DISS. ETH NO. 23804

Novel Pentafluorosulfanyl-Substituted Building Blocks and Evaluation of their Physicochemical Properties and Polycationic Hexasaccharides Derived from α-Cyclodextrin

A thesis submitted to attain the degree of

DOCTOR OF SCIENCES of ETH ZURICH

(Dr. sc. ETH ZURICH)

presented by

ADRIEN JOLITON

Master of Science and Diplôme d'Ingénieur, INSA Rouen

born on 19.07.1987

citizen of France

accepted on the recommendation of

Prof. Dr. Erick M. Carreira, examiner

Prof. Dr. Karl-Heinz Altmann, co-examiner

2016

Acknowledgements

First and foremost, I would like to express my gratitude to Prof. Dr. Erick M. Carreira for giving me the opportunity to join his group and for supervising my doctoral studies. I am thankful for the freedom I had in managing the projects, and for his trust and patience when things did not work as anticipated. I also thank him for his helpful advice and creative ideas.

I further want to thank Prof. Dr. Karl-Heinz Altmann for accepting the co-examination of this thesis without hesitation. His valuable comments and corrections have resulted in a significant improvement of this manuscript.

I would like to thank Dr. Jean-Marc Plancher from F. Hoffmann La Roche for the collaboration on the pentafluorosulfanyl project. He accepted without hesitation to help us, and always answered my questions about the interpretation of the results we obtained with enthusiasm.

I am also grateful to Hannes Zipfel for his huge help with the hexasaccharides. As a pioneer on this project, he taught me all the important subtilities to know about these compounds.

I was fortunate to be a member of the G338 laboratory, endowed with a fantastic working atmosphere. Having great labmates definitely makes easier the life as a PhD student. Therefore, big thanks go to all past and present members of G338, who will remain *Inglourious Basterds* forever, Dr. Sébastien Goudreau, Dr. Simon Breitler, Dr. Nikolas Huwyler, Christian Ebner, Stefan Fisher, Leonardo Nannini and Michael Imhof, for all the memorable moments we shared in the lab, and also outside ETH.

I would also like to thank all the former and current members of the Carreira group for the stimulating environment. It was a formidable experience to be surrounded with so many brillant and motivated scientists, who were always very helpful. In particular, I am grateful to Prof. Dr. David Sarlah for his support, his mentorship and all the interesting discussions during his evening lab tours.

I am indebted to the proofreaders of this thesis, Johannes Boshkow, Christian Ebner, Stefan Fischer, Robert Gillespie, Leonardo Nannini, Matthias Westphal, Hannes Zipfel, Thibault Harmand and Dr. Christopher White. Their comments and suggestions helped considerably to improve the quality of this manuscript.

In addition, the excellent infrastructure at ETH Zurich as well as its helpful staff were essential to the achievement of this work. Therefore, I would like to thank the members of the

NMR service (Dr. Marc-Olivier Ebert, René Arnold, Rainer Frankenstein and Stephan Burkhardt), the SMoCC team (Dr. Michael D. Wörle, Dr. Nils Trapp and Michael Solar), the MS service (Dr. Xiangyang Zhang, Louis Bertschi, Oswald Greter and Rolf Häfliger), the HCI-shop, the glassware cleaning team and all the other facilities. Special thanks also go to Anke Kleint for her inestimable administrative support.

During my time at ETH, football was an important activity in my time outside the lab. I would like to thank all the players who joined the Thursday afternoon sessions, as well as all the members of the *Don't Panic* team. I also wish the Carreira group to win the PharmaCup again.

J'ai la chance de conserver de formidables amis depuis mon départ de Normandie. Il est fantastique que l'on ait pu garder contact et que l'on puisse se voir régulièrement malgré la distance qui nous sépare les uns des autres. Je tiens à remercier en particulier Benoit Delpeuch, Denis Blougorn, Aurore Sergent et Kevin Simon pour tous les moments inoubliables passés ensemble depuis maintenant plus de dix ans. Merci pour toutes les soirées de rigolade épiques qui font complètement sortir de la réalité ! J'adresse aussi une dédicace à Takahiro Hayashi et à Thibault Harmand, champion de chat-bite, pour la soirée "spéciale" qui fut une des plus grandes péripéties durant mes années de doctorat.

Je remercie ma famille, et en particulier mes parents Philippe et Marie-Isabelle ainsi que mon frère Hugo pour leur soutien durant mes parcours scolaire et universitaire qui ont abouti à cette thèse. Je leur suis reconnaissant pour l'éducation dont j'ai bénéficié, qui m'a offert des valeurs d'intégrité et d'ouverture d'esprit, et sans laquelle je ne serais pas arrivé là où j'en suis aujourd'hui.

Enfin, rien n'aurait été possible sans la présence de Claudia Elena Murar à mes côtés. Sa patience, son réconfort et son aide sans faille ont été déterminants dans l'accomplissement de ce travail. Le bonheur et le soutien qu'elle m'a apporté durant ces dernières années sont tout simplement inestimables. Mulţumesc Claudia, te iubesc.

Publications

A. Joliton, E. M. Carreira, *Org. Lett.* **2013**, *15*, 5147–5149

Ir-Catalyzed Preparation of SF_5-Substituted Potassium Aryl Trifluoroborates via C–H Borylation and their Application in the Suzuki–Miyaura Reaction

A. Joliton, E. M. Carreira, *Synlett* **2015**, 737–740

Novel SF_5-Anilines and SF_5-Aryl Ethers from SF_5-Subtituted Potassium Aryl Trifluoroborates

A. Joliton, J.-M. Plancher, E. M. Carreira, *Angew. Chem. Int. Ed.* **2016**, *55*, 2113–2117

Formation of α-SF_5-Enolate enables Preparation of 3-SF_5-Quinolin-2-ones, 3-SF_5-Pyridin-2-ones: Evaluation of their Physicochemical Properties

Poster Presentation

SSCI-Symposium, Zürich, Switzerland, January 2016

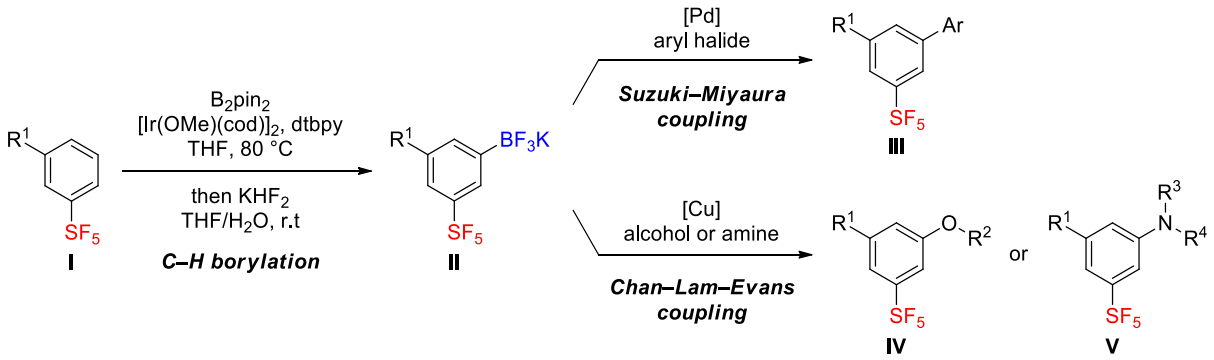
Generation of α-SF_5-Enolate: Preparation of Novel SF_5-Heterocycles

Table of Contents

Abstract

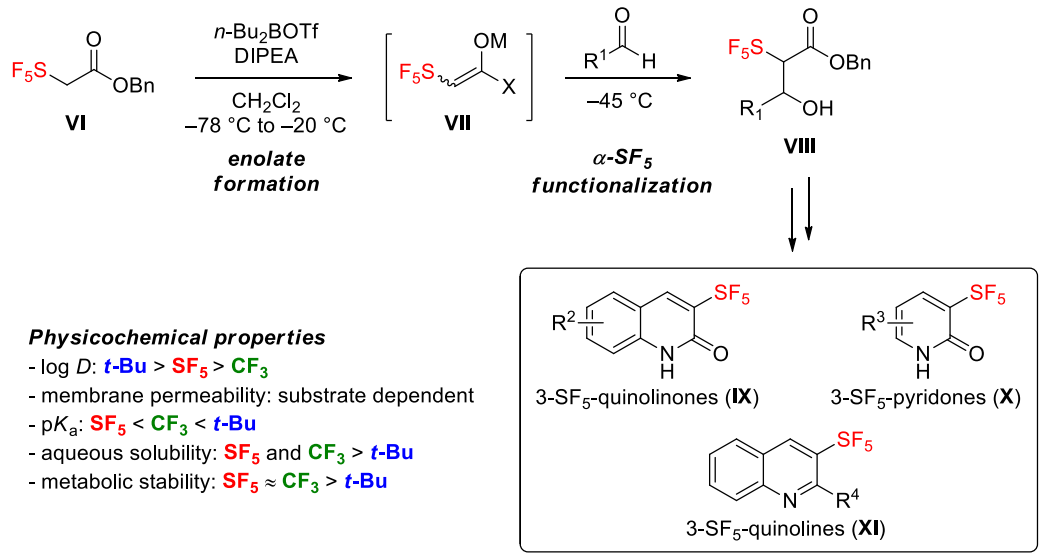
Among the fluorine-containing substituents, the pentafluorosulfanyl group (SF_5) is emerging as an attractive entity because of its unique combination of properties. For example, it is more electron-withdrawing, more lipophilic, and more chemically and thermally stable than the trifluoromethyl group. Despite these assets, and the reported potential utility of this substituent in pharmaceuticals, agrochemicals and materials, more extensive applications of the SF_5 group are limited due to the scarcity of methods to prepare SF_5-substituted building blocks, in particular SF_5 heterocycles. In this context, the first part of this thesis describes the synthesis of unprecedented SF_5 compounds as well as the investigation of their reactivity.

Firstly, regioselective iridium catalyzed C–H borylation of 3-substituted SF_5-aryl compounds **I** delivered novel SF_5-substituted potassium aryltrifluoroborates **II** (Scheme I). The versatility of these boron reagents was demonstrated by using them in Suzuki–Miyaura and Chan–Lam–Evans cross-coupling reactions. This methodology enabled access to a variety of uncommon 1,3,5-trisubstituted SF_5-substituted aryl compounds, such as biaryls **III**, aryl ethers **IV**, and anilines **V**.



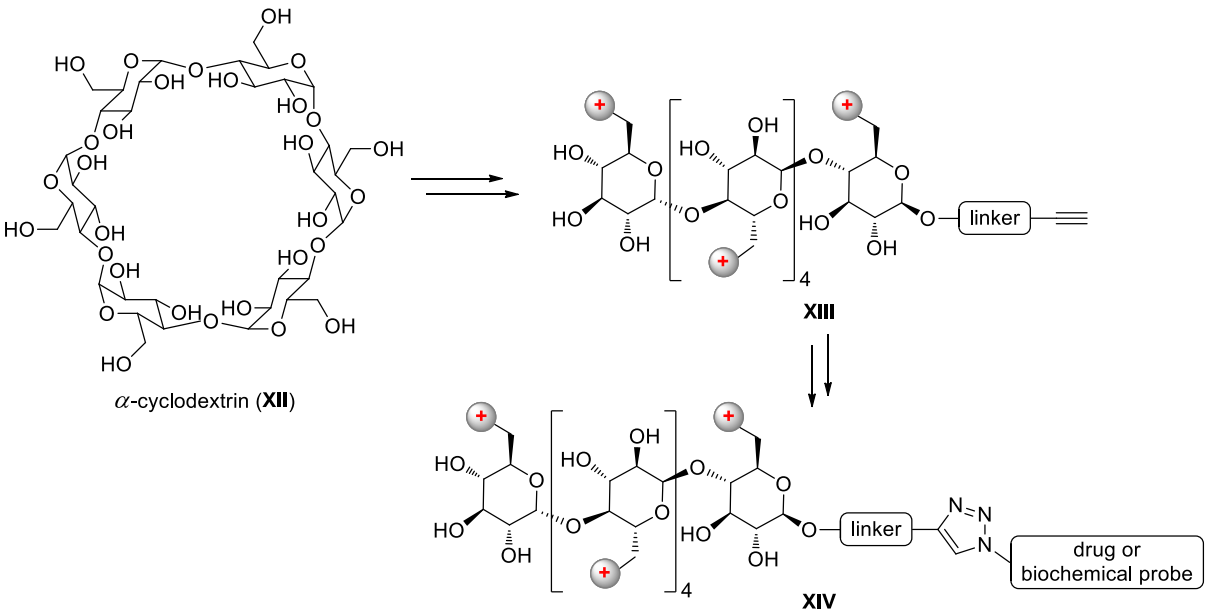
Scheme I. Preparation of 1,3,5-trisubstituted SF_5-aryl compounds *via* C–H borylation.

Subsequently, efforts towards the synthesis of novel SF_5-containing *N*-heterocycles were achieved. Initial approaches involving direct pentafluorosulfanylation of aryl compounds were unfruitful. Therefore, the boron-mediated generation of an α-SF_5-enolate **VII** from benzyl SF_5-acetate **VI** and its participation in aldol reactions was developed (Scheme II). This unprecedented α-functionalization of the SF_5 group afforded adducts **VIII** in high yields. Further elaborations culminated in the synthesis of 3-SF_5-quinolones **IX**, 3-SF_5-pyridones **X**, and 3-SF_5-quinolines **XI**. Moreover, the comparison of their physicochemical data with those of their trifluoromethyl and *tert*-butyl analogues was performed, and it was confirmed that the SF_5 group can be considered as a surrogate for these substituents with property-modulating effects.



Scheme II. Synthesis of 3-SF_5-quinolones, 3-SF_5-pyridones, and 3-SF_5-quinolines *via* generation of an α-SF_5-enolate.

The second part of this thesis describes the concise preparation of a clickable polycationic hexasaccharide **XIII** derived from α-cyclodextrin **XII** (Scheme III). The synthesis relies on ring cleavage, followed by glycosylation of a linker and cationization at 6-positions. One example of conjugation with biotin by click chemistry was also performed.



Scheme III. Preparation of a polycationic hexasaccharide from α-cyclodextrin and its conjugation by click chemistry.

Résumé

Parmi les substituants fluorés, le groupe pentafluorure de soufre (SF_5) est en train d'émerger comme une entité attractive du fait de la combinaison particulière de ses propriétés. En effet, il possède un effet électronique plus attracteur que le groupe trifluorométhyle, et est également plus lipophile, et plus stable chimiquement et thermiquement. Malgré ces atouts, et les quelques rapports sur le potentiel bénéfice de ce substituant en chimie pharmaceutique, en agrochimie et dans la science des matériaux, l'utilisation à plus grande échelle du groupe SF_5 reste limitée. Cela est dû à la rareté des méthodes connues pour préparer des composés incluant ce substituant, en particulier des hétérocycles. Ainsi, la première partie de cette thèse décrit la synthèse de composés inédits substitués avec un groupe SF_5, ainsi que l'investigation de leur réactivité.

Tout d'abord, de nouveaux aryltrifluoroborates de potassium **II**, comprenant le groupe SF_5, ont été préparés à partir de pentafluorures de soufre arylés **I**, substitués en position 3, *via* borylation par activation C–H catalysée par l'iridium (Schéma I). L'utilisation de ces dérivés boroniques dans les réaction de couplage de Suzuki–Miyaura et de Chan–Lam–Evans a illustré leur polyvalence. Cette méthode a ainsi permis d'accéder à des composés benzéniques 1,3,5-trisubstitués incorporant un groupe SF_5 sans précédent, tels que des biaryles **III**, des éthers d'aryle **IV**, et des anilines **V**.

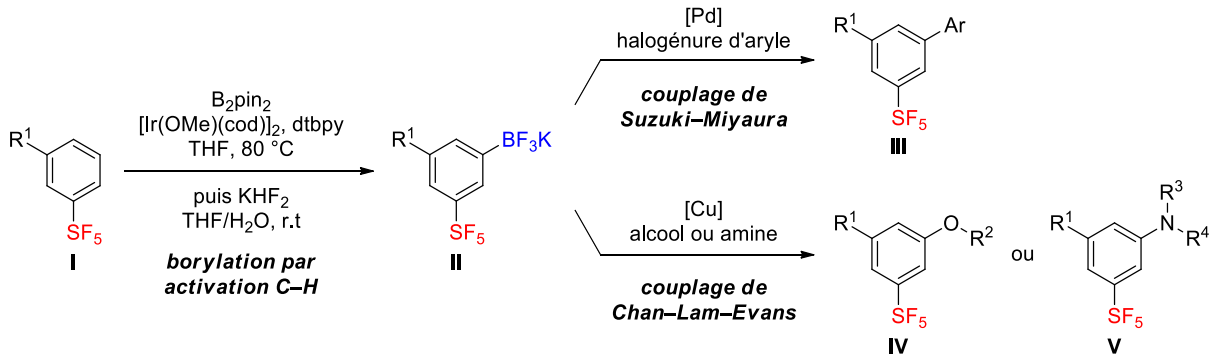


Schéma I. Préparation de composés 1,3,5-trisubstitués comprenant le groupe SF_5 *via* borylation par activation C–H catalysée par l'iridium.

Par la suite, les efforts ont été concentrés sur la synthèse de nouveaux hétérocycles azotés comprenant le groupe SF_5. Les approches initiales impliquant une introduction directe du substituent SF_5 sur un cycle aromatique ont échouées. Par conséquent, la génération d'un énolate de bore en position α du SF_5 **VII** à partir de l'acetate de benzyle **VI**, et sa participation dans des aldolisations, ont été développées avec succès (Schéma II). Cette fonctionnalisation inédite en position *α* du groupe SF_5 a ainsi permis la préparation de produits d'addition **VIII** avec de hauts rendements. La transformation de ces composés a ensuite culminé avec la

synthèse de 3-SF_5-quinolones **IX**, de 3-SF_5-pyridones **X**, et de 3-SF_5-quinolines **XI**. De plus, la comparaison de leurs données physico-chimiques avec celles de leurs analogues trifluorométhylés and *tert*-butylés a été effectuée, et a confirmée que le SF_5 peut être considéré comme un substitut de ces groupes fonctionnels conférant une modulation des propriétés.

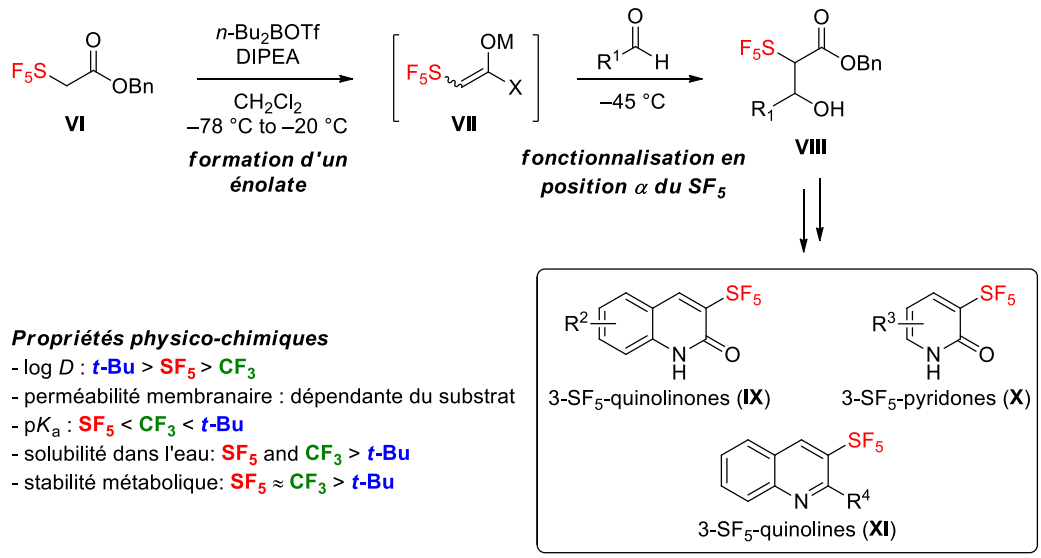


Schéma II. Synthèse de 3-SF_5-quinolones, de 3-SF_5-pyridones, et de 3-SF_5-quinolines *via* génération d'un énolate en position α du groupe SF_5.

La seconde partie de cette thèse décrit la préparation concise d'un hexasaccharide polycationique fonctionnalisable par chimie click **XIII**, À partir de l'α-cyclodextrine **XII** (Schéma III). La synthèse repose sur l'ouverture de la cyclodextrine, suivie de la glycosylation d'un lieur et de la cationisation aux positions 6. Un exemple de conjugaison avec la biotine par cycloaddition a aussi été réalisé.

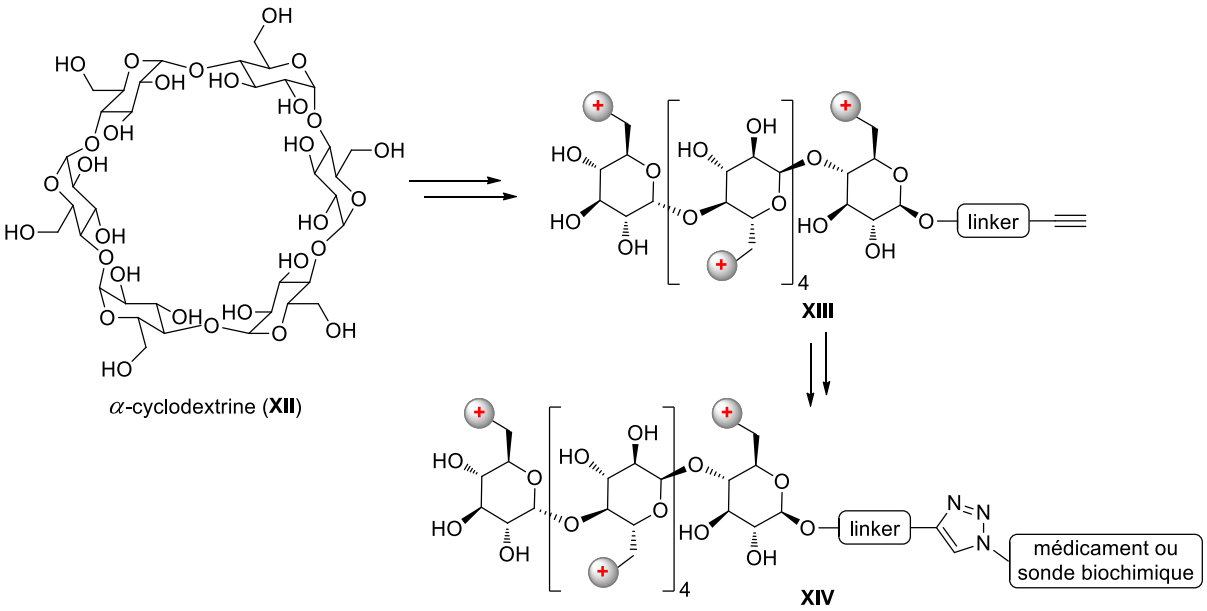


Schéma III. Préparation d'un hexasaccharide polycationique à partir de l'α-cyclodextrine et sa conjugaison par chimie click.

List of Abbreviations

$[\alpha]^{T}_{D}$	specific rotation at temperature T at the sodium D line
Å	ångström
Ac	acetyl
acac	acetylacetonate
AIBN	2,2'-azobisisobutyronitrile
aq.	aqueous
Ar	aryl
atm	atmosphere
BBB	blood-brain-barrier
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
b.p.	boiling point
bpy	2,2'-bipyridine
br	broad
Bu	butyl
c	centi
°C	degree Celsius
CAM	cerium ammonium molybdate
cat.	catalytic
Cl	intrinsic clearance rate
cm	centimeter
CNS	central nervous system
cod	1,5-cyclooctadiene
conc.	concentrated
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
δ	NMR chemical shift in ppm
$\Delta\varepsilon$	dielectric anisotropy
d	doublet, day
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
4-DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
dppf	1,1'-bis(diphenylphosphino)ferrocene

d.r.	diastereomeric ratio
dtbpy	4,4'-di-*tert*-butyl-2,2'-dipyridyl
E	electrophile
EDC	1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide
EDTA	ethylenediaminetetraacetic acid
EI	electron impact ionization
equiv	equivalent
e.r.	enantiomeric ratio
ESI	electronspray ionization
Et	ethyl
g	gram
GAG	glycosaminoglycan
GlcA	glucuronic acid
GC-MS	gas chromatography-mass spectrometry
GlcN	glucosamine
GlcNAc	*N*-acetylglucosamine
h	hour
h	Planck constant
Hex	hexanes
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HS	heparan sulfate
Hz	hertz
i	*iso*
IC_{50}	half maximal inhibitory concentration
IdoA	iduronic acid
IR	infrared
J	coupling constant
L	liter
LC-MS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
Log *D*	logarithm of the 1-octanol/H_2O partition coefficient
μ	micro
m	milli, multiplet, meter
M	mega, molar
MALDI	matrix-assisted laser desorption/ionization
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minute
mol	mole
m.p.	melting point
Ms	methanesulfonyl
MS	molecular sieves, mass spectrometry
v	vibration frequency in cm^{-1}

n	nano
n	normal, unbranched alkyl chain
n/a	not available
NBS	*N*-bromoosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
[O]	oxidation
π	hydrophobic parameter
p	pentuplet
PDC	pyridinium dichromate
PG	protecting group
Ph	phenyl
pH	negative logarithm of hydrogen ion concentration
pin	pinacolato
pK_a	negative logarithm of the acid dissociation constant
PPA	polyphosphoric acid
ppm	parts per million
Pr	propyl
q	quartet
quant.	quantitative
R_f	retention factor
rpm	revolutions per minute
r.t.	room temperature
σ	Hammett substituent constant
s	singlet
SCE	saturated calomel electrode
T	temperature
t	triplet
t	*tert*
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TC	thiophene-2-carboxylate
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFP	tri(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylene-1,2-diamine
TMS	trimethylsilyl
t_R	retention time
Ts	*para*-toluenesulfonyl
UV	ultraviolet
V	volt
W	watt

1

Novel Pentafluorosulfanyl-Substituted Building Blocks and Evaluation of their Physicochemical Properties

1. Novel Pentafluorosulfanyl-Substituted Building Blocks and Evaluation of their Physicochemical Properties

1.1. Introduction

1.1.1. General Properties of the Pentafluorosulfanyl Group

Since the preparation of the fluorinated drugs fludrocortisone (**1**)[1] and 5-fluoroacil (**2**)[2] in the 1950s (Figure 1.1.1), the role of fluorine in life sciences considerably increased in the last six decades. Nowadays, it is well known that the introduction of fluorine into a molecule can have a remarkable impact on various parameters, such as conformation, pK_a, intrinsic potency, membrane permeability, metabolic stability, or pharmacokinetic properties.[3] Incorporation of fluorine is now nearly systematic in drug development programs to enhance the properties of a compound and around a fifth of all marketed drugs contain at least one fluorine atom. Examples include the antidepressant fluoxetine (Prozac) (**3**), the top-selling cholesterol-lowering drug atorvastatin (Lipitor) (**4**), and the antibacterial ciprofloxacin (Ciprobay) (**5**).

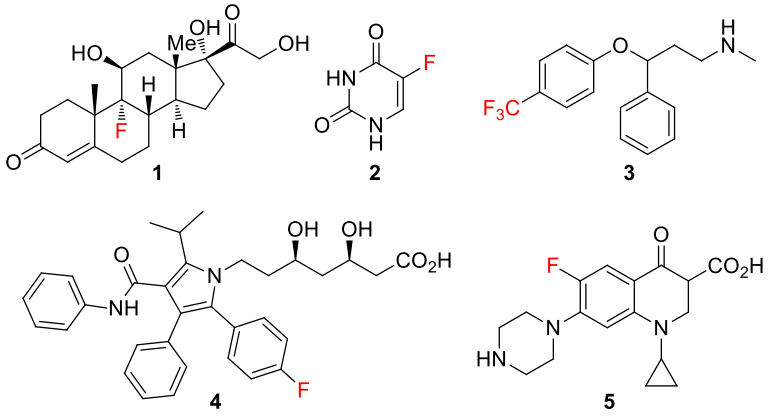


Figure 1.1.1. Structures of fludrocortisone (**1**), 5-fluorouracil (**2**), fluoxetine (**3**), atorvastatin (**4**), and ciprofloxacin (**5**).

Such fluorinated molecules contain either single fluorine substituents (aliphatic in **1**, or aromatic in **2**, **4** and **5**), or substituents containing several fluorine atoms, such as the trifluoromethyl group in fluoxetine (**3**). Because the presence of multiple fluorine atoms exerts significant changes on relevant parameters, those fluorinated substituents are used to adjust the

[1] J. Fried, E. F. Sabo, *J. Am. Chem. Soc.* **1954**, *76*, 1455–1456.
[2] C. Heidelberger, N. K. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E. Pleven, J. Scheiner, *Nature* **1957**, *179*, 663–666.
[3] a) K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; c) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015,** *58*, 8315–8359**.**

properties of bioactive compounds. The CF_3 group is certainly the most common of the fluorine-containing functional groups in drug molecules and agrochemicals, and the early interest in this substituent[4] encouraged organic chemists to design synthetic methods for its introduction. This resulted in the development of various reagents and strategies allowing the preparation of numerous CF_3 intermediates and CF_3 building blocks by electrophilic, nucleophilic and radical trifluoromethylation.[5] In addition, other fluorine-containing moieties are more and more popular due to their potential in life sciences, and have attracted the interest of organic chemists. Thus, efficient methods have been recently described for the direct introduction of fluorinated groups[5e] such as pentafluoroethyl (CF_2CF_3),[6] difluoromethyl (CHF_2),[7] trifluoromethoxy (OCF_3),[8] or trifluoromethylthio (SCF_3).[9] In comparison with these substituents, other fluorine-containing groups are underrepresented, mainly because of the scarcity of methods to access the corresponding building blocks. For a long time, this was the case for the pentafluorosulfanyl substituent (SF_5). However, this functional group has gained increasing attention in the last decade, and the number of reports with biological applications is exploding.[10]

The relatively recent history of the SF_5 substituent started in 1933 with the discovery of the dimer of SF_5, disulfur decafluoride S_2F_{10}, as a side product in the synthesis of sulfur hexafluoride SF_6 by exposure of S_8 to F_2.[11] SF_5-compounds are considered to be organic derivatives of SF_6. Accordingly, the sulfur atom adopts a hypervalent hexacoordinated state with an octahedral geometry, bearing four equatorial and one axial fluorine atoms. X-ray analyses of organic compounds containing a SF_5 substituent showed that the equatorial fluorine atoms are actually twisted out of the equatorial plane by 2-4° towards the axial fluorine, resulting in an additional component to the overall dipole moment (*vide infra*). For example, the F_{ax}–S–F_{eq}

[4] H. L. Yale, *J. Med. Pharm. Chem.* **1959**, *1*, 121–133.
[5] For reviews about trifluoromethylation methods, see: a) J. A. Ma, D. Cahard, *Chem. Rev.* **2008**, *108*, Pr1–Pr43; b) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475–4521; c) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477; d) X. F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2012**, *7*, 1744–1754; e) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264; f) C. Alonso, E. M. de Marigorta, G. Rubiales, F. Palacios, *Chem. Rev.* **2015**, *115*, 1847–1935.
[6] For recent examples of pentafluoroethylation, see: a) C. Pooput, W. R. Dolbier, M. Medebielle, *J. Org. Chem.* **2006**, *71*, 3564–3568; b) I. Popov, S. Lindeman, O. Daugulis, *J. Am. Chem. Soc.* **2011**, *133*, 9286–9289; c) N. D. Litvinas, P. S. Fier, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 536–539; d) A. Lishchynskyi, V. V. Grushin, *J. Am. Chem. Soc.* **2013**, *135*, 12584–12587; e) H. Serizawa, K. Aikawa, K. Mikami, *Org. Lett.* **2014**, *16*, 3456–3459; f) L. I. Panferova, F. M. Miloserdov, A. Lishchynskyi, M. M. Belmonte, J. Benet-Buchholz, V. V. Grushin, *Angew. Chem. Int. Ed.* **2015**, *54*, 5218–5222.
[7] For recent examples of difluoromethylation, see: a) K. Fujikawa, Y. Fujioka, A. Kobayashi, H. Amii, *Org. Lett.* **2011**, *13*, 5560–5563; b) Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond, P. S. Baran, *J. Am. Chem. Soc.* **2012**, *134*, 1494–1497; c) P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 5524–5527; d) C. Matheis, K. Jouvin, L. J. Goossen, *Org. Lett.* **2014**, *16*, 5984–5987; e) C. D. Shao, G. F. Shi, Y. H. Zhang, S. L. Pan, X. H. Guan, *Org. Lett.* **2015**, *17*, 2652–2655.
[8] For recent examples of trifluoromethoxylation, see: a) C. H. Huang, T. Liang, S. Harada, E. Lee, T. Ritter, *J. Am. Chem. Soc.* **2011**, *133*, 13308–13310; b) K. N. Hojczyk, P. J. Feng, C. B. Zhan, M. Y. Ngai, *Angew. Chem. Int. Ed.* **2014**, *53*, 14559–14563. For a review, see: F. R. Leroux, B. Manteau, J. P. Vors, S. Pazenok, *Beilstein J. Org. Chem.* **2008**, *4*, 13.
[9] For recent reviews about trifluoromethylthiolation methods, see: a) F. Toulgoat, S. Alazet, T. Billard, *Eur. J. Org. Chem.* **2014**, 2415–2428; b) X. H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731–764.
[10] For reviews about the chemistry and applications of SF_5-compounds, see: a) J. T. Welch in *Fluorine in Pharmaceutical and Medicinal Chemistry. From Biophysical Aspects to Clinical Applications* (Eds: V. Gouverneur, K. Müller), Imperial College Press, London, **2012**, pp.175–207; b) S. Altomonte, M. Zanda, *J. Fluorine Chem.* **2012**, *143*, 57–93; c) P. R. Savoie, J. T. Welch, *Chem. Rev.* **2015**, *115*, 1130–1190.
[11] a) K. G. Denbigh, R. Whytlaw-Gray, *Nature* **1933**, *131*, 763; b) K. G. Denbigh, R. Whytlaw-Gray, *J. Chem. Soc.* **1934**, 1346–1352.

bond angle in 3-SF_5-benzoic acid has been determined to be 87.6° (Figure 1.1.2).[12] The bond lengths follow the trend S–F_{eq} < S–F_{ax} < S–C; in the case of 3-SF_5-benzoic acid, they are 1.561 Å, 1.587 Å and 1.804 Å, respectively. The distinct shape of the SF_5 group is also well visualized by ^{19}F NMR spectroscopy. Indeed, SF_5-containing compounds display characteristic AB_4-type spectra, with a coupling constant $^2J(F_{ax}–F_{eq})$ usually ranging between 145 and 150 Hz (Figure 1.1.2 shows the ^{19}F NMR spectrum of 4-SF_5-benzoic acid).

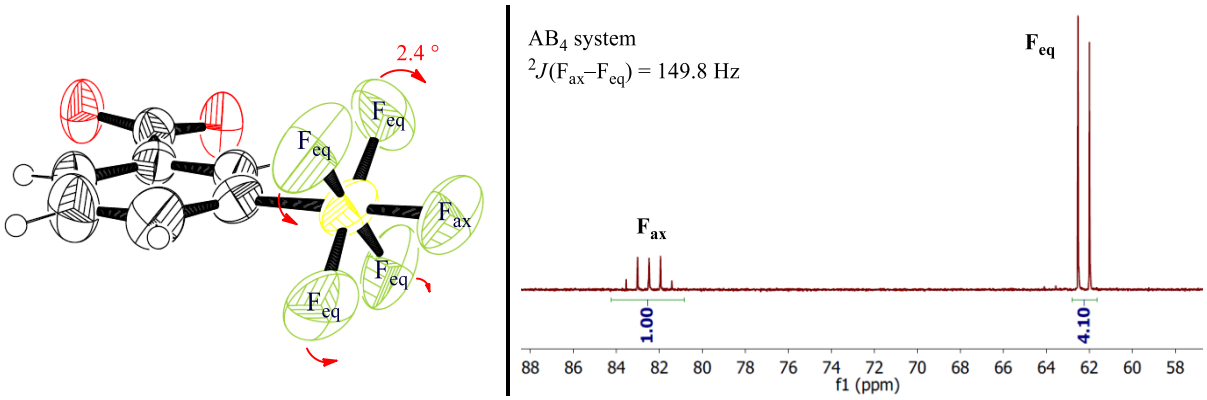


Figure 1.1.2. Left: X-ray crystal structure of 3-SF_5-benzoic acid; right: ^{19}F NMR spectrum of 4-SF_5-benzoic acid.

The pentafluorosulfanyl group possesses a unique set of properties, which are potentially attractive to implement in structures of interest. In terms of size, the SF_5 group is situated between the CF_3 and *t*-Bu groups. Indeed, the bigger size of the SF_5-substituent compared to the CF_3 have been illustrated using space-filling molecular models with diameters of 6.4 Å and 6.1 Å, respectively (Figure 1.1.3).[13]

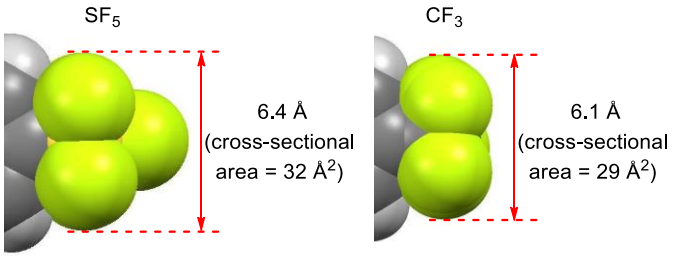


Figure 1.1.3. Size comparison of SF_5 and CF_3 groups.

With five fluorine atoms, the pentafluorosulfanyl group is expected to show high lipophilicity. Indeed, comparison of its hydrophobic parameter (π_X) with other relevant functional groups point up this lipophilic character (Table 1.1.1).[14] This parameter, introduced by Hansch and describing the contribution of a substituent to the lipophilicity of a compound,

[12] C. Zarantonello, A. Guerrato, E. Ugel, R. Bertani, F. Benetollo, R. Milani, A. Venzo, A. Zaggia, *J. Fluorine Chem.* **2007**, *128*, 1449–1453.
[13] P. G. Nixon, R. Winter, D. G. Castner, N. R. Holcomb, D. W. Grainger, G. L. Gard, *Chem. Mater.* **2000**, *12*, 3108–3112.
[14] C. Hansch, A. Leo, S. H. Unger, K. H. Kim, Nikaitan.D, E. J. Lien, *J. Med. Chem.* **1973**, *16*, 1207–1216.

represents the difference in the logarithms of partition coefficients of substituted and unsubstituted compounds ($\pi_X = \log P_X - \log P_H$). In the present case, the values were measured for substituted benzenes. According to these data, the pentafluorosulfanyl group ($\pi_{SF_5} = 1.23$) exhibits a higher lipophilicity than the trifluoromethoxy group ($\pi_{OCF_3} = 1.04$) and the trifluoromethyl group ($\pi_{CF_3} = 0.88$). However it is less lipophilic than the (trifluoromethyl)thio group ($\pi_{SCF_3} = 1.44$) and the *tert*-butyl group ($\pi_{t\text{-Bu}} = 1.98$).

Table 1.1.1. Hydrophobic parameters of several substituents from benzene solute system.

$\pi_X = \log P_X - \log P_H$

X	*t*-Bu	SCF_3	SF_5	OCF_3	CF_3	Cl	CH_3	F	H	NO_2
π_X	1.98	1.44	1.23	1.04	0.88	0.71	0.56	0.14	0	–0.28

The SF_5 group is known as a very strong electron-withdrawing substituent. The comparisons of the dissociation constants of *meta*- and *para*-substituted benzoic acids, and of the Hammett parameters σ_m and σ_p, enable an evaluation of the electron-withdrawing effect of the SF_5 substituent (Table 1.1.2).[14,15] The values reported show that among the fluorine-containing functional groups, the SF_5 group possesses the strongest electron-withdrawing effect. In addition, the dipole moments of (pentafluorosulfanyl)benzene and (trifluoromethyl)benzene, 3.44 D and 2.60 D, respectively,[15a] also emphasize this trend.

Table 1.1.2. Dissociation constants of *meta*- and *para*-substituted benzoic acids and Hammett parameters.[a]

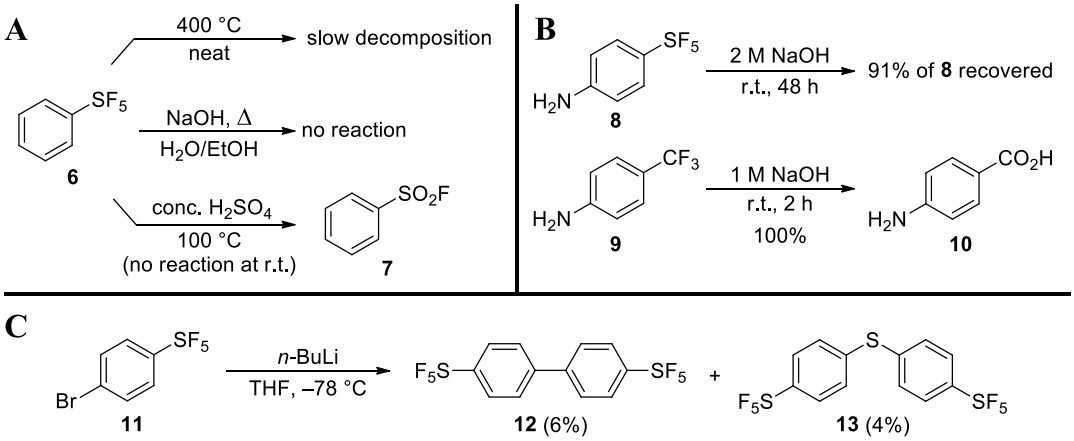
X	**p*K*a (*meta*)**	**p*K*a (*para*)**	**σ_m**	**σ_p**
NO_2	4.66	4.53	0.73	0.77
SF_5	4.82	4.70	0.61	0.69
SCF_3	5.13	4.98	0.41	0.51
OCF_3	5.15	5.19	0.39	0.36
CF_3	5.11	4.95	0.43	0.53

a) In EtOH:H_2O (1:1) at 25 °C.

It is known that SF_5-aryl compounds have good thermal and chemical stability, at least equal to their CF_3-equivalents.[16] Phenylsulfur pentafluoride (**6**) suffers from minor degradation when

[15] (a) W. A. Sheppard, *J. Am. Chem. Soc.* **1962**, *84*, 3072–3076; (b) W. A. Sheppard, *J. Am. Chem. Soc.* **1965**, *87*, 2410–2420; (c) C. J. Byrne, D. A. R. Happer, M. P. Hartshorn, H. K. J. Powell, *J. Chem. Soc., Perkin Trans. 2* **1987**, 1649–1653; (d) J. Shorter, *Pure Appl. Chem.* **1997**, *69*, 2497–2510.
[16] W. A. Sheppard, *J. Am. Chem. Soc.* **1962**, *84*, 3064–3072.

it is heated at 400 °C for several hours in a sealed glass tube (Scheme 1.1.1. A). No decomposition was observed when it was refluxed in a solution of sodium hydroxide in aqueous ethanol, as well as in presence of concentrated sulfuric acid at room temperature. However, similarly to (trifluoromethyl)benzene, **6** is hydrolyzed to benzenesulfonyl fluoride **7** when it is heated at 100 °C in concentrated sulfuric acid. Moreover, a study reported by Philp showed that the hydrolysis of 4-(pentafluorosulfanyl)aniline (**8**) in aqueous sodium hydroxide solution is much slower than for 4-(trifluoromethyl)aniline (**9**) (Scheme 1.1.1.B).[17] The SF_5-substituent is also generally tolerant to various conditions for common synthetic transformations (oxidizing and reducing agents, strong acids and bases, Ni-, Pd- and Pt-catalyzed hydrogenation or C–C coupling reactions). One limitation has been found when lithiation of 1-bromo-4-(pentafluorosulfanyl)benzene (**11**) was attempted by treatment with *n*-BuLi (Scheme 1.1.1.C).[18] The reaction led to a complex mixture of products, including **12** and **13** in very low yields (6% and 4%, respectively). Degradation of SF_5-organyl compounds was also recently reported by treatment with a binuclear rhodium hydrido complex *via* defluorination.[19]



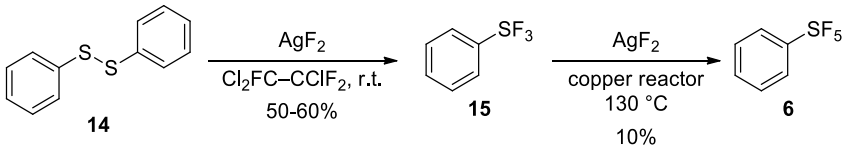
Scheme 1.1.1. Thermal and chemical stability of the SF_5 group.

1.1.2. Synthesis and Chemistry of SF_5-Substituted Compounds

1.1.2.1. SF_5-Aryl Compounds

The first synthesis of pentafluorosulfanylbenzene was documented by Sheppard in 1960 by stepwise oxidative fluorination of the corresponding phenyl disulfide (**14**) (Scheme 1.1.2).[20] Treatment of **14** with silver difluoride in trichlorotrifluoroethane afforded the intermediate phenylsulfur trifluoride **15**, which upon heating to 130 °C in a copper reactor in presence of AgF_2, was converted into **6**, isolated in about 10% yield after distillation.

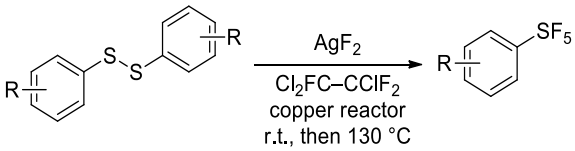
[17] R. D. Bowden, P. J. Comina, M. P. Greenhall, B. M. Kariuki, A. Loveday, D. Philp, *Tetrahedron* **2000**, *56*, 3399–3408.
[18] P. Kirsch, M. Bremer, M. Heckmeier, K. Tarumi, *Angew. Chem. Int. Ed.* **1999**, *38*, 1989–1992.
[19] L. Zámostná, T. Braun, B. Braun, *Angew. Chem. Int. Ed.* **2014**, *53*, 2745–2749.
[20] W. A. Sheppard, *J. Am. Chem. Soc.* **1960**, *82*, 4751–4752.

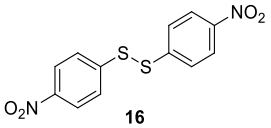
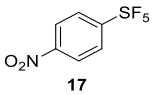
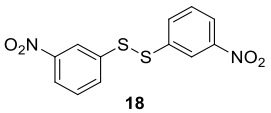
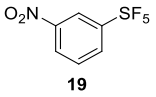
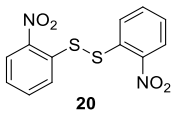
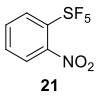
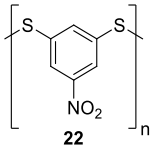
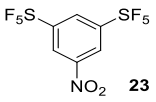


Scheme 1.1.2. First preparation of pentafluorosulfanylbenzene.

Using a modified one-pot procedure, Sheppard then reported other examples of SF_5-substituted arenes, all of them incorporating a nitro group (Table 1.1.3).[16] In this way, *para*- and *meta*-nitro-(pentafluorosulfanyl)benzene could be synthesized in 15% and 30% yield, respectively. The use of bis-(*o*-nitrophenyl)-disulfide (**20**) failed to give the desired SF_5-product (Entry 3). The corresponding phenylsulfur trifluoride was observed, but underwent decomposition upon heating. Interestingly, aromatic compound **23** bearing two SF_5-substituents could be prepared from the polymeric disulfide **22** in 11% yield.

Table 1.1.3. Oxidative fluorination of aryl disulfides.



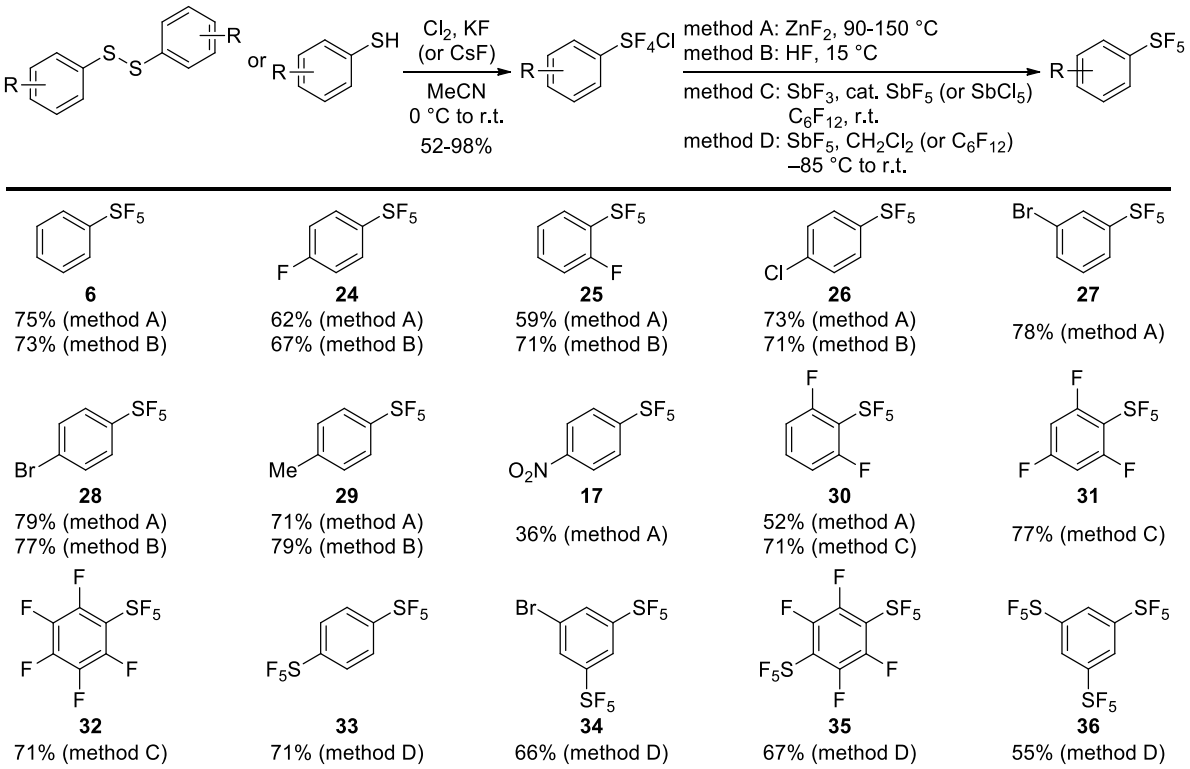
Entry	$(Ar–S)_2$	Product	Yield
1	 **16**	 **17**	15%
2	 **18**	 **19**	30%
3	 **20**	 **21**	0%
4	 **22**	 **23**	11%

Because of the low yields obtained as well as the poor reproducibility in the Sheppard's method, the chemistry of SF_5-aryl compounds was almost completely abandoned. Interest in these compounds revived in the 1990s,[21] and few modifications of the original procedure were developed, such as the use of XeF_2 instead of AgF_2.[22] A significant advance was achieved when

[21] (a) A. K. S. Clair, T. L. S. Clair, J. S. Thrasher, *US 5220070*, **1993**; (b) A. G. Williams, N. R. Foster, *WO 94/22817*, **1994**.
[22] X. B. Ou, A. F. Janzen, *J. Fluorine Chem.* **2000**, *101*, 279–283.

elemental fluorine (F_2/N_2) was used,[17,23] converting **16** and **18** into the corresponding SF_5-arenes in 39% and 41%, respectively. This convenient access to larger quantities of SF_5-substituted nitrobenzenes generalized their commercialization. Shortly after, Thrasher reported the synthesis of phenylsulfur pentafluoride compounds with substituents other than nitro using Sheppard's procedure.[24] In this way, building blocks with fluorine in *ortho*-position or chlorine in *para*-position of the SF_5 were documented. Thrasher also disclosed that the presence of copper was essential for the reaction to succeed (either as added strips, or as the reactor itself).[24,25]

A breakthrough in the synthesis of pentafluorosulfanylarenes has recently been achieved by Umemoto.[26] This two-step method, avoiding the use of elemental fluorine, relies on the preparation of arylsulfur chlorotetrafluoride intermediates by treating diaryl disulfides or aryl thiols with chlorine in presence of an alkali metal fluoride in acetonitrile (Scheme 1.1.3).



Scheme 1.1.3. Preparation of SF_5-arenes using Umemoto's procedure.

After purification by distillation or crystallization, the $ArSF_4Cl$ products were converted into their corresponding SF_5-aryl products by displacement of the chloride with a fluoride source,

[23] (a) R. D. Bowden, M. P. Greenhall, J. S. Moillet, J. Thomson, *WO 97/05106*, **1997**; (b) R. D. Chambers, R. C. H. Spink, *Chem. Commun.* **1999**, 883–884.
[24] (a) A. M. Sipyagin, C. P. Bateman, Y. T. Tan, J. S. Thrasher, *J. Fluorine Chem.* **2001**, *112*, 287–295; (b) A. M. Sipyagin, V. S. Enshov, S. A. Kashtanov, C. P. Bateman, B. D. Mullen, Y. T. Tan, J. S. Thrasher, *J. Fluorine Chem.* **2004**, *125*, 1305–1316.
[25] A. M. Sipyagin, C. P. Bateman, A. V. Matsev, A. Waterfeld, R. E. Jilek, C. D. Key, G. J. Szulczewski, J. S. Thrasher, *J. Fluorine Chem.* **2014**, *167*, 203–210.
[26] (a) T. Umemoto, *WO 2008/118787*, **2008** ; (b) T. Umemoto, L. M. Garrick, N. Saito, *Beilstein J. Org. Chem.* **2012**, *8*, 461–471.

such as ZnF_2, HF or SbF_3 and SbF_5. This practical, scalable and high yielding method provided access to new SF_5-building blocks with substituents such as bromide or chloride, as well as polyfluorinated arylsulfurpentafluorides and bis- and tris-SF_5-arenes.

1.1.2.2. SF_5-Alkyl Compounds

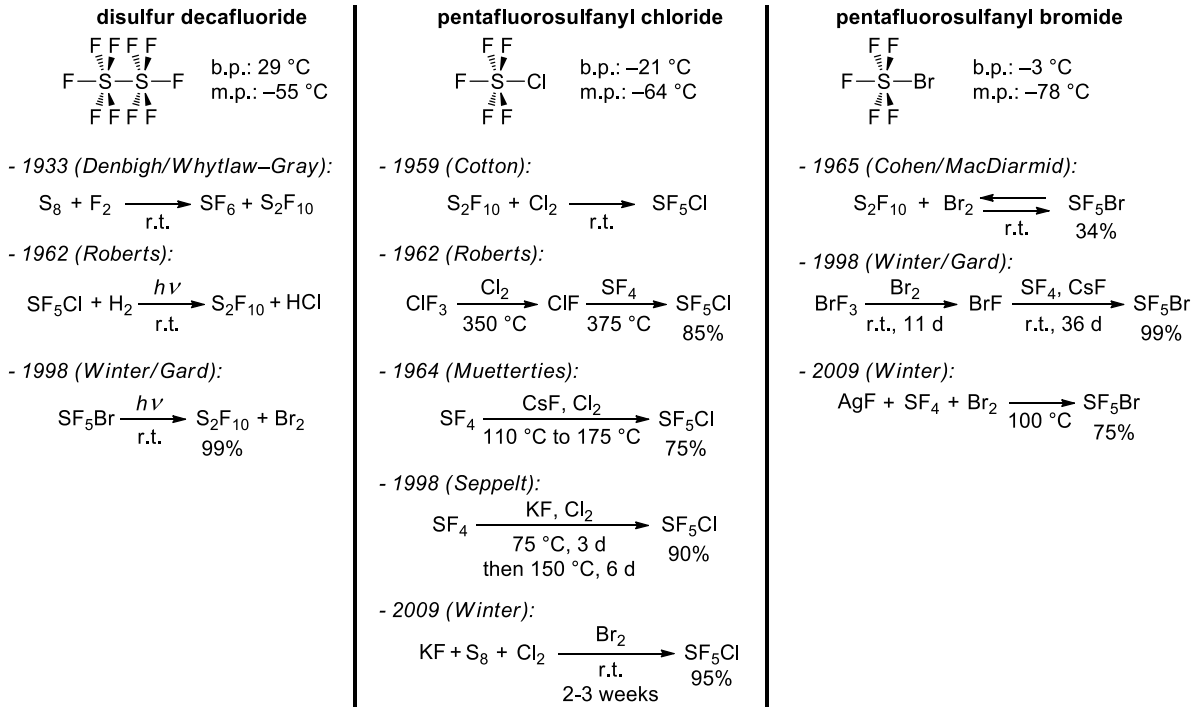
Synthesis of aliphatic SF_5-compounds started in the 1950s with the preparation of CF_3SF_5 by direct fluorination of CH_3SH and CS_2 using cobalt trifluoride in up to 40% yield.[27] Following this accomplishment, the same process was performed by electrochemical fluorination in HF.[28] Such direct fluorination methods necessitate harsh conditions, limiting the number of suitable starting materials. Consequently, most SF_5-containing alkyl derivatives are prepared by radical addition of SF_5X (X = Cl, Br, SF_5) to alkenes and alkynes. Nevertheless, the chemistry of pentafluosulfanyl aliphatic compounds is still underdeveloped because of the difficulty to prepare these pentafluorosulfanylating reagents.

As previously mentioned (cf. Chapter 1.1.1),[11] disulfur decafluoride (S_2F_{10}) was observed for the first time as a minor side product during the preparation of SF_6 by fluorination of S_8 with F_2 (Scheme 1.1.4, left). This highly toxic chemical (four times as toxic as phosgene) was considered a potential chemical pulmonary agent during World War II, because it does not cause lacrimation and skin irritation, providing little warning of exposure.[29] Several years later, S_2F_{10} was prepared more conveniently by ultraviolet irradiation of SF_5Cl under H_2 atmosphere.[30] The most recent reported method involves the efficient photochemical decomposition of SF_5Br in a quartz vessel.[31]

Pentafluorosulfanyl chloride (SF_5Cl) is the most important agent for introducing the SF_5 group into organic molecules, because of its relative availability and lower toxicity compared to S_2F_{10} and SF_5Br, as well as its ability to undergo relatively clean addition through formation of radicals. The first synthesis of SF_5Cl was reported in 1959, by treatment of S_2F_{10} with chlorine gas (Scheme 1.1.4, middle).[32] In the following years, several improvements were achieved in the preparation of this reagent. The need to start from the difficult to access S_2F_{10} was avoided when ClF_3, Cl_2 and sulfur tetrafluoride (SF_4) were used to obtain SF_5Cl in good yield, allowing its large-scale production.[33] Further optimizations of this process using CsF or KF were later

[27] G. A. Silvey, G. H. Cady, *J. Am. Chem. Soc.* **1950**, *72*, 3624–3626.
[28] (a) G. A. Silvey, G. H. Cady, *J. Am. Chem. Soc.* **1952**, *74*, 5792–5793; (b) A. F. Clifford, H. K. Elshamy, H. J. Emeleus, R. N. Haszeldine, *J. Chem. Soc.* **1953**, 2372–2375; (c) R. N. Haszeldine, F. Nyman, *J. Chem. Soc.* **1956**, 2684–2689; (d) R. D. Dresdner, J. A. Young, *J. Am. Chem. Soc.* **1959**, *81*, 574–577; (e) J. A. Young, R. D. Dresdner, *J. Org. Chem.* **1959**, *24*, 1021–1022.
[29] H. Johnston, *Chemical Warfare Civilian During World War II*, World Scientific, **2003**, pp. 33–36.
[30] H. L. Roberts, *J. Chem. Soc.* **1962**, 3183–3185.
[31] R. Winter, P. G. Nixon, G. L. Gard, *J. Fluorine Chem.* **1998**, *87*, 85–86.
[32] J. W. George, F. A. Cotton, *Proc. Chem. Soc.* **1959**, 317–318.
[33] (a) F. Nyman, H. L. Roberts, *J. Chem. Soc.* **1962**, 3180–3183; (b) F. Nyman, H. L. Roberts, *Inorg. Synth.* **1966**, *8*, 160–165.

described.[34] A significant advance was recently reported in the patent literature by AvantBio (AvantFluor), suggesting an important reduction of the production cost in the future.[35] In this method, elemental sulfur, dry potassium fluoride and chlorine were mixed in a reactor in the presence of bromine, which acts as a catalyst (no reaction was observed in absence of Br_2). After two to three weeks at room temperature, SF_5Cl was obtained in excellent yield *via* formation of SF_4. Currently, SF_5Cl is the only commercially available pentafluorosulfanylating reagent, and ABCR is the only chemical company supplying this product in Europe.

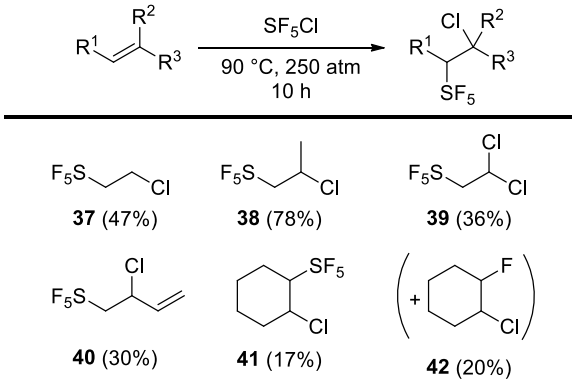


Scheme 1.1.4. Preparation of pentafluorosulfanylating reagents.

Preparation and isolation of pentafluorosulfanyl bromide (SF_5Br) is more challenging than its chloride analogue due to its lower stability. Similarly to SF_5Cl, SF_5Br was prepared for the first time in modest yield by treating S_2F_{10} with bromine (Scheme 1.1.4, right).[36] The non-complete conversion of the S_2F_{10} suggested that the reaction is reversible. In a comparable strategy to the one applied for SF_5Cl, an improvement was developed with the use of BrF_3 as starting material, which was reacted with bromine to give BrF.[37] The latter was subsequently treated with SF_4 and CsF to afford SF_5Br in quantitative yield. Finally, in the AvantBio's (AvantFluor's) patent previously mentioned, a new process for the preparation of SF_5Br was also disclosed, by reaction of AgF, SF_4 and Br_2 at 100 °C.

[34] (a) C. W. Tullock, D. D. Coffman, E. L. Muetterties, *J. Am. Chem. Soc.* **1964**, *86*, 357–361; (b) U. Jonethal, R. Kuschel, K. Seppelt, *J. Fluorine Chem.* **1998**, *88*, 3–4.
[35] R. Winter, *WO 2009/152385*, **2009**.
[36] B. Cohen, MacDiarmid, *Inorg. Chem.* **1965**, *4*, 1782–1785.
[37] R. Winter, R. J. Terjeson, G. L. Gard, *J. Fluorine Chem.* **1998**, *89*, 105–106.

As previously explained, the chemistry of pentafluorosulfanylating reagents mainly involves formation of free radicals which can add to alkenes and alkynes. SF_5Br is the most reactive of the three reagents, but it also has the lowest thermal stability. It starts to decompose in an inert vessel at 150 °C, whereas SF_5Cl is stable up to 400 °C. S_2F_{10} is the least used, because it is the most difficult to access and it has the lowest reactivity towards olefins. Its thermal decomposition also occurred at around 400 °C (although slow decomposition was observed at 150 °C).[38] A seminal report of Roberts described that SF_5Cl is able to add thermally at 250 atm to simple olefins (Scheme 1.1.5).[39]



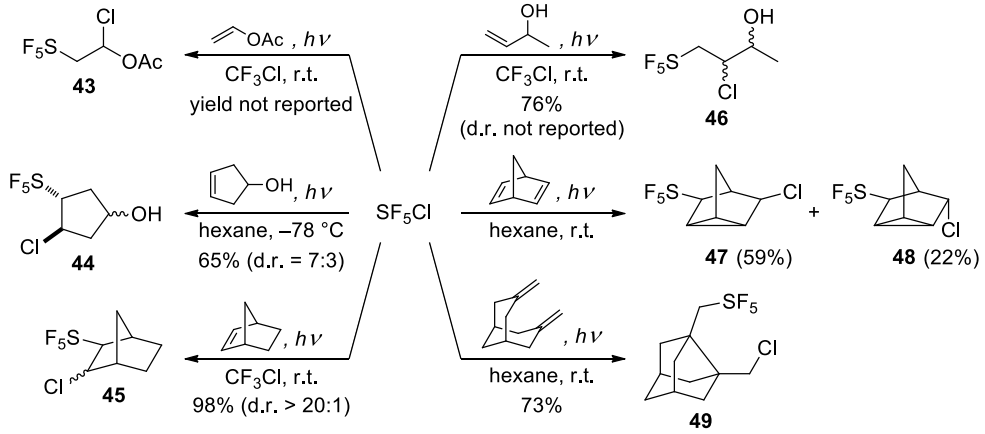
Scheme 1.1.5. Thermal addition of SF_5Cl to olefins.

The pentafluorosulfanyl radical always adds to the least substituted position of the alkene. Under these conditions, isobutene and styrene underwent polymerization. Interestingly, with cyclohexene as starting material, the major product observed was chlorofluorocyclohexane **42**, probably *via* an ionic pathway in which the olefin reacts as a nucleophile with SF_5Cl to form a chloronium ion and SF_5^-, which readily decomposes into the stable SF_4 and a fluoride ion. In this report, the authors also carried out SF_5Cl addition to olefins by ultraviolet irradiation, but the yields were not specified. Addition to acetylene and propyne was also mentioned to occur, but yields were not indicated either. Reaction of SF_5Cl with fluoro-olefins was found to be more difficult, and it had to be done in an autoclave at 100 °C in the presence of a radical initiator, dibenzoyl peroxide.[40]

In the following years, several reports of SF_5Cl addition to other relatively simple systems under photochemical conditions were reported (Scheme 1.1.6).[41] Among these examples, addition to vinyl acetate was found to be possible and afforded **43**, albeit no yield was reported.[41a] Moreover, free hydroxyl groups are tolerated under these conditions as shown in the

[38] (a) W. C. Schumb, *Ind. Eng. Chem.* **1947**, *39*, 421–423; (b) W. R. Trost, R. L. Mcintosh, *Can. J. Chem.* **1951**, *29*, 508–525.
[39] J. R. Case, N. H. Ray, H. L. Roberts, *J. Chem. Soc.* **1961**, 2066–1970.
[40] J. R. Case, H. L. Roberts, N. H. Ray, *J. Chem. Soc.* **1961**, 2070–2075.
[41] (a) R. Winter, G. L. Gard, *J. Fluorine Chem.* **1994**, *66*, 109–116; (b) A. Klauck, K. Seppelt, *Angew. Chem. Int. Ed.* **1994**, *33*, 93–95; (c) V. K. Brel, *Synthesis* **2005**, 1245–1250; (d) M. V. Ponomarenko, Y. A. Serguchev, G. V. Roschenthaler, *J. Fluorine Chem.* **2010**, *131*, 270–273.

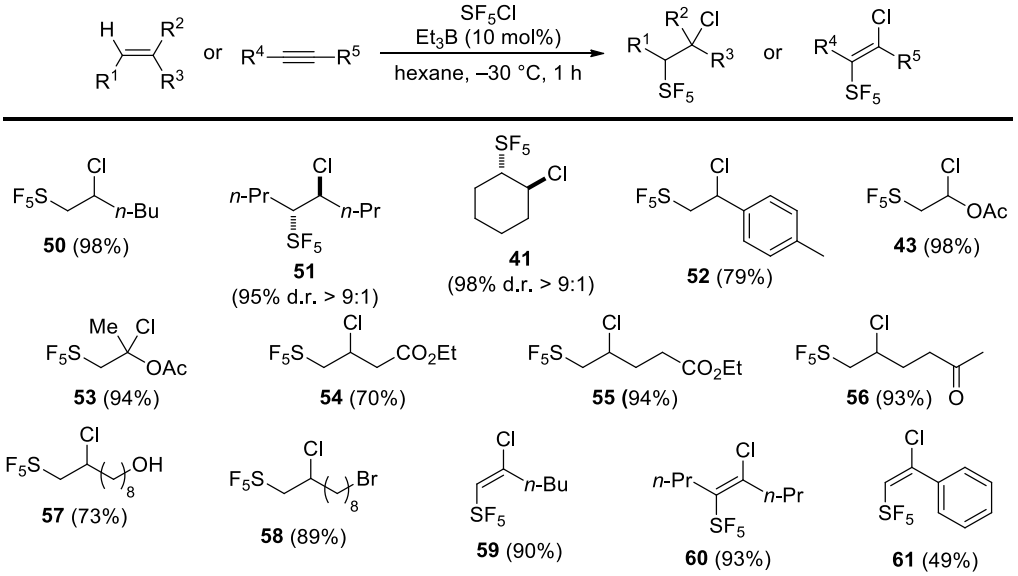
addition of SF_5Cl to 3-cyclopentenol to obtain **44** with slight diastereocontrol (d.r. = 7:3, the major diastereoisomer was not identified).[41b] Treatment of norbornene with SF_5Cl formed **45** as a single unidentified diastereoisomer in very high yield.[41b] Addition to 3-buten-2-ol was also disclosed, giving compound **46**.[41c] Finally, radical transannular cyclizations occurred when SF_5Cl was added to non-conjugated dienes such as 3,7-dimethylenebicyclo[3.3.1]nonane or norbornadiene, leading to products **47**, **48** and **49**.[41d]



Scheme 1.1.6. Examples of SF_5Cl addition under photochemical conditions.

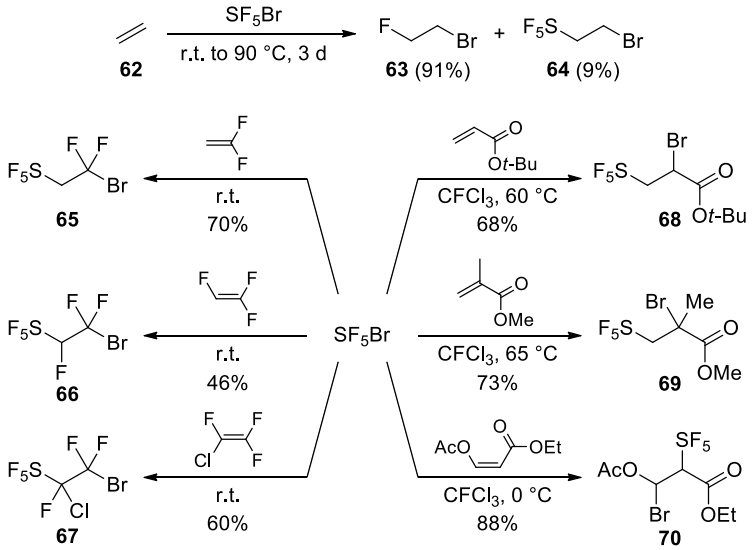
An important improvement in the SF_5Cl addition was achieved by Dolbier in 2002, with the use of catalytic amount of triethylborane (Scheme 1.1.7).[42] Under these conditions, the reaction proceeds cleanly in high yield under mild conditions and in short reaction times. Another advantage of this method is the possibility to run the reaction in the liquid phase (the boiling point of SF_5Cl is –21 °C). This facilitates the preparation SF_5-substituted compounds in a standard laboratory because it avoids the need for specialized equipment such as metal pressure reactors or photochemical reactors. This convenient method was applied to a variety of alkenes and alkynes, affording the corresponding addition products in generally high yields. Interestingly, in contrast with previous observations under thermal or photochemical activation,[39] styrene was a suitable starting material under these conditions, providing **52** without polymerization. Other compatible functional groups include esters (**43**, **53**, **54**, **55**), ketones (**56**), free alcohols (**57**) and even bromine (**58**). Addition to simple alkynes could also be achieved in good yields. However, the reaction with phenyl acetylene gave **61** in only 49% yield, because of competing formation of a 2:1 adduct.

[42] (a) S. Ait-Mohand, W. R. Dolbier, *Org. Lett.* **2002**, *4*, 3013–3015; (b) W. R. Dolbier, S. Ait-Mohand, T. D. Schertz, T. A. Sergeeva, J. A. Cradlebaugh, A. Mitani, G. L. Gard, R. W. Winter, J. S. Thrasher, *J. Fluorine Chem.* **2006**, *127*, 1302–1310.



Scheme 1.1.7. Addition of SF_5Cl with Et_3B initiation.

Compared to its chloride counterpart, pentafluorosulfanyl bromide SF_5Br is more reactive, and is less studied because of its higher toxicity, instability and its propensity to undergo ionic reactions (Scheme 1.1.8).



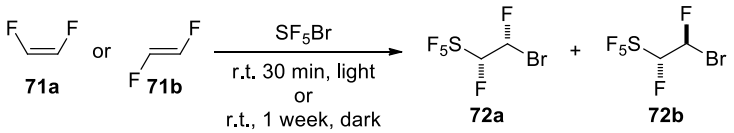
Scheme 1.1.8. SF_5Br addition to olefins.

For example, the addition of SF_5Br to ethylene afforded 1-bromo-2-fluoroethane (**63**) as major product, resulting from formation of a bromonium intermediate.[43] However, early studies showed that SF_5Br readily adds to fluoro-olefins at room temperature.[44] Moreover, contrary to SF_5Cl, it can add to other electron-poor olefins such as *α,β*-unsaturated esters.[41a,45]

[43] R. J. Terjeson, G. L. Gard, *J. Fluorine Chem.* **1987**, *35*, 653–662.
[44] J. Steward, L. Kegley, H. F. White, G. L. Gard, *J. Org. Chem.* **1969**, *34*, 760–762.
[45] R. Winter, G. L. Gard, *J. Fluorine Chem.* **2000**, *102*, 79–87.

A study of the SF_5Br addition to both *cis*- and *trans*-1,2-difluoroethylene by Fox supports the radical pathway of the reaction (Table 1.4).[46] The absence of stereospecificity and the fact that the reaction is much faster in the presence of light suggest that it goes through a radical intermediate instead of a bromonium ion.

Table 1.1.4. Product distribution of SF_5Br addition to 1,2-difluoroethylene.



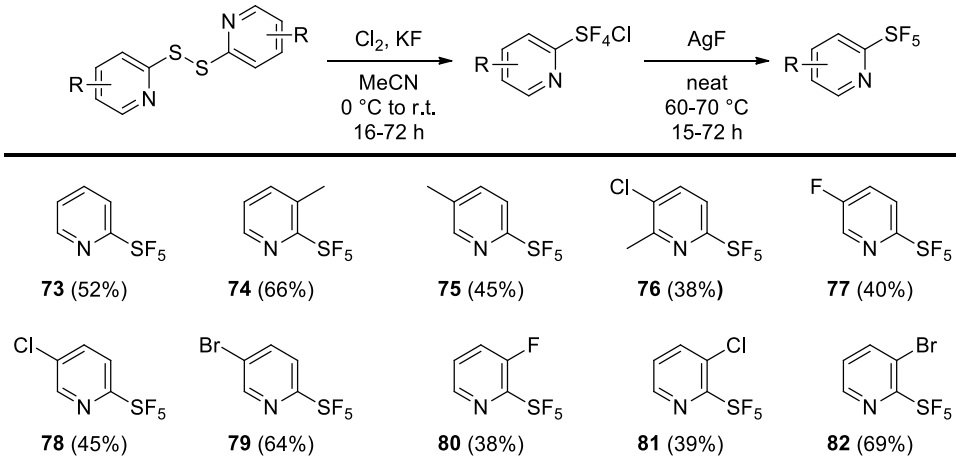
Configuration	Conditions	Conv. (%)	Yield (%)	72a:72b
trans	dark	87	66	1.83:1
trans	light	100	75	1.94:1
cis	dark	86	60	2.17:1
cis	light	100	74	2.15:1

1.1.2.3. SF_5-Heterocycles

Due to the lack of methods for the introduction of the SF_5 group, and their relatively low substrate scope, only a small number of SF_5 heterocycles are reported in the literature. To date, five different strategies have been followed for their preparation: 1) Oxidative fluorination of pyridyl disulfides using Umemoto's method, for the synthesis of SF_5-pyridines. 2) Functionalization of SF_5-aryl compounds, giving access to benzannulated heterocycles where the SF_5 group is attached to the benzene moiety. 3) 1,3-Dipolar cycloaddition reactions with SF_5-alkynes or SF_5-alkenes, affording nitrogen or sulfur-containing 5-membered heterocycles. 4) Retro-Diels–Alder reactions of bridged SF_5-containing precursors for the preparation of SF_5-furans. 5) Oxidation of SF_5-substituted anisoles, affording SF_5-mucolactone.

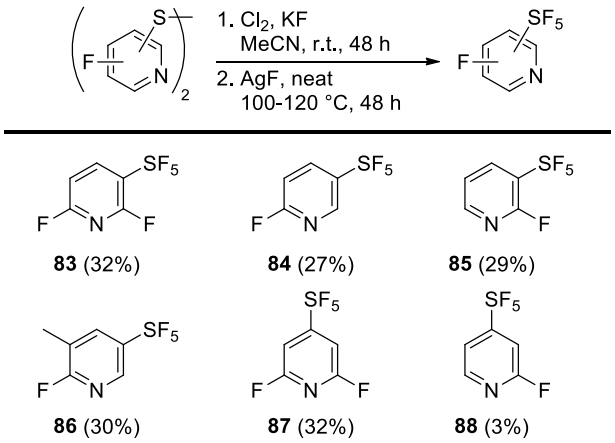
Recently, Dolbier described the preparation of 2-SF_5-pyridines following Umemoto's strategy (Scheme 1.1.9).[47] Thus, oxidative fluorination of 2,2'-dipyridyl disulfide with potassium fluoride and chlorine in acetonitrile affording the 2-SF_4Cl-pyridine intermediates. After extensive screening of reaction conditions, the authors found that the final fluorination step had to be done with silver(I) fluoride AgF, and without solvent. This method turned out to be compatible with 2,2'-dipyridyl disulfide only. Indeed, when the oxidative fluorination was attempted with 3,3'-dipyridyl disulfide and 4,4'-dipyridyl disulfide, no SF_4Cl-pyridine intermediate was formed, and only decomposition of the starting material occurred.

[46] A. D. Berry, W. B. Fox, *J. Org. Chem.* **1978**, *43*, 365–367.
[47] O. S. Kanishchev, W. R. Dolbier, *Angew. Chem. Int. Ed.* **2015**, *54*, 280–284.



Scheme 1.1.9. Synthesis of 2-SF_5-pyridines.

Shibata and co-workers just disclosed a way to obtain 3- and 4-SF_5-pyridines with this two-step procedure by using dipyridyl disulfide precursors bearing fluorine atoms in *ortho* position (Scheme 1.1.10).[48]



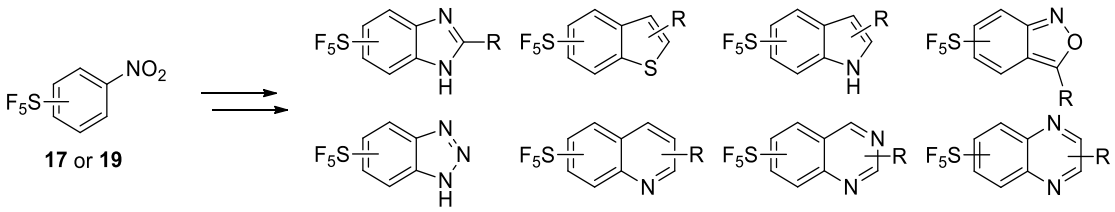
Scheme 1.1.10. Synthesis of 3- and 4-SF_5-pyridines

The authors suggested that the presence of fluorine atoms is important during the chlorotetrafluorination step to reduce the nucleophilicity of the pyridine, and therefore avoid intermolecular decomposition of the SF_4Cl-pyridine intermediates. Thus, six examples of 2-fluorinated SF_5-pyridines were prepared in yields ranging from 3% to 32%. Moreover, these compounds could be further derivatized by nucleophilic substitution of the *ortho*-fluorine by nitrile, azide, thiols, amines and alcohols.

A variety of pentafluorosulfanyl-containing benzannulated heterocycles with the SF_5 moiety on the non-heterocyclic ring were obtained by functionalization of commercially available *para*-

[48] M. Kosobokov, B. Cui, A. Balia, K. Matsuzaki, E. Tokunaga, N. Saito, N. Shibata, *Angew. Chem. Int. Ed.* **2016**, *55*, 10781–10785.

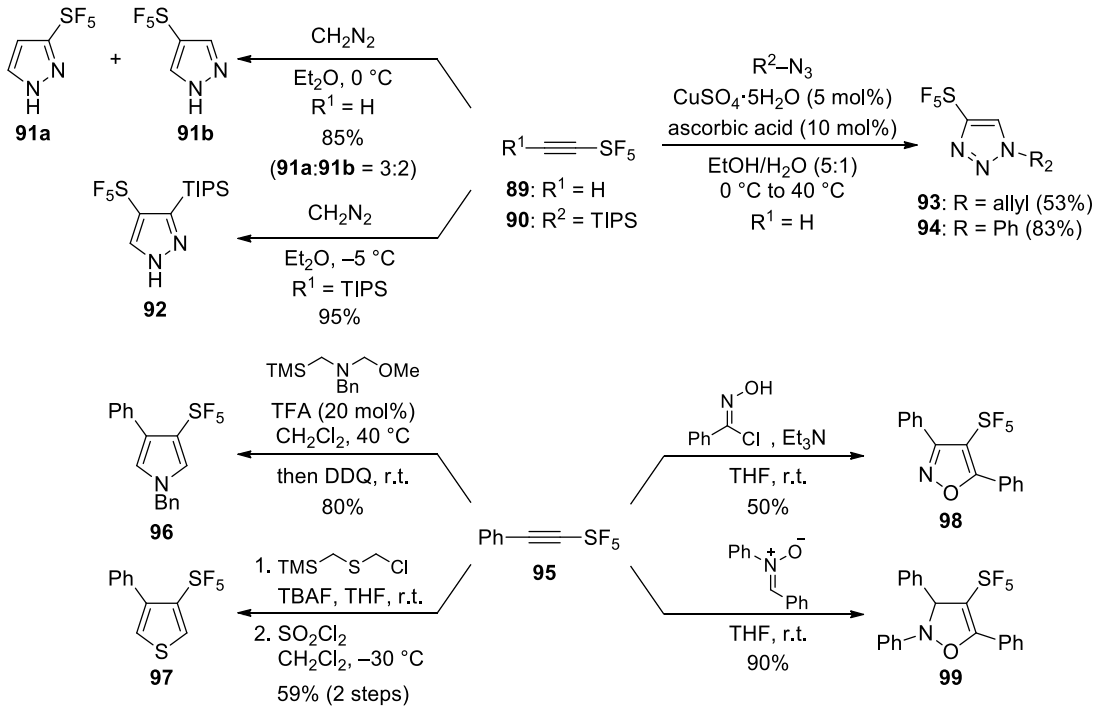
and *meta*-SF_5-substituted nitrobenzenes (Scheme 1.1.11).[49] In this way, Beier applied vicarious nucleophilic substitution (cf. Chapter 1.2.1) in the synthesis of SF_5-heterocyclic system of benzimidazoles,[49a] benzotriazoles,[49a] quinoxalines,[49a] indoles,[49c] benzisoxazoles,[49d] quinolines,[49d] and quinazolines.[49d] Moreover, Knochel prepared magnesium reagents by Br/Mg exchange with *i*-PrMgCl·LiCl and by directed metalation with $TMP_2Mg·2LiCl$, and used these reagents for the synthesis of SF_5-indoles and SF_5-benzo[*b*]thiophenes.[49b] Xu and co-workers also reported a method for the preparation of SF_5-quinolines by multicomponent coupling reactions of SF_5-anilines.[49e]



Scheme 1.1.11. Preparation of SF_5-benzannulated heterocycles.

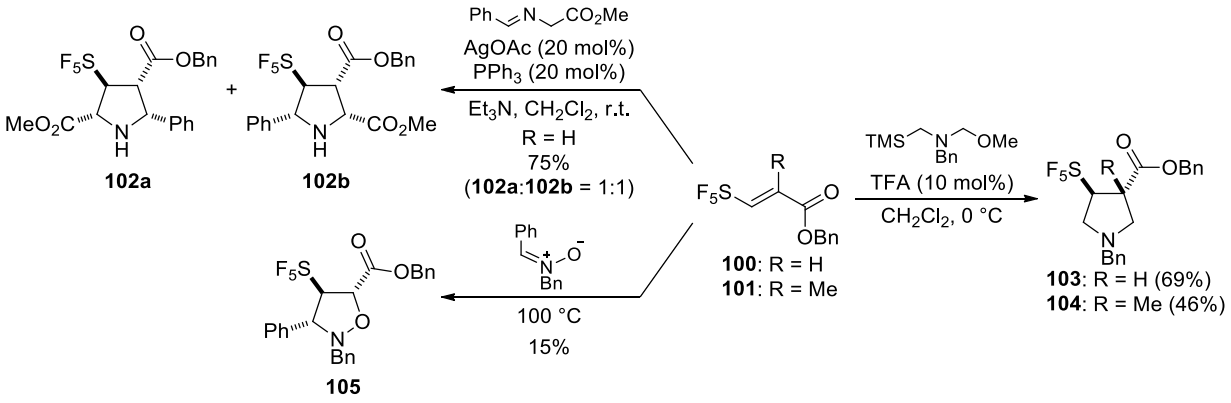
An important class of SF_5-heterocycles is accessible by 1,3-dipolar cycloaddition reactions of SF_5-substituted alkynes and alkenes. This strategy affords access to a number of 5-membered SF_5-heterocycles. The first example of such reaction was reported in the 1960s by Hoover and Coffman with the treatment of SF_5-acetylene **89**[50] with diazomethane (Scheme 1.1.12).[51] SF_5-pyrazole **91** was obtained as a mixture of inseparable regioisomers (**91a**:**91b** = 3:2) in 85% yield. Forty years later, this reaction was investigated again by Shreeve in order to prepare SF_5-energetic materials.[52a] Addition of diazomethane to TIPS-protected SF_5-acetylene gave only one regioisomer **92**. SF_5-triazoles were also prepared by treatment of **90** with organic azides.[52] Reaction of SF_5-alkynes with azomethine and thiocarbonyl ylides precursors was also employed for the synthesis of protected SF_5-pyrroles and SF_5-thiophenes.[53] Isoxazoles and isoxazolines could also be prepared by 1,3-dipolar cycloaddition reactions.[54]

[49] (a) T. Pastyrikova, G. Iakobson, N. Vida, R. Pohl, P. Beier, *Eur. J. Org. Chem.* **2012**, 2123–2126; (b) A. Frischmuth, A. Unsinn, K. Groll, H. Stadtmuller, P. Knochel, *Chem. Eur. J.* **2012**, *18*, 10234–10238; (c) G. Iakobson, T. Posta, P. Beier, *Synlett* **2013**, *24*, 855–859; (d) P. Beier, T. Pastyrikova, *Beilstein J. Org. Chem.* **2013**, *9*, 411–416; (e) X. L. Mi, J. Chen, L. J. Xu, *Eur. J. Org. Chem.* **2015**, 1415–1418.
[50] SF_5-acetylene was prepared by hydrogen bromide elimination from the corresponding bromoalkene.
[51] F. W. Hoover, D. D. Coffman, *J. Org. Chem.* **1964**, *29*, 3567–3570.
[52] (a) C. F. Ye, G. L. Gard, R. W. Winter, R. G. Syvret, B. Twamley, J. M. Shreeve, *Org. Lett.* **2007**, *9*, 3841–3844; (b) T. Abe, G. H. Tao, Y. H. Joo, R. W. Winter, G. L. Gard, J. M. Shreeve, *Chem. Eur. J.* **2009**, *15*, 9897–9904; (c) S. Garg, J. M. Shreeve, *J. Mater. Chem.* **2011**, *21*, 4787–4795.
[53] (a) W. R. Dolbier, Z. Y. Zheng, *J. Org. Chem.* **2009**, *74*, 5626–5628; (b) W. R. Dolbier, Z. Y. Zheng, *J. Fluorine Chem.* **2011**, *132*, 389–393.
[54] S. E. Lopez, A. Mitani, P. Pena, I. Ghiviriga, W. R. Dolbier, *J. Fluorine Chem.* **2015**, *176*, 121–126.



Scheme 1.1.12. Cycloaddition reactions with SF_5-alkynes.

Using the same strategy with SF_5-substituted acrylic esters and amides, Jubault, Bouillon and co-workers disclosed the first syntheses of SF_5-pyrrolidines such as **102**, **103** and **104** (Scheme 1.1.13).[55]

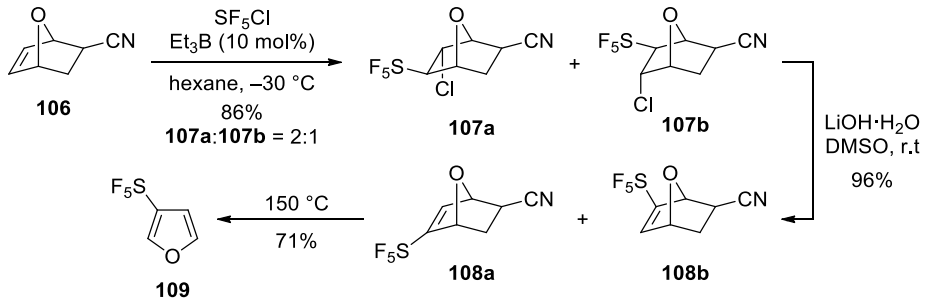


Scheme 1.1.13. Cycloaddition reaction with SF_5-alkenes.

Tetrasubstituted pyrrolidines were obtained as a mixture of regioisomers. SF_5-isoxazolidines were also accessible, albeit in a less efficient way. For example, isoxazolidine **105** was obtained as a single diastereoisomer in 15% yield. Replacing the phenyl substituent by an ester resulted in the formation of mixtures of diastereoisomers.

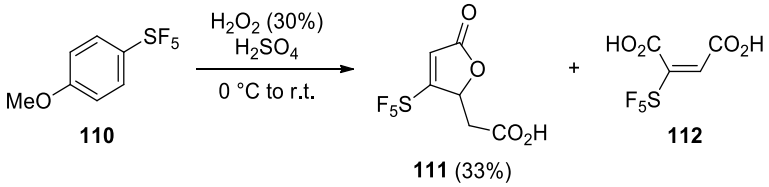
[55] (a) E. Falkowska, V. Tognetti, L. Joubert, P. Jubault, J. P. Bouillon, X. Pannecoucke, *RSC Adv.* **2015**, *5*, 6864–6868; (b) E. Falkowska, M. Y. Laurent, V. Tognetti, L. Joubert, P. Jubault, J. P. Bouillon, X. Pannecoucke, *Tetrahedron* **2015**, *71*, 8067–8076.

Another example of reported SF_5 heterocycle is pentafluorosulfanylfuran **109**, prepared by a three-step sequence from furan-acrylonitrile *exo*-adduct **106** (Scheme 1.1.14).[56] Radical addition of SF_5Cl to **106** afforded **107** as a mixture of regioisomers, which were converted to the corresponding alkenes **108** by elimination with lithium hydroxide. Finally, heating **108** at 150 °C triggered the desired retro-Diels–Alder reaction, affording 3-SF_5-furan in 71% yield.



Scheme 1.1.14. Preparation of 3-SF_5-furan.

The last example of described SF_5-substituted heterocycle involves oxidation of 3- and 4-SF_5-substituted anisoles.[57] Beier and co-workers showed that treatment of 4-SF_5-anisole **110** with a mixture of aqueous hydrogen peroxide and concentrated sulfuric acid afforded 3-SF_5-mucolactone **111** in 33% yield (Scheme 1.1.15). One side product in the reaction was SF_5-maleic acid **112**. Starting from 3-SF_5-anisole also delivered **111**, albeit in lower yield.



Scheme 1.1.15. Preparation of 3-SF_5-mucolactone.

1.1.3. Applications

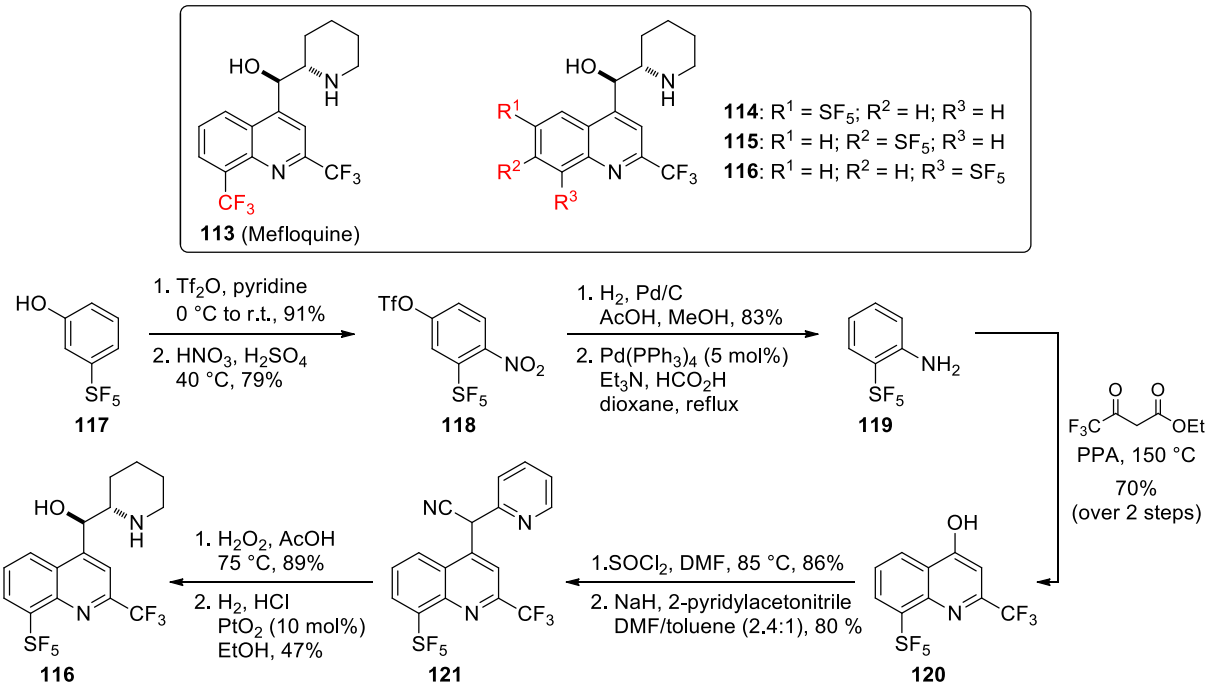
Because of the very recent interest it received, and the lack of methods to access relevant building blocks, there are only a few applications of the pentafluorosulfanyl group in life science. However, several reports have shown that SF_5 derivatives can outperform their CF_3 analogues in pharmaceuticals and agrochemicals. Moreover, enhancement of the properties of several materials has been observed with the introduction of the pentafluorosulfanyl group. Finally, a few examples of reactions involving SF_5-substituted catalysts have been documented. Selected examples of each type of application are described in this section.

[56] W. R. Dolbier, A. Mitani, W. Xu, I. Ghiviriga, *Org. Lett.* **2006**, *8*, 5573–5575.
[57] (a) N. Vida, T. Pastyrikova, B. Klepetarova, P. Beier, *J. Org. Chem.* **2014**, *79*, 8906–8911; (b) N. Vida, J. Vaclavik, P. Beier, *Beilstein J. Org. Chem.* **2016**, *12*, 110–116.

1.1.3.1. Pharmaceuticals

In recent years, there has been an explosion of the number of SF_5 compounds exhibiting a biological activity in both patent and non-patent literature databases.[10] As the pentafluorosulfanyl group is often compared to the trifluoromethyl and *tert*-butyl groups, many of these reports include a comparison of SF_5-compounds with their CF_3 and *t*-Bu analogues, to illustrate the consequent alterations in bioactivity or in physicochemical properties.

For instance, Wipf and co-workers realized a study of the biological activity of SF_5 analogues of mefloquine (Scheme 1.1.16).[58] Mefloquine **113** is an antimalarial drug used against chloroquine-resistant strains. Until 2009, it was notably the preventive treatment used by the U. S. army for deployments in areas where malaria is endemic. However, its antimalarial activity is associated with serious side effects such as anxiety, depression, hallucinations or seizures.



Scheme 1.1.16. Structure of mefloquine and synthesis of 8-SF_5-mefloquine.

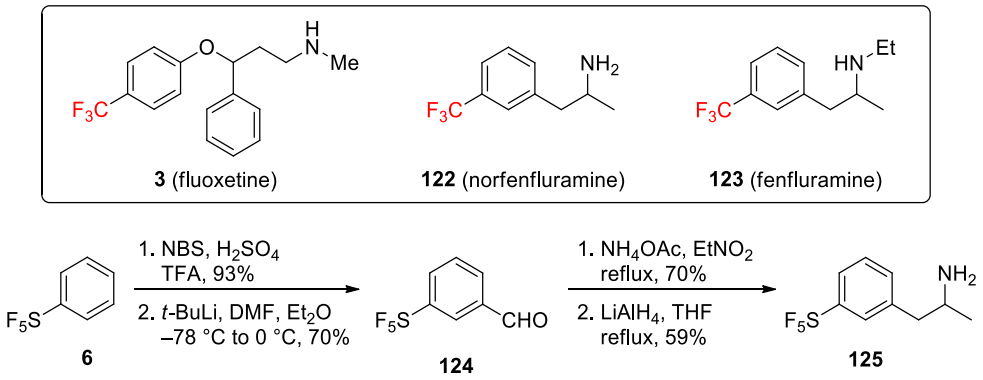
Preparation of 6- and 7-SF_5-mefloquines **114** and **115** were achieved from 3- and 4-SF_5-anilines,[58a] whereas the exact 8-SF_5-analogue of the drug required the synthesis of 2-SF_5-aniline **119** from 3-SF_5-phenol **117**.[58b] After removal of the necessary directing hydroxyl group, the synthetic strategy followed a similar pathway to the route for 6- and 7-SF_5-mefloquines.

[58] (a) P. Wipf, T. T. Mo, S. J. Geib, D. Caridha, G. S. Dow, L. Gerena, N. Roncal, E. E. Milner, *Org. Biomol. Chem.* **2009**, *7*, 4163–4165; (b) T. T. Mo, X. L. Mi, E. E. Milner, G. S. Dow, P. Wipf, *Tetrahedron Lett.* **2010**, *51*, 5137–5140; (c) G. S. Dow, E. E. Milner, P. Wipf, T. Mo, *WO 2010/144434*, **2010**.

Conrad–Limpach condensation with ethyl trifluoroacetoacetate afforded quinoline **120**, which was converted into the desired target in four steps.

Determination of IC_{50} against four drug resistant strains of *Plasmodium falciparum* and a mammalian cell line showed that **114** and **115** exhibit similar antimalarial activities and greater selectivity than their CF_3 congeners and mefloquine **113**.[58a] Moreover, 8-SF_5-mefloquine **116** was administrated in infected mice, and displayed a higher activity than mefloquine itself.[58c]

Another early example of the beneficial effect of SF_5-introduction has been reported by Welch.[59] In this work, SF_5 analogues of serotonin (5-hydroxytryptamine; 5-HT) uptake inhibitors fluoxetin **3**, norfenfluramine **122**, and fenfluramine **123**, were prepared and their biological activity was evaluated (Scheme 1.1.17).



Scheme 1.1.17. Structures of fluoxetine, norfenfluramine and fenfluramine, and synthesis of SF_5-norfenfluramine.

The synthesis of SF_5-norfenfluramine **125** was achieved by electrophilic bromination of SF_5-benzene (**6**), followed by metalation with *t*-BuLi and subsequent formylation to obtain **124**. Treatment with nitroethane afforded the corresponding nitroalkene intermediate, which was then reduced with $LiAlH_4$ to form SF_5-norfenfluramine. Compared to the parent trifluoromethylated compounds, all the SF_5 analogues showed increased selectivity between different 5-HT receptors. For example, SF_5-norfenfluramine **125** possesses enhanced affinity for 5-HT_{2b}, 5-HT_{2c} and 5-HT_6 relative to norfenfluramine **122**, whereas its affinity for 5-HT_{1a} is lower (Figure 1.1.4).

[59] J. T. Welch, D. S. Lim, *Bioorg. Med. Chem.* **2007**, *15*, 6659–6666.

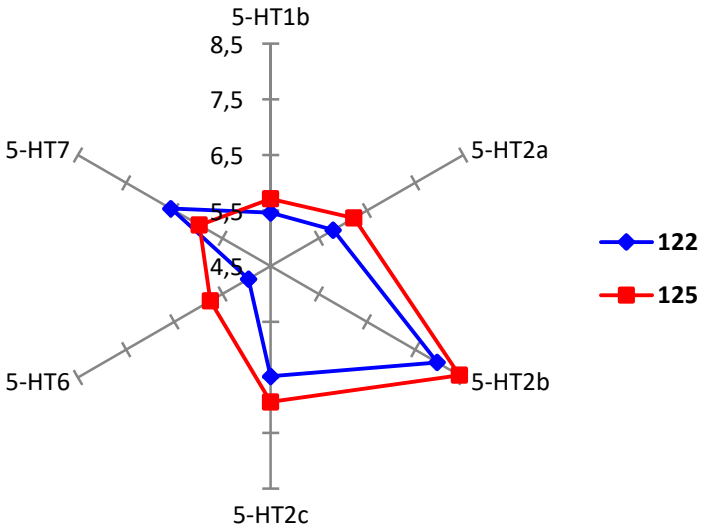
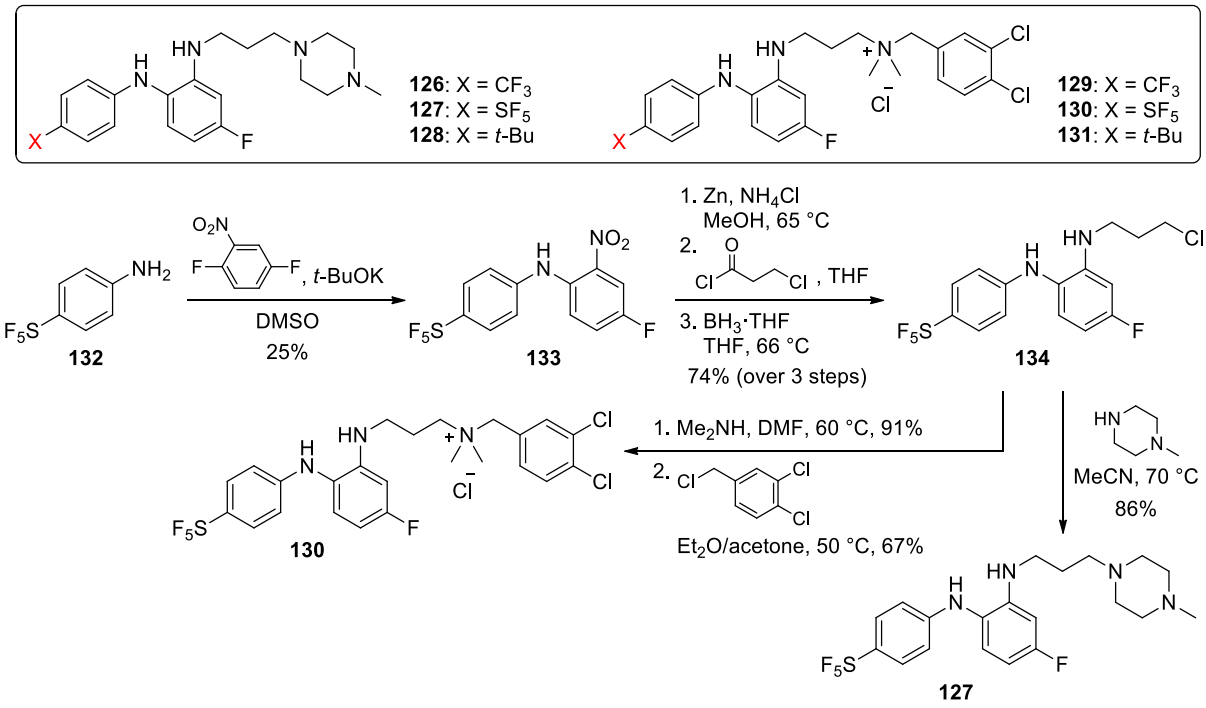


Figure 1.1.4. Comparison of pK_i values for a series of 5-HT receptors (adapted from ref. 59 with the permission from Elsevier).

Diederich and co-workers realized an evaluation of novel SF_5-diarylamine inhibitors of trypanothione reductase, and compared them to their CF_3 and *t*-Bu analogues (Scheme 1.1.18).[60] This enzyme is a promising target for the treatment of diseases caused by parasitic trypanosomes, such as *Trypanosoma brucei* or *Trypanosoma cruzi*.



Scheme 1.1.18. Structure of trypanothione reductase inhibitors and synthesis of SF_5 analogues.

SF_5 analogues **127** and **130** were prepared from 4-SF_5-aniline (**132**), which participated in nucleophilic aromatic substitution with 2,5-difluoronitrobenzene to afford **133**. Reduction of the

[60] B. Stump, C. Eberle, W. B. Schweizer, M. Kaiser, R. Brun, R. L. Krauth-Siegel, D. Lentz, F. Diederich, *ChemBioChem* **2009**, *10*, 79–83.

nitro group, followed by acylation and subsequent reduction of the resulting amide gave alkyl chloride **134**. Finally, treatment with *N*-methylpiperazine was performed to obtain **127**. Alternatively, **134** was converted into **130** by nucleophilic substitution with dimethylamine followed by treatment with treatment with 3,4-dichlorobenzyl chloride to form the quaternary ammonium salt.

Activity against *T. brucei* as well as cytotoxicity of the piperazine inhibitors are presented in Table 1.1.1. The three compounds display similar inhibitory properties with similar micromolar affinities to the enzyme. However, the SF_5-compound **127** possesses the lowest cytotoxicity. Similarly, **129**, **130** and **131** exhibit comparable activities against *T. cruzi*, with the lowest cytotoxicity for **130**. Moreover, the two SF_5 analogues **127** and **130** show good membrane permeability.

Table 1.1.5. In vivo activity against *T. brucei* and cytotoxicity of piperazines **126**, **127** and **128**.

Compound	*T. brucei* IC_{50} (µM)	Cytotoxicity IC_{50} (µM)
126	2.4	27.9
127	4.4	> 192.1
128	2.5	31.9

Other recent comparative studies of bioactive *tert*-butyl, trifluoromethyl and pentafluorosulfanyl-containing compounds have been achieved by Westphal and Carreira,[61] as well as by other research groups.[62] If no considerable improvement of the activity was observed in these examples, the implementation of the SF_5 group generated specific fluctuations of the physicochemical properties of the compounds studied, and showed its bioisosterism with the CF_3 and *t*-Bu groups.

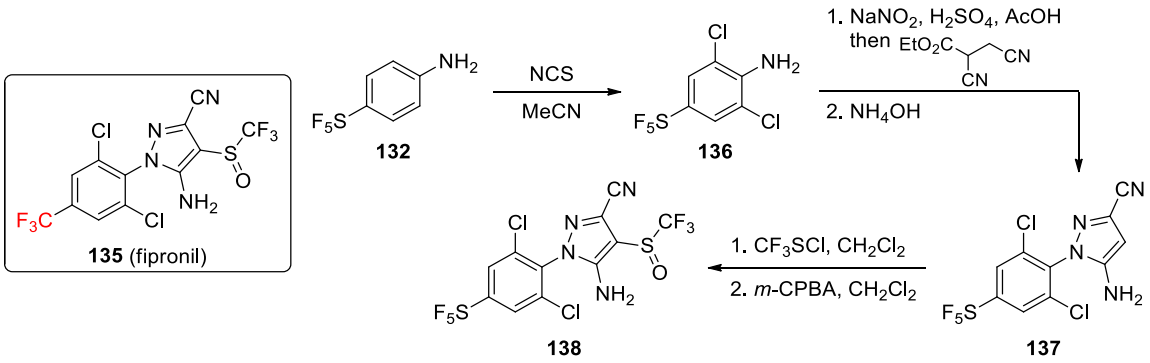
1.1.3.2. Agrochemicals

The first example describing the utility of the pentafluorosulfanyl group in life sciences was reported in a patent in 1963, where SF_5-substituted aryl ureas were tested as herbicides.[63] A number of patents have subsequently claimed the benefit of SF_5 compounds as pesticides from

[61] M. V. Westphal, B. T. Wolfstädter, J. M. Plancher, J. Gatfield, E. M. Carreira, *ChemMedChem* **2015**, *10*, 461–469.
[62] For examples, see: (a) P. W. Chia, S. C. Brennan, A. M. Z. Slawin, D. Riccardi, D. O'Hagan, *Org. Biomol. Chem.* **2012**, *10*, 7922–7927; (b) S. Altomonte, G. L. Baillie, R. A. Ross, J. Riley, M. Zanda, *RSC Adv.* **2014**, *4*, 20164–20176; (c) C. Alverez, M. R. Arkin, S. L. Bulfer, R. Colombo, M. Kovaliov, M. G. LaPorte, C. Lim, M. Liang, W. J. Moore, R. J. Neitz, Y. Z. Yan, Z. Z. Yue, D. M. Huryn, P. Wipf, *ACS Med. Chem. Lett.* **2015**, *6*, 1225–1230; (d) C. M. M. Hendriks, T. M. Penning, T. Z. Zang, D. Wiemuth, S. Grunder, I. A. Sanhueza, F. Schoenebeck, C. Bolm, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4437–4440.
[63] M. S. Raasch, *US3073861*, **1963**.

the 1990s.[10] Comparative studies of the activity SF_5 pesticides with their CF_3 analogues have also been reported.

Fipronil (**135**) is a trifluoromethyl-containing insecticide which was used against houseflies and cockroaches until 2013. One weakness of this compound was the low activity observed against field strains of these pests that developed an inherited resistance to dieldrin, another insecticide previously used commercially. Salmon and co-workers synthesized the SF_5 analogue of fipronil, along with SF_5 analogues of others pesticides, and investigated its relative activity compared to fipronil.[64] Synthesis of **138** started by electrophilic bischlorination of 4-SF_5-aniline affording **136**, which was converted into pyrazole **137** *via* formation of the azo compound with ethyl 1,2-dicyanopropionate and subsequent treatment with aqueous ammonia (Scheme 1.1.19). Completion of the synthesis was achieved by treatment with trifluoromethylsulfenyl chloride, followed by oxidation with *m*-CPBA (the synthetic yields of this sequence were not specified).



Scheme 1.1.19. Structure of fipronil, and synthesis of its SF_5 analogue.

Screening of **135** and **138** against both susceptible and resistant (to dieldrin) strains of *Musca domestica* houseflies and susceptible *Blattella germanica* coackroaches showed not only that the SF_5-analogue is more active, but also that it overcomes the cross-resistance with no loss of potency (Table 1.1.6).

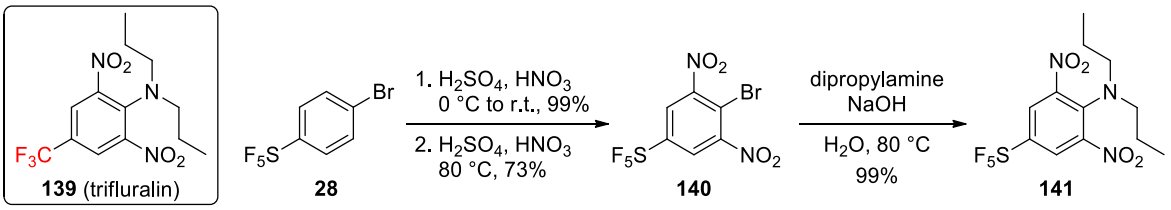
Table 1.1.6. Comparison of insecticidal activity of CF_3- and SF_5-fipronil.[a]

Compound	*Musca*	*Musca* (R)[b]	*Blattella*
135	15.42	143.4	0.5[c]
138	1.38	3.21	1[c]

a) LC_{50} (ppm); b) (R) indicates a strain resistant to dieldrin; c) Relative potency.

[64] (a) R. Salmon, *WO 93/06089*, **1993**; (b) P. J. Crowley, G. Mitchell, R. Salmon, P. A. Worthington, *Chimia* **2004**, *58*, 138–142.

Welch and co-workers reported a comparative study of trifluralin (**139**), a trifluoromethyl-containing herbicide, with its SF_5 analogue **141**.[65] The latter was accessed by two successive electrophilic nitrations of 4-bromo-(pentafluorosulfanyl)benzene (**28**), followed by nucleophilic substitution with dipropylamine (Scheme 1.1.20).



Scheme 1.1.20. Structure of trifluralin and synthesis of its SF_5-analogue.

The comparison of the herbicidal activity on several grass and leaf species of trifluralin and its SF_5 derivative **141** showed that the replacement of the CF_3 group by a SF_5 group does not bring any apparent benefit in post-emergence application (12 days after planting). However, in pre-emergence application (2 days after planting), the herbicidal performance of the SF_5 analogue is higher (Figure 1.1.5). Even if trifluralin **139** can effectively control several plant growing at 4 kg/ha, **141** displays a stronger activity towards grass weeds. Indeed, the same level of activity was observed with only 0.67 kg/ha of **141**. With barnyard grass and crabgrass, 0.168 kg/ha was even enough to obtain 90% of inhibition. Moreover, crops were relatively more tolerant to **141** than **139**. With application of trifluralin **139** at 4 and 1 kg/ha, the crop damage for corn was 100% and 20%, respectively. On the other hand, the crop injury using **141** is less pronounced with only 10% of inhibition at 2.68 kg/ha. In conclusion, in pre-emergence application, the SF_5 analogue **141** is more selective and more potent towards the unwanted grass weeds.

[65] D. S. Lim, J. S. Choi, C. S. Pak, J. T. Welch, *J. Pestic. Sci.* **2007**, *32*, 255–259.

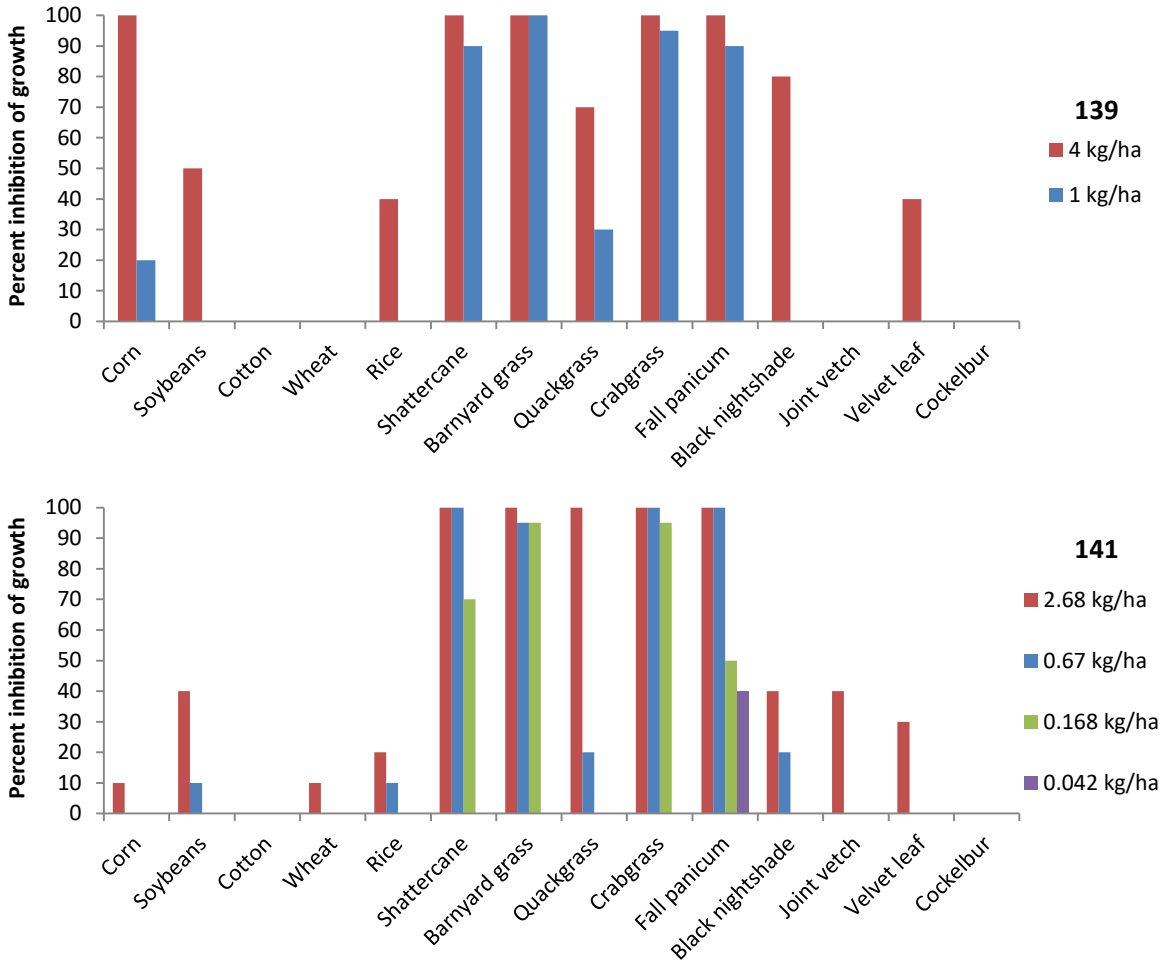


Figure 1.1.5. Herbicidal activity of trifluralin and SF_5-trifluralin in pre-emergence application (adapted from ref. 65 with the permission from the Pesticide Science Society of Japan).

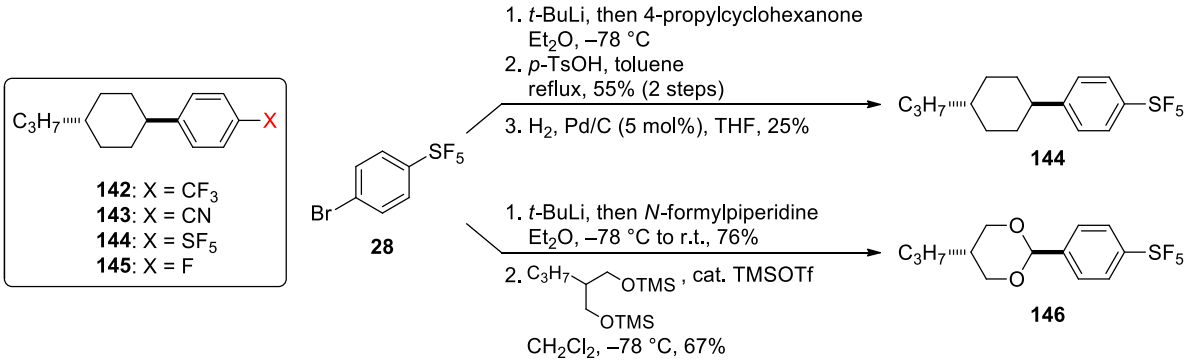
1.1.3.3. Materials

Introduction of the SF_5 substituent in several types of materials have been investigated. Its high thermal and chemical stability, as well as its electronic properties, make it a valuable group to ameliorate the performances of selected materials.

One of the earliest applications of the pentafluorosulfanyl group was in the preparation of liquid crystals.[18,66] Liquid crystals with high dielectric anisotropy ($\Delta\varepsilon$) are desirable in order to be able to decrease the necessary driving voltage of active matrice liquid crystal displays (AM-LCD). The most efficient way to increase $\Delta\varepsilon$ is by introducing a polar terminal group with the highest possible dipole moment. The best group compatible with AM-LCD technology was the trifluoromethyl substituent like in compound **142** (Scheme 1.1.21) with $\Delta\varepsilon = 8.6$ (Table 1.1.7). A much higher $\Delta\varepsilon$ can be obtained with the use of a terminal cyano group (e.g. **143**, $\Delta\varepsilon = 21.1$),

[66] (a) P. Kirsch, M. Bremer, *Angew. Chem. Int. Ed.* **2000**, *39*, 4217–4235; (b) P. Kirsch, M. Bremer, M. Heckmeier, K. Tarumi, *Mol. Cryst. Liq. Cryst.* **2000**, *346*, 29–33; (c) P. Kirsch, A. Hahn, *Eur. J. Org. Chem.* **2005**, 3095–3100; (d) P. Kirsch, A. Hahn, *Eur. J. Org. Chem.* **2006**, 1125–1131.

but it is unfortunately not suitable for active matrix displays. Indeed, the cyano group solvates ionic contaminants, resulting in low voltage holding ratio, which causes observable reduction of the contrast of the display and flicker phenomena. Synthesis of **144**, the SF_5 analogue of **142**, was achieved by lithiation of 4-bromo-(pentafluorosulfanyl)benzene **28**, treatment with propylcyclohexanone and elimination, followed by hydrogenation of the resulting alkene.



Scheme 1.1.21. Structure of liquid crystals containing a polar terminal group, and synthesis of SF_5-substituted liquid crystals **144** and **146**.

As expected, due to the higher electronegativity of the pentafluorosulfanyl group compared to the trifluoromethyl group, liquid crystal **144** possesses a stronger dielectric anisotropy than **142** (Table 1.1.7). Other SF_5-containing liquid crystals have been prepared and tested, like **146** for example, with a dioxane component instead of the cyclohexyl ring. The $\Delta\varepsilon$ obtained with **146** is comparable to the $\Delta\varepsilon$ of the liquid crystal with the terminal cyano group **143**. However, one inconvenience resulting from the introduction of the SF_5 group is the increase in rotational viscosity, an important parameter influencing the switching time of the display.

Table 1.1.7. Dielectric anisotropy of liquid crystals.

Compound	**142**	**143**	**144**	**145**	**146**
$\Delta\varepsilon$	8.6	21.1	12.0	4.3	20.3

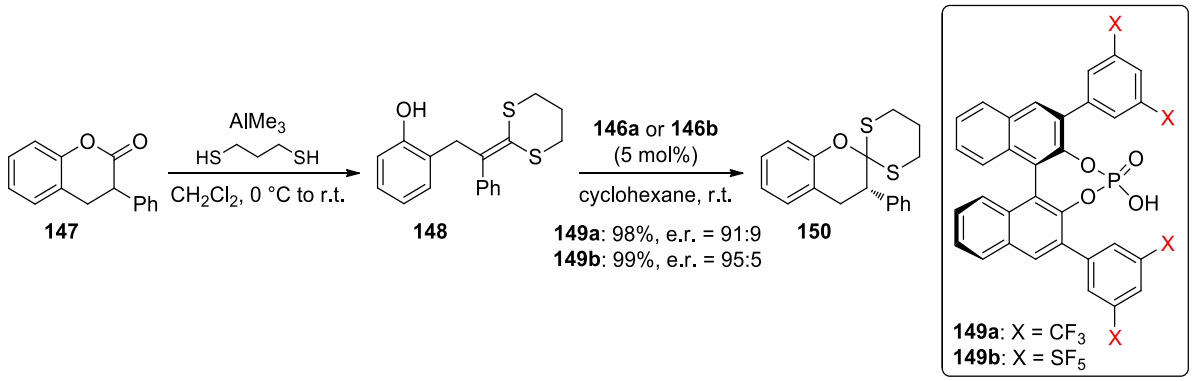
Other applications of the pentafluorosulfanyl group in material sciences include the preparation of polymers,[67] as well as its implementation in dyes such as phthalocyanines,[68] and BODIPYs.[69] Moreover, the introduction of the SF_5 substituent in energetic materials resulted in an increase of the density and a diminution of the impact sensitivity.[52,70]

[67] (a) R. Winter, P. G. Nixon, G. L. Gard, D. G. Castner, N. R. Holcomb, Y. H. Hu, D. W. Grainger, *Chem. Mater.* **1999**, *11*, 3044–3049; (b) P. G. Nixon, R. Winter, D. G. Castner, N. R. Holcomb, D. W. Grainger, G. L. Gard, *Chem. Mater.* **2000**, *12*, 3108–3112.
[68] (a) N. Iida, E. Tokunaga, N. Saito, N. Shibata, *J. Fluorine Chem.* **2014**, *168*, 93–98; (b) N. Iida, E. Tokunaga, N. Saito, N. Shibata, *J. Fluorine Chem.* **2015**, *171*, 120–123; (c) N. Iida, K. Tanaka, E. Tokunaga, S. Mori, N. Saito, N. Shibata, *ChemistryOpen* **2015**, *4*, 698–702.
[69] H. R. A. Golf, H. U. Reissig, A. Wiehe, *J. Org. Chem.* **2015**, *80*, 5133–5143.
[70] (a) M.E. Sitzmann, W. H. Gilligan, D. L. Ornellas, J. S. Thrasher, *J. Energ. Mat.* **1990**, *8*, 352–374; (b) H. Martinez, Z. Y. Zheng, W. R. Dolbier, *J. Fluorine Chem.* **2012**, *143*, 112–122.

1.1.3.4. Catalysts

The development of reagents or catalysts bearing the pentafluorosulfanyl group is still at its infancy. Only two examples of reactions efficiently catalyzed with SF_5-containing catalysts are reported in the literature, both developed by the research group of List.

List and co-workers described the first approach to enantiopure *α*-arylated hydrocoumarins using a deracemization strategy (Scheme 1.1.22).[71] Thus, racemic *α*-arylated hydrocoumarin **147** was converted into the corresponding opened ketene dithioacetal **148**. Then, catalytic asymmetric protonation of the latter in presence of phosphoric acid afforded the dithioacetal-protected hydrocoumarin **150**. Various chiral phosphoric acids were screened, and the two most successful were **149a** and **149b**, containing electron-withdrawing substituents CF_3 and SF_5, respectively. The reaction carried out with catalyst **149a** afforded **150** in excellent yield and with good enantioselectivity (91:9 er). However, the reaction could be optimized by using the catalyst **149b**, containing the 3,5-bis(pentafluorosulfanyl)phenyl substituents, delivering the cyclization product with higher enantioselectivity (95:5 er).

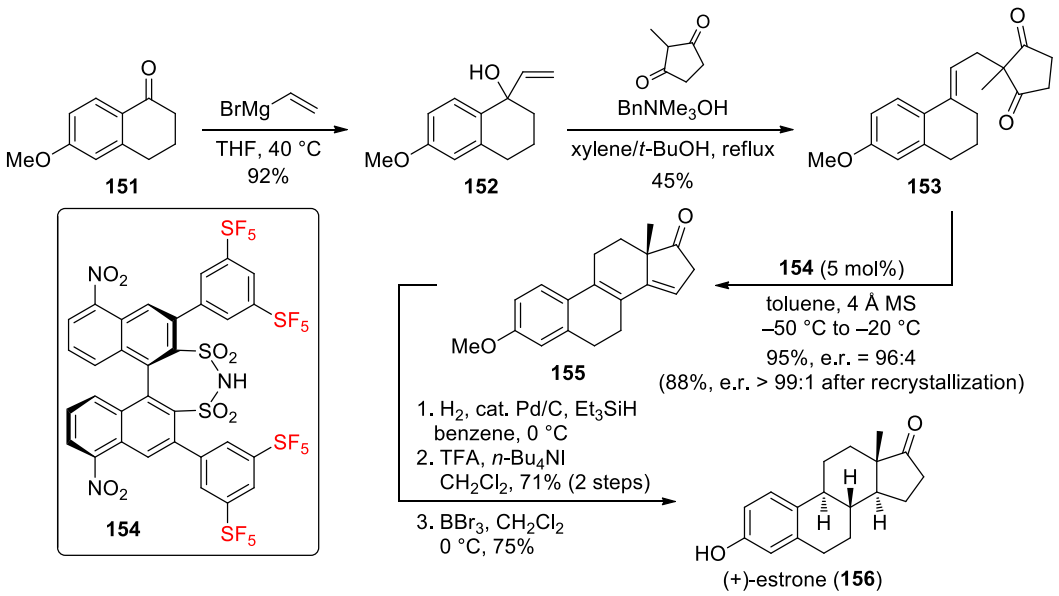


Scheme 1.1.22. Deracemization of *α*-aryl hydrocoumarin.

In a recent paper, List reported the use of another SF_5-containing catalyst in the asymmetric Torgov cyclization.[72] This reaction was applied as the key step of a very short synthesis of (+)-estrone (Scheme 1.1.23). The diketone **153**, precursor for the asymmetric cyclization, was prepared in two steps from commercially available 6-methoxy-1-tetralone (**151**). Among the chiral Brønsted acids screened to trigger the Torgov reaction, disulfonimide **154**, bearing two 3,5-bis(pentalfuorosulfanyl)phenyl substituents, afforded the best results in terms of enantioselectivity. Thus, treatment of **153** with 5 mol% of **154** in toluene at low temperature afforded the desired diene **155** in 95% yield and with 96:4 er. After a single recrystallization,

[71] J. W. Lee, B. List, *J. Am. Chem. Soc.* **2012**, *134*, 18245–18248.
[72] S. Prevost, N. Dupre, M. Leutzsch, Q. G. Wang, V. Wakchaure, B. List, *Angew. Chem. Int. Ed.* **2014**, *53*, 8770–8773.

providing enantiopure **155**, the completion of the synthesis was achieved by reduction followed by methyl ether deprotection.



Scheme 1.1.23. Total synthesis of (+)-estrone.

1.1.4. Conclusion

The utility of the pentafluorosulfanyl group is just beginning to be demonstrated. Its peculiar combination of properties can bring advantageous effects on biologically active compounds which go beyond the similarity with trifluoromethyl-substituted molecules.

Even if improvements have been recently achieved in the development of methods for the preparation of SF_5-substituted aryl and alkyl compounds, the pentafluorosulfanyl group lacks visibility compared to other fluorine-containing functional groups. The number of available building blocks incorporating the pentafluorosulfanyl group is still low and their chemical behavior is rather unexplored. This statement is particularly valid concerning heterocycles, which are omnipresent in agrochemicals and pharmaceuticals. Consequently, new strategies to access unprecedented SF_5-heterocycles are highly desirable. Moreover, the modulating effects of the SF_5 group are not completely understood because of the paucity of physicochemical property data of these building blocks.

In this context, the goal of this project was to design, prepare and study novel building blocks featuring the pentafluorosulfanyl group. Two subclasses of compounds were successfully synthesized using two different strategies: 1) Ir-catalyzed C–H borylation gave access to novel SF_5-substituted potassium aryltrifluoroborates. The usefulness of these building blocks was showcased in Suzuki–Miyaura and Chan–Lam–Evans coupling reactions. 2) Unprecedented

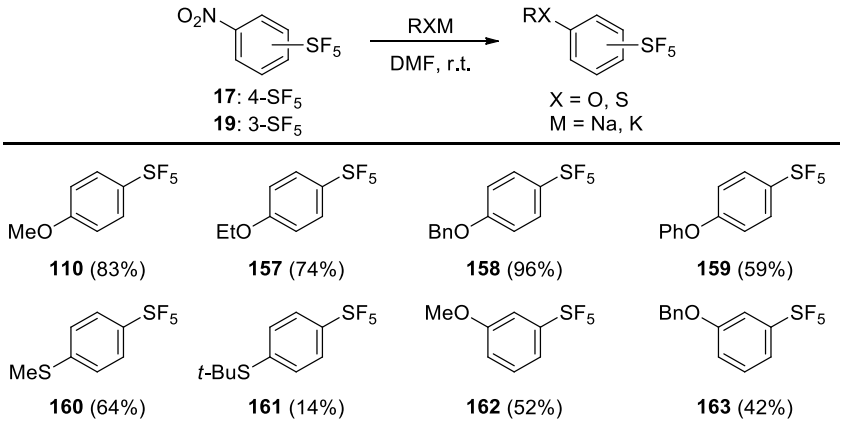
SF_5-heterocycles, namely 3-SF_5-quinolin-2-ones, 3-SF_5-quinolines and 3-SF_5-pyridin-2-ones, were prepared using a *de novo* strategy. These compounds are the first examples of *N*-heterocycles incorporating a SF_5 group in 3-position.[73] The key step in these synthetic sequences was the generation of an enolate in α-position of the SF_5-group, which underwent aldol reactions. The chemistry of these heterocycles was also explored. Furthermore, investigation of their physicochemical properties and comparative analysis with those of their trifluoromethyl and *tert*-butyl analogues were achieved.

[73] The work of Shibata describing the synthesis of 3- and 4-SF_5 pyridines (ref. 48) was disclosed after the publication of our study (ref. 129).

1.2. Preparation and Applications of Novel SF_5-Aryl Boron Reagents

1.2.1. Access to Versatile SF_5-Aryl Building Blocks

One restriction to the widespread application of the SF_5-substituted compounds is the limited number of available methods to synthesize versatile SF_5 building blocks and to use them in the construction of complex molecules of interest. In the majority of cases, aromatic SF_5 compounds are prepared by derivatization of the two commercially available 3- and 4-(pentafluorosulfanyl)nitrobenzene (**17** and **19**), accessible in large quantity. Beier investigated on the reactivity and the possibility for simple functionalization of these compounds. For example, by taking advantage of the electron withdrawing effect of the pentafluorosulfanyl group, he reported the aromatic nucleophilic substitution of the nitro group with alkoxides and thiolates to generate substituted 4- and 3-SF_5-arenes (Scheme 1.2.1).[74]

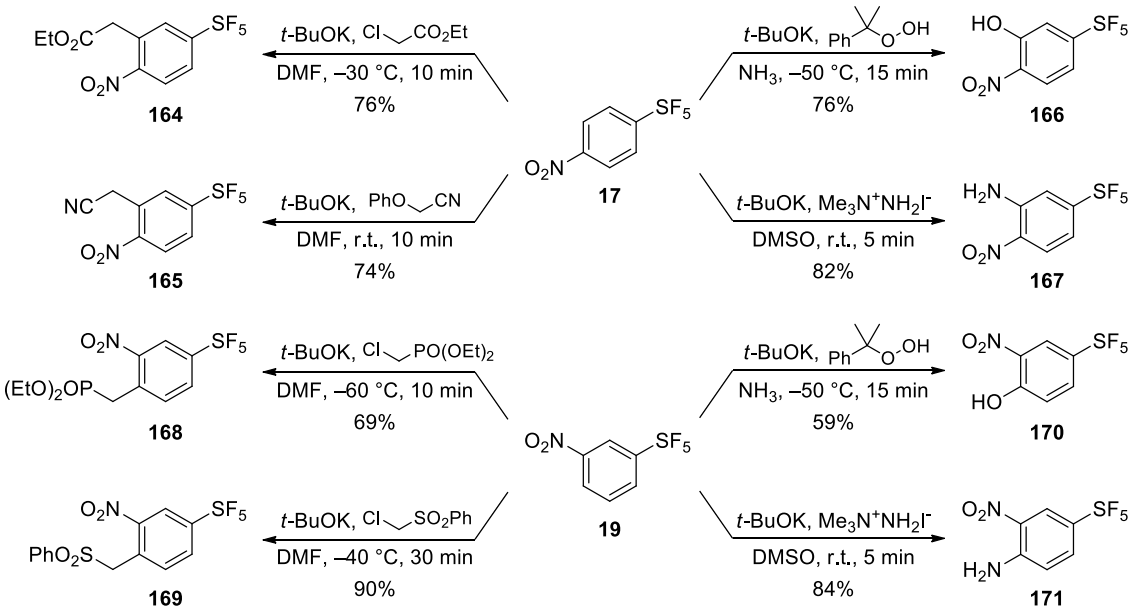


Scheme 1.2.1. S_NAr of 3- and 4-SF_5-nitrobenzenes.

The reaction was successful with 4-(pentafluorosulfanyl)nitrobenzene (**17**), and aryl ethers could be obtained in modest to good yield with simple aliphatic alcohols and unsubstituted phenol. Reaction with aliphatic thiolates was limited to three examples, and attempts to realize substitution with thiophenol failed. On the other hand, the reaction using 3-(pentafluorosulfanyl)nitrobenzene (**19**) as starting material was less efficient. Indeed, of the three examples reported, the best yield was 52%, obtained by treatment of **19** with MeONa to give **162**. Moreover, phenols, and thiolates were found to be not suitable for this reaction. Therefore, obtaining 3-SF_5-substituted aryl compounds using this method remains difficult.

[74] P. Beier, T. Pastyrikova, N. Vida, G. Iakobson, *Org. Lett.* **2011**, *13*, 1466–1469.

Beier also disclosed the vicarious nucleophilic substitutions of 3- and 4-nitro (pentafluorosulfanyl)benzenes.[49,75] This reaction, widely explored by Mąkosza, allows the nucleophilic replacement of an hydrogen in *ortho* or *para* position of the nitro group.[76]



Scheme 1.2.2. Vicarious nucleophilic substitutions of 3- and 4-SF_5-nitrobenzenes.

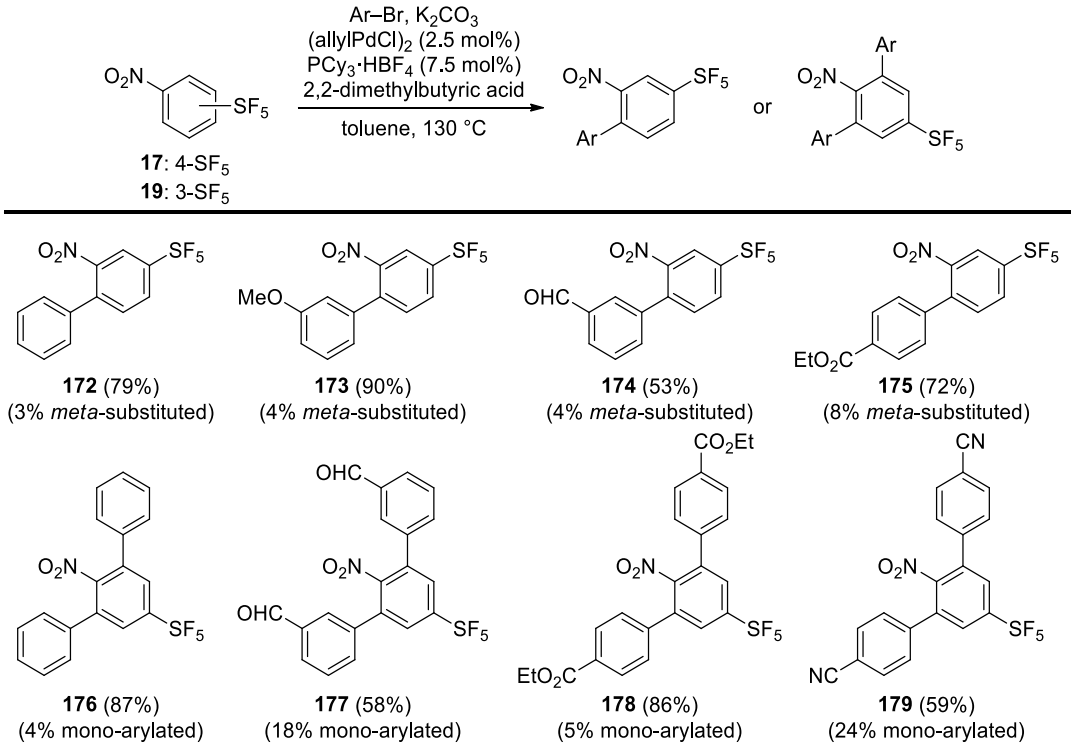
By using this strategy, Beier and co-workers were able to prepare a collection of 3,4-disubstituted pentafluorosulfanylbenzenes by addition of appropriate nucleophiles (Scheme 1.2.2). Short exposure of **17** and **19** to carbanions having a leaving group at the nucleophilic center afforded the corresponding substitution products (**164**, **165**, **168** and **169**) in good yields.[75a] In the case of the 3-(pentafluorosulfanyl)nitrobenzene **19**, only minor amounts of the other possible regioisomer with the substitution in *para* position of the nitro group was observed (2-15%). Hydroxylation *via* vicarious nucleophilic substitution was also possible, by generating anion of cumene hydroperoxide in liquid ammonia, giving access to **166** and **170**.[75b] Only 5% of the regioisomer with the hydroxyl group in *para* position of the nitro was formed when **19** was used as starting material. Similarly, amination was accomplished with trimethylhydrazinium iodide, affording **167** and **171** in good yields.[49a] Oxidative nucleophilic substitution of hydrogen was also reported by addition alkyl Grignard and alkyl lithium reagents, quickly followed by treatment with potassium permanganate in liquid ammonia.[75c] However this reaction was limited to only a small number of reagents, excluding aryl

[75] (a) P. Beier, T. Pastyrikova, G. Iakobson, *J. Org. Chem.* **2011**, *76*, 4781–4786; (b) P. Beier, T. Pastyrikova, *Tetrahedron Lett.* **2011**, *52*, 4392−4394; (c) N. Vida, P. Beier, *J. Fluorine Chem.* **2012**, *143*, 130–134; (d) G. Iakobson, P. Beier, *Beilstein J. Org. Chem.* **2012**, *8*, 1185−1190.

[76] (a) M. Mąkosza, B. Chylinska, B. Mudryk, *Liebigs. Ann. Chem.* **1984**, 8–14; (b) M. Mąkosza, T. Glinka, A. Kinowski, *Tetrahedron* **1984**, *40*, 1863–1868; (c) M. Mąkosza, J. Golinski, J. Baran, D. Dziewonskabaran, *Chem. Lett.* **1984**, 1619–1622; (d) M. Mąkosza, J. Winiarski, *Chem. Lett.* **1984**, 1623–1624; (e) M. Mąkosza, K. Stalinski, *Chem. Eur. J.* **1997**, *3*, 2025–2031; (f) N. Moskalev, M. Barbasiewicz, M. Mąkosza, *Tetrahedron* **2004**, *60*, 347–358; (g) M. Mąkosza, *Chem. Soc. Rev.* **2010**, *39*, 2855–2868.

derivatives. The addition with *meta*-derivative **19** was rather not regioselective, probably due to the high reactivity of these organometallic compounds.

Moreover, concurrently to the work described in this chapter, Zhang and co-workers reported the palladium-catalyzed direct arylation of electron-deficient (pentafluorosulfanyl)nitrobenzenes (Scheme 1.2.3).[77] When 3-(pentafluorosulfanyl)nitrobenzene was treated with aryl bromides, catalytic amounts of $(allylPdCl)_2$ and $PCy{\cdot}HBF_4$, 2,2-dimethylbutyric acid, as well as K_2CO_3, high regioselectivity was observed with arylation in *ortho*-position of the nitro group. Traces amounts of the corresponding compounds with *meta*-arylation were also observed. On the other hand, direct arylation of 4-(pentafluorosulfanyl)nitrobenzene mainly afforded bis-arylated products in both *ortho*-positions of the nitro group, along with variable amounts of mono-arylated products.



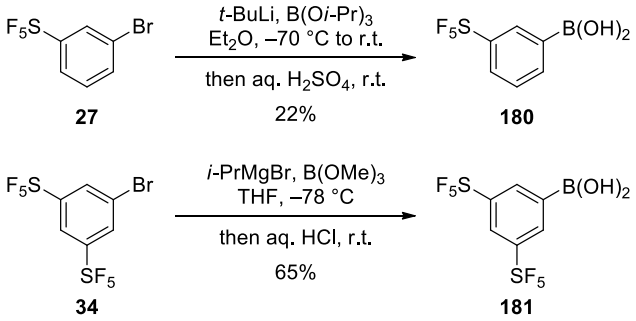
Scheme 1.2.3. Pd-catalyzed direct arylation of (pentafluorosulfanyl)nitrobenzenes.

Boronic acids and their derivatives represent one of the most important classes of versatile building blocks.[78] Due to their ease of preparation, low toxicity, and high reactivity, these reagents of choice are widely used for the formation of carbon–carbon and carbon–heteroatom bonds by transition metal-catalyzed coupling reactions in the construction of complex

[77] C. Wang, Y. B. Yu, S. L. Fan, X. G. Zhang, *Org. Lett.* **2013**, *15*, 5004–5007.
[78] Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials (Volume 1 and 2), Second Edition (Ed: D. G. Hall) Wiley-VCH, Weinheim, **2011**.

molecules. The usefulness and popularity of these compounds incited research groups to develop novel synthetic methods to prepare them.

At the time when the work described in this chapter was realized, reports of pentafluorosulfanyl substituted aryl boron reagents were rare in both patent and research journal literature.[79] The first example of preparation of aryl boronic acids featuring the SF_5 group dates from 2005, in which the routine method involving metal–halogen exchange, followed by treatment with trialkoxyborane and subsequent hydrolysis was performed (Scheme 1.2.4).[79a] However, this approach suffers from low yields, the best one being obtained *via* lithiation of 3-bromo(pentalfluorosulfanyl)benzene using *t*-BuLi to form the corresponding boronic acid **180** in only 22% yield. Similar outcomes were observed when the reaction was applied in the synthesis of BACE-1 inhibitors.[79b] Interestingly, 3,5-bis(pentafluorosulfanyl)phenyl boronic acid **181** could be obtained in a good yield of 65% by generating the Grignard reagent from 1,3-bis(pentafluorosulfanyl)-5-bromobenzene (**34**) with *i*-PrMgBr followed by treatment with trimethyl borate.[79c]



Scheme 1.2.4. Preparation of SF_5-containing aryl boronic acids.

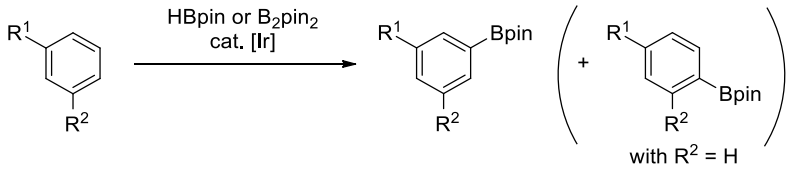
Because of the paucity of SF_5-substituted aryl boronic reagents, straightforward access to novel members of this class of building blocks would be highly desirable. If successful, such a methodology would create new opportunities to synthesize complex molecules bearing the SF_5 group.

1.2.2. Iridium-Catalyzed C–H Borylation[80]

Among the modern methods to synthesize boronic acid derivatives, direct borylation by C–H activation has emerged as one of the most striking in the two last decades.[81] This reaction offers the advantage that it does not require aryl or alkyl halides to prepare the corresponding boronic

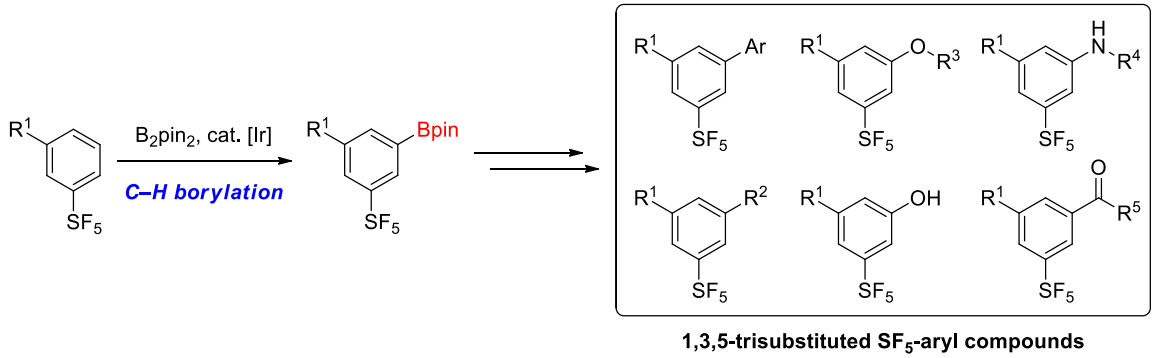
[79] (a) J. Sherrington, *WO 2005/123749 A1*, **2005**; (b) A. W. Stamford, J. N. Cumming, *WO 2011/044184 A1*, **2011**; (c) Y. D. Yang, X. Lu, E. Tokunaga, N. Shibata, *J. Fluorine Chem.* **2012**, *143*, 204–209.
[80] The results of the study presented in this section were published: A. Joliton, E. M. Carreira, *Org. Lett.* **2013**, *15*, 5147–5149.
[81] I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890–931.

reagents. In a pioneering study, Smith reported the iridium-catalyzed C–H borylation of arenes using HBpin and Cp* or phosphine-based ligands at temperatures between 100 and 150 °C.[82] The reaction, in which the regioselectivity is determined by steric factors, provided a mixture of arylboronate esters from monosubstituted arenes, and 3,5-disubstituted arylboronate esters from 1,3-disubstituted arenes (Scheme 1.2.5).



Scheme 1.2.5. Regioselectivity in the iridium-catalyzed C–H borylation.

The method was concurrently improved further by Hartwig, Ishayama and Miyaura with the use of B_2pin_2 and bipyridine ligands.[83] The reactions realized in presence of this powerful catalytic system are performed at room temperature up to 80 °C. The initial reports were followed by the elaboration of several one-pot processes *via* C–H borylation, providing access to 1,3,5-trisubstituted aryl compounds, which would be more difficult to obtain by other methods. Thus, one pot preparation of 3,5-disubstituted phenols,[84a] aryl halides,[84b-c] or aryl cyanides[84d] were described, as well as borylation/cross-coupling sequences.[82b, 84e-g]



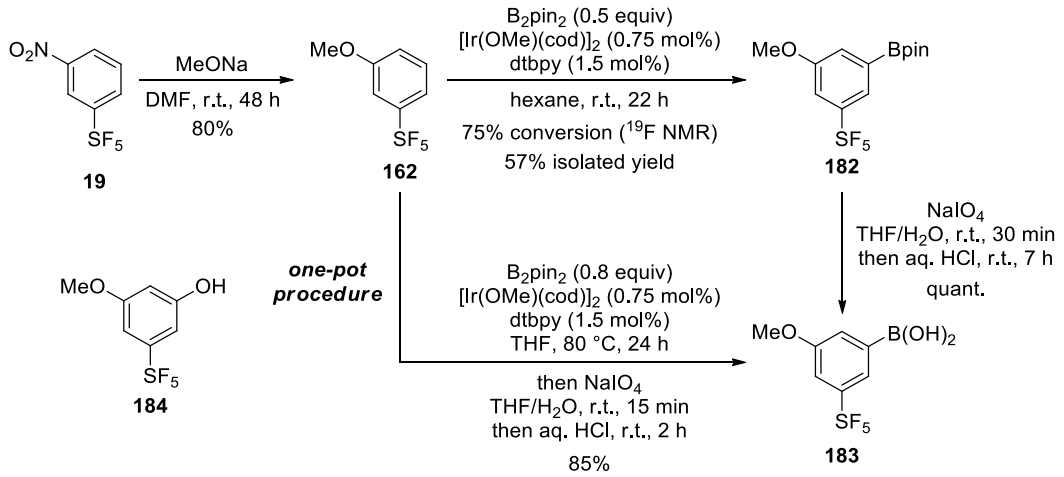
Scheme 1.2.6. Access to 1,3,5-trisubstituted SF_5-aryl compounds *via* C–H borylation.

Applying this methodology to *meta*-substituted SF_5-aryl compounds would give access to unprecedented and otherwise difficult to obtain 3,5-disubstituted pentafluorosulfanylbenzenes (Scheme 1.2.6). Except the 1,3-bis(pentafluorosulfanyl)-5-bromobenzene (**34**), there is only one

[82] (a) C. N. Iverson, M. R. Smith, *J. Am. Chem. Soc.* **1999**, *121*, 7696–7697; (b) J. Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, M. R. Smith, *Science* **2002**, *295*, 305–308.
[83] (a) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 390-391; (b) T. Ishiyama, J. Takagi, J. F. Hartwig, N. Miyaura, *Angew. Chem. Int. Ed*. **2002**, *41*, 3056–3058; (c) T. M. Boller, J. M. Murphy, M. Hapke, T. Ishiyama, N. Miyaura, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 14263–14278.
[84] (a) R. E. Maleczka, F. Shi, D. Holmes, M. R. Smith, *J. Am. Chem. Soc.* **2003**, *125*, 7792–7793; (b) J. M. Murphy, X. Liao, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 15434–15435; (c) B. M. Partridge, J. F. Hartwig, *Org. Lett.* **2013**, *15*, 140–143; (d) C. W. Liskey, X. B. Liao, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 11389–11391; (e) T. Ishiyama, Y. Nobuta, J. F. Hartwig, N. Miyaura, *Chem. Commun.* **2003**, 2924–2925; (f) T. Kikuchi, Y. Nobuta, J. Umeda, Y. Yamamoto, T. Ishiyama, N. Miyaura, *Tetrahedron* **2008**, *64*, 4967–4971; (g) D. W. Robbins, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2013**, *52*, 933–937.

example of preparation of a SF_5-aryl compound with such a substitution pattern, by aromatic electrophilic substitution of 3-(pentafluorosulfanyl)nitrobenzene with NBS in sulfuric acid.[49b] However, with other substituents than a nitro group in the *meta*-position of the SF_5, such as *ortho*/*para* directing group halogens or alkoxy groups, electrophilic substitution would give 1,2,4-trisubstituted products because of electronic factors. On the other hand, the regioselectivity of iridium-catalyzed borylation is controlled by steric factors. Therefore, iridium catalyzed C–H borylation of 3-SF_5-substituted arenes would install the boronate ester in the *meta*-position of both the SF_5 group and the second substituent. This strategy would then offer the benefits of the boron reagent versatility to access a collection of novel 1,3,5-trisubstituted pentafluorosulfanylbenzenes, which are potentially important building blocks for drug discovery and agrochemicals.

Consequently, we decided to examine the feasibility of the iridium-catalyzed C–H borylation on *meta*-substituted SF_5 aryl compounds. Because of the absence of nitro groups in all reported examples of the substrate scope for this reaction, we decided to start our investigation with the known 3-methoxy(pentafluorosulfanyl)benzene (**162**), which was prepared following Beier's protocol (Scheme 1.2.7).[74] We then attempted to expose **162** to the initial conditions described by Hartwig, Miyaura and Ishayama,[83b] by treatment with 0.5 equiv of B_2pin_2 in presence of 0.75 mol% of $[Ir(OMe)(cod)]_2$ and 1.5 mol% of dtbpy in hexane at room temperature. Satisfyingly, the corresponding boronate ester **182** was cleanly formed and a maximum conversion of 75% was reached after 22 h, according to ^{19}F NMR monitoring. To the best of our knowledge, this is the first example of C–H activation with a pentafluorosulfanyl-containing aryl system.



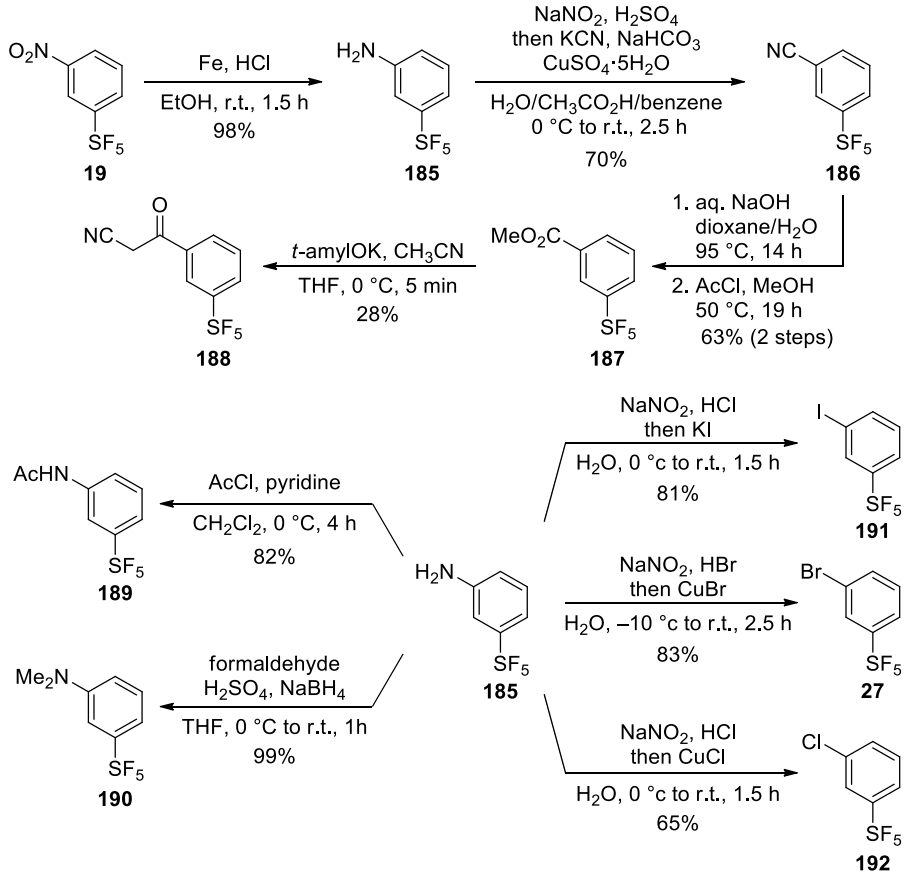
Scheme 1.2.7. C–H borylation of **160** and convertion to the corresponding boronic acid.

Surprisingly, the isolation of **182** was found to be troublesome. In general, purification of pinacol boronic esters by column chromatography on silica gel is a trivial process, this factor being even an advantage when these species are compared to their corresponding boronic acid derivatives. However, in our case, **182** was tailing on the column even when it was eluted with pure EtOAc, and could not be collected without substantial loss of material. Because of the higher reactivity towards cross-coupling reactions of aryl boronic acids compared to the boronate esters, we converted **182** into boronic acid **183** by oxidative cleavage of the pinacol group with $NaIO_4$.[85] The efficiency and cleanness of this reaction encouraged us to try a one-pot method to obtain directly **183** from 3-methoxy(pentafluorosulfanyl)benzene **162**, as previously disclosed by Hartwig.[86] Thus, the C–H borylation was performed in THF at 80 °C, which afforded the boronate ester with complete conversion, according to ^{19}F NMR analysis. In addition to be more powerful regarding the conversion, these reaction conditions also offered the advantage of using a solvent which can also dissolve more polar substrates than the hexane previously employed, making this method more versatile. The second step of this one-pot process had to be carefully monitored. Indeed, long reaction times, as described in the Hartwig report (reactions performed for 16 h), resulted in the formation of phenol **184** in variable amounts (10-50%), arising from periodate mediated oxidation of **183**. Consequently, the reaction was stopped after 2 h, and isolation of the SF_5-aryl boronic acid was achieved by precipitation from Et_2O with hexane to obtain desired product in 85% yield and high purity, according to ^1H and ^{19}F NMR spectra. The optimization of the isolation conditions was primordial, since like the majority of boronic acids, purification of **183** by column chromatography was not convenient.

With efficient conditions for the direct formation of pentafluorosulfanyl substituted aryl boronic acids in hand, we explored the possibility to expand this transformation to other *meta*-substituted pentafluorosulfanylbenzenes. Therefore, a collection of substrates was synthesized from 3-SF_5-aniline (**185**) (Scheme 1.2.8). Importantly, except for **188**, **189** and **190**, all these compounds are commercially available, even if they were prepared in our laboratory in the present case. Formation of the aryl diazonium salt followed by Sandmeyer reaction with KCN and $CuSO_4$ afforded 3-cyano(pentafluorosulfanyl)benzene (**186**). The latter could be hydrolyzed under basic conditions to form the carboxylic acid which was converted into the corresponding methyl ester **187**. The *β*-keto nitrile **188** was also prepared, *via* addition of acetonitrile, as it could be a precursor of various heterocycles, such as pyrimidines. Moreover, acetylation of

[85] S. J. Coutts, J. Adams, D. Krolikowski, R. J. Snow, *Tetrahedron Lett.* **1994**, *35*, 5109–5112.
[86] J. M. Murphy, C. C. Tzschucke, J. F. Hartwig, *Org. Lett.* **2007**, *9*, 757–760.

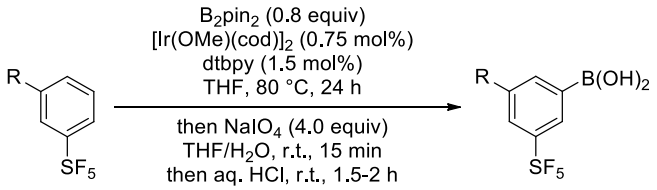
3-SF_5-aniline gave amide **189** in good yield. Reductive alkylation with formaldehyde of **185** was also performed to obtain dimethylaniline **190**. Finally, 3-SF_5 aryl halides **27**, **191** and **192** were accessed by Sandmeyer reaction.

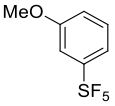
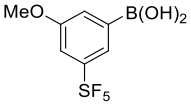
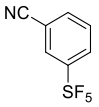
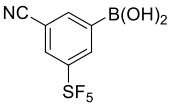
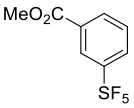
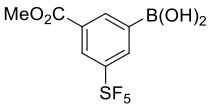
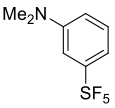
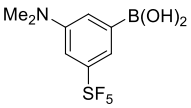


Scheme 1.2.8. Preparation of 3-substituted SF_5-aryl compounds.

Next, we investigated the generality of the C–H borylation/oxidative cleavage sequence on the newly prepared *meta*-substituted SF_5-arenes (Table 1.2.1). The iridium-catalyzed C–H borylation was always performed in a complete and clean way, as judged by ^1H and ^{19}F NMR analyses of reaction aliquots. However, it rapidly became obvious that the isolation of the formed arylboronic acids would represent an obstacle. Indeed, conversion of the pinacol boronic esters into the corresponding boronic acids was less trivial, and unpredictable amounts of phenol and other unidentified compounds were formed during this step. Moreover, the purification method by precipitation from Et_2O with hexane, which proved to be efficient for methoxy derivative **183** (Entry 1), failed to give clean products for the other attempted substrates (Entries 2-4). Efforts to identify conditions for their isolation were unsuccessful and only resulted in lowering the purity of the compounds, attributed to decomposition of the boron reagent as well as probable formation of trimeric cyclic anhydrides.

Table 1.2.1. Substrate scope of C–H borylation/oxidative cleavage sequence.



Entry	3-SF_5-Arene	Conversion for C–H borylation[a]	Product	Yield	Estimated purity[b]
1	 **162**	100%	 **183**	85%	>95%
2	 **186**	100%	 **193**	84%	60%
3	 **187**	100%	 **194**	85%	90%
4[c]	 **190**	100%	 **195**	n/a	<50%

a) Determined by ^{1}H and ^{19}F NMR analyses of an aliquot; b) Estimation made by integration of the signals of aromatic protons in ^{1}H NMR spectra; c) Reaction mixture neutralized with aq. $NaHCO_3$ prior to isolation.

Nevertheless, the iridium-catalyzed C–H borylation seemed to be effective and only the isolation step was problematic. Consequently, we envisaged to avoid these purification issues by converting the boronate ester into another boron derivative, more stable and easier to isolate. One solution would be the use of potassium aryltrifluoroborates reagents, boron ate complex derivatives.[87] Potassium organotrifluoroborates, which emerged in the 1960s,[88] display exceptional stabilities towards nucleophilic compounds as well as air and moisture compared to trivalent organoboranes. Moreover, their isolation is generally straightforward, by precipitation or recrystallization from acetone with diethyl ether. The expansion of potassium organotrifluoroborate chemistry was initiated with the improvement of their preparation. In 1995, Vedejs and co-workers disclosed that treatment of arylboronic acids with potassium hydrogen difluoride KHF_2 efficiently afforded the corresponding potassium

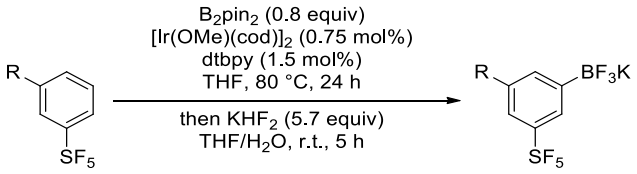
[87] For a review about potassium organotrifluoborates, see: S. Darses, J. P. Genet, *Chem. Rev.* **2008**, *108*, 288–325.
[88] (a) R. D. Chambers, H. C. Clark, C. J. Willis, *J. Am. Chem. Soc.* **1960**, *82*, 5298–5301; (b) S. L. Stafford, *Can. J. Chem.* **1963**, *41*, 807–808; (c) R. D. Chambers, T. Chivers, D. A. Pyke, *J. Chem. Soc.* **1965**, 5144–5145.

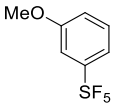
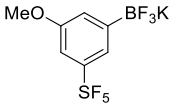
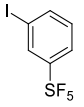
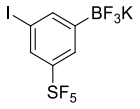
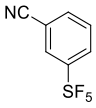
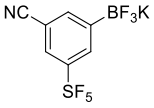
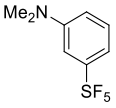
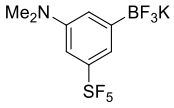
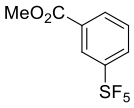
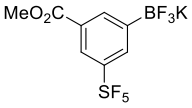
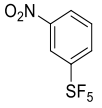
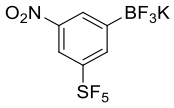
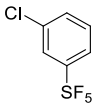
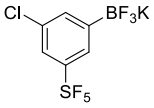
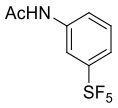
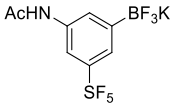
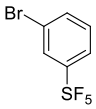
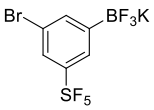
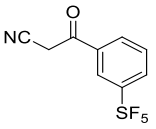
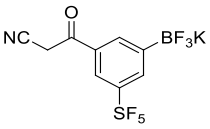
aryltrifluoroborates.[89] Following the report of this straightforward protocol, a number of publications showed that potassium organotrifluoroborate can participate in a large variety of reactions with comparable reactivity to boronic acids.

Attracted by the promising advantages of the potassium trifluoroborate species, we attempted to apply the one-pot procedure described by Hartwig in order to obtain pentafluorosulfanyl-substituted potassium aryltrifluoroborates (Table 1.2.2).[86] Thus, after iridium-catalyzed C–H borylation, simple addition of water and KHF_2, followed by stirring at room temperature for 5 hours, afforded complete conversion to the desired SF_5-substituted potassium aryltrifluoroborates. Interestingly, unlike the majority of the potassium organotrifluoroborates, SF_5-$ArBF_3K$ are soluble in diethyl ether. Consequently, a solvent system that would remove the pinacol byproduct from the prepared SF_5-aryl trifluoroborates had to be identified. We found that all these compounds could be isolated by precipitation from acetone with chloroform or dichloromethane. The residual pinacol could be removed by additional washing of the obtained solid to afford the pentafluorosulfanyl substituted aryltrifluoroborates in high purity, according to ^1H and ^{19}F NMR spectra. The scope of substrates includes various substituents in the *meta*-position of the SF_5 group, such as methoxy (Entry 1), nitrile (Entry 2), methyl ester (Entry 3), halogens (Entries 4-6) and tertiary amine (Entry 7). In all these cases, the iridium-catalyzed C–H borylation was achieved with complete conversion, and the SF_5-substituted potassium aryltrifluoroborates were obtained in good to excellent yields. It is important to notice that these compounds were very stable, and they could be stored on the laboratory bench for months. Moreover, a multigram scale reaction was conducted with **162** in 92% yield, affording more than 3 g of **196**, underscoring the efficiency, simplicity, and suitability of this method for the preparation of large quantities of SF_5-substituted building blocks. However, the iridium-catalyzed C–H borylation was unsuccessful with compounds bearing an acidic protons (Entries 9-10) such as amide **189**[90] and *β*-keto nitrile **188**[91], which gave a mixture of unidentified compounds with a conversion below 30%. 3-(pentafluorosulfanyl)nitrobenzene **19** was also unsuitable for C–H borylation (Entry 8), with no conversion observed.

[89] E. Vedejs, R. W. Chapman, S. C. Fields, S. Lin, M. R. Schrimpf, *J. Org. Chem.* **1995**, *60*, 3020–3027.
[90] *N*-phenylacetamide: pK_a = 21.5 in DMSO, therefore the p*K*a of **187** is lower due to the electron withdrawing effect of the SF_5; F. G. Bordwell, G. Z. Ji, *J. Am. Chem. Soc.* **1991**, *113*, 8398–8401.
[91] benzoylacetonitrile: pK_a = 10.2 in DMSO; F. G. Bordwell, M. Vanderpuy, N. R. Vanier, *J. Org. Chem.* **1976**, *41*, 1883–1885.

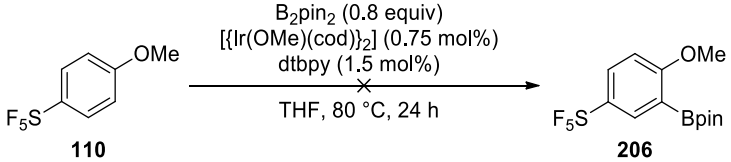
Table 1.2.2. One-pot synthesis of SF_5-substituted potassium aryltrifluoroborates.



Entry	3-SF_5-Arene	Product	Yield	Entry	3-SF_5-Arene	Product	Yield
1	 **162**	 **196**	94%	6	 **191**	 **201**	72%[a]
2	 **186**	 **197**	88%	7	 **190**	 **202**	81%
3	 **187**	 **198**	65%	8	 **19**	 **203**	0%[b]
4	 **192**	 **199**	89%	9	 **189**	 **204**	n/a[c]
5	 **27**	 **200**	76%	10	 **188**	 **205**	n/a[c]

a) C–H borylation was conducted for 48 h; b) No conversion during C–H borylation; c) C–H borylation gave mixtures.

We also attempted the iridium-catalyzed C–H borylation with 4-methoxy(pentafluorosulfanyl)benzene (**110**), in order to provide alternatives to methods of Beier and Zhang[74-75,77] to obtain pentafluorosulfanylbenzenes with 1,2,4-trisubstitution pattern (Scheme 1.2.9). However, formation of the borylated product **206** was not observed, probably due to the importance of the steric hindrance generated by the two substituents in **110**.



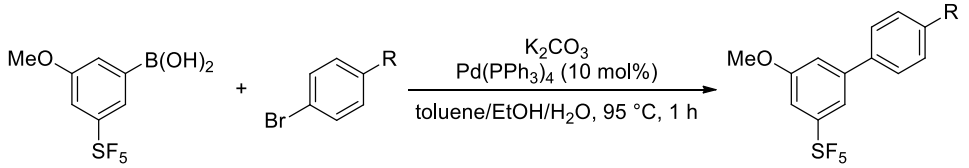
110 **206**

Scheme 1.2.9. Attempted C–H borylation on 4-methoxy(pentalfuorosulfanyl)benzene.

1.2.3. Application in Suzuki–Miyaura Coupling Reaction

1.2.3.1. With SF_5-Substituted Arylboronic Acid

With novel pentafluorosulfanyl-substituted aryl boron reagents in hands, we wanted to demonstrate their usefulness to access unprecedented 3,5-disubstituted SF_5-aryl compounds. Thus, we explored their reactivity in the Suzuki–Miyaura cross-coupling reaction. As it was described in the previous section, we initially prepared the 3-methoxy-5-(pentafluorosulfanyl)aryl boronic acid (**183**). Consequently, we submitted the latter to standard Suzuki–Miyaura reaction conditions with aryl bromides (Scheme 1.2.10).



Scheme 1.2.10. Suzuki–Miyaura cross-coupling reaction of SF_5-$ArB(OH)_2$ with aryl halides.

SF_5-$ArB(OH)_2$ **183** was a suitable substrate for this palladium-catalyzed cross-coupling reaction and it could be converted to the corresponding SF_5-biaryls with 4-bromotoluene and 4-bromochlorobenzene in 83% and 69% yield, respectively. Since we identified that SF_5-substituted potassium aryltrifluoroborates were generally easier to access than the boronic acid, the efforts towards the preparation of more SF_5-biaryl compounds from SF_5-aryl boronic acids were not pursued, although other types of transition metal-catalyzed reactions were investigated with those substrates (*vide infra*).

1.2.3.2. With SF_5-substituted potassium aryltrifluoroborates

Even if they are less commonly used than boronic acids, performances of potassium organotrifluoroborates in palladium catalyzed cross-coupling reactions have been explored, in particular for the Suzuki–Miyaura cross-coupling, and suitable reaction conditions have been identified. Initial investigations were achieved by Genet and co-workers, who successfully demonstrated that organotrifluoroborates can couple with aryldiazonium ions.[92] Then Molander and co-workers reported cross-coupling reactions of potassium alkyl, alkenyl and alkynyltrifluoroborates with aryl and alkenyl halides and triflates.[93] Batey and Quach described

[92] (a) S. Darses, T. Jeffery, J. L. Brayer, J. P. Demoute, J. P. Genet, *Bull. Soc. Chim. Fr.* **1996**, *133*, 1095–1102; (b) S. Darses, J. P. Genet, J. L. Brayer, J. P. Demoute, *Tetrahedron Lett.* **1997**, *38*, 4393–4396; (c) S. Darses, G. Michaud, J. P. Genet, *Tetrahedron Lett.* **1998**, *39*, 5045–5048; (d) S. Darses, G. Michaud, J. P. Genet, *Eur. J. Org. Chem.* **1999**, 1875–1883.

[93] (a) G. A. Molander, T. Ito, *Org. Lett.* **2001**, *3*, 393–396; (b) G. A. Molander, C. R. Bernardi, *J. Org. Chem.* **2002**, *67*, 8424–8429; (c) G. A. Molander, B. W. Katona, F. Machrouhi, *J. Org. Chem.* **2002**, *67*, 8416–8423; (d) G. A. Molander, M. R. Rivero, *Org. Lett.* **2002**, *4*, 107–109.

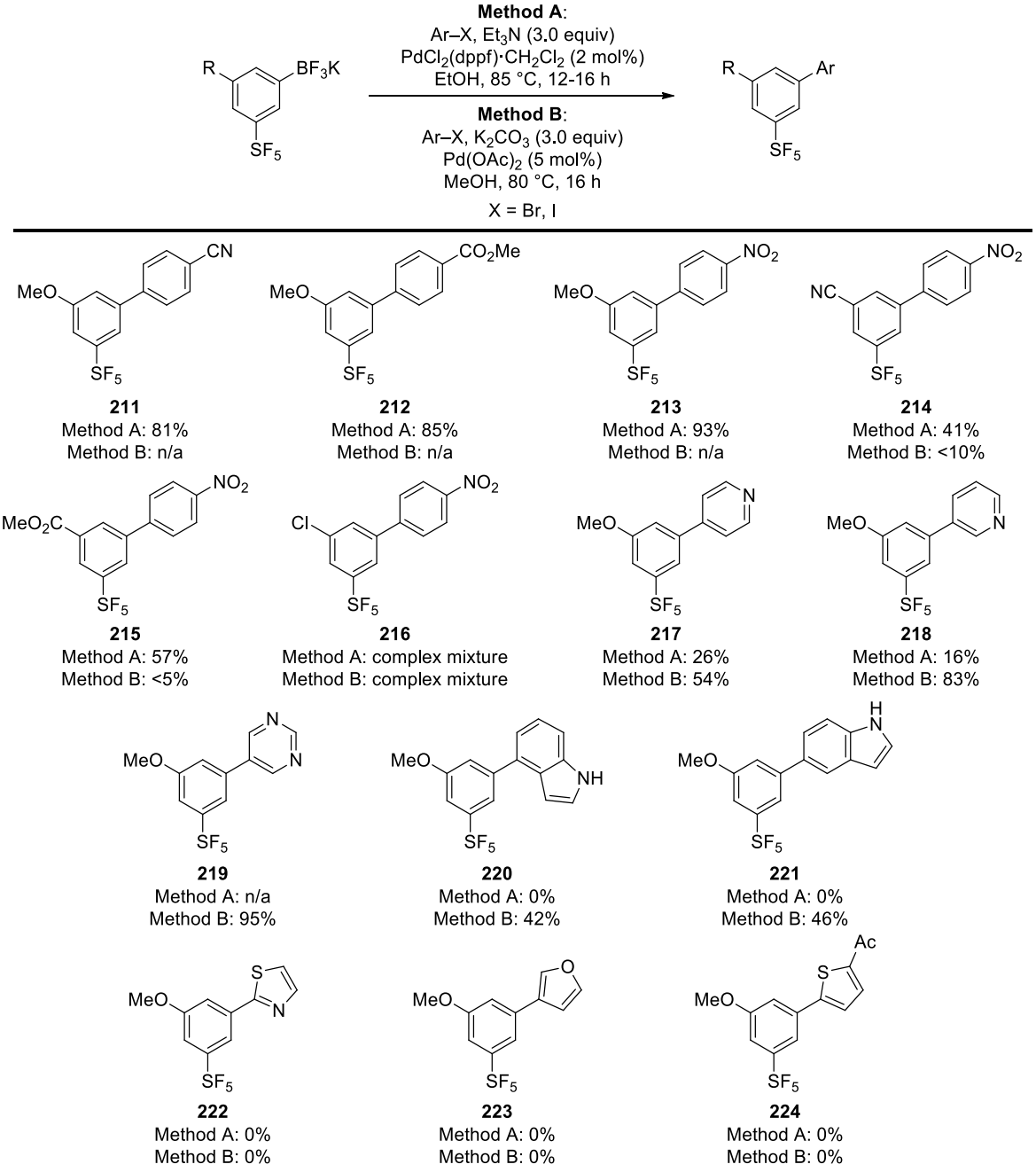
the synthesis of tetrabutylammonium organotrifluoroborate salts and their cross-coupling reactions with alkenyl and aryl halides.[94] Finally, several set of conditions for the coupling of potassium aryltrifluoroborates and aryl halides were disclosed by Molander and co-workers.[95]

Therefore, we explored the reactivity of the prepared pentafluorosulfanyl-substituted potassium aryltrifluoroborates in Suzuki–Miyaura coupling reaction. After screening of conditions, we identified that slight modification of the original procedures were necessary and that the choice of the method was dependent on the aryl halide used (Scheme 1.2.11). Cross-coupling of the *meta*-methoxy derivative of SF_5-$ArBF_3K$ **196** with 4-bromobenzonitrile could be achieved by employing 2 mol% of $PdCl_2(dppf)\cdot CH_2Cl_2$ with 3 equivalents of triethylamine in ethanol at 85 °C (Method A), affording biaryl **211** in 81% yield. Importantly, while Molander and co-workers stated that the reaction could be carried out under an open atmosphere,[95b] it was important in our case to degas the mixture prior to addition of the palladium catalyst and to conduct the reaction under nitrogen atmosphere (**211** was obtained in only 60% yield without degassing and under open atmosphere). Moreover, the initial Molander procedure requires only 0.5 mol% of palladium catalyst, whereas the reaction with the pentafluorosulfanyl-substituted derivatives gave low conversion with a catalyst loading below 2 mol%. Under the thus established conditions, **196** was also coupled in excellent yields with methyl 4-bromobenzoate and 4-bromonitrobenzene to afford **212** and **213**, respectively. The reaction of SF_5-$ArBF_3K$ bearing another electron withdrawing group such as a nitrile or a methyl ester gave **214** and **215** with lower conversion. This finding might be explained by the lower efficiency of the transmetallation step during the catalytic cycle. Additionally, using *meta*-chlorine derivative of SF_5-$ArBF_3K$ **199** gave a mixture of inseparable compounds, one of them tentatively assigned as the desired biaryl **216**. This observation could be due to competitive oxidative addition into the C–Cl bond of the boron reagent **199**, which can be enhanced by the electron withdrawing effect of the pentafluorosulfanyl group.

The Suzuki–Miyaura cross-coupling reaction of **196** with heteroaryl halides was not satisfying under the reaction conditions of Method A. Very poor yields were obtained with pyridines and no reaction occurred with indole derivatives. However, the reaction was improved by using $Pd(OAc)_2$ with potassium carbonate in MeOH at 80 °C (Method B). This set of reaction conditions was suitable for the cross-coupling of **196** with 4-iodopyridine and 3-bromopyridine to give **217** and **218** in 54% and 83% yield, respectively. Diheteroaryl halide

[94] R. A. Batey, T. D. Quach, *Tetrahedron Lett.* **2001**, *42*, 9099–9103.
[95] (a) G. A. Molander, B. Biolatto, *Org. Lett.* **2002**, *4*, 1867–1870; (b) G. A. Molander, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302–4314; (c) G. A. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, *40*, 275–286.

5-bromopyrimidine also participated in the reaction to afford **219** in excellent yields. Furthermore, bromoindoles could be coupled with SF_5-$ArBF_3K$ in modest yields.



Scheme 1.2.11. Suzuki–Miyaura cross-coupling reactions of SF_5-$ArBF_3K$ with aryl halides (n/a: experiment not conducted).

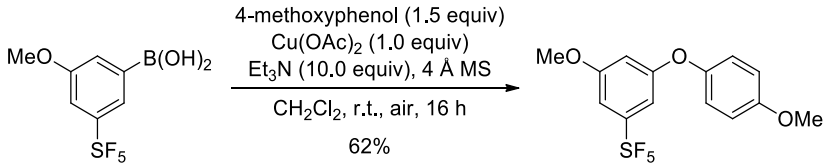
Several substrates were found to be unsuitable under both sets of conditions. Thus, attempts to realize cross-coupling reaction with 2-bromothiazole, 3-bromofuran and 2-acetyl-5-bromothiophene failed to give any product. Another set of conditions involving Pd_2dba_3 (2 mol%), Xphos ligand (4 mol%) and potassium phosphate was also unsuccessful for these 5-membered heterocyclic substrates.

1.2.4. Application in Chan–Lam–Evans Coupling Reaction[96]

1.2.4.1. With SF_5-Substituted Arylboronic Acid

Evaluation of the available anilines and aryl ethers featuring a SF_5 group shows limitations. 3- and 4-SF_5-anilines are mainly obtained by reduction of SF_5-substituted nitrobenzenes. However, there is only one reported example of 3-SF_5-aniline incorporating an additional substituent in *meta*-position.[49b] Similarly, only the Beier procedure involving nucleophilic substitution of the nitro group is known to give access to SF_5-aryl ethers.[74] As previously mentioned, this method afforded satisfying results with 4-SF_5-nitrobenzene, but the substrate scope and yields with 3-SF_5-nitrobenzene are largely reduced. Therefore, in the light of the omnipresence of anilines and aryl ethers in pharmaceutical, agricultural, and material science research, we considered the possibility to perform the Chan–Lam–Evans cross-coupling reaction with the pentafluorosulfanyl-substituted potassium aryltrifluoroborates. This copper-mediated reaction revolutionized the formation of aryl carbon–heteroatom bonds.[97] Initial reports of this reaction were independently published by Chan,[98] Evans[99] and Lam[100] in 1998 and described the *N*- and *O*-arylation with aryl boronic acids. This transformation overcomes disavantages associated with Ullmann and Goldberg reactions as well as the palladium-catalyzed Buchwald–Hartwig coupling reaction such as the need for high temperatures or strong bases.

Like for the Suzuki–Miyaura cross-coupling reaction, our initial investigations for the Chan–Lam–Evans reaction were achieved with the SF_5-substituted aryl boronic acid **183**. We first attempted the synthesis of diarylether using conditions reported by Evans (Scheme 1.2.12).



183 **225**

Scheme 1.2.12. Chan–Lam–Evans reaction of SF_5-$ArB(OH)_2$ with 4-methoxyphenol.

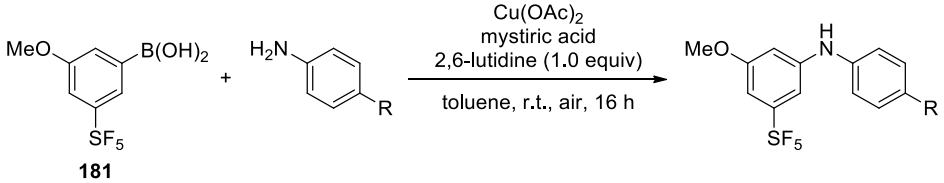
Arylation of 4-methoxyphenol with methoxy derivative SF_5-$ArB(OH)_2$ **183** was possible in presence of stoichiometric amount of copper(II) acetate and triethylamine as a base, to afford SF_5-substituted diaryl ether **225** in 62% yield. Addition of powdered molecular sieves was

[96] The results of the study presented in this section were published: A. Joliton, E. M. Carreira, *Synlett* **2015**, *26*, 737–740.
[97] For reviews about copper-mediated aryl C–heteroatom formation, see: (a) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449: (b) J. X. Qiao, P. Y. S. Lam in *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials (Volume 1 and 2), Second Edition* (Ed: D. G. Hall) Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2011, pp 315–361.
[98] D. M. T. Chan, K. L. Monaco, R. P. Wang, M. P. Winters, *Tetrahedron Lett.* **1998**, *39*, 2933–2936.
[99] D. A. Evans, J. L. Katz, T. R. West, *Tetrahedron Lett.* **1998**, *39*, 2937–2940.
[100] P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan, A. Combs, *Tetrahedron Lett.* **1998**, *39*, 2941–2944.

important to avoid the conversion of **183** into the corresponding phenol which could react itself with the boronic acid **183** remaining in the reaction mixture.

We also briefly examined the possibility to arylate amines with the pentafluorosulfanyl-substituted boron reagent **183**. We first applied the exact reaction conditions of the catalytic version described by Buchwald (Table 1.2.3, Entry 1), namely copper(II) acetate (10 mol%), in presence of mystiric acid (0.2 equiv) and 2,6-lutidine (1.0 equiv).[101] Surprisingly, the corresponding diarylamine **226** was obtained in only 18% yield. In a second experiment, we used the boronic acid as limiting reagent, in order to avoid waste of the more precious SF_5-containing material (Entry 2). The amounts of catalyst (30 mol%), base (2.0 equiv) and acid additive (0.6 equiv) were also increased, which resulted in a yield improvement by almost 30%. Exchanging the *para*-substituent of the aniline to make it more electron-rich did not have a beneficial effect (Entry 3). Finally, employing stoichiometric amount of copper-catalyst slightly increased the yield of the reaction to a maximum of 52% (Entry 4).

Table 1.2.3. Chan–Lam–Evans reaction of SF_5-ArB$(OH)_2$ with anilines.

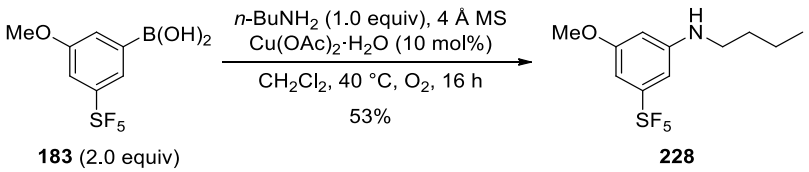


Entry	R	Product	176	Aniline	$Cu(OAc)_2$	Mistyric acid	Yield[a]
1	Cl	**226**	1.5 equiv	1.0 equiv	0.1 equiv	0.2 equiv	18%
2	Cl	**226**	1.0 equiv	2.0 equiv	0.3 equiv	0.6 equiv	46%
3	OMe	**227**	1.0 equiv	2.0 equiv	0.3 equiv	0.6 equiv	37%
4	Cl	**226**	1.0 equiv	2.0 equiv	1.0 equiv	2.0 equiv	52%

a) Isolated yield.

One example of Chan–Lam–Evans cross-coupling with an aliphatic amine was also attempted. Initially, arylation of primary and secondary amines with arylboronic acids were problematic, however Batey disclosed efficient conditions for this transformation in 2003.[102] We subjected **183** to this procedure with *n*-butylamine, using catalytic copper(II) acetate and molecular sieves in dichloromethane at 40 °C under an atmosphere of oxygen. The corresponding aniline **228** was obtained in 53 % yield.

[101] J. C. Antilla, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 2077–2079.
[102] T. D. Quach, R. A. Batey, *Org. Lett.* **2003**, *5*, 4397–4400.



183 (2.0 equiv) **228**

Scheme 1.2.13. Chan–Lam–Evans reaction of SF_5-$ArB(OH)_2$ with aliphatic amine.

In the same way than for the Suzuki–Miyaura cross-coupling reaction, the rest of the study towards the preparation of novel SF_5-anilines and SF_5-aryl ethers was achieved from the SF_5-substituted potassium aryltrifluoroborates, since they were easier to access than their boronic acid couterparts.

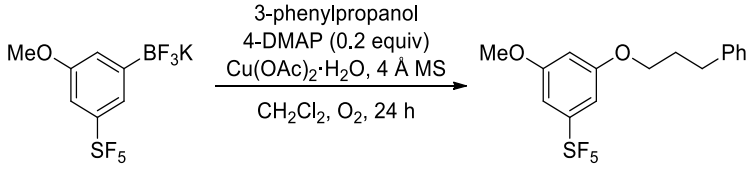
1.2.4.2. With SF_5-Substituted Potassium Aryltrifluoroborates

Since the discovery of the Chan–Lam–Evans cross-coupling reaction, important advances have subsequently been made, resulting in an enlargement of the scope. In this respect, Batey disclosed the synthesis of aryl ethers[103] and anilines[102] from potassium aryltrifluoroborates.

Slight optimization of the method was necessary to obtain SF_5-substituted aryl ethers in satisfactory yields (Table 1.2.4). We first attempted to use the exact same conditions than Batey (10 mol% of $Cu(OAc)_2·H_2O$, 0.2 equivalents of 4-DMAP, 4 Å MS in CH_2Cl_2 at room temperature under oxygen atmosphere), with the exception of the inversion of stoichiometry between the alcohol (3-phenylpropanol) and the $ArBF_3K$ reagent (**196**), in order to set the SF_5-containing material as the limiting reagent. Unfortunately, only traces of aryl ether product were formed, and most of the SF_5-$ArBF_3K$ **196** was recovered (entry 1). Because of the low solubility of **196** in CH_2Cl_2, we tried without success to add a phase transfer agent (Entries 2-3). We then found that the desired aryl ether could be obtained in 45% yield using stoichiometric copper(II) acetate (Entry 4). Since formation of tentatively assigned homocoupling product of **196** was observed, we used an excess of boron reagent, but this had no influence on the yield (Entry 5). We eventually found that the reaction temperature was a crucial factor. Thus, the coupling realized at 60 °C in DCE afforded the desired aryl ether **229** in a satisfactory yield of 77% (Entry 6).

[103] T. D. Quach, R. A. Batey, *Org. Lett.* **2003**, *5*, 1381–1384.

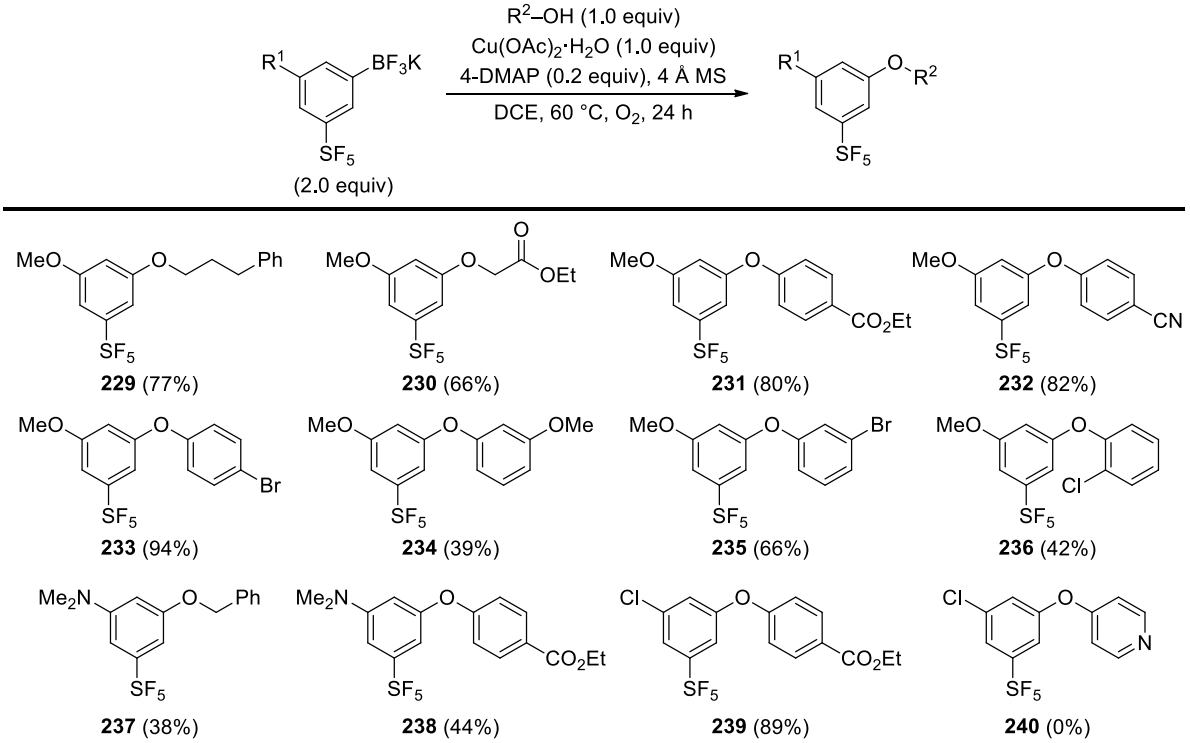
Table 1.2.4. Optimization of Chan–Lam–Evans reaction conditions between SF_5-$ArBF_3K$ **196** and 3-phenylpropanol.



Entry	189	$Ph(CH_2)_3OH$	$Cu(OAc)_2·H_2O$	Temperature	Yield[a]
1	1.0 equiv	2.0 equiv	0.1 equiv	r.t.	<5%
2[b]	1.0 equiv	2.0 equiv	0.1 equiv	r.t.	0%
3[b]	1.0 equiv	2.0 equiv	1.0 equiv	r.t.	0%
4	1.0 equiv	2.0 equiv	1.0 equiv	r.t.	45%
5	2.0 equiv	1.0 equiv	1.0 equiv	r.t.	47%
6[c]	2.0 equiv	1.0 equiv	1.0 equiv	60 °C	77%

a) Isolated yield; b) *n*-Bu_4NBr (1.0 equiv) added; c) DCE used as solvent.

With suitable conditions in hand for the etherification of pentafluorosulfanyl-substituted potassium aryltrifluoroborates, we embarked on the preparation of a small library of diverse SF_5-substituted aryl ethers (Scheme 1.2.14).



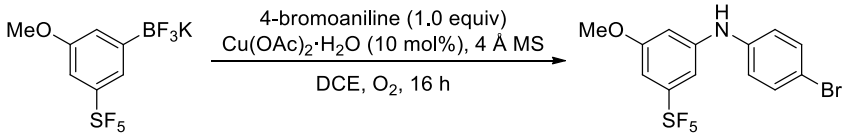
Scheme 1.2.14. Chan–Lam–Evans reaction of SF_5-$ArBF_3K$ with alcohols.

Alkyl alcohols and *para*-substituted phenols reacted smoothly with methoxy derivative of SF_5-$ArBF_3K$ **196** to give the corresponding aryl ethers in good to excellent yield (**229**, **230**, **231**, **232** and **233**). *Ortho*- and *meta*-substituted phenols were also compatible substrates for this

reactions, although the yields obtained were lower (**234**, **235**, and **236**). Modifying the substituent in *meta*-position of the SF_5 group influenced the efficiency of the cross-coupling. Thus, products resulting from coupling with dimethylamine derivative of SF_5-$ArBF_3K$ **202** were isolated in modest yield (**237** and **238**). On the other hand, a substrate with an halogen such as chlorine derivative **199** afforded **239** in excellent yield. Attempts to realize cross-coupling with heterocycles such as hydroxypyridines were unsuccessful, as it afforded complex mixtures and none of the desired products could be isolated.

Having demonstrated the usefulness of SF_5-$ArBF_3K$ for the preparation of unprecedented SF_5-aryl ethers, we then explored the reactivity of these boron reagents towards amines and anilines. As for the reaction with alcohols, the original conditions described by Batey (10 mol% of $Cu(OAc)_2 \cdot H_2O$, no base, 4 Å MS in CH_2Cl_2 at 40 °C under oxygen atmosphere)[102] afforded poor conversion of the starting materials, along with formation of unidentified side products. Thus, we investigated the effects of temperature and addition of base on the Chan–Lam–Evans reaction between 4-bromoaniline and SF_5-$ArBF_3K$ **196** (Table 1.2.5).

Table 1.2.5. Optimization of Chan–Lam–Evans reaction conditions between SF_5-$ArBF_3K$ **196** and 4-bromoaniline.



196 (2.0 equiv) **241**

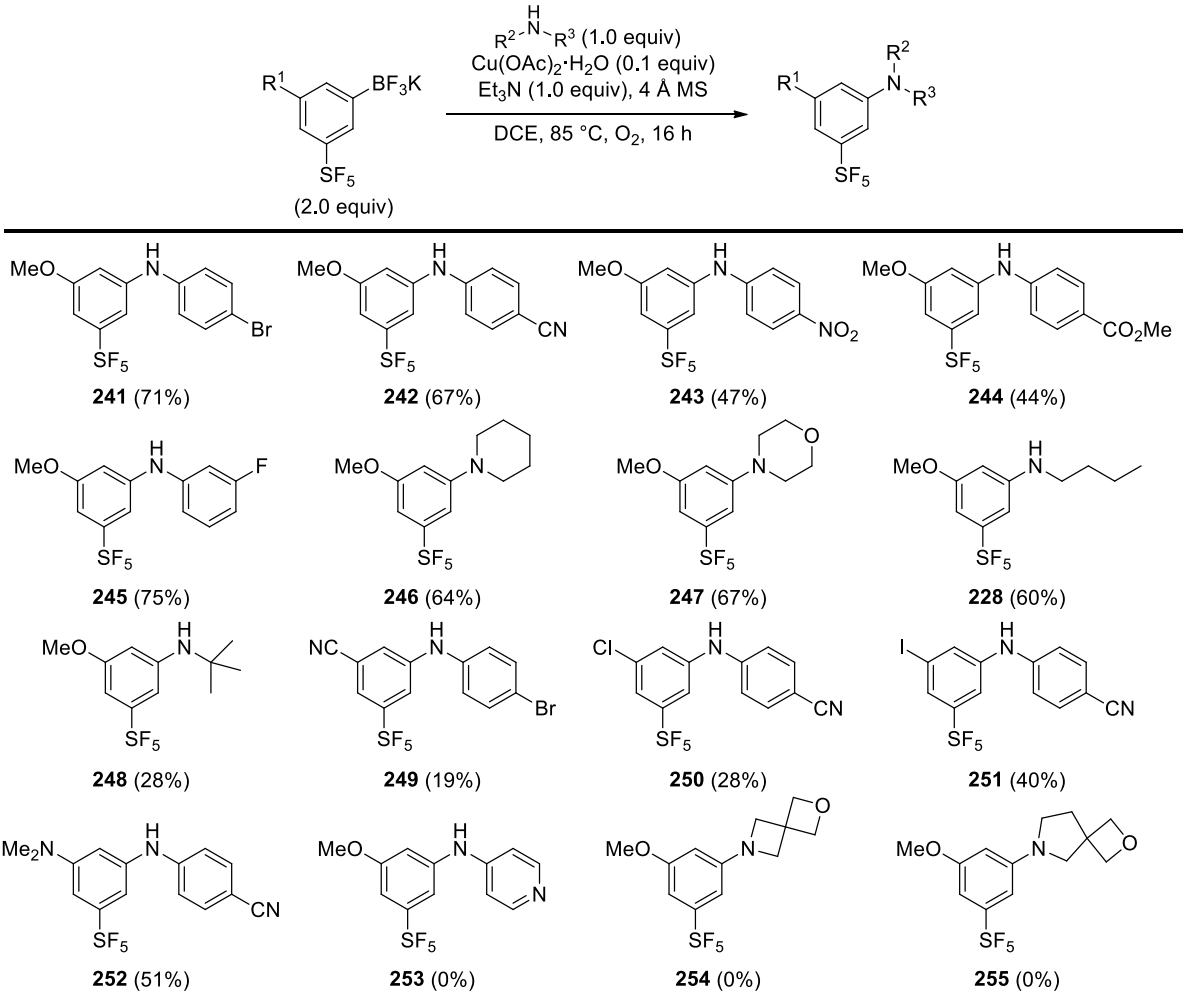
Entry	Base (equiv)	Temperature	Conversion[a]	Yield[b]
1	none	60 °C	73%	53%
2[c]	none	60 °C	58%	n.d.[d]
3	none	85 °C	77%	n.d.[d]
4	4-DMAP (0.2)	60 °C	100%	<25%[e]
5	2,6-lutidine (2.0)	60 °C	0%	n.d.[d]
6	Et_3N (2.0)	60 °C	77%	48%
7	Et_3N (0.2)	85 °C	100%	64%
8	Et_3N (0.5)	85 °C	100%	63%
9	Et_3N (1.0)	85 °C	100%	71%
10	Et_3N (2.0)	85 °C	100%	70%

a) Determined by ^1H NMR analysis of the crude material; b) Isolated yield; c) Reaction conducted with 1.0 equiv of $Cu(OAc)_2 \cdot H_2O$; d) Purification was not conducted; e) Product could not be obtained pure.

Similarly to the preparation of SF_5-aryl ethers, two equivalents of SF_5-$ArBF_3K$ were unfortunately necessary in order to compensate competitive homocoupling. Conducting the reaction with 10 mol% of $Cu(OAc)_2 \cdot H_2O$ at 60 °C resulted in 73% conversion of the aniline,

and only 53% of isolated diarylamine **241** (Table 1.2.5, Entry 1). Using stoichiometric copper had a negative effect on the conversion (Entry 2), and increasing the temperature to 85 °C did not entail a significant benefit (Entry 3). We then attempted to add a base to the reaction mixture, like in the procedure with boronic acid derivatives. 4-DMAP gave a complex mixture, from which the desired product could not be obtained in pure form. The addition of 2,6-lutidine inhibited the cross-coupling reaction. Pleasingly, we found that the combination of adding triethylamine and increasing the temperature to 85 °C improved both conversion and cleanness of the reaction (Entries 7-10). It was finally identified that satisfying conditions were met with one equivalent of triethylamine (Entry 9).

With the thus developed reaction conditions, we undertook the preparation of a collection of novel SF_5-containing anilines (Scheme 1.2.15).



Scheme 1.2.15. Chan–Lam–Evans reaction of SF_5-$ArBF_3K$ with amines.

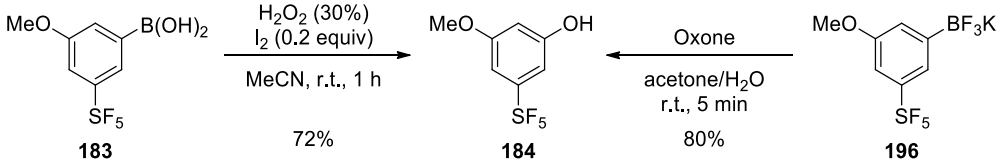
Para-substituted anilines could be converted into the corresponding diarylamines in modest to good yields (**241**, **242**, **243** and **244**). 3-fluoroaniline reacted efficiently with **196** to furnish **245** in 75% yield. Moreover, aliphatic amines were compatible substrates. Thus, cyclic amines

such as piperidine and morpholine underwent cross-coupling in 64% and 67% yield, respectively. The reaction with *n*-butylamine also gave **228** in good yield. However, the sterically hindered *t*-butylamine afforded the corresponding aniline **248** in only 28% yield. Altering the substituent in *meta*-position of the SF_5 had a consequential effect on the efficiency of the reaction. Thus, nitrile, chloro, iodo and dimethylamine derivatives of SF_5-$ArBF_3K$ reacted with anilines in low to modest yield (**249**, **250**, **251** and **252**). Unfortunately, reaction with 4-aminopyridine gave a complex mixture and no desired coupling product could be isolated. Moreover, spirocyclic *N*-heterocycles,[104] promising scaffolds for drug discovery, were unreactive under these reaction conditions.[105]

1.2.5. Other Functionalizations

1.2.5.1. Oxidation

Besides Suzuki–Miyaura and Chan–Lam–Evans cross-coupling reactions, others types of reactions were explored with the pentafluorosulfanylsubstituted aryl boron reagents prepared. It is well known that organoboron compounds can be oxidized to the corresponding alcohols. Thus we applied reported protocols to methoxy derivatives of the boronic acid **183** and the potassium trifluoroborate **196** to convert them into phenol **184** (Scheme 1.2.16).



Scheme 1.2.16. Oxidation of SF_5-aryl boron reagents.

Treatment of **183** with hydrogen peroxide in presence of catalytic iodine in acetonitrile at room temperature afforded **184** in 72% yield.[106] Alternatively, SF_5-$ArBF_3K$ **196** was rapidly oxidized using Oxone®[107] in a mixture of acetone and water at room temperature to obtain phenol **184** in 80% yield.[108] These experiments show the attractiveness of the iridium-catalyzed C–H borylation method for the generation of *meta*-substituted 3-pentafluorosulfanylphenols incorporating *ortho*/*para* directing group, such as a methoxy or halogens.

---

[104] (a) J. Burkhard, E. M. Carreira, *Org. Lett.* **2008**, *10*, 3525–3526; (b) G. Wuitschik, M. Rogers-Evans, A. Buckl, M. Bernasconi, M. Marki, T. Godel, H. Fischer, B. Wagner, I. Parrilla, F. Schuler, J. Schneider, A. Alker, W. B. Schweizer, K. Muller, E. M. Carreira, *Angew. Chem. Int. Ed.* **2008**, *47*, 4512–4515; (c) D. B. Li, M. Rogers-Evans, E. M. Carreira, *Org. Lett.* **2011**, *13*, 6134–6136; (d) D. B. Li, M. Rogers-Evans, E. M. Carreira, *Org. Lett.* **2013**, *15*, 4766–4769; (e) for a review, see: E. M. Carreira, T. C. Fessard, *Chem. Rev.* **2014**, *114*, 8257–8322.

[105] The spirocyclic amines were generously supplied by Spirochem in their oxalate salt form, and treated with 2.0 equiv of triethylamine prior to use.

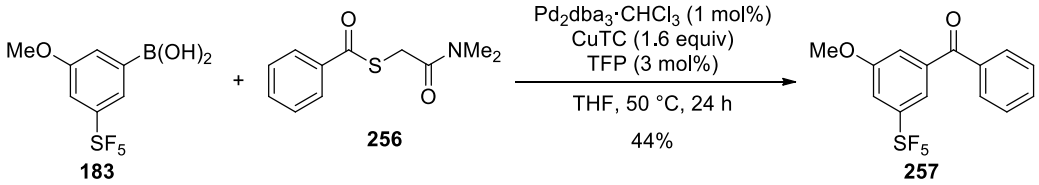
[106] A. Gogoi, U. Bora, *Synlett* **2012**, 1079–1081.

[107] Oxone is a trademark of Dupont and used for the triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$. The active ingredient is potassium peroxymonosulfate ($KHSO_5$).

[108] G. A. Molander, L. N. Cavalcanti, *J. Org. Chem.* **2011**, *76*, 623–630.

1.2.5.2. Liebeskind–Srogl coupling

Preparation of ketones by palladium-catalyzed cross-coupling reaction between arylboronic acids and thioesters has been reported in 2000 by Liebeskind and Srogl.[109] This C–C bond forming process requires the use of stoichiometric copper(I) thiophenecarboxylate (CuTC) as a thiophilic metal cofactor. Applying this method to our SF_5-boron reagent would give a straightforward access to unusual SF_5-containing aryl ketones. Indeed, **183** could be converted into aryl ketone **257** by coupling with thioester **256** using $Pd_2dba_3{\cdot}CHCl_3$/tri(2-furyl)phosphine (TFP) as catalytic system in the presence of Cu(I) thiophene-2-carboxylate (Scheme 1.2.17). Even if a modest yield of 44% was obtained and no further investigation to improve this result was conducted, this example opens a way for opportunities for the preparation of new promising SF_5-containing building blocks.



Scheme 1.2.17. Liebeskind–Srogl reaction of SF_5-$ArB(OH)_2$.

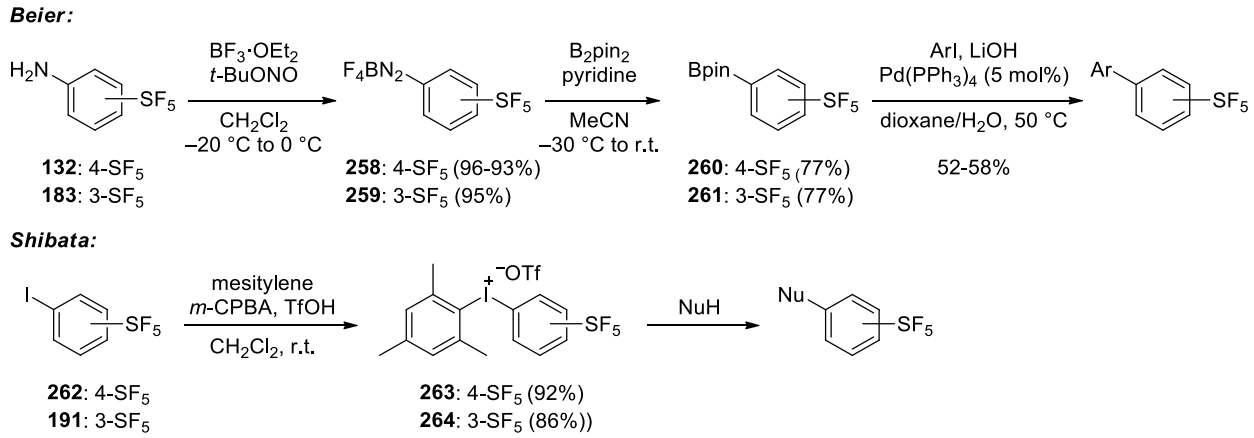
1.2.6. Conclusion

In summary, we have described the preparation of a set of new 3,5-disubstituted aryl boron reagents incorporating a pentafluorosulfanyl group *via* regioselective iridium-catalyzed C–H borylation. The choice to convert the arylboronic esters in one-pot into their corresponding potassium trifluoroborates was justified by the simplicity of their isolation as well as their stability. The versatility of these reagents was illustrated with examples of applications in various types of reactions. Thus, their compatibility in the Suzuki–Miyaura cross-coupling reaction was demonstrated with various aryl and heteroaryl halides, giving access to unprecedented SF_5-substituted biaryl compounds. Moreover, Chan–Lam–Evans cross-coupling reaction was also investigated with alkyl alcohols, phenols, alkyl amines and anilines. The resulting uncommon 3-SF_5-aryl ethers were generally obtained in good yields, whereas the reaction affording SF_5-anilines seemed to be more limited. Oxidation of these substrates was also efficiently achieved to prepare 3-SF_5-substituted phenol, and one example of implementation of a pentafluorosulfanyl-substituted arylboronic acid in the Liebeskind–Srogl cross-coupling was realized to prepare a 3-SF_5-aryl ketone. Obviously, the usefulness of these

[109] (a) L. S. Liebeskind, J. Srogl, *J. Am. Chem. Soc.* **2000**, *122*, 11260–11261; (b) For a review about Liebeskind–Srogl cross-coupling reaction, see: H. Prokopcova, C. O. Kappe, *Angew. Chem. Int. Ed.* **2009**, *48*, 2276–2286.

reagents is not limited to the reactions presented in this section and other transformations involving boron derivatives could be employed. Their simple preparation and promising versatility open new opportunities to access novel 1,3,5-trisubstituted SF_5-aryl compounds, potential important building blocks for drug discovery and agrochemicals.

Following the publication of our work described in this section, Beier and co-workers reported the preparation of 3- and 4-SF_5-arylpinacolborates *via* pyridine-promoted dediazotation of SF_5-aryldiazonium tetrafluoroborates (Scheme 1.2.18, top).[110] The pentafluorosulfanyl-substituted aryl boron derivatives **260** and **261** were obtained in good yield, however their performance in Suzuki–Miyaura cross-coupling reaction gave *lower* yields, and no example of trisubstituted SF_5-arylpinacolborate was described. Another example of versatile SF_5-aryl building blocks was also disclosed by Shibata and co-workers with the synthesis of 3- and 4-SF_5-arylaryliodonium as well as 3,5-bis-SF_5-arylaryliodonium salts (Scheme 1.2.18, bottom).[111] These reagents could be subjected to nucleophilic substitutions with C-, O-, N-, and S-nucleophiles in good to excellent yield. Nevertheless, like in the example of Beier, no example of trisubstituted SF_5-aryliodonium salt was depicted.



Scheme 1.2.18. Subsequent developments of versatile SF_5 building blocks.

[110] G. Iakobson, J. Y. Du, A. M. Z. Slawin, P. Beier, *Beilstein J. Org. Chem.* **2015**, *11*, 1494–1502.
[111] K. Matsuzaki, K. Okuyama, E. Tokunaga, N. Saito, M. Shiro, N. Shibata, *Org. Lett.* **2015**, *17*, 3038–3041.

1.3. Preparation of Novel SF_5-Heterocycles and Study of their Physicochemical Properties

1.3.1. Introduction

As previously described in this thesis (cf. Chapter 1.1.2.3), the preparation of heterocycles incorporating the pentafluorosulfanyl group remains a challenging task. Therefore we focused our efforts on the development of new strategies towards the synthesis of unprecedented SF_5-heterocycles. Ultimately, the physicochemical properties of these compounds could be studied in order to evaluate the impact of these building blocks in pharmaceutical and agrochemical industries. We first examined the possibility of direct pentafluorosulfanylation of aryl compounds and would then apply this late-stage functionalization on heteroaryl compounds. As an alternative, we also considered *de novo* syntheses, where the SF_5 group would be introduced into organic compounds at an early stage *via* known radical addition. Synthetic manipulations of these SF_5 compounds, involving investigations of their reactivity, could give access to various novel SF_5 heterocycles.

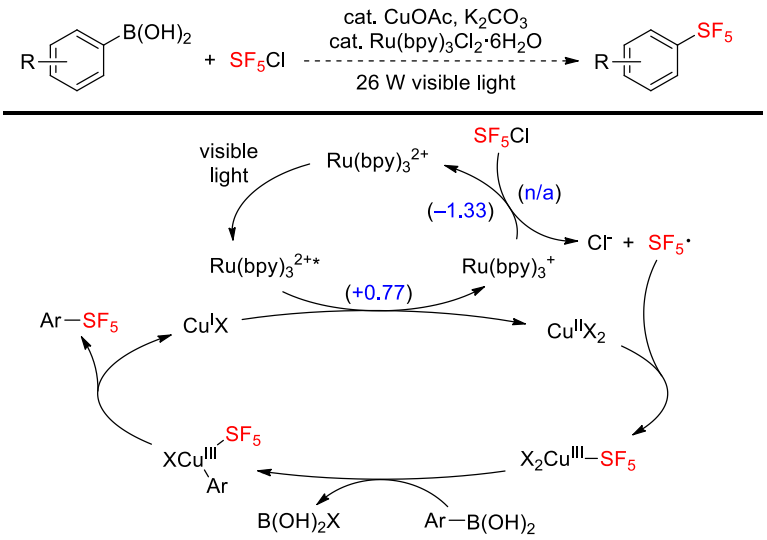
1.3.2. Unsuccessful Strategies

1.3.2.1. Late-Stage Introduction of SF_5

Direct methods for trifluoromethylation are nowadays common and allow access to a multitude of CF_3-containing building blocks, including CF_3 heterocycles.[5] The equivalent strategy for the introduction of the SF_5 group is still unknown and would be ideal for rapid production of various SF_5-aryl and SF_5-heteroaryl compounds. Importantly, it is known that the SF_5Cl reagent is prone to generate SF_5 radicals. Therefore, we considered that conditions for radical addition of the trifluoromethyl group could be promising for direct pentafluorosulfanylation. Recent important developments have been achieved in radical trifluoromethylation reactions.[112] In particular, the Cu-catalyzed/Ru-photocatalyzed trifluoromethylation of arylboronic acids reported by Sanford appeared very attractive.[112d] This reaction is performed by formation of the trifluoromethyl radical from CF_3I in DMF at 60 °C. Importantly, heterocycles such as pyridines, furans and thiophenes were suitable substrates for this method. We speculated that SF_5Cl gas could behave in a similar way to CF_3I and generate a

[112] (a) For a review about radical trifluoromethylation methods, see: A. Studer, *Angew. Chem. Int. Ed.* **2012**, *51*, 8950–8958; For recent examples of radical trifluoromethylation of arenes and heteroarenes, see: (b) Y. N. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond, P. S. Baran, *Proc. Natl. Acad. Sci.* **2011**, *108*, 14411–14415; (c) D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224–228; (d) Y. D. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2012**, *134*, 9034–9037; (e) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95–99; (f) Y. D. Ye, S. A. Künzi, M. S. Sanford, *Org. Lett.* **2012**, *14*, 4979–4981; (g) J. J. Dai, C. Fang, B. Xiao, J. Yi, J. Xu, Z. J. Liu, X. Lu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 8436–8439; (h) J. Xie, X. G. Yuan, A. Abdukader, C. J. Zhu, J. Ma, *Org. Lett.* **2014**, *16*, 1768–1771; (i) G. F. Shi, C. D. Shao, S. L. Pan, J. X. Yu, Y. H. Zhang, *Org. Lett.* **2015**, *17*, 38–41; (j) K. Zhang, X. H. Xu, F. L. Qing, *J. Org. Chem.* **2015**, *80*, 7658–7665.

SF_5 radical that could participate in a comparable catalytic system as proposed by Sanford (Scheme 1.3.1).



Scheme 1.3.1. Poosible catalyzed direct pentafluorosulfanylation of aryl boronic acids; redox potential (in blue) are given in volts versus saturated calomel electrode (SCE).

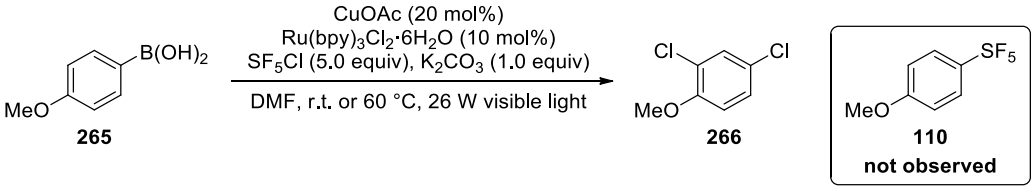
Photoexcitation of $Ru(bpy)_3^{2+}$ would generate $Ru(bpy)_3^{2+*}$ which would undergo one-electron reduction with Cu^I to form $Ru(bpy)_3^{+}$ and Cu^{II}. We hypothesized that $Ru(bpy)_3^{+}$ could reduce SF_5Cl to afford the radical species $SF_5\cdot$ and Cl^-. This event occurs in the case of CF_3, as indicated by the literature reduction potential of $Ru(bpy)_3^{+}$ (–1.33 V vs SCE)[113] and CF_3I (–1.22 V vs SCE).[114] Unfortunately, the reduction potential of SF_5Cl is not reported, rendering a prevision of the feasibility of this step impossible. The $SF_5\cdot$ could then form a $Cu^{III}(SF_5)$ intermediate with Cu^{II}. Then, transmetalation with the arylboronic acid, followed by reductive elimination, would generate the desired SF_5-aryl product.

Although our ultimate goal was the preparation of SF_5-heterocyclic compounds, we began exploring this possibility with 4-methoxyphenylboronic acid (**265**), namely for of two reasons: 1) It is one of the most efficient substrates for trifluoromethylation in the scope investigated by Sanford. 2) Formation of the desired 4-methoxy(pentafluorosulfanyl)benzene (**110**) could be smoothly monitored by GC-MS and NMR analyses, as it is a known compound and a reference could be prepared using Beier nucleophilic substitution on 4-(pentafluorosulfanyl)nitrobenzene with sodium methoxide (cf. Chapter 1.2.1).[74]

Unfortunately, direct introduction of SF_5 group using photocatalysis and transition-metal catalysis proved unsuccessful (Scheme 1.3.2). Treating arylboronic acid **265** with

[113] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363.
[114] S. M. Bonesi, R. Erra-Balsells, *J. Chem. Soc., Perkin Trans. 2* **2000**, 1583–1595.

5.0 equivalents of SF_5Cl in presence of CuOAc (20 mol%), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (10 mol%) and K_2CO_3 (1.0 equiv) in DMF at 60 °C under visible light (26 W compact fluorescent light bulb) for 8 h only resulted in complete formation of dichloromethoxybenzene **266** (as confirmed by GC-MS and ^1H NMR analysis of the crude material). Interestingly, when an aliquot of the reaction mixture was analyzed by ^{19}F NMR analysis, no characteristic signal corresponding to the SF_5 group was visible. Instead, one singlet with a chemical shift of 75 ppm (in $CDCl_3$) was observed, attributed to sulfur tetrafluoride (SF_4).[115] Disappearance of this signal upon concentration of the reaction mixture under *vacuum* strengthened the assumption that SF_4 was formed.

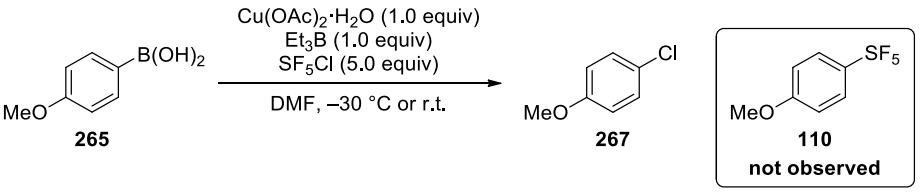


Scheme 1.3.2. Attempted direct pentafluorosulfanylation by photocatalysis and copper catalysis.

We actually identified SF_5Cl reagent to be unstable in DMF and undergoing slow decomposition to produce SF_4, and that this process is faster at elevated temperatures (*vide infra*). Consequently, we attempted to achieve the reaction at room temperature. Nevertheless no change occurred in the outcome of the reaction and only formation of dichloromethoxybenzene **266** and SF_4 was observed.

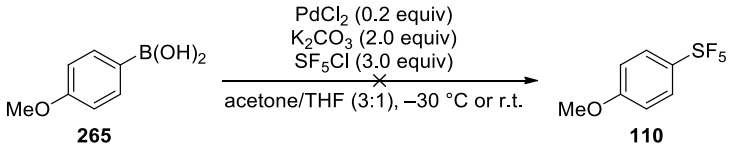
Since it was not clear if the ruthenium photocatalyst even promoted the formation of the radical $SF_5\cdot$, we envisaged to trigger this process with a different method. Because triethylborane is known to initiate homolytic cleavage of SF_5Cl for its addition to alkenes, we considered to use this reagent for the direct introduction of the SF_5 group into aryl compounds (Scheme 1.3.3).[42] When **265** was treated with SF_5Cl in presence of stoichiometric amounts of Et_3B and $Cu(OAc)_2 \cdot H_2O$ in DMF at room temperature or –30 °C, complete conversion of the boronic acid to 4-chloroanisole (**257**) was observed. Similarly to the attempt with the photocatalyst, sulfur tetrafluoride was formed during the course of the reaction. ^{19}F NMR analysis of aliquots of the reaction after 1 h at room temperature and at –30 °C indicated that the ratios of SF_5Cl:SF_4 were 1:10.4 and 1:1.1, respectively. Similar outcomes were observed when the reaction was carried out in CH_2Cl_2, whereas only protodeborylation occurred in THF.

[115] The ^{19}F NMR spectrum of SF_4 at room temperature consists of one singlet, due to rapid interconversion of axial and equatorial fluorines, two triplets can be observed at –60 °C; J. Bacon, R. J. Gillespie, J. W. Quail, *Can. J. Chem.* **1963**, *41*, 1016–1018.



Scheme 1.3.3. Attempted direct pentafluorosulfanylation by activation with Et_3B.

We next explored the possibility of a palladium-catalyzed pentafluorosulfanylation, speculating that oxidative addition of SF_5Cl to the transition-metal could occur, because such reactivity has been reported with sulfonyl chloride for the synthesis of sulfonyl compounds.[116] Inspired by the sulfonylation method of Bandgar, which is performed at room temperature,[116a] we treated **265** with SF_5Cl in presence of $PdCl_2$ (20 mol%) and K_2CO_3 (Scheme 1.3.4). Unfortunately, no pentafluorosulfanylation took place, only rapid formation of SF_4 was detected by ^{19}F NMR analysis, and boronic acid **265** was recovered.



Scheme 1.3.4. Attempted direct pentafluorosulfanylation *via* oxidative addition of SF_5Cl to transition metal.

During these studies for direct pentafluorosulfanylation, stock solutions of SF_5Cl in DMF, THF, and CH_2Cl_2 were prepared by bubbling the gas through the different solvents for a few seconds. This facilitated the handling of the SF_5Cl and gave the possibility to achieve multiple reactions with accurate measuring of the reagent amount used. The concentration of these solutions was calculated based on the mass of the SF_5Cl added.[117] The solutions were stored in Schlenk flask at –78 °C. However, as mentioned earlier, the SF_5Cl slowly decomposed in these solvents to generate SF_4 as indicated by ^{19}F NMR analysis, probably with formation of FCl not detected in the range of measurement.[118] The NMR spectra in Figure 1.3.1 show the evolution of SF_5Cl solutions in DMF at –78 °C and 0 °C. While the consumption of SF_5Cl at –78 °C seems relatively slow,[119] its disproportionation at 0 °C is much faster, with around 50% of conversion into SF_4 after 1 h. The decomposition patterns in THF and CH_2Cl_2 were similar.

[116] (a) B. P. Bandgar, S. V. Bettigeri, J. Phopase, *Org. Lett.* **2004**, *6*, 2105–2108; (b) X. D. Zhao, E. Dimitrijevic, V. M. Dong, *J. Am. Chem. Soc.* **2009**, *131*, 3466–3467; (c) J. R. DeBergh, N. Niljianskul, S. L. Buchwald, *J. Am. Chem. Soc.* **2013**, *135*, 10638–10641; (d) Y. H. Xu, M. Wang, P. Lu, T. P. Loh, *Tetrahedron* **2013**, *69*, 4403–4407.

[117] The concentration of the prepared solutions usually varied between 0.45 and 0.60 M; the additional volume of the SF_5Cl introduced was neglected in the calculation of the concentration.

[118] FCl has a chemical shift of –450 ppm, in the present case the range of measurement was between –200 and 140 ppm.

[119] The times of preparation of the sample and transport to the NMR apparatus have to be taken into account, hence the amount of SF_4 in the solution is probably lower than observed in the ^{19}F NMR spectra.

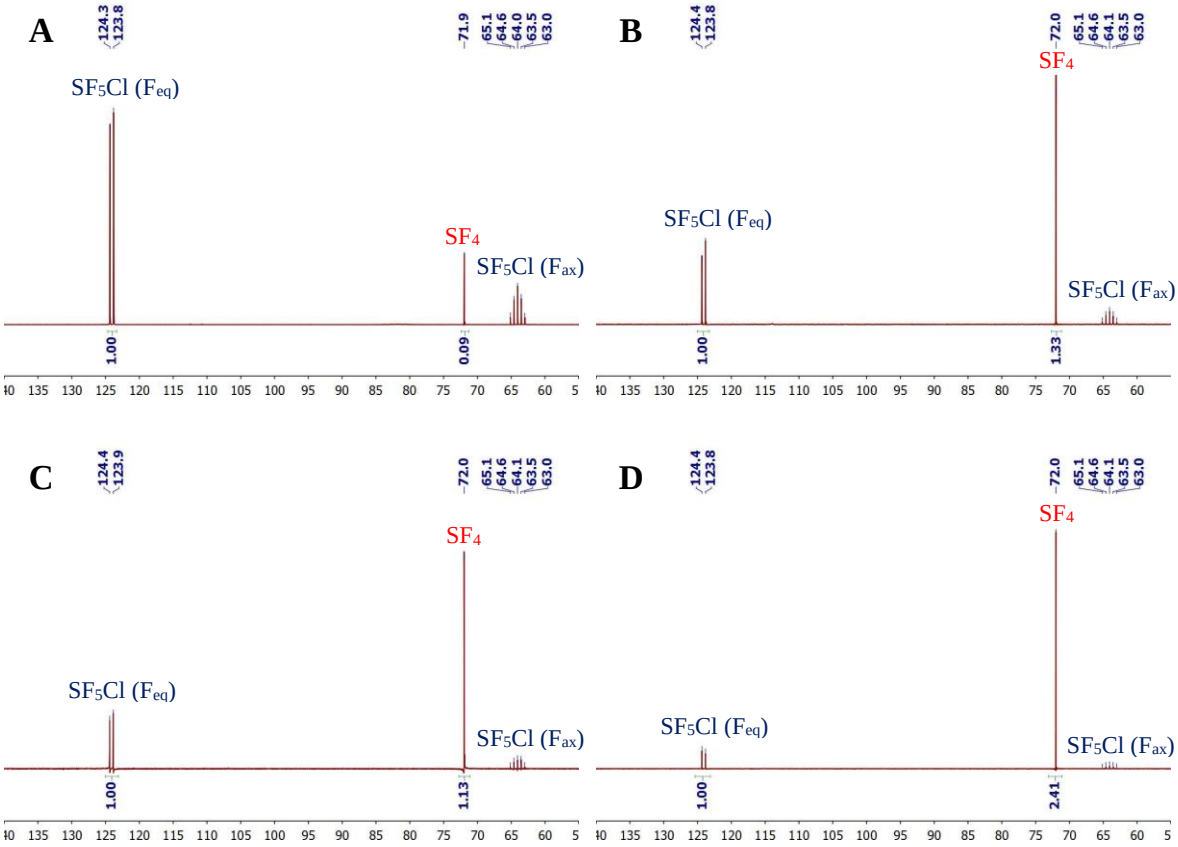
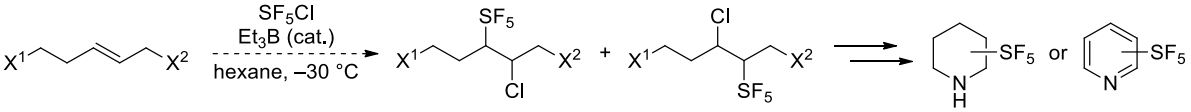


Figure 1.3.1. Evolution of SF_5Cl in DMF; **A**: after 12 h at –78 °C; **B**: after 96 h at –78 °C; **C**: after 1 h at 0 °C, **D**: after 3 h at 0 °C; chemical shifts in ppm.

The issue regarding the stability of the SF_5Cl in solution associated with its low availability[120] convinced us to explore other strategies, relying on the known reactivity of the gas towards alkenes and alkynes.

1.3.2.2. SF_5Cl Addition to Internal Olefins

Parallel to the investigation of direct pentafluorosulfanylation, *de novo* synthesis of heterocycles *via* radical addition of SF_5Cl to olefins incorporated into a chain bearing two functionalizable extremities was also explored (Scheme 1.3.5).



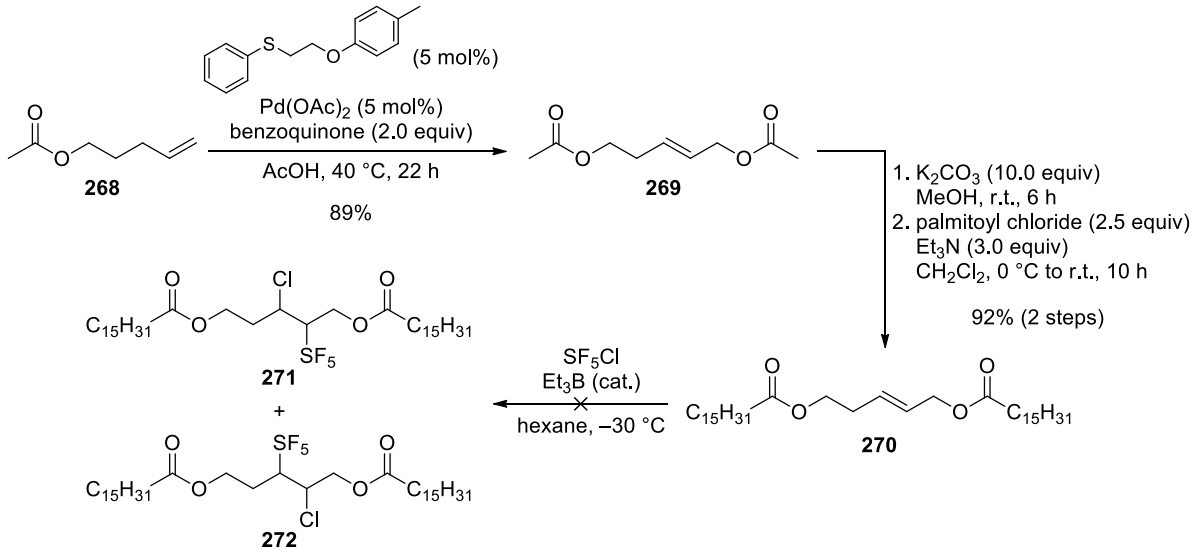
Scheme 1.3.5. Synthetic plan to prepare six-membered *N*-heterocycles *via* SF_5Cl addition to internal olefins.

Thus, a five-carbon chain could give access to six-membered *N*-heterocycles such as pyridines or piperidines, after synthetic manipulation. In addition to the feasibility of the SF_5Cl

[120] ABCR had only limited amount of SF_5Cl gas in stock, therefore we could not afford to waste large quantities of the reagent.

addition, another question arising from this approach is the regioselectivity of the reaction, since two different regioisomers could be obtained. These two regioisomers would then afford 3- and 4-SF_5-*N*-heterocycles.

The choice of the internal olefin was dictated by required functional groups on the two extremities of the carbon chain. Thus, the known (*E*)-diester **269** was prepared by palladium-catalyzed allylic oxidation of 4-penten-1-yl acetate (**268**) using a thioether ligand (Scheme 1.3.6).[121] Radical addition of SF_5Cl to **269** was impossible because of the insolubility of the alkene in hexane, the solvent required for this reaction. Therefore, the two acetates were hydrolyzed and then replaced by long aliphatic chains in order to improve the solubility of the substrate. Diester **270** was then subjected to SF_5Cl addition using Dolbier's procedure.[42] Surprisingly, no desired SF_5Cl addition product was formed, and only olefin **270** was recovered.



Scheme 1.3.6. Attempted SF_5Cl addition to internal olefin **270**.

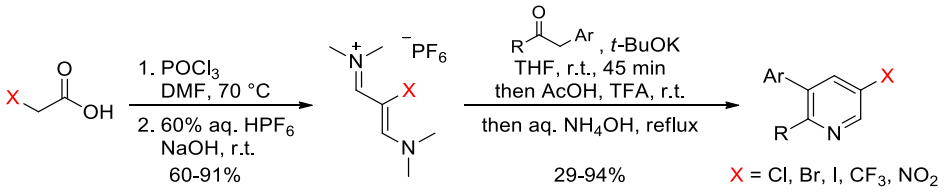
With this result, the strategy involving the use of internal olefins as precursors of SF_5-heterocycles did not appear realistic. Thus, assuming that the success of the SF_5Cl radical addition to olefin is substrate-dependent, we decided to start our *de novo* synthesis of SF_5-containing heterocycles from an alkene which is known to undergo such an addition.

1.3.2.3. Vinamidinium Hexafluorophosphate Salts for the Preparation of SF_5-Pyridines

During the course of the synthesis of COX-2 specific inhibitors, researchers at Merck disclosed the efficient preparation of substituted pyridines by annulation of ketones and vinamidinium hexafluorophosphate salts bearing electron-withdrawing groups at the *β*-position

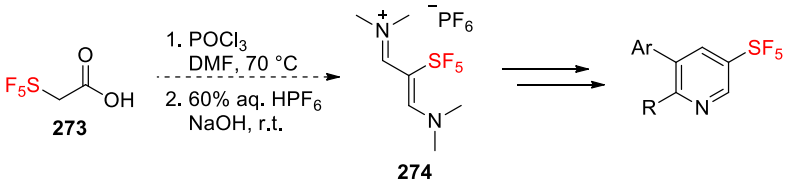
[121] W. H. Henderson, C. T. Check, N. Proust, J. P. Stambuli, *Org. Lett.* **2010**, *12*, 824–827.

(Scheme 1.3.7).[122] In a one-pot procedure, the ketone enolate was reacted with the vinamidinium salt, and after quenching of the adduct with a mixture of acetic acid and TFA, ring closure of the pyridine ring was performed upon heating under reflux in presence of aqueous ammonium hydroxide. The electron-withdrawing substituents include halogens, trifluoromethyl and nitro. Considering these functional groups, we suspected that a SF_5 group could also be compatible under these reaction conditions, giving the opportunity to access various 3-SF_5-substituted pyridines.



Scheme 1.3.7. Synthesis of 3-substituted pyridines by annulation of ketones with vinamidinium hexafluorophosphates salts.

The substituted vinamidinium salts were prepared by treatment of *α*-substituted acetic acid with $POCl_3$ in DMF at 70°C, followed by exchange of the chloride counterion with a hexafluorophosphate ion.[123] Importantly, the use of hexafluorophosphate as the counterion was primordial for the stability of the salt towards hydrolysis. This strategy seemed very attractive because of the compatibility with halogens, trifluoromethyl and nitro groups. Consequently, we were interested in submitting *α*-SF_5-substituted acetic acid **273** to this two-step sequence in order to obtain a vinamidinium hexafluorophosphate salt with a pentafluorosulfanyl group in the *β*-position, which could be itself converted into 3-SF_5-substituted pyridines (Scheme 1.3.8).



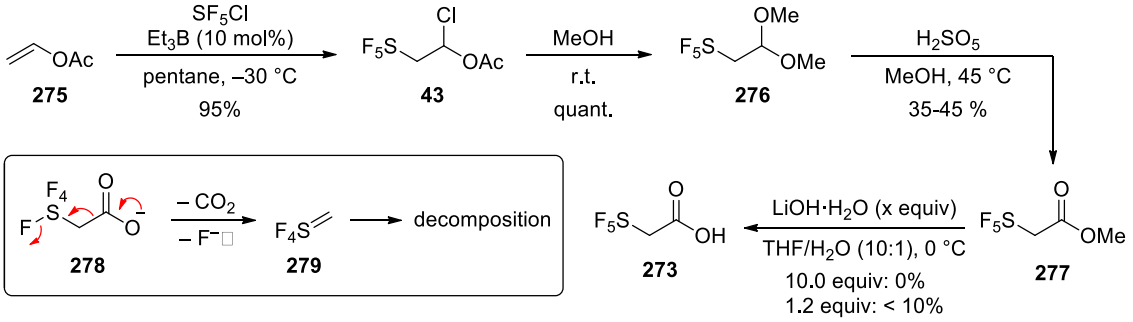
Scheme 1.3.8. Plan to prepare 3-SF_5-pyridines *via* formation of vinamidinium salt.

In the course of the preparations of methyl sulfur pentafluoride and methylene sulfur tetrafluoride, Kleemann and Seppelt reported the synthesis of 2-(pentafluorosulfanyl)acetic acid (**263**) by addition of SF_5Cl to ketene, followed by hydrolysis of the resulting *α*-SF_5 acetyl

[122] (a) J. F. Marcoux, E. G. Corley, K. Rossen, P. Pye, J. Wu, M. A. Robbins, I. W. Davies, R. D. Larsen, P. J. Reider, *Org. Lett.* **2000**, *2*, 2339–2341; (b) J. F. Marcoux, F. A. Marcotte, J. Wu, P. G. Dormer, I. W. Davies, D. Hughes, P. J. Reider, *J. Org. Chem.* **2001**, *66*, 4194–4199.
[123] I. W. Davies, J. F. Marcoux, J. Wu, M. Palucki, E. G. Corley, M. A. Robbins, N. Tsou, R. G. Ball, P. Dormer, R. D. Larsen, P. J. Reider, *J. Org. Chem.* **2000**, *65*, 4571–4574.

chloride.[124] However, their SF_5Cl addition step required special equipment such as an autoclave and the isolation of the α-SF_5 acetyl chloride was done by distillation, which could be hazardous considering potential unreacted toxic ketene and SF_5Cl gas or subproducts such as SF_4. Therefore, we sought to develop a new synthesis of α-SF_5-substituted acetic acid, which would be more convenient and adapted to a common organic chemistry laboratory.

The preparation of the corresponding methyl ester **277** has been disclosed by Winter and Gard in 1994.[41a] This three-step sequence relies on the SF_5Cl addition to vinyl acetate, followed by treatment with methanol to obtain dimethyl acetal protected α-SF_5 acetaldehyde **276**, which was converted into the corresponding methyl ester by oxidation with *m*-CPBA. Dolbier and co-workers published an improved synthesis of the methyl α-SF_5-acetate, applying the same strategy, but taking advantage of the high-yielding Et_3B mediated SF_5Cl addition, and conducting the oxidation with persulfuric acid (Scheme 1.3.9).[42b] We hypothesized that the carboxylic acid **273** could be conveniently generated by hydrolysis of the corresponding ester.

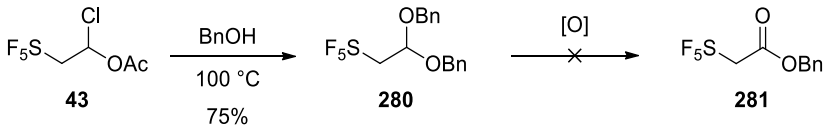


Scheme 1.3.9. Attempted synthesis of acid **263** by hydrolysis of known methyl ester **267**.

Unfortunately, hydrolysis of **277** under standard conditions failed to provide carboxylic acid **273** in synthetically useful yields. Using a large excess of lithium hydroxide resulted in complete decomposition of the material, as indicated by ^{19}F NMR analysis after 1 h, with no SF_5 signal observed. One could assume that after formation of the carboxylate **278**, rapid decarboxylation with concomitant fluoride elimination would generate methylene sulfur tetrafluoride, which would decompose in the basic reaction medium. Reducing the amount of lithium hydroxide to 1.2 equivalents allowed us to observe formation of the acid **273** by NMR, but the longer rate required for full conversion of the ester in that case entailed significant decomposition of the acid. Because of the instability of the carboxylic acid in basic medium, we considered using neutral reaction conditions. Moreover, the preparation of the methyl ester **277** was unreliable on small scale (< 500 mg) because of its high volatility. Therefore, we turned

[124] (a) D. D. Coffman, W. Tullock, *US 3102903A*, **1963**; (b) G. Kleemann, K. Seppelt, *Angew. Chem. Int. Ed.* **1978**, *17*, 516–518; (c) G. Kleemann, K. Seppelt, *Chem. Ber.* **1979**, *112*, 1140–1146; (d) G. Kleemann, K. Seppelt, *Chem. Ber.* **1983**, *116*, 645–658.

ourselves towards the preparation of benzyl ester **281** using the same route as for **277** (Scheme 1.3.10). Subsequent hydrogenolysis was expected to give the desired α-SF_5 acetic acid **273**.



Scheme 1.3.10. Attempted synthesis of benzyl SF_5-acetate.

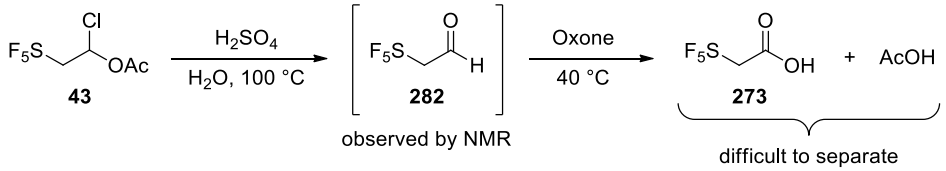
Although Winter and Gard claimed in their report that formation of the dibenzyl acetal was not possible,[41a] we found that treating chloroacetate **43** in benzyl alcohol at 100 °C for 72 h cleanly afforded acetal **280** in 75% yield. Unfortunately, oxidation of **280** using persulfuric acid only led to a complex mixture of products including several SF_5-containing compounds which could not be isolated. Attempts with *m*-CPBA and catalytic sulfuric acid let to a similar outcome, as well as *m*-CPBA in the presence of DBU and $BF_3{\cdot}OEt_2$, which has been described as an efficient procedure for dibenzyl acetal oxidation.[125] It was actually ascertained later during the course of the project, when **281** was efficiently prepared (*vide infra*), that one of the products in these mixtures was the desired benzyl ester, albeit formed in low ratio (< 20% according to ^{19}F NMR analysis of the crude materials). Others attempts involving Oxone® and catalytic sulfuric acid were also vain, with only starting material recovered.

We then attempted to hydrolyze the SF_5Cl addition adduct of vinyl acetate **43** in order to obtain the corresponding α-SF_5 acetaldehyde (**272**), with the aim of oxidizing the latter to obtain **273**. After treatment of **43** with 0.5 equivalents of H_2SO_4 in water at 100 °C for 1 h, and extraction with diethyl ether, we were able to observe partial conversion to the desired aldehyde according to ^1H and ^{19}F NMR analyses (**43**:**282** = 1:1) of the crude material. However, the high volatility of this aldehyde made the isolation tedious. Therefore, direct oxidation of the aldehyde to the corresponding carboxylic acid in the same reaction flask was carried out (Scheme 1.3.11). After complete formation of **282** using 1.0 equivalent of H_2SO_4 in H_2O at 100 °C for 2 h, addition of 2.0 equivalents of Oxone and stirring for 12 h at 40 °C provided clean conversion to the desired carboxylic acid **273**.

Nevertheless, problems encountered at this stage were once more related to the isolation of the α-SF_5 acetic acid **273**. One byproduct in this reaction was acetic acid, which was difficult to remove without concomitant loss of **273**, because of their similar solubility properties and

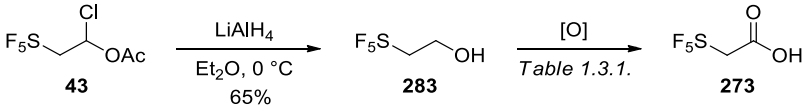
[125] H. Rhee, J. Y. Kim, *Bull. Korean Chem. Soc.* **2000**, *21*, 355–357.

boiling points. Since acetic acid would definitely compete with **273** during the preparation of the vinamidinium salt, we had to find a way to circumvent this problem.



Scheme 1.3.11. Synthesis of α-SF_5-acetic acid **273** by one-pot hydrolysis–oxidation of **43**.

We examined the possibility of using SF_5-substituted ethanol **283** as precursor of the desired carboxylic acid. Eventually, we found that reduction of **43** with $LiAlH_4$ at 0 °C in Et_2O afforded clean conversion to 2-pentafluorosulfanylethanol (**283**) within 15 min (Scheme 1.3.12). The product could be smoothly isolated by distillation (b.p. = 80-90 °C/80 mbar) or by column chromatography in 65% yield. The undesired ethanol generated during the reaction by the reduction of the acetate moiety could also be removed from by careful concentration of the crude mixture on a rotary evaporator without substantial loss of **283**.

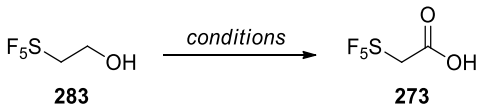


Scheme 1.3.12. Synthesis of α-SF_5-acetic acid **263** by oxidation of SF_5-ethanol **273**.

We next probed the conditions for the oxidation of alcohol **283** into **273** (Table 1.3.1). Jones oxidation resulted in complete consumption of **283**. However concurrent formation of inseparable acetic acid *via* proto-depentafluorosulfanylation discouraged us to use this method (Entry 1). We noticed that the amount of acetic acid formed was related to the concentration of sulfuric acid in the Jones reagent. Oxidation using potassium permanganate and sodium hydroxide caused decomposition of α-SF_5 acetic acid **273** (Entry 2), validating its low stability under basic conditions. Therefore, Corey-Schmidt oxidation,[126] which is performed under essentially neutral conditions, was attempted but proceeded with low conversion of the alcohol (Entry 3). Ultimately, catalytic CrO_3 oxidation in the presence of periodic acid reported by Zhao and co-workers,[127] afforded clean and complete conversion of **283** into **273** (Entry 4). Simple treatment with an aqueous solution of Na_2HPO_4 followed by extraction with Et_2O furnished the carboxylic acid which could be used without any further purification.

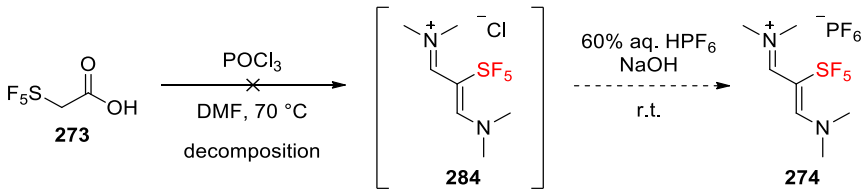
[126] E. J. Corey, G. Schmidt, *Tetrahedron Lett.* **1979**, 399–402.
[127] M. Z. Zhao, J. Li, Z. G. Song, R. Desmond, D. M. Tschaen, E. J. J. Grabowski, P. J. Reider, *Tetrahedron Lett.* **1998**, *39*, 5323–5326.

Table 1.3.1. Oxidation of SF_5-ethanol **273**.



Entry	Conditions	Result
1	CrO_3, H_2SO_4, acetone, 0 °C	concurrent formation of acetic acid
2	$KMnO_4$, NaOH, H_2O, 0 °C	decomposition of **273**
3	PDC, DMF, r.t.	conversion < 10%
4	H_5IO_6, CrO_3 (1 mol%), wet MeCN, 0 °C	clean conversion, quantitative

With an efficient and practical method to prepare α-SF_5-acetic acid **273** in hand, we next turned our attention to the synthesis of the desired SF_5-substituted vinamidinium hexafluorophosphate salt **274**, a potential precursor of 3-SF_5-pyridines. Unfortunately, our efforts to give any product under the described conditions failed (Scheme 1.3.13). The intermediate vinamidinium chloride **284** was not observed and only decomposition of the SF_5 moiety occurred, according to ^{19}F NMR analysis.

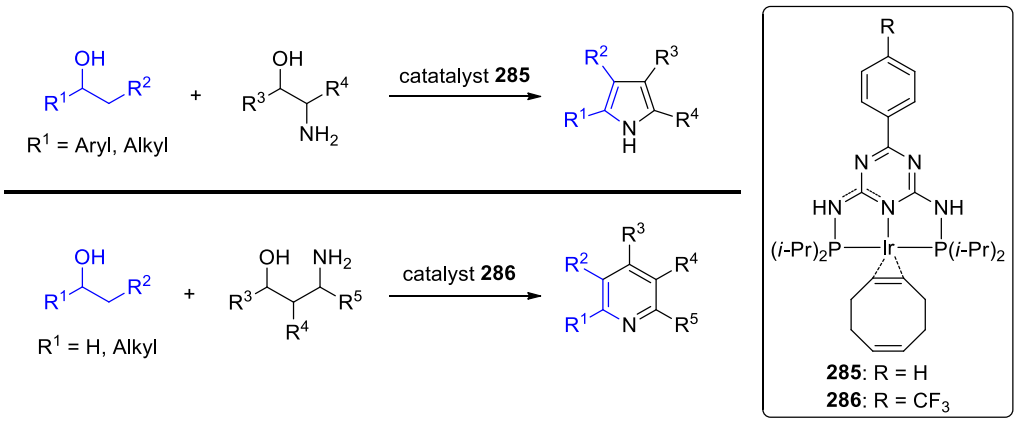


Scheme 1.3.13. Attempted preparation of SF_5-substituted vinamidinium salt from acid **263**.

1.3.2.4. Dehydrogenative Condensation of SF_5-Ethanol with Amino Alcohols

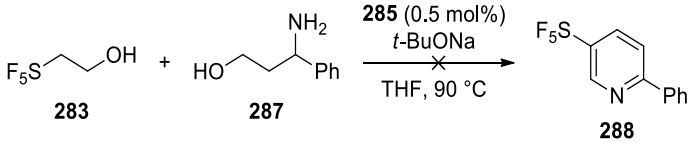
The next strategy to obtain SF_5-susbtituted heterocycles that we explored was based on the successful preparation of SF_5-ethanol **283**. In 2013, Michlik and Kempe reported the synthesis of pyrroles and pyridines by dehydrogenative condensation of aliphatic alcohols and amino alcohols using an iridium-based catalyst (Scheme 1.3.14).[128] Selective Ir-catalyzed oxidation of the alcohol followed by condensation of the resulting carbonyl with the amino alcohol produces an imine intermediate. The remaining hydroxyl group in the imine intermediate is then oxidized by the Ir-catalyst and subsequent ring closure *via* condensation affords the heterocycle. In the case of pyrroles, only examples with secondary alcohols are reported, in order to have selective oxidation.[128a] However, primary alcohols were suitable substrates when reacted with 1,3-amino alcohols to make pyridines.[128b]

[128] (a) S. Michlik, R. Kempe, *Nat. Chem.* **2013**, *5*, 140–144; (b) S. Michlik, R. Kempe, *Angew. Chem. Int. Ed.* **2013**, *52*, 6326–6329.



Scheme 1.3.14. Synthesis of pyrroles and pyridines by Ir-catalyzed dehydrogenative condensation.

We aspired to apply this method to SF_5-ethanol **283** in order to obtain 3-SF_5-pyridines. Therefore, amino alcohol **287** was treated with an excess of **283** (3.0 equiv) in presence of catalyst **285** (0.5 mol%) and sodium *tert*-butoxide in THF at 90 °C (Scheme 1.3.15). We used iridium catalyst **285** instead of **286** because of the higher availability of the benzoguanamine precursor than its trifluoromethyl-substituted analogue. We premised that formation of the desired pyridine **288** could be observed with **285**, and that further optimization could be pursued later on. After 24 h, alcohol **283** did not react and thus pyridine **288** was not observed. Instead, it appeared that **287** underwent self-condensation. Oxidation of the hydroxyl group in **283** was presumably prevented by the electron-withdrawing effect of the SF_5 substituent.



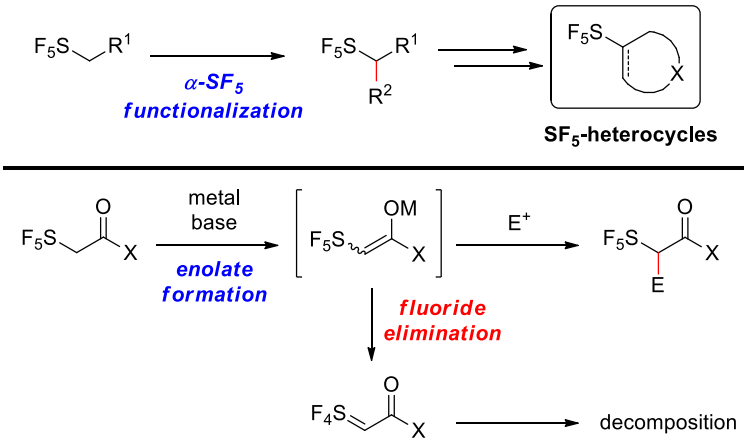
Scheme 1.3.15. Attempted synthesis of SF_5-pyridine by Ir-catalyzed dehydrogenative condensation of **283**.

1.3.3. Synthesis of 3-SF_5-Heterocycles[129]

1.3.3.1. Generation of an *α*-SF_5-Enolate and Aldol Reaction

After the unsuccessful attempts discussed in the previous chapter, we decided to explore alternative routes. In particular, it became obvious that creating a new bond in *α*-position of the SF_5 group was the most critical issue. Solving this problem would afford a non-terminal pentafluorosulfanyl-containing compound, which could be converted into SF_5-heterocycles *via* synthetic manipulation of the two extremities in R^1 and R^2 (Scheme 1.3.16, top).

[129] The results of the study presented in this chapter were published: A. Joliton, J. M. Plancher, E. M. Carreira, *Angew. Chem. Int. Ed.* **2016**, *55*, 2113–2117.



Scheme 1.3.16. α-SF_5 functionalization *via* formation of an α-SF_5-enolate.

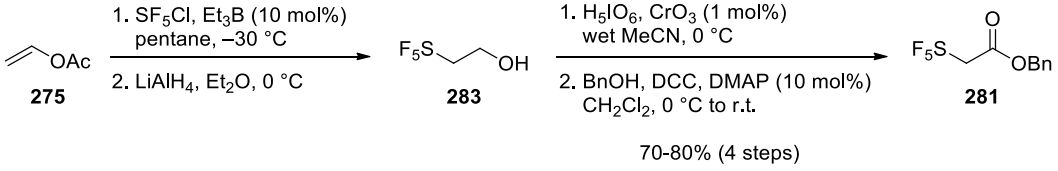
Interestingly, to the best of our knowledge, no report of C–C bond formation on a pentafluorosulfanylmethyl moiety was reported in the literature when we started this project. While we were carrying out the work described in this chapter, one example of functionalization in the α-position of the SF_5 group was published by Thrasher, Haufe and co-workers, in which Ireland–Claisen rearrangements followed by esterification of allyl SF_5-acetates were achieved.[130] However, this report suffers from yields ranging from 3 to 33% and limited substrate scope.

We envisioned that such an α-functionalization of the pentafluorosulfanyl group could be accomplished by generation of an enolate in the α-position, which could react with suitable electrophiles (Scheme 1.3.16, bottom). We anticipated that one obstacle in this strategy could be the inherent instability of the intermediate enolate because of its potential propensity to undergo fluoride elimination leading to an alkylidenesulfur tetrafluoride entity with subsequent decomposition in the reaction medium. Such sulfur alkylidenetetrafluoride species have already been prepared by Seppelt and co-workers, by fluorine elimination following bromine/lithium exchange in α-position of the SF_5.[124b,131] The authors could isolate these compounds despite their rapid decomposition at room temperature,[131a] but further studies on their reactivity was not reported.

In order to explore the possibility of using an α-SF_5-enolate in synthetic sequences for the preparation of novel SF_5-heterocycles, an α-SF_5 substituted carbonyl precursor such as benzyl ester **281** was required. The choice of the benzyl ester was justified on the basis of its assumed low volatility, making it convenient to handle. Fortunately, with a solid route to SF_5-acetic acid **283** in hand, a simple esterification would furnish **281**. Satisfyingly, Steglich conditions with

[130] A. L. Dreier, A. V. Matsnev, J. S. Thrasher, G. Haufe, *J. Fluorine Chem.* **2014**, *167*, 84–90.
[131] (a) B. Potter, K. Seppelt, *Inorg. Chem.* **1982**, *21*, 3147–3150; (b) T. Krugerke, J. Buschmann, G. Kleemann, P. Luger, K. Seppelt, *Angew. Chem. Int. Ed.* **1987**, *26*, 799–801; (c) J. Buschmann, T. Koritsanszky, R. Kuschel, P. Luger, K. Seppelt, *J. Am. Chem. Soc.* **1991**, *113*, 233–238.

benzyl alcohol were found to be effective and afforded the desired ester in 97% yield. With the aim of gaining convenience, the four-step sequence from the vinyl acetate could be improved with merely a single purification by column chromatography at the end affording **281** in high yield on multigram-scale (Scheme 1.3.17).



Scheme 1.3.17. Synthesis of benzyl SF_5-acetate **281**.

After a reliable route to benzyl SF_5-acetate **281** was secured, we next turned our attention to the generation and reaction of the corresponding enolate. Dolbier and co-workers attempted without success to alkylate methyl SF_5-acetate using various bases.[42b] No reaction was observed at low temperature and decomposition of the SF_5 moiety occurred when the reaction was warmed to room temperature. However, they proved the formation of the enolate by deuterium quench experiment using sodium methoxide in CD_3OD. In a similar manner, our attempts to generate lithium or sodium enolates of **281** using strong bases such LDA or NaH, followed by treatment with electrophiles such as methyl iodide or benzaldehyde, failed to give any product.

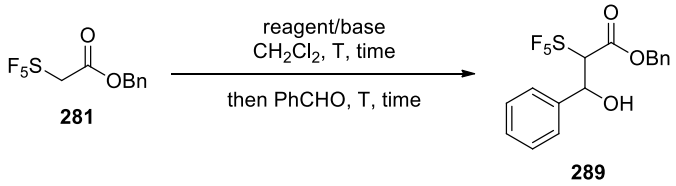
Interestingly, the similar instability of α-CF_3-enolates has been reported in the literature.[132] Nevertheless, several publications have described that titanium and boron enolates of α-CF_3-carbonyl derivatives can be engaged in aldol additions.[133] With the electron-withdrawing properties of the pentafluorosulfanyl increasing the acidity of the α-protons, we suspected that such soft enolization conditions would be compatible with benzyl SF_5-acetate **281**.

We thus set out to examine the possibility to form a boron α-SF_5-enolate and to treat it with benzaldehyde (Table 1.3.2). An initial attempt using dicyclohexylboron triflate with triethylamine did not afford any aldol adduct, and only starting material **281** was recovered (Entry 1). However, exchanging the base to DIPEA proved to be essential for the success of the reaction. Indeed, alcohol **289** was formed with a conversion of 31% (Entry 2). Following this promising result, we examined the effect of the boron ligands. Gratifyingly, the reaction performed with dibutylboron triflate, gave higher conversion of the benzyl SF_5-acetate (Entries 3-5). Control of the influence of the temperature during formation of the

[132] T. Ishihara, M. Kuroboshi, K. Yamaguchi, Y. Okada, *J. Org. Chem.* **1990**, *55*, 3107–3114.
[133] (a) Y. Itoh, M. Yamanaka, K. Mikami, *J. Am. Chem. Soc.* **2004**, *126*, 13174–13175; (b) K. Mikami, Y. Itoh, *Chem. Rec.* **2006**, *6*, 1–11; (c) T. Shimada, M. Yoshioka, T. Konno, T. Ishihara, *Org. Lett.* **2006**, *8*, 1129–1131; (d) X. Franck, B. Seon-Meniel, B. Figadere, *Angew. Chem. Int. Ed.* **2006**, *45*, 5174–5176; (e) P. V. Ramachandran, G. Parthasarathy, P. D. Gagare, *Org. Lett.* **2010**, *12*, 4474–4477; (f) P. V. Ramachandran, P. D. Gagare, G. Parthasarathy, *Tetrahedron Lett.* **2011**, *52*, 6055–6057; (g) P. V. Ramachandran, G. Parthasarathy, P. D. Gagare, *Tetrahedron Lett.* **2011**, *52*, 5359–5362.

enolate (30 min at −78 °C, followed by 30 min at –20 °C) and during aldehyde addition (1 h at –45 °C) allowed us to find efficient reaction conditions, affording the aldol adduct in 84% yield after isolation by column chromatography (Entry 5).

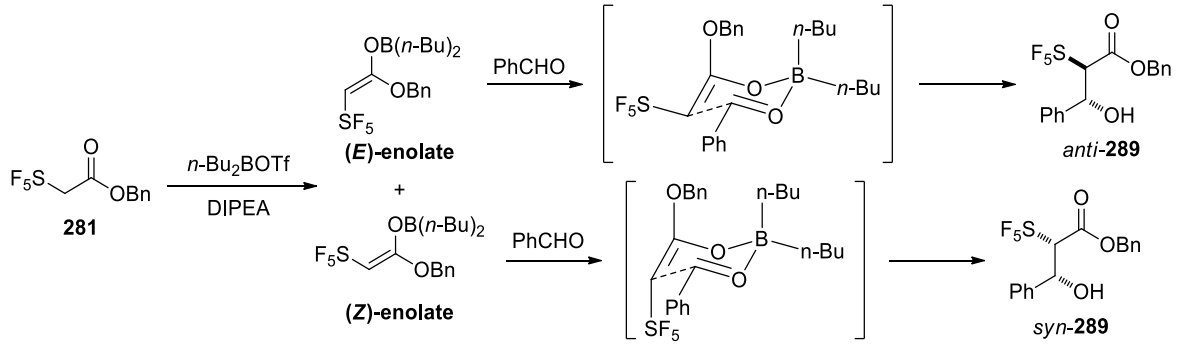
Table 1.3.2. Optimization of the boron-mediated aldol reaction of **281**.



Entry	Reagent (equiv)	Base (equiv)	Conditions enolate formation	Conditions aldol addition	Conv.[a]	*syn*:*anti*[a]
1	*n*-Cy_2BOTf (2.0)	Et_3N (2.0)	–78 °C, 0.5 h then 0 °C, 0.5 h	–78 °C, 1 h then 0 °C, 1 h	0%	-
2	*n*-Cy_2BOTf (2.0)	DIPEA (2.0)	–78 °C, 0.5 h then 0 °C, 0.5 h	–78 °C, 1 h then 0 °C, 1 h	31%	1:3.6
3	*n*-Bu_2BOTf (2.0)	DIPEA (2.0)	–78 °C, 0.5 h then 0 °C, 0.5 h	–78 °C, 1 h then 0 °C, 1 h	90%	1:4.0
4	*n*-Bu_2BOTf (2.0)	DIPEA (2.0)	–78 °C, 1 h	–78 °C, 1 h then 0 °C, 1 h	80%	1:1.2
5	*n*-Bu_2BOTf (2.0)	DIPEA (2.0)	–78 °C, 0.5 h then –20 °C, 0.5 h	–45 °C, 1 h	95% (84)[b]	1:2.7

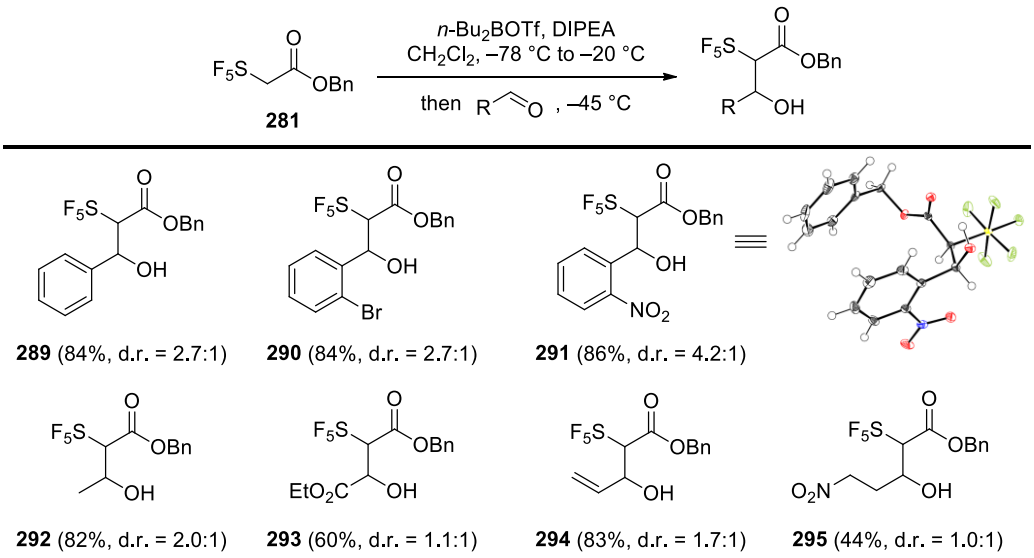
a) Determined by ^{19}F NMR analysis of the crude material; b) Isolated yield.

Although it was not a crucial parameter for us, this aldol reaction was achieved with some level of diastereocontrol. Formation of the *anti*-product as the major diastereoisomer was proven by X-ray crystallographic analysis of a nitro-derivative (*vide infra*). Considering that the reaction proceeds *via* a six-membered transition state with a chair conformation following the Zimmerman–Traxler model, the *anti*-product arises from a (*E*)-enolate, whereas the *syn*-product is generated from a (*Z*)-enolate (Scheme 1.3.18).



Scheme 1.3.18. Formation of (*Z*)- and (*E*)-enolates leading to *syn*- and *anti*-**279**.

With satisfying conditions in hand, we explored the feasibility of this α-SF_5 functionalization of benzyl SF_5-acetate **281** with others aldehydes, in order to prepare aldol adducts which have the potential to be converted into heterocycles (Scheme 1.3.19).



Scheme 1.3.19. Substrate scope of the boron-mediated aldol reaction with α-SF_5-enolate and X-ray crystal structure of *anti*-**281**.

The reaction with nitro- or bromo-substituted benzaldehydes gave the corresponding aldol adducts (**290** and **291**) in high yields. In addition to aromatic aldehydes, aliphatic aldehydes are also suitable substrates. Thus, acetaldehyde, ethyl glyoxalate, acrolein and 3-nitropropanal[134] underwent aldol reaction to give the desired products (**292**, **293**, **294** and **295**, respectively) in 44 to 83% yield. All these aldol adducts could be stored for months at –20 °C without noticeable decomposition. However, they have the propensity to undergo retro-aldol reaction in presence of base (*vide infra*). Isolation of the major diastereoisomer of **291** by preparative TLC and recrystallization from fluorobenzene afforded crystals confirming that the *anti*-isomer was favored. Interestingly, in the ^{19}F NMR spectra of all the aldol products, the signal of the equatorial fluorines of the *syn*-diastereoisomer appears as a simple doublet, coupling only with the axial fluorine of the SF_5 group. On the other hand, the signal of the equatorial fluorines of the *anti*-diastereoisomer is more complex, with additional multiplicity probably due to coupling with nearby protons under a specific conformation.

Under the described reaction conditions, other electrophiles than aldehydes, including acyl chlorides, ketones or acrylonitrile failed to give any product resulting from addition of the

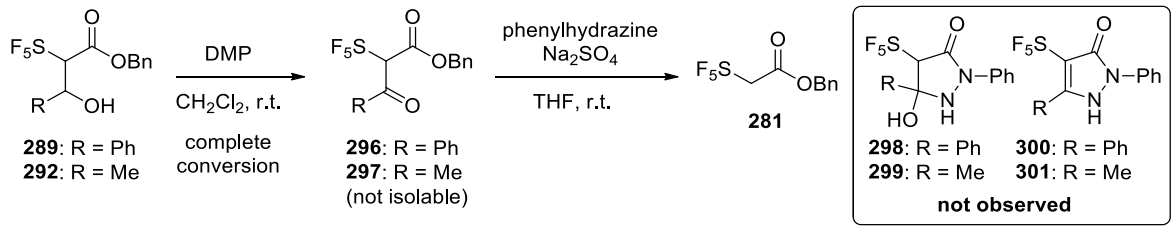
[134] 3-Nitropropanal was prepared following a reported procedure: (a) R. Ohrlein, W. Schwab, R. Ehrler, V. Jager, *Synthesis* **1986**, 535–538; (b) H. Griesser, R. Öhrlein, W. Schwab, R. Ehrler, C. Jäger, *Org. Synth.* **2000**, *77*, 236.

formed α-SF_5-enolate. However, we found that *N*-Boc-imines could be added using a modified procedure, albeit in modest yields (see Chapter 1.3.3.5).

1.3.3.2. Unsuccessful Routes Towards SF_5-Heterocycles from Aldol Adducts.

With an unprecedented and reliable method to create a key C–C bond in the α-position of the pentafluorosulfanyl group, we turned ourselves towards the *de novo* synthesis of novel SF_5-heterocycles. Indeed, with the SF_5 moiety already implemented in the chain, synthetic modification of its extremities could afford cyclized products.

The first attempted approaches involved condensation or Michael addition using modified aldol adducts and hydrazines in order to obtain SF_5-pyrazolidinones or SF_5-pyrazolones. Therefore, we performed a Dess–Martin oxidation on both aldol adducts **289** and **292** (Scheme 1.3.20). Complete conversion into the corresponding ketone was observed in both cases. However, these compounds could not be purified by column chromatography because of their propensity to suffer from retro-Claisen C–C cleavage reaction in presence of silica gel, leading to the recovery of benzyl SF_5-acetate **281**.



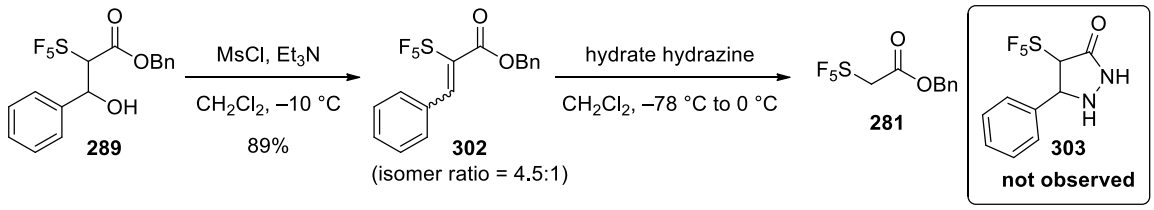
Scheme 1.3.20. Attempted synthesis of SF_5-pyrazolidinones and SF_5-pyrazolones *via* oxidation of aldol adducts.

Consequently, we treated crude **296** or **297** with phenylhydrazine in presence of sodium sulfate as drying agent. Formation of fluorinated pyrazolidinones has been documented from α-fluoro-β-ketoesters using a similar procedure.[135] However, with the SF_5 group, no heterocycle formation was observed under these conditions. Instead, only benzyl SF_5-acetate **281** was generated with complete conversion. We assumed that nucleophilic attack of hydrazine on the ketone functional group triggers also a retro-Claisen reaction releasing **281**.

Next, we explored the possibility of preparing SF_5-pyrazolidinones by addition of hydrazine to an α-SF_5-acrylic system obtained by dehydration of aldol product **289** (Scheme 1.3.21).[136] Mesylation of the latter and subsequent elimination afforded α,β-unsaturated ester **302** in 89% yield. The product was obtained as a mixture of unassigned *E* and *Z* isomers in a ratio of 4.5:1.

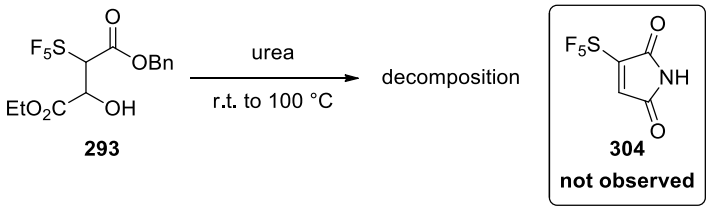
[135] C. Portella, M. Iznaden, *Synthesis* **1991**, 1013–1014.
[136] S. Aoki, T. Kawasaki-Takasuka, T. Yamazaki, *Tetrahedron* **2011**, *67*, 4845–4851.

Unfortunately, treatment of **302** with hydrazine did not furnish the desired SF_5-heterocycle **303**. Once more, only benzyl SF_5-acetate **281** was formed. We hypothesized that after conjugate addition of hydrazine to **302**, the intermediate underwent a retro-Mannich reaction under the reaction conditions to give **281**.



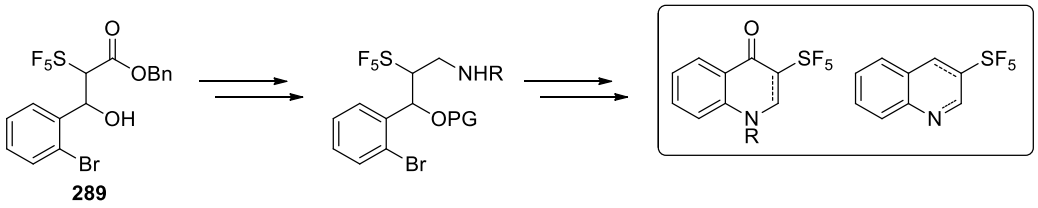
Scheme 1.3.21. Attempted synthesis of SF_5-pyrazolydinones *via* dehydration of **289**.

We also tried to prepare SF_5-maleimide **304** by treatment of aldol adduct **293** with urea (Scheme 1.3.22).[137] However, no reaction was observed at room temperature, and increasing the reaction temperature only resulted in decomposition of the pentafluorosulfanyl moiety, according to ^{19}F NMR analysis.



Scheme 1.3.22. Attempted synthesis of SF_5-maleimide **304**.

We next planned to use bromobenzyl derivative **289** as precursor of benzannulated *N*-heterocycles such as dihydroquinolones, tetrahydroquinolines, quinolones and quinolines, where the SF_5 group would be attached to the heterocyclic part (Scheme 1.3.23).[138] To achieve this goal, the strategy would be to convert the ester group into an amine, followed by ring-closure employing Buchwald–Hartwig cross-coupling reaction.

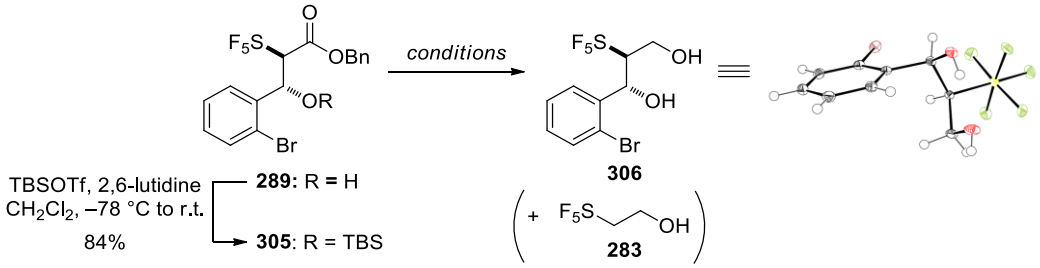


Scheme 1.3.23. Strategy towards SF_5-substituted benzannulated *N*-heterocycles from **289**.

[137] T. Katoh, K. Nishide, M. Node, H. Ogura, *Heterocycles* **1999**, *50*, 833–841.
[138] Quinolines with a SF_5 group on the non-heterocyclic ring have already been reported (cf. chapter 1.1.2.3)

As a matter of convenience during this study, we only used the major *anti*-diastereoisomer of **289**, which was obtained nearly pure by column chromatography. In order to access the desired amine precursor for cyclization, we focused on the establishment of conditions for the reduction of the ester group (Table 1.3.3). This step was not trivial due to the ability of **289** to undergo competitive retro-aldol reaction.

Table 1.3.3. Attempts of reduction of benzyl esters **289** and **305**.



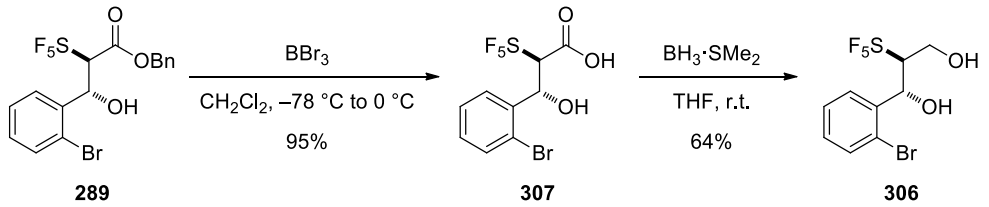
Entry	Substrate	Conditions	Result[a]
1	**289**	$LiAlH_4$, Et_2O, –78 °C	mainly **283** + SF_5 decomposition traces of **306**
2	**289**	DIBAL, Et_2O, –78 °C	no reaction
3	**289**	DIBAL, Et_2O, 0 °C	**306** (42%)[b] + SF_5 decomposition
4	**289**	Li(*n*-Bu)(*i*-Bu)$_2$AlH THF –78°C to –30 °C	SF_5 decomposition
5	**289**	$LiBH_4$, $LiEtBH_3$ (10 mol%) Et_2O, 0 °C	mainly **283** + SF_5 decomposition
6	**305**	$LiAlH_4$, Et_2O, –78 °C	mainly SF_5 decomposition traces of **306**
7	**305**	DIBAL, Et_2O, –78 °C to 0 °C	**306** (53%)[b] + SF_5 decomposition
8	**305**	$LiBH_4$, $LiEtBH_3$ (10 mol%) Et_2O, 0 °C to r.t.	no reaction

a) Determined by ^1H and ^{19}F NMR analyses of the crude material; b) Isolated yield.

Indeed, treatment with $LiAlH_4$ mainly resulted in formation of SF_5-ethanol **283** along with decomposition of the SF_5 moiety and only traces of the desired diol **306** (Entry 1). Using DIBAL at 0 °C gave promising results and furnished **306** in 42% yield, although with substantial decomposition into non-fluorinated compounds (Entry 3). The latter could by recrystallized by vapor diffusion of pentane in Et_2O, affording crystals suitable for X-ray analysis and giving another confirmation of the formation of *anti*-**289** as the major diastereoisomer during the aldol reaction. Since we surmised that the decomposition of the substrate induced by DIBAL could be initiated by coordination of the free hydroxyl group to the aluminium, we tried to use the ate complex of DIBAL and *n*-butyllithium, which does not

possess a vacant coordination site.[139] Unfortunately, these conditions failed to give any product (Entry 4). The attempt to use conditions reported by Brown involving reaction with $LiBH_4$ in presence of catalytic amounts of lithium triethylborohydride was also unsuccessful with formation of **283** *via* a retro-aldol process as the major product (Entry 5).[140] In order to avoid this side reaction to occur, we planned to protect the free hydroxyl group. Among the numerous protection reaction conditions examined, only treatment of **289** with TBSOTf and 2,6-lutidine efficiently afforded the corresponding silyl-ether **305**. Unfortunately, the protection was fruitless since cleavage of the silyl group was observed when **305** was reduced with $LiAlH_4$, affording only traces of **306** (Entry 6). A similar outcome was observed when DIBAL was used, however, the desired diol was obtained in slightly higher yield than with the unprotected ester **289** (Entry 7).On the other hand, **305** did not react in presence of $LiBH_4$ and catalytic lithium triethylborohydride and only starting material was recovered (Entry 8).

Ultimately, the synthesis of diol **306** could be improved by preliminary formation of carboxylic acid **307** (Scheme 1.3.24). Benzyl cleavage could be cleanly achieved by treatment with boron tribromide. Hydrogenolysis with Pd/C was not suitable because of concomitant aromatic debromination. Reduction of the acid was then accomplished using borane dimethylsulfide, affording diol **306** in 64% yield.

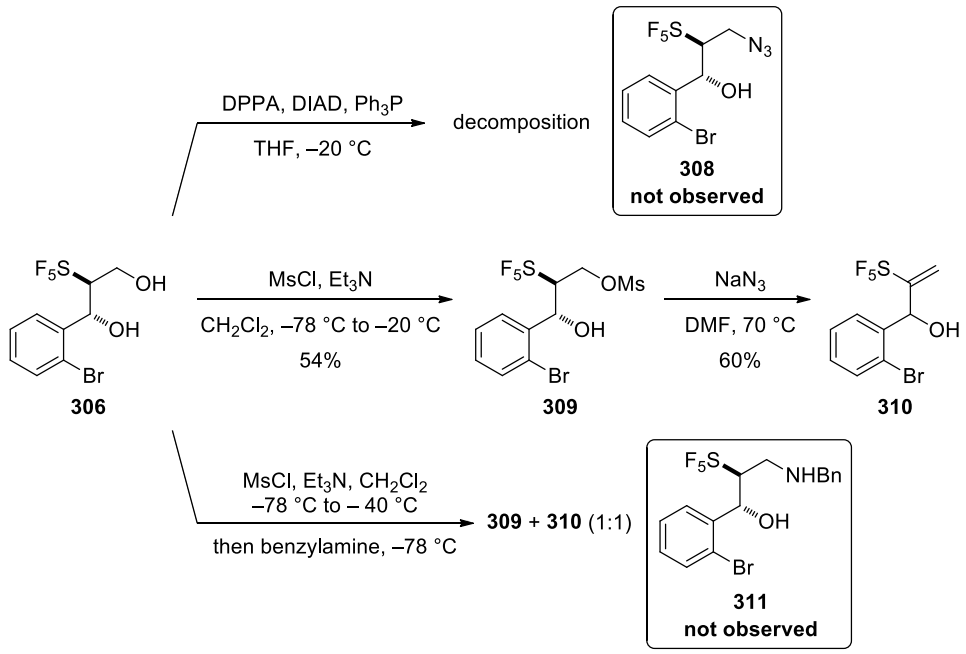


Scheme 1.3.24. Synthesis of diol **306** by reduction of carboxylic acid **307**.

Next, we turned our attention to the conversion of the terminal hydroxyl group into an amine (Scheme 1.3.25). We attempted to selectively install a terminal azide group using the Bose–Mitsunobu method with DPPA.[141] Unfortunately, under these conditions, decomposition of the SF_5 moiety occurred, with only unidentified signals observed in the ^{19}F NMR spectrum, with chemical shifts between –80 and –10 ppm. Therefore we tried to employ a mesylate intermediate. Regioselective mesylation of the terminal alcohol was possible by careful control of the reaction temperature, affording **309** in 54% yield. However, nucleophilic substitution with sodium azide was unsuccessful. Instead, elimination of the mesylate, probably facilitated by the electron-withdrawing effect of the pentafluorosulfanyl group, furnished olefin **310** in 60% yield.

[139] S. Kim, K. H. Ahn, *J. Org. Chem.* **1984**, *49*, 1717–1724.
[140] H. C. Brown, S. Narasimhan, *J. Org. Chem.* **1982**, *47*, 1604–1606.
[141] B. Lal, B. N. Pramanik, M. S. Manhas, A. K. Bose, *Tetrahedron Lett.* **1977**, 1977–1980.

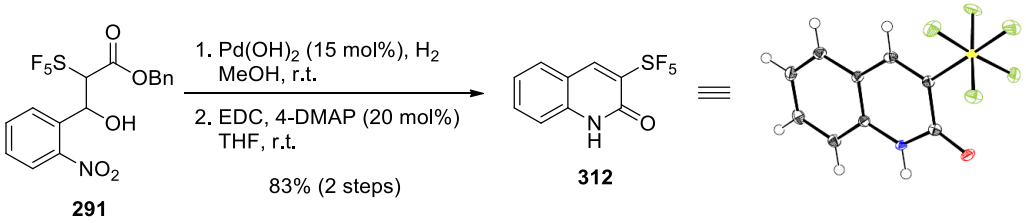
One-pot mesylation–amination with benzyl amine was investigated as well, but elimination of the mesylate intermediate was also faster than the desired substitution.



Scheme 1.3.25. Attempted amination of diol **306**.

1.3.3.3. Synthesis of 3-SF_5-Quinolones and 3-SF_5-Quinolines

Facing the difficulties associated with the amination, we decided to start the *de novo* synthesis of SF_5-substituted *N*-heterocycles from a substrate which already incorporates the nitrogen atom. Therefore we chose aldol product **291** as precursor of 3-SF_5-quinolones and 3-SF_5-quinolines. We hypothesized that these heterocycles could be prepared by simultaneous reduction of the nitro group and cleavage of the benzyl group in **291**, followed by cyclization and subsequent elimination of the hydroxyl group (Scheme 1.3.26).

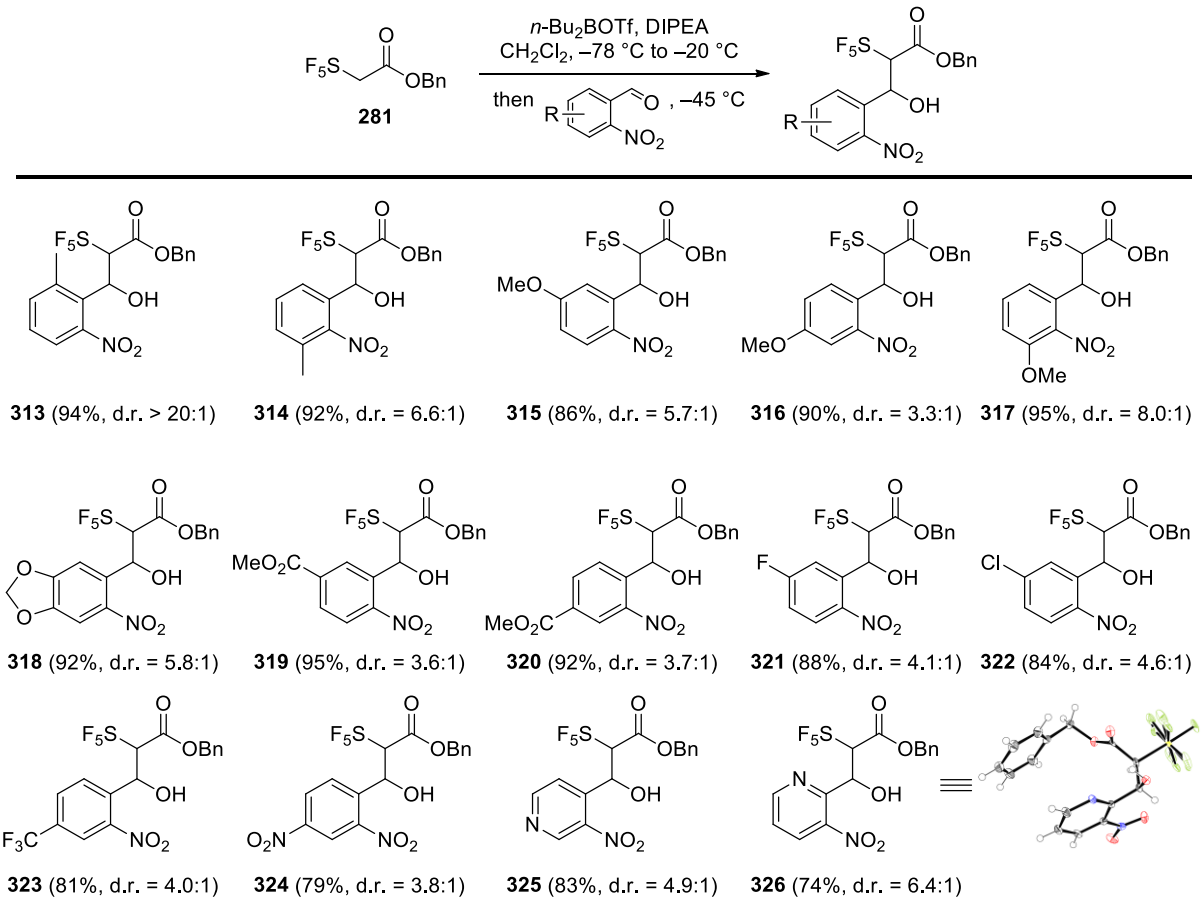


Scheme 1.3.26. Synthesis of 3-SF_5-quinolin-2-one **312**.

To our delight, treatment of **291** with Pearlman's catalyst under hydrogen atmosphere in methanol for 2.5 h at room temperature afforded a mixture of cyclized and non-cyclized products, as indicated by ^{19}F NMR spectroscopy. Then, completion of the cyclization with concomitant hydroxyl elimination was achieved by reacting the crude mixture with EDC in presence of 4-DMAP in THF. This two-step sequence afforded 3-SF_5-quinolin-2-one (**312**) in

83% yield on gram scale. Recrystallization from ethyl acetate afforded crystals suitable for X-ray analysis.

With an efficient synthesis of SF_5-heterocycle **312** in hand, we showcased the generality of this method for the preparation of a range of 3-SF_5-quinolones. The aldol reaction with benzyl SF_5-acetate **281** was thus applied to other substituted nitrobenzaldehydes (Scheme 1.3.27).

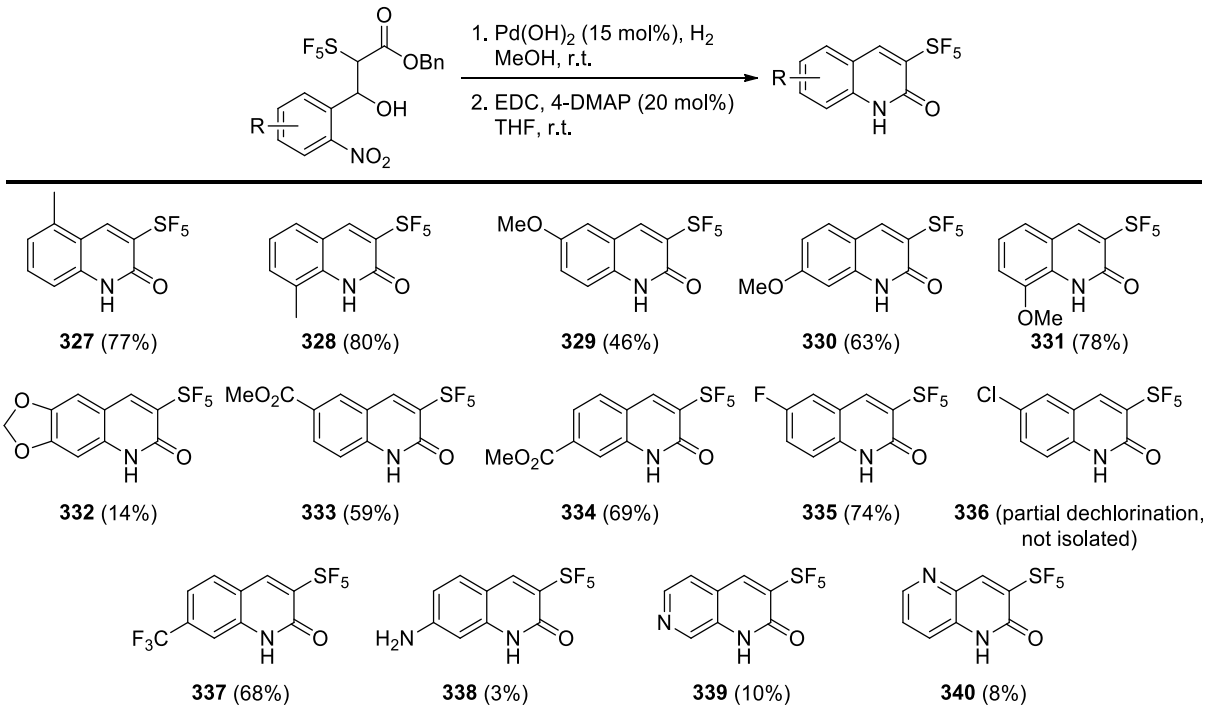


Scheme 1.3.27. Nitrobenzaldehyde scope of aldol reaction with benzyl SF_5-acetate.

The reaction could be performed on a large number of substrates in high yields varying from 74% to 95%. Aldol adducts with various functional groups on the aryl moiety were accessible. Methyl substituted nitrobenzaldehydes afforded **313** and **314** in excellent yields. Interestingly, a methyl group in *ortho*-position of the aldehyde has a significant influence on the diastereoselectivity of the reaction (d.r. > 20:1). Products bearing electron-donating groups such as methoxy (**315**, **316**, **317**) or methylenedioxy (**318**) could also be efficiently prepared. Electron-withdrawing substituents such as esters (**319**, **320**), halogens (**321**, **322**), trifluoromethyl (**323**) and additional nitro (**324**) were also compatible with the aldol reaction conditions. In addition to nitrobenzaldehydes, nitropyridinecarboxaldehydes were also suitable substrates, furnishing heteroaryl derivatives **325** and **326** in 83% and 74% yield, respectively.

The major isomer of the latter could be recrystallized from chloroform, furnishing crystals suitable for X-ray analysis and corroborating the favored formation of the *anti*-diastereoisomer.

We then turned our attention to the preparation of a collection of 3-SF_5-quinolones from the nitro-substituted aldol adducts by using the thus developed two-step reduction–cyclization sequence (Scheme 1.3.28).



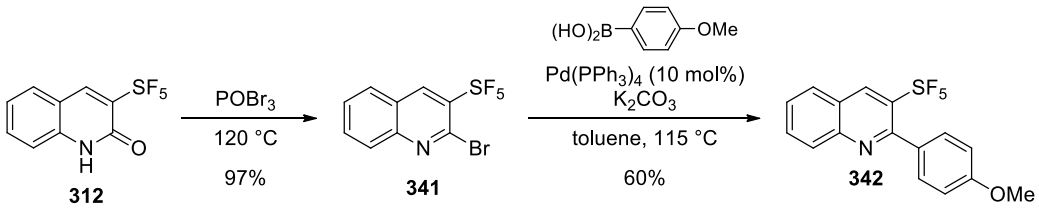
Scheme 1.3.28. Preparation of 3-SF_5-quinolones.

5- and 8-methyl derivatives **327** and **328** were obtained in high yields. In addition, methoxy-substituted quinolones were prepared in 46 to 78% yields (**329**, **330**, **331**). Moreover, SF_5-quinolines bearing esters such as **333** and **334** were accessible in 59% and 69% yield, respectively. Reactions with fluorine or trifluoromethyl derivatives were suitable and gave **335** and **336** in good yields.

However, not all of the prepared nitro-substituted aldol adducts were efficiently converted into the corresponding 3-SF_5-quinolones. For example, methylenedioxy derivative **318** afforded SF_5-quinolone **332** in only 14% yield. Formation of a black tar in the flask suggested decomposition or polymerization of the product. Similar outcomes were observed with dinitro-derivative **324** and pyridyl compounds **325** and **326**. Indeed, amino-quinolone **338** and naphthyridinones **339** and **340** were obtained in yields below 10%. Another limitation was observed when chloro-substituted aldol adduct **322** was used as starting material with partial hydrodechlorination during the reduction step, resulting in the formation of an inseparable

mixture of **336** and **312** after cyclization (1.5:1 according to ^{19}F NMR analysis of the crude material).

In order to illustrate the synthetic utility of these novel 3-SF_5-quinolones, we next focused on the synthesis of 3-SF_5-quinolines by modification of **312**. Treatment of the latter with neat $POBr_3$ at 120 °C furnished 2-Br-3-SF_5-quinoline (**341**) in 97% yield (Scheme 1.3.29). This compound could be further functionalized with by Suzuki–Miyaura cross-coupling reaction with 4-methoxyphenylboronic acid, affording 2-aryl-substituted 3-SF_5-quinoline **342** in 60% yield. On the other hand, attempts of Buchwald–Hartwig cross-coupling for the installation of amine substituents, following a procedure suitable for similar heterocyclic substrates,[142] gave only traces of the desired 2-aminoquinoline products.

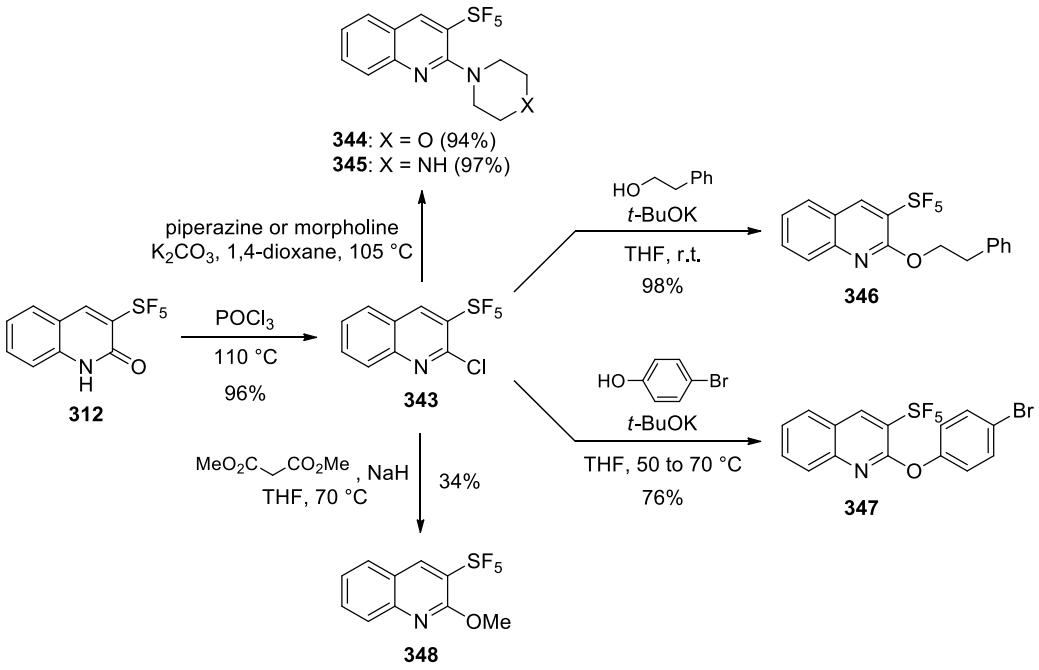


Scheme 1.3.29. Dehydroxybromination of 3-SF_5-quinolone **302** and Suzuki–Miyaura cross-coupling reaction.

Alternatively, 3-SF_5-quinolone **312** was treated with $POCl_3$ to give 2-Cl-3-SF_5-quinoline **343** in 96% yield (Scheme 1.3.30). The latter was expected to be an optimal platform for nucleophilic substitution. Indeed, the chloride could be displaced by amines such as morpholine or piperazine, in presence of potassium carbonate in dioxane at 105 °C, to obtain compounds **344** and **345** in excellent yields. The analogous reaction with anilines did not afford the corresponding diaryl amine compounds and resulted in recovery of the starting material. However, both alcohols and phenols were suitable substrates for aromatic nucleophilic substitution. Indeed, treatment of **343** with phenylethanol in THF at room temperature furnished **346** in 98% yield. The reaction with 4-bromophenol necessitated higher temperature and longer reaction time to give **347** in 76% yield. Interestingly, nucleophilic substitution of **343** with dimethyl malonate did not afford the expected formation of a new C–C bond. Instead, the methoxy derivative **348** was isolated in 34% yield. Other attempts of functionalization of 2-Cl-3-SF_5-quinoline were met with failure. For example, **343** was unreactive towards iron-catalyzed alkylation following Fürstner's report with $Fe(acac)_3$ and EtMgBr.[143] Furthermore, nucleophilic substitutions with Grignard reagents such as PhMgBr, allylMgBr and

[142] S. Wagaw, S. L. Buchwald, *J. Org. Chem.* **1996**, *61*, 7240–7241.
[143] (a) A. Fürstner, A. Leitner, *Angew. Chem. Int. Ed.* **2002**, *41*, 609–612; (b) A. Fürstner, A. Leitner, M. Mendez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863.

EtMgBr were fruitless. No reaction occurred at room temperature, and traces of protodehalogenation with formation of 3-SF_5-quinoline (**349**) were observed at higher temperature.



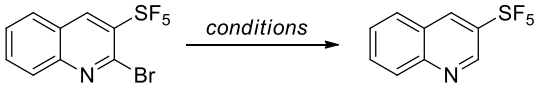
Scheme 1.3.30. Dehydroxychlorination of 3-SF_5-quinolone and nucleophilic substitution reactions.

We next turned our attention to the synthesis of the 3-SF_5-quinoline (**349**), as we planned to evaluate its physicochemical properties (*vide infra*). Surprisingly, the reduction of 2-halogeno-3-SF_5-quinolines **341** and **343** was not as trivial as expected (Table 1.3.4). We first tried to take advantage of the ability of **343** to undergo aromatic nucleophilic substitution. However, displacement of the chloride with a hydride was unfruitful. Treatment with $LiAlH_4$ at –20 °C resulted in complete decomposition of the SF_5 moiety within five minutes (Entry 1), as no signal could be observed in the ^{19}F NMR spectrum of the crude material. On the other hand, **343** did not react in presence of DIBAL (Entry 2). We then attempted several Pd-catalyzed hydrogenation procedures, reported for similar 2-halogenoheterocycles. Ammonium formate in presence of Pd/C (Entry 3),[144] or hydrogen gas in presence of $PdCl_2$ and base (Entry 4)[145] were inefficient reaction conditions. Reduction of **343** with $NaBH_4$ in presence of TMEDA and

[144] B. Manteau, P. Genix, L. Brelot, J. P. Vors, S. Pazenok, F. Giornal, C. Leuenberger, F. R. Leroux, *Eur. J. Org. Chem.* **2010**, 6043–6066.
[145] (a) X. B. Chen, Q. P. Hu, Q. J. Yuan, W. Ding, J. M. Ren, B. B. Zeng, *Tetrahedron Lett.* **2012**, *53*, 3798–3801; (b) E. Kiselev, K. Agama, Y. Pommier, M. Cushman, *J. Med. Chem.* **2012**, *55*, 1682–1697.

catalytic $PdCl_2$(dppf) gave poor results with a conversion of only 10% (Entry 5).[146] Pd-catalyzed hydrogenation on the bromo-derivative **341** was also met with failure (Entry 6).[147]

Table 1.3.4. Synthesis of 3-SF_5-quinoline (**349**).



341: X = Br
343: X = Cl

349

Entry	X	Conditions	Result[a]
1	Cl	$LiAlH_4$, THF, –20 °C	decomposition of SF_5
2	Cl	DIBAL, THF, 0 °C to r.t.	no reaction
3	Cl	NH_4HCO_2, Pd/C (10 mol%) MeOH, 55 °C	no reaction
4	Cl	H_2, $PdCl_2$ (10 mol%), AcONa, MeOH, r.t.	no reaction
5	Cl	$NaBH_4$, TMEDA, $PdCl_2$(dppf) THF, r.t. to 60 °C	**343**:**349** = 9:1
6	Br	H_2, Pd/C, KOH EtOH, r.t. to 75 °C	no reaction
7	Br	*n*-BuLi, THF, –78 °C, then MeOH	**341**:**349** = 1:1 + decomposition
8	Br	*i*-PrMgCl·LiCl, 0 °C then MeOH	**341**:**349** = 1:0.5 + decomposition
9	Br	Zn, aq. NaOH, r.t. to 80 °C	no reaction
10	Br	Zn, EtOH/AcOH, 80 °C	**349** (15%)[b] + decomposition
11	Br	Zn, AcOH/H_2O, 80 °C	mainly 3-SF_5-quinolone **312**
12	Br	*n*-Bu_3SnH, AIBN (2 mol%) benzene, 85 °C	**349** (84%)[b]

a) Determined by ^1H and ^{19}F NMR analyses of the crude material; b) Isolated yield.

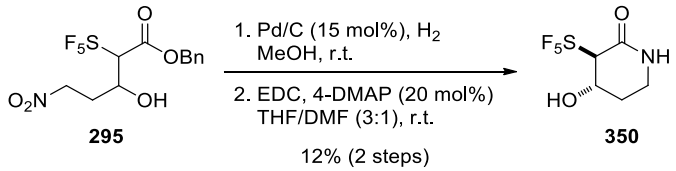
We then explored the possibility of reduction *via* metal–halogen exchange. Treatment with *n*-BuLi at low temperature followed by addition of MeOH afforded a 1:1 mixture of brominated and reduced products, along with substantial decomposition (Entry 7).[148] Using milder conditions with *i*-PrMgCl·LiCl did not improve the method (Entry 8). Reductive dehalogenation with zinc in aqueous alkaline media was also unsuccessful (Entry 9).[149] Debromination with zinc in boiling ethanolic acetic acid afforded only 15% of the reduced product (Entry 10).[150] Using aqueous acetic acid instead of ethanol gave hydrolyzed 3-SF_5-quinolone **312** as the major

[146] G. Chelucci, *Tetrahedron Lett.* **2010**, *51*, 1562–1565.
[147] N. Nishimura, A. Siegmund, L. B. Liu, K. Yang, M. C. Bryan, K. L. Andrews, Y. X. Bo, S. K. Booker, S. Caenepeel, D. Freeman, H. Y. Liao, J. McCarter, E. L. Mullady, T. San Miguel, R. Subramanian, N. Tamayo, L. Wang, D. A. Whittington, L. Zalameda, N. Zhang, P. E. Hughes, M. H. Norman, *J. Med. Chem.* **2011**, *54*, 4735–4751.
[148] F. Cottet, M. Marull, O. Lefebvre, M. Schlosser, *Eur. J. Org. Chem.* **2003**, 1559–1568.
[149] M. Schlosser, C. Bobbio, *Eur. J. Org. Chem.* **2002**, 4174–4180.
[150] J. B. Paine, *J. Heterocycl. Chem.* **1987**, *24*, 351–355.

product (Entry 11).[151] Ultimately, we found that radical dehalogenation with *n*-Bu_3SnH and catalytic AIBN was the ideal approach to obtain 3-SF_5-quinoline (**349**) in 84% yield.[152]

1.3.3.4. Synthesis of 3-SF_5-Pyridones

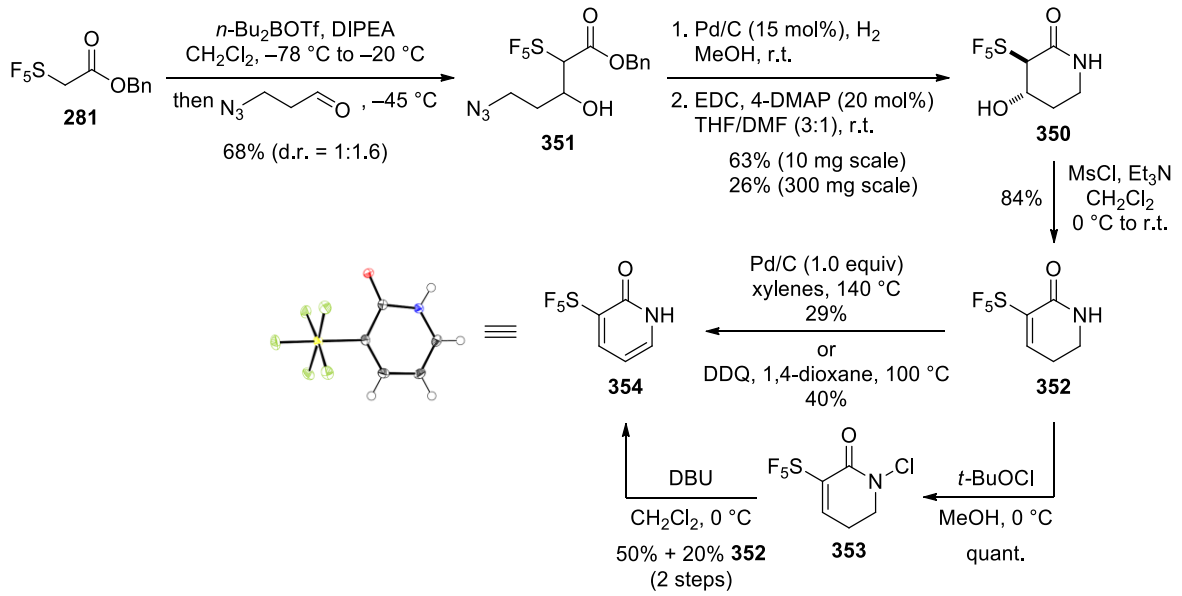
After securing a route for the preparation of novel SF_5-substituted benzannulated *N*-heterocycles, we were optimistic that a similar strategy could be employed for the synthesis of six-membered aromatic *N*-heterocycles, such as 3-SF_5-pyridones. Therefore, we planned to apply the same conditions to the aldol adduct **295**, generated from 3-nitropropanal. We expected that after cyclization, elimination of the hydroxyl group and further oxidation would afford the aromatic ring. Unfortunately, the reduction–cyclization sequence was not as efficient as previously, and hydroxyl *δ*-lactam **350** was obtained in only 12% yield (Scheme 1.3.31). Interestingly, from a 1:1 mixture of diastereoisomers *anti*- and *syn*-**295**, the cyclization product **350** was formed as a single isomer, tentatively assigned as the *trans*-diastereoisomer. This observation was probably due to epimerization in presence of base.



Scheme 1.3.31. Reduction–cyclization sequence of nitro derivative **295**.

It appeared that the inefficient step in this sequence was the reduction, giving a complex mixture according to ^1H and ^{19}F NMR analyses. Other reduction conditions involving palladium, platinum or nickel catalysts failed to improve the outcome. Facing this issue, in addition to the moderate yield of 44% obtained in the aldol reaction (cf. Chapter 1.3.3.1), we decided to change the substrate for the reduction–cyclization sequence. Therefore, we prepared azido derivative **351** by aldol reaction of 3-azidopropanal[153] with benzyl SF_5-acetate **281** (Scheme 1.3.32). Reduction of the azide with concomitant benzyl ether cleavage, followed by cyclization afforded the desired *δ*-lactam **350** in 63%. Unfortunately, while this process gave satisfying result on small scale (ca. 10 mg), attempts to reproduce this route on larger scale failed to give synthetically useful yields. Therefore, we aspired to improve the route in order to enable the synthesis of large quantities of SF_5-building blocks (*vide infra*).

[151] M. Arshad, M. A. Fernandez, E. M. McGarrigle, V. K. Aggarwal, *Tetrahedron: Asymmetry* **2010**, *21*, 1771–1776.
[152] E. Barbu, J. J. Wolff, I. Bolocan, F. Cuiban, *Heterocycl. Commun.* **2000**, *6*, 25–28.
[153] 3-Azidopropanal was prepared following a reported procedure: K. Ii, S. Ichikawa, B. Al-Dabbagh, A. Bouhss, A. Matsuda, *J. Med. Chem.* **2010**, *53*, 3793–3813.



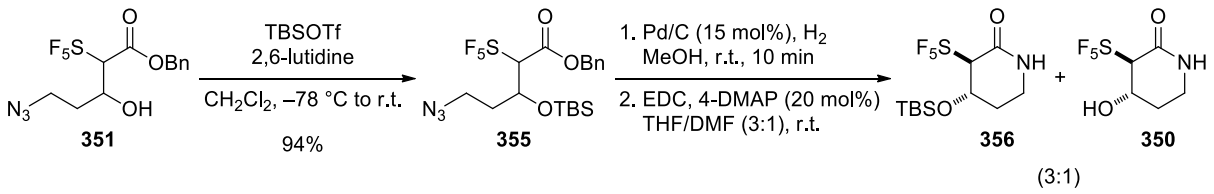
Scheme 1.3.32. First generation synthesis of 3-SF_5-pyridone **354**.

Nevertheless, with sufficient material in hand, we pursued the proposed route to SF_5-pyridone **354**. Elimination of the hydroxyl group *via* formation of a mesylate intermediate afforded unsaturated lactam **352** in 84% yield. Two strategies were explored to complete the last ring desaturation. First, a two-step procedure involving formation *N*-chlorination followed by dehydrochlorination was investigated. Treatment of **352** with *tert*-butyl hypochlorite afforded *N*-chlorolactam **353** quantitavely.[154] The crude material obtained was then directly subjected to elimination conditions. Exposure to DBU furnished the desired 3-SF_5-pyridone **354** in 50% yield along with 20% recovery of **352**, most likely formed by chloride exchange from the lactam to the base. Using a hindered base such as 2,6-lutidine did not improve the ratio of **354** versus **352**. Alternatively, dehydrogenation of the lactam could be achieved using Pd/C in refluxing xylenes, albeit in only 29% yield.[155] DDQ oxidation in refluxing dioxane gave slightly better yield of 40%.[156] Recrystallization of 3-SF_5-pyridone from ethyl acetate afforded crystals suitable for X-ray analysis, confirming the success of its formation. Optimization of the desaturation of **352**, for example by photolytic dehydrochlorination of **353**, was not further investigated, since a different route was ultimately found for the synthesis of **354**.

As previously mentioned, scaling up the reduction–cyclization sequence on **351** was challenging. This problem was attributed to the low stability of the hydroxyl-substituted amino acid intermediate, which partially decomposed during the hydrogenation step. To circumvent

[154] (a) R. C. F. Jones, C. E. Dawson, M. J. O'Mahony, P. Patel, *Tetrahedron Lett.* **1999**, *40*, 4085–4088; (b) R. C. F. Jones, A. K. Choudhury, C. E. Dawson, C. Lumley, V. McKee, *Arkivoc* **2012**, 12–24.
[155] For an example of Pd-mediated dehydrogenation of lactam, see: Z. Pi, J. Lloyd, J. X. Qiao, T. C. Wang, G. O. Tora, *WO 2013/048930 A1*, **2013**, p. 67.
[156] M. J. Thompson, J. C. Louth, S. M. Little, M. P. Jackson, Y. Boursereau, B. N. Chen, I. Coldham, *ChemMedChem* **2012**, *7*, 578–586.

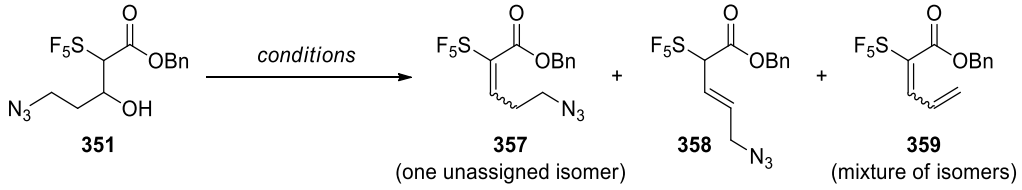
this obstacle, we first tried to protect the alcohol, in order to prevent potential side reactions. Unfortunately, when TBS-protected **355** was subjected to the reduction conditions, partial deprotection of the hydroxyl group was observed even after only 10 min, resulting in a 3:1 mixture of **356** and **350** after cyclization (Scheme 1.3.33).



Scheme 1.3.33. Reduction–cyclization sequence of TBS-protected **355**.

We then studied the possibility of eliminating the hydroxyl group prior to reduction. We hypothesized that the size of the pentafluorosulfanyl group would favor formation of the *trans*-isomer, necessary to enable the subsequent cyclization. However, under various reaction conditions, we were confronted with competitive formation of other side products, including isomer **358**, double elimination product **359** and other SF_5-containing unidentified compounds (Table 1.3.5). An initial attempt using MsCl (2.0 equiv) and Et_3N (5.0 equiv) at –20 °C only gave **359**, resulting from hydroxyl and azide elimination (Entry 1). When the reaction temperature and the amount of base were decreased, the formation of a mixture of mono elimination products **357** and **358** was observed (Entry 2). These two compounds were difficult to separate by column chromatography, and the geometry of **357**, obtained as a single *cis*- or *trans*-isomer, could not be assigned. However, formation of the *trans*-isomer of **358** was confirmed by the vicinal coupling constant $^3J_{HH}$ of 15.4 Hz. Employing a weaker base such as pyridine in order to suppress azide elimination resulted in low conversion as well as major formation of **358** (Entry 3). Exchanging the mesylate leaving group for a triflate accelerated the reaction, but favored isomer **358** (Entry 4). The regioselectivity could be improved by forming the acetate in presence of 4-DMAP at –78 °C, but other unidentified SF_5-containing compounds were also observed (Entry 5). Increasing the temperature resulted in a more significant generation of double elimination product **359** (Entries 6-7).

Table 1.3.5. Hydroxyl elimination on aldol adduct **351**.



Entry	Conditions	Result[a]
1	MsCl (2.0 equiv), Et_3N (5.0 equiv) CH_2Cl_2, –20 °C	only **359** (89%)[b]
2	MsCl (1.1 equiv), Et_3N (2.0 equiv) CH_2Cl_2, –78 °C	**357**:**358**:**359** = 2:1:4
3	MsCl (1.1 equiv), pyridine (2.2 equiv) CH_2Cl_2, –78 °C to r.t.	**357**:**358** = 1:21 (25% conversion)
4	Tf_2O (1.1 equiv), pyridine (2.2 equiv) CH_2Cl_2, –78 °C to r.t.	**357**:**358** = 1:4.5 (98%)[b]
5	Ac_2O (1.5 equiv), 4-DMAP (2.0 equiv) CH_2Cl_2, –78 °C	**357**:**358** = 3.0:1 (+ ca 15% of other unidentified SF_5-compounds)
6	Ac_2O, 4-DMAP CH_2Cl_2, –20 °C	**357**:**359**: = 5.9:1 (+ ca 7% of other unidentified SF_5-compounds)
7	Ac_2O, 4-DMAP CH_2Cl_2, 0 °C	**357**:**359**: = 3:1 (+ ca 20% of other unidentified SF_5-compounds)

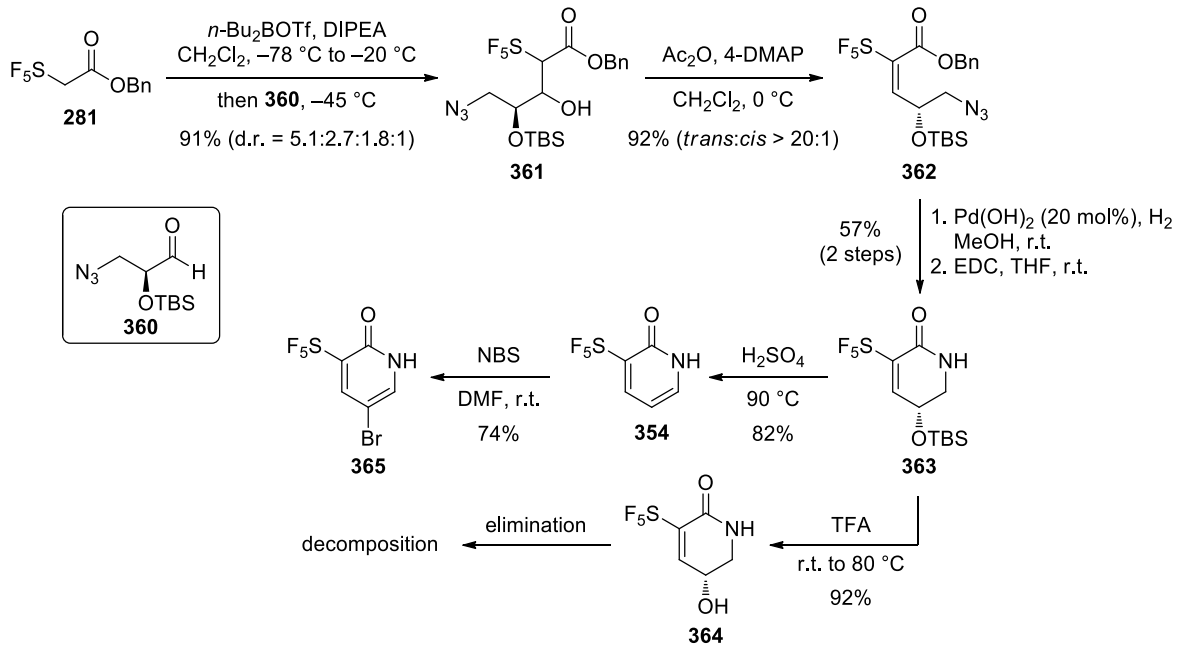
a) Determined by ^1H and ^{19}F NMR analyses of the crude material; b) Isolated yield.

In order to suppress the competitive formation of isomer **358**, and azide elimination product **359**, we surmised that a substituent in the γ-position of the ester would be beneficial. Moreover, we could take advantage of this additional substitution to achieve the last desaturation of the ring. Therefore, we decided to use aldehyde **360** in the aldol reaction with α-SF_5 enolate (Scheme 1.3.34). **360** was prepared on multigram scale from L-ascorbic acid,[157] and offered the advantage to be easier to handle than 3-azidopropanal because of its higher molecular weight, inducing a higher boiling point as well as a lower propensity to undergo explosion.

Aldol adduct **361** was obtained as a mixture of four diastereoisomers in 91% yield. Then, treatment of this mixture with Ac_2O and 4-DMAP led to the generation of a single elimination compound **362** in an excellent yield of 92%. At this stage, formation of the *trans*-isomer could not be confirmed. Validation of the correct stereoselectivity during the elimination step was ascertained when execution of the reduction–cyclization sequence afforded **363** in 57% yield. Using Pearlman's catalyst instead of palladium on carbon resulted in faster and cleaner conversion to the corresponding amino acid. Moreover, it was found that the cyclization step was more efficient in the absence of 4-DMAP. Elimination of the TBS-protected hydroxyl

[157] See the experimental section for details about the preparation of **360**.

group could be achieved by heating **363** in neat sulfuric acid to afford the desired SF_5-pyridone **354** in 82% yield. The tolerance of the SF_5 group to such harsh reaction conditions is noticeable, and underscores its strong stability in acidic *media*. The desired elimination could not be achieved upon treatment of **363** with softer acids such as TFA, even at elevated temperatures. Under these conditions, the deprotected unsaturated δ-lactam **364** was obtained in 92% yield. Attempts to effect elimination were met with failure with various conditions, such as Ac_2O/4-DMAP or MsCl/Et_3N. Only decomposition of the SF_5 group occurred, attributed to initial conjugate addition of the base to the unsaturated lactam.



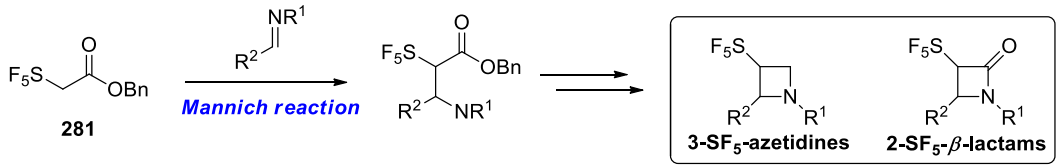
Scheme 1.3.34. Second generation synthesis of 3-SF_5-pyridone **354**.

Using this route, the preparation of 3-SF_5-pyridone could be achieved on a synthetically useful scale (> 250 mg). Moreover, in order to open perspectives towards further functionalization of this building block, we prepared the potentially versatile pyridone **365** by regioselective electrophilic bromination.

1.3.3.5. Addition to Imines, Towards 3-SF_5-Azetidines

The preceding chapters described the development of an unprecedented aldol reaction with an α-SF_5-enolate, and its application to the synthesis of novel SF_5-heterocycles, namely quinolines, quinolones and pyridones. We next endeavoured to operate this useful α-SF_5-functionalization with other electrophiles than aldehydes, in order to access distinct SF_5-heterocycles.

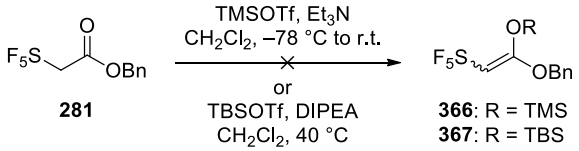
Therefore, we reasoned that SF_5-substituted four-membered *N*-heterocycles such as 3-SF_5-azetidines or 3-SF_5-β-lactams could be reached by synthetic manipulation of compounds arising from Mannich reactions involving an α-SF_5-enolate generated from benzyl SF_5-acetate **281** (Scheme 1.3.35).



Scheme 1.3.35. Synthetic strategy for the construction of SF_5-substituted four-membered *N*-heterocycles.

Four-membered *N*-heterocycles have emerged as important scaffolds in medicinal chemistry in the last decade, and outstanding development in their preparation has been achieved.[158] Thus, examples of synthesis of β-lactams arising from Mannich reactions have been reported.[159] Moreover, preparation of 2-CF_3-β-lactam from a β-amino carbonyl compound has already been described.[160] Therefore, we were optimistic about the possibility to prepare pentafluorosulfanyl-substituted analogues.

Since several reports about the addition of silyl ketene acetal to imines have been disclosed,[161] we first attempted to prepare the silyl ketene acetal of benzyl SF_5-acetate **281** (Scheme 1.3.36). We assumed that formation of **366** would be possible since trimethylsilyl ketene acetal of α-CF_3 esters have been prepared and could even be isolated.[162] However, our efforts were unsuccessful, and only starting material was recovered after aqueous work-up under controlled pH. Because we believed that **366** could be hydrolyzed upon addition of water, we tried to prepare the putatively more stable TBS-analogue **367**.



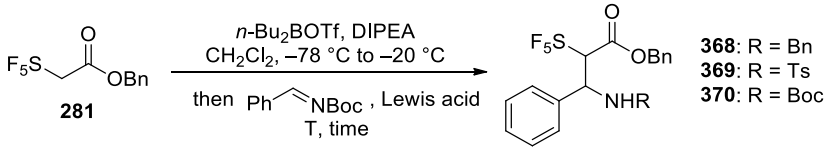
Scheme 1.3.36. Attemptde formation of SF_5-substituted ketene silyl acetal from **281**.

[158] For recent reviews about the preparation of four-membered *N*-heterocycles, see: (a) A. Brandi, S. Cicchi, F. M. Cordero, *Chem. Rev.* **2008**, *108*, 3988–4035; (b) T. M. Bott, F. G. West, *Heterocycles* **2012**, *84*, 223–264.
[159] (a) C. Gianelli, L. Sambri, A. Carlone, G. Bartoli, P. Melchiorre, *Angew. Chem. Int. Ed.* **2008**, *47*, 8700–8702; (b) M. Hatano, T. Horibe, K. Ishihara, *J. Am. Chem. Soc.* **2010**, *132*, 56–57; (c) Y. P. Lou, C. W. Zheng, R. M. Pan, Q. W. Jin, G. Zhao, Z. Li, *Org. Lett.* **2015**, *17*, 688–691.
[160] V. Jurcik, A. M. Z. Slawin, D. O'Hagan, *Beilstein J. Org. Chem.* **2011**, *7*, 759–766.
[161] For selected examples, see : (a) G. Guanti, E. Narisano, L. Banfi, *Tetrahedron Lett.* **1987**, *28*, 4331–4334; (b) B. C. Ranu, S. Samanta, S. K. Guchhait, *Tetrahedron* **2002**, *58*, 983–988; (c) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965; (d) G. T. Notte, J. M. B. Vu, J. L. Leighton, *Org. Lett.* **2011**, *13*, 816–818; (e) Q. G. Wang, M. Leutzsch, M. van Gemmeren, B. List, *J. Am. Chem. Soc.* **2013**, *135*, 15334–15337.
[162] T. Yokozawa, T. Nakai, N. Ishikawa, *Tetrahedron Lett.* **1984**, *25*, 3987–3990.

Monitoring the reaction by ^{19}F NMR analysis showed slow conversion of **281** to a new single SF_5-containing compound (50% conversion after 4 days at 40 °C). However, after aqueous work-up using pH 7 phosphate buffer, only **281** was recovered. Attempts to directly add *N*-Boc phenylimine to the ketene silyl acetal did not afford any addition product.

Hence, we decided to form the α-SF_5-enolate and add it to imines. The main challenge arising from this strategy was the lower electrophilicity of imines compared to aldehydes, therefore we suspected that Lewis acid activation would be necessary. Indeed, when the conditions established for aldol reaction were applied to *N*-Ts or *N*-Bn phenylimines, no reaction occurred (Table 1.3.6, Entries 1-2), whereas reaction with *N*-Boc phenylimine afforded only traces of **370** (Entry 3). However, it was found that addition of $BF_3{\cdot}OEt_2$ after introduction of the imine resulted in conversion into 30% of the desired **370** as a mixture of diastereoisomers (d.r. = 1.7:1) along with 25% of other unidentified compounds (Entry 5).[163] Replacing $BF_3{\cdot}OEt_2$ with Ti(O*i*-Pr)$_4$ only led to formation of traces of **370** (Entry 6).

Table 1.3.6. Mannich reaction *via* generation of boron enolate of **281**.



Entry	R	Lewis acid (equiv)	Conditions imine addition	Result[a]
1	Bn	none	–45 °C to 0 °C, 2 h	no reaction
2	Ts	none	–45 °C to 0 °C, 2 h	no reaction
3	Boc	none	–45 °C to 0 °C, 2 h	traces of **370** (< 5%)
4	Ts	$BF_3{\cdot}OEt_2$ (2.0)	–45 °C, 4 h	no reaction
5	Boc	$BF_3{\cdot}OEt_2$ (2.0)	–45 °C, 4 h	**370** (ca. 30%, d.r. = 1.7:1) + 25% side products
6	Boc	Ti(O*i*-Pr)$_4$ (2.0)	–45 °C, 4 h	traces of **370** (< 10%)

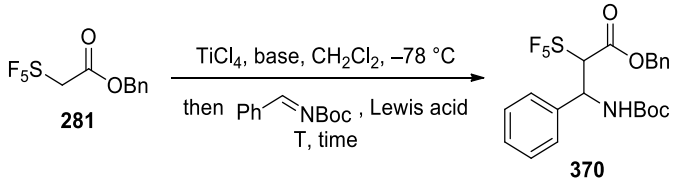
a) Conversions determined by ^1H and ^{19}F NMR analyses of the crude material.

At the same time, extensive investigation involving the use of other soft enolates of benzyl SF_5-acetate **281** was conducted. Promising results were obtained when the corresponding titanium enolate was formed (Table 1.3.7). Treatment of **281** with $TiCl_4$ followed by addition of base at –78 °C resulted in a color change of the reaction mixture to dark red, attributed to the generation of the corresponding enolate. Subsequent addition of *N*-Boc phenylimine had no effect without additional Lewis acid or when DIPEA was used as base (Entries 1-3). However,

[163] Assignment of the diastereoisomers could not be performed.

the enolate generated from Et_3N added to the imine in presence of Ti(O*i*-Pr)$_4$ with 53% conversion (Entry 4). No reaction was observed when *N*-Ts or *N*-Bn phenylimines were used as electrophiles. Interestingly when the titanium enolate was treated with benzaldehyde, no aldol reaction occurred. Increasing the reaction time and keeping the reaction temperature at –78 °C resulted in a cleaner reaction with better conversion (Entry 5). On the other hand, higher amount of Lewis acid decreased the conversion to ca. 50% (Entry 6).

Table 1.3.7. Mannich reaction *via* generation of titanium enolate of **281**.[a]



Entry	$TiCl_4$ (equiv)	Base (equiv)	Lewis acid (equiv)	Conditions imine addition	Result[b]
1	1.2	DIPEA (1.4)	none	–78 °C to r.t, 4 h	no reaction
2	1.2	Et_3N (1.4)	none	–78 °C to r.t, 4 h	no reaction
3	1.2	DIPEA (1.4)	Ti(O*i*-Pr)$_4$ (1.2)	–78 °C to r.t, 4 h	no reaction
4	1.2	Et_3N (1.4)	Ti(O*i*-Pr)$_4$ (1.2)	–78 °C to r.t, 4 h	**370** (53%, d.r. = 3.4:1) + 5% side products
5[c]	1.2	Et_3N (1.4)	Ti(O*i*-Pr)$_4$ (1.2)	–78 °, 15 h	**370** (84%, d.r. = 3.3:1) + 7% side products
6	1.2	Et_3N (1.4)	Ti(O*i*-Pr)$_4$ (3.0)	–78 °, 15 h	**370** (42%, d.r. = 2.5:1) + 7% side products
7	1.2	Et_3N (1.4)	$TiCl_4$ (1.2)	–78 °, 5 h	**273** (ca. 20%)
8	3.5	Et_3N (1.4)	Ti(O*i*-Pr)$_4$ (2.0)	–78 °, 5 h	**370** (<10%); **371** (ca. 50%)
9	6.0	Et_3N (2.0)	Ti(O*i*-Pr)$_4$ (1.2)	–78 °, 1 h	**371** (100%)

a) The titanium enolate was formed by stirring a mixture of $TiCl_4$ and **281** at 0 °C for 10 min, followed by addition of base at –78 °C and additional stirring for 30 min; b) Conversions determined by ^{1}H and ^{19}F NMR analyses of the crude material; c) Enolate was stirred for only 10 min at −78 °C prior to imine addition.

Switching Ti(O*i*-Pr)$_4$ to $TiCl_4$ inhibited formation of the desired Mannich product, and starting material along with 20% of SF_5-acetic acid were observed in the crude material (Entry 7). Interestingly, using an excess of $TiCl_4$ during the enolate formation gave rise to a new compound **371** (Entries 8-9). The latter, which could be isolated as a colorless liquid by column chromatography, is believed to be the alkylidenesulfur tetrafluoride compound emanating from HF elimination from **281** (Figure 1.3.2, A). The ^{1}H and ^{19}F spectra of the isolated product corroborated this assumption. In the ^{1}H NMR spectrum, the signal multiplicity for the methine

proton (δ = 4.03 ppm) is a ddt: two doublets by coupling with F_c and F_d (J = 39.3 Hz, 12.2 Hz), and a triplet by coupling with F_a and F_b (J = 8.7 Hz). The planar configuration between the methine proton, the carbonyl group, and the two axial fluorine atoms F_c and F_d of such sulfur tetrafluoride compounds has been documented with the low-temperature crystal structure analysis of the corresponding fluorocarbonylmethylidenesulfur tetrafluoride.[131b] Moreover, comparison of ^{19}F NMR analyses of **371** and ethylidenesulfur tetrafluoride[131a] revealed spectra with a similar pattern, namely a A_2BC system (Figure 1.3.2, C and D). The coupling constants between axial fluorine atoms and equatorial fluorine atoms are between 160 and 165 Hz, which is in agreement with literature data.[131b] However, doubts are still subsisting about the structure of compound **371** because the corresponding mass could not be detected by HRMS.[164]

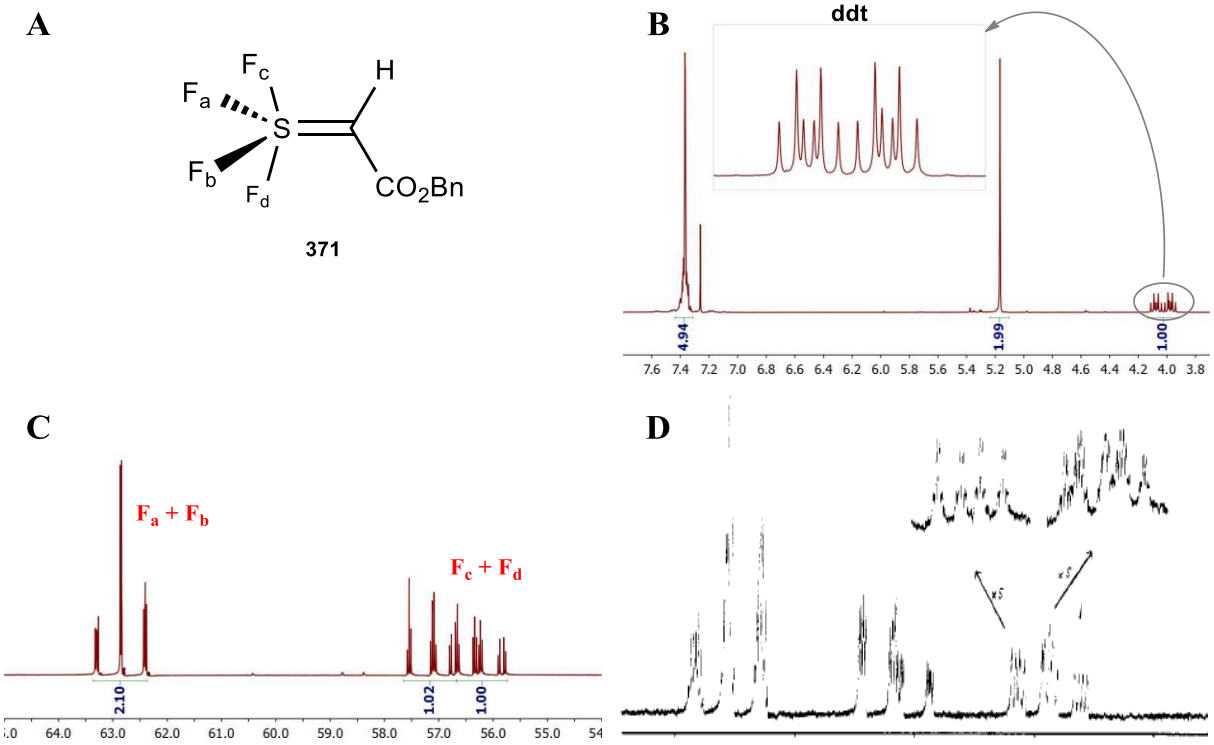


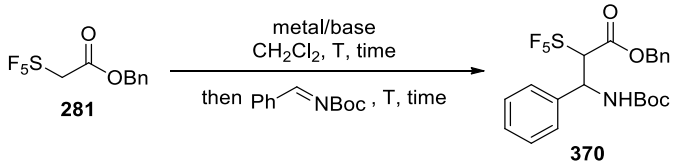
Figure 1.3.2. A: proposed structure for **371**; **B**: ^1H NMR spectrum of **371**; **C**: ^{19}F NMR spectrum of **371**; **D**: ^{19}F NMR spectrum of ethylidenesulfur tetrafluoride (reproduced from ref. 131a with the permission of the publisher American Chemical Society).

Additional experiments for the Mannich reaction *via* generation of tin or magnesium enolates of **281** did not improve of the outcome (Table 1.3.8). Thus, reaction of *N*-Boc phenyl imine with tin *α*-SF_5-enolate prepared with $Sn(OTf)_2$ and Et_3N gave a conversion of only 20% (Entry 1). However, the reaction was cleaner than with the titanium enolate, with no formation of side products observed. Using DIPEA as base, or adding TMSOTf to activate the imine inhibited the reaction (Entries 2-3). On the other hand, the magnesium enolate formed with MgI_2 and Et_3N or

[164] ESI and EI ionization techniques were attempted.

DIPEA as base also gave a cleaner transformation than with the titanium enolate, but with mediocre conversion (Entries 4-5).

Table 1.3.8. Mannich reaction *via* generation of tin and magnesium enolates of **281**.



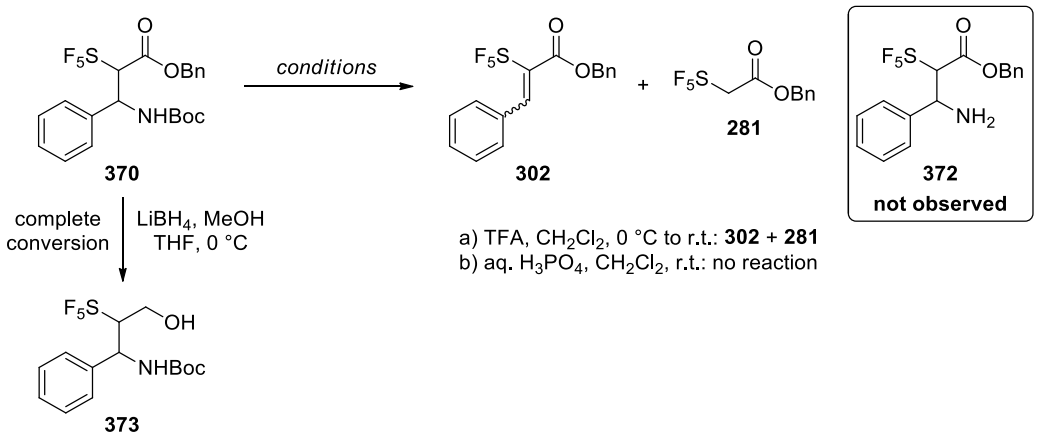
Entry	Metal (equiv)	Base (equiv)	Conditions enolate formation	Conditions imine addition	Result[a]
1	$Sn(OTf)_2$ (1.2)	Et_3N (1.4)	–78 °C, 0.5 h	–78 °C to r.t., 15 h	**370** (17%, d.r. = 1.8:1)
2	$Sn(OTf)_2$ (1.2)	DIPEA (1.4)	–78 °C, 0.5 h	–78 °C to r.t., 15 h	no reaction
3[b]	$Sn(OTf)_2$ (1.2)	Et_3N (1.4)	–78 °C, 0.5 h	–78 °C to r.t., 15 h	no reaction
4	MgI_2 (1.4)	Et_3N (1.6)	–45 °C, 0.5 h	–45 °C to r.t., 15 h	**370** (30%, d.r. = 4:1)
5	MgI_2 (1.4)	DIPEA (1.6)	–45 °C, 0.5 h	–45 °C to r.t., 15 h	**370** (17%, d.r. = 16:1)

a) Conversions determined by ^1H and ^{19}F NMR analyses of the crude material; b) TMSOTf (1.1 equiv) was added after addition of imine.

Unfortunately, at this time, ABCR announced that they could not furnish the SF_5Cl reagent anymore due to a stock shortage for an undetermined period of time. Therefore, we were unable to achieve additional optimization of the Mannich reaction, or to carry on the reaction with the best conditions identified (Table 1.3.7, Entry 5) on a scale large enough to obtain a relevant isolated yield.

However, by combining all the material obtained during the investigation of the Mannich reaction, we could briefly explore the reactivity of Mannich adduct **370** (Scheme 1.3.37). Attempts of *N*-Boc deprotection were fruitless. Indeed, employing TFA gave a mixture of elimination product **302** and retro-Mannich product **281**. On the other hand, **370** did not react with milder deprotection conditions using aqueous phosphoric acid.[165] Therefore, we next turned our attention to the identification of suitable conditions for the reduction of the ester. While $LiAlH_4$ resulted in decomposition of the material, we found that amino alcohol **373** could be obtained with full conversion using $LiBH_4$ and MeOH in THF at 0 °C. Interestingly, when the pure major diastereoisomer of **370** was used as starting material, a mixture of diastereoisomers of **373** (d.r. = 4.9:1) was obtained, suggesting partial epimerization prior to the reduction.

[165] B. Li, M. Berliner, R. Buzon, C. K. F. Chiu, S. T. Colgan, T. Kaneko, N. Keene, W. Kissel, T. Le, K. R. Leeman, B. Marquez, R. Morris, L. Newell, S. Wunderwald, M. Witt, J. Weaver, Z. J. Zhang, Z. L. Zhang, *J. Org. Chem.* **2006**, *71*, 9045-–050.



Scheme 1.3.37. Attempted *N*-Boc deprotection and reduction of **370**.

Further exploration of the reactivity of **373** in order to prepare 3-SF_5-azetidines could not be achieved because of the stock shortage of SF_5Cl. One option could be to close the ring under Mitsunobu conditions, since the synthesis of four-membered *N*-heterocycles using this strategy has already been reported.[166]

1.3.4. Evaluation of the Physicochemical Properties

In order to assess the effect of the pentafluorosulfanyl group on the synthesized heterocycles, we measured several physicochemical parameters of 3-SF_5-quinoline (**349**), 3-SF_5-quinolin-2-one (**312**), and 3-SF_5-pyrid-2-one (**354**).[167] As previously explained, the SF_5 group is considered as a bioisostere of CF_3 and *t*-Bu groups.[58-62] Therefore, it would be interesting to compare the collected data for these three SF_5 heterocycles to those of their CF_3 and *t*-Bu analogues (Figure 1.3.3).[168] While comparative evaluations of the properties between CF_3-, *t*-Bu- and SF_5-substituted compounds have been previously reported with aromatic compounds, it is the first time that such analysis is perfomed with heterocycles.

[166] For examples, see: (a) M. M. Meloni, M. Taddei, *Org. Lett.* **2001**, *3*, 337–340; (b) W. P. Malachowski, C. Tie, K. Wang, R. L. Broadrup, *J. Org. Chem.* **2002**, *67*, 8962–8969; (c) T. B. Durham, M. J. Miller, *J. Org. Chem.* **2003**, *68*, 35–42; (d) R. Angelaud, Y. L. Zhong, P. Maligres, J. Lee, D. Askin, *J. Org. Chem.* **2005**, *70*, 1949–1952; (e) H. Bittermann, P. Gmeiner, *J. Org. Chem.* **2006**, *71*, 97–102; (f) M. Bouazaoui, J. Martinez, F. Cavelier, *Eur. J. Org. Chem.* **2009**, 2729–2732; (g) Y. J. Xu, G. Lu, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2009**, *48*, 3353–3356.

[167] These measurements were performed at F. Hoffmann-La Roche in Basel, under the supervision of Dr. Jean-Marc Plancher.

[168] **378** was purchased from Fluorochem; for details about the preparation of **374**, **375**, **376**, **377** and **379**: see experimental part.

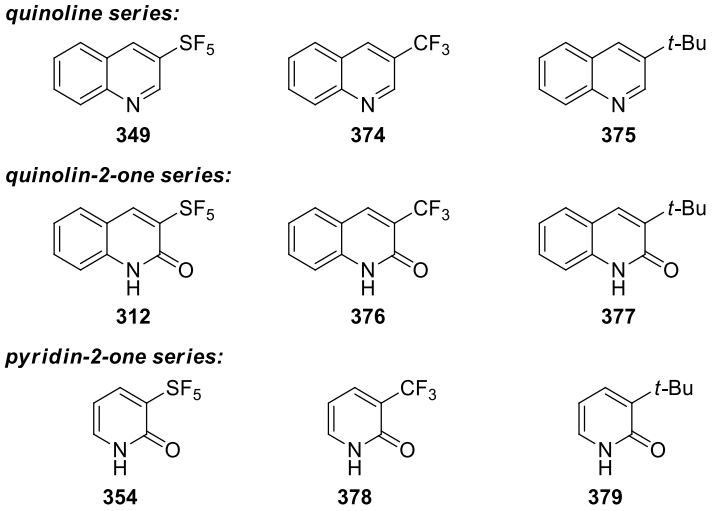
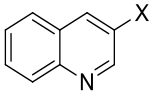


Figure 1.3.3. Compounds studied for the comparative evaluation of the physicochemical properties.

1.3.4.1. Quinolines

The physicochemical properties determined for the three quinolones are presented in Table 1.3.9. Unfortunately, the lipophilicity of SF_5, CF_3 and *t*-Bu quinoline could not be compared, because measures of the log *D* for **349** and **374** failed. Moreover, the membrane permeability of **374** could not be determined because of its low UV absorption. However PAMPA values obtained for **349** and **375** showed that the *t*-Bu analogue exhibits a higher permeability than the SF_5 compound. The change in pK_a highlights the high electronegativity of the SF_5 group compared to the CF_3 group.

Table 1.3.9. Measured physicochemical properties of quinoline series.



Compound	Log *D*[a]	PAMPA[b]	PAMPA Details[c]	pK_a[d]
349 (X = SF_5)	n/a[g]	4.16±1.12	11; 86; 2	1.59±0.01
374 (X = CF_3)	n/a[g]	n/a[h]	n/a[h]	2.47±0.01
375 (X = *t*-Bu)	2.95±0.08	8.71±1.49	9; 88; 3	5.37±0.02
Compound	**LYSA[e]**	**hCl[f]**	**mCl[f]**	**rCl[f]**
349 (X = SF_5)	< 0.1	47±17	23±10	45±8
374 (X = CF_3)	< 0.1	46±12	26±10	43±17
375 (X = *t*-Bu)	< 0.1	87±8	34±11	52±9

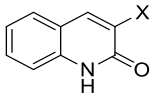
a) Log *D* = intrinsic distribution coefficient between octanol and aqueous buffer (pH = 7.4); b) Membrane permeability ($nm \cdot s^{-1}$) as derived from the parallel artificial membrane permeability assay (PAMPA); c) PAMPA retention values (%): in donor compartment; in membrane; in acceptor compartment; d) Acidities of the conjugate ammonium determined spectrophotometrically at 23±1 °C; e) Solubility ($mg \cdot L^{-1}$) determined by lyophilization solubility assay (LYSA) at pH 6.5; f) Metabolic stability; values describe intrinsic clearance ($\mu M \cdot min^{-1} \cdot mg^{-1}$) in human (h), mouse (m), and rat (r) microsomes; g) Out of range (no MS peak detected); h) UV absorption too low.

The effect of these three substituents on the solubility in water could not be evaluated with quinolines, as the values were too low to be measured. Intrinsic clearances in human, mouse and rat microsomes were also measured in order to assess the metabolic stability of these compounds. The three quinoline derivatives display comparable metabolic stability in mouse and rat microsomes. However, the CF_3 and SF_5 analogues possess a lower clearance rate than the *t*-Bu quinoline **375** in human microsomes.

1.3.4.2. Quinolin-2-ones

Table 1.3.10 contains the data collected for the quinolin-2-one series. The log *D* values illustrate the expected lipophilicity of the SF_5 group, higher than CF_3 but lower than *t*-Bu. Interestingly, no correlation between the lipophilicity and the membrane permeability was discerned. Indeed, the values increase in the order SF_5 < *t*-Bu < CF_3. As in the quinoline series, the pK_a values reflect the electron-withdrawing effect of the pentafluorosulfanyl group, with **312** containing the most acidic proton. Moreover, *t*-Bu-quinolin-2-one **377** shows low solubility, whereas introduction of SF_5 or CF_3 considerably increases the LYSA value. Concerning the metabolic stability, the three compounds possess similar intrinsic clearance rates in human and rat microsomes. However, *t*-Bu analogue **377** displays significantly lower stability than its SF_5 and CF_3 counterparts in mouse microsomes.

Table 1.3.10. Measured physicochemical properties of quinolin-2-one series.



Compound	Log *D*[a]	PAMPA[b]	PAMPA Details[c]	pK_a[d]
312 (X = SF_5)	2.80±0.02	4.22±1.61	69; 18; 13	10.30±0.01
376 (X = CF_3)	2.18±0.04	9.32±0.81	68; 2; 28	10.75±0.01
377 (X = *t*-Bu)	3.59±0.02	7.00±0.28	26; 66; 8	> 12.00
Compound	**LYSA[e]**	**hCl[f]**	**mCl[f]**	**rCl[f]**
312 (X = SF_5)	23[g]	44±10	15±8	17±10
376 (X = CF_3)	42±3	42±9	26±6	< 10
377 (X = *t*-Bu)	1.9±0.1	42±13	116±12	16±10

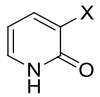
a) Log *D* = intrinsic distribution coefficient between octanol and aqueous buffer (pH = 7.4); b) Membrane permeability ($nm \cdot s^{-1}$) as derived from the parallel artificial membrane permeability assay (PAMPA); c) PAMPA retention values (%): in donor compartment; in membrane; in acceptor compartment; d) Acidities determined spectrophotometrically at 23±1 °C; e) Solubility ($mg \cdot L^{-1}$) determined by lyophilization solubility assay (LYSA) at pH 6.5; f) Metabolic stability; values describe intrinsic clearance ($\mu M \cdot min^{-1} \cdot mg^{-1}$) in human (h), mouse (m), and rat (r) microsomes; g) Measured only once.

1.3.4.3. Pyridin-2-ones

Finally, the physicochemical properties measured for the pyridine-2-one series are compiled in Table 1.3.11. Although the log *D* value for the SF_5-pyridin-2-one **354** could not be

determined, we premised that it is comprised between the values of the CF_3 and *t*-Bu analogues. Contrary to the quinolin-2-one series, the membrane permeability trend corresponds to the supposed lipophilicity with PAMPA values increasing in the order CF_3 < SF_5 < *t*-Bu. It came as no surprise that the p*K*a values of the pyridine-2-ones follow the same inclination that those obtained with quinolin-2-ones, the electronegative SF_5 increasing the acidity of the amide proton in **354**. Moreover, like in the quinolin-2-one series, the *t*-Bu analogue **379** possesses a much lower solubility than the SF_5 and CF_3 analogues. For example, the LYSA value for **354** is four times bigger than for **379**. The three pyridone derivatives display similar intrinsic clearance rates in human microsomes. However, replacement of the *t*-Bu by a CF_3 or SF_5 group improves the stability in mouse and rat microsomes, with clearance rates below 10 $\mu M \cdot min^{-1} \cdot mg^{-1}$.

Table 1.3.11. Measured physicochemical properties of pyridin-2-one series.



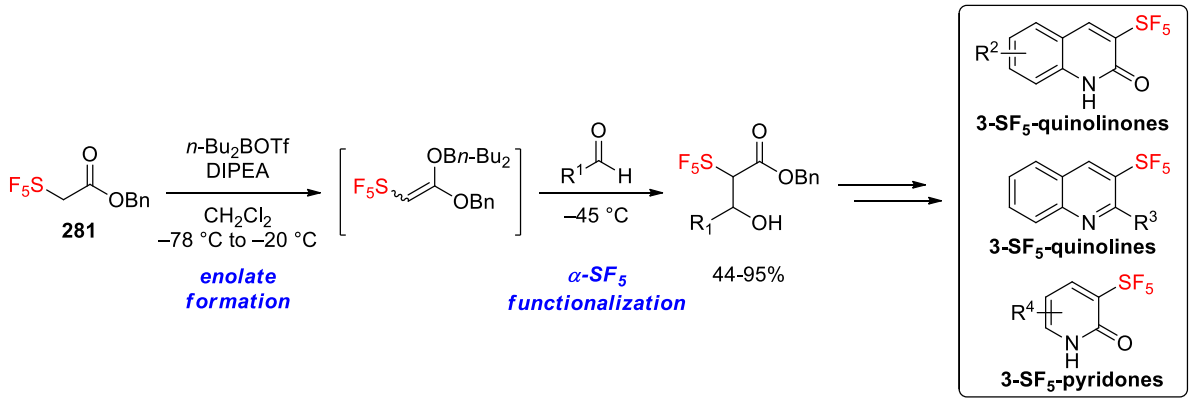
Compound	Log *D*[a]	PAMPA[b]	PAMPA Details[c]	p*K*a[d]
354 (X = SF_5)	n/a[g]	3.78±0.16	85; 0; 15	9.24±0.01
378 (X = CF_3)	0.43±0.06	1.19±0.05	88; 7; 5	9.92±0.01
379 (X = *t*-Bu)	1.87±0.01	13.82±0.04	64; 2; 35	> 12.00
Compound	**LYSA[e]**	**hCl[f]**	**mCl[f]**	**rCl[f]**
354 (X = SF_5)	200±8	< 10	< 10	< 10
378 (X = CF_3)	152±2	< 10	< 10	< 10
379 (X = *t*-Bu)	55±1	12±10	38±7	32±11

a) Log *D* = intrinsic distribution coefficient between octanol and aqueous buffer (pH = 7.4); b) Membrane permeability ($nm \cdot s^{-1}$) as derived from the parallel artificial membrane permeability assay (PAMPA); c) PAMPA retention values (%): in donor compartment; in membrane; in acceptor compartment; d) Acidities determined spectrophotometrically at 23±1 °C; e) Solubility ($mg \cdot L^{-1}$) determined by lyophilization solubility assay (LYSA) at pH 6.5; f) Metabolic stability; values describe intrinsic clearance ($\mu M \cdot min^{-1} \cdot mg^{-1}$) in human (h), mouse (m), and rat (r) microsomes; g) Out of range (no MS peak detected).

1.3.5. Conclusion

In conclusion, we have undertaken studies that culminated in the synthesis of unprecedented SF_5-substituted *N*-heterocycles. Our first approaches *via* direct introduction of the pentafluorosulfanyl group into aryl compounds were met with failure. Therefore, we had to change our strategy and use *de novo* synthesis. After extensive exploration of potential routes for the construction of branched SF_5-compounds, we discovered that a boron enolate in the *α*-position of the SF_5 group could be generated from benzyl SF_5-acetate **281** (Scheme 1.3.38), efficiently prepared in four steps from vinyl acetate on multigram scale. This enolate was then engaged in aldol reactions to achieve *α*-SF_5 functionalization in high yields. By careful choice of the aldehydes used in this transformation, we were able to obtain suitable precursors for the preparation of novel SF_5-heterocyclic compounds, namely 3-SF_5-quinolin-2-ones, 3-SF_5-

quinolines, and 3-SF_5-pyridin-2-ones. Although the obtained α-SF_5-β-hydroxy esters were prone to undergo retro-aldol reactions, we could identify suitable conditions to convert these compounds into the targeted heterocycles. Thus, aldol adducts resulting from the reaction between **281** and 2-nitrobenzaldehydes were submitted to a two-step reduction–cyclization sequence to give 3-SF_5-quinolin-2-ones. Investigation of the reactivity of these compounds led us to achieve further elaboration of 3-SF_5-quinolin-2-one (**312**) to produce a number of 3-SF_5-quinolines. In a similar way, addition of α-SF_5-enolate to aldehyde **360** was the key step for the preparation of 3-SF_5-pyridin-2-ones. These compounds represent the first synthesized members of six-membered *N*-heterocycles with a SF_5 group in *meta*-position.



Scheme 1.3.38. Preparation of 3-SF_5-quinolin-2-ones, 3-SF_5-quinolines, and 3-SF_5-pyridin-2-ones *via* generation of an α-SF_5-enolate.

After the publication of this work, Thrasher, Haufe, and co-workers reported the *anti*-selective aldol reaction of octyl SF_5-acetate mediated by dicyclohexylborane and triethylamine.[169] Although the level of diastereoselectivity obtained was high, the method suffers from low yields for several substrates, in particular aliphatic aldehydes. Moreover, no subsequent downstream chemistry on these aldol adducts was described. It is probable that the choice of the octyl ester hampered the possibility for further synthetic elaboration, and that the authors were confronted with similar obstacles as we met during the course of our studies, associated with the poor stability of the aldol products. In another recent report, Ponomarenko and co-workers described a one-pot preparation of α-SF_5-α-β-unsaturated carbonyl compounds *via* titanium-mediated enolization of methyl SF_5-acetate and subsequent reaction with aldehydes.[170] They also disclosed a few examples where they could isolate the aldol adduct with *syn*-selectivity when the reaction was conducted in CH_2Cl_2.

[169] F. W. Friese, A. L. Dreier, A. V. Matsnev, C. G. Daniliuc, J. S. Thrasher, G. Haufe, *Org. Lett.* **2016**, *18*, 1012–1015.
[170] M. V. Ponomarenko, S. Grabpwsky, R. Pal. G.-V. Röschenthaler, A. A. Fokin, *J. Org. Chem.* **2016**, *81*, 6783–6791.

With several novel SF_5-heterocycles in hand, the influence of the pentafluorosulfanyl group on the physicochemical properties was investigated. Thus, collection of the parameters for 3-SF_5-quinolin-2-one (**312**), 3-SF_5-quinoline (**349**), 3-SF_5-pyridin-2-one (**354**), as well as for their CF_3 and *t*-Bu analogues enabled a direct comparison between these three functional groups (Figure 1.3.4). This unprecedented study on heterocycles confirmed that the pentafluorosulfanyl substituent can be regarded as a surrogate for trifluoromethyl and *tert*-butyl groups with property-modulating effects, due to its high electronegativity combined with high lipophilicity. On the one hand, replacing a *t*-Bu group with a SF_5 group is accompanied by increased polarity and volume reduction, as well as higher solubility and metabolic stability. On the other hand, substituting a CF_3 group with a SF_5 group offers increased lipophilicity and volume augmentation.

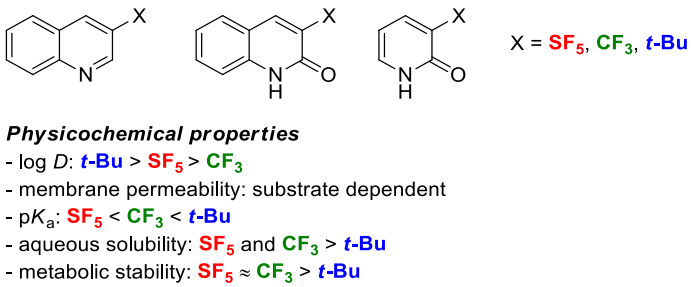


Figure 1.3.4. Comparative study of the physicochemical properties of SF_5-, CF_3- and *t*-Bu-derivatives of quinoline, quinolin-2-one and pyridin-2-one (Adapted from ref. 129 with the permission of the publisher John Wiley and Sons).

We also started to explore the possibility to engage an α-SF_5-enolate in Mannich reactions with the aim to synthesize SF_5-containing four-membered *N*-heterocycles such as 3-SF_5-β-lactams or 3-SF_5-azetidines. Promising results were obtained when titanium enolate was generated. However, further investigation towards the preparation of novel SF_5-heterocycles could not be achieved because of a stock shortage of SF_5Cl reagent at ABCR, which is the only supplier in Europe.

1.4. Conclusion and Outlook

Among the fluorine-containing functional groups, the pentafluorosulfanyl substituent is underrepresented in the various areas of organic chemistry. The main reason for this lack of appearance is the scantiness of efficient methods to prepare SF_5-contaning scaffolds, especially SF_5-heterocycles. However, due to its uncommon combination of properties, the SF_5 group has recently gained increasing attention, and examples of its benefits for bioactive molecules and materials have been reported. Therefore, the development of new protocols for the synthesis of SF_5-building blocks is of high interest. In this regard, the first part of this thesis describes the preparation of a number of unprecedented SF_5-substituted compounds.

Firstly, regioselective iridium-catalyzed C–H borylation afforded a collection of SF_5-substituted potassium aryltrifluoroborates. The synthetic utility of these reagents was illustrated by applying them in Suzuki–Miyaura and in Chan–Lam–Evans cross-coupling reactions, furnishing a library of unprecedented 1,3,5-trisubstituted SF_5-aryl compounds.

We then focused our efforts on the synthesis of novel SF_5-containing *N*-heterocycles. A key feature in this study was the possibility to generate a boron enolate in the α-position of the pentafluorosulfanyl group and its use in aldol reactions. This transformation was applied in short synthetic sequences for the preparation of 3-SF_5-quinolin-2-ones, 3-SF_5-quinolines and 3-SF_5-pyridin-2-ones. This aldol reaction, allowing unprecedented functionalization in the α-position of the SF_5 group, provides new opportunities for the expansion of the pentafluorosulfanyl chemistry. We also opened a way towards the synthesis of 3-SF_5-azetidines and 3-SF_5-β-lactams by using titanium α-SF_5-enolate in Mannich reactions.

In order to assess the impact of the introduction of a SF_5 group into heterocyclic scaffolds, physicochemical parameters of the prepared SF_5 heterocycles were collected and analyzed. A comparison with the properties of the CF_3 and *t*-Bu analogues demonstrated the influence of the pentafluorosulfanyl group. In this respect, the SF_5 group can be considered as a suitable surrogate for these functional groups with potential fine-tuning effect.

The pentafluorosulfanyl group is still emerging, and further breakthroughs in its chemistry, such as an efficient method for direct pentafluorosulfanylation of molecules, are necessary to expect more applications in agrochemicals, pharmaceuticals and materials. Nevertheless, the disclosure of novel strategies to access original scaffolds bearing the pentafluorosulfanyl group as well as a better understanding of its modulating effect on compound properties will encourage scientists to widen its implementation into their research programs.

2

Polycationic Hexasaccharides Derived from α-Cyclodextrin

2. Polycationic Hexasaccharides Derived from α-Cyclodextrin

2.1. Introduction

2.1.1. Polyanionic Hexasaccharides as Heparan Sulfate Mimetics[171]

2.1.1.1. Heparin and Heparan Sulfate

Heparan sulfate is a highly sulfated member of the glycosaminoglycan (GAG) family of polysaccharides, with a structure closely related to heparin.[172] It is biosynthesized as a proteoglycan, consisting of GAG chains covalently linked to a core protein through an *O*-glycosidic bond to a serine residue, and located on cell surface and extracellular matrix.[173] Heparin and heparan sulfate are composed of uronic acid-(1→4)-D-glucosamine repeating disaccharide units, with different levels of sulfation, and where the uronic acid can be an α-L-glucuronic acid (GlcA) or a β-D-iduronic acid (IdoA) (Figure 2.1.1).[172]

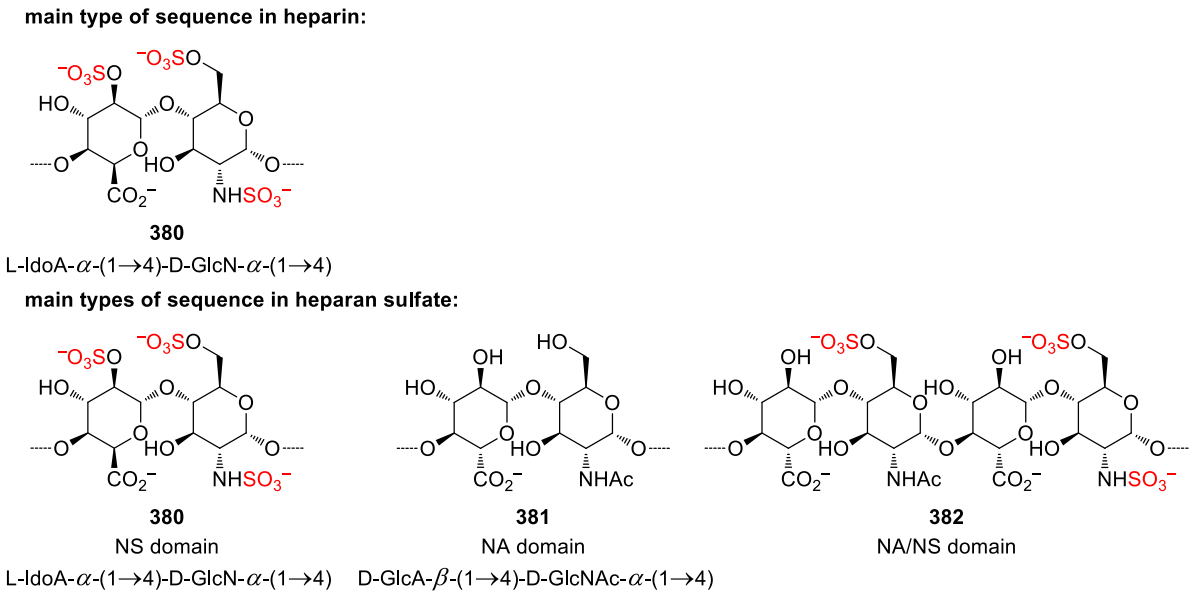


Figure 2.1.1. Most abundant subunits in heparin and heparan sulfate.

The main structural difference between heparin and heparan sulfate is the number of sulfate groups. Indeed, heparin is more sulfated and contains a lower level of acetylated glucosamine

[171] The work presented in this chapter was achieved by Hannes Zipfel in the course of his doctoral studies in the Carreira group; for more details, see: H. F. Zipfel, Diss. ETH No. 23528, pp. 49–108.
[172] (a) For a review about the structure and function of heparin and heparan sulfate, see: D. L. Rabenstein, *Nat. Prod. Rep.* **2002**, *19*, 312–331; (b) U. Lindahl, L. Kjellen, *Thromb. Haemost.* **1991**, *66*, 44–48.
[173] (a) R. Sasisekharan, R. Raman, V. Prabhakar, *Annu. Rev. Biomed. Eng.* **2006**, *8*, 181–231; (b) N. S. Gandhi, R. L. Mancera, *Chem. Biol. Drug Des.* **2008**, *72*, 455–482.

than heparan sulfate. Moreover, L-iduronic acid constitutes up to 90% of the uronic acid residues in heparin. In a distinct way, heparan sulfate displays different distributions of disaccharide units. Indeed, heparan sulfate chains consist of three different types of region: 1) Highly sulfated, heparin-like sequences (NS domains); 2) Non-sulfated GlcA-(1→4)-GlcNAc (acetylated glucosamine) sequences (NA domain), which are the most abundant; 3) Sequences alternating *N*-acetylated and *N*-sulfated residues (NA/NS domains). Other modifications are also found to a lesser extent, such as sulfation at 3-position.[174]

Heparan sulfate proteoglycans play a key role in a wide range of biological functions, such as signal transduction,[175] regulation of cell growth,[176] cell proliferation,[177] developmental processes,[177] blood coagulation,[178] or angiogenesis.[179] The heparan sulfate chains of heparan sulfate proteoglycans can bind to proteins by electrostatic interactions between the anionic sites on heparan sulfates and cationic ammoniums, guanidinium and imidazolium residues on proteins. Glycosaminoglycans are also involved in infection by pathogens (bacteria, viruses, parasites) as they facilitate the specific interaction between host and pathogen.[180] These interactions arise from pathogen surface proteins capable of binding with glycosaminoglycan proteoglycans, which act as coreceptors on host cell surfaces.[181]

2.1.1.2. Role of Heparan Sulfate in HIV-1 Infection Cycle.

The first step of the human immunodeficiency virus (HIV-1) replication cycle is the binding and entry into the host cell ($CD4^+$ T cells and macrophages).[182] This step is mediated by the HIV envelope complex consisting of the surface trimer glycoprotein gp120 and the transmembrane glycoprotein gp41, which are bound in a non-covalent way (Figure 2.1.2). Firstly, attachment of the gp120 to a surface CD4 receptor triggers important structural modifications in the envelope protein, involving extension of the variable loop V3 and shifts of variable loops V1 and V2. This event induces exposure of a new region called CD4 induced epitope (CD4i), which establishes a binding site for a surface chemokine receptor (CCR5 or CXCR4) together with the relocated V3 loop. Then exposure of the gp41 leads to fusion of the virus with the host cell membrane.

---

[174] J. D. Esko, U. Lindahl, *J. Clin. Invest.* **2001**, *108*, 169–173.
[175] U. Hacker, K. Nybakken, N. Perrimon, *Nat. Rev. Mol. Cell. Bio.* **2005**, *6*, 530–541.
[176] M. Lyon, J. T. Gallagher, *Matrix Biol.* **1998**, *17*, 485–493.
[177] N. Perrimon, M. Bernfield, *Nature* **2000**, *404*, 725–728.
[178] J. Liu, L. C. Pedersen, *Appl. Microbiol. Biotechnol.* **2007**, *74*, 263–272.
[179] R. V. Iozzo, J. D. San Antonio, *J. Clin. Invest.* **2001**, *108*, 349–355.
[180] (a) R. S. Aquino, E. S. Lee, P. W. Park, *Prog. Mol. Biol. Transl. Sci.* **2010**, *93*, 373–394; (b) E. Kamhi, E. J. Joo, J. S. Dordick, R. J. Linhardt, *Biol. Rev.* **2013**, *88*, 928–943.
[181] A. H. Bartlett, P. W. Park, *Expert Rev. Mol. Med.* **2010**, *12*, e5.
[182] (a) A. Engelman, P. Cherepanov, *Nat. Rev. Microbiol.* **2012**, *10*, 279–290; (b) C. B. Wilen, J. C. Tilton, R. W. Doms, *Cold Spring Harb. Perspect. Med.* **2012**, *2*, a006866.

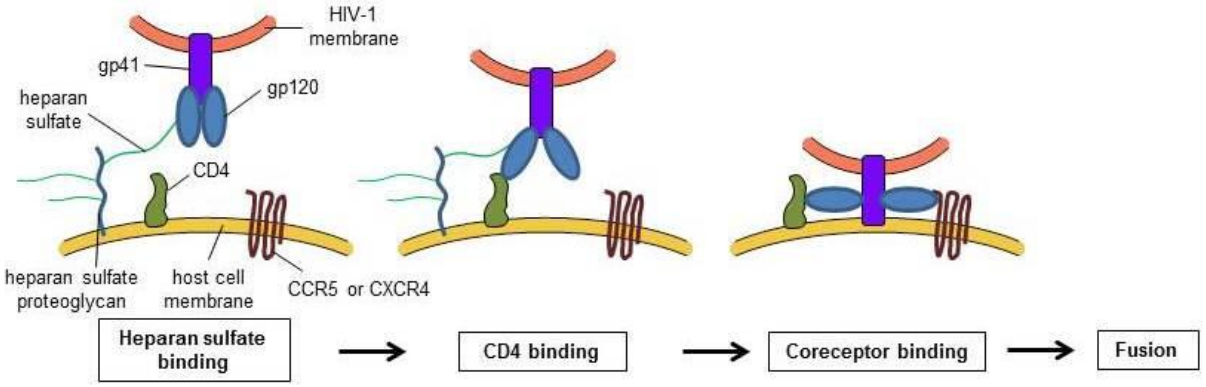


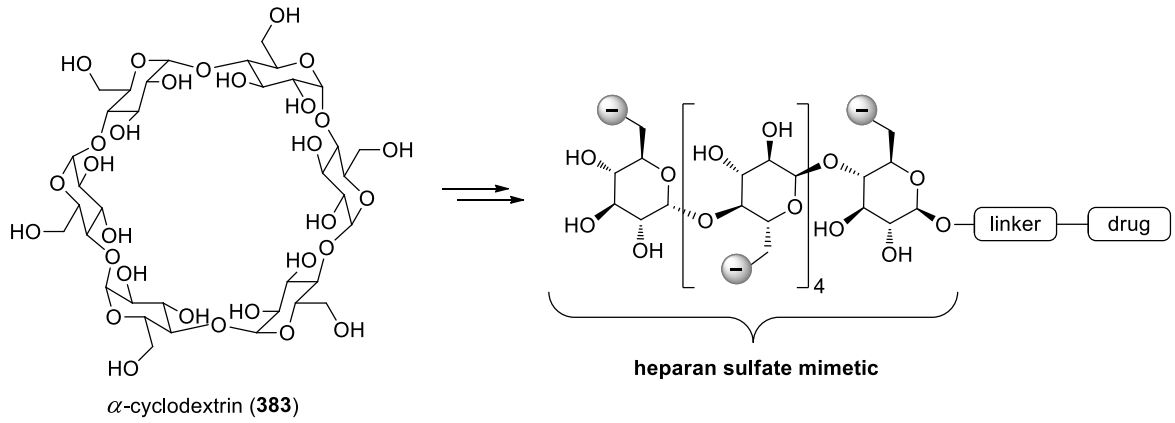
Figure 2.1.2. HIV-1 entry mechanism.

It has been suggested that heparan sulfate proteoglycans also interact with HIV-1, prior to CD4 recognition.[183] This binding promotes pathogen infection by concentrating the virions at the cell surface.[184] Moreover, it was shown that heparan sulfate binds to the V3 domain of gp120 and that heparan sulfate oligosaccharides can compete with cell surface heparan sulfates.[185] Based on these observations, Lortat-Jacob and co-workers developed a CD4 mimetic peptide linked to a heparan sulfate dodecasaccharide (HS_{12}) which can bind to gp120, exposing the CD4i domain subsequently blocked by the HS_{12}.[186] This compound displayed high activities against several HIV strains with doses causing 90% inhibition (ED_{90}) ranged from 3 nM to 11 nM. Interestingly, the activities of the CD4 mimetic peptide alone and of the HS_{12} alone were weaker, demonstrating the importance of the multivalent binding. In a recent paper,[187] the same research group showed that the replacement of the difficult to prepare HS_{12} by a mimetic anionic peptide led to similar antiviral activities.

2.1.1.3. Synthesis of Polyanionic Hexasaccharides

The chemical synthesis of structurally defined heparan sulfates and of glycosaminoglycans in general, remains extremely complex.[188] It relies on a large number of steps, because of the successive glycosylation reactions, combined with the related protecting group manipulations. In addition, their preparation is associated with low selectivities leading to low yields and tedious separation processes. In this context, Zipfel and Carreira investigated the preparation of glycosaminoglycan mimetic polyanionic hexasaccharides from α-cyclodextrin (Scheme 2.1.1).

[183] B. J. Connell, H. Lortat-Jacob, *Front. Immunol.* **2013**, *4*, 00385.
[184] A. C. S. Saphire, M. D. Bobardt, Z. Zhang, G. David, P. A. Gallay, *J. Virol.* **2001**, *75*, 9187–9200.
[185] (a) G. Roderiquez, T. Oravecz, M. Yanagishita, D. C. Bouhabib, H. Mostowski, M. A. Norcross, *J. Virol.* **1995**, *69*, 2233–2239; (b) R. R. Vives, A. Imberty, Q. J. Sattentau, H. Lortat-Jacob, *J Biol Chem* **2005**, *280*, 21353–21357.
[186] F. Baleux, L. Loureiro-Morais, Y. Hersant, P. Clayette, F. Arenzana-Seisdedos, D. Bonnaffe, H. Lortat-Jacob, *Nat. Chem. Biol.* **2009**, *5*, 743–748.
[187] B. J. Connell, F. Baleux, Y. M. Coic, P. Clayette, D. Bonnaffe, H. Lortat-Jacob, *Chem. Biol.* **2012**, *19*, 131–139.
[188] For a recent review about the the chemical synthesis og glycosaminoglycans, see: M. Mende, C. Bennarek, M. Wawryszyn, P. Sauter, M. B. Biskup, U. Schepers, S. Bräse, *Chem. Rev.* **2016**, 116, 8193–8255.



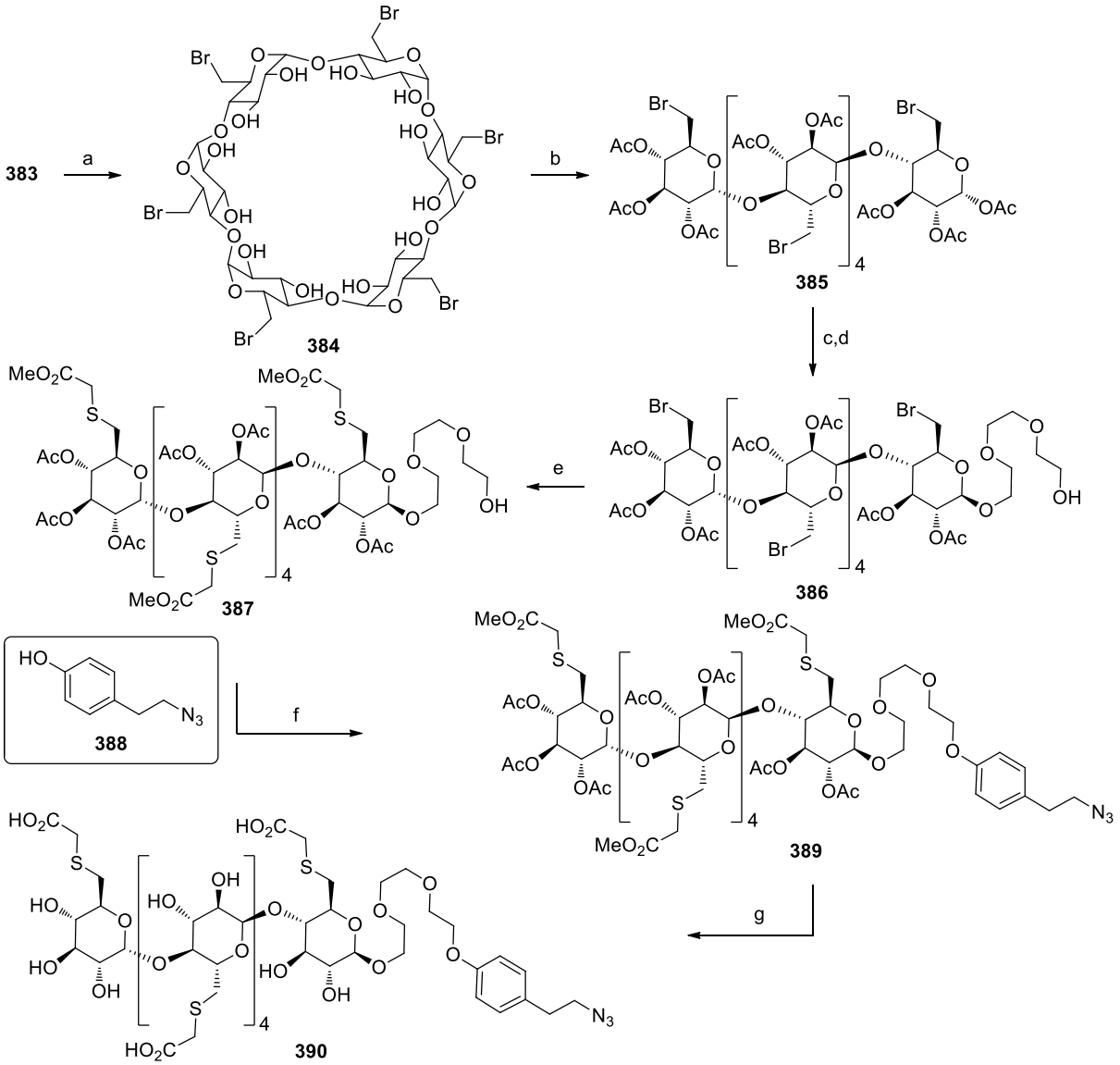
Scheme 2.1.1. Preparation of heparan sulfate mimetic from α-cyclodextrin.

This strategy relied on ring opening and introduction of negatively charged groups at 6-positions and allowed an expeditive synthesis of a heparan sulfate mimetic. The latter was conjugated with known gp120-binding HIV entry inhibitors, as well as biochemical probes *via* a linker.

The synthesis started with hexabromination at 6-positions of α-cyclodextrin using Thatcher's conditions,[189] *via* formation of Vilsmeier reagent,[190] affording **384** in 86% yield (Scheme 2.1.2). Cyclodextrin cleavage was then performed using a modified procedure of the one reported by Vasella.[191] Treatment of **384** with $HClO_4$ in acetic anhydride furnished the peracetylated saccharide **385** predominantly as its α-anomer. Due to additional cleavage, the product was obtained as a mixture of oligomers (hexa-:penta-:tetra-:tri-:disaccharide = 68:9:9:7:7), as determined by LC-MS. After extensive experimentation, the anomeric bromide was identified as the best glycosyl donor for the subsequent glycosylation step. Therefore, after bromination using an excess of HBr in AcOH, glycosylation of triethyleneglycol was achieved using $ZnBr_2$ as promoter in presence of 4 Å molecular sieves to give glycoside **386** in 34% yield. Nucleophilic displacement of the primary bromides with methyl-2-mercaptoacetate was performed to install the protected carboxylic acids, which later play the role of the negatively charged functional groups. In order to implement a site for conjugation with drugs or probes, introduction of an azide functionality at the terminal position of the linker was achieved by Mitsunobu reaction with phenol **388**. At this stage the fully protected compound was still a mixture of oligomers (hexa-:penta-:tetra-:tri-:di-:monosaccharide = 59:13:12:10:5:1). Purification by preparative HPLC afforded pure hexasaccharide **389** in 30% yield. Finally, global hydrolysis afforded

[189] D. Vizitiu, C. S. Walkinshaw, B. I. Gorin, G. R. J. Thatcher, *J. Org. Chem.* **1997**, *62*, 8760–8766.
[190] D. R. Hepburn, H. R. Hudson, *J. Chem. Soc., Perkin Trans. 1* **1976**, 754–757.
[191] B. Hoffmann, D. Zanini, I. Ripoche, R. Burli, A. Vasella, *Helv. Chim. Acta* **2001**, *84*, 1862–1888.

clickable heparan sulfate mimetic **390**, which was used without any further purification in the subsequent conjugations.



Scheme 2.1.2. Synthesis of heparan sulfate mimetic anionic hexasaccharide. Reagents and conditions: a) Br_2 (15 equiv), Ph_3P (15 equiv), DMF, 75 °C, 14 h, 86%; b) $HClO_4$ (8.3 equiv), Ac_2O, r.t., 24 h, 62%; c) 30% HBr in AcOH (108 equiv), DCE, r.t., 45 min; d) triethyleneglycol (7.0 equiv), $ZnBr_2$ (11.0 equiv), 4 Å MS, DCE, r.t., 18 h, 34% (2 steps); e) methyl-2-mercaptoacetate (30 equiv), Et_3N (20 equiv), DMF, 60 °C, 40 h, 86%; f) **388** (6.0 equiv), Ph_3P (3.0 equiv), DEAD (3.0 equiv), 0 °C to r.t., 2 h, 30% after preparative HPLC; g) MeONa (50 equiv), THF, 0 °C, 2 min, then dropwise addition of H_2O, r.t., 4 h, then AcOH (200 equiv).

Conjugation with probes for chemical biology and with HIV entry inhibitors was achieved by a copper-free variant of the azide–alkyne cycloaddition.[192] Therefore, strained cyclooctyne derivatives were used as the alkyne partners in the click reaction with hexasaccharide **390**. In this way, four heparansulfate mimetic–HIV entry inhibitor conjugate were prepared by treating

[192] J. C. Jewett, C. R. Bertozzi, *Chem. Soc. Rev.* **2010**, *39*, 1272–1279.

390 with compounds **391**, **392**, **393** and **394** (Figure 2.1.3). The biological activity of these compounds is currently under investigation. Moreover, biochemical probes such as a biotin, a fluorescent dye and a photoaffinity label were also attached to the heparan sulfate mimetic with the same method.

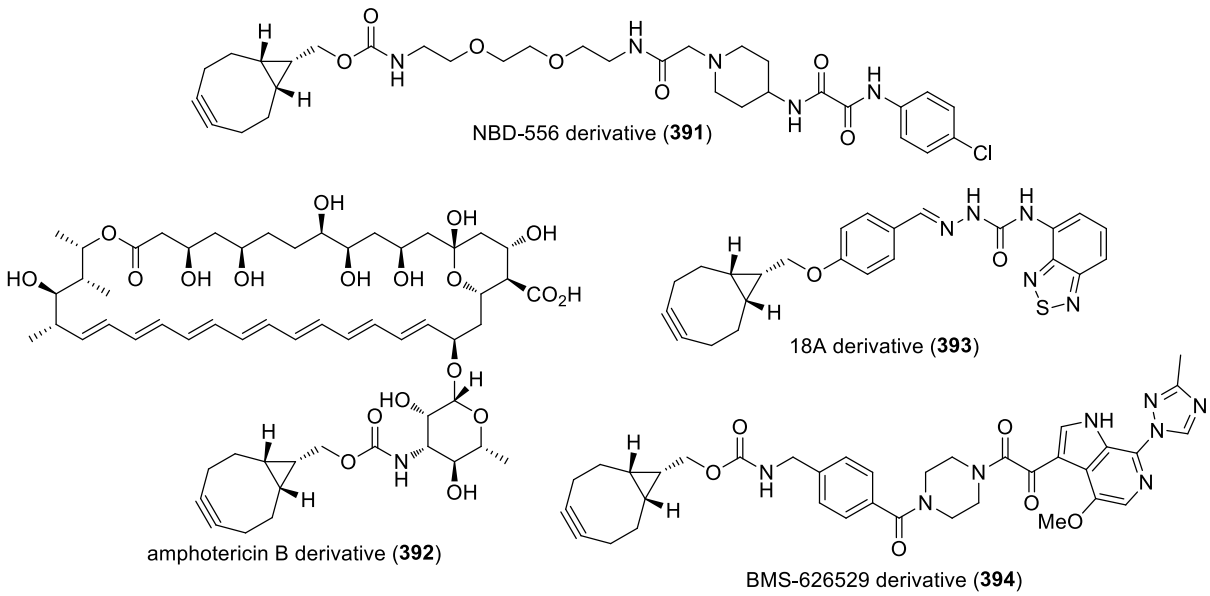
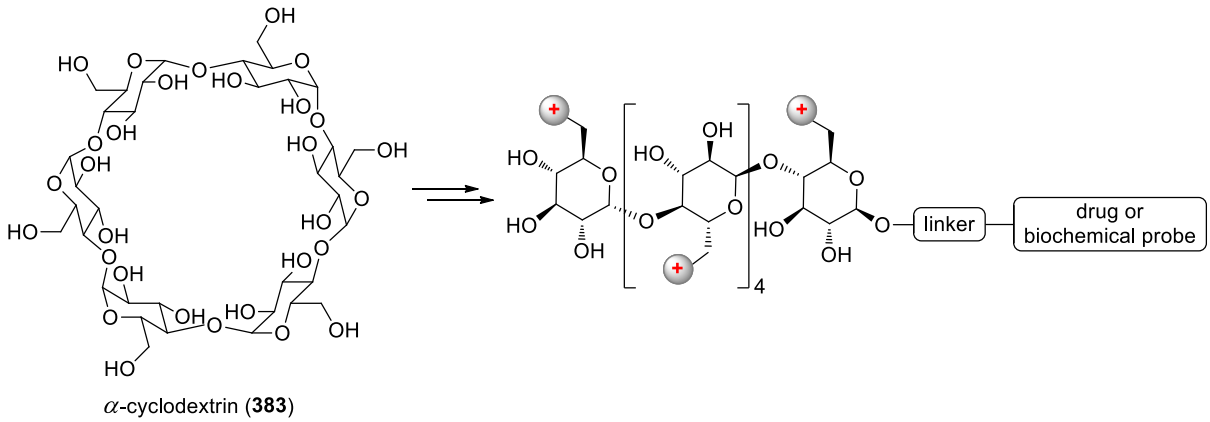


Figure 2.1.3. HIV entry inhibitors conjugated to heparan sulfate mimetic **390**.

2.1.2. Polycationic Hexasaccharides as Potential Carrier in Adsoptive-Mediated Transcytosis

Following the development of this fast and chemically robust method for the synthesis of negatively charged hexasaccharides, we explored the possibility of taking advantage of the same strategy to prepare the oppositely charged cationic hexasaccharides (Scheme 2.1.3).



Scheme 2.1.3. Preparation of polycationic hexasacharides from α-cyclodextrin.

The preparation of well-defined polycationic hexasaccharides could lead to several applications by targeting negatively charged biomolecules. For example, one possibility would be to use them as carriers in adsorptive-mediated transcytosis.

A big challenge in the development of therapeutics for brain diseases is penetration of the blood-brain-barrier (BBB).[193] The BBB is formed by tightly joined endothelial cells preventing the uncontrolled passage of substances from the circulating blood to the central nervous system (CNS). These substances include invading organisms and unwanted substances, but also drugs for the treatment of CNS associated diseases. Nevertheless, several routes for the transport of molecules through the BBB have been established. Small hydrophilic molecules are able to diffuse through the tight junctions between the endothelial cells, although to only low extent. Small lipophilic molecules can diffuse transcellularly though the membrane. However, transport of other bigger molecules, including proteins,[194] are excluded by diffusion because of their hydrophilicity and high molecular weight. Therefore, other types of transport pathways are involved, such as carrier-mediated transport,[195] receptor-mediated transcytosis,[196]or adsorptive-mediated transcytosis.[197]

Adsorptive-mediated transcytosis is a vesicle-based process relying on electrostatic interactions between a positively charged substance and the negatively charged surface of endothelial cells at the luminal side (Figure 2.1.4). The luminal surface of endothelial cells is decorated with sialo-glycoconjugates and heparan sulfate proteoglycans,[198] providing the anionic sites that can bind to cationic molecules. Endocytosis of the transported molecule in the cell is possible through pits coated with clathrin proteins, or caveolae combining caveolin proteins and lipids. Then formation of vesicle and transport of the cationized molecule across the BBB take place. Importantly, anionic sites are also present at the abluminal side of the cell surface, and facilitate the release of the cationic species in the brain interstitium.

[193] For recent reviews about the strategies for CNS drug delivery, see: (a) Y. Chen, L. H. Liu, *Adv. Drug Deliv. Rev.* **2012**, *64*, 640–665; (b) W. A. Banks, *Nat. Rev. Drug Discov.* **2016**, *15*, 275–292.
[194] A. Lalatsa, A. G. Schatzlein, I. F. Uchegbu, *Mol. Pharm.* **2014**, *11*, 1081–1093.
[195] (a) G. Lee, S. Dallas, M. Hong, R. Bendayan, *Pharmacol. Rev.* **2001**, *53*, 569–596; (b) A. Lindqvist, J. Rip, P. J. Gaillard, S. Bjorkman, M. Hammarlund-Udenaes, *Mol. Pharm.* **2013**, *10*, 1533–1541.
[196] W. M. Pardridge, *Int. Congr. Ser.* **2005**, *1277*, 49–62.
[197] For a review about adsoptive-mediated transcytosis, see: F. Herve, N. Ghinea, J. M. Scherrmann, *AAPS J.* **2008**, *10*, 455–472.
[198] A. W. Vorbrodt, *J. Neurocytol.* **1989**, *18*, 359–368.

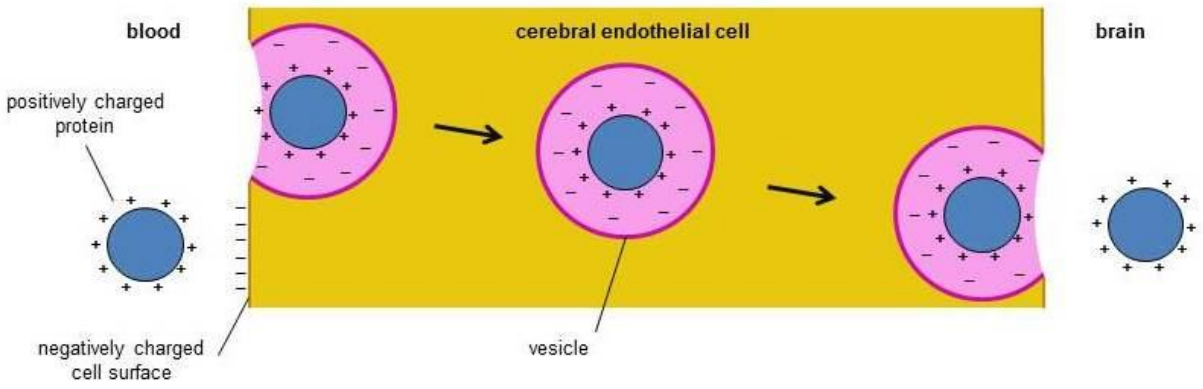


Figure 2.1.4. Transport across the BBB *via* adsorptive-mediated transcytosis.

Since adsorptive-mediated transcytosis is triggered by interaction of cationic molecules with the anionic cell surface, chemical cationization or vectorization with cell-penetrating peptides (CCP) are methods employed for the delivery of peptide drugs to the brain. Cationization of proteins is most commonly done by multiple amidation with diamines.[197,199] However, this process can alter the native conformation of proteins, resulting in loss of their biological activity. Cell-penetrating peptides, or Trojan horse peptides, are short peptides (usually 10-27 amino acid residues) containing a large abundance of positively charged amino acids (lysine or arginine).[197,200] Because of the high density of the capillary network in the brain, it is expected that the surface of the BBB displays a large concentration of negative charges. Nevertheless, one problem that can arise with these methods is the random distribution in the organism because of the anionic sites found in all living cell surfaces. This lack of selectivity can induce toxic effects, and the development of protein-based neurotherapeutics delivery to the brain often requires a case-by-case study.

Moreover, chitosan nanoparticules have been used as delivery system to target the brain.[201] Chitosan is a polysaccharide composed of β-(1→4)-linked acetyl-D-glucosamine and D-glucosamine units (Figure 2.1.5), with variable degrees of *N*-acetylation. It is obtained by deacetylation with NaOH of chitin, a polysaccharide found in the exoskeleton of crustaceans and cell walls of fungi.[202] The amino groups in chitosan are protonated at physiological pH,

[199] (a) J. F. Poduslo, G. L. Curran, *J. Neurochem.* **1996**, *66*, 1599–1609; (b) J. Futami, M. Kitazoe, H. Murata, H. Yamada, *Expert Opin. Drug Discov.* **2007**, *2*, 261–269.
[200] (a) F. Heitz, M. C. Morris, G. Divita, *Brit. J. Pharmacol.* **2009**, *157*, 195–206; (b) S. Reissmann, *J. Pept. Sci.* **2014**, *20*, 760–784.
[201] (a) S. L. Wang, T. Y. Jiang, M. X. Ma, Y. C. Hu, J. H. Zhang, *Int. J. Pharmaceut.* **2010**, *386*, 249–255; (b) B. Wilson, M. K. Samanta, K. Santhi, K. P. S. Kumar, M. Ramasamy, B. Suresh, *nanomedicine* **2010**, *6*, 144–152; (c) C. F. Lien, E. Molnar, P. Toman, J. Tsibouklis, G. J. Pilkington, D. C. Gorecki, E. Barbu, *Biomacromolecules* **2012**, *13*, 1067–1073.
[202] M. Dash, F. Chiellini, R. M. Ottenbrite, E. Chiellini, *Prog. Polym. Sci.* **2011**, *36*, 981–1014.

resulting in possible binding to negatively charged surfaces. Therefore, chitosan-based systems have found several applications in drug delivery.[202,203]

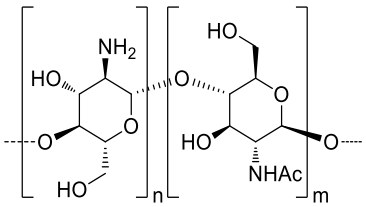


Figure 2.1.5. Structure of chitosan.

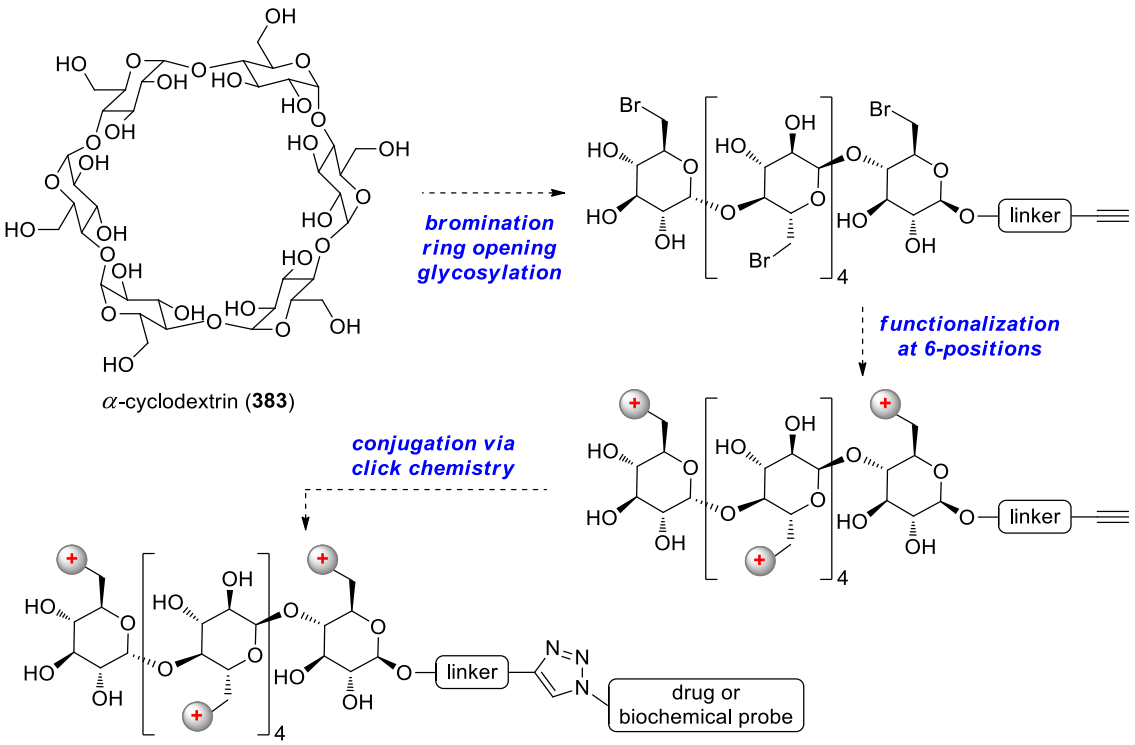
Due to the cationic character of chitosan, it has been hypothesized that it crosses the BBB *via* adsorptive mediated transcytosis.[201c] In the same way that anionic hexasaccharides were expected to be mimetic of heparan sulfates (cf. Chapter 2.1.1), cationic hexasaccharides functionalized with amino groups could be considered as mimetics of chitosan.

Therefore, because they are positively charged, like cationized proteins or cell-penetrating peptides, polycationic hexasaccharides could be tested as carriers of neuropharmaceuticals into the CNS. Importantly, a flexible route to structurally defined compounds would be valuable for structure-activity relationship studies, and would give alternatives to the currently employed transporters.

[203] (a) S. R. Mao, W. Sun, T. Kissel, *Adv. Drug Deliv. Rev.* **2010**, *62*, 12–27; (b) K. Nagpal, S. K. Singh, D. N. Mishra, *Chem. Pharm. Bull.* **2010**, *58*, 1423–1430; (c) A. Bernkop-Schnürch, S. Dünnhaupt, *Eur. J. Pharm. Biopharm.* **2012**, *81*, 463–469.

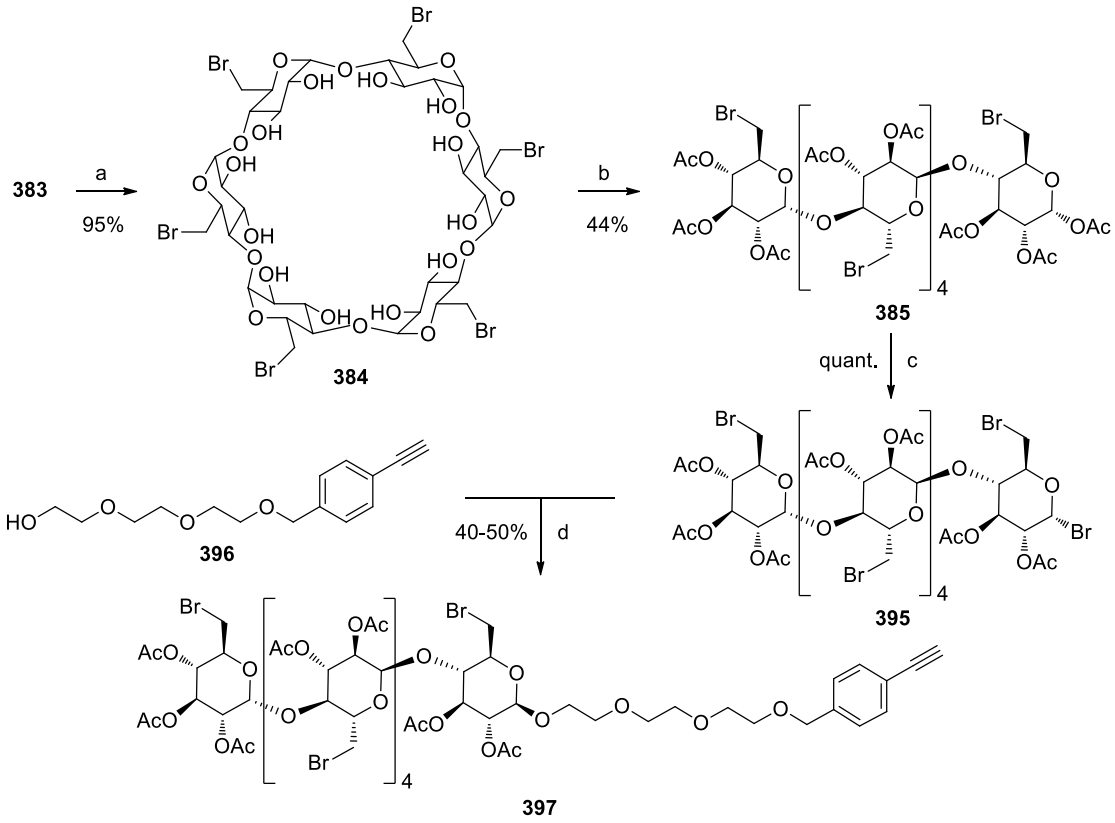
2.2. Synthesis of Polycationic Hexasaccharides

To access polycationic hexasaccharides, we planned to use the same approach as for polyanionic hexasaccharides (cf. Chapter 2.1.1). However, because we anticipated that ammonium hexasaccharides could be obtained by azidation at 6-positions followed by Staudinger reduction, a different linker without a terminal azide function group had to be selected. A linker featuring a terminal alkyne would be ideal, as it would allow conjugation of the hexasaccharide with drugs or biochemical probes *via* click chemistry. Moreover, a common versatile deprotected precursor which already contains the final linker would be desirable, in order to have the possibility of varying the type of cations introduced at 6-positions in a rapid way (Scheme 2.2.1).



Scheme 2.2.1. Synthetic strategy for the preparation of polycationic hexasacharides.

Thus, the synthesis of the opened peracetylated hexasaccharide **385** was performed following the procedure presented in the previous chapter (Scheme 2.2.2). After bromination of *α*-cyclodextrin at 6-positions in high yield, ring-opening was achieved by treatment with $HClO_4$ in acetic anhydride. Although the cleavage was not complete after 24 h, and presence of peracetylated *α*-cyclodextrin was still observed, the reaction was stopped because of competitive extra cleavage resulting in the formation of shorter oligomer. However, careful purification by column chromatography afforded the hexamer **385** in 44% yield as a mixture of anomers, prevailing *α*-stereoisomer (*α*:*β* = 7:1; *α*: $^3J_{H_1H_2}$ = 3.5 Hz; *β*: $^3J_{H_1H_2}$ = 8.0 Hz).



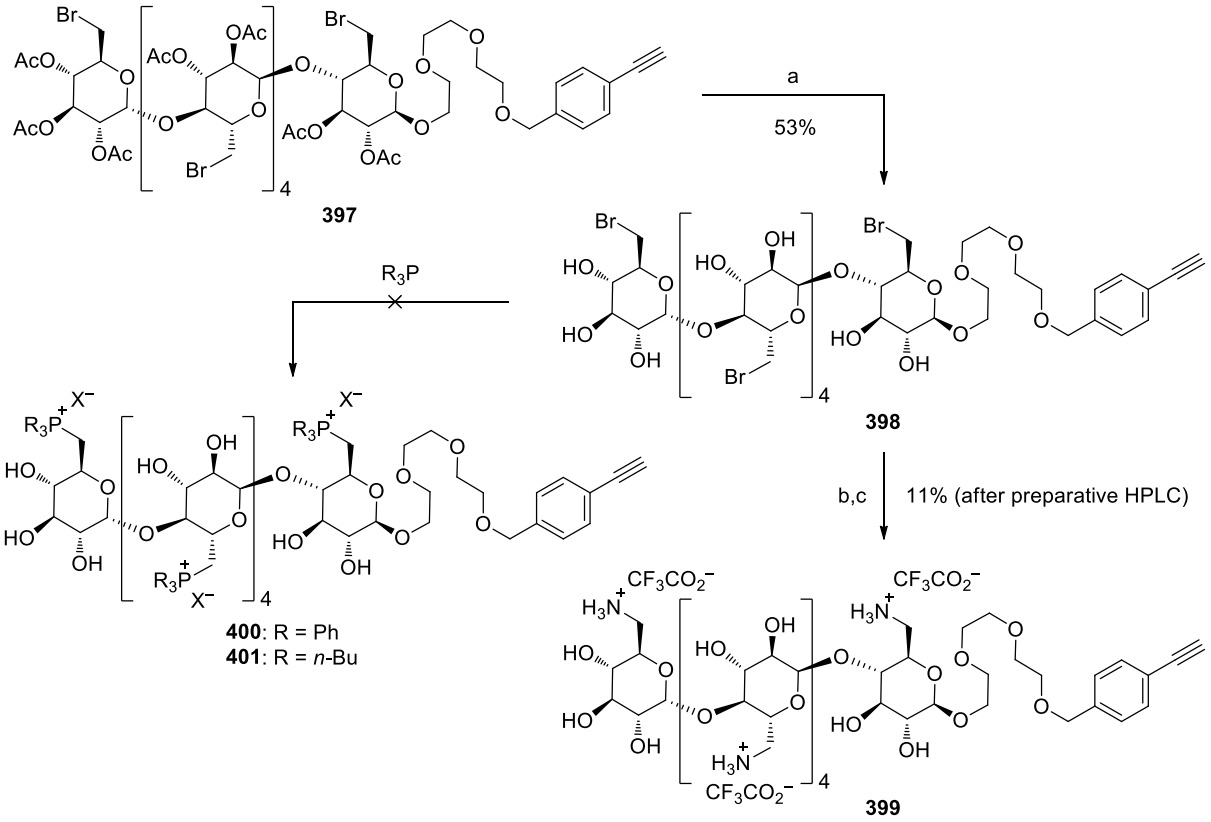
Scheme 2.2.2. Synthesis of glycoside **397**. Reagents and conditions: a) Br_2 (15 equiv), Ph_3P (15 equiv), DMF, 75 °C, 16 h, 95%; b) $HClO_4$ (8.3 equiv), Ac_2O, r.t., 24 h, 44%, α:β = 7:1; c) 30% HBr in AcOH (100 equiv), DCE, r.t., 30 min, quant.; d) **395** (1.5 equiv), $ZnBr_2$ (5.0 equiv), 4 Å MS, DCE, r.t., 16-20 h, 40-50%.

During the course of his studies towards the synthesis of polyanionic hexasaccharides, Zipfel reported the synthesis of glycoside **397** by glycosylation of bromide **395** with alkyne-containing alcohol **396**, albeit in low yield, under the developed optimized conditions using $ZnBr_2$.[171] Indeed, after preparation of α-anomeric **395** ($^3J_{H_1H_2}$ = 4.0 Hz), glycosylation of **396** afforded **397** in only 24% yield as a mixture with the excess of linker, which could not be separated by column chromatography. In addition of the inability to obtain the product in pure form, another identified problem was the additional internal glycosylations, resulting in formation of smaller oligomers, as judged by LC-MS analysis. Therefore, slight modification of the procedure was investigated in order to have access to pure **397** in a reliable and more efficient way. Exchanging the promoter to silver triflate afforded the desired product in only 22% yield.[204] We quickly came back to $ZnBr_2$, and premised that using the linker as limiting reagent with an excess of carbohydrate would reduce undesired sugar cleavage. Moreover, complete consumption of the linker would facilitate the isolation of the hexasaccharide by column chromatography. Indeed, using an excess of **395** (1.5 equiv), in presence of $ZnBr_2$ (5.0 equiv) and molecular sieves led to

[204] Z. C. Pei, H. Yu, M. Theurer, A. Walden, P. Nilsson, M. D. Yan, O. Ramstrom, *ChemBioChem* **2007**, *8*, 166–168.

complete glycosylation of the linker **396**. Shorter oligomers were still formed, albeit at a lower level, and careful purification by column chromatography furnished pure hexamer **397** as the *β*-anomer ($^3J_{H_1H_2}$ = 7.6 Hz) in 40-50% yield.

After successful installation of the linker on the hexasaccharide, we performed hydrolysis of the acetate protecting groups by treatment with sodium methoxide at 0 °C, affording **398** in 53% yield (Scheme 2.2.3).



Scheme 2.2.3. Synthesis of polycationic hexasaccharide **399**. Reagents and conditions: a) MeONa (15.0 equiv), THF/MeOH (2:1), 0 °C, 1 h, then Amberlyst® 15, 53%; b) NaN_3 (12.0 equiv), DMF, 70 °C, 24 h, quant.; c) Ph_3P (9.0 equiv), DMF/H_2O (10:1), r.t. then 70 °C, 24 h, then preparative HPLC, 11%.

With a precursor for insertion of cations at 6-positions in hand, we first investigated the introduction of ammonium groups *via* an azidation–reduction sequence. Analogous functionalization at 6-position of mono- and disaccharides,[205] as well as cyclodextrins,[206] have already been reported. Gratifyingly, azidation of **398** was conducted with success in quantitative yield. The subsequent Staudinger reduction necessitated heating to 70 °C in order to reach full conversion. One problem arose during the purification process: although it was possible to

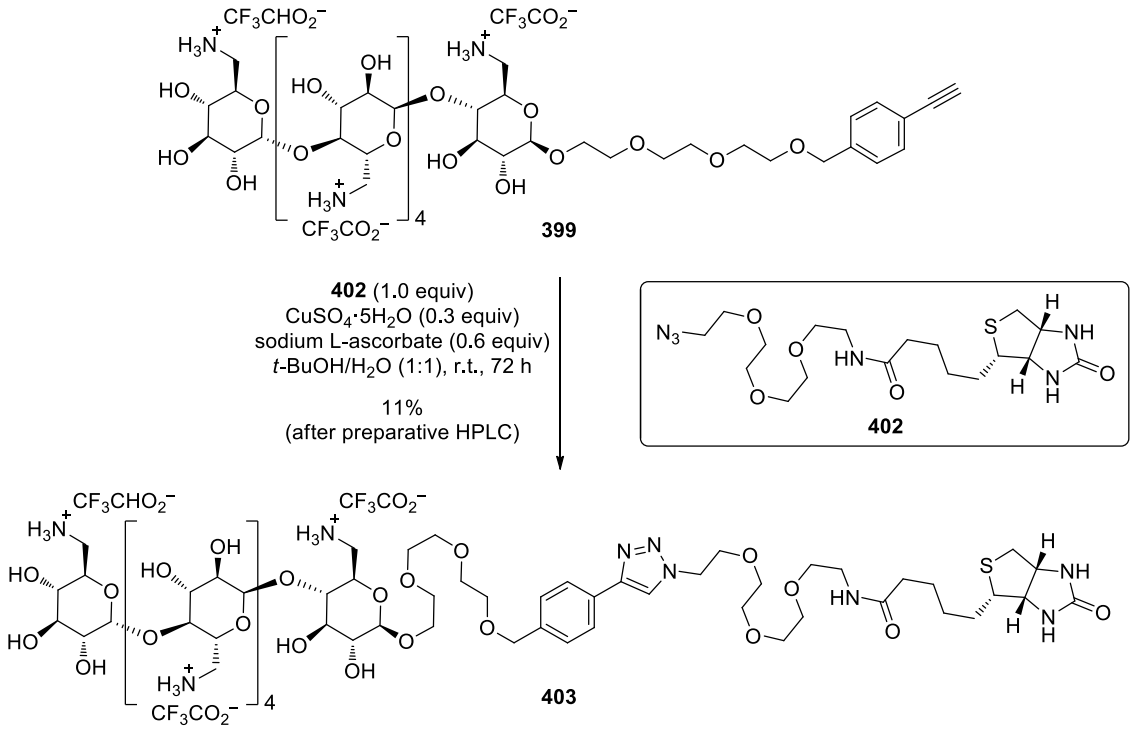
[205] (a) M. V. Reddington, *J. Chem. Soc., Perkin Trans. 1* **1998**, 143–147; (b) S. Fort, V. Boyer, L. Greffe, G. Davies, O. Moroz, L. Christiansen, M. Schulein, S. Cottaz, H. Driguez, *J. Am. Chem. Soc.* **2000**, *122*, 5429–5437; (c) K. Agoston, P. Fugedi, *Carbohydr. Res.* **2014**, *389*, 50–56.
[206] (a) B. I. Gorin, R. J. Riopelle, G. R. J. Thatcher, *Tetrahedron Lett.* **1996**, *37*, 4647–4650; (b) V. Mojr, M. Budesinsky, R. Cibulka, T. Kraus, *Org. Biomol. Chem.* **2011**, *9*, 7318–7326.

identify satisfying conditions for the isolation of **399** by HPLC on analytical scale, switching these conditions to preparative scale led to elution of the majority of the material with the solvent front. Therefore only 11% of pure polycationic hexasaccharide could be collected after one run. The impure part collected with the front solvent could be resubjected to purification in order to gain more material.

We also attempted to synthesize polycationic hexasaccharides containing phosphonium cations. Dondoni and co-workers reported the phosphanation by substitution of iodide with triphenylphosphine at 6-position of monosaccharides in order to use the corresponding phosphonium salts in Wittig reactions.[207] However, treating **398** with an excess of Ph_3P in DMF at 90 °C did not deliver satisfying results. After one week, complete consumption of the starting hexabromide was observed along with formation of the monosubstituted product (detected by MALDI analysis). Longer reaction time led to a complex mixture of products, in which the desired **400** could not be identified. Increasing the temperature up to 130 °C gave a black tar, presumably resulting from polymerization. Addition of NaI to the reaction mixture accelerated the conversion of **398**, but a complex mixture was also obtained. Finally, we tried to use the more nucleophilic *n*-Bu_3P, but similar mixtures were generated with no identification of the desired **401** possible.

Finally, with the targeted hexaammonium saccharide **399** in hand, we investigated its conjugation by click chemistry. As a proof of concept, we chose to install a biotin label, widely used in molecular biology because of its strong affinity with streptavidin and its homologs.[208] For example, proteins binding to cationic polysaccharide **399** could be identified *via* detection using streptavidin coated solid supports. Copper-catalyzed cycloaddition reaction of **399** with biotin azide **402** was performed using copper sulfate and sodium ascorbate in a mixture of *t*-BuOH and H_2O at room temperature (Scheme 2.2.4). The conversion into **403** was complete, as indicated by HPLC monitoring. However, similarly to **399**, the purification of **403** by preparative HPLC of the resulting polyammonium was troublesome. Only 11% of the desired cycloaddition product could be isolated in pure form, and a major impure fraction was collected with the solvent front.

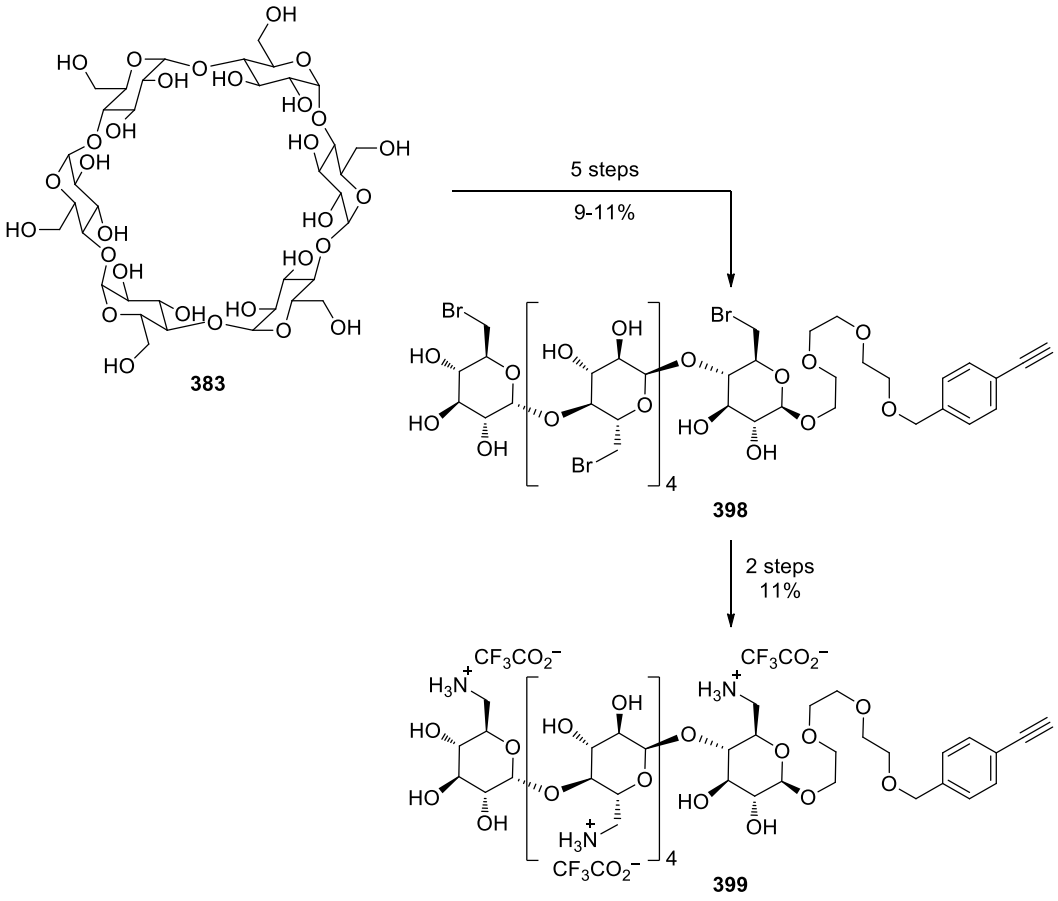
[207] a) A. Dondoni, H. M. Zuurmond, A. Boscarato, *J. Org. Chem.* **1997**, *62*, 8114–8124; b) A. Dondoni, A. Marra, M. Mizuno, P. P. Giovannini, *J. Org. Chem.* **2002**, *67*, 5444–5444.
[208] C. M. Dundas, D. Demonte, S. Park, *Appl. Microbiol. Biotechnol.* **2013**, *97*, 9343–9353.



Scheme 2.2.4. Conjugation of polycationic hexasaccharide **399** to biotin.

2.3. Conclusion and Outlook

In summary, the preparation of a clickable polycationic hexasaccharide from *α*-cyclodextrin in seven steps was described in the second part of this thesis. The strategy relies on ring cleavage followed by glycosylation and deprotection to give hexabrominated saccharide **398**, which features a linker bearing a terminal alkyne (Scheme 2.3.1). Azidation and subsequent Staudinger reduction afforded the desired hexaammonium saccharide **399**. Importantly, intermediate **398** could be used for the introduction of other types of cationic species, allowing the quick preparation of modified polycationic hexasaccharides for structure-activity relationship studies. Moreover, the possibility of conjugating relevant molecules was demonstrated with the synthesis of a biotin derivative.



Scheme 2.3.1. Summary of the preparation of polycation hexasaccharide **399**.

These polycationic hexasaccharides could be used in several applications by taking advantage of their possible electrostatic interaction with negatively charged biomolecules. This potential affinity could make them valuable carriers for drug delivery, for example by targeting the central nervous system *via* adsorptive-mediated transcytosis through the blood-brain-barrier.

3

Experimental Part

3. Experimental Part

3.1. General Methods and Materials

Chemicals and solvents: All chemicals and solvents were purchased from ABCR, Acros, Aldrich, Fluka, TCI, Combi-Blocks, Merck or Fluorochem and were used as received from the commercial supplier without further purification unless mentioned otherwise. Deuterated solvents for NMR spectroscopy were obtained from Armar Chemicals. THF, Et_2O, CH_2Cl_2, MeCN and toluene were dried using an LC TECHNOLOGY SOLUTIONS SP-1 solvent purification system under an atmosphere of dry N_2. DCE, DMSO and DMF were stored over 4 Å molecular sieves. Et_3N and DIPEA were distilled from CaH_2 under an atmosphere of dry N_2. Pyridine and *i*-Pr_2NH were distilled from KOH under an atmosphere of dry N_2.

General procedures: All non-aqueous reactions were realized under an inert atmosphere of dry nitrogen in glassware dried with heat gun. Reactions were monitored by thin layer chromatography (TLC) or ^{19}F NMR. TLC was performed on Merck silica gel 60 F_{254} TLC glass plates, and visualized with UV light (254 nm) and potassium permanganate, cerium ammonium molybdate (CAM), or Seebach's CAM stain. Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure. Column chromatographic purification was performed as flash column chromatography at 0.3-0.5 bar pressure using Fluka silica gel 60 (high purity grade, 230-400 mesh, 60 Å) or Silicycle UltraPure P60 silica gel (230-400 mesh, 60 Å) as stationary phase.[209] Yields refer to chromatographically pure compounds, unless stated otherwise.

Analytics: Nuclear Magnetic Resonance (NMR) spectra were recorded on Varian Mercury (300 MHz), Bruker AV and DRX (400 MHz) or Bruker AVIII (600 MHz with cryoprobe). All measurements were carried out at ambiant temperature (ca. 22 °C). Chemical shifts (δ) are reported in ppm, and are referenced to the residual solvent signal as internal standard (deuterated chloroform at 7.26 ppm for ^1H NMR, and 77.16 ppm for ^{13}C NMR; deuterated methanol at 3.31 ppm for ^1H NMR, and 49.00 ppm for ^{13}C NMR; deuterated DMSO at 2.50 ppm for ^1H NMR, and 39.52 ppm for ^{13}C NMR; deuterated acetonitrile at 1.94 ppm for ^1H NMR, and 1.32 ppm and 118.26 ppm for ^{13}C NMR; deuterated dichloromethane at 5.32 ppm for ^1H NMR, and 53.84 ppm for ^{13}C NMR). ^{19}F NMR spectra are referenced relative to $CFCl_3$ in $CDCl_3$, CD_3OD, $(CD_3)_2SO$, CD_3CN and CD_2Cl_2. Coupling constants (*J*) are reported in Hz. Multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p

[209] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

(pentuplet), m (multiplet or unresolved) and br (broad signal). Measurements on the Bruker AVIII (600 MHz with cryoprobe, calibration with tetramethylsilane) were performed by the NMR service team of the *Laboratorium für Organische Chemie* at *ETH Zürich* by René Arnold, Rainer Frankenstein and Philipp Zumbrunnen under the direction of Dr. Marc-Olivier Ebert.

High resolution mass spectrometric (HRMS) measurements were performed on a Waters' Micromass AutoSpec Ultima for EI, a Bruker's solariX for MALDI, or a Bruker's maXis for ESI, by the mass spectrometry service of the *Laboratorium für Organische Chemie* at *ETH Zürich* by Louis Bertschi, Oswald Greter and Rolf Häfliger, under the direction of Dr. Xiangyang Zhang.

Infrared (IR) spectra were recorded neat on a Perkin-Elmer Spectrum Two FT-IR spectrometer. The peaks are reported as absorption maxima (n, cm^{-1}).

Optical rotations were measured on a JASCO P-2000 Polarimeter equipped with a 10 cm cell.

X-ray diffraction experiments were carried out on a Bruker Kappa Apex II or on a Bruker Appex II Duo diffractometer by Dr. Nils Trapp and Michael Solar of the *Small Molecule Chrystallography Center* at *ETH Zürich*.

Preparative and analytical HPLC were performed at ambient temperature on a Waters Autopurification System using mixtures of H_2O (+ 0.1 vol% TFA) and MeCN (+ 0.1 vol% TFA) as mobile phase. Compounds were detected by UV absorption. For analytical HPLC, a Reprosil-Gold 120 C18, 5 μm, 125 x 4.6 mm was used with a flow rate of 1.40 $mL \cdot min^{-1}$. For preparative HPLC, a Reprosil-Gold 120 C18, 5 μm, 120 x 20 mm was used with a flow rate of 26.5 $mL \cdot min^{-1}$.

Physicochemical assays:

Determination of lipophilicities (log *D* pH = 7.4): The high-throughput assay method is derived from the conventional 'shake flask' method: The compound of interest is distributed between a 50 mM aqueous TAPSO buffer at pH 7.4 and 1-octanol. The distribution coefficient is then calculated from the difference in concentration in the aqueous phase before and after partitioning and the volume ratio of the two phases. To measure log*D* values within the range of –1 to 3.5, it is necessary to carry out the procedure at four different octanol/water ratios. The "one-phase-analysis" experiment starts with 2 or 9 μL of a pure DMSO solution of the compound, which is dispensed into, respectively, 38 or 171 μL of the aqueous buffer solution,

bringing the compound concentration to approximately c = 0.5 mM. A small part of this solution is then analyzed by UV. The observed optical density corresponds to the concentration of the substance before partitioning. To a measured aliquot of the aqueous solution a matching aliquot of 1-octanol is added, and the mixture is incubated by quiet shaking for 2 hours at 23±1 °C. The emulsion is allowed to stand overnight at the same temperature to ensure that the partition equilibrium is reached. Then, thorough centrifugation at 3000 rpm for 10 min is applied to separate the layers, and the concentration of the compound in the aqueous phase is determined again by measuring the UV absorption under the same conditions as the reference.

Membrane permeability determination (PAMPA): Permeabilities are determined *via* PAMPA (Parallel Artificial Membrane Permeation Assay). The small intestine, being the major site of oral absorption, is simulated by a three compartment model. Drugs permeate by passive diffusion from the donor compartment (320 µL, Roche Teflon plate), which is separated by a phospholipid coated filter (4.5 µL, Millipore MAIPN4550), to the acceptor compartment (280 µL, Millipore MAIPN4550). Donor buffer: 0.05 M MOPSO at pH 6.5 + 0.5% (w/v) Glycocholic acid. Acceptor buffer: 0.05 M MOPSO at pH 6.5. Membrane: 10% (w/v) Egg Lecithin in Dodecane + 0.5% (w/v) Cholesterol. The permeation constant Pe [10^{-6} cm·s^{-1}] as well as the sample distribution can be retrieved by UV analytics of donor (t_{start}), donor (t_{end}) and acceptor (t_{end}) using the pION PAMPA Evolution software.

High-throughput measurement of ionization constants (pK_a): Ionization constants are determined at 23±1 °C by spectrophotometry using a ProfilerSGA SIRIUS instrument in buffered water solution at ionic strength of 150 mM. To this end the UV-spectrum of a compound is measured at different pH values. The solution of the sample is injected at constant flow rate into a flowing pH gradient. Changes in UV absorbance are monitored as a function of the pH gradient. The pK_a values are found and determined where the rate of change of absorbance is at a maximum. The pH gradient is established by proportionally mixing two flowing buffer solutions. The buffer solutions contain mixtures of weak acids and bases that are UV-spectroscopically transparent above 240 nm. It is necessary to calibrate the gradient in order to know exactly the pH at any given time. This is achieved by introducing standard compounds with known pKa values.

Solubility: Lyophilisation Solubility Assay (LYSA): Samples were prepared in duplicate from 10 mM DMSO stock solutions. After evaporation (1 h) of DMSO with a centrifugal vacuum evaporator (Genevac Technologies), the compounds were dissolved in 0.05 M phosphate buffer (pH 6.5), stirred for one hour and shaken two hours. After one night, the

solutions were filtered using a microtiter filter plate (Millipore MSDV N65) and the filtrate and its 1/10 dilution were analyzed by direct UV measurement or by HPLC-UV. In addition a four point calibration curve is prepared from the 10 mM stock solutions and used for the solubility determination of the compounds. The results are expressed in $\mu g \cdot mL^{-1}$.

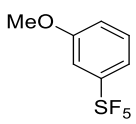
Determination of metabolic stability in liver microsomes: Microsomal incubations were carried out in 96-well plates in 200 µL of liver microsome incubation medium containing potassium phosphate buffer (50 mM, pH 7.4), $MgCl_2$ (10 mM), EDTA (1 mM), $NADP^+$ (2 mM), glucose-6-phosphate·$2H_2O$ (20 mM), glucose-6-phosphate dehydrogenase (4 units/mL) with 0.1 mg of liver microsomal protein per mL. Test compounds were incubated at 2 µM for up to 30 min at 37 °C under vortexing at 500 rpm. The reaction was stopped by transferring 30 µL incubation aliquots to 90 µL of ice-cold methanol. Levels of un-metabolized drug were determined by high-performance liquid chromatography (HPLC) coupled with tandem mass spectrometry (LC/MS/MS). The system consisted of a Shimadzu binary gradient HPLC system, a Waters XTerra® MS C18 column (1mm x 50mm) and a Sciex API 2000 mass spectrometer. A two component mobile phase pumped at 0.15 $mL \cdot min^{-1}$ contained the following solvents: solvent A (1% aqueous formic acid and MeOH 80:20) and solvent B (MeOH). An initial isocratic step of 0.5 min solvent A was followed by a gradient of 0 to 80% solvent B within 1 min. Detection was performed in positive mode. The intrinsic clearance (CL) was determined in semilogarithmic plots of compound concentrations versus time.

3.2. Novel Pentafluorosulfanyl-Substituted Building Blocks

3.2.1. Preparation and Applications of Novel SF_5-Aryl Boron Reagents

3.2.1.1. Preparation of SF_5-Aryl Boron Reagents

1-Methoxy-3-(pentafluorosulfanyl)benzene (162)

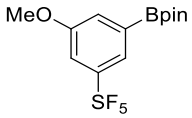


Following a slightly modified procedure described by Beier,[74] MeONa (185 mg, 1.5 equiv) was added in one portion to a solution of 3-(pentafluorosulfanyl)nitrobenzene (405 mg, 1.54 mmol) in DMF (1.6 mL) at room temperature. Then NaOMe was added in portions (185 mg, 1.5 equiv) every hour until complete conversion was observed by ^{19}F NMR. Saturated aqueous NH_4Cl was added and extraction was done with Et_2O (3x). The combined organic layers were washed with water (3x), then once with brine, dried with $MgSO_4$, and concentrated

under reduced pressure. Purification was performed by column chromatography (100% Hex) to afford **162** as a colorless oil (294 mg, 1.26 mmol, 80%).

TLC: R_f = 0.40 (Hex/EtOAc 95:5); NMR spectra consistent with those found in the literature: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.42 – 7.32 (m, 2H), 7.30 – 7.27 (m, 1H), 7.04 (dt, *J* = 7.1, 2.3 Hz, 1H), 3.85 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.5, 154.9 (p, $^2J_{CF}$ = 17.8 Hz), 129.5, 118.3 (p, $^3J_{CF}$ = 4.8 Hz), 117.3, 112.3 (p, $^3J_{CF}$ = 4.8 Hz), 55.8; **^{19}F NMR** (282 MHz, $CDCl_3$) AB_4 system, δ 84.7 (p, $^2J_{FF}$ = 149.9 Hz, 1F), 62.66 (d, $^2J_{FF}$ = 149.9 Hz, 4F); **IR** (neat): 2946, 2828, 1605, 1493, 1484, 1297, 1249, 1111, 1038, 837, 789 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_7H_7F_5OS$ $[M]^+$ 234.0138, found 234.0138.

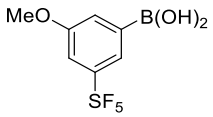
2-(3-Methoxy-5-(pentafluorosulfanyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (182)



In a round-bottom flask was introduced $[Ir(OMe)(cod)]_2$ (5.2 mg, 7.05 μmol, 0.75 mol%), dtbpy (3.9 mg, 14 μmol, 1.5 mol%) and pin_2B_2 (120 mg, 0.47 mmol, 0.5 equiv). The flask was flushed 5 min with N_2, and hexane (2 mL) was introduced. Then a solution of **162** (220 mg, 0.94 mmol) in hexane (1 mL) was added, and the reaction mixture was stirred at r.t. for 24h (no evolution of conversion was observed by ^{19}F NMR). The mixture was concentrated under reduced pressure. Purification was performed by column chromatography (100% Hex to Hex/EtOAc 1:1) to afford **182** as a white solid (191 mg, 0.53 mmol, 57%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.43 (s, 1H), 7.36 (s, 1H), 3.87 (s, 3H), 1.35 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.0, 154.5 (apparent m), 124.0 (p, $^3J_{CF}$ = 4.6 Hz), 122.2, 115.6 (p, $^3J_{CF}$ = 4.4 Hz), 84.6, 56.0, 25.0. (C–B not observed); **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 84.5 (apparent m, 1F), 62.7 (d, $^2J_{FF}$ = 149.5 Hz, 4F); **HRMS** (EI): *m/z* calculated for $C_{13}H_{18}BF_5O_3S$ $[M]^+$ 359.1021, found 359.1020.

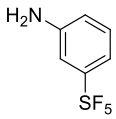
(3-Methoxy-5-(pentafluorosulfanyl)phenyl)boronic acid (183)



In a round-bottom flask was introduced $[Ir(OMe)(cod)]_2$ (25 mg, 34 µmol, 0.75 mol%), dtbpy (19 mg, 68 µmol, 1.5 mol%) and pin_2B_2 (929 mg, 3.62 mmol, 0.8 equiv). The flask was flushed 5 min with N_2, and THF (4.5 mL) was introduced. Then a solution of **162** (1.06 g, 4.53 mmol) in THF (2.0 mL) was added. The flask was sealed and the reaction mixture was stirred at 80 °C for 24h. The mixture was allowed to cool at r.t. and THF (30 mL) and H_2O (9 mL) were added, followed by $NaIO_4$ (3.87 g, 18.1 mmol, 4.0 equiv). After stirring for 15 min at r.t., 1 M HCl solution (4.5 mL, 4.5 mmol, 1.0 equiv) was added, and the mixture was stirred at r.t. for 2.5 h. Then H_2O and Et_2O were added, extraction was made with Et_2O (3x), and the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in a minimum amount of Et_2O, precipitated with the addition of hexane, and then filtered. Repeating this process a second time afforded **183** as a tanned solid (1.07 g, 3.86 mmol, 85%).

^{1}H NMR (300 MHz, CD_3CN): δ 7.76 (d, *J* = 1.9 Hz, 1H), 7.51 (d, *J* = 2.3 Hz, 1H), 7.41 (t, *J* = 2.3 Hz, 1H), 6.28 (s, 2H), 3.86 (s, 3H); **^{13}C**: n/a; **^{19}F NMR** (282 MHz, CD_3CN): AB_4 system, δ 84.6 (apparent m, 1F), 62.2 (d, $^2J_{FF}$ = 145.6 Hz, 4F); **HRMS** (EI): *m/z* calculated for $C_7H_8BF_5O_3S$ $[M]^+$ 277.0239, found 277.0239.

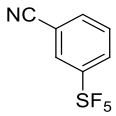
3-(Pentafluorosulfanyl)aniline (185)



Following a slightly modified reported procedure,[49b] HCl (conc., 5 mL, 58.3 mmol, 5.1 equiv) was dropwisely added to a suspension of 3-(pentafluorosulfanyl)nitrobenzene (3.00 g, 11.43 mmol) and Fe (3.83 g, 68.6 mmol, 6.0 equiv) powder in EtOH at room temperature. The reaction was stirred for 1.5 h and then quenched with an excess of NH_4OH (25%). The mixture was filtered and the filtrate was extracted with CH_2Cl_2 (3x). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 9:1) to afford **185** as an orange solid after storage at −20°C (2.46 g, 11.23 mmol, 98%).

TLC: R_f = 0.29 (Hex/EtOAc 8:2); NMR spectra consistent with those found in the literature: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.21 (tt, *J* = 8.0, 1.2 Hz, 1H), 7.11 (ddd, *J* = 8.3, 2.3, 0.9 Hz, 1H), 7.04 (t, *J* = 2.2 Hz, 1H), 6.77 (dd, *J* = 8.0, 2.2 Hz, 1H), 3.86 (br, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.0 (apparent m), 146.8, 129.5, 117.8, 115.8 (p, $^3J_{FF}$ = 4.8 Hz), 112.3 (p, $^3J_{FF}$ = 4.7 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 85.2 (apparent m, 1F), 62.4 (d, $^2J_{FF}$ = 149.8 Hz, 4F); **IR** (neat): 3473, 3445, 3365, 3218, 1737, 1621, 1494, 1459, 1324, 1278, 1128, 1093, 904, 772 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_6H_6F_5NS$ $[M]^+$ 219.0136, found 219.0128.

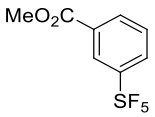
3-(Pentafluorosulfanyl)benzonitrile (186)



To a solution of **185** (1.11 g, 5.06 mmol) in water (2.5 mL) and acetic acid (2.5 mL) was added concentrated sulfuric acid (570 µL, 10.13 mmol, 2.0 equiv). The mixture was cooled down to 0°C and a solution of $NaNO_2$ (384 mg, 5.57 mmol, 1.1 equiv) in water (0.5 mL) was dropwisely added over 2 min. In a separated flask, a solution of KCN (1.65 g, 25.3 mmol, 5.0 equiv) in water (5 mL) was added to a solution of $CuSO_4 \cdot 5H_2O$ (0.97 g, 6.08 mmol, 1.2 equiv) in water (5 mL) and the resulting mixture was cooled down at 0°C. $NaHCO_3$ (4.25 g, 50.6 mmol, 10 equiv) and benzene (5 mL) were added followed by the solution of aryl diazonium (in a very dropwisely manner). The reaction was allowed to warm at room temperature. After 2.5 h, Et_2O was added and the layers were separated. Aqueous layer was extracted with Et_2O (2x), and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 98:2) to afford **186** as a yellowish solid after storage at -20°C (812 mg, 3.54 mmol, 70 %).

TLC: R_f = 0.44 (Hex/EtOAc 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.06 (t, *J* = 1.9 Hz, 1H), 8.01 (ddd, *J* = 8.4, 2.3, 1.0 Hz, 1H), 7.83 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 135.2, 130.4 (p, $^3J_{CF}$ = 4.6 Hz), 130.1 (apparent m, 2C), 117.1, 113.7. (C–SF_5 not observed); **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 81.4 (p, $^2J_{FF}$ = 151.9 Hz, 1F), 62.5 (d, $^2J_{FF}$ = 152.2 Hz, 4F); **IR** (neat): 3082, 3057, 2234, 1927, 1834, 1737, 1602, 1574, 1481, 1425, 1114, 878, 831, 775 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_7H_4F_5NS$ $[M]^+$ 228.9980, found 228.9980.

3-(Pentafluorosulfanyl)benzoic acid methyl ester (187)



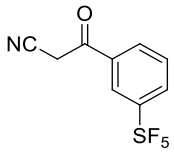
To a solution of **186** (760 mg, 3.32 mmol) in 1,4-dioxane (10 mL) was added 2 N NaOH solution (10 mL, 20.0 mmol, 6.0 equiv). The reaction was refluxed overnight. After cooling down to r.t., the mixture was diluted with water, washed with Et_2O (2x), acidified to pH 2 with 10% HCl, and extracted with Et_2O (3x). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure to afford the carboxylic acid as a white solid, which was used without any further purification.

NMR spectra consistent with those found in the literature:[12] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.51 (t, J = 1.9 Hz, 1H), 8.27 (m, 1H), 8.02 (ddd, J = 8.4, 2.4, 1.0 Hz, 1H), 7.63 (t, J = 8.1 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.0, 154.3 (apparent m), 133.2, 131.2 (p, $^3J_{CF}$ = 4.6 Hz), 130.3, 129.4 , 128.1 (p, $^3J_{CF}$ = 4.6Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 82.7 (p, $^2J_{FF}$ = 149.8 Hz, 1F), 62.6 (d, $^2J_{FF}$ = 149.8 Hz, 4F); **IR** (neat): 2970, 2861, 2669, 2549, 1694, 1605, 1581, 1448, 1412, 1278, 1144, 1090, 830, 797, 754 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_7H_4F_5O_2S$ $[M]^-$ 246.9858, found 246.9857.

To a solution of the crude 3-(pentafluorosulfanyl)benzoic acid in MeOH (17 mL) was added acetyl chloride (2.4 mL, 33.2 mmol, 10 equiv). The reaction was stirred overnight at 50 °C. After cooling down at room temperature, the mixture was concentrated under reduced pressure. The residue was partitioned between saturated aqueous $NaHCO_3$ and Et_2O. Extraction was made with Et_2O (3x). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried with $MgSO_4$, and concentrated under reduced pressure. Purification was performed by column chromatography (Hex to Hex/EtOAc 96:4) to afford **187** as a yellowish oil (545 mg, 2.08 mmol, 63% after two steps).

TLC: R_f = 0.44 (Hex/EtOAc 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.43 (t, *J* = 1.9 Hz, 1H), 8.22 – 8.17 (m, 1H), 7.95 (ddd, *J* = 8.3, 2.4, 1.0 Hz, 1H), 7.60 – 7.52 (m, 1H), 3.97 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.3, 153.9 (apparent m), 132.5, 131.1, 130.08 (p, $^3J_{CF}$ = 4.5 Hz), 129.0, 127.27 (p, $^3J_{CF}$ = 4.6 Hz), 52.7; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 83.36 (p, $^2J_{FF}$ = 151.0 Hz, 1F), 62.60 (d, $^2J_{FF}$ = 151.0 Hz, 4F); **IR** (neat): 3018, 2970, 2954, 1735, 1441, 1365, 1278, 1217, 1130, 844, 818 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_8H_7F_5O_2S$ $[M]^+$ 262.0082, found 262.0080.

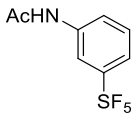
3-(Pentafluorosulfanyl)benzoylacetonitrile (188)



To a solution of MeCN (0.40 mL, 7.63 mmol, 4.0 equiv) in THF (5 mL) was dropwisely added potassium *tert*-pentylate (25% in toluene, 3.32 mL, 5.72 mmol, 3.0 equiv). The mixture was cooled down at 0°C and a solution of **187** (500 mg, 1.907 mmol) in THF (2.6 mL) was slowly added. After 5 min, the reaction was quenched with saturated aqueous NH_4Cl, and then extraction was made with EtOAc (3x). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 8:2 to 6:4) to afford **188** as an orange oil (145 mg, 0.535 mmol, 28%).

TLC: R_f = 0.50 (Hex/EtOAc 1:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.31 (t, *J* = 1.9 Hz, 1H), 8.12 – 8.01 (m, 2H), 7.69 (t, *J* = 8.0 Hz, 1H), 4.13 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 185.7, 154.7 (apparent t, $^2J_{CF}$ = 18.6 Hz), 135.0, 131.84 (p, $^3J_{CF}$ = 4.6 Hz), 131.3, 130.1, 126.2 (p, $^3J_{CF}$ = 4.7 Hz), 113.1, 29.8; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 82.1 (apparent m, 1F), 62.5 (d, $^2J_{FF}$ = 151.2 Hz, 4F); **IR** (neat): 3079, 2961, 2924, 2268, 1702, 1599, 1426, 1391, 1333, 1219, 1014, 939, 832, 796, 710, 685, 666 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_9H_6F_5NNaOS$ $[M+Na]^+$ 293.9982, found 293.9983.

3-Pentafluorosulfanylacetanilide (189)

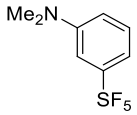


To a solution of **185** (1.06 g, 4.84 mmol) in CH_2Cl_2 (9.7 mL) at 0°C was added pyridine (0.59 mL, 7.25 mmol, 1.5 equiv) and then acetyl chloride (0.41 mL, 5.80 mmol, 1.2 equiv). The reaction was stirred from 0°C to room temperature for 4h. Saturated aqueous NH_4Cl was added and extraction was made with CH_2Cl_2 (3x). The combined organic layers were washed with aqueous $CuSO_4$, dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 8:2 to 6:4) to afford **189** as a white solid (1.04 g, 3.98 mmol, 82%).

TLC: R_f = 0.42 Hex / EtOAc 3:7; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.90 (t, *J* = 2.1 Hz, 1H), 7.74 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.55 – 7.35 (m, 3H), 2.21 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.7, 138.3, 129.4, 122.9, 121.7 (apparent m), 117.6 (apparent m), 24.7 (C–SF_5 not

observed); **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 84.0 (apparent m, 1F), 62.6 (d, $^2J_{FF}$ = 149.7 Hz, 4F); **IR** (neat): 3302, 3264, 3194, 3132, 3095, 1738, 1671, 1600, 1547, 1479, 1426, 1375, 1325, 1294, 1268, 916, 834, 806, 784, 737 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_8H_8F_5NOS$ $[M+H]^+$ 262.0320, found 262.0322.

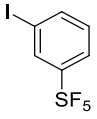
1-(Dimethylamino)-3-(pentafluorosulfanyl)benzene (190)



To a solution of **185** (1.31 g, 5.98 mmol) in THF (10 mL) was added $NaBH_4$ (1.36 g, 35.9 mmol, 6.0 equiv). The resulting suspension was then dropwisely added at 0°C to a solution of formaldehyde (37% in H_2O, 1.82 mL, 24.51 mmol, 4.1 equiv) and conc. H_2SO_4 (1.54 mL, 28.4 mmol, 4.7 equiv) in 12 mL (12 mL). The mixture was slowly warmed at room temperature. After 1 h, H_2O (15 mL) was added, and then KOH in pellets until pH reached about 10. The mixture was filtered and then extracted with Et_2O (3x). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (100% Hex to Hex/EtOAc 95:5) to afford **190** as a white solid (1.46 g, 5.90 mmol, 99 %).

TLC: R_f = 0.41 (Hex/EtOAc 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31 – 7.23 (m, 1H), 7.09 – 7.02 (m, 2H), 6.80 (dd, *J* = 8.4, 2.3 Hz, 1H), 2.99 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.3 (apparent m), 150.5, 129.1, 115.0, 113.5 (p, $^3J_{CF}$ = 4.8 Hz), 109.5 (p, $^3J_{CF}$ = 4.8 Hz), 40.6; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 85.8 (p, $^2J_{FF}$ = 148.5, 1F), 62.4 (d, $^2J_{FF}$ = 148.5 Hz, 4F); **IR** (neat): 3091, 2919, 2820, 1926, 1737, 1603, 1505, 1440, 1360, 1230, 1176, 815, 754 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_8H_{11}F_5NS$ $[M+H]^+$ 248.0527, found 248.0527.

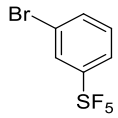
3-Iodopentafluorosulfanylbenzene (191)



To a suspension of **185** (975 mg, 4.45 mmol) in conc. HCl (2 mL) and H_2O (3 mL) at 0°C was slowly added a solution of $NaNO_2$ (368 mg, 5.34 mmol, 1.2 equiv) in H_2O (3 mL). The resulting solution was stirred 5 min at 0°C and then slowly added to a solution of KI (1.48 g, 8.90 mmol, 2.0 eq) in H_2O (25 mL) at 0°C. The reaction was slowly warmed to r.t. and stirred for 1.5 h. Then extraction was made with pentane (3x). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (100% pentane) to afford **191** as a colorless oil (1.19 g, 3.60 mmol, 81%).

TLC: R_f = 0.53 (Hex); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.08 (t, *J* = 1.9 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.74 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.25 – 7.16 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 154.5 (apparent m), 140.8, 130.4, 134.8 (p, $^3J_{CF}$ = 4.8 Hz), 125.4 (p, $^3J_{CF}$ = 4.7 Hz), 93.2; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 82.7 (apparent m, 1F), 62.7 (d, $^2J_{FF}$ = 151.0 Hz, 4F); **IR** (neat): 3098, 1574, 1464, 1417, 1110, 1064, 996, 835, 781, 710, 661 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_6H_4FI_5S$ $[M]^+$ 329.8994, found 329.8989.

3-Bromopentafluorosulfanylbenzene (27)

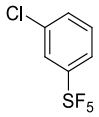


To a suspension of **185** (1.44 g, 6.57 mmol) in 48% HBr (6.6 mL) at -10°C was dropwisely added a solution of $NaNO_2$ (0.68 g, 9.86 mmol, 1.5 equiv) in water (2 mL). The resulting mixture was stirred for 1 h between –10°C and –5°C and was then added to a solution of CuBr (1.04 g, 7.23 mmol, 1.1 equiv) in HBr (6.6 mL). The reaction was stirred at room temperature for 2.5 h and was then poured into iced water. Extraction was made with Et_2O (3x).The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried with $MgSO_4$, and concentrated under reduced pressure. Purification was performed by column chromatography (pentane) to afford **27** as a colorless oil (1.54 g, 5.44 mmol, 83%).

TLC: R_f = 0.51 (Hex); NMR spectra consistent with those found in the literature:[210] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.91 (t, *J* = 2.0 Hz, 1H), 7.71 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.36 (tt, *J* = 8.2, 1.2 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 154.7 (apparent t, $^2J_{CF}$ = 17.9 Hz), 134.9, 130.3, 129.3 (p, $^3J_{CF}$ = 5.0 Hz), 124.80 (p, $^3J_{CF}$ = 4.8 Hz), 122.4; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 82.9 (p, $^2J_{FF}$ = 151.2 Hz, 1F), 62.8 (d, $^2J_{FF}$ = 151.2 Hz, 4F); **IR** (neat): 3101, 2976, 1738, 1578, 1466, 1422, 1365, 1216, 840 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_6H_4BrF_5S$ $[M]^+$ 281.9137, found 281.9130.

[210] T. A. Sergeeva, W. R. Dolbier, *Org. Lett.* **2004**, *6*, 2417–2419.

3-Chloropentafluorosulfanylbenzene (192)

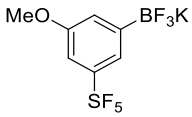


To a suspension of **185** (1.00 g, 4.56 mmol) in conc. HCl (4.6 mL) at 0°C was dropwisely added a solution of $NaNO_2$ (472 mg, 6.89 mmol, 1.5 equiv) in H_2O (2.0 mL). The mixture was stirred 5 min at 0°C until everything dissolved. The resulting solution was then added to solution CuCl (0.7 g, 6.84 mmol, 1.5 equiv) in conc. HCl (6.0 mL) at 0°C. The reaction temperature was slowly warmed to r.t. and stirred for 1.5 h. Extraction was made with pentane (3x), and combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the crude material was performed by column chromatography (100% pentane) to afford **192** as a colorless oil (704 mg, 2.95 mmol, 65%).

TLC: R_f = 0.49 (Hex); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.77 (t, *J* = 2.0 Hz, 1H), 7.66 (dt, *J* = 8.1, 1.5 Hz, 1H), 7.51 (dt, *J* = 8.1, 1.3 Hz, 1H), 7.42 (tt, *J* = 8.2, 1.2 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 154.5 (apparent m), 134.8, 132.0, 130.0, 126.6 (p, $^3J_{CF}$ = 4.8 Hz), 124.4 (p, $^3J_{CF}$ = 4.7 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 82.8 (apparent m, 1F), 62.8 (d, $^2J_{FF}$ = 149.8 Hz, 4F); **IR** (neat): 1585, 1470, 1418, 1121, 840, 745, 601 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_6H_4ClF_5S$ $[M]^+$ 237.9637, found 237.9641.

General procedure for the preparation of SF_5-substituted potassium aryltrifluoroborates: In a round-bottom flask was introduced $[Ir(OMe)(cod)]_2$ (11.1 mg, 0.015 mmol, 0.75 mol%), dtbpy (8.3 mg, 0.030 mmol, 1.5 mol%) and pin_2B_2 (360 mg, 1.40 mmol, 0.7 equiv). The flask was flushed 5 min with N_2, and THF (2.0 mL) was introduced. Then a solution of **162** (470 mg, 2.01 mmol) in THF (1.0 mL) was added. The flask was sealed and the reaction mixture was stirred at 80 °C for 24h. The mixture was allowed to cool down to r.t. and H_2O (1.8 mL) and KHF_2 (894 mg, 11.44 mmol, 5.7 equiv) were added. After stirring for 5 h, the mixture was concentrated under reduced pressure to dryness. The residue was extracted into hot acetone, and the resulting filtrate was concentrated under reduced pressure. The solid was dissolved into a minimum amount of acetone, precipitated with the addition of chloroform, and then filtered. This process was repeated a second time to afford **196** as a tanned solid after drying under high *vacuum* (639 gm, 1.88 mmol, 94%).

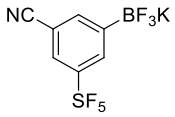
Potassium 3-methoxy-5-(pentafluorosulfanyl)phenyltrifluoroborate (196)



^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.50 (d, *J* = 2.3 Hz, 1H), 7.26 (d, *J* = 2.5 Hz, 1H), 7.04 (t, *J* = 2.3 Hz, 1H), 3.81 (s, 3H); **^{13}C NMR** (101 MHz, $(CD_3)_2CO$): δ 159.3, 154.5 (apparent m), 121.6 (apparent m), 121.0, 109.5 (p, $^{3}J_{CF}$ = 4.8 Hz), 55.7 (C–B not observed); **^{19}F NMR** (282 MHz, $(CD_3)_2CO$): δ 87.0 (apparent m), 62.4 (d, $^{2}J_{FF}$ = 147.1 Hz), –143.9 (br); **^{11}B NMR** (160 MHz, $(CD_3)_2CO$): δ 2.72 (q, $^{1}J_{BF}$ = 50.3 Hz); **IR** (neat): 1705, 1574, 1420, 1323, 1276, 1255, 1175, 989, 959, 735 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_7H_6BF_8OS$ $[M–K]^-$ 301.0108, found 301.0111.

Multigram scale reaction: Following the general procedure, **162** (2.34 g, 9.99 mmol) was converted into **196** as a tanned solid (3.12 g, 9.17 mmol, 92%).

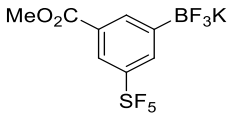
Potassium 3-cyano-5-(pentafluorosulfanyl)phenyltrifluoroborate (197)



Following the general procedure, **186** (405 mg, 1.77 mmol) was converted into **19** as an orange solid (521 mg, 1.55 mmol, 88%).

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 8.13 (d, *J* = 2.4 Hz, 1H), 7.99 (t, *J* = 2.0 Hz, 1H), 7.95 (br, 1H); **^{13}C NMR** (101 MHz, $(CD_3)_2CO$): δ 153.7 (apparent m), 139.2, 133.3 (apparent m), 127.2 (p, $^{3}J_{CF}$ = 4.8 Hz), 119.0, 112.3 (C–B not observed); **^{19}F NMR** (282 MHz, $(CD_3)_2CO$): δ 84.0 (apparent m), 62.0 (d, $^{2}J_{FF}$ = 147.0 Hz), –144.74 (br); **^{11}B NMR** (160 MHz, $(CD_3)_2CO$): δ 2.27 (q, $^{1}J_{BF}$ = 47.7 Hz); **IR** (neat): 3099, 2239, 1701, 1413, 1371, 1246, 1170, 1023, 964, 834, 737, 692, 656 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_7H_3BF_8NS$ $[M–K]^-$ 295.9960, found 295.9960.

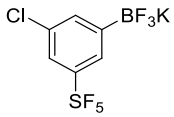
Potassium 3-methoxycarbonyl-5-(pentafluorosulfanyl)phenyltrifluoroborate (198)



Following the general procedure, **187** (445 mg, 1.70 mmol) was converted into **198** as a slightly tanned solid (403 mg, 1.10 mmol, 65%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 8.37 (br, 1H), 8.17 – 8.09 (m, 2H), 3.92 (s, 3H); **^{13}C NMR** (101 MHz, $(CD_3)_2CO$): δ 166.9, 153.9 (p, $^{2}J_{CF}$ = 15.0 Hz), 136.6, 133.3, 130.1, 124.6 (apparent m), 52.5 (C–B not observed); **^{19}F NMR** (282 MHz, $(CD_3)_2CO$): δ 85.7 (apparent m), 62.2 (d, $^{2}J_{FF}$ = 147.0 Hz), –144.17 (br); **^{11}B NMR** (160 MHz, $(CD_3)_2CO$): δ 2.58 (q, $^{1}J_{BF}$ = 49.8 Hz); **IR** (neat): 3105, 2960, 1714, 1607, 1445, 1213, 969, 828, 774, 742, 663 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_8H_6BF_8O_2S$ $[M–K]^-$ 329.0061, found 329.0051.

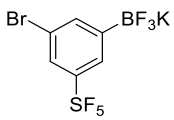
Potassium 3-chloro-5-(pentafluorosulfanyl)phenyltrifluoroborate (199)



Following the general procedure, **192** (490 mg, 2.05 mmol) was converted into **199** as a slightly tanned solid (627 mg, 1.82 mmol, 89%).

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.82 (d, *J* = 2.3 Hz, 1H), 7.64 (d, *J* = 1.9 Hz, 1H), 7.55 (t, *J* = 2.1 Hz, 1H); **^{13}C NMR** (101 MHz, $(CD_3)_2CO$): δ 155.3 (apparent m), 135.7, 133.3, 127.5 (apparent m), 123.2 (apparent m) (C–B not observed); **^{19}F NMR** (282 MHz, $(CD_3)_2CO$): δ 85.3 (apparent m), 62.4 (d, $^{2}J_{FF}$ = 147.0 Hz), –144.4 (br); **^{11}B NMR** (160 MHz, $(CD_3)_2CO$): δ 2.34 (q, $^{1}J_{BF}$ = 48.9 Hz); **IR** (neat): 1567, 1402, 1215, 1017, 829, 773, 726, 649, 613 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_6H_3BClF_8S$ $[M–K]^-$ 304.9616, found 304.9648.

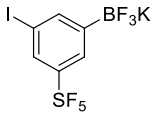
Potassium 3-bromo-5-(pentafluorosulfanyl)phenyltrifluoroborate (200)



Following the general procedure, **27** (243 mg, 0.59 mmol) was converted into **200** as a slightly tanned solid (176 mg, 0.45 mmol, 76%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.90 – 7.86 (m, 1H), 7.83 – 7.80 (m, 1H), 7.69 (t, *J* = 2.1 Hz, 1H); **^{13}C NMR** (101 MHz, $(CD_3)_2CO$): δ 154.6 (apparent m), 138.8, 127.9 (apparent m), 125.9 (p, $^{3}J_{CF}$ = 5.0 Hz), 121.5 (C–B not observed); **^{19}F NMR** (282 MHz, $(CD_3)_2CO$): δ 85.3 (m), 62.4 (d, $^{2}J_{FF}$ = 147.0 Hz), –144.3 (br); **^{11}B NMR** (160 MHz, $(CD_3)_2CO$): δ 2.24 (q, $^{1}J_{BF}$ = 48.9 Hz); **IR** (neat): 3080, 2970, 1738, 1559, 1365, 1215, 1009, 957, 987, 828, 750, 719 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_6H_3BBrF_8S$ $[M–K]^-$ 348.9111, found 348.9112.

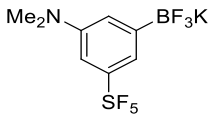
Potassium 3-iodo-5-(pentafluorosulfanyl)phenyltrifluoroborate (201)



Following the general procedure, **191** (651 mg, 1.97 mmol) was converted into **201** as a slightly tanned solid (622 mg, 1.43 mmol, 72%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 8.02 (br, 1H), 7.88 (d, *J* = 2.3 Hz, 1H), 7.86 (t, *J* = 2.0 Hz, 1H); **^{13}C NMR** (101 MHz, $(CD_3)_2CO$): δ 154.6 (apparent m), 145.0, 131.5 (p, $^{3}J_{CF}$ = 4.8 Hz), 128.3 (apparent m), 93.3 (C–B not observed); **^{19}F NMR** (282 MHz, $(CD_3)_2CO$): δ 85.5 (apparent m), 62.3 (d, $^{2}J_{FF}$ = 147.1 Hz), –144.3 (br); **^{11}B NMR** (160 MHz, $(CD_3)_2CO$): δ 2.10 (q, $^{1}J_{BF}$ = 49.4 Hz); **IR** (neat): 1552, 1394, 1211, 1117, 985, 827, 710, 646, 592 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_6H_3BF_8IS$ $[M–K]^-$ 396.8972, found 396.8938.

Potassium 3-(dimethylamino)-5-(pentafluorosulfanyl)phenyltrifluoroborate (202)

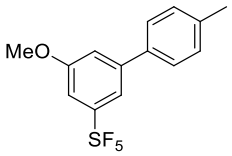


Following the general procedure, **190** (410 mg, 1.66 mmol) was converted into **202** as a slightly tanned solid (477 mg, 1.35 mmol, 81%).

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.27 (d, *J* = 2.2 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 6.85 (t, *J* = 2.4 Hz, 1H), 2.93 (s, 6H); **^{13}C NMR** (101 MHz, $(CD_3)_2CO$): δ 155.1 (apparent m), 150.8, 120.3, 118.0 (apparent m), 107.6 (p, $^{3}J_{CF}$ = 4.6 Hz), 40.9 (C–B not observed); **^{19}F NMR** (282 MHz, $(CD_3)_2CO$): δ 88.6 (apparent m), 62.4 (d, $^{2}J_{FF}$ = 147.0 Hz), –143.4 (br); **^{11}B NMR** (160 MHz, $(CD_3)_2CO$): δ 2.95 (q, $^{1}J_{BF}$ = 52.0 Hz); **IR** (neat): 2970, 2815, 1728, 1598, 1492, 1430, 1355, 1228, 1057, 984, 828, 793, 731 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_8H_9BF_8NS$ $[M–K]^-$ 314.0428, found 314.0420.

3.2.1.2. SF_5-Aryl Boron Reagents in the Suzuki–Miyaura Coupling Reaction

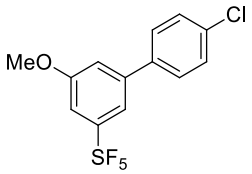
3-Methoxy-4'-methyl-5-(pentafluorosulfanyl)-1,1'-biphenyl (209)



To a solution of **183** (58 mg, 0.21 mmol) in toluene (1 mL), EtOH (350 µL) and H_2O (700 µL) were added 1-bromo-4-methylbenzene (31 µL, 0.25 mmol, 1.2 equiv) and K_2CO_3 (115 mg, 0.83 mmol, 4.0 equiv). The mixture was degazed with Ar for 10 min, then $Pd(PPh_3)_4$ (24 mg, 0.02 mmol, 0.1 equiv) was added and the reaction was stirred at 95 °C for 1 h. After cooling down to r.t., saturated aqueous NH_4Cl solution and extraction was made with CH_2Cl_2 (3x). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (100% Hex to Hex/EtOAc 99:1) to afford the **209** as a white solid (56 mg, 0.17 mmol, 83%).

TLC: R_f = 0.46 (Hex/EtOAc 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54 (t, *J* = 1.7 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 7.27 – 7.19 (m, 2H), 3.90 (s, 3H), 2.41 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.7, 155.2 (p, $^2J_{CF}$ = 17.8 Hz), 143.3, 138.5, 136.8, 129.9, 127.2, 117.2 (p, $^3J_{CF}$ = 4.7 Hz), 115.9, 110.6 (p, $^3J_{CF}$ = 4.6 Hz), 56.0, 21.3; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 84.6 (apparent m, 1F), 62.8 (d, $^2J_{FF}$ = 149.8 Hz, 4F); **IR** (neat): 3104, 3022, 2942, 2843, 1607, 1460, 1208, 1038, 832 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{14}H_{13}F_5OS$ $[M]^+$ 324.0602, found 324.0597.

4'-Chloro-3-methoxy-5-(pentafluorosulfanyl)-1,1'-biphenyl (210)



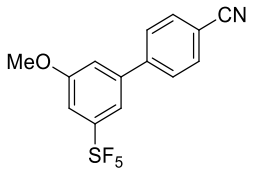
To a solution of **183** (112 mg, 0.40 mmol, 1.2 equiv) in toluene (1.7 mL), EtOH (560 µL) and H_2O (1.1 mL) were added 1-bromo-4-chlorobenzene (64 mg, 0.33 mmol) and K_2CO_3 (185 mg, 1.34 mmol, 4.0 equiv). The mixture was degazed with Ar for 10 min, then $Pd(PPh_3)_4$ (39 mg, 0.03 mmol, 0.1 equiv) was added and the reaction was stirred at 95 °C for 1 h. After cooling down to r.t., saturated aqueous NH_4Cl solution and extraction was made with CH_2Cl_2 (3x). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure.

Purification was performed by column chromatography (100% Hex to Hex/EtOAc 99:1) to afford **210** as a white solid (79 mg, 0.23 mmol, 69%).

TLC: R_f = 0.48 (Hex/EtOAc 95:5); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.52 – 7.47 (m, 3H), 7.46 – 7.41 (m, 2H), 7.27 (t, *J* = 2.2 Hz, 1H), 7.19 (t, *J* = 1.9 Hz, 1H), 3.91 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.9, 155.4 (p, $^2J_{CF}$ = 17.4 Hz), 142.1, 138.1, 134.7, 129.4, 128.7, 117.2 (p, $^3J_{CF}$ = 4.9 Hz), 116.0, 111.1 (p, $^3J_{CF}$ = 4.6 Hz), 56.0; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 84.3 (apparent m, 1F), 62.8 (d, $^2J_{FF}$ = 148.6 Hz, 4F); **IR**: n/a; **HRMS** (EI): *m/z* calculated for $C_{13}H_{10}ClF_5OS$ $[M]^+$ 344.0056, found 344.0044.

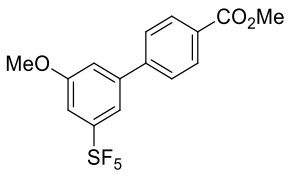
*General procedure for the preparation of biaryl compounds from SF_5-substituted potassium aryltrifluoroborates using **Method A***: In a two-necked round bottom flask was introduced 4-bromobenzonitrile (40.0 mg, 99%, 0.218 mmol), **196** (89 mg, 0.261 mmol, 1.2 equiv), triethylamine (91 μL, 0.653 mmol, 3.0 equiv) and EtOH (1 mL). The mixture was degased for 10 min with nitrogen, and $PdCl_2(dppf)\cdot CH_2Cl_2$ (3.6 mg, 4.4 μmol, 2 mol%) was added. The reaction was refluxed for 16 h. Then the mixture was concentrated and the residue partitioned between H_2O and Et_2O. Extraction was made with Et_2O (3x). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 96:4) to afford **211** as a white solid (59.0 mg, 0.218 mmol, 81%).

4-(3-Methoxy-5-(pentafluorosulfanyl)phenyl)benzonitrile (211)



TLC: R_f = 0.33 (Hex/EtOAc 8:2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.80 – 7.74 (m, 2H), 7.69 – 7.64 (m, 2H), 7.54 – 7.51 (m, 1H), 7.33 (t, *J* = 2.2 Hz, 1H), 7.22 (t, *J* = 1.8 Hz, 1H), 3.92 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.0, 155.5 (apparent m), 144.0, 141.3, 133.0, 128.1, 118.6, 117.3 (p, $^3J_{CF}$ = 4.5 Hz), 112.3, 112.0 (p, $^3J_{CF}$ = 4.9, 4.3 Hz), 56.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 83.8 (apparent m), 62.7 (d, $^2J_{FF}$ = 148.6 Hz); **IR** (neat): 3104, 3020, 2970, 2945, 2846, 2225, 1738, 1604, 1461, 1218, 1039, 825, 774, 728 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{14}H_{10}F_5NOS$ $[M]^+$ 335.0398, found 335.0397.

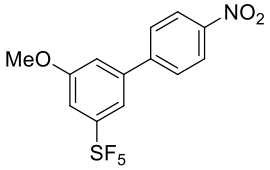
4-(3-Methoxy-5-(pentafluorosulfanyl)phenyl)benzoic acid methyl ester (212)



Following Method A, 4-bromobenzoic acid methyl ester (44.1 mg, 98%, 0.201 mmol) and **196** (82 mg, 0.241 mmol, 1.2 equiv) were converted into **212** as a white solid (63.2 mg, 0.172 mmol, 85%) after purification by column chromatography (Hex/EtOAc 95:5).

TLC: R_f = 0.40 (Hex/EtOAc 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.56 (t, *J* = 1.7 Hz, 1H), 7.30 (t, *J* = 2.2 Hz, 1H), 7.27 – 7.22 (m, 1H), 3.96 (s, 3H), 3.92 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.8, 159.9, 155.4 (p, $^2J_{CF}$ = 17.7 Hz), 143.9, 142.1, 130.4, 130.1, 127.4, 117.4 (p, $^3J_{CF}$ = 4.7 Hz), 116.3, 111.6 (p, $^3J_{CF}$ = 4.4 Hz), 56.1, 52.4; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 84.1 (apparent m), 62.8 (d, $^2J_{FF}$ = 150.0 Hz); **IR** (neat): 3106, 3020, 2970, 2944, 2845, 1715, 1606, 1434, 1281, 1216, 1111, 1039, 831, 748, 655 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{15}H_{13}F_5O_3S$ $[M]^+$ 368.0500, found 368.0488.

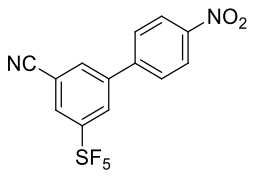
4-(3-Methoxy-5-(pentafluorosulfanyl)phenyl)nitrobenzene (213)



Following Method A, 4-bromonitrobenzene (43.0 mg, 95%, 0.202 mmol) and **196** (83 mg, 0.243 mmol, 1.2 equiv) were converted into **213** as a white solid (67.0 mg, 0.189 mmol, 93%) after purification by column chromatography (Hex/EtOAc 96:4).

TLC: R_f = 0.47 (Hex/EtOAc 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.36 – 8.29 (m, 2H), 7.76 – 7.69 (m, 2H), 7.56 (t, *J* = 1.7 Hz, 1H), 7.35 (t, *J* = 2.1 Hz, 1H), 7.26 – 7.24 (m, 1H), 3.93 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.1, 155.6 (apparent m), 147.9, 145.8, 140.8, 128.3, 124.4, 117.5 (p, $^3J_{CF}$ = 4.7 Hz), 116.5, 112.2 (p, $^3J_{CF}$ = 4.7 Hz), 56.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 83.7 (apparent m), 62.7 (d, $^2J_{FF}$ = 148.9 Hz); **IR** (neat): 3456, 3109, 3022, 2945, 2845, 1738, 1598, 1514, 1462, 1343, 1218, 1108, 1035, 900, 822, 749, 690, 650 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{13}H_{11}F_5NO_3S$ $[M+H]^+$ 356.0374, found 356.0378; for $C_{13}H_{10}F_5NNaO_3S$ $[M+Na]^+$ 378.0194, found 378.0197.

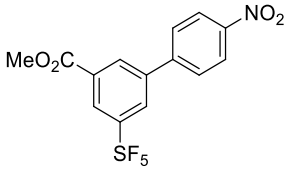
4-(3-Methoxy-5-(pentafluorosulfanyl)phenyl)nitrobenzene (214)



Following Method A, 4-bromonitrobenzene (42.0 mg, 95%, 0.198 mmol) and **197** (79.0 mg, 0.237 mmol, 1.2 equiv) were converted into **214** as a white solid (28.0 mg, 0.080 mmol, 41%) after purification by column chromatography (Hex/EtOAc 95:5).

TLC: R_f = 0.29 (Hex/EtOAc 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.47 – 8.36 (m, 2H), 8.19 (t, *J* = 1.9 Hz, 1H), 8.12 (t, *J* = 1.7 Hz, 1H), 8.04 (d, *J* = 1.5 Hz, 1H), 7.80 – 7.72 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.0 (apparent m), 148.6, 143.3, 141.6, 133.8, 129.7 (p, $^3J_{CF}$ = 4.6 Hz), 129.2 (p, $^3J_{CF}$ = 4.5 Hz), 128.5, 124.9, 116.7, 114.7; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 80.8 (apparent m), 62.8 (d, $^2J_{FF}$ = 150.9 Hz); **IR** (neat): 3087, 2922, 2857, 2238, 1600, 1520, 1448, 1345, 1132, 1109, 198, 846, 751, 684, 659 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{13}H_7F_5N_2O_2S$ $[M]^+$ 350.0143, found 350.0133.

4-(3-Methoxycarbonyl-5-(pentafluorosulfanyl)phenyl)nitrobenzene (215)

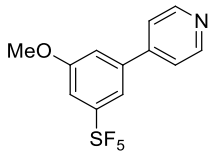


Following Method A, 4-bromonitrobenzene (44.0 mg, 95%, 0.207 mmol) and **198** (91.0 mg, 0.248 mmol, 1.2 equiv) were converted into **215** as a white solid (45.0 mg, 0.117 mmol, 57%) after purification by column chromatography (Hex/EtOAc 95:5).

TLC: R_f = 0.36 (Hex/EtOAc 8:2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.51 – 8.47 (m, 1H), 8.44 (d, *J* = 1.6 Hz, 1H), 8.41 – 8.34 (m, 2H), 8.16 (t, *J* = 1.9 Hz, 1H), 7.87 – 7.73 (m, 2H), 4.02 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.0, 154.8 (p, $^2J_{CF}$ = 17.8 Hz), 148.2, 144.6, 140.4, 132.2, 131.4, 128.9 (q, $^3J_{CF}$ = 4.5 Hz), 128.4, 127.3 (p, $^3J_{CF}$ = 4.6, 4.1 Hz), 124.6, 53.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 82.7 (apparent m), 62.8 (d, $^2J_{FF}$ = 150.7 Hz); **IR** (neat): 3081, 2960, 2848, 2237, 1725, 1599, 1520, 1345, 1246, 1128, 834, 751, 686, 657 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{14}H_{10}F_5NO_4S$ $[M]^+$ 383.0246, found 383.0238.

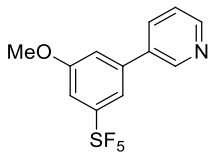
*General procedure for the preparation of biaryl compounds from SF_5-substituted potassium aryltrifluoroborates using **Method B***: In a round-bottom flask was introduced 4-iodopyridine (24.0 mg, 96%, 0.112 mmol), **196** (76.1 mg, 0.225 mmol, 2.0 equiv), K_2CO_3 (46.6 mg, 0.337 mmol, 3.0 equiv) and MeOH (0.6 mL). The solution was degased 5 min with nitrogen, then $Pd(OAc)_2$ (1.3 mg, 5.6 μmol, 5 mol%) was added. The flask was sealed and the reaction mixture was stirred at 85°C for 16 h. Then the mixture was concentrated and the residue partitioned between H_2O and EtOAc. Extraction was made with EtOAc (3x). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 6:4 to 4:6) to afford **217** as a slightly yellow solid (19.0 mg, 0.061 mmol, 54%)

4-(3-Methoxy-5-(pentafluorosulfanyl)phenyl)pyridine (217)



TLC: R_f = 0.39 (Hex/EtOAc 3:7); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.75 – 8.69 (m, 2H), 7.57 (t, J = 1.7 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.34 (t, J = 2.1 Hz, 1H), 7.28 – 7.25 (m, 1H), 3.92 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.1, 155.6 (apparent m), 150.7, 146.8, 140.4, 121.9, 117.1 (p, $^3J_{CF}$ = 4.7 Hz), 116.1, 112.4 (p, $^3J_{CF}$ = 4.4 Hz), 56.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 83.8 (apparent m), 62.7 (d, $^2J_{FF}$ = 148.4 Hz); **IR** (neat): 3081, 2950, 2850, 1726, 1597, 1520, 1449, 1346, 1308, 1221, 1127, 831, 819, 658 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{12}H_{11}F_5NOS$ $[M+H]^+$ 312.0476, found 312.0476; for $C_{12}H_{10}F_5NNaOS$ $[M+Na]^+$ 334.0295, found 334.0296.

3-(3-Methoxy-5-(pentafluorosulfanyl)phenyl)pyridine (218)

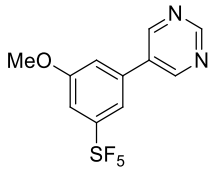


Following Method B, 3-bromopyridine (32.1 mg, 99%, 0.201 mmol) and **196** (136 mg, 0.401 mmol, 2.0 equiv) were converted into **218** as a slightly yellow (51.6 mg, 0.166 mmol, 83%) solid after purification by column chromatography (Hex/EtOAc 1:1).

TLC: R_f = 0.30 (Hex/EtOAc 3:7); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.83 (s, 1H), 8.67 (s, 1H), 7.86 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.52 (t, *J* = 1.7 Hz, 1H), 7.41 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.32 (t, *J* =

2.1 Hz, 1H), 7.22 (t, *J* = 1.7 Hz, 1H), 3.92 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.0, 155.5 (p, $^2J_{CF}$ = 17.9 Hz), 149.7, 148.4, 140.0, 135.3 , 134.7 , 123.9 , 117.3 (p, $^3J_{CF}$ = 4.7 Hz), 116.2 , 111.6 (p, $^3J_{CF}$ = 4.6 Hz), 56.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 84.1 (m), 62.7 (d, $^2J_{FF}$ = 149.7 Hz); **IR** (neat): 3099, 3022, 2923, 2846, 1602, 1582, 1460, 1433, 1327, 1226, 1053, 1021, 823, 752, 709, 650 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{12}H_{10}F_5NOS$ $[M]^+$ 311.0398, found 311.0393.

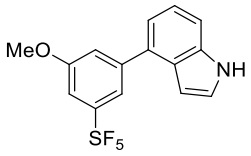
5-(3-Methoxy-5-(pentafluorosulfanyl)phenyl)-pyrimidine (219)



Following Method B, 5-bromopyrimidine (26.9 mg, 98%, 0.166 mmol) and **196** (113 mg, 0.332 mmol, 2.0 equiv) were converted into **219** as a white solid (49.3 mg, 0.158 mmol, 95%) after purification by column chromatography (Hex/EtOAc 1:1).

TLC: R_f = 0.29 (Hex/EtOAc 3:7); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.28 (s, 1H), 8.94 (s, 2H), 7.52 (t, *J* = 1.7 Hz, 1H), 7.37 (t, *J* = 2.2 Hz, 1H), 7.21 (t, *J* = 1.8 Hz, 1H), 3.93 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.3, 158.5 , 155.7 (apparent m), 155.2, 136.4 , 133.2 , 117.0 (p, $^3J_{CF}$ = 4.9 Hz), 116.13 , 112.49 (p, $^3J_{CF}$ = 4.7 Hz), 56.17; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 83.3 (apparent m), 62.7 (d, $^2J_{FF}$ = 148.7 Hz); **IR** (neat): 3090, 3058, 2970, 2943, 2842, 1739, 1602, 1561, 1466, 1418, 1322, 1235, 1190, 1034, 897, 828, 759, 718, 682, 652, 635 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{11}H_9F5N_2OS$ $[M]^+$ 312.0357, found 312.0351.

4-(3-Methoxy-5-(pentafluorosulfanyl)phenyl)-1H-indole (220)

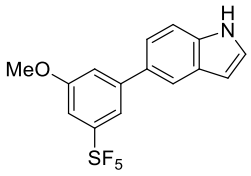


Following Method B, 4-bromoindole (29.0 mg, 97%, 0.143 mmol) and **196** (98 mg, 0.287 mmol, 2.0 equiv) were converted into **220** as a white solid (21.1 mg, 0.060 mmol, 42%) after purification by column chromatography (Hex/EtOAc 9:1 to 87:13).

TLC: R_f = 0.39 (Hex/EtOAc 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.32 (br, 1H), 7.72 (t, *J* = 1.7 Hz, 1H), 7.46 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.38 (t, *J* = 1.7 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.21 (dd, *J* = 7.3, 1.0 Hz, 1H), 6.68 (ddd, *J* = 3.2, 2.0, 1.0 Hz, 1H), 3.92 (s, 3H); **^{13}C NMR**

(101 MHz, $CDCl_3$): δ 159.5 , 154.9 (apparent m), 143.2 , 136.4 , 132.6 , 126.1 , 125.2 , 122.5 , 120.0 , 118.9 (p, $^3J_{CF}$ = 4.6 Hz), 117.3 , 111.4 , 110.8 (p, $^3J_{CF}$ = 4.6 Hz), 101.7 , 56.0; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 85.0 (apparent m), 62.9 (d, $^2J_{FF}$ = 150.0 Hz); **IR** (neat): 3415, 2936, 2842, 1725, 1600, 1504, 1460, 1401, 1357, 1226, 1128, 1050, 894, 830, 786, 751, 719, 657 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{15}H_{12}F_5NOS$ $[M]^+$ 349.0555, found 349.0558.

5-(3-Methoxy-5-(pentafluorosulfanyl)phenyl)-1H-indole (221)

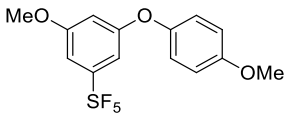


Following Method B, 5-bromoindole (19.0 mg, 99%, 0.096 mmol) and **196** (65 mg, 0.192 mmol, 2.0 equiv) were converted into as a white solid **221** (15.3 mg, 0.044 mmol, 46%) after purification by column chromatography (Hex/EtOAc 9:1 to 85:15).

TLC: R_f = 0.38 (Hex/EtOAc 7:3); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.23 (br, 1H), 7.85 (d, *J* = 2.0 Hz, 1H), 7.62 (t, *J* = 1.7 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.41 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.27-7.32 (m, 2H), 7.23 (t, *J* = 2.1 Hz, 1H), 6.64 (dd, *J* = 3.3, 2.1 Hz, 1H), 3.92 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.0, 155.2 (apparent m), 144.7, 135.9, 131.8, 128.8, 125.4, 121.8, 119.7, 117.6 (p, $^3J_{CF}$ = 4.6 Hz), 116.2, 111.7, 110.0 (p, $^3J_{CF}$ = 4.7 Hz), 103.3, 56.0; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 85.0 (apparent m), 62.9 (d, $^2J_{FF}$ = 149.9 Hz); **IR** (neat): 3479, 3398, 3100, 3022.5, 2952, 2846, 1600, 1464, 1421, 1223, 1030, 821, 739, 660 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{15}H_{12}F_5NOS$ $[M]^+$ 349.0555, found 349.0549.

3.2.1.3. SF_5-Aryl Boron Reagents in the Chan–Lam–Evans Coupling Reaction

1-Methoxy-3-(4-methoxyphenoxy)-5-(pentafluorosulfanyl)benzene (225)

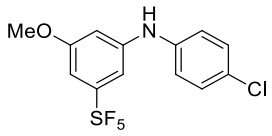


To a solution of 4-methoxyphenol (81.0 mg, 99%, 0.646 mmol) in CH_2Cl_2 (6.5 mL) under air atmosphere was added 4 Å molecular sieves (650 mg), triethylamine (450 µL, 3.23 mmol, 5.0 equiv), $Cu(OAc)_2$ (120.0 mg, 0.646 mmol, 1.0 equiv) and **183** (216 mg, 0.775 mmol, 1.2 equiv). After stirring for 16 h at r.t., the reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. Purification was performed by column

chromatography (Hex to Hex/EtOAc 99:1) to afford **225** as a colorless oil (145 mg, 0.407 mmol, 63%).

TLC: R_f = 0.52 (Hex/EtOAc 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.04 – 6.95 (m, 3H), 6.95 – 6.87 (m, 3H), 6.59 (t, *J* = 2.2 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.4, 159.6, 156.8, 155.3 (p, $^2J_{CF}$ = 18.0 Hz), 148.8, 121.4, 115.3, 107.83 (p, $^3J_{CF}$ = 4.7 Hz), 106.33 (p, $^3J_{CF}$ = 4.9 Hz), 106.1, 55.9, 55.8; **^{19}F NMR** (376 MHz, $CDCl_3$): AB_4 system, δ 86.60 – 79.89 (m), 62.63 (d, *J* = 150.2 Hz); **IR** (neat): 2949, 2839, 2169, 1737, 1604, 1503, 1206, 1145, 1035, 825, 770, 663 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{14}H_{13}F_5O_3S$ $[M]^+$ 356.0500, found 356.0498.

***N*-(4-chlorophenyl)-3-methoxy-5-(pentafluorosulfanyl)aniline (226)**



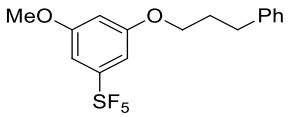
To a suspension of **183** (52.0 mg, 0.187 mmol) in toluene (6.5 mL) under air atmosphere was added $Cu(OAc)_2$ (34.7 mg, 0.187 mmol, 1.0 equiv), mystiric acid (85.0 mg, 0.374 mmol, 2.0 equiv) and 2,6-lutidine (21.8 μL, 0.187 mmol, 1.0 equiv). The mixture was stirred for 5 min at r.t. (until complete dissolution of the reagents), and 4-chloroaniline (47.7 mg, 0.374 mmol, 2.0 equiv) was added. After stirring for 24 h at r.t., the reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 9:1) to afford **226** as an orange solid (35.0 mg, 0.097 mmol, 52%).

TLC: R_f = 0.33 (Hex/EtOAc 8:2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.29 – 7.22 (m, 2H), 7.05 – 6.98 (m, 2H), 6.94 (t, *J* = 1.9 Hz, 1H), 6.81 (t, *J* = 2.1 Hz, 1H), 6.64 (t, *J* = 2.0 Hz, 1H), 5.78 (s, 1H), 3.78 (s, 3H); **^{13}C NMR** (300 MHz, $CDCl_3$): δ 160.4, 155.7 (p, $^2J_{CF}$ = 17.4 Hz), 144.6, 140.2, 129.8, 127.7, 120.8, 107.5 (t, $^3J_{CF}$ = 4.8 Hz), 105.2, 104.4 (t, $^3J_{CF}$ = 4.8 Hz), 55.9; **^{19}F NMR** (376 MHz, $CDCl_3$): AB_4 system, δ 84.7 (apparent m), 62.4 (d, *J* = 149.6 Hz); IR (neat): 3424, 3088, 3038, 2541, 1586, 1491, 1355, 1256, 1174, 815, 770, 644 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{13}H_{11}ClF_5NOS$ $[M+H]^+$ 360.0243, found 360.0243.

General procedure for the preparation of aryl ethers from SF_5-substituted potassium aryltrifluoroborates: A suspension of **196** (82.0 mg, 0.240 mmol, 2.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (24.0 mg, 0.120 mmol, 1.0 equiv), DMAP (2.9 mg, 0.024 mmol, 0.2 equiv) and powdered 4 Å molecular sieves (200 mg) in DCE (1.2 mL) was stirred for 5 min to room temperature. Then 3-phenylpropan-1-ol (16.7 mg, 98%, 0.120 mmol) was added, a condenser was set up and the

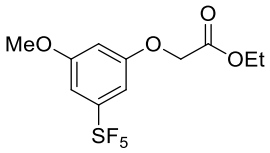
reaction mixture was stirred at 60 °C under an atmosphere of oxygen (balloon) for 24 h. The reaction mixture was cooled down to room temperature, filtered through a pad of celite, and concentrated under reduced pressure. Purification was performed by preparative TLC (Hex/EtOAc 95:5) to afford **229** as a colorless oil (33.9 mg, 0.092 mmol, 77%).

1-Methoxy-3-(pentafluorosulfanyl)-5-(3-phenylpropoxy)benzene (229)



TLC: R_f = 0.38 (Hex/EtOAc 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37 – 7.28 (m, 2H), 7.22 (ddd, *J* = 6.1, 2.9, 1.7 Hz, 3H), 6.89 (d, *J* = 2.2 Hz, 2H), 6.56 (t, *J* = 2.2 Hz, 1H), 3.97 (t, *J* = 6.2 Hz, 2H), 3.82 (s, 3H), 2.82 (dd, *J* = 8.3, 6.8 Hz, 2H), 2.16 – 2.03 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.3, 159.8, 155.3 (apparent m), 141.3, 128.6 (m, 2C), 126.2, 105.5 (p, $^3J_{CF}$ = 4.7 Hz), 104.8 (p, $^3J_{CF}$ = 4.7 Hz), 103.8, 67.7, 55.9, 32.2, 30.8; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 84.5 (apparent m), 62.6 (d, $^2J_{FF}$ = 148.8 Hz); **IR** (neat): 3029, 2943, 2676, 1609, 1454, 1432, 1290, 1198, 1163, 1065, 1039, 834, 770, 750, 699, 680, 663, 597 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{16}H_{17}F_5O_2S$ $[M]^+$ 368.0864, found 368.0855.

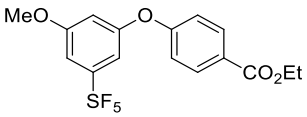
Ethyl 2-(3-methoxy-5-(pentafluorosulfanyl)phenoxy)acetate (230)



Following general procedure, ethyl glycolate (24.7 mg, 95%, 0.237 mmol) and **196** (161.0 mg, 0.475 mmol, 2.0 equiv) were converted into **230** as a white solid (53.0 mg, 0.158 mmol, 70%) after purification by column chromatography (Hex/toluene 1:1 to 3:7).

TLC: R_f = 0.25 (Hex/EtOAc 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.93 (t, *J* = 2.1 Hz, 1H), 6.89 (t, *J* = 2.0 Hz, 1H), 6.60 (t, *J* = 2.1 Hz, 1H), 4.62 (s, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.2, 160.4, 158.5, 155.3 (apparent m), 106.0 (p, $^3J_{CF}$ = 4.8 Hz), 105.4 (p, $^3J_{CF}$ = 4.9 Hz), 104.3, 65.8, 61.8, 56.0, 14.3; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 84.2 (apparent m), 62.6 (d, $^2J_{FF}$ = 151.0 Hz); **IR** (neat): 3108, 2985, 2943, 2843, 1756, 1608, 1469, 1297, 1213, 1194, 1162, 889, 834, 764, 661, 598, 570 cm^{-1}; **HRMS** (EI): calculated for $C_{11}H_{13}F_5O_4S$ $[M]^+$ 336.0450, found 336.0444.

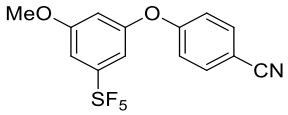
Ethyl 4-(3-methoxy-5-(pentafluorosulfanyl)phenoxy)benzoate (231)



Following general procedure, ethyl 4-hydroxybenzoate (31.2 mg, 99%, 0.186 mmol) and **196** (126.0 mg, 0.372 mmol, 2.0 equiv) were converted into **231** as a colorless oil (60.2 mg, 0.151 mmol, 80%) after purification by column chromatography (Hex/EtOAc 95:5).

TLC: R_f = 0.30 (Hex/EtOAc 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.8 Hz, 2H), 7.09 (t, *J* = 2.1 Hz, 1H), 7.06 – 7.01 (m, 3H), 6.71 (t, *J* = 2.2 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.0, 160.7, 160.3, 156.9, 155.4 (apparent m), 132.0, 126.3, 118.2, 109.9 (p, $^3J_{CF}$ = 4.7 Hz), 108.3 (m, 2C), 61.2, 56.1, 14.5; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 83.7 (apparent m), 62.6 (d, $^2J_{FF}$ = 149.8 Hz); **IR** (neat): 3407, 3104, 1714, 1600, 1588, 1504, 1467, 1448, 1274, 1222, 1162, 1147, 1099, 894, 835, 814, 760, 662, 597 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{16}H_{15}F_5O_4S$ $[M]^+$ 398.0606, found 398.0603.

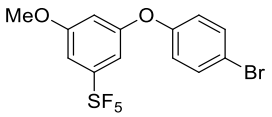
4-(3-Methoxy-5-(pentafluorosulfanyl)phenoxy)benzonitrile (232)



Following general procedure, 4-hydroxybenzonitrile (26.0 mg, 97%, 0.212 mmol) and **196** (144.0 mg, 0.423 mmol, 2.0 equiv) were converted into **232** as a colorless oil (61.3 mg, 0.174 mmol, 82%) after purification by column chromatography (Hex/EtOAc 96:4).

TLC: R_f = 0.25 (Hex/EtOAc 9:1); **^{1}H NMR** 300 MHz, $CDCl_3$): δ 7.70 – 7.62 (m, 2H), 7.14 (t, J = 2.0 Hz, 1H), 7.10 – 7.03 (m, 3H), 6.73 (t, J = 2.2 Hz, 1H), 3.84 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.9, 160.4, 155.7 (apparent m, 2C), 134.6 118.7, 118.6, 110.4 (p, $^3J_{CF}$ = 4.5 Hz), 109.0 (apparent m, 2C), 107.4, 56.2; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 83.0 (apparent m), 62.7 (d, $^2J_{FF}$ = 149.9 Hz); **IR** (neat): 3108, 3016, 2957, 2850, 2226, 1773, 1599, 1587, 1501, 1498, 1449, 1435, 1292, 1226, 1172, 1149, 1059, 832, 817, 763, 662, 650, 594, 571, 556, 536 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{14}H_{10}F_5NO_2S$ $[M]^+$ 351.0547, found 351.0354.

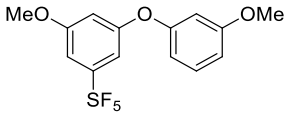
1-(4-Bromophenoxy)-3-methoxy-5-(pentafluorosulfanyl)benzene (233)



Following general procedure, 4-bromophenol (25.2 mg, 98%, 0.146 mmol) and **196** (99.0 mg, 0.291 mmol, 2.0 equiv) were converted into **233** as a colorless oil (55.2 mg, 0.136 mmol, 95%) after purification by column chromatography (Hex/EtOAc 95:5).

TLC: R_f = 0.38 (Hex/EtOAc 95:5); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.56 – 7.38 (m, 2H), 7.03 (t, *J* = 2.0 Hz, 1H), 6.97 (t, *J* = 2.0 Hz, 1H), 6.95 – 6.88 (m, 2H), 6.64 (t, *J* = 2.2 Hz, 1H), 3.81 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.6, 157.9, 155.3 (apparent m, 2C), 133.2, 121.2, 117.2, 109.0 (p, $^3J_{CF}$ = 4.8 Hz), 107.6 (p, $^3J_{CF}$ = 4.7 Hz), 107.4, 56.0; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 83.5 (apparent m), 62.6 (d, $^2J_{FF}$ = 151.6 Hz); **IR** (neat): 3103, 3011, 2943, 2840, 1607, 1578, 1482, 1431, 1290, 1215, 1146, 1058, 894, 812, 763, 662, 597 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{13}H_{10}BrF_5O_2S$ $[M]^+$ 403.9500, found 403.9490.

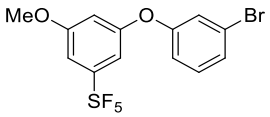
1-Methoxy-3-(3-methoxyphenoxy)-5-(pentafluorosulfanyl)benzene (234)



Following general procedure, 3-methoxyphenol (24.4 mg, 97%, 0.191 mmol) and **196** (130.0 mg, 0.381 mmol, 2.0 equiv) were converted into **234** as a colorless oil (26.4 mg, 0.074 mmol, 39%) after purification by column chromatography (Hex/EtOAc 96:4).

TLC: R_f = 0.28 (Hex/EtOAc 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35 – 7.17 (m, 1H), 7.01 (apparent m, 2H), 6.73 (ddd, *J* = 8.3, 2.3, 0.9 Hz, 1H), 6.67 (t, *J* = 2.2 Hz, 1H), 6.64 – 6.57 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.3, 160.5, 158.2, 157.1, 155.3 (apparent m), 130.6, 111.6, 110.2, 109.1 (p, $^3J_{CF}$ = 4.9 Hz), 107.4, 107.2 (p, $^3J_{CF}$ = 4.9 Hz), 105.6, 56.0, 55.6; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 83.6 (apparent m), 62.6 (d, $^2J_{FF}$ = 149.2 Hz); **IR** (neat): 2944, 2840, 1585, 1431, 1286, 1154, 889, 834, 681, 659, 599 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{14}H_{13}F_5O_3S$ $[M]^+$ 356.0500, found 356.0490.

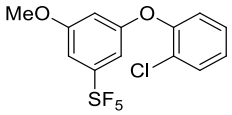
1-(3-Bromophenoxy)-3-methoxy-5-(pentafluorosulfanyl)benzene (235)



Following general procedure, 3-bromophenol (25.0 mg, 98%, 0.142 mmol) and **196** (96.0 mg, 0.283 mmol, 2.0 equiv) were converted into **235** as a colorless oil (37.9 mg, 0.094 mmol, 66%) after purification by column chromatography (Hex/EtOAc 99:1).

TLC: R_f = 0.37 (Hex/EtOAc 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.27 – 7.21 (m, 1H), 7.20 (t, *J* = 2.1 Hz, 1H), 7.06 (t, *J* = 2.1 Hz, 1H), 7.00 (t, *J* = 2.0 Hz, 1H), 6.96 (ddd, *J* = 8.1, 2.4, 1.1 Hz, 1H), 6.66 (t, *J* = 2.2 Hz, 1H), 3.82 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.6, 157.5, 157.0, 155.3 (apparent m), 131.3, 127.6, 123.3, 122.6, 117.9, 109.3 (p, $^3J_{CF}$ = 4.6 Hz), 107.8 (m, 2C), 56.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 83.6 (apparent m), 62.6 (d, $^2J_{FF}$ = 150.8 Hz); **IR** (neat): 3102, 2941, 2838, 1579, 1467, 1212, 1147, 1058, 832, 764, 676, 661, 599, 580 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{13}H_{10}BrF_5O_2S$ $[M]^+$ 403.9500, found 403. 9494.

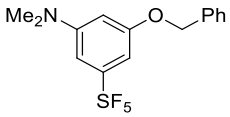
1-(2-Chlorophenoxy)-3-methoxy-5-(pentafluorosulfanyl)benzene (236)



Following general procedure, 2-chlorophenol (24.5 mg, 98%, 0.187 mmol) and **196** (127.0 mg, 0.374 mmol, 2.0 equiv) were converted into **236**as a colorless oil (28.4 mg, 0.079 mmol, 42%) after purification by column chromatography (Hex/EtOAc 99:1).

TLC: R_f: 0.35 (Hex/EtOAc 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.29 (td, *J* = 7.8, 1.6 Hz, 1H), 7.18 (td, *J* = 7.7, 1.6 Hz, 1H), 7.07 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.02 (t, *J* = 2.1 Hz, 1H), 6.94 (t, *J* = 2.0 Hz, 1H), 6.58 (t, *J* = 2.2 Hz, 1H), 3.81 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.5, 158.0, 155.4 (apparent m), 151.1, 131.3, 128.4, 126.6, 126.2, 121.9, 108.0 (p, $^3J_{CF}$ = 4.8 Hz), 107.1 (p, $^3J_{CF}$ = 4.8 Hz), 106.3, 56.0; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 83.8 (apparent m), 62.6 (d, $^2J_{FF}$ = 149.9 Hz); **IR** (neat): 3105, 2954, 2841, 1609, 1579, 1475, 1228, 1148, 1061, 834, 775, 755, 681, 663, 601, 585, 563 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{13}H_{10}ClF_5O_2S$ $[M]^+$ 360.0005, found 360.0005.

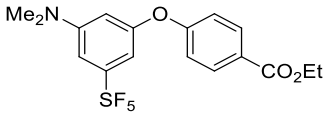
3-(Benzyloxy)-N,N-dimethyl-5-(pentafluorosulfanyl)aniline (237)



Following general procedure, benzyl alcohol (25.9 mg, 99%, 0.237 mmol) and **202** (167.0 mg, 0.474 mmol, 2.0 equiv) were converted into **237** as a white solid (31.6 mg, 0.089 mmol, 38%) after purification by column chromatography (Hex/EtOAc 97:3).

TLC: R_f: 0.32 (Hex/EtOAc 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.48 – 7.31 (m, 5H), 6.74 (t, *J* = 2.0 Hz, 1H), 6.70 (t, *J* = 2.1 Hz, 1H), 6.40 (t, *J* = 2.2 Hz, 1H), 5.06 (s, 2H), 2.97 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.3, 155.8 (p, $^2J_{CF}$ = 15.6 Hz), 151.2, 136.5, 128.8, 128.3, 127.8, 103.4 (p, $^3J_{CF}$ = 4.9 Hz), 102.0, 100.6 (p, $^3J_{CF}$ = 4.7 Hz), 70.6, 40.6; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 85.9 (apparent m), 62.5 (d, $^2J_{FF}$ = 149.7 Hz); **IR** (neat): 3039, 2926, 2881, 1611, 1563, 1361, 1240, 1153, 1048, 835, 816, 750, 699, 662, 597, 562 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{15}H_{16}F_5NOS$ $[M]^+$ 353.0868, found 353.0871.

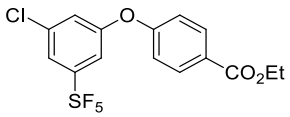
Ethyl 4-(3-(dimethylamino)-5-(pentafluorosulfanyl)phenoxy)benzoate (238)



Following general procedure, ethyl 4-hydroxybenzoate (25.0 mg, 99%, 0.150 mmol) and **202** (106.0 mg, 0.301 mmol, 2.0 equiv) were converted into **238** as a white solid (27.3 mg, 0.066 mmol, 44%) after purification by column chromatography (Hex/EtOAc 95:5).

TLC: R_f: 0.24 (Hex/EtOAc 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13 – 7.91 (m, 2H), 7.06 – 6.95 (m, 2H), 6.85 (t, *J* = 2.1 Hz, 1H), 6.74 (t, *J* = 2.0 Hz, 1H), 6.47 (t, *J* = 2.2 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 2.98 (s, 6H), 1.39 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.2, 161.1, 156.3, 155.8 (apparent m), 151.5, 131.9, 125.6, 117.6, 106.1, 105.8 (p, $^3J_{CF}$ = 4.9 Hz), 105.33 (p, $^3J_{CF}$ = 4.7 Hz), 61.1, 40.5, 14.5; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 84.8 (apparent m), 62.5 (d, $^2J_{FF}$ = 149.0 Hz); **IR** (neat): 2984, 2907, 2817, 1713, 1600, 1502, 1273, 1236, 1162, 1099, 834, 769, 753, 659, 596 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{17}H_{18}F_5NO_3S$ $[M]^+$ 411.0922, found 411.0916.

Ethyl 4-(3-chloro-5-(pentafluorosulfanyl)phenoxy)benzoate (239)

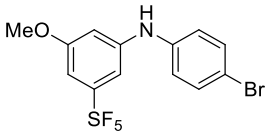


Following general procedure, ethyl 4-hydroxybenzoate (25.0 mg, 99%, 0.150 mmol) and **199** (106.0 mg, 0.301 mmol, 2.0 equiv) were converted into **239** as a colorless oil (54.2 mg, 0.135 mmol, 90%) after purification by column chromatography (Hex/EtOAc 99:1).

TLC: R_f = 0.42 (Hex/EtOAc 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.14 – 8.06 (m, 2H), 7.53 (t, *J* = 1.8 Hz, 1H), 7.34 (t, *J* = 2.0 Hz, 1H), 7.15 (t, *J* = 2.0 Hz, 1H), 7.10 – 7.01 (m, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.8, 159.4, 157.0, 155.2 (apparent m), 135.7, 132.2, 127.1, 122.3, 121.8 (p, $^3J_{CF}$ = 4.9 Hz), 118.7, 115.7 (p, $^3J_{CF}$ = 4.7 Hz), 61.3, 14.5; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 82.1 (m), 62.9 (d, $^2J_{FF}$ = 150.3 Hz); **IR** (neat): 3101, 2985, 1715, 1586, 1503, 1275, 1245, 1162, 1100, 843, 735, 703, 664 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{15}H_{12}ClF_5O_3S$ $[M]^+$ 402.0111, found 402.0119.

General procedure for the preparation of anilines from SF_5-substituted potassium aryltrifluoroborates: A suspension of **196** (118.0 mg, 0.347 mmol, 2.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (3.5 mg, 0.017 mmol, 10 mol%), Et_3N (24 µL, 0.174 mmol, 1.0 equiv) and powdered 4 Å molecular sieves (230 mg) in DCE (1.7 mL) was stirred for 5 min at room temperature. Then 4-bromoaniline (31.1 mg, 96%, 0.174 mmol) was added, a condenser was set up and the reaction mixture was stirred at 85 °C under an atmosphere of oxygen (balloon) for 16 h. The reaction mixture was cooled down to room temperature, filtered through a pad of celite, and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/toluene 8:2 to 7:3) to afford **241** as a yellowish solid (50.1 mg, 0.124 mmol, 71%).

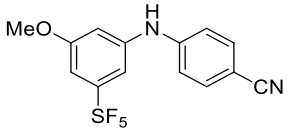
***N*-(4-bromophenyl)-3-methoxy-5-(pentafluorosulfanyl)aniline (241)**



TLC: R_f = 0.25 (Hex/EtOAc 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.47 – 7.35 (m, 2H), 7.02 – 6.93 (m, 3H), 6.83 (t, *J* = 2.0 Hz, 1H), 6.67 (t, *J* = 2.1 Hz, 1H), 5.79 (s, 1H), 3.80 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.4, 155.7 (p, $^2J_{CF}$ = 16.8 Hz), 144.4, 140.8, 132.7, 121.0, 115.0, 107.7 (p, $^3J_{CF}$ = 4.8 Hz), 105.4, 104.6 (p, $^3J_{CF}$ = 4.6 Hz), 55.9; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 84.4 (apparent m), 62.4 (d, $^2J_{FF}$ = 148.4 Hz); **IR** (neat): 3406, 2940,

2841, 1608, 1586, 1487, 1256, 1197, 1114, 896, 832, 768, 660, 595 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{13}H_{11}BrF_5NOS$ $[M]^+$ 402.9660, found 402.9663.

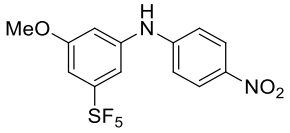
4-((3-Methoxy-5-(pentafluorosulfanyl)phenyl)amino)benzonitrile (242)



Following general procedure, 4-aminobenzonitrile (24.6 mg, 98%, 0.204 mmol) and **196** (139.0 mg, 0.408 mmol, 2.0 equiv) were converted into **242** as a white solid (48.2 mg, 0.138 mmol, 67%) after purification by column chromatography (Hex/EtOAc 9:1 to 85:15).

TLC: R_f = 0.38 (Hex/EtOAc 7:3); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.61 – 7.49 (m, 2H), 7.12 (t, *J* = 2.0 Hz, 1H), 7.08 – 7.00 (m, 2H), 6.98 (t, *J* = 2.0 Hz, 1H), 6.83 (t, *J* = 2.1 Hz, 1H), 6.15 (s, 1H), 3.84 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.5, 155.7 (apparent m), 146.6, 141.7, 134.1, 119.5, 116.3, 110.5 (p, $^3J_{CF}$ = 4.6 Hz), 108.7, 106.9 (p, $^3J_{CF}$ = 4.7 Hz), 103.5, 56.0; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 83.9 (apparent m), 62.4 (d, $^2J_{FF}$ = 148.4 Hz); **IR** (neat): 3327, 2215, 1599, 1470, 1343, 1273, 1167, 901, 859, 820, 783, 657, 544 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{14}H_{11}F_5N_2OS$ $[M]^+$ 350.0507, found 350.0504.

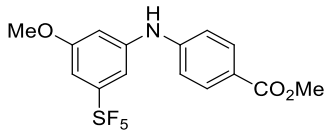
3-Methoxy-*N*-(4-nitrophenyl)-5-(pentafluorosulfanyl)aniline (243)



Following general procedure, 4-nitroaniline (30.0 mg, 99%, 0.215 mmol) and **196** (146.0 mg, 0.430 mmol, 2.0 equiv) were converted into **243** as an orange solid (37.2 mg, 0.100 mmol, 47%) after purification by column chromatography (Hex/EtOAc 85:15).

TLC: R_f = 0.35 (Hex/EtOAc 7:3); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.28 – 8.04 (m, 2H), 7.16 (t, *J* = 1.9 Hz, 1H), 7.09 – 6.92 (m, 3H), 6.88 (t, *J* = 2.1 Hz, 1H), 6.33 (s, 1H), 3.85 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.6, 155.8 (apparent m), 148.7, 141.3, 141.2, 126.4, 115.1, 111.2 (p, $^3J_{CF}$ = 4.4 Hz), 109.5, 107.62 (p, $^3J_{CF}$ = 4.7 Hz), 56.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 83.5 (apparent m), 62.5 (d, $^2J_{FF}$ = 148.4 Hz); **IR** (neat): 3379, 3109, 2942, 2849, 1582, 1500, 1462, 1306, 1270, 1165, 1110, 902, 852, 823, 780, 750, 663, 597 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{13}H_{11}F_5N_2O_3S$ $[M]^+$ 370.0405, found 370.0391.

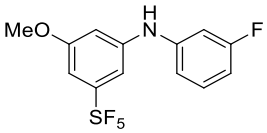
Methyl 4-((3-methoxy-5-(pentafluorosulfanyl)phenyl)amino)benzoate (244)



Following general procedure, methyl 4-aminobenzoate (30.1 mg, 98%, 0.195 mmol) and **196** (133.0 mg, 0.390 mmol, 2.0 equiv) were converted into **244** as a yellowish solid (32.9 mg, 0.086 mmol, 44%) after purification by column chromatography (Hex/EtOAc 95:5 to 85:15).

TLC: R_f = 0.21 (Hex/EtOAc 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.07 – 7.79 (m, 2H), 7.11 (t, *J* = 1.9 Hz, 1H), 7.08 – 7.00 (m, 2H), 6.93 (t, *J* = 2.1 Hz, 1H), 6.83 (t, *J* = 2.0 Hz, 1H), 6.13 (s, 1H), 3.89 (s, 3H), 3.83 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.9, 160.4, 155.6 (apparent m), 146.5, 142.7, 131.7, 123.0, 116.1, 109.7 (p, $^3J_{CF}$ = 4.7 Hz), 107.7, 106.1 (p, $^3J_{CF}$ = 4.7 Hz), 56.0, 52.0; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 84.2 (apparent m), 62.4 (d, $^2J_{FF}$ = 148.4 Hz); **IR** (neat): 3350, 2950, 2849, 1705, 1468, 1344, 1285, 1270, 1170, 833, 777, 761, 710, 660, 594, 190 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{15}H_{14}F_5NO_3S$ $[M]^+$: 383.0609, found 383.0599.

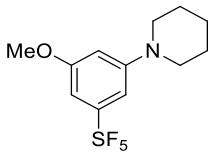
***N*-(3-fluorophenyl)-3-methoxy-5-(pentafluorosulfanyl)aniline (245)**



Following general procedure, 3-fluoroaniline (25.0 mg, 99%, 0.223 mmol) and **196** (151.0 mg, 0.445 mmol, 2.0 equiv) were converted into **245** as a yellowish oil (57.3 mg, 0.167 mmol, 75%) after purification by column chromatography (Hex/toluene 8:2).

TLC: R_f = 0.38 (Hex/EtOAc 8:2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.25 (td, *J* = 8.1, 6.5 Hz, 1H), 7.02 (t, *J* = 1.9 Hz, 1H), 6.89 – 6.76 (m, 3H), 6.76 – 6.64 (m, 2H), 5.88 (s, 1H), 3.82 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 162.7 (d, $^1J_{CF}$ = 467.5 Hz), 162.6, 155.7 (p, $^2J_{CF}$ = 16.2 Hz), 143.9, 143.6 (d, $^3J_{CF}$ = 10.3 Hz), 130.9 (d, $^3J_{CF}$ = 9.8 Hz), 114.2 (d, $^4J_{CF}$ = 2.7 Hz), 109.1 (d, $^2J_{CF}$ = 21.2 Hz), 108.4 (p, $^3J_{CF}$ = 4.9 Hz), 106.2, 105.6 (d, $^2J_{CF}$ = 24.7 Hz), 105.0 (p, $^3J_{CF}$ = 4.8 Hz), 55.9; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 84.6 (apparent m), 62.4 (d, $^2J_{FF}$ = 149.8 Hz), -111.4 (dd, $^3J_{FH}$ = 16.9, $^3J_{FH}$ = 8.3 Hz); **IR** (neat): 3436, 3096, 2940, 2845, 1599, 1492, 1467, 1201, 1176, 1163, 1144, 891, 831, 769, 678, 657, 598 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{13}H_{11}F_6NOS$ $[M]^+$ 343.0460, found 343.0458.

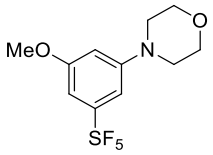
1-(3-Methoxy-5-(pentafluorosulfanyl)phenyl)piperidine (246)



Following general procedure, piperidine (24.6 mg, 99%, 0.286 mmol) and **196** (195.0 mg, 0.572 mmol, 2.0 equiv) were converted into **246** as a white solid (57.9 mg, 0.182 mmol, 64%) upon storage at -20 °C after purification by column chromatography (Hex/EtOAc 99:1 to 98:2).

TLC: R_f = 0.33 (Hex/EtOAc 98:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.89 (t, *J* = 2.0 Hz, 1H), 6.71 (t, *J* = 2.1 Hz, 1H), 6.53 (t, *J* = 2.2 Hz, 1H), 3.81 (s, 3H), 3.21 – 3.13 (m, 4H), 1.80 – 1.65 (m, 4H), 1.64 – 1.55 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.1, 155.7 (apparent m), 153.0, 107.1 (p, $^3J_{CF}$ = 4.4 Hz), 105.1, 102.0 (p, $^3J_{CF}$ = 5.4 Hz), 55.7, 50.4, 25.7, 24.3; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 85.5 (apparent m), 62.5 (d, $^2J_{FF}$ = 148.5 Hz); **IR** (neat): 3092, 2941, 2845, 1598, 1464, 1442, 1208, 1185, 1126, 890, 863, 830, 800, 738, 654, 590 cm^{-1}; HRMS (EI): *m/z* calculated for $C_{12}H_{16}F_5NOS$ $[M]^+$ 316.0789, found 316.0792.

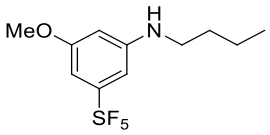
4-(3-Methoxy-5-(pentafluorosulfanyl)phenyl)morpholine (247)



Following general procedure, morpholine (23.5 mg, 99%, 0.267 mmol) and **196** (182.0 mg, 0.534 mmol, 2.0 equiv) were converted into **247** as a white solid (57.2 mg, 0.179 mmol, 67%) after purification by column chromatography (Hex/EtOAc 94:6 to 85:15).

TLC: R_f = 0.32 (Hex/EtOAc 8:2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.88 (t, *J* = 2.0 Hz, 1H), 6.78 (t, *J* = 2.0 Hz, 1H), 6.52 (t, *J* = 2.1 Hz, 1H), 3.89 – 3.83 (m, 4H), 3.82 (s, 3H), 3.27 – 3.01 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.2, 155.8 (p, $^2J_{CF}$ = 17.7 Hz), 152.3, 106.4 (p, $^3J_{CF}$ = 4.8 Hz), 104.7, 102.9 (p, $^3J_{CF}$ = 4.8 Hz), 66.8, 55.8, 49.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 85.1 (apparent m), 62.4 (d, $^2J_{FF}$ = 149.8 Hz); **IR** (neat): 2979, 2843, 1602, 1579, 1450, 1265, 1205, 1119, 848, 810, 743, 662, 648, 590 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{11}H_{14}F_5NO_2S$ $[M]^+$ 319.0660, found 319.0670.

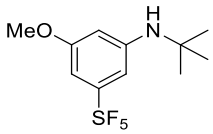
***N*-(*n*-butyl)-3-methoxy-5-(pentafluorosulfanyl)aniline (228)**



Following general procedure, *n*-butylamine (20.9 mg, 99%, 0.283 mmol) and **196** (192.0 mg, 0.566 mmol, 2.0 equiv) were converted into **228** as a colorless oil (60.0 mg, 0.170 mmol, 60%) after purification by column chromatography (Hex/EtOAc 99:1).

TLC: R_f = 0.35 (Hex/EtOAc 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.59 (t, *J* = 2.0 Hz, 1H), 6.57 (t, *J* = 2.0 Hz, 1H), 6.21 (t, *J* = 2.1 Hz, 1H), 3.79 (m, 4H), 3.10 (t, *J* = 7.0 Hz, 2H), 1.67 – 1.54 (m, 2H), 1.50 – 1.36 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.4, 155.8 (apparent m), 149.4, 103.6 (p, $^3J_{CF}$ = 5.0 Hz), 100.6, 100.5 (p, $^3J_{CF}$ = 4.7 Hz), 55.7, 43.7, 31.5, 20.4, 14.0; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 85.2 (apparent m), 62.3 (d, $^2J_{FF}$ = 149.9 Hz); **IR** (neat): 3427, 2962, 2935, 2875, 1605, 1464, 1207, 1175, 887, 827, 762, 659, 595 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{11}H_{16}F_5NOS$ $[M]^+$ 305.0868, found 305.0869.

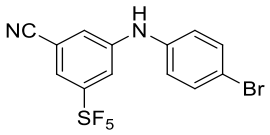
***N*-(*tert*-butyl)-3-methoxy-5-(pentafluorosulfanyl)aniline (248)**



Following general procedure, *tert*-butylamine (19.6 mg, 98%, 0.263 mmol) and **196** (179.0 mg, 0.525 mmol, 2.0 equiv) were converted into **248** as a colorless oil (22.3 mg, 0.073 mmol, 28%) after purification by column chromatography (Hex/EtOAc 99:1).

TLC: R_f = 0.41 (Hex/EtOAc 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.67 (t, *J* = 2.0 Hz, 1H), 6.61 (t, *J* = 2.0 Hz, 1H), 6.36 (t, *J* = 2.1 Hz, 1H), 3.79 (s, 4H), 1.36 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.0 155.4 (apparent m), 147.8, 106.9 (p, $^3J_{CF}$ = 4.5 Hz), 104.2, 100.6 (p, $^3J_{CF}$ = 4.5 Hz), 55.7, 51.7, 29.9; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 85.6 (apparent m), 62.3 (d, $^2J_{FF}$ = 149.7 Hz); **IR** (neat): 3429, 2938, 2977, 1604, 1478, 1463, 1206, 1173, 882, 832, 775, 733, 650, 596 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{11}H_{16}F_5NOS$ $[M]^+$ 305.0868, found 305.0870.

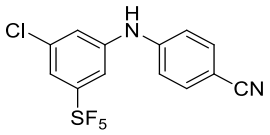
3-((4-Bromophenyl)amino)-5-(pentafluorosulfanyl)benzonitrile (249)



Following general procedure, 4-bromoaniline (28.0 mg, 96%, 0.156 mmol) and **197** (105.0 mg, 0.313 mmol, 2.0 equiv) were converted into **249** as a brown solid (12.6 mg, 0.032 mmol, 20%) after purification by column chromatography (Hex/EtOAc 95:5).

TLC: R_f = 0.35 (Hex/EtOAc 8:2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.57 – 7.43 (m, 4H), 7.30 (t, *J* = 1.5 Hz, 1H), 7.20 – 6.84 (m, 2H), 6.01 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.2 (apparent m), 145.3, 138.8, 122.6, 122.5, 120.6 (apparent m, 2C), 117.4 (apparent m, 2C), 117.3, 114.2; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 81.8 (apparent m), 62.3 (d, $^2J_{FF}$ = 150.0 Hz); **IR** (neat): 3355, 2923, 2237, 1585, 1486, 1453, 1335, 1309, 1071, 1010, 843, 763, 719, 661, 594, 488 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{13}H_8BrF_5N_2S$ $[M]^+$ 397.9507, found 397.9524.

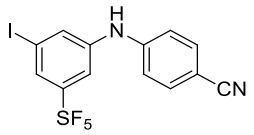
4-((3-Chloro-5-(pentafluorosulfanyl)phenyl)amino)benzonitrile (250)



Following general procedure, 4-aminobenzonitrile (24.0 mg, 98%, 0.199 mmol) and **199** (137.0 mg, 0.398 mmol, 2.0 equiv) were converted into **250** as a white solid (20.0 mg, 0.056 mmol, 28%) after purification by column chromatography (Hex/EtOAc 9:1 to 8:2).

TLC: R_f = 0.31 (Hex/EtOAc 7:3): **^{1}H NMR** (300 MHz, CD_2Cl_2): δ 7.68 – 7.52 (m, 2H), 7.42 (dd, *J* = 2.0, 1.0 Hz, 2H), 7.32 (t, *J* = 1.9 Hz, 1H), 7.22 – 7.01 (m, 2H), 6.34 (s, 1H); **^{13}C NMR** (101 MHz, CD_2Cl_2): δ 146.3, 143.3, 136.2, 134.8, 122.6, 120.9 (p, $^3J_{CF}$ = 6.8 Hz), 119.8, 117.7, 116.0 (apparent m), 105.3 (C-SF_5 not observed); **^{19}F NMR** (282 MHz, CD_2Cl_2): AB_4 system, δ 82.4 (apparent m), 62.3 (d, $^2J_{FF}$ = 148.9 Hz); **IR** (neat): 3328, 3197, 2217, 1587, 1531, 1507, 1455, 1336, 1176, 1122, 830, 819, 756, 736, 655, 595, 544 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{13}H_8ClF_5N_2S$ $[M]^+$ 354.0012, found 354.0007.

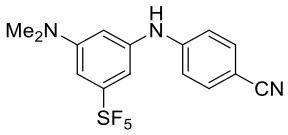
4-((3-Iodo-5-(pentafluorosulfanyl)phenyl)amino)benzonitrile (251)



Following general procedure, 4-aminobenzonitrile (24.0 mg, 98%, 0.199 mmol) and **201** (174.0 mg, 0.313 mmol, 2.0 equiv) were converted into **251** as a white solid (35.9 mg, 0.080 mmol, 40%) after purification by column chromatography (Hex/EtOAc 9:1).

TLC: R_f = 0.31 (Hex/EtOAc 8:2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.73 (t, *J* = 1.6 Hz, 1H), 7.63 (t, *J* = 1.6 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.47 (t, *J* = 1.9 Hz, 1H), 7.10 – 7.00 (m, 2H), 6.16 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 155.3 (apparent m), 145.2, 142.3, 134.2, 131.0, 129.0 (p, J = 4.5 Hz), 119.2, 117.0 (apparent m, 2C), 104.6, 93.8; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 82.6 (apparent m), 62.7 (d, $^2J_{FF}$ = 149.9 Hz); **IR** (neat): 3319, 2221, 1605, 1581, 1528, 1507, 1450, 1338, 1173, 824,716, 654, 594, 544 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{13}H_8F_5IN_2S$ $[M]^+$ 445.9368, found 445.9373.

4-((3-(Dimethylamino)-5-(pentafluorosulfanyl)phenyl)amino)benzonitrile (252)

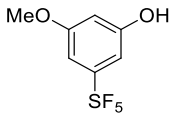


Following general procedure, 4-aminobenzonitrile (24.0 mg, 98%, 0.199 mmol) and **202** (141.0 mg, 0.398 mmol, 2.0 equiv) were converted into **252** as a tanned solid (37.1 mg, 0.102 mmol, 51%) after purification by column chromatography (Hex/EtOAc 9:1 to 8:2).

TLC: R_f = 0.51 (Hex/EtOAc 6:4); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.64 – 7.39 (m, 2H), 7.07 – 6.94 (m, 2H), 6.87 (t, *J* = 1.9 Hz, 1H), 6.78 (t, *J* = 2.1 Hz, 1H), 6.55 (t, *J* = 2.1 Hz, 1H), 6.13 (s, 1H), 2.99 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 156.0 (p, $^2J_{CF}$ = 16.5 Hz), 151.2, 147.5, 141.1, 134.0, 119.8, 115.7, 106.8, 106.4 (p, $^3J_{CF}$ = 4.6 Hz), 105.4 (p, $^3J_{CF}$ = 4.5 Hz), 102.6, 40.6; **^{19}F NMR** (282 MHz, $CDCl_3$) AB_4 system, δ 85.4 (apparent m), 62.3 (d, $^2J_{FF}$ = 149.8 Hz); **IR** (neat): 3326, 2217, 1582, 1508, 1440, 1414, 1324, 1169, 823, 757, 655, 591, 543 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{15}H_{14}F_5N_3S$ $[M]^+$ 362.0745, found 362.0737.

3.2.1.4. Other Functionalizations of SF_5-Aryl Boron Reagents

3-Methoxy-5-(pentafluorosulfanyl)phenol (184)

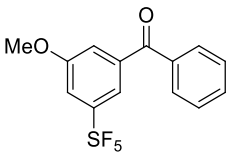


*Procedure from boronic acid **183***: To a solution of **183** (79 mg, 0.28 mmol) in MeCN (0.5 mL) were added 30% H_2O_2 solution (570 µL) and then I_2 (14.5 mg, 0.06 mmol, 0.2 equiv). The reaction was stirred for 1 h at r.t., then H_2O was added and extraction was made with Et_2O (3x). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ solution, dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 95:5 to 8:2) to afford **184** as a white solid (51 mg, 0.20 mmol, 72%).

*Procedure from potassium aryltrifluoroborate **196***: To a solution of **196** (100 mg, 0.29 mmol) in acetone (1.5 mL) was added a solution of Oxone® (90 mg, 0.29 mmol, 1.0 equiv) in H_2O (1.5 mL). The reaction was stirred for 5 min at r.t., then H_2O (3 mL) was added followed by 0.1 M HCl (1.8 mL). Extraction was made with CH_2Cl_2 (3x). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 9:1 to 8:2) to afford **184** as a white solid (59 mg, 0.24 mmol, 80%).

TLC: R_f = 0.46 (Hex/EtOAc 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.89 (t, *J* = 2.1 Hz, 1H), 6.84 (t, *J* = 2.0 Hz, 1H), 6.53 (t, *J* = 2.3 Hz, 1H), 5.15 (s, 1H), 3.82 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.5, 156.2, 155.3 (p, $^2J_{CF}$ = 16.8 Hz), 106.3 (p, $^3J_{CF}$ = 4.8 Hz), 105.4 (p, $^3J_{CF}$ = 4.9 Hz), 104.6, 56.0; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 83.7 (apparent m, 1F), 62.09 (d, $^2J_{FF}$ = 148.4 Hz, 4F); **IR** (neat): 3390, 2952, 2847, 1615, 1461, 1437, 1333, 1300, 1196, 1157, 1058, 830, 765, 661, 599 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_7H_7F_5O_2S$ $[M]^+$ 250.0082, found 250.0085.

(3-Methoxy-5-(pentafluorosulfanyl)phenyl)(phenyl)methanone (257)



183 (90 mg, 0.32 mmol, 1.2 equiv), CuTC (82 mg, 0.43 mmol, 1.6 equiv), $Pd_2dba_3{\cdot}CHCl_3$ (2.8 mg, 2.7 µmol, 1 mol%), thioester **256**[109a] (60 mg, 0.27 mmol) and tris-2-furylphosphine

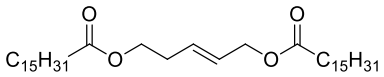
(2.0 mg, 8.1 μmol, 3 mol%) were introduced in a flask that was then flushed with argon for 5 min, then THF (3.4 mL) was introduced and the mixture was stirred for 18 h at 50 °C. Then 5% aqueous HCl solution was added and extraction was made with Et_2O (3x), the combined organic layers were washed with H_2O, then brine, dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex to Hex/EtOAc 98:2) to afford **257** as a yellowish oil (40 mg, 0.12 mmol, 44%).

TLC: R_f = 0.27 (Hex/EtOAc 95:5); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.86 – 7.76 (m, 2H), 7.73 (dd, *J* = 2.0, 1.3 Hz, 1H), 7.69 – 7.59 (m, 1H), 7.57 – 7.44 (m, 4H), 3.91 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 194.6, 159.6, 154.4 (apparent m), 139.3, 136.6, 133.3, 130.2, 128.8, 119.9 (p, $^3J_{CF}$ = 4.8 Hz), 117.7, 116.4 (p, $^3J_{CF}$ = 5.2 Hz), 56.2; **^{13}F NMR**: n/a; **IR**: n/a; **HRMS** (EI): *m/z* calculated for $C_{14}H_{11}F_5O_2S$ $[M]^+$ 338.0395, found: 338.0396.

3.2.2. Preparation of Novel SF_5-Heterocycles

3.2.2.1. Unsuccessful Strategies

(*E*)-pent-2-ene-1,5-diyl dipalmitate (270)



To a solution of **269**[121] (604 mg, 3.24 mmol) in MeOH (32 mL) was added K_2CO_3 (4.4 g, 32.4 mmol, 10.0 equiv). The mixture was stirred at r.t. for 6 h, then filtered and concentrated under reduced pressure. Purification was performed by column chromatography (CH_2Cl_2/MeOH 98:2) to afford the diol as a yellow oil in quantitative yield.

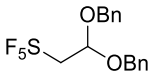
^{1}H NMR spectrum in accordance with literature:[211] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.84 – 5.54 (m, 2H), 4.08 (d, *J* = 4.6 Hz, 2H), 3.65 (t, *J* = 6.1 Hz, 2H), 2.65 (s, 1H), 2.58 (s, 1H), 2.37 – 2.21 (m, 2H).

To a solution of (*E*)-pent-2-ene-1,5-diol (100 mg, 0.979 mmol) in 9.8 mL CH_2Cl_2 (9.8 mL) at 0 °C was added Et_3N (410 μL, 2.94 mmol, 3.0 equiv) followed by palmitoyl chloride (743 μL, 2.45 mmol, 2.5 equiv). The mixture was stirred for 10 h at r.t. Saturated aqueous $NaHCO_3$ solution was added, the layers were separated and extraction was made with CH_2Cl_2 (3x). Combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 95:5) to afford **270** as a white solid (522 mg, 0.902 mmol, 92%).

[211] J. R. Coombs, F. Haeffner, L. T. Kliman, J. P. Morken, *J. Am. Chem. Soc.* **2013**, *135*, 11222–11231.

TLC: R_f = 0.24 (Hex/EtOAc 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.79 – 5.60 (m, 2H), 4.52 (dd, *J* = 5.9, 0.9 Hz, 2H), 4.11 (t, *J* = 6.7 Hz, 2H), 2.39 (qd, *J* = 6.7, 1.0 Hz, 2H), 2.29 (td, *J* = 7.6, 6.2 Hz, 4H), 1.69 – 1.51 (m, 4H), 1.37 – 1.18 (m, 48H), 0.92 – 0.83 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.9, 173.7, 131.0, 126.9, 64.7, 63.2, 34.5, 32.1, 31.8, 29.94 – 29.72 (m, 12C), 29.6 (2C) , 29.5 (2C) , 29.4 (2C) , 29.3 (2C) , 25.13 (2C) , 25.11 (2C) , 22.9 (2C) , 14.3 (2C); **IR** (neat): 2955, 2916, 2849, 1733, 1473, 1462, 1394, 1309, 1287, 1265, 1242, 1219, 1195, 1174, 1099, 961, 730, 719 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{37}H_{74}NO_4$ $[M+NH_4]^+$ 596.5612, found 596.5606.

(((2-Pentafluorosulfanylethane-1,1-diyl)bis(oxy))bis(methylene))dibenzene (280)

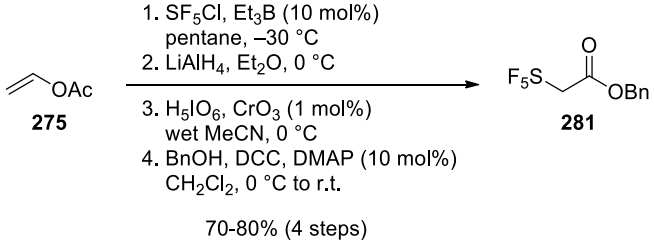


A mixture of **43**[42] (55 mg, 0.19 mmol) and benzyl alcohol (135 µL, 1.30 mmol, 6.9 equiv) was stirred at 100 °C for 72 h. After cooling down to r.t., H_2O was added and extraction was made with Et_2O (3x). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/toluene 9:1 to 8:2) to afford **280** as a colorless oil (52 mg, 0.14 mmol, 75%).

TLC: R_f = 0.54 (Hex/EtOAc 95:5); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.46 – 7.31 (m, 10H), 5.27 (t, *J* = 5.1 Hz, 1H), 4.71 (d, *J* = 11.5 Hz, 2H), 4.63 (d, *J* = 11.5 Hz, 2H), 3.94 (pd, *J* = 8.3, 5.0 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 136.9, 128.7, 128.2, 128.0, 97.7 (p, $^3J_{CF}$ = 5.3 Hz), 72.5 (p, $^2J_{CF}$ = 12.4 Hz), 69.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 83.6 (apparent m, 1F), 67.58 (dt, $^2J_{FF}$ = 146.9, $^3J_{HF}$ = 7.9 Hz, 4F); **IR** (neat): 3067, 3034, 2876, 1118, 1046, 815, 734, 695, 630, 594 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{16}H_{17}F_5NaO_2S$ $[M+Na]^+$ 391.0762, found 391.0763.

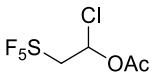
3.2.2.2. Aldol Reactions with *α*-SF_5-Enolate

*Four-step preparation of benzyl SF_5-acetate **281***:



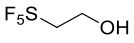
Scheme 3.2.1. Preparation of benzyl SF_5-acetate **281**.

1-Chloro-2-pentafluorosulfanylethyl acetate (43)



Following a slightly modified procedure described by Dolbier,[42] in a two-necked flask equipped with a dry ice reflux condenser was introduced pentane (160 mL), which was then cooled down at –78 °C. SF_5Cl (7.7 g, 46.4 mmol, 1.2 equiv) and vinyl acetate (3.6 mL, 38.7 mmol) were added. The solution was warmed at –40 °C and Et_3B was dropwisely added (3.9 mL, 1.0 M in hexane, 3.9 mmol, 0.1 equiv). The mixture was stirred for 1.5 h between –30 and –20 °C and then warmed at room temperature. Then aqueous $NaHCO_3$ solution was added, the layers were separated and extraction was made with Et_2O (2x). Combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure to afford **43** as a colorless oil, which was used in the next step without any further purification. NMR spectra consistent with those found in the literature.

2-Pentafluorosulfanylethan-1-ol (283)

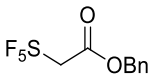


To a solution of crude **43** in Et_2O (260 mL) at 0 °C was slowly added $LiAlH_4$ (9.7 mL, 4.0 M in Et_2O, 38.7 mmol, 1.0 equiv). After 15 min, aqueous Rochelle salt solution was added and the mixture was stirred for 1 h at room temperature. Extraction was made with Et_2O (3x), and the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure (400 mPa, 40 °C). The crude alcohol was used in the next step without any further purification. NMR spectra consistent with those found in the literature.[212]

TLC: R_f = 0.39 (Hex/EtOAc 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.20 – 4.00 (m, 2H), 3.99 – 3.79 (m, 2H), 1.88 (t, J = 6.5 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 73.5 (p, $^2J_{CF}$ = 11.5 Hz), 58.6 (p, $^3J_{CF}$ = 4.7 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 84.4 (apparent m, 1F), 66.1 (dt, $^2J_{FF}$ = 145.1 Hz, $^3J_{FH}$ = 7.9 Hz, 4F); **IR** (neat): 3360, 2972, 1079, 1041, 8071, 637, 552 cm^{-1}.

[212] R. W. Winter, G. L. Gard, *J. Fluorine Chem.* **2006**, *127*, 1188–1194.

Benzyl 2-pentafluorosulfanylacetate (281)

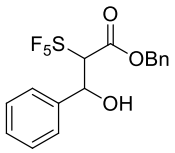


Following Zhao's oxidation procedure,[127] to a solution of crude **283** in wet MeCN (200 mL, containing 1% of H_2O) at 0 °C was dropwisely added a solution of H_5IO_6 (30.9 g, 135.0 mmol, 3.5 equiv) and CrO_3 (40 mg, 0.39 mmol, 0.01 equiv) in wet MeCN (200 mL). The reaction was stirred at 0 °C for 2 h and then quenched with a solution of Na_2HPO_4 (12 g in 200 mL H_2O). Extraction was made with Et_2O (3x), and the combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The crude SF_5-acetic acid **273** was then dissolved in CH_2Cl_2 (260 mL), and benzyl alcohol (8.0 mL, 77.0 mmol, 2.0 equiv) and 4-DMAP (0.47 g, 3.87 mmol, 0.1 equiv) were added. The mixture was cooled down at 0 °C and DCC (12.0 g, 58.0 mmol, 1.5 equiv) was added. After stirring for 2 h at r.t., the reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 99:1 to 98:2) to afford **2** as a colorless oil (8.50 g, 30.8 mmol, 80%).

TLC: R_f = 0.35 (Hex/EtOAc 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 – 7.31 (m, 5H), 5.24 (s, 2H), 4.34 (p, $^3J_{FH}$ = 7.6 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 162.2 (p, $^3J_{CF}$ = 4.7 Hz), 134.5, 129.0, 128.9, 128.7, 70.7 (p, $^2J_{CF}$ = 17.0 Hz), 68.5; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 78.9 (apparent m, 1F), 71.0 (apparent m, $^2J_{FF}$ = 148.4 Hz, 4F); **IR** (neat): 3040, 2928, 1746, 1307, 1264, 1156, 828, 696, 537 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_9H_9F_5O_2S$ $[M]^+$ 276.0238, found 276.0240.

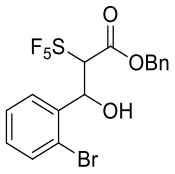
*General procedure for the aldol reaction with benzyl SF_5-acetate **281***: To a solution of **281** (20 mg, 0.073 mmol) in 0.35 mL CH_2Cl_2 (0.35 mL) at –78 °C was slowly added *n*-Bu_2BOTf (146 µL, 1.0 M in CH_2Cl_2, 0.146 mmol, 2.0 equiv), and then DIPEA (38 µL, 0.218 mmol, 3.0 equiv). The mixture was stirred for 30 min at –78 °C and then for 30 min at –20 °C. Then the mixture was cooled down to –45 °C and benzaldehyde (9.3 mg, 0.087 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) was slowly added. The reaction was stirred at –45 ° for 1 h and then quenched with pH 7 phosphate buffer (0.8 mL). MeOH (0.8 mL) and 30% H_2O_2 solution (0.8 mL) were added and the mixture was vigorously stirred at r.t. for 8 h. Extraction was made with CH_2Cl_2 (3x), the combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Ultrapure Silica from SiliCycle, Hex/EtOAc 95:5 to 9:1) to afford the title compound as a colorless oil (23 mg, 0.061 mmol, 84%, d.r. = 2.7:1).

Benzyl 3-hydroxy-3-phenyl-2-(pentafluorosulfanyl)propanoate (289)



TLC: R_f = 0.37 (Hex/EtOAc 85:15); NMR data for the major diastereoisomer only: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 – 7.27 (m, 8H), 7.15 – 7.10 (m, 2H), 5.54 (dd, *J* = 9.1, 3.8 Hz, 1H), 5.13 (d, *J* = 2.2 Hz, 2H), 4.80 – 4.68 (m, 1H), 4.25 (d, *J* = 9.2 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.4 (apparent m), 139.1, 134.0, 129.0, 128.9, 128.8, 128.7, 128.4, 126.1, 86.6 (p, $^2J_{CF}$ = 9.4 Hz), 72.6 (p, $^3J_{CF}$ = 3.0 Hz), 68.7; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 80.4 (apparent m, 1F), 66.4 (apparent m, $^2J_{FF}$ = 147.0 Hz, 4F); **IR** (neat): 3492, 2926, 1745, 1456, 1159, 827, 788, 746, 696, 649, 569 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{16}H_{15}F_5NaO_3S$ $[M+Na]^+$ 405.0554, found 405.0553.

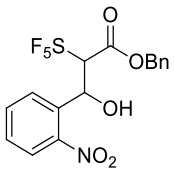
Benzyl 3-(2-bromophenyl)-3-hydroxy-2-(pentafluorosulfanyl)propanoate (290)



Following general procedure, **281** (20 mg, 0.072 mmol) and 2-bromobenzaldehyde (16 mg, 0.087 mmol, 1.2 equiv) were converted into **290** as a white solid (28 mg, 0.061 mmol, 84%, d.r. = 2.7:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/EtOAc 95:5 to 9:1).

TLC: R_f = 0.33 (Hex/EtOAc 9:1); NMR data for the major diastereoisomer only: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.38 – 7.26 (m, 4H), 7.23 – 7.20 (m, 1H), 7.20 – 7.13 (m, 2H), 7.09 – 7.04 (m, 1H), 5.81 (dd, *J* = 9.9, 2.4 Hz, 1H), 5.07 (s, 2H), 4.93 – 4.83 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$); δ 165.5 (p, $^3J_{CF}$ = 2.9 Hz), 137.6, 133.9, 133.3, 130.2, 128.9, 128.8, 128.5, 128.2, 128.1, 121.7, 83.5 (p, ^2JCF = 10.5 Hz), 72.1 (p, $^3J_{CF}$ = 2.7 Hz), 68.7; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 80.0 (apparent m, 1F), 66.4 (apparent m, $^2J_{FF}$ = 147.0 Hz, 4F); **IR** (neat): 3492, 2989, 1721, 1343, 1249, 1163, 820, 784, 745, 699, 593, 560 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{16}H_{14}BrF_5NaO_3S$ $[M+Na]^+$ 482.9659, found 482.9653.

benzyl 3-hydroxy-3-(2-nitrophenyl)-2-(pentafluorosulfanyl)propanoate (291)

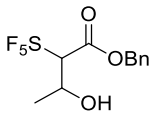


Following general procedure, **281** (1.40 g, 5.05 mmol) and 2-nitrobenzaldehyde (919 mg, 6.1 mmol, 1.2 equiv) were converted into **291** as a yellowish solid (1.87 g, 4.381 mmol, 86%, d.r. = 4.2:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/CH_2Cl_2 1:1 to 2:8). Diastereoisomers could be separated by preparative TLC ($CHCl_3$/EtOAc 99.5:0.5; three successive runs) for characterization. Crystals suitable for X-ray analysis of the major diastereoisomer were produced by recrystallization from fluorobenzene by slow evaporation.

Minor diastereoisomer (*syn*): **TLC**: R_f = 0.27 (Hex/EtOAc 8:2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.87 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.68 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.56 (td, *J* = 7.6, 1.4 Hz, 1H), 7.47 – 7.37 (m, 1H), 7.35 – 7.28 (m, 3H), 7.21 – 7.10 (m, 2H), 6.07 (d, *J* = 7.5 Hz, 1H), 5.13 – 5.00 (m, 2H), 4.96 (d, *J* = 12.0 Hz, 1H), 3.65 (br, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.3 (apparent m), 148.1, 133.7, 133.6, 133.1, 129.73, 129.69, 128.8, 128.7, 128.6, 125.1, 87.5 (p, $^2J_{CF}$ = 9.7 Hz), 68.7 (apparent m), 68.6; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 80.5 (apparent m, 1F), 68.8 (d, $^2J_{FF}$ = 145.6 Hz, 4F); **IR** (neat): 3506, 2941, 1743, 1529, 1349, 1161, 841, 786, 754, 697, 598, 574 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{16}H_{14}F_5NNaO_5S$ $[M+Na]^+$ 450.0405, found 450.0414.

Major diastereoisomer (*anti*): **TLC**: R_f = 0.27 (Hex/EtOAc 8:2); **1H NMR** (300 MHz, $CDCl_3$): δ 8.10 – 8.02 (m, 1H), 7.59 – 7.54 (m, 1H), 7.54 – 7.41 (m, 2H), 7.36 – 7.27 (m, 3H), 7.17 – 7.09 (m, 2H), 6.14 (dd, J = 9.4, 2.7 Hz, 1H), 5.11 (d, J = 4.4 Hz, 2H), 5.07 (m, 1H), 4.88 (d, J = 9.4 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.7 (apparent m), 147.3, 134.7, 134.2, 133.8, 129.8, 129.2, 129.0, 128.8, 128.7, 125.5, 84.1 (p, $^2J_{CF}$ = 11.2 Hz), 69.1 (p, $^3J_{CF}$ = 3.3 Hz), 68.9; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 79.5 (apparent m, 1F), 66.7 (apparent m, $^2J_{FF}$ = 147.1 Hz, 4F); **IR** (neat): 3473, 3012, 1721, 1529, 1344, 1165, 860, 837, 820, 789, 737 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{16}H_{14}F_5NNaO_5S$ $[M+Na]^+$ 450.0405, found 450.0408.

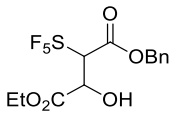
Benzyl 3-hydroxy-2-(pentafluorosulfanyl)butanoate (292)



Following general procedure, **281** (19 mg, 0.069 mmol) and acetaldehyde (83 μL, 1.0 M solution in CH_2Cl_2 prepared with freshly distilled acetaldehyde, 0.083 mmol, 1.2 equiv) were converted into **292** as a colorless oil (18 mg, 0.056 mmol, 82%, d.r. = 2.0:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/EtOAc 95:5 to 9:1).

TLC: R_f = 0.30 (Hex/EtOAc 85:15); minor diastereoisomer (*syn*): **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.45 – 7.31 (m, 5H), 5.28 (d, *J* = 0.9 Hz, 2H), 4.65 – 4.51 (m, 1H), 4.45 – 4.28 (m, 1H), 3.12 (d, *J* = 8.1 Hz, 1H), 1.36 (dt, *J* = 6.5, 0.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.5 (p, $^3J_{CF}$ = 3.0 Hz), 134.3, 129.0, 128.9, 128.6, 87.4 (p, $^2J_{CF}$ = 9.8 Hz), 68.7, 66.7 (p, $^3J_{CF}$ = 3.0 Hz), 22.0 (apparent m); **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 80.0 (apparent m, 1F), 66.3 (dd, $^2J_{FF}$ = 146.0, J= 5.8 Hz, 4F); major diastereoisomer (*anti*): **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.45 – 7.31 (m, 5H), 5.23 (s, 2H), 4.65 – 4.51 (m, 1H), 4.51 – 4.40 (m, 1H), 2.52 (s, 1H), 1.29 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.6 (p, $^3J_{CF}$ = 3.3 Hz), 134.3, 129.0, 128.9, 128.7, 90.2 (p, $^2J_{CF}$ = 8.5 Hz), 68.6, 67.4 (p, $^3J_{CF}$ = 2.4 Hz), 20.7 (apparent m); **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 81.8 (apparent m, 1F), 67.3 (dd, $^2J_{FF}$ = 145.3, *J* = 5.3 Hz, 4F); **IR** (neat): 3475, 2925, 1743, 1303, 1256, 1168, 830, 786, 749, 697, 599 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{11}H_{13}F_5NaO_3S$ $[M+Na]^+$ 343.0398, found 343.0399.

1-Benzyl 4-ethyl 3-hydroxy-2-(pentafluorosulfanyl)succinate (293)

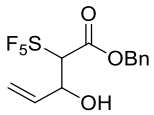


Following general procedure, **281** (17 mg, 0.062 mmol) and ethyl glyoxalate (27 mg, 30% solution in toluene, 0.092 mmol, 1.5 equiv) were converted into **293** as a colorless oil (14 mg, 0.037 mmol, 60%, d.r. = 1.1:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/EtOAc 9:1).

TLC: R_f = 0.30 (Hex/EtOAc 8:2); NMR data for mixture of two diastereoisomers: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.44 – 7.32 (m, 10H), 5.27 – 5.22 (m, 4H), 4.94 – 4.71 (m, 4H), 4.30 – 4.07 (m, 4H), 4.00 (d, *J* = 10.1 Hz, 1H), 3.42 (d, *J* = 4.7 Hz, 1H), 1.33 – 1.17 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.1, 169.9, 164.5 (apparent m), 163.9 (apparent m), 134.3, 134.1, 129.1, 129.0, 128.87, 128.85, 128.73, 128.70, 84.3 (p, $^2J_{CF}$ = 11.7 Hz), 82.8 (p, $^2J_{CF}$ =

12.7 Hz), 70.5 (p, $^{3}J_{CF}$ = 3.0 Hz), 70.4 (t, $^{3}J_{CF}$ = 2.6 Hz), 69.0, 68.9, 63.1, 63.0, 14.1, 14.0; **^{19}F NMR** (282 MHz, $CDCl_3$): 2 x AB_4 system δ 81.4 – 77.6 (apparent m, 2F), 69.2 (apparent m, $^{2}J_{FF}$ = 147.1 Hz, 4F), 67.0 (apparent m, $^{2}J_{FF}$ = 148.3 Hz, 4F); **IR** (neat): 3475, 2927, 1739, 1303, 1240, 1168, 1020, 843, 797, 752, 698, 601 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{13}H_{15}F_5NaO_5S$ $[M+Na]^+$ 401.0453, found 401.0454.

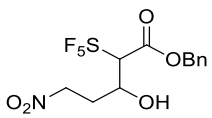
Benzyl 3-hydroxy-2-(pentafluorosulfanyl)pent-4-enoate (294)



Following general procedure, **281** (21 mg, 0.076 mmol) and acrolein (90 μL, 1.0 M in CH_2Cl_2 prepared with freshly distilled acrolein, 0.091 mmol, 1.2 equiv) were converted into **294** as a colorless oil (21 mg, 0.063 mmol, 83%, d.r. = 1.7:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/EtOAc 9:1).

TLC: R_f = 0.28 (Hex/EtOAc 85:15); NMR data for mixture of two diastereoisomers: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.45 – 7.28 (m, 10H), 5.92 – 5.73 (m, 2H), 5.51 – 5.36 (m, 2H), 5.31 – 5.21 (m, 4H), 5.20 (s, 2H), 4.98 – 4.81 (m, 2H), 4.58 – 4.39 (m, 2H), 3.58 (d, *J* = 9.1 Hz, 1H), 2.48 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.2 (p, $^{3}J_{CF}$ = 3.1 Hz), 164.0 (p, $^{3}J_{CF}$ = 3.2 Hz), 135.5 (apparent t, $^{4}J_{CF}$ = 1.7 Hz), 134.5 (apparent t, $^{4}J_{CF}$ = 1.6 Hz), 134.3, 134.2, 129.0, 128.9, 128.9, 128.8, 128.8, 128.7, 120.4, 118.8, 88.4 (p, $^{2}J_{CF}$ = 9.0 Hz), 85.2 (p, $^{2}J_{CF}$ = 10.0 Hz), 71.9 (p, $^{3}J_{CF}$ = 2.6 Hz), 71.1 (p, $^{3}J_{CF}$ = 3.1 Hz), 68.8, 68.5; **^{19}F NMR** (282 MHz, $CDCl_3$): 2 x AB_4 system δ 81.3 (apparent m, 1F) 80.4 (apparent m, 1F), 67.8 (apparent m, $^{2}J_{FF}$ = 147.0 Hz, 4F), 66.80 (apparent m, $^{2}J_{FF}$ = 147.1 Hz, 4F); **IR** (neat): 3444, 2956, 1745, 1699, 1674, 1452, 1380, 1238, 1167, 836, 790, 739, 696, 598, 569 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{12}H_{13}F_5NaO_3S$ $[M+Na]^+$ 355.0394, found 355.0394.

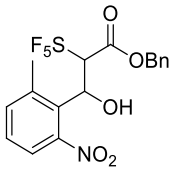
Benzyl 3-hydroxy-5-nitro-2-(pentafluorosulfanyl)pentanoate (295)



Following general procedure, **281** (258 mg, 0.93 mmol) and 3-nitropropanal (116 mg, 1.12 mmol, 1.2 equiv) were converted into **295** as a yellowish solid (154 mg, 0.41 mmol, 44%, d.r. = 1.0:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/EtOAc 9:1 to 8:2).

TLC: R_f = 0.25 (Hex/EtOAc 8:2); NMR data for mixture of two diastereoisomers: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.43 – 7.33 (m, 10H), 5.30 (s, 2H), 5.26 (d, *J* = 1.4 Hz, 2H), 4.69 – 4.35 (m, 8H), 3.39 (d, *J* = 8.4 Hz, 1H), 2.99 (s, 1H), 2.53 – 2.35 (m, 1H), 2.35 – 2.10 (m, 2H), 2.11 – 1.92 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.3 (p, $^3J_{CF}$ = 3.0 Hz), 164.4 (apparent m), 134.0, 133.9, 129.3, 129.2, 129.0, 128.95, 128.9, 128.8, 88.2 (p, $^2J_{CF}$ = 9.7 Hz), 85.7 (p, $^2J_{CF}$ = 11.1 Hz), 71.7, 71.6, 69.3, 69.1, 68.2 (apparent m), 67.5 (apparent m), 32.5, 31.1; **^{19}F NMR** (282 MHz, $CDCl_3$): 2 x AB_4 system δ 81.0 (apparent m, 1F) 80.0 (apparent m, 1F), 68.5 (d, $^2J_{FF}$ = 146.1 Hz, 4F), 66.9 (d, $^2J_{FF}$ = 147.0 Hz, 4F); **IR** (neat): 3533, 3037, 2967, 1731, 1548, 1380, 1180, 833, 740, 696, 595 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{12}H_{14}F_5NNaO_5S$ $[M+Na]^+$ 402.0405, found 402.0405.

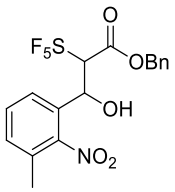
Benzyl 3-(2-methyl-6-nitrophenyl)-3-hydroxy-2-(pentafluorosulfanyl)propanoate (313)



Following general procedure, **281** (209 mg, 0.757 mmol) and 2-methyl-6-nitrobenzaldehyde (150 mg, 0.908 mmol, 1.2 equiv) were converted into **313** as a yellow oil (313 mg, 0.709 mmol, 94%, d.r. > 20:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/ CH_2Cl_2 1:1 to 3:7).

TLC: R_f = 0.39 (Hex/EtOAc 8:2); NMR data for the major diastereoisomer only: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.70 – 7.64 (m, 1H), 7.51 (ddd, *J* = 7.6, 1.5, 0.7 Hz, 1H), 7.43 – 7.33 (m, 6H), 5.98 (apparent t, *J* = 10.2 Hz, 1H), 5.37 (d, *J* = 12.2 Hz, 1H), 5.31 (d, *J* = 12.3 Hz, 1H), 5.10 (dp, *J* = 10.4, 6.1 Hz, 1H), 4.00 (d, *J* = 9.9 Hz, 1H), 2.59 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.1 (p, $^3J_{CF}$ = 3.4 Hz), 140.4, 136.7, 134.6, 130.6, 129.4, 128.8 (s with shoulder, 2C) , 128.5, 123.7, 84.8 (p, $^2J_{CF}$ = 9.6 Hz), 68.8, 67.4 (p, $^3J_{CF}$ = 3.7 Hz), 20.6; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 80.0 (apparent m, 1F), 66.7 (apparent m, $^2J_{FF}$ = 147.3 Hz, 4F); **IR** (neat): 3507, 3036, 2963, 1749, 1530, 1308, 1165, 892, 844, 795, 753, 697, 599 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{17}H_{20}F_5N_2O_5S$ $[M+NH_4]^+$ 459.1008, found 459.1007.

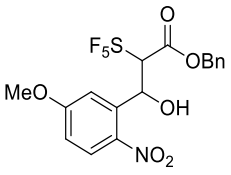
Benzyl 3-hydroxy-3-(3-methyl-2-nitrophenyl)-2-(pentafluorosulfanyl)propanoate (314)



Following general procedure, **281** (202 mg, 0.731 mmol) and 3-methyl-2-nitrobenzaldehyde (145 mg, 0.878 mmol, 1.2 equiv) were converted into **314** as a yellowish solid (297 mg, 0.673 mmol, 92%, d.r. = 6.6:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/toluene 3:7 to remove remaining aldehyde, followed by Hex/EtOAc 9:1 to 8:2).

TLC: R_f = 0.29 (Hex/EtOAc 8:2); NMR data for the major diastereoisomer only: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38 – 7.31 (m, 3H), 7.29 – 7.26 (m, 3H), 7.24 – 7.19 (m, 2H), 5.52 (dd, *J* = 8.8, 3.5 Hz, 1H), 5.18 (s, 2H), 4.91 (pd, *J* = 6.2, 3.5 Hz, 1H), 4.67 (d, *J* = 8.8 Hz, 1H), 2.34 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.5 (p, $^3J_{CF}$ = 3.6 Hz), 149.5, 133.9, 132.5, 132.2, 131.1, 130.8, 129.1, 128.8, 128.7, 125.6, 84.7 (p, $^2J_{CF}$ = 10.7 Hz), 69.0, 68.7 (p, $^3J_{CF}$ = 3.3 Hz), 17.9; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 79.2 (apparent m, 1F), 66.6 (apparent m, $^2J_{FF}$ = 146.2 Hz, 4F); **IR** (neat): 3482, 3036, 1745, 1530, 1456, 1366, 1167, 851, 793, 751, 600 cm^{-1}; **HRMS** (ESI) *m/z* calculated for $C_{17}H_{16}F_5NNaO_5S$ $[M+Na]^+$ 464.0562, found 464.0556.

Benzyl 3-(5-methoxy-2-nitrophenyl)-3-hydroxy-2-(pentafluorosulfanyl)propanoate (315)

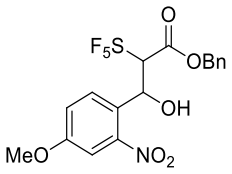


Following general procedure, **281** (196 mg, 0.710 mmol) and 5-methoxy-2-nitrobenzaldehyde (154 mg, 0.851 mmol, 1.2 equiv) were converted into **315** (280 mg, 0.612 mmol, 86%, d.r. = 5.7:1) as a slightly tanned solid after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/CH_2Cl_2 1:1 to 2:8).

TLC: R_f = 0.40 (Hex/EtOAc 7:3); NMR data for the major diastereoisomer only: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.17 (d, *J* = 9.3 Hz, 1H), 7.36 – 7.26 (m, 3H), 7.12 – 7.02 (m, 3H), 6.88 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.26 (dd, *J* = 9.6, 2.5 Hz, 1H), 5.15 (d, *J* = 12.2 Hz, 1H), 5.10 – 5.00 (m, 2H), 4.90 (d, *J* = 9.7 Hz, 1H), 3.79 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.7 (p, $^3J_{CF}$ =

3.2 Hz), 164.2, 139.8, 138.0, 133.9, 128.9, 128.8, 128.6, 128.2, 114.6, 114.3, 83.8 (p, $^2J_{CF}$ = 11.4 Hz), 69.6 (p, $^3J_{CF}$ = 3.2 Hz), 68.7, 56.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 79.6 (apparent m, 1F), 66.7 (apparent m, $^2J_{FF}$ = 147.1 Hz, 4F); **IR** (neat): 3481, 3035, 2946, 2845, 1748, 1582, 1517, 1335, 1293, 1243, 1166, 858, 844, 800, 698 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{17}H_{16}F_5NNaO_6S$ $[M+Na]^+$ 480.0511, found 480.0512.

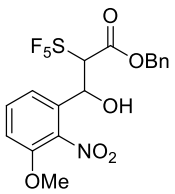
Benzyl 3-hydroxy-3-(4-methoxy-2-nitrophenyl)-2-(pentafluorosulfanyl)propanoate (316)



Following general procedure, **281** (195 mg, 0.706 mmol) and 4-methoxy-2-nitrobenzaldehyde (153 mg, 0.847 mmol, 1.2 equiv) were converted into **316** as a yellow solid (291 mg, 0.636 mmol, 90%, d.r. = 3.3:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/CH_2Cl_2 1:1 to 2:8).

TLC: R_f = 0.43 (Hex/EtOAc 85:15); NMR data for the major diastereoisomer only: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.54 (d, *J* = 2.5 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.36 – 7.24 (m, 3H), 7.17 – 7.11 (m, 2H), 6.98 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.06 (dd, *J* = 9.4, 2.8 Hz, 1H), 5.16 (d, *J* = 12.1 Hz, 1H), 5.08 (d, *J* = 11.8 Hz, 1H), 5.08 – 4.97 (m, 1H), 4.76 (d, *J* = 9.3 Hz, 1H), 3.87 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.7 (p, $^3J_{CF}$ = 2.8 Hz), 160.1, 147.9, 133.9, 130.2, 129.0, 128.7, 128.7, 126.3, 120.5, 110.0, 84.3 (p, $^2J_{CF}$ = 10.8 Hz), 68.9 (apparent m), 68.7, 56.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 79.8 (apparent m, 1F), 66.61 (apparent m, $^2J_{FF}$ = 147.0 Hz, 4F); IR (neat): 3492, 2962, 2844, 1742, 1620, 1534, 1164, 846, 800 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{17}H_{20}F_5N_2O_6S$ $[M+NH_4]^+$ 475.0957, found 457.0950.

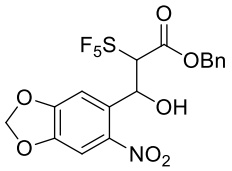
Benzyl 3-hydroxy-3-(3-methoxy-2-nitrophenyl)-2-(pentafluorosulfanyl)propanoate (317)



Following general procedure, **281** (200 mg, 0.724 mmol) and 3-methoxy-2-nitrobenzaldehyde (157 mg, 0.869 mmol, 1.2 equiv) were converted into **317** as a yellowish solid (315 mg, 0.689 mmol, 95%, d.r. = 8.0:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/ CH_2Cl_2 4:6 to 2:8).

TLC: R_f = 0.28 (Hex/EtOAc 7:3);); NMR data for the major diastereoisomer only: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37 – 7.31 (m, 3H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.25 – 7.19 (m, 2H), 7.03 – 6.90 (m, 2H), 5.51 (dd, *J* = 8.8, 3.5 Hz, 1H), 5.18 (s, 2H), 4.88 (pd, *J* = 6.0, 3.5 Hz, 1H), 4.68 (d, *J* = 8.8 Hz, 1H), 3.89 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.5 (p, $^3J_{CF}$ = 2.7 Hz), 151.2, 139.6, 133.9, 132.3, 131.6, 129.0, 128.8, 128.7, 118.9, 113.2, 84.6 (p, $^2J_{CF}$ = 11.1 Hz), 69.0, 68.5 (p, $^3J_{CF}$ = 3.3 Hz), 56.7; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 79.2 (apparent m, 1H), 66.5 (apparent m, $^2J_{FF}$ = 147.1 Hz, 4H); **IR** (neat): 3484, 3035, 2949, 2848, 1742, 1586, 1533, 1370, 1283, 1166, 1059, 846, 753, 698, 601 cm^{-1}; **HRMS** (ESI) *m/z* calculated for $C_{17}H_{20}F_5NN_2O_6S$ $[M+NH_4]^+$ 475.0957, found 475.0958.

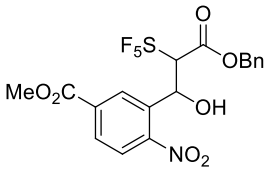
Benzyl 3-hydroxy-3-(6-nitrobenzo[d][1,3]dioxol-5-yl)-2-(pentafluorosulfanyl)propanoate (318)



Following general procedure, **281** (201 mg, 0.728 mmol) and 6-nitropiperonal (176 mg, 0.873 mmol, 1.2 equiv) were converted into **318** as a white solid (317 mg, 0.673 mmol, 92%, d.r. = 5.8:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/CH_2Cl_2 4:6 to 2:8).

TLC: R_f = 0.34 (Hex/EtOAc 7:3); NMR data for the major diastereoisomer only: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.34 – 7.29 (m, 3H), 7.17 – 7.14 (m, 2H), 6.99 (d, *J* = 0.6 Hz, 1H), 6.15 (dd, *J* = 9.3, 2.6 Hz, 1H), 6.11 (d, *J* = 1.2 Hz, 1H), 6.09 (d, *J* = 1.2 Hz, 1H), 5.22 (d, *J* = 12.1 Hz, 1H), 5.08 (d, *J* = 12.1 Hz, 1H), 5.06 – 4.99 (m, 1H), 4.81 (d, *J* = 9.4 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.7 (apparent m), 152.9, 148.2, 141.4, 134.0, 132.3, 128.9, 128.8, 128.5, 108.0, 106.0, 103.5, 83.9 (p, $^2J_{CF}$ = 11.0 Hz), 69.4 (q, $^3J_{CF}$ = 3.5 Hz), 68.7; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 79.6 (apparent m, 1F), 66.7 (apparent m, $^2J_{FF}$ = 147.1 Hz, 4F); **IR** (neat): 3450, 3009, 2926, 1713, 1519, 1506, 1487, 1330, 1266, 1169, 1039, 836, 808, 750, 697 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{17}H_{14}F_5NNaO_7S$ $[M+Na]^+$ 494.0303, found 494.0301.

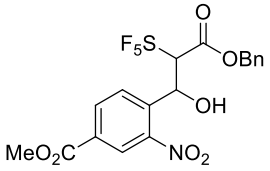
Methyl 3-(3-(benzyloxy)-1-hydroxy-3-oxo-2-pentafluorosulfanylpropyl)-4-nitrobenzoate (319)



Following general procedure, **281** (190 mg, 0.688 mmol) and methyl 3-formyl-4-nitrobenzoate (173 mg, 0.825 mmol, 1.2 equiv) were converted into **319** as a yellow solid (316 mg, 0.651 mmol, 95%, d.r. = 3.6:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/CH_2Cl_2 3:7 to 1:9).

TLC: R_f = 0.48 (Hex/EtOAc 7:3); NMR data for the major diastereoisomer only: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26 (dt, *J* = 1.8, 0.6 Hz, 1H), 8.10 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.08 – 8.04 (m, 1H), 7.34 – 7.21 (m, 3H), 7.15 – 7.08 (m, 2H), 6.12 (dd, *J* = 9.3, 3.1 Hz, 1H), 5.19 (d, *J* = 12.0 Hz, 1H), 5.12 – 5.00 (m, 2H), 4.86 (d, *J* = 9.3 Hz, 1H), 3.98 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.4 (p, $^3J_{CF}$ = 2.5, 1.9 Hz), 164.6, 149.8, 135.0, 134.9, 133.8, 131.0, 130.7, 129.0, 128.7, 128.5, 125.5, 84.1 (p, $^2J_{CF}$ = 11.4 Hz), 69.0, 68.8 (apparent m), 53.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 79.4 (apparent m, 1H), 66.9 (apparent m, $^2J_{FF}$ = 147.0 Hz, 4H); **IR** (neat): 3477, 3036, 2958, 1730, 1535, 1297, 1170, 850, 811, 742, 600 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{18}H_{20}F_5N_2O_7S$ $[M+NH_4]^+$ 503.0906, found 503.0903.

Methyl 4-(3-(benzyloxy)-1-hydroxy-3-oxo-2-pentafluorosulfanylpropyl)-3-nitrobenzoate (320)

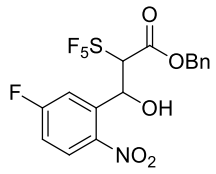


Following general procedure, **281** (197 mg, 0.713 mmol) and methyl 4-formyl-3-nitrobenzoate (179 mg, 0.856 mmol, 1.2 equiv) were converted into **320** as a yellow solid (320 mg, 0.659 mmol, 92%, d.r. = 3.7:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/CH_2Cl_2 1:1 to 3:7).

TLC: R_f = 0.46 (Hex/EtOAc 7:3); NMR data for the major diastereoisomer only: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.64 (d, *J* = 1.8 Hz, 1H), 8.01 (ddd, *J* = 8.3, 1.8, 0.5 Hz, 1H), 7.61 (dt, *J* = 8.2, 0.5 Hz, 1H), 7.39 – 7.22 (m, 3H), 7.16 – 7.07 (m, 2H), 6.17 (dd, *J* = 9.3, 2.8 Hz, 1H), 5.17 (d, *J* = 11.9 Hz, 1H), 5.10 – 4.98 (m, 2H), 4.91 (d, *J* = 9.3 Hz, 1H), 4.00 (s, 3H); **^{13}C NMR**

(101 MHz, $CDCl_3$): δ 165.45 (apparent m), 164.4, 147.2, 138.8, 134.5, 133.7, 131.9, 129.7, 129.2, 128.9, 128.8, 126.4, 83.7 (p, $^2J_{CF}$ = 11.8 Hz), 69.2 – 68.9 (m, 2C), 53.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 79.1 (apparent m, 1F), 66.9 (apparent m, $^2J_{FF}$ = 147.6 Hz, 4F); **IR** (neat): 3480, 2959, 1729, 1538, 1350, 1297, 1162, 851, 750, 698 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{18}H_{20}F_5N_2O_7S$ $[M+NH_4]^+$ 503.0906, found 503.0904.

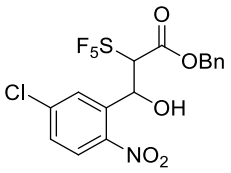
Benzyl 3-(5-fluoro-2-nitrophenyl)-3-hydroxy-2-(pentafluorosulfanyl)propanoate (321)



Following general procedure, **281** (197 mg, 0.713 mmol) and 5-fluoro-2-nitrobenzaldehyde (145 mg, 0.856 mmol, 1.2 equiv) were converted into **321** as a white solid (279 mg, 0.626 mmol, 88%, d.r. = 4.1:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/CH_2Cl_2 4:6 to 2:8).

TLC: R_f = 0.41 (Hex/EtOAc 8:2); NMR data for the major diastereoisomer only: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.15 (dd, *J* = 9.1, 5.0 Hz, 1H), 7.38 – 7.25 (m, 4H), 7.19 – 7.04 (m, 3H), 6.19 (dd, *J* = 9.4, 2.5 Hz, 1H), 5.19 (d, *J* = 12.0 Hz, 1H), 5.08 (d, *J* = 11.9 Hz, 1H), 5.05 – 4.99 (m, 1H), 4.96 (d, *J* = 9.4 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.6 (apparent t, $^3J_{CF}$ = 2.8 Hz), 165.5 (d, $^1J_{CF}$ = 259.5 Hz), 143.1 (d, $^4J_{CF}$ = 3.2 Hz), 138.9 (d, $^3J_{CF}$ = 8.3 Hz), 133.7, 129.2, 128.9, 128.7, 128.6 (d, $^3J_{CF}$ = 8.6 Hz), 116.9 (d, $^2J_{CF}$ = 23.2 Hz), 116.8 (d, $^2J_{CF}$ = 25.7 Hz), 83.50 (p, $^2J_{CF}$ = 11.8 Hz), 69.2 – 69.0 (m, 2C); **^{19}F NMR** (376 MHz, $CDCl_3$): AB_4 system, δ 79.2 (apparent m, 1F), 66.8 (apparent m, $^2J_{FF}$ = 146.0 Hz, 4F), –100.8 (s, 1F); **IR** (neat): 4357, 3118, 3013, 1719, 1589, 1528, 1345, 1167, 836, 804, 756, 698 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{16}H_{13}F_6NNaO_5S$ $[M+Na]^+$ 468.0311, found 468.0309.

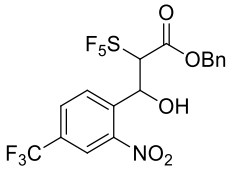
Benzyl 3-(5-chloro-2-nitrophenyl)-3-hydroxy-2-(pentafluorosulfanyl)propanoate (322)



Following general procedure, **281** (225 mg, 0.815 mmol) and 5-chloro-2-nitrobenzaldehyde (180 mg, 0.977 mmol, 1.2 equiv) were converted into **322** as a yellow solid (315 mg, 0.682 mmol, 84%, d.r. = 4.6:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/EtOAc 9:1 to 85:15).

TLC: R_f = 0.41 (Hex/EtOAc 8:2); NMR data for the major diastereoisomer only: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 2.1 Hz, 1H), 7.43 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.37 – 7.29 (m, 3H), 7.18 – 7.11 (m, 2H), 6.17 (dd, *J* = 9.3, 2.6 Hz, 1H), 5.19 (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 12.1 Hz, 1H), 5.07 – 4.96 (m, 1H), 4.93 (d, *J* = 9.3 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.5 (p, $^3J_{CF}$ = 2.8 Hz), 145.4, 141.3, 136.9, 133.7, 130.0, 129.7, 129.2, 128.9, 128.5, 127.1, 83.7 (p, $^2J_{CF}$ = 11.7 Hz), 69.0 (apparent m, 2C); **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, minor isomer: δ 79.2 (apparent m, 1F), 66.85 (apparent m, $^2J_{FF}$ = 146.8, 4F); **IR** (neat): 3459, 3113, 0308, 1744, 1719, 1567, 1523, 1332, 1166, 1114, 957, 830, 795, 750, 696, 601, 504 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{16}H_{13}ClF_5NNaO_5S$ $[M+Na]^+$ 484.0015, found 484.0020.

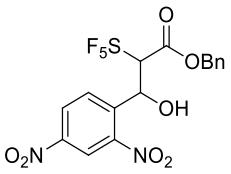
Benzyl 3-hydroxy-3-(2-nitro-4-(trifluoromethyl)phenyl)-2-(pentafluorosulfanyl)propanoate (323)



Following general procedure, **281** (195 mg, 0.706 mmol) and 2-nitro-4-(trifluoromethyl)benzaldehyde (186 mg, 0.847 mmol, 1.2 equiv) were converted into **323** as a slightly yellow solid (282 mg, 0.569 mmol, 81%, d.r. = 4.0:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/CH_2Cl_2 4:6 to 2:8).

TLC: minor diastereoisomer: R_f = 0.49 (Hex/EtOAc 8:2); major diastereoisomer: R_f = 0.57 (Hex/EtOAc 8:2); NMR data for the major diastereoisomer only: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.29 (dt, *J* = 1.8, 0.6 Hz, 1H), 7.64 (dq, *J* = 8.4, 0.7 Hz, 1H), 7.62 – 7.54 (m, 1H), 7.37 – 7.27 (m, 3H), 7.17 – 7.12 (m, 2H), 6.17 (dd, *J* = 9.2, 2.6 Hz, 1H), 5.24 (d, *J* = 11.9 Hz, 1H), 5.08 – 4.97 (m, 2H), 4.97 (d, *J* = 9.2 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.5 (apparent m), 147.2, 138.5, 133.7, 132.4 (q, $^2J_{CF}$ = 34.5 Hz), 130.3 – 130.5 (m, 2C), 129.3, 129.1, 128.8, 122.7 (q, $^3J_{CF}$ = 3.8 Hz), 122.5 (q, $^1J_{CF}$ = 273.0 Hz), 83.5 (p, $^2J_{CF}$ = 12.2 Hz), 69.2, 68.9 (p, $^3J_{CF}$ = 3.5 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 79.1 (apparent m, 1F), 66.8 (apparent m, $^2J_{FF}$ = 147.0 Hz, 4F), –63.5 (s, 3F); **IR** (neat): 3473, 3096, 3037, 3967, 1746, 1544, 1326, 1143, 1086, 848, 798, 699 cm^{-1}; **HRMS** (ESI) *m/z* calculated for $C_{17}H_{17}F_8N_2O_5S$ $[M+NH_4]^+$ 513.0725, found 513.0721.

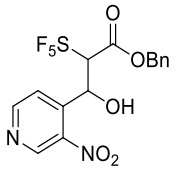
Benzyl 3-(2,4-dinitrophenyl)-3-hydroxy-2-(pentafluorosulfanyl)propanoate (324)



Following general procedure, **281** (204 mg, 0.739 mmol) and 2,4-dinitrobenzaldehyde (174 mg, 0.886 mmol, 1.2 equiv) were converted into **324** as a yellow solid (274 mg, 0.580 mmol, 79%, d.r. = 3.8:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, Hex/CH_2Cl_2 4:6 to 1:9).

TLC: minor diastereoisomer: R_f = 0.30 (Hex/EtOAc 8:2); major diastereoisomer: R_f = 0.23 (Hex/EtOAc 8:2); NMR data for the major diastereoisomer only: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.82 (d, *J* = 2.3 Hz, 1H), 8.04 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.39 – 7.30 (m, 1H), 7.30 – 7.23 (m, 2H), 7.20 – 7.10 (m, 2H), 6.21 (dd, *J* = 9.1, 2.6 Hz, 1H), 5.27 (d, *J* = 11.7 Hz, 1H), 5.01 – 4.94 (m, 2H), 4.92 (d, *J* = 9.2 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.2 (p, $^3J_{CF}$ = 2.8 Hz), 147.8, 147.1, 140.8, 133.7, 131.0, 129.4, 129.3, 128.8, 127.8, 120.7, 83.2 (p, $^2J_{CF}$ = 13.5 Hz), 69.2, 69.0 (apparent t, $^3J_{CF}$ = 3.5 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 79.0 (apparent m, 1F), 67.1 (apparent m, $^2J_{FF}$ = 146.9 Hz, 4F); **IR** (neat): 3483, 3110, 2953, 2884, 1745, 1608, 1538, 1347, 1166, 847, 790, 738, 699 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{16}H_{13}F_5N_2NaO_7S$ $[M+Na]^+$ 495.0256, found 495.0256.

Benzyl 3-hydroxy-3-(3-nitropyridin-4-yl)-2-(pentafluorosulfanyl)propanoate (325)

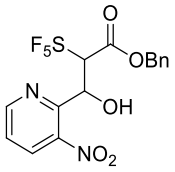


Following general procedure, **281** (197 mg, 0.713 mmol) and 3-nitroisonicotinaldehyde (130 mg, 0.856 mmol, 1.2 equiv) were converted into **235** as a white solid (253 mg, 0.591 mmol, 83%, d.r. = 4.9:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, CH_2Cl_2/EtOAc 95:5 to 9:1).

TLC: R_f = 0.24 (Hex/EtOAc 7:3); NMR data for the major diastereoisomer only: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.22 (s, 1H), 8.59 (d, *J* = 5.2 Hz, 1H), 7.46 (d, *J* = 5.2 Hz, 1H), 7.40 – 7.28 (m, 3H), 7.20 – 7.10 (m, 2H), 6.18 (d, *J* = 2.9 Hz, 1H), 5.18 (d, *J* = 11.9 Hz, 1H), 5.08 (d, *J* = 11.9 Hz, 1H), 4.99 (pd, $^3J_{FH}$ = 5.7, 2.8 Hz, 1H); **13C NMR** (101 MHz, $CDCl_3$): δ 165.4 (apparent m), 154.7, 146.6, 143.7, 142.9, 133.6, 129.4, 128.9, 128.9, 123.0, 83.0 (p, $^2J_{CF}$ =

12.8 Hz), 69.3, 68.5 (p, $^3J_{CF}$ = 3.0 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 78.8 (apparent m, 1F), 67.0 (apparent m, $^2J_{FF}$ = 144.3 Hz, 4F); **IR** (neat): 3473, 3070, 2875, 1747, 1603, 1533, 1349, 1165, 844, 794, 751, 698, 597 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{15}H_{14}F_5N_2O_5S$ $[M+H]^+$ 429.0538, found 429.0541.

Benzyl 3-hydroxy-3-(3-nitropyridin-2-yl)-2-(pentafluorosulfanyl)propanoate (326)

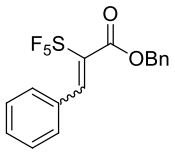


Following general procedure, **281** (196 mg, 0.710 mmol) and 3-nitropicolinaldehyde (130 mg, 0.856 mmol, 1.2 equiv) were converted into **326** as a white solid (226 mg, 0.528 mmol, 74%, d.r. = 6.4:1) after purification by column chromatography (Ultrapure Silica from SiliCycle, CH_2Cl_2/EtOAc 99:1). The major diastereoisomer could be isolated, and crystals suitable for X-ray analysis were obtained by slow evaporation from $CDCl_3$.

TLC: Minor diastereoisomer: R_f = 0.28 (CH_2Cl_2/EtOAc 99:1); Major diastereoisomer: R_f = 0.39 (CH_2Cl_2/EtOAc 99:1); NMR data for the major diastereoisomer only: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.46 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.31 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.43 (dd, *J* = 8.2, 4.7 Hz, 1H), 7.40 – 7.34 (m, 3H), 7.34 – 7.29 (m, 2H), 6.25 (dd, *J* = 10.5, 3.6 Hz, 1H), 5.32 – 5.20 (m, 2H), 5.15 (d, *J* = 12.1 Hz, 1H), 4.75 (d, *J* = 10.6 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.7 (p, $^3J_{CF}$ = 2.9 Hz), 152.5, 152.2, 144.7, 134.5, 133.5, 128.9, 128.8 (s with shoulder, 2C), 124.5, 84.0 (p, $^2J_{CF}$ = 11.4 Hz), 69.0 (p, $^3J_{CF}$ = 3.5 Hz), 68.5; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 80.0 (apparent m, 1F), 66.8 (apparent m, $^2J_{FF}$ = 146.4 Hz, 4F); **IR** (neat): 3476, 3079, 3036, 1747, 1534, 1348, 1157, 842, 794, 749, 698, 598 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{15}H_{14}F_5N_2O_5S$ $[M+H]^+$ 429.0538, found 429.0536.

3.2.2.3. Unsuccessful Routes towards SF_5-Heterocycles from Aldol Adducts

Benzyl 2-pentalfuorosulfanyl-3-phenylacrylate (302)



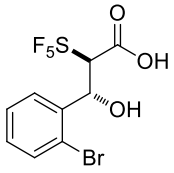
To a solution of **289** (55 mg, 0.137 mmol) in CH_2Cl_2 (1.4 mL) at –10 °C was added MsCl (22 µL, 0.273 mmol, 2.0 equiv) followed by Et_3N (114 µL, 0.820 mmol, 6.0 equiv). After stirring at –10 °C for 30 min, saturated aqueous NH_4Cl solution was added and extraction was

made with CH_2Cl_2 (3x), the combined organic layers dried over Na_2SO_4, and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 98:2) to afford **302** as a mixture of unassigned (*Z*) and (*E*)-isomers (44.5 mg, 0.112 mmol, 89%, isomer ratio: 4.5:1). The two isomers could be separated by preparative TLC (Hex/EtOAc 95:5, three elutions).

Minor isomer: **TLC**: R_f = 0.67 (Hex/EtOAc 8:2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.46 – 7.35 (m, 8H), 7.36 – 7.27 (m, 2H), 7.25 (s, 1H), 5.33 (s, 2H); **^{13}C NMR**: n/a; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 81.1 (apparent m, 1F), 71.3 (apparent m, $^2J_{FF}$ = 152.8 Hz, 4F); **HRMS** (EI): calculated for $C_{16}H_{13}F_5O_2S$ $[M]^+$ 257.0054, found 257.0054.

Major isomer: **TLC**: R_f = 0.67 (Hex/EtOAc 8:2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.42 – 7.21 (m, 8H), 7.22 – 7.12 (m, 2H), 5.20 (s, 2H); **^{13}C NMR**: n/a; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 81.6 (apparent m, 1F), 65.0 (d, $^2J_{FF}$ = 150.7 Hz, 4F); **HRMS** (EI): *m/z* calculated for $C_{16}H_{13}F_5O_2S$ $[M]^+$ 257.0054, found 257.0054.

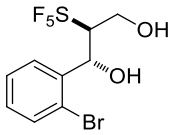
Anti-3-(2-bromophenyl)-3-hydroxy-2-pentafluorosulfanylpropanoic acid (307)



To a solution of **289** (55 mg, 0.119 mmol) in CH_2Cl_2 (1.2 mL) at –78 °C was slowly added BBr_3 (356 µL, 1.0 M in CH_2Cl_2, 0.356 mmol, 3.0 equiv). The mixture was stirred 30 min at −78 °C then quenched with H_2O. The layers were separated and extraction was made with EtOAc (3x). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (CH_2Cl_2/MeOH 85:15) to afford **307** as a colorless solid (42 mg, 0.113 mmol, 95%).

TLC: R_f = 0.48 (CH_2Cl_2/MeOH 8:2); **^{1}H NMR** (300 MHz, CD_3OD): δ 7.64 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.56 (ddd, *J* = 8.1, 5.0, 1.2 Hz, 1H), 7.37 (td, *J* = 7.6, 1.2 Hz, 1H), 7.26 – 7.15 (m, 1H), 5.68 (d, *J* = 1.9 Hz, 1H), 4.56 (pd, *J* = 6.9, 1.7 Hz, 1H); **^{13}C NMR** (101 MHz, CD_3OD): δ 170.7, 141.1, 133.9, 130.8, 130.2, 128.9, 122.6, 88.6 (p, $^2J_{CF}$ = 5.4 Hz), 72.6 (apparent t, $^3J_{CF}$ = 3.2 Hz); **^{19}F NMR** (282 MHz, CD_3OD): AB_4 system, δ 83.0 (apparent m, 1F), 63.8 (dd, *J* = 144.4, 6.9 Hz, 4F); **IR** (neat): 3332, 2951, 1615, 1386, 1024, 842, 826, 794, 752, 552 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_9H_8BrF_5NaO_3S$ $[M+Na]^+$ 392.9190, found 392.9193.

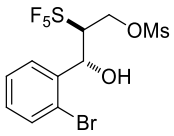
***Anti*-1-(2-bromophenyl)-2-pentalfuorosulfanylpropane-1,3-diol (306)**



To a solution of **307** (35 mg, 0.094 mmol) in THF (940 µL) at 0 °C was slowly added $BH_3 \cdot SMe_2$ (283 µL, 1.0 M in THF, 0.283 mmol, 3.0 equiv). The mixture was let warmed to r.t. overnight, then additional $BH_3 \cdot SMe_2$ (283 µL, 1.0 M in THF, 0.283 mmol, 3.0 equiv) was added and the mixture was stirred for 24 h. H_2O and EtOAc were added, the layers were separated and extraction was made with EtOAc (3 x). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 85:15) to afford **306** as a white solid (21.4 mg, 0.060 mmol, 64%). Recrystallization from Et_2O by gaseous diffusion of pentane afforded crystals suitable for X-ray analysis.

TLC: R_f = 0.44 (Hex/EtOAc 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.74 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.58 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.43 (td, *J* = 7.7, 1.1 Hz, 1H), 7.23 (td, *J* = 7.7, 1.7 Hz, 1H), 5.88 (d, *J* = 6.8 Hz, 1H), 4.25 (ddd, *J* = 11.6, 5.8, 1.9 Hz, 1H), 4.13 (tdd, *J* = 9.5, 6.3, 4.7 Hz, 2H), 3.79 (d, *J* = 6.8 Hz, 1H), 2.44 (t, *J* = 6.5 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 139.2, 133.5, 130.2, 128.4, 128.1, 121.4, 88.7 (p, $^2J_{CF}$ = 5.3 Hz), 73.7 (p, $^3J_{CF}$ = 3.4 Hz), 60.2 (p, $^3J_{CF}$ = 3.4 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 85.2 (apparent m, 1F), 60.2 (dd, $^2J_{FF}$ = 144.0, $^3J_{HF}$ = 5.3 Hz, 4F); **IR** (neat): 3350, 2928, 1467, 1439, 1076, 1025, 829, 733 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_9H_{10}BrF_5O_2S$ $[M]^+$ 355.9500, found 355.9512.

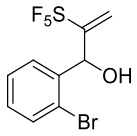
***Anti*-3-(2-bromophenyl)-3-hydroxy-2-pentafluorosulfanyl methanesulfonate (309)**



To a solution of **306** (15 mg, 0.042 mmol) in 420 µL CH_2Cl_2 (420 µL) at –78 °C was slowly added MsCl (3.5 µL, 0.044 mmol, 1.05 equiv) followed by Et_3N (6 µL, 0.044 mmol, 1.05 equiv). The mixture was stirred for 1 h at –78 °C and then 1 h at –20 °C. The reaction was quenched with 0.5 M HCl solution. Then Extraction was made with CH_2Cl_2 (3x). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 9:1 to 8:2) to afford **309** as a white solid (10 mg, 0.023 mmol, 54%).

^{1}H NMR (300 MHz, $CHCl_3$): δ 7.72 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.60 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.44 (td, *J* = 7.7, 1.3 Hz, 1H), 7.31 – 7.19 (m, 1H), 5.86 (d, *J* = 5.0 Hz, 1H), 4.85 (dd, *J* = 12.5, 7.1 Hz, 1H), 4.70 – 4.55 (m, 1H), 4.55 – 4.43 (m, 1H), 2.83 (s, 3H), 2.55 (d, *J* = 4.8 Hz, 1H); **^{13}C NMR**; n/a; **^{19}F NMR** (282 MHz, $CHCl_3$): AB_4 system, δ 84.3 (apparent m, 1F), 60.8 (d, $^{2}J_{FF}$ = 144.2 Hz, 4F).

1-(2-Bromophenyl)-2-(pentafluorosulfanyl)prop-2-en-1-ol (310)



To a solution of **309** (8.5 mg, 0.020 mmol) in DMF 200 µL was added NaN_3 (5.1 mg, 0.078 mmol, 4.0 equiv). The mixture was stirred for 1 h at 70 °C. Then H_2O and EtOAc were added. Extraction was made with EtOAc (3x). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 9:1 to 85:15) to afford **310** (4 mg, 0.012 mmol, 60%).

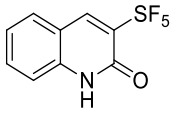
^{1}H NMR (300 MHz, $CHCl_3$): δ 7.60 (ddd, *J* = 8.0, 4.1, 1.6 Hz, 2H), 7.39 (td, *J* = 7.6, 1.3 Hz, 1H), 7.22 (td, *J* = 7.6, 1.7 Hz, 1H), 6.19 (d, *J* = 2.8 Hz, 1H), 6.05 (d, *J* = 4.7 Hz, 1H), 5.83 – 5.69 (m, 1H), 2.57 (d, *J* = 4.0 Hz, 1H); **^{13}C NMR** (101 MHz, $CHCl_3$): δ 133.4, 130.2, 128.4, 127.9, 123.1, 122.8 apparent (t, $^{3}J_{CF}$ = 5.4 Hz), 71.9 (apparent m); C_{Ar}–$C_{benzylic}$ and C–SF_5 not visible; **^{19}F NMR** (282 MHz, $CHCl_3$): AB_4 system, δ 84.1 (apparent m, 1F), 60.5 (apparent m, $^{2}J_{FF}$ = 148.3 Hz, 4F); **HRMS** (EI): *m/z* calculated for $C_9H_8BrF_5OS$ $[M]^+$ 337.9394, found 337.9388.

3.2.2.4. Synthesis of 3-SF_5-quinolones and 3-SF_5-quinolines

General procedure for the preparation of 3-SF_5-quinolones: To a solution of **291** (1.99 g, 4.66 mmol) in MeOH (47 mL) was added $Pd(OH)_2$ (0.33 mg, 0.47 mmol, 0.15 equiv). H_2 atmosphere was set up (balloon) and the mixture was vigorously stirred at r.t. for 2.5 h. The mixture was filtered through a pad of celite and concentrated under reduced pressure to afford a mixture of reduced non-cyclized, cyclized and aromatized products (5 signals visible by ^{19}F NMR). The crude material was suspended in THF (47 mL) and EDC (1.86 g, 9.31 mmol, 2.0 equiv) and DMAP (0.11 g, 0.93 mmol, 0.2 equiv) were added. After stirring for 14 h, H_2O was added and extraction was made with EtOAc (3x). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (dry loading, Hex/EtOAc 9:1 to 7:3) to afford **312** as

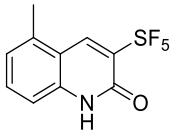
a white solid (1.05 g, 3.86 mmol, 83%). Crystals suitable for X-ray analysis were produced by recrystallization from ethyl acetate by slow evaporation.

3-(Pentafluorosulfanyl)quinolin-2(1H)-one (312)



TLC: R_f = 0.35 (Hex/EtOAc 7:3); **^{1}H NMR** (600 MHz, CD_3OD, cryoprobe): δ 8.76 (s, 1H), 7.89 – 7.81 (m, 1H), 7.70 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H), 7.38 (ddt, *J* = 8.4, 1.2, 0.7 Hz, 1H), 7.34 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H); **^{13}C NMR** (151 MHz, CD_3OD, cryoprobe): δ 157.2, 144.9 (p, $^3J_{CF}$ = 4.9 Hz), 144.4 (p, $^2J_{CF}$ = 14.2 Hz), 141.2, 135.1, 131.3, 124.6, 118.2, 116.2; **^{19}F NMR** (282 MHz, CD_3OD): AB_4 system, δ 83.5 (apparent m, 1F), 66.2 (d, $^2J_{FF}$ = 150.5 Hz, 4F); **IR** (neat): 2234, 2189, 2118, 1639, 1620, 1592, 1455, 1231, 1011, 831, 783, 759, 677, 558, 464 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_9H_7F_5NOS$ $[M+H]^+$ 272.0163, found 272.0163.

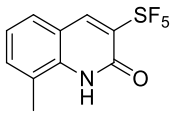
5-Methyl-3-(pentafluorosulfanyl)quinolin-2(1H)-one (327)



Following general procedure, **313** (305 mg, 0.691 mmol) was converted into **327** as a tanned solid (151 mg, 0.529 mmol, 77%) after purification by column chromatography (dry loading, Hex/EtOAc 8:2 to 1:1).

TLC: R_f = 0.32 (Hex/EtOAc 7:3); **^{1}H NMR** (500 MHz, CD_3OD, cryoprobe): δ 8.73 (d, *J* = 0.7 Hz, 1H), 7.57 (dd, *J* = 8.3, 7.4 Hz, 1H), 7.22 (dp, *J* = 8.4, 0.7 Hz, 1H), 7.19 (dp, *J* = 7.3, 0.9 Hz, 1H), 2.62 (s, 3H); **^{13}C NMR** (126 MHz, CD_3OD, cryoprobe): δ 156.9, 143.4 (p, $^2J_{CF}$ = 15.2 Hz), 141.9, 141.1 (p, $^3J_{CF}$ = 4.7 Hz), 139.5, 135.2, 125.8, 117.0, 114.6, 18.5; **^{19}F NMR** (282 MHz, CD_3OD): AB_4 system, δ 83.6 (apparent m, 1F), 66.4 (d, $^2J_{FF}$ = 150.6 Hz, 4F); **IR** (neat): 3021, 2960, 2871, 1669, 1611, 1440, 1256, 1034, 835, 814, 736, 671, 577, 563 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{10}H_9F_5NOS$ $[M+H]^+$ 286.0320, found 286.0318.

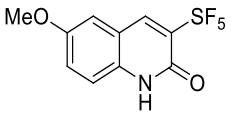
8-Methyl-3-(pentafluorosulfanyl)quinolin-2(1H)-one (328)



Following general procedure, **314** (287 mg, 0.650 mmol) was converted into **328** as a white solid (149 mg, 0.522 mmol, 80%) after purification by column chromatography (dry loading, Hex/EtOAc 9:1 to 7:3).

TLC: R_f = 0.44 (Hex/EtOAc 7:3); **^{1}H NMR** (600 MHz, CD_3OD, cryoprobe): δ 8.73 (s, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.57 – 7.55 (m, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 2.49 (s, 3H); **^{13}C NMR** (151 MHz, CD_3OD, cryoprobe): δ 157.4, 145.4 (apparent t, $^3J_{CF}$ = 4.2 Hz), 144.1 (p, $^2J_{CF}$ = 15.2 Hz), 139.7, 136.3, 129.5, 125.1, 124.4, 118.3, 17.1; **^{19}F NMR** (282 MHz, CD_3OD): AB_4 system, δ 83.4 (apparent m, 1F), 66.2 (d, $^2J_{FF}$ = 149.9 Hz, 4F); **IR** (neat): 3175, 3058, 2963, 1652, 1608, 1455, 1094, 839, 814, 764, 743, 671, 566, 539 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{10}H_9F_5NOS$ $[M+H]^+$ 286.0320, found 286.0319.

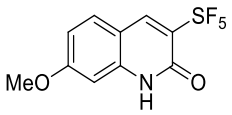
6-Methoxy-3-(pentafluorosulfanyl)quinolin-2(1H)-one (329)



Following general procedure, **315** (275 mg, 0.601 mmol) was converted into **329** as a yellow solid (84 mg, 0.279 mmol, 46%) after purification by column chromatography (dry loading, CH_2Cl_2/EtOAc 9:1).

TLC: R_f = 0.35 (Hex/EtOAc 7:3); **^{1}H NMR** (600 MHz, $(CD_3)_2SO$, cryoprobe): δ 12.39 (s, 1H), 8.86 (s, 1H), 7.51 (d, *J* = 2.8 Hz, 1H), 7.37 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.32 (d, *J* = 9.1 Hz, 1H), 3.80 (s, 3H); **^{13}C NMR** (151 MHz, $(CD_3)_2SO$, cryoprobe): δ 154.5, 153.8, 143.0 (p, $^2J_{CF}$ = 11.1 Hz), 142.7, 134.8, 123.9, 116.5, 116.3, 110.3, 55.4; **^{19}F NMR** (282 MHz, $(CD_3)_2SO$): AB_4 system, δ 83.7 (apparent m, 1F), 66.3 (d, $^2J_{FF}$ = 150.1 Hz, 4F); **IR** (neat): 2844, 1657, 1496, 1238, 1044, 805, 817, 599, 571, 562 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{10}H_9F_5NO_2S$ $[M+H]^+$ 302.0269, found 302.0269.

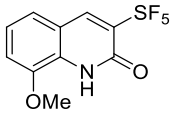
7-Methoxy-3-(pentafluorosulfanyl)quinolin-2(1H)-one (330)



Following general procedure, **316** (282 mg, 0.617 mmol) was converted into **330** as a tanned solid (117 mg, 0.388 mmol, 63%) after purification by column chromatography (dry loading, CH_2Cl_2/EtOAc 95:5 to 8:2).

TLC: R_f = 0.42 (Hex/EtOAc 6:4); **^{1}H NMR** (600 MHz, CD_3OD, cryoprobe): δ 8.63 (t, *J* = 0.5 Hz, 1H), 7.72 (d, *J* = 8.9 Hz, 1H), 6.94 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.82 (d, *J* = 2.4 Hz, 1H), 3.91 (s, 3H); **^{13}C NMR** (151 MHz, CD_3OD, cryoprobe): δ 166.2, 157.6, 144.5 (apparent t, $^3J_{CF}$ = 4.7 Hz), 143.6, 141.4 (p, $^2J_{CF}$ = 15.1 Hz), 132.8, 115.0, 112.4, 98.0, 56.4; **^{19}F NMR** (282 MHz, CD_3OD): AB_4 system, δ 84.8 (apparent m, 1F), 66.7 (d, $^2J_{FF}$ = 149.9 Hz, 4F); **IR** (neat): 2940, 2816, 1655, 1629, 1279, 1246, 1142, 1024, 840, 803, 674, 581, 551 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{10}H_9F_5NO_2S$ $[M+H]^+$ 302.0269, found 302.0269.

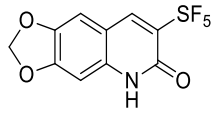
8-Methoxy-3-(pentafluorosulfanyl)quinolin-2(1H)-one (331)



Following general procedure, **317** (299 mg, 0.654 mmol) was converted into **331** as a slightly tanned solid (153 mg, 0.508 mmol, 78%) after purification by column chromatography (dry loading, Hex/EtOAc 7:3 to 1:1).

TLC: R_f = 0.40 (Hex/EtOAc 6:4); **^{1}H NMR** (600 MHz, CD_3OD, cryoprobe): δ 8.72 (d, *J* = 0.4 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.30 – 7.25 (m, 2H), 4.02 (s, 3H); **^{13}C NMR** (151 MHz, CD_3OD, cryoprobe): δ 156.8, 147.3, 145.4 – 144.7 (m, 2C), 131.5, 124.7, 122.5, 118.5, 114.4, 56.8; **^{19}F NMR** (282 MHz, CD_3OD): AB_4 system, δ 83.4 (apparent m, 1F), 66.2 (d, $^2J_{FF}$ = 150.8 Hz, 4F); **IR** (neat): 3156, 2948, 2846, 1642, 1611, 1474, 1295, 1268, 1238, 1123, 1034, 835, 809, 756, 735, 667, 589, 550, 471 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{10}H_9F_5NO_2S$ $[M+H]^+$ 302.0269, found 302.0269.

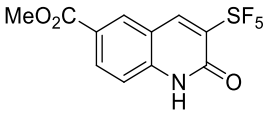
7-(Pentafluorosulfanyl)-[1,3]dioxolo[4,5-g]quinolin-6(5H)-one (332)



Following general procedure, **318** (305 mg, 0.647 mmol) was converted into **332** as a slightly tanned solid (29 mg, 0.092 mmol, 14%) after purification by column chromatography (dry loading, CH_2Cl_2/EtOAc 9:1 to 7:3).

TLC: R_f = 0.27 (Hex/EtOAc 6:4); **^{1}H NMR** (600 MHz, CD_3OD): δ 8.59 (s, 1H), 7.20 (s, 1H), 6.82 (s, 1H), 6.12 (s, 2H); **^{13}C NMR** (151 MHz, CD_3OD): δ 157.1, 155.6, 146.8, 144.0, 141.6 (p, $^2J_{CF}$ = 16.0 Hz), 139.7, 113.0, 107.1, 104.2, 95.7; **^{19}F NMR** (282 MHz, CD_3OD) AB_4 system, δ 84.5 (apparent m, 1F), 66.6 (d, $^2J_{FF}$ = 148.7 Hz, 4F); **IR** (neat): 2815, 1649, 1574, 1478, 1459, 1419, 1258, 1038, 829, 780, 677, 584, 560 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{10}H_6F_5NO_3S$ $[M]^+$ 314.9983, found 314.9984; for $C_{10}H_7F_5NO_3S$ $[M+H]^+$ 316.0061, found 316.0062; for $C_{10}H_6F_5NNaO_3S$ $[M+Na]^+$ 337.9881, found 337.9882; for $C_{10}H_6F_5KNO_3S$ $[M+K]^+$ 353.9620, found 353.9622.

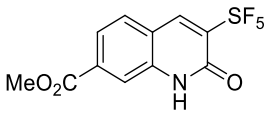
Methyl 2-oxo-3-(pentafluorosulfanyl)-1,2-dihydroquinoline-6-carboxylate (333)



Following general procedure, **319** (315 mg, 0.649 mmol) was converted into **333** as a slightly tanned solid (125 mg, 0.380 mmol, 59%) after purification by column chromatography (dry loading, Hex/EtOAc 8:2 to 1:9).

TLC: R_f = 0.44 (Hex/EtOAc 6:4); **^{1}H NMR** (600 MHz, $(CD_3)_2SO$, cryoprobe): δ 12.76 (bs, 1H), 9.14 (s, 1H), 8.65 (d, *J* = 1.9 Hz, 1H), 8.19 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 1H), 3.88 (s, 3H); **^{13}C NMR** (151 MHz, $(CD_3)_2SO$, cryoprobe): δ 165.16 , 154.5, 143.7, 143.3 (p, $^2J_{CF}$ = 11.0 Hz), 142.8, 133.5, 132.5, 123.8, 115.7, 115.4, 52.2; **^{19}F NMR** (282 MHz, $(CD_3)_2SO$): AB_4 system, δ 86.5 (p, $^2J_{FF}$ = 154.1 Hz, 1F), 67.5 (d, $^2J_{FF}$ = 152.6 Hz, 4F); **IR** (neat): 3070, 2995, 2822, 1713, 1657, 1624, 1570, 1443, 1275, 1257, 1231, 1214, 1109, 844, 823, 797, 772, 676, 575, 564 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{11}H_9F_5NO_3S$ $[M+H]^+$ 330.0218, found 330.0218.

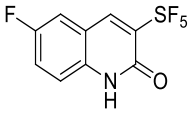
Methyl 2-oxo-3-(pentafluorosulfanyl)-1,2-dihydroquinoline-7-carboxylate (334)



Following general procedure, **320** (302 mg, 0.622 mmol) was converted into **334** as a slightly tanned solid (142 mg, 0.431 mmol, 69%) after purification by column chromatography (dry loading, Hex/EtOAc 8:2 to 1:1).

TLC: R_f = 0.41 (Hex/EtOAc 7:3); **^{1}H NMR** (600 MHz, CD_3OD, cryoprobe): δ 8.82 (s, 1H), 8.01 – 7.99 (m, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.88 (dd, *J* = 8.3, 1.5 Hz, 1H), 3.96 (s, 3H); **^{13}C NMR** (151 MHz, CD_3OD, cryoprobe): δ 167.1, 157.0, 146.3 (p, $^2J_{CF}$ = 15.9 Hz), 144.3, 141.0, 135.9, 131.7, 124.3, 121.1, 117.6, 53.2; **^{19}F NMR** (282 MHz, CD_3OD): AB_4 system, δ 82.5 (apparent m, 1F), 66.0 (d, $^2J_{FF}$ = 150.5 Hz, 4F); **IR** (neat): 3053, 2941, 2843, 1665, 1312, 1255, 1217, 831, 772, 756, 584, 565 cm^{-1}; **HRMS** (MALDI): *m/z* calcualted for $C_{11}H_9F_5NO_3S$ $[M+H]^+$ 330.0218, found 330.0218.

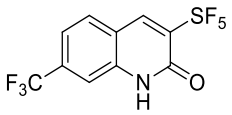
6-Fluoro-3-(pentafluorosulfanyl)quinolin-2(1H)-one (335)



Following general procedure, **321** (266 mg, 0.597 mmol) was converted into **335** as a tanned solid (128 mg, 0.443 mmol, 74%) after purification by column chromatography (dry loading, Hex/EtOAc 8:2 to 1:1).

TLC: R_f = 0.34 (Hex/EtOAc 7:3); **1H NMR** (600 MHz, CD_3OD, cryoprobe): δ 8.76 (s, 1H), 7.62 (ddt, *J* = 8.4, 2.8, 0.5 Hz, 1H), 7.52 (ddd, *J* = 9.1, 8.4, 2.8 Hz, 1H), 7.40 (ddt, *J* = 9.1, 4.5, 0.5 Hz, 1H); **^{13}C NMR** (151 MHz, CD_3OD, cryoprobe): δ 159.7 (d, $^1J_{CF}$ = 242.3 Hz), 156.8, 145.5 (p, $^2J_{CF}$ = 15.1), 144.2 (d, $^4J_{CF}$ = 4.4 Hz), 138.0, 123.5 (d, $^2J_{CF}$ = 25.2 Hz), 118.9 (d, $^3J_{CF}$ = 9.4 Hz), 118.3 (d, $^3J_{CF}$ = 8.6 Hz), 115.5 (d, $^2J_{CF}$ = 23.5 Hz); **^{19}F NMR** (282 MHz, CD_3OD): AB_4 system, δ 82.9 (apparent m, 1F), 66.1 (d, $^2J_{FF}$ = 150.1 Hz, 1F), –119.0 (apparent td, *J* = 8.4, 4.2 Hz, 1F); **IR** (neat): 3092, 3004, 2927, 2824, 1658, 1499, 1241, 1043, 842, 822, 764, 678, 562, 471 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_9H_6F_6NOS$ $[M+H]^+$ 290.0069, found 290.0068.

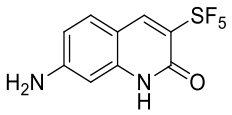
7-(Trifluoromethyl)-3-(pentafluorosulfanyl)quinolin-2(1H)-one (337)



Following general procedure, **323** (277 mg, 0.559 mmol) was converted into **337** as a slightly yellow solid (129 mg, 0.380 mmol, 68%) after purification by column chromatography (dry loading, CH_2Cl_2/EtOAc 98:2 to 9:1).

TLC: R_f = 0.27 (Hex/EtOAc 8:2); **1H NMR** (600 MHz, CD_3OD, cryoprobe): δ 8.85 (s, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.66 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.60 – 7.54 (m, 1H); **^{13}C NMR** (151 MHz, CD_3OD, cryoprobe): δ 156.9, 146.5 (p, $^2J_{CF}$ = 15.3 Hz), 144.3, 141.1, 135.8 (q, $^2J_{CF}$ = 32.9 Hz), 132.8, 124.9 (q, $^1J_{CF}$ = 272.2 Hz), 120.5, 120.3 (q, $^3J_{CF}$ = 3.5 Hz), 113.5 (q, $^3J_{CF}$ = 4.4 Hz); **^{19}F NMR** (282 MHz, CD_3OD): AB_4 system, δ 82.1 (apparent m, 1F), 65.9 (d, $^2J_{FF}$ = 150.9 Hz, 4F), -63.1 (s, 3F); **IR** (neat): 3181, 3070, 2878, 1671, 1324, 1178, 1137, 1071, 848, 803, 737 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{10}H_5F_8NNaOS$ $[M+Na]^+$ 361.9856, found 361.9858.

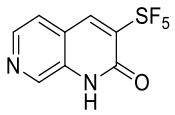
7-Amino-3-(pentafluorosulfanyl)quinolin-2(1H)-one (338)



Following general procedure, **324** (265 mg, 0.561 mmol) was converted into **338** as a red solid (5 mg, 0.017 mmol, 3%) after purification by column chromatography (dry loading, CH_2Cl_2/MeOH 98:2 to 95:5).

TLC: R_f = 0.45 (CH_2Cl_2/MeOH 95:5); **^{1}H NMR** (600 MHz, CD_3OD): δ 8.37 (s, 1H), 7.45 (d, *J* = 8.7 Hz, 1H), 6.65 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.40 (d, *J* = 1.9 Hz, 1H); **^{13}C NMR** (151 MHz, CD_3OD): δ 158.2, 156.2, 144.1 (apparent m), 144.0, 137.8 (p, $^2J_{CF}$ = 14.7 Hz), 132.6, 114.5, 109.6, 96.3; **^{19}F NMR** (282 MHz, CD_3OD): AB_4 system, δ 86.5 (apparent m, 1F), 67.4 (d, $^2J_{FF}$ = 150.2 Hz, 4F); **IR** (neat): 3355, 2926, 2855, 1620, 1245, 838, 788, 670, 498 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_9H_7F_5N_2OS$ $[M]^+$ 286.0194, found 286.0193; for $C_9H_8F_5N_2OS$ $[M+H]^+$ 287.0272, found 287.0272; for $C_9H_7F_5N_2NaOS$ $[M+Na]^+$ 309.0091, found 309.0092; for $C_9H_7F_5N_2KOS$ $[M+K]^+$ 324.9831, found 324.9831.

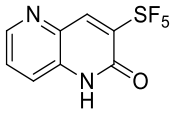
3-(Pentafluorosulfanyl)-1,7-naphthyridin-2(1H)-one (339)



Following general procedure, **325** (244 mg, 0.570 mmol) was converted into **339** as a white yellow solid (16 mg, 0.059 mmol, 10%) after purification by column chromatography (dry loading, Hex/EtOAc 2:8 to 5:95).

TLC: R_f = 0.35 (Hex/EtOAc 1:9); **^{1}H NMR** (600 MHz, $(CD_3)_2SO$, cryoprobe): δ 12.75 (s, 1H), 9.03 (s, 1H), 8.76 (s, 1H), 8.45 (d, J = 5.2 Hz, 1H), 7.87 (dd, J = 5.3, 0.8 Hz, 1H); **^{13}C NMR** (151 MHz, $(CD_3)_2SO$, cryoprobe): δ 154.0, 146.7 (p, $^2J_{CF}$ = 12.6 Hz), 142.2, 141.9, 138.4, 134.7, 122.0, 120.4; **^{19}F NMR** (282 MHz, $(CD_3)_2SO$): AB_4 system, δ 85.2 (apparent m, 1F), 67.0 (d, $^2J_{FF}$ = 154.0 Hz, 4F); **IR** (neat): 2925, 2855, 1648, 1441, 1277, 1226, 845, 830, 799, 592, 567, 541 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_8H_6F_5N_2OS$ $[M+H]^+$ 273.0116, found 273.0116.

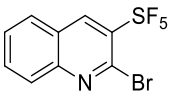
3-(Pentafluorosulfanyl)- 1,5-naphthyridin-2(1H)-one (340)



Following general procedure, **326** (192 mg, 0.448 mmol) was converted into **340** as a white solid (10mg, 0.037 mmol, 8%)) after purification by column chromatography (dry loading, Hex/EtOAc 3:7 to 2:8).

TLC: R_f = 0.51 (Hex/EtOAc 2:8); **^{1}H NMR** (600 MHz, $(CD_3)_2SO$, cryoprobe): δ 8.70 (s, 1H), 8.64 (dd, *J* = 4.3, 1.5 Hz, 1H), 7.79 – 7.75 (m, 1H), 7.70 (dd, *J* = 8.5, 4.3 Hz, 1H); **^{13}C NMR** (151 MHz, $(CD_3)_2SO$, cryoprobe): δ 154.0, 146.4, 145.6 (p, $^2J_{CF}$ = 11.9 Hz), 143.4, 137.2, 133.1, 127.6, 123.3; **^{19}F NMR** (282 MHz, $(CD_3)_2SO$): AB_4 system, δ 85.9 (p, $^2J_{FF}$ = 153.0 Hz, 1F), 67.2 (d, $^2J_{FF}$ = 152.6 Hz, 4F); **IR** (neat): 2853, 2193, 1666, 1644, 845, 811 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_8H_6F_5N_2OS$ $[M+H]^+$ 273.0116, found 273.0116.

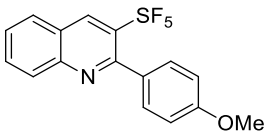
2-Bromo-3-(pentafluorosulfanyl)quinoline (341)



A mixture of **312** (433 mg, 1.60 mmol) and $POBr_3$ (2.5 g, 8.72 mmol, 5.5 equiv) was stirred at 120 °C for 16 h. After cooling down to room temperature, iced-cold water was carefully added. Saturated aqueous K_2CO_3 solution and EtOAc were added, layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 97:3) to afford **341** as a white solid (517 mg, 1.55 mmol, 97%).

TLC: R_f = 0.25 (Hex/EtOAc 95:5); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.11 (dt, *J* = 8.6, 1.0 Hz, 1H), 8.00 – 7.83 (m, 2H), 7.80 – 7.61 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 147.9 (m, 2C), 139.8 (p, $^3J_{CF}$ = 5.2 Hz), 133.6, 133.4 128.91, 128.90, 128.7, 125.4. **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 81.1 (apparent m, 1F), 66.6 (apparent m, $^2J_{FF}$ = 152.5 Hz, 4F); **IR** (neat): 3058, 2926, 1617, 1554, 1486, 1377, 1329, 1120, 978, 840, 798, 774, 751, 970, 581, 566 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_9H_6BrF_5NS$ $[M+H]^+$ 333.9319, found 333.9319.

2-(4-Methoxyphenyl)-3-(pentafluorosulfanyl)quinoline (342)

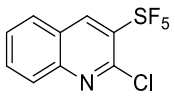


To a solution of **341** (51 mg, 0.15 mmol) in toluene (1.5 mL) was added (4-methoxyphenyl)boronic acid (46 mg, 0.30 mmol, 2.0 equiv) and K_2CO_3 (42 mg, 0.30 mmol, 2.0 equiv). The mixture was degassed with Argon for 10 min, $Pd(PPh_3)_4$ (18 mg, 0.015 mmol, 0.1 equiv) was added and the reaction was stirred for 48 h at 115 °C. After cooling down to r.t., H_2O was added and extraction was made with Et_2O (3x). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 9:1 to 8:2) to afford **342** as a white solid (33 mg, 0.09 mmol, 60%).

TLC: R_f = 0.31 (Hex/EtOAc 85:15); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.89 – 8.54 (m, 1H), 8.30 – 8.09 (m, 1H), 8.06 – 7.96 (m, 1H), 7.87 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.69 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.09 – 6.81 (m, 2H), 3.88 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.6, 155.0, 148.5 (p, $^2J_{CF}$ = 13.3 Hz), 147.4, 137.3 (p, $^3J_{CF}$ = 5.5 Hz),

134.1, 132.7, 129.9, 129.5, 128.7, 128.3, 125.8, 113.2, 55.5; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 83.9 (apparent m, 1F), 70.0 (d, $^2J_{FF}$ = 151.5 Hz, 4F); **IR** (neat): 3091, 3022, 2963, 2844, 1613, 1517, 1410, 1291, 1247, 1180, 2030, 894, 834, 812, 782, 758, 669, 574 cm^{-1}; **HRMS** (EI): *m/z* calculated for $[C_{16}H_{12}F_5NOS]^+$ 361.0555, found 361.0561.

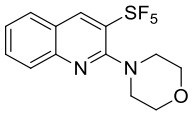
2-Chloro-3-(pentafluorosulfanyl)quinoline (343)



A solution of **312** (101 mg, 0.372 mmol) in $POCl_3$ (1.2 mL) was stirred at 110 °C for 14 h. After cooling down to room temperature, the mixture was poured into a stirring mixture of ice and water. Saturated aqueous K_2CO_3 solution and EtOAc were added, layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 97:3) to afford **343** as a white solid (104 mg, 0.359 mmol, 96%).

TLC: R_f = 0.36 (Hex/EtOAc 95:5); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.17 – 7.99 (m, 1H), 8.01 – 7.79 (m, 2H), 7.69 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 147.5, 145.7 (p, $^2J_{CF}$ = 18.3 Hz),143.0 140.2 (p, $^3J_{CF}$ = 5.2 Hz), 133.6, 128.8 (m, 2C), 128.5, 125.5; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 81.1 (apparent m, 1F), 66.8 (apparent m, $^2J_{FF}$ = 151.4 Hz 4F); **IR** (neat): 3061, 2957, 2923, 2853, 1619, 1559, 1488, 1377, 1331, 1163, 1132, 991, 899, 865, 841, 806, 786, 775, 752, 672, 601, 568, 525 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_9H_6ClF_5NS$ $[M+H]^+$ 289.9824, found 289.9824.

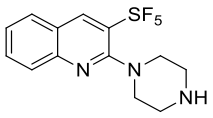
4-(3-(Pentafluorosulfanyl)quinolin-2-yl)morpholine (344)



To a solution of **343** (10.0 mg, 0.035 mmol) in dioxane (400 µL) was added K_2CO_3 (9.5 mg, 0.069 mmol, 2.0 equiv) and morpholine (20 µL, 0.23 mmol, 6.6 equiv), and the reaction mixture was stirred for 48h at 105 °C. After cooling down to room temperature, H_2O was added, and extraction was made with Et_2O (3x). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 9:1) to afford **344** as a white solid (11.0 mg, 0.032 mmol, 94%).

TLC: R_f = 0.27 (Hex/EtOAc 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.66 (s, 1H), 8.05 – 7.99 (m, 1H), 7.91 – 7.86 (m, 1H), 7.82 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.60 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 3.89 (t, *J* = 4.5 Hz, 4H), 3.11 (t, *J* = 4.5 Hz, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.1, 147.9, 145.2 (p, $^3J_{CF}$ = 16.7 Hz), 139.7 (p, $^2J_{CF}$ = 5.2 Hz), 132.3, 128.8, 128.4, 127.6, 125.8, 67.5, 52.6; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 84.5 (apparent m, 1F), 68.9 (d, $^2J_{FF}$ = 151.3 Hz, 4F); **IR** (neat): 2955, 2917, 2857, 1585, 1556, 1490, 1447, 1412, 1368, 1258, 1227, 1109, 1011, 851, 838, 812, 782, 760, 720, 571 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{13}H_{13}F_5N_2OS$ $[M]^+$ 340.0664, found 340.0660.

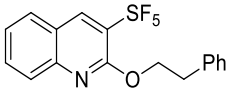
2-(Piperazin-1-yl)-3-(pentafluorosulfanyl)quinoline (345)



To a solution of **343** (43.0 mg, 0.148 mmol) in dioxane (1.5 mL) was added K_2CO_3 (103 mg, 0.742 mmol, 5.0 equiv) and piperazine (153 mg, 1.781 mmol, 12.0 equiv), and the reaction mixture was stirred for 24 h at 105 °C. After cooling down to room temperature, H_2O was added, and extraction was made with Et_2O (3x). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification was made by column chromatography (CH_2Cl_2/MeOH/Et_3N 95:5:1) to afford **345** as a yellow oil (49.0 mg, 0.144 mmol, 97%).

TLC: R_f = 0.27 (CH_2Cl_2/MeOH 95:5); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.04 – 7.96 (m, 1H), 7.87 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.80 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.59 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 4.21 (bs, 1H), 3.15 (s, 8H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.4, 147.9, 145.1 (p, $^2J_{CF}$ = 14.4 Hz), 139.6 (p, $^3J_{CF}$ = 5.2, 4.7 Hz), 132.2, 128.7, 128.4, 127.5, 125.7, 53.2, 46.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 84.5 (apparent m, 1F), 68.8 (d, $^2J_{FF}$ = 152.3 Hz, 4F); **IR** (neat): 3061, 2946, 2837, 1618, 1587, 1556, 1451, 1414, 1231, 1012, 843, 813, 785, 635, 572 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{13}H_{15}F_5N_3S$ $[M+H]^+$ 340.0901, found 340.0906.

3-Pentafluorosulfanyl-2-phenethoxyquinoline (346)

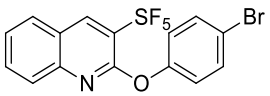


To a solution of potassium *tert*-butoxide (8.7 mg, 0.078 mmol, 1.5 equiv) in THF (200 μL) at r.t. was added 2-phenylethanol (9.5 μL, 0.079 mmol, 1.5 equiv). The mixture was stirred for

10 min and then a solution of **343** (15.0 mg, 0.052 mmol) in THF (320 µL) was slowly added. After stirring for 15 h, H_2O was added and extraction was made with EtOAc (3x). The combined organic layers were dried over $MgSO_4$, washed with brine, and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 99:1) to afford **346** as a colorless oil (19.0 mg, 0.051 mmol, 98 %).

TLC: R_f = 0.50 (Hex/EtOAc 95:5); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.51 (s, 1H), 8.00 – 7.65 (m, 3H), 7.46 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.40 – 7.10 (m, 5H), 4.78 (t, *J* = 7.0 Hz, 2H), 3.19 (t, *J* = 7.0 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 154.1, 146.9, 139.7 (p, $^3J_{CF}$ = 5.2, 4.8 Hz), 138.5, 137.9 (apparent m), 132.4, 129.3, 128.9, 128.6, 127.0, 126.6, 125.5, 123.5, 68.3, 35.5; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 82.8 (apparent m), 67.5 (d, $^2J_{FF}$ = 151.2 Hz); **IR** (neat): 3065, 3029, 2960, 1620, 1597, 1566, 1495, 1476, 1422, 1343, 1273, 1259, 834, 784, 775, 730, 698, 669, 597, 574, 508, 476 cm^{-1}; **HRMS** (MALDI): calculated for $C_{17}H_{15}F_5NOS$ $[M+H]^+$ 376.0789, found 376.0788.

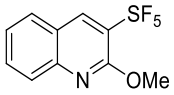
2-(4-Bromophenoxy)-3-(pentafluorosulfanyl)quinoline (347)



To a solution of potassium *tert*-butoxide (15.1 mg, 0.135 mmol, 1.5 equiv) in THF (500 µL) at r.t. was added 4-bromophenol (23.3 mg, 0.135 mmol, 1.5 equiv). The mixture was stirred for 10 min and then a solution of **343** (26.1 mg, 0.090 mmol) in THF (400 µL) was slowly added. After stirring for 48 h at 50 °C, another portion of 15.1 mg of potassium *tert*-butoxide and 23.3 mg of 4-bromophenol were added and the reaction was stirred for 48 h at 70 °C. H_2O was added and extraction was made with EtOAc (3x). The combined organic layers were dried over $MgSO_4$, washed with brine, and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 98:2 to 85:5) to afford **348** as a white solid (29.2 mg, 0.069 mmol, 76 %).

TLC: R_f = 0.51 (Hex/EtOAc 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.66 (s, 1H), 7.87 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.79 – 7.64 (m, 2H), 7.65 – 7.43 (m, 3H), 7.19 – 7.07 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 153.3, 152.3, 146.5, 140.5 (p, $^3J_{CF}$ = 5.0 Hz), 137.6 (p, $^2J_{CF}$ = 19.6 Hz), 132.8, 132.6, 128.8, 127.5, 126.5, 124.4, 123.8, 118.2; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 81.9 (apparent m, 1F), 67.6 (d, $^2J_{FF}$ = 151.1 Hz, 4F); **IR** (neat): 3101, 3060, 2960, 2924, 1568, 1482, 1408, 1348, 1254, 1201, 1042, 1012, 869, 857, 814, 791, 661, 599, 571, 455 cm^{-1}; **HRMS** (EI): *m/z* calculated for $[C_{15}H_9BrF_5NOS]^+$ 424.9503, found 424.9507.

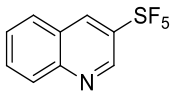
2-Methoxy-3-(pentafluorosulfanyl)quinolone (348)



To a suspension of NaH (8.3 mg, 60%, 0.207 mmol, 2.0 equiv) in THF (500 µL) at 0 °C was slowly added dimethyl malonate (15 µL, 0.131 mmol, 1.3 equiv). The mixture was stirred for 30 min at r.t. and then a solution of **343** (30 mg, 0.104 mmol) in THF (600 µL) was added at 0 °C. The reaction mixture was stirred at 70 °C for 60 h. After cooling down to r.t., H_2O and EtOAc added. Extraction was made with EtOAc (3x), combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 99:1 to 98:2) to afford **348** as a white solid (10 mg, 0.0.35 mmol, 34%).

TLC: R_f = 0.35 (Hex/EtOAc 99:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.52 (s, 1H), 7.92 – 7.84 (m, 1H), 7.84 – 7.78 (m, 1H), 7.75 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.47 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 4.17 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 154.6, 146.9, 139.7 (p, $^3J_{CF}$ = 5.6 Hz), 137.8 (apparent m), 132.5, 128.9, 127.1, 125.5, 123.5, 54.6; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 82.5 (apparent m, 1F), 67.2 (d, $^2J_{FF}$ = 151.4 Hz, 4F); **IR** (neat): 2994, 2937, 2857, 1623, 1598, 1481, 1402, 1345, 1261, 996, 961, 828, 797, 783, 773, 668, 575, 469 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{10}H_8F_5NOS$ $[M]^+$ 285.0247, found 285.0255.

3-(Pentafluorosulfanyl)quinolone (349)



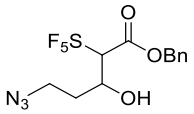
A solution of **341** (152 mg, 0.45 mmol) in benzene (4.5 mL) was degased with argon for 5 min, then *n*-Bu_3SnH (170 µL, 0.64 mmol, 1.4 equiv) was added. The mixture was heated at 80 °C and AIBN (1.5 mg, 9.1 µmol, 0.02 equiv) was added. After stirring for 24 h at 85 °C, aqueous NaOH solution (1.0 M, 5 mL) was added and the resulting biphasic mixture was vigorously stirred for 2 h at room temperature. The layers were separated and extraction was made with Et_2O (3x), the combined organic layers were washed with 1.0 M NaOH solution, dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 95:5) to afford **349** as a white solid (97 mg, 0.38 mmol, 84%).

TLC: R_f = 0.35 (Hex/EtOAc 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.20 (d, *J* = 2.5 Hz, 1H), 8.57 (d, *J* = 2.5 Hz, 1H), 8.18 (dt, *J* = 8.6, 0.9 Hz, 1H), 7.96 – 7.91 (m, 1H), 7.88 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.69 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 148.4, 147.4 (p, $^2J_{CF}$ = 19.6, 18.3 Hz), 145.7 (p, $^3J_{CF}$ = 4.8 Hz), 134.5 (p, $^3J_{CF}$ = 4.8 Hz), 132.4, 129.6, 129.2, 128.5, 126; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 82.3 (apparent m, 1F), 65.08 (d, $^2J_{FF}$ = 151.3 Hz, 4F); **IR** (neat): 3051, 2925, 2854, 1620, 1569, 1497, 1380, 1090, 959, 832, 800, 785, 752, 671, 572 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_9H_6F_5NS$ $[M]^+$ 255.0136, found 255.0138.

3.2.2.5. Synthesis of 3-SF_5-pyridones

*3.2.2.5.1. First generation synthesis of 3-SF_5-pyridone **354**:*

Benzyl 5-azido-3-hydroxy-2-(pentafluorosulfanyl)pentanoate (351)

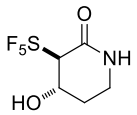


To a solution of **281** (378 mg, 1.37 mmol) in CH_2Cl_2 (5.0 mL) at –78 °C was slowly added *n*-Bu_2BOTf (2.74 mL, 1.0 M in CH_2Cl_2, 2.74 mmol, 2.0 equiv), and then DIPEA (710 µL, 4.11 mmol, 3.0 equiv). The mixture was stirred 30 min at –78 °C and then 30 min at –20 °C. The mixture was cooled down at –45 °C and 3-azidopropanal (281 mg, 1.64 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) was slowly added. The reaction was stirred at –45 °C for 1 h and then quenched with pH 7 phosphate buffer (5.0 mL). MeOH (5.0 mL) and 30% H_2O_2 solution (5.0 mL) were added and the mixture was vigorously stirred at r.t. for 8 h. Extraction was made with CH_2Cl_2 (3x), the combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Ultrapure Silica from SiliCycle, Hex/EtOAc 9:1 to 8:2) to afford the **351** as a yellowish solid upon storage at –20 °C (349 mg, 0.93 mmol, 68%, d.r. = 1.6:1).

TLC: R_f = 0.46 (Hex/EtOAc 8:2); minor diastereoisomer (*syn*): **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.46 – 7.31 (m, 5H), 5.25 (d, *J* = 1.6 Hz, 2H), 4.47 – 4.35 (m, 2H), 3.51 (td, *J* = 7.5, 5.3 Hz, 2H), 2.95 – 2.85 (apparent m, 1H), 1.91 – 1.71 (m, 1H), 1.71 – 1.59 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.5 (apparent t, $^3J_{CF}$ = 3.2 Hz), 134.2, 129.1, 128.9, 128.8, 88.7 (p, $^2J_{CF}$ = 8.8 Hz), 68.8, 68.4 (apparent t, $^3J_{CF}$ = 2.3 Hz), 47.9, 33.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 81.5 (apparent m, 1F), 68.1 (d, $^2J_{FF}$ = 146.4 Hz, 4F); major diastereoisomer (*trans*): **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.46 – 7.31 (m, 5H), 5.28 (s, 2H), 4.58 – 4.42 (m, 2H), 3.51 (td, *J* = 7.5, 5.3 Hz, 2H), 3.39 (d, *J* = 8.7 Hz, 1H), 1.82 (m, 1H), 1.64 (m, 1H); **^{13}C NMR**

(101 MHz, $CDCl_3$): δ 165.5 (apparent m), 134.1, 129.1, 128.9, 128.7, 85.9 (p, $^2J_{CF}$ = 10.3 Hz), 69.0, 67.8 (p, $^3J_{CF}$ = 3.1 Hz), 47.8, 34.7; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 80.7 (apparent m, 1F), 66.6 (apparent m, $^2J_{FF}$ = 147.1 Hz, 4F); **IR** (neat): 3507, 2953, 2100, 1742, 1456, 1381, 1306, 1253, 1170, 832, 795, 752, 696, 596 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{12}H_{14}F_5N_3NaO_3S$ $[M+Na]^+$ 398.0568, found 398.0568.

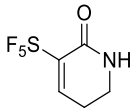
(*Anti*)-4-hydroxy-3-(pentafluorosulfanyl)piperidin-2-one (350)



To a solution of **351** (310 mg, 0.826 mmol) in MeOH (8.3 mL) was added Pd/C (132 mg, 10%, 0.124 mmol, 0.15 equiv). The reaction was stirred under H_2 atmosphere (balloon) at r.t. for 2 h. The mixture was filtered thought a pad of celite, and concentrated under reduced pressure. The crude amino acid was disolved in THF (14.2 mL) and DMF (2.4 mL), EDC (317 mg, 1.651 mmol, 2.0 equiv) and DMAP (10.1 mg, 0.083 mmol, 0.1 equiv) were added and the mixture was stirred at r.t. for 20 h. H_2O and EtOAc were added, the layers were separated and extraction was made with EtOAc (3x). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 3:7 to 2:8) to afford **350** as a white solid (53 mg, 0.220 mmol, 26%).

TLC: R_f = 0.45 (Hex/EtOAc 3:7); **^{1}H NMR** (300 MHz, CD_3OD): δ 4.69 (dt, *J* = 4.4, 2.3 Hz, 1H), 4.32 (pt, *J* = 7.5, 1.9 Hz, 1H), 3.53 (ddd, *J* = 12.5, 11.1, 5.3 Hz, 1H), 3.31 – 3.24 (m, 1H), 2.24 – 2.05 (m, 1H), 1.95 (dtd, *J* = 9.2, 4.5, 2.1 Hz, 1H); **^{13}C NMR** (101 MHz, CD_3OD): δ 164.3 (p, $^3J_{CF}$ = 3.4 Hz), 86.1 (p, $^2J_{CF}$ = 6.9 Hz), 65.9 (p, $^3J_{CF}$ = 3.7 Hz), 38.0, 25.9; **^{19}F NMR** (282 MHz, CD_3OD): AB_4 system, δ 83.9 (apparent m, 1F), 64.8 (dd, *J* = 144.5, 7.9 Hz); **IR** (neat): 3586, 2955, 2388, 1652, 1087, 885, 829, 783, 626, 541 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_5H_9F_5NO_2S$ $[M+H]^+$ 242.0269, found 242.0272.

3-Pentafluorosulfanyl-5,6-dihydropyridin-2(1H)-one (352)

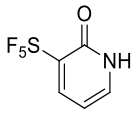


To a solution of **350** (9 mg, 0.037 mmol) in CH_2Cl_2 (380 μL) at –20 °C was added MsCl (5.6 μL, 0.075 mmol, 2.0 equiv), and then Et_3N (15.5 μL, 0.112 mmol, 3.0 equiv). The reaction was slowly let warmed to room temperature. After 2h, additional of MsCl (5.6 μL, 0.075 mmol,

2.0 equiv) and Et_3N (15.5 µL, 0.112 mmol, 3.0 equiv) were added. After stirring for three more hours at r.t., saturated aqueous NH_4Cl solution was added. The layers were separated, extraction was made with EtOAc (3x). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 3:7) to afford **352** as a white solid (7 mg, 0.031 mmol, 84%).

TLC: R_f = 0.47 (Hex/EtOAc 1:9); **^{1}H NMR:** (300 MHz, $CDCl_3$) δ 7.46 (t, *J* = 4.8 Hz, 1H), 6.05 (s, 1H), 3.45 (td, *J* = 6.9, 2.8 Hz, 2H), 2.65 (dtq, *J* = 6.6, 4.8, 1.6 Hz, 2H); **^{13}C NMR:** (101 MHz, $CDCl_3$) δ 146.0 (apparent m), 38.8, 24.8, (sample was not concentrated enough, C–SF_5 and C=O signals were not detected); **^{19}F NMR:** (282 MHz, $CDCl_3$) AB_4 system, δ 82.4 (apparent m, 1F), 66.0 (d, $^2J_{FF}$ = 153.2 Hz, 4F); **HRMS** (ESI): *m/z* calculated for $C_5H_6F_5NOS$ $[M]^+$ 223.0085, found 223.0085; for $C_5H_7F_5NOS$ $[M+H]^+$ 224.0163, found 224.0163; for $C_5H_6F_5NNaOS$ $[M+Na]^+$ 245.9982, found 245.9983.

3-(Pentafluorosulfanyl)pyridin-2(1*H*)-one (354)



<u>*Via N-chlorination*</u>: To a solution of 3**52** (6 mg, 0.027 mmol) in MeOH (270 µL) at 0 °C and protected from light was dropwisely added freshly prepared *tert*-butyl hypochlorite (7 µL, 0.062 mmol, 2.3 equiv). After stirring for 1.5 h at 0 °C, the mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with H_2O, dried with $MgSO_4$ and concentrated under reduced pressure to afford *N*-chlorolactam **353** which was used without any further purification. To a solution of crude **353** in CH_2Cl_2 (270 µL) at 0 °C and protected from light was dropwisely added DBU (4.8 µL, 0.032 mmol, 1.2 equiv). After stirring for 30 min at 0 °C, saturated aqueous NH_4Cl solution was added. Extraction was made with CH_2Cl_2 (3x), the combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 3:7) to afford **354** as a white solid (3 mg, 0.014 mmol, 50%) along with **352** (1.2 mg, 5.4 µmol, 20%). Crystals suitable for X-ray analysis were obtained by recrystallization from ethyl acetate by slow evaporation

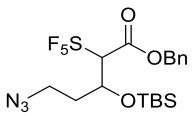
<u>*Pd/C oxidation*</u>: To a solution of **352** (7 mg, 0.031 mmol) in xylene (315 µL) was added Pd/C (33 mg, 10%, 0.031 mol, 1.0 equiv) and the mixture was stirred at 140 °C for 24 h. After cooling down to r.t., the mixture was filtered through a pad of celite, and the filtrate was

concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 3:7) to afford **354** as a white solid (2 mg, 0.009 mmol, 29%).

DDQ oxidation: To a solution of **352** (12 mg, 0.054 mmol) in 1,4-dioxane (600 μL) was added DDQ (14.7 mg, 0.065 mol, 1.2 equiv) and the mixture was stirred at 100 °C for 24 h. After cooling down to r.t., EtOAc and saturated aqueous $NaHCO_3$ solution were added. Extraction was made with EtOAc (3x) and the combined organic layers were concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 3:7) to afford **354** as a white solid (5 mg, 0.054 mmol, 40%).

TLC: R_f = 0.31 (Hex/EtOAc 2:8); **^{1}H NMR** (400 MHz, CD_3CN): δ 10.34 (bs, 1H), 8.12 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.56 (dd, *J* = 6.4, 2.0 Hz, 1H), 6.35 – 6.24 (m, 1H); **^{13}C NMR** (101 MHz, CD_3CN): δ 156.3, 144.4 (p, $^3J_{CF}$ = 4.9 Hz), 143.4 (p, $^2J_{CF}$ = 14.6 Hz), 141.7, 104.4; **^{19}F NMR** (282 MHz, CD_3CN): AB_4 system, δ 85.7 (apparent m, 1F), 65.7 (d, $^2J_{FF}$ = 149.7 Hz, 4F); **IR** (neat): 3137, 3080, 2998, 2924, 2861, 2802, 1650, 1611, 1581, 1553, 1478, 1337, 1234, 1045, 837, 803, 787, 764, 634, 580, 539 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_5H_4F_5NOS$ $[M]^+$ 220.9929, found 220.9931.

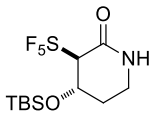
Benzyl 5-azido-3-((*tert*-butyldimethylsilyl)oxy)-2-pentafluorosulfanylpentanoate (355)



To a solution of **351** (202 mg, 0.54 mmol) in CH_2Cl_2 (5.4 mL) at –78 °C was 2,6-lutidine (140 μL, 1.18 mmol, 2.2 equiv), and then TBSOTf (250 μL, 1.08 mmol, 2.0 equiv). The mixture was slowly let warmed at r.t. overnight. Saturated aqueous $NaHCO_3$ solution added and extraction was made with CH_2Cl_2 (3x), the combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 99:1) to afford **355** as a colorless solid (249 mg, 0.51 mmol, 94%, d.r. = 1.6:1).

NMR data for mixture of two diastereoisomers: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.46 – 7.29 (m, 5H), 5.34 – 5.08 (m, 2H), 4.73 – 4.43 (m, 2H), 3.57 – 3.20 (m, 2H), 2.32 – 1.97 (m, 2H), 0.87 and 0.83 (two s, 9H), 0.14 – 0.08 (m, 6H); **^{13}C NMR**: n/a; **^{19}F NMR** (282 MHz, $CDCl_3$): two AB_4 systems, δ 83.94 – 80.87 (m, 8F), 68.41 (d, $^2J_{FF}$ = 144.7 Hz, 1F), 67.67 (dd, $^2J_{FF}$ = 144.8, $^3J_{HF}$ = 6.5 Hz, 1F).

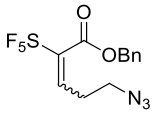
(3*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-3-(pentafluorosulfanyl)-2-one (356)



A solution of **355** (110 mg, 0.225 mmol) and Pd/C (36 mg, 10%, 0.034 mmol, 0.15 equiv) in MeOH (2.2 mL) was stirred under H_2 atmosphere (balloon) for 10 min. After filtering through a pad of celite, the mixture was concentrated under reduced pressure to afford the amino acid as a white solid (partial TBS-deprotection observed). The crude material was disolved in THF (1.8 mL) and DMF (0.45 mL), EDC (90 mg, 0.45 mmol, 2.0 equiv) was added, followed by DMAP (5.5 mg, 0.045 mmol, 0.2 equiv) and the reaction was stirred for 5 h at room temperature. H_2O was added and extraction was made with EtOAc (3x). Combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 8:2 to 2:8) to afford **356** as a white solid (44 mg, 0.124 mmol, 55%) along with **350** (10 mg, 0.041 mmol, 18%).

TLC: R_f = 0.33 (Hex/EtOAc 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.58 (s, 1H), 4.71 (dt, J = 3.7, 1.6 Hz, 1H), 4.19 (p, J = 7.1 Hz, 1H), 3.66 – 3.53 (m, 1H), 3.31 (dddd, J = 11.5, 5.8, 3.1, 1.9 Hz, 1H), 2.19 (td, J = 12.8, 6.3 Hz, 1H), 1.85 (d, J = 14.3 Hz, 1H), 0.87 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 162.5, 84.7 (p, $^2J_{CF}$ = 6.7 Hz), 66.1 (apparent m), 37.6, 25.8, 25.7, 18.0, -4.9, -5.0; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 82.7 (apparent m, 1F), 64.1 (dd, *J* = 146.1, 7.2 Hz, 4F); **IR** (neat): 3243, 2954, 2932, 2860, 1688, 1256, 1114, 1098, 1030, 827, 778, 660, 556 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{11}H_{23}F_5NO_2SSi$ $[M+H]^+$ 356.1133, found 356.1133.

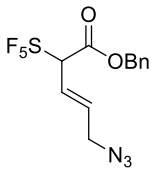
Benzyl 5-azido-2-(pentalfuorosulfanyl)pent-2-enoate (357)



To a solution of **351** (15 mg, 0.040 mmol) in CH_2Cl_2 (400 µL) at –78 °C was added pyridine (7.1 µL, 0.088 mmol, 2.2 equiv) and then dropwisely Tf_2O (7.4 µL, 0.044 mmol, 1.1 equiv). The mixture was stirred for 1h at –78 °C and then slowly let warmed at r.t. overnight. Saturated aqueous NH_4Cl solution was added, then extraction was made with CH_2Cl_2 (3x). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 95:5) to afford a mixture of isomers **357** and **358** (7.5 mg, 0.021 mmol, 98%, **357**:**358** = 1:4.5).

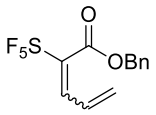
TLC: R_f = 0.55 (Hex/EtOAc 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 – 7.32 (m, 5H), 6.70 (t, J = 7.7 Hz, 1H), 5.31 (s, 2H), 3.39 (t, J = 6.7 Hz, 2H), 2.44 – 2.36 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.32 (apparent m), 148.9 (apparent m), 137.7 (p, $^3J_{CF}$ = 5.9 Hz), 134.5, 129.0, 128.9, 128.8, 68.6, 49.5, 28.9; **^{19}F NMR** (282 MHz, $CDCl_3$): δ 81.0 (apparent m, 1F), 64.6 (d, $^2J_{FF}$ = 151.0 Hz, 4F).

(*E*)-benzyl 5-azido-2-(pentafluorosulfanyl)pent-3-enoate (358)



TLC: R_f = 0.55 (Hex/EtOAc 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 – 7.31 (m, 5H), 6.31 – 6.15 (m, 1H), 5.98 (dt, *J* = 15.4, 5.8 Hz, 1H), 5.24 (s, 2H), 4.99 (dp, *J* = 10.7, 5.4 Hz, 1H), 3.90 (d, *J* = 6.0 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.0 (p, *J* = 3.0 Hz), 135.0, 134.4, 128.9, 128.8, 128.6, 124.8 (p, $^2J_{CF}$ = 3.1 Hz), 85.7 (p, $^3J_{CF}$ = 13.8 Hz), 68.7, 51.7; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 78.8 (apparent m, 1F), 62.1 (dd, $^2J_{FF}$ = 145.9, $^3J_{HF}$ = 5.3 Hz, 4F).

Benzyl 2-pentafluorosulfanyl-2,4-dienoate (359)

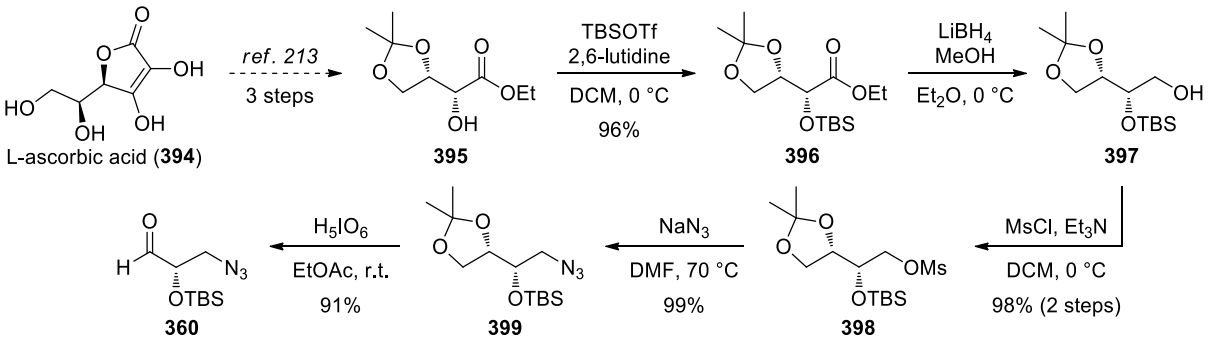


To a solution of **351** (50.5 mg, 0.135 mmol) in CH_2Cl_2 (1.3 mL) at –20 °C was added MsCl (21 µL, 0.270 mmol, 2.0 equiv) and then dropwisely Et3N (94 µL, 0.673 mmol, 5.0 equiv). The mixture was stirred for 2h at –20 °C. Saturated aqueous NH_4Cl solution was added, then extraction was made with CH_2Cl_2 (3x). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 98:2 to 95:5) to afford **359** as a colorless oil (37.5 mg, 0.119 mmol, 89%).

TLC: R_f = 0.39 (Hex/EtOAc 95:5); NMR data for the major isomer only: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 – 7.31 (m, 5H), 7.07 (d, *J* = 11.1 Hz, 1H), 6.40 (dt, *J* = 16.7, 10.5 Hz, 1H), 5.76 (d, *J* = 16.7 Hz, 1H), 5.66 (d, *J* = 10.0 Hz, 1H), 5.32 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 161.4 (apparent m), 139.4 (p, $^2J_{CF}$ = 6.0 Hz), 134.7, 134.2, 130.7, 129.8, 128.9, 128.8, 128.6, 68.5; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 81.4 (apparent m, 1F), 65.2 (d, $^2J_{FF}$ =

150.9 Hz, 4F); **IR** (neat): 3037, 1739, 1223, 1174, 853, 799, 600 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{12}H_{15}F_5NO_2S$ $[M+NH_4]^+$ 332.0738, found 332.0740.

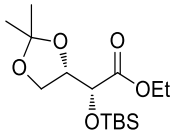
*3.2.2.5.2. Synthesis of aldehyde **360***



Scheme 3.2.2. Synthesis of aldehyde **360**.

Ester **395** was prepared from L-ascorbic acid on multigram scale following reported procedure.[213]

(*R*)-ethyl 2-((tert-butyldimethylsilyl)oxy)-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)acetate (396)

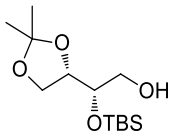


To a solution of **395** (8.25 g, 40.4 mmol) in CH_2Cl_2 (202 mL) at 0 °C was added 2,6-lutidine (5.6 mL, 48.5 mmol, 1.2 equiv) and then TBSOTf (11.1 mL, 48.5 mmol, 1.2 equiv). The mixture was stirred for 1.5 h at 0 °C, and quenched with saturated aqueous NH_4Cl solution. Extraction was made with CH_2Cl_2 (3x), and the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 95:5) to afford **396** as a colorless oil (12.4 g, 38.9 mmol, 96%).

TLC: R_f = 0.43 (Hex/EtOAc 9:1), **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.31 (td, *J* = 6.4, 5.4 Hz, 1H), 4.25 – 4.15 (m, 3H), 4.03 (dd, *J* = 8.5, 6.6 Hz, 1H), 3.95 (dd, *J* = 8.6, 6.3 Hz, 1H), 1.40 (d, *J* = 0.7 Hz, 3H), 1.35 – 1.31 (m, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.2, 109.8, 77.3, 73.5, 65.7, 61.1, 26.4, 25.8, 25.5, 18.5, 14.3, -4.8, -5.1; **IR** (neat): 2985, 2932, 2858, 1735, 1473, 1370, 1252, 1154, 1072, 1006, 778 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{15}H_{30}NaO_5Si$ $[M+Na]^+$ 341.1755, found 341.1756; $[\alpha]^{23}_D$ = +26.3 (*c* 1.0, $CHCl_3$).

[213] C. André, J. Bolte, C. Demuynck, *Tetrahedron: Asymmetry* **1998**, *9*, 1359-1367.

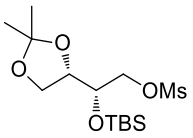
(*S*)-2-((*tert*-butyldimethylsilyl)oxy)-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (397)



To a solution of **396** (11.7 g, 36.6 mmol) in Et_2O (185 mL) at 0 °C was slowly added $LiBH_4$ (1.6 g, 73.3 mmol, 2.0 equiv) and then MeOH (3.0 mL, 73.3 mmol, 2.0 equiv) in a dropwise manner. The mixture was stirred for 1.5 h at 0 °C, and quenched with 0.5 M HCl solution. Extraction was made with EtOAc (3x), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, then brine, dried with $MgSO_4$ and concentrated under reduced pressure. The resulting alcohol **397** was used in the next step without any further purification.

TLC: R_f = 0.32 (Hex/EtOAc 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.19 (td, *J* = 6.8, 5.7 Hz, 1H), 4.02 – 3.94 (m, 1H), 3.89 – 3.75 (m, 2H), 3.66 (dt, *J* = 10.4, 5.0 Hz, 1H), 3.53 (ddd, *J* = 11.3, 6.4, 4.7 Hz, 1H), 2.17 (t, *J* = 6.2 Hz, 1H), 1.42 (s, 3H), 1.34 (s, 3H), 0.89 (s, 9H), 0.10 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 109.5, 77.3, 72.9, 65.5, 63.8, 26.5, 25.9, 25.3, 18.3, –4.5, –4.6; **IR** (neat): 3467, 2986, 2953, 2931, 2888, 2858, 1473, 1371, 1253, 1214, 1117, 1063, 943, 835, 778 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{12}H_{25}O_4Si$ $[M–CH_3]^+$ 261.1517, found 261.1523; **$[\alpha]^{23}_D$** = –13.0 (*c* 1.0, $CHCl_3$).

(*S*)-2-((*tert*-butyldimethylsilyl)oxy)-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl methanesulfonate (398)

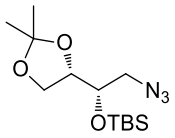


To a solution of crude **397** in CH_2Cl_2 (245 mL) at 0 °C was added MsCl (4.3 mL, 55.0 mmol, 1.5 equiv) and then Et_3N (10.2 mL, 73.3 mmol, 2.0 equiv) in a dropwise manner. The mixture was stirred for 1.5 h at 0 °C, and the saturated aqueous NH_4Cl solution added. Extraction was made with CH_2Cl_2 (3x), and the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 85:15 to 8:2) to afford **398** as a colorless oil (12.7 g, 35.9 mmol, 98%).

TLC: R_f = 0.42 (Hex/EtOAc 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.31 (dd, *J* = 10.2, 4.2 Hz, 1H), 4.21 – 4.08 (m, 2H), 4.00 (dq, *J* = 6.8, 4.3 Hz, 2H), 3.87 (dd, *J* = 8.6, 6.3 Hz, 1H), 3.03 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (101 MHz,

$CDCl_3$): δ 109.8, 76.2, 70.7, 70.3, 65.1, 37.5, 26.4, 25.9, 25.2, 18.2, -4.4, -4.7; **IR** (neat): 2986, 2954, 2932, 2889, 2858, 1473, 1358, 1254, 1215, 1176, 1070, 958, 834, 778, 528 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{14}H_{31}O_6SSi$ $[M+H]^+$ 355.1605, found 355.1600; $[\alpha]^{22}_D$ = –7.3 (*c* 1.0, $CHCl_3$).

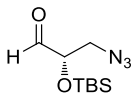
((*S*)-2-azido-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethoxy)(tert-butyl)dimethylsilane (399)



To a solution of **398** (12.7 g, 35.9 mmol) in DMF (180 mL) was added NaN_3 (7.0 g, 108.0 mmol, 3.0 equiv). The mixture was stirred at 70 °C for 24 h. After cooling down to r.t., EtOAc and H_2O were added Extraction was made with EtOAc (3x), and the combined organic layers were washed with H_2O (5x), then with brine, dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 95:5) to afford **399** as a colorless oil (10.75 g, 35.7 mmol, 99%).

TLC: R_f = 0.32 (Hex/EtOAc 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.15 (td, *J* = 6.6, 5.3 Hz, 1H), 3.97 (dd, *J* = 8.5, 6.7 Hz, 1H), 3.90 – 3.78 (m, 2H), 3.40 (dd, *J* = 12.6, 3.9 Hz, 1H), 3.17 (dd, *J* = 12.6, 6.9 Hz, 1H), 1.40 (s, 3H), 1.33 (s, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 109.6, 76.8, 72.3, 65.1, 53.45, 26.4, 25.9, 25.1, 18.2, -4.6, -4.7; **IR** (neat): 2987, 2954, 2931, 2859, 2101, 1473, 1371, 1256, 1214, 1115, 1073, 951, 838, 779 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{13}H_{27}N_3NaO_3Si$ $[M+Na]^+$ 324.1714, found 324.1710; $[\alpha]^{23}_D$ = –6.0 (*c* 1.0, $CHCl_3$).

(*S*)-3-azido-2-((tert-butyldimethylsilyl)oxy)propanal (360)



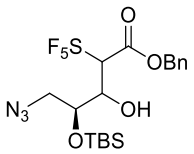
To a solution of **399** (1.75 g, 5.81 mmol) in EtOAc (29 mL) at r.t. was added H_5IO_6 (1.59 g, 6.97 mmol, 1.2 equiv). The mixture was stirred for 1 h, filtered through a pad of celite and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 9:1) to afford **360** as a colorless oil (1.13 g, 4.93 mmol, 85%).

TLC: R_f = 0.42 (Hex/EtOAc 85:15); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.66 (d, *J* = 0.5 Hz, 1H), 4.15 (ddd, *J* = 5.8, 3.7, 0.9 Hz, 1H), 3.49 (dd, *J* = 12.8, 3.7 Hz, 1H), 3.39 (dd, *J* = 12.9, 5.8 Hz,

1H), 0.95 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 202.3, 77.5, 53.2, 25.8, 18.3, -4.7, -4.9; **IR** (neat): 2954, 2931, 2859, 2100, 1737, 1472, 1290, 1254, 1124, 964, 837, 809, 779, 671 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_5H_{10}N_3O_2Si$ $[M–t\text{-Bu}]^+$ 172.0542, found 172.0536; $[\alpha]^{25}_D$ = –91.0 (*c* 1.0, $CHCl_3$).

*3.2.2.5.3. Second generation synthesis of 3-SF_5-pyridone **354***

(4*S*)-benzyl 5-azido-4-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2-(pentafluorosulfanyl)-pentanoate (361)



To a solution of **281** (248 mg, 0.796 mmol) in CH_2Cl_2 (2.7 mL) at –78 °C was slowly added *n*-Bu_2BOTf (1.80 mL, 1.0 M in CH_2Cl_2, 1.80 mmol, 2.0 equiv), and then DIPEA (311 µL, 1.80 mmol, 2.0 equiv). The mixture was stirred 30 min at –78 °C and then 30 min at –20 °C. The mixture was cooled down at –45 °C and **360** (247 g, 1.077 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was slowly added. The reaction was stirred at –45 °C for 1 h and then quenched with pH 7 phosphate buffer (3 mL). MeOH (3 mL) and 30% H_2O_2 solution (3 mL) were added and the mixture was vigorously stirred at r.t. for 8 h. Extraction was made with CH_2Cl_2 (3x), the combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Ultrapure Silica from SiliCycle, Hex/ CH_2Cl_2 7:3 to 1:1) to afford **361** as a colorless oil (411 mg, 0.813 mmol, 91%, d.r.: A:B:C:D = 1.8:1.0:5.1:2.7).

Isomers were partially separated by preparative TLC (Hex/EtOAc 95:5) for characterization: Diastereoisomers A and B were obtained as a mixture whereas diastereoisomers C and D could be isolated. Diastereoisomers A and B were then separated by preparative HPLC: *column*: Reprosil-Gold 120 C18, 5 µm, 120 x 20 mm; *method*: isocratic flow, 26.5 $mL \cdot min^{-1}$, H_2O (+ 0.1% TFA):MeCN (+ 0.1% TFA) = 35:65; *retention times*: $t_{R_{diaA}}$ = 15.64 min; $t_{R_{diaB}}$ = 14.61 min; *wavelength of detection* λ = 120 nm.

Diastereoisomer A: **TLC**: R_f = 0.37 (Hex/EtOAc 95:5), **^{1}H NMR** (600 MHz, $CDCl_3$, cryoprobe): δ 7.48 – 7.33 (m, 5H), 5.29 (d, *J* = 12.1 Hz, 1H), 5.23 (d, *J* = 12.0 Hz, 1H), 4.69 – 4.59 (m, 1H), 4.34 – 4.29 (m, 1H), 3.90 (q, *J* = 4.9 Hz, 1H), 3.50 – 3.32 (m, 2H), 3.22 (d, *J* = 2.5 Hz, 1H), 0.90 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$, cryoprobe): δ 165.2 (apparent t, $^3J_{CF}$ = 3.4 Hz), 134.1, 129.1, 128.9, 128.8, 84.1 (p, $^2J_{CF}$ = 10.2 Hz), 72.8, 71.9,

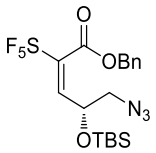
68.9, 52.2, 25.9, 18.1, -4.2, -5.0; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 81.0 (apparent m, 1F), 69.5 (d, $^2J_{FF}$ = 146.7 Hz, 4F); **IR** (neat): 3541, 2954, 2930, 2858, 2106, 1745, 1259, 1168, 1108, 841, 780, 697 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{18}H_{28}F_5N_3NaO_4SSi$ $[M+Na]^+$ 528.1382, found 528.1381; **$[\alpha]^{24}_D$** = 8.8 (*c* 0.3, $CHCl_3$).

Diastereoisomer B: **TLC**: R_f = 0.37 (Hex/EtOAc 95:5); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.45 – 7.32 (m, 5H), 5.31 (d, *J* = 12.0 Hz, 1H), 5.18 (d, *J* = 11.9 Hz, 1H), 4.45 – 4.34 (m, 2H), 3.51 – 3.44 (m, 2H), 3.34 – 3.26 (m, 1H), 2.63 (d, *J* = 10.4 Hz, 1H), 0.87 (s, 9H), 0.02 (s, 3H), -0.05 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$, cryoprobe): δ 163.9 (apparent t, $^3J_{CF}$ = 3.1 Hz), 134.1, 129.3, 129.2, 128.9, 86.6 (p, $^2J_{CF}$ = 9.5 Hz), 71.1, 70.2, 68.8, 53.5, 25.9, 18.1, -4.1, -5.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 81.8 (apparent m, 1F), 68.4 (d, $^2J_{FF}$ = 149.1 Hz, 4F); **IR** (neat): 3532, 2930, 2859, 2106, 1745, 1259, 1118, 1076, 843, 781, 697, 600 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{18}H_{29}F_5N_3O_4SSi$ $[M+H]^+$ 506.1563, found 506.1565; **$[\alpha]^{23}_D$** = –18.4 (*c* 0.1, $CHCl_3$).

Diastereoisomer C: **TLC**: R_f = 0.32 (Hex/EtOAc 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 – 7.34 (m, 5H), 5.27 (s, 2H), 4.76 – 4.59 (m, 1H), 4.45 (ddd, *J* = 9.9, 5.0, 3.2 Hz, 1H), 4.19 (d, *J* = 9.9 Hz, 1H), 4.05 (td, *J* = 5.2, 3.2 Hz, 1H), 3.41 (dd, *J* = 12.6, 5.7 Hz, 1H), 3.19 (dd, *J* = 12.5, 4.8 Hz, 1H), 0.90 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.7 (p, $^3J_{CF}$ = 3.0 Hz), 134.2, 129.0, 128.8, 128.7, 82.4 (p, $^2J_{CF}$ = 10.1 Hz), 72.1, 71.0 (p, $^3J_{CF}$ = 3.2 Hz), 68.8, 52.2, 25.8, 18.1, -4.4, -5.0; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 81.1 (apparent m, 1F), 65.5 (apparent m, $^2J_{FF}$ = 147.2 Hz, 4F); **IR** (neat): 3475, 2955, 2932, 2860, 2106, 1718, 1259, 1173, 1110, 844, 780, 697 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{18}H_{28}F_5N_3NaO_4SSi$ $[M+Na]^+$ 528.1382, found 528.1379; **$[\alpha]^{22}_D$** = –22.4 (*c* 0.5, $CHCl_3$).

Diastereoisomer D: **TLC**: R_f = 0.25 (Hex/EtOAc 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 – 7.31 (m, 5H), 5.32 (d, *J* = 12.0 Hz, 1H), 5.22 (d, *J* = 12.0 Hz, 1H), 4.88 (pd, *J* = 6.7, 1.1 Hz, 1H), 4.55 – 4.45 (m, 1H), 4.37 (ddd, *J* = 10.6, 7.6, 1.6 Hz, 1H), 3.66 – 3.54 (m, 2H), 3.54 – 3.46 (m, 1H), 0.87 (s, 9H), 0.10 (s, 3H), -0.05 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.5 (p, $^3J_{CF}$ = 2.3 Hz), 133.7, 129.2, 128.9 (2C), 81.0 (p, $^2J_{CF}$ = 11.7 Hz), 73.7 (apparent t, $^4J_{CF}$ = 1.5 Hz), 72.0 (apparent m), 69.1, 53.6, 25.8, 18.0, -3.7, -5.4; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 80.2 (apparent m, 1F), 66.0 (apparent m, $^2J_{FF}$ = 151.3 Hz, 4F); **IR** (neat): 3497, 2956, 2933, 2861, 2106, 1726, 1260, 1175, 1108, 840, 780, 750, 697 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{18}H_{28}F_5N_3NaO_4SSi$ $[M+Na]^+$ 528.1382, found 528.1380; **$[\alpha]^{22}_D$** = –15.7 (*c* 1.0, $CHCl_3$).

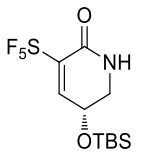
(*R*,*E*)-benzyl 5-azido-4-((*tert*-butyldimethylsilyl)oxy)-2-(pentafluorosulfanyl)pent-2-enoate (362)



To a solution of **361** (148 mg, 2.93 mmol) in CH_2Cl_2 (29 mL) at 0 °C was added acetic anhydride (415 μL, 4.39 mmol, 1.5 equiv), and then DMAP (715 mg, 5.85 mmol, 2.0 equiv). The mixture was stirred for 1 h at 0 °C and then quenched with 1.0 M HCl. Extraction was made with CH_2Cl_2 (3x), the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 99:1) to afford **362** as a colorless oil (1.31 g, 2.69 mmol, 92%).

TLC: R_f = 0.36 (Hex/EtOAc 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 – 7.34 (m, 5H), 6.62 (dt, *J* = 8.4, 0.7 Hz, 1H), 5.50 – 5.12 (m, 2H), 4.34 (dtt, *J* = 8.6, 5.2, 0.8 Hz, 1H), 3.21 (d, *J* = 5.0 Hz, 2H), 0.86 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.9 (apparent m), 146.8 (p, $^2J_{CF}$ = 18.5 Hz), 141.8 (p, $^3J_{CF}$ = 5.6 Hz), 134.3, 129.2, 129.1, 129.0, 70.1, 68.9, 56.0, 25.7, 18.1, -4.8, -5.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 79.2 (apparent m, 1F), 64.0 (d, $^2J_{FF}$ = 150.2 Hz, 4F); **IR** (neat): 2956, 2932, 2888, 2860, 2100, 1744, 1257, 1196, 1101, 853, 838, 779, 697, 668, 602 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{18}H_{26}F_5N_3NaO_3SSi$ $[M+Na]^+$ 510.1277, found 510.1276; **$[\alpha]^{23}_D$** = –5.7 (*c* 0.5, $CHCl_3$).

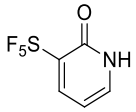
(*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-(pentafluorosulfanyl)-5,6-dihydropyridin-2(1H)-one (363)



A solution of **362** (1.29 g, 2.65 mmol) and $Pd(OH)_2$ (370 mg, 20%, 0.53 mmol, 0.2 equiv) in MeOH (27 mL) was stirred under H_2 atmosphere (balloon) for 15 min. After filtering through a pad of celite, the mixture was concentrated under reduced pressure to afford the corresponding amino acid as a white solid. The crude material was suspended in THF (27 mL), EDC (1.05 g, 5.30 mmol, 2.0 equiv) was added, and the reaction was stirred for 2 h at room temperature. H_2O was added and extraction was made with EtOAc (3x). Combined organic layers were washed with brine and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 7:3) to afford **363** as a yellowish oil (533 mg, 1.51 mmol, 57%).

TLC: R_f = 0.35 (Hex/EtOAc 7:3); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.21 (d, *J* = 2.6 Hz, 1H), 6.61 (s, 1H), 4.73 (t, *J* = 8.5 Hz, 1H), 3.47 – 3.33 (m, 2H), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 158.2, 149.8 (p, $^3J_{CF}$ = 4.8 Hz), 145.8 (p, $^2J_{CF}$ = 15.8 Hz), 65.0, 46.2, 25.7, 18.1, -4.7, -4.7; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 80.8 (apparent m, 1F), 65.4 (d, $^2J_{FF}$ = 152.4 Hz, 4F); **IR** (neat): 3285, 2933, 2891, 1693, 1473, 1259, 1124, 1007, 850, 807, 779, 671 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_7H_{11}F_5NO_2SSi$ $[M–C_4H_9]^+$ 296.0195, found 296.0198; **$[\alpha]^{22}_D$** = –9.3 (*c* 0.5, $CHCl_3$).

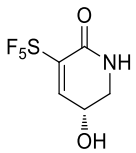
3-(Pentafluorosulfanyl)pyridin-2(1*H*)-one (354)



A mixture of **363** (520 mg, 1.47 mmol) and concencetrated H_2SO_4 (7.4 mL) was heated at 90 °C for 1 h. After cooling down to room temperature, the mixture was poured into ice and 5.0 M aqueous NaOH was added (until pH reaches 7-8). Extraction was made with EtOAc (3x), the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification was performed by column chromatography (dry loading, Hex/EtOAc 3:7) to afford **354** as a white solid (268 mg, 1.21 mmol, 82%).

TLC: R_f = 0.31 (Hex/EtOAc 2:8); **^{1}H NMR** (400 MHz, CD_3CN): δ 10.34 (bs, 1H), 8.12 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.56 (dd, *J* = 6.4, 2.0 Hz, 1H), 6.35 – 6.24 (m, 1H); **^{13}C NMR** (101 MHz, CD_3CN): δ 156.3, 144.4 (p, $^3J_{CF}$ = 4.9 Hz), 143.4 (p, $^2J_{CF}$ = 14.6 Hz), 141.7, 104.4; **^{19}F NMR** (282 MHz, CD_3CN): AB_4 system, δ 85.7 (apparent m, 1F), 65.7 (d, $^2J_{FF}$ = 149.7 Hz, 4F); **IR** (neat): 3137, 3080, 2998, 2924, 2861, 2802, 1650, 1611, 1581, 1553, 1478, 1337, 1234, 1045, 837, 803, 787, 764, 634, 580, 539 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_5H_4F_5NOS$ $[M]^+$ 220.9929, found 220.9931.

(*R*)-5-hydroxy-3-(pentafluorosulfanyl)-5,6-dihydropyridin-2(1H)-one (364)

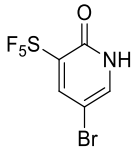


A solution of **363** (21 mg, 0.059 mmol) in TFA (450 μL) was stirred at r.t. for 24 h. Ice cold H_2O and EtOAc were added, and extraction was made with EtOAc (3x). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was

performed by column chromatography (Hex/EtOAc 2:8) to afford **364** as a white solid (13 mg, 0.054 mmol, 92%).

TLC: R_f = 0.20 (Hex/EtOAc 3:7); **^{1}H NMR** (600 MHz, $(CD_3)_2CO$): δ 7.48 (d, *J* = 3.5 Hz, 1H), 7.10 (br, 1H), 5.07 (d, *J* = 6.3 Hz, 1H), 4.84 – 4.70 (m, 1H), 3.56 (dddd, *J* = 12.8, 5.7, 3.8, 0.9 Hz, 1H), 3.43 – 3.36 (m, 1H); **^{13}C NMR** (151 MHz, $(CD_3)_2CO$): δ 157.5, 150.0 (p, $^3J_{CF}$ = 4.9 Hz), 147.1 (p, $^2J_{CF}$ = 13.3 Hz), 64.1, 46.4; **^{19}F NMR** (282 MHz, $(CD_3)_2CO$): AB_4 system, δ 85.7 (apparent m, 1F), 66.5 (d, $^2J_{FF}$ = 149.6 Hz, 4F); **IR** (neat): 3305, 2926, 1682, 850 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_5H_7F_5NNaO_2S$ $[M+H]^+$ 240.0112, found 240.0112; **$[\alpha]^{23}_D$** = −6.9 (*c* 0.15, $CHCl_3$).

5-Bromo-3-(pentafluorosulfanyl)pyridin-2(1*H*)-one (365)

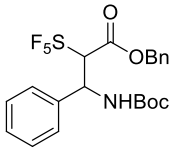


To a solution of **354** (102 mg, 0.461 mmol) in DMF (4.6 mL) was added NBS (purified prior to use by recrystallization from H_2O, 86 mg, 484 mmol, 1.05 equiv). After stirring at r.t. for 4 h, EtOAc and H_2O were added, and extraction was made with EtOAc (3x). The combined organic layers were washed with H_2O (4x), then brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification was performed by column chromatography (CH_2Cl_2/EtOAc 9:1 to 8:2) to afford **365** as a white solid (103 mg, 0.343 mmol, 74%).

TLC: R_f = 0.39 (Hex/EtOAc 1:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.78 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.1, 146.0, 143.0 (apparent m), 140.9, 97.1; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 81.1 (apparent m, 1F), 64.8 (d, $^2J_{FF}$ = 152.6 Hz, 4F); **IR** (neat): 3152, 3072, 2967, 2897, 1662, 1604, 849, 815, 662 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_5H_3BrF_5NOS$ $[M]^+$ 298.9034, found 298.9038.

3.2.2.6. Mannich Reactions with *α*-SF_5-Enolate

Benzyl 3-((*tert*-butoxycarbonyl)amino)-3-phenyl-2-(pentafluorosulfanyl)propanoate (370)



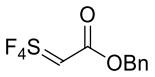
To a solution of **281** (12 mg, 0.044 mmol) in CH_2Cl_2 (200 µL) at 0 °C was added $TiCl_4$ (106 µL, 0.5 M in CH_2Cl_2, 0.053 mmol, 1.2 equiv), the mixture was stirred 10 min at 0 °C and then cooled down to –78 °C. Et_3N (62 µL, 1.0 M in CH_2Cl_2, 0.062 mmol, 1.4 equiv) was added and the mixture was stirred for 10 min. Then (*E*)-*tert*-butyl benzylydenecarbamate (10.8 mg, 0.053 mmol, 1.2 equiv) in CH_2Cl_2 (200 µL) was added followed by Ti(O*i*-Pr)$_4$ (106 µL, 0.5 M in CH_2Cl_2, 0.053 mmol, 1.2 equiv). The reaction was stirred from –78 °C to –65 °C for 15 h, then quenched with pH 7 phosphate buffer (1 mL), and the mixture was let warmed to r.t., Extraction was made with CH_2Cl_2 (3x), the combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. ^{19}F NMR spectrum of the crude material indicated a conversion of 91% into **370** as a mixture of diastereoisomers (67% + 17%), and traces of two unidentified side products (3% + 4%). Purification was performed by column chromatography (Ultrapure Silica from SiliCycle, Hex/EtOAc 98:2 to 9:1) to afford the major diastereoisomer as a white solid and the minor diastereoisomer as a colorless oil (isolated yield not determined).

Minor diastereoisomer: **TLC**: R_f = 0.54 (Hex/EtOAc 85:15); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34 – 7.25 (m, 6H), 7.25 – 7.18 (m, 2H), 7.09 – 6.97 (m, 2H), 6.87 (d, *J* = 9.2 Hz, 1H), 5.72 (dd, *J* = 9.0, 2.5 Hz, 1H), 5.07 (d, *J* = 12.2 Hz, 1H), 5.02 (d, *J* = 12.2 Hz, 1H), 4.76 – 4.62 (m, 1H), 1.44 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.1, 154.9, 137.9, 134.0, 129.2, 128.8, 128.7, 128.5, 128.3, 126.6, 84.9 (p, $^3J_{CF}$ = 9.5 Hz), 80.2, 68.6, 54.2, 28.5; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 79.9 (apparent m, 1F), 65.0 (apparent m, 4F); **IR** (neat): 3441, 2979, 2932, 1740, 1721, 1497, 1167, 899, 863, 837, 788, 751, 698 cm^{-1}; **HRMS** (MALDI) *m/z* calculated for $C_{21}H_{24}F_5NNaO_4S$ $[M+Na]^+$ 504.1238, found 504.1239.

Major diastereoisomer: **TLC**: R_f = 0.48 (Hex/EtOAc 85:15); **^{1}H NMR** (400 MHz, $(CD_3)_2CO$): δ 7.45 (ddd, *J* = 6.0, 2.7, 1.5 Hz, 2H), 7.36 – 7.28 (m, 6H), 7.17 – 7.08 (m, 2H), 6.98 (d, *J* = 9.8 Hz, 1H), 5.56 (t, *J* = 10.6 Hz, 1H), 5.32 (dp, *J* = 11.6, 5.8 Hz, 1H), 4.91 (d, *J* = 12.2 Hz, 1H), 4.79 (d, *J* = 12.2 Hz, 1H), 1.35 (s, 9H); **^{13}C NMR** (101 MHz, $(CD_3)_2CO$): δ 164.0 (p, $^3J_{CF}$ = 2.9 Hz), 155.0, 139.8, 135.5, 129.6, 129.4, 129.31, 129.30, 129.28, 129.0, 88.0 (p, $^2J_{CF}$ = 7.3 Hz), 79.7, 68.7, 56.1, 28.5; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 79.9

(apparent m, 1F), 65.0 (apparent m, 4F); **IR** (neat): 3412, 3038, 2979, 2932, 1748, 1689, 1518, 1309, 1168, 894, 869, 841, 830, 792, 773, 701 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{21}H_{24}F_5NNaO_4S$ $[M+Na]^+$ 504.1238, found 504.1237.

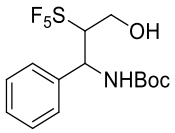
Benzyl 2-(tetrafluoro-λ^6-sulfanylidene)acetate (371)



To a solution of **281** (18 mg, 0.065 mmol) in CH_2Cl_2 (650 µL) at 0 °C was added $TiCl_4$ (260 µL, 1.5 M in CH_2Cl_2, 0.391 mmol, 6.0 equiv), the mixture was stirred 10 min at 0 °C and then cooled down to −78 °C. Et_3N (130 µL, 1.0 M in CH_2Cl_2, 0.130 mmol, 2.0 equiv) was added and the mixture was stirred for 30 min. Then (*E*)-*tert*-butyl benzylydenecarbamate (16.0 mg, 0.078 mmol, 1.2 equiv) in 200 µL CH_2Cl_2 (300 µL) was added followed by Ti(O*i*-Pr)$_4$ (155 µL, 0.5 M in CH_2Cl_2, 0.078 mmol, 1.2 equiv). The reaction was stirred at –78 °C for 1 h, then quenched with pH 7 phosphate buffer (1 mL), and the mixture was let warmed to r.t., Extraction was made with CH_2Cl_2 (3x), the combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Ultrapure Silica from SiliCycle, Hex/EtOAc 95:5) to afford **371** as a colorless oil (isolated yield not determined).

TLC: R_f = 0.48 (Hex/EtOAc 85:15); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45 – 7.30 (m, 5H), 5.17 (s, 2H), 4.03 (ddt, J = 39.3, 12.2, 8.7 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.0 (apparent m), 135.4, 128.8, 128.7, 128.6, 67.7, 57.9 (apparent m); **^{19}F NMR** (376 MHz, $CDCl_3$): A_2BC system, δ 62.8 (apparent m, 2F), 57.1 (apparent m, 1F), 56.3 (apparent m, 1F).

***Tert*-butyl (3-hydroxy-2-pentafluorosulfanyl-1-phenylpropyl)carbamate (373)**



To a solution of **370** (9 mg, 0.019 mmol) in THF (370 µL) at 0 °C was slowly added $LiBH_4$ (0.8 mg, 0.037 mmol, 2.0 equiv), and then MeOH (1.5 µL, 0.037 mmol, 2.0 equiv). After stirring for 1.5 h at 0 °C, additional $LiBH_4$ (0.8 mg, 0.037 mmol, 2.0 equiv) and MeOH (1.5 µL, 0.037 mmol, 2.0 equiv) were added. After stirring for 2 h, saturated aqueous NH_4Cl solution was added. Extraction was made with EtOAc (3x), and the combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by preparative TLC (CH_2Cl_2/EtOAc 95:5) to afford both isolated isomers as a

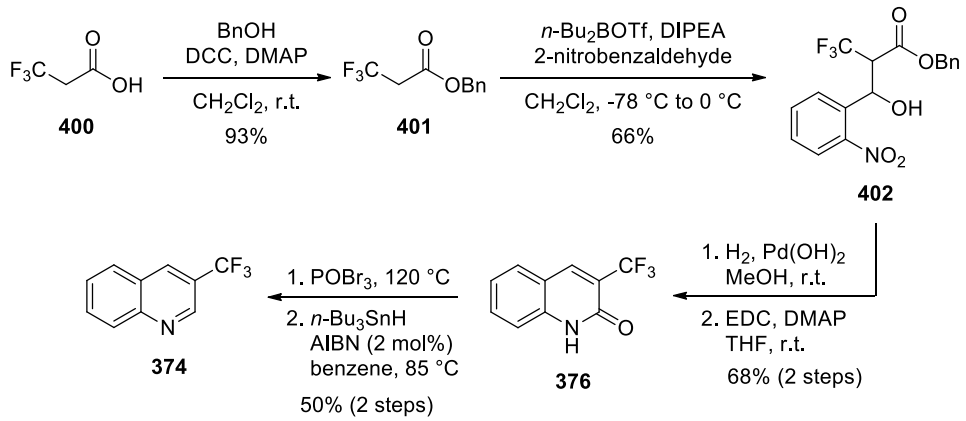
white solid (major diastereoisomer) and a colorless oil (minor diastereoisomer), d.r. = 4.9:1 (according to ^{19}F NMR of the crude material).

Minor diastereoisomer: **TLC**: R_f = 0.30 (Hex / EtOAc 8:2); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.42 – 7.34 (m, 4H), 7.34 – 7.28 (m, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 5.73 (s, 1H), 4.37 – 4.25 (m, 1H), 4.06 – 3.78 (m, 2H), 2.31 (s, 1H), 1.43 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 155.2, 140.2, 129.2, 128.2, 126.5, 89.0, 80.1, 60.1, 56.1, 28.5; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 85.3 (apparent m, 1F), 59.2 (d, $^2J_{FF}$ = 142.7 Hz, 4F); **IR** (neat): 3387, 2979, 1691, 1509, 1368, 1252, 1169, 832, 701, 586 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{14}H_{20}F_5NNaO_3S$ $[M+Na]^+$ 400.0976, found 400.0971.

Major diastereoisomer: **TLC**: R_f = 0.38 (Hex / EtOAc 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 – 7.35 (m, 2H), 7.34 – 7.26 (m, 3H), 5.73 (s, 1H), 5.47 (d, *J* = 10.7 Hz, 1H), 4.21 (ddd, *J* = 12.2, 9.4, 3.8 Hz, 1H), 4.10 (td, *J* = 9.1, 6.5 Hz, 1H), 4.02 – 3.87 (m, 1H), 1.49 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.3, 137.9, 128.6, 127.6, 125.8, 92.3, 81.8, 59.7 (apparent m), 51.6, 28.4; **^{19}F NMR** (282 MHz, $CDCl_3$): AB_4 system, δ 86.4 (apparent m, 1F), 66.9 (d, $2J_{FF}$ = 143.0 Hz, 4F); **IR** (neat): 3387, 2979, 1691, 1509, 1368, 1252, 1169, 832, 701, 586 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{14}H_{20}F_5NNaO_3S$ $[M+Na]^+$ 400.0976, found 400.0978.

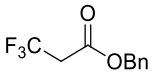
3.2.2.7. Preparation of CF_3 and *t*-Bu analogues

3-(Trifluoromethyl)-pyridin-2(1H)-one **378** was purchased from Fluorochem. The five other analogues were prepared using the following procedures:



Scheme 3.2.3. Preparation of CF_3-quinolone **376** and CF_3-quinoline **374**.

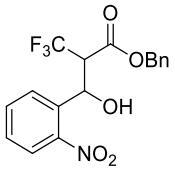
Benzyl 3,3,3-trifluoropropanoate (401)



To a solution of 3,3,3-trifluoropropanoic acid (2.51 g, 19.60 mmol) in CH_2Cl_2 (130 mL) were added benzyl alcohol (4.0 mL, 39.20 mmol, 2.0 equiv) and 4-DMAP (0.24 g, 1.96 mmol, 0.1 equiv). The mixture was cooled down at 0 °C and DCC (6.07 g, 29.4 mmol, 1.5 equiv) was added. After stirring for 2 h at r.t., the reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/ CH_2Cl_2 9:1 to 8:2) to afford **401** as a colorless oil (3.96 g, 18.15 mmol, 93%).

NMR spectra consistent with those found in the literature:[133e] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 – 7.31 (m, 5H), 5.22 (s, 2H), 3.23 (q, J = 10.1 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.1 (q, $^3J_{CF}$ = 4.2 Hz), 135.0, 128.8, 128.7, 123.5 (q, $^1J_{CF}$ = 276.2 Hz), 67.6, 39.76 (q, $^2J_{CF}$ = 31.1 Hz).

Benzyl 3,3,3-trifluoro-2-(hydroxy(2-nitrophenyl)methyl)propanoate (402)

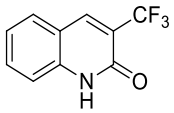


To a solution of **401** (1.50 g, 6.88 mmol) in CH_2Cl_2 (20 mL) at –78 °C was slowly added *n*-Bu_2BOTf (13.7 mL, 1.0 M in CH_2Cl_2, 13.7 mmol, 2.0 equiv), and then DIPEA (2.4 mL, 13.7 mmol, 2.0 equiv). The mixture was stirred 30 min at –78 °C and then 30 min at 0 °C. The mixture was cooled down at –45 °C and 2-nitrobenzaldehyde (1.25 g, 8.25 mmol, 1.2 equiv) in 2.0 mL CH_2Cl_2 was slowly added. The reaction was stirred at –45 °C for 1 h and then quenched with pH 7 phosphate buffer (20 mL). MeOH (20 mL) and 30% H_2O_2 solution (20 mL) were added and the mixture was vigorously stirred at r.t. for 10 h. Extraction was made with CH_2Cl_2 (3x), the combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Ultrapure Silica from SiliCycle, Hex/ CH_2Cl_2 4:6 to 2:8) to afford **S10** as a yellow oil (1.67 g, 4.53 mmol, 66%, d.r. > 20:1).

TLC: R_f = 0.30 (Hex/EtOAc 8:2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.97 (dd, J = 8.2, 1.5 Hz, 1H), 7.80 – 7.75 (m, 1H), 7.60 (td, J = 7.6, 1.4 Hz, 1H), 7.45 (ddd, J = 8.8, 7.3, 1.5 Hz, 1H), 7.38 – 7.28 (m, 3H), 7.25 – 7.18 (m, 2H), 5.82 (t, J = 5.8 Hz, 1H), 5.12 (d, J = 1.6 Hz, 2H), 3.96

(qd, *J* = 8.1, 6.2 Hz, 1H), 3.41 (d, *J* = 5.1 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.2 (q, $^3J_{CF}$ = 3.2 Hz), 147.8, 134.52, 134.50, 134.0, 129.9, 129.6, 128.8, 128.7, 128.5, 125.2, 123.9 (q, $^1J_{CF}$ = 282.0 Hz), 68.1, 68.0 (q, $^3J_{CF}$ = 1.9 Hz), 55.2 (q, $^2J_{CF}$ = 25.9 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$): δ –62.6 (d, $^3J_{FH}$ = 8.4 Hz); **IR** (neat): 3515, 3037, 2962, 1742, 1527, 1345, 1255, 1156, 1117, 1001, 752, 697 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{17}H_{18}F_3N_2O_5$ $[M+NH_4]^+$ 387.1162, found 387.1163.

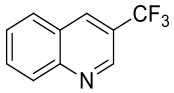
3-(Trifluoromethyl)quinolin-2(1H)-one (376)



To a solution of **402** (1.00 g, 2.71 mmol) in MeOH (40 mL) was added $Pd(OH)_2$ (0.28 g, 20%, 0.41 mmol, 0.15 equiv). Then H_2 atmosphere was set up (balloon), and the reaction was stirred for 2.5 h at room temperature. The mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude material was disolved in THF (30 mL) and EDC (1.04 g, 5.42 mmol, 2.0 equiv) and DMAP (66 mg, 0.54 mmol, 0.2 equiv) were added. After stirring for 14 h, H_2O was added and extraction was made with EtOAc (3x). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (dry loading, Hex/EtOAc 8:2 to 7:3) to afford **376** as a white solid (391 mg, 1.83 mmol, 68%).

TLC: R_f = 0.42 (Hex/EtOAc 7:3); **^{1}H NMR** (400 MHz, CD_3OD): δ 8.45 (s, 1H), 7.81 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.67 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.33 (ddd, *J* = 8.1, 7.3, 1.1 Hz, 1H); **^{13}C NMR** (101 MHz, CD_3OD): δ 160.3, 142.2 (apparent m), 141.2, 134.4, 130.8, 124.5, 124.0 (q, $^1J_{CF}$ = 269.7 Hz), 122.1 (q, $^2J_{CF}$ = 30.8 Hz), 119.1, 116.6; **^{19}F NMR** (282 MHz, CD_3OD): δ –65.3; **IR** (neat): 3018, 2959, 2854, 1669, 1327, 1212, 1119, 1215, 760, 734, 585, 600, 472 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{10}H_7F_3NO$ $[M+H]^+$ 214.0474, found 214.0477.

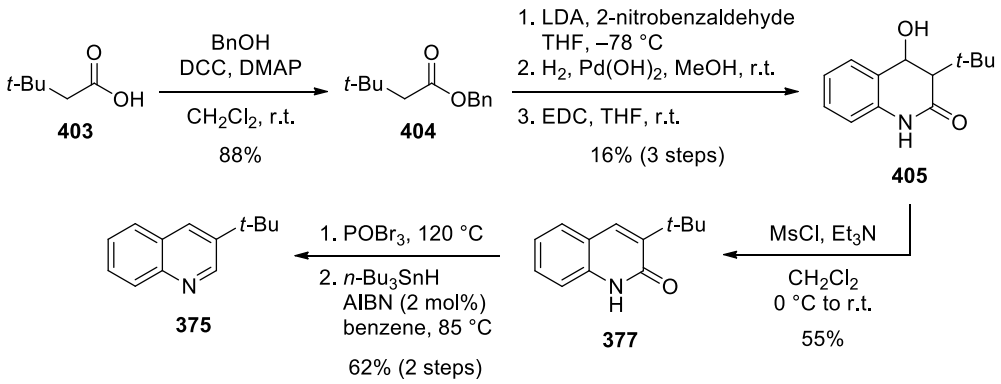
3-(Trifluoromethyl)quinolone (374)



A mixture **376** (350 mg, 1.64 mmol) and $POBr_3$ (2.35 g, 8.21 mmol, 5.0 equiv) was stirred at 120 °C for 16 h. After cooling down at room temperature, iced-cold water was carefully added. Saturated aqueous K_2CO_3 solution and EtOAc were added, layers were separated and the

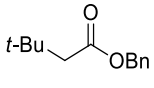
aqueous layer was extracted twice with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The resulting brown solid was disolved in benzene (16 mL), the solution was degased with Ar for 10 min and then *n*-Bu_3SnH (650 µL, 2.44 mmol, 1.5 equiv) was added. The mixture was heated at 80 °C and AIBN (5.3 mg, 0.03 mmol, 0.02 equiv) was added. After stirring for 24 h at 85 °C, aqueous NaOH solution (1.0 M, 5 mL) was added and the resulting biphasic mixture was vigorously stirred for 2 h at room temperature. The layers were separated and extraction was made with Et_2O (3x), the combined organic layers were washed with 1.0 M NaOH solution, dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 95:5) to afford the title compound as a white solid (161 mg, 0.82 mmol, 50%).

NMR spectra consistent with those found in the literature:[214] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.11 (d, *J* = 2.2 Hz, 1H), 8.49 – 8.39 (m, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.86 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.67 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.5, 146.2 (q, $^3J_{CF}$ = 3.3 Hz), 134.1 (q, $^3J_{CF}$ = 4.2 Hz), 131.9, 129.8, 128.7, 128.1, 126.4, 123.8 (q, $^1J_{CF}$ = 272.3 Hz), 123.7 (q, $^2J_{CF}$ = 32.8 Hz); **^{19}F NMR** (282 MHz, $CDCl_3$) δ −62.3.



Scheme 3.2.4. Preparation of *t*-Bu-quinolone **377** and *t*-Bu-quinoline **375**.

Benzyl 3,3-dimethylbutanoate (404)



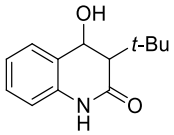
To a solution of 3,3-dimethylbutanoic acid (1.50 g, 12.91 mmol) in CH_2Cl_2 (90 mL) were added benzyl alcohol (2.7 mL, 25.80 mmol, 2.0 equiv) and DMAP (0.16 g, 1.29 mmol, 0.1 equiv). The mixture was cooled down at 0 °C and DCC (4.00 g, 19.37 mmol, 1.5 equiv) was added. After stirring for 2 h at r.t., the reaction mixture was filtered through a pad of celite and

[214] T. F. Liu, Q. L. Shen, *Org. Lett.* **2011**, *13*, 2342-2345.

concentrated under reduced pressure. Purification was performed by column chromatography (Hex/ CH_2Cl_2 8:2 to 6:4) to afford **404** as a colorless oil (2.34 g, 11.34 mmol, 88%).

NMR spectra consistent with those found in literature:[215] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.43 – 7.28 (m, 5H), 5.11 (s, 2H), 2.26 (s, 2H), 1.04 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.3, 136.3, 128.6, 128.4, 128.2, 66.0, 48.1, 31.0, 29.8.

3-(*Tert*-butyl)-4-hydroxy-3,4-dihydroquinolin-2(1H)-one (405)

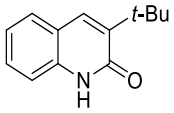


To a solution of freshly prepared LDA (2.55 mmol, 1.05 equiv) in THF (10 mL) at –78 °C was slowly added a solution of **404** (500 mg, 2.42 mmol) in THF (2.0 mL). The solution was stirred 30 min at –78 °C and then 2-nitrobenzaldehyde in THF (1.5 mL) was added. After stirring for 5 h at –78 °C, saturated aqueous NH_4Cl solution was added. Extraction was made with EtOAc (3x), the combined organic layers were washed with brine, dried with MgSO4, and concentrated under reduced pressure. Partial purification was performed by column chromatography (Hex/EtOAc 8:2) to afford the aldol product (574 mg) as a mixture of diastereoisomers along with unidentified side products. The mixture was dissolved in MeOH (16.1 mL), $Pd(OH)_2$ (113 mg, 20%, 0.16 mmol, 0.1 equiv) was added, and the mixture was stirred under hydrogen atmosphere (balloon) for 3.5 h. The mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude material was suspended in THF (16 mL) and EDC (641 mg, 3.21 mmol, 2.0 equiv) and DMAP (39 mg, 0.32 mmol, 0.2 equiv) were added. After stirring for 14 h, H_2O was added and extraction was made with EtOAc (3x). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (CH_2Cl_2/EtOAc 9:1 to 8:2) to afford **405** as a white solid (76 mg, 0.35 mmol, 14% after 3 steps).

TLC: R_f = 0.36 (Hex/EtOAc 7:3); **^{1}H NMR** (400 MHz, CD_3OD): δ 7.28 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.25 – 7.17 (m, 1H), 6.99 (td, *J* = 7.5, 1.2 Hz, 1H), 6.87 (dd, *J* = 7.8, 1.0 Hz, 1H), 4.98 (d, *J* = 3.3 Hz, 1H), 2.36 (d, *J* = 3.3 Hz, 1H), 1.25 (s, 9H); **^{13}C NMR** (101 MHz, CD_3OD): δ 172.8, 138.4, 129.9, 129.0, 128.4, 123.6, 116.2, 69.7, 55.9, 33.5, 30.0; **IR** (neat): 3268, 2952, 2810, 2431, 1668, 1599, 1489, 1384, 1362, 1277, 1252, 1210, 1076, 964, 759, 607, 493 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{13}H_{18}NO_2$ $[M+H]^+$ 220.1332, found: 220.1332.

[215] M. Ochiai, A. Yoshimura, Md. M. Hoque, T. Okubo, M. Saito, K. Miyamoto, *Org. Lett.* **2011**, *13*, 5568–5571.

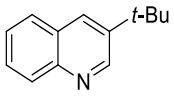
3-(*Tert*-butyl)quinolin-2(1H)-one (377)



To a solution of **405** (58 mg, 0.26 mmol) in MeCN (5.3 mL) at –0 °C was added MsCl (62 µL, 0.79 mmol, 3.0 equiv) and then Et_3N (135 µL, 1.32 mmol, 5.0 equiv). After stirring for 3 h at r.t., H_2O was added and extraction was made with EtOAc (3x). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (DCM/EtOAc 9:1 to 8:2) to afford **377** as a white solid (29 mg, 0.14 mmol, 55%).

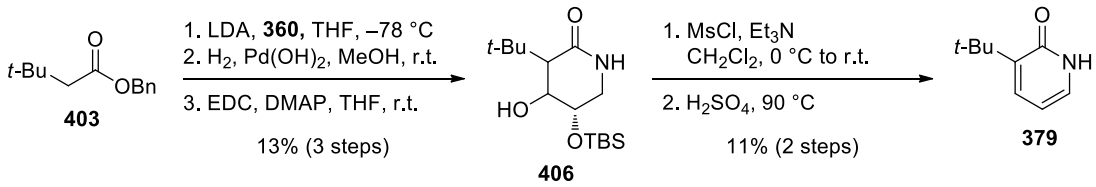
TLC: R_f = 0.35 (Hex/EtOAc 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 12.35 (s, 1H), 7.68 (s, 1H), 7.54 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.45 (ddd, *J* = 8.4, 7.1, 1.4 Hz, 1H), 7.37 (ddt, *J* = 8.2, 1.2, 0.6 Hz, 1H), 7.17 (ddd, *J* = 7.8, 7.1, 1.2 Hz, 1H), 1.51 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.1, 141.1, 137.9, 134.7, 129.5, 127.6, 122.2, 120.2, 115.1, 35.3, 29.0; **IR** (neat): 3002, 2952, 2887, 1649, 1567, 1430, 1356, 1226, 749, 596 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{13}H_{16}NO$ $[M+H]^+$ 202.1226, found 202.1226.

3-(*Tert*-butyl)quinolone (375)



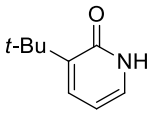
A mixture of **377** (75 mg, 0.34 mmol) and $POBr_3$ (490 mg, 1.71 mmol, 5.0 equiv) was stirred at 120 °C for 16 h. After cooling down at room temperature, iced-cold water was carefully added. Saturated aqueous K_2CO_3 solution and EtOAc were added, layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The resulting brown solid was disolved in benzene (3.4 mL), the solution was degased with Ar for 10 min and then *n*-Bu_3SnH (130 µL, 0.48 mmol, 1.4 equiv) was added. The mixture was heated at 80 °C and AIBN (1.1 mg, 6.8 µmol, 0.02 equiv) was added. After stirring for 24 h at 85 °C, aqueous NaOH solution (1.0 M, 4 mL) was added and the resulting biphasic mixture was vigorously stirred for 2 h at room temperature. The layers were separated and extraction was made with Et_2O (3x), the combined organic layers were washed with 1.0 M NaOH solution, dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 9:1) to afford **375** as a yellow oil (39 mg, 0.21 mmol, 62%).

TLC: R_f = 0.40 (Hex/EtOAc 8:2); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.03 (d, *J* = 2.5 Hz, 1H), 8.07 (dd, *J* = 8.6, 1.0 Hz, 1H), 8.03 (dd, *J* = 2.5, 0.8 Hz, 1H), 7.78 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.65 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.51 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 1.45 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 150.3, 146.6, 143.5, 131.0, 129.2, 128.8, 128.1, 127.9, 126.7, 34.0, 31.2; **IR** (neat): 2962, 2908, 2871, 1572, 1492, 1374, 1095, 969, 904, 787, 750 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_{13}H_{15}N$ $[M]^+$ 185.1199, found 185.1201.



Scheme 3.2.5. Preparation of *t*-Bu-pyridone **379**.

3-(*Tert*-butyl)pyridin-2(1H)-one (379)



To a solution of freshly prepared LDA (9.60 mmol, 1.1 equiv) in THF (75 mL) at –78 °C was slowly added a solution of **403** (1.8 g, 8.73 mmol) in THF (5.0 mL). The solution was stirred 30 min at –78 °C and then aldehyde **360** in THF (1.5 mL) was added. After stirring for 2 h at −78 °C, saturated aqueous NH_4Cl solution was added. Extraction was made with EtOAc (3x), the combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. Partial purification was performed by column chromatography (Hex/EtOAc 95:5 to 9:1) to afford the aldol product (2.83 g) as a mixture of diastereoisomers along with unidentified side products.

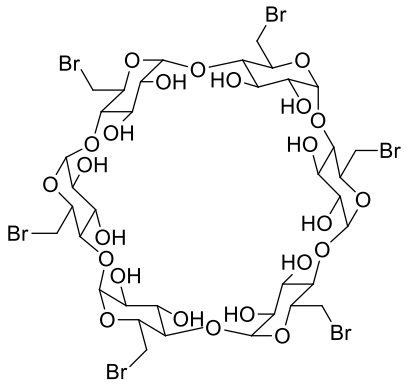
To 1.4 g (theoretically 3.21 mmol) of the mixture in MeOH (32 mL) was added $Pd(OH)_2$ (451 mg, 20%, 0.64 mmol, 0.2 equiv), and the mixture was stirred under hydrogen atmosphere (balloon) for 30 min. The mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude material was suspended in THF (32 mL) and EDC (1.27 g, 6.38 mmol, 2.0 equiv) and DMAP (78 mg, 0.64 mmol, 0.2 equiv) were added. After stirring for 14 h, H_2O was added and extraction was made with EtOAc (3x). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 8:2 to 6:4) to afford **406** as a mixture of non-separable diastereoisomers which was not characterized (391 mg, 1.30 mmol, 13% after three steps).

The mixture was dissolved in CH_2Cl_2 (13 mL), the solution was cooled down at 0 °C and MsCl (300 μL, 3.89 mmol, 3.0 equiv) was slowly added followed by Et_3N (1.1 mL, 7.78 mmol, 6.0 equiv). The reaction was let stirred at r.t. for 3 h and saturated aqueous NH_4Cl was added. Layers were separated and extraction was made with CH_2Cl_2 (3x). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The crude material was dissolved in concentrated H_2SO_4 (6.5 mL) and the mixture was stirred at 90 °C for 90 min. After cooling down to r.t., the mixture was poured into ice and 5.0 M aqueous NaOH was added (until pH reaches 7-8). Extraction was made with EtOAc (3x), the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 4:6 to 2:8) to afford **379** as a slightly tanned solid (21 mg, 0.14 mmol, 11% after two steps).

TLC: R_f = 0.31 (Hex/EtOAc 2:8); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 12.51, (br, 1H), 7.38 – 7.33 (m, 1H), 7.28 – 7.24 (m, 1H), 6.20 (t, *J* = 6.7 Hz, 1H), 1.37 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.3, 140.5, 135.6, 132.3, 106.3, 34.9, 28.5; **IR** (neat): 3130, 2952, 2868, 1637, 1554, 1454, 1361, 1058, 761 562 cm^{-1}; **HRMS** (EI): *m/z* calculated for $C_9H_{13}NO$ $[M]^+$ 151.0992, found 151.0994.

3.3. Polycationic Hexasaccharides

Hexa-6-bromo-6-deoxy-*α*-cyclodextrin (384)

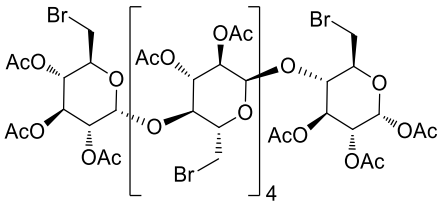


Following a reported procedure,[189] to a solution of triphenylphosphine (227 g, 865 mmol, 15.4 equiv) in DMF (1.5 L) at 0 °C was added bromine (44 mL, 848 mmol, 15.1 equiv) in a dropwise manner over 30 min. The mixture was let stirred at r.t. for 30 min and then pre-dried (under high-*vacuum* at 120 °C for 15 h) *α*-cyclodextrin (54.5 g, 56 mmol) was added. The resulting yellow suspension was stirred at r.t. for 15 min then at 75 °C for 16 h. The brown solution was cooled down to r.t. and concentrated under reduced pressure. The residue was dissolved in 1 L MeOH and MeONa (ca. 150 g) was added portionwise at 0 °C until pH > 7.

After stirring for 1 h at 0 °C, the mixture was poored into 2 L of iced water. The precipitate was filtered, washed with H_2O (1 L) and MeOH (3 x 1 L), and lyophilized to afford **384** as a slightly tanned solid contamined with 8% triphenylphosphine oxide (77.8 g, 53 mmol, 95%).

NMR spectra consistent with those found in the literature;[216] **^{1}H NMR** (400 MHz, $(CD_3)_2SO$): δ 5.76 (br, 12H), 4.94 (d, J = 3.5 Hz, 6H), 3.99 – 3.86 (m, 12H), 3.86 – 3.69 (m, 12H), 3.48 – 3.26 (m, 12H); **^{13}C NMR** (101 MHz, $(CD_3)_2SO$): δ 101.9, 84.7, 72.5, 71.6, 70.6, 34.9.

2,3,4-Tri-*O*-acetyl-6-bromo-6-deoxy-*α*-D-glucopyranosyl-[(1→4)-2,3-di-*O*-acetyl-6-bromo-6-deoxy-*α*-D-glucopyranosyl]$_4$-(1→4)-1,2,3-tri-*O*-acetyl-6-bromo-6-deoxy-*α*-D-glucopyranoside (385)



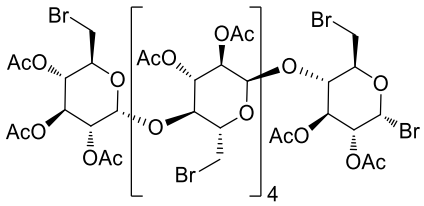
To a suspension of **384** (77.7 g, 52.9 mmol) in Ac_2O (2.6 L) at 0 °C was dropwisely 70% $HClO_4$ (37.6 mL, 438 mmol, 8.3 equiv) over 15 min. The mixture was allowed to warm to r.t. and stirred for 24 h. Pyridine (86 mL) was added and themixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (1 L) and 1 M HCl (1 L) and filtered through a pad of celite. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (1 L) and brine (1 L), dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Solid deposit, Hex/EtOAc 6:4 to 1:9) to afford **385** as a yellow solid (45.9 g, 23.46 mmol, 44%, α:β = 7:1).

TLC: R_f = 0.30 (Hex / EtOAc 3:7); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.28 (d, *J* = 3.5 Hz, 1H), 5.55 (dd, *J* = 10.1, 8.7 Hz, 1H), 5.50 (d, *J* = 4.0 Hz, 1H), 5.48 – 5.36 (m, 9H), 5.09 (t, *J* = 9.7 Hz, 1H), 4.95 (dd, *J* = 10.1, 3.7 Hz, 1H), 4.85 (dd, *J* = 10.6, 4.0 Hz, 1H), 4.78 – 4.70 (m, 4H), 4.27 – 3.74 (m, 21H), 3.67 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.44 (dd, *J* = 11.6, 4.2 Hz, 1H), 2.23 (s, 3H), 2.10 – 1.95 (m, 39H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.7, 170.6, 170.2, 170.1, 170.0, 169.9, 169.4, 169.1, 95.7, 95.6, 95.5, 77.2, 73.8, 73.6, 72.2, 71.7, 71.6, 71.4, 70.6, 70.5, 70.4, 70.2, 69.9, 69.8, 69.3, 69.2, 69.0, 68.9, 68.8, 34.7, 34.6, 34.3, 33.9, 31.9, 21.2, 21.1, 20.8, 20.8, 20.8, 20.7, 20.7, 20.6; **IR** (neat): 2958, 1749, 1437, 1369, 1235, 1216, 1030, 941, 912,

[216] W. Xue, L. Zhang, *Synthesis*, **2011**, 3612-3614.

730 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{64}H_{88}Br_6NO_{39}$ $[M+NH_4]^+$ 1968.0028, found 1968.0005; $[\alpha]^{22}_D$ = 123.3 (*c* 1.0, $CHCl_3$).

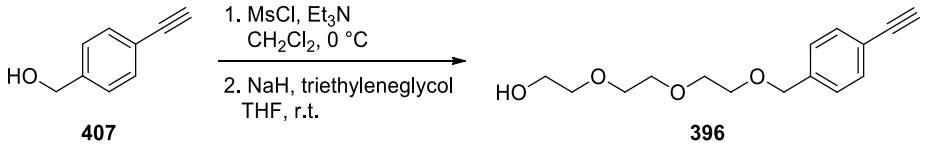
2,3,4-Tri-*O*-acetyl-6-bromo-6-deoxy-*α*-D-glucopyranosyl-[(1→4)-2,3-di-*O*-acetyl-6-bromo-6-deoxy-*α*-D-glucopyranosyl]$_4$-(1→4)-2,3-di-*O*-acetyl-6-bromo-6-deoxy-*α*-D-glucopyranosyl bromide (395)



To a solution of **385** (1.11 g, 0.568 mmol) in DCE (9.5 mL) at r.t. was added HBr (9.35 mL, 33% in AcOH, 56.8 mmol, 100.0 equiv). The mixture was stirred for 30 min and then poured into ice-cold water (40 mL). CH_2Cl_2 (35 mL) was added and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 x 25 mL) and brine, dried with Na_2SO_4 and concentrated under reduced pressure. The crude material was used without any further purification.

TLC: R_f = 0.50 (Hex / EtOAc 4:6); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.54 (d, *J* = 4.0 Hz, 1H), 5.64 (t, *J* = 9.4 Hz, 1H), 5.50 – 5.35 (m, 9H), 5.08 (t, *J* = 9.7 Hz, 1H), 4.85 (dd, *J* = 10.6, 3.9 Hz, 1H), 4.79 – 4.69 (m, 3H), 4.68 (dd, *J* = 9.9, 4.0 Hz, 1H), 4.37 – 3.70 (m, 23H), 3.66 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.44 (dd, *J* = 11.5, 4.0 Hz, 1H), 2.08 – 1.97 (m, 39H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.8, 170.7, 170.6, 170.6, 170.6, 170.2, 170.1, 170.0, 169.9, 169.9, 169.9, 169.8, 169.6, 169.4, 95.7, 95.6, 95.6, 95.4, 86.1, 73.7, 73.7, 73.6, 72.7, 72.3, 72.1, 71.6, 71.6, 71.5, 71.4, 71.3, 70.6, 70.6, 70.5, 70.4, 70.4, 70.2, 69.3, 69.2, 69.1, 69.1, 69.0, 68.9, 68.8, 68.8, 34.7, 34.6, 34.3, 33.1, 31.9, 21.1, 21.1, 21.0, 21.0, 20.8, 20.8, 20.7, 20.7, 20.7, 20.7 (due to the large number of overlapping signals, not every carbon atom could be detected); **IR** (neat): 2958, 1753, 1421, 1369, 1238, 1036, 756 cm^{-1}; **HRMS** (ESI) *m/z* calculated for $C_{62}H_{85}Br_7NO_{37}$ $[M+NH_4]^+$ 1987.9079, found 1987.9043; $[\alpha]^{20}_D$ = 148.5 (*c* 2.0, $CHCl_3$).

2-(2-(2-((4-Ethynylbenzyl)oxy)ethoxy)ethoxy)ethanol (396)



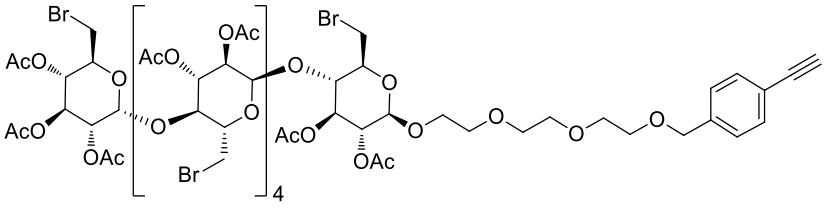
407 **396**

To a solution of (4-ethynylphenyl)methanol (2.5 g, 18.92 mmol) in CH_2Cl_2 (95 mL) at 0 °C was added MsCl (2.95 mL, 37.8 mmol, 2.0 equiv) followed by Et_3N (7.91 mL, 56.7 mmol, 3.0 equiv). The mixture was let stirred at 0 °C for 1 h and saturated aqueous NH_4Cl solution was added. The layers were separated and extraction was made with CH_2Cl_2 (3x), the combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The crude mesylate was used in the next without further purification.

To a suspension of triethyleneglycol (28.4 g, 189 mmol, 10.0 equiv) in THF (85 mL) at 0 °C was slowly added NaH (1.06 g, 26.50 mmol, 1.4 equiv). After stirring for 20 min at r.t., a solution of the mesylate intermediate in THF (10 mL) was added at 0 °C. After stirring for 16 h, saturated aqueous NH4Cl solution was added. EtOAc was added and the layers were separated. Extraction was made with EtOAc (3x). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography to afford **396** as a yellow oil (4.26 g, 16.12 mmol, 85%).

TLC: R_f = 0.31 (Hex/EtOAc 1:9); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.56 (s, 2H), 3.76 – 3.56 (m, 12H), 3.06 (s, 1H), 2.38 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 139.2, 132.3, 127.6, 121.4, 83.7, 77.3, 72.9, 72.6, 70.8, 70.7, 70.5, 69.7, 61.9; **IR** (neat): 3462, 3282, 2868, 1718, 1350, 1274, 1094, 821 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{15}H_{20}NaO_4$ $[M+Na]^+$ 287.1254, found 287.1258.

2-(2-(2-((4-Ethylnylbenzyl)oxy)ethoxy)ethoxy)ethyl 2,3,4-tri-O-acetyl-6-bromo-6-deoxy-α-D-glucopyranosyl-[(1→4)-2,3-di-O-acetyl-6-bromo-6-deoxy-α-D-glucopyranosyl]$_4$-(1→4)-2,3-di-O-acetyl-6-bromo-6-deoxy-1-β-D-glucopyranoside (397)

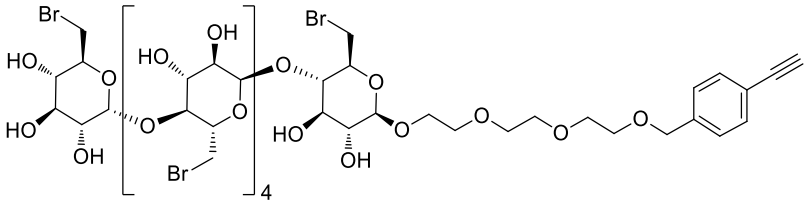


To a solution of linker **396** (100 mg, 0.378 mmol) crude **395** (1.12 g, 0.568 mmol, 1.5 equiv) in DCE (19 mL) at r.t. was added 4 Å molecular sieves (2.2 g) and the mixture was stirred for

1 h. Then $ZnBr_2$ (426 mg, 1.89 mmol, 5.0 equiv) was added and the reaction was vigorously stirred at r.t. for 20 h. The mixture was filtered and diluted with CH_2Cl_2. The organic layer was washed with 1 M HCl (2 x 50 mL), then brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification was performed by column chromatography (Hex/EtOAc 3:7 to 100% EtOAc) to afford **397** as a white solid (349 mg, 0.161 mmol, 43%).

TLC: R_f = 0.29 (Hex/EtOAc 3:7); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.49 – 7.43 (m, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 5.51 – 5.32 (m, 10H), 5.23 (t, *J* = 9.0 Hz, 1H), 5.07 (t, *J* = 9.7 Hz, 1H), 4.88 – 4.78 (m, 2H), 4.78 – 4.67 (m, 4H), 4.62 (d, *J* = 7.6 Hz, 1H), 4.55 (s, 2H), 4.16 – 3.98 (m, 6H), 4.00 – 3.71 (m, 15H), 3.71 – 3.56 (m, 13H), 3.43 (dd, *J* = 11.7, 4.2 Hz, 1H), 3.10 (s, 1H), 2.06 – 1.94 (m, 39H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.6, 170.5, 170.5, 170.2, 170.2, 170.0, 169.9, 169.8, 169.7, 169.4, 139.4, 132.3, 127.5, 121.3, 100.1, 95.6, 95.5, 95.5, 95.4, 83.6, 75.3, 74.0, 73.7, 73.7, 72.8, 72.2, 71.9, 71.6, 71.6, 71.5, 71.3, 70.8, 70.8, 70.7, 70.6, 70.4, 70.4, 70.3, 70.1, 69.8, 69.2, 69.1, 69.1, 69.0, 68.8, 68.7, 68.6, 34.7, 34.5, 34.4, 34.2, 33.4, 31.9, 21.0, 21.0, 21.0, 20.8, 20.7, 20.7, 20.7, 20.6, 20.6 (due to the large number of overlapping signals, not every carbon atom could be detected); **IR** (neat): 3029, 2950, 1752, 1421, 1369, 1237, 1033, 757 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{77}H_{104}Br_6NO_{41}$ $[M+NH_4]^+$ 2172.1179, found 2172.1127; **$[\alpha]^{21}_D$** = 110.1 (*c* 2.0, $CHCl_3$).

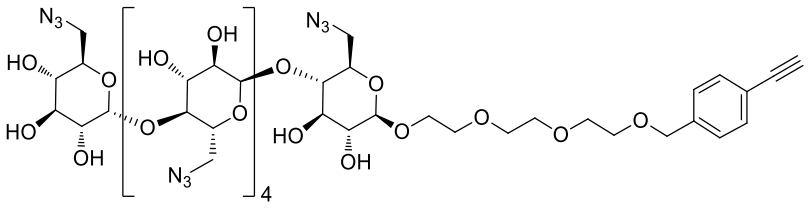
2-(2-(2-((4-Ethylnylbenzyl)oxy)ethoxy)ethoxy)ethyl 6-bromo-6-deoxy-*α*-D-glucopyranosyl-[(1→4)-6-bromo-6-deoxy-*α*-D-glucopyranosyl]$_4$-(1→4)-6-bromo-6-deoxy-1-*β*-D-glucopyranoside (398)



To a solution of **397** (360 mg, 0.167 mmol) in MeOH/THF (1:2, 8.3 mL) at 0 °C was dropwisely added MeONa (5.4 mL in MeOH, 460 µL, 2.499 mmol, 15.0 equiv). After stirring for 1 h at 0 °C, Amberlyst® 15 acidic cation exchange resin (1.5 g, prealably washed with MeOH/THF 1:1) was added and the mixture was stirred at 0 °C until pH = 6, then quickly filtered and the filter cake was washed with MeOH (50 mL) and MeOH/THF (1:1, 50 mL). The filtrate was concentrated under reduced pressure to ca. 10 mL, H_2O was added (precipitate formed) and the crude material was lyophilized. Purification was performed by column chromatography (MeCN/H_2O 99:1 to 95:5) to afford **398** as a white solid (143 mg, 0.089 mmol, 53%).

TLC: R_f = 0.43 (MeCN/ H2O 9:1); **^{1}H NMR** (400 MHz, CD_3OD): δ 7.49 – 7.45 (m, 2H), 7.39 – 7.34 (m, 2H), 5.25 – 5.15 (m, 5H), 4.58 (s, 2H), 4.39 (d, *J* = 7.8 Hz, 1H), 4.00 – 3.82 (m, 15H), 3.82 – 3.60 (m, 20H), 3.58 – 3.43 (m, 12H), 3.30 – 3.20 (m, 2H); **^{13}C NMR** (101 MHz, CD_3OD): δ 140.6, 133.1, 128.8, 122.9, 104.1, 103.1, 102.8, 102.8, 102.8, 102.7, 84.4, 84.2, 84.1, 84.1, 84.1, 84.0, 78.9, 77.2, 74.7, 74.6, 74.4, 74.4, 74.4, 74.1, 74.0, 73.7, 73.6, 72.4, 72.4, 71.5, 71.5, 71.5, 70.8, 69.9, 34.6, 34.4, 34.3 (due to the large number of overlapping signals, not every carbon atom could be detected); **IR** (neat): 3340, 2921, 1418, 1363, 1258, 1147, 1065, 1037 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{51}H_{78}Br_6NO_{28}$ $[M+NH_4]^+$ 1625.9805, found 1625.9771; **$[\alpha]^{22}_D$** = 73.2 (*c* 1.0, MeOH).

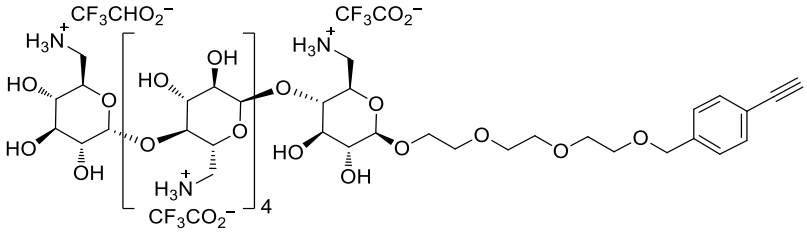
2-(2-(2-((4-Ethylnylbenzyl)oxy)ethoxy)ethoxy)ethyl 6-azido-6-deoxy-*α*-D-glucopyranosyl -[(1→4)-6-azido-6-deoxy-*α*-D-glucopyranosyl]$_4$-(1→4)-6-azido-6-deoxy-1-*β*-D-glucopyranoside (408)



To a solution of **398** (310 mg, 0.192 mmol) in DMF (9.6 mL) was added NaN_3 (150 mg, 2.304 mmol, 12.0 equiv), and the mixture was heated at 70 °C for 24 h. After cooling down to r.t., the mixture was concentrated under reduced pressure. H_2O was added to the residue and the crude material was lyophilized. Partial purification was performed by column chromatography (MeCN/H_2O 97:3 to 90:10) to afford **408** along with additional salts as a white solid (282 mg, theoretical mass: 266 mg).

TLC: R_f = 0.43 (MeCN/ H_2O 9:1); **^{1}H NMR** (300 MHz, CD_3OD): δ 7.47 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 5.23 – 5.13 (m, 5H), 4.71 – 4.55 (m, 2H), 4.48 (d, *J* = 7.7 Hz, 1H), 4.09 – 3.96 (m, 1H), 3.95 – 3.80 (m, 8H), 3.80 – 3.41 (m, 38H), 3.31 – 3.21 (m, 2H); **^{13}C NMR** (101 MHz, CD_3OD): δ 140.1, 133.1, 129.0, 123.0, 103.1, 102.8, 102.6, 102.5, 102.5, 82.5, 82.4, 82.4, 82.3, 77.1, 75.3, 74.5, 74.5, 74.4, 74.4, 73.9, 73.7, 73.5, 73.4, 72.2, 72.1, 72.0, 70.9, 70.8, 70.8, 70.6, 70.0, 69.2, 53.1, 52.8, 52.4 (due to the large number of overlapping signals, not every carbon atom could be detected); **IR** (neat): 3315, 2921, 2101, 1439, 1350, 1285, 1150, 1074, 1047 cm^{-1}; **HRMS** (ESI): *m/z* calculated for $C_{51}H_{78}N_{19}O_{28}$ $[M+NH_4]^+$ 1404.5258, found 1404.5257; **$[\alpha]^{22}_D$** = 50.3 (*c* 1.0, MeOH).

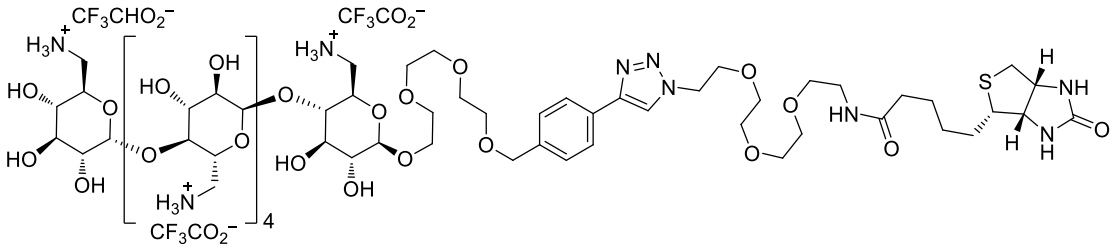
2-(2-(2-((4-Ethylnylbenzyl)oxy)ethoxy)ethoxy)ethyl 6-ammonio-6-deoxy-*α*-D-glucopyranosyl-[(1→4)-6-ammonio-6-deoxy-*α*-D-glucopyranosyl]$_4$-(1→4)-6-ammonio-6-deoxy-1-*β*-D-glucopyranoside hexatrifluoroacetate salt (399)



To a solution of **408** (266 mg, 0.192 mmol) in DMF (8.7 mL) was added Ph_3P (453 mg, 1.726 mmol, 9.0 equiv) and then 880 μL H_2O. The mixture was stirred at r.t. for 2 h and then at 70 °C for 24 h. After cooling down to r.t., 1 M HCl was added until pH = 3, then H_2O was added. The aqueous layer was washed with EtOAc (3x) and then lyophilized. Purification was performed by flash preparative HPLC (see details below) to afford pure **399** as a white solid (42 mg, 0.022 mmol, 11%), and a large fraction of impure **399** eluting with the solvent front (260 mg).

^{1}H NMR (400 MHz, CD_3OD): δ 7.45 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 5.31 – 5.21 (m, 5H), 4.56 (s, 2H), 4.37 (d, *J* = 7.8 Hz, 1H), 4.19 – 4.01 (m, 5H), 3.97 – 3.85 (m, 5H), 3.79 – 3.62 (m, 14H), 3.61 – 3.55 (m, 5H), 3.55 – 3.42 (m, 13H), 3.26 – 3.06 (m, 7H); **^{13}C NMR** (101 MHz, CD_3OD): δ 162.9 (q, $^2J_{CF}$ = 36.1 Hz, TFA), 140.5, 133.0, 128.8, 123.0, 104.2, 102.0, 101.2, 101.2, 100.9, 100.7, 84.3, 82.8, 82.7, 82.6, 82.3, 78.7, 76.4, 74.6, 74.2, 73.7, 73.5, 73.5, 73.4, 73.4, 73.3, 73.2, 73.2, 73.1, 72.9, 71.5, 71.5, 71.4, 70.7, 70.5, 70.1, 68.9, 68.7, 68.7, 42.2, 42.1, 42.1 (due to the large number of overlapping signals, not every carbon atom could be detected); **^{19}F NMR** (282 MHz, CD_3OD): δ –75.2 (TFA); **IR** (neat): 3283, 3091, 2924, 1672, 1519, 1432, 1200, 1130, 1086, 1028, 838, 799, 722 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{51}H_{78}N_{19}O_{28}$ (free amine) $[M+H]^+$ 1231.5563, found 1231.5550; **$[\alpha]^{22}_D$** = 93.1 (*c* 1.0, MeOH); **HPLC**: *analytical*: H_2O (+0.1% TFA):MeCN (+0.1% TFA) = 85:15 (*t* = 0.00 min) → 85:15 (*t* = 1.00 min) → 75:25 (*t* = 9.00 min) → 10:90 (*t* = 12.00 min) → 85:15 (*t* = 12.10 min), t_R = 8.01 min, λ = 240 nm; *preparative*: H_2O (+0.1% TFA):MeCN (+0.1% TFA) = 90:10 (*t* = 0.00 min) → 90:10 (*t* = 3.00 min) → 85:15 (*t* = 4.00 min) → 75:25 (*t* = 12.00 min) → 10:90 (*t* = 15.00 min) → 90:10 (*t* = 15.10 min), t_R = 8.88 min, λ = 240 nm.

Polycationic hexasaccharide-biotin conjugate (403)



To a solution of **399** (80 mg, 0.042 mmol) and Biotin-PEG3-azide (18.6 mg, 0.042 mmol, 1.0 equiv) in *t*-BuOH/H_2O (1:1, 950 μL) was added $CuSO_4 \cdot 5H_2O$ (3.1 mg, 0.013 mmol, 0.3 equiv) and sodium L-ascorbate (5.0 mg, 0.025 mmol, 0.6 equiv). The mixture was stirred at r.t. for 72 h and then lyophilized. Purification was performed by flash preparative HPLC (see details below) to afford pure **403** as a white solid (11 mg, 4.66 μmol, 11%), and a large fraction of impure **403** eluting with the solvent front (60 mg).

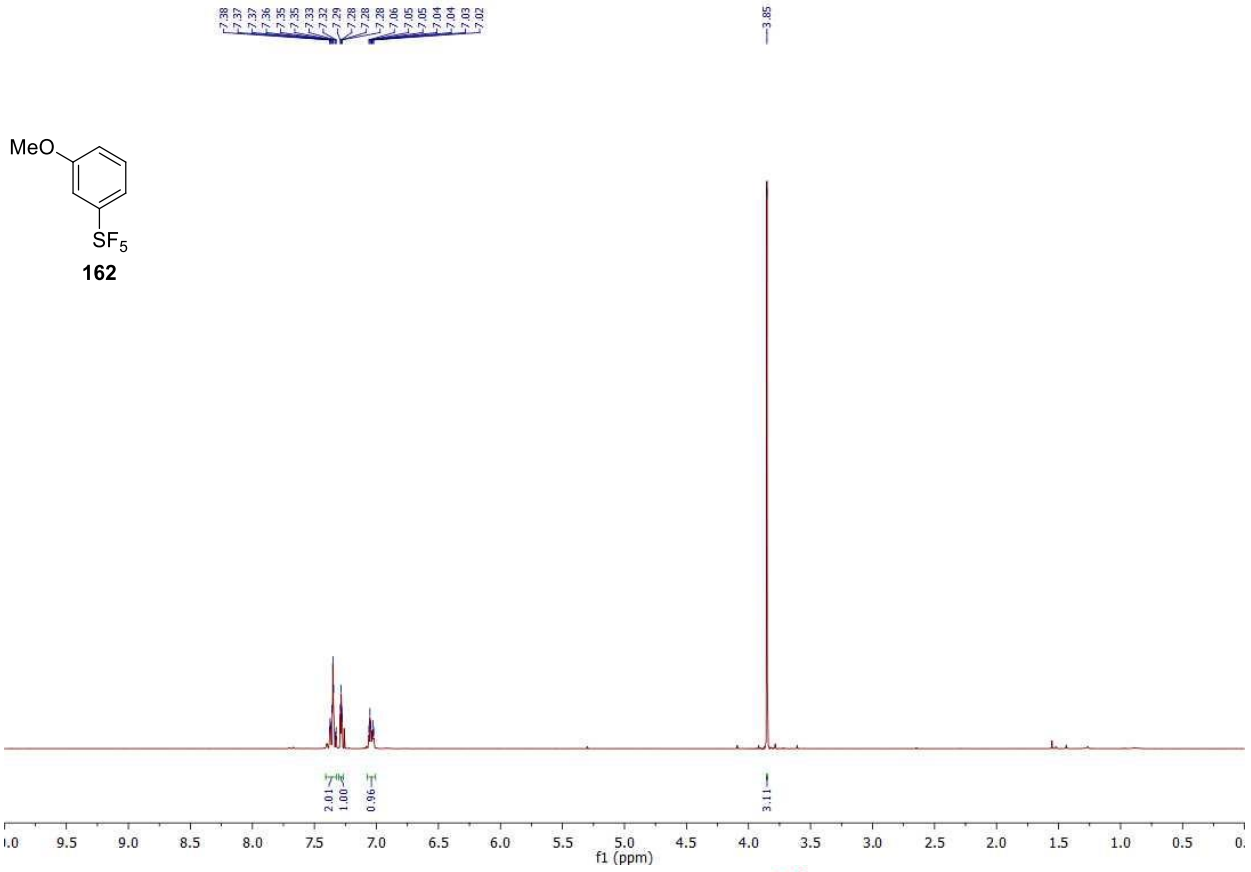
^{1}H NMR (600 MHz, CD_3OD): δ 8.39 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 5.31 – 5.22 (m, 5H), 4.67 – 4.64 (m, 2H), 4.60 (s, 2H), 4.52 – 4.45 (m, 2H), 4.37 (d, *J* = 7.8 Hz, 1H), 4.29 (ddd, *J* = 16.1, 7.8, 4.4 Hz, 2H), 4.21 – 4.09 (m, 3H), 4.08 – 4.02 (m, 1H), 3.98 – 3.94 (m, 2H), 3.95 – 3.87 (m), 3.80 – 3.60 (m), 3.60 – 3.43 (m), 3.40 – 3.34 (m), 3.26 – 3.06 (m), 2.92 (ddd, *J* = 14.0, 12.8, 5.0 Hz, 2H), 2.75 – 2.65 (m), 2.25 – 2.20 (m), 2.17 (t, *J* = 7.4 Hz, 2H), 1.80 – 1.51 (m), 1.49 – 1.35 (m); **^{13}C NMR** (151 MHz, CD_3OD): δ 176.1, 166.1, 162.6 (apparent m, TFA), 148.5, 139.9, 131.2, 129.6, 126.8, 123.3, 104.4, 101.9, 101.2, 100.9, 100.3, 82.8, 82.7, 82.1, 76.4, 74.7, 74.3, 73.8, 73.7, 73.5, 73.5, 73.5, 73.4, 73.3, 73.2, 73.1, 73.0, 71.7, 71.6, 71.6, 71.6, 71.5, 71.5, 71.4, 71.3, 71.3, 71.2, 71.1, 70.7, 70.6, 70.5, 70.5, 70.3, 70.2, 68.9, 68.8, 68.7, 63.4, 61.6, 57.0, 51.8, 51.6, 42.3, 42.2, 42.1, 41.1, 41.0, 40.4, 40.3, 36.7, 36.7, 35.4, 29.8, 29.5, 29.5, 26.9 (due to the large number of overlapping signals, not every carbon atom could be detected); **^{19}F NMR** (282 MHz, CD_3OD): δ –75.2 (TFA); **IR** (neat): 3283, 2924, 2111, 1672, 1533, 1457, 1431, 1201, 1128, 1086, 1062, 1028, 836, 799, 722 cm^{-1}; **HRMS** (MALDI): *m/z* calculated for $C_{69}H_{119}N_{12}O_{33}S$ (free amine) $[M+H]^+$ 1675.7718, found 1675.7709; **HPLC**: *analytical*: H_2O (+0.1% TFA):MeCN (+0.1% TFA) = 80:20 (*t* = 0.00 min) → 80:20 (*t* = 9.00 min) → 10:90 (*t* = 11.00 min) → 80:20 (*t* = 13.00 min), t_R = 3.53 min, λ = 249 nm; *preparative*: H_2O (+ 0.1% TFA):MeCN (+ 0.1% TFA) = 95:5 (*t* = 0.00 min) → 95:5 (*t* = 3.00 min) → 80:20 (*t* = 4.00 min) → 80:20 (*t* = 12.00 min) → 10:90 (*t* = 15.00 min) → 95:5 (*t* = 15.10 min) t_R = 7.01 min, λ = 249 nm.

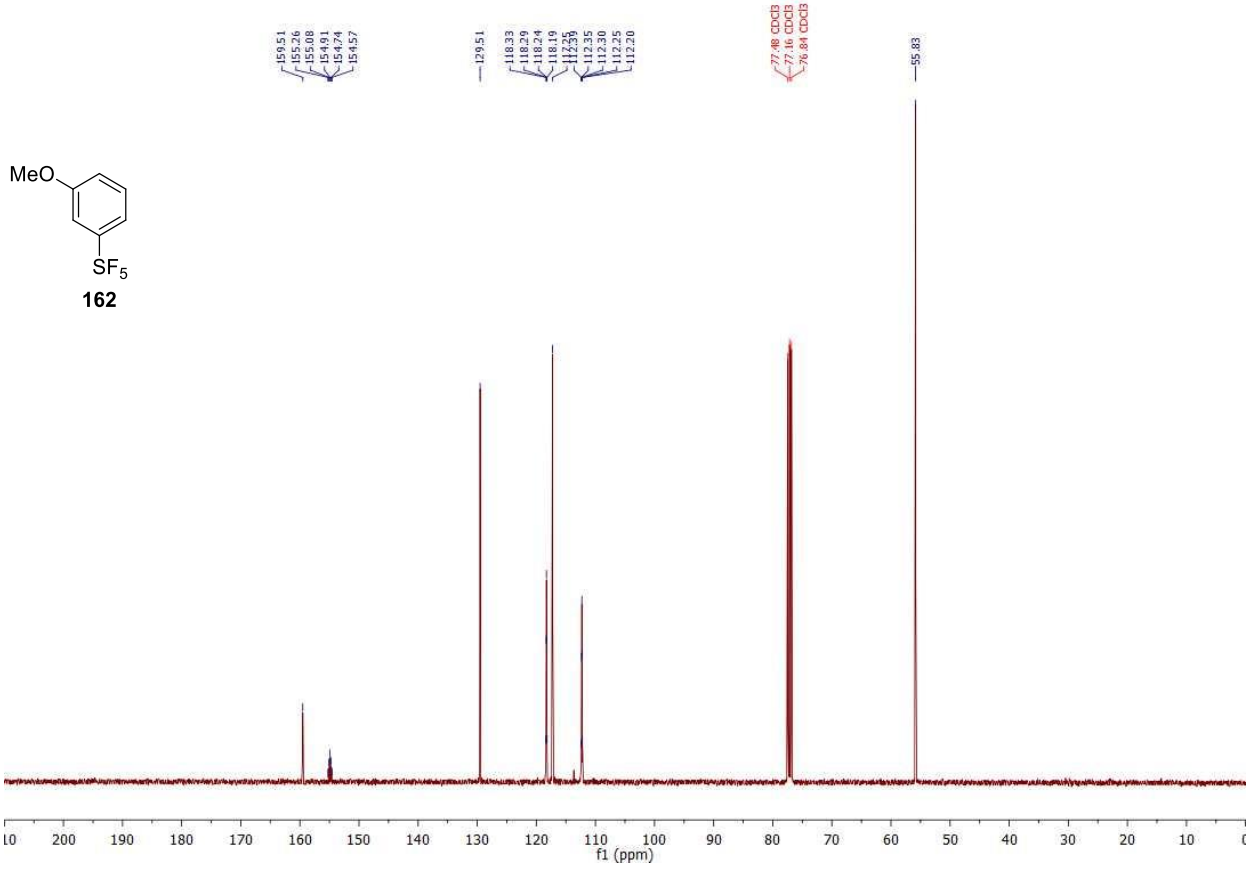
4

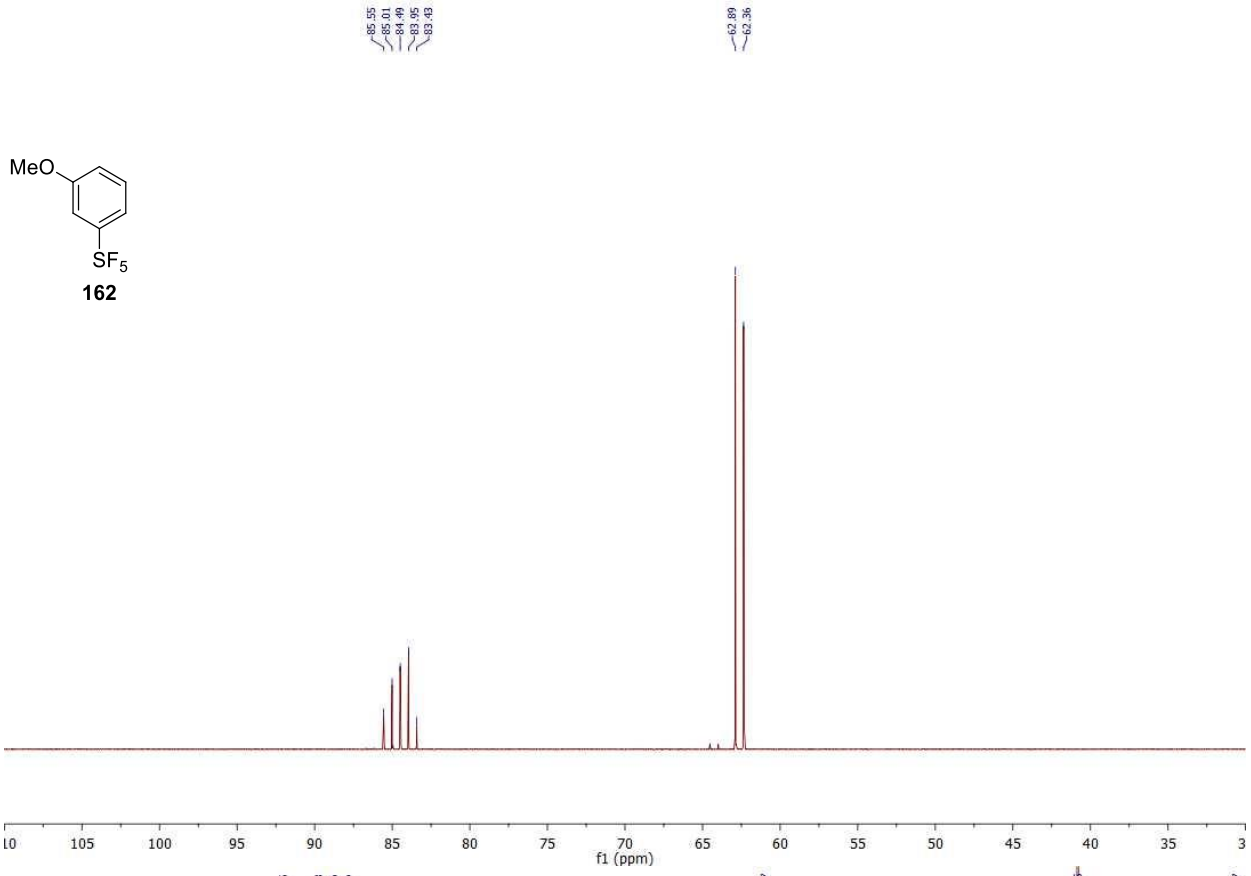
Appendix

4. Appendix

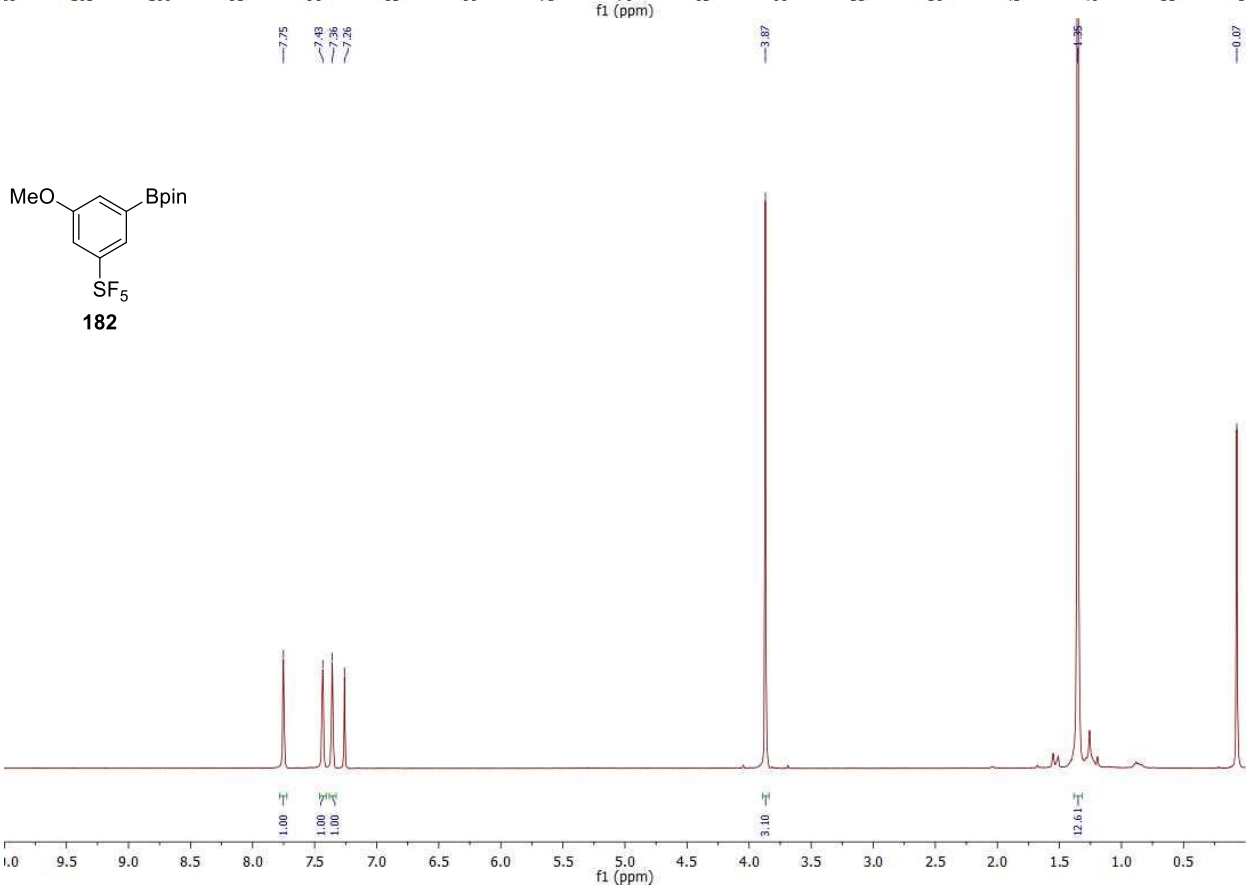
4.1. NMR Spectroscopic Data



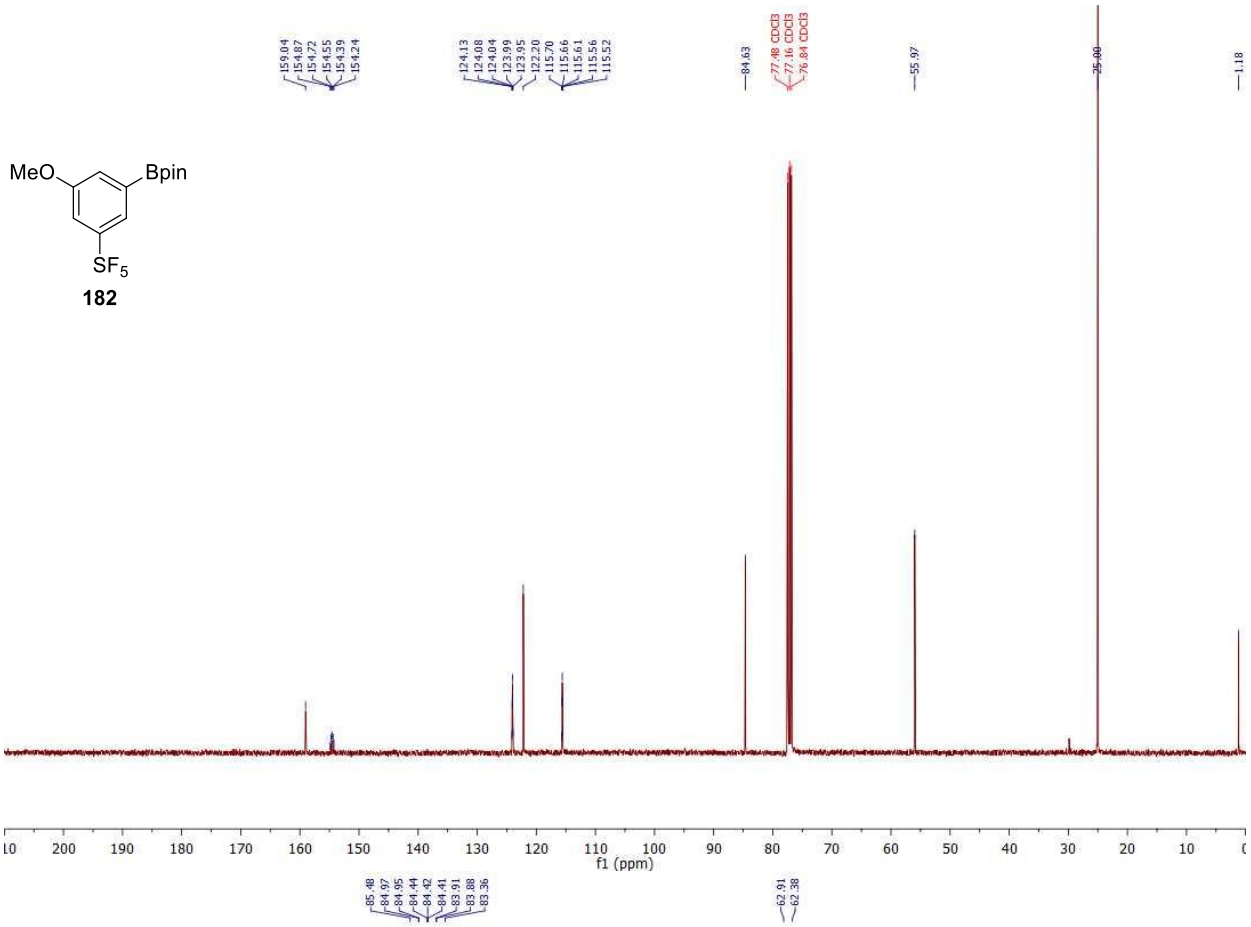


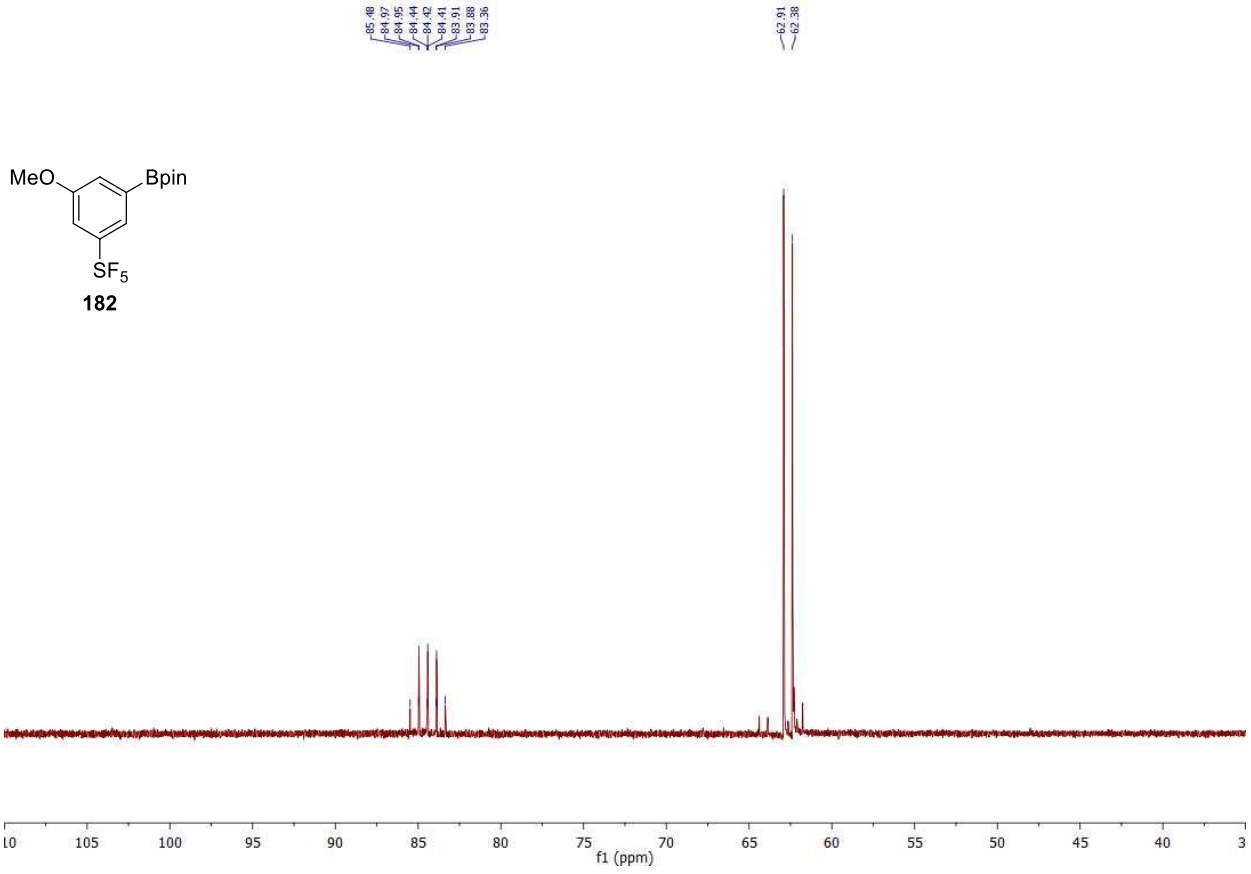

85.55
85.01
84.49
83.95
83.43
62.89
62.36
MeO
SF5
f1 (ppm)

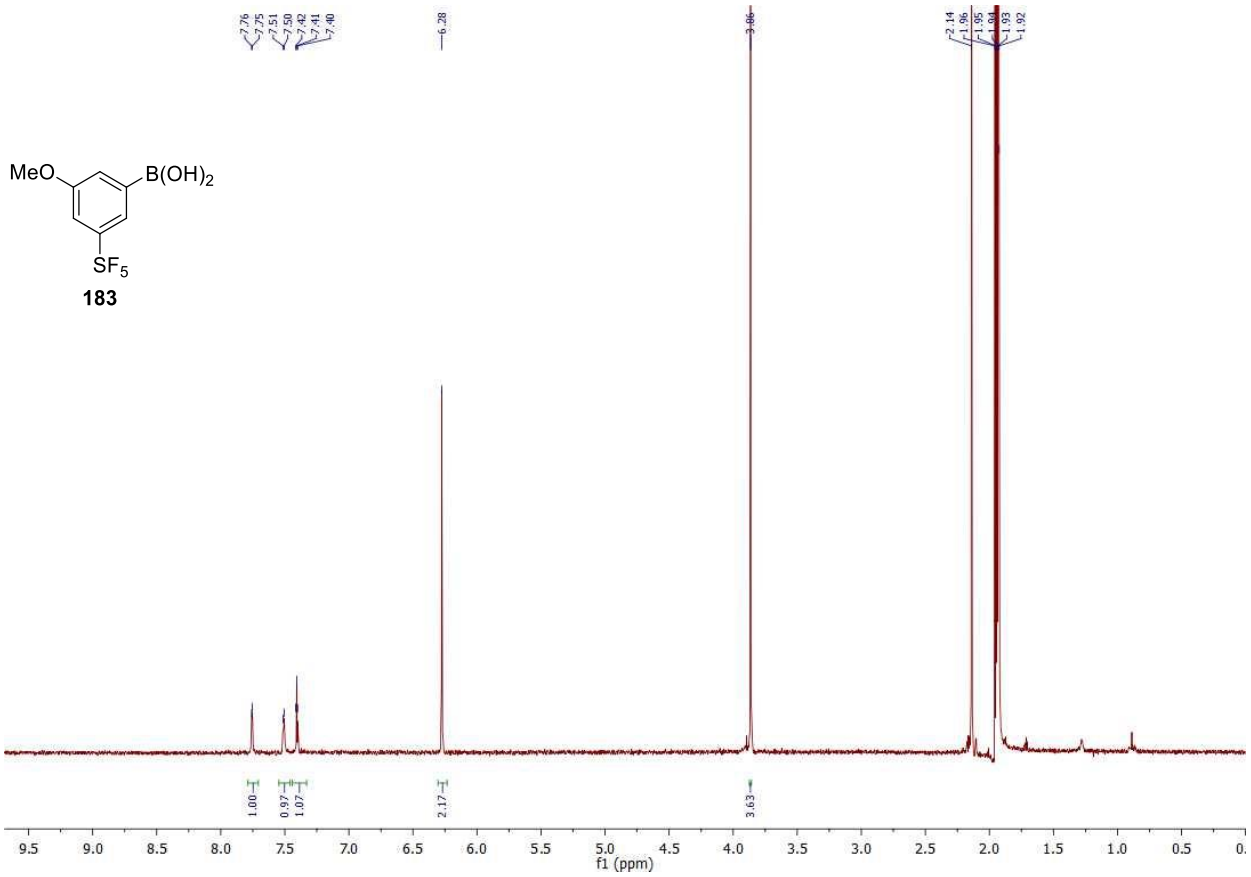
162

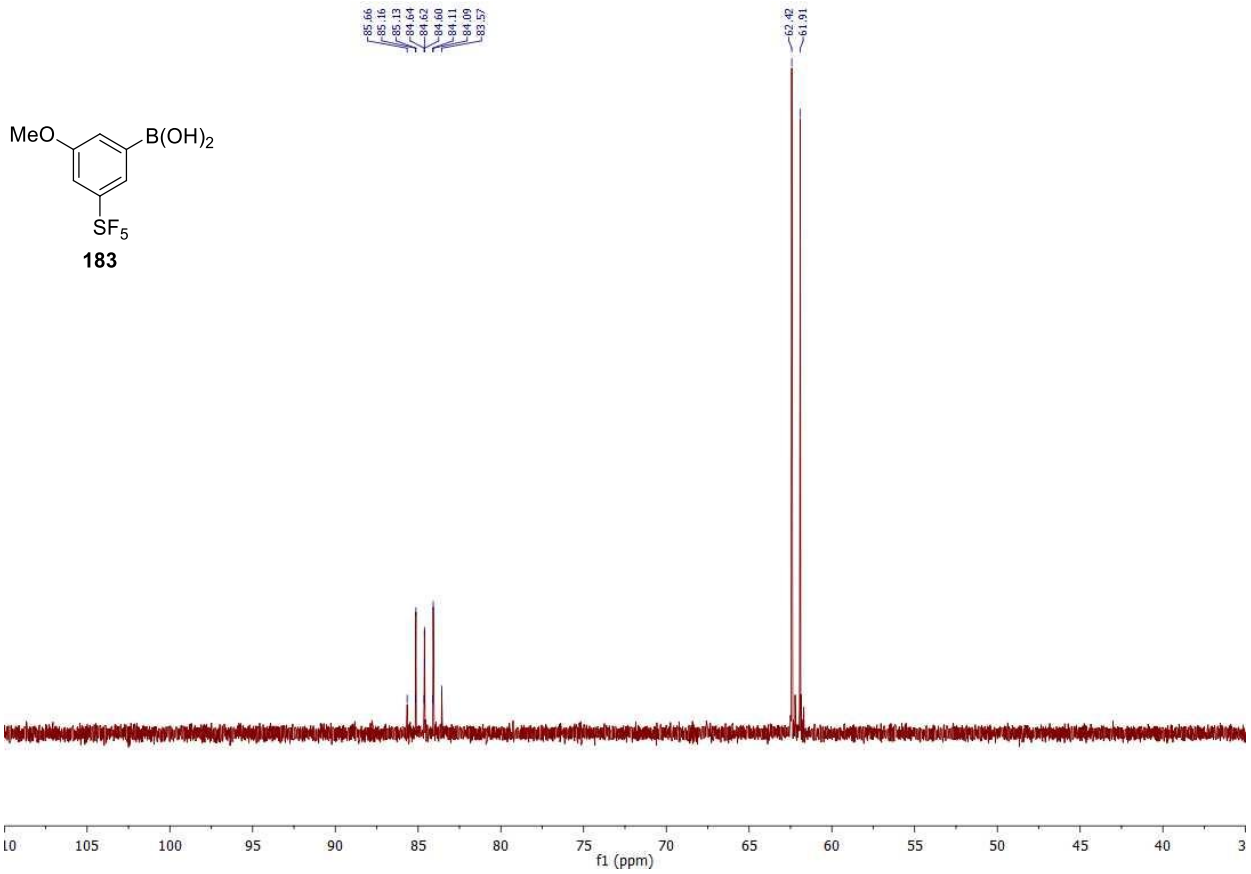

7.75
7.43
7.36
7.26
3.87
1.35
0.07
MeO
Bpin
SF5
1.00
1.00
1.00
3.10
12.61
f1 (ppm)

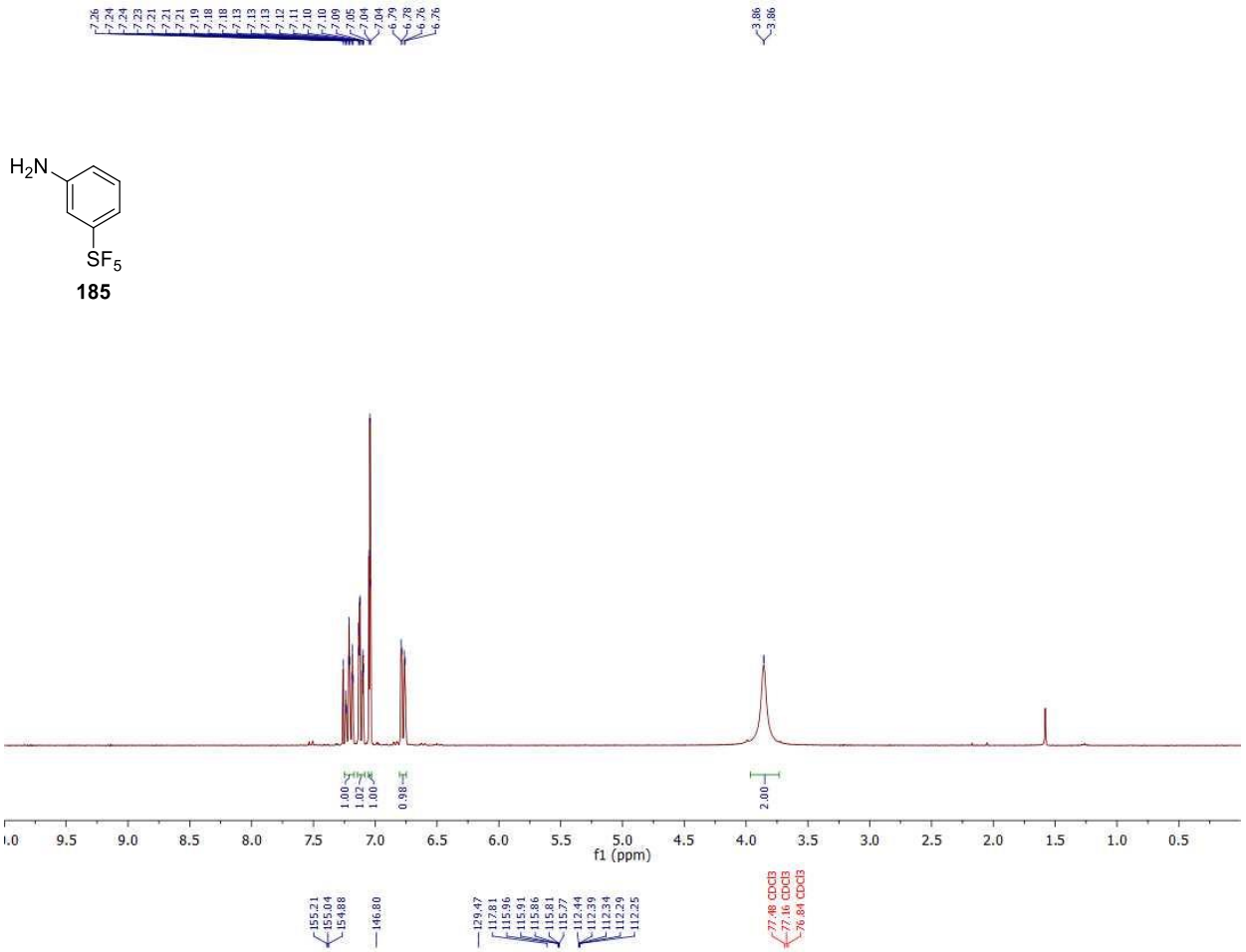
182

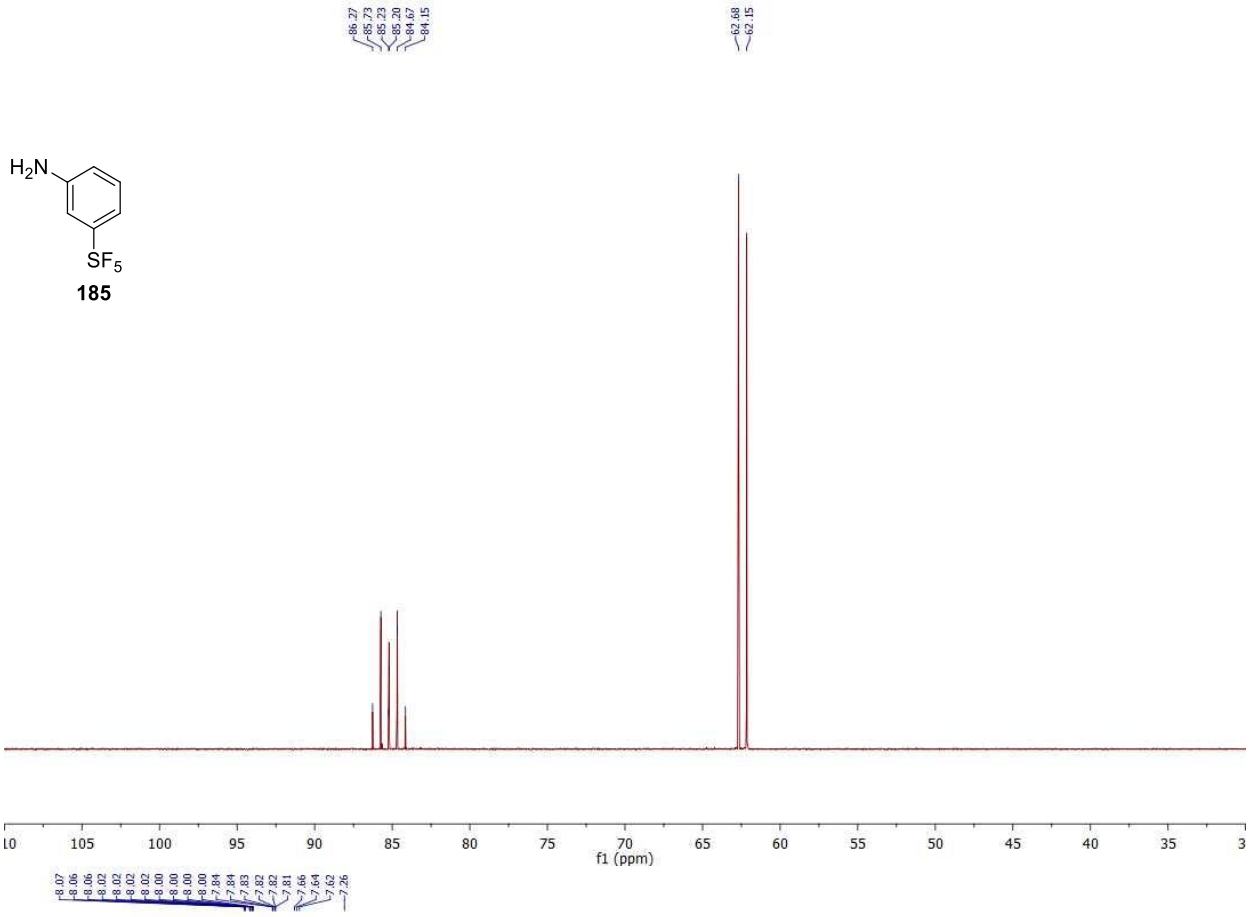

159.04
154.87
154.72
154.55
154.39
154.24
124.13
124.08
124.04
123.99
123.95
122.20
115.70
115.66
115.61
115.56
115.52
84.63
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.97
25.00
1.18
MeO
Bpin
SF5
182
f1 (ppm)


85.48
84.97
84.95
84.44
84.42
84.41
83.91
83.88
83.36
62.91
62.38
MeO
Bpin
SF5
182
f1 (ppm)

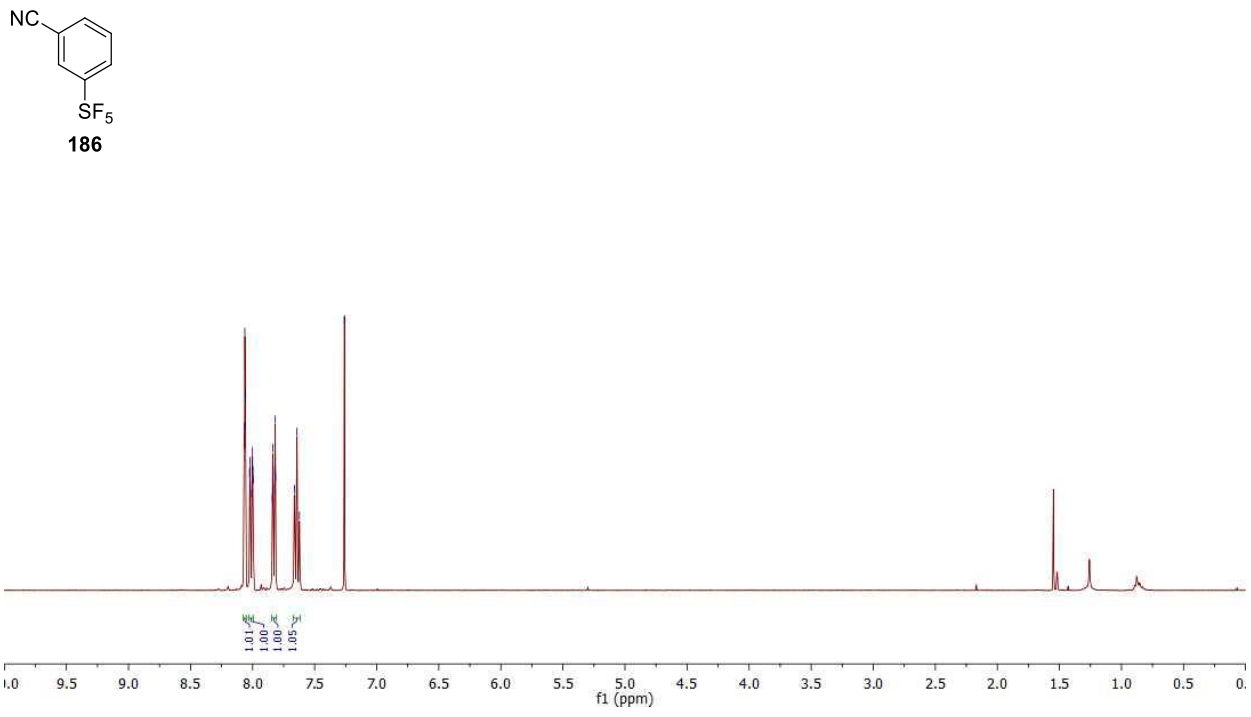

MeO
B(OH)2
SF5
183
7.76
7.75
7.51
7.50
7.42
7.41
7.40
6.28
3.86
2.14
1.96
1.95
1.94
1.93
1.92
1.00
0.97
1.07
2.17
3.63
f1 (ppm)


MeO
B(OH)2
SF5
183
85.66
85.16
85.13
84.64
84.62
84.60
84.11
84.09
83.57
62.42
61.91
f1 (ppm)

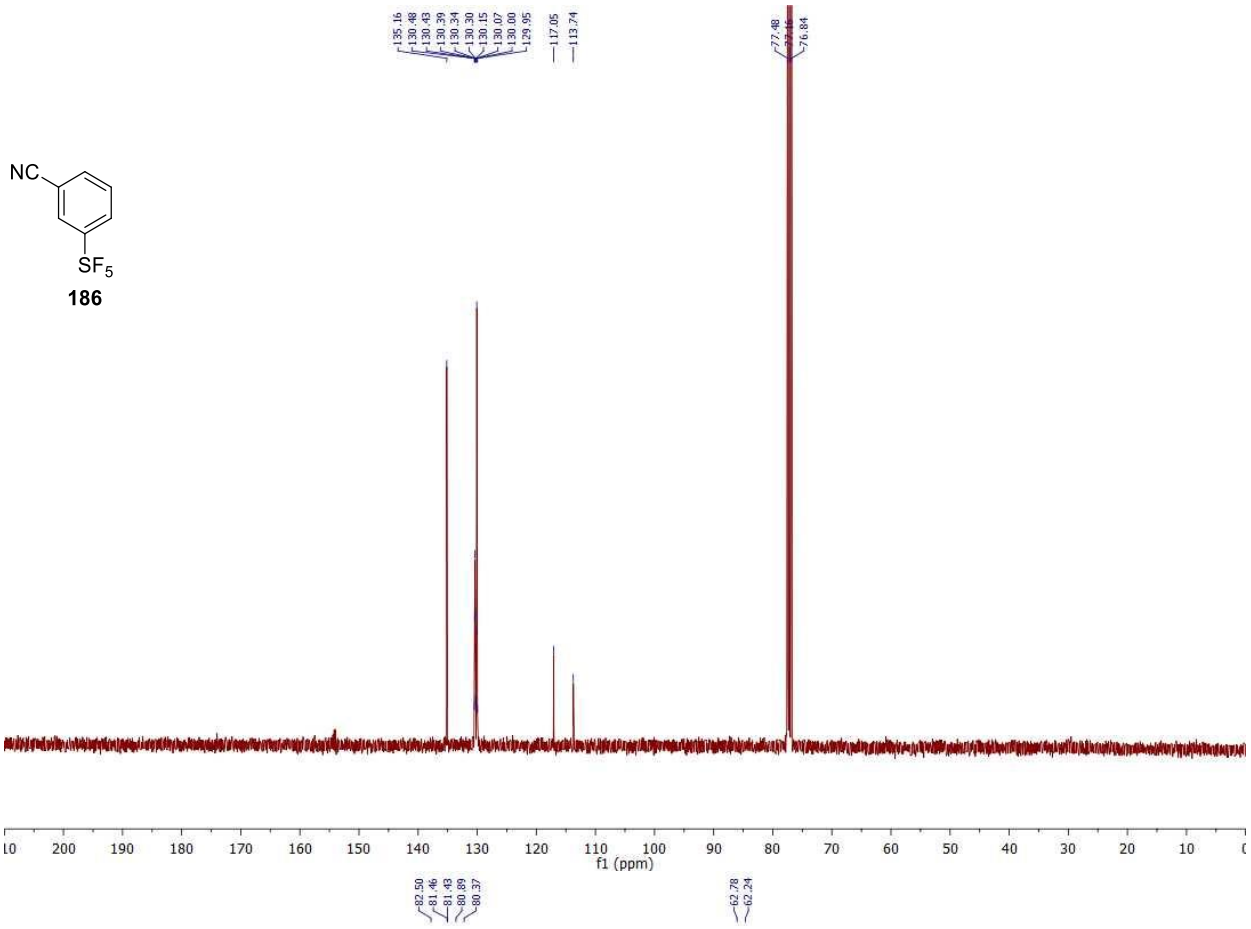

7.26
7.24
7.24
7.23
7.21
7.21
7.21
7.19
7.18
7.18
7.13
7.13
7.13
7.12
7.11
7.10
7.10
7.09
7.05
7.04
7.04
6.79
6.78
6.76
6.76
3.86
3.86
H2N
SF5
185
1.00
1.02
1.00
0.98
2.00
f1 (ppm)
155.21
155.04
154.88
146.80
129.47
117.81
115.96
115.91
115.86
115.81
115.77
112.44
112.39
112.34
112.29
112.25
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
H2N
SF5
185
f1 (ppm)

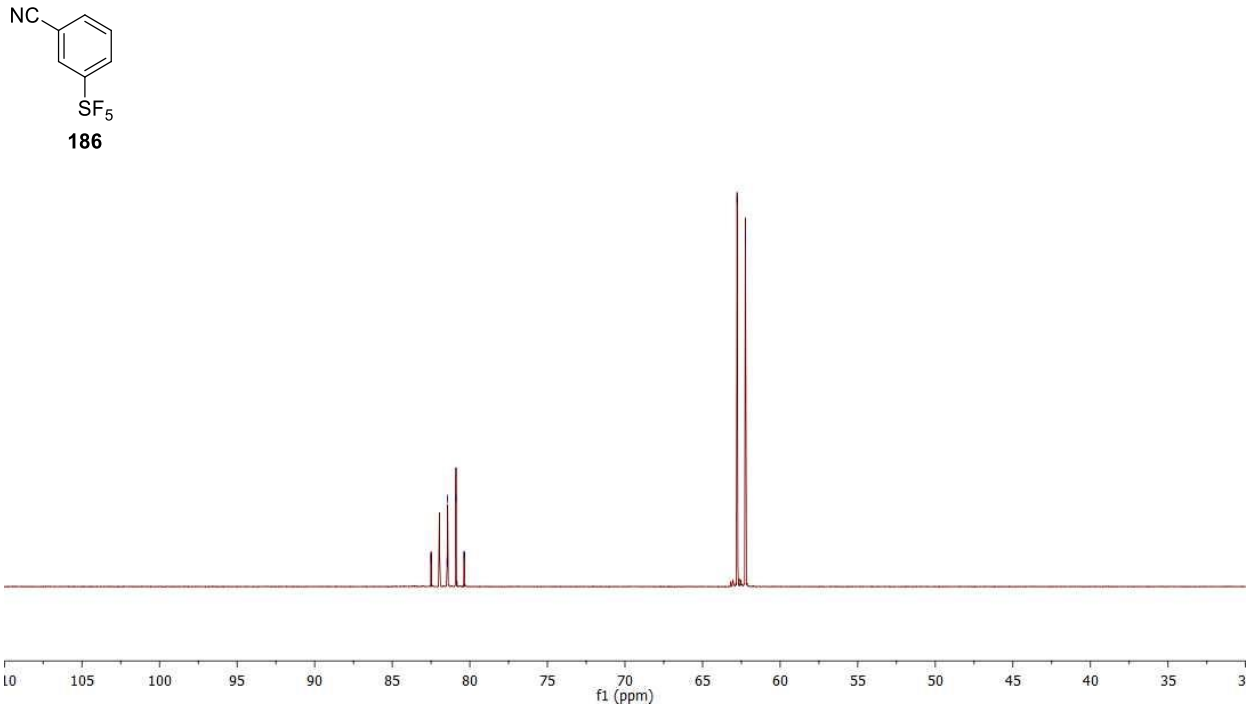

86.27
85.73
85.23
85.20
84.67
84.15
62.68
62.15
H_2N
SF_5
f1 (ppm)

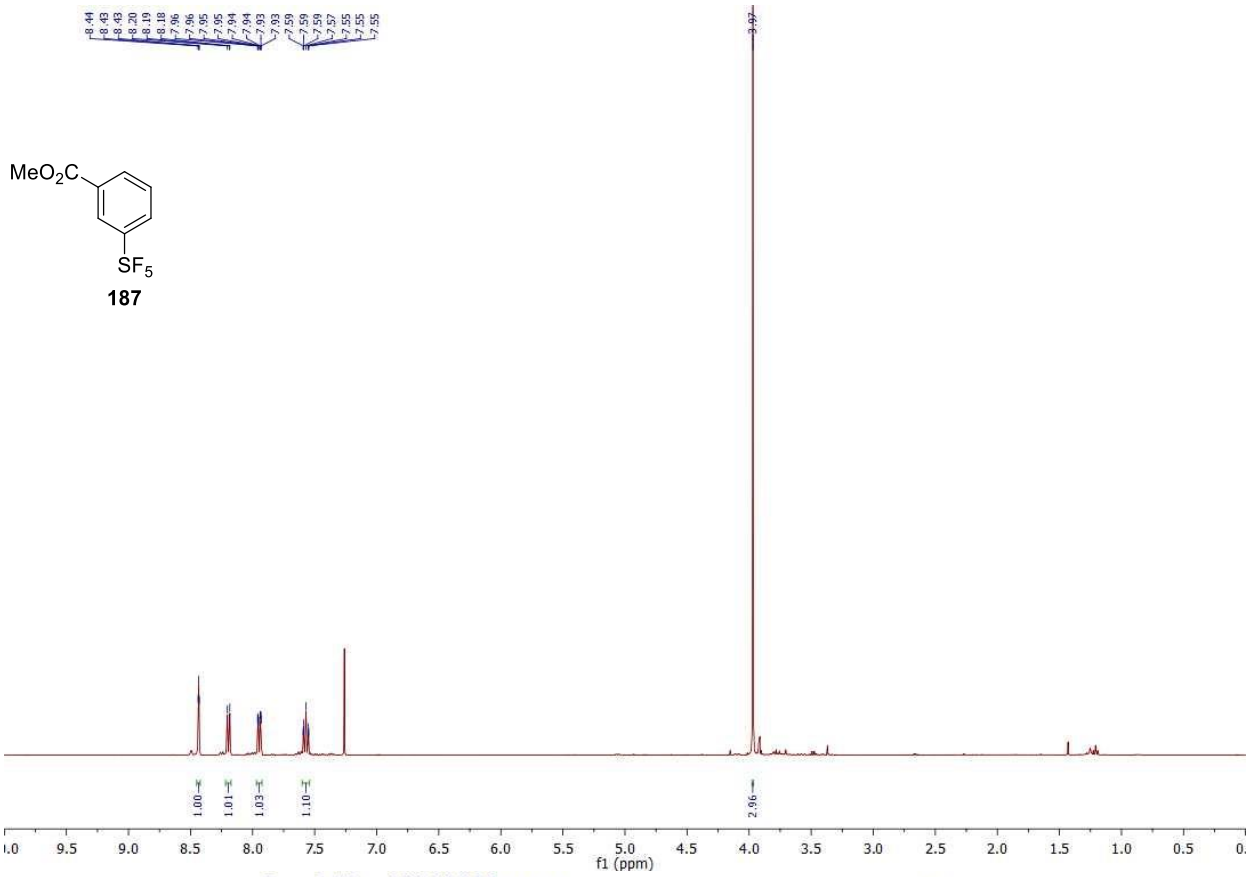
185

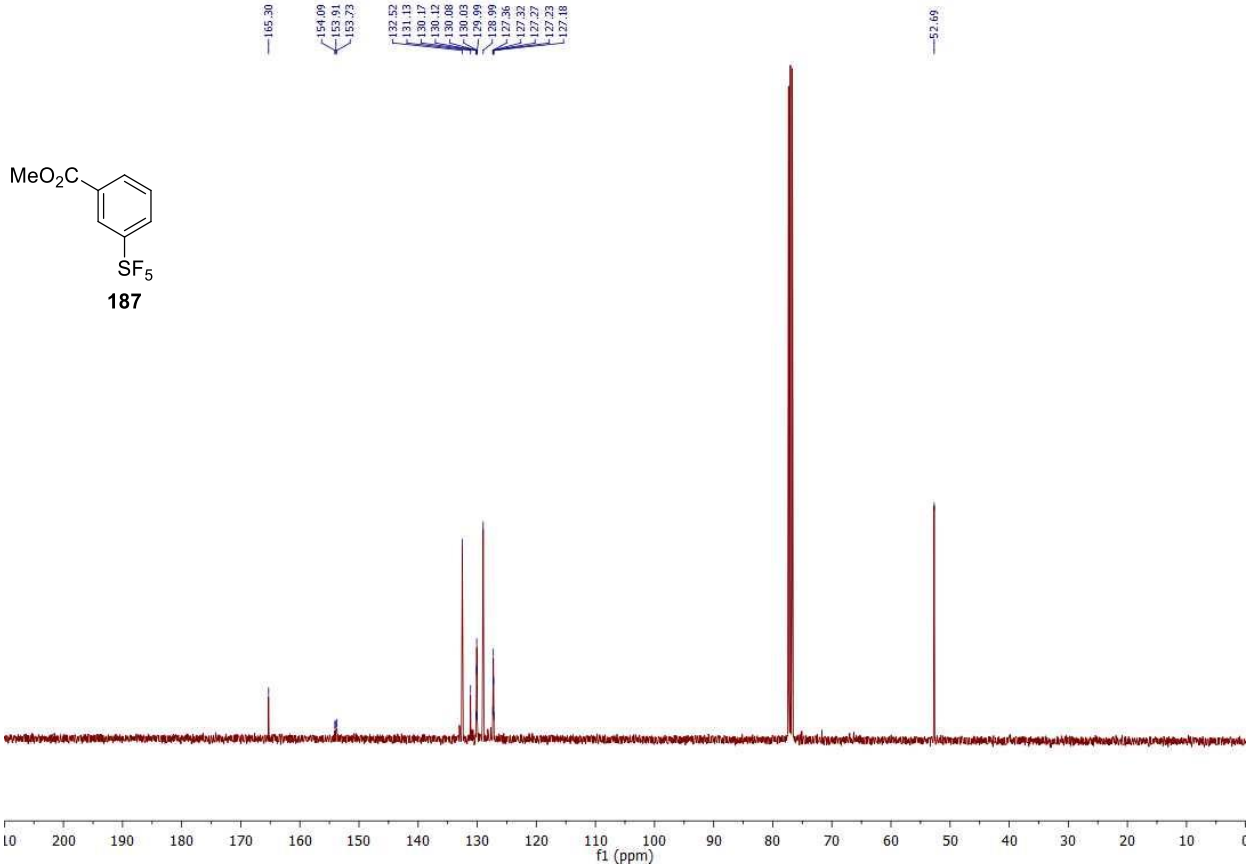

NC
SF_5
f1 (ppm)

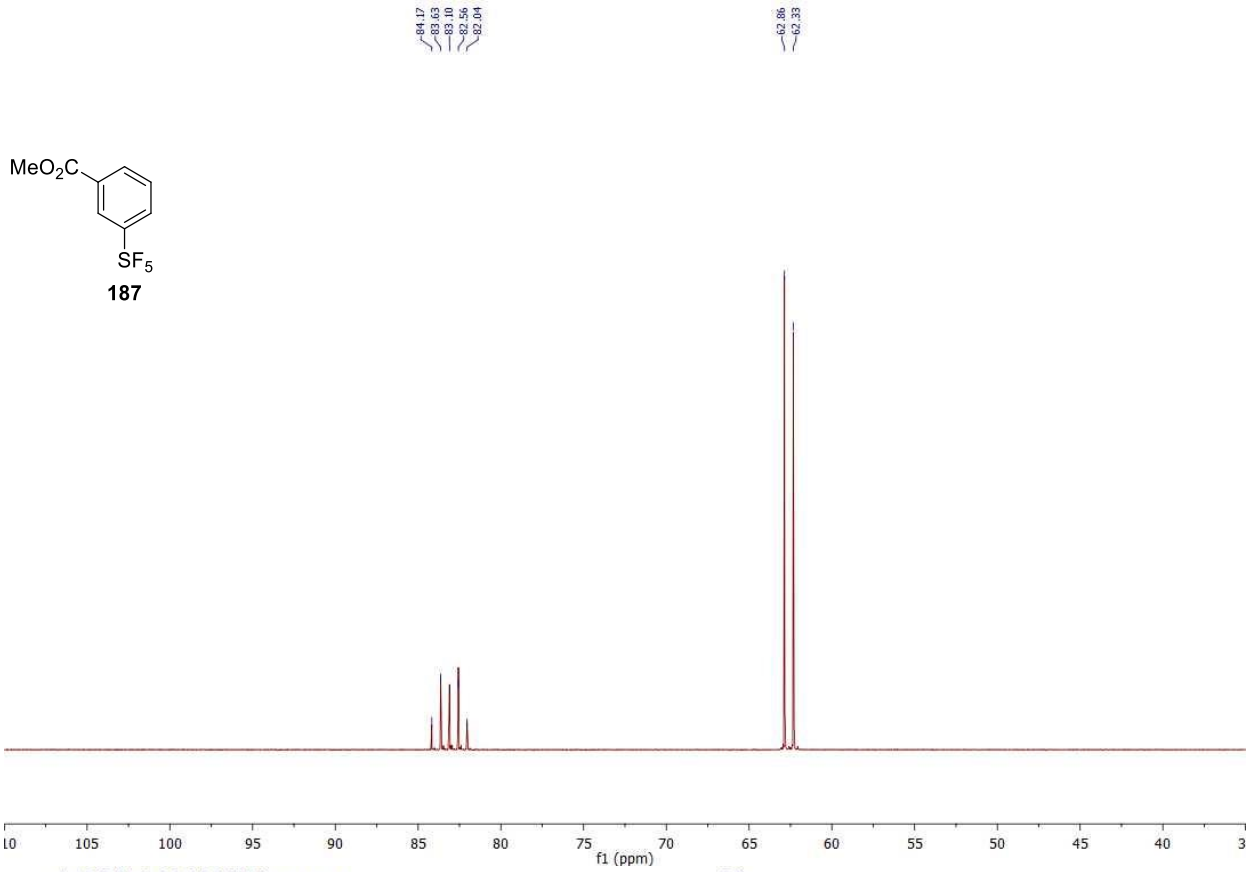
186


135.16
130.48
130.43
130.39
130.34
130.30
130.15
130.07
130.00
129.95
117.05
113.74
77.48
77.16
76.84
NC
SF5
186
f1 (ppm)
82.50
81.46
81.43
80.89
80.37
62.78
62.24

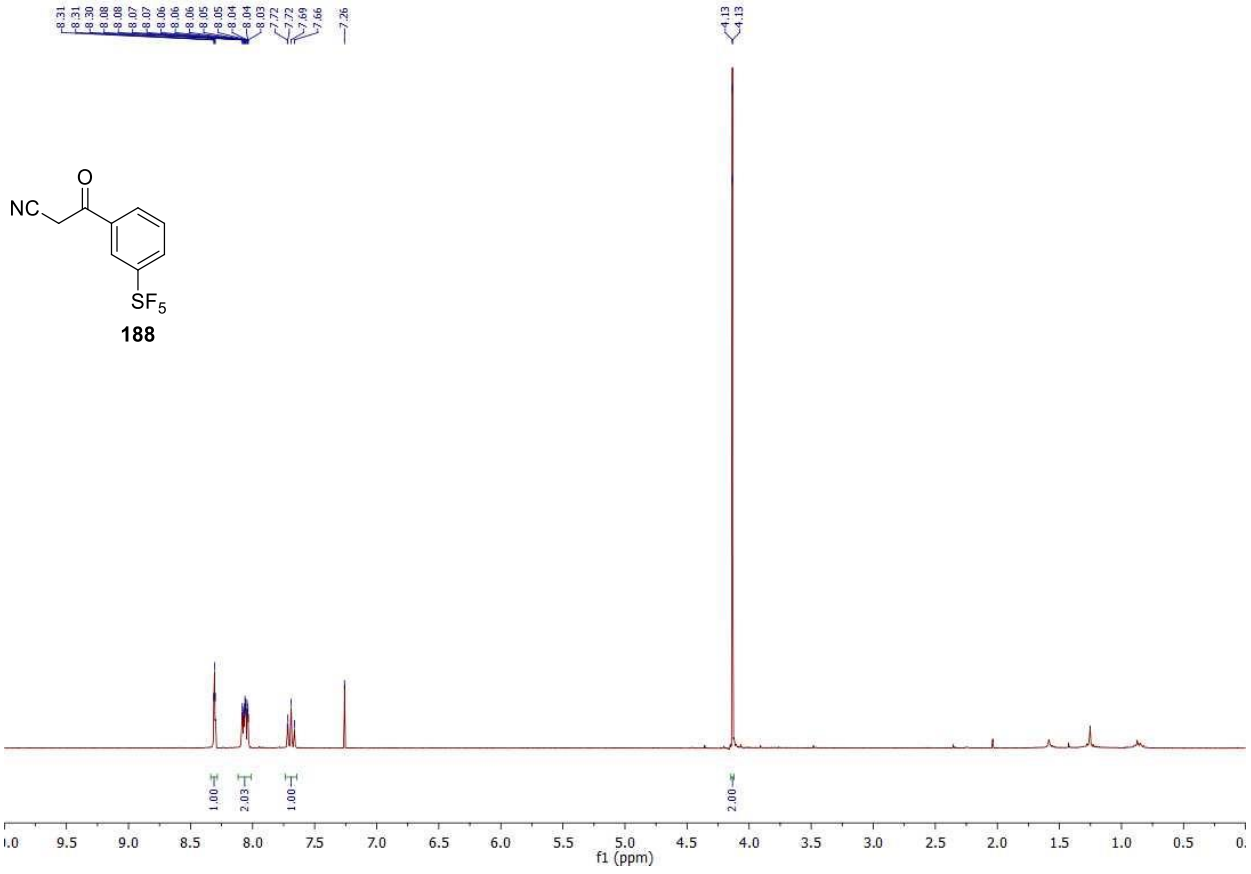

NC
SF5
186
f1 (ppm)


MeO2C
SF5
187
f1 (ppm)

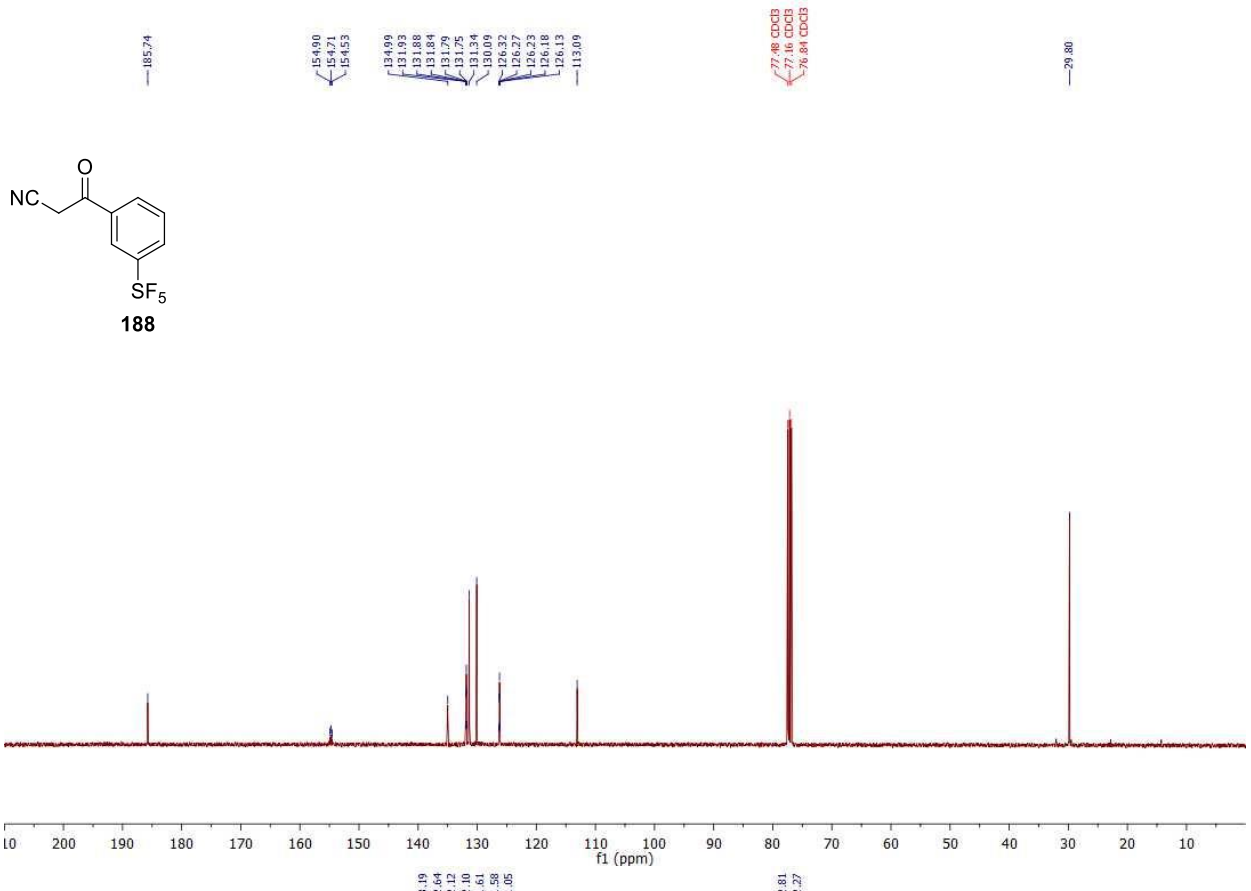

MeO2C
SF5
187
f1 (ppm)


84.17
83.63
83.10
82.56
82.04
62.86
62.33
f1 (ppm)

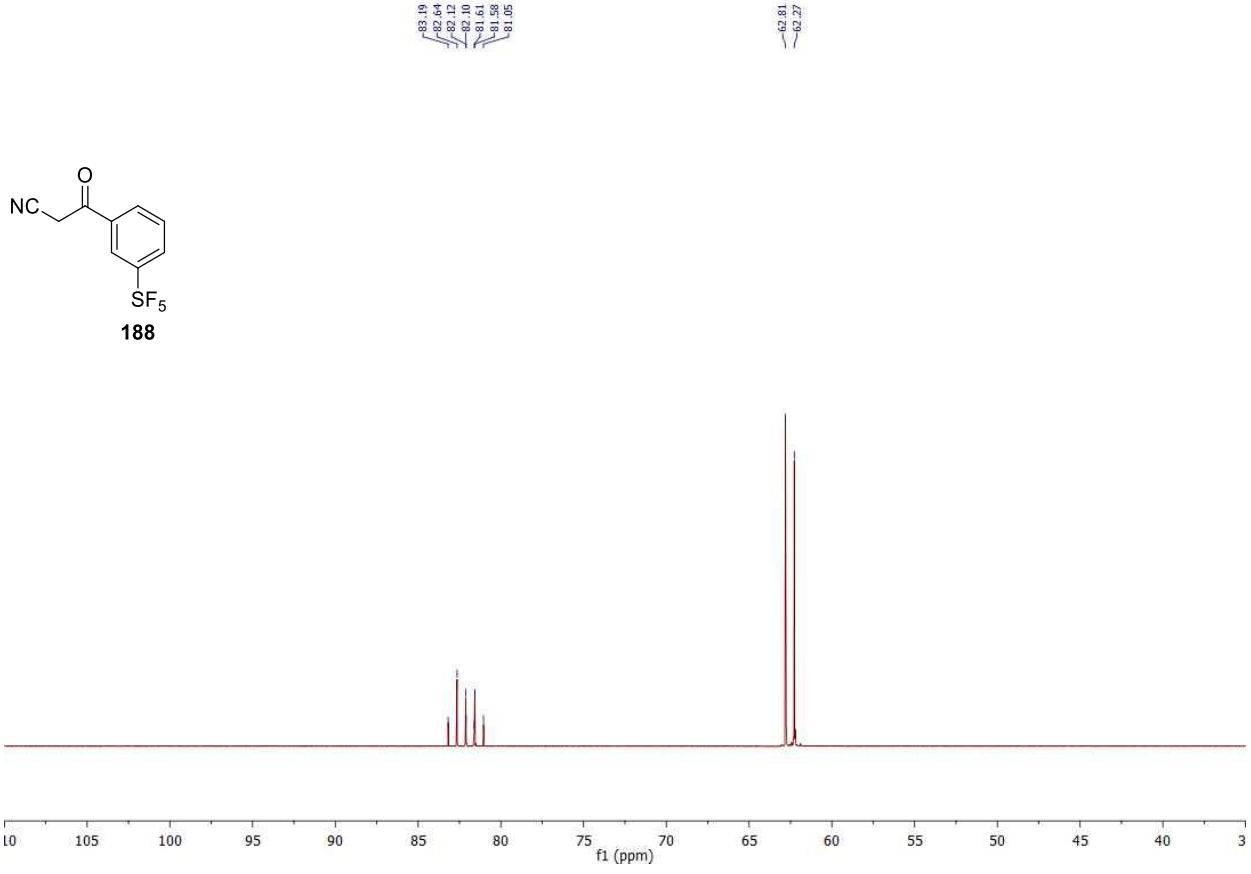
187


8.31
8.31
8.30
8.08
8.08
8.07
8.07
8.06
8.06
8.06
8.06
8.05
8.05
8.04
8.04
8.03
7.72
7.72
7.69
7.66
7.26
4.13
4.13
1.00
2.03
1.00
2.00
f1 (ppm)

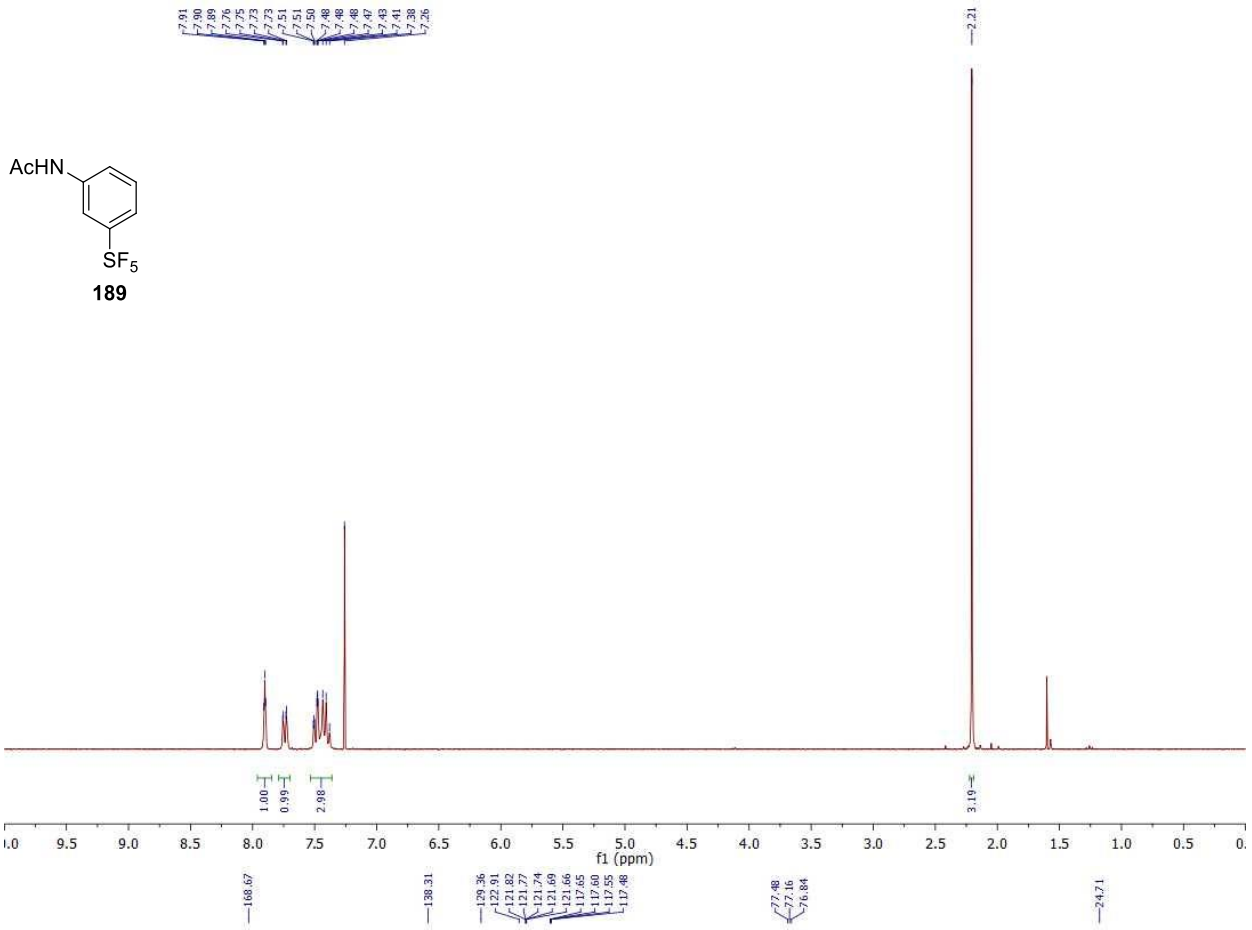
188

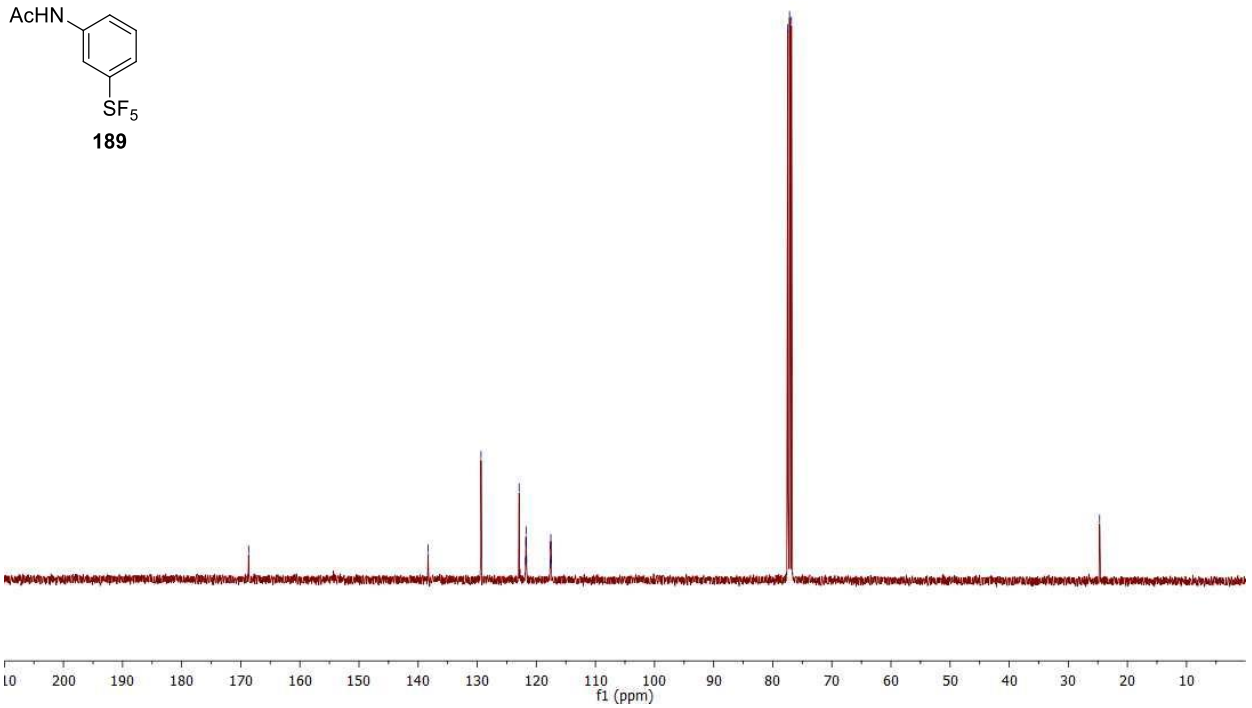

185.74
154.90
154.71
154.53
134.99
131.93
131.88
131.84
131.79
131.75
131.34
130.09
126.32
126.27
126.23
126.18
126.13
113.09
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
29.80
NC
O
SF5
f1 (ppm)

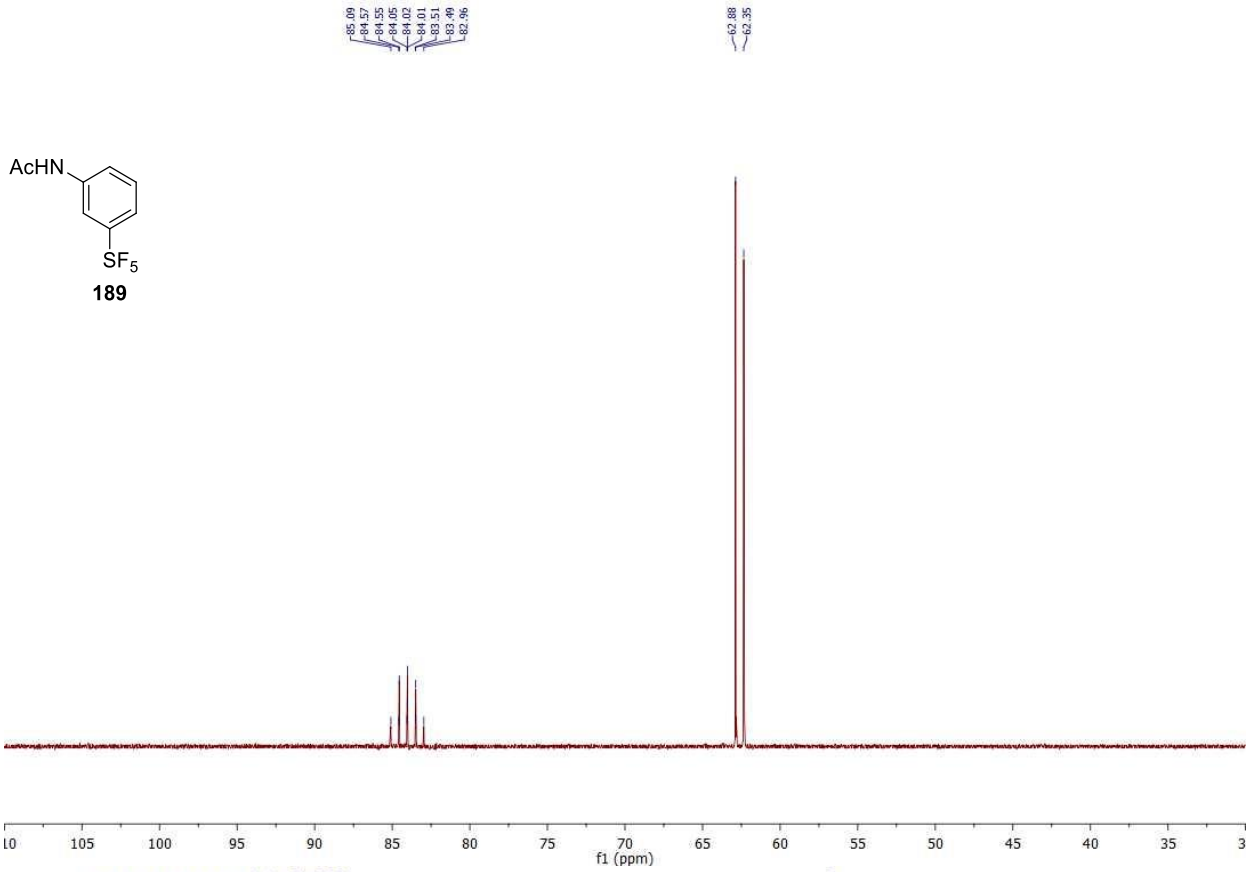
188

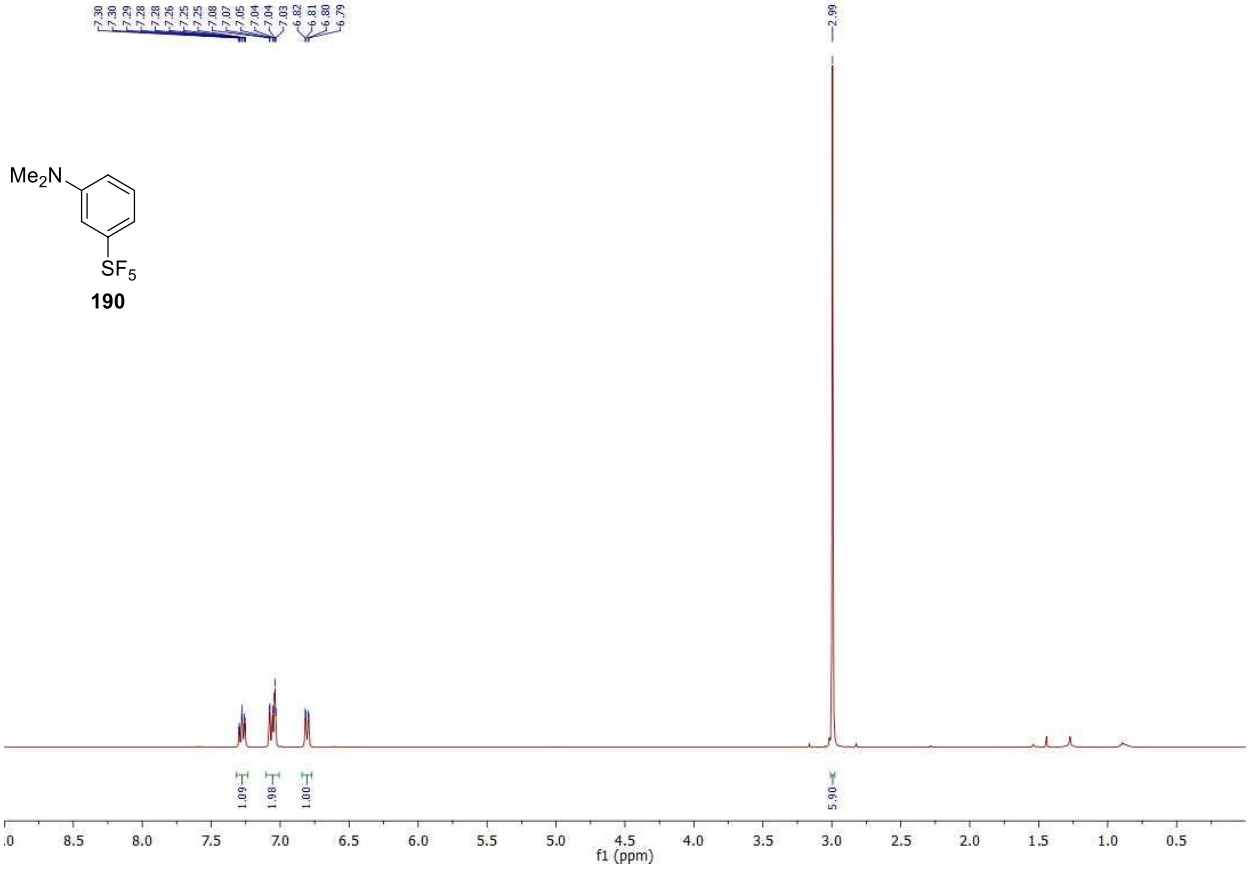

83.19
82.64
82.12
82.10
81.61
81.58
81.05
62.81
62.27
NC
O
SF5
f1 (ppm)

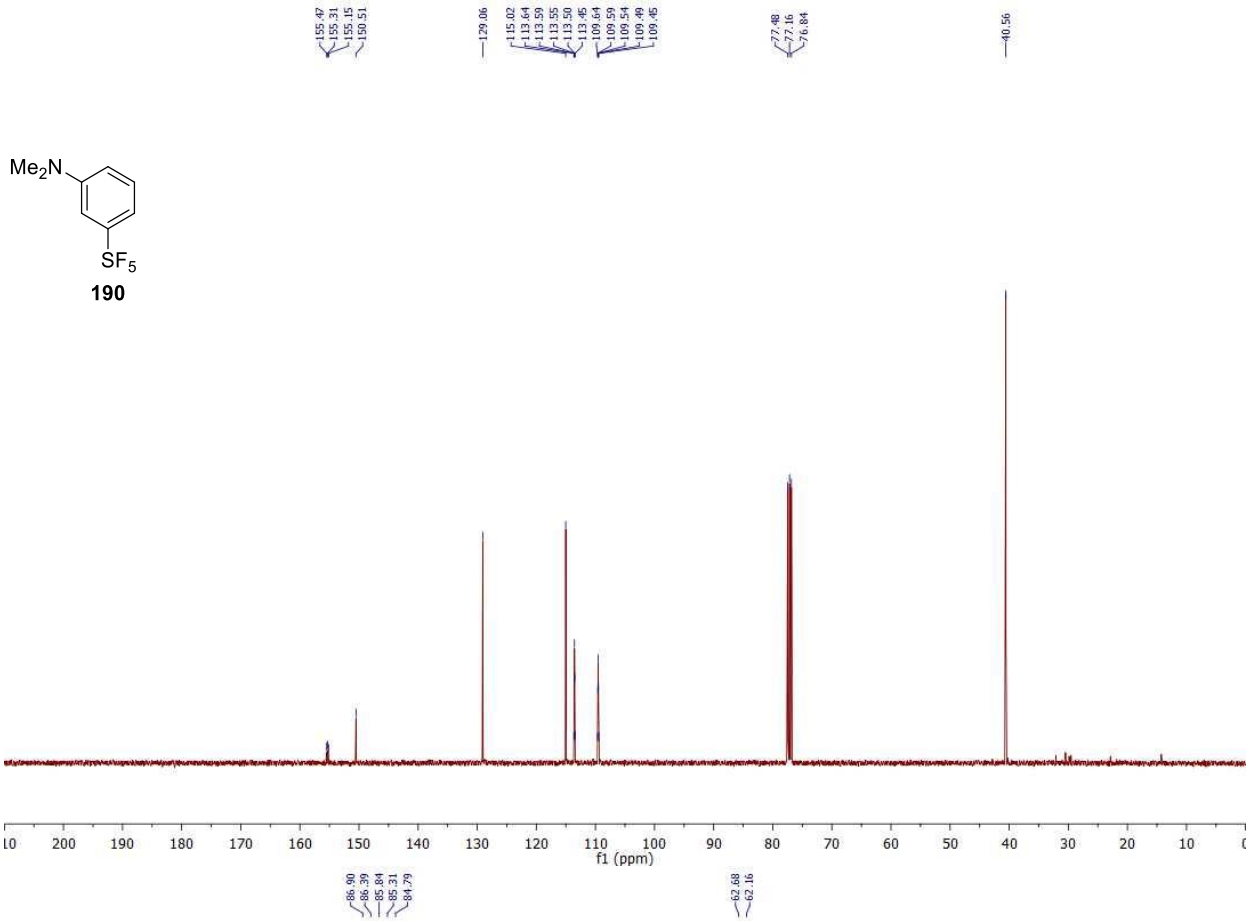
188

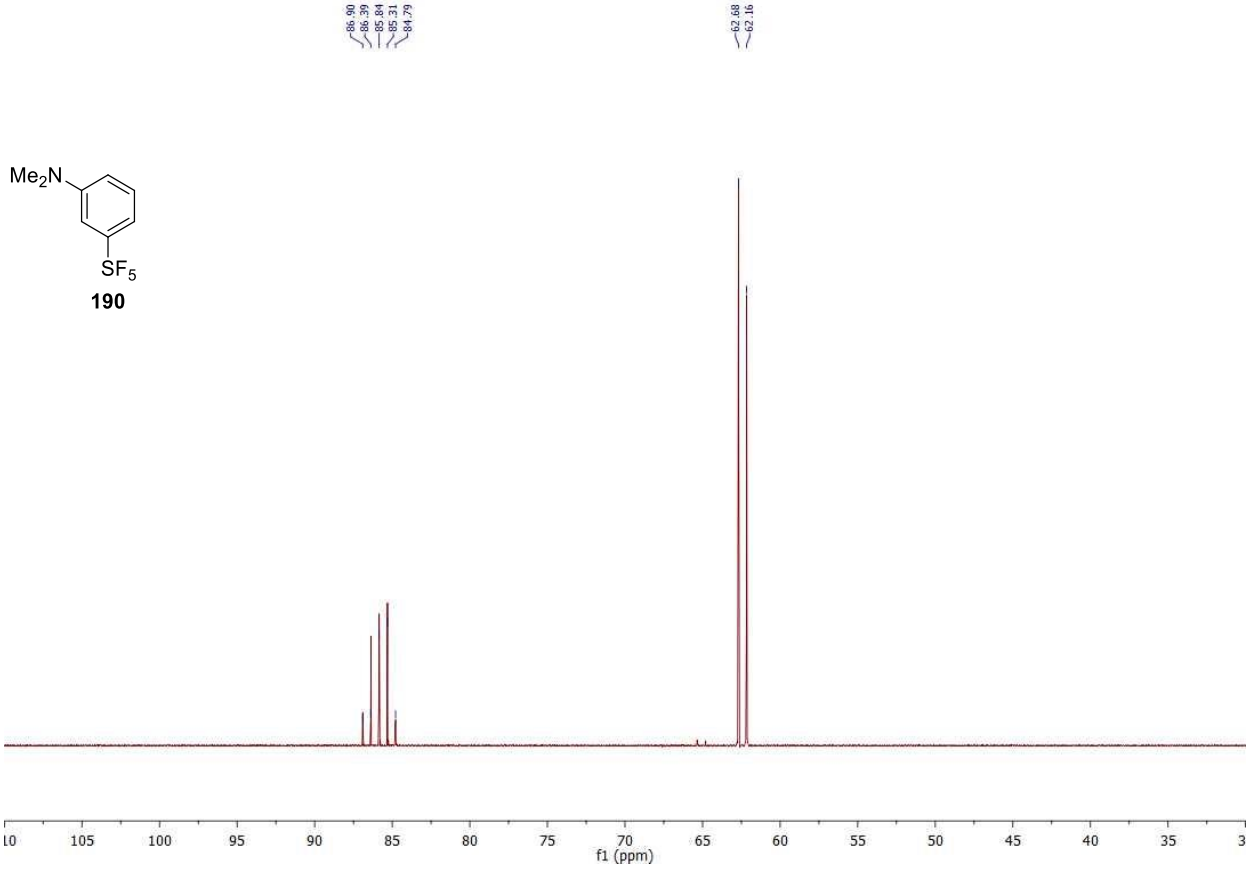

AcHN
SF5
189
f1 (ppm)

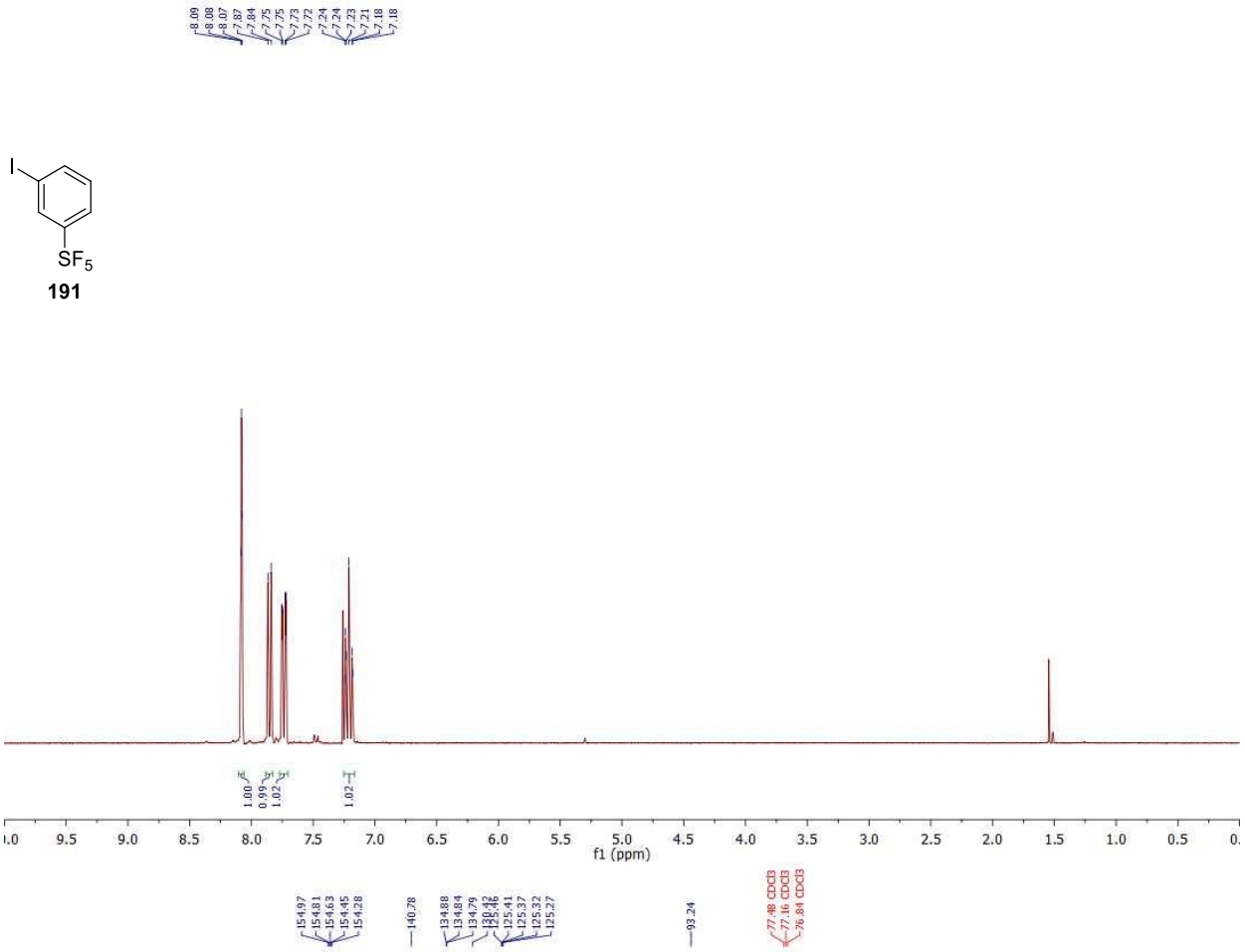

AcHN
SF5
189
f1 (ppm)

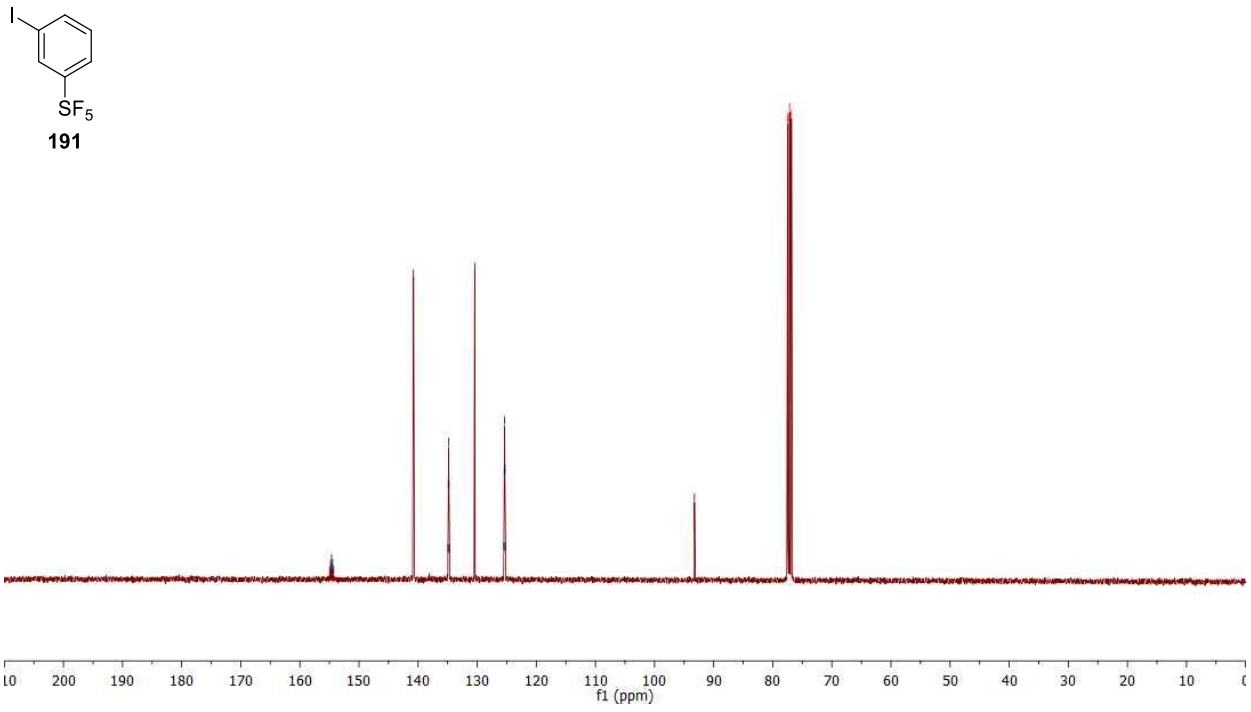

85.09
84.57
84.55
84.05
84.02
84.01
83.51
83.49
82.96
62.88
62.35
AcHN
SF5
189
f1 (ppm)

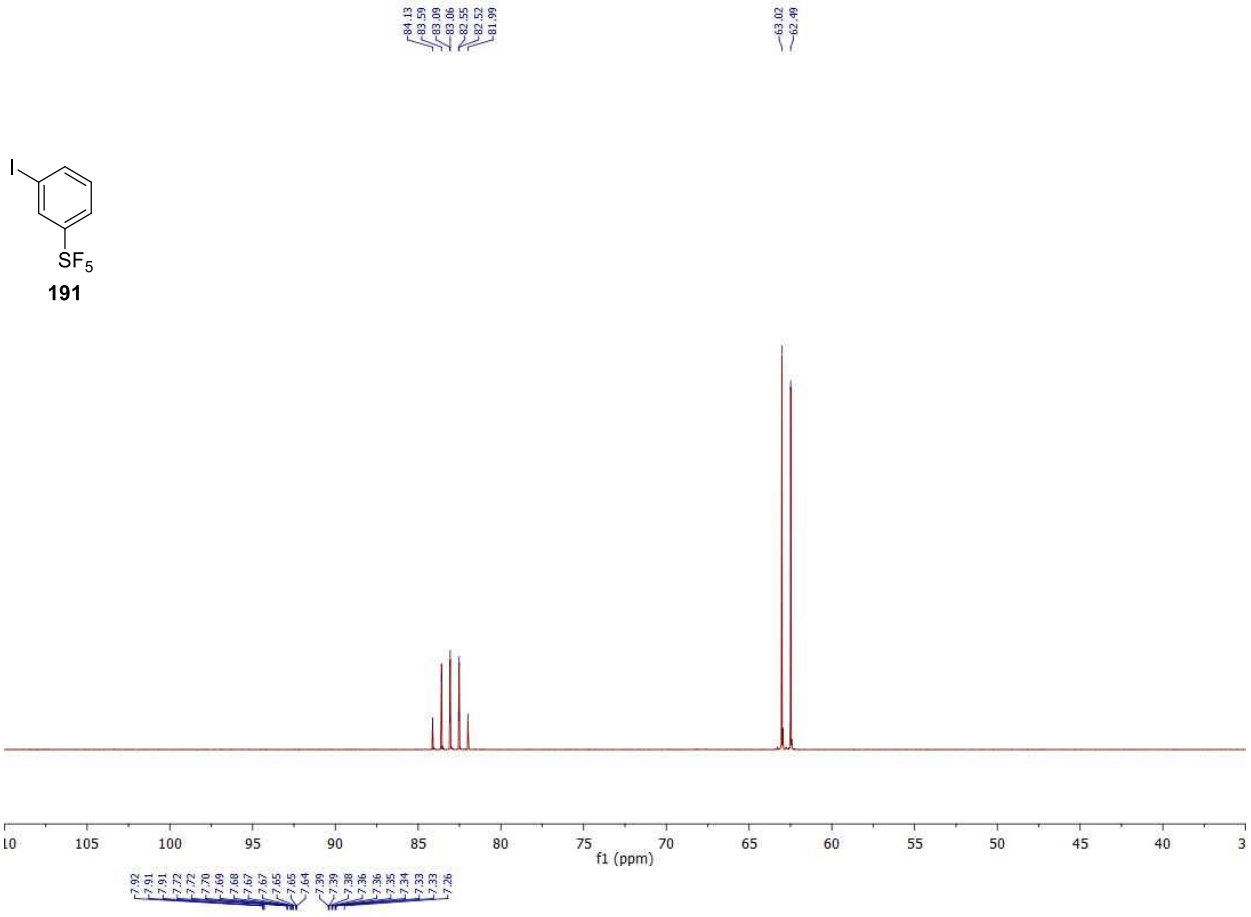

7.30
7.30
7.29
7.28
7.28
7.26
7.25
7.25
7.08
7.07
7.05
7.04
7.04
7.03
6.82
6.81
6.80
6.79
2.99
Me2N
SF5
190
1.09
1.98
1.00
5.90
f1 (ppm)

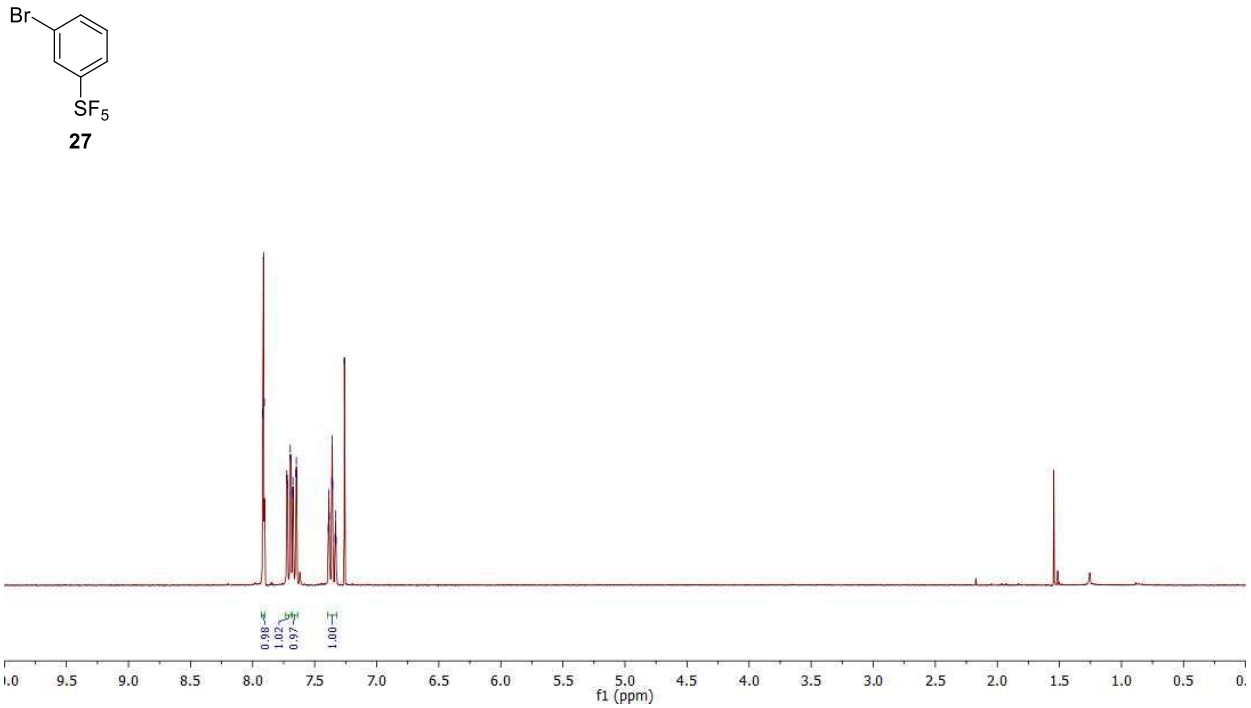

155.47
155.31
155.15
150.51
129.06
115.02
113.64
113.59
113.55
113.50
113.45
109.64
109.59
109.54
109.49
109.45
77.48
77.16
76.84
40.56
Me2N
SF5
190
f1 (ppm)

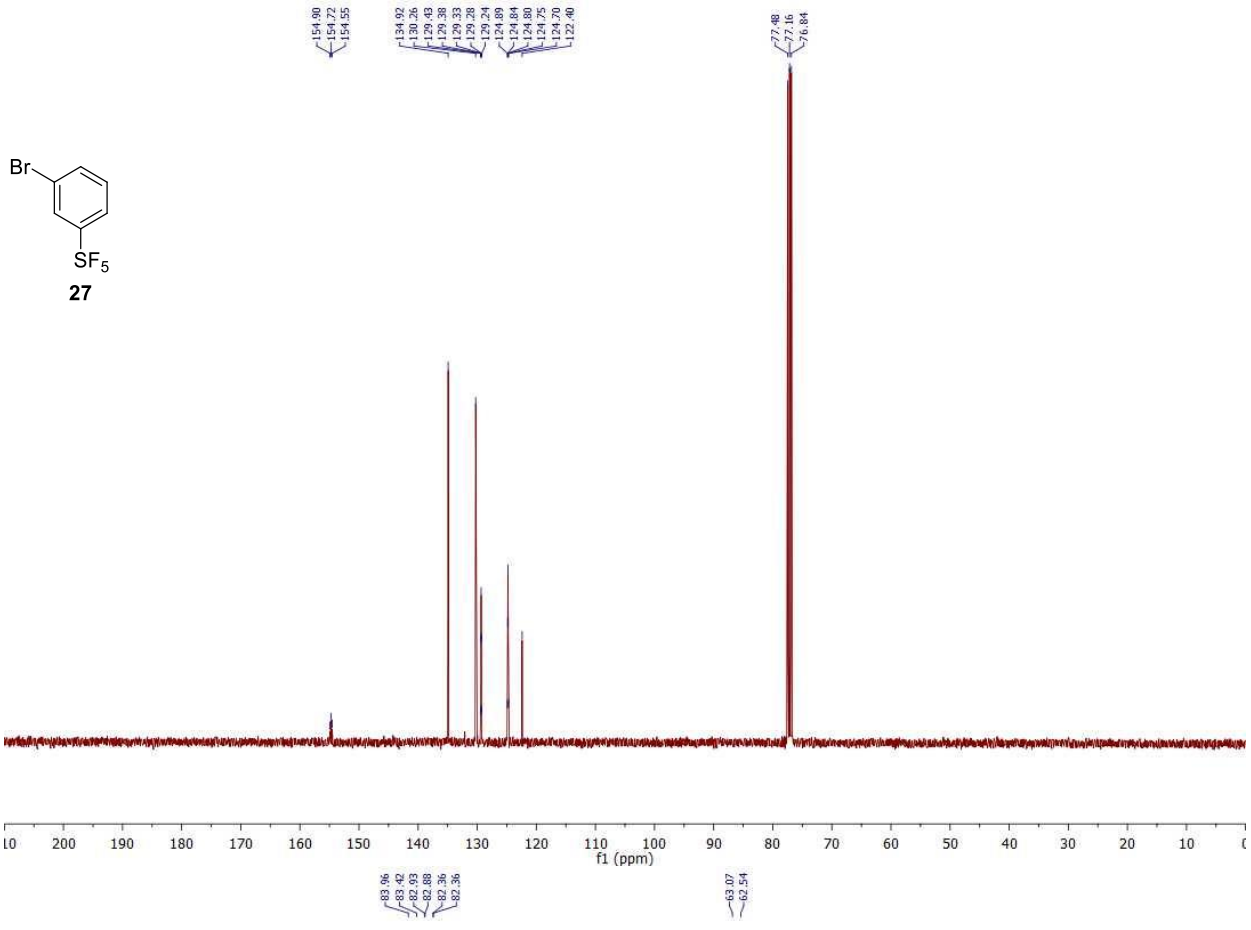

86.90
86.39
85.84
85.31
84.79
62.68
62.16
Me2N
SF5
190
f1 (ppm)


8.09
8.08
8.07
7.87
7.84
7.75
7.75
7.73
7.72
7.24
7.24
7.23
7.21
7.18
7.18
I
SF5
191
1.00
0.99
1.02
1.02
f1 (ppm)
154.97
154.81
154.63
154.45
154.28
140.78
134.88
134.84
134.79
125.41
125.37
125.32
125.27
93.24
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3

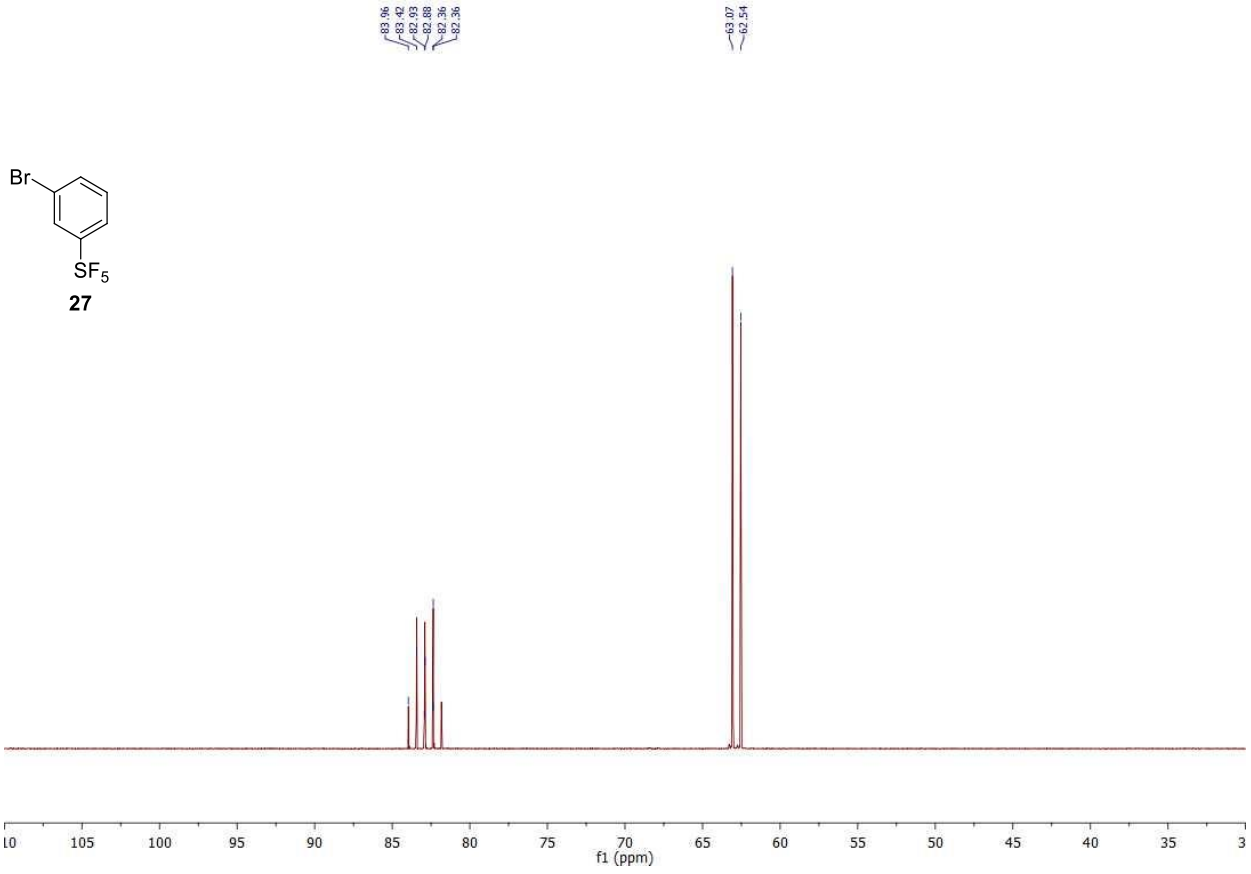

I
SF5
191
f1 (ppm)


84.13
83.59
83.09
83.06
82.55
82.52
81.99
63.02
62.49
I
SF5
191
f1 (ppm)
7.92
7.91
7.91
7.72
7.72
7.70
7.69
7.68
7.67
7.67
7.65
7.65
7.64
7.39
7.38
7.36
7.36
7.35
7.34
7.33
7.33
7.26

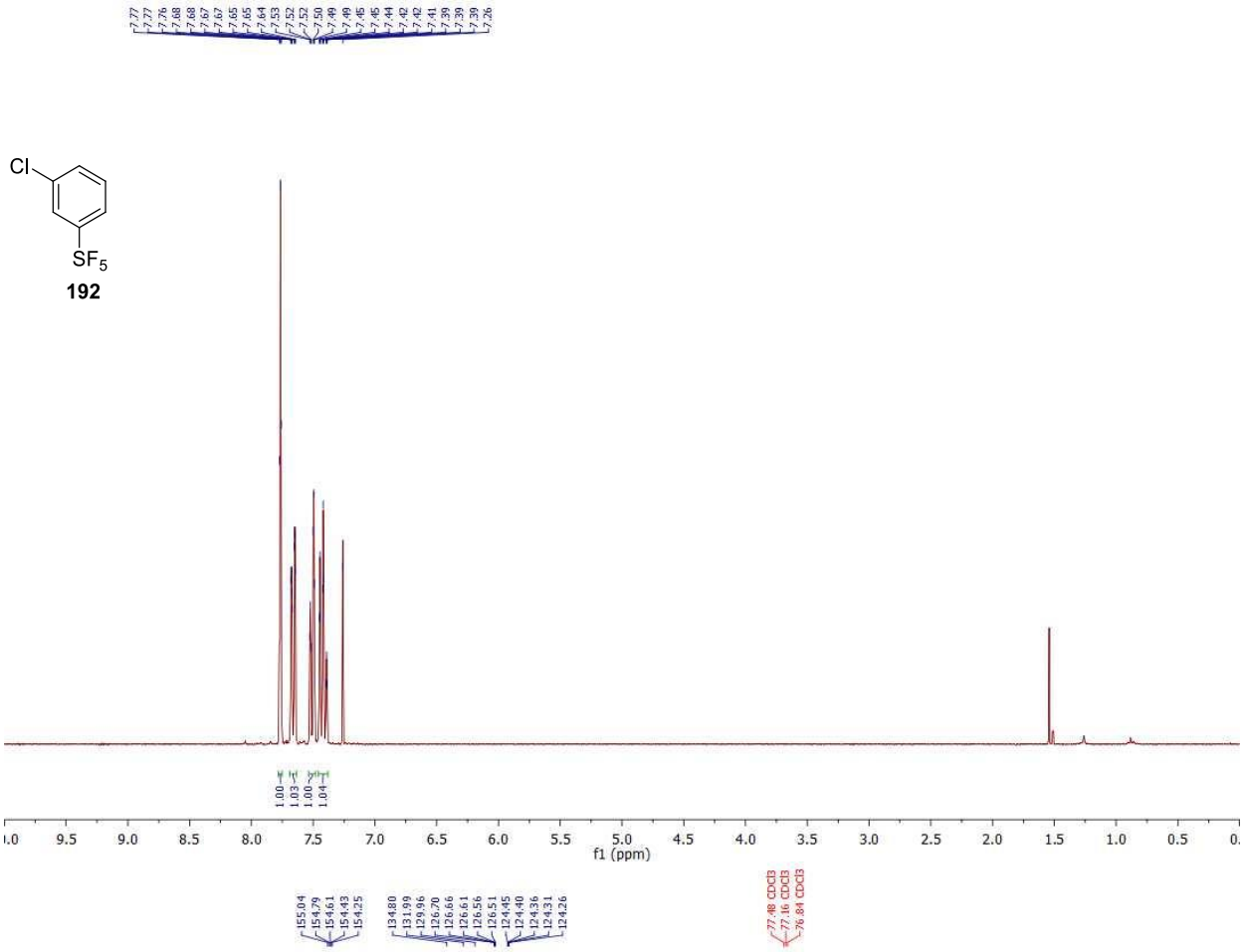

Br
SF5
27
0.98
1.02
0.97
1.00
f1 (ppm)

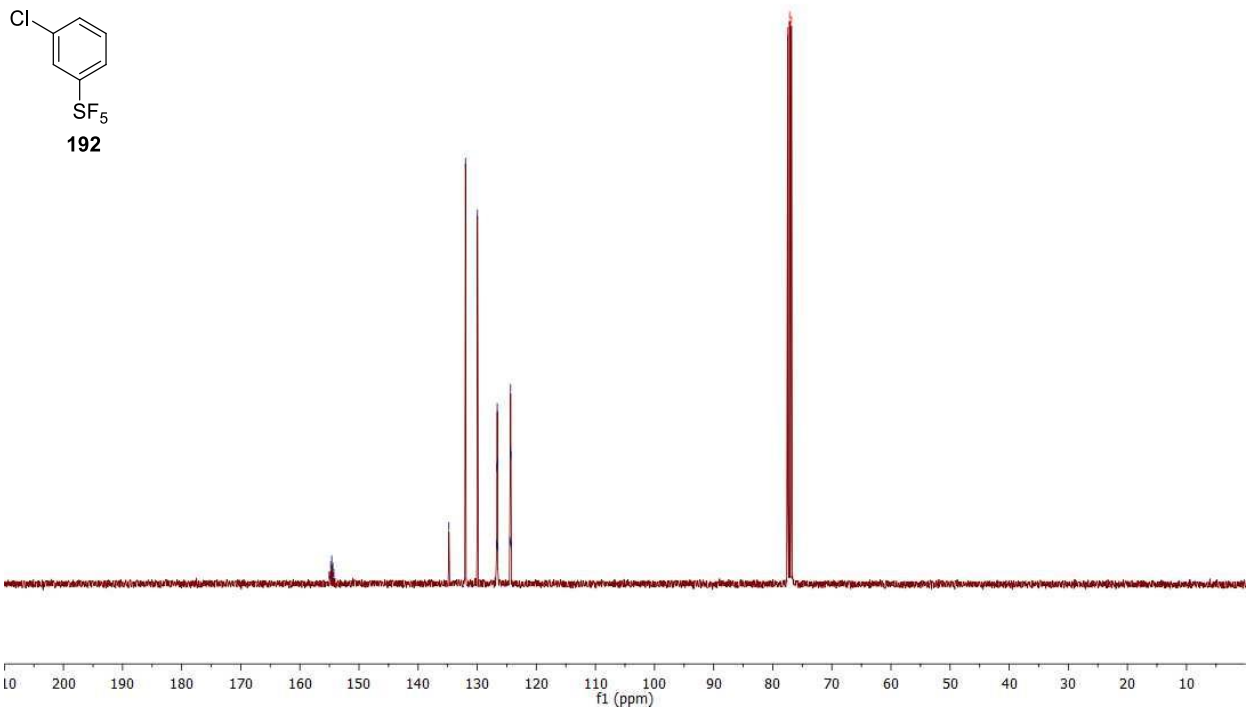

154.90
154.72
154.55
134.92
130.26
129.43
129.38
129.33
129.28
129.24
124.89
124.84
124.80
124.75
124.70
122.40
77.48
77.16
76.84
Br
SF5
f1 (ppm)

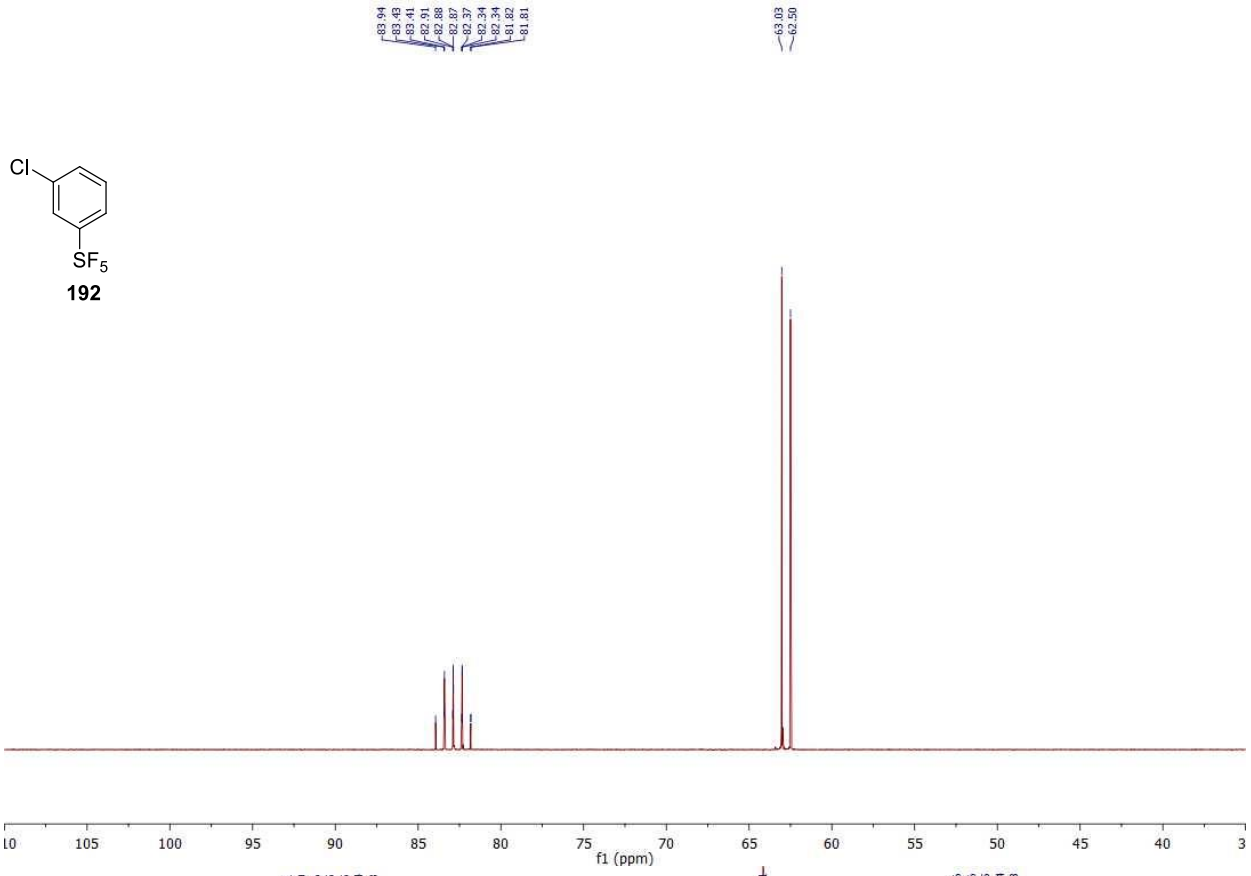
27


-83.96
-83.42
-82.93
-82.88
-82.36
-82.36
-63.07
-62.54
Br
SF5
f1 (ppm)

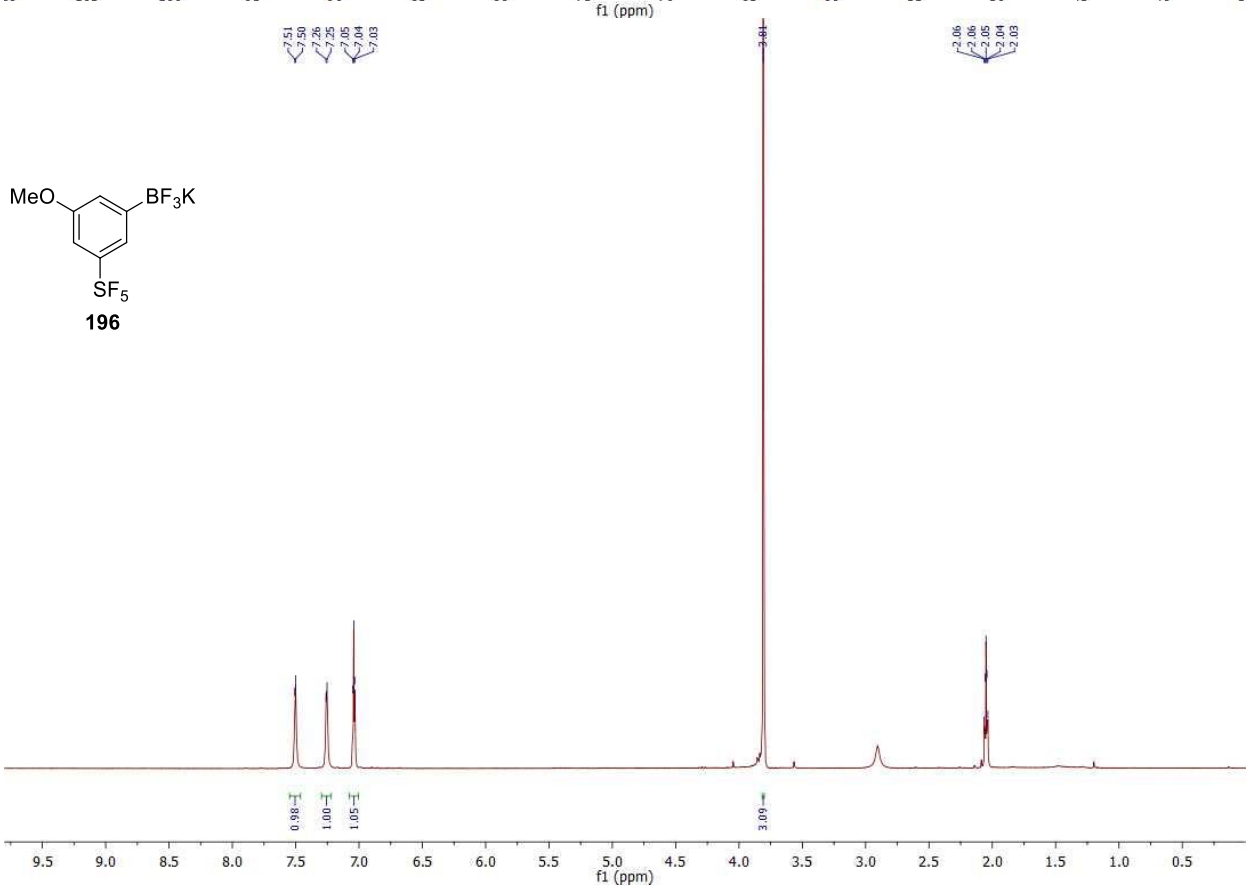
27


Cl
SF5
192
f1 (ppm)

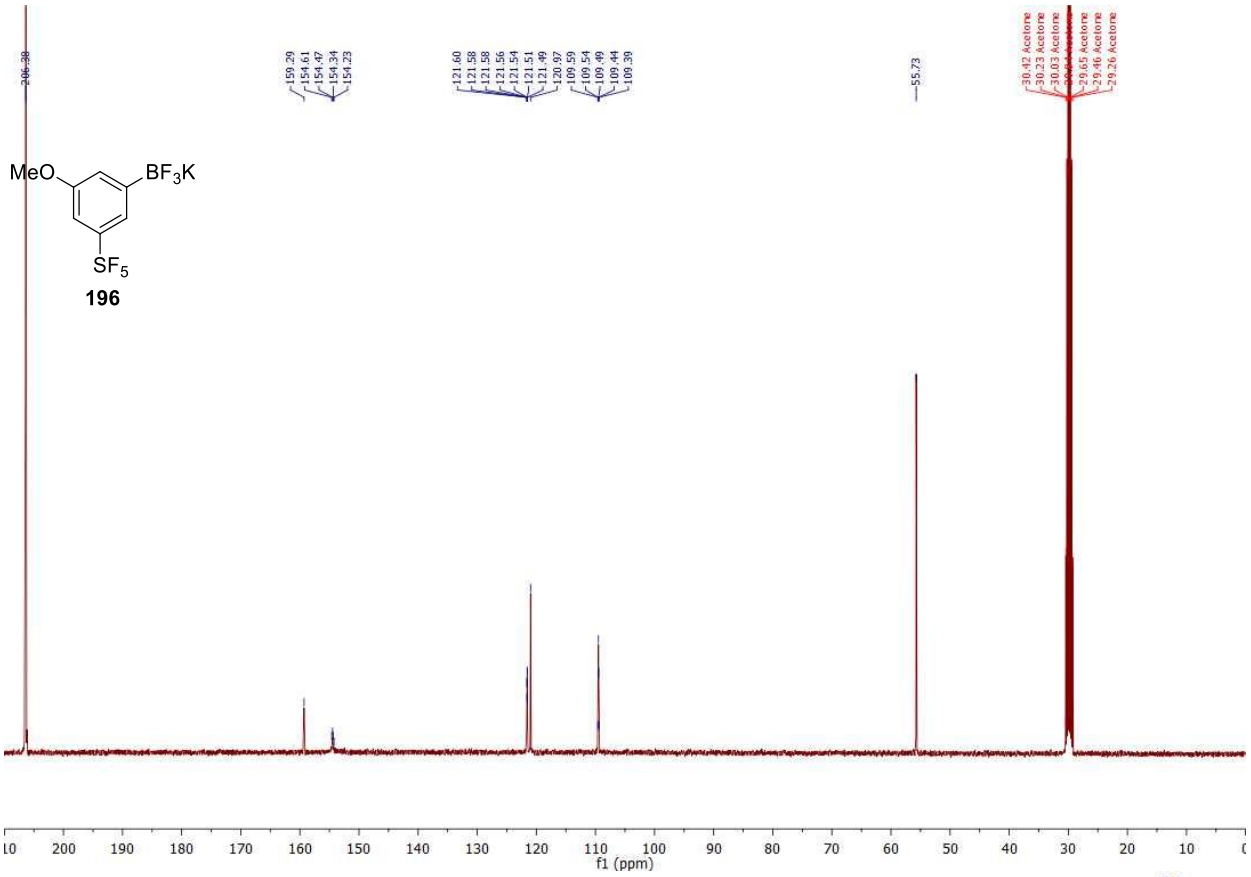

Cl
SF5
192
f1 (ppm)

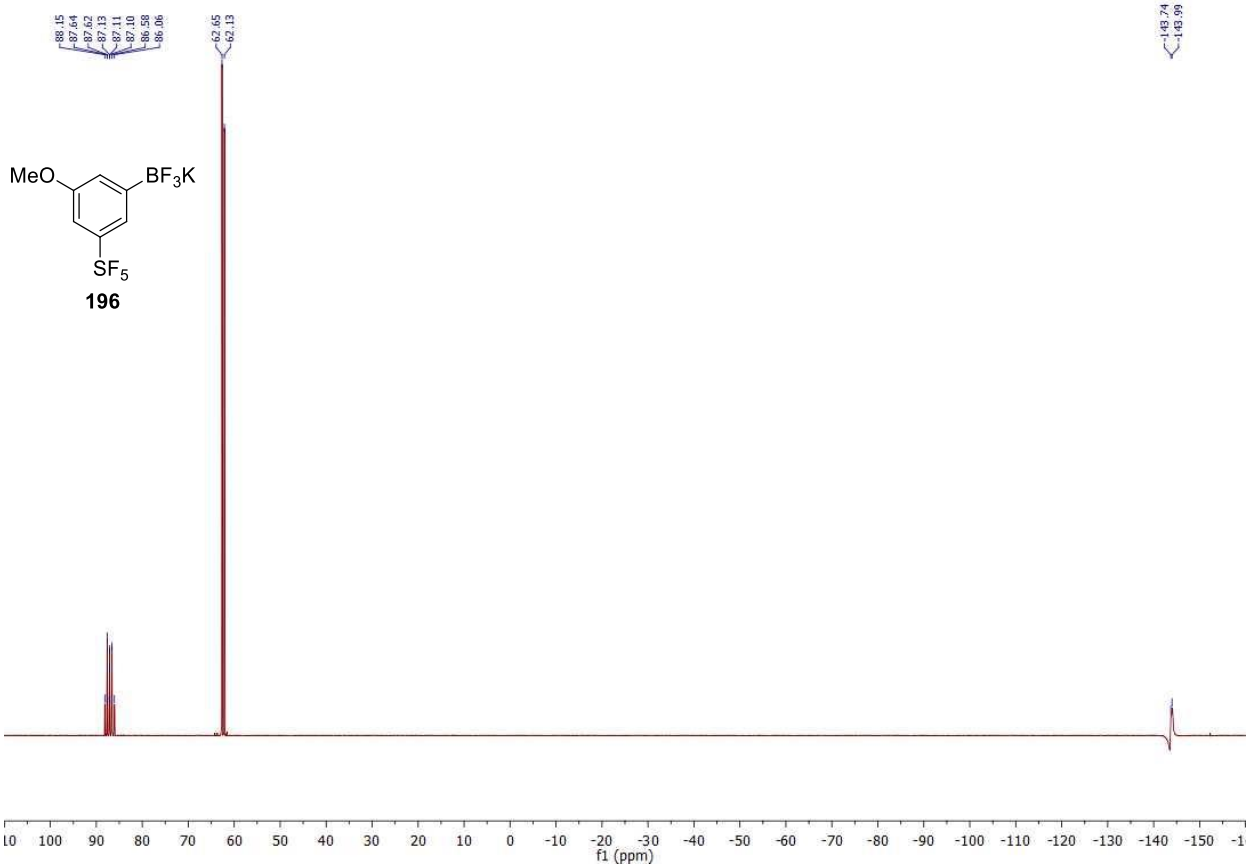

83.94
83.43
83.41
82.91
82.88
82.87
82.37
82.34
82.34
81.82
81.81
63.03
62.50
Cl
SF5
f1 (ppm)

192

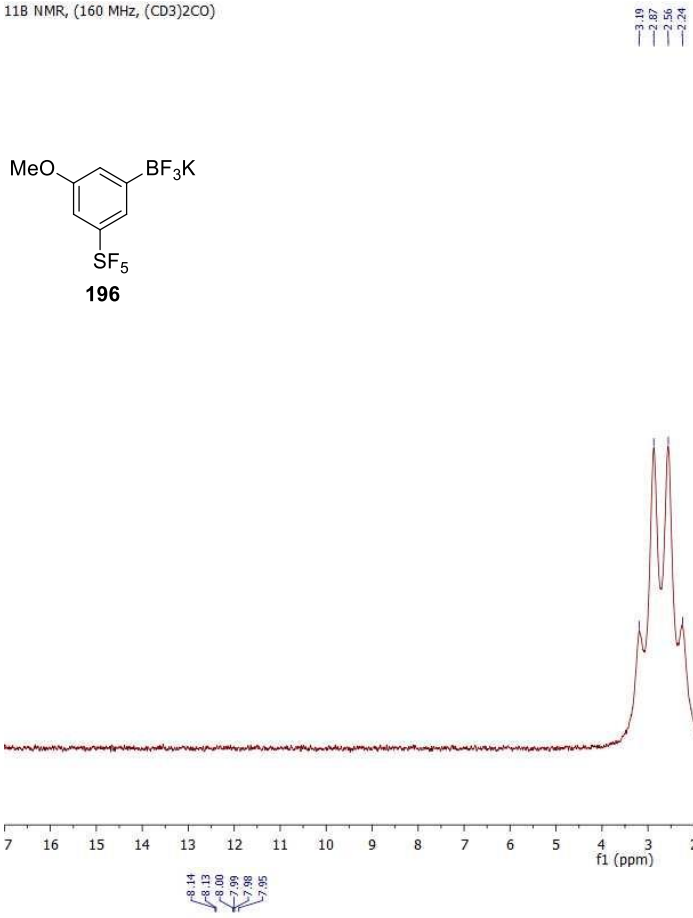

7.51
7.50
7.26
7.25
7.05
7.04
7.03
3.81
2.06
2.06
2.05
2.04
2.03
MeO
BF3K
SF5
0.98
1.00
1.05
3.09
f1 (ppm)

196

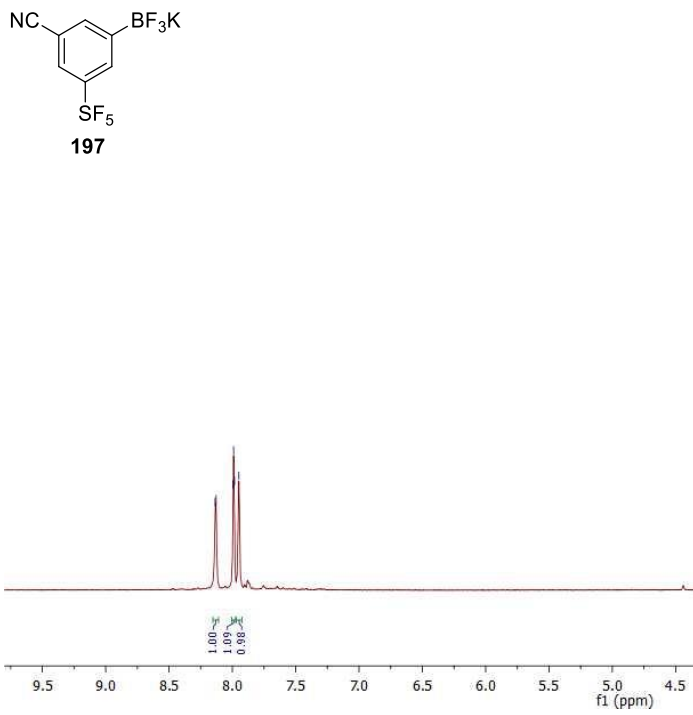

MeO
BF3K
SF5
196
206.38
159.29
154.61
154.47
154.34
154.23
121.60
121.58
121.58
121.56
121.54
121.51
121.49
120.97
109.59
109.54
109.49
109.44
109.39
55.73
30.42 Acetone
30.23 Acetone
30.03 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
f1 (ppm)


MeO
BF3K
SF5
196
88.15
87.64
87.62
87.13
87.11
87.10
86.58
86.06
62.65
62.13
-143.74
-143.99
f1 (ppm)

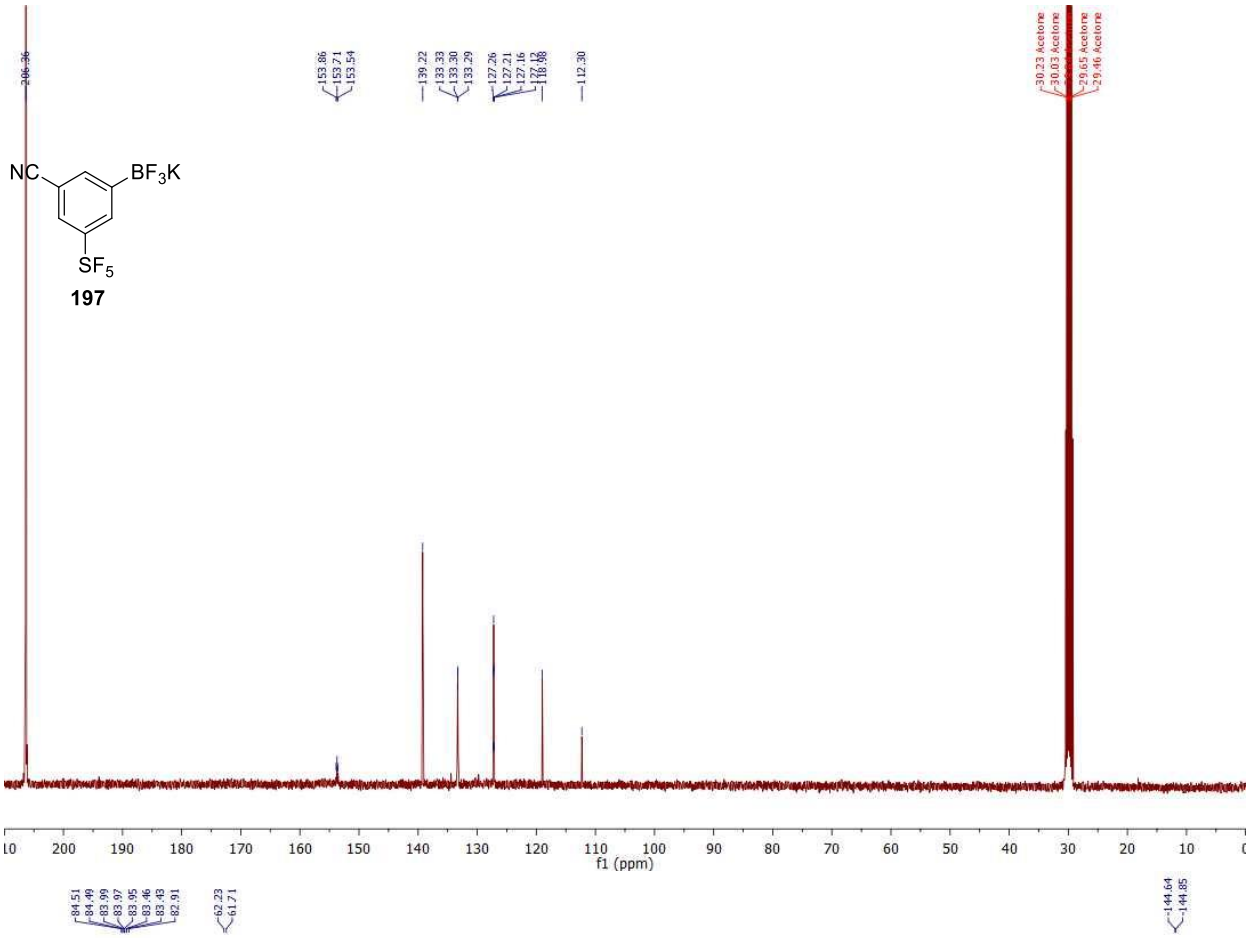
11B NMR, (160 MHz, (CD3)2CO)

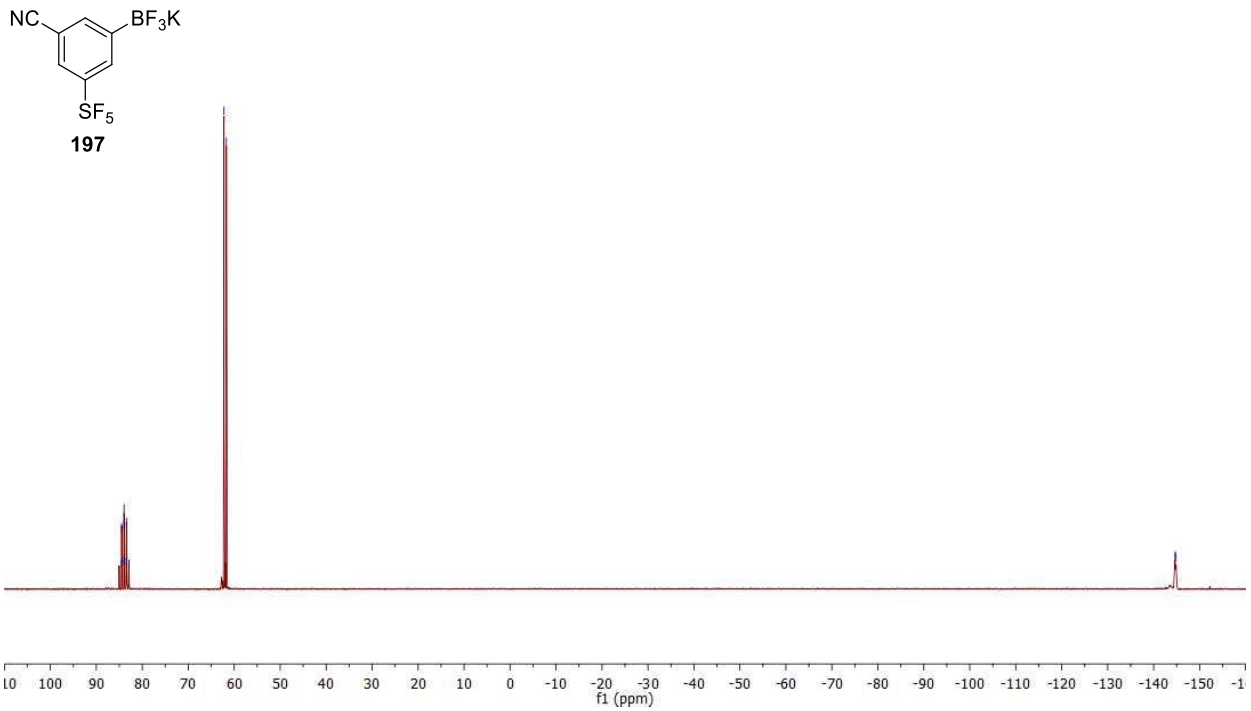


196

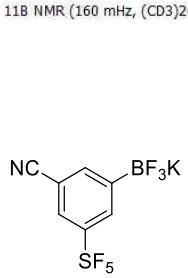


197

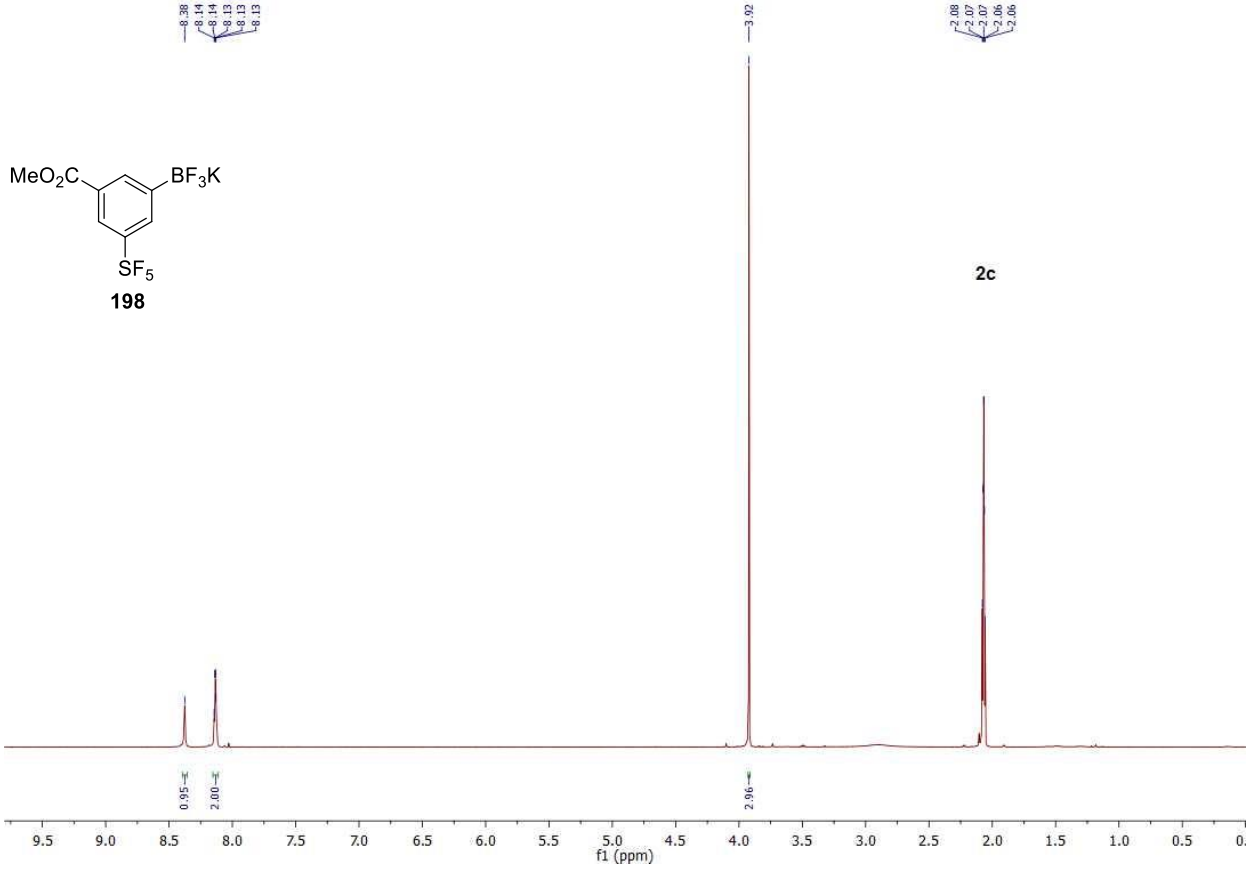

206.36
153.86
153.71
153.54
139.22
133.33
133.30
133.29
127.26
127.21
127.16
112.30
30.23 Acetone
30.03 Acetone
29.65 Acetone
29.46 Acetone
NC
BF3K
SF5
197
f1 (ppm)
84.51
84.49
83.99
83.97
83.95
83.46
83.43
82.91
62.23
61.71
144.64
144.85


NC
BF3K
SF5
197
f1 (ppm)

11B NMR (160 mHz, (CD3)2CO)

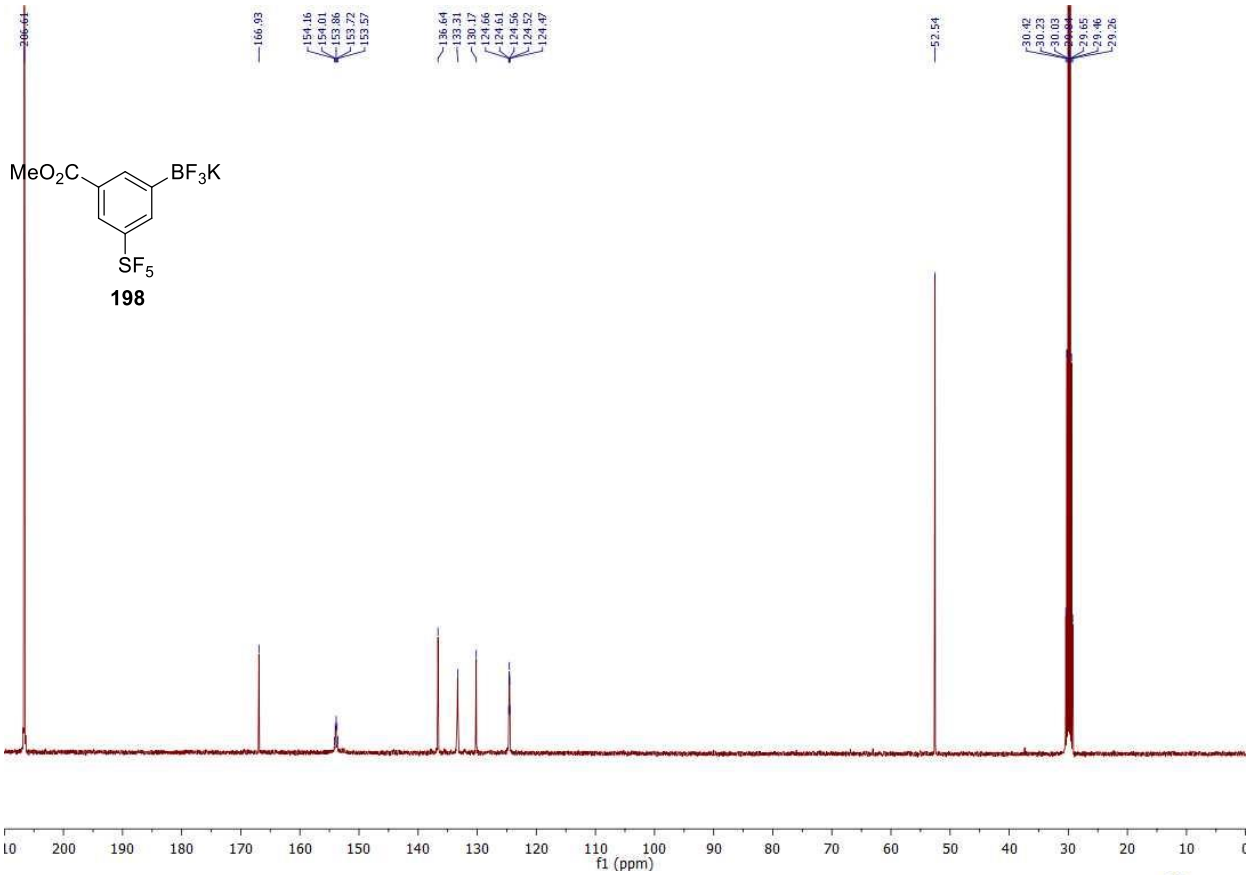


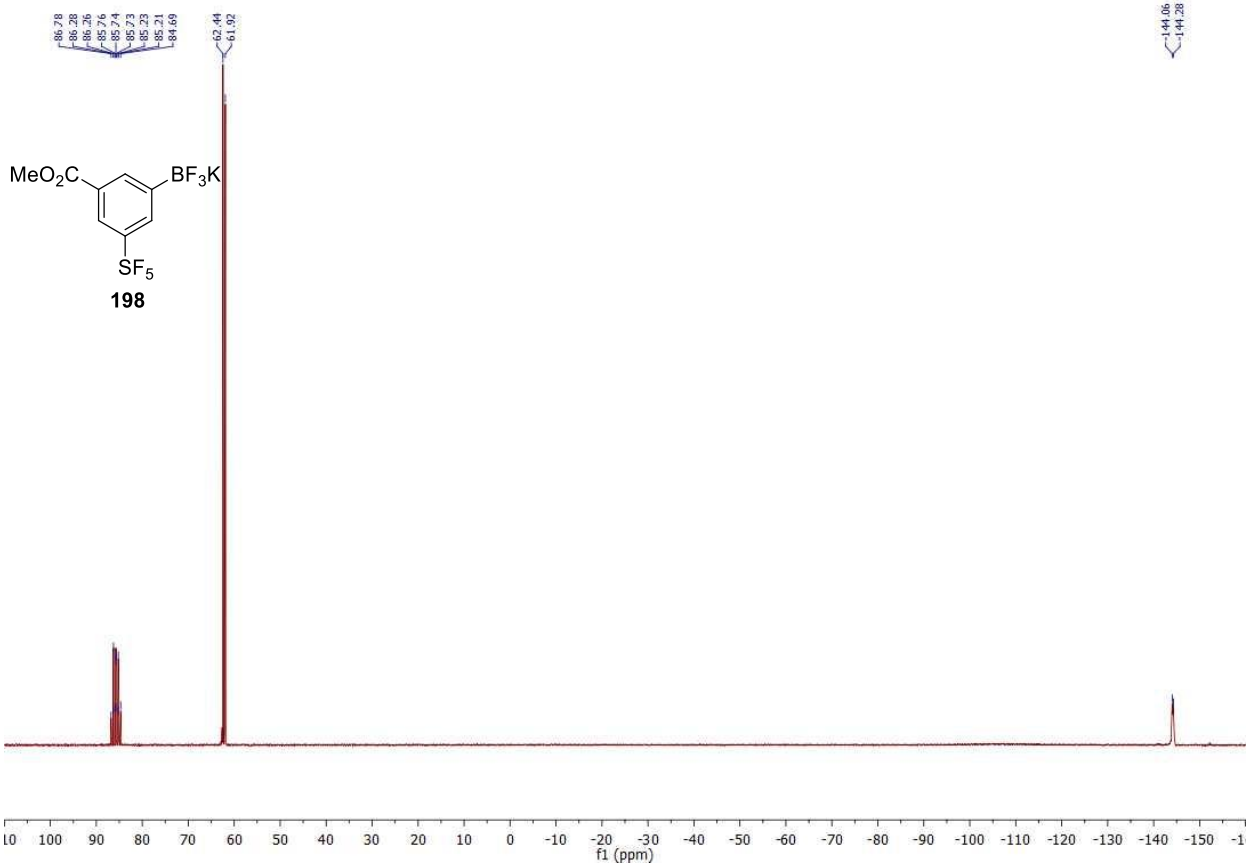
197



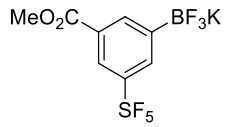
198

2c

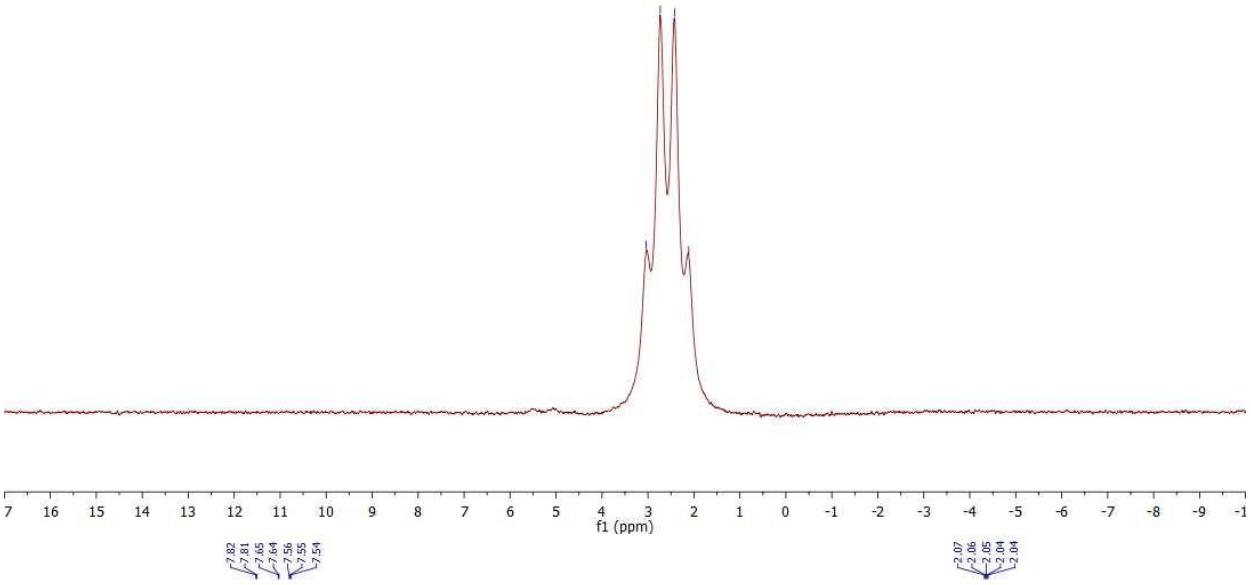

MeO2C
BF3K
SF5
198
f1 (ppm)

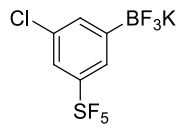

MeO2C
BF3K
SF5
198
f1 (ppm)

11B NMR (160 MHz, (CD3)2CO)

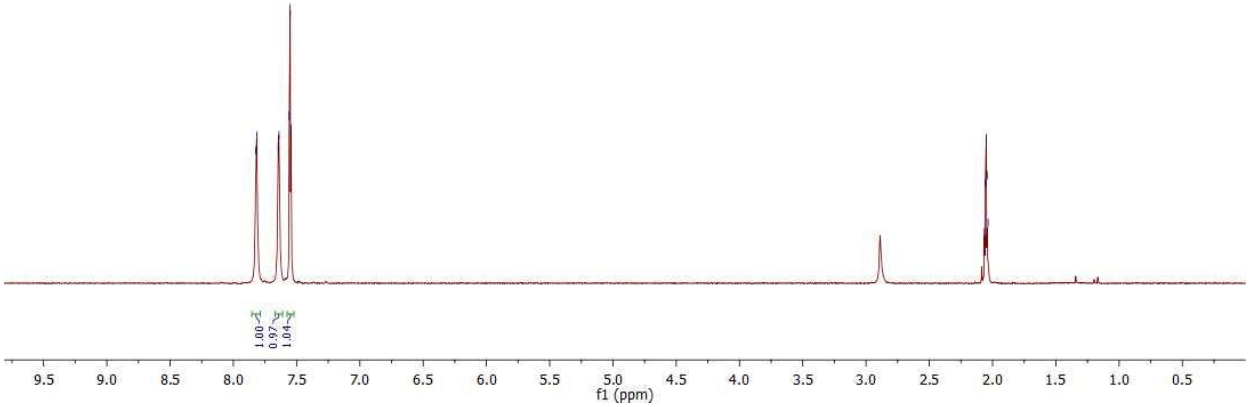


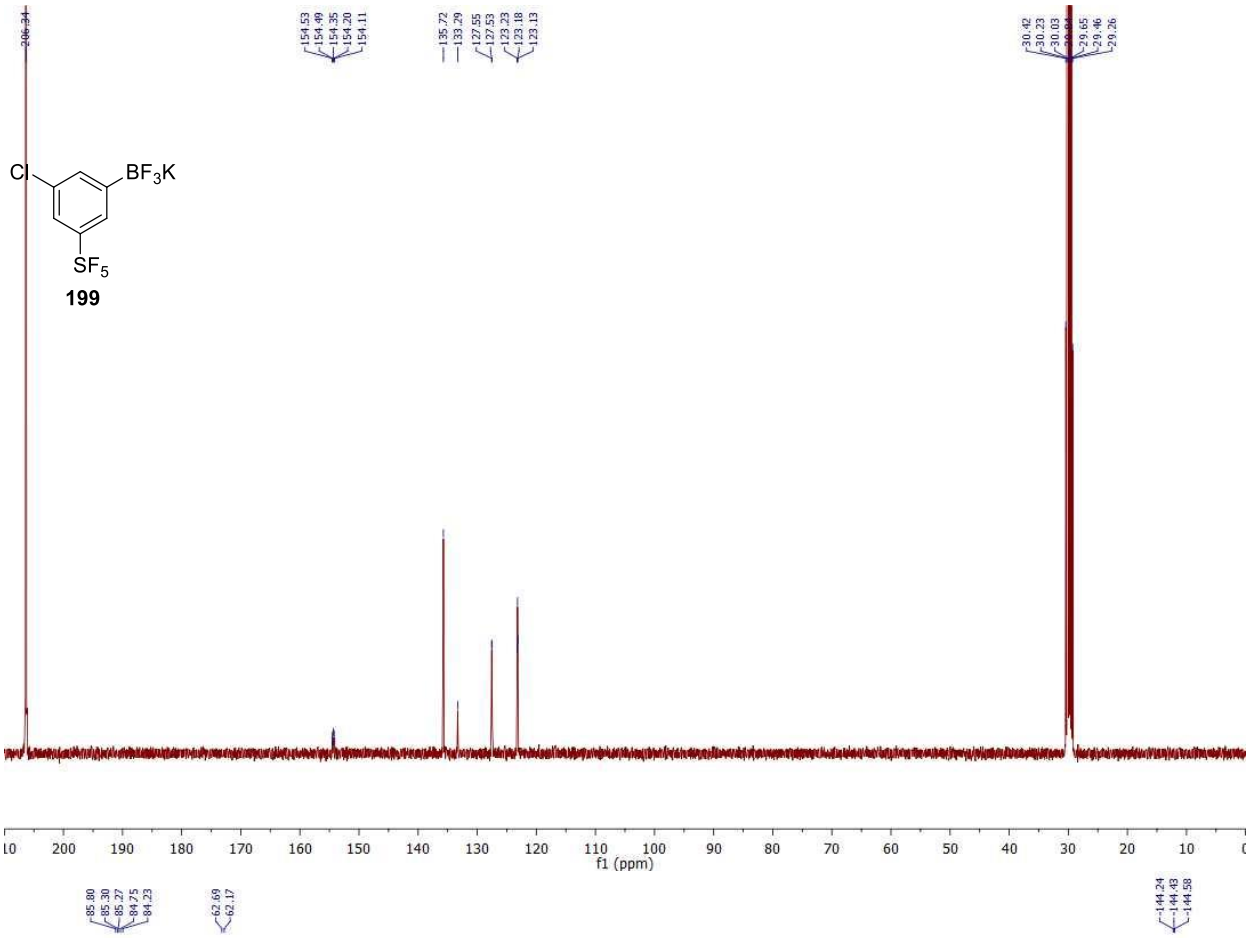
198

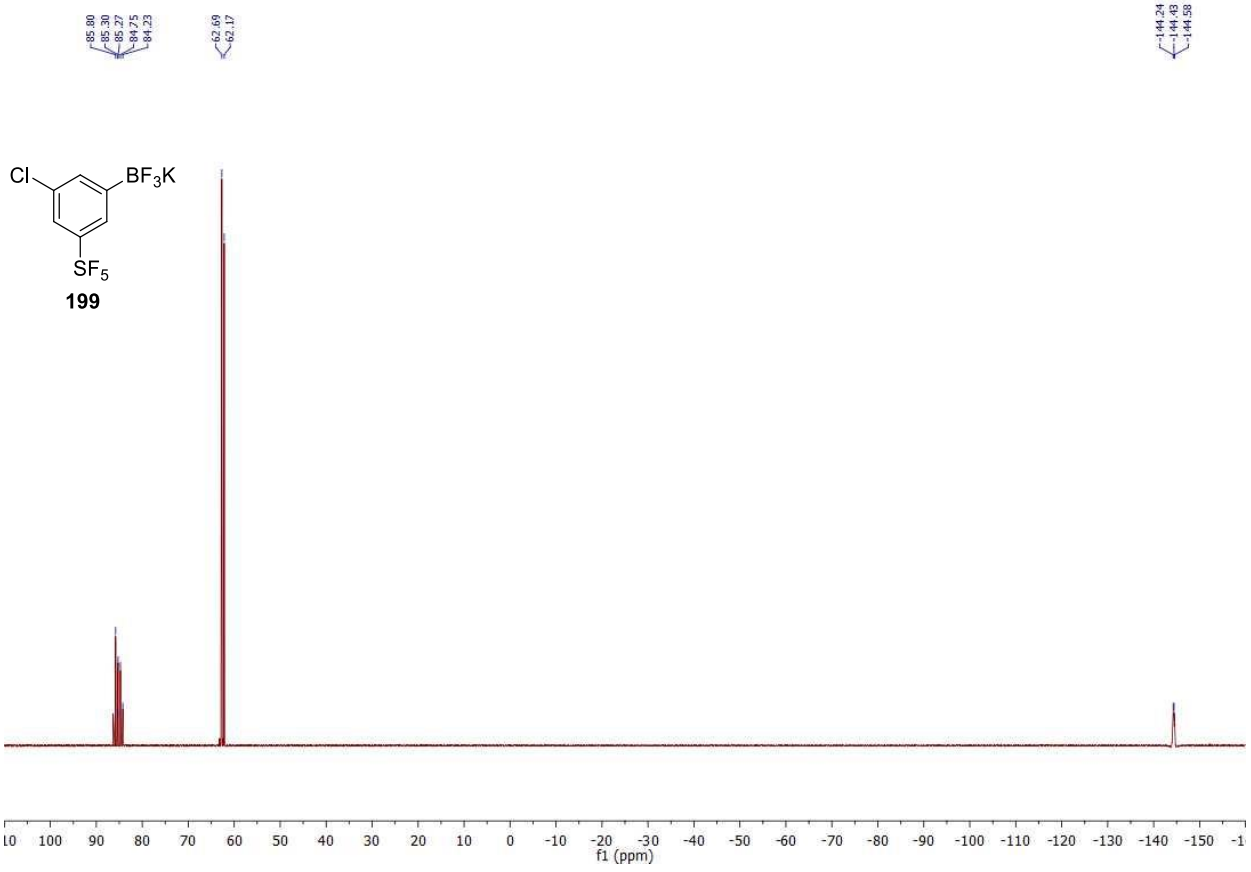




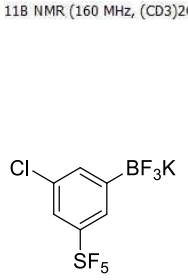
199



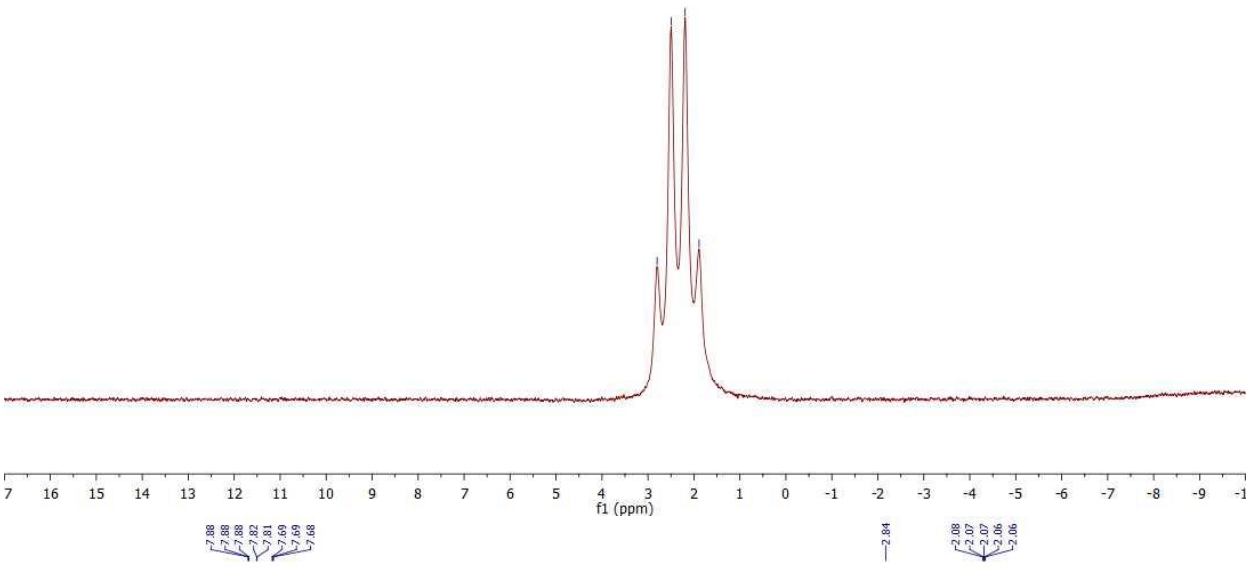

206.34
154.53
154.49
154.35
154.20
154.11
135.72
133.29
127.55
127.53
123.23
123.18
123.13
30.42
30.23
30.03
29.65
29.46
29.26
Cl
BF3K
SF5
199
f1 (ppm)

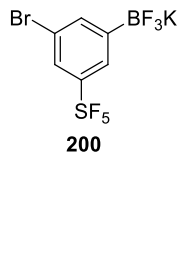

85.80
85.30
85.27
84.75
84.23
62.69
62.17
144.24
144.43
144.58
Cl
BF3K
SF5
199
f1 (ppm)

11B NMR (160 MHz, (CD3)2CO)

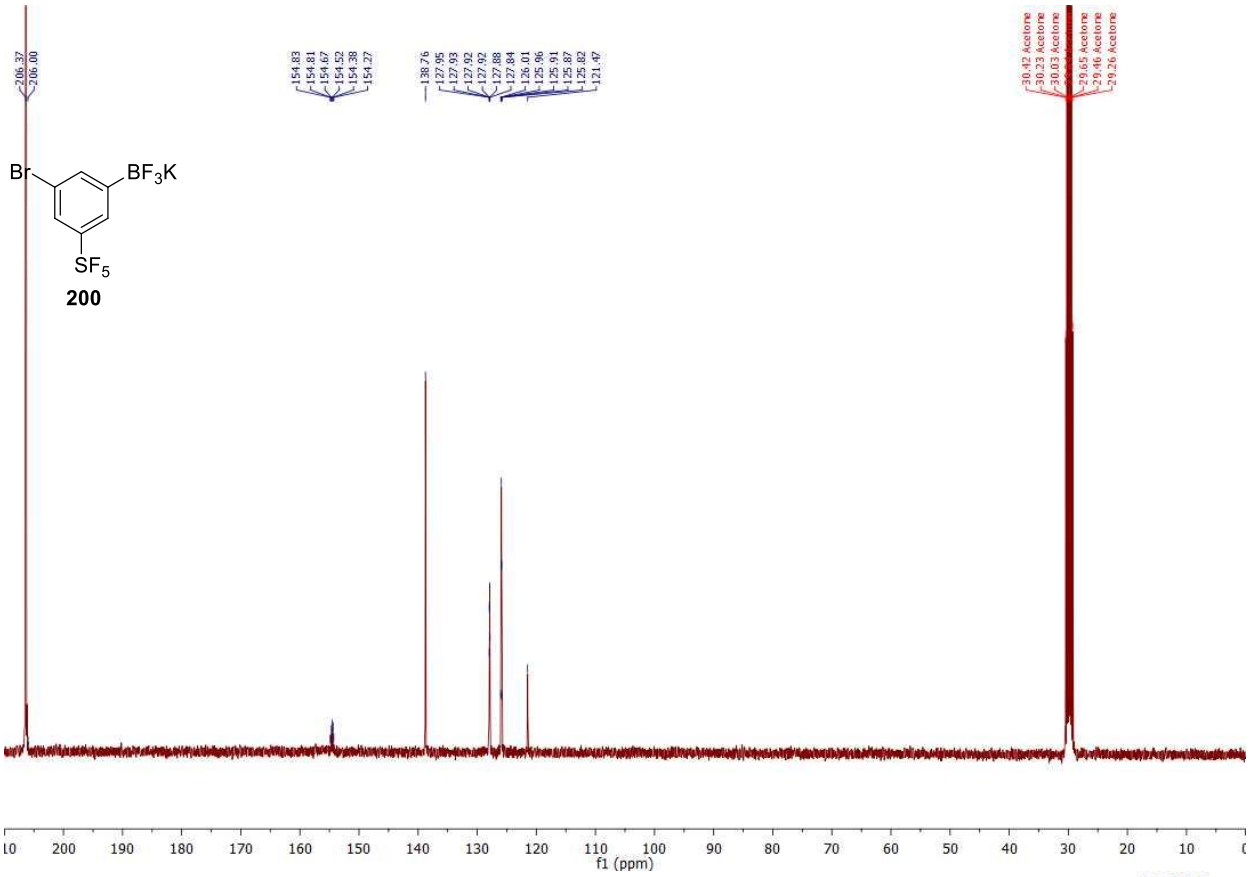


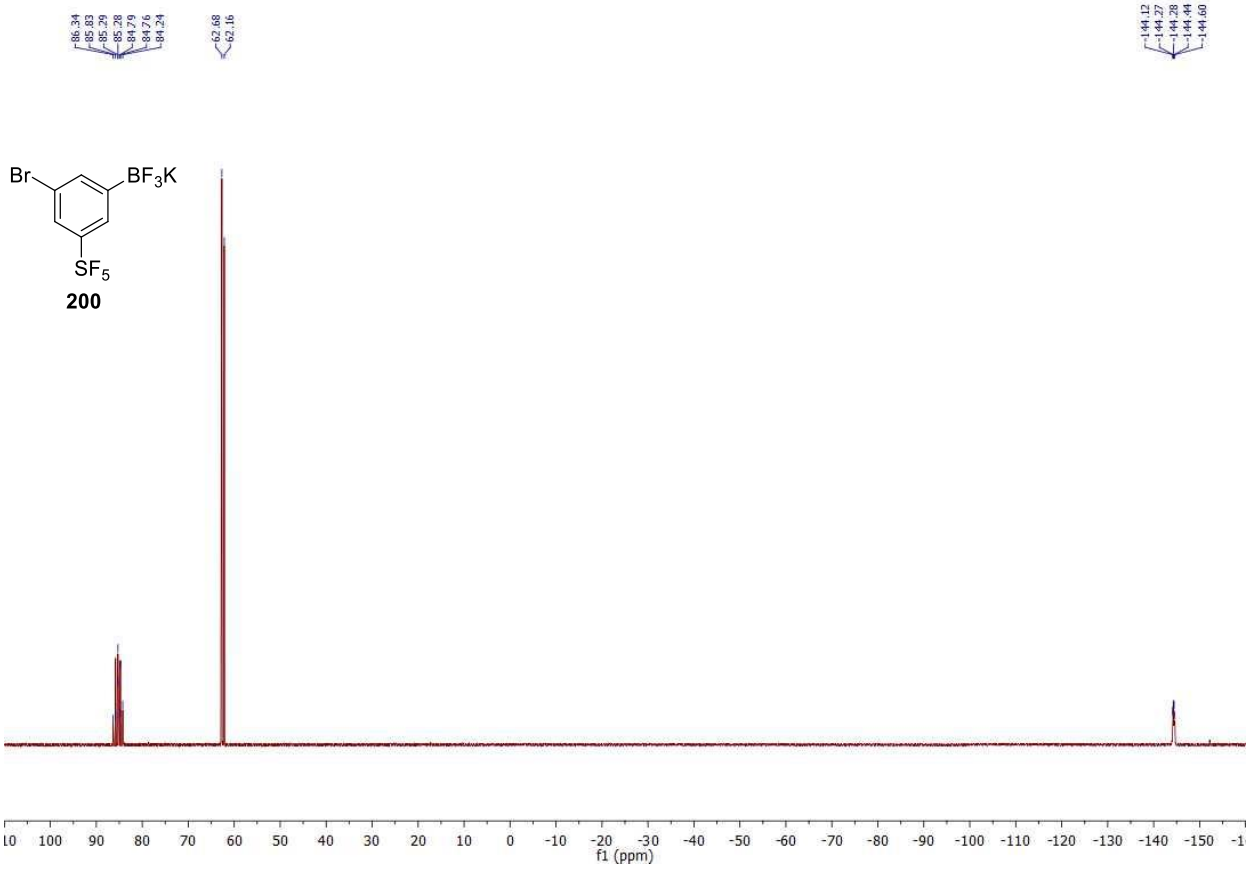
199



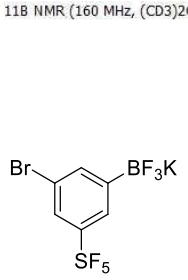


200

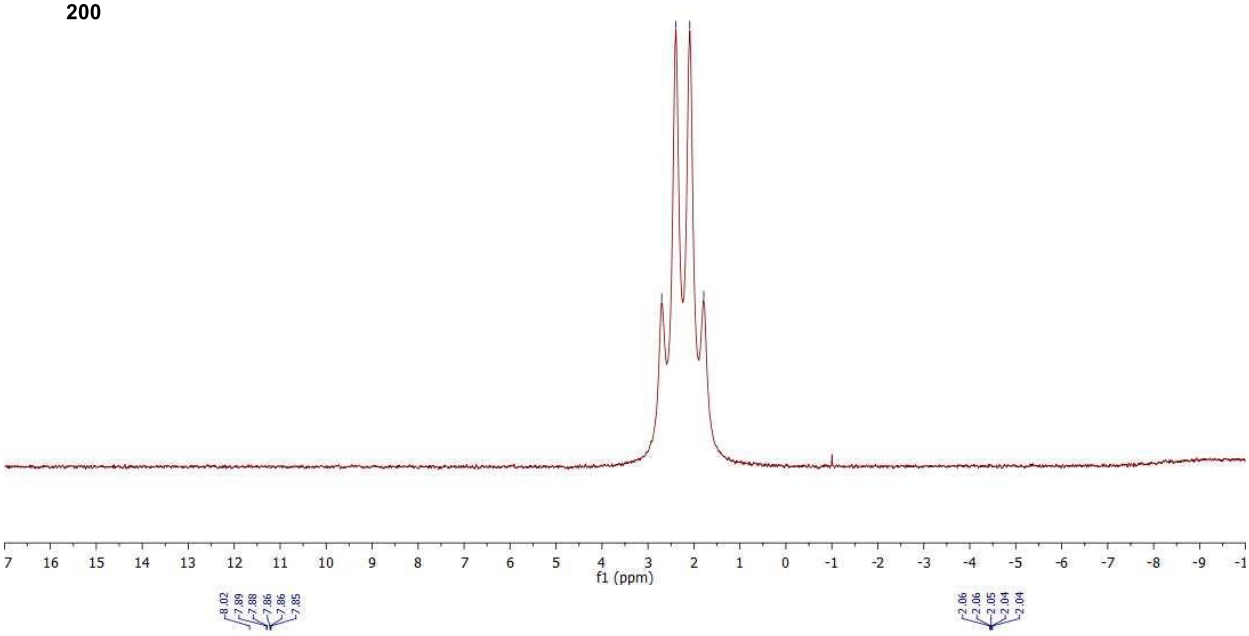

206.37
206.00
154.83
154.81
154.67
154.52
154.38
154.27
138.76
127.95
127.93
127.92
127.92
127.88
127.84
126.01
125.96
125.91
125.87
125.82
121.47
30.42 Acetone
30.23 Acetone
30.03 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
Br
BF3K
SF5
200
f1 (ppm)

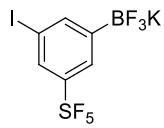

86.34
85.83
85.29
85.28
84.79
84.76
84.24
62.68
62.16
144.12
144.27
144.28
144.44
144.60
Br
BF3K
SF5
200
f1 (ppm)

11B NMR (160 MHz, (CD3)2CO)

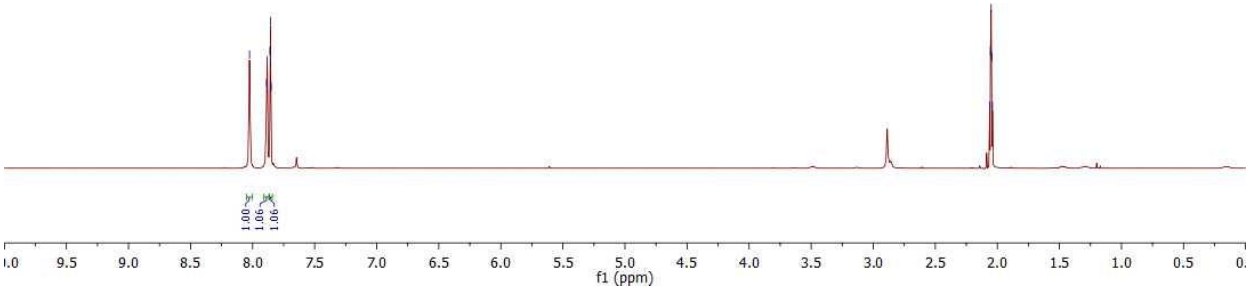


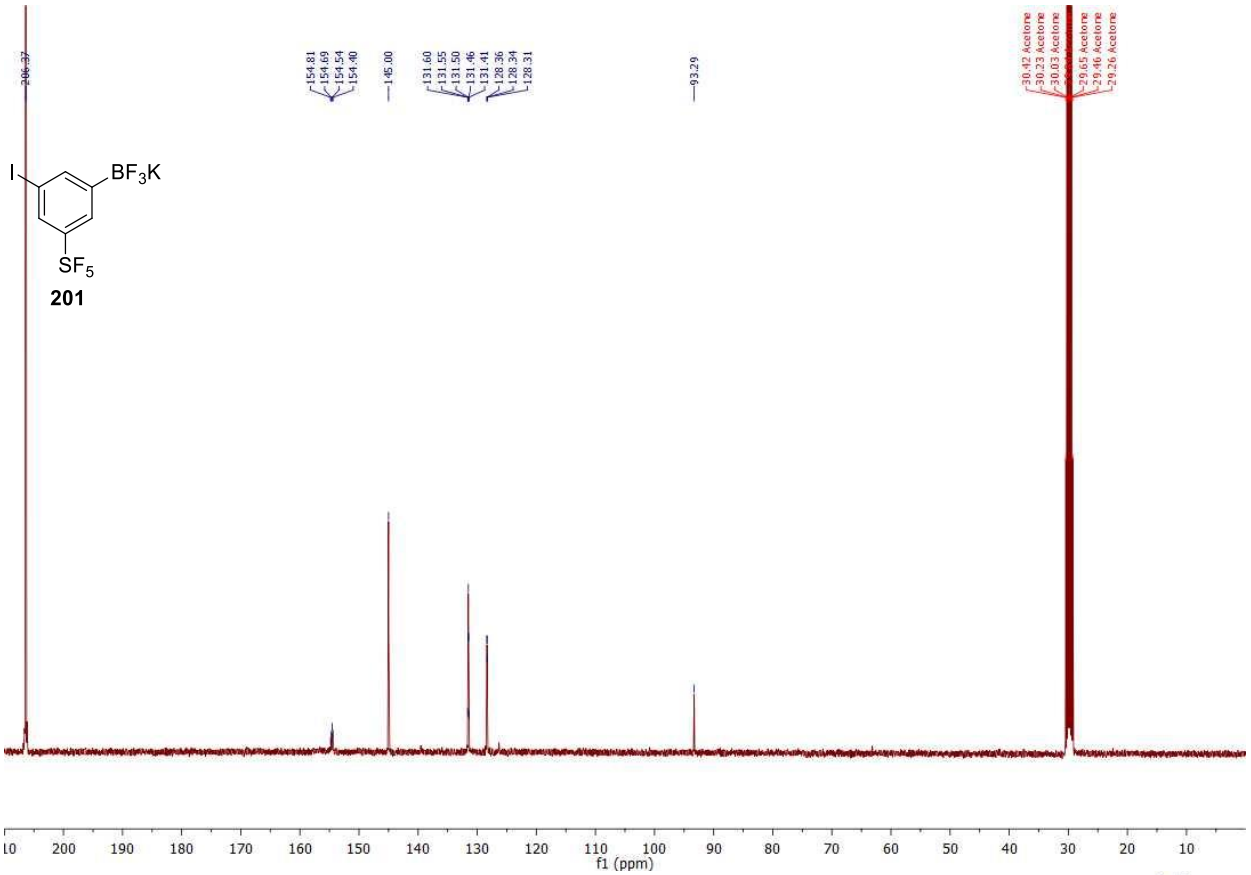
200

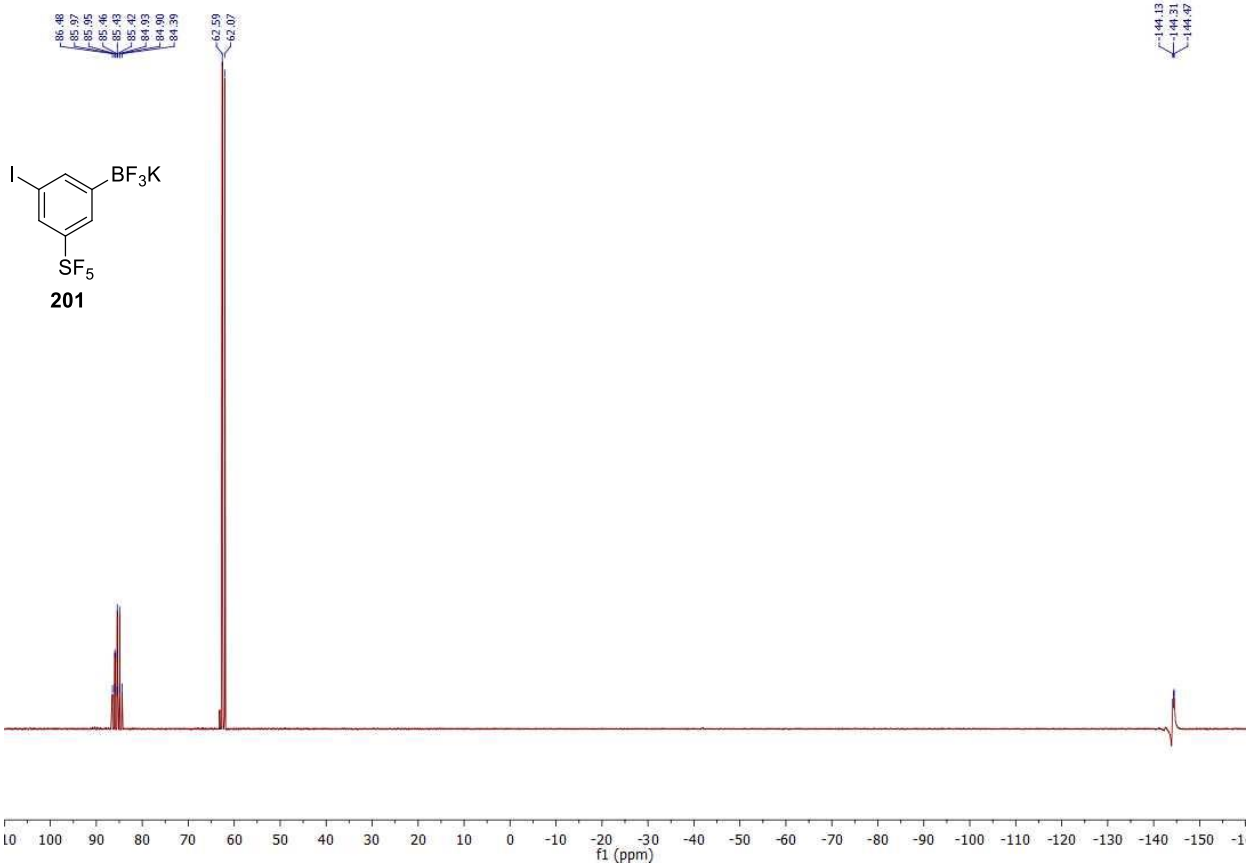




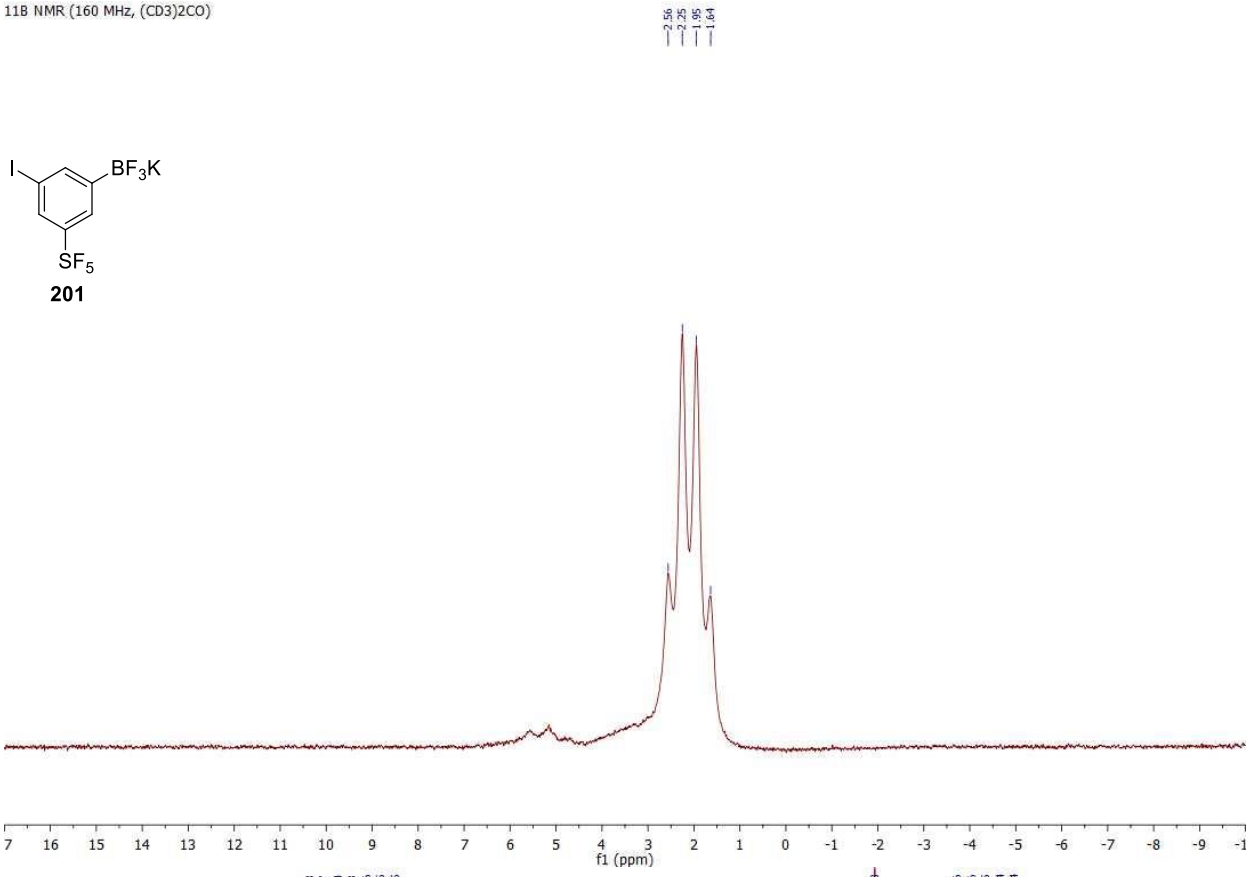
201



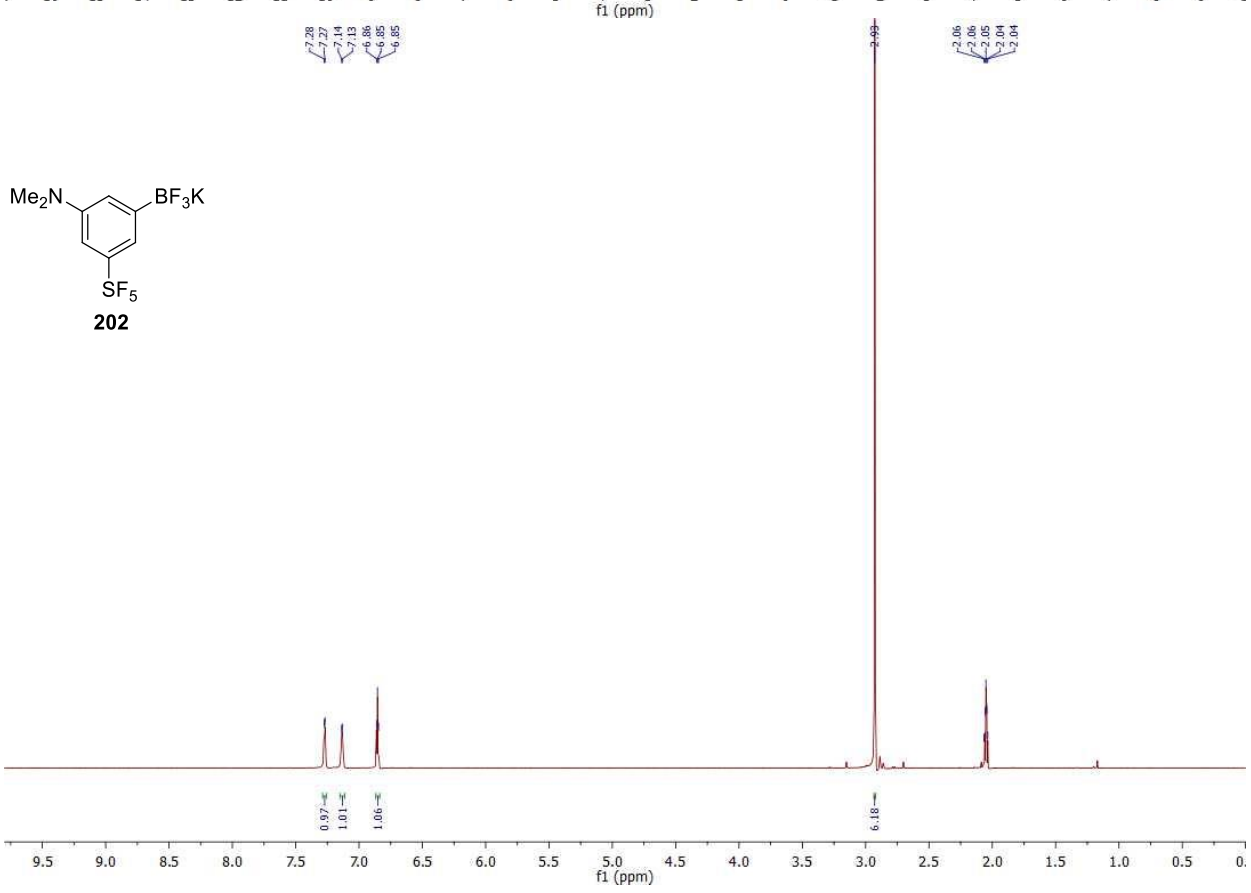

206.37
154.81
154.69
154.54
154.40
145.00
131.60
131.55
131.50
131.46
131.41
128.36
128.34
128.31
93.29
30.42 Acetone
30.23 Acetone
30.03 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
I
BF3K
SF5
201
f1 (ppm)


86.48
85.97
85.95
85.46
85.43
85.42
84.93
84.90
84.39
62.59
62.07
144.13
144.31
144.49
I
BF3K
SF5
201
f1 (ppm)

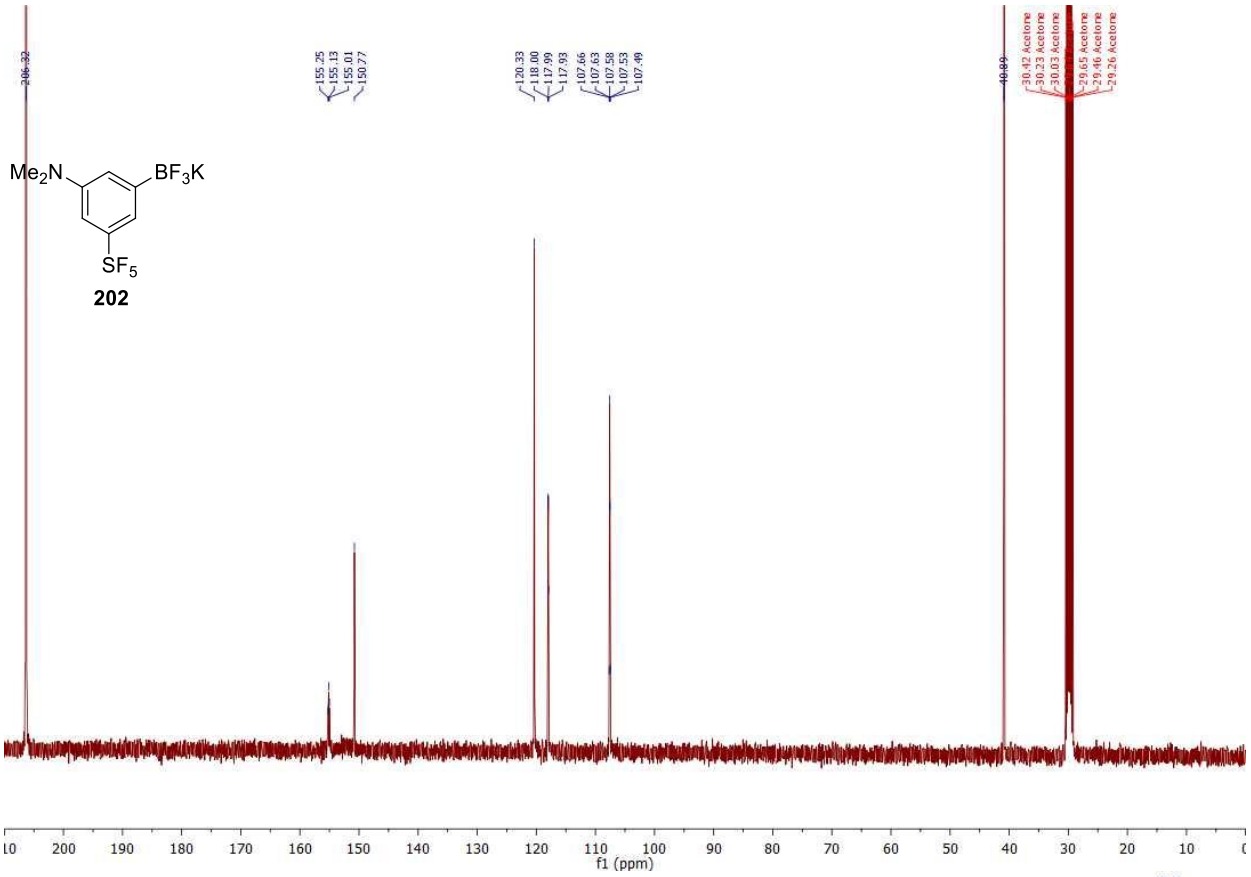
11B NMR (160 MHz, (CD3)2CO)

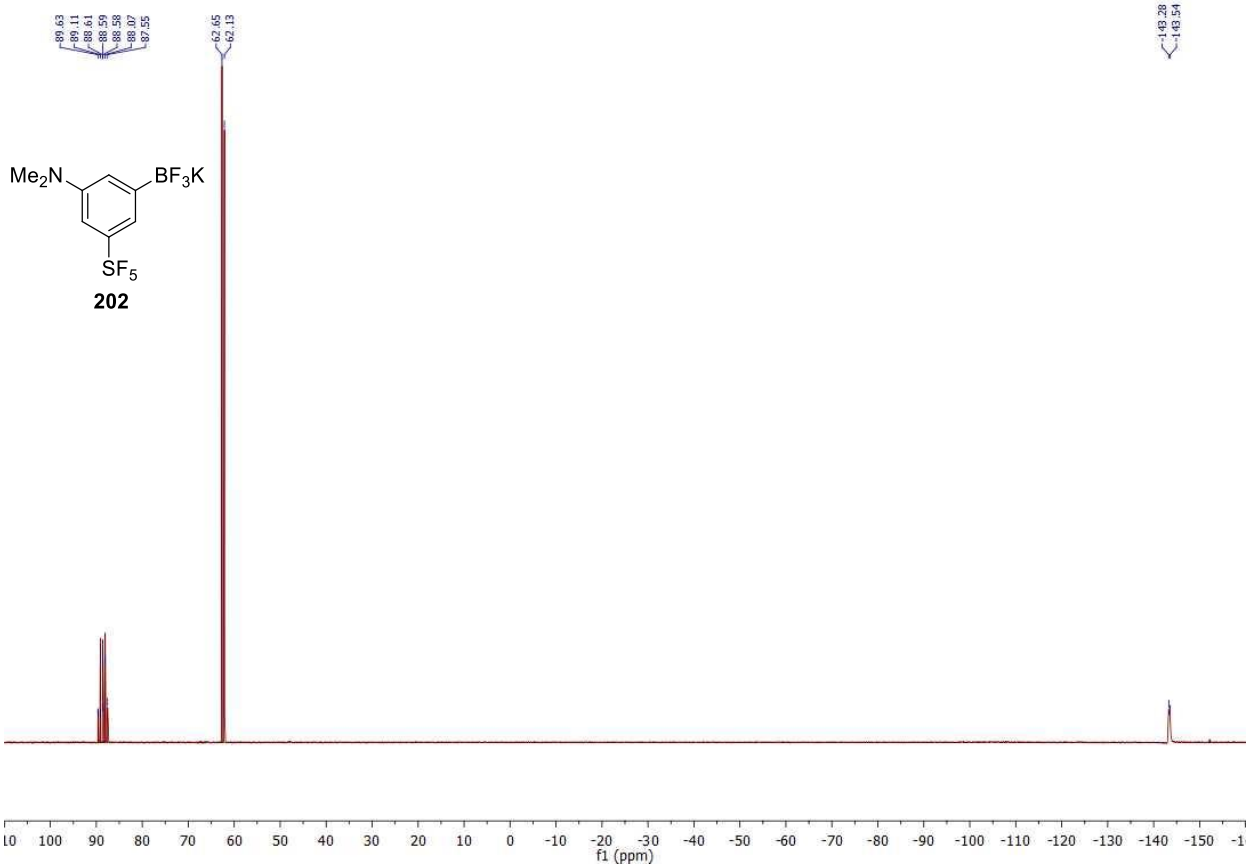


201

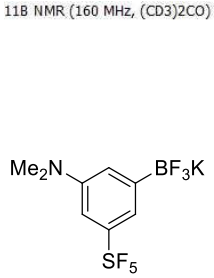


202

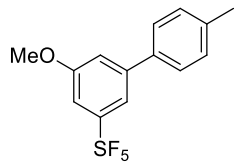

206.32
155.25
155.13
155.01
150.77
120.33
118.00
117.99
117.93
107.66
107.63
107.58
107.53
107.49
40.89
30.42 Acetone
30.23 Acetone
30.03 Acetone
29.65 Acetone
29.46 Acetone
29.26 Acetone
Me2N
BF3K
SF5
202
f1 (ppm)


89.63
89.11
88.61
88.59
88.58
88.07
87.55
62.65
62.13
-143.28
-143.54
Me2N
BF3K
SF5
202
f1 (ppm)

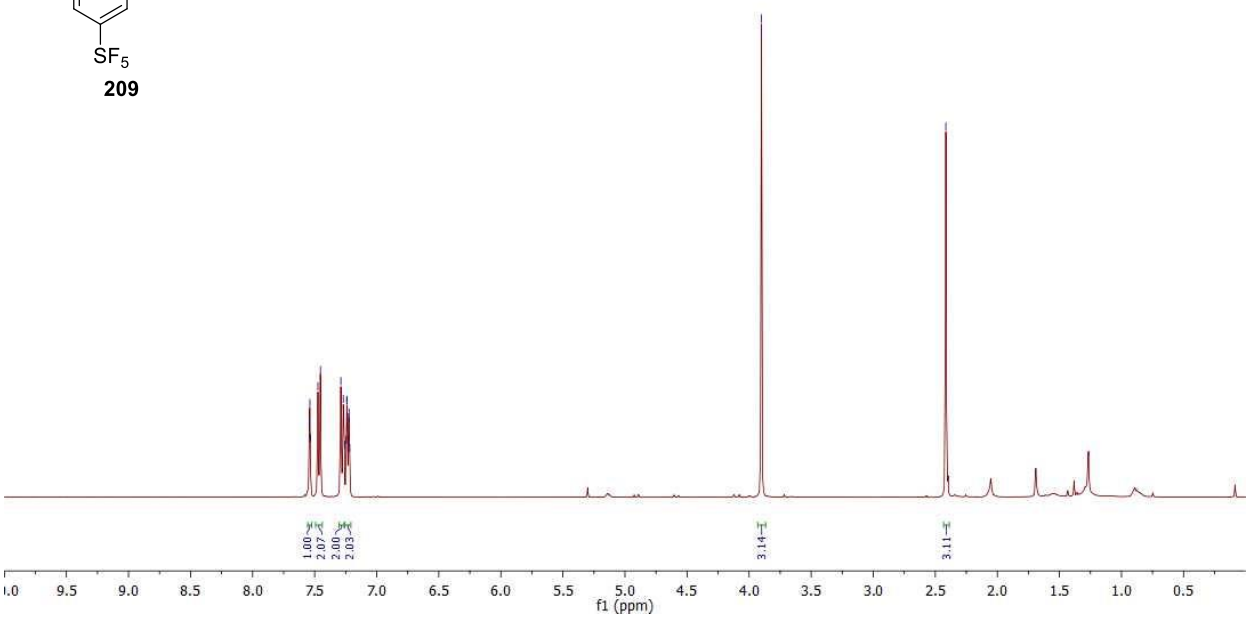
11B NMR (160 MHz, (CD3)2CO)

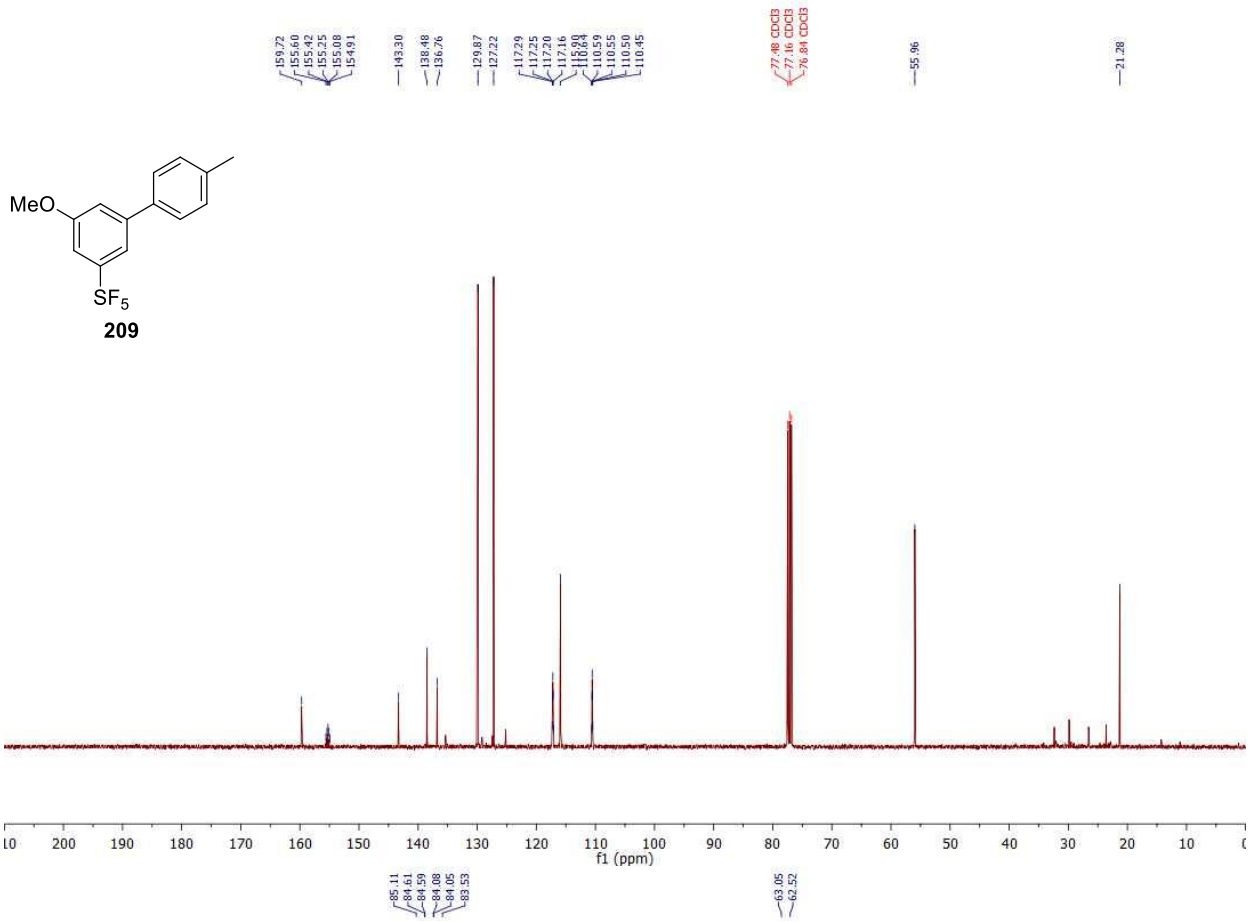


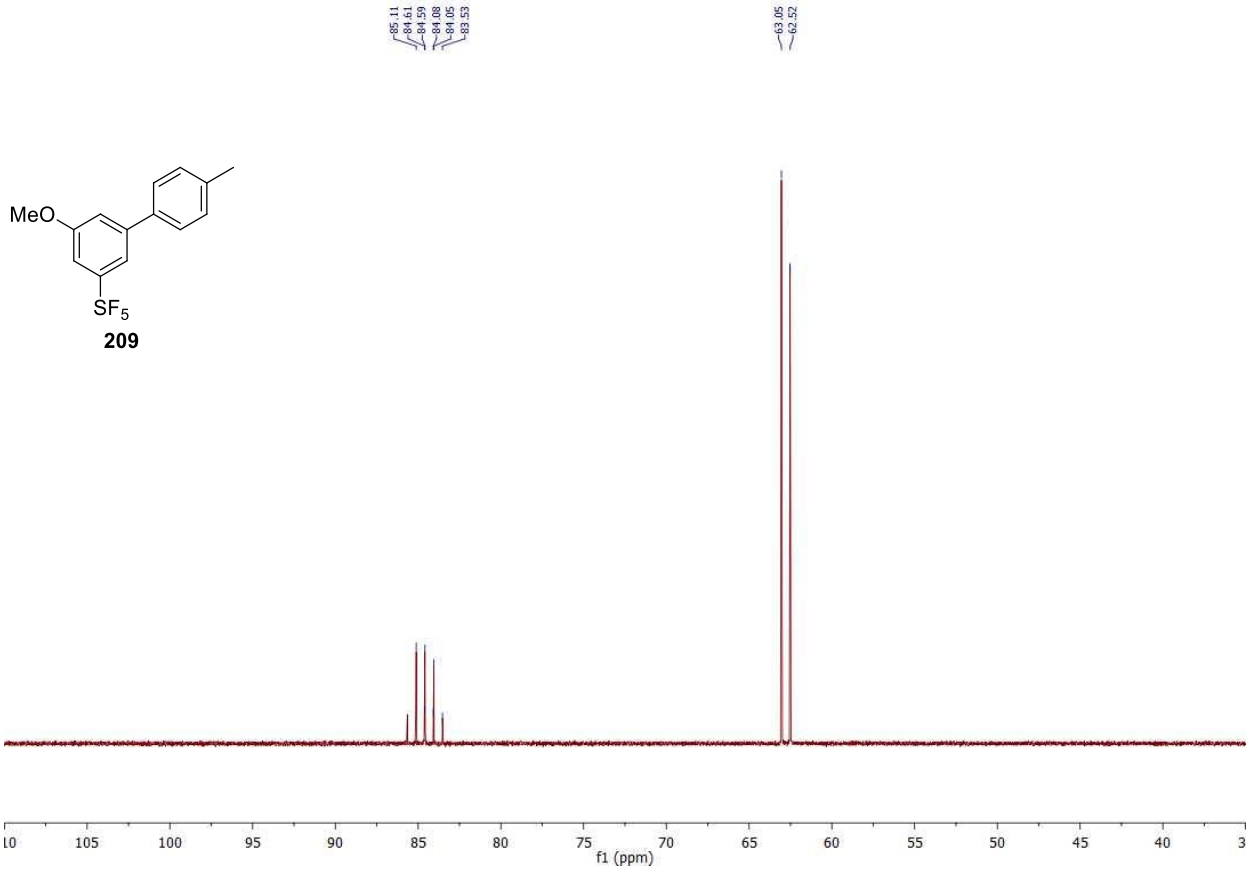
202

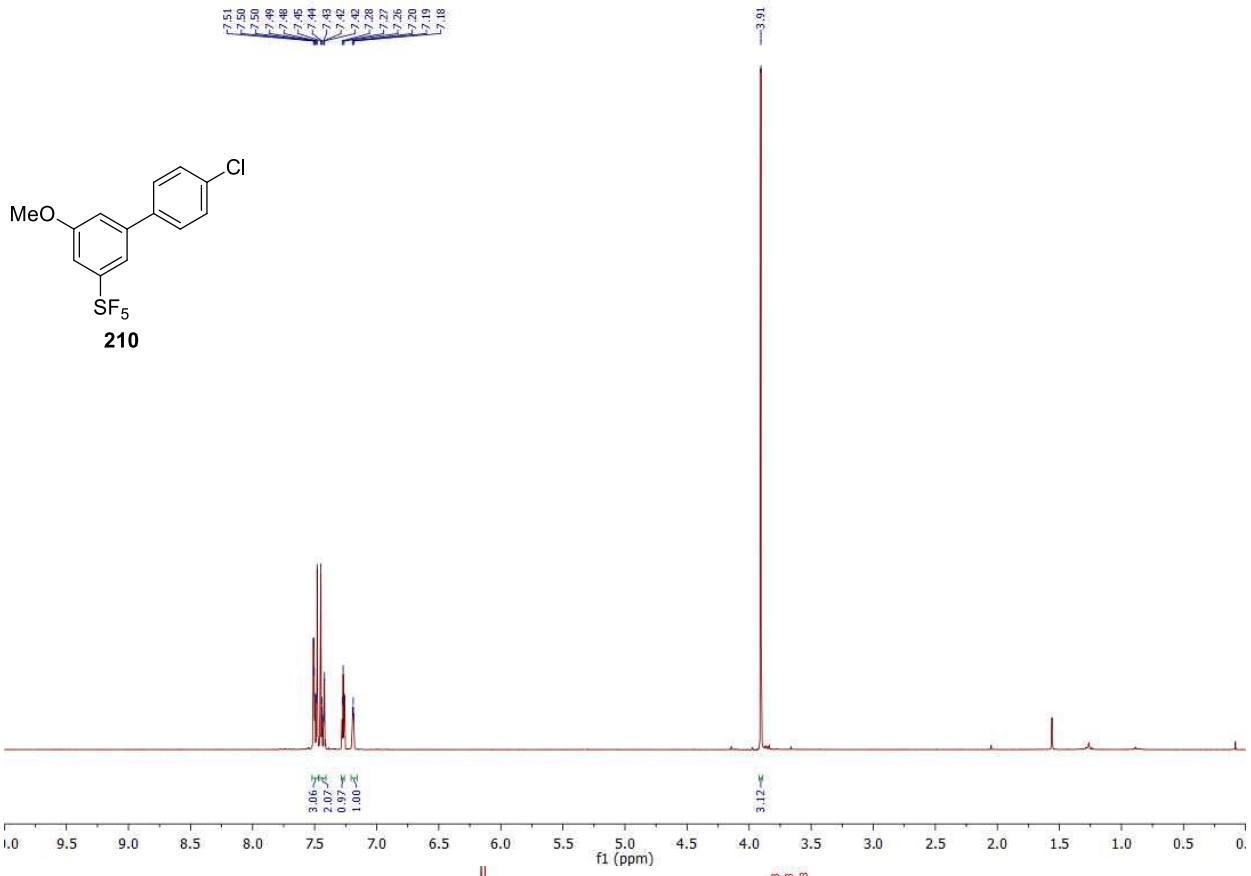


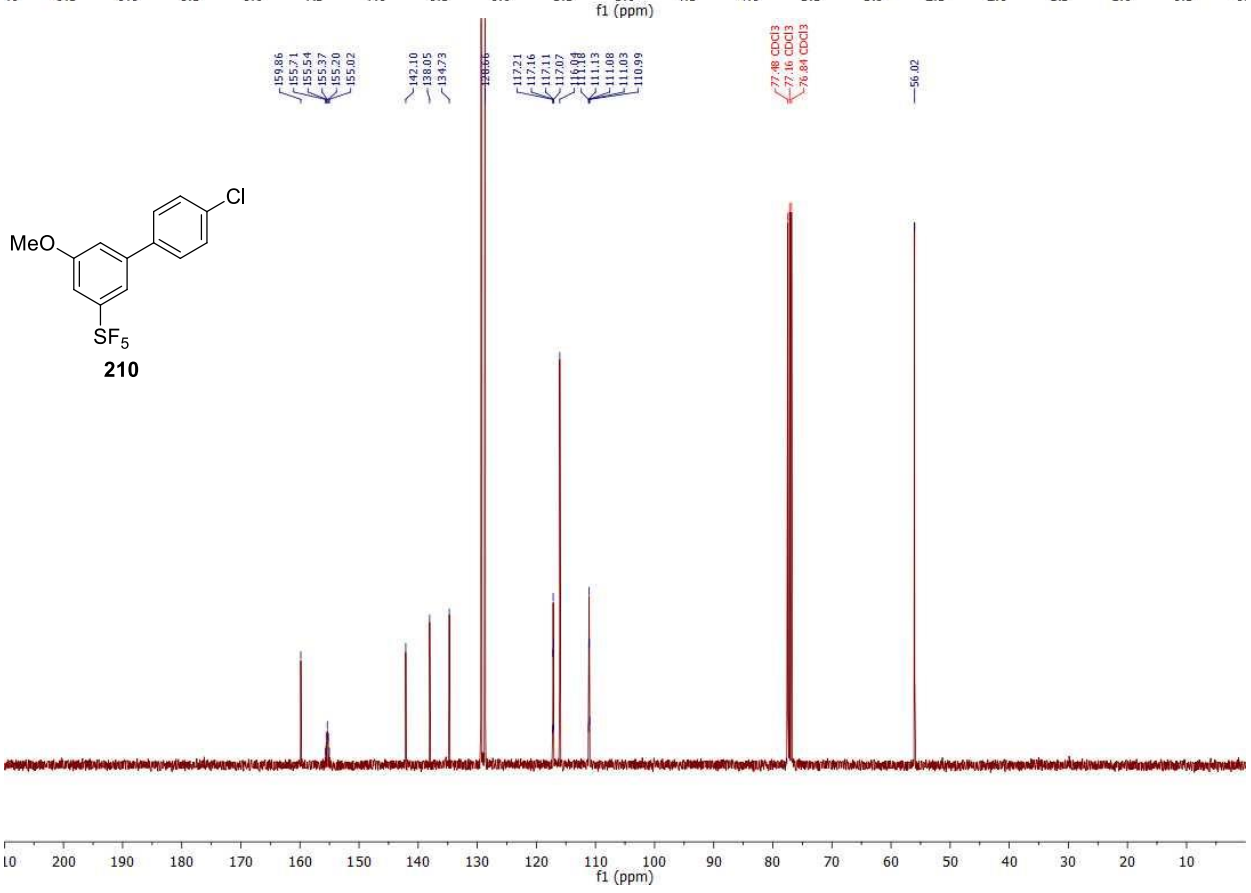
209

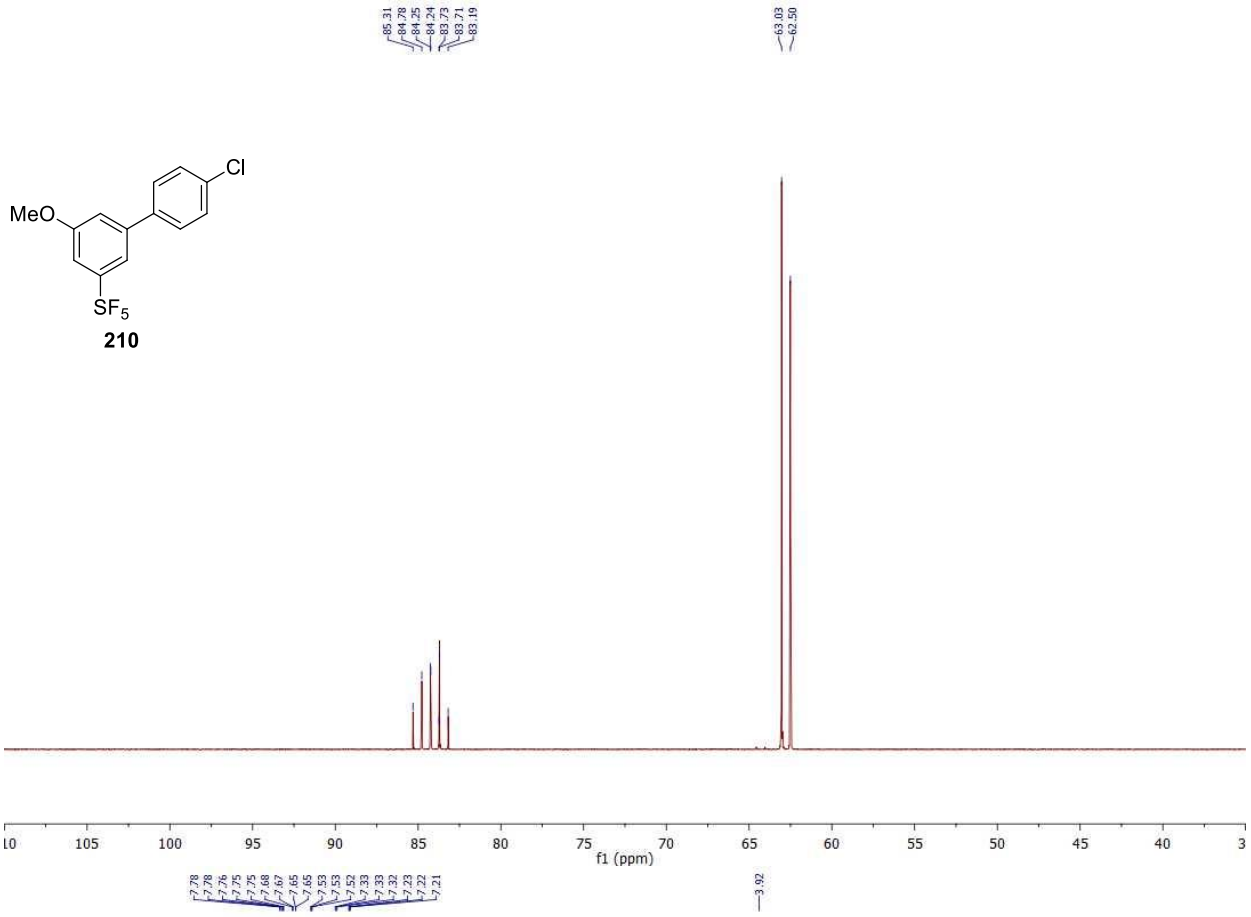


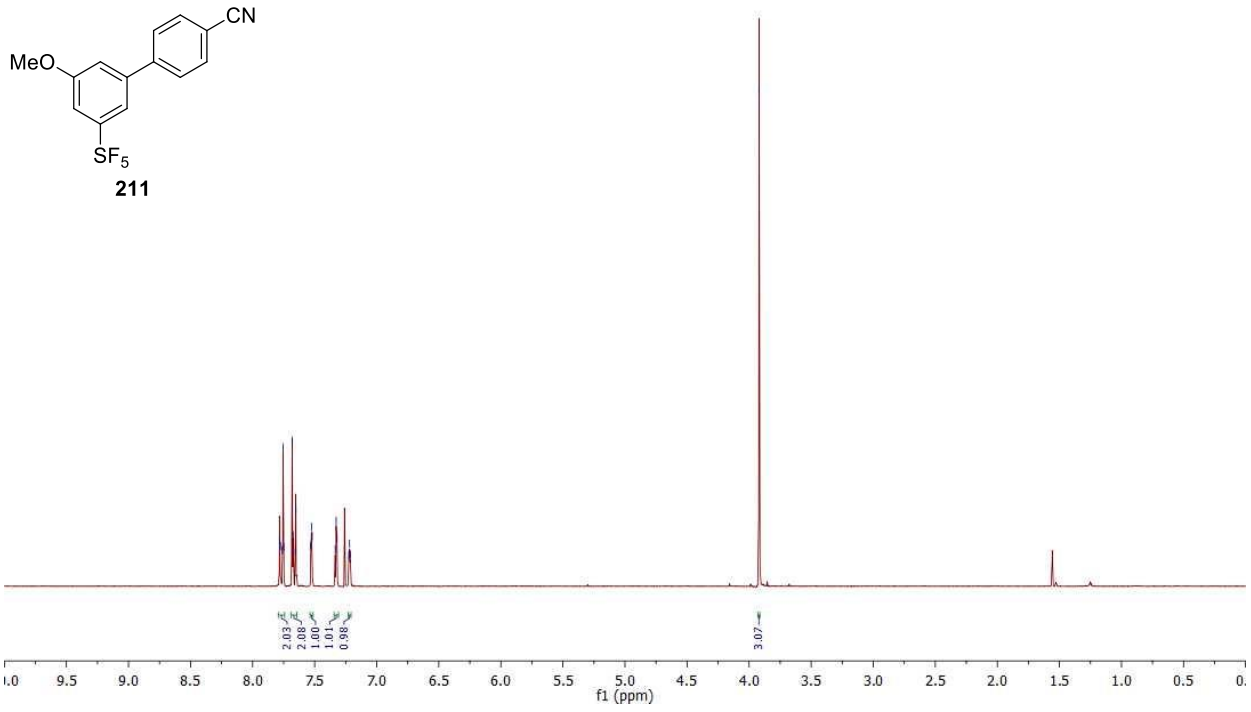

159.72
155.60
155.42
155.25
155.08
154.91
143.30
138.48
136.76
129.87
127.22
117.29
117.25
117.20
117.16
110.59
110.55
110.50
110.45
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.96
21.28
MeO
SF5
209
f1 (ppm)

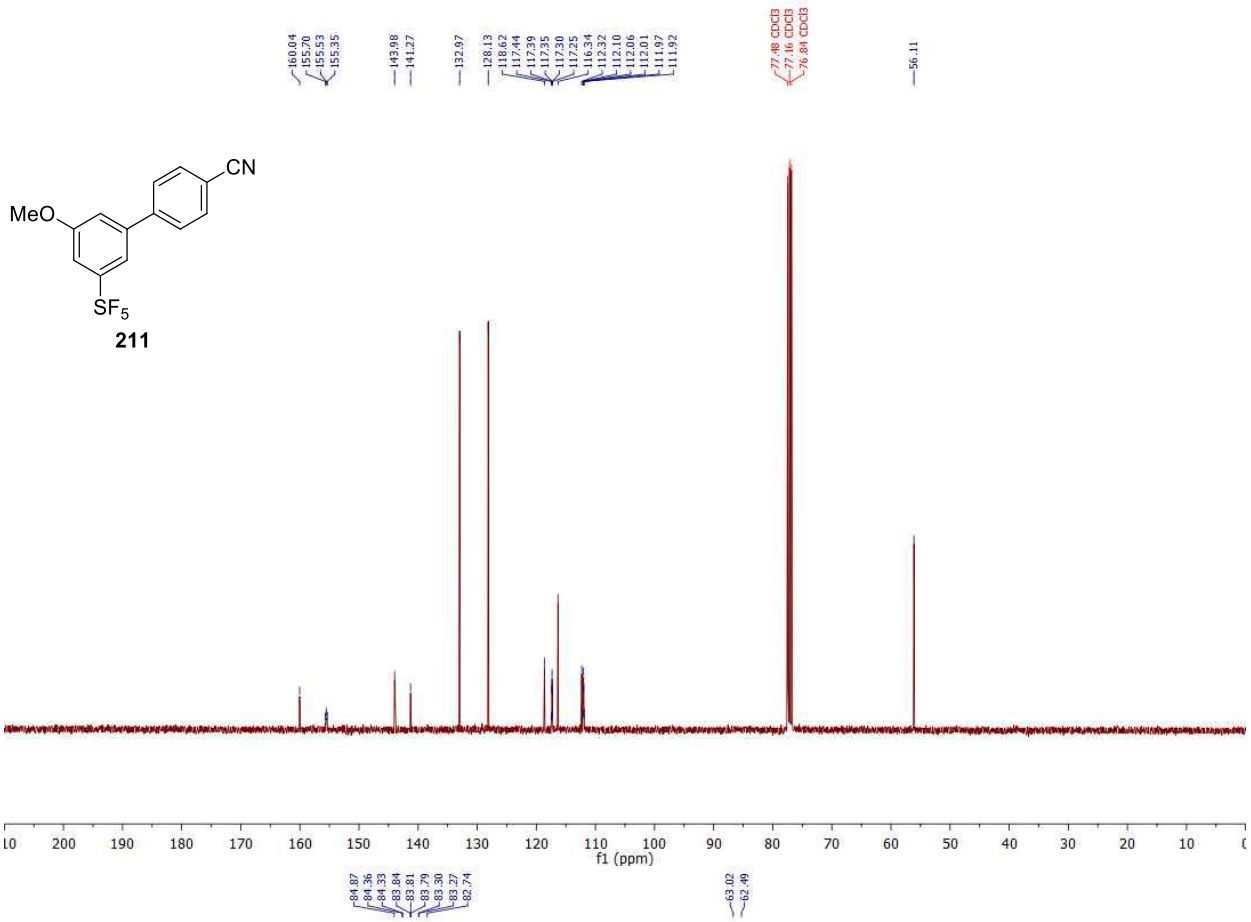

85.11
84.61
84.59
84.08
84.05
83.53
63.05
62.52
MeO
SF5
209
f1 (ppm)

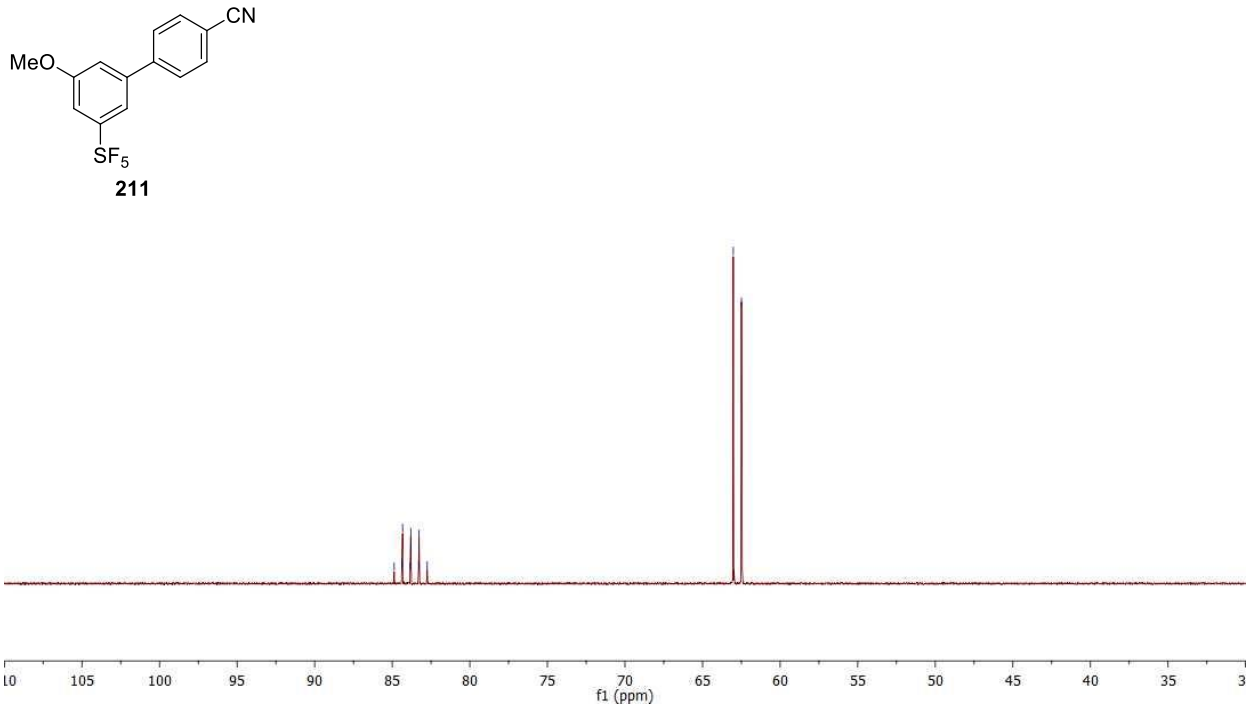

7.51
7.50
7.50
7.49
7.48
7.45
7.44
7.43
7.42
7.42
7.28
7.27
7.26
7.20
7.19
7.18
3.91
Cl
MeO
SF5
210
3.06
2.07
0.97
1.00
3.12
f1 (ppm)

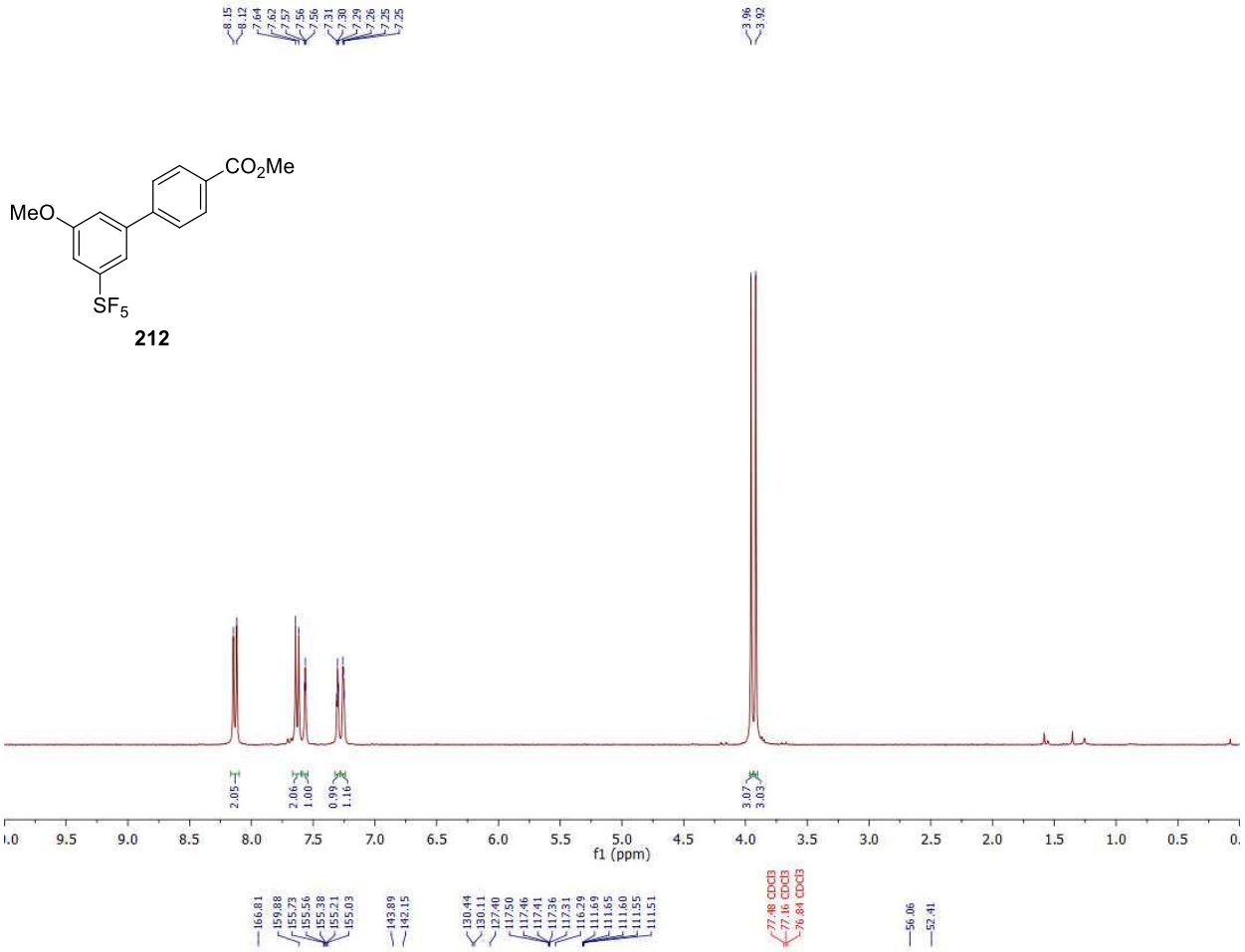

159.86
155.71
155.54
155.37
155.20
155.02
142.10
138.05
134.73
128.66
117.21
117.16
117.11
117.07
111.13
111.08
111.03
110.99
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.02
Cl
MeO
SF5
210
f1 (ppm)

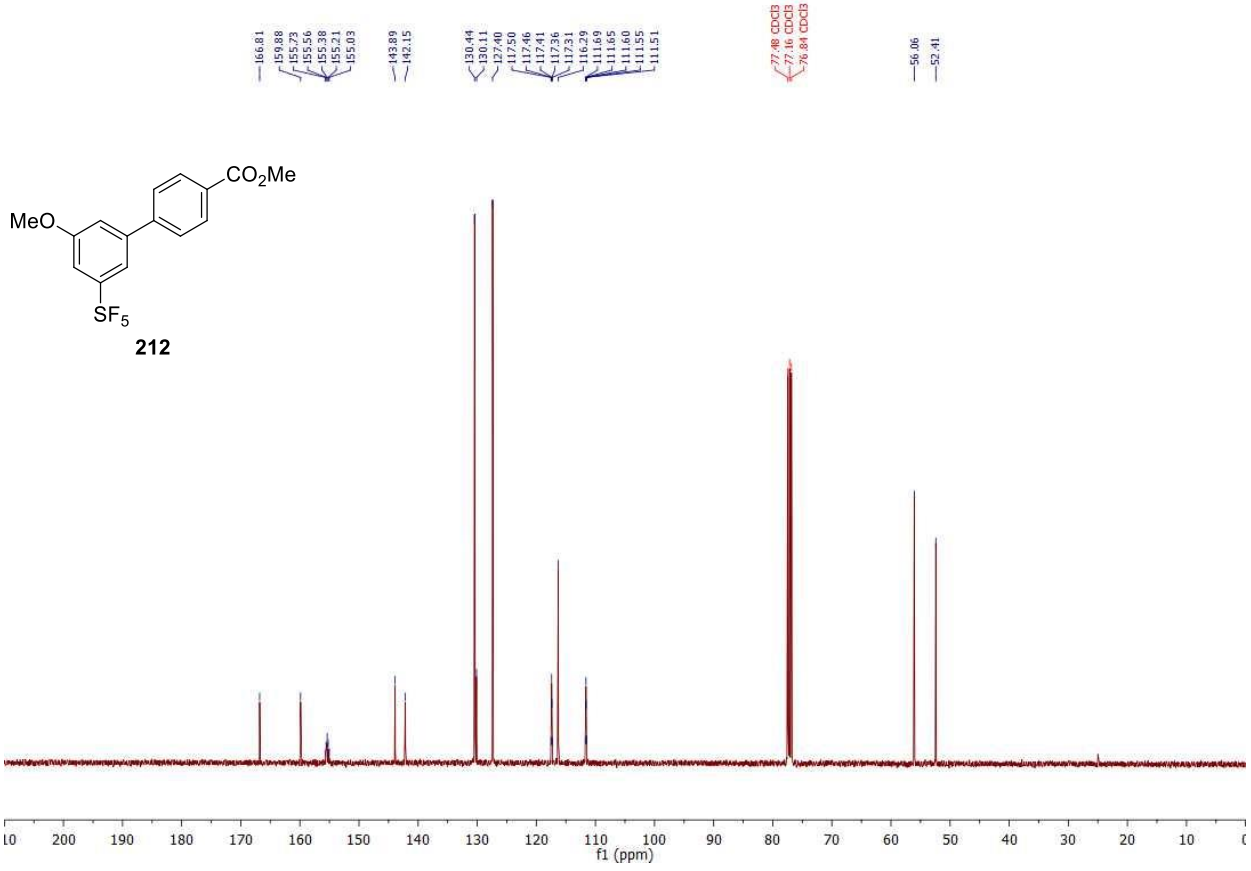

85.31
84.78
84.25
84.24
83.73
83.71
83.19
63.03
62.50
Cl
MeO
SF5
210
f1 (ppm)
7.78
7.76
7.75
7.68
7.67
7.65
7.53
7.52
7.33
7.32
7.23
7.22
7.21
3.92

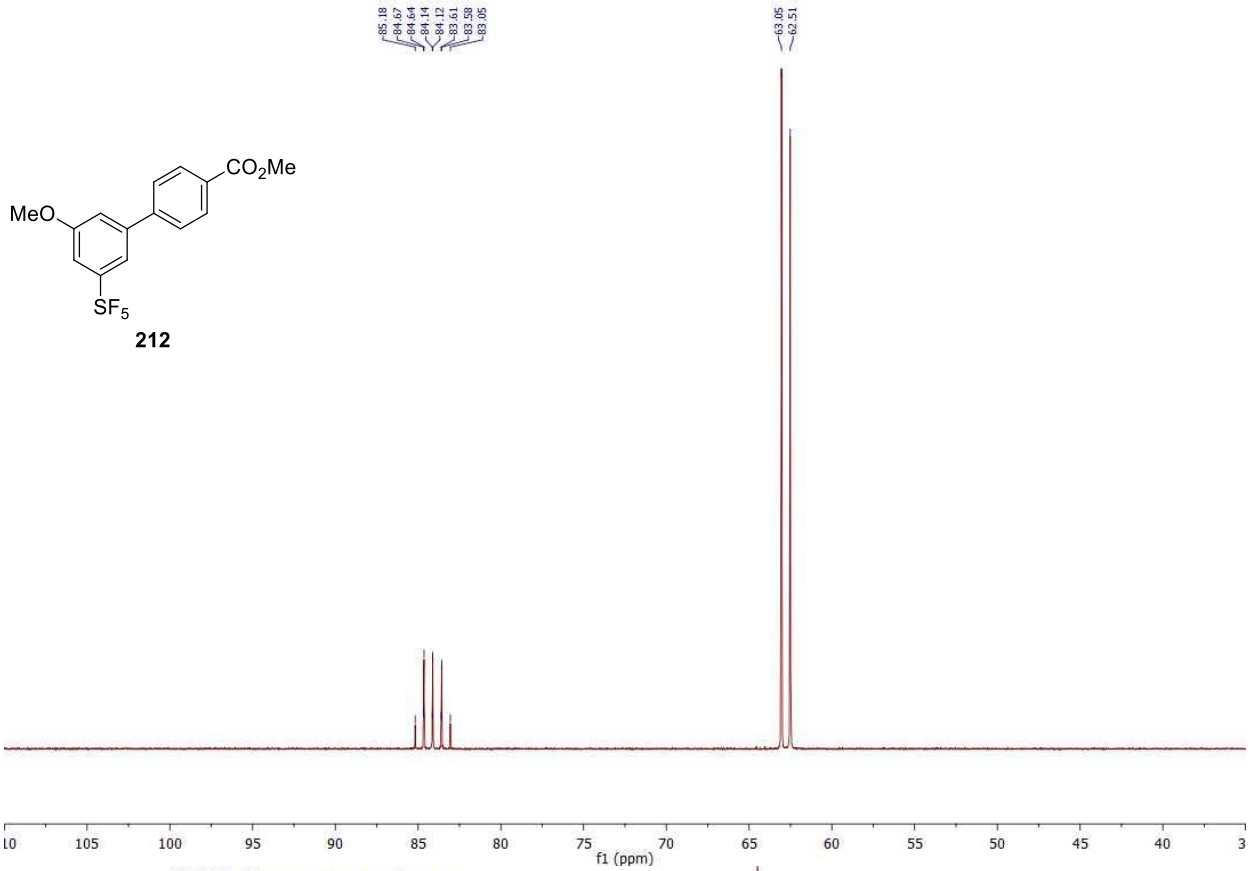

CN
MeO
SF5
211
f1 (ppm)
2.03
2.08
1.00
1.01
0.98
3.07


160.04
155.70
155.53
155.35
143.98
141.27
132.97
128.13
118.62
117.44
117.39
117.35
117.30
117.25
116.34
112.32
112.10
112.06
112.01
111.97
111.92
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.11
CN
MeO
SF5
211
f1 (ppm)

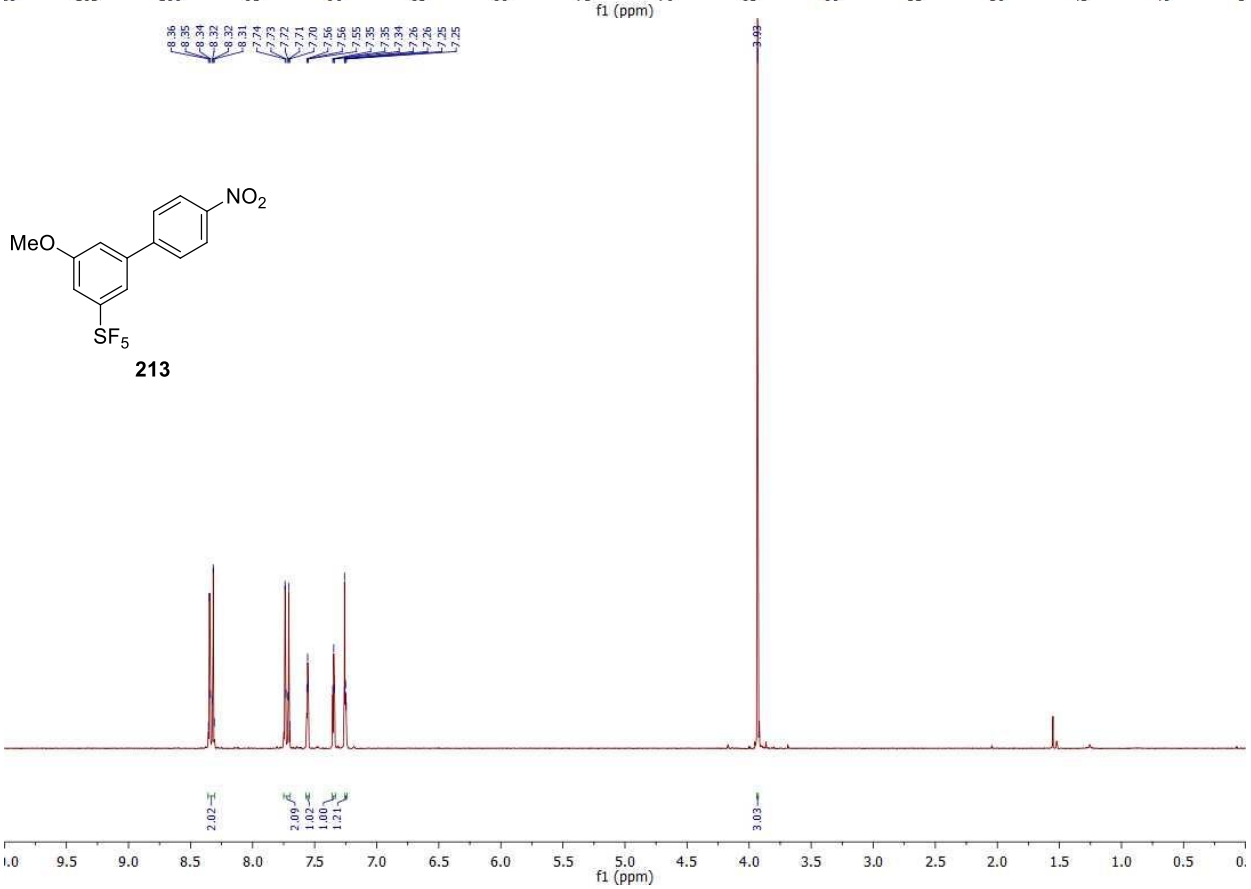

84.87
84.36
84.33
83.84
83.81
83.79
83.30
83.27
82.74
63.02
62.49
CN
MeO
SF5
211
f1 (ppm)


8.15
8.12
7.64
7.62
7.57
7.56
7.56
7.31
7.30
7.29
7.26
7.25
7.25
3.96
3.92
CO2Me
MeO
SF5
212
2.05
2.06
1.00
0.99
1.16
3.07
3.03
f1 (ppm)

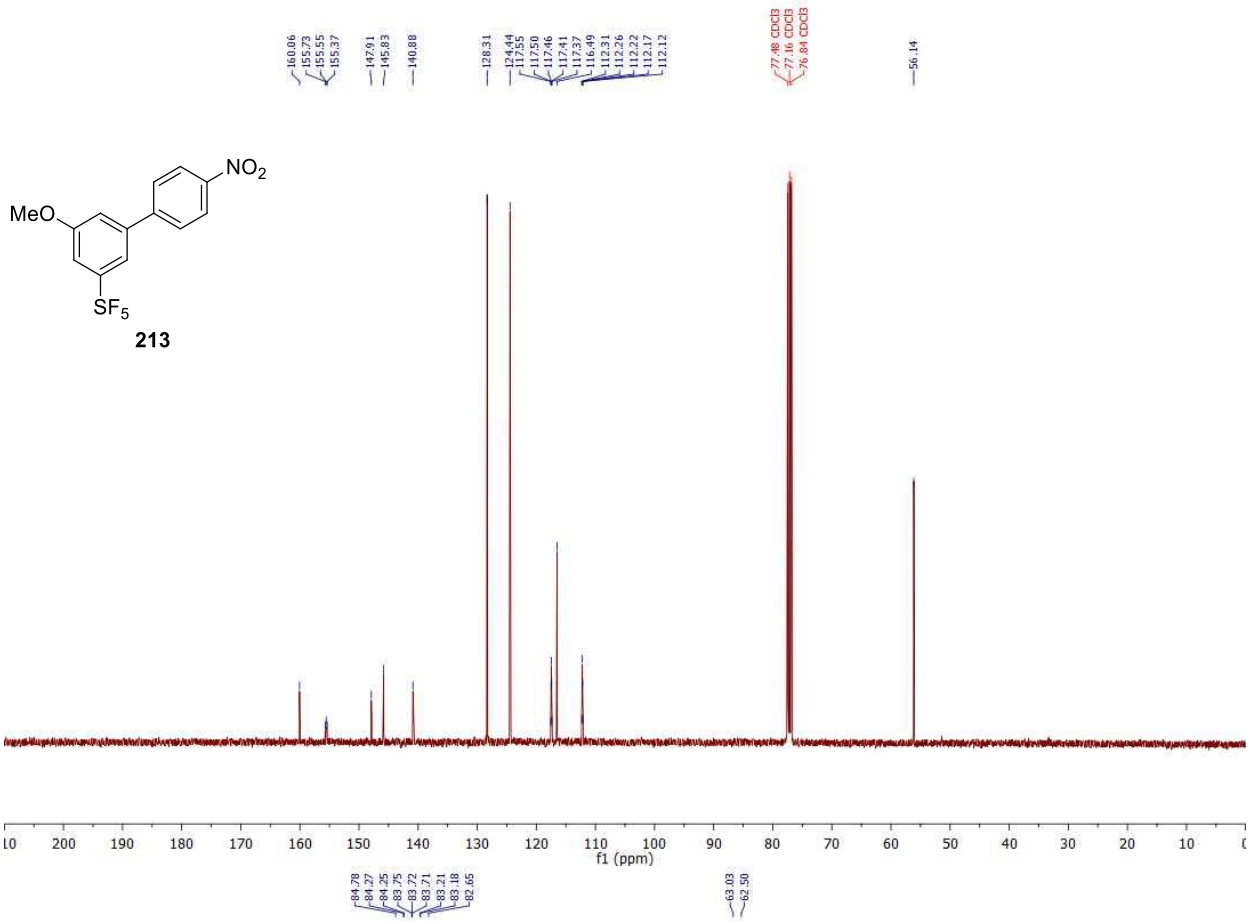

166.81
159.88
155.73
155.56
155.38
155.21
155.03
143.89
142.15
130.44
130.11
127.40
117.50
117.46
117.41
117.36
117.31
116.29
111.69
111.65
111.60
111.55
111.51
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.06
52.41
CO2Me
MeO
SF5
212
f1 (ppm)

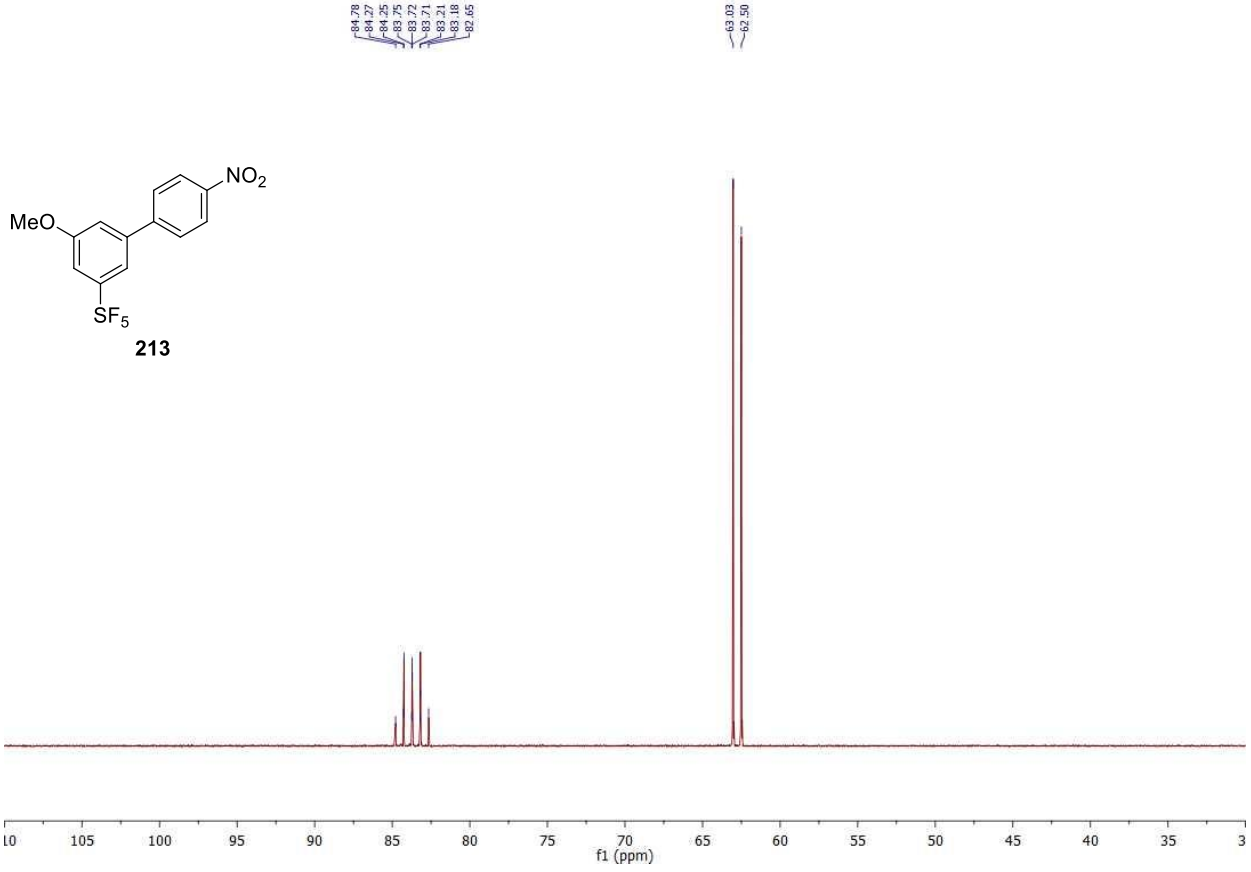

85.18
84.67
84.64
84.14
84.12
83.61
83.58
83.05
63.05
62.51
CO2Me
MeO
SF5
f1 (ppm)

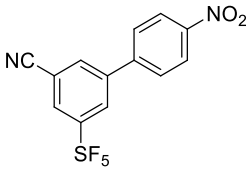
212


8.36
8.35
8.34
8.32
8.31
7.74
7.73
7.72
7.71
7.70
7.56
7.55
7.35
7.34
7.26
7.25
7.25
3.03
NO2
MeO
SF5
2.02
2.09
1.02
1.00
1.21
3.03
f1 (ppm)

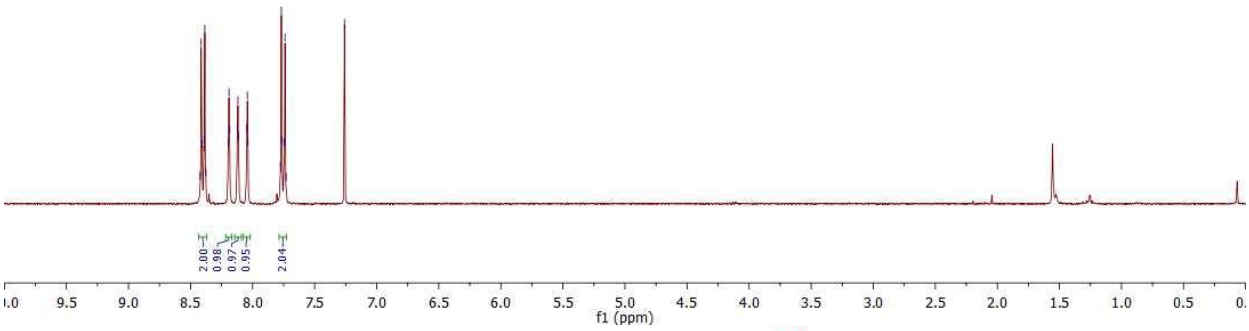
213

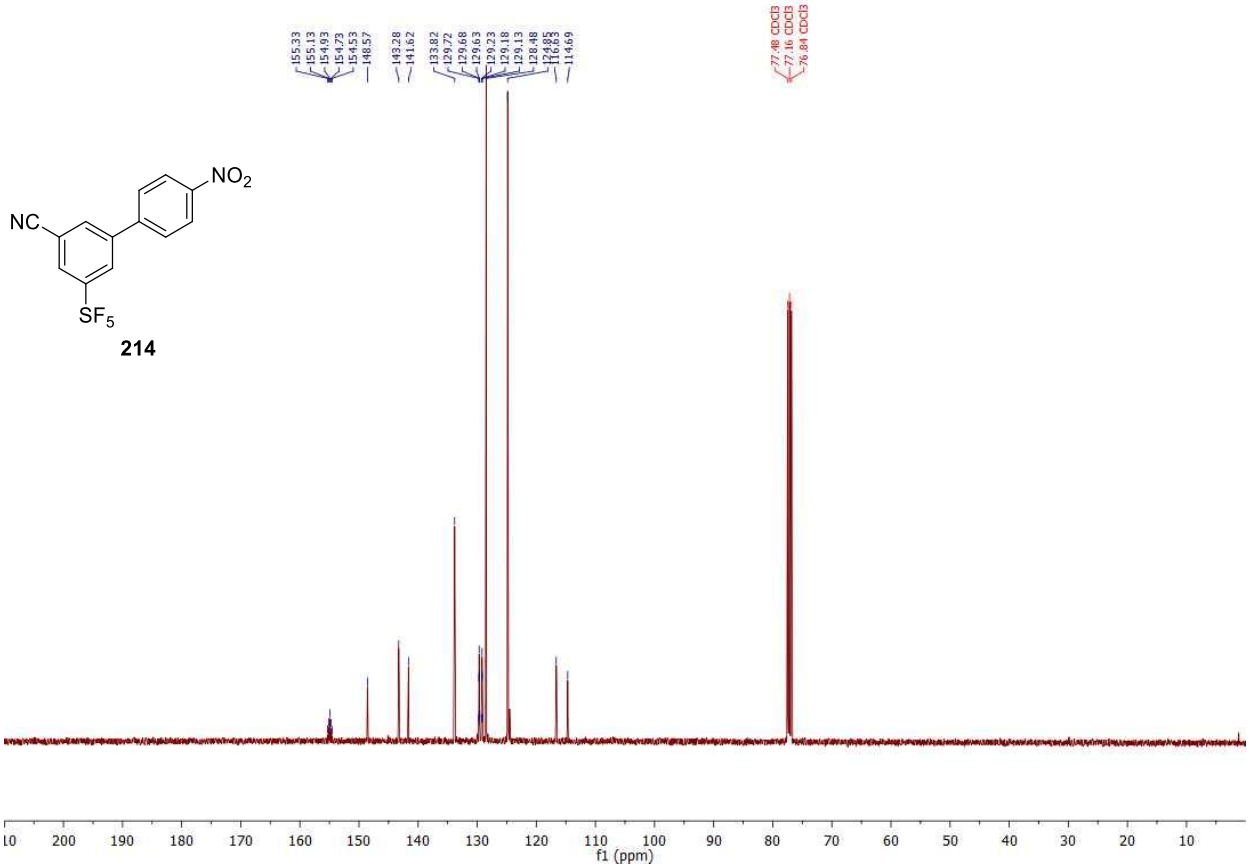

160.06
155.73
155.55
155.37
147.91
145.83
140.88
128.31
124.44
117.55
117.50
117.46
117.41
117.37
116.49
112.31
112.26
112.22
112.17
112.12
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.14
NO2
MeO
SF5
213
f1 (ppm)


84.78
84.27
84.25
83.75
83.72
83.71
83.21
83.18
82.65
63.03
62.50
NO2
MeO
SF5
213
f1 (ppm)


NO2
NC
SF5

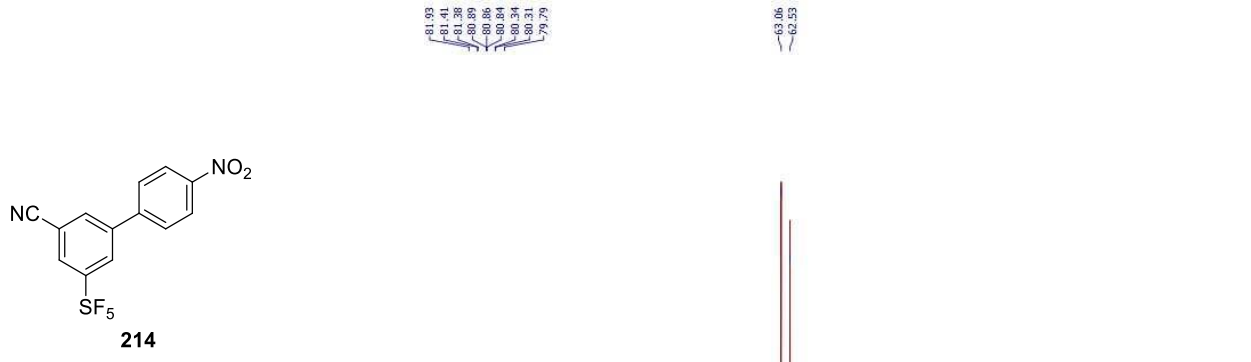
214


2.00
0.98
0.97
0.95
2.04
f1 (ppm)


155.33
155.13
154.93
154.73
154.53
148.57
143.28
141.62
133.82
129.72
129.68
129.63
129.23
129.18
129.13
128.48
114.69
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
f1 (ppm)

NO2
NC
SF5

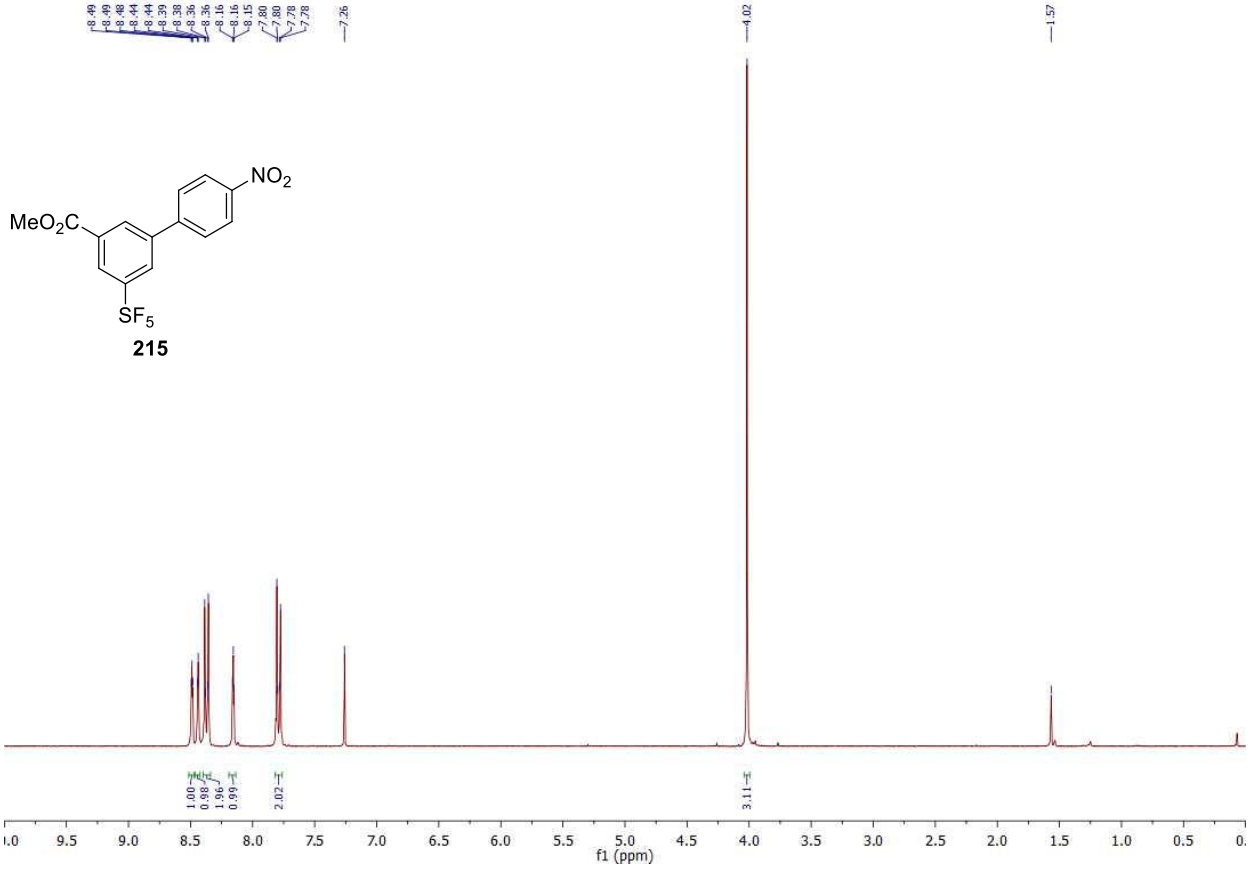
214


81.93
81.41
81.38
80.89
80.86
80.84
80.34
80.31
79.79
63.06
62.53

NO2
NC
SF5

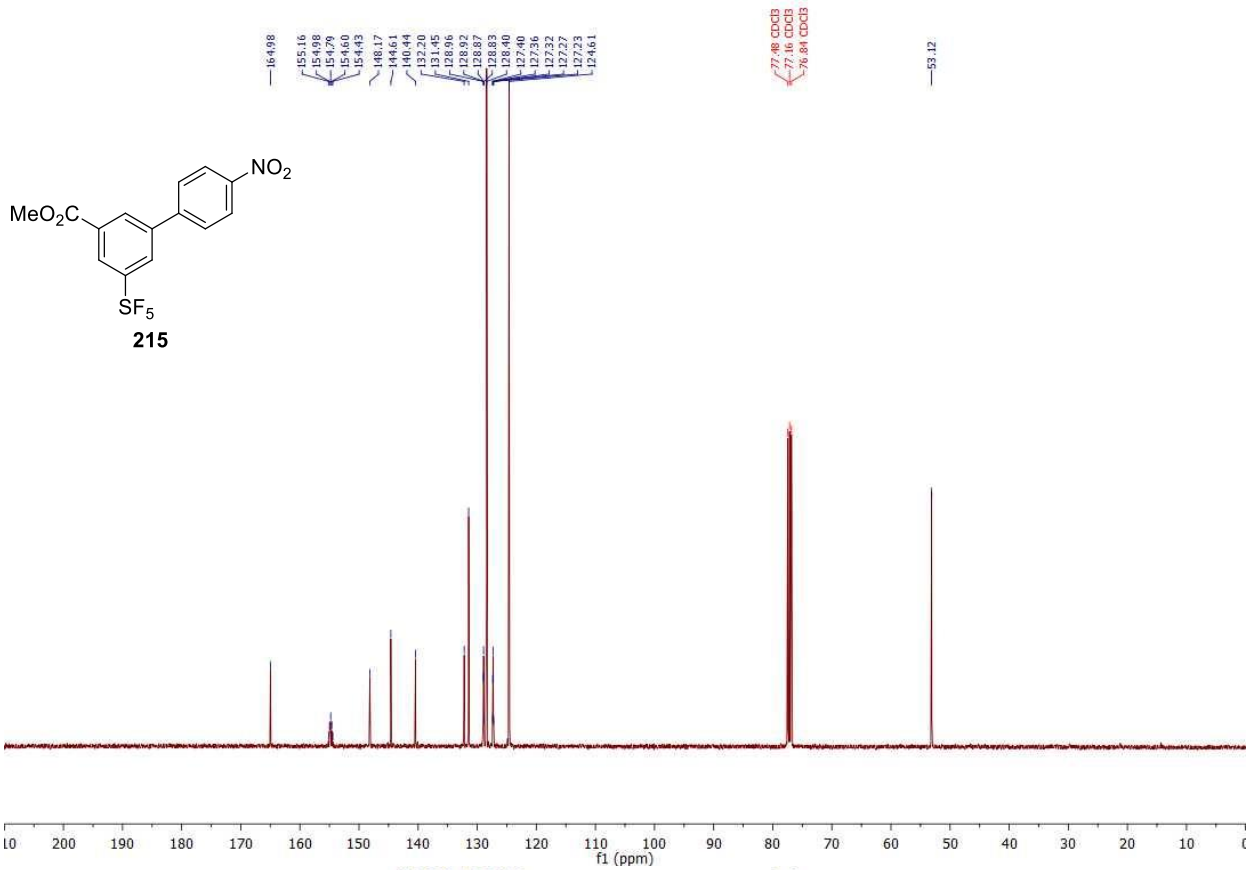
214

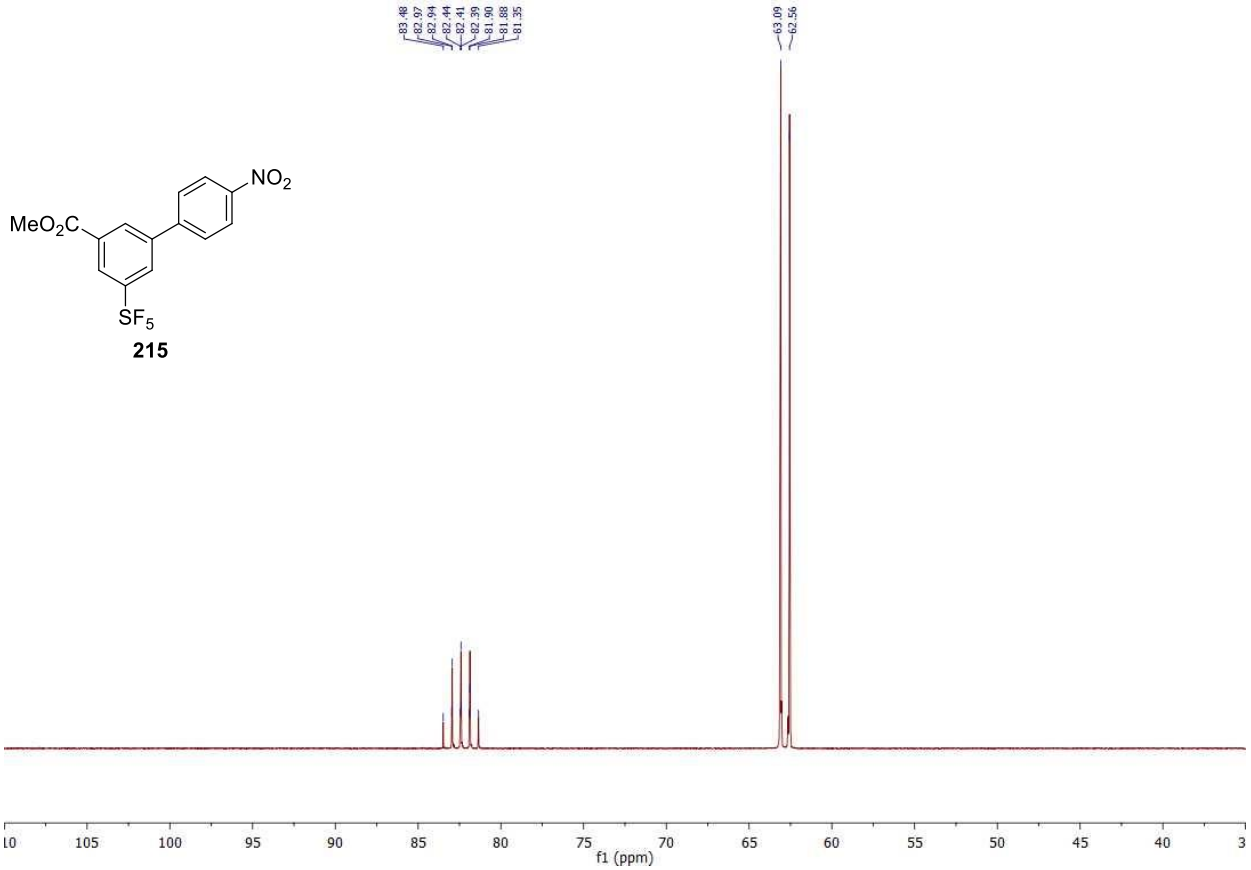
f1 (ppm)

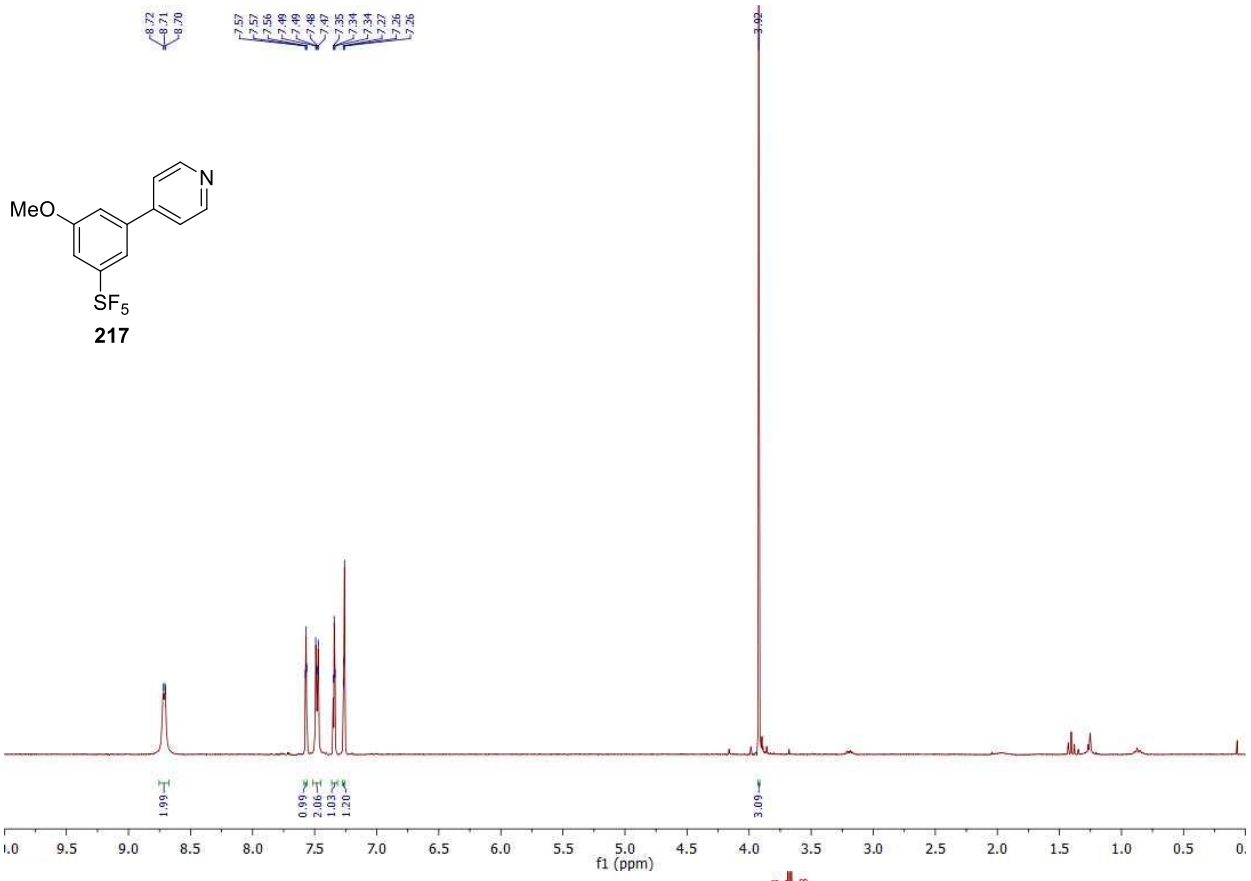

8.49
8.49
8.48
8.44
8.44
8.39
8.38
8.36
8.36
8.16
8.15
7.80
7.78
7.78
7.26
4.02
1.57
1.00
0.98
1.96
0.99
2.02
3.11
f1 (ppm)

NO2
MeO2C
SF5

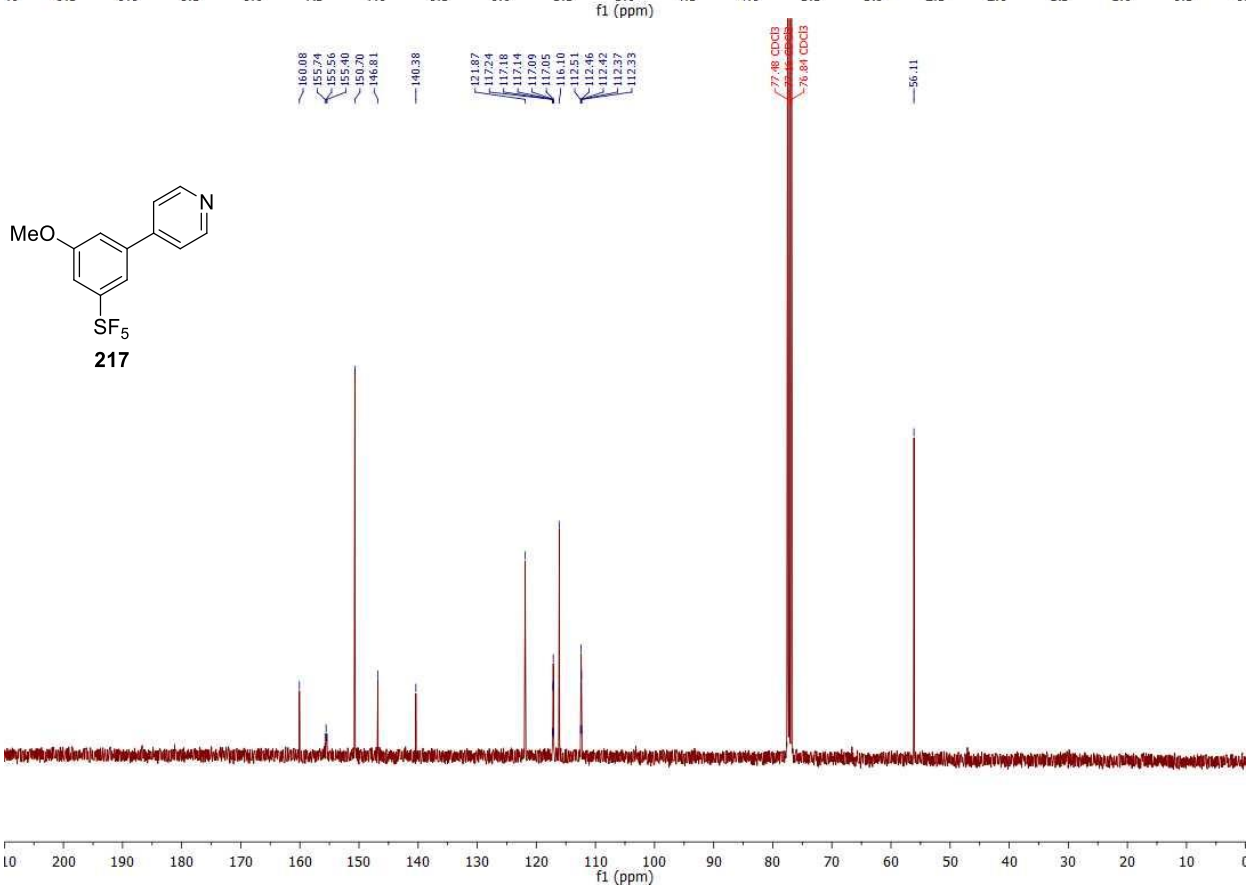
215


164.98
155.16
154.98
154.79
154.60
154.43
148.17
144.61
140.44
132.20
131.45
128.96
128.92
128.87
128.83
128.40
127.40
127.36
127.32
127.27
127.23
124.61
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
53.12
MeO2C
NO2
SF5
215
f1 (ppm)

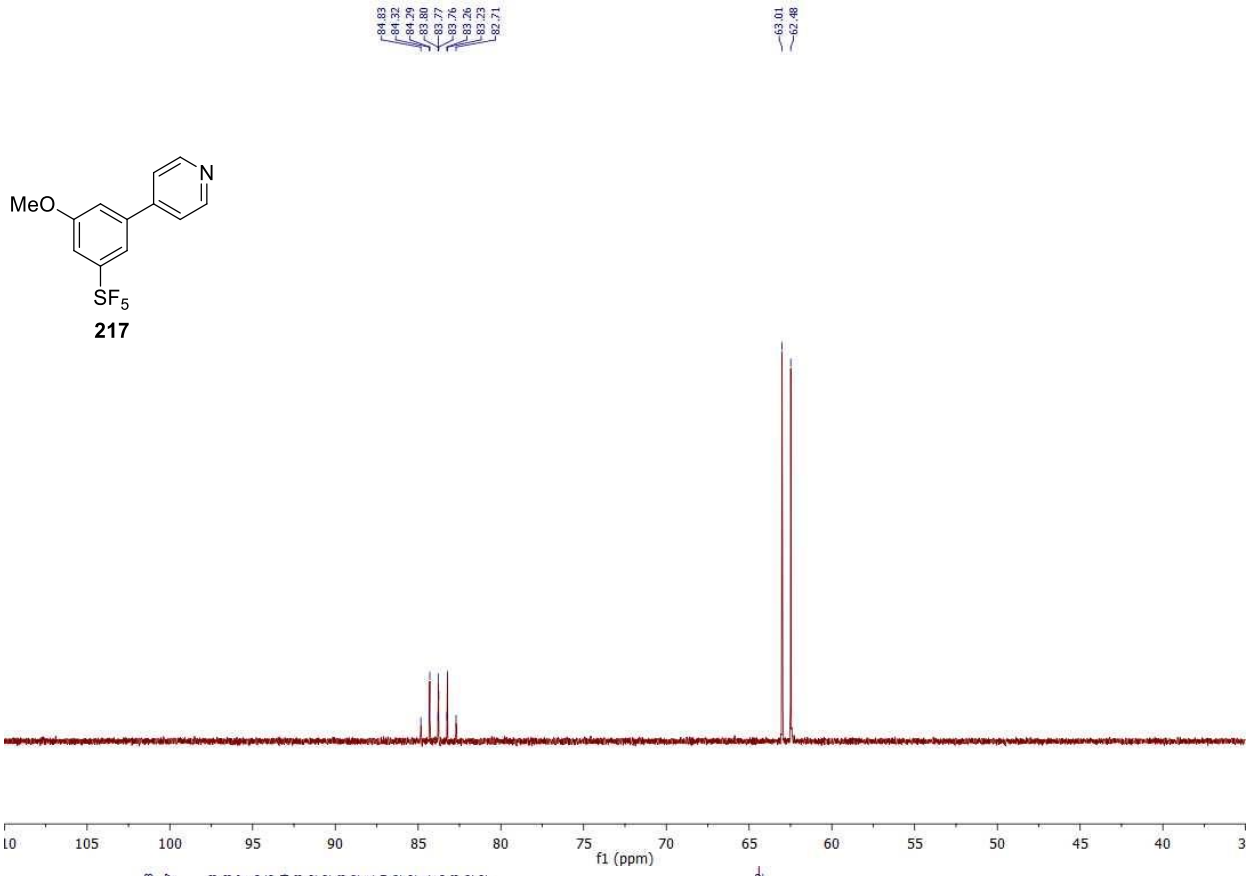

83.48
82.97
82.94
82.44
82.41
82.39
81.90
81.88
81.35
63.09
62.56
MeO2C
NO2
SF5
215
f1 (ppm)


8.72
8.71
8.70
7.57
7.57
7.56
7.49
7.49
7.48
7.47
7.35
7.34
7.34
7.27
7.26
7.26
3.93
MeO
N
SF5
1.99
0.99
2.06
1.03
1.20
3.09
f1 (ppm)

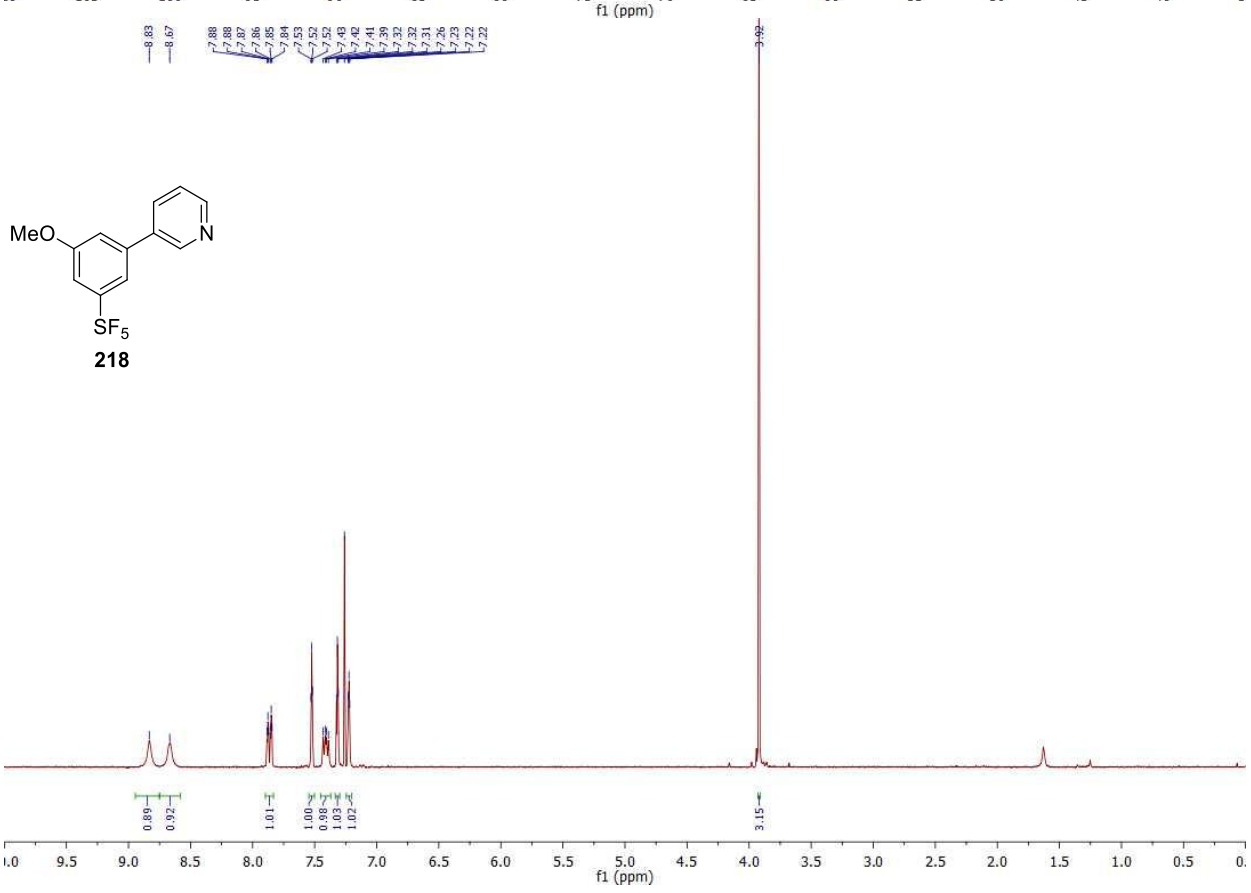
217


160.08
155.74
155.56
155.40
150.70
146.81
140.38
121.87
117.24
117.18
117.14
117.09
117.05
116.10
112.51
112.46
112.42
112.37
112.33
77.48 CDCl3
76.84 CDCl3
56.11
MeO
N
SF5
f1 (ppm)

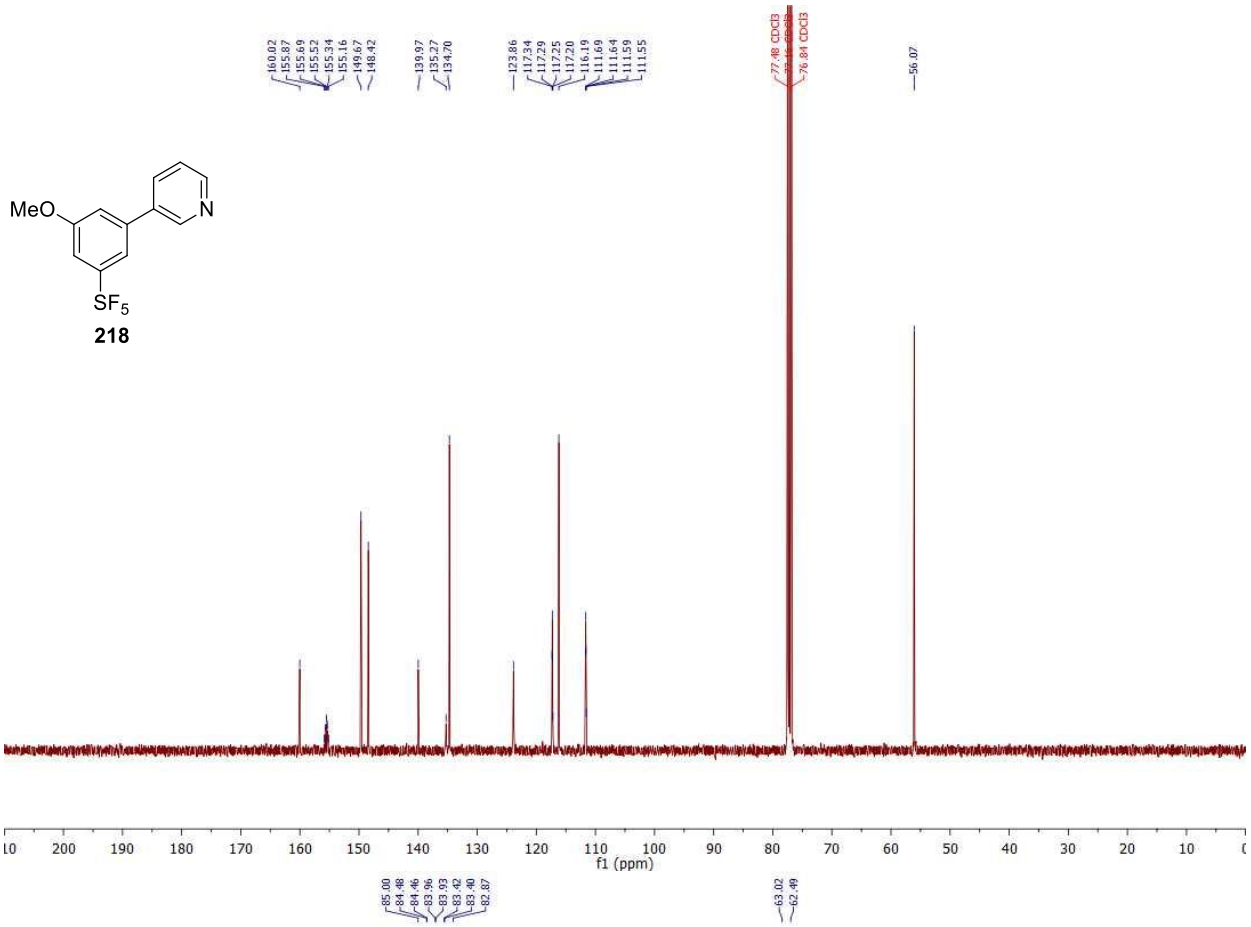
217

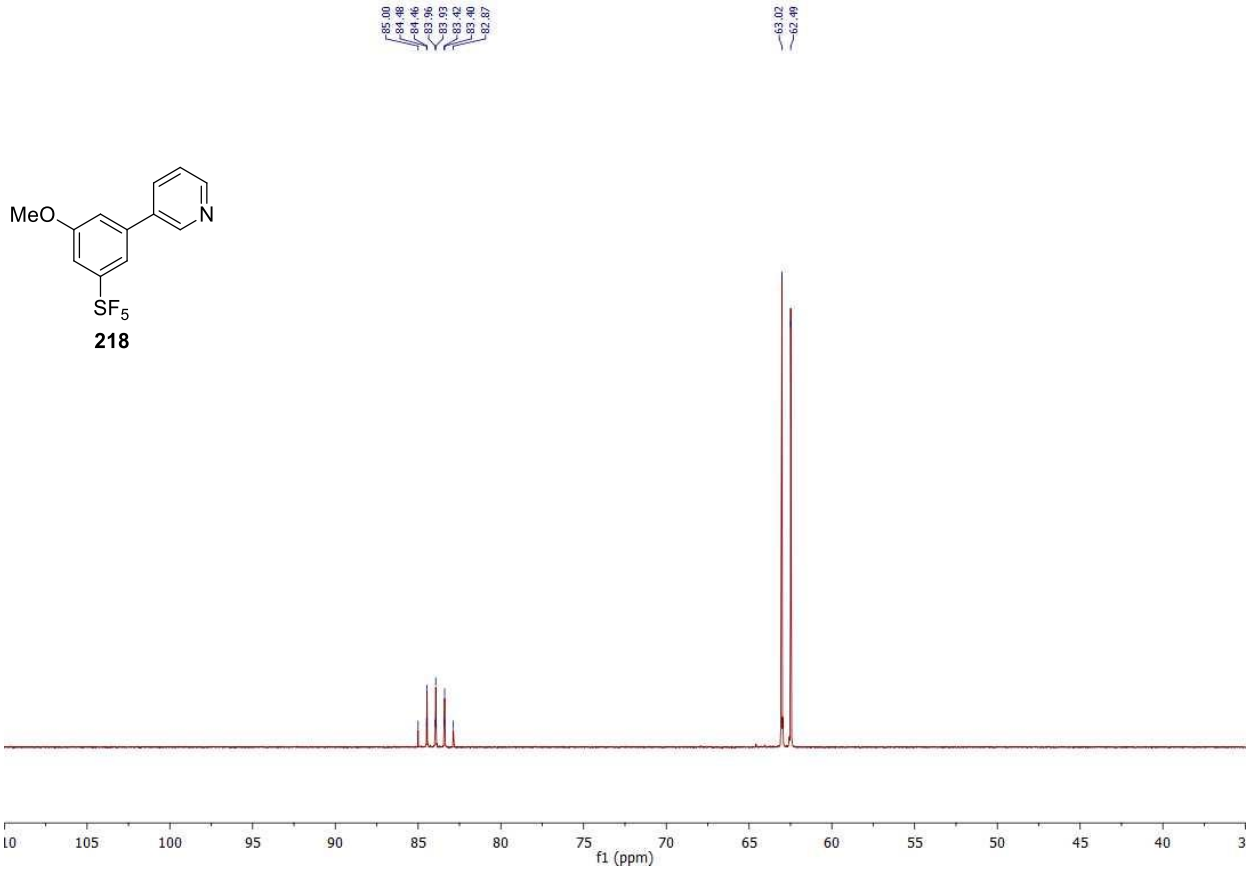

84.83
84.32
84.29
83.80
83.77
83.76
83.26
83.23
82.71
63.01
62.48
MeO
N
SF5
f1 (ppm)

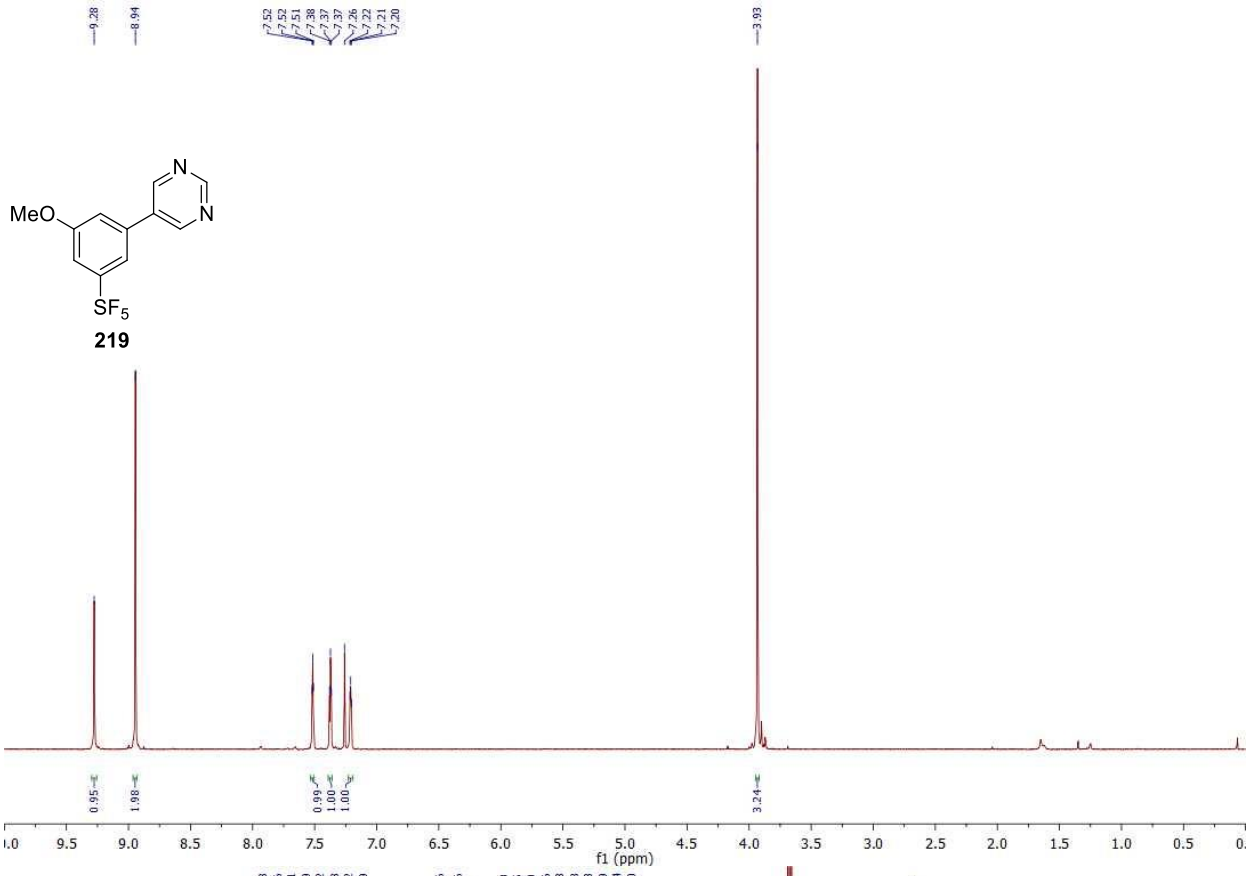
217


8.83
8.67
7.88
7.88
7.87
7.86
7.85
7.84
7.53
7.52
7.52
7.43
7.42
7.41
7.39
7.32
7.32
7.31
7.26
7.23
7.22
7.22
3.92
MeO
N
SF5
0.89
0.92
1.01
1.00
0.98
1.03
1.02
3.15
f1 (ppm)

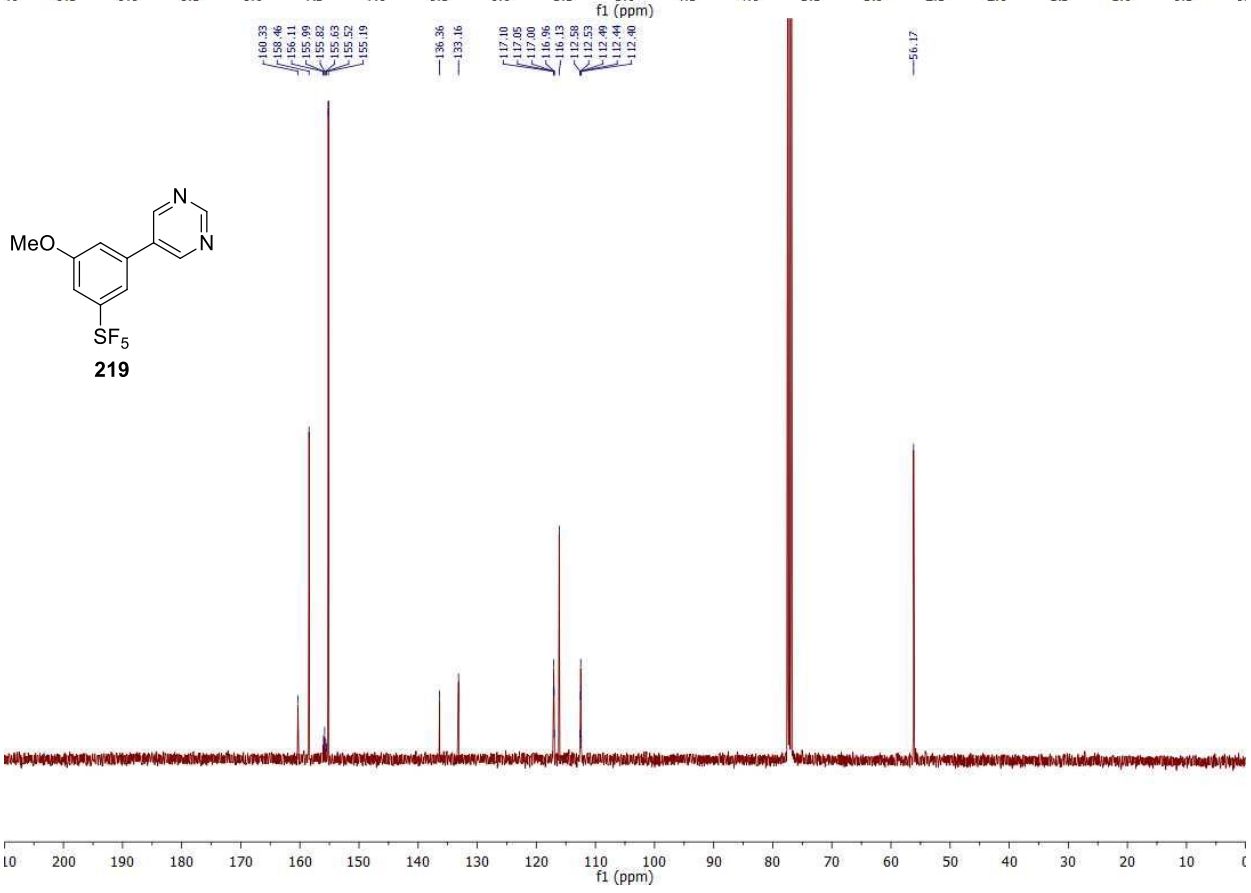
218


160.02
155.87
155.69
155.52
155.34
155.16
149.67
148.42
139.97
135.27
134.70
123.86
117.34
117.29
117.25
117.20
116.19
111.69
111.64
111.59
111.55
77.48 CDCl3
76.84 CDCl3
56.07
MeO
N
SF5
218
f1 (ppm)

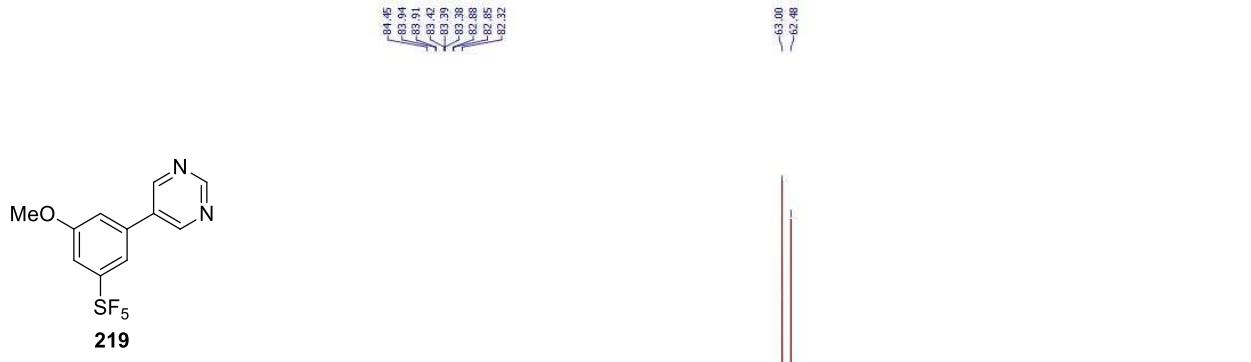

85.00
84.48
84.46
83.96
83.93
83.42
83.40
82.87
63.02
62.49
MeO
N
SF5
218
f1 (ppm)


9.28
8.94
7.52
7.52
7.51
7.38
7.37
7.37
7.26
7.22
7.21
7.20
3.93
MeO
N
N
SF5
0.95
1.98
0.99
1.00
1.00
3.24
f1 (ppm)

219


160.33
158.46
156.11
155.99
155.82
155.63
155.52
155.19
136.36
133.16
117.10
117.05
117.00
116.96
116.13
112.58
112.53
112.49
112.44
112.40
56.17
MeO
N
N
SF5
f1 (ppm)

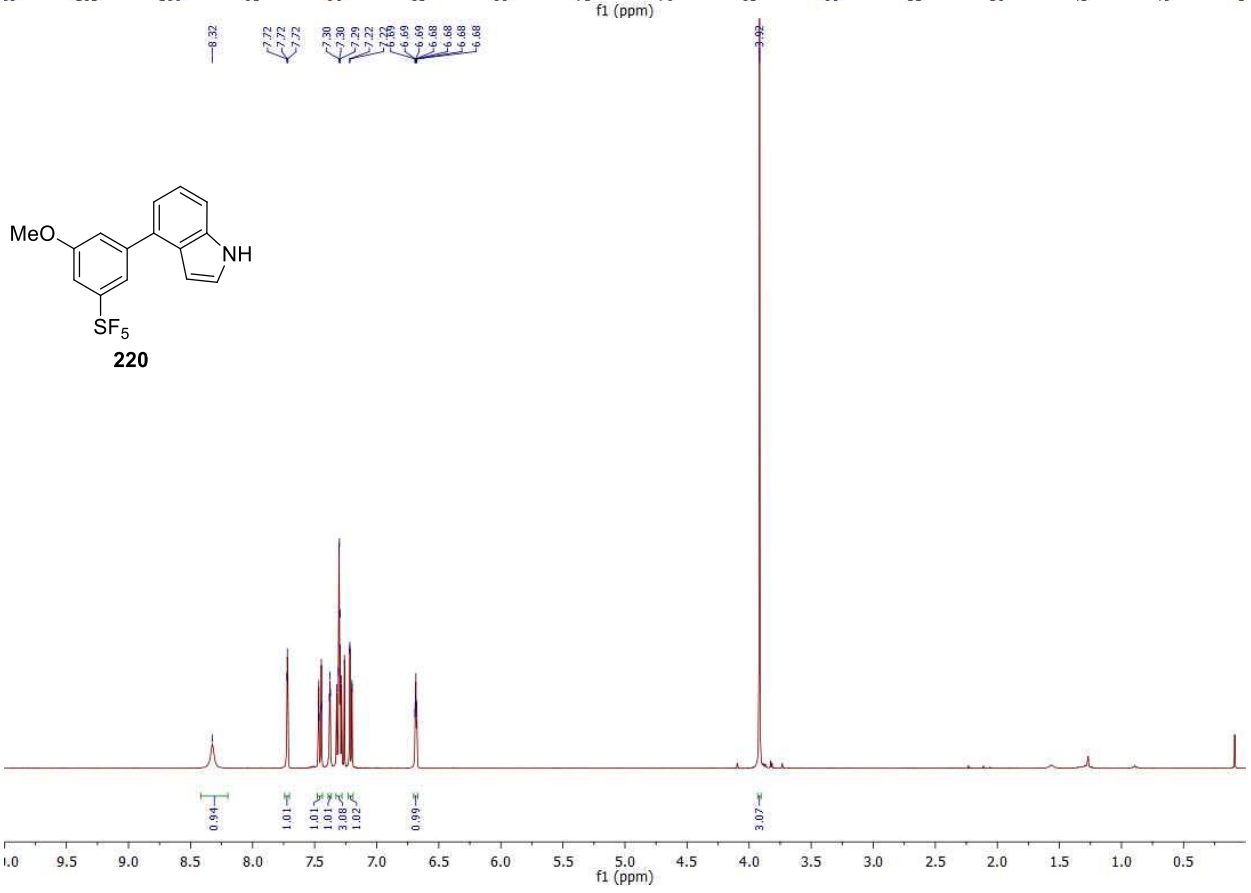
219


84.45
83.94
83.91
83.42
83.39
83.38
82.88
82.85
82.32
63.00
62.48

MeO
N
N
SF5

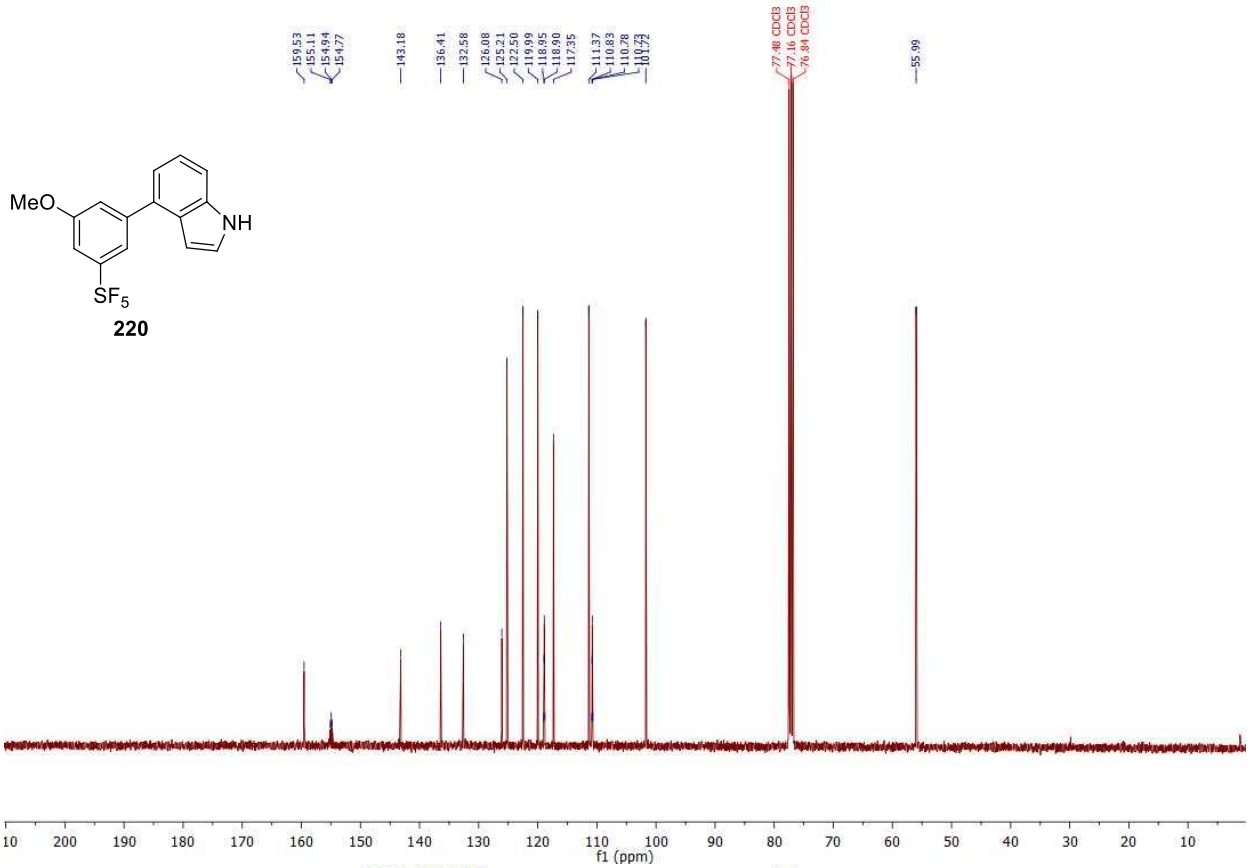
219

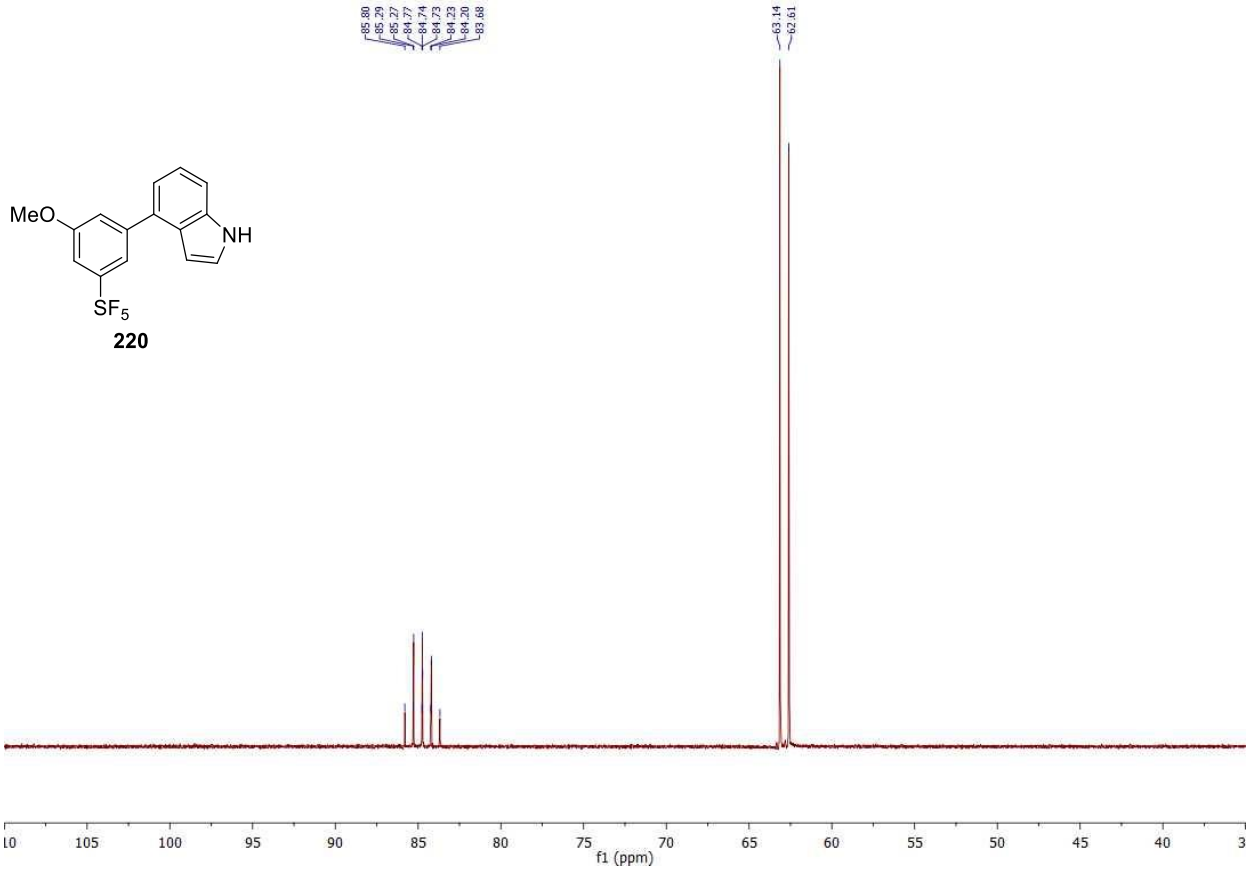
f1 (ppm)

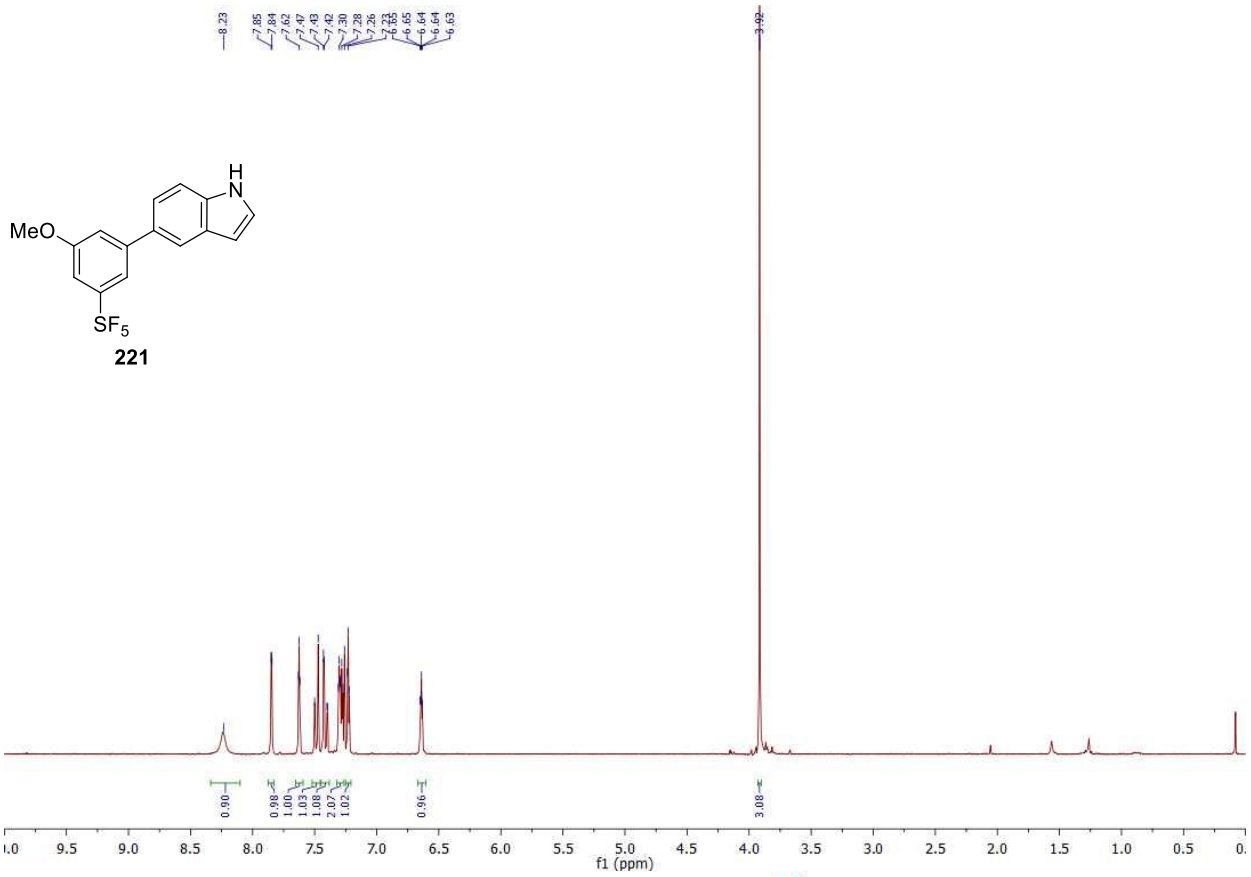

8.32
7.72
7.72
7.72
7.30
7.30
7.29
7.22
6.69
6.68
6.68
6.68
6.68
3.92
0.94
1.01
1.01
1.01
3.08
1.02
0.99
3.07
f1 (ppm)

MeO
NH
SF5

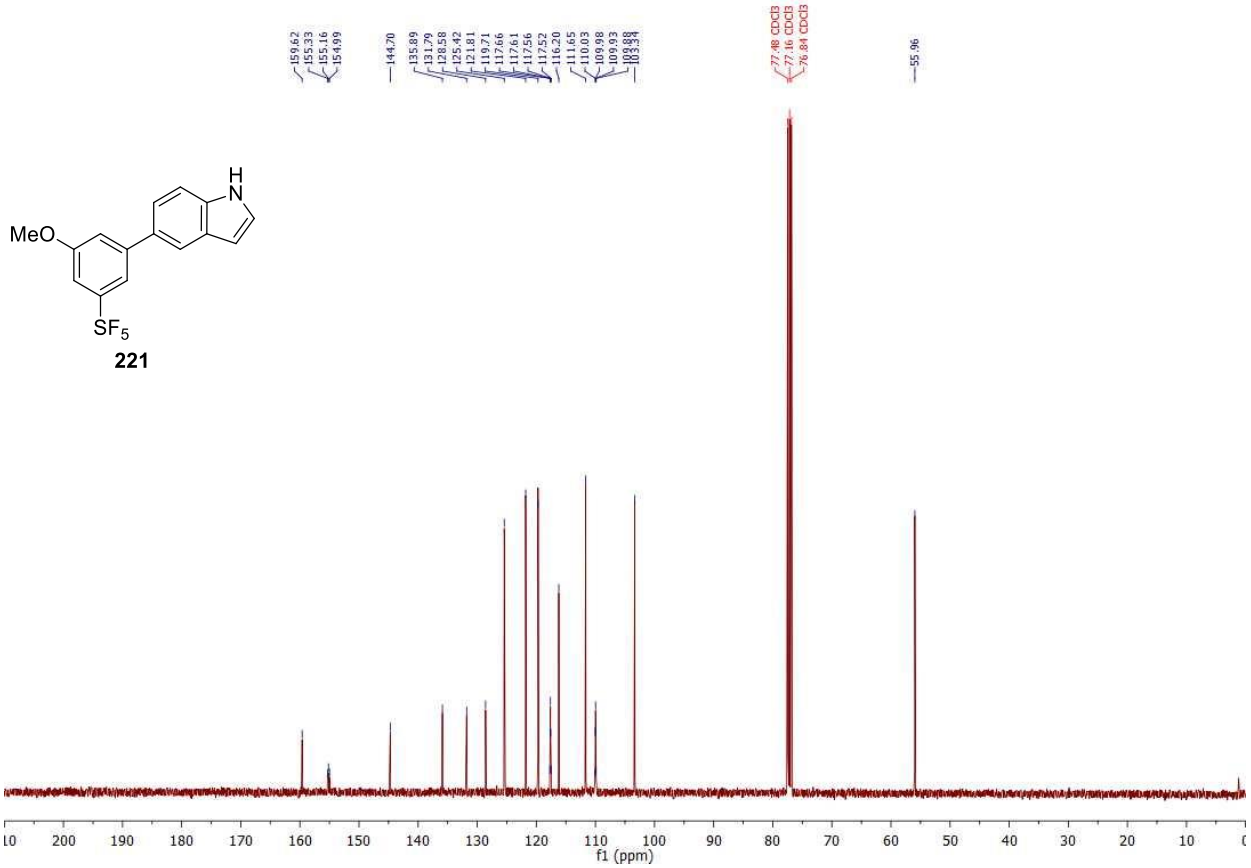
220


159.53
155.11
154.94
154.77
143.18
136.41
132.58
126.08
125.21
122.50
119.99
118.95
118.90
117.35
111.37
110.83
110.78
110.73
101.72
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.99
MeO
NH
SF5
220
f1 (ppm)

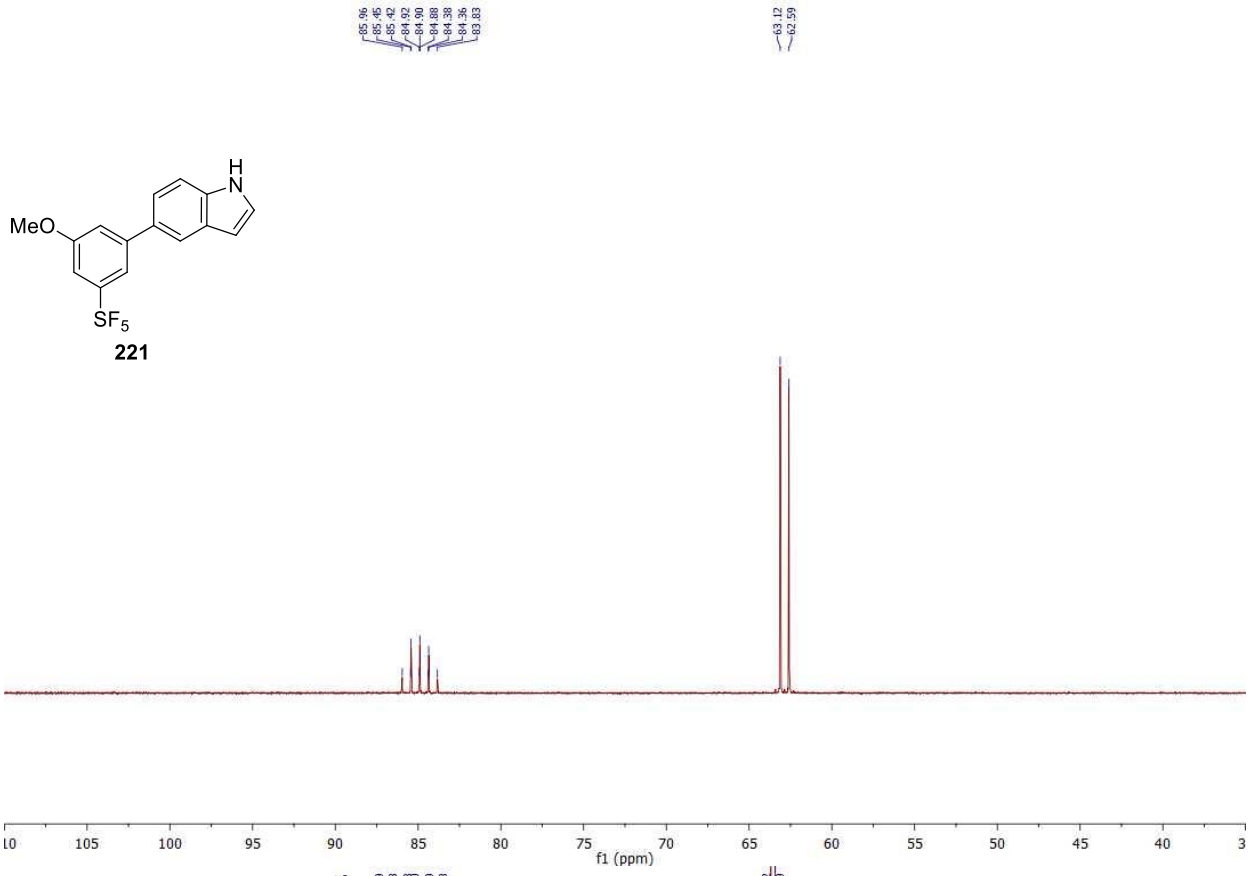

85.80
85.29
85.27
84.77
84.74
84.73
84.23
84.20
83.68
63.14
62.61
MeO
NH
SF5
220
f1 (ppm)

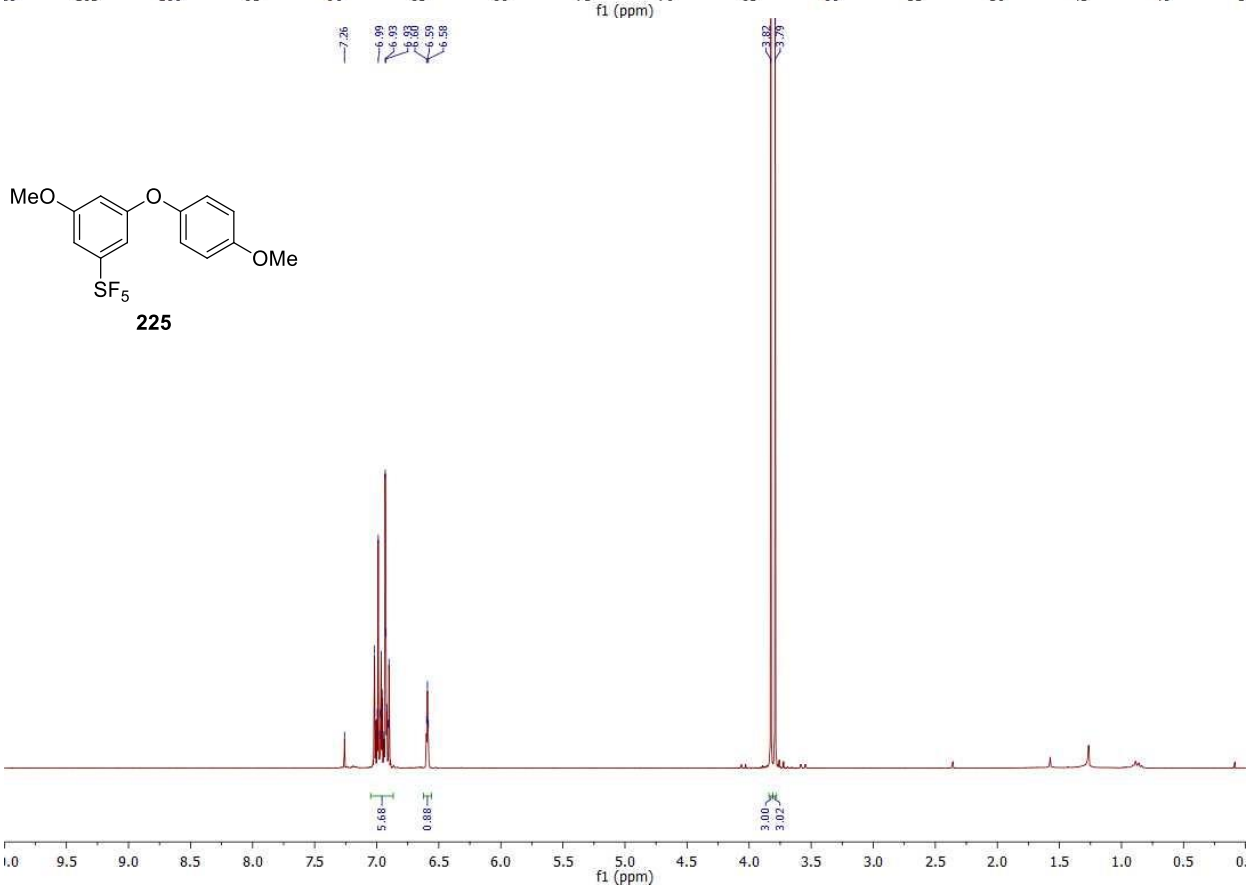

8.23
7.85
7.84
7.62
7.47
7.43
7.42
7.30
7.28
7.26
7.23
6.65
6.64
6.64
6.63
3.92
MeO
H
N
SF5
0.90
0.98
1.00
1.03
1.08
2.07
1.02
0.96
3.08
f1 (ppm)

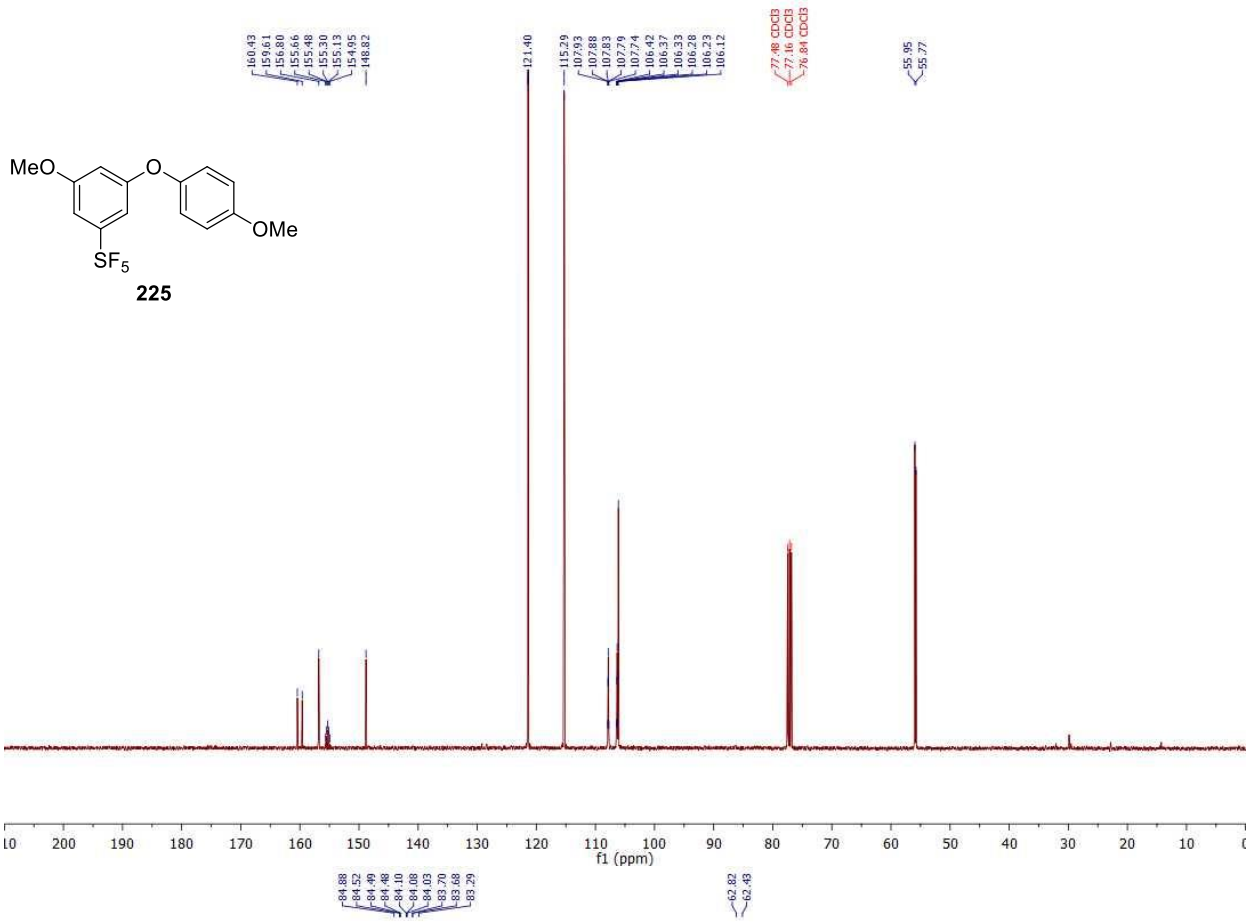
221

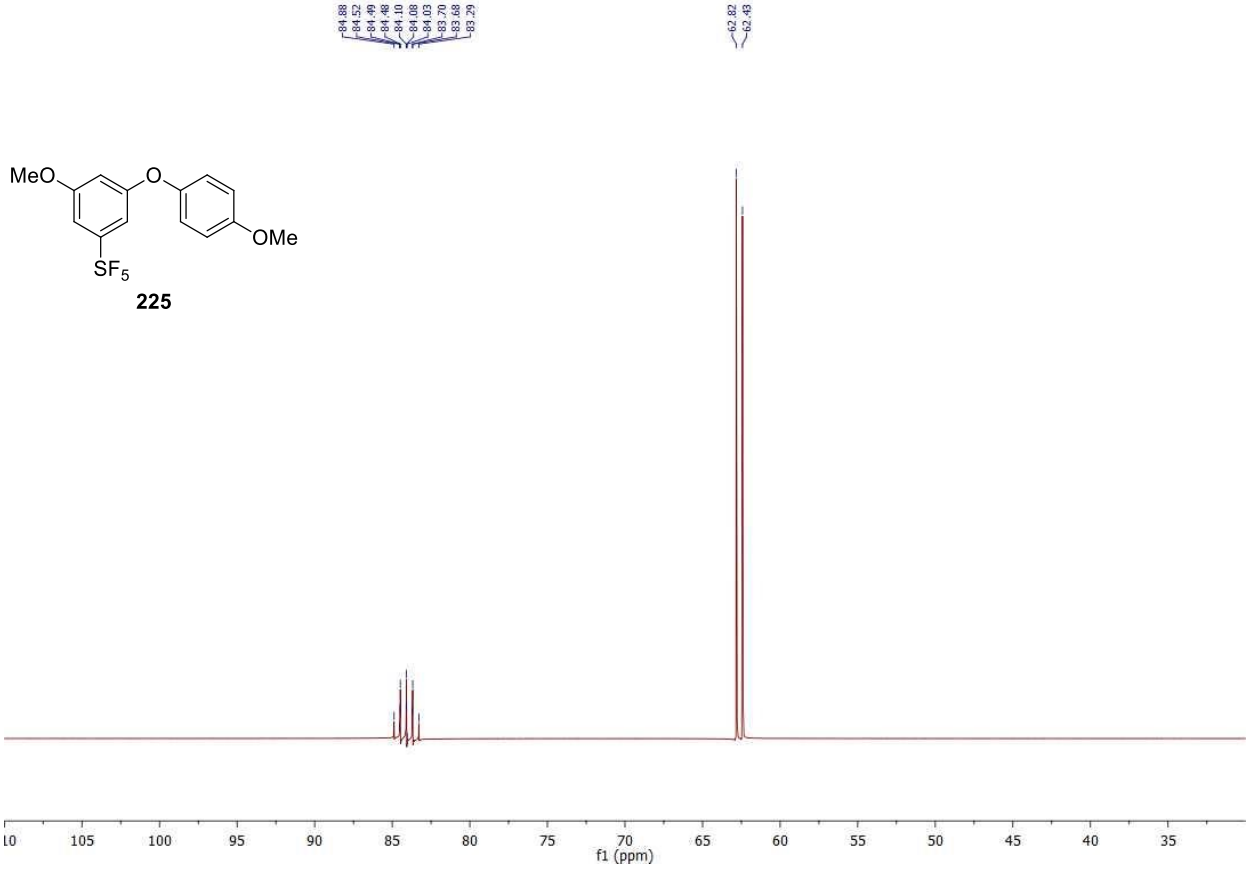

159.62
155.33
155.16
154.99
144.70
135.89
131.79
128.58
125.42
121.81
119.71
117.66
117.61
117.56
117.52
116.20
111.65
110.03
109.98
109.93
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.96
MeO
H
N
SF5
f1 (ppm)

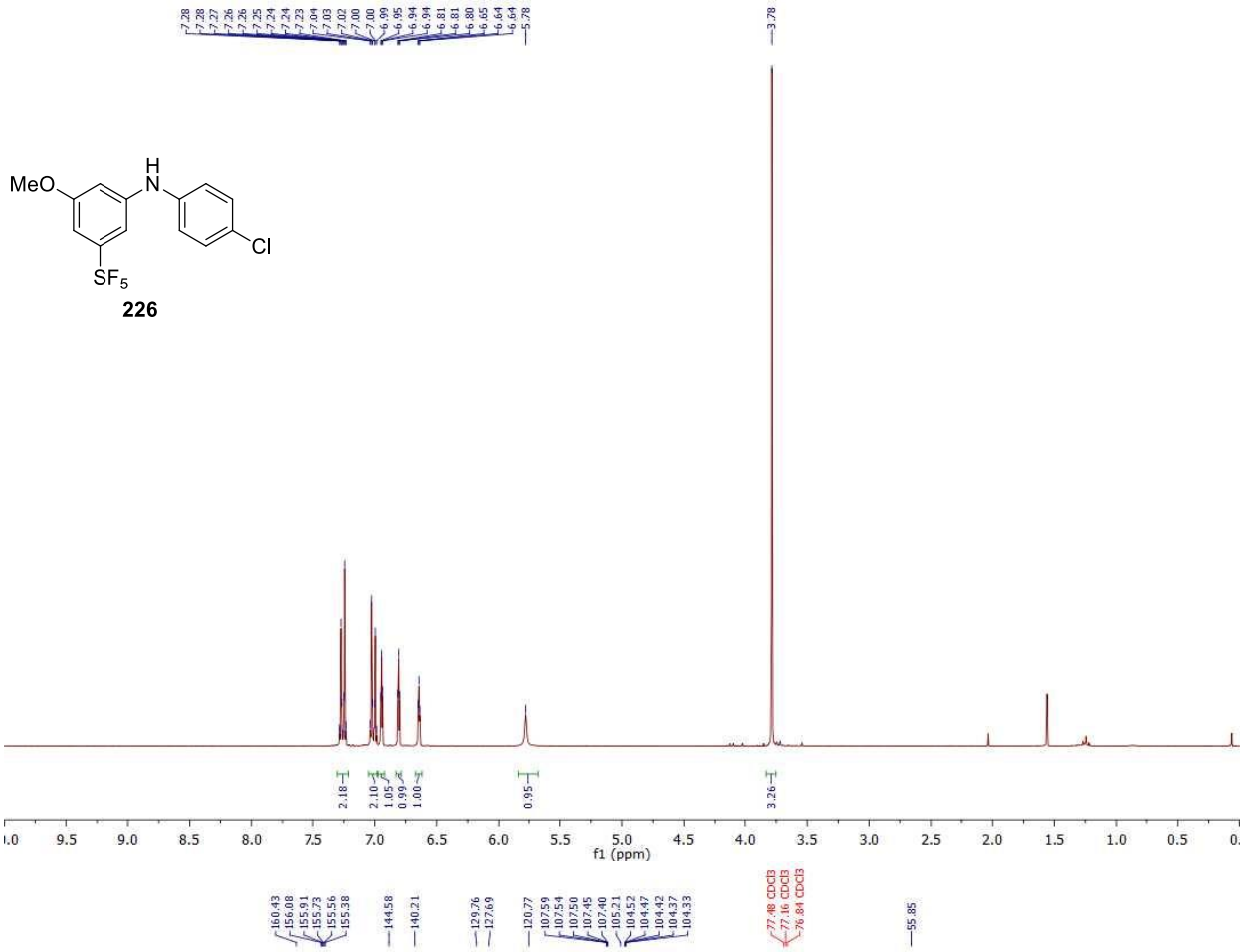
221

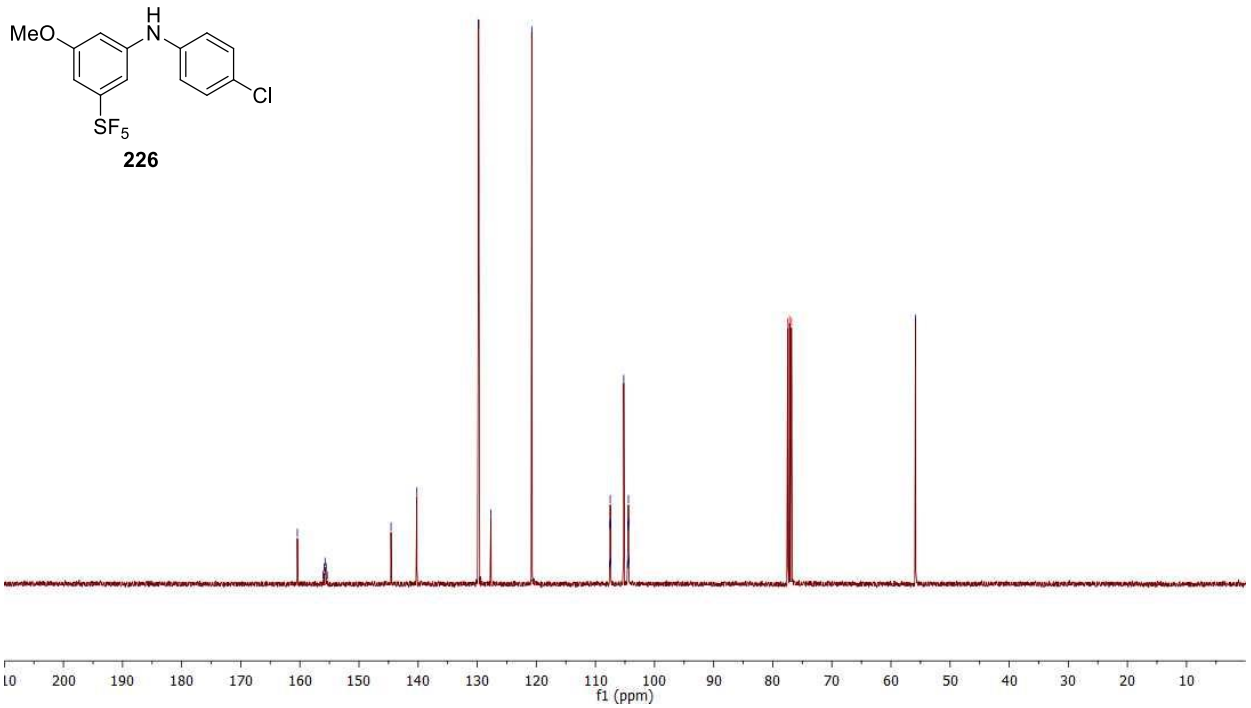

MeO
H
N
SF5
221
f1 (ppm)

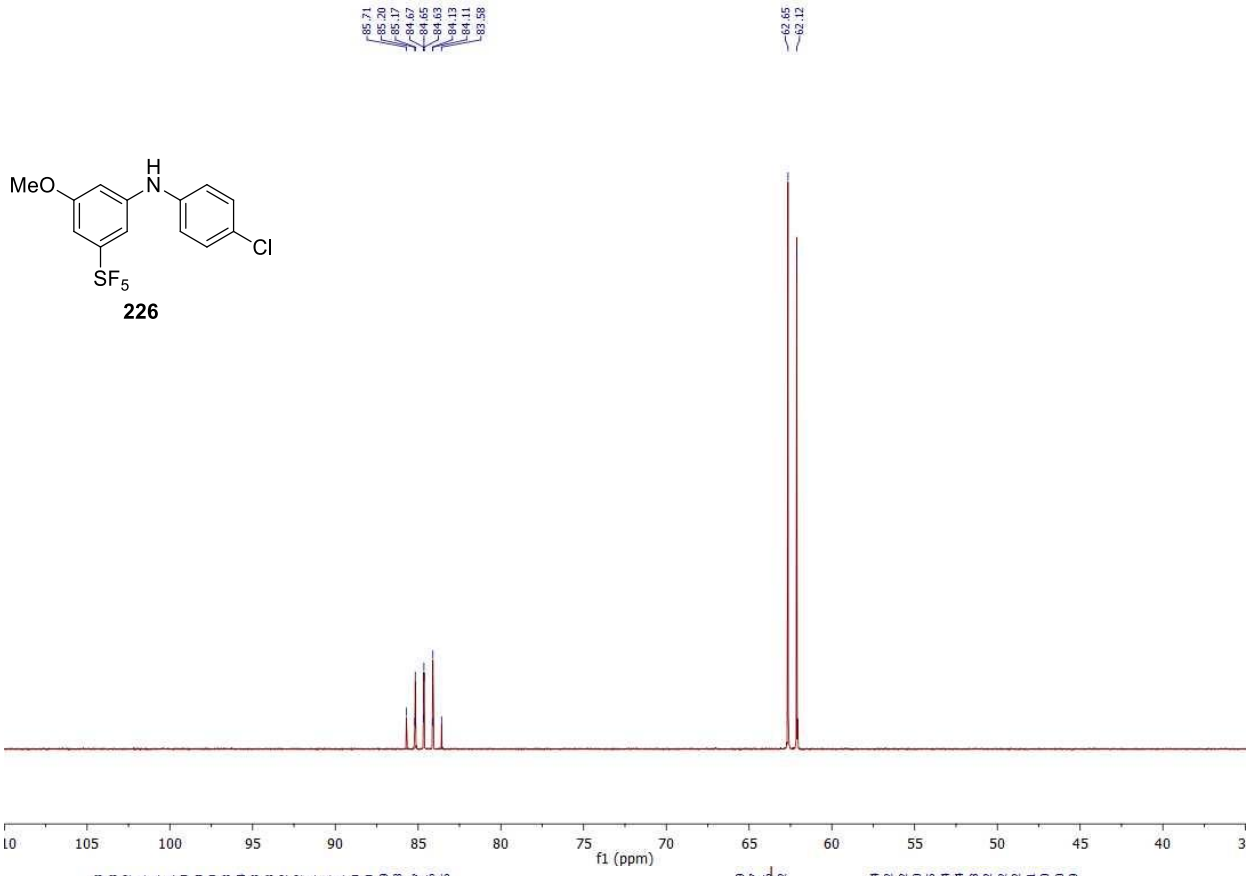

MeO
O
OMe
SF5
225
f1 (ppm)


160.43
159.61
156.80
155.66
155.48
155.30
155.13
154.95
148.82
121.40
115.29
107.93
107.88
107.83
107.79
107.74
106.42
106.37
106.33
106.28
106.23
106.12
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.95
55.77
MeO
O
OMe
SF5
225
f1 (ppm)

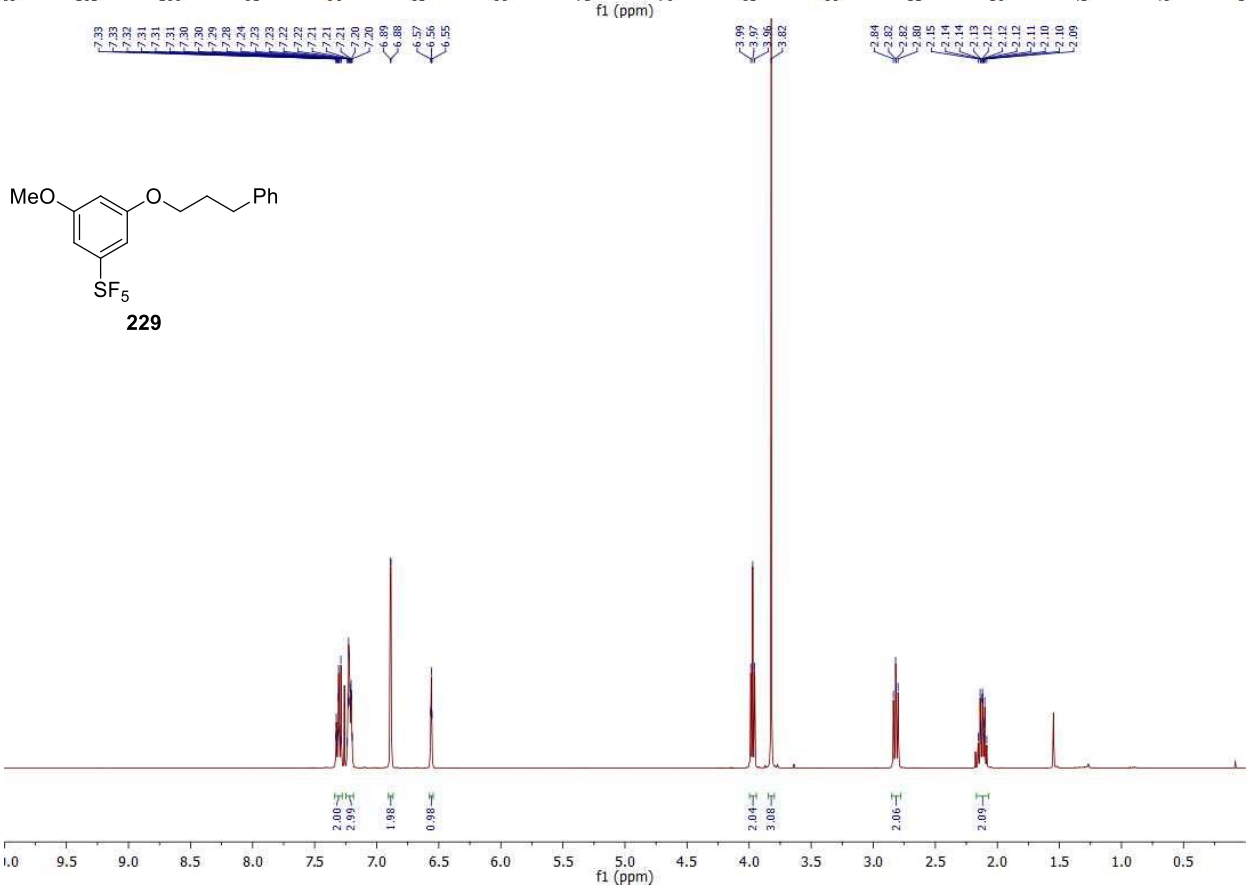

84.88
84.52
84.49
84.48
84.10
84.08
84.03
83.70
83.68
83.29
62.82
62.48
MeO
O
OMe
SF5
225
f1 (ppm)


MeO
H
N
Cl
SF5
226
f1 (ppm)

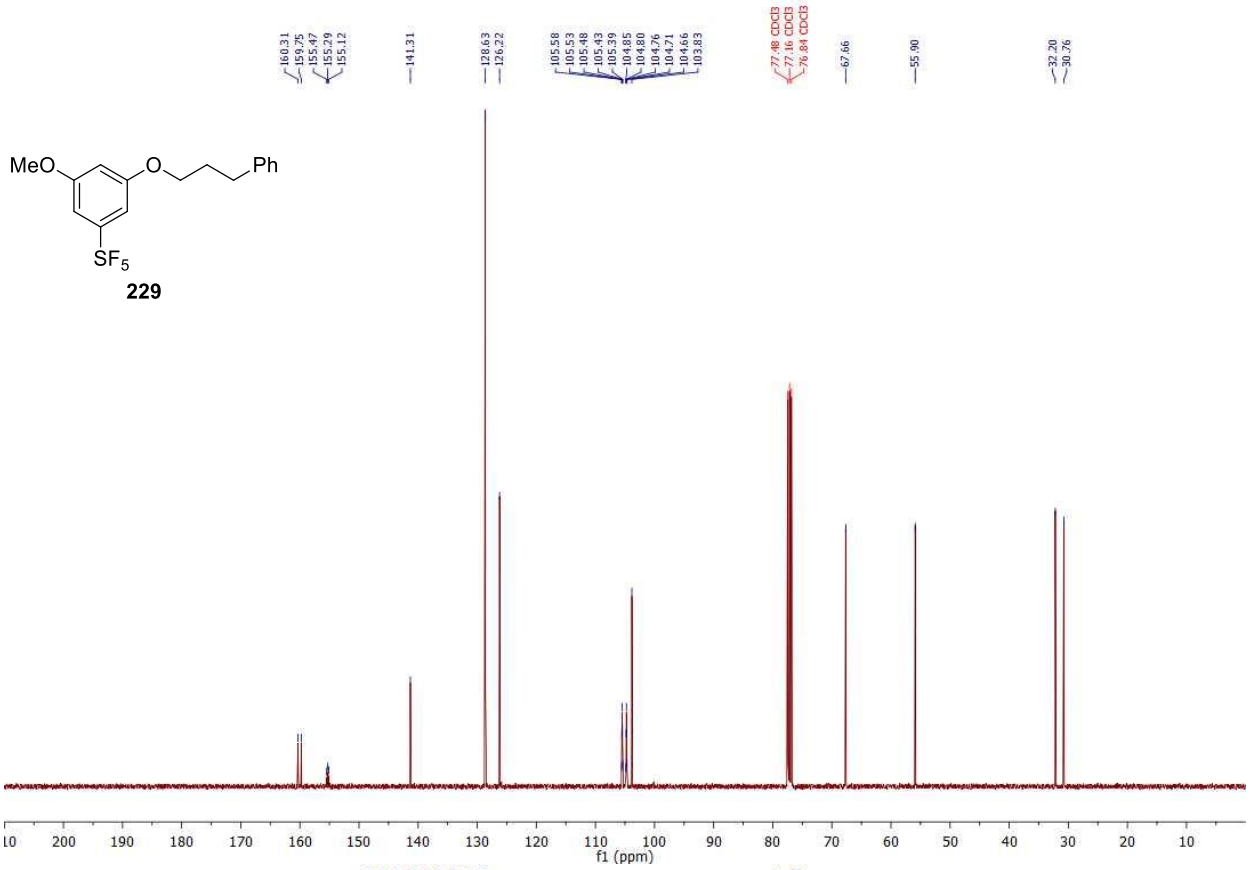

MeO
H
N
Cl
SF5
226
f1 (ppm)

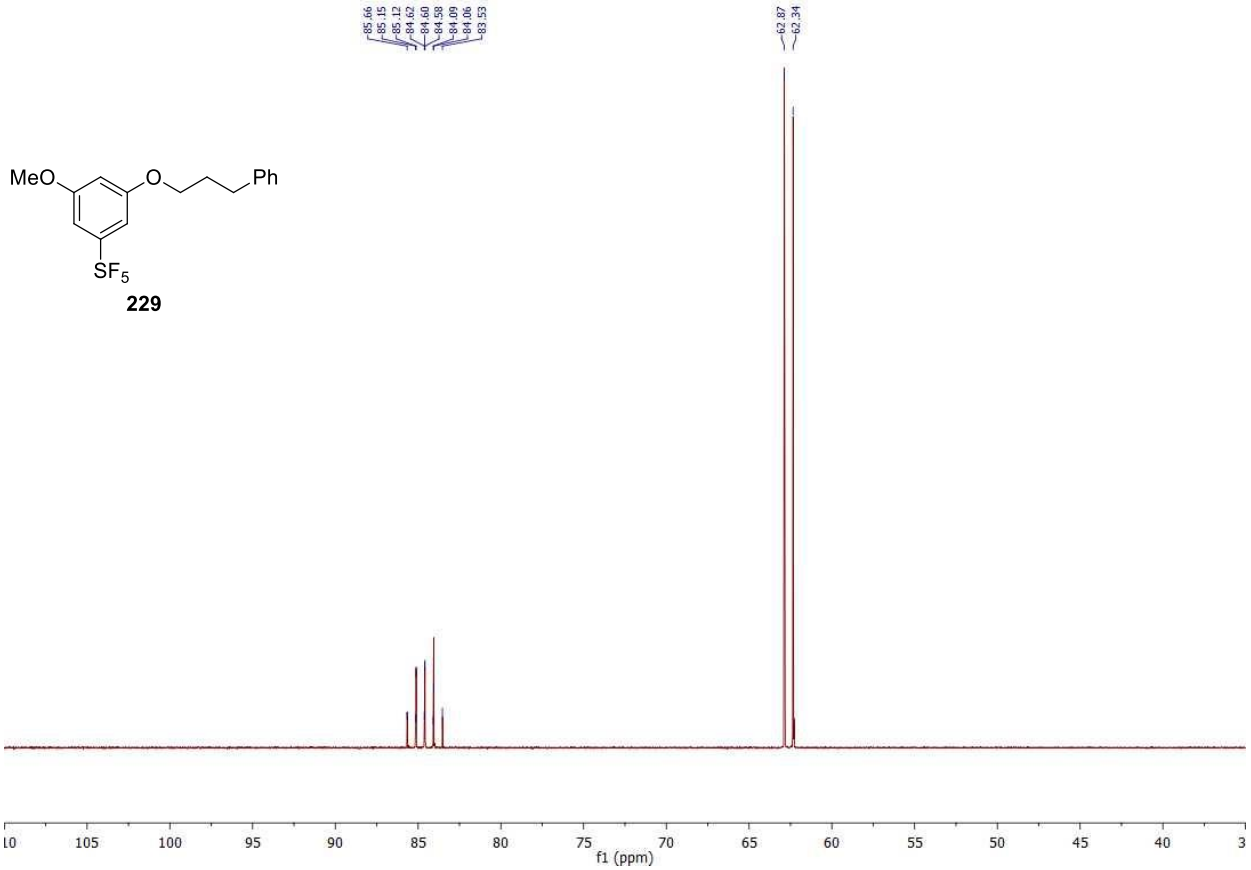


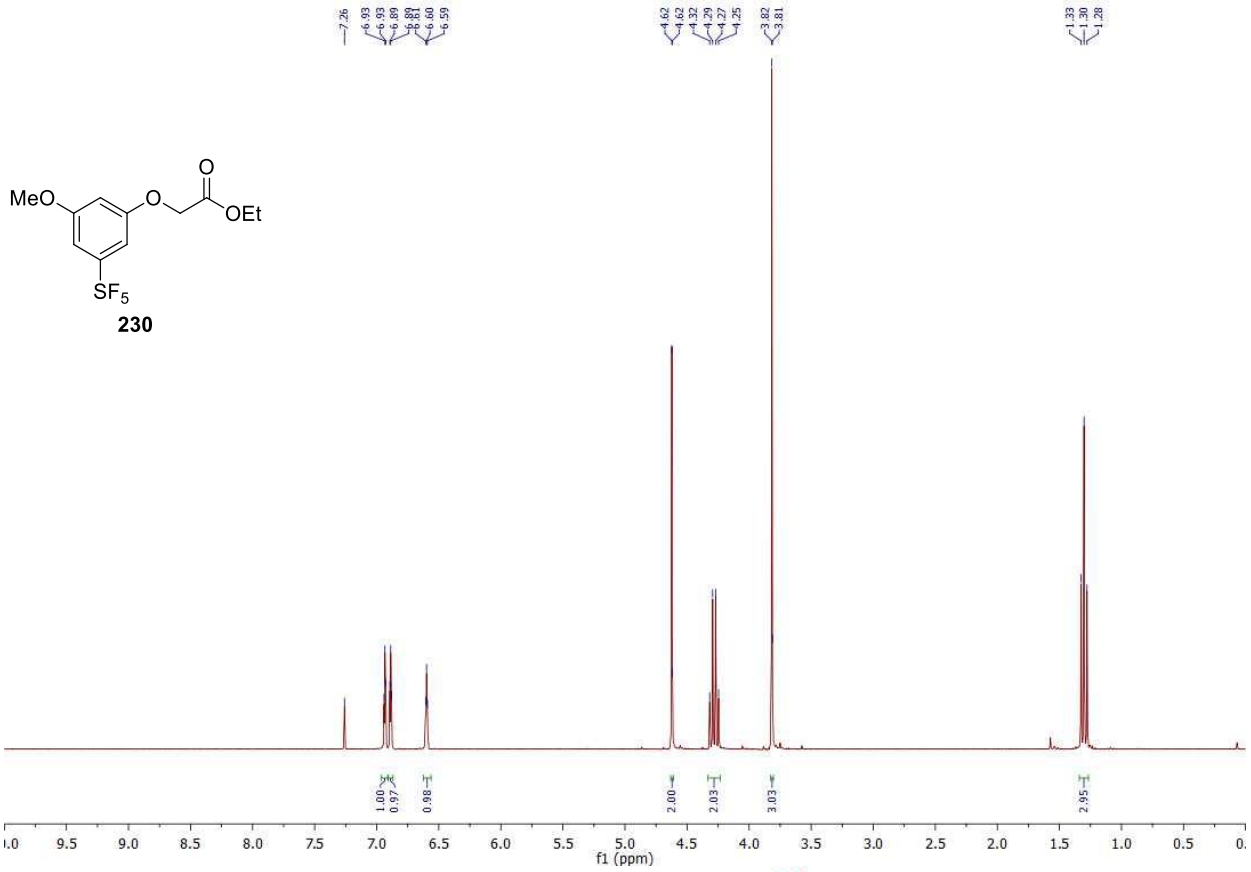
226

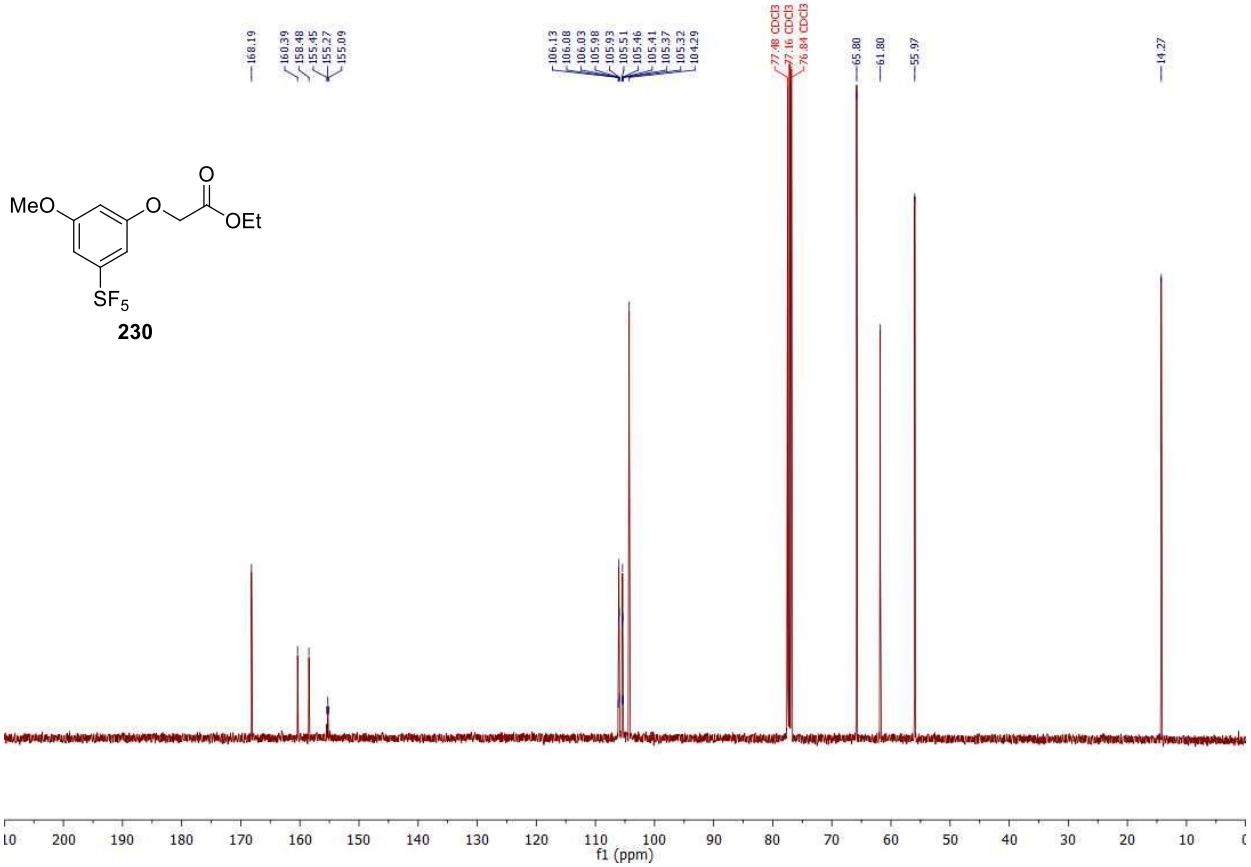


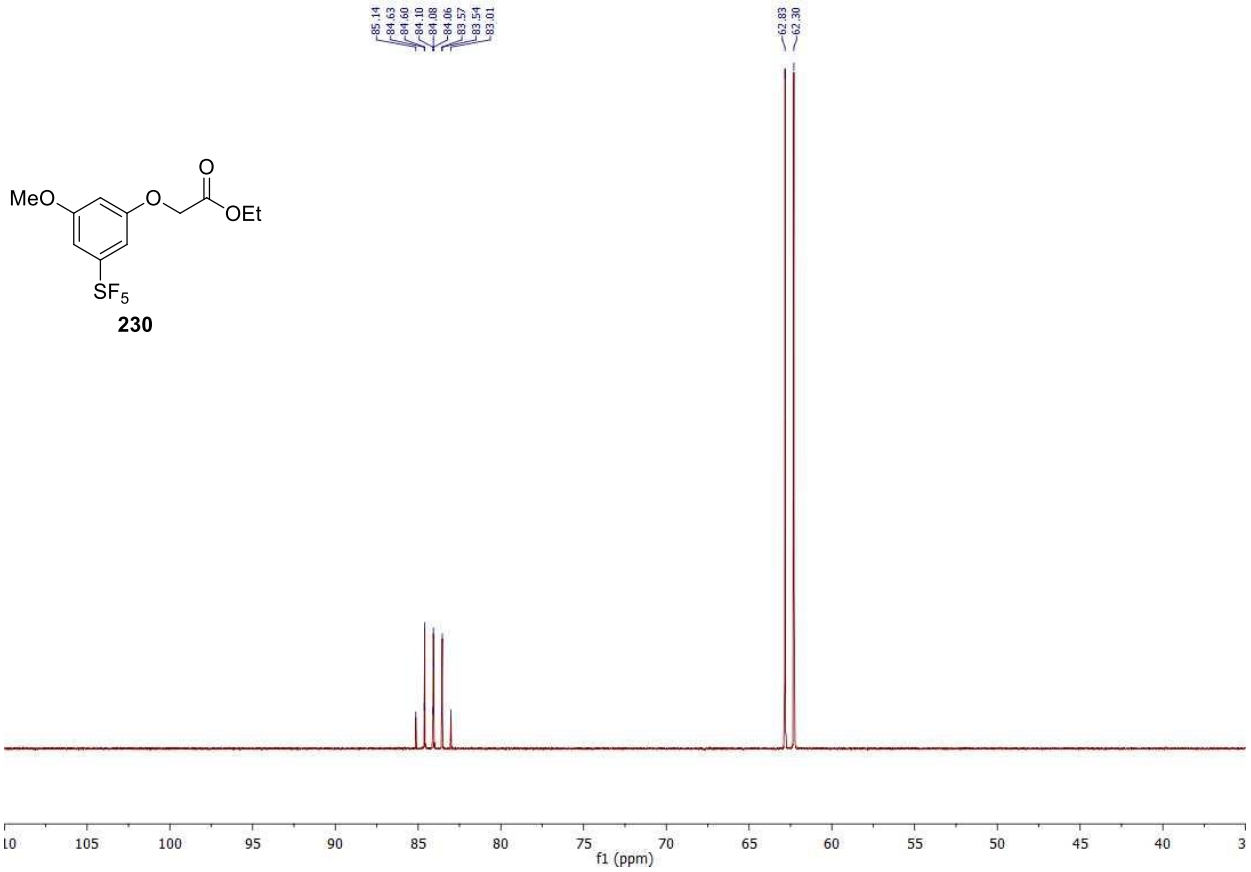
229

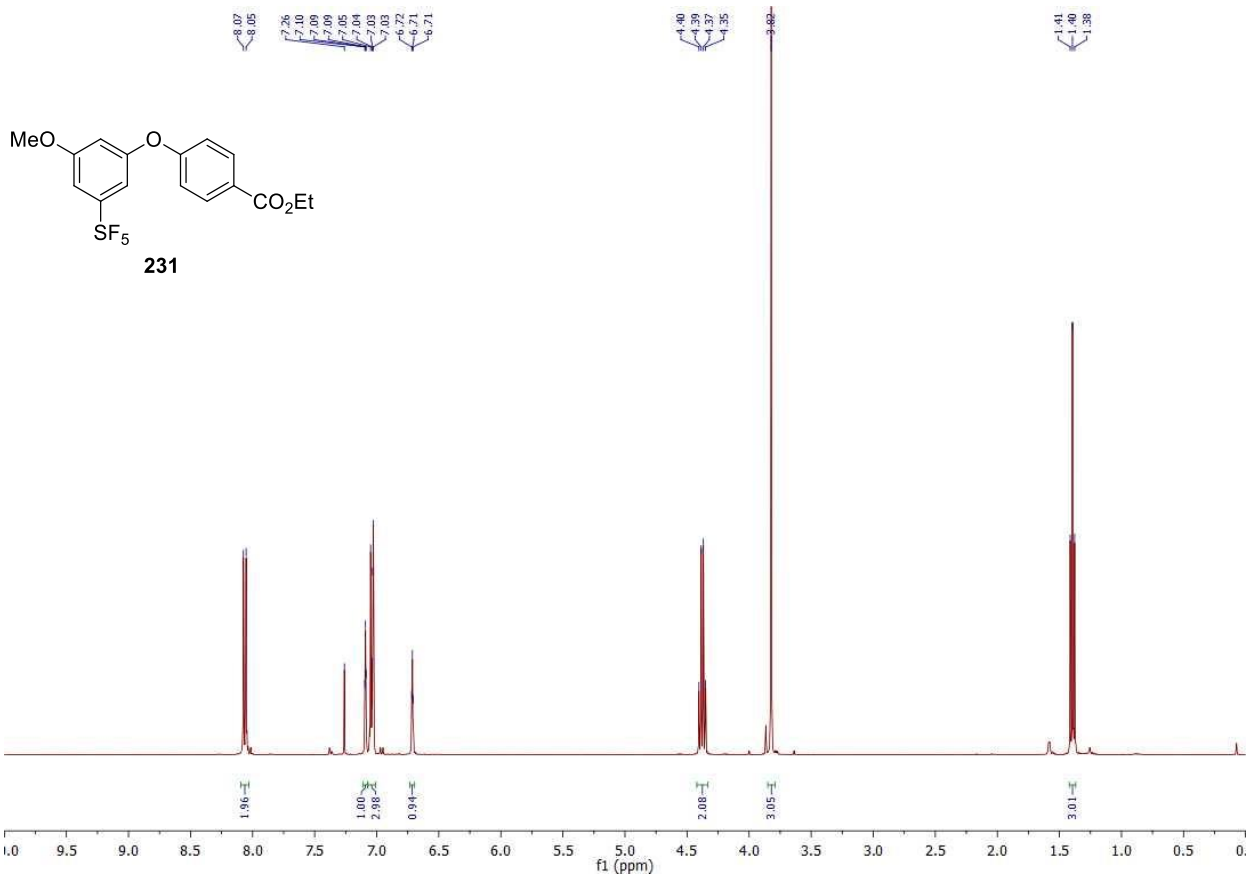

160.31
159.75
155.47
155.29
155.12
141.31
128.63
126.22
105.58
105.53
105.48
105.43
105.39
104.85
104.80
104.76
104.71
104.66
103.83
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
67.66
55.90
32.20
30.76
MeO
O
Ph
SF5
229
f1 (ppm)

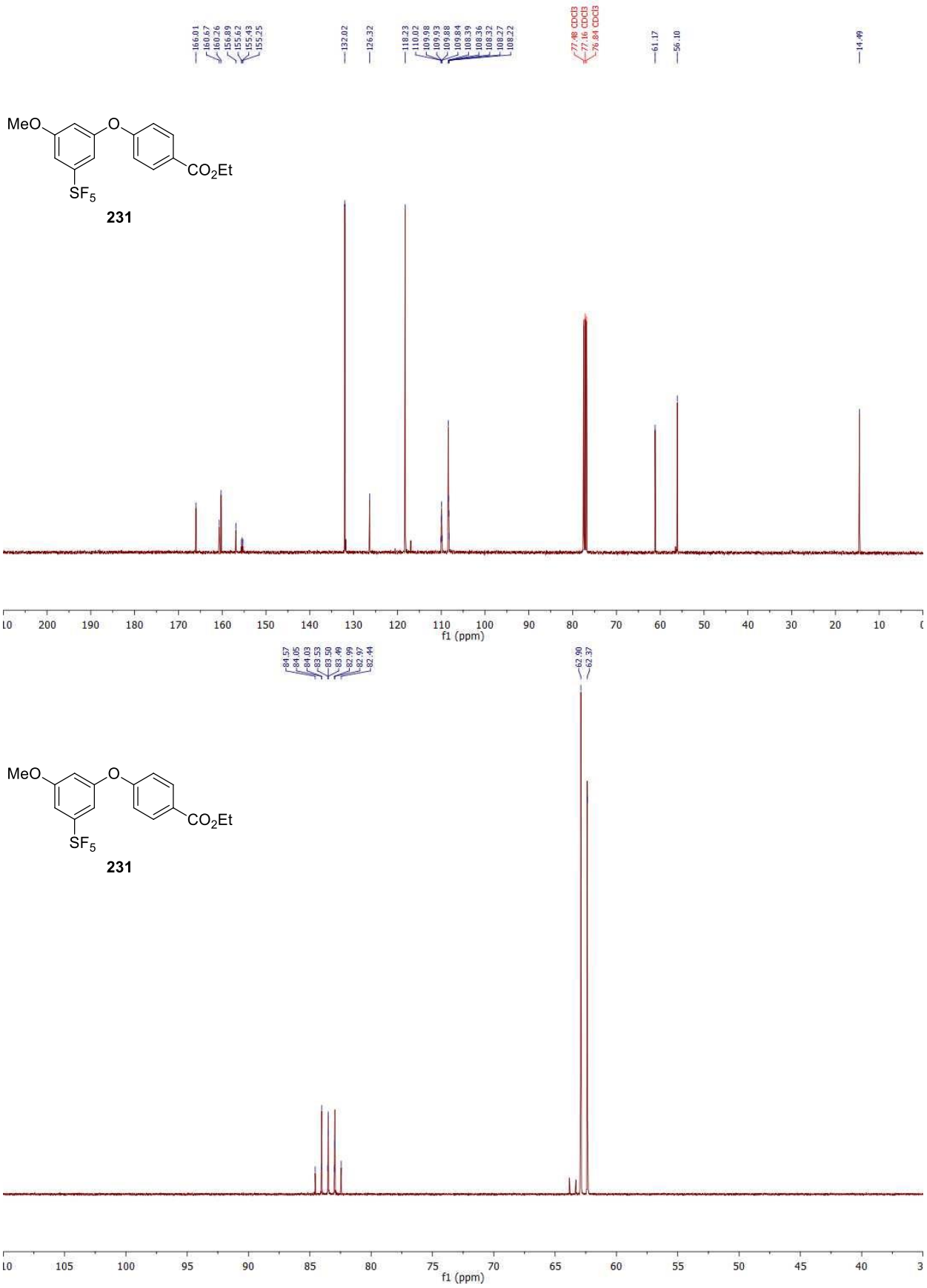

85.66
85.15
85.12
84.62
84.60
84.58
84.09
84.06
83.53
62.87
62.34
MeO
O
Ph
SF5
229
f1 (ppm)

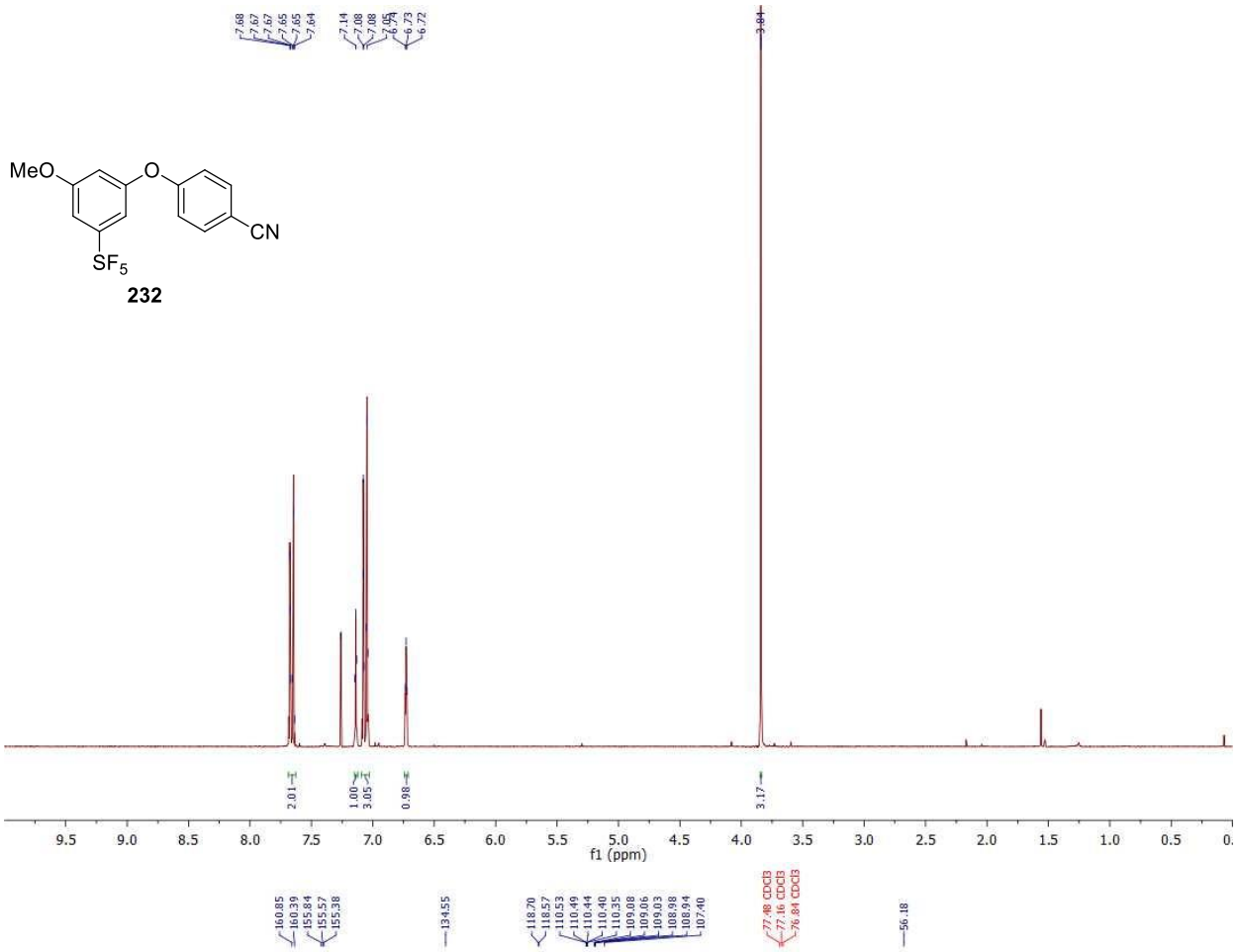

MeO
O
O
OEt
SF5
230
f1 (ppm)

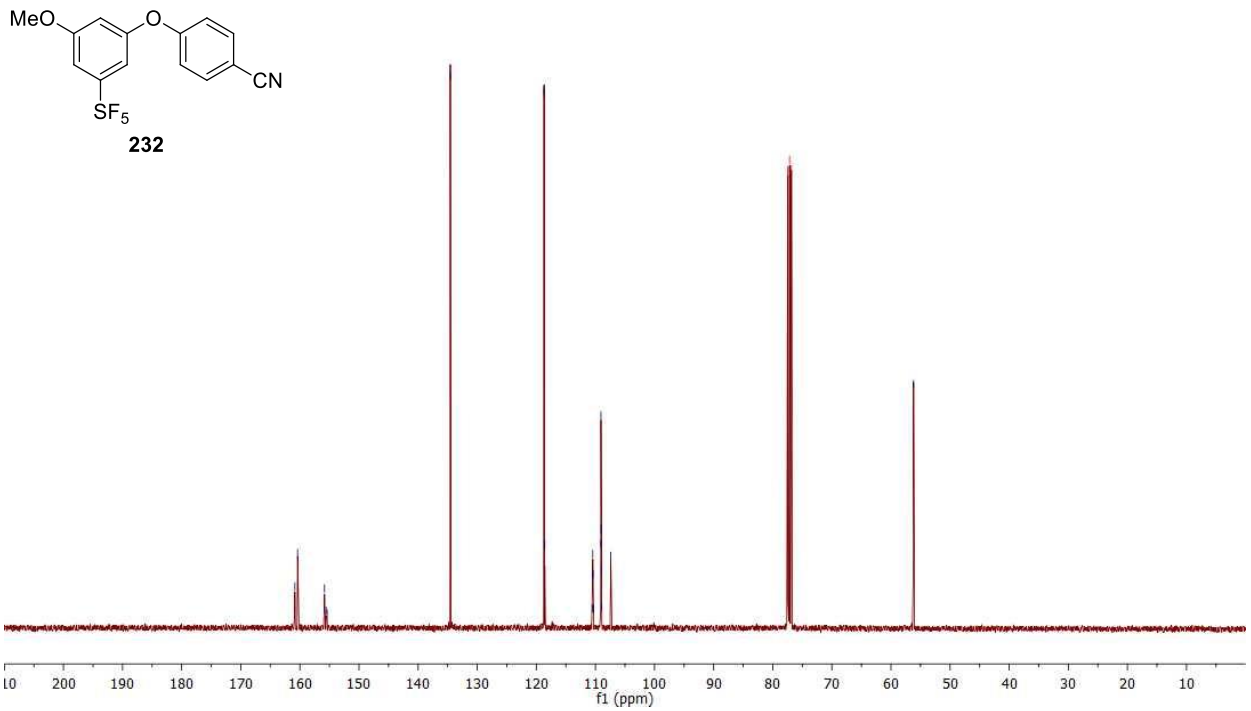

MeO
O
O
OEt
SF5
230
f1 (ppm)

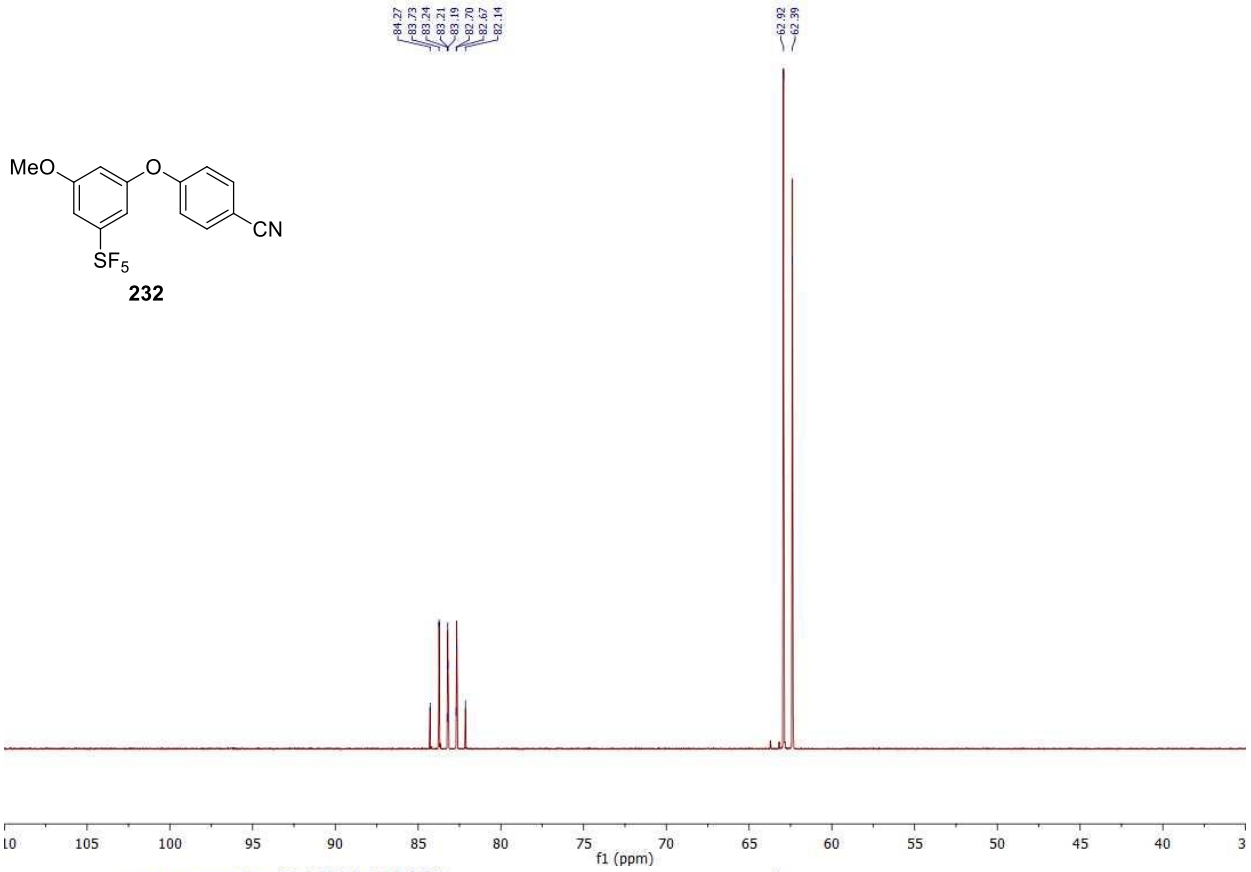

85.14
84.63
84.60
84.10
84.08
84.06
83.57
83.54
83.01
62.83
62.30
MeO
O
O
OEt
SF5
230
f1 (ppm)


8.07
8.05
7.26
7.10
7.09
7.09
7.05
7.04
7.03
7.03
6.72
6.71
6.71
4.40
4.39
4.37
4.35
3.82
1.41
1.40
1.38
MeO
O
CO2Et
SF5
231
1.96
1.00
2.98
0.94
2.08
3.05
3.01
f1 (ppm)

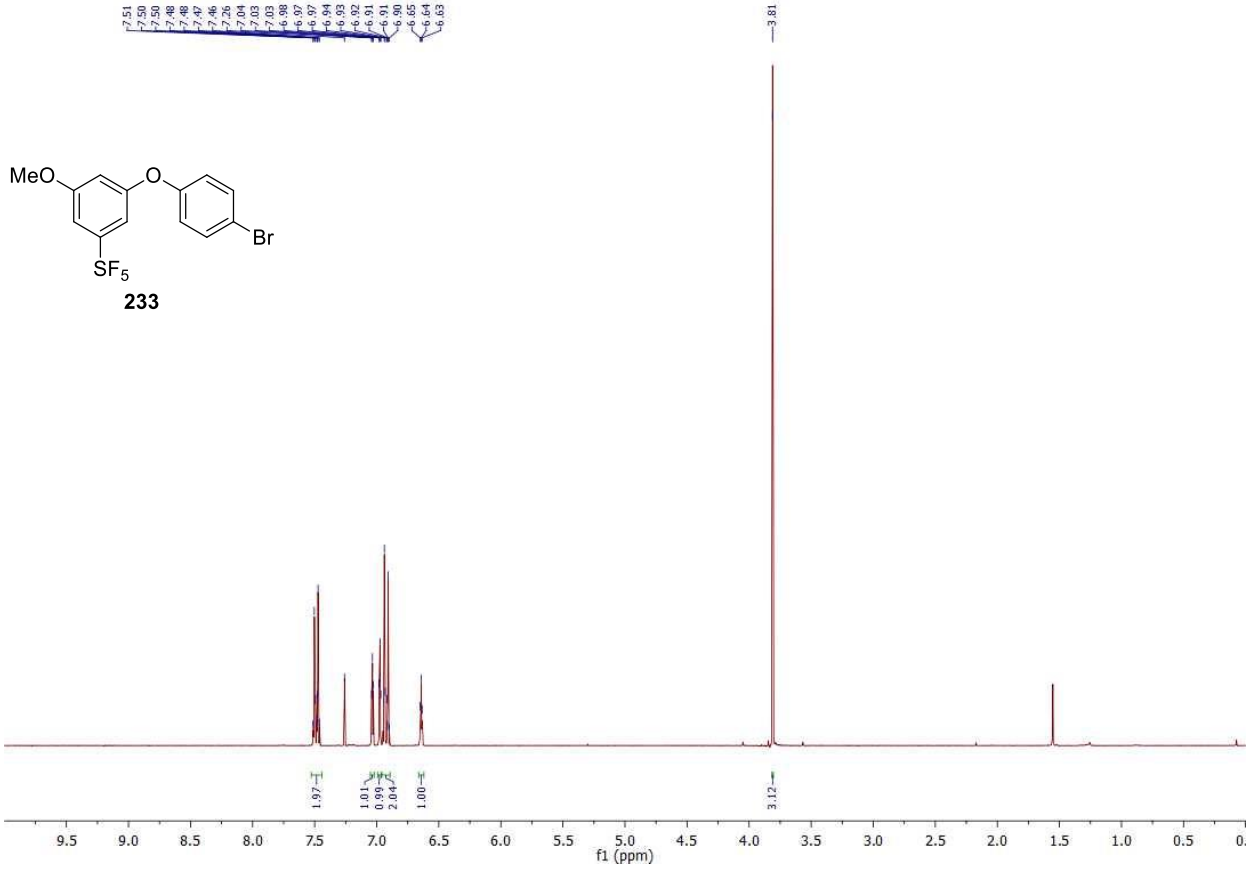

166.01
160.67
160.26
156.89
155.62
155.43
155.25
132.02
126.32
118.23
110.02
109.98
109.93
109.88
109.84
108.39
108.36
108.32
108.27
108.22
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
61.17
56.10
14.49
MeO
O
CO2Et
SF5
231
f1 (ppm)
84.57
84.05
84.03
83.53
83.50
83.49
82.99
82.97
82.44
62.90
62.37
MeO
O
CO2Et
SF5
231
f1 (ppm)


MeO
O
CN
SF5
232
f1 (ppm)

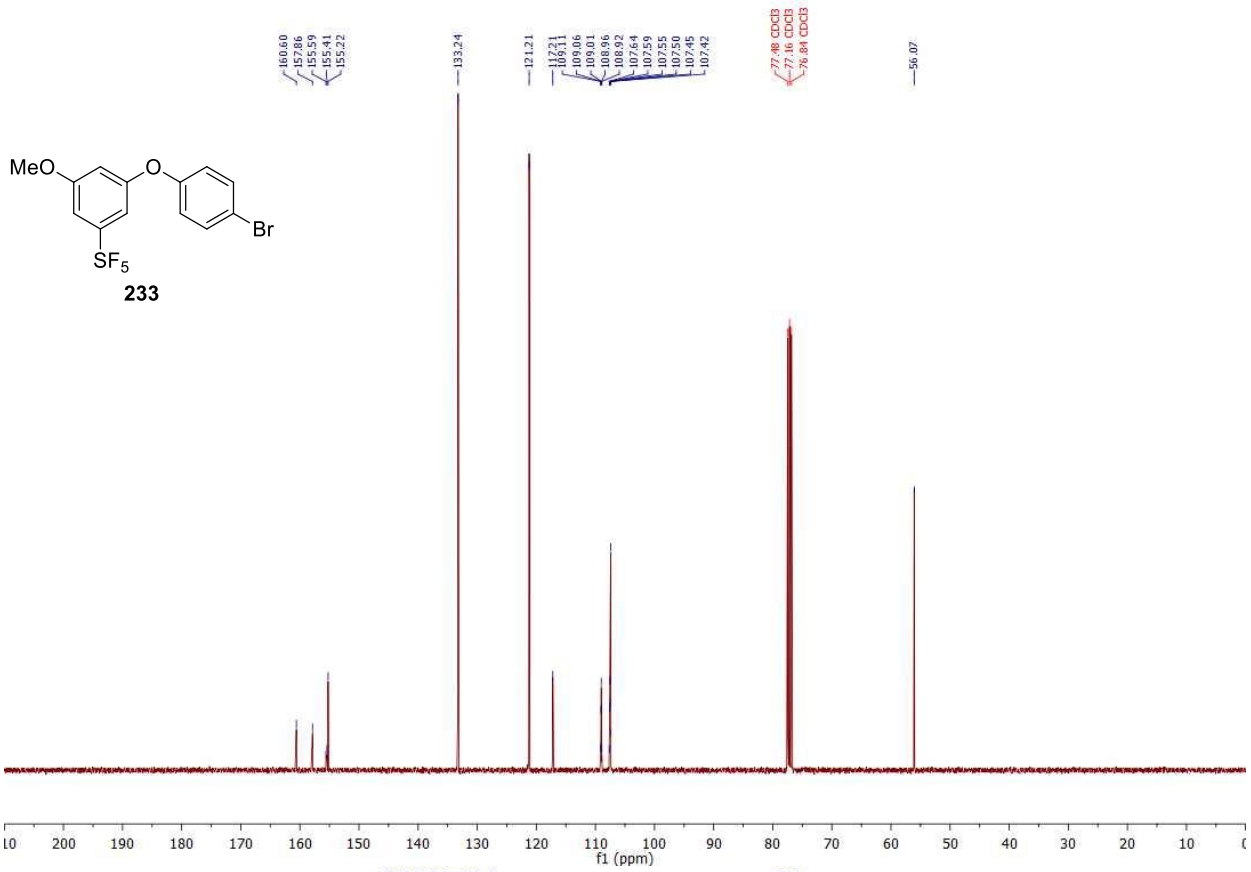

MeO
O
CN
SF5
232
f1 (ppm)

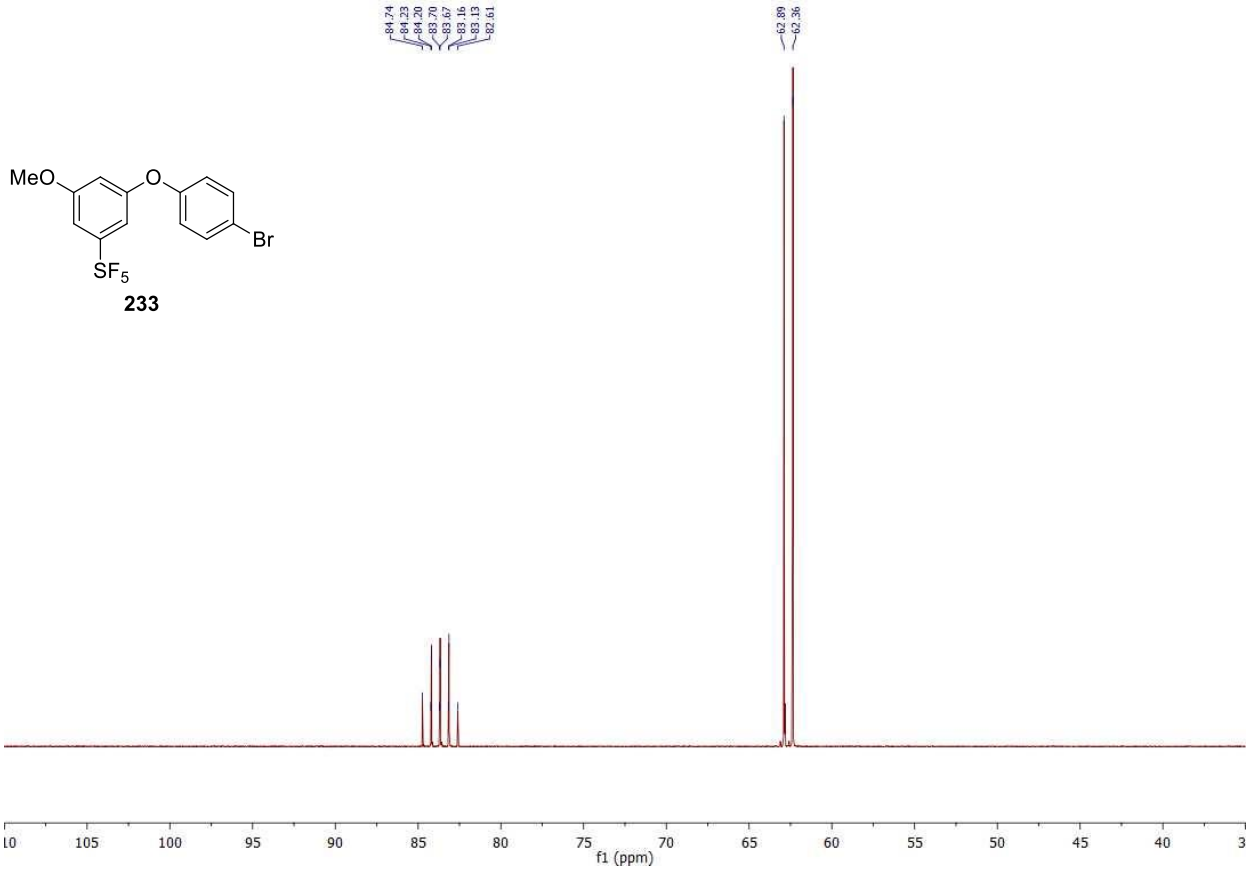

84.27
83.73
83.24
83.21
83.19
82.70
82.67
82.14
62.92
62.39
MeO
O
CN
SF5
f1 (ppm)

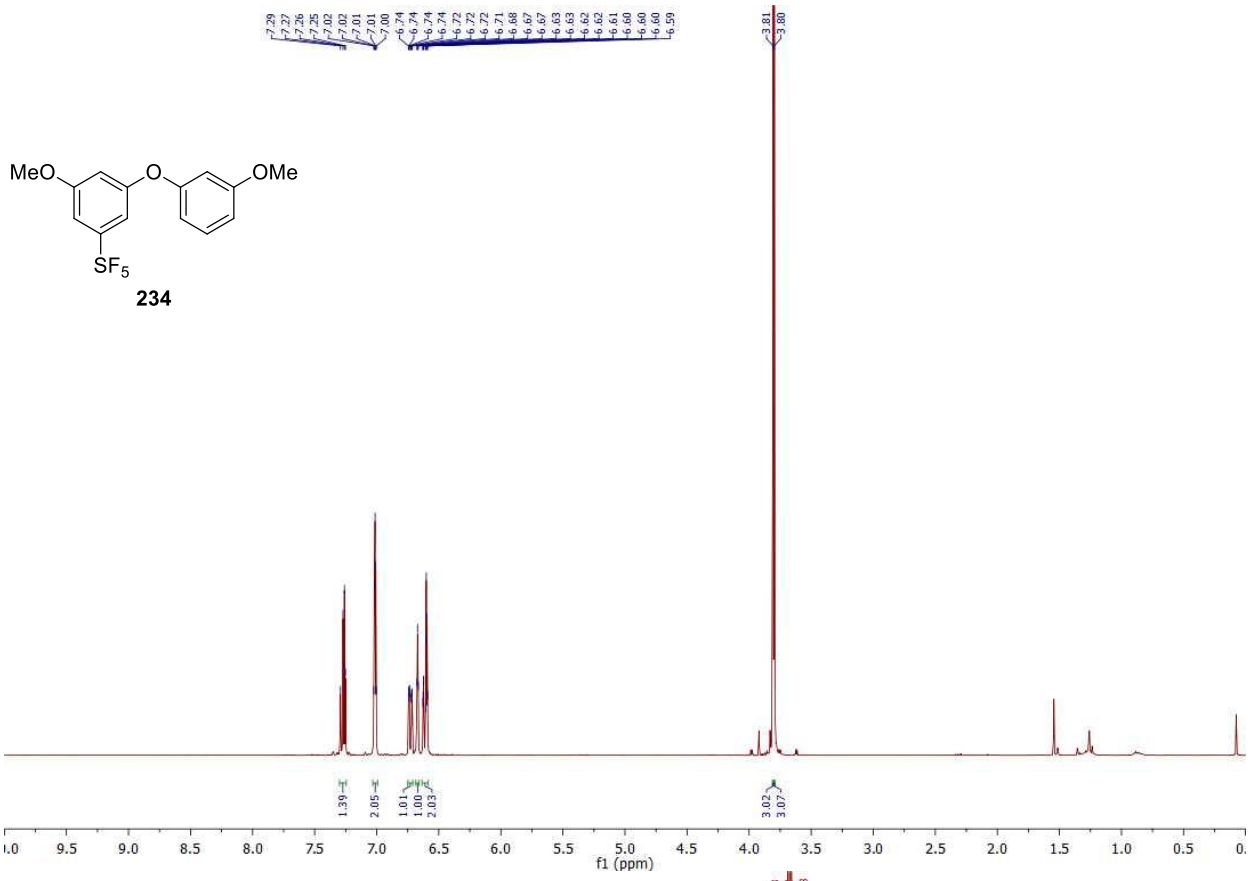
232

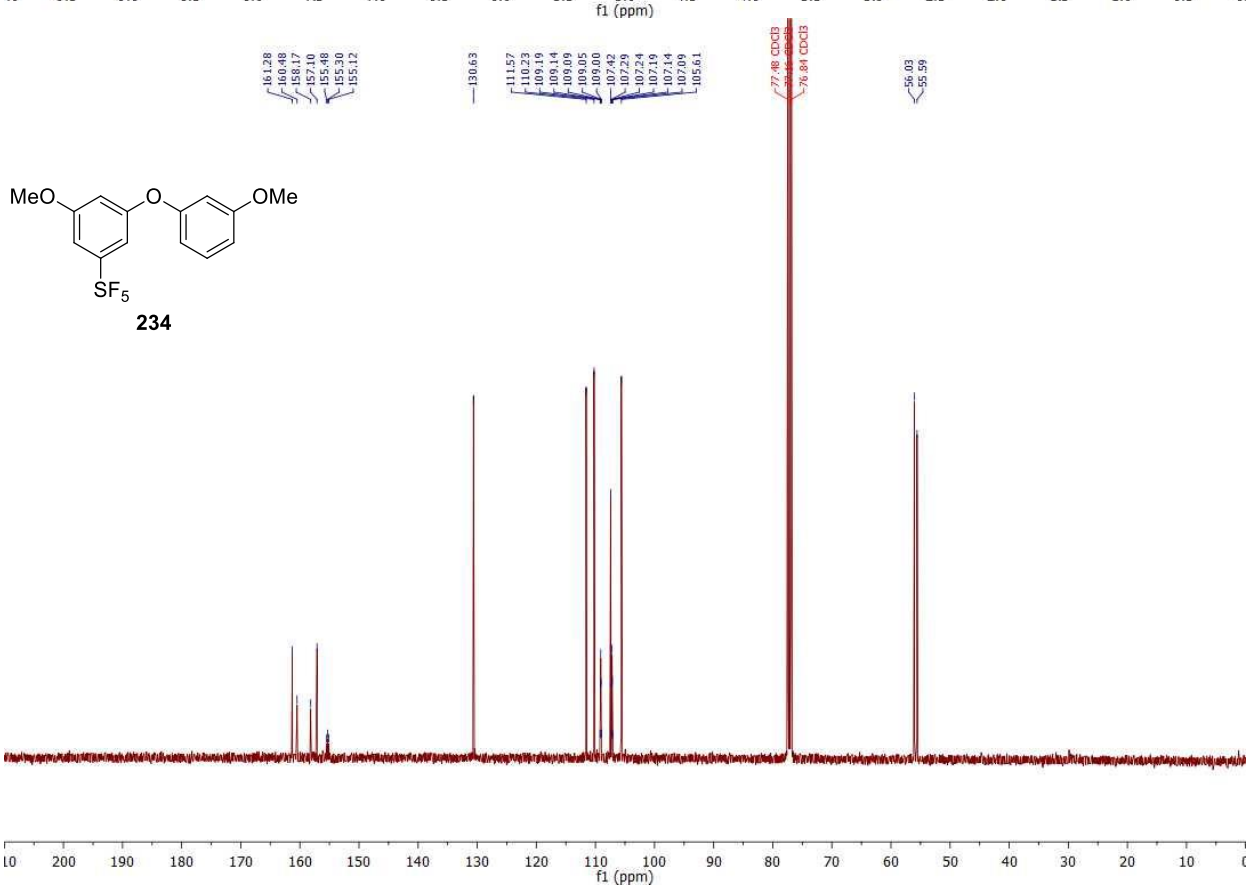

7.51
7.50
7.50
7.48
7.48
7.47
7.46
7.26
7.04
7.03
7.03
6.98
6.97
6.94
6.93
6.92
6.91
6.91
6.90
6.65
6.64
6.63
3.81
MeO
O
Br
SF5
1.97
1.01
0.99
2.04
1.00
3.12
f1 (ppm)

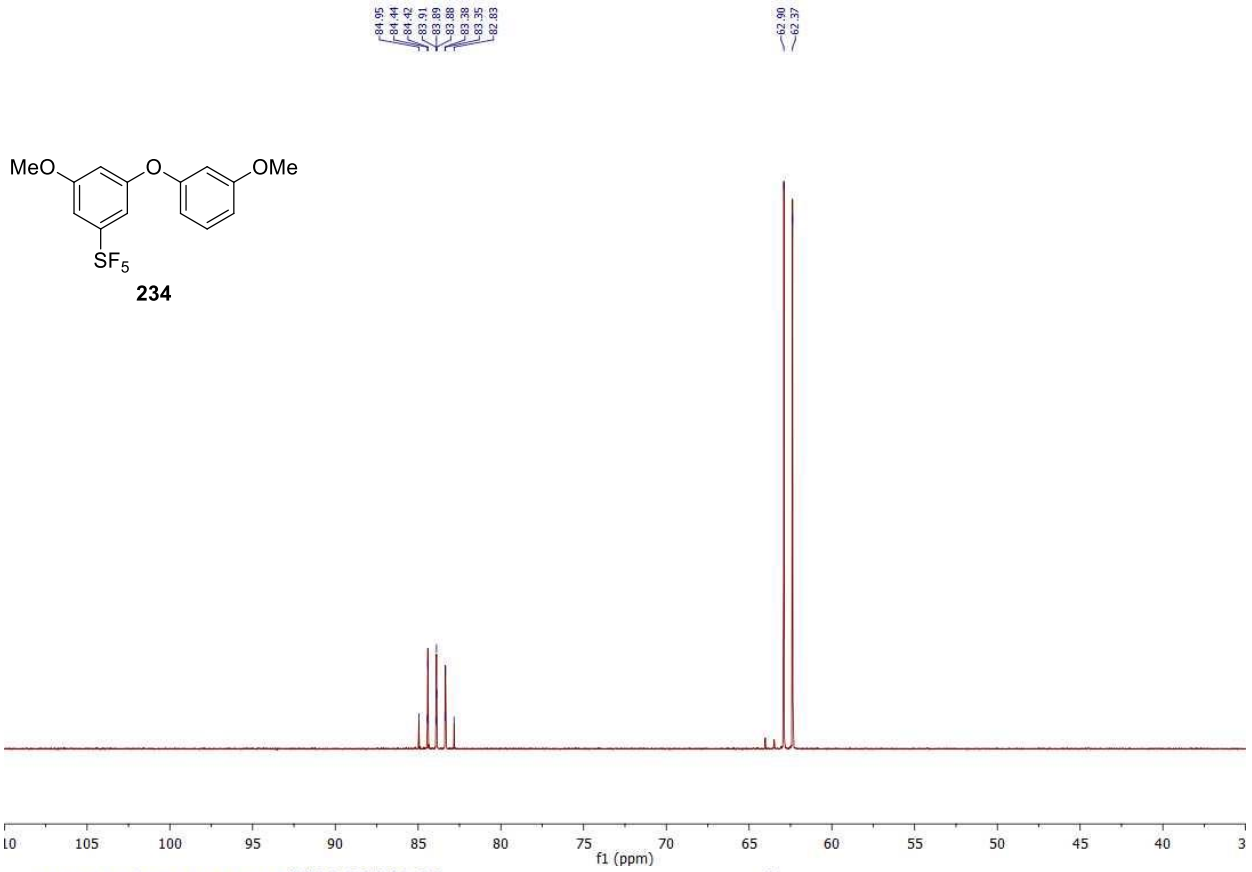
233

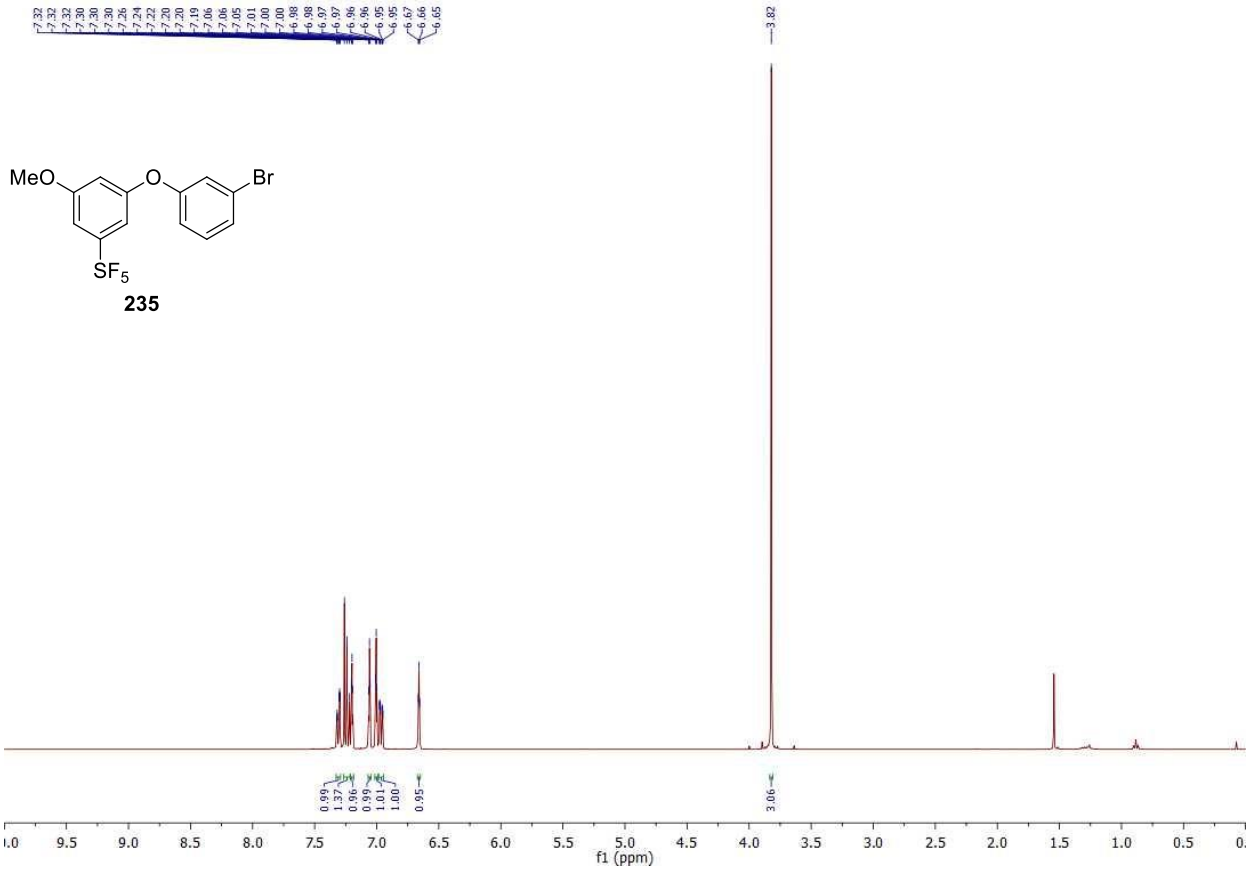

160.60
157.86
155.59
155.41
155.22
133.24
121.21
117.21
109.11
109.06
109.01
108.96
108.92
107.64
107.59
107.55
107.50
107.45
107.42
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.07
MeO
O
Br
SF5
233
f1 (ppm)

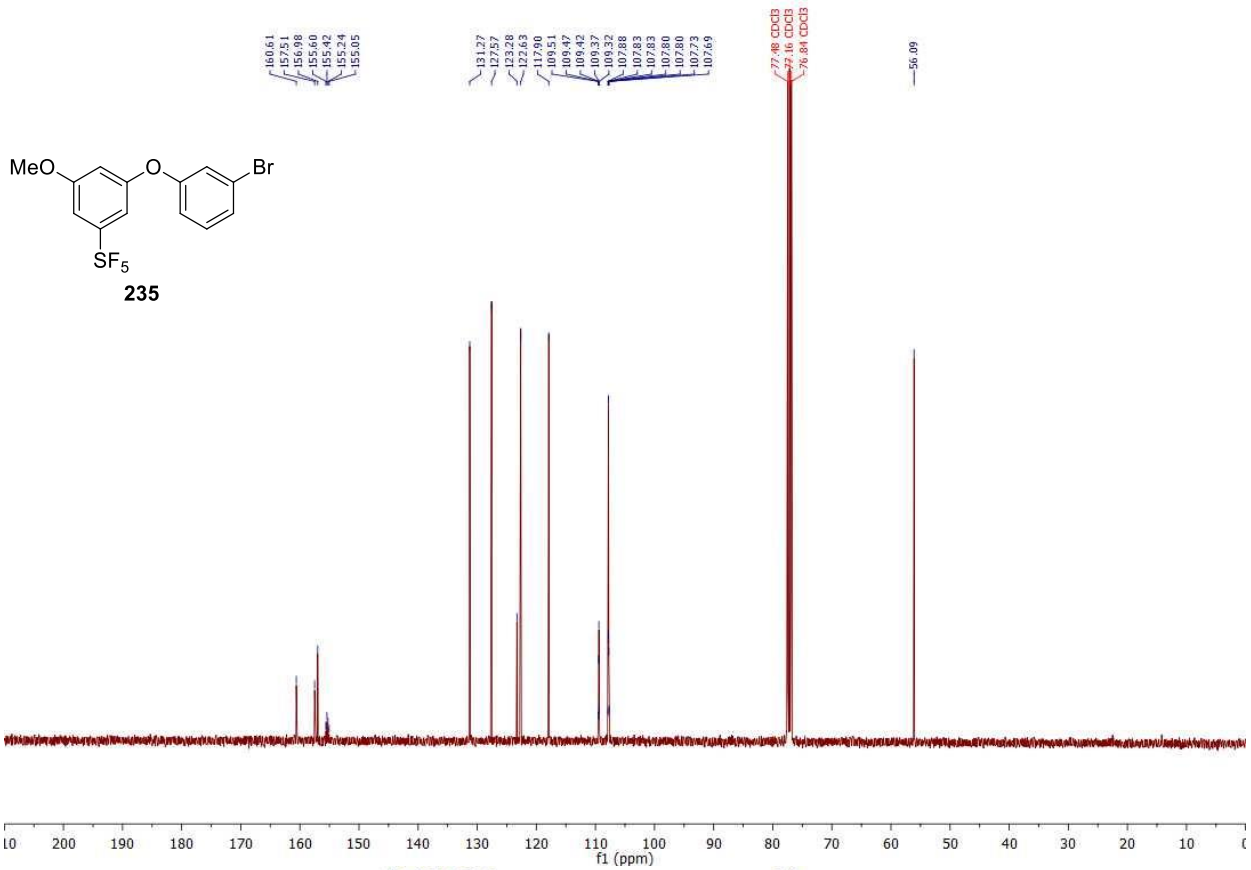

84.74
84.23
84.20
83.70
83.67
83.16
83.13
82.61
62.89
62.36
MeO
O
Br
SF5
233
f1 (ppm)

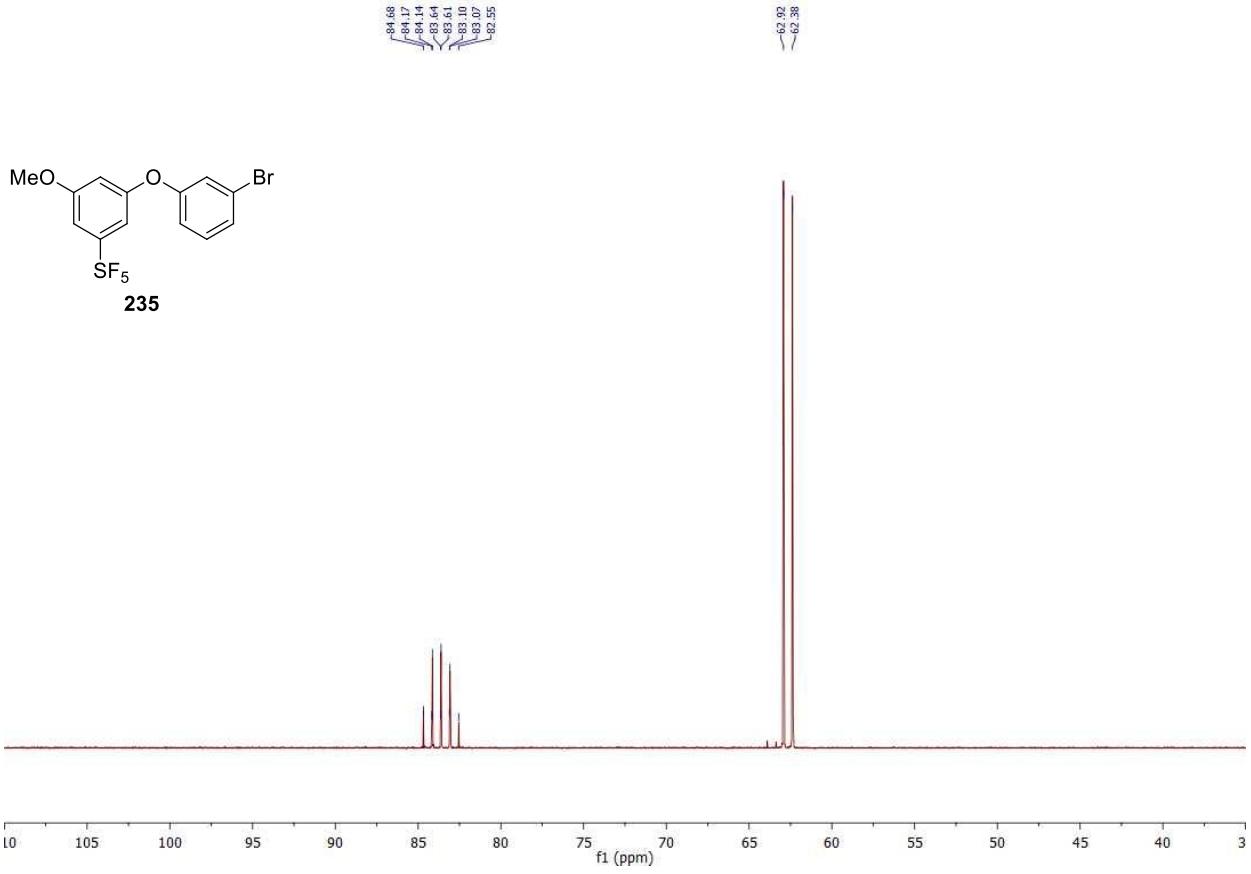

MeO
O
OMe
SF5
234
f1 (ppm)

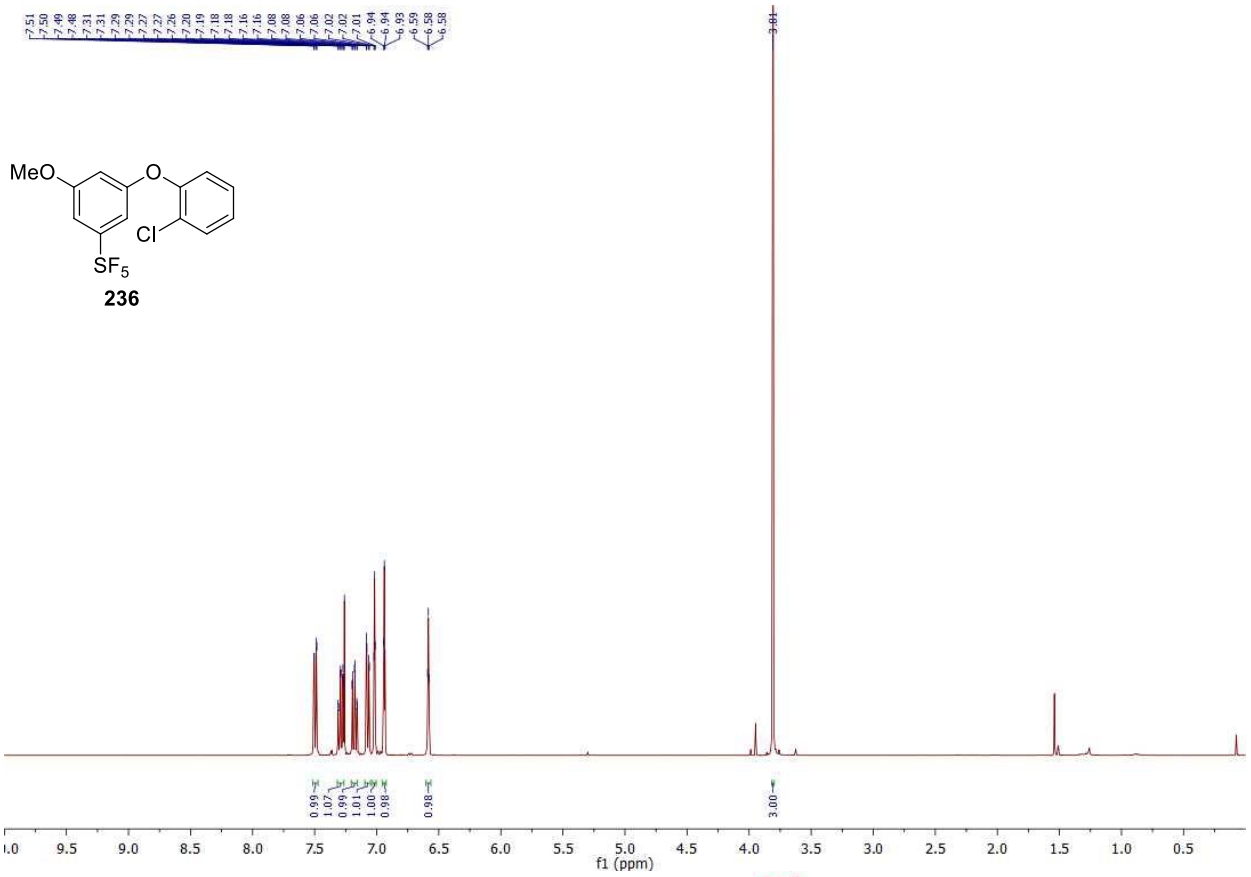

MeO
O
OMe
SF5
234
f1 (ppm)

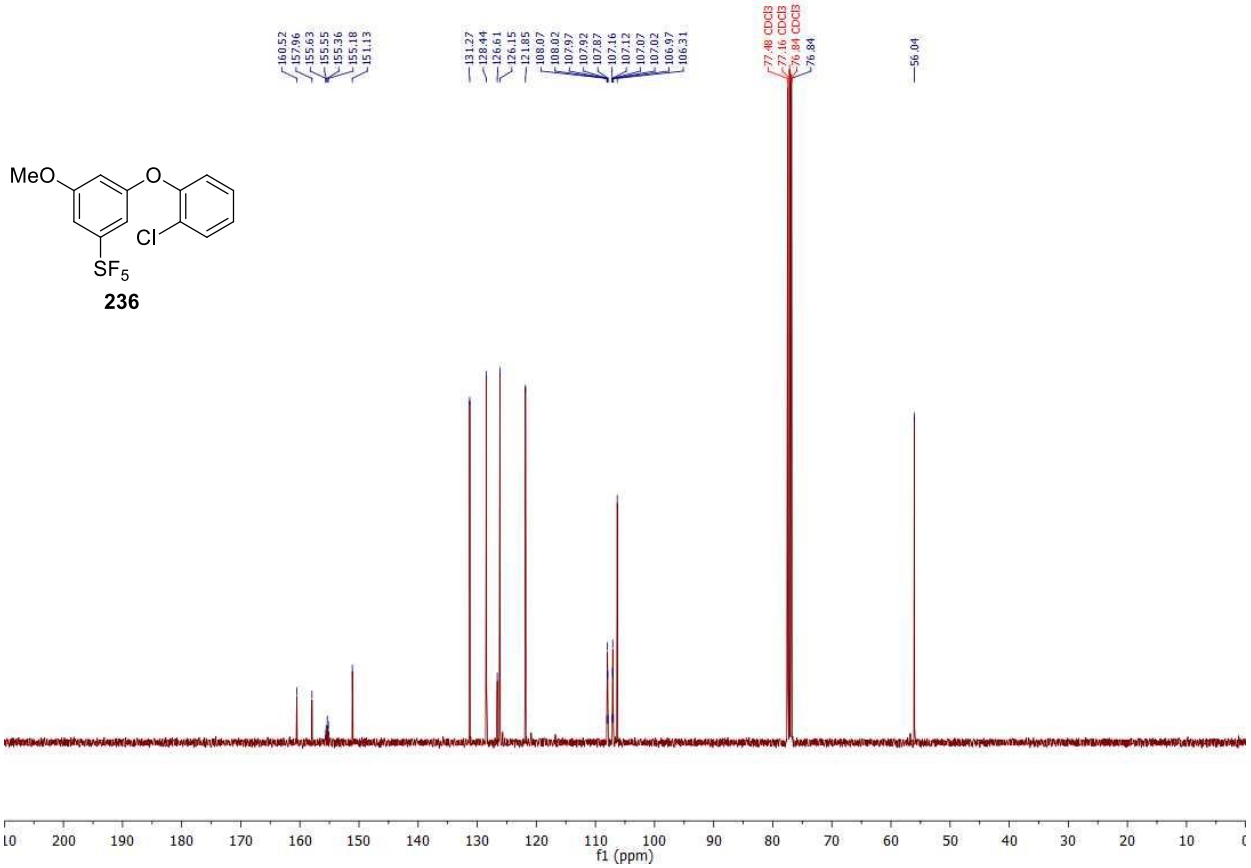

MeO
O
OMe
SF5
234
f1 (ppm)

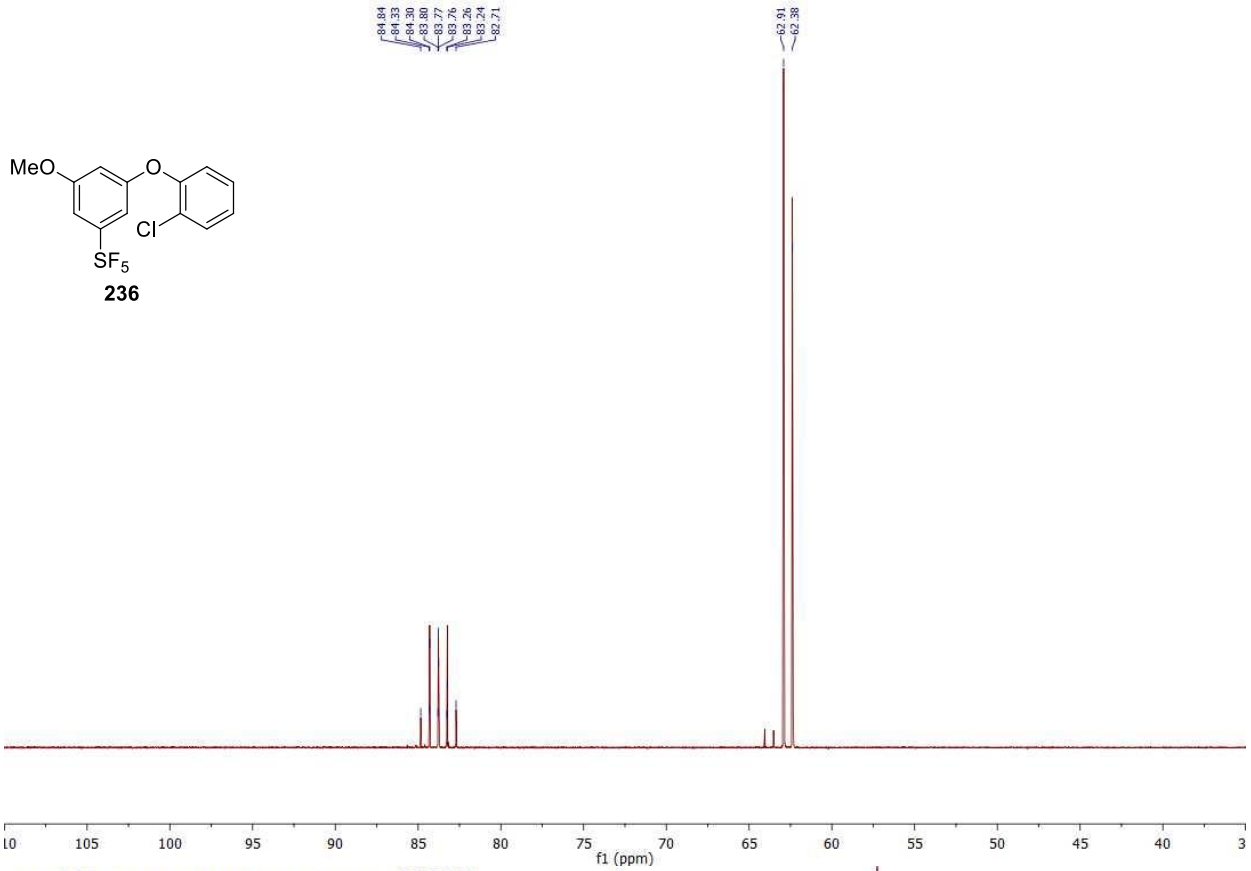

MeO
O
Br
SF5
235
f1 (ppm)

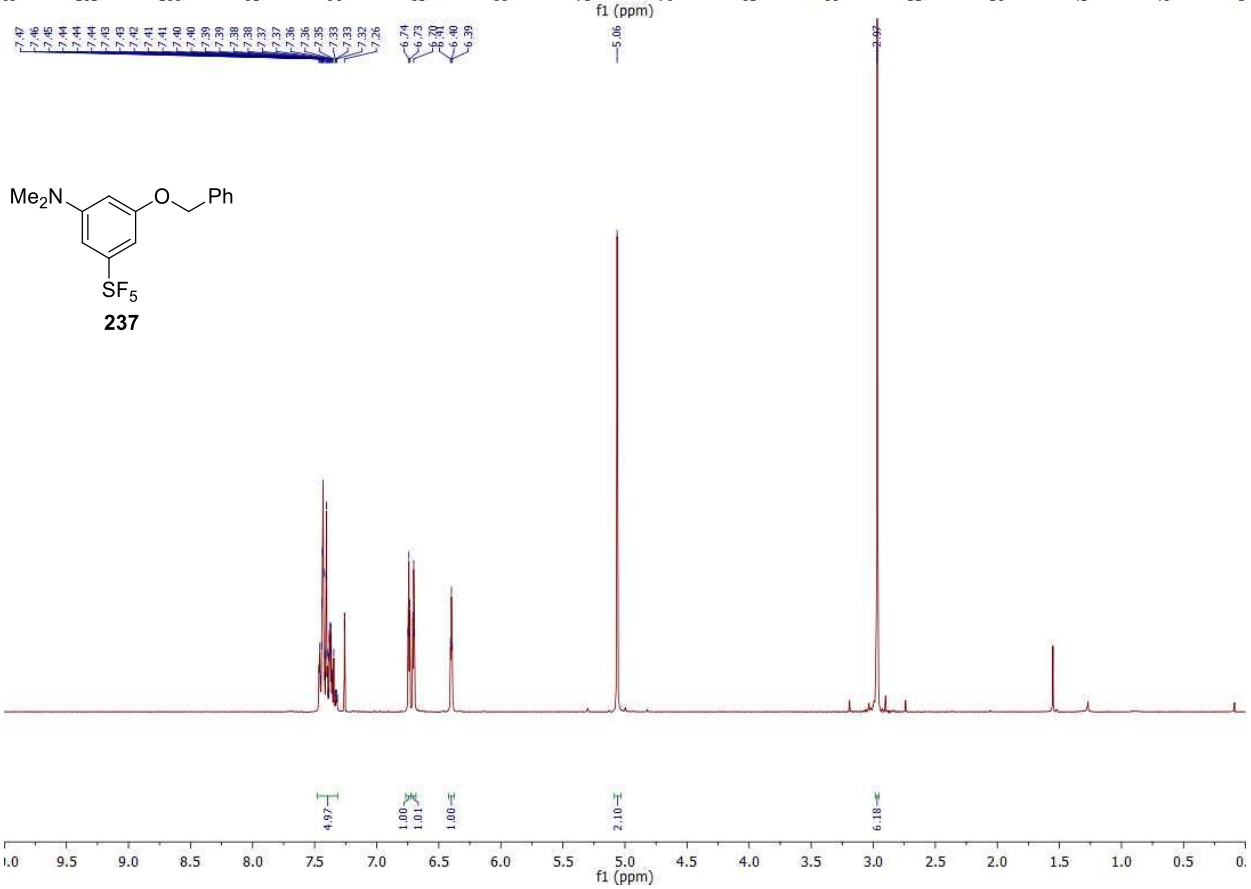

160.61
157.51
156.98
155.60
155.42
155.24
155.05
131.27
127.57
123.28
122.63
117.90
109.51
109.47
109.42
109.37
109.32
107.88
107.83
107.80
107.80
107.73
107.69
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.09
MeO
O
Br
SF5
235
f1 (ppm)

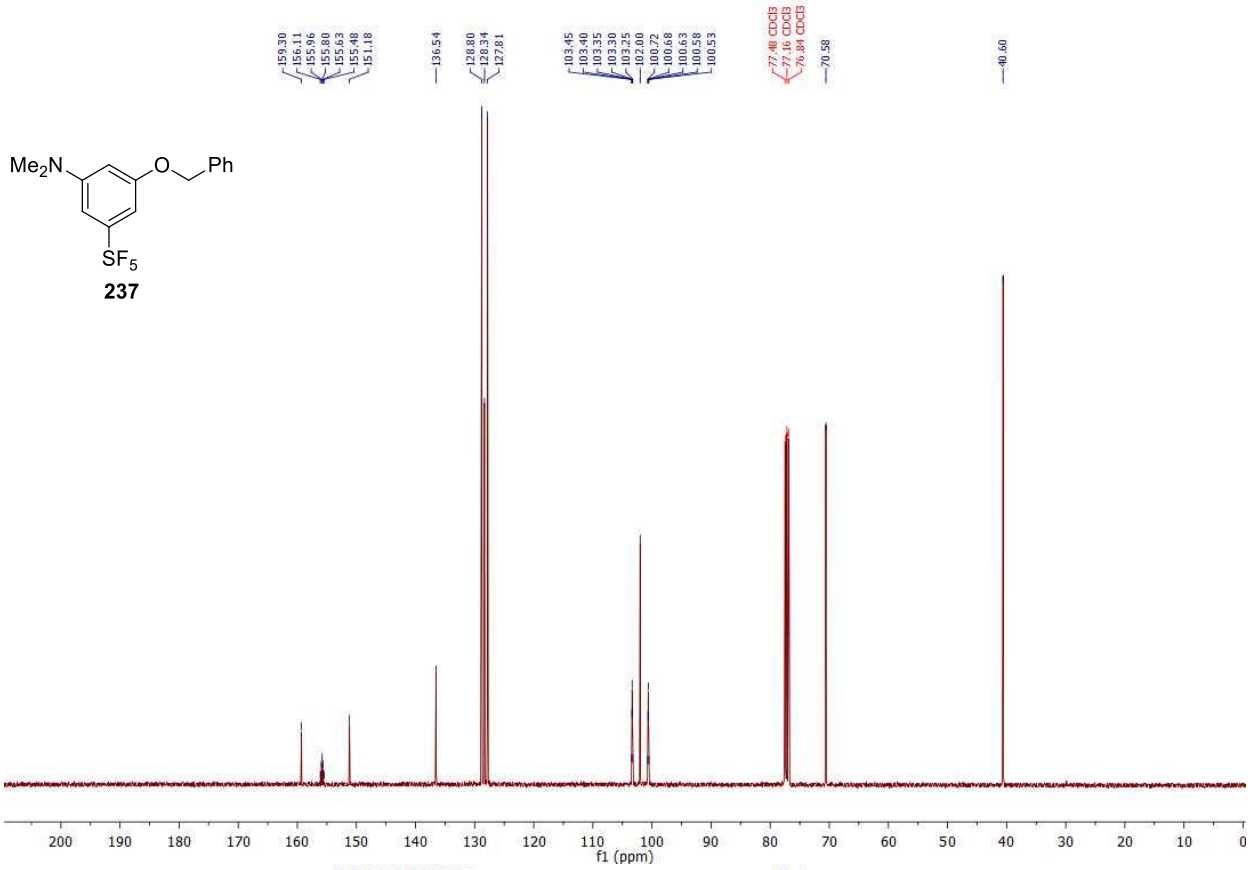

84.68
84.17
84.14
83.64
83.61
83.10
83.07
82.55
62.92
62.38
MeO
O
Br
SF5
235
f1 (ppm)

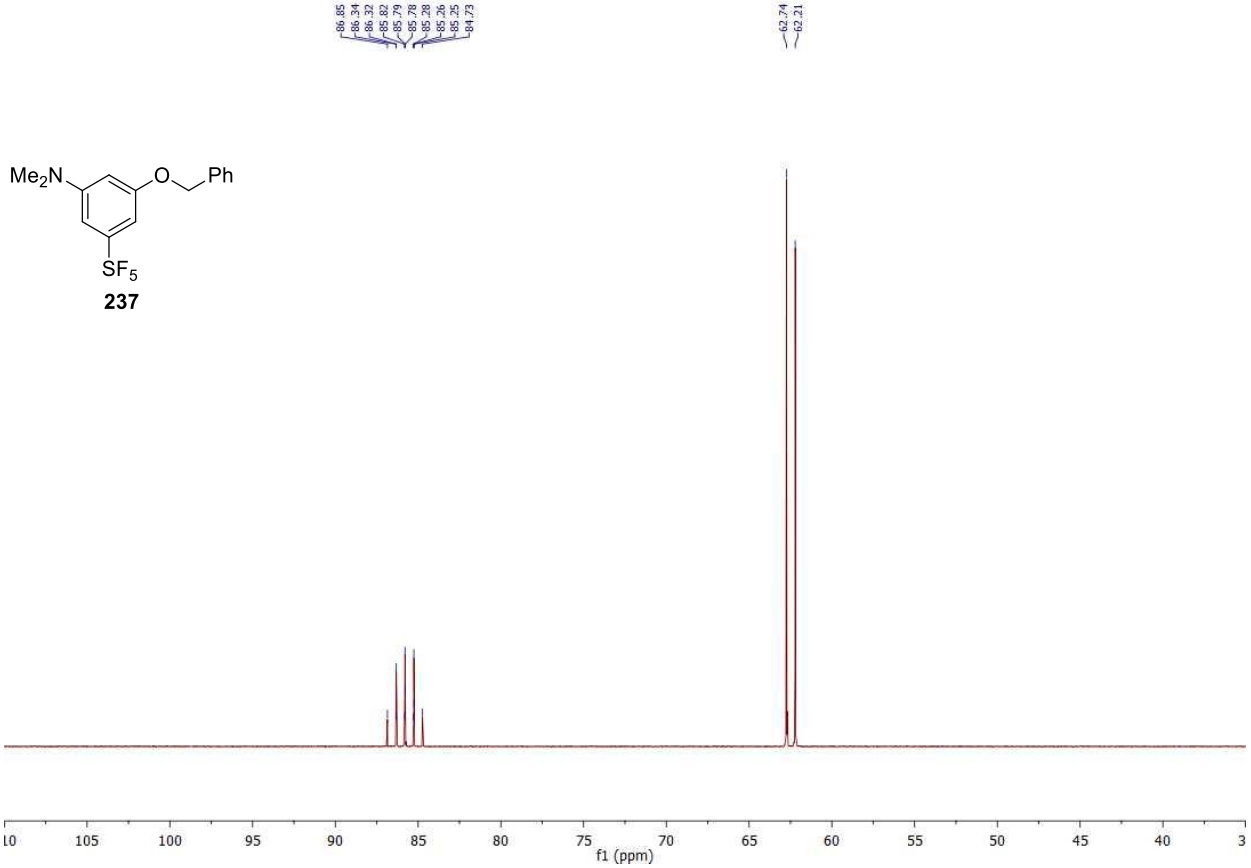

MeO
O
Cl
SF5
236
f1 (ppm)

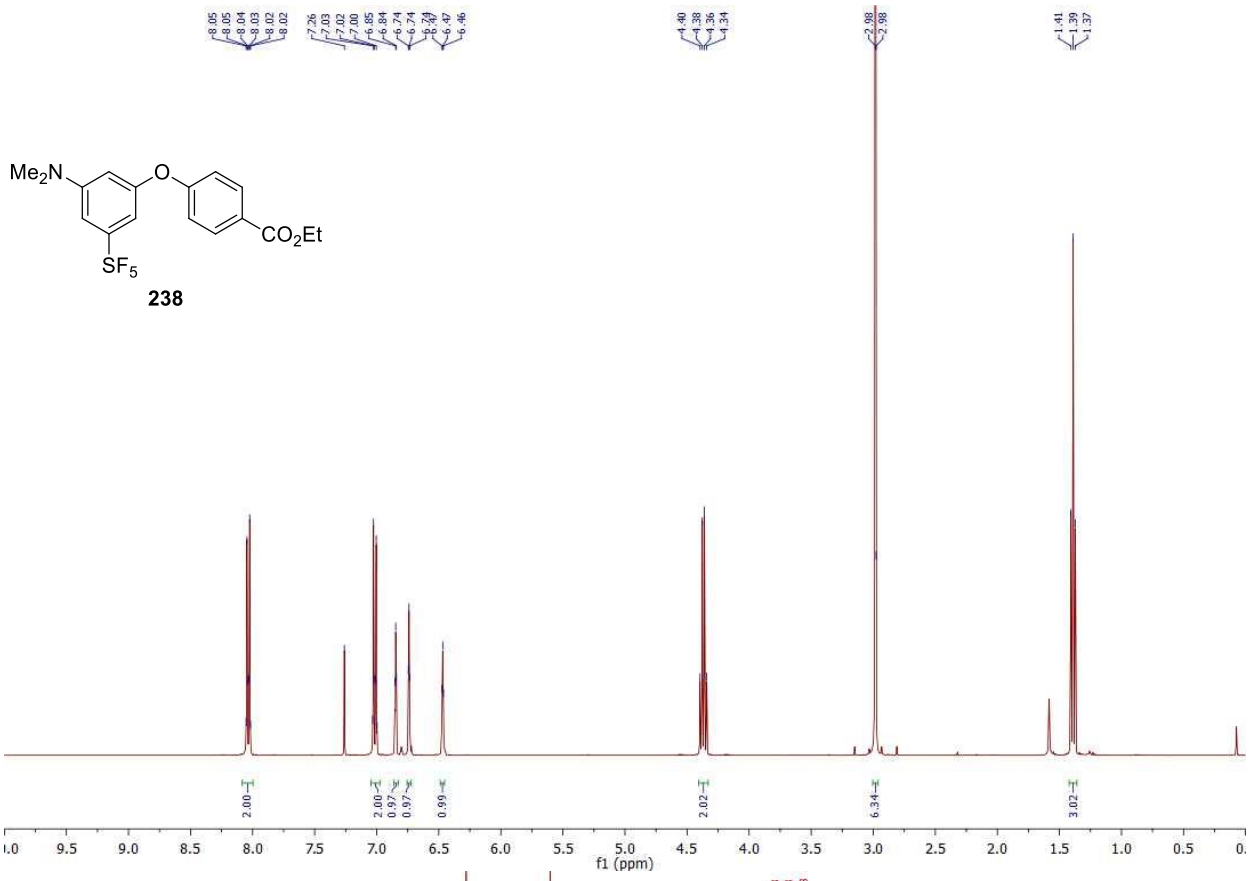

MeO
O
Cl
SF5
236
f1 (ppm)

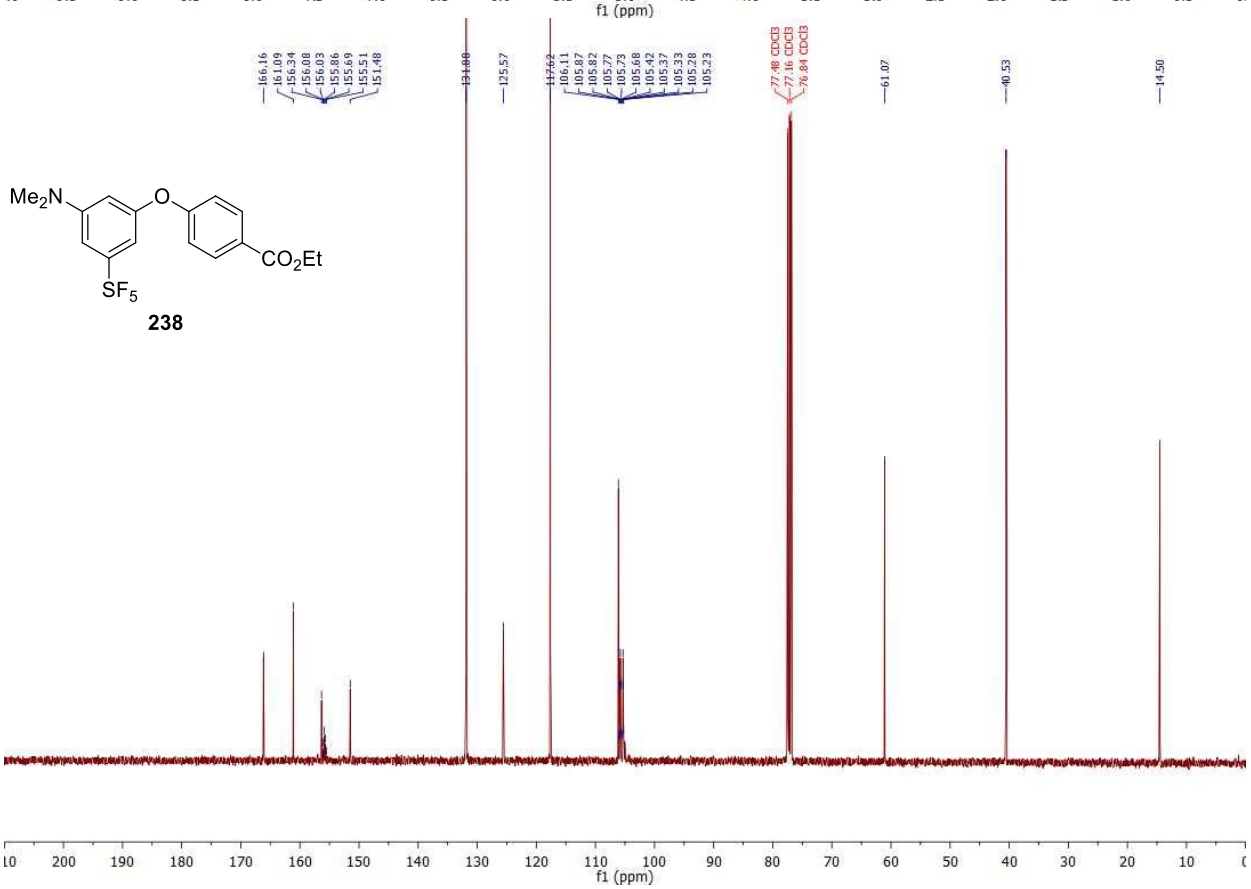

MeO
O
Cl
SF5
236
f1 (ppm)

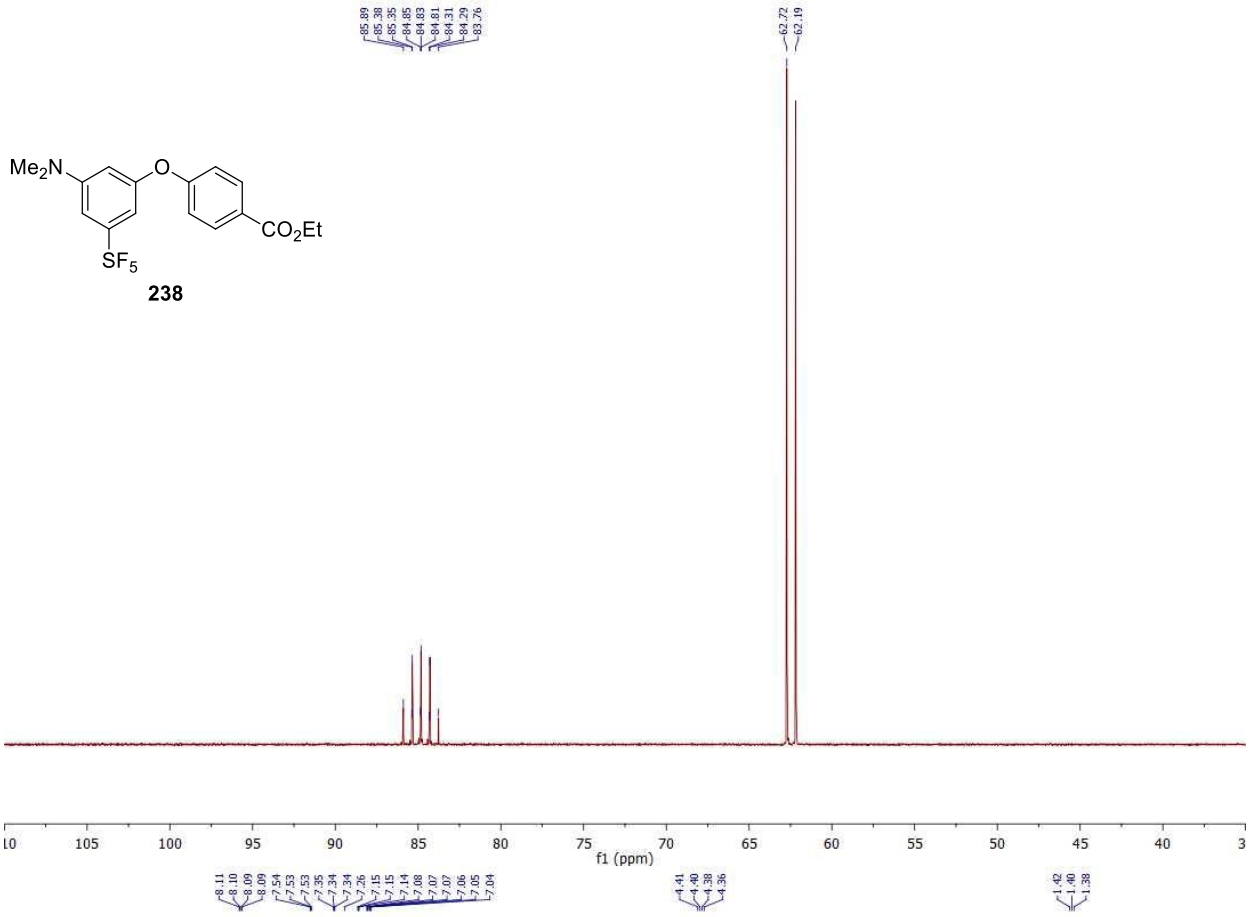

Me2N
O
Ph
SF5
237
f1 (ppm)


159.30
156.11
155.96
155.80
155.63
155.48
151.18
136.54
128.80
128.34
127.81
103.45
103.40
103.35
103.30
103.25
102.00
100.72
100.68
100.63
100.58
100.53
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
70.58
40.60
Me2N
O
Ph
SF5
237
f1 (ppm)

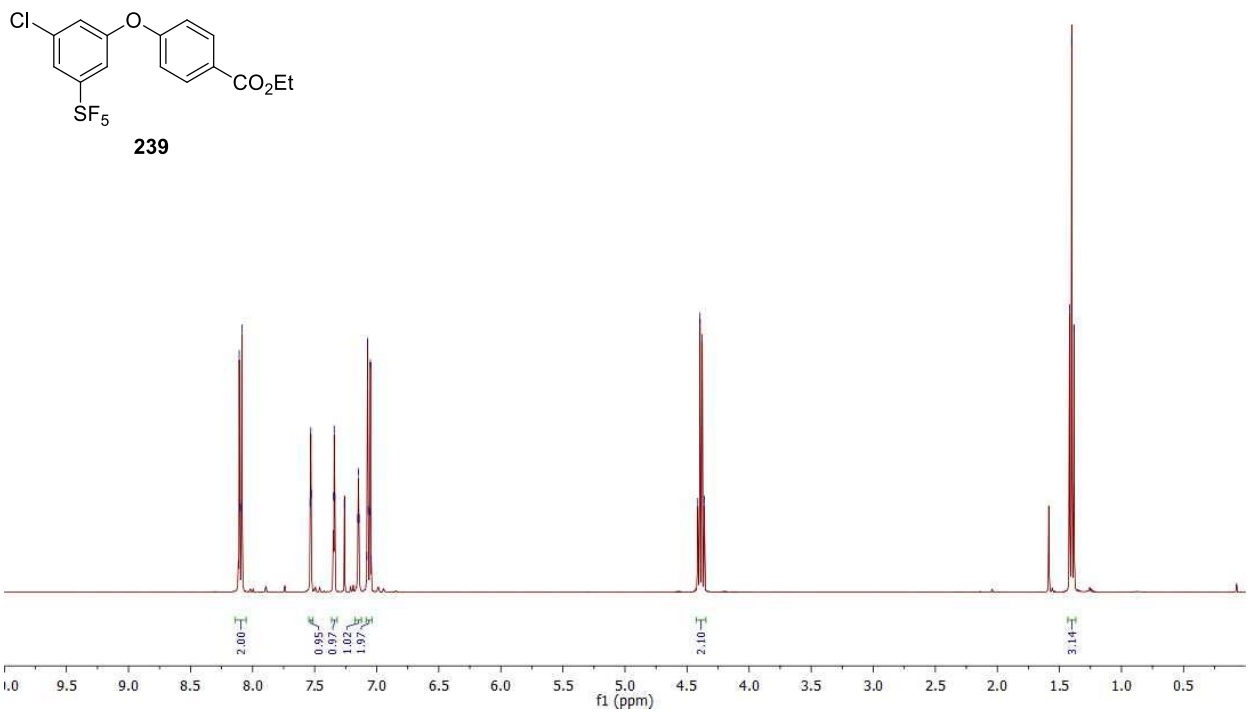

86.85
86.34
86.32
85.82
85.79
85.78
85.28
85.26
85.25
84.73
62.74
62.21
Me2N
O
Ph
SF5
237
f1 (ppm)


Me2N
O
CO2Et
SF5
238
f1 (ppm)

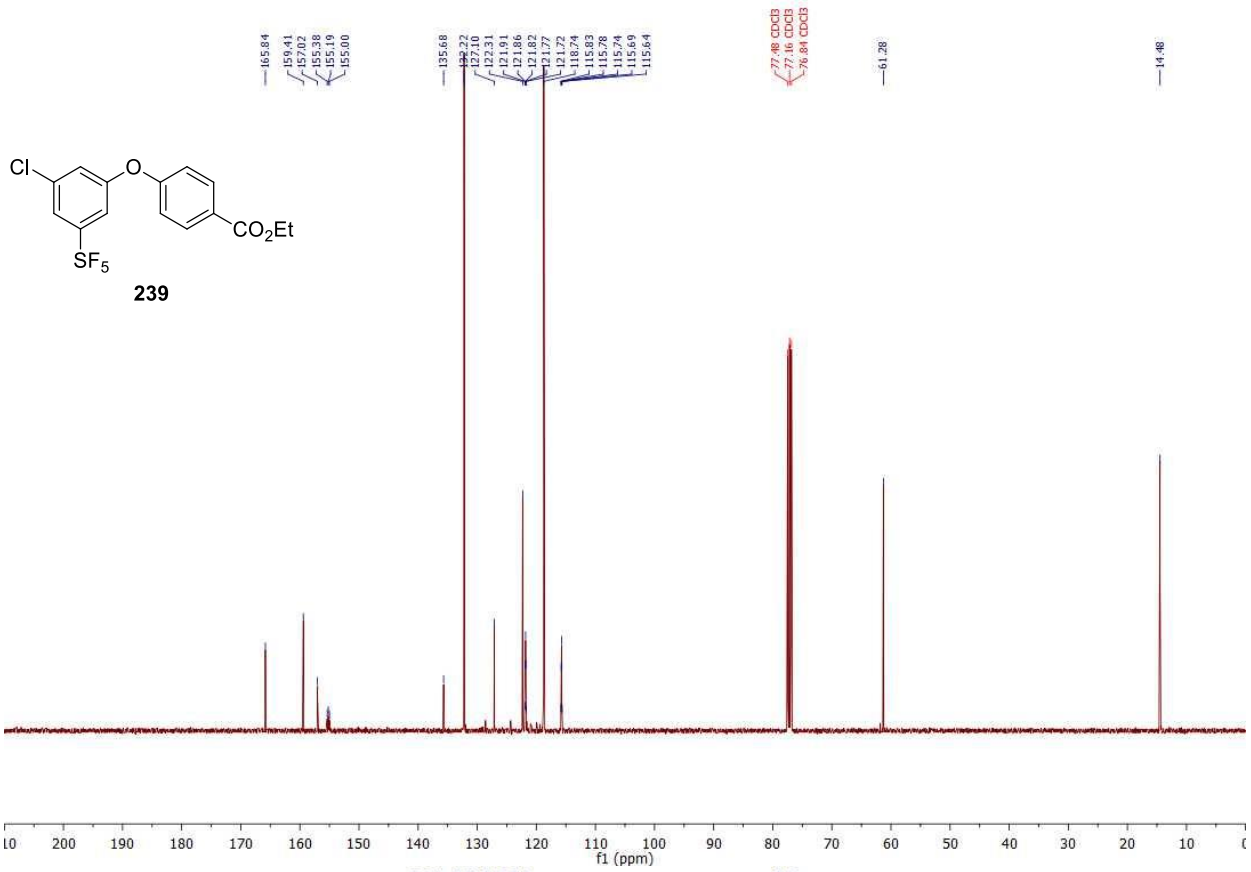

Me2N
O
CO2Et
SF5
238
f1 (ppm)

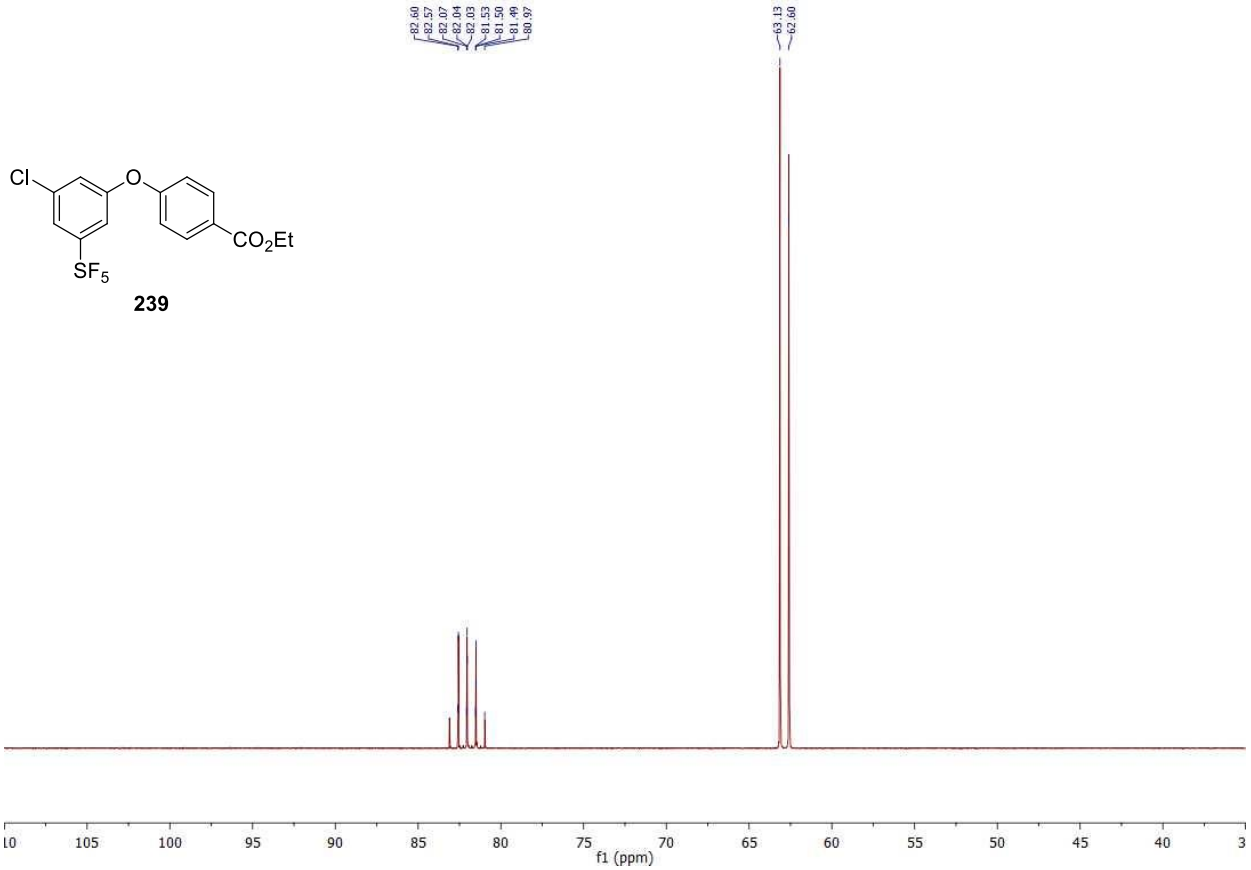


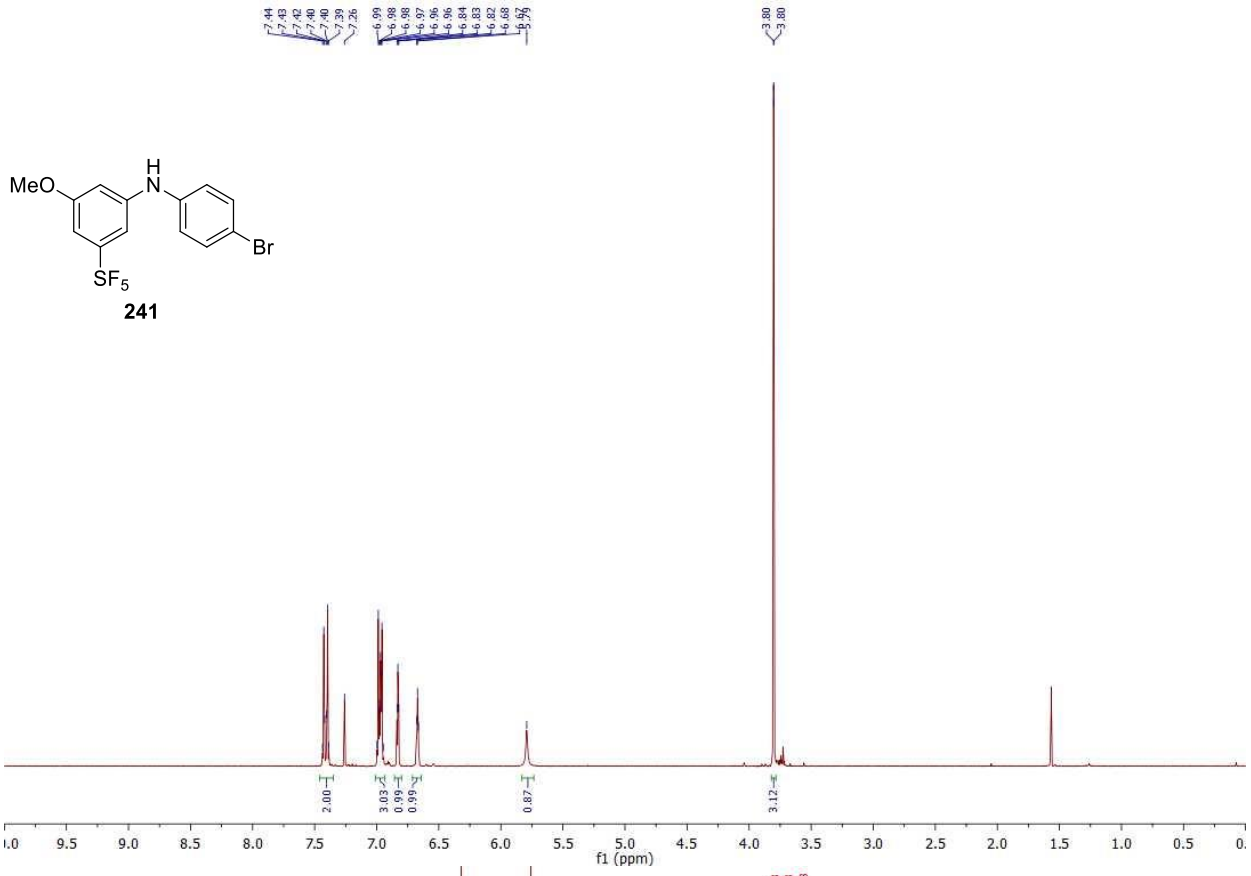
238

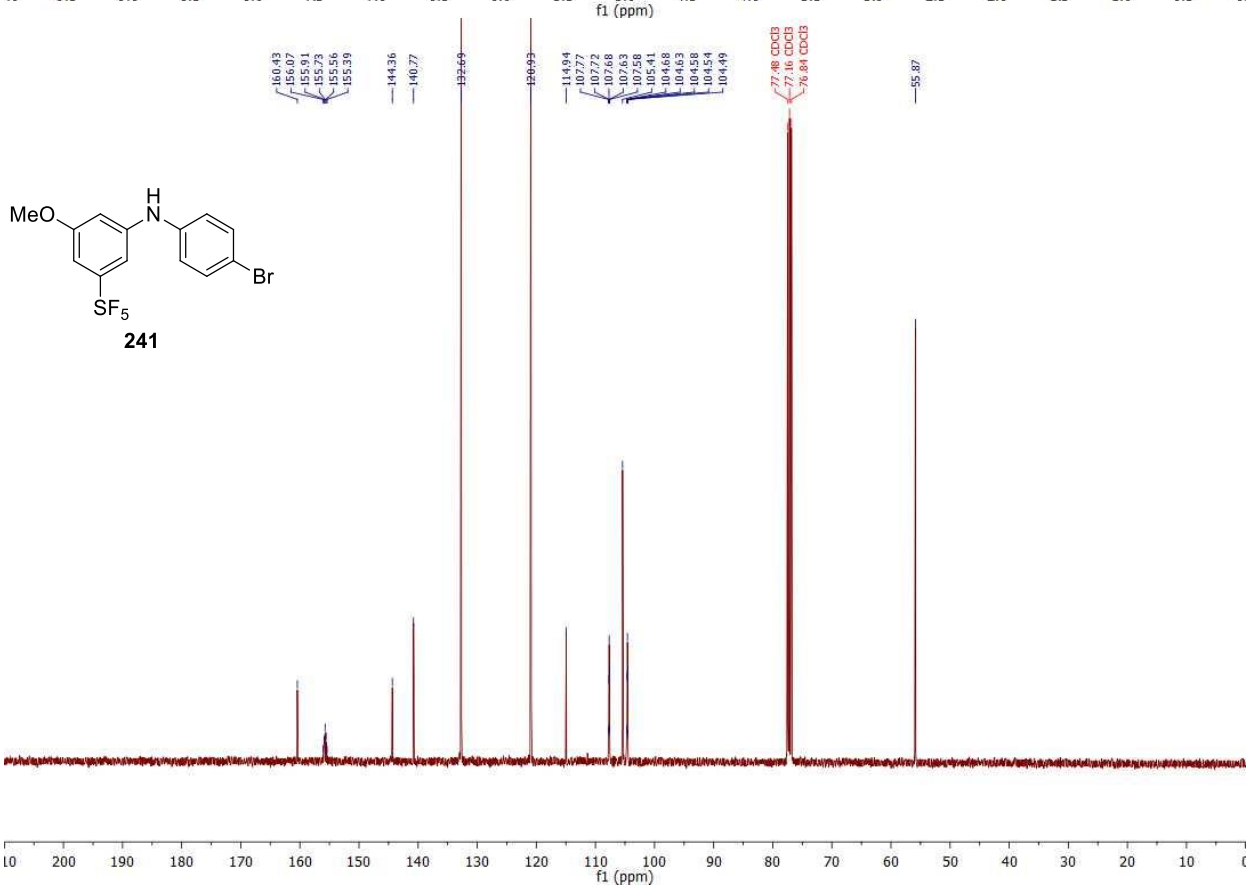


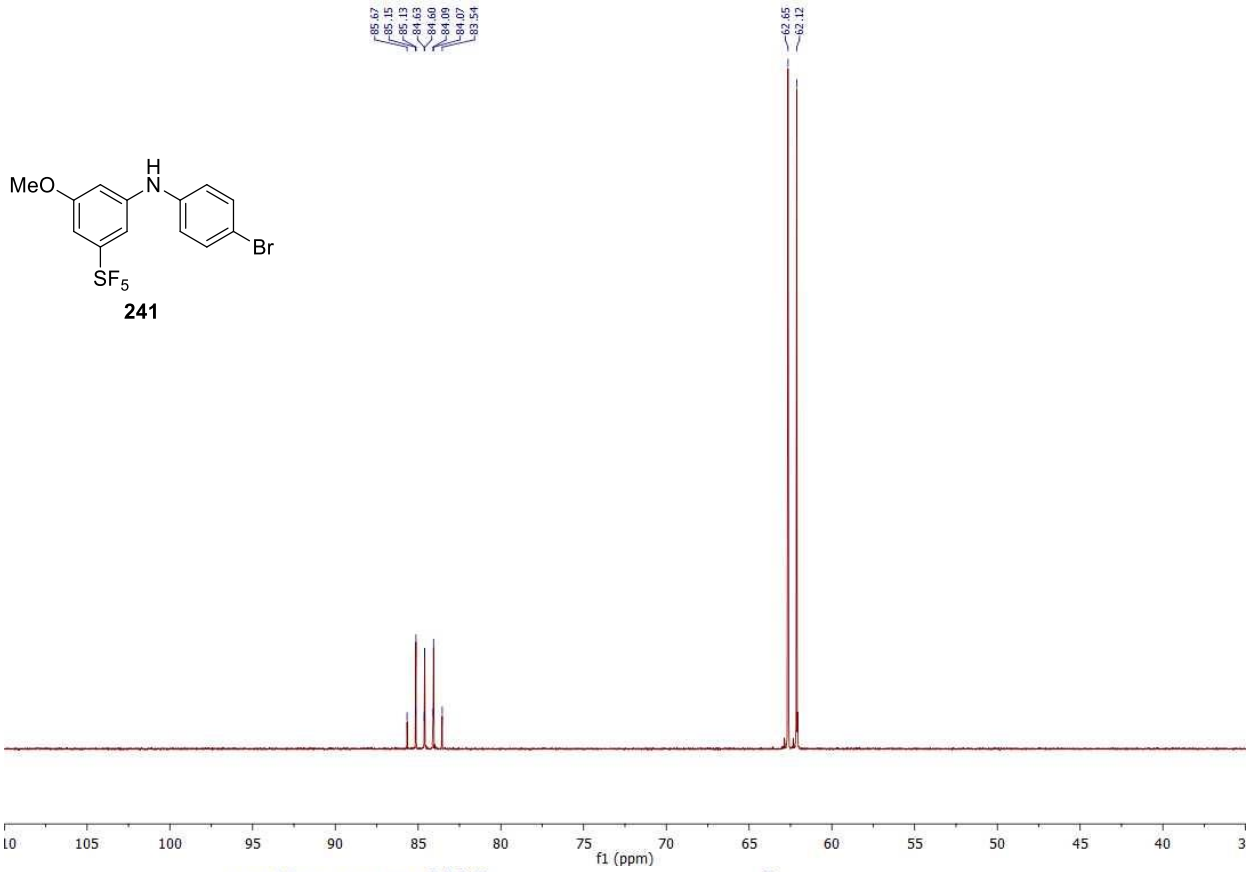
239

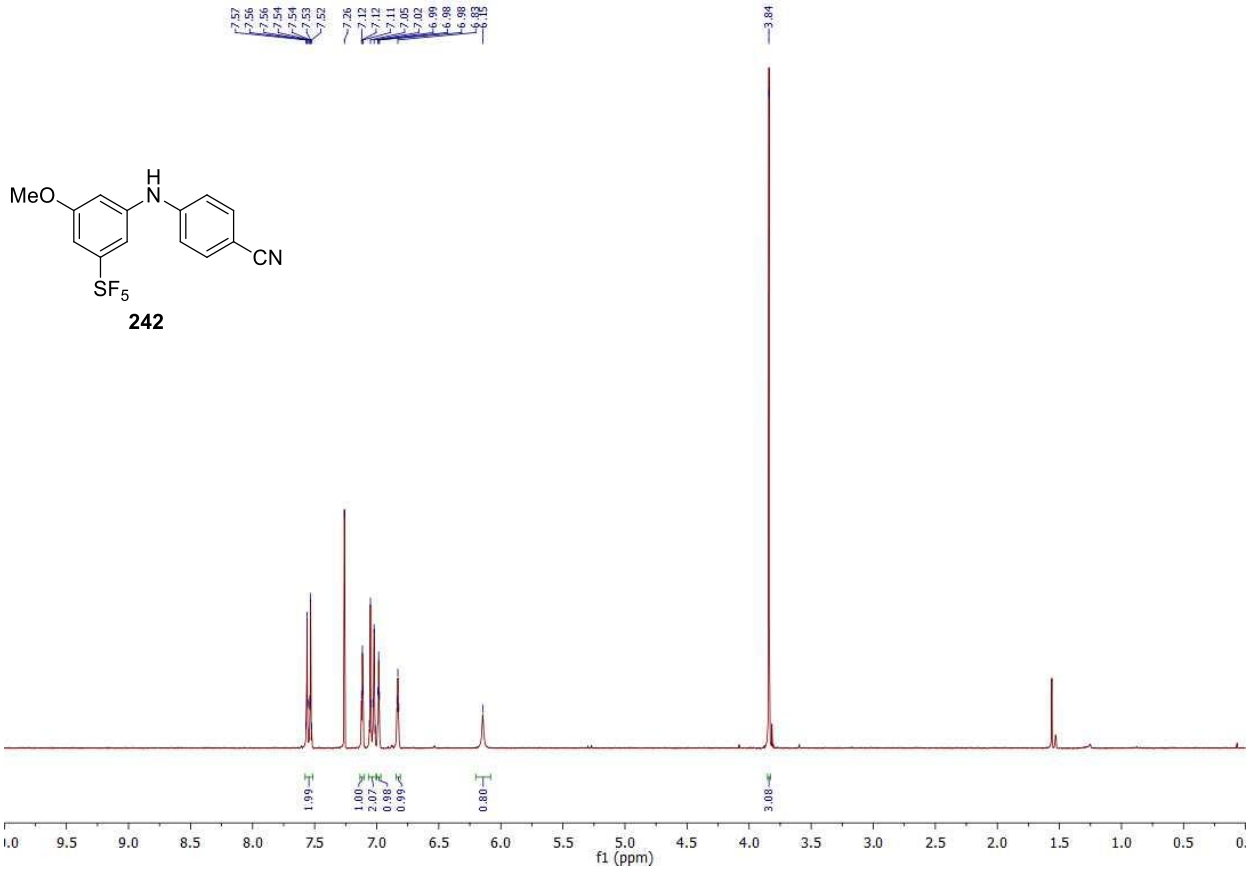

165.84
159.41
157.02
155.38
155.19
155.00
135.68
132.22
127.10
122.31
121.91
121.86
121.82
121.77
121.72
118.74
115.83
115.78
115.74
115.69
115.64
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
61.28
14.48
Cl
O
CO2Et
SF5
239
f1 (ppm)

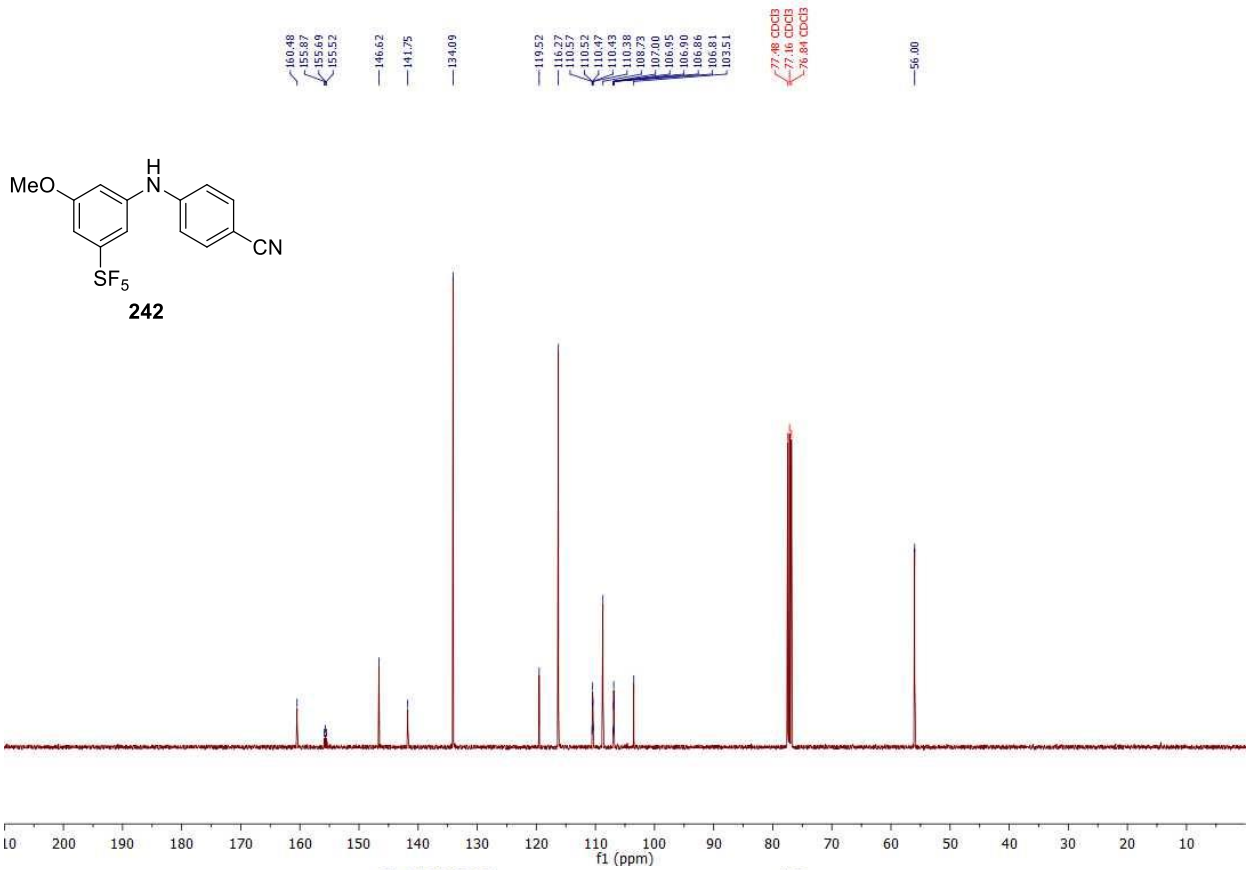

82.60
82.57
82.07
82.04
82.03
81.53
81.50
81.49
80.97
63.13
62.60
Cl
O
CO2Et
SF5
239
f1 (ppm)

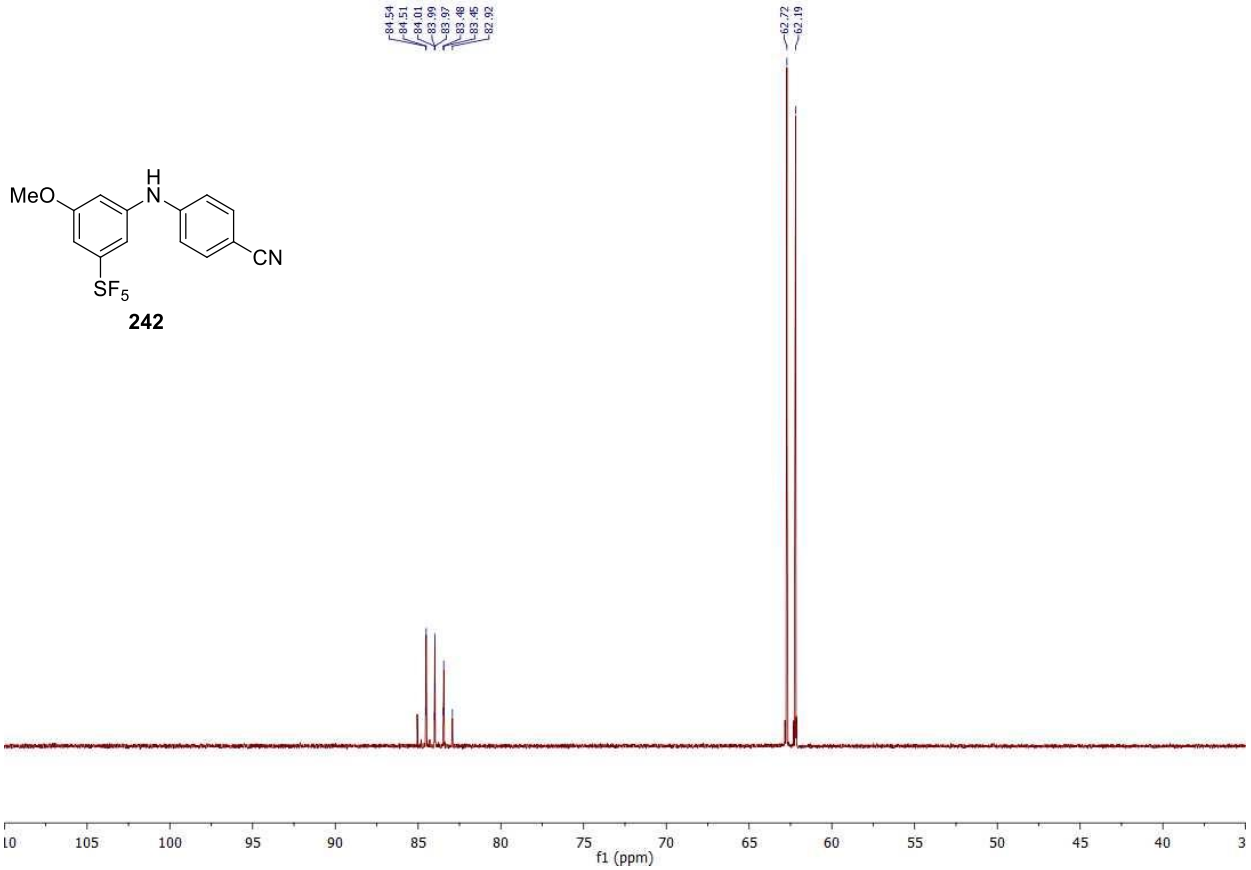

MeO
H
N
Br
SF5
241
f1 (ppm)

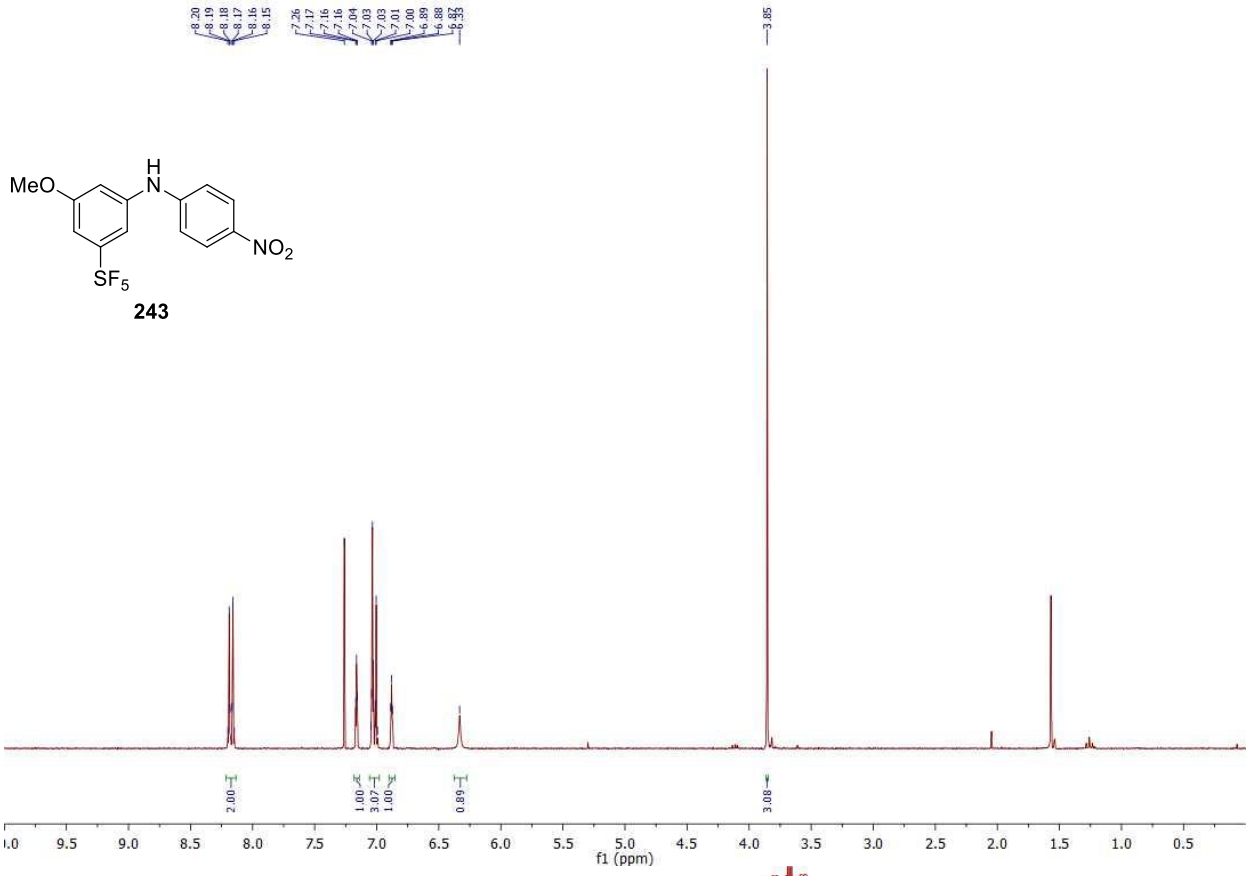

MeO
H
N
Br
SF5
241
f1 (ppm)

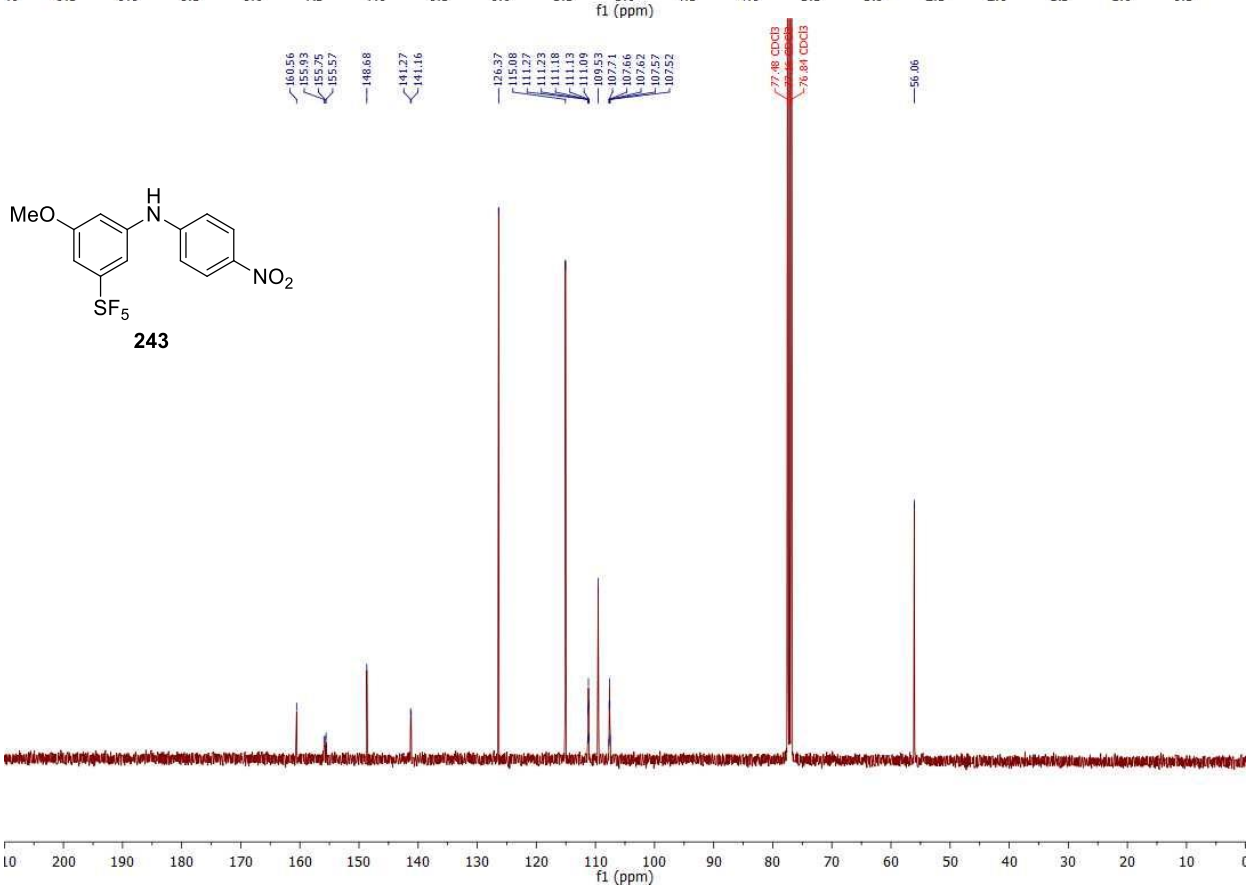

MeO
H
N
Br
SF5
241
f1 (ppm)

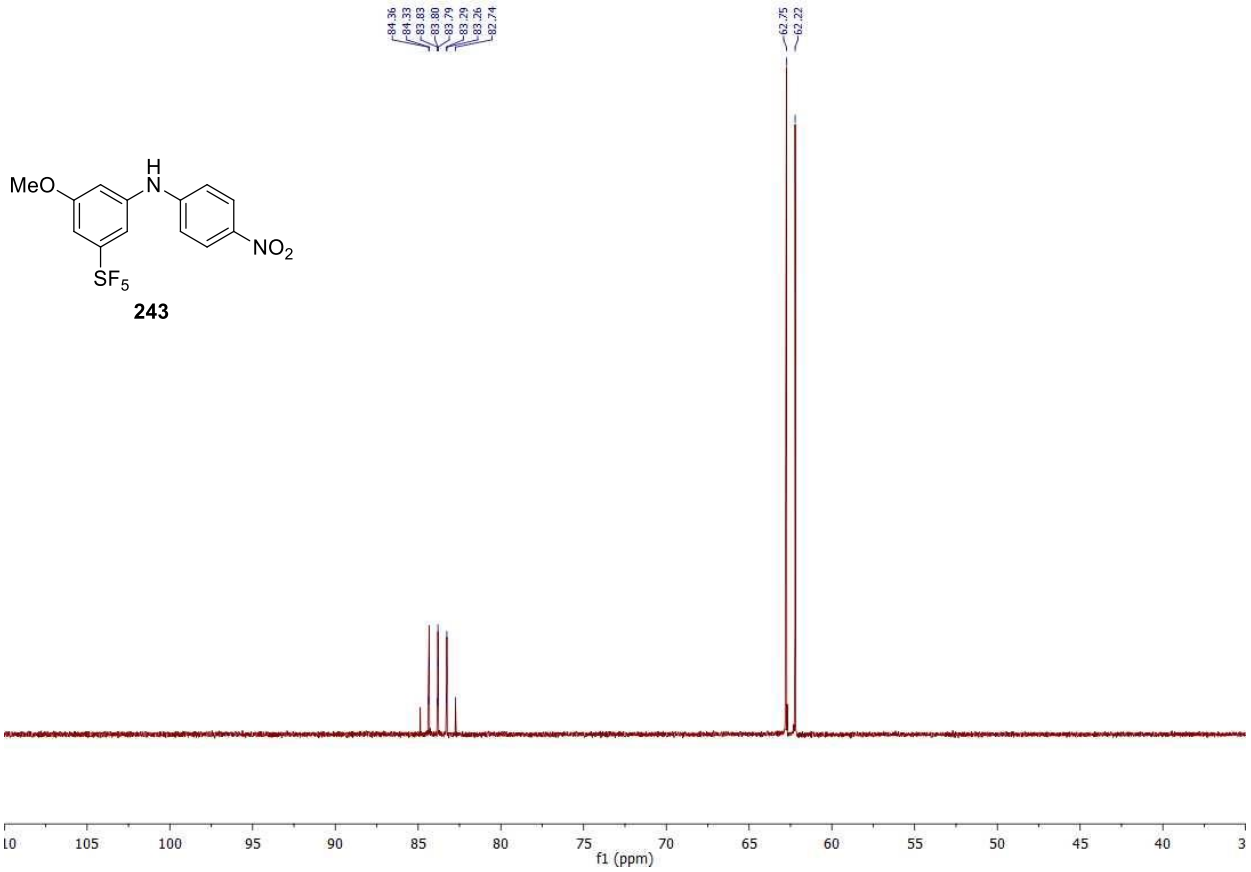

MeO
H
N
CN
SF5
242
f1 (ppm)


160.48
155.87
155.69
155.52
146.62
141.75
134.09
119.52
116.27
110.57
110.52
110.47
110.43
110.38
108.73
107.00
106.95
106.90
106.86
106.81
103.51
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.00
MeO
H
N
CN
SF5
242
f1 (ppm)

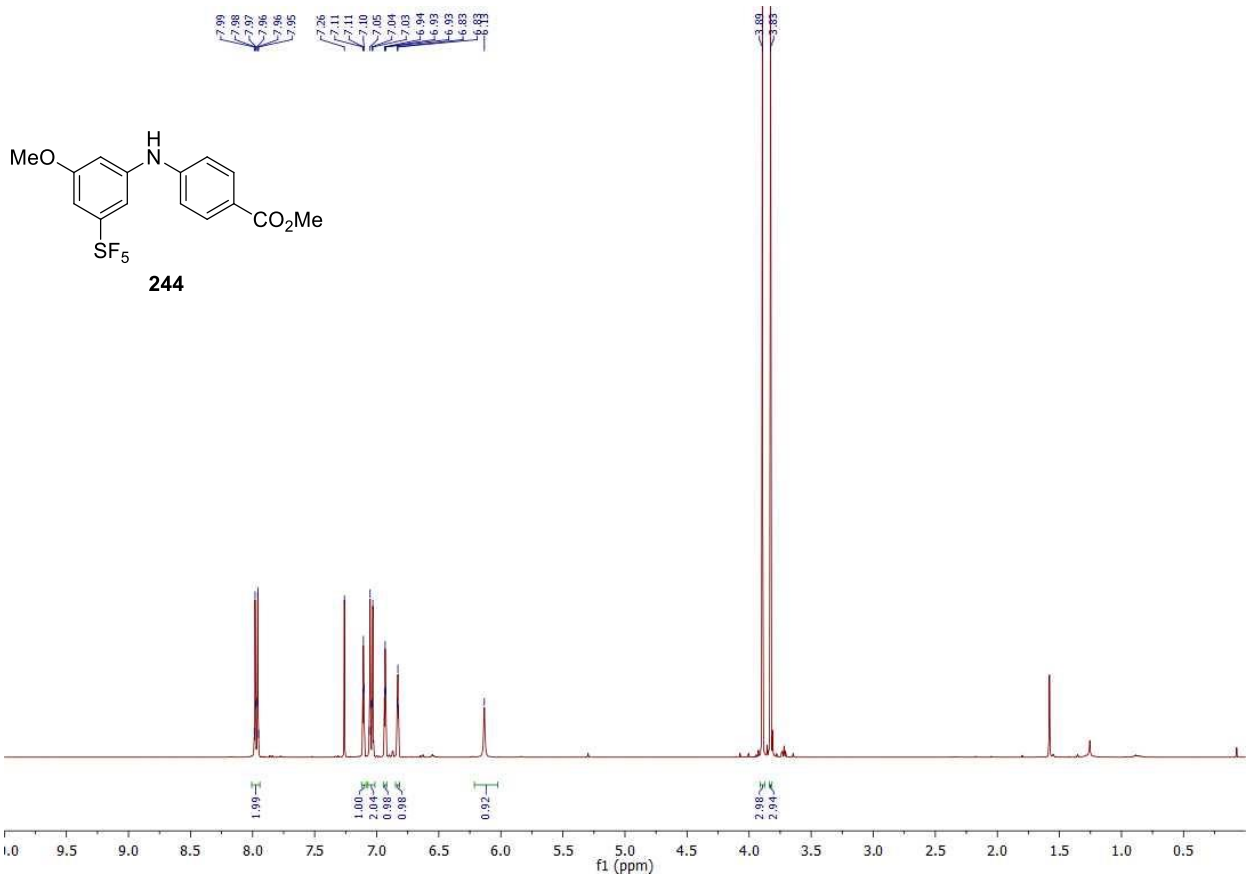

84.54
84.51
84.01
83.99
83.97
83.48
83.45
82.92
62.72
62.19
MeO
H
N
CN
SF5
242
f1 (ppm)


MeO
H
N
NO2
SF5
243
f1 (ppm)

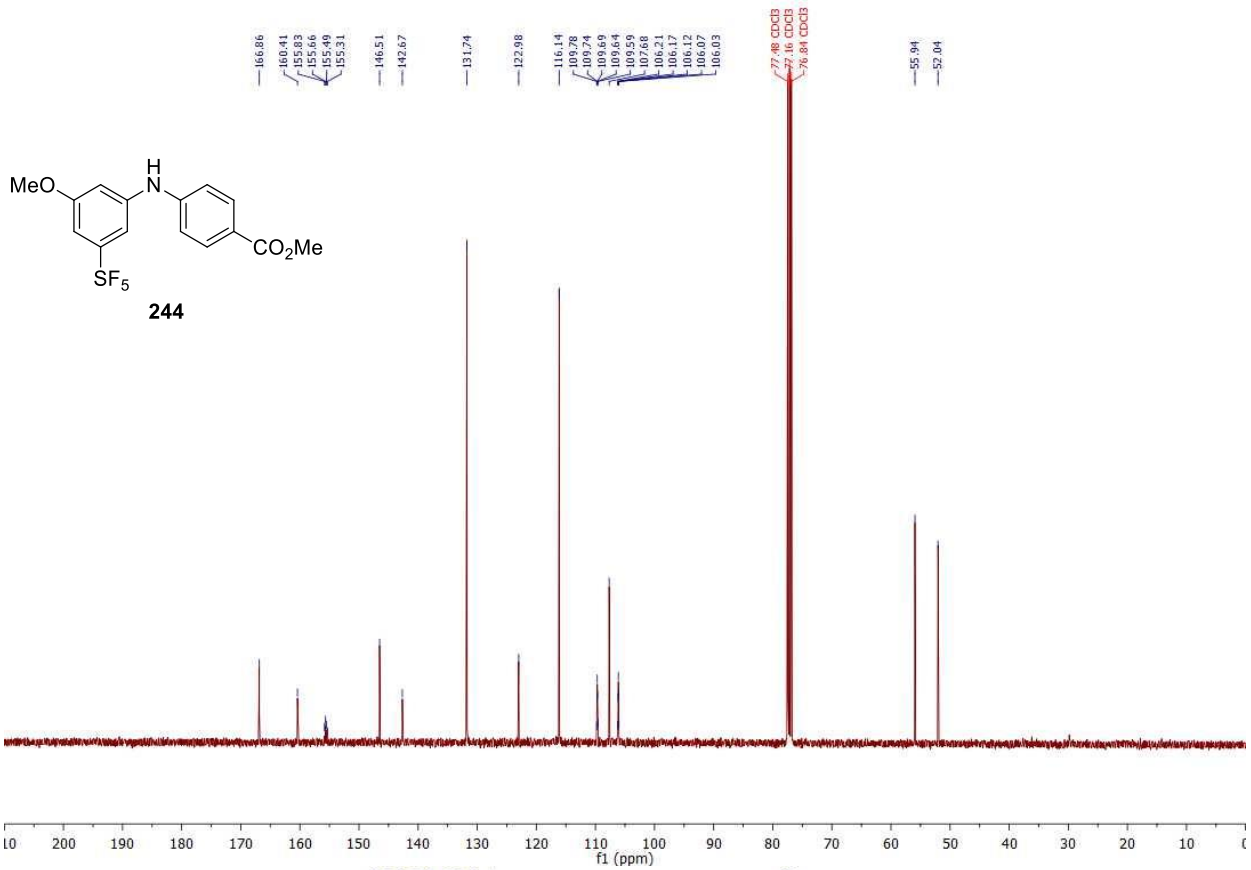

MeO
H
N
NO2
SF5
243
f1 (ppm)

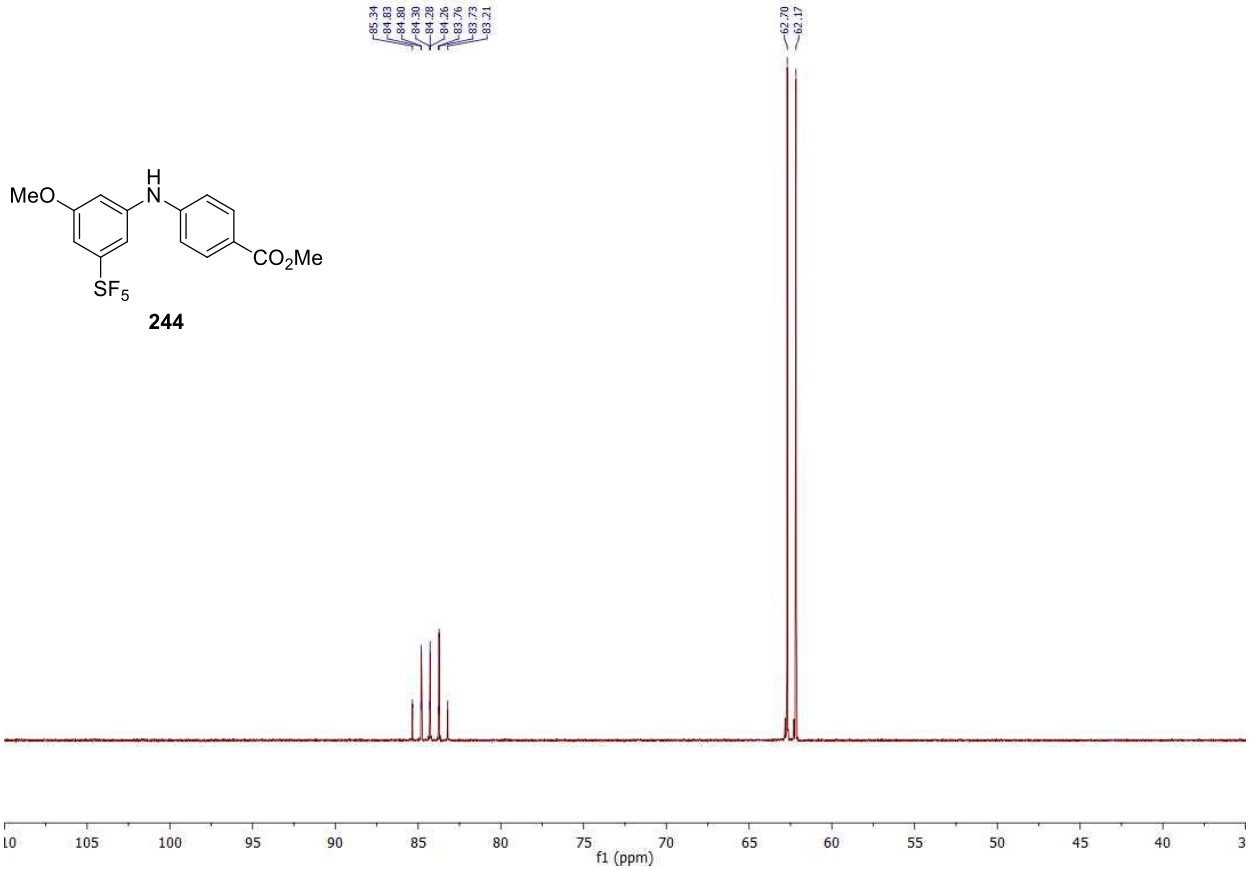

84.36
84.33
83.83
83.80
83.79
83.29
83.26
82.74
62.75
62.22
MeO
H
N
NO2
SF5
f1 (ppm)

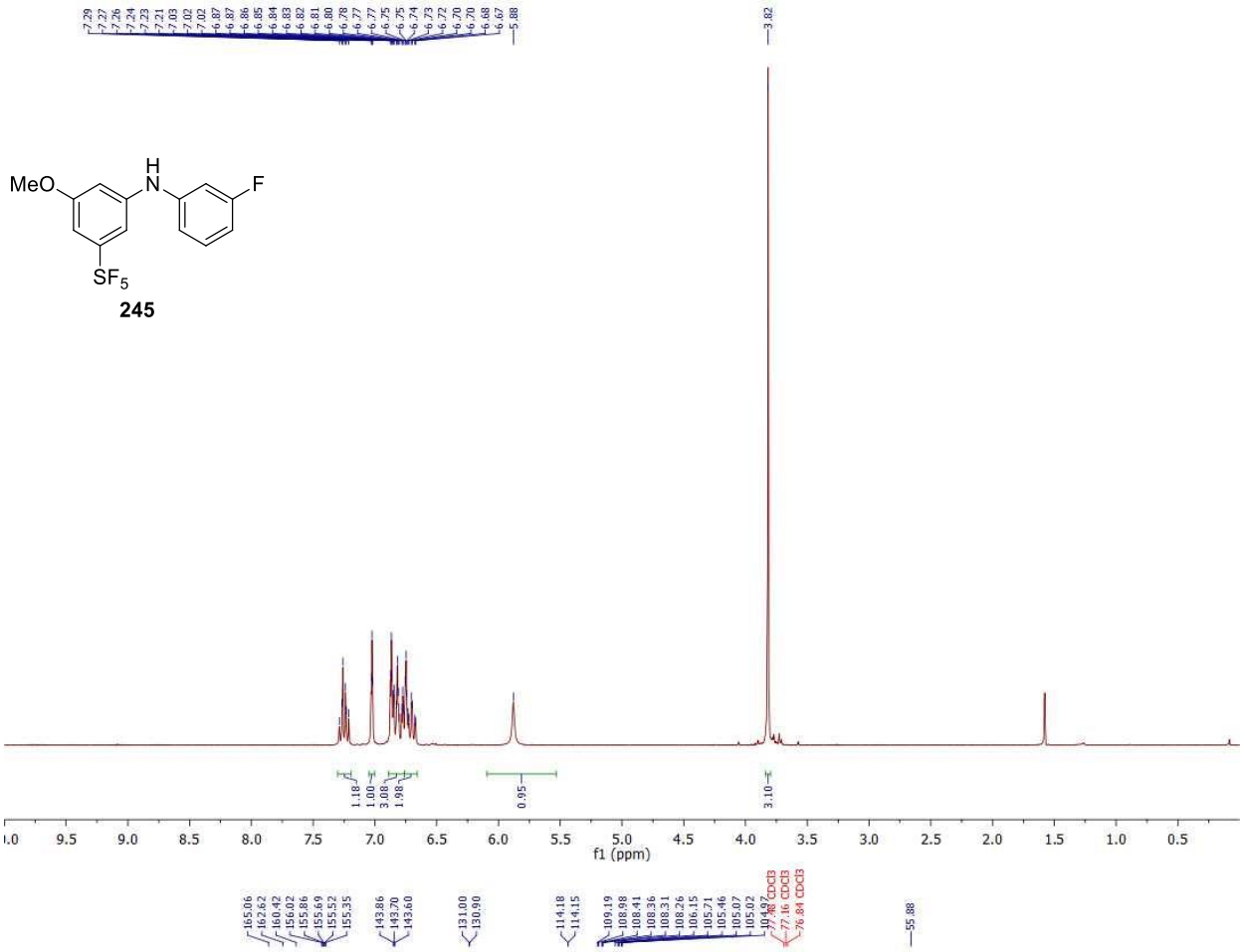
243

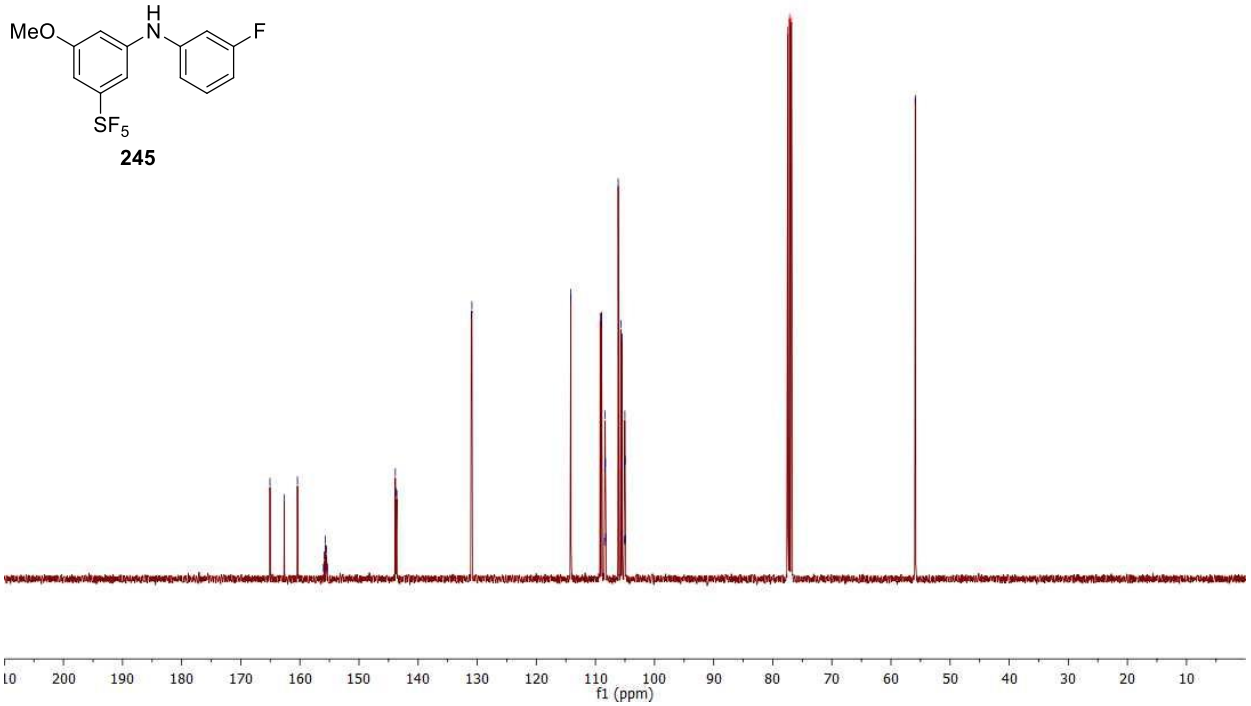

7.99
7.98
7.97
7.96
7.96
7.95
7.26
7.11
7.11
7.10
7.05
7.04
7.03
6.94
6.93
6.93
6.83
6.83
3.89
3.85
MeO
H
N
CO2Me
SF5
1.99
1.00
2.04
0.98
0.98
0.92
2.98
2.94
f1 (ppm)

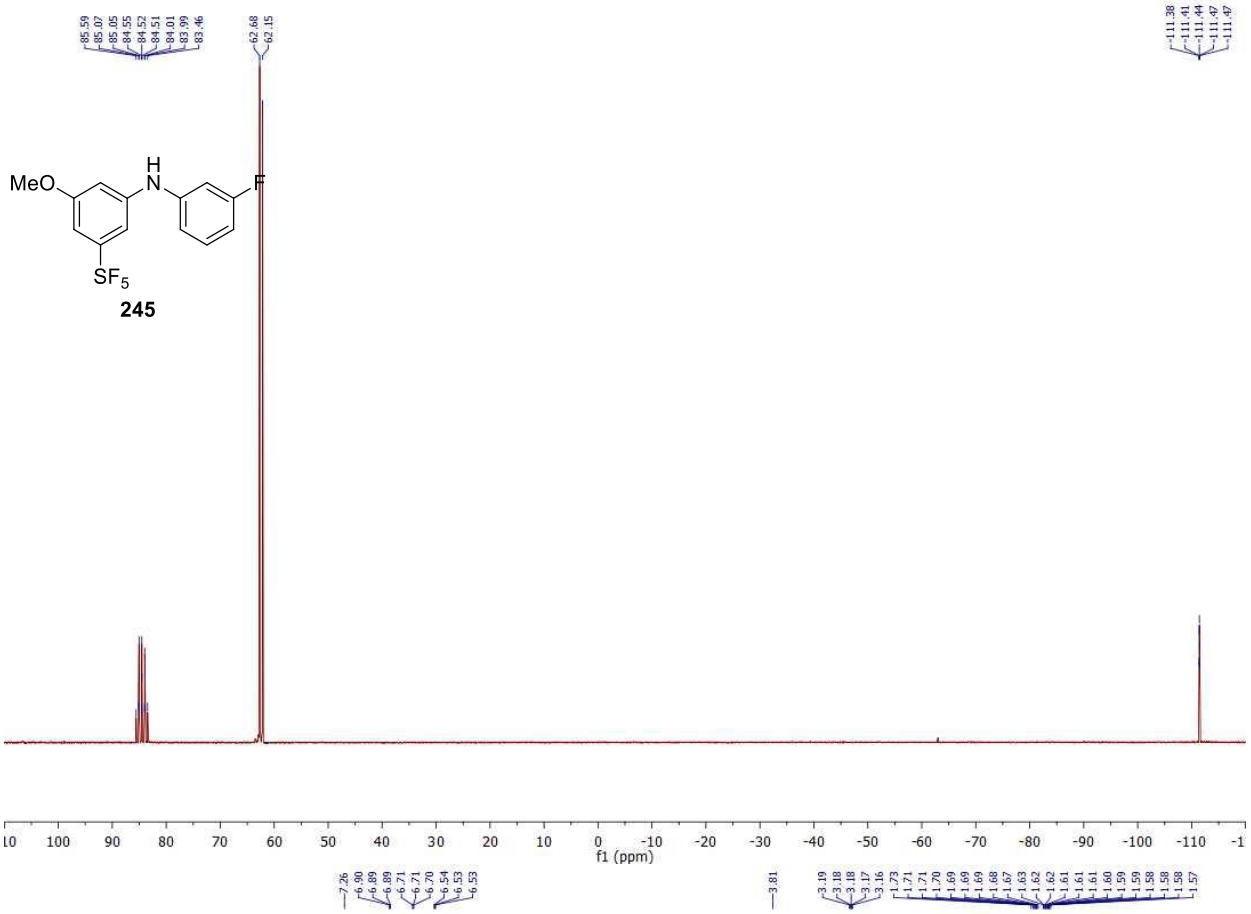
244

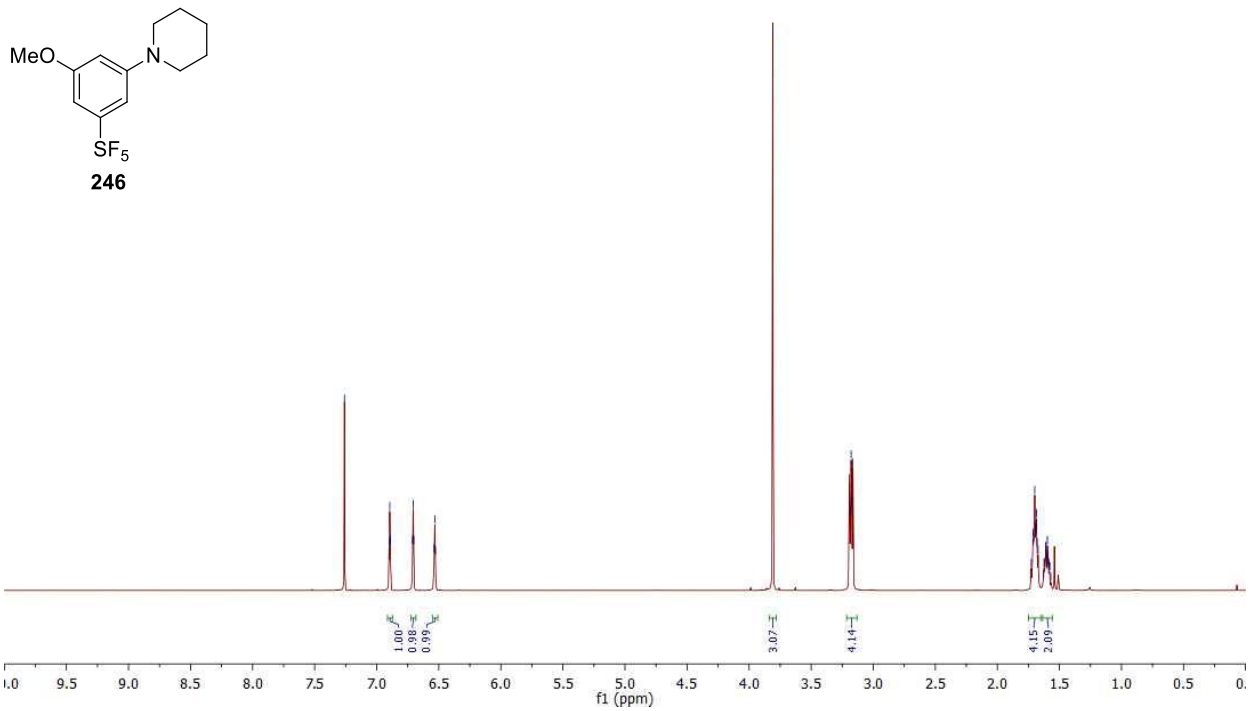

166.86
160.41
155.83
155.66
155.49
155.31
146.51
142.67
131.74
122.98
116.14
109.78
109.74
109.69
109.64
109.59
107.68
106.21
106.17
106.12
106.07
106.03
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.94
52.04
MeO
H
N
CO2Me
SF5
244
f1 (ppm)

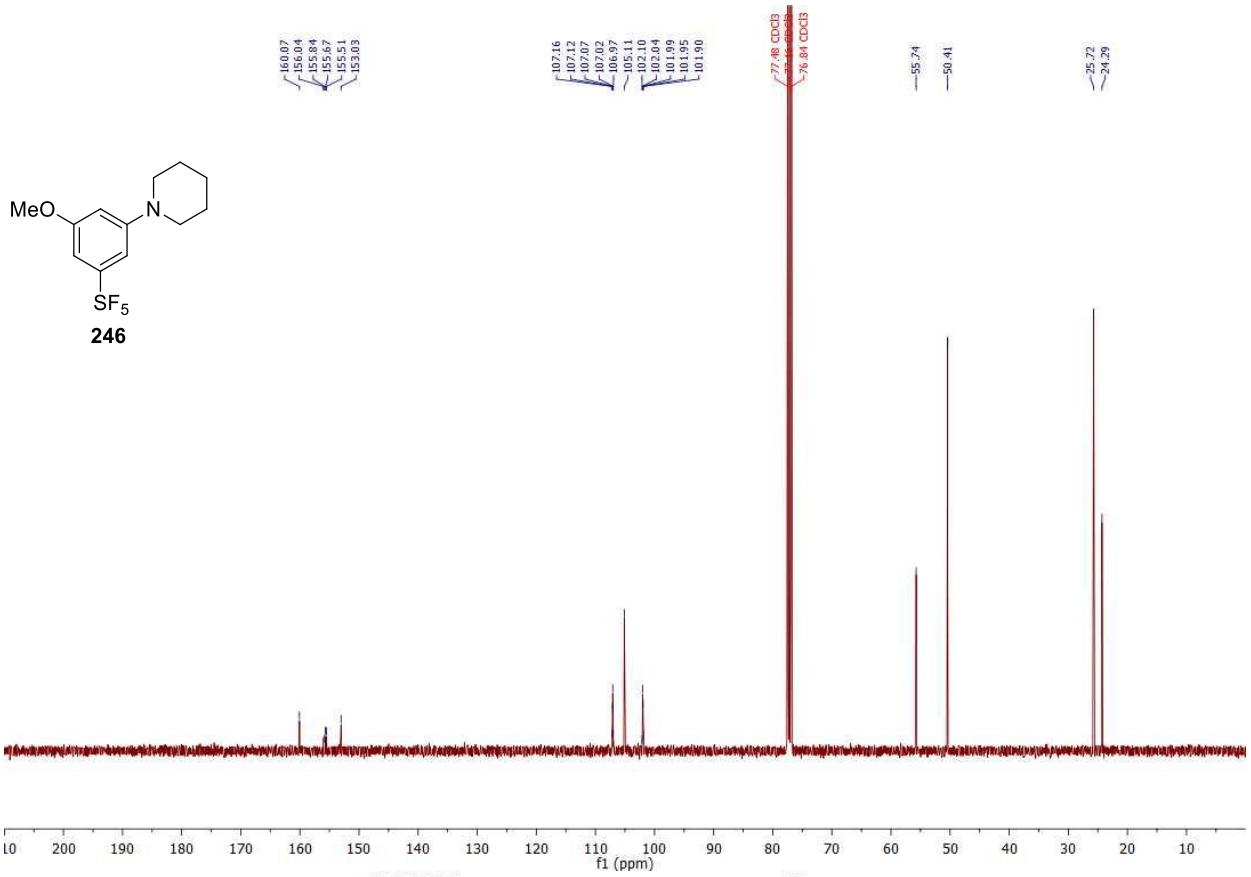

85.34
84.83
84.80
84.30
84.28
84.26
83.76
83.73
83.21
62.70
62.17
MeO
H
N
CO2Me
SF5
244
f1 (ppm)

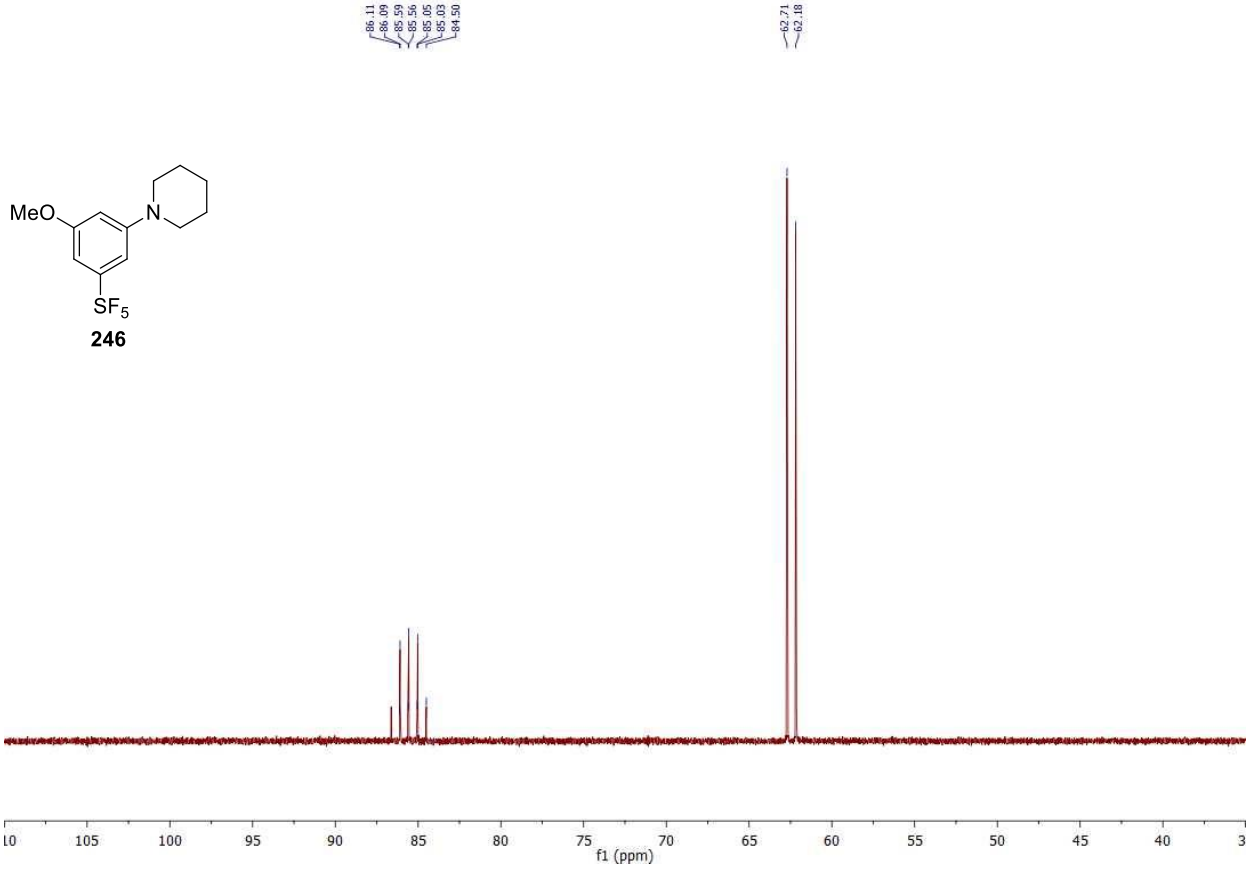

MeO
H
N
F
SF5
245
f1 (ppm)

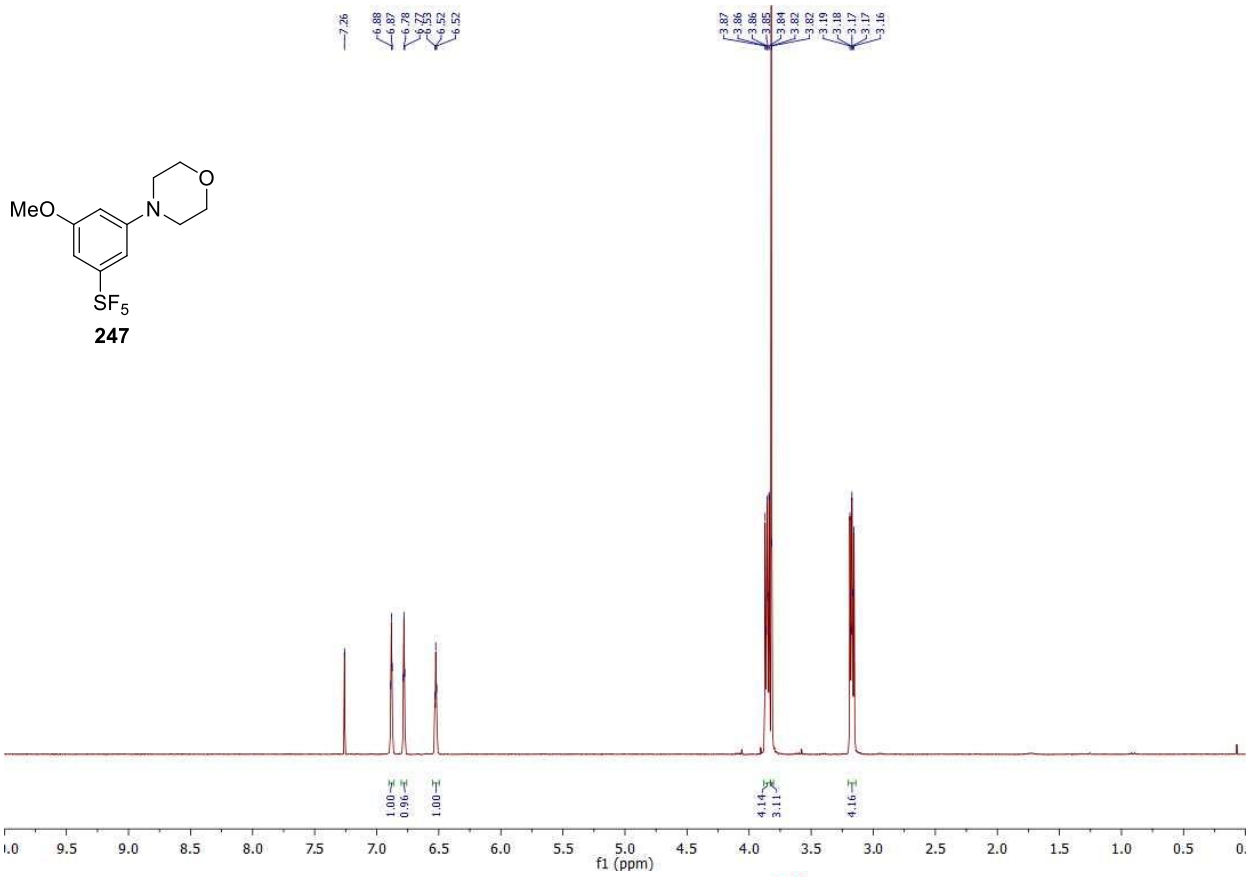

MeO
H
N
F
SF5
245
f1 (ppm)

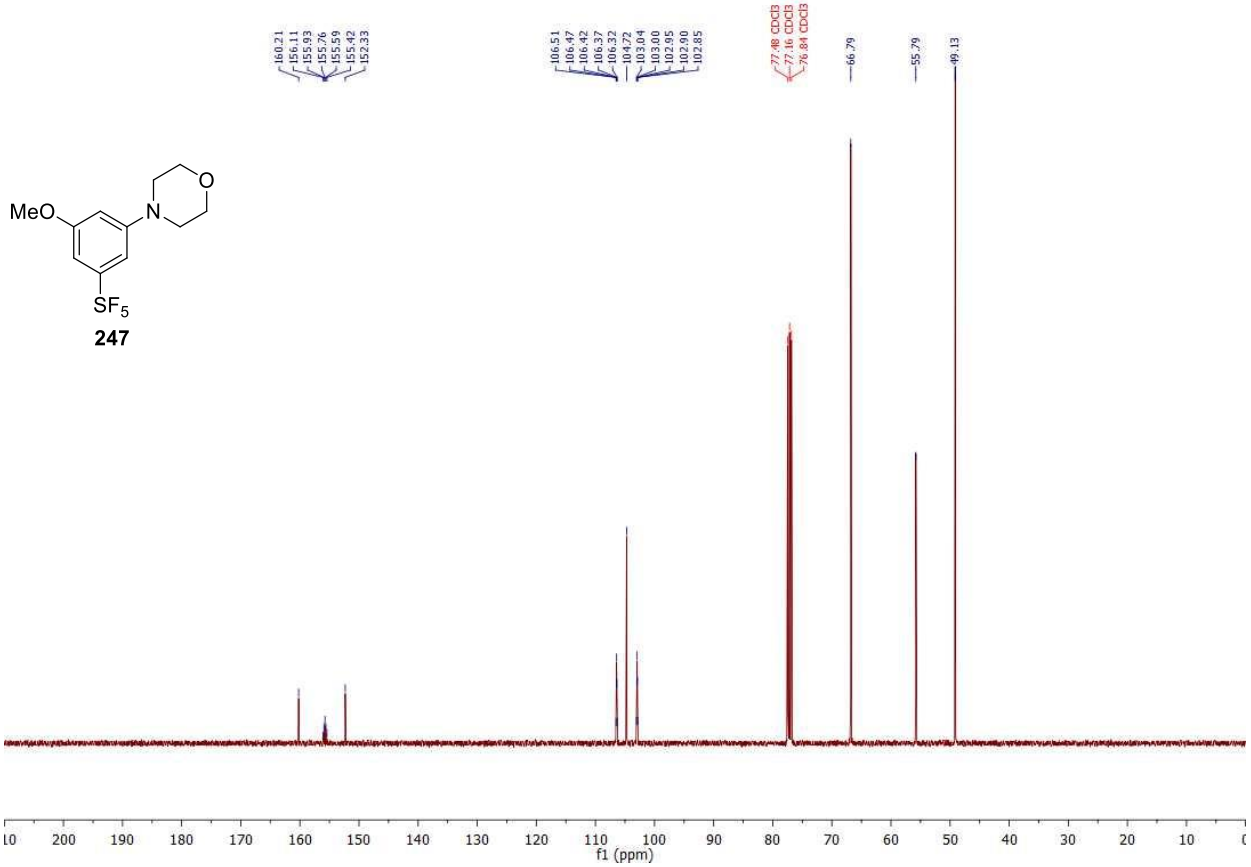

MeO
H
N
F
SF5
245
f1 (ppm)

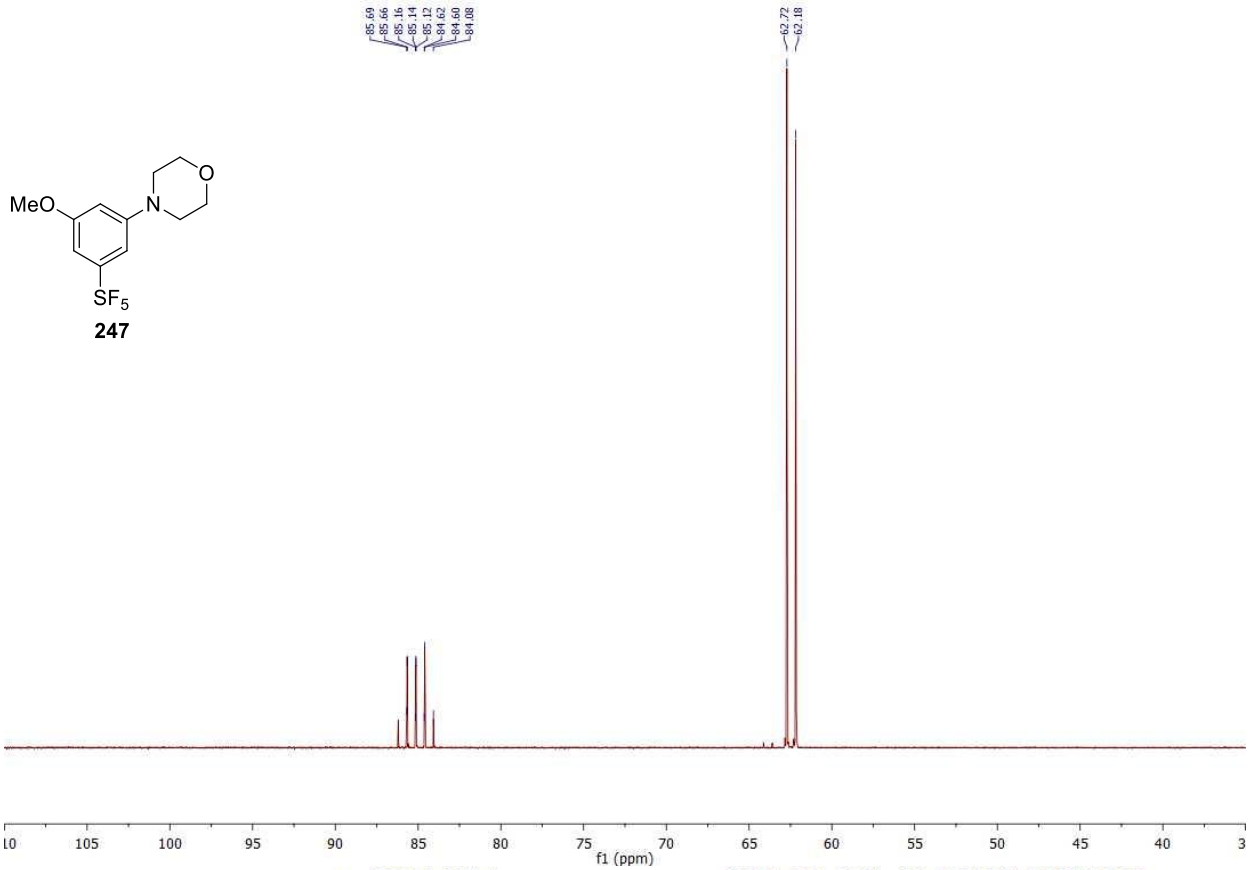

MeO
N
SF5
246
f1 (ppm)


160.07
156.04
155.84
155.67
155.51
153.03
107.16
107.12
107.07
107.02
106.97
105.11
102.10
102.04
101.99
101.95
101.90
77.48 CDCl3
76.84 CDCl3
55.74
50.41
25.72
24.29
MeO
N
SF5
246
f1 (ppm)

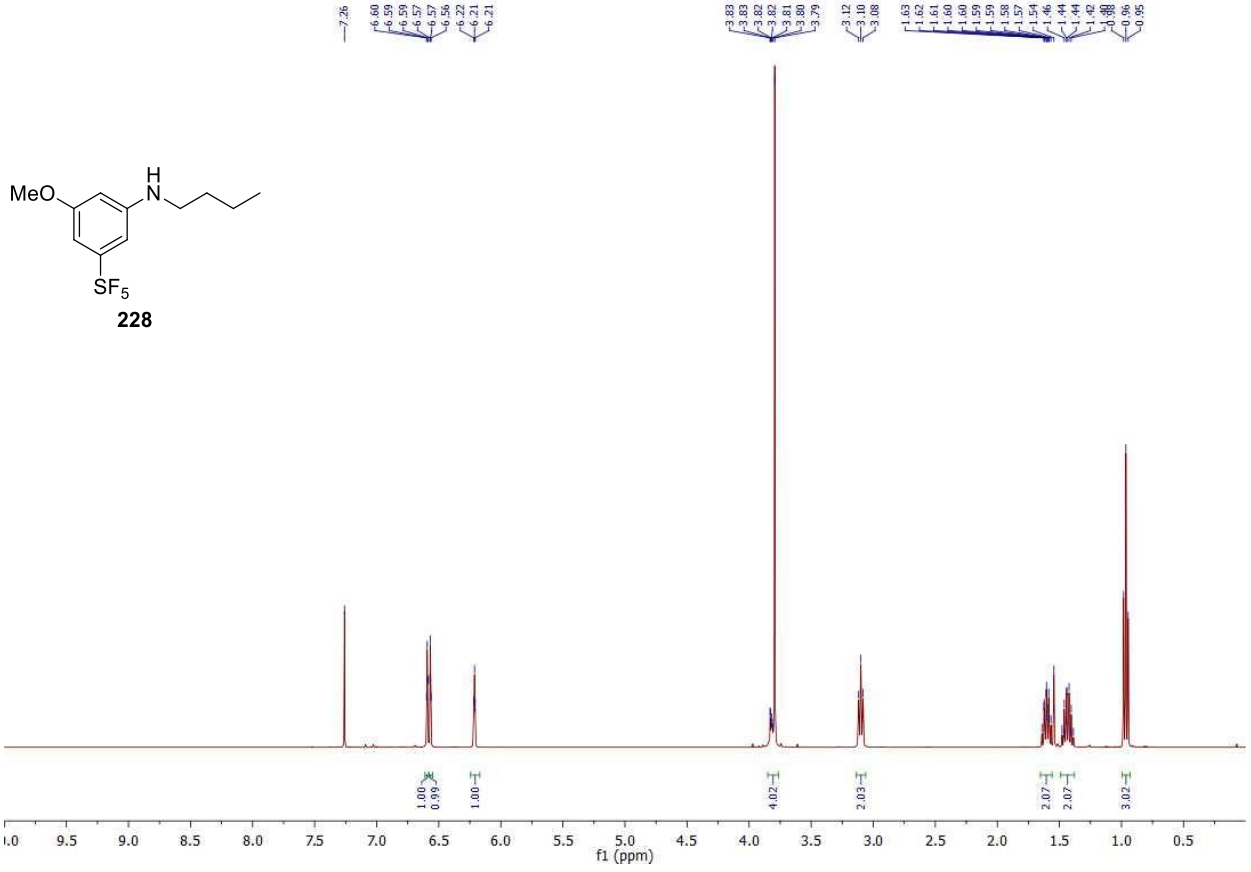

86.11
86.09
85.59
85.56
85.05
85.03
84.50
62.71
62.18
MeO
N
SF5
246
f1 (ppm)


MeO
N
O
SF5
247
f1 (ppm)

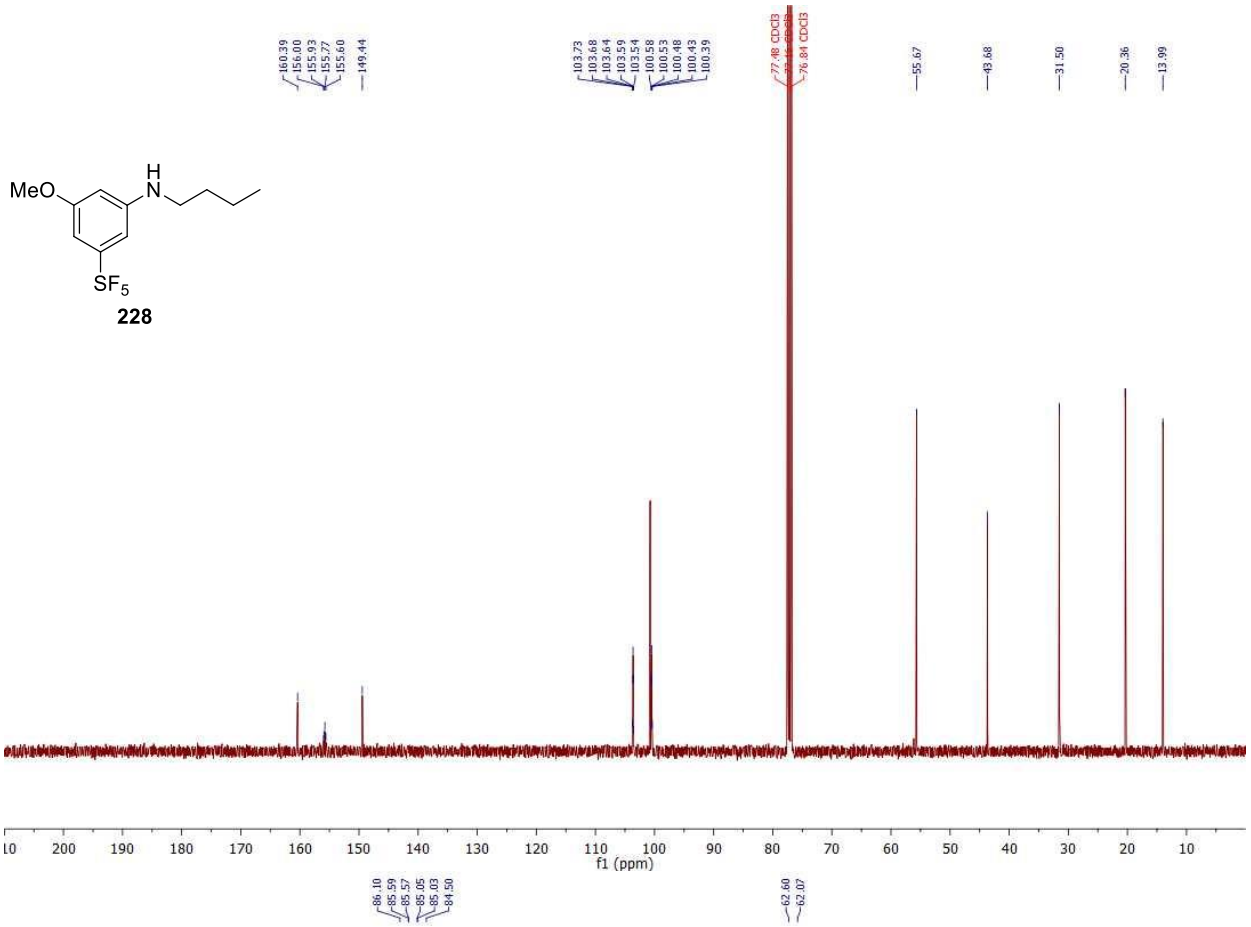

MeO
N
O
SF5
247
f1 (ppm)

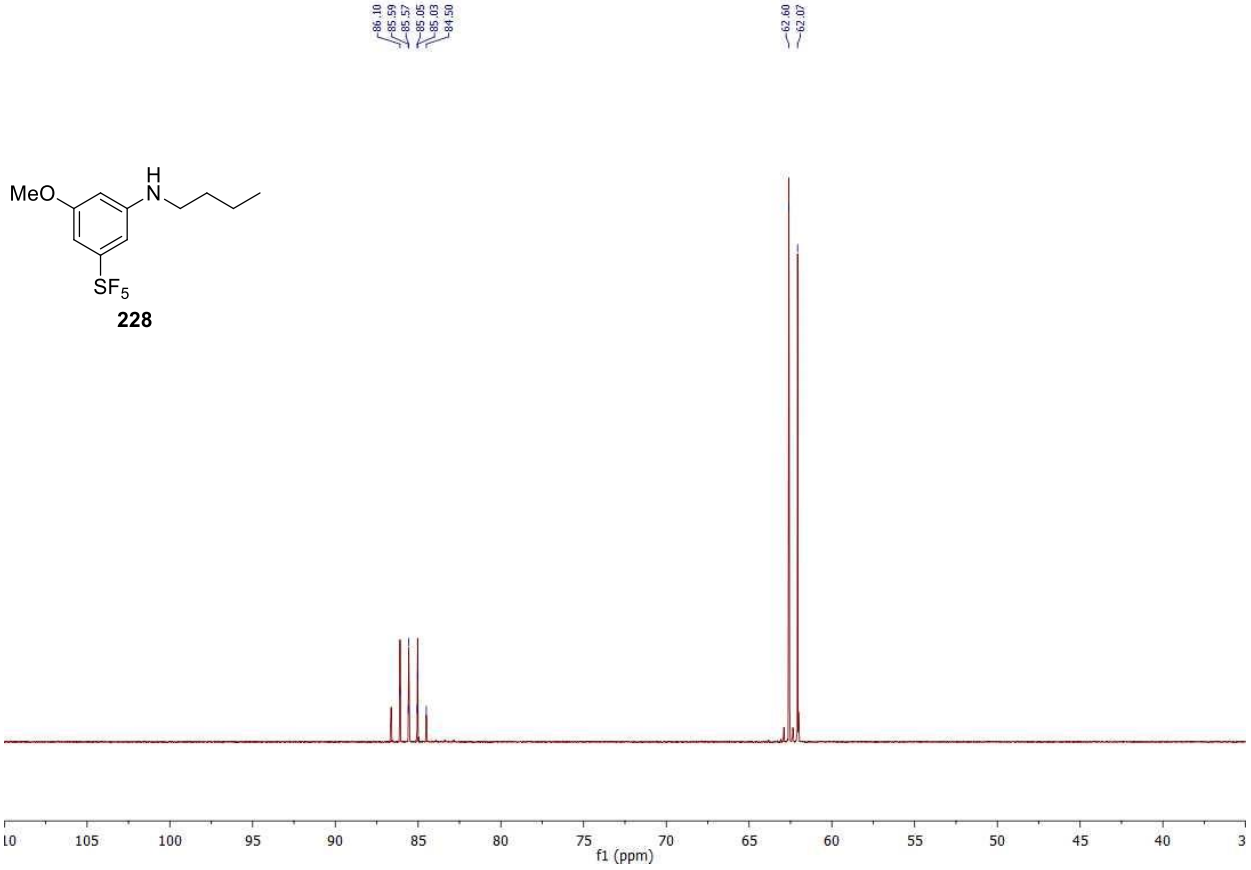

85.69
85.66
85.16
85.14
85.12
84.62
84.60
84.08
62.72
62.18
MeO
O
N
SF5
f1 (ppm)

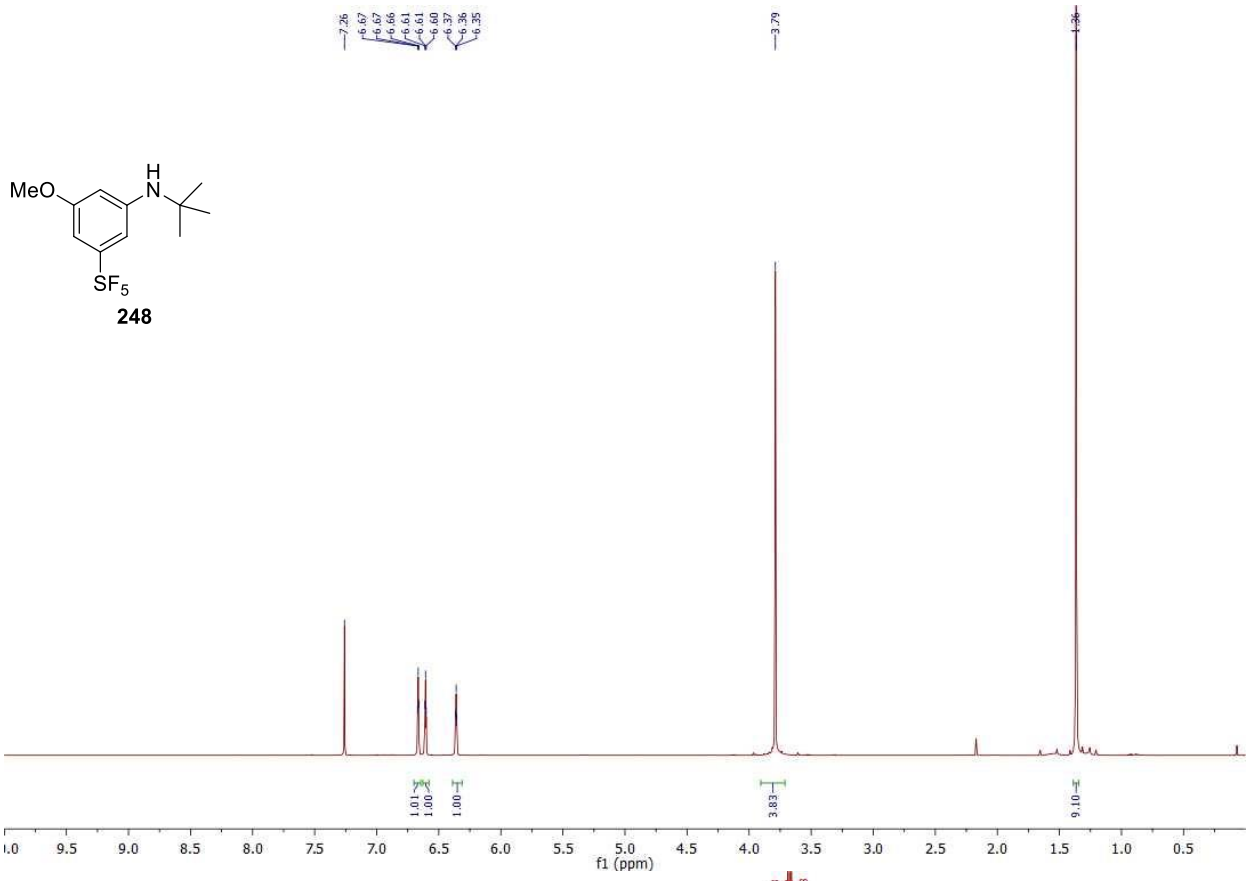
247


7.26
6.60
6.59
6.59
6.57
6.57
6.56
6.22
6.21
6.21
3.83
3.83
3.82
3.82
3.81
3.80
3.79
3.12
3.10
3.08
1.63
1.62
1.61
1.60
1.60
1.59
1.59
1.58
1.57
1.54
1.46
1.44
1.44
1.42
0.98
0.96
0.95
MeO
H
N
SF5
1.00
0.99
1.00
4.02
2.03
2.07
2.07
3.02
f1 (ppm)

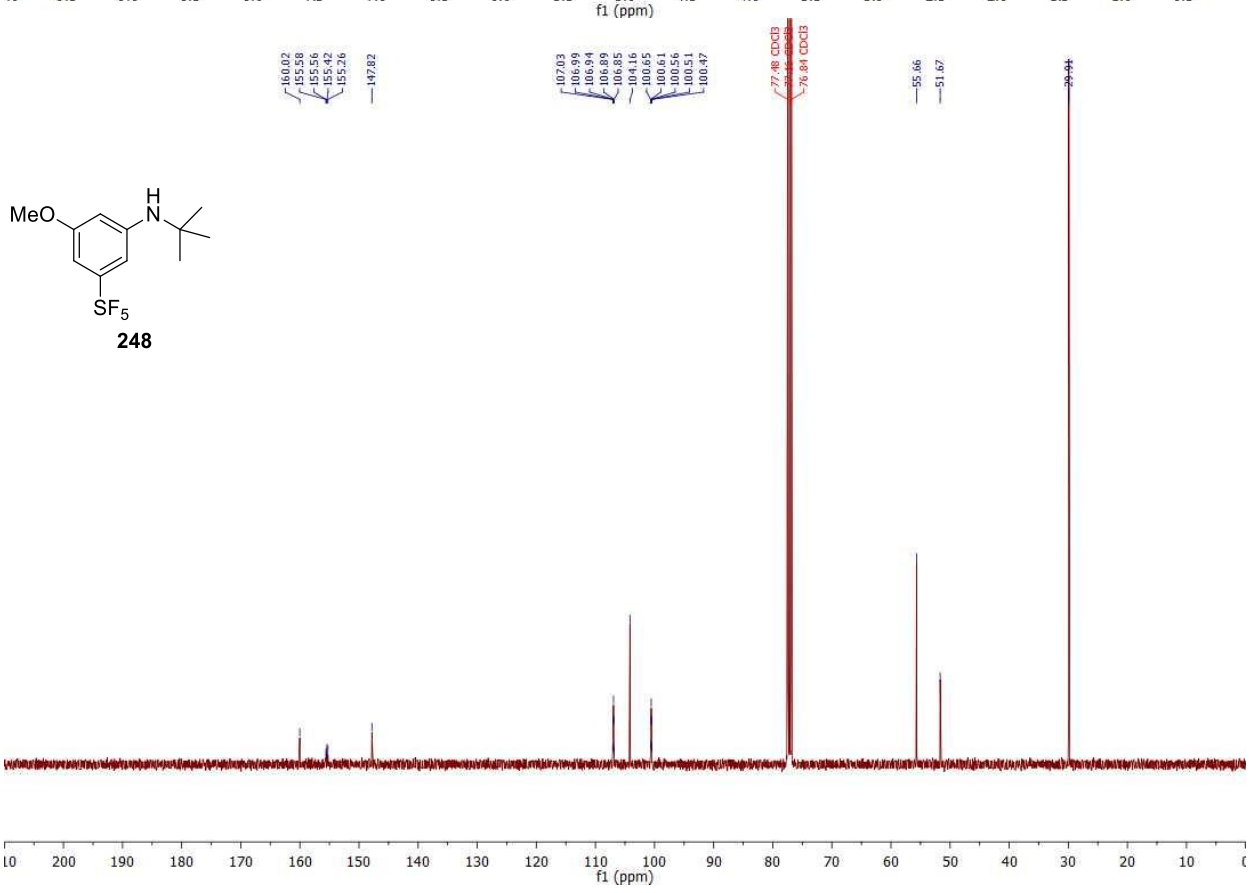
228


160.39
156.00
155.93
155.77
155.60
149.44
103.73
103.68
103.64
103.59
103.54
100.58
100.53
100.48
100.43
100.39
77.48 CDCl3
76.84 CDCl3
55.67
43.68
31.50
20.36
13.99
MeO
H
N
SF5
228
f1 (ppm)

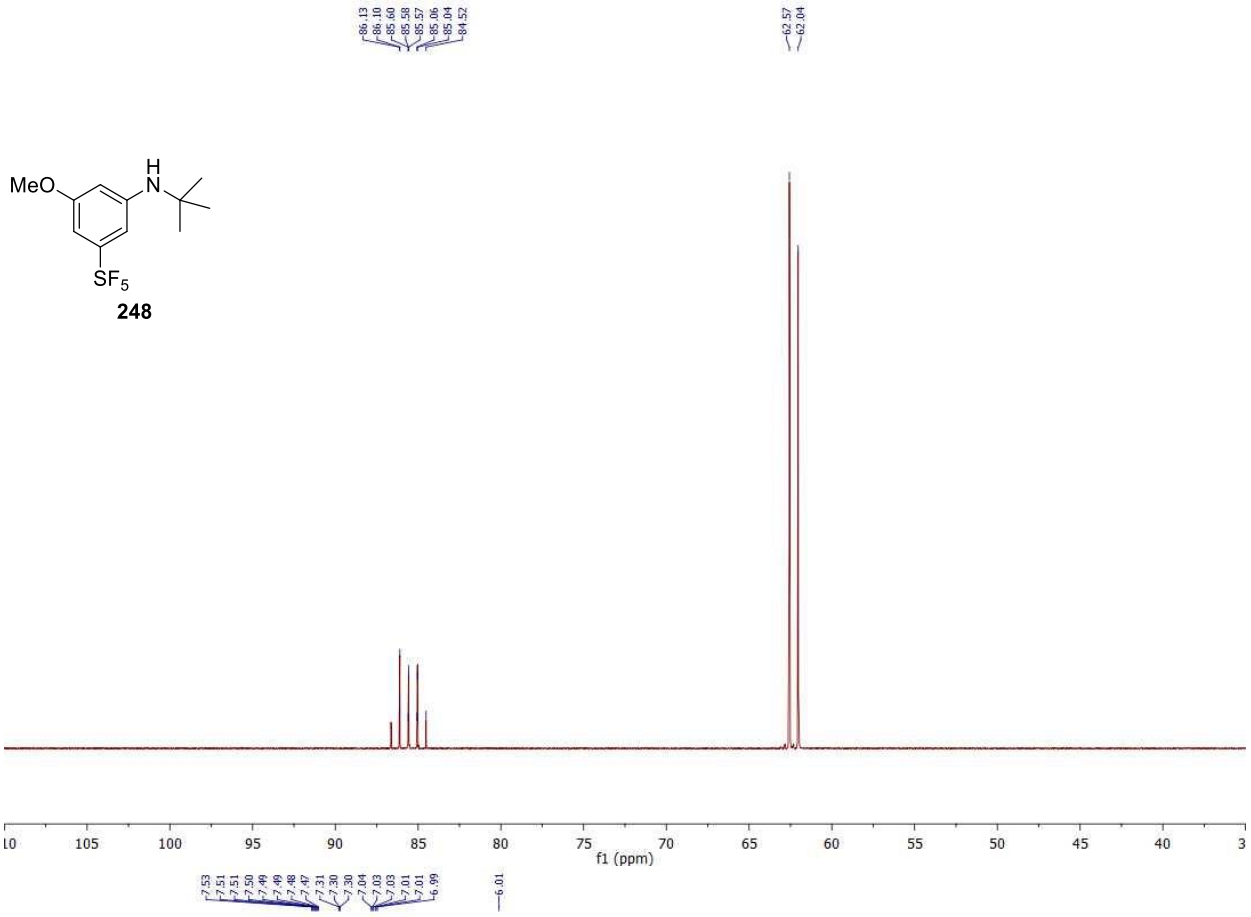

86.10
85.99
85.57
85.05
85.03
84.50
62.60
62.07
MeO
H
N
SF5
228
f1 (ppm)


7.26
6.67
6.67
6.66
6.61
6.61
6.60
6.37
6.36
6.35
3.79
1.36
MeO
H
N
SF5
1.01
1.00
1.00
3.83
9.10
f1 (ppm)

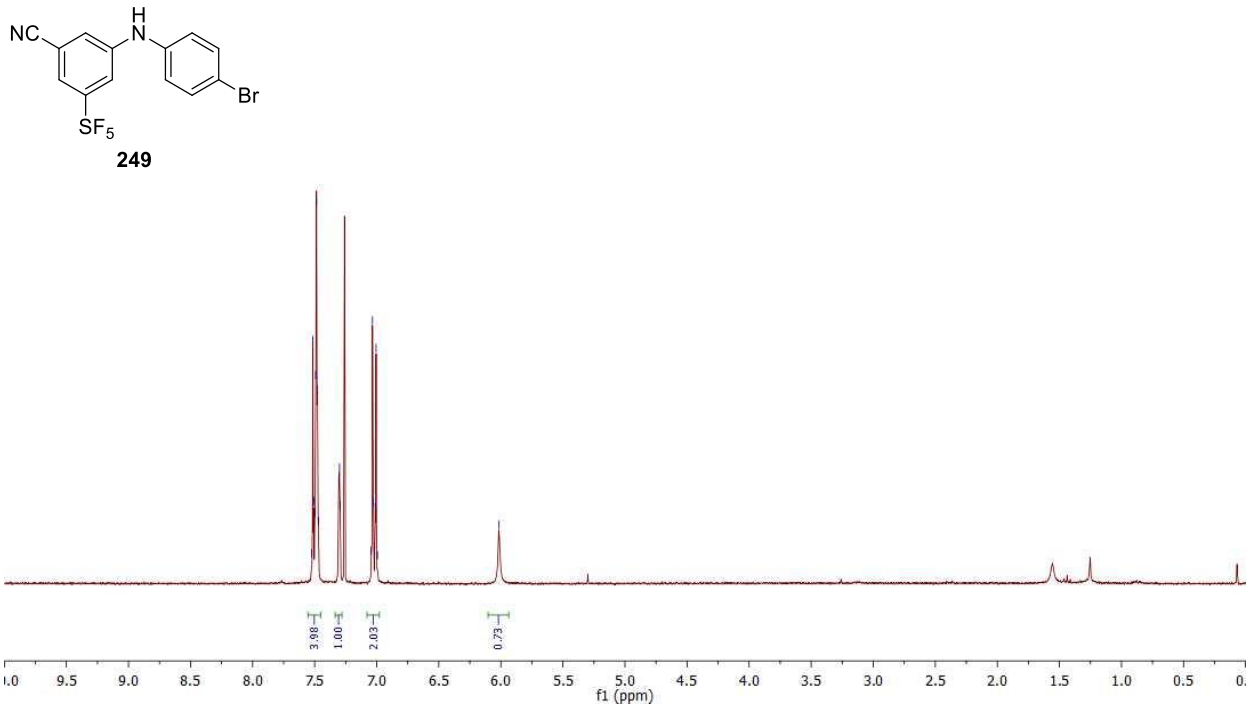
248


160.02
155.58
155.56
155.42
155.26
147.82
107.03
106.99
106.94
106.89
106.85
104.16
100.65
100.61
100.56
100.51
100.47
77.48 CDCl3
76.84 CDCl3
55.66
51.67
29.71
MeO
H
N
SF5
f1 (ppm)

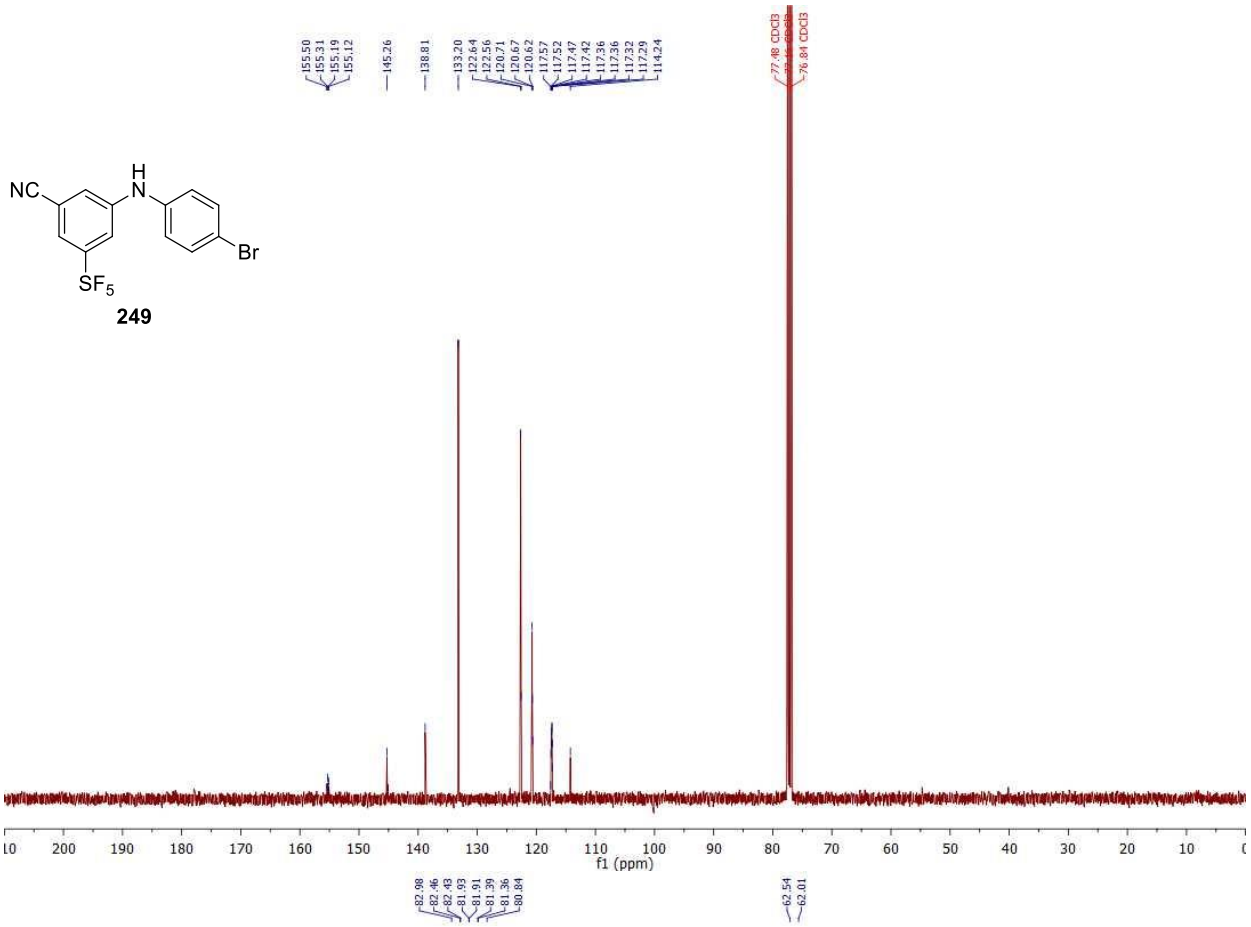
248

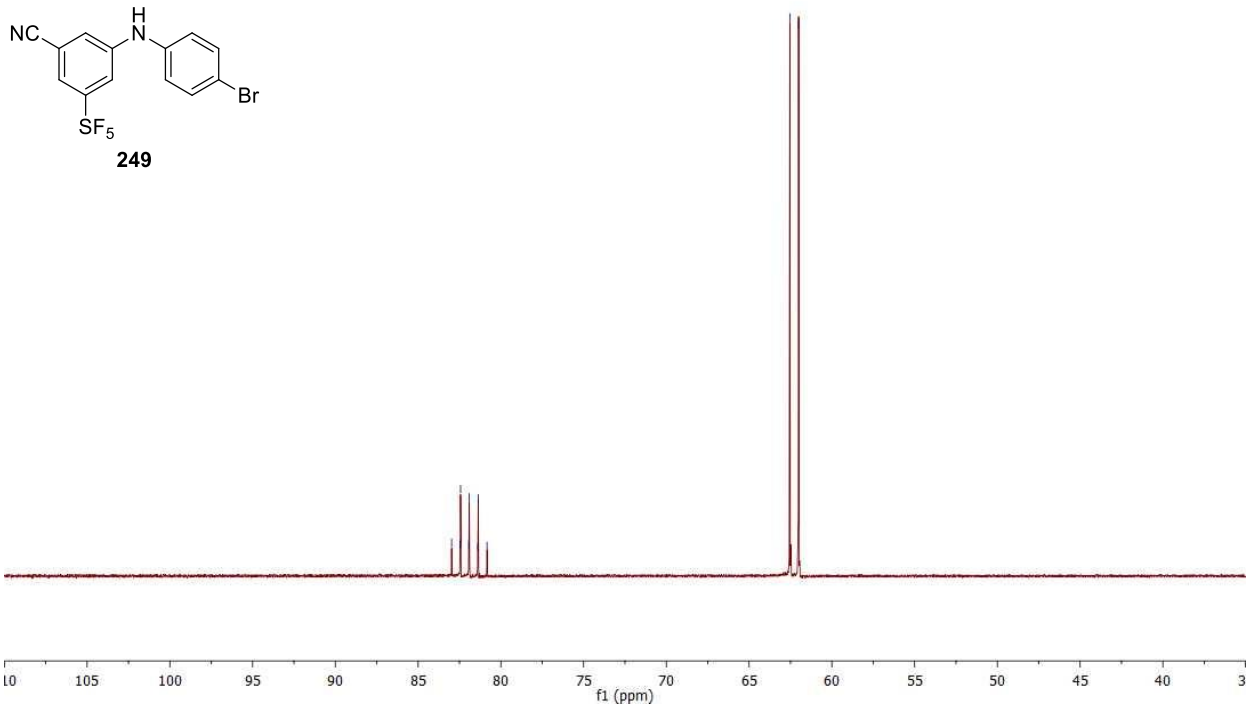

86.13
86.10
85.60
85.58
85.57
85.06
85.04
84.52
62.57
62.04
MeO
H
N
SF5
f1 (ppm)
7.53
7.51
7.51
7.50
7.49
7.49
7.48
7.47
7.31
7.30
7.30
7.04
7.03
7.03
7.01
7.01
6.99
6.01

248

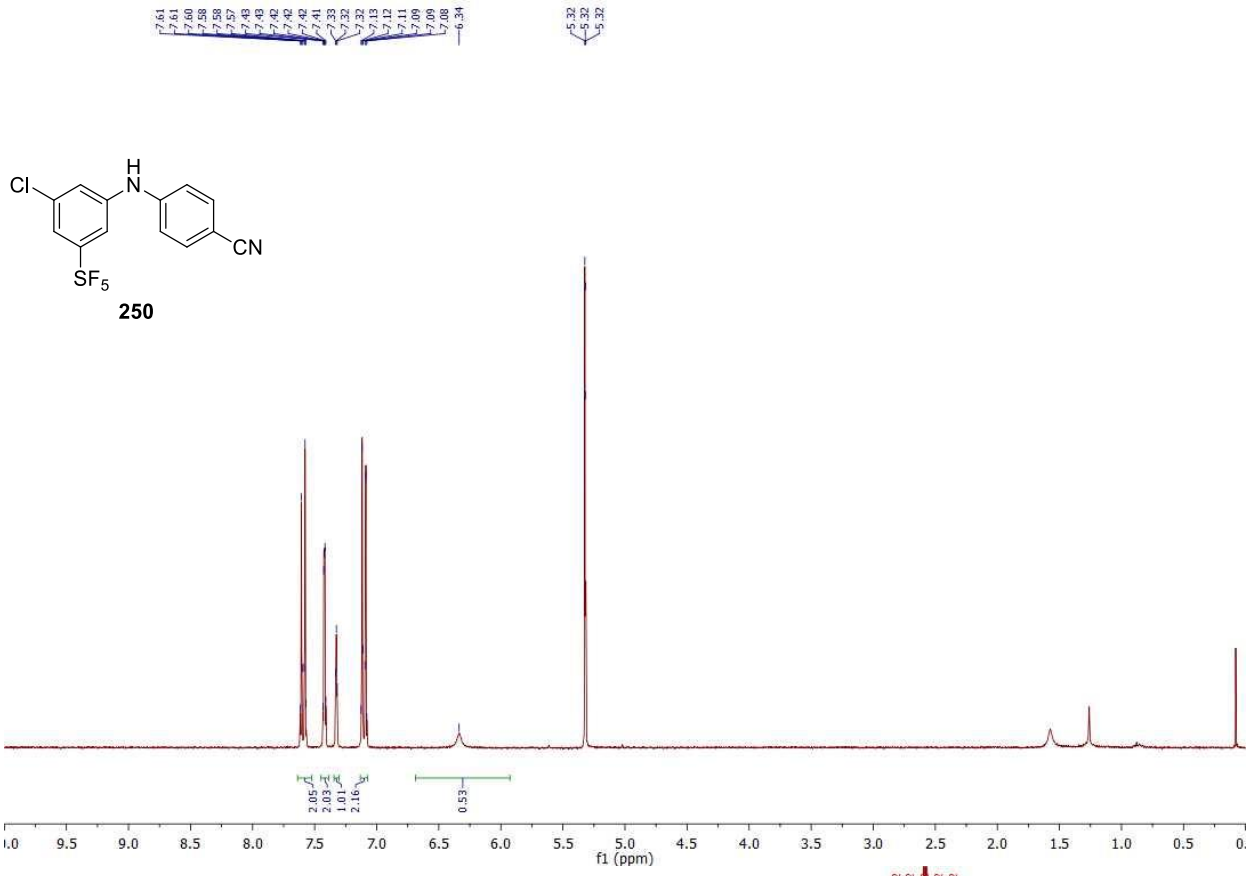

NC
H
N
Br
SF5
3.98
1.00
2.03
0.73
f1 (ppm)

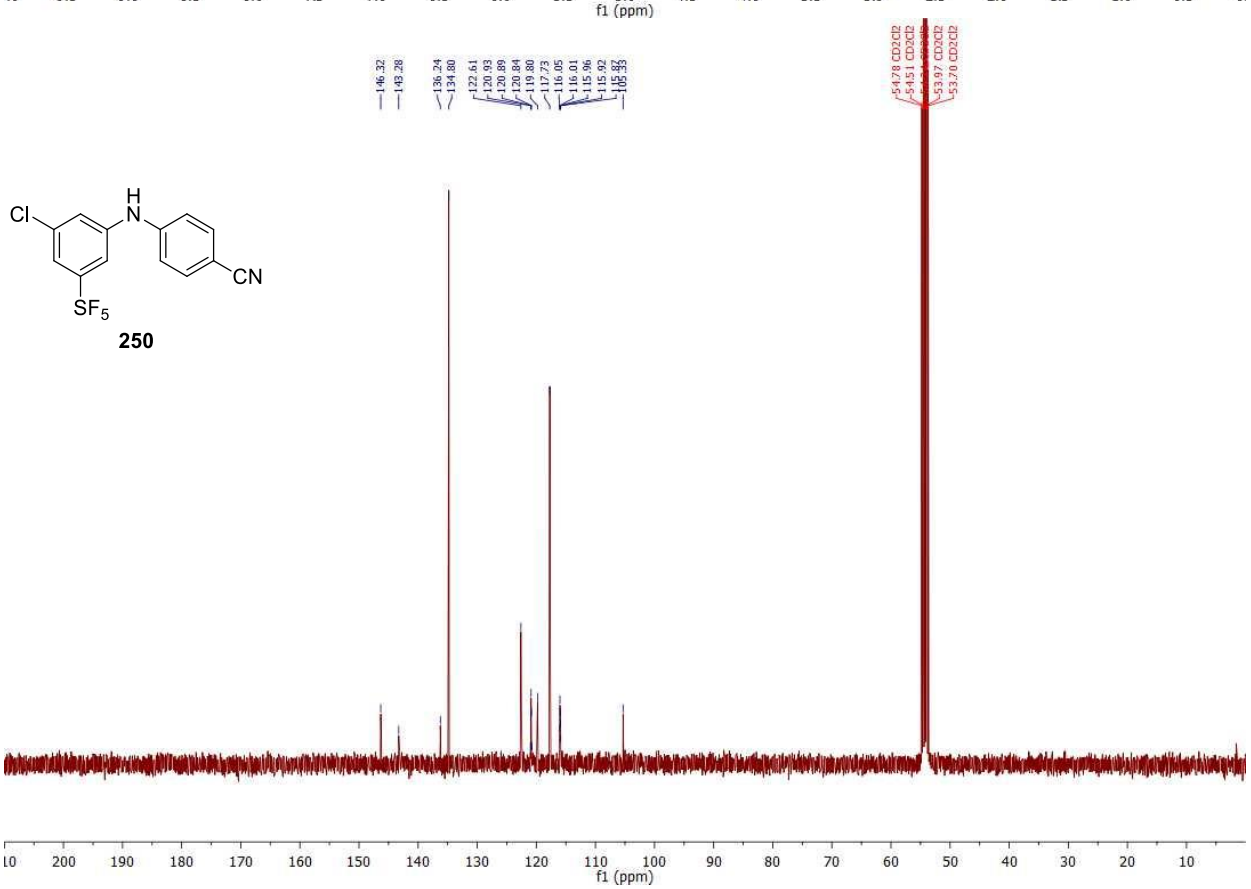
249

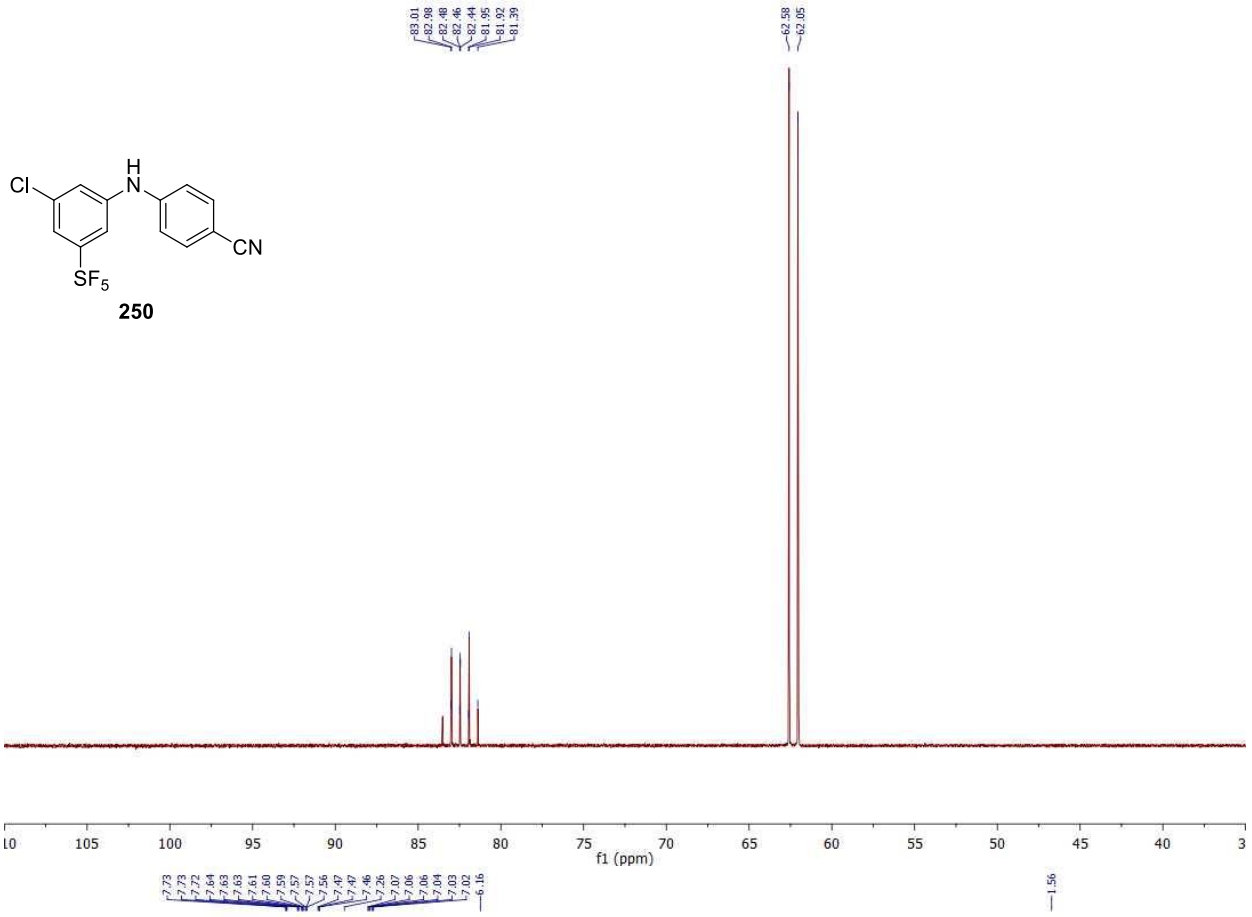

155.50
155.31
155.19
155.12
145.26
138.81
133.20
122.64
122.56
120.71
120.67
120.62
117.57
117.52
117.47
117.42
117.36
117.36
117.32
117.29
114.24
77.48 CDCl3
76.84 CDCl3
f1 (ppm)
82.98
82.46
82.43
81.93
81.91
81.39
81.36
80.84
62.54
62.01


f1 (ppm)

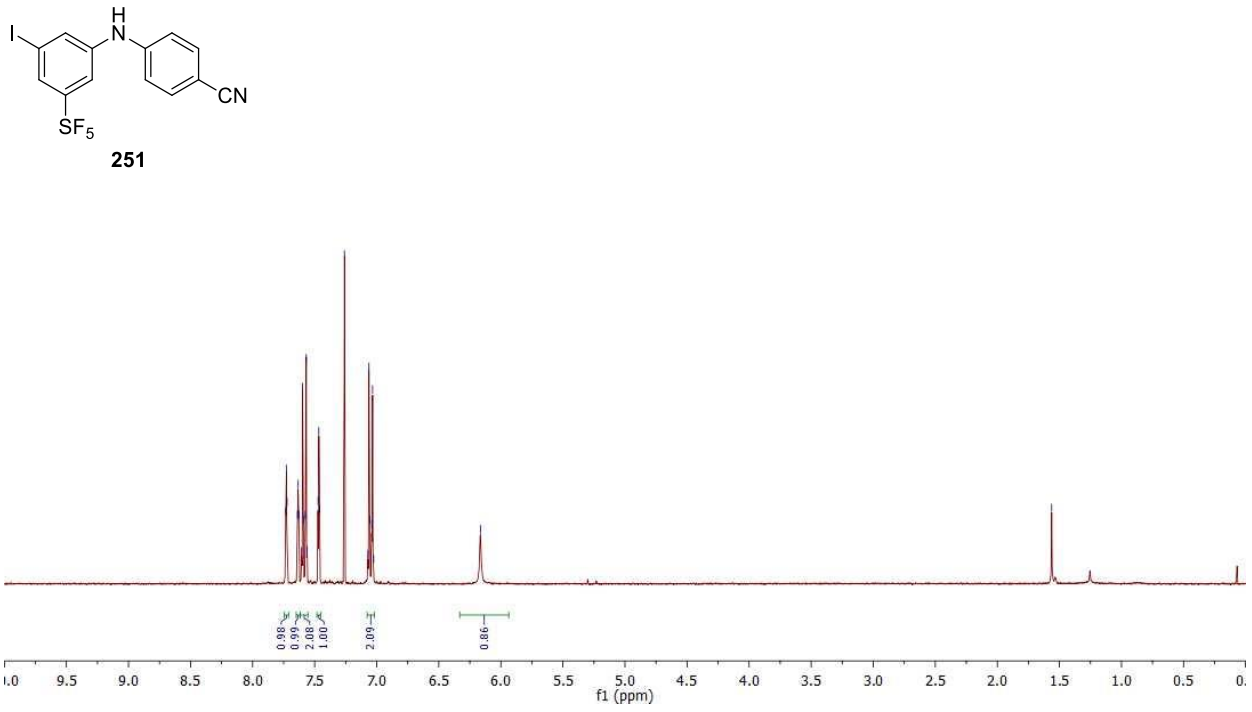
249


Cl
H
N
CN
SF5
250
f1 (ppm)

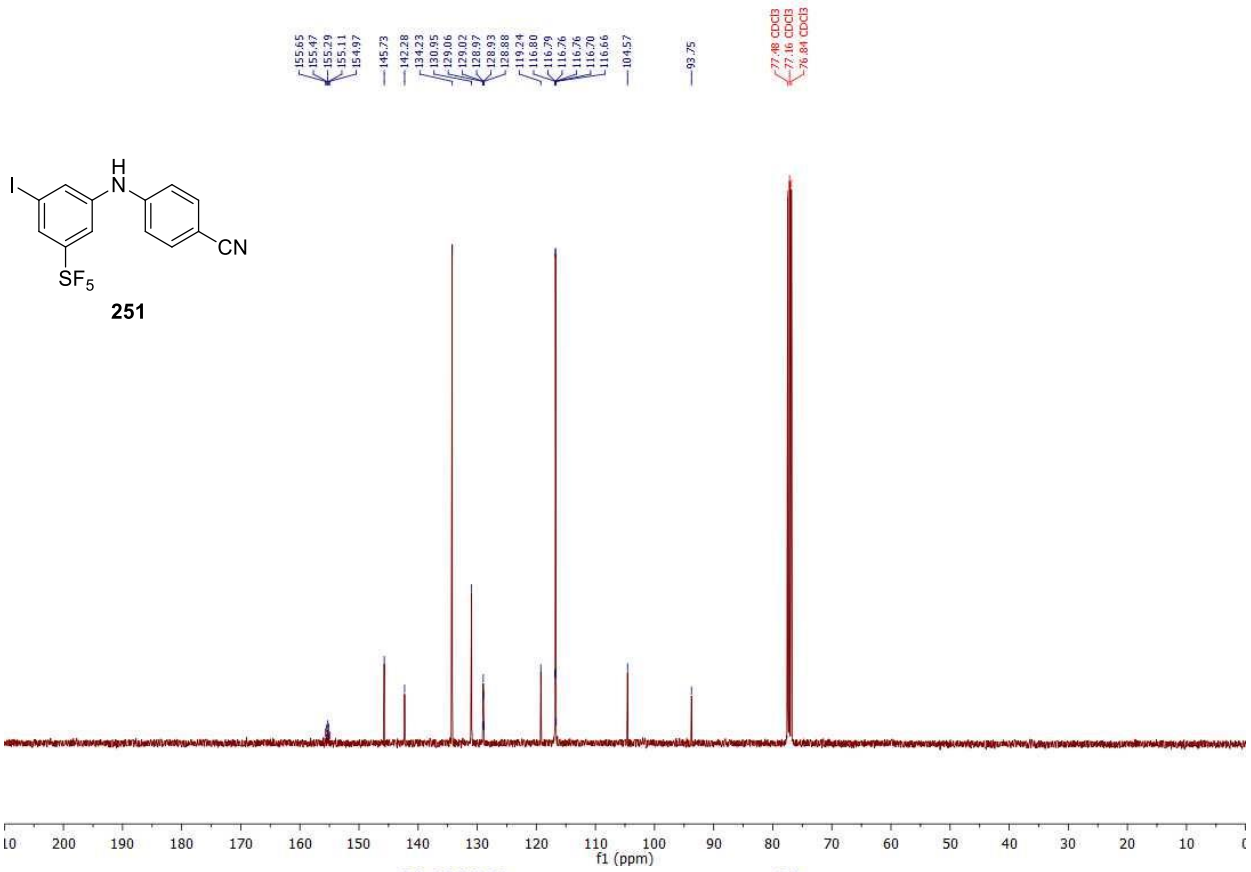

Cl
H
N
CN
SF5
250
f1 (ppm)

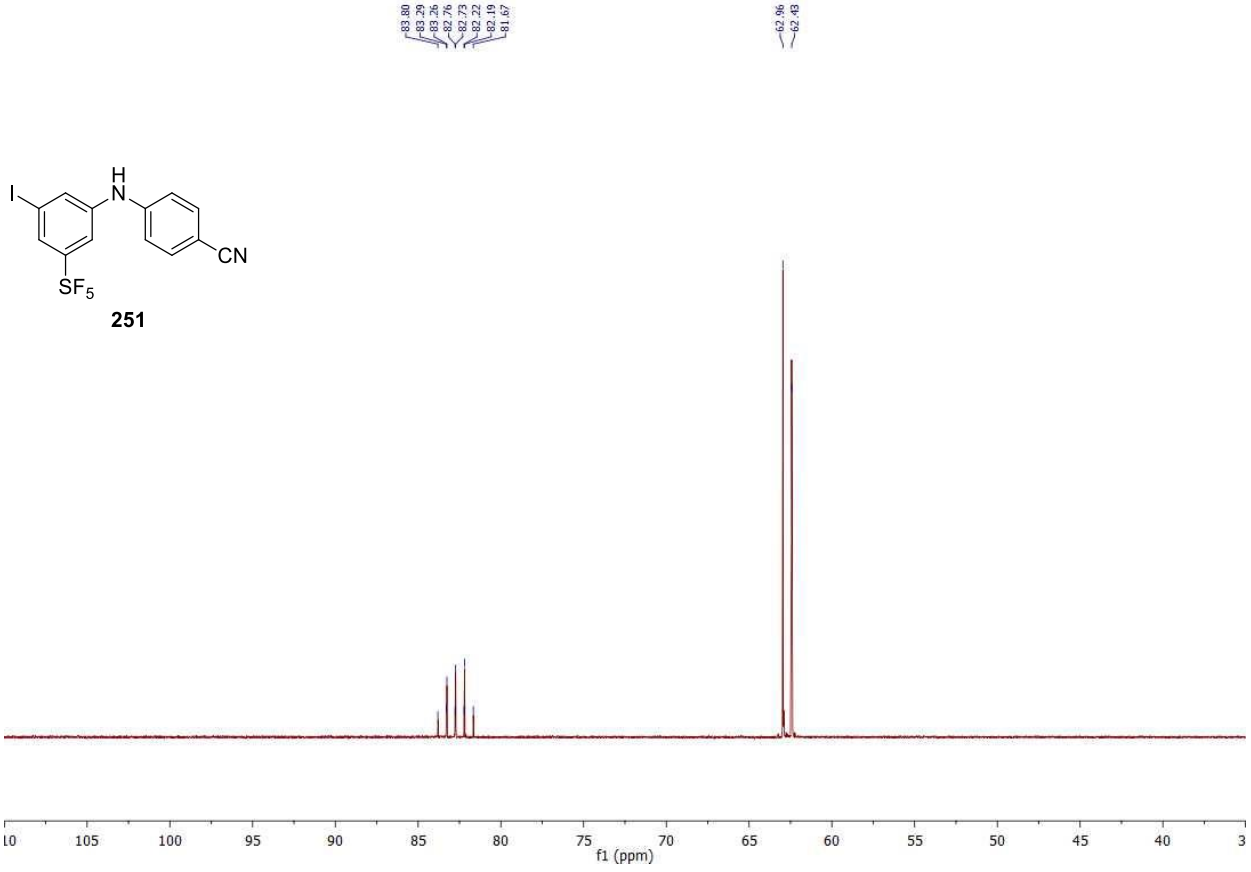

83.01
82.98
82.48
82.46
82.44
81.95
81.92
81.39
62.58
62.05
Cl
H
N
CN
SF5
f1 (ppm)
7.73
7.73
7.72
7.64
7.63
7.63
7.61
7.60
7.59
7.57
7.57
7.56
7.47
7.47
7.46
7.26
7.07
7.06
7.04
7.03
7.02
6.16
1.56

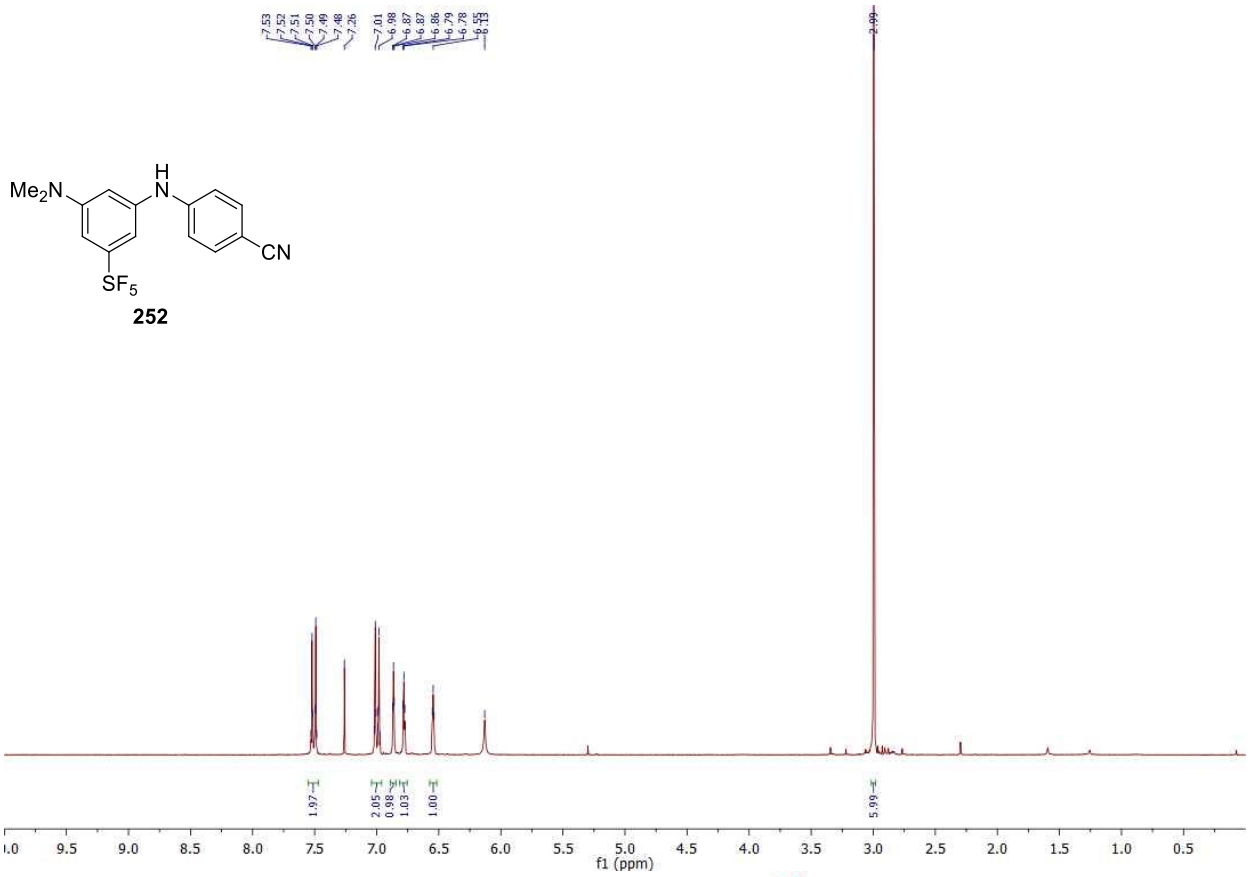
250

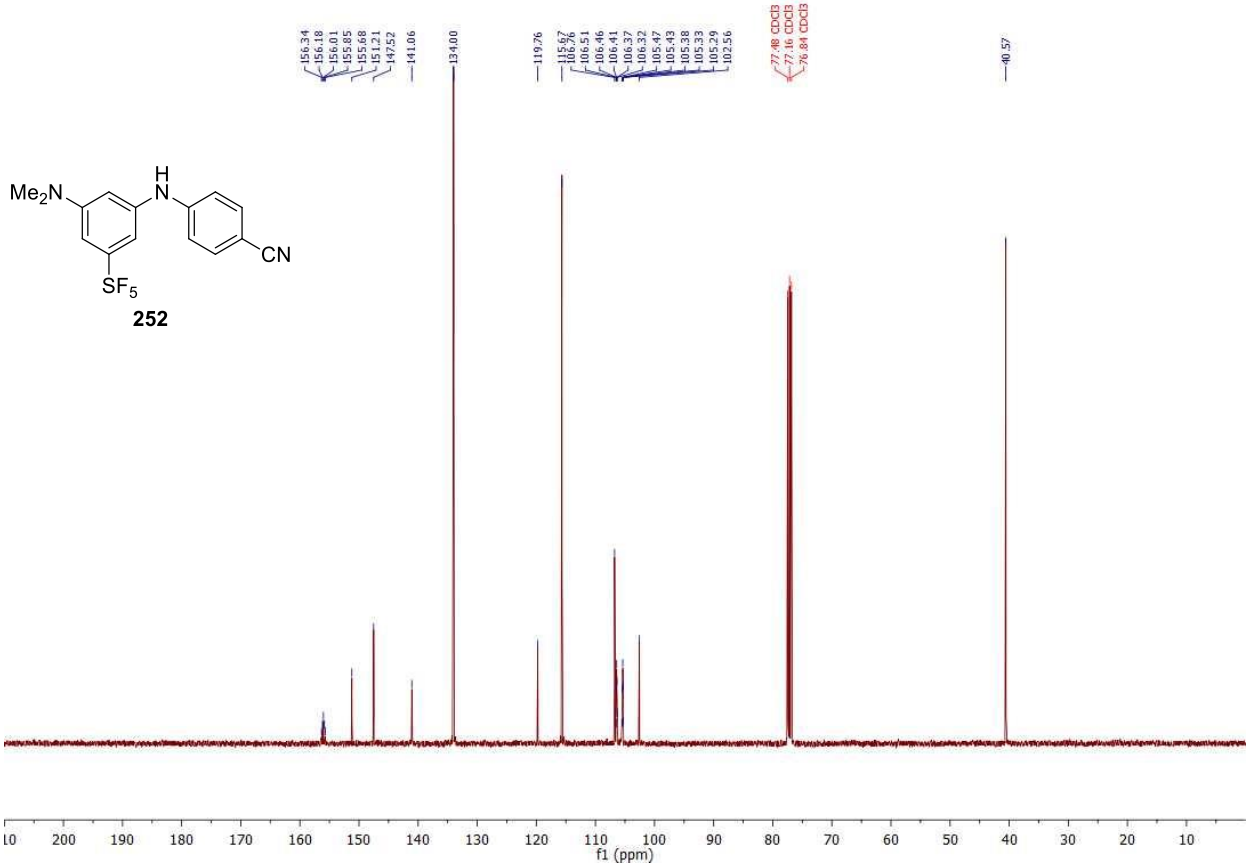

I
H
N
CN
SF5
f1 (ppm)
0.98
0.99
2.08
1.00
2.09
0.86

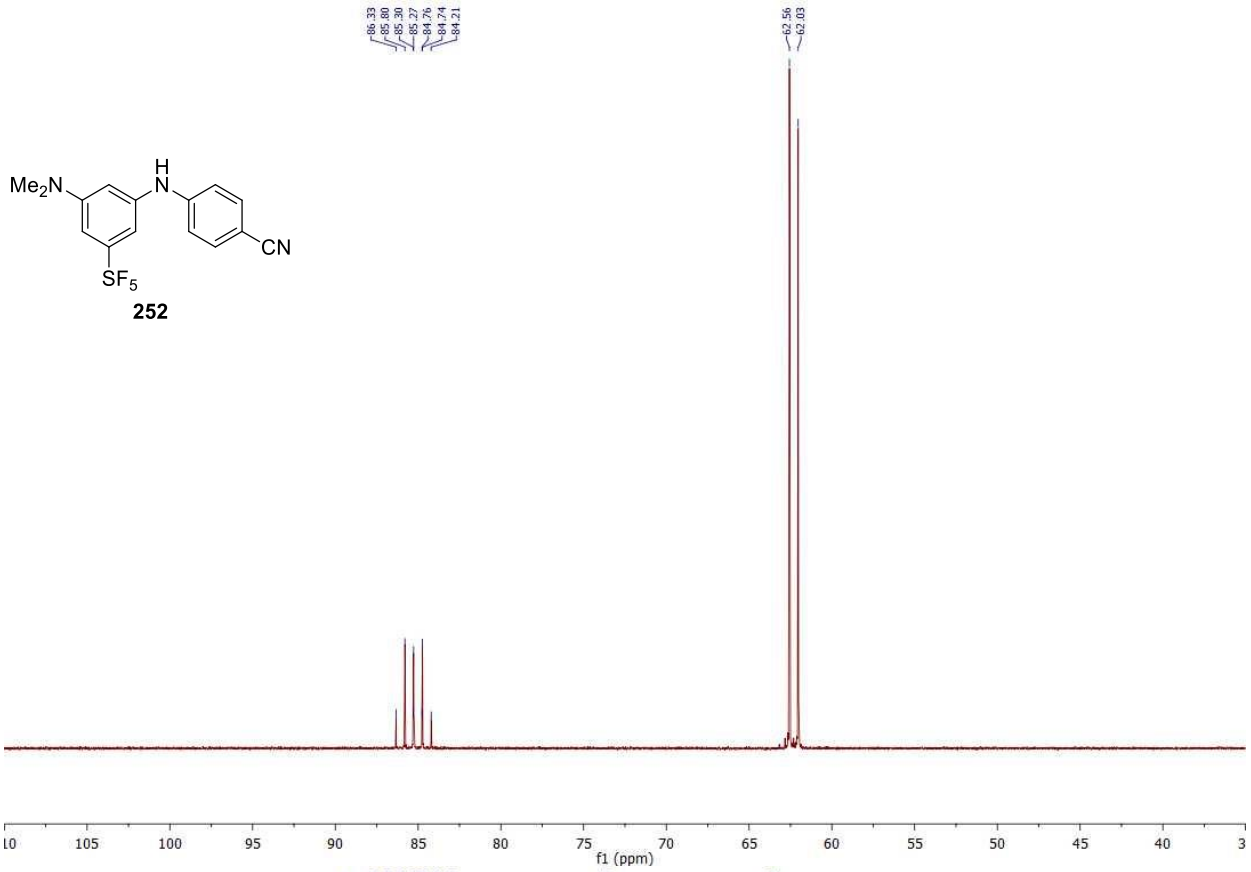
251

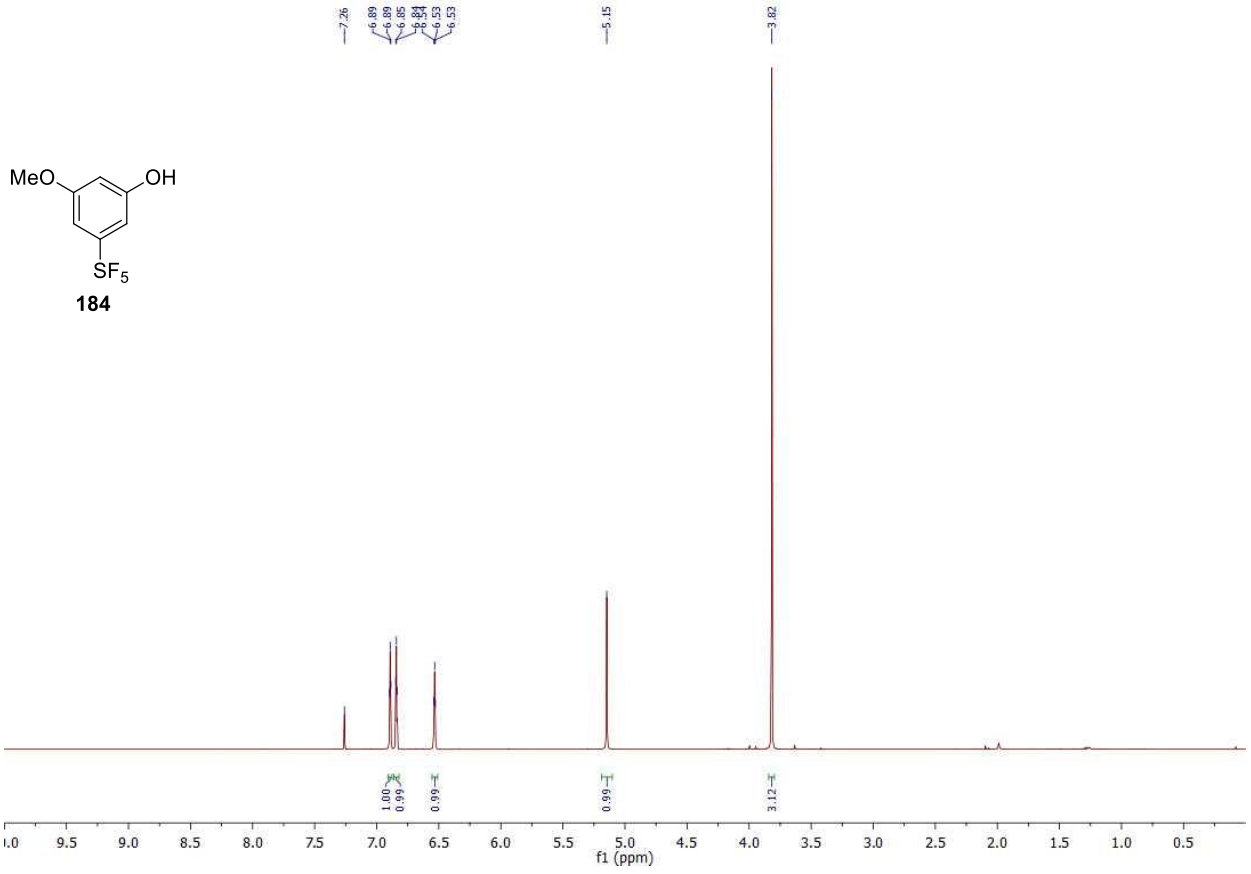

155.65
155.47
155.29
155.11
154.97
145.73
142.28
134.23
130.95
129.06
129.02
128.97
128.93
128.88
119.24
116.80
116.79
116.76
116.76
116.70
116.66
104.57
93.75
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
H
N
I
CN
SF5
251
f1 (ppm)

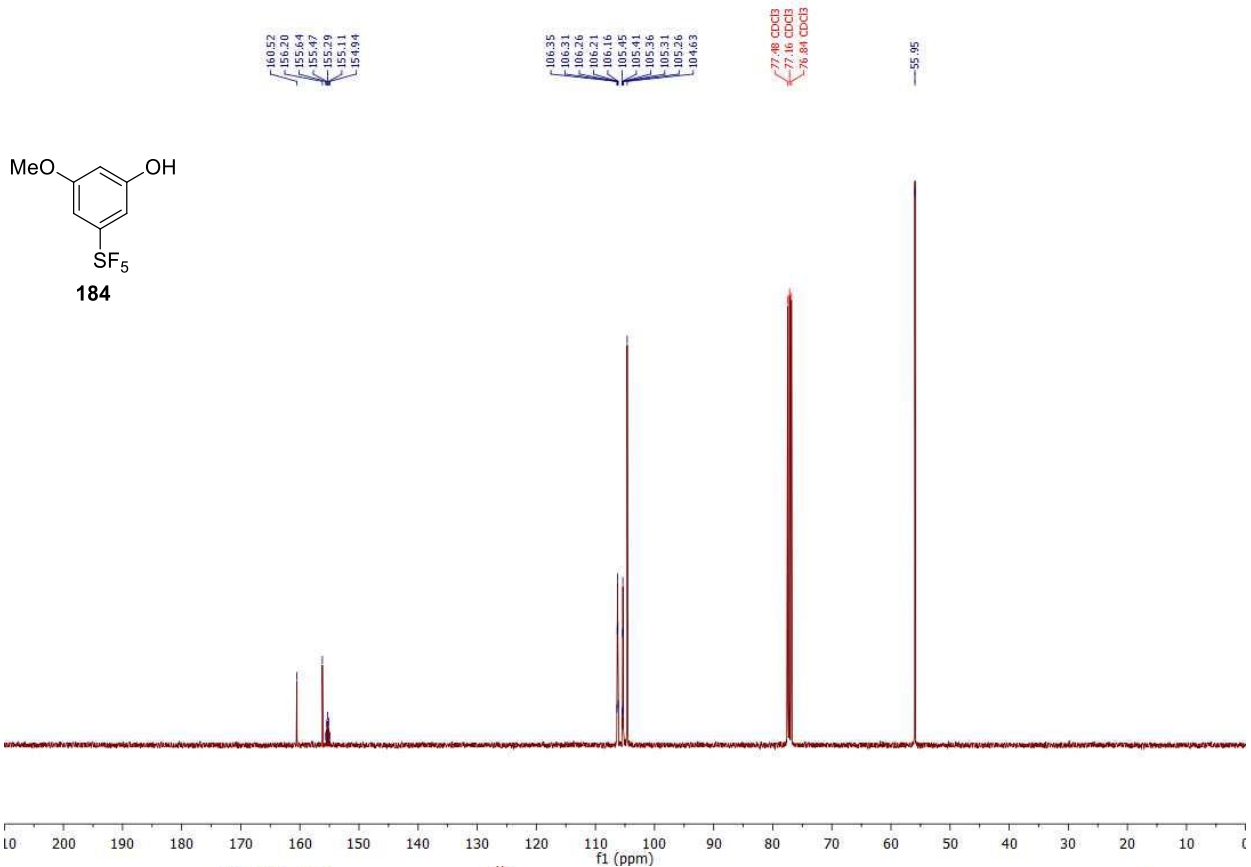

83.80
83.29
83.26
82.76
82.73
82.22
82.19
81.67
62.96
62.43
H
N
I
CN
SF5
251
f1 (ppm)

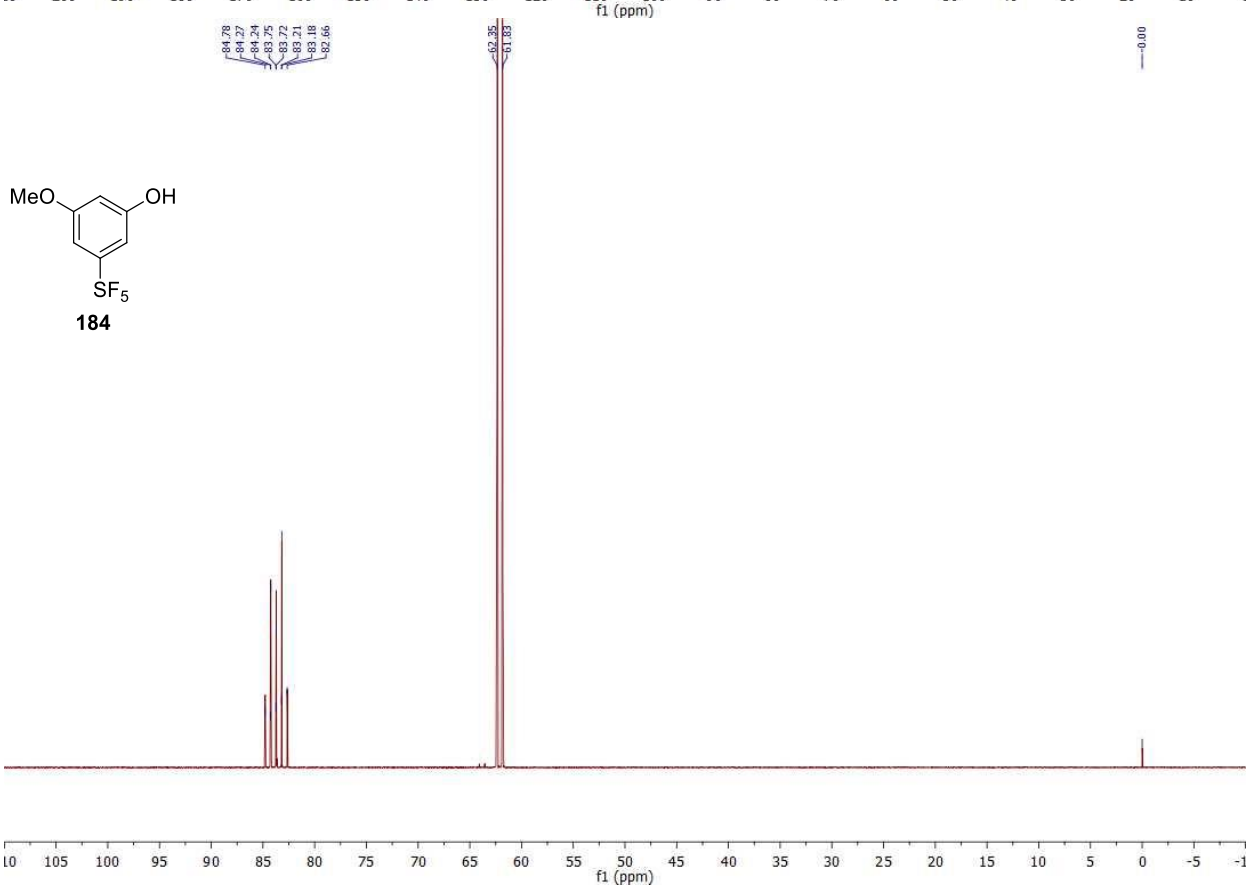

Me2N
H
N
CN
SF5
252
f1 (ppm)

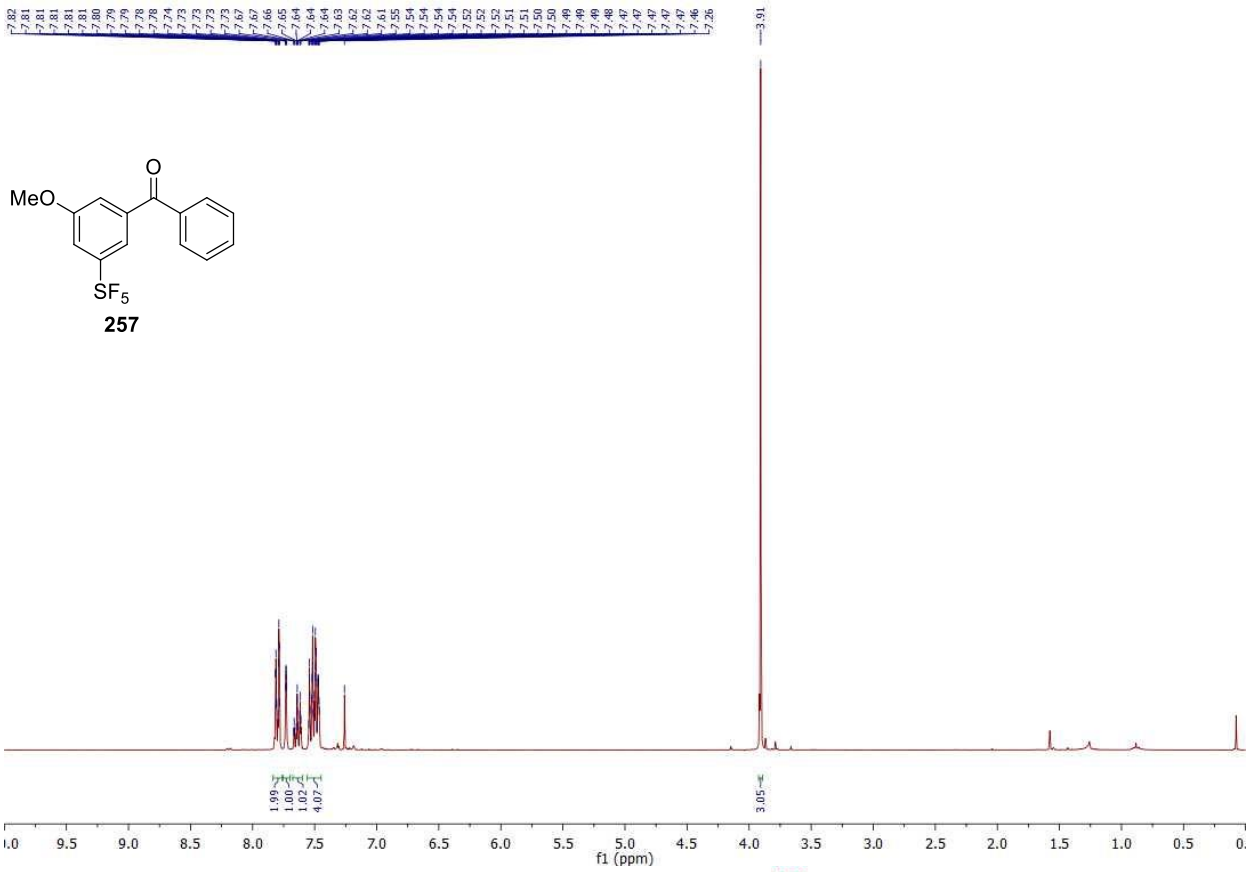

Me2N
H
N
CN
SF5
252
f1 (ppm)

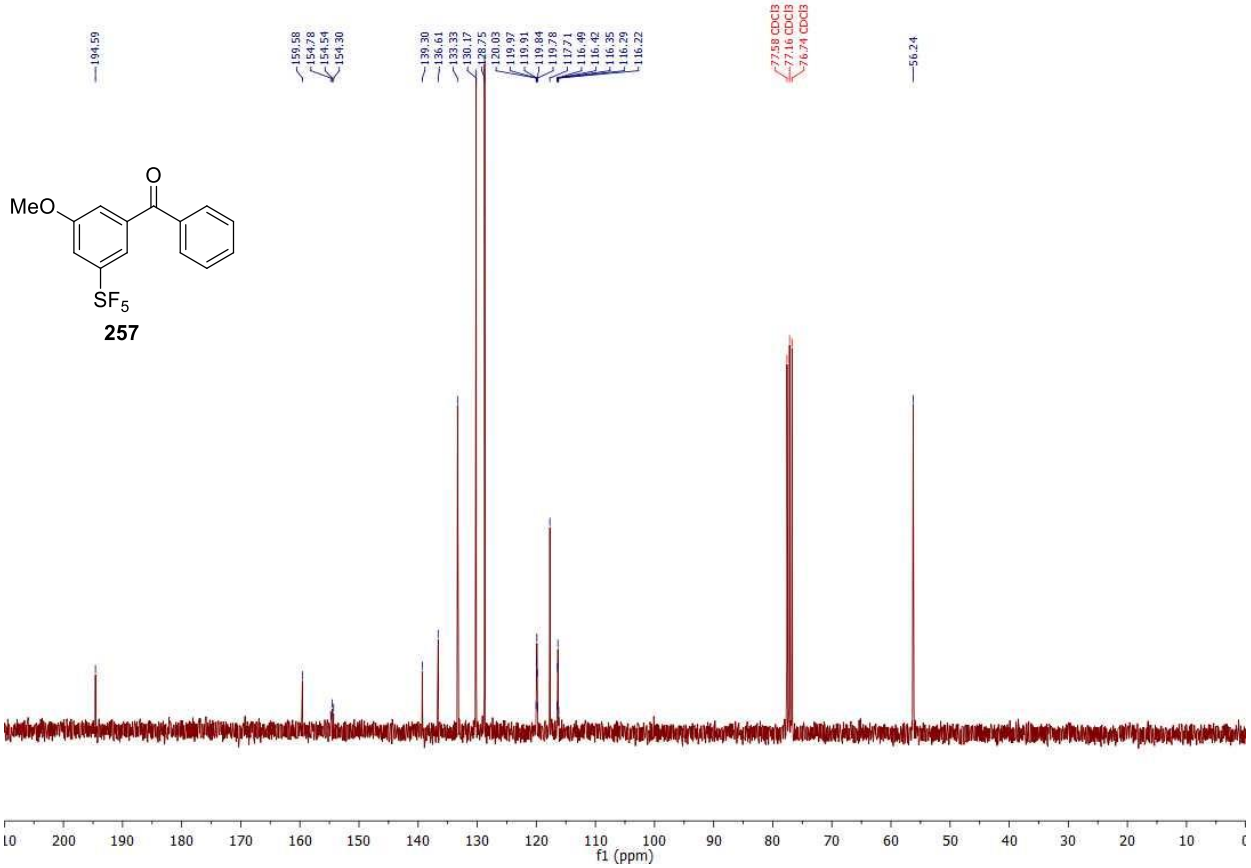

86.33
85.80
85.30
85.27
84.76
84.74
84.21
62.56
62.03
Me2N
H
N
CN
SF5
252
f1 (ppm)

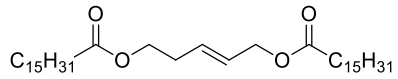

7.26
6.89
6.89
6.85
6.84
6.84
6.53
6.53
5.15
3.82
MeO
OH
SF5
184
1.00
0.99
0.99
0.99
3.12
f1 (ppm)


160.52
156.20
155.64
155.47
155.29
155.11
154.94
106.35
106.31
106.26
106.21
106.16
105.45
105.41
105.36
105.31
105.26
104.63
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.95
MeO
OH
SF5
184
f1 (ppm)


84.78
84.27
84.24
83.75
83.72
83.21
83.18
82.66
62.35
61.83
0.00
MeO
OH
SF5
184
f1 (ppm)

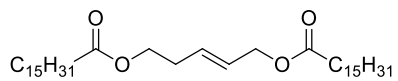

MeO
O
SF5
257
f1 (ppm)


MeO
O
SF5
257
f1 (ppm)


O
O
O
O
C15H31
C15H31

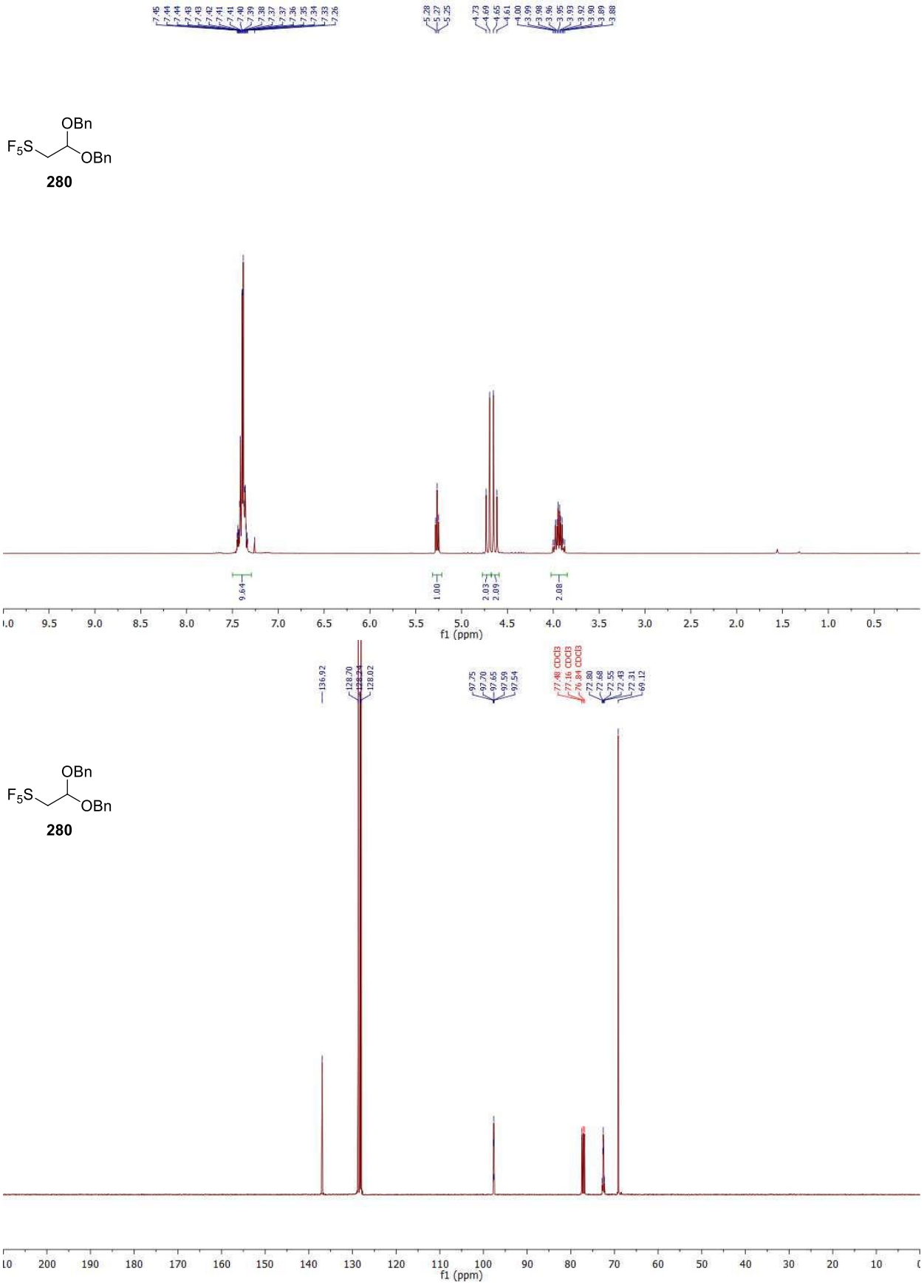
270

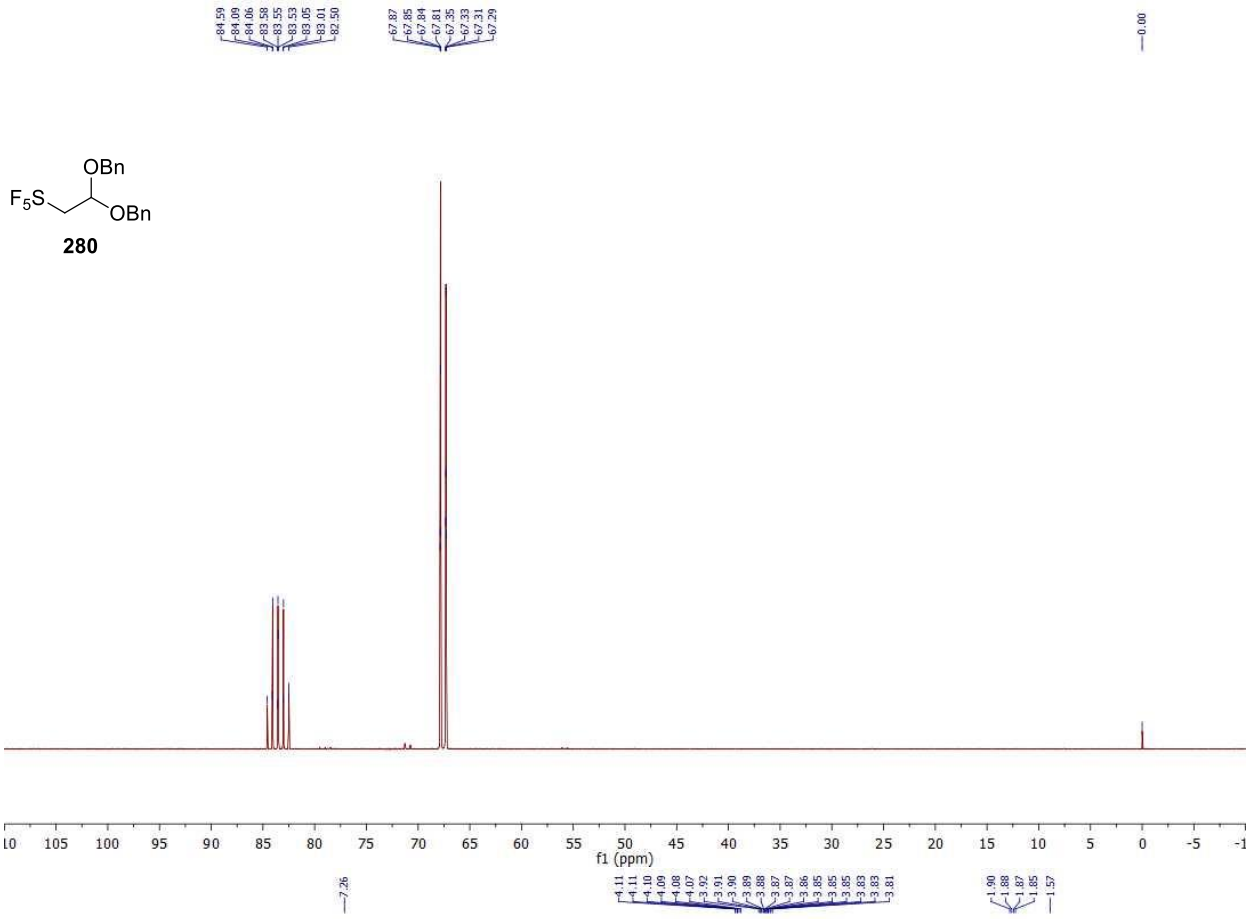
7.26
5.76
5.75
5.73
5.72
5.71
5.70
5.69
5.68
5.67
5.66
5.65
5.63
4.52
4.51
4.13
4.11
4.09
2.41
2.40
2.39
2.38
2.36
2.32
2.30
2.28
2.27
1.62
1.60
1.28
1.27
0.89
0.88
0.87
0.86
0.85
1.99
1.89
2.00
1.96
4.15
4.46
51.02
6.26
f1 (ppm)

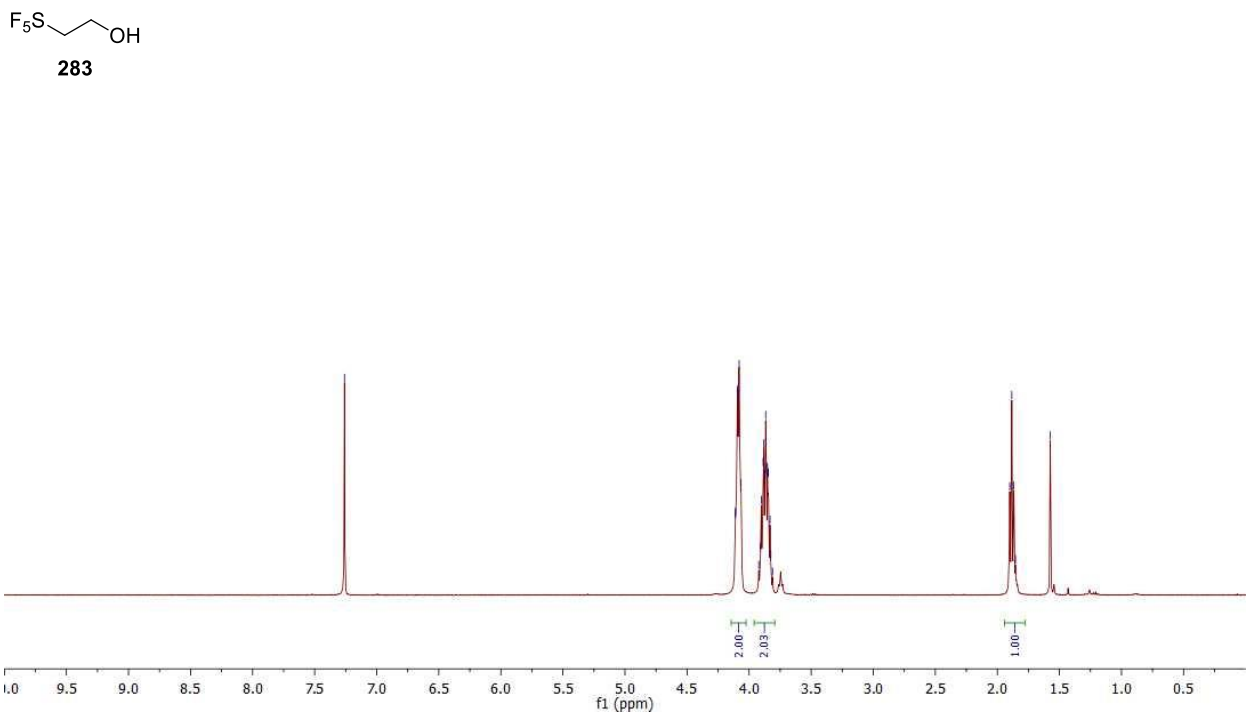

O
O
O
O
C15H31
C15H31

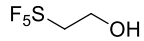
270

173.93
173.70
131.03
126.95
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
64.70
63.19
34.47
32.08
31.82
29.85
29.84
29.81
29.76
29.63
29.52
29.48
29.32
25.13
25.11
22.85
14.27
f1 (ppm)


OBn
F5S
OBn
280
f1 (ppm)
OBn
F5S
OBn
280
f1 (ppm)

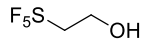

OBn
F5S
OBn
280
f1 (ppm)


F5S
OH
283
f1 (ppm)



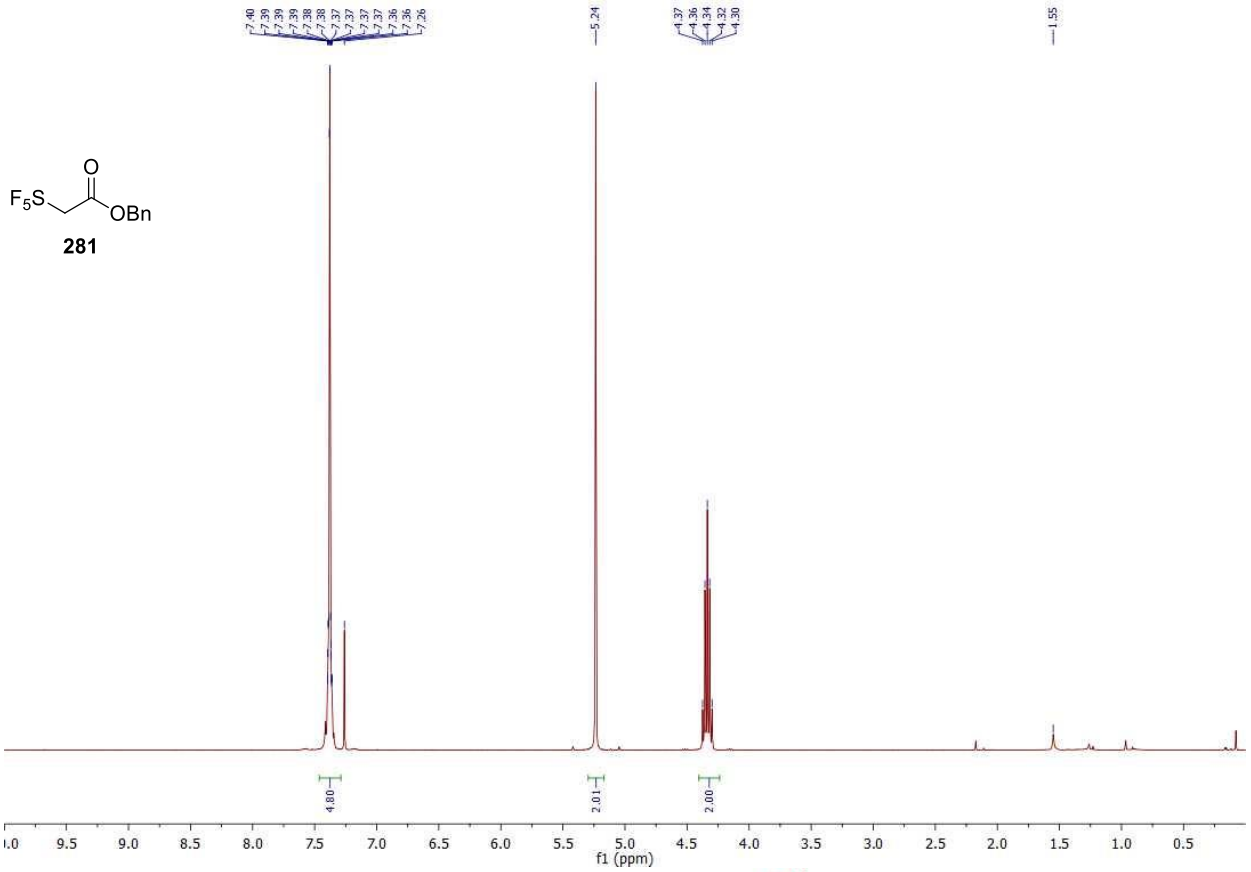
283

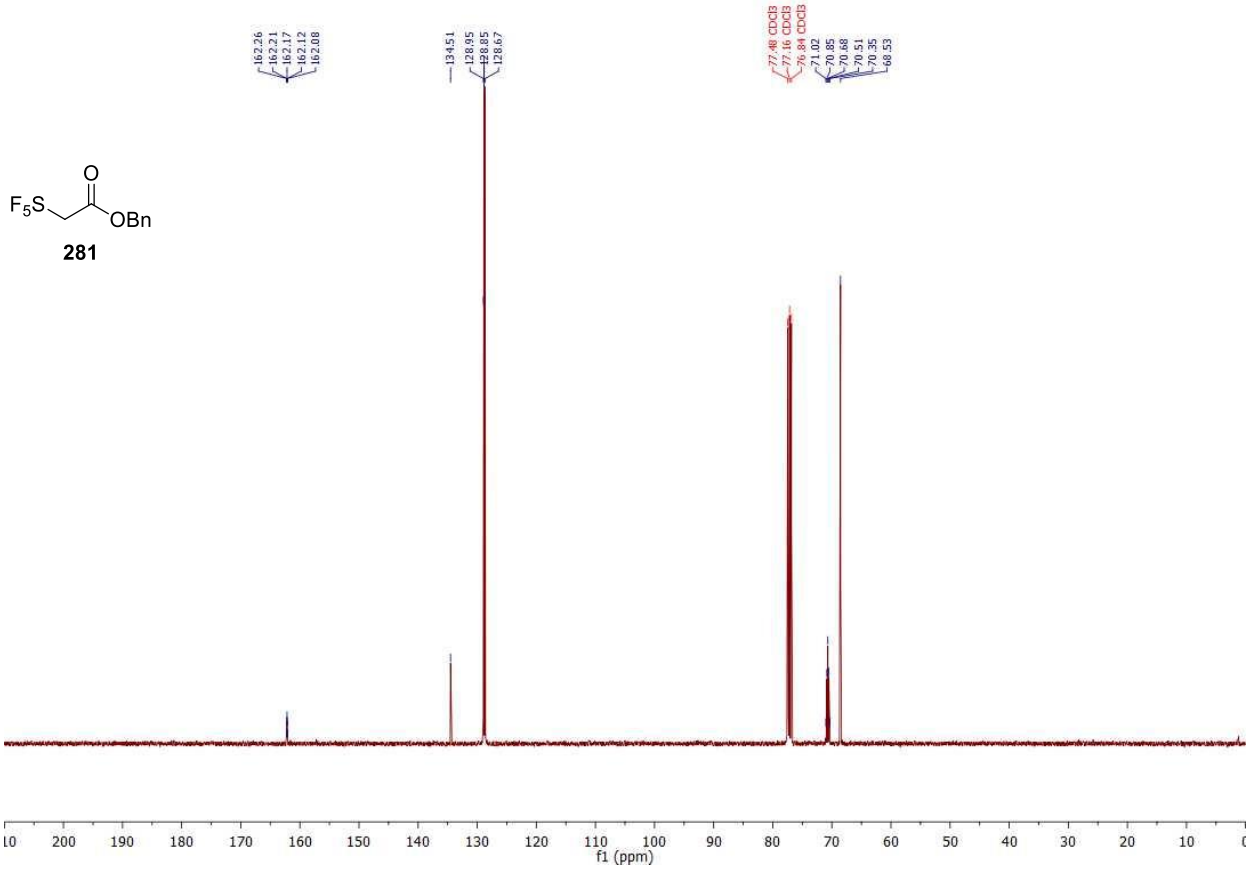
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
73.71
73.60
73.48
73.37
73.25
58.69
58.65
58.60
58.55
58.51
f1 (ppm)
85.47
84.97
84.95
84.46
84.44
83.94
83.92
83.41
66.38
66.35
66.32
65.86
65.84
65.81



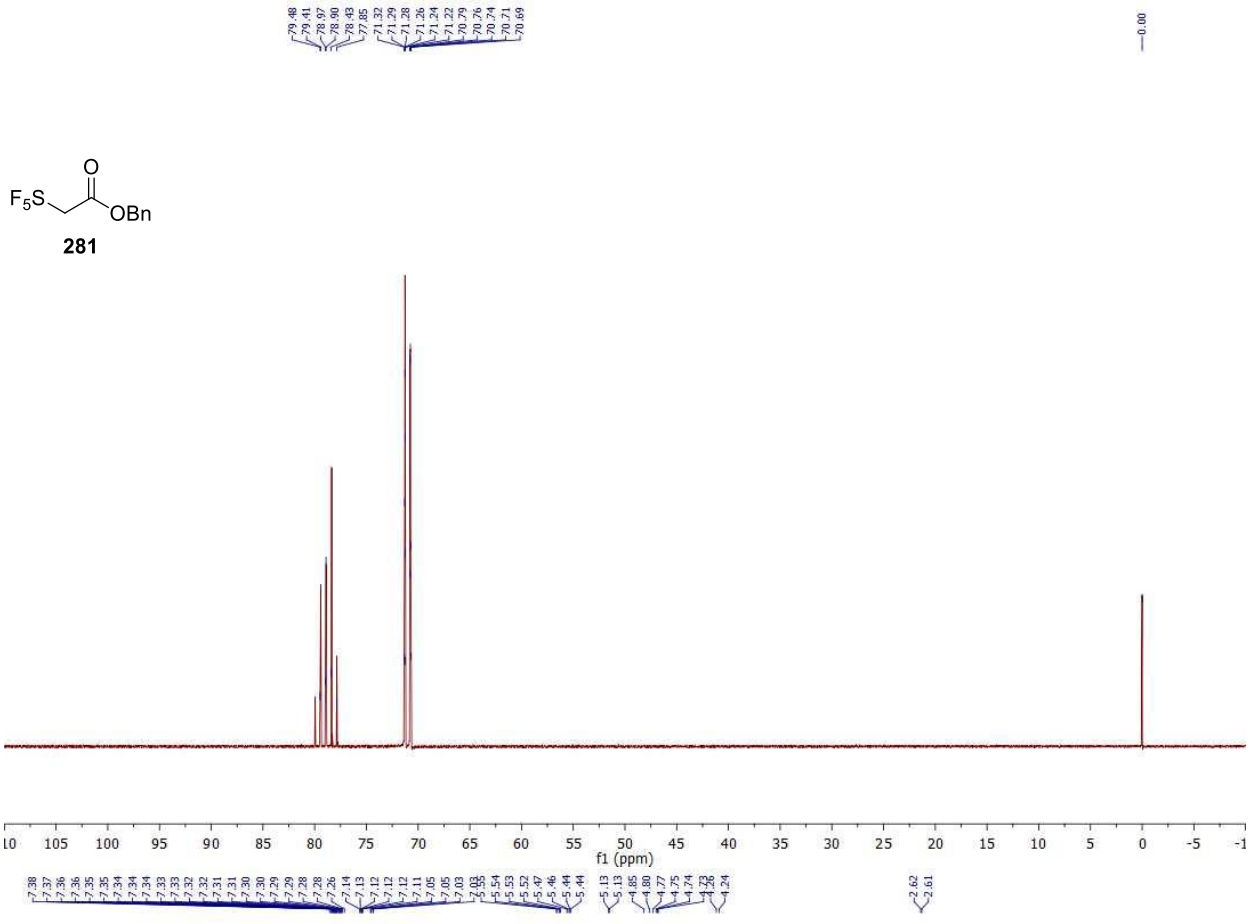
283

f1 (ppm)

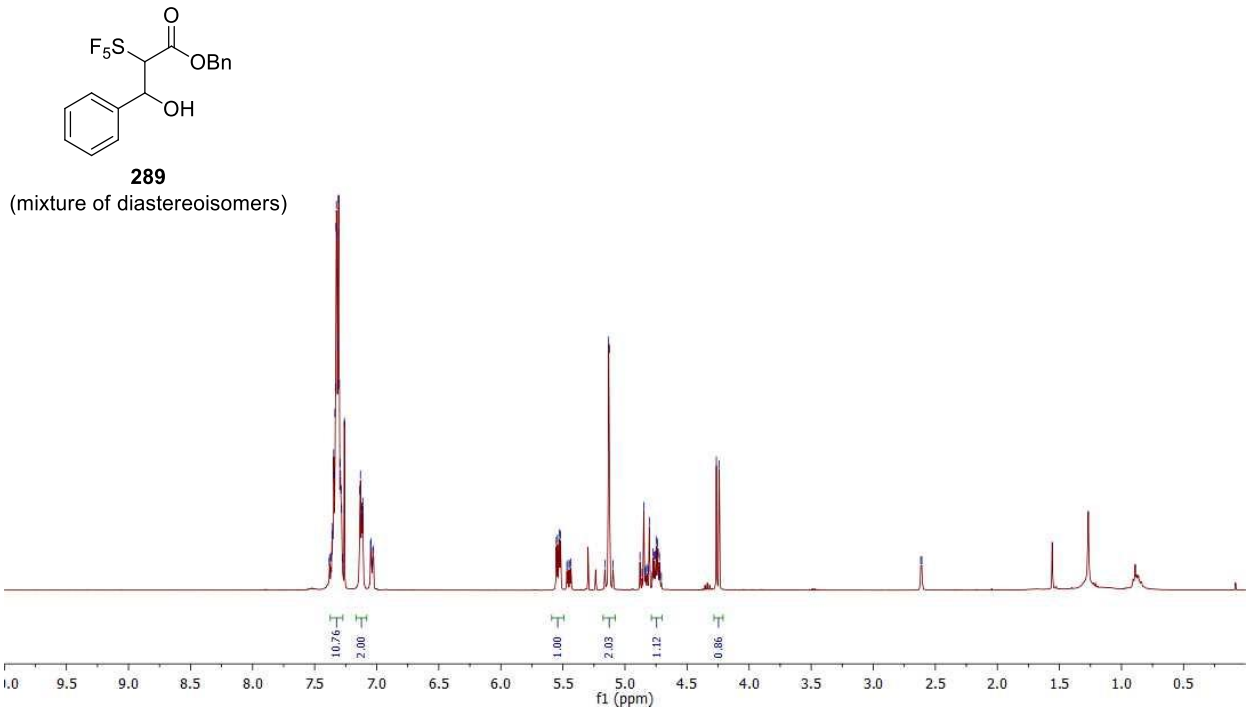

7.40
7.39
7.39
7.39
7.38
7.38
7.37
7.37
7.37
7.37
7.37
7.36
7.36
7.26
5.24
4.37
4.36
4.34
4.32
4.30
1.55
4.80
2.01
2.00
f1 (ppm)


162.26
162.21
162.17
162.12
162.08
134.51
128.95
128.85
128.67
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
71.02
70.85
70.68
70.51
70.35
68.53
f1 (ppm)

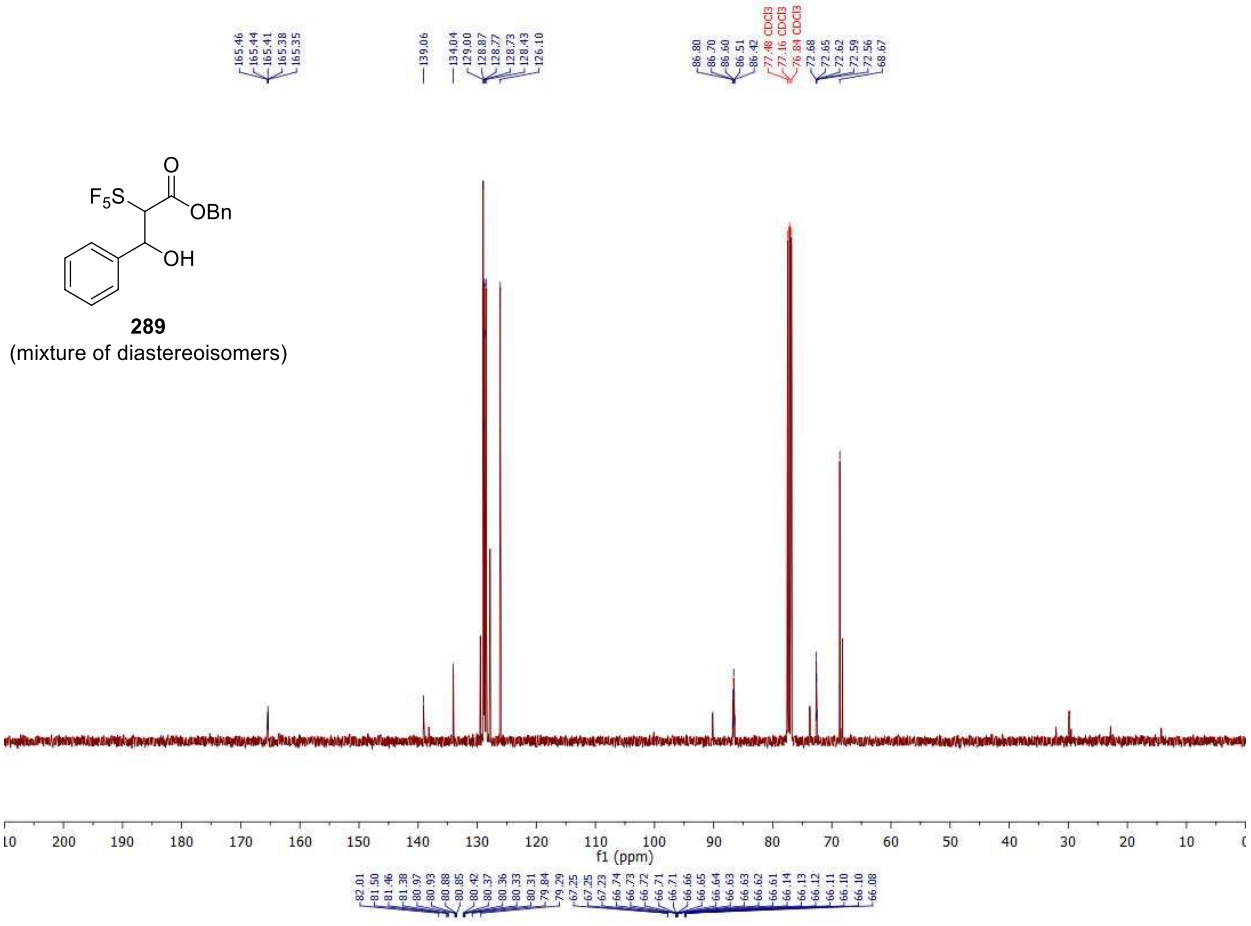
281



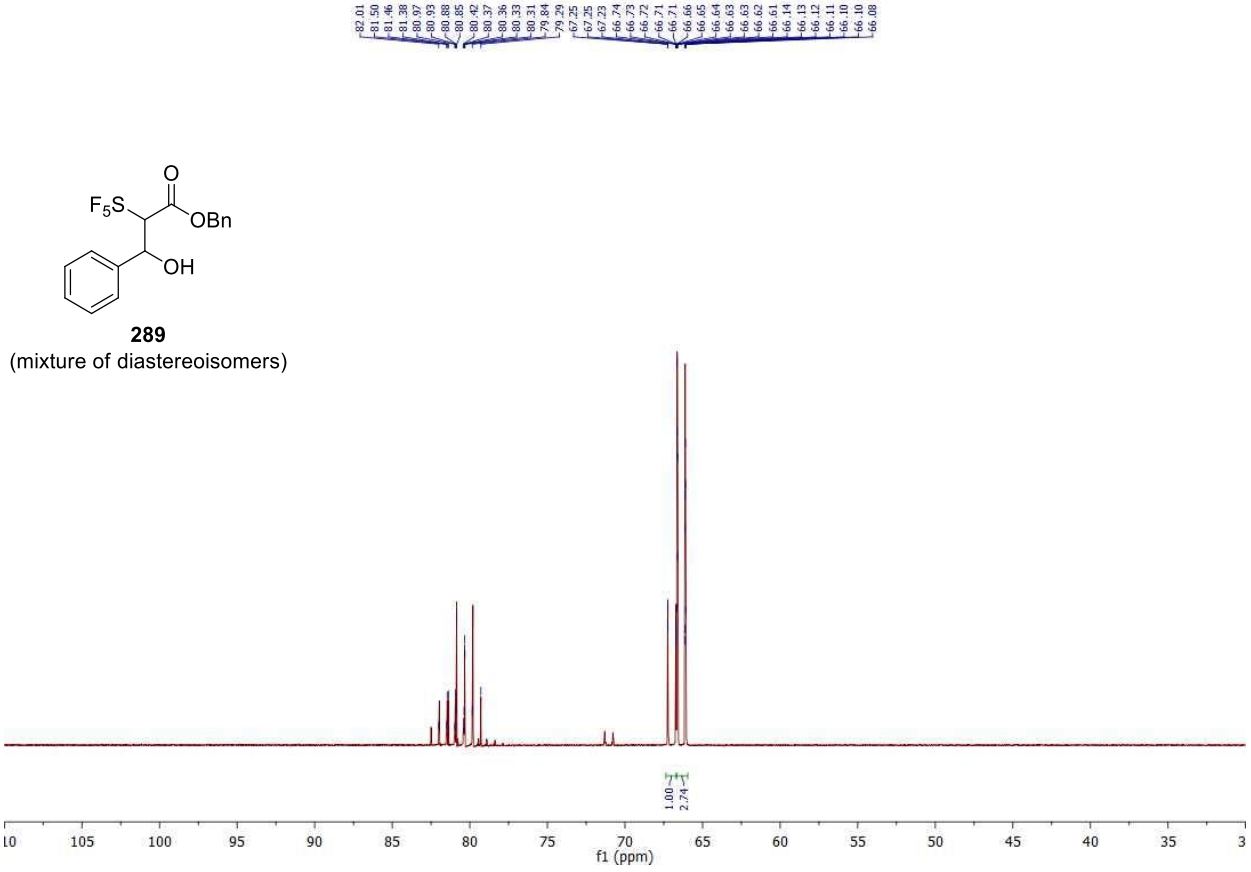
281



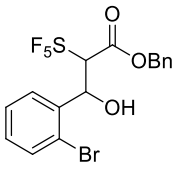
289
(mixture of diastereoisomers)



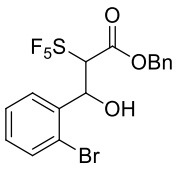
289
(mixture of diastereoisomers)



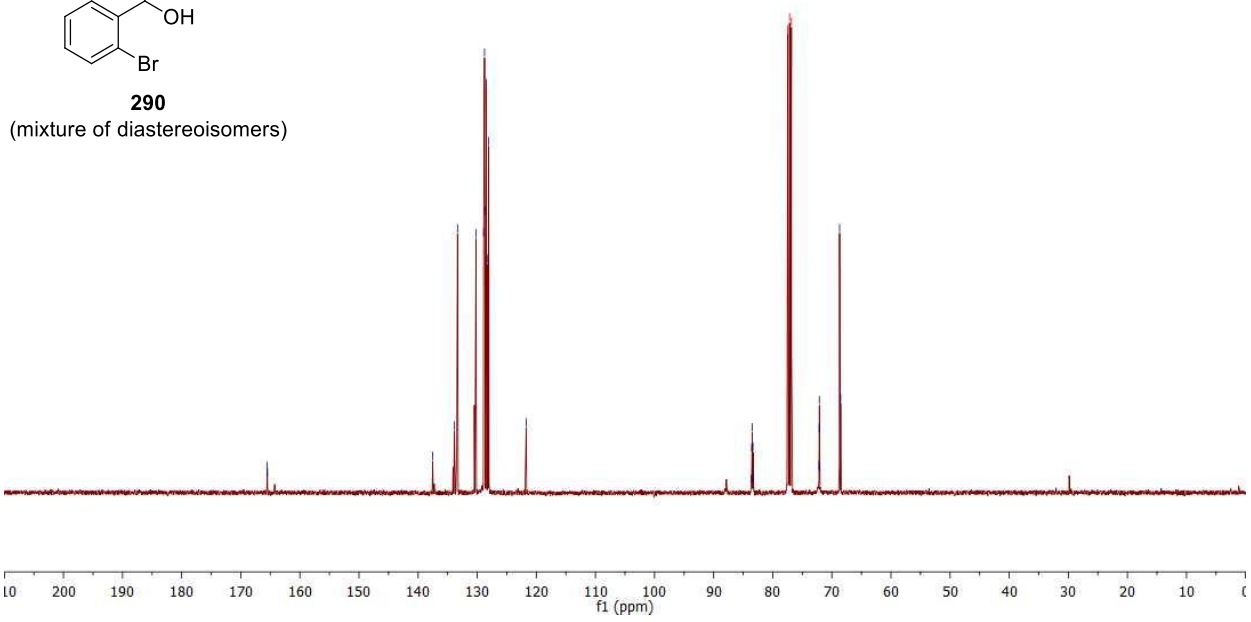
289
(mixture of diastereoisomers)

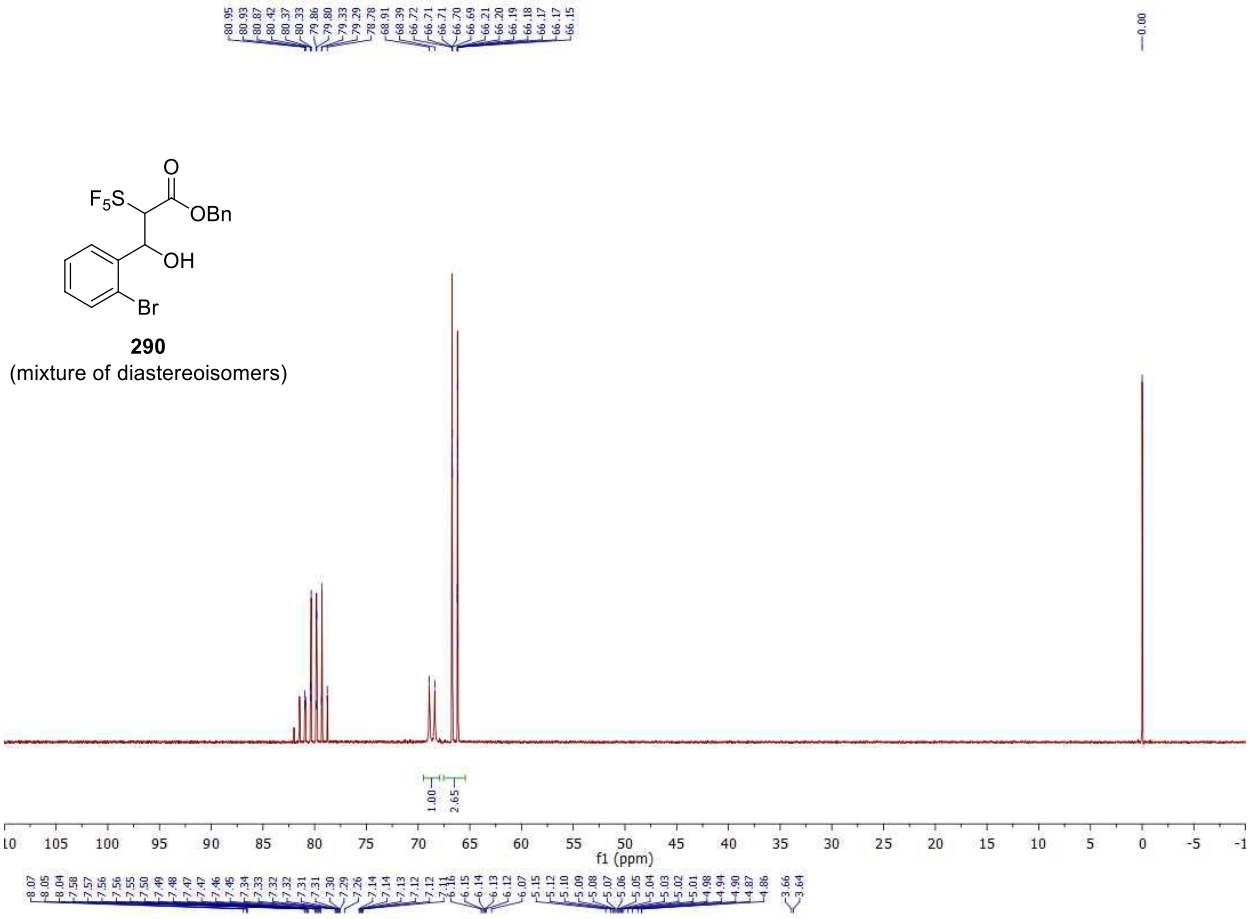


290
(mixture of diastereoisomers)

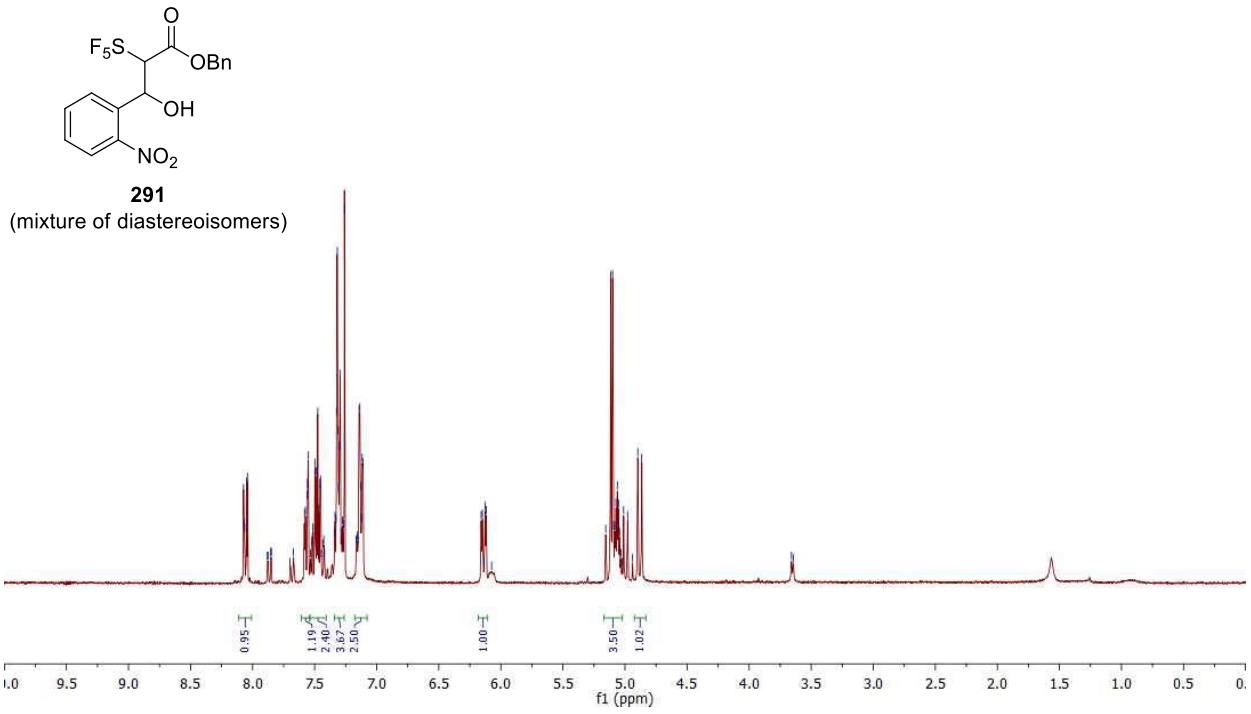


290
(mixture of diastereoisomers)

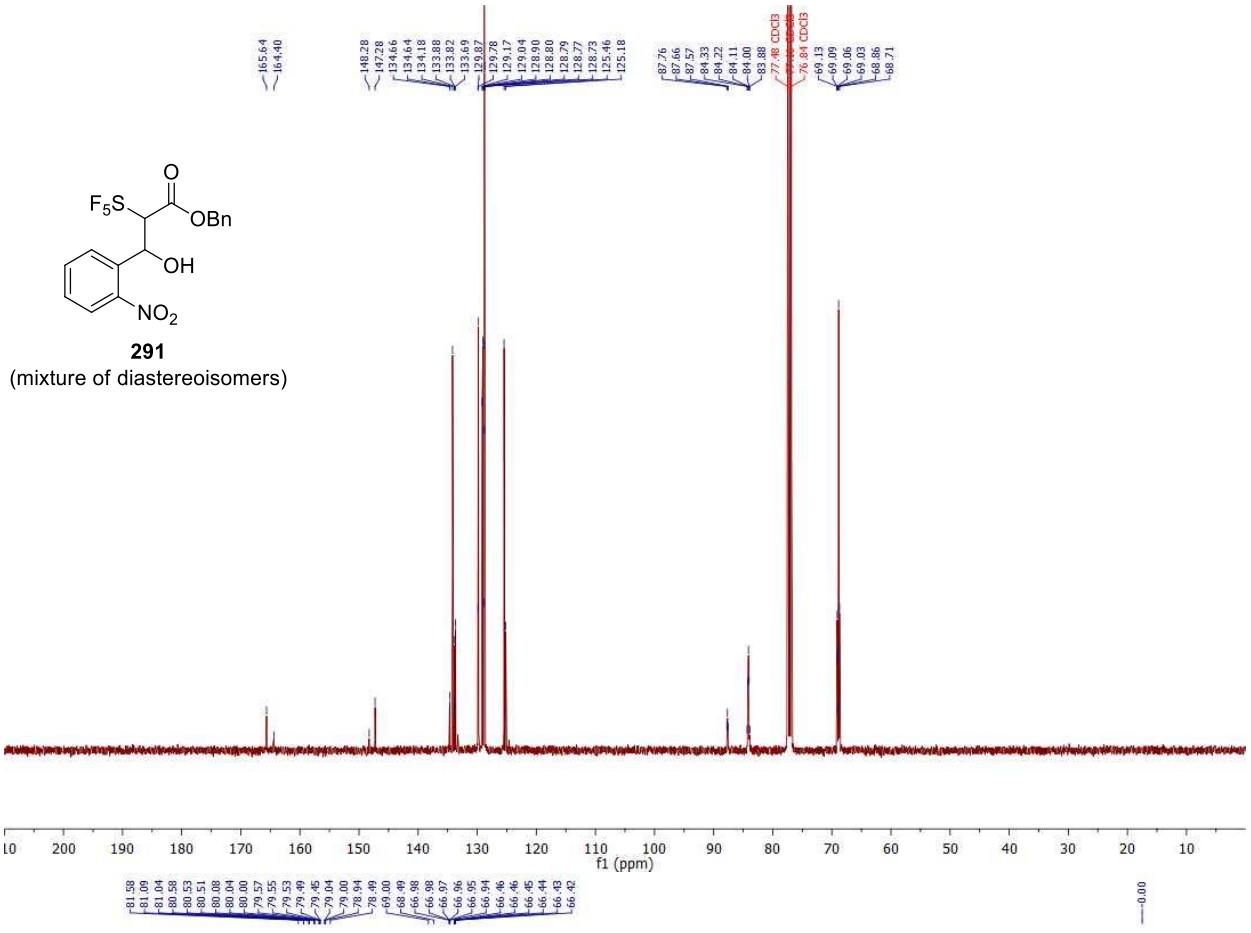




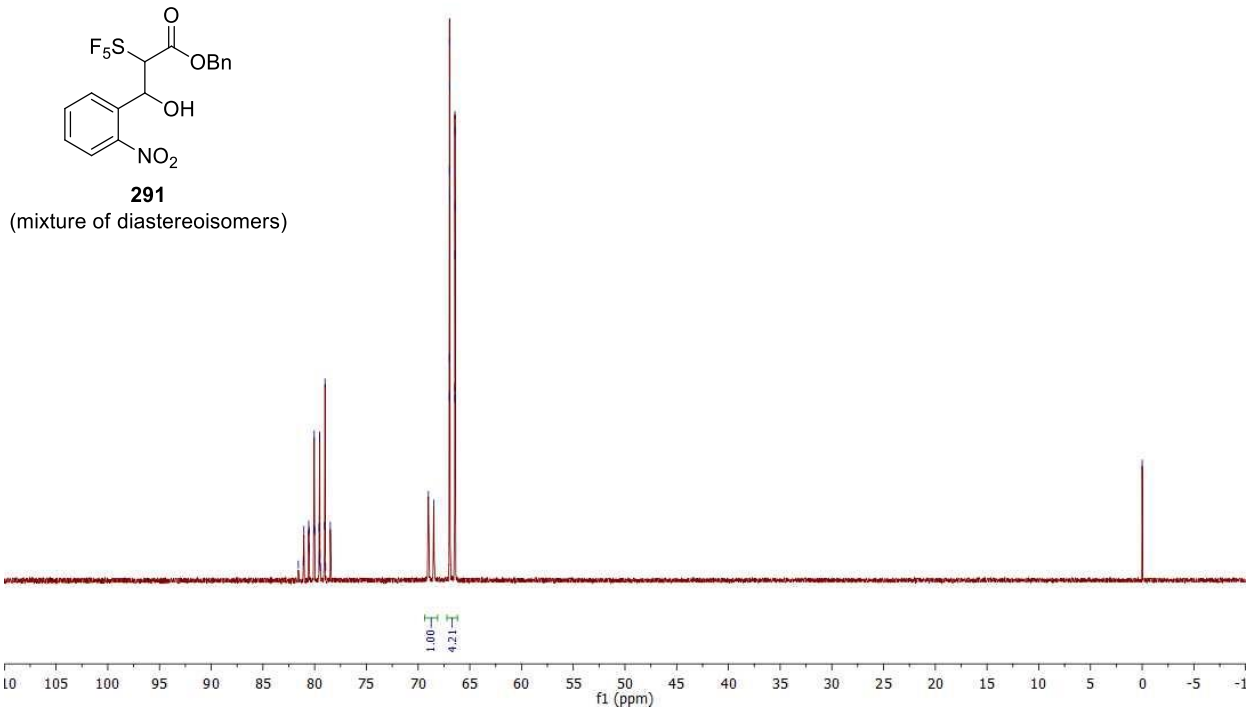
290
(mixture of diastereoisomers)



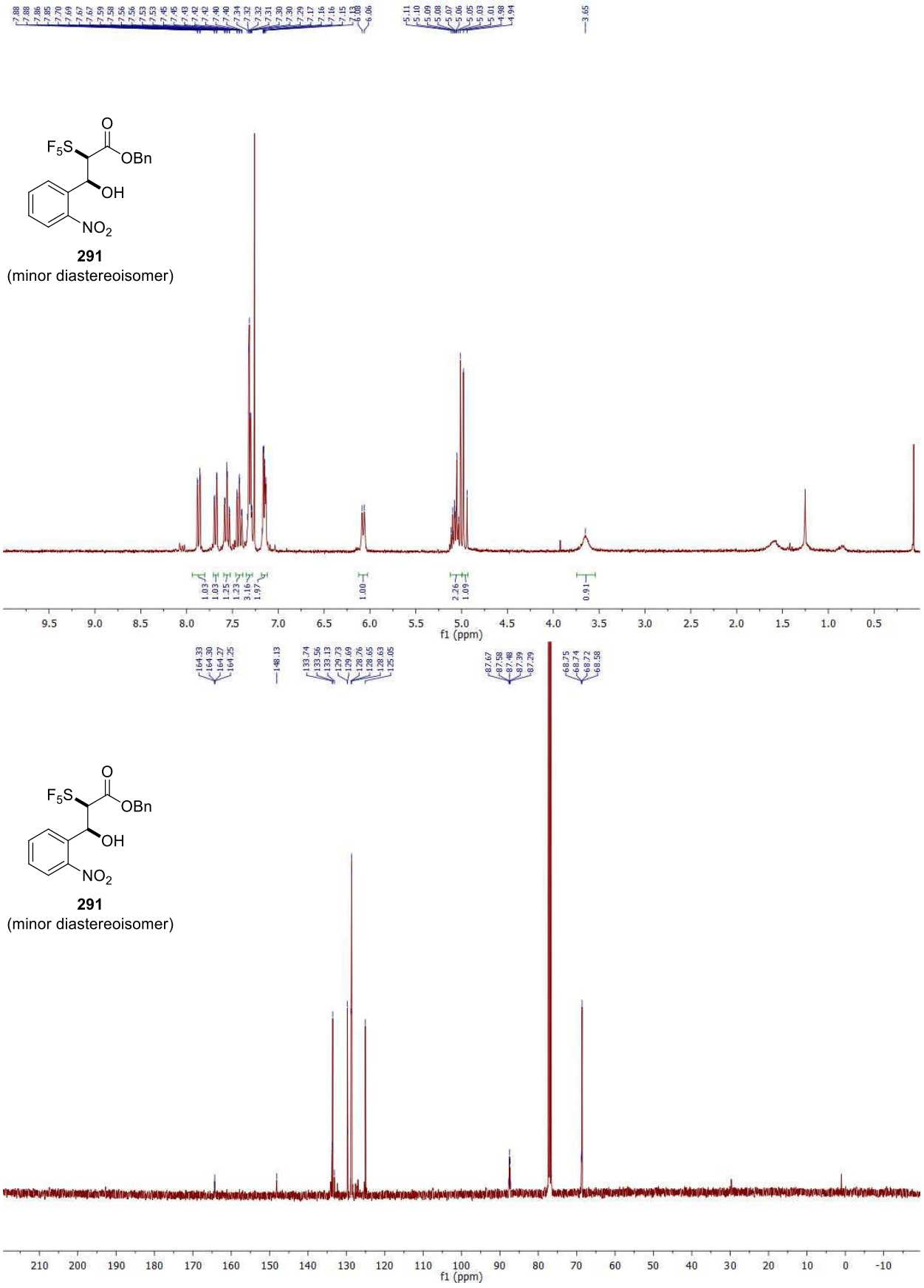
291
(mixture of diastereoisomers)

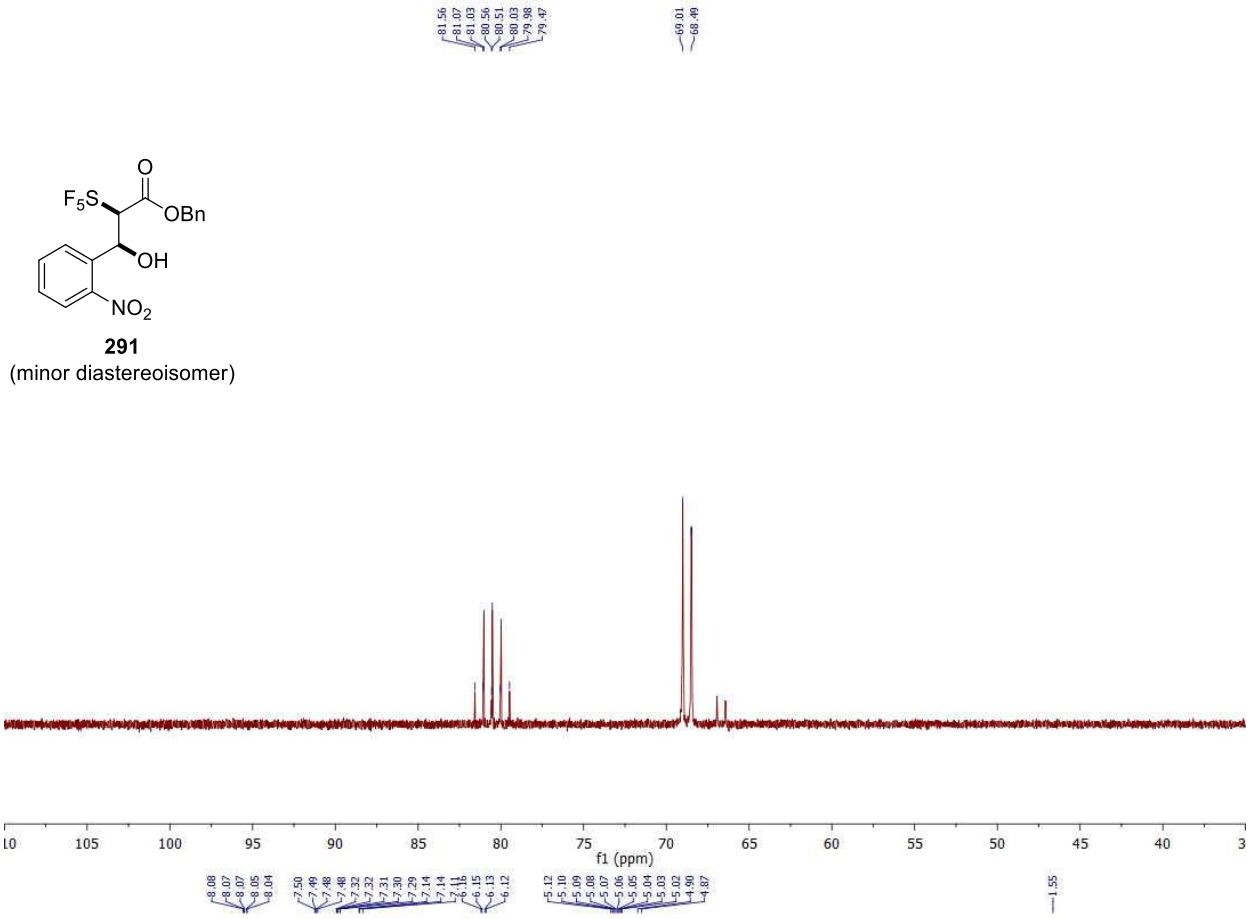


291
(mixture of diastereoisomers)

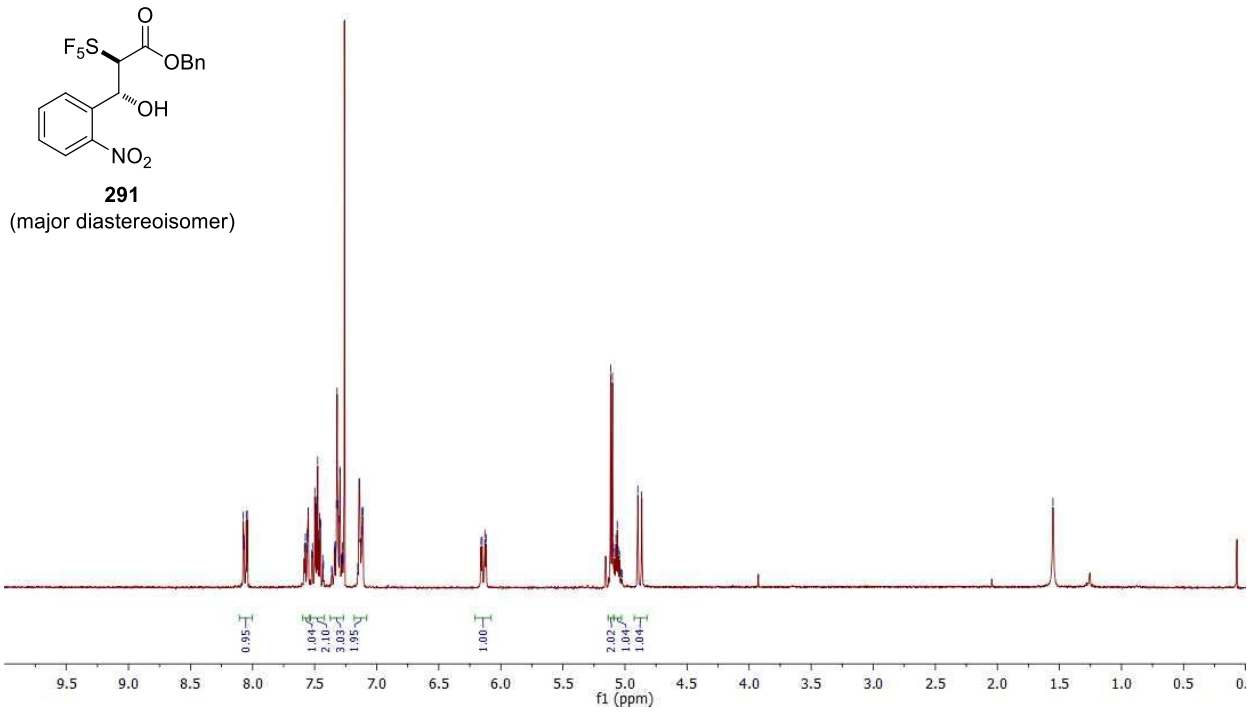


291
(mixture of diastereoisomers)

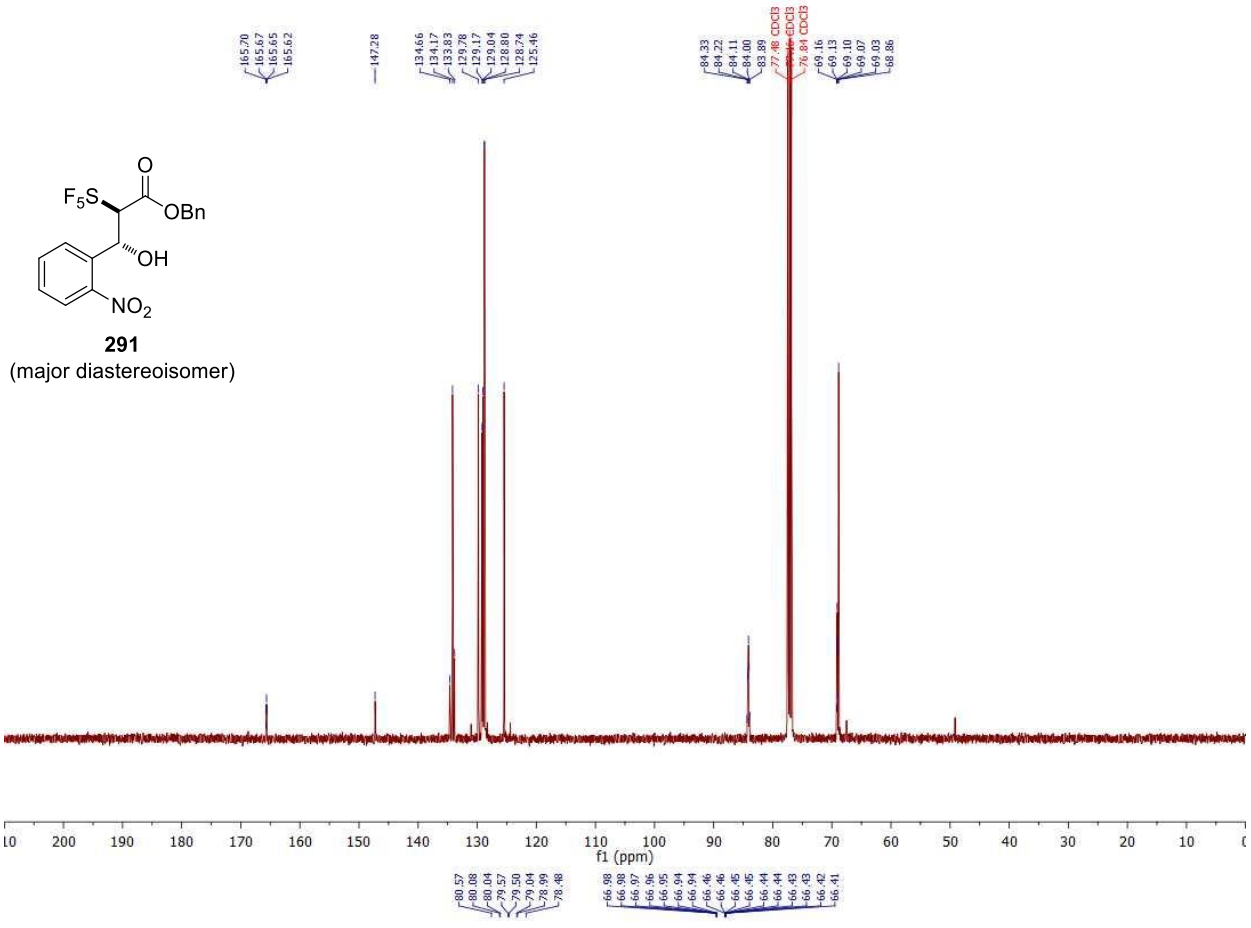

F5S
O
OBn
OH
NO2
291
(minor diastereoisomer)
f1 (ppm)
F5S
O
OBn
OH
NO2
291
(minor diastereoisomer)
f1 (ppm)

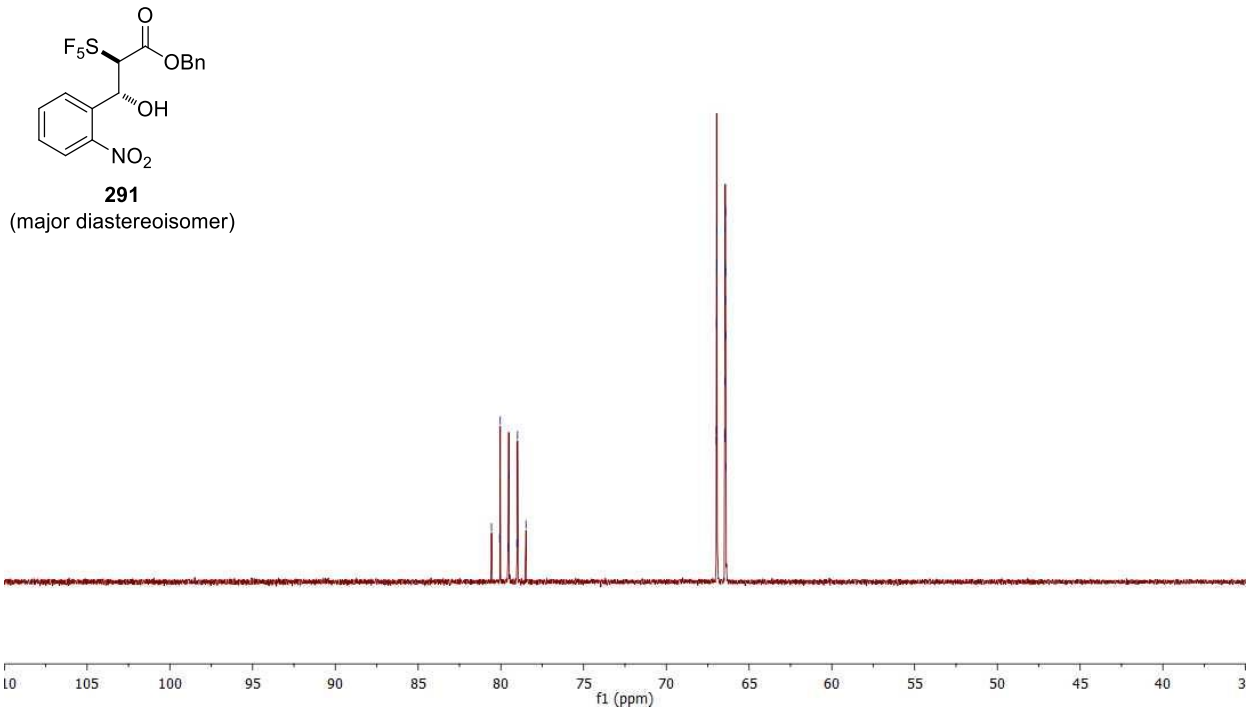


291
(minor diastereoisomer)

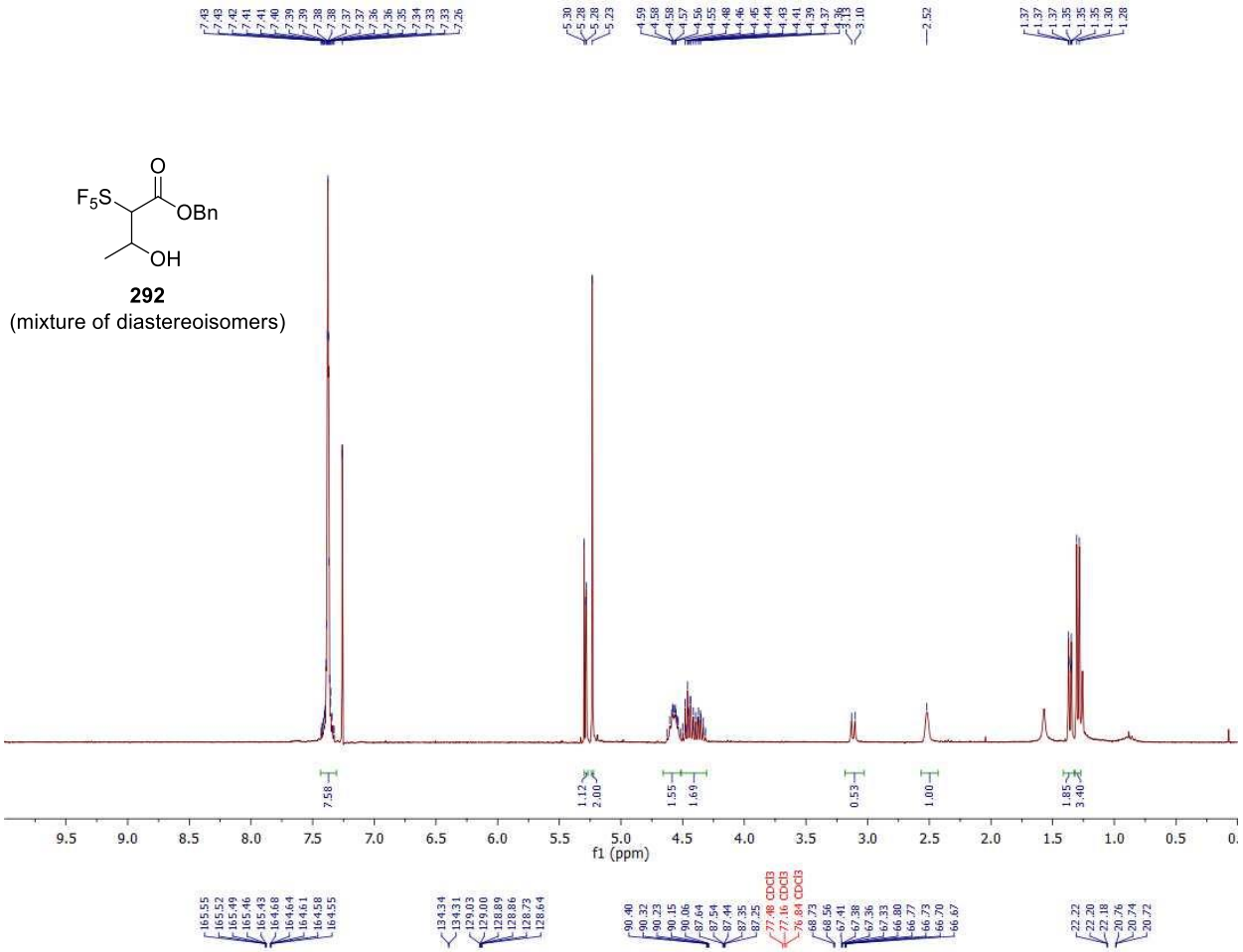


291
(major diastereoisomer)

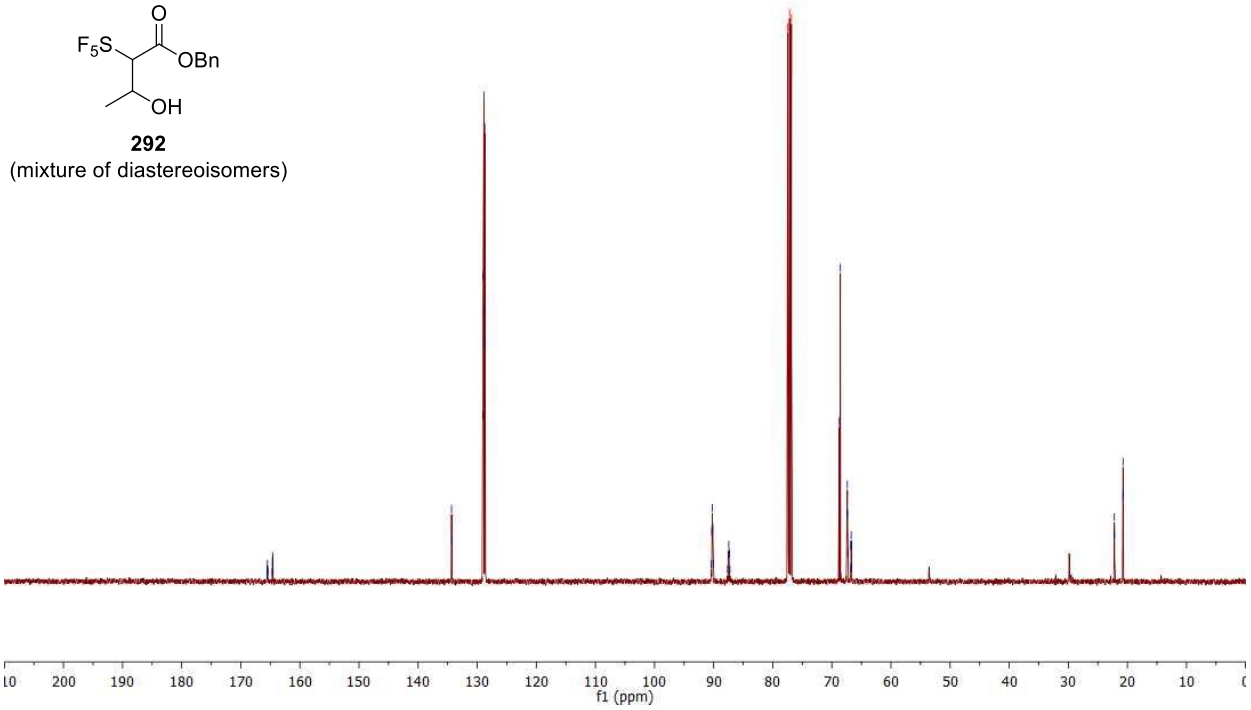




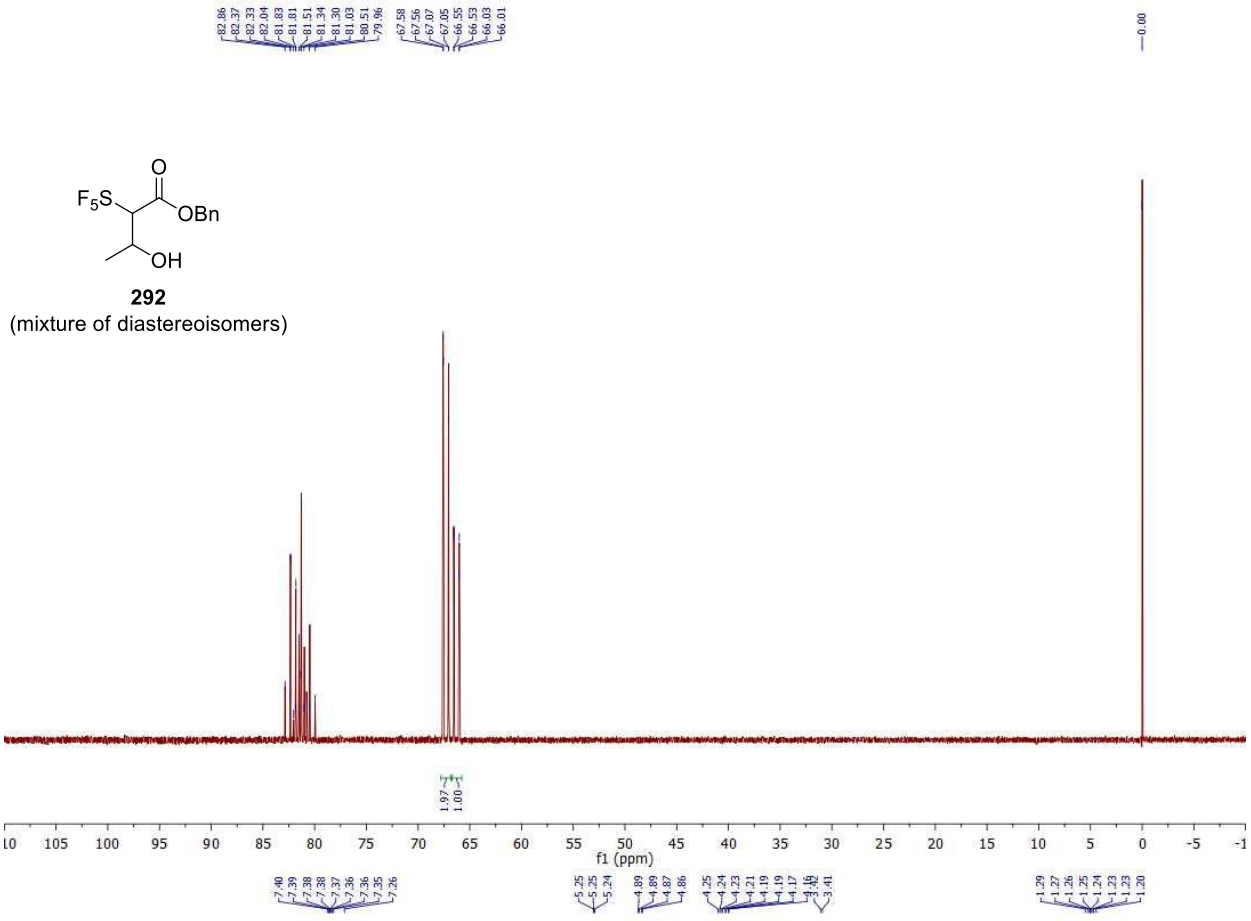
291
(major diastereoisomer)



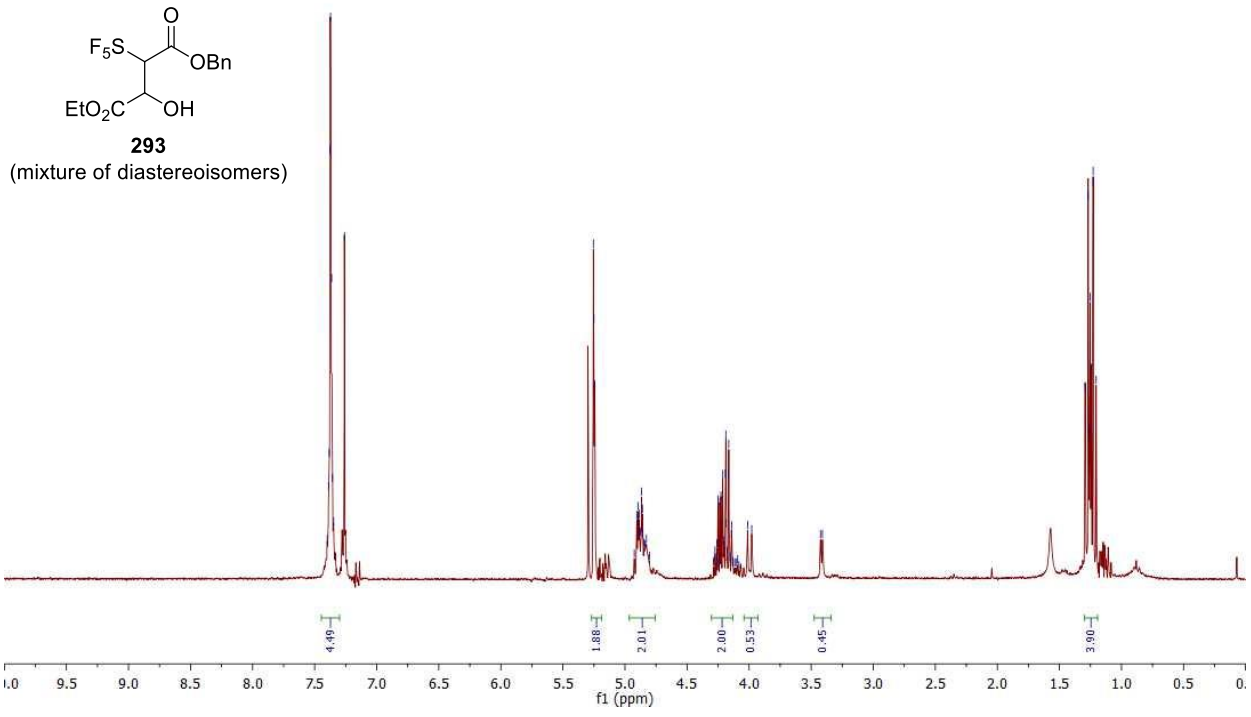
292
(mixture of diastereoisomers)



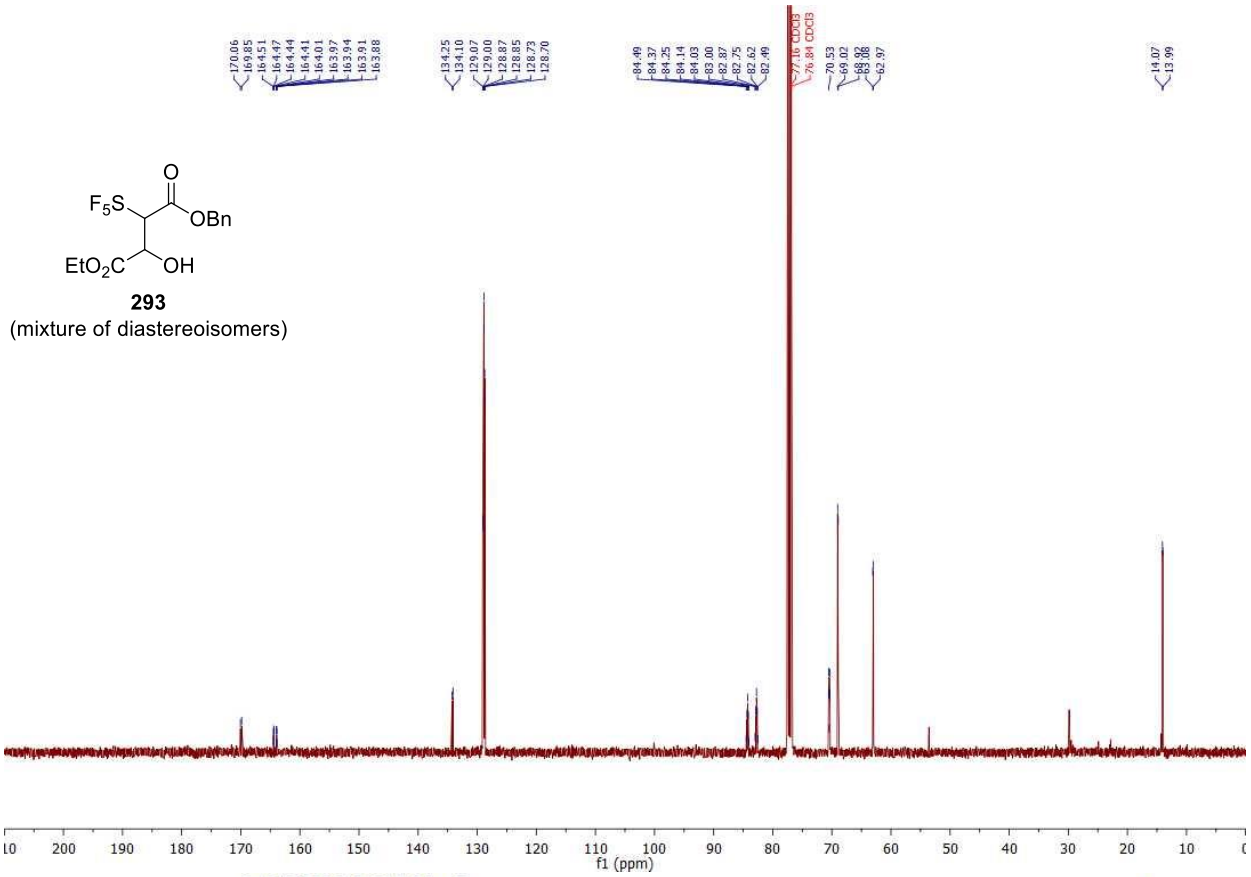
292
(mixture of diastereoisomers)

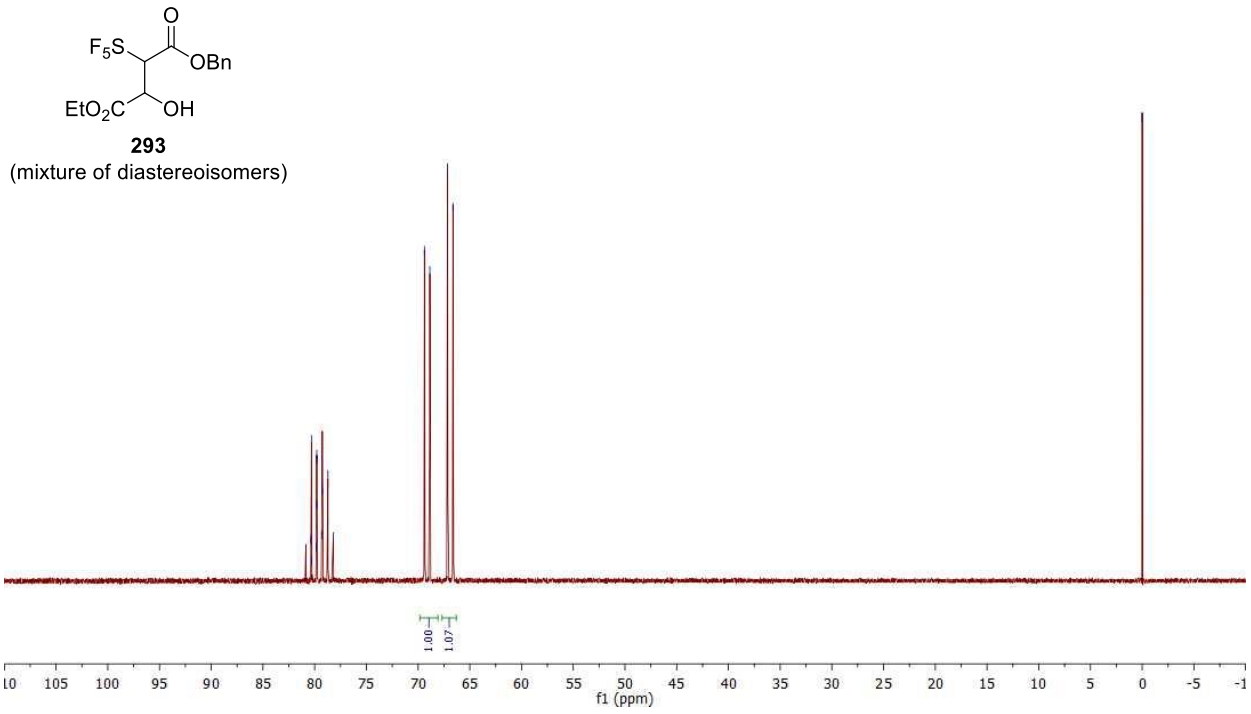


292
(mixture of diastereoisomers)

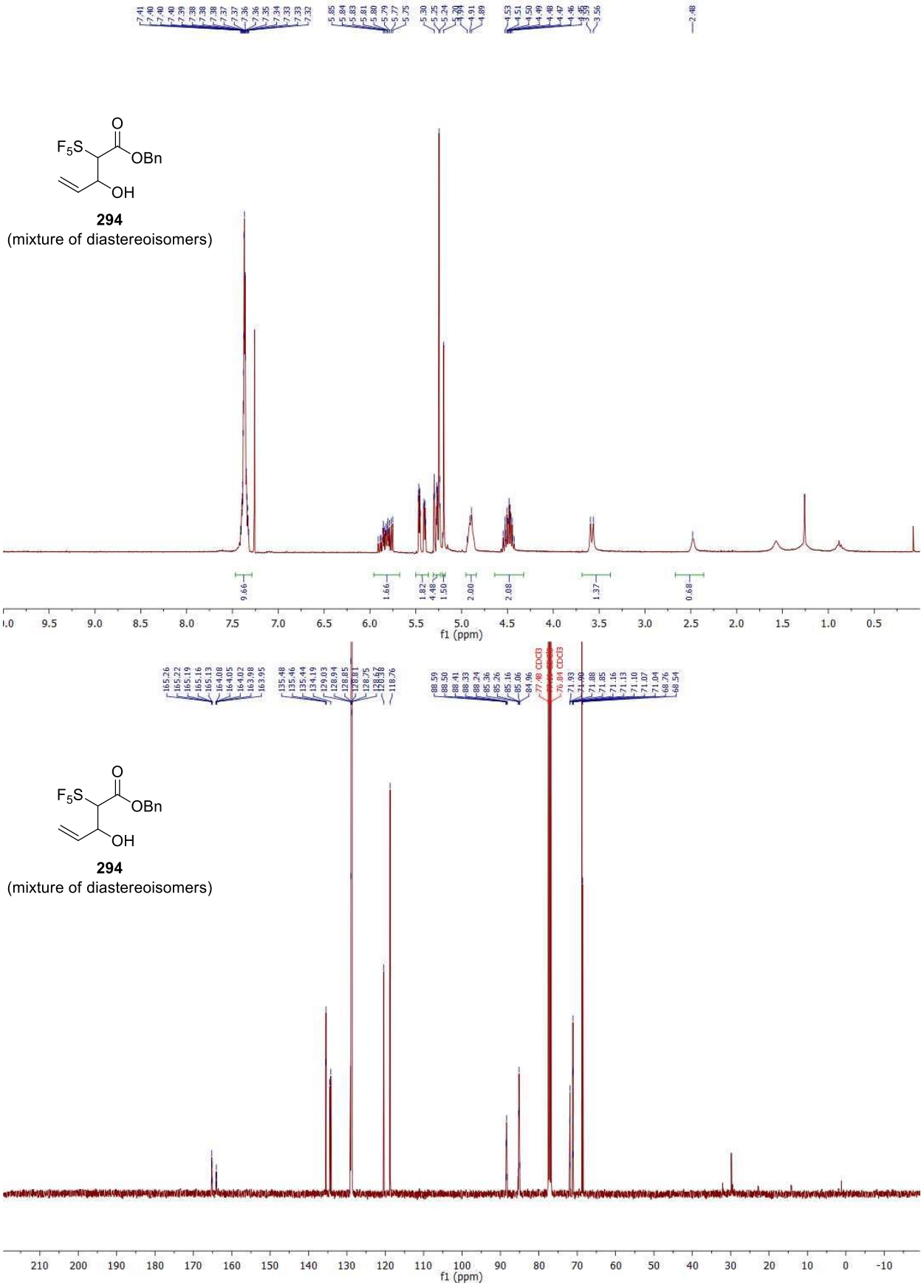


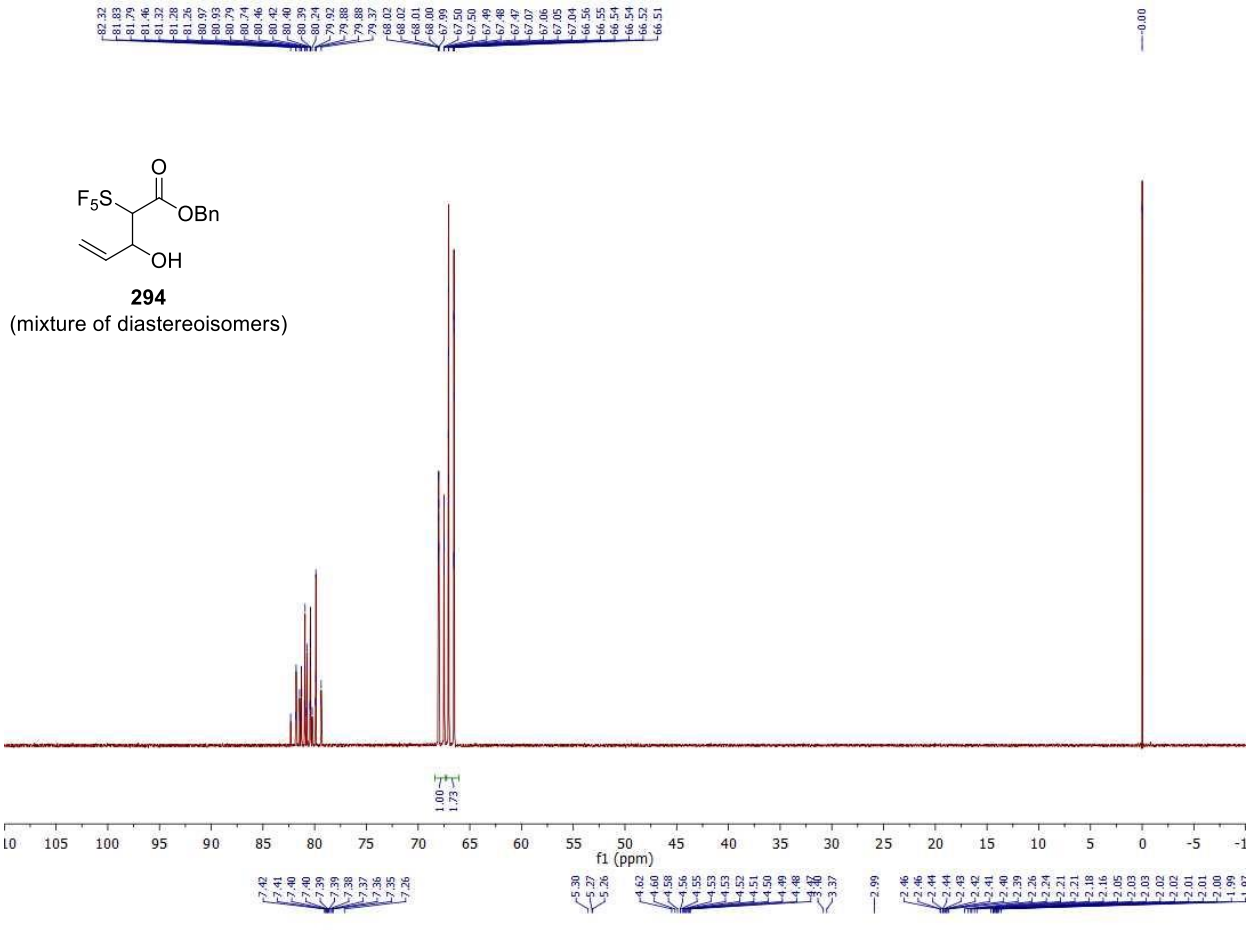
293
(mixture of diastereoisomers)



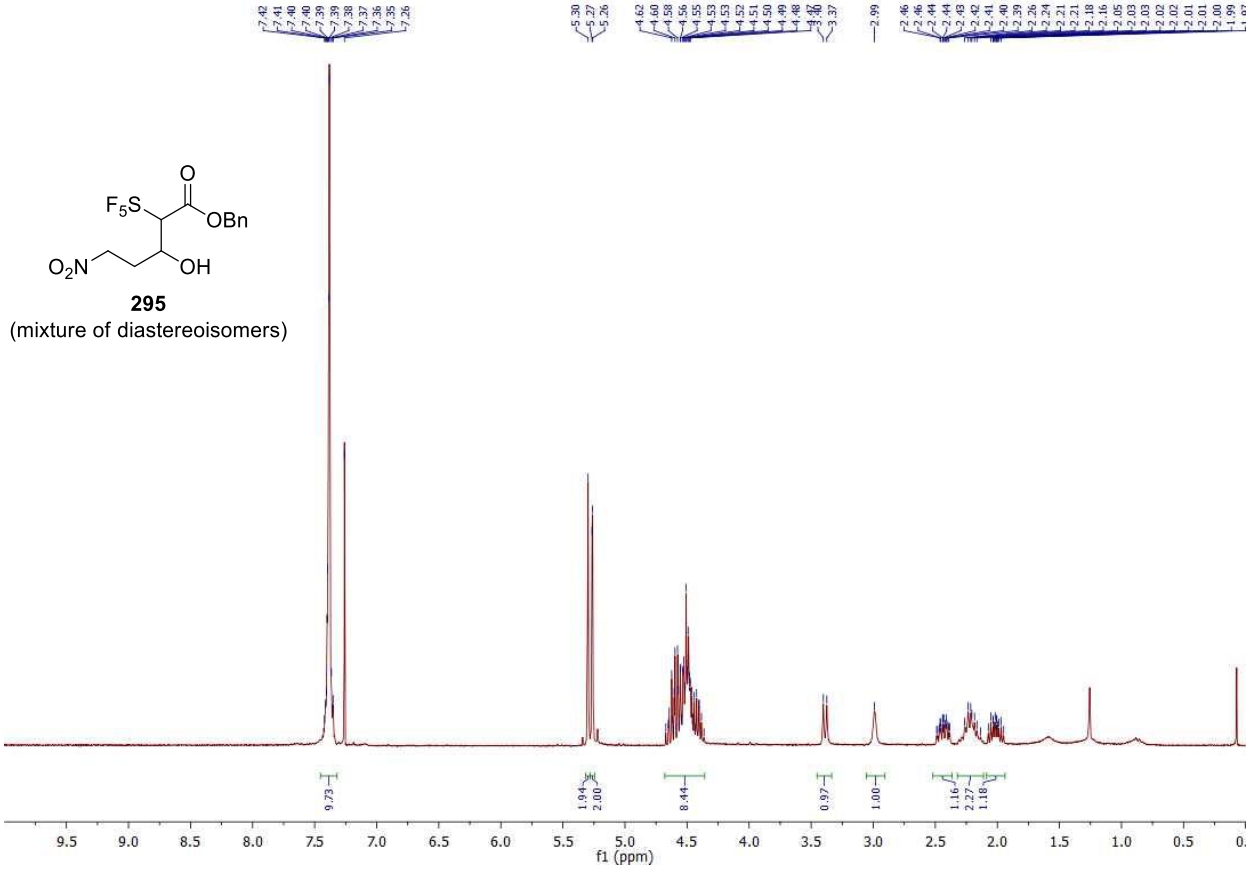


293
(mixture of diastereoisomers)

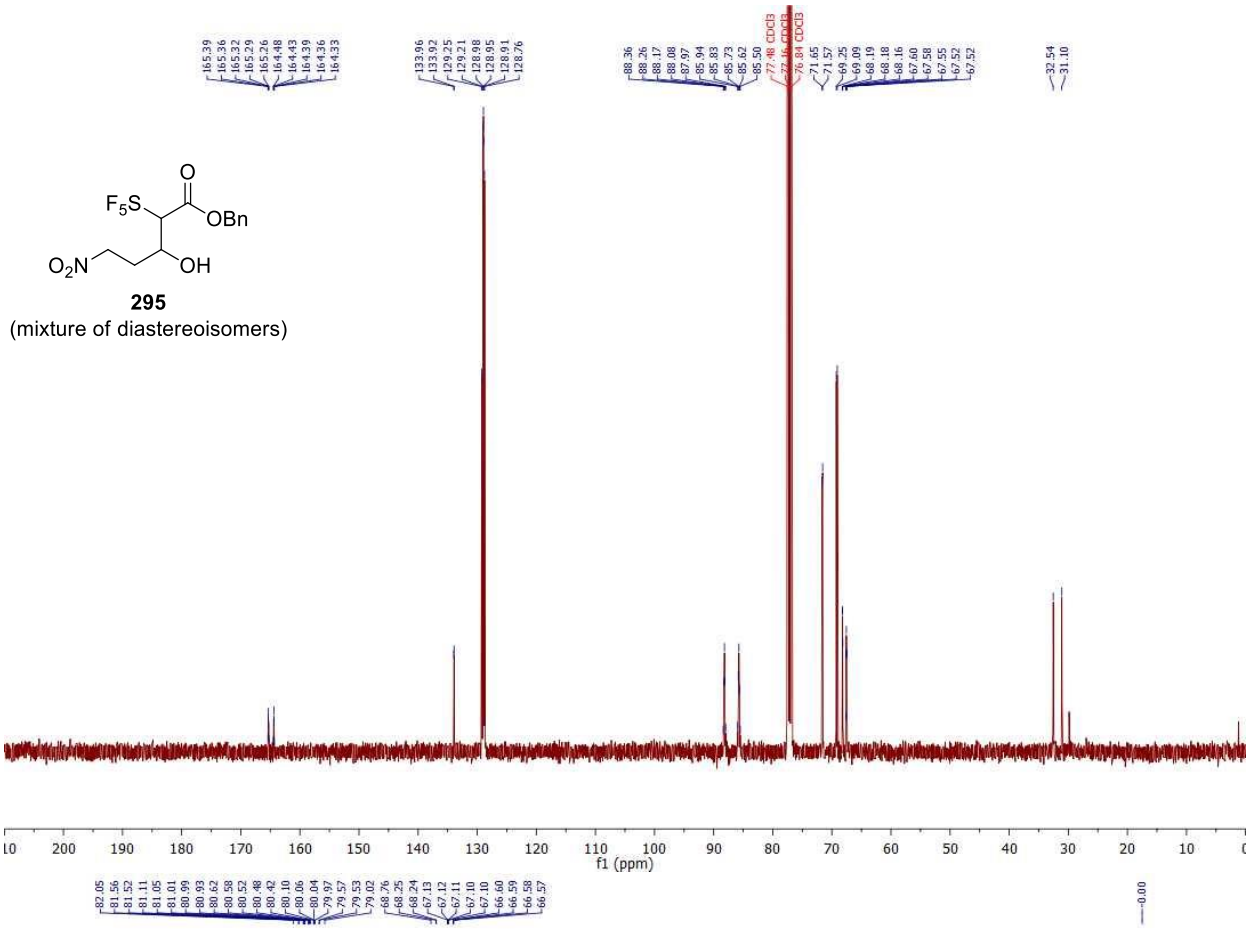

F5S
O
OBn
OH
294
(mixture of diastereoisomers)
f1 (ppm)
F5S
O
OBn
OH
294
(mixture of diastereoisomers)
f1 (ppm)



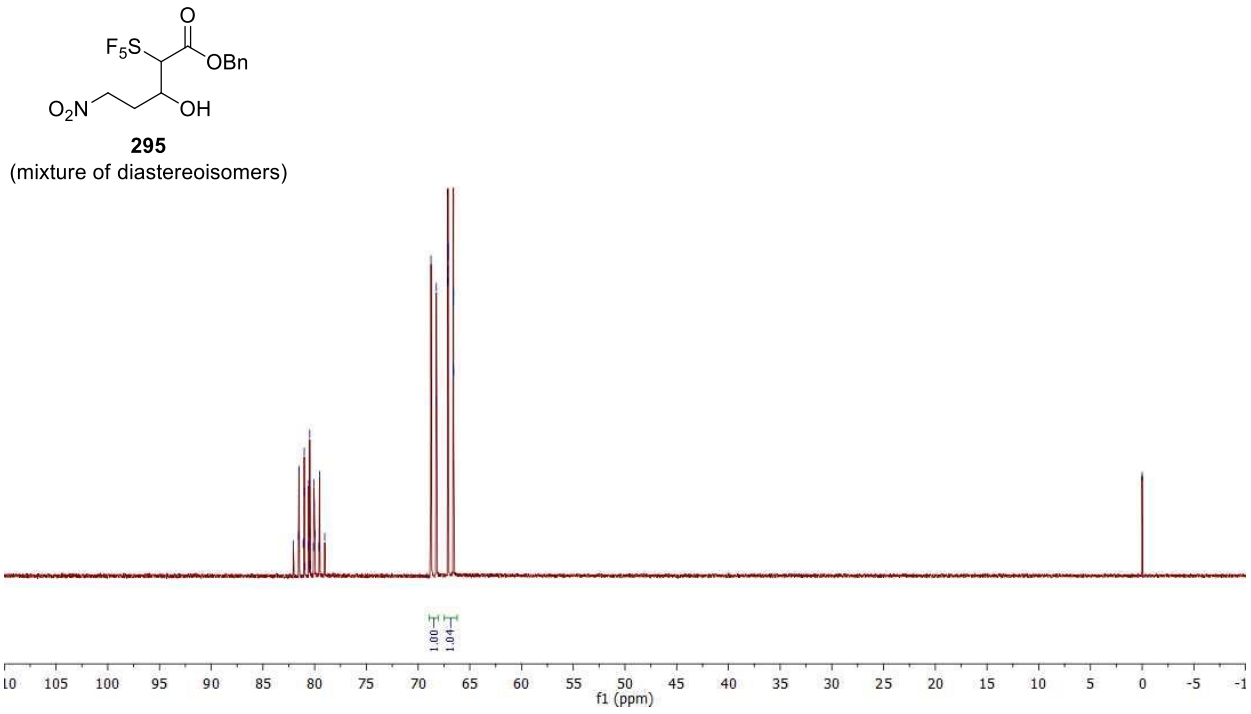
294
(mixture of diastereoisomers)



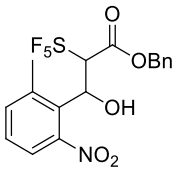
295
(mixture of diastereoisomers)



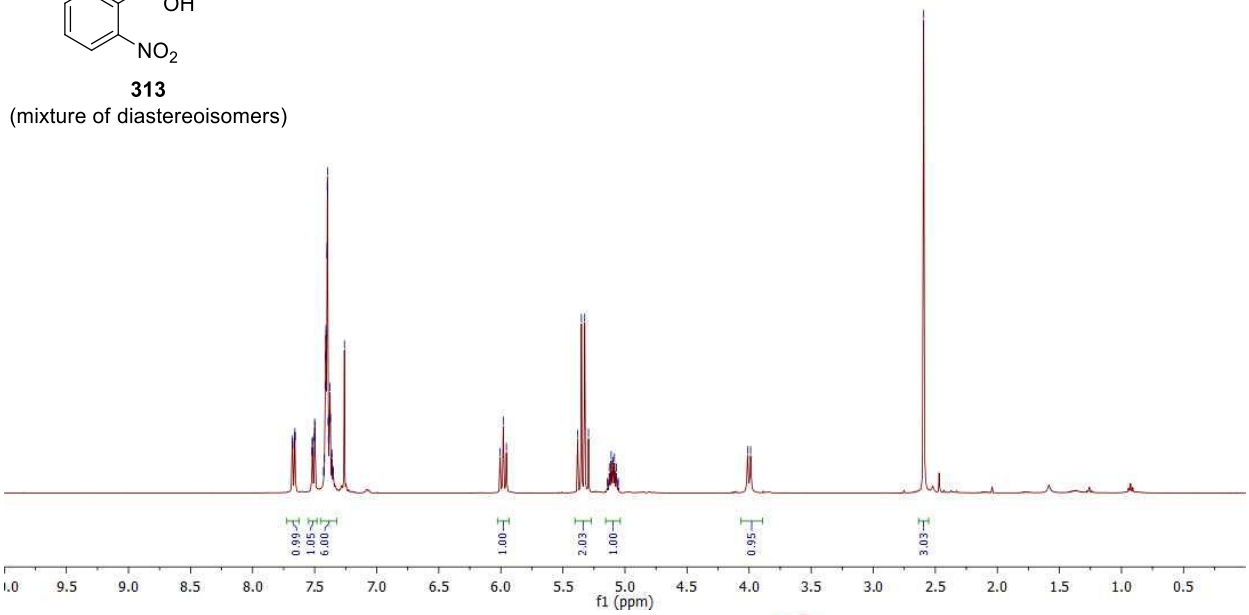
295
(mixture of diastereoisomers)

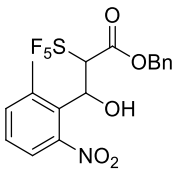


295
(mixture of diastereoisomers)

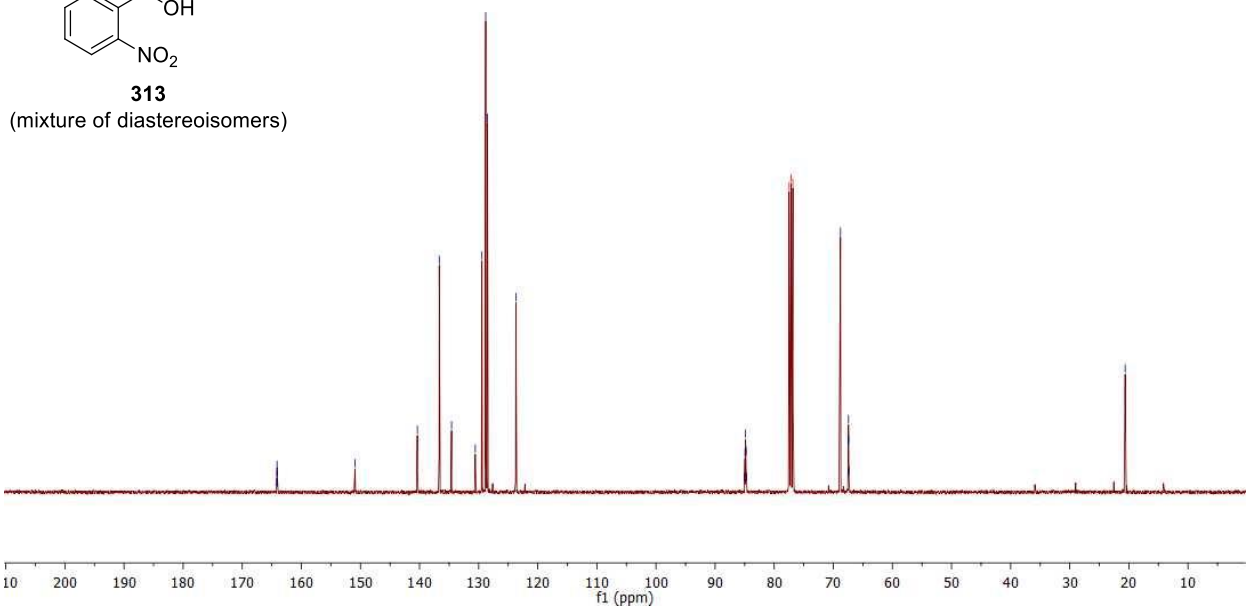


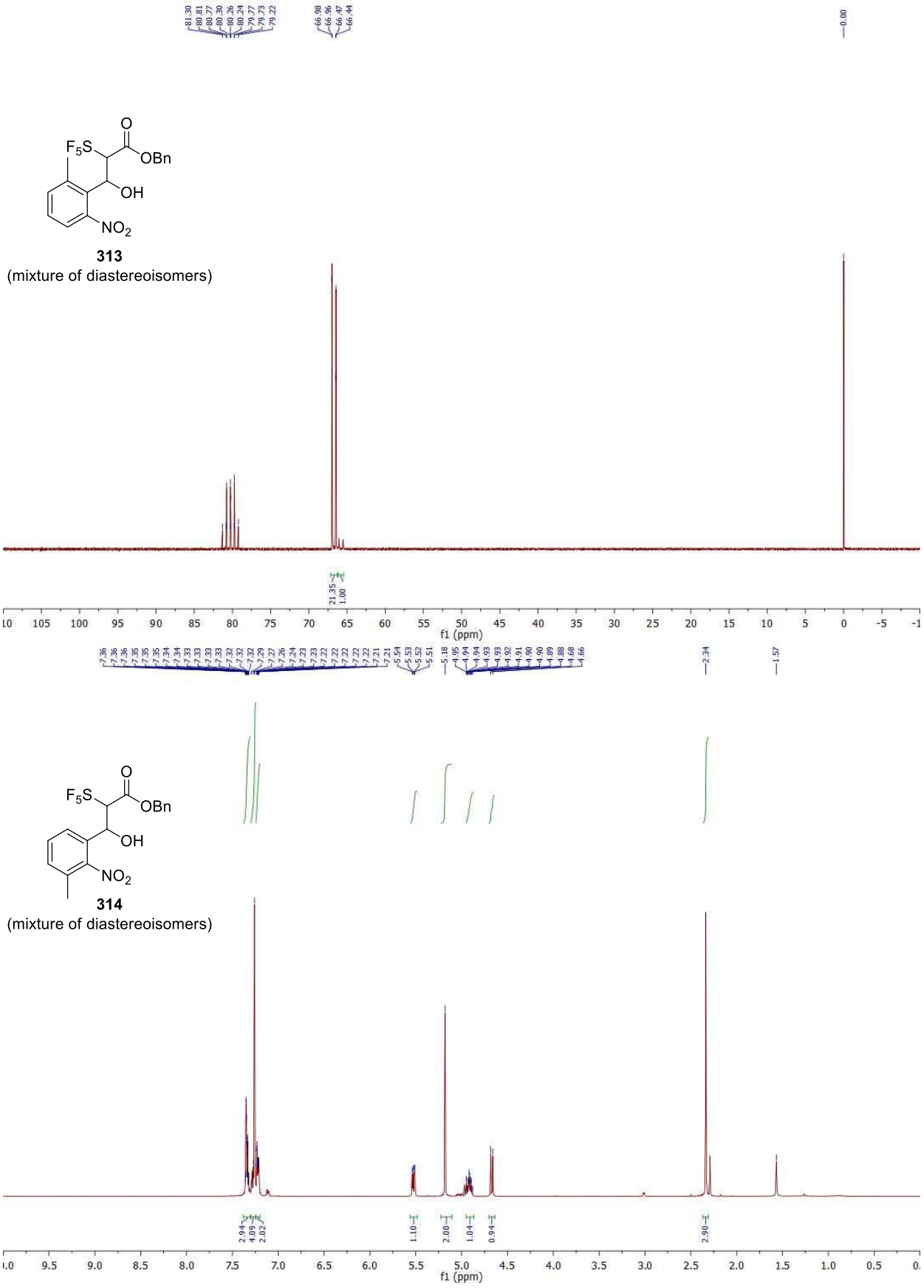
313
(mixture of diastereoisomers)





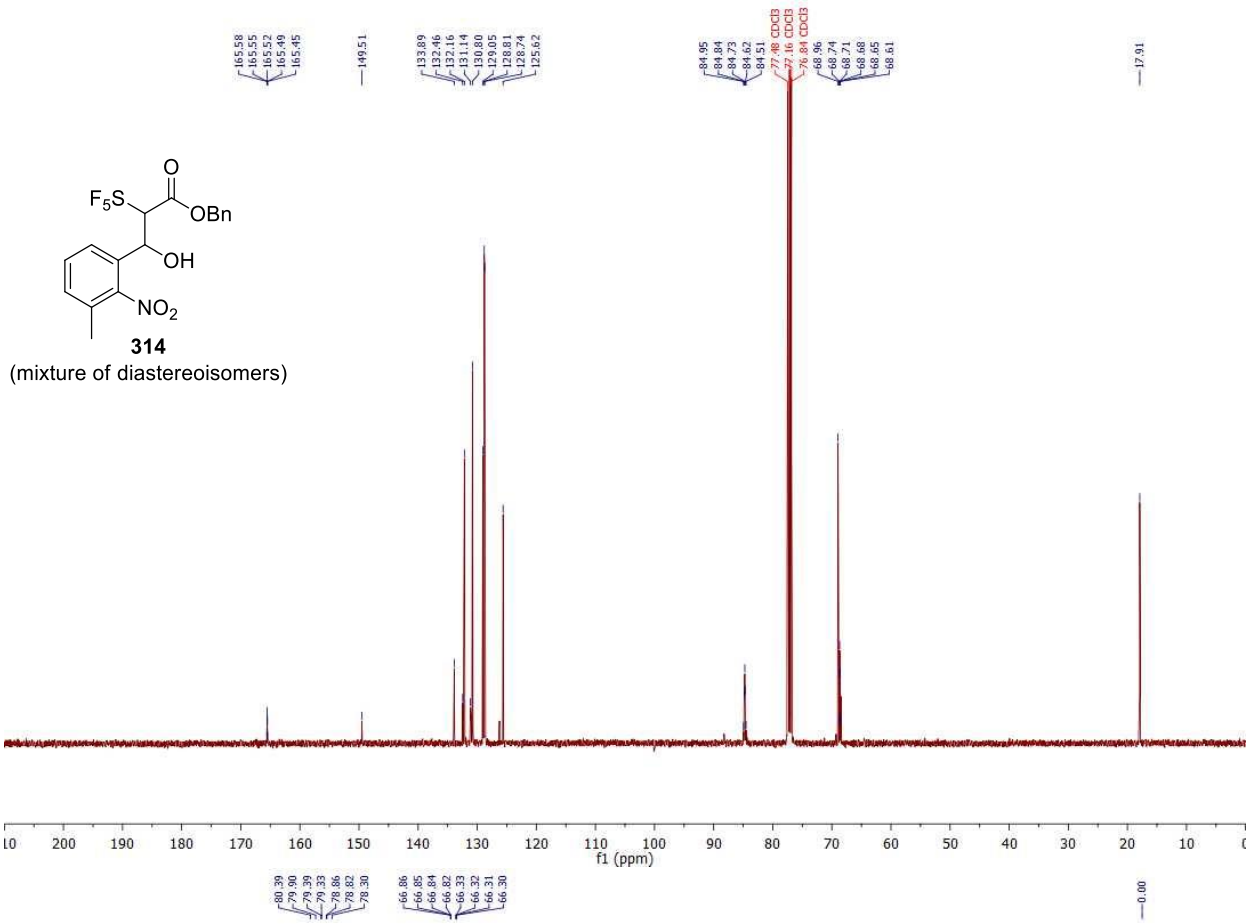
313
(mixture of diastereoisomers)

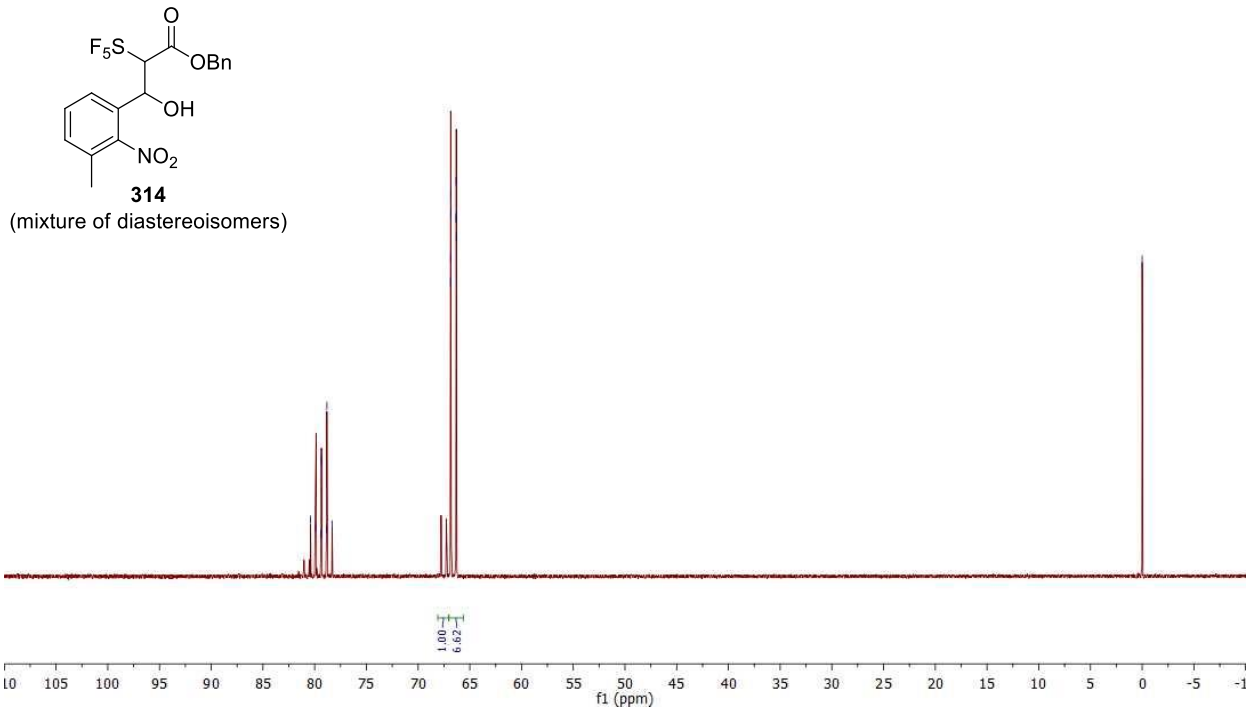




313
(mixture of diastereoisomers)

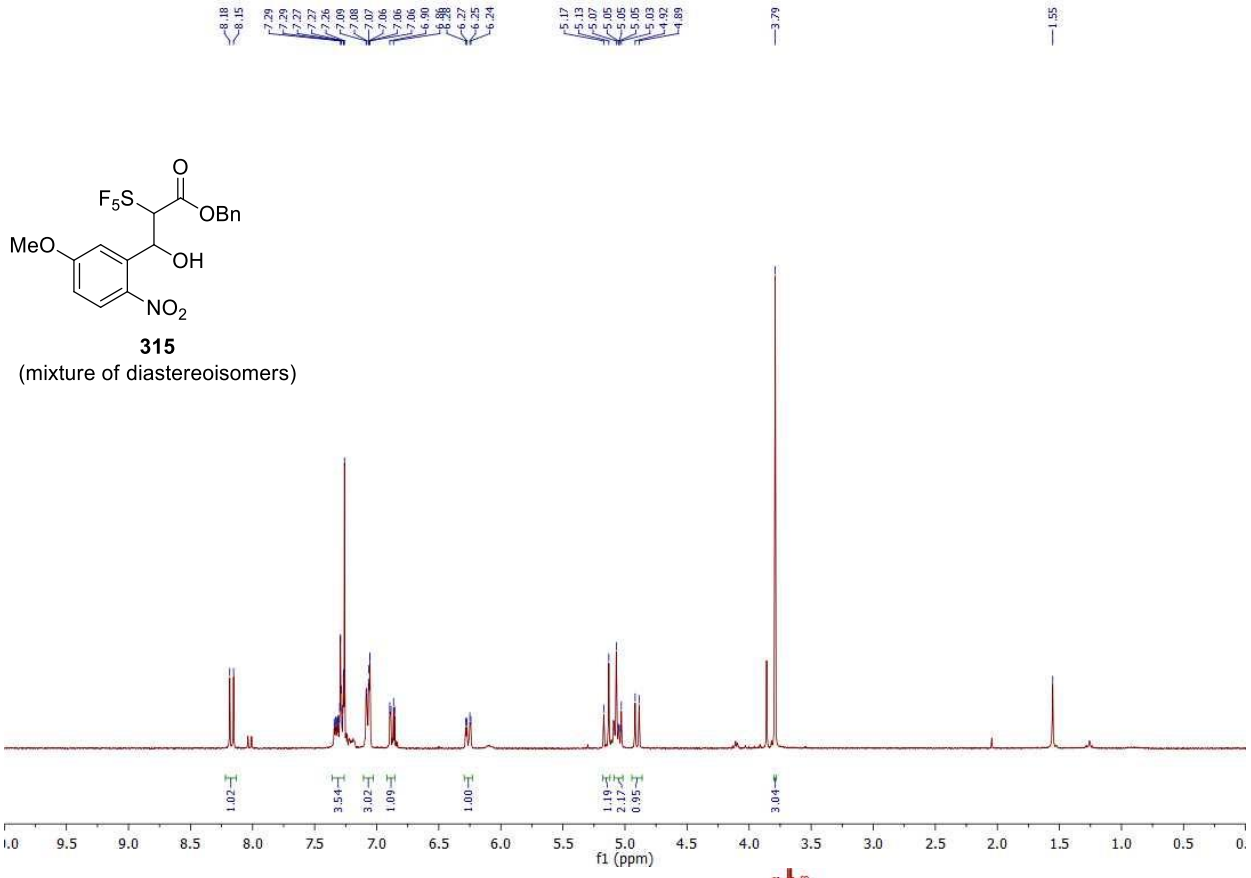
314
(mixture of diastereoisomers)



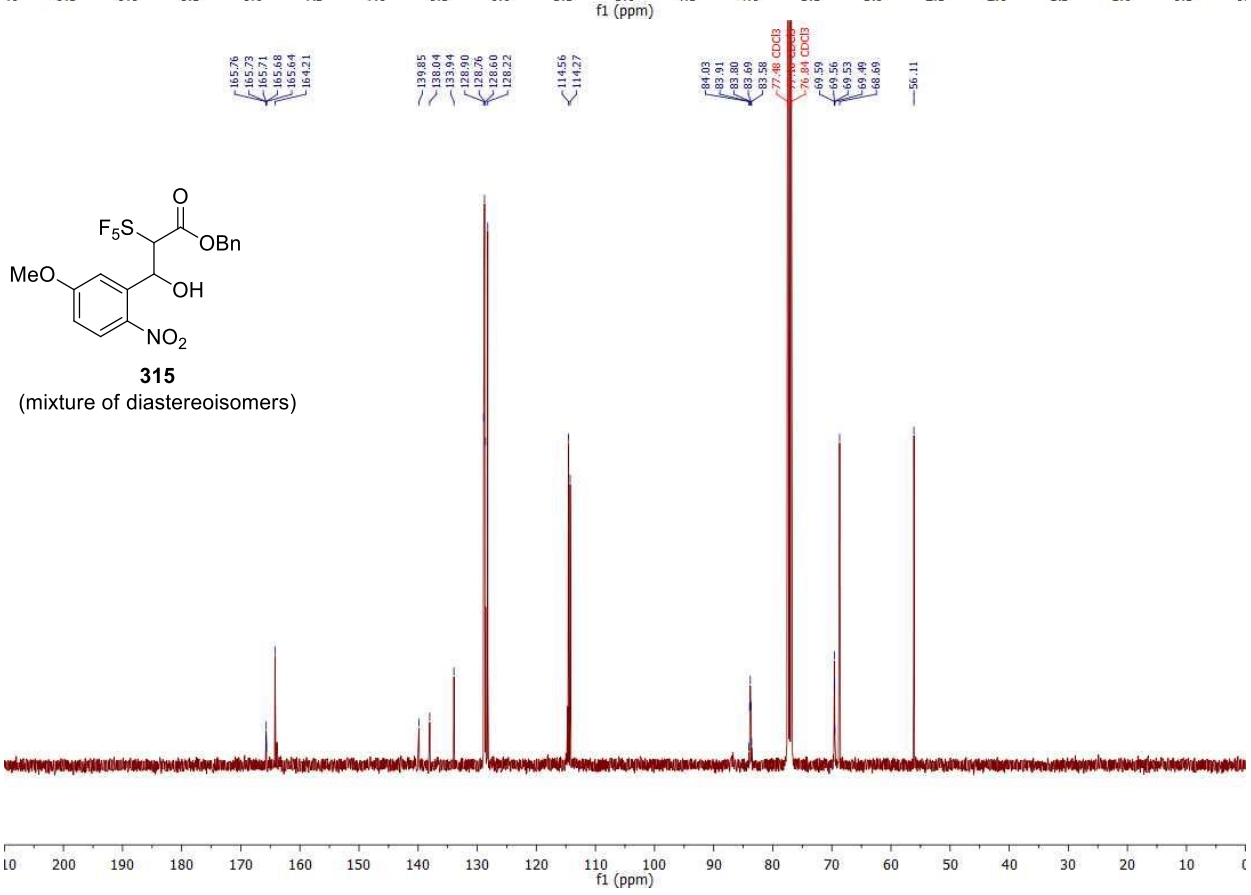


314
(mixture of diastereoisomers)

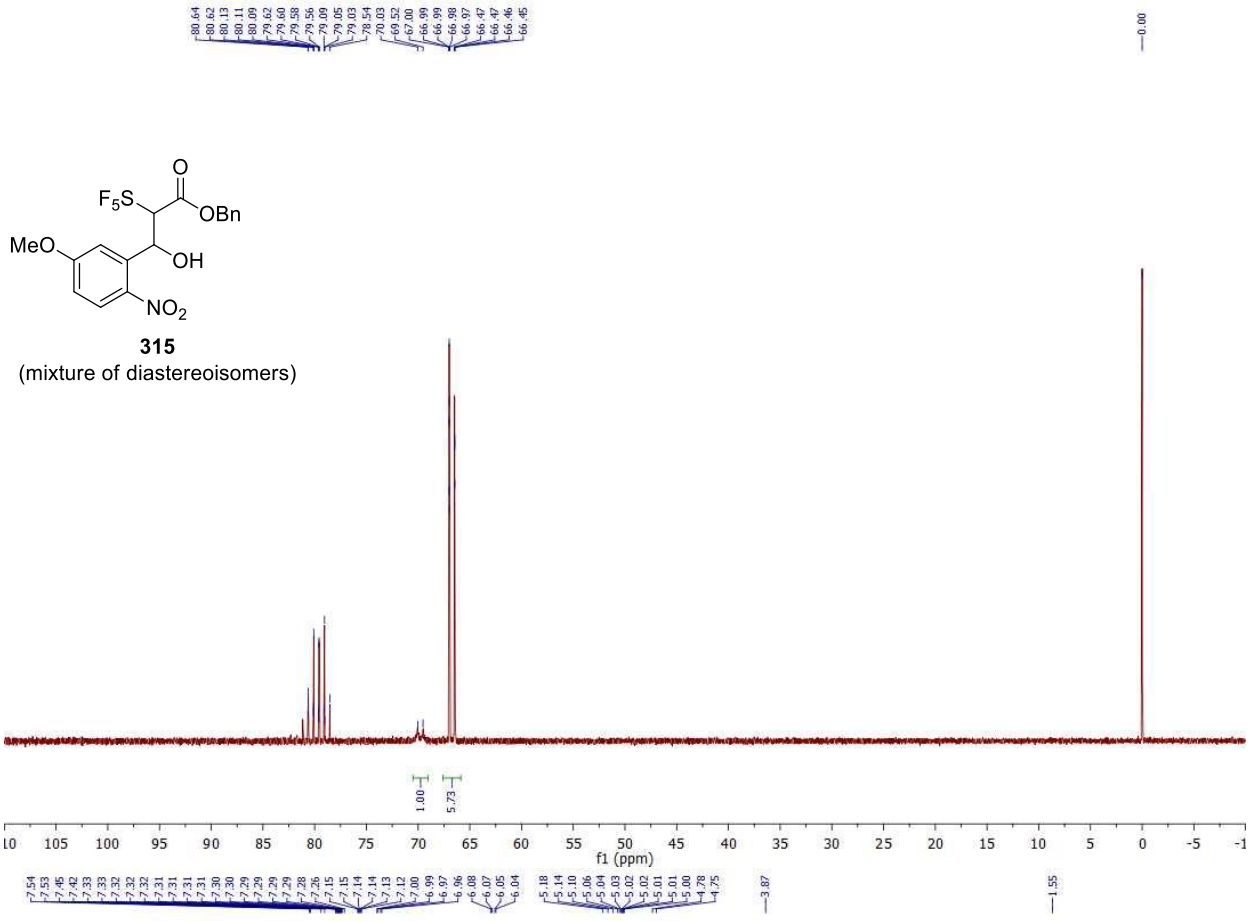
314
(mixture of diastereoisomers)



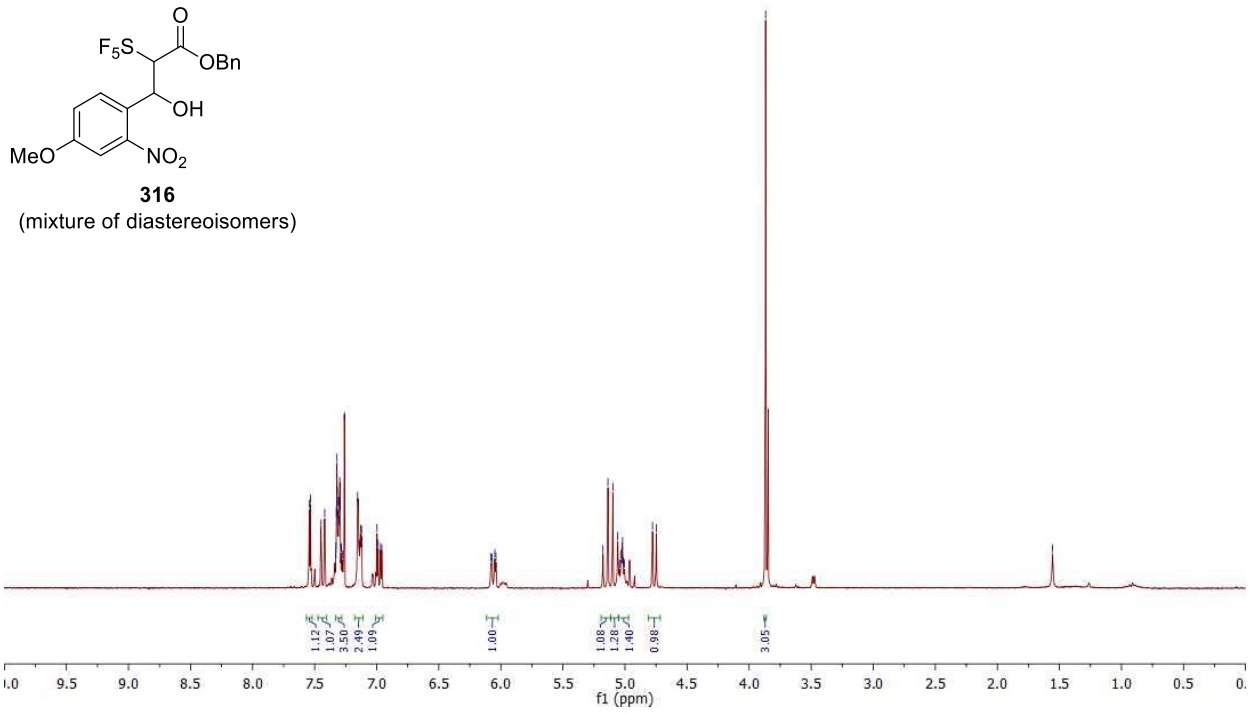
315
(mixture of diastereoisomers)



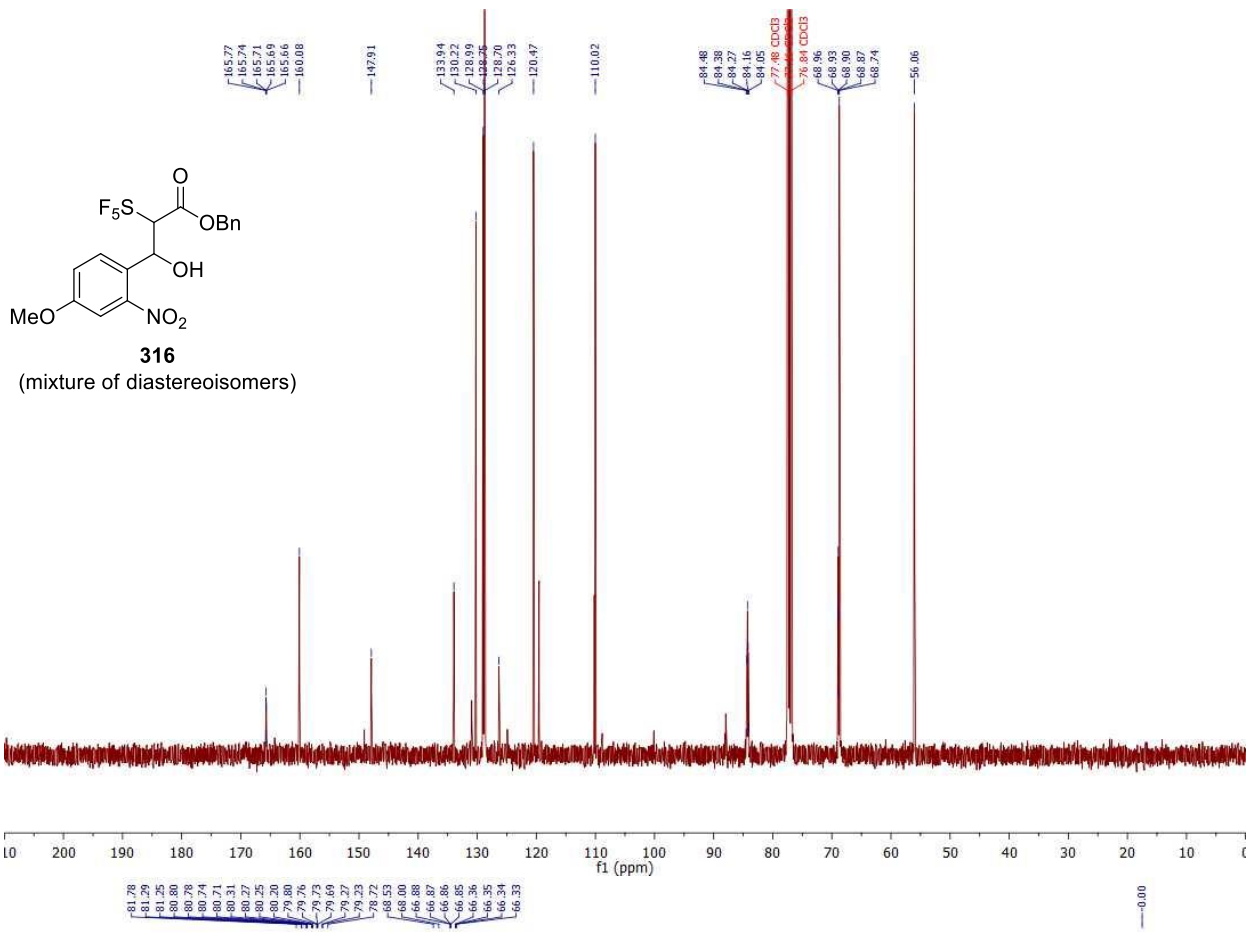
315
(mixture of diastereoisomers)

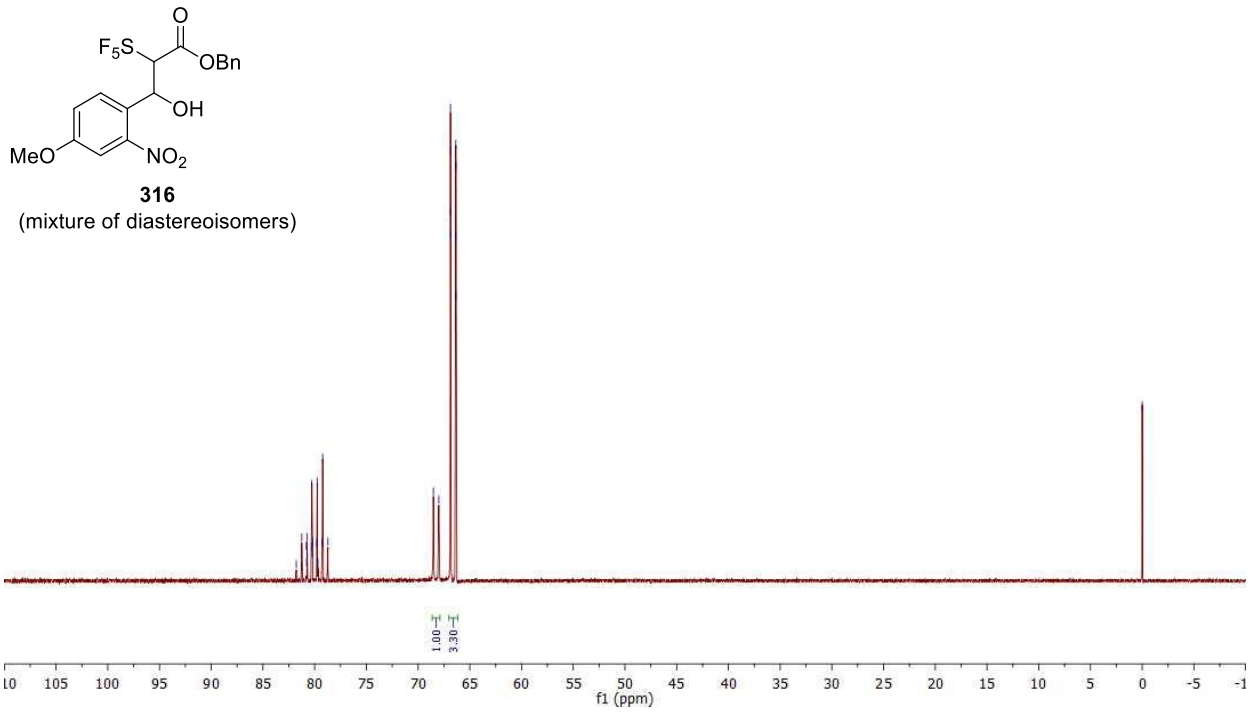


315
(mixture of diastereoisomers)



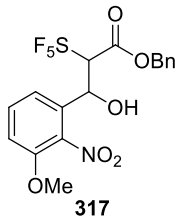
316
(mixture of diastereoisomers)



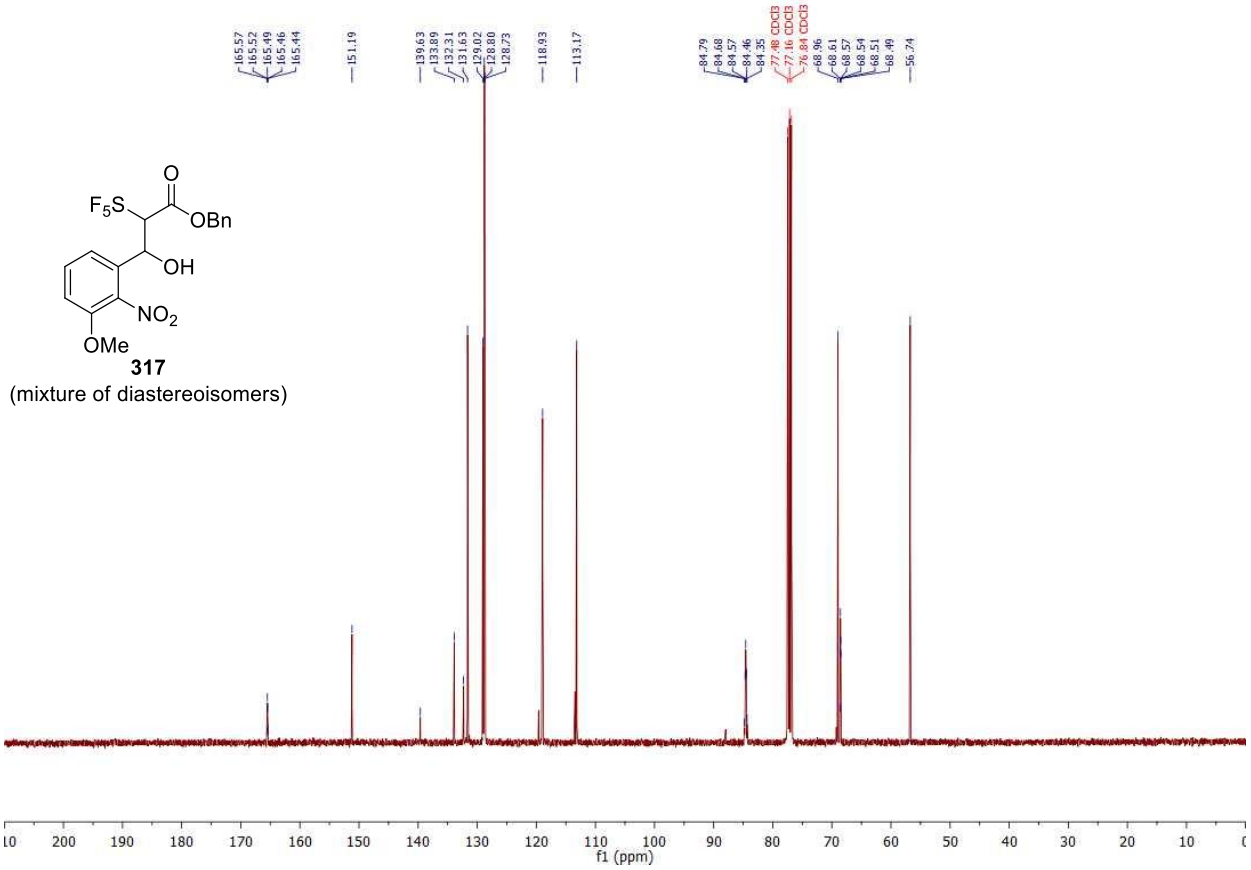


316
(mixture of diastereoisomers)

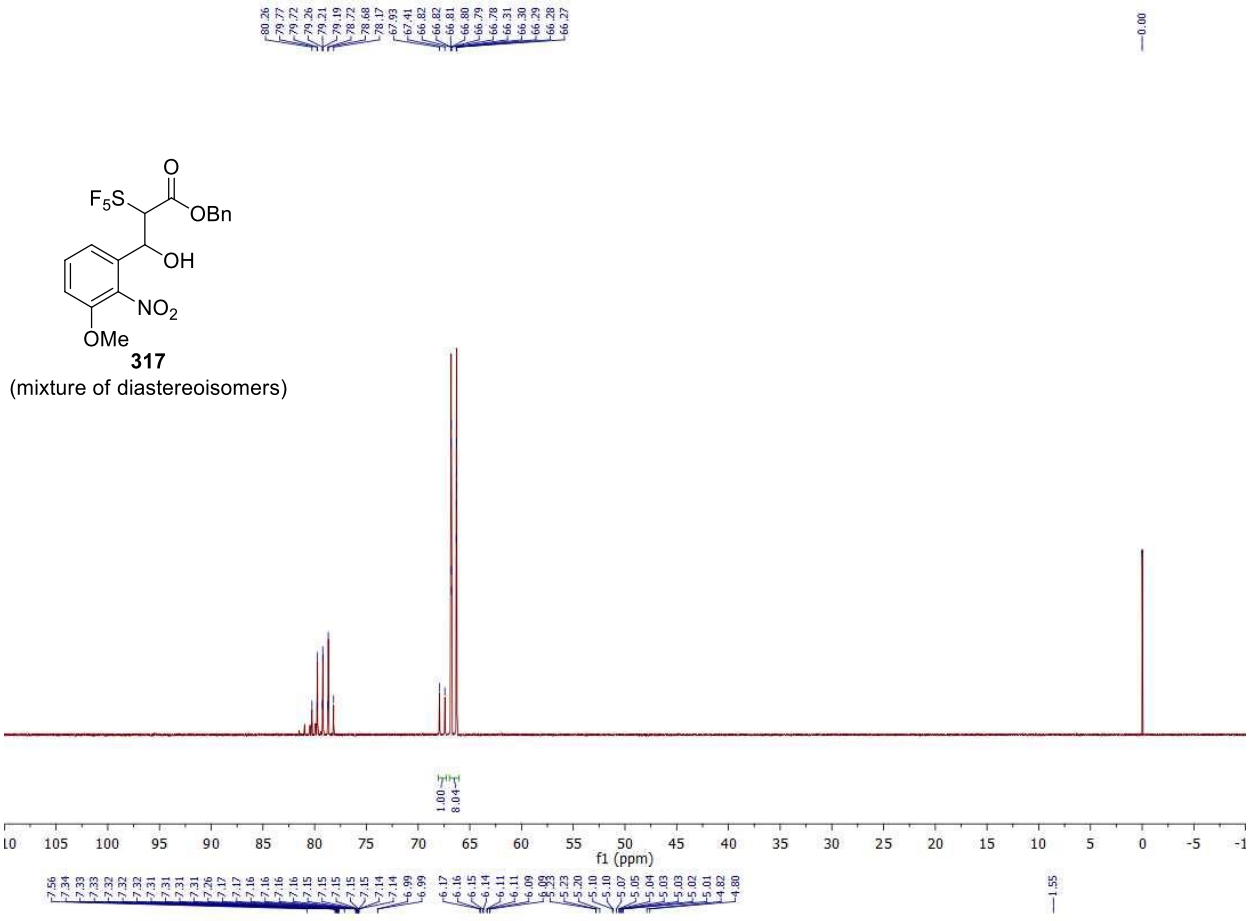
316
(mixture of diastereoisomers)



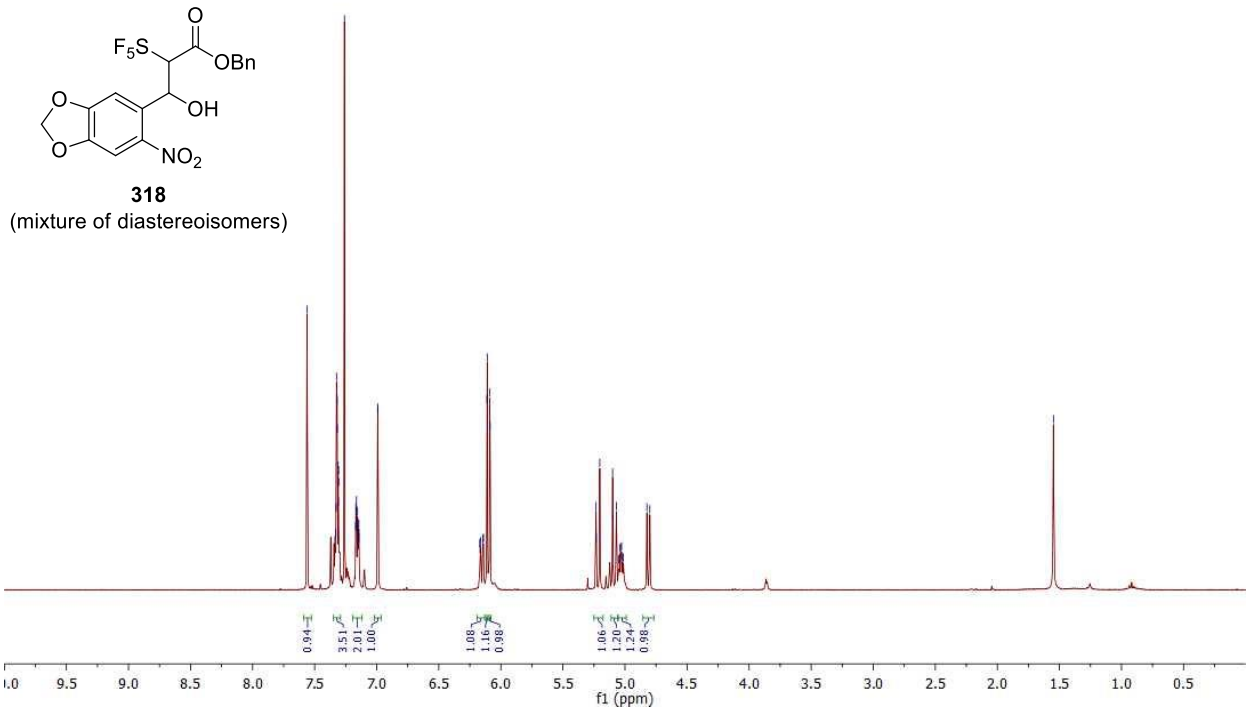
317
(mixture of diastereoisomers)



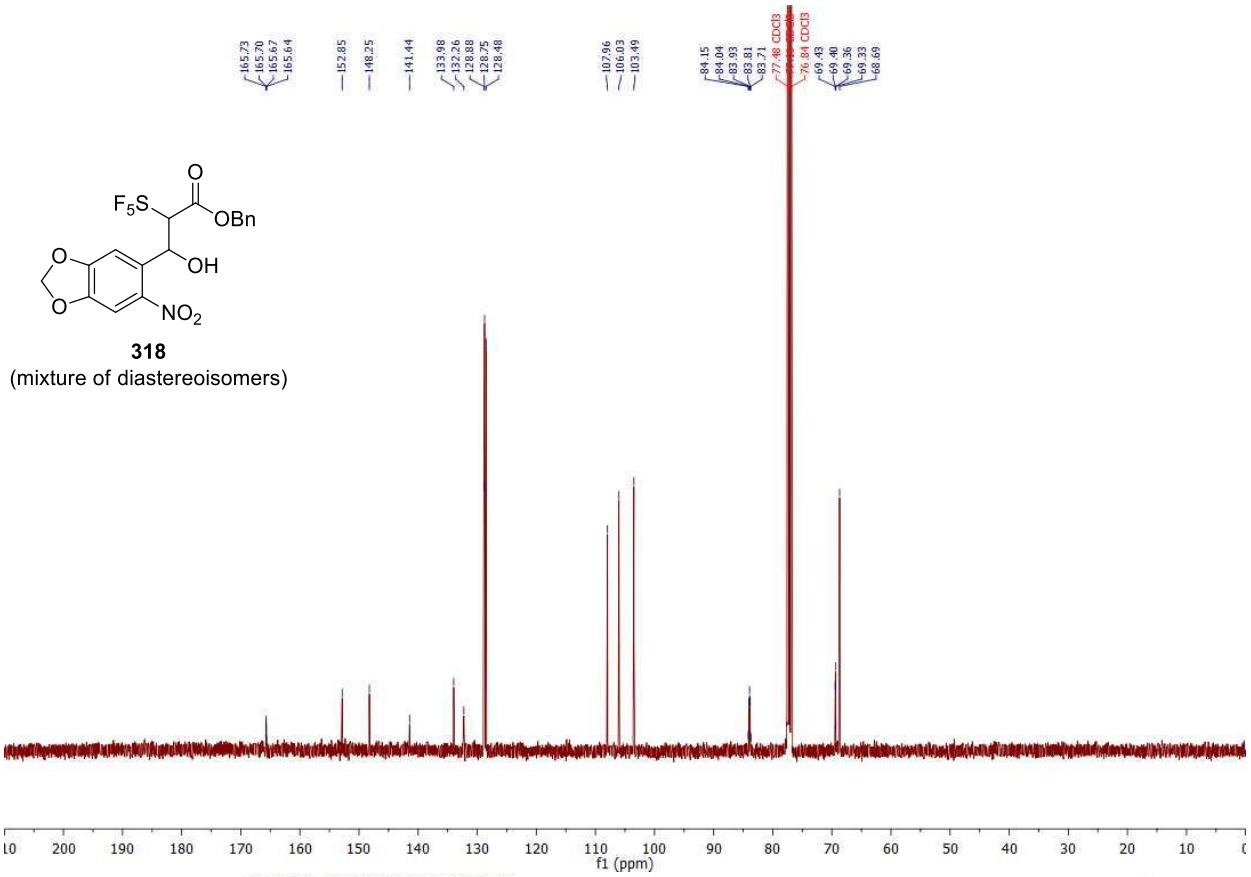
317
(mixture of diastereoisomers)



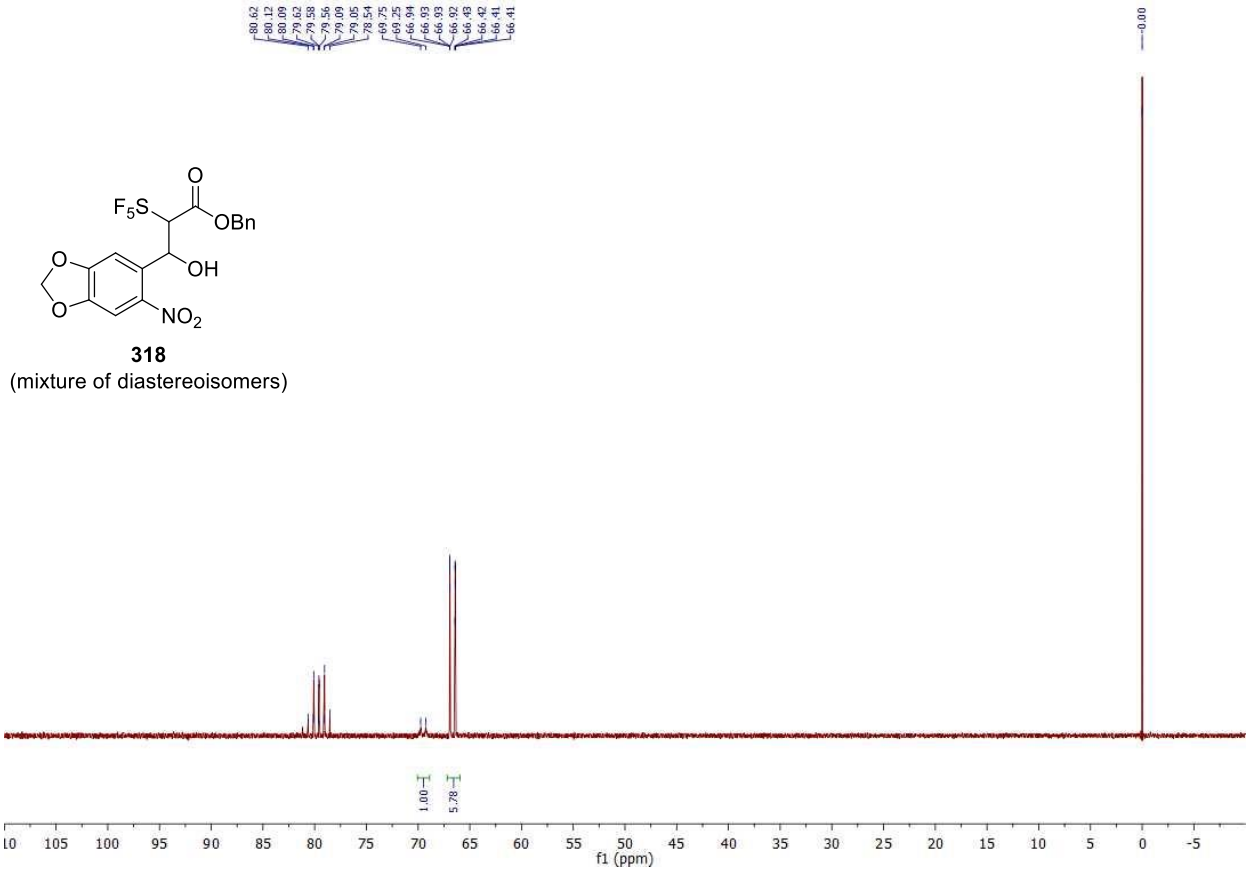
317
(mixture of diastereoisomers)



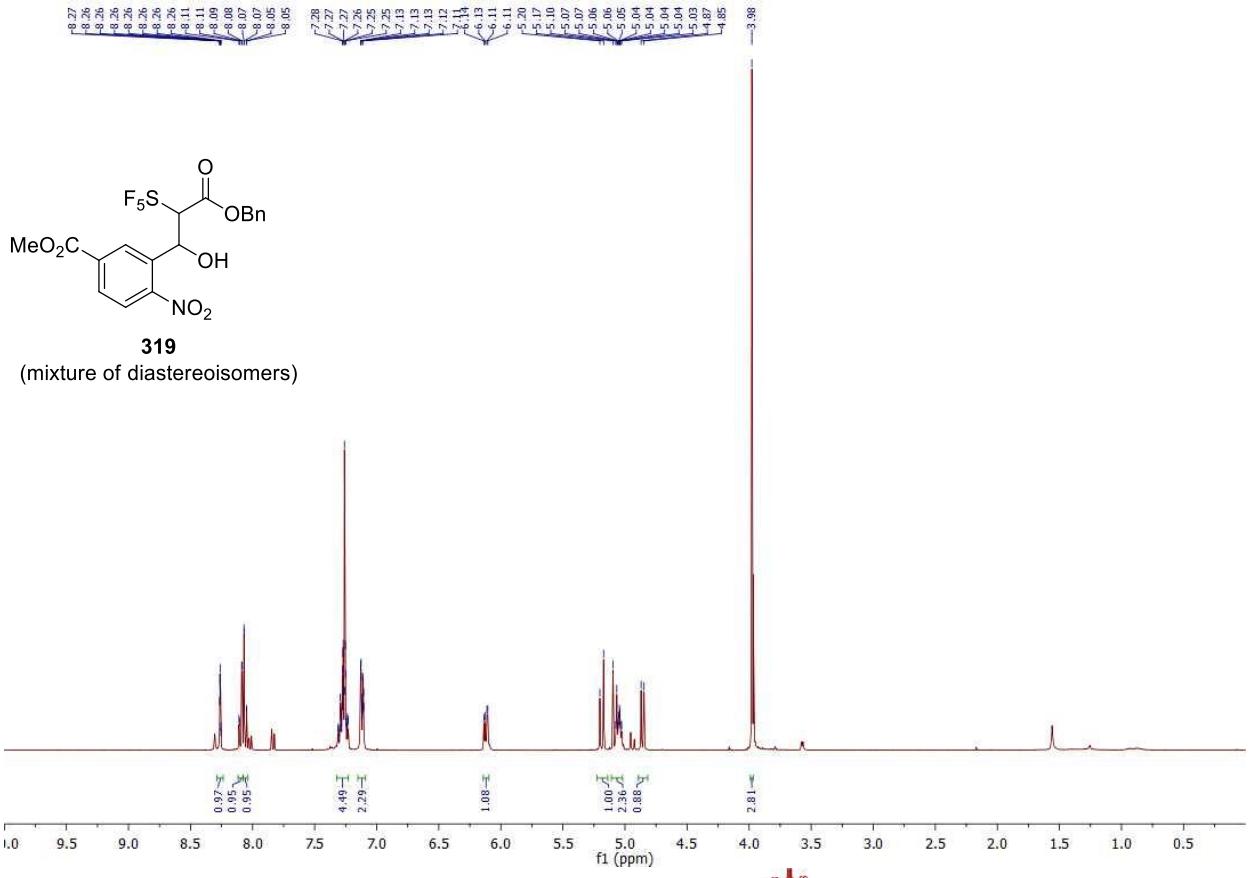
318
(mixture of diastereoisomers)

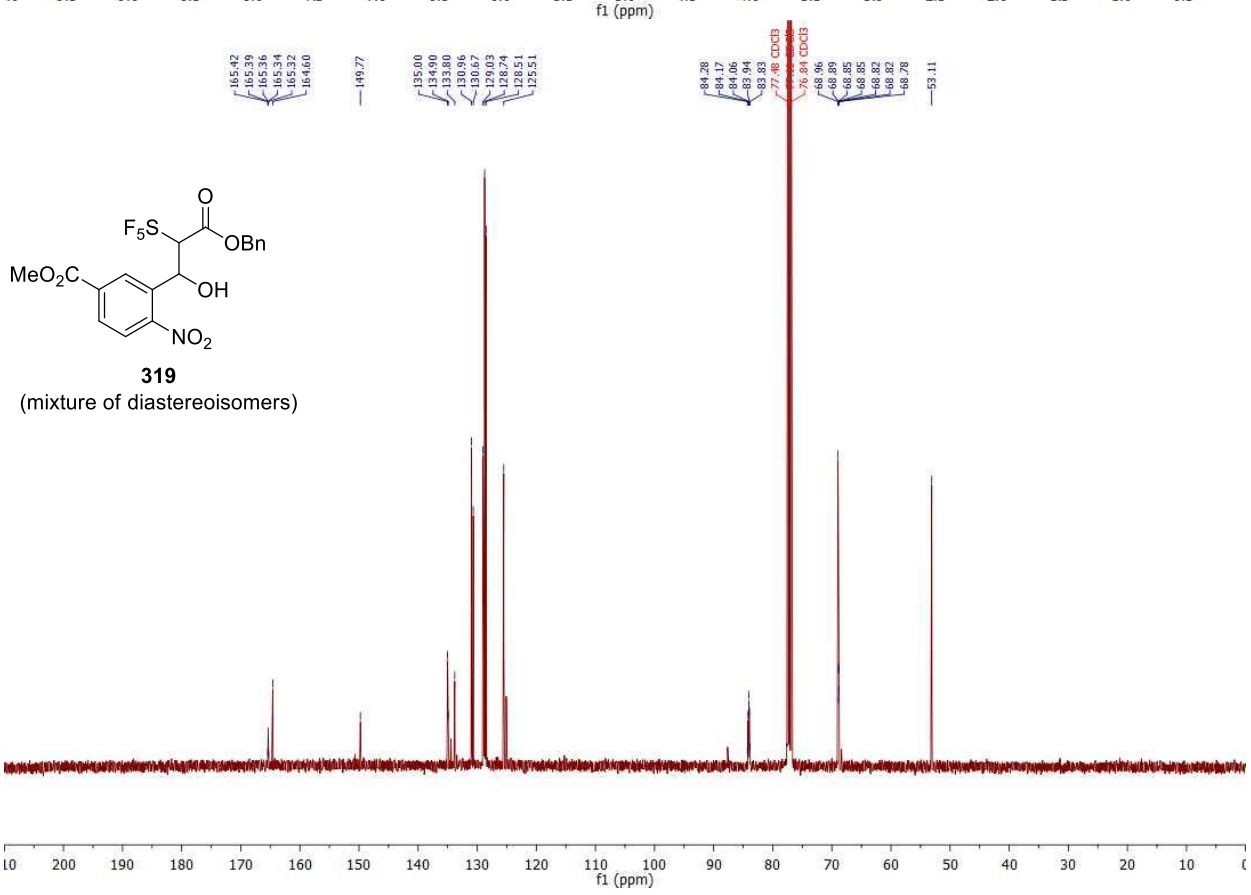


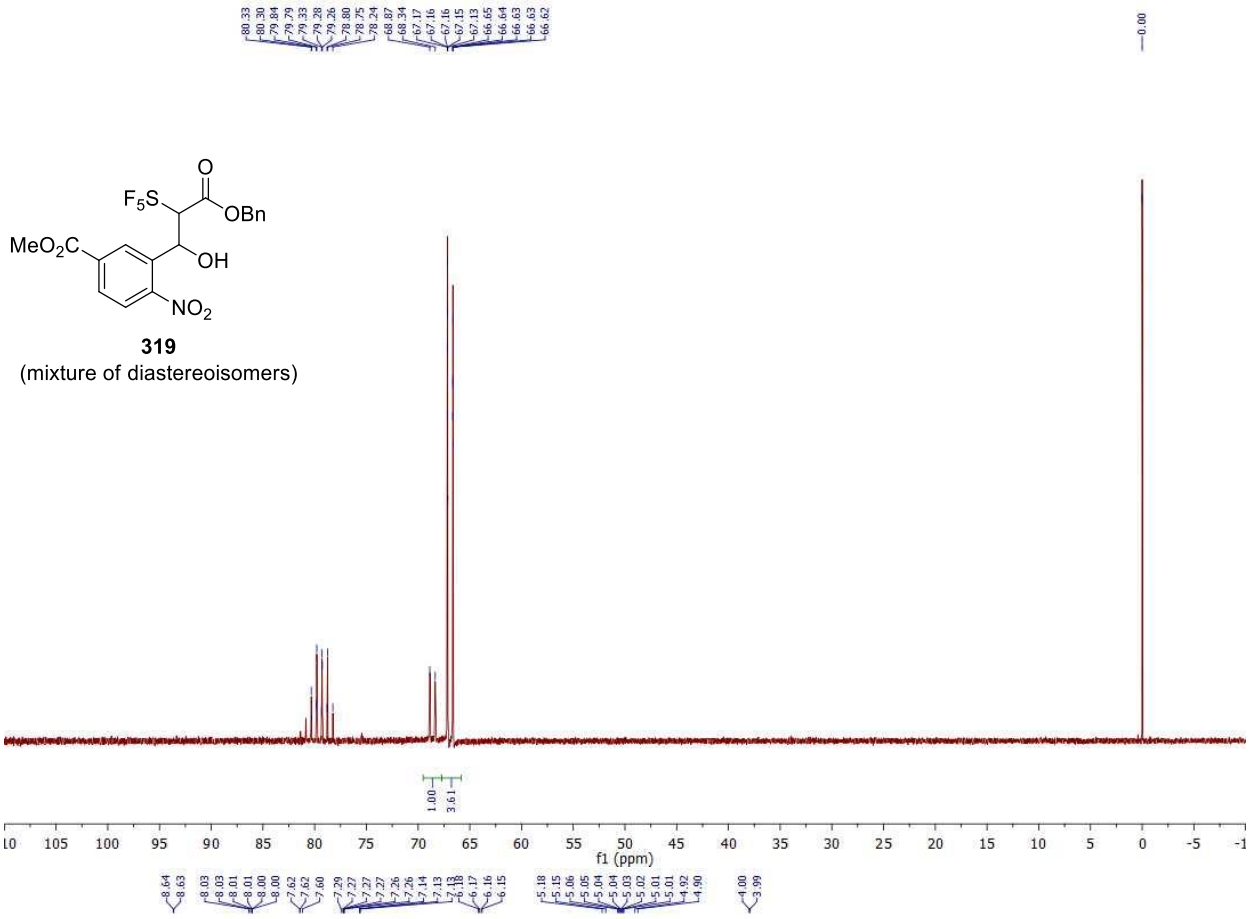
318
(mixture of diastereoisomers)



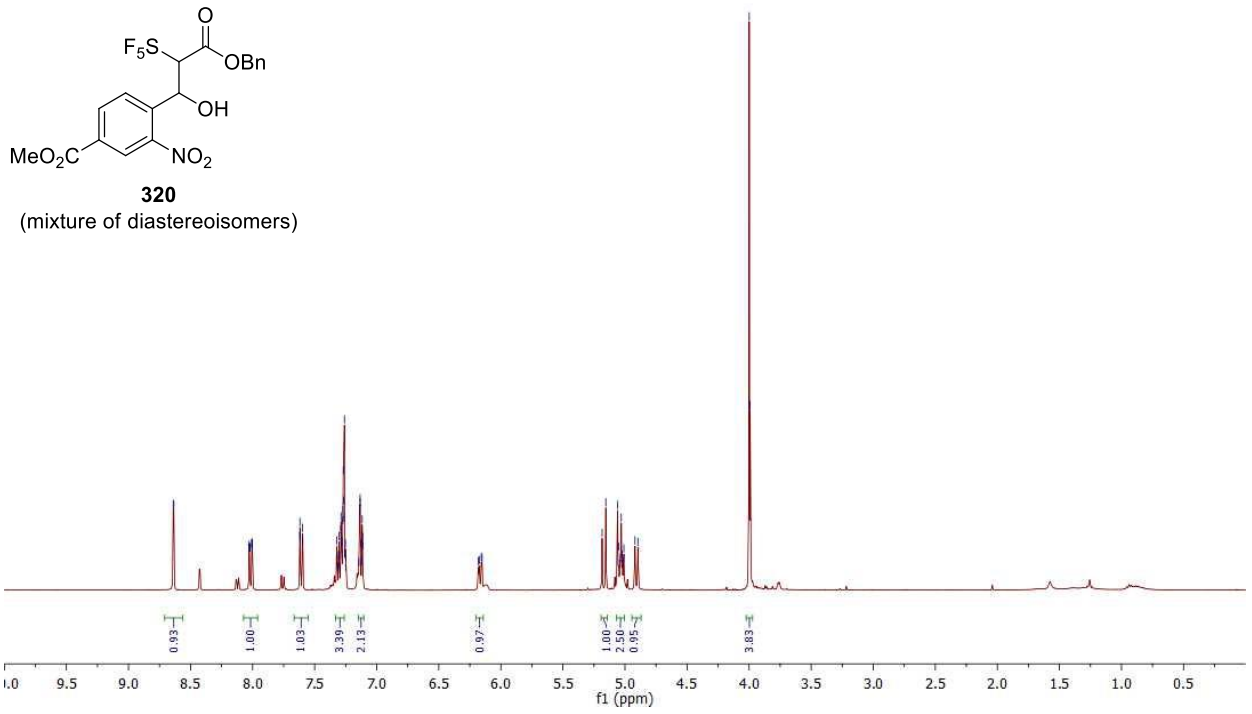
318
(mixture of diastereoisomers)


8.27
8.26
8.26
8.26
8.26
8.26
8.26
8.26
8.26
8.11
8.11
8.09
8.08
8.07
8.07
8.05
8.05
7.28
7.27
7.27
7.27
7.26
7.25
7.25
7.13
7.13
7.13
7.12
7.11
6.14
6.13
6.11
6.11
5.20
5.17
5.10
5.07
5.07
5.06
5.06
5.05
5.04
5.04
5.04
5.04
5.03
4.87
4.85
3.98
O
F5S
OBn
MeO2C
OH
NO2
319
(mixture of diastereoisomers)
0.97
0.95
0.95
4.49
2.29
1.08
1.00
2.36
0.88
2.81
f1 (ppm)

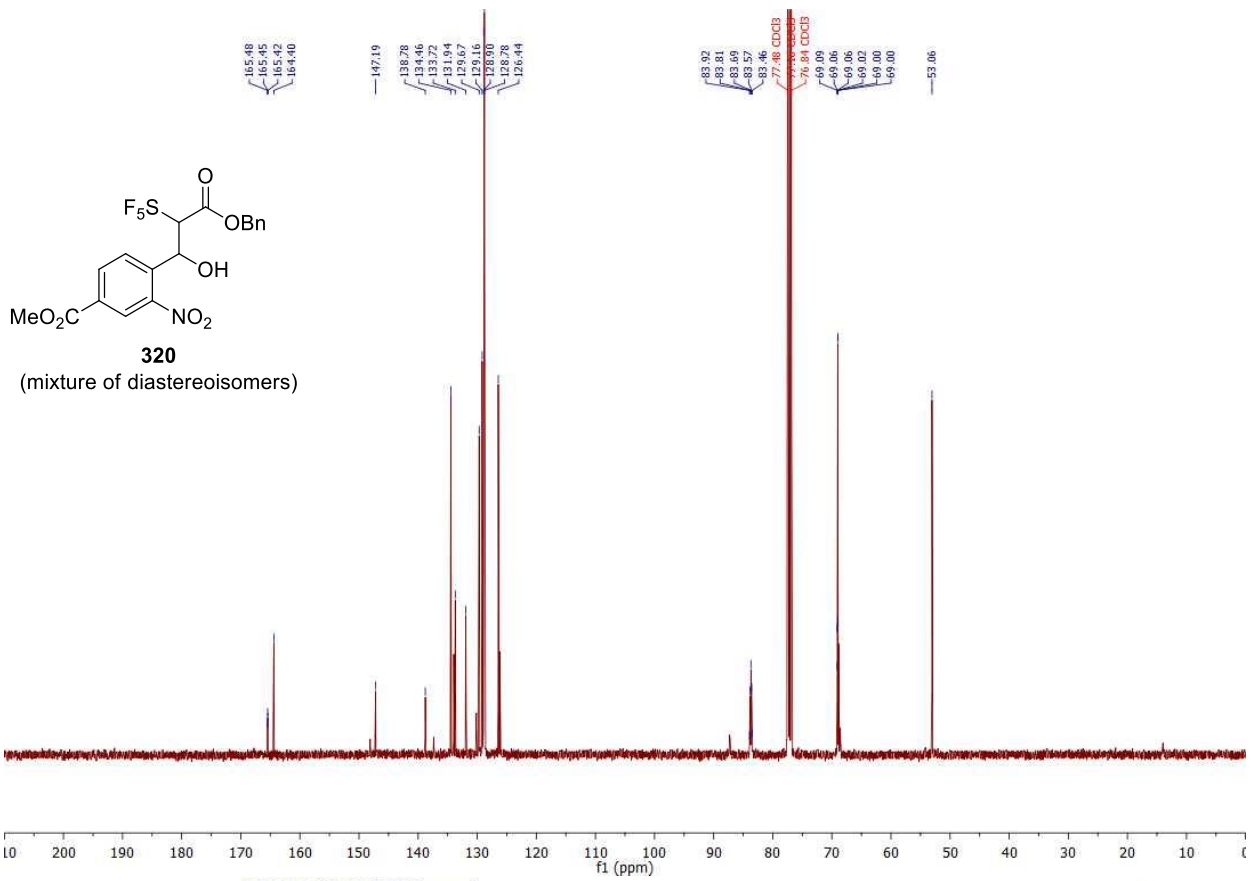

165.42
165.39
165.36
165.34
165.32
164.60
149.77
135.00
134.90
133.80
130.96
130.67
129.03
128.74
128.51
125.51
84.28
84.17
84.06
83.94
83.83
77.48 CDCl3
76.84 CDCl3
68.96
68.89
68.85
68.85
68.82
68.82
68.78
53.11
O
F5S
OBn
MeO2C
OH
NO2
319
(mixture of diastereoisomers)
f1 (ppm)

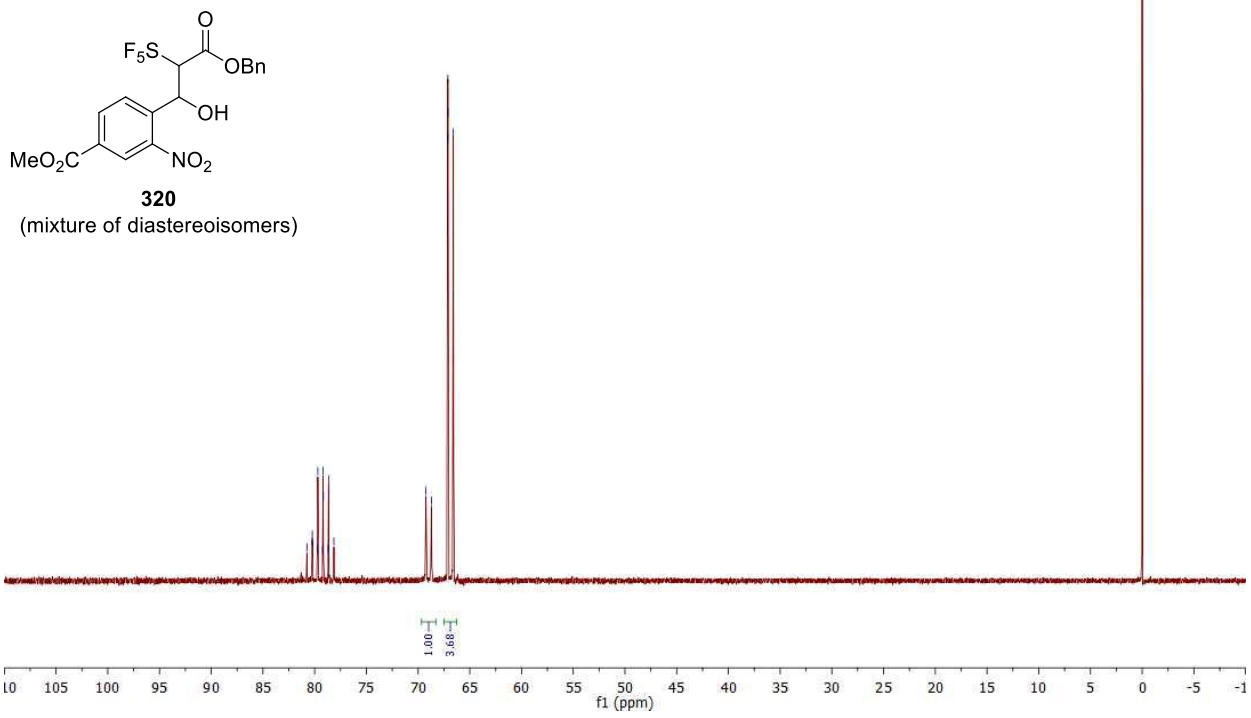


319
(mixture of diastereoisomers)



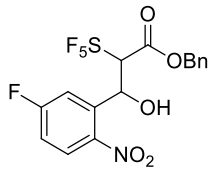
320
(mixture of diastereoisomers)



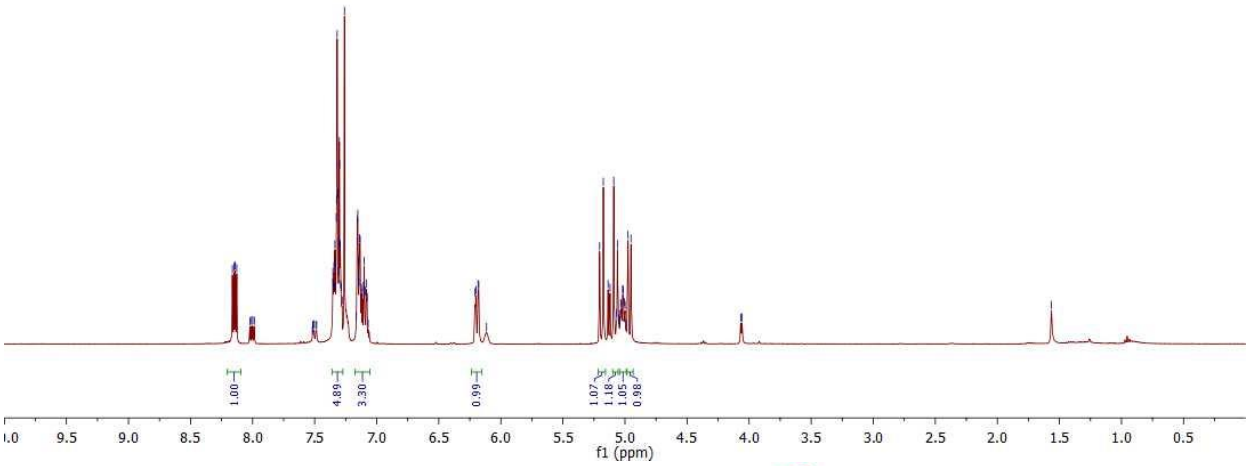


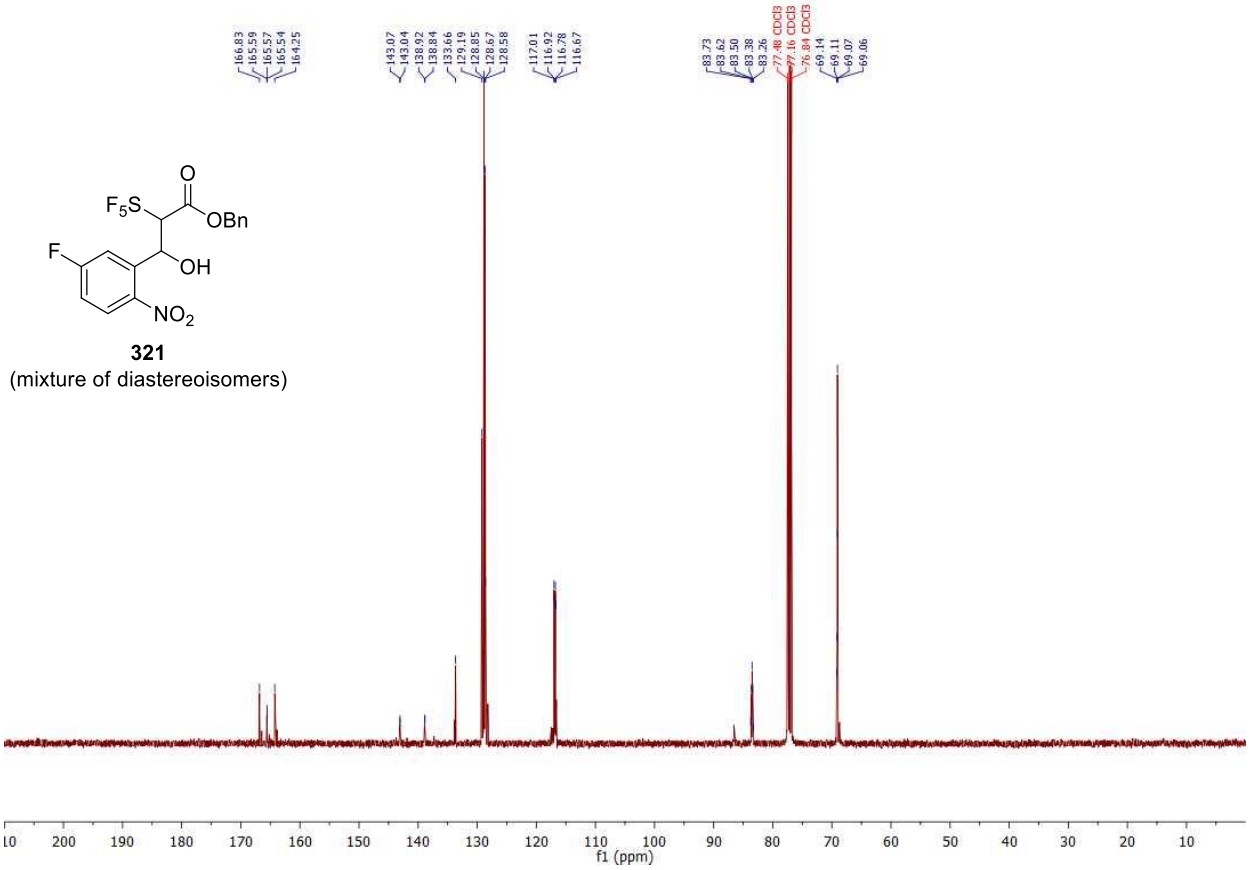
320
(mixture of diastereoisomers)

320
(mixture of diastereoisomers)

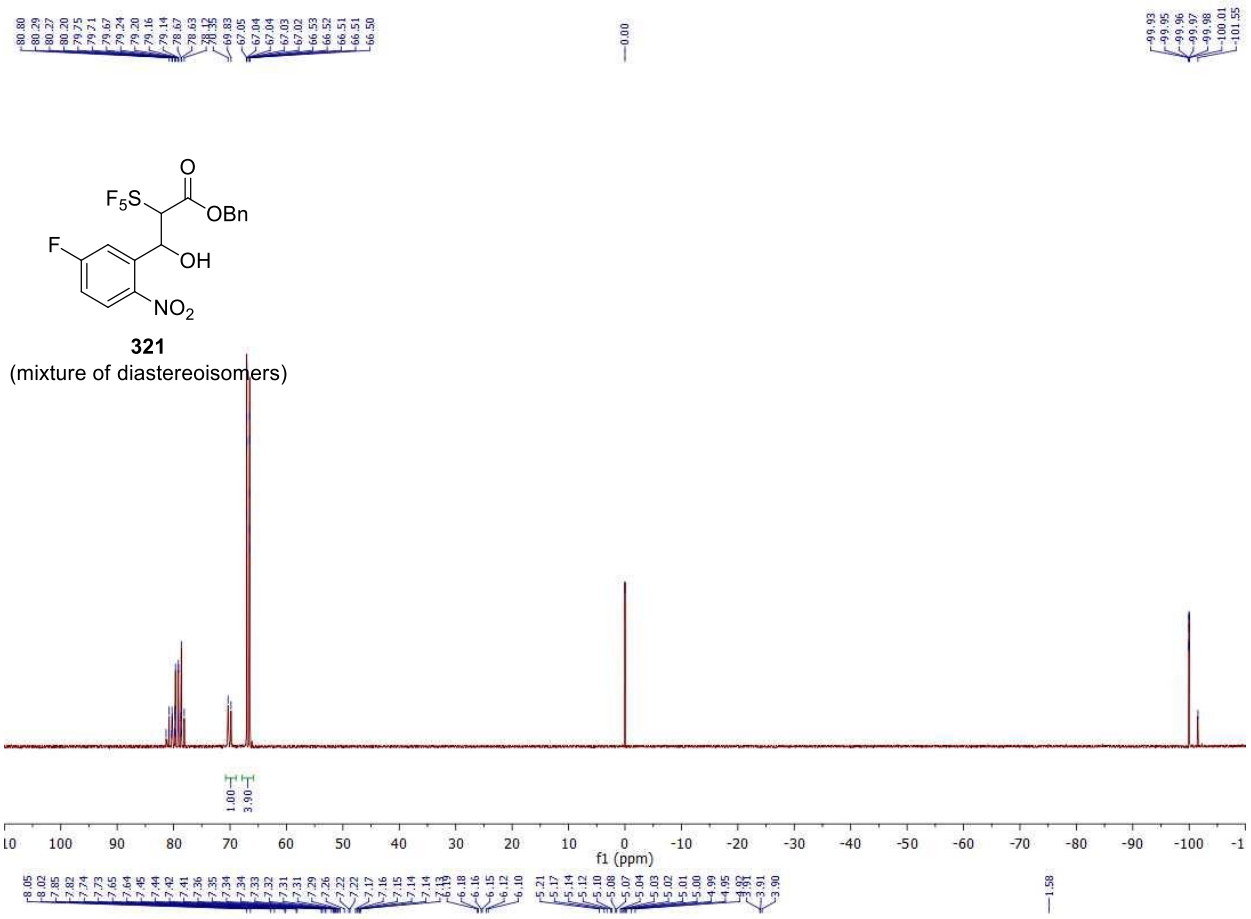


321
(mixture of diastereoisomers)

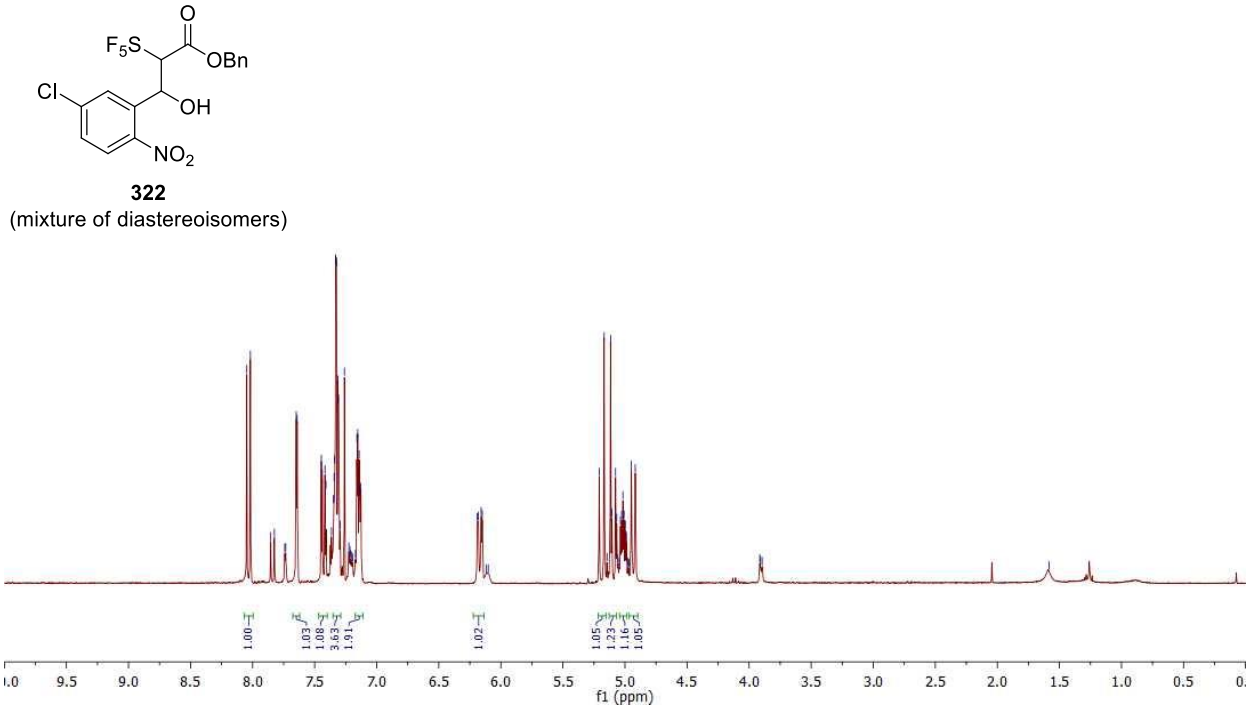




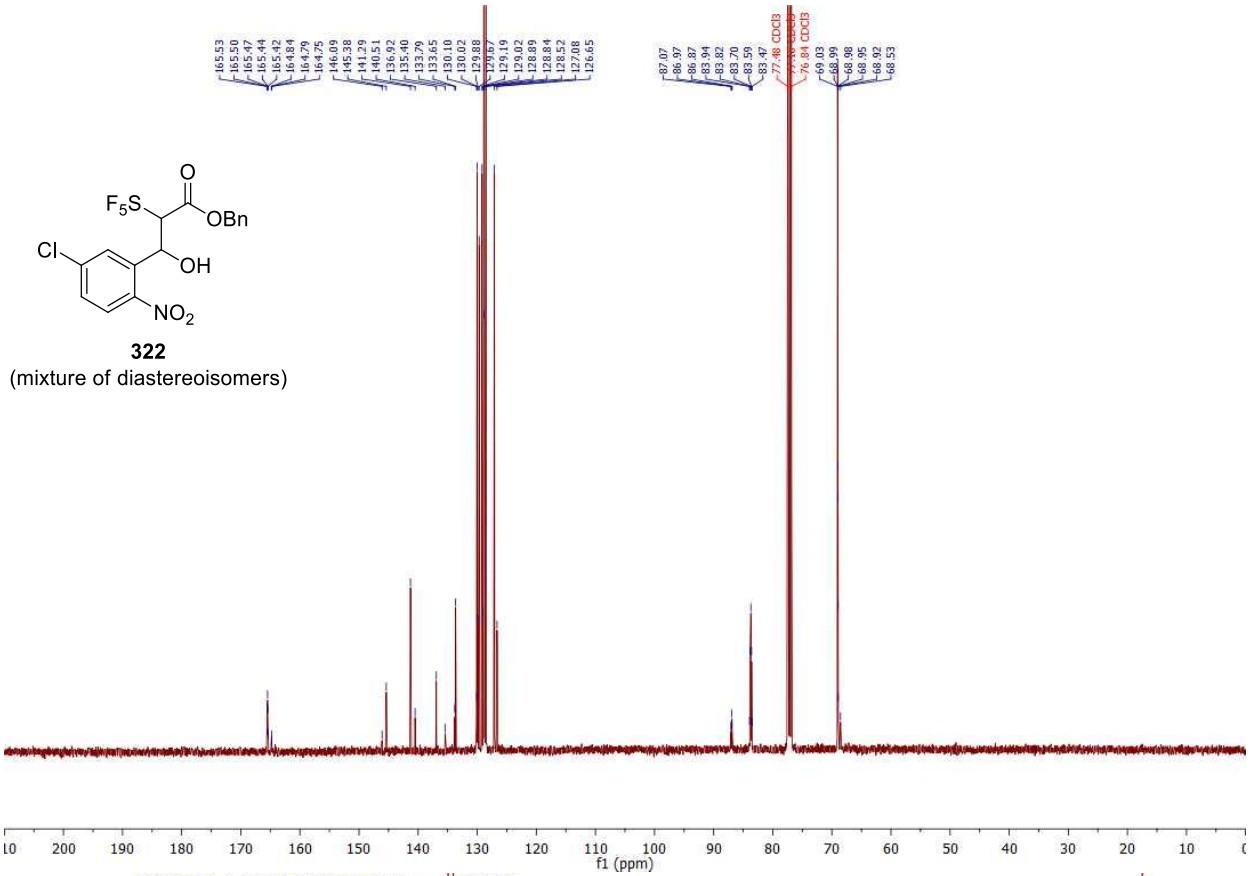
321
(mixture of diastereoisomers)



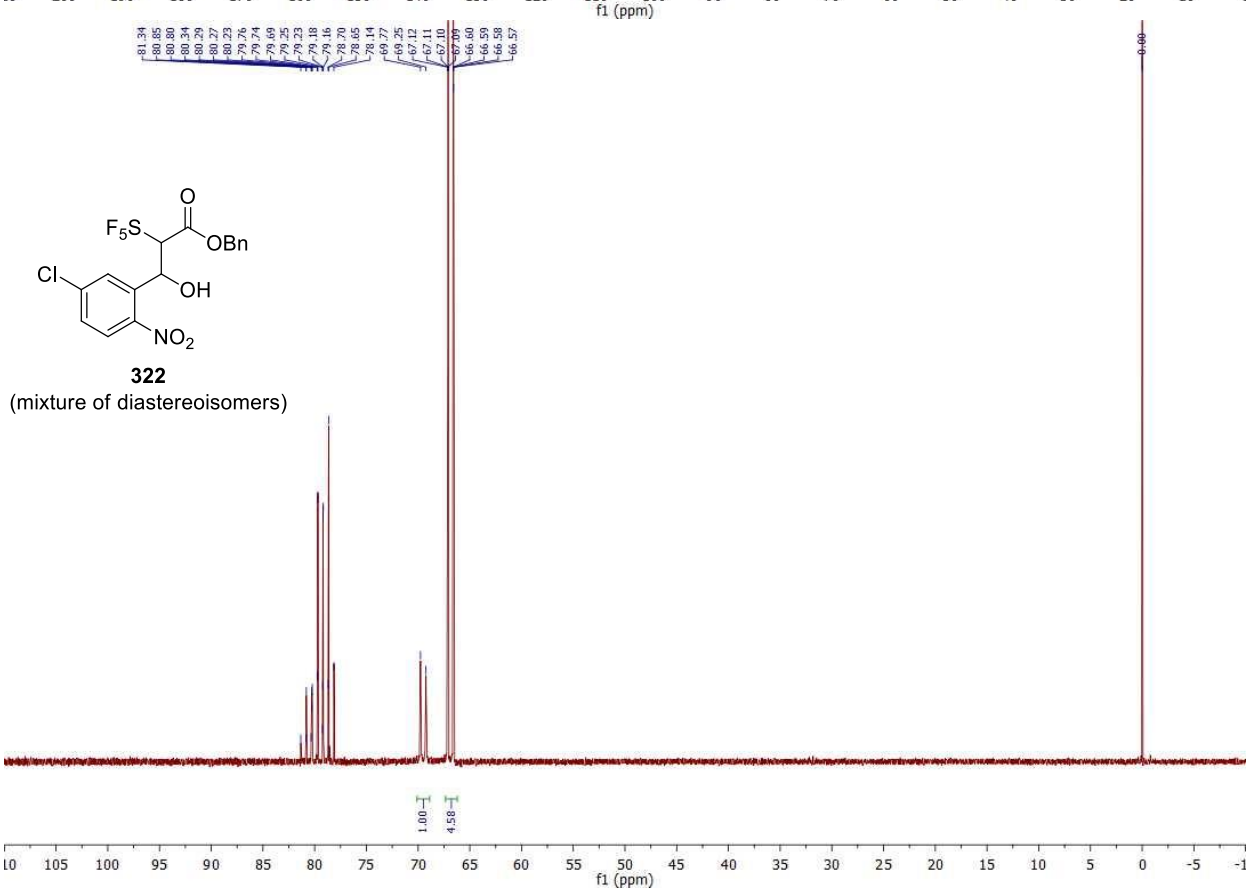
321
(mixture of diastereoisomers)



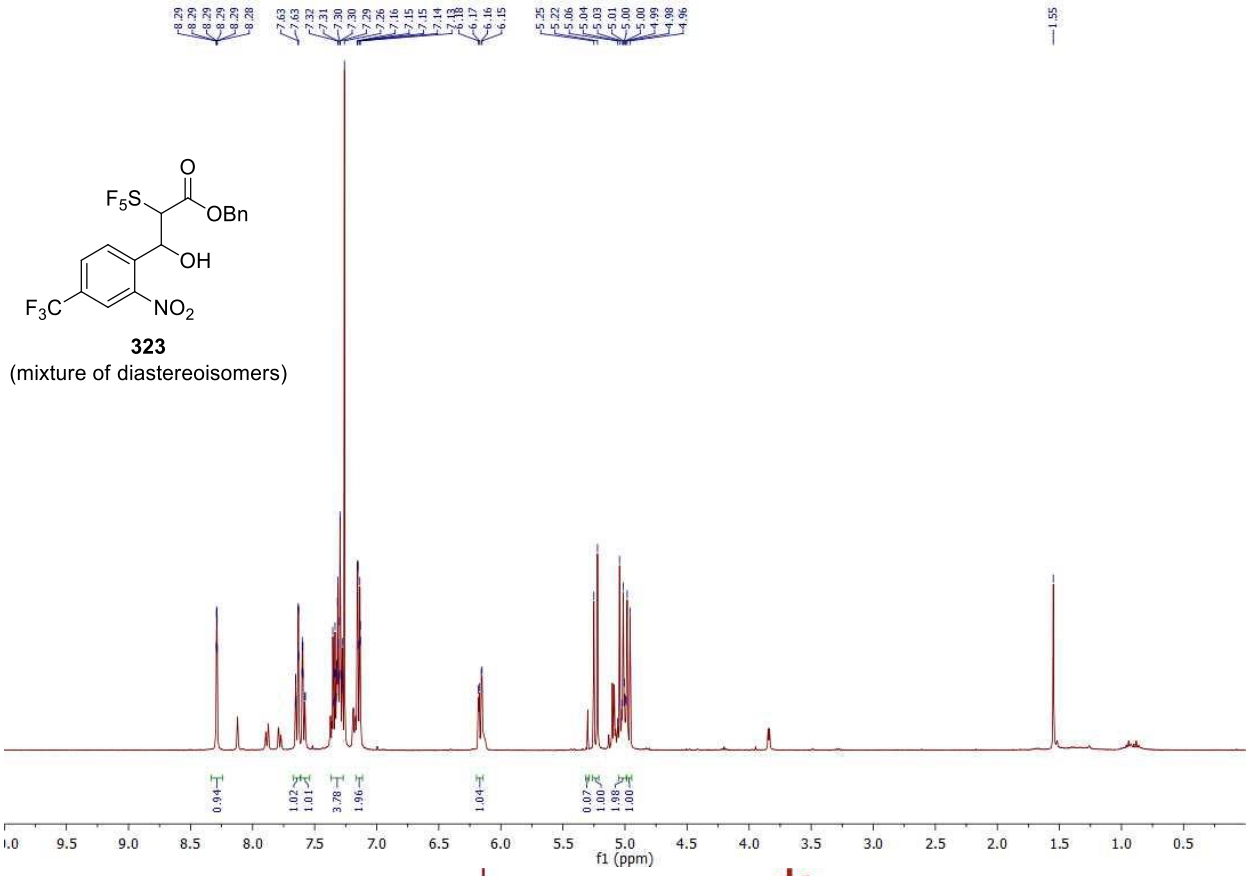
322
(mixture of diastereoisomers)



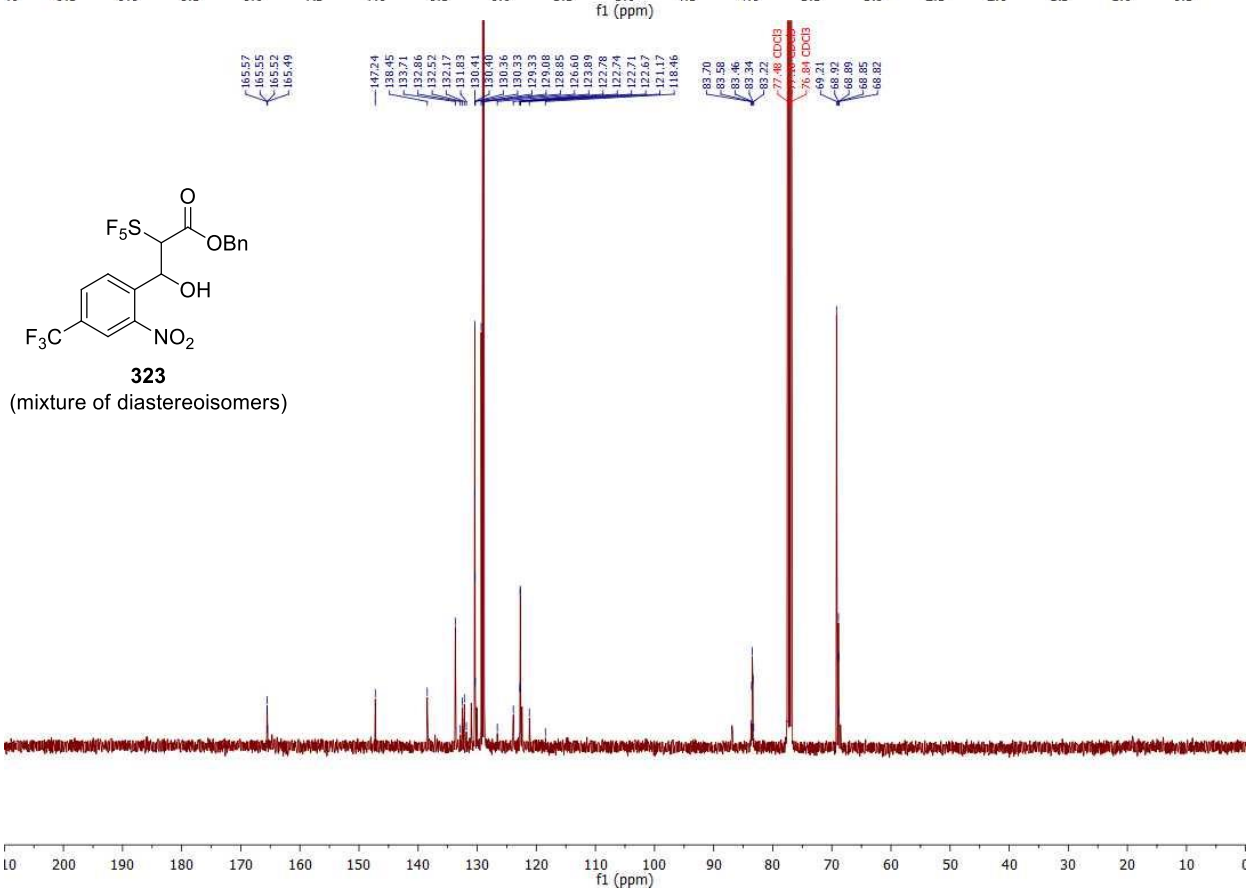
322
(mixture of diastereoisomers)



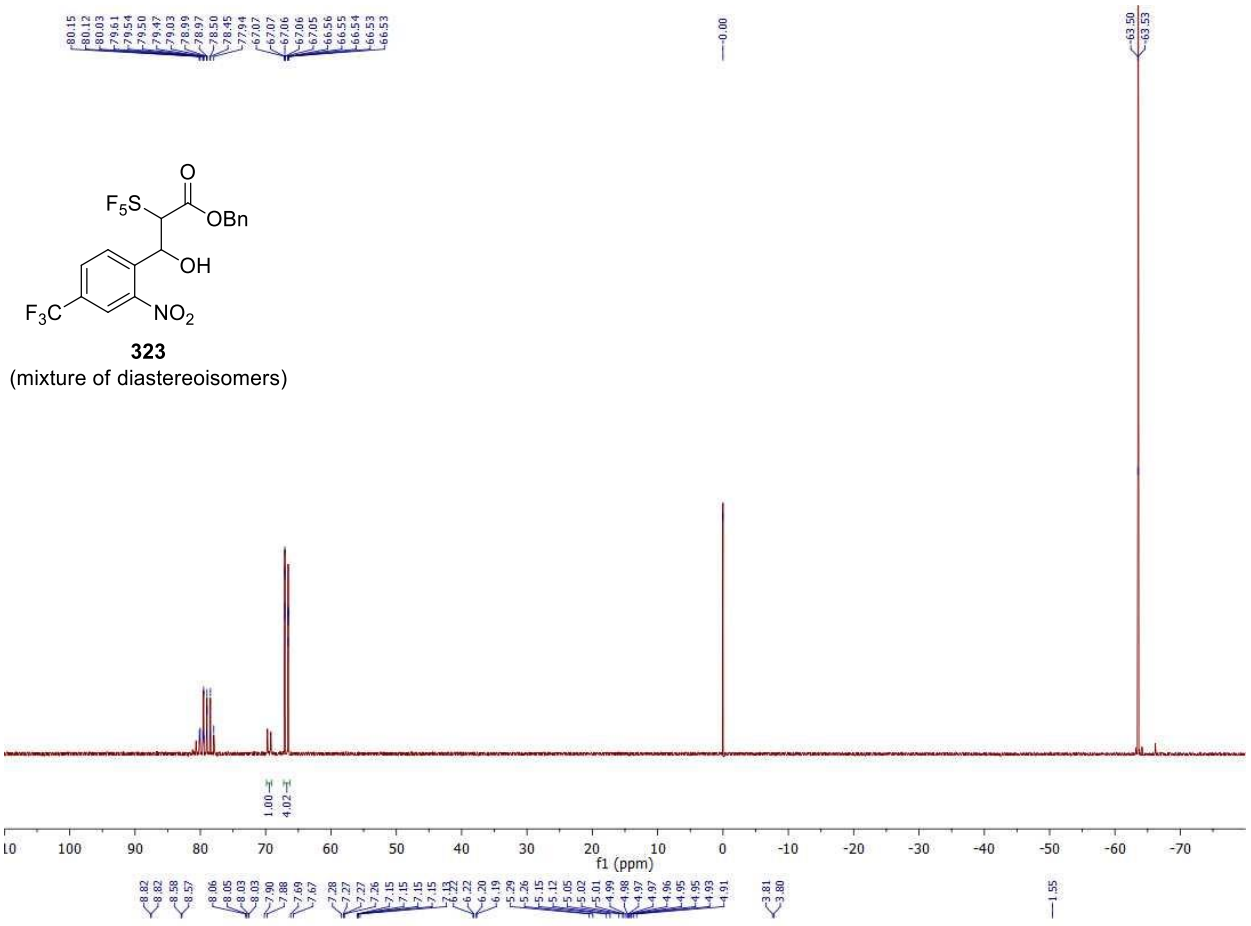
322
(mixture of diastereoisomers)



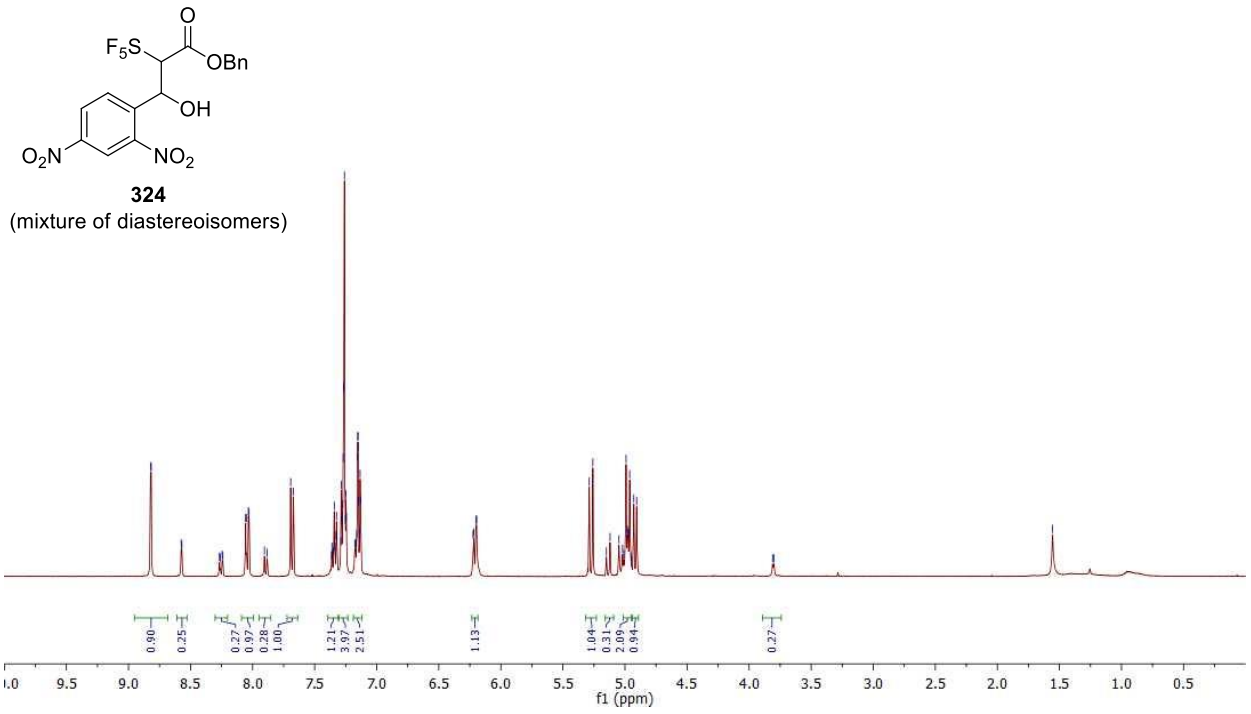
323
(mixture of diastereoisomers)



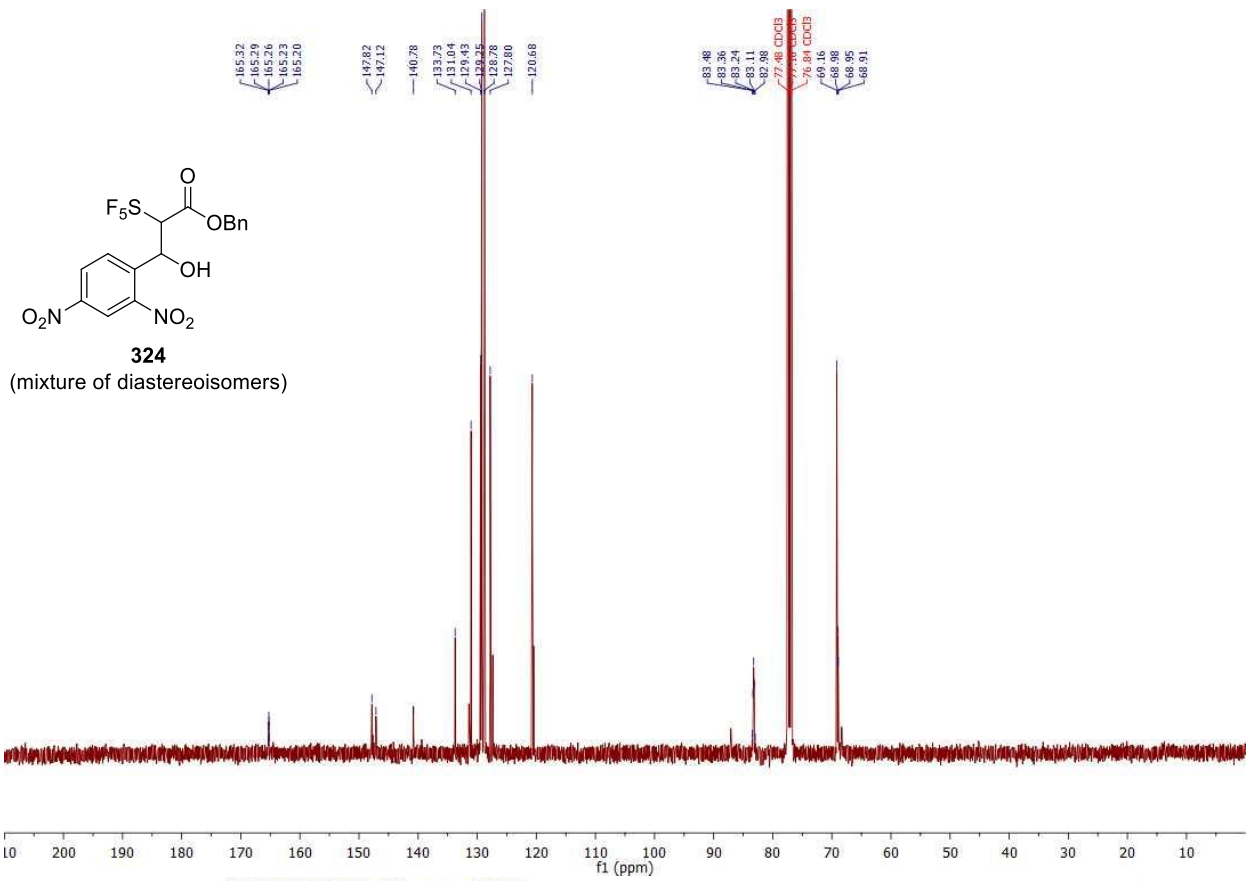
323
(mixture of diastereoisomers)



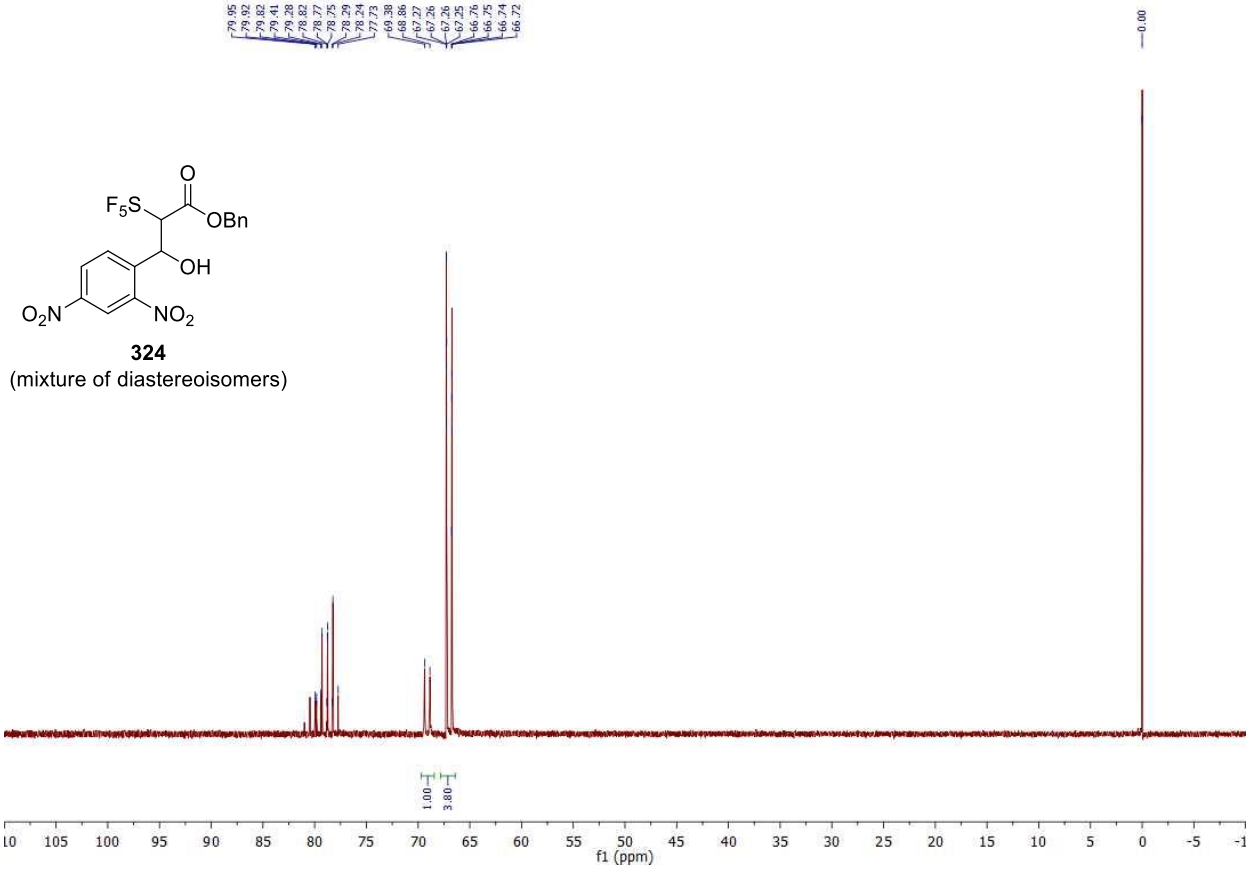
323
(mixture of diastereoisomers)



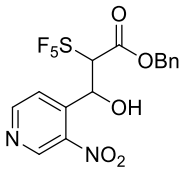
324
(mixture of diastereoisomers)



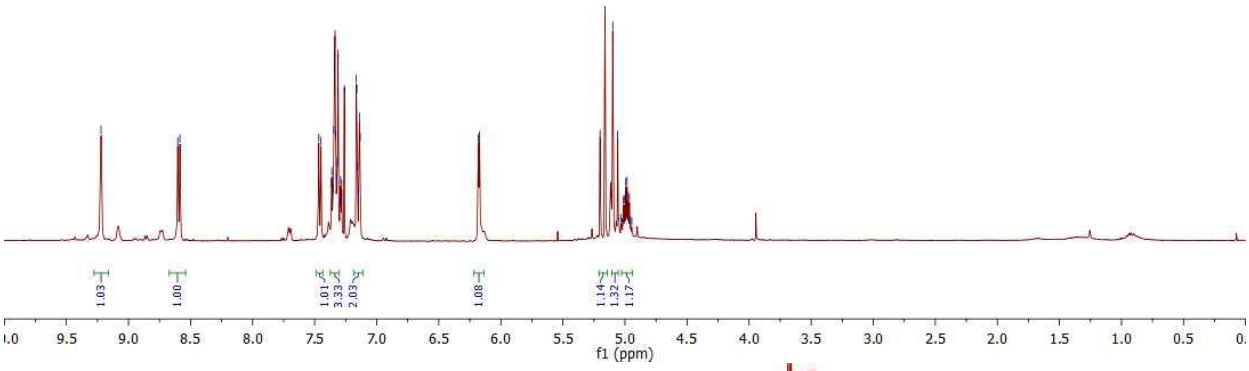
324
(mixture of diastereoisomers)

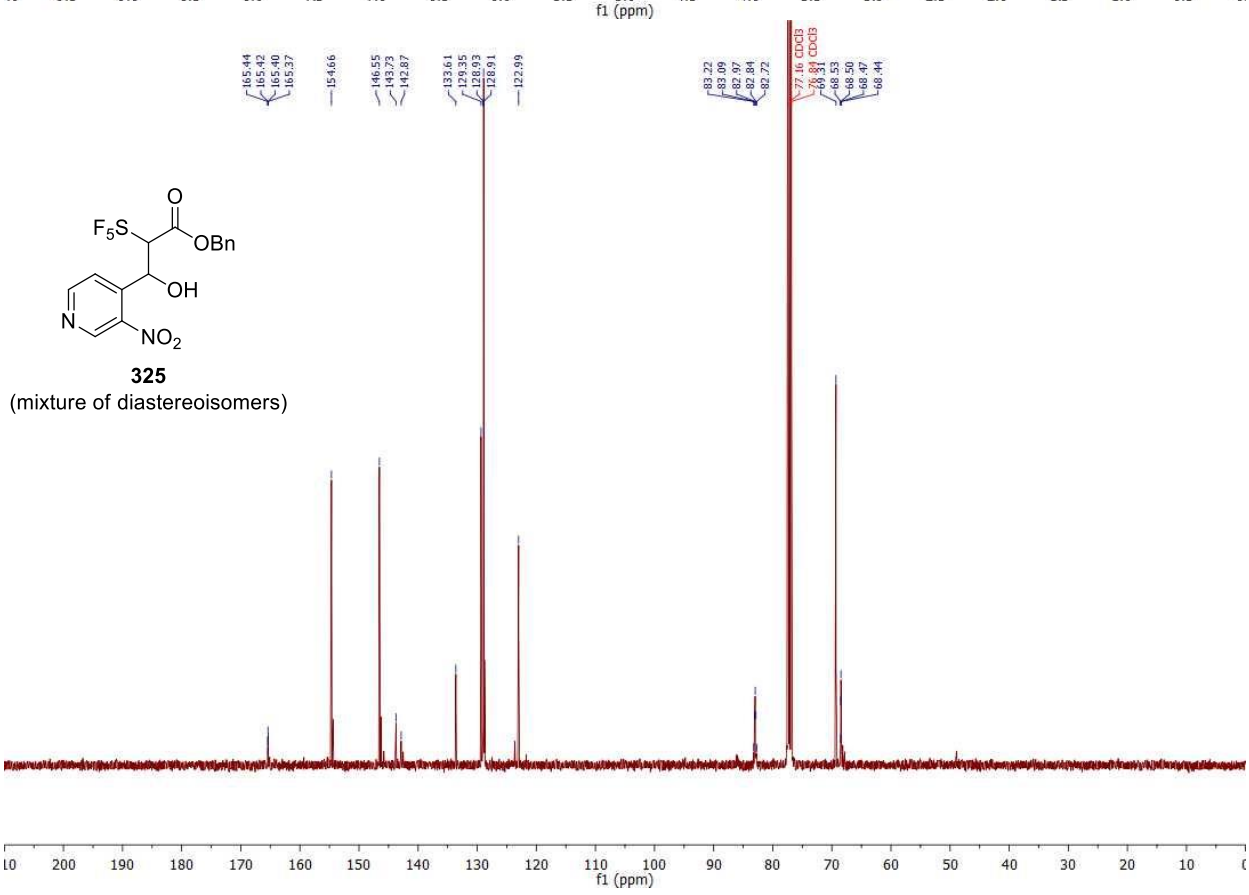


324
(mixture of diastereoisomers)

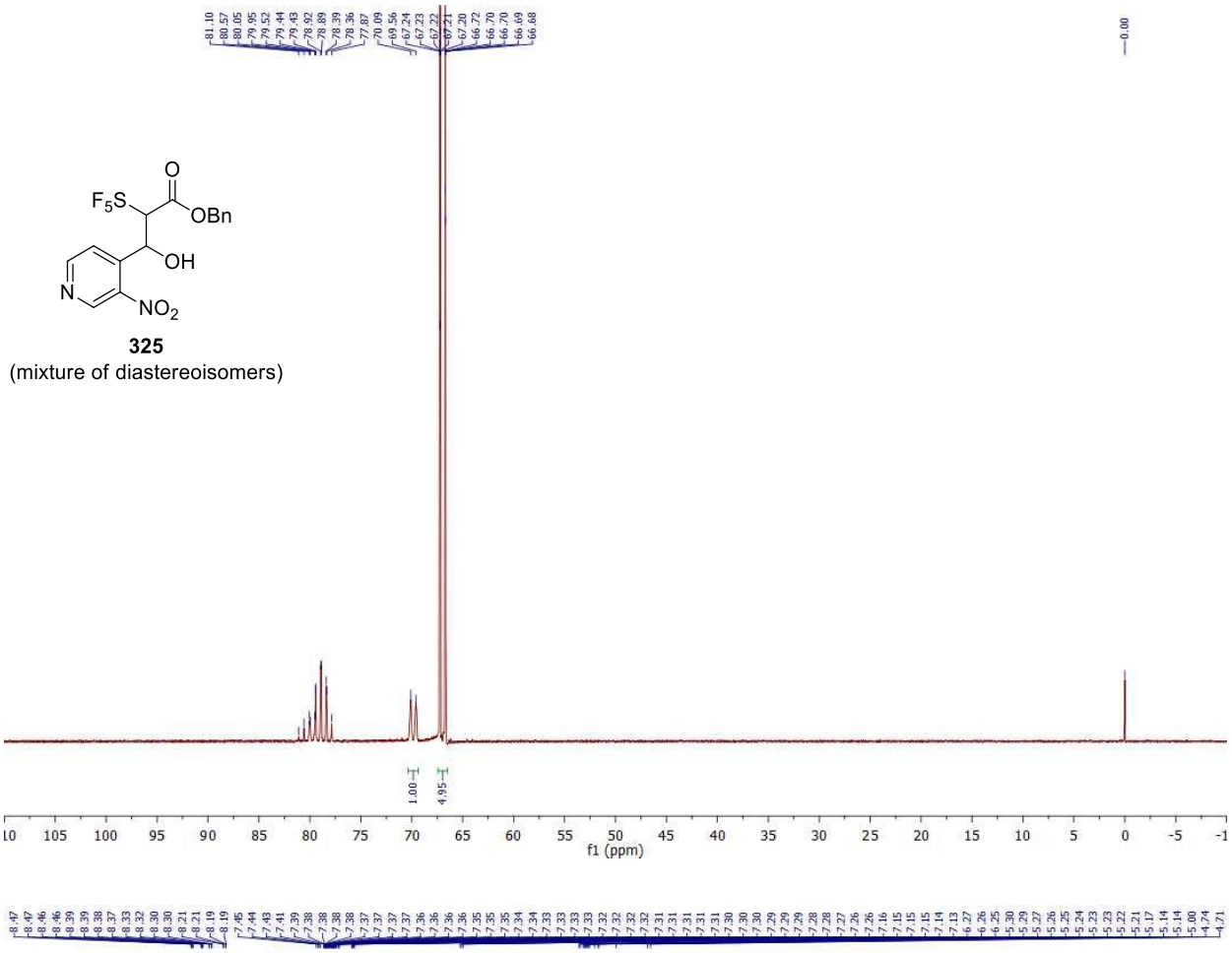


325
(mixture of diastereoisomers)

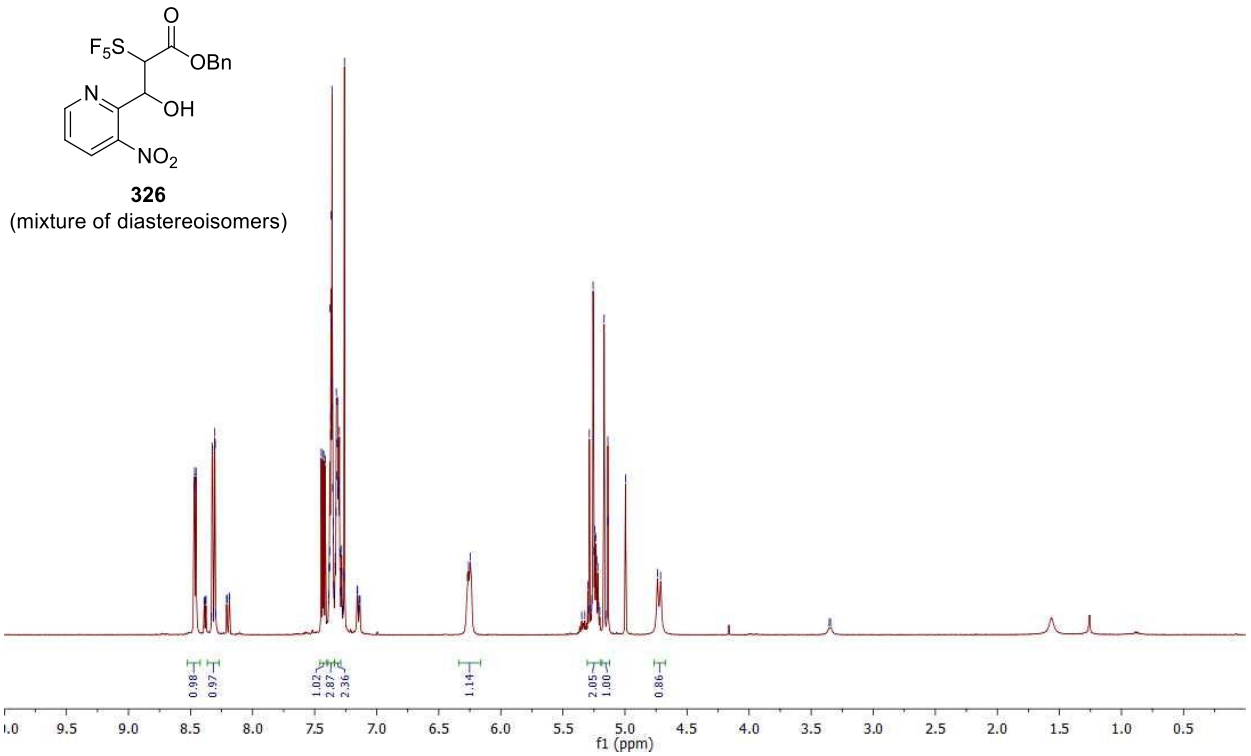




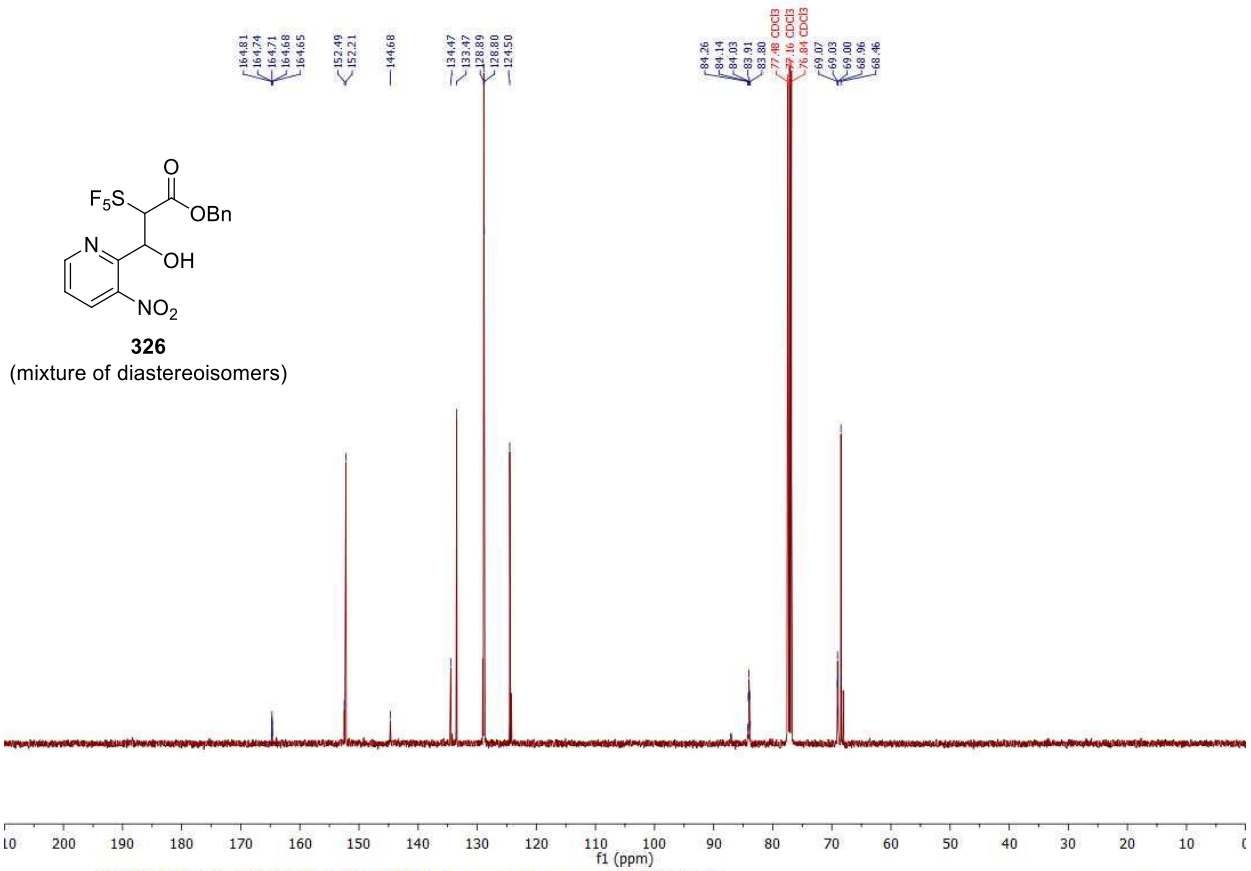
325
(mixture of diastereoisomers)



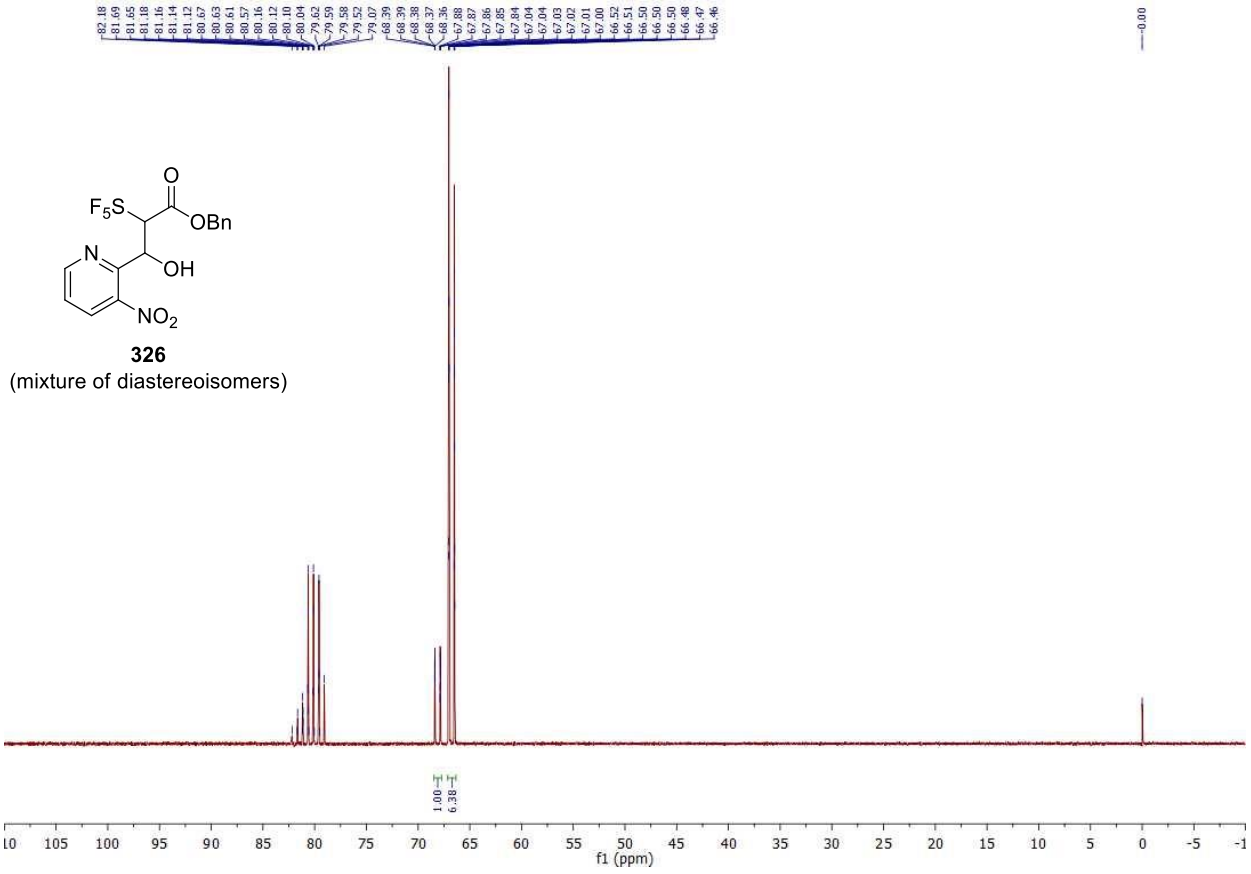
325
(mixture of diastereoisomers)



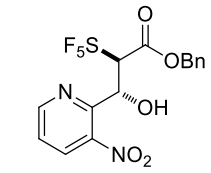
326
(mixture of diastereoisomers)



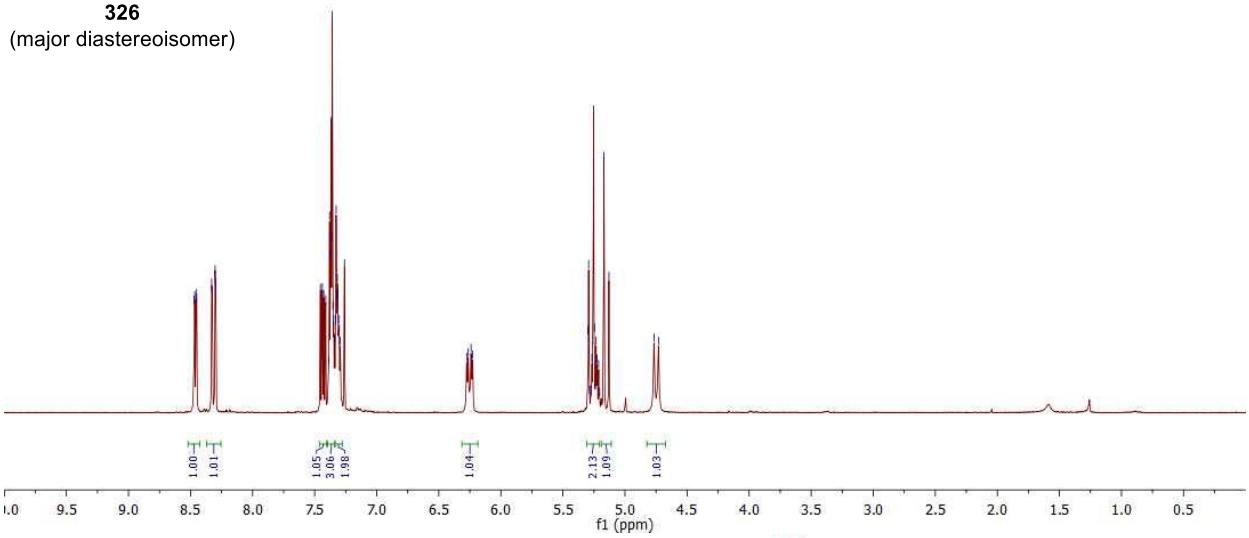
326
(mixture of diastereoisomers)

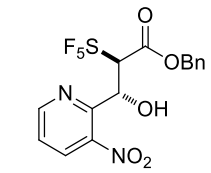


326
(mixture of diastereoisomers)

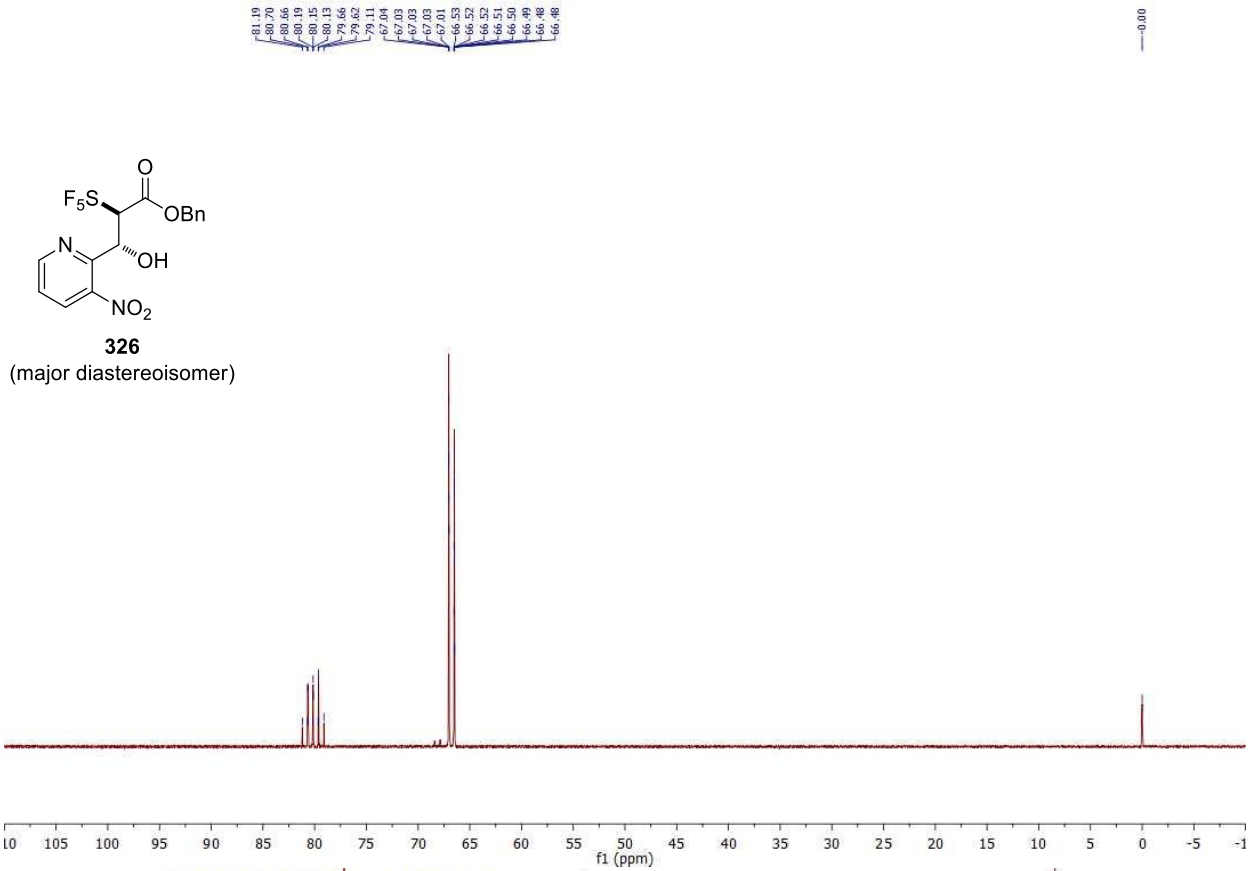


326
(major diastereoisomer)

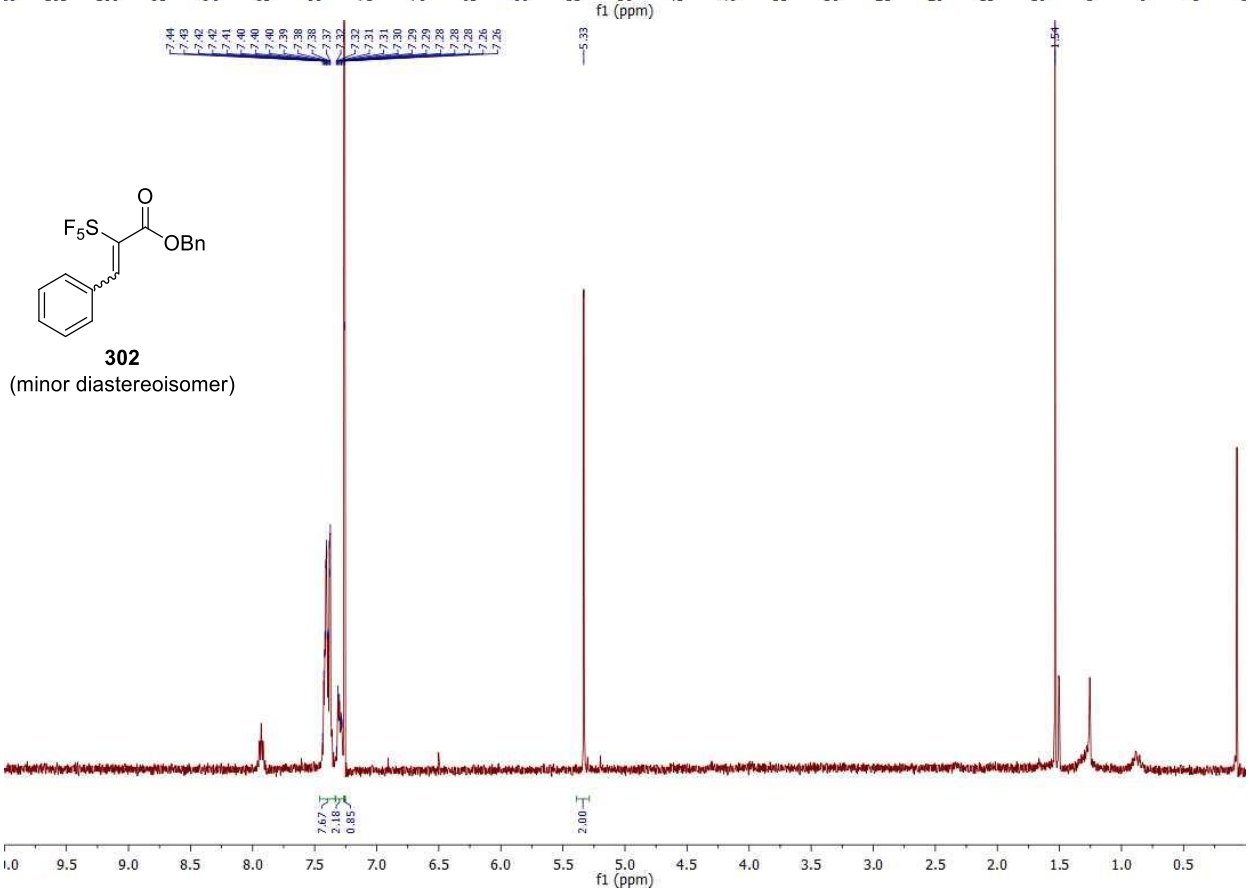




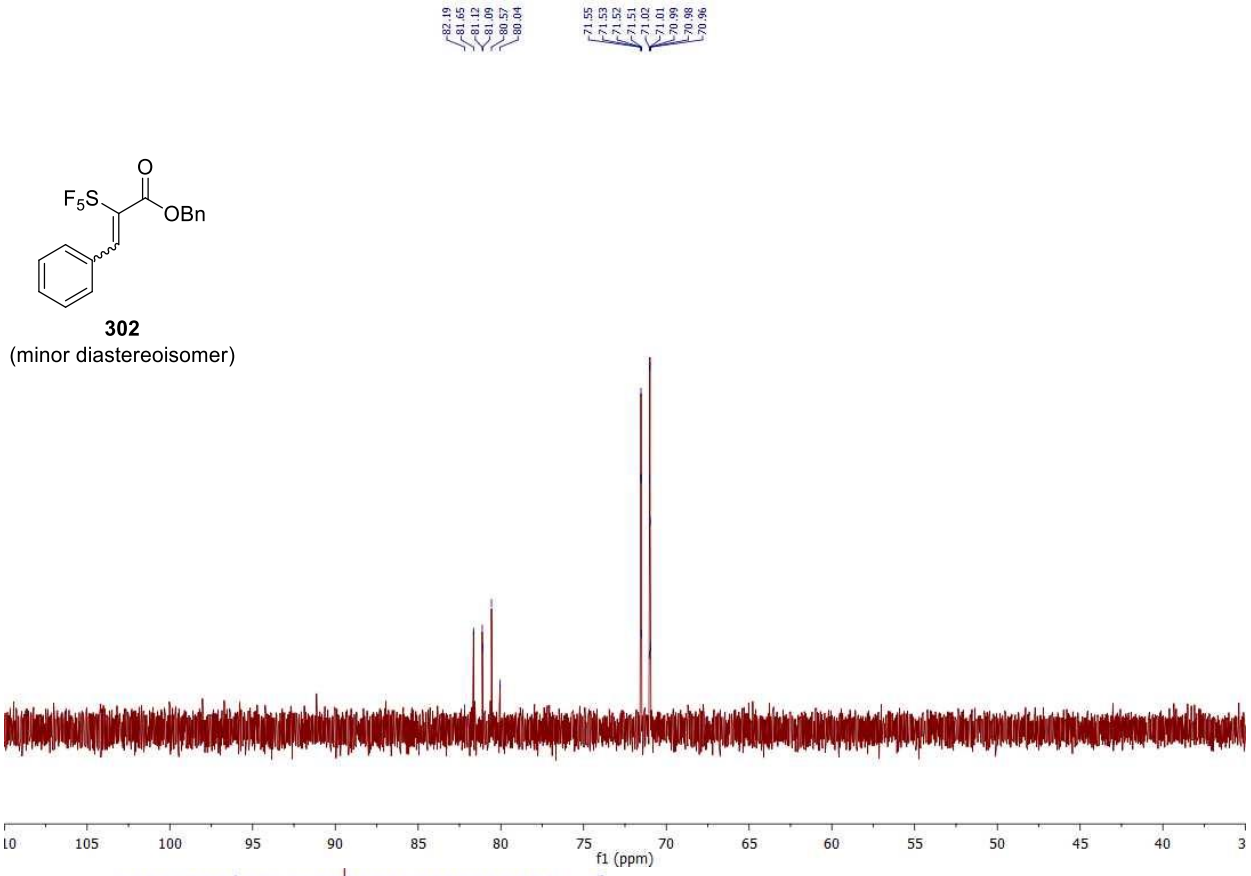
326
(major diastereoisomer)



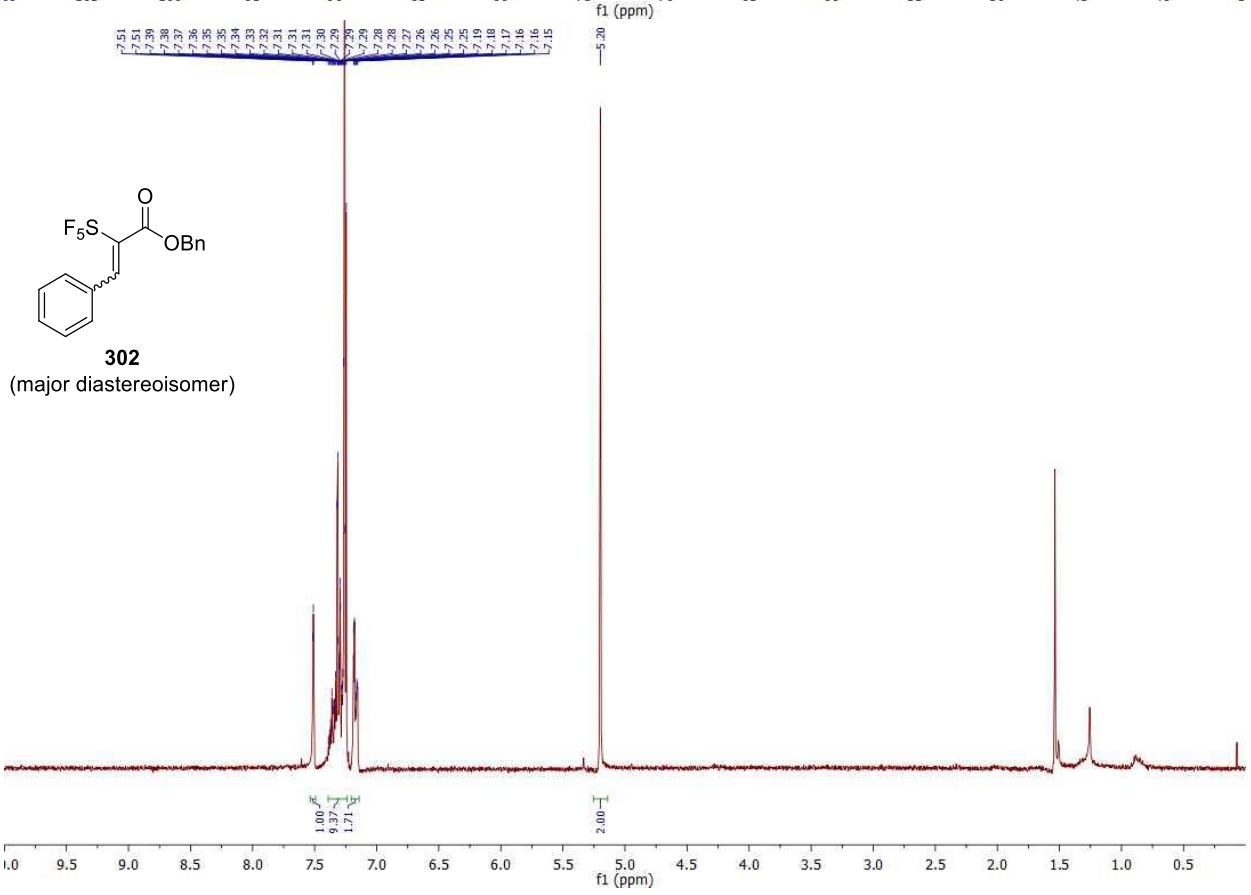
326
(major diastereoisomer)



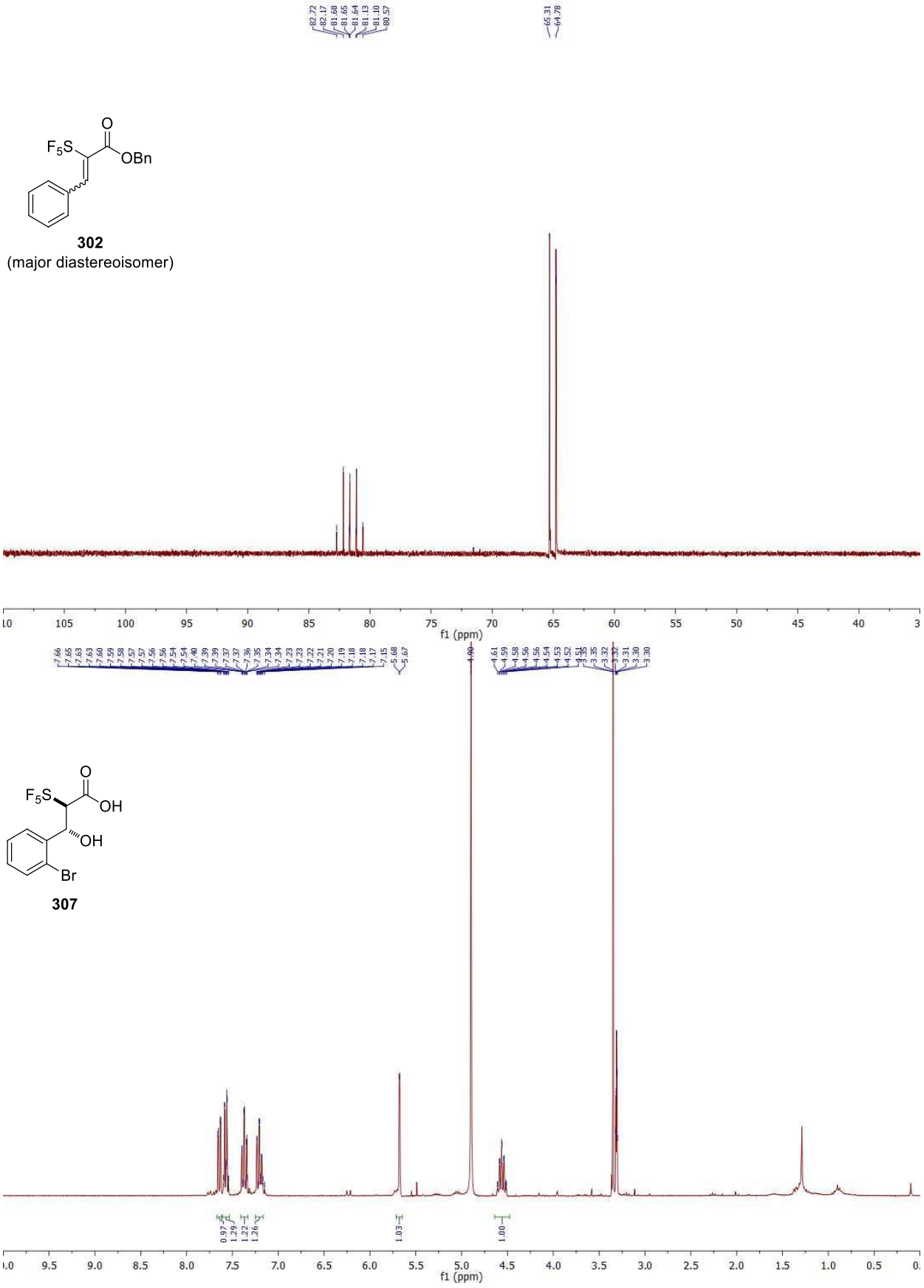
302
(minor diastereoisomer)



302
(minor diastereoisomer)

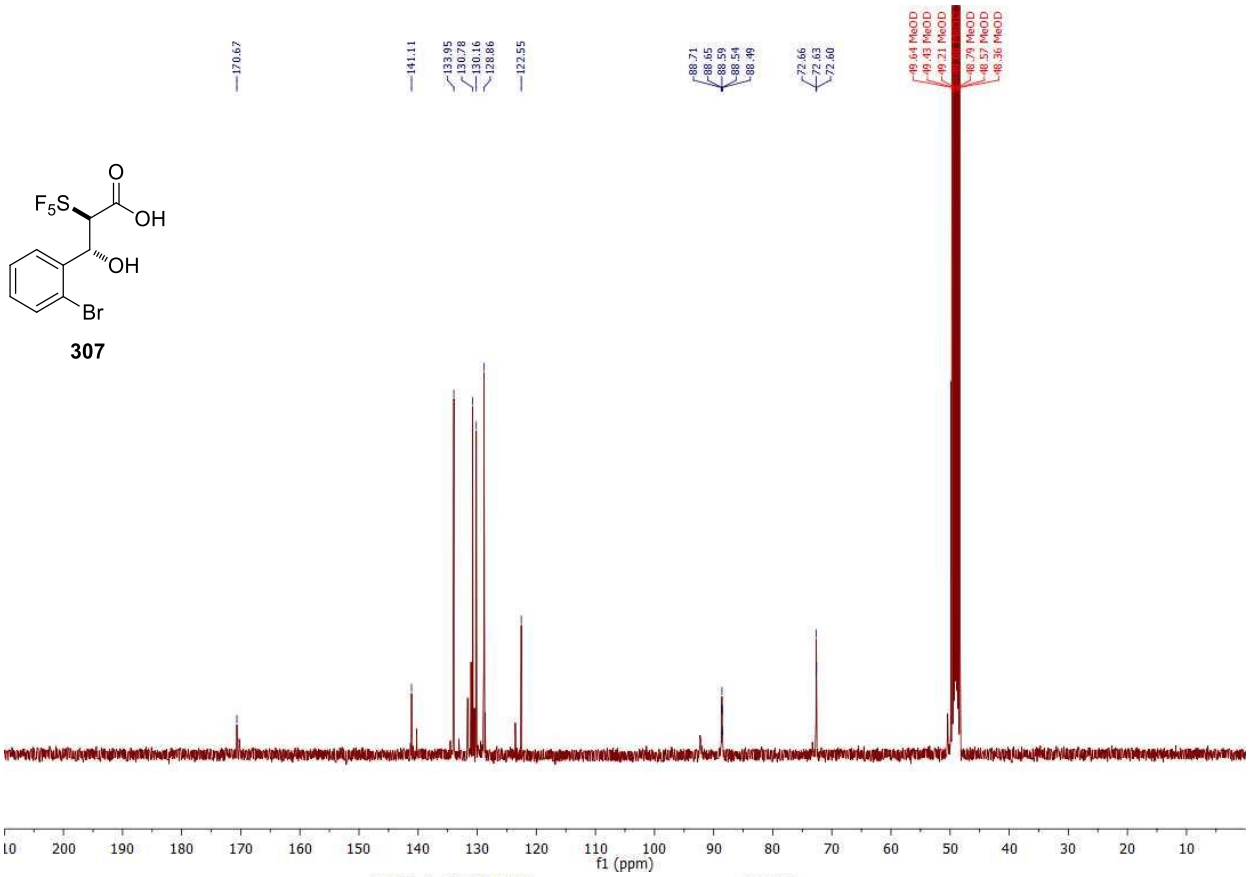


302
(major diastereoisomer)



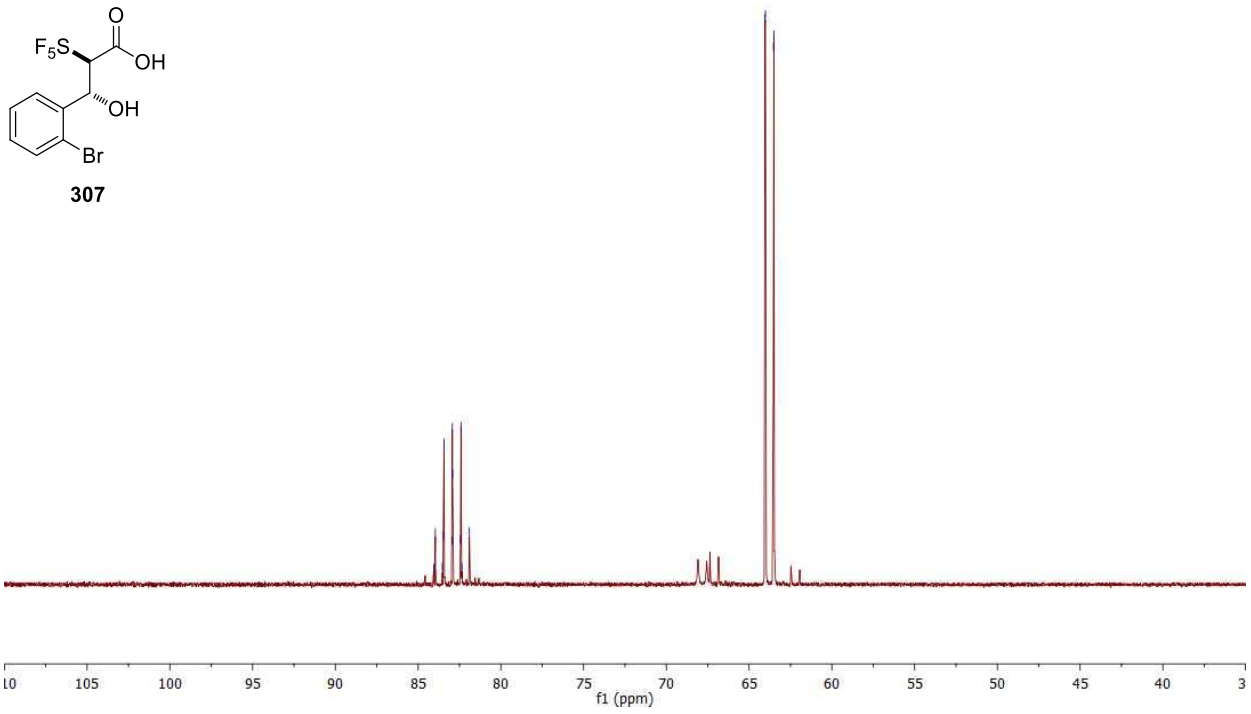
302
(major diastereoisomer)

307


170.67
141.11
133.95
130.78
130.16
128.86
122.55
88.71
88.65
88.59
88.54
88.49
72.66
72.63
72.60
49.64 MeOD
49.43 MeOD
49.21 MeOD
48.79 MeOD
48.57 MeOD
48.36 MeOD
f1 (ppm)

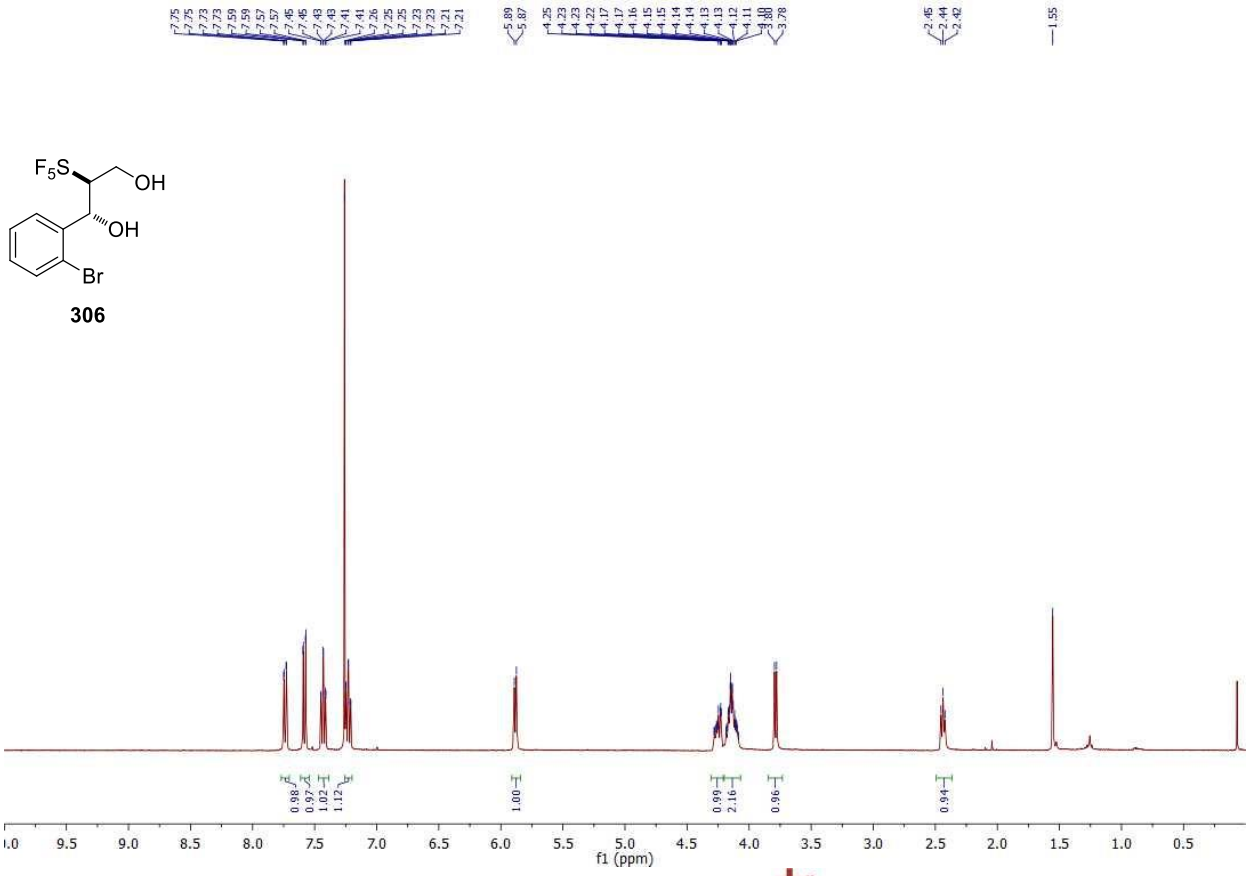
O
F5S
OH
OH
Br

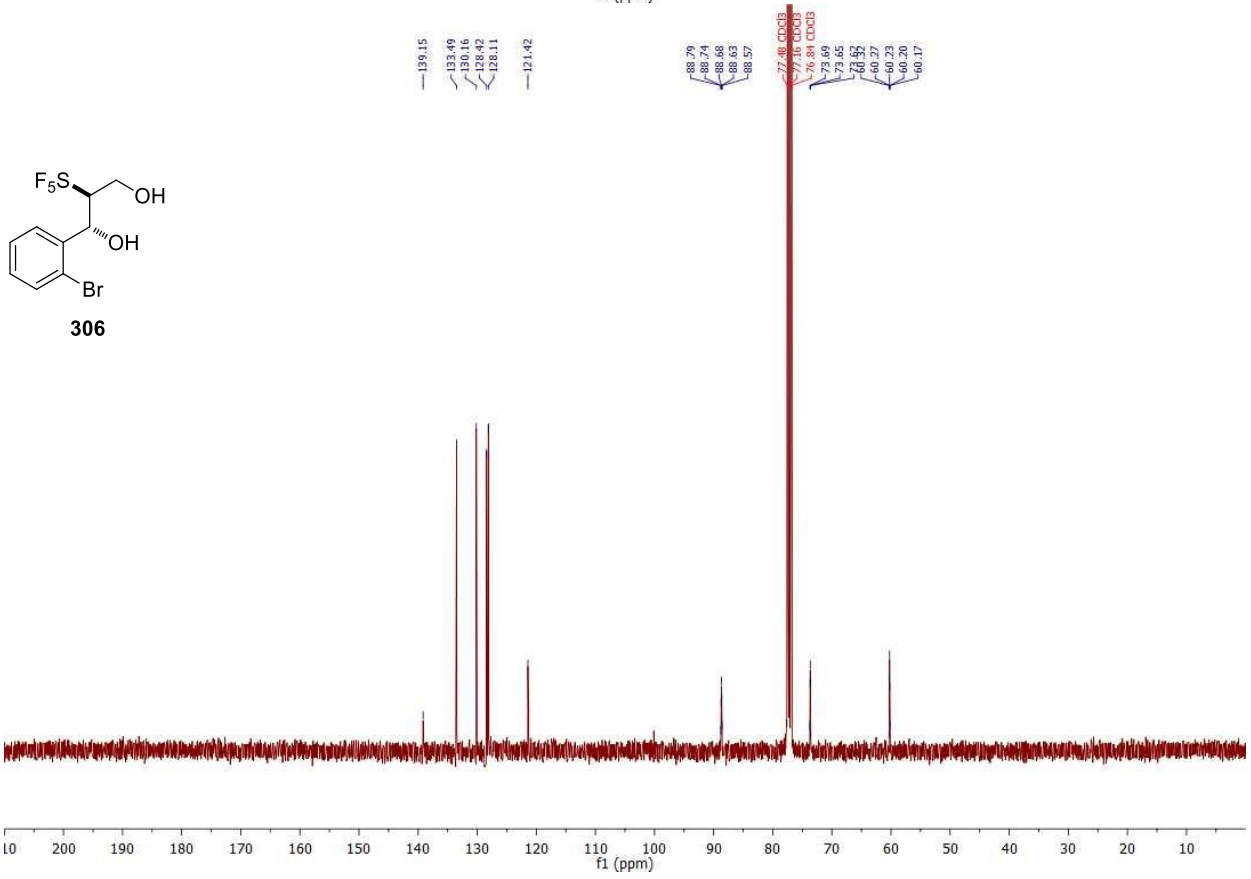
307

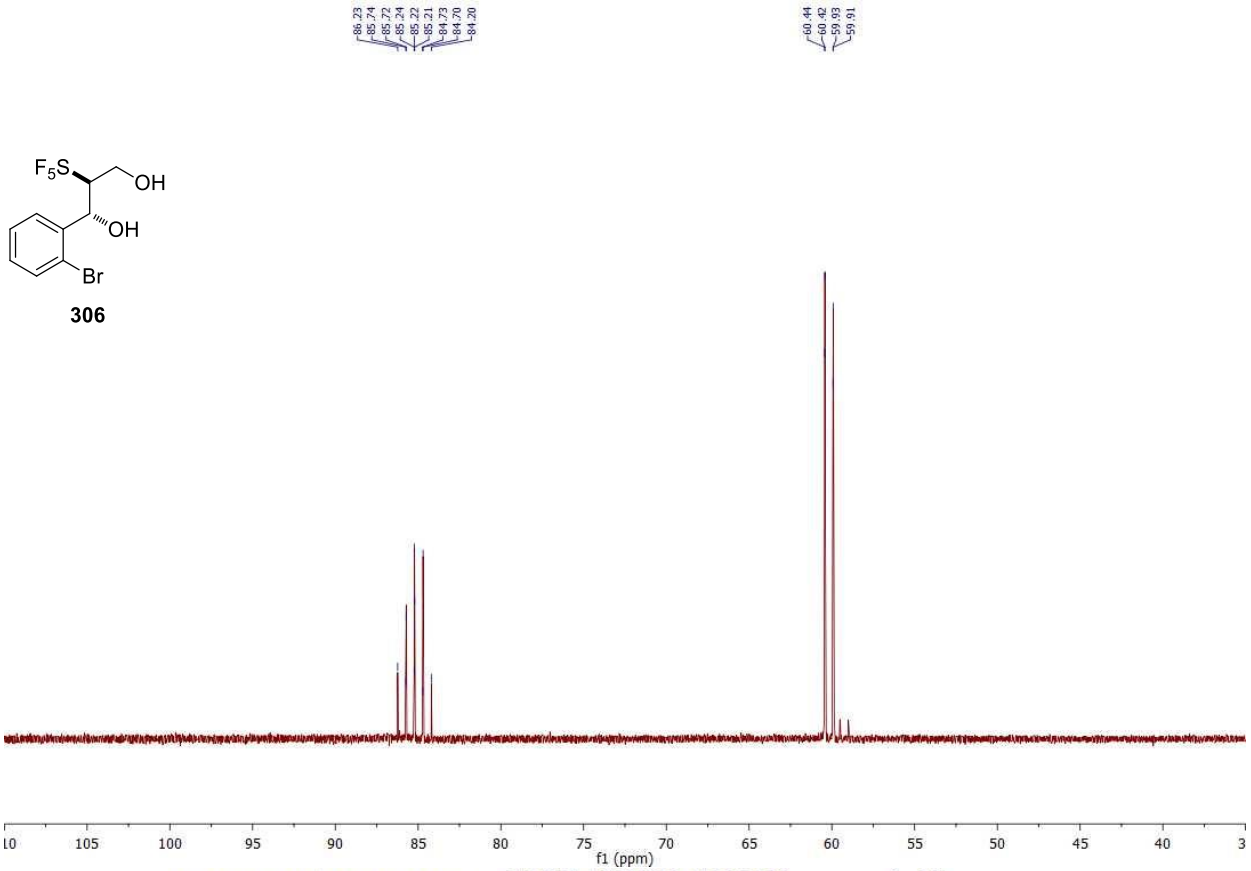

84.06
83.96
83.54
83.47
83.44
82.96
82.93
82.92
82.44
82.41
82.35
81.90
64.04
64.02
63.53
63.50
f1 (ppm)

O
F5S
OH
OH
Br

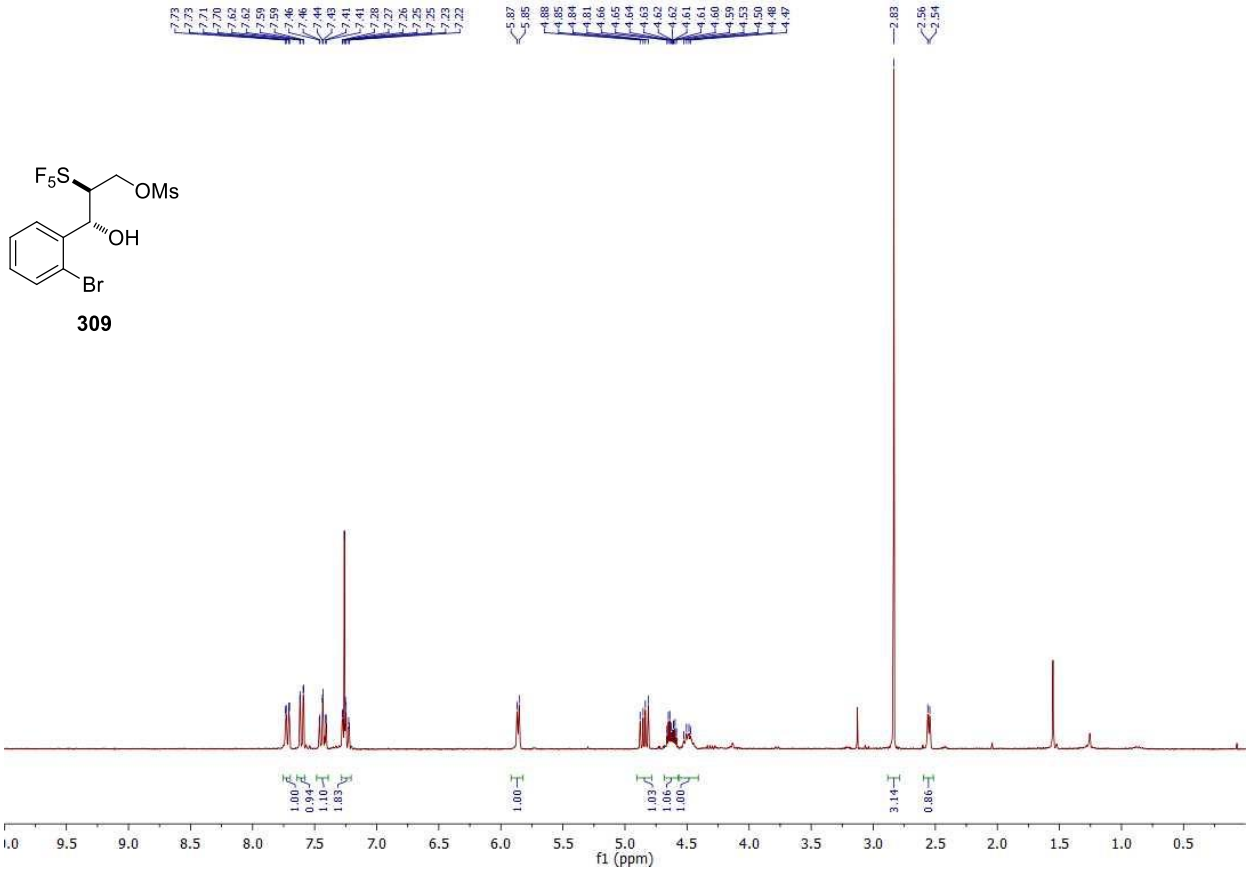
307


F5S
OH
OH
Br
306
f1 (ppm)

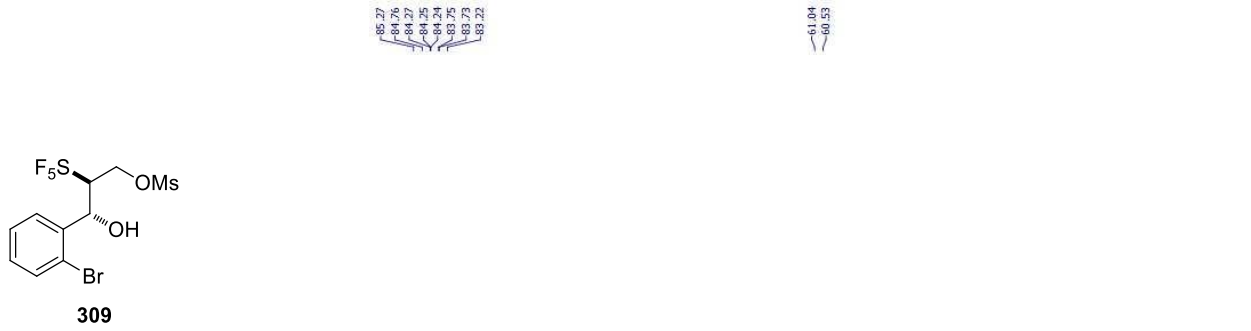

F5S
OH
OH
Br
306
f1 (ppm)


86.23
85.74
85.72
85.24
85.22
85.21
84.73
84.70
84.20
60.44
60.42
59.93
59.91
F5S
OH
OH
Br
f1 (ppm)

306

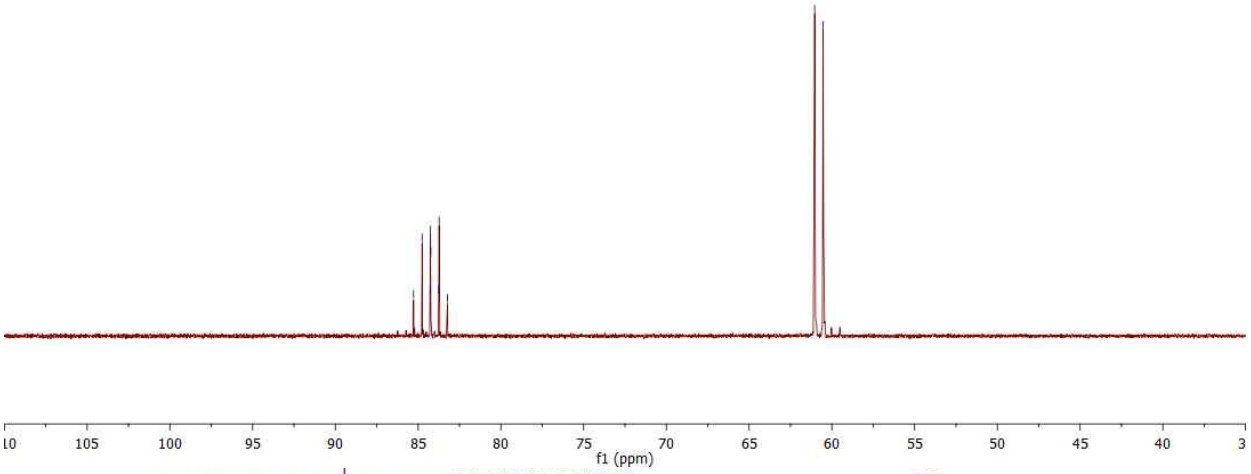

7.73
7.73
7.71
7.70
7.62
7.62
7.59
7.59
7.46
7.46
7.44
7.43
7.41
7.41
7.28
7.27
7.26
7.25
7.25
7.23
7.22
5.87
5.85
4.88
4.85
4.84
4.81
4.66
4.65
4.64
4.63
4.62
4.62
4.61
4.61
4.60
4.59
4.53
4.50
4.48
4.47
2.83
2.56
2.54
F5S
OMs
OH
Br
1.00
0.94
1.10
1.83
1.00
1.03
1.06
1.00
3.14
0.86
f1 (ppm)

309

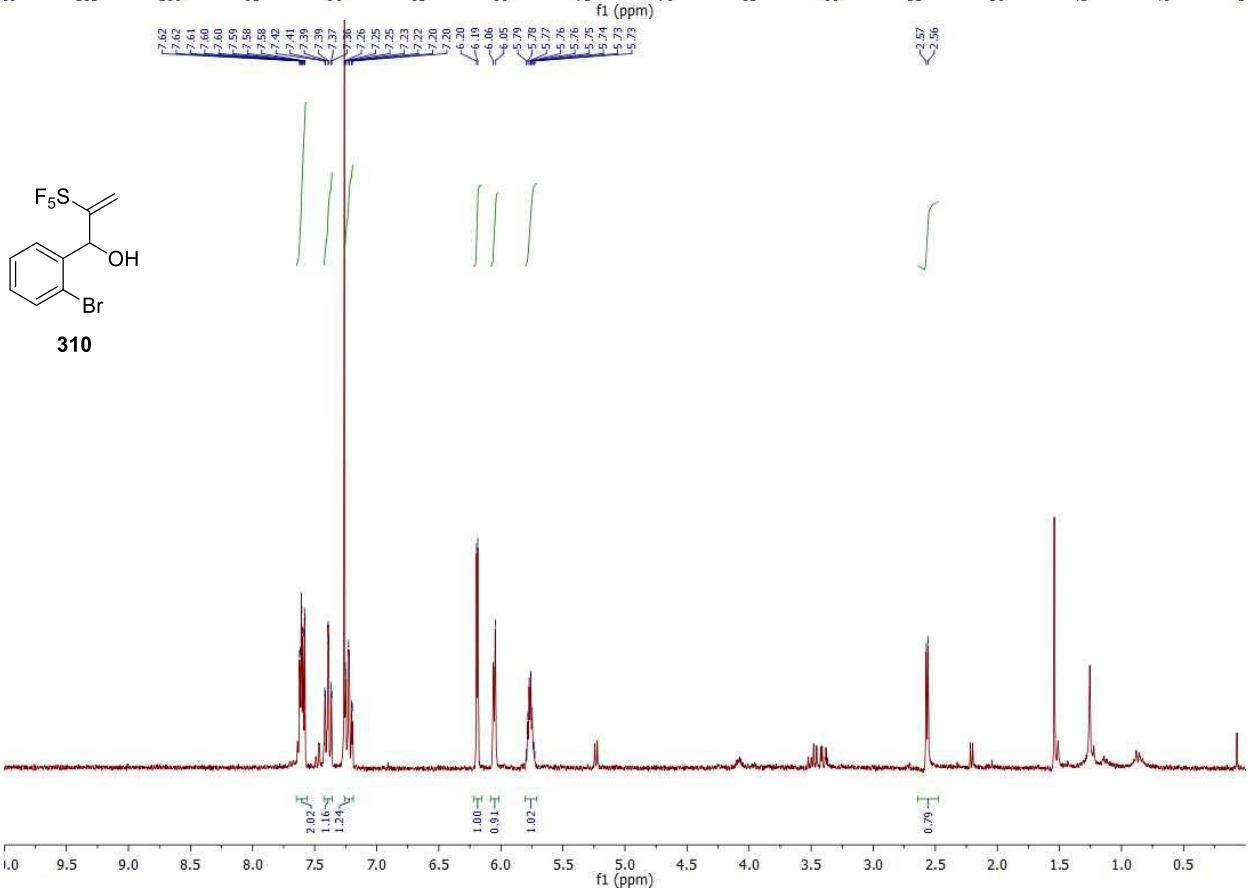

85.27
84.76
84.27
84.25
84.24
83.75
83.73
83.22
61.04
60.53

F5S
OMs
OH
Br

309

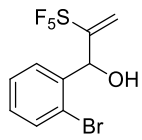


f1 (ppm)


7.62
7.62
7.61
7.60
7.60
7.59
7.58
7.58
7.42
7.41
7.39
7.39
7.37
7.36
7.26
7.25
7.25
7.23
7.22
7.20
7.20
6.20
6.19
6.06
6.05
5.79
5.78
5.77
5.76
5.76
5.75
5.74
5.73
5.73
2.57
2.56
2.02
1.16
1.24
1.00
0.91
1.02
0.79
f1 (ppm)

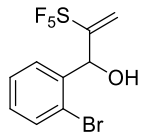
F5S
OH
Br

310


F5S
OH
Br

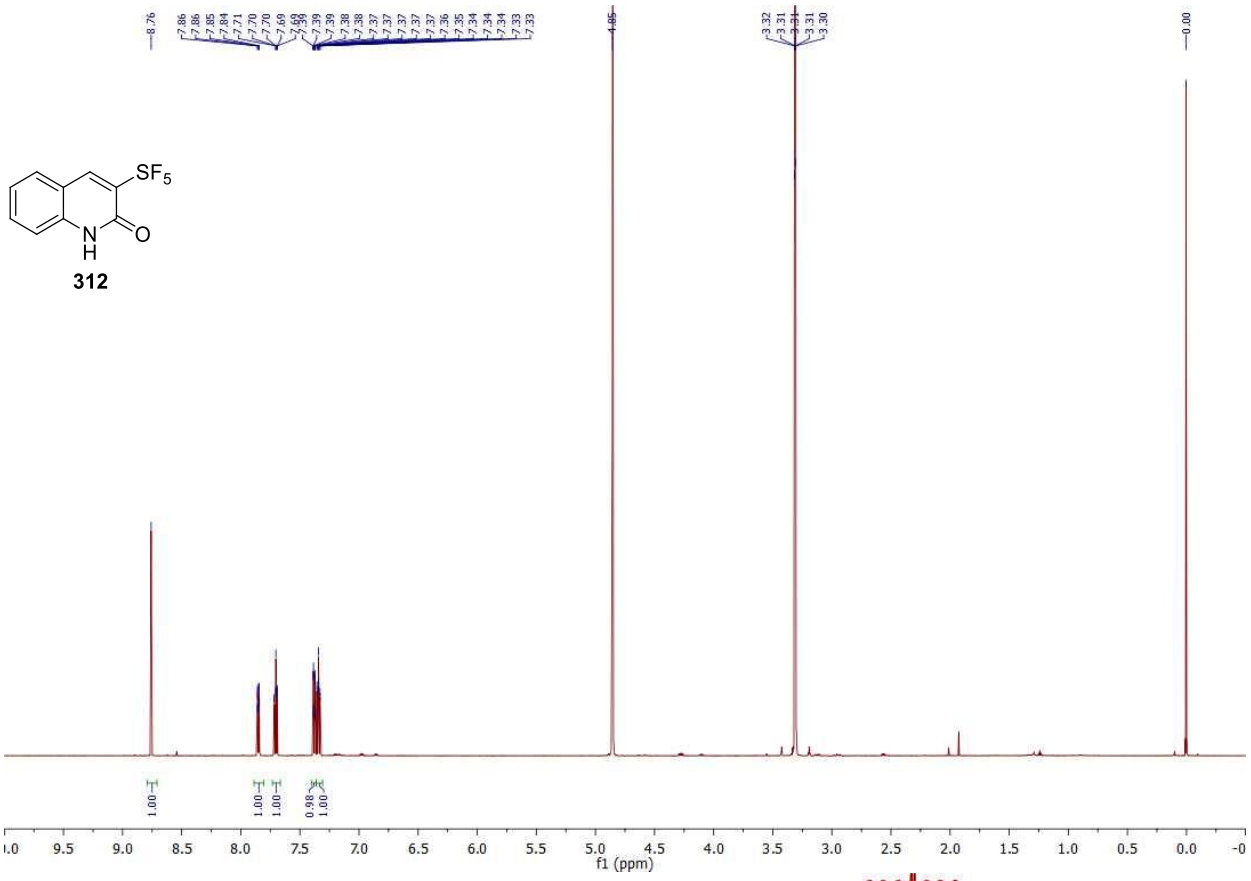
310

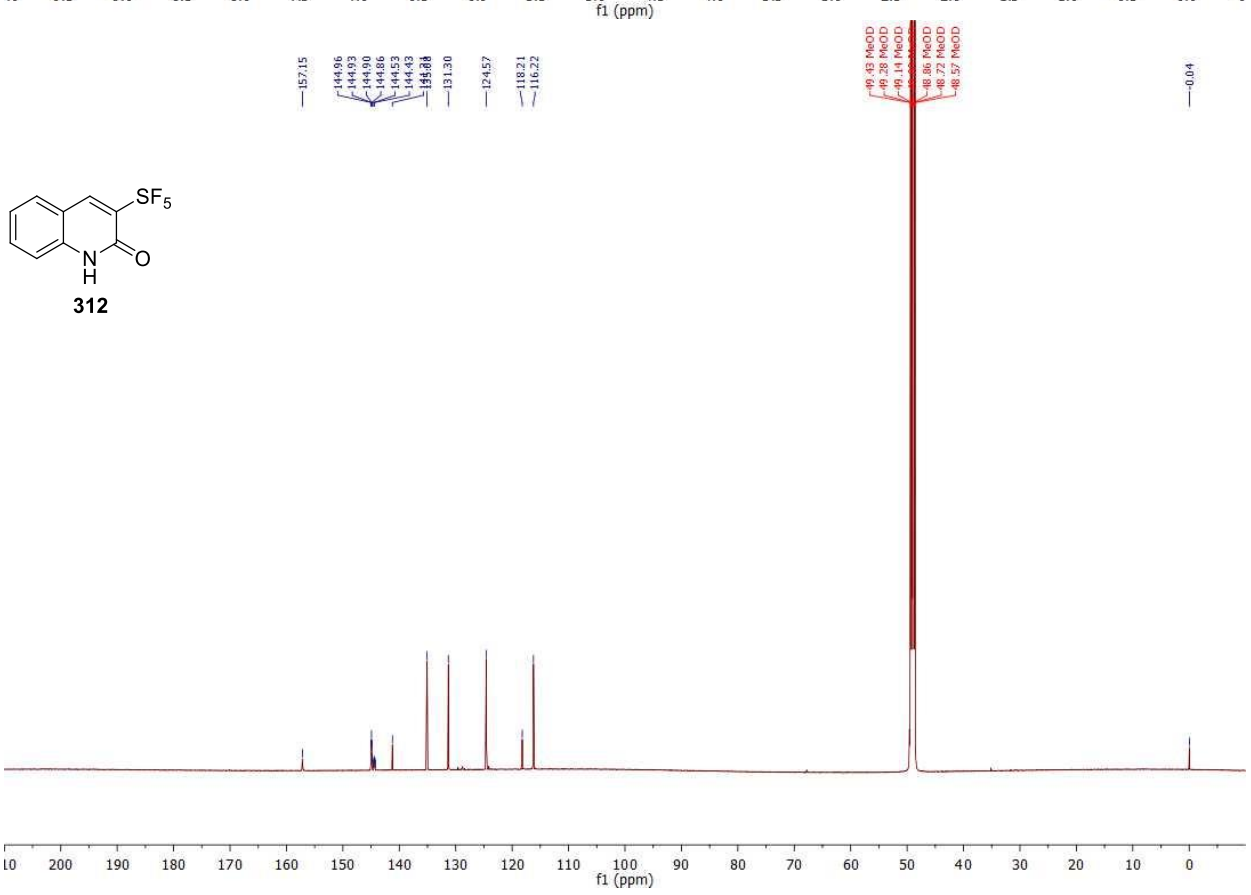
133.42
130.16
128.42
127.89
123.11
122.86
122.81
122.76
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
71.95
71.91
71.88
f1 (ppm)
85.16
84.63
84.11
84.10
83.58
83.06
60.72
60.70
60.19
60.18

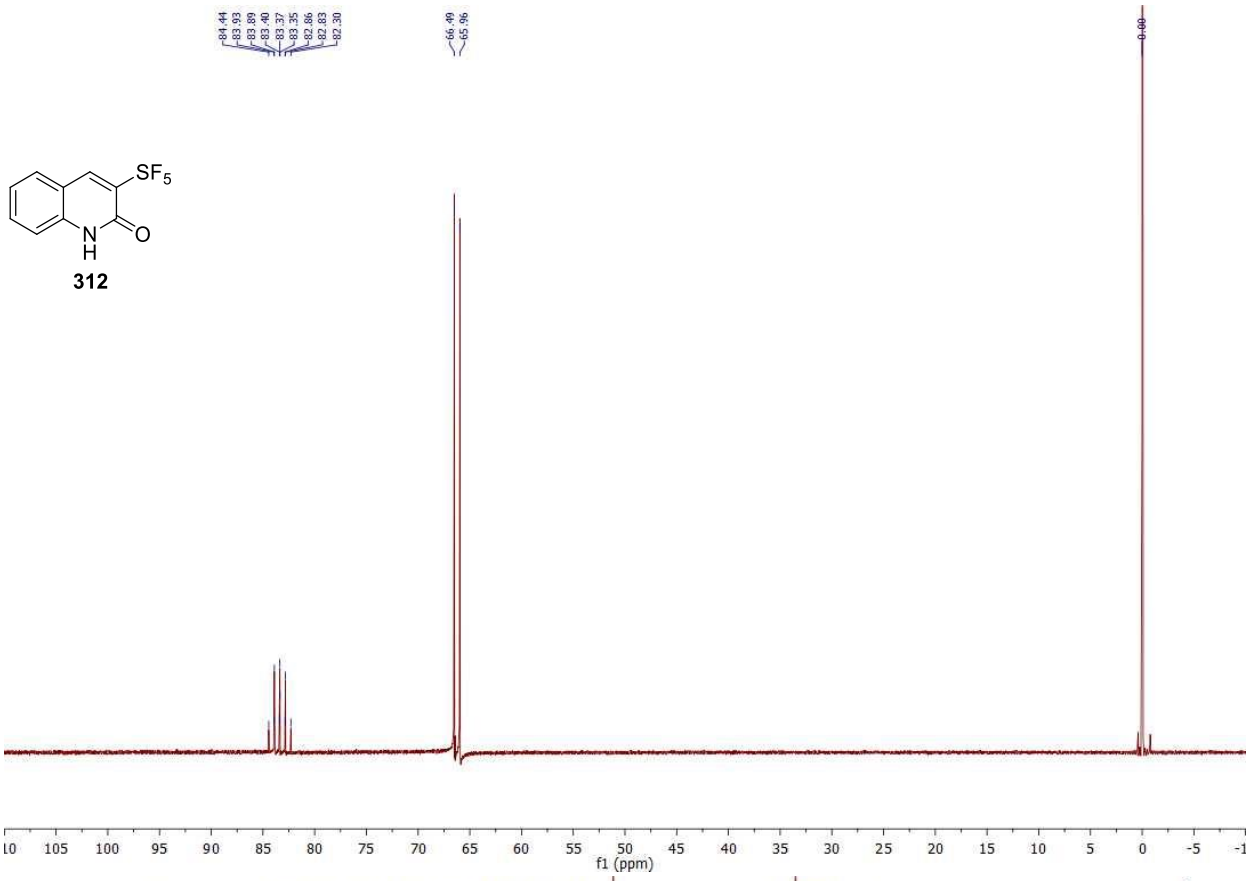

F5S
OH
Br

310

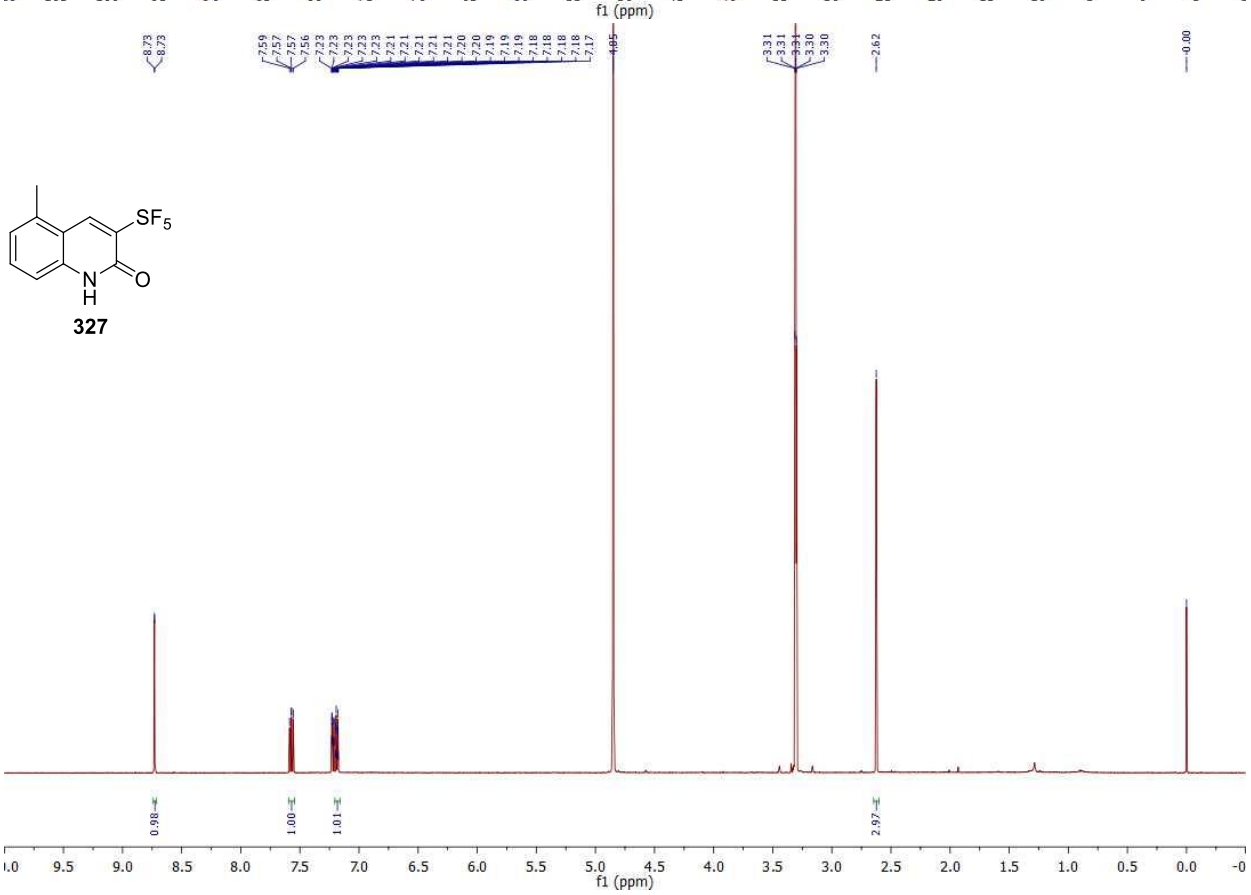
f1 (ppm)


8.76
7.86
7.86
7.85
7.84
7.71
7.70
7.70
7.69
7.39
7.39
7.38
7.38
7.37
7.37
7.37
7.37
7.37
7.36
7.35
7.34
7.34
7.34
7.33
7.33
4.86
3.32
3.31
3.31
3.31
3.30
0.00
SF5
N
H
O
312
1.00
1.00
1.00
0.98
1.00
f1 (ppm)

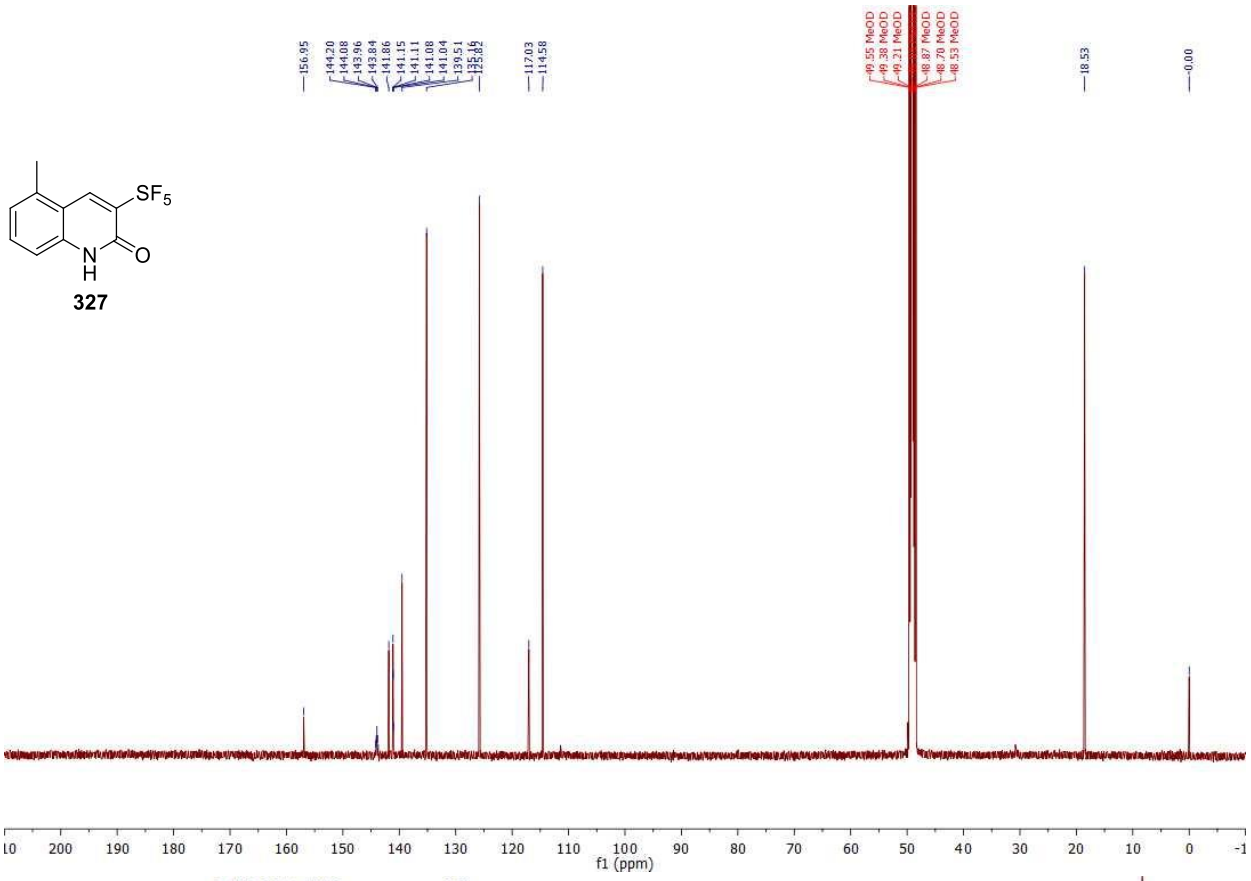

157.15
144.96
144.93
144.90
144.86
144.53
144.43
131.30
124.57
118.21
116.22
49.43 MeOD
49.28 MeOD
49.14 MeOD
48.86 MeOD
48.72 MeOD
48.57 MeOD
0.04
SF5
N
H
O
312
f1 (ppm)

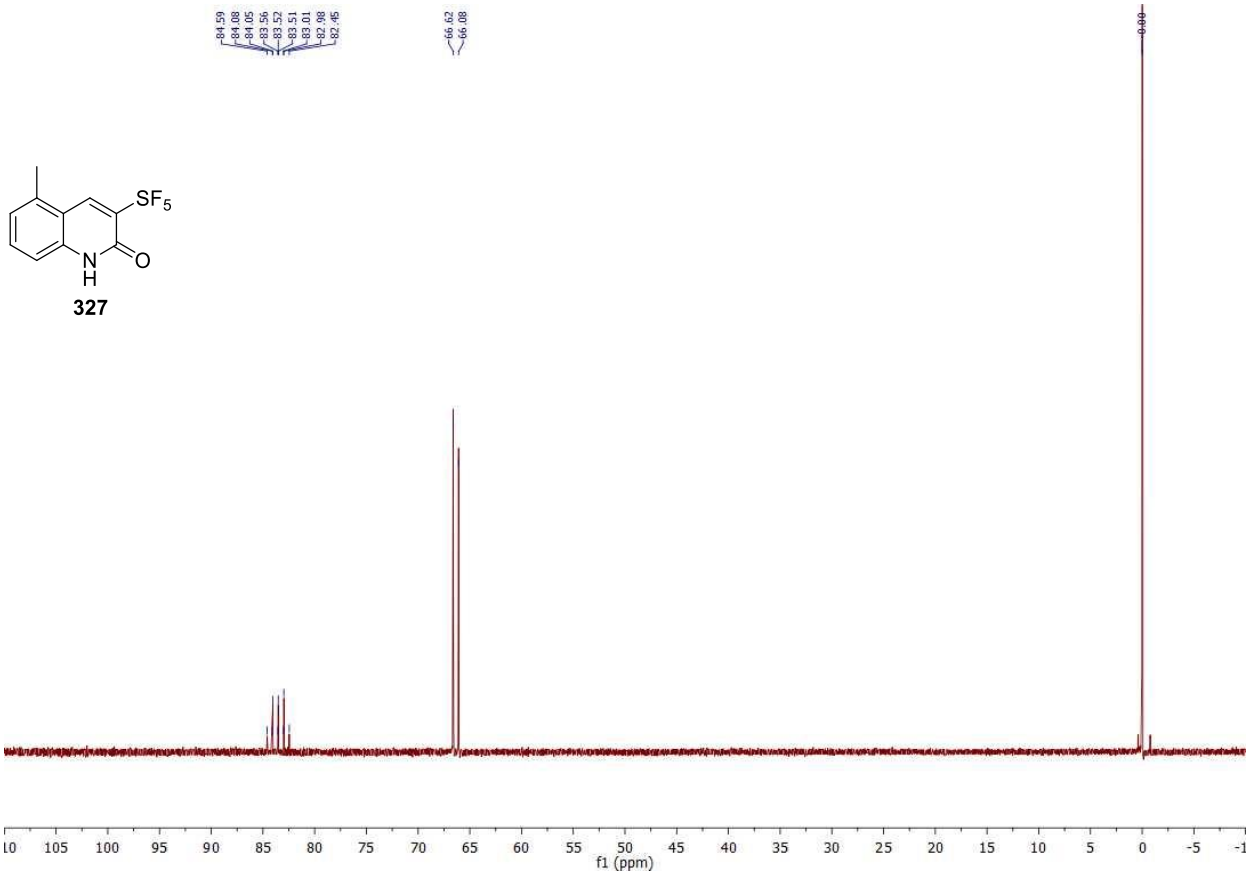

84.44
83.93
83.89
83.40
83.37
83.35
82.86
82.83
82.30
66.49
65.96
0.00
f1 (ppm)

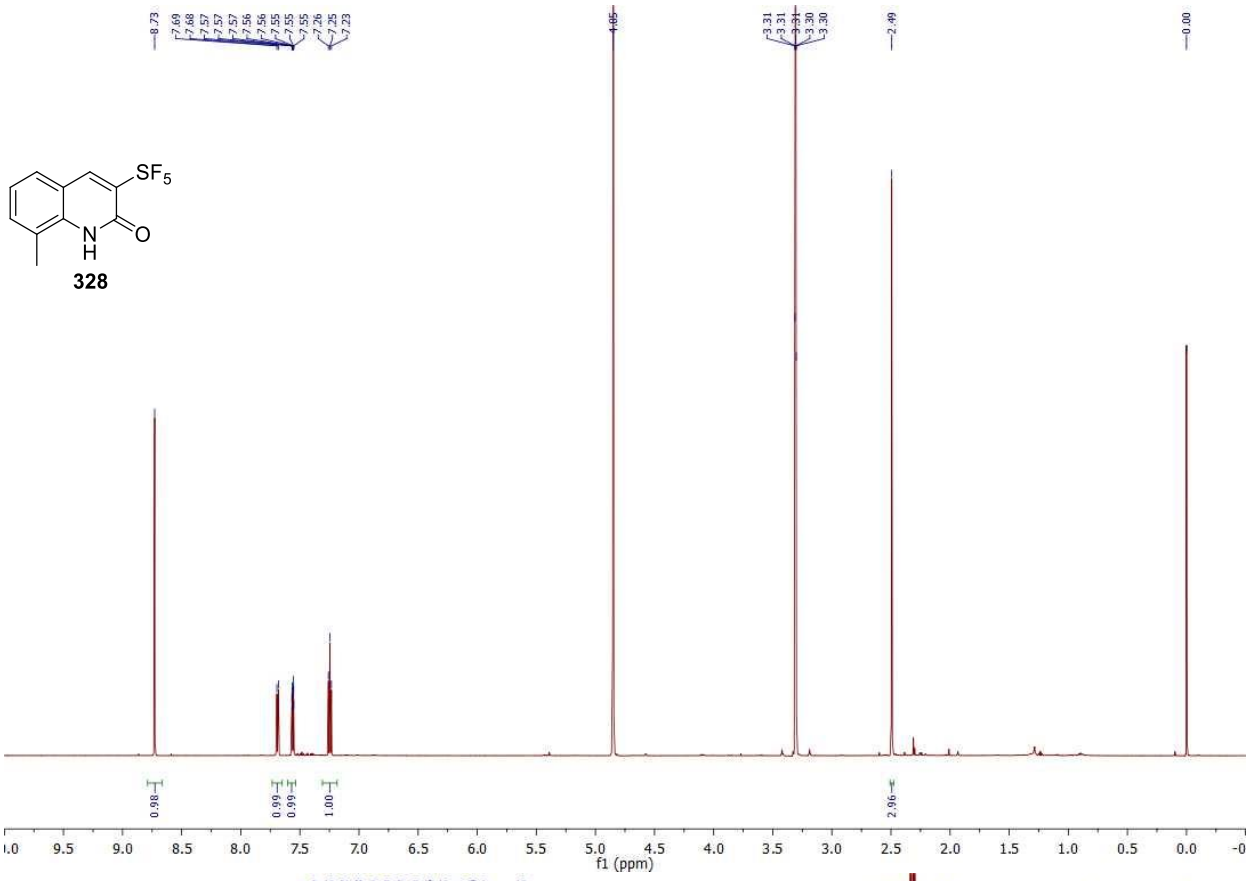
312


8.73
8.73
7.59
7.57
7.57
7.56
7.23
7.23
7.23
7.23
7.21
7.21
7.21
7.21
7.21
7.20
7.20
7.19
7.19
7.19
7.18
7.18
7.18
7.18
7.17
4.85
3.31
3.31
3.31
3.30
3.30
2.62
-0.00
0.98
1.00
1.01
2.97
f1 (ppm)

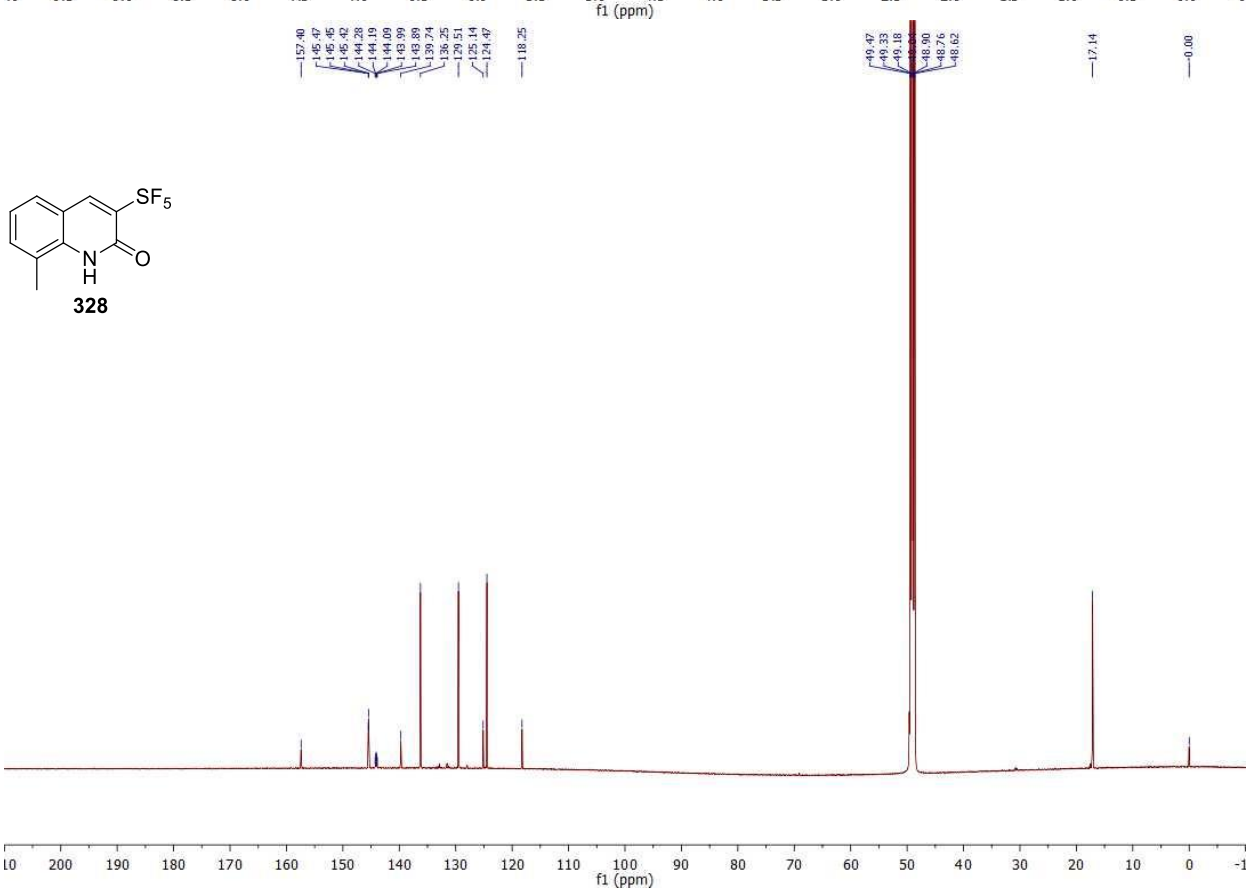
327


156.95
144.20
144.08
143.96
143.84
141.86
141.15
141.11
141.08
141.04
139.51
135.16
125.82
117.03
114.58
49.55 MeOD
49.38 MeOD
49.21 MeOD
48.87 MeOD
48.70 MeOD
48.53 MeOD
18.53
0.00
SF5
N
H
O
327
f1 (ppm)

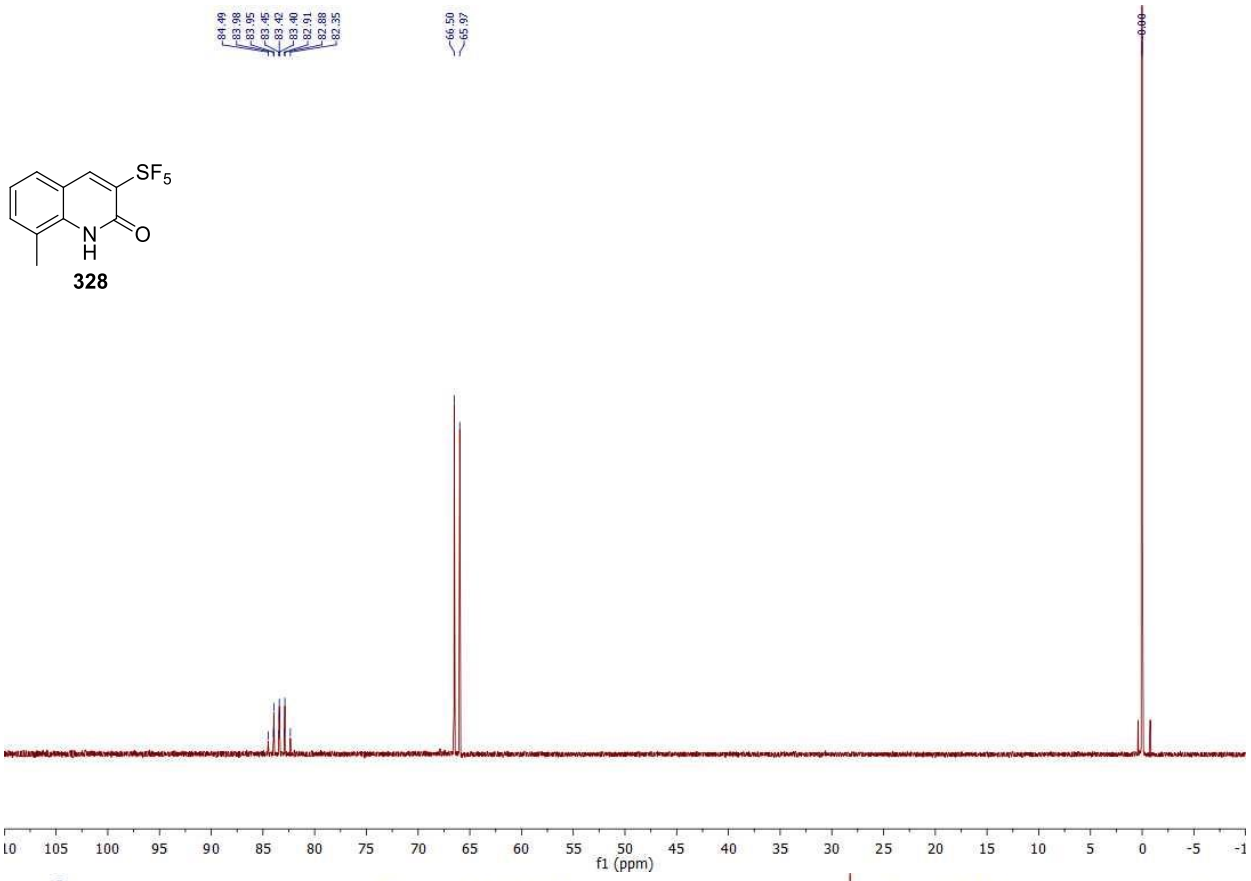

84.59
84.08
84.05
83.56
83.52
83.51
83.01
82.98
82.45
66.62
66.08
0.00
SF5
N
H
O
327
f1 (ppm)


8.73
7.69
7.68
7.57
7.57
7.57
7.57
7.56
7.56
7.55
7.55
7.55
7.26
7.25
7.23
1.85
3.31
3.31
3.31
3.30
3.30
2.49
0.00
SF5
N
H
O
0.98
0.99
0.99
1.00
2.96
f1 (ppm)

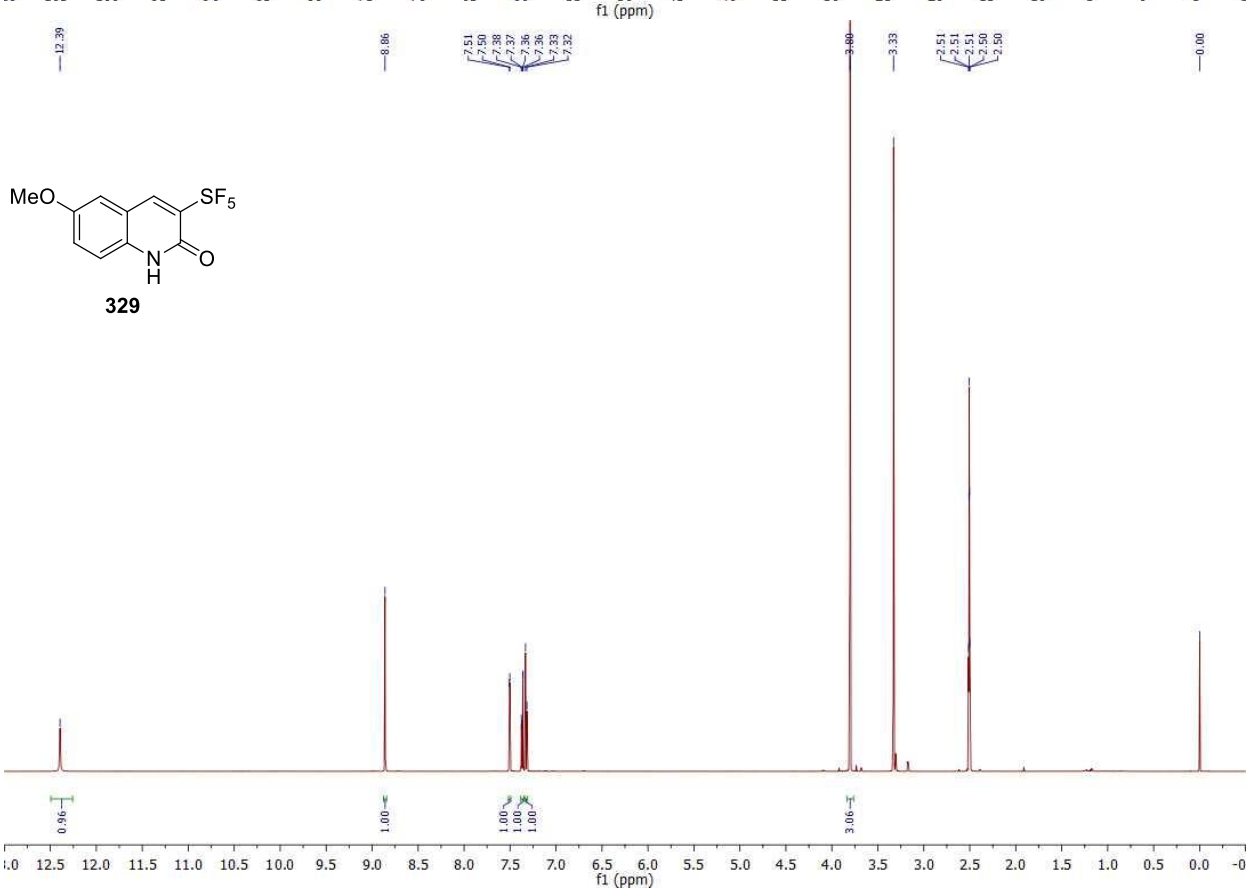
328


157.40
145.47
145.45
145.42
144.28
144.19
144.09
143.99
143.89
139.74
136.25
129.51
125.14
124.47
118.25
49.47
49.33
49.18
48.90
48.76
48.62
17.14
0.00
SF5
N
H
O
f1 (ppm)

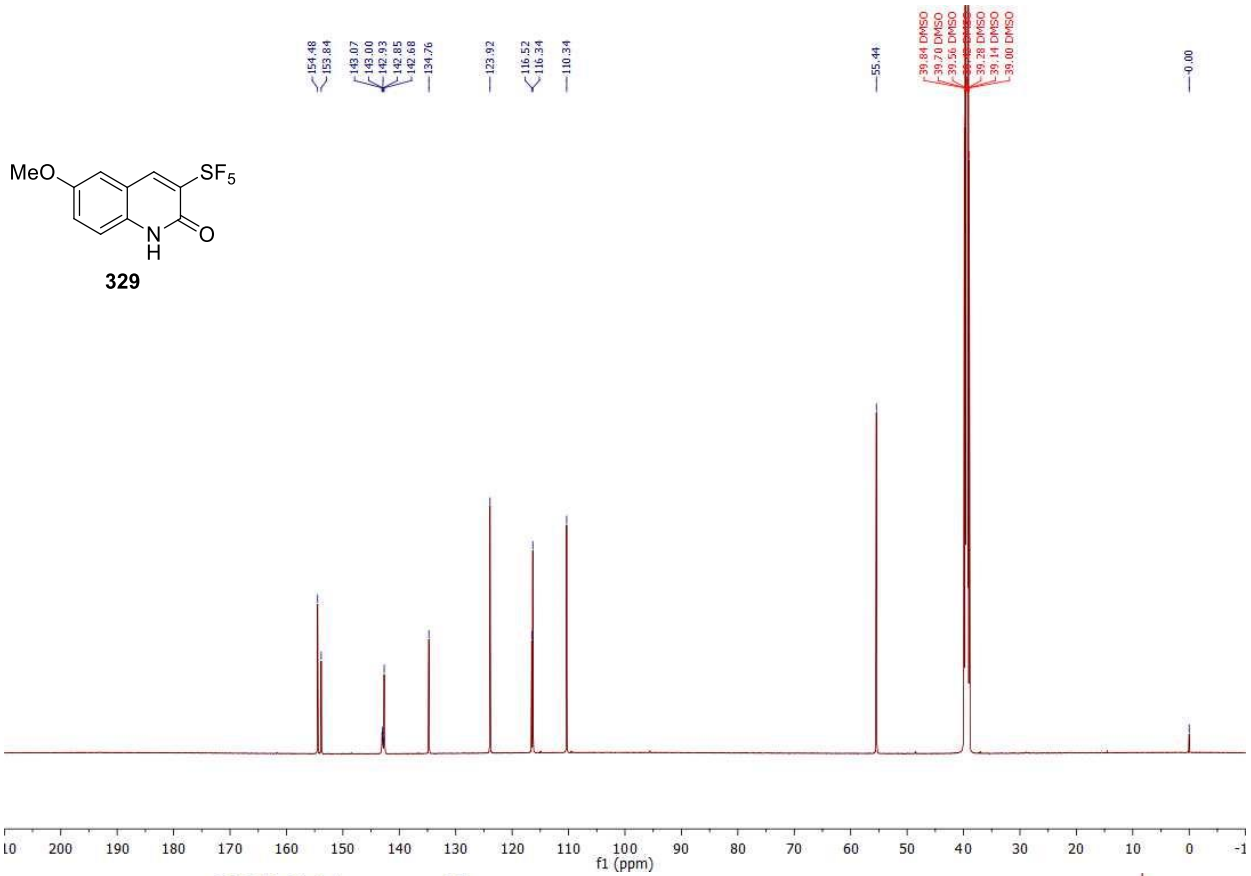
328


84.49
83.98
83.95
83.45
83.42
83.40
82.91
82.88
82.35
66.50
65.97
0.00
SF5
N
H
O
f1 (ppm)

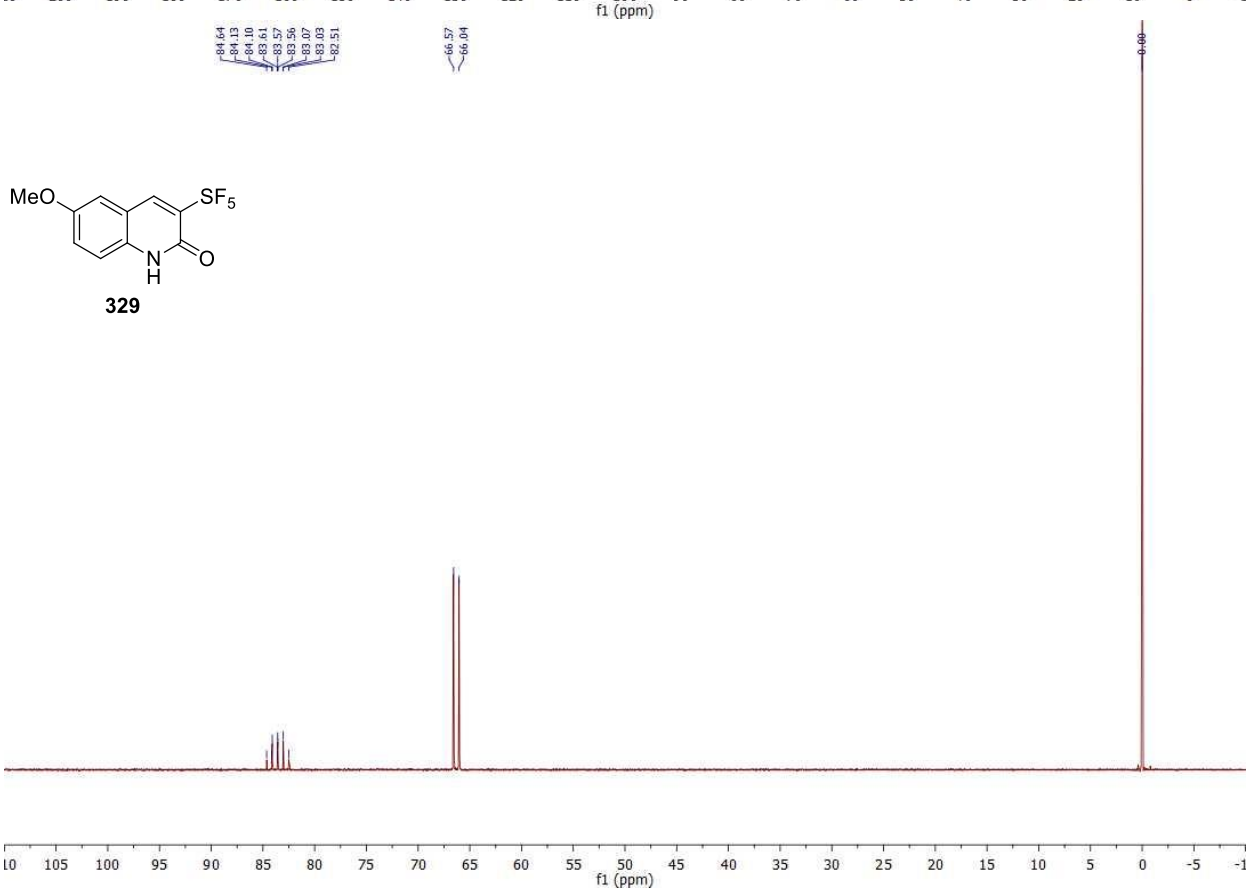
328


12.39
8.86
7.51
7.50
7.38
7.37
7.36
7.36
7.33
7.32
3.80
3.33
2.51
2.51
2.51
2.50
2.50
0.00
MeO
SF5
N
H
O
0.96
1.00
1.00
1.00
1.00
3.06
f1 (ppm)

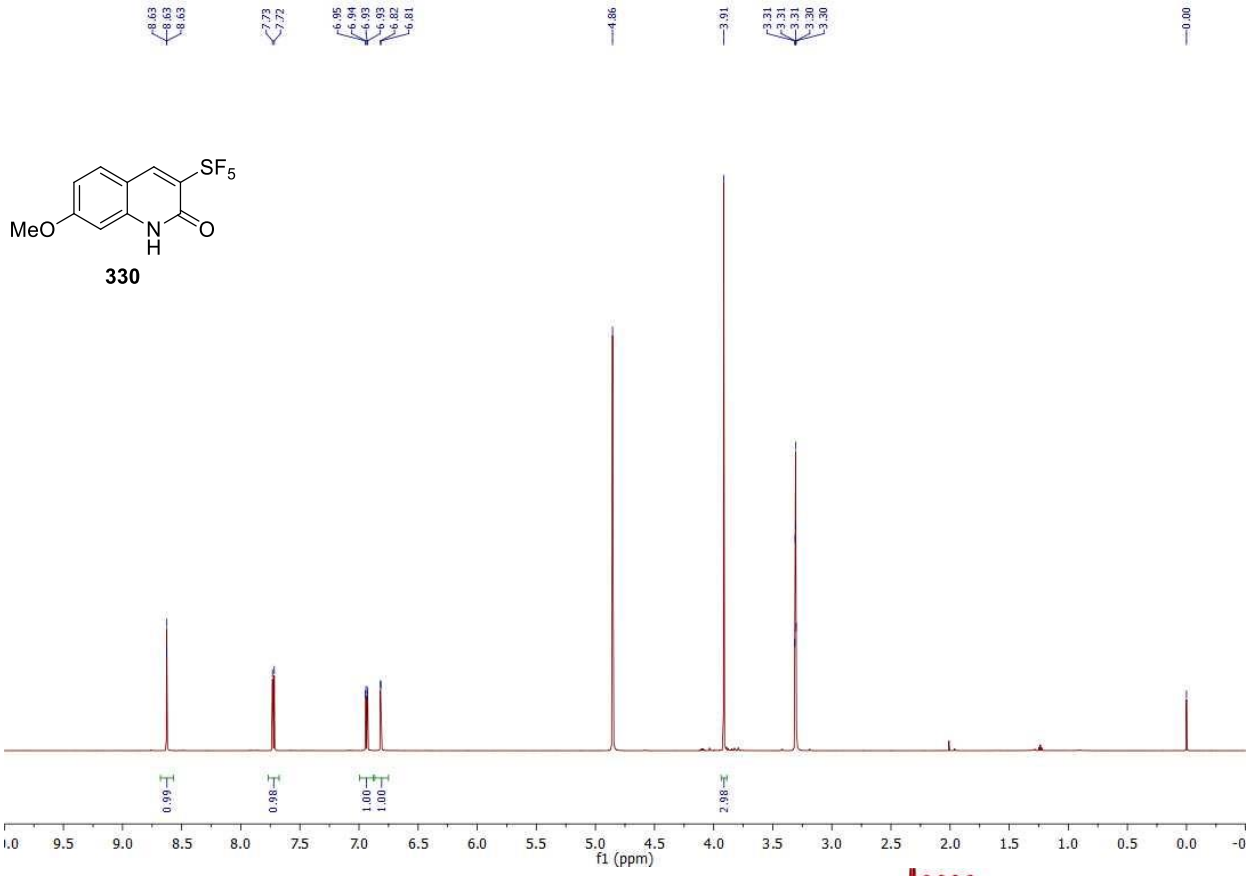
329

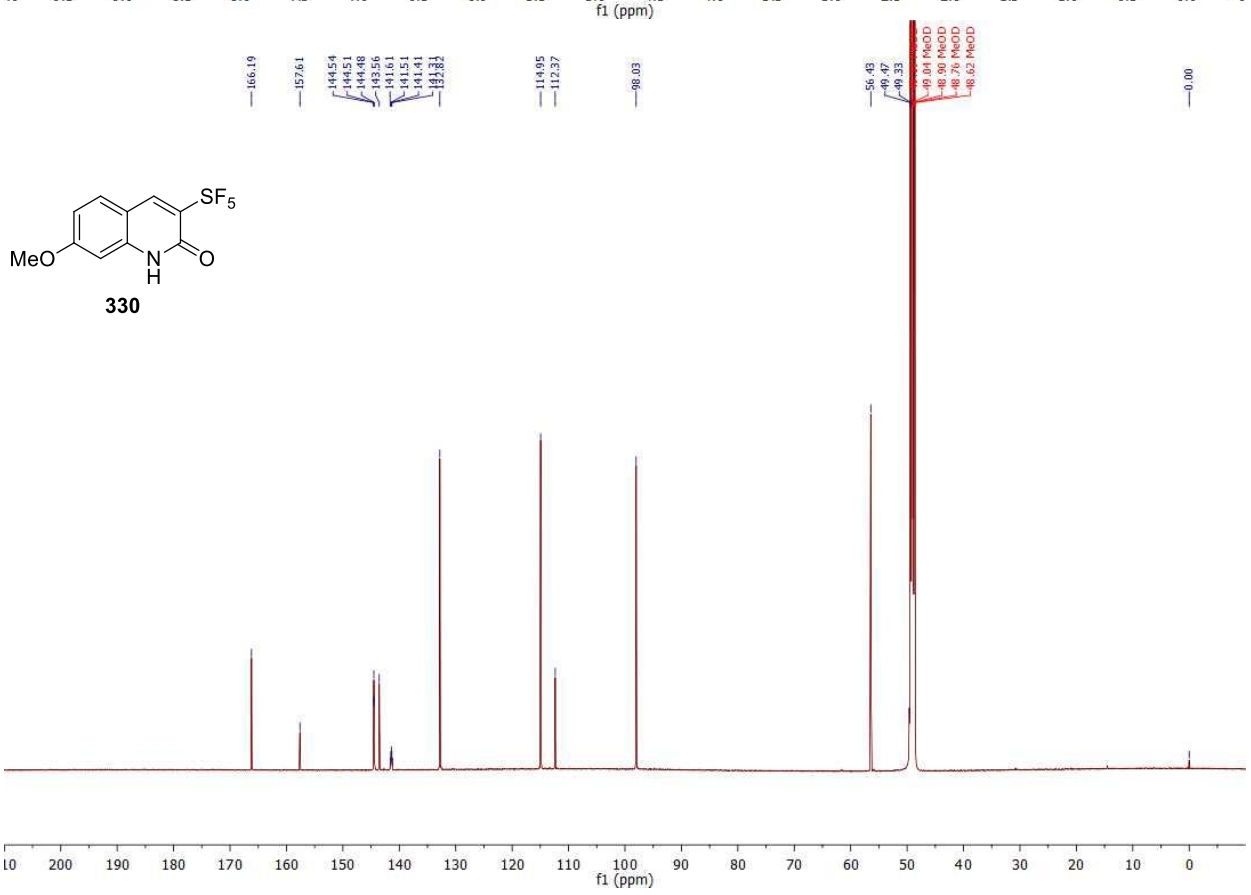

154.48
153.84
143.07
143.00
142.93
142.85
142.68
134.76
123.92
116.52
116.34
110.34
55.44
39.84 DMSO
39.70 DMSO
39.56 DMSO
39.28 DMSO
39.14 DMSO
39.00 DMSO
0.00
MeO
SF5
N
H
O
f1 (ppm)

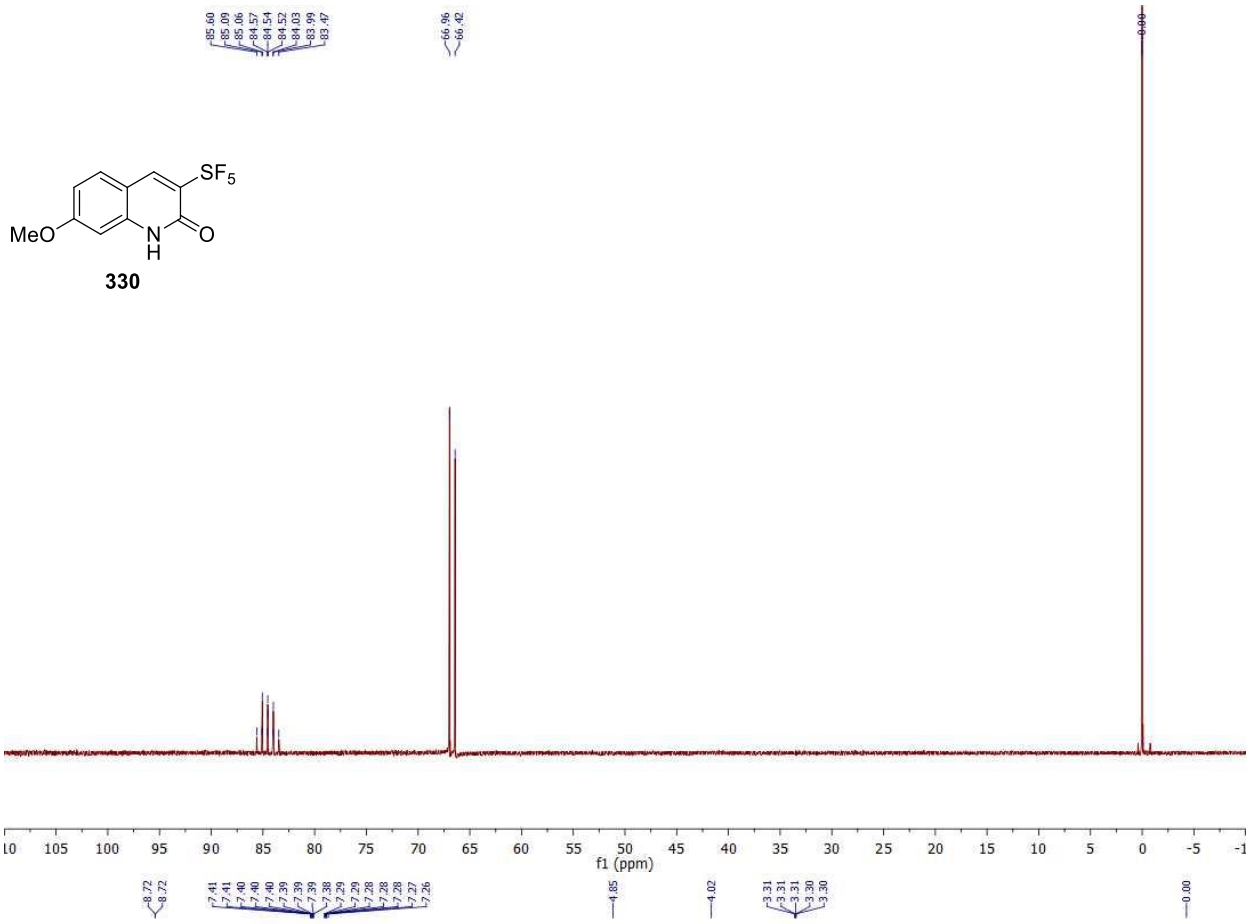
329


84.64
84.13
84.10
83.61
83.57
83.56
83.07
83.03
82.51
66.57
66.04
0.00
MeO
SF5
N
H
O
f1 (ppm)

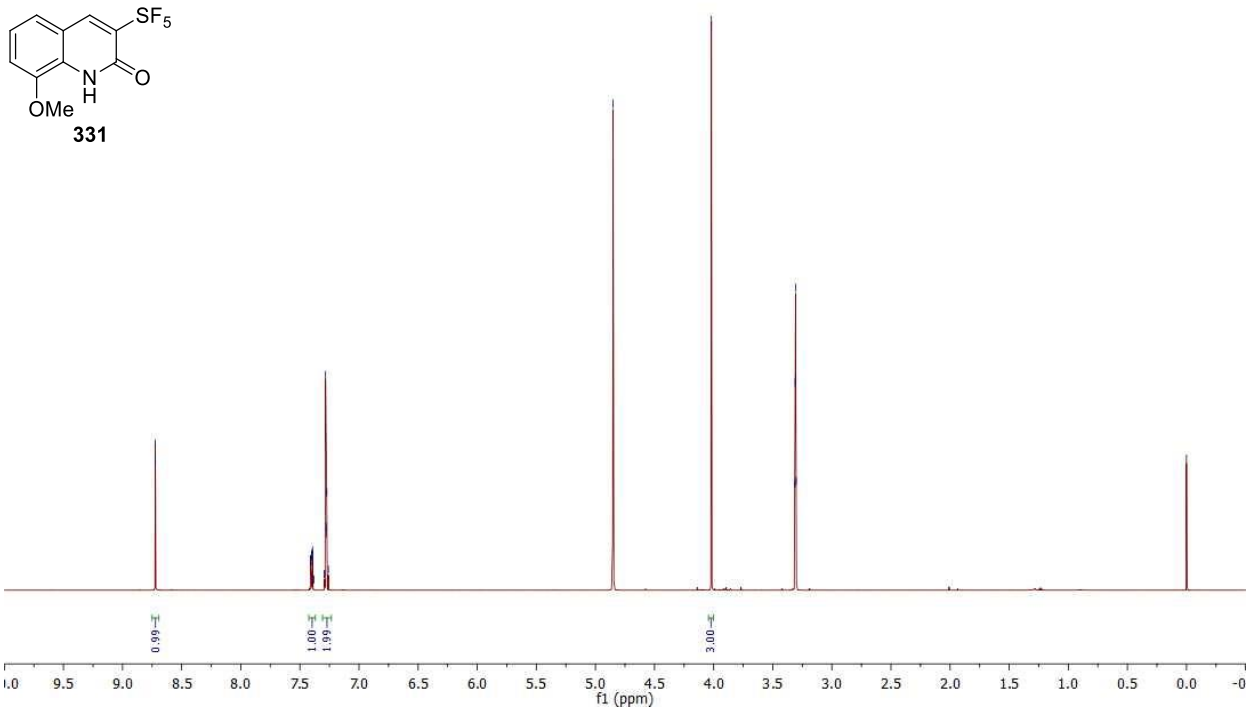
329


8.63
8.63
8.63
7.73
7.72
6.95
6.94
6.93
6.93
6.82
6.81
4.86
3.91
3.31
3.31
3.31
3.30
3.30
0.00
SF5
MeO
N
H
O
330
0.99
0.98
1.00
1.00
2.98
f1 (ppm)

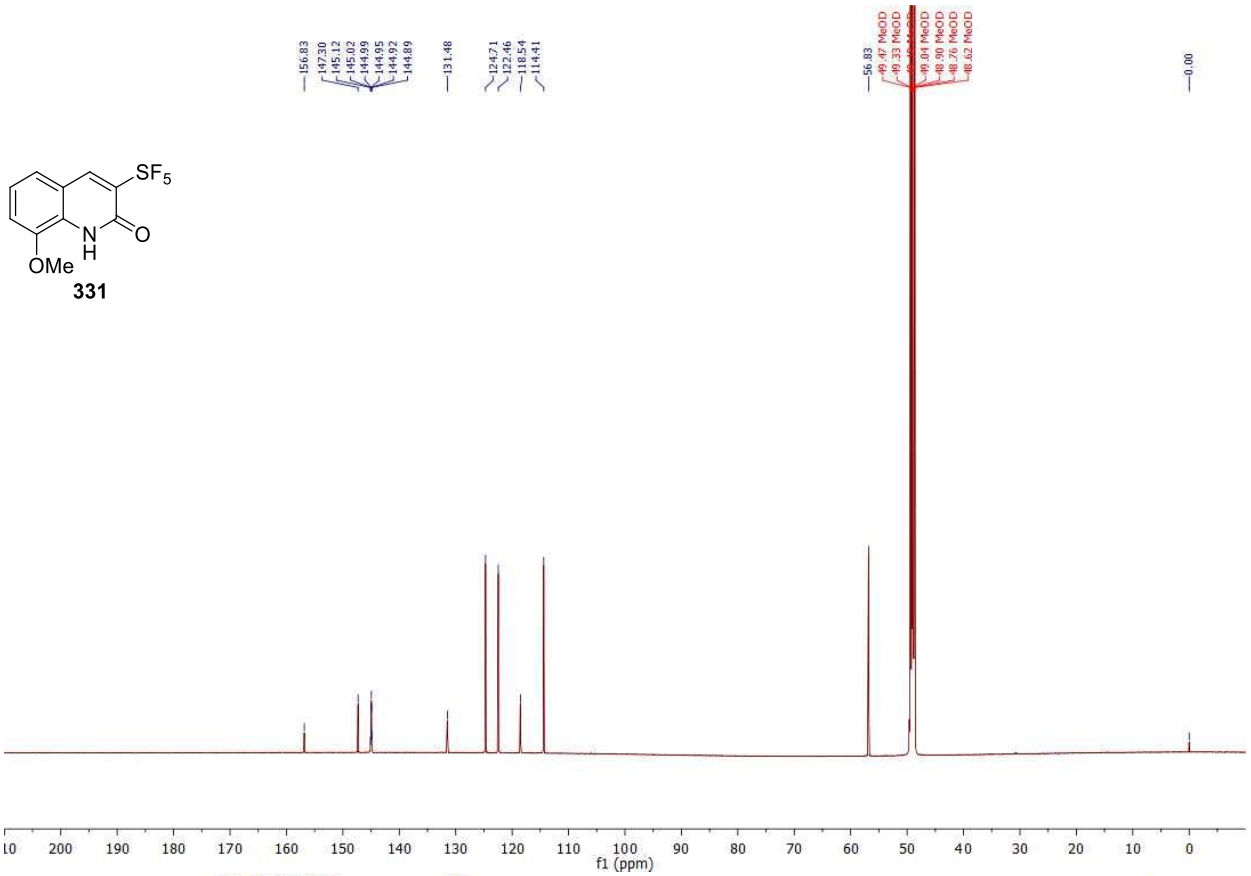

166.19
157.61
144.54
144.51
144.48
143.56
141.61
141.51
141.41
141.31
132.82
114.95
112.37
98.03
56.43
49.47
49.33
49.04 MeOD
48.90 MeOD
48.76 MeOD
48.62 MeOD
0.00
SF5
MeO
N
H
O
330
f1 (ppm)

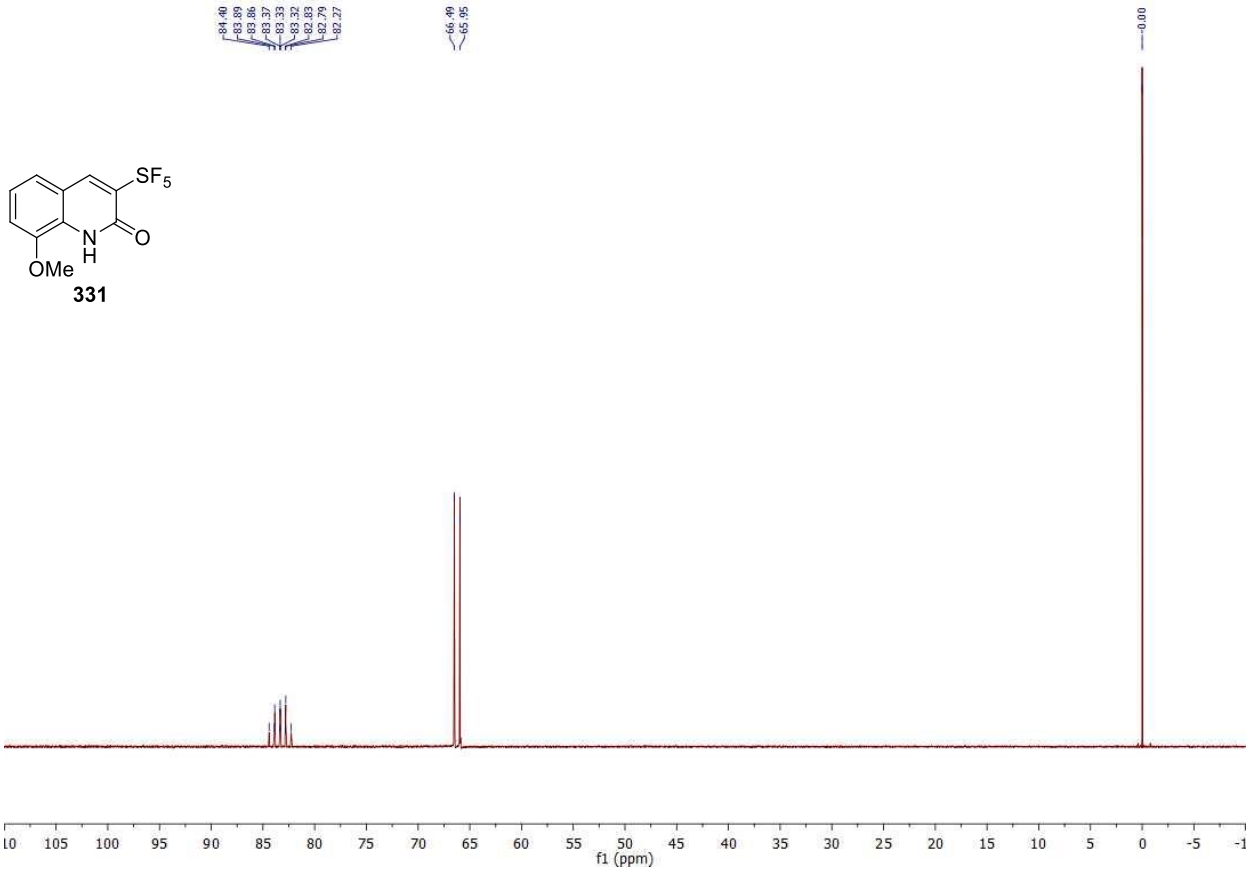

85.60
85.09
85.06
84.57
84.54
84.52
84.03
83.99
83.47
66.96
66.42
0.00
SF5
MeO
N
H
O
f1 (ppm)
8.72
8.72
7.41
7.41
7.40
7.40
7.40
7.39
7.39
7.39
7.38
7.29
7.29
7.28
7.28
7.28
7.27
7.26
4.85
4.02
3.31
3.31
3.31
3.30
3.30
0.00

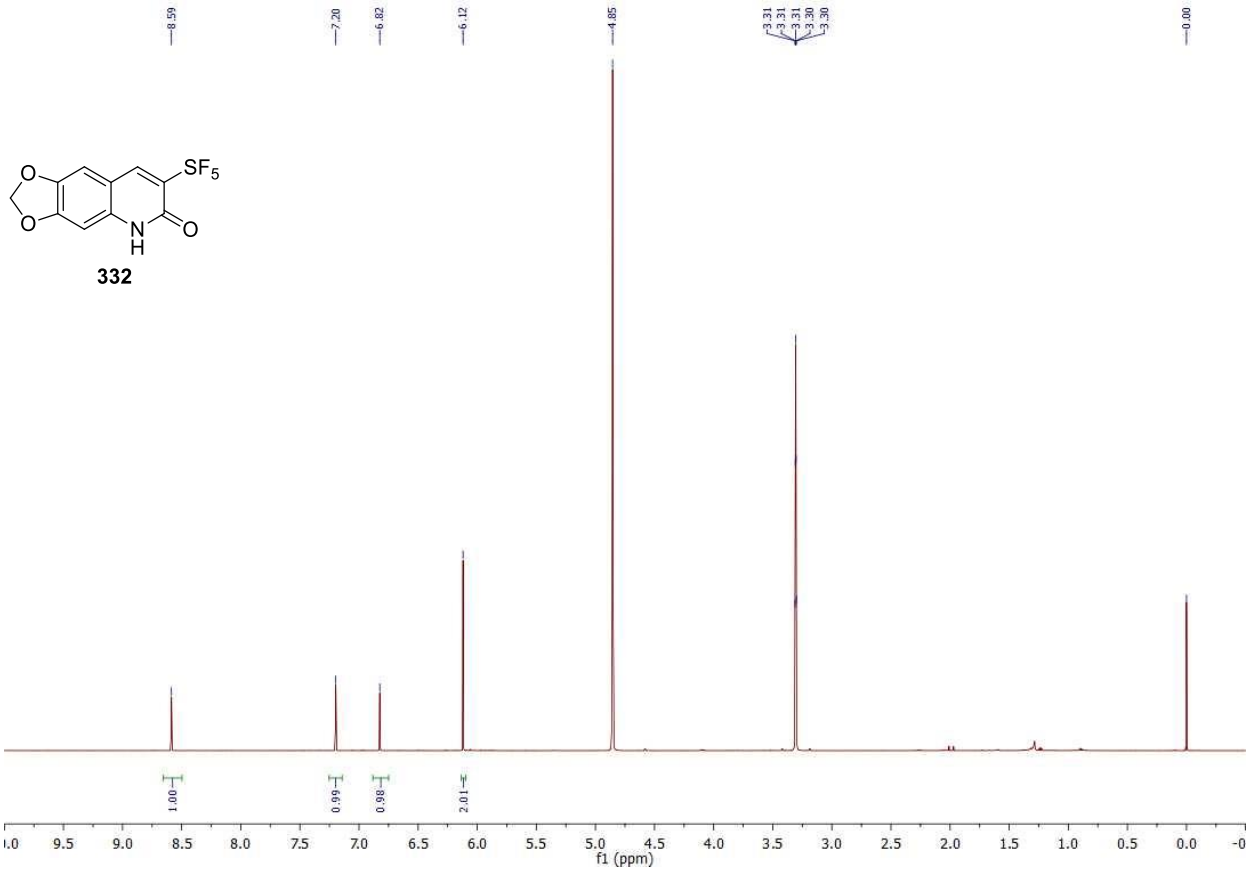
330

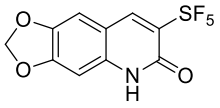

SF5
N
H
O
OMe
f1 (ppm)
0.99
1.00
1.99
3.00

331


156.83
147.30
145.12
145.02
144.99
144.95
144.92
144.89
131.48
124.71
122.46
118.54
114.41
56.83
49.47 MeOD
49.33 MeOD
49.19 MeOD
49.04 MeOD
48.90 MeOD
48.76 MeOD
48.62 MeOD
0.00
SF5
N
H
O
OMe
331
f1 (ppm)


84.40
83.89
83.86
83.37
83.33
83.32
82.83
82.79
82.27
66.49
65.95
0.00
SF5
N
H
O
OMe
331
f1 (ppm)


8.59
7.20
6.82
6.12
4.85
3.31
3.31
3.31
3.30
3.30
0.00
1.00
0.99
0.98
2.01
f1 (ppm)

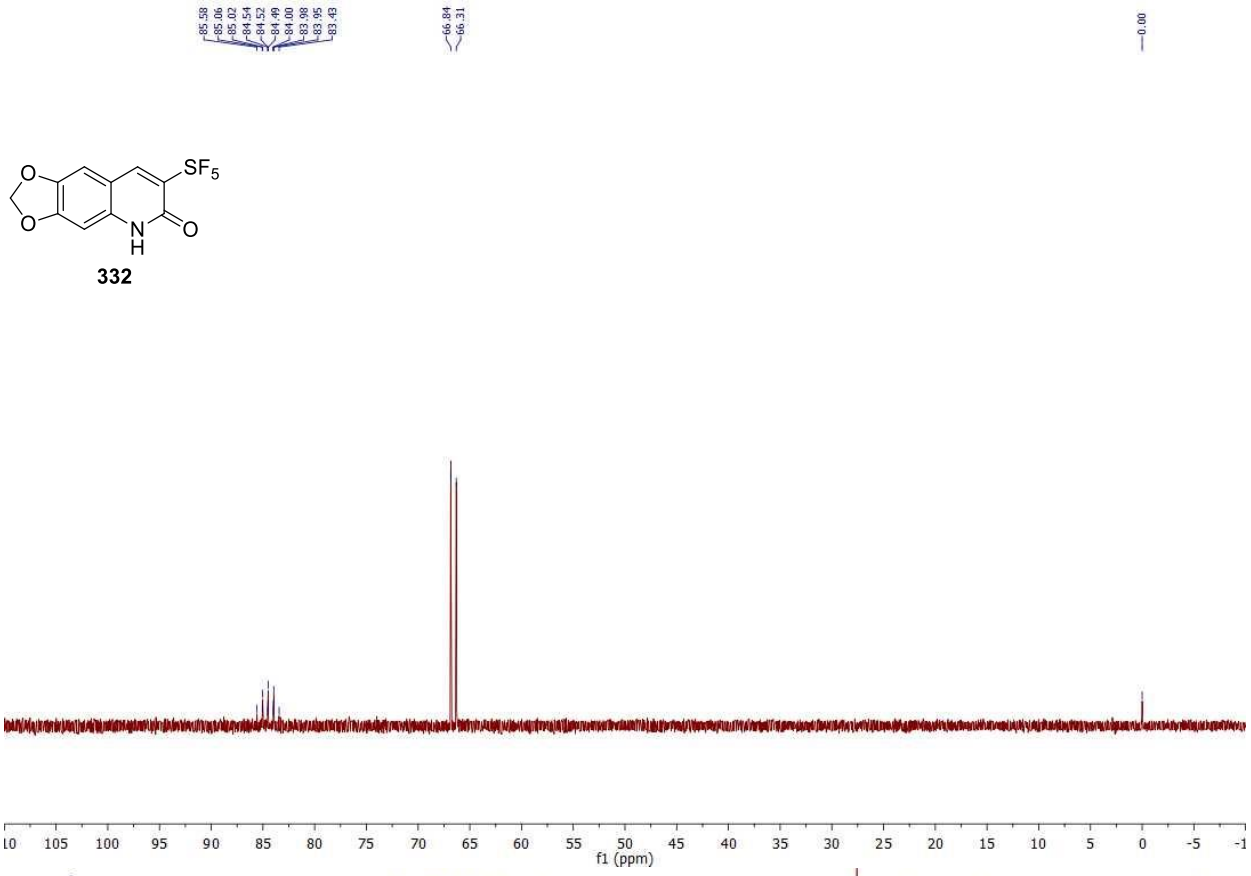

SF5
O
O
N
H
O

332

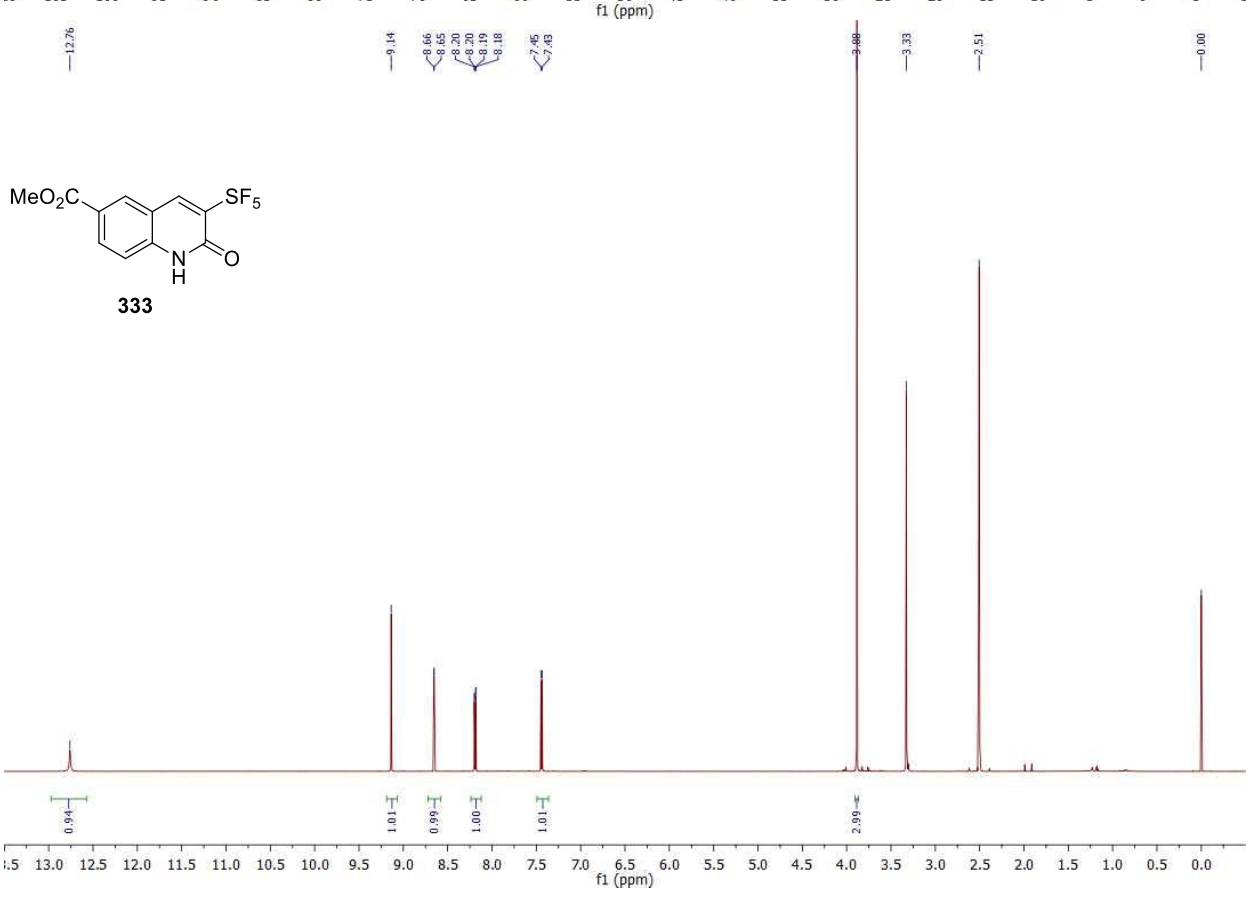
157.12
155.63
146.84
144.04
141.84
141.74
141.65
141.55
141.44
139.68
112.95
107.13
104.24
95.71
49.47 MeOD
49.33 MeOD
49.18 MeOD
48.90 MeOD
48.76 MeOD
48.62 MeOD
0.00
f1 (ppm)

SF5
O
O
N
H
O

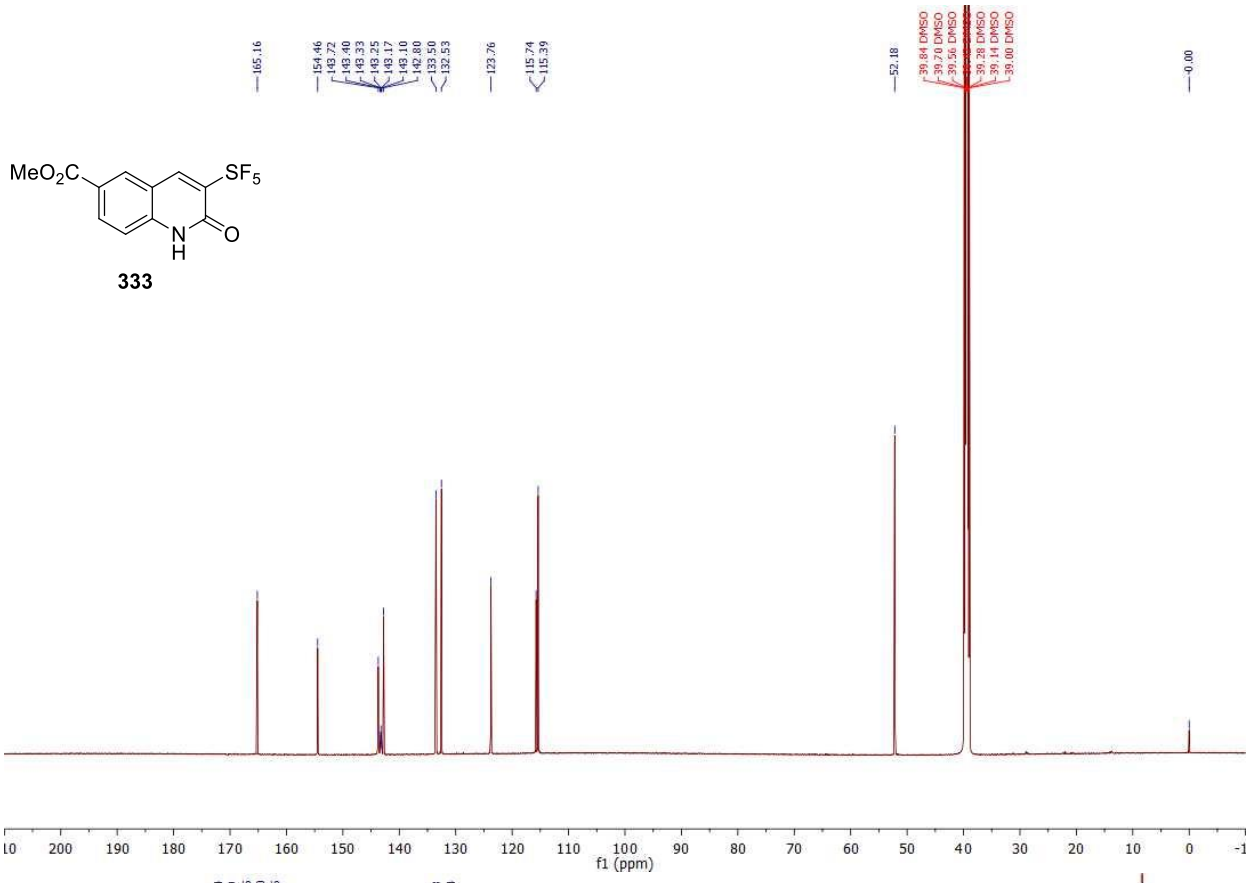
332


85.58
85.06
85.02
84.54
84.52
84.49
84.00
83.98
83.95
83.43
66.84
66.31
0.00
O
O
N
H
O
SF5
f1 (ppm)

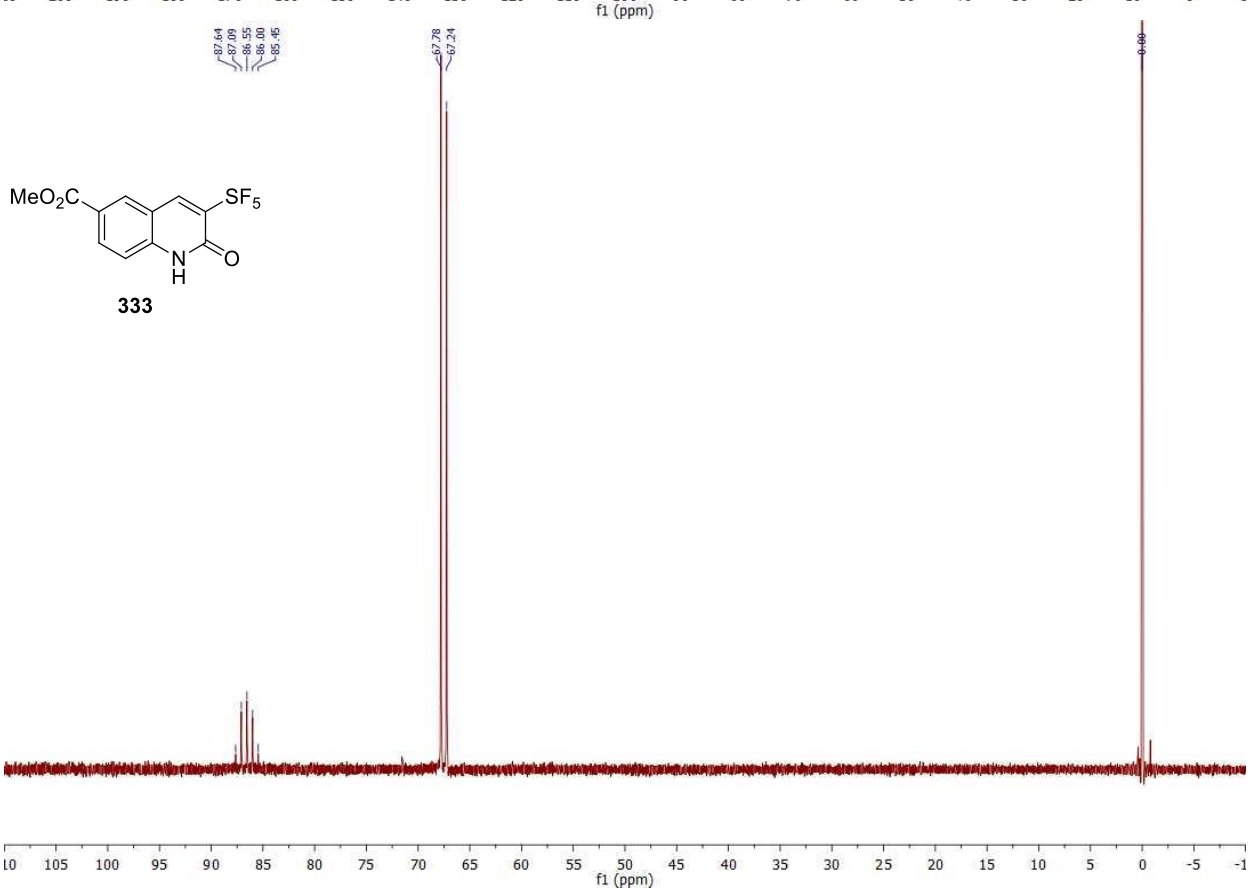
332


12.76
9.14
8.66
8.65
8.20
8.20
8.19
8.18
7.45
7.43
3.88
3.33
2.51
0.00
MeO2C
SF5
N
H
O
0.94
1.01
0.99
1.00
1.01
2.99
f1 (ppm)

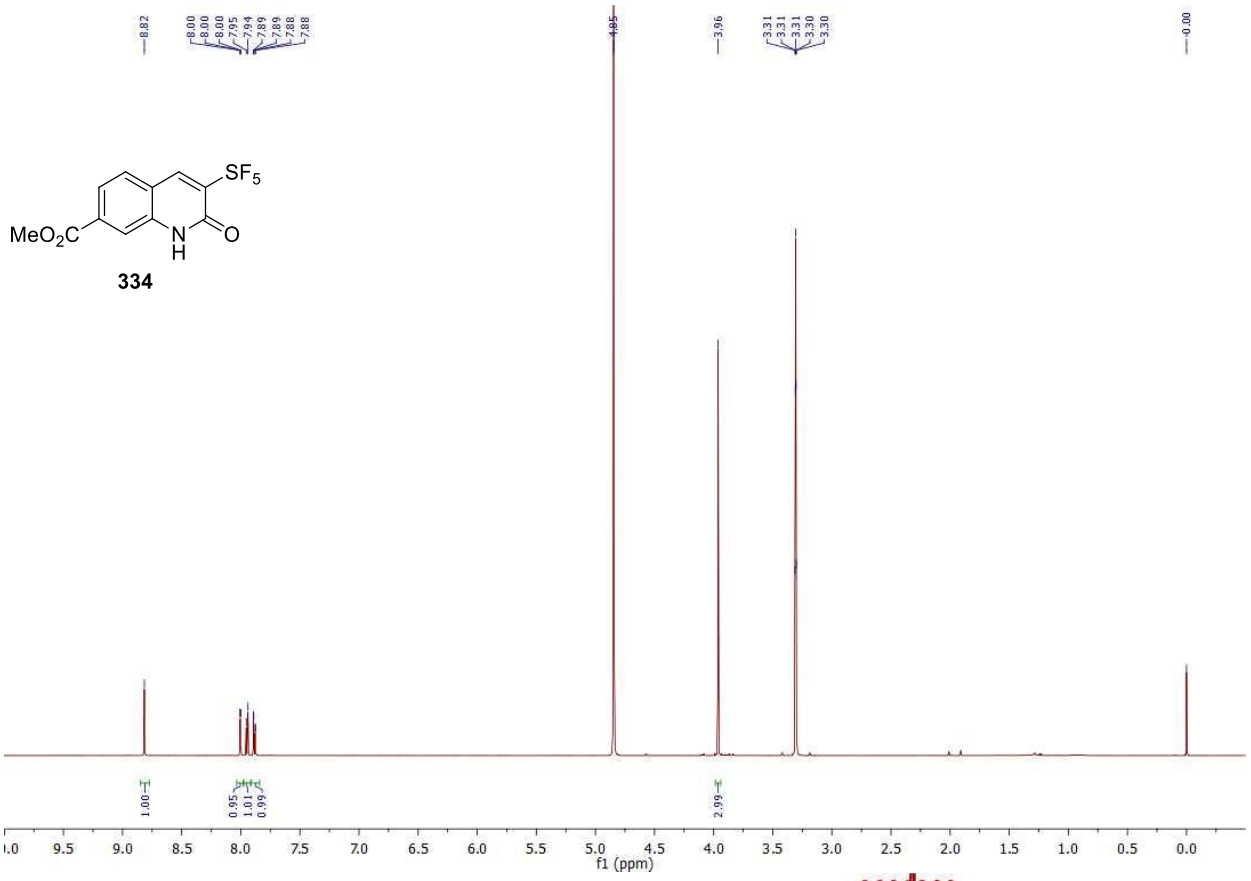
333


165.16
154.46
143.72
143.40
143.33
143.25
143.17
143.10
142.80
133.50
132.53
123.76
115.74
115.39
52.18
39.84 DMSO
39.70 DMSO
39.56 DMSO
39.28 DMSO
39.14 DMSO
39.00 DMSO
0.00
MeO2C
SF5
N
H
O
f1 (ppm)

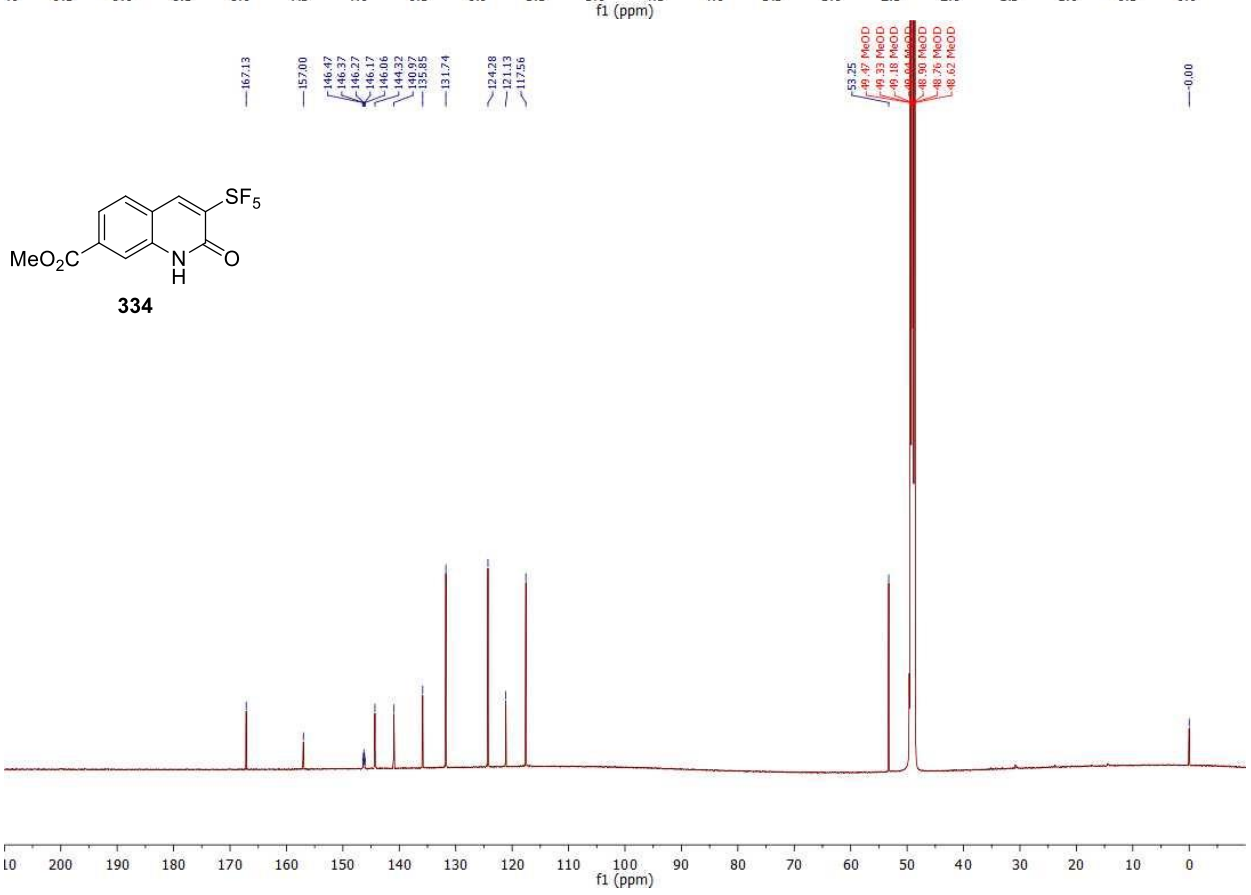
333


87.64
87.09
86.55
86.00
85.45
67.78
67.24
0.00
MeO2C
SF5
N
H
O
f1 (ppm)

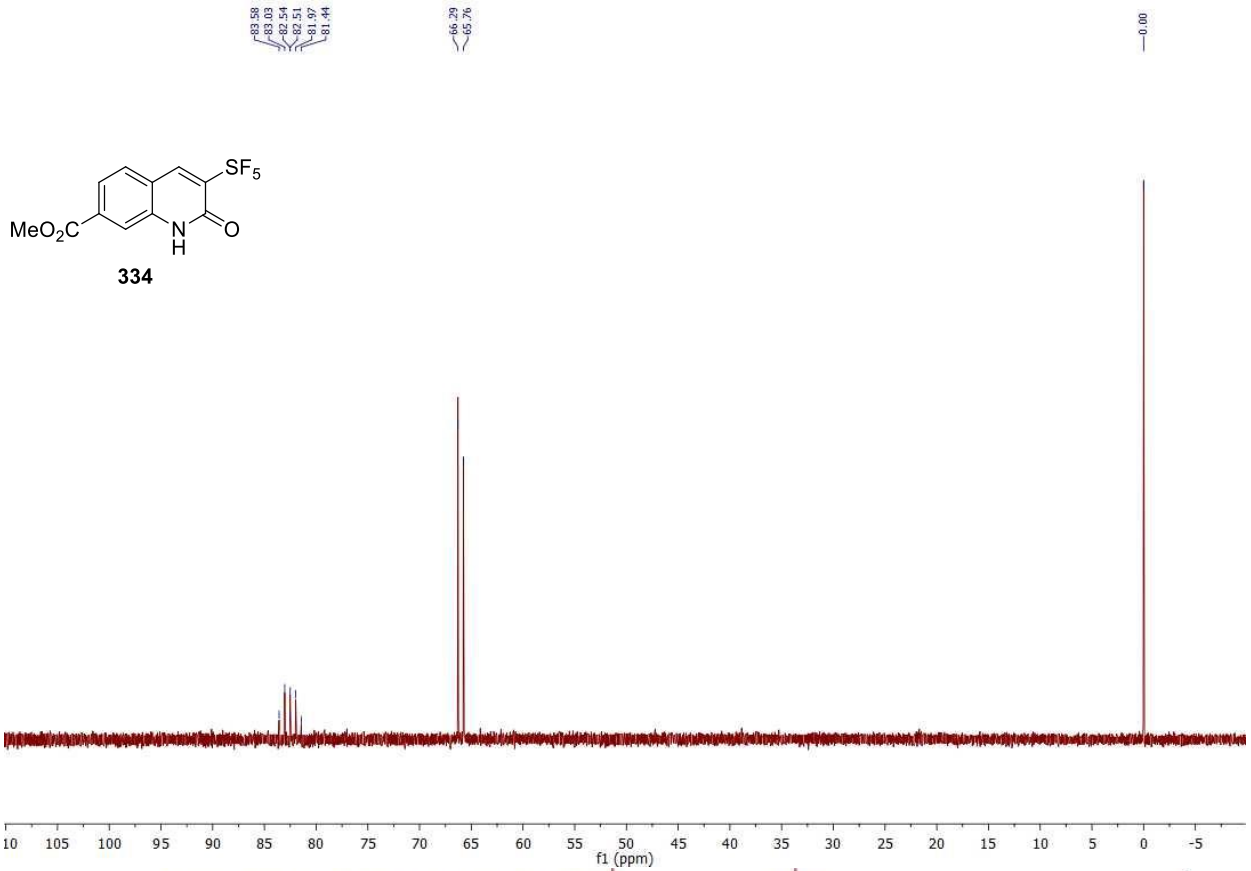
333


8.82
8.00
8.00
8.00
7.95
7.94
7.89
7.89
7.88
7.88
4.05
3.96
3.31
3.31
3.31
3.30
3.30
0.00
SF5
MeO2C
N
H
O
1.00
0.95
1.01
0.99
2.99
f1 (ppm)

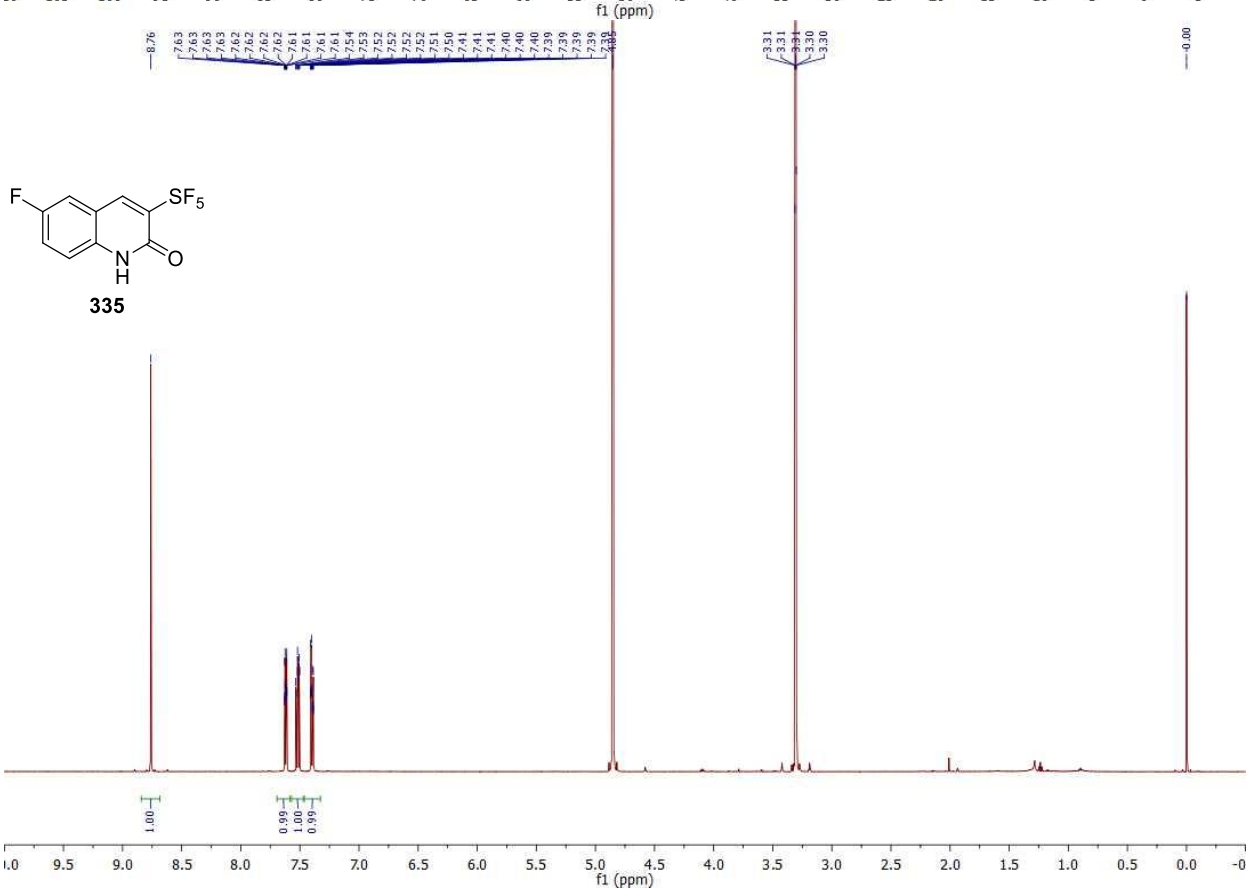
334


167.13
157.00
146.47
146.37
146.27
146.17
146.06
144.32
140.97
135.85
131.74
124.28
121.13
117.56
53.25
49.47 MeOD
49.33 MeOD
49.18 MeOD
48.90 MeOD
48.76 MeOD
48.62 MeOD
0.00
SF5
MeO2C
N
H
O
f1 (ppm)

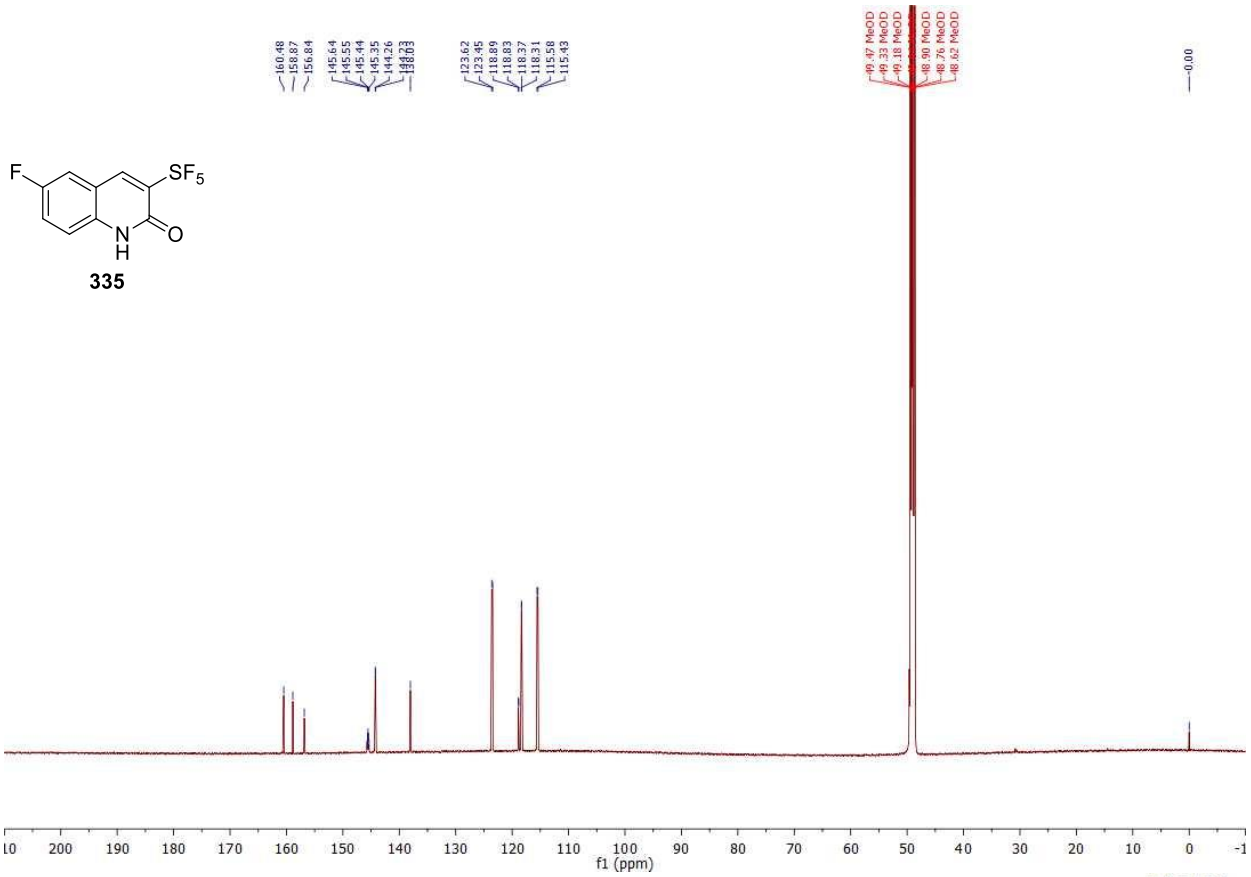
334

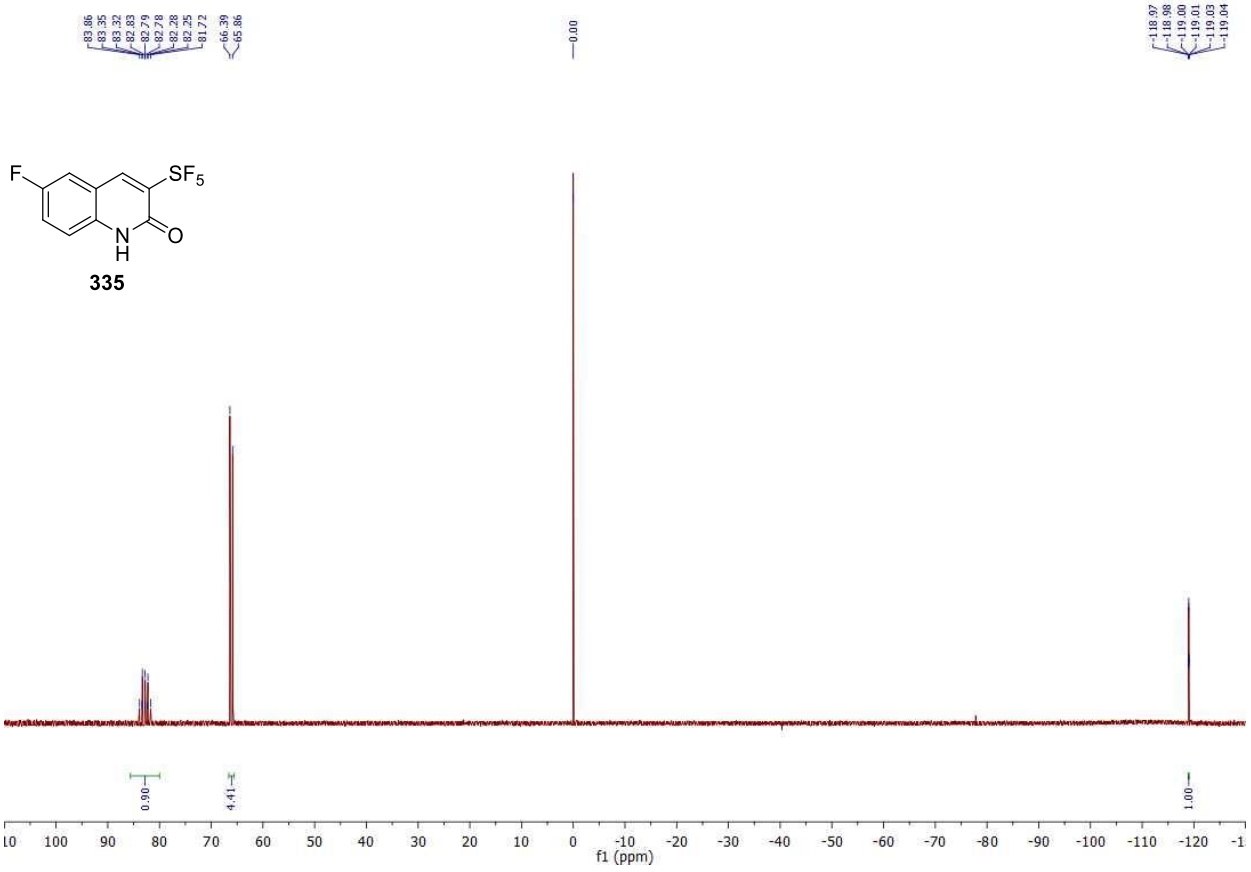

83.58
83.03
82.54
82.51
81.97
81.44
66.29
65.76
0.00
SF5
MeO2C
N
H
O
f1 (ppm)

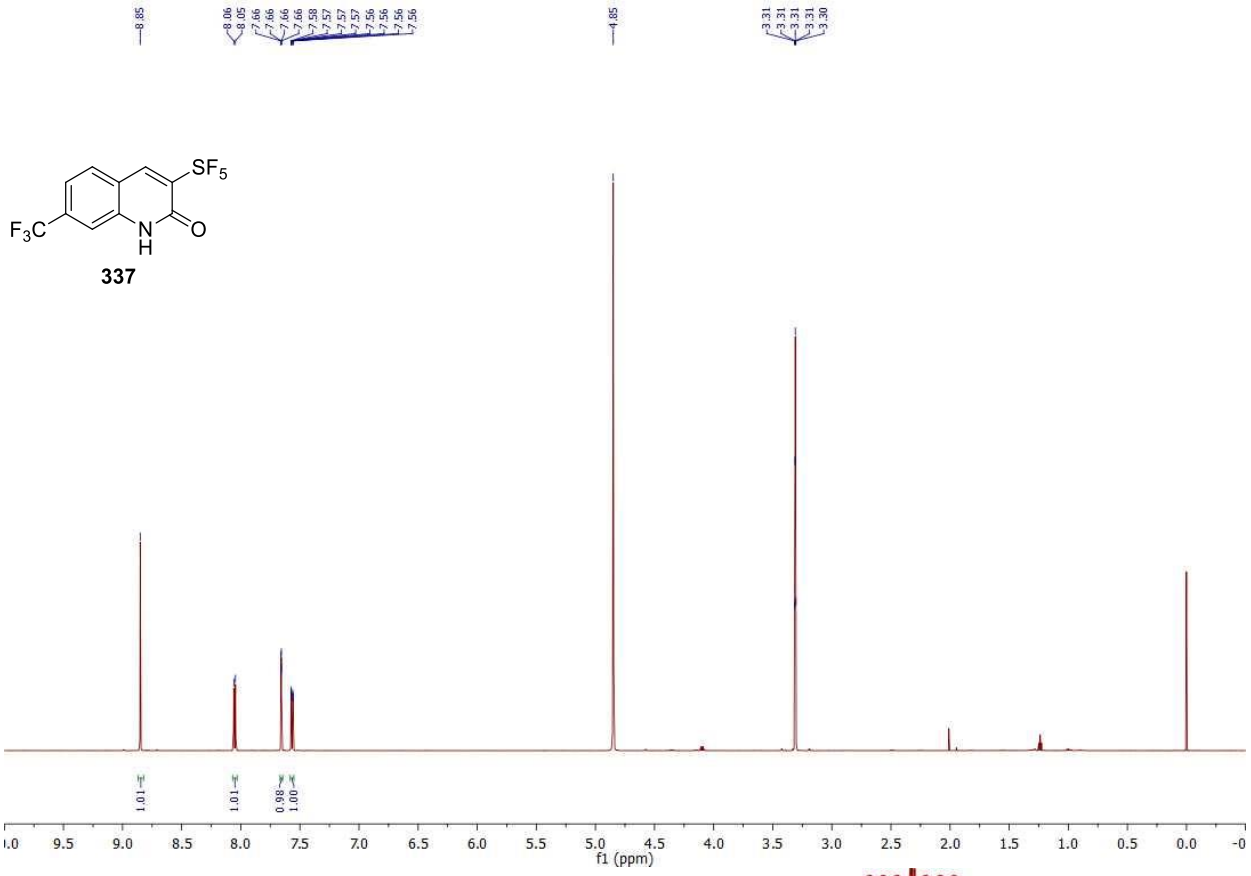
334

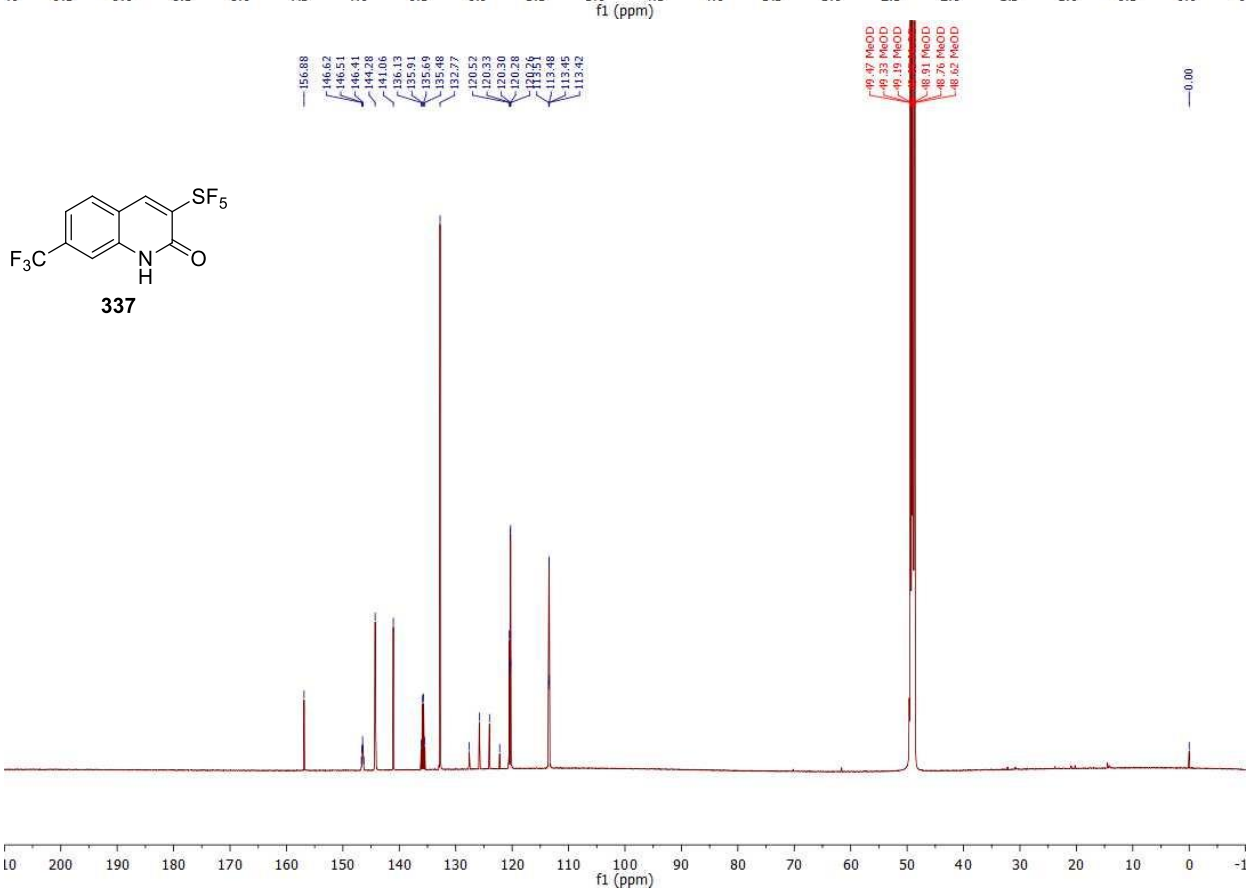

8.76
7.63
7.62
7.61
7.54
7.53
7.52
7.51
7.50
7.41
7.40
7.39
7.38
3.31
3.30
0.00
F
SF5
N
H
O
1.00
0.99
1.00
0.99
f1 (ppm)

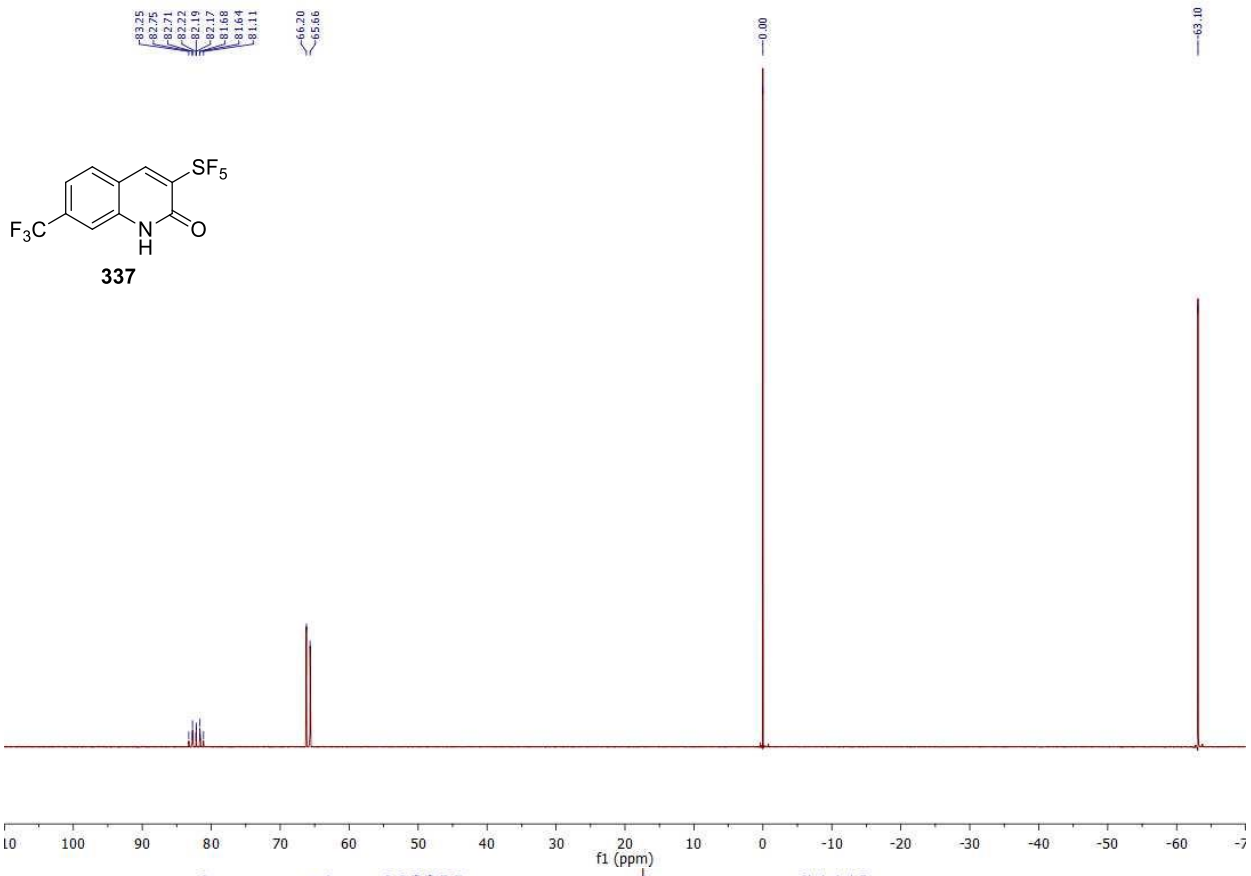
335


F
SF5
N
H
O
335
160.48
158.87
156.84
145.64
145.55
145.44
145.35
144.26
138.03
123.62
123.45
118.89
118.83
118.37
118.31
115.58
115.43
49.47 MeOD
49.33 MeOD
49.18 MeOD
48.90 MeOD
48.76 MeOD
48.62 MeOD
0.00
f1 (ppm)

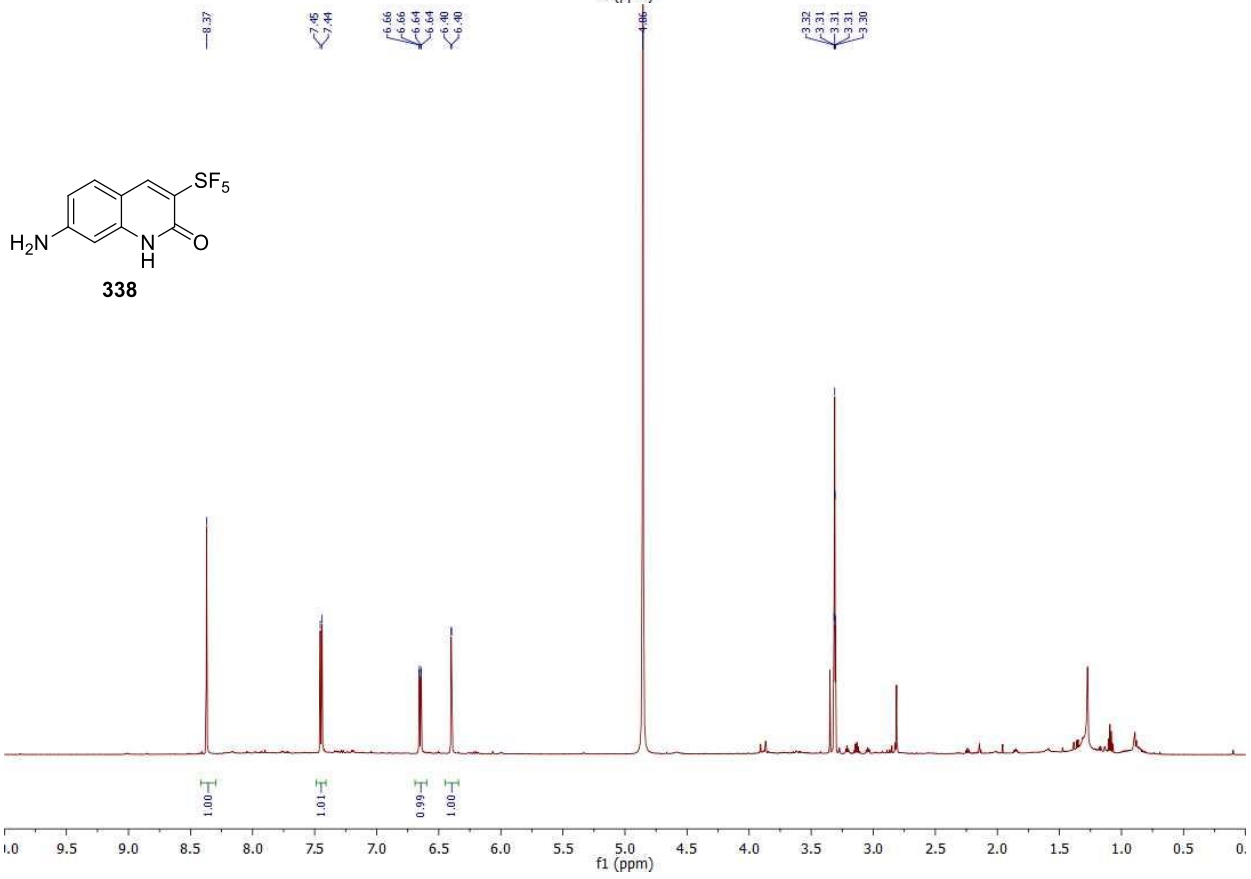

83.86
83.35
83.32
82.83
82.79
82.78
82.28
82.25
81.72
66.39
65.86
0.00
118.97
118.98
119.00
119.01
119.03
119.04
F
SF5
N
H
O
335
0.90
4.41
1.00
f1 (ppm)


8.85
8.06
8.05
7.66
7.66
7.66
7.58
7.57
7.57
7.57
7.56
7.56
7.56
7.56
4.85
3.31
3.31
3.31
3.31
3.30
SF5
F3C
N
H
O
337
1.01
1.01
0.98
1.00
f1 (ppm)

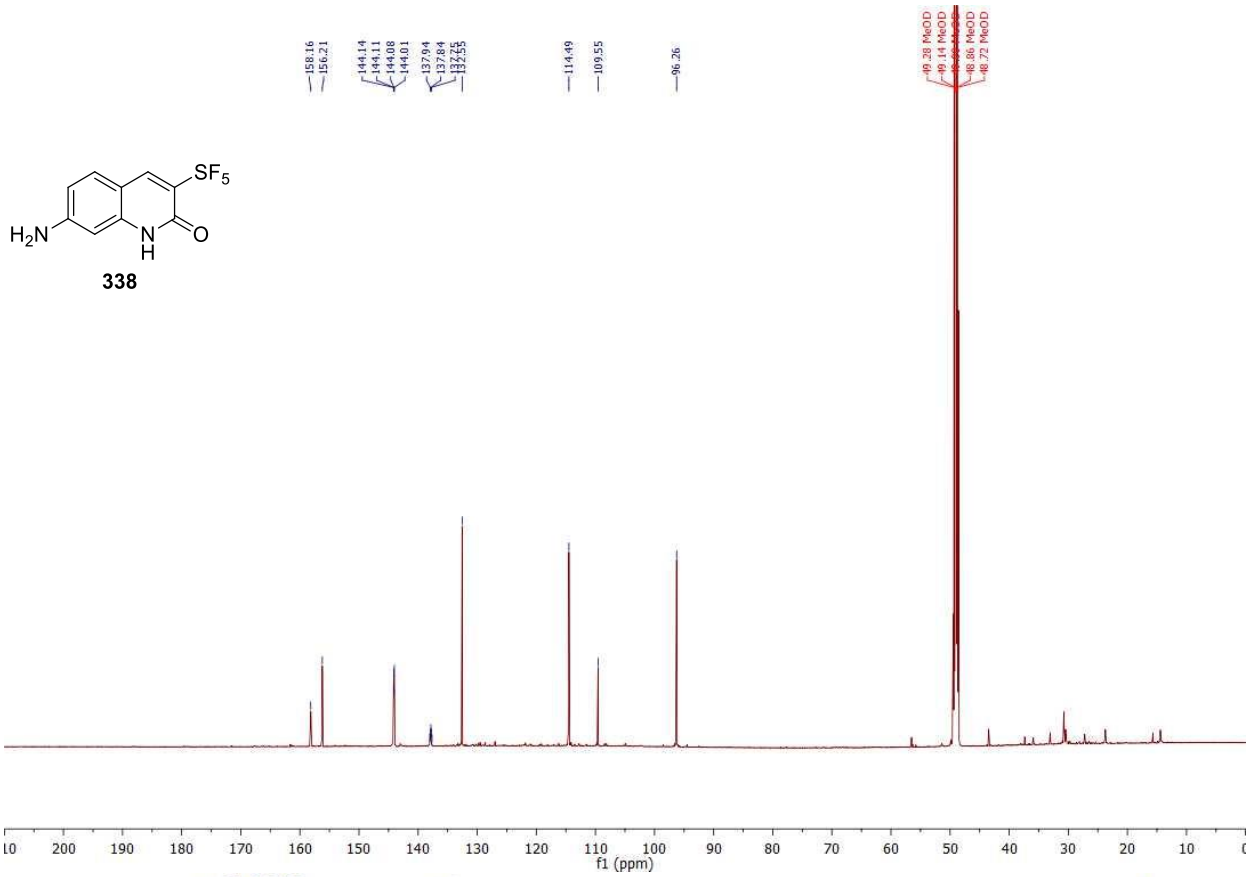

156.88
146.62
146.51
146.41
144.28
141.06
136.13
135.91
135.69
135.48
132.77
120.52
120.33
120.30
120.28
120.26
119.51
113.48
113.45
113.42
49.47 MeOD
49.33 MeOD
49.19 MeOD
48.91 MeOD
48.76 MeOD
48.62 MeOD
0.00
SF5
F3C
N
H
O
337
f1 (ppm)

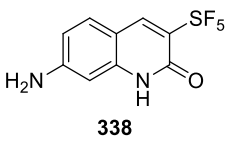

83.25
82.75
82.71
82.22
82.19
82.17
81.66
81.64
81.11
66.20
65.66
0.00
-63.10
SF5
F3C
N
H
O
f1 (ppm)

337


8.37
7.45
7.44
6.66
6.66
6.64
6.64
6.40
6.40
3.32
3.31
3.31
3.31
3.30
SF5
H2N
N
H
O
1.00
1.01
0.99
1.00
f1 (ppm)

338


158.16
156.21
144.14
144.11
144.08
144.01
137.94
137.84
132.55
114.49
109.55
96.26
49.28 MeOD
49.14 MeOD
48.86 MeOD
48.72 MeOD
f1 (ppm)

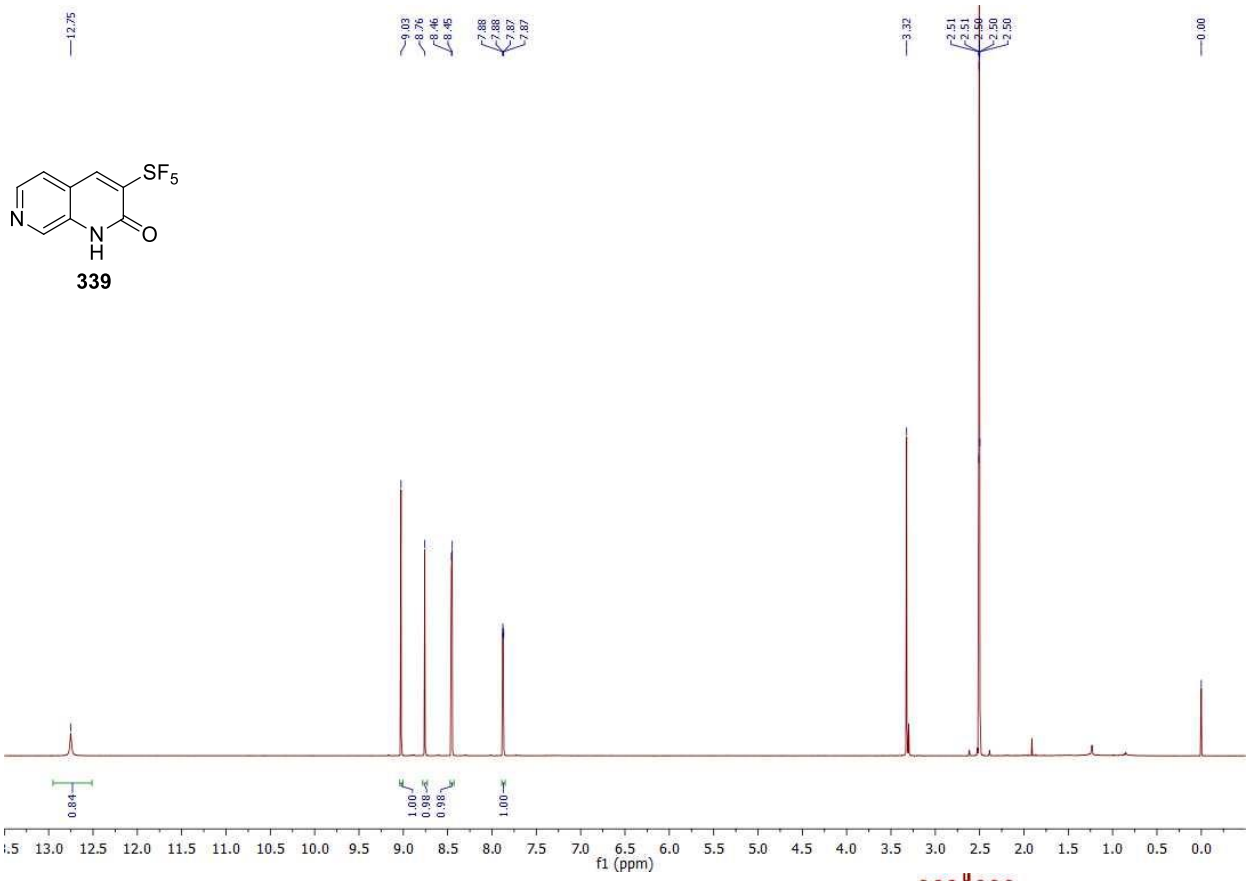

SF5
H2N
N
H
O

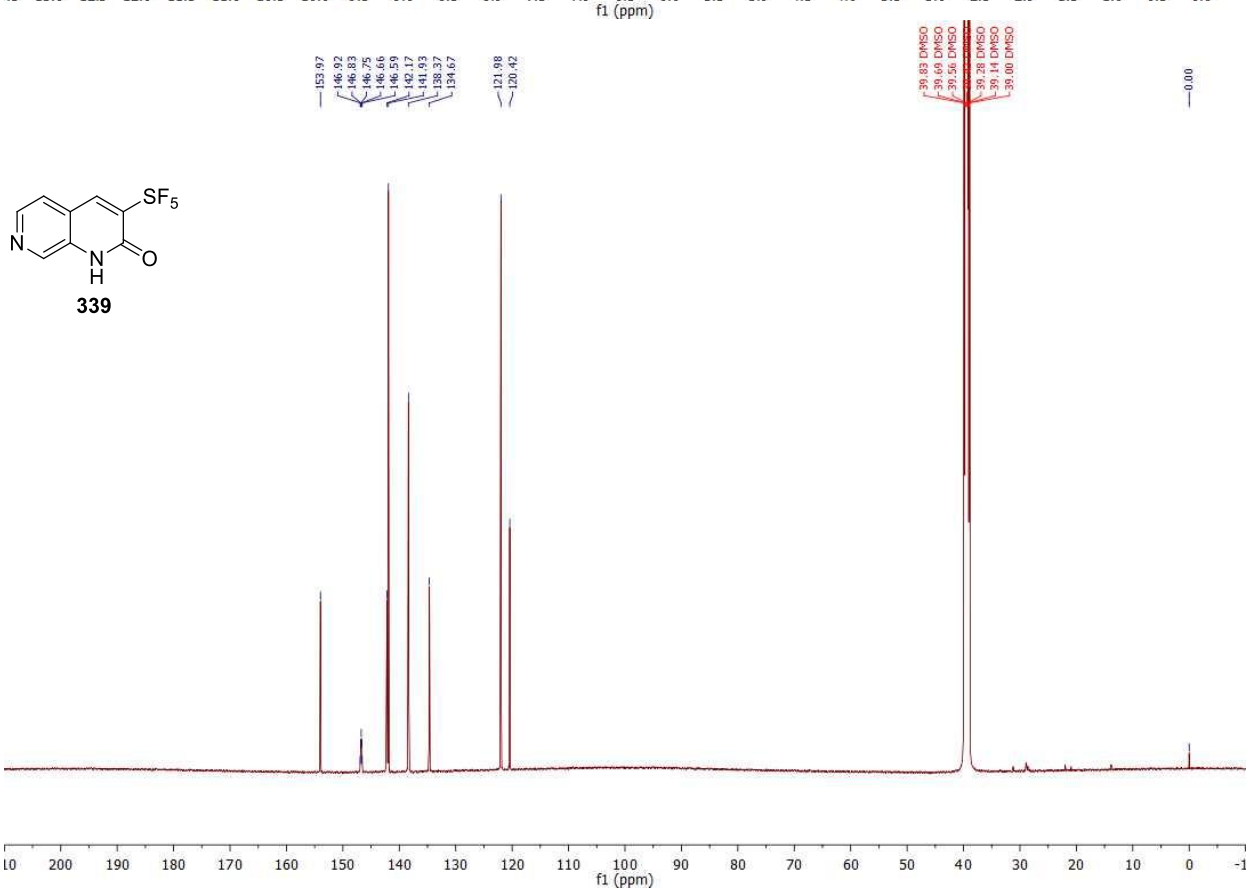
338

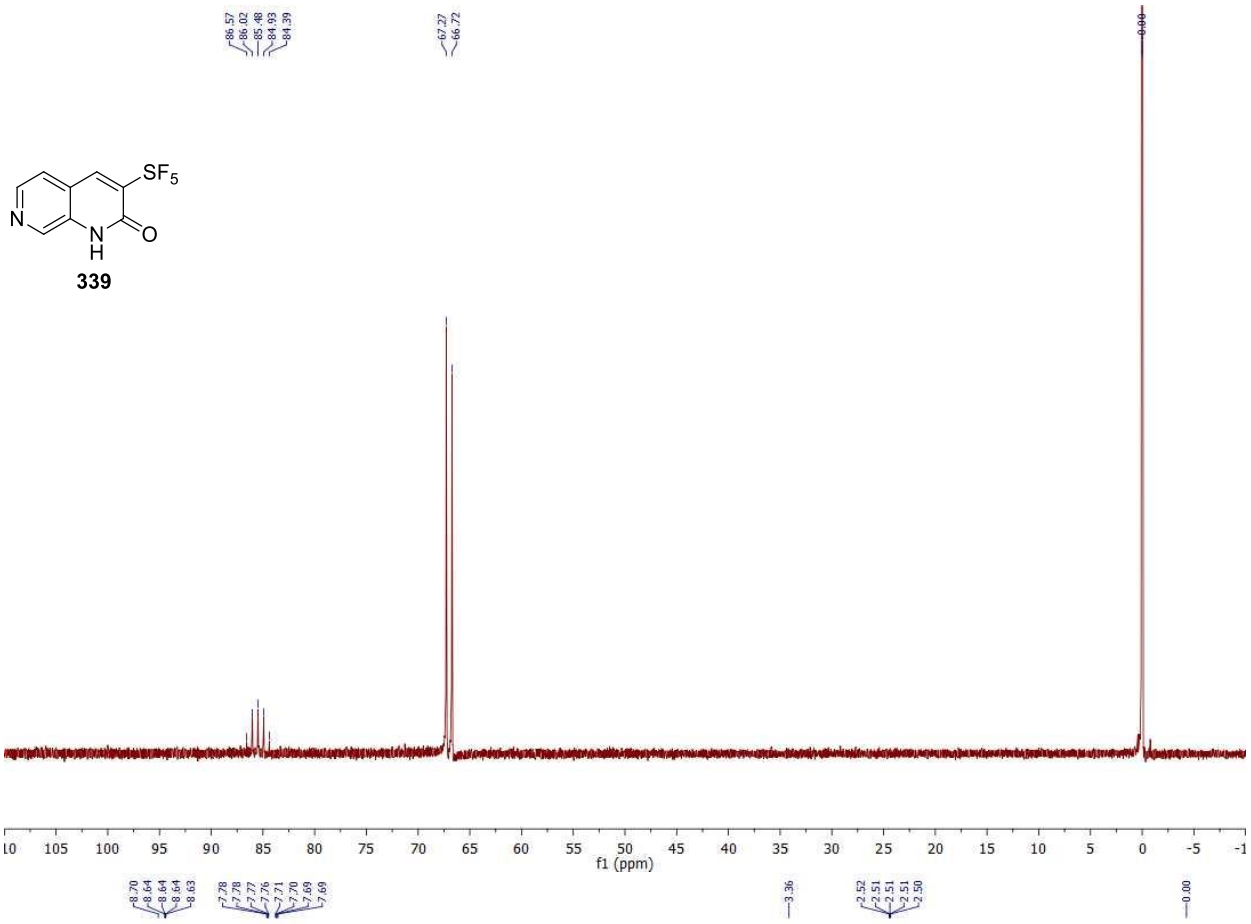
87.53
87.02
86.99
86.47
86.45
85.96
85.93
85.40
67.67
67.14
0.00
f1 (ppm)

SF5
H2N
N
H
O

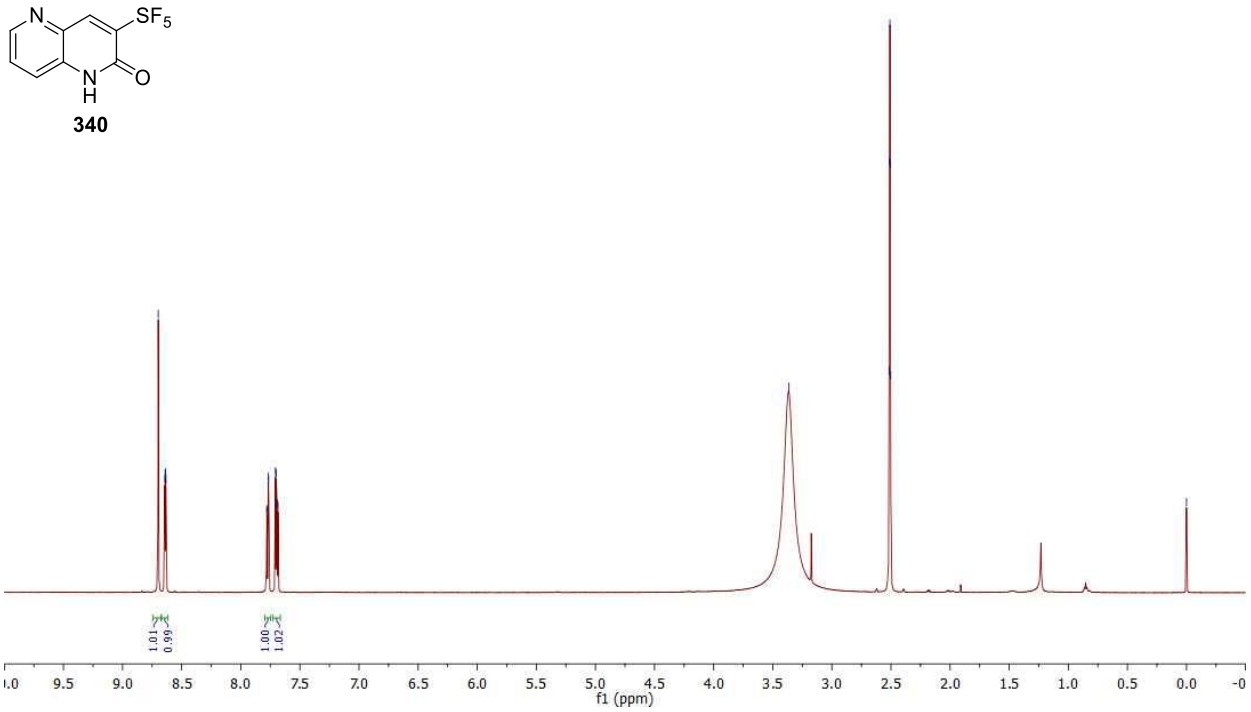
338


12.75
9.03
8.76
8.46
8.45
7.88
7.88
7.87
7.87
3.32
2.51
2.51
2.50
2.50
0.00
SF5
N
N
H
O
339
0.84
1.00
0.98
0.98
1.00
f1 (ppm)

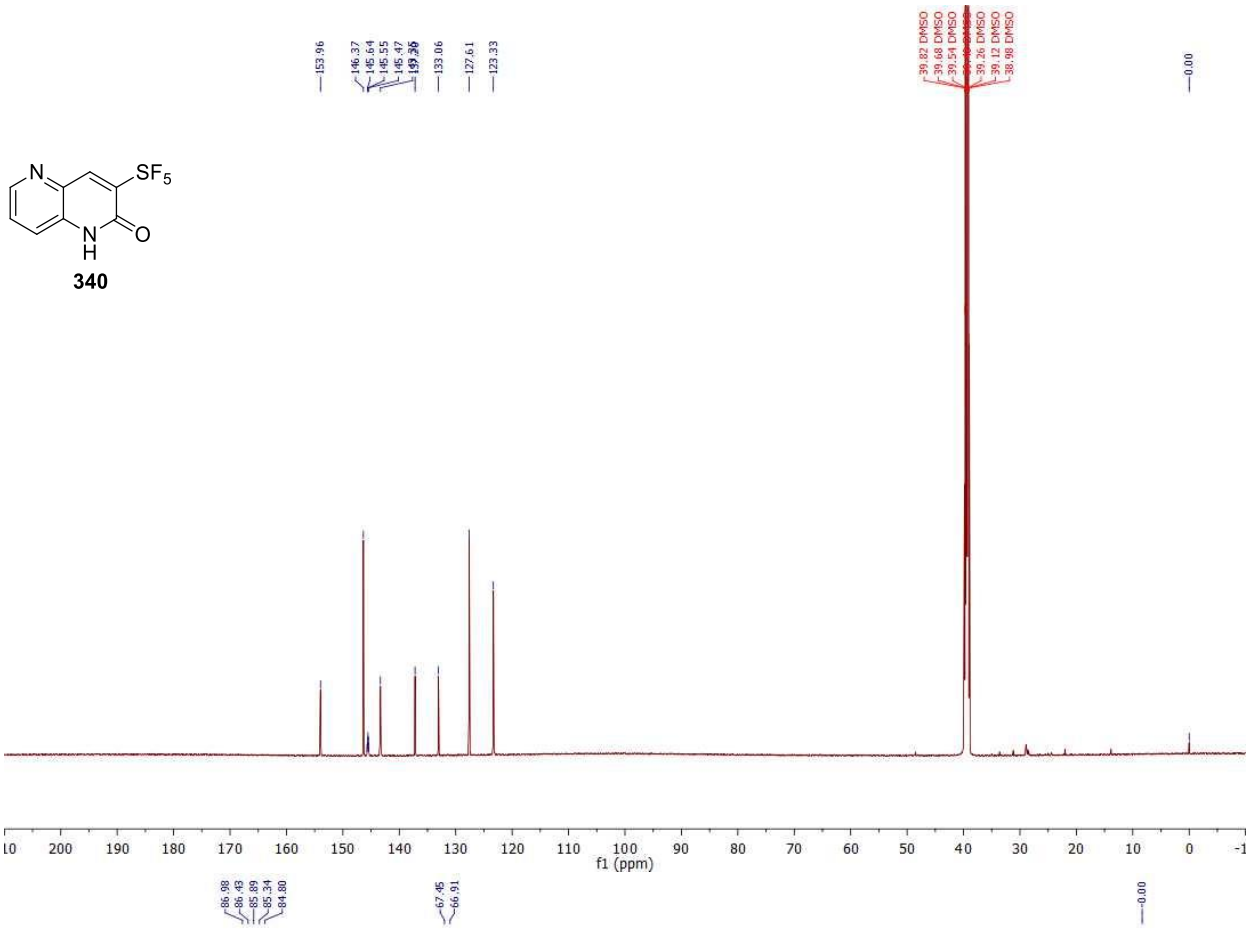

153.97
146.92
146.83
146.75
146.66
146.59
142.17
141.93
138.37
134.67
121.98
120.42
39.83 DMSO
39.69 DMSO
39.56 DMSO
39.28 DMSO
39.14 DMSO
39.00 DMSO
0.00
SF5
N
N
H
O
339
f1 (ppm)

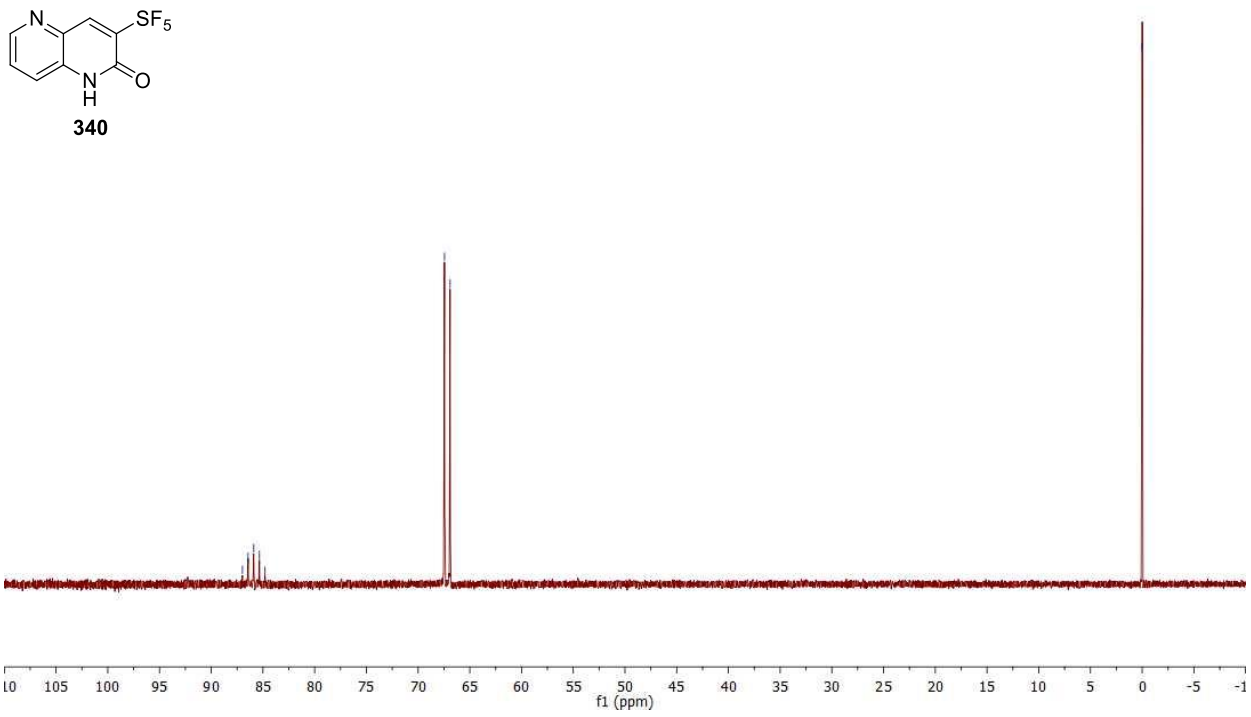

86.57
86.02
85.48
84.93
84.39
67.27
66.72
0.00
SF5
N
N
H
O
f1 (ppm)
8.70
8.64
8.64
8.64
8.63
7.78
7.78
7.77
7.76
7.71
7.70
7.69
7.69
3.36
2.52
2.51
2.51
2.51
2.50
0.00

339

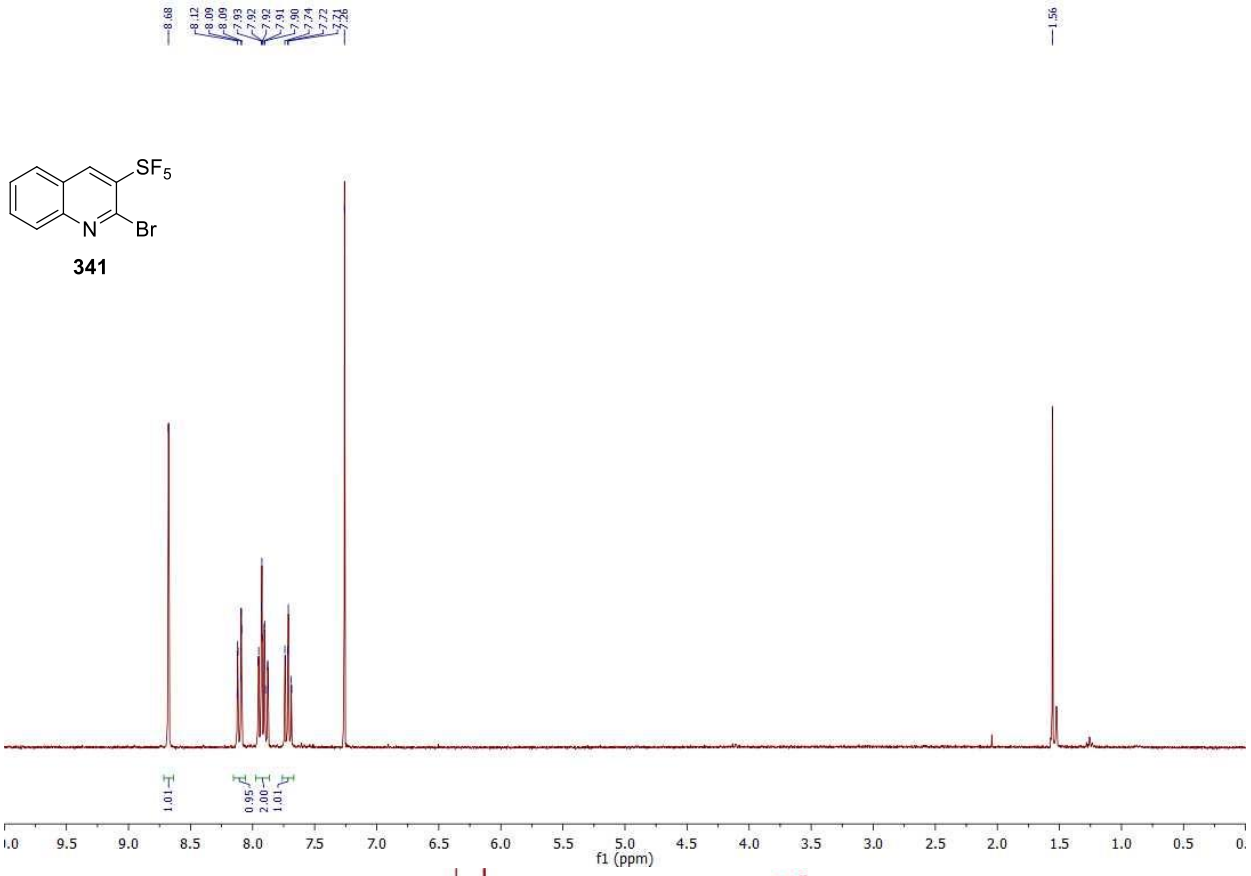

SF5
N
N
H
O
1.01
0.99
1.00
1.02
f1 (ppm)

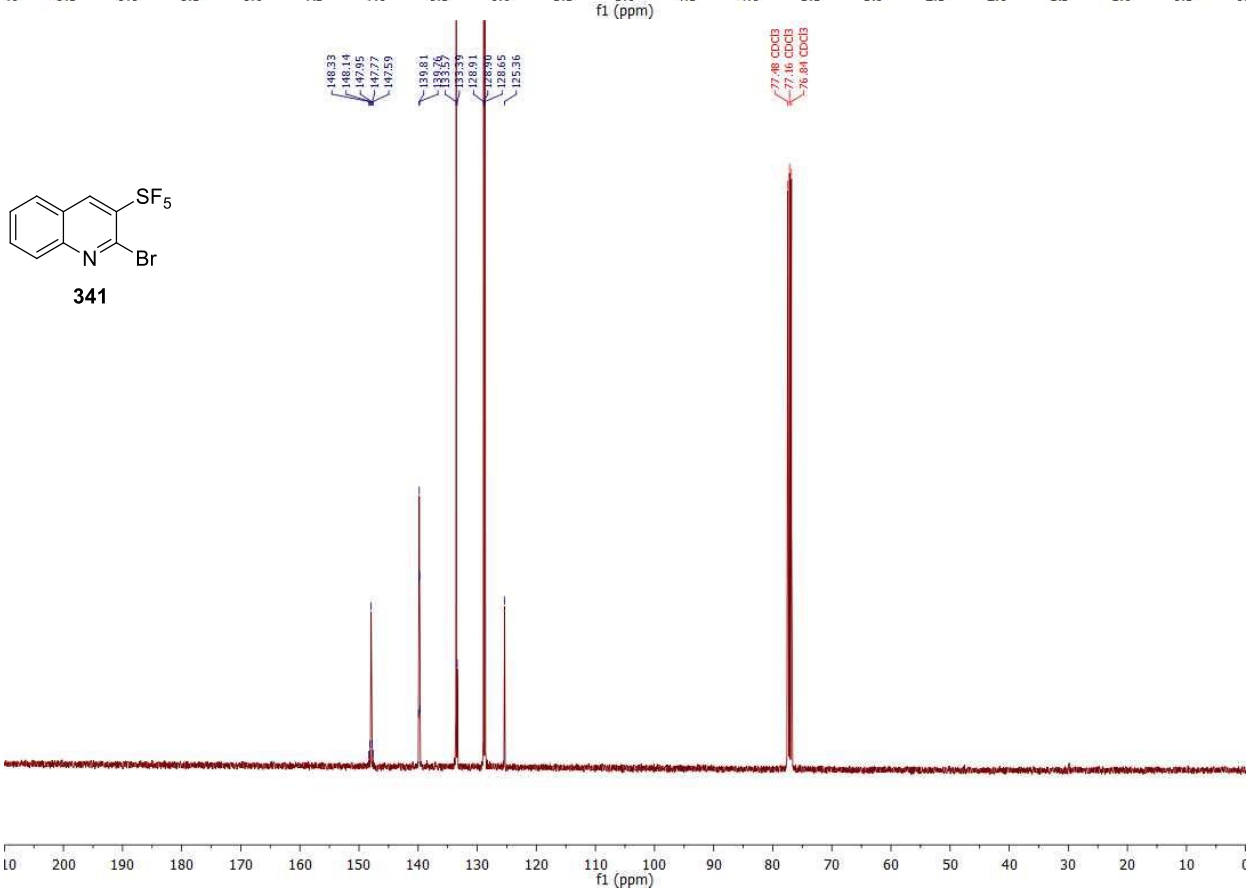
340

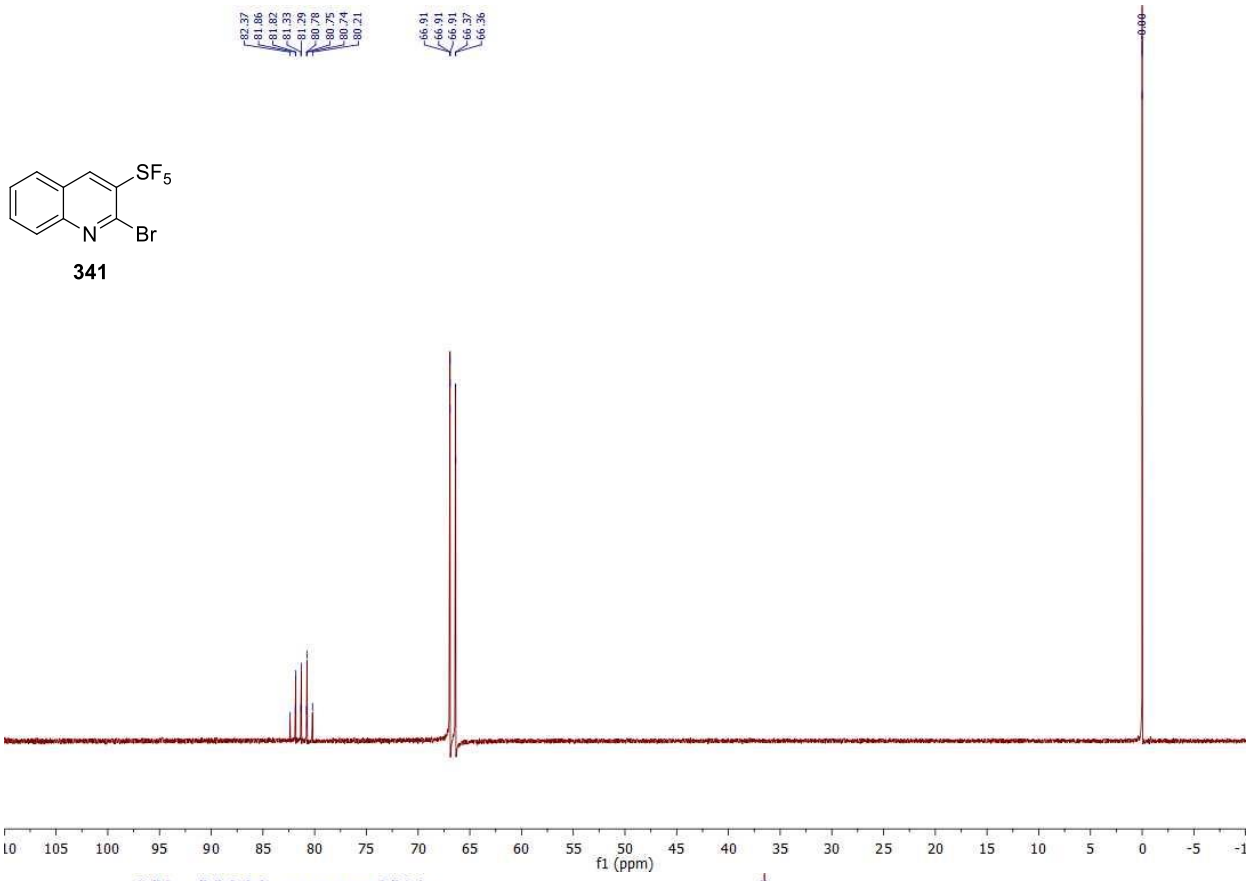

153.96
146.37
145.64
145.55
145.47
133.06
127.61
123.33
39.82 DMSO
39.68 DMSO
39.54 DMSO
39.26 DMSO
39.12 DMSO
38.98 DMSO
0.00
f1 (ppm)


86.98
86.48
85.89
85.34
84.80
67.45
66.91
0.00
f1 (ppm)

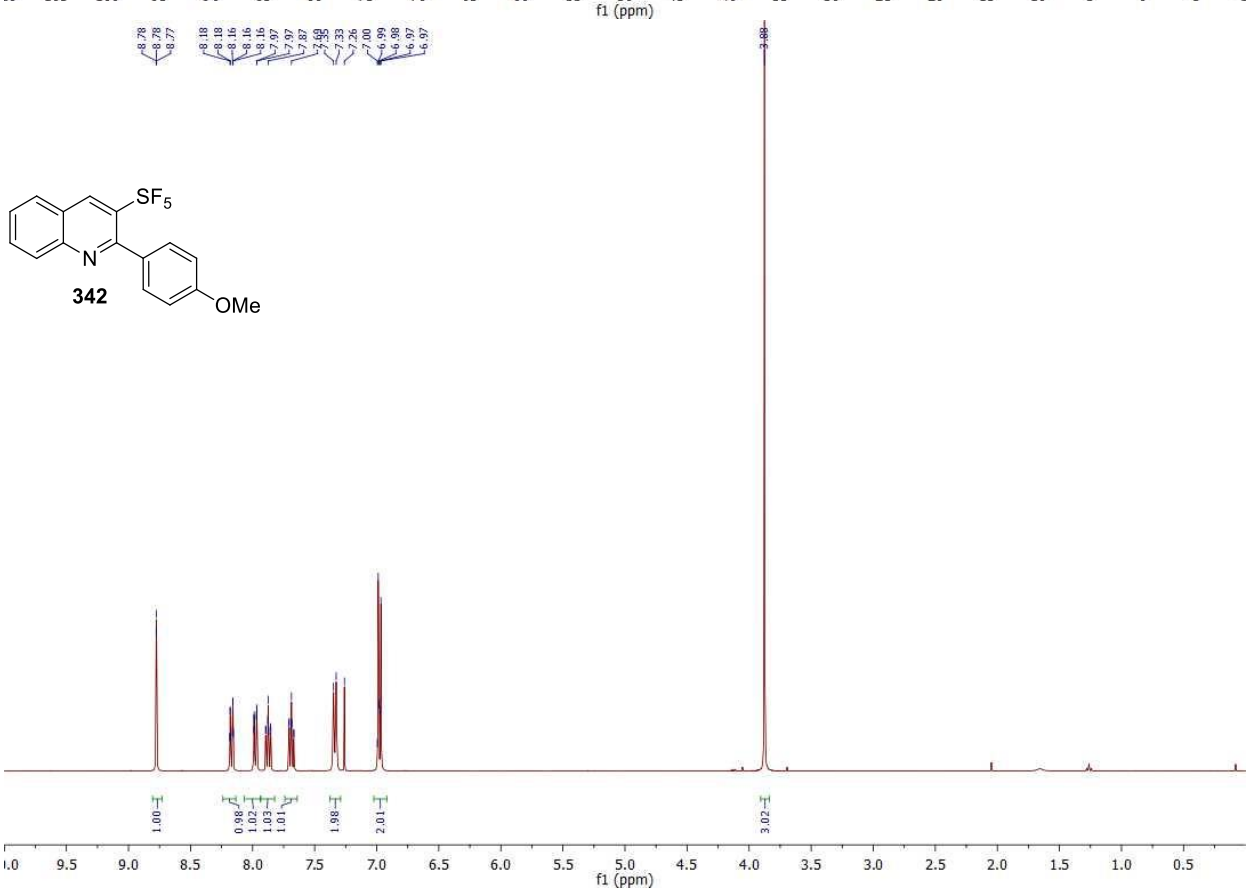
340


8.68
8.12
8.09
8.09
8.09
7.93
7.92
7.92
7.91
7.90
7.74
7.72
7.71
7.26
1.56
SF5
Br
341
1.01
0.95
2.00
1.01
f1 (ppm)

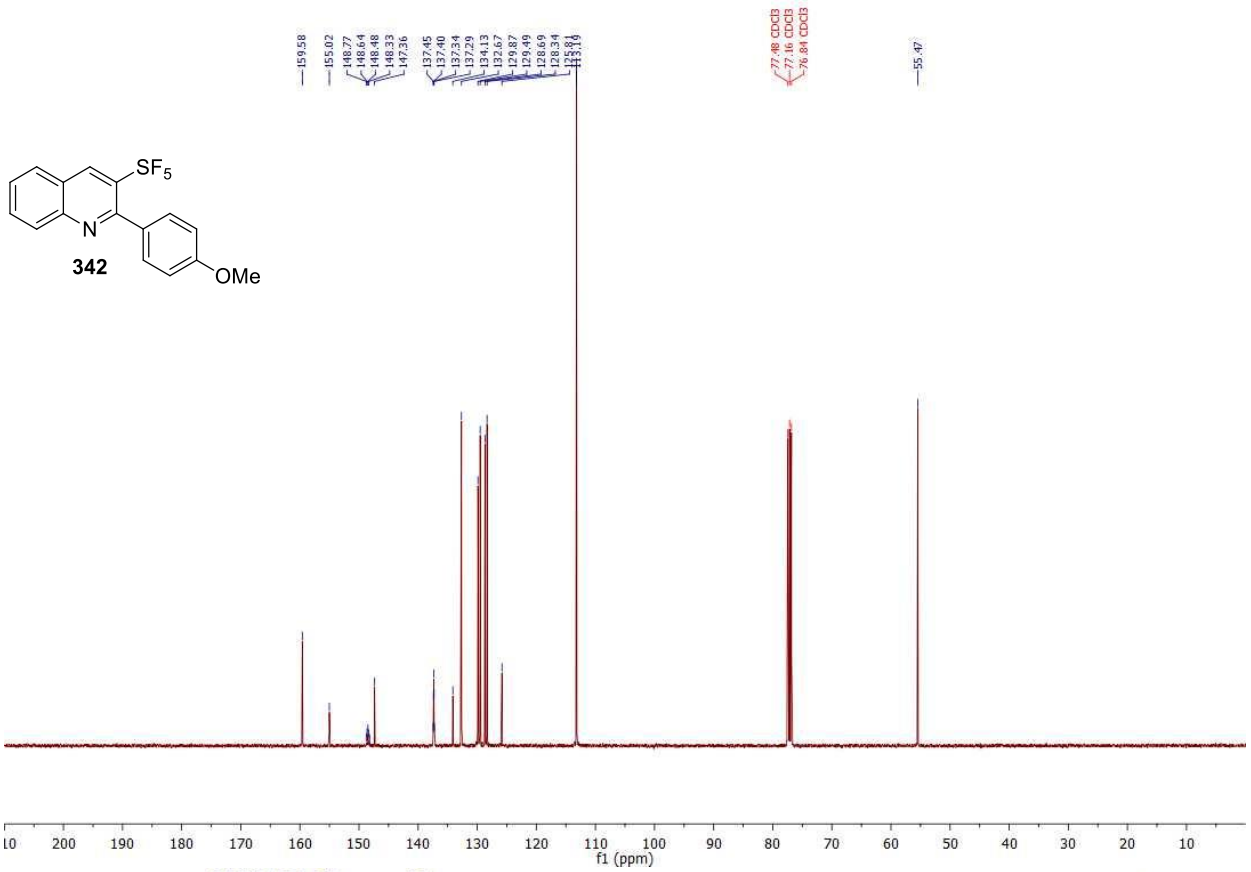

148.33
148.14
147.95
147.77
147.59
139.81
133.55
128.91
128.90
128.65
125.36
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
SF5
Br
341
f1 (ppm)

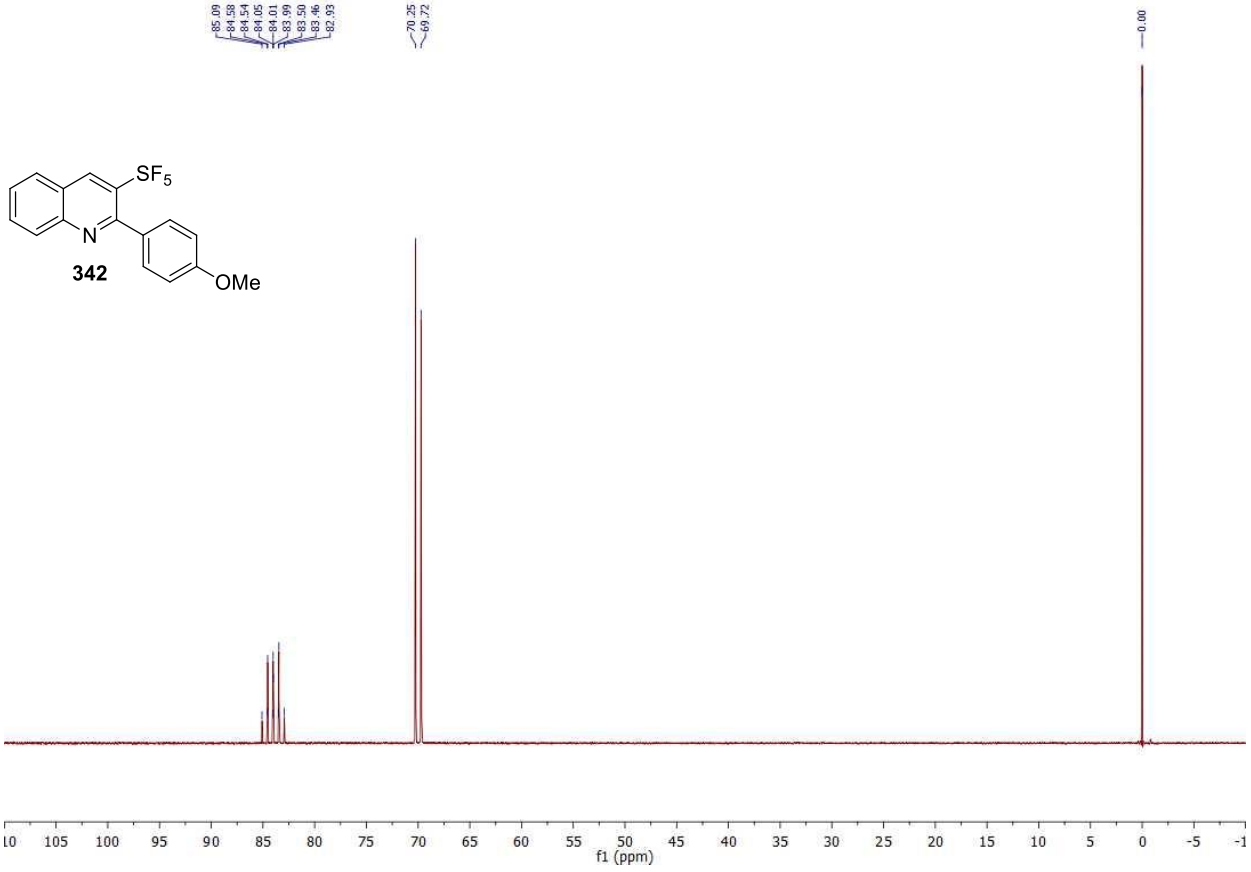


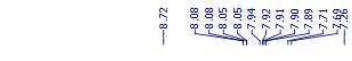
341

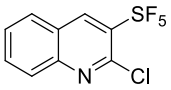


342

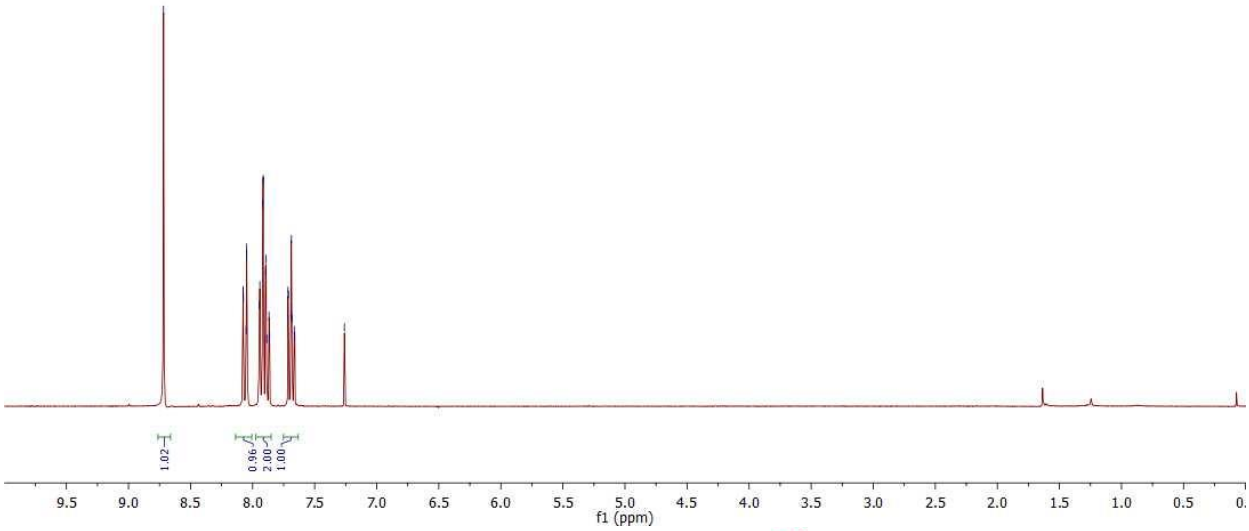

159.58
155.02
148.77
148.64
148.48
148.33
147.36
137.45
137.40
137.34
137.29
134.13
132.67
129.87
129.49
128.69
128.34
125.81
113.19
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.47
SF5
N
OMe
342
f1 (ppm)


85.09
84.58
84.54
84.05
84.01
83.99
83.50
83.46
82.93
70.25
69.72
0.00
SF5
N
OMe
342
f1 (ppm)

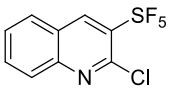

8.72
8.08
8.08
8.05
8.05
7.94
7.92
7.91
7.90
7.89
7.71
7.68
7.68


SF5
N
Cl

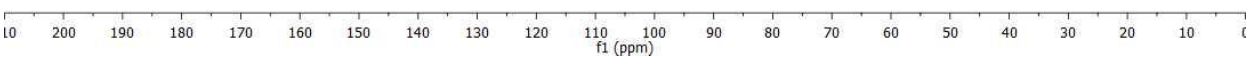
343

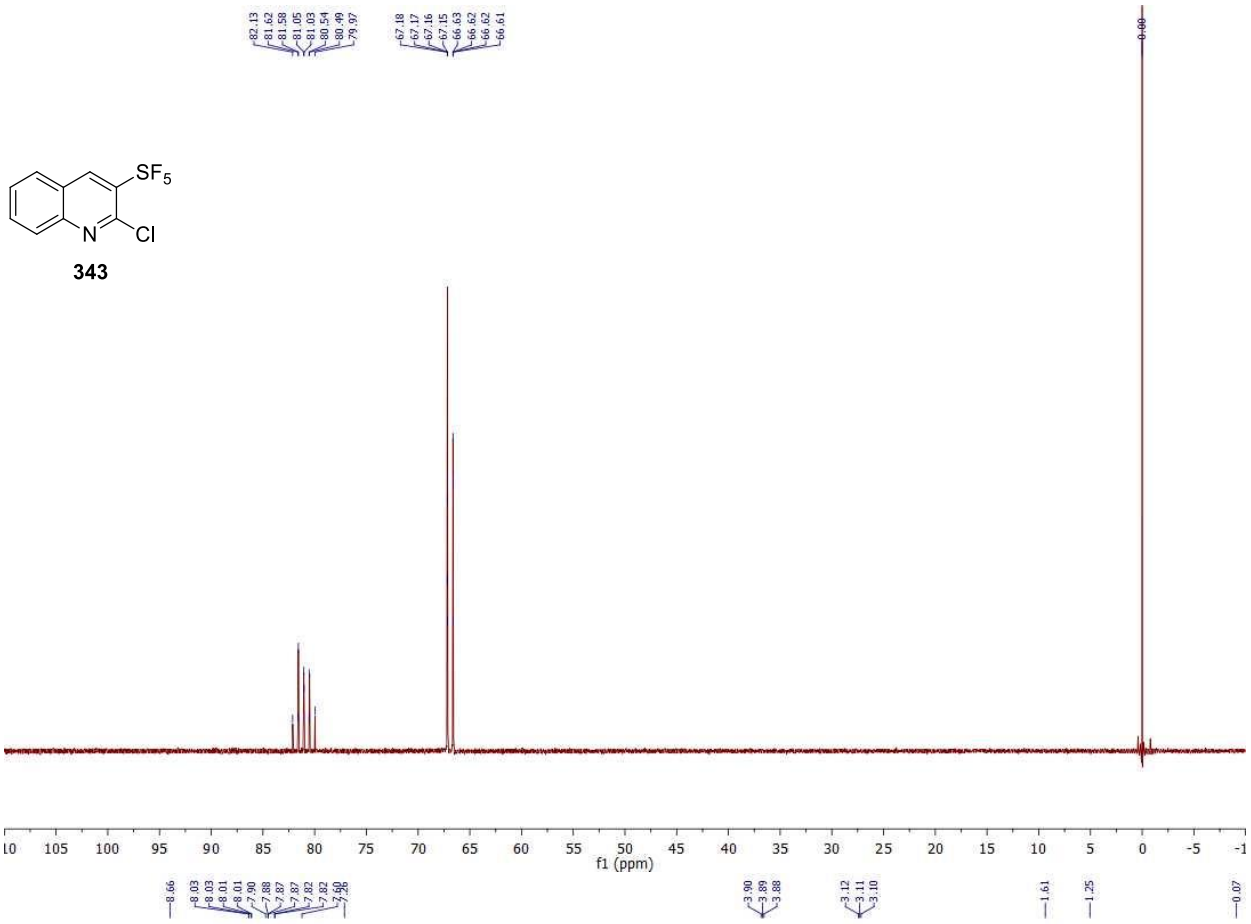

1.02
0.96
2.00
1.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


147.48
146.04
145.85
145.66
145.48
145.30
142.96
140.35
140.29
140.24
140.19
140.14
133.58
128.83
128.79
128.49
125.54
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3

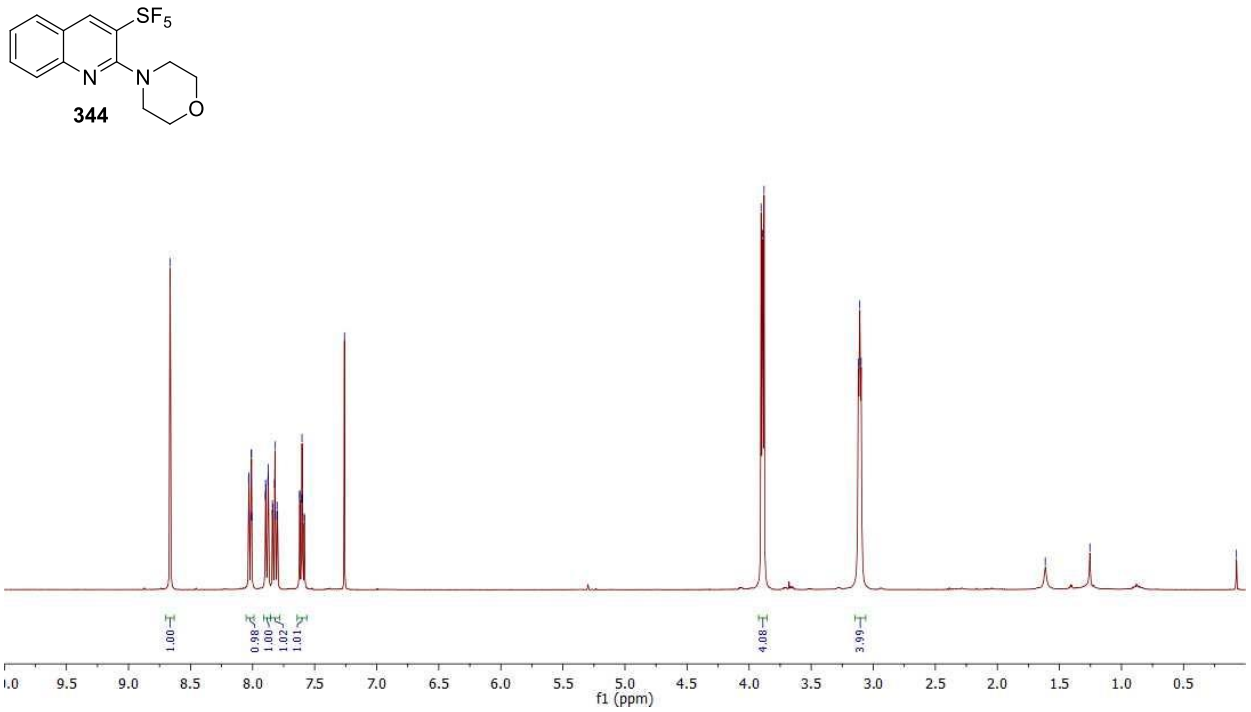

SF5
N
Cl

343

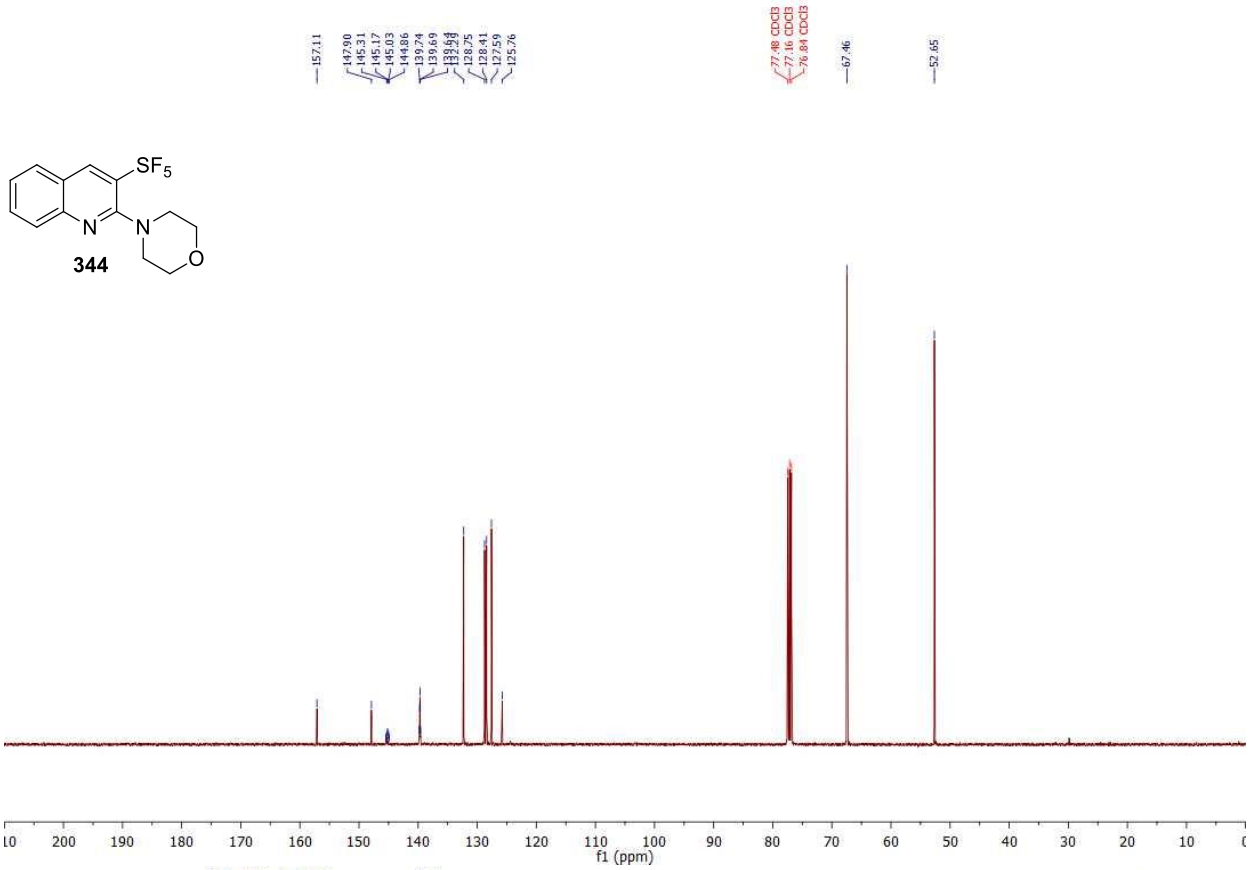

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

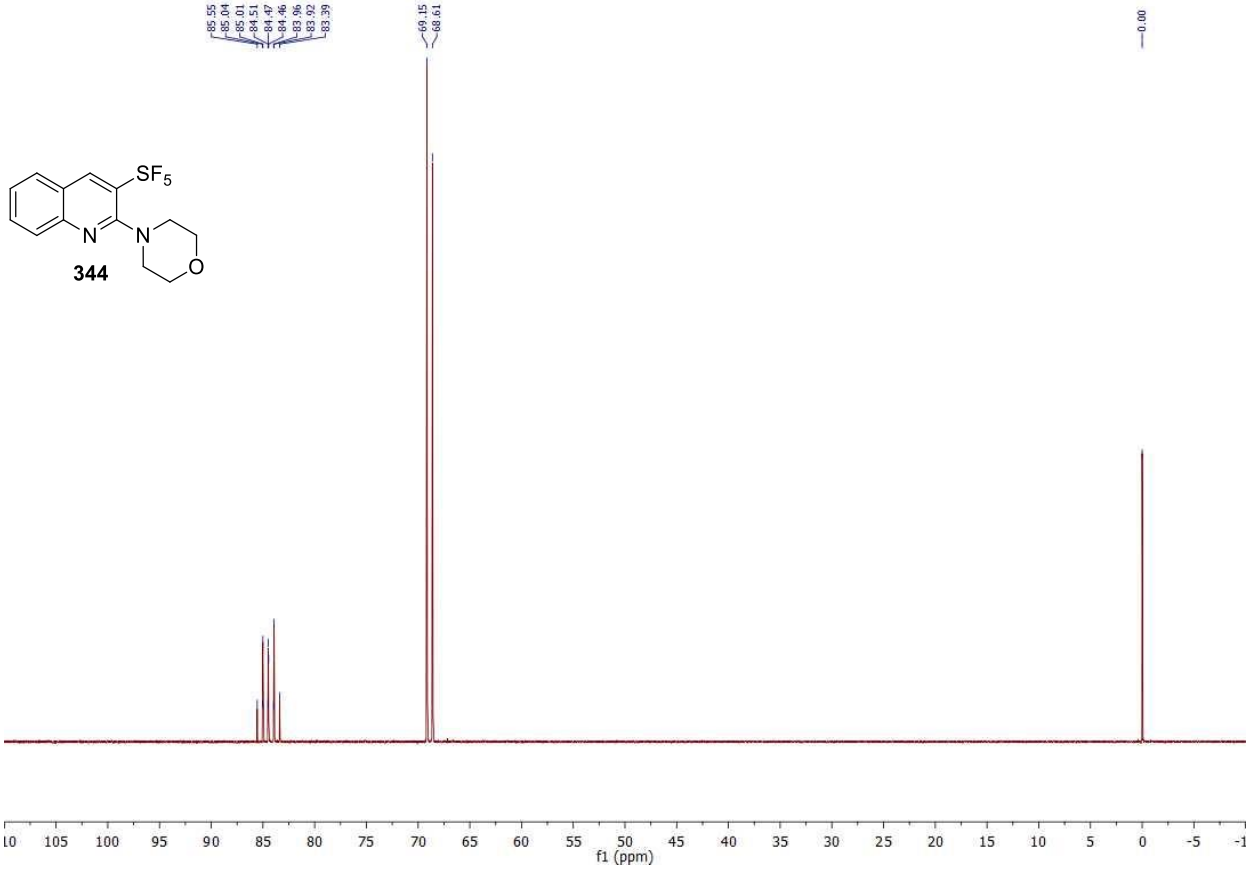

82.13
81.62
81.58
81.05
81.03
80.54
80.49
79.97
67.18
67.17
67.16
67.15
66.63
66.62
66.62
66.61
0.00
f1 (ppm)
8.66
8.03
8.03
8.01
8.01
7.90
7.88
7.87
7.87
7.82
7.82
7.80
3.90
3.89
3.88
3.12
3.11
3.10
1.61
1.25
0.07

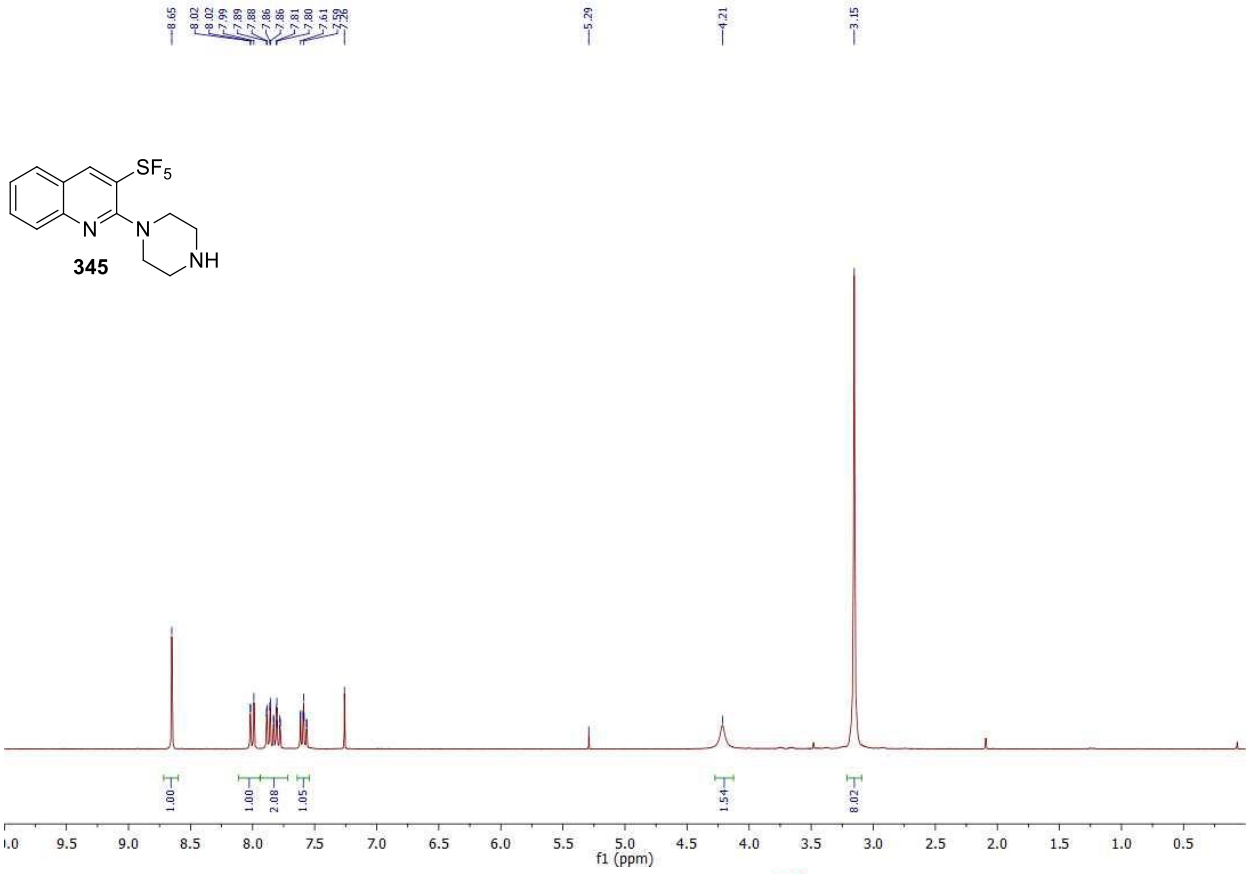
343

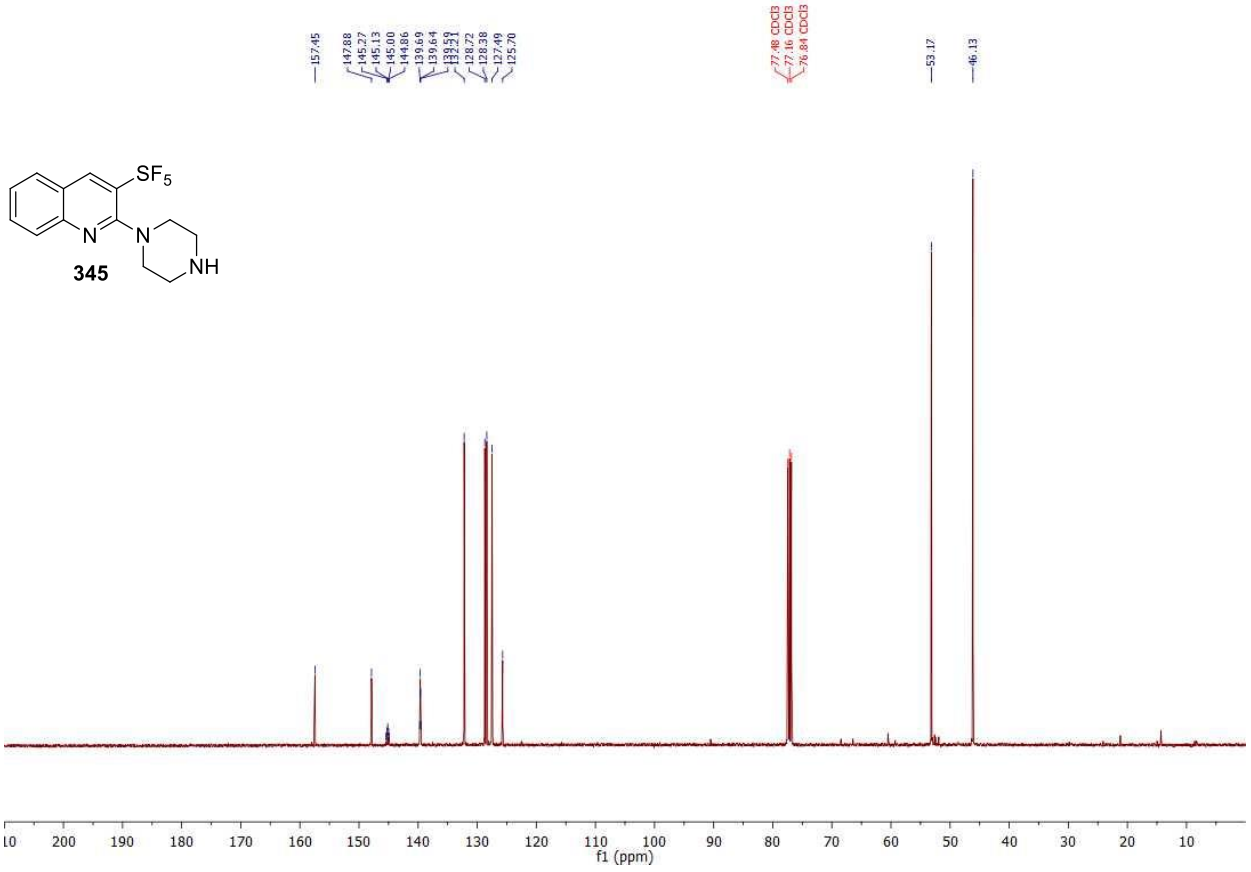

1.00
0.98
1.00
1.02
1.01
4.08
3.99
f1 (ppm)

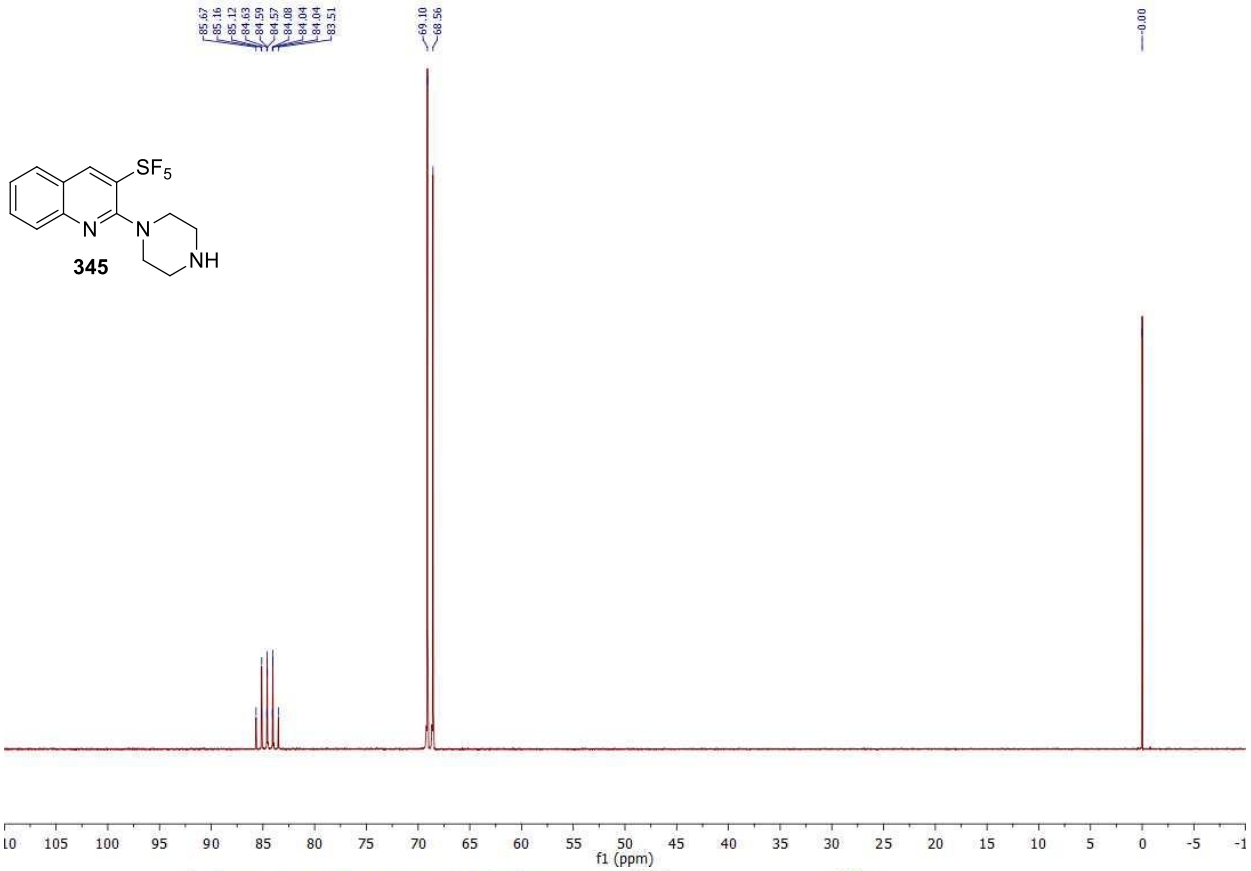
344

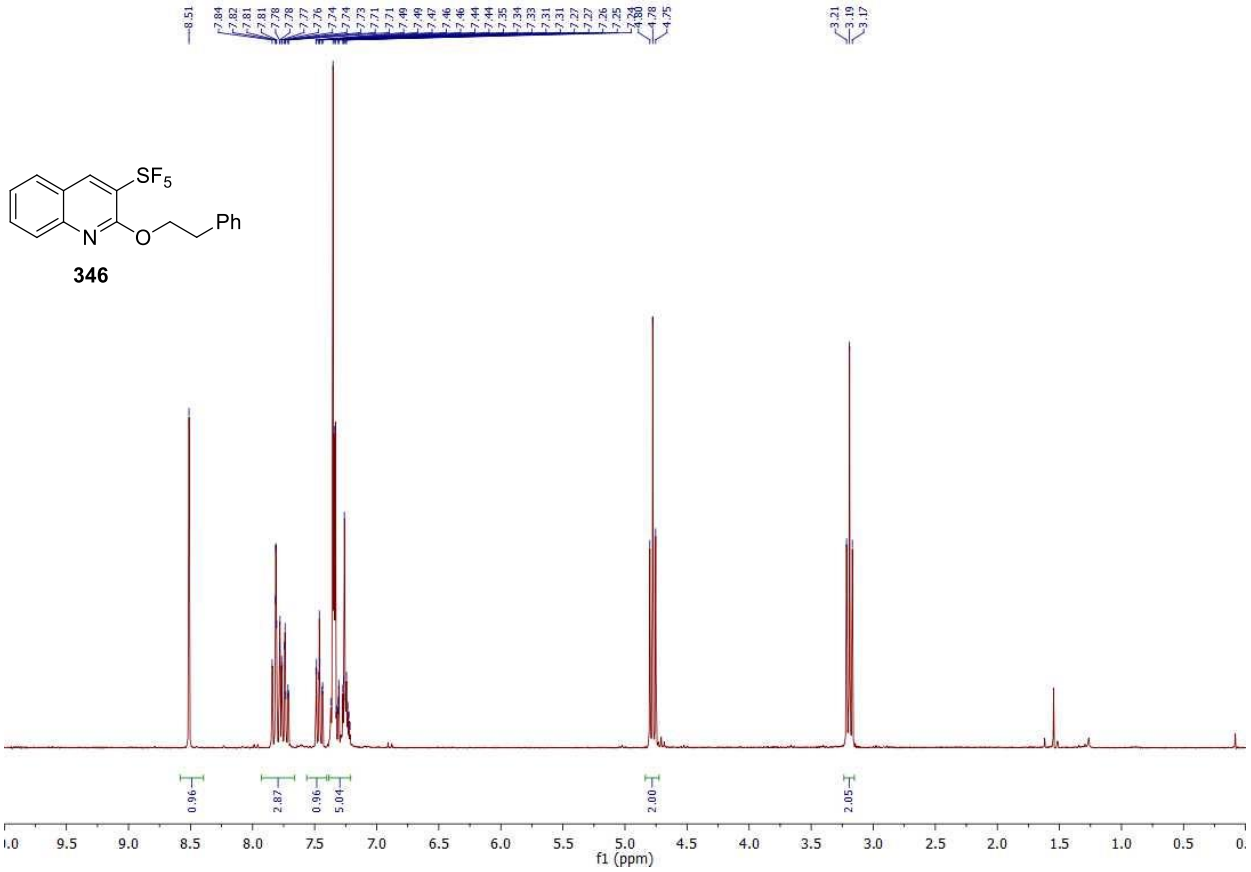

157.11
147.90
145.31
145.17
145.03
144.86
139.74
139.69
133.59
133.44
128.75
128.41
127.59
125.76
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
67.46
52.65
SF5
N
N
O
344
f1 (ppm)

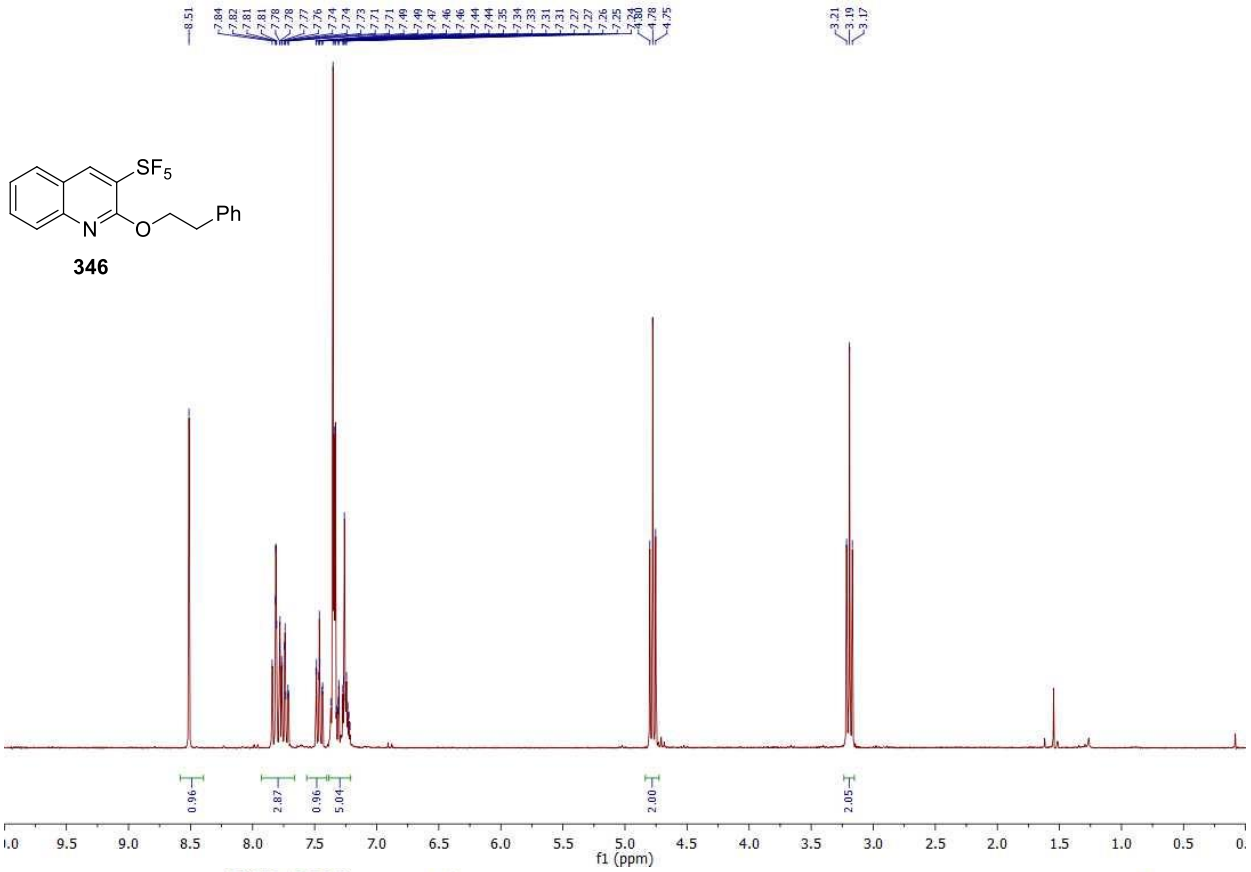

85.55
85.04
85.01
84.51
84.47
84.46
83.96
83.92
83.39
69.15
68.61
0.00
SF5
N
N
O
344
f1 (ppm)

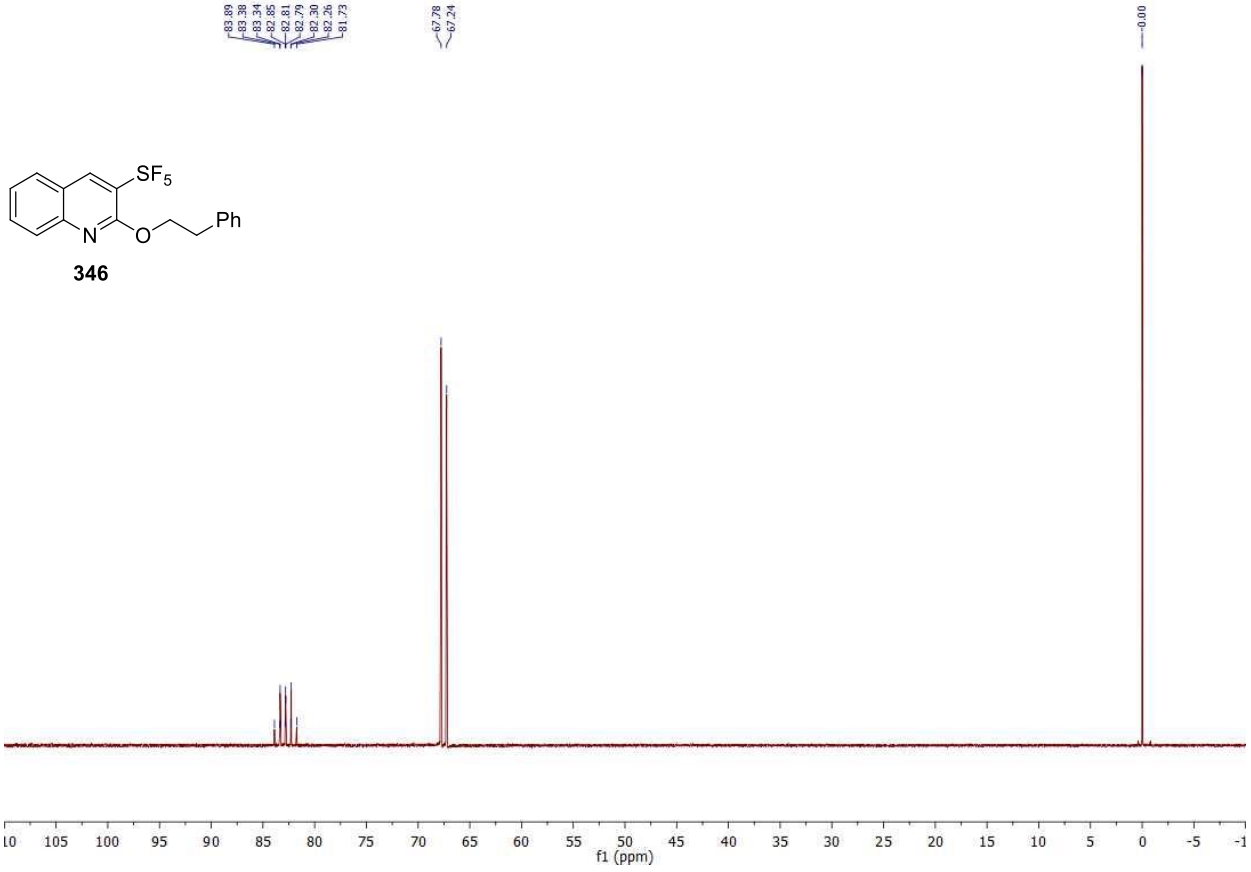

8.65
8.02
8.02
7.99
7.89
7.88
7.86
7.86
7.81
7.80
7.61
7.58
7.58
5.29
4.21
3.15
SF5
N
N
NH
345
1.00
1.00
2.08
1.05
1.54
8.02
f1 (ppm)

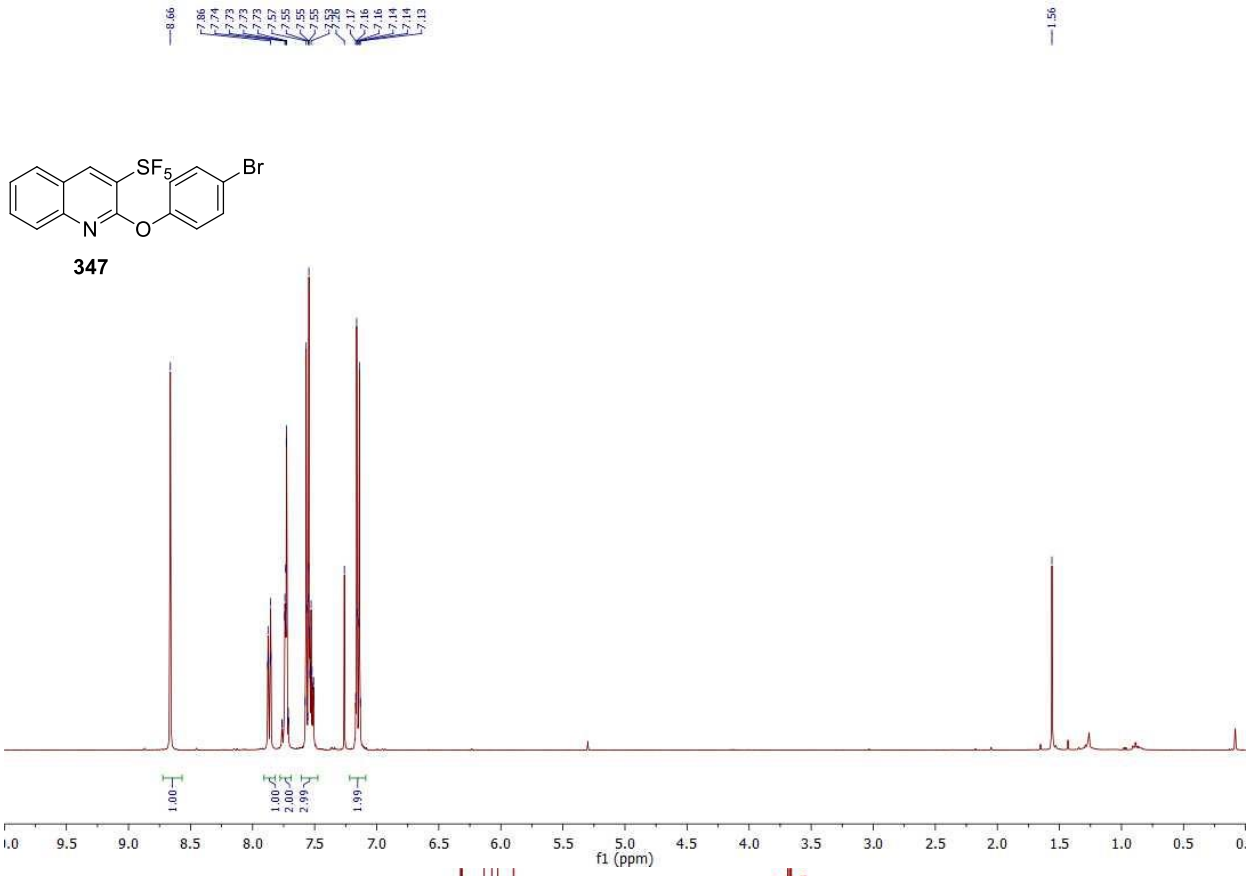

157.45
147.88
145.27
145.13
145.00
144.86
139.69
139.64
133.51
133.21
128.72
128.38
127.49
125.70
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
53.17
46.13
SF5
N
N
NH
345
f1 (ppm)

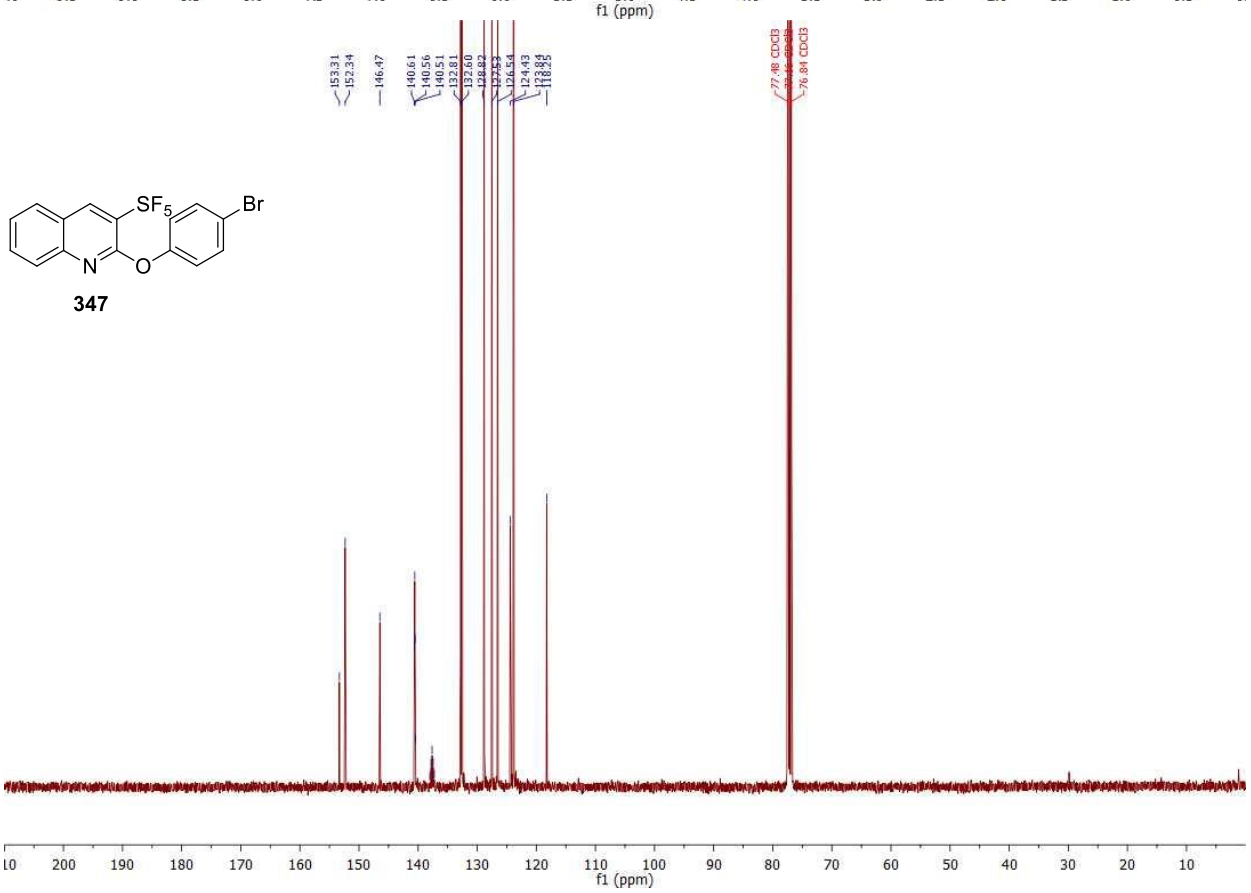

SF5
N
N
NH
345
f1 (ppm)

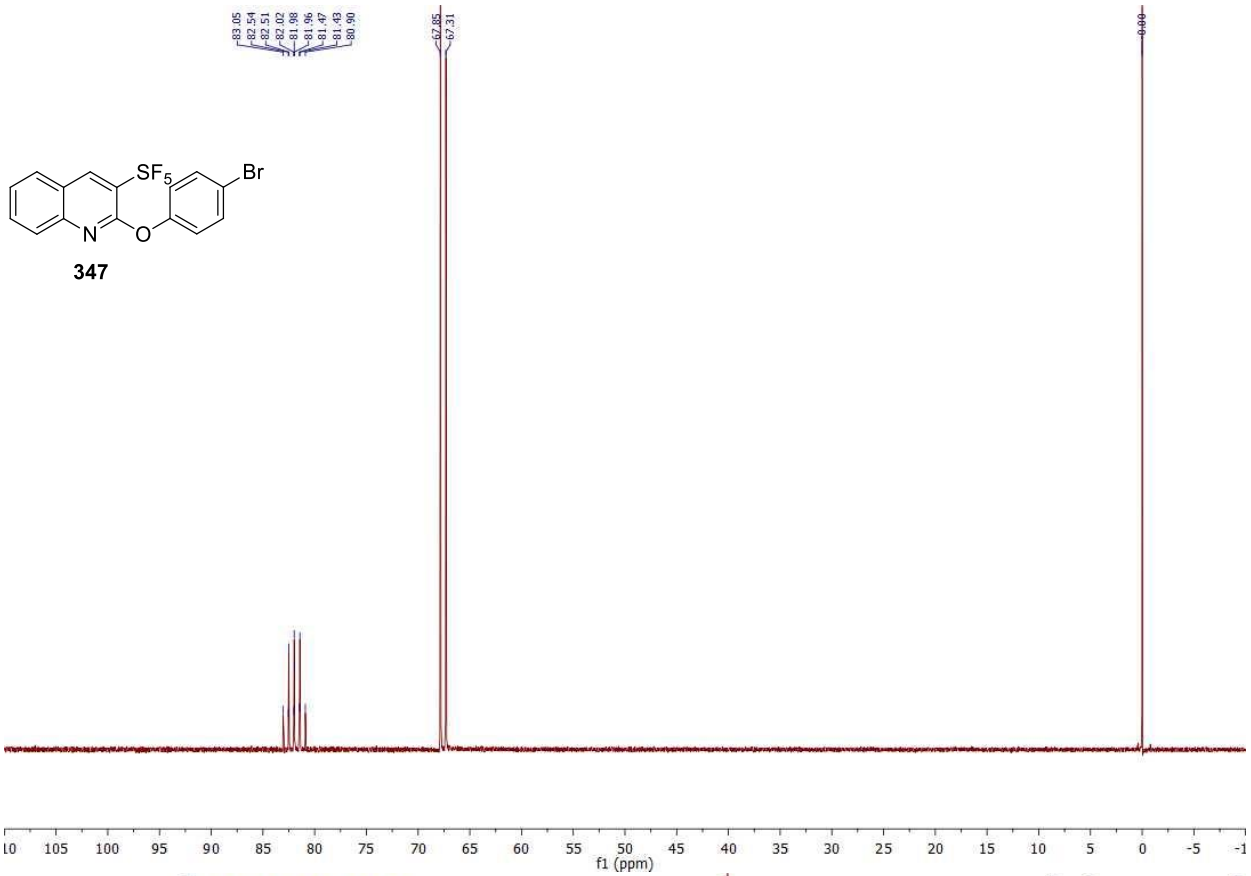

SF5
N
O
Ph
346
f1 (ppm)


SF5
N
O
Ph
346
f1 (ppm)

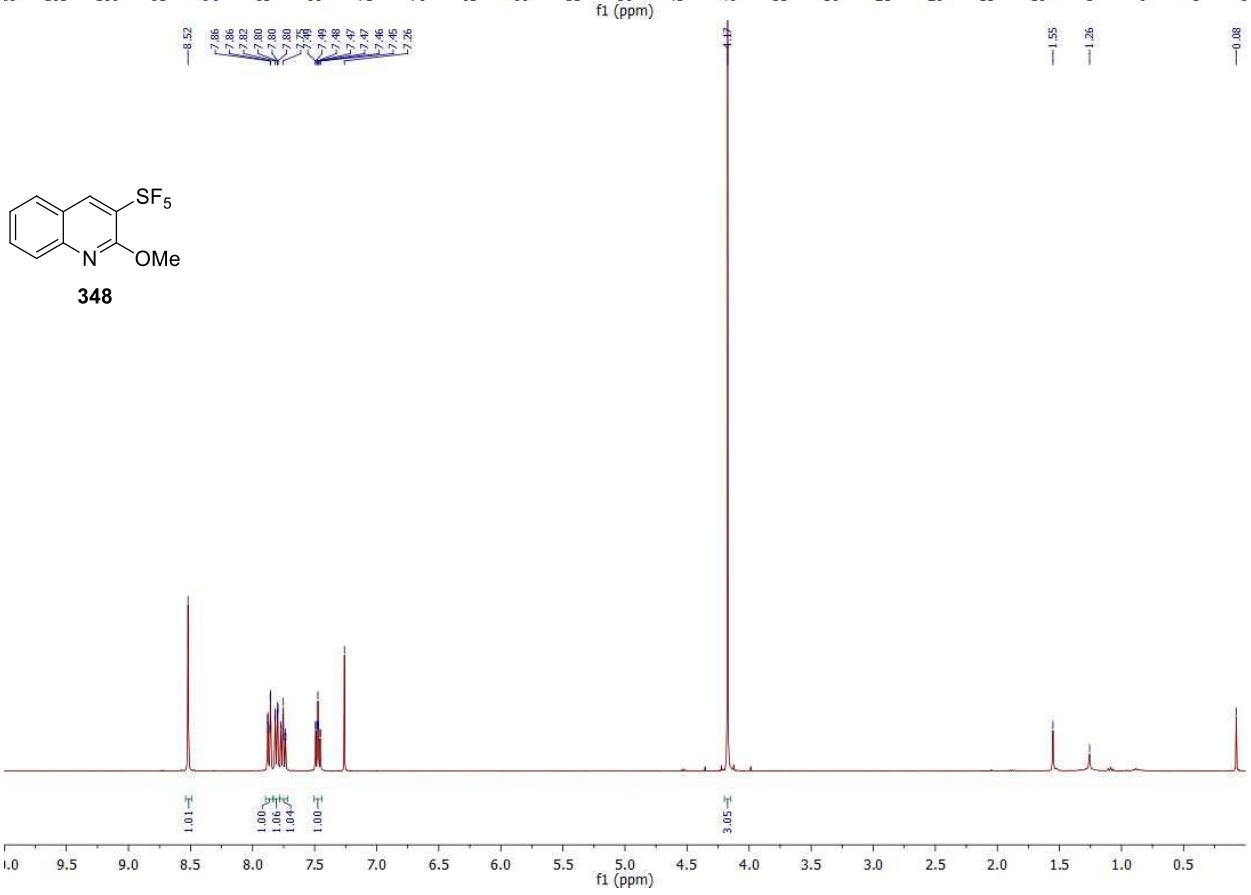

SF5
N
O
Ph
346
f1 (ppm)


8.66
7.86
7.74
7.73
7.73
7.73
7.57
7.55
7.55
7.55
7.53
7.26
7.17
7.16
7.16
7.14
7.14
7.13
1.56
SF5
Br
N
O
347
1.00
1.00
2.00
2.99
1.99
f1 (ppm)

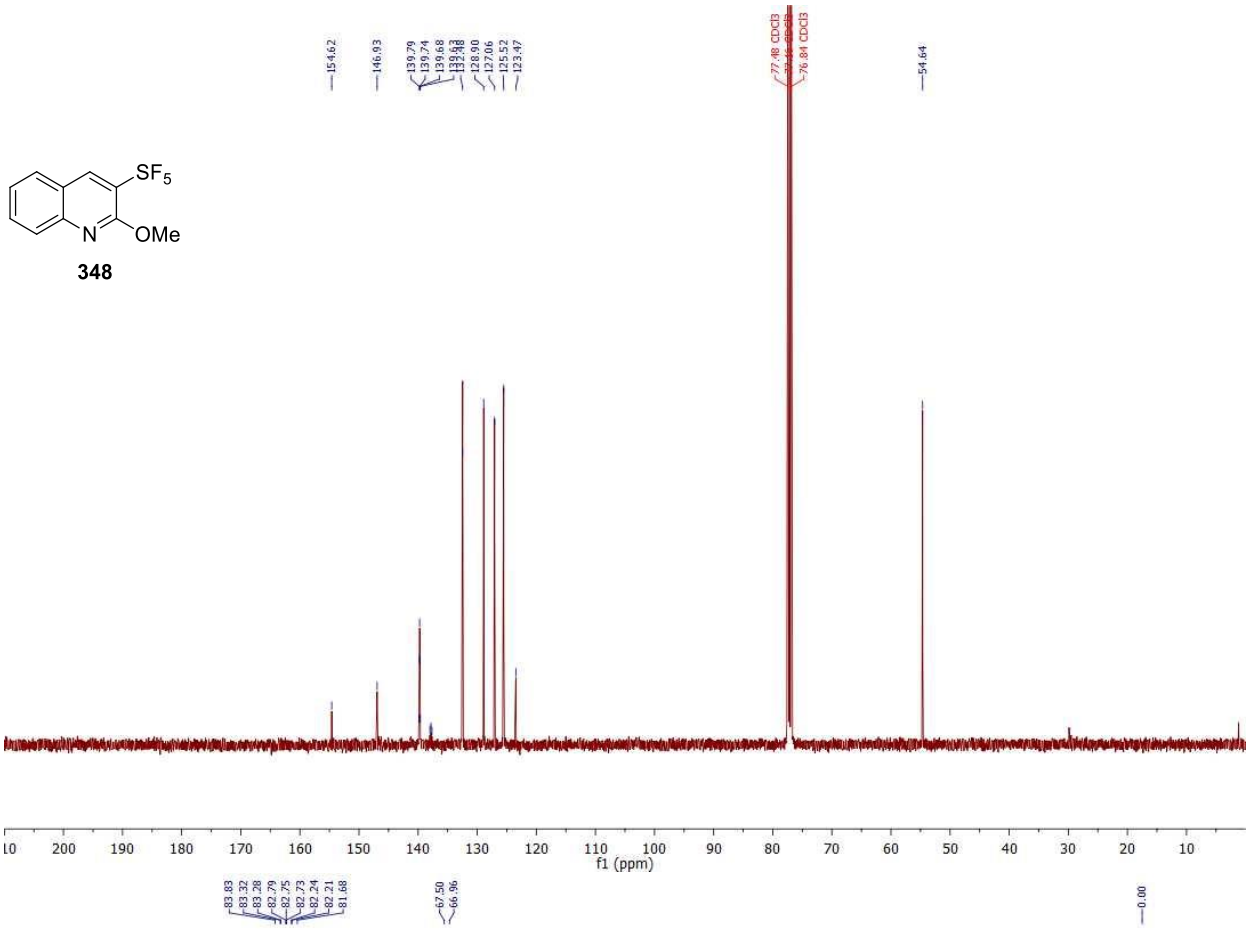

153.31
152.34
146.47
140.61
140.56
140.51
132.81
132.60
128.82
127.63
126.54
124.43
118.25
77.48 CDCl3
76.84 CDCl3
SF5
Br
N
O
347
f1 (ppm)

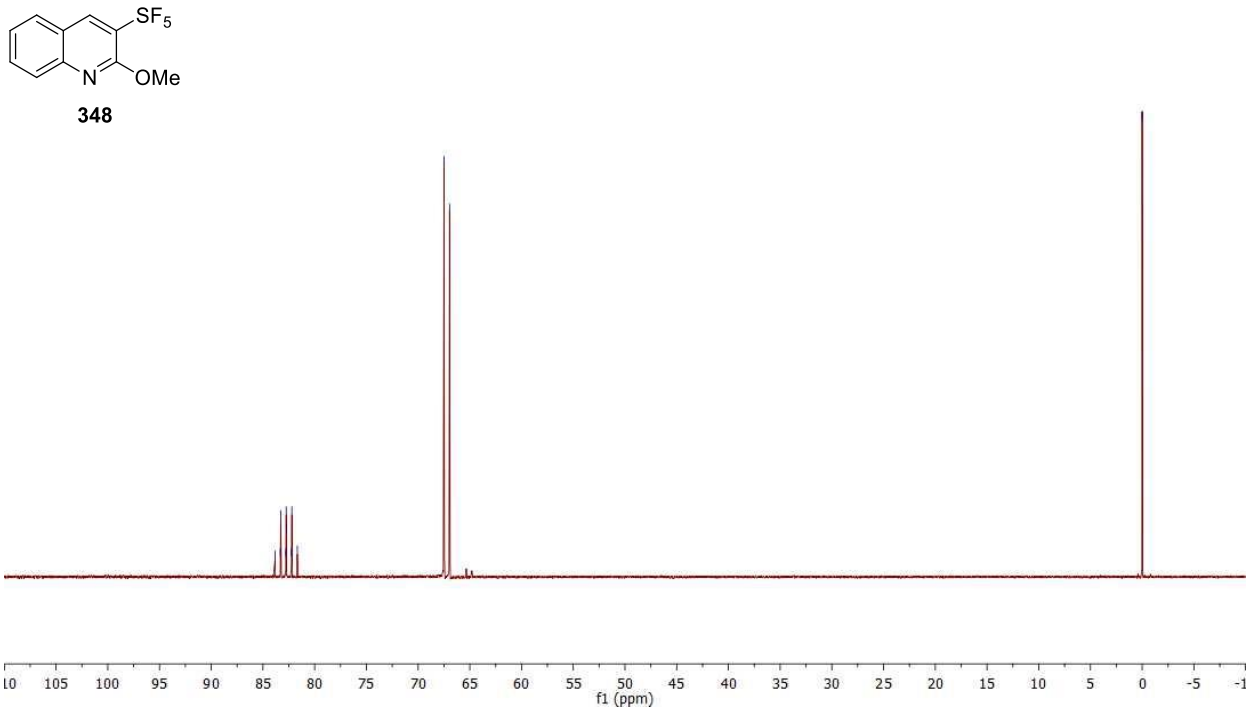

83.05
82.54
82.51
82.02
81.98
81.96
81.47
81.43
80.90
67.85
67.31
0.00
SF5
Br
N
O
f1 (ppm)

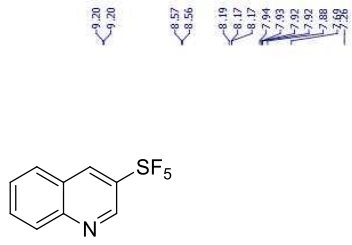
347


8.52
7.86
7.86
7.82
7.80
7.80
7.79
7.79
7.49
7.48
7.47
7.47
7.46
7.45
7.26
1.17
1.55
1.26
0.08
SF5
N
OMe
1.01
1.00
1.06
1.04
1.00
3.05
f1 (ppm)

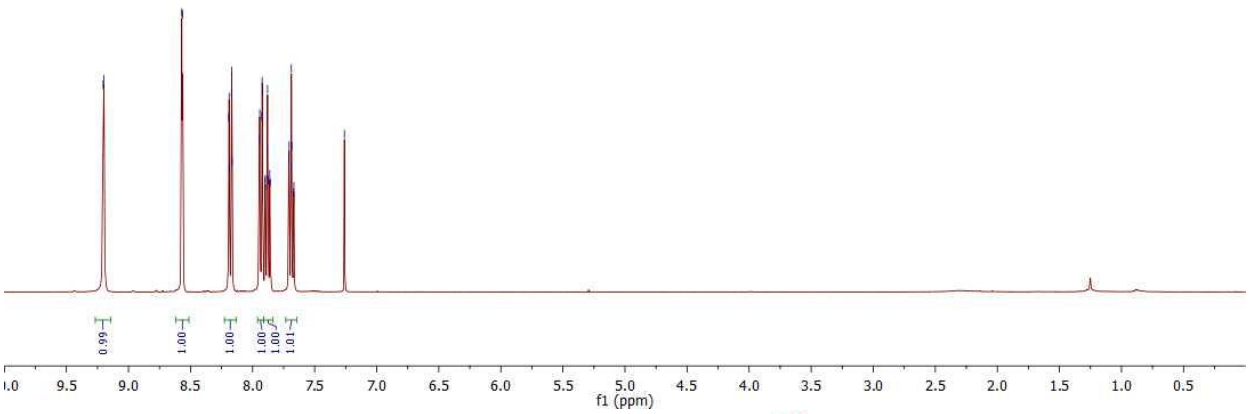
348

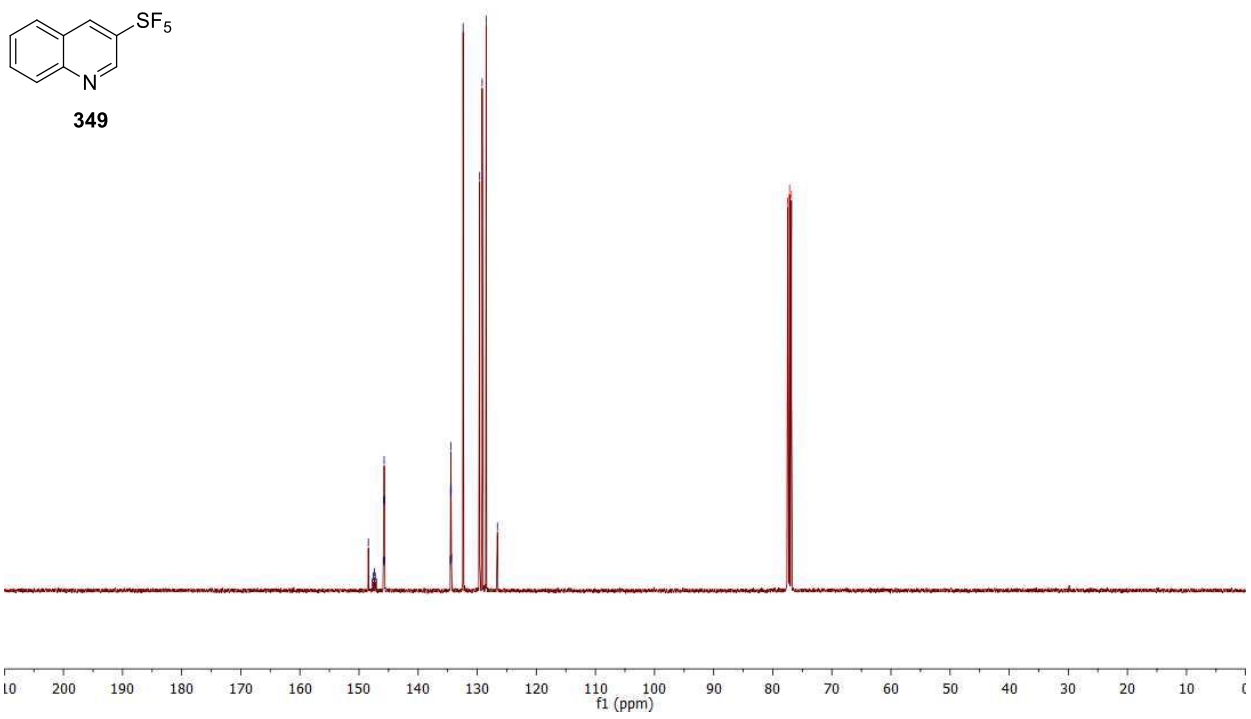

154.62
146.93
139.79
139.74
139.68
128.90
127.06
125.52
123.47
77.48 CDCl3
76.84 CDCl3
54.64
SF5
N
OMe
348
f1 (ppm)
83.83
83.32
83.28
82.79
82.75
82.73
82.24
82.21
81.68
67.50
66.96
0.00


SF5
N
OMe
348
f1 (ppm)

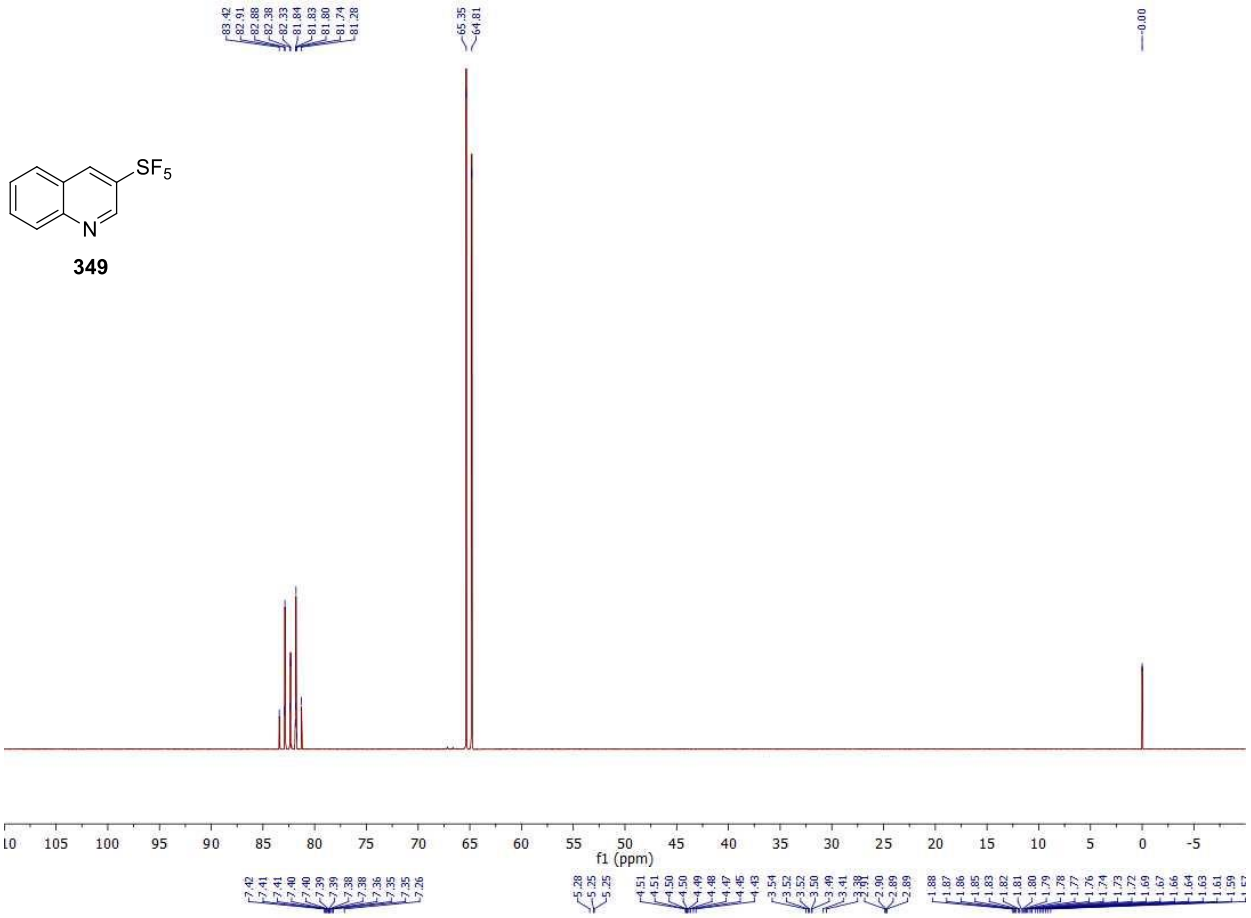


349

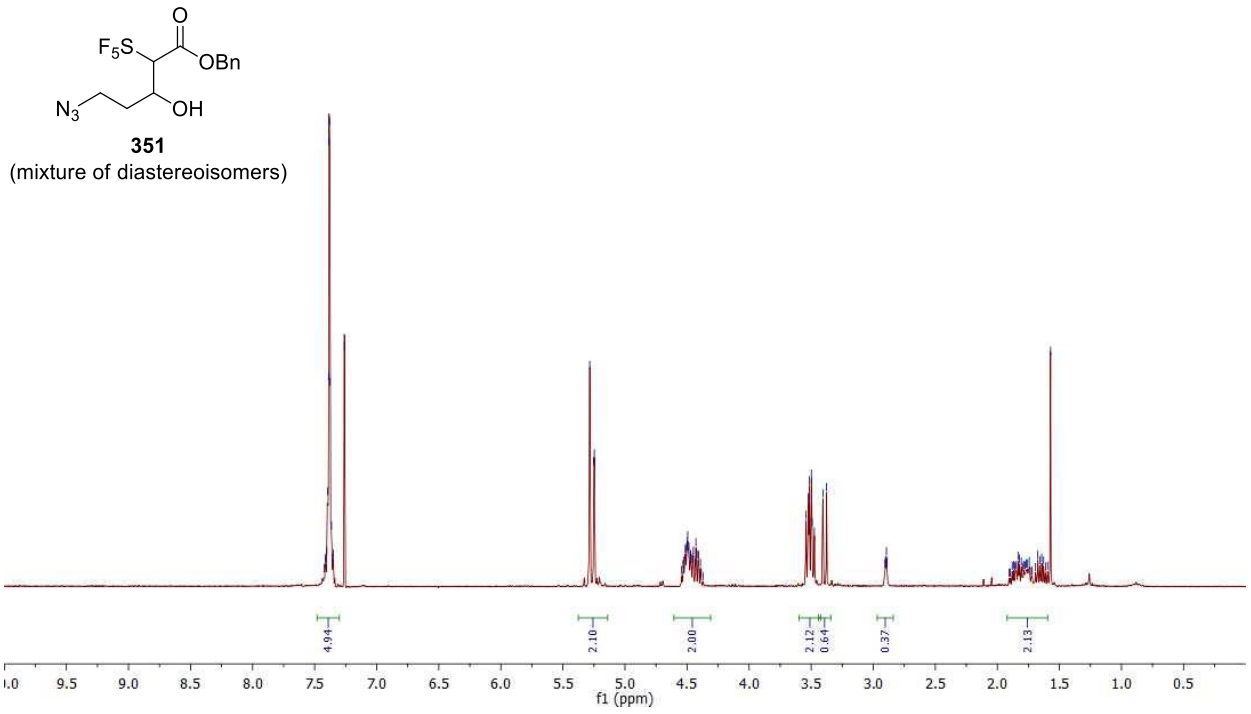




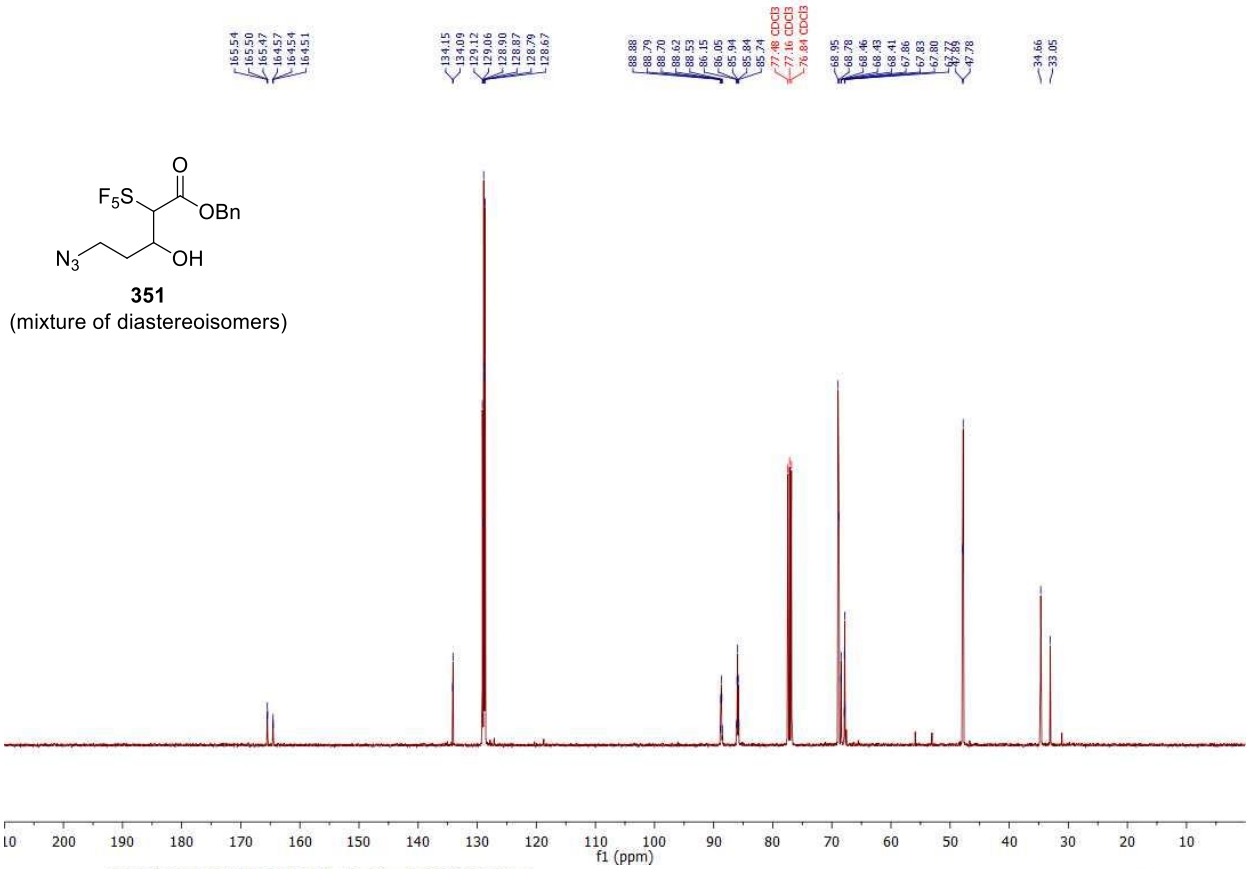
349



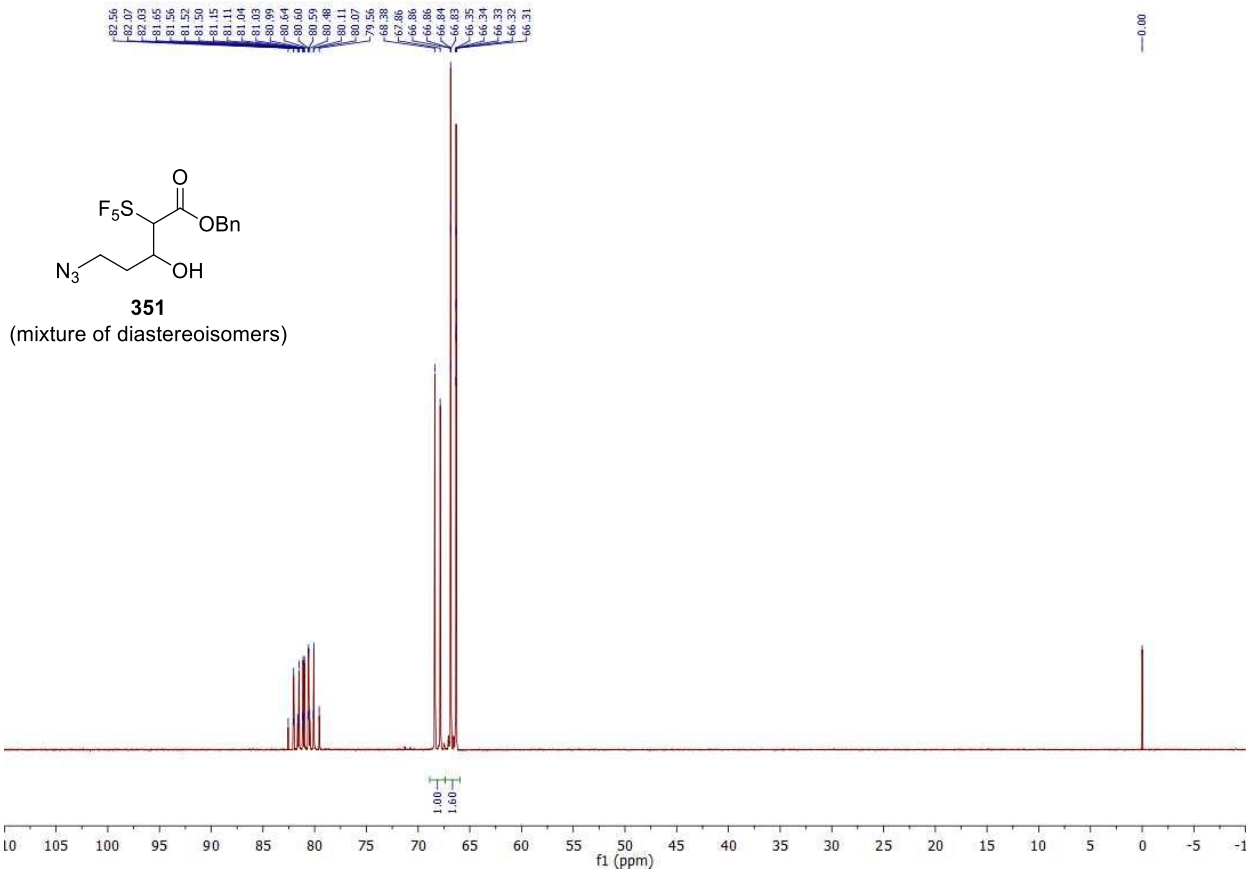
349



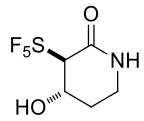
351
(mixture of diastereoisomers)



351
(mixture of diastereoisomers)

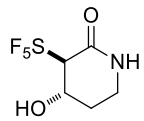


351
(mixture of diastereoisomers)



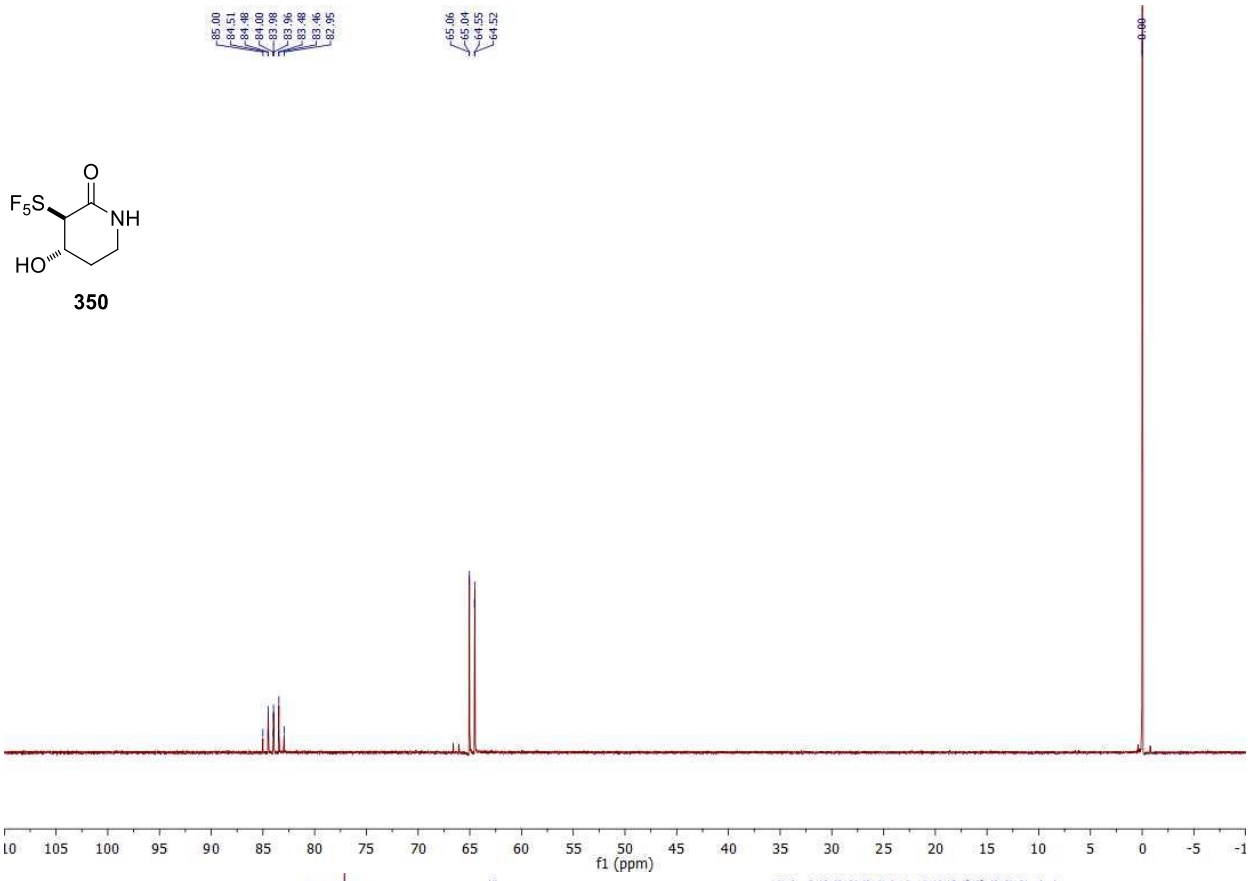
350

4.70
4.69
4.68
4.67
4.34
4.32
4.31
4.29
3.54
3.52
3.50
3.48
3.30
3.29
3.28
3.27
3.25
2.21
2.20
2.19
2.16
2.15
2.14
2.13
2.12
2.12
2.10
2.10
1.99
1.98
1.97
1.97
1.96
1.95
1.94
1.93
1.93
1.92
1.08
1.00
1.14
0.94
1.27
1.14
f1 (ppm)

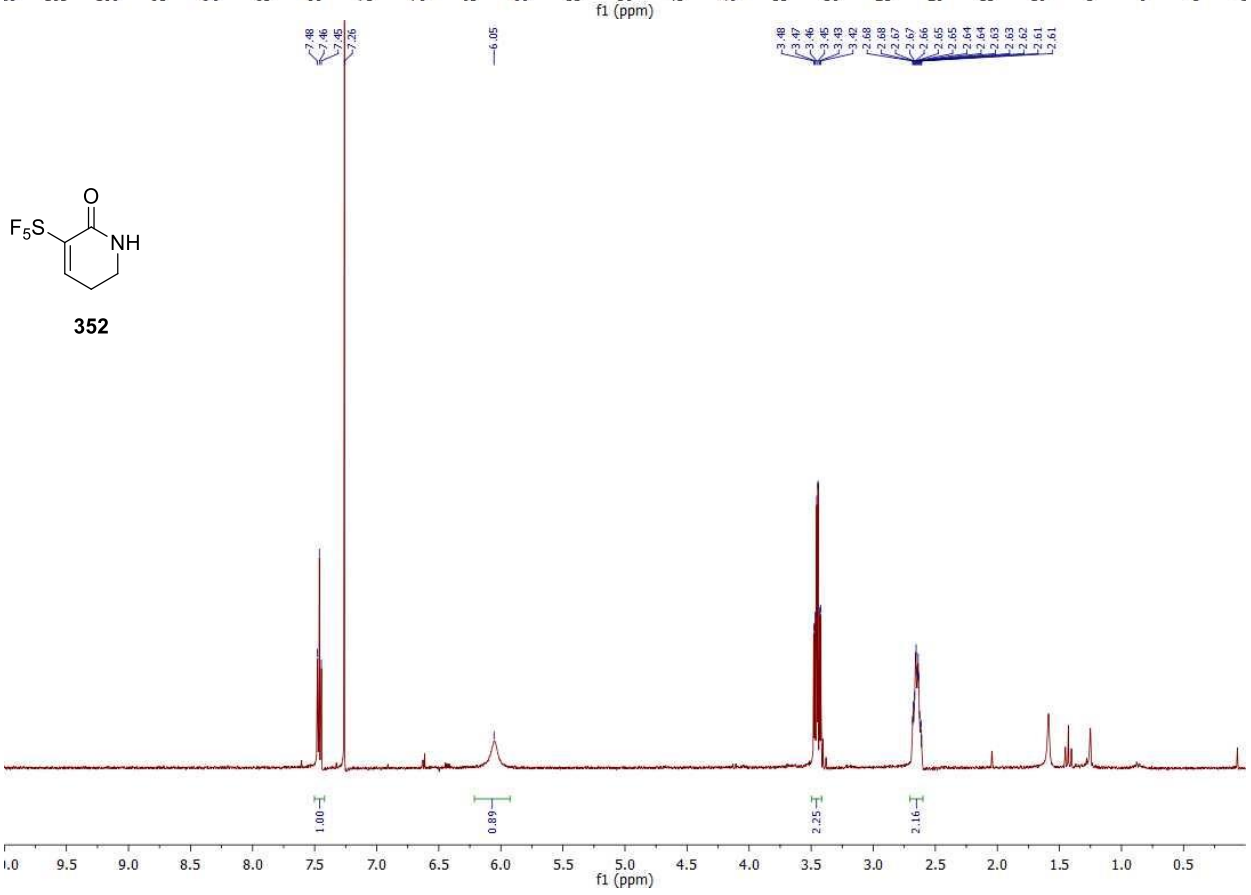


350

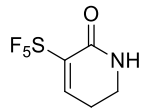
164.36
164.33
164.31
164.29
164.25
86.25
86.18
86.11
86.04
85.98
65.97
65.94
65.90
65.86
65.82
49.64 MeOD
49.43 MeOD
49.21 MeOD
48.79 MeOD
48.57 MeOD
48.36 MeOD
38.04
25.88
f1 (ppm)


85.00
84.51
84.48
84.00
83.98
83.96
83.48
83.46
82.95
65.06
65.04
64.55
64.52
0.00
f1 (ppm)

350

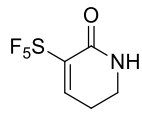

7.48
7.46
7.45
7.26
6.05
3.48
3.47
3.46
3.45
3.43
3.42
2.68
2.67
2.66
2.65
2.64
2.63
2.62
2.61
1.00
0.89
2.25
2.16
f1 (ppm)

352

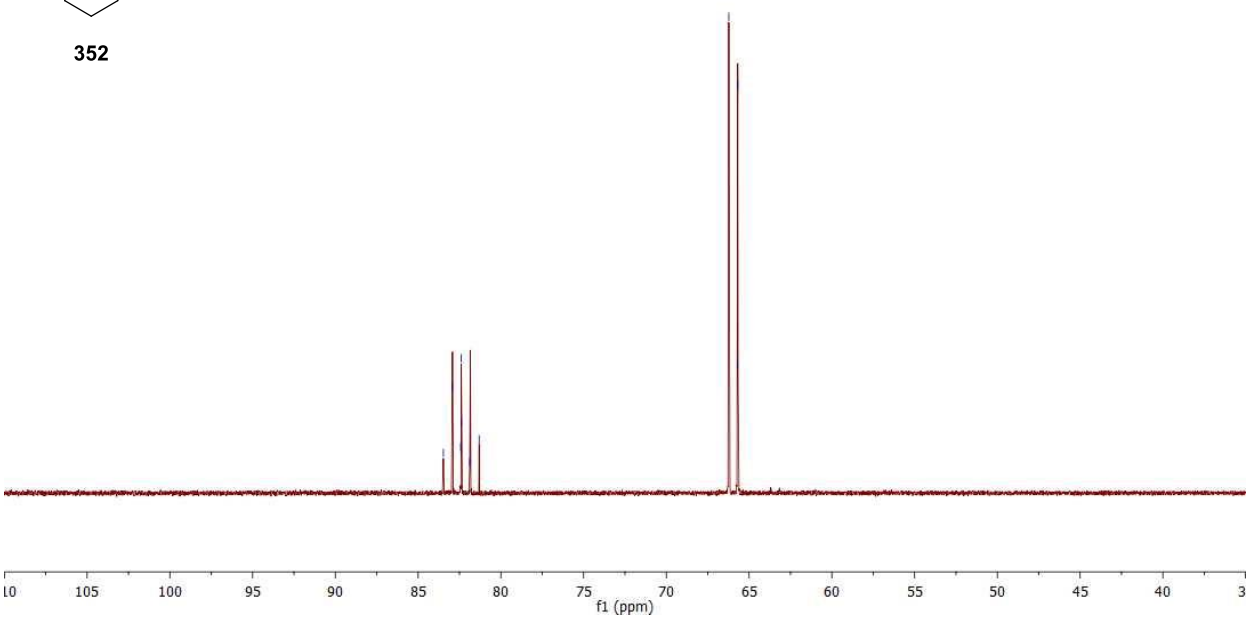

O
F5S
NH

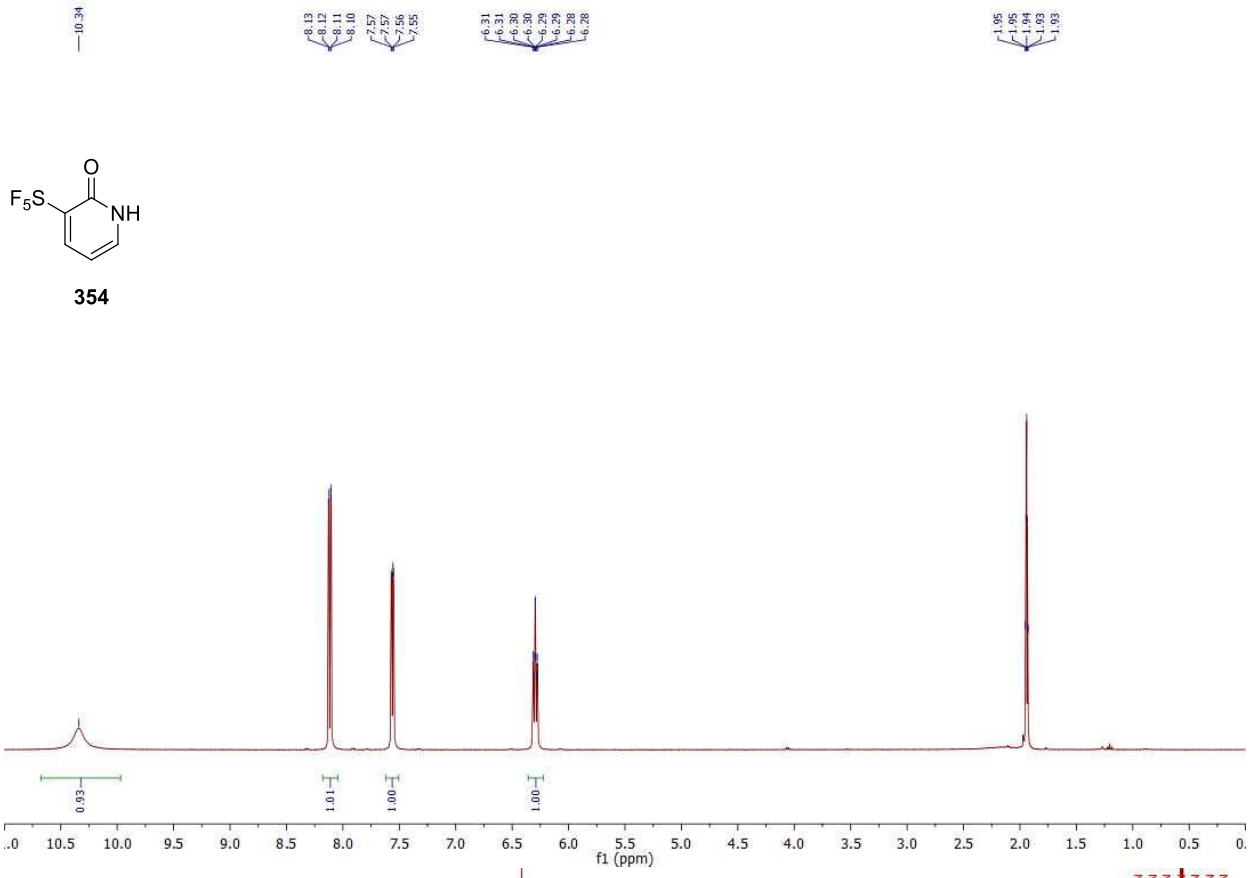
352

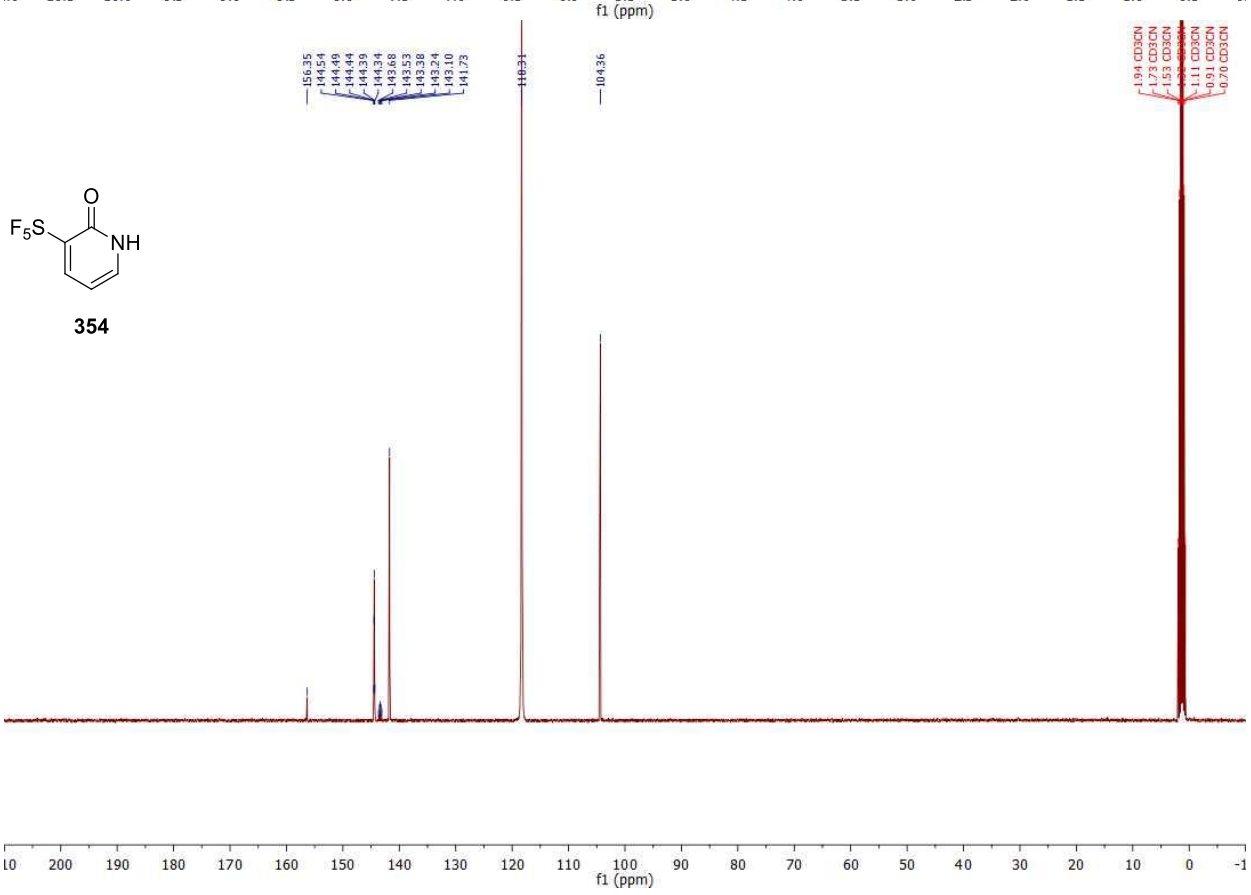
146.06
146.01
145.96
77.48 CDCl3
76.84 CDCl3
38.80
24.82
f1 (ppm)
83.47
82.92
82.45
82.39
82.37
81.88
81.31
66.23
65.70
65.68

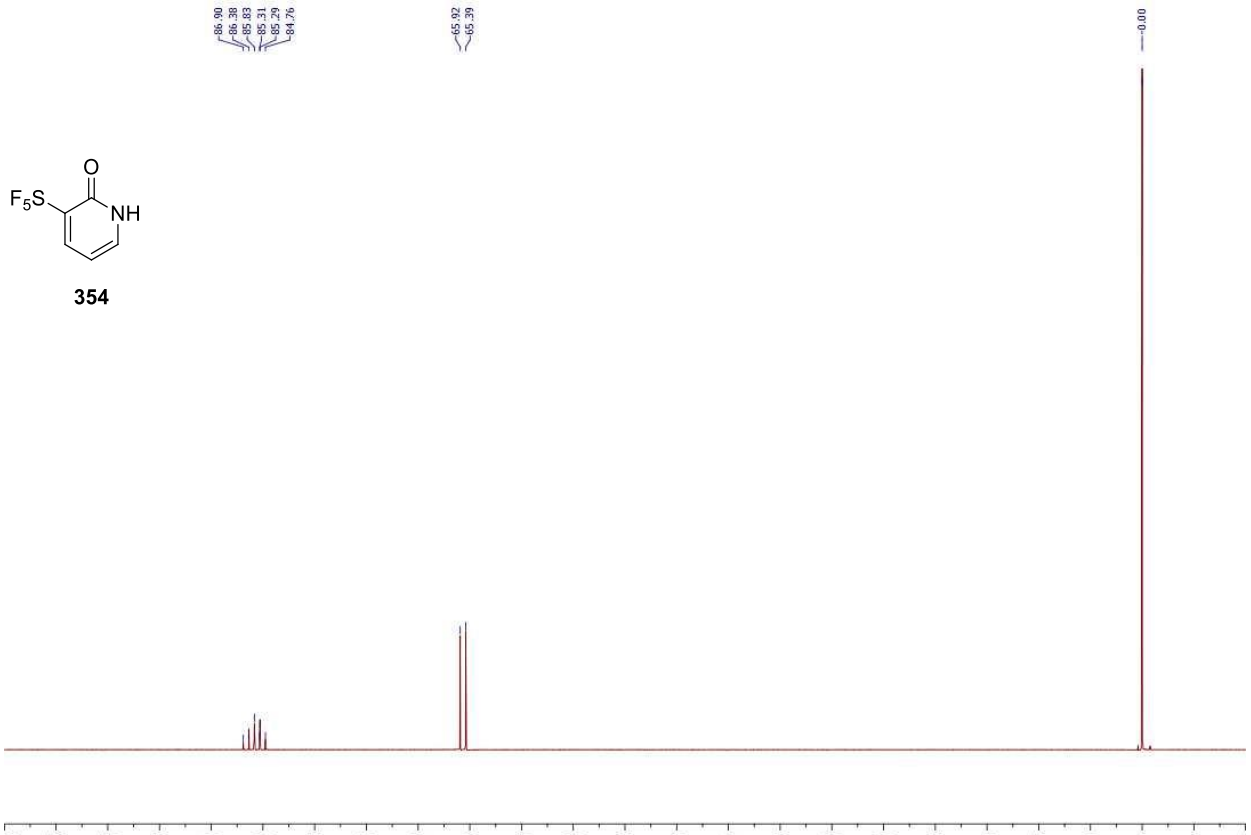

O
F5S
NH

352

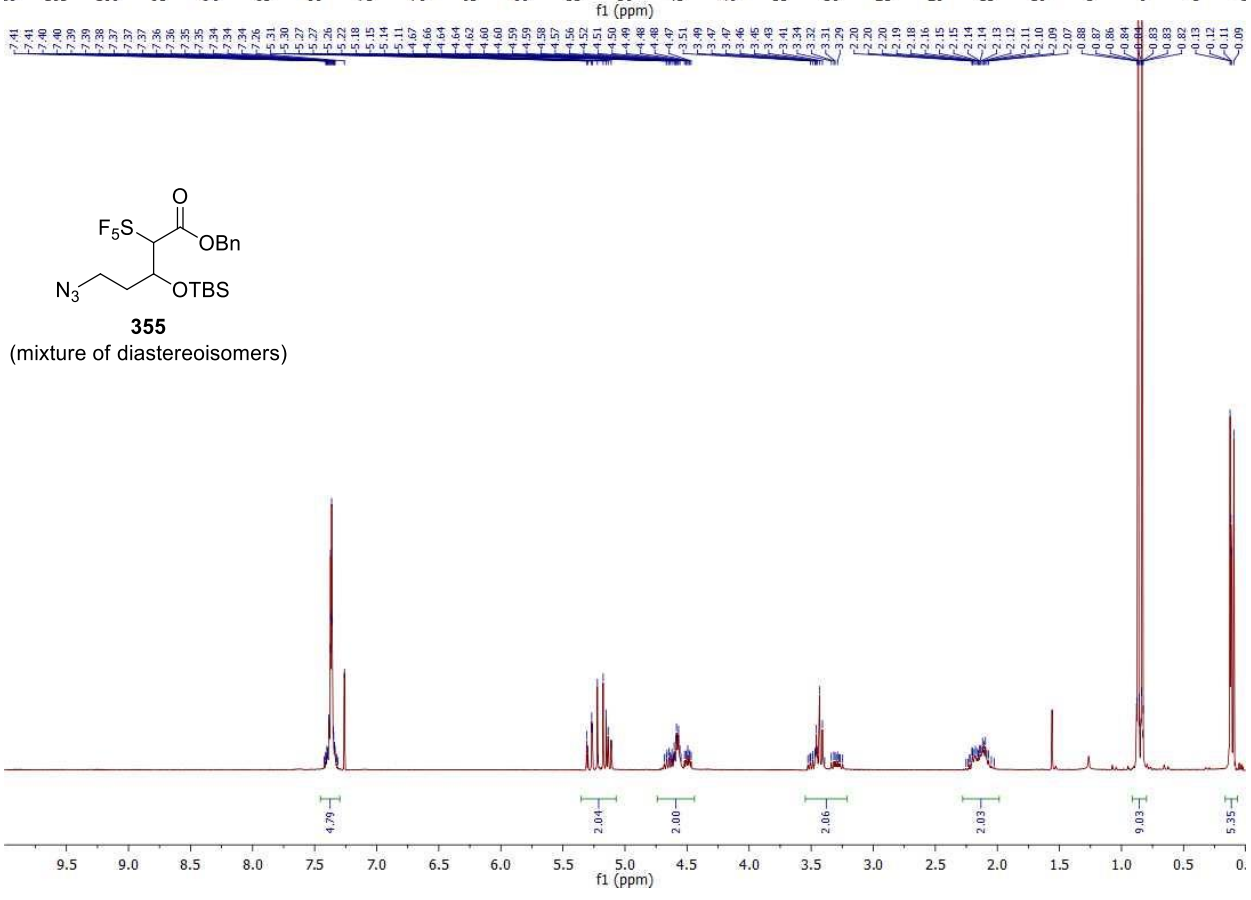

f1 (ppm)


10.34
8.13
8.12
8.11
8.10
7.57
7.57
7.56
7.55
6.31
6.31
6.30
6.30
6.29
6.29
6.28
6.28
1.95
1.95
1.94
1.93
1.93
O
F5S
NH
354
0.93
1.01
1.00
1.00
f1 (ppm)

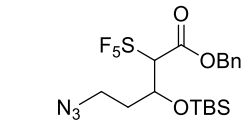

156.35
144.54
144.49
144.44
144.39
144.34
143.68
143.53
143.38
143.24
143.10
141.73
118.31
104.36
1.94 CD3CN
1.73 CD3CN
1.53 CD3CN
1.11 CD3CN
0.91 CD3CN
0.70 CD3CN
O
F5S
NH
354
f1 (ppm)



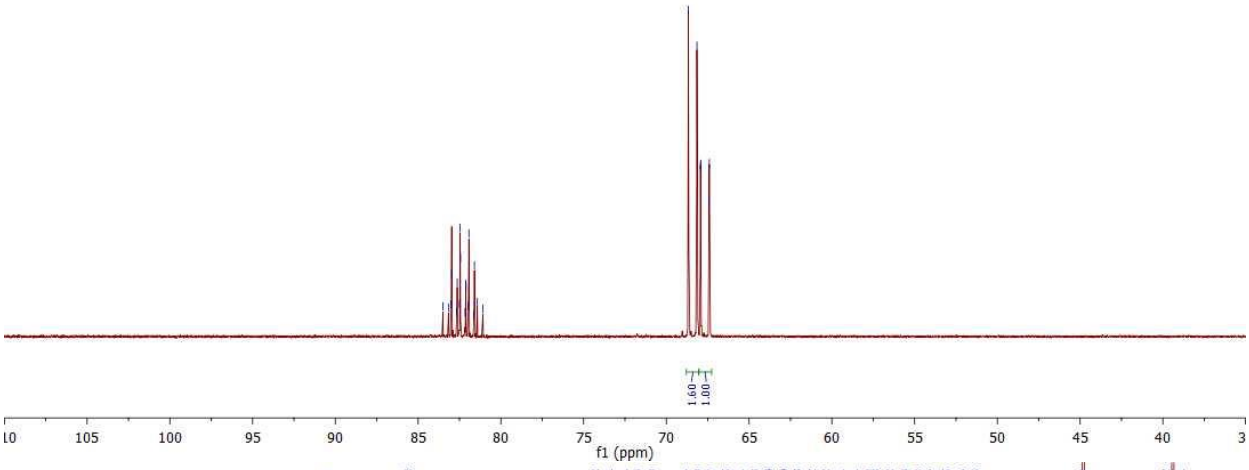
354

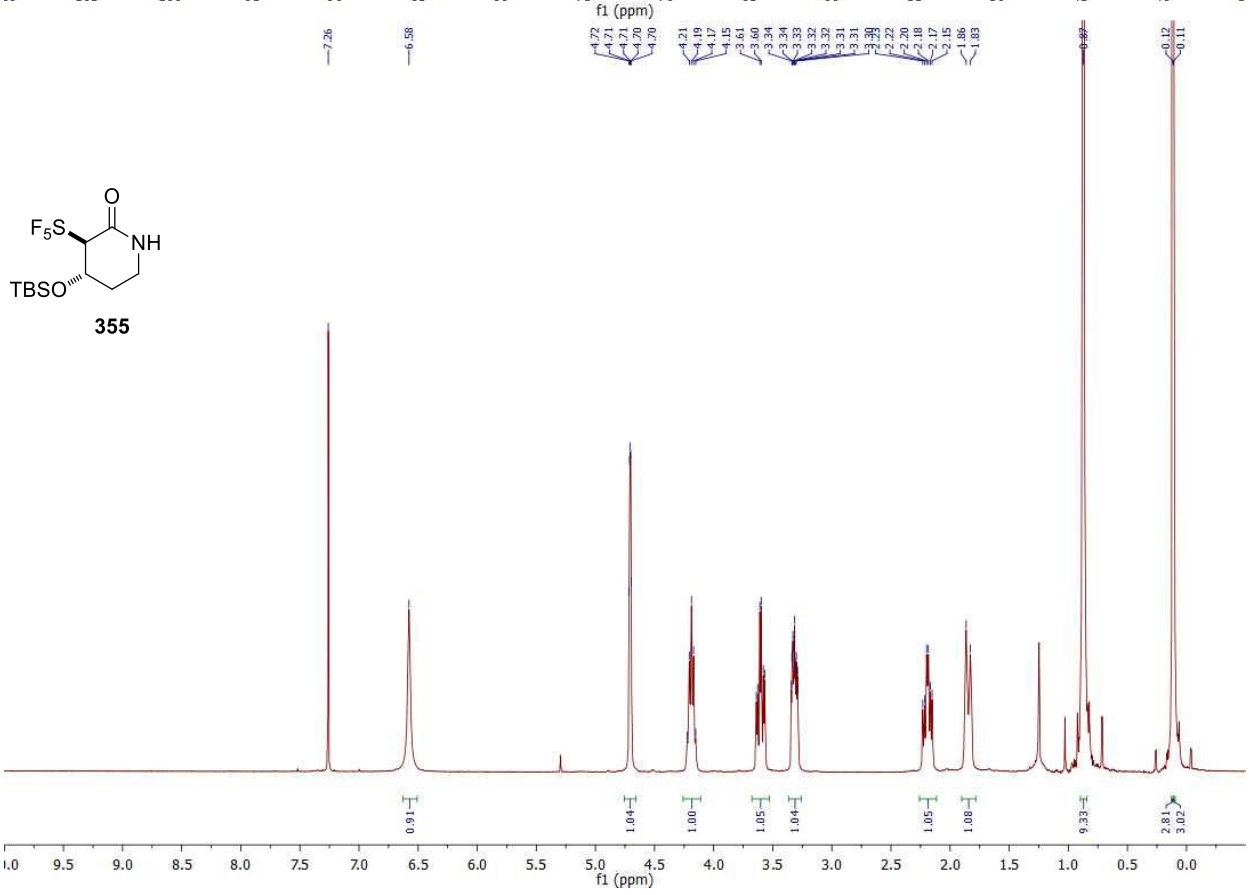


355
(mixture of diastereoisomers)

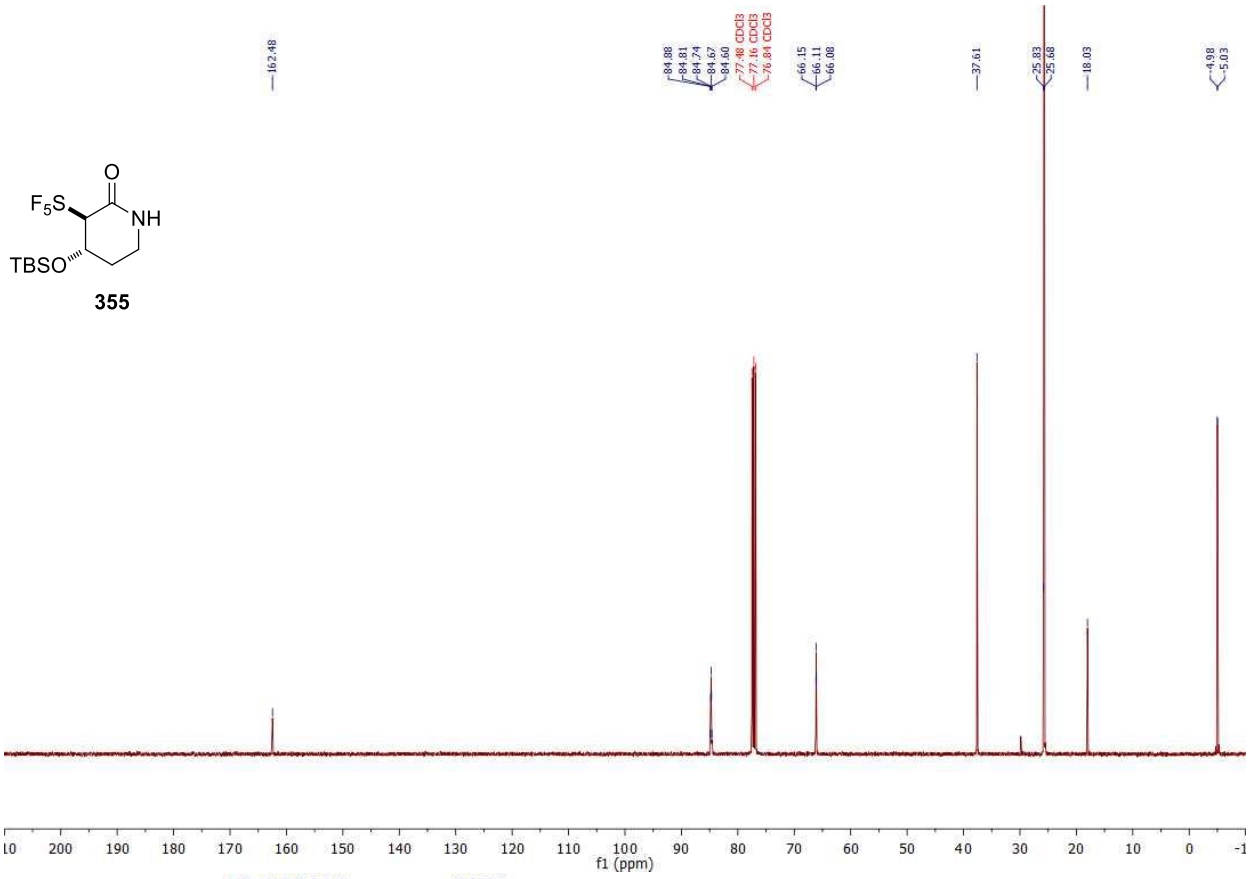


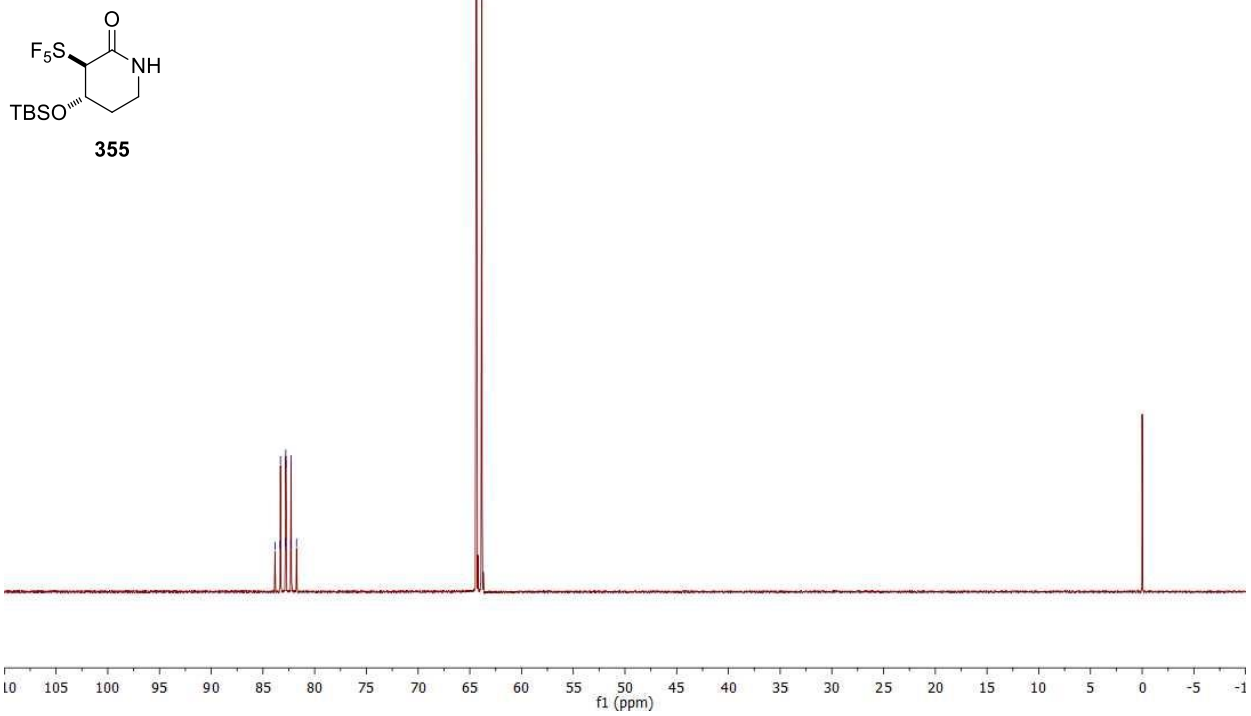
355
(mixture of diastereoisomers)



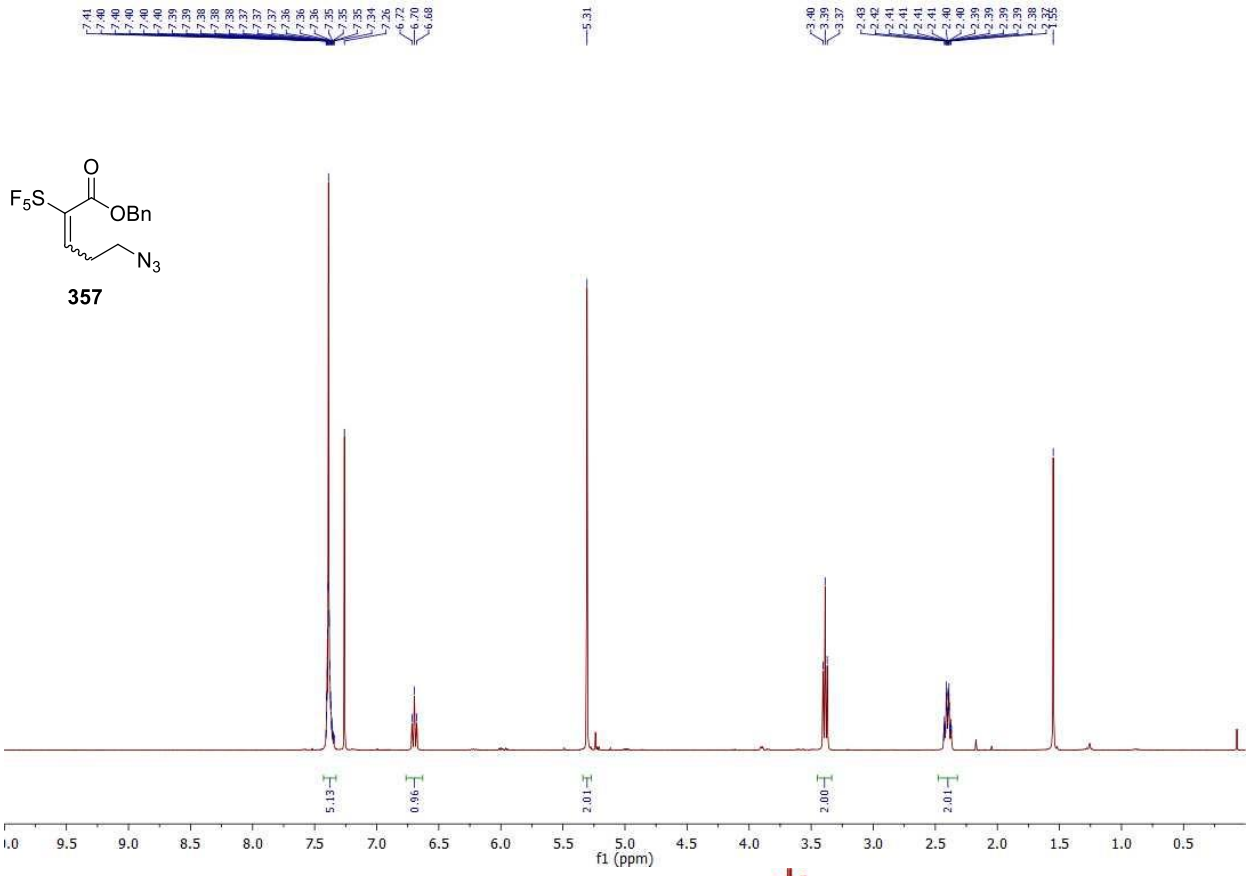


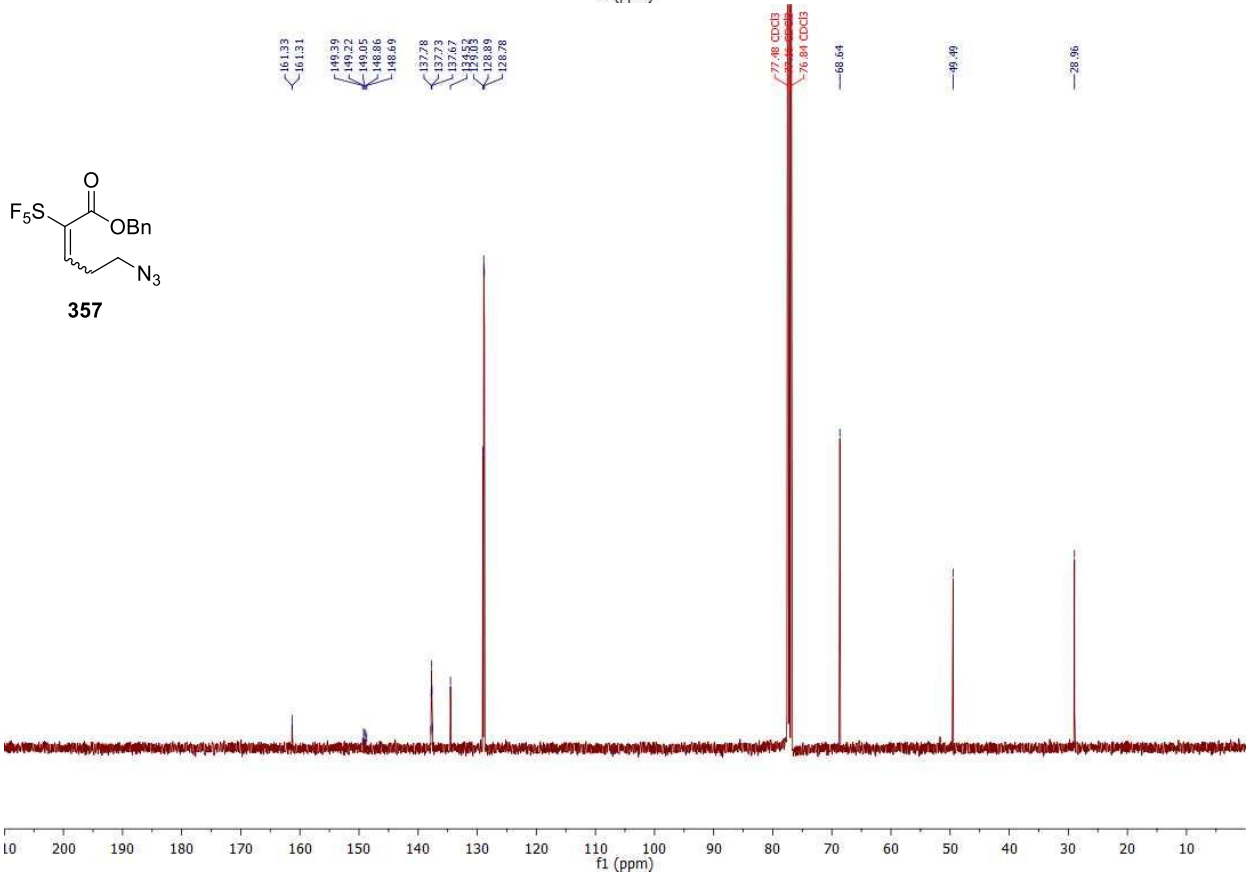
355

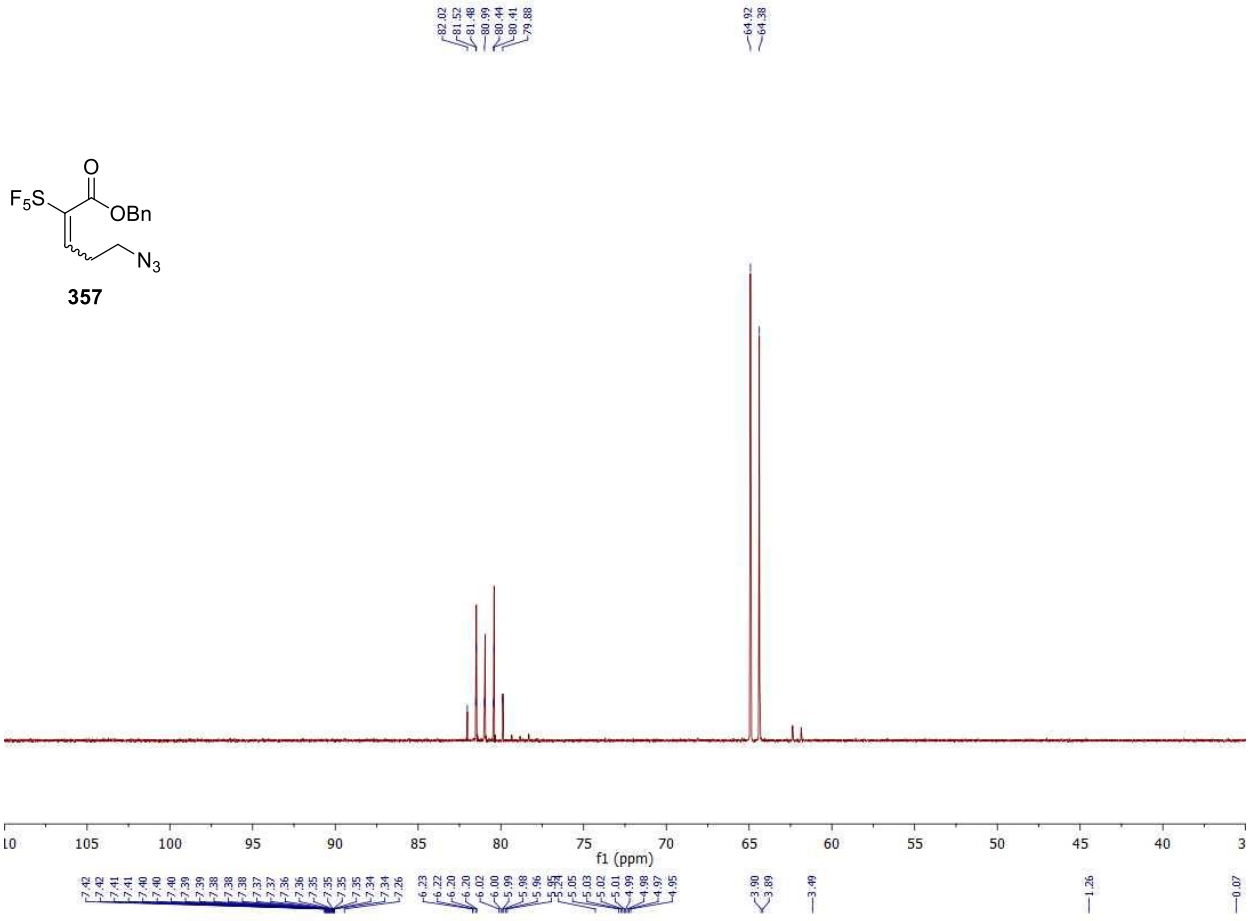

162.48
84.88
84.81
84.74
84.67
84.60
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
66.15
66.11
66.08
37.61
25.83
25.68
18.03
-4.98
-5.03
f1 (ppm)

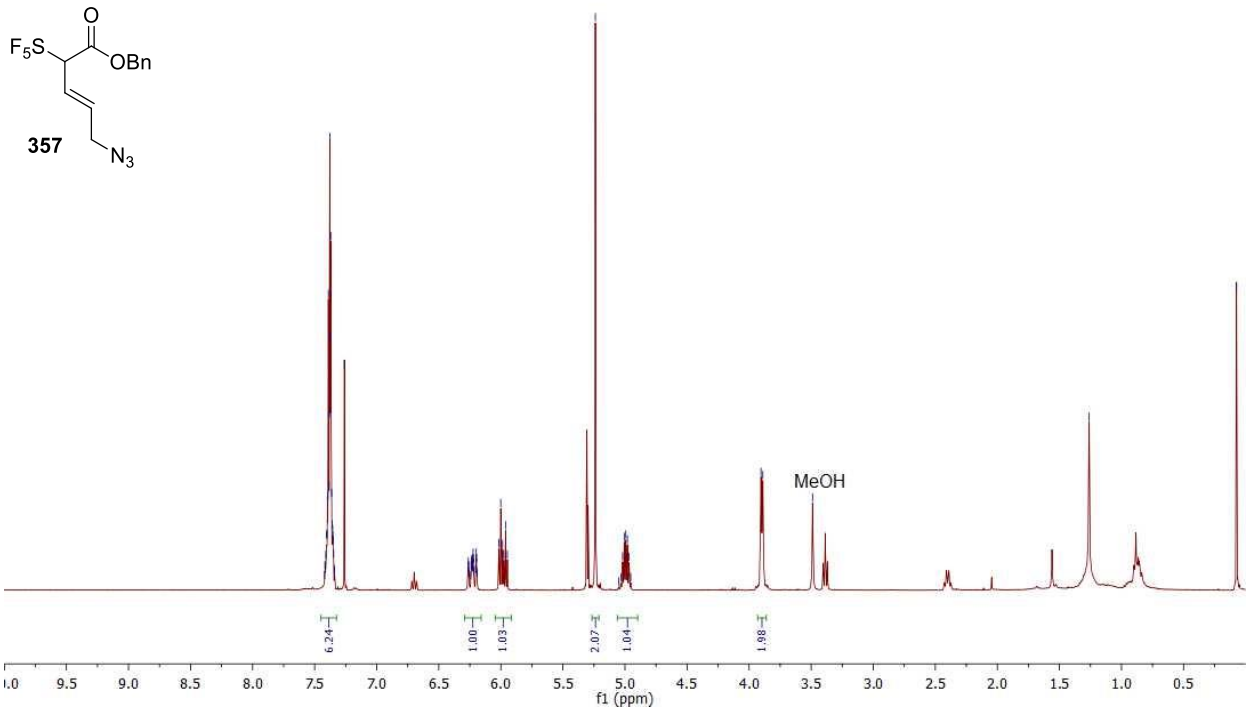

83.83
83.34
83.31
82.82
82.79
82.78
82.30
82.27
81.75
64.38
64.35
63.86
63.83
f1 (ppm)

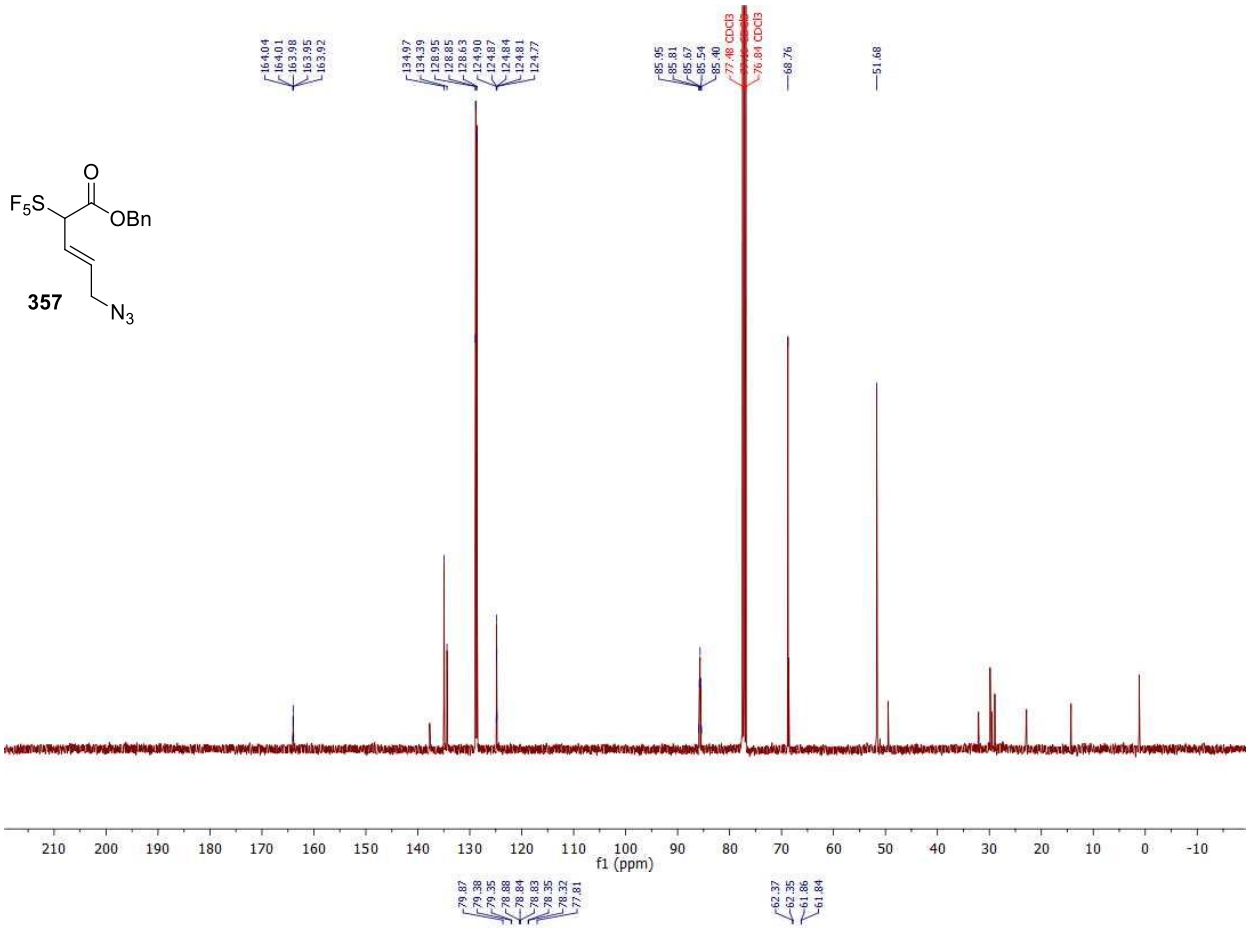
355

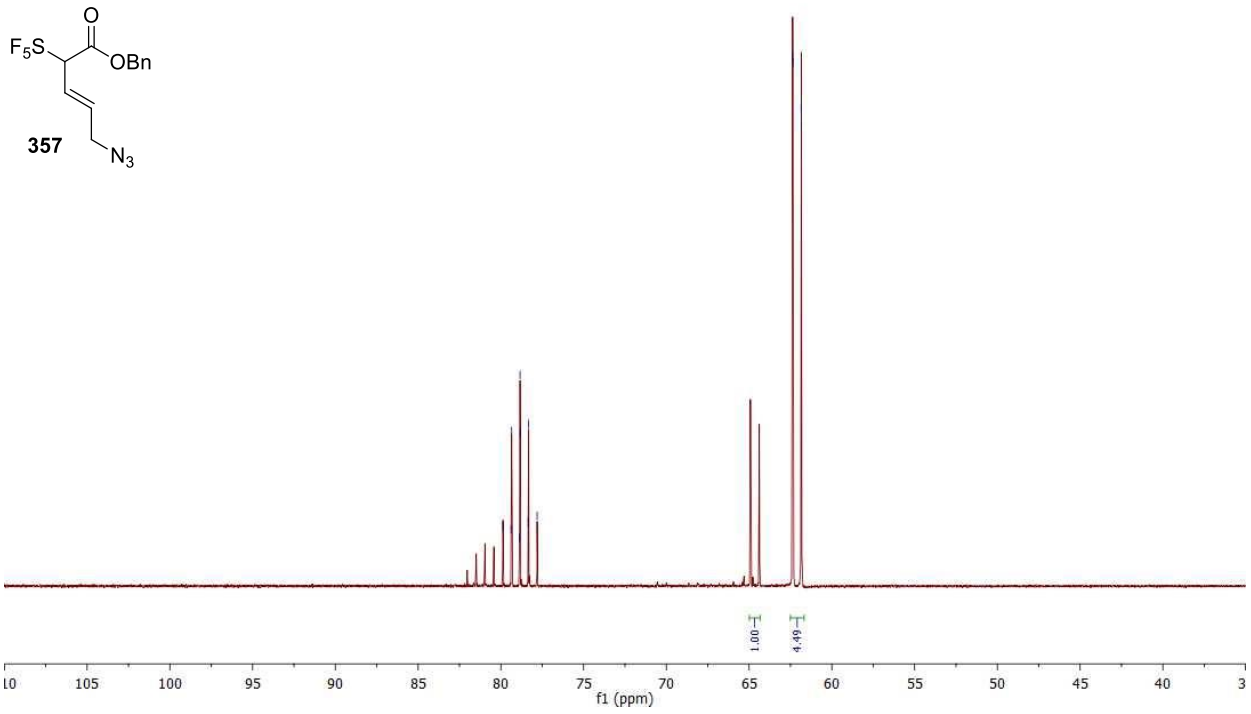

F5S
O
OBn
N3
357
f1 (ppm)

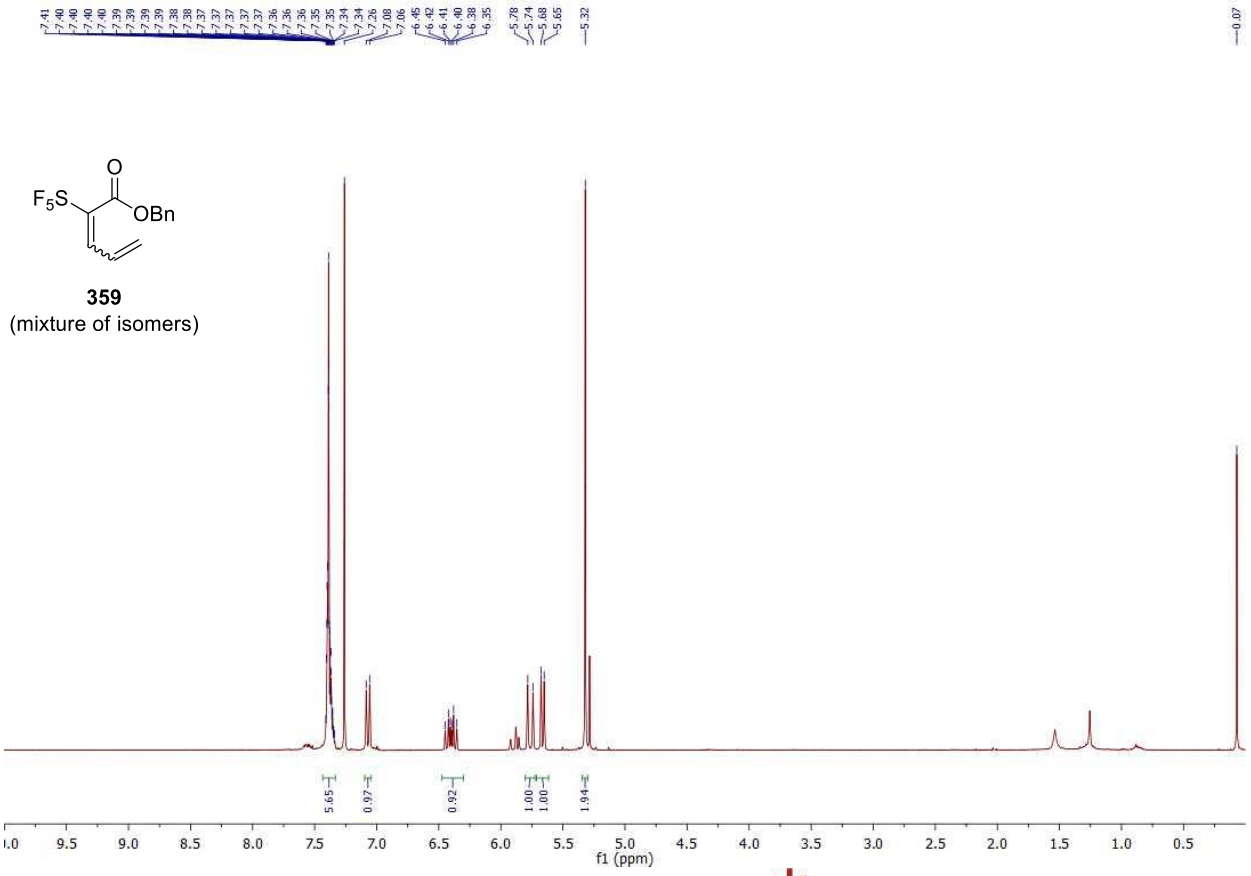

F5S
O
OBn
N3
357
f1 (ppm)

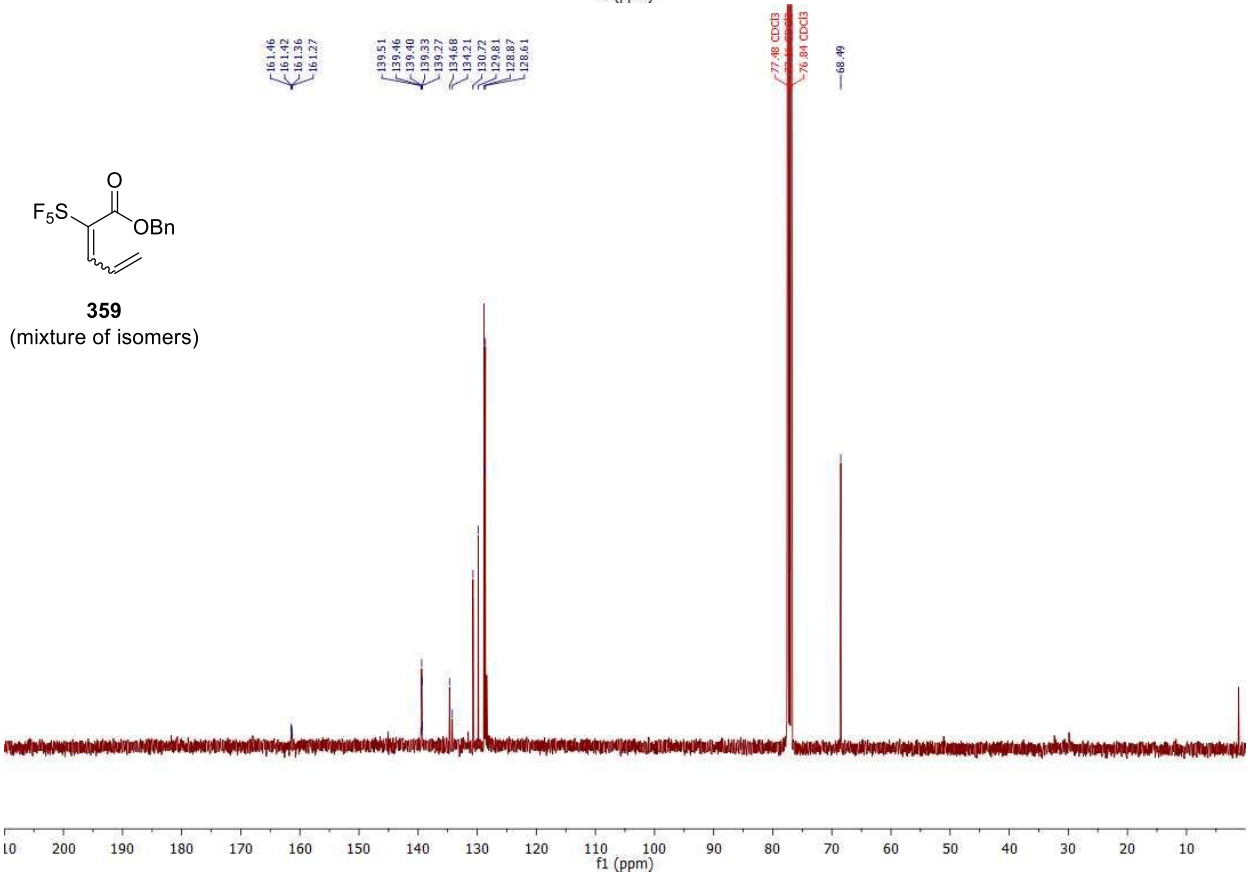

82.02
81.52
81.48
80.99
80.44
80.41
79.88
64.92
64.38
O
F5S
OBn
N3
357
f1 (ppm)
7.42
7.42
7.41
7.41
7.40
7.40
7.40
7.39
7.39
7.38
7.38
7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.35
7.35
7.34
7.34
7.26
6.23
6.22
6.20
6.20
6.02
6.00
5.99
5.98
5.96
5.95
5.94
5.05
5.03
5.02
5.01
4.99
4.98
4.97
4.95
3.90
3.89
3.49
1.26
0.07

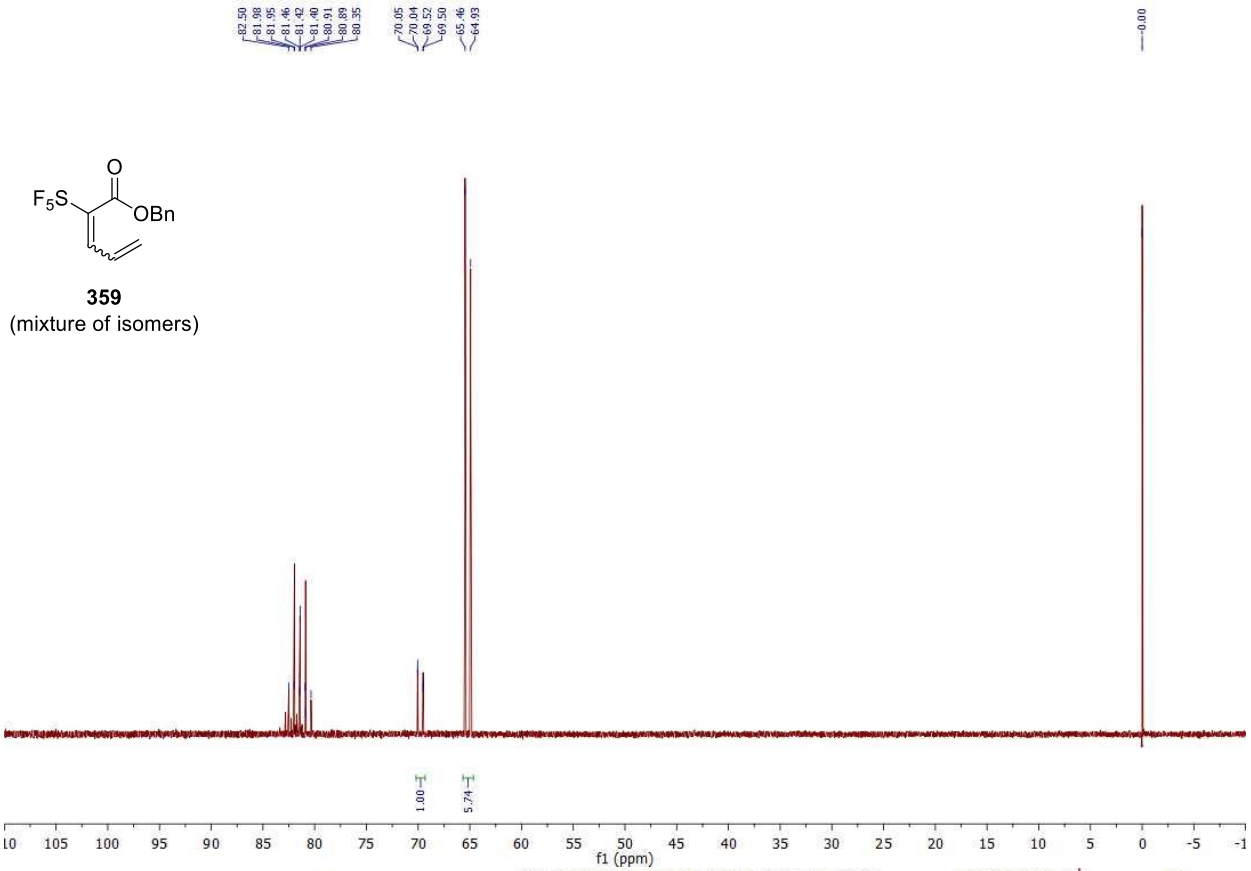

O
F5S
OBn
357
N3
MeOH
6.24
1.00
1.03
2.07
1.04
1.98
f1 (ppm)


164.04
164.01
163.98
163.95
163.92
134.97
134.39
128.95
128.85
128.63
124.90
124.87
124.84
124.81
124.77
85.95
85.81
85.67
85.54
85.40
77.48 CDCl3
76.84 CDCl3
68.76
51.68
f1 (ppm)
79.87
79.38
79.35
78.88
78.84
78.83
78.35
78.32
77.81
62.37
62.35
61.86
61.84

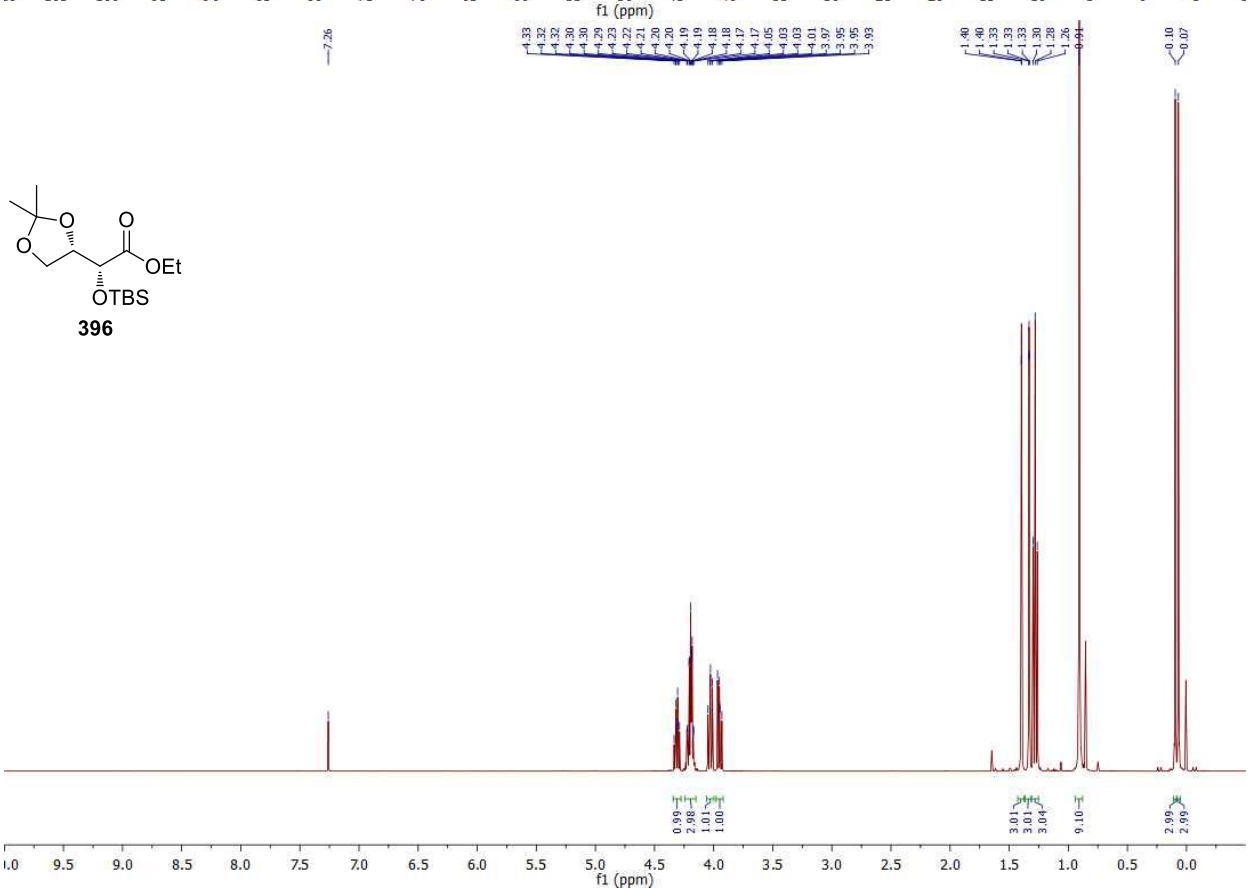

1.00
4.49
f1 (ppm)


F5S
O
OBn
359
(mixture of isomers)
f1 (ppm)

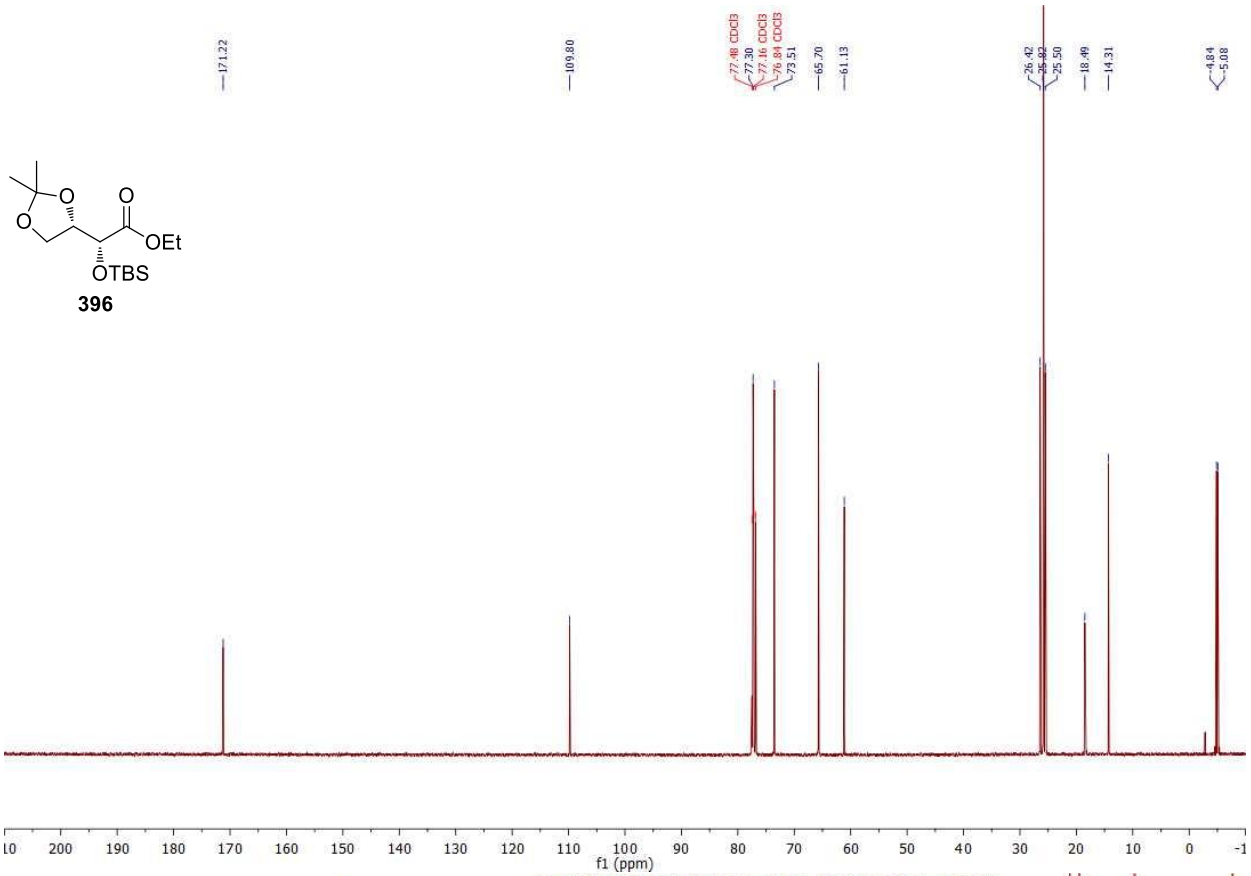

F5S
O
OBn
359
(mixture of isomers)
f1 (ppm)



359
(mixture of isomers)

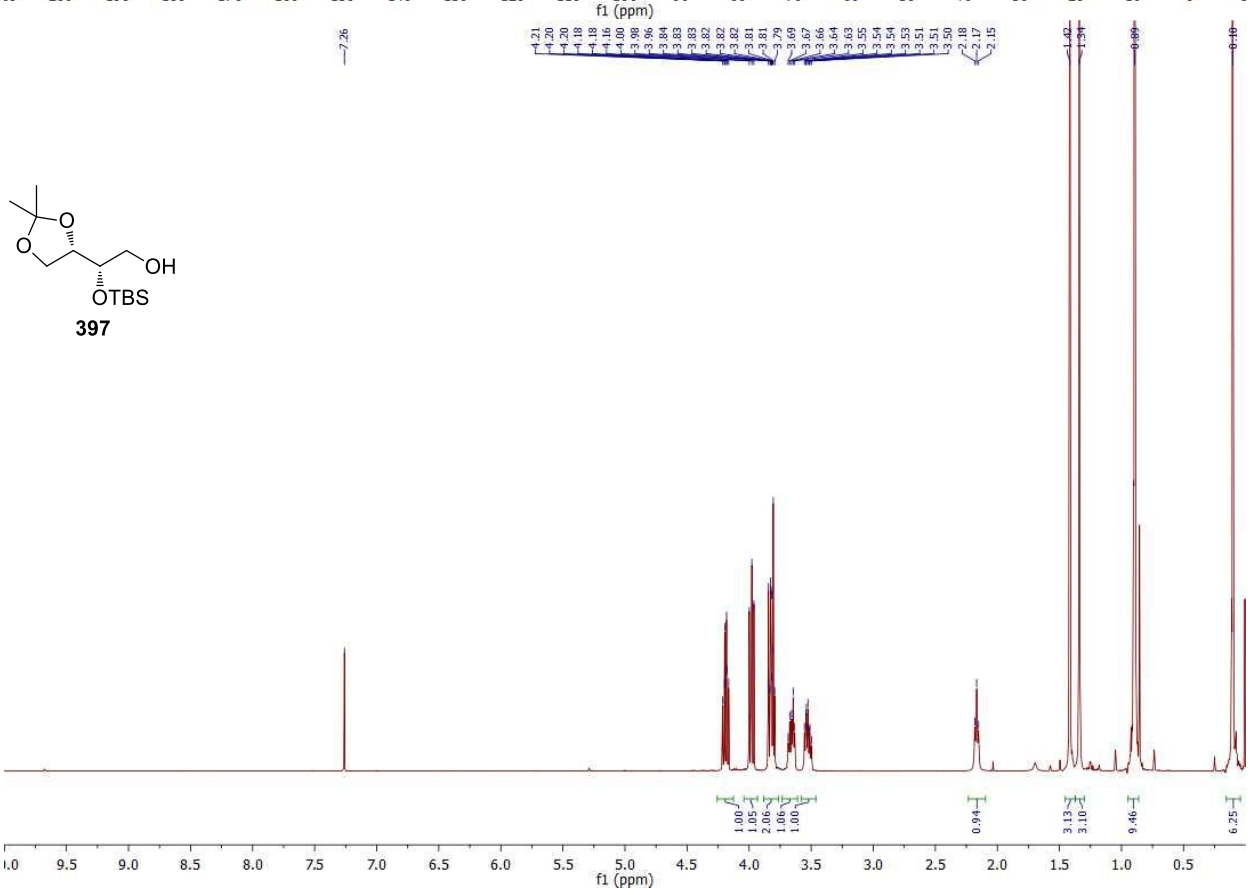


396


171.22
109.80
77.48 CDCl3
77.30
77.16 CDCl3
76.84 CDCl3
73.51
65.70
61.13
26.42
25.92
25.50
18.49
14.31
-4.84
-5.08
f1 (ppm)

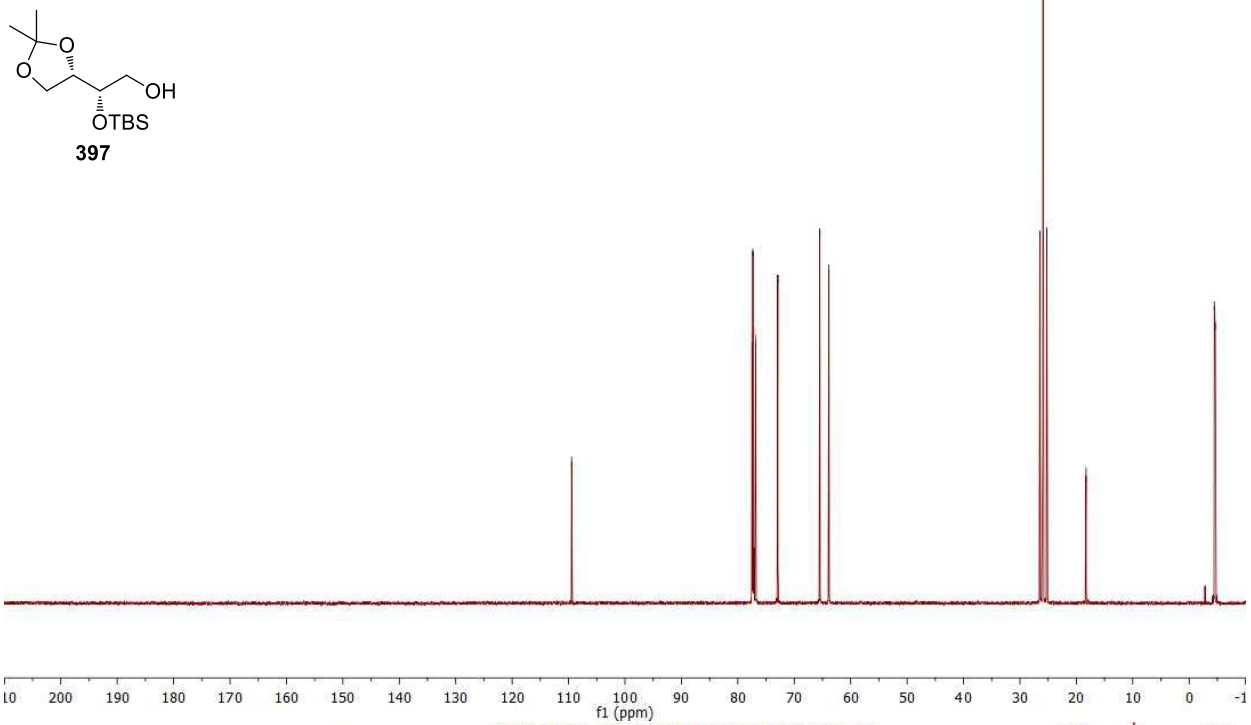
O
O
O
OEt
OTBS

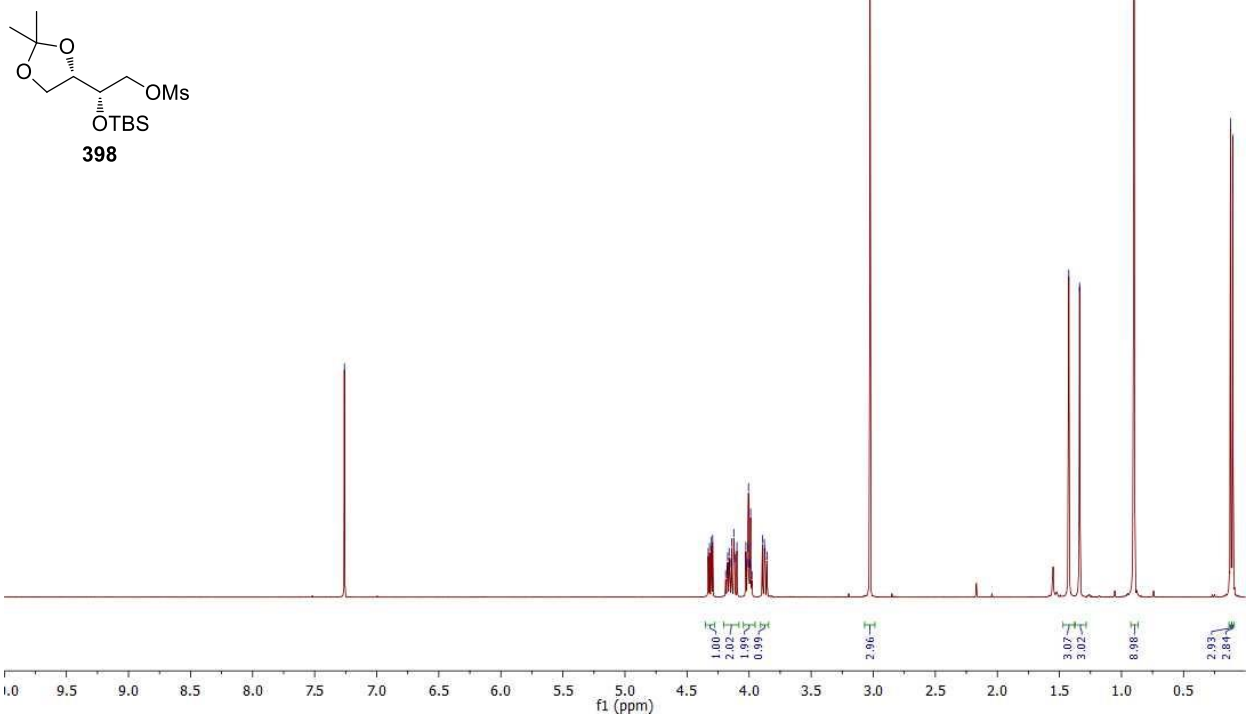
396


7.26
4.21
4.20
4.20
4.18
4.18
4.16
4.00
3.98
3.96
3.84
3.83
3.83
3.82
3.82
3.82
3.81
3.81
3.79
3.69
3.67
3.66
3.64
3.63
3.55
3.54
3.54
3.53
3.51
3.51
3.50
2.18
2.17
2.15
1.42
1.34
0.89
0.10
1.00
1.05
2.06
1.06
1.00
0.94
3.13
3.10
9.46
6.25
f1 (ppm)

O
O
OH
OTBS

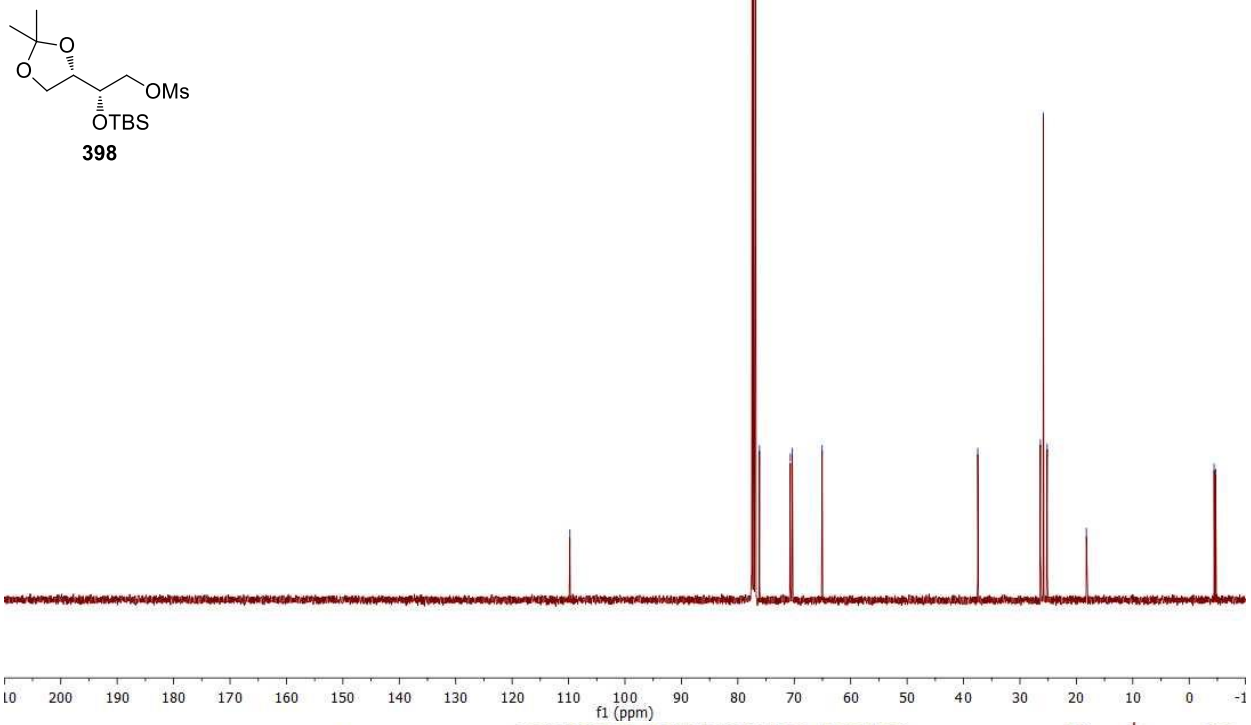
397


109.46
77.48 CDCl3
77.33
77.16 CDCl3
76.84 CDCl3
72.91
65.47
63.85
26.47
25.94
25.25
18.28
4.46
4.61
f1 (ppm)

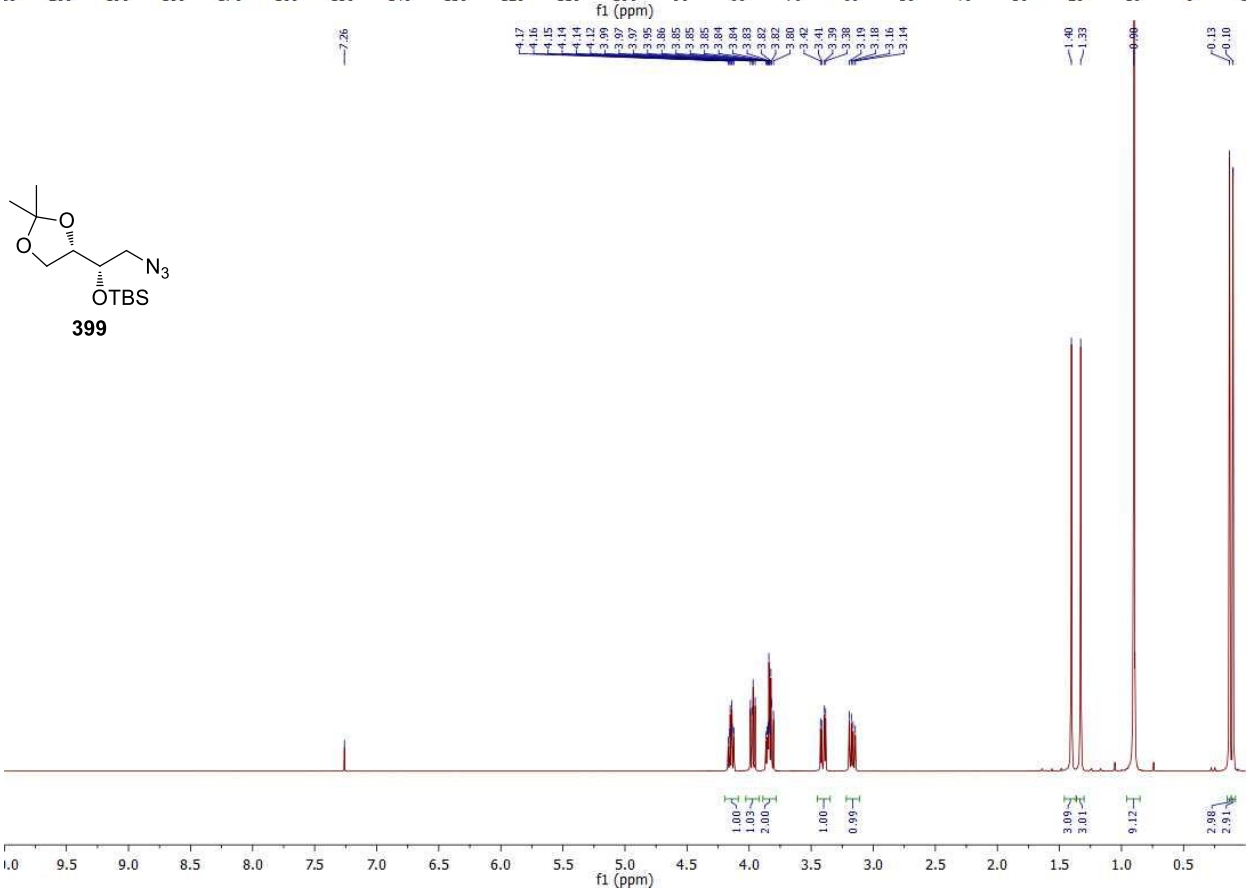

7.26
4.33
4.32
4.30
4.29
4.19
4.18
4.17
4.16
4.16
4.14
4.14
4.12
4.12
4.10
4.03
4.02
4.01
4.00
4.00
3.99
3.99
3.98
3.89
3.88
3.87
3.86
3.03
1.42
1.34
0.00
0.12
0.10
1.00
2.02
1.99
0.99
2.96
3.07
3.02
8.98
2.93
2.84
f1 (ppm)

O
O
OMs
OTBS

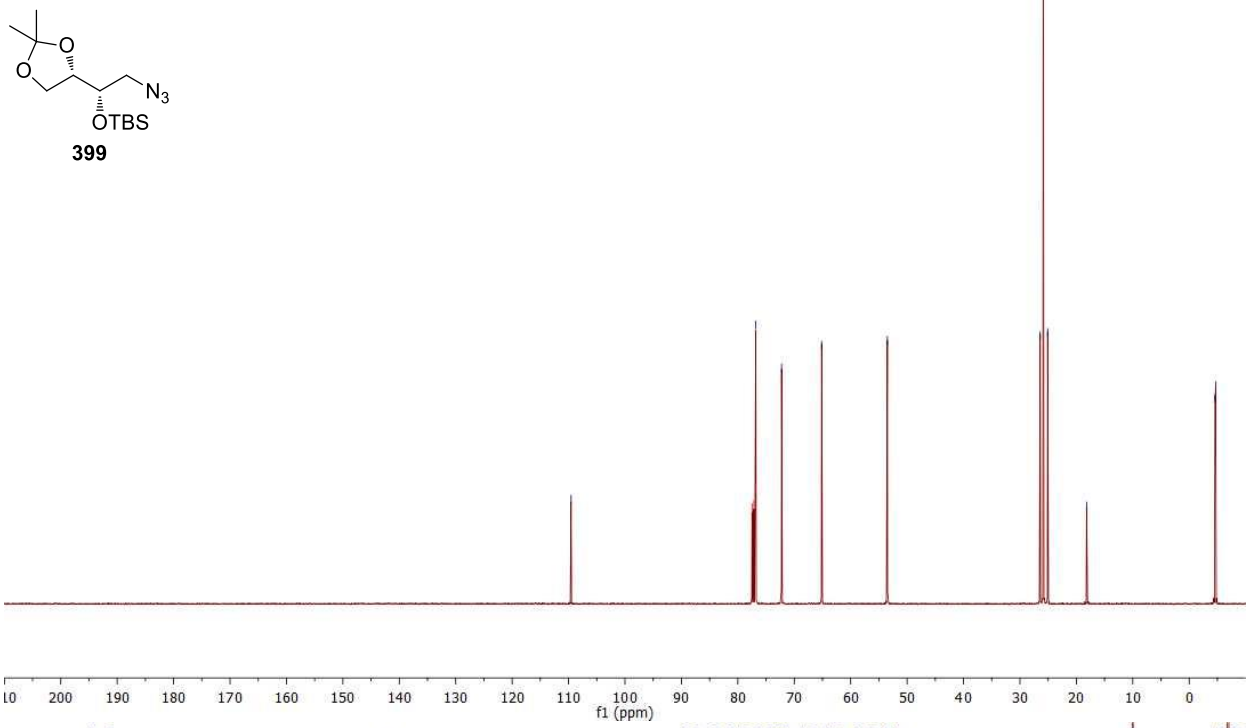
398

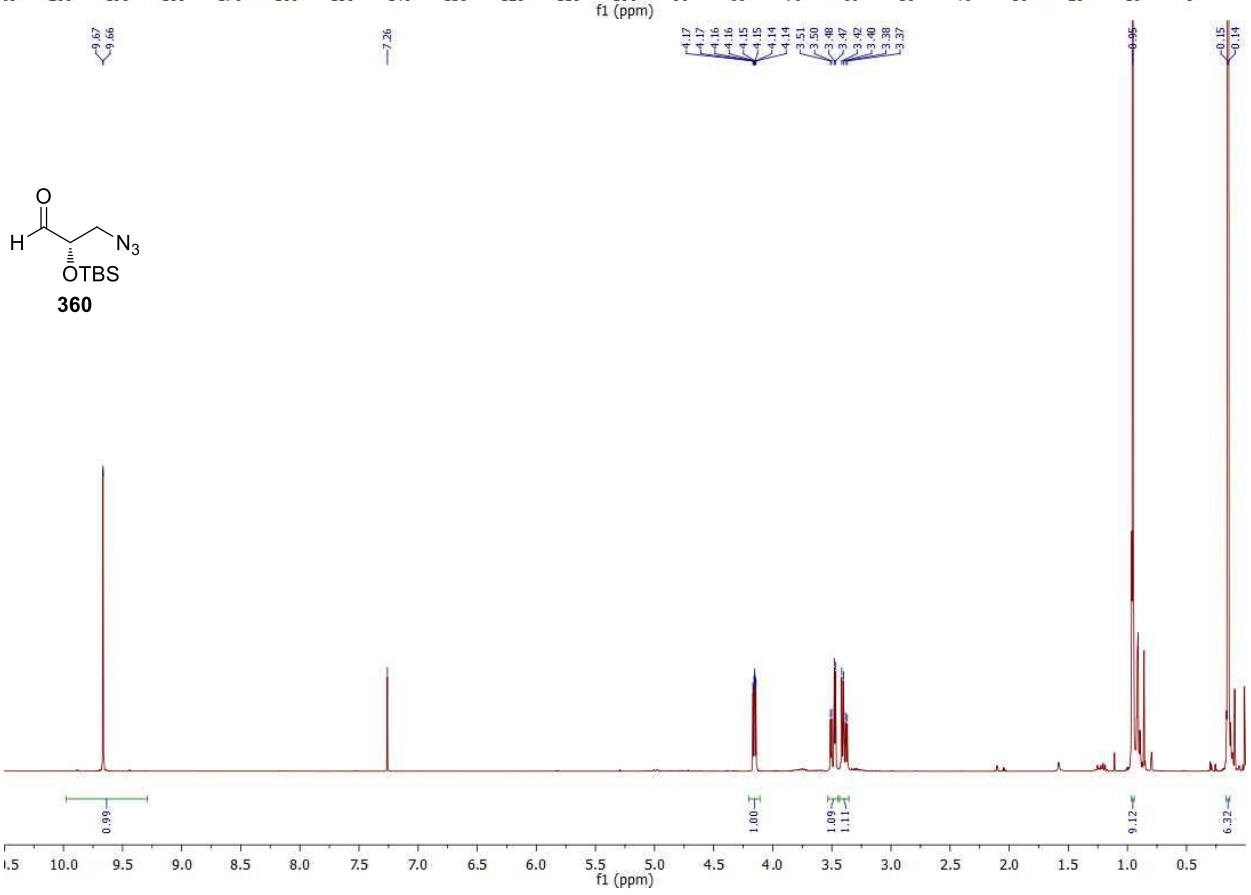

109.76
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
76.15
70.69
70.33
65.05
37.48
26.37
25.85
25.16
18.23
-4.41
-4.69
OMs
OTBS
f1 (ppm)

398


7.26
4.17
4.16
4.15
4.14
4.14
4.12
3.99
3.97
3.97
3.95
3.86
3.85
3.85
3.85
3.84
3.84
3.83
3.82
3.82
3.80
3.42
3.41
3.39
3.38
3.19
3.18
3.16
3.14
1.40
1.33
0.00
0.13
0.10
N3
OTBS
1.00
1.03
2.00
1.00
0.99
3.09
3.01
9.12
2.98
2.91
f1 (ppm)

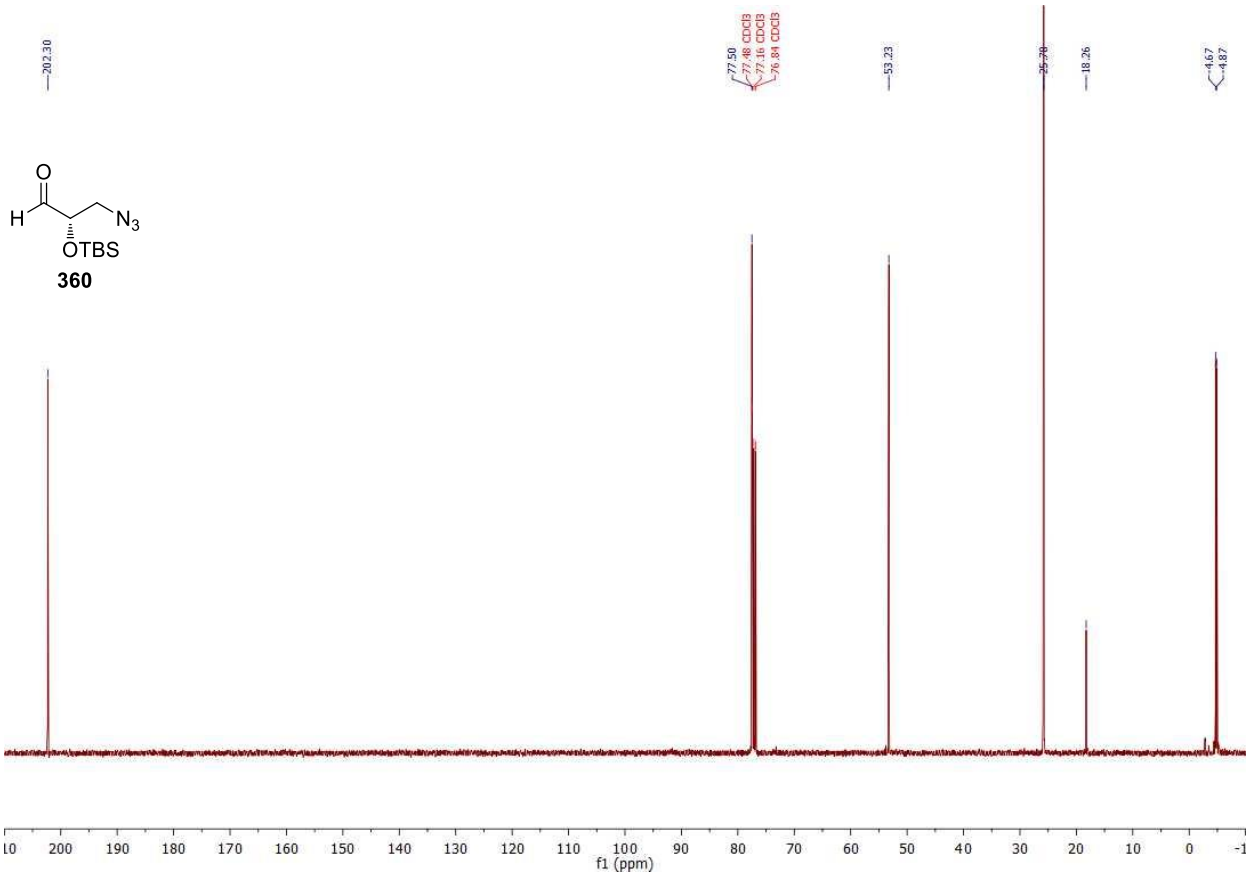
399


109.56
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
76.82
72.25
65.14
53.49
26.41
25.86
25.08
18.18
4.57
4.69
f1 (ppm)

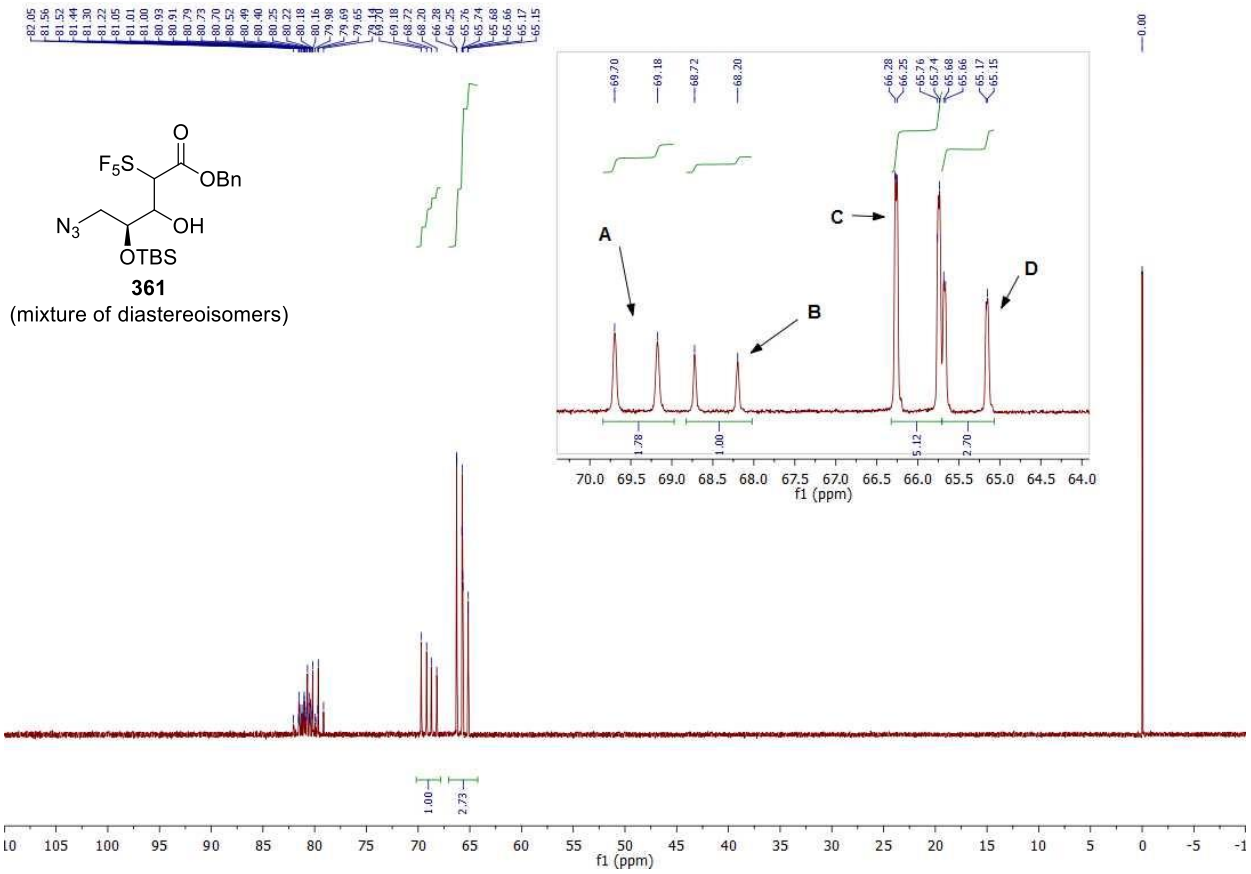

9.67
9.66
7.26
4.17
4.17
4.16
4.16
4.15
4.15
4.14
4.14
3.51
3.50
3.48
3.47
3.42
3.40
3.38
3.37
0.15
0.14
0.99
1.00
1.09
1.11
9.12
6.32
f1 (ppm)

399

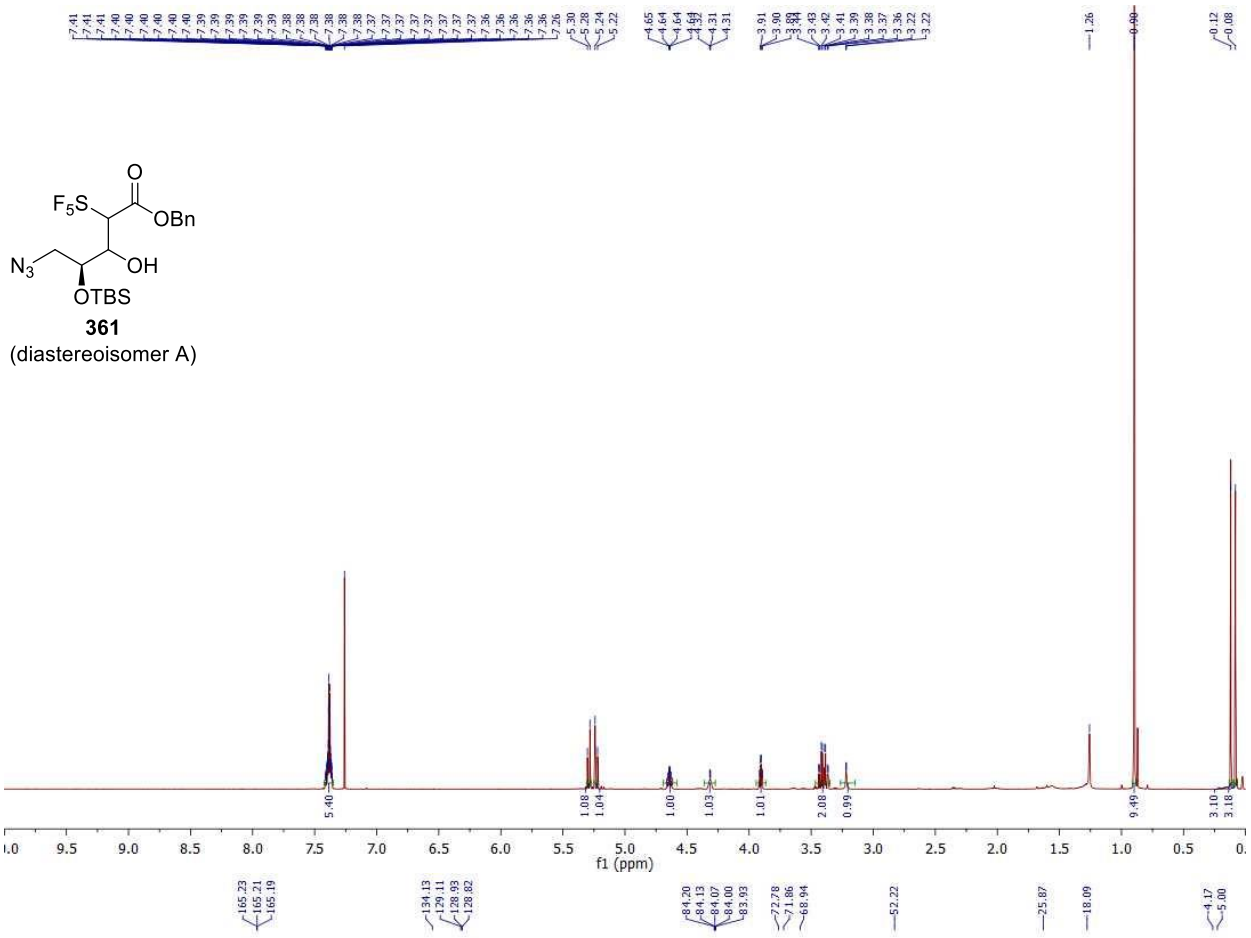
360



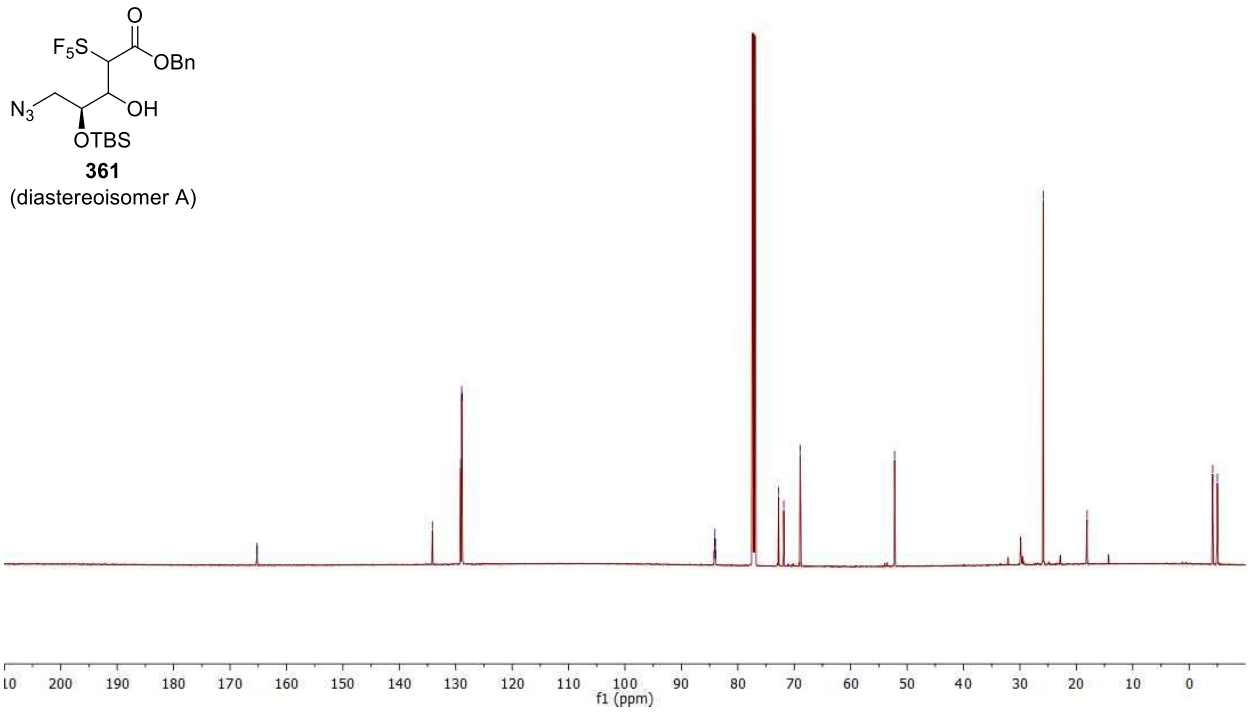
360



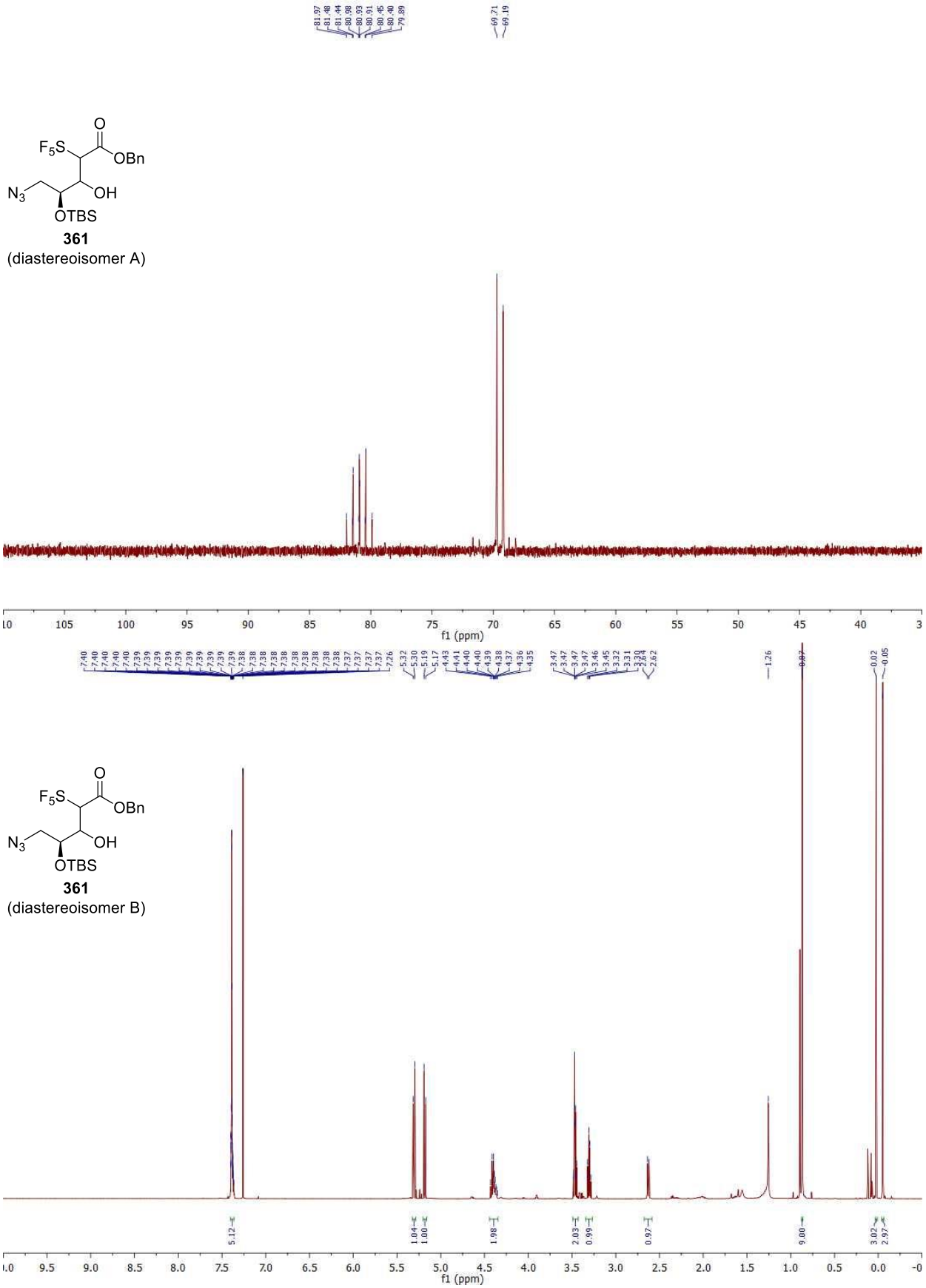
361
(mixture of diastereoisomers)

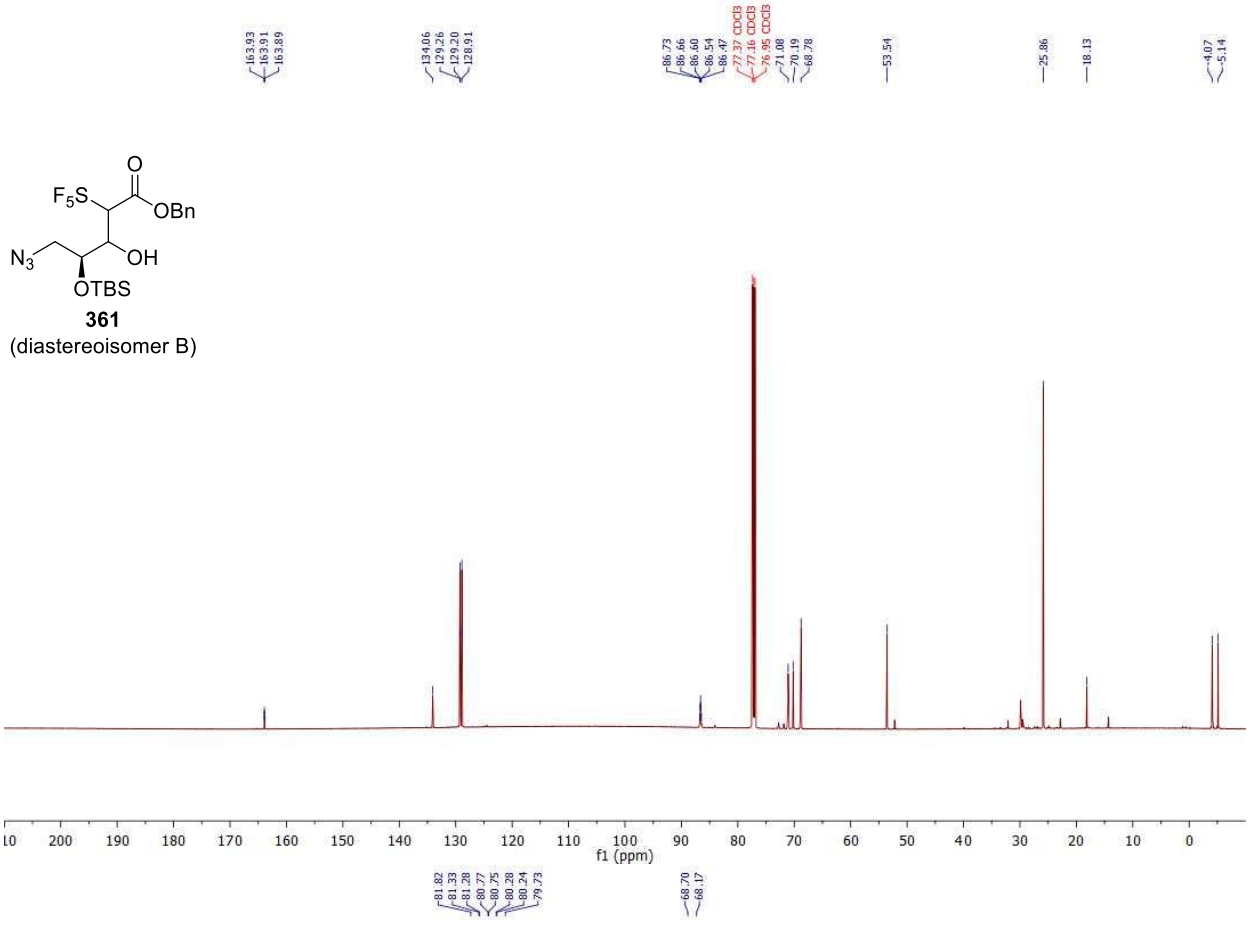


361
(diastereoisomer A)

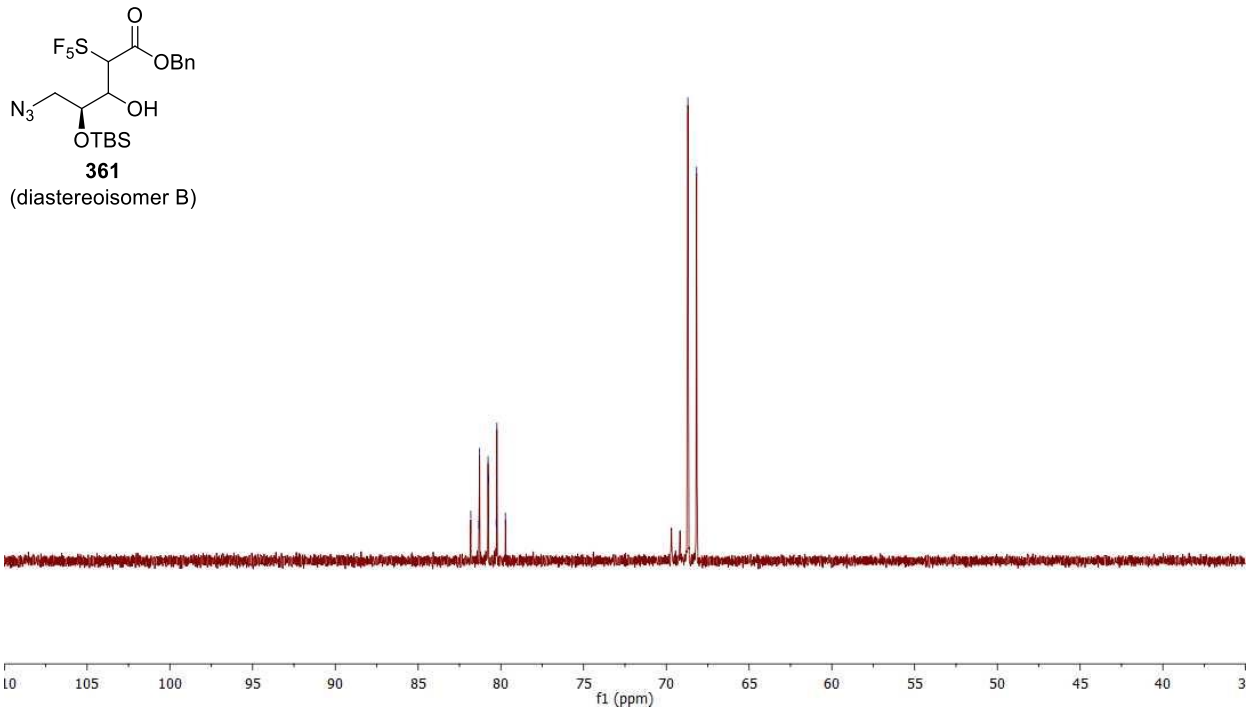


361
(diastereoisomer A)

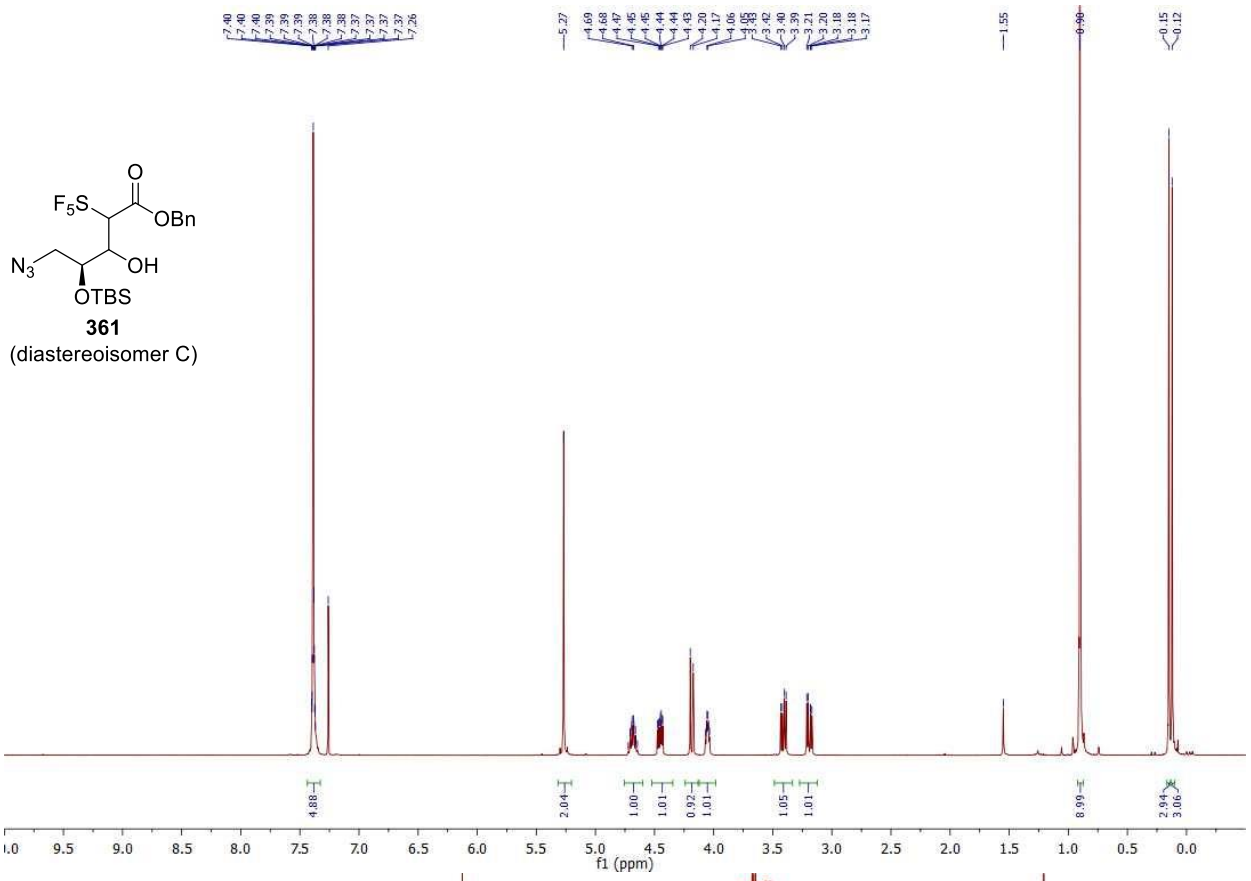

81.97
81.48
81.44
80.98
80.93
80.91
80.45
80.40
79.89
69.71
69.19
O
F5S
OBn
N3
OH
OTBS
361
(diastereoisomer A)
f1 (ppm)
7.40
7.39
7.38
7.37
7.26
5.32
5.30
5.19
5.17
4.43
4.41
4.40
4.39
4.38
4.37
4.36
4.35
3.47
3.46
3.45
3.32
3.31
2.64
2.62
1.26
0.87
0.02
0.05
O
F5S
OBn
N3
OH
OTBS
361
(diastereoisomer B)
5.12
1.04
1.00
1.98
2.03
0.99
0.97
9.00
3.02
2.97
f1 (ppm)

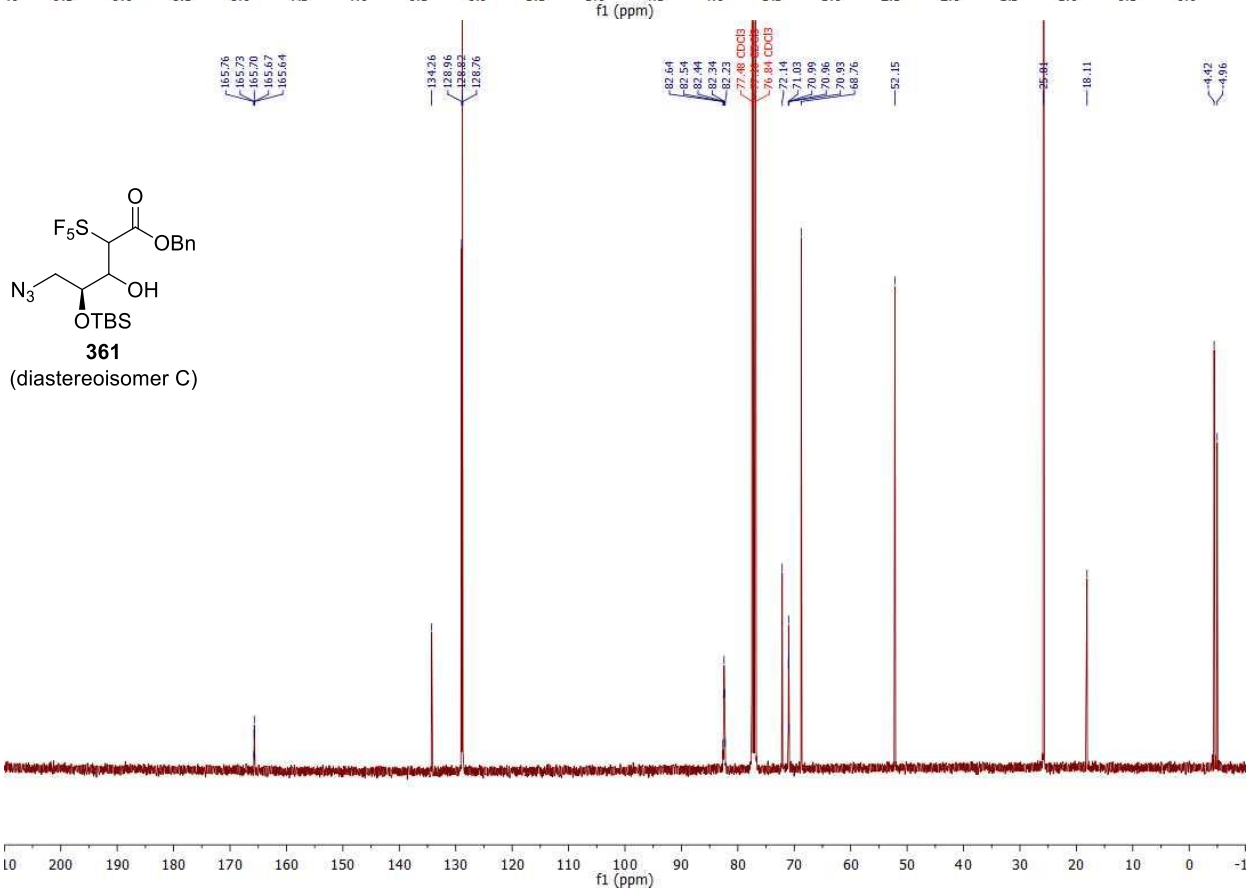


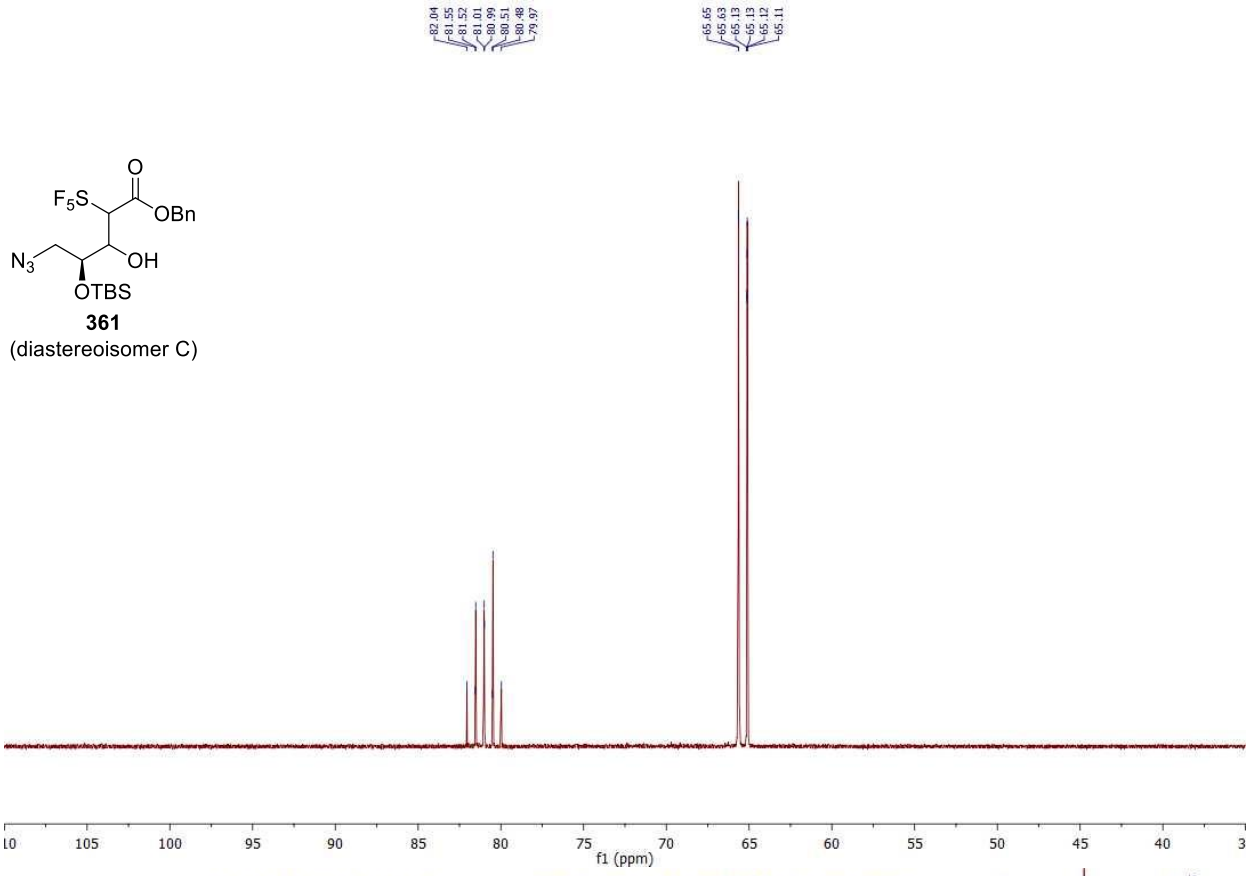
361
(diastereoisomer B)



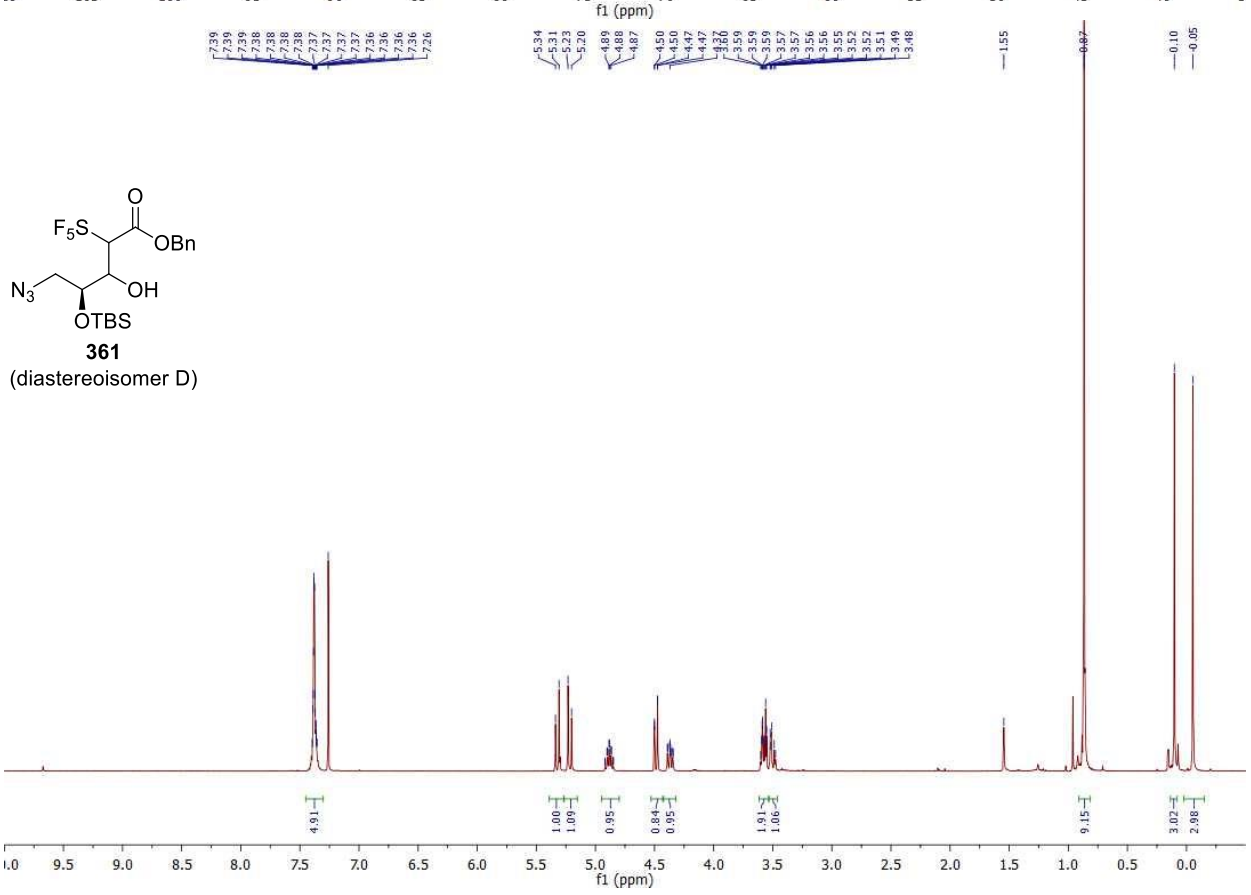
361
(diastereoisomer B)


F5S
O
OBn
N3
OH
OTBS
361
(diastereoisomer C)
f1 (ppm)

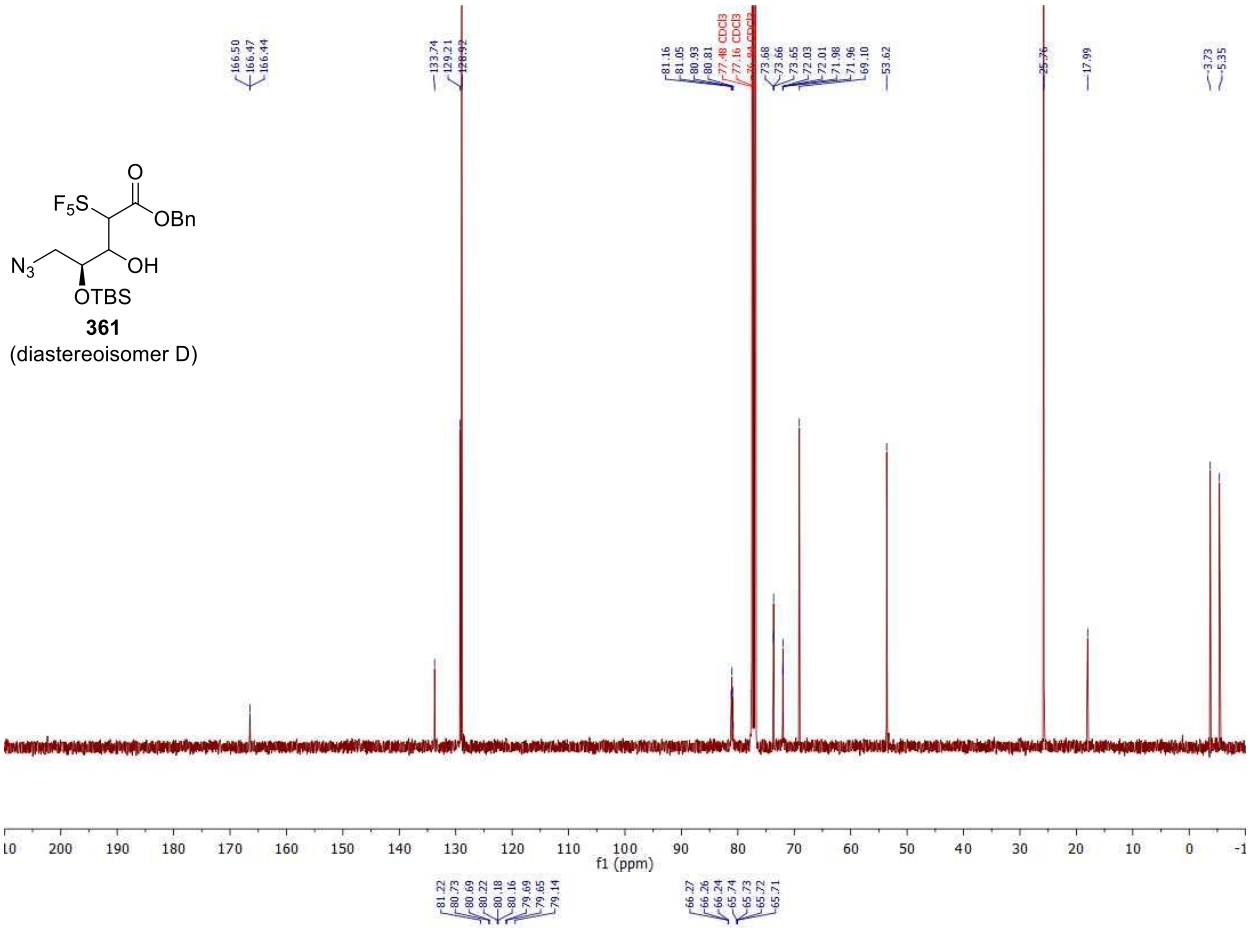

F5S
O
OBn
N3
OH
OTBS
361
(diastereoisomer C)
f1 (ppm)



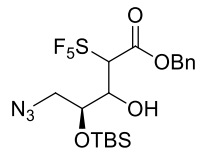
361
(diastereoisomer C)



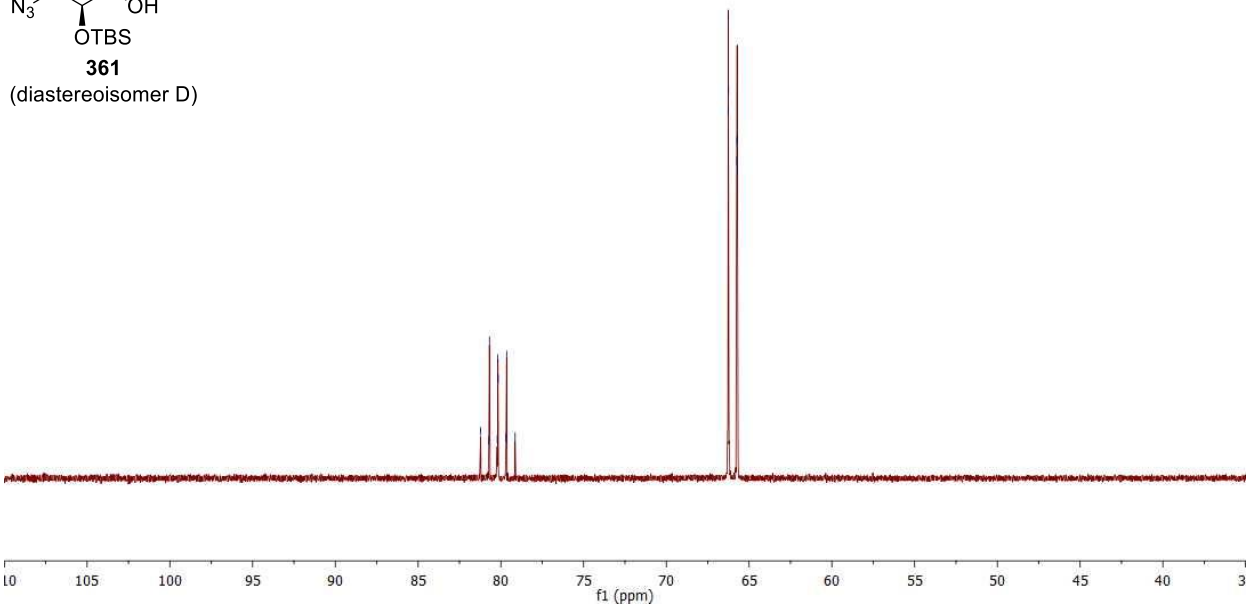
361
(diastereoisomer D)

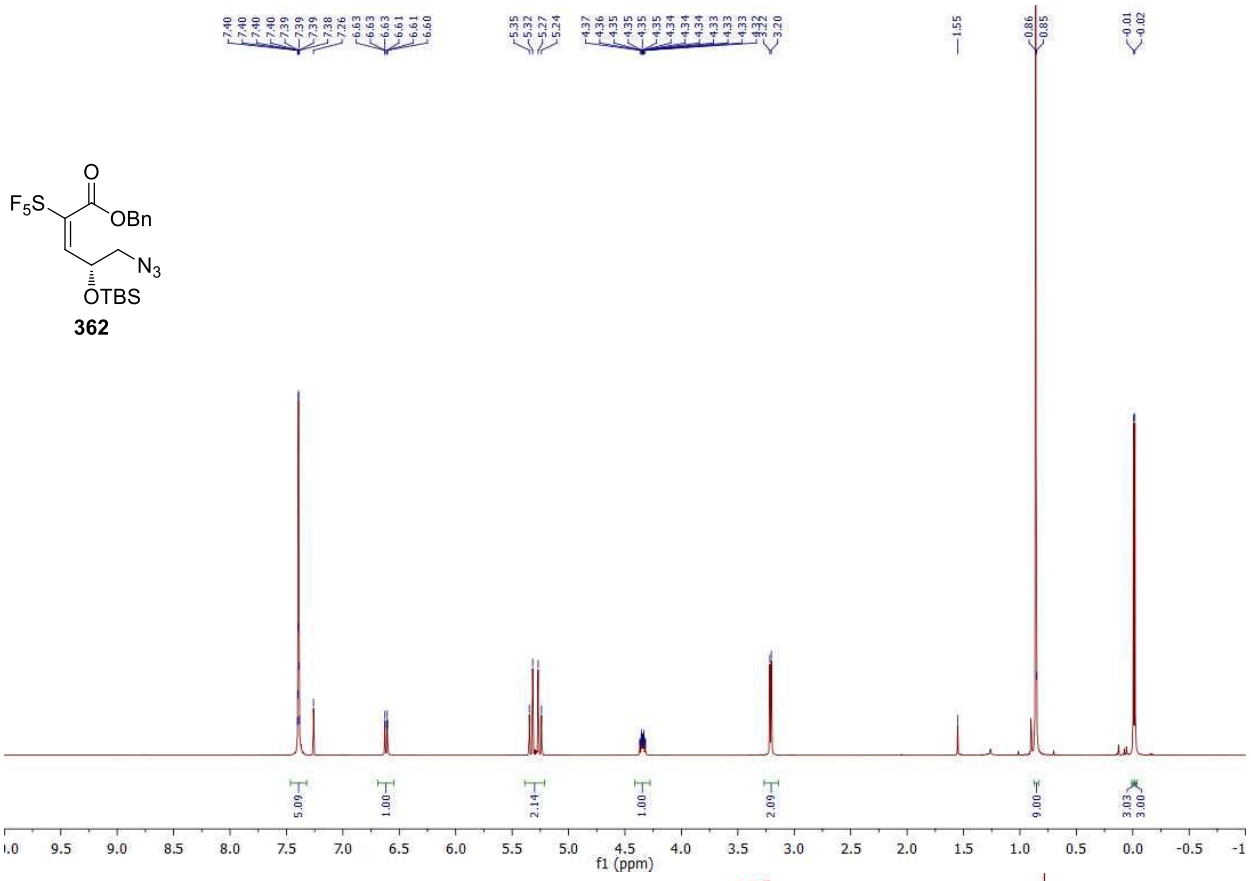


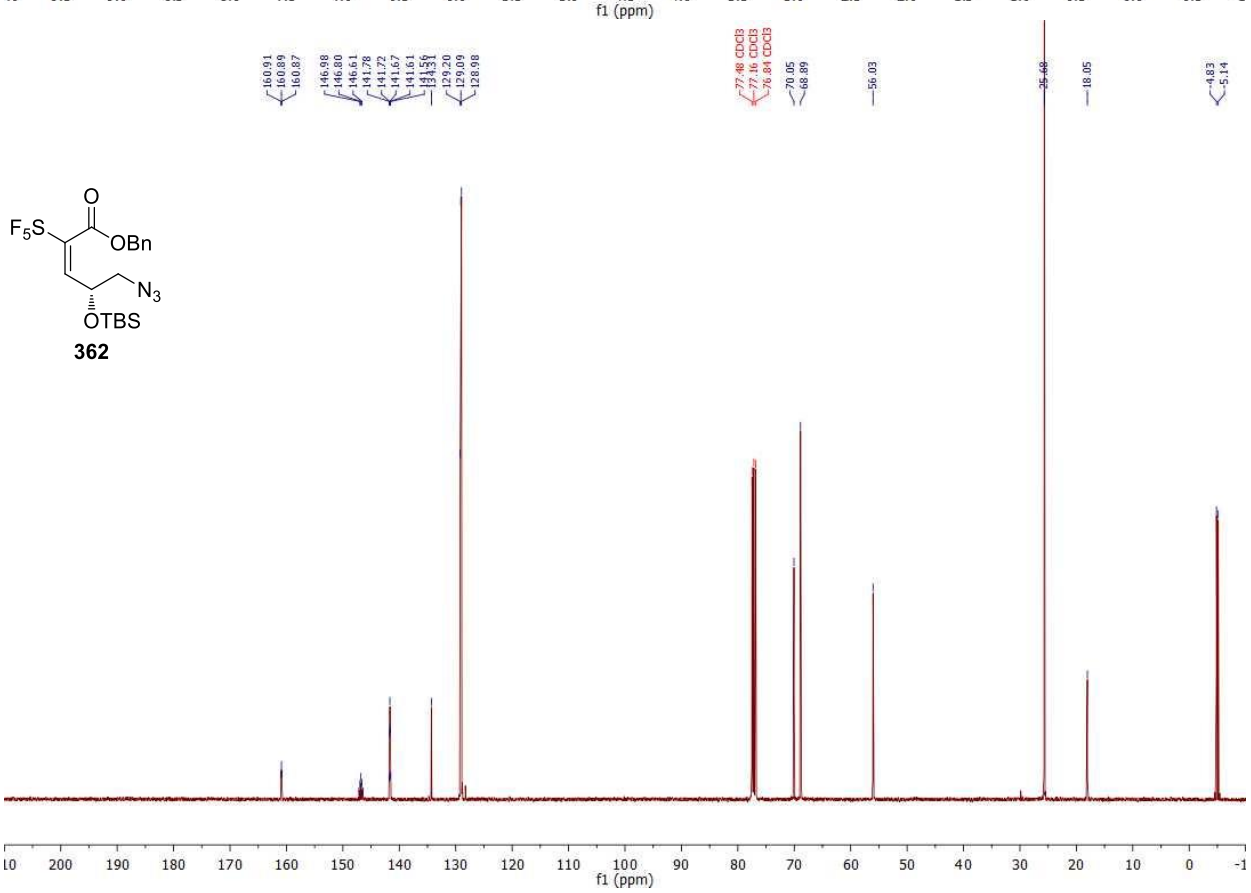
361
(diastereoisomer D)

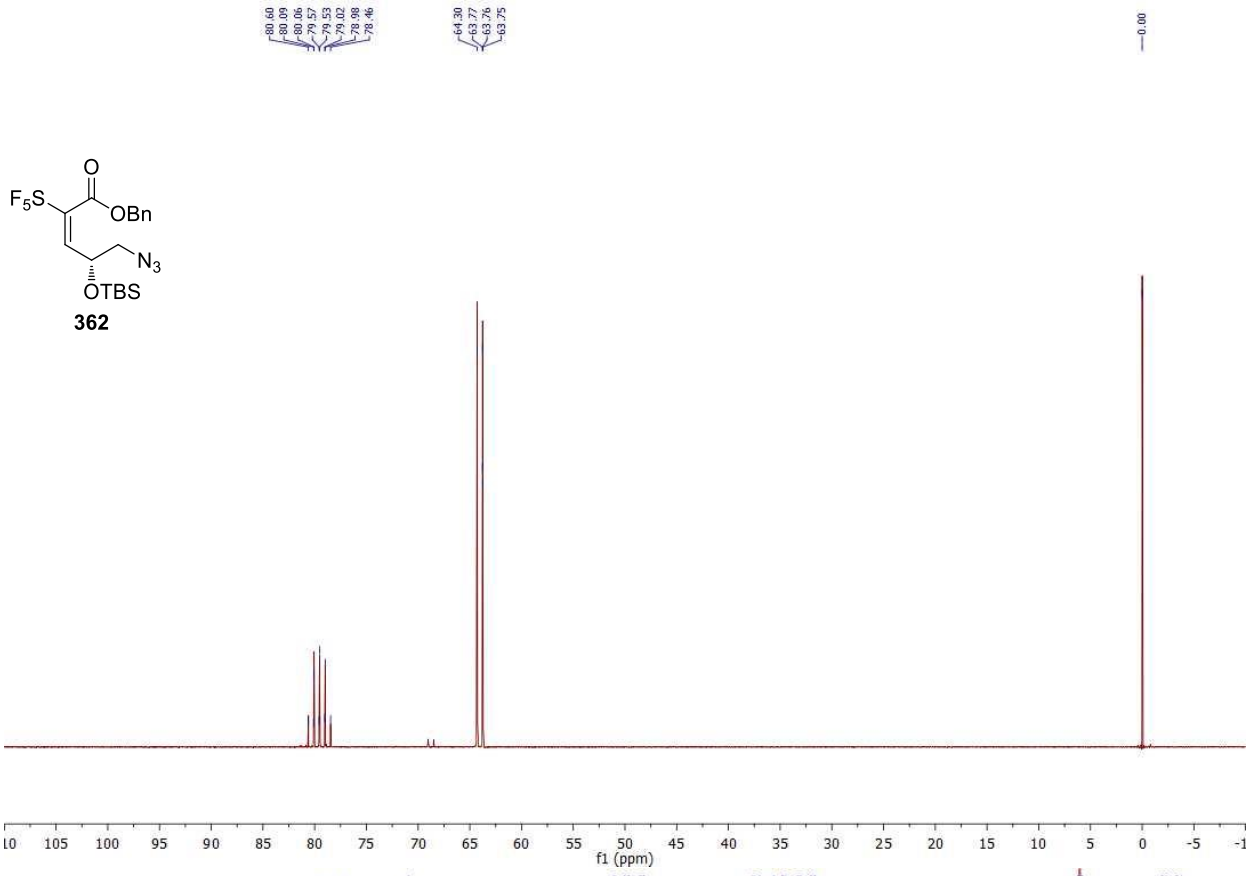


361
(diastereoisomer D)

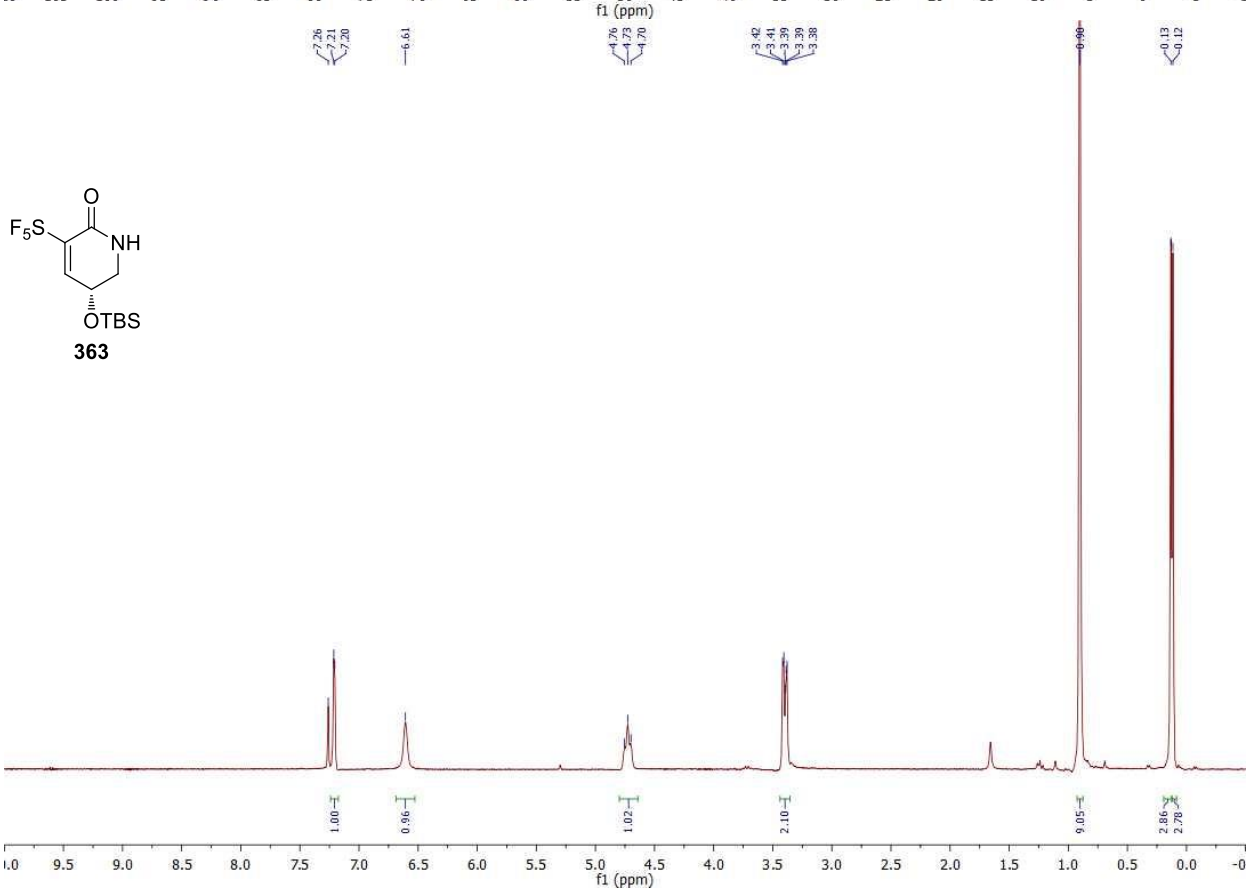



F5S
O
OBn
N3
OTBS
362
f1 (ppm)

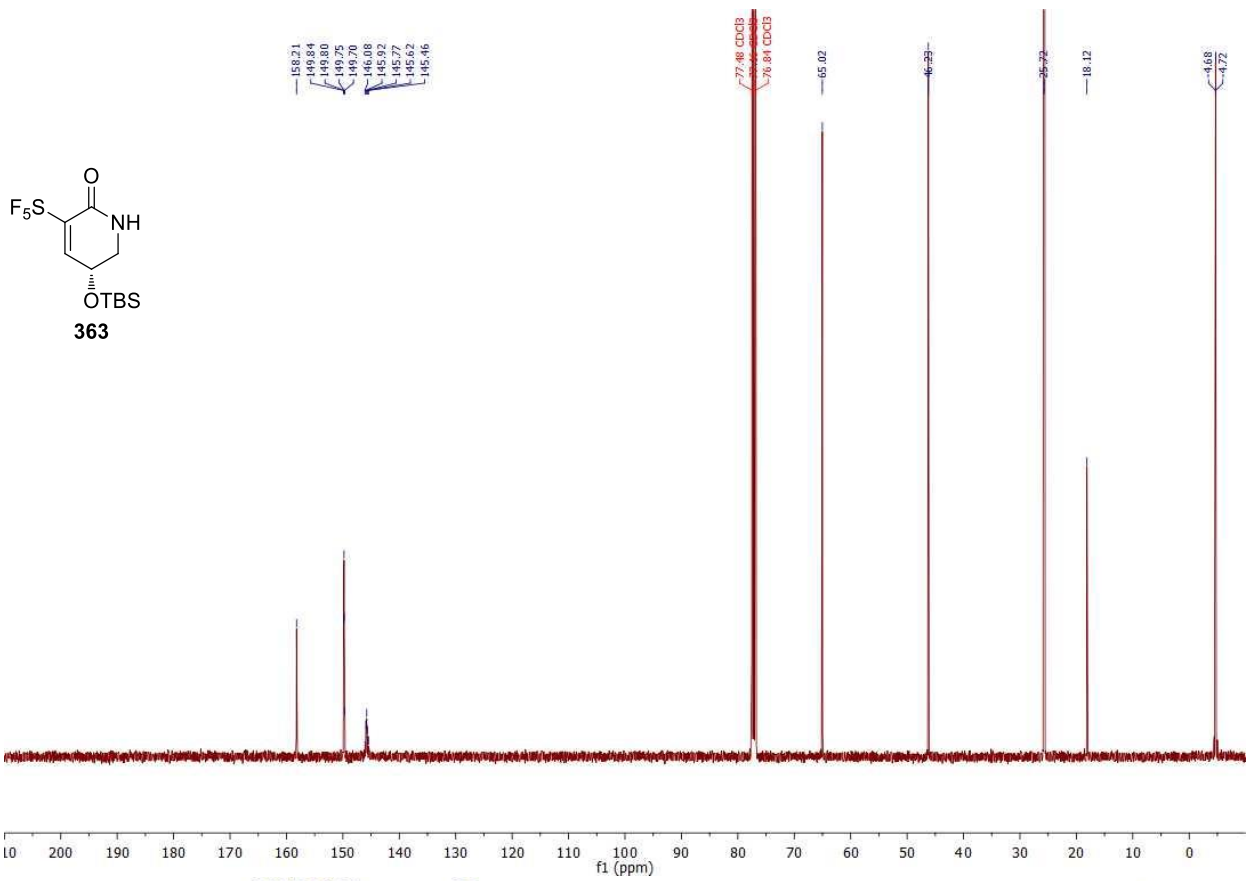

F5S
O
OBn
N3
OTBS
362
f1 (ppm)

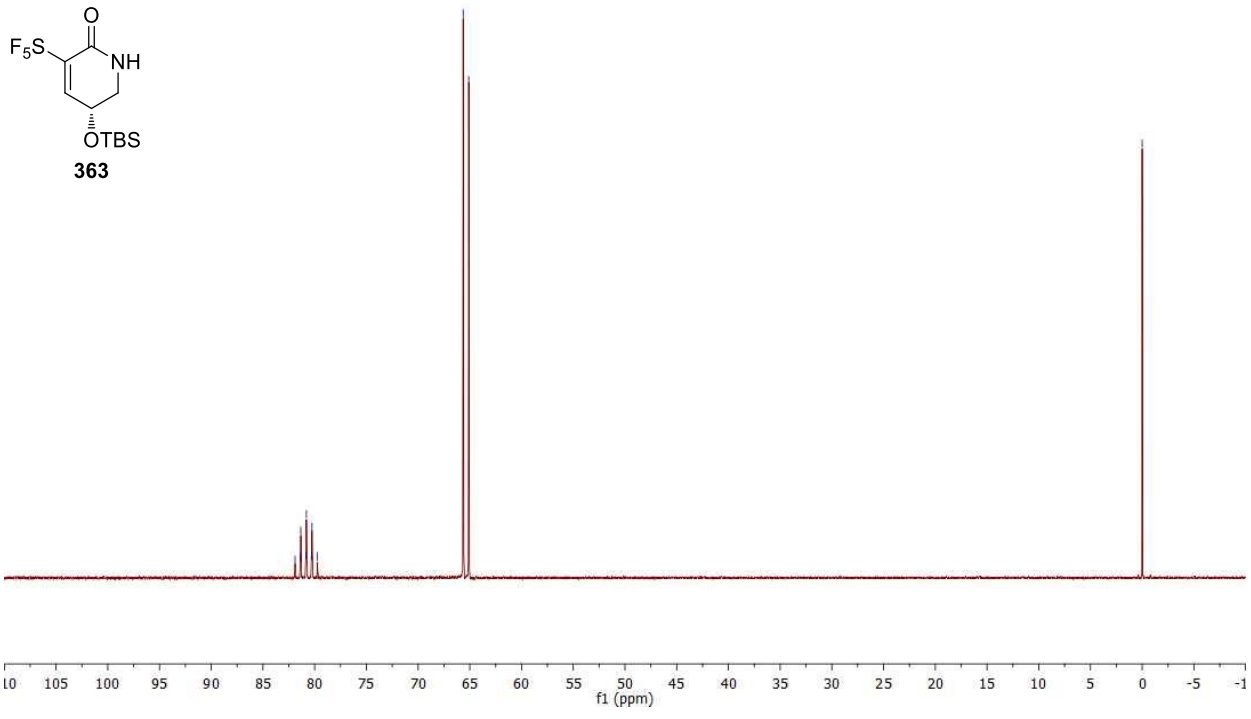

80.60
80.09
80.06
79.57
79.53
79.02
78.98
78.46
64.30
63.77
63.76
63.75
0.00
O
F5S
OBn
N3
OTBS
f1 (ppm)

362


7.26
7.21
7.20
6.61
4.76
4.73
4.70
3.42
3.41
3.39
3.39
3.38
0.00
0.13
0.12
O
F5S
NH
OTBS
1.00
0.96
1.02
2.10
9.05
2.86
2.78
f1 (ppm)

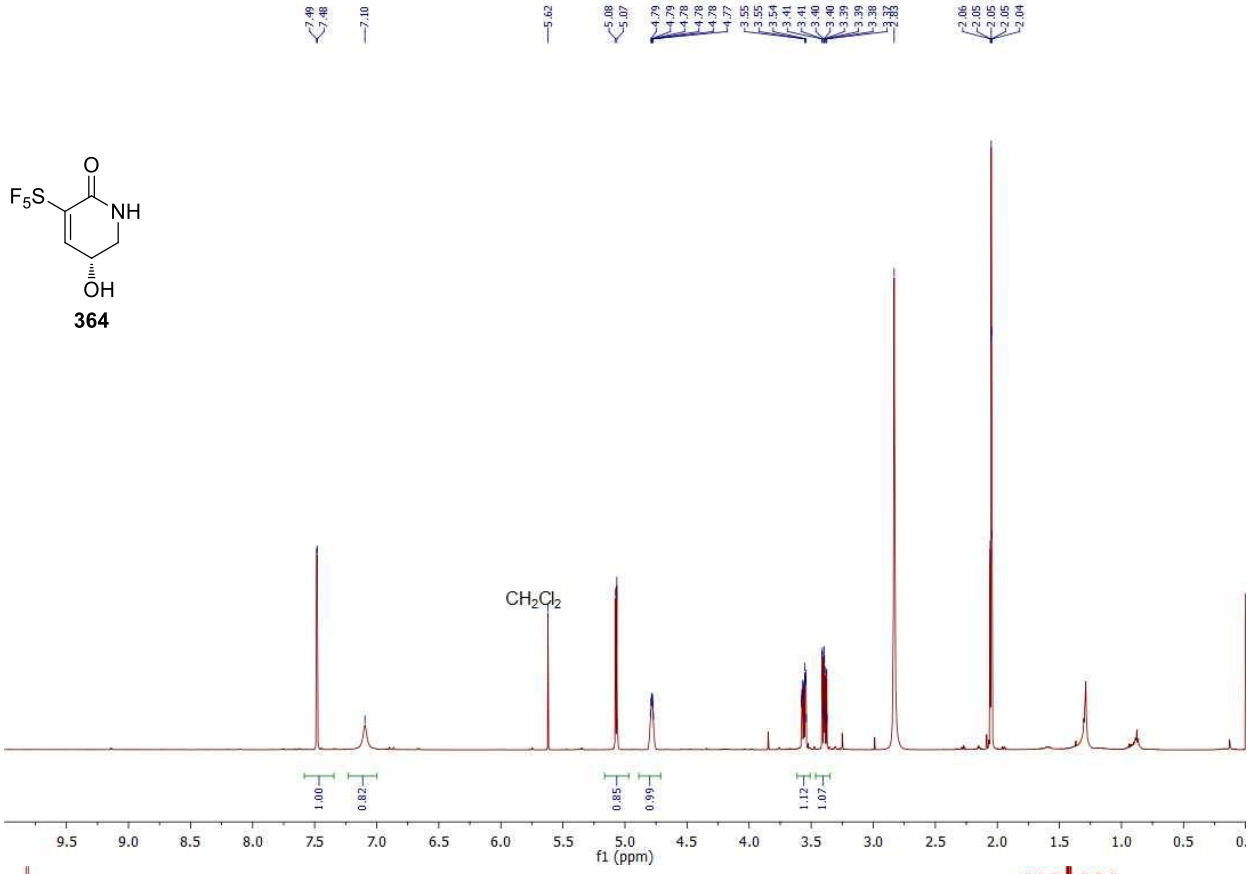
363

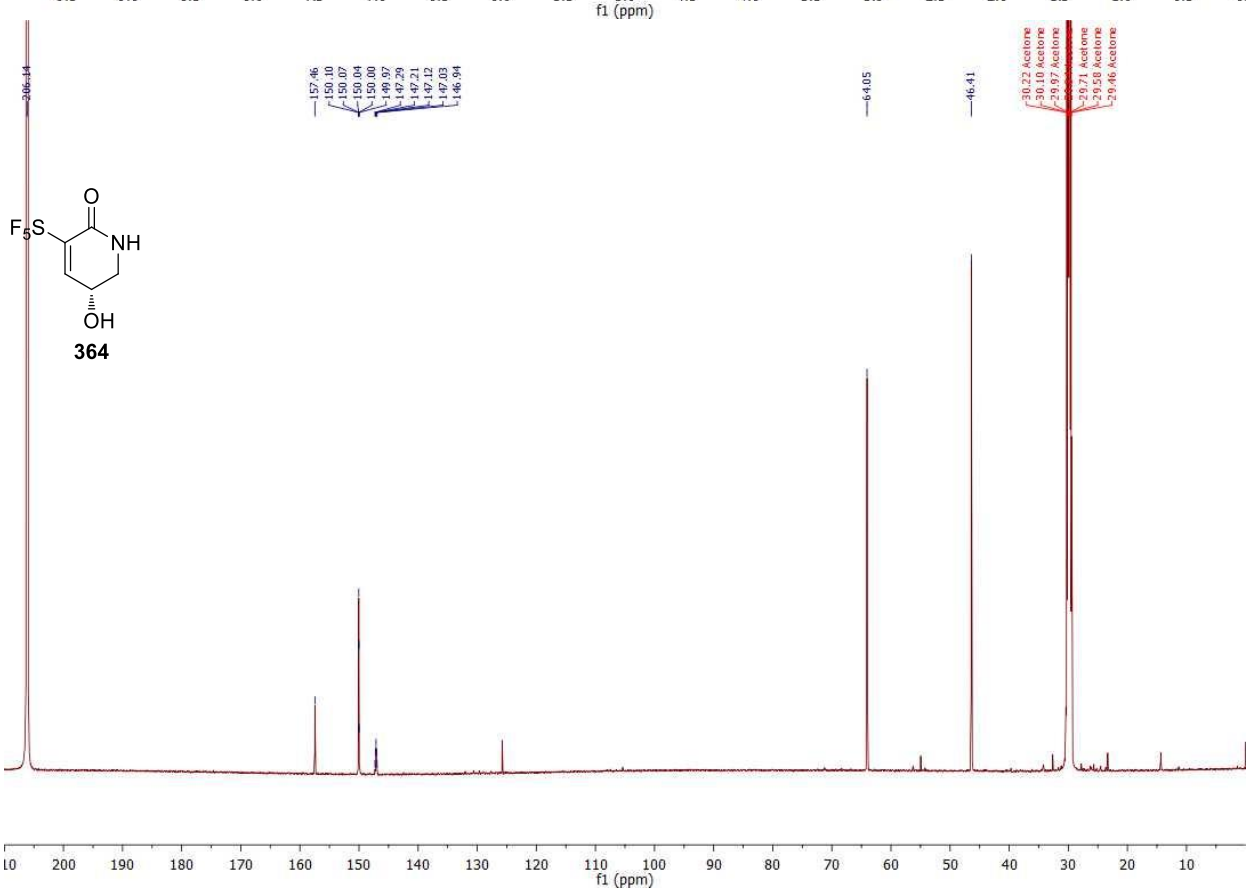

158.21
149.84
149.80
149.75
149.70
146.08
145.92
145.77
145.62
145.46
77.48 CDCl3
76.84 CDCl3
65.02
46.33
25.72
18.12
4.68
4.72
f1 (ppm)

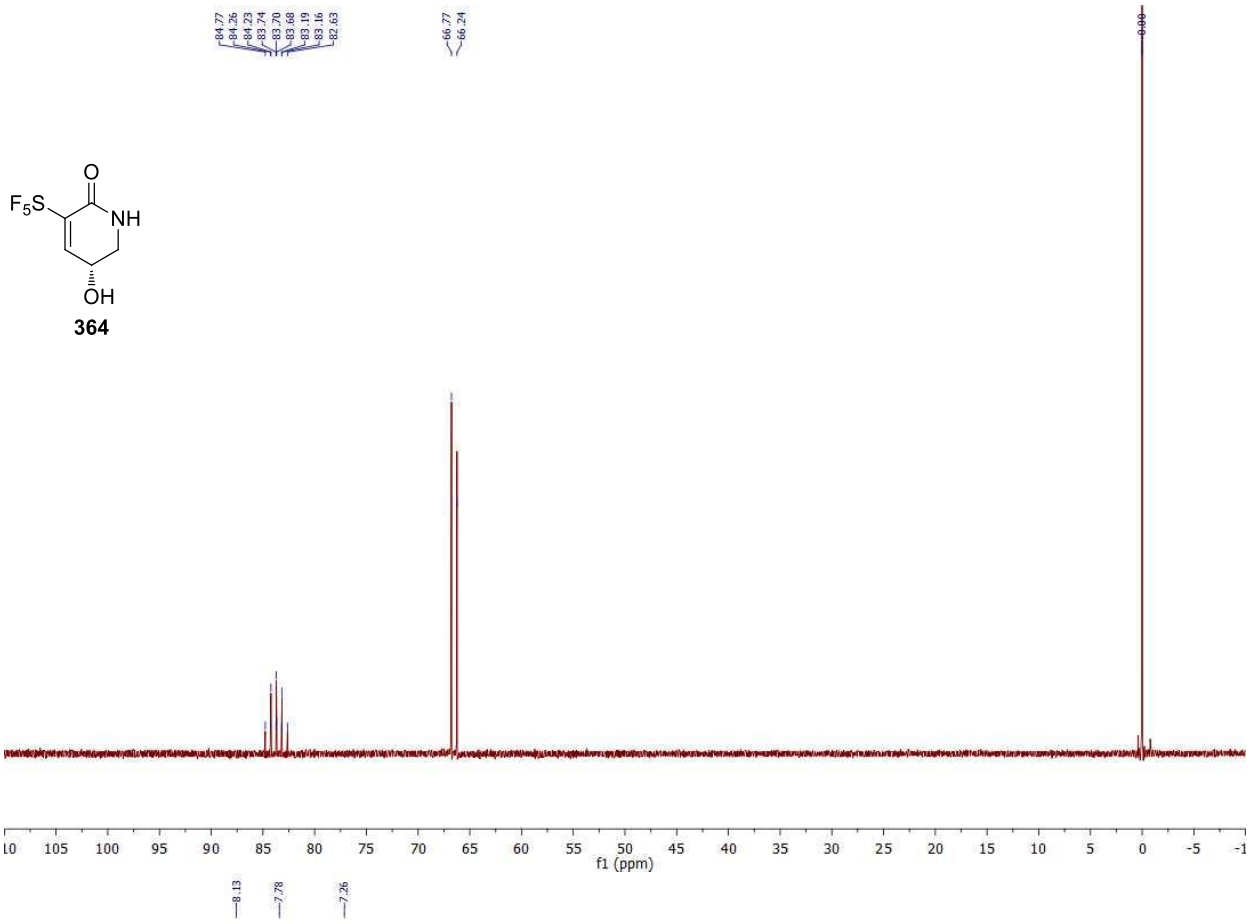

81.89
81.38
81.34
80.85
80.80
80.30
80.26
79.73
65.64
65.10
0.00
f1 (ppm)

363

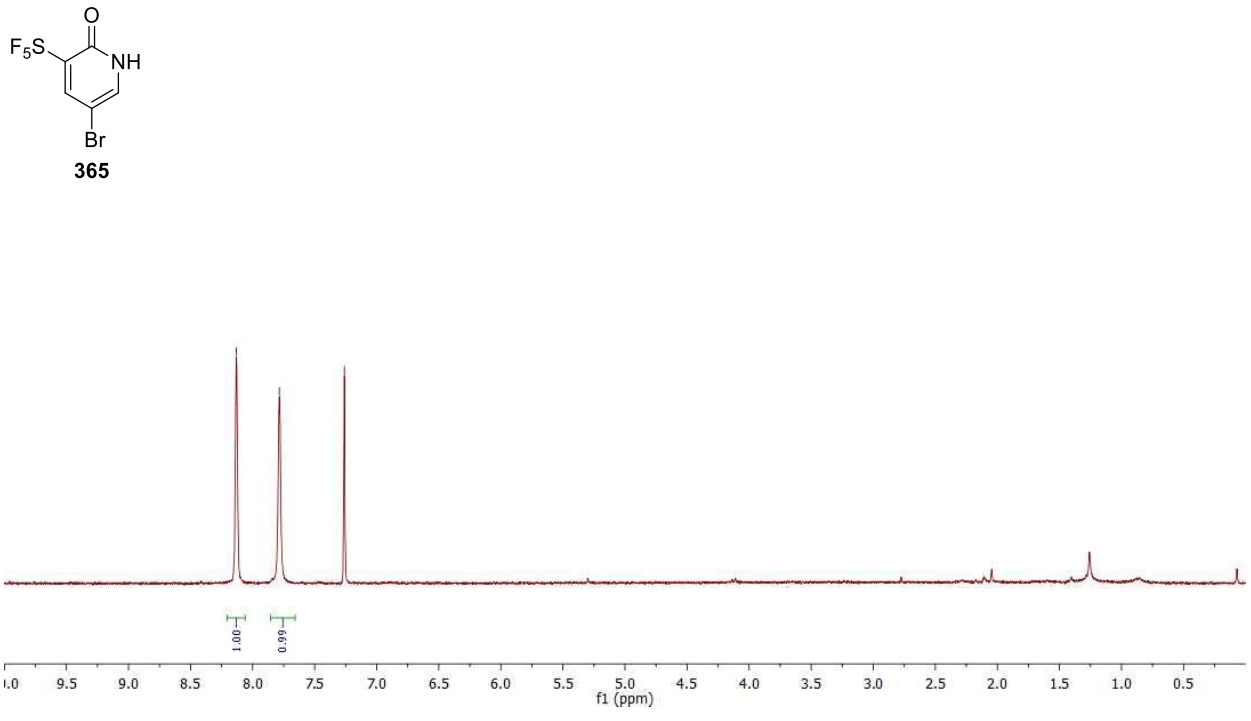
363


7.49
7.48
7.10
5.62
5.08
5.07
4.79
4.79
4.78
4.78
4.78
4.77
3.55
3.55
3.54
3.41
3.41
3.40
3.40
3.39
3.39
3.38
2.06
2.05
2.05
2.05
2.04
O
F5S
NH
OH
364
CH2Cl2
1.00
0.82
0.85
0.99
1.12
1.07
f1 (ppm)

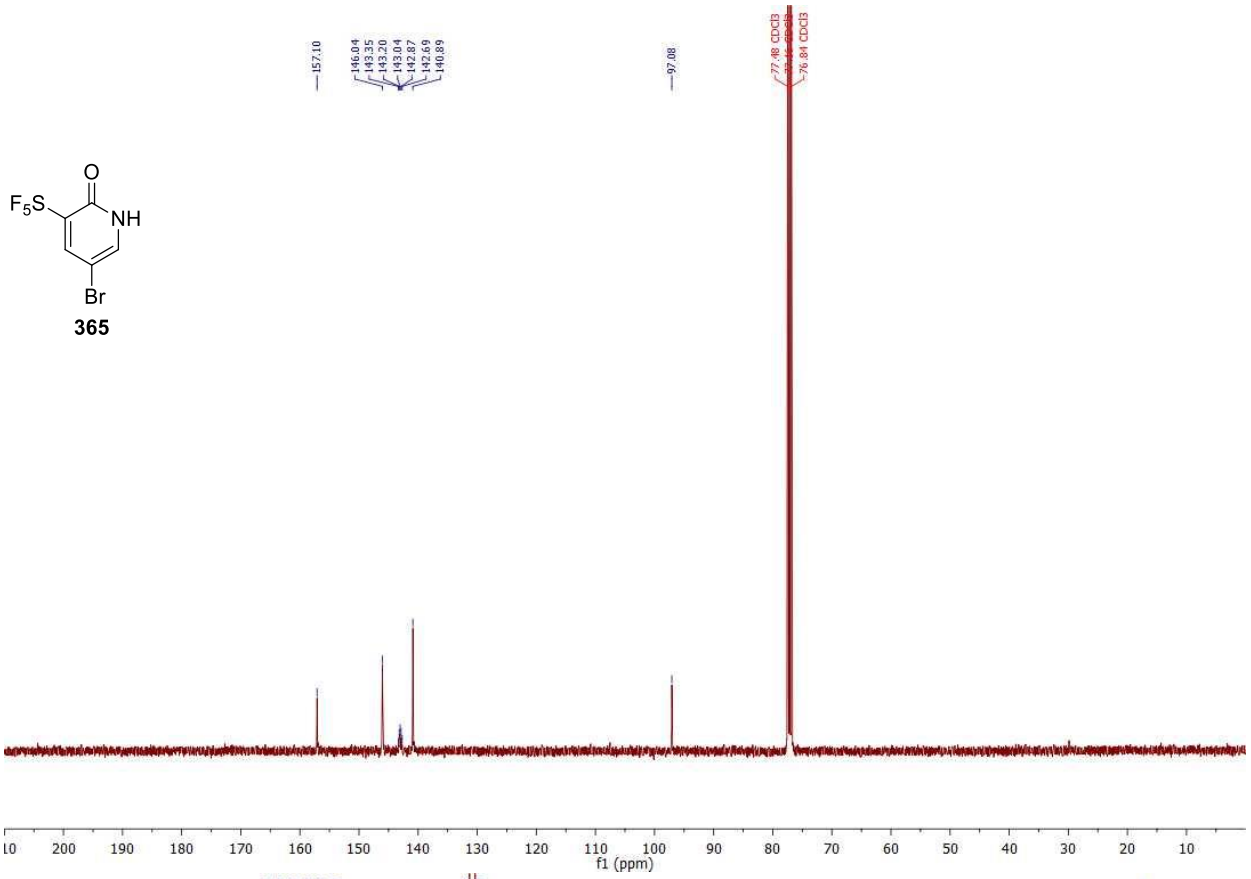

206.14
157.46
150.10
150.07
150.04
150.00
149.97
147.29
147.21
147.12
147.03
146.94
64.05
46.41
30.22 Acetone
30.10 Acetone
29.97 Acetone
29.71 Acetone
29.58 Acetone
29.46 Acetone
O
F5S
NH
OH
364
f1 (ppm)


84.77
84.26
84.23
83.74
83.70
83.68
83.19
83.16
82.63
66.77
66.24
0.00
f1 (ppm)
8.13
7.78
7.26

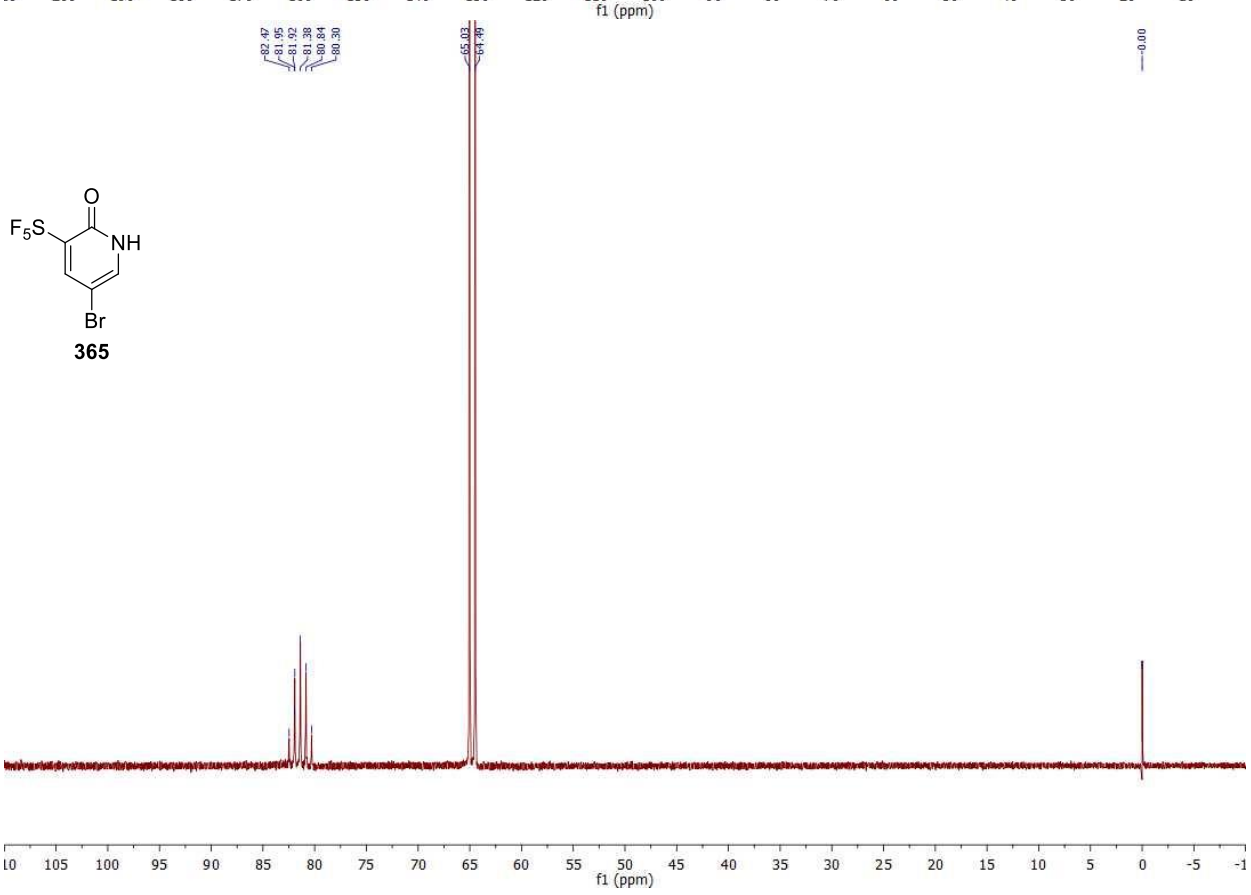
364


1.00
0.99
f1 (ppm)

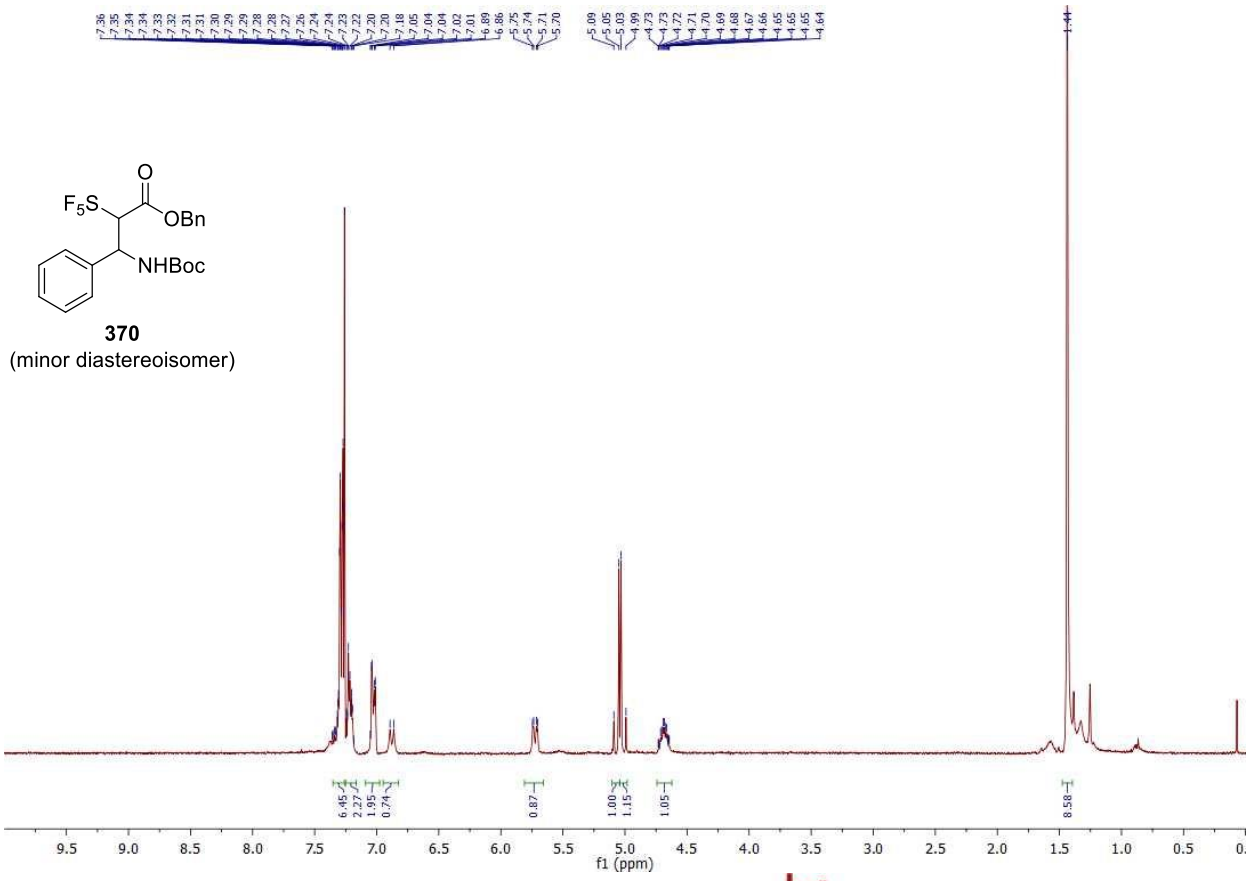
365


157.10
146.04
143.35
143.20
143.04
142.87
142.69
140.89
97.08
77.48 CDCl3
76.84 CDCl3
f1 (ppm)

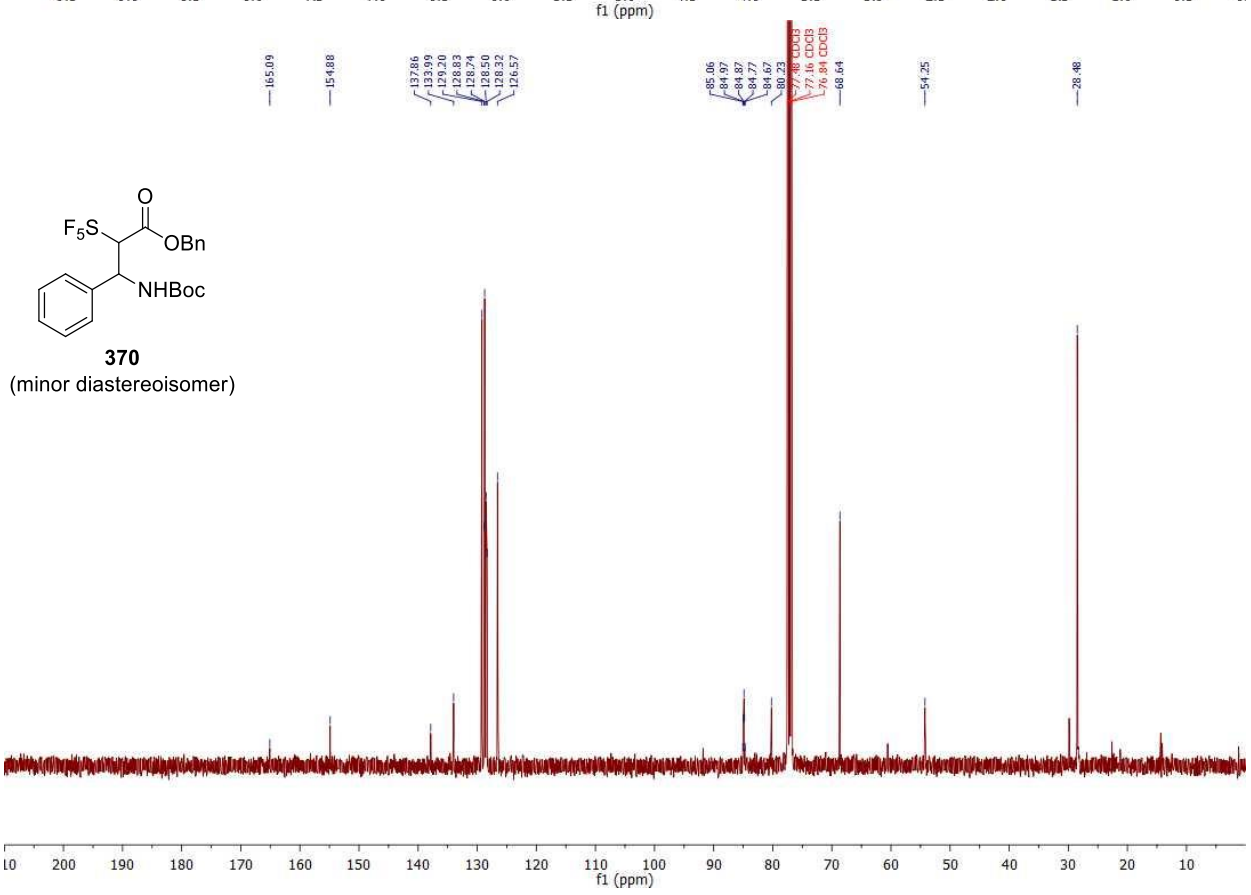
365


82.47
81.95
81.92
81.38
80.84
80.30
65.03
64.49
0.00
f1 (ppm)

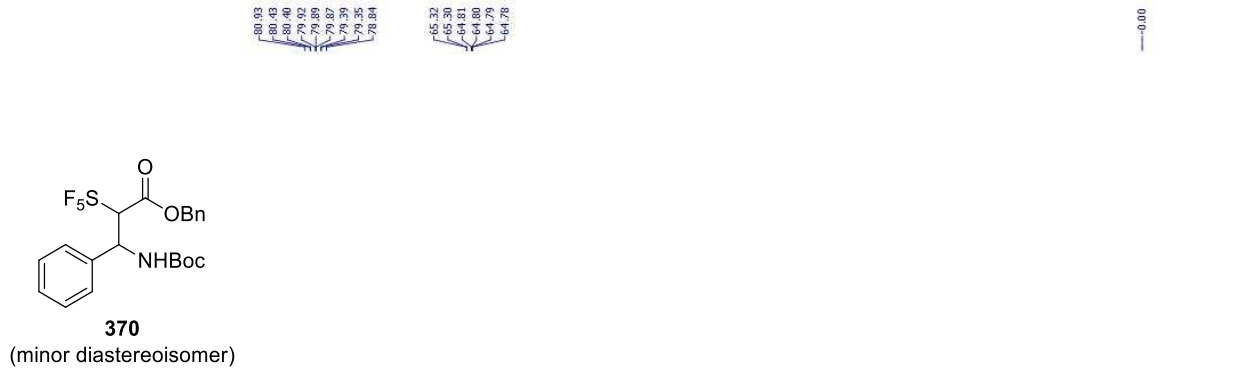
365



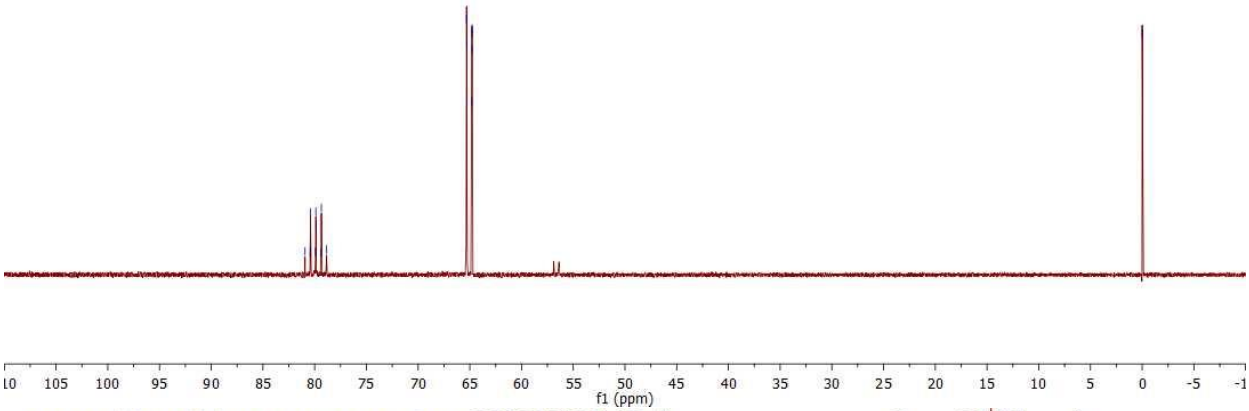
370
(minor diastereoisomer)

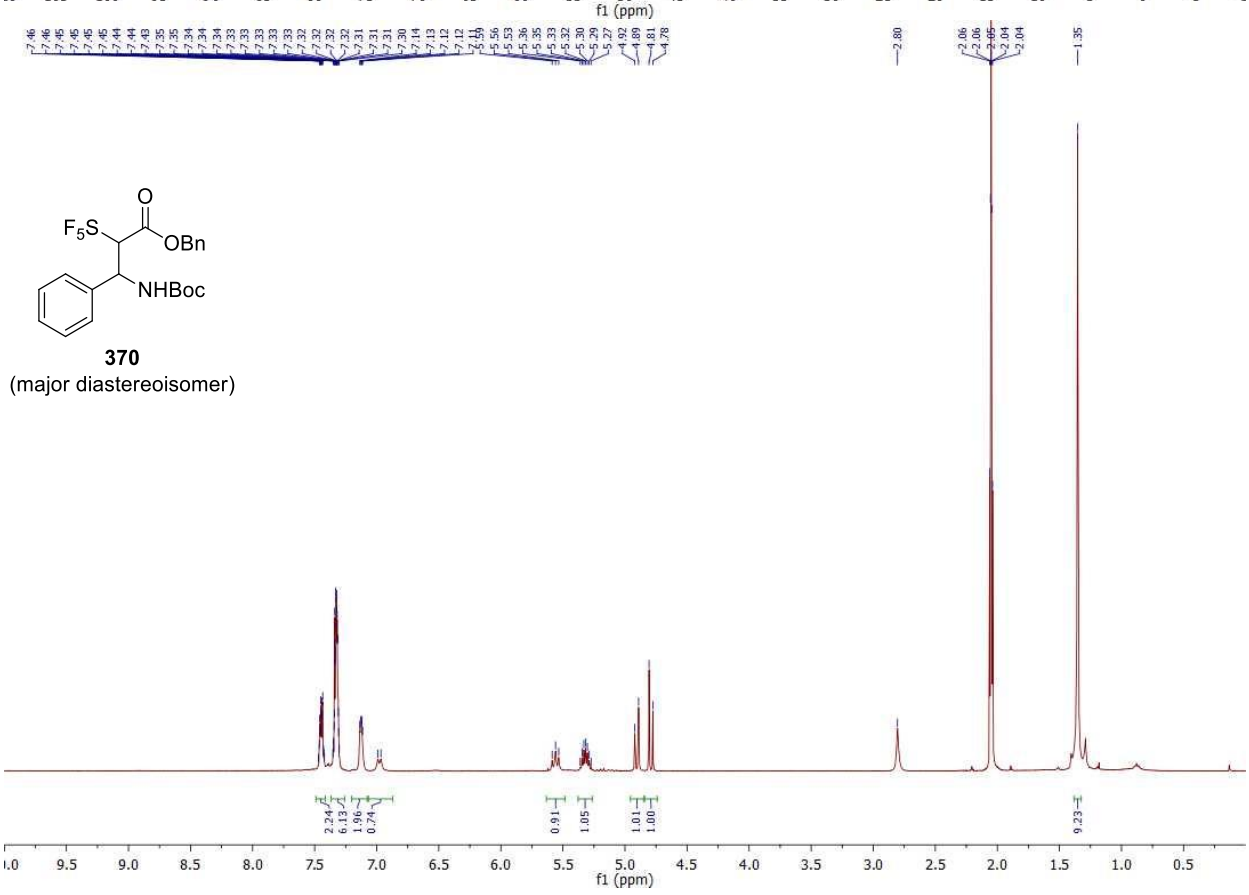


370
(minor diastereoisomer)

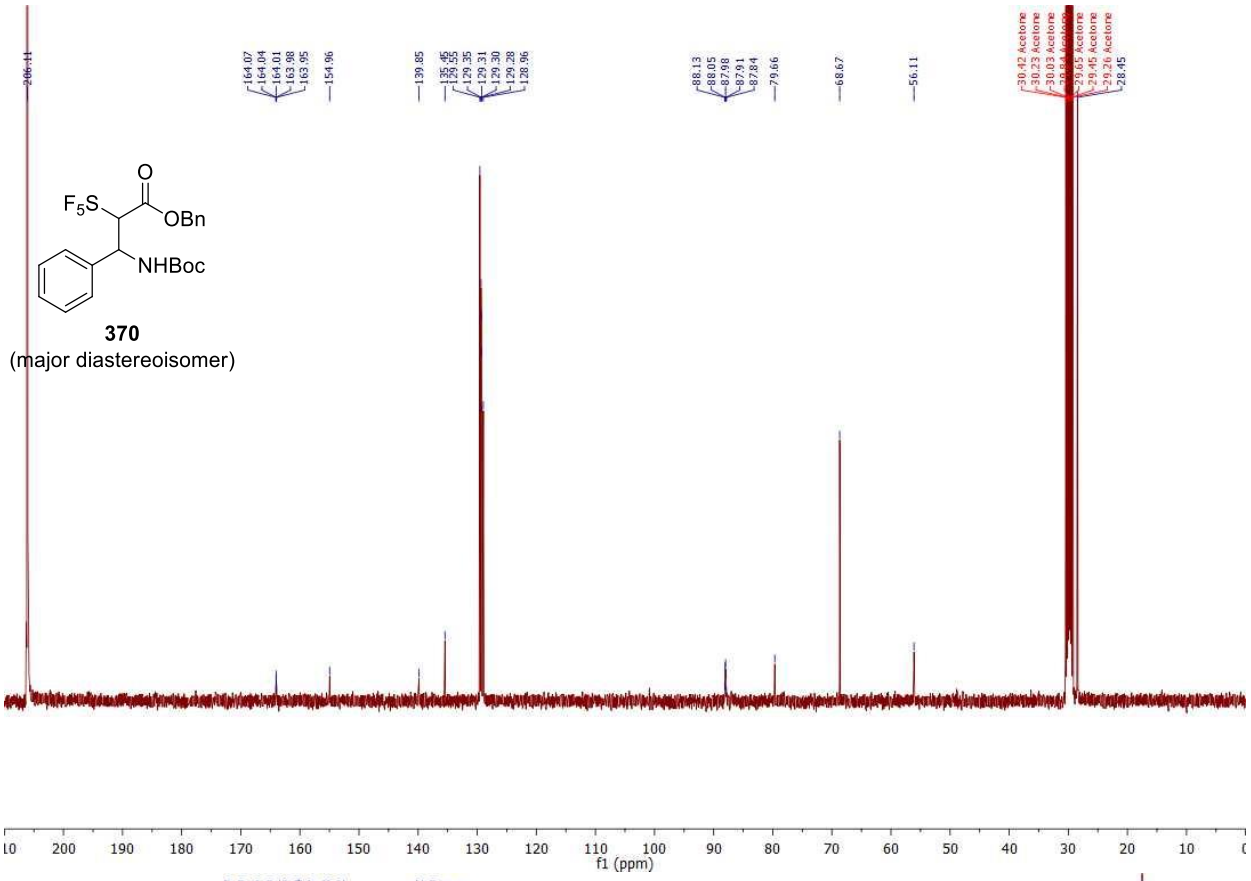


370
(minor diastereoisomer)

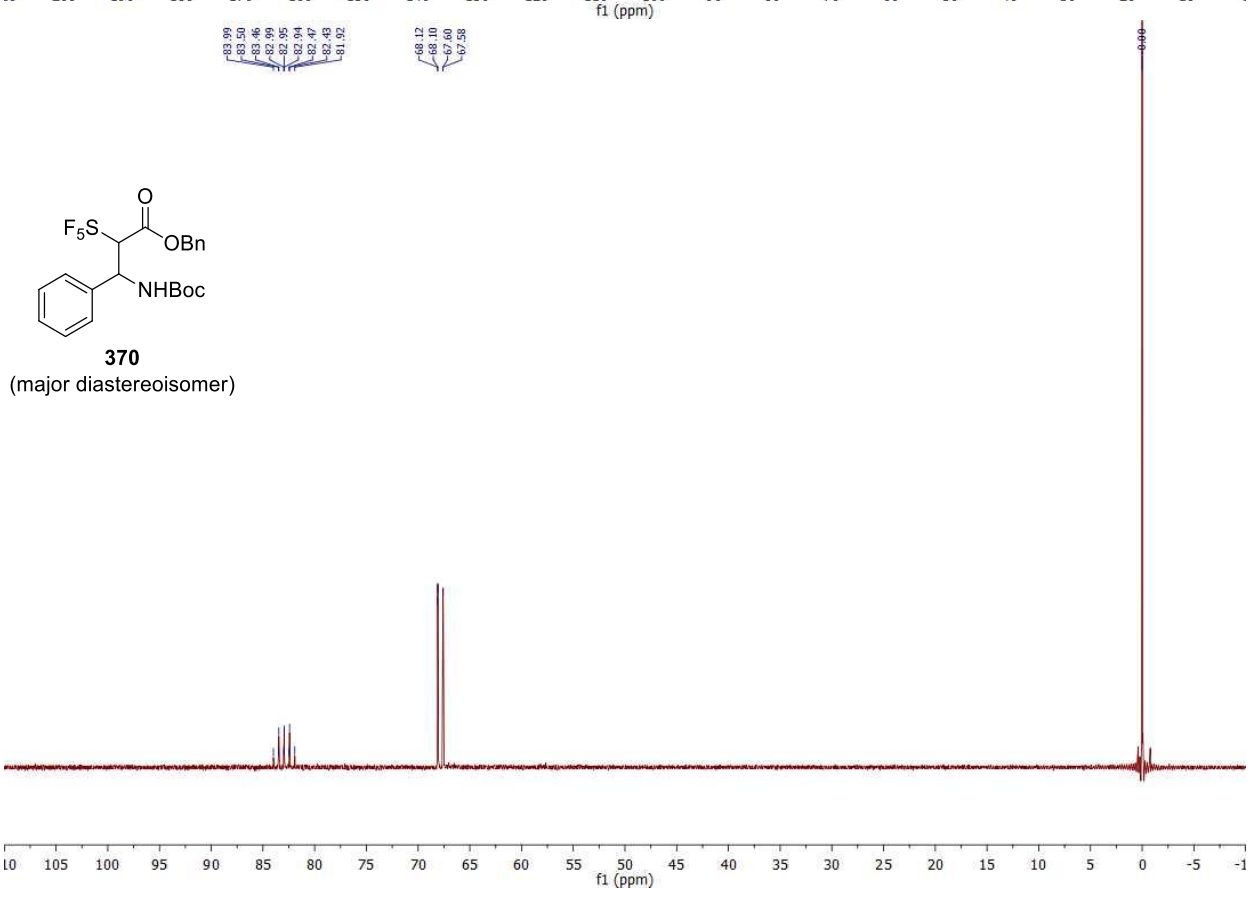




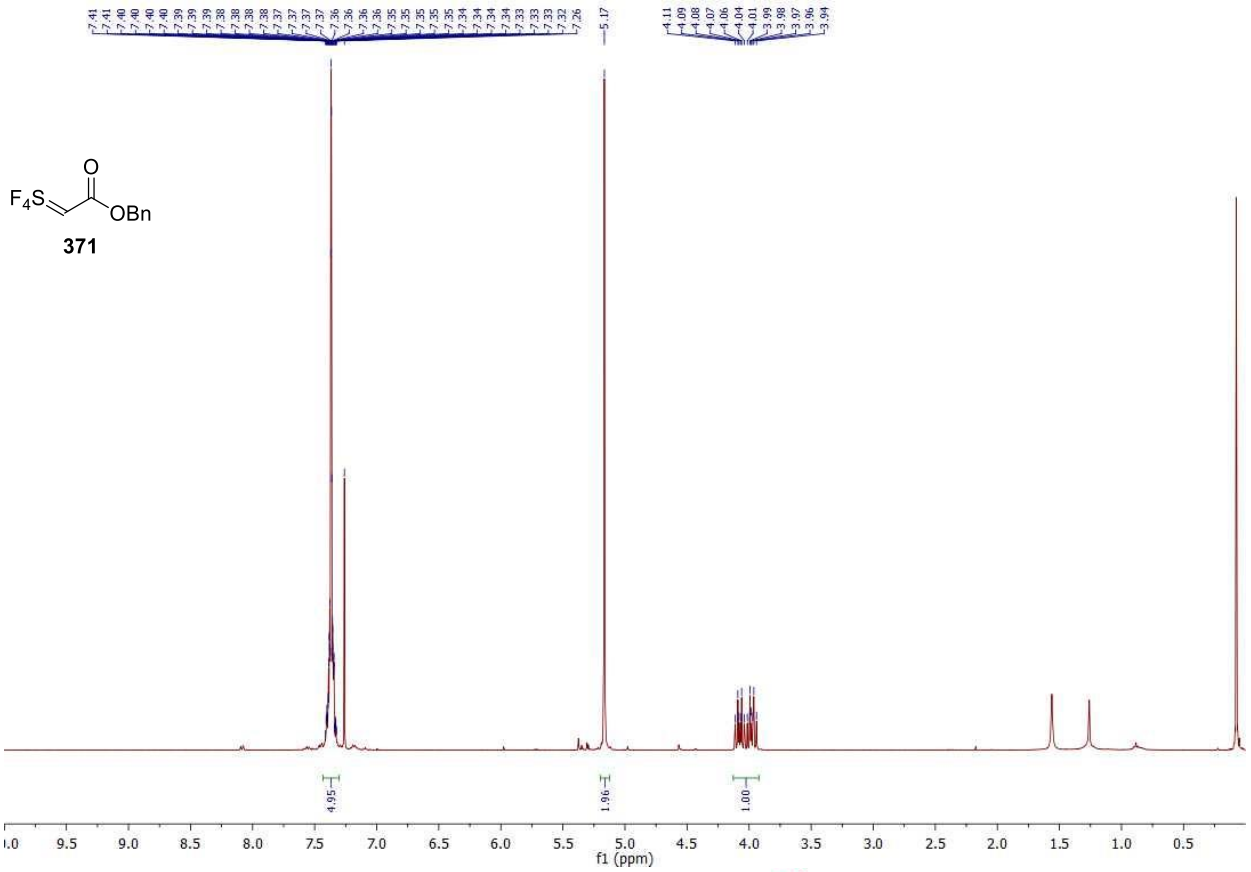
370
(major diastereoisomer)

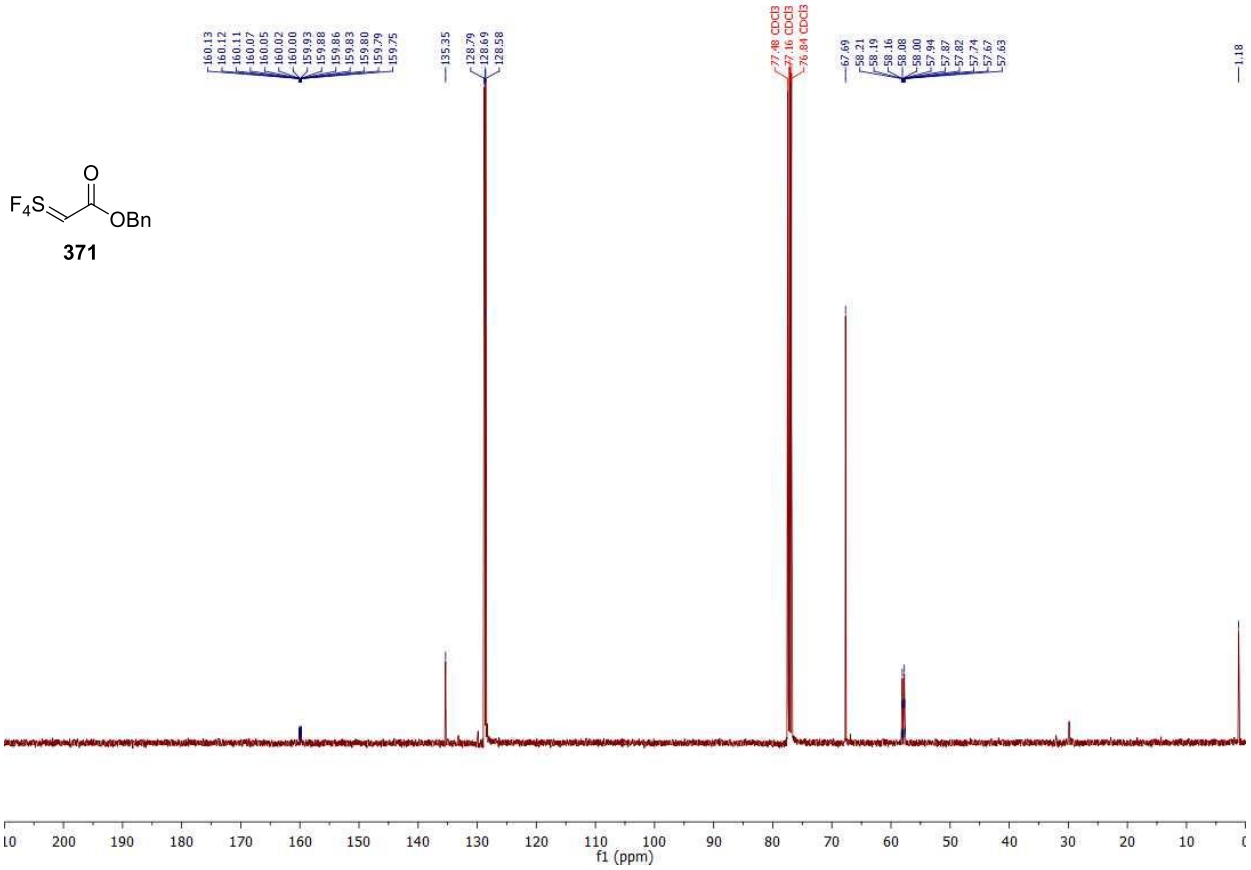


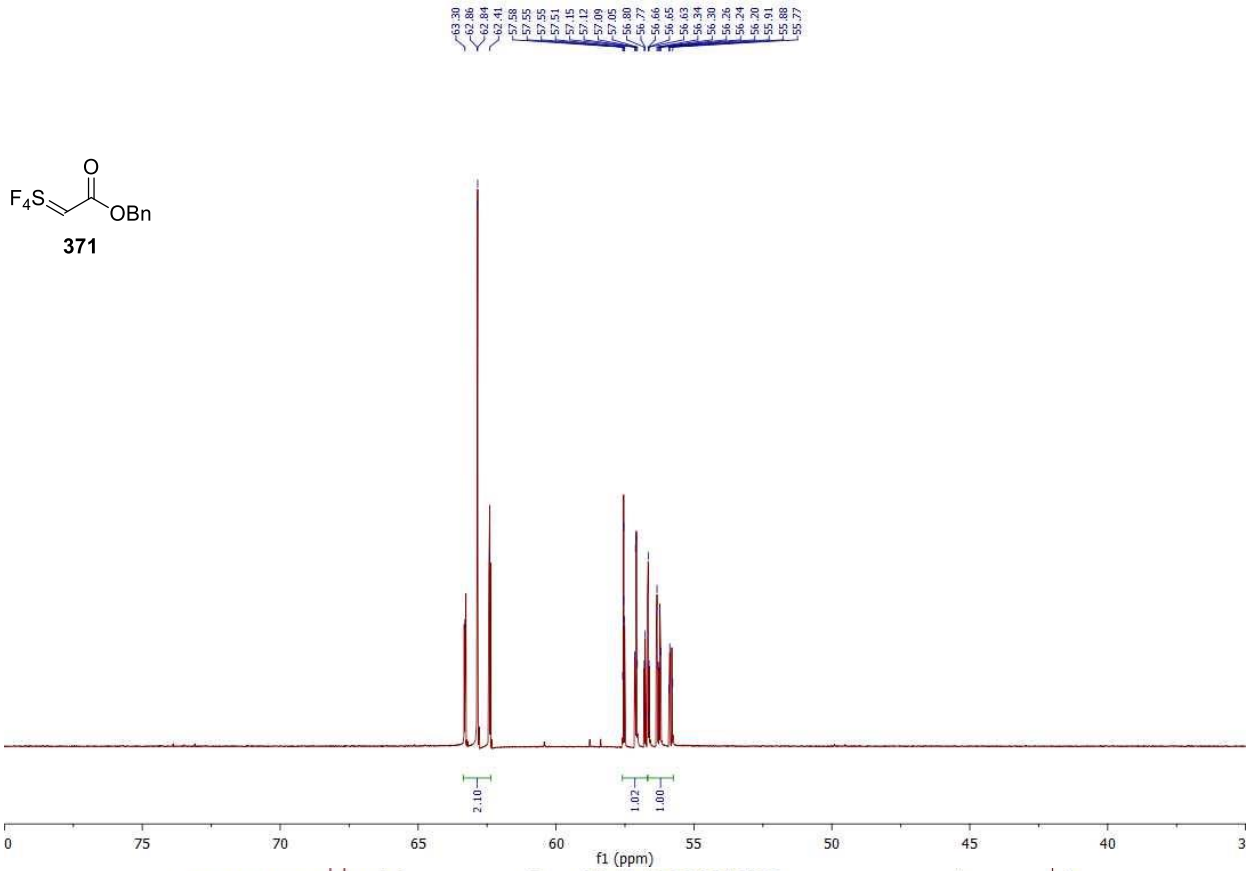
370
(major diastereoisomer)



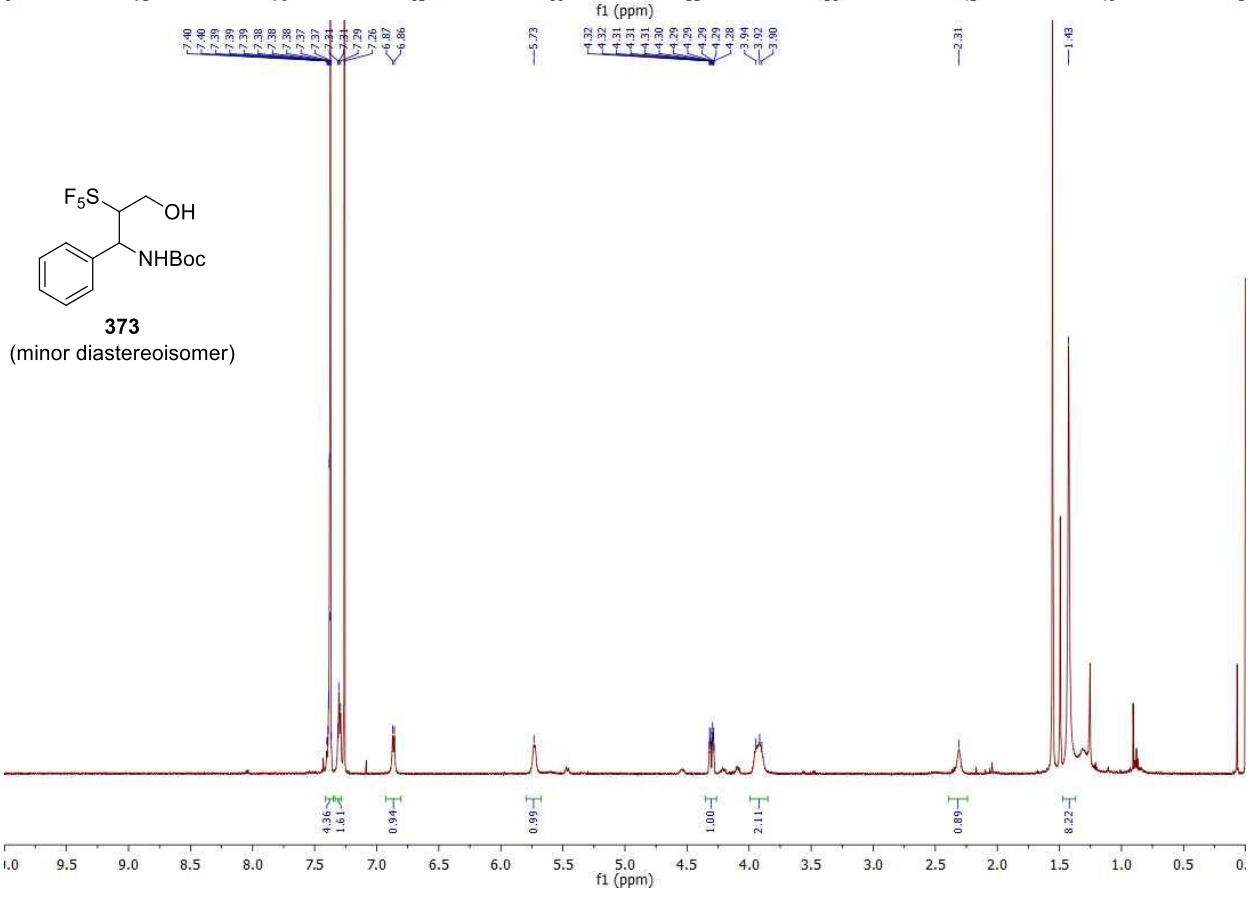
370
(major diastereoisomer)


F4S
O
OBn
371
4.95
1.96
1.00
f1 (ppm)

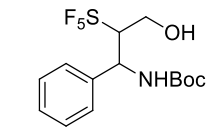

F4S
O
OBn
371
f1 (ppm)



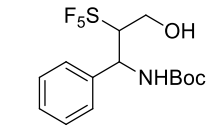
371



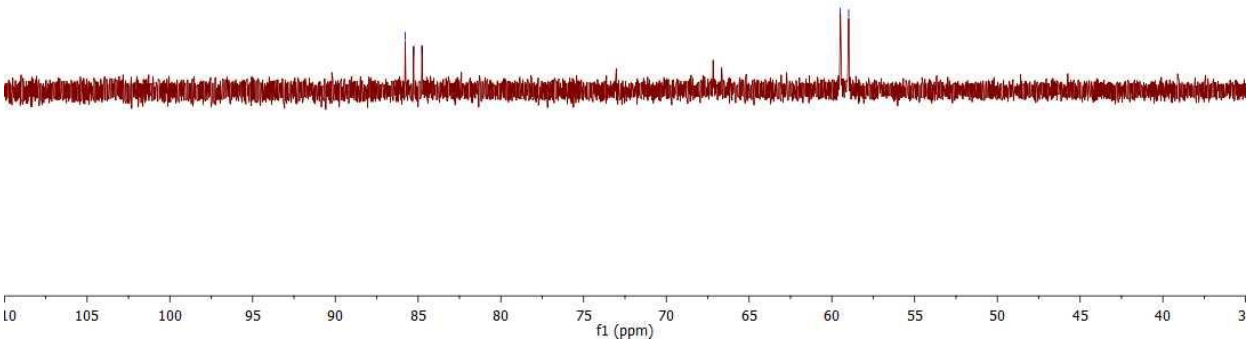
373
(minor diastereoisomer)

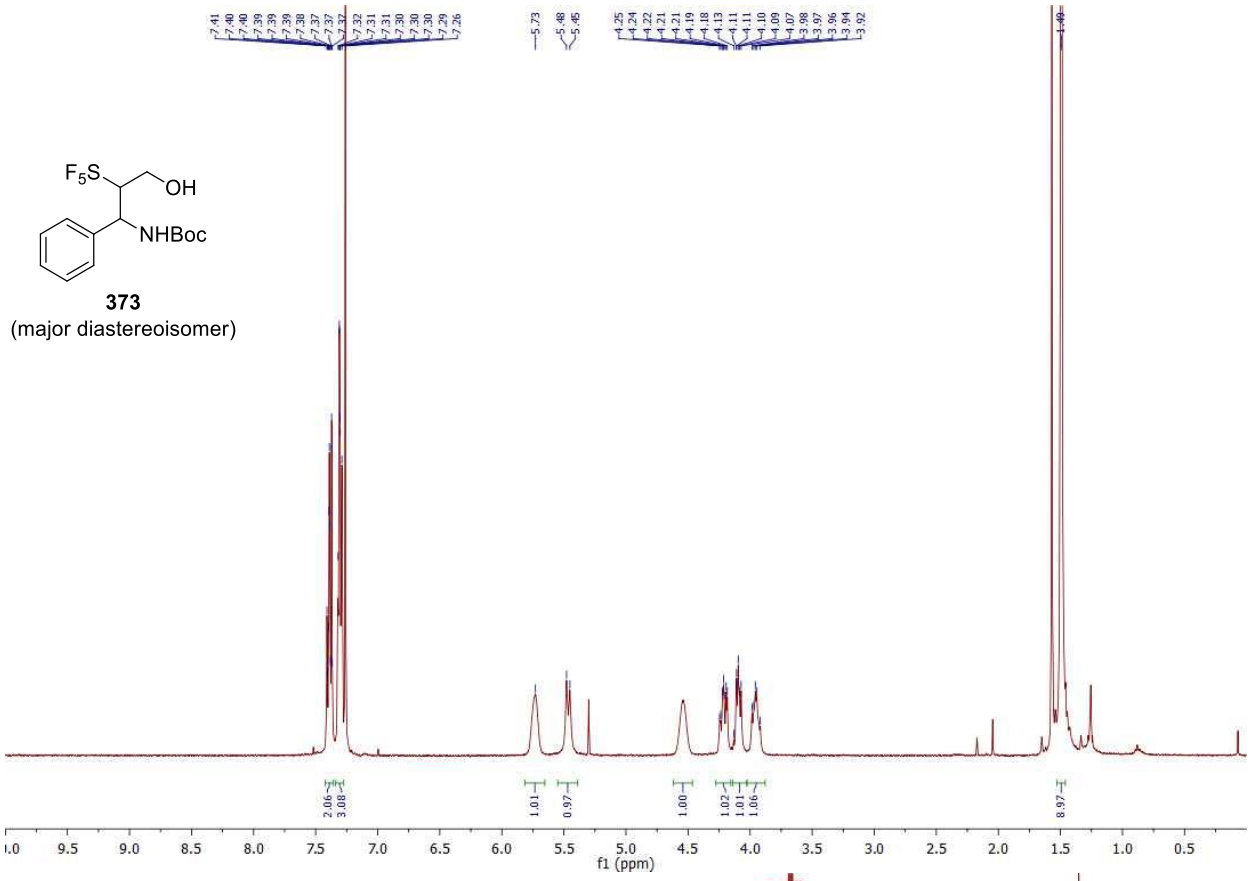


373
(minor diastereoisomer)

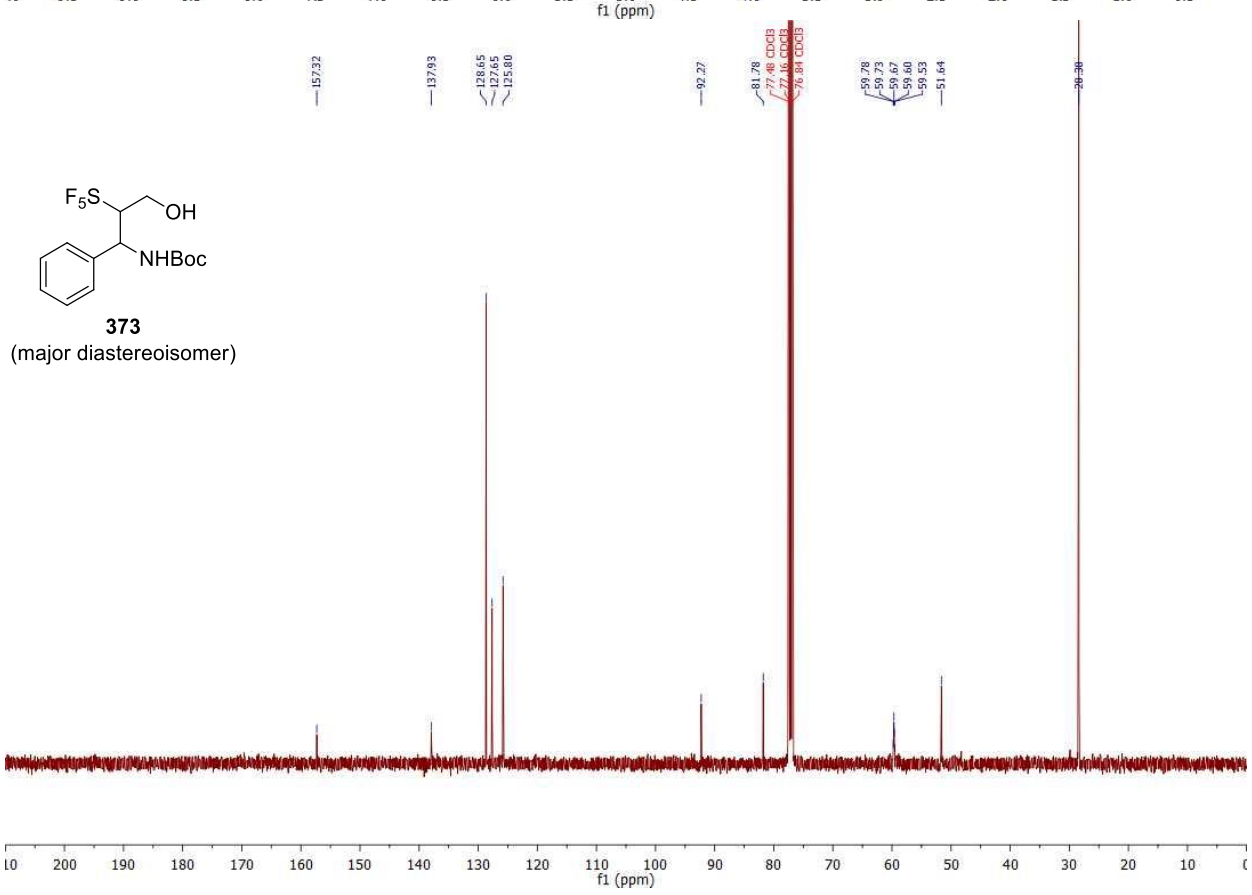


373
(minor diastereoisomer)

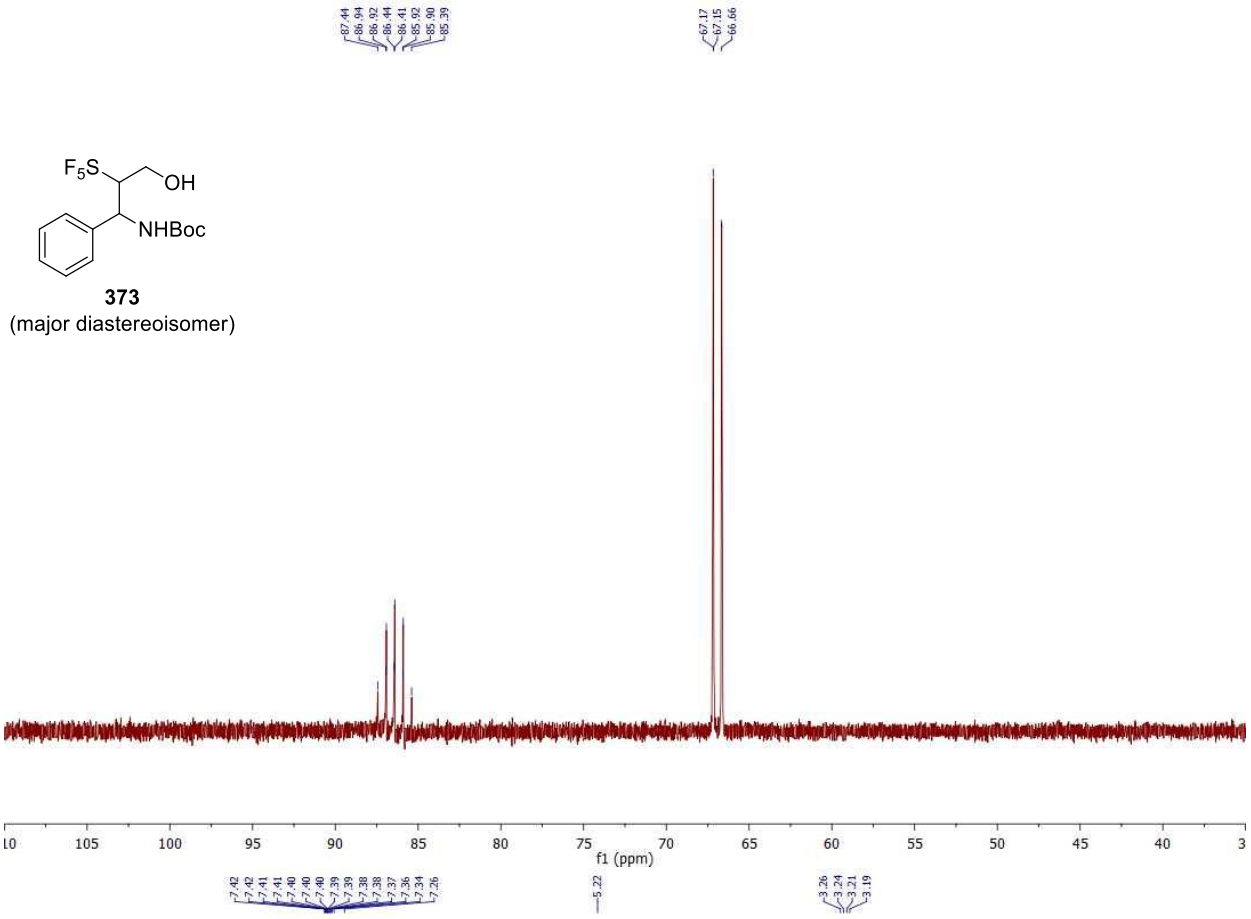




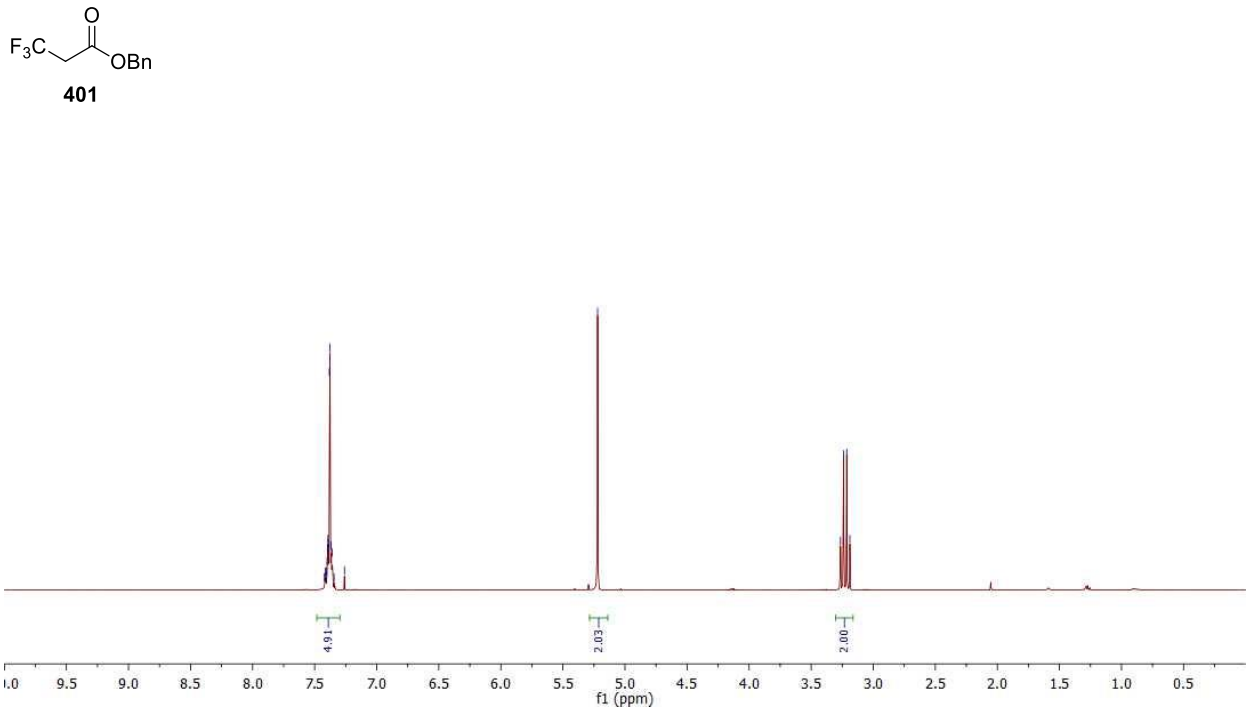
373
(major diastereoisomer)



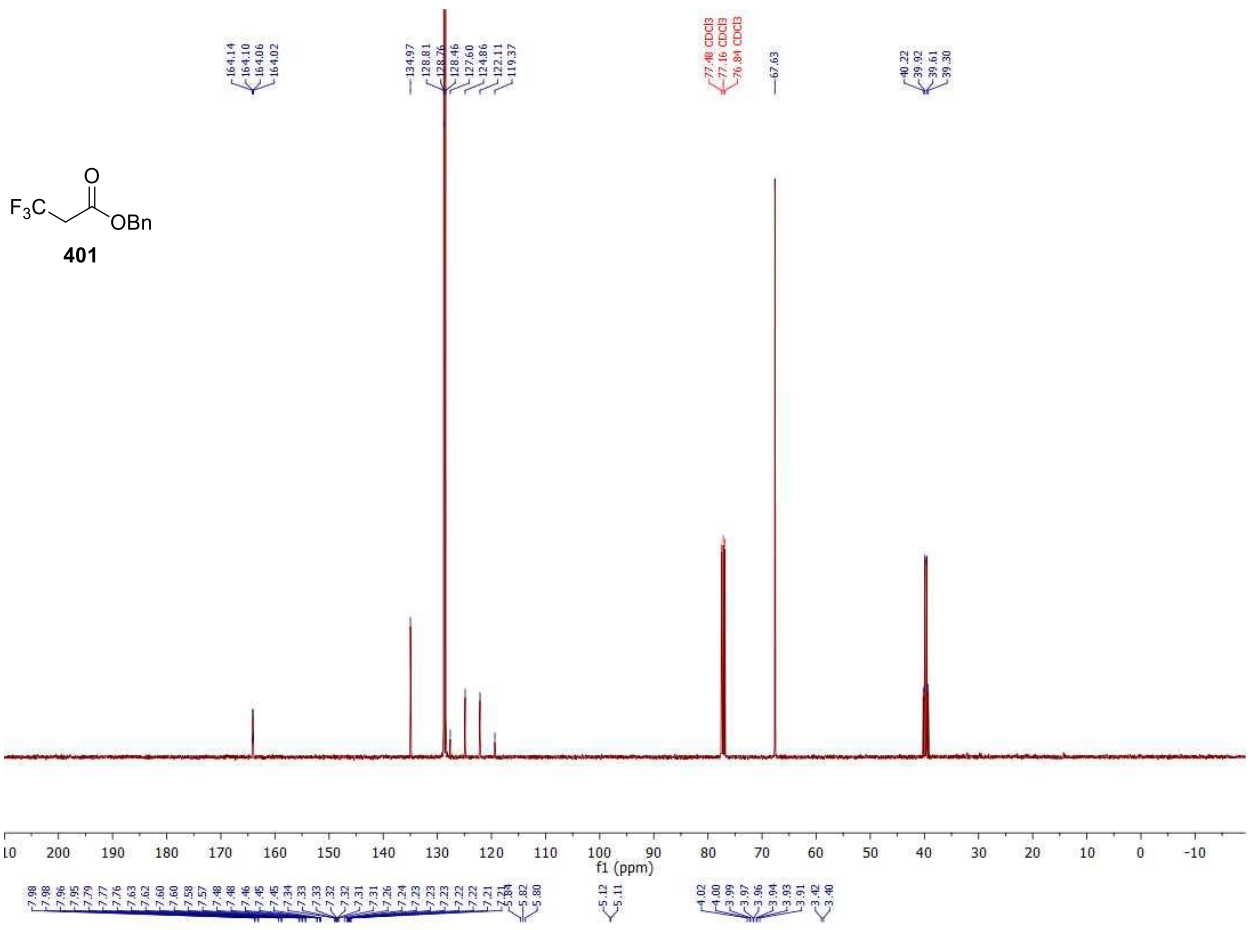
373
(major diastereoisomer)



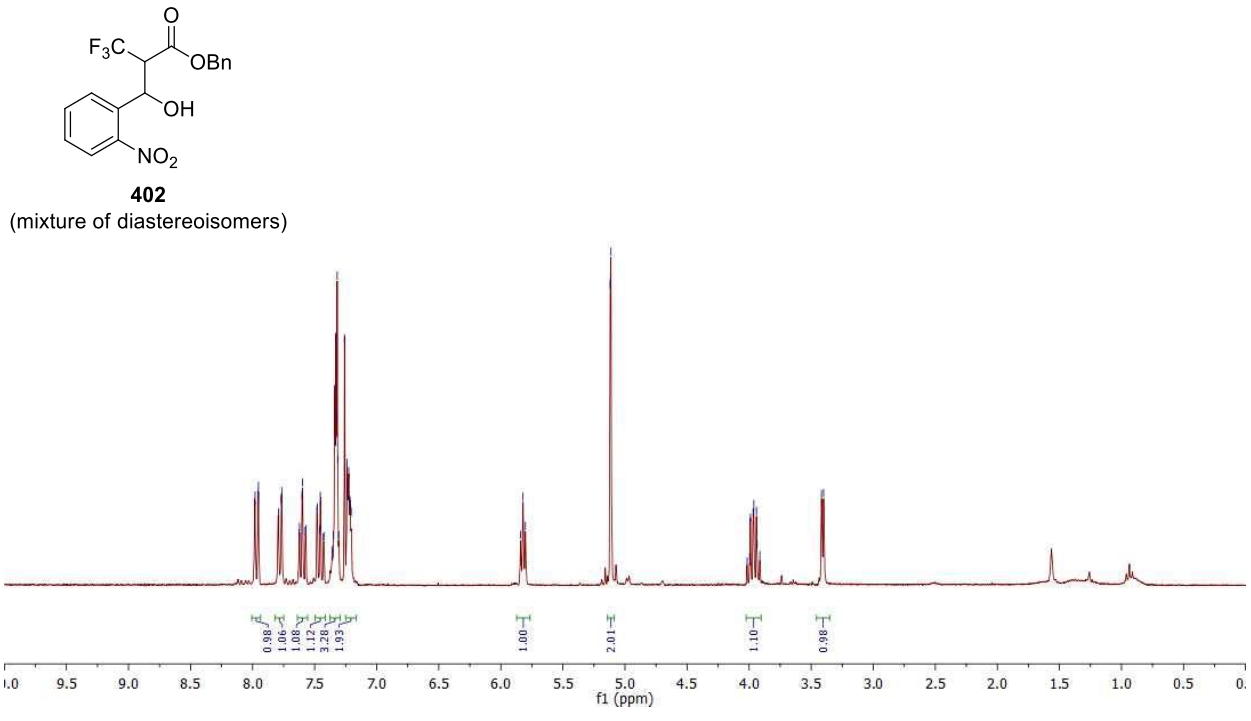
373
(major diastereoisomer)



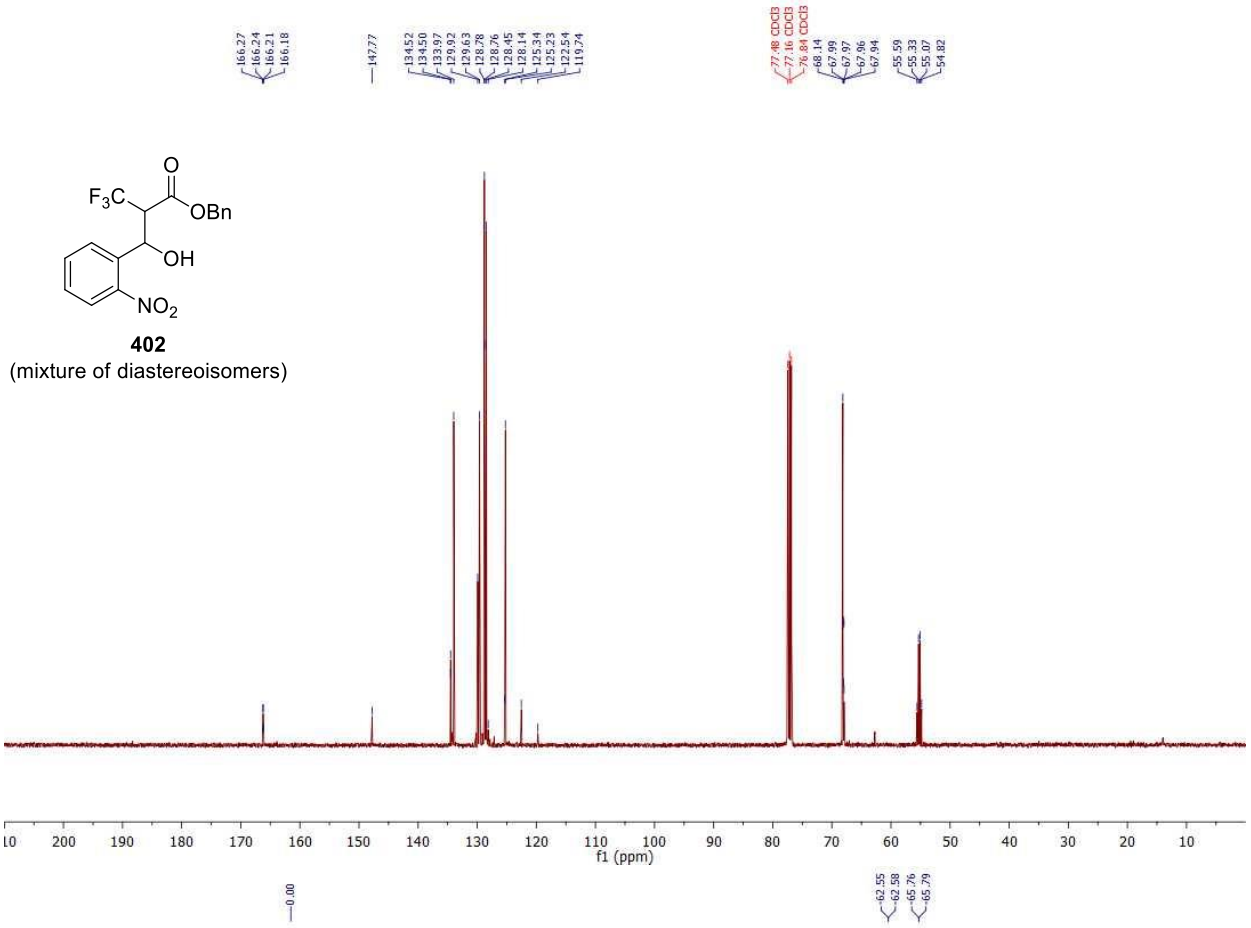
401



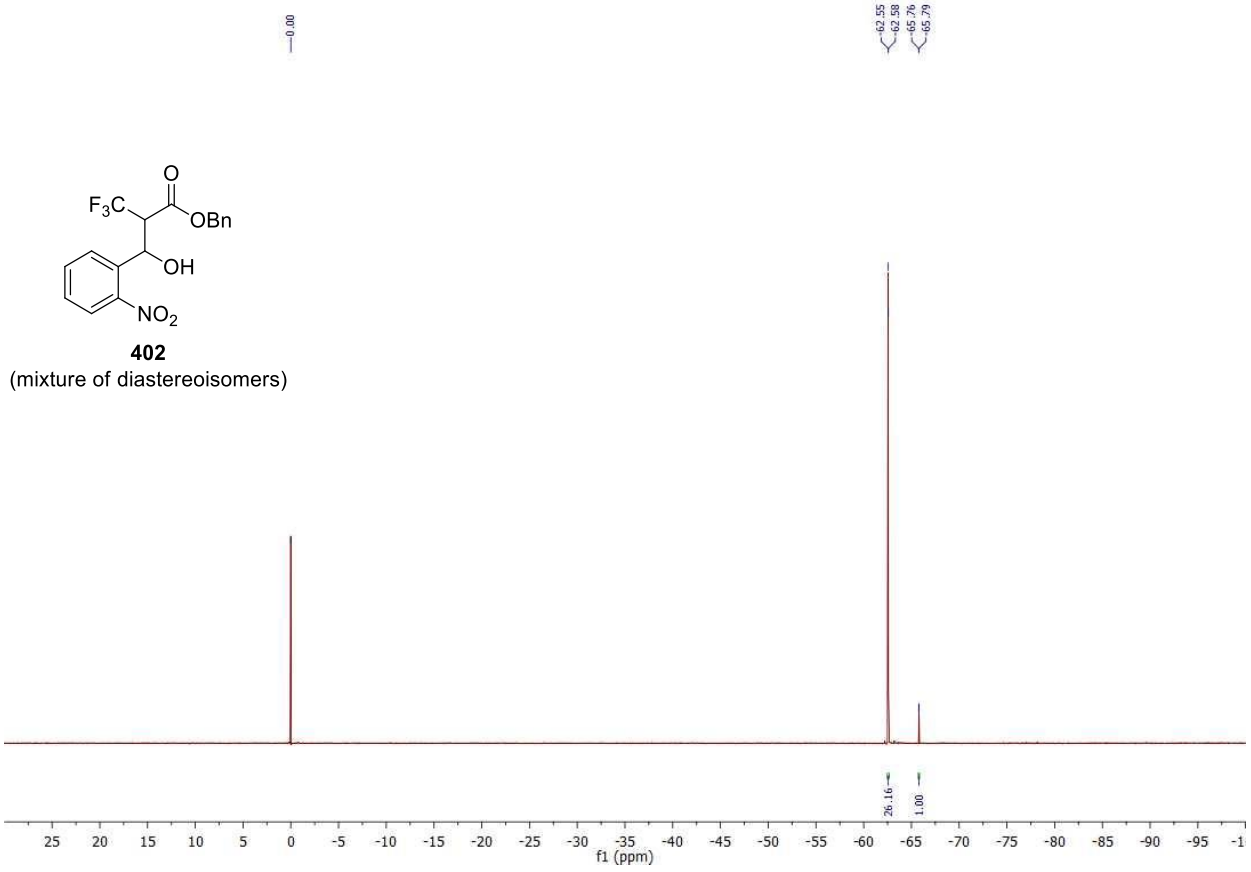
401



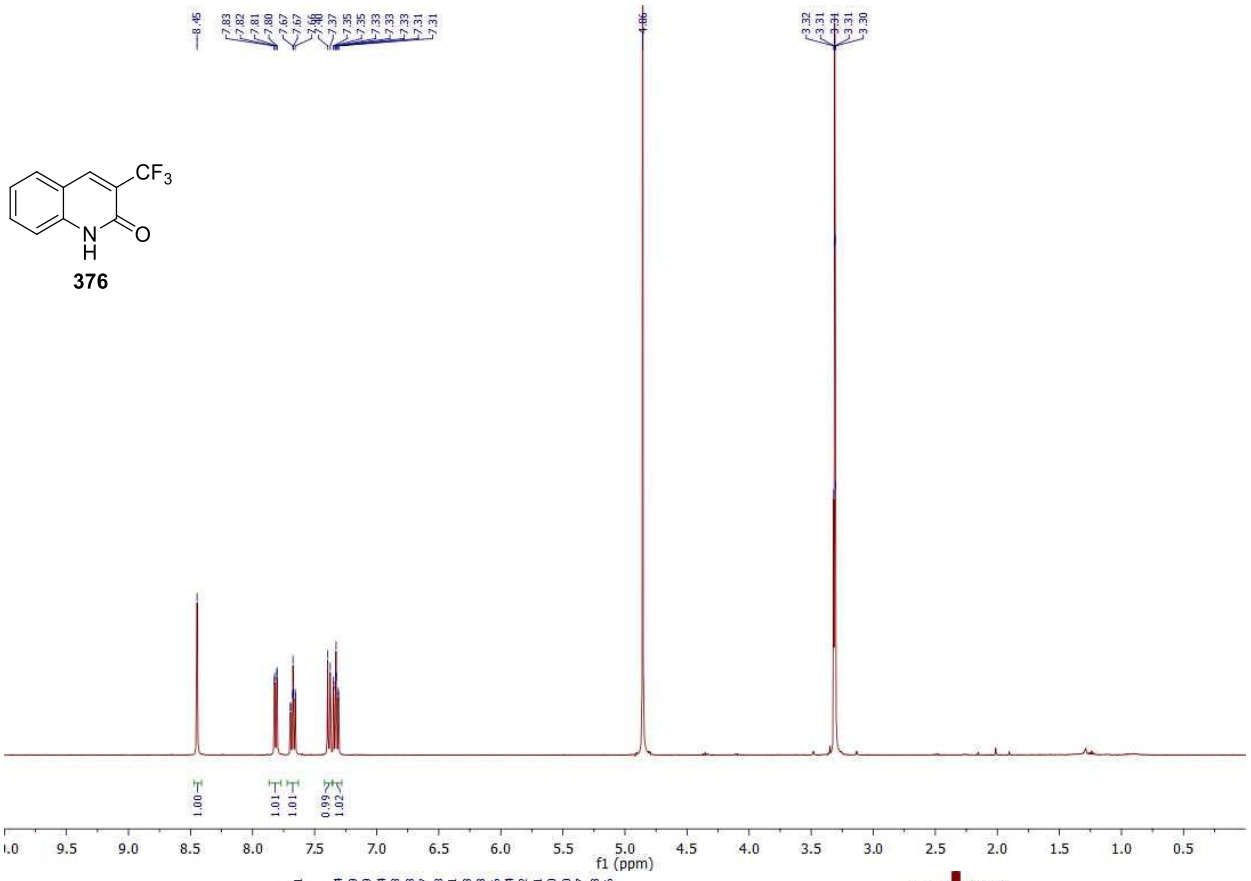
402
(mixture of diastereoisomers)

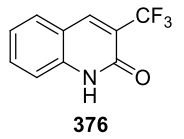


402
(mixture of diastereoisomers)



402
(mixture of diastereoisomers)

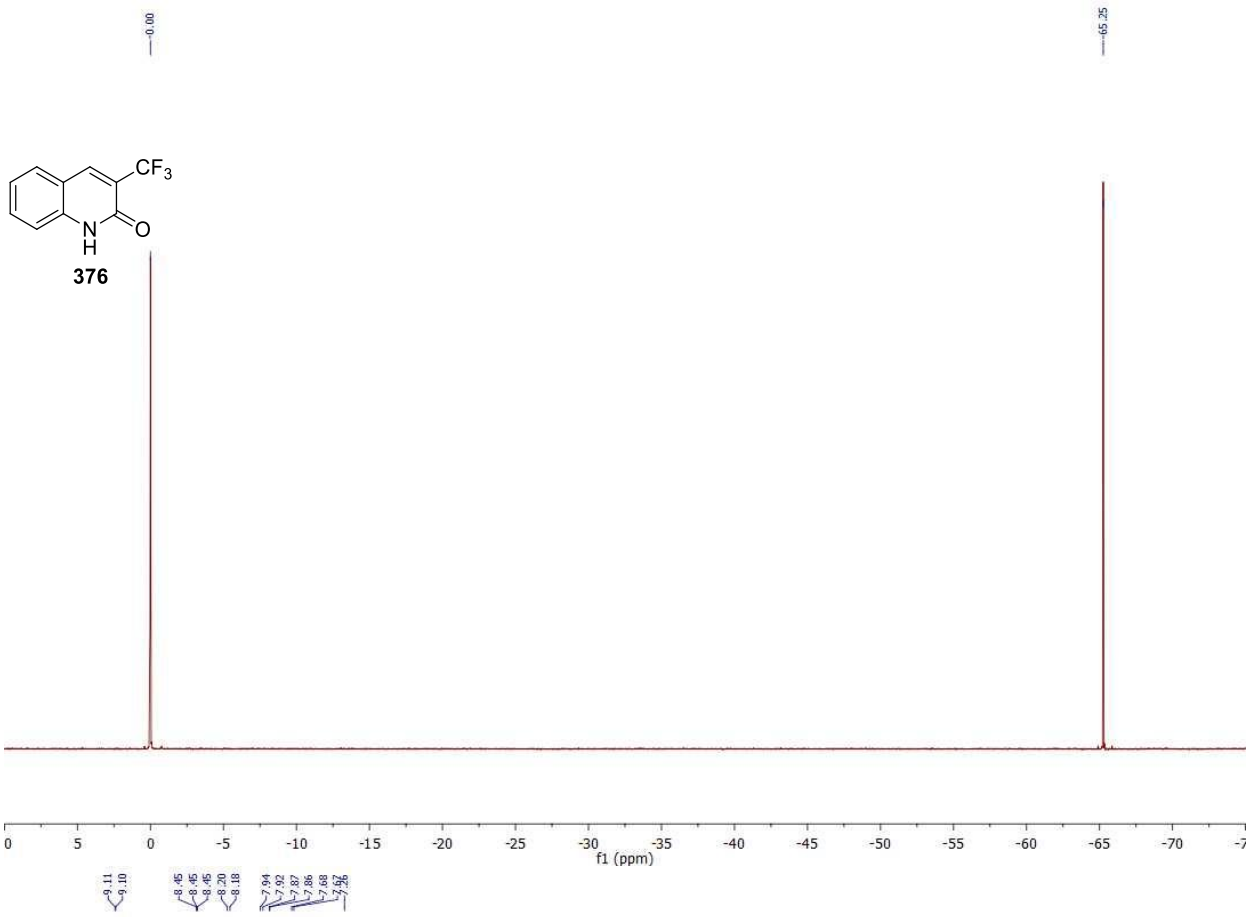

8.45
7.83
7.82
7.81
7.80
7.67
7.67
7.66
7.66
7.37
7.35
7.33
7.33
7.33
7.31
7.31
3.32
3.31
3.31
3.31
3.30
1.00
1.01
1.01
0.99
1.02
f1 (ppm)



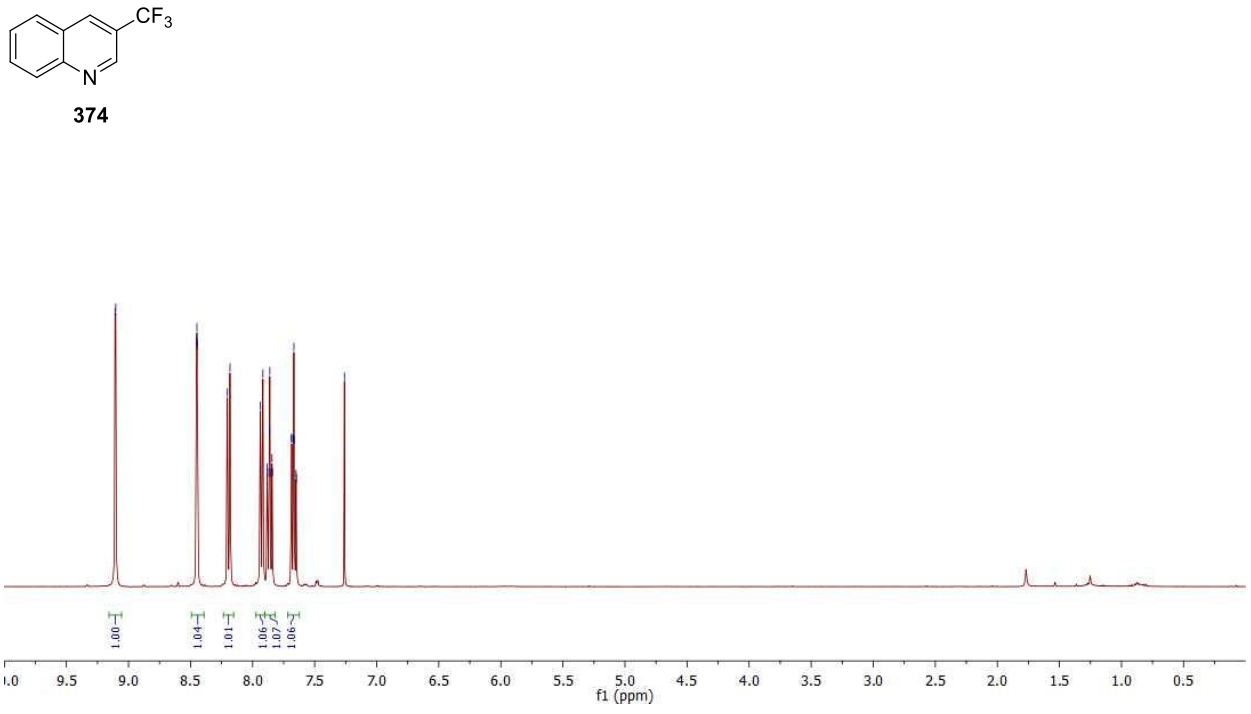
376

160.31
142.34
142.29
142.29
142.24
142.18
142.13
141.17
134.38
130.81
128.03
125.33
124.46
122.64
122.52
122.21
121.90
121.60
119.97
119.13
116.56
49.64
49.42
49.21
48.79
48.57
48.36
f1 (ppm)

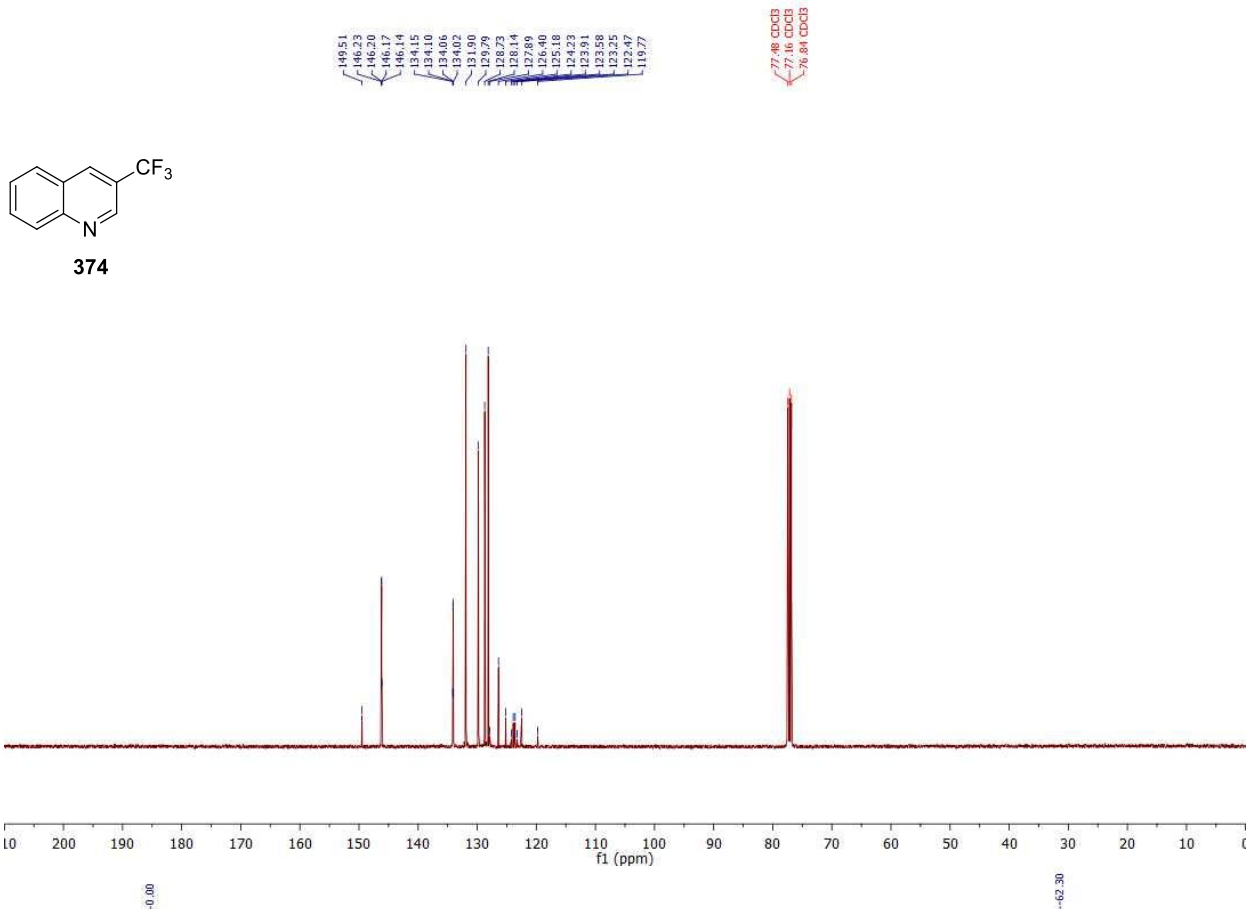
376



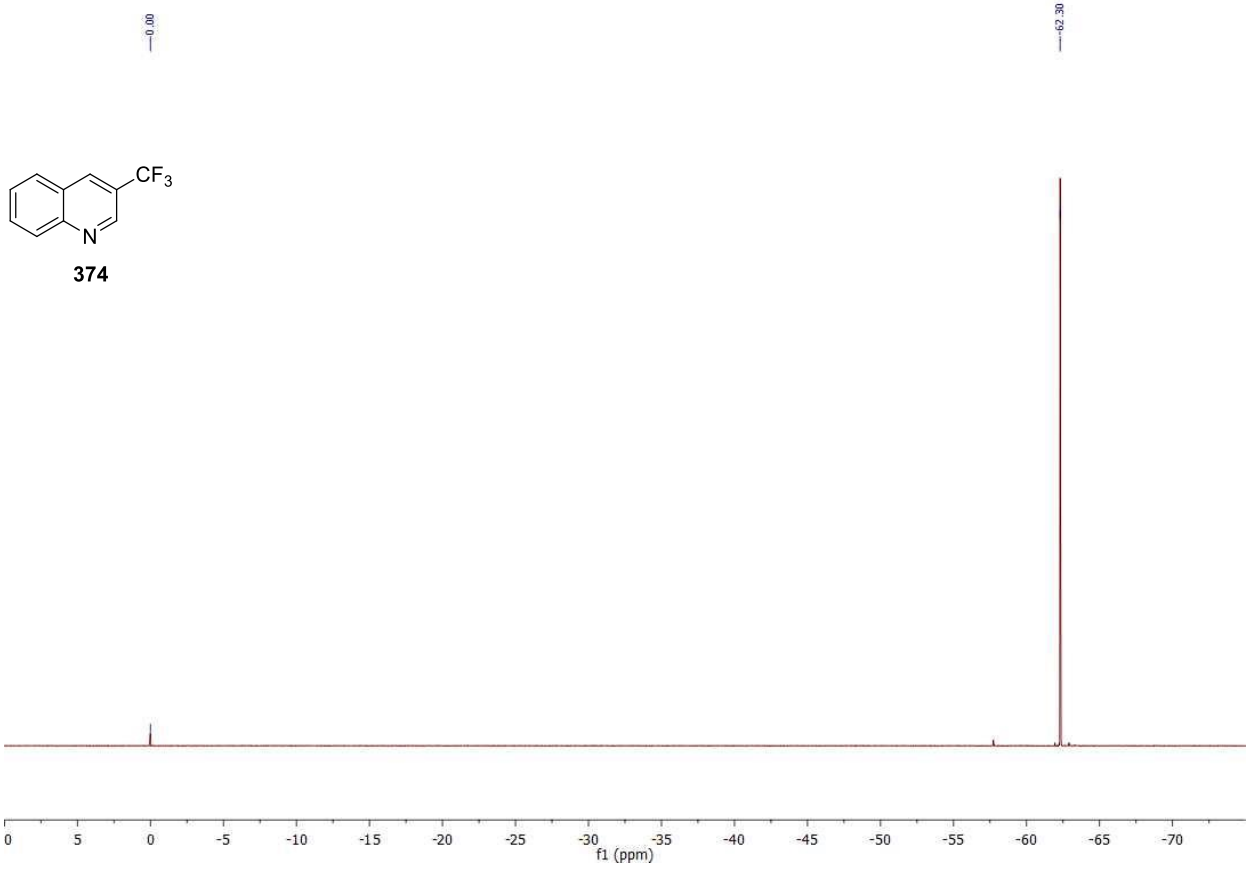
376



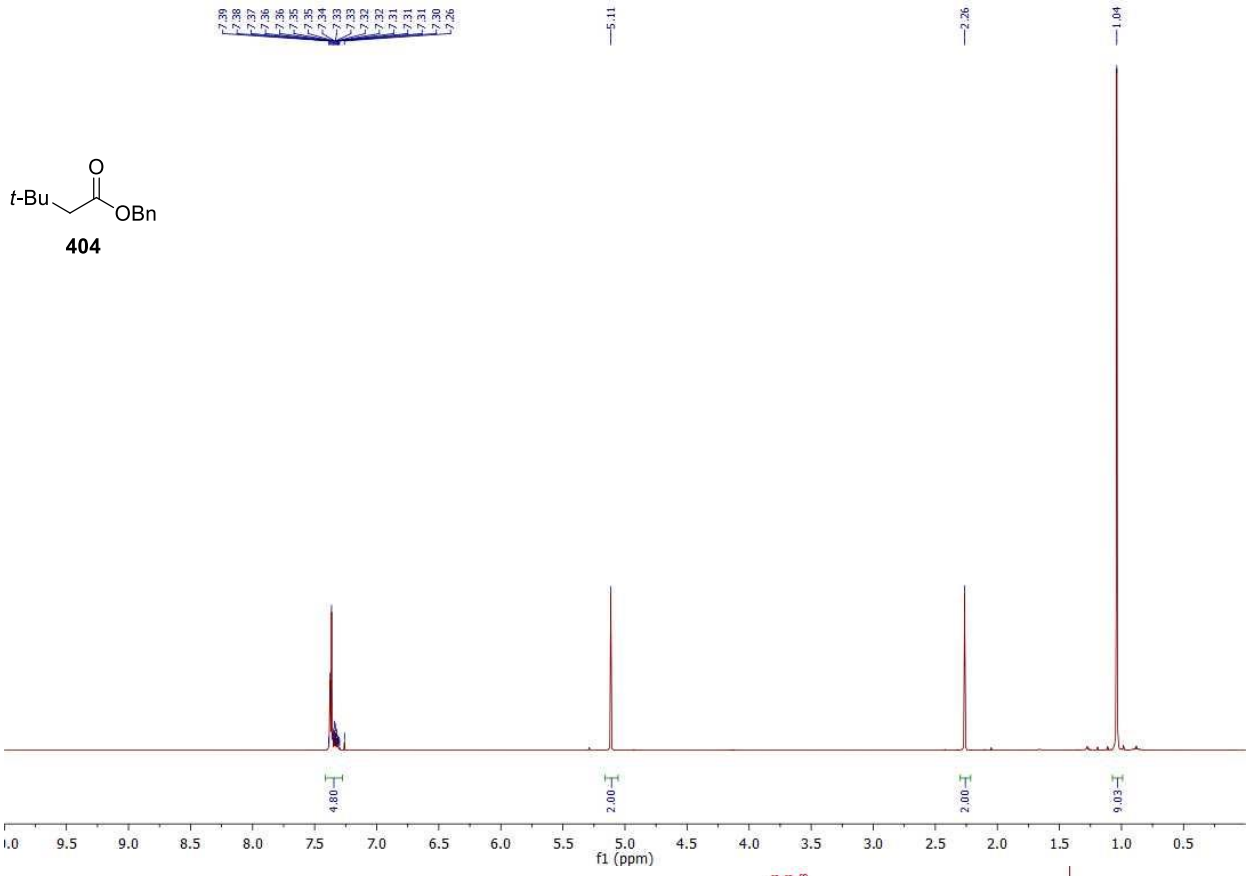
374

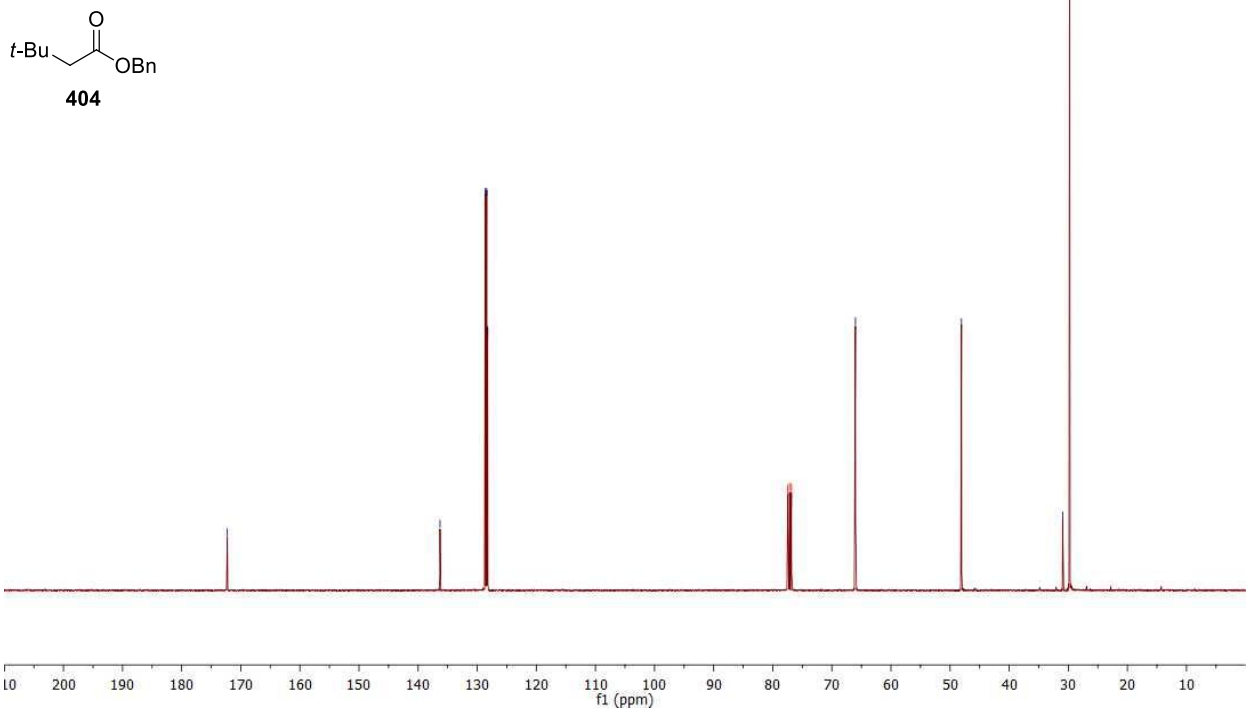

149.51
146.23
146.20
146.17
146.14
134.15
134.10
134.06
134.02
131.90
129.79
128.73
128.14
127.89
126.40
125.18
124.23
123.91
123.58
123.25
122.47
119.77
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
f1 (ppm)

374


0.00
-62.30
f1 (ppm)

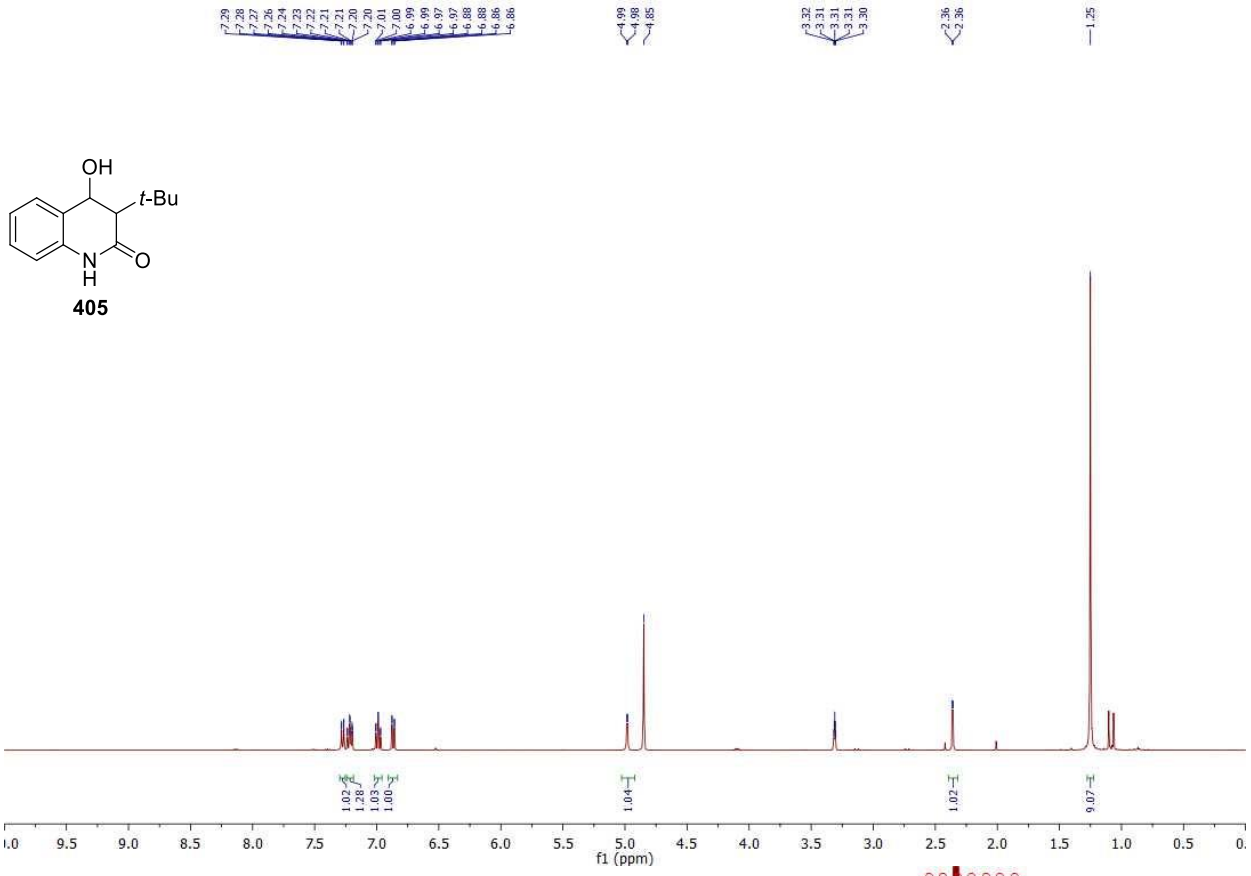
374

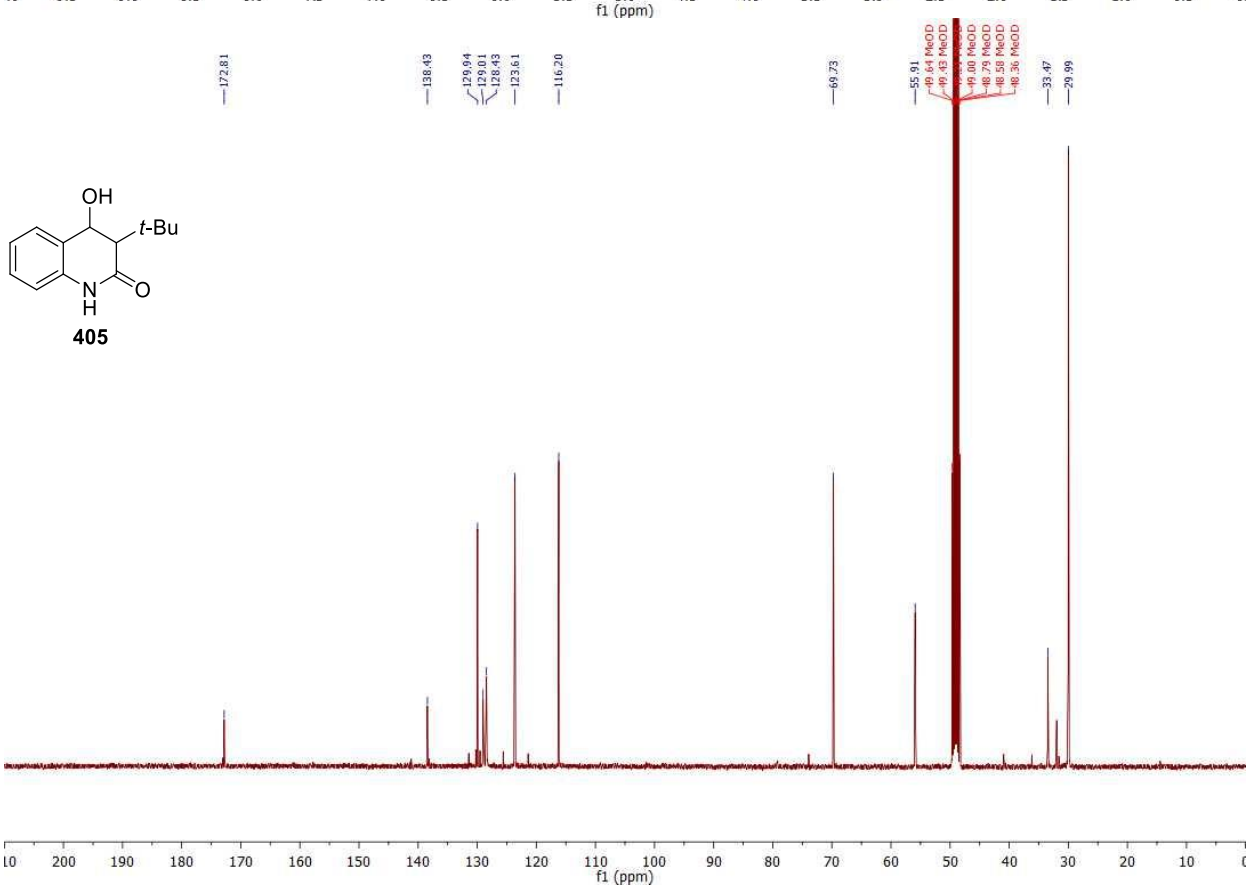

7.39
7.38
7.37
7.36
7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.31
7.30
7.26
5.11
2.26
1.04
4.80
2.00
2.00
9.03
f1 (ppm)

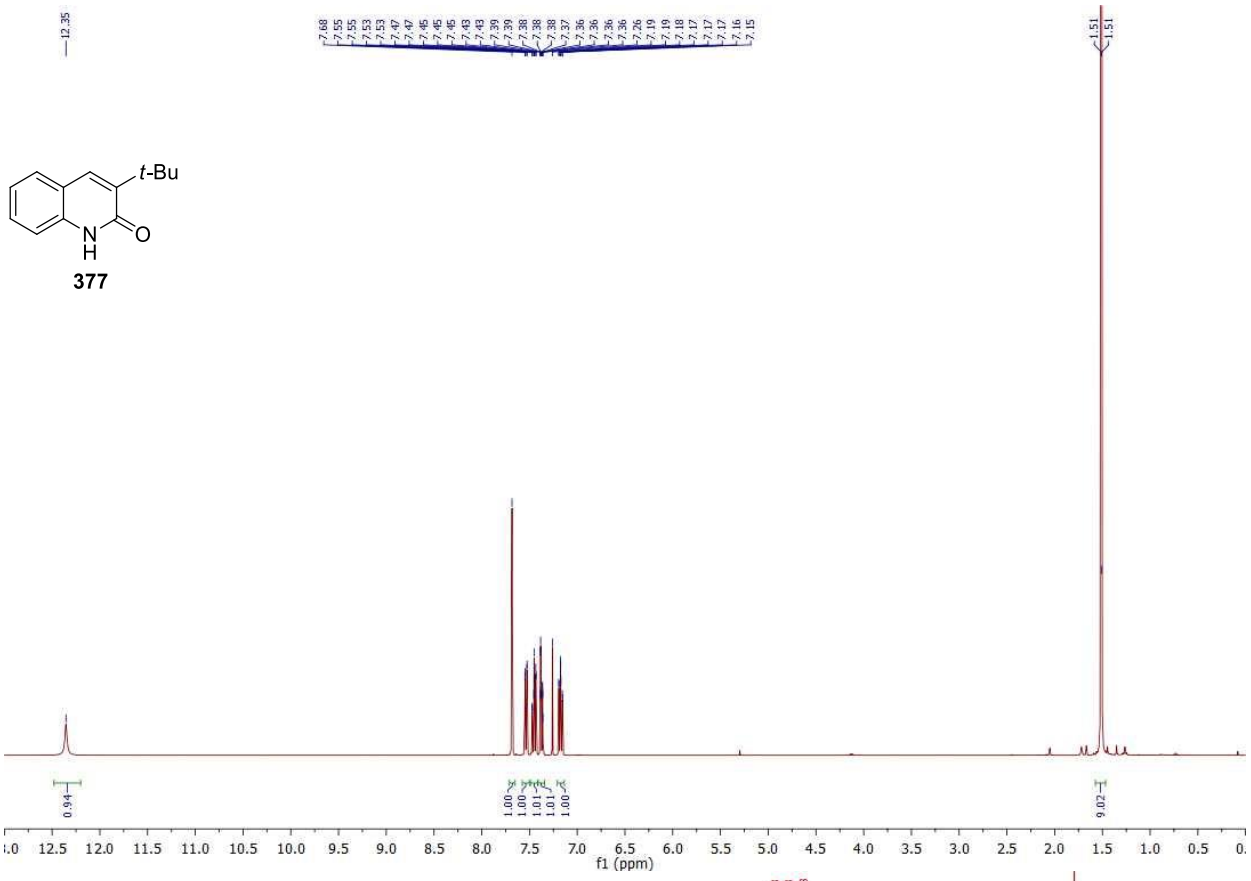

172.27
136.29
128.63
128.39
128.24
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
66.01
48.07
30.95
29.77
f1 (ppm)

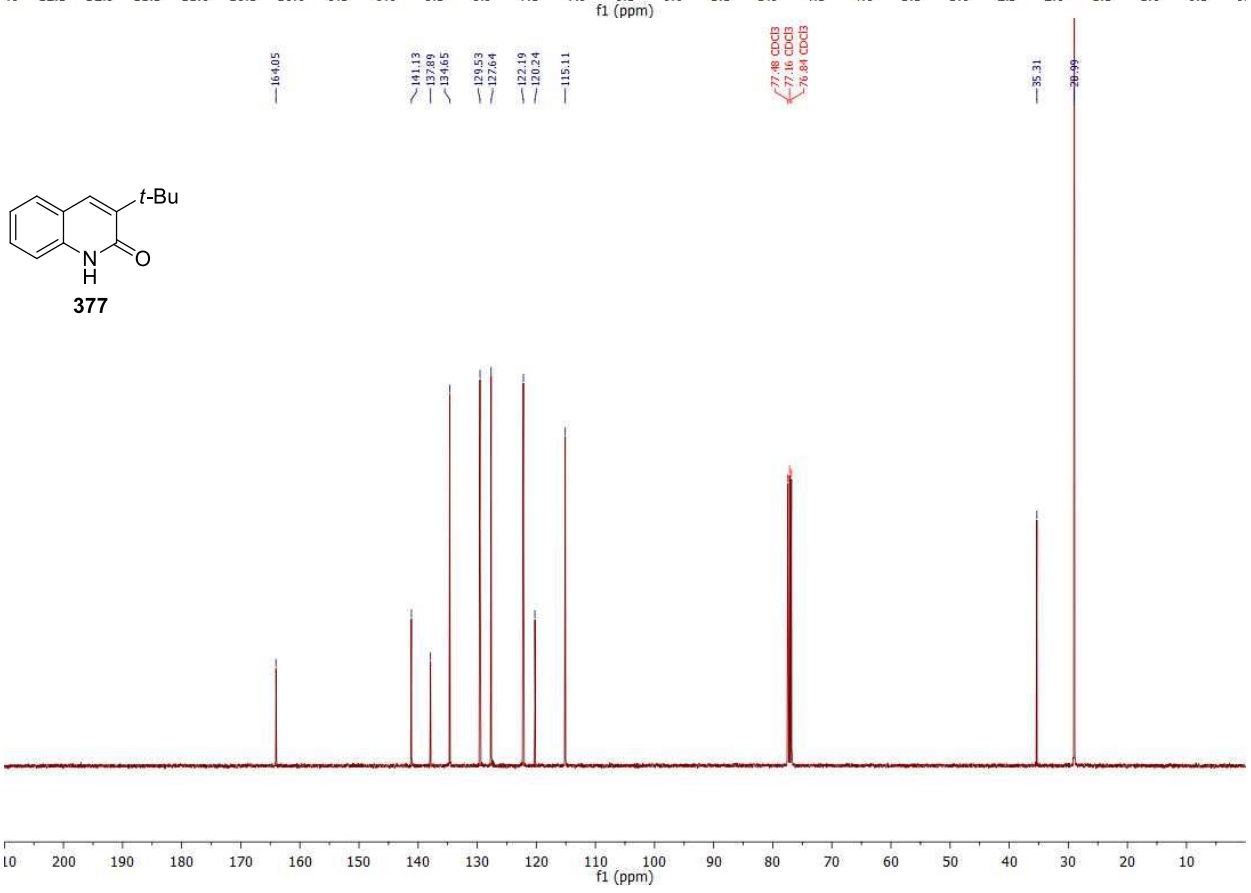
t-Bu OBn

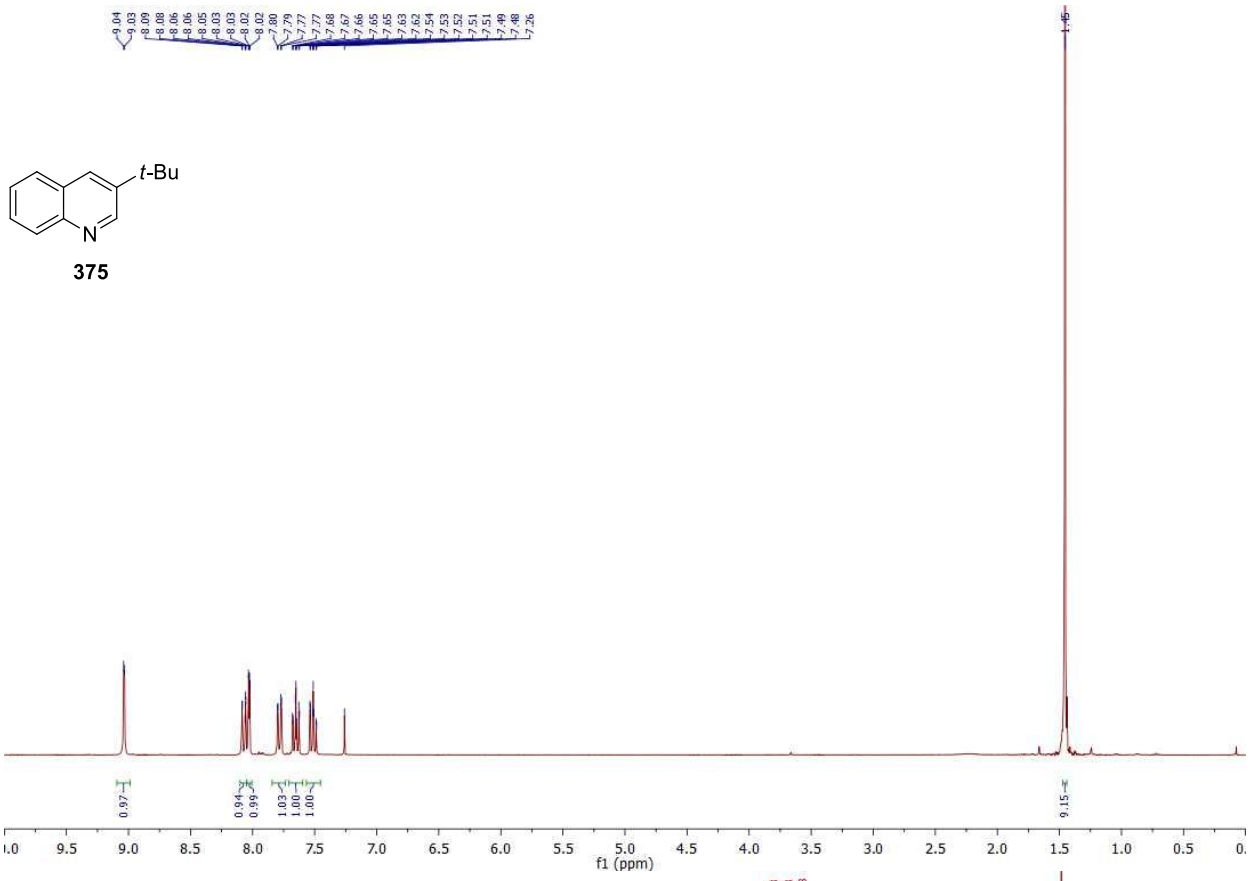
404

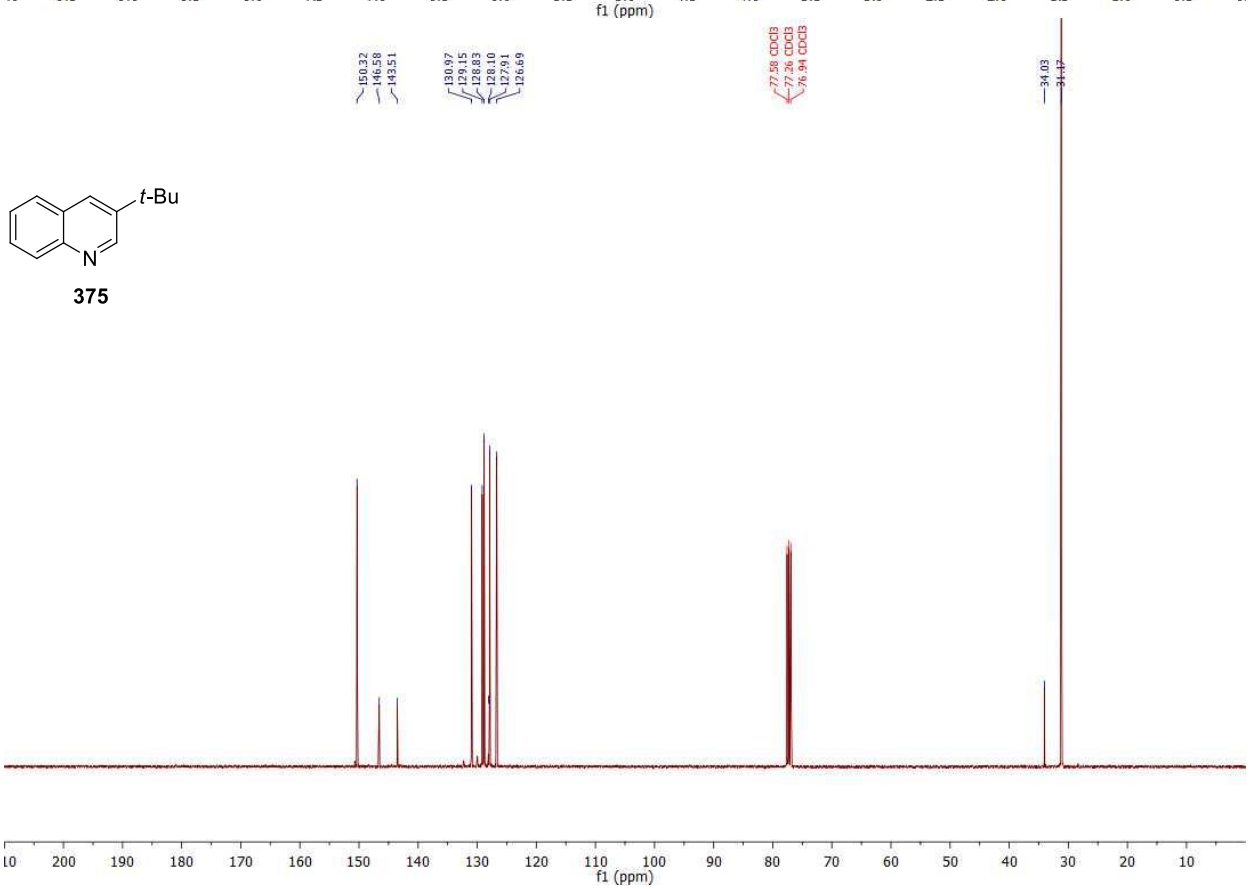

OH
t-Bu
N
H
O
405
f1 (ppm)

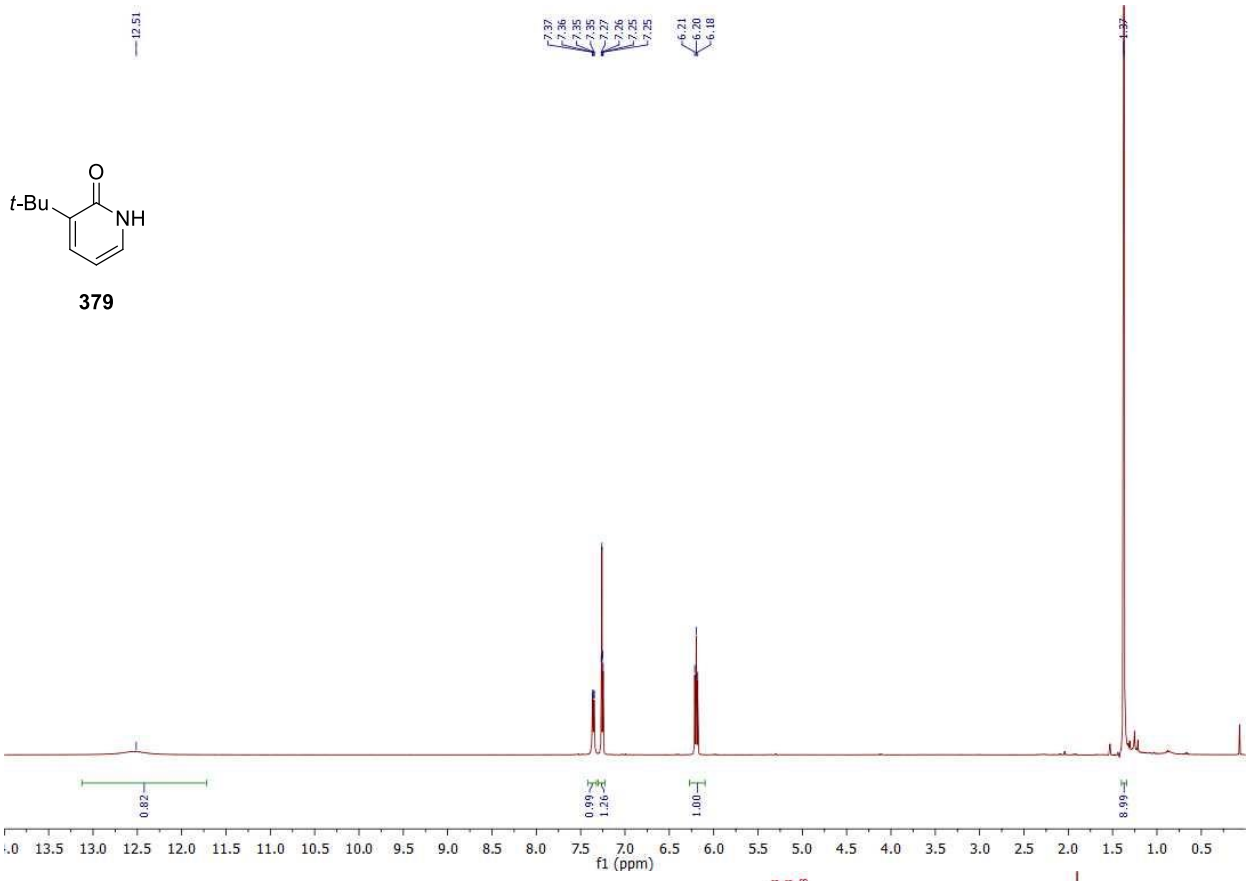

OH
t-Bu
N
H
O
405
f1 (ppm)

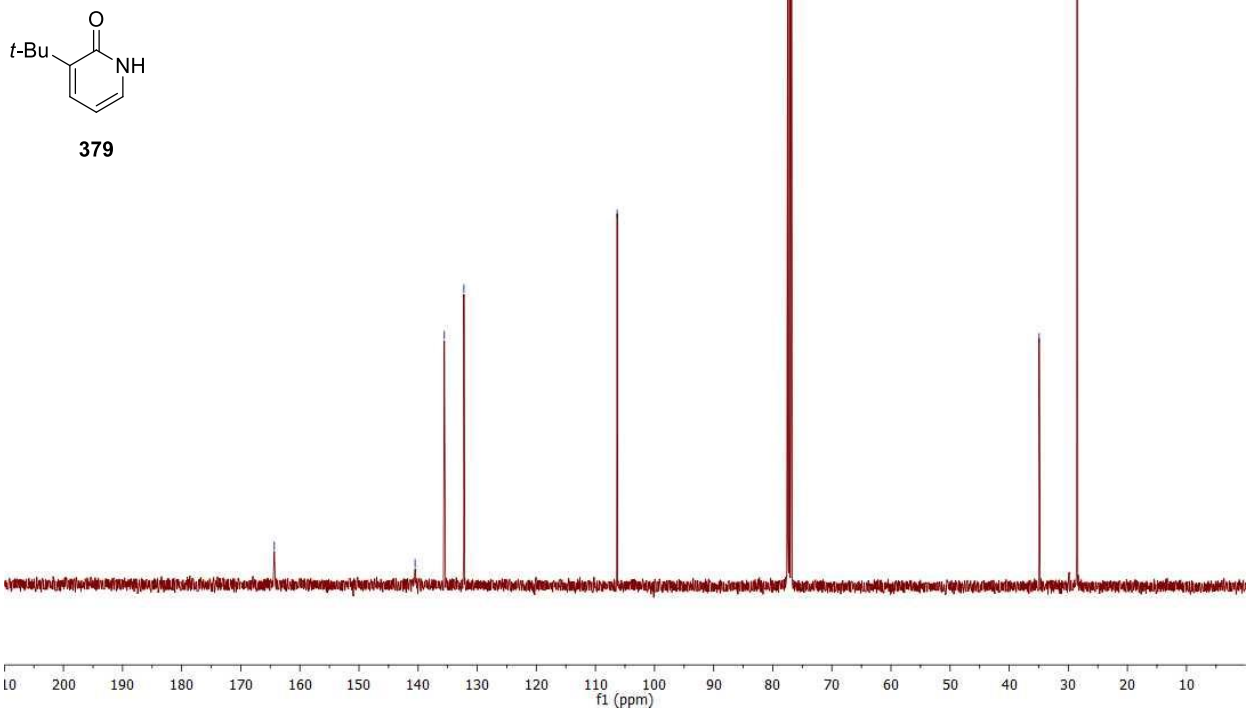

12.35
7.68
7.55
7.55
7.53
7.53
7.47
7.47
7.45
7.45
7.43
7.43
7.39
7.39
7.38
7.38
7.38
7.37
7.36
7.36
7.36
7.26
7.19
7.18
7.17
7.17
7.16
7.15
1.51
1.51
t-Bu
N
H
O
377
0.94
1.00
1.00
1.01
1.01
1.00
9.02
f1 (ppm)


164.05
141.13
137.89
134.65
129.53
127.64
122.19
120.24
115.11
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
35.31
28.49
t-Bu
N
H
O
377
f1 (ppm)


t-Bu
N
375
f1 (ppm)


t-Bu
N
375
f1 (ppm)


12.51
7.37
7.36
7.35
7.35
7.27
7.26
7.25
7.25
6.21
6.20
6.18
1.37
0.82
0.99
1.26
1.00
8.99
f1 (ppm)

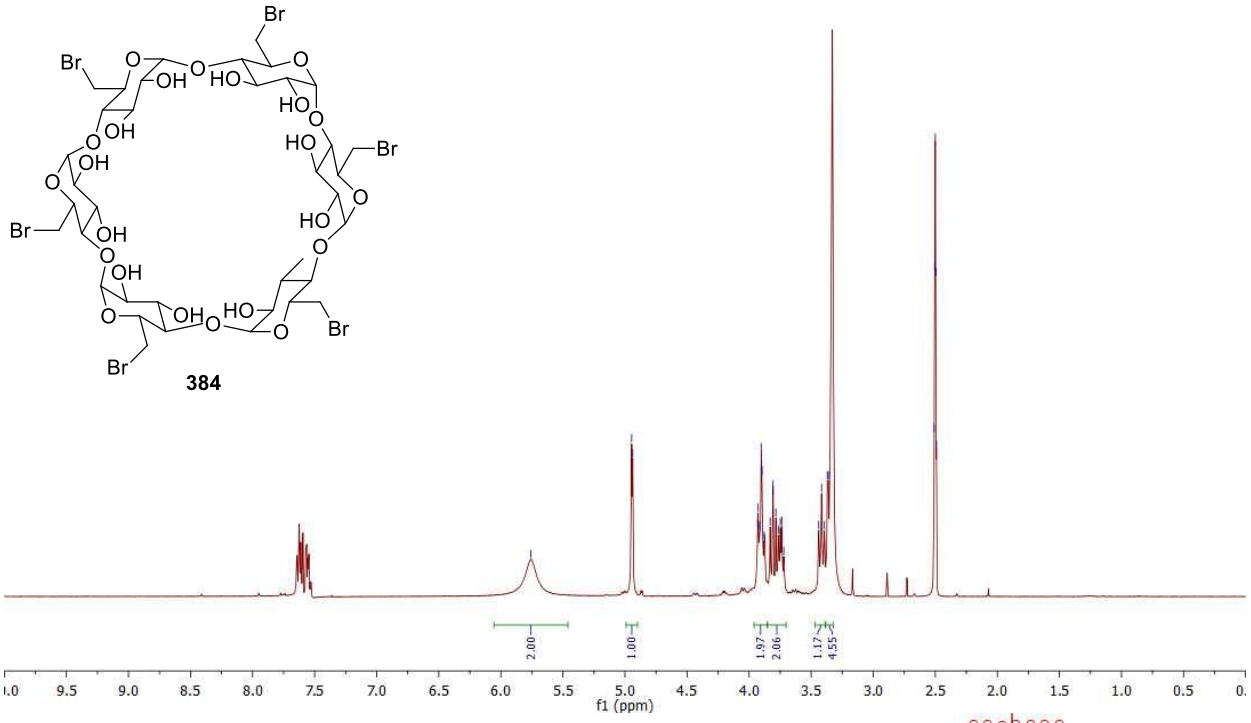

164.33
140.51
135.57
132.25
106.32
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
34.93
28.52
f1 (ppm)

O
t-Bu
NH

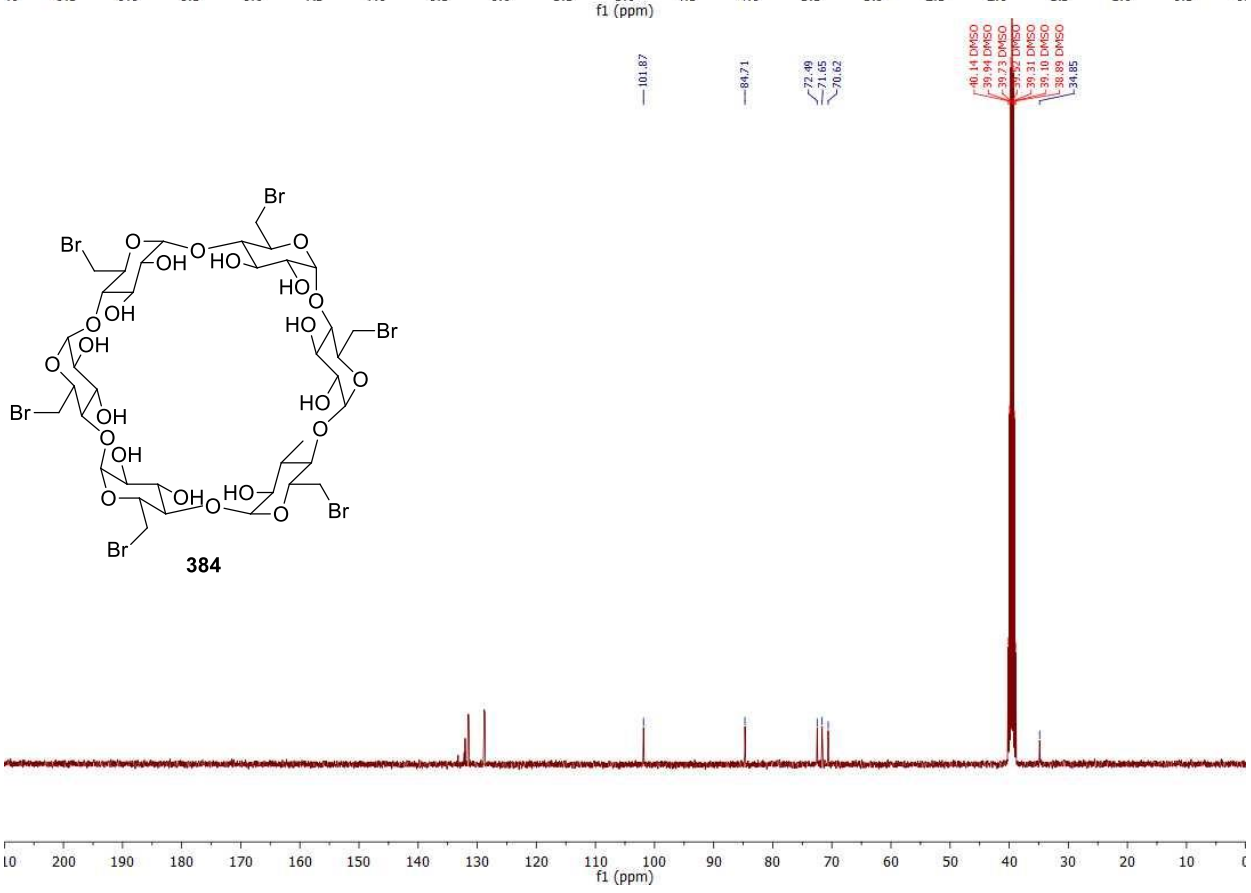
379

O
t-Bu
NH

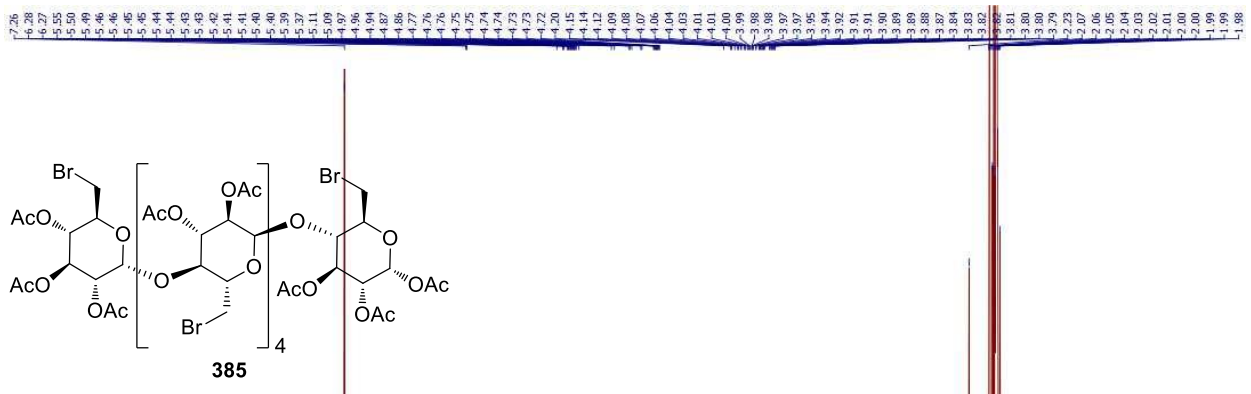
379


5.76
4.95
4.94
3.93
3.90
3.90
3.83
3.81
3.81
3.81
3.78
3.75
3.44
3.42
3.39
3.37
3.36
2.51
2.50
2.50
2.50
2.49
2.00
1.00
1.97
2.06
1.17
4.55
f1 (ppm)

384


101.87
84.71
72.49
71.65
70.62
40.14 DMSO
39.94 DMSO
39.73 DMSO
39.52 DMSO
39.31 DMSO
39.10 DMSO
38.89 DMSO
34.85
f1 (ppm)

384


Br
AcO
AcO
OAc
O
OAc
AcO
O
O
Br
4
Br
O
AcO
OAc
OAc

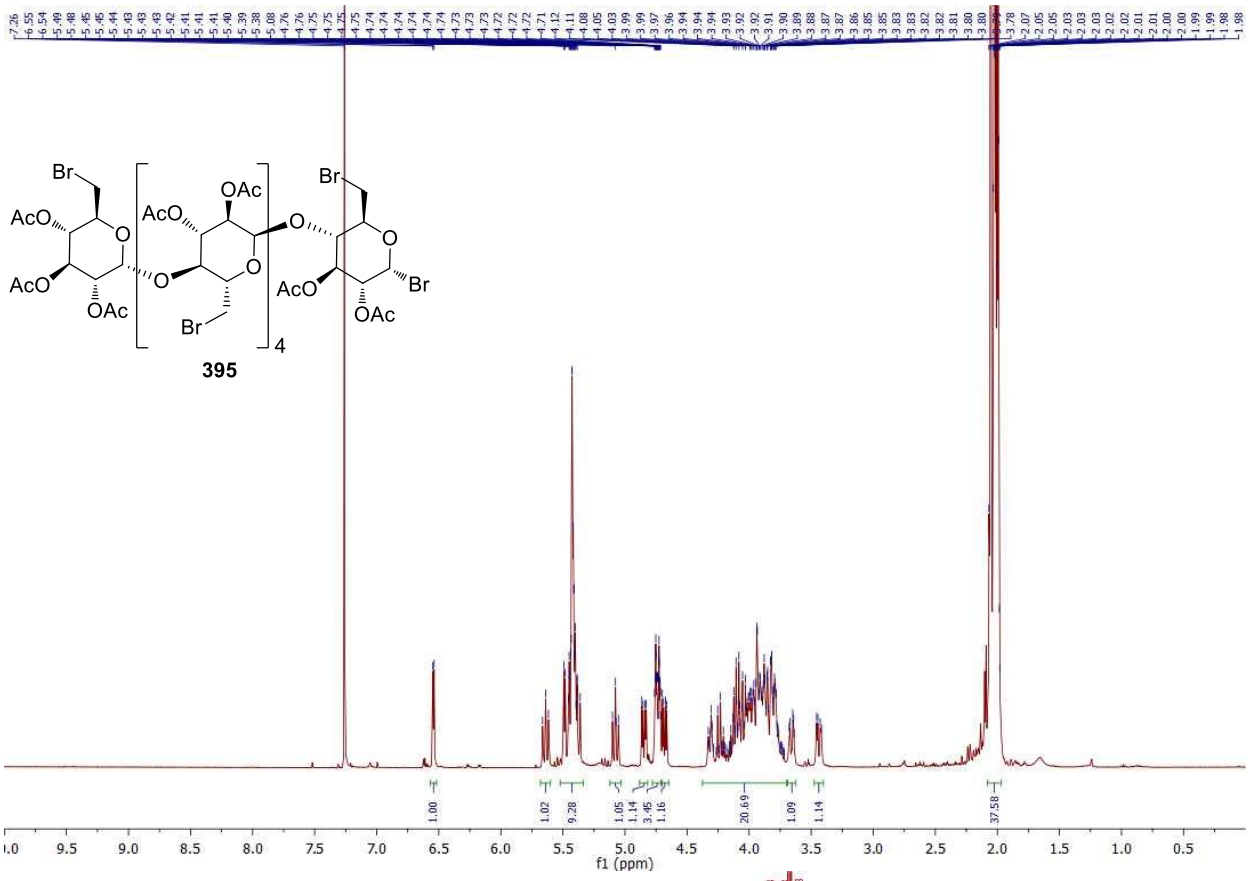
385

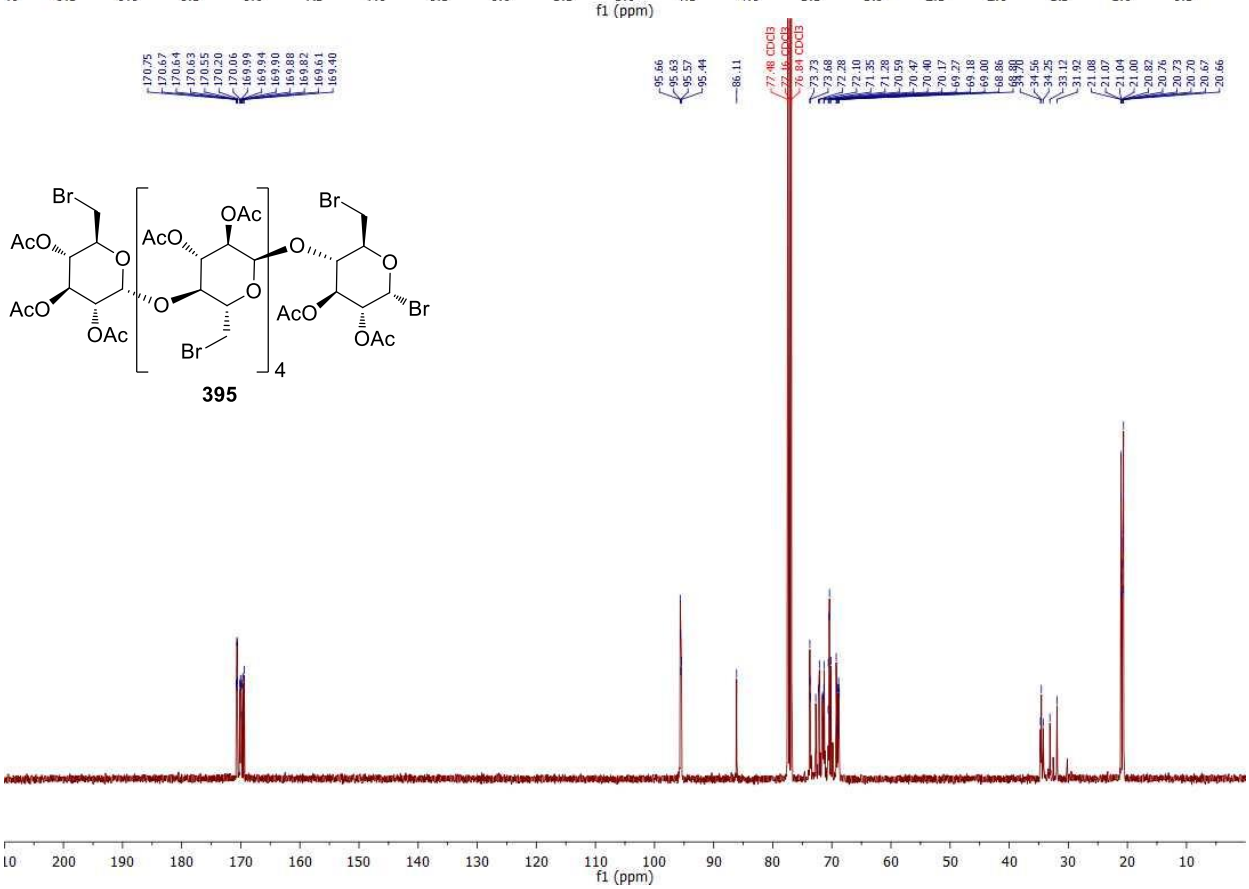
1.00
1.04
1.22
9.06
1.23
1.09
1.14
3.85
21.61
1.15
1.19
2.88
41.24
f1 (ppm)

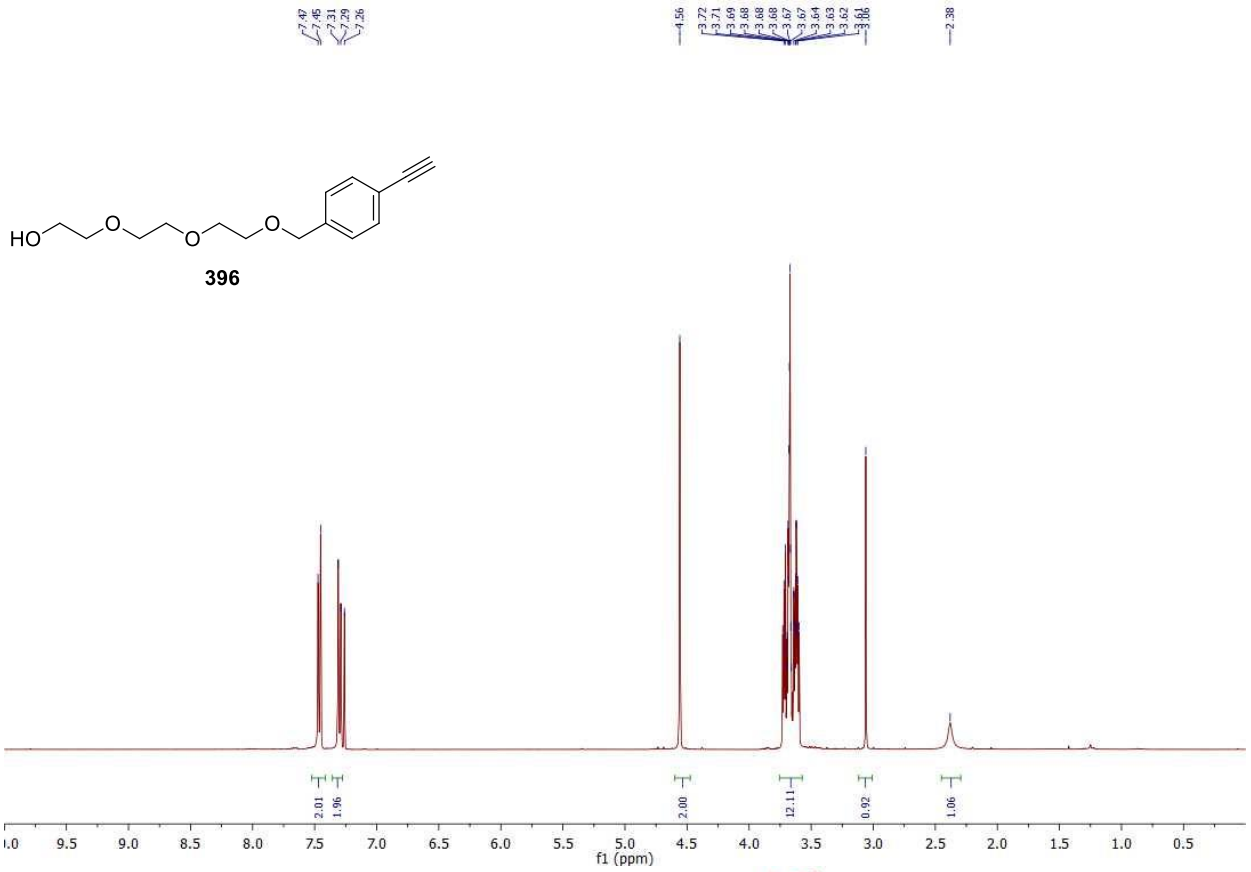

Br
AcO
AcO
OAc
O
OAc
AcO
O
O
Br
4
Br
O
AcO
OAc
OAc

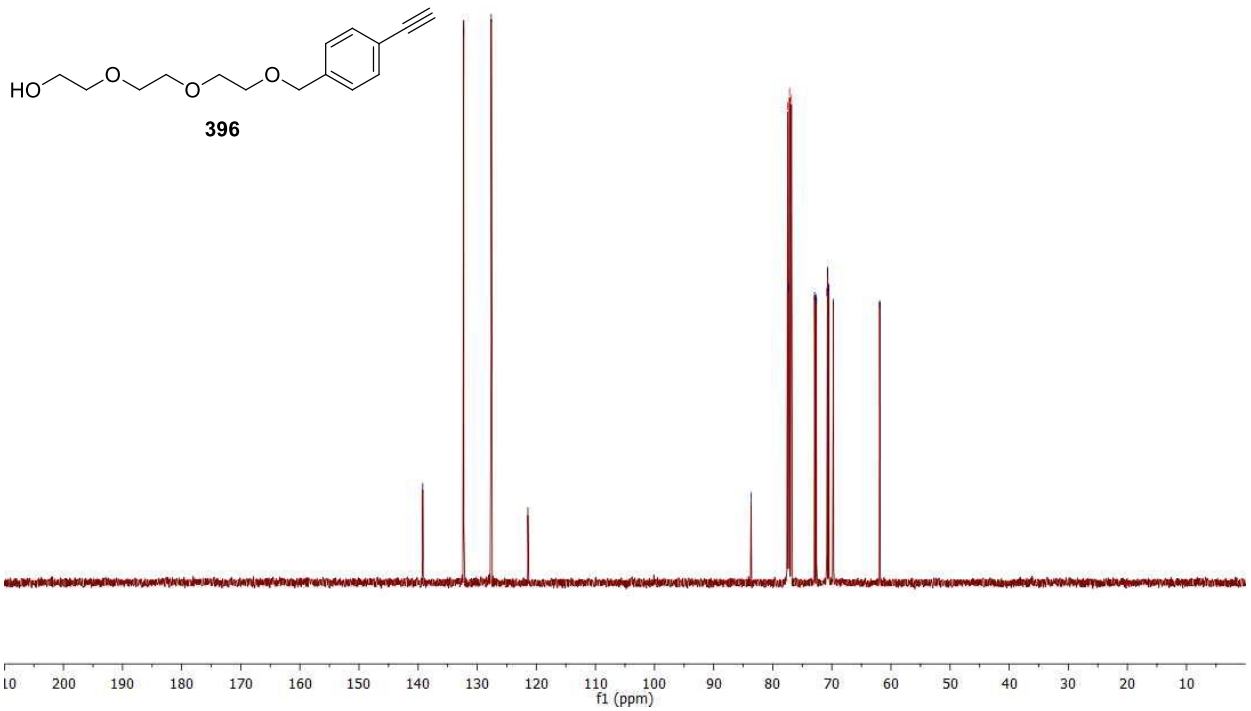
385

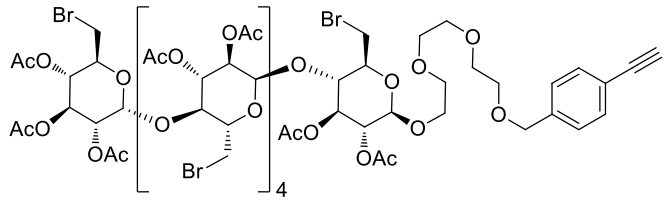
f1 (ppm)


Br
AcO
OAc
AcO
OAc
O
Br
4
395
f1 (ppm)

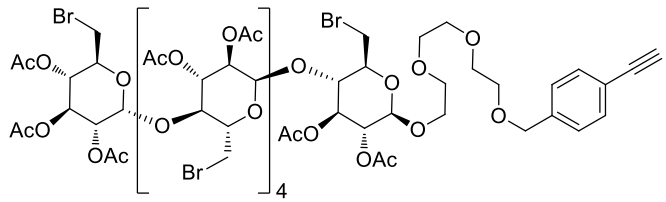

Br
AcO
OAc
AcO
OAc
O
Br
4
395
f1 (ppm)


HO
O
O
O
396
f1 (ppm)

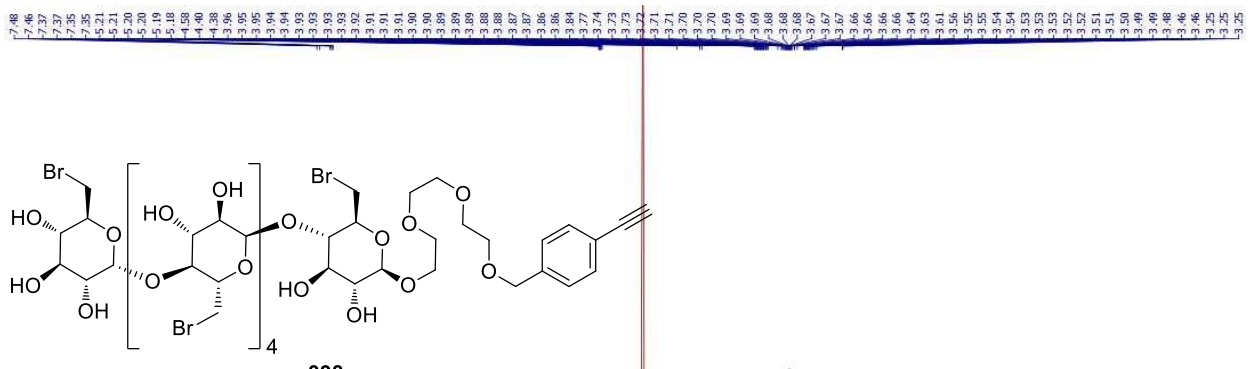

HO
O
O
O
396
f1 (ppm)



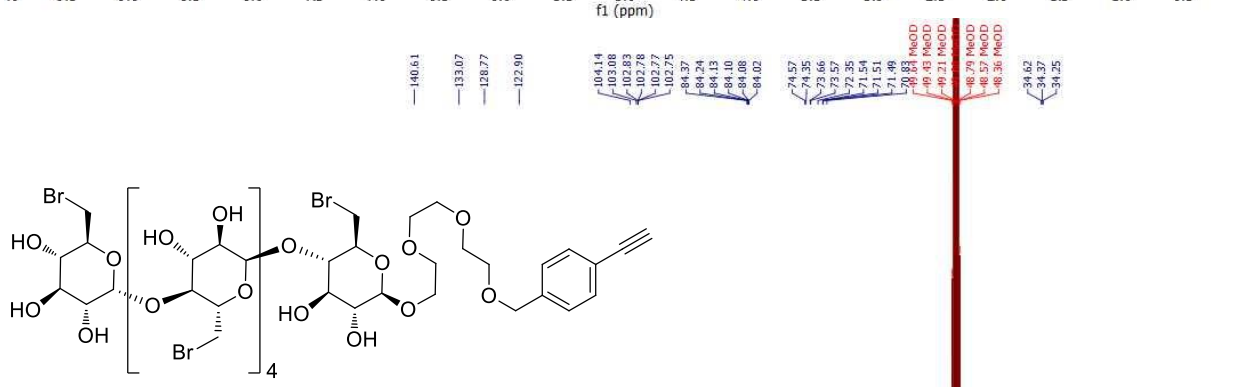
397



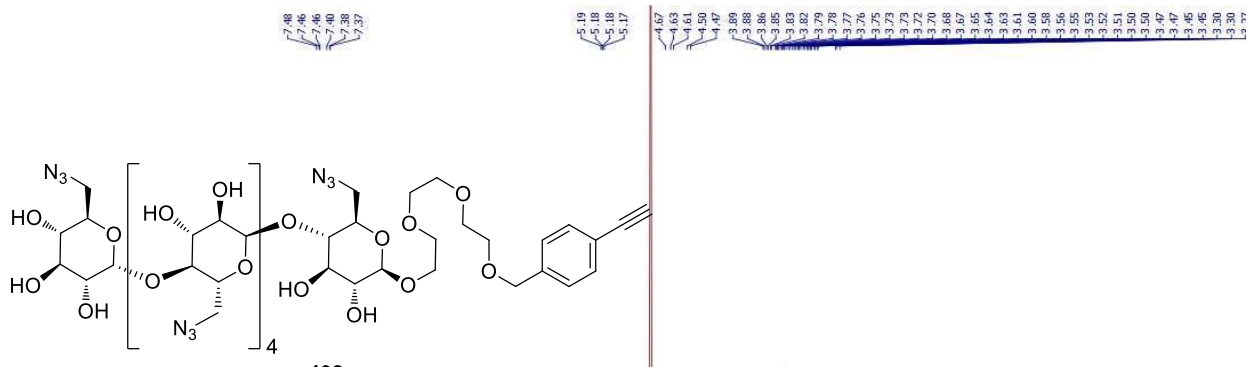
397



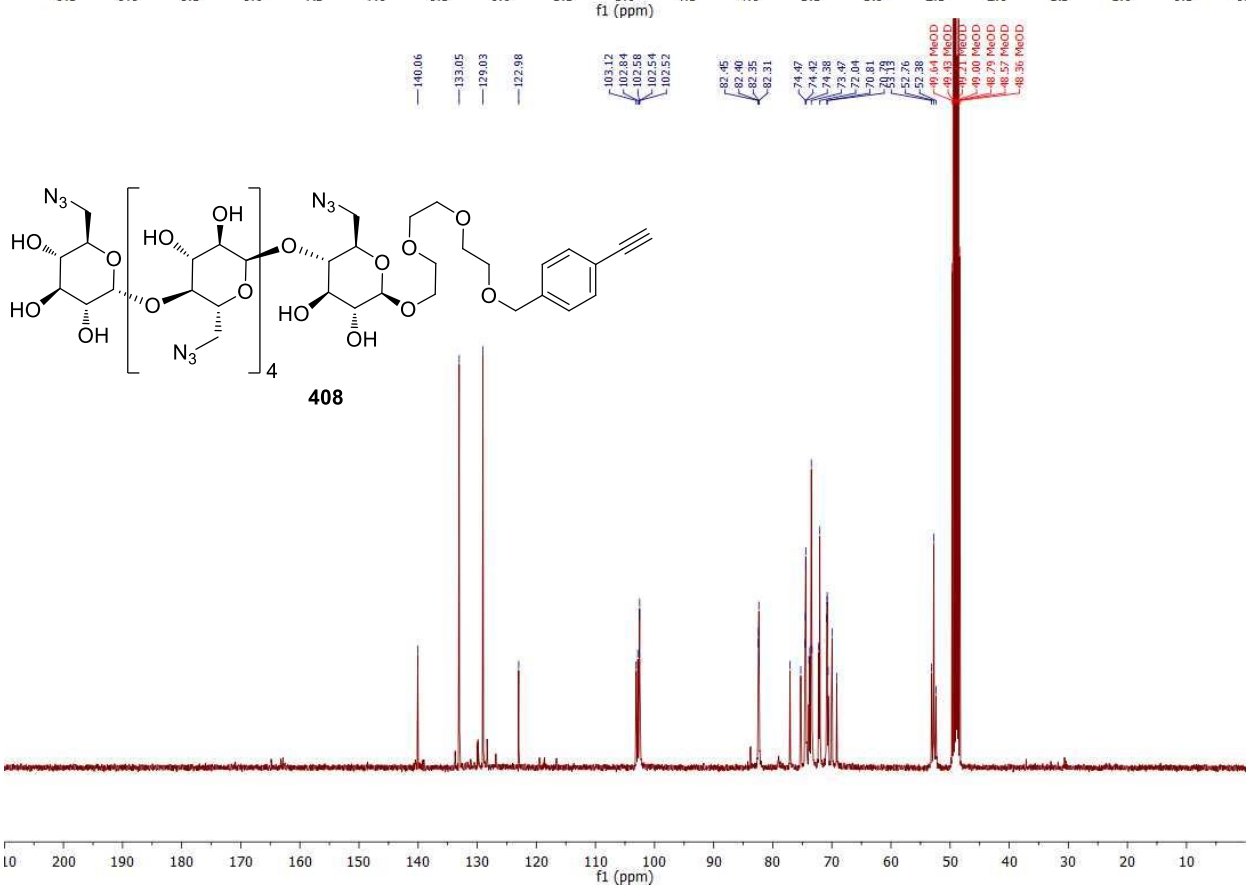
398



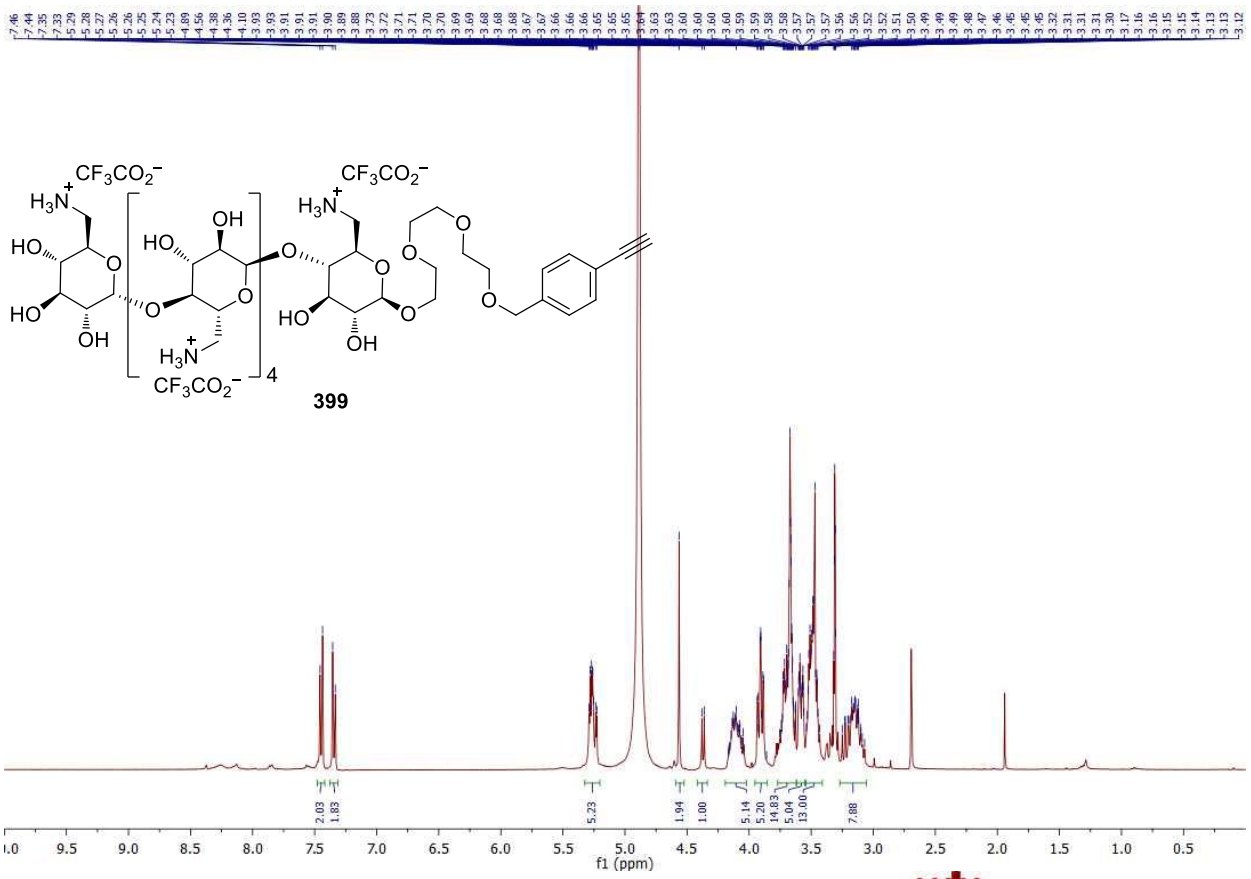
398

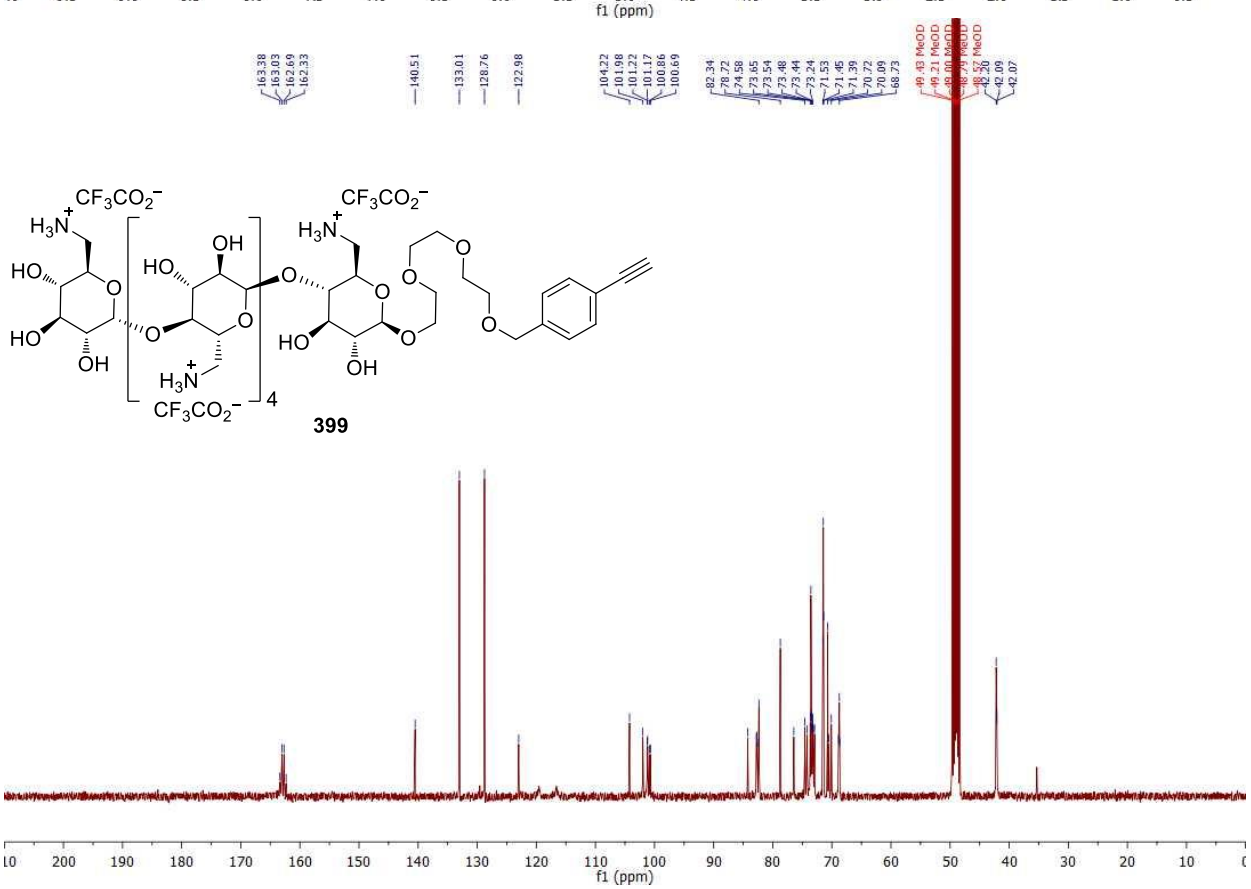


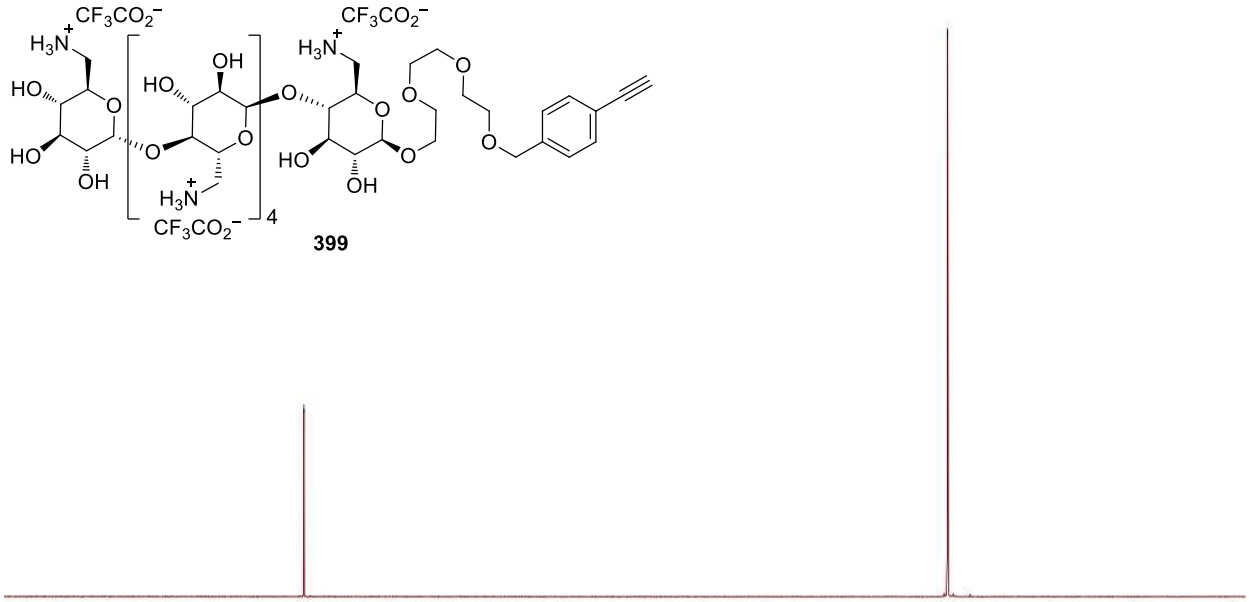
408



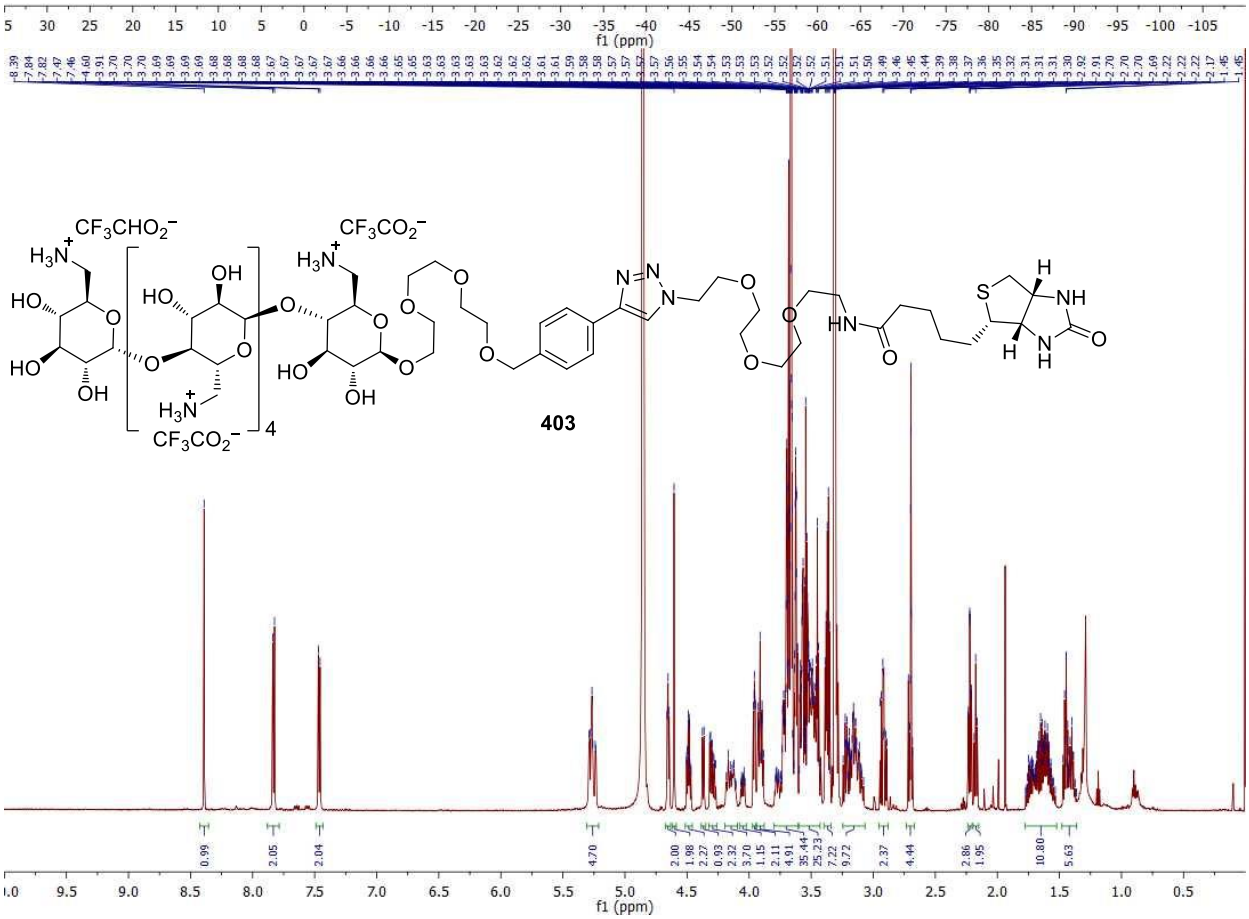
408


399
f1 (ppm)

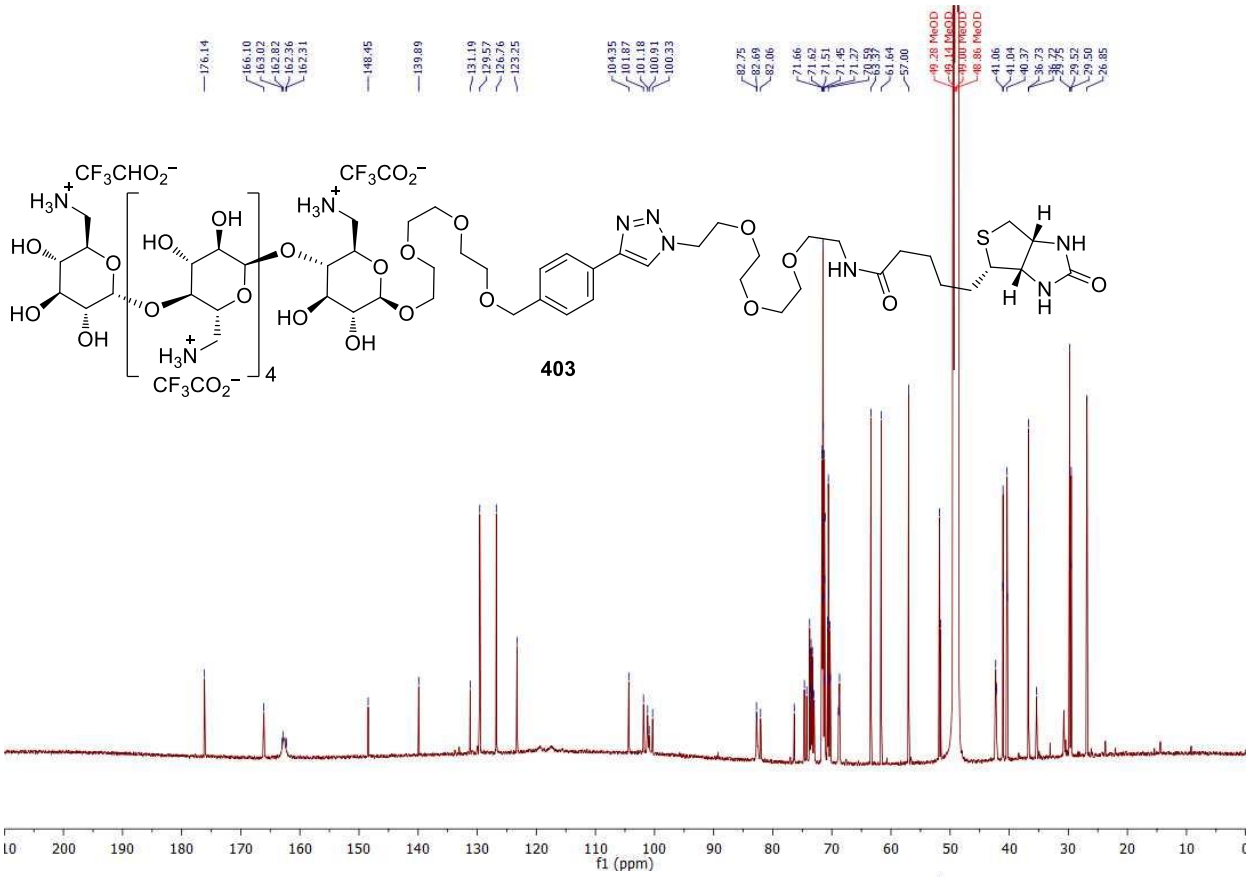

399
f1 (ppm)

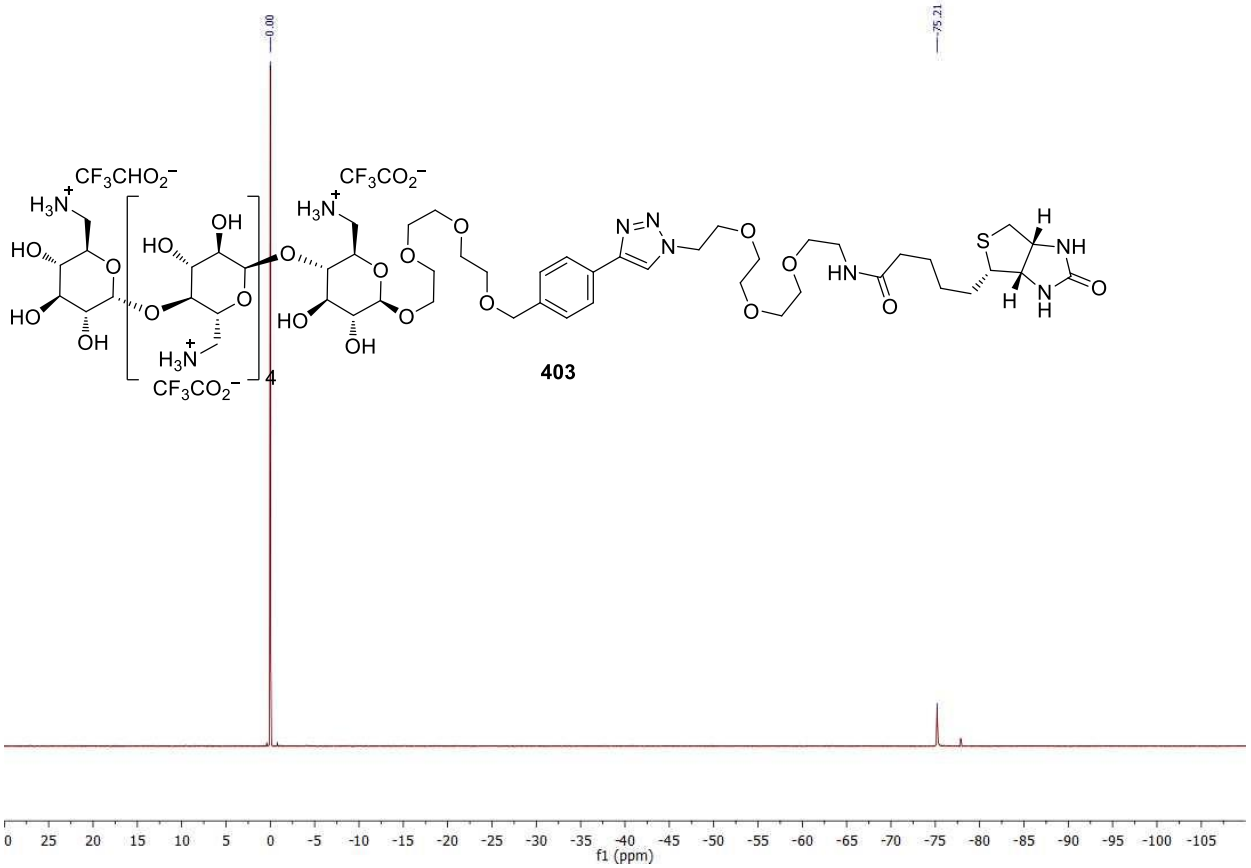


399



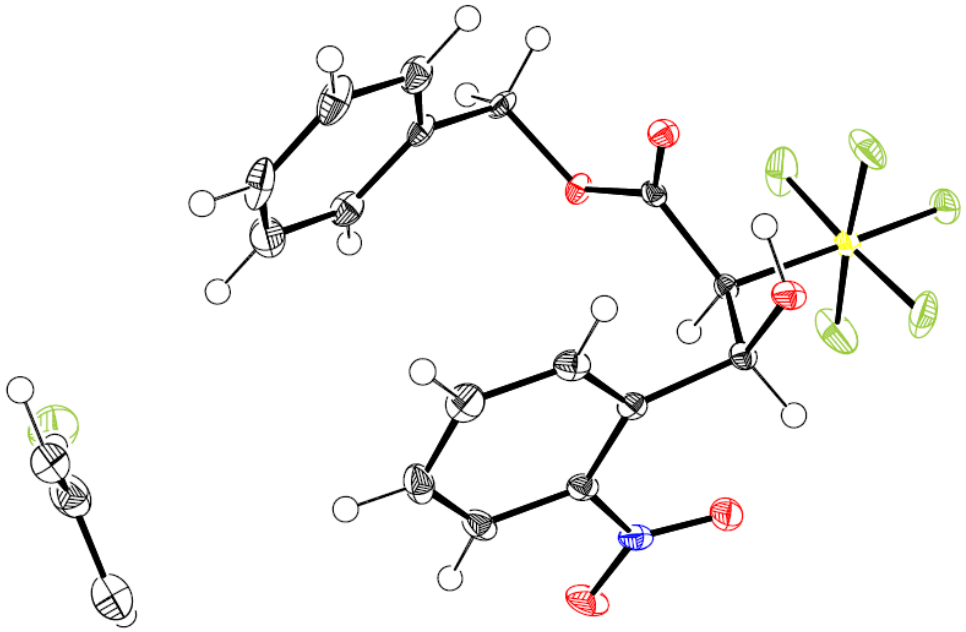
403


403
f1 (ppm)


403
f1 (ppm)

4.2. X-ray Crystallographic Data

***Anti*-benzyl 3-hydroxy-3-(2-nitrophenyl)-2-(pentafluorosulfanyl)propanoate (291)**



Structure deposited at the Cambridge Crystallographic Data Centre (CCDC 1415085)

Experimental: recrystallization of *anti*-**291** from fluorobenzene by slow evaporation afforded crystals suitable for X-ray analysis. Remark about the crystal: disordered fluorobenzene on special position (inversion). A colorless rod-like specimen of $C_{19}H_{16.5}F_{5.5}NO_5S$, approximate dimensions 0.24 mm x 0.08 mm x 0.01 mm, was used for the X-ray crystallographic analysis.

CCDC deposition number 1415085

Chemical formula $C_{19}H_{16.5}F_{5.5}NO_5S$

Formula weight 475.39

Crystal system triclinic

Space group P-1

Unit cell dimensions a = 5.4561(12) Å α = 74.382(8)°

b = 11.595(2) Å β = 80.977(9)°

c = 15.970(3) Åγ = 80.794(9)°

Volume 953.6(3) $Å^3$

Z 2

Density (calculated) 1.656 $g \cdot cm^{-3}$

Absorption coefficient 0.257 mm^{-1}

F(000) 486.0

Temperature 100.0(2) K

Radiation MoKα (0.71073 Å)

2θ range for data collection 5.054° to 55.084°

Index ranges $-6 \leq h \leq 7$, $-15 \leq k \leq 15$, $-20 \leq l \leq 20$

Reflections collected 15193

Independent reflections 4308 [R_{int} = 0.0414, R_{sigma} = 0.0546]

Data / restraints / parameters 4308/1/292

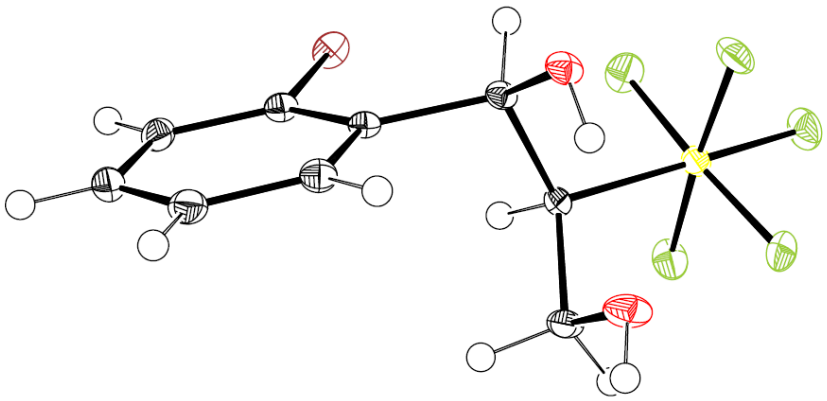
Goodness-of-fit on F^2 1.017

Final R indexes I>2σ(I) R_1 = 0.0405; wR_2 = 0.0818

all data R_1 = 0.0660; wR_2 = 0.0921

Largest diff. peak and hole 0.36/–0.45 $eÅ^{-3}$

***Anti*-1-(2-bromophenyl)-2-pentalfuorosulfanylpropane-1,3-diol (306)**



Experimental: recrystallization of **306** from Et_2O by gaseous diffusion of pentane afforded crystals suitable for X-ray analysis. A colorless plate-like specimen of $C_9H_{10}BrF_5O_2S$, approximate dimensions 0.32 mm x 0.16 mm x 0.12 mm, was used for the X-ray crystallographic analysis.

CCDC deposition number structure not deposited

Chemical formula $C_9H_{10}BrF_5O_2S$

Formula weight 357.14

Crystal system monoclinic

Space group $P2_1/c$

Unit cell dimensions a = 7.1277(4) Å α = 90°

b = 21.9474(12) Å β = 130.382(3)°

c = 9.6622(4) Å γ =90°

Volume 1151.37(11) $Å^3$

Z 4

Density (calculated) 2.060 $g \cdot cm^{-3}$

Absorption coefficient 3.809 mm^{-1}

F(000) 704.0

Temperature 100.0(2) K

Radiation MoKα (0.71073 Å)

2θ range for data collection 5.838° to 61.28°

Index ranges $-10 \le h \le 10$, $-31 \le k \le 31$, $-13 \le l \le 13$

Reflections collected 49699

Independent reflections 3545 [R_{int} = 0.0242, R_{sigma} = 0.0121]

Data / restraints / parameters 3545/2/169

Goodness-of-fit on F^2 1.054

Final R indexes I>2σ(I) R_1 = 0.0192; wR_2 = 0.0500

all data R_1 = 0.0227; wR_2 = 0.0514

Largest diff. peak and hole 0.47/–0.48 eÅ^{-3}

*Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **306**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.*

Atom	***x***	***y***	***z***	**U(eq)**
Br1	367.2(2)	4880.3(2)	2303.7(2)	16.31(4)
S1	6249.8(6)	3580.0(2)	3803.6(4)	12.61(6)
F1	5711.1(15)	3074.5(4)	4665.8(11)	19.12(17)
F2	7072.8(15)	4085.8(4)	3102.0(12)	19.70(17)
F3	9045.3(15)	3562.2(4)	5625.5(12)	21.07(18)
F4	6938.1(16)	3068.4(4)	3046.4(12)	19.26(17)
F5	5833.8(16)	4097.5(4)	4733.4(12)	20.53(18)
O1	2226(2)	2741.1(5)	-8.0(14)	19.2(2)
O2	887.8(18)	2826.0(4)	1948.4(13)	13.67(18)
C1	-5931(3)	4253.1(7)	-2618.9(19)	17.5(3)
C2	-4193(3)	4608.4(6)	-1115.7(19)	15.5(2)
C3	-1935(2)	4355.8(6)	324.4(17)	12.6(2)
C4	-1365(2)	3750.0(6)	320.9(17)	11.1(2)
C5	1105(2)	3465.6(6)	1884.9(17)	10.7(2)
C6	3004(2)	3655.1(6)	1680.5(17)	10.9(2)
C7	2514(3)	3383.6(6)	22.2(18)	14.3(2)

C8	-5403(2)	3650.0(7)	-2663.7(19)	16.6(3)
C9	-3152(2)	3402.4(6)	-1209.8(18)	14.0(2)

*Anisotropic Displacement Parameters ($Å^2×10^3$) for **306**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+...]$.*

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
Br1	18.10(7)	12.23(7)	20.03(7)	-4.07(5)	12.98(6)	-2.19(5)
S1	11.89(13)	13.20(14)	11.95(14)	1.56(10)	7.37(12)	0.67(10)
F1	16.7(4)	22.8(4)	15.0(4)	8.0(3)	8.9(3)	0.7(3)
F2	15.5(4)	18.9(4)	23.7(4)	6.1(3)	12.3(4)	-1.2(3)
F3	11.2(4)	26.9(5)	15.9(4)	2.9(3)	4.7(3)	0.5(3)
F4	19.5(4)	17.6(4)	20.9(4)	2.4(3)	13.2(4)	7.2(3)
F5	18.2(4)	23.0(4)	15.9(4)	-7.6(3)	9.1(3)	-1.2(3)
O1	31.9(6)	13.6(5)	17.2(5)	-4.0(4)	18.2(5)	-2.2(4)
O2	19.7(4)	8.7(4)	15.0(4)	1.9(3)	12.3(4)	0.1(3)
C1	13.9(6)	23.9(7)	15.5(6)	5.3(5)	9.9(5)	3.4(5)
C2	18.0(6)	13.8(6)	19.4(6)	4.3(5)	14.3(5)	4.0(5)
C3	14.4(5)	12.4(6)	13.4(6)	-0.4(4)	10.1(5)	-1.0(4)
C4	12.8(5)	11.7(5)	11.1(5)	0.3(4)	8.8(5)	-0.6(4)
C5	13.6(5)	8.6(5)	10.9(5)	0.5(4)	8.4(5)	-0.3(4)
C6	11.4(5)	10.5(5)	10.4(5)	1.9(4)	6.9(5)	1.2(4)
C7	19.1(6)	14.3(6)	12.4(5)	1.0(4)	11.5(5)	0.9(5)
C8	14.3(6)	22.4(7)	13.5(6)	-1.6(5)	9.2(5)	-2.0(5)
C9	15.5(6)	13.8(6)	13.5(6)	-1.3(4)	9.8(5)	-0.9(4)

*Bond Lengths for **306**.*

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
Br1	C3	1.8997(13)	C1	C2	1.386(2)
S1	F1	1.5769(9)	C1	C8	1.385(2)
S1	F2	1.5974(9)	C2	C3	1.3902(18)
S1	F3	1.5892(9)	C3	C4	1.3908(18)
S1	F4	1.5816(9)	C4	C5	1.5247(17)
S1	F5	1.5907(9)	C4	C9	1.3968(18)
S1	C6	1.8541(13)	C5	C6	1.5466(17)
O1	C7	1.4225(17)	C6	C7	1.5228(18)
O2	C5	1.4179(15)	C8	C9	1.3864(19)

*Bond Angles for **306**.*

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
F1	S1	F2	174.41(5)	C1	C2	C3	119.59(13)
F1	S1	F3	87.55(5)	C2	C3	Br1	116.79(10)
F1	S1	F4	89.98(5)	C2	C3	C4	121.97(12)
F1	S1	F5	90.32(5)	C4	C3	Br1	121.24(10)
F1	S1	C6	95.21(5)	C3	C4	C5	122.71(11)
F2	S1	C6	90.38(5)	C3	C4	C9	117.21(12)
F3	S1	F2	86.88(5)	C9	C4	C5	120.07(11)
F3	S1	F5	87.17(5)	O2	C5	C4	111.10(10)
F3	S1	C6	176.30(5)	O2	C5	C6	113.63(10)
F4	S1	F2	89.30(5)	C4	C5	C6	107.89(10)
F4	S1	F3	87.30(5)	C5	C6	S1	113.75(8)
F4	S1	F5	174.44(5)	C7	C6	S1	113.62(9)
F4	S1	C6	95.16(5)	C7	C6	C5	113.95(10)
F5	S1	F2	89.86(5)	O1	C7	C6	109.96(10)
F5	S1	C6	90.33(5)	C1	C8	C9	120.18(13)
C8	C1	C2	119.61(13)	C8	C9	C4	121.44(13)

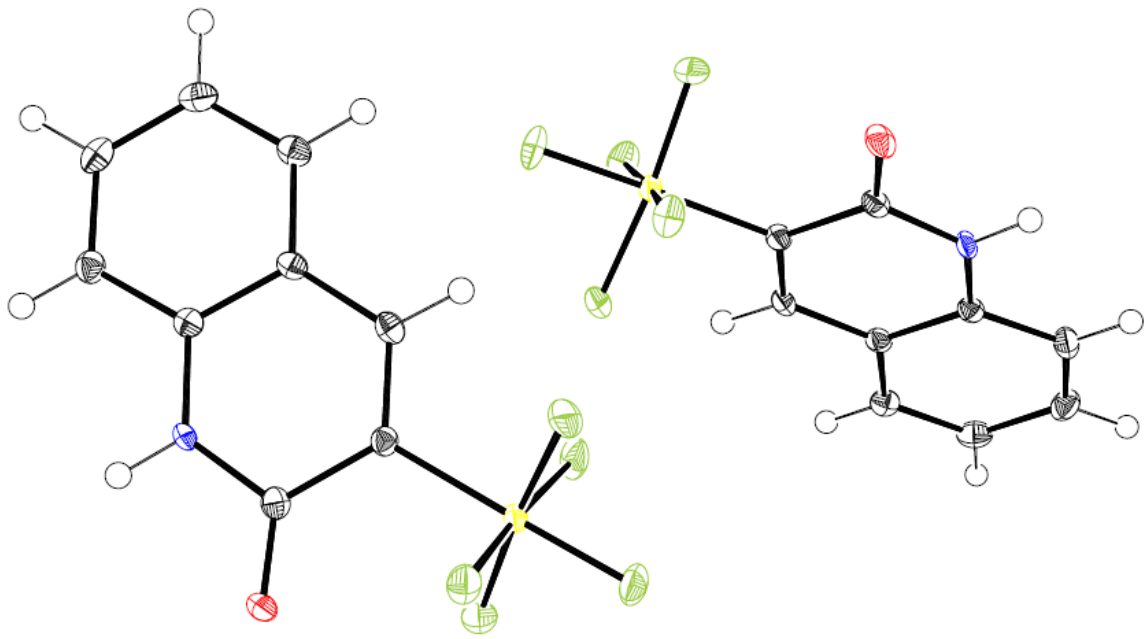
*Torsion Angles for **306**.*

A	B	C	D	Angle/°	A	B	C	D	Angle/°
Br1	C3	C4	C5	0.36(17)	C1	C8	C9	C4	-0.4(2)
Br1	C3	C4	C9	-178.64(9)	C2	C1	C8	C9	0.3(2)
S1	C6	C7	O1	80.49(12)	C2	C3	C4	C5	179.81(12)
F1	S1	C6	C5	24.98(9)	C2	C3	C4	C9	0.81(19)
F1	S1	C6	C7	-107.58(9)	C3	C4	C5	O2	155.01(12)
F2	S1	C6	C5	-155.23(9)	C3	C4	C5	C6	-79.82(14)
F2	S1	C6	C7	72.20(9)	C3	C4	C9	C8	-0.15(19)
F4	S1	C6	C5	115.43(9)	C4	C5	C6	S1	160.46(8)
F4	S1	C6	C7	-17.13(10)	C4	C5	C6	C7	-67.13(13)
F5	S1	C6	C5	-65.38(9)	C5	C4	C9	C8	-179.18(12)
F5	S1	C6	C7	162.06(9)	C5	C6	C7	O1	-51.99(14)
O2	C5	C6	S1	-75.88(12)	C8	C1	C2	C3	0.3(2)
O2	C5	C6	C7	56.53(14)	C9	C4	C5	O2	-26.02(16)
C1	C2	C3	Br1	178.56(10)	C9	C4	C5	C6	99.16(13)
C1	C2	C3	C4	-0.9(2)					

*Hydrogen Atom Coordinates ($Å \times 10^4$) and Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **306**.*

Atom	*x*	*y*	*z*	U(eq)
H1	1780(40)	2593(10)	-950(20)	29
H2	1100(40)	2678(9)	1280(20)	21
H1A	-7477	4422	-3612	21
H2A	-4543	5022	-1070	19
H5	1640	3643	3046	13
H6	2749	4103	1437	13
H7A	1001	3565	-1097	17
H7B	3905	3478	61	17
H8	-6585	3405	-3694	20
H9	-2818	2987	-1256	17

3-(Pentafluorosulfanyl)quinolin-2(1H)-one (312)



Structure deposited at the Cambridge Crystallographic Data Centre (CCDC 1415086)

Experimental: recrystallization of **312** from ethyl acetate by slow evaporation afforded crystals suitable for X-ray analysis. Remarks about the crystal: 15% twinning in the measured crystal; two symmetry-unrelated molecules in the asymmetric unit. A colorless plate-like specimen of $C_9H_6F_5NOS$, approximate dimensions 0.56 mm x 0.22 mm x 0.14 mm, was used for the X-ray crystallographic analysis.

CCDC deposition number 1415086

Chemical formula $C_9H_6F_5NOS$

Formula weight 271.21

Crystal system monocyclic

Space group $P2_1/c$

Unit cell dimensions a = 20.8140(17) Å α = 90°

b = 5.8333(5) Å β = 115.119(2)°

c = 17.7237(14) Å γ = 90°

Volume 1948.4(3) $Å^3$

Z 8

Density (calculated) 1.849 $g \cdot cm^{-3}$

Absorption coefficient 0.390 mm^{-1}

F(000) 1088.0

Temperature 100.0(2) K

Radiation MoKα (0.71073 Å)

2θ range for data collection 3.972° to 55.09°

Index ranges $-27 \le h \le 27$, $-7 \le k \le 7$, $-23 \le l \le 23$

Reflections collected 21167

Independent reflections 4485 [R_{int} = 0.0344, R_{sigma} = 0.0282]

Data / restraints / parameters 4485/2/314

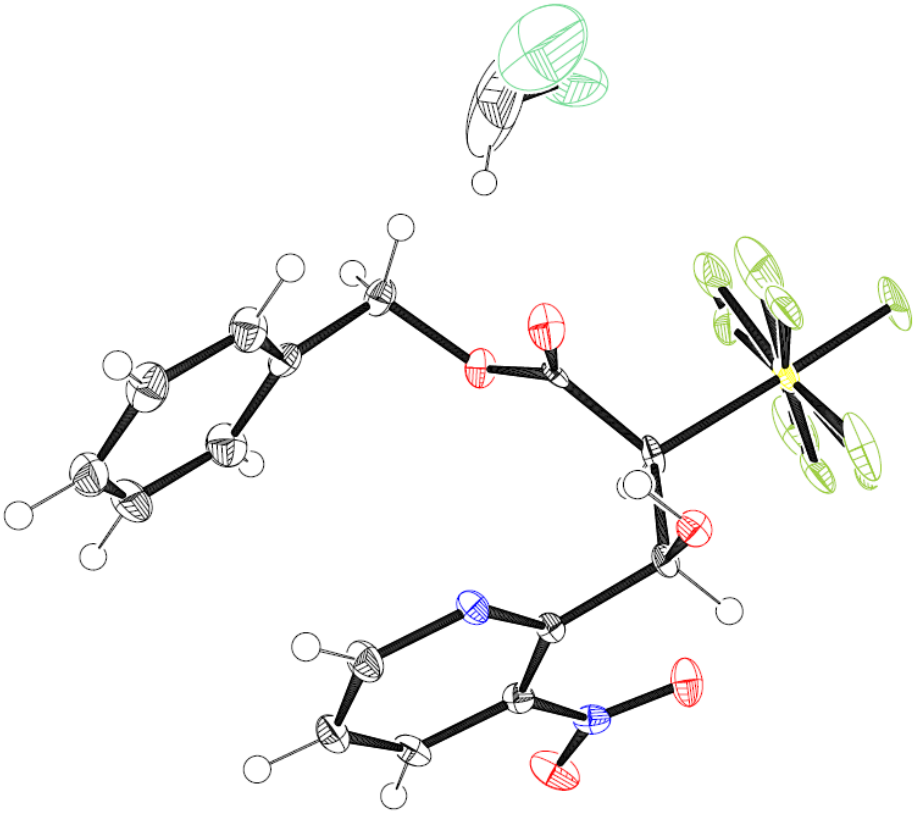
Goodness-of-fit on F^2 1.014

Final R indexes $I>2\sigma(I)$ R_1 = 0.0511; wR_2 = 0.1391

all data R_1 = 0.0554; wR_2 = 0.1434

Largest diff. peak and hole 1.15/–0.32 $eÅ^{-3}$

***Anti*-benzyl 3-hydroxy-3-(3-nitropyridin-2-yl)-2-(pentafluorosulfanyl)propanoate (326)**



Experimental: recrystallization of *anti*-**326** from CDCl3 by slow evaporation afforded crystals suitable for X-ray analysis. Remarks about the crystal: 1/2 chloroforme per asymmetric unit is disordered around a center of inversion in such a way that all chlorine positions are shared between neighbouring carbons and it forms a linear channel running through the crystal. The SF5 ligand is also disordered (about 90:10, 2 positions by rotation around the C-S bond). A colorless plate-like specimen of $C_{15.5}H_{13.5}Cl_{1.5}F_5N_2O_5S$, approximate dimensions 0.32 mm x 0.28 mm x 0.12 mm, was used for the X-ray crystallographic analysis.

CCDC deposition number structure not deposited

Chemical formula $C_{15.5}H_{13.5}Cl_{1.5}F_5N_2O_5S$

Formula weight 488.02

Crystal system monoclinic

Space group $P2_1/c$

Unit cell dimensions a = 31.279(4) Å α = 90°

b = 10.9690(13) Å β = 170.241(6)°

c = 31.674(4) Å γ =90°

Volume 1842.1(5) $Å^3$

Z 4

Density (calculated) 1.760 g·cm^{-3}

Absorption coefficient 0.477 mm^{-1}

F(000) 988.0

Temperature 100.0(2) K

Radiation MoKα (0.71073 Å)

2θ range for data collection 3.934° to 55.006°

Index ranges –40≤h≤40, –13≤k≤14, –41≤l≤40

Reflections collected 28680

Independent reflections 4192 [R_{int} = 0.0699, R_{sigma} = 0.0513]

Data / restraints / parameters 4192/222/303

Goodness-of-fit on F^2 10.82

Final R indexes I>2σ(I) R_1 = 0.0997; wR_2 = 0.2593

all data R_1 = 0.1144; wR_2 = 0.2685

Largest diff. peak and hole 1.59/–1.83 eÅ^{-3}

*Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **326**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.*

Atom	***x***	***y***	***z***	**U(eq)**
S1	727(2)	5309.8(10)	2217(2)	18.7(3)
O3	-2853(6)	2878(3)	-1142(6)	15.0(7)
O5	304(7)	2846(3)	1192(7)	19.3(7)
O6	5232(7)	1924(4)	7825(7)	24.5(8)
F7	241(7)	6724(3)	1682(7)	33.4(8)
O8	4326(6)	2766(3)	5318(6)	15.4(7)
F9	-1376(10)	5326(6)	519(10)	31.5(11)
F10	2782(10)	5688(4)	4544(9)	40.5(11)
O11	2646(7)	3298(3)	5086(7)	21.4(8)
F12	2789(8)	5406(3)	3857(8)	30.6(10)
C13	1905(9)	3063(4)	3002(8)	11.6(8)
N14	-263(8)	838(4)	1389(7)	15.0(8)
N15	3517(8)	2257(4)	5929(8)	15.7(8)
C17	1478(8)	3677(4)	3015(8)	11.8(8)
C18	-506(8)	2949(4)	1342(8)	11.9(8)
C19	5027(9)	2135(5)	5609(9)	16.5(9)
C20	2433(9)	1378(4)	4575(9)	13.3(8)
C21	4531(9)	793(5)	5152(9)	15.4(9)
C22	3343(9)	191(5)	5489(9)	16.7(9)
C23	632(10)	-302(5)	2291(10)	19.8(9)
C24	2419(9)	-665(5)	4319(9)	19.2(10)
C25	2644(10)	265(5)	3078(9)	19.9(10)

C26	612(8)	1687(4)	2507(8)	11.2(8)
C27	5700(11)	-1193(5)	6543(11)	28.3(11)
C28	6056(10)	53(5)	6886(10)	23.6(11)
C29	2293(11)	-993(5)	2742(11)	25.3(11)
C30	3816(11)	-1717(5)	4469(11)	27.1(11)
F1	-1352(8)	5062(4)	-148(7)	25.5(8)
Cl1	9581(5)	6196(2)	9792(5)	93.2(6)
C2	7969(10)	4859(13)	8113(8)	137(7)
Cl2	4973(11)	4980(30)	4982(6)	133.6(13)
F12A	3500(40)	5530(30)	4780(40)	31.5(11)
F10A	1750(60)	5500(30)	3680(50)	25.5(8)
F9A	-1940(40)	5190(40)	-150(40)	27(7)
F1A	-340(70)	5190(30)	720(70)	40.5(11)

Anisotropic Displacement Parameters ($Å^2×10^3$) for **326**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
S1	23.7(3)	5.6(5)	23.2(3)	1.5(4)	23.1(2)	1.7(4)
O3	10.2(7)	16.5(16)	9.7(7)	0.6(13)	9.7(6)	0.5(13)
O5	17.7(7)	18.7(17)	16.3(7)	0.9(14)	16.6(7)	1.7(14)
O6	24.6(8)	23.8(19)	20.1(8)	-5.6(15)	21.9(7)	-7.0(15)
F7	41.0(9)	5.0(13)	41.7(9)	6.0(13)	40.6(8)	5.8(13)
O8	11.7(7)	16.3(16)	11.7(7)	-0.5(13)	11.4(6)	0.1(13)
F9	45.6(8)	16(2)	50.7(9)	12(2)	47.7(8)	12(2)
F10	52.6(11)	10.8(18)	43.3(10)	-2.4(17)	47(1)	-0.9(18)
O11	18.6(8)	17.9(18)	16.9(8)	1.0(14)	17.3(7)	2.4(14)
F12	34.0(9)	11.9(17)	39.1(9)	1.9(16)	35.9(8)	0.3(15)
C13	12.2(9)	5.0(18)	12.0(9)	0.3(15)	11.9(8)	-0.4(15)
N14	14.1(8)	9.4(18)	13.8(8)	-3.3(15)	13.7(8)	-3.4(15)
N15	15.2(8)	16.7(19)	14.8(8)	-5.2(16)	14.8(7)	-5.5(16)
C17	9.1(9)	7.2(19)	8.8(9)	2.0(15)	8.6(8)	2.2(15)
C18	8.2(9)	11(2)	7.9(9)	2.5(16)	7.8(8)	2.4(16)
C19	13.3(9)	19(2)	14.8(9)	-1.1(18)	13.8(9)	-0.5(18)
C20	13.1(9)	12(2)	12.9(9)	-3.3(17)	12.8(8)	-3.3(17)
C21	10.7(9)	18(2)	11.9(9)	-1.6(18)	11.1(9)	-1.3(17)
C22	15.5(10)	14(2)	15.1(10)	-0.2(18)	15.0(9)	-1.3(18)
C23	24(1)	12(2)	23.1(10)	-2.7(19)	23.2(10)	-2.6(19)
C24	18.1(10)	12(2)	18.4(11)	0.9(18)	17.9(10)	0.6(18)
C25	16.7(10)	23(3)	16.2(10)	2.7(19)	16.1(9)	3.3(19)
C26	8.7(8)	10(2)	8.7(9)	-1.3(16)	8.5(8)	-1.4(16)
C27	31.9(12)	23(3)	31.4(12)	12(2)	31.2(12)	11(2)

C28	17.9(11)	26(3)	16.7(11)	4(2)	16.9(11)	4(2)
C29	23.2(11)	23(3)	24.0(12)	-7(2)	23.2(11)	-6(2)
C30	36.1(11)	18(2)	39.3(12)	0(2)	37.3(11)	0(2)
F1	30.4(8)	14.1(17)	26.9(8)	9.1(15)	28.2(7)	8.6(15)
Cl1	183.4(6)	47.9(13)	176.5(6)	-9.5(15)	179.2(5)	-10.9(16)
C2	188(6)	65(12)	220(5)	-57(9)	202(5)	-46(9)
Cl2	243.2(14)	58(3)	256.2(14)	-70(3)	248.4(12)	-67(3)
F12A	45.6(8)	16(2)	50.7(9)	12(2)	47.7(8)	12(2)
F10A	30.4(8)	14.1(17)	26.9(8)	9.1(15)	28.2(7)	8.6(15)
F9A	27(4)	14(14)	23(4)	6(8)	24(3)	7(7)
F1A	52.6(11)	10.8(18)	43.3(10)	-2.4(17)	47(1)	-0.9(18)

Bond Lengths for **326**.

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
S1	F7	1.585(3)	N14	C26	1.340(6)
S1	F9	1.569(4)	N15	C20	1.469(6)
S1	F10	1.558(4)	C17	C18	1.552(6)
S1	F12	1.601(4)	C18	C26	1.526(6)
S1	C17	1.847(5)	C19	C21	1.498(7)
S1	F1	1.570(4)	C20	C22	1.392(7)
S1	F12A	1.557(14)	C20	C26	1.387(6)
S1	F10A	1.596(14)	C21	C25	1.379(7)
S1	F9A	1.583(15)	C21	C28	1.393(7)
S1	F1A	1.554(15)	C22	C24	1.362(7)
O3	C18	1.398(5)	C23	C24	1.377(7)
O5	C13	1.189(6)	C25	C29	1.392(8)
O6	N15	1.216(6)	C27	C28	1.379(8)
O8	C13	1.330(6)	C27	C30	1.382(9)
O8	C19	1.468(6)	C29	C30	1.373(8)
O11	N15	1.232(6)	Cl1	C2	1.733(8)
C13	C17	1.534(7)	C2	Cl2	1.733(8)
N14	C23	1.341(6)			

Bond Angles for **326**.

Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
F7	S1	F12	87.5(2)	O5	C13	C17	125.3(4)
F7	S1	C17	176.9(2)	O8	C13	C17	109.5(4)
F7	S1	F10A	92.5(11)	C26	N14	C23	118.7(4)
F9	S1	F7	87.7(3)	O6	N15	O11	123.4(4)
F9	S1	F12	175.1(3)	O6	N15	C20	118.5(4)

F9	S1	C17	94.8(3)	O11	N15	C20	118.1(4)
F9	S1	F1	89.4(3)	C13	C17	S1	110.9(3)
F10	S1	F7	86.3(2)	C13	C17	C18	109.9(4)
F10	S1	F9	91.6(3)	C18	C17	S1	114.4(3)
F10	S1	F12	89.3(3)	O3	C18	C17	113.2(4)
F10	S1	C17	91.8(2)	O3	C18	C26	111.6(4)
F10	S1	F1	174.4(2)	C26	C18	C17	106.7(4)
F12	S1	C17	90.0(2)	O8	C19	C21	111.9(4)
F1	S1	F7	88.3(2)	C22	C20	N15	115.9(4)
F1	S1	F12	89.3(2)	C26	C20	N15	123.2(4)
F1	S1	C17	93.6(2)	C26	C20	C22	120.9(4)
F12A	S1	F7	88.2(11)	C25	C21	C19	120.7(5)
F12A	S1	C17	88.7(11)	C25	C21	C28	119.1(5)
F12A	S1	F10A	85.9(17)	C28	C21	C19	120.1(5)
F12A	S1	F9A	169.7(18)	C24	C22	C20	118.6(5)
F10A	S1	C17	86.8(11)	N14	C23	C24	124.1(5)
F9A	S1	F7	89.5(18)	C22	C24	C23	117.9(5)
F9A	S1	C17	93.5(18)	C21	C25	C29	120.4(5)
F9A	S1	F10A	84.2(17)	N14	C26	C18	113.3(4)
F1A	S1	F7	84.6(13)	N14	C26	C20	119.8(4)
F1A	S1	C17	96.0(13)	C20	C26	C18	126.9(4)
F1A	S1	F12A	95(2)	C28	C27	C30	120.4(5)
F1A	S1	F10A	176.9(16)	C27	C28	C21	120.2(5)
F1A	S1	F9A	94.6(19)	C30	C29	C25	120.1(5)
C13	O8	C19	116.1(4)	C29	C30	C27	119.8(5)
O5	C13	O8	125.2(5)	Cl1	C2	Cl2	117.8(13)

Torsion Angles for **326**.

A	**B**	**C**	**D**	**Angle/°**	**A**	**B**	**C**	**D**	**Angle/°**
S1	C17	C18	O3	65.1(5)	C17	C18	C26	C20	77.6(6)
S1	C17	C18	C26	-171.8(3)	C19	O8	C13	O5	0.8(7)
O3	C18	C26	N14	24.5(5)	C19	O8	C13	C17	178.3(4)
O3	C18	C26	C20	-158.2(4)	C19	C21	C25	C29	176.1(5)
O5	C13	C17	S1	-71.5(5)	C19	C21	C28	C27	-176.0(5)
O5	C13	C17	C18	56.0(6)	C20	C22	C24	C23	0.3(7)
O6	N15	C20	C22	5.2(6)	C21	C25	C29	C30	0.5(8)
O6	N15	C20	C26	-174.8(4)	C22	C20	C26	N14	-1.0(7)
O8	C13	C17	S1	111.0(4)	C22	C20	C26	C18	-178.1(4)
O8	C13	C17	C18	-121.6(4)	C23	N14	C26	C18	178.4(4)
O8	C19	C21	C25	110.9(5)	C23	N14	C26	C20	0.9(7)
O8	C19	C21	C28	-72.1(6)	C25	C21	C28	C27	1.0(8)

F9	S1	C17	C13	139.1(4)	C25	C29	C30	C27	0.0(8)
F9	S1	C17	C18	14.2(4)	C26	N14	C23	C24	-0.3(8)
F10	S1	C17	C13	-129.2(4)	C26	C20	C22	C24	0.4(7)
F10	S1	C17	C18	105.9(4)	C28	C21	C25	C29	-0.9(8)
O11	N15	C20	C22	-175.2(4)	C28	C27	C30	C29	0.1(9)
O11	N15	C20	C26	4.8(7)	C30	C27	C28	C21	-0.6(9)
F12	S1	C17	C13	-39.9(4)	F1	S1	C17	C13	49.4(4)
F12	S1	C17	C18	-164.8(4)	F1	S1	C17	C18	-75.5(4)
C13	O8	C19	C21	-83.2(5)	F12A	S1	C17	C13	-70.0(15)
C13	C17	C18	O3	-60.4(5)	F12A	S1	C17	C18	165.1(15)
C13	C17	C18	C26	62.8(5)	F10A	S1	C17	C13	-156.0(13)
N14	C23	C24	C22	-0.3(8)	F10A	S1	C17	C18	79.1(13)
N15	C20	C22	C24	-179.7(4)	F9A	S1	C17	C13	120.1(13)
N15	C20	C26	N14	179.1(4)	F9A	S1	C17	C18	-4.8(13)
N15	C20	C26	C18	2.0(7)	F1A	S1	C17	C13	25.1(16)
C17	C18	C26	N14	-99.6(4)	F1A	S1	C17	C18	-99.8(16)

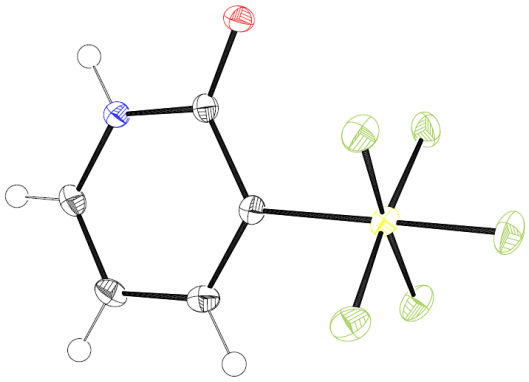
Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **326**.

Atom	***x***	***y***	***z***	**U(eq)**
H3	-2694	2515	-1220	23
H17	3106	3630	4758	14
H18	-737	3361	1396	14
H19A	6841	2271	7317	20
H19B	4056	2483	4426	20
H22	4584	-19	6901	20
H23	-8	-897	1478	24
H24	2989	-1485	4884	23
H25	1578	763	1871	24
H27	6756	-1694	7740	34
H28	7344	407	8308	28
H29	997	-1351	1315	30
H30	3576	-2575	4239	33
H2	7899(8)	4342(10)	8304(7)	164

Atomic Occupancy for **326**.

Atom	***Occupancy***	**Atom**	***Occupancy***	**Atom**	***Occupancy***
F9	0.880(7)	F10	0.880(7)	F12	0.880(7)
F1	0.880(7)	C2	0.5	H2	0.5
Cl2	0.5	F12A	0.120(7)	F10A	0.120(7)
F9A	0.120(7)	F1A	0.120(7)		

3-(pentafluorosulfanyl)pyridin-2(1*H*)-one (354)



Structure deposited at the Cambridge Crystallographic Data Centre (CCDC 1415087)

Experimental: recrystallization of **354** from ethyl acetate by slow evaporation afforded crystals suitable for X-ray analysis. A colorless plate-like specimen of $C_5H_4F_5NOS$, approximate dimensions 0.30 mm x 0.22 mm x 0.07 mm, was used for the X-ray crystallographic analysis.

CCDC deposition number 1415087

Chemical formula $C_5H_4F_5NOS$

Formula weight 221.15

Crystal habit colorless plate

Crystal system monocyclic

Space group $P2_1/c$

Unit cell dimensions a = 10.972(2) Å α = 90°

b = 5.4764(13) Å β = 119.104(2)°

c = 13.691(2) Å γ = 90°

Volume 718.8 $Å^3$

Z 4

Density (calculated) 2.044 $g \cdot cm^{-3}$

Absorption coefficient 0.502 mm^{-1}

F(000) 440.0

Temperature 100.0(2) K

Radiation MoKα (0.71073 Å)

2θ range for data collection 4.248° to 55.25°

Index ranges $-14 \leq h \leq 14$, $-7 \leq k \leq 7$, $-17 \leq l \leq 17$

Reflections collected 10050

Independent reflections 1660 [R_{int} = 0.0196, R_{sigma} = 0.0112]

Data / restraints / parameters 1660/1/121

Goodness-of-fit on F^2 1.088

Final R indexes I>2σ(I) R_1 = 0.0224; wR_2 = 0.0606

all data R_1 = 0.0237; wR_2 = 0.0617

Largest diff. peak and hole 0.41/–0.35eÅ^{-3}

Curriculum Vitae

Adrien Joliton

Born 19.07.1987 in Cherbourg, France

Education and Research Experience

10/2012 – present	Doctoral studies (Supervisor: Prof. Erick M. Carreira) ETH Zurich, Switzerland Title: *Novel Pentafluorosulfanyl-Substituted Building Blocks and Evaluation of their Physicochemical Properties And Polycationic Hexasaccharides Derived from α-Cyclodextrin*
02/2012 – 07/2012	Master thesis Spirochem AG, Zurich, Swizerland Title: *Design and Synthesis of Novel Molecules for Pharmaceutical Application*
09/2011 – 07/2012	M. Sc. in Chemistry INSA (National Institute of Applied Sciences) et Université de Rouen, France
07/2010 – 07/2011	Internship as research chemist Broad Institute of Harvard and MIT, Cambridge, MA, USA
05/2010 – 06/2010	Research project in the group of Prof. Philippe Jubault IRCOF (Research Institute in Fine Organic Chemistry) Rouen, France
06/2009 – 08/2009	Research project in the group of Prof. Olof Ramström KTH (Royal Institute of Technology), Stockholm, Sweden
09/2008 – 09/2012	Diplôme d'Ingénieur in Chemistry INSA (National Institute of Applied Sciences), Rouen, France
02/2008 – 04/2008	Research project in the group of Prof. Janine Mauzeroll UQAM (University from Quebec in Montreal), Montreal, Canada
09/2006 – 07/2008	DUT (Diplôme Universitaire de Technologie) in Chemistry Institute of technology, Rouen, France

Teaching Experience

Falls 2014 and 2015	Teaching assistant for the lecture *Organic Chemistry III*, ETH Zurich
Spring 2014	Teaching assistant for the laboratory course *OACP1*, ETH Zurich

Journal Publications

E. Comer, H. Liu, A. Joliton, A. Clabaut, C. Johnson, L. B. Akella, L. A. Marcaurelle, *Proc. Natl. Acad. Sci.* **2011,** *108,* 6751–6756

Fragment-based domain shuffling approach for the synthesis of pyran-based macrocycles

J. T. Lowe, A. Joliton, L. A. Marcaurelle *et al., J. Org. Chem.* **2012**, 77, 7187–7211

Synthesis and Profiling of a Diverse Collection of Azetidine-Based Scaffolds for the Development of CNS-Focused Lead-Like Libraries

L. Deng, X. Wang, S. Uppalapati, O. Norberg, H. Dong, A. Joliton, M. Yan, O. Ramström, *Pure Appl. Chem.* **2013**, *85*, 1789–1801

Stereocontrolled 1-S-Glycosylation and Comparative Binding Studies of Photoprobe-Thiosaccharide Conjugates with their O-Linked Analogs

A. Joliton, E. M. Carreira, *Org. Lett.* **2013**, *15*, 5147–5149

Ir-Catalyzed Preparation of SF_5-Substituted Potassium Aryl Trifluoroborates via C–H Borylation and their Application in the Suzuki–Miyaura Reaction

A. Joliton, E. M. Carreira, *Synlett* **2015**, 737–740

Novel SF_5-Anilines and SF_5-Aryl Ethers from SF_5-Subtituted Potassium Aryl Trifluoroborates

A. Joliton, J.-M. Plancher, E. M. Carreira, *Angew. Chem. Int. Ed.* **2016**, *55*, 2113–2117

Formation of α-SF_5-Enolate enables Preparation of 3-SF_5-Quinolin-2-ones, 3-SF_5-Pyridin-2-ones: Evaluation of their Physicochemical Properties

Poster Presentations

Gordon Research Seminar, High Throughput Chemistry & Chemical Biology, New London, NH, USA, June 2011

A Fragment-Based Domain Shuffling Strategy for the Generation of a Library of Pyran-Containing Macrocycles

Gordon Research Conference, High Throughput Chemistry & Chemical Biology, New London, NH, USA, June 2011

Diversity-Oriented Synthesis of a Diazaspirocyclic Library

SSCI-Symposium, Zurich, Switzerland, January 2016

Generation of α-SF_5-Enolate: Preparation of Novel SF_5-Heterocycles