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Studies Toward the Synthesis of Bafilomycin A_1 and Fusidilactone C

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presented by

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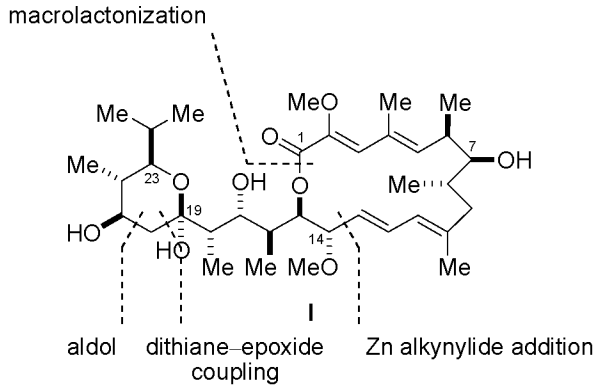
Abstract

The macrolide bafilomycin A_1 (**I**) was isolated in 1983 by *Werner* and *Hagenmeier* from cultures of *Streptomyces griseus* sp. *sulfurus*. **I** displays a broad spectrum of biological activities, the most remarkable of which is the unprecedented selective inhibition of vacuolar ATPases.

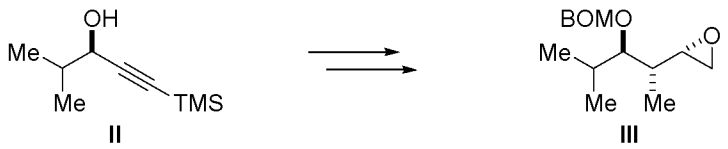
According to our retrosynthetic analysis (Scheme 1), we envisioned the preparation of bafilomycin A_1 by zinc-mediated addition of a C1–C13 enyne to a C14 aldehyde and subsequent macrolactonization.



Scheme 1. Retrosynthetic analysis of bafilomycin A_1.

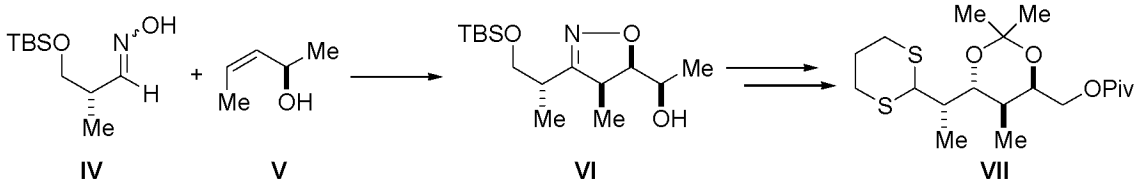
Part I of this thesis describes two convergent approaches toward the synthesis of bafilomycin A_1's C14–C25 subunit, the first one focusing on a dithiane–epoxide coupling and the second one on an aldol reaction.

The synthesis of epoxide **III** commenced with the enantioselective zinc-catalyzed addition of trimethylsilyl acetylene to isobutyraldehyde to afford propargylic alcohol **II** in 77% yield and 92% enantiomeric excess (Scheme 2). Further elaboration of **II** relied on a diastereoselective conjugate addition–hydroxylation sequence.



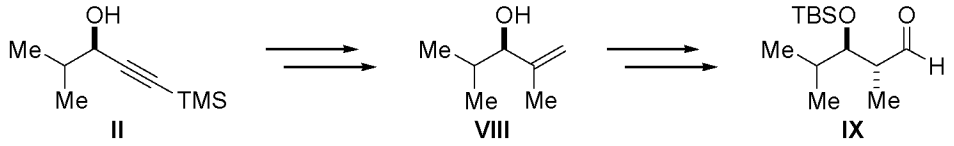
Scheme 2.

The hydroxy-directed nitrile oxide cycloaddition between oxime **IV** and allylic alcohol **V** furnished isoxazoline **VI** in 80% yield with complete diastereoselectivity (Scheme 3). Its transformation to dithiane **VII** involved the palladium-catalyzed transfer hydrogenation of a vinyl triflate, the reductive opening of the isoxazoline moiety using Raney-Nickel, and the *anti*-selective reduction of a β-hydroxy ketone. However, the coupling of both functionalized intermediates **III** and **VII** failed to give the desired product, which prompted us to investigate an alternative strategy.



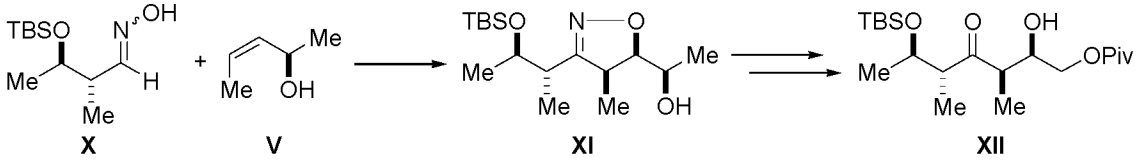
Scheme 3.

The aldol approach toward bafilomycin A_1 commenced with the stereoselective synthesis of aldehyde **IX** (Scheme 4). Allylic alcohol **VIII** was prepared from the optically active propargylic alcohol **II** by zirconium-mediated carboalumination of the derived terminal alkyne. Installation of the α-stereogenic center present in **IX** was achieved by diastereoselective hydroboration. Aldehyde **IX** was thus prepared in six steps and 31% overall yield.



Scheme 4.

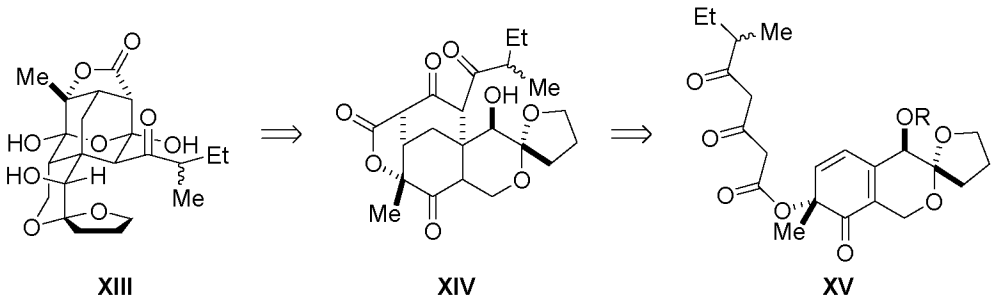
The magnesium-mediated nitrile oxide cycloaddition between optically active oxime **X**, which was accessed by *Frater–Seebach* alkylation, and allylic alcohol **V** served as the key step for the synthesis of bafilomycin A_1's C14–C20 fragment **XII** (Scheme 5). Isoxazoline **XI** was obtained in 60% yield with a diastereomeric ratio of 95:5.



Scheme 5.

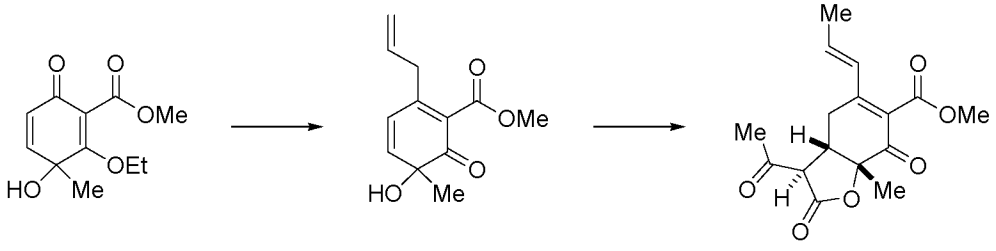
Part II of the present thesis describes our studies toward the total synthesis of fusidilactone C (**XIII**). The isolation of this natural product from the fungal endophyte *Fusidium sp.* was reported in 2002 by *Krohn* and co-workers (Scheme 6). Fusidilactone C possesses only weak biological activity, but its unusual densely functionalized hexacyclic structure incorporating an oxoadamantyl bishemiacetal renders it a formidable target for chemical synthesis.

Our retrosynthetic analysis is based on an intramolecular tandem 1,6–1,4-addition to a cyclohexadienone moiety as a key step.



Scheme 6. Retrosynthetic analysis of fusidilactone C.

Vinylogous ester **XVI** was prepared in four steps and submitted to allyl *Grignard* addition and subsequent acid-catalyzed elimination of ethanol to give tertiary alcohol **XVII** in 41% yield (Scheme 7). Treatment of **XVII** with diketene and triethylamine led to the formation of the corresponding acetoacetate, which, under the mild reaction conditions, spontaneously underwent in situ 1,6-addition to afford the bicyclic lactone (±)-**XVIII** in 43% unoptimized yield. All attempts to convert the tertiary alcohol into a β,δ-diketoester moiety failed and thus precluded the development of the planned 1,6–1,4-addition.

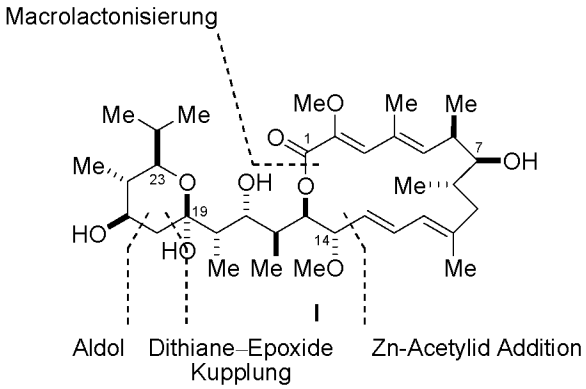


Scheme 7.

Zusammenfassung

Das Makrolid Bafilomycin A_1 (**I**) wurde 1983 von *Werner* und *Hagenmeier* aus einer *Streptomyces griseus* sp. *sulfurus*-Kultur isoliert. **I** besitzt ein breites Spektrum biologischer Aktivitäten, insbesondere die erstmals beobachtete Fähigkeit, vakuoläre ATPasen selektiv zu inhibieren.

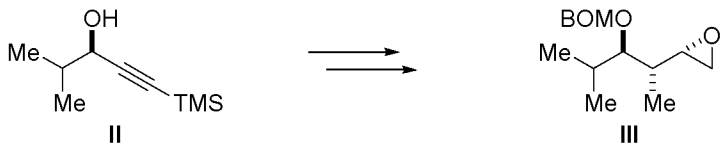
Unsere Syntheseplanung basiert auf der Zink-katalysierten Addition eines C1–C13 Enins an einen C14 Aldehyden und einer anschliessender Macrolactonisierung (Scheme 8).



Scheme 8. Syntheseplanung für Bafilomycin A_1.

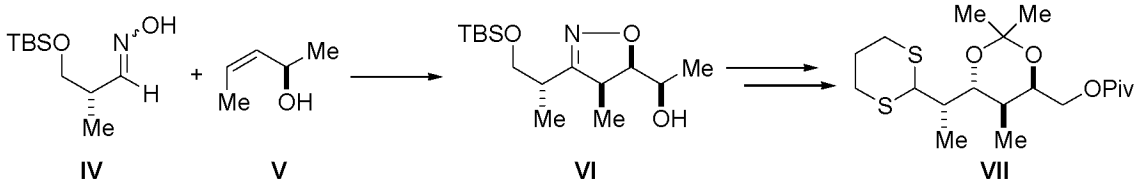
Teil I der vorliegenden Arbeit beschreibt zwei Ansätze für die Synthese von Bafilomycin A_1's C14–C25 Fragment: Der erste beruht auf einer Dithian–Epoxid Kupplung, der zweite auf einer Aldol Reaktion.

Die Synthese von Epoxid **III** begann mit der Zink-katalysierten enantioselektiven Addition von Trimethylsilylacetylen an Isobutyraldehyd zum propargylischen Alkohol **II**, der auf diese Weise in 77% Ausbeute und 92% Enantiomerenüberschuss hergestellt wurde (Scheme 9). Die Überführung von **II** in Epoxid **III** beruhte auf einer diastereoselektiven Sequenz von *Michael*-Addition und Hydroxylierung.



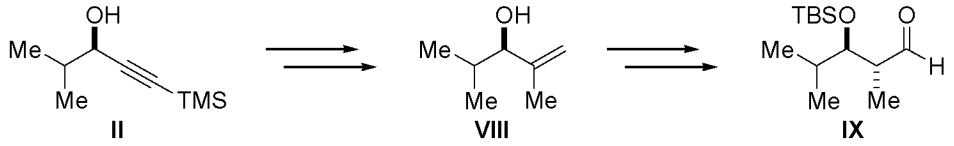
Scheme 9.

Die Hydroxy-dirigierte Nitriloxid-Cycloaddition zwischen dem Oxim **IV** und dem allylischen Alkohol **V** lieferte das Isoxazolin **VI** in 80% Ausbeute und mit vollständiger Diastereoselektivität (Scheme 10). Die Umwandlung von **VI** in Dithian **VII** umfasste die Palladium-katalysierte Transferhydrierung eines Vinyltriflats, die reduktive Spaltung des Isoxazolin-Rings mit Raney-Nickel und die *anti*-selektive Reduktion eines β-Hydroxyketons. Da die Kupplung der beiden fortgeschrittenen Intermediate **III** und **VII** fehlschlug, widmeten wir uns der Erkundung einer Alternativroute.



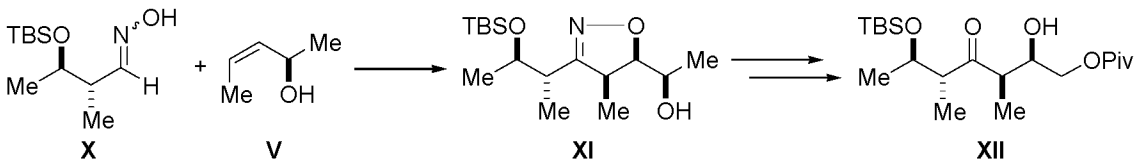
Scheme 10.

Die stereoselektive Darstellung von Aldehyd **IX** legte den Grundstein zu unserem Aldol-Ansatz (Scheme 11). Dazu wurde der propargylische Alkohol **II** desilyliert und mittels Zirkonium-katalysierter Carboaluminierung in den allylischen Alkohol **VIII** überführt. Das stereogene α-Zentrum des Aldehyds **IX** wurde durch eine diastereoselektive Hydroborierung generiert. Diese sechsstufige Syntheseroute lieferte **IX** in einer Gesamtausbeute von 31%.



Scheme 11.

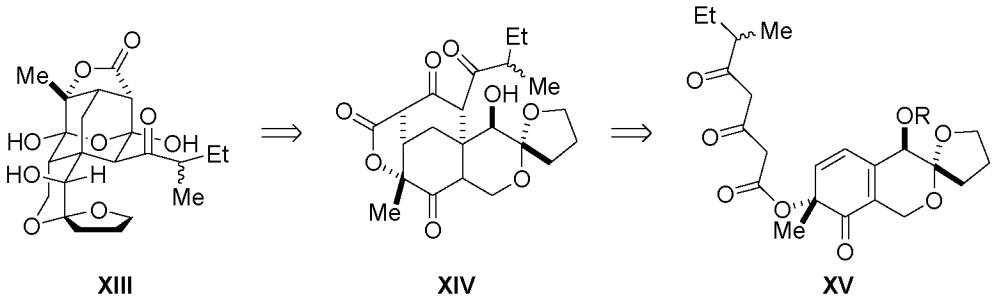
Die diastereoselektive Nitriloxid-Cycloaddition zwischen Oxim **X**, dessen Darstellung auf einer *Frater–Seebach* Alkylierung basierte, und dem allylischen Alkohol **V** diente als Schlüsselschritt der Synthese von Bafilomycin A_1's C14–C20 Fragment **XII** (Scheme 12). Das Isoxazolin **XI** wurde so in 60% Ausbeute und mit einem Diastereomerenverhältnis von 95:5 hergestellt.



Scheme 12.

Teil II dieser Doktorarbeit beschreibt unsere Bemühungen mit dem Ziel einer Totalsynthese von Fusidilactone C (**XIII**). Die Isolierung dieses Naturstoffs aus dem Pilz-Endophyten *Fusidium* sp. wurde 2002 von *Krohn* et al. publiziert. Fusidilactone C besitzt nur schwache biologische Aktivität, aber seine aussergewöhnliche, auf einem Oxoadamantan-Bishemiacetal basierende hexacyclische Struktur macht es zu einer interessanten Zielverbindung für eine chemische Synthese.

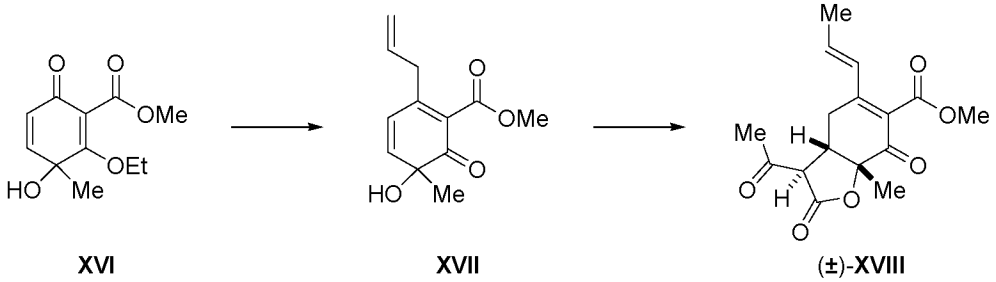
Unsere Syntheseplanung konzentrierte sich auf eine intramolekulare Tandem-1,6–1,4-Addition an eine Cyclohexadienon-Einheit als Schlüsselschritt (Scheme 13).



XIII **XIV** **XV**

Scheme 13. Syntheseplanung für Fusidilactone C.

Allyl-*Grignard*-Addition an den in vier Stufen hergestellten vinylogen Ester **XVI** und nachfolgende Säure-katalysierte Eliminierung lieferten den tertiären Alkohol **XVII** in 41% Ausbeute (Scheme 14). Umsetzung von **XVII** mit Diketen und Triethylamin führte zur Bildung des entsprechenden Acetoacetats, welches unter den milden Reaktionsbedingungen spontan in einer 1,6-Addition zum Lacton (±)-**XVIII** reagierte (43% Ausbeute, unoptimiert). Alle Versuche, den tertiären Alkohol in einen β,δ-Diketoester zu überführen, schlugen fehl und verhinderten damit die Ausarbeitung der geplanten 1,6–1,4-Addition.



XVI **XVII** (±)-**XVIII**

Scheme 14.

List of Abbreviations, Acronyms, and Symbols

2D-NOESY	two dimensional nuclear *Overhauser* enhanced spectroscopy
9-BBN	9-Borabicyclo[3.3.1]nonane
$[\alpha]^{T}_{D}$	specific rotation at temperature T at the sodium D line
Å	Ångstrom
Ac	acetyl
acac	acetylacetonato
AIBN	2,2'-azoisobutyronitrile
ATP	adenosin-5'-triphosphate
aq.	aqueous
binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOM	benzyloxymethyl
br	broad
Bu	butyl
Bz	benzoyl
° C	degree centigrade
calcd	calculated
CAN	ceric ammonium nitrate
cat.	catalytic
CDI	*N,N'*-carbonyldiimidazole
CI	chemical ionization

cm^{-1}	reciprocal centimeters
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cp*	pentamethyl cyclopentadienyl
CSA	10-camphorsulfonic acid
Cy	cyclohexyl
δ	NMR chemical shift in ppm downfield from a standard
d	day, doublet
DAST	diethylaminosulfur trifluoride
dba	(*E*,*E*)-dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAL-H	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DMAP	4-*N*,*N*-dimethylamino pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethyl formamide
DMP	*Dess–Martin* periodinane

DMSO	dimethyl sulfoxide
DMT	4,4'-dimethoxytriphenylmethyl
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EDC·HCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	enantiomeric excess
EI	electron impact ionization
ent	reversal of stereocenters
equiv	equivalent
Et	ethyl
et al.	and others
eV	electronvolt
FD	field desorption
g	gram
h	hour
HMBC	heteronuclear multiple bond correlation
HMDS	1,1,1,3,3,3,-hexamethyldisilazide
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
IBX	2-iodoxybenzoic acid
INDOR	internuclear double resonance
IR	infrared
J	coupling constant

kcal	kilocalorie
LDA	lithium diisopropyl amide
L-Selectride	lithium tri-*sec*-butylborohydride
m	multiplet
m	*meta*
M	molar
MALDI	matrix-assisted laser desorption ionization
*m*CPBA	3-chloroperoxybenzoic acid
Me	methyl
mg	milligram
min	minute
ml	milliliter
µl	microliter
mmol	millimole
µmol	micromole
mol %	mole per cent
MOM	methoxymethyl
Ms	methylsulfonyl
MS	molecular sieves, mass spectrometry
MTr	4-methoxytriphenylmethyl
NCS	*N*-chlorosuccinimide
n.d.	not determined
NME	*N*-methyl ephedrine
NMO	*N*-methyl morpholine *N*-oxide

NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
n*O*e	nuclear *Overhauser* enhancement
o	*ortho*
p	*para*
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
pH	negative logarithm of hydrogen ion concentration
Ph	phenyl
Piv	2,2-dimethylpropanoyl
PMB	4-methoxybenzyl
PMP	4-methoxyphenyl
ppm	parts per million
PPTS	pyridinium 4-toluenesulfonate
Pr	propyl
PTLC	preparative TLC
py	pyridine
q	quartet
quant.	quantitative
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
R_f	retention factor
rt	room temperature
s	singlet
sat.	saturated

SFORD	single frequency off-resonance decoupling
Super-Hydride	lithium triethylborohydrate
t	triplet
T	temperature, tesla
TAS-F	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl radical
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	4-methylphenylsulfonyl
TPAP	tetra-*n*-propylammonium perruthenate
UV	ultraviolet
vs	versus
wt%	weight percent

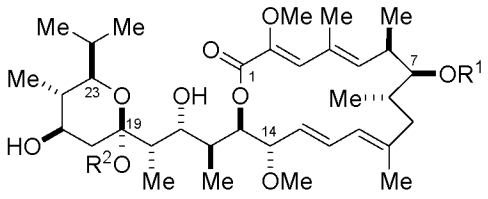
Part I:

Studies Toward the Synthesis of Bafilomycin A_1

1 Introduction

1.1 Isolation of Bafilomycin A_1

Bafilomycin A_1 (**1**) and the closely related bafilomycins A_2, B_1, B_2, C_1, and C_2 (Figure 1) were originally isolated from the culture medium of the actinobacterium *Streptomyces griseus* sp. *sulphurus* (Figure 2) in 1983 by *Werner* and *Hagenmeier*, [1,2] and later on also from the culture of *Actinomyces* sp. A239 and a strain of *Kitasatospora cheerisanensis* YC75.[3,4] The bafilomycins A_1, B_1 and C_1 are native, whereas their C19 methoxy analogs A_2, B_2 and C_2 are formed during the isolation procedure.[5]



Bafilomycins

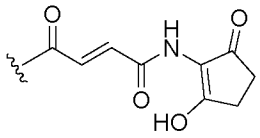
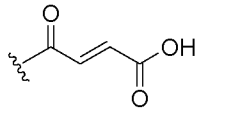
	R^1	R^2
A_1 (**1**)	H	H
A_2		Me
B_1		H
B_2		Me
C_1		H
C_2		Me

Figure 1. Structures of the bafilomycins.

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1 G. Werner, H. Hagenmaier, K. Albert, H. Kohlshorn, H. Drautz, *Tetrahedron Lett.* **1983**, *24*, 5193–5196.

2 G. Werner, H. Hagenmaier, H. Drautz, A. Baumgartner, H. Zahner, *J. Antibiot.* **1984**, *37*, 110–117.

3 E. Lacey, J. H. Gill, M. L. Power, R. W. Rickards, M. G. Oshea, J. M. Rothschild, *Int. J. Parasitol.* **1995**, *25*, 349–357.

4 S. S. Moon, W. H. Hwang, Y. R. Chung, J. Shin, *J. Antibiot.* **2003**, *56*, 856–861.

5 Throughout the text, the atom numbering introduced by *Werner* and *Hagenmeier* will be used; see ref. 1.

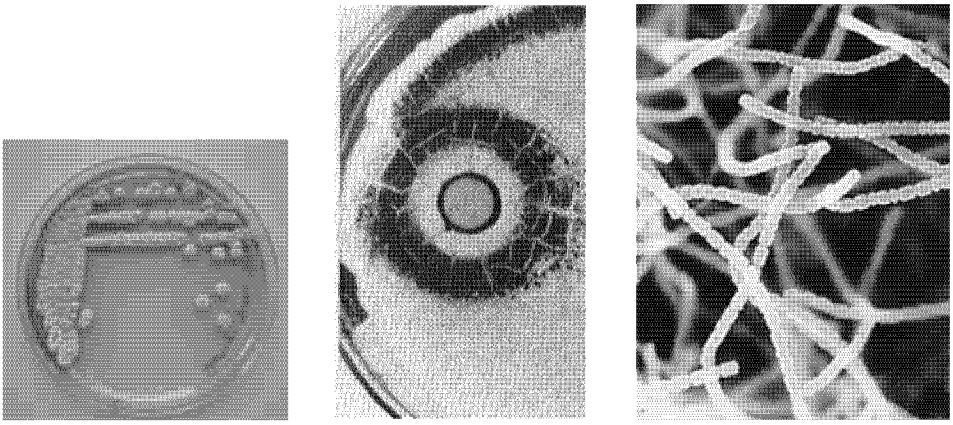

Figure 2. Left: *Streptomyces griseus* in culture medium.[6] Middle: Close-up of *Streptomyces griseus* M-1027.[7] Right: Scanning electron microscope photography of *Streptomyces griseus*.[8]

For the isolation of the bafilomycins, the antibiotic-producing microorganism TÜ 1922, a *Streptomyces griseus* sp. *sulphurus* strain, was cultured in a 100-liter fermentor at 27 °C in a medium consisting of 2% meat meal, 2% malt extract and 1% $CaCO_3$ at pH 7.2.[2] After adjusting the culture filtrate to pH 10, a brown residue containing the bafilomycins was obtained by extraction with ethyl acetate and concentration of the organic phase. Three sequential column chromatographies and finally purification by HPLC afforded 45 mg of bafilomycin A_1 and 36 mg of bafilomycin A_2. Bafilomycin A_1 is a colorless amorphous powder with a melting point of 98–106 °C (decomposition) and an R_f value of 0.51 ($CHCl_3$/MeOH 9:1).

All bafilomycins are readily soluble in acetone, methanol and chloroform, are unstable under acidic (pH < 6) and basic (pH > 11) conditions, and decompose at their respective melting point. The bafilomycins belong to the plecomacrolide family of naturally occurring macrolide antibiotics (formerly known as the hygrolide family), which also includes the hygrolidins,[9] concanamycins,[10] formamicin,[11] and elaiophylin.[12] These natural products are

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6 This illustration was taken from: www.uni-bielefeld.de/biologie/Didaktik/BotZell/text/forschung_micro_unterricht.html, 05.03.2007.

7 This illustration was taken from: www.bt.a.u-tokyo.ac.jp/_kougaku/04/main206.html, 05.03.2007.

8 This illustration was taken from: www.nsf.gov/news/speeches/colwell/rc03_compass/sld014.htm; S. Amano, S. Maydoh, T. Shomura, The Society for Actinomycetes Japan, 05.03.2007.

9 (a) H. Seto, I. Tajima, H. Akao, K. Furihata, N. Otake, *J. Antibiot.* **1984**, *37*, 610–613; (b) H. Seto, H. Akao, K. Furihata, N. Otake, *Tetrahedron Lett.* **1982**, *23*, 2667–2670.

typically composed of a 16- or 18-membered macrolactone with two conjugated diene units, a hemiacetal side chain, and a three-carbon linker between the two subunits.

1.2 Structure Elucidation of Bafilomycin A_1

The constitution of bafilomycin A_1 was proposed by *Werner* and *Hagenmeier* based on IR, UV, mass, and NMR spectroscopy.[1,2] The EI-mass spectrum showed several fragment ion peaks up to m/z = 568, but the molecular ion peak of m/z = 622 corresponding to $C_{35}H_{58}O_9$ only appeared in the FD-mass spectrum. The ^{13}C NMR spectrum revealed 9 x CH_3, 2 x CH_2, 6 x CH, 2 x CH_3O, 6 x CHO, 1 x O–C–O, 5 x CH=, 3 x C=, and 1 x COO, which were correlated to the proton resonances by SFORD. Analysis of the ^1H NMR spectrum by conventional proton spin decoupling, INDOR spectra, and n*O*e experiments led to the determination of three fragments, which were combined to bafilomycin A_1's full skeleton.

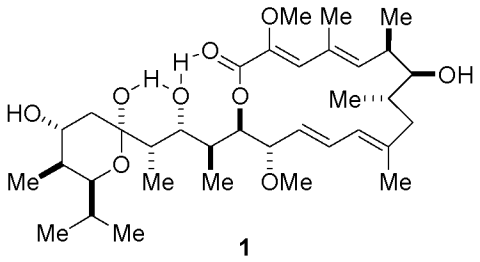

Figure 3. Structure and hydrogen bonding network of bafilomycin A_1.

The configuration and intramolecular hydrogen-bonding network—this biologically important structural motif is common to all plecomacrolides—of bafilomycin A_1 was originally proposed by *Corey* based on NMR analysis and molecular modeling, and was later confirmed by X-ray crystallographic analysis (Figure 3).[13,14] By interpretation of proton–proton coupling constants, ^1H nuclear *Overhauser* enhancements and ^{13}C spin–lattice relaxation times, bafilomycin A_1's conformations in solution have been determined to be very

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[10] (a) J. W. Westley, C. M. Liu, L. H. Sello, R. H. Evans, N. Troupe, J. F. Blount, A. M. Chiu, L. J. Todaro, P. A. Miller, *J. Antibiot.* **1984**, *37*, 1738–1740; (b) H. Kinashi, K. Someno, K. Sakaguchi, T. Higashijima, T. Miyazawa, *Tetrahedron Lett.* **1981**, *22*, 3861–3864.

[11] M. Igarashi, H. Makamura, H. Naganawa, T. Takauchi, *J. Antibiot.* **1997**, *50*, 932–936.

[12] M. Gerlitz, P. Hammann, R. Thiericke, J. Rohr, *J. Org. Chem.* **1992**, *57*, 4030–4033.

[13] E. J. Corey, J. W. Ponder, *Tetrahedron Lett.* **1984**, *25*, 4325–4328.

[14] G. H. Baker, P. J. Brown, R. J. J. Dorgan, J. R. Everett, S. V. Ley, A. M. Z. Slawin, D. J. Williams, *Tetrahedron Lett.* **1987**, *28*, 5565–5568.

similar to its crystalline state (Figure 4), with the intramolecular hydrogen-bonding staying intact in $CDCl_3$ solution.[15]

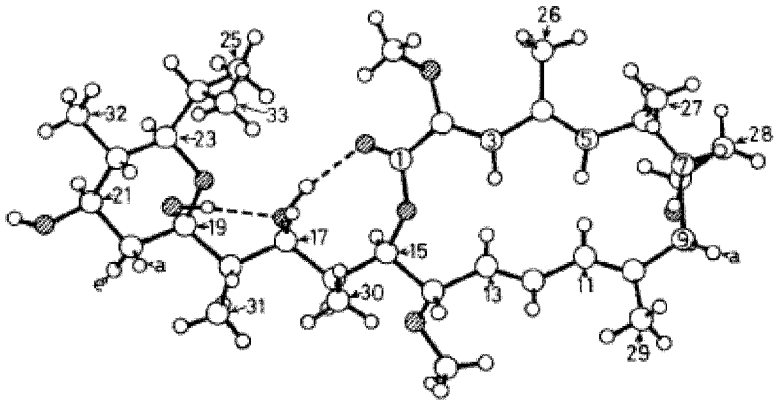

Figure 4. Crystal structure of bafilomycin A_1 (oxygen atoms are shaded and the hydrogen bonds shown as dotted lines).[15]

1.3 Biological Activity of Bafilomycin A_1

In a disc diffusion assay, the bafilomycins displayed a broad activity spectrum against *Gram*-positive bacteria, fungi, and yeast.[2] The antibacterial effects increased in the order A < B < C and were in general far less pronounced than the antifungal activity.

Bowman and co-workers investigated the effect of bafilomycin A_1 (**1**) on various membrane ATPases from microorganisms, animal cells, and plant cells.[16] These ion-pumping membrane proteins are typically divided into three structural types:

- F-type or F_1F_0 ATPases using the electrochemical H^+- or occasionally K^+-gradient to synthesize ATP,
- P-type or E_1E_2 ATPases, for which the energy release by hydrolysis of ATP is coupled to the translocation of cations across the membrane, and
- V-type or vacuolar ATPases, apparently hydrolyzing ATP and generating a proton gradient, which is used for the acidification of certain cell compartments.

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[15] G. H. Baker, P. J. Brown, R. J. J. Dorgan, J. R. Everett, *J. Chem. Soc., Perkin Trans. 2* **1989**, 1073–1079.

[16] E. J. Bowman, A. Siebers, K. Altendorf, *Proc. Natl. Acad. Sci. U. S. A.* **1988**, *85*, 7972–7976.

While bafilomycin A_1 showed little to no effect on the tested E_1E_2 and F_1F_0 ATPases, it proved highly active for the inhibition of vacuolar ATPases even at nanomolar concentration. **1** being the first relatively specific potent inhibitor for V-type ATPases, the least understood category of membrane ATPases at the time, it appeared an excellent candidate for probing their structure and function.

The vacuolar proton ATPase, a universal component of eukaryotic organisms, is found in the membranes of many organelles, such as fungal and plant vacuoles, coated vesicles or chromaffin granules.[17] The V-ATPase is a multi-subunit enzyme composed of a cytosolic, ATP-hydrolyzing sector and a membrane sector, which is responsible for proton translocation across the membrane (Figure 5). Bafilomycin A_1 appears to inhibit its functioning by interaction with the later.

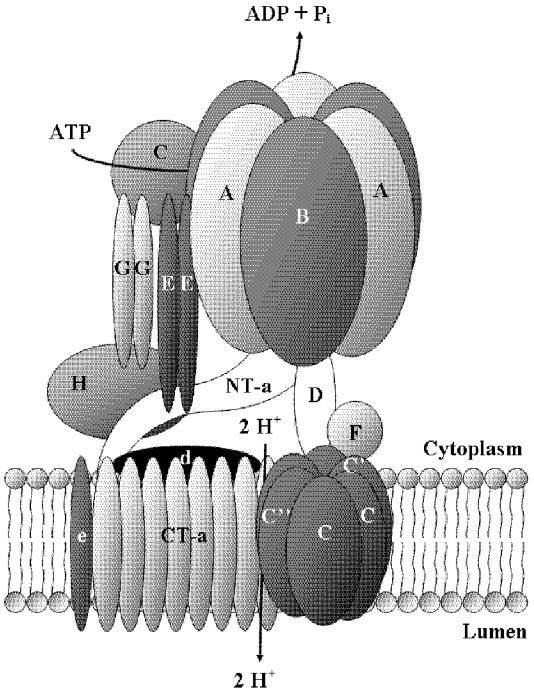

Figure 5. Simplified schematic model of vacuolar ATPases.

The fact that the vacuolar ATPase is highly expressed on the membrane of bone-resorbing osteoclasts—they are responsible for the acidic environment required for bone resorption—renders them an interesting potential target for treating metabolic diseases related to

[17] For a review on vacuolar ATPases see: (a) M. E. Finbow, M. A. Harrison, *Biochem. J.* **1997**, *324*, 697–712; (b) M. Forgac, *J. Biol. Chem.* **1999**, *274*, 12951–12954.

overstimulated bone resorption such as osteoporosis.[18] As a specific inhibitor of V-ATPases, bafilomycin A_1 would be predestined for such an application. But its inability to distinguish among the vacuolar ATPases located in different cells, tissues, and cell compartments leads to generalized inhibition of all of them causing substantial toxicity. To date, all attempts to prepare a derivative or analog with retained inhibitory activity but increased selectivity for the osteoclast enzyme were unsuccessful.[19]

Structure–activity relationship studies of bafilomycin A_1 and its analogs revealed that modification of the C19 or C21 hydroxy group had little or no effect on the interaction with the tested V-ATPases, whereas the presence of an alcohol at the C7 position was crucial for activity. Drastic modifications of the macrolactone ring, such as partial or full hydrogenation of the two diene units, were detrimental to the activity, while opening of this ring only led to a 100-fold decrease. Finally, the hemiacetal moiety was extensively modified without affecting biological activity; but replacement of the entire scaffold by carboxylic or carbomethoxy groups afforded inactive compounds.

1.4 Synthetic Approaches toward Bafilomycin A_1

1.4.1 Introduction

Bafilomycin A_1 combines a very particular biological activity and several unusual structural features such as the 16-membered macrolactone, the tetrahydropyrane hemiacetal, the C2–C5 diene unit bearing a methyl enol ether, a total of twelve stereogenic centers, and the unique hydrogen bonding network. As a consequence, this macrolide antibiotic has attracted considerable synthetic interest:[20] To date, four total syntheses have been reported (by *Evans*,[21] *Toshima*,[22] *Roush*,[23] and *Hanessian*[24]), as well as six partial syntheses (by *Paterson*,[25]

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18 S. Gagliardi, M. Rees, C. Farina, *Curr. Med. Chem.* **1999**, *6*, 1197–1212.

19 (a) S. Drose, K. U. Bindseil, E. J. Bowman, A. Siebers, A. Zeeck, K. Altendorf, *Biochemistry* **1993**, *32*, 3902–3906; (b) S. Gagliardi, P. A. Gatti, P. Belfiore, A. Zocchetti, G. D. Clarke, C. Farina, *J. Med. Chem.* **1998**, *41*, 1883–1893.

20 For a review see: W. M. Dai, Y. C. Guan, J. Jin, *Curr. Med. Chem.* **2005**, *12*, 1947–1993.

21 D. A. Evans, M. A. Calter, *Tetrahedron Lett.* **1993**, *34*, 6871–6874.

22 (a) K. Toshima, T. Jyojima, H. Yamaguchi, Y. Noguchi, T. Yoshida, H. Murase, M. Nakata, S. Matsumura, *J. Org. Chem.* **1997**, *62*, 3271–3284; (b) K. Toshima, T. Jyojima, H. Yamaguchi, H. Murase, T. Yoshida, S. Matsumura, M. Nakata, *Tetrahedron Lett.* **1996**, *37*, 1069–1072; (c) K. Toshima, H. Yamaguchi, T. Jyojima, Y. Noguchi, M. Nakata, S. Matsumura, *Tetrahedron Lett.* **1996**, *37*, 1073–1076.

Breit,[26] *Marshall*,[27] *Prunet*,[28] *Cossy*,[29] and *Lett*[30]), and several synthetic studies starting from the natural product.[31]

Typically, the largest fragments were assembled by a *Stille* or *Suzuki* cross-coupling to form the C11–C12 bond and subsequent macrolactonization under *Yamaguchi* or *Keck* conditions (Figure 6).[21–24] Alternatively, an intermolecular esterification followed by intramolecular *Stille* coupling has been developed.[30] For the installation of the C2–C5 diene unit, an iterative *Wittig* and *Horner–Wadsworth–Emmons* olefination protocol has been widely used.[22,23,27] Regarding the construction of the polypropionate side chain, the application of a diastereoselective aldol reaction was the most popular approach.[21–23,25]

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[23] (a) K. A. Scheidt, A. Tasaka, T. D. Bannister, M. D. Wendt, W. R. Roush, *Angew. Chem., Int. Ed.* **1999**, *38*, 1652–1655; (b) K. A. Scheidt, T. D. Bannister, A. Tasaka, M. D. Wendt, B. M. Savall, G. J. Fegley, W. R. Roush, *J. Am. Chem. Soc.* **2002**, *124*, 6981–6990; (c) W. R. Roush, T. D. Bannister, M. D. Wendt, J. A. Jablonowski, K. A. Scheidt, *J. Org. Chem.* **2002**, *67*, 4275–4283; (d) W. R. Roush, T. D. Bannister, *Tetrahedron Lett.* **1992**, *33*, 3587–3590; (e) W. R. Roush, T. D. Bannister, M. D. Wendt, *Tetrahedron Lett.* **1993**, *34*, 8387–8390.

[24] (a) S. Hanessian, J. G. Ma, W. G. Wang, *J. Am. Chem. Soc.* **2001**, *123*, 10200–10206; (b) S. Hanessian, K. Sumi, *Synthesis* **1991**, 1083–1089; (c) S. Hanessian, Y. H. Gai, W. G. Wang, *Tetrahedron Lett.* **1996**, *37*, 7473–7476.

[25] I. Paterson, S. Bower, M. D. McLeod, *Tetrahedron Lett.* **1995**, *36*, 175–178.

[26] B. Breit, S. K. Zahn, *Tetrahedron Lett.* **1998**, *39*, 1901–1904.

[27] (a) J. A. Marshall, N. D. Adams, *Org. Lett.* **2000**, *2*, 2897–2900; (b) J. A. Marshall, N. D. Adams, *J. Org. Chem.* **2002**, *67*, 733–740.

[28] (a) R. Lopez, J. C. Poupon, J. Prunet, J. P. Ferezou, L. Ricard, *Synthesis* **2005**, 644–661; (b) J. C. Poupon, E. Demont, J. Prunet, J. P. Ferezou, *J. Org. Chem.* **2003**, *68*, 4700–4707.

[29] (a) F. Eustache, P. I. Dalko, J. Cossy, *J. Org. Chem.* **2003**, *68*, 9994–10002; (b) F. Eustache, P. I. Dalko, J. Cossy, *Tetrahedron Lett.* **2003**, *44*, 8823–8826.

[30] (a) E. Queron, R. Lett, *Tetrahedron Lett.* **2004**, *45*, 4539–4543; (b) E. Queron, R. Lett, *Tetrahedron Lett.* **2004**, *45*, 4527–4531; (c) E. Queron, R. Lett, *Tetrahedron Lett.* **2004**, *45*, 4533–4537.

[31] (a) M. Deeg, H. Hagenmaier, A. Kretschmer, *J. Antibiot.* **1987**, *40*, 320–328; (b) S. Hanessian, Q. C. Meng, E. Olivier, *Tetrahedron Lett.* **1994**, *35*, 5393–5396; (c) S. Hanessian, A. Tehim, Q. C. Meng, K. Granberg, *Tetrahedron Lett.* **1996**, *37*, 9001–9004; (d) P. A. Gatti, S. Gagliardi, A. Cerri, M. Visconti, C. Farina, *J. Org. Chem.* **1996**, *61*, 7185–7188; (e) K. L. Granberg, K. M. Edvinsson, K. Nilsson, *Tetrahedron Lett.* **1999**, *40*, 755–758.

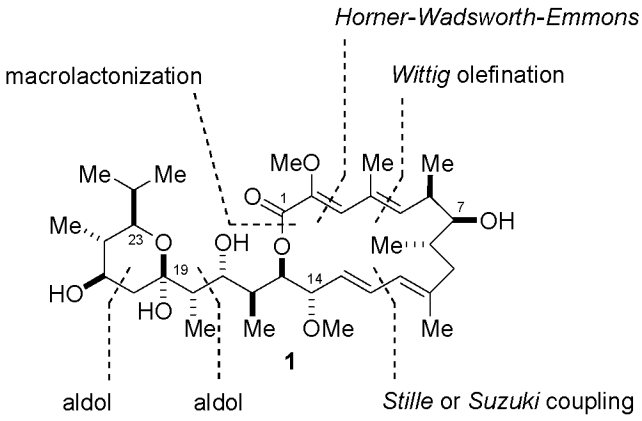


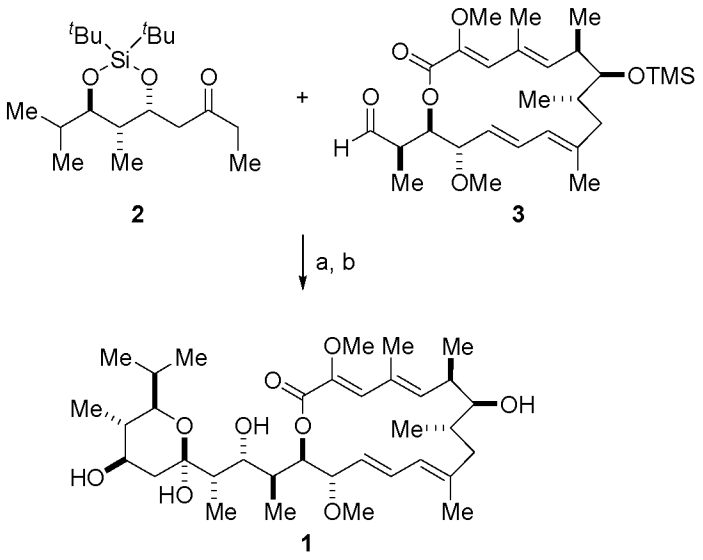
Figure 6. Key bond forming reactions used in bafilomycin A_1 syntheses.

Some interesting methodology has been developed for the selective installation of bafilomycin A_1's stereogenic centers, including addition of in situ generated γ-methoxyallylchromium,[22] γ-methoxyallenyltin[23] and enantioenriched allenylzinc[27] reagents, allylation and crotylation reactions,[23,25] iterative conjugate addition–hydroxylation,[24] hydroformylation of acyclic olefins,[26] Bu_3SnH promoted radical reductive deoxygenation–cyclopropane ring opening,[27] and dynamic kinetic resolution of 1,3-diketones.[29]

1.4.2 An Aldol Approach by *Evans*

The first total synthesis of bafilomycin A_1 was reported by *Evans* and *Calter* in 1993.[21] For the key bond construction, a late stage diastereoselective aldol reaction between a fully elaborated macrocyclic aldehyde and an appropriate ketone fragment was envisioned.

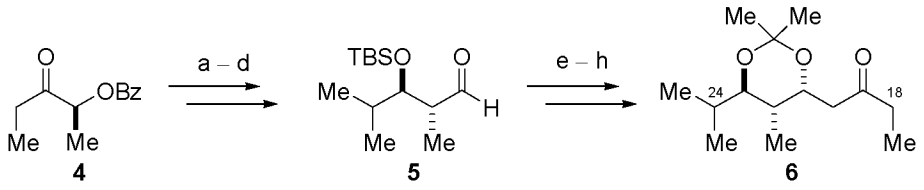
In extensive model studies, it was found that the best results in terms of yield and selectivity were obtained with the rarely used $PhBCl_2/{}^iPr_2NEt$ as enolizing agent in combination with cyclic constrainment of the diol by careful choice of a suitable protective group. With these findings in hand, *Evans* and co-workers proceeded to the key fragment coupling of ketone **2** to aldehyde **3** and were pleased to obtain the desired aldol product in 60% yield as a single diastereomer (Scheme 15). Final deprotection under mild conditions afforded bafilomycin A_1 in high yield.



Scheme 15: (a) $PhBCl_2$, $^iPr_2NEt$, CH_2Cl_2, –78 °C, 60%, dr > 95:5; (b) HF·py, THF, rt, 94%.

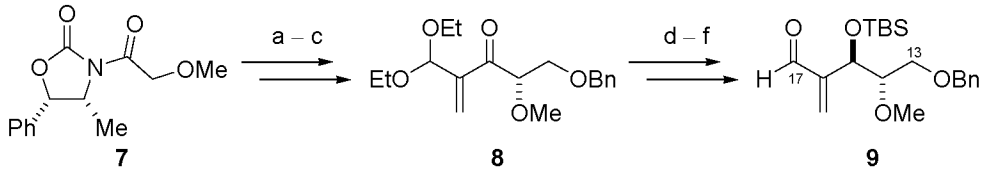
1.4.3 Synthesis of the C13–C25 Fragment by *Paterson*

The distinctive features of the *Paterson* synthesis of the C13–C25 fragment are a boron-mediated, *syn*-aldol coupling for the formation of the C17–C18 bond and a hydroxyl-directed hydrogenation to set the C16 stereocenter.[25] The utilized 11-step sequence resulted in 26% overall yield and 73% diastereoselectivity for the introduction of nine stereogenic centers.



Scheme 16: (a) Cy_2BCl, Me_2NEt, Et_2O, 0 °C, 3 h, then ^iPrCHO, –78 °C to –20 °C, 15 h, then aq. MeOH, H_2O_2, 0 °C, 1 h, 97%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 2 h; (c) $NaBH_4$, MeOH, 0 °C, 30 min, then K_2CO_3, MeOH, rt, 3 h; (d) $NaIO_4$, aq. MeOH, rt, 30 min, 81% over 3 steps; (e) trimethyl-(2-methylenebutyl)silane, $TiCl_4$, CH_2Cl_2, –94 °C, 10 min, 84%, 97% de; (f) TBAF, THF, rt, 30 min; (g) $(MeO)_2CMe_2$, PPTS, CH_2Cl_2, rt, 4 h; (h) OsO_4, NMO, ^tBuOH, THF, H_2O, rt, 4 h, then $NaIO_4$, pH 7 buffer, 10 min, 81% over 3 steps.

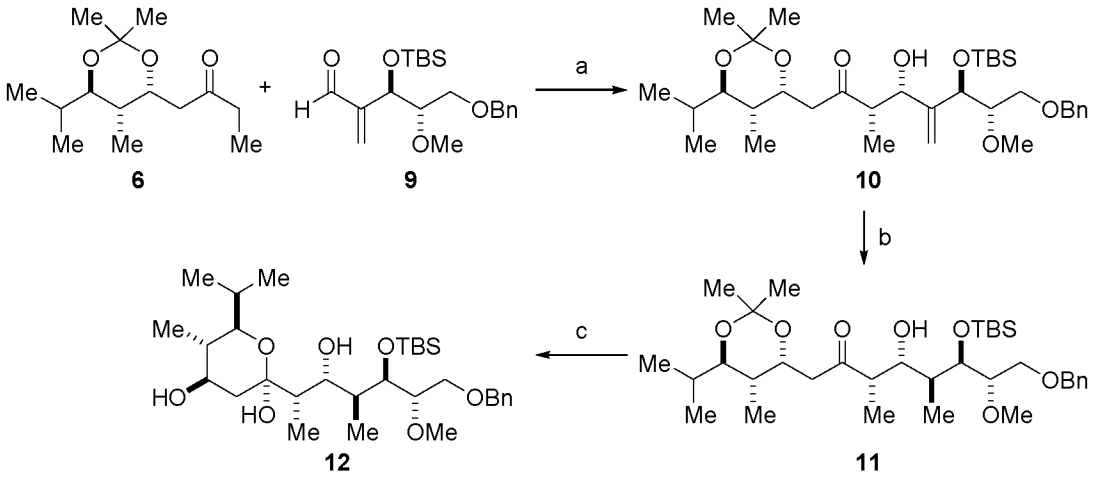
The synthesis of ketone **6**, starting from (*S*)-lactate derivative **4**, made use of a diastereoselective aldol coupling and a $TiCl_4$ promoted, *Felkin–Anh* controlled allylation reaction (Scheme 16). The synthesis of aldehyde **9**, on the other hand, relied on an *Evans*-type alkylation and an *anti*-selective *Luche* reduction (Scheme 17).



Scheme 17: (a) $TiCl_4$, $^iPr_2NEt$, CH_2Cl_2, 0 °C, 1 h, then BOMCl, 0 °C, 16 h, 85%; (b) MeONHMe·HCl, $AlMe_3$, CH_2Cl_2, –15 °C to rt, 20 h; (c) (3,3-diethoxyprop-1-en-2-yl)lithium, THF, –78 °C, 2 h, 75% over two steps; (d) $CeCl_3·7H_2O$, $NaBH_4$, EtOH, –78 °C, 1.5 h, 97%; (e) TBSOTf, 2,6-lutidine, THF, 0 °C, 20 min, then EtOH; (f) $(CO_2H)_2$, wet THF, rt, 20 h, 74% over 2 steps.

Separate investigation of the π-facial selectivities of each of the two coupling partners in boron-, tin- and titanium-mediated *syn*-aldol additions showed that with boron and tin(II) enolates, a *si*-face attack on the aldehyde was preferred for both the aldehyde and the enolate, suggesting matched double diastereodifferentiation. *Paterson* and co-workers therefore proceeded to the $^nBu_2BOTf$-mediated aldol addition of ketone **6** to aldehyde **9**, which afforded the desired hydroxy ketone **10** in 69% yield and 82% diastereomeric excess (Scheme 18).

The C16 stereogenic center was introduced by hydroxyl-directed hydrogenation of alkene **10** using *Wilkinson*'s catalyst. Finally, removal of the acetonide and formation of the cyclic hemiacetal was accomplished under mild acidic conditions to afford bafilomycin A_1's C13–C25 segment.

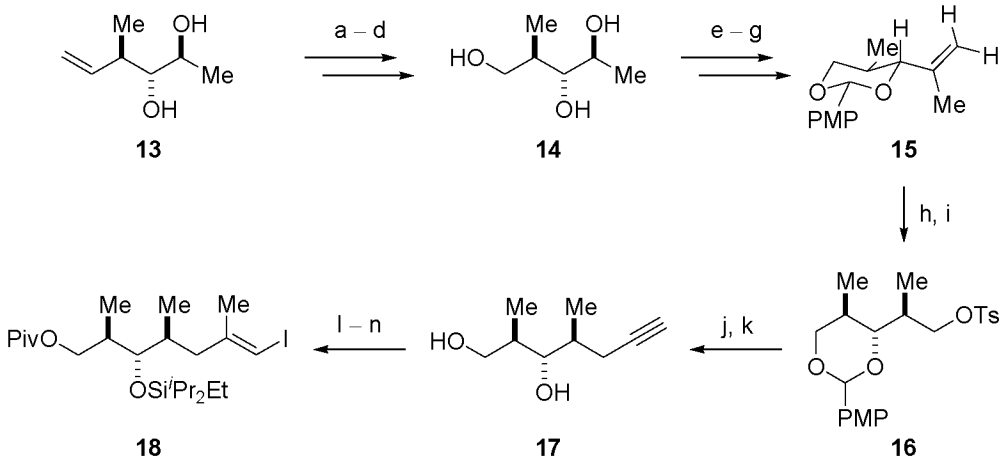


Scheme 18: (a) **6**, Bu_2OTf, $^iPr_2NEt$, CH_2Cl_2, –78 °C, then **9**, –78 °C to –25 °C, 16 h, 69%, 82% de; (b) H_2 (15 bar), PhH, $(Ph_3P)_3RhCl$, 16 h, 96%; (c) 40% aq. HF, MeCN, H_2O, rt, 1 h, 83%.

1.4.4 The Aldol Approach by *Toshima*

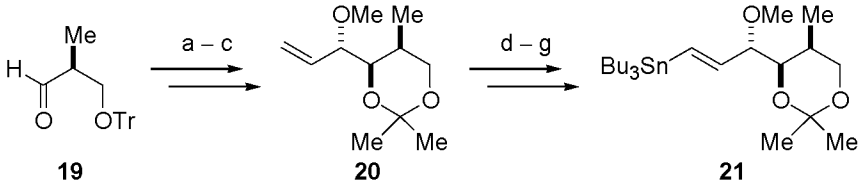
Toshima and co-workers' highly convergent total synthesis of bafilomycin A_1 was based upon efficient fragment connection by a *Stille* cross-coupling reaction and a subsequent diastereoselective aldol addition.[22] During the assembly of the three key intermediates, each of which was chiral pool derived, several interesting observations were made:

- En route to vinyl iodide **18** (Scheme 19), the observed complete stereoselectivity in the hydroboration reaction with dicyclohexylborane was rationalized by the substrate adopting exclusively conformation **15**, in which only the *re*-face of the olefin was accessible.
- Prior deprotection of the diol was crucial for high yields in the carbozirconation reaction of **17**.
- The scarcely used ethyldiisopropylsilyl ether protective group in **18** was chosen because it offered sufficient stability in the subsequent reactions while still allowing for removal under mild acidic conditions.



Scheme 19: (a) Ac_2O, DMAP, EtOAc, rt, 1 h, quant.; (b) O_3, MeOH, CH_2Cl_2, –78 °C, then Me_2S; (c) $NaBH_4$, MeOH, CH_2Cl_2, rt, 30 min; (d) NaOMe, MeOH, rt, 3 h, 94% over 3 steps; (e) $(MeO)_2CHC_6H_4OMe$, CSA, DMF, rt, 90 min, 94%; (f) PCC, 3 Å MS, CH_2Cl_2, rt, 90 min, quant.; (g) $Ph_3P{=}CH_2$, PhH, rt, 1 h, 95%; (h) $BH_3{\cdot}SMe_2$, C_6H_{10}, THF, rt, 1 h, then aq. NaOH, H_2O_2, 88%; (i) TsCl, py, rt, 90 min, quant.; (j) lithium acetylide, DMSO, rt, 90 min, 66%; (k) 80% AcOH in H_2O, 40 °C, 13 h , 77%; (l) Cp_2ZrCl_2, $AlMe_3$, I_2, DCE, rt, 13 h, 82%; (m) PivCl, NEt_3, CH_2Cl_2, rt, 14 h, 97%; (n) ^{i}Pr$_2$EtSiOTf, 2,6-lutidine, CH_2Cl_2, rt, 4 h, quant..

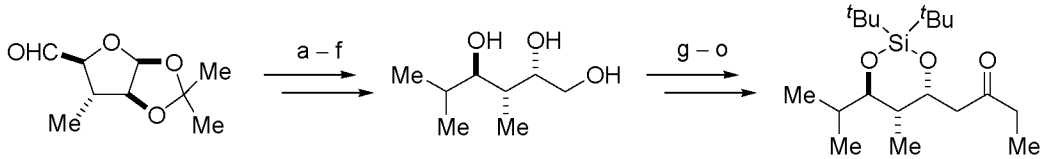
- During the synthesis of the C12–C17 segment **21** (Scheme 20), the addition of an in situ generated γ-methoxyallylchromium reagent to aldehyde **19** proceeded in good stereoselectivity.



19 **20** **21**

Scheme 20: (a) $CrCl_2$, CH_2=CHCH$(OMe)_2$, TMSI, THF, –42 °C, 16 h, 62%, dr 100:11:5; (b) 1% HCl in MeOH, rt, 30 min, quant.; (c) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt, 16 h; (d) OsO_4, NMO, acetone, H_2O, rt, 16 h; (e) $NaIO_4$, THF, H_2O, rt, 30 min; (f) $CrCl_2$, CHI_3, THF, rt, 14 h, 38% over 4 steps; (g) Bu_3SnCl, ^{n}BuLi, THF, –78 °C, 1 h, 69%.

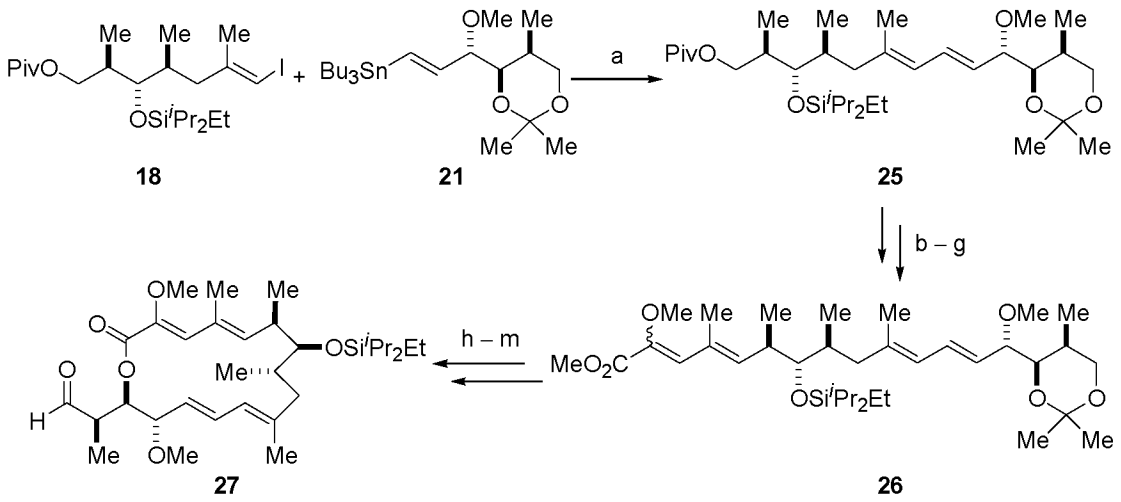
- The cyclic protection of the diol moiety in **24** (Scheme 21) was chosen in view of the imminent final aldol coupling and the results obtained by *Evans*[21] and *Paterson*[25] in their respective aldol reactions.



22 **23** **24**

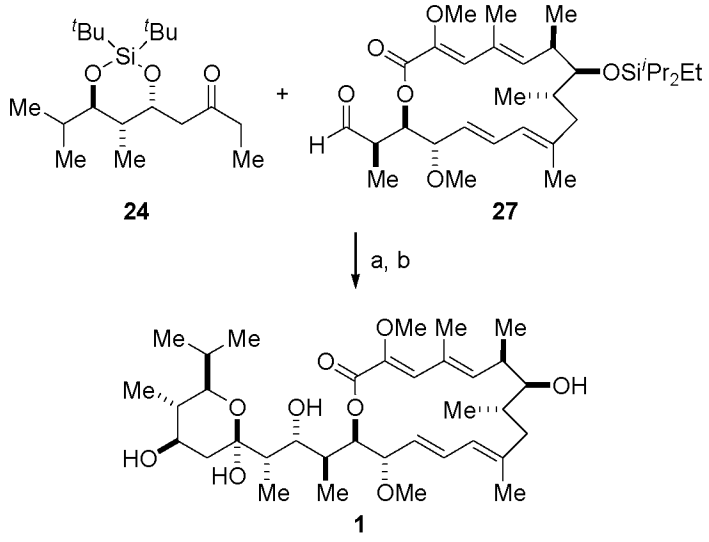
Scheme 21: (a) MeMgI, Et_2O, rt, 30 min, 94%; (b) PCC, 3 Å MS, CH_2Cl_2, rt, 30 min, 94%; (c) Ph_3P=CH_2, PhH, rt, 30 min, 81%; (d) H_2, Raney-Ni (W4), dioxane, rt, 24 h, 92%; (e) 50% AcOH in H_2O, 80 °C, 2 h, 93%; (f) $LiAlH_4$, THF, 60 °C, 16 h, 77%; (g) CDI, CH_2Cl_2, rt, 2.5 h, 85%; (h) TBSCl, imidazole, DMF 40 °C, 16 h, 87%; (i) 1 M aq. NaOH, MeOH, rt, 16 h; (j) TsCl, py, rt, 16 h; (k) NaOMe, MeOH, CH_3Cl, rt, 16 h, 46% over 3 steps; (l) 2-ethyl-1,3-dithiane, ^{n}BuLi, THF, –20 °C, 1 h; (m) TBAF, THF, rt, 2.5 h, 97% over 2 steps; (n) ^{t}Bu$_2$Si$(OTf)_2$, DMF, rt, 2 h, 95%; (o) $CaCO_3$, MeI, MeCN, H_2O, rt, 6 h, 69%.

With all three key fragments in hand, *Toshima* and co-workers focused on the cross-coupling reaction between vinyl iodide **18** and vinyl stannane **21** (Scheme 22). Several palladium catalysts were tested under *Stille* conditions, and $PdCl_2$(dppf) was found to give the highest yield. Interestingly, the ^{1}H NMR of diene **25** showed an inseparable 3:1 mixture of isomers. Since this phenomenon disappeared after the macrolactonization step, it was assumed to be a matter of conformational isomers.



Scheme 22: (a) $PdCl_2(dppf)$, DMF, 50 °C, 15 h, 60%; (b) MeLi, Et_2O, rt, 30 min, 79%; (c) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C, 20 min; (d) $Ph_3P{=}C(Me)CO_2Et$, PhMe, 100 °C, 14 h, 98% over 2 steps; (e) DIBAL-H, PhMe, –78 °C, 5 min, 97%; (f) MnO_2, CH_2Cl_2, rt, 2 h, quant.; (g) $(EtO)_2P(O)CH(OMe)CO_2Me$, NaHMDS, THF, rt, 30 min, 89%; (h) PPTS, MeOH, rt, 30 min, 96%; (i) MTrCl, NEt_3, DMAP, CH_2Cl_2, rt, 3.5 h, quant.; (j) 1 M aq. KOH, dioxane, 80 °C, 2 h, 64%; (k) 2,4,6-trichlorobenzoyl chloride, NEt_3, THF, DMAP, PhMe (0.002 M), 110 °C, 16 h, 42%; (l) PPTS, MeOH, rt, 14 h, 80%; (m) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, –78 °C, 20 min, 74%.

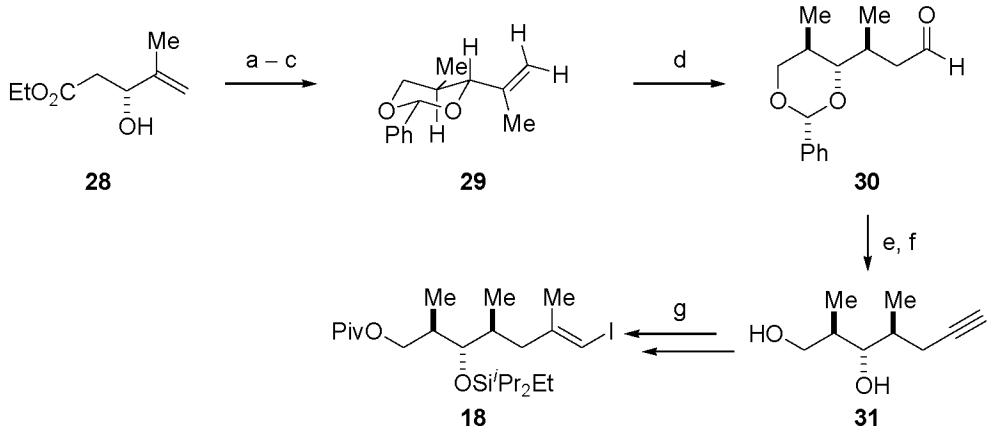
For the final key bond formation between ketone **24** and aldehyde **27**, *Evans*'s recently disclosed *syn*-selective aldol reaction[21] led to optimal results with regard to yield and selectivity (Scheme 23). The subsequent global deprotection using TBAF in THF/AcOH afforded bafilomycin A_1 (**1**) in 26% yield from the macrocyclic aldehyde **27**.



Scheme 23: (a) $PhBCl_2$, ^{i}Pr$_2$NEt, CH_2Cl_2, 2.5 h, 58%; (b) TBAF, AcOH, THF, 60 °C, 12 h, 45%.

1.4.5 *Breit*'s Hydroformylation Approach to the C5–C11 Fragment

Breit and co-workers applied their recently developed diastereoselective hydroformylation of acyclic olefins to the formal synthesis of bafilomycin A_1's C5–C11 fragment (Scheme 24).[26] Hydroformylation of substrate **29** afforded aldehyde **30** in high yield and as a single diastereomer. This observation was in agreement with 2D-NOESY experiments and MACROMODEL/MM3 calculations that revealed a strong preference for **29** to adopt the depicted chair-like conformation with the external olefin oriented in a single well-defined position and the olefin's *re*-face efficiently blocked by the equatorial methyl group in the back.

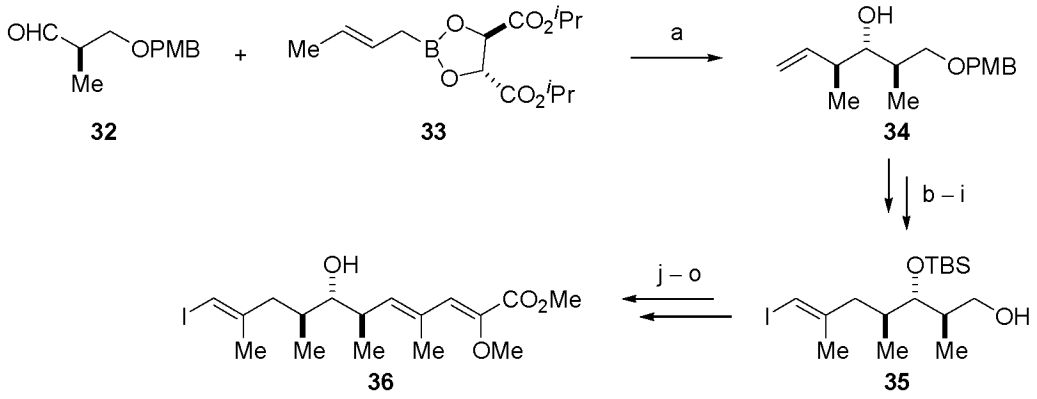


Scheme 24: (a) LDA, MeI, HMPA, THF, –78 °C; (b) $LiAlH_4$, Et_2O, 0 °C, 83%; (c) $PhCH(OMe)_2$, TsOH, CH_2Cl_2, rt, 86%; (d) 0.7 mol % [$Rh(CO)_2$acac/4 $P(OPh)_3$], PhMe, 70 °C, 20 bar (H_2/CO 1:1), 36 h, 80%; (e) CBr_4, PPh_3, then ^{n}BuLi, THF, 64%; (f) 80% aq. AcOH, THF, 50 °C, 70%; (g) see ref. 22.

1.4.6 The Total Synthesis by *Roush*

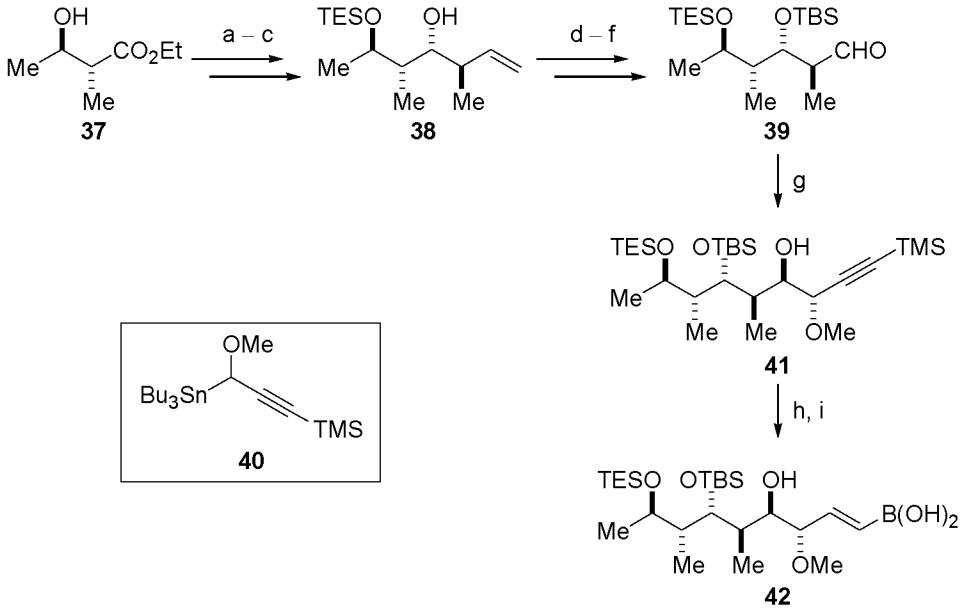
The key bond constructions of *Roush*'s total synthesis of bafilomycin A_1 involved *E*-selective double asymmetric crotylborations in both the matched and mismatched approach, a *Suzuki* cross-coupling, and a *Mukaiyama*-type aldol reaction.[23]

Selective installation of the C1–C11 fragment's *anti–anti* stereotriad by crotylboration was achieved in good 85:15 diastereomeric ratio, given that it was a mismatched case (Scheme 25). In accord with *Toshima*'s observations,[22] the introduction of the trisubstituted vinyl iodide by *Negishi*'s carbozirconation methodology was only successful if the substrate contained at least one hydroxy group.



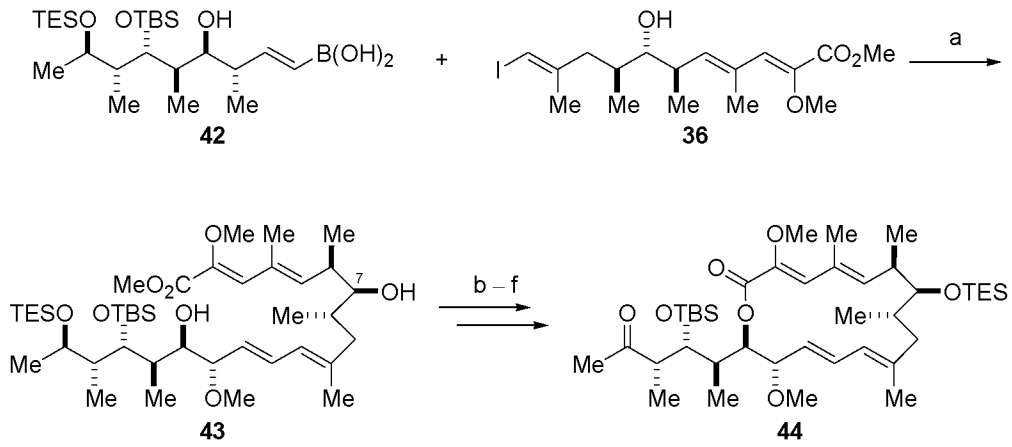
Scheme 25: (a) 4 Å MS, PhMe, –78 °C, 78%, dr 85:15; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, –50 °C, 99%; (c) catecholborane, $(Ph_3P)_3RhCl$ (2 mol %), THF, –5 °C, then MeOH, H_2O_2, aq. NaOH, rt, 87%; (d) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C, 99%; (e) CBr_4, PPh_3, CH_2Cl_2, 89%; (f) ^{n}BuLi, THF, –78 °C, 99%; (g) DDQ, CH_2Cl_2, pH 7 buffer, 0 °C, 96%; (h) Cp_2ZrCl_2, $AlMe_3$, DCE, 60 °C; (i) I_2, THF, 65% over 2 steps; (j) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C; (k) $Ph_3P{=}CMeCO_2Me$, PhMe, 60 °C, 90% over 2 steps; (l) DIBAL-H, THF, –78 °C, 99%; (m) MnO_2, CH_2Cl_2, rt, 97% over 2 steps; (n) KHMDS, THF, $(^iPrO)_2P(O)CH(OMe)CO_2Me$, 18-crown-6, 0 °C to rt, 85%; (o) TBAF, THF, rt, 82%.

Roush's second generation approach to vinylboronic acid **41** involved a matched double asymmetric crotylboration reaction and the addition of a γ-methoxyallenyltin reagent (Scheme 26). Propargylstannane **42** was prepared as a stable precursor, which could then be transformed to the corresponding allenylstannane in situ and added to aldehyde **39**. Given the unsuccessful attempts at developing an enantioselective route to **42**, *Roush* and co-workers resorted to a kinetic resolution under the reaction conditions. In the event, treatment of aldehyde **39** with $BuSnCl_3$ and five equivalents of **42** not only afforded homopropargylic alcohol **40** in high yield but also with an impressive diastereomeric ratio of 20:1.



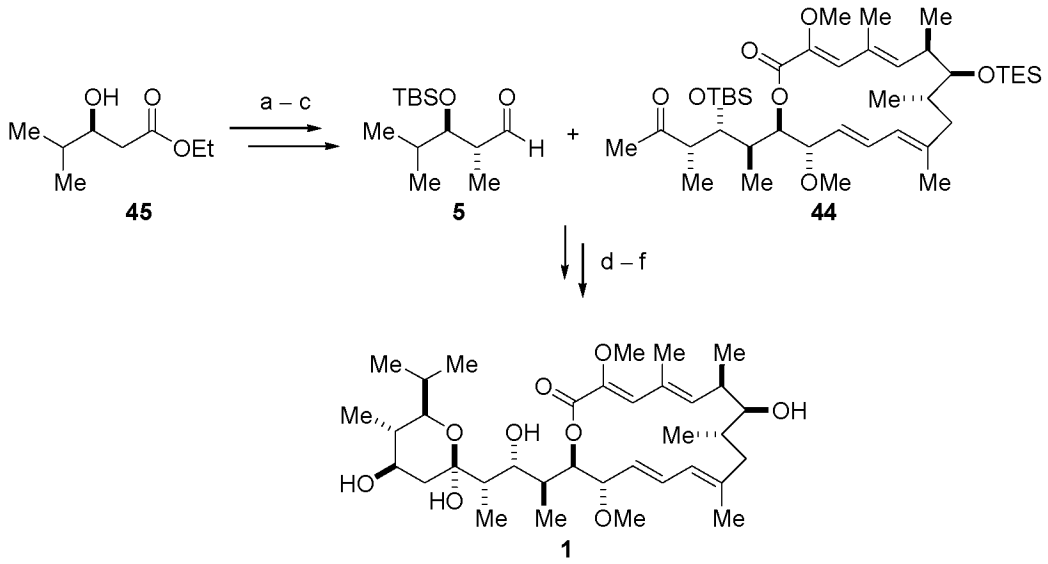
Scheme 26: (a) TESCl, py, CH_2Cl_2, rt, 1 h, 95%; (b) DIBAL-H, CH_2Cl_2, –78 °C, 1 h; (c) *ent*-**33**, PhMe, –78 °C, 4 h, 70% over 2 steps; (d) TBSOTf, $^iPr_2NEt$, DMF, –20 °C, 14 h, 93%; (e) OsO_4 (cat.), NMO, THF, acetone, pH 7 buffer, rt, 14 h; (f) $NaIO_4$, THF, pH 7 buffer, rt, 3 h, 98% over 2 steps; (g) **40** (5.0 equiv), $BuSnCl_3$, hexane, –40 °C to –45 °C, 2 h, 84%, dr 20:1; (h) Amberlyst A-26, MeOH, rt, 16 h, 93%; (i) catecholborane, 9-BBN (cat.), THF, 60 °C, then pH 7 buffer, rt, 71%.

After failure of the *Horner–Wadsworth–Emmons* and *Julia* olefination protocols, a *Suzuki* cross-coupling reaction was envisioned for the upcoming C11–C12 bond formation. The key fragments **36** and **42** were thus treated with $Pd(PPh_3)_4$ and TlOH according to *Kishi*'s modification of the *Suzuki* reaction (Scheme 27). Saponification of the methyl ester set the stage for the macrolactonization step. Once again, *Yamaguchi* conditions showed the best results, but a large excess of acid chloride and base was necessary to prevent formation of the symmetrical anhydride. Furthermore, it was crucial for successful cyclization that the C7 hydroxy group be unprotected. Molecular models showed that a protective group at that position led to strong interactions with the C6 methyl substituent or the C9 methylene, thereby causing the *seco*-acid to adopt a different conformation, which proved unsuitable for macrolactonization.



Scheme 27: (a) 20 mol % $Pd(PPh_3)_4$, aq. TlOH, THF, rt, 65%; (b) KOH, dioxane, 80 °C; (c) 2,4,6-trichlorobenzoyl chloride, $^iPr_2NEt$, THF, then DMAP, PhMe, Δ, 52% over 2 steps; (d) TESOTf, 2,6-lutidine, CH_2Cl_2, –50 °C, 85%; (e) TFA, THF, H_2O, 5 °C, 90%; (f) DMP, py, CH_2Cl_2, 0 °C, 98%.

While chlorotitanium enolates gave the best results in *Roush*'s model studies, they failed to provide useful levels of stereoselectivity for the coupling of **5** and **44**. A *Mukaiyama* aldol reaction, which had shown excellent *Felkin* selectivity for reactions of 2,3-*anti*-*β*-hydroxy aldehydes,[32] finally afforded the desired product in > 95:5 diastereomeric ratio (Scheme 28).



Scheme 28: (a) LDA, THF, rt, then MeI, HMPA, rt, then TBSOTf, 70%; (b) DIBAL-H, THF, –78 °C; (c) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C, 83% over 2 steps; (d) **44**,

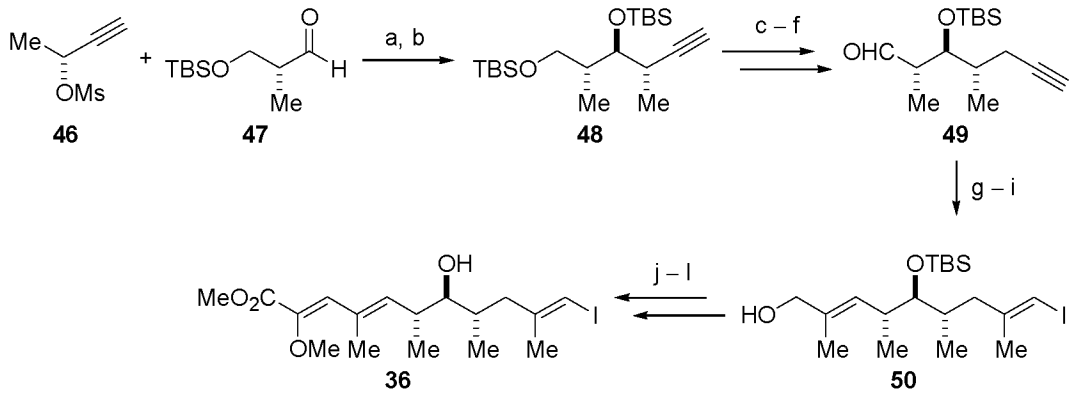
[32] (a) D. A. Evans, M. J. Dart, J. L. Duffy, M. G. Yang, *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343; (b) I. Paterson, J. G. Cumming, J. D. Smith, R. A. Ward, *Tetrahedron Lett.* **1994**, *35*, 441–444; (c) K. Yasue, W. R. Roush, unpublished results.

TMSCl, NEt_3, LHMDS, CH_2Cl_2, –78 °C; (e) **5**, $BF_3{\cdot}OEt_2$, –78 °C, 85% over 2 steps; (f) TAS-F, DMF, H_2O, rt, 93%.

1.4.7 *Marshall*'s Total Synthesis of Bafilomycin V_1

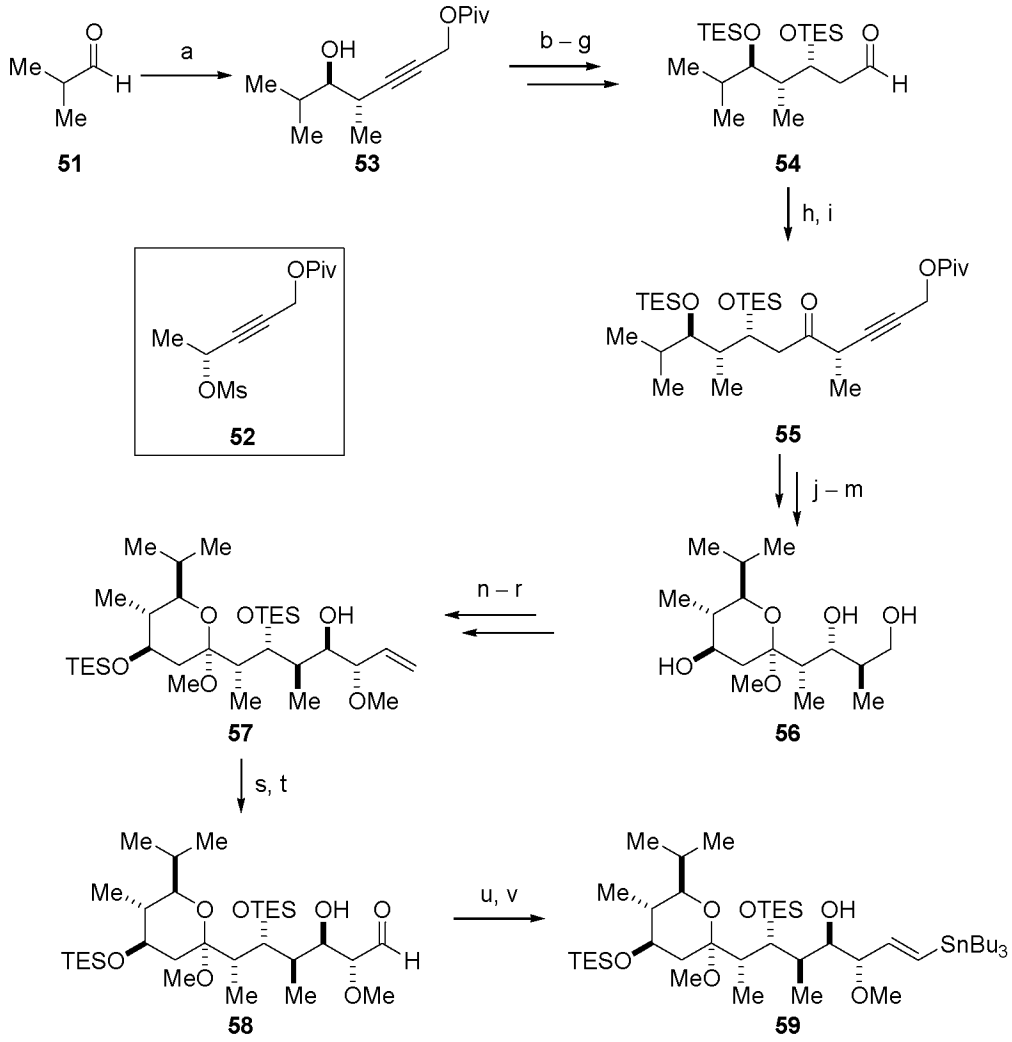
The attempted synthesis of bafilomycin A_1 by *Marshall* and co-workers failed at the penultimate step after assembly of the full carbon skeleton.[27] They then turned their attention to the *semi*-synthetic derivative bafilomycin V_1 (**61**), which was first described by *Farina* and co-workers in the course of structure–activity relationship studies of bafilomycin analogs.[19b] The open chain *seco*-ester bafilomycin V_1 was originally prepared by methanolysis of bafilomycin C_2 and was found to inhibit vacuolar ATPases, albeit to lesser extent than bafilomycin A_1.

The construction of the key building blocks featured several additions of enantioenriched allenylzinc reagents to aldehydes, a method recently developed in the *Marshall* group.[33] The chiral allenylzinc reagents were prepared in situ by treatment of the corresponding propargylic mesylates with a palladium(0)-phosphine catalyst and diethylzinc, and then applied to the synthesis of the C1–C11 vinyl iodide **36** (Scheme 29) and the C12–C25 fragment **59** (Scheme 30).



Scheme 29: (a) $Pd(OAc)_2$, PPh_3 (5 mol %), Et_2Zn, THF, –20 °C, 70%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 96%; (c) Cy_2BH, DME, 0 °C to rt, then H_2O_2, NaOH, 81%; (d) $(EtO)_2P(O)CHN_2$, KO^{t}Bu, THF, –78 °C to 0 °C, 96%; (e) PPTS, MeOH, rt, 79%; (f) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C, 91%; (g) $Ph_3P{=}C(Me)CO_2Et$, PhMe, 100 °C, 92%; (h) DIBAL-H, CH_2Cl_2, –78 °C, 92%; (i) Cp_2ZrCl_2, $AlMe_3$, DCE, 50 °C, then I_2, THF, –30 °C to 0 °C, 65%; (j) MnO_2, CH_2Cl_2, rt, 95%; (k) $(^iPrO)_2P(O)CH(OMe)CO_2Me$, KHMDS, 18-crown-6 (cat.), THF, 0 °C to rt, 89%; (l) TBAF, THF, rt, 81%.

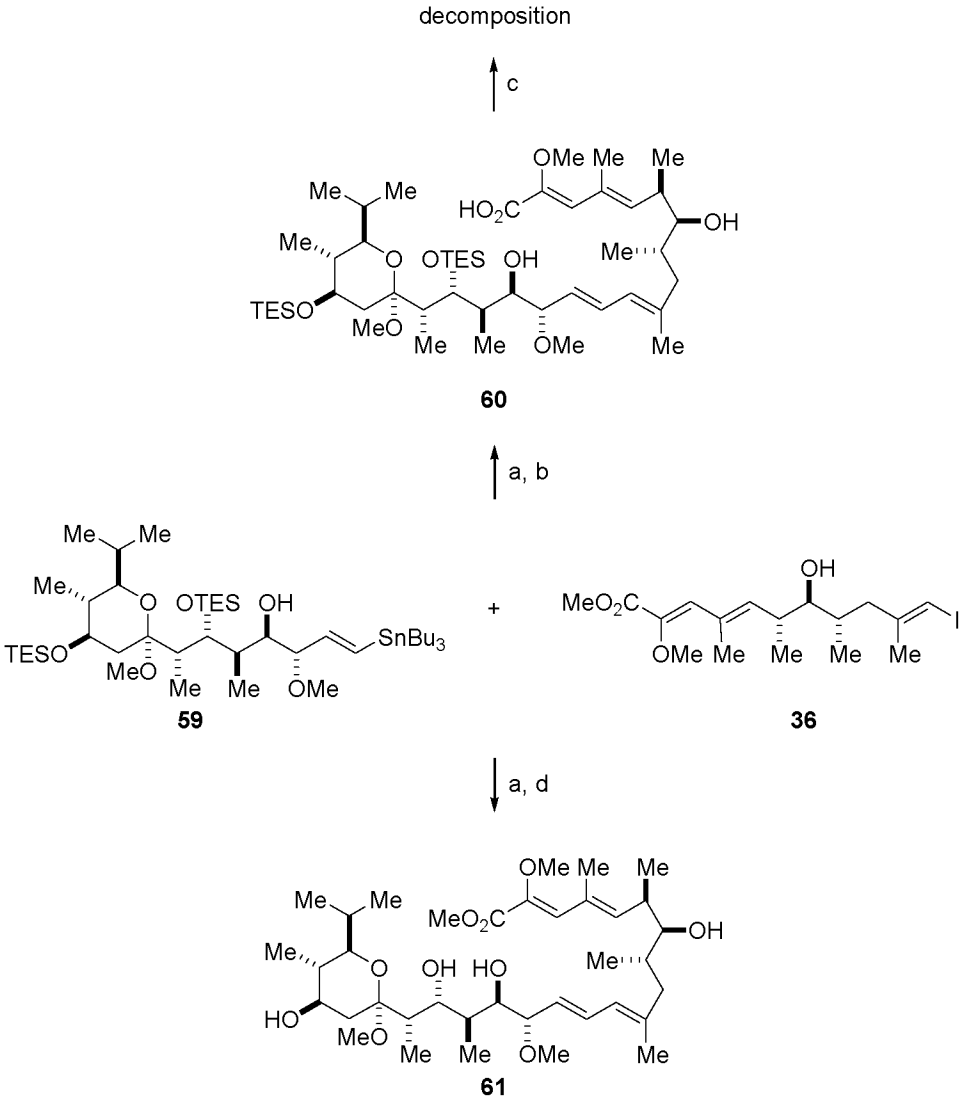
[33] J. A. Marshall, N. D. Adams, *J. Org. Chem.* **1999**, *64*, 5201–5204.



Scheme 30: (a) **52**, $Pd(OAc)_2$, PPh_3 (5 mol %), Et_2Zn, THF, –78 °C to –20 °C, 76%; (b) $LiAlH_4$, THF, 55 °C, 82%; (c) (+)-DIPT, TBHP, $Ti(O^iPr)_4$, CH_2Cl_2, –40 °C, 86%; (d) Red-Al, THF, rt, 93%; (e) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 99%; (f) AcOH, H_2O, THF, rt, 82%; (g) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C, 99%; (h) **52**, $Pd(OAc)_2$, PPh_3 (5 mol %), Et_2Zn, THF, –78 °C to –20 °C, 70%; (i) DMP, $NaHCO_3$, CH_2Cl_2; (j) PPTS, MeOH, 84% over 2 steps; (k) Red-Al, THF, 0 °C to rt; (l) (+)-DIPT, TBHP, $Ti(O^iPr)_4$, –20 °C, 80% over 2 steps; (m) $(LiMe)_2$·CuCN, THF, 0 °C to rt, 90%; (n) PivCl, NEt_3, DMAP, CH_2Cl_2, 0 °C, 87%; (o) TESCl, imidazole, DMF, rt, 94%; (p) DIBAL-H, CH_2Cl_2, –78 °C, 92%; (q) DMP, $NaHCO_3$, CH_2Cl_2; (r) $Me_2C(OMe)_2$, TMSI, $CrCl_2$, THF, –78 °C to 0 °C, 61% over 2 steps; (s) OsO_4 (5 mol %), NMO, THF, pH 7 buffer, 85%; (t) $NaIO_4$, THF, H_2O, 99%; (u) $(MeO)_2P(O)C(N_2)C(O)Me$, K_2CO_3, MeOH, 0 °C to rt, 63%; (v) Bu_3SnH, $Pd(PPh_3)_2Cl_2$, CH_2Cl_2, 70%.

After the successful *Stille* cross-coupling between vinylstannane **59** and vinyl iodide **36**, the completion of the bafilomycin A_1 synthesis seemed close (Scheme 31). But the *Yamaguchi* lactonization of intermediate **60** failed. A rationale was found in the instability of the C18–C25 pyranoside moiety under the reaction conditions, since cyclization of a similar

seco-acid had been effective in the *Evans* synthesis.[21] An attempt to invert the two coupling steps was doomed because the intermolecular esterification failed, too. With bafilomycin A_1 apparently out of reach, *Marshall* and co-workers completed the total synthesis of the vacuolar ATPase-inhibitor bafilomycin V_1 (**61**).

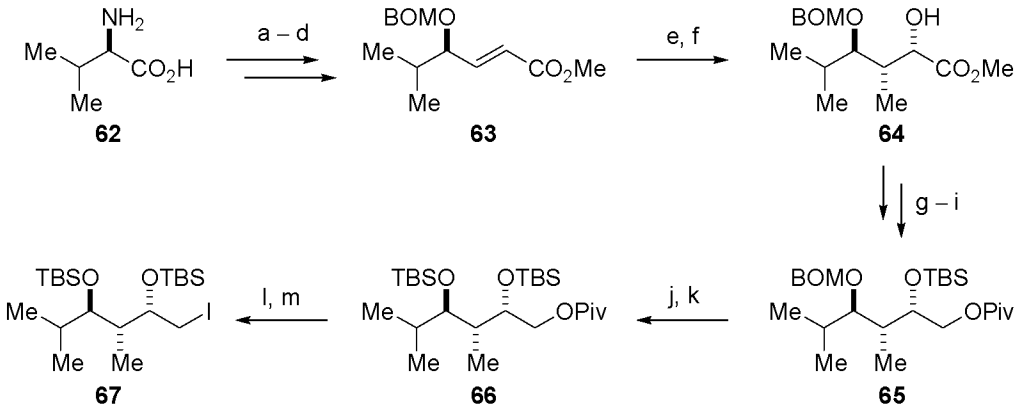


Scheme 31: (a) $Pd_2(dba)_3$, $AsPh_3$, LiCl, NMP (0.08 M), rt, 76%; (b) KOTMS, THF, rt, quant. (crude); (c) 2,4,6-trichlorobenzoyl chloride, $^iPr_2NEt$, THF (0.01 M), rt, then DMAP, PhMe, 110 °C; (d) TBAF, AcOH, THF, rt, 80%.

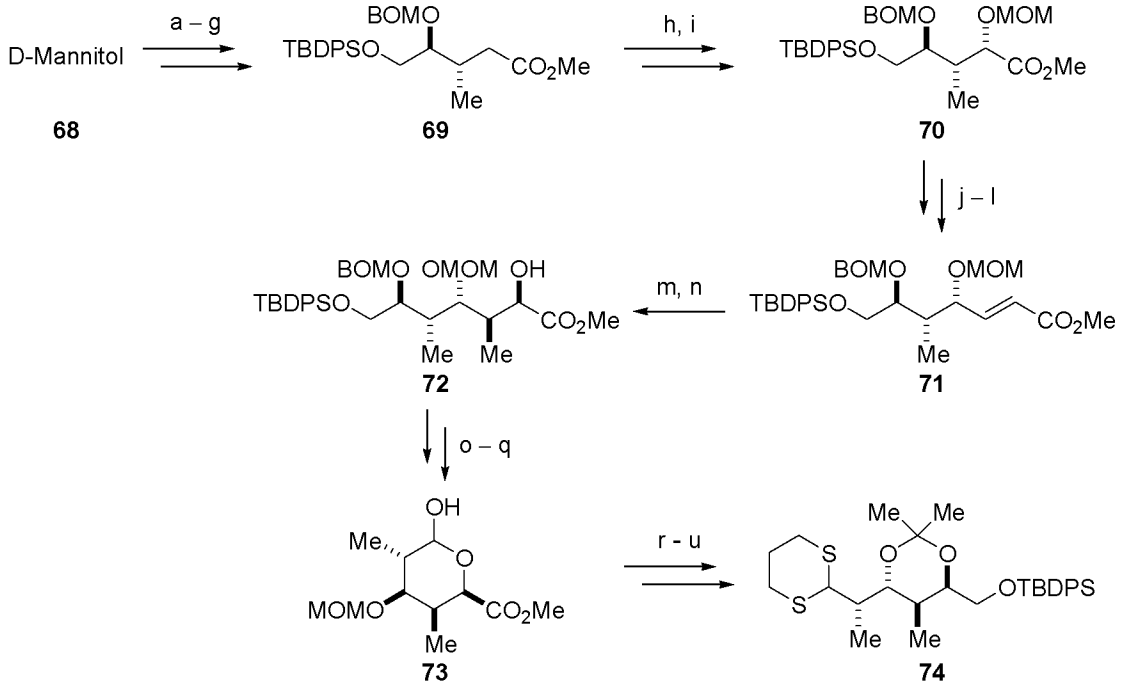
1.4.8 *Hanessian*'s Total Synthesis of Bafilomycin A_1

Hanessian's synthesis started from D-valine (**62**) and D-mannitol (**68**) as sources of homochirality.[24] The construction of the propionate units relied on the *anti*-selective 1,4-

addition to acyclic substrates and the *syn*-selective hydroxylation that had been recently described by the same authors (Schemes 32–34).

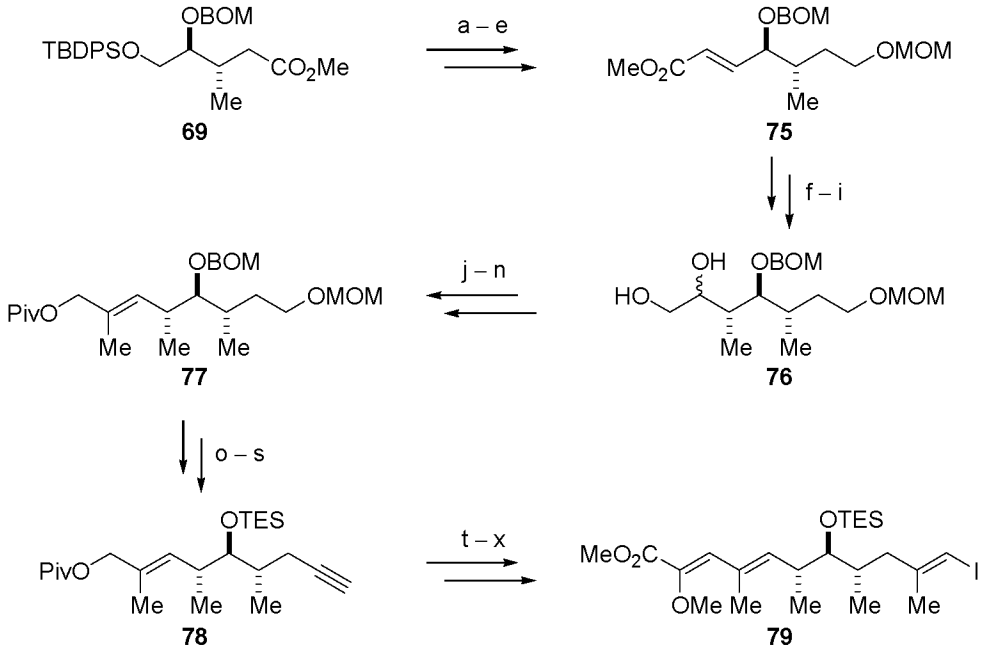


Scheme 32: (a) $NaNO_2$, H_2SO_4, then CH_2N_2, 53%; (b) BOMCl, $^iPr_2NEt$, CH_2Cl_2, 85%; (c) DIBAL-H, PhMe, 87%; (d) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C, then $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 86%; (e) Me_2CuLi, TMSCl, THF, –78 °C, 90%; (f) KHMDS, THF, then *Davis*' oxaziridine, 80%; (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 94%; (h) DIBAL-H, PhMe, 86%; (i) PivCl, py, 88%; (j) H_2, $Pd(OH)_2$/C, MeOH; (k) TBSOTf, 2,6-lutidine, CH_2Cl_2, 95% over 2 steps; (l) DIBAL-H, PhMe, 91%; (m) I_2, imidazole, PPh_3, PhMe, 84%.



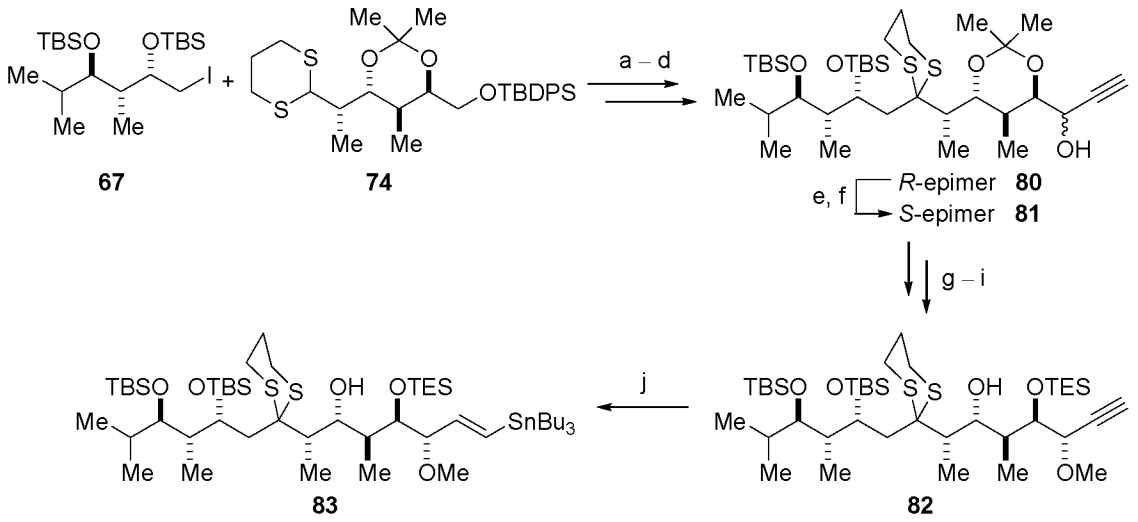
Scheme 33: (a) $Me_2C(OMe)_2$, TsOH, DMF, rt, 80%; (b) $NaIO_4$, $NaHCO_3$, H_2O, rt; (c) $(EtO)_2PCH_2CO_2Et$, K_2CO_3, H_2O, rt, 86% over 2 steps; (d) AcOH, H_2O, rt; (e) TBDPSCl, DMAP, imidazole, DMF, rt, 73% over 2 steps; (f) BOMCl, $^iPr_2NH$, CH_2Cl_2, rt, 94%; (g) Me_2CuLi, TMSCl, THF, –78 °C, 95%; (h) KHMDS, THF, then *Davis*' oxaziridine, –78 °C, 90%; (i) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 80%; (j) DIBAL-H, THF, –78 °C to 0 °C, 97%; (k) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C; (l) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 96% over 2 steps;

(m) Me_2CuLi, TMSCl, THF, –78 °C, 85%; (n) KHMDS, THF, then *Davis*' oxaziridine, –78 °C, 75%; (o) TBAF, AcOH, THF, rt, 95%; (p) $Pd(OH)_2/C$, MeOH, H_2, rt; (q) $NaIO_4$, MeOH, H_2O; (r) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, 0 °C, 65% over 3 steps; (s) $NaBH_4$, THF, H_2O, rt, 95%; (t) TBDPSCl, imidazole, THF, rt, 88%; (u) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt, 95%.



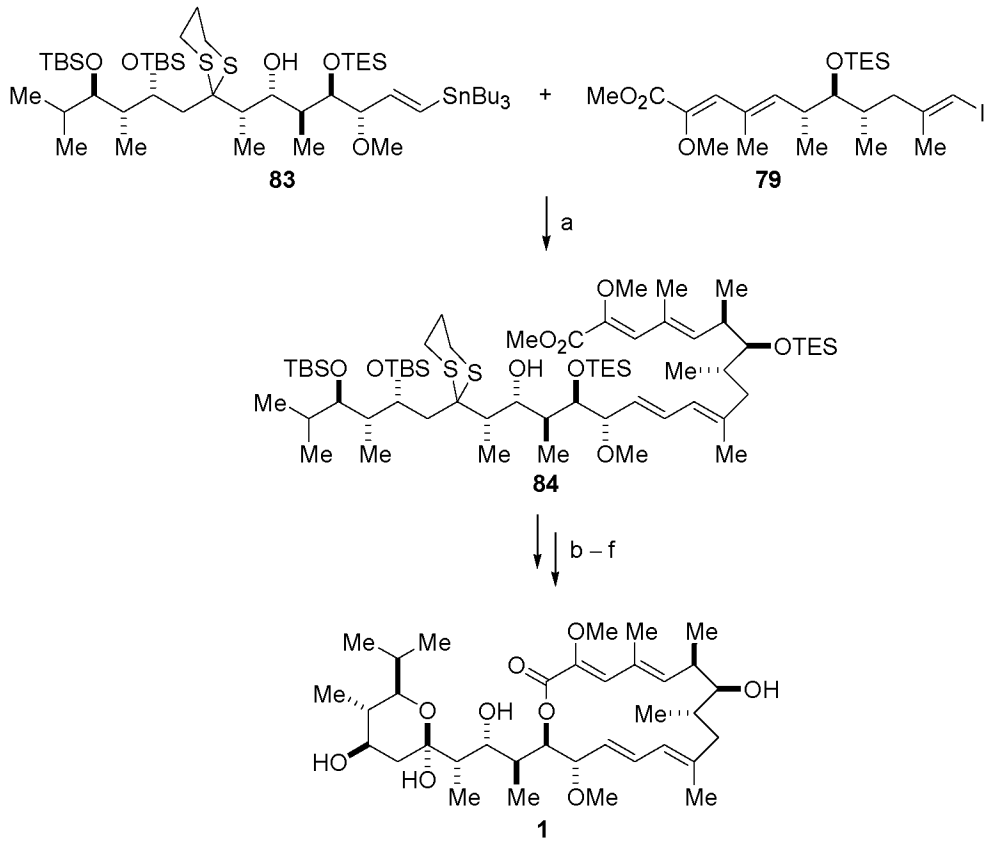
Scheme 34: (a) DIBAL-H, PhMe, –78 °C, 89%; (b) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 92%; (c) TBAF, THF, 92%; (d) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C; (e) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 87% over 2 steps; (f) Me_2CuLi, TMSCl, THF, –78 °C, 90%; (g) KHMDS, *Davis*' oxaziridine, THF, 84%; (h) $LiBH_4$, MeOH, 92%; (i) H_2, $Pd(OH)_2/C$, MeOH, 90%; (j) $NaIO_4$, wet CH_2Cl_2; (k) $Ph_3P{=}CMeCO_2Et$, PhH, Δ, 85% over 2 steps; (l) TESCl, 2,6-lutidine, THF, 95%; (m) DIBAL-H, PhMe, –78 °C, 89%; (n) PivCl, py, CH_2Cl_2, 95%; (o) *B*-bromocatecholborane, CH_2Cl_2, –78 °C, 90%; (p) TESOTf, 2,6-lutidine, CH_2Cl_2, 95%; (q) PPTS, CH_2Cl_2, MeOH, 93%; (r) DMP, CH_2Cl_2, 93%; (s) dimethyl (1-diazo-2-oxopropyl)phosphonate, K_2CO_3, MeOH, 91%; (t) Cp_2ZrCl_2, $AlMe_3$, H_2O (cat.), –30 °C, then I_2, 78%; (u) DIBAL-H, PhMe, –78 °C, 92%; (v) MnO_2, CH_2Cl_2, 90%; (w) methyl methoxyacetate, LHMDS, THF, 86%; (x) MsCl, py, DBU, 80%.

The *C*-alkylation of dithiane **74** with iodide **67** under standard conditions was high yielding (Scheme 35). As an additional advantage, the coupling product already bore the later on important dithiane-masking of the C19 ketone. The completion of vinyl stannane **83** set the stage for the key fragment coupling between the C1–C11 and the C12–C25 subunits.



Scheme 35: (a) **74**, ^{t}BuLi, THF, HMPA, –78 °C, then **67**, 84%; (b) TBAF, AcOH, THF, 91%; (c) DMSO, NEt_3, SO_3·py, PhMe, rt, 89%; (d) ethynylmagnesium bromide, THF, –10 °C, 89%; (e) DMP, CH_2Cl_2, 92%; (f) Super-Hydride, CH_2Cl_2, –78 °C, 93%; (g) KO^{t}Bu, MeI, THF, 86%; (h) MeOH, CSA, 86% (based on 40% recovered starting material); (i) TESCl, DMAP, THF, DMF, 89%; (j) Bu_3SnH, Ph_2PdCl_2 (cat.), THF, 87%.

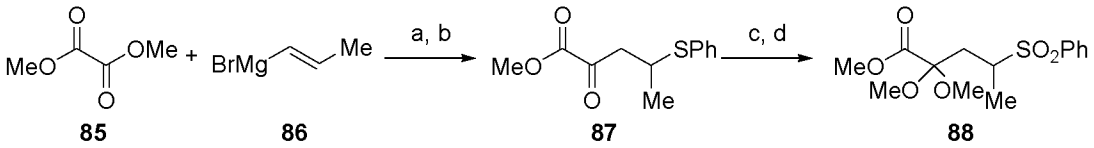
Hanessian and co-workers envisioned a *Stille* cross-coupling reaction between the fully elaborated vinyl iodide **79** and vinyl stannane **83**, bearing the potentially problematic dithiane group (Scheme 36). Preliminary studies were discouraging, because the use of the standard reagents did not afford any of the desired product and in some cases even led to decomposition. It was only when *Hünig*'s base was added to the reaction that the authors were able to isolate some coupling product, albeit in low yield. The real breakthrough was achieved when Pd(dppf)Cl_2 was used in combination with *Hünig*'s base and $AsPh_3$, furnishing **84** in 60% yield. The synthesis was completed by macrolactonization according to the *Keck* protocol and global deprotection.



Scheme 36: (a) $Pd(dppf)Cl_2$, $^iPr_2NEt$, $AsPh_3$, THF, DMF, 50 °C, 60%; (b) TBAF, AcOH, THF, 87%; (c) KOH, dioxane, 80 °C, 88%; (d) EDC, DMAP, CH_2Cl_2, Δ, 65%; (e) TsOH, MeOH, 86%; (f) $HgCl_2$, $CaCO_3$, CH_3CN, H_2O, 85%.

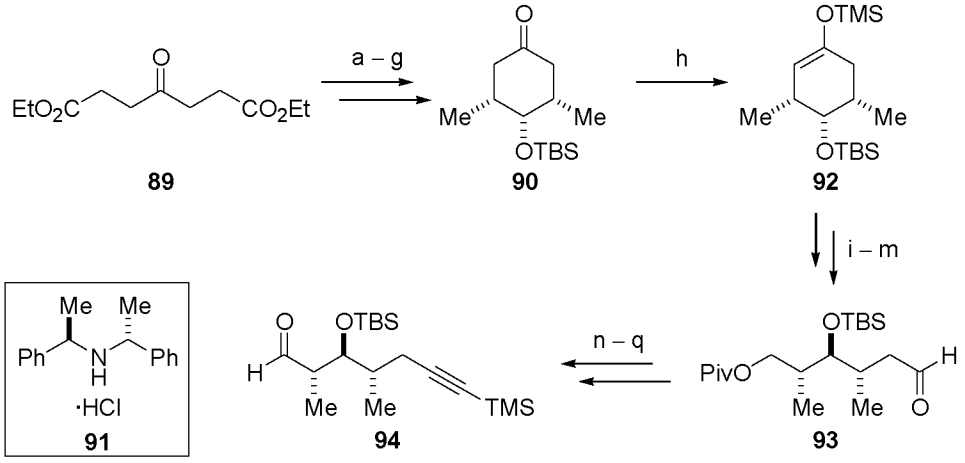
1.4.9 *Prunet*'s Synthesis of the C1–C11 and C12–C25 Fragments

Prunet and co-workers reported the synthesis of two advanced intermediates under way to bafilomycin A_1.[27] A classical *Julia* olefination between racemic sulfone **88** (Scheme 37) and chiral aldehyde **94** was envisioned for the construction of the C1–C11 subunit.



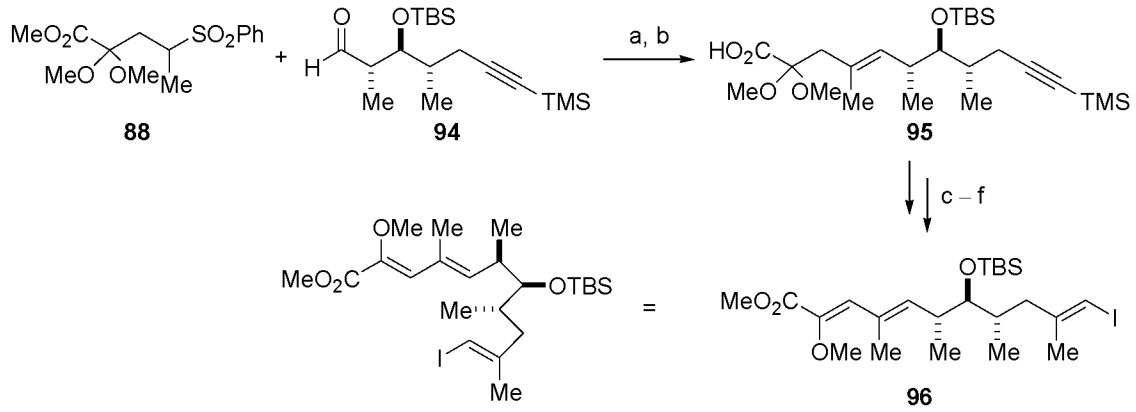
Scheme 37: (a) Et_2O, –40 °C; (b) PhSH, NEt_3, CH_2Cl_2, 0 °C to rt; (c) $HC(OMe)_3$, MeOH, TsOH, Δ, 30% over 3 steps; (d) *m*CPBA, CH_2Cl_2, 0 °C, 94%.

The enantioselective synthesis of aldehyde **94** relied on a desymmetrization protocol: Treatment of *meso*-ketone **90** with *Koga*'s chiral base (**91**) afforded TMS enol ether **92** in 80% yield and 94% enantiomeric excess (Scheme 38).

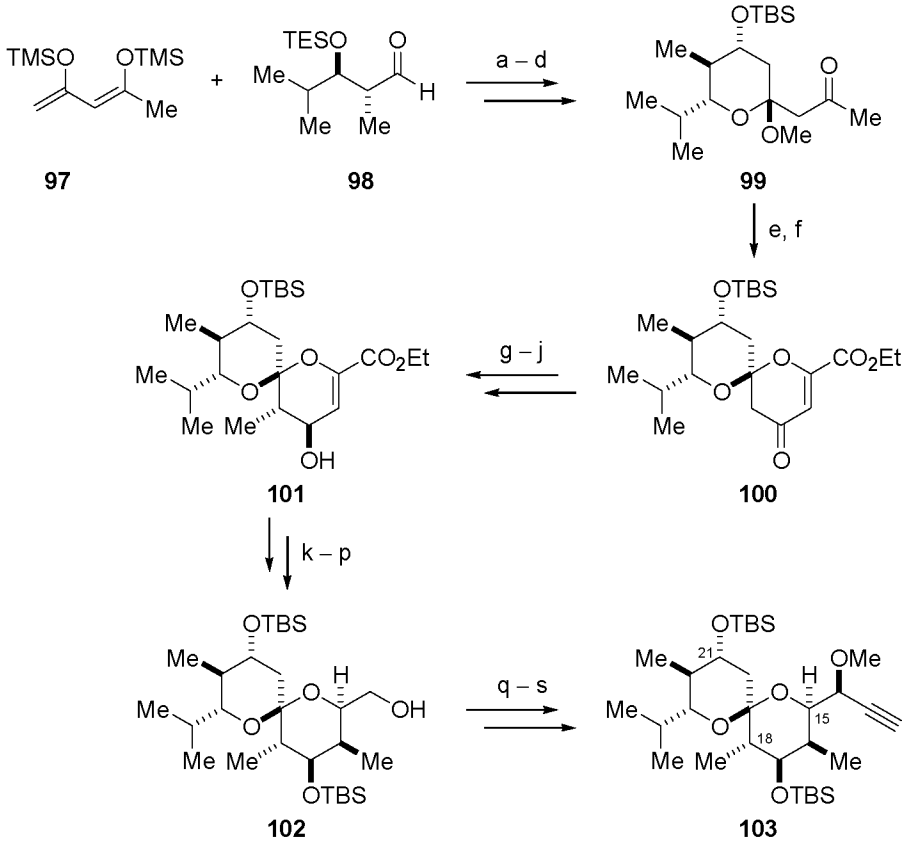


Scheme 38: (a) $(HOCH_2)_2$, TsOH, PhH, Δ; (b) NaH, THF, Δ, 73% over 2 steps; (c) NaH, THF, 0 °C, then ^{t}BuLi, –78 °C, HMPA, then MeI, –78 °C to rt; (d) NaOH, EtOH, Δ, 72% over 2 steps; (e) L-Selectride, THF, –78 °C, 84%; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 98%; (g) TsOH, acetone, Δ; (h) **91**, ^{n}BuLi, TMSCl, THF, –110 °C to –78 °C, 80%, 94% ee; (i) O_3, CH_2Cl_2, MeOH, –78 °C, then $NaBH_4$, –78 °C to rt; (j) CH_2N_2, Et_2O, 75% over 2 steps; (k) PivCl, py, 87%; (l) DIBAL-H, THF, –78 °C to –20 °C; (m) IBX, THF, DMSO; (n) $MeC(O)C(N_2)P(O)(OMe)_2$, K_2CO_3, MeOH, 0 °C to rt; (o) DIBAL-H, PhMe, –78 °C, 70% over 4 steps; (p) ^{n}BuLi, TMSCl, then NEt_3, then 2 M HCl, 88%; (q) IBX, THF, DMSO, 90%.

Fragment coupling was achieved in a two-step *Julia* olefination process with $LiNEt_2$ as the optimal base and the terminal methyl ester as an internal acylating agent for the intermediary alkoxide (Scheme 39). *Prunet* and co-workers completed the synthesis of the C1–C11 subunit **96**—which was identical to *Roush*'s[23] and *Marshall*'s[27] key fragment—in 21 steps and 3.3% overall yield.



Scheme 39: (a) $LiNEt_2$, THF, –78 °C to 0 °C, 83%; (b) Na/Hg, MeOH, –40 °C, *E*/*Z* 13:1; (c) CSA, PhH, Δ; (d) CH_2N_2, Et_2O, 50% over 2 steps; (e) K_2CO_3, MeOH; (f) Cp_2ZrCl_2, $AlMe_3$, H_2O, CH_2Cl_2, then I_2, THF, –78 °C to 0 °C, 60% over 2 steps.



Scheme 40: (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C, 93:7 dr; (b) TBAF, DMF, rt, 3 h, 82% over 2 steps; (c) Montmorillonite K10, MeOH, $MeNO_2$; (d) TBSCl, DMF, imidazole, 0 °C to 20 °C, 86% over 2 steps; (e) LDA, THF, –78 °C, then $(CO_2Et)_2$, –78 °C to 0 °C; (f) Montmorillonite K10, $MeNO_2$, 82% over 2 steps; (g) NaHMDS (3.5 equiv), THF, HMPA, MeI (excess), 76%, 95:5 dr; (h) $NaBH_4$, $CeCl_3$, MeOH, –78 °C to 0 °C, 69%; (i) DEAD, PPh_3, *p*-nitrobenzoic acid, PhH, hexane, –5 °C; (j) K_2CO_3, EtOH, rt, 68% over 2 steps; (k) CH_2I_2, Et_2Zn, PhMe, O_2; (l) TBSOTf, 2,6-lutidine, CH_2Cl_2, 75% over 2 steps; (m) DIBAL-H, THF, –78 °C to 0 °C, 92%; (n) NaH, CS_2, MeI; (o) Bu_3SnH, AIBN, PhMe, Δ; (p) $BH_3{\cdot}THF$, then aq. NaOH, H_2O_2, 86% over 3 steps; (q) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C; (r) TMSC≡CLi, THF, –110 °C, 53% over 2 steps, 7:2 dr; (s) NaH, MeI, then MeOH, 89%.

For the C12–C25 building block, *Prunet* and co-workers chose spiroketal **100** as a useful synthon, whose preparation relied on aldehyde **98** as the single source of homochirality (Scheme 40). Selective installation of the additional stereogenic centers was achieved by taking advantage of the spiroketal's rigid framework:

- methylation at C18 afforded a 95:5 mixture of diastereomers
- *Luche* reduction of the C17 ketone gave the secondary alcohol with 11:2 diastereomeric ratio
- C17-OH-directed *Simmons–Smith* reaction occurred exclusively from the top face

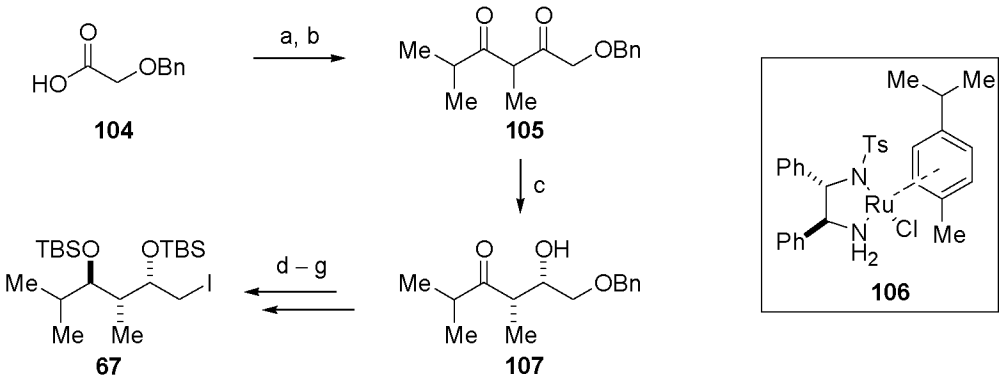
- hydroboration of the *exo*-methylene took place from its sterically less hindered *si*-face
- acetylide addition to the C14 aldehyde occurred in 7:2 *syn*/*anti*-selectivity

The method used for the introduction of the C16 methyl substituent and the *exo*-methylene unit is also noteworthy: Cyclopropanation and subsequent Bu_3SnH promoted radical reductive deoxygenation–cyclopropane ring opening installed the two substituents in a rather unusual but straightforward way.[34]

The elaboration of **103** to a suitable vinyl stannane, its *Stille* cross-coupling to vinyl iodide **96**, and the completion of the bafilomycin A_1 total synthesis are subject to ongoing studies.

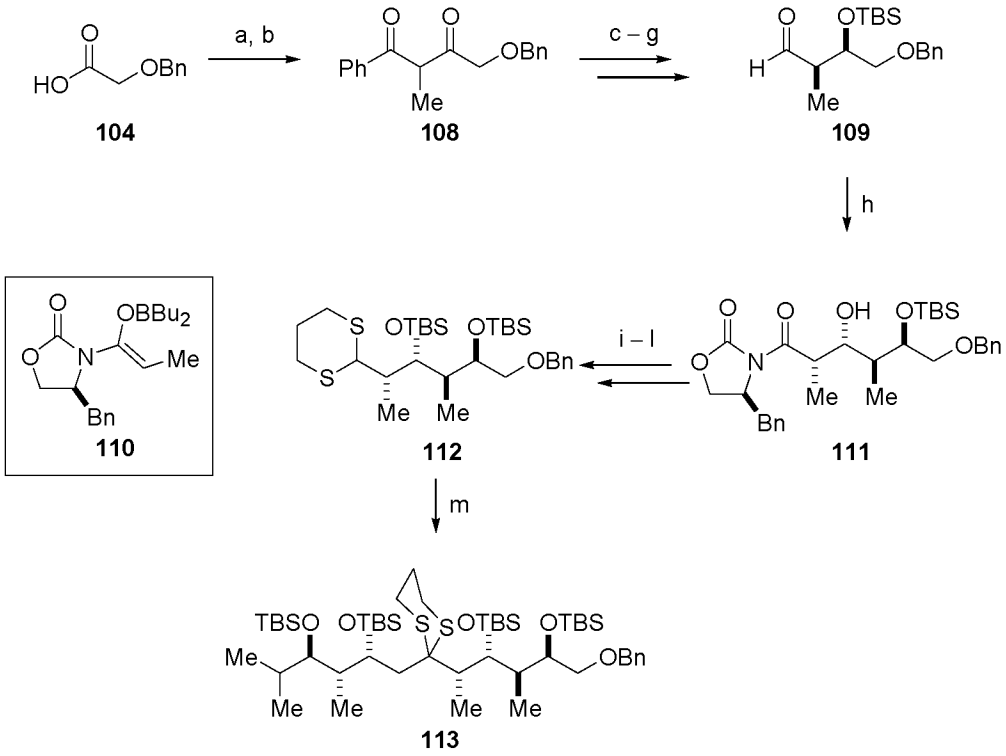
1.4.10 *Cossy*'s Dynamic Kinetic Resolution Approach to C14–C25

The two key intermediates in *Cossy*'s synthesis of bafilomycin A_1's C14–C25 subunit were both prepared *via* a dynamic kinetic resolution approach (Schemes 41 and 42).[29] Thus, the easily available diketones **105** and **108** were reduced under asymmetric transfer hydrogenation conditions using opposite enantiomers of *Noyori*'s chiral ruthenium catalyst (**106** and *ent*-**106**, respectively). Further elaboration of the two hydroxy ketones involved the 1,3-*anti* selective reduction of **107** en route to iodide **67**, and an *anti*-*Felkin*-type *Evans* aldol reaction, producing the required *syn*–*anti*–*syn*-stereotetrad observed in dithiane **112**. Coupling of the two fragments was finally realized using *Hanessian*'s[24] conditions.



Scheme 41: (a) DCC, benzotriazole, rt, 96%; (b) LDA, THF, 2-methylpentan-3-one, 72%; (c) **106** (1 mol %), NEt_3, HCO_2H, CH_2Cl_2, 92%, 72:28 dr, 94% ee; (d) $Me_4NBH(OAc)_3$, AcOH, 76%, 90:10 dr; (e) TBSOTf, 2,6-lutidine, 90%; (f) H_2, Pd/C (10%), K_2CO_3, EtOAc, 71%; (g) I_2, imidazole, PPh_3, PhMe, 95%.

[34] For detailed model studies and alternative reaction pathways see: J. C. Poupon, R. Lopez, J. Prunet, J. P. Ferezou, *J. Org. Chem.* **2002**, *67*, 2118–2124.

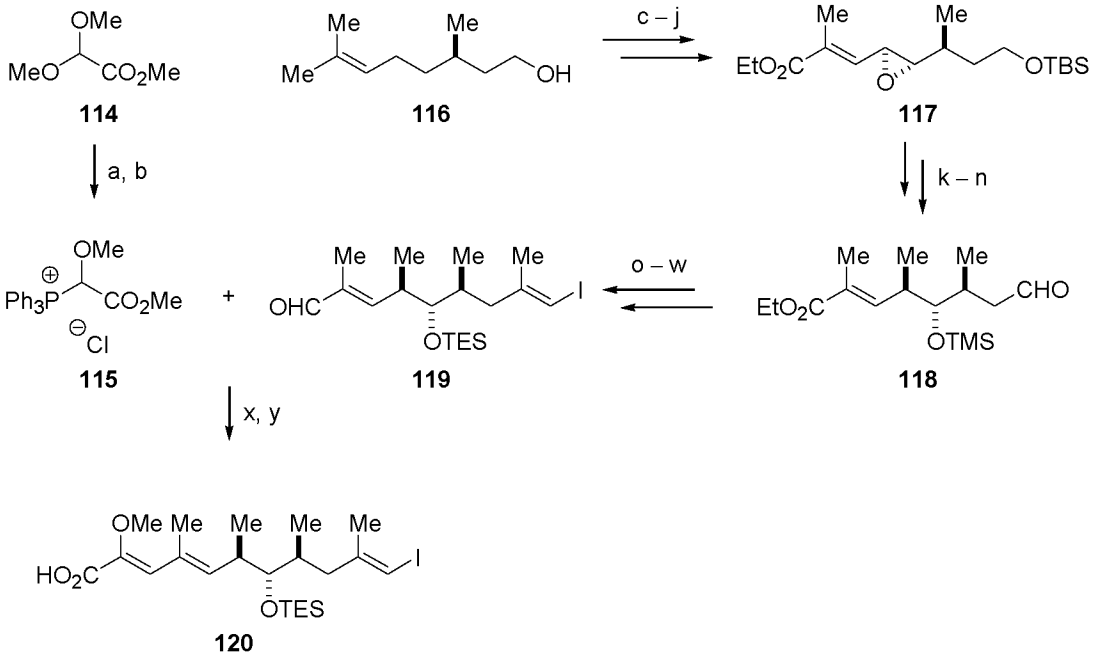


Scheme 42: (a) DCC, benzotriazole, rt, 96%; (b) propiophenone, LDA, THF, 72%; (c) *ent*-**106** (1 mol %), HCO_2H, NEt_3, CH_2Cl_2, 89%, 68:32 dr, 93% ee; (d) Cy-1,2-$(NHTs)_2$, $SnCl_2$, $(TMS)_2O$, then AcOH, THF, H_2O, 78%; (e) TBSOTf, 2,6-lutidine, quant.; (f) DIBAL-H, PhMe, –78 °C, quant.; (g) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C, 90%; (h) **110**, 80%; (i) (MeO)NHMe·HCl, $AlMe_3$, 97%; (j) TBSCl, 2,6-lutidine, 97%; (k) DIBAL-H, THF, 89%; (l) $HS(CH_2)_3SH$, $TiCl_4$, 98%; (m) ^{t}BuLi, HMPA, THF, then **67**, 28%.

1.4.11 *Lett*'s Intramolecular *Stille* Coupling

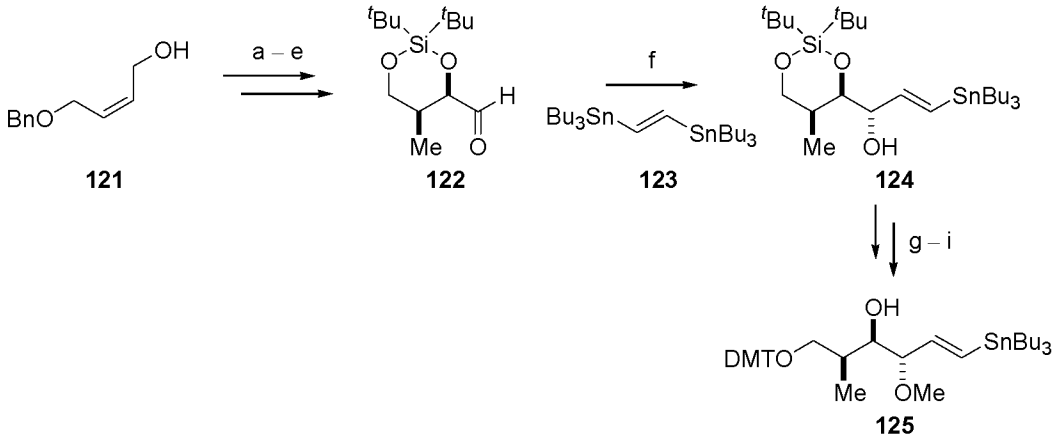
In contrast to virtually all of the previous approaches, *Lett* and co-workers' synthetic outline did not involve a macrolactonization step, but rather an intermolecular esterification followed by an intramolecular *Stille* coupling.[30]

Acid **120** was prepared in 18 steps and 4% overall yield from (*R*)-citronellol (**116**) utilizing a *Sharpless* epoxidation, regioselective epoxide opening under *Miyashita* conditions ($AlMe_3$/ H_2O), and a stereoselective *Wittig*-type olefination with phosphonium salt **115** (Scheme 43).



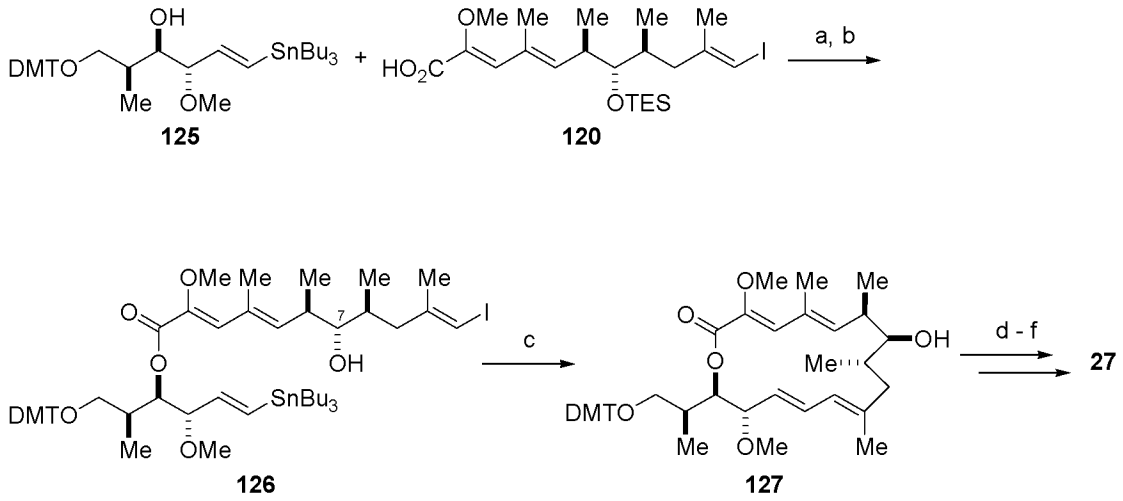
Scheme 43: (a) PCl_5, 140 °C, 1.5 h, 93%; (b) PPh_3, CH_2Cl_2, rt, 60 h, 94%; (c) TBSCl, imidazole, DMF, rt, quant.; (d) NaOH, MeOH, CH_2Cl_2, –78 °C, O_3, 80%; (e) LDA, THF, –78 °C, 30 min, then $(PhSe)_2$, –78 °C to rt, 2 h, 88%; (f) 30% H_2O_2, CH_2Cl_2, py, 0 °C, 92%; (g) DIBAL-H, PhMe, –78 °C, 3 h, 93%; (h) $Ti(O^iPr)_4$, (+)-DET, CH_2Cl_2, TBHP, –30 °C, 16 h, 72%; (i) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C; (j) $Ph_3P{=}C(Me)CO_2Et$, THF, rt, 3 h, 85% over 2 steps; (k) DCE, H_2O, rt, then –30 °C, $AlMe_3$, 4 h, 75%; (l) TBAF, THF, rt, 2 h; (m) TMSCl, NEt_3, DMF, rt, 2 h, 86% over 2 steps; (n) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C, 80%; (o) PPh_3, CBr_4, CH_2Cl_2, then NEt_3, rt, 15 min, then –78 °C to rt, 7 h, 91%; (p) DIBAL-H, PhMe, –78 °C, 3 h; (q) TBAF, THF, rt, 2 h, 91% over 2 steps; (r) ^{n}BuLi, THF, –78 °C to rt, 3 h, 86%; (s) $AlMe_3$, Cp_2ZrCl_2, DCE, rt, 20 h, then –30 °C, I_2, –30 °C to rt, 1 h, 74%; (t) TMSCl, NEt_3, DMF, rt, 1.5 h, 91%; (u) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C, 75%: (v) HF·py, py, THF, rt, 4 h; (w) TESOTf, ^{i}Pr$_2$NEt, DMF, rt, 3 h, 87% over 2 steps; (x) **115**, NEt_3, CH_2Cl_2, rt, 15 min, then **119**, Δ, 4 d, then **115**, NEt_3, Δ, 2 d, 67–70%, *Z*/*E* = 87:13–92:8; (y) 1 M aq. NaOH, THF, Δ, 30 h, 83%.

The synthesis of the C12–C17 fragment **125** was achieved in 10% yield and 80% enantiomeric excess over nine steps (Scheme 44). The pivotal addition of in situ prepared *E*-1-lithio-2-tributlystannylethylene to a chiral aldehyde only proceeded with useful diastereo-selectivity if the aldehyde's diol portion was protected as a cyclic silyl ketal.



Scheme 44: (a) $Ti(O^iPr)_4$, (–)-DET, CH_2Cl_2, –30 °C, 30 min, then **121**, –30 °C, 1 h, then TBHP, –30 °C, 4 d, 76%, 80% ee; (b) CuI, MeLi, Et_2O, 0 °C, then –40 °C, 5 h, dr 70:30; (c) 2,6-lutidine, $^tBu_2Si(OTf)_2$, CH_2Cl_2, rt, 3 h, 58% over 2 steps; (d) Pd/C (10%), H_2, 95% EtOH, rt, 4 h, 84%; (e) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C, 90%; (f) **123**, ^{n}BuLi, THF, –78 °C to rt, then **122**, –78 °C, 7 h, 40%; (g) ^{n}BuLi, MeI, THF, –78 °C to rt, 1 h, then HMPA, rt, 16 h, 89%; (h) TBAF, THF, rt, 3 d, 88%; (i) $DMTBF_4$, DTBMP, MeCN, rt, 4 h, 97%.

After successful intermolecular esterification, *Lett* and co-workers turned their attention to the upcoming *Stille* coupling step (Scheme 45). Through extensive screening of reagents, solvents, temperature, and dilution effects, the optimal cyclization conditions were found to furnish **127** in 28% yield (33% based on recovered starting material). As previously observed in several cases for the macrolactonization, it was crucial for the reaction to take place that the precursor's C7 hydroxy group be unprotected. The formal synthesis of bafilomycin A_1 was finally completed by interception with *Toshima*'s[22] macrocyclic intermediate **27**.



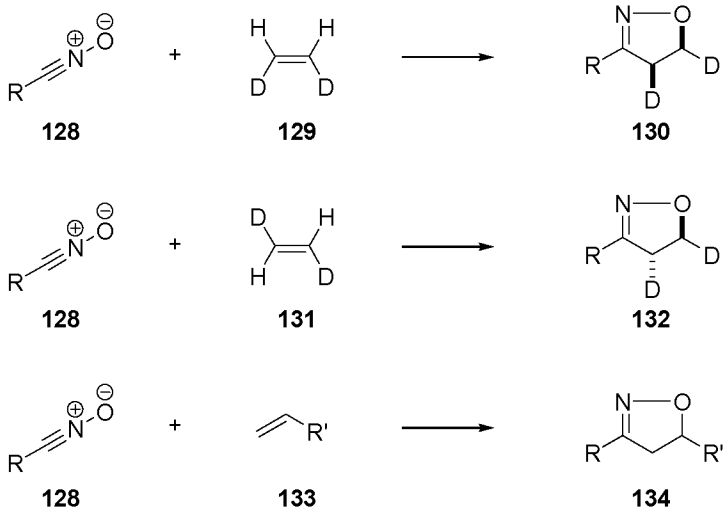
Scheme 45: (a) **120**, PhMe (0.1 M), DMAP, rt, then NEt_3, 2,4,6-trichlorobenzoyl chloride, then **115**, rt, 24 h, 89%; (b) TBAF, THF, rt, 4 h, 87%; (c) $Pd_2(dba)_3$ (cat.), $AsPh_3$, $^iPr_2NEt$,

DMF, rt, then **126** (0.001 M), 40 °C, 30 h, 28%; (d) $^{i}PrEt_2SiOTf$, $^{i}Pr_2NEt$, DMF, rt, 3 h, 88%; (e) PPTS, MeOH, rt, 4 h, 62%; (f) $(COCl)_2$, DMSO, NEt_3, –78 °C, 20 min, 74%.

1.5 The Hydroxy-Directed Nitrile Oxide Cycloaddition

1.5.1 Introduction

It has been known for more than a century that nitrile oxides can undergo 1,3-dipolar cycloaddition with suitable dipolarophiles such as alkenes, alkynes, or carbonyls.[35] According to a concerted [3+2] mechanism, the addition of nitrile oxides to alkenes proceeds stereospecifically, with *E*-olefins leading to the *trans*- and *Z*-olefins to the *cis*-isoxazolines, respectively (Scheme 46).[36] Furthermore, complete regioselectivity is generally observed in the case of terminal alkenes,[37] a fact that correlates well with calculated frontier molecular orbital coefficients.[38]



Scheme 46.

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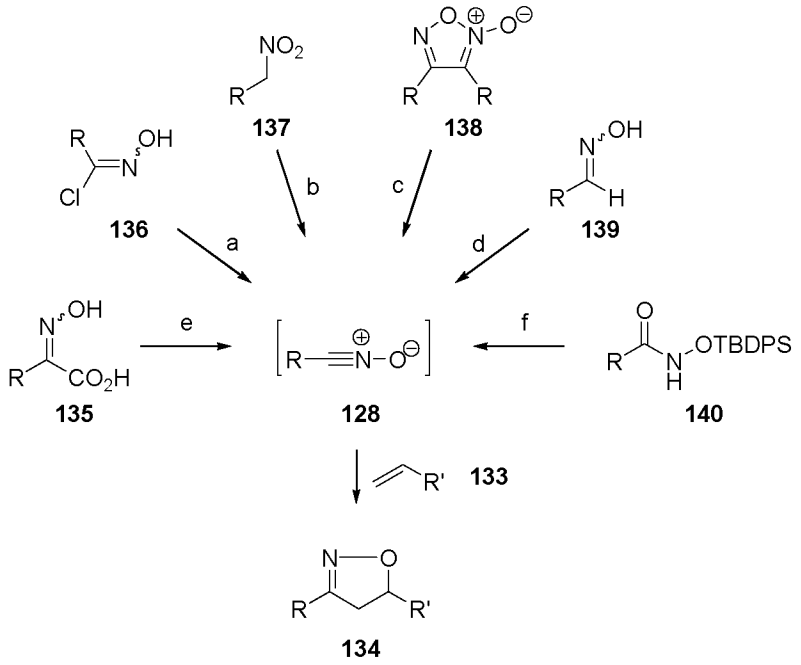
[35] For a review, see: (a) *1,3-Dipolar Cycloaddition Chemistry;* A. Padwa, Ed.; General Heterocyclic Chemistry Series (Taylor/Weissberger), Vol. 1; John Wiley & Sons: New York **1984**; (b) C. J. Easton, C. M. M. Hughes, G. P. Savage, G. W. Simpson, *Adv. Heterocycl. Chem.* **1994**, *60*, 261–327.

[36] K. N. Houk, R. A. Firestone, L. L. Munchausen, P. H. Mueller, B. H. Arison, L. A. Garcia, *J. Am. Chem. Soc.* **1985**, *107*, 7227–7228.

[37] M. Christl, R. Huisgen, *Chem. Ber.* **1973**, *106*, 3345–3367.

[38] For a review, see: K. N. Houk in *1,3-Dipolar Cycloaddition Chemistry;* A. Padwa, Ed.; General Heterocyclic Chemistry Series (Taylor/Weissberger), Vol. 2; John Wiley & Sons: New York **1984**.

Nitrile oxides are highly reactive and tend to dimerize to the corresponding furoxans. For this reason, they are usually prepared in situ and immediately trapped by a dipolarophile. Typical methods involve treatment of a hydroxymoyl chloride **136** with a base or a silver(I) salt,[39] dehydration of a primary nitro compound **137**,[40] thermolysis of a furoxan **138**,[41] oxidation of an aldoxime **139** or an α-hydroxyimino carboxylic acid **135**,[42] or the dehydration of O-silylated hydroxamic acids **140**[43] (Scheme 47).



Scheme 47: (a) NEt_3, or $AgNO_3$, or PhMe/Δ, or 4 Å MS, or $(Bu_3Sn)_2O$, or AgOAc; (b) MeNCO/NEt_3, or *Burgess* reagent/NEt_3, or DAST/NEt_3, or $POCl_3$/NEt_3, or Boc_2O/DMAP; (c) 135–165 °C; (d) 1-chlorobenzotriazole, or $(Bu_3Sn)_2O$/^{t}BuOCl, or MnO_2; (e) CAN; (f) Tf_2O, NEt_3, –40 °C to 0 °C.

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[39] (a) P. A. Wade, M. K. Pillay, S. M. Singh, *Tetrahedron Lett.* **1982**, *23*, 4563–4566; (b) P. Caldirola, M. Deamici, C. Demicheli, P. Pevarello, *Heterocycles* **1985**, *23*, 2479–2482; (c) J. N. Kim, E. K. Ryu, *Heterocycles* **1990**, *31*, 1693–1697; (d) Y. Tokunaga, M. Ihara, K. Fukumoto, *Heterocycles* **1996**, *43*, 1771–1775.

[40] (a) T. Mukaiyama, T. Hoshino, *J. Am. Chem. Soc.* **1960**, *82*, 5339–5342; (b) B. H. Kim, P. B. Jacobs, R. L. Elliott, D. P. Curran, *Tetrahedron* **1988**, *44*, 3079–3092; (c) N. Maugein, A. Wagner, C. Mioskowski, *Tetrahedron Lett.* **1997**, *38*, 1547–1550; (d) Y. Basel, A. Hassner, *Synthesis* **1997**, 309–312.

[41] (a) D. P. Curran, C. J. Fenk, *J. Am. Chem. Soc.* **1985**, *107*, 6023–6028.

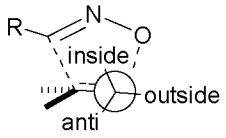
[42] (a) J. N. Kim, E. K. Ryu, *Synth. Commun.* **1990**, *20*, 1373–1377; (b) O. Moriya, H. Takenaka, M. Iyoda, Y. Urata, T. Endo, *J. Chem. Soc., Perkin Trans. 1* **1994**, 413–417; (c) J. Kiegiel, M. Poplawska, J. Jozwik, M. Kosior, J. Jurczak, *Tetrahedron Lett.* **1999**, *40*, 5605–5608; (d) N. Arai, M. Iwakoshi, K. Tanabe, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2277–2285.

[43] D. Muri, J. W. Bode, E. M. Carreira, *Org. Lett.* **2000**, *2*, 539–541.

1.5.2 Stereoselective 1,3-Dipolar Nitrile Oxide Cycloadditions

Even though the 1,3-dipolar cycloaddition of nitrile oxides with olefins has been known for a long time, stereoselective versions only started to evolve in the early 1980's:[44] Both chiral nitrile oxides[45] and alkenes[46] were used for the diastereoselective formation of 2-isoxazolines.

Houk and co-workers calculated the transition state energies for the nitrile oxide cycloaddition of chiral allylic ethers and alcohols (model **141**, Figure 7).[47] They showed that hydroxy groups preferentially occupied the *outside* position to maximize hydrogen bonding with the nitrile oxide oxygen, while alkyl substituents favored the sterically least crowded *anti* position. In the case of alkoxy groups, the *inside* position allows for optimal orbital overlap and electron donation into the $\pi_{C=C}$ orbital, leading to a stabilized transition state. From a pure sterical point of view, the *inside* position seems to be less demanding than the *outside* position.[48] This proposal is in good agreement with experimental data.



141

Figure 7. *Houk*'s transition state model.

In 1991, *Kanemasa* and co-workers reported the generation of nitrile oxides by treatment of hydroxymoyl chlorides with organometallic reagents and their subsequent cycloaddition to allylic alcohols.[49] It was shown that the reaction of hydroxymoyl chloride **142** with the chiral

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[44] For a review on asymmetric 1,3-dipolar cycloadditions, see: K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863–909.

[45] For selected examples, see: (a) A. P. Kozikowski, Y. Kitagawa, J. P. Springer, *J. Chem. Soc., Chem. Comm.* **1983**, 1460–1462; (b) B. H. Kim, Y. J. Chung, G. C. Keum, J. H. Kim, K. M. Kim, *Tetrahedron Lett.* **1992**, *33*, 6811–6814.

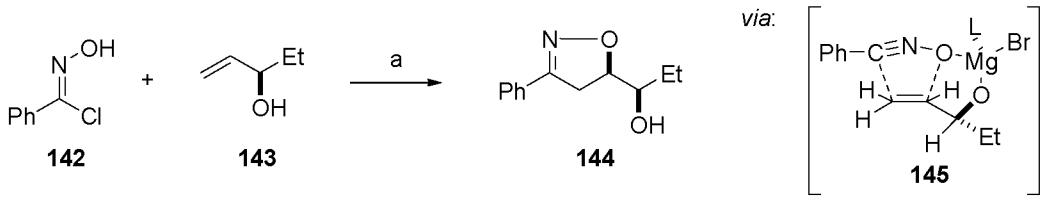
[46] For selected examples, see: (a) D. P. Curran, B. H. Kim, J. Daugherty, T. A. Heffner, *Tetrahedron Lett.* **1988**, *29*, 3555–3558; (b) S. Kanemasa, K. Onimura, *Tetrahedron* **1992**, *48*, 8645–8658; (c) C. Baldoli, P. Delbuttero, S. Maiorana, G. Zecchi, M. Moret, *Tetrahedron Lett.* **1993**, *34*, 2529–2532; (d) B. M. Kellybasetti, M. F. Mackay, S. M. Pereira, G. P. Savage, G. W. Simpson, *Heterocycles* **1994**, *37*, 529–539; (e) P. Bravo, L. Bruche, M. Crucianelli, A. Farina, S. V. Meille, A. Merli, P. Seresini, *J. Chem. Res., Synop.* **1996**, 348–349.

[47] K. N. Houk, S. R. Moses, Y. D. Wu, N. G. Rondan, V. Jager, R. Schohe, F. R. Fronczek, *J. Am. Chem. Soc.* **1984**, *106*, 3880–3882.

[48] K. N. Houk, H. Y. Duh, Y. D. Wu, S. R. Moses, *J. Am. Chem. Soc.* **1986**, *108*, 2754–2755.

[49] (a) S. Kanemasa, S. Kobayashi, M. Nishiuchi, H. Yamamoto, E. Wada, *Tetrahedron Lett.* **1991**, *32*, 6367–6370; (b) S. Kanemasa, M. Nishiuchi, E. Wada, *Tetrahedron Lett.* **1992**, *33*, 1357–1360; (c) S. Kanemasa,

allylic alcohol **143** in the presence of EtMgBr proceeded in high yield and excellent diastereoselectivity (Scheme 48). Transition state **145** was postulated to account for both the regio- and the diastereoselectivity of the reaction.



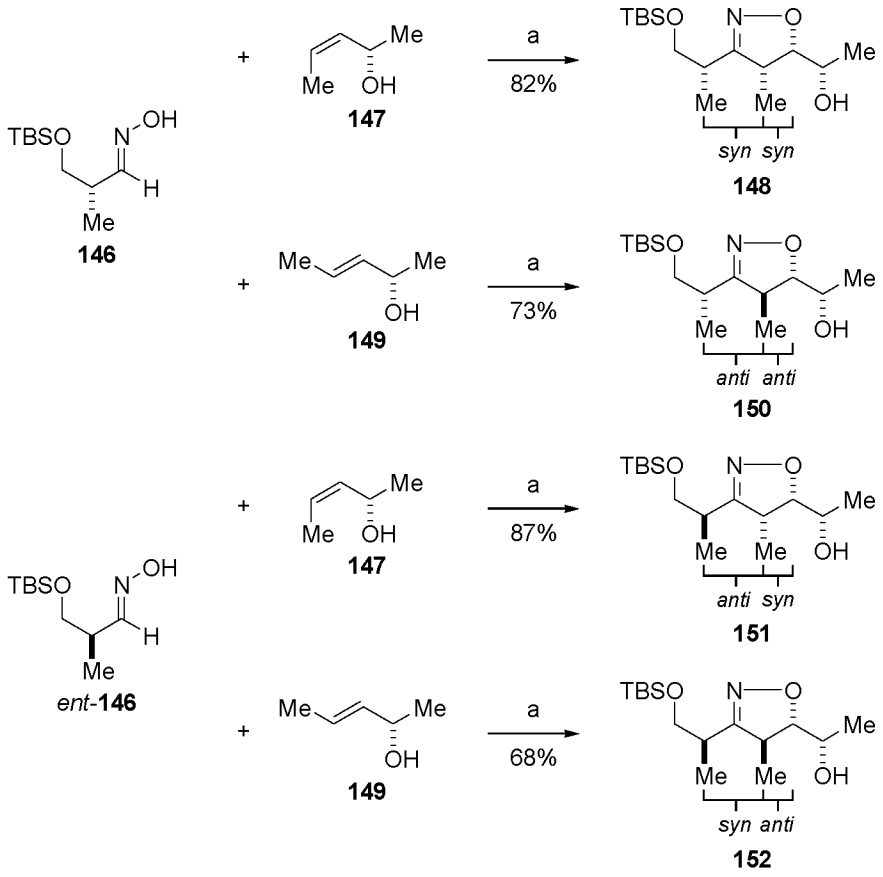
Scheme 48: (a) EtMgBr, THF, –30 °C, 41 h, 75% yield, 95:5 dr.

The scope of the hydroxy-directed nitrile oxide cycloaddition reaction was significantly expanded by *Carreira* and co-workers: It was shown that, in addition to the aromatic nitrile oxides reported earlier, chiral aliphatic ones also undergo completely regio- and stereoselective cycloaddition to chiral allylic alcohols (Scheme 49).[50] The newly developed reaction conditions are very convenient and broadly applicable.

Most importantly, *Carreira*'s method allows for the preparation of all possible *syn/anti*-combinations starting from the same set of reagents (*E*- or *Z*-allylic alcohol and (*R*)- or (*S*)-oxime). As isoxazolines are generally considered aldol surrogates (see section 1.5.3), this reaction provides an entry to all possible polyketide diastereomers.

M. Nishiuchi, A. Kamimura, K. Hori, *J. Am. Chem. Soc.* **1994**, *116*, 2324–2339; (d) S. Kanemasa, K. Okuda, H. Yamamoto, S. Kaga, *Tetrahedron Lett.* **1997**, *38*, 4095–4098; (e) H. Yamamoto, S. Watanabe, K. Kadotani, M. Hasegawa, M. Noguchi, S. Kanemasa, *Tetrahedron Lett.* **2000**, *41*, 3131–3136.

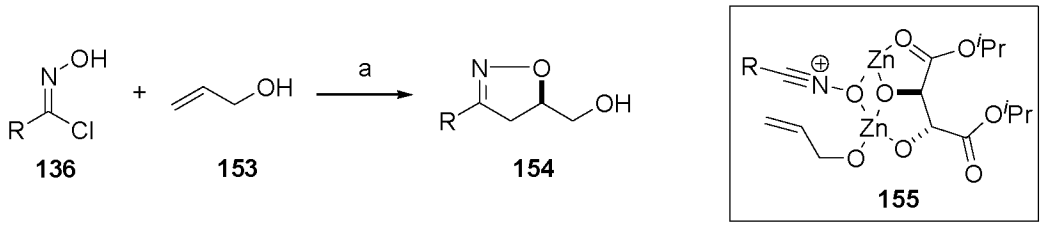
[50] J. W. Bode, N. Fraefel, D. Muri, E. M. Carreira, *Angew. Chem., Int. Ed.* **2001**, *40*, 2082–2085.



Scheme 49: (a) oxime, ^{t}BuOCl, CH_2Cl_2, –78 °C, 2 h, then allylic alcohol, EtMgBr, ^{i}PrOH, 0 °C to rt, 12 h.

The first and so far only catalytic enantioselective nitrile oxide cycloadditions have been reported by *Ukaji* and *Inomata* using $ZnEt_2$/(+)-diisopropyl tartrate (Scheme 50).[51] Achiral aromatic as well as aliphatic nitrile oxides have been successfully added to allyl alcohol, whereas the use of more substituted allylic alcohols led to lower yield and stereoselectivity. The authors proposed a bridged transition state **(155)** to account for the enantioselectivity observed in this remarkable reaction.

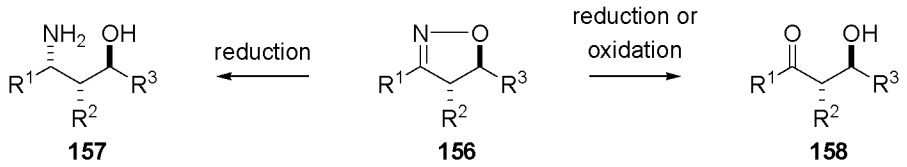
[51] (a) Y. Ukaji, K. Sada, K. Inomata, *Chem. Lett.* **1993**, 1847–1850; (b) M. Shimizu, Y. Ukaji, K. Inomata, *Chem. Lett.* **1996**, 455–456; (c) Y. Yoshida, Y. Ukaji, S. Fujinami, K. Inomata, *Chem. Lett.* **1998**, 1023–1024.



Scheme 50: (a) **153**, $ZnEt_2$, (+)-DIPT, $CHCl_3$, 0 °C, 1 h, then $ZnEt_2$, **136**, 0 °C, 12 h, 62–98% yield, 84–93% ee.

1.5.3 Applications

Isoxazolines **156** can undergo a wide range of transformations, such as oxidation, reduction, nucleophilic addition, or deprotonation followed by addition to an electrophile.[35b] From a synthetic point of view, the preparation of β-amino alcohols **157**[52] and especially of β-hydroxy ketones **158** offers the greatest opportunities (Scheme 51).



Scheme 51. Important transformations of isoxazolines.

The reduction of isoxazolines to β-hydroxy ketones is typically affected by hydrogenation using *Raney*-Nickel,[53] $Mo(CO)_6$[54] or Pd/C.[55] Alternatives include treatment with EtMgBr and $Ti(O^iPr)_4$,[56] reduction with SmI_2,[57] Ni-catalyzed electrolysis,[58] or ozonolysis.[59] Isoxazolines, whose diastereoselective synthesis by hydroxy-directed nitrile oxide cycloaddition has been

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52 A. R. Minter, A. A. Fuller, A. K. Mapp, *J. Am. Chem. Soc.* **2003**, *125*, 6846–6847.

53 (a) D. P. Curran, *J. Am. Chem. Soc.* **1982**, *104*, 4024–4026; (b) D. P. Curran, *J. Am. Chem. Soc.* **1983**, *105*, 5826–5833; (c) D. P. Curran, S. A. Scanga, C. J. Fenk, *J. Org. Chem.* **1984**, *49*, 3474–3478.

54 (a) P. G. Baraldi, A. Barco, S. Benetti, S. Manfredini, D. Simoni, *Synthesis* **1987**, 276–278; (b) S. Cicchi, A. Goti, A. Brandi, A. Guarna, F. Desarlo, *Tetrahedron Lett.* **1990**, *31*, 3351–3354; (c) G. J. McGarvey, J. A. Mathys, K. J. Wilson, *J. Org. Chem.* **1996**, *61*, 5704–5705.

55 (a) K. Torssell, O. Zeuthen, *Acta Chem. Scand. Ser. B* **1978**, *32*, 118–124; (b) M. Asaoka, T. Mukuta, H. Takei, *Tetrahedron Lett.* **1981**, *22*, 735–738.

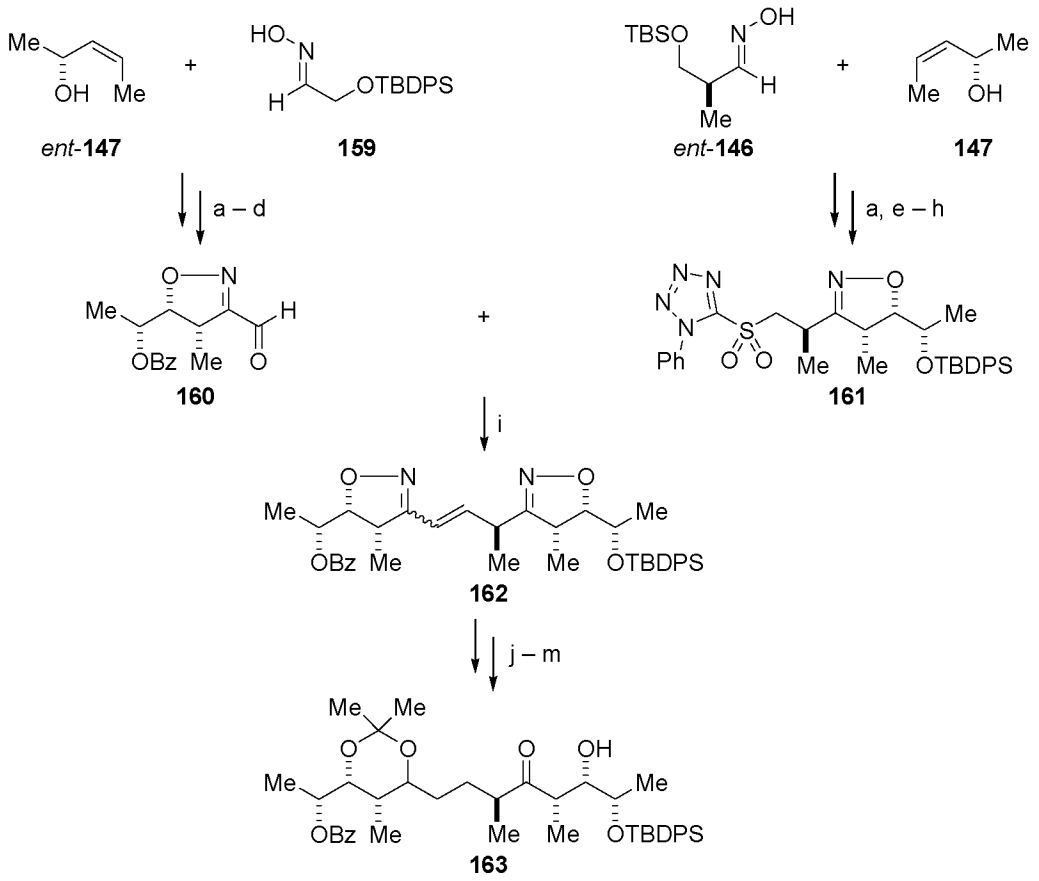
56 D. H. Churykau, V. G. Zinovich, O. G. Kulinkovich, *Synlett* **2004**, 1949–1952.

57 J. W. Bode, E. M. Carreira, *Org. Lett.* **2001**, *3*, 1587–1590.

58 V. F. Caetano, F. W. J. Demnitz, F. B. Diniz, R. M. Mariz, M. Navarro, *Tetrahedron Lett.* **2003**, *44*, 8217–8220.

59 A. P. Kozikowski, M. Adamczyk, *Tetrahedron Lett.* **1982**, *23*, 3123–3126.

discussed in section 1.5.2, can therefore serve as protected aldol surrogates: While only a few natural products contain an isoxazoline moiety,[60] several total syntheses have made use of their stereoselective construction by 1,3-dipolar nitrile oxide cycloaddition and facile opening to the corresponding β-hydroxy ketones.[61]



Scheme 52: (a) ^{t}BuOCl, **159** or *ent*-**146**, CH_2Cl_2, –78 °C, then *ent*-**147** or **147**, EtMgBr, ^{i}PrOH, CH_2Cl_2, 0 °C to rt; (b) BzCl, NEt_3, DMAP, CH_2Cl_2, 72% over 2 steps; (c) TBAF, THF, 93%; (d) DMP, CH_2Cl_2, 88%; (e) TBDPSCl, imidazole, DMF, 85% over 2 steps; (f) AcOH, THF, H_2O, 95%; (g) 1-phenyl-1*H*-tetrazole-5-thiol, Ph_3P, DEAD, THF, 99%; (h) $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, H_2O_2, EtOH, 92%; (i) **161**, KHMDS, THF, –78 °C, then **160**, 96%; (j) SmI_2, THF, H_2O, 55–70%; (k) $Me_4NBH(OAc)_3$, AcOH, MeCN; (l) $Me_2C(OMe)_2$, TsOH, 85% over 2 steps; (m) H_2, Raney-Ni, MeOH, H_2O, $B(OH)_3$, 90%.

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[60] For selected examples, see: (a) D. M. Vyas, Y. Chiang, T. W. Doyle, *Tetrahedron Lett.* **1984**, *25*, 487–490; (b) G. M. Nicholas, G. L. Newton, R. C. Fahey, C. A. Bewley, *Org. Lett.* **2001**, *3*, 1543–1545.

[61] For selected examples, see: (a) S. F. Martin, M. S. Dappen, B. Dupre, C. J. Murphy, J. A. Colapret, *J. Org. Chem.* **1989**, *54*, 2209–2216; (b) J. W. Bode, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 3611–3612; (c) J. W. Bode, E. M. Carreira, *J. Org. Chem.* **2001**, *66*, 6410–6424.

Fader and *Carreira* recently reported the diastereoselective synthesis of pentaketides *via* nitrile oxide cycloaddition (Scheme 52).[62] Coupling of the two highly functionalized isoxazolines **165** and **166** was achieved according to the *Kocieński* modification of the *Julia–Lythgoe* olefination. Selective reduction of the 3-alkenyl isoxazoline moiety with SmI_2 then allowed for differentiation between the two aldol surrogates.[57]

1.6 The Enantioselective Zinc Alkynylide Addition

1.6.1 Introduction

Propargylic alcohols are versatile building blocks for organic synthesis and are readily further elaborated by hydroboration, carbometalation, or hydrosilylation, for instance.[63] Their enantioselective synthesis has therefore attracted considerable interest. The enantioselective addition of alkynylides to carbonyl compounds will be discussed in greater detail in section 1.6.3. Alternative methods for the synthesis of optically active propargylic alcohols involve enzymatic resolution,[64] asymmetric reduction of ynones,[65] and reductive cleavage of chiral α,β-alkynyl acetals.[66]

1.6.2 Formation of Alkynylides

The relatively low pK_a (~ 25) of terminal acetylenes allows for facile deprotonation with alkyl lithium or *Grignard* reagents, as well as with alkali metal alkoxides or hydroxides.[67] Because of the incompatibility of these reagents with electrophiles, the alkynylide formation and the nucleophilic addition have to be carried out in two separate steps.

Over the last few decades, several methods for the in situ deprotonation of terminal alkynes with weaker bases and under catalytic conditions have been developed.[68] The resulting

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[62] L. D. Fader, E. M. Carreira, *Org. Lett.* **2004**, *6*, 2485–2488.

[63] For a review, see: *Modern Acetylene Chemistry*; P. J. Stang, F. Diederich, Eds.; VCH Weinheim, **1995**.

[64] D. W. Xu, Z. Y. Li, S. M. Ma, *Tetrahedron Lett.* **2003**, *44*, 6343–6346.

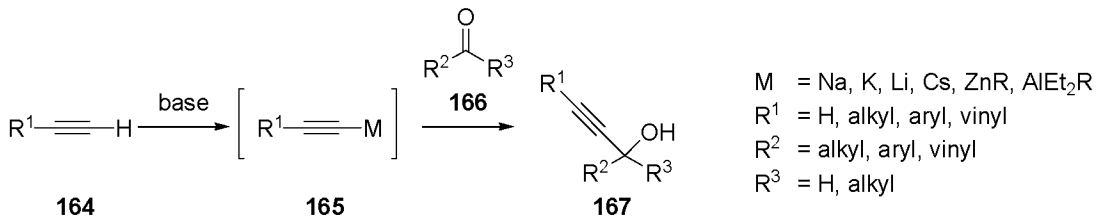
[65] For a review, see: (a) V. K. Singh, *Synthesis* **1992**, 605–617; (b) E. J. Corey, C. J. Helal, *Angew. Chem., Int. Ed.* **1998**, *37*, 1987–2012.

[66] K. Ishihara, A. Mori, I. Arai, H. Yamamoto, *Tetrahedron Lett.* **1986**, *27*, 983–986.

[67] For an early application, see: W. Reif, H. Grassner, *Chem. Ing. Tech.* **1973**, *45*, 646–652.

[68] For selected examples, see; (a) N. Shachat, J. J. Bagnell, *J. Org. Chem.* **1962**, *27*, 1498–1504; (b) M. Yamaguchi, A. Hayashi, M. Hirama, *Chem. Lett.* **1992**, 2479–2482; (c) J. H. Ahn, M. J. Joung, N. M. Yoon,

alkynylides readily undergo nucleophilic addition not only to aldehydes and ketones (Scheme 53), but also to acetals, nitrones, aldimines, and iminium ions.



Scheme 53.

1.6.3 Enantioselective Alkynylide Addition

The first asymmetric alkynylide addition to aldehydes was achieved by *Mukaiyama* and *Suzuki* in 1979 by the use of a lithium base and a proline-derived ligand.[69] Thereafter, several groups reported the application of tin, zinc, nickel, aluminum or titanium alkynylides with a wide variety of chiral ligands for the formation of optically active propargylic alcohols.[70,71] In addition, several methods for the enantioselective alkynylide addition to ketones,[72] iminium ions,[73] and nitrones[74] have been developed.

J. Org. Chem. **1995**, *60*, 6173–6175; (d) J. Busch-Petersen, Y. X. Bo, E. J. Corey, *Tetrahedron Lett.* **1999**, *40*, 2065–2068; (e) D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **1999**, *121*, 11245–11246; (f) T. Ishikawa, T. Mizuta, K. Hagiwara, T. Aikawa, T. Kudo, S. Saito, *J. Org. Chem.* **2003**, *68*, 3702–3705; (g) T. Weil, P. R. Schreiner, *Eur. J. Org. Chem.* **2005**, 2213–2217; (h) R. B. Lettan, K. A. Scheidt, *Org. Lett.* **2005**, *7*, 3227–3230.

[69] (a) T. Mukaiyama, K. Suzuki, K. Soai, T. Sato, *Chem. Lett.* **1979**, 447–448; (b) T. Mukaiyama, K. Suzuki, *Chem. Lett.* **1980**, 255–256.

[70] For a review, see: L. Pu, *Tetrahedron* **2003**, *59*, 9873–9886.

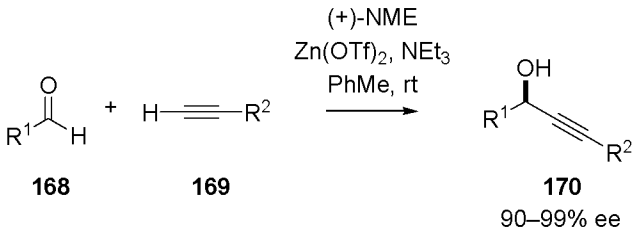
[71] For selected examples, see: (a) E. J. Corey, K. A. Cimprich, *J. Am. Chem. Soc.* **1994**, *116*, 3151–3152; (b) D. Moore, L. Pu, *Org. Lett.* **2002**, *4*, 1855–1857; (c) M. Nakajima, M. Saito, S. Hashimoto, *Tetrahedron: Asymmetry* **2002**, *13*, 2449–2452; (d) A. L. Braga, H. R. Appelt, C. C. Silveira, L. A. Wessjohann, P. H. Schneider, *Tetrahedron* **2002**, *58*, 10413–10416; (e) R. M. Kamble, V. K. Singh, *Tetrahedron Lett.* **2003**, *44*, 5347–5349; (f) M. Li, X. Z. Zhu, K. Yuan, B. X. Cao, X. L. Hou, *Tetrahedron: Asymmetry* **2004**, *15*, 219–222; (g) S. Dahmen, *Org. Lett.* **2004**, *6*, 2113–2116.

[72] For selected examples, see: (a) P. G. Cozzi, *Angew. Chem., Int. Ed.* **2003**, *42*, 2895–2898; (b) Y. F. Kang, L. Liu, R. Wang, Y. F. Zhou, W. J. Yan, *Adv. Synth. Catal.* **2005**, *347*, 243–247; (c) G. Lu, X. S. Li, Y. M. Li, F. Y. Kwong, A. S. C. Chan, *Adv. Synth. Catal.* **2006**, *348*, 1926–1933.

[73] (a) N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem., Int. Ed.* **2003**, *42*, 5763–5766; (b) C. Fischer, E. M. Carreira, *Synthesis* **2004**, 1497–1503; (c) C. Fischer, E. M. Carreira, *Org. Lett.* **2004**, *6*, 1497–1499; (d) T. E. Knöpfel, P. Aschwanden, T. Ichikawa, T. Watanabe, E. M. Carreira, *Angew. Chem., Int. Ed.* **2004**, *43*, 5971–5973; (e) P. Aschwanden, C. R. J. Stephenson, E. M. Carreira, *Org. Lett.* **2006**, *8*, 2437–2440; (f) C. M. Wei, J. T. Mague, C. J. Li, *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5749–5754.

[74] (a) S. Pinet, S. U. Pandya, P. Y. Chavant, A. Ayling, Y. Vallee, *Org. Lett.* **2002**, *4*, 1463–1466; (b) D. Topic, P. Aschwanden, R. Fässler, E. M. Carreira, *Org. Lett.* **2005**, *7*, 5329–5330.

In 1999, *Carreira* and co-workers reported the in situ generation of zinc(II) alkynylides using 10 mol % $Zn(OTf)_2$ and 25 mol % *Hünig*'s base, followed by addition to nitrones, aldehydes, ketones, or *N*-tosyl aldimines.[68e] The use of stoichiometric amounts of $Zn(OTf)_2$, NEt_3 and of commercially available (+)-*N*-methyl ephedrine led to the enantioselective addition of various zinc alkynylides to a wide range of aldehydes (Scheme 54).[75] Mechanistic studies based on infrared spectroscopy supported the anticipated formation of a zinc alkynylide intermediate.[76]



Scheme 54.

The first catalytic enantioselective addition of terminal alkynes to aldehydes was developed by *Anand* and *Carreira* (Scheme 55).[77] High yields and enantiomeric excesses were obtained for a wide range of substrates. Over the last five years, several other catalyst systems that only require substoichiometric amounts of metal have been developed.[78] Furthermore, the catalytic enantioselective alkynylation of α-ketoesters was reported recently.[79]

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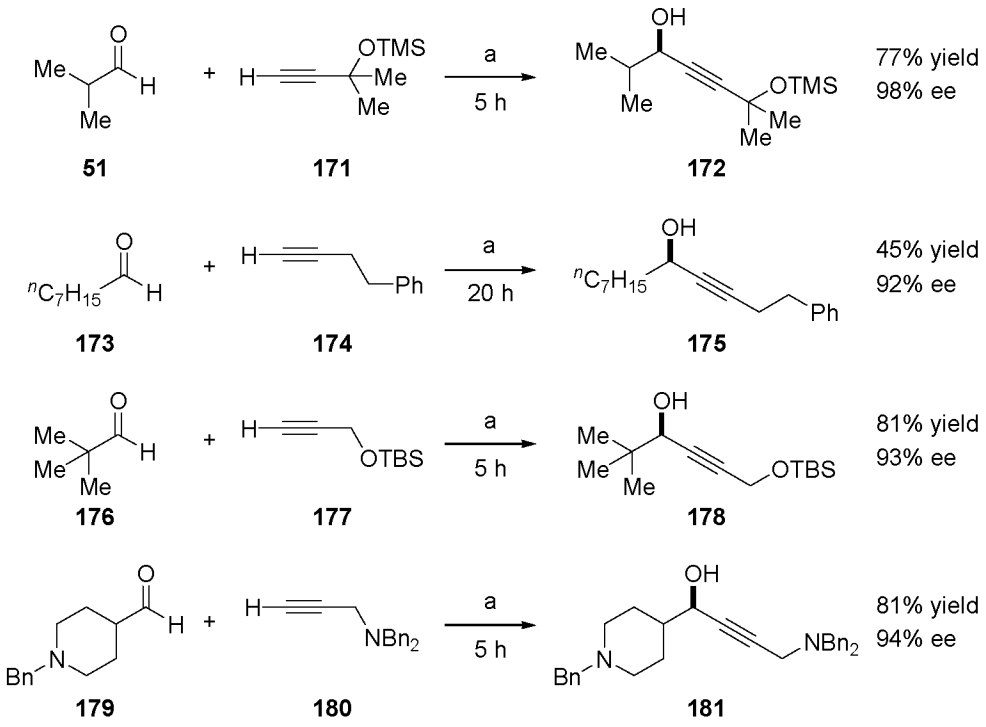
[75] (a) D. E. Frantz, R. Fässler, C. S. Tomooka, E. M. Carreira, *Acc. Chem. Res.* **2000**, *33*, 373–381; (b) D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807; (c) D. Boyall, F. Lopez, H. Sasaki, D. Frantz, E. M. Carreira, *Org. Lett.* **2000**, *2*, 4233–4236; (d) E. El-Sayed, N. K. Anand, E. M. Carreira, *Org. Lett.* **2001**, *3*, 3017–3020; (e) D. Boyall, D. E. Frantz, E. M. Carreira, *Org. Lett.* **2002**, *4*, 2605–2606.

[76] R. Fässler, C. S. Tomooka, D. E. Frantz, E. M. Carreira, *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5843–5845.

[77] N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688.

[78] (a) Z. L. Chen, W. N. Xiong, B. Jiang, *Chem. Commun.* **2002**, 2098–2099; (b) R. Takita, Y. Fukuta, R. Tsuji, T. Ohshima, M. Shibasaki, *Org. Lett.* **2005**, *7*, 1363–1366; (c) M. Yamashita, K. Yamada, K. Tomioka, *Adv. Synth. Catal.* **2005**, *347*, 1649–1652; (d) R. Takita, K. Yakura, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 13760–13761; (e) J. Ekstrom, A. B. Zaitsev, H. Adolfsson, *Synlett* **2006**, 885–888.

[79] B. Jiang, Z. L. Chen, X. X. Tang, *Org. Lett.* **2002**, *4*, 3451–3453.



Scheme 55: (a) $Zn(OTf)_2$ (20 mol %), (+)-NME (22 mol %), NEt_3 (50 mol %), PhMe, rt, 2 h, then alkyne (1.2 equiv), rt, 15 min, then aldehyde (1.0 equiv), 60 °C.

The enantioselective alkynylide addition to aldehydes has been used in the synthesis of several natural products and other biologically active compounds, including efavirenz,[80] leucascandrolide A,[81] (+)-gigantecin,[82] and epoxomycin.[83] Equally noteworthy are the highly stereoselective preparation of an alk-2-yn-1,4-diol (**184**)[84] as well as the stereodivergent synthesis of several tetrahydrofuran moieties[85] such as **188**, which could potentially be applied to the synthesis of *annonaceous* acetogenins[86] in the future (Scheme 56).

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[80] M. E. Pierce, R. L. Parsons, L. A. Radesca, Y. S. Lo, S. Silverman, J. R. Moore, Q. Islam, A. Choudhury, J. M. D. Fortunak, D. Nguyen, C. Luo, S. J. Morgan, W. P. Davis, P. N. Confalone, C. Y. Chen, R. D. Tillyer, L. Frey, L. S. Tan, F. Xu, D. L. Zhao, A. S. Thompson, E. G. Corley, E. J. J. Grabowski, R. Reamer, P. J. Reider, *J. Org. Chem.* **1998**, *63*, 8536–8543.

[81] (a) A. Fettes, E. M. Carreira, *Angew. Chem., Int. Ed.* **2002**, *41*, 4098–4101; (b) A. Fettes, E. M. Carreira, *J. Org. Chem.* **2003**, *68*, 9274–9283.

[82] M. T. Crimmins, J. She, *J. Am. Chem. Soc.* **2004**, *126*, 12790–12791.

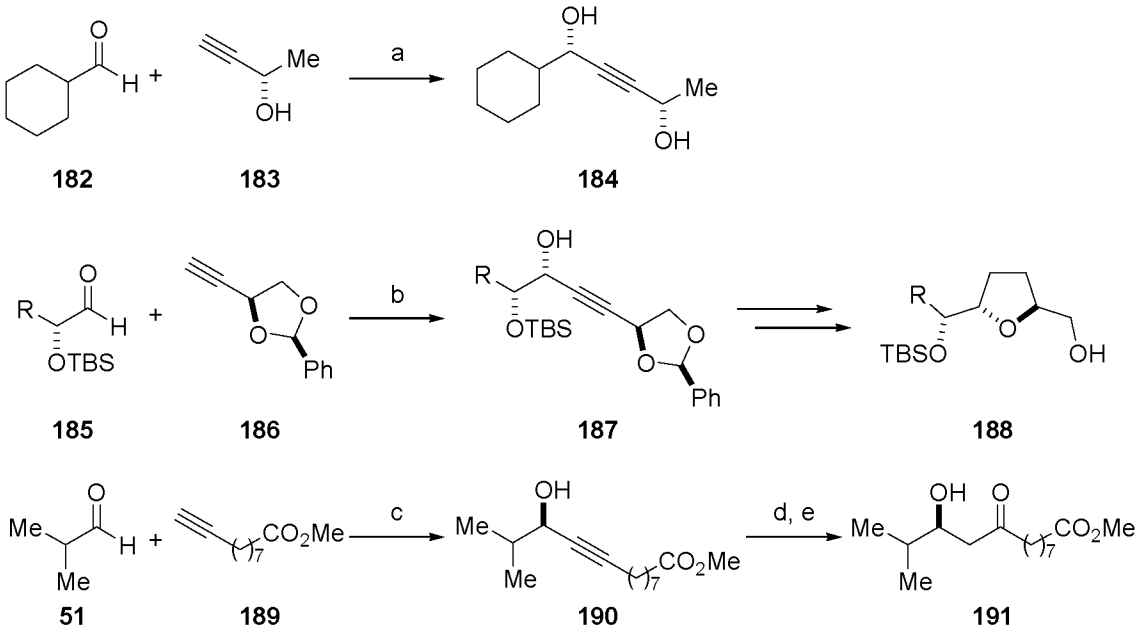
[83] S. Katukojvala, K. N. Barlett, S. D. Lotesta, L. J. Williams, *J. Am. Chem. Soc.* **2004**, *126*, 15348–15349.

[84] M. Amador, X. Ariza, J. Garcia, J. Ortiz, *Tetrahedron Lett.* **2002**, *43*, 2691–2694.

[85] N. Maezaki, N. Kojima, M. Asai, H. Tominaga, T. Tanaka, *Org. Lett.* **2002**, *4*, 2977–2980.

[86] For a review on *annonaceous* acetogenins, see: F. Q. Alali, X. X. Liu, J. L. McLaughlin, *J. Nat. Prod.* **1999**, *62*, 504–540.

Trost and co-workers recently reported the preparation of optically active propargylic alcohols according to *Carreira*'s catalytic procedure and their conversion to the corresponding *β*-hydroxy ketones (e.g. **191**) by an elegant hydrosilylation–oxidation protocol.[87] To date, the catalytic version of the enantioselective zinc alkynylide addition has not been applied yet to the total synthesis of a natural product.



Scheme 56: (a) (−)-NME, $Zn(OTf)_2$, NEt_3, PhMe, 60–70 °C, 3 h, 82% yield, 95:5 dr; (b) (−)-NME, $Zn(OTf)_2$, NEt_3, PhMe, rt, 116 h, 86% yield, 95:5 dr; (c) $Zn(OTf)_2$, (+)-NME, NEt_3, PhMe, 60 °C, 81% yield, 94% ee; (d) $BzMe_2SiH$, $[Cp^*Ru(NCMe)_3]PF_6$, acetone, 0 °C to rt; (e) TBAF, then H_2O_2, MeOH, $KHCO_3$, 80% over 2 steps.

1.7 Conclusion

Bafilomycin A_1 is very attractive to synthetic organic chemists, not only because of its unique structural features but also due to its inhibitory effect on vacuolar ATPases and the resulting potential for pharmaceutical applications. This widespread fascination has given rise to several total and partial syntheses which have been discussed in detail.

Many important observations have been made in the course of these synthetic studies, especially with regard to suitable protective groups and the rather delicate macrolactonization

[87] B. M. Trost, Z. T. Ball, T. Joge, *Angew. Chem., Int. Ed.* **2003**, *42*, 3415–3418.

step. These findings may provide helpful guidance for designing a new route directed at the total synthesis of bafilomycin A_1.

The hydroxy-directed nitrile oxide cycloaddition reaction appears to be an excellent method for the stereoselective construction of the polyketide portion; and an enantioselective enynyl zinc addition seems predestinated for the key C13–C14 bond formation, thereby potentially enabling a very convergent approach to bafilomycin A_1.

2 The Dithiane–Epoxide Approach

2.1 Synthetic Planning

2.1.1 Introduction

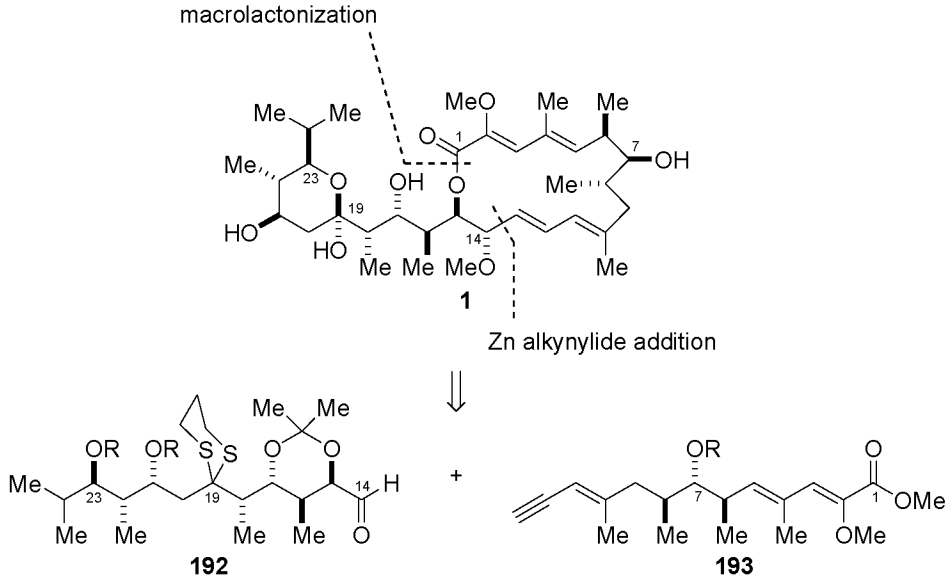
At the outset of this project, several of the aforementioned total syntheses of bafilomycin A_1 had already been reported. Our goal was therefore to showcase the utility of the recently developed hydroxy-directed nitrile oxide cycloaddition in the preparation of a densely functionalized natural product.

The C10–C13 diene unit offered the opportunity to apply our enantioselective zinc alkynylide addition to aldehydes with regard to an enyne substrate. This would allow for a very convergent synthesis of bafilomycin A_1. With these considerations in mind, we proceeded to the retrosynthetic analysis.

2.1.2 Retrosynthetic Analysis

With the obvious disconnection at the C1 ester linkage of the macrolactone, a final macrolactonization of a fully functionalized linear intermediate was envisioned (Scheme 57). Although *Marshall* and co-workers had not been able to effect the lactonization of a substrate that already contained the C19 hemiacetal,[27] *Hanessian*'s linear precursor, bearing a dithiane-protected ketone to prevent ketalization, furnished the desired macrolactone under *Keck* conditions.[24] Thus, protection of the C19 carbonyl group appeared to be crucial for successful macrolactonization.

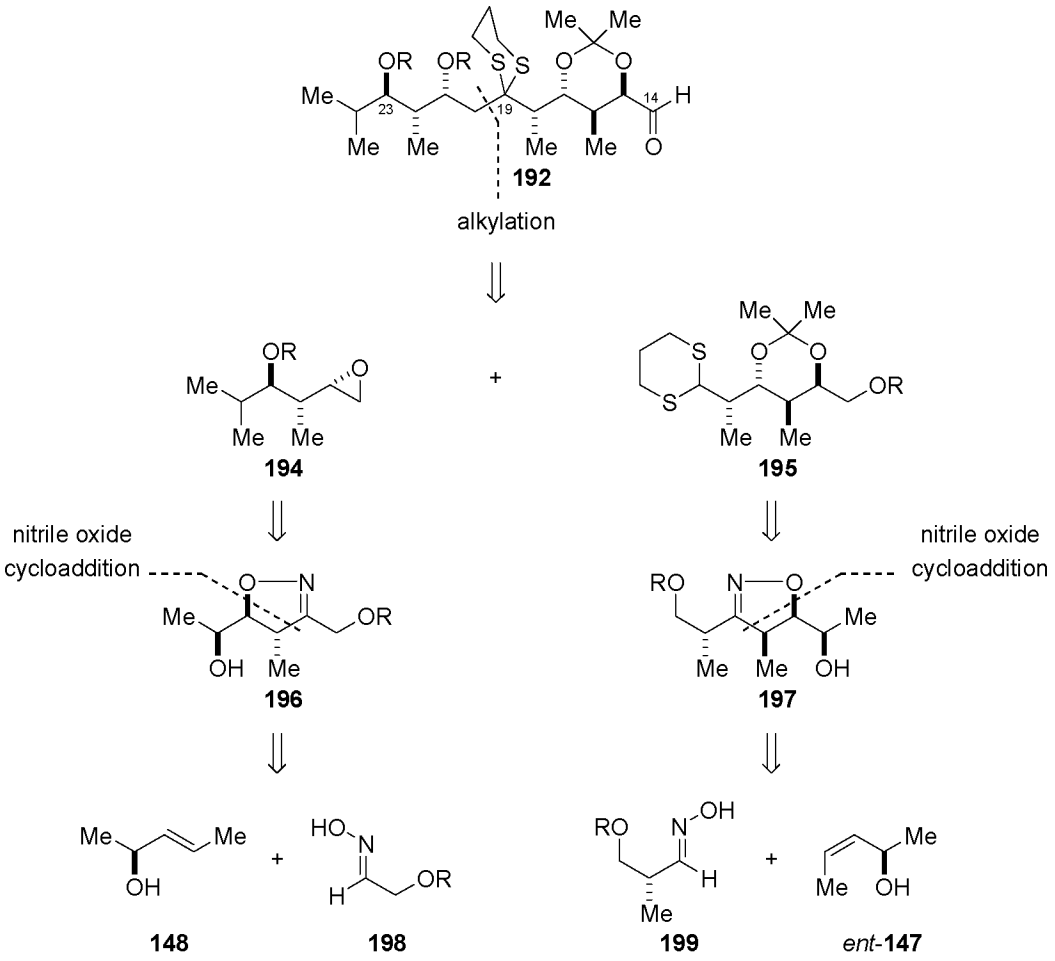
For the convergent assembly of bafilomycin A_1's carbon skeleton, we planned the enantioselective addition of an enynyl zinc species derived from alkyne **193** to the C14–C25 aldehyde **192**. The zinc alkynylide addition to highly functionalized aldehydes has been shown to proceed in high yield and good stereoselectivity,[82] but is unprecedented for conjugated enynes. The preparation of the polyene subunit **193** will be discussed elsewhere.[88]



Scheme 57.

Construction of bafilomycin A_1's densely functionalized polyketide portion **192** was planned to arise from the *C*-alkylation of a dithiane **195** with an epoxide **194**, which would render an additional protection of the C19 carbonyl moiety unnecessary (Scheme 58). Epoxide **194** and dithiane **195** were both envisioned to be derived from an isoxazoline (**196** or **197**, respectively), which would allow for the selective installation of all six stereogenic centers by hydroxy-directed nitrile oxide cycloaddition. The two chiral allylic alcohols **148** and *ent*-**147**, as well as the two aldoximes **198** and **199** would therefore serve as the starting points for our synthetic studies.

[88] The synthesis of bafilomycin A_1's C1–C13 fragment will be part of *Florian Kleinbeck*'s doctoral thesis.



Scheme 58.

2.2 Results and Discussion

2.2.1 Synthesis of the C20–C25 Fragment *via* Nitrile Oxide Cycloaddition

Synthesis of Oxime 202

The synthesis of the epoxide fragment **194** commenced with the preparation of aldoxime **202** according to *Fader* and *Carreira*[62] in a high yielding four-step sequence starting from allyl alcohol (**153**) (Scheme 59).[89] Following suitable protection as TBDPS ether,[90,91]

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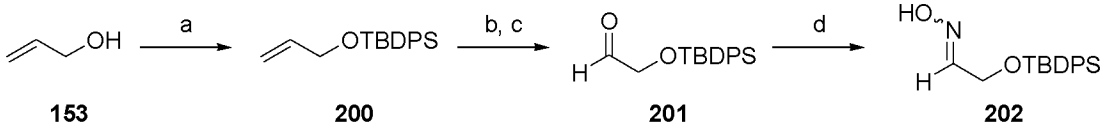
[89] This route was devised and partially executed by Dr. *Lee Fader* who is gratefully acknowledged.

[90] For a general review on protective groups, see: T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Edition, John Wiley & Sons, Inc.: New York, **1999**.

[91] For a general review on silyl protective groups, see: M. Lalonde, T. H. Chan, *Synthesis* **1985**, 817–845.

dihydroxylation of **200** using K_2OsO_4 and subsequent oxidative cleavage of the diol with $NaIO_4$ afforded aldehyde **201**, which was immediately converted to the more stable oxime **202** by treatment with *N*-hydroxylamine.



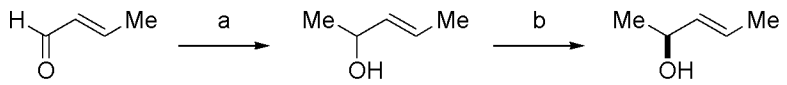
153 **200** **201** **202**

Scheme 59: (a) TBDPSCl, imidazole, DMF, rt, 15 h, 99%; (b) NMO, $K_2OsO_4 \cdot 2\ H_2O$, THF, ^{t}BuOH, H_2O, 0 °C to rt, 20 h; (c) $NaIO_4$, THF, H_2O, 0 °C, 4 h; (d) $HONH_2 \cdot HCl$, NEt_3, EtOH, 5 h, rt, 82% over 3 steps.

The ^{1}H NMR spectrum of aldoxime **202** revealed a mixture of unassigned *E/Z*-isomers with respect to the C=N double bond, as evidenced by the signals at δ 7.49, 4.27, and 1.07 ppm (major) and 6.97, 4.55, and 1.06 ppm (minor), respectively.[92] Its subsequent transformation to the corresponding nitrile oxide, though, rendered the separation of the two stereoisomers unnecessary.

Synthesis of Chiral Allylic Alcohol 148

The chiral allylic alcohol **148** was prepared by methyl *Grignard* addition to crotonaldehyde (**203**), followed by kinetic resolution of (±)-**148** (Scheme 60). Thus, a *Sharpless* asymmetric epoxidation[93] afforded alcohol **148** in 30% yield and 95% enantiomeric excess, as estimated by comparison of the optical rotation.[94]



203 (±)-**148** **148**

Scheme 60: (a) MeMgBr, Et_2O, 0 °C to rt, 100 min, 60%; (b) $Ti(O^iPr)_4$, (–)-DIPT, TBHP, 4 Å MS, CH_2Cl_2, –20 °C, 40 h, 30%, 95% ee.

Compared to the four-step protocol previously employed for the preparation of *ent*-**148** (Scheme 61),[50] which involved alkynylation of acetaldehyde (**205**), TPAP oxidation,[95]

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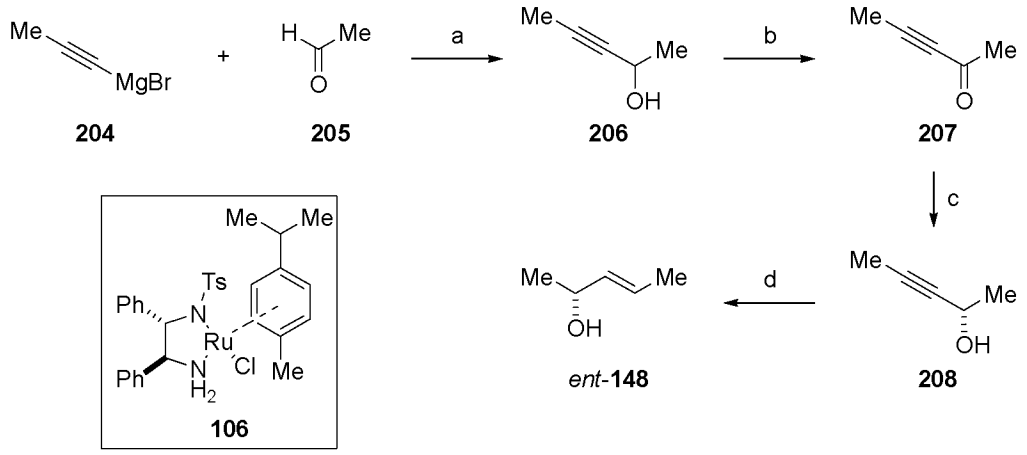
92 For a review, see: H. Metzger in *Nitro-, Nitroso- und Hydroxylamin-Verbindungen, Methoden der organischen Chemie (Houben-Weyl)*, Band 10, Teil 4, Georg Thieme Verlag: Stuttgart, **1971**; pp 282–290.

93 Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.

94 H. J. Gais, T. Jagusch, N. Spalthoff, F. Gerhards, M. Frank, G. Raabe, *Chem. Eur. J.* **2003**, *9*, 4202–4221.

95 W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc., Chem. Comm.* **1987**, 1625–1627.

asymmetric transfer hydrogenation using *Noyori*'s catalyst **106**,[96] and reduction of the propargylic alcohol **208**, the new route offered much faster access to optically active allylic alcohols.



Scheme 61: (a) Et_2O, 0 °C to rt, 5 h, 90%; (b) TPAP (cat.), NMO, 4 Å MS, CH_2Cl_2, rt, 3 h, 89%; (c) **106** (1.5 mol %), ^{i}PrOH, rt, 4.5 d, 85%, 92% ee; (d) $LiAlH_4$, Et_2O, 40 °C, 2 d, 72%.

Nitrile Oxide Cycloaddition and Introduction of the Isopropyl Moiety

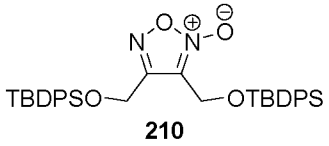
A hydroxy-directed nitrile oxide cycloaddition served as the key step for the synthesis of the C20–C25 fragment (Scheme 62). Aldoxime **202** was treated with ^{t}BuOCl at low temperature to give the typical deep blue solution of the corresponding intermediate hydroxymoyl chloride. The nitrile oxide was then formed in situ upon dropwise addition of the hydroxymoyl chloride to a solution containing the magnesium alkoxide derived from **148**.

Scheme 62: (a) **202**, ^{t}BuOCl, CH_2Cl_2, –78 °C, 2 h, then slow addition to **148**, ^{i}PrOH, EtMgBr, CH_2Cl_2, 0 °C to rt, 29 h, 30–50%, 88:12 dr.

To avoid dimerization of the nitrile oxide, it was very important to perform the addition very slowly over several hours. As a matter of fact, we isolated 10–20% of furoxan **210** (Figure 8) upon fast addition of the hydroxymoyl chloride solution to the alkoxide, while the

[96] K. J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285–288.

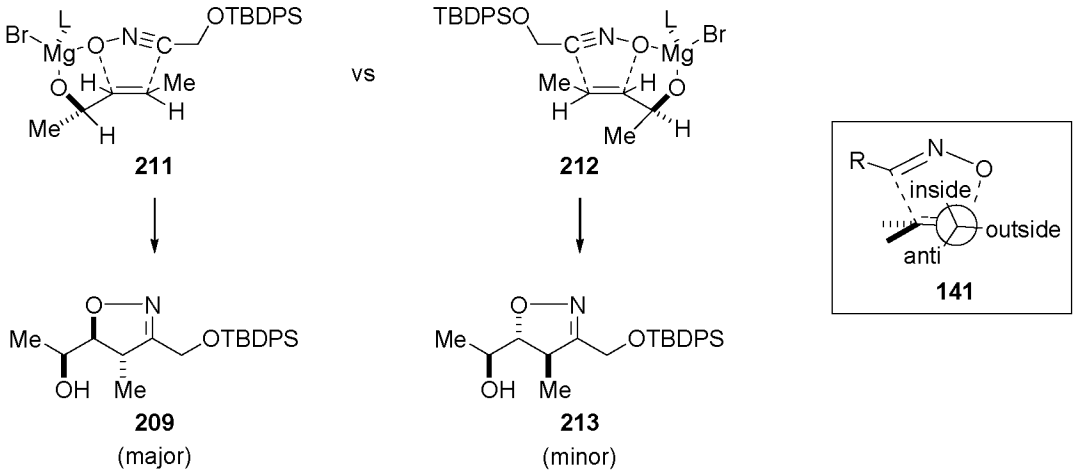
yield of isoxazoline **209** decreased. Furthermore, we chose to use isopropyl alcohol as an additive because it was earlier found to lead to an increase in yield.[49c]



210

Figure 8.

With regard to the diastereoselectivity, transition states **211** and **212** (Scheme 63) have to be considered: Both of them involve chelation of the *Lewis* acidic magnesium ion, which forces the olefin's hydroxy group to adopt the *outside* position according to *Houk*'s transition state model **141**. In transition state **211**, however, the methyl group occupies the sterically least crowded *anti* position, while **212** places the methyl group into the less favored *inside* position.



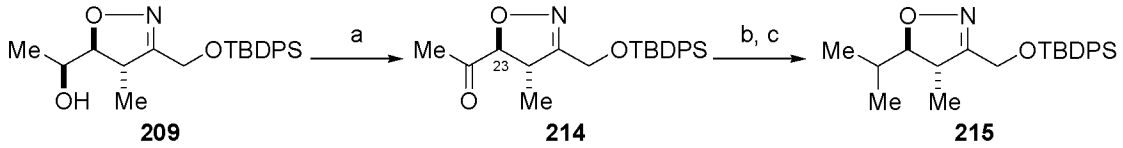
211 **212** **209** (major) **213** (minor) **141**

Scheme 63

Isoxazoline **209** was obtained as a 88:12 mixture of diastereomers, as estimated by integration of the ^{1}H NMR signals around δ 3.22 and 3.44 ppm, respectively. The yields of only 30–50% in combination with the limited scalability of the reaction rendered this nitrile oxide cycloaddition the bottleneck for the synthesis of bafilomycin A_1's C20–C25 subunit.

The transformation of the secondary alcohol **209** to the corresponding isopropyl isoxazoline **215** is depicted in Scheme 64. TPAP oxidation to ketone **214** proceeded in 96% yield and occurred without detected epimerization at C23, as judged by analysis of the C23-H

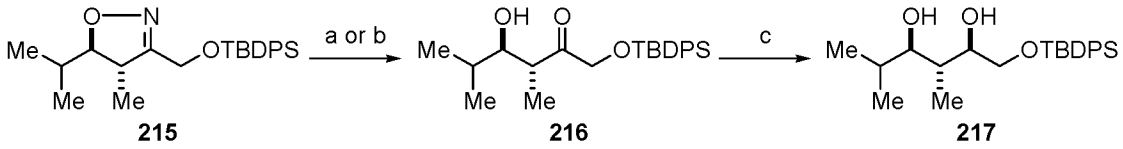
signal at δ 4.48 ppm. *Wittig* olefination and heterogeneous hydrogenation of the intermediary olefin afforded **215** in essentially quantitative yield.



Scheme 64: (a) TPAP (cat.), NMO, 4 Å MS, CH_2Cl_2, 0 °C to rt, 45 min, 96%; (b) Ph_3PMeBr, ^{n}BuLi, THF, –78 °C to 0 °C, 30 min, then –78 °C, **214**, –78 °C to 0 °C, 30 min, 99%; (c) Pd/C, H_2, EtOH, rt, 1 h, quant..

Further Elaboration of Isoxazoline 215

Reductive opening of the isoxazoline moiety was tackled both by Raney-Nickel catalyzed hydrogenation and with $Mo(CO)_6$, respectively (Scheme 65). The desired *β*-hydroxy ketone **216** was obtained in 25–40% yield under various reaction conditions. *Syn*-selective *Prasad* reduction[97] then furnished diol **217** in 53% yield. Analysis of the diol's ^{1}H NMR spectrum prior to purification revealed a diastereomeric ratio of 81:19, as determined by integration of the signals at δ 3.34 ppm (major) and 3.48 ppm (minor).



Scheme 65: (a) Raney-Ni, H_2, $B(OH)_3$, MeOH, H_2O, rt, 20–30 min, 26–34%; (b) $Mo(CO)_6$, MeCN, H_2O, reflux, 3–6 h, 25–40%; (c) BEt_3, $NaBH_4$, THF, MeOH, –78 °C, 4.5 h, 53% yield, 81:19 dr.

At this point, we were several steps away from the C20–C25 epoxide **221** (Scheme 66).[61b] In view of the rather lengthy sequence for the introduction of the isopropyl moiety, the unexpected low yields for the nitrile oxide cycloaddition, the reductive opening of the isoxazoline, and the *Prasad* reduction, as well as the limited scalability of several steps, we decided to devise an alternative route to **221**.

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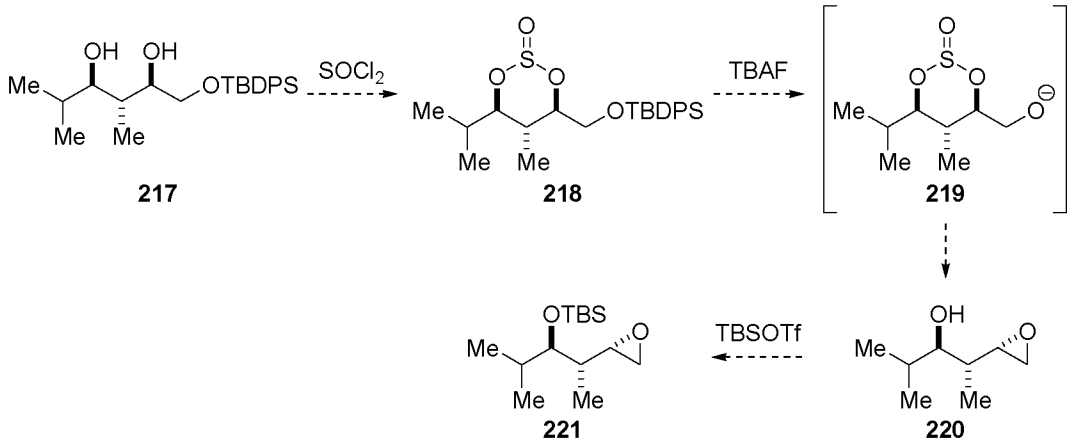
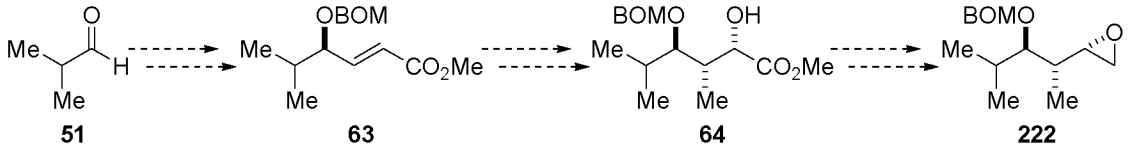
[97] K. M. Chen, K. G. Gunderson, G. E. Hardtmann, K. Prasad, O. Repic, M. J. Shapiro, *Chem. Lett.* **1987**, 1923–1926.



Scheme 66: Final steps originally planned for the synthesis of epoxide **221**.

2.2.2 Synthesis of the C20–C25 Epoxide *via* Zinc Alkynylide Addition

For our second generation approach to the C20–C25 epoxide (Scheme 67), we decided to make use of a catalytic asymmetric zinc alkynylide addition. We planned to intercept *Hanessian*'s α,β-unsaturated ester intermediate **63** and to apply his conjugate addition–hydroxylation protocol to obtain **64**,[24] which would then finally be converted to epoxide **222**.



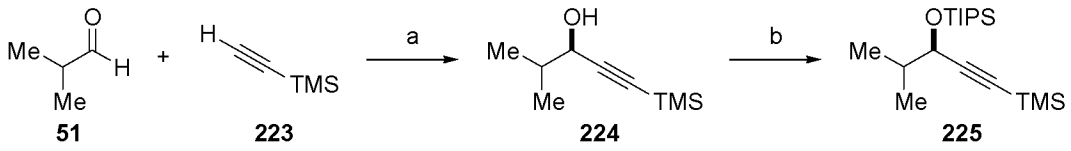
Scheme 67: Revised synthetic plan for the preparation of epoxide **222**.

Synthesis of Acetylenic Ester 227

We began our synthesis with the catalytic enantioselective zinc alkynylide addition of trimethylsilyl acetylene (**223**) to isobutyraldehyde (**51**) (Scheme 68).[77] Thus, alkyne **223** was treated with 20 mol % zinc triflate, 22 mol % (+)-*N*-methyl ephedrine, and 50 mol % triethylamine to form the zinc alkynylide, which was then added to aldehyde **51** to give the chiral propargylic alcohol **224** in 77% yield. In order to determine the enantioselectivity of the alkynylide addition, **224** was subjected to gas chromatographic analysis,[98] which revealed an enantiomeric excess of 92%. The upcoming replacement of the trimethylsilyl group by an

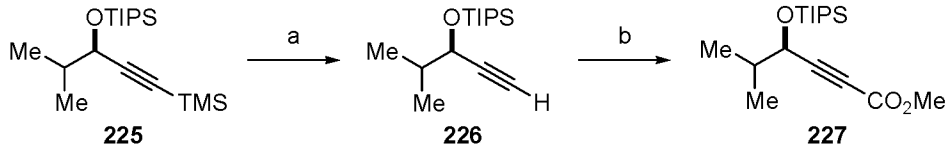
[98] 60–100 °C, ramp 0.5 °C per min, retention times: 32.7 min (minor), 33.3 min (major).

ester moiety necessitated protection of the secondary alcohol, which was consequently converted to the silyl ether **225** in 82% yield.



Scheme 68: (a) $Zn(OTf)_2$ (20 mol %), (+)-NME (22 mol %), NEt_3 (50 mol %), PhMe, 60 °C, 12 h, 77% yield, 92% ee; (b) TIPSOTf, imidazole, DMF, rt, 3 h, 82%.

The trimethylsilyl group was selectively removed using potassium carbonate in methanol (Scheme 69). [99] Treatment of the terminal alkyne **226** with methyl chloroformate and base afforded the corresponding ester **227** in 91% yield over two steps.



Scheme 69: (a) K_2CO_3, MeOH, rt, 20.5 h; (b) ^{n}BuLi, $ClCO_2Me$, THF, –78 °C, 2 h, 91% over 2 steps.

Reduction to Allylic Alcohol 236

The *E*-selective reduction of acetylenic esters was studied in detail by *Meta* and *Koide* (Scheme 70).[100] When sodium borohydride in methanol at –34 °C was used as reducing agent, substrate **228** bearing a free hydroxy group in γ-position was converted to the α,β-unsaturated ester **229** in high yield and complete *E*-selectivity. TBS ether **230**, on the other hand, proved reluctant to reduction even at 0 °C, and **231** was obtained in poor yield and as a 1:2 *E*/*Z*-mixture. The authors concluded that the reactions proceeded *via* intermediate **234**, which secured an intramolecular hydride delivery.[101]

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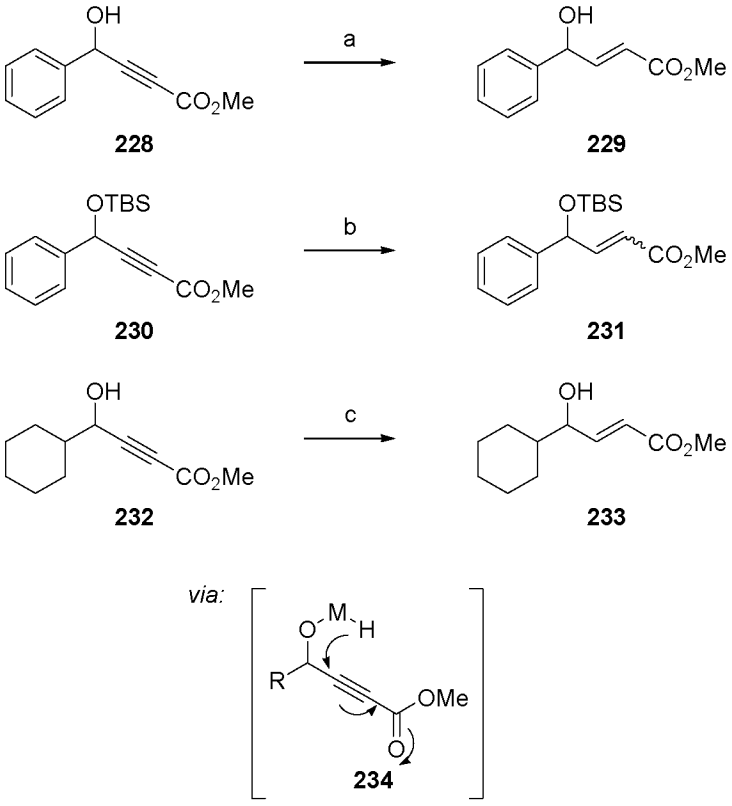
[99] C. Cai, A. Vasella, *Helv. Chim. Acta* **1995**, *78*, 732–757.

[100] C. T. Meta, K. Koide, *Org. Lett.* **2004**, *6*, 1785–1787; for an application, see also: E. M. Carreira, J. Dubois, *J. Am. Chem. Soc.* **1995**, *117*, 8106–8125.

[101] A similar effect was previously described for intramolecular hydrosilylation reactions; see: S. E. Denmark, W. T. Pan, *Org. Lett.* **2003**, *5*, 1119–1122 and references therein.

For the reduction of the aliphatic propargylic alcohol **232**, Red-Al[102] proved superior to sodium borohydride. The desired γ-hydroxy-α,β-unsaturated ester **233** was obtained in 80% yield as a single isomer.



Scheme 70: (a) $NaBH_4$, MeOH, –34 °C, 86%; (b) $NaBH_4$, MeOH, 0 °C, ~15% **233** and 80% **230**, *E*:*Z* (**233**) = 1:2; (c) Red-Al, THF, –72 °C, 25 min, 80%.

On the basis of *Koide*'s results, desilylation of **227** with TBAF afforded propargylic alcohol **235**, which was subjected to Red-Al reduction. The reaction proceeded smoothly at −78 °C and furnished allylic alcohol **236** in 75% yield and with complete *E*-selectivity, as judged by analysis of the ^{1}H NMR spectrum: The signals of the vinyl protons at δ 6.96 and 6.05 ppm (the only ones detected in this region) showed a vicinal coupling constant of J = 15.9 Hz, which is characteristic for *E*-olefins.[103]

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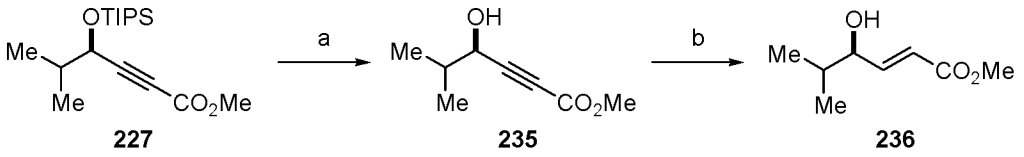
[102] V. Bazant, M. Capka, M. Cerny, V. Chvalovsky, K. Kochloefl, M. Kraus, J. Malek, *Tetrahedron Lett.* **1968**, *9*, 3303–3306.

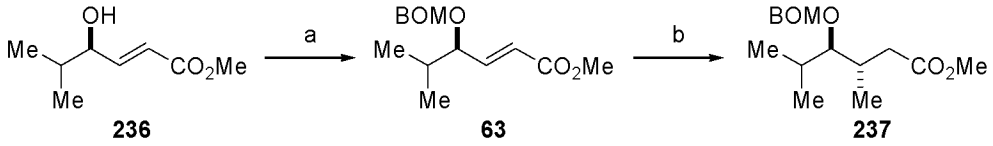
[103] E. Pretsch, P. Bühlmann, C. Affolter; ^{1}H NMR Spectroscopy in *Structure Determination of Organic Compounds*, 3rd Edition; Springer-Verlag: Heidelberg, **2000**.



Scheme 71: (a) TBAF, THF, 0 °C, 20 min, 77%; (b) Red-Al, THF, –78 °C, 25 min, 77%.

Completion of the Epoxide Synthesis

With **236** in hand, we were only one protection step away from *Hanessian*'s intermediate **63**. Alcohol **236** was converted to the benzyloxymethyl ether under standard conditions (Scheme 72). Following *Hanessian*'s protocol, **63** was subjected to diastereoselective 1,4-addition of methyl cuprate. The methyl cuprate was preformed by stirring a suspension of copper(I) iodide in THF with methyllithium at –15 °C to 0 °C for 30 min, was cooled to –78 °C, and was then treated with TMSCl[104] and the α,β-unsaturated ester **63** to give **237** in 84% yield.



Scheme 72: (a) BOMCl, $^{i}Pr_2NEt$, DMAP, CH_2Cl_2, rt, 18 h, 87%; (b) MeLi·LiI, CuI, TMSCl, THF, –78 °C, 4 h, 84%.

The *anti*-selectivity observed in the conjugate addition reaction can be rationalized by *Roush*'s adaptation of the polar *Felkin–Anh* model for additions to carbonyl groups (Figure 9),[105] predicting that

- nucleophilic attack should occur exclusively from the side opposite the electron with-drawing ether substituent, avoiding electrostatic interactions between the electronegative group and the incoming nucleophile,
- and that allylic 1,3-interactions should be minimized.

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[104] (a) E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1985**, *26*, 6019–6022; (b) E. Nakamura, S. Matsuzawa, Y. Horiguchi, I. Kuwajima, *Tetrahedron Lett.* **1986**, *27*, 4029–4032; (c) C. R. Johnson, T. J. Marren, *Tetrahedron Lett.* **1987**, *28*, 27–30.

[105] W. R. Roush, B. M. Lesur, *Tetrahedron Lett.* **1983**, *24*, 2231–2234.

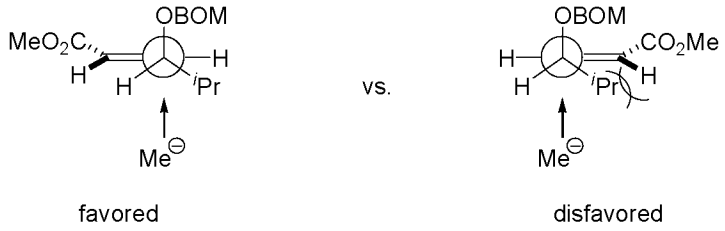
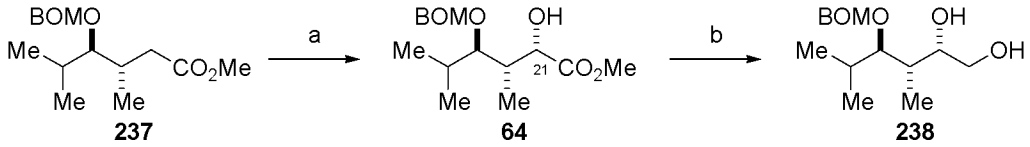


Figure 9. *Roush*'s Adaptation of the polar *Felkin–Anh* model for the 1,4-addition of a nucleophile.

Stereoselective introduction of the C21 hydroxy group was achieved by enolate hydroxylation with *Davis*' oxaziridine[106] (Scheme 73). Transition state **239** (Figure 10) accounts for the observed *syn*-selectivity of >20:1. Reduction of ester **64** with $LiBH_4$ furnished diol **238** in 71% yield.[107]



Scheme 73: (a) KHMDS, THF, then *Davis*' oxaziridine, –78 °C, 9.5 h, 63%; (b) $LiBH_4$, THF, MeOH, 0 °C to rt, 4 h, 71%.

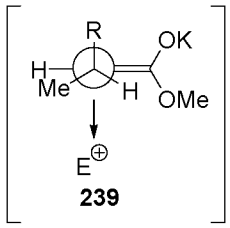


Figure 10.

The primary alcohol of diol **238** was selectively sulfonylated with mesitylenesulfonyl chloride to give α-hydroxy sulfonate **240** (Scheme 74). Subsequent treatment of **240** with base afforded the desired C20–C25 epoxide **222**.

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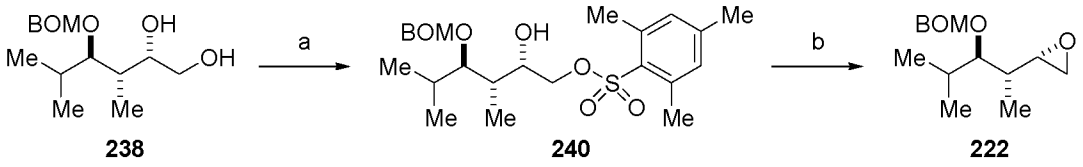
[106] F. A. Davis, O. D. Stringer, *J. Org. Chem.* **1982**, *47*, 1774–1775.

[107] H. C. Brown, S. Narasimhan, Y. M. Choi, *J. Org. Chem.* **1982**, *47*, 4702–4708.



Scheme 74: (a) mesitylenesulfonyl chloride, DMAP, CH_2Cl_2, 0 °C, 3 h; (b) LHMDS, THF, –78 °C to 0 °C, 2.5 h, 53% over 2 steps.

2.2.3 Synthesis of the C14–C19 Dithiane *via* Nitrile Oxide Cycloaddition

The preparation of the dithiane subunit[108] commenced with the asymmetric synthesis of isoxazoline *ent*-**151** (Figure 11), whose enantiomer had been reported by *Carreira* and co-workers in 2001 (Scheme 49).[50] Along the same lines, we planned to access *ent*-**151** *via* the hydroxy-directed nitrile oxide cycloaddition between allylic alcohol *ent*-**147** and aldoxime **146**.

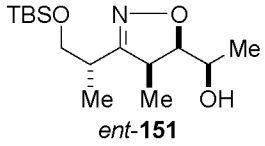
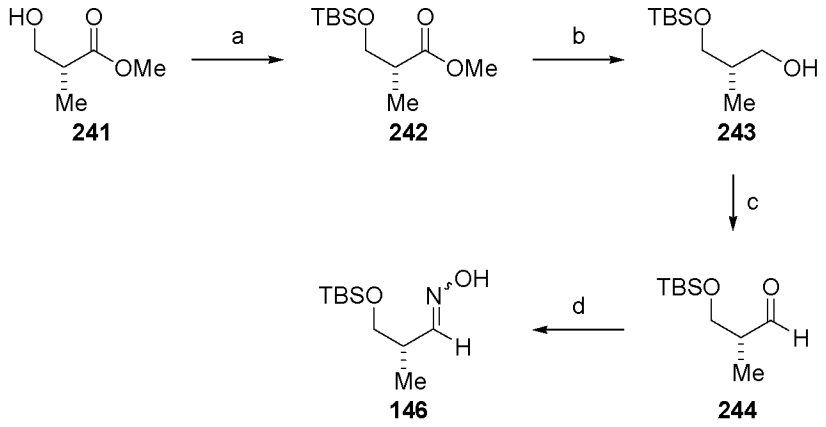


Figure 11.

Synthesis of Chiral Oxime 146

Aldoxime **146** was prepared according to the four-step sequence reported for its enantiomer[50] (Scheme 75). *tert*-Butyldimethylsilyl protection of commercially available (*R*)-3-hydroxy-2-methyl-propionic acid methyl ester (**241**) under standard conditions afforded silyl ether **242** in essentially quantitative yield. Aldehyde **244** was obtained by ester reduction with DIBAL-H and subsequent TPAP oxidation of the intermediary primary alcohol **243**, and was immediately converted to aldoxime **146**. Once again, analysis of the ^{1}H NMR spectrum revealed an inconsequential *E*/*Z*-mixture with respect to the C=N double bond, which was determined to be ~2:1 by integration of the signals at δ 7.41 ppm (major) and 6.66 ppm (minor).

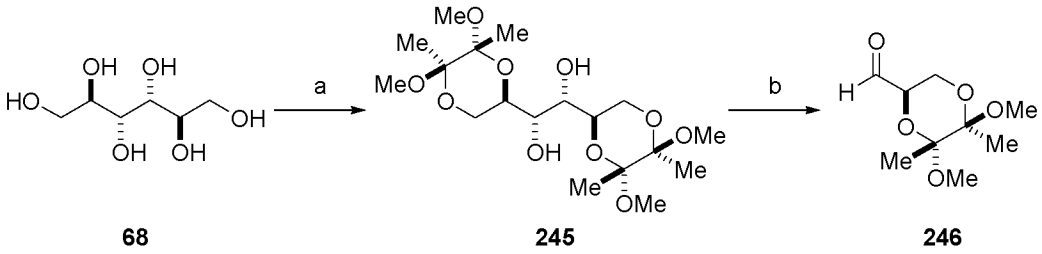
[108] Part of this synthesis was devised by Dr. *Lee Fader* and *Florian Kleinbeck* who are gratefully acknowledged.



Scheme 75: (a) TBSCl, imidazole, DMF, rt, 12 h; (b) DIBAL-H, CH_2Cl_2, –78 °C, 90 min; (c) TPAP (cat.), NMO, 4 Å MS, CH_2Cl_2, 0 °C to rt, 3 h; (d) $NH_2OH{\cdot}HCl$, py, EtOH, rt, 14 h, 55% over 4 steps.

Synthesis of Chiral Allylic Alcohol *ent*-147

We next turned our attention to redesigning the dipolarophile synthesis. Commercially available D-mannitol **(68)** was converted to aldehyde **246** according to *Ley*'s procedure (Scheme 76).[109] Selective protection of the terminal diol units with butanedione and trimethyl orthoformate under acidic conditions afforded the diprotected intermediate **245**. Aldehyde **246** was then obtained by oxidative cleavage of the middle diol moiety using $NaIO_4$.



Scheme 76: (a) butanedione, $HC(OMe)_3$, $BF_3{\cdot}THF$, MeOH, rt, 4 h, 40%; (b) $NaIO_4$, CH_2Cl_2, sat. aq. $NaHCO_3$, rt, 14 h.

Selective access to *Z*-olefin **247**[110] was achieved by *Wittig* olefination of aldehyde **246** (Scheme 77).[111] Analysis of the ^1H NMR spectrum revealed a *Z*/*E*-ratio of 92:8, as determined

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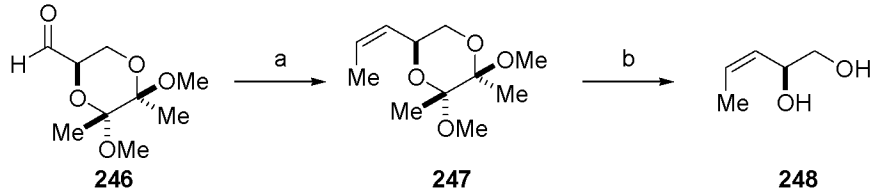
[109] P. Michel, S. V. Ley, *Synthesis* **2003**, 1598–1602.

[110] The preferential formation of the *Z*-double bond was later confirmed by comparison of the spectral data for *ent*-**147** to the previously reported data; see: O. Hamed, P. M. Henry, *Organometallics* **1997**, *16*, 4903–4909.

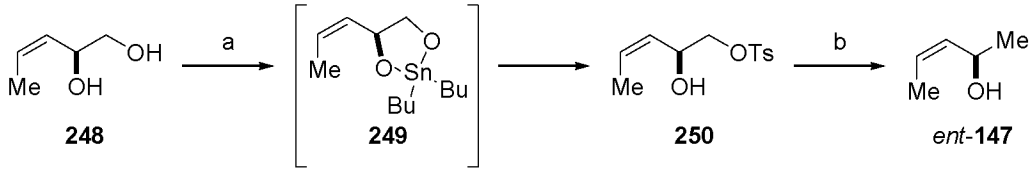
[111] For a review, see: E. Vedejs, M. J. Peterson, *Top. Stereochem.* **1994**, *21*, 1–157.

by integration of the methoxy signals at δ 3.37/3.36 (minor) and 3.33/3.28 (major) ppm. Removal of the butane diacetal under acidic conditions afforded diol **248** in 93% yield.



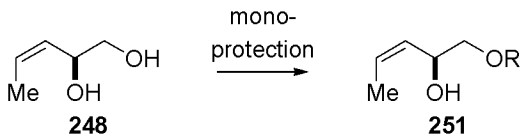
Scheme 77: (a) Ph_3PEtBr, ^nBuLi, THF, 0 °C, 30 min, then **246**, –78 °C to rt, 10 h, 60% from diol **245**, *Z*/*E* = 92:8; (b) AcOH, H_2O, 60 °C, 6.5 h, then rt, 11 h, 93%.

The synthesis of chiral allylic alcohol *ent*-**147** was completed by selective tosylation of the primary hydroxy group to give **250** in 80% yield, followed by $LiAlH_4$ reduction (Scheme 78). During the first step, stannylene intermediate **249** is formed and converted in situ to mono-tosylate **250** by treatment with TBAB and TsCl.[112] This sequence was more efficient than direct mono-tosylation of the parent diol, which afforded **250** in only 56% yield.



Scheme 78: (a) Bu_2SnO, PhH, 90 °C, 2 h, then 90 °C to 50 °C, 1 h, then TBAB, TsCl, 50 °C, 1 h, 80%; (b) $LiAlH_4$, Et_2O, 0 °C, 2.5 h, 72%.

Z-olefin *ent*-**147** was thus prepared in six steps and 15% overall yield from commercially available D-mannitol on a multi-gram scale. Furthermore, the diol intermediate **248** offered access to mono-protected diols **251** (Scheme 79), which were later tested as alternative dipolarophiles in the hydroxy-directed nitrile oxide cycloaddition (see section 3.2.2).

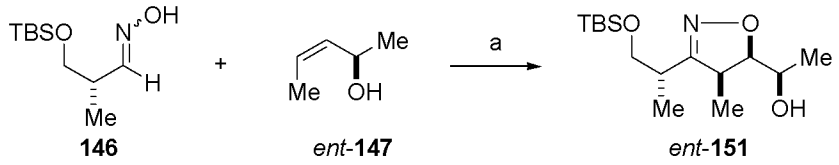


Scheme 79.

[112] (a) M. J. Martinelli, R. Vaidyanathan, V. Van Khau, *Tetrahedron Lett.* **2000**, *41*, 3773–3776; (b) A. R. L. Cecil, Y. L. Hu, M. J. Vicent, R. Duncan, R. C. D. Brown, *J. Org. Chem.* **2004**, *69*, 3368–3374.

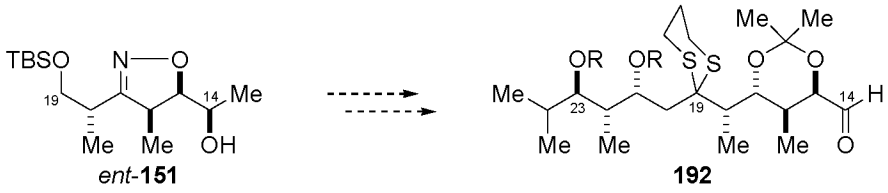
The Nitrile Oxide Cycloaddition

The key nitrile oxide cycloaddition between oxime **146** and allylic alcohol *ent*-**147** under standard conditions proceeded uneventfully (Scheme 80).[50] The desired isoxazoline *ent*-**151** was obtained in 80% yield and with complete diastereoselectivity as judged by analysis of the ^{1}H NMR signals between 3.50 ppm and 4.00 ppm.



Scheme 80: (a) **146**, ^{t}BuOCl, CH_2Cl_2, –78 °C, 2 h, then *ent*-**147**, ^{i}PrOH, EtMgBr, 0 °C to rt, 12 h, 80%.

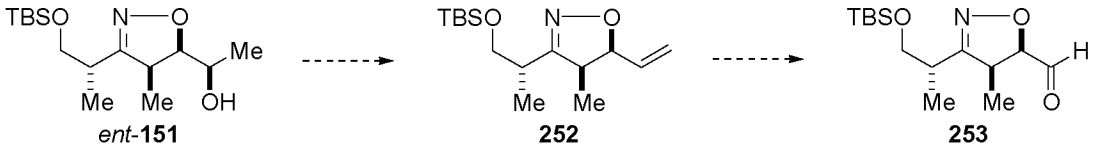
The main drawback of this approach utilizing the diastereoselective cycloaddition, however, is the need for a stereogenic center located at the dipolarophile's allylic C14 position in order for the selective formation of *ent*-**151**. Since we envisioned the formation of the C13–C14 bond by enynyl zinc addition to aldehyde **192**, the terminal methyl group present in *ent*-**151** had to be cleaved (Scheme 81).



Scheme 81.

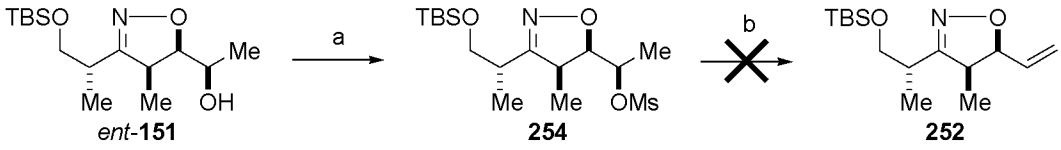
The Elimination Problem

Looking for a fast approach to the C14 aldehyde **253**, dehydration of isoxazoline *ent*-**151** to the terminal olefin **252** and subsequent oxidative cleavage of the double bond seemed promising (Scheme 82). It is important to use a mild dehydrating reagent to avoid side reactions, such as removal of the silyl ether protective group under acidic conditions, epimerization, or elimination of the *O*-functionalities in β-position to the C=N bond.



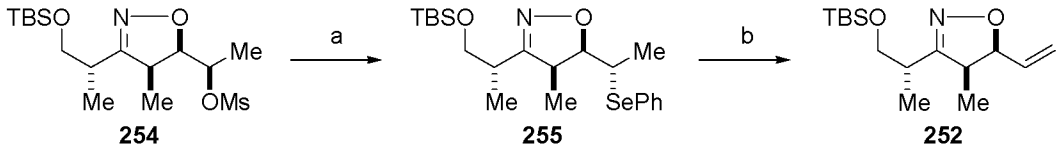
Scheme 82.

We decided to investigate the transformation of the isoxazoline's secondary alcohol into a good leaving group followed by base-promoted elimination.[113] Difficulties potentially arising from such an approach are epimerization at C16 or C18 under the elimination conditions or the formation of the internal C14=C15 double bond. Alcohol *ent*-**151** was converted to the corresponding mesylate **254** using methanesulfonyl chloride and triethylamine (Scheme 83). But when **254** was treated with a large variety of commonly used bases, none of the desired olefin **252** was isolated.



Scheme 83: (a) MsCl, NEt_3; (b) NaOH or KH or KO^{t}Bu or KHMDS or DBU/Δ.

In a further attempt, mesylate **254** was converted to selenide **255** and subsequently treated with H_2O_2 (Scheme 84). Although this procedure finally furnished the desired alkene **252**, the yields were varying from 10–40% over the two steps. These rather unsatisfying results prompted the search for better alternatives.



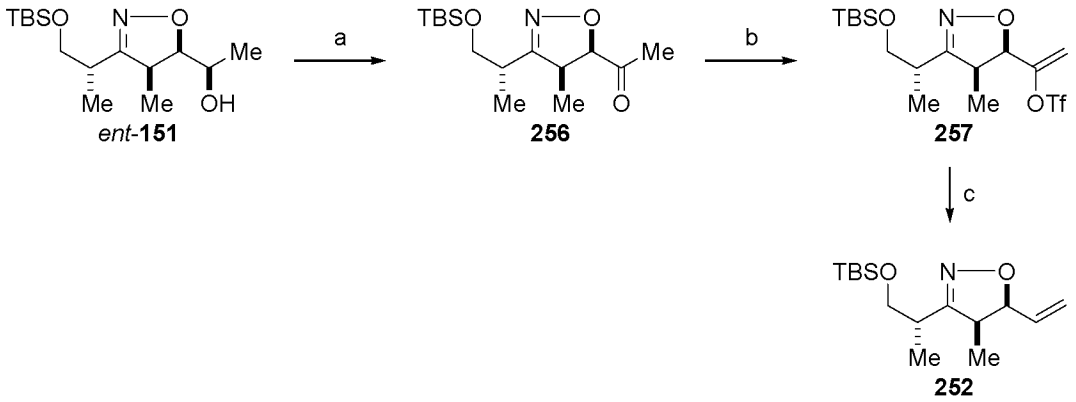
Scheme 84: (a) $(PhSe)_2$, $NaBH_4$; (b) H_2O_2, 10–40% over 2 steps.

Therefore, the Pd-catalyzed reduction of a vinyl triflate intermediate **257** was examined (Scheme 85).[114] Ketone **256** was prepared in 93% yield by TPAP oxidation of the secondary alcohol *ent*-**151**. Conversion of the former to the corresponding terminal vinyl triflate proved somewhat challenging, but when $PhNTf_2$ was added to the substrate prior to the base, triflate

[113] These elimination studies were performed by Dr. *Lee Fader* who is gratefully acknowledged.

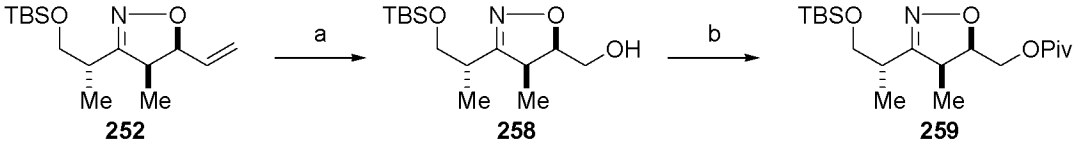
[114] Further optimization of this route will be discussed in *Florian Kleinbeck*'s doctoral thesis.

257 was obtained in 43% yield along with 39% of unreacted starting material. Transfer hydrogenation of triflate **257** afforded olefin **252** in 89% yield.



Scheme 85: (a) TPAP (cat.), NMO, 4 Å MS, CH_2Cl_2, 0 °C to rt, 3 h, 93%; (b) KHMDS, THF, –78 °C, 30 min, $PhNTf_2$, –78 °C, 50 min, 43% (70% based on recovered starting material); (c) $Pd(OAc)_2$, PPh_3, HCO_2H, NEt_3, DMF, 60 °C, 15 min, 89%.

Ozonolysis of the terminal alkene **252** in methanol at −78 °C, followed by reductive work-up furnished the primary alcohol **258** (Scheme 86). Before proceeding to the isoxazoline opening, alcohol **258** had to be protected and was therefore converted to the corresponding pivaloate **259**, which would allow for the selective removal of the ester group at a later stage.

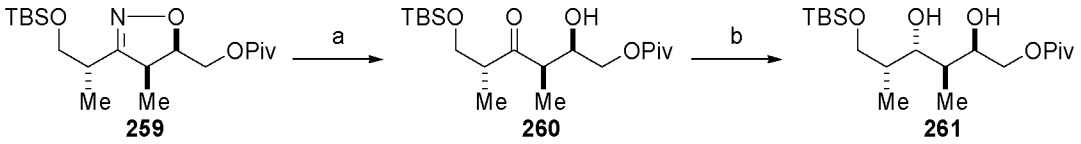


Scheme 86: (a) O_3, MeOH, –78 °C, 10 min, then $NaBH_4$, –78 °C to rt, 1 h; (b) PivCl, py, rt, 10.5 h, 65% over 2 steps.

Opening of the Isoxazoline and 1,3-*anti* Reduction

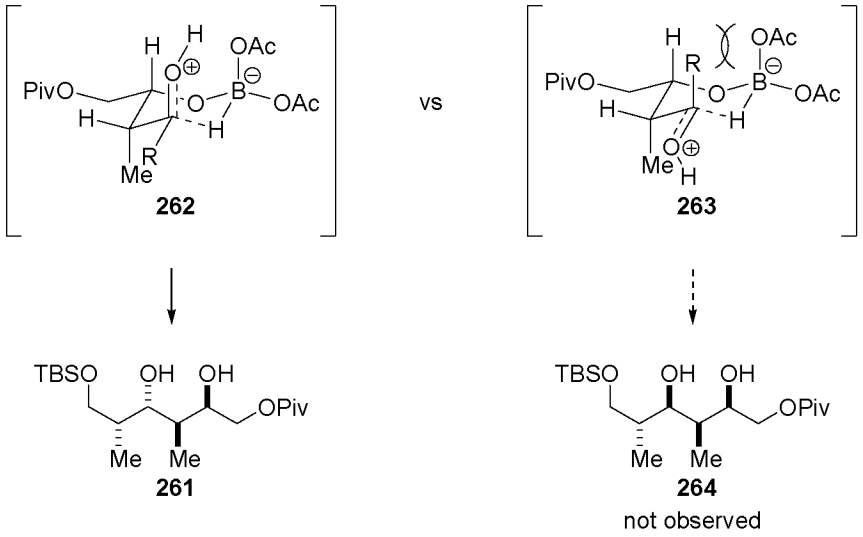
The reductive opening of the isoxazoline moiety using Raney-Nickel afforded *β*-hydroxy ketone **260** in very high yield of 95% (Scheme 87). For the 1,3-*anti* selective reduction to diol **261**, we applied the method developed by *Evans* and co-workers.[115] It was shown by these authors that omitting the acetic acid additive had a detrimental effect on both conversion and diastereoselectivity of the reaction, which led to the conclusion that acidic activation of the carbonyl group was necessary for the hydride attack to occur.

[115] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.



Scheme 87: (a) H_2, Raney-Ni, $B(OH)_3$, MeOH, H_2O, rt, 45 min, 95%; (b) $Me_4NBH(OAc)_3$, MeCN, AcOH, rt, 20 min, then –20 °C, **260**, –20 °C, 24 h, then rt, 1 h.

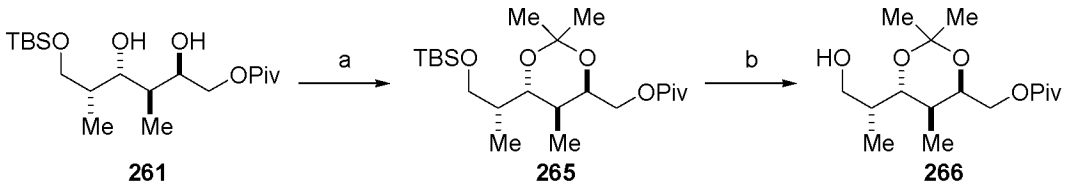
The observed *anti*-selectivity was explained by a directed intramolecular hydride transfer *via* the competing six-membered transition states **262** and **263** (Scheme 88): The more pronounced 1,3-diaxial interactions between R and OAc destabilize **263** to a greater extent than the interactions between HO^+ and OAc found in **262**.



Scheme 88.

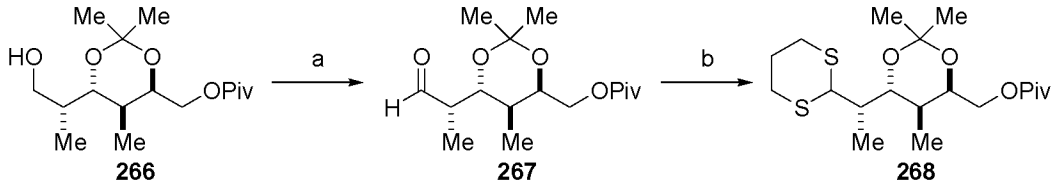
Completion of the Dithiane Synthesis

With diol **261** in hand, we were very close to the completion of the C14–C19 fragment. Protection of the diol moiety and removal of the *tert*-butyldimethylsilyl group furnished hydroxy acetal **266** (Scheme 89).



Scheme 89: (a) $Me_2C(OMe)_2$, TsOH, rt, 1 h, 51% over 2 steps; (b) TBAF, THF, rt, 4 h, 92%.

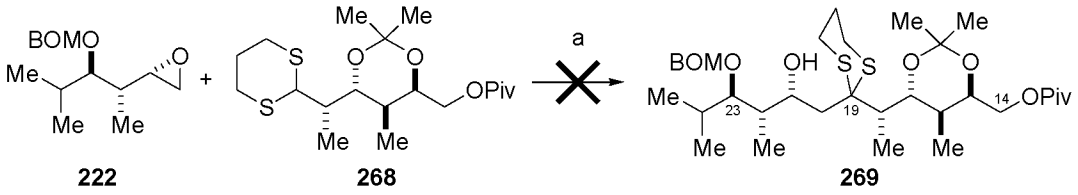
Alcohol **266** was oxidized to aldehyde **267** using *Ley*'s conditions (Scheme 90). During the acid-catalyzed synthesis of dithiane **268**, partial deprotection of the diol moiety was observed, which was reversed in situ by the addition of 2,2-dimethoxypropane.



Scheme 90: (a) TPAP (cat.), NMO, 4 Å MS, CH_2Cl_2, 0 °C to rt, 1.5 h, 93%; (b) $BF_3{\cdot}OEt_2$, $HS(CH_2)_3SH$, CH_2Cl_2, 0 °C to rt, 4.5 h, then $Me_2C(OMe)_2$, rt, 30 min, 71%.

2.2.4 Attempted Dithiane–Epoxide Coupling

The stage was set for the key fragment coupling between dithiane **268** and epoxide **222**, and we were eager to test the scope of the projected alkylation. Dithiane **222** was deprotonated with ^{t}BuLi (1.1 equiv) to give a yellow solution of the anion, to which epoxide **268** was added. To our great disappointment, we were not able to isolate any of the desired coupling product **269**, nor were we able to recover the dithiane starting material **268**. Epoxide **222**, on the other hand, seemed unreactive under the employed conditions.[116] After a number of unsuccessful attempts, we decided to reconsider our overall approach.



Scheme 91: (a) **268**, ^{t}BuLi, HMPA, THF, –78 °C, 1 h, then **222**, –78 °C, 5.5 h.

2.2.5 Conclusion

In the course of our first generation approach to the synthesis of bafilomycin A_1's C20–C25 fragment, the advanced diol intermediate **217** was prepared in ten steps and 5% overall yield from commercially available allyl alcohol. The selective introduction of the stereogenic

[116] To further examine the reactivity of epoxide **222**, it was treated with lithiated 2-isopropyl-[1,3]dithiane (1.2 equiv): once again, **222** was recovered.

centers relied on the key nitrile oxide cycloaddition between allylic alcohol **148** and oxime **202**.

Our second generation approach to epoxide **222** was based on a catalytic enantioselective zinc alkynylide addition to isobutyraldehyde. Further elaboration of the optically active propargylic alcohol involved a diastereoselective conjugate addition–hydroxylation sequence and finally furnished epoxide **222** in twelve steps and 6% overall yield.

Bafilomycin A_1's C14–C19 subunit **268** was prepared in 18 steps from D-mannitol, making use of a hydroxy-directed nitrile oxide cycloaddition reaction. Subsequently, the conversion to the derived primary alcohol was achieved *via* palladium-catalyzed transfer hydrogenation of a vinyl triflate and successive ozonolysis. Reductive opening of the isoxazoline moiety and selective reduction to the 1,3-*anti*-diol both proceeded in very high yield.

In conclusion, we have accomplished the synthesis of two advanced intermediates, namely epoxide **222** and dithiane **268**, which we planned to connect and further elaborate to the macrolide antibiotic bafilomycin A_1. Although the coupling of the two fragments **222** and **268** was unsuccessful, we were able to demonstrate the utility of the zinc-catalyzed alkynylide addition and the hydroxy-directed nitrile oxide cycloaddition for the stereoselective preparation of highly functionalized polyketide building blocks and thus to contribute to the consolidation of these valuable methods among the standard reactions of organic synthesis.

3 The Aldol Approach

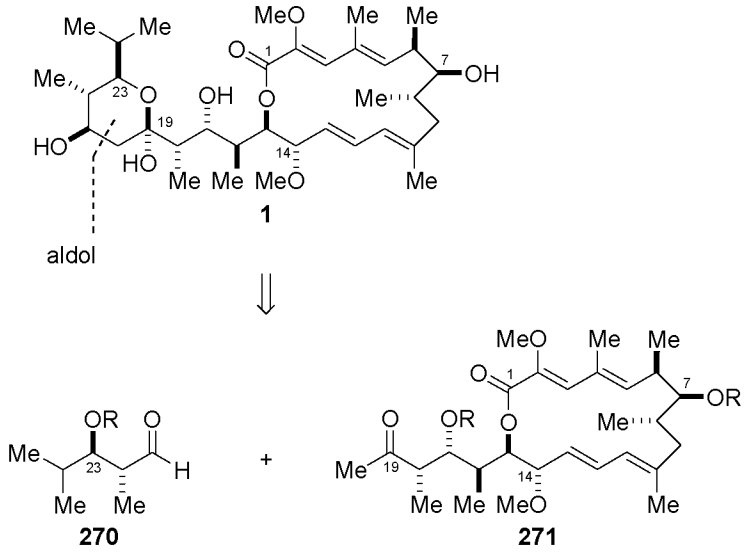
3.1 Synthetic Planning

3.1.1 Introduction

In the course of our dithiane–epoxide approach to bafilomycin A_1, we gained useful insights with regard to suitable protective groups, viable reaction sequences leading to enantio- and diastereomerically pure intermediates, and potential pitfalls along the way. We wished to design a new route that would combine our previously elaborated methodology with a more dependable fragment coupling strategy. With these considerations in mind, we proceeded to amend our earlier synthetic planning.

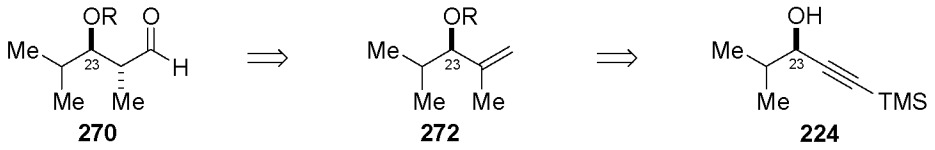
3.1.2 Retrosynthetic Analysis

Our second generation approach to bafilomycin A_1 (**1**) focused on a late-stage aldol coupling of an aldehyde **270** to a macrocyclic ketone **271** (Scheme 57). The same strategy for the C13–C14 bond formation was previously pursued by *Roush* and co-workers during their synthesis of **1**[23] and would offer an opportunity to intercept intermediates thereof.



Scheme 92.

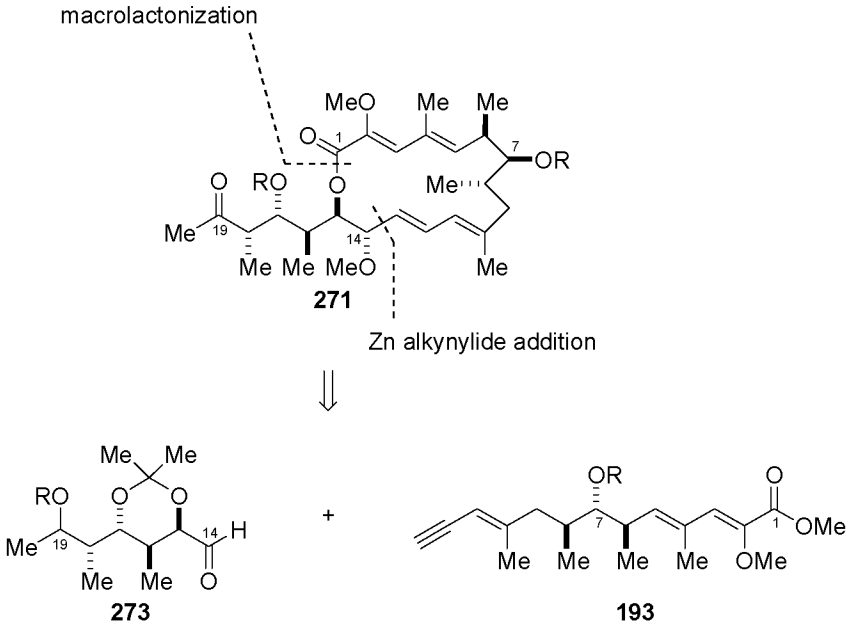
We planned to access aldehyde **270** from the optically active propargylic alcohol **224** (Scheme 93), which had been synthesized in the course of our dithiane–epoxide approach (see section 2.2.2). Intermediate **272** was envisioned to emerge from a carbometalation reaction and to be further elaborated by hydroboration.



Scheme 93.

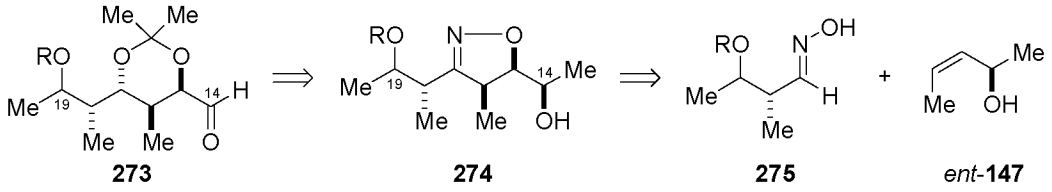
With regard to the macrolactone **271**, we intended to pursue our original plan and attempt the enynyl zinc addition of a polyene fragment **193**[117] to an aldehyde **273** (Scheme 94). Macrolactonization under the previously successful *Yamaguchi* or *Keck* conditions would then afford the macrocyclic ketone **271**.[22–24]

[117] The synthesis of bafilomycin A_1's C1–C13 fragment will be part of *Florian Kleinbeck*'s doctoral thesis.



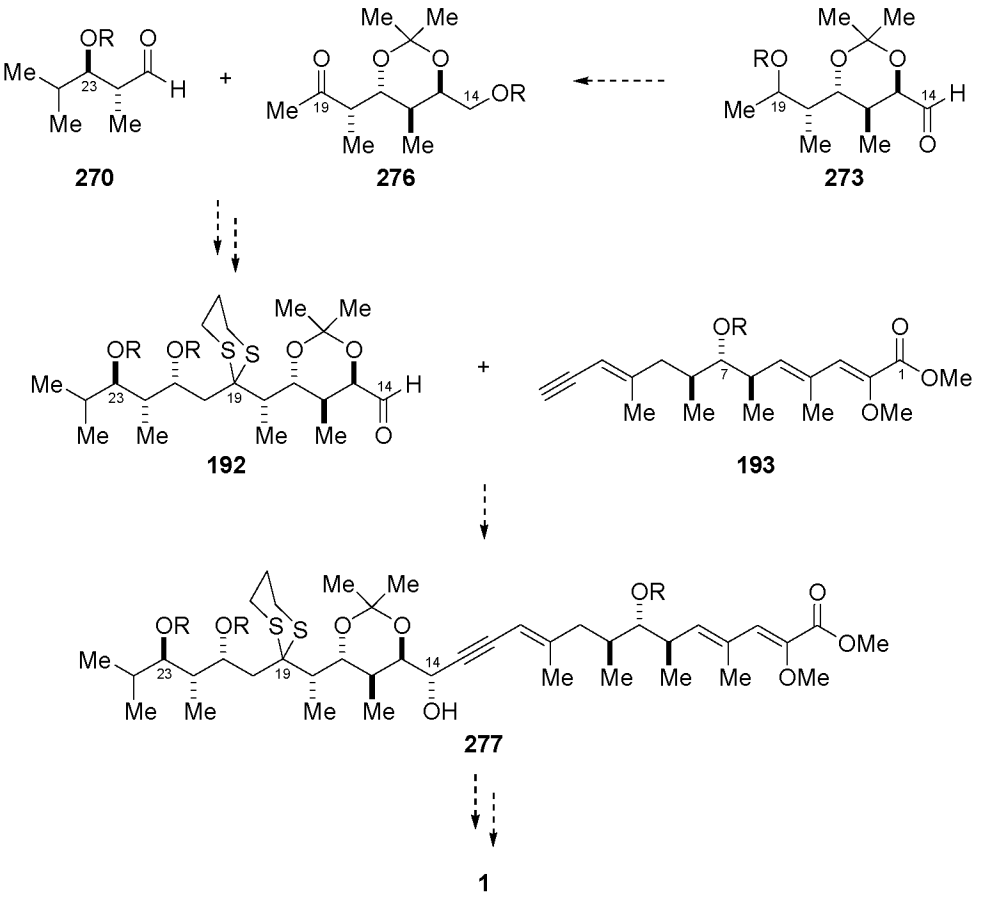
Scheme 94.

For the synthesis of aldehyde **273**, we planned the hydroxy-directed nitrile oxide cycloaddition between a chiral oxime **275** and allylic alcohol *ent*-**147**. Further processing of isoxazoline **274** would then involve reductive opening of the heterocycle and 1,3-*anti* reduction of the intermediary *β*-hydroxy ketone. Since the protected alcohol at C19 will be oxidized to a ketone for the final aldol coupling step, the configuration at C19 is inconsequential and can thus be chosen based on the accessibility of the respective oxime precursor **275**.



Scheme 95.

The projected key fragments, aldehyde **270**, aldehyde **273**, and enyne **193** would also allow for an alternative coupling sequence along the lines of our previous dithiane–epoxide approach (Scheme 96): Aldol reaction between ketone **276** and aldehyde **270**, followed by enynyl zinc addition of **193** to **192** to give the linear bafilomycin A_1 precursor **277**.



Scheme 96.

This alternative coupling order gives us additional flexibility for the elaboration of a convergent synthesis of bafilomycin A_1 and provides a backup strategy. Our second generation approach will therefore commence with the preparation of three chiral components, namely propargylic alcohol **224**, oxime **275**, and allylic alcohol *ent*-**147**, and will involve an enynyl zinc addition and an aldol reaction for the key coupling events.

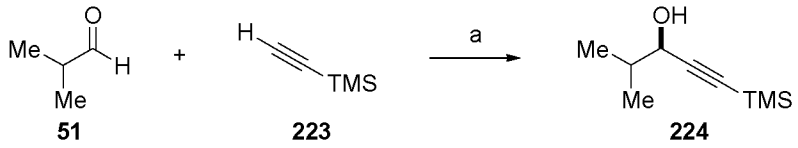
3.2 Results and Discussion

3.2.1 Synthesis of the C21–C25 Aldehyde *via* Zinc Alkynylide Addition

Synthesis of the Propargylic Silyl Ether 279

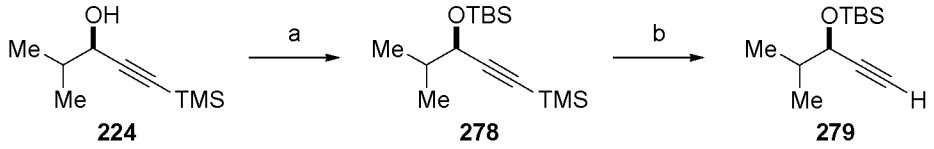
Our synthesis of aldehyde **5** commenced with the Zn-catalyzed addition of alkyne **223** to aldehyde **51** (Scheme 68), which was discussed in the course of our dithiane–epoxide

approach (see section 2.2.2). Both reactants as well as the reagents being commercially available, this reliable reaction was typically performed on a 50 mmol scale. Alcohol **224** was obtained in 77% yield and 92% enantiomeric excess, as determined by gas chromatographic analysis.[98]



Scheme 97: (a) $Zn(OTf)_2$ (20 mol %), (+)-NME (22 mol %), NEt_3 (50 mol %), PhMe, 60 °C, 12 h, 77% yield, 92% ee.

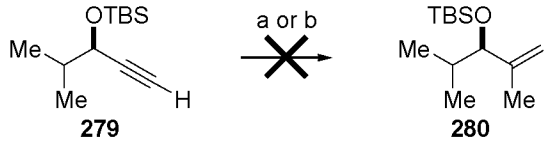
Protection of the propargylic alcohol **224** using *tert*-butyldimethylsilyl chloride and imidazole in DMF afforded silyl ether **278** in 95% yield (Scheme 98).[90,91] Subsequently, the terminal alkyne **279** was obtained by selective removal of the trimethylsilyl group with K_2CO_3 in methanol.[99]



Scheme 98: (a) TBSCl, imidazole, DMF, rt, 15.5 h, 95%; (b) K_2CO_3, MeOH, rt, 6.5 h, 75%.

The Carbometalation Reaction

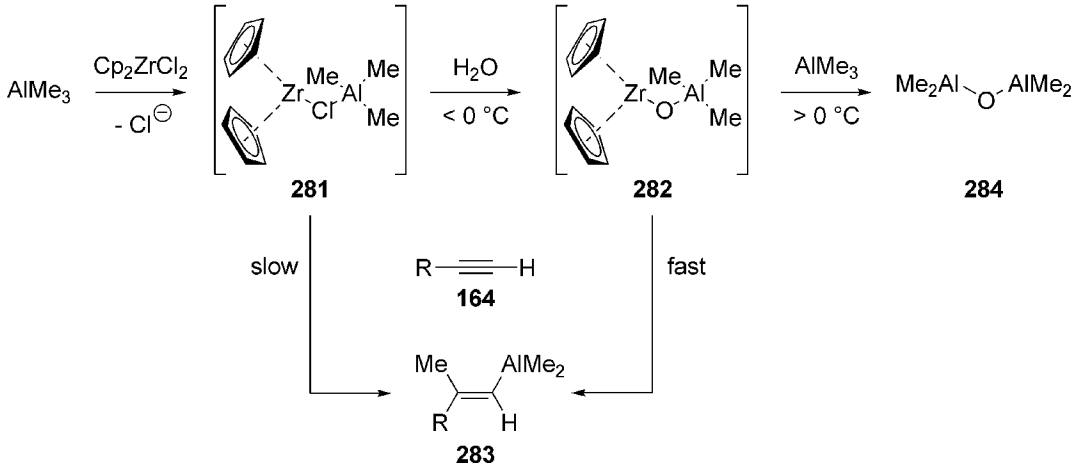
With alkyne **279** in hand, the stage was set for the key carbometalation reaction. Thus, **279** was subjected to a zirconium-mediated carboalumination according to *Negishi*'s procedure (Scheme 99).[118] To our disappointment, alkyne **279** proved resistant to carbometalation under these reaction conditions and only starting material was isolated.



Scheme 99: (a) Cp_2ZrCl_2, $AlMe_3$, CH_2Cl_2, rt, 40 h; (b) Cp_2ZrCl_2, $AlMe_3$, CH_2Cl_2, H_2O, −23 °C, 10 min, then **279**, −23 °C, 45 min, then H_2O, −23 °C to rt, 2 h.

[118] D. E. Van Horn, E. Negishi, *J. Am. Chem. Soc.* **1978**, *100*, 2252–2254.

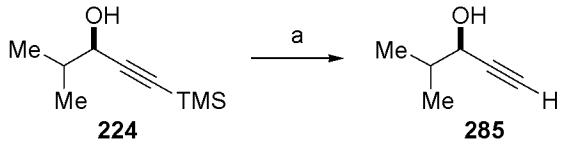
Wipf's water-accelerated carboalumination[119] employing $AlMe_3$ (3.10 equiv), Cp_2ZrCl_2 (0.22 equiv), and H_2O (1.55 equiv) seemed to provide a solution for our problem. The authors propose a thermodynamically labile, but catalytically highly active oxygen-bridged intermediate **282**, while the earlier mentioned classical variant is thought to involve the less reactive chloro-bridged analog **281** (Scheme 100). But even under the more forceful conditions, the carbometalation of alkyne **279** failed.



Scheme 100.

We suspected that the rather large silyl protective group in **279** was shielding the alkyne towards the attack of the sterically very demanding reagents **281** and **282**, respectively. We therefore decided to investigate the carbometalation of an unprotected propargylic alcohol.

Removal of the trimethylsilyl group present in **224** was effected under basic conditions to afford the terminal alkyne **285** (Scheme 101). Because of its high volatility, intermediate **285** was used as a solution in CH_2Cl_2, the concentration of which was typically in the range of 65–75 wt%, as determined by integration of the ^1H NMR signals.[120]



Scheme 101: (a) K_2CO_3, MeOH, rt, 7.5 h.

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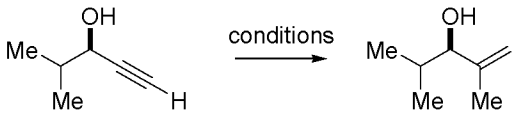
[119] P. Wipf, S. Lim, *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068–1071.

[120] The concentration of **285** in CH_2Cl_2 was determined by integration of the ^1H NMR signals at δ 5.29 ppm (CH_2Cl_2, 2 H) and 4.68 (**285**, 1 H).

We then turned our attention to the carboalumination of alkyne **285**. The results of our studies are summarized in Table 1. Under the reaction conditions typically used by *Wipf* and *Lim*—combining $AlMe_3$ (3.10 equiv) with Cp_2ZrCl_2 (0.22 equiv) in CH_2Cl_2 at −23 °C, adding H_2O (1.55 equiv) and after ten minutes a solution of the alkyne and $AlMe_3$ (0.33 equiv) in CH_2Cl_2, and warming the obtained mixture to room temperature—the conversion was very low (entry 1). By increasing the amount of reagents and/or the reaction time, we were able to considerably improve the conversion (entries 2–6). An attempt to reach full conversion with less Cp_2ZrCl_2 and $AlMe_3$ but at higher temperature failed (entry 6).



285 **286**

entry	Cp_2ZrCl_2 (equiv)	$AlMe_3$ (equiv)	H_2O (equiv)	temperature (°C)	time[121] (h)	conversion[122] (%)
1	0.22	3.10 + 0.33	1.55	−23 to rt	3.5	< 30
2	0.22	3.10 + 0.33	1.55	−23 to rt	24	50
3	1.00	14.1 + 1.50	7.05	−23 to rt	2	75
4	1.05	14.7 + 1.56	7.10	−23 to rt	24	> 95
5	2.00	28.2 + 3.00	7.05	−23 to rt	6	> 95
6	0.46	6.50 + 0.69	1.55	−23 to 40	24	60
7	1.00	14.0 + 1.50	7.00	0 to rt	24	> 95
8	0.50	14.0 + 1.50	3.50	0 to rt	36	90
9	1.00	7.00 + 1.50	7.00	0 to rt	36	75

Table 1.

When the active catalyst was preformed at 0 °C instead of −23 °C, the reaction looked cleaner (entry 7). Furthermore, it was found that decreasing the amount of $AlMe_3$ had a more drastic effect on the conversion than the amount of Cp_2ZrCl_2 (entries 8 and 9, respectively).

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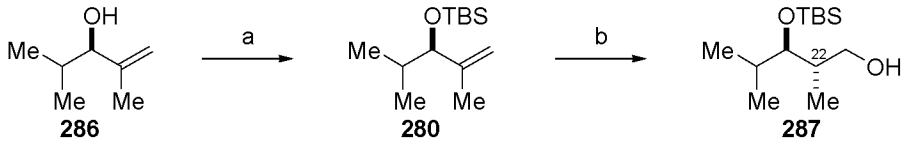
[121] Starting material and product cannot be distinguished by TLC analysis. The reaction times indicated were chosen based on the results of the preceding reactions.

[122] The conversion was estimated based on integration of the crude product's ^1H NMR signals at δ 4.15 ppm (starting material, 1 H) and 4.98–4.82 ppm (product, 2 H).

In an attempt to further optimize our conditions, the reaction was run in deoxygenated solvent. We were pleased to detect full conversion to alkene **286** within 24 hours using 0.22 equivalent of Cp_2ZrCl_2 and 6.20 equivalent of $AlMe_3$.[123]

Final Steps to Aldehyde 5

Allylic alcohol **286** was subjected to silyl protection to furnish **280** in 71% yield from propargylic alcohol **224** (Scheme 102). The diastereoselective hydroboration of (±)-**280** using 9-BBN was previously described by *Evans* and co-workers.[124] Alcohol **287**[23c,125] was thus obtained in 69% yield and a diastereomeric ratio of 96:4, as estimated by integration of the ^1H NMR signals at δ 3.61/3.41 ppm (major) and 3.80/3.50 ppm (minor).



Scheme 102: (a) TBSCl, imidazole, DMF, rt, 18 h, 71% from **224** (3 steps); (b) 9-BBN, THF, −78 °C to rt, 13.5 h, then THF/EtOH, 2 M aq. NaOH, 30% aq. H_2O_2, rt, 2 h, 69% yield, 96:4 dr.

The observed strong preference for the *anti* product can be rationalized by comparison of the respective transition states **288** and **290** (Scheme 103):[126] In both cases, the influence of the sterically demanding hydroborating agent 9-BBN forces the allylic proton into the *inside* position. The unfavorable 1,2-allylic interactions, however, appear to be far less pronounced in the case of **290** (Me ↔ OTBS) than for **288** (Me ↔ ^{i}Pr), resulting in the preferential formation of alcohol **287**.

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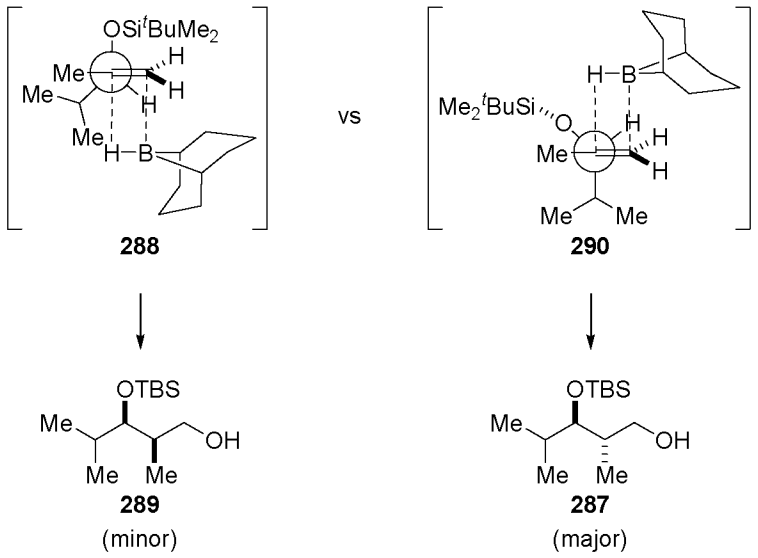
[123] To avoid loss of material during the isolation process, allylic alcohol **287** was directly converted to the corresponding, less volatile silyl ether **280**, the yield being determined thereafter.

[124] D. A. Evans, G. C. Fu, A. H. Hoveyda, *J. Am. Chem. Soc.* **1992**, *114*, 6671–6679.

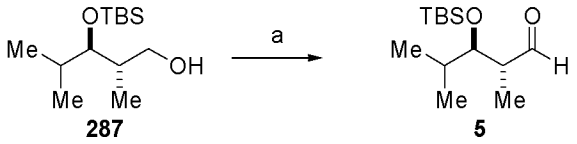
[125] The synthesis of alcohol **287** has been reported previously: (a) R. Baker, J. C. Head, C. J. Swain, *J. Chem. Soc., Perkin Trans. 1* **1988**, 85–97; (b) L. C. Dias, L. J. Steil, V. D. Vasconcelos, *Tetrahedron: Asymmetry* **2004**, *15*, 147–150.

[126] W. C. Still, J. C. Barrish, *J. Am. Chem. Soc.* **1983**, *105*, 2487–2489.



Scheme 103.

Swern oxidation[127] of alcohol **287** finally afforded the C21–C25 aldehyde **5** in 81% yield (Scheme 104).[125c] The synthesis of **5** was thus completed in six steps and 31% overall yield from commercially available isobutyraldehyde (**51**).



Scheme 104: (a) $(COCl)_2$, DMSO, NEt_3, −78 °C, 70 min, 81%.

3.2.2 Synthesis of the C14–C20 Diol *via* Nitrile Oxide Cycloaddition

Synthesis of the Chiral Oxime 296

We chose (*R*)-3-hydroxy-butyric acid ethyl ester (**291**) as the starting point for our oxime synthesis (Scheme 105). *Frater–Seebach* alkylation[128] afforded intermediate **37** in 84% yield and a diastereomeric ratio of 94:6, as determined by integration of the ^{1}H NMR signals at δ 4.06 ppm (minor) and 3.87 ppm (major), respectively.[129] Alcohol **37** was then converted to silyl ether **292** in 97% yield using standard conditions.

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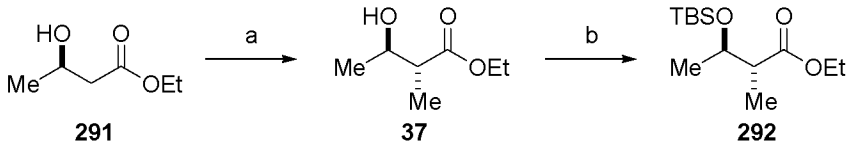
[127] A. J. Mancuso, D. Swern, *Synthesis* **1981**, 165–185.

[128] (a) G. Frater, *Helv. Chim. Acta* **1979**, *62*, 2825–2828; (b) D. Seebach, D. Wasmuth, *Helv. Chim. Acta* **1980**, *63*, 197–200.

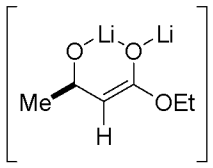
[129] M. A. Sutter, D. Seebach, *Liebigs Ann. Chem.* **1983**, 939–949.



291 **37** **292**

Scheme 105: (a) $^{i}Pr_2NH$, MeLi, THF, −50 °C to −30 °C, then MeI, HMPA, −30 °C, 15 min, 84% yield, 94:6 dr; (b) TBSCl, imidazole, DMF, rt, 14 h, 97%.

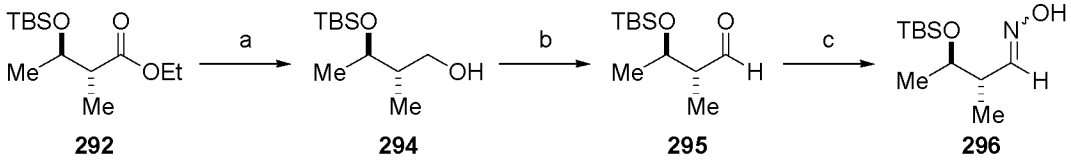
The *anti*-selectivity observed in the alkylation step was interpreted by *Seebach* and *Wasmuth* as the result of the cyclic transition state **293** (Figure 12): The enolate's top face being shielded by the methyl substituent in β-position, the electrophile is forced to approach from the back side.



293

Figure 12.

Reduction of ester **292** with DIBAL-H afforded the primary alcohol **294** in 95% yield (Scheme 106). Oxime **296** was finally obtained by oxidation according to *Ley*'s procedure[95] and subsequent treatment of the intermediary unstable aldehyde **295** with *N*-hydroxylamine.

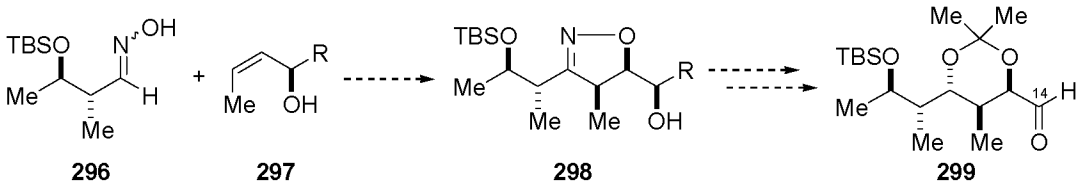


292 **294** **295** **296**

Scheme 106: (a) DIBAL-H, CH_2Cl_2, −78 °C to rt, 3 h, 95%; (b) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 2 h; (c) $NH_2OH{\cdot}HCl$, NEt_3, EtOH, rt, 15 h, 85% over 2 steps.

The Nitrile Oxide Cycloaddition

With aldoxime **296** in hand, we were ready to investigate the key step for our synthesis of bafilomycin A_1's C14–C20 subunit. We intended to perform a hydroxy-directed nitrile oxide cycloaddition between **296** and an allylic alcohol **297** (Scheme 107). Isoxazoline **298** would then have to be further elaborated to aldehyde **299**.



Scheme 107.

In the course of our dithiane–epoxide approach, we had used allylic alcohol *ent*-**147** (corresponding to **297** with R = Me) in the nitrile oxide cycloaddition and encountered major difficulties in the subsequent elimination reaction (see section 2.2.3). We wished to circumvent these problems by the use of an alternative dipolarophile in the cycloaddition reaction, which would allow for a more facile installation of the C14 aldehyde. We decided to investigate the 1,3-dipolar cycloaddition of the achiral allylic alcohol **300** (Figure 13),[130] several mono-protected diols **251** (R = H, Bz, TES, TBDPS, Tr), and the racemic[131] hydroxy silanes **301** (R'_3 = Me_2Ph, $^tBuPh_2$, $^tBuMe_2$).

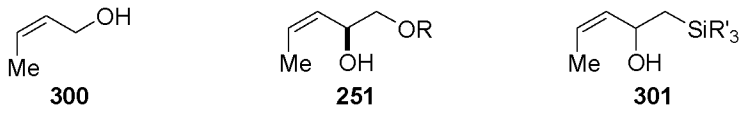


Figure 13.

The hydroxysilanes **301** were prepared from the corresponding α-silyl aldehydes **303** (Scheme 108).[132] In the case of the dimethylphenylsilane, alkene **302** served as the starting point. Hydroboration of **302** with 9-BBN dimer and subsequent *Swern* oxidation afforded aldehyde **303**.[133] The TBS and TBDPS aldehydes were accessed from imine **304**,[134] which was treated with LDA and the respective silyl chloride.[135] Addition of 1-propynylmagnesium bromide to the aldehydes **303** furnished the racemic propargylic alcohols **305**, which were reduced to the corresponding allylic alcohols **301** using *Lindlar*'s catalyst.

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[130] Alcohol **300** was prepared by hydrogenation of commercially available but-2-ynol using *Lindlar*'s catalyst.

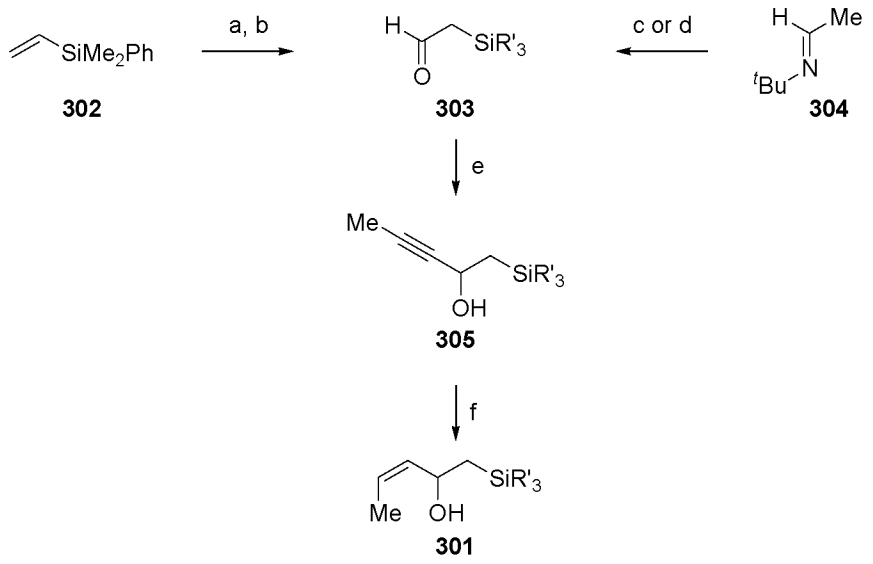
[131] The racemate **301** served as a model for the optically active hydroxy silanes, which we intended to use for the synthesis of bafilomycin A_1.

[132] The indicated yields were obtained under unoptimized reaction conditions.

[133] B. S. Gerstenberger, J. P. Konopelski, *J. Org. Chem.* **2005**, *70*, 1467–1470.

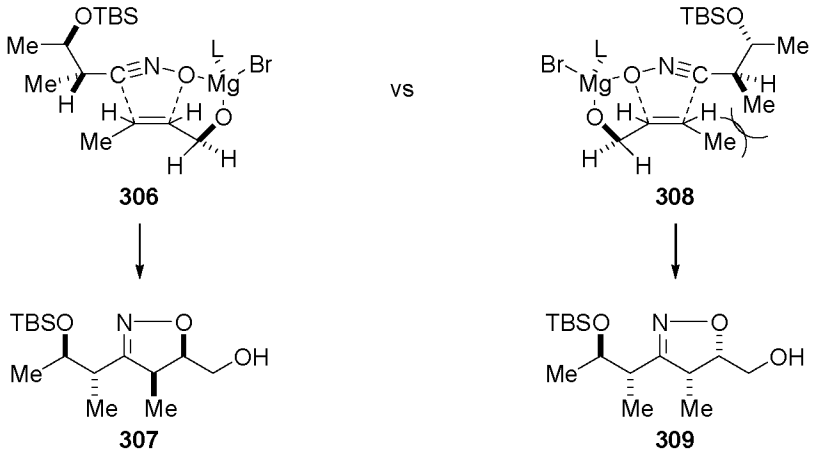
[134] K. N. Campbell, A. H. Sommers, B. K. Campbell, *J. Am. Chem. Soc.* **1944**, *66*, 82–84.

[135] L. F. Tietze, T. Neumann, M. Kajino, M. Pretor, *Synthesis* **1995**, 1003–1006.



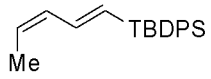
Scheme 108: (a) 9-BBN dimer, THF, rt, 2 h, then H_2O, sat. aq. NaOH, 30% aq. H_2O_2, rt, 1 h; (b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C to rt, 2 h; (c) LDA, THF, 0 °C, 30 min, then TBSCl, Bu_4NI, rt, 4 h, 51%; (d) LDA, THF, 0 °C, 30 min, then TBDPSCl, Bu_4NI, rt, 4 h; (e) MeCCMgBr, Et_2O, −78 °C to rt, 2 h, 54% for TBS, 66% over 2 steps for TBDPS, 72% over 3 steps for $SiMe_2Ph$; (f) *Lindlar*'s catalyst, H_2, EtOAc, rt, 3–6 h, 57% for TBS, 62% for TBDPS, 90% for $SiMe_2Ph$.

For the cycloaddition of the achiral olefin **300** with oxime **296,** we anticipated the two competing transition states **306** and **308** depicted in Scheme 109. We were hoping that the oxime's α-stereogenic center would be able to influence the stereochemical outcome of the cycloaddition. Thus, transition state **308** (Me ↔ Me) should be slightly disfavored compared to **306** (Me ↔ H). In practice, however, the nitrile oxide cycloaddition of **300** afforded the corresponding isoxazoline in 67% yield as an inseparable 55:45-mixture of diastereomers.



Scheme 109.

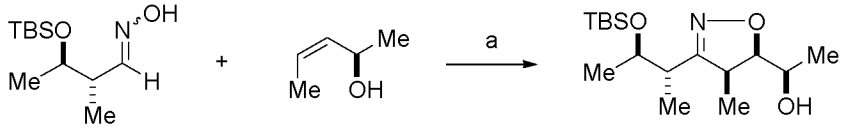
When we attempted the cycloaddition of oxime **296** to the diols **251** or silanes **301**, no isoxazolines were formed. As a matter of fact, diene **310** (Figure 14) was isolated in the case of the *tert*-butyldiphenylsilane, which indicates that the hydroxy silanes were unstable under the reaction conditions, resulting in the elimination of water.



310

Figure 14.

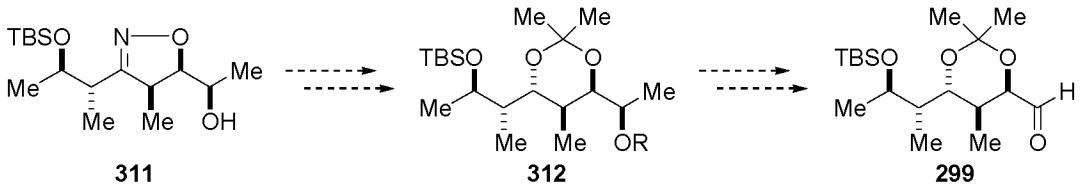
We finally decided to stick to the conventional allylic alcohol *ent*-**147**[136] and to further investigate the subsequent elimination reaction. Thus, oxime **296** was subjected to the 1,3-dipolar cycloaddition with *ent*-**147**, which furnished isoxazoline **311** in 60% yield (Scheme 110). Integration of the ^{1}H NMR signals at δ 3.35 ppm (minor) and 3.26 ppm (major) revealed a diastereomeric ratio of 95:5 for **311**.



296 *ent*-**147** **311**

Scheme 110: (a) **296**, ^{t}BuOCl, CH_2Cl_2, –78 °C, 2 h, then *ent*-**147**, ^{i}PrOH, EtMgBr, 0 °C to rt, 23 h, 60% yield, 95:5 dr.

During our dithiane–epoxide approach, the C14 aldehyde was accessed by installation of a primary hydroxy group at C14 and subsequent reductive opening of the isoxazoline. We now also wished to examine an alternative route which would involve opening of the isoxazoline moiety prior to the dehydration step (Scheme 111). This would allow for a shorter and presumably higher yielding access to the C14 aldehyde **299**.

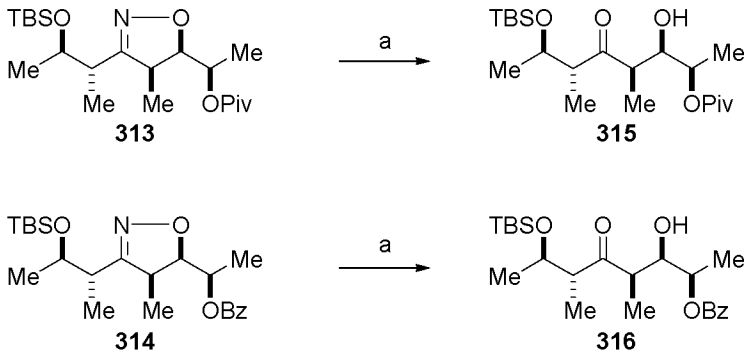


311 **312** **299**

Scheme 111.

[136] For the synthesis of alcohol *ent*-**147**, see section 2.2.3.

We prepared the two isoxazolines **313** and **314** by esterification of alcohol **311** and subjected them to Raney-Nickel catalyzed reduction (Scheme 112). The corresponding *β*-hydroxy ketones **315** and **316** were isolated in 38% and 15% yield, respectively. These results prompted us to address the direct dehydration of isoxazoline **311**.



Scheme 112: (a) H_2, Raney-Ni, $B(OH)_3$, MeOH, H_2O, rt, 20 min, 38% for **315**, 15% for **316**.

The Dehydration to Alkene 317

With regard to the dehydration of isoxazoline **311**, the use of the very mild *Martin* sulfurane[137] **(318)** seemed promising.[138] As this reagent has been successfully employed for the dehydration of a variety of substrates in a wide range of solvents,[139] we wished to investigate the effect of the solvent on the yield obtained for the reaction with alcohol **311** (Table 2).

To our surprise, dehydration using *Martin* sulfurane in $CHCl_3$ failed, even though its successful use for other substrates has been reported.[139d,e] Among the tested solvents, CCl_4 and toluene turned out to be the best choices, furnishing alkene **317** in 45% and 48% isolated yield, respectively (entries 1 and 5). To determine the effect of dilution, the dehydration was also conducted at higher (0.100 M) or lower (0.025 M) concentration of the substrate in CCl_4

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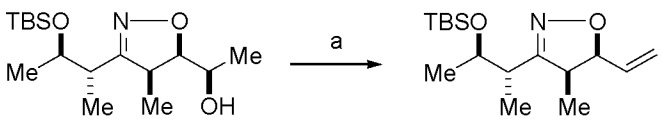
137 J. C. Martin, R. J. Arhart, *J. Am. Chem. Soc.* **1971**, *93*, 4327–4329.

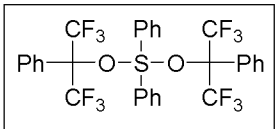
138 We have investigated several alternatives for the dehydration of an almost identical substrate in the course of our dithiane–epoxide approach: see section 2.2.3.

139 For selected examples, see: (a) S. J. Shiuey, I. Kulesha, E. G. Baggiolini, M. R. Uskokovic, *J. Org. Chem.* **1990**, *55*, 243–247; (b) S. Zimmermann, S. Bick, P. Welzel, H. Meuer, W. S. Sheldrick, *Tetrahedron* **1995**, *51*, 2947–2952; (c) A. G. Myers, M. Siu, F. Ren, *J. Am. Chem. Soc.* **2002**, *124*, 4230–4232; (d) C. H. Heathcock, M. McLaughlin, J. Medina, J. L. Hubbs, G. A. Wallace, R. Scott, M. M. Claffey, C. J. Hayes, G. R. Ott, *J. Am. Chem. Soc.* **2003**, *125*, 12844–12849; (e) P. S. Baran, J. M. Richter, *J. Am. Chem. Soc.* **2004**, *126*, 7450–7451; (f) A. Kuramochi, H. Usuda, K. Yamatsugu, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 14200–14201.

and toluene. In all four cases, alkene **317** was isolated in lower yield than for the originally used 0.050 M solutions. Under the optimal conditions using a 0.050 M solution of alcohol **311** in toluene, olefin **317** was obtained in 48% yield.



311 **317**



318

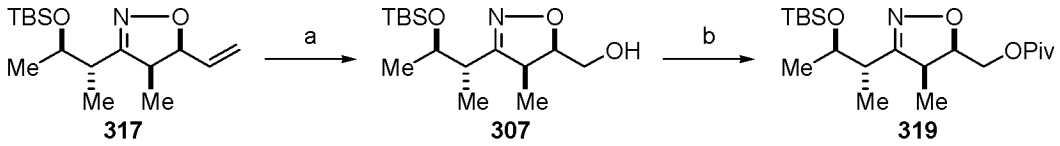
entry	solvent	yield (0.025 M)	yield (0.050 M)	yield (0.100 M)
1	CCl_4	36%	45%	36%
2	$CHCl_3$	n.d.	-	n.d.
3	CH_2Cl_2	n.d.	36%	n.d.
4	PhH	n.d.	33%	n.d.
5	PhMe	34%	48%	45%
6	*o*-xylene	n.d.	39%	n.d.
7	hexane	n.d.	30%	n.d.

Table 2. Typical reaction conditions involved addition of a solution of alcohol **311** to a solution of *Martin* sulfurane (1.1 equiv) at 0 °C and stirring the resulting mixture at room temperature for 60 min, before the reaction was stopped by addition of H_2O.

This one-step conversion of alcohol **311** to olefin **317** was more efficient than the three-step sequence involving oxidation to the ketone, vinyl triflate formation, and palladium-catalyzed transfer hydrogenation thereof, which we had used earlier for a very similar substrate (36% over three steps).[140] We decided to settle for the *Martin* sulfurane dehydration and to move on to the oxidative cleavage of the C=C double bond.

Ozonolysis of alkene **317** in methanol and subsequent reductive work-up with $NaBH_4$ afforded alcohol **307**, which was converted to the corresponding pivaloate **319** in 74% yield over two steps (Scheme 113). The ester protective group was chosen because it can be selectively removed in the presence of silyl ether and acetonide functionalities, both of which we intended to include in our aldehyde fragment **299**.

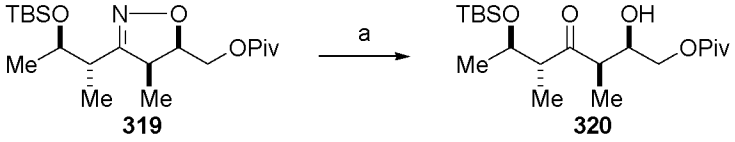
[140] See section 2.2.3.



Scheme 113: (a) O_3, MeOH, –78 °C, 8 min, then $NaBH_4$, –78 °C to rt, 80 min, 85%; (b) PivCl, py, rt, 9 h, 87%.

The Reductive Isoxazoline Opening

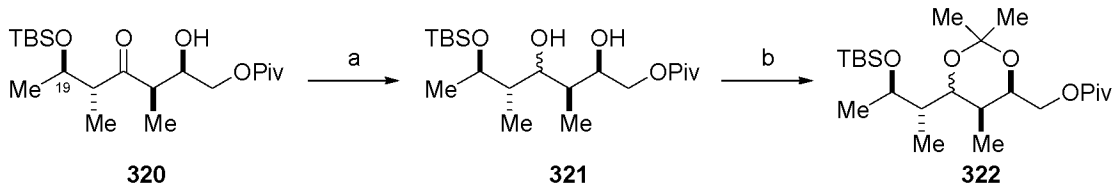
Our next task was the reductive opening of the isoxazoline moiety. Thus, **319** was subjected to Raney-Nickel catalyzed hydrogenation and in situ hydrolysis with $H_2O/B(OH)_3$ (Scheme 87). By slightly increasing the substrate concentration (from 0.020 M to 0.025 M) and by decreasing the reaction time from 30 to 20 minutes, the yield of *β*-hydroxy ketone **320** was improved from 56% to 70%.



Scheme 114: (a) H_2, Raney-Ni, $B(OH)_3$, MeOH, H_2O, rt, 20 min, 70%.

The 1,3-*anti* Reduction

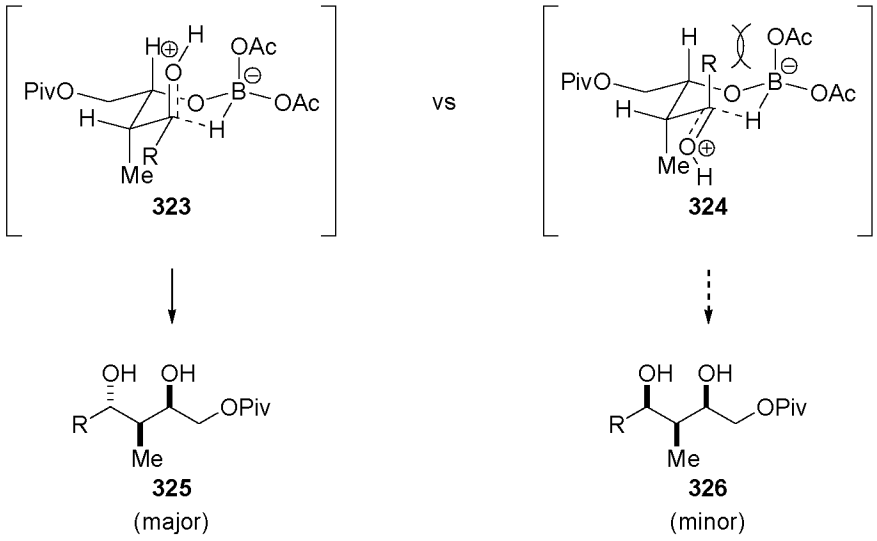
The 1,3-*anti* reduction of *β*-hydroxy ketone **320** was tackled using $Me_4NBH(OAc)_3$ in acetonitrile/acetic acid according to *Evans'* procedure[115] (Scheme 115): Diol **321** was obtained in 49% yield and as an inseparable 2:1 mixture of diastereomers.[141] Acid-catalyzed acetonide formation finally afforded **322** in 69% yield as an inseparable diastereomeric mixture.



Scheme 115: (a) $Me_4NBH(OAc)_3$, MeCN, AcOH, rt, 20 min, then –20 °C, **320**, MeCN, –20 °C to rt, 3 d, 49%; (b) TsOH, $Me_2C(OMe)_2$, rt, 90 min, 69%.

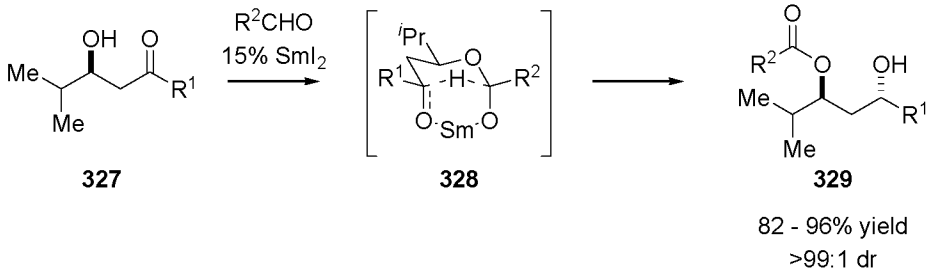
[141] The diastereomeric ration was estimated by integration of the ^1H NMR signals at δ 1.01/0.80 ppm (major) and 0.95/0.74 ppm (minor).

The poor stereoselectivity in the $Me_4NBH(OAc)_3$ reduction of **320** was unexpected, as we had successfully used the same method for the reduction of the closely related *β*-hydroxy ketone **260**, lacking the C19 methyl group in comparison to **320** (see section 2.2.3). By analysis of the transition state model typically invoked for this reaction (Scheme 116),[115] the additional C19 methyl group should increase the steric bulk of the R group, leading to stronger interactions in the case of **324** and additionally favoring the formation of the *anti*-diol **325**.



Scheme 116.

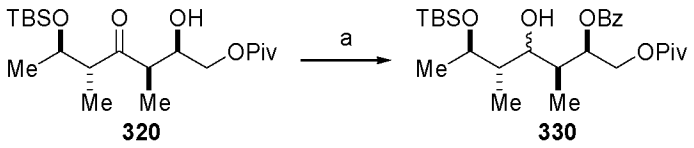
The SmI_2-catalyzed *Tishchenko* reaction,[142] which is known to furnish 1,3-*anti*-diol monoesters with high diastereoselectivity (Scheme 117), seemed a good alternative to the $Me_4NBH(OAc)_3$ reduction. The *Tishchenko* reaction is thought to involve a cyclic transition state **328**, leading to stereoselective intramolecular hydride delivery.



Scheme 117.

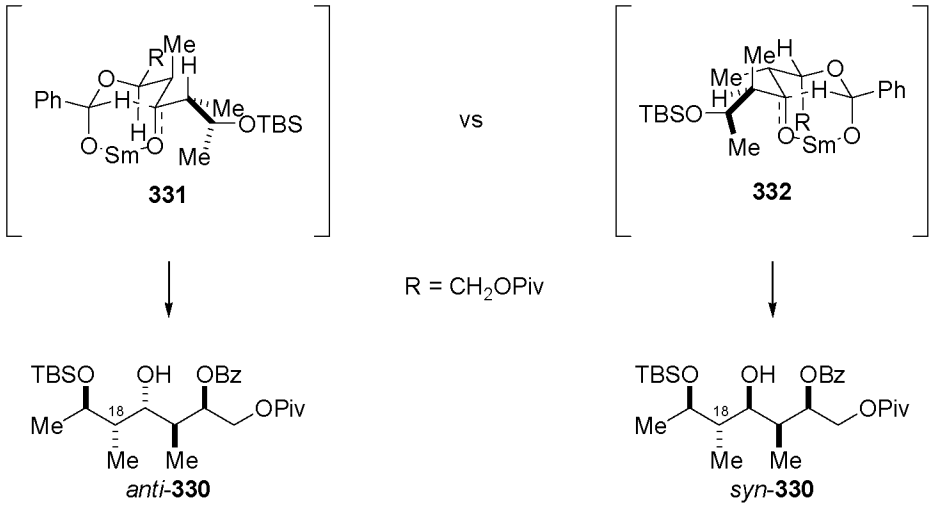
[142] D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.

Treatment of β-hydroxy ketone **320** with benzaldehyde and SmI_2 afforded a mixture of diastereomeric products **330** along with 37% of unreacted starting material (Scheme 118). With respect to **330**, we were able to isolate 27% of the major and 5% of the minor diastereomer.



Scheme 118: (a) SmI_2, PhCHO, THF, –10 °C, 22.5 h, 27% major, 5% minor, 37% **320**.

The diastereoselectivity being rather poor, we decided to examine the proposed respective transition states **332** and **331** for the formation of the *syn* and *anti* products (Scheme 119). The 1,3-diaxial interactions between R, the alkoxide, and the carbonyl group should destabilize **332** compared to **331**, favoring the formation of *anti*-**330**. The orientation of the C18 methyl group (axial in **331** and equatorial in **332** should have a much smaller influence on the stereochemical outcome of the reaction, as there are no other axial substituents in the upper hemisphere.



Scheme 119.

The envisioned application of the SmI_2-catalyzed *Tishchenko* reaction to the synthesis of the C14 aldehyde **299** renders optimization of this reaction inevitable. Alternatively, *Keck*'s

recently developed SmI_2-reduction of β-alkoxy ketones[143] might provide an entry to bafilomycin A_1's C14–C20 subunit.

3.2.3 Conclusion

In the course of our aldol approach to bafilomycin A_1, the C21–C25 subunit was prepared in six steps and 31% overall yield. The concise synthesis of aldehyde **5** relied on the catalytic enantioselective zinc alkynylide addition of trimethylsilyl acetylene to isobutyraldehyde, a water-accelerated carboalumination, and a highly diastereoselective hydroboration reaction.

The synthesis of β-hydroxy ketone **320**, an advanced intermediate *en route* to the C14–C20 aldehyde **299**, was achieved *via* the hydroxy-directed nitrile oxide cycloaddition of alcohol *ent*-**147** to oxime **296**. The subsequent steps involved dehydration using *Martin* sulfurane and reductive opening of the isoxazoline moiety. The 1,3-*anti*-selective reduction of **320** to the corresponding diol and its elaboration to aldehyde **299** are subject to further investigations.

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[143] (a) G. E. Keck, C. A. Wager, T. Sell, T. T. Wager, *J. Org. Chem.* **1999**, *64*, 2172–2173; (b) G. E. Keck, C. A. Wager, *Org. Lett.* **2000**, *2*, 2307–2309.

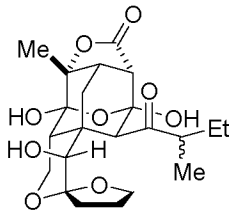
Part II:

Studies Toward the Synthesis of Fusidilactone C

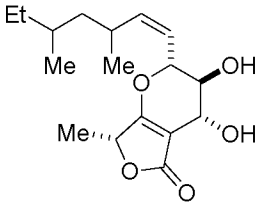
4 Introduction

4.1 Isolation of Fusidilactone C

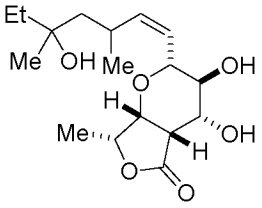
The isolation of fusidilactone C (**333**) from the fungal endophyte *Fusidium* sp. was reported in 2002 by *Krohn* and co-workers (Figure 15).[144] Along with **333**, the fungus was found to produce the bicyclic fusidilactones A (**334**) and B (**335**) and the previously known[145] *cis*-4-hydroxy-6-deoxyscytalone (**336**).



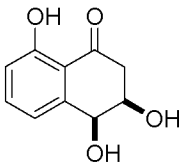
Fusidilactone C (**333**)



Fusidilactone A (**334**)



Fusidilactone B (**335**)



336

Figure 15. Structures of the *Fusidium* sp. metabolites.

Fusidium sp., which belongs to the mitosporic fungi, was isolated from the leaves of *Mentha arvensis*, a mint species native to most of Europe and Asia. The fungus was cultivated

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[144] K. Krohn, C. Biele, K. H. Drogies, K. Steingrover, H. J. Aust, S. Draeger, B. Schulz, *Eur. J. Org. Chem.* **2002**, 2331–2336.

[145] U. Sanakawa, H. Shimada, T. Sato, T. Kinoshita, K. Yanasaki, *Chem. Pharm. Bull.* **1981**, *29*, 3536–3542.

on biomalt semi-solid agar medium or alternatively in biomalt liquid culture. Ethyl acetate extraction of the homogenized cultures furnished a mixture of the fusidilactones, which exhibited antifungal activity against *Eurotium repens* and *Fusarium oxysporum*, weak antibacterial activity against *Escherichia coli* and *Bacillus megaterium*, and also inhibited the alga *Chlorella fusca*.

Separation of the metabolites by flash column chromatography afforded the individual fusidilactones which were further purified by PTLC and HPLC. Fusidilactone A was isolated from the least polar fraction as a colorless oil, while purification of the second and third fractions afforded solid fusidilactone B and triol **336**, respectively.

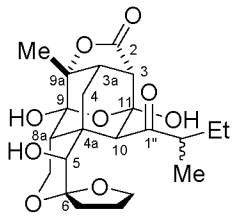
With an R_f value of 0.52 in pure MeO^{t}Bu, fusidilactone C was the most polar of the four metabolites. The melting point of this colorless solid was determined to be 197 °C. Unfortunately, the preparation of suitable crystals for X-ray crystallographic analysis failed.

4.2 Structure Elucidation of Fusidilactone C

The molecular composition of fusidilactone C was determined by CI-mass spectrometry in accordance with the NMR spectroscopic data.[144] Thus, the detected molecular ion peak at m/z = 438.1881 was assigned to $C_{22}H_{30}O_9$. The IR spectrum revealed the presence of a hydroxyl group, an ether, a γ-lactone, and a ketone.

Based on analysis of the ^{1}H and ^{13}C NMR and the correlations observed in the HMBC spectrum, *Krohn* and co-workers assigned four independent structural motifs that were subsequently combined to fusidilactone C's oxoadamantane skeleton. The relative configuration at C5, C8a, C9a, and C10 was elucidated based on n*O*e experiments (Figure 16):[146] Crosspeaks from the proton at C10 to the ones at C5 and C8 revealed the axial orientation of the C5 hydroxy group. In addition, the C9a methyl group was shown to be proximal to the C4 and C8a protons. The proposed relative configuration was further supported by several W-couplings of the equatorial protons on the oxoadamantane scaffold. Apart from the stereogenic center at C2'', only the absolute stereochemistry remains to be determined.

[146] Throughout the text, the atom numbering introduced by *Krohn* et al. will be used; see ref. 144.



333

Figure 16.

Fusidilactone C possesses several unusual structural features: An oxoadamantane skeleton was previously only found in a single natural product, the alkaloid 5,15-oxidolycopodane.[147] Also the ether-bridged bishemiacetal is very rare in nature. Overall, the polyoxygenated hexacycle fusidilactone C contains nine stereogenic centers, one of which is a quaternary carbon.

4.3 Synthetic Approaches toward Fusidilactone C

To date, only one synthetic approach towards fusidilactone C has been reported.[148] Additionally, *Gao* and *Snider* described the synthesis of the fusidilactone B ring system by an iodoetherification.[149] This seeming lack of interest is rather surprising, given that the structure has been known for several years now and appears to offer copious synthetic challenges.

4.3.1 An Approach to the 2-Oxadecalin Spiroketal of Fusidilactone C

In 2004, *Hsung* and co-workers reported an approach to the 2-oxadecalin spiroketal portion of fusidilactone C.[148] Their key step made use of an *endo*-selective intramolecular *Diels–Alder* reaction, in which a ketal-tether gave rise to the observed high stereoselectivity.

Preparation of diene **338** was achieved in seven steps and 52% overall yield from diol **337** through two sequential *Wittig* olefinations (Scheme 120). The dihydrofurane intermediate **341**, on the other hand, was derived from **339** and **340**. Acid-catalyzed fragment coupling afforded **342**, which was then converted into the *Diels–Alder* precursor **343**.

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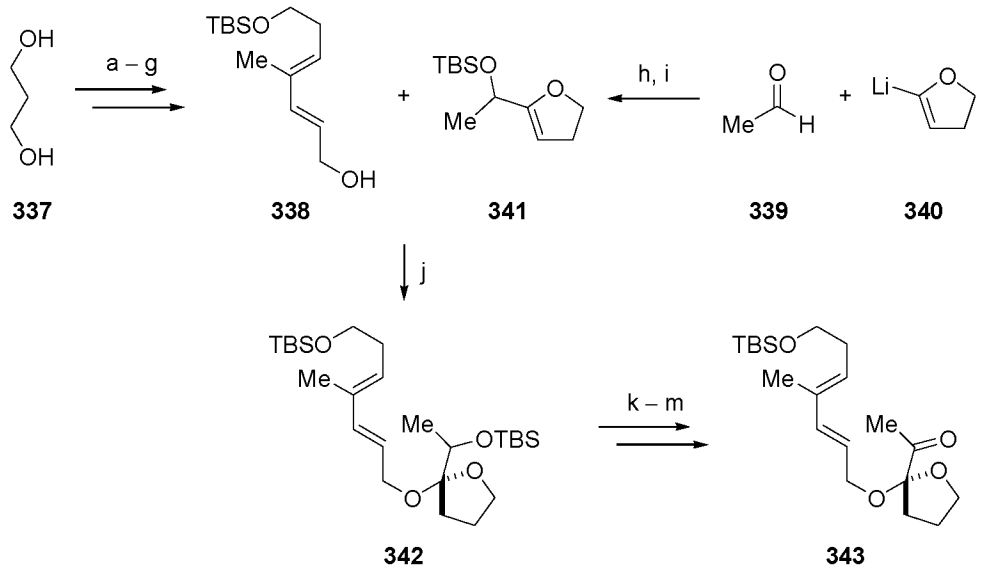
147 W. A. Ayer, L. M. Browne, A. W. Elgersma, P. P. Singer, *Can. J. Chem.* **1990**, *68*, 1300–1304.

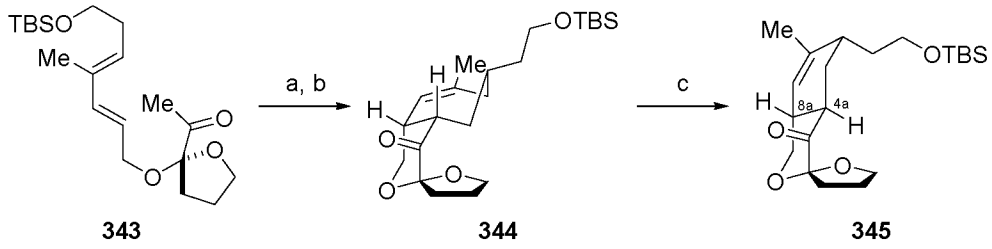
148 J. S. Wang, R. P. Hsung, S. K. Ghosh, *Org. Lett.* **2004**, *6*, 1939–1942.

149 X. L. Gao, B. B. Snider, *J. Org. Chem.* **2004**, *69*, 5517–5527.



Scheme 120: (a) NaH, TBSCl, THF, 0 °C to rt, 3 h, 95%; (b) SO_3·py, DMSO, NEt_3, CH_2Cl_2, 0 °C to rt, 2 h, 86%; (c) $EtO_2CC(Me)PPh_3$, PhMe, Δ, 12 h, 88% yield, *E*/*Z* = 20:1; (d) DIBAL-H, CH_2Cl_2, −78 °C, 2 h, 86%; (e) SO_3·py, DMSO, NEt_3, CH_2Cl_2, 0 °C to rt, 2 h, 95%; (f) $EtO_2CCHPPh_3$, PhMe, Δ, 12 h, 96%; (g) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 93%; (h) THF, −78 °C; (i) TBSCl, imidazole, DMF, rt; (j) PPTS, CH_2Cl_2, 0 °C to rt; (k) TBAF, THF, rt; (l) TBSCl, imidazole, DMF, 0 °C to rt, 41% from **342**; (m) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 2 h, 93%.

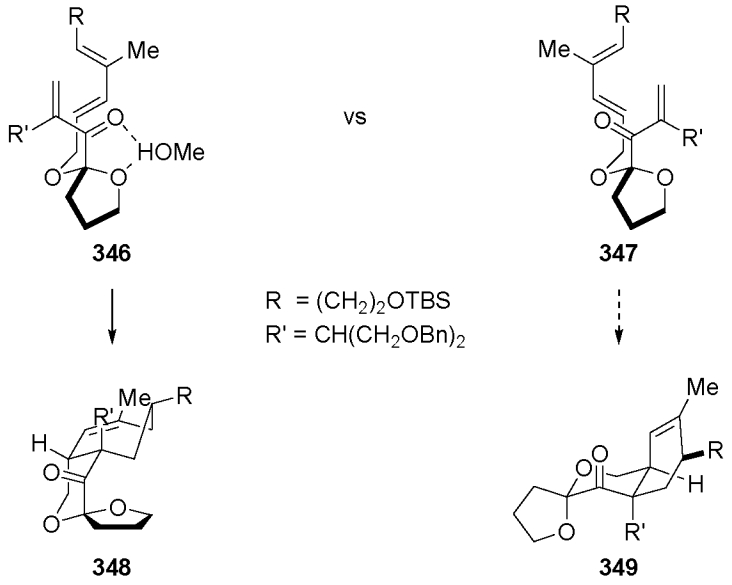
Ketone **343** was treated with *Eschenmoser*'s salt to give the intermediary *β*-amino ketone, which was then subjected to methylation and subsequent base-promoted elimination (Scheme 121). In the course of this second reaction step, which was carried out in methanol at room temperature, also the intramolecular *Diels–Alder* cyclization took place and directly furnished spiroketal **344**. Epimerization of C4a with K_2CO_3 finally afforded the *trans*-2-oxodecalin spiroketal **345** in 90% yield as a 5:1 mixture of diastereomers.



Scheme 121: (a) LHMDS, THF, −78 °C to 0 °C, 1 h, then $Me_2N{=}CH_2I$, −78 °C to rt, 1 h, 61%; (b) Na_2CO_3, MeI, MeOH, rt, 12 h, 45%; (c) K_2CO_3, MeOH, rt, 12 h, 90% yield, 5:1 dr.

With regard to the intramolecular *Diels–Alder* reaction, the authors proposed the tricyclic product **344** to arise from a ketal-tethered *endo* transition state similar to **346** (Scheme 122).

Calculations (Spartan: G-31G*/B3LYP) suggested that **346** should be favored over **347** by about 0.11 kcal mol^{-1}. In addition, *Hsung* and co-workers argued that the furan oxygen should be stronger coordinating than the allylic ether, leading to preferential chelation of methanol by the carbonyl group and the furan oxygen. This chelate formation should further promote the cycloaddition *via* **346**.



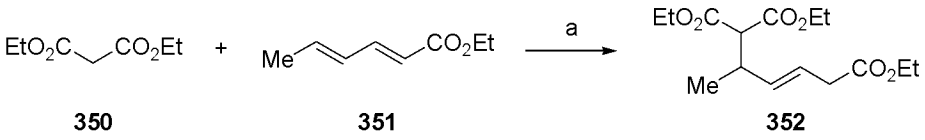
Scheme 122.

4.4 Inter- and Intramolecular 1,6-Additions

At the beginning of the twentieth century, several groups reported the use of 1,6-addition reactions, most of which involved the reduction of doubly unsaturated acids or esters.[150] An early example of a carbon-based nucleophile was described by *Weissheimer* and *Sponnagel* in 1906: Treatment of the $\alpha,\beta,\gamma,\delta$-unsaturated ester **351** with sodium malonate afforded the 1,6-addition product **352** (Scheme 123).[151]

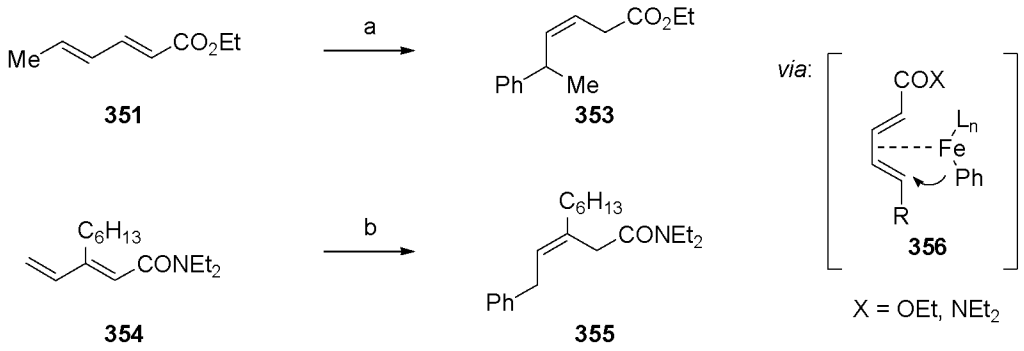
[150] For an early review, see: E. P. Kohler, K. R. Butler, *J. Am. Chem. Soc.* **1926**, *48*, 1036–1048.

[151] P. Weissheimer, F. Sponnagel, *Liebigs Ann. Chem.* **1906**, *345*, 227–233. Unfortunately, the authors did not report the yield obtained for this reaction.



Scheme 123: (a) NaOH, PhH, 50–60 °C, 8 h.

This lead result prompted more detailed studies of carbon nucleophiles in conjugate addition reactions. 1,6-Addition of organolithium or *Grignard* reagents to doubly unsaturated ketones, cyanides, quinones, epoxides, or diesters typically afforded the derived products in less than 50% yield,[152] while the yields arising from cuprate addition were slightly higher.[153] Significant improvement resulted from the use of an iron(II) catalyst, as illustrated by two selected examples (Scheme 124).[154] The exclusive formation of the *Z*-products can be rationalized by an *s-cis*-diene–iron complex (**356**), promoting intramolecular aryl transfer and biasing the future double bond geometry. A very similar complex (**359**) is thought to be involved in the iridium-catalyzed 1,6-addition of aryl boronic acids to doubly unsaturated ketones, esters and amides, which was recently reported by *Hayashi* and co-workers (Scheme 125).[155]



Scheme 124: (a) PhMgBr, $FeCl_2$, THF, −45 °C to −35 °C, 3 h, 78%; (b) PhMgBr, $FeCl_2$, THF, −45 °C to −35 °C, 3 h, 86%.

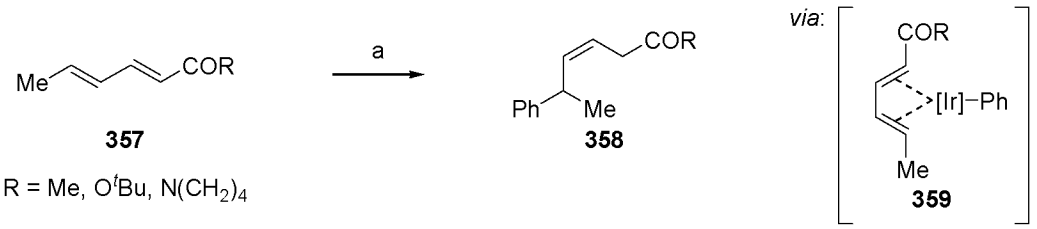
---

[152] For selected examples, see: (a) R. C. Fuson, J. R. Larson, *J. Am. Chem. Soc.* **1959**, *81*, 2149–2150; (b) G. Rio, B. Sillion, *Bull. Soc. Chim. Fr.* **1961**, 831–836; (c) J. A. Marshall, H. Roebke, *J. Org. Chem.* **1966**, *31*, 3109–3113; (d) C. H. Foster, G. A. Berchtold, *J. Am. Chem. Soc.* **1971**, *93*, 3831–3832; (e) G. A. Holmberg, L. Jalander, H. Norrgard, B. Pettersson, *Acta Chem. Scand. Ser. B* **1974**, *B 28*, 909–912; (f) D. W. Cameron, M. Mingin, *Aust. J. Chem.* **1977**, *30*, 859–863.

[153] For selected examples, see: (a) J. A. Marshall, R. A. Ruden, L. K. Hirsch, M. Phillippe, *Tetrahedron Lett.* **1971**, *12*, 3795–3798; (b) B. R. Davis, S. J. Johnson, *J. Chem. Soc., Perkin Trans. 1* **1979**, 2840–2844; (c) F. Barbot, A. Kadibelban, P. Miginiac, *Tetrahedron Lett.* **1983**, *24*, 5089–5090.

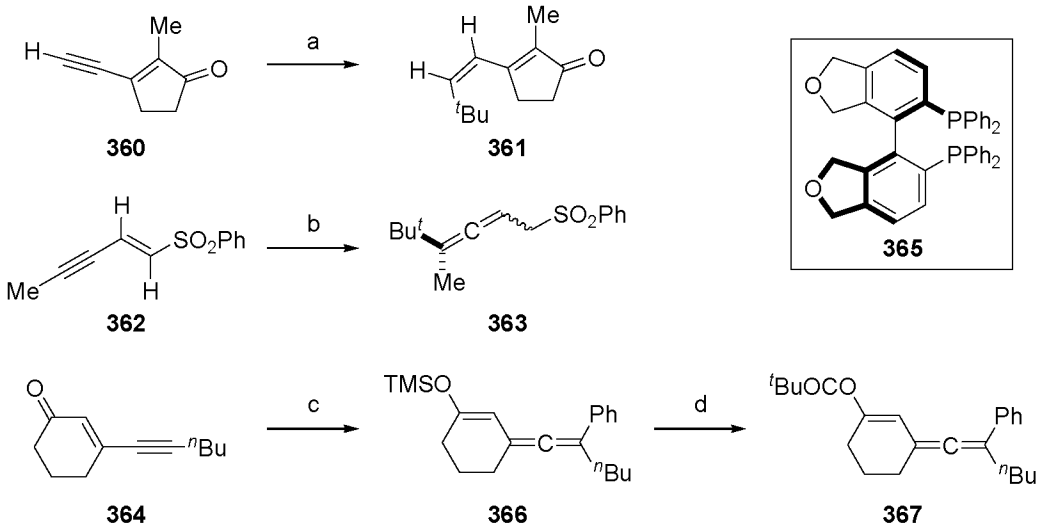
[154] K. Fukuhara, H. Urabe, *Tetrahedron Lett.* **2005**, *46*, 603–606.

[155] T. Nishimura, Y. Yasuhara, T. Hayashi, *Angew. Chem., Int. Ed.* **2006**, *45*, 5164–5166.



Scheme 125: (a) $(PhBO)_3$, [{Rh(OH)(cod)}$_2$], H_2O, PhH, 80 °C, 3 h, 86% (R = Me), 82% (R = O^{t}Bu), 90% (R = N(CH$_2$)$_4$).

Hulce[156] and *Krause*[157] have successfully used the 1,6-addition of organocuprates to electron-poor enynes for the formation of dienones and allenes, such as **361** and **363** (Scheme 126). This method was subsequently expanded to the rhodium-catalyzed enantioselective preparation of allenes by *Hayashi* and co-workers, furnishing the desired products **367** in up to 92% enantiomeric excess.[158]



Scheme 126: (a) ^{t}Bu$_2$Cu(CN)Li$_2$, Et$_2$O, −78 °C, 1.5 h, 93% yield, *Z*/*E* = 34:1 ; (b) ^{t}Bu$_2$Cu(CN)Li$_2$, Et$_2$O, −20 °C, 1 h, 91%; (c) PhTi(O^{i}Pr)$_4$Li, [RhCl(C$_2$H$_4$)$_2$]$_2$, **365**, TMSCl, THF, rt, 30 min; (d) MeLi, Et$_2$O, −78 °C to 0 °C, 30 min, then ^{t}BuCOCl, rt, 30 min, 86% yield, 90% ee.

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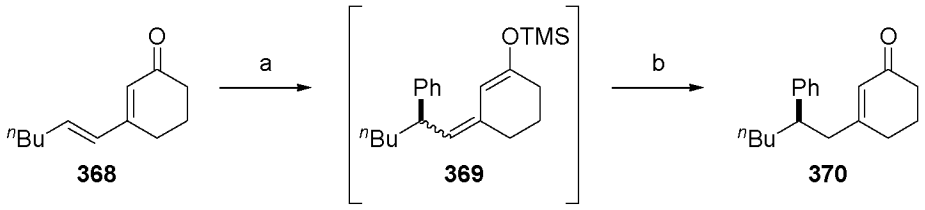
156 (a) M. Hulce, *Tetrahedron Lett.* **1988**, *29*, 5851–5854; (b) M. Y. Cheng, M. Hulce, *J. Org. Chem.* **1990**, *55*, 964–975.

157 (a) N. Krause, *Chem. Ber.* **1990**, *123*, 2173–2180; (b) N. Krause, *Liebigs Ann. Chem.* **1993**, 521–525; (c) A. Haubrich, M. Vanklaveren, G. Vankoten, G. Handke, N. Krause, *J. Org. Chem.* **1993**, *58*, 5849–5852; (d) G. Handke, N. Krause, *Tetrahedron Lett.* **1993**, *34*, 6037–6040; (e) M. Hohmann, N. Krause, *Chem. Ber.* **1995**, *128*, 851–860; (f) M. Uerdingen, N. Krause, *Tetrahedron* **2000**, *56*, 2799–2804; (g) J. Canisius, T. A. Mobley, S. Berger, N. Krause, *Chem. Eur. J.* **2001**, *7*, 2671–2675.

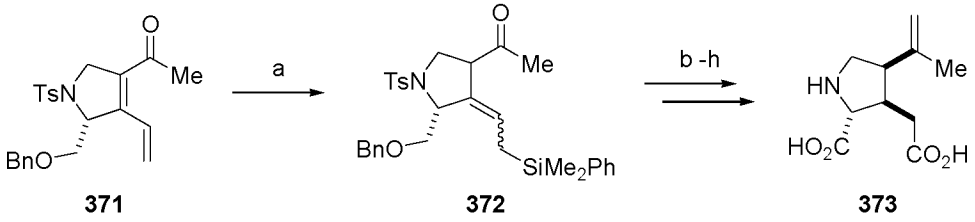
158 T. Hayashi, N. Tokunaga, K. Inoue, *Org. Lett.* **2004**, *6*, 305–307.

Equally noteworthy in the context of catalytic 1,6-additions is the recently reported asymmetric 1,6-addition of aryl zinc reagents to dienones (Scheme 127).[159] The intermediary dienol silyl ether was hydrolyzed under acidic conditions to give the α,β-unsaturated ketone **370** in to 96% enantiomeric excess.



Scheme 127: (a) PhZnCl, TMSCl, [{RhCl[(*S*)-binap]}$_2$], THF, rt, 2 h, *Z*/*E* = 4:1; (b) aq. HCl, 99% over 2 steps, 96% ee.

Applications of the 1,6-addition in the course of a total synthesis are very scarce. In 2003, *Trost* and *Rudd* reported the asymmetric synthesis of (+)-α-kainic acid (**373**), which involved the 1,6-addition of a silyl anion to the $\alpha,\beta,\gamma,\delta$-unsaturated ketone **371** (Scheme 128).[160] The silicon moiety was used as a stable oxygen surrogate, since the direct hydroboration of **371** had proven unfeasible due to decomposition or formation of product mixtures under a variety of conditions.



Scheme 128: (a) LiSiMe$_2$Ph, CuCN, THF, −78 °C to 0 °C, 5 h; (b) DBU, PhH, Δ, 7 h, 87% over 2 steps, 96% ee; (c) Pd/C, 1:1 formic acid/MeOH, rt, 4 h, 93%; (d) H_2, [Ir(cod)py(PCy$_3$)]PF$_6$, B(O^{i}Pr)$_3$, rt, 24 h, 65%; (e) TMSCH$_2$Li, THF, −78 °C, 5 h, 65%; (f) HF, MeCN, rt, 1 h; (g) KH, TBHP, TBAF, DMF, 65 °C, 4 h, 90% over 2 steps; (h) CrO_3, H_2SO_4, H_2O, acetone, rt, 1.5 h; (i) Li, NH_3, THF, −78 °C, 30 min, 80% over 2 steps.

The 1,6-addition of an α-sulfonyl carbanion to quinone methide **374** has been applied to the synthesis of the antiarthritic drug candidate S-2474 (**377**, Scheme 129).[161] The initially

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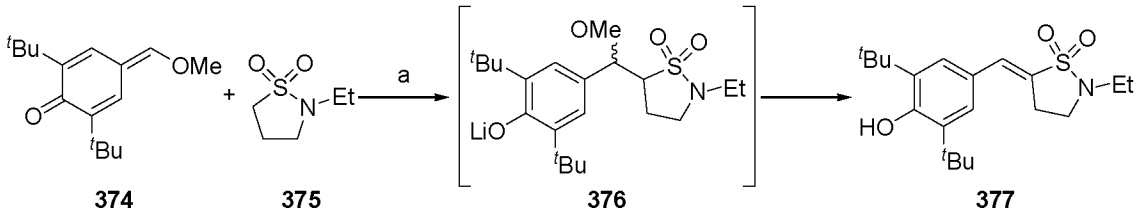
[159] T. Hayashi, S. Yamamoto, N. Tokunaga, *Angew. Chem., Int. Ed.* **2005**, *44*, 4224–4227.

[160] B. M. Trost, M. T. Rudd, *Org. Lett.* **2003**, *5*, 1467–1470.

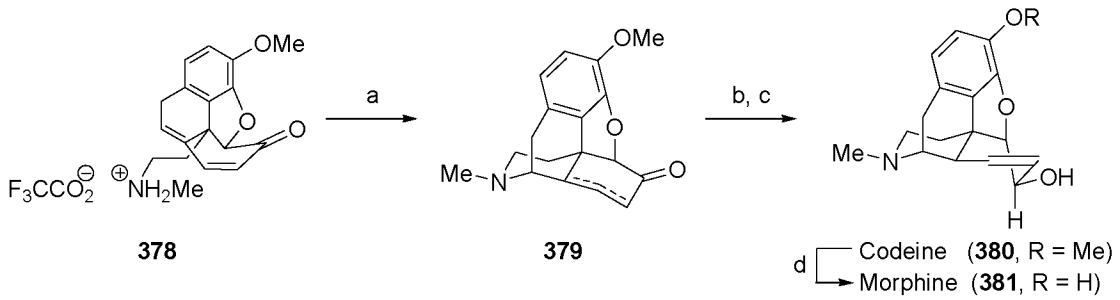
[161] M. Inagaki, N. Haga, M. Kobayashi, N. Ohta, S. Kamata, T. Tsuri, *J. Org. Chem.* **2002**, *67*, 125–128.

formed addition product **376** was converted in situ to **377** by elimination of MeOH, rendering the separation of the two diastereomers unnecessary.



Scheme 129: (a) LDA, THF, −78 °C, 2 h, 61%.

In the course of their morphine synthesis, *Toth* and *Fuchs* developed an intramolecular 1,6-addition of an amine.[162] Thus, ammonium salt **378** spontaneously underwent conjugate addition to the dienone moiety upon neutralization (Scheme 130).



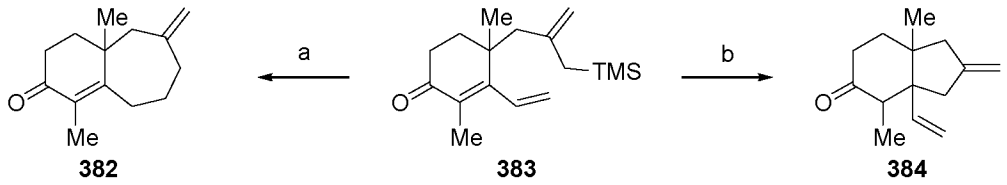
Scheme 130: (a) aq. $NaHCO_3$, CH_3Cl, rt, 20 min, 60%; (b) HCl, Et_2O, CH_2Cl_2, rt, 30 min, then 0.2 M aq. NaOH, $CHCl_3$, 95%; (c) $NaBH_4$, MeOH, rt, 30 min, 95%; (d) BBr_3, $CHCl_3$, rt, 30 min, 55%.

The intramolecular 1,6-addition of a carbon nucleophile was first reported by *Majetich* and co-workers in 1985.[163] It was shown that the regioselectivity of the reaction was determined by the mode of activation, *Lewis* acids leading to the formation of the 1,6-addition product **382** and fluoride ions favoring the 1,4-addition to **384**, respectively (Scheme 131). Subsequent studies dealt with the application of this intramolecular *Sakurai* reaction to the synthesis of

[162] (a) J. E. Toth, P. L. Fuchs, *J. Org. Chem.* **1986**, *51*, 2594–2596; (b) J. E. Toth, P. L. Fuchs, *J. Org. Chem.* **1987**, *52*, 473–475.

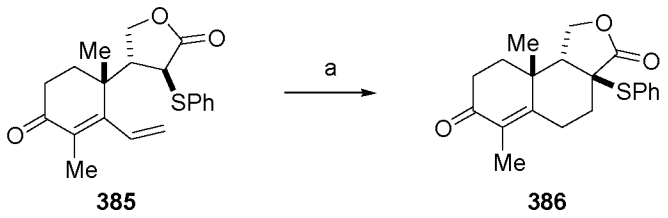
[163] (a) G. Majetich, K. Hull, J. Defauw, R. Desmond, *Tetrahedron Lett.* **1985**, *26*, 2747–2750; (b) G. Majetich, K. Hull, R. Desmond, *Tetrahedron Lett.* **1985**, *26*, 2751–2754.

bicyclic natural products.[164] A very similar intramolecular cyclization of allylsilanes was described by *Schinzer* and co-workers.[165]



Scheme 131: (a) $EtAlCl_2$, PhMe, 0 °C, 30 min, 90%; (b) TBAF, 4 Å MS, HMPA, DMF, rt, 1 h, 54%.

Concurrently, *Holton* and co-workers made use of an intramolecular 1,6-addition for a stereospecific annulation (Scheme 132).[166] Upon treatment of **385** with base, the tricyclic product **386** was obtained in quantitative yield as a single diastereomer.



Scheme 132: (a) NaOMe, MeOH, rt, 1 h, quant..

The scope of the intramolecular 1,6-addition was further expanded by *Majetich* and co-workers, who reported the reaction of unactivated alkenes **387**[167] and the *Friedel–Crafts* annulation of aryl substituted dienones, such as **389**[168] (Scheme 133). The derived bicyclic product **388** was obtained in 60% yield, while tricycle **390** was isolated in 75% yield.

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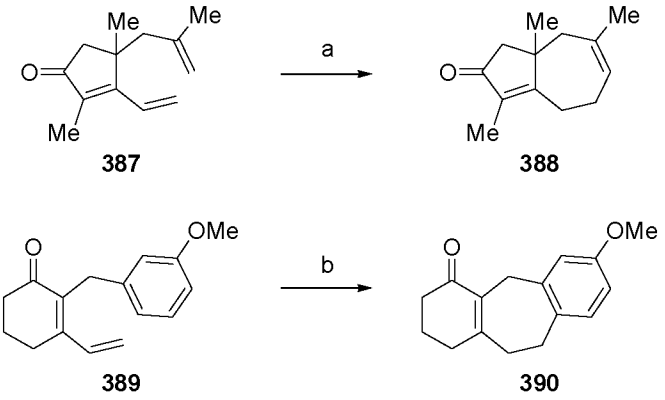
[164] For selected examples, see: (a) G. Majetich, J. Defauw, C. Ringold, *J. Org. Chem.* **1988**, *53*, 50–68; (b) G. Majetich, J. S. Song, C. Ringold, G. A. Nemeth, M. G. Newton, *J. Org. Chem.* **1991**, *56*, 3973–3988; (c) G. Majetich, J. S. Song, A. J. Leigh, S. M. Condon, *J. Org. Chem.* **1993**, *58*, 1030–1037.

[165] D. Schinzer, G. Dettmer, M. Ruppelt, S. Solyom, J. Steffen, *J. Org. Chem.* **1988**, *53*, 3823–3828.

[166] M. E. Krafft, R. M. Kennedy, R. A. Holton, *Tetrahedron Lett.* **1986**, *27*, 2087–2090.

[167] G. Majetich, V. Khetani, *Tetrahedron Lett.* **1990**, *31*, 2243–2246.

[168] G. Majetich, Y. Zhang, T. L. Feltman, V. Belfoure, *Tetrahedron Lett.* **1993**, *34*, 441–444.



Scheme 133: (a) Amberlyst Resin, CH_2Cl_2, Δ, 60%; (b) $BF_3{\cdot}OEt_2$, rt, 75%.

4.5 Conclusion

The fungal metabolite fusidilactone C possesses unique structural features which promise several challenging and enthralling synthetic tasks. Its complexity has even been compared to that of tetrodotoxin, the poison of the Japanese pufferfish.[144] Despite fusidilactone C's very intriguing structure, only one attempt at its synthesis has been published to date. This offers ample freedom for the selection of a synthetic strategy.

1,6-additions to acceptor-substituted dienes are very rare, especially compared to the widely used 1,4-additions, and have only scarcely been applied in syntheses. In particular the intramolecular version is still poorly conceived. We therefore decided to investigate the scope of an intramolecular 1,6-addition in view of a potential application in our studies toward the synthesis of fusidilactone C.

5 A 1,6-Addition Approach to Fusidilactone C

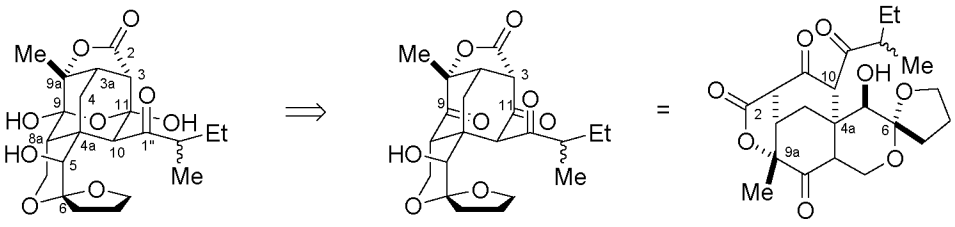
5.1 Synthetic Planning

5.1.1 Introduction

At the outset of this project, the isolation of fusidilactone C (**333**) had only recently been reported.[144] Intrigued by its very unusual structure, we decided to devise a synthetic approach which would allow for the preparation of **333**. The expedient construction of fusidilactone C's oxoadamantane scaffold is key to a concise and elegant synthesis.

5.1.2 Retrosynthetic Analysis

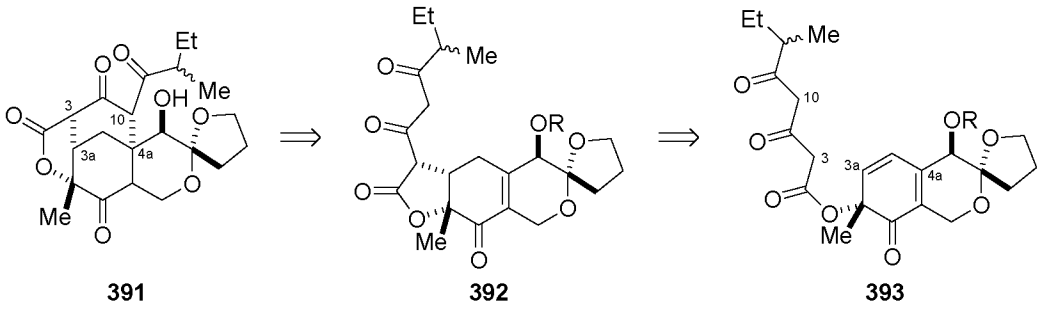
We expected the oxoadamantyl bishemiacetal present in fusidilactone C (**333**) to be formed by addition of H_2O to the parent triketone **391** (Scheme 134). It seemed likely that the conformation of **391** would facilitate acetal formation to an extent that the triketone could be converted to the natural product under very mild conditions.



333 **391** **391**

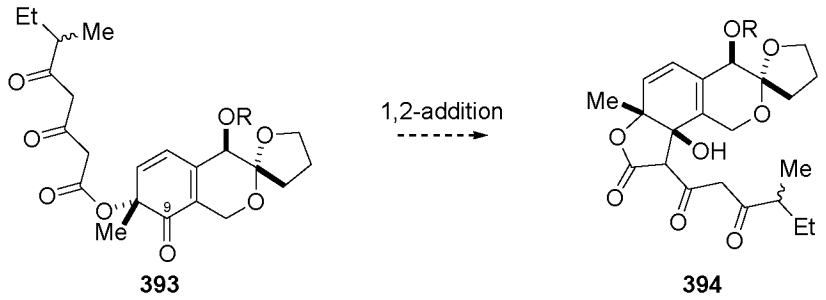
Scheme 134.

The key disconnection of our approach is an unprecedented tandem 1,6–1,4-addition of a β,δ-diketoester to a cyclohexadienone moiety (Scheme 135), which would lead to the considerably simplified tricyclic structure **393**.



Scheme 135.

While competitive 1,2-addition to the C9 ketone affording **394** seems reasonable (Scheme 136), we postulated that (i) this undesired pathway was reversible and (ii) the 1,6-addition product should be thermodynamically favored because the C=O double bond stays intact. Moreover, **392** could react further in an intramolecular 1,4-addition, giving rise to an additional C–C bond (83 kcal mol^{-1}), while the product resulting from 1,2-addition (**394**) would be a less stable hydroxy diene.

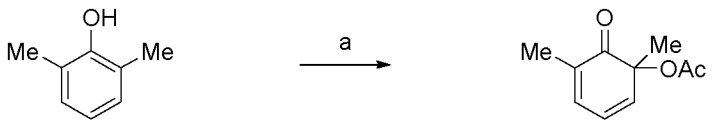


Scheme 136.

5.2 Results and Discussion

5.2.1 Preliminary Studies I

Since only a few examples of intramolecular 1,6-additions had previously been reported,[169] we decided to test the feasibility of the key step on a simplified model system. The known cyclohexadienone **396**,[170] available from 2,6-dimethylphenol (**395**) in 63% yield by $Pb(OAc)_4$-mediated oxidation (Scheme 137), was chosen as a starting point for these preliminary studies.



395 **396**

Scheme 137: (a) $Pb(OAc)_4$, CH_2Cl_2, rt, 2 h, 63%.

Deprotonation of cyclohexadienone **396** under dilute conditions should give rise to an intramolecular 1,2- or 1,6-addition reaction, leading to the formation of alcohol **397** or enone **398**, respectively (Scheme 138). A rough estimate of the relative stability of these two compounds can be obtained by analysis of their bond energies:[171] **398** incorporates a C=O double bond (173–181 kcal mol^{-1}), and an additional C–C (83–85 kcal mol^{-1}) and C–H (96–99 kcal mol^{-1}) single bond; **397** possesses an additional C=C double bond (146–151 kcal mol^{-1}), a C–O (85–91 kcal mol^{-1}), and an O–H (110–111 kcal mol^{-1}) bond.[172] By comparison of the average bond energies, enone **398** should be favored by about 12 kcal mol^{-1}, whereas summation of the highest values for **397** and the lowest values for **398** ("worst case") results in an energy difference of 1 kcal mol^{-1} in favor of the 1,2-addition product **397**.[173] Based on these estimates, the assumption that the 1,6-addition is thermodynamically favored seems scientifically tenable.

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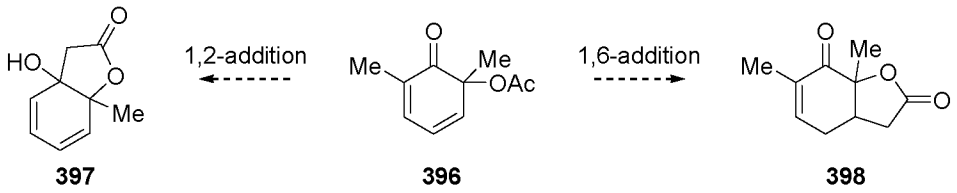
169 See section 4.4.

170 H. Auksi, P. Yates, *Can. J. Chem.* **1981**, *59*, 2510–2517.

171 Only the energies of bonds which are not common to both products were compared.

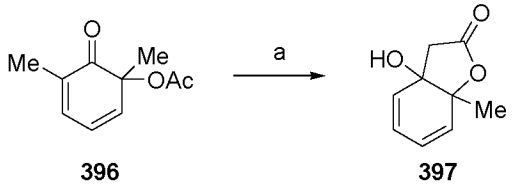
172 These bond energies were taken from: M. B. Smith, J. March; *March's Advanced Organic Chemistry*, 5th edition; John Wiley & Sons: New York, **2001**; p. 24.

173 The "best case" scenario suggests an energy difference of 24 kcal mol^{-1} in favor of **398**.



Scheme 138.

To investigate the reactivity of dienone **396** upon deprotonation, it was treated with LDA at –78 °C (Scheme 139). The reaction afforded the 1,2-addition product **397** in 54% yield with no detected 1,6-addition product, suggesting that the formation of the 1,2-addition product **397** was kinetically favored.



Scheme 139: (a) LDA, THF, −78 °C, 30 min, 54%.

Based on the assumption that **397** was the kinetically controlled product and that its formation was reversible, we undertook a number of experiments aimed at obtaining the thermodynamically favored 1,6-addition product **398**. The parameters studied include (i) the base used for deprotonation; (ii) the reaction temperature; (iii) the reaction time (Table 3).

In several cases, the 1,2-addition product **397** was isolated (entries 1–3 and 7). On the other hand, increased temperature, which would be consistent with thermodynamic control, led either to decomposition (entry 4) or to dimerization (entry 5), affording the intermolecular 1,2-addition product **399** (Figure 17).

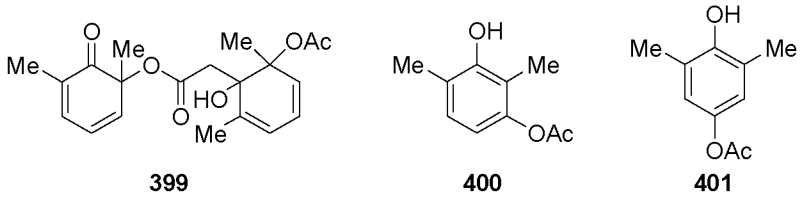
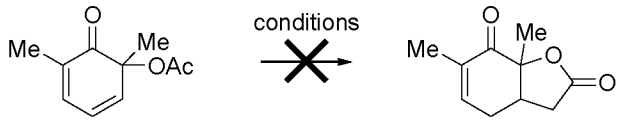


Figure 17.



396 **398**

entry	conditions	results
1	LHMDS, THF, –78 °C, 30 min	1,2-addition
2	KO^{t}Bu, THF, –78 °C, 90 min	1,2-addition
3	KO^{t}Bu, ^{t}BuOH, rt, 3 d	1,2-addition
4	KO^{t}Bu, ^{t}BuOH, 50 °C, 20 h	decomposition
5	KO^{t}Bu, ^{t}BuOH, 85 °C, 3 h	dimerization
6	LDA, THF, rt, 1 h	1,2-addition
7	CuO^{t}Bu,[174] THF,[175] –78 °C to rt, 15 h	no reaction
8	CuO^{t}Bu,[174] THF,[175] 30 °C, 19 h	no reaction
9	KHMDS, CuBr·SMe_2, THF, –78 °C to rt, 16 h	no reaction
10	KHMDS, CuBr·SMe_2, SMe_2, THF, 0 °C to rt, 17 h	no reaction
11	NEt_3, $SnCl_4$, CH_2Cl_2, –78 °C, 90 min	acetate migration
12	NEt_3, $TiCl_4$, CH_2Cl_2, –78 °C to rt, 17 h	acetate migration

Table 3.

Since cuprates are known to readily undergo conjugate addition reactions,[176] we decided to examine copper-based reagents. Upon treatment with CuO^{t}Bu (entries 7 and 8) and with KHMDS/CuBr (entries 9 and 10), acetate **396** proved unreactive.

Finally, we turned our attention to the *Lewis* acid activation of the dienone system with either $TiCl_4$ or $SnCl_4$ (entries 11 and 12). These reactions failed to afford the 1,6-addition product **398**, giving two highly UV-active compounds instead, which were assigned to the structures **400** and **401**, wherein acetate migration—presumably *via* acid-catalyzed dienone–phenol rearrangement[177]—had occurred.

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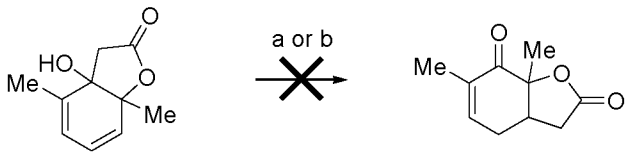
[174] Constantin Czekelius is gratefully acknowledged for the preparation of CuO^{t}Bu.

[175] For the reactions with CuO^{t}Bu, THF was deoxygenated prior to use.

[176] For a review, see: J. A. Kozlowski in *Comprehensive Organic Synthesis*; B. M. Trost, I. Fleming, Eds.; Pergamon: Oxford, **1991**; Vol. 4, 169–198.

[177] For a review, see: B. Miller, *Acc. Chem. Res.* **1975**, *8*, 245–256.

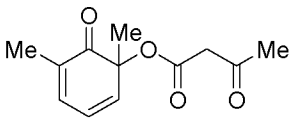
As we expected the 1,2-addition process to be reversible under suitable reaction conditions, we attempted equilibration by 1,2-elimination/1,6-addition to give **398** (Scheme 140). Alcohol **397** was therefore treated with potassium hydride and 18-crown-6. Both at 0 °C and at ambient temperature, the reaction mixture turned dark brown within a short time, and TLC analysis showed complete consumption of the starting material. However, NMR analysis of the reaction mixture revealed decomposition.



397 **398**

Scheme 140: (a) KH, 18-crown-6, THF, 0 °C, 30 min; (b) KH, 18-crown-6, THF, rt, 5 min.

At this point in time, it was unclear why the intramolecular 1,6-addition did not take place and we started questioning the viability of our model substrate: indeed, for the planned synthesis of fusidilactone C, the nucleophile in the 1,6-addition process was a β-ketoester, which is considerably more acidic than the acetate group in our model system **396** (pK_a 11 vs 24 in H_2O). Thus, the second-generation model substrate **402** incorporating an acetoacetate side chain was envisaged (Figure 18), which would offer the opportunity to investigate the tandem 1,6–1,4-addition reaction.

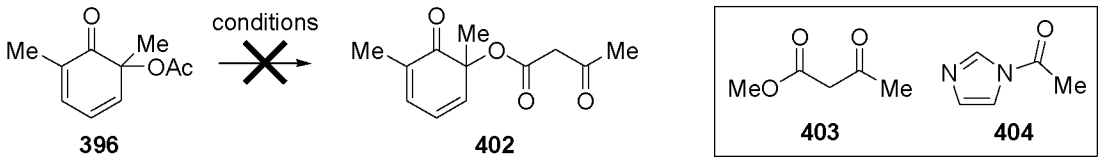


402

Figure 18: Second-generation model substrate.

We tried to access acetoacetate **402** from the parent acetate **396** (Scheme 141). Transesterification[178] with **403** was unsuccessful, returning only unreacted starting material even after prolonged reaction times; treatment of acetate **396** with an acylating agent under basic conditions afforded a mixture of starting material and the previously described 1,2-addition product **397**.

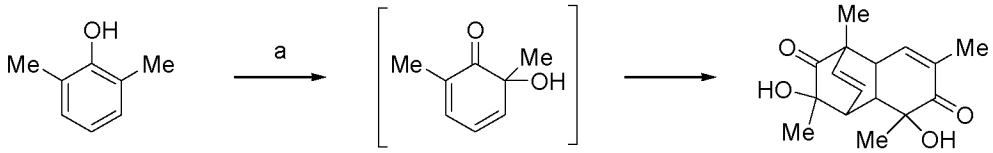
[178] For a review, see: J. Otera, *Chem. Rev.* **1993**, *93*, 1449–1470.



396 **402** **403** **404**

Scheme 141: (a) KCN, **403**, rt, 7 d; (b) **403**, NaOMe, rt, 3 d; (c) LHMDS, AcCl, THF, −78 °C, 2 h; (d) NaHMDS, AcCl, THF, −78 °C, 2 h; (e) LHMDS, **404**,[179] THF, −78 °C to 0 °C, 2 h; (f) NaHMDS, **404**, THF, −78 °C to 0 °C, 2 h.

Esterification of alcohol **405** would allegedly allow for a fast access to acetoacetate **402**. While **405** is well known to undergo dimerization by *Diels–Alder* reaction even at room temperature (Scheme 142),[180] esterification of its dimer **406** followed by retro *Diels–Alder* reaction is literature known.[181]



395 **405** **406**

Scheme 142: (a) $NaIO_4$, H_2O, rt, 30 min, 64%.

In view of these reports, we tackled the esterification of dimer **406** (Scheme 143). For the transformation to **407**, diketene—which is sufficiently reactive to esterify tertiary alcohols[182]—seemed to be the reagent of choice, but failed to provide the desired product. Also, **406** proved recalcitrant to transesterification with methylacetoacetate (**403**). Thus, we suspected that diol **406** might be sterically too crowded for acylation. Our assumption was further supported by the inertness of **406** towards Ac_2O in the presence of catalytic amounts of DMAP in pyridine.

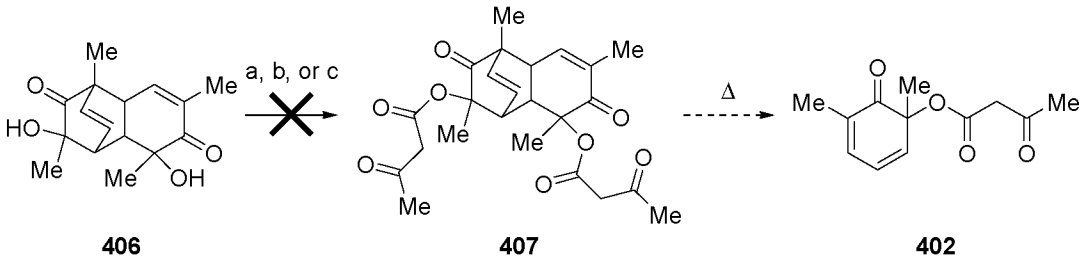
---

[179] M. E. Nelson, N. D. Priestley, *J. Am. Chem. Soc.* **2002**, *124*, 2894–2902.

[180] E. Adler, J. Dahlen, G. Westin, *Acta Chem. Scand.* **1960**, *14*, 1580–1596.

[181] V. K. Singh, P. T. Deota, B. N. S. Raju, *Synth. Commun.* **1987**, *17*, 115–124.

[182] For selected examples, see: (a) A. Nudelman, R. Kelner, N. Broida, H. E. Gottlieb, *Synthesis* **1989**, 387–388; (b) K. Fukushima, Y. Q. Lu, T. Ibata, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 3289–3295.



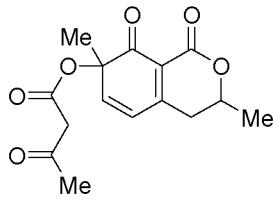
406 **407** **402**

Scheme 143: (a) diketene, DMAP, THF, rt to 50 °C, 2 h; (b) diketene, py, PhMe, rt, 2 d; (c) **403**, TsOH, 80 °C, 3 h.

At this point, we decided to discontinue the investigation of our dienone model system **396** and to look for more promising alternatives. In particular, we were hoping to find suitable substituents for the dienone moiety, which would prevent *Diels–Alder* dimerization and thus enable the preparation of a 2-hydroxy-cyclohexa-3,5-dienone.

5.2.2 Preliminary Studies II

For our third-generation model substrate, we wished to incorporate more of the structural features present in **393** (Scheme 135), the envisaged precursor for our synthesis of fusidilactone C. Acetoacetate **408** (Figure 19) would not only bear the cyclohexadienone moiety necessary for the envisioned intramolecular 1,6-addition reaction, but also possess the [4.4.0]bicyclic scaffold of **393**. Additionally, we expected the lactone to render the dienone system less electron-rich and thus (i) less prone to dimerization by *Diels–Alder* reaction and (ii) more reactive toward the desired 1,6-addition pathway.



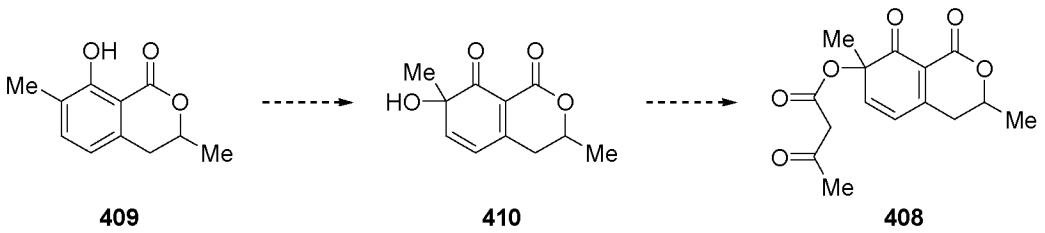
408

Figure 19: Third-generation model system.

We intended to access acetoacetate **408** from the known phenol **409**[183] (Scheme 144). $NaIO_4$-promoted oxidation of **409** should furnish cyclohexadienone **110**, which we were expecting to be sufficiently electron-deficient to avoid dimerization by *Diels–Alder* reaction.

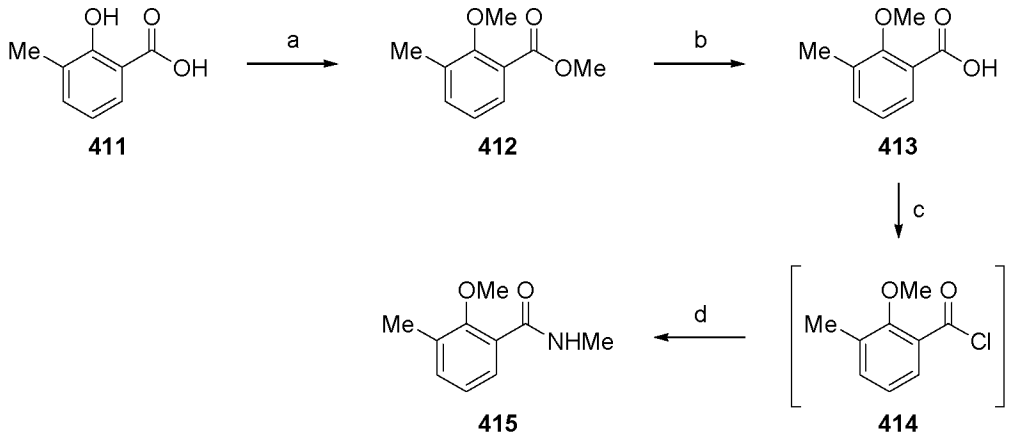
[183] H. J. Bestmann, F. Kern, D. Schäfer, M. C. Witschel, *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 795–796.

Esterification of the tertiary hydroxy group present in **410** with diketene should then afford acetoacetate **408**.



Scheme 144.

Acid **413** was prepared from salicylic acid (**411**) in two steps and 86% overall yield (Scheme 145).[184] Dimethylation of **411** afforded ester **412**, which was subsequently saponified to acid **413**. Treatment of **413** with thionyl chloride afforded acid chloride **414**, the conversion of which into amid **415** was effected with methylamine in 43% yield over two steps.[183]



Scheme 145: (a) K_2CO_3, MeI, DMF, 90 °C, 15 h, 94%; (b) NaOH, MeOH, H_2O, rt, 15 h, 92% (c) $SOCl_2$, DMF, rt, 5 h; (d) aq. $MeNH_2$, rt, 18 h, 43% over 2 steps.

Ortholithiation[185] of amide **415** and subsequent addition of (±)-propylene oxide furnished alcohol **416** (Scheme 146). Methyl ether cleavage using BBr_3 gave diol **417**. The synthesis of phenol **409** was completed by lactonization of amide **417** under acidic conditions.

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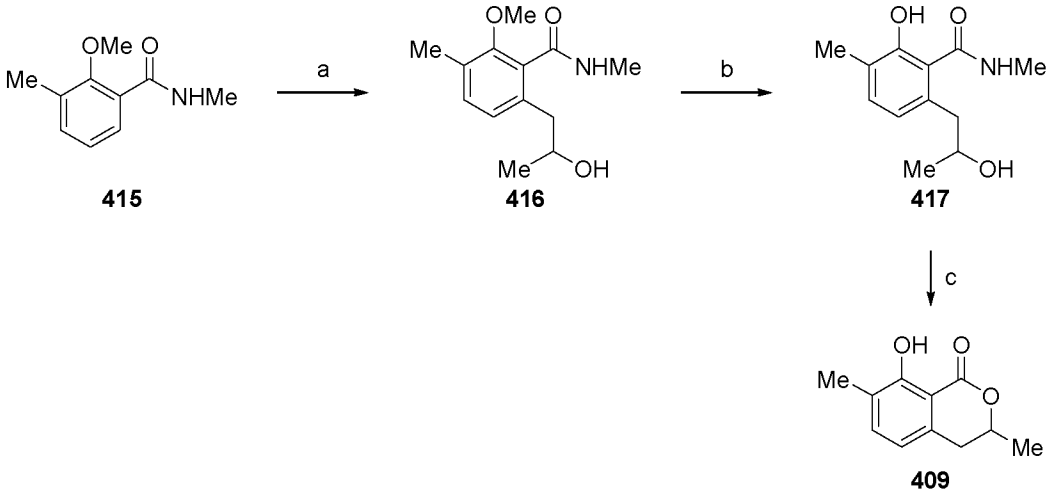
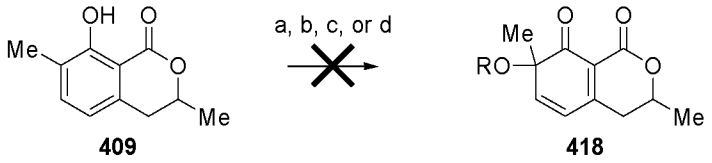
[184] S. M. Cohen, M. Meyer, K. N. Raymond, *J. Am. Chem. Soc.* **1998**, *120*, 6277–6286.

[185] For a review on directed metalation, see: V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933.



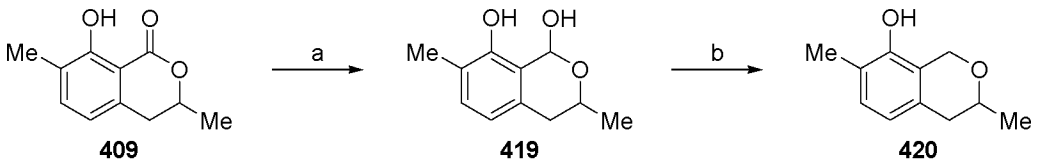
Scheme 146: (a) TMEDA, ^{s}BuLi, THF, −78 °C, 4 h, then 2-methyloxirane, −78 °C to rt, 14 h; (b) BBr_3, CH_2Cl_2, −78 °C to rt, 15 h; (c) 15% aq. HCl, 100 °C, 15 h, 12% over 3 steps.

With phenol **409** in hand, we turned our attention to its planned transformation to the corresponding cyclohexadienone **418**. However, **409** proved unreactive under a variety of typical oxidative conditions (Scheme 147). We suspected that the electron-withdrawing lactone rendered the aromatic π-system too electron poor to undergo oxidation. Therefore, the lactone was reduced to the cyclic ether, which should provide the phenol with sufficient electron density to permit its transformation to the cyclohexadienone.



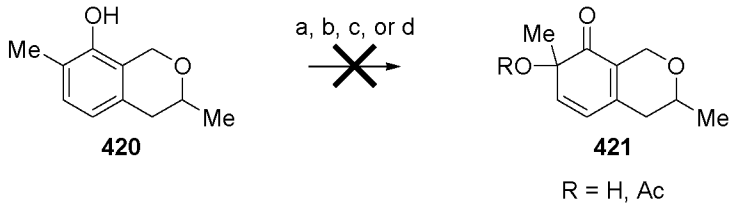
Scheme 147: (a) $NaIO_4$, H_2O, 50 °C, 3 d; (b) $Pb(OAc)_4$, CH_2Cl_2, rt, 4 d; (c) $(PhSeO)_2O$, CH_2Cl_2, 45 °C, 6 d; (d) $Pb(OAc)_4$, AcOH, rt, 4 h.

Treatment of lactone **409** with DIBAL-H afforded lactol **419** in 93% yield (Scheme 148). Further reduction to ether **420** was achieved with triethylsilane under acidic conditions.



Scheme 148: (a) DIBAL-H, THF, −78 °C to rt, 1 h, 93%; (b) NH_4F, Et_3SiH, CF_3CO_2H, CH_2Cl_2, 0 °C to rt, 140 min, 46%.

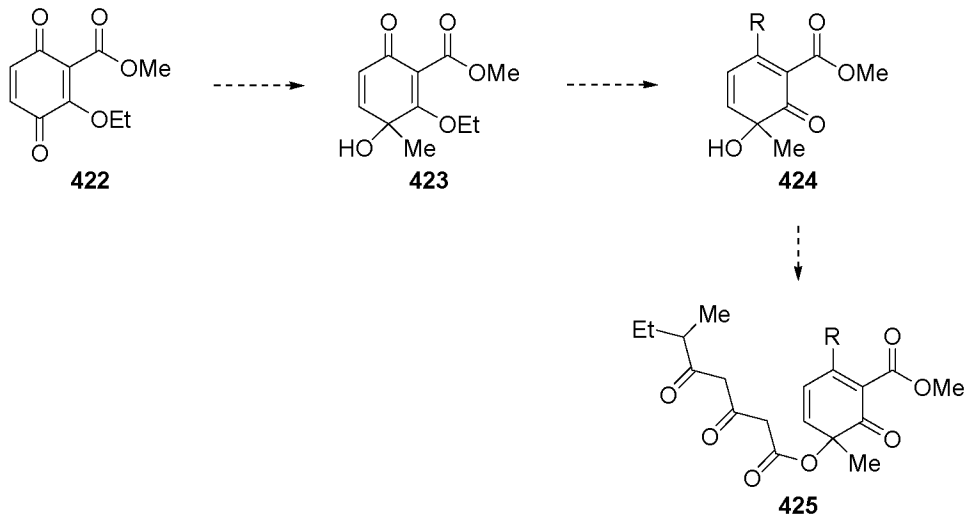
We attempted to prepare cyclohexadienone **421** by oxidation of isochromanol **420** using sodium periodate in water/methanol, phenylseleninic anhydride in methylene chloride, and lead tetraacetate in acetic acid, respectively, but without success (Scheme 149): In all three cases, the starting material decomposed under the employed reaction conditions. When **420** was treated with lead tetraacetate in methylene chloride at ambient temperature, we observed the formation of a complicated mixture of several products, which were not isolated or further characterized.



Scheme 149: (a) $NaIO_4$, H_2O, MeOH, rt, 5 d; (b) $(PhSeO)_2O$, CH_2Cl_2, 40 °C, 75 min; (c) $Pb(OAc)_4$, AcOH, rt, 2 d; (d) $Pb(OAc)_4$, CH_2Cl_2, rt, 2 h.

5.2.3 Intramolecular Conjugate Addition Reactions

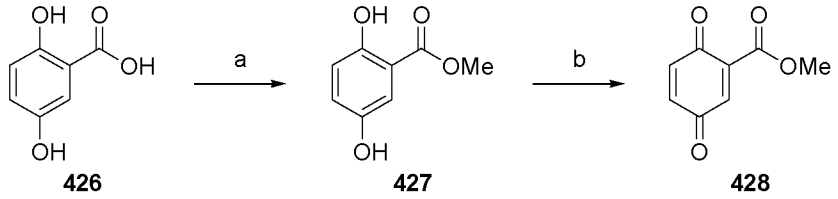
In view of the difficulties encountered during the attempted oxidation of the phenols **409** and **420**, we decided to pursue a completely different approach toward a 2-hydroxy cyclohexadienone **425**: We envisioned preparing tertiary alcohol **423** by methylation of quinone **422** (Scheme 150). Nucleophilic addition to the vinylogous ester followed by β-elimination of ethanol would afford cyclohexadienone **424**, which we intended to convert into β,δ-diketoester **425** by esterification.



Scheme 150: Revised synthetic planning.

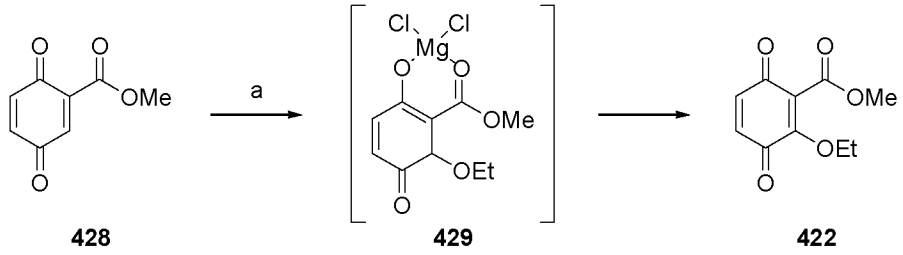
Synthesis of Tertiary Alcohol 423

The synthesis of the known quinone **428**[186] commenced with the acid-catalyzed esterification of 2,5-dihydroxy benzoic acid (**426**), which afforded **427** in almost quantitative yield (Scheme 151).[187] Hydroquinone **427** was subsequently oxidized to the corresponding quinone **428** using silver(II) oxide.[186]



Scheme 151: (a) H_2SO_4, MeOH, 65 °C, 24 h, 98%; (b) $MgSO_4$, Ag_2O, Et_2O, rt, 25 h, 92%.

Introduction of the ethoxy substituent was achieved under conditions similar to those used by *Hormi* and *Moilanen*.[188] Thus, magnesium chloride served as a *Lewis* acid, activating the quinone ester **428** towards 1,4-addition of ethanol (Scheme 152). In contrast to *Hormi*'s protocol requiring two equivalents of quinone **428**, our modification is based on the addition of stoichiometric amounts of DDQ to oxidize the intermediary hydroquinone, giving **422** in 72% yield.

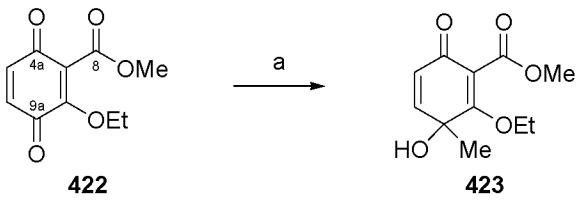


Scheme 152: (a) $MgCl_2$, DDQ, EtOH, PhMe, rt, 20 h, 72%.

For the introduction of the tertiary hydroxy alcohol, we had envisioned methyl addition to the C9a ketone. Comparison of the three carbonyl groups present in quinone **422** suggests that the nucleophilic attack should preferentially occur at the C9a ketone, since the other two carbonyl groups are part of an ester (C8) or a vinylogous ester (C4a) group, which are

[186] M. Nakazaki, K. Naemura, *J. Org. Chem.* **1981**, *46*, 106–111.
[187] F. Mazzini, E. Alpi, P. Salvadori, T. Netscher, *Eur. J. Org. Chem.* **2003**, 2840–2844.
[188] O. E. O. Hormi, A. M. Moilanen, *Tetrahedron* **1998**, *54*, 1943–1952.

generally less reactive electrophiles.[189] In the event, treatment of **422** with MeLi afforded alcohol **423** as a single product in 58% yield (Scheme 153).

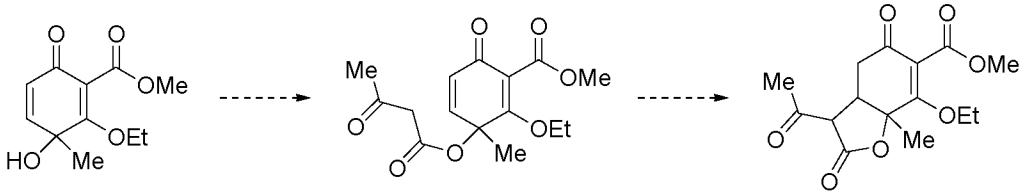


422 **423**

Scheme 153: (a) MeLi, THF, −78 °C, 1 h, 58%.

Intramolecular 1,4-Addition

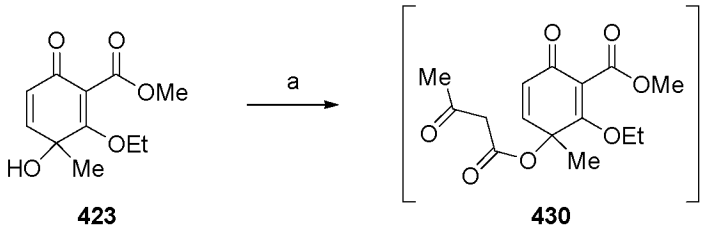
At this point, we decided to slightly deviate from our original plan and to investigate the esterification of alcohol **423** and the subsequent intramolecular 1,4-addition to lactone **431** (Scheme 154). Our goal was to gain information about (i) the reactivity of the tertiary hydroxy group towards acylation and (ii) the feasibility of an intramolecular conjugate addition reaction of a β-ketoester.



423 **430** **431**

Scheme 154.

Alcohol **423** was treated with diketene and pyridine (Scheme 155). While the ^{1}H NMR spectrum of the unpurified product showed formation of **430**, its isolation in pure form by flash column chromatography failed because of extensive decomposition on silica gel.

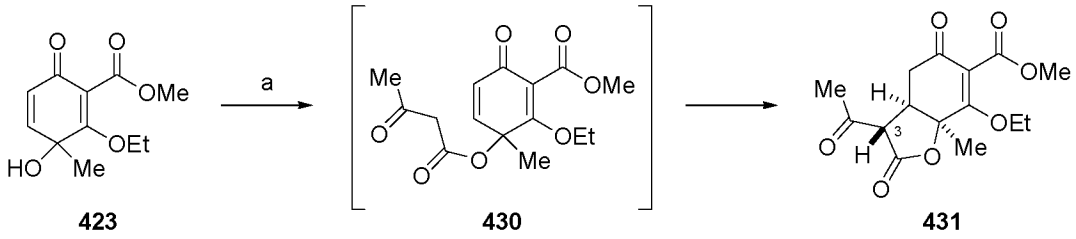


423 **430**

Scheme 155: (a) diketene, py, PhMe, rt, 20 h.

[189] F. A. Carey, R. J. Sundberg, *Reaktionen von Carbonylverbindungen*; in *Organische Chemie*; H. J. Schäfer, D. Hoppe, G. Erker, Eds.; VCH: Weinheim **1995**; pp. 425–482.

Encouraged by this positive result, we hypothesized that, under slightly more basic conditions, the activated methylene group in **430** could undergo nucleophilic conjugate addition to the α,β-unsaturated ketone in situ, furnishing bicyclic lactone **431** directly and avoiding the difficult isolation of **430**. Indeed, when pyridine ($pK_a \approx 5.2$) was replaced by triethylamine ($pK_a \approx 10.7$), cyclization of the intermediate β-ketoester was observed, affording the stable lactone **431** in good 53% yield.[190]



423 **430** **431**

Scheme 156: (a) diketene, NEt_3, CH_2Cl_2, rt, 40 h, 53%.

Moreover, we were able to obtain crystals of **431** suitable for single crystal X-ray analysis. The structure obtained unambiguously confirmed the *cis* ring fusion and the relative configuration at C3 (Figure 20).

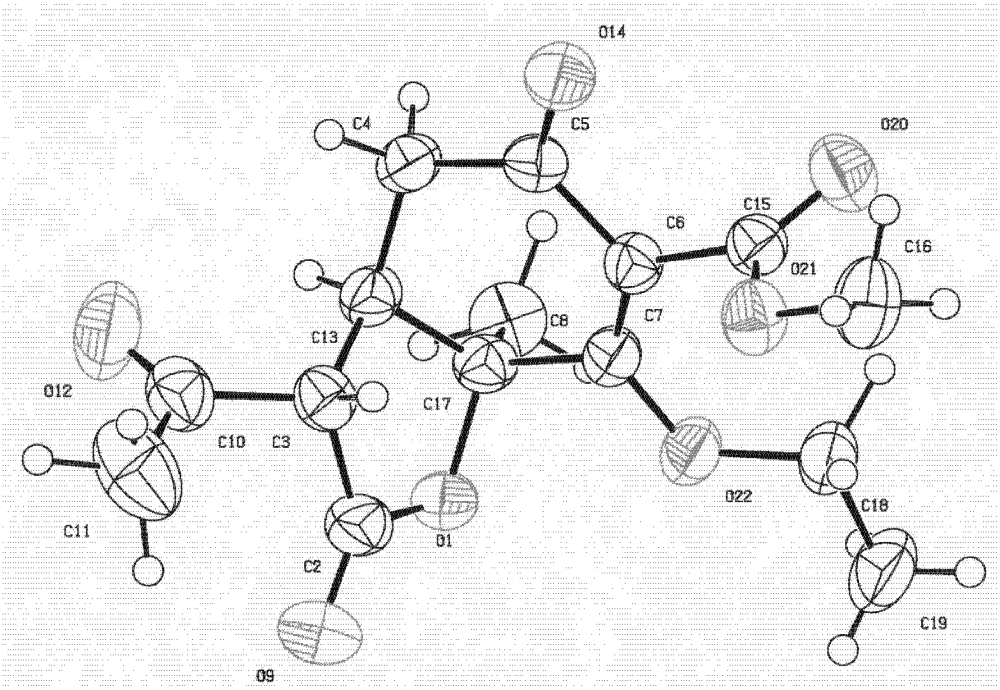
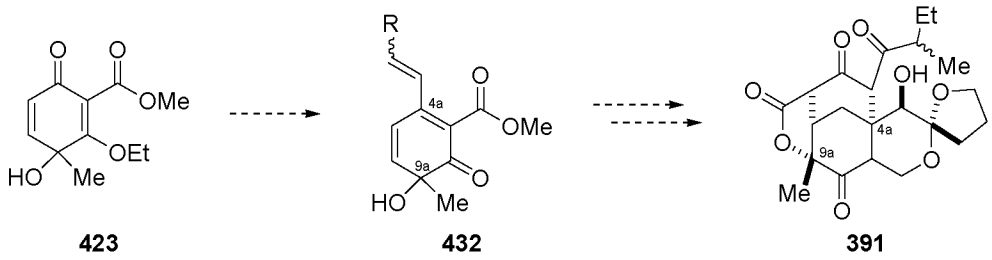


Figure 20. X-ray structure of lactone **431**.

[190] All compounds were prepared in racemic form. The depicted stereodescriptors only describe the relative configuration.

Intramolecular 1,6-Addition

After the first successful intramolecular 1,4-addition reaction, we decided to return to the originally devised route. We needed to introduce an adequate substituent at the C4a position, which would allow for the installation of the α-hydroxy ketal at a later stage (Scheme 157). In this respect, a (substituted) vinyl group seemed promising, as its conversion to the corresponding C4a carbaldehyde by oxidative cleavage should be feasible. We envisioned preparing the cyclohexadienone **432** from **423** by *Grignard* addition[191] to the C4a carbonyl group and subsequent acid-promoted elimination, similar to the second step in the *Stork–Danheiser* alkylation.[192]



423 **432** **391**

Scheme 157.

Vinyl- and allylmagnesium bromide were chosen for the planned addition reaction (Scheme 158): Vinylogous ester **423** was treated with two equivalents of *Grignard* reagent, one of which was needed for deprotonation of the tertiary alcohol. The reaction was quenched by the addition of 1 M aqueous HCl to effect the acid-promoted elimination of ethanol from intermediate **433**. The desired cyclohexadienones **434** and **435** were obtained in 39% and 41% unoptimized yield, respectively.

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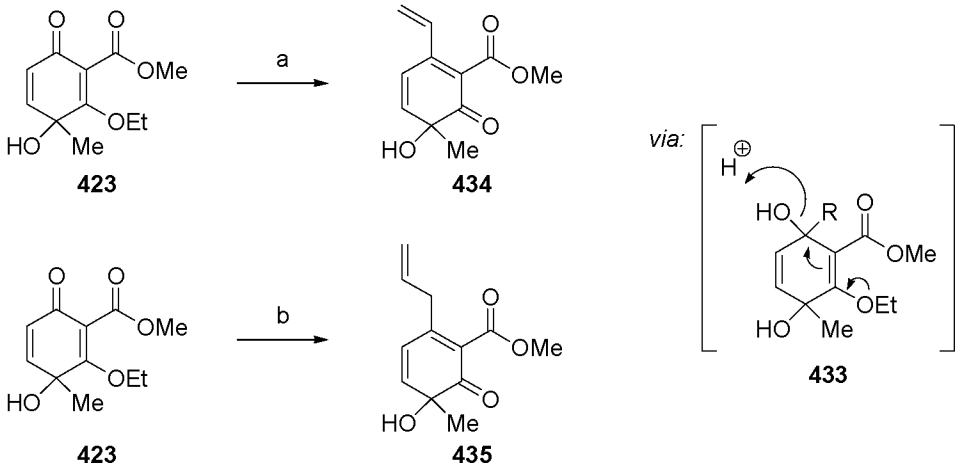
[191] (a) V. Grignard, *Acad. Sci.* **1900**, 1322–1324; (b) V. Grignard, *Ann. Chim.* **1901**, *7*, 433–490.

[192] (a) G. Stork, R. L. Danheiser, *J. Org. Chem.* **1973**, *38*, 1775–1776; for selected examples, see: (b) A. Matzeit, H. J. Schafer, C. Amatore, *Synthesis* **1995**, 1432–1444; (c) G. B. Dudley, K. S. Takaki, D. D. Cha, R. L. Danheiser, *Org. Lett.* **2000**, *2*, 3407–3410; (d) T. J. Greshock, R. L. Funk, *J. Am. Chem. Soc.* **2002**, *124*, 754–755.

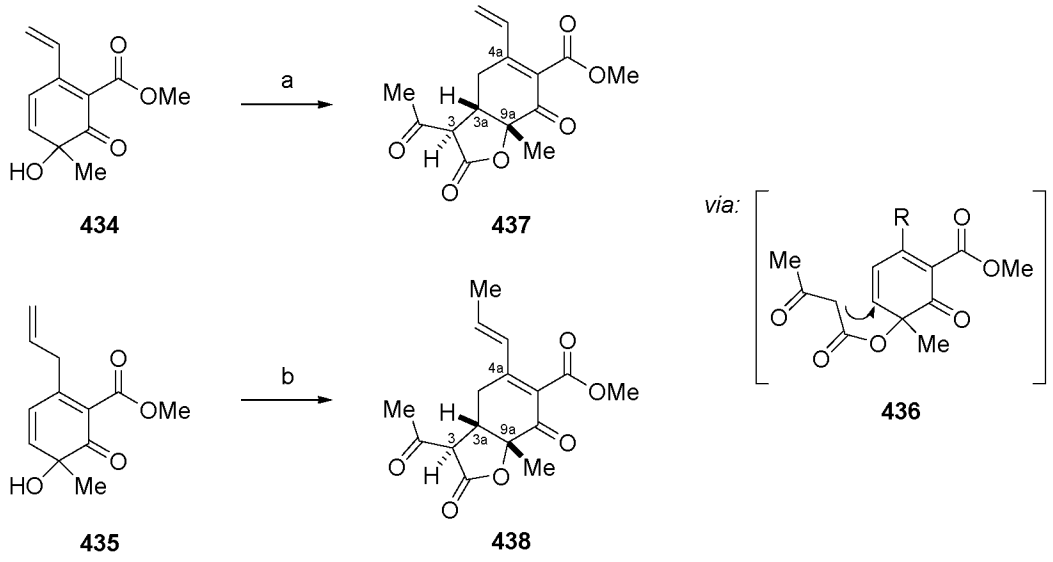


Scheme 158: (a) $CH_2CHMgBr$, Et_2O, −78 °C, 90 min, then 1 M aq. HCl, 39%; (b) CH_2CHCH_2MgBr, Et_2O, −78 °C, 90 min, then 1 M aq. HCl, 41%.

Before tackling the conversion of the above cyclohexadienones **434** and **435** to β,δ-diketoester **425**, we wished to explore the feasibility of our key step, the intramolecular 1,6-addition, with the corresponding acetoacetate **436**. To our delight, the conditions developed previously (diketene, NEt_3, CH_2Cl_2, rt) for esterification of **423** and in situ intramolecular 1,4-addition to give **431** could also be applied to the 1,6-addition of **436**, giving the desired bicyclic lactones **437** and **438** in 26% and 43% unoptimized yield (Scheme 159).

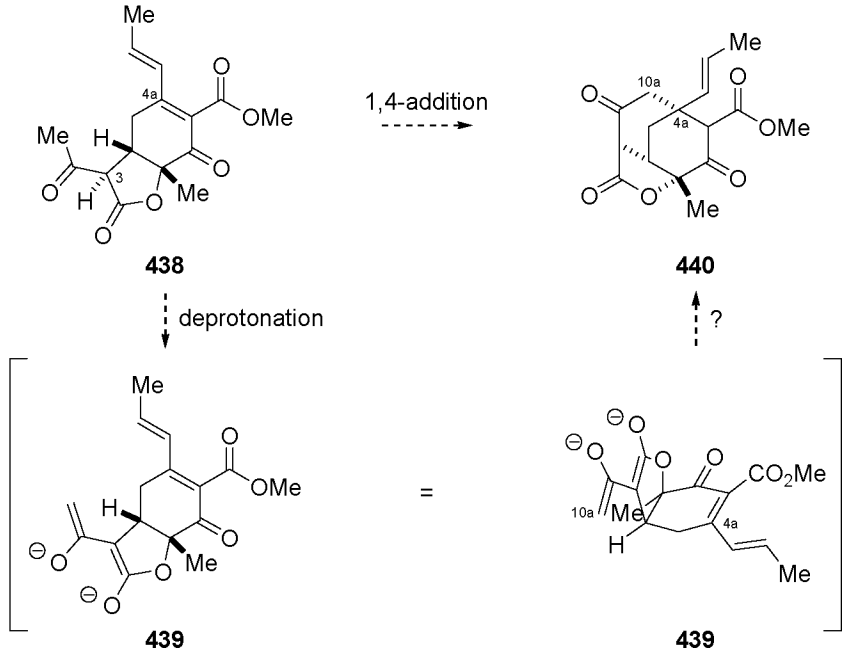
These reactions represent the first examples of such processes, and the mild conditions are noteworthy. Additionally, in the case of **438**, concomitant isomerization of the monosubstituted *E*-double bond[193] to the thermodynamically more stable (ca. 1 kcal mol^{-1}) 1,2-disubstituted olefin was observed. The relative configuration at C3, C3a and C9a was tentatively assigned by analogy to the previously described lactone **431** (Figure 20).

[193] The double bond configuration was assigned based on the ^1H NMR spectrum, which showed a vicinal coupling constant of J = 15.9 Hz.



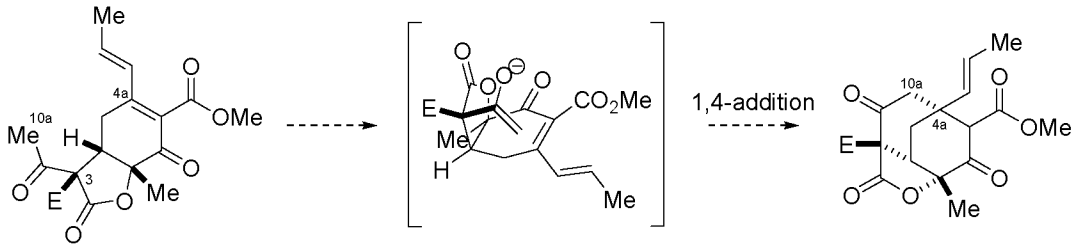
Scheme 159: (a) diketene, NEt_3, CH_2Cl_2, rt, 14 h, 26%; (b) diketene, NEt_3, CH_2Cl_2, rt, 16 h, 43%.

The upcoming attempted intramolecular 1,4-addition was investigated only with **438**. Indeed, its higher yielding access as compared to **437** combined with the advantageous double bond isomerization rendered this substrate more attractive for further studies. Close analysis of the structure of dianion **439** (Scheme 160) needed for the formation of tricycle **440** revealed that, because of the flat dienolate structure, the reactive sites at C10a and C4a were out of reach for intramolecular cyclization.



Scheme 160.

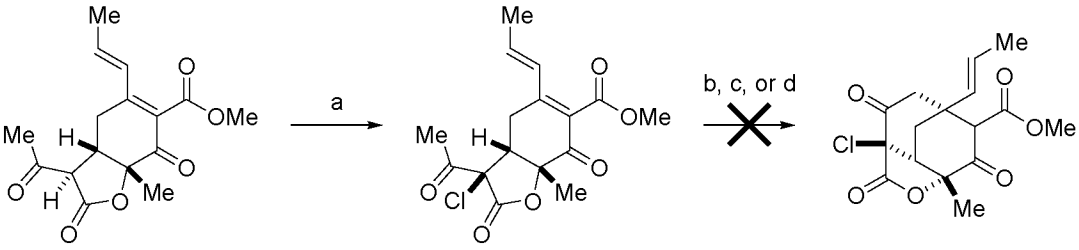
By reacting the activated C3 position with a suitable electrophile (e.g. chlorine), the newly formed quaternary center at C3 would arrange the methyl ketone in close proximity of the C4a–C8a double bond by stereoselective approach of the electrophile from the bicycle's *exo* face (Scheme 161).



441 **442** **443**

Scheme 161.

Chlorination of **438** using sodium hydride and *N*-chlorosuccinimide gave **444** in 32% unoptimized yield (Scheme 162). However, the attempted intramolecular 1,4-addition under basic conditions failed, leading to decomposition ($CsCO_3$) or isolation of unreacted starting material (LDA, NaH).

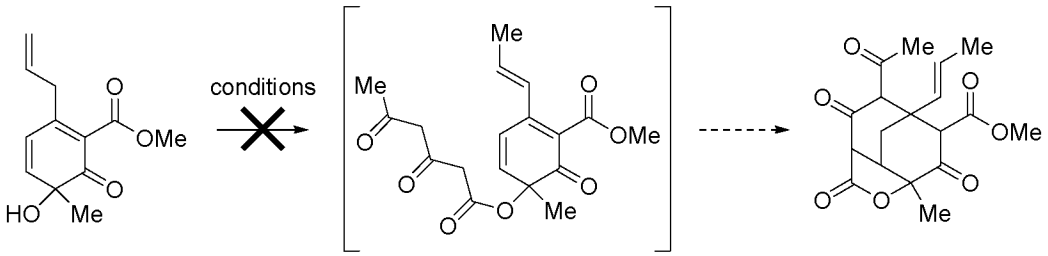


438 **444** **445**

Scheme 162: (a) NaH, NCS, THF, rt, 14 h, 32%; (b) $CsCO_3$, MeCN, 85 °C, 2 h; (c) LDA, Et_2O, –78 °C, 2 h; (d) NaH, THF, rt, 8 h.

Toward an Intramolecular Tandem 1,6–1,4-Addition

Having shown the feasibility of an intramolecular 1,6-addition, we were poised to attempt the envisioned tandem 1,6–1,4-addition reaction of β,δ-diketoester **446**, which we intended to access from alcohol **435** (Table 4).



435 **446** **447**

entry	conditions	results
1	**448**, PhMe, Δ, 2 d	no reaction
2	**448**, PhMe, 80 °C,[194] 2 d	no reaction
3	**448**, PhMe, 4 Å MS, rt, 2 d	no reaction
4	**448**, PhMe, Δ, 2 d	decomposition
5	KH, THF, 0 °C, then **448**, 30 min	no reaction
6	KH, 4 Å MS, THF, 0 °C, then **448**, 30 min	no reaction
7	**449**, cyanuric chloride, $PhNMe_2$, MeCN, 0 °C to rt, 4 d	**435** and **452**
8	**449**, 2,4,6-trichlorobenzoyl chloride, NEt_3, CH_2Cl_2, T, 1 d	**435** and **452**
9	**449**, HCCOEt, $[RuCl_2(p\text{-cymene})]_2$, PhMe, 0 °C to rt, 1 d	decomposition
10	**450**, py (1 equiv), PhMe, Δ, 4 h	no reaction
11	**450**, py (3 equiv), PhMe, Δ, 4 h	no reaction
12	**450**, K_2CO_3, $Zn(NO_3)_2$, DMF, rt, 2.5 d	no reaction
13	**450**, NEt_3 (3 equiv), PhMe, Δ, 4 h	decomposition
14	**450**, NEt_3 (1 equiv), PhMe, Δ, 4 h	decomposition
15	**450**, NEt_3 (3 equiv), PhMe, rt, 2 d, then 50 °C, 1 d, then 70 °C, 3 d	**452**
16	**450**, NEt_3 (1 equiv), PhMe, rt, 2 d, then 50 °C, 1 d, then 70 °C, 3 d	**452**
17	**451**, py, CH_2Cl_2, rt, 2 d	no reaction
18	**451**, NEt_3, CH_2Cl_2, rt, 4 d, then 40 °C, 2 d	**452**
19	**451**, KH, THF, rt, 90 min	decomposition
20	**451**, CSA, THF, 50 °C, 2 d, then 70 °C, 1 d	no reaction
21	**451**, TsOH, THF, 50 °C, 2 d, then 70 °C, 1 d	no reaction

Table 4.

[194] This reaction was conducted in a distillation apparatus to remove methanol.

The attempted transesterification of **448**[195] (Figure 21) at high temperature or under basic conditions either furnished unreacted starting material or led to decomposition (entries 1–6). When **435** was treated with acid **449** and cyanuric chloride (entry 7) or the *Yamaguchi* reagent (entry 8), we observed partial isomerization of the terminal double bond to give **452**. Ruthenium-catalyzed formation of a 1-ethoxyvinyl ester and subsequent esterification according to *Kita*'s method[196] was equally unsuccessful (entry 9), leading to decomposition of alcohol **435**.

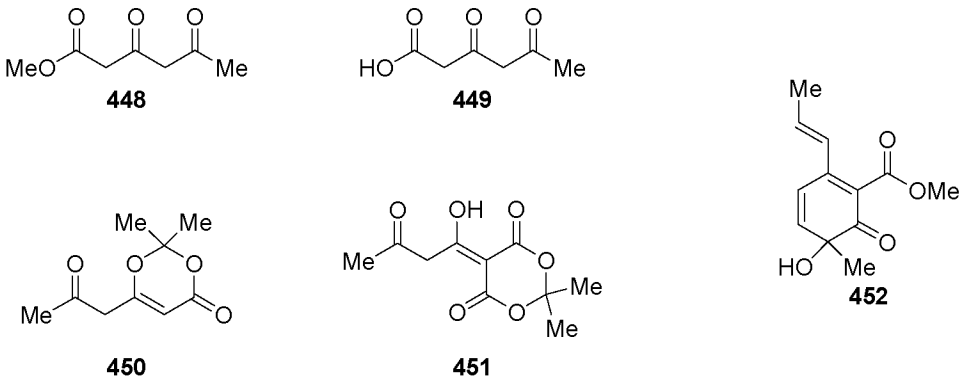


Figure 21.

We then turned our attention to dioxinone **450**[197] (Figure 21), analogs of which have been successfully used for the thermal esterification of tertiary alcohols.[198] In most cases, starting material **435** (Table 4, entries 10–12) or its double bond isomer **452**[199] were isolated (entries 15 and 16), while decomposition was observed under slightly more harsh conditions (entries 13 and 14).

Finally, we attempted the esterification of **435** with *Meldrum*'s acid derivative[200] **451**. Depending on the base used, either starting material (entry 17) or its double bond isomer **452**

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195 Diketoester **448** was prepared by heating dehydroacetic acid to 85 °C in the presence of MeOH and Mg turnings; see: J. G. Batelaan, *Synth. Commun.* **1976**, *6*, 81–83.

196 Y. Kita, H. Maeda, K. Omori, T. Okuno, Y. Tamura, *Synlett* **1993**, 273–274.

197 Compound **450** was prepared according to *Sato* and *Kaneko*'s procedure, which involved treatment of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one with LDA and acetyl chloride; see: M. Sato, J. Sakaki, Y. Sugita, S. Yasuda, H. Sakoda, C. Kaneko, *Tetrahedron* **1991**, *47*, 5689–5708.

198 For selected examples, see: (a) R. J. Clemens, J. A. Hyatt, *J. Org. Chem.* **1985**, *50*, 2431–2435; (b) U. Jahn, P. Hartmann, I. Dix, P. G. Jones, *Eur. J. Org. Chem.* **2002**, 718–735; (c) P. S. Skerry, N. A. Swain, D. C. Harrowven, D. Smyth, G. Bruton, R. C. D. Brown, *Chem. Commun.* **2004**, 1772–1773.

199 The double bond configuration was assigned based on the 1H NMR spectrum, which showed a vicinal coupling constant of J = 17.4 Hz.

200 Y. Oikawa, K. Sugano, O. Yonemitsu, *J. Org. Chem.* **1978**, *43*, 2087–2088.

(entry 18) were obtained, while the use of potassium hydride (entry 19) led to decomposition. Even under acidic conditions using camphorsulfonic acid (entry 20) or *para*-toluenesulfonic acid (entry 21), alcohol **435** proved resistant to esterification with **451**. At this point, we decided to discontinue our studies toward fusidilactone C because of the unexpected difficulties in preparing the requisite β,δ-diketoester **446**.

5.2.4 Conclusion

In summary, our synthetic studies toward fusidilactone C have progressed through a number of model systems. While, retrospectively, the first model system incorporating an acetate as nucleophile for 1,6-addition was an oversimplification compared to the natural product, more and more sophisticated model substrates were designed after careful examination and analysis of the gathered data.

Finally, model substrate **435** was prepared in a five-step synthesis from 2,5-dihydroxy benzoic acid (**426**). To our delight, **435** underwent the desired esterification and in situ 1,6-addition under very mild conditions in 43% overall yield. Our lack of success in accessing the corresponding β,δ-diketoester **447**, required for tandem 1,6–1,4-addition, precluded the further elaboration of this approach.

6 Experimental Section

6.1 General Methods

All non-aqueous reactions were carried out using oven-dried (110 °C) glassware under a positive pressure of dry argon unless otherwise noted.

Tetrahydrofuran, diethyl ether, toluene, acetonitrile and methylene chloride were dried over activated alumina under an argon atmosphere (H_2O content < 30 ppm as determined by *Karl–Fischer* titration).[201] Diethyl ether was distilled from a mixture of $FeSO_4 \cdot 7\ H_2O$ and Na_2SO_4 prior to drying. Benzene was distilled from sodium/benzophenone ketyl under an atmosphere of dry nitrogen. Triethylamine, diisopropylamine, and pyridine were distilled from potassium hydroxide under an atmosphere of dry nitrogen. Ethyldiisopropylamine (*Hünig*'s base) was distilled from sodium hydride under an atmosphere of dry nitrogen. Methanol was distilled from magnesium turnings under an atmosphere of dry nitrogen. Trimethylchlorosilane was distilled from calcium hydride. Chloroform was distilled from calcium chloride. Crotonaldehyde, isobutyraldehyde, trimethylsilyl acetylene, and diketene were distilled prior to use. Ethylmagnesium bromide, methyllithium, *n*-butyllithium, *sec*-butyllithium, and *tert*-butyllithium were titrated with ^{s}BuOH/phenanthroline.[202] All other commercially available reagents were used without further purification. Phenyl bistriflimide,[203] tetra-*n*-propylammonium perruthenate,[204] *Davis*' oxaziridine,[205] *Martin*

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[201] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518–1520.

[202] S. C. Watson, J. F. Eastham, *J. Organomet. Chem.* **1967**, *9*, 165–168.

[203] J. B. Hendrickson, R. Bergeron, *Tetrahedron Lett.* **1973**, *14*, 4607–4610.

[204] W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc., Chem. Comm.* **1987**, 1625–1627.

[205] L. C. Vishwakarma, O. D. Stringer, F. A. Davis, *Org. Synth.* **1988**, *66*, 203–210.

sulfurane,[206] tetramethylammonium triacetoxyborohydride,[115] and samarium(II) iodide[207] were prepared according to literature procedures.

Except if indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography using Merck Silica Gel F_{254} plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained using ceric ammonium molybdate or potassium permanganate stain.

Chromatographic purification of products (flash column chromatography) was performed on E. Merck Silica Gel 60 (230–400 mesh) using a forced flow of eluant at 0.3–0.5 bar.[208] Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure. Purified compounds were further dried for 12–48 h under high vacuum (0.01–0.05 Torr). Yields refer to chromatographically purified and spectroscopically pure compounds, unless stated otherwise.

Melting points: melting points were measured on a Büchi B-540 melting point apparatus. All melting points were measured in open capillaries and are uncorrected.

Optical rotations: optical rotations were measured on a Jasco DIP-1000 polarimeter operating at the sodium D line with a 100 mm path length cell, and are reported as follows: $[\alpha]^{T}_{D}$, concentration (g/100 ml), and solvent.

NMR spectra: NMR spectra were recorded on a Varian Mercury 300 spectrometer operating at 300 MHz and 75 MHz for ^{1}H and ^{13}C acquisitions, respectively. Chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard relative to chloroform (δ 7.26 for ^{1}H and 77.0 for ^{13}C). All ^{13}C spectra were measured with complete proton decoupling. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentaplet, m = multiplet; coupling constants in Hz.

IR spectra: IR spectra were recorded on a Varian 800 FT-IR or a Perkin Elmer Spectrum RX-I FT-IR spectrometer. Absorptions are given in wavenumbers (cm^{-1}).

Mass spectra: mass spectra were recorded by the MS service at ETH Zürich. EI-MS (*m/z*): EI-HIRES Micromass Autospel-ULTIMA spectrometer at 70 eV. ESI-MS (*m/z*): IONSPEC

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[206] J. C. Martin, R. J. Arhart, J. A. Franz, E. F. Perozzi, L. J. Kaplan, *Org. Synth.* **1988**, *50-9*, 163–166.

[207] P. Girard, J. L. Namy, H. B. Kagan, *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.

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

Ultima ESI-FT-ICR spectrometer at 4.7 T. MALDI-MS (*m/z*): Ion Spec Ultima HR FT-ICR MS MALDI-FT-ICR MS using the 2,5-dihydroxy-benzoic acid two layers method at 4.7 T.

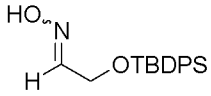
Elemental analyses: elemental analyses were performed by the Mikrolabor der ETH Zürich.

Gas chromatography: gas chromatographic measurements were performed on a Hewlett Packard 6890 Series gas chromatograph using a Supelco fused silica column *β*-Dex 120 (length: 30 m, diameter: 0.25 cm, film thickness: 0.25 µl), hydrogen as the carrier gas, and an FID detector.

Chemical names: chemical names were generated with AutoNom 4.01 (Beilstein Informationssysteme GmbH).

6.2 Experimental Procedures: Bafilomycin A_1

6.2.1 Synthesis of the C20–C25 Fragment *via* Nitrile Oxide Cycloaddition



(*tert*-Butyl-diphenyl-silanyloxy)-acetaldehyde oxime (202): To a solution of imidazole (1.78 g, 26.2 mmol, 1.80 equiv) in DMF (4.0 ml) was added TBDPSCl (3.80 ml, 14.6 mmol, 1.00 equiv) and allyl alcohol (3.00 ml, 44.0 mmol, 3.00 equiv). The mixture was stirred for 15 h at room temperature. The layers were separated and the top layer was diluted with Et_2O (100 ml), washed with H_2O (2 x 50 ml), dried over Na_2SO_4, filtered, and carefully concentrated under reduced pressure to afford silyl ether **200** (4.30 g, 14.5 mmol).

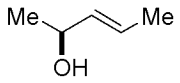
A solution of unpurified silyl ether **200** (2.84 g, 9.57 mmol, 1.00 equiv) in 1:1:1 THF/ ^{t}BuOH/H_2O (90 ml) was cooled to 0 °C. NMO (1.23 g, 10.5 mmol, 1.10 equiv) and $K_2OsO_4 \cdot 2\,H_2O$ (32 mg, 0.10 mmol, 1.0 mol % equiv) was added. The mixture was stirred for 20 h and allowed to warm to ambient temperature. Na_2SO_3 (19 g) and saturated aqueous $NaHCO_3$ (200 ml) were added and the mixture was stirred for 30 min. The mixture was extracted with EtOAc (3 x 300 ml) and the combined organic phases were dried over Na_2SO_4, filtered, and carefully concentrated under reduced pressure to give the diol intermediate, which was used without further purification.

To a solution of the diol in THF (10 ml) and H_2O (10 ml) was added $NaIO_4$ (4.50 g, 21.1 mmol, 2.20 equiv). The mixture was stirred for 3 h at room temperature. H_2O (100 ml) and CH_2Cl_2 (100 ml) was added and the layers were separated. The organic phase was washed with H_2O (2 x 100 ml), dried over Na_2SO_4, filtered, and carefully concentrated under reduced pressure to provide aldehyde intermediate **201**, which was used immediately in the next step.

To a solution of aldehyde **201** in EtOH (30 ml) was added $NH_2OH{\cdot}HCl$ (1.96 g, 28.7 mmol, 3.00 equiv) and NEt_3 (4.00 ml, 30.0 mmol, 3.13 equiv). The solution was stirred for 5 h at ambient temperature before it was diluted with H_2O (100 ml). The mixture was extracted with EtOAc (3 x 100 ml) and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (5–10% EtOAc in hexane) provided known oxime **202** (1.18 g, 67% yield over three steps) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, * denotes signal corresponding to the minor oxime diastereomer): δ 7.68–7.64 (m, 4 H), 7.49 (t, 1 H, J = 5.6 Hz), 7.45–7.26 (m, 6 H), 6.97* (t, 1 H, J = 3.4 Hz), 4.55* (d, 2 H, J = 3.4 Hz), 4.27 (d, 2 H, J = 5.6 Hz), 1.07 (s, 9 H), 1.06* (s, 9 H).

These spectral characteristics are identical to those previously reported.[62]



(*E*)-(*S*)-Pent-3-en-2-ol (148): A solution of (*E*)-But-2-enal (41.0 ml, 502 mmol, 1.00 equiv) in Et_2O (250 ml) was cooled to 0 °C. MeMgBr (180 ml, 540 mmol, 1.08 equiv) was slowly added. The solution was stirred for 40 min at 0 °C, the ice-bath was removed, and the reaction mixture was stirred for another 60 min at ambient temperature. Saturated aqueous NH_4Cl (100 ml) was carefully added and the layers were separated. The aqueous phase was diluted with H_2O (100 ml) and extracted with Et_2O (3 x 200 ml). The combined organic phases were dried over $MgSO_4$, filtered, and carefully concentrated under reduced pressure. Distillation (50 °C, 25–30 mbar) afforded the racemic allylic alcohol (26.1 g, 60% yield) as a colorless liquid.

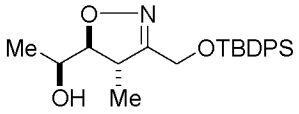
A solution of the racemic allylic alcohol (26.1 g, 303 mmol, 1.00 equiv) in CH_2Cl_2 (1.3 l) was cooled to –20 °C. 4 Å molecular sieves (18.1 g), (–)-DIPT (9.70 ml, 46.0 mmol, 0.150 equiv), and $Ti(O^iPr)_4$ (7.50 ml, 30.8 mmol, 0.100 equiv) was added. After stirring for 30 min at –20 °C, TBHP (36.0 ml, 198 mmol, 0.650 equiv) was added. The resulting mixture

was stirred for 42 h at –20 °C. A solution of $Fe_2SO_4 \cdot 7\ H_2O$ (282 g) and tartaric acid (86 g) in H_2O (850 ml) was added and the resulting mixture was let warm to ambient temperature. The layers were separated, the organic phase was added to aqueous NaOH (30 wt%, 725 ml), and the mixture was stirred for 30 min at room temperature. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 500 ml). The combined organic phases were washed with H_2O (1 l) and brine (1 l), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (CH_2Cl_2) afforded allylic alcohol **148** (7.83 g, 30% yield) as a colorless liquid. The enantomeric excess obtained was estimated to be 95% by comparison to the previously reported optical rotation.[94]

Optical Rotation: $[\alpha]^{23}_D$ (*c* 0.97, $CHCl_3$) = −17.6.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.66−5.55 (m, 2 H), 4.31−4.20 (m, 1 H), 1.69 (d, 3 H, *J* = 5.7 Hz), 1.25 (d, 3 H, *J* = 6.3 Hz).

These spectral characteristics are identical to those previously reported.[94]



(*S*)-1-((4*S*,5*S*)-3-((*tert*-Butyl-diphenyl-silanyloxymethyl)-4-methyl-4,5-dihydro-isoxazol-5-yl)-ethanol (209): A solution of oxime **202** (1.40 g, 4.46 mmol, 1.00 equiv) in CH_2Cl_2 (50 ml) was cooled to –78 °C. ^{t}BuOCl (506 mg, 4.68 mmol, 1.05 equiv) was added dropwise over 20 min. The resulting deep blue solution was stirred for 2 h at –78 °C and then used directly in the next step.

A solution of allylic alcohol **148** (498 mg, 5.79 mmol. 1.30 equiv) in CH_2Cl_2 (100 ml) was cooled to 0 °C. ^{i}PrOH (1.11 ml, 14.7 mmol, 3.30 equiv) was added, followed by dropwise addition of EtMgBr (4.5 ml, 3.0 M in Et_2O, 13 mmol, 3.0 equiv). After stirring for 30 min at 0 °C, the deep blue solution from above was added via cannula over 6 h. The reaction was then stirred for 5 h at 0 °C, allowed to warm to room temperature and stirred for another 24 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (300 ml) and EtOAc (300 ml). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 300 ml). The combined organic phases were washed with H_2O (300 ml) and brine (300 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% EtOAc in hexane) provided isoxazoline **209** (1.18 g, 67%

yield) as a colorless gum. The diastereomeric ratio of 88:12 was estimated by integration of the ^{1}H NMR signals around δ 3.22 and 3.44 ppm, respectively.

R_f = 0.32 (hexane/EtOAc 2:1)

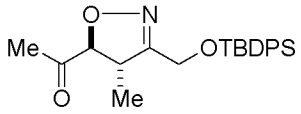
Optical Rotation: $[\alpha]^{31}_D$ (*c* 0.68, $CHCl_3$) = +65.4.

^{1}H NMR (300 MHz, $CDCl_3$,* denotes signal corresponding to the minor diastereomer): δ 7.68–7.63 (m, 4 H), 7.46–7.37 (m, 6 H), 4.48 (d, 1 H, *J* = 12.9 Hz), 4.38 (dd, 1 H, *J* = 13.2, 0.6 Hz), 4.26* (q, 1 H, *J* = 5.1 Hz), 3.94 (t, 1 H, *J* = 6.3 Hz), 3.71–3.63 (m, 1 H), 3.51−3.40* (m, 1 H), 3.25–3.16 (m, 1 H), 2.28 (d, 1H, *J* = 4.5 Hz), 2.05* (d, 1 H, *J* = 6.6 Hz), 1.24–1.21 (m, 6 H), 1.07 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1, 135.7, 132.9, 132.7, 130.2, 128.1, 91.8, 68.5, 58.1, 44.6, 26.9, 19.4, 18.6, 16.6.

IR (thin film): ν 3422, 3072, 2932, 1472, 1462, 1428, 1391, 1258, 1113 cm^{-1}.

HRMS (MALDI): calcd for $C_{23}H_{31}NO_3SiNa$ $[M+Na]^+$ 420.1965; found 420.1961.



1-[(4*S*,5*S*)-3-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-methyl-4,5-dihydro-isoxazol-5-yl]-ethanone (214): A solution of alcohol **209** (902 mg, 2.27 mmol, 1.00 equiv), 4 Å molecular sieves (345 mg), and NMO (345 mg, 2.95 mmol, 1.30 equiv) in CH_2Cl_2 (5.0 ml) was cooled to 0 °C and stirred for 30 min. To the reaction was added TPAP (80.0 mg, 0.230 mmol, 10 mol %) in one portion. The reaction was stirred for 45 min and allowed to warm to room temperature. Upon completion of the reaction, silica gel was added (1 g) and the mixture concentrated under reduced pressure. The resulting solid was then applied to a plug of silica gel (5 g) and the product was eluted with CH_2Cl_2 (ca. 50 ml). Evaporation of the filtrate provided analytically pure ketone **214** (854 mg, 96% yield).

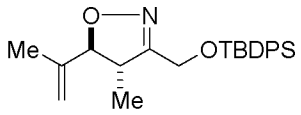
Optical Rotation: $[\alpha]^{28}_D$ (*c* 0.47, $CHCl_3$) = +29.1.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67–7.61 (m, 4 H), 7.46–7.36 (m, 6 H), 4.48 (d, 1 H, *J* = 11.4 Hz), 4.41–4.36 (m, 2 H), 3.61–3.52 (m, 1 H), 2.27 (s, 3 H), 1.27 (d, 3 H, *J* = 7.2 Hz), 1.06 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 208.2, 161.7, 135.7, 132.7, 132.6, 130.2, 128.1, 91.1, 57.8, 46.4, 26.9, 19.4, 17.0.

IR (thin film): ν 3071, 2933, 2859, 1718, 1472, 1428, 1360, 1188, 1113 cm^{-1}.

HRMS (MALDI): calcd for $C_{23}H_{29}NO_3SiNa$ $[M+Na]^+$ 418.1809; found 418.1807.



(4*S*,5*S*)-3-(*tert*-Butyl-diphenyl-silanyloxymethyl)-5-isopropenyl-4-methyl-4,5-dihydro-isoxazole (453): A solution of methyltriphenylphosphonium bromide (2.98 g, 8.36 mmol, 2.32 equiv) in THF (100 ml) was cooled to –78 °C and ^{n}BuLi (3.7 ml, 1.6 M, 5.8 mmol, 1.6 equiv) was added dropwise over 5 min. The reaction was stirred for 5 min at –78 °C and then allowed to warm to 0 °C over 30 min. The deep yellow solution was cooled to –78 °C again and a solution of ketone **214** (1.42 g, 3.60 mmol, 1.00 equiv) in THF (5.0 ml) was added dropwise over 5 min. The reaction was stirred for 5 min at –78 °C and then warmed to 0 °C over 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (50 ml) and the layers were separated. The aqueous phase was extracted with EtOAc (3 x 100 ml) and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (ca. 0.5 ml) and filtered through a plug of silica gel with CH_2Cl_2 washing (ca. 75 ml). Evaporation of the filtrate provided analytically pure olefin **453** (1.40 g, 99% yield) as a colorless gum.

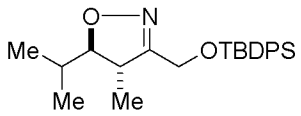
Optical Rotation: $[\alpha]^{29}_D$ (*c* 0.81, $CHCl_3$) = +62.4.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69–7.63 (m, 4 H), 7.45–7.36 (m, 6 H), 5.20–5.03 (m, 1 H), 4.91–4.90 (m, 1 H), 4.51–4.46 (m, 2 H), 4.37 (dd, 1 H, *J* = 12.6, 0.9 Hz), 3.30–3.20 (m, 1 H), 1.75 (m, 3 H), 1.24 (d, 3 H, *J* = 6.9 Hz), 1.06 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0, 142.7, 135.8, 133.0, 132.8, 130.2, 128.1, 113.5, 91.9, 58.2, 46.8, 26.9, 19.4, 17.1, 16.6.

IR (thin film): ν 3072, 2961, 2932, 2859, 1654, 1622, 1590, 1472, 1457, 1428, 1196, 1113, 1087 cm^{-1}.

HRMS (MALDI): calcd for $C_{24}H_{31}NO_2SiNa$ $[M+Na]^+$ 416.2016; found 416.2014.



(4*S*,5*R*)-3-(*tert*-Butyl-diphenyl-silanyloxymethyl)-5-isopropyl-4-methyl-4,5-dihydro-isoxazole (215): Olefin **453** (495 mg, 1.26 mmol, 1.00 equiv) and Pd/C (100 mg) was slurried with EtOH (5.0 ml) in a *Schlenk* flask. The flask was then evaporated to ca. 100 mbar and refilled with H_2 from a balloon. This procedure was repeated twice. The mixture was stirred for 1 h at room temperature, filtered through celite, and the filter cake was washed with EtOAc (50 ml). The filtrate was concentrated under reduced pressure and the residue taken up in CH_2Cl_2 (ca. 0.3 ml). This solution was filtered through a plug of silica gel and the plug was washed with CH_2Cl_2 (ca. 40 ml). Evaporation of the filtrate provided analytically pure isopropylisoxazoline **215** (495 mg, quantitative yield) as a colorless gum.

$\mathbf{R}_f$ = 0.74 (hexane/EtOAc 2:1)

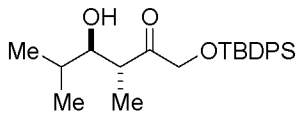
Optical Rotation: $[\alpha]^{28}_{D}$ (*c* 0.81, $CHCl_3$) = +54.2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69–7.64 (m, 4 H), 7.45–7.36 (m, 6 H), 4.46 (d, 1 H, *J* = 12.9 Hz), 4.36 (dd, 1 H, *J* = 12.9, 0.9 Hz), 3.90 (t, 1 H, *J* = 6.6 Hz), 3.20–3.10 (m, 1 H), 1.88–1.77 (m, 1 H), 1.19 (d, 3 H, *J* = 7.2 Hz), 1.06 (s, 9 H), 0.97 (d, 3 H, *J* = 6.6 Hz), 0.93 (d, 3 H, *J* = 6.6 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 135.8, 133.1, 132.2, 130.2, 128.1, 93.3, 58.2, 44.7, 32.3, 27.0, 19.4, 18.0, 17.9, 17.6.

IR (thin film): ν 3072, 3030, 2961, 2932, 2859, 1621, 1590, 1472, 1428, 1390, 1365, 1113, 1087 cm^{-1}.

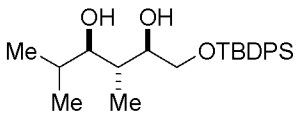
HRMS (MALDI): calcd for $C_{24}H_{33}NO_2SiNa$ $[M+Na]^+$ 418.2173; found 418.2168.



(3*R*,4*R*)-1-(*tert*-Butyl-diphenyl-silanyloxy)-4-hydroxy-3,5-dimethyl-hexan-2-one (216): To a solution of isoxazoline **215** (45.8 mg, 0.140 mmol, 1.00 equiv) in MeOH (5.0 ml) and H_2O (1.0 ml) in a 20 ml *Schlenk* flask was added $B(OH)_3$ (138 mg, 2.23 mmol, 15.9 equiv)

and Raney-Nickel until the reaction mixture stayed black upon stirring. The flask was partially evaporated and refilled with H_2 from a balloon. The reaction mixture was stirred under H_2-atmosphere for 20 min at room temperature, before being filtered over celite. The filter cake was rinsed with EtOAc (50 ml) and the combined organic phases were concentrated under reduced pressure. The residue was taken up in 1:1 EtOAc/hexane (160 ml), filtered over a plug of silica gel, and concentrated under reduced pressure to give *β*-hydroxy ketone **216** (20.5 mg, 37% yield).

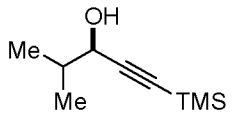
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.64 (m, 4 H), 7.47–7.36 (m, 6 H), 3.39 (dt, 1 H, *J* = 6.9, 4.8 Hz), 2.97 (p, 1 H, *J* = 7.2 Hz), 2.28 (d, 1 H, *J* = 7.5 Hz), 1.70–1.60 (m, 1 H), 1.11 (s, 9 H), 1.02 (d, 3 H, *J* = 7.2 Hz), 0.89 (d, 3 H, *J* = 5.7 Hz), 0.87 (d, 3 H, *J* = 5.4 Hz).



(2*R*,3*R*,4*R*)-1-(*tert*-Butyl-diphenyl-silanyloxy)-3,5-dimethyl-hexane-2,4-diol (217): A mixture of THF (0.34 ml) and MeOH (0.07 ml) was cooled to 0 °C, before BEt_3 (56.0 µl, 55.4 µmol, 1.05 equiv) was added. The solution was stirred for 70 min at ambient temperature and then cooled to −78 °C. A solution of *β*-hydroxy ketone **216** (21.0 mg, 52.7 µmol, 1.00 equiv) in THF (0.25 ml) was added. The reaction mixture was stirred for 25 min at −78 °C, $NaBH_4$ (13.3 mg, 0.350 mmol, 6.64 equiv) was added, and everything was stirred for another 4 h at −78 °C. After dilution with EtOAc (10 ml) and saturated aqueous NH_4Cl (10 ml), the two layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 ml). The combined organic phases were washed with brine (30 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was taken up in MeOH (3 ml) and again concentrated under reduced pressure. This procedure was repeated three times. Purification by flash column chromatography (10% EtOAc in hexane) afforded diol **217** (11.1 mg, 53% yield) with a diastereomeric ratio of 81:19.

^{1}H NMR (300 MHz, $CDCl_3$, * denotes signal corresponding to the minor diastereomer): δ 7.68–7.64 (m, 4 H), 7.48–7.36 (m, 6 H), 3.96–3.91 (m, 1 H), 3.72–3.65 (m, 2 H), 3.49* (br d, 1 H, *J* = 9.3 Hz), 3.34 (br d, 1 H, *J* = 9.0 Hz), 2.88 (br s, 2 H), 1.86–1.77 (m, 1 H), 1.76–1.62 (m, 1 H), 1.06 (s, 9 H), 1.00 (d, 3 H, *J* = 6.6 Hz), 0.88* (d, 3 H, *J* = 7.2 Hz), 0.83 (d, 3 H, *J* = 5.7 Hz), 0.80 (d, 3 H, *J* = 5.4 Hz), 0.78* (d, 3 H, *J* = 5.4 Hz).

6.2.2 Synthesis of the C20–C25 Epoxide *via* Zinc Alkynylide Addition



(*R*)-4-Methyl-1-trimethylsilanyl-pent-1-yn-3-ol (224): Zinc triflate (3.64 g, 10.0 mmol, 0.200 equiv) was placed in a *Schlenk* tube, heated to 125 °C under high vacuum for 13 h, and then cooled to ambient temperature. (+)-*N*-methyl ephedrine (1.97 g, 11.0 mmol, 0.220 equiv) was added and the solids were stirred under high vacuum for 30 min before the *Schlenk* tube was filled with Argon. After addition of toluene (50 ml) and NEt_3 (3.50 ml, 25.1 mmol, 0.500 equiv), the cloudy mixture was stirred for 2 h at room temperature. Trimethylsilyl-acetylene (8.50 ml, 60.2 mmol, 1.19 equiv) was added, the mixture was stirred for 15 min at room temperature, and then freshly distilled isobutyraldehyde (4.60 ml, 50.7 mmol, 1.00 equiv) was added. The cloudy mixture was heated to 60 °C for 12 h and let cool to ambient temperature. Et_2O (50 ml) and saturated aqueous NH_4Cl (100 ml) was added, the layers were separated, and the aqueous phase was extracted with Et_2O (2 x 100 ml). The combined organic phases were washed with brine (200 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (20–50% Et_2O in pentane) afforded propargylic alcohol **224** as a slightly yellowish oil (6.62 g, 77% yield). The enantiomeric excess of 92% was determined by gas chromatographic analysis.

$\mathbf{R}_f$ = 0.61 (hexane/EtOAc 3:1)

Optical Rotation: $[\alpha]^{25}_D$ (*c* 1.05, $CHCl_3$) = +0.81

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.14 (t, 1 H, *J* = 5.9 Hz), 1.94 (d, 1 H, *J* = 5.7 Hz), 1.91−1.80 (m, 1 H), 0.99 (d, 3 H, *J* = 5.1 Hz), 0.97 (d, 3 H, *J* = 5.1 Hz), 0.16 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 105.6, 90.1, 68.2, 34.4, 18.0, 17.4, −0.1.

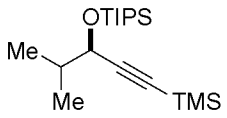
IR (thin film): ν 3408, 2961, 2900, 2875, 2174, 1470, 1409, 1385, 1368, 1321, 1252, 1178, 1130, 1104, 1031 cm^{-1}.

HRMS (EI): calcd for $C_6H_{11}OSi$ $[M–C_3H_7]^+$ 127.0571; found 127.0571.

Anal. calcd for $C_9H_{18}OSi$: C 63.47%, H 10.65%, O 9.39%; found: C 63.21%, H 10.65%.

GC: 60–100 °C, ramp 0.5 °C per min; t_1 = 32.7 min (minor), t_2 = 33.3 min (major).

These spectral characteristics are identical to those previously reported.[209]



(*R*)-4-Methyl-3-triisopropylsilanyloxy-1-trimethylsilanyl-pent-1-yne (225): To a solution of alcohol **224** (1.85 g, 10.9 mmol, 1.00 equiv) in DMF (7.25 ml) was added imidazole (1.85 g, 27.2 mmol, 2.49 equiv) and triisopropylsilyl triflate (3.50 ml, 13.0 mmol, 1.19 equiv). The solution was stirred for 3 h at ambient temperature. Saturated aqueous NH_4Cl (20 ml) was added and the mixture was extracted with Et_2O (3 x 20 ml). The combined organic phases were washed with brine (50 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (pentane) afforded silyl ether **225** (2.90 g, 82% yield).

$\mathbf{R}_f$ = 0.88 (hexane/EtOAc 5:1)

Optical Rotation: $[\alpha]^{25}_{D}$ (*c* 0.98, $CHCl_3$) = +31.7

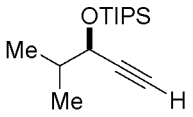
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.27 (d, 1 H, *J* = 5.1 Hz), 1.92−1.77 (m, 1 H), 1.12−1.06 (m, 21 H), 0.99 (d, 3 H, *J* = 6.6 Hz), 0.96 (d, 3 H, *J* = 6.6 Hz), 0.15 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 106.6, 89.0, 68.7, 35.5, 18.2, 17.5, 12.4, 0.0.

IR (thin film): ν 2955, 2868, 2174, 1741, 1464, 1380, 1251, 1096, 1027 cm^{-1}.

HRMS (EI): calcd for $C_{15}H_{31}OSi_2$ $[M-C_3H_7]^+$ 283.1908; found 283.1908.

Anal. calcd for $C_{18}H_{38}OSi_2$: C 66.18%, H 11.72%, O 4.90%; found: C 66.17%, H 11.56%.



Triisopropyl-((*R*)-1-isopropyl-prop-2-ynyloxy)-silane (226): To a solution of trimethylsilyl alkyne **225** (12.9 g, 39.5 mmol, 1.00 equiv) in MeOH (120 ml) was added K_2CO_3 (2.74 g, 19.8 mmol, 0.500 equiv). The originally cloudy solution became clear after about 3 h

[209] S. Niwa, K. Soai, *J. Chem. Soc. Perkin. Trans. 1* **1990**, 937–943.

and was stirred for a total of 20.5 h at ambient temperature. Saturated aqueous NH_4Cl (150 ml) was added and the mixture was extracted with Et_2O (3 x 200 ml). The combined organic phases were washed with brine (500 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (pentane) afforded terminal alkyne **226** as a colorless solution in Et_2O, which was directly taken on to the next step.

$\mathbf{R}_f$ = 0.83 (hexane/EtOAc 5:1)

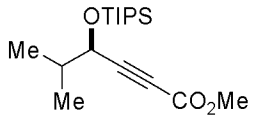
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.32 (dd, 1 H, *J* = 5.1, 2.1 Hz), 2.35 (d, 1 H, *J* = 2.1 Hz), 1.94–1.82 (m, 1 H), 1.12–1.06 (m, 21 H), 1.02 (d, 3 H, *J* = 6.9 Hz), 0.97 (d, 3 H, *J* = 6.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 84.1, 72.7, 68.2, 35.3, 18.1, 16.9, 12.3.

IR (thin film): ν 3312, 2950, 2870, 1466, 1385, 1250, 1098 cm^{-1}.

HRMS (EI): calcd for $C_{15}H_{30}OSi$ $[M]^+$ 254.2060; found 254.2060.

Anal. calcd for $C_{15}H_{30}OSi$: C 70.80%, H 11.88%, O 6.29%; found: C 70.54%, H 11.77%.



(*R*)-5-Methyl-4-triisopropylsilanyloxy-hex-2-ynoic acid methyl ester (227): A solution of the above obtained terminal alkyne **226** in THF (120 ml) was cooled to –78 °C. ^{n}BuLi (27.5 ml, 1.6 M in hexane, 44 mmol, 1.1 equiv) was added and the solution was stirred for 15 min. Methyl chloroformate (3.50 ml, 45.3 mmol, 1.15 equiv) was added and the solution was stirred for 2 h at –78 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl (100 ml) and Et_2O (250 ml), the mixture was allowed to come to ambient temperature, and the layers were separated. The aqueous phase was extracted with Et_2O (2 x 250 ml) and the combined organic phases were washed with brine (500 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (5% Et_2O in pentane) yielded ester **227** (11.2 g, 91% yield over two steps) as a colorless oil.

$\mathbf{R}_f$ = 0.34 (hexane/EtOAc 5:1)

Optical Rotation: $[\alpha]^{20}_D$ (*c* 1.10, $CHCl_3$) = +30.4

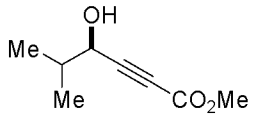
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.43 (d, 1 H, *J* = 4.8 Hz), 3.77 (s, 3 H), 2.02–1.88 (m, 1 H), 1.12–1.06 (m, 21 H), 1.03 (d, 3 H, *J* = 6.6 Hz), 0.99 (d, 3 H, *J* = 6.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 153.8, 88.2, 68.1, 52.7, 35.4, 18.1, 18.1, 17.3, 12.3.

IR (thin film): ν 2949, 2869, 2235, 1723, 1464, 1386, 1353, 1251, 1182, 1101, 1064, 1007 cm^{-1}.

HRMS (EI): calcd for $C_{14}H_{25}O_3Si$ $[M–C_3H_7]^+$ 269.1567; found 269.1562.

Anal. calcd for $C_{17}H_{32}O_3Si$: C 65.33%, H 10.32%, O 15.36%; found: C 65.38%, H 10.11%.



(*R*)-4-Hydroxy-5-methyl-hex-2-ynoic acid methyl ester (235): A solution of silyl ether **227** (11.1 g, 35.5 mmol, 1.00 equiv) in THF (120 ml) was cooled to 0 °C. TBAF (40 ml, 1.0 M in THF, 40 mmol, 1.1 equiv) was added and the solution was stirred for 20 min at 0 °C. Et_2O (200 ml) and saturated aqueous NH_4Cl (200 ml) was added, the layers were separated, and the aqueous phase was extracted with Et_2O (3 x 300 ml). The combined organic phases were washed with brine (500 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (4–20% Et_2O in pentane) afforded alcohol **235** (4.25 g, 77% yield).

R_f = 0.31 (hexane/EtOAc 3:1)

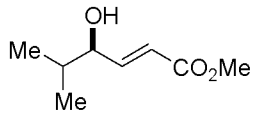
Optical Rotation: $[\alpha]^{26}_D$ (*c* 0.96, $CHCl_3$) = +18.2

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.29 (d, 1 H, *J* = 5.7 Hz), 3.79 (s, 3 H), 2.04–1.89 (m, 2 H), 1.05 (d, 3 H, *J* = 4.2 Hz), 1.02 (d, 3 H, *J* = 4.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 153.6, 87.1, 67.6, 52.8, 34.3, 18.0, 17.6.

IR (thin film): ν 3421, 2966, 2880, 2236, 1718, 1572, 1438, 1381, 1257, 1135, 1037 cm^{-1}.

Anal. calcd for $C_8H_{12}O_3$: C 61.52%, H 7.74%, O 30.73%; found: C 61.49%, H 7.74%.



(*E*)-(*R*)-4-Hydroxy-5-methyl-hex-2-enoic acid methyl ester (236): A solution of Red-Al (15.5 ml, 3.5 M in toluene, 54 mmol, 2.0 equiv) in THF (120 ml) was cooled to –78 °C. A solution of alkyne **235** (4.20 g, 26.9 mmol, 1.00 equiv) in THF (100 ml) was added dropwise *via* cannula during which time the solution turned yellow and a gas evolved. The solution was stirred for 25 min at –78 °C. The reaction was quenched by slow addition of aqueous 0.2 M HCl (400 ml) and the mixture was allowed to come to ambient temperature. The mixture was extracted with Et_2O (3 x 450 ml) and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (250 ml) and brine (250 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (4–10% Et_2O in pentane) afforded alkene **236** (3.27 g, 77% yield) as a colorless oil.

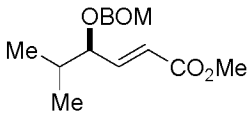
$\mathbf{R}_f$ = 0.21 (hexane/EtOAc 3:1)

Optical Rotation: $[\alpha]^{21}_D$ (*c* 1.05, $CHCl_3$) = –30.5

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (dd, 1 H, *J* = 15.9, 5.1 Hz), 6.05 (dd, 1 H, *J* = 15.9, 1.5 Hz), 4.11 (dt, 1 H, *J* = 5.1, 1.5 Hz), 3.75 (s, 3 H), 1.89–1.74 (m, 1 H), 1.74 (br s, 1 H), 0.96 (d, 3 H, *J* = 2.7 Hz), 0.93 (d, 3 H, *J* = 2.7 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 148.9, 120.7, 75.9, 51.7, 33.8, 18.3, 17.5.

IR (thin film): ν 3450, 2962, 2880, 1720, 1660, 1439, 1280, 1173, 1079, 1034 cm^{-1}.

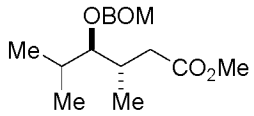


(*E*)-(*R*)-4-Benzyloxymethoxy-5-methyl-hex-2-enoic acid methyl ester (63): To a solution of alcohol **236** (554 mg, 3.50 mmol, 1.00 equiv) in CH_2Cl_2 (12 ml) was added $^iPr_2NEt$ (3.05 ml, 17.5 mmol, 5.00 equiv), BOMCl (1.50 ml, 10.8 mmol, 3.09 equiv), and DMAP (51.3 mg, 4.20 mmol, 1.20 equiv). The solution was stirred for 18 h at room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (10 ml) and the mixture was extracted with Et_2O (3 x 20 ml). The combined organic phases were washed with brine

(50 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography afforded ether **63** (849 mg, 87% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.30 (m, 5 H), 6.85 (dd, 1 H, J = 15.8, 6.7 Hz), 6.00 (dd, 1 H, J = 15.8, 1.2 Hz), 4.80–4.65 (m, 3 H), 4.55 (d, 1 H, J = 11.7 Hz), 4.05 (t, 1 H, J = 6.0 Hz), 3.75 (s, 3 H), 1.95–1.80 (m, 1 H), 0.99 (d, 3 H, J = 6.8 Hz), 0.94 (d, 3 H, J = 6.8 Hz).

These spectral characteristics are identical to those previously reported.[24a]

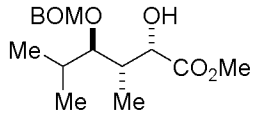


(3*S*,4*R*)-4-Benzyloxymethoxy-3,5-dimethyl-hexanoic acid methyl ester (237): A suspension of CuI (107 mg, 562 µmol, 4.97 equiv) in THF (2.70 ml) was cooled to −15 °C. After slow addition of MeLi·LiI (1.1 ml, 1.0 M in Et_2O, 1.1 mmol, 10 equiv), the resulting mixture was stirred for 30 min and allowed to warm to 0 °C and was then cooled to −78 °C. TMSCl (0.290 ml, 2.28 mmol, 20.2 equiv) was added, followed by a solution of α,β-unsaturated ester **63** (31.4 mg, 113 µmol, 1.00 equiv) in THF (0.70 ml). The resulting mixture was stirred for 4 h at −78 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl (10 ml), the mixture was let warm to room temperature and extracted with EtOAc (3 x 10 ml). The combined organic phases were washed with 1:1 saturated aqueous NH_4Cl/ NH_4OH (20 ml), saturated aqueous NH_4Cl (20 ml), and brine (20 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (2–4% EtOAc in hexane) afforded ester **237** (28.0 mg, 84% yield).

$\mathbf{R}_f$ = 0.40 (hexane/EtOAc 5:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.26 (m, 5 H), 4.79 (dd, 2 H, J = 12.3, 6.8 Hz), 4.66 (dd, 2 H, J = 17.1, 11.8 Hz), 3.66 (s, 3 H), 3.11 (t, 1 H, J = 5.4 Hz), 2.63 (dd, 1 H, J = 15.0, 3.6 Hz), 2.30–2.20 (m, 1 H), 2.16 (dd, 1 H, J = 15.0, 9.6 Hz), 1.90–1.80 (m, 1 H), 1.00 (d, 3 H, J = 6.8 Hz), 0.97 (d, 3 H, J = 3.4 Hz), 0.96 (d, 3 H, J = 3.4 Hz).

These spectral characteristics are identical to those previously reported.[24a]

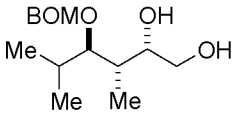


(2*S*,3*S*,4*R*)-4-Benzyloxymethoxy-2-hydroxy-3,5-dimethyl-hexanoic acid methyl ester (64): A solution of ester **237** (28.0 mg, 95.1 µmol, 1.00 equiv) in THF (1.40 ml) was cooled to −78 °C. Solid KHMDS (40.2 mg, 202 µmol, 2.12 equiv) was added, the solution was stirred for 30 min at −78 °C, and a solution of *Davis*' oxaziridine (75.3 mg, 288 µmol, 3.03 equiv) in THF (0.20 ml) was added. The resulting mixture was stirred for 9.5 h at −78 °C, before the reaction was quenched by addition of saturated aqueous NH_4Cl (5 ml). The mixture was warmed to room temperature and extracted with EtOAc (3 x 10 ml). The combined organic phases were washed with brine (20 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (5−10% EtOAc in hexane) afforded hydroxy ester **64** (18.7 mg, 63% yield).

$\mathbf{R}_f$ = 0.28 (hexane/EtOAc 3:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.26 (m, 5 H), 4.88 (d, 1 H, *J* = 6.5 Hz), 4.80 (d, 1 H, *J* = 6.5 Hz), 4.67 (s, 2 H), 4.66 (d, 1 H, *J* = 2.1 Hz), 3.79 (s, 3 H), 3.38 (dd, 3 H, *J* = 9.1, 3.0 Hz), 2.20–2.10 (m, 1 H), 1.90–1.80 (m, 1 H), 1.01 (d, 3 H, *J* = 6.9 Hz), 0.92 (d, 3 H, *J* = 6.8 Hz), 0.82 (d, 3 H, *J* = 6.9 Hz).

These spectral characteristics are identical to those previously reported.[24a]



(2*S*,3*S*,4*R*)-4-Benzyloxymethoxy-3,5-dimethyl-hexane-1,2-diol (238): A solution of ester **64** (18.7 mg, 60.0 µmol, 1.00 equiv) in THF (0.56 ml) was cooled to 0 °C. $LiBH_4$ (17.8 mg, 0.820 mmol, 13.6 equiv) and MeOH (14 µl) was added, the cooling bath was removed, and the solution was stirred for 4 h at ambient temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (10 ml) and EtOAc (10 ml). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 ml). The combined organic phases were washed with brine (30 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (20–40% EtOAc in hexane) gave diol **238** (12.0 mg, 71% yield) as a colorless oil.

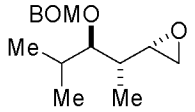
R_f = 0.21 (hexane/EtOAc 1:1)

Optical Rotation: $[\alpha]^{20}_{D}$ (*c* 0.23, $CHCl_3$) = –85.3

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.32 (m, 5 H), 4.83 (dd, 2 H, *J* = 33.3, 6.9 Hz), 4.68 (dd, 2 H, *J* = 43.2, 12.0 Hz), 4.78–4.12 (m, 1 H), 3.66 (t, 1 H, *J* = 10.5 Hz), 4.38 (dt, 2 H, *J* = 9.3, 4.2 Hz), 3.30 (dd, 1 H, *J* = 7.2 Hz, 4.2 Hz), 1.99–1.89 (m, 2 H), 1.77 (dp, 1 H, *J* = 7.2, 2.1 Hz), 1.61 (br s, 1 H), 0.05 (d, 3 H, *J* = 6.9 Hz), 0.91 (d, 3 H, *J* = 3.0 Hz), 0.88 (d, 3 H, *J* = 3.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 137.1, 128.5, 128.0, 127.8, 97.5, 88.6, 70.8, 70.8, 65.3, 36.8, 30.0, 20.3, 16.4, 10.9.

IR (thin film): ν 3424, 2962, 2881, 1455, 1380, 1149, 1078, 1022 cm^{-1}.



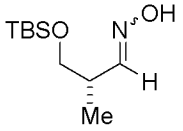
(*S*)-2-((1*R*,2*R*)-2-Benzyloxymethoxy-1,3-dimethyl-butyl)-oxirane (222): A solution of triol **238** (13.2 mg, 46.7 µmol, 1.00 equiv) in CH_2Cl_2 (0.20 ml) was cooled to 0 °C. DMAP (12.1 mg, 99.1 µmol, 1.95 equiv) and 2,4,6-trimethyl-benzenesulfonyl chloride (12.6 mg, 57.6 µmol, 1.23 equiv) was added. The obtained mixture was stirred for 3 h at 0 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl (5 ml) and Et_2O (5 ml). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 5 ml). The combined organic phases were washed with brine (10 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Sulfonate **240** was used for the next step without further purification.

A solution of unpurified sulfonate **240** in THF (0.50 ml) was cooled to −78 °C. LHMDS (54 µl, 1.0 M in THF, 54 µmol, 1.2 equiv) was added, and the solution was stirred for 1 h at −78 °C and for another 90 min at 0 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl (5 ml) and Et_2O (5 ml). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 5 ml). The combined organic phases were washed with brine (10 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10% Et_2O in pentane) gave epoxide **222** (6.5 mg, 53% yield over two steps).

$\mathbf{R}_f$ = 0.52 (hexane/EtOAc 3:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.34 (m, 5 H), 4.82 (d, 2 H, *J* = 1.5 Hz), 4.67 (d, 2 H, *J* = 1.5 Hz), 3.30 (dd, 1 H, *J* = 6.3, 4.8 Hz), 2.95–2.90 (m, 1 H), 2.82 (dd, 1 H, *J* = 5.1, 3.9 Hz), 2.65 (dd, 1 H, *J* = 5.1, 3.0 Hz), 1.99–1.88 (m, 1 H), 1.32–1.24 (m, 1 H), 1.08 (d, 3 H, *J* = 6.9 Hz), 1.00 (d, 3 H, *J* = 6.9 Hz), 0.94 (d, 3 H, *J* = 6.9 Hz).

6.2.3 Synthesis of the C14–C19 Dithiane *via* Nitrile Oxide Cycloaddition



(*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-propionaldehyde oxime (146): To a solution of imidazole (15.4 g, 226 mmol, 2.50 equiv) and TBSCl (16.3 g, 108 mmol, 1.20 equiv) in DMF (15 ml) was added a solution of (*R*)-3-hydroxy-2-methyl-propionic acid methyl ester (10.0 ml, 90.2 mmol, 1.00 equiv) in DMF (15 ml). The solution was stirred for 12 h at room temperature. After addition of Et_2O (250 ml) and H_2O (60 ml), the layers were separated and the organic phase was washed with H_2O (3 x 60 ml) and brine (60 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting colorless oil, silyl ether **242**, was used without further purification.

A solution of unpurified silyl ether **242** in CH_2Cl_2 (600 ml) was cooled to −78 °C. Neat DIBAL-H (48.2 ml, 271 mmol, 3.00 equiv) was added and the solution was stirred for 90 min at −78 °C. MeOH (10 ml) was added carefully, the mixture was stirred for 10 min at −78 °C, and saturated aqueous sodium potassium tartrate (300 ml) was added. The mixture was stirred for 12 h and allowed to warm to room temperature. Et_2O (600 ml) was added, the layers were separated and the aqueous layer was extracted with Et_2O (2 x 300 ml). The combined organic phases were washed with brine (600 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting colorless liquid, alcohol **243**, was used without further purification.

To a solution of unpurified alcohol **243** in CH_2Cl_2 (400 ml) was added NMO (15.9 g, 135 mmol, 1.50 equiv) and 4 Å molecular sieves (45 g). The mixture was stirred for 30 min at room temperature and then cooled to 0 °C. TPAP (984 mg, 2.80 mmol, 3.00 mol %) was

added. The mixture was stirred for 15 min at 0 °C, the cooling bath was removed, and the mixture was stirred for another 3 h at room temperature. The mixture was diluted with pentane (400 ml) and filtered through a pad of silica gel (elution with 33% Et_2O in pentane). The filtrate was carefully concentrated under reduced pressure to a slightly yellow liquid, aldehyde **244**, which was used without further purification.

To a solution of unpurified aldehyde **244** in EtOH (800 ml) was added $NH_2OH{\cdot}HCl$ (9.41 g, 135 mmol, 1.50 equiv) and pyridine (110 ml). The mixture was stirred for 14 h at room temperature and then concentrated under reduced pressure. The residue was taken up in EtOAc (600 ml), washed with H_2O (3 x 200 ml) and brine (200 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The pyridine was removed by co-evaporation with cyclohexane (6 x 200 ml). Purification by flash column chromatography (10% EtOAc in hexane) afforded oxime **146** (10.7 g, 55% yield over four steps) as a colorless oil.

$\mathbf{R}_f$ = 0.60 (hexane/EtOAc 2:1)

Optical Rotation: $[\alpha]^{22}_{D}$ (*c* 1.10, $CHCl_3$) = +6.6.

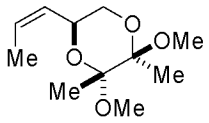
^{1}H NMR (300 MHz, $CDCl_3$, * denotes signal corresponding to the minor oxime diastereomer): δ 7.41 (d, 1 H, *J* = 6.2 Hz), 6.66* (d, 1 H, *J* = 7.2 Hz), 3.66–3.56 (m, 2 H), 3.32–3.19* (m, 1 H), 2.62–2.48 (m, 1 H), 1.09 (d, 3 H, *J* = 6.9 Hz), 1.08* (d, 3 H, *J* = 6.9 Hz), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$, * denotes signal corresponding to the minor oxime diastereomer): δ 155.1*, 154.5, 66.0, 65.2*, 37.3, 25.8, 18.3, 14.2, 13.9*, –5.4.

IR (thin film): ν 3306, 2956, 2930, 2885, 2858, 1472, 1462, 1389, 1362, 1257, 1104, 1032, 1007 cm^{-1}.

Anal. calcd for $C_{10}H_{23}NO_2Si$: C 55.25%, H 10.66%, N 6.44%; found: C 55.43%, H 10.64%, N 6.47%.

These spectral characteristics are identical to those previously reported.[50]



(2*R*,3*R*,6*S*)-2,3-Dimethoxy-2,3-dimethyl-5-((*Z*)-propenyl)-[1,4]dioxane (247): A suspension of Ph_3PEtBr (94.5 g, 255 mmol, 1.40 equiv) in THF (400 ml) was cooled to 0 °C. Upon dropwise addition of ^{n}BuLi (148 ml, 1.60 M in hexane, 267 mmol, 1.30 equiv), the solid dissolved and the resulting solution became deep red. The solution was stirred for 30 min at 0 °C and then cooled to −78 °C. A solution of aldehyde **246**[109] (ca. 182 mmol) in THF (35 ml) was added *via* cannula over 15 min. The resulting orange suspension was stirred for 10 h and allowed to warm to ambient temperature, before it was poured into saturated aqueous NH_4Cl (300 ml). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 500 ml). The combined organic phases were washed with brine (300 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (15–50% Et_2O in pentane) afforded alkene **247** (23.6 g, 60% yield over two steps) as a 92:8 mixture of diastereomers.

$\mathbf{R}_f$ = 0.77 (hexane/EtOAc 1:1)

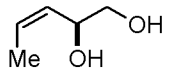
Optical Rotation: $[\alpha]^{20}_D$ (*c* 1.31, $CHCl_3$) = −225.8.

^{1}H NMR (300 MHz, $CDCl_3$, * denotes signal corresponding to the minor diastereomer): δ 5.75–5.65 (m, 1 H), 5.39–5.31 (m, 1 H), 4.80–4.73 (m, 1 H), 3.60 (t, 1 H, *J* = 11.6 Hz), 3.37* (s, 3 H), 3.63* (s, 3 H), 3.33 (s, 3 H), 3.28 (s, 3 H), 1.71 (dd, 3 H, *J* = 7.9, 1.9 Hz), 1.56 (s, 1 H), 1.31 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 129.7, 126.1, 99.0, 97.7, 64.0, 62.2, 48.1, 48.0, 24.8, 18.0, 17.6, 13.5.

IR (thin film): ν 3019, 2985, 2950, 2918, 2831, 2359, 2341, 1456, 1372, 1336, 1285, 1210, 1164, 1143, 1121, 1076, 1058, 1038 cm^{-1}.

Anal. calcd for $C_{11}H_{20}O_4$: C 61.09%, H 9.32%, O 29.59%; found: C 61.02%, H 9.42%.



(*Z*)-(*S*)-Pent-3-ene-1,2-diol (248): To acetal **247** (35.2 g, 163 mmol, 1.00 equiv) was added H_2O (200 ml) and AcOH (200 ml). The mixture was stirred for 6.5 h at 60 °C and for another 11 h at room temperature. Co-evaporation with toluene (5 x 300 ml) afforded the crude diol, which was purified by flash column chromatography (50–60% EtOAc in hexane) to give alkene **248** (15.5 g, 93% yield) as a clear colorless oil.

$\mathbf{R}_f$ = 0.12 (hexane/EtOAc 1:1)

Optical Rotation: $[\alpha]^{20}_{D}$ (*c* 1.08, $CHCl_3$) = +28.5.

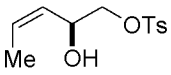
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.74–5.63 (m, 1 H), 5.42–5.35 (m, 1 H), 4.62–4.55 (m, 1 H), 3.59 (dd, 1 H, *J* = 11.2, 3.7 Hz), 3.50 (dd, 1 H, *J* = 10.9, 7.8 Hz), 2.13 (br s, 2 H), 1.71 (dd, 3 H, *J* = 6.8, 1.5 Hz).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 129.3, 128.5, 68.6, 66.5, 13.7.

IR (thin film): ν 3366, 3019, 2922, 2872, 2360, 1660, 1446, 1396, 1315, 1268, 1239, 1214, 1073, 1027 cm^{-1}.

HRMS (EI): calcd for C_4H_7O $[M-CH_3O]^+$ 71.0491; found 71.0490.

Anal. calcd for $C_5H_{10}O_2$: C 58.80%, H 9.87%, O 31.33%; found: C 58.57%, H 9.66%.



Toluene-4-sulfonic acid (*Z*)-(*S*)-2-hydroxy-pent-3-enyl ester (250): To a solution of diol **248** (371 mg, 3.63 mmol, 1.00 equiv) in benzene (37 ml) was added Bu_2SnO (1.08 g, 4.34 mmol, 1.20 equiv). The suspension was heated to reflux for 2 h, during which time it became a clear solution, which was stirred for 1 h while cooling to 50 °C. TsCl (748 mg, 3.92 mmol, 1.08 equiv) and TBAB (581 mg, 1.80 mmol, 0.500 equiv) was added, the resulting mixture was stirred for 1 h at 50 °C, and then cooled to room temperature. After addition of silica gel, the mixture was concentrated under reduced pressure. The solid residue was subjected to two consecutive flash column chromatographies (10–50% and 12–20% EtOAc in hexane, respectively) to afford tosylate **250** (745 mg, 80% yield) as a colorless oil.

R_f = 0.55 (hexane/EtOAc 1:1)

Optical Rotation: $[\alpha]^{20}_D$ (*c* 0.80, $CHCl_3$) = +65.7.

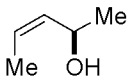
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82–7.78 (m, 2 H), 7.37–7.33 (m, 2 H), 5.74–5.62 (m, 1 H), 5.33–5.25 (m, 1 H), 4.72 (dt, 1 H, *J* = 7.8, 3.4), 3.99 (dd, 1 H, *J* = 10.3, 3.7 Hz), 3.90 (dd, 1 H, *J* = 10.3, 7.8 Hz), 2.45 (s, 3 H), 2.15 (br s, 1 H), 1.65 (dd, 3 H, *J* = 6.8, 5.3 Hz).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 144.9, 132.6, 129.9, 129.8, 127.8, 126.7, 72.6, 65.8, 21.7, 13.7.

IR (thin film): ν 3527, 3431, 3022, 2950, 2922, 2359, 1661, 1598, 1495, 1448, 1401, 1358, 1308, 1292, 1212, 1190, 1176, 1121, 1096, 1019 cm^{-1}.

HRMS (MALDI): calcd for $C_{12}H_{16}O_4SNa$ $[M+Na]^+$ 279.0667; found 279.0662.

Anal. calcd for $C_{12}H_{16}O_4S$: C 56.23%, H 6.29%, O 12.51%; found: C 55.98%, H 6.34%.



(*Z*)-(*R*)-Pent-3-en-2-ol (*ent*-147): To a suspension of $LiAlH_4$ (1.01 g, 25.3 mmol, 3.24 equiv) in Et_2O (50 ml) at 0 °C was added a solution of tosylate **250** (2.00 g, 7.80 mmol, 1.00 equiv) in Et_2O (10 ml) *via* cannula. The mixture was stirred for 130 min at 0 °C. The reaction was quenched by addition of $Na_2SO_4 \cdot 10\ H_2O$, and the resulting slurry was stirred for 30 min at room temperature. After filtration, the solvent was removed by distillation over a Vigreux column. Purification by Kugelrohr distillation (130 °C, 45 mbar) afforded allylic alcohol *ent*-**147** (486 mg, 72% yield) as a clear colorless liquid.

R_f = 0.30 (CH_2Cl_2/Et_2O 9:1)

Optical Rotation: $[\alpha]^{20}_D$ (*c* 1.30, $CHCl_3$) = +11.1.

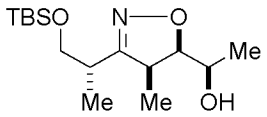
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.56–5.40 (m, 1 H), 4.72–4.64 (m, 1 H), 1.68 (d, 3 H, *J* = 5.6 Hz), 1.47 (br s, 1 H), 1.25 (d, 3 H, *J* = 6.2 Hz).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 134.7, 125.4, 63.6, 23.4, 13.1.

IR (thin film): ν 3350, 3016, 2971, 2923, 1660, 1448, 1406, 1370, 1314, 1289, 1240, 1144, 1108, 1061, 1022 cm^{-1}.

HRMS (EI): calcd for C_4H_7O $[M–CH_3]^+$ 71.0497; found 71.0490.

These spectral characteristics are identical to those previously reported.[210]



(*R*)-1-{(4*S*,5*R*)-3-[(*S*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-methyl-ethyl]-4-methyl-4,5-dihydro-isoxazol-5-yl}-ethanol (*ent*-151): A solution of oxime **146** (1.09 g, 5.00 mmol, 1.00 equiv) in CH_2Cl_2 (50 ml) was cooled to –78 °C. ^{t}BuOCl (543 mg, 5.00 mmol, 1.00 equiv) was added dropwise over 20 min. The resulting deep blue solution was stirred for 2 h at –78 °C and then used directly in the next step.

A solution of allylic alcohol *ent*-**147** (560 mg, 6.50 mmol, 1.30 equiv) in CH_2Cl_2 (100 ml) was cooled to 0 °C. ^{i}PrOH (1.25 ml, 16.5 mmol, 3.30 equiv) was added, followed by dropwise addition of EtMgBr (5.0 ml, 3.0 M in Et_2O, 15 mmol, 3.0 equiv). After stirring for 30 min at 0 °C, the deep blue solution from above was added *via* cannula over 6 h. The reaction was then stirred for 12 h and allowed to warm to room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (300 ml) and EtOAc (300 ml). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 300 ml). The combined organic phases were washed with H_2O (300 ml) and brine (300 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (20% EtOAc in hexane) provided isoxazoline *ent*-**151** (1.21 g, 80% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.16 (dd, 1 H, J = 9.7, 5.3 Hz), 3.95–3.90 (m, 1 H), 3.90 (dd, 1 H, J = 10.0, 5.6 Hz), 3.66–3.60 (m, 1 H), 3.31–3.21 (m, 1 H), 2.67–2.60 (m, 1 H), 2.02 (s, 1 H), 1.26 (d, 3 H, J = 6.2 Hz), 1.19 (d, 3 H, J = 7.5), 1.18 (d, 3 H, J = 7.2 Hz), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H).

These spectral characteristics are identical to those previously reported.[50]

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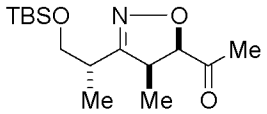
[210] O. Hamed, P. M. Henry, *Organometallics* **1997**, *16*, 4903–4909.



1-{(4*S*,5*R*)-3-[(*S*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-methyl-ethyl]-4-methyl-4,5-dihydro-isoxazol-5-yl}-ethanone (256): To a solution of alcohol *ent*-**151** (6.60 g, 21.9 mmol, 1.00 equiv) in CH_2Cl_2 (50 ml) was added NMO (3.33 g, 28.5 mmol, 1.30 equiv) and 4 Å molecular sieves (5.30 g). The mixture was stirred for 20 min at room temperature before TPAP (389 mg, 1.10 mmol, 0.500 equiv) was added. After stirring for 165 min, the mixture was diluted with pentane (50 ml) and filtered through a thin pad of celite. To the filtrate was added silica gel and the mixture was concentrated under reduced pressure. The resulting solid was applied to a plug of silica gel (5.5 x 10 cm) and elution with CH_2Cl_2 provided ketone **256** (6.10 g, 93% yield) as a colorless gum.

$\mathbf{R}_f$ = 0.57 (hexane/EtOAc 7:3)

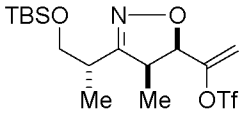
Optical Rotation: $[\alpha]^{27}_{D}$ (*c* 2.91, $CHCl_3$) = +37.2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.71 (d, 1 H, *J* = 10.8 Hz), 3.91 (dd, 1 H, *J* = 10.2, 5.7 Hz), 3.66 (dd, 1 H, *J* = 9.9, 7.5 Hz), 3.62–3.51 (m, 1 H), 2.69–2.58 (m, 1 H), 2.23 (s, 3 H), 1.17 (d, 3 H, *J* = 7.2 Hz), 1.06 (d, 3 H, *J* = 7.5 Hz), 0.87 (s, 9 H), 0.04 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 208.2, 164.3, 86.8, 65.4, 47.1, 35.0, 28.5, 26.1, 18.5, 16.0, 12.2, –5.2.

IR (thin film): ν 2956, 2931, 2858, 1716, 1474, 1464, 1359, 1095 cm^{-1}.

HRMS (ESI): calcd for $C_{15}H_{29}NO_3SiNa$ $[M+Na]^+$ 322.1809; found 322.1804.



Trifluoro-methanesulfonic acid 1-{(4*S*,5*R*)-3-[(*S*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-ethyl]-4-methyl-4,5-dihydro-isoxazol-5-yl}-vinyl ester (257): A solution of ketone **256** (1.00 g, 3.34 mmol, 1.00 equiv) in THF (40 ml) was cooled to –78 °C. To the solution was added a precooled (–78 °C) solution of KHMDS (730 mg, 3.66 mmol, 1.10 equiv) in THF (30.0 ml). After stirring the solution for 1 h, a precooled (–78 °C) solution of $PhNTf_2$

(1.30 g, 3.64 mmol, 1.09 equiv) in THF (7.0 ml) was added via cannula and the reaction was monitored by TLC (20% EtOAc in hexane). Upon completion, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (10 ml) and the mixture was warmed to room temperature. The layers were separated and the aqueous phase was extracted with EtOAc (3 x 50 ml). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (3% EtOAc in hexane) gave vinyl triflate **257** (607 mg, 43% yield) as a colorless gum, along with ketone **256** (390 mg, 39%).

$\mathbf{R}_f$ = 0.61 (hexane/EtOAc 4:1)

Optical Rotation: $[\alpha]^{27}_{D}$ (*c* 1.23, $CHCl_3$) = –1.9.

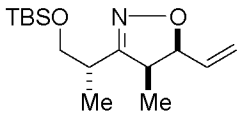
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.41–5.38 (m, 2 H), 4.94 (d, 1 H, *J* = 10.0 Hz), 3.87 (dd, 1 H, *J* = 9.9, 5.7 Hz), 3.63 (dd, 1 H, *J* = 11.0, 7.8 Hz), 3.51–3.40 (m, 1 H), 2.69–2.58 (m, 1 H), 1.18 (d, 3 H, *J* = 7.2 Hz), 1.14 (d, 3 H, *J* = 7.5 Hz), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.04 (s, 3 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ –73.6.

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8, 150.3, 118.5 (q, CF_3, *J* = 319 Hz), 106.7, 81.0, 65.4, 46.4, 35.2, 26.1, 18.5, 16.0, 12.2, –5.1.

IR (thin film): ν 2956, 2934, 2885, 2858, 1668, 1483, 1474, 1425, 1252, 1214, 1093 cm^{-1}.

HRMS (ESI): calcd for $C_{16}H_{29}NO_5F_3SSiNa$ $[M+Na]^+$ 454.1302; found 454.1296.



(4*S*,5*S*)-3-[(*S*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-methyl-ethyl]-4-methyl-5-vinyl-4,5-dihydro-isoxazole (252): To a solution of vinyl triflate **257** (1.98 g, 4.59 mmol, 1.00 equiv) in DMF (5.0 ml) was added PPh_3 (240 mg, 0.920 mmol, 0.200 equiv) and NEt_3 (1.92 ml, 13.8 mmol, 3.01 equiv). To the solution was added HCO_2H (346 µl, 9.18 mmol, 2.00 equiv) and $Pd(OAc)_2$ (103 mg, 0.460 mmol, 0.100 equiv), and the reaction was heated to 60 °C for 15 min. The reaction was quenched by addition of H_2O (15 ml) and the mixture was extracted with EtOAc (3 x 15 ml). The combined organic phases were washed with H_2O (3 x 15 ml),

dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (1.5% EtOAc in hexane) provided olefin **252** (1.15 g, 89% yield) as a colorless oil.

$\mathbf{R}_f$ = 0.63 (hexane/EtOAc 1:1)

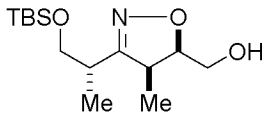
Optical Rotation: $[\alpha]^{29}_{D}$ (*c* 0.63, $CHCl_3$) = +36.2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.91–5.79 (m, 1 H), 5.40–5.28 (m, 2 H), 4.83–4.77 (m, 1 H), 3.91 (dd, 1 H, *J* = 9.9, 5.1 Hz), 3.65 (dd, 1 H, *J* = 9.9, 7.8 Hz), 3.28–3.18 (m, 1 H), 2.69–2.58 (m, 1 H), 1.19 (d, 3 H, *J* = 7.2 Hz), 1.05 (d, 3 H, *J* = 7.2 Hz), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 132.4, 119.7, 84.5, 65.6, 46.6, 35.4, 26.2, 16.3, 12.4, –5.0, –5.1.

IR (thin film): ν 2956, 2930, 2858, 1644, 1613, 1475, 1462, 1389, 1088 cm^{-1}.

HRMS (ESI): calcd for $C_{15}H_{29}NO_2SiNa$ $[M+Na]^+$ 306.1860; found 306.1856.



{(4*S*,5*R*)-3-[(*S*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-methyl-ethyl]-4-methyl-4,5-dihydro-isoxazol-5-yl}-methanol (258): A solution of olefin **252** (145 mg, 0.510 mmol, 1.00 equiv) in MeOH (2.0 ml) was flushed with O_2 and then cooled to –78 °C while continuing to bubble O_2 through the solution. Ozone was then passed through the solution until a blue color persisted. Excess ozone was removed from the solution by bubbling O_2 and N_2 through the solution. $NaBH_4$ (77.2 mg, 2.04 mmol, 4.00 equiv) was added and the mixture was allowed to warm to room temperature and stir for 1 h. The reaction was quenched by addition of H_2O (0.75 ml) and 2 M aqueous NaOH (0.25 ml). After stirring for 30 min, EtOAc (10 ml) and H_2O (10 ml) were added and the layers separated. The aqueous phase was extracted with EtOAc (3 x 10 ml) and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide alcohol **258** (145 mg) as a colorless oil, which was directly used in the next step.

$\mathbf{R}_f$ = 0.46 (hexane/EtOAc 1:1)

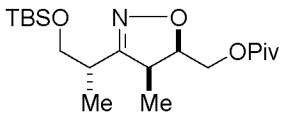
Optical Rotation: $[\alpha]^{28}_{D}$ (*c* 0.34, $CHCl_3$) = –20.3.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.51–4.45 (m, 1 H), 3.87 (dd, 1 H, *J* = 9.9, 5.4 Hz), 3.70 (d, 2 H, *J* = 5.1 Hz), 3.60 (dd, 1 H, *J* = 9.9, 8.1 Hz), 3.40–3.29 (m, 1 H), 2.65–2.53 (m, 1 H), 2.23 (br s, 1 H), 1.14 (d, 3 H, *J* = 7.2 Hz), 0.86 (s, 9 H), 0.02 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 82.2, 65.4, 61.2, 44.7, 35.0, 26.2, 18.5, 16.0, 10.6, −5.1, –5.1.

IR (thin film): ν 3417, 2929, 2858, 1462, 1389, 1255, 1089 cm^{-1}.

HRMS (ESI): calcd for $C_{14}H_{29}NO_3SiNa$ $[M+Na]^+$ 310.1809; found 310.1803.



2,2-Dimethyl-propionic acid (4*S*,5*R*)-3-[(*S*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-ethyl]-4-methyl-4,5-dihydro-isoxazol-5-ylmethyl ester (259): To a solution of alcohol **258** (145 mg, 0.510 mmol, 1.00 equiv) in pyridine (2.00 ml) was added trimethylacetyl chloride (125 µl, 1.01 mmol, 2.00 equiv). The mixture was stirred for 10.5 h at room temperature, MeOH (2 ml) was added, and the mixture was stirred for another 30 min. The reaction was quenched by addition of H_2O (5 ml) and EtOAc (5 ml). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 5 ml). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (5–10% EtOAc in hexane) provided pivaloate **259** (181 mg, 65% yield over two steps) as a colorless oil.

$\mathbf{R}_f$ = 0.50 (hexane/EtOAc 4:1)

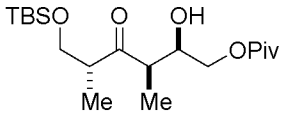
Optical Rotation: $[\alpha]^{27}_{D}$ (*c* 0.62, $CHCl_3$) = –13.9.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.58–4.51 (m, 1 H), 4.26 (dd, 1 H, *J* = 11.7, 4.8 Hz), 4.11 (dd, 1 H, *J* = 11.7, 6.0 Hz), 3.88 (dd, 1 H, *J* = 10.2, 5.4 Hz), 3.62 (dd, 1 H, *J* = 9.9, 8.1 Hz), 3.38–3.27 (m, 1 H), 2.66–2.54 (m, 1 H), 1.17–1.10 (m, 15 H), 0.86 (s, 9 H), 0.02 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 178.2, 164.7, 79.5, 65.4, 62.3, 44.9, 39.0, 35.1, 27.4, 26.1, 18.5, 16.1, 10.9, –5.1, –5.3.

IR (thin film): ν 2957, 2931, 2878, 1732, 1462, 1396, 1362, 1282, 1256, 1159, 1089 cm^{-1}.

HRMS (ESI): calcd for $C_{19}H_{37}NO_4SiNa$ $[M+Na]^+$ 394.2384; found 394.2379.



2,2-Dimethyl-propionic acid (2*R*,3*R*,5*R*)-6-(*tert*-butyl-dimethyl-silanyloxy)-2-hydroxy-3,5-dimethyl-4-oxo-hexyl ester (260): To a solution of isoxazoline **259** (136 mg, 0.370 mmol, 1.00 equiv) in 5:1 MeOH/H_2O (10 ml) was added $B(OH)_3$ (246 mg, 3.98 mmol, 10.8 equiv) and Raney-Nickel (ca. 40 mg, moist with H_2O). The *Schlenk* tube was partially evacuated and refilled with H_2 from a balloon. The mixture was stirred vigorously under an H_2 atmosphere for 45 min at room temperature. The mixture was filtered over celite, the filter pad was washed with EtOAc (30 ml), and the filtrate was concentrated under reduced pressure. The residue was then taken up in 40% EtOAc in hexane (1 ml) and filtered through a plug of silica gel (ca. 2 g, elution with 40% EtOAc in hexane). The filtrate was concentrated under reduced pressure to provide hydroxy ketone **260** (130 mg, 95% yield, > 95% pure as determined by ^1H NMR) as a colorless oil.

$\mathbf{R_f}$ = 0.46 (hexane/EtOAc 2:1)

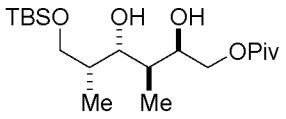
Optical Rotation: $[\alpha]^{29}_D$ (*c* 0.52, $CHCl_3$) = –24.7.

^1H NMR (300 MHz, $CDCl_3$): δ 7.56 (dd, 1 H, *J* = 9.6, 8.7 Hz), 4.15–4.04 (m, 3 H), 3.54 (dd, 1 H, *J* = 9.3, 4.8 Hz), 3.06–2.94 (m, 2 H), 2.78 (dq, 1 H, *J* = 7.2, 4.2 Hz), 1.20 (s, 9 H), 1.17 (d, 3 H, *J* = 7.2 Hz), 0.99 (d, 3 H, *J* = 6.9 Hz), 0.84 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 216.9, 178.5, 69.9, 66.0, 65.7, 48.0, 47.6, 39.0, 27.4, 26.1, 18.5, 13.6, 13.3, 10.2, –5.3, –5.3.

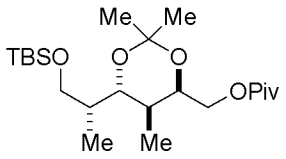
IR (thin film): ν 3500, 2958, 2858, 1732, 1713, 1462, 1388, 1362, 1284, 1258, 1159, 1099, 1005 cm^{-1}.

HRMS (ESI): calcd for $C_{19}H_{38}O_5SiNa$ $[M+Na]^+$ 397.2381; found 397.2375.



2,2-Dimethyl-propionic acid (2*R*,3*S*,4*S*,5*R*)-6-(*tert*-butyl-dimethyl-silanyloxy)-2,4-dihydroxy-3,5-dimethyl-hexyl ester (261): A solution of $Me_4NBH(OAc)_3$ (970 mg, 3.69 mmol, 5.00 equiv) in 1:1 MeCN/AcOH (7.4 ml) was stirred for 20 min at room temperature, cooled to –20 °C, and added via cannula to a precooled (–20 °C) solution of hydroxy ketone **260** (276 mg, 0.740 mmol, 1.00 equiv) in MeCN (1.8 ml). The reaction was stirred for 24 h at –20 °C and 1 h at room temperature, and then quenched by addition of saturated aqueous sodium potassium tartrate (4 ml). The mixture was stirred at room temperature for 30 min, H_2O (5 ml) was added, and the mixture was extracted with EtOAc (6 x 10 ml). The combined organic phases were dried over Na_2SO_4, filtered, diluted with toluene (30 ml), and concentrated under reduced pressure. The residue was taken up in 1:1 EtOAc/hexane and filtered through a plug of silica gel, eluting with EtOAc (25 ml). The filtrate was concentrated under reduced pressure to provide diol **261,** which was used immediately in the next step.

$\mathbf{R}_f$ = 0.36 (hexane/EtOAc 2:1)



2,2-Dimethyl-propionic acid (4*R*,5*S*,6*S*)-6-[(*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-ethyl]-2,2,5-trimethyl-[1,3]dioxan-4-yl methyl ester (265): To a solution of diol **261** (279 mg, 0.740 mmol, 1.00 equiv) in 2,2-dimethoxypropane (5.0 ml) was added TsOH (65.0 mg, 0.340 mmol, 0.460 equiv). After stirring for 1 h at room temperature, NEt_3 (700 ml) was added and the solution was concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (ca. 0.5 ml) and filtered through a plug of silica gel (washing with CH_2Cl_2). The filtrate was concentrated under reduced pressure to provide analytically pure acetonide **265** (156 mg, 51% yield over two steps) as a colorless oil.

$\mathbf{R}_f$ = 0.85 (hexane/EtOAc 2:1)

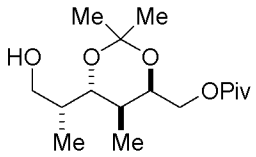
Optical Rotation: $[\alpha]^{29}_D$ (*c* 0.19, $CHCl_3$) = –19.4.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.17–3.94 (m, 3 H), 3.51–3.38 (m, 3 H), 1.95–1.84 (m, 1 H), 1.71–1.59 (m, 1 H), 1.30 (s, 3 H), 1.28 (s, 3 H), 1.18 (s, 9 H), 0.87–0.81 (m, 15 H), 0.02 (s, 3 H), 0.01 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 178.6, 100.8, 73.3, 67.9, 65.0, 64.1, 38.8, 35.2, 27.4, 26.1, 25.1, 23.8, 18.4, 11.7, 10.8, –5.2, –5.2.

IR (thin film): ν 2958, 2933, 2858, 1733, 1462, 1380, 1282, 1256, 1226, 1160, 1101, 1024 cm^{-1}.

HRMS (ESI): calcd for $C_{22}H_{44}O_5SiNa$ $[M+Na]^+$ 439.2850; found 439.2844.



2,2-Dimethyl-propionic acid (4*R*,5*S*,6*S*)-6-[(*R*)-2-hydroxy-1-methyl-ethyl]-2,2,5-trimethyl-[1,3]dioxan-4-ylmethyl ester (266): To a solution of silyl ether **265** (30.0 mg, 70.0 μmol, 1.00 equiv) in THF (1.0 ml) was added TBAF (70 μl, 1.0 M in THF, 70 μmol, 1.0 equiv). The solution was stirred for 4 h at room temperature, silica gel (300 mg) was added, and the mixture was concentrated under reduced pressure. The solid was then applied to a silica gel column and purified by flash column chromatography (50% EtOAc in hexane) to give alcohol **266** (20.0 mg, 92% yield).

R_f = 0.44 (hexane/EtOAc 2:1)

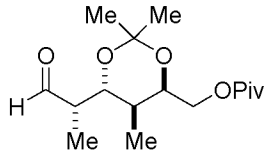
Optical Rotation: $[\alpha]^{28}_D$ (*c* 0.42, $CHCl_3$) = –15.4.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.12–3.97 (m, 3 H), 3.63–3.61 (m, 2 H), 3.51 (dd, 1 H, *J* = 8.1, 2.7 Hz), 2.17 (br s, 1 H), 2.01–1.90 (m, 1 H), 1.86–1.74 (m, 1 H), 1.34 (s, 3 H), 1.29 (s, 3 H), 1.17 (s, 9 H), 0.95 (d, 3 H, *J* = 7.2 Hz), 0.84 (d, 3 H, *J* = 6.6 Hz) .

^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 100.9, 76.9, 68.0, 36.9, 39.0, 37.5, 34.7, 27.4, 25.2, 23.8, 12.3, 10.9.

IR (thin film): ν 3347, 2972, 2878, 1731, 1481, 1459, 1381, 1284, 1226, 1164, 1022 cm^{-1}.

HRMS (ESI): calcd for $C_{16}H_{30}O_5Na$ $[M+Na]^+$ 325.1985; found 325.1983.

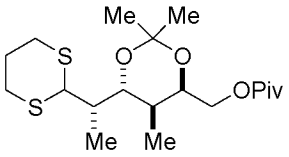


2,2-Dimethyl-propionic acid (4*R*,5*S*,6*R*)-2,2,5-trimethyl-6-[(*S*)-1-methyl-2-oxo-ethyl]-[1,3]dioxan-4-ylmethyl ester (267): A solution of alcohol **266** (50.0 mg, 0.530 mmol, 1.00 equiv), 4 Å molecular sieves (41 mg), and NMO (29.0 mg, 0.800 mmol, 1.51 equiv) in CH_2Cl_2 (2.00 ml) was stirred for 45 min at room temperature. The mixture was cooled to 0 °C and TPAP (6.0 mg, 0.020 mmol, 4.0 mol %) was added in one portion. The mixture was stirred for 45 min and allowed to warm to room temperature. Upon completion of the reaction, silica gel (100 mg) was added and the mixture was concentrated under reduced pressure. The resulting solid was applied to a plug of silica gel (1 g) which was eluted with 10% EtOAc in CH_2Cl_2 (ca. 15 ml). The filtrate was concentrated under reduced pressure to provide aldehyde **267** (46.0 mg, 93% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.62 δ (d, 1 H, J = 0.9 Hz), 4.09−3.90 (m, 5 H), 3.77 (dd, 1 H, J = 8.1, 3.0 Hz), 2.41−2.33 (m, 1 H), 2.02−1.91 (m, 1 H), 1.29 (s, 3 H), 1.24 (s, 3 H), 1.14 (s, 9 H), 1.10 (d, 3 H, J = 6.9 Hz), 0.85 (d, 3 H, J = 6.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 203.8, 178.2, 101.1, 73.4, 67.7, 63.6, 48.5, 39.0, 34.8, 27.4, 24.8, 23.7, 12.0, 8.0.

HRMS (MALDI): calcd for $C_{16}H_{28}O_5SiNa$ $[M+Na]^+$ 323.1829; found 323.1837.



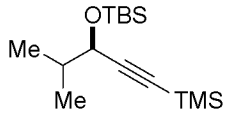
2,2-Dimethyl-propionic acid (4*R*,5*S*,6*R*)-6-((*S*)-1-[1,3]dithian-2-yl-ethyl)-2,2,5-trimethyl-[1,3]dioxan-4-ylmethyl ester (268): To a solution of aldehyde **267** (9.8 mg, 0.030 mmol, 1.0 equiv) in CH_2Cl_2 (0.25 ml) at 0 °C was added propanedithiol (10 µl, 0.10 mmol, 3.3 equiv) and $BF_3{\cdot}OEt_2$ (4.0 µl, 0.030 mmol, 1.0 equiv). The resulting solution was stirred for 3 h and allowed to warm to room temperature. Additional propanedithiol (10 µl, 0.10 mmol, 3.3 equiv) was added and the solution was stirred for another 90 min at ambient temperature. After the addition of 2,2-dimethoxy propane (0.050 ml, 0.41 mmol, 14 equiv), the solution was stirred for 30 min at room temperature. The mixture was diluted

with CH_2Cl_2 (10 ml) and saturated aqueous $NaHCO_3$ (10 ml), the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic phases were washed with saturated aqueous NH_4Cl (25 ml) and brine (25 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography afforded dithiane **268** (9.0 mg, 71% yield).

$\mathbf{R}_f$ = 0.37 (hexane/EtOAc 2:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.50 (d, 1 H, *J* = 9.9 Hz), 4.53 (s, 1 H), 4.19 (dd, 1 H, *J* = 11.4, 3.0 Hz), 3.97 (dd, 1 H, *J* = 8.7, 7.2 Hz), 3.69–3.58 (m, 1 H), 2.99–2.81 (m, 6 H), 2.61–2.49 (m, 1 H), 2.15–2.07 (m, 1 H), 1.83 (s, 6 H), 1.23–1.22 (m, 12 H), 1.08 (d, 3 H, *J* = 6.6 Hz).

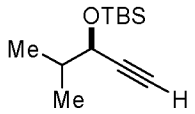
6.2.4 Synthesis of the C21–C25 Aldehyde *via* Zinc Alkynylide Addition



(*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-1-trimethylsilanyl-pent-1-yne (278): To a solution of alcohol **224** (172 mg, 1.01 mmol, 1.00 equiv) in DMF (1.40 ml) was added TBSCl (181 mg, 1.20 mmol, 1.19 equiv) and imidazole (152 mg, 2.23 mmol, 2.21 equiv). The resulting solution was stirred for 15.5 h at ambient temperature. The reaction was quenched by addition of H_2O (20 ml) and EtOAc (20 ml). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 20 ml). The combined organic phases were washed with 1 M aqueous HCl (50 ml) and brine (50 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (4% Et_2O in pentane) gave silyl ether **278** (272 mg, 95% yield).

$\mathbf{R}_f$ = 0.89 (hexane/EtOAc 4:1)

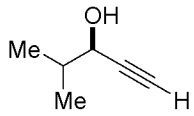
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.07 (d, 1 H, *J* = 6.0 Hz), 1.84–1.73 (m, 1 H), 0.96 (d, 3 H, *J* = 4.2 Hz), 0.94 (d, 3 H, *J* = 4.2 Hz), 0.90 (s, 9 H), 0.15 (s, 9 H), 0.13 (s, 3 H), 0.10 (s, 3 H).



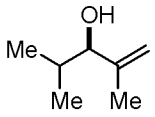
***tert*-Butyl-((*R*)-1-isopropyl-prop-2-ynyloxy)-dimethyl-silane (279)**: To a solution of alkyne **278** (272 mg, 0.960 mmol, 1.00 equiv) in MeOH (10 ml) was added K_2CO_3 (199 mg, 1.44 mmol, 1.50 equiv). The resulting cloudy mixture became clear after being stirred for 6.5 h at ambient temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 ml) and Et_2O (30 ml). The layers were separated and the aqueous phase was extracted with Et_2O (2 x 30 ml). The combined organic phases were washed with brine (50 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (4% Et_2O in pentane) gave alkyne **279** (151 mg, 75% yield).

$\mathbf{R}_f$ = 0.89 (hexane/EtOAc 3:1)

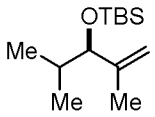
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.11 (dd, 1 H, *J* = 5.7, 2.4 Hz), 2.35 (d, 1 H, *J* = 2.1 Hz), 1.88–1.77 (m, 1 H), 0.98 (d, 3 H, *J* = 6.0 Hz), 0.96 (d, 3 H, *J* = 6.0 Hz), 0.91 (s, 9 H), 0.14 (s, 3 H), 0.10 (s, 3 H).



(*R*)-4-Methyl-pent-1-yn-3-ol (285): To a solution of trimethylsilyl alkyne **224** (3.17 g, 18.6 mmol, 1.00 equiv) in MeOH (190 ml) was added K_2CO_3 (3.85 g, 27.9 mmol, 1.50 equiv). The originally cloudy mixture became clear upon stirring for 7.5 h at room temperature. MeOH was partially removed by distillation. The residue was taken up in 1 M aqueous HCl (50 ml) which was then extracted with Et_2O (3 x 50 ml). The combined organic phases were washed with brine (100 ml), dried over $MgSO_4$, filtered, and carefully concentrated under reduced pressure. Co-evaporation with CH_2Cl_2 (3 x 50 ml) afforded **284** as a colorless solution in CH_2Cl_2, which was directly used in the next step. Typically, a concentration of 65–75 wt% was employed, as determined by integration of the ^{1}H NMR signals at δ 5.29 ppm (CH_2Cl_2, 2 H) and 4.68 ppm (**285**, 1 H).



(*R*)-2,4-Dimethyl-pent-1-en-3-ol (286): A suspension of Cp_2ZrCl_2 (321 mg, 1.10 mmol, 0.220 equiv) in degassed CH_2Cl_2 (18.5 ml) was cooled to 0 °C. After the addition of $AlMe_3$ (15.5 ml, 2.0 M in hexane, 31 mmol, 6.2 equiv), H_2O (0.140 ml, 7.75 mmol, 1.55 equiv) was added drop by drop. The mixture was stirred for 10 min at 0 °C, before a solution of alkyne **285** (682 mg, 72 wt% in Et_2O, 5.0 mmol, 1.0 equiv) and $AlMe_3$ (1.65 ml, 2.0 M in hexane, 3.3 mmol, 0.66 equiv) in degassed CH_2Cl_2 (8.0 ml) was added. The cooling bath was removed and the cloudy mixture was stirred for 24 h at room temperature. The reaction was quenched by careful addition of 3 M aqueous HCl until gas evolution stopped, followed by addition of $MgSO_4$. The resulting slurry was stirred for 30 min at room temperature and then filtered. The filter cake was washed with Et_2O (50 ml), and the combined organic phases were carefully concentrated under reduced pressure. The resulting colorless liquid was directly used in the next step.



***tert*-Butyl-((*R*)-1-isopropyl-2-methyl-allyloxy)-dimethyl-silane (280)**: To a solution of alcohol **286** in DMF (7.5 ml) was added imidazole (1.03 g, 15.1 mmol, 3.02 equiv) and TBSCl (830 mg, 5.51 mmol, 1.10 equiv). The solution was stirred for 18 h at ambient temperature, MeOH (2 ml) was added, and the resulting mixture was stirred for another 30 min. After addition of H_2O (20 ml), the mixture was extracted with CH_2Cl_2 (3 x 25 ml). The combined organic phases were washed with brine (50 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was filtered over a plaque of silica gel, which was washed with pentane (100 ml) to give pure silyl ether **280** (812 mg, 71% yield over three steps).

R_f = 0.77 (hexane)

Optical Rotation: $[\alpha]^{22}_D$ (*c* 0.99, $CHCl_3$) = +7.9.

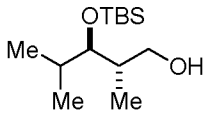
^{1}H NMR (300 MHz, $CDCl_3$, * denotes signal corresponding to the minor rotamer): δ 4.90–4.88* (m, 2 H), 4.81–4.78 (m, 2 H), 3.66* (d, 1 H, *J* = 6.9 Hz), 3.59 (d, 1 H, *J* = 7.5 Hz),

2.17–1.84* (m, 1 H), 1.75–1.60 (m, 1 H), 1.65–1.64 (m, 3 H), 0.89 (s, 3 H), 0.88 (d, 3 H, J = 6.9 Hz), 0.78* (d, 3 H, J = 6.9 Hz), 0.77 (d, 3 H, J = 6.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$* denotes signal corresponding to the minor rotamer): δ 152.4*, 146.9, 111.9, 109.4*, 82.8, 82.6*, 31.9*, 31.7, 25.9, 25.7*, 22.8*, 19.7*, 19.4, 18.6, 18.3*, 17.2, 11.9*, –2.9*, –4.6, –5.1.

IR (thin film): ν 3339, 2956, 2860, 1650, 1465, 1381, 1253, 1062, 1008 cm^{-1}.

Anal. calcd for $C_{13}H_{28}OSi$: C 68.35%, H 12.35%, O 7.00%; found: C 68.09%, H 12.17%.



(2*S*,3*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2,4-dimethyl-pentan-1-ol (287): 9-BBN (12.0 ml, 0.50 M in THF, 6.0 mmol, 3.0 equiv) was cooled to −78 °C. Alkene **280** (577 mg, 2.00 mmol, 1.00 equiv) was added and the solution was stirred for 13.5 h and allowed to warm to ambient temperature. 1:1 THF/EtOH (4 ml) was added, followed by 2 M aqueous NaOH (4 ml) and 30% aqueous H_2O_2 (4 ml). The obtained mixture was stirred for 2 h at room temperature before being diluted with EtOAc (25 ml). The layers were separated and the organic phase was washed with brine (20 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc in hexane) afforded alcohol **287** (342 mg, 69% yield) as a colorless liquid.

R_f = 0.58 (hexane/EtOAc 1:1)

Optical Rotation: $[\alpha]^{23}_D$ (*c* 1.01, $CHCl_3$) = −7.2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.69–3.53 (m, 2 H), 3.41 (t, 1 H, J = 4.9 Hz), 2.71 (t, 1 H, J = 5.7 Hz), 1.91–1.78 (m, 2 H), 0.97 (d, 3 H, J = 6.9 Hz), 0.91 (d, 3 H, J = 6.6 Hz), 0.90 (d, 3 H, J = 6.6 Hz), 0.91 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H).

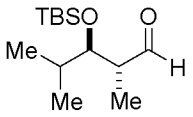
^{13}C NMR (75 MHz, $CDCl_3$): δ 82.3, 65.0, 37.0, 33.1, 26.2, 19.1, 18.5, 18.4, 16.6, –3.8, –3.9.

IR (thin film): ν 3357, 2956, 2933, 2886, 2861, 1466, 1385, 1367, 1253, 1034 cm^{-1}.

HRMS (EI): calcd for $C_{10}H_{23}O_2Si$ $[M-C_3H_7]^+$ 203.1462; found 203.1459.

Anal. calcd for $C_{13}H_{30}O_2Si$: C 63.35%, H 12.27%, O 12.98%; found: C 63.62%, H 11.98%.

These spectral characteristics are identical to those previously reported.[211]



(2*R*,3*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2,4-dimethyl-pentanal (5): A solution of $(COCl)_2$ (0.100 ml, 1.14 mmol, 1.60 equiv) in CH_2Cl_2 (4.2 ml) was cooled to −78 °C. DMSO (0.160 ml, 2.26 mmol, 3.18 equiv) was added and the solution was stirred for 10 min at −78 °C, before a solution of alcohol **287** (175 mg, 0.710 mmol, 1.00 equiv) in CH_2Cl_2 (2.8 ml) was added. The resulting solution was stirred for 15 min at −78 °C, NEt_3 (0.520 ml, 3.74 mmol, 5.27 equiv) was added, and the solution was stirred for another 70 min at −78 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl (2 ml) and was let warm to room temperature. CH_2Cl_2 (10 ml) and saturated aqueous NH_4Cl (10 ml) was added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic phases were washed with brine (25 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (50% CH_2Cl_2 in hexane) afforded aldehyde **5** (141 mg, 81% yield) as a colorless liquid.

$\mathbf{R_f}$ = 0.68 (hexane/CH_2Cl_2 1:1)

Optical Rotation: $[\alpha]^{20}_D$ (*c* 1.05, $CHCl_3$) = −31.6.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.78 (d, 1 H, *J* = 2.4 Hz), 3.67 (dd, 1 H, *J* = 5.1, 4.2 Hz), 2.58–2.49 (m, 1 H), 1.89–1.76 (m, 1 H), 1.10 (d, 3 H, *J* = 7.2 Hz), 0.92 (d, 3 H, *J* = 6.9 Hz), 0.90 (s, 9 H), 0.90 (d, 3 H, *J* = 6.9 Hz), 0.07 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 204.9, 79.2, 49.9, 32.9, 26.0, 18.9, 18.3, 12.1, –3.9, –4.1.

IR (thin film): ν 2956, 2934, 2887, 2860, 1710, 1466, 1387, 1367, 1254, 1185, 1053 cm^{-1}.

HRMS (ESI): calcd for $C_{13}H_{28}O_3SiNa$ $[M+NaO]^+$ 283.1700; found 283.1697.

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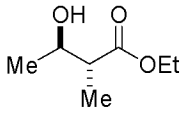
[211] R. Baker, J. C. Head, C. J. Swain, *J. Chem. Soc., Perkin Trans. 1* **1988**, 85–97.

6.2.5 Synthesis of the C14–C20 Diol *via* Nitrile Oxide Cycloaddition

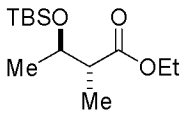


(2*R*,3*R*)-3-Hydroxy-2-methyl-butyric acid ethyl ester (37): A solution of $^{i}Pr_2NH$ (14.5 ml, 111 mmol, 2.22 equiv) in THF (26 ml) was cooled to 0 °C. MeLi (69 ml, 1.6 M, 0.11 mol, 2.2 equiv) was added, the mixture was cooled to −50 °C, and (*R*)-3-hydroxy-butyric acid ethyl ester **(291)** (6.50 ml, 50.0 mmol, 1.00 equiv) was slowly added. The mixture was stirred for 15 min at −30 °C before a solution of MeI (4.70 ml,75.0 mmol, 1.50 equiv) in HMPA (12.5 ml) was added. After stirring the mixture for another 15 min, it was poured onto ice-water and the resulting biphasic mixture was extracted with Et_2O (3 x 200 ml). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10−50% Et_2O in pentane) afforded alcohol **37** (6.13 g, 84% yield) as a colorless oil. The diastereomeric ratio of 94:6 was determined by integration of the ^{1}H NMR signals at δ 4.06 ppm (major) and 3.87 ppm (minor), respectively.

Optical Rotation: $[\alpha]^{22}_{D}$ (*c* 0.96, $CHCl_3$) = −17.4.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.17 (q, 2 H, *J* = 7.2 Hz), 3.87 (h, 1 H, *J* = 6.3 Hz), 2.71 (d, 1 H, *J* = 5.7 Hz), 2.44 (p, 1 H, *J* = 7.2 Hz), 1.28 (t, 3 H, *J* = 7.2 Hz), 1.22 (d, 3 H, *J* = 6.3 Hz), 1.19 (d, 3 H, *J* = 7.2 Hz).

These spectral characteristics are identical to those previously reported.[129]



(2*R*,3*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-butyric acid ethyl ester (292): To a solution of alcohol **37** (6.13 g, 42.0 mmol, 1.00 equiv) in DMF (75 ml) was added TBSCl (9.22 g, 61.2 mmol, 1.46 equiv) and imidazole (7.64 g, 122 mmol, 2.91 equiv). The resulting solution was stirred for 14 h at room temperature. EtOAc (200 ml) and H_2O (300 ml) was added, the layers were separated, and the aqueous phase was extracted with EtOAc (2 x 200 ml). The combined organic phases were washed with 1 M aqueous HCl (300 ml) and

brine (300 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc in hexane) afforded silyl ether **292** (10.6 g, 97% yield) as a colorless liquid.

R_f = 0.72 (hexane/EtOAc 3:1)

Optical Rotation: $[\alpha]^{26}_{D}$ (*c* 1.00, $CHCl_3$) = −36.5.

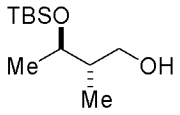
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.16−4.07 (m, 2 H), 4.06−3.97 (m, 1 H), 2.48 (p, 1 H, *J* = 7.2 Hz), 1.26 (t, 3 H, *J* = 7.2 Hz), 1.12 (d, 3 H, *J* = 6.3 Hz), 1.08 (d, 3 H, *J* = 6.9 Hz), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 70.2, 60.1, 48.2, 25.8, 20.6, 18.0, 14.3, 12.8, −4.2, −5.0.

IR (thin film): ν 2935, 2892, 2859, 1737, 1464, 1376, 1318, 1253, 1184, 1110, 1067 cm^{-1}.

HRMS (EI): calcd for $C_9H_{19}O_3Si$ $[M-C_4H_9]^+$ 203.1098; found 203.1099.

Anal. calcd for $C_{13}H_{28}O_3Si$: C 59.95%, H 10.84%, O 18.43%; found: C 60.06%, H 10.92%.



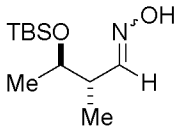
(2*R*,3*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-butan-1-ol (294): A solution of ester **292** (10.6 g, 40.7 mmol, 1.00 equiv) in CH_2Cl_2 (380 ml) was cooled to −78 °C. After the addition of neat DIBAL-H (15.0 ml, 89.2 mmol, 2.19 equiv), the resulting solution was stirred for 2 h at −78 °C, the cooling bath removed, and the solution stirred for another 1 h at room temperature. The reaction was quenched by addition of saturated aqueous sodium potassium tartrate (200 ml). The resulting biphasic mixture was stirred for 30 min at room temperature, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 200 ml). The combined organic phases were washed with H_2O (500 ml) and brine (500 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (5−20% Et_2O in pentane) afforded alcohol **294** (8.42 g, 95% yield) as a colorless oil.

R_f = 0.41 (hexane/EtOAc 3:1)

Optical Rotation: $[\alpha]^{21}_{D}$ (*c* 0.96, $CHCl_3$) = −24.1.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.67 (ddd, 1 H, *J* = 10.7, 6.0, 4.4 Hz), 3.57 (ddd, 1 H, *J* = 11.1, 5.7, 5.7 Hz), 3.42 (dd, 1 H, *J* = 5.0, 5.0 Hz), 1.90–1.82 (m, 2 H), 0.97 (d, 3 H, *J* = 7.1 Hz), 0.94 (d, 3 H, *J* = 7.2 Hz), 0.92 (s, 9 H), 0.91 (, 3 H, *J* = 5.7 Hz), 0.11 (s, 3 H), 0.08 (s, 3 H).

These spectral characteristics are identical to those previously reported.[212]



(2*R*,3*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-butyraldehyde oxime (296): To a solution of alcohol **294** (8.42 g, 38.6 mmol, 1.00 equiv) in CH_2Cl_2 (390 ml) was added 4 Å molecular sieves (19.3 g) and NMO (7.90 g, 67.5 mmol, 1.75 equiv). The resulting mixture was stirred for 30 min at room temperature and then cooled to 0 °C. TPAP (730 mg, 2.31 mmol, 6.00 mol %) was added in portions. The resulting mixture was stirred for 10 min at 0 °C, the ice-bath was removed, and the mixture was stirred for 2 h at ambient temperature. Pentane (250 ml) was added and everything filtered over silica gel. The filter cake was washed with 1:2 Et_2O/pentane (500 ml) and the combined organic phases were concentrated under reduced pressure to afford aldehyde **295**, which was used in the next step without further purification.

To a solution of unpurified aldehyde **295** in EtOH (114 ml) was added NEt_3 (11.4 ml) and $NH_2OH{\cdot}HCl$ (5.42 g, 78.0 mmol, 2.02 equiv). The resulting solution was stirred for 15 h at room temperature and then concentrated under reduced pressure. The residue was taken up in H_2O (100 ml) and EtOAc (100 ml), the layers were separated, and the aqueous phase was extracted with EtOAc (2 x 100 ml). The combined organic phases were washed with brine (200 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (5−20% Et_2O in pentane) afforded oxime **296** (7.60 g, 85% yield over two steps).

R_f = 0.51 (hexane/EtOAc 3:1)

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[212] H. J. Bestmann, B. Liepold, A. Kress, A. Hofmann, *Chem. Eur. J.* **1999**, *5*, 2984–2989.

Optical Rotation: $[\alpha]^{24}_{D}$ (*c* 0.97, $CHCl_3$) = −3.6.

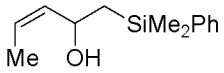
^{1}H NMR (300 MHz, $CDCl_3$, * denotes signal corresponding to the minor oxime diastereomer): δ 8.25* (br d, 1 H, *J* = 32.7 Hz), 8.02 (br d, 1 H, *J* = 32.7 Hz), 7.39 (d, 1 H, *J* = 7.5 Hz), 6.75* (d, 1 H, *J* = 7.8 Hz), 3.87−3.81* (m, 1 H), 3.84−3.76 (m, 1 H), 3.20−3.09* (m, 1 H), 2.41−2.31 (m, 1 H), 1.12 (d, 3 H, *J* = 6.3 Hz), 1.12* (d, 3 H, *J* = 6.3 Hz), 1.08 (d, 3 H, *J* = 6.9 Hz), 1.06* (d, 3 H, *J* = 6.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$, * denotes signal corresponding to the minor oxime diastereomer): δ 167.8*, 154.4, 71.0, 70.2*, 42.0, 37.0*, 25.8, 25.6*, 22.0*, 21.7, 18.0, 14.8, 14.2*, −4.3, −5.0.

IR (thin film): ν 3245, 3110, 2956, 2860, 1737, 1464, 1378, 1255, 1124, 1036 cm^{-1}.

HRMS (EI): calcd for $C_7H_{16}NO_2Si$ $[M-C_4H_9]^+$ 174.0945; found 174.0946.

Anal. calcd for $C_{11}H_{25}NO_2Si$: C 57.09%, H 10.89%, N 6.05%, O 13.83%; found: C 57.25%, H 10.60%, N 5.97%.



(*Z*)-1-(Dimethyl-phenyl-silanyl)-pent-3-en-2-ol (301a): To a solution of dimethylphenylvinylsilane (1.01 g, 6.22 mmol, 1.00 equiv) in THF (6.3 ml) was added a solution of 9-BBN dimer (1.55 g, 6.35 mmol, 1.02 equiv) in THF (13.3 ml) over 20 min. The resulting solution was stirred for 2 h at room temperature. H_2O (6.3 ml) and saturated aqueous NaOH (6.3 ml) was added, followed by slow addition of 30% aqueous H_2O_2 (6.9 ml) at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The layers were separated and the aqueous phase was extracted with EtOAc (3 x 30 ml). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (5–15% EtOAc in hexane) afforded 2-(dimethyl-phenyl-silanyl)-ethanol in quantitative yield.

A solution of $(COCl)_2$ (0.340 ml, 3.92 mmol, 1.41 equiv) in CH_2Cl_2 (15 ml) was cooled to −78 °C. A solution of DMSO (0.480 ml, 6.76 mmol, 2.43 equiv) in CH_2Cl_2 (0.52 ml) was added and the resulting solution was stirred for 45 min at −78 °C. A solution of 2-(dimethyl-phenyl-silanyl)-ethanol (501 mg, 2.78 mmol, 1.00 equiv) in CH_2Cl_2 (12.5 ml) was added and the resulting solution was stirred for 1 h at −78 °C. After the addition of NEt_3 (1.55 ml,

11.1 mmol, 3.99 equiv), the cooling bath was removed and the solution stirred for 1 h at ambient temperature. The solution was diluted with Et_2O (50 ml) and washed with 1 M aqueous HCl (2 x 30 ml) and H_2O (30 ml). The combined aqueous phases were extracted with Et_2O (3 x 100 ml). The combined organic phases were washed with H_2O (200 ml) and brine (200 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give aldehyde **303a**, which was used in the next step without further purification.

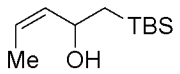
A solution of aldehyde **303a** in Et_2O (27.5 ml) was cooled to −78 °C. 1-Propynylmagnesium bromide (6.0 ml, 0.50 M, 3.0 mmol, 1.1 equiv) was added and the resulting solution was stirred for 1 h at −78 °C. The reaction was quenched by addition of H_2O (30 ml) and the resulting mixture was extracted with Et_2O (3 x 30 ml). The combined organic phases were washed with brine (100 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10−20% Et_2O in pentane) furnished propargylic alcohol **305a** (433 mg, 72% yield over three steps).

To a solution of propargylic alcohol **305a** (271 mg, 1.24 mmol, 1.00 equiv) in EtOAc (6 ml) was added *Lindlar*'s catalyst (61.2 mg). The *Schlenk* tube was partially evaporated and refilled with H_2 from a balloon. The reaction mixture was stirred for 9 h at room temperature under H_2 before it was filtered over celite and concentrated under reduced pressure. Purification by flash column chromatography (12% Et_2O in pentane) afforded allylic alcohol **301a** (247 mg, 90% yield).

$\mathbf{R}_f$ = 0.27 (hexane/EtOAc 4:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54−7.50 (m, 2 H), 7.36−7.34 (m, 3 H), 5.44−5.40 (m, 2 H), 4.68−4.59 (m, 1 H), 1.58 (d, 3 H, J = 5.1 Hz), 1.30−1.27 (m, 2 H), 0.33 (s, 3 H), 0.32 (s, 3 H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 138.9, 135.3, 133.5, 128.8, 127.7, 124.9, 65.0, 26.1, 13.2, −2.0, −2.2.



(*Z*)-1-(*tert*-Butyl-dimethyl-silanyl)-pent-3-en-2-ol (301b): A solution of ^{i}PrNH$_2$ (0.290 ml, 2.21 mmol, 1.09 equiv) in THF (2.0 ml) was cooled to 0 °C. ^{n}BuLi (1.3 ml, 1.6 M, 2.0 mmol, 1.0 equiv) was added and the solution was stirred for 30 min at 0 °C. After the

addition of *tert*-butyl-ethylidene-amine[134] (204 mg, 2.06 mmol, 1.02 equiv), the reaction mixture was stirred for 30 min at 0 °C, for 5 min at room temperature, and then cooled to 0 °C. A solution of TBSCl (304 mg, 2.02 mmol, 1.00 equiv) in THF (1.0 ml) was added, followed by Bu_4NI (37.2 mg, 0.100 mmol, 5.00 mol %). The resulting yellow mixture was stirred for 15 min at 0 °C and for 4 h at room temperature. After dilution with Et_2O (10 ml) and H_2O (10 ml), the layers were separated and the aqueous phase was extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with brine (25 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (0–4% EtOAc in hexane) afforded aldehyde **303b** (167 mg, 51% yield), which was immediately used in the next step.

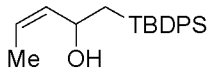
A solution of aldehyde **303b** (1.52 g, 9.60 mmol, 1.00 equiv) in Et_2O (100 ml) was cooled to −78 °C. 1-Propynylmagnesium bromide (20.5 ml, 0.50 M, 10 mmol, 1.1 equiv) was added and the resulting solution was stirred for 30 min at −78 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl (50 ml), and the resulting mixture was extracted with Et_2O (3 x 50 ml). The combined organic phases were washed with H_2O (200 ml) and brine (200 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10−20% Et_2O in pentane) furnished propargylic alcohol **305b** (1.02 g, 54% yield).

To a solution of propargylic alcohol **305b** (1.02 g, 4.15 mmol, 1.00 equiv) in EtOAc (22 ml) was added *Lindlar*'s catalyst (221 mg). The *Schlenk* tube was partially evaporated and refilled with H_2 from a balloon. The reaction mixture was stirred for 3 h at room temperature under H_2 before it was filtered over celite and concentrated under reduced pressure. Purification by flash column chromatography (5−10% Et_2O in pentane) afforded allylic alcohol **301b** (474 mg, 57% yield).

$\mathbf{R_f}$ = 0.48 (hexane/EtOAc 3:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.52−5.39 (m, 2 H), 4.70−4.62 (m, 1 H), 1.70 (d, 3 H, J = 5.4 Hz), 1.37−1.26 (m, 2 H), 1.10−0.98 (m, 1 H), 0.87 (s, 9 H), −0.01 (s, 3 H), −0.02 (s, 3 H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 135.6, 124.8, 65.2, 26.5, 22.4, 16.5, 14.3, 13.4, −5.4.



(*Z*)-1-(*tert*-Butyl-diphenyl-silanyl)-pent-3-en-2-ol (301c): A solution of $^{i}PrNH_2$ (2.90 ml, 22.1 mmol, 1.03 equiv) in THF (20 ml) was cooled to 0 °C. $^{n}BuLi$ (14 ml, 1.6 M, 22 mmol, 1.1 equiv) was added and the solution was stirred for 30 min at 0 °C. After the addition of *tert*-butyl-ethylidene-amine[134] (2.01 g, 20.3 mmol, 1.00 equiv), the reaction mixture was stirred for 30 min at 0 °C. A solution of TBDPSCl (5.80 ml, 22.3 mmol, 1.10 equiv) in THF (10.0 ml) was added, followed by Bu_4NI (374 mg, 1.01 mmol, 5.00 mol %). The resulting yellow mixture was stirred for 2.5 h at room temperature. After dilution with Et_2O (50 ml) and H_2O (50 ml), the layers were separated and the aqueous phase was extracted with Et_2O (3 x 50 ml). The combined organic phases were washed with brine (100 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (0–10% Et_2O in pentane) afforded aldehyde **303c** (5.01 g, 88% yield), which was immediately used in the next step.

A solution of aldehyde **303c** (5.01 g, 17.9 mmol, 1.00 equiv) in Et_2O (180 ml) was cooled to −78 °C. 1-Propynylmagnesium bromide (35.5 ml, 0.50 M, 18 mmol, 1.0 equiv) was added and the resulting solution was stirred for 45 min at −78 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl (100 ml) and the resulting mixture was extracted with Et_2O (3 x 100 ml). The combined organic phases were washed with H_2O (200 ml) and brine (200 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10−20% Et_2O in pentane) furnished propargylic alcohol **305c** (4.33 g, 75% yield).

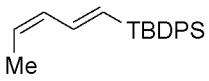
To a solution of propargylic alcohol **305c** (4.33 g, 13.4 mmol, 1.00 equiv) in EtOAc (33 ml) was added *Lindlar*'s catalyst (330 mg). The *Schlenk* tube was partially evaporated and refilled with H_2 from a balloon. The reaction mixture was stirred for 4 h at room temperature under H_2, before it was filtered over celite and concentrated under reduced pressure. Purification by flash column chromatography (5−10% Et_2O in pentane) afforded allylic alcohol **301b** (2.69 g, 62% yield).

$\mathbf{R}_f$ = 0.34 (hexane/EtOAc 3:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.62 (m, 4 H), 7.41–7.34 (m, 6 H), 5.41–5.19 (m, 2 H), 4.66–4.57 (m, 1 H), 1.68 (dd, 1 H, J = 15.0, 7.5 Hz), 1.54–1.43 (m, 2 H), 1.34 (dd, 3 H, J = 6.9, 0.9 Hz), 1.04 (s, 9 H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 136.0, 135.1, 134.3, 134.1, 129.1, 129.0, 127.6, 127.4, 124.4, 64.8, 27.8, 20.4, 18.2, 13.1.

IR (thin film): ν 3569, 3368, 3072, 3048, 3014, 2997, 2960, 2930, 2890, 2857, 2361, 1957, 1886, 1824, 1654, 1589, 1488, 1471, 1446, 1427, 1391, 1362, 1256, 1191, 1106, 1031 cm^{-1}.



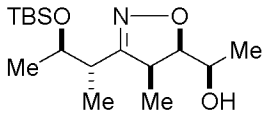
***tert*-Butyl-diphenyl-(penta-1,3-dienyl)silane (310)**: A solution of oxime **296** (81.2 mg, 0.340 mmol, 1.00 equiv) in CH_2Cl_2 (3.5 ml) was cooled to –78 °C. ^{t}BuOCl (37.2 mg, 0.340 mmol, 1.00 equiv) was added dropwise over 15 min. The resulting deep blue solution was stirred for 2 h at –78 °C and then used directly in the next step.

A solution of allylic alcohol **301c** (319 mg, 0.890 mmol, 2.60 equiv) in CH_2Cl_2 (7.0 ml) was cooled to 0 °C. ^{i}PrOH (54 µl, 0.71 mmol, 2.1 equiv) was added, followed by dropwise addition of EtMgBr (0.34 ml, 3.0 M in Et_2O, 1.0 mmol, 3.0 equiv). After stirring for 30 min at 0 °C, the deep blue solution from above was added via cannula over 15 min. The reaction was then stirred for 19 h and allowed to warm to room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (10 ml) and EtOAc (10 ml). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 ml). The combined organic phases were washed with H_2O (20 ml) and brine (20 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (0–8% Et_2O in pentane) provided diene **310** (147 mg, 54% yield).

R_f = 0.90 (hexane/EtOAc 3:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64–7.61 (m, 4 H), 7.43–7.33 (m, 2 H), 6.52 (dd, 1 H, J = 15.3, 9.9 Hz), 6.26 (ddd, 1 H, J = 15.3, 10.2, 1.8 Hz), 6.20 (d, 1 H, J = 18.6 Hz), 5.77–5.65 (m, 1 H), 1.79 (dd, 3 H, J = 6.6, 1.2 Hz), 1.10 (s, 9 H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 149.2, 136.1, 134.7, 134.7, 131.3, 128.9, 127.4, 123.6, 27.8, 18.4, 18.2.



(*R*)-1-{(4*S*,5*R*)-3-[(1*S*,2*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-methyl-propyl]-4-methyl-4,5-dihydro-isoxazol-5-yl}-ethanol (311): A solution of oxime **296** (1.17 g, 5.06 mmol, 1.00 equiv) in CH_2Cl_2 (50 ml) was cooled to –78 °C. ^{t}BuOCl (544 mg, 5.01 mmol, 0.990 equiv) was added dropwise over 15 min. The resulting deep blue solution was stirred for 2 h at –78 °C and then used directly in the next step.

A solution of allylic alcohol *ent*-**147** (565 mg, 6.56 mmol, 1.30 equiv) in CH_2Cl_2 (100 ml) was cooled to 0 °C. ^{i}PrOH (1.30 ml, 17.0 mmol, 3.36 equiv) was added, followed by dropwise addition of EtMgBr (5.0 ml, 3.0 M in Et_2O, 15 mmol, 3.0 equiv). After stirring for 40 min at 0 °C, the deep blue solution from above was added via cannula over 3 h. The reaction was then stirred for 23 h and allowed to warm to room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (300 ml) and EtOAc (300 ml). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 300 ml). The combined organic phases were washed with H_2O (300 ml) and brine (300 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10–20% EtOAc in hexane) provided isoxazoline **311** (952 mg, 60% yield) as a 95:5 mixture of diastereomers.

R_f = 0.37 (hexane/EtOAc 2:1)

Optical Rotation: $[\alpha]^{24}_D$ (*c* 1.01, $CHCl_3$) = –8.5.

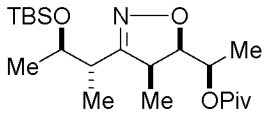
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.13–3.96 (m, 3 H), 3.31–3.21 (m, 1 H), 2.67–2.59 (m, 1 H), 2.09 (br t, 1 H, *J* = 5.4 Hz), 1.26 (d, 3 H, *J* = 6.0 Hz), 1.19–1.14 (m, 9 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 86.4, 70.0, 66.0, 44.7, 40.2, 25.9, 21.1, 20.1, 18.1, 14.8, 11.2, –4.3, –4.6.

IR (thin film): ν 3419, 2955, 2889, 1463, 1378, 1254, 1102, 1029 cm^{-1}.

HRMS (ESI): calcd for $C_{16}H_{33}NO_3SiNa$ $[M+Na]^+$ 338.2122; found 338.2122.

Anal. calcd for $C_{16}H_{33}NO_3Si$: C 60.91%, H 10.54%, N 4.44%, O 15.21%; found: C 60.65%, H 10.35%, N 4.51%.



2,2-Dimethyl propionic acid (*R*)-1-{(4*S*,5*R*)-3-[(1*S*,2*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-propyl]-4-methyl-4,5-dihydro-isoxazol-5-yl}-ethyl ester (313): To a solution of alcohol **311** (237 mg, 0.750 mmol, 1.00 equiv) in pyridine (3.7 ml) was added PivCl (0.280 ml, 2.27 mmol, 3.00 equiv). The resulting clear solution was stirred for 14.5 h at room temperature. After the addition of MeOH (4 ml), the solution was stirred for 30 min and then diluted with EtOAc (50 ml) and saturated aqueous NH_4Cl (50 ml). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 50 ml). The combined organic phases were washed with brine (100 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (4−20% EtOAc in hexane) provided ester **313** (265 mg, 89% yield).

R_f = 0.73 (hexane/EtOAc 2:1)

Optical Rotation: $[\alpha]^{21}_D$ (*c* 0.95, $CHCl_3$) = −26.9.

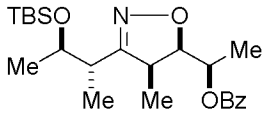
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.16−5.08 (m, 1 H), 4.28 (dd, 1 H, *J* = 9.0, 6.9 Hz), 4.10 (dq, 1 H, *J* = 6.0, 3.3 Hz), 3.31−3.21 (m, 1 H), 2.64 (dq, 1 H, *J* = 7.2, 3.3 Hz), 1.28 (d, 3 H, *J* = 6.3 Hz), 1.20 (s, 9 H), 1.18 (d, 3 H, *J* = 7.2 Hz), 1.16 (d, 3 H, *J* = 6.3 Hz), 1.10 (d, 3 H, *J* = 7.2 Hz), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1, 84.3, 69.9, 68.4, 44.6, 40.0, 38.8, 27.2, 25.9, 25.7, 20.9, 18.1, 17.5, 14.5, 11.0, −4.3, −4.7.

IR (thin film): ν 2960, 2935, 2884, 2863, 1729, 1465, 1377, 1283, 1256, 1161, 1099, 1028 cm^{-1}.

HRMS (MALDI): calcd for $C_{21}H_{41}NO_4SiNa$ $[M+Na]^+$ 422.2697; found 422.2700.

Anal. calcd for $C_{21}H_{41}NO_4Si$: C 63.11%, H 10.34%, N 3.50%, O 16.01%; found: C 62.88%, H 10.12%, N 3.65%.



Benzoic acid (*R*)-1-{(4*S*,5*R*)-3-[(1*S*,2*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-propyl]-4-methyl-4,5-dihydro-isoxazol-5-yl}-ethyl ester (314): A solution of alcohol **311** (206 mg, 0.550 mmol, 1.00 equiv) in CH_2Cl_2 (6.0 ml) was cooled to 0 °C. NEt_3 (0.180 ml, 1.29 mmol, 2.35 equiv), BzCl (0.150 ml, 1.29 mmol, 2.35 equiv), and DMAP (15.5 mg, 0.130 mmol, 0.230 equiv) was added. The cooling bath was removed and the solution was stirred for 15 h at room temperature. Et_2O (20 ml) and saturated aqueous $NaHCO_3$ (20 ml) was added, the layers were separated, and the aqueous phase was extracted with Et_2O (2 x 20 ml). The combined organic phases were washed with brine (50 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (4–20% EtOAc in hexane) provided ester **314** (240 mg, 88% yield).

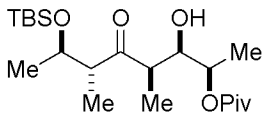
$\mathbf{R}_f$ = 0.65 (hexane/EtOAc 2:1)

Optical Rotation: $[\alpha]^{20}_D$ (*c* 0.98, $CHCl_3$) = −78.0.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09–8.04 (m, 2 H), 7.58–7.52 (m, 1 H), 7.45–7.39 (m, 2 H), 5.37 (p, 1 H, *J* = 3.3 Hz), 4.44 (dd, 1 H, *J* = 9.3, 6.0 Hz), 3.41–3.31 (m, 1 H), 2.66 (dq, 1 H, *J* = 7.2, 3.6 Hz), 1.45 (d, 3 H, *J* = 6.6 Hz) 1.17 (d, 3 H, *J* = 6.0 Hz), 1.15 (d, 6 H, *J* = 7.2 Hz), 0.87 (s, 9 H), 0.05 (s, 3 H), 0.01 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 164.9, 132.9, 130.5, 130.1, 129.7, 128.8, 128.2, 84.2, 70.1, 69.3, 44.9, 40.1, 25.9, 21.1, 18.0, 17.7, 14.7, 11.1, −4.4, −4.7.

IR (thin film): ν 2935, 2886, 2859, 1790, 1721, 1603, 1457, 1379, 1272, 1213, 1175, 1110, 1027 cm^{-1}.



2,2-Dimethyl propionic acid (1*R*,2*R*,3*R*,5*R*,6*R*)-6-(*tert*-butyl-dimethyl-silanyloxy)-2-hydroxy-1,3,5-trimethyl-4-oxo-hepthyl ester (315): To a solution of isoxazoline **313** (106 mg, 0.270 mmol, 1.00 equiv) in MeOH (8.5 ml) was added H_2O (1.7 ml), $B(OH)_3$ (252 mg, 4.08 mmol, 15.1 equiv), and Raney-Nickel (1 spatula, so the mixture stayed black

upon stirring). The *Schlenk* tube was partially evaporated and refilled with H_2 from a balloon. The mixture was stirred vigorously under an H_2 atmosphere for 60 min at room temperature. The mixture was filtered over celite, the filter pad was washed with EtOAc (30 ml), silica gel was added to the filtrate, and the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (4–8% EtOAc in hexane) to give *β*-hydroxy ketone **315** (41.1 mg, 38% yield).

R_f = 0.70 (hexane/EtOAc 2:1)

Optical Rotation: $[\alpha]^{24}_{D}$ (*c* 0.48, $CHCl_3$) = −7.7.

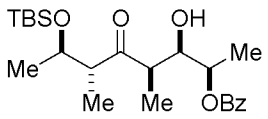
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.90–4.82 (m, 1 H), 4.04–3.91 (m, 2 H), 2.86–2.74 (m, 1 H), 2.71–2.62 (m, 1 H), 2.46 (d, 1 H, *J* = 5.4 Hz), 1.20 (d, 3 H, *J* = 6.9 Hz), 1.20 (s, 9 H), 1.15 (d, 3 H, *J* = 7.2 Hz), 1.13 (d, 3 H, *J* = 6.0 Hz), 0.95 (d, 3 H, *J* = 7.2 Hz), 0.83 (s, 9 H), 0.05 (s, 3 H), −0.04 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 215.3, 177.7, 73.6, 71.8, 70.7, 52.2, 48.9, 38.9, 27.2, 25.9, 21.4, 18.0, 16.7, 13.9, 9.4, −4.5, −4.6.

IR (thin film): ν 3444, 2962, 1723, 1463, 1376, 1285, 1163, 1058, 1011 cm^{-1}.

HRMS (ESI): calcd for $C_{21}H_{42}O_5SiNa$ $[M+Na]^+$ 425.2694; found 425.2692.

Anal. calcd for $C_{21}H_{42}O_5Si$: C 62.64%, H 10.51%, O 19.87%; found: C 62.35%, H 10.42%.



Benzoic acid (1*R*,2*R*,3*R*,5*R*,6*R*)-6-(*tert*-butyl-dimethyl-silanyloxy)-2-hydroxy-1,3,5-trimethyl-4-oxo-heptyl ester (316): To a solution of isoxazoline **314** (102 mg, 0.240 mmol, 1.00 equiv) in MeOH (8.0 ml) was added H_2O (1.6 ml), $B(OH)_3$ (240 mg, 3.88 mmol, 16.2 equiv), and Raney-Nickel (1 spatula, so the mixture stayed black upon stirring). The *Schlenk* tube was partially evacuated and refilled with H_2 from a balloon. The mixture was stirred vigorously under an H_2 atmosphere for 30 min at room temperature and then filtered over celite. The filter pad was washed with CH_2Cl_2 (30 ml), silica gel was added to the filtrate, and the mixture was concentrated under reduced pressure. The residue was purified by

flash column chromatography (8–10% EtOAc in hexane) to give β-hydroxy ketone **316** (15.5 mg, 15% yield).

R_f = 0.61 (hexane/EtOAc 2:1)

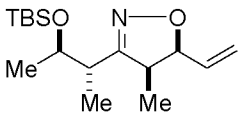
Optical Rotation: $[\alpha]^{24}_{D}$ (*c* 0.36, $CHCl_3$) = +1.2.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12–8.08 (m, 2 H), 7.61–7.55 (m, 1 H), 7.48–7.43 (m, 2 H), 5.35–5.28 (m, 1 H), 4.13–4.05 (m, 1 H), 3.76–3.71 (m, 1 H), 3.65–3.59 (m, 1 H), 3.02–2.89 (m, 2 H), 1.44 (d, 3 H, *J* = 6.3 Hz), 1.14 (d, 3 H, *J* = 6.3 Hz), 1.06 (d, 3 H, *J* = 7.2 Hz), 0.98 (d, 3 H, *J* = 6.9 Hz), 0.86 (s, 9 H), 0.07 (s, 3 H), 0.01 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 217.7, 165.8, 132.9, 130.1, 129.6, 128.3, 75.7, 71.1, 70.5, 53.9, 49.7, 25.9, 20.9, 18.1, 16.6, 13.2, 12.9, −4.6, −4.6.

IR (thin film): ν 3415, 2934, 2886, 2860, 1711, 1604, 1457, 1377, 1269, 1109, 1024 cm^{-1}.

HRMS (MALDI): calcd for $C_{23}H_{38}O_5SiNa$ $[M+Na]^+$ 445.2381; found 445.2376.



(4*S*,5*S*)-3-[(1*S*,2*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-methyl-propyl]-4-methyl-5-vinyl-4,5-dihydro-isoxazole (317): A solution of *Martin* sulfurane (117 mg, 0.170 mmol, 1.06 equiv) in toluene (2.50 ml) was cooled to 0 °C. A solution of alcohol **311** (50.5 mg, 0.160 mmol, 1.00 equiv) in toluene (0.60 ml) was added. The cooling bath was removed and the solution was stirred for 1 h at room temperature. CH_2Cl_2 (10 ml) and H_2O (10 ml) was added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 ml). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (0–2% EtOAc in hexane) provided olefin **317** (22.9 mg, 48% yield).

R_f = 0.40 (hexane/EtOAc 4:1)

Optical Rotation: $[\alpha]^{25}_{D}$ (*c* 1.02, $CHCl_3$) = +34.7.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.95–5.84 (m, 1 H), 5.43–5.31 (m, 2 H), 4.78 (dd, 1 H, *J* = 8.7, 7.8 Hz), 4.12–4.40 (m, 1 H), 3.31–3.20 (m, 1 H), 2.65 (dq, 1 H, *J* = 7.2, 4.2 Hz), 1.18 (d,

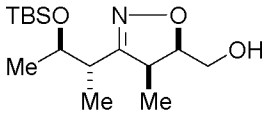
3 H, *J* = 7.8 Hz), 1.16 (d, 3 H, *J* = 6.3 Hz), 1.06 (d, 3 H, *J* = 7.5 Hz), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 132.2, 119.7, 84.8, 70.2, 46.7, 40.3, 38.1, 36.4, 25.8, 21.1, 18.0, 15.1, 12.6, −4.4, −4.8.

IR (thin film): ν 2956, 2935, 2889, 2860, 2361, 1463, 1379, 1255, 1189, 1107, 1029 cm^{-1}.

HRMS (ESI): calcd for $C_{16}H_{31}NO_2SiNa$ $[M+Na]^+$ 320.2016; found 320.2020.

Anal. calcd for $C_{16}H_{31}NO_2Si$: C 64.59%, H 10.50%, N 4.71%, O 10.76%; found: C 64.55%, H 10.21%, N 4.60%.



{(4*S*,5*R*)-3-[(1*S*,2*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-methyl-propyl]-4-methyl-4,5-dihydro-isoxazol-5-yl}-methanol (307): A solution of olefin **317** (238 mg, 0.800 mmol, 1.00 equiv) in MeOH (7.5 ml) was flushed with O_2 and cooled to −78 °C. The solution was flushed with O_3 until a blue color persisted (8 min), then with O_2 and N_2 to remove excess O_3. $NaBH_4$ (120 mg, 3.17 mmol, 3.96 equiv) was added, the cooling bath was removed, and the mixture was stirred for 80 min at room temperature. H_2O (0.6 ml) and 2 M aqueous NaOH (0.2 ml) was added and the resulting mixture was stirred for 20 min at room temperature. EtOAc (20 ml) and H_2O (20 ml) was added, the layers were separated, and the aqueous phase was extracted with EtOAc (3 x 20 ml). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10−20% EtOAc in hexane) provided alcohol **307** (204 mg, 85% yield).

R_f = 0.40 (hexane/EtOAc 1:1)

Optical Rotation: $[\alpha]^{20}_D$ (*c* 0.97, $CHCl_3$) = −31.5.

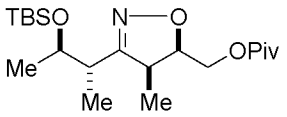
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.49 (p, 1 H, *J* = 5.1 Hz), 4.12−4.05 (m, 1 H), 3.78 (br t, 2 H, *J* = 5.1 Hz), 3.44−3.33 (m, 1 H), 2.66−2.58 (m, 1 H), 1.95 (br t, 1 H, *J* = 5.1 Hz), 1.17 (d, 3 H, *J* = 7.5 Hz), 1.16 (d, 3 H, *J* = 7.5 Hz), 1.15 (d, 3 H, *J* = 6.3 Hz), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.9, 82.3, 69.9, 61.0, 45.0, 40.1, 25.9, 21.0, 18.1, 14.6, 11.1, −4.3, −4.6.

IR (thin film): ν 3401, 2933, 2887, 2859, 1741, 1615, 1463, 1378, 1253, 1100, 1026 cm^{-1}.

HRMS (ESI): calcd for $C_{15}H_{31}NO_3SiNa$ $[M+Na]^+$ 324.1965; found 324.1968.

Anal. calcd for $C_{15}H_{31}NO_3Si$: C 59.76%, H 10.36%, N 4.65%, O 15.92%; found: C 59.72%, H 10.43%, N 4.59%.



2,2-Dimethyl-propionic acid (4*S*,5*R*)-3-[(1*S*,2*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-propyl]-4-methyl-4,5-dihydro-isoxazol-5-ylmethyl ester (319): To a solution of alcohol **307** (123 mg, 0.410 mmol, 1.00 equiv) in pyridine (1.60 ml) was added PivCl (0.10 ml, 0.81 mmol, 2.0 equiv). The solution was stirred for 9 h at room temperature. EtOAc (10 ml) and H_2O (10 ml) was added, the layers were separated, and the aqueous phase was extracted with EtOAc (3 x 10 ml). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc in hexane) provided pivaloate **319** (137 mg, 87% yield).

$\mathbf{R}_f$ = 0.86 (hexane/EtOAc 1:1)

Optical Rotation: $[\alpha]^{21}_D$ (*c* 1.12, $CHCl_3$) = −23.7.

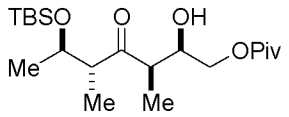
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.58−4.51 (m, 1 H), 4.33 (dd, 1 H, *J* = 11.7, 5.4 Hz), 4.22 (dd, 1 H, *J* = 11.7, 6.6 Hz), 4.13−4.04 (m, 1 H), 3.43−3.32 (m, 1 H), 2.65 (dq, 1 H, *J* = 7.5, 6.9 Hz), 1.21 (s, 9 H), 1.18 (d, 3 H, *J* = 7.2 Hz), 1.15 (d, 3 H, *J* = 6.3 Hz), 1.13 (d, 3 H, *J* = 7.5 Hz), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 178.0, 164.9, 79.8, 70.1, 62.0, 45.1, 40.1, 38.8, 27.2, 25.9, 21.3, 18.1, 15.1, 11.3, −4.3, −4.6.

IR (thin film): ν 2960, 2934, 2886, 2862, 1733, 1464, 1376, 1281, 1255, 1150, 1101, 1028 cm^{-1}.

HRMS (MALDI): calcd for $C_{20}H_{40}NO_4Si$ $[M+H]^+$ 386.2721; found 386.2711.

Anal. calcd for $C_{20}H_{39}NO_4Si$: C 62.29%, H 10.19%, N 3.63%, O 16.60%; found: C 62.30%, H 10.06%, N 3.75%.



2,2-Dimethyl-propionic acid (2*R*,3*R*,5*R*,6*R*)-6-(*tert*-butyl-dimethyl-silanyloxy)-2-hydroxy-3,5-dimethyl-4-oxo-heptyl ester (320): To a solution of isoxazoline **319** (293 mg, 0.760 mmol, 1.00 equiv) in MeOH (25 ml) was added H_2O (5.0 ml), $B(OH)_3$ (761 mg, 12.1 mmol, 16.2 equiv), and Raney-Nickel (1 spatula, so the mixture stayed black upon stirring). The *Schlenk* tube was partially evacuated and refilled with H_2 from a balloon. The mixture was stirred vigorously under an H_2 atmosphere for 20 min at room temperature. The mixture was filtered over celite, the filter pad was washed with CH_2Cl_2 (100 ml), silica gel was added to the filtrate, and the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc in hexane) to give β-hydroxy ketone **320** (208 mg, 70% yield) as a white solid.

R_f = 0.47 (hexane/EtOAc 3:1)

MP: 60–65 °C

Optical Rotation: $[\alpha]^{21}_D$ (*c* 0.81, $CHCl_3$) = −19.3.

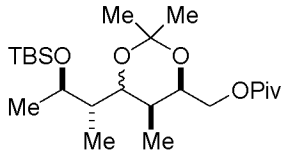
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22−4.15 (m, 1 H), 4.12−3.98 (m, 3 H), 2.90 (br d, 1 H, *J* = 3.3 Hz), 2.84−2.68 (m, 2 H), 1.21 (s, 9 H), 1,17 (d, 3 H, *J* = 7.2 Hz), 1.14 (d, 3 H, *J* = 6.0 Hz), 0.98 (d, 3 H, *J* = 7.2 Hz), 0.84 (s, 9 H), 0.06 (s, 3 H), −0.02 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 216.5, 178.6, 70.2, 69.4, 65.9, 52.7, 48.1, 38.8, 27.2, 25.8, 21.2, 17.9, 13.8, 9.3, −4.7, −4.8.

IR (thin film): ν 3419, 2962, 2932, 2882, 2858, 1735, 1700, 1472, 1379, 1362, 1279, 1257, 1146, 1104, 1063, 1023 cm^{-1}.

HRMS (MALDI): calcd for $C_{20}H_{40}O_5SiNa$ $[M+Na]^+$ 411.2537; found 411.2538.

Anal. calcd for $C_{20}H_{40}O_5Si$: C 61.81%, H 10.37%, O 20.58%; found: C 61.87%, H 10.29%.



2,2-Dimethyl-propionic acid (4*R*,5*S*)-6-[(1*S*,2*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-propyl]-2,2,5-trimethyl-[1,3]dioxan-4-ylmethyl ester (322): A solution of $Me_4NBH(OAc)_3$ (113 mg, 430 µmol, 5.00 equiv) in 1:1 MeCN/AcOH (1.80 ml) was stirred for 20 min at room temperature. This solution was added dropwise to a solution of *β*-hydroxy ketone **320** (33.4 mg, 85.9 µmol, 1.00 equiv) in MeCN (0.20 ml) at −20 °C. The resulting mixture was stirred for 27 h at −20 °C, for 22 h at 0 °C, and for 29 h at room temperature (TLC did not show any progress). The reaction was quenched by addition of saturated aqueous sodium potassium tartrate (10 ml) and the mixture was stirred for 1 h at room temperature. The mixture was extracted with EtOAc (3 x 20 ml) and the combined organic phases were washed with brine (50 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (5−10% EtOAc in hexane) afforded diol **321** (16.6 mg, 49% yield) as a 2:1 mixture of diastereomers, which was immediately used in the next step.

To a solution of diol **321** (16.6 mg, 42.5 µmol, 1.00 equiv) in $Me_2C(OMe)_2$ (0.30 ml) was added $TsOH{\cdot}H_2O$ (6.2 mg, 32.6 µmol, 0.77 equiv). The resulting mixture was stirred for 90 min at room temperature. NEt_3 (0.05 ml) was added and the mixture was concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (20 ml) and filtered over a plaque of silica gel to provide a 2:1 diastereomeric mixture of acetonide **322** (12.7 mg, 69% yield).

$\mathbf{R}_f$ = 0.87 (hexane/EtOAc 3:1)

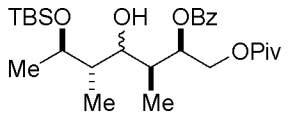
^{1}H NMR (300 MHz, $CDCl_3$,* denotes signal corresponding to the minor diastereomer): δ 4.18−3.94 (m, 4 H), 3.73 (p, 1 H, *J* = 6.3 Hz), 3.54* (dd, 1 H, *J* = 10.5, 2.1 Hz), 3.50 (dd, 1 H, *J* = 8.1, 1.5 Hz), 1.86−1.74 (m, 1 H), 1.37* (s, 3 H), 1.33 (s, 3 H), 1.29 (s, 3 H), 1.20 (s, 9 H), 1.10 (d, 3 H, *J* = 6.3 Hz), 0.97* (d, 3 H, *J* = 6.3 Hz), 0.88 (s, 9 H), 0.85 (d, 3 H, *J* = 7.2 Hz), 0.84 (d, 3 H, *J* = 6.6 Hz), 0.74* (d, 3 H, *J* = 6.9 Hz), 0.06 (s, 3 H), 0.04 (s, 3 H), 0.03* (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$,* denotes signal corresponding to the minor diastereomer): δ 178.4, 100.4, 98.7*, 74.3*, 73.7, 71.6*. 70.3, 67.6, 67.4*, 65.1*, 63.9, 44.6, 40.1*, 38.7,

35.9*, 30.8*, 29.7, 27.2, 25.9, 24.9, 24.0, 20.9, 19.3*, 18.1*, 17.2*, 11.5, 8.8, 7.9*, 4.8*, −3.5, −4.6*, −4.8.

IR (thin film): ν 2962, 2934, 2896, 2862, 1734, 1464, 1379, 1282, 1252, 1225, 1151, 1098, 1074, 1022 cm^{-1}.

HRMS (ESI): calcd for $C_{23}H_{46}O_5SiNa$ $[M+Na]^+$ 453.3007; found 543.3009.



Benzoic acid (1*R*,2*S*,4*S*,5*R*)-5-(*tert*-butyl-dimethyl-silanyloxy)-1-(2,2-dimethyl-propionyloxymethyl)-3-hydroxy-2,4-dimethyl-hexyl ester (330): A solution of *β*-hydroxy ketone **320** (52.3 mg, 135 μmol, 1.00 equiv) in degassed THF (0.40 ml) was cooled to −10 °C. PhCHO (66.0 μl, 649 μmol, 4.81 equiv) was added, followed by addition of SmI_2 (1.30 ml, 0.10 M in degassed THF, 0.13 mmol, 0.96 equiv) upon which the mixture turned yellow and then greenish-brown. The resulting suspension was stirred for 22.5 h at −10 °C. Et_2O (10 ml) and saturated aqueous $NaHCO_3$ (10 ml) was added, the layers were separated, and the aqueous phase was extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with brine (10 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (2−5% EtOAc in hexane) afforded two diastereomers of benzoate **330** (major: 18.0 mg, 27% yield; minor: 3.6 mg, 5% yield) along with some unreacted starting material (19.1 mg, 37%).

Major diastereomer:

R_f = 0.61 (hexane/EtOAc 3:1)

Optical Rotation: $[\alpha]^{24}_D$ (*c* 0.52, $CHCl_3$) = −10.4.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05−8.02 (m, 2 H), 7.59−7.54 (m, 1 H), 7.46−7.41 (m, 2 H), 5.87−5.82 (m, 1 H), 4.46 (dd, 1 H, *J* = 11.7, 8.7 Hz), 4.25 (dd, 1 H, *J* = 11.4, 3.9 Hz), 3.89 (t, 1 H, *J* = 6.0 Hz), 3.78 (br d, 1 H, *J* = 9.9 Hz), 3.56 (d, 1 H, *J* = 2.1 Hz), 1.94−1.83 (m, 1 H), 1.53−1.45 (m, 1 H), 1.18 (d, 3 H, *J* = 6.3 Hz), 1.10 (s, 9 H), 0.94−0.87 (m, 6 H), 0.76 (s, 9 H), 0.03 (s, 3 H), −0.01 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 166.5, 133.0, 129.7, 128.3, 72.5, 71.8, 69.8, 65.0, 40.4, 38.7, 37.9, 27.0, 25.7, 22.1, 17.8, 10.3, 10.0, −4.2, −5.2.

IR (thin film): ν 3499, 2962, 2934, 2888, 2862, 1726, 1602, 1460, 1378, 1272, 1154, 1109, 1072, 1028, 1001 cm^{-1}.

HRMS (ESI): calcd for $C_{27}H_{46}O_6SiNa$ $[M+Na]^+$ 517.2956; found 517.2952.

Minor diastereomer:

R_f = 0.46 (hexane/EtOAc 3:1)

Optical Rotation: $[\alpha]^{23}_D$ (*c* 0.19, $CHCl_3$) = −21.9.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05−8.02 (m, 2 H), 7.61−7.54 (m, 1 H), 7.48−7.43 (m, 2 H), 5.36−5.30 (m, 1 H), 4.37−4.25 (m, 2 H), 3.99 (dq, 1 H, *J* = 6.6, 3.3 Hz), 3.89 (br d, 1 H, *J* = 8.1 Hz), 3.68 (d, 1 H, *J* = 1.2 Hz), 2.17−2.08 (m, 1 H), 1.79−1.70 (m, 1 H), 1.26 (d, 3 H, *J* = 6.3 Hz), 1.16 (d, 3 H, *J* = 6.9 Hz), 1.11 (d, 3 H, *J* = 7.5 Hz), 1.04 (s, 9 H), 0.89 (s, 9 H), 0.09 (s, 3 H).

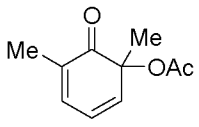
^{13}C NMR (75 MHz, $CDCl_3$): δ 178.3, 166.0, 133.1, 130.0, 129.6, 128.4, 73.5, 73.0, 71.4, 62.7, 40.4, 38.7, 38.2, 27.0, 25.8, 21.2, 17.9, 11.4, 10.8, −4.4, −5.1.

IR (thin film): ν 3488, 2962, 2935, 2888, 2862, 1725, 1602, 1459, 1373, 1267, 1152, 1104, 1029 cm^{-1}.

HRMS (ESI): calcd for $C_{27}H_{46}O_6SiNa$ $[M+Na]^+$ 517.2956; found 517.2962.

6.3 Experimental Procedures: Fusidilactone C

6.3.1 Preliminary Studies I



Acetic acid 1,5-dimethyl-6-oxo-cyclohexa-2,4-dienyl ester (396): To a solution of $Pb(OAc)_4$ (10.3 g, 23.2 mmol, 1.15 equiv) in CH_2Cl_2 (190 ml) was added a solution of 2,6-dimethylphenol (2.46, 20.1 mmol, 1.00 equiv) in CH_2Cl_2 (20 ml). The mixture was stirred for

2 h at room temperature before the addition of ethane-1,2-diol (1 ml), filtration, and concentration under reduced pressure. The residue was taken up in toluene (70 ml), washed with water (50 ml), saturated aqueous sodium bicarbonate solution (50 ml), and brine (50 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (3% EtOAc in hexane) gave cyclohexadienone **396** (2.27 g, 63% yield) as a yellow oil.

$\mathbf{R}_f$ = 0.48 (hexane/EtOAc 2:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.79–6.75 (m, 1 H), 6.16 (dd, 1 H, J = 9.6, 2.7 Hz), 6.10 (dd, 1 H, J = 9.6, 1.5 Hz), 2.06 (s, 3 H), 1.91 (d, 3 H, J = 1.2 Hz), 1.35 (s, 3 H).

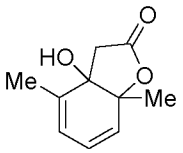
^{13}C NMR (75 MHz, $CDCl_3$): δ 198.8, 169.3, 139.6, 136.7, 138.8, 121.7, 78.9, 23.9, 20.6, 15.4.

IR (thin film): ν 2985, 2928, 1738, 1672, 1584, 1445, 1370, 1248, 1172, 1071, 1018 cm^{-1}.

HRMS (EI): calcd for $C_{10}H_{12}O_3$ $[M]^+$ 180.0781; found 180.0780.

Anal. calcd for $C_{10}H_{12}O_3$: C 66.65%, H 6.71%, O 26.64%; found: C 66.65%, H 6.75%.

These spectral characteristics are identical to those previously reported.[170]



3a-Hydroxy-4,7a-dimethyl-3a,7a-dihydro-3*H*-benzofuran-2-one (397): A solution of ^{i}Pr$_2$NH (0.310 ml, 2.37 mmol, 2.03 equiv) in THF (10 ml) was cooled to 0 °C and ^{n}BuLi (1.5 ml, 1.6 M in hexane, 2.4 mmol, 2.1 equiv) was added. The solution was stirred for 20 min at 0 °C and then cooled to –78 °C. A solution of cyclohexadienone **396** (210 mg, 1.17 mmol, 1.00 equiv) in THF (5.0 ml) was added dropwise. The solution was stirred for 30 min at –78 °C. After addition of H_2O (30 ml), the mixture was extracted with CH_2Cl_2 (3 x 50 ml). The combined organic phases were washed with brine (100 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (20–30% EtOAc in hexane) gave lactone **397** (114 mg, 54% yield) as a yellow oil, which became solid upon standing.

$\mathbf{R}_f$ = 0.25 (hexane/EtOAc 2:1)

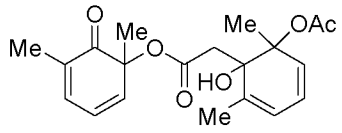
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.80 (dd, 1 H, *J* = 9.6, 5.4 Hz), 5.64 (d, 1 H, *J* = 9.6 Hz), 5.60 (dt, 1 H, *J* = 5.4, 1.5 Hz), 2.97 (s, 1H), 2.77 (dd, 2 H, *J* = 55.8, 17.4 Hz), 1.88 (s, 3 H), 1.43 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2, 139.3, 129.0, 123.3, 118.4, 91.2, 79.6, 42.8, 19.0, 18.0.

IR (thin film): ν 3412, 3359, 3037, 2983, 2938, 2360, 2191, 1739, 1601, 1141, 1372, 1332, 1266, 1234, 1149. 1090, 1049 cm^{-1}.

HRMS (EI): calcd for $C_{10}H_{12}O_3$ $[M]^+$ 180.0781; found 180.0780.

Anal. calcd for $C_{10}H_{12}O_3$: C 66.65%, H 6.71%, O 26.64%; found: C 66.47%, H 6.70%.

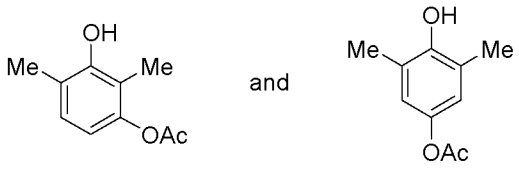


(6-Acetoxy-1-hydroxy-2,6-dimethyl-cyclohexa-2,4-dienyl)-acetic acid 1,5-dimethyl-6-oxo-cyclohexa-2,4-dienyl ester (399): A solution of cyclohexadienone **396** (58.1 mg, 0.320 mmol, 1.00 equiv) and KO^{t}Bu (51.4 mg, 0.460 mmol, 1.44 equiv) in ^{t}BuOH (10 ml) was heated to reflux for 5 h. After addition of EtOAc (20 ml) and H_2O (20 ml), the layers were separated and the aqueous phase was extracted with EtOAc (3 x 20 ml). The combined organic phases were washed with brine (50 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (5–10% EtOAc in hexane) afforded dimer **399**.

$\mathbf{R}_f$ = 0.36 (hexane/EtOAc 1:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.91–6.85 (m, 2 H), 6.64 (dd, 1 H, *J* = 7.5, 6.6 Hz), 6.21 (dd, 1 H, *J* = 7.5, 1.5 Hz), 5.88 (d, 1 H, *J* = 9.6 Hz), 5.83 (dd, 1 H, *J* = 6.9, 1.2 Hz), 5.61 (s, 1 H), 4.68 (s, 1 H), 4.30 (dd, 1 H, *J* = 6.6, 1.8 Hz), 4.20 (s, 1 H), 3.33–3.22 (m, 2 H), 2.84 (t, 1 H, *J* = 6.0 Hz), 2.34 (s, 3 H), 2.24 (s, 3 H), 1.68 (s, 3 H), 1.48 (s, 3 H), 1.45 (s, 3 H), 1.23 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 194.3, 188.8, 155.9, 153.8, 153.2, 146.1, 136.3, 136.0, 133.0, 128.7, 121.8, 109.5, 91.3, 80.0, 53.1, 50.9, 48.7, 46.2, 44.4, 30.9, 29.8, 26.3, 22.8, 18.7, 18.3, 16.4, 13.2, 11.5.



Acetic acid 3-hydroxy-2,4-dimethyl-phenyl ester (400) and **acetic acid 4-hydroxy-3,5-dimethyl-phenyl ester (401)**: A solution of cyclohexadienone **396** (53.1 mg, 0.290 mmol, 1.00 equiv) in CH_2Cl_2 (9.0 ml) was cooled to –78 °C and $SnCl_4$ (0.20 ml, 0.67 mmol, 2.31 equiv) was added. The solution was stirred for 20 min at –78 °C, before NEt_3 (50 µl, 0.36 mmol, 1.2 equiv) was. The solution was stirred for 90 min at –78 °C. After addition of saturated aqueous NH_4Cl (10 ml), the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic phases were washed with brine (20 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (3–5% EtOAc in hexane) gave a mixture of **400** and **401** (45.3 mg, 85% yield).

$\mathbf{R}_f$ = 0.58 (hexane/EtOAc 4:1)

Phenol **400**:

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.97 (d, 1 H, J = 8.1 Hz), 6.55 (d, 1 H, J = 8.1 Hz), 4.68 (s, 1 H), 2.31 (s, 3 H), 2.23 (s, 3 H), 2.06 (s, 3 H).

These spectral characteristics are identical to those previously reported.[213]

Phenol **401**:

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (s, 2 H), 4.52 (s, 1 H), 2.26 (s, 3 H), 2.13 (s, 6 H).

These spectral characteristics are identical to those previously reported.[214]

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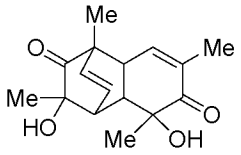
[213] G. Quinkert, E. Kleiner, B. J. Freitag, J. Glenneberg, U. M. Billhardt, F. Cech, K. R. Schmieder, C. Schudok, H. C. Steinmetzer, J. W. Bats, G. Zimmermann, G. Durner, D. Rehm, E. F. Paulus, *Helv. Chim. Acta* **1986**, *69*, 469–537.

[214] I. K. Boddy, R. C. Cambie, G. Dixon, P. S. Rutledge, P. D. Woodgate, *Aust. J. Chem.* **1983**, *36*, 803–813.



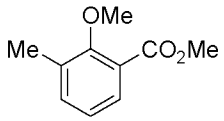
3,10-Dihydroxy-3,5,8,10-tetramethyl-tricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (406): To a suspension of 2,6-dimethylphenol (1.01 g, 8.27 mmol, 1.00 equiv) in H_2O (275 ml) was added a solution of $NaIO_4$ (4.11 g, 19.2 mmol, 2.32 equiv) in H_2O (135 ml). The resulting yellow mixture was stirred for 45 min at room temperature before the reaction was quenched by addition of ethane-1,2-diol (5 ml). The aqueous mixture was extracted with CH_2Cl_2 (3 x 500 ml). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Addition of hexane (50 ml) and subsequent concentration under reduced pressure afforded a yellow solid, which was recrystallized from 1:1 benzene/hexane to give dimer **406** (690 mg, 60% yield) as a slightly yellow solid.

$\mathbf{R}_f$ = 0.16 (hexane/EtOAc 2:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.30–6.24 (m, 2 H), 5.51 (ddd, 1 H, *J* = 8.1, 1.8, 0.6 Hz), 4.01 (s, 1 H), 3.39 (dt, 1 H, *J* = 6.6, 1.8 Hz), 3.25 (dd, 1 H, *J* = 8.4, 2.1 Hz), 2.90–2.85 (m, 1 H), 2.31 (s, 1 H), 1.85 (t, 3 H, *J* = 1.5 Hz), 1.35 (s, 3 H), 1.32 (s, 3 H), 1.24 (s, 3 H).

These spectral characteristics are identical to those previously reported.[215]

6.3.2 Preliminary Studies II



2-Methoxy-3-methyl-benzoic acid methyl ester (412): To a solution of 2-hydroxy-3-methylbenzoic acid (15.2 g, 100 mmol, 1.00 equiv) in DMF (200 ml) was added K_2CO_3 (41.5 g, 300 mmol, 3.00 equiv) and MeI (16.0 ml, 257 mmol, 2.57 equiv). The mixture was heated to 90 °C for 15 h, cooled to room temperature, filtered, and concentrated under reduced

[215] E. Adler, J. Dahlen, G. Westin, *Acta Chem. Scand.* **1960**, *14*, 1580–1596.

pressure. Purification by flash column chromatography (CH_2Cl_2) gave methyl ester **412** (16.4 g, 94% yield) as a colorless oil.

R_f = 0.67 (hexane/EtOAc 1:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65–7.62 (m, 1H), 7.36–7.33 (m, 1 H), 7.05 (t, 1 H, *J* = 7.8 Hz), 3.92 (s, 3 H), 3.83 (s, 3 H), 2.32 (s, 3 H).

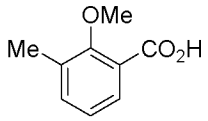
^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 158.2, 135.0, 132.6, 129.0, 124.4, 123.4, 61.5, 52.2, 16.1.

IR (thin film): ν 2949, 2864, 1724, 1593, 1467, 1433, 1290, 1264, 1229, 1190, 1137, 1089, 1008 cm^{-1}.

HRMS (EI): calcd for $C_{10}H_{12}O_3$ $[M]^+$ 180.0781; found 180.0779.

Anal. calcd for $C_{10}H_{12}O_3$: C 66.65%, H 6.71%, O 26.64%; found: C 66.38%, H 6.67%.

These spectral characteristics are identical to those previously reported.[184]



2-Methoxy-3-methylbenzoic acid (413): To a solution of methyl ester **412** (16.4 g, 94.0 mmol, 1.00 equiv) in methanol (100 ml) and water (100 ml) was added NaOH (24.1 g, 603 mmol, 6.41 equiv). The solution was stirred for 15 h at room temperature and then concentrated under reduced pressure. The resulting white solid was redissolved in water. Addition of 6 M aqueous HCl led to precipitation of a white solid which was filtered and dried under high vacuum to give analytically pure acid **413** (14.4 g, 92% yield).

R_f = 0.28 (hexane/EtOAc 1:1)

MP: 84–86 °C

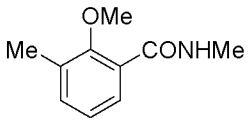
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (dd, 1 H, *J* = 7.8, 1.5 Hz), 7.44 (ddd, 1 H, *J* = 7.8, 1.8, 0.6 Hz), 7.20 (t, 1 H, *J* = 7.8 Hz), 3.94 (s, 3 H), 2.39 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 116.1, 157.6, 136.9, 131.4, 130.6, 125.0, 121.8, 62.2, 16.1.

IR (KBr): ν 2949, 2854, 2708, 2589, 2342, 1699, 1675, 1593, 1476, 1429, 1374, 1314, 1223, 1187, 1172, 1155, 1091 cm^{-1}.

HRMS (EI): calcd for $C_9H_{10}O_3$ $[M]^+$ 166.0624; found 166.0623.

These spectral characteristics are identical to those previously reported.[184]



2-Methoxy-*N*,3-dimethyl-benzamid (415): To acid **413** (10.0 g, 60.2 mmol, 1.00 equiv) was added DMF (5 drops) and dropwise $SOCl_2$ (10.0 ml, 137 mmol, 2.28 equiv). The mixture was stirred for 5 h at room temperature and then concentrated under reduced pressure to give acid chloride **414**, which was directly used for the next step.

To unpurified acid chloride **414** was added dropwise aqueous methylamine solution (115 ml, 1.52 mol, 25.2 equiv) and the mixture was stirred for 18 h at room temperature. 1 M aqueous HCl (50 ml) was added and the aqueous phase was extracted with EtOAc (3 x 200 ml). The combined organic phases were washed with brine (400 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography gave amid **415** (4.62 g, 43% over two steps) as a white solid.

R_f = 0.25 (hexane/EtOAc 1:1)

MP: 73–74 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (dd, 1 H, *J* = 7.8, 1.8 Hz), 7.73 (br s, 1 H), 7.31−7.28 (m, 1 H), 7.12 (t, 1H, *J* = 7.5 Hz), 3.76 (s, 3 H), 3.03 (d, 3 H, *J* = 5.1 Hz), 2.32 (s, 3 H).

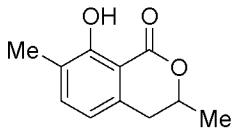
^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 156.3, 134.3, 131.3, 129.2, 126.4, 124.5, 61.3, 26.7, 16.1.

IR (KBr): ν 3352, 3065, 3007, 2968, 2941, 2361, 1981, 1830, 1638, 1584, 1534, 1465, 1413, 1302, 1254, 1221, 1194, 1171, 1156, 1127, 1088, 1030 cm^{-1}.

HRMS (EI): calcd for $C_{10}H_{13}NO_2$ $[M]^+$ 179.0941; found 179.0943.

Anal. calcd for $C_{10}H_{13}NO_2$: C 67.02%, H 7.31%, N 7.82%, O 17.85%; found: C 67.09%, H 7.15%, N 7.83%.

These spectral characteristics are identical to those previously reported.[183]



8-Hydroxy-3,7-dimethyl-isochroman-1-one (409): A solution of TMEDA (1.45 ml, 9.61 mmol, 2.44 equiv) in THF (30 ml) was cooled to –78 °C. Addition of ^{s}BuLi (6.50 ml, 1.47 M in cyclohexane, 9.56 mmol, 2.43 equiv) gave a yellow solution which turned orange-brown upon addition of a solution of amid **415** (706 mg, 3.94 mmol, 1.00 equiv) in THF (20 ml). The resulting solution was stirred for 4 h at –78 °C, before a solution of 2-methyloxirane (0.30 ml, 4.3 mmol, 1.1 equiv) in THF (5.0 ml) was added. The obtained solution was slowly let warm to room temperature over night (14 h) and turned yellow upon addition of saturated aqueous ammonium chloride (50 ml). The mixture was extracted with EtOAc (3 x 50 ml) and the combined organic phases were washed with brine (100 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give alcohol **416**, which was directly used in the next step.

Unpurified alcohol **416** was dissolved in CH_2Cl_2 (10 ml) and the solution was cooled to −78 °C. BBr_3 (17 ml, 1.0 M in CH_2Cl_2, 17 mmol, 4.4 equiv) was added and the now dark red solution was slowly let warm to room temperature over night (15 h). The reaction was quenched by slow addition of 10% aqueous HCl (10 ml) and the mixture was extracted with CH_2Cl_2 (3 x 25 ml). The combined organic phases were washed with brine (50 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (20% EtOAc in hexane) gave the demethylated phenol **417** as a brown oil.

Hydroxy amide **417** was suspended in 15% aqueous HCl (50.0 ml) and heated to 100 °C for 15 h. The mixture was extracted with EtOAc (3 x 50 ml), and the combined organic phases were washed with brine (100 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc in hexane) gave lactone **409** (83 mg, 12% yield over three steps) as a white solid.

R_f = 0.61 (hexane/EtOAc 1:1)

MP: 88–91 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ 11.26 (s, 1 H), 7.27 (d, 1 H, J = 7.5 Hz), 6.59 (d, 1 H, J = 7.5 Hz), 4.77–4.65 (m, 1 H), 2.90 (d, 2 H, J = 7.2 Hz), 2.42 (s, 3 H), 1.52 (d, 3 H, J = 6.3 Hz).

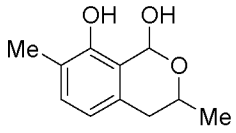
^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 160.3, 136.7, 136.4, 125.1, 117.0, 107.4, 76.3, 34.6, 20.9, 15.6.

IR (thin film): ν 3039, 2980, 2934, 1734, 1656, 1625, 1508, 1462, 1420, 1375, 1289, 1246, 1172, 1122, 1059 cm^{-1}.

HRMS (EI): calcd for $C_{11}H_{12}O_3$ $[M]^+$ 192.0781; found 192.0781.

Anal. calcd for $C_{11}H_{12}O_3$: C 68.74%, H 6.29%, O 24.97%; found: C 68.45%, H 6.33%.

These spectral characteristics are identical to those previously reported.[183]



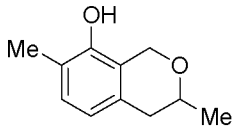
3,7-Dimethyl-isochroman-1,8-diol (419): A solution of lactone **409** (100 mg, 0.520 mmol, 1.00 equiv) in THF (3.5 ml) was cooled to –78 °C and DIBAL-H (0.20 ml, 1.2 mmol, 2.3 equiv) was added. The solution was stirred for 1 h at –78 °C and then let warm to room temperature (1 h). Saturated aqueous K^+/Na^+-tartrate (5 ml) was added and the mixture was stirred for 30 min at room temperature. The mixture was diluted with water (10 ml) and extracted with EtOAc (3 x 20 ml). The combined organic phases were washed with brine (50 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10–20% EtOAc in hexane) gave lactol **419** (94.4 mg, 93% yield).

$\mathbf{R}_f$ = 0.17 (hexane/EtOAc 1:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (br s, 1 H), 6.99 (d, 1 H, J = 7.8 Hz), 6.60 (d, 1 H, J = 7.8 Hz), 4.76 (s, 2 H), 3.87–3.77 (m, 1 H), 2.67 (s, 1 H), 2.65 (d, 1 H, J = 2.4 Hz), 2.19 (s, 3 H), 1.21 (d, 3 H, J = 6.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.3, 134.7, 130.1, 124.0, 123.6, 121.8, 69.1, 65.8, 58.8, 41.7, 23.2, 15.8, 15.3.

IR (thin film): ν 3303, 2969, 2928, 2248, 1704, 1582, 1421, 1376, 1318, 1228, 1071 cm^{-1}.



3,7-Dimethyl-isochroman-8-ol (420): A solution of lactol **419** (94.4 mg, 0.490 mmol, 1.00 equiv) and NH_4F (48.3 mg, 1.30 mmol, 2.68 equiv) in CH_2Cl_2 (2.5 ml) was cooled to 0 °C. Et_3SiH (0.21 ml, 1.3 mmol, 2.7 equiv) and CF_3CO_2H (40 µl, 0.52 mmol, 1.1 equiv) was added, the mixture was stirred for 20 min at 0 °C, the ice-bath was removed, and the mixture was stirred for 2 h at room temperature. Ice cold water was added (20 ml) and the mixture was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (50 ml) and brine (50 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (2–8% EtOAc in hexane) gave cyclic ether **420** (39.7 mg, 46% yield) as a colorless oil.

$\mathbf{R_f}$ = 0.69 (hexane/EtOAc 1:1)

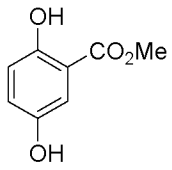
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.94 (d, 1 H, J = 7.8 Hz), 6.62 (d, 1 H, J = 7.8 Hz), 4.98 (d, 1 H, J = 15.6 Hz), 4.70 (d, 1 H, J = 15.6 Hz), 4.48 (s, 1 H), 3.81−3.70 (m, 1 H), 2.66 (d, 2 H, J = 5.4 Hz), 2.21 (s, 3 H), 1.35 (d, 3 H, J = 6.3 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 128.1, 120.5, 109.8, 70.4, 64.5, 35.6, 21.6, 15.2.

IR (KBr): ν 3334, 2958, 2927, 2871, 2359, 1728, 1671, 1583, 1463, 1377, 1244, 1113, 1080, 1012 cm^{-1}.

HRMS (EI): calcd for $C_{11}H_{14}O_2$ $[M]^+$ 178.0989; found 178.0990.

6.3.3 Intramolecular Conjugate Addition Reactions



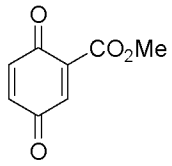
2,5-Dihydroxy-benzoic acid methyl ester (427): To a solution of 2,5-dihydroxybenzoic acid (101 g, 655 mmol, 1.00 equiv) in methanol (660 ml, 16.3 mol, 24.8 equiv) was added H_2SO_4 (44 ml, 0.78 mol, 1.2 equiv). The mixture was heated to 65 °C for 24 h and then cooled

to ambient temperature. After concentration under reduced pressure, the residue was taken up in H_2O. The aqueous phase was extracted with Et_2O. The organic phase was washed with water until the pH of the aqueous phase was neutral and with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give methyl ester **427** (107 g, 98% yield) as a slightly beige solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.33 (s, 1 H), 7.28 (dd, 1 H, J = 3.1, 0.3 Hz), 7.01 (dd, 1 H, J = 8.9, 3.1 Hz), 6.89 (dd, 1 H, J = 8.9, 0.3 Hz), 4.52 (s, 1 H), 3.94 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 155.7, 147.5, 124.0, 118.5, 114.6, 112.1, 52.4.

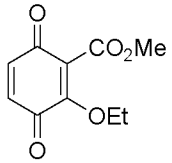
These spectral characteristics are identical to those previously reported.[186]



3,6-Dioxo-cyclohexa-1,4-dienecarboxylic acid methyl ester (428): To a solution of hydroquinone **427** (106 g, 630 mmol, 1.00 equiv) in Et_2O (2.0 l) was added $MgSO_4$ (232 g, 1.93 mol, 3.06 equiv) and Ag_2O (183 g, 790 mmol, 1.25 equiv). The mixture was stirred with a mechanical stirrer for 25 h at room temperature, filtered, and concentrated under reduced pressure. The obtained orange solid **428** (96.5 g, 92% yield) was used for the next step without purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (t, 1 H, J = 0.9 Hz), 6.83 (d, 2 H, J = 1.7 Hz), 3.92 (s, 3 H).

These spectral characteristics are identical to those previously reported.[186]



2-Ethoxy-3,6-dioxo-cyclohexa-1,4-dienecarboxylic acid methyl ester (422): To a solution of quinone **428** (92.0 g, 554 mmol, 1.00 equiv) in toluene (3.0 l) was added $MgCl_2$ (107 g, 1.12 mol, 2.03 equiv), DDQ (126 g, 555 mmol, 1.00 equiv), and EtOH (72 ml,

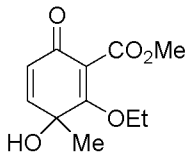
1.2 mol, 2.2 equiv). The mixture was stirred with a mechanical stirrer for 20 h at ambient temperature, cooled to 0 °C, filtered, and concentrated under reduced pressure. Ether **422** (83.5 g, 72% yield) was obtained as an orange-brown oil and was used without further purification.

$\mathbf{R}_f$ = 0.66 (hexane/EtOAc 1:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (s, 2 H), 4.36 (q, 2 H, *J* = 7.0 Hz), 3.90 (s, 3 H), 1.39 (t, 3 H, *J* = 7.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 183.9, 181.6, 163.5, 135.7, 134.2, 68.3, 52.6, 15.0.

IR (thin film): ν 3068, 2989, 2956, 1682, 1650, 1596, 1477, 1438, 1379, 1323, 1232, 1197, 1098, 1040, 1005 cm^{-1}.



2-Ethoxy-3-hydroxy-3-methyl-6-oxo-cyclohexa-1,4-dienecarboxylic acid methyl ester (423): A solution of quinone **422** (2.60 g, 12.4 mmol, 1.00 equiv) in THF (140 ml) was cooled to –78 °C. Upon addition of MeLi (7.80 ml, 1.58 M in Et_2O, 12.3 mmol, 1.00 equiv), the previously colorless solution turned dark green. After stirring for 1 h at –78 °C, saturated NH_4Cl (50 ml) was added. The mixture was allowed to warm to ambient temperature and was extracted with EtOAc (3 x 150 ml). The combined organic phases were washed with H_2O (400 ml) and brine (400 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (30–50% EtOAc in hexane) gave tertiary alcohol **423** (1.62 g, 58% yield) as a dark brown oil.

$\mathbf{R}_f$ = 0.20 (hexane/EtOAc 1:1)

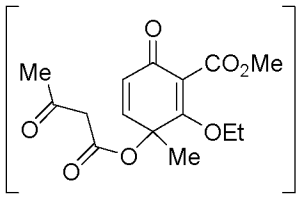
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (d, 1 H, *J* = 10.0 Hz), 6.12 (d, 1 H, *J* = 10.0 Hz), 4.30–4.11 (m, 2 H), 3.86 (s, 3 H), 2.56 (br s, 1 H), 1.41 (t, 3 H, *J* = 7.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 184.0, 169.8, 166.7, 146.8, 125.8, 69.2, 67.0, 52.8, 27.9, 15.2.

IR (thin film): ν 3440, 2987, 2954, 1729, 1661, 1629, 1593, 1436, 1374, 1317, 1244, 1197, 1184, 1141, 1113, 1045, 1011 cm^{-1}.

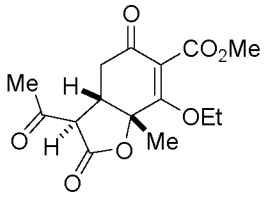
HRMS (EI): calcd for $C_{11}H_{14}O_5$ $[M]^+$ 226.0836; found 226.0838.

Anal. calcd for $C_{11}H_{14}O_5$: C 58.40%, H 6.24%, O 35.36%; found: C 58.42%, H 6.18%.



2-Ethoxy-3-methyl-6-oxo-3-(3-oxo-butyryloxy)-cyclohexa-1,4-dienecarboxylic acid methyl ester (430): To a solution of alcohol **423** (48.0 mg, 0.210 mmol, 1.00 equiv) in toluene (1.0 ml) was added pyridine (3 drops) and diketene (20 µl, 0.26 mmol, 1.2 equiv). The solution was stirred for 28 h at room temperature and the reaction was quenched by addition of saturated aqueous NH_4Cl (5 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic phases were washed with brine (20 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give acetoacetate **430**, which proved unstable to silica gel.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.59 (d, 1 H, J = 9.9 Hz), 6.20 (d, 1 H, J = 9.9 Hz), 4.26–4.16 (m, 1 H), 4.12–3.96 (m, 1 H), 3.84 (s, 3 H), 3.46 (d, 2 H, J = 4.2 Hz), 2.26 (s, 3 H), 1.60 (s, 3 H), 1.32 (t, 3 H, J = 6.9 Hz).



(3*R,3a*S**,7a*R**)-3-Acetyl-7-ethoxy-7a-methyl-2,5-dioxo-2,3,3a,4,5,7a-hexahydro-benzofuran-6-carboxylic acid methyl ester (431)**: To a solution of alcohol **423** (199 mg, 0.880 mmol, 1.00 equiv) in CH_2Cl_2 (10 ml) was added NEt_3 (0.190 ml, 1.36 mmol, 1.55 equiv) and diketene (110 µl, 1.44 mmol, 1.63 equiv). The solution was stirred for 40 h at room temperature and the reaction was quenched by addition of saturated aqueous NH_4Cl (10 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x

10 ml). The combined organic phases were washed with brine (20 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (20% EtOAc in hexane) gave lactone **431** (145 mg, 53% yield) as a white solid.

R_f = 0.20 (hexane/EtOAc 1:1)

MP: 172–174 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.24–4.09 (m, 2 H), 3.84 (s, 3 H), 3.64 (d, 1 H, *J* = 12.0 Hz), 3.33 (ddd, 1 H, *J* = 12.0, 5.7, 2.4 Hz), 2.74 (dd, 1 H, *J* = 17.4, 5.7 Hz), 2.58 (dd, 1 H, *J* = 17.4, 2.4 Hz), 2.47 (s, 3 H), 1.79 (s, 3 H), 1.39 (t, 3 H, *J* = 6.9 Hz).

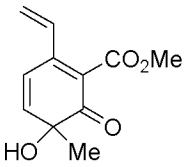
^{13}C NMR (75 MHz, $CDCl_3$): δ 198.9, 191.8, 169.4, 166.4, 165.9, 114.4, 81.4, 67.8, 56.8, 52.9, 40.7, 35.3, 30.1, 22.8, 15.0.

IR (thin film): ν 2919, 2855, 1774, 1727, 1657, 1602, 1445, 1410, 1376, 1318, 1237, 1095, 1023 cm^{-1}.

HRMS (EI): calcd for $C_{15}H_{18}O_7$ $[M]^+$ 310.1047; found 310.1046.

Anal. calcd for $C_{15}H_{18}O_7$: C 58.06%, H 5.85%, O 36.09%; found: C 58.35%, H 5.87%.

X-ray crystallographic analysis: see appendix A.



5-Hydroxy-5-methyl-6-oxo-2-vinyl-cyclohexa-1,3-dienecarboxylic acid methyl ester (434): A solution of ketone **423** (7.15 g, 31.6 mmol, 1.00 equiv) in Et_2O (360 ml) was cooled to –78 °C. Vinylmagnesium bromide (70 ml, 1.0 M in THF, 70 mmol, 2.2 equiv) was added and the resulting solution was stirred for 90 min at –78 °C. 1 M aqueous HCl (200 ml) was added and the mixture was let warm to ambient temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 200 ml). The combined organic phases were washed with water (600 ml) and brine (600 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10–20% EtOAc in hexane) gave cyclohexadienone **434** (2.57 g, 39% yield) as an orange-brown oil.

$\mathbf{R}_f$ = 0.34 (hexane/EtOAc 1:1)

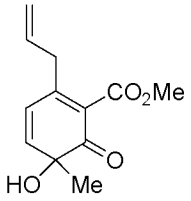
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89 (d, 1 H, *J* = 9.9 Hz), 6.49 (dd, 1 H, *J* = 17.7, 11.7 Hz), 6.15 (d, 1 H, *J* = 9.9 Hz), 6.06 (dd, 1 H, *J* = 17.7, 1.5 Hz), 5.67 (dd, 1 H, *J* = 11.7, 1.5 Hz), 3.83 (s, 3 H), 2.74 (s, 1 H), 1.54 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 182.1, 166.4, 154.9, 153.0, 130.8, 130.6, 126.0, 125.4, 68.9, 52.6, 27.4.

IR (thin film): ν 3410, 2987, 1735, 1659, 1437, 1244, 1153, 1052, 1010 cm^{-1}.

HRMS (ESI): calcd for $C_{11}H_{12}O_4Na$ $[M+Na]^+$ 231.0628; found 231.0634.

Anal. calcd for $C_{11}H_{12}O_4$: C 63.45%, H 5.81%, O 30.74%; found: C 63.50%, H 6.06%.



2-Allyl-5-hydroxy-5-methyl-6-oxo-cyclohexa-1,3-dienecarboxylic acid methyl ester (435): A solution of ketone **423** (1.14 g, 5.04 mmol, 1.00 equiv) in Et_2O (60 ml) was cooled to –78 °C. Allylmagnesium bromide (11 ml, 1.0 M in Et_2O, 11 mmol, 2.2 equiv) was added and the resulting solution was stirred for 90 min at –78 °C. 1 M aqueous HCl (30 ml) was added and the mixture was let warm to ambient temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 30 ml). The combined organic phases were washed with water (100 ml) and brine (100 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (20–30% EtOAc in hexane) gave cyclohexadienone **435** (462 mg, 41% yield) as an orange-brown oil.

$\mathbf{R}_f$ = 0.37 (hexane/EtOAc 1:1)

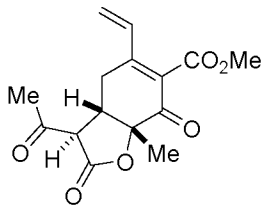
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.88 (d, 1 H, *J* = 10.2 Hz), 6.14 (d, 1 H, *J* = 10.2 Hz), 5.87 –5.73 (m, 1 H), 5.19 (m, 2 H), 3.81 (s, 3 H), 3.27 (qdt, 2 H, *J* = 15.0, 6.0, 1.5 Hz), 2.33 (s, 1 H), 1.49 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 181.7, 166.2, 159.1, 152.3, 134.0, 126.1, 118.1, 52.3, 33.6, 29.7, 26.4.

IR (thin film): ν 3464, 2984, 1734, 1373, 1243, 1150, 1080, 1035 cm^{-1}.

HRMS (ESI): calcd for $C_{12}H_{14}O_4Na$ $[M+Na]^+$ 245.0784; found 245.0784.

Anal. calcd for $C_{12}H_{14}O_4$: C 64.85%, H 6.35%, O 28.80%; found: C 64.85%, H 6.44%.



(3*R,3a*S**,7a*R**)-3-Acetyl-7a-methyl-2,7-dioxo-5-vinyl-2,3,3a,4,7,7a-hexahydro-benzofuran-6-carboxylic acid methyl ester (437)**: To a solution of alcohol **434** (260 mg, 1.25 mmol, 1.00 equiv) in CH_2Cl_2 (17 ml) was added NEt_3 (0.35 ml, 2.5 mmol, 2.0 equiv) and diketene (0.20 ml, 2.6 mmol, 2.1 equiv). After stirring for 14 h at room temperature, saturated aqueous NH_4Cl (20 ml) was added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases were washed with brine (60 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc in hexane) gave lactone **437** (95.2 mg, 26% yield) as a white solid.

$\mathbf{R}_f$ = 0.55 (hexane/EtOAc 1:1)

MP: 180–182 °C

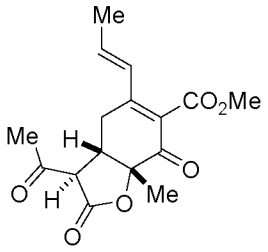
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.37 (dd, 1 H, *J* = 17.7, 11.7 Hz), 6.06 (dd, 1 H, *J* = 17.7, 0.9 Hz), 5.76 (dd, 1 H, *J* = 11.7, 0.9 Hz), 3.84 (s, 3 H), 3.63 (d, 1 H, *J* = 12.6 Hz), 3.39 (ddd, 1 H, *J* = 12.6, 5.7, 2.4 Hz), 2.80 (dd, 1 H, *J* = 17.7, 5.7 Hz), 2.67 (dd, 1 H, *J* = 17.7, 2.4 Hz), 2.48 (s, 3 H), 1.84 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 199.0, 191.5, 168.8, 165.5, 150.5, 132.6, 130.0, 128.3, 81.4, 56.4, 52.8, 42.8, 35.3, 30.2, 24.2.

IR (thin film): ν 2964, 2905, 1767, 1735, 1666, 1614, 1575, 1445, 1381, 1346, 1266, 1227, 1159, 1096, 1040 cm^{-1}.

HRMS (EI): calcd for $C_{15}H_{16}O_6$ $[M]^+$ 292.0941; found 292.0942.

Anal. calcd for $C_{15}H_{16}O_6$: C 61.64%, H 5.52%, O 32.84%; found: C 61.38%, H 5.49%.



(3*R,3a*S**,7a*R**)-3-Acetyl-7a-methyl-2,7-dioxo-5-((*E*)-propenyl)-2,3,3a,4,7,7a-hexahydro-benzofuran-6-carboxylic acid methyl ester (438)**: To a solution of alcohol **435** (210 mg, 0.900 mmol, 1.00 equiv) in CH_2Cl_2 (12.0 ml) was added NEt_3 (0.190 ml, 1.36 mmol, 1.51 equiv) and diketene (0.110 ml, 1.44 mmol, 1.59 equiv). After stirring for 16 h at room temperature, saturated aqueous NH_4Cl (10 ml) was added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic phases were washed with brine (30 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10–20% EtOAc in hexane) gave lactone **438** (119 mg, 43% yield) as a white solid.

R_f = 0.33 (hexane/EtOAc 1:1)

MP: 188–190 °C

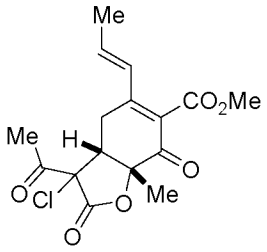
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.69 (dq, 1 H, *J* = 15.9, 6.9 Hz), 6.05 (dq, 1 H, *J* = 15.9, 1.5 Hz), 3.85 (s, 3 H), 3.63 (d, 1 H, *J* = 12.6 Hz), 3.36 (ddd, 1 H, *J* = 12.6, 5.4, 2.4 Hz), 2.79 (dd, 1 H, *J* = 18.0, 5.7 Hz), 2.65 (dd, 1 H, *J* = 18.0, 2.4 Hz), 2.47 (s, 3 H), 1.92 (dd, 3 H, *J* = 6.9, 1.8 Hz), 1.84 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 198.7, 191.0, 168.6, 150.2, 142.1, 124.3, 81.4, 46.2, 52.5, 42.8, 35.0, 30.1, 24.4, 20.2.

IR (thin film): ν 2963, 2908, 1771, 1729, 1665, 1629, 1574, 1443, 1345, 1264, 1228, 1158, 1096, 1020 cm^{-1}.

HRMS (EI): calcd for $C_{16}H_{18}O_6$ $[M]^+$ 306.1098; found 306.1098.

Anal. calcd for $C_{16}H_{18}O_6$: C 62.74%, H 5.92%, O 31.34%; found: C 62.77%, H 5.86%.



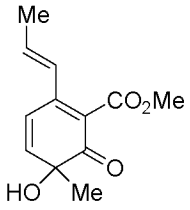
(3a*R,7a*R**)-3-Acetyl-3-chloro-7a-methyl-2,7-dioxo-5-((*E*)-propenyl)-2,3,3a,4,7,7a-hexahydro-benzofuran-6-carboxylic acid methyl ester (444)**: To a suspension of NaH (5.9 mg, 0.25 mmol, 1.3 equiv) in THF (2.0 ml) was added a solution of ketoester **438** (59.6 mg, 195 µmol, 1.00 equiv) in THF (6.0 ml). The obtained yellow mixture was stirred for 30 min at room temperature. NCS (34.5 mg, 258 µmol, 1.32 equiv) was added and the resulting mixture was stirred for 14 h at room temperature. CH_2Cl_2 (10 ml) and saturated aqueous NH_4Cl (10 ml) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml) and the combined organic phases were washed with brine (30 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (15–20% EtOAc in hexane) gave chloride **444** (21.0 mg, 32% yield) as a slightly yellow oil.

$\mathbf{R}_f$ = 0.45 (hexane/EtOAc 1:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (dq, 1 H, *J* = 15.9, 6.9 Hz), 6.07 (dq, 1 H, *J* = 15.9, 1.8 Hz), 3.84 (s, 3 H), 3.78 (dd, 1 H, *J* = 6.9, 1.8 Hz), 2.83 (dd, 1 H, *J* = 18.9, 6.9 Hz), 2.72 (dd, 1 H, *J* = 18.9, 1.8 Hz), 2.62 (s, 3 H), 1.92 (dd, 3 H, *J* = 6.9, 1.8 Hz), 1.88 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 197.3, 190.1, 148.7, 141.6, 124.3, 81.7, 69.9, 52.7, 46.8, 33.5, 29.8, 26.9, 26.1, 20.4.

HRMS (MALDI): calcd for $C_{16}H_{17}ClO_6$ $[M+Na]^+$ 363.0606; found 363.0602.



5-Hydroxy-5-methyl-6-oxo-2-((*E*)-propenyl)-cyclohexa-1,3-dienecarboxylic acid methyl ester (452): To a solution of alcohol **435** (19.3 mg, 86.8 µmol, 1.00 equiv) and **450**

(23.6 mg, 128 μmol, 1.47 equiv) in Toluene (2.0 ml) was added NEt_3 (3 drops). After stirring the resulting solution for 50 h at room temperature, saturated aqueous NH_4Cl (10 ml) was added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic phases were washed with brine (30 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford internal olefin **452**.

$\mathbf{R}_f$ = 0.32 (hexane/EtOAc 1:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86 (d, 1 H, *J* = 9.9 Hz), 6.78–6.66 (m, 1 H), 6.18 (dq, 1 H, *J* = 17.4, 1.8 Hz), 6.15 (d, 1 H, *J* = 9.9 Hz), 3.85 (s, 3 H), 2.40 (s, 1 H), 1.91 (dd, 3 H, *J* = 6.9, 1.8 Hz), 1.55 (s, 3 H).

Curriculum Vitae

Born March 29, 1978 in Winterthur, Switzerland, to *Jana* and *Alfred Marti-Kassowitz*.

1991 – 1998	Matura Typus B at Kantonsschule Rychenberg, Winterthur
1998 – 2002	Chemistry studies at ETH Zürich
Spring 2001	Exchange Semester at Purdue University, West Lafayette, USA ("*Asymmetric Synthesis of Boronolide via Chiral Organoboranes*") under the supervision of Prof. *P. V. Ramachandran*
Spring 2002	Internship in the group of Prof. *Antonio Togni* at ETH Zürich ("*Catalytic Enantioselective Dihalogenation of β-Ketoesters*")
2002 – 2003	Diploma thesis ("*Vannusal A: Introduction of the Quaternary Carbon at C13*") under the supervision of Dr. *Michael P. Jennings* in the group of Prof. *K. C. Nicolaou* at The Scripps Research Institute, La Jolla, USA ETH Medal for best Diploma thesis in chemistry, 2003
2003 – 2007	Ph.D. studies ("*Studies Toward the Synthesis of Bafilomycin A_1 and Fusidilactone C*") under the supervision of Prof. *Erick M. Carreira* at ETH Zürich

During my Diploma studies and my Ph.D. thesis, I was teaching assistant for two introductory-level organic chemistry laboratory courses as well as for five chemistry exercises and lectures.

Zürich, May 2007

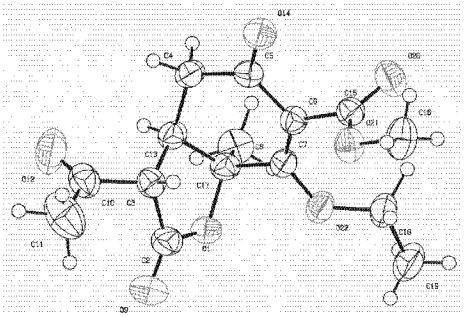
Gabriela Jana Marti

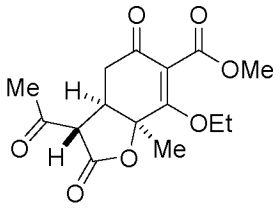
Appendix A:

X-ray Crystallographic

Data

A.1 Crystallographic Data for Lactone 431





431

Experimental

Crystal data

$C_{15}H_{18}O_7$, M_r = 310.302
Monoclinic $P2_1/n$
a = 5.9643 (2) Å
b = 20.3161 (5) Å
c = 12.6189 (8) Å
α = 90.00 °
β = 90.757 (2) °
γ = 90.00 °
V = 1528.92 (12) Å^3
Z = 4
D_x = 1.348 Mg m^{-3}
Density measured by: not measured
fine-focus sealed tube
Mo *K*α radiation λ = 0.71073

Cell parameters from 4283 refl.
θ = 0.998—26.373 °
μ = 0.108 mm^{-1}
T = 298 K

Cube 0.4 x 0.2 x 0.2 mm
Colourless
Crystal source: G. Marti

Data collection

KappaCCD
CCD
Absorption correction: none
9112 measured reflections
3099 independent reflections
2301 observed reflections

Criterion: >2sigma(I)
R_{int} = 0.055
θ_{max} = 26.36 °
h = –6 →7
k = –25 →25
l = –14 →15

Refinement

Refinement on F^2
fullmatrix least squares refinement
R(all) = 0.0935
R(gt) = 0.0669
wR(ref) = 0.1952
wR(gt)= 0.1772
S(ref) = 1.279
3099 reflections
271 parameters
0 restraints

All H-atom parameters refined
Calculated weights calc
Δ/σ_{max} = 0.287
$\Delta\rho_{max}$ = 0.342eÅ^3
$\Delta\rho_{min}$ = –0.371eÅ^3
Extinction correction: none
Atomic scattering factors from International Tables Vol C Tables 4.2.6.8 and 6.1.1.4

Data collection: KappaCCD
Cell refinement: HKL Scalepack[216]
Data reduction: Denzo and Scalepak[216]
Program(s) used to solve structure: *SIR*97[217]
Program(s) used to refine structure: *SHELXL*-97[218]

	x	y	z	U_{eq}	Occ
O1	0.1517 (3)	0.18793 (8)	0.25279 (12)	0.0487 (5)	1
O9	-0.0964 (4)	0.15105 (11)	0.36759 (16)	0.0742 (6)	1
O12	0.2551 (4)	-0.00320 (12)	0.3462 (2)	0.0883 (8)	1
O14	0.1584 (3)	0.03050 (8)	-0.08498 (13)	0.0545 (5)	1
O20	0.0428 (3)	0.16323 (10)	-0.19871 (14)	0.0617 (5)	1
O21	-0.2548 (3)	0.13552 (8)	-0.10377 (13)	0.0516 (5)	1

[216] Z. Otwinowski, W. Minor; in *Methods in Enzymology*, *276*; C. W. Carter, Jr., R. M. Sweet, Eds.; Academic Press: New York **1997**, pp 307–326.

[217] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. Moliterni, R. Spagna, *J. Appl. Cryst.* **1999,** *32*, 115–119.

[218] G. M. Sheldrick: *SHELXL*97. Program for the Refinement of Crystal Structures. University of Göttingen, Germany **1997**.

O22	0.0638 (3)	0.24163 (8)	0.06969 (13)	0.0536 (5)	1
C2	0.0254 (4)	0.13996 (12)	0.29558 (19)	0.0493 (6)	1
C3	0.0696 (4)	0.07524 (11)	0.23934 (18)	0.0447 (6)	1
C4	0.3320 (4)	0.04958 (12)	0.08312 (18)	0.0466 (6)	1
C5	0.1871 (4)	0.06870 (10)	-0.01081 (16)	0.0407 (5)	1
C6	0.0922 (4)	0.13505 (10)	-0.01556 (17)	0.0401 (5)	1
C7	0.1315 (4)	0.17926 (10)	0.06297 (17)	0.0403 (5)	1
C8	0.4972 (5)	0.19802 (14)	0.1565 (2)	0.0566 (7)	1
C10	0.0770 (5)	0.01805 (13)	0.3183 (2)	0.0579 (7)	1
C11	-0.1409 (8)	-0.0075 (2)	0.3560 (3)	0.0900 (12)	1
C13	0.2863 (4)	0.08929 (11)	0.18227 (17)	0.0423 (5)	1
C15	-0.0373 (4)	0.14732 (11)	-0.11668 (18)	0.0421 (5)	1
C16	-0.3951 (6)	0.14301 (18)	-0.1983 (3)	0.0640 (8)	1
C17	0.2729 (4)	0.16313 (11)	0.16095 (17)	0.0417 (5)	1
C18	-0.0383 (5)	0.27711 (12)	-0.0186 (2)	0.0527 (6)	1
C19	-0.0666 (8)	0.34631 (15)	0.0197 (3)	0.0760 (10)	1
H19A	-0.162 (7)	0.349 (2)	0.078 (4)	0.094 (13)	1
H19B	-0.112 (6)	0.3715 (19)	-0.035 (3)	0.083 (10)	1
H19C	0.096 (7)	0.3592 (17)	0.041 (3)	0.079 (10)	1
H13	0.422 (5)	0.0833 (13)	0.225 (2)	0.049 (6)	1
H18A	-0.189 (5)	0.2588 (14)	-0.040 (2)	0.061 (8)	1
H11A	-0.112 (7)	-0.045 (2)	0.409 (4)	0.100 (12)	1
H11B	-0.168 (11)	-0.037 (3)	0.325 (5)	0.15 (2)	1
H11C	-0.213 (9)	0.030 (3)	0.404 (4)	0.140 (18)	1
H3	-0.049 (5)	0.0680 (12)	0.193 (2)	0.043 (6)	1
H18B	0.048 (5)	0.2723 (15)	-0.091 (3)	0.069 (8)	1
H16A	-0.360 (8)	0.181 (2)	-0.235 (4)	0.113 (14)	1
H4A	0.510 (6)	0.0570 (13)	0.066 (2)	0.061 (8)	1
H4B	0.302 (4)	-0.0008 (13)	0.103 (2)	0.050 (7)	1
H16B	-0.339 (8)	0.117 (2)	-0.259 (4)	0.108 (13)	1
H16C	-0.499 (8)	0.113 (2)	-0.192 (3)	0.105 (14)	1
H8	0.569 (8)	0.192 (2)	0.231 (4)	0.126 (15)	1
H8B	0.477 (6)	0.248 (2)	0.139 (3)	0.090 (11)	1
H8C	0.586 (6)	0.1845 (17)	0.091 (3)	0.083 (10)	1

Table 5. Fractional atomic coordinates and equivalent isotropic thermal parameters (Å^2); $U_{eq} = 1/3\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* a_i.a_j$

	U_{11}	U_{12}	U_{13}	U_{22}	U_{23}	U_{33}
O1	0.0588 (10)	0.0076 (8)	0.0030 (7)	0.0445 (9)	-0.0074 (6)	0.0429 (9)
O9	0.0764 (14)	0.0155 (11)	0.0232 (11)	0.0835 (14)	-0.0044 (10)	0.0633 (13)
O12	0.0912 (18)	0.0142 (13)	-0.0022 (13)	0.0813 (15)	0.0372 (12)	0.0923 (16)
O14	0.0672 (12)	0.0016 (8)	-0.0053 (8)	0.0481 (9)	-0.0096 (7)	0.0481 (9)
O20	0.0552 (11)	0.0013 (10)	0.0003 (8)	0.0845 (13)	0.0103 (8)	0.0453 (10)
O21	0.0405 (10)	-0.0033 (7)	-0.0058 (7)	0.0607 (10)	0.0082 (7)	0.0536 (10)

O22	0.0725 (12)	0.0129 (8)	-0.0080 (8)	0.0412 (9)	-0.0006 (6)	0.0468 (9)
C2	0.0453 (14)	0.0100 (11)	-0.0008 (10)	0.0599 (14)	-0.0024 (10)	0.0427 (13)
C3	0.0450 (13)	-0.0016 (10)	-0.0033 (10)	0.0486 (13)	-0.0011 (9)	0.0404 (12)
C4	0.0492 (14)	0.0112 (11)	-0.0023 (10)	0.0434 (12)	-0.0047 (9)	0.0472 (12)
C5	0.0413 (12)	0.0003 (9)	0.0016 (9)	0.0412 (11)	-0.0041 (8)	0.0397 (11)
C6	0.0387 (12)	0.0016 (9)	-0.0013 (9)	0.0420 (11)	0.0018 (8)	0.0395 (11)
C7	0.0395 (11)	0.0017 (9)	0.0007 (9)	0.0374 (11)	0.0025 (8)	0.0439 (12)
C8	0.0494 (15)	-0.0087 (12)	-0.0050 (12)	0.0576 (16)	-0.0048 (12)	0.0625 (16)
C10	0.0758 (19)	-0.0050 (14)	-0.0010 (12)	0.0524 (14)	-0.0009 (10)	0.0456 (13)
C11	0.105 (3)	-0.041 (3)	0.014 (2)	0.093 (3)	0.010 (2)	0.072 (2)
C13	0.0426 (12)	0.0072 (10)	-0.0057 (9)	0.0428 (11)	-0.0023 (8)	0.0412 (11)
C15	0.0431 (13)	0.0007 (10)	-0.0010 (9)	0.0421 (11)	-0.0007 (9)	0.0410 (12)
C16	0.0535 (17)	-0.0063 (15)	-0.0223 (14)	0.0694 (19)	0.0126 (15)	0.0686 (19)
C17	0.0436 (12)	0.0020 (10)	-0.0023 (9)	0.0416 (11)	-0.0067 (8)	0.0399 (12)
C18	0.0657 (17)	0.0072 (12)	-0.0081 (12)	0.0435 (12)	0.0061 (10)	0.0487 (14)
C19	0.110 (3)	0.0218 (18)	-0.017 (2)	0.0460 (15)	0.0017 (14)	0.072 (2)

Table 6. Anisotropic displacement parameters ($Å^2$)

O1—C2	1.349 (3)	C13—C17	1.526 (3)
O1—C17	1.463 (3)	C18—C19	1.497 (4)
O9—C2	1.193 (3)	C3—H3	0.92 (3)
O12—C10	1.196 (4)	C4—H4A	1.10 (3)
O14—C5	1.226 (3)	C4—H4B	1.07 (3)
O20—C15	1.191 (3)	C8—H8	1.03 (5)
O21—C15	1.331 (3)	C8—H8B	1.05 (4)
O21—C16	1.457 (3)	C8—H8C	1.03 (4)
O22—C7	1.333 (3)	C11—H11A	1.03 (5)
O22—C18	1.453 (3)	C11—H11B	0.73 (6)
C2—C3	1.519 (3)	C11—H11C	1.06 (6)
C3—C13	1.515 (3)	C13—H13	0.98 (3)
C3—C10	1.531 (3)	C16—H16A	0.93 (5)
C4—C5	1.508 (3)	C16—H16B	1.00 (5)
C4—C13	1.516 (3)	C16—H16C	0.88 (5)
C5—C6	1.463 (3)	C18—H18A	1.01 (3)
C6—C7	1.356 (3)	C18—H18B	1.05 (3)
C6—C15	1.504 (3)	C19—H19A	0.94 (5)
C7—C17	1.523 (3)	C19—H19B	0.90 (4)
C8—C17	1.515 (4)	C19—H19C	1.04 (4)
C10—C11	1.483 (5)		

Table 7. Geometric Parameters I (Å)

C2—O1—C17	110.65 (17)	C5—C4—H4A	110.7 (14)
C15—O21—C16	115.5 (2)	C13—C4—H4A	106.0 (15)
C7—O22—C18	123.16 (18)	C5—C4—H4B	109.6 (13)
O9—C2—O1	121.2 (2)	C13—C4—H4B	106.6 (14)
O9—C2—C3	129.1 (3)	H4A—C4—H4B	110 (2)
O1—C2—C3	109.7 (2)	C17—C8—H8	106 (3)
C13—C3—C2	102.31 (19)	C17—C8—H8B	111 (2)
C13—C3—C10	115.8 (2)	H8—C8—H8B	110 (3)
C2—C3—C10	110.90 (19)	C17—C8—H8C	112 (2)
C5—C4—C13	113.82 (19)	H8—C8—H8C	119 (3)
O14—C5—C6	120.1 (2)	H8B—C8—H8C	99 (3)
O14—C5—C4	120.6 (2)	C10—C11—H11A	109 (2)
C6—C5—C4	119.14 (18)	C10—C11—H11B	108 (5)
C7—C6—C5	121.17 (19)	H11A—C11—H11B	77 (5)
C7—C6—C15	126.33 (19)	C10—C11—H11C	107 (3)
C5—C6—C15	112.44 (18)	H11A—C11—H11C	103 (4)
O22—C7—C6	128.8 (2)	H11B—C11—H11C	143 (6)
O22—C7—C17	108.53 (18)	C3—C13—H13	114.6 (16)
C6—C7—C17	122.6 (2)	C4—C13—H13	103.7 (16)
O12—C10—C11	123.9 (3)	C17—C13—H13	105.2 (15)
O12—C10—C3	118.9 (3)	O21—C16—H16A	111 (3)
C11—C10—C3	117.1 (3)	O21—C16—H16B	112 (3)
C3—C13—C4	117.1 (2)	H16A—C16—H16B	89 (4)
C3—C13—C17	103.07 (18)	O21—C16—H16C	104 (3)
C4—C13—C17	112.77 (19)	H16A—C16—H16C	143 (4)
O20—C15—O21	123.9 (2)	H16B—C16—H16C	86 (3)
O20—C15—C6	125.1 (2)	O22—C18—H18A	112.9 (17)
O21—C15—C6	110.90 (19)	C19—C18—H18A	109.2 (17)
O1—C17—C7	107.13 (17)	O22—C18—H18B	114.3 (17)
O1—C17—C8	108.31 (18)	C19—C18—H18B	115.0 (17)
C7—C17—C8	110.4 (2)	H18A—C18—H18B	100 (2)
O1—C17—C13	102.94 (17)	C18—C19—H19A	112 (2)
C7—C17—C13	112.43 (17)	C18—C19—H19B	108 (2)
C8—C17—C13	115.0 (2)	H19A—C19—H19B	113 (4)
O22—C18—C19	105.5 (2)	C18—C19—H19C	102 (2)
C13—C3—H3	112.5 (16)	H19A—C19—H19C	111 (3)
C2—C3—H3	107.3 (15)	H19B—C19—H19C	109 (3)
C10—C3—H3	107.7 (15)		

Table 8. Geometric Parameters II (°)

C17—O1—C2—O9	-175.7 (2)	C10—C3—C13—C17	-150.51 (19)
C17—O1—C2—C3	5.1 (2)	C5—C4—C13—C17	-46.9 (3)

O9—C2—C3—C13	-162.9 (3)	C16—O21—C15—O20	0.3 (3)
O1—C2—C3—C13	16.3 (2)	C16—O21—C15—C6	-177.3 (2)
O9—C2—C3—C10	-38.8 (4)	C7—C6—C15—O20	94.1 (3)
O1—C2—C3—C10	140.3 (2)	C5—C6—C15—O20	-82.9 (3)
C13—C4—C5—O14	-159.2 (2)	C7—C6—C15—O21	-88.3 (3)
C13—C4—C5—C6	24.6 (3)	C5—C6—C15—O21	94.7 (2)
O14—C5—C6—C7	-176.5 (2)	C2—O1—C17—C7	94.5 (2)
C4—C5—C6—C7	-0.3 (3)	C2—O1—C17—C8	-146.4 (2)
O14—C5—C6—C15	0.7 (3)	C2—O1—C17—C13	-24.2 (2)
C4—C5—C6—C15	176.9 (2)	O22—C7—C17—O1	46.4 (2)
C18—O22—C7—C6	-10.7 (4)	C6—C7—C17—O1	-134.7 (2)
C18—O22—C7—C17	168.1 (2)	O22—C7—C17—C8	-71.3 (3)
C5—C6—C7—O22	178.0 (2)	C6—C7—C17—C8	107.6 (3)
C15—C6—C7—O22	1.2 (4)	O22—C7—C17—C13	158.81 (19)
C5—C6—C7—C17	-0.7 (3)	C6—C7—C17—C13	-22.3 (3)
C15—C6—C7—C17	-177.5 (2)	C3—C13—C17—O1	33.0 (2)
C13—C3—C10—O12	14.6 (4)	C4—C13—C17—O1	160.28 (19)
C2—C3—C10—O12	-101.4 (3)	C3—C13—C17—C7	-81.9 (2)
C13—C3—C10—C11	-165.7 (3)	C4—C13—C17—C7	45.3 (3)
C2—C3—C10—C11	78.3 (3)	C3—C13—C17—C8	150.6 (2)
C2—C3—C13—C4	-154.22 (19)	C4—C13—C17—C8	-82.2 (3)
C10—C3—C13—C4	85.1 (3)	C7—O22—C18—C19	-174.5 (3)
C2—C3—C13—C17	-29.8 (2)		

Table 9. Geometric Parameters III (°)

Appendix B:

Spectroscopic Data

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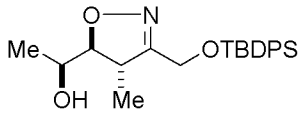

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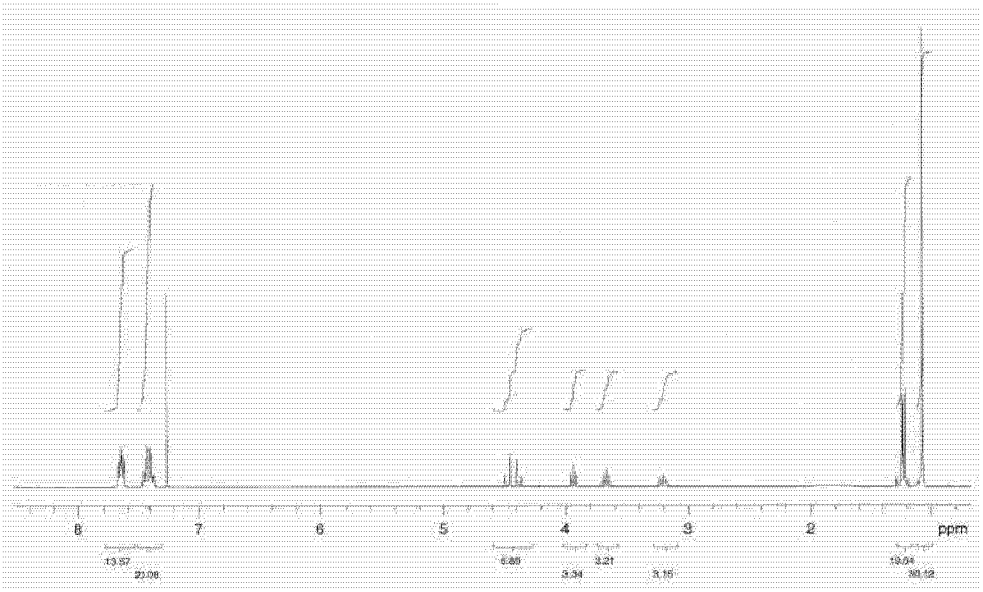

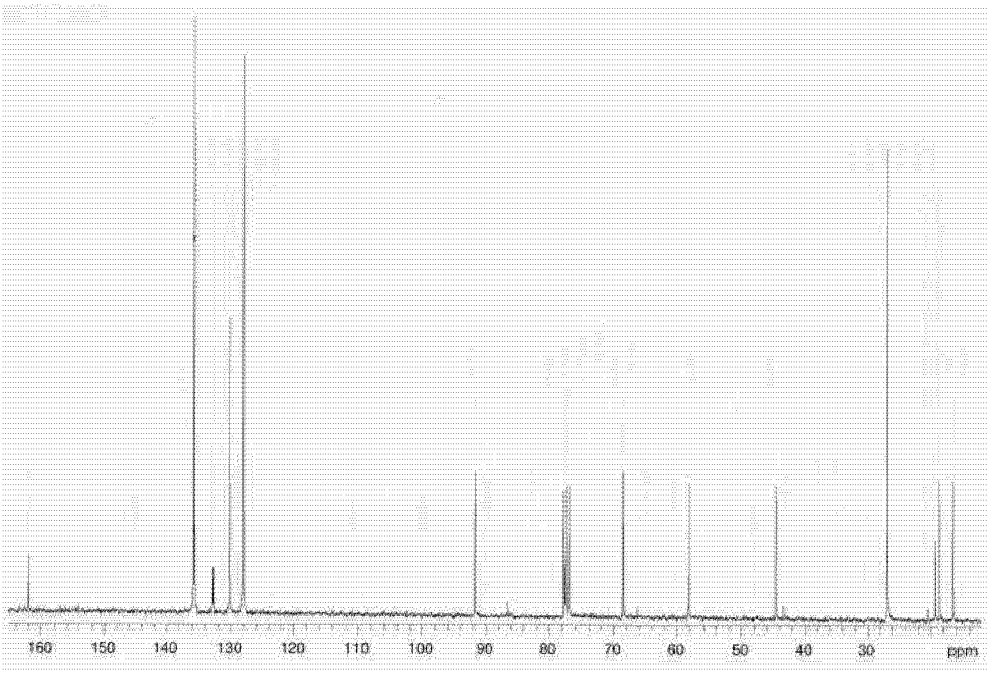
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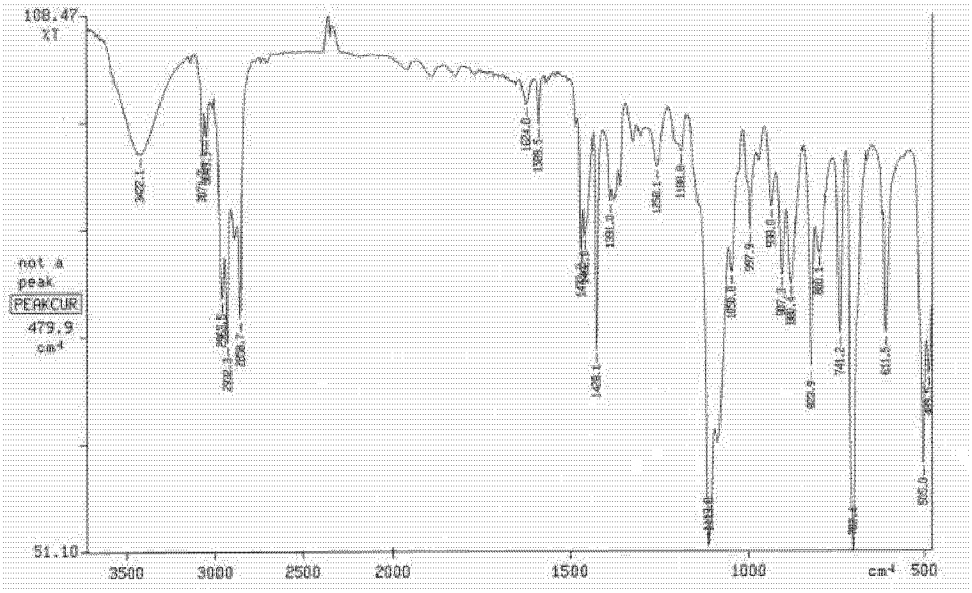
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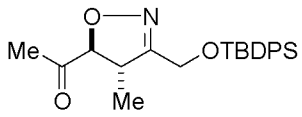
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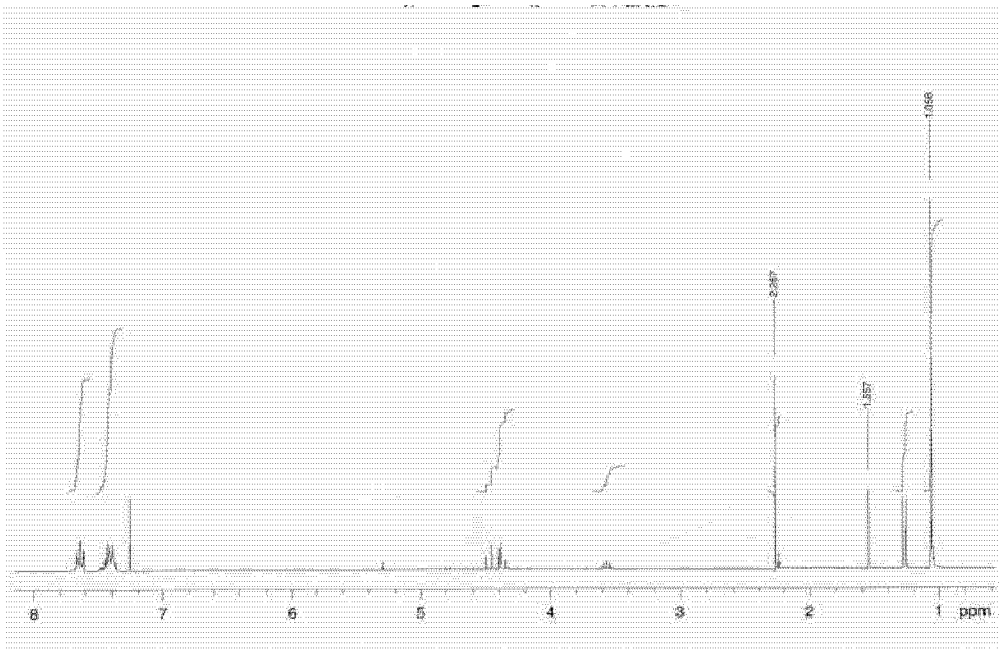
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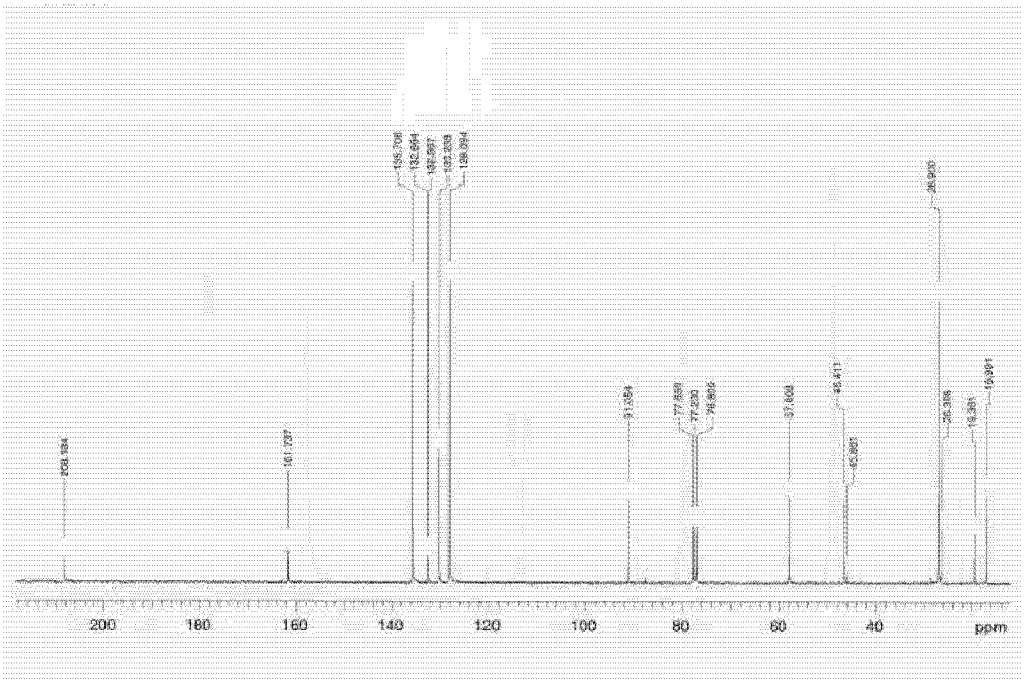
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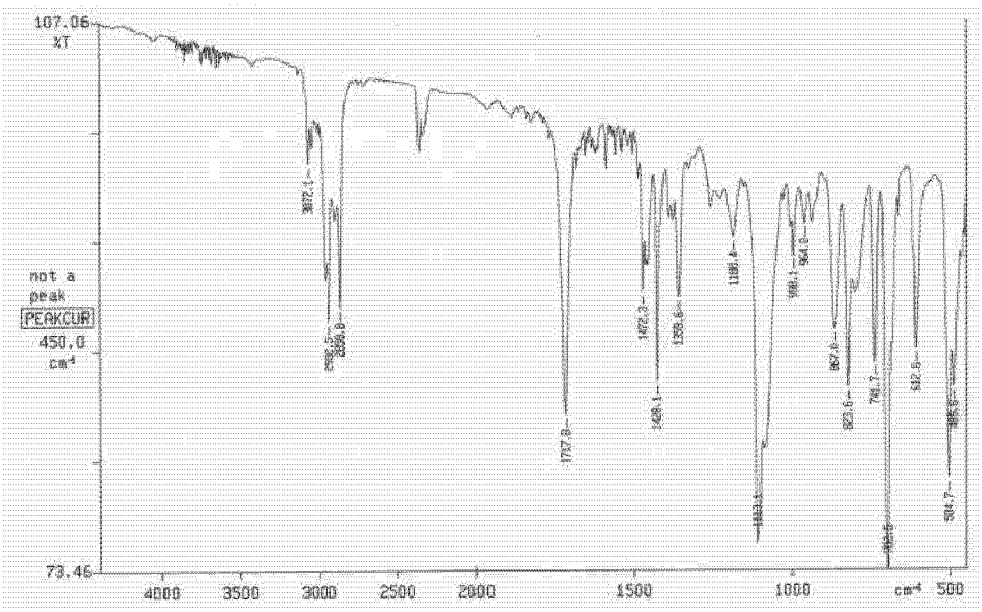
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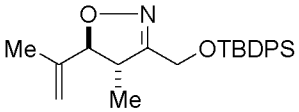
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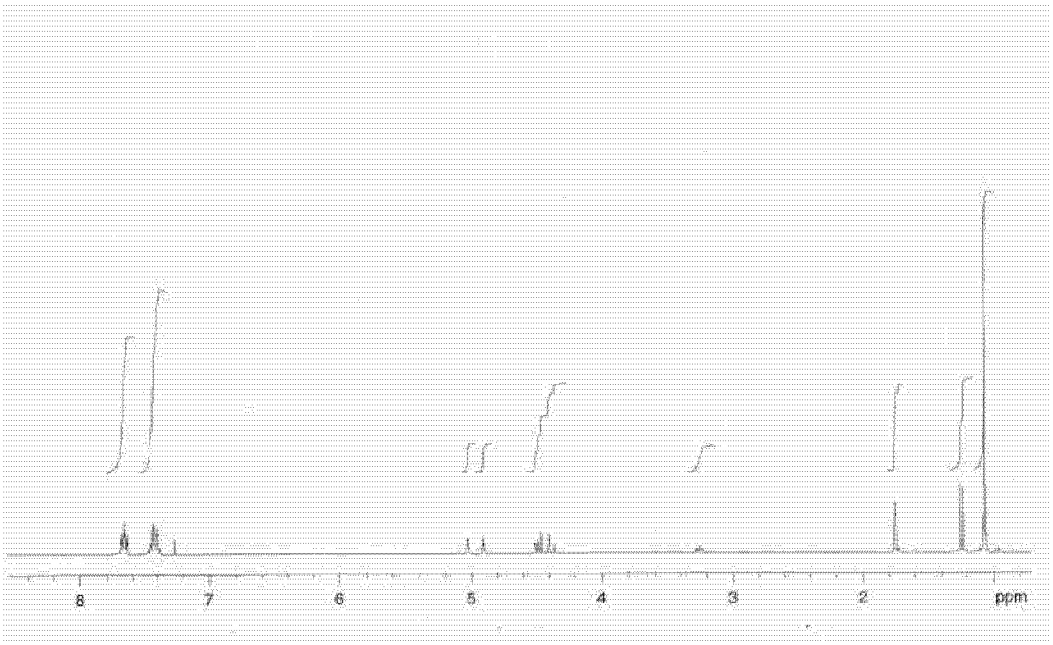
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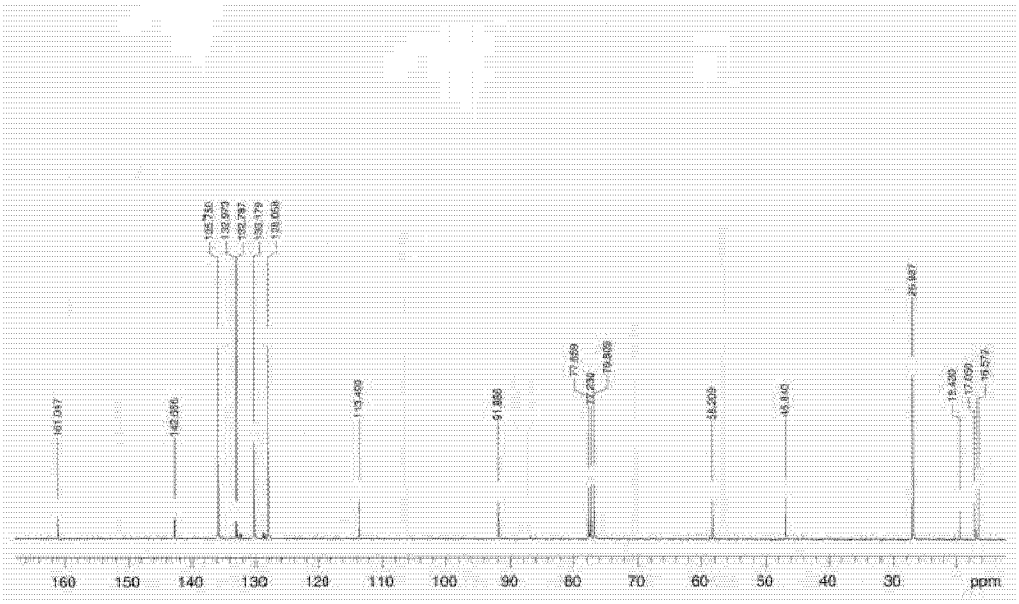
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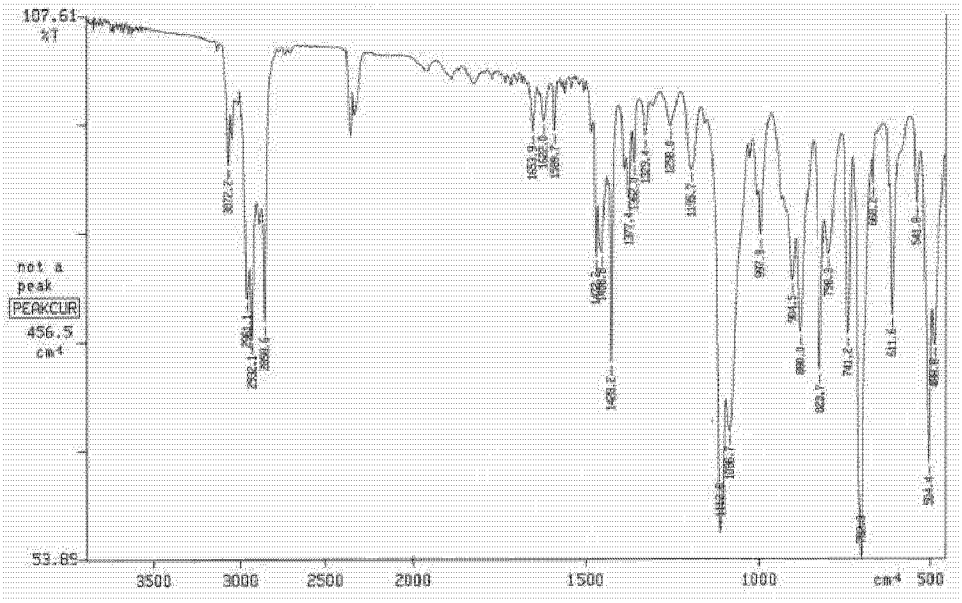
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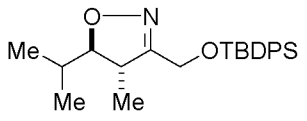
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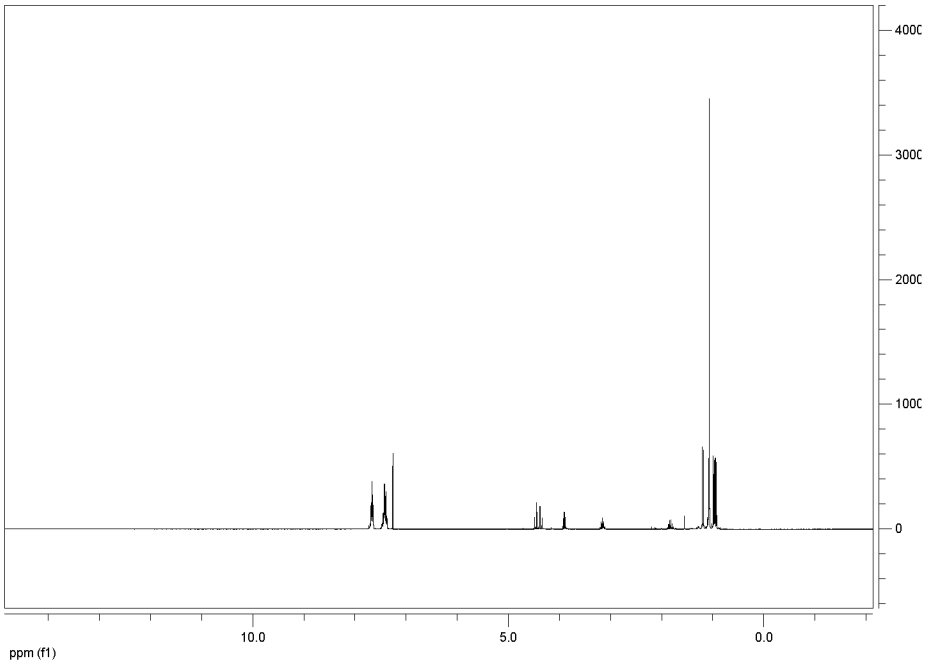
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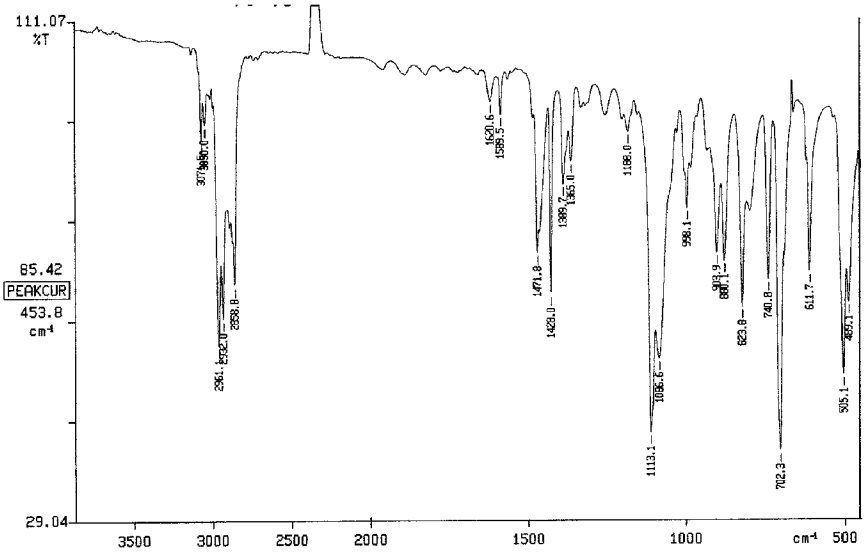
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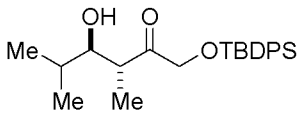
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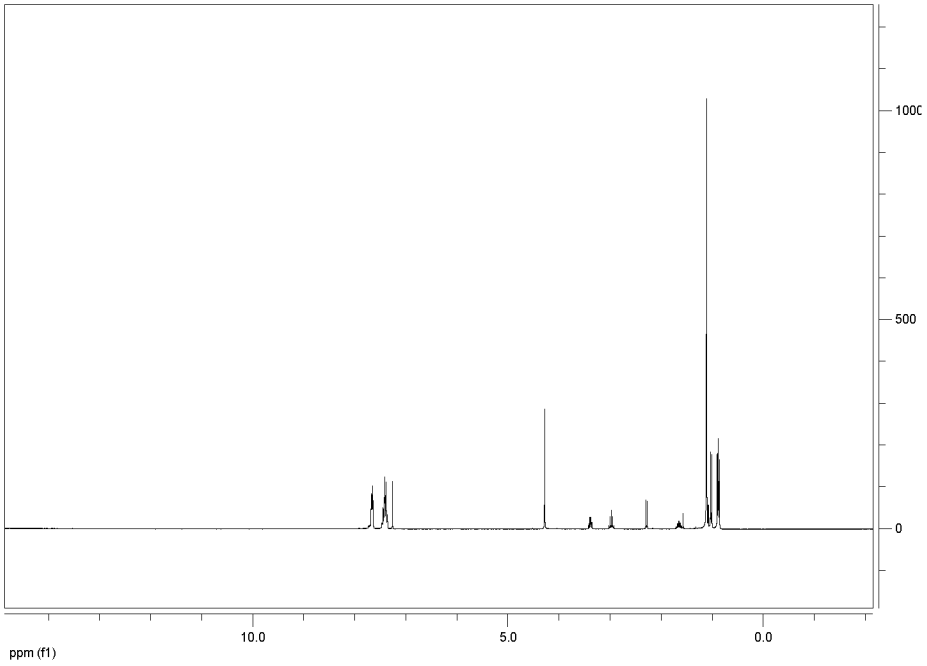
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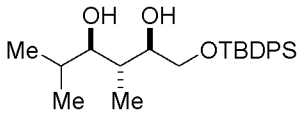
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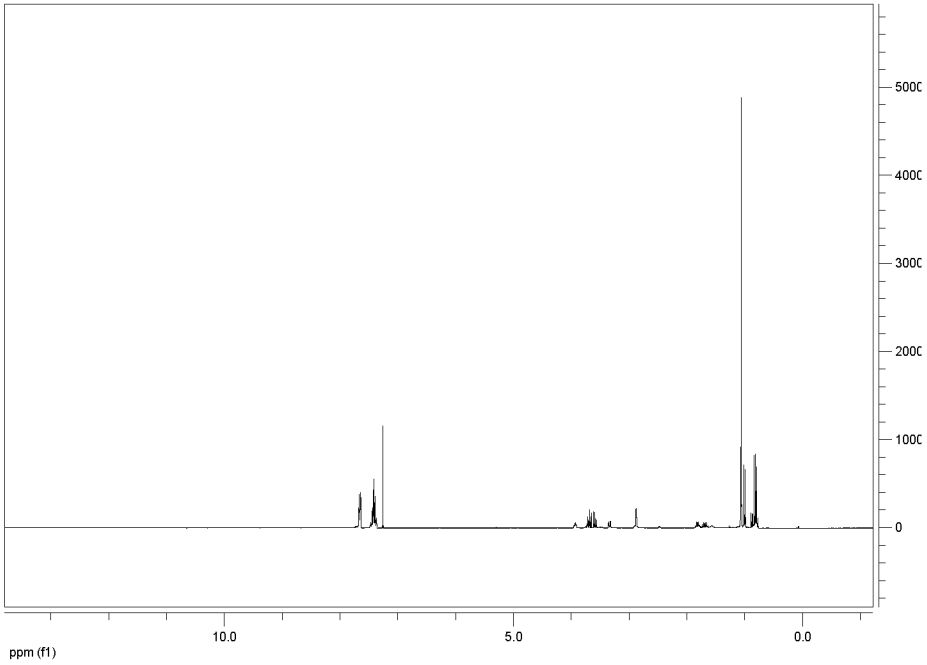
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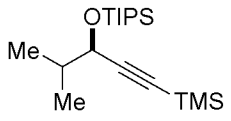
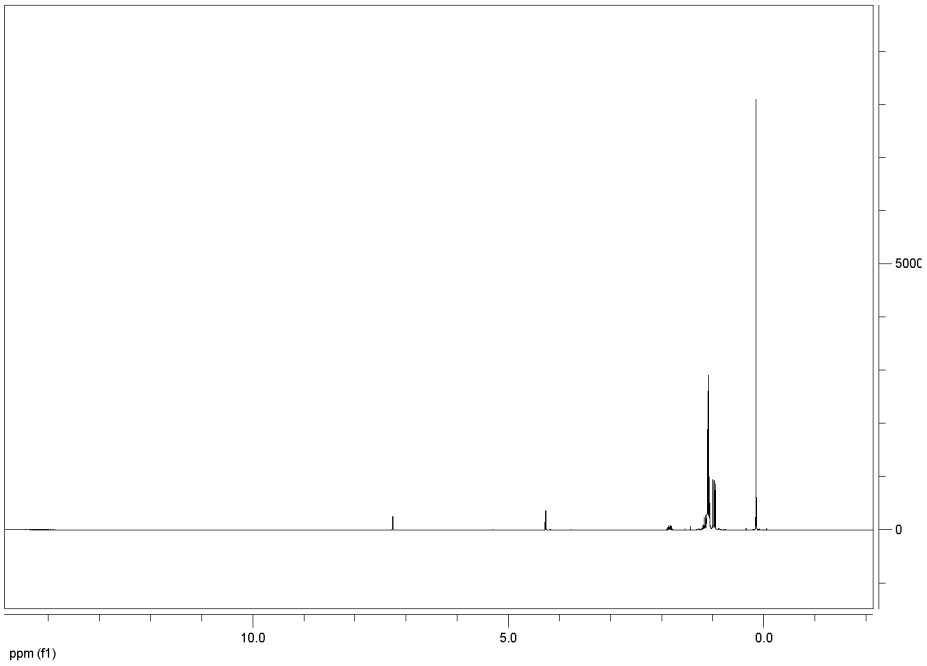
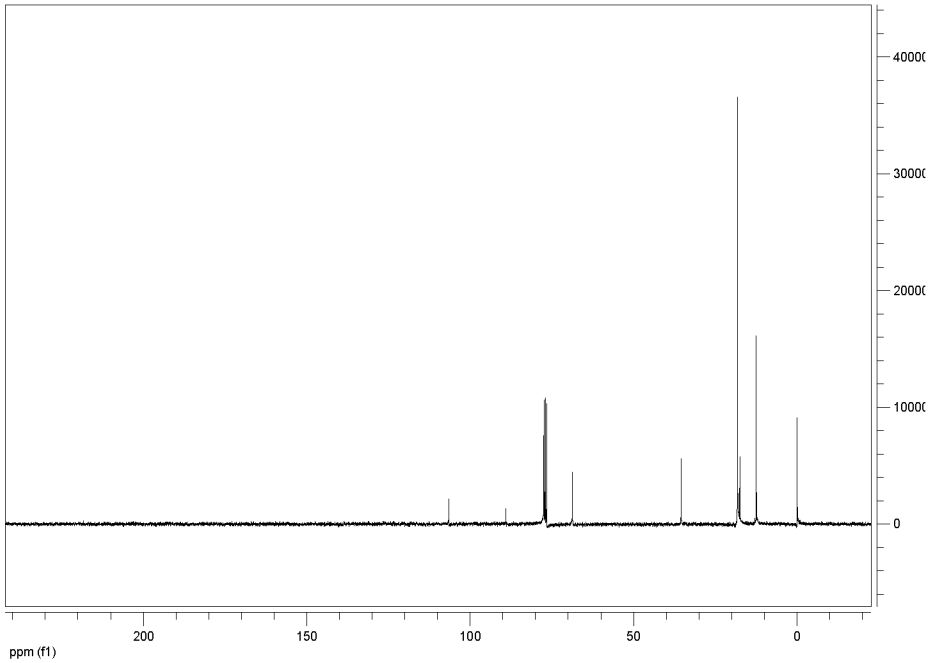
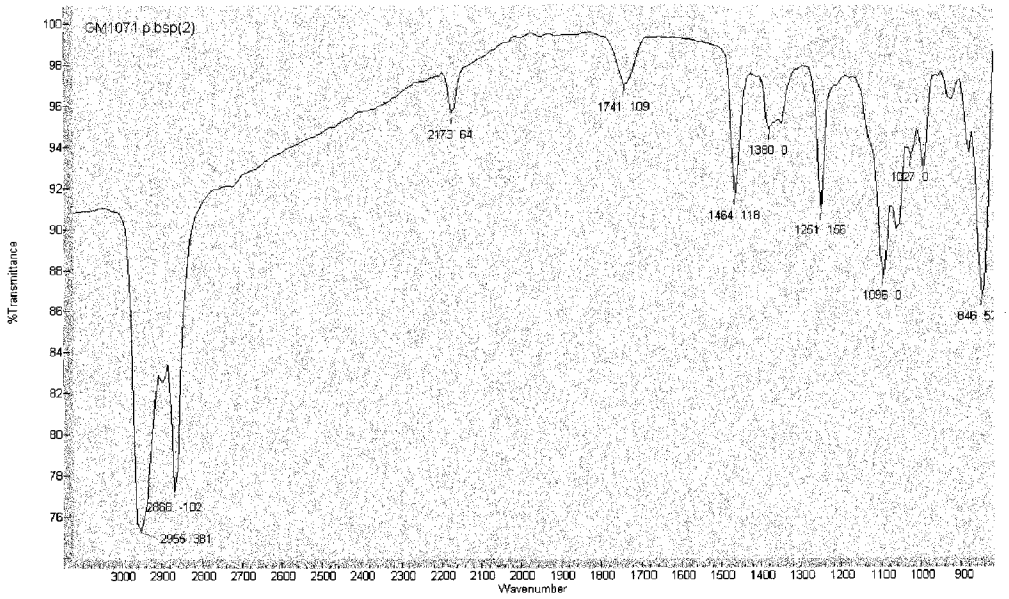
ppm (f1)

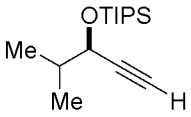

OTIPS
Me
Me
TMS

225

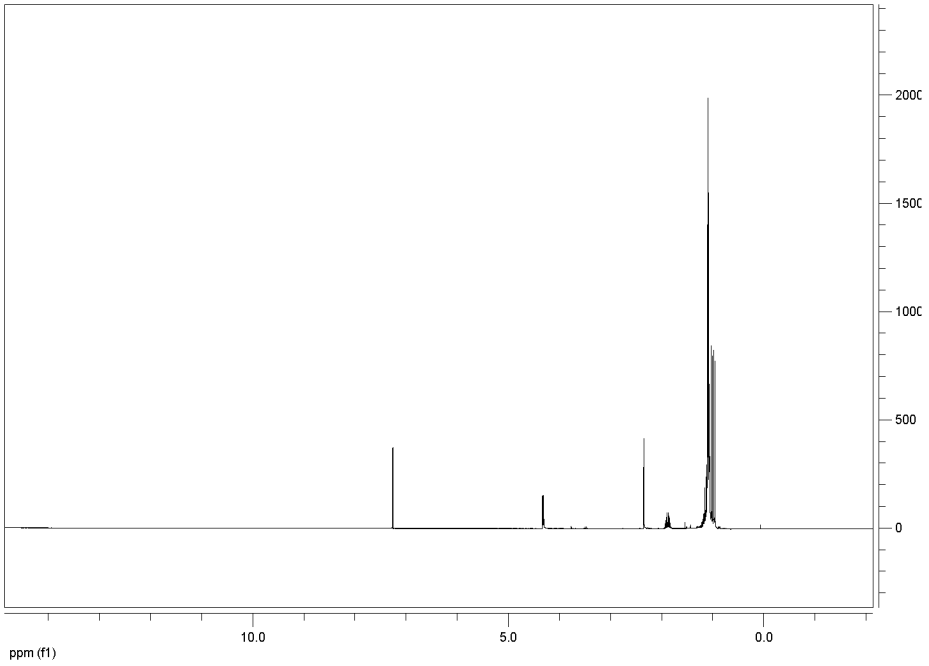

5000
0
10.0
5.0
0.0
ppm (f1)

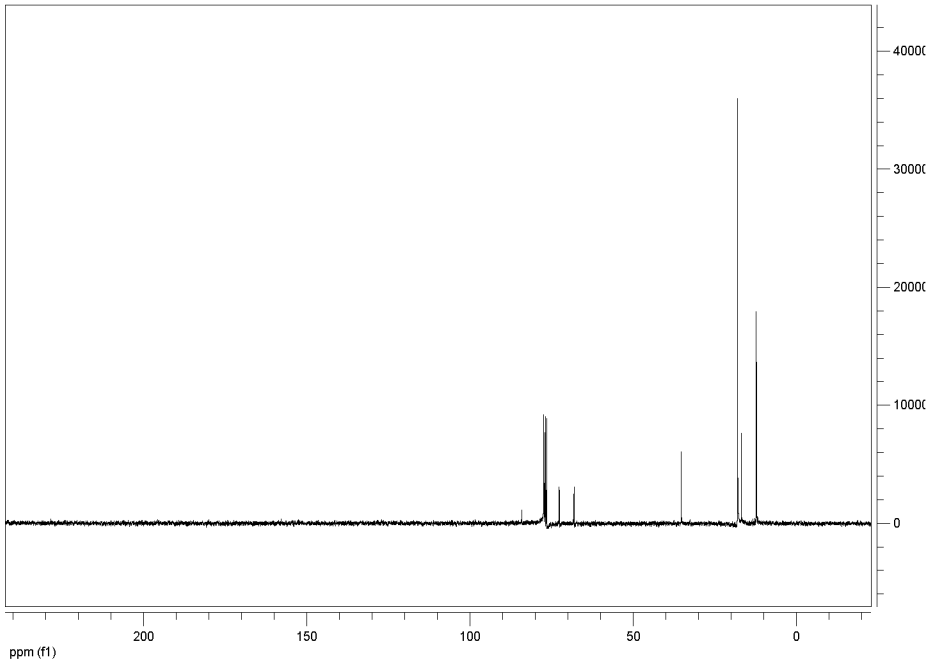

40000
30000
20000
10000
0
200
150
100
50
0
ppm (f1)

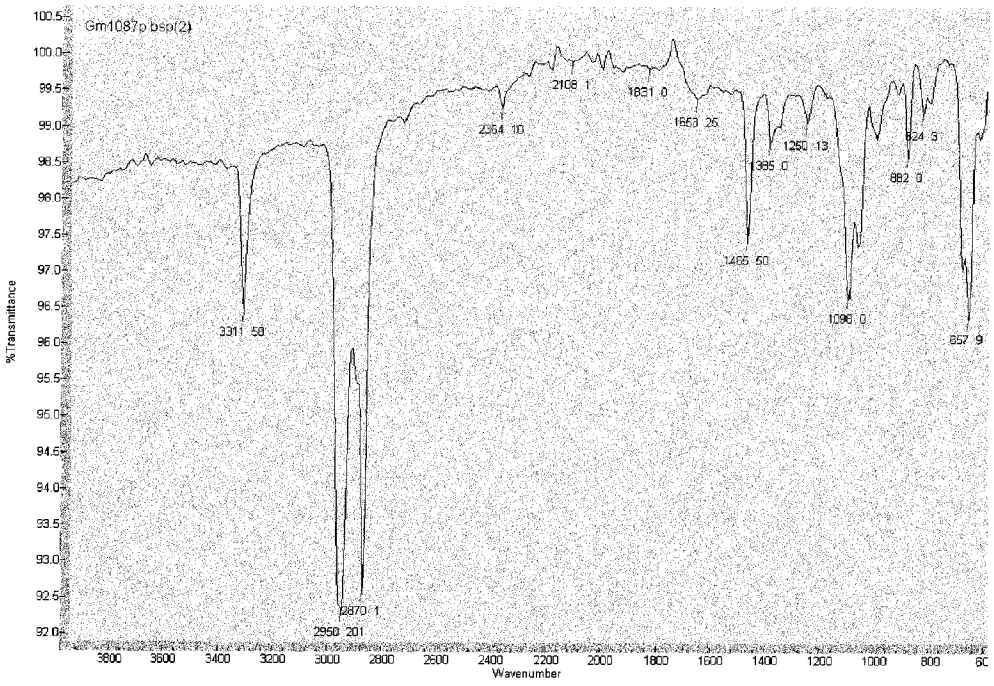

CM1071 p.bsp(2)
%Transmittance
Wavenumber
2173.64
1741.109
1380.0
1464.118
1251.166
1027.0
1095.0
846.5
2866.102
2955.381

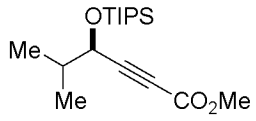

OTIPS
Me
Me
H

226

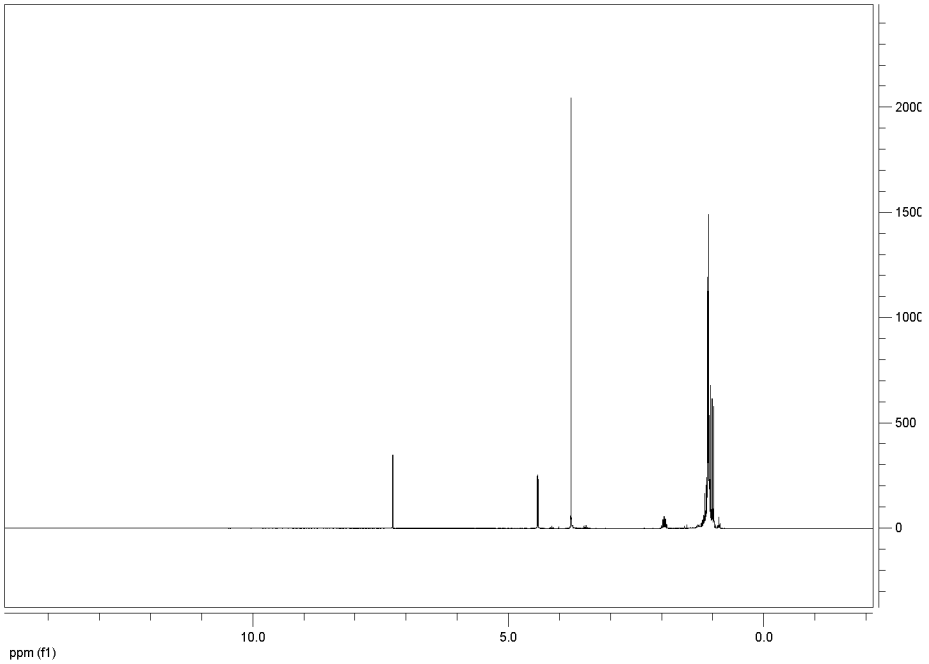

ppm (f1)
10.0
5.0
0.0

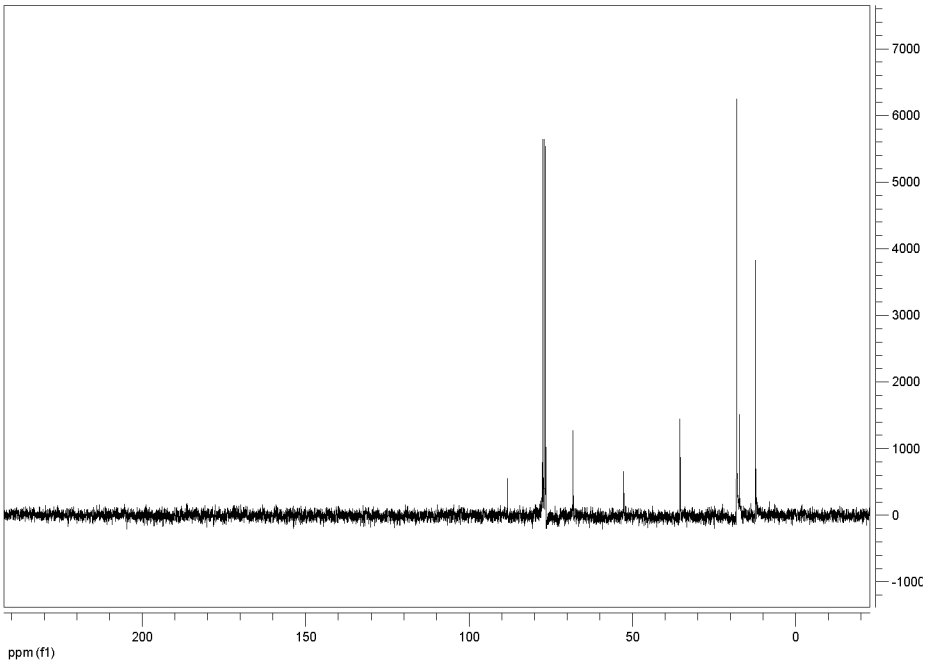

40000
30000
20000
10000
0
200
150
100
50
0
ppm (f1)

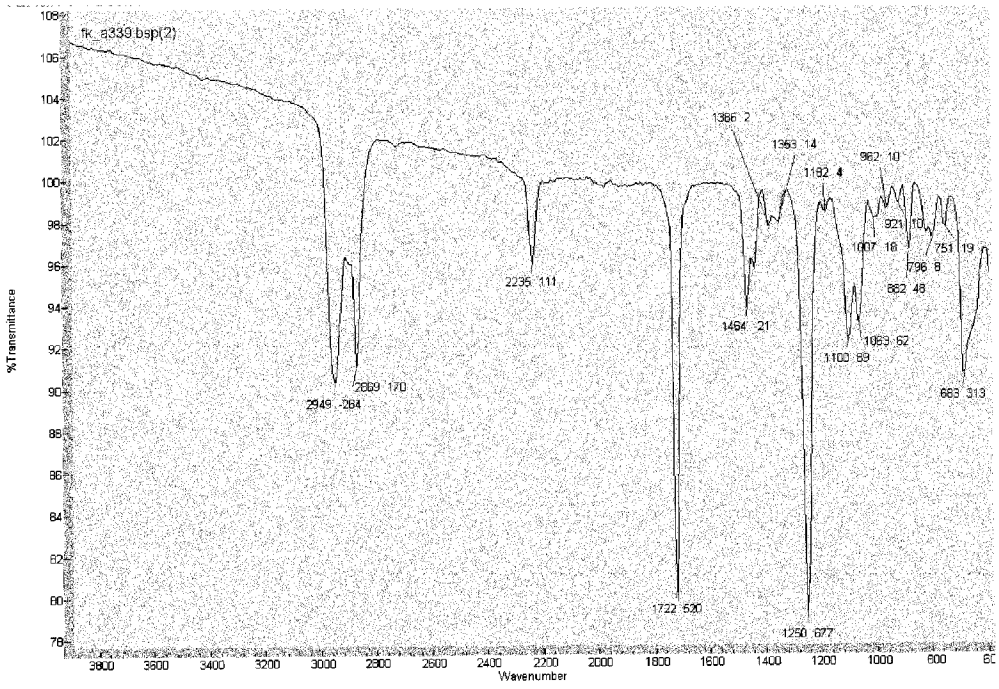

Gm1087p bsp(2)
%Transmittance
Wavenumber
3311 58
2870 1
2950 201
2364 10
2108 1
1831 0
1663 25
1465 50
1395 0
1250 13
1098 0
882 0
824 5
657 9

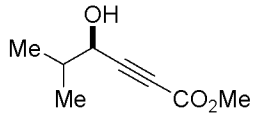

OTIPS
Me
Me
CO2Me

227

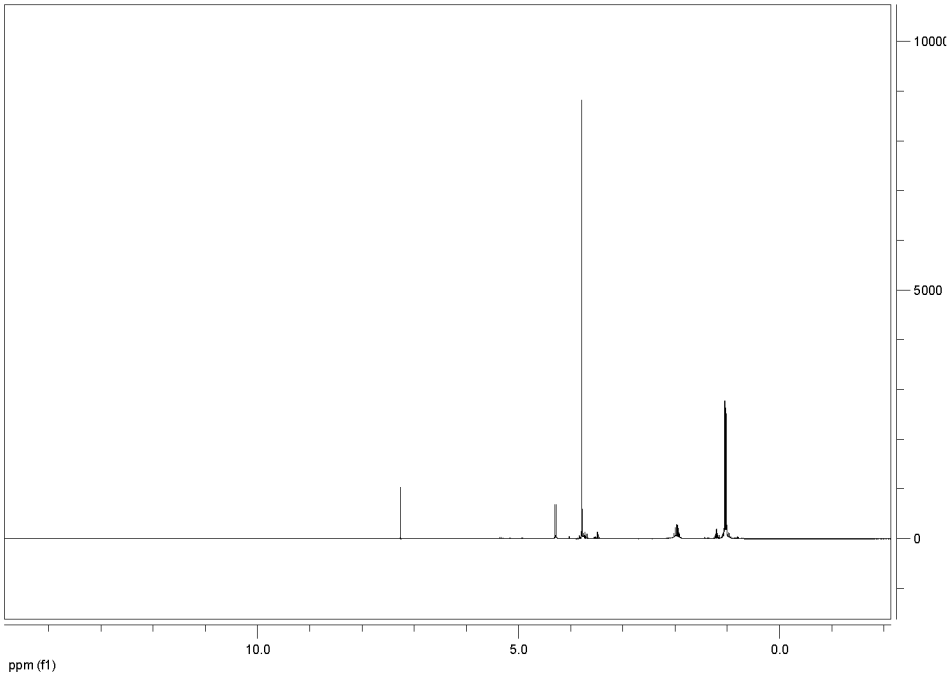

2000
1500
1000
500
0
10.0
5.0
0.0
ppm (f1)

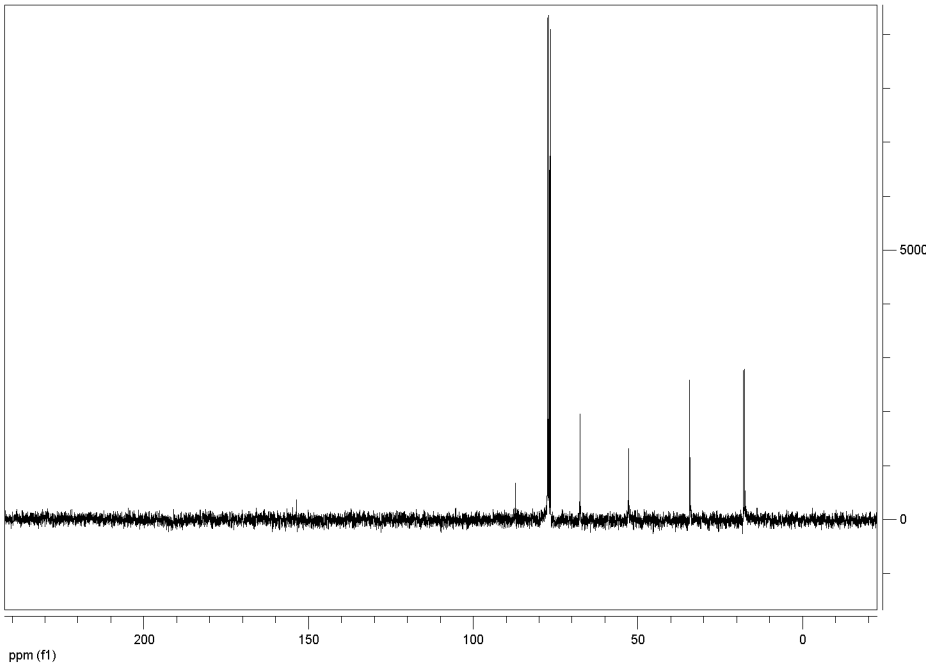

7000
6000
5000
4000
3000
2000
1000
0
-1000
200
150
100
50
0
ppm (f1)

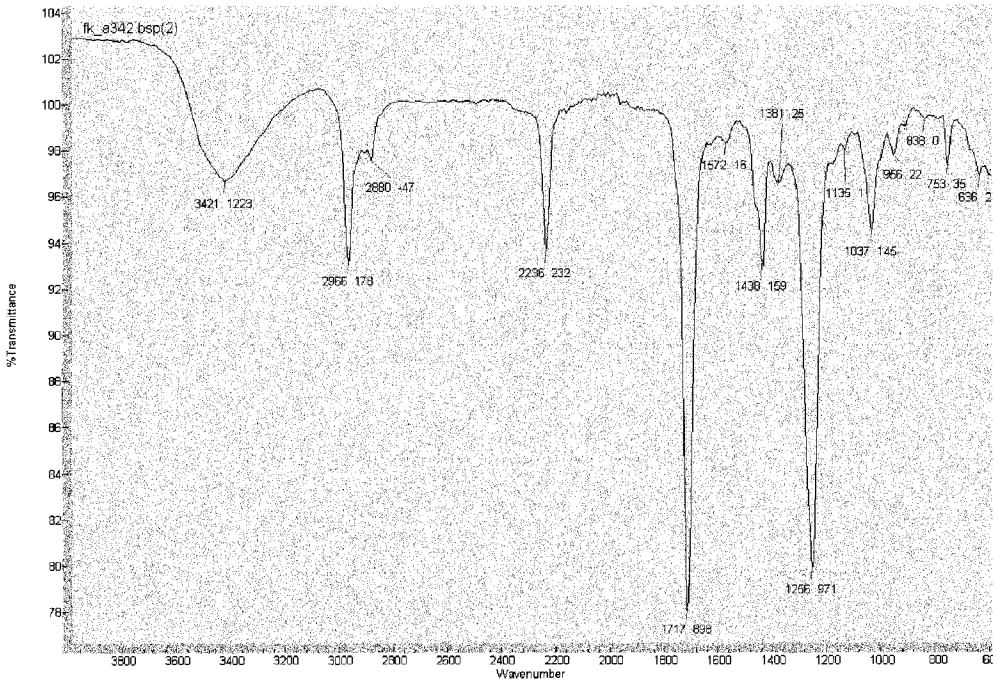

fk_a339 bsp(2)
%Transmittance
Wavenumber
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
2949 264
2869 170
2235 111
1722 520
1494 21
1366 2
1363 14
1192 4
1250 677
1100 89
1063 62
1007 16
962 10
921 10
882 48
796 8
751 19
683 313

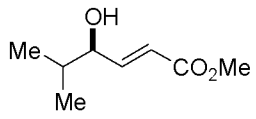

OH
Me
Me
CO_2Me

235

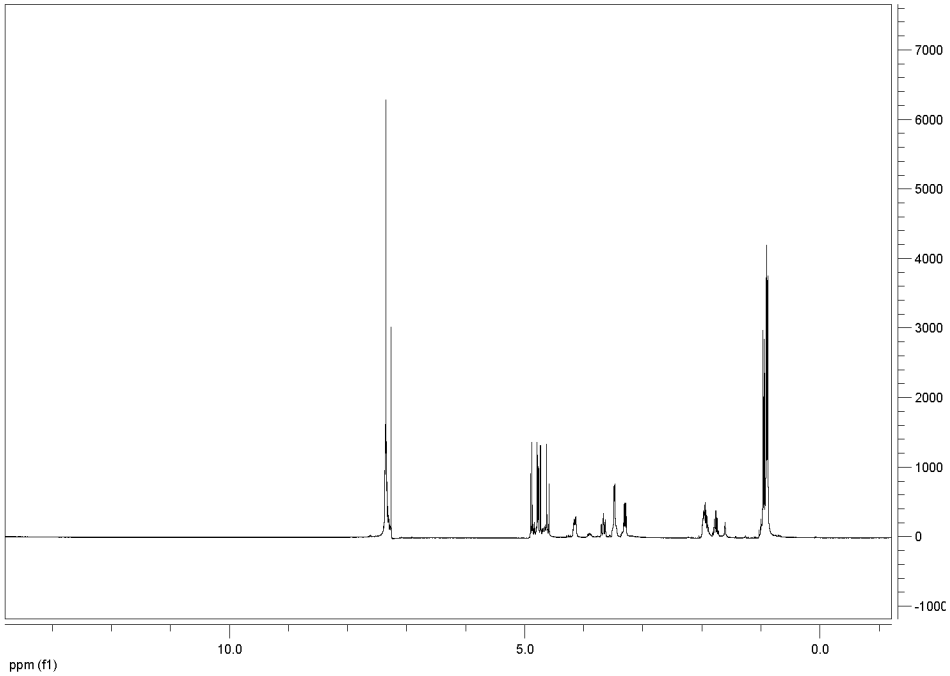

10000
5000
0
10.0
5.0
0.0
ppm (f1)

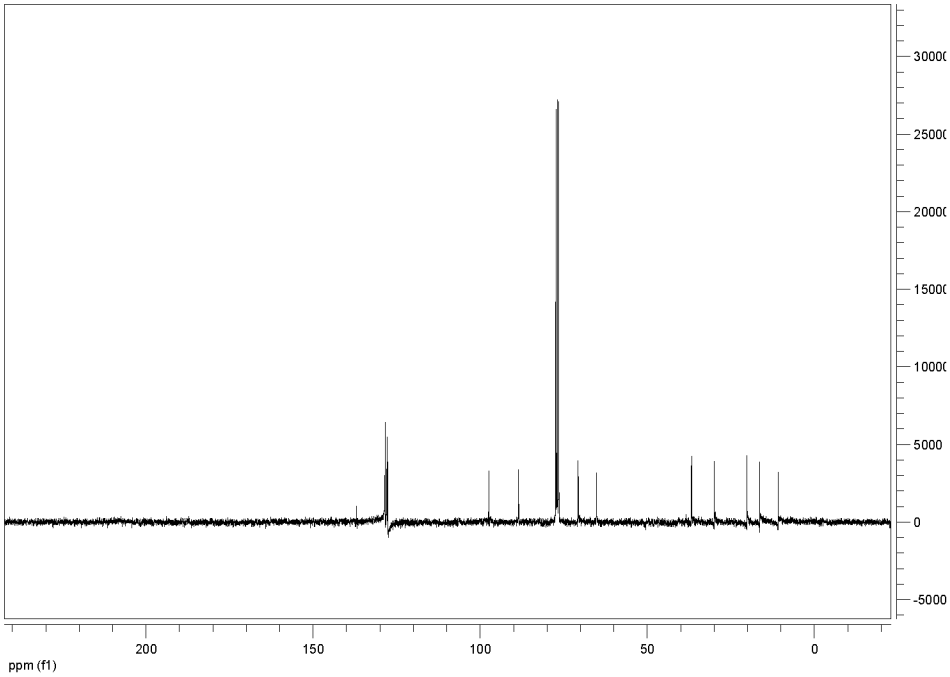

5000
0
200
150
100
50
0
ppm (f1)

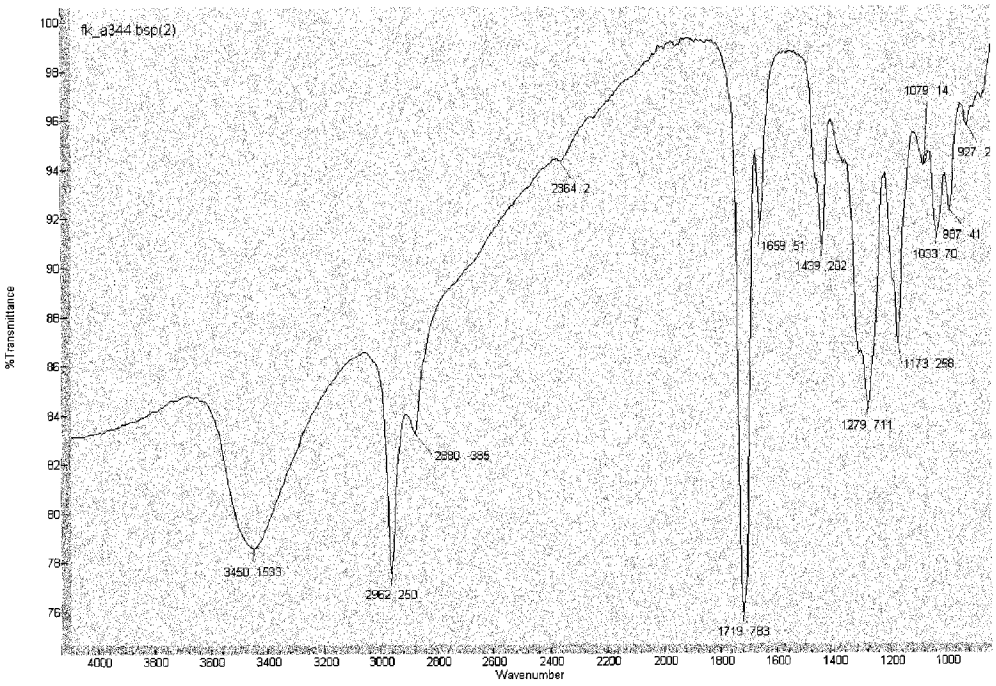

fk_a342.bsp(2)
%Transmittance
Wavenumber
3421 1223
2966 178
2880 47
2236 232
1717 898
1572 15
1381 25
1436 159
1296 971
1135 1
1037 145
966 22
938 0
753 35
636 2

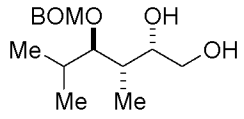

OH
Me
Me
CO_2Me

236

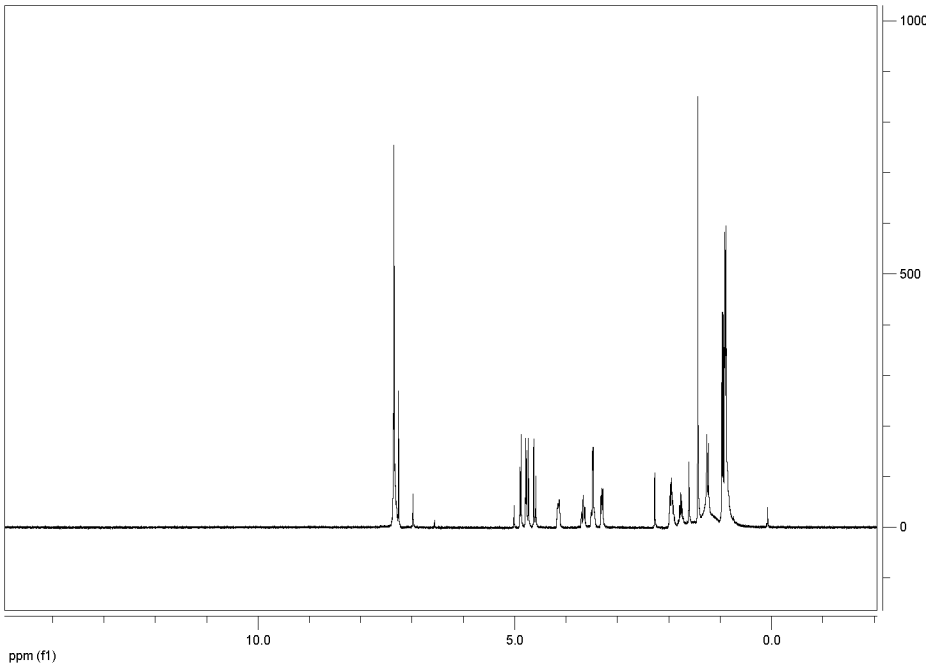

7000
6000
5000
4000
3000
2000
1000
0
-1000
10.0
5.0
0.0
ppm (f1)

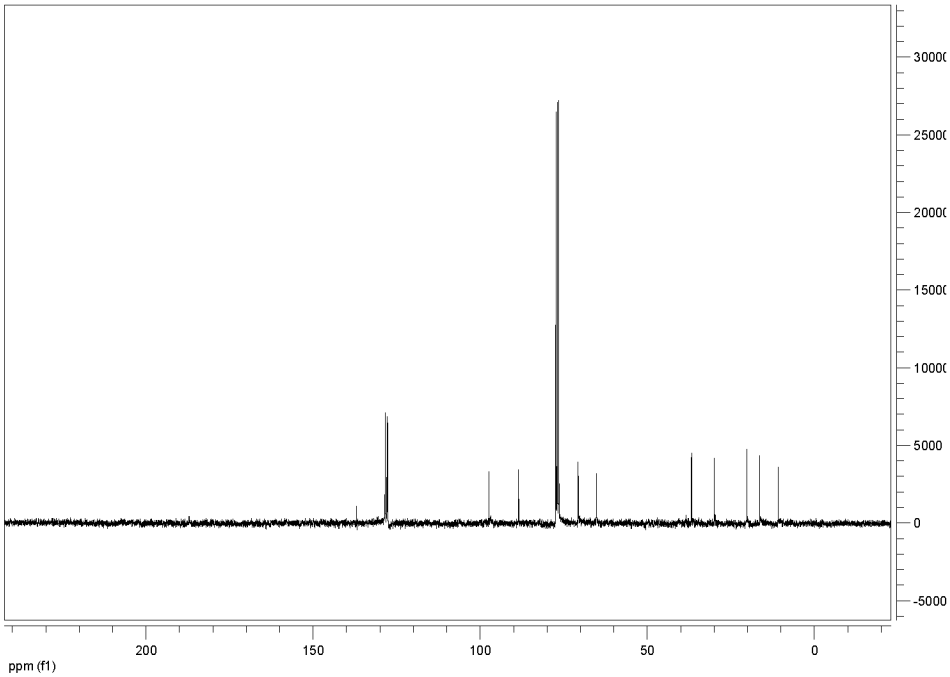

30000
25000
20000
15000
10000
5000
0
-5000
200
150
100
50
0
ppm (f1)

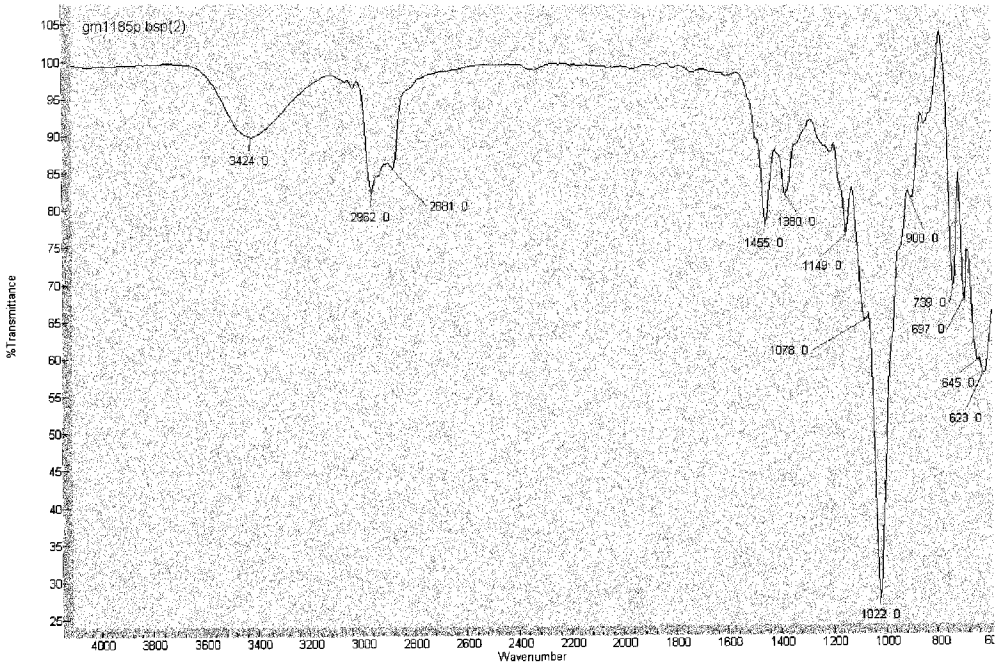

fk_a344 bsp(2)
%Transmittance
Wavenumber
3450.1533
2962.250
2880.395
2364.2
1719.783
1659.51
1439.202
1279.711
1173.268
1079.14
1033.70
987.41
927.2

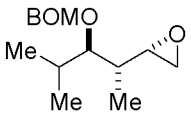

BOMO
OH
Me
OH
Me
Me

238

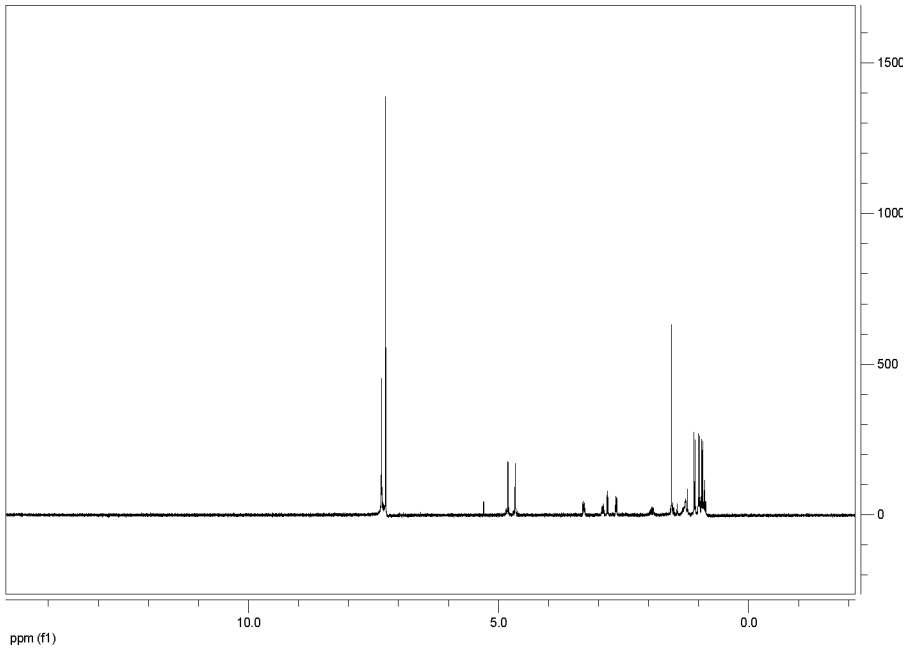

1000
500
0
10.0
5.0
0.0
ppm (f1)

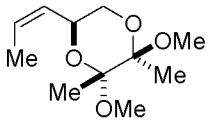

3000
2500
2000
1500
1000
5000
0
-5000
200
150
100
50
0
ppm (f1)


gm1185p.esp(2)
%Transmittance
Wavenumber
3424.0
2962.0
2681.0
1455.0
1380.0
1149.0
1078.0
1022.0
900.0
739.0
697.0
645.0
623.0

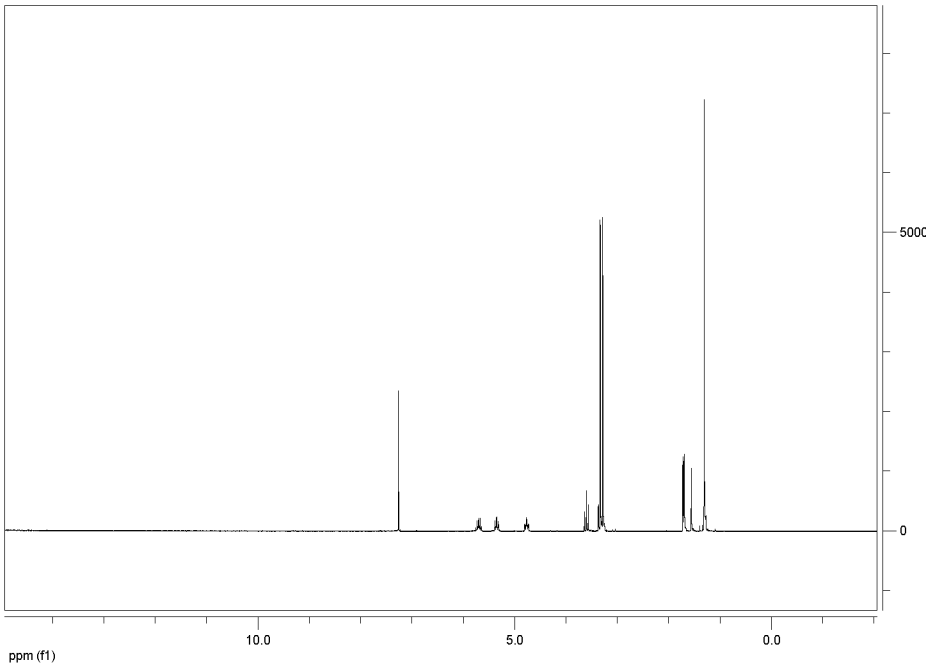

BOMO
Me
Me
Me
O

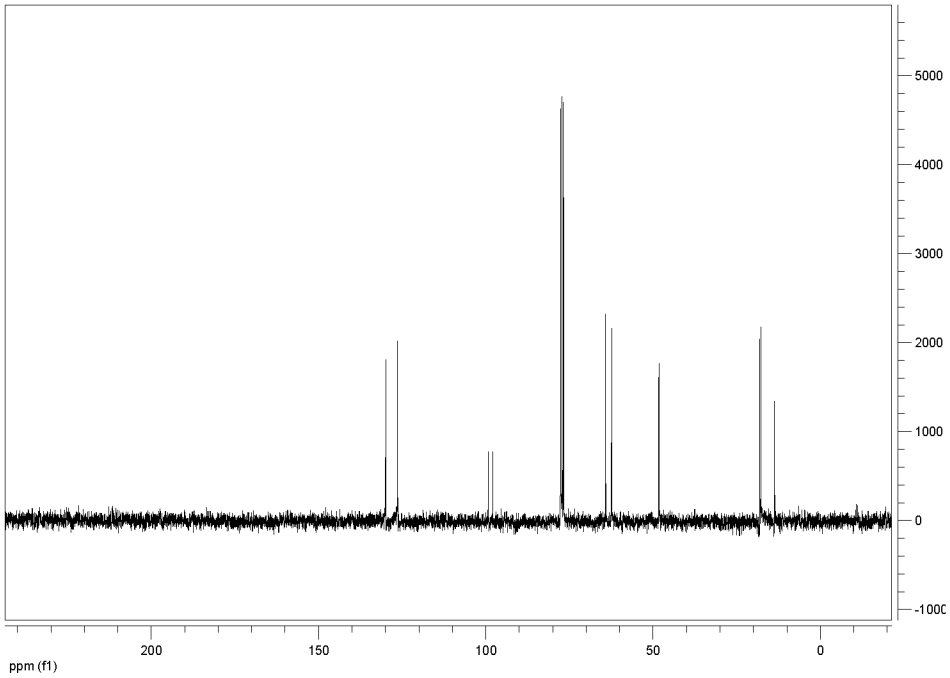
222

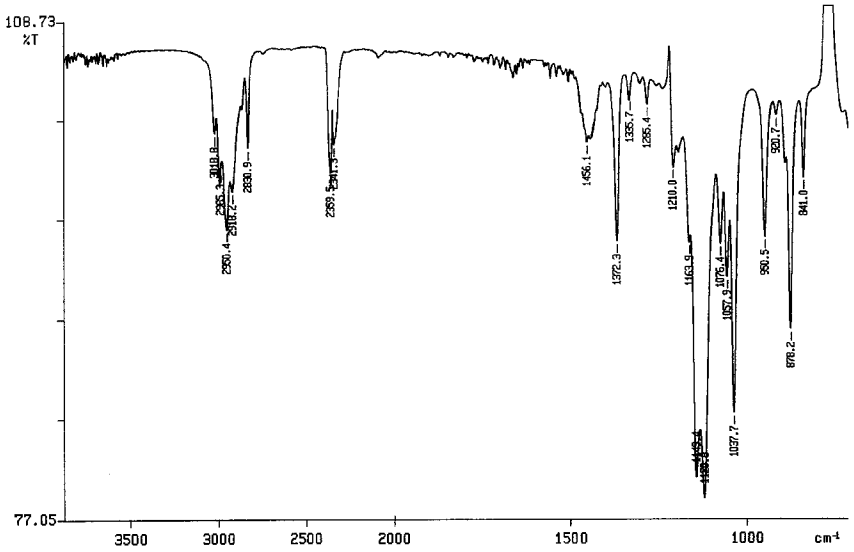

1500
1000
500
0
10.0
5.0
0.0
ppm (f1)

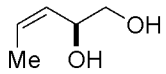

Me
O
O
OMe
Me
Me
OMe

247

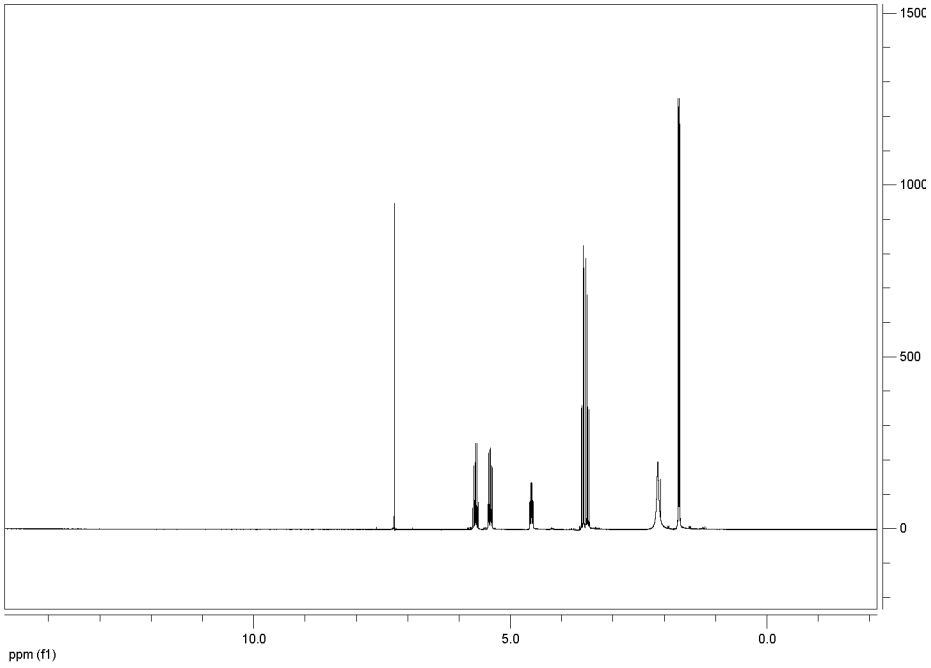

5000
0
10.0
5.0
0.0
ppm (f1)

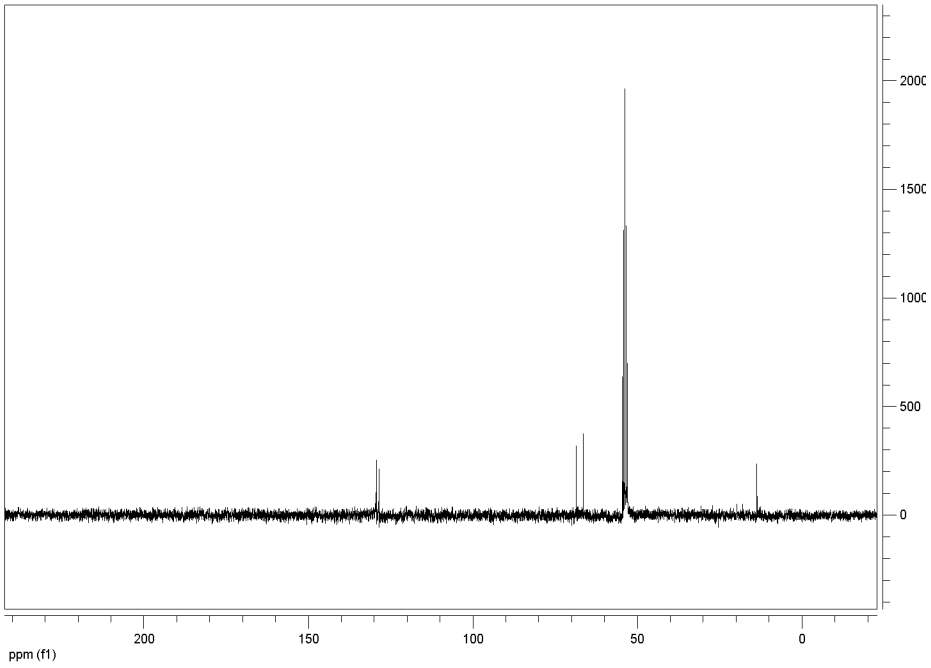

5000
4000
3000
2000
1000
0
-1000
200
150
100
50
0
ppm (f1)

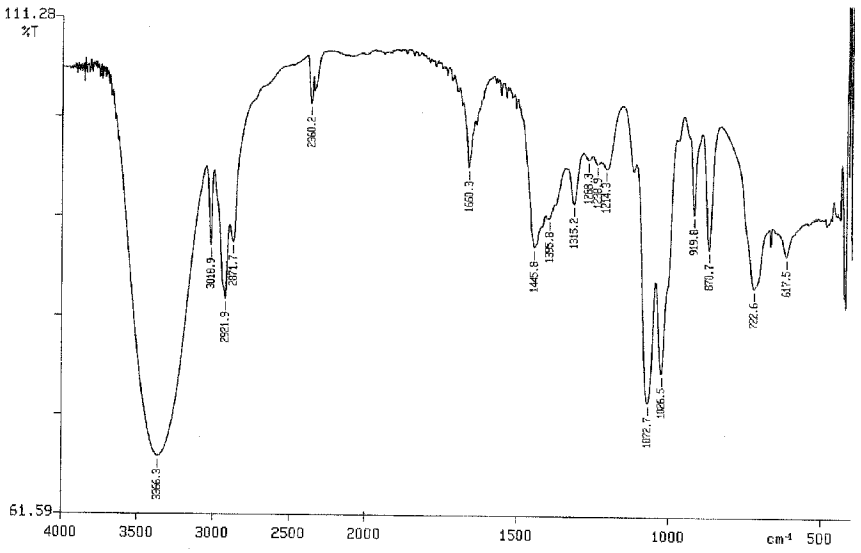

108.73
%T
77.05
3500
3000
2500
2000
1500
1000
cm-1
2930.9
2850.4
2389.5
1456.1
1372.3
1335.7
1285.4
1210.0
1163.9
1076.4
1057.9
1037.7
980.5
920.7
878.2
841.0

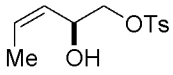

OH
Me
OH

248

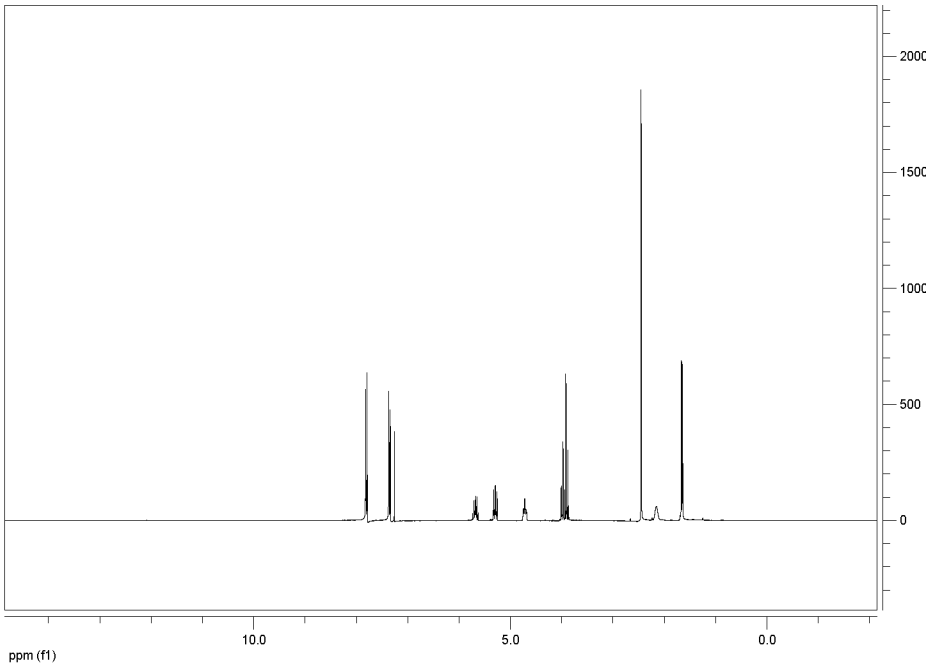

1500
1000
500
0
10.0
5.0
0.0
ppm (f1)

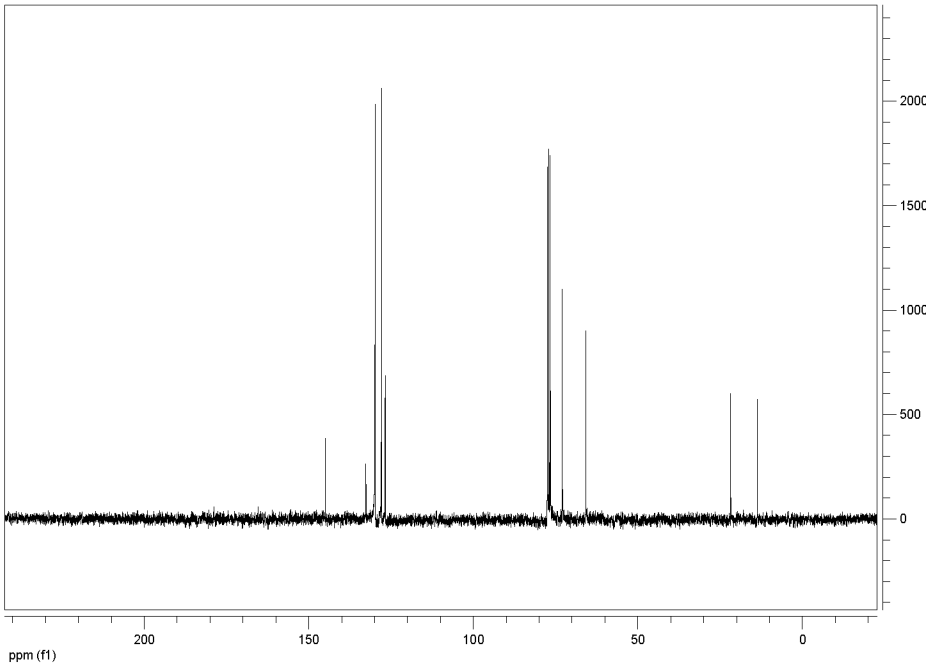

2000
1500
1000
500
0
200
150
100
50
0
ppm (f1)

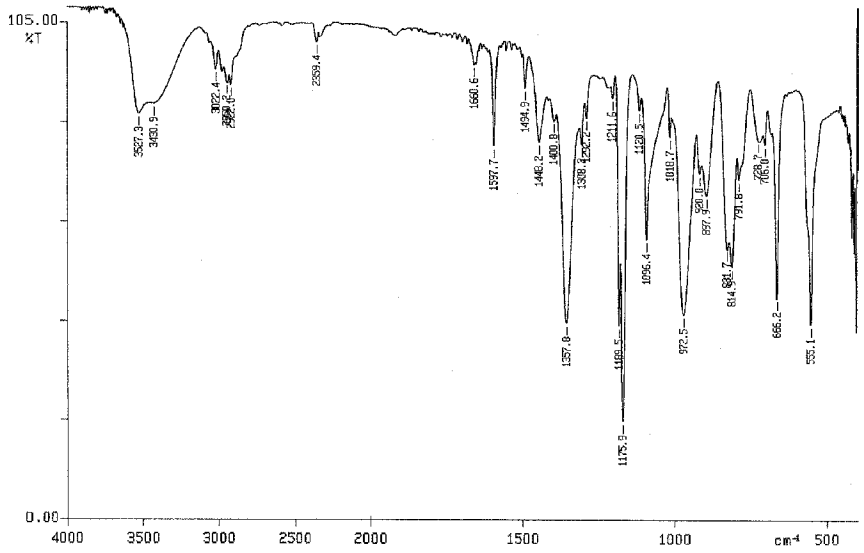

111.28
%T
61.59
4000
3500
3000
2500
2000
1500
1000
cm-1
500
3356.3
3016.9
2921.9
2871.7
2360.2
1650.3
1445.8
1395.8
1315.2
1072.7
1006.5
919.8
870.7
722.6
617.5

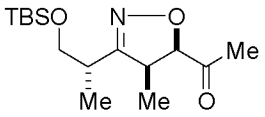

OTs
Me
OH

250

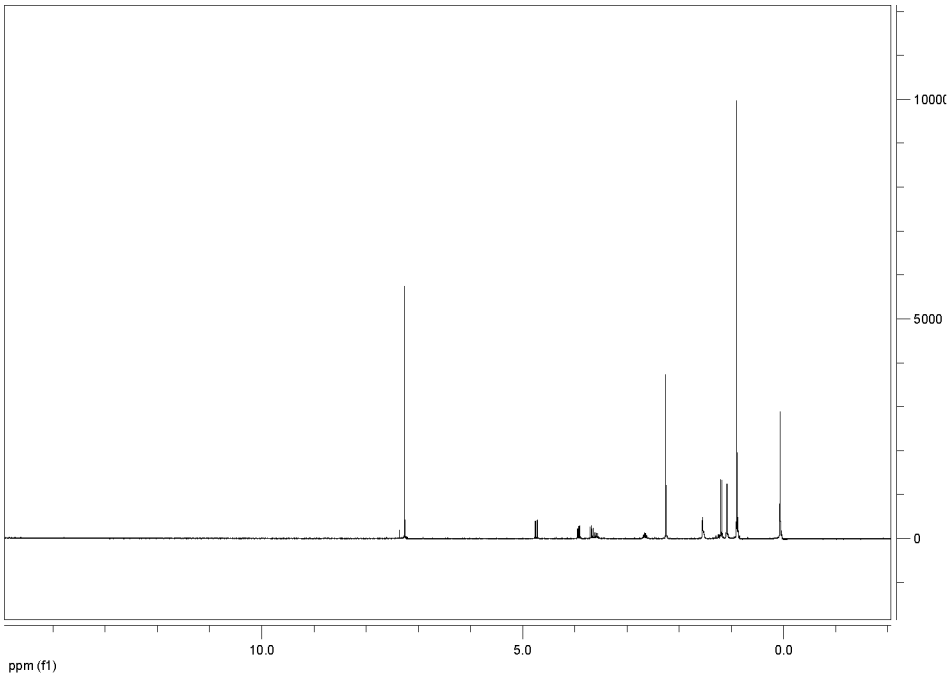

2000
1500
1000
500
0
10.0
5.0
0.0
ppm (f1)

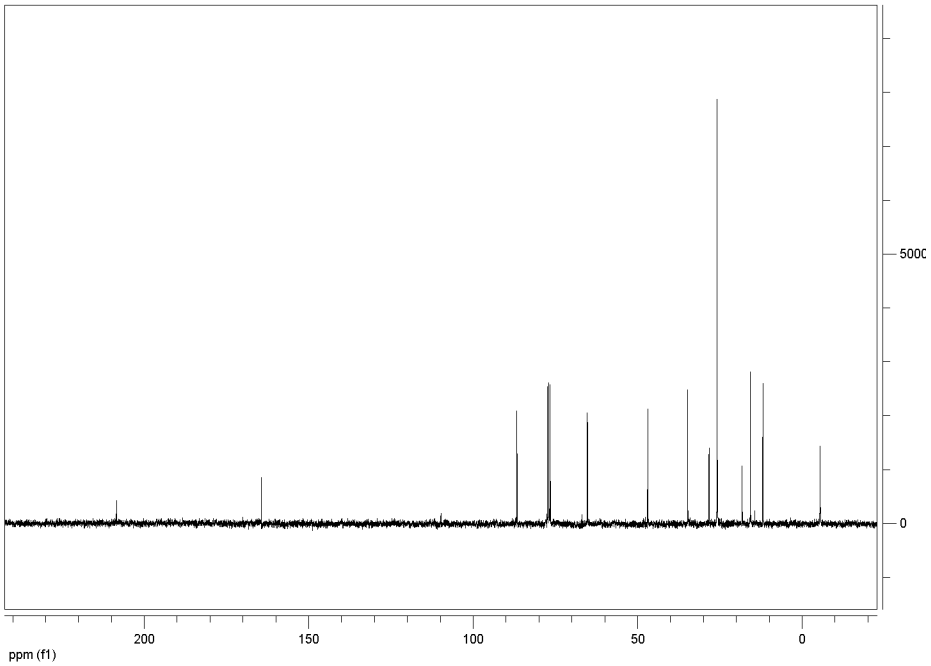

2000
1500
1000
500
0
200
150
100
50
0
ppm (f1)

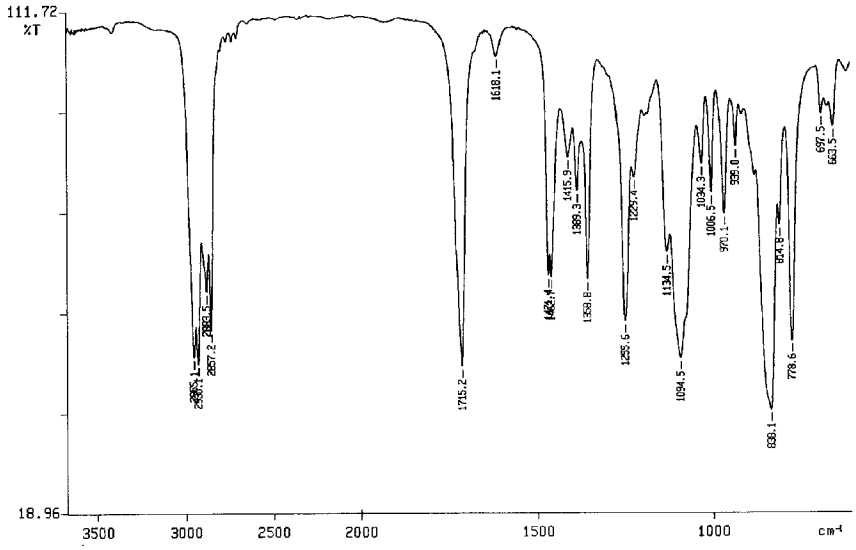

105.00
%T
0.00
4000
3500
3000
2500
2000
1500
1000
500
cm-1
3527.3
3430.9
2359.4
1660.6
1597.7
1494.9
1446.2
1400.8
1357.0
1211.6
1175.9
1096.4
1018.7
972.5
857.9
814.3
791.8
728.2
705.0
666.2
555.1

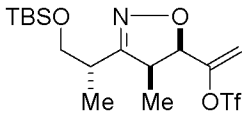

TBSO
N
O
Me
Me
Me
O

256

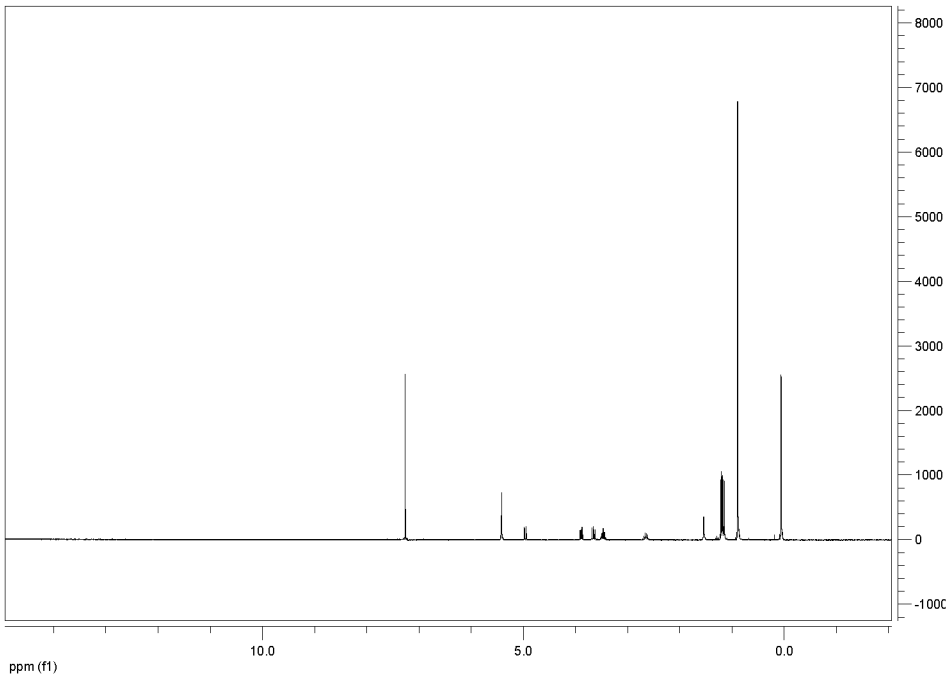

10000
5000
0
10.0
5.0
0.0
ppm (f1)

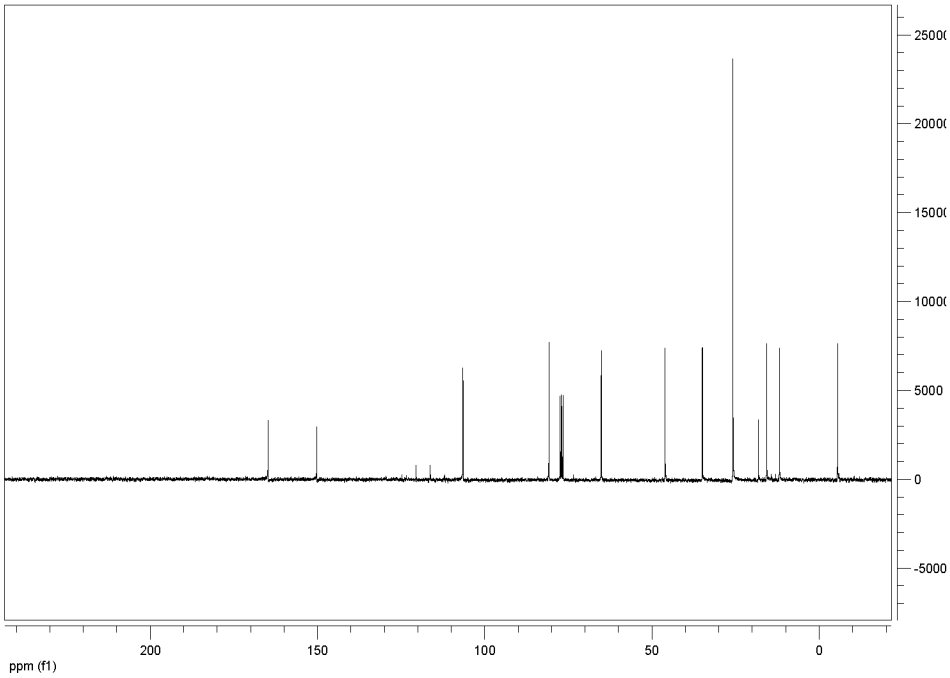

5000
0
200
150
100
50
0
ppm (f1)

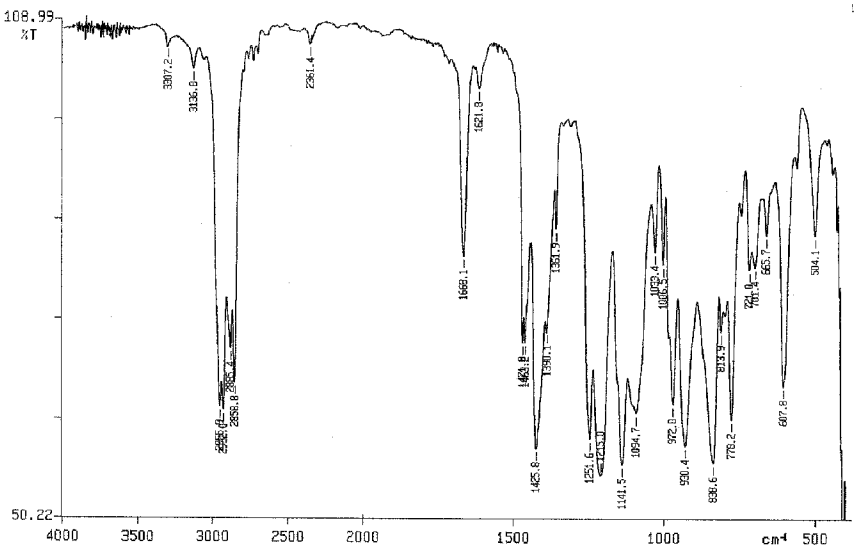

111.72
%T
18.96
3500
3000
2500
2000
1500
1000
cm-1
1715.2
1618.1
1359.8
1255.6
1094.5
778.6
698.1

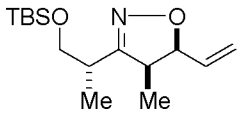

TBSO
N
O
Me
Me
OTf

257

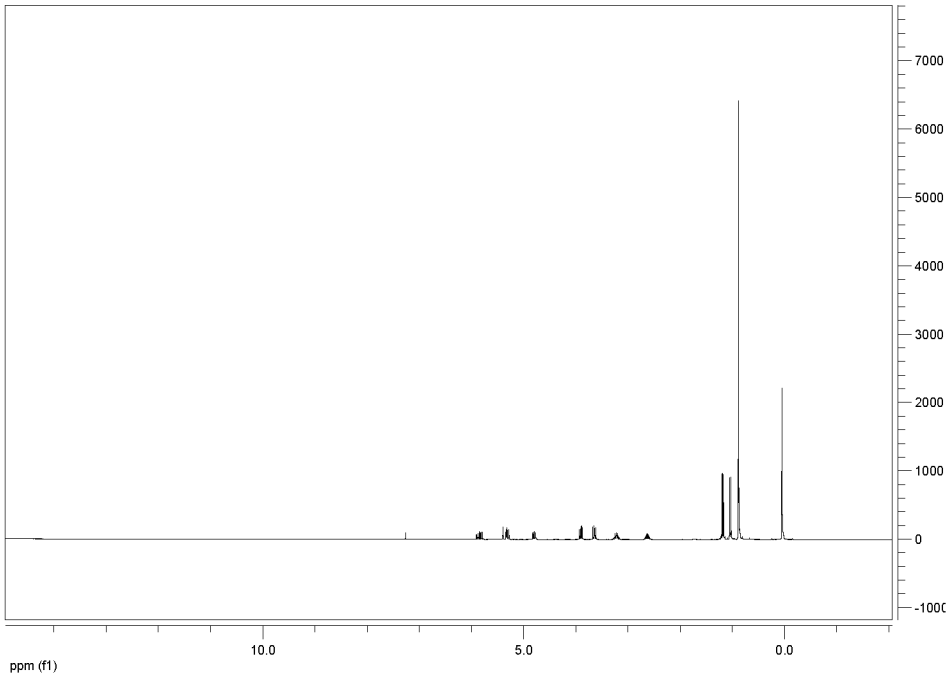

8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10.0
5.0
0.0
ppm (f1)

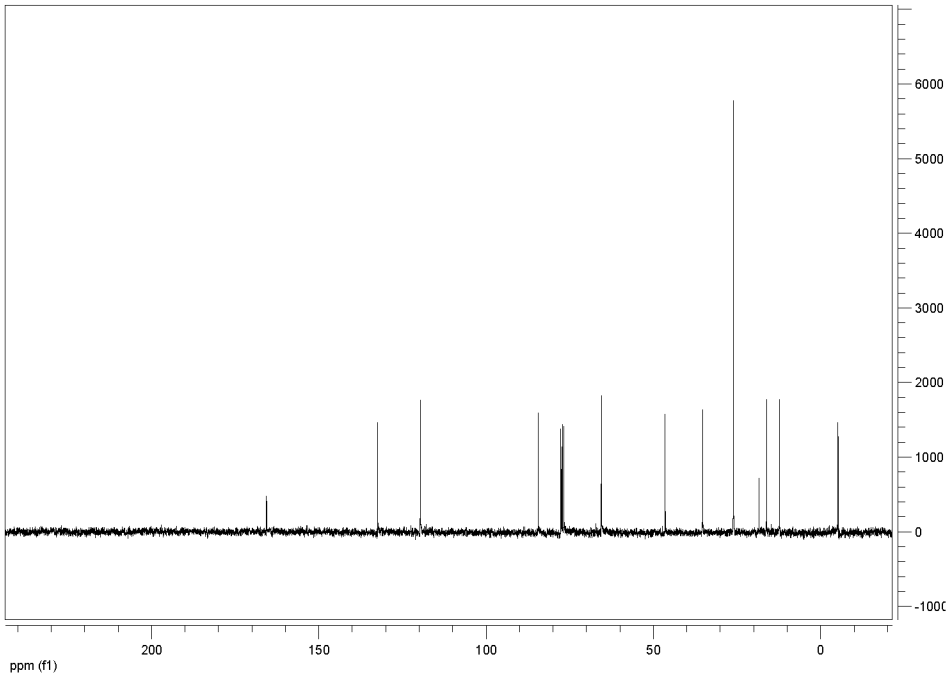

25000
20000
15000
10000
5000
0
-5000
200
150
100
50
0
ppm (f1)

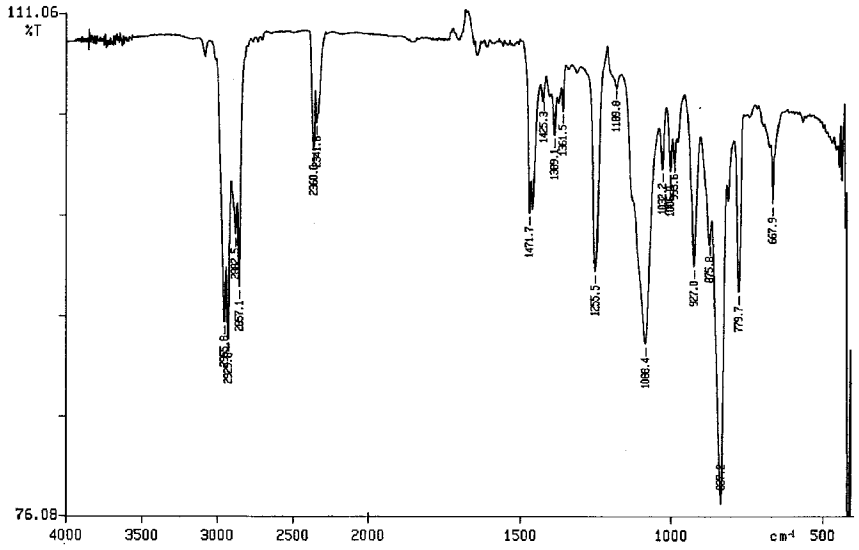

108.99
%T
50.22
3397.2
3136.8
2961.4
1668.1
1621.8
1425.8
1390.1
1361.9
1251.6
1213.3
1141.5
1054.7
1023.4
1002.5
972.8
930.4
838.6
778.2
721.0
701.4
665.7
607.8
504.1
4000
3500
3000
2500
2000
1500
1000
cm-1
500

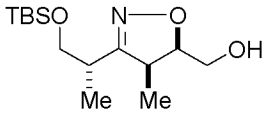

TBSO
N
O
Me
Me

252

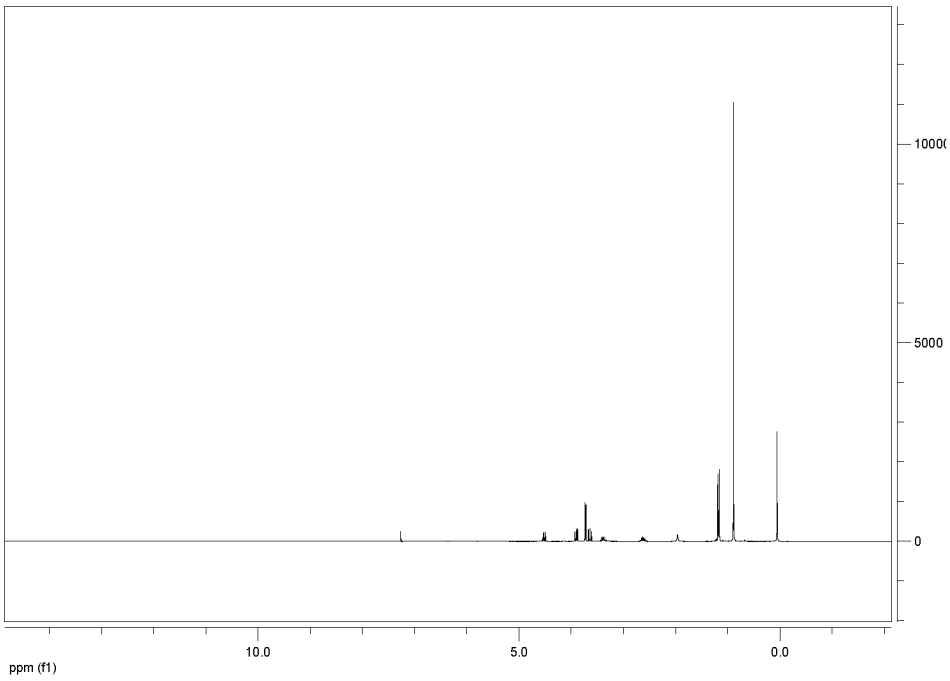

7000
6000
5000
4000
3000
2000
1000
0
-1000
10.0
5.0
0.0
ppm (f1)

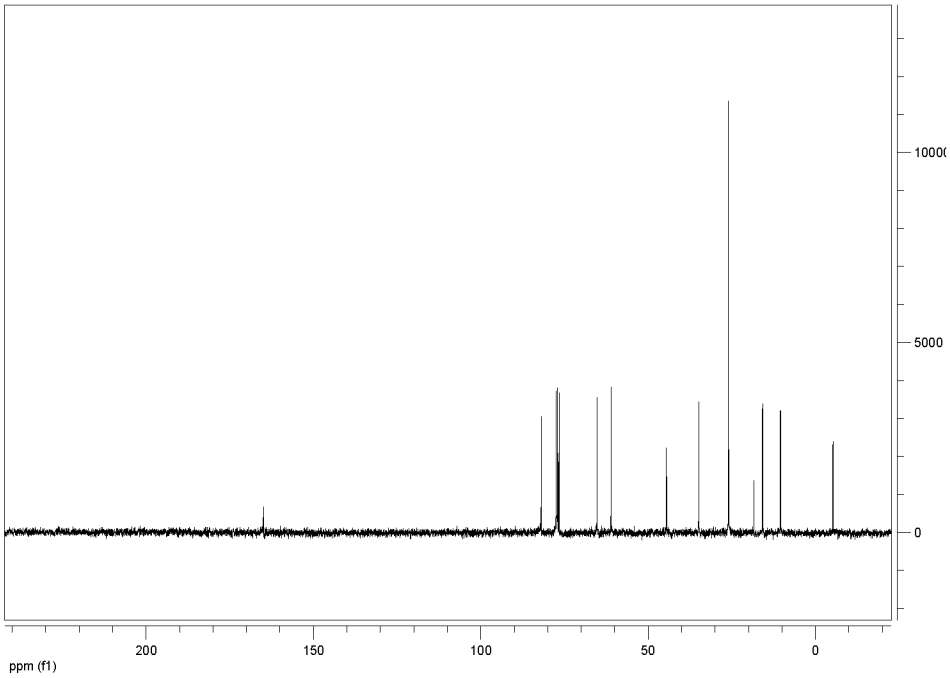

6000
5000
4000
3000
2000
1000
0
-1000
200
150
100
50
0
ppm (f1)

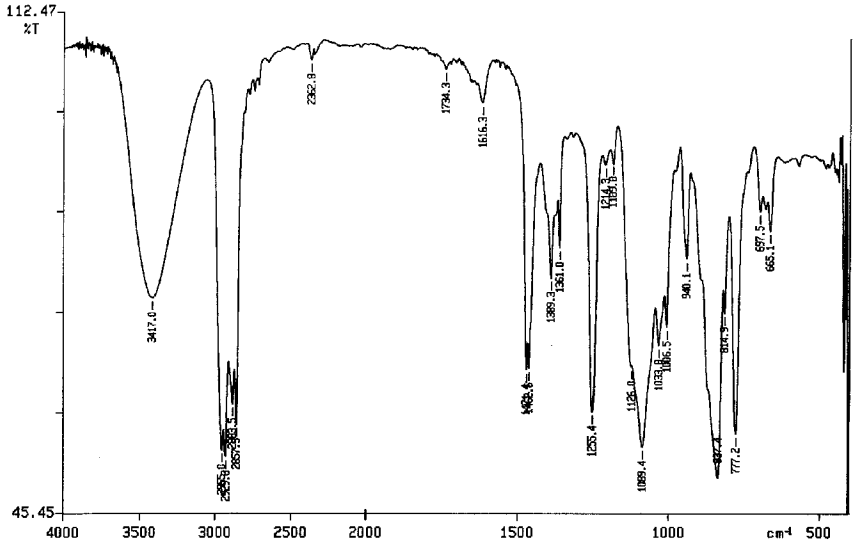

111.06
%T
76.08
4000
3500
3000
2500
2000
1500
1000
cm-1
500
2957.1
2360.0
1471.7
1425.3
1389.1
1351.5
1255.5
1189.8
1086.4
927.0
875.8
779.7
667.9

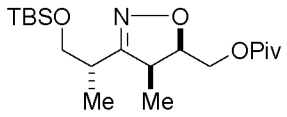

TBSO
N
O
OH
Me
Me

258

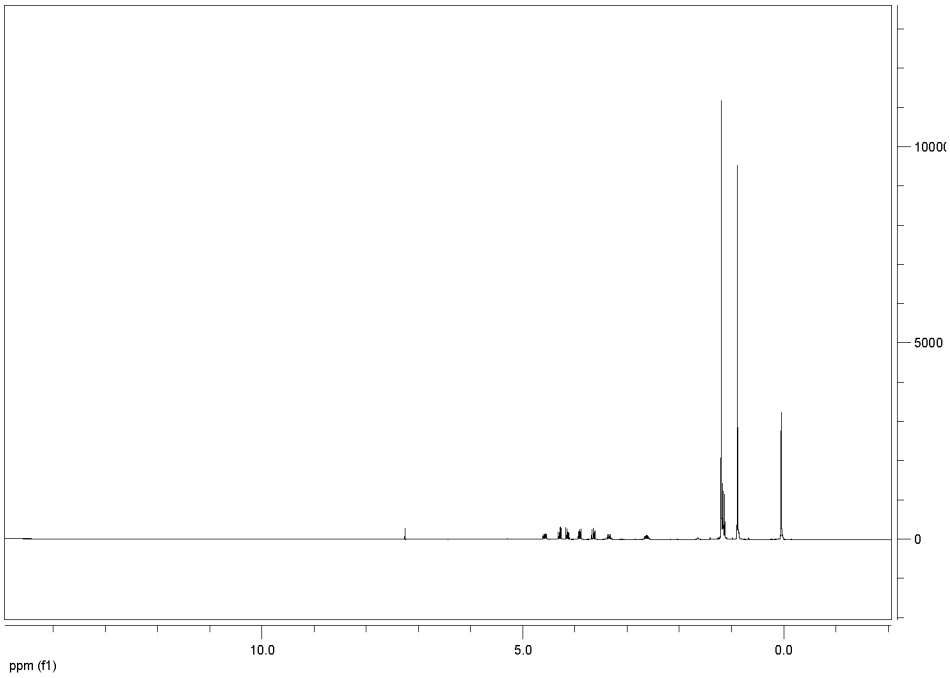

10000
5000
0
10.0
5.0
0.0
ppm (f1)

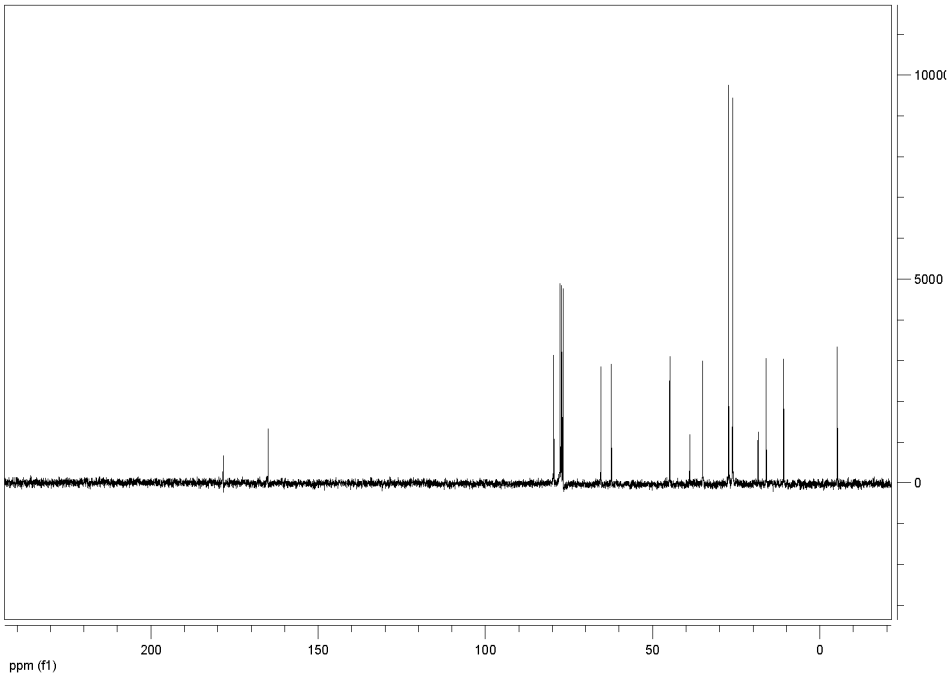

10000
5000
0
200
150
100
50
0
ppm (f1)

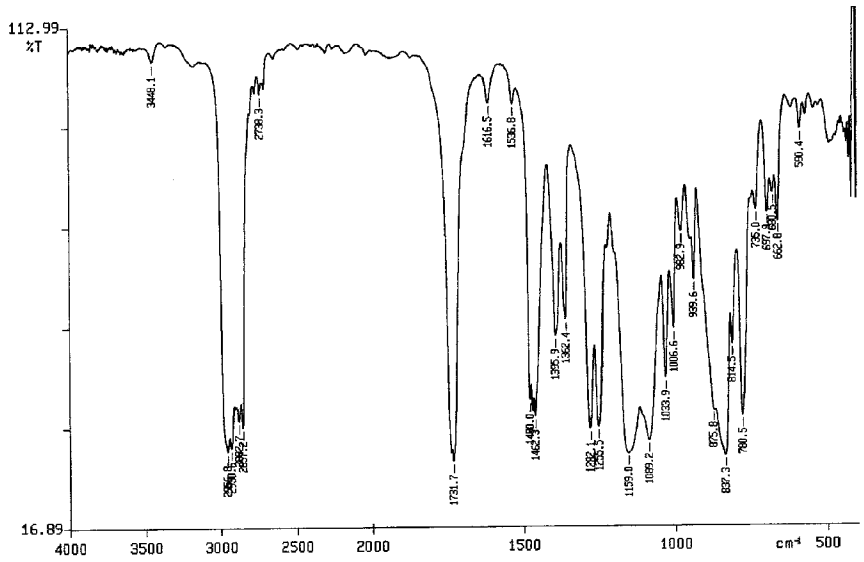

112.47
%T
45.45
3417.0
2362.8
1734.3
1616.3
1389.3
1361.0
1255.4
1089.4
940.1
777.2
697.5
665.1
4000
3500
3000
2500
2000
1500
1000
cm-1
500

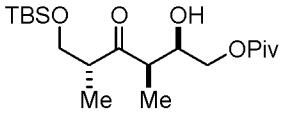

TBSO
N
O
OPiv
Me
Me

259

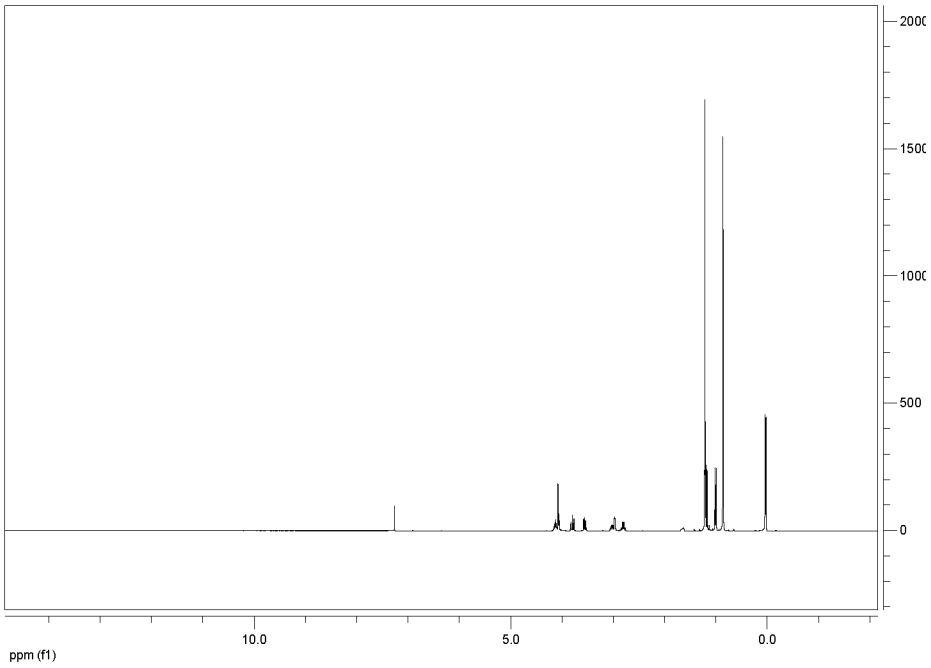

10000
5000
0
10.0
5.0
0.0
ppm (f1)

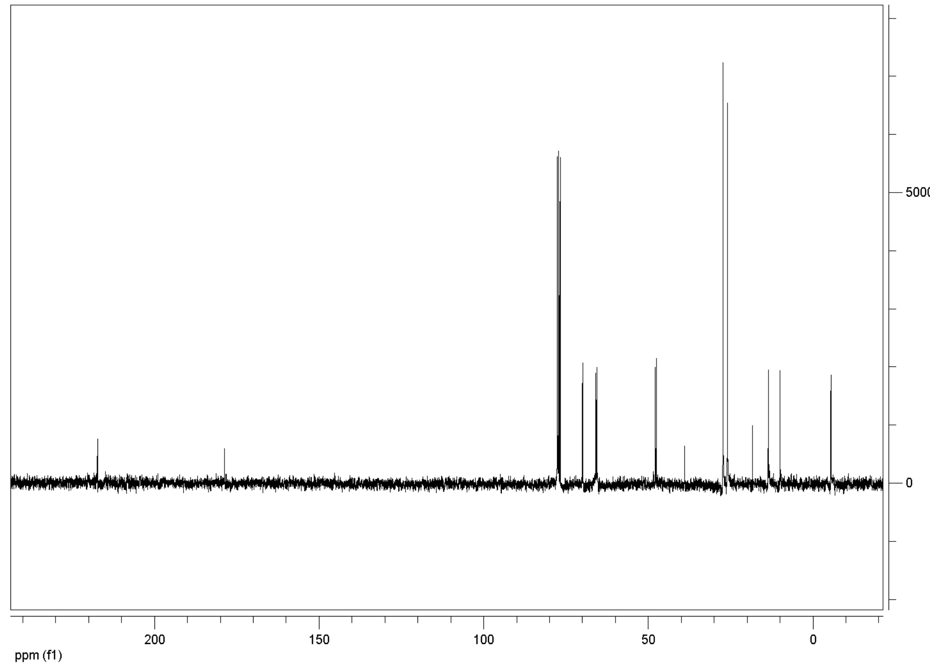

10000
5000
0
200
150
100
50
0
ppm (f1)

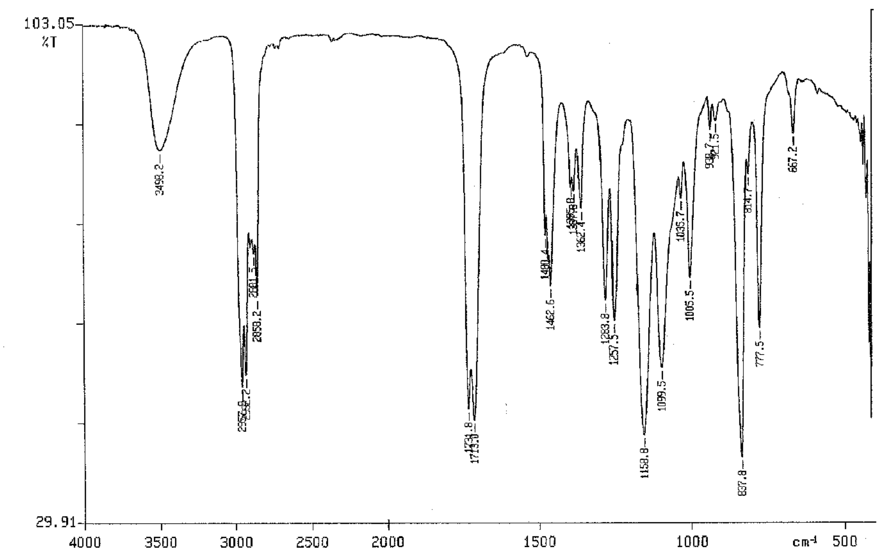

112.99
%T
16.89
4000
3500
3000
2500
2000
1500
1000
cm-1
500
3446.1
2738.3
1731.7
1616.5
1536.8
1462.0
1295.9
1362.4
1159.0
1089.2
1033.9
1006.6
982.3
939.6
875.8
837.3
814.5
780.5
735.0
690.5
662.8
590.4

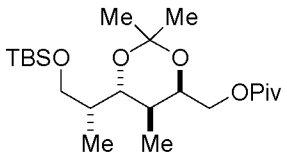

TBSO
O
OH
OPiv
Me
Me

260

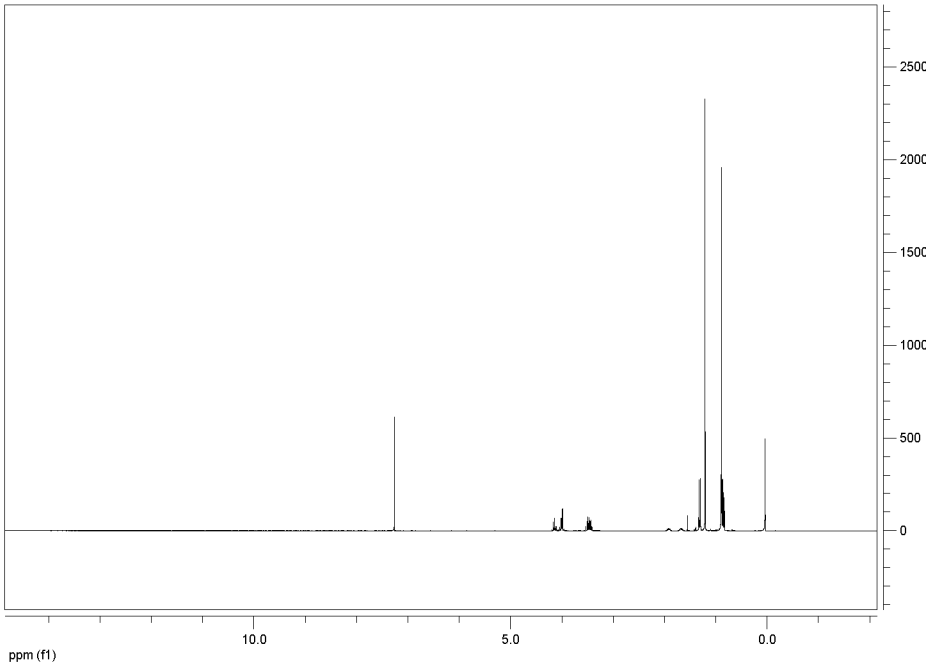

2000
1500
1000
500
0
10.0
5.0
0.0
ppm (f1)

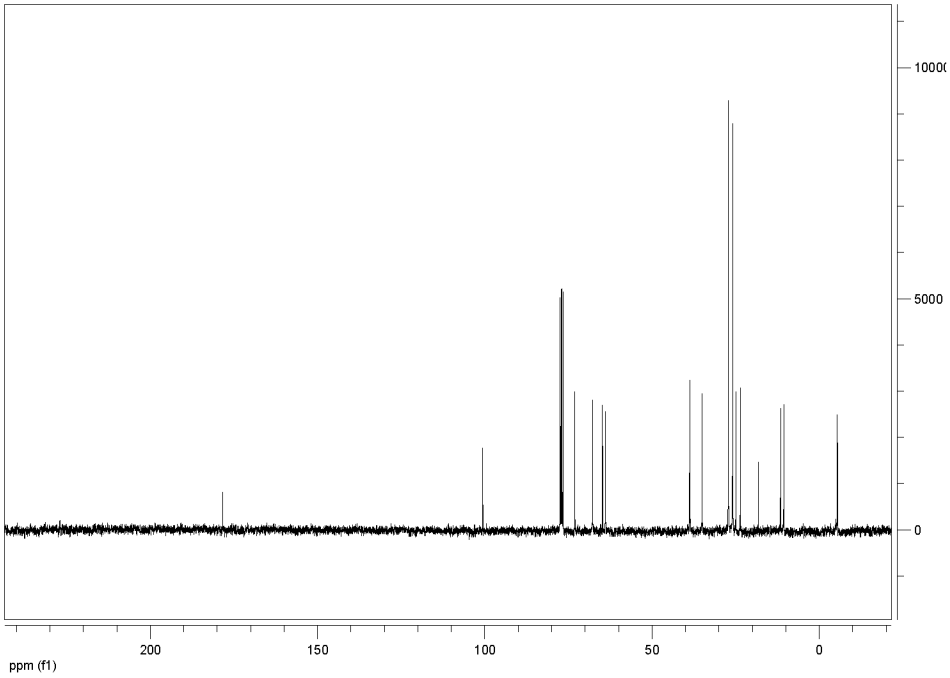

5000
0
200
150
100
50
0
ppm (f1)

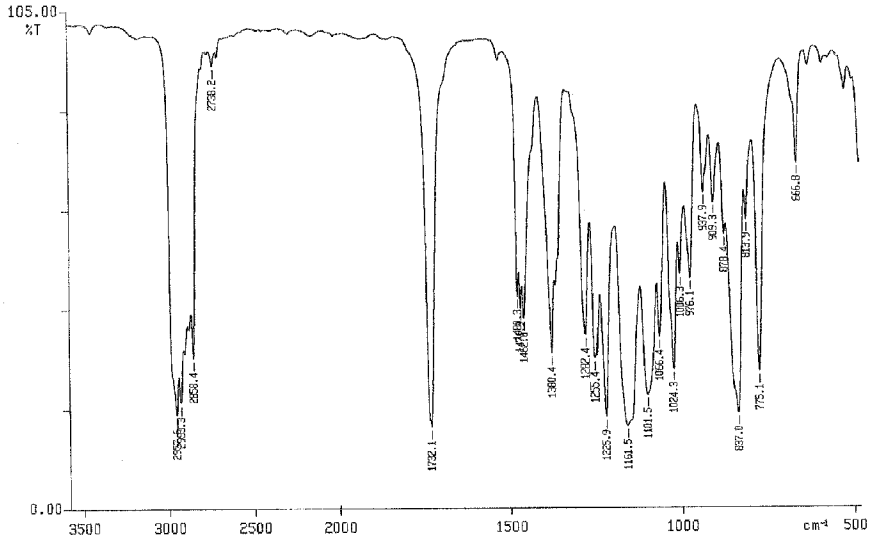

103.05
%T
29.91
4000
3500
3000
2500
2000
1500
1000
cm-1
500
3498.2
2859.2
1731.8
1462.6
1362.4
1283.8
1257.5
1158.8
1099.5
1035.7
1005.5
837.8
777.5
814.7
667.2

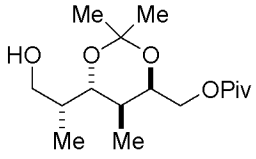

Me
Me
TBSO
O
O
OPiv
Me
Me

265

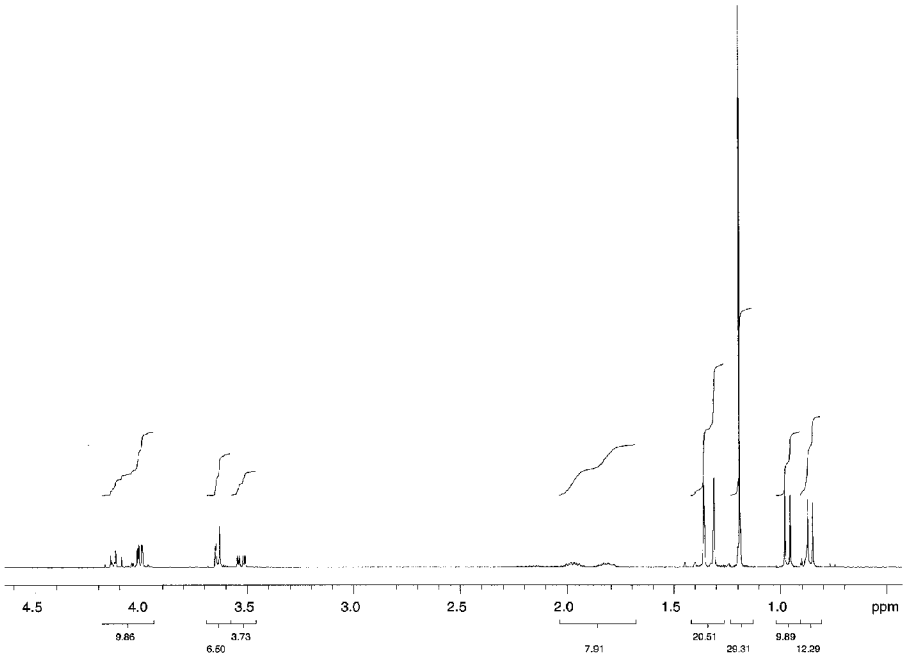

2500
2000
1500
1000
500
0
10.0
5.0
0.0
ppm (f1)

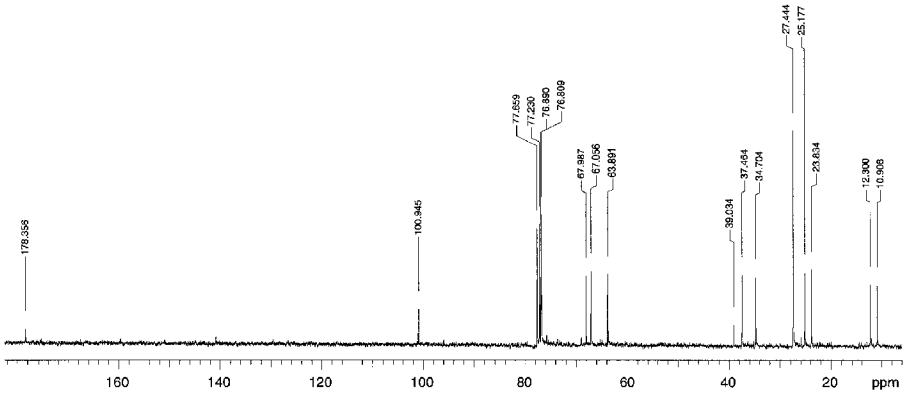

10000
5000
0
200
150
100
50
0
ppm (f1)

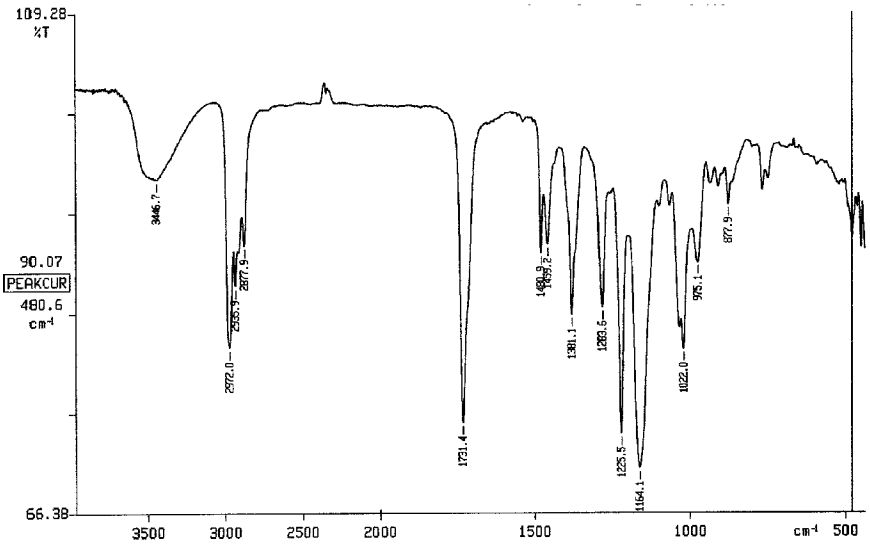

105.00
%T
0.00
3500
3000
2500
2000
1500
1000
cm-1
500
2958.3
2850.4
1732.1
1380.4
1232.4
1225.9
1161.5
1101.5
1024.3
976.1
957.9
905.3
857.0
775.1
666.8

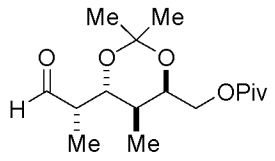

Me
Me
HO
O
O
OPiv
Me
Me

266

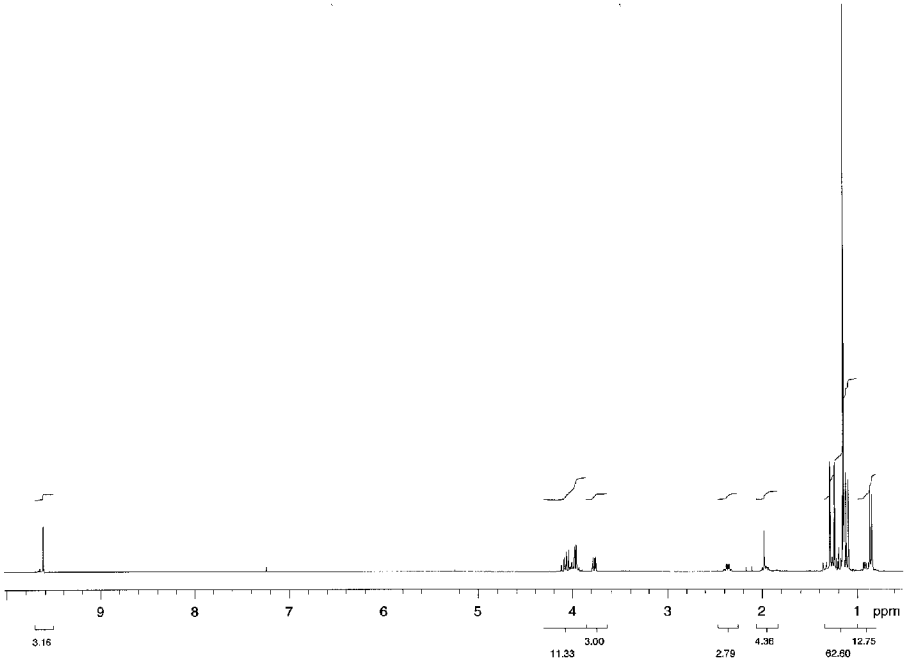

4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
9.86
3.73
6.60
7.91
20.51
28.31
9.89
12.29

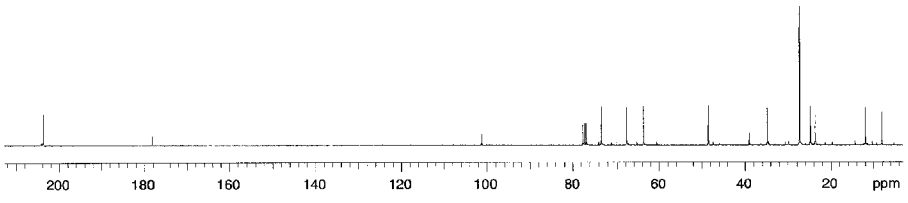

178.358
100.945
77.659
77.250
76.980
76.809
67.987
67.056
63.891
39.034
37.464
34.704
27.444
25.177
23.634
12.900
10.968
160
140
120
100
80
60
40
20
ppm

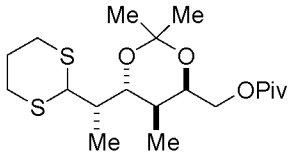

109.28
%T
90.07
PEAKCUR
480.6
cm-1
66.38
3446.7
2972.0
2935.9
2877.9
1731.4
1459.2
1381.1
1263.6
1225.5
1164.1
1022.0
975.1
877.9
3500
3000
2500
2000
1500
1000
cm-1
500


Me
Me
O
O
O
H
OPiv
Me
Me

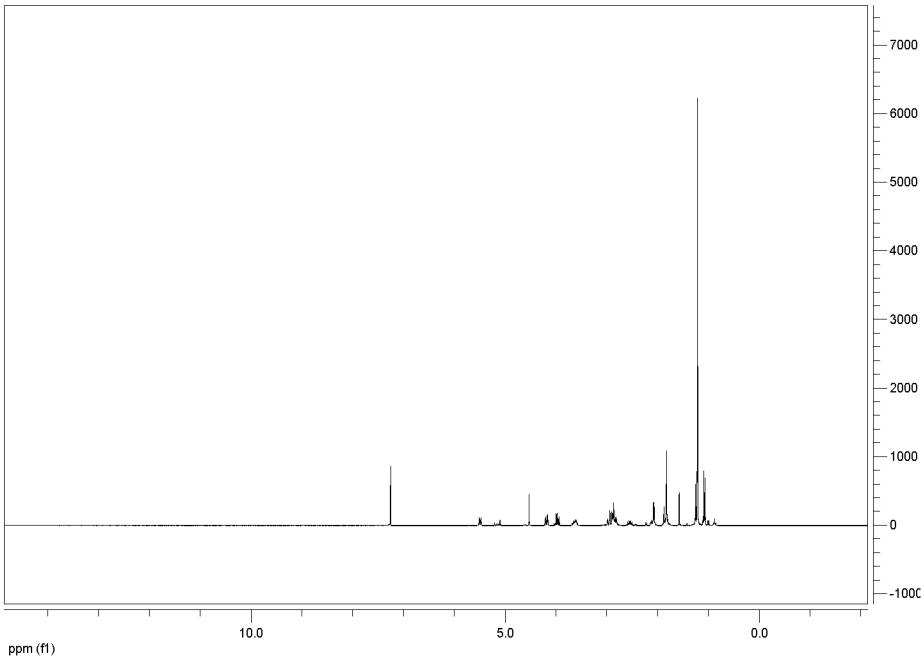
267

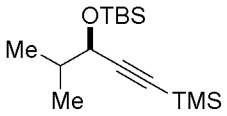

9
8
7
6
5
4
3
2
1
ppm
3.16
11.33
3.00
2.79
4.36
62.60
12.75


200
180
160
140
120
100
80
60
40
20
ppm

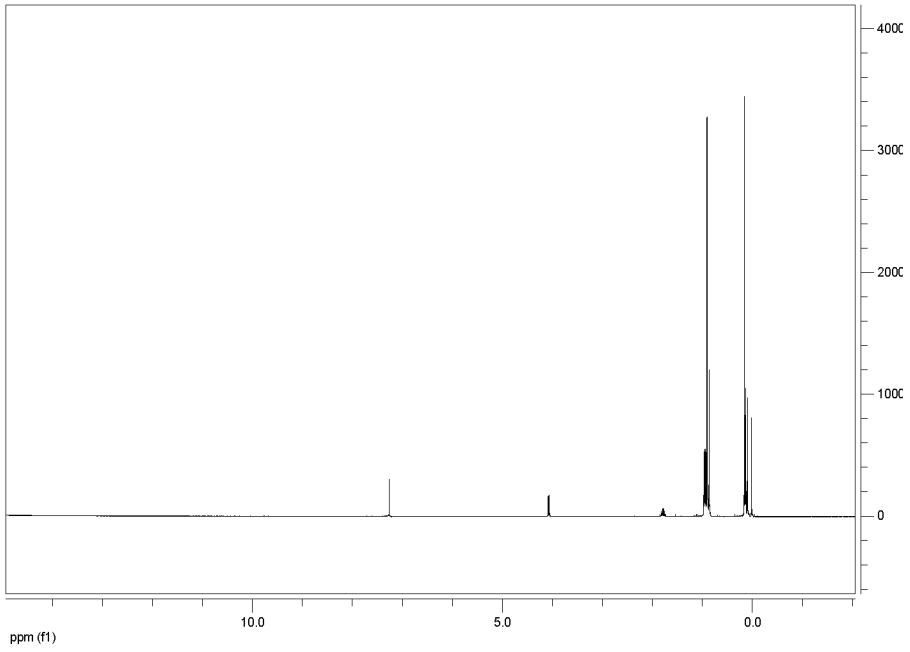

Me
Me
S
O
O
OPiv
S
Me
Me

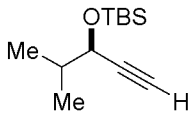
268


7000
6000
5000
4000
3000
2000
1000
0
-1000
10.0
5.0
0.0
ppm (f1)

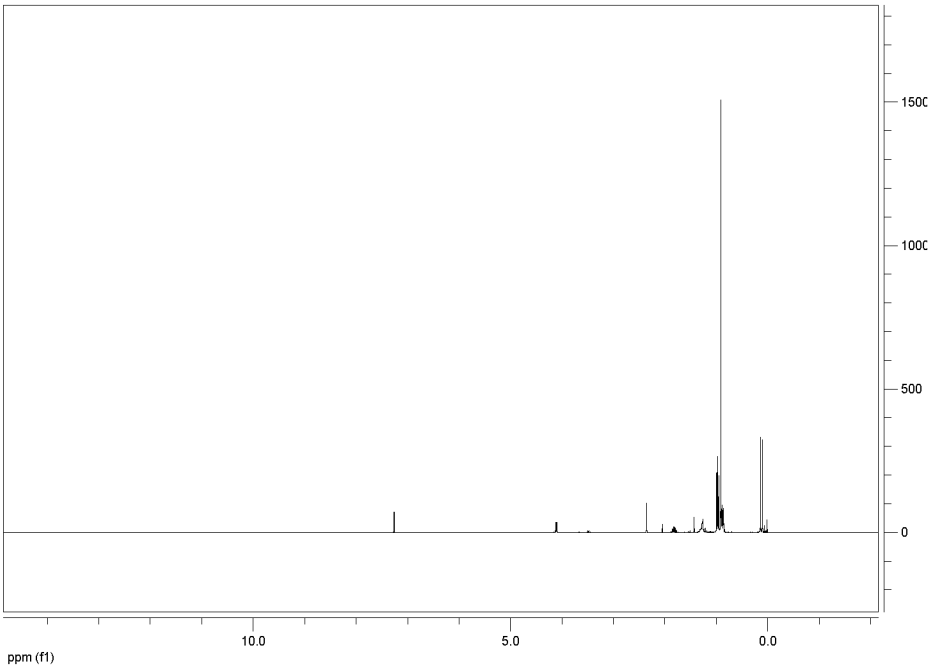

OTBS
Me
Me
TMS

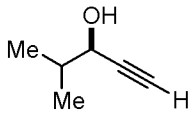
278


4000
3000
2000
1000
0
10.0
5.0
0.0
ppm (f1)

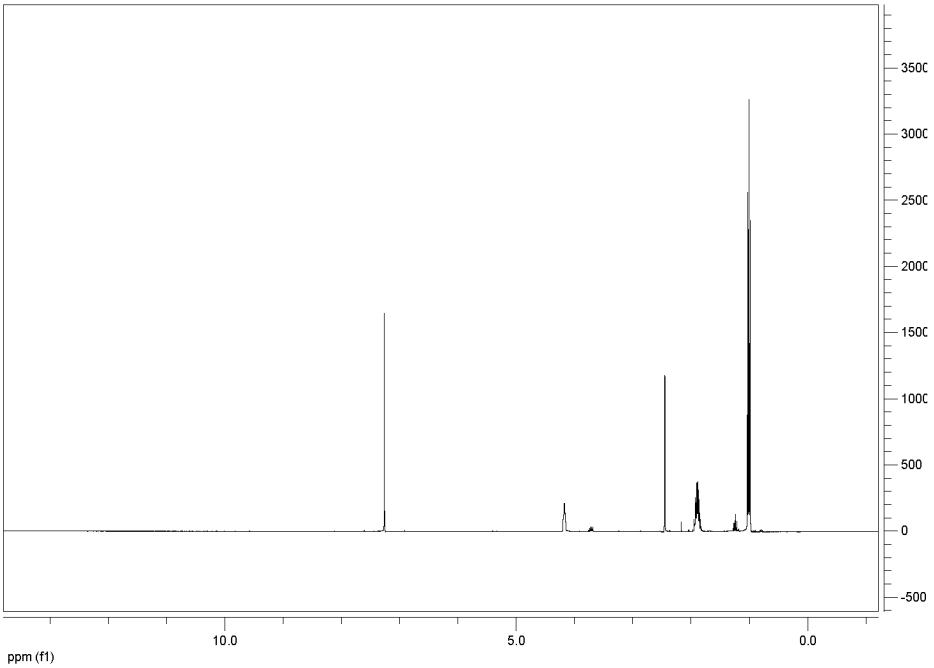

OTBS
Me
Me
H

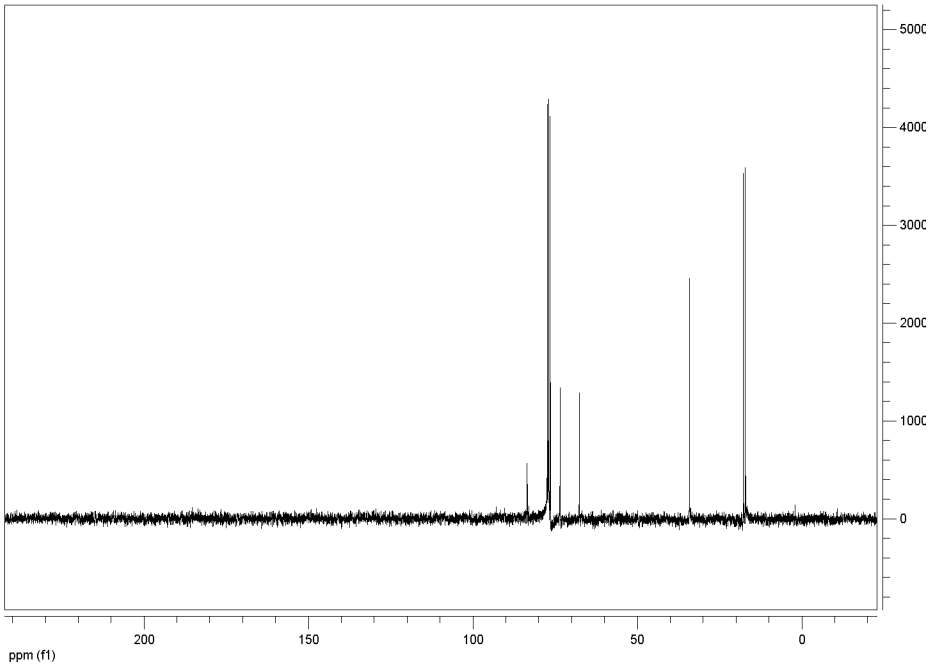
279

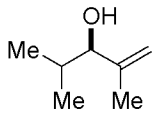

1500
1000
500
0
10.0
5.0
0.0
ppm (f1)


OH
Me
Me
H

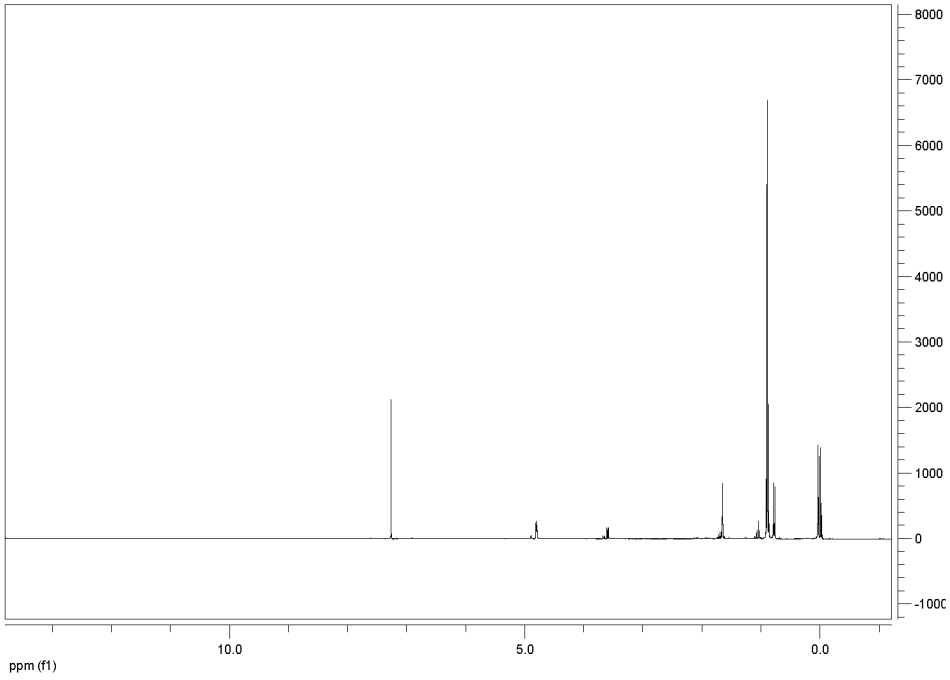
285

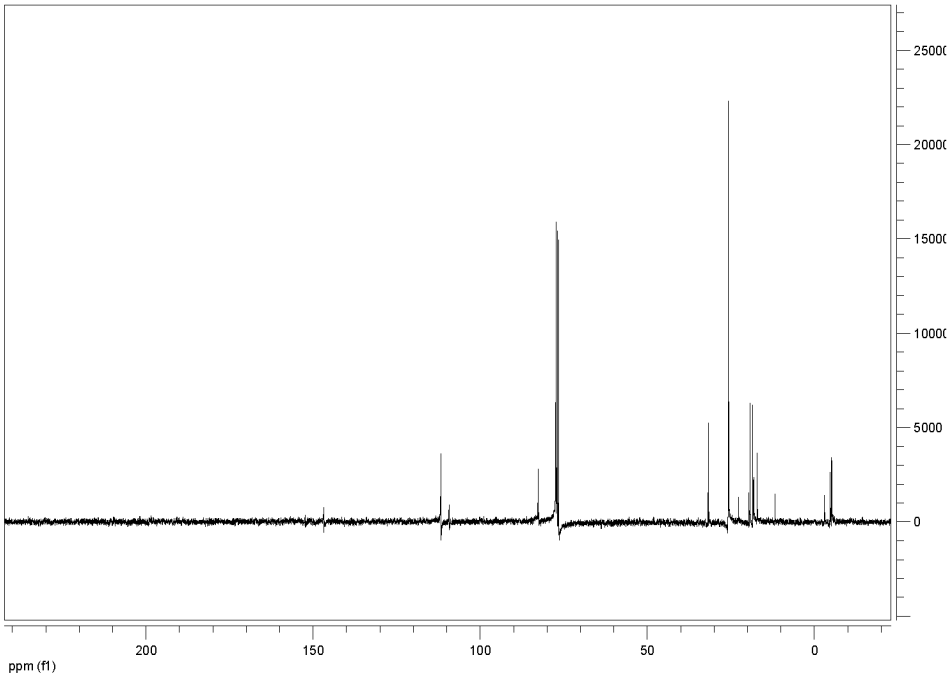

3500
3000
2500
2000
1500
1000
500
0
-500
10.0
5.0
0.0
ppm (f1)

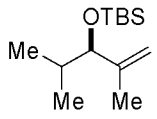

5000
4000
3000
2000
1000
0
200
150
100
50
0
ppm (f1)


OH
Me
Me
Me

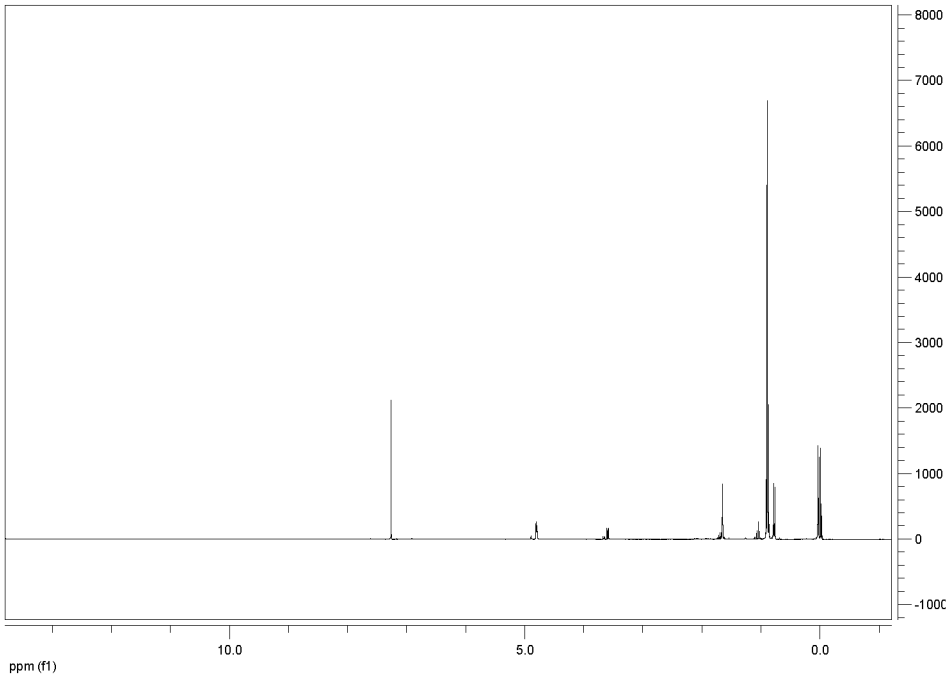
286

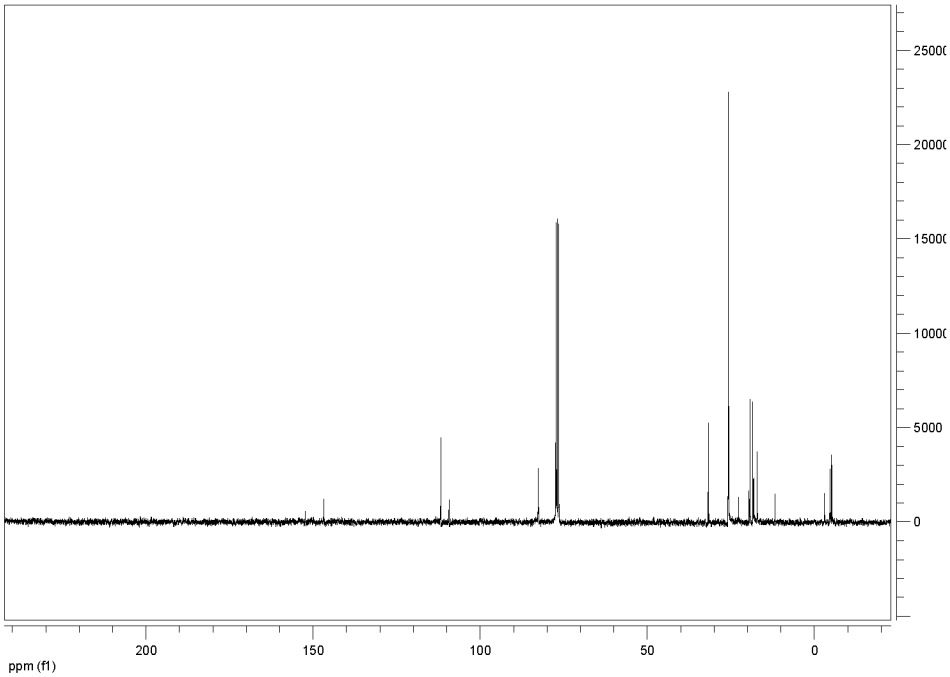

8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10.0
5.0
0.0
ppm (f1)

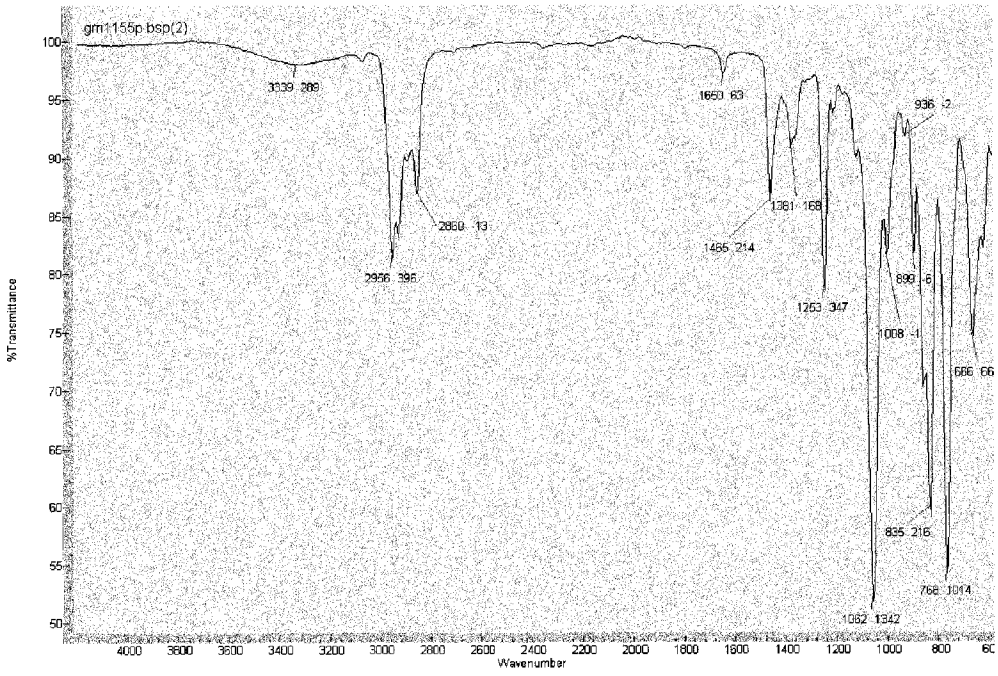

25000
20000
15000
10000
5000
0
200
150
100
50
0
ppm (f1)

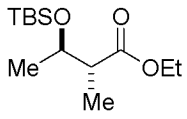

OTBS
Me
Me
Me

280

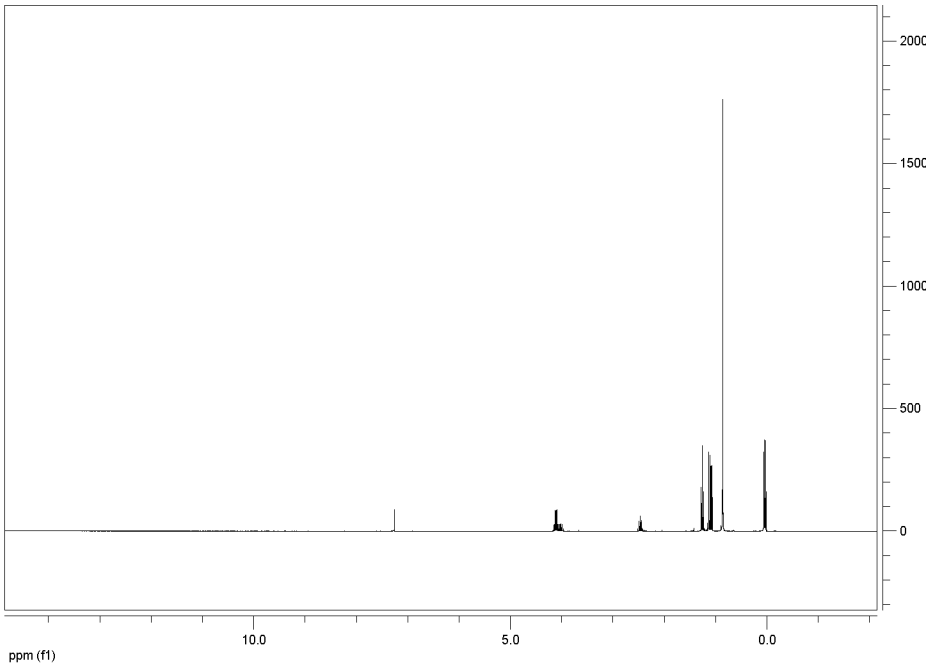

8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10.0
5.0
0.0
ppm (f1)

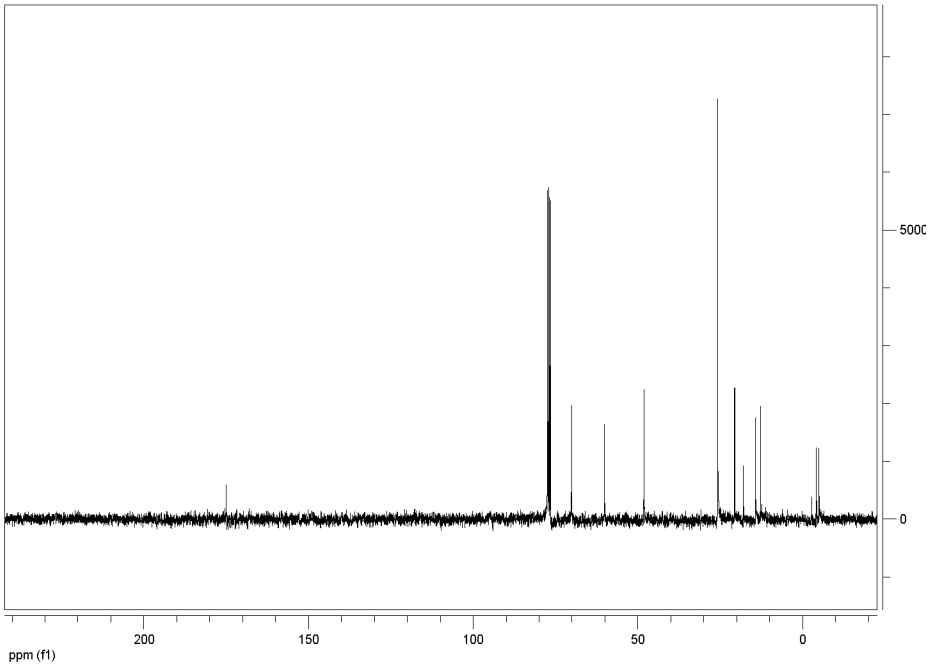

25000
20000
15000
10000
5000
0
200
150
100
50
0
ppm (f1)

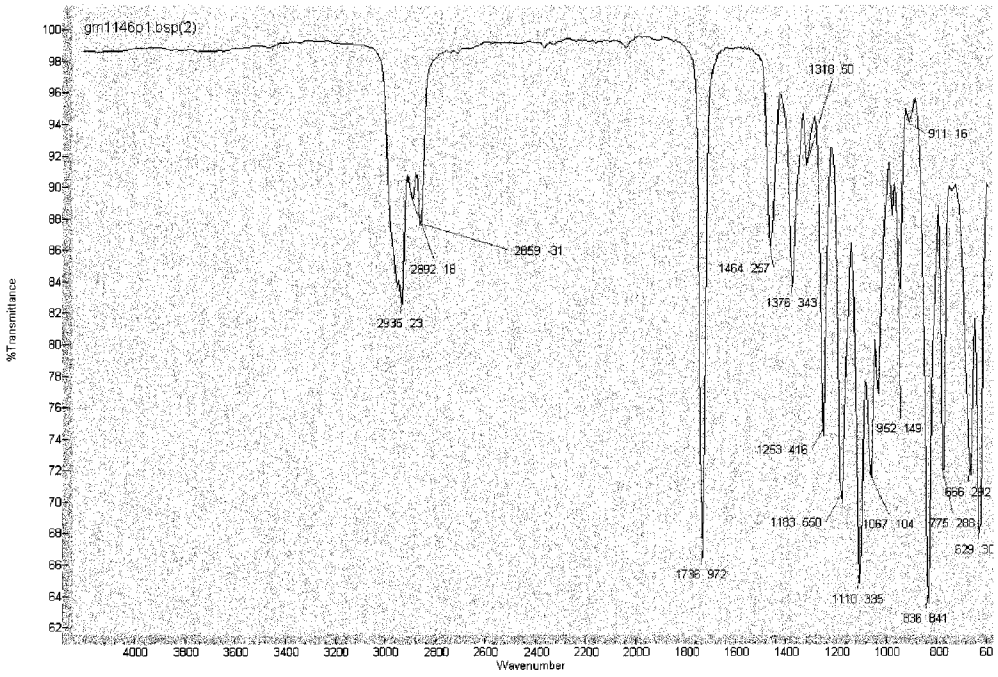

gm1155p.bsp(2)
%Transmittance
Wavenumber
3039 89
2956 96
2869 13
1650 63
1485 214
1381 168
1253 347
1062 1342
1008 -1
936 -2
899 -6
835 216
768 1014
686 66
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800

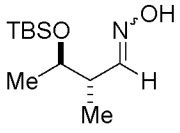

TBSO
O
Me
OEt
Me

292

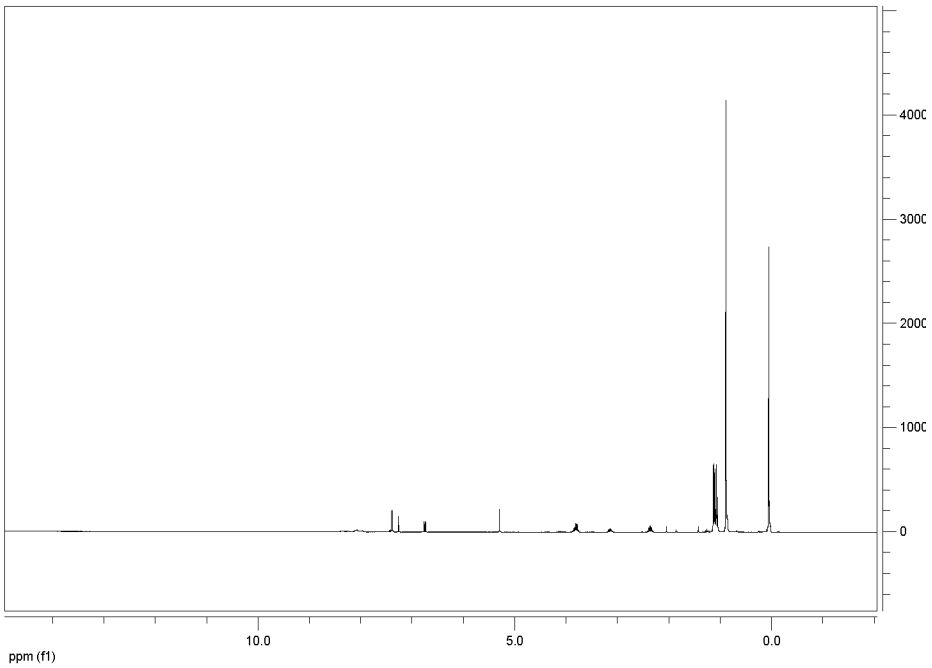

2000
1500
1000
500
0
10.0
5.0
0.0
ppm (f1)

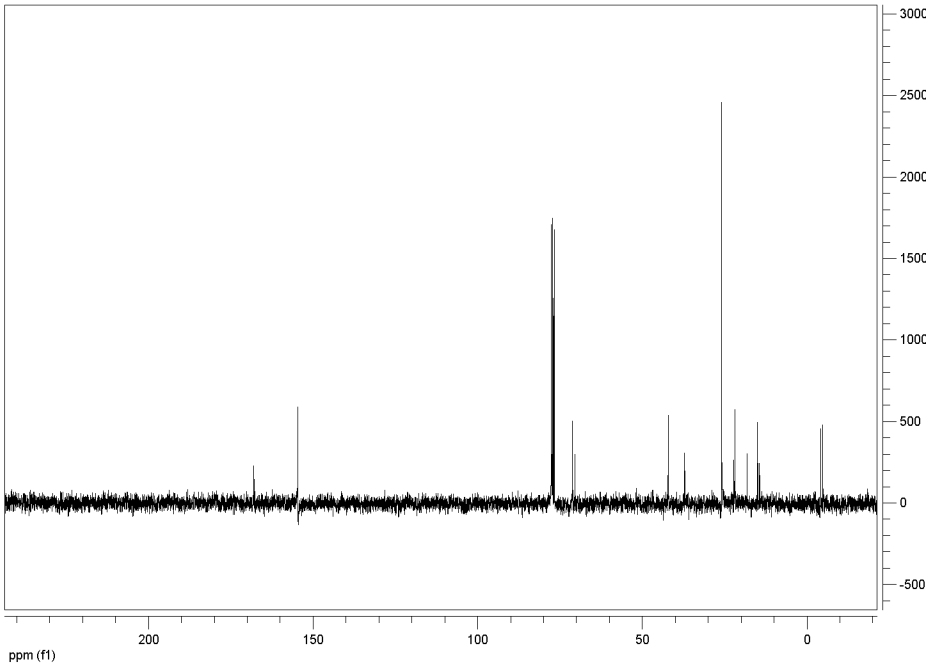

5000
0
200
150
100
50
0
ppm (f1)

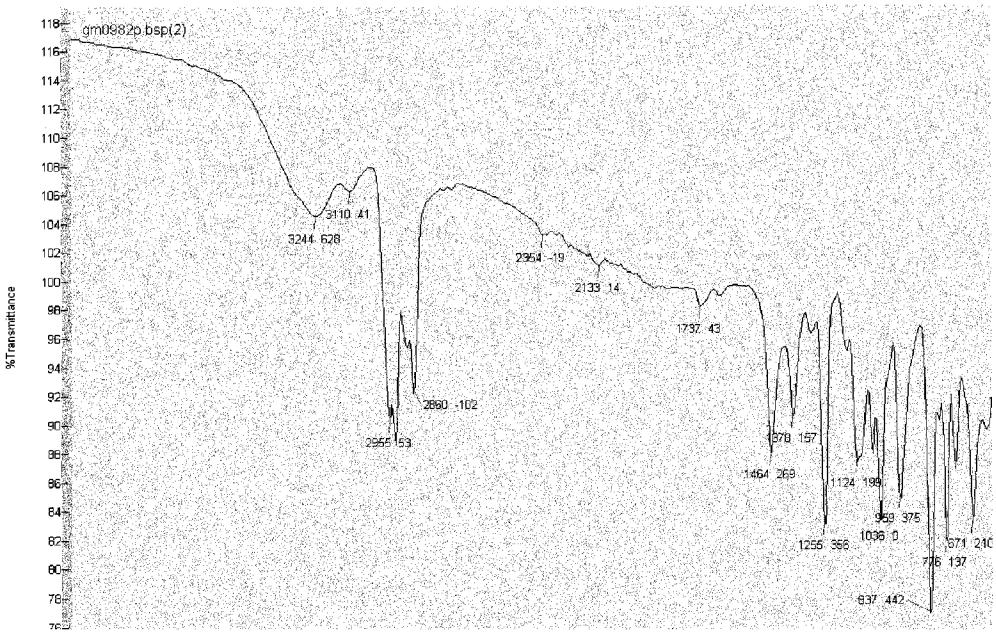

gm1146p1.bsp(2)
%Transmittance
Wavenumber
2935 23
2892 18
2859 31
1736 972
1464 257
1376 343
1318 60
1253 416
1183 650
1110 335
1067 104
952 149
911 16
836 841
775 283
656 292
629 30

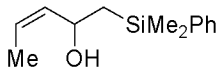

TBSO
N
OH
Me
H
Me

296

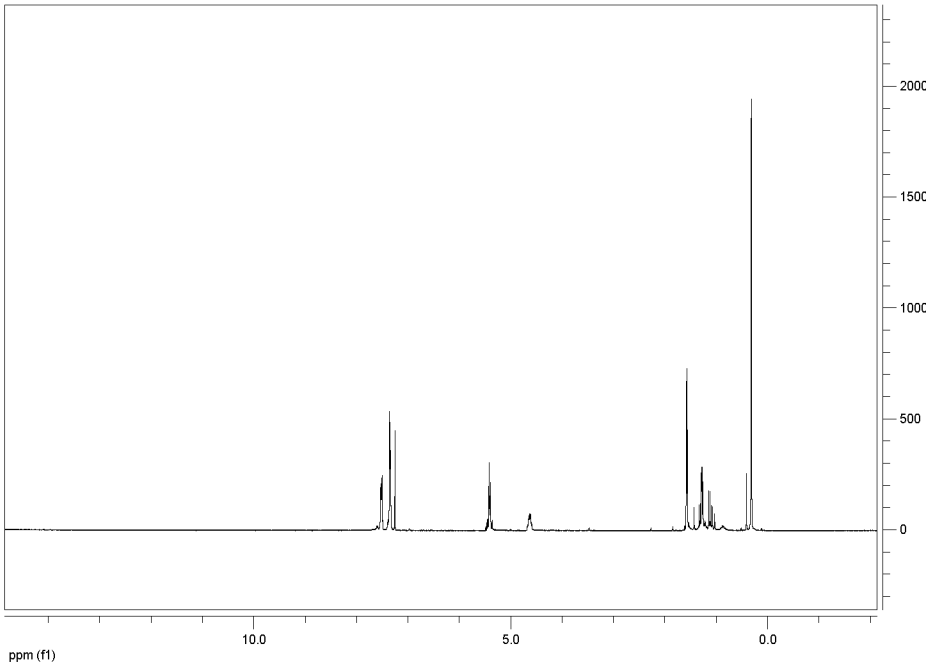

ppm (f1)
10.0
5.0
0.0
4000
3000
2000
1000
0

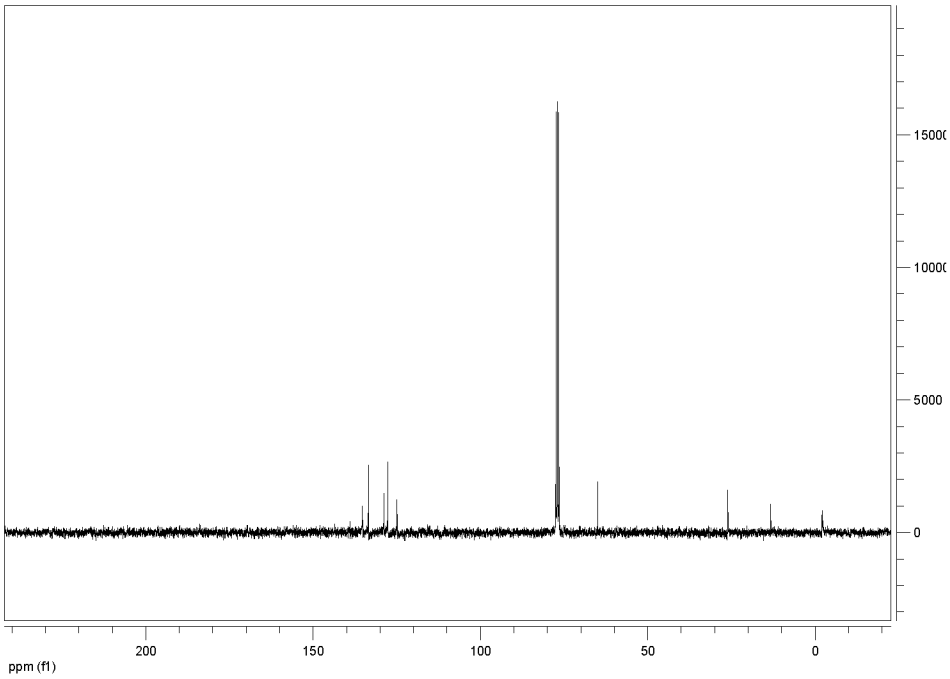

3000
2500
2000
1500
1000
500
0
-500
200
150
100
50
0
ppm (f1)

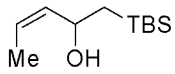

gm0982p.bsp(2)
%Transmittance
3110 41
3244 628
2954 -19
2133 14
1737 43
2890 -102
2955 53
1378 157
1464 269
1124 199
959 375
1036 0
1255 366
971 210
776 137
837 442


SiMe2Ph
Me
OH

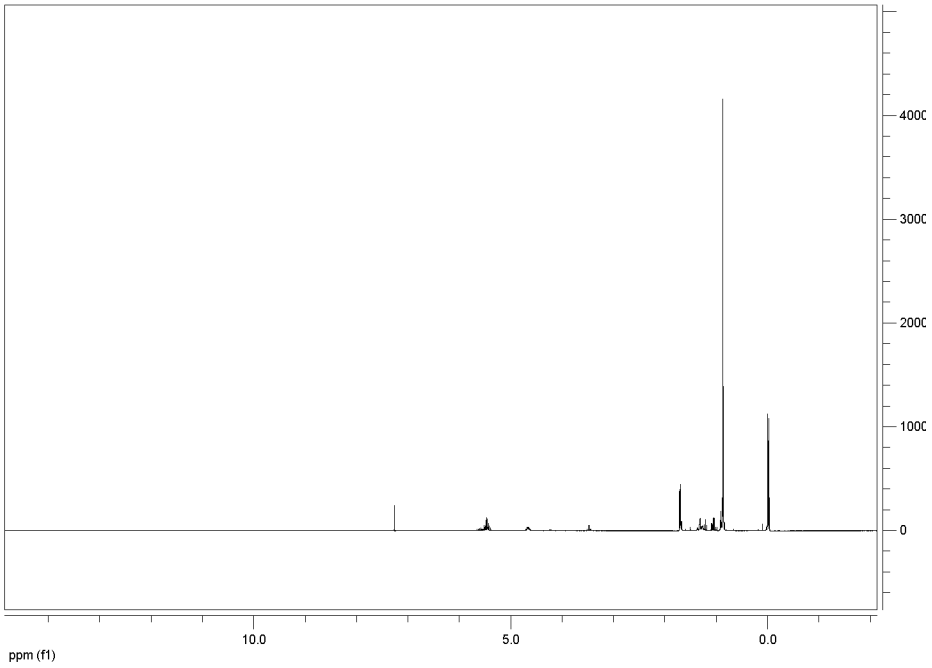
301a

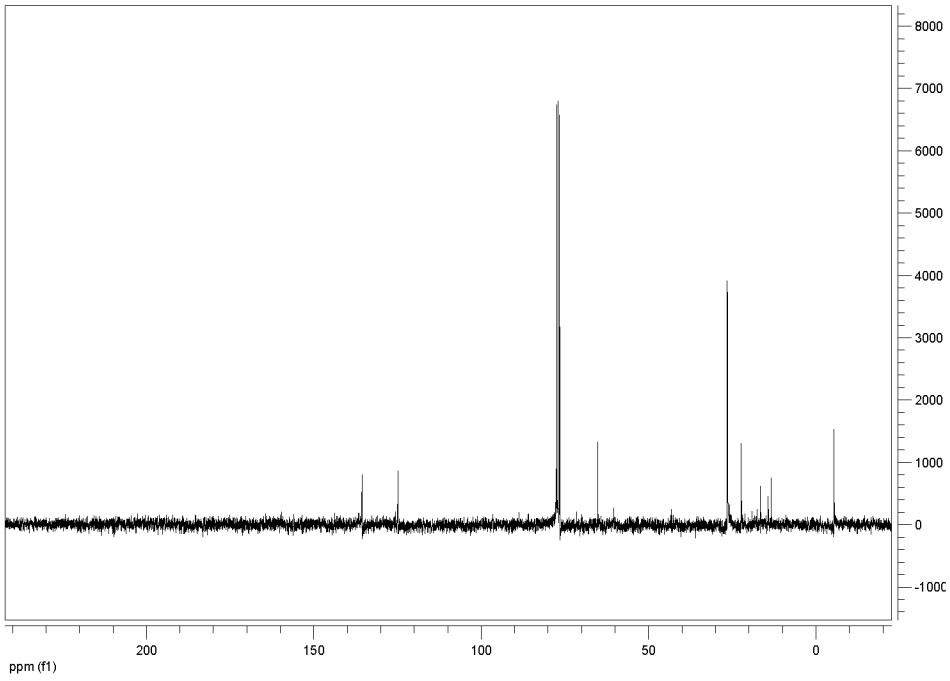

2000
1500
1000
500
0
10.0
5.0
0.0
ppm (f1)

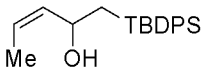

15000
10000
5000
0
200
150
100
50
0
ppm (f1)


TBS
Me
OH

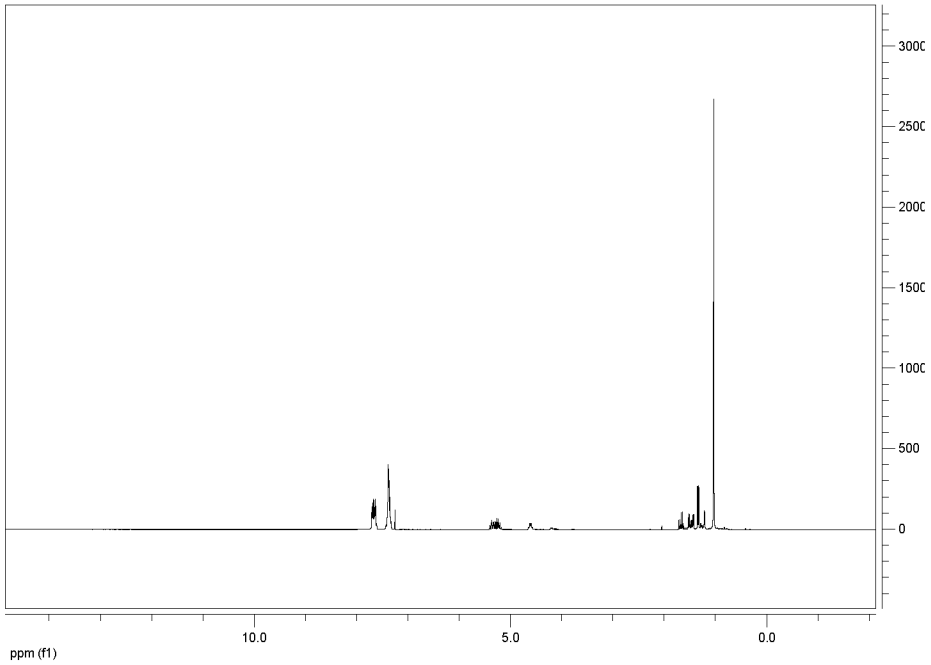
301b

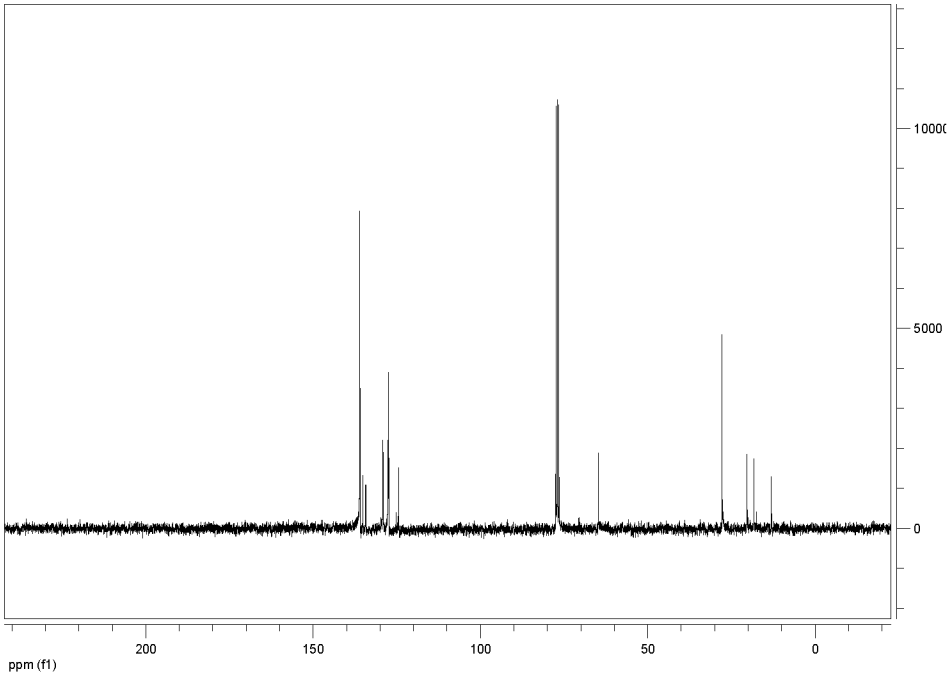

4000
3000
2000
1000
0
10.0
5.0
0.0
ppm (f1)

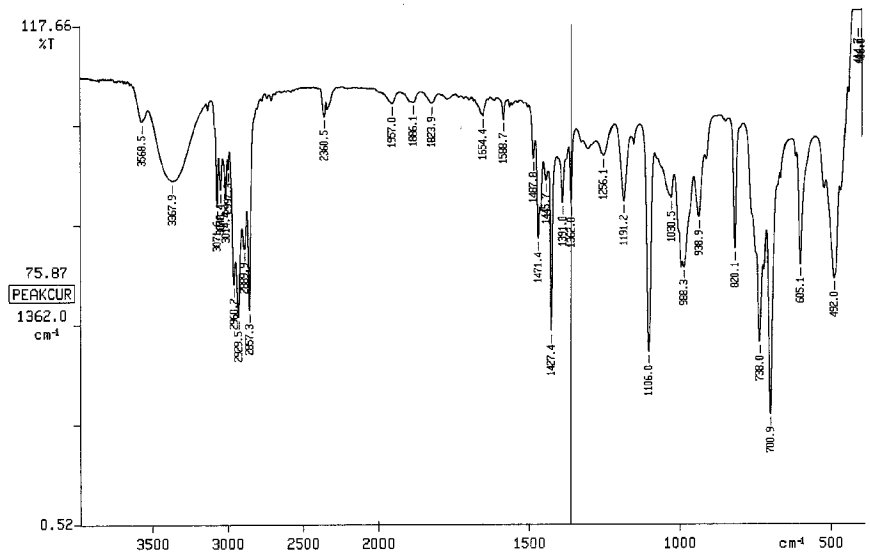

8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
200
150
100
50
0
ppm (f1)

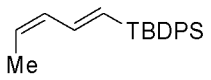

TBDPS
Me
OH

301c

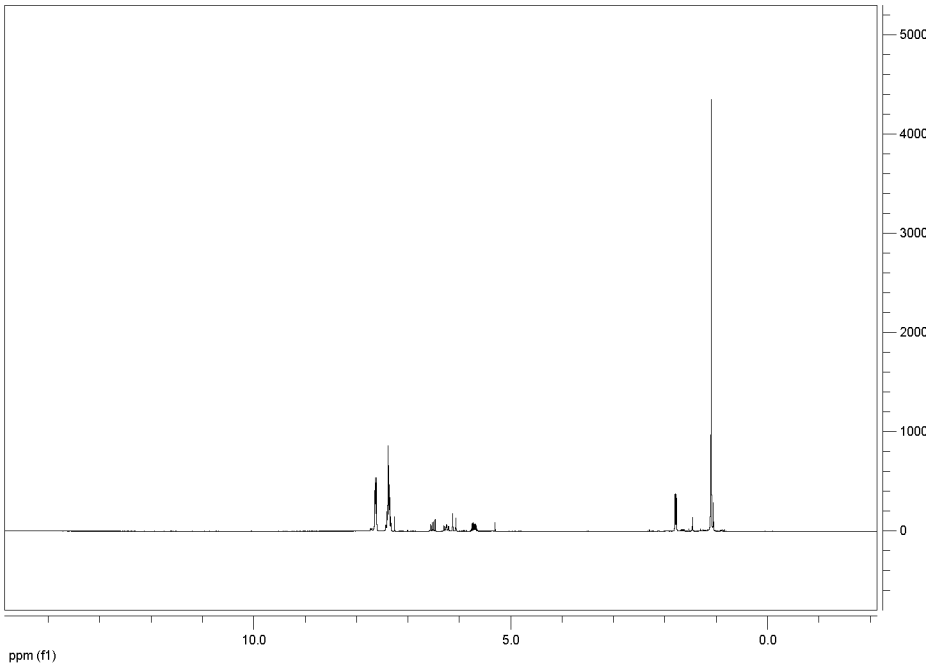

3000
2500
2000
1500
1000
500
0
10.0
5.0
0.0
ppm (f1)

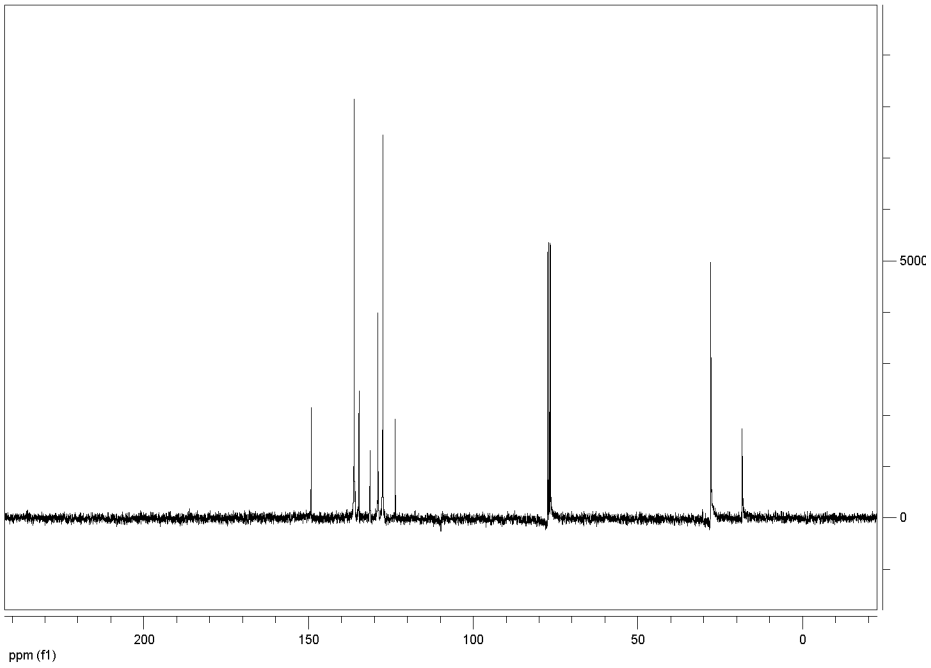

10000
5000
0
200
150
100
50
0
ppm (f1)

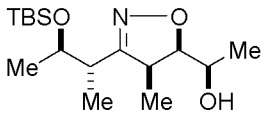

117.66
%T
75.87
PEAKCUR
1362.0
cm-1
0.52
3568.5
3367.9
2360.5
1957.0
1886.1
1823.9
1554.4
1588.7
1471.4
1427.4
1256.1
1191.2
1106.0
1030.3
988.3
938.9
820.1
738.0
700.9
605.1
492.0
3500
3000
2500
2000
1500
1000
cm-1
500


TBDPS
Me

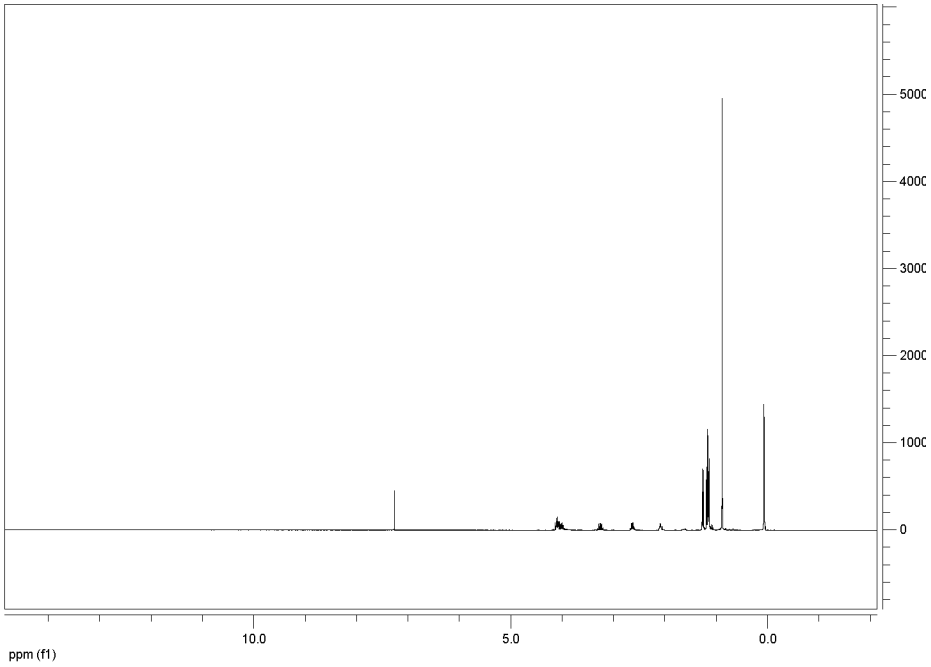
310

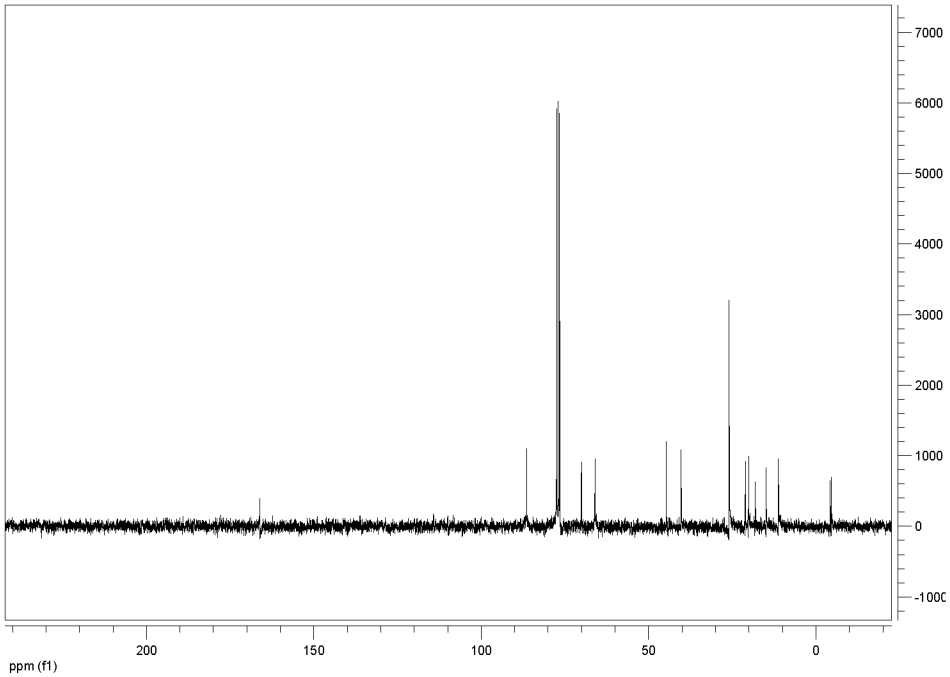

5000
4000
3000
2000
1000
0
10.0
5.0
0.0
ppm (f1)

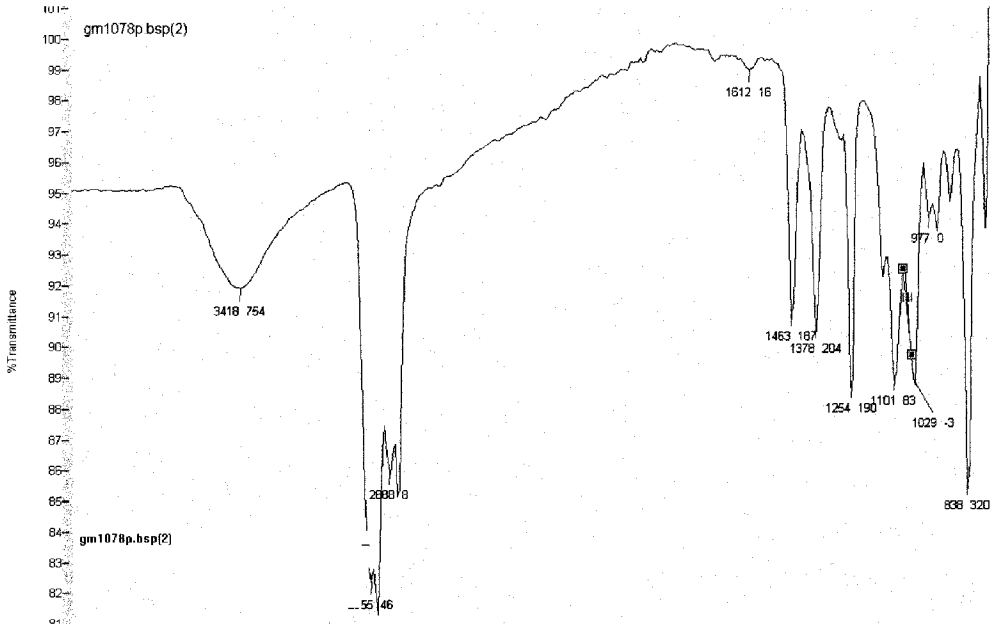

5000
0
200
150
100
50
0
ppm (f1)

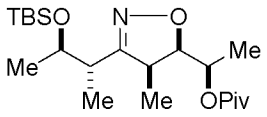

TBSO
N
O
Me
Me
Me
Me
OH

311

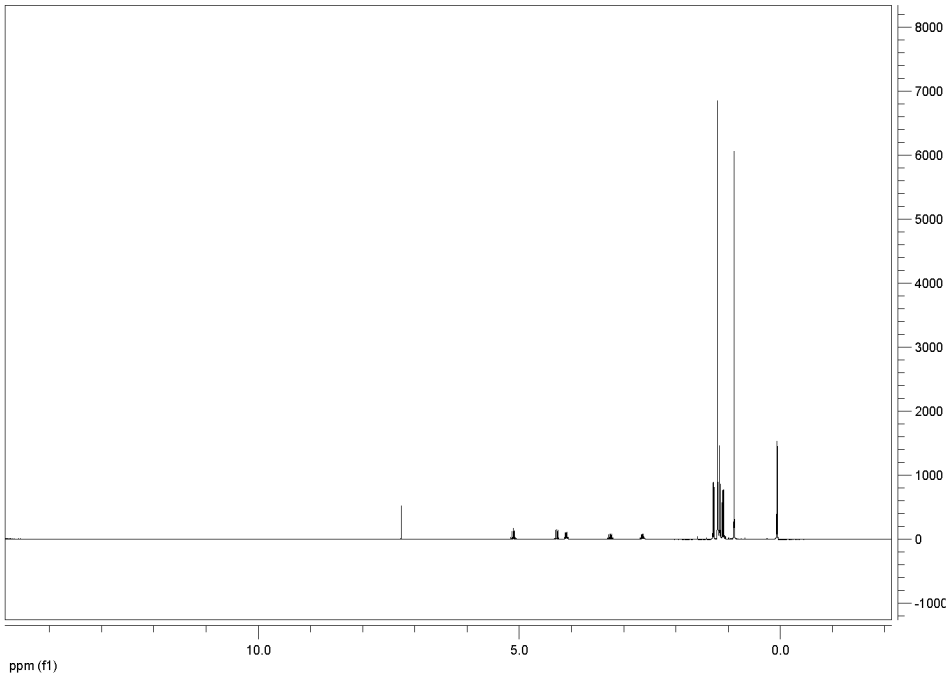

5000
4000
3000
2000
1000
0
10.0
5.0
0.0
ppm (f1)

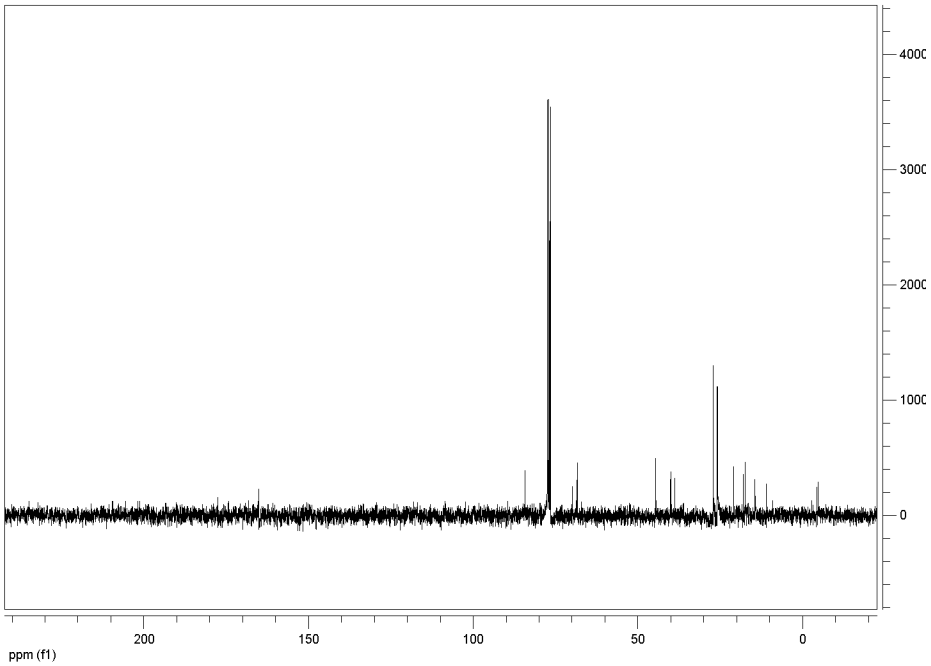

7000
6000
5000
4000
3000
2000
1000
0
-1000
200
150
100
50
0
ppm (f1)

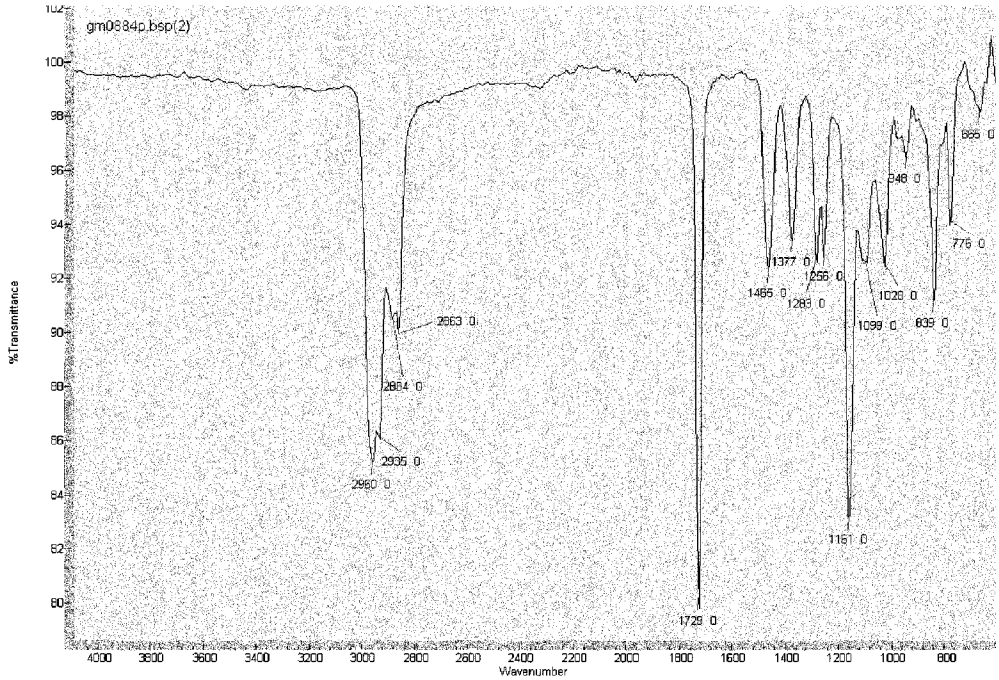

gm1078p bsp(2)
%Transmittance
3418 754
1612 16
1463 187
1378 204
1254 190
1101 83
1029 -3
977 0
838 320
gm1078p.bsp(2)

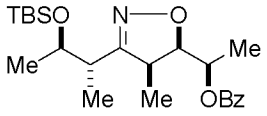

TBSO
N
O
Me
Me
Me
Me
OPiv

313

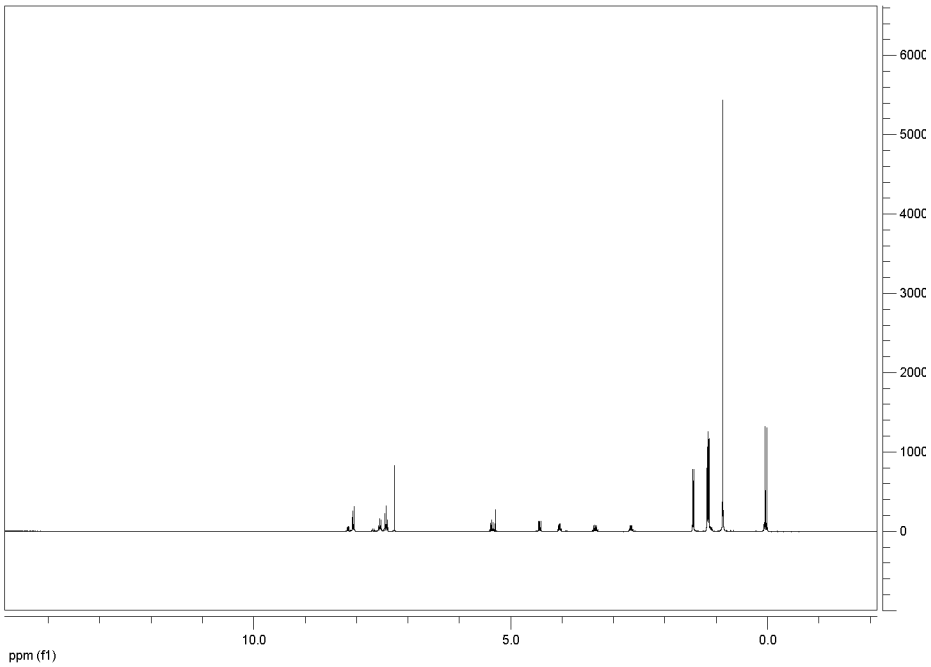

8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10.0
5.0
0.0
ppm (f1)

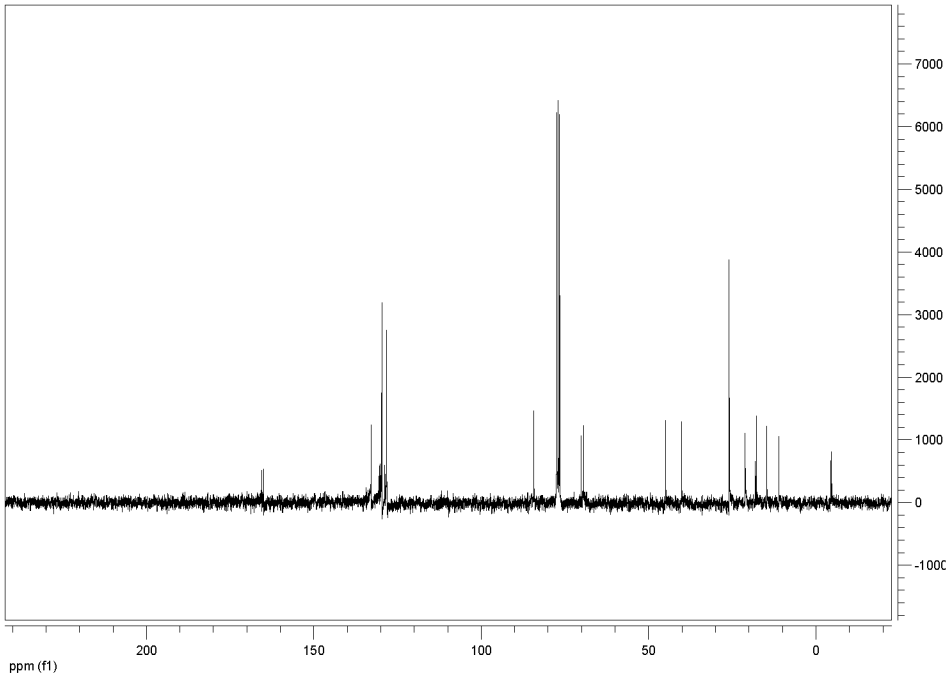

4000
3000
2000
1000
0
200
150
100
50
0
ppm (f1)

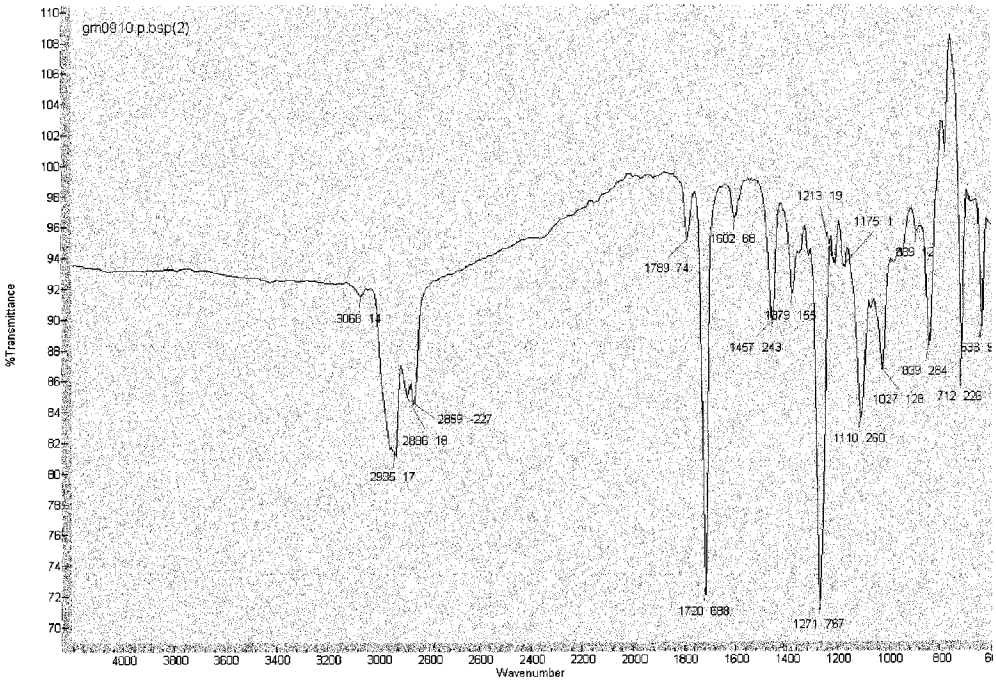

gm0884p.bsp(2)
%Transmittance
Wavenumber
2963.0
2864.0
2935.0
2980.0
1729.0
1465.0
1377.0
1256.0
1288.0
1161.0
1099.0
1029.0
848.0
839.0
776.0
665.0

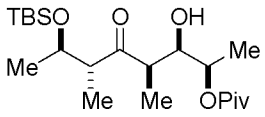

TBSO
N
O
Me
Me
Me
Me
OBz

314

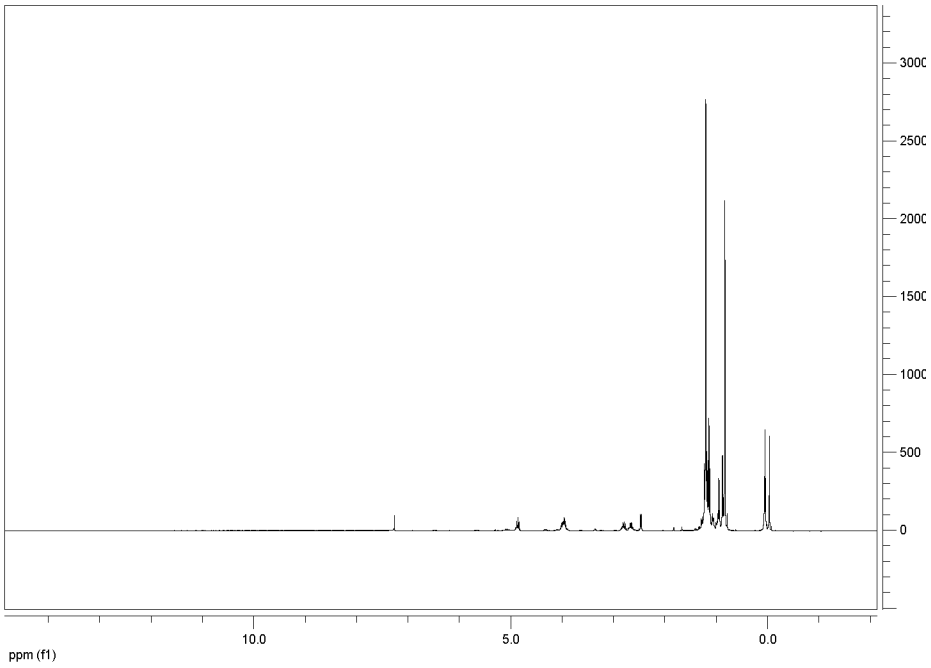

ppm (f1)
10.0
5.0
0.0

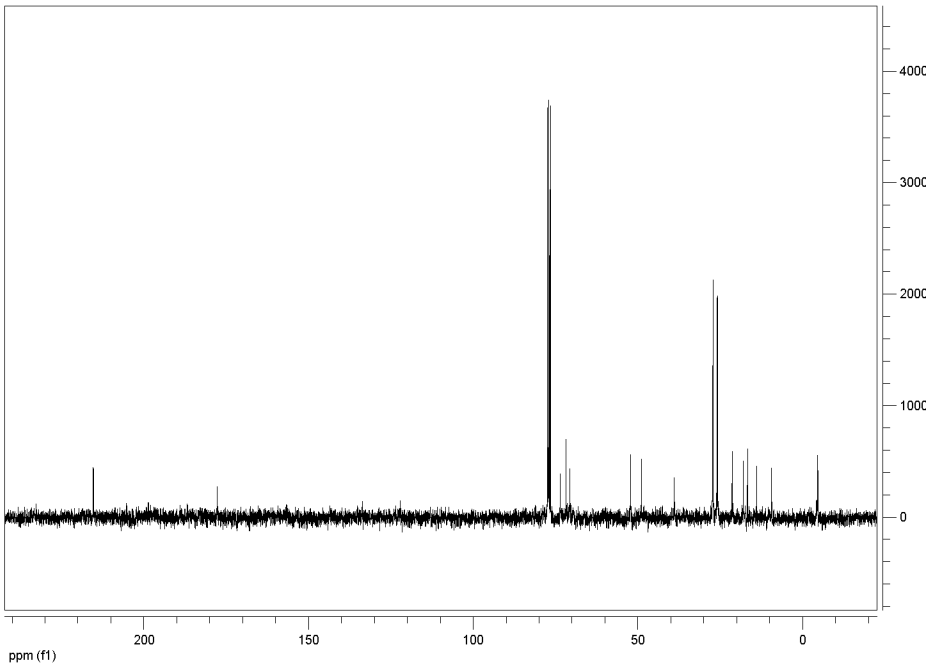

7000
6000
5000
4000
3000
2000
1000
0
-1000
200
150
100
50
0
ppm (f1)

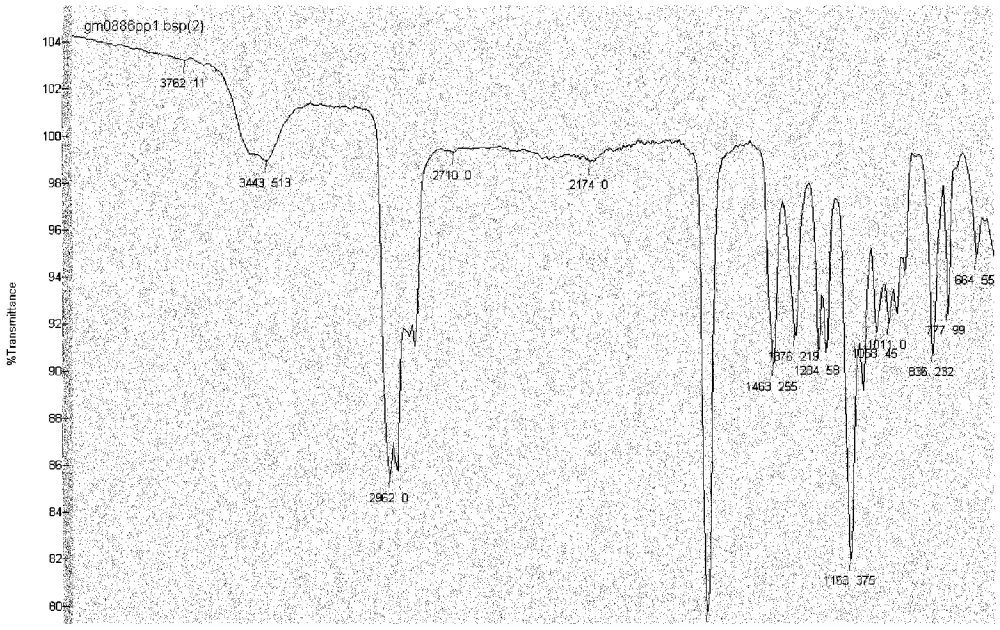

gm0910.p.bsp(2)
%Transmittance
Wavenumber
3068 14
2936 17
2886 18
2859 -227
1789 74
1720 688
1602 68
1457 243
1379 155
1271 787
1213 19
1175 1
1110 260
1027 128
839 284
712 226

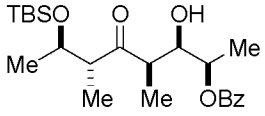

TBSO
O
OH
Me
Me
Me
Me
OPiv

315

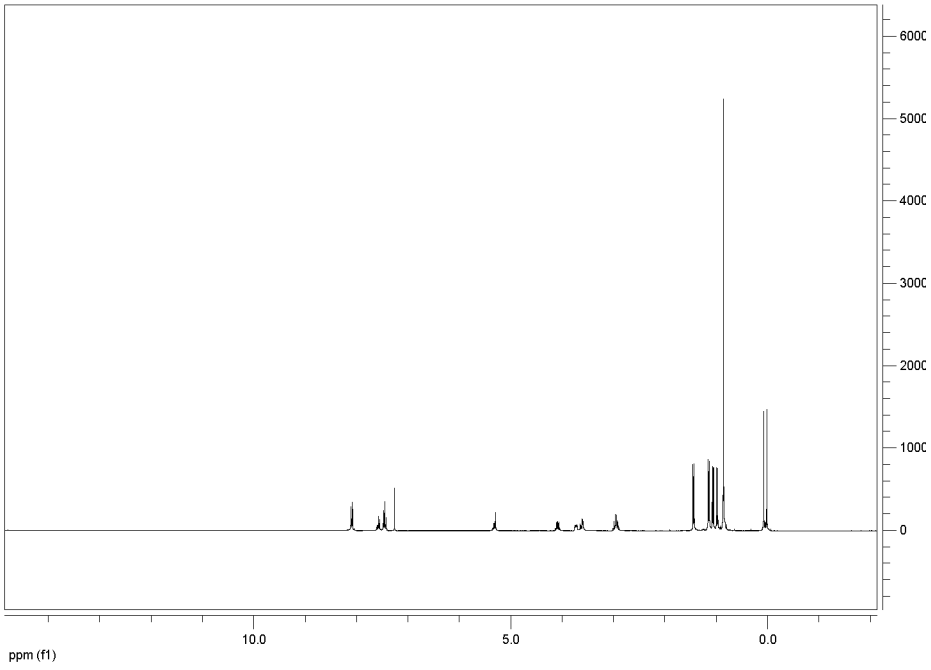

3000
2500
2000
1500
1000
500
0
10.0
5.0
0.0
ppm (f1)

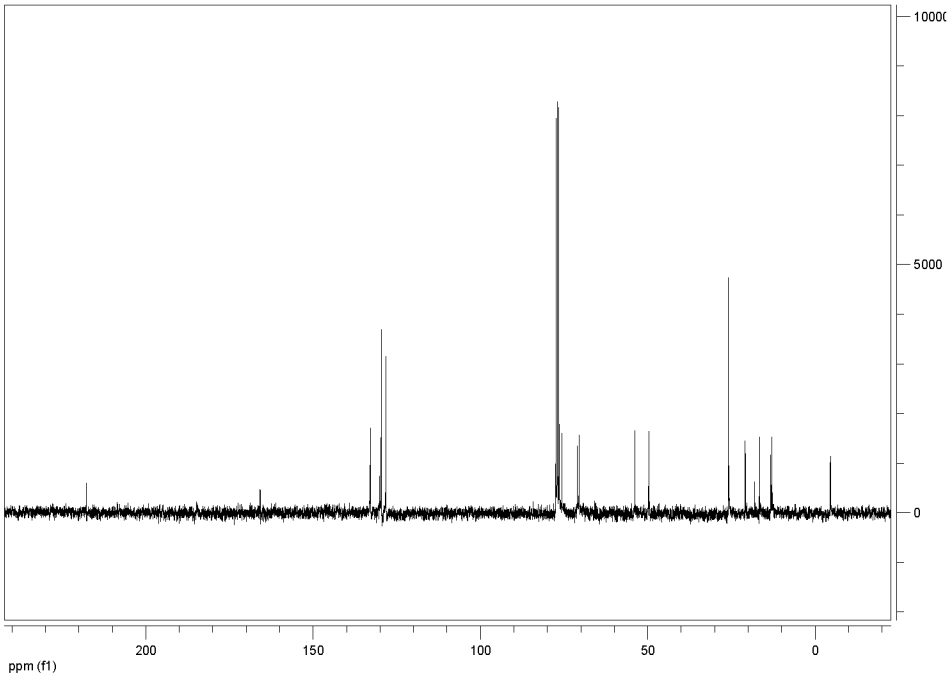

4000
3000
2000
1000
0
200
150
100
50
0
ppm (f1)

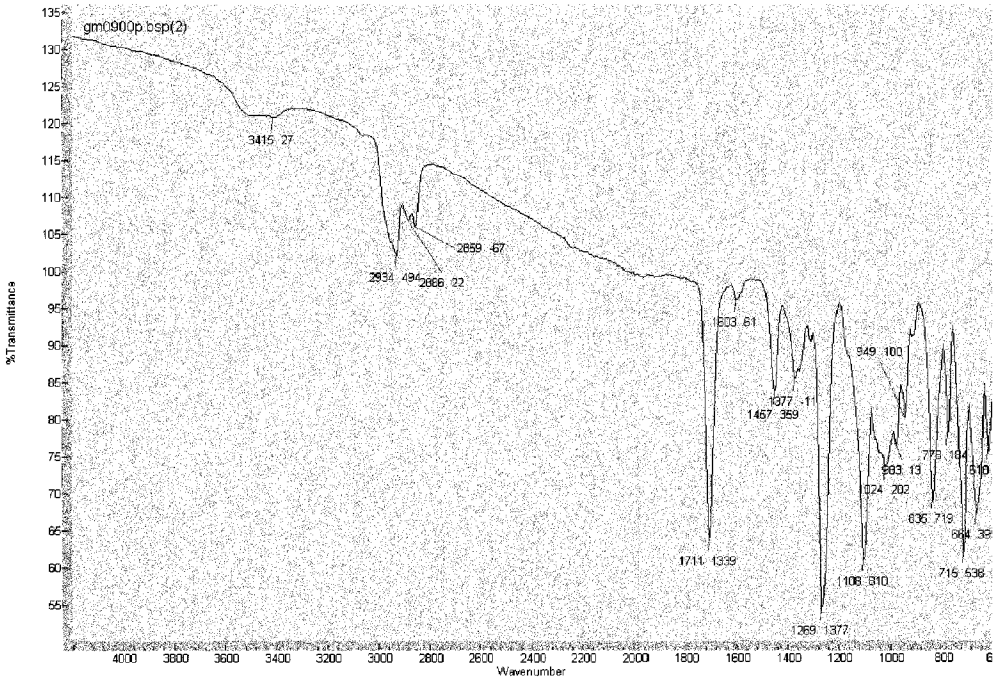

gm0886pp1 bsp(2)
%Transmittance
3762.11
3443.513
2962.0
2710.0
2174.0
1676.219
1463.255
1204.58
1163.375
1093.46
1011.0
836.252
777.99
664.55

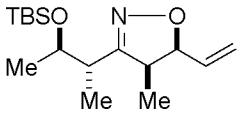

TBSO
O
OH
Me
Me
Me
Me
OBz

316

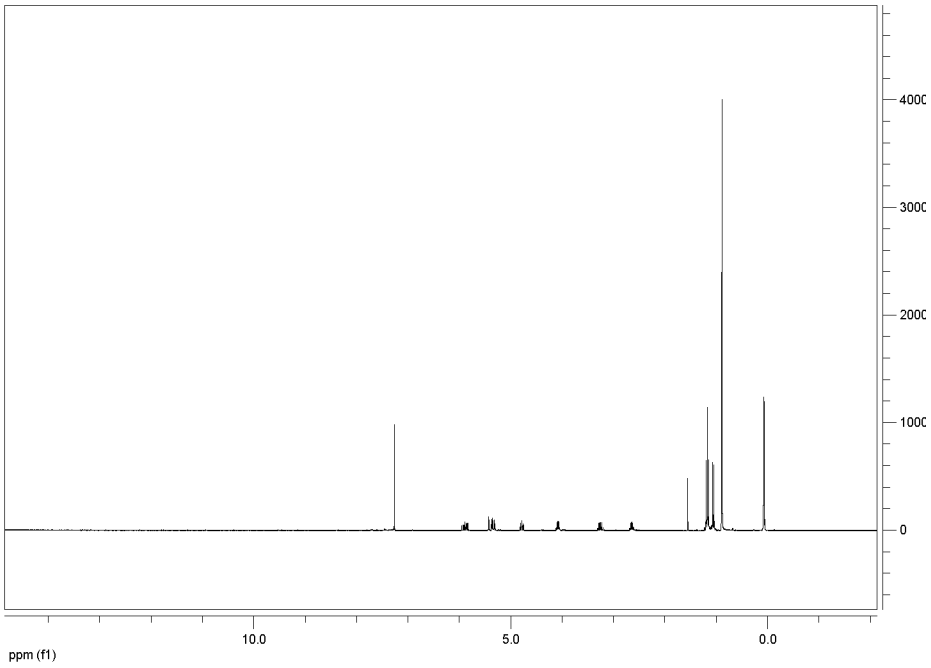

6000
5000
4000
3000
2000
1000
0
10.0
5.0
0.0
ppm (f1)

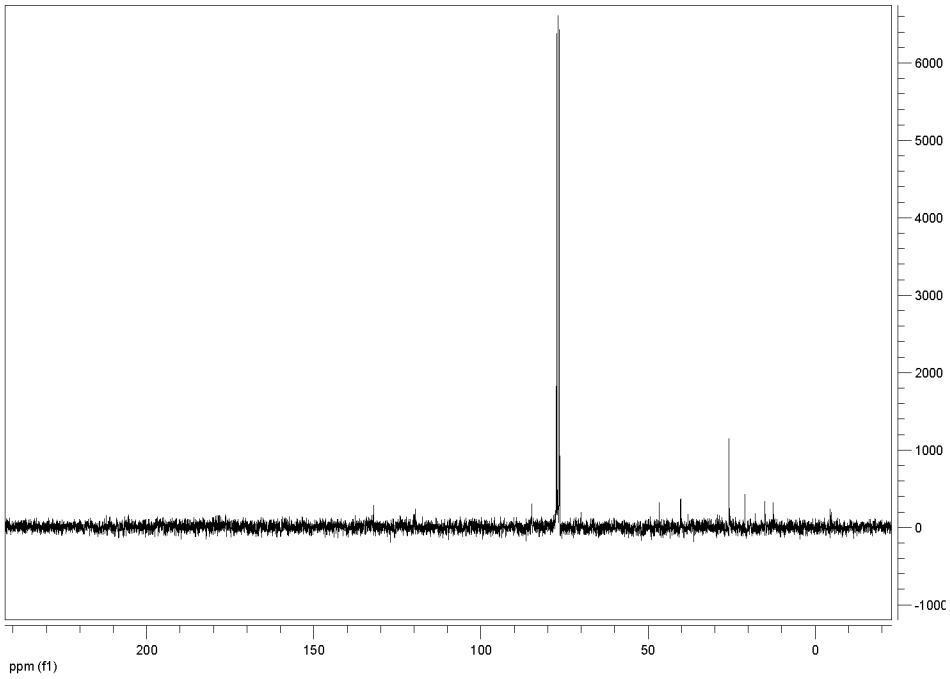

10000
5000
0
200
150
100
50
0
ppm (f1)

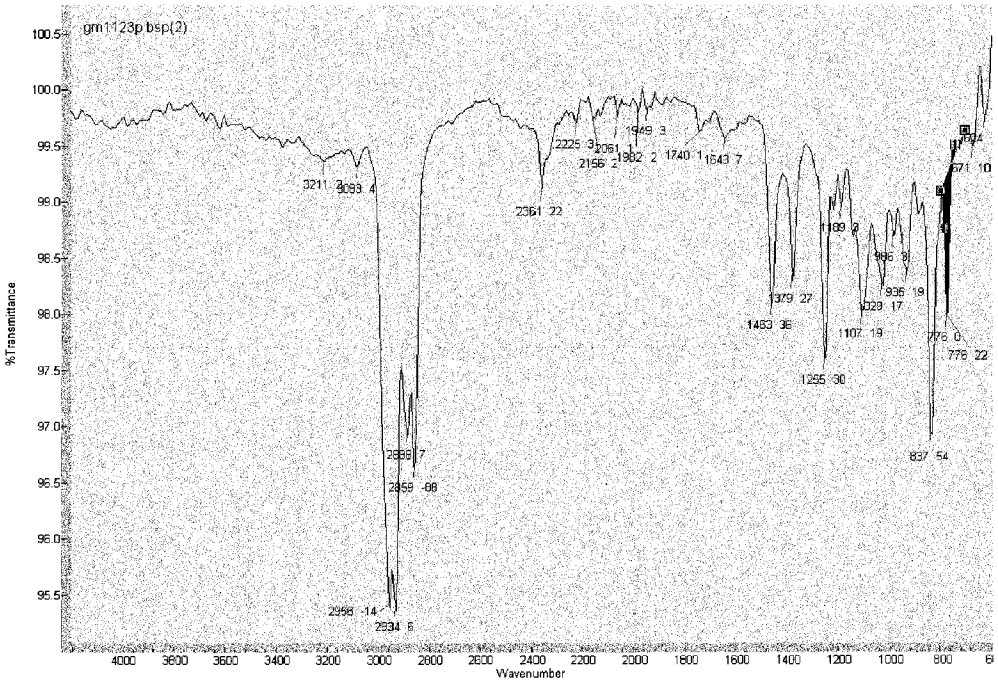

gm0900p.bsp(2)
%Transmittance
Wavenumber
3415.27
2934.49
2859.67
2888.22
1803.81
1711.13
1457.39
1377.11
1269.13
1108.81
949.10
903.13
824.20
715.53

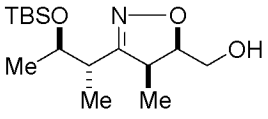

TBSO
N
O
Me
Me
Me

317

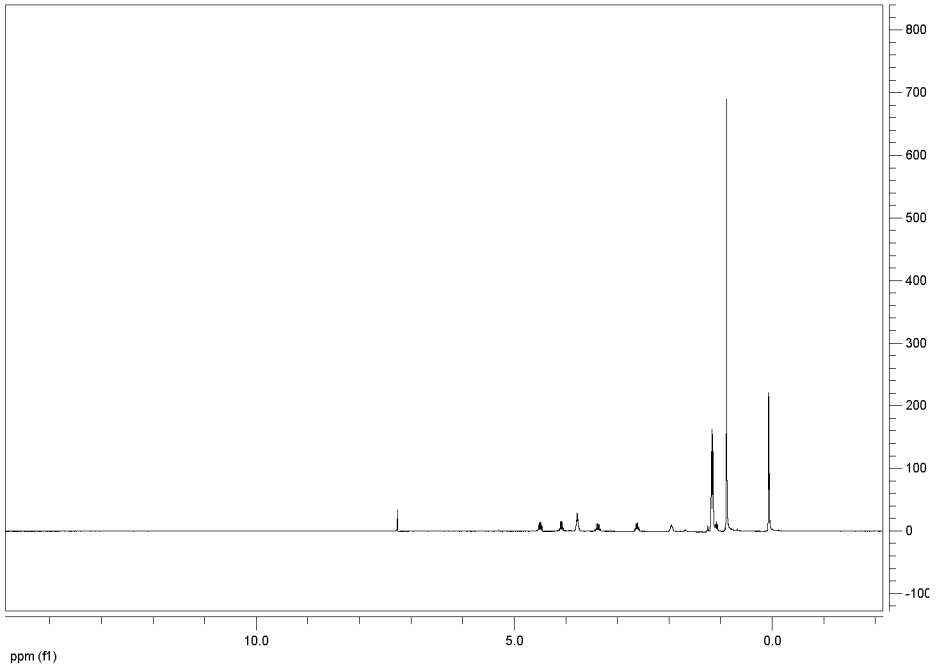

4000
3000
2000
1000
0
10.0
5.0
0.0
ppm (f1)

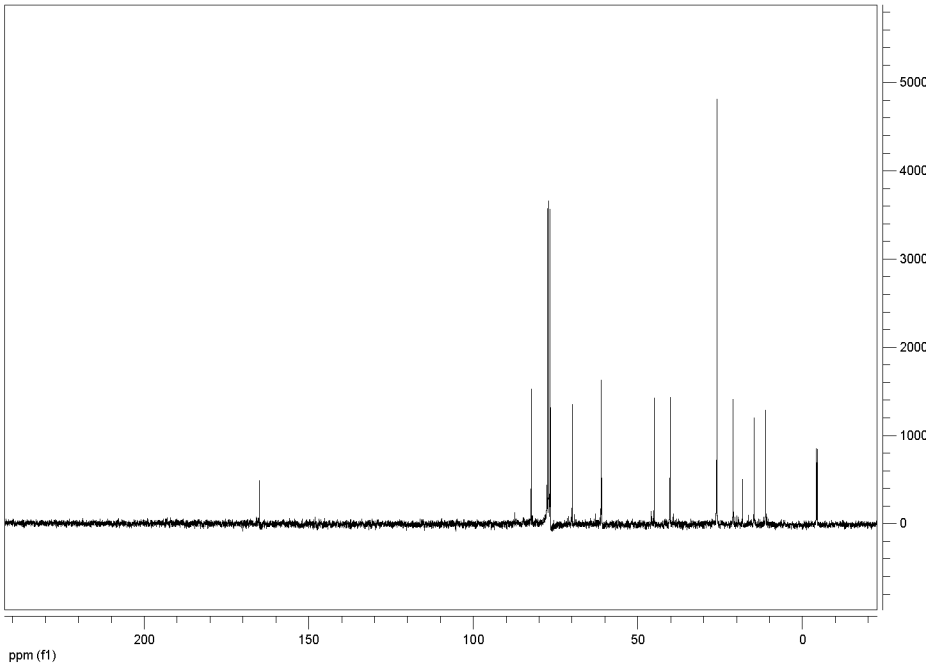

6000
5000
4000
3000
2000
1000
0
-1000
200
150
100
50
0
ppm (f1)

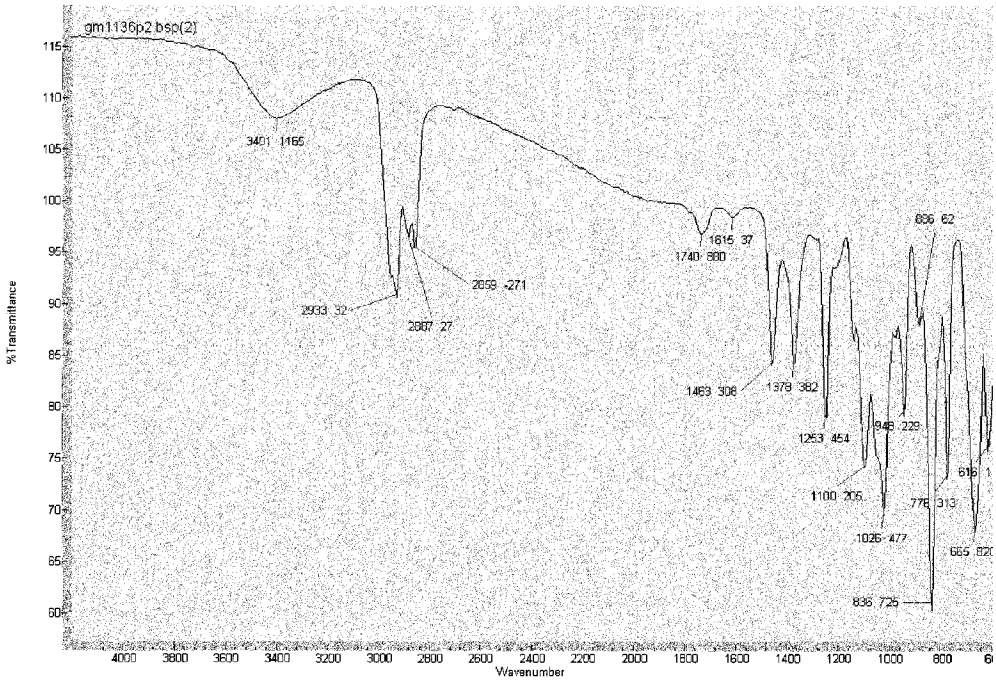

gm1123p bsp(2)
%Transmittance
Wavenumber
3211 3
3093 4
2361 22
2225 3
2156 2
2061 1
1949 3
1902 2
1740 1
1643 7
1483 36
1379 27
1255 30
1107 19
1029 17
996 9
936 19
837 54
778 22
2958 14
2934 6
2859 68

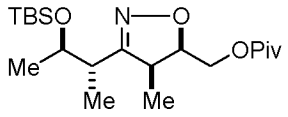

TBSO
N
O
OH
Me
Me
Me

307

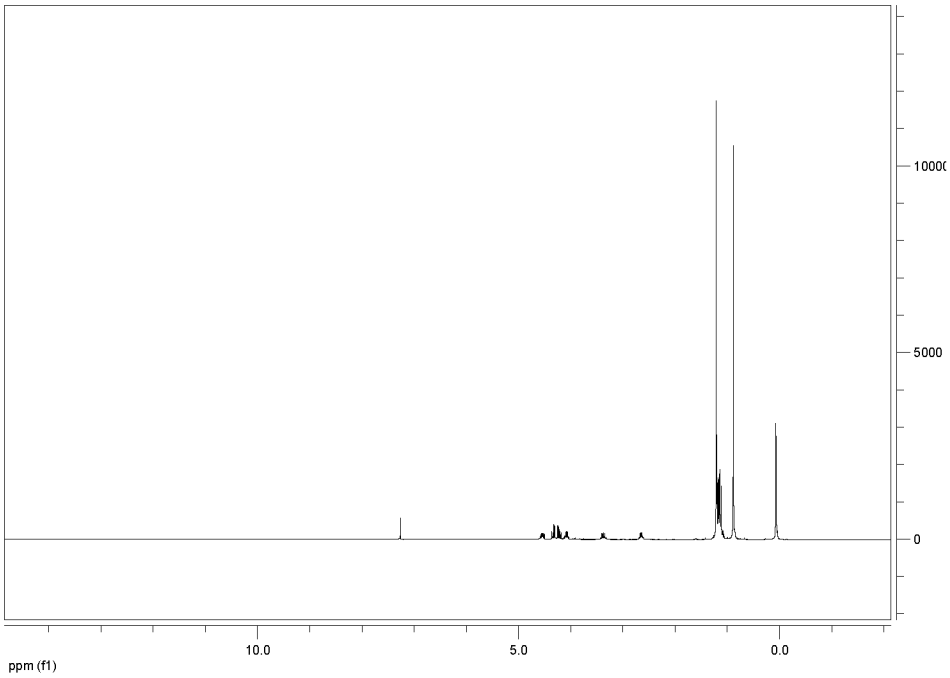

ppm (f1)
10.0
5.0
0.0

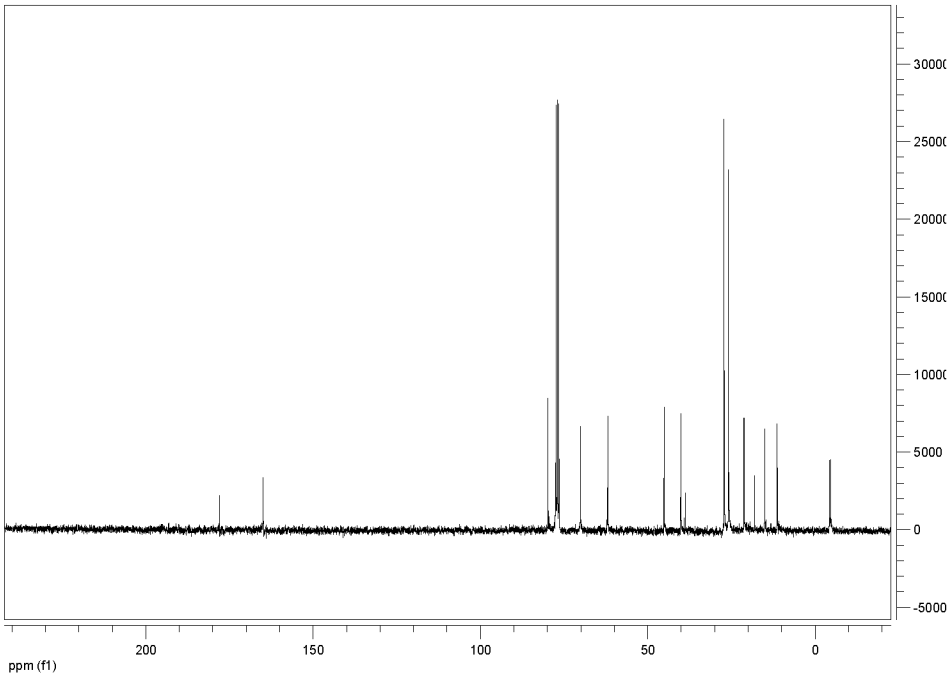

5000
4000
3000
2000
1000
0
200
150
100
50
0
ppm (f1)

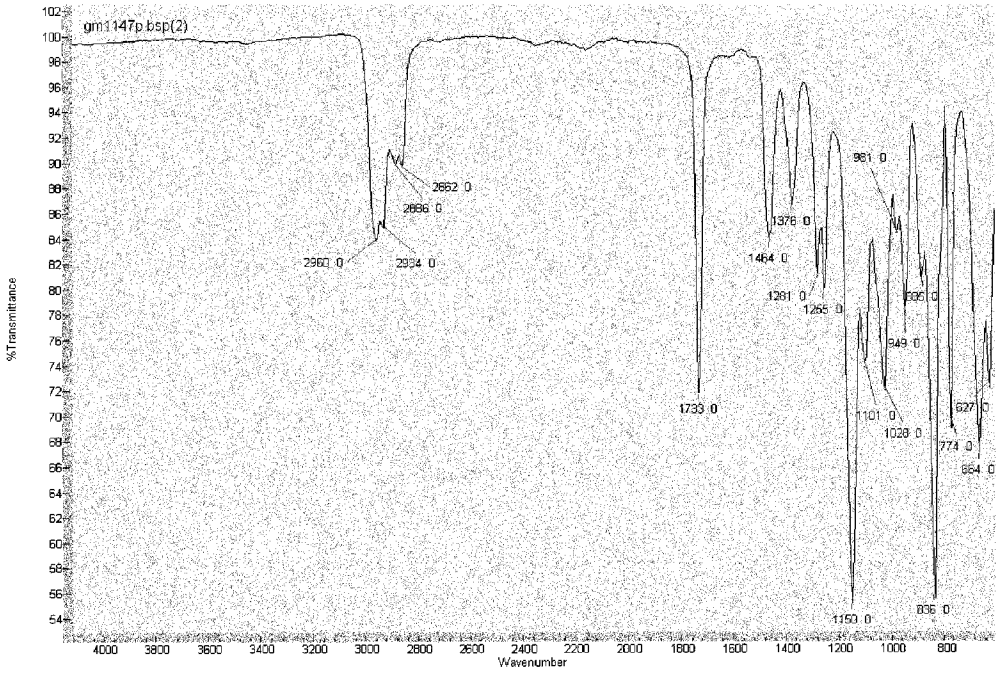

gm1136p2.bsp(2)
%Transmittance
Wavenumber
3401 1165
2933 32
2859 271
2887 27
1740 880
1615 37
1463 308
1378 382
1253 454
1100 205
1026 477
946 229
836 62
836 725
778 313
685 82
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800

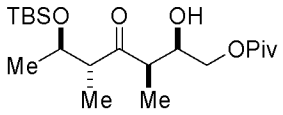

TBSO
N
O
OPiv
Me
Me
Me

319

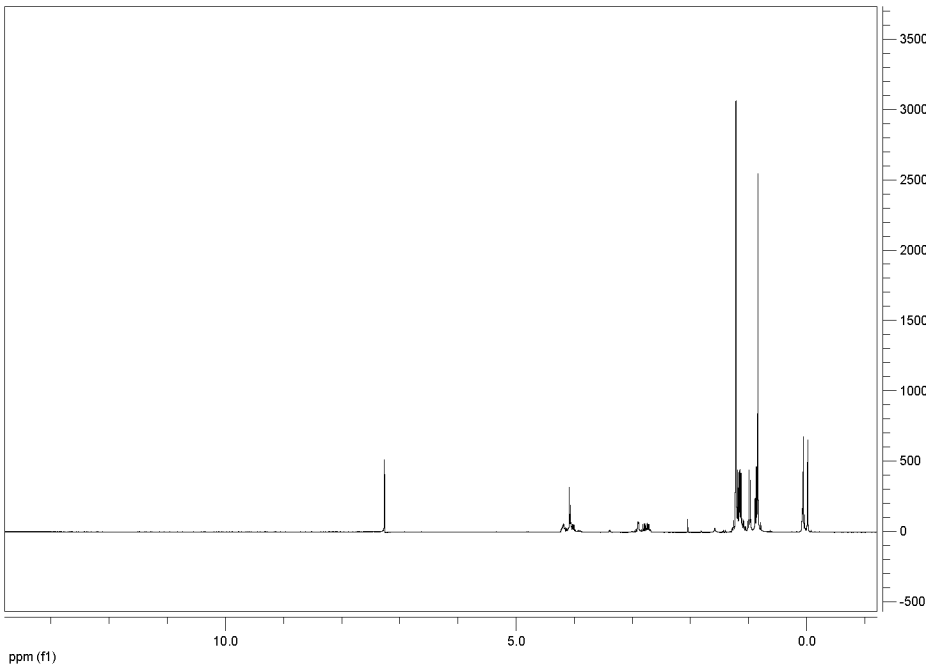

10000
5000
0
10.0
5.0
0.0
ppm (f1)

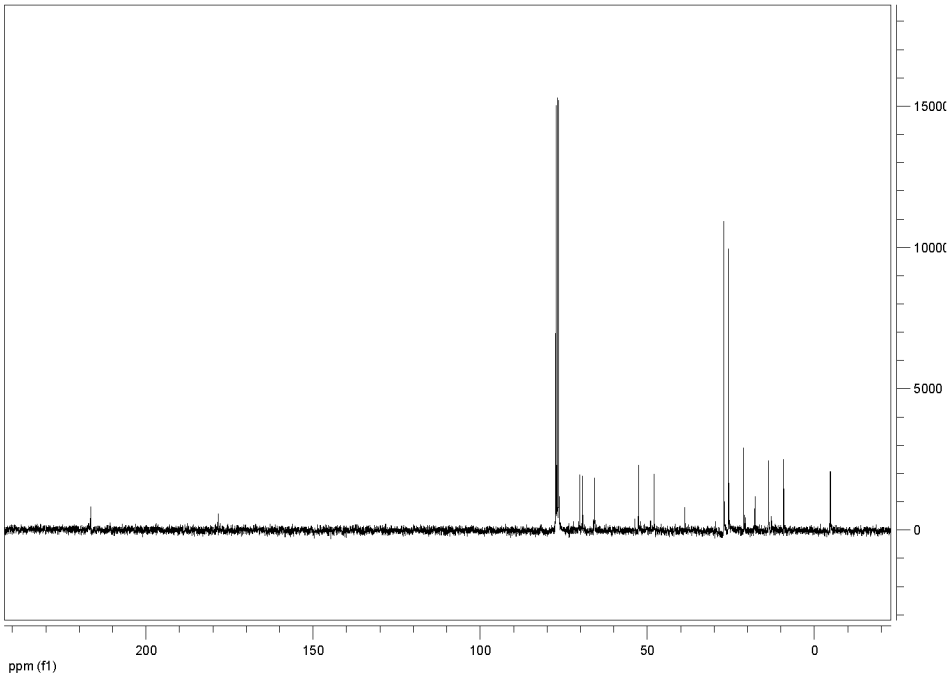

30000
25000
20000
15000
10000
5000
0
-5000
200
150
100
50
0
ppm (f1)

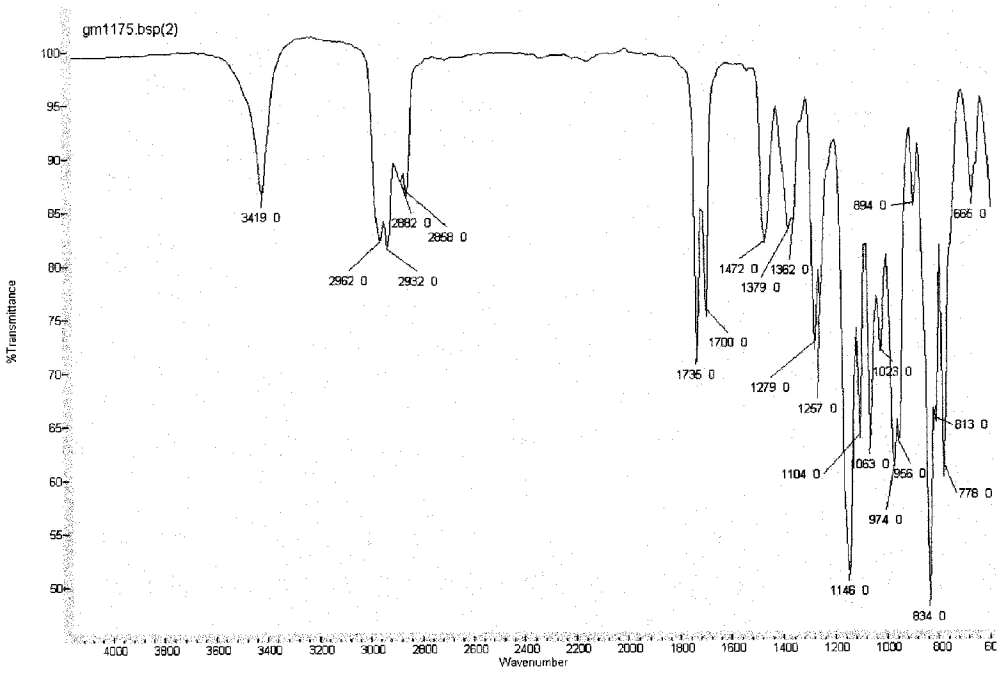

gm1147p.bsp(2)
%Transmittance
Wavenumber
2960.0
2934.0
2882.0
2856.0
1733.0
1464.0
1378.0
1281.0
1255.0
1150.0
1101.0
1028.0
981.0
949.0
895.0
836.0
774.0
664.0
627.0

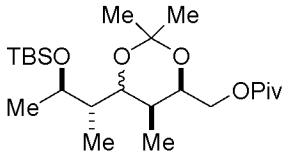

TBSO
O
OH
OPiv
Me
Me
Me

320

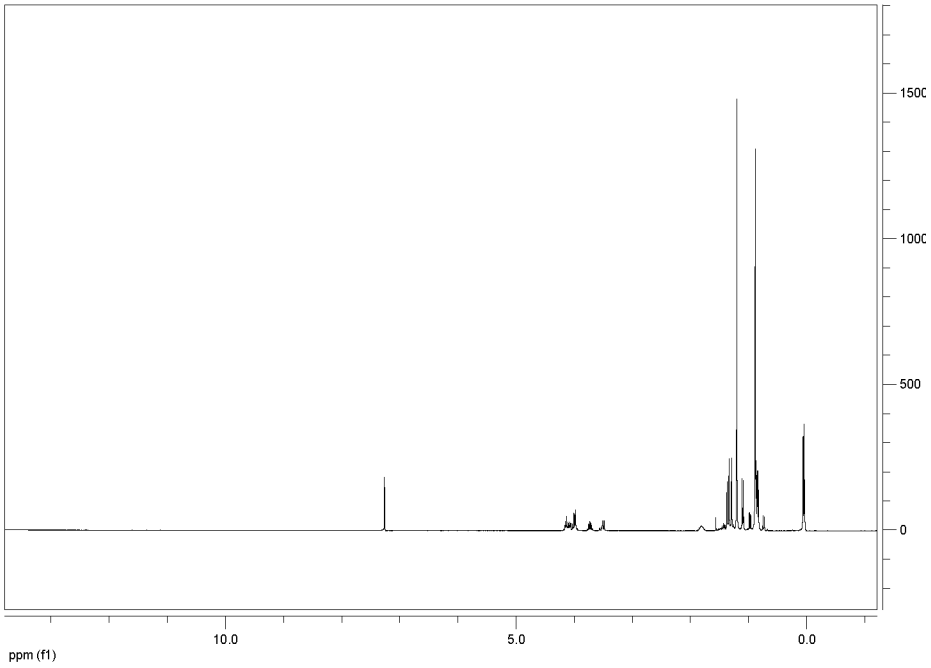

ppm (f1)
10.0
5.0
0.0

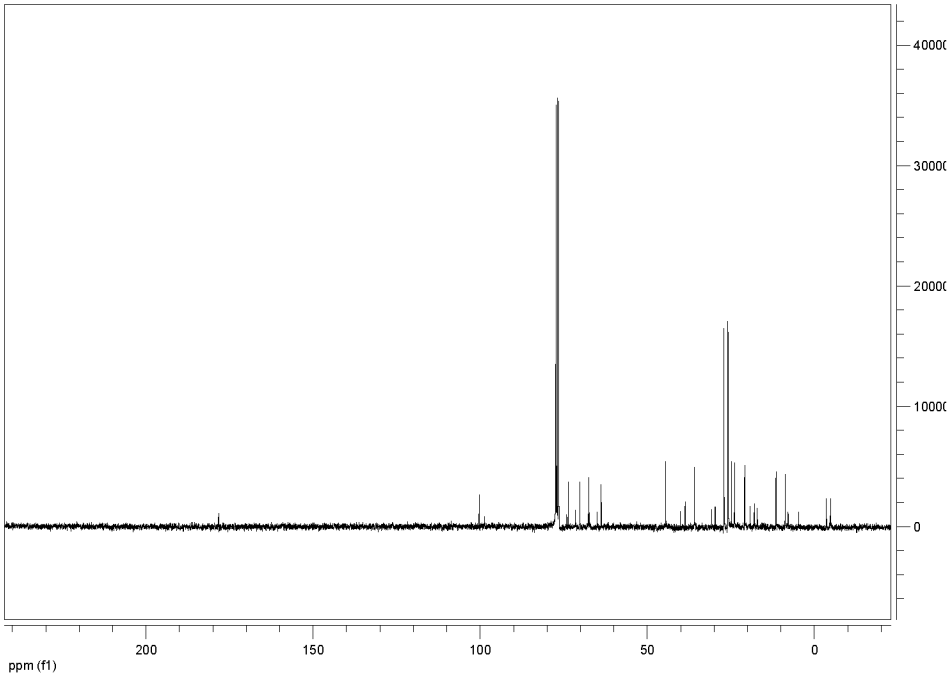

15000
10000
5000
0
200
150
100
50
0
ppm (f1)

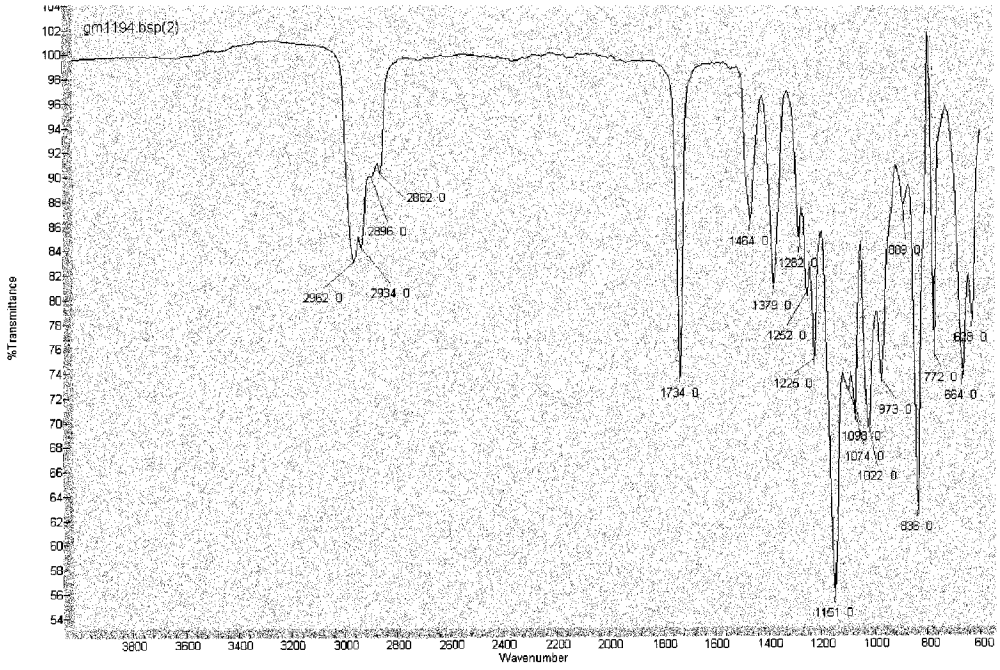

gm1175.bsp(2)
%Transmittance
Wavenumber
3419 0
2962 0
2932 0
2882 0
2858 0
1735 0
1700 0
1472 0
1379 0
1362 0
1279 0
1257 0
1146 0
1104 0
1063 0
1023 0
974 0
956 0
894 0
834 0
813 0
778 0
666 0

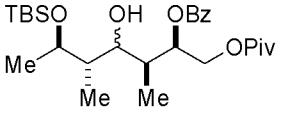

Me
Me
TBSO
O
O
OPiv
Me
Me
Me

322


1500
1000
500
0
10.0
5.0
0.0
ppm (f1)

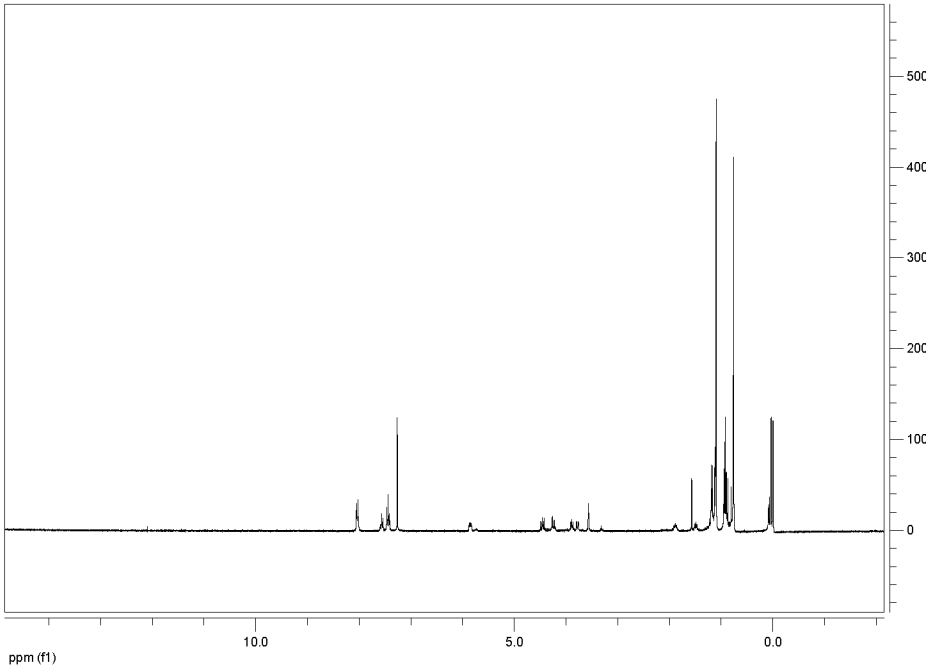

40000
30000
20000
10000
0
200
150
100
50
0
ppm (f1)

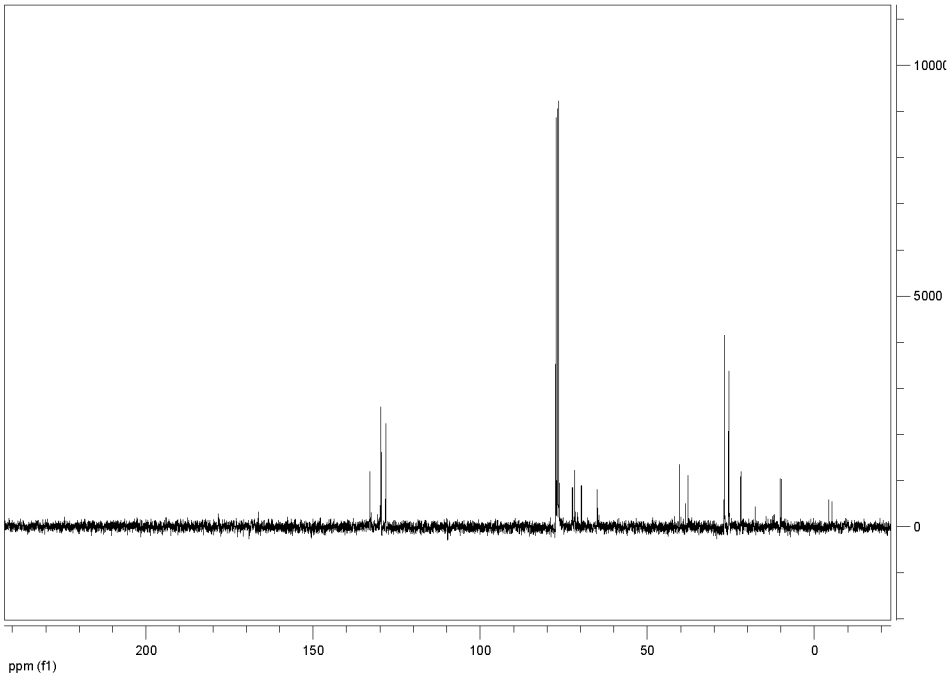


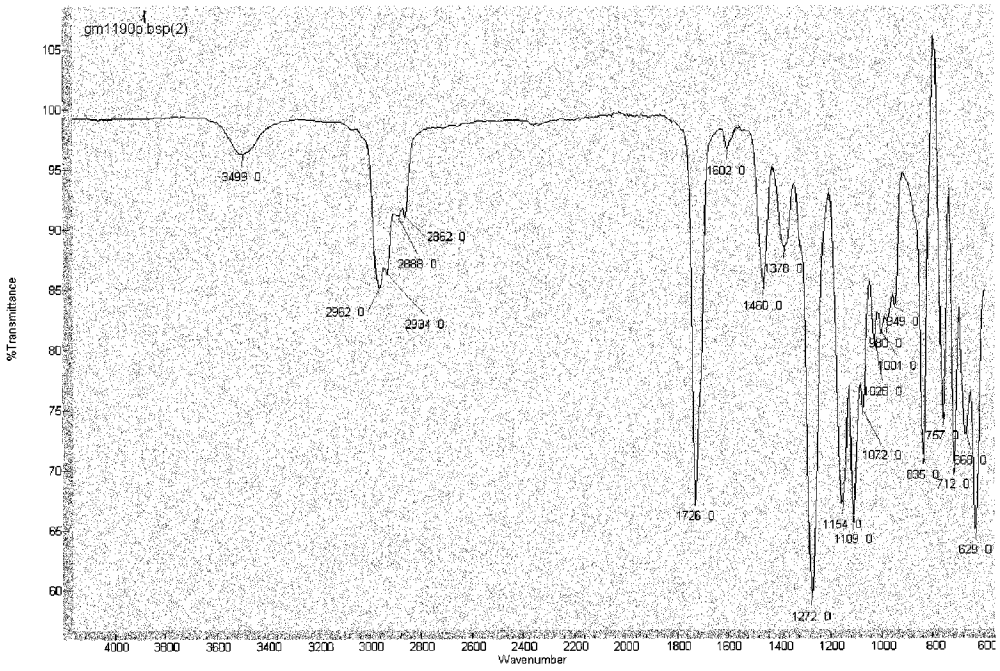


330

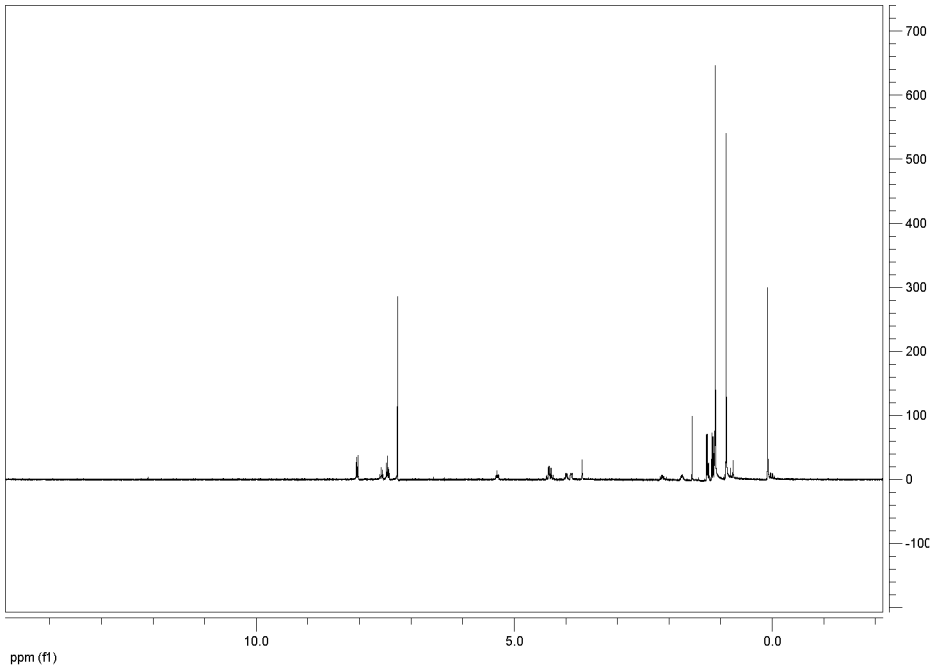
Major diastereomer:

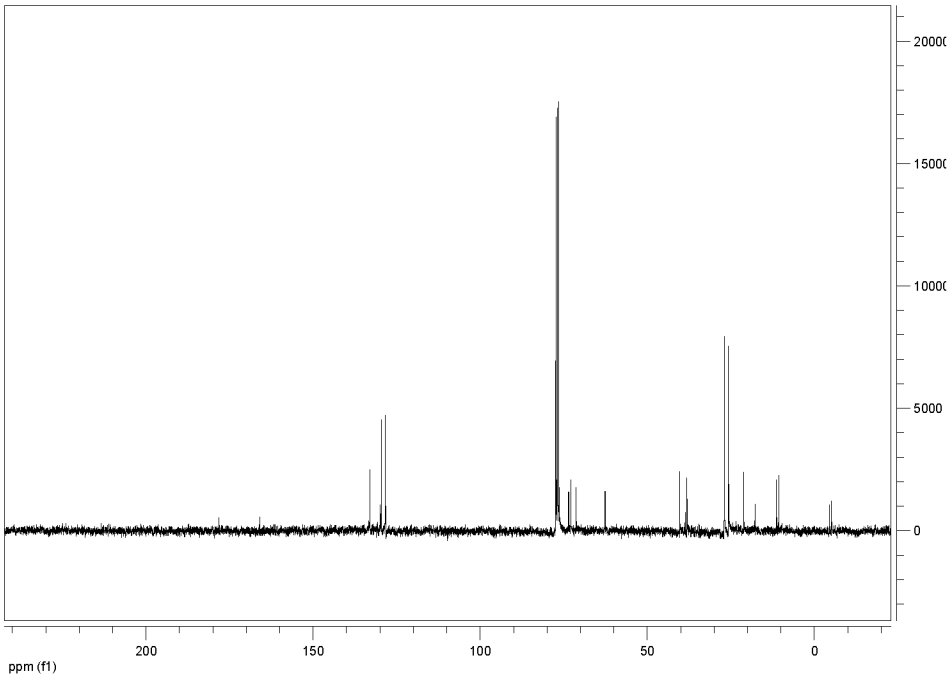


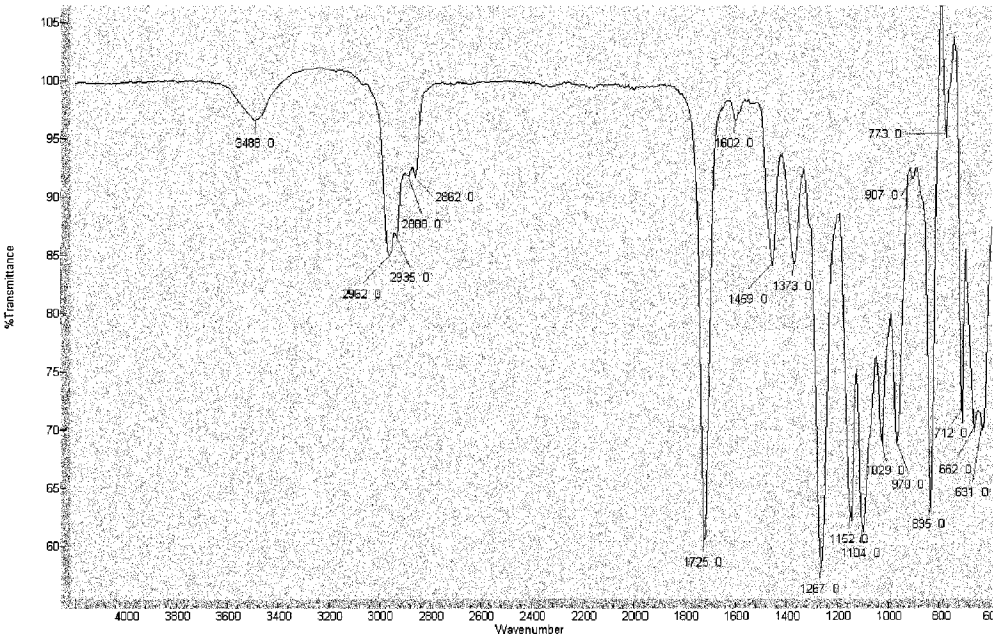

10000
5000
0
200
150
100
50
0
ppm (f1)


gm1190p.bsp(2)
%Transmittance
Wavenumber
3499.0
2962.0
2934.0
2888.0
2862.0
1726.0
1602.0
1460.0
1378.0
1272.0
1154.0
1109.0
1072.0
1026.0
1001.0
980.0
949.0
757.0
712.0
629.0

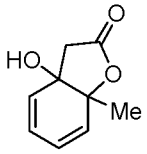
Minor diastereomer:



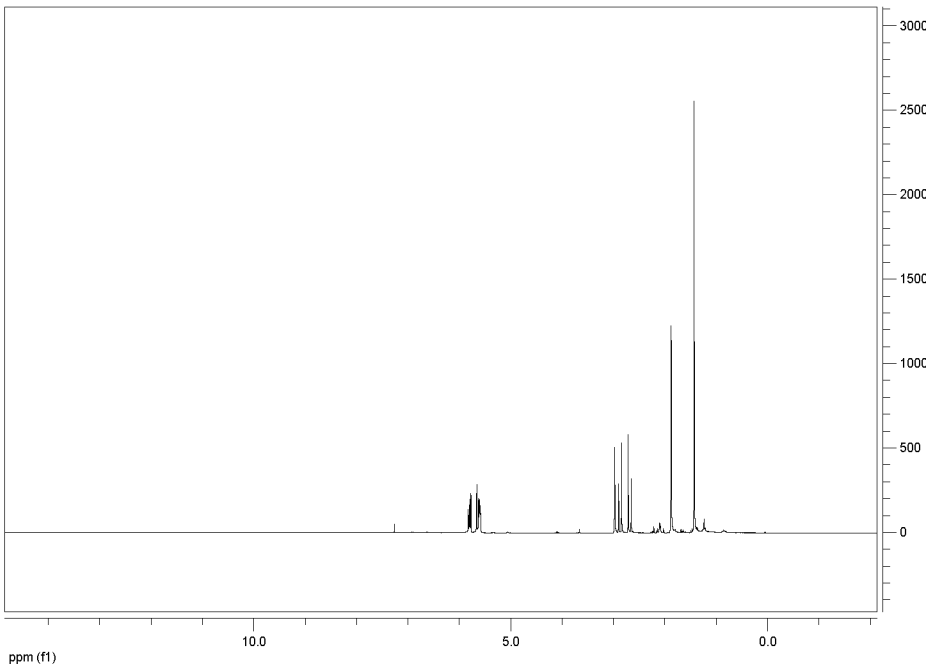


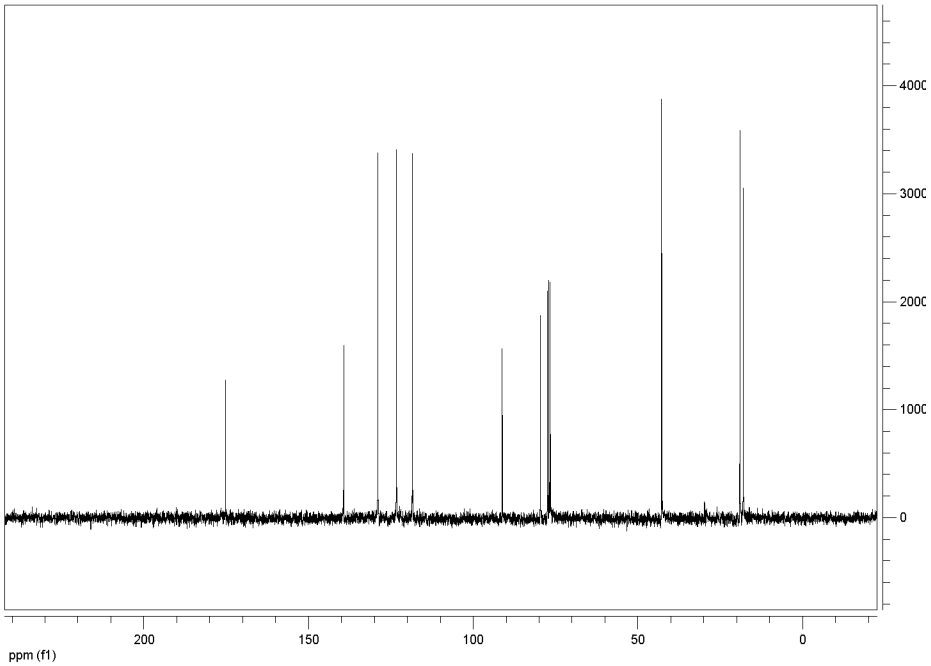


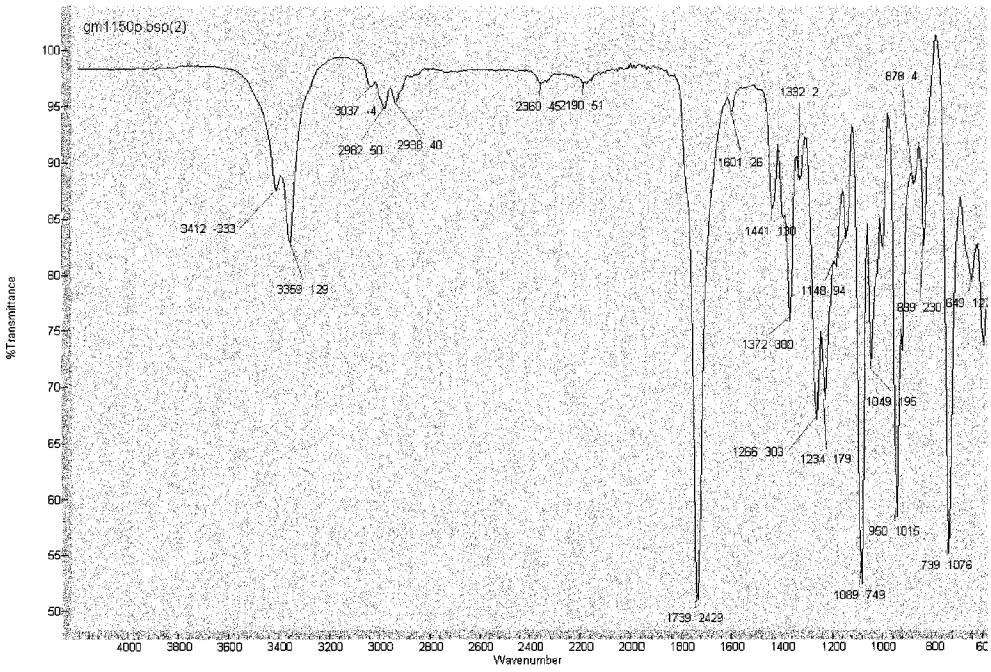
B.2 Fusidilactone C

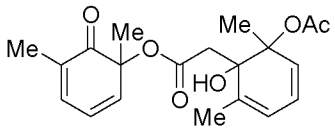


397

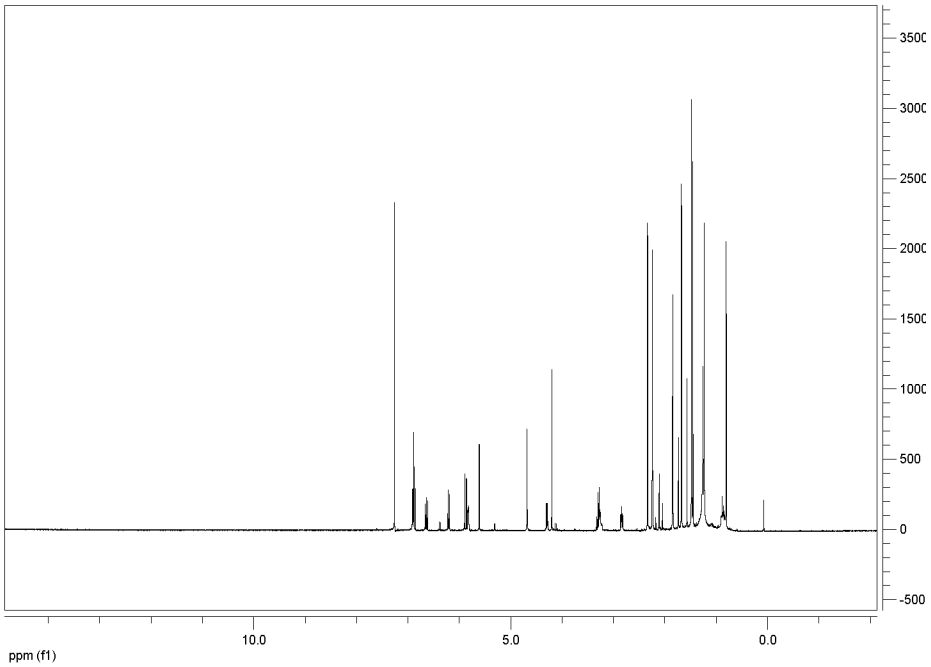


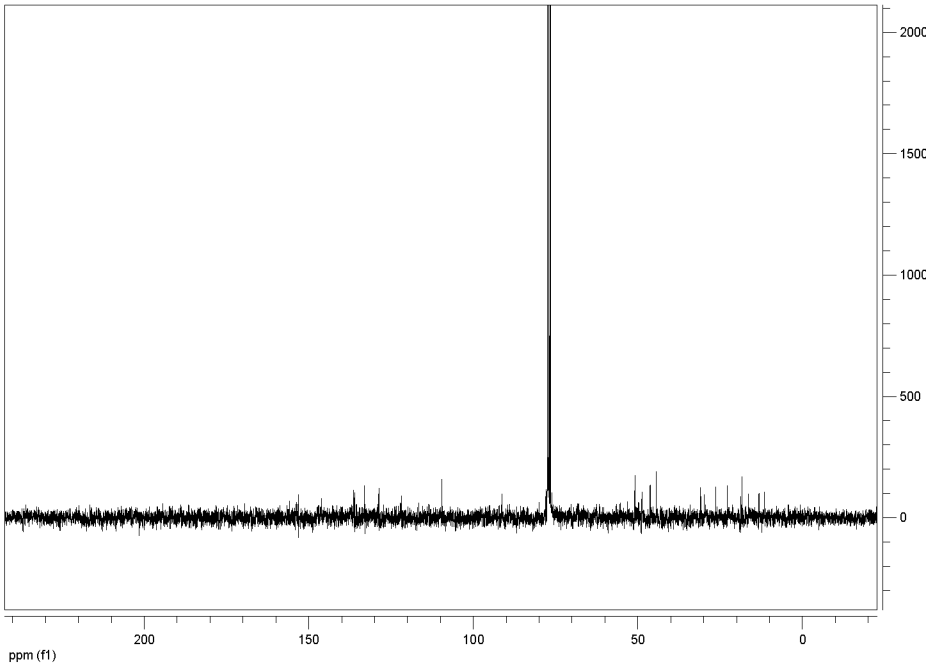

4000
3000
2000
1000
0
200
150
100
50
0
ppm (f1)

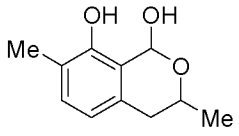

gm1150b.bsp(2)
%Transmittance
Wavenumber
3412 333
3358 129
3037 4
2982 50
2938 40
2360 45
2190 51
1739 2423
1601 26
1441 100
1392 2
1372 980
1266 303
1234 179
1148 94
1089 749
1049 195
950 1015
899 230
878 4
849 12
739 1076


O
Me
Me
O
Me
OAc
HO
O
Me

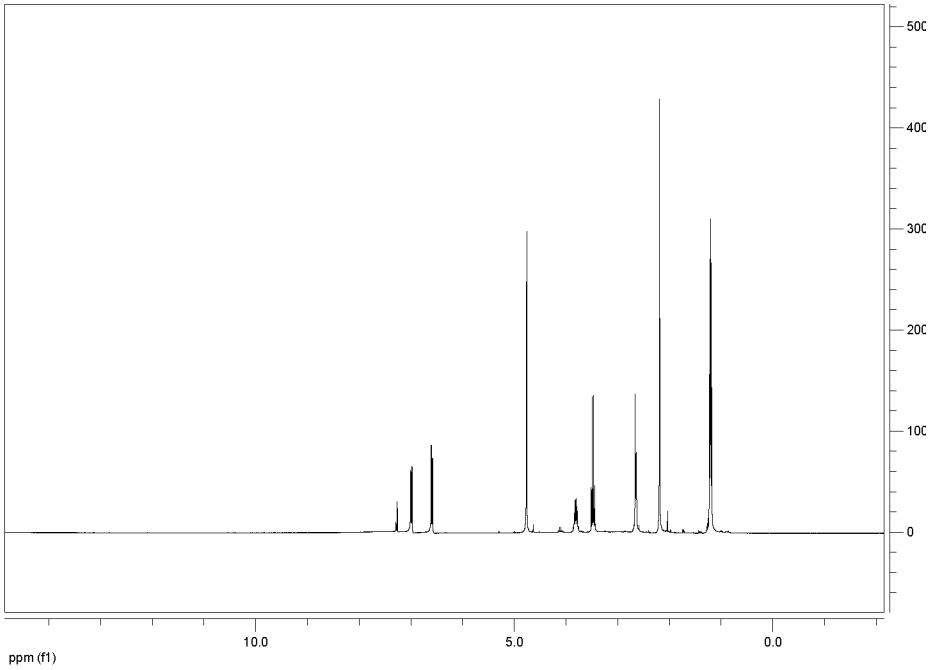
399

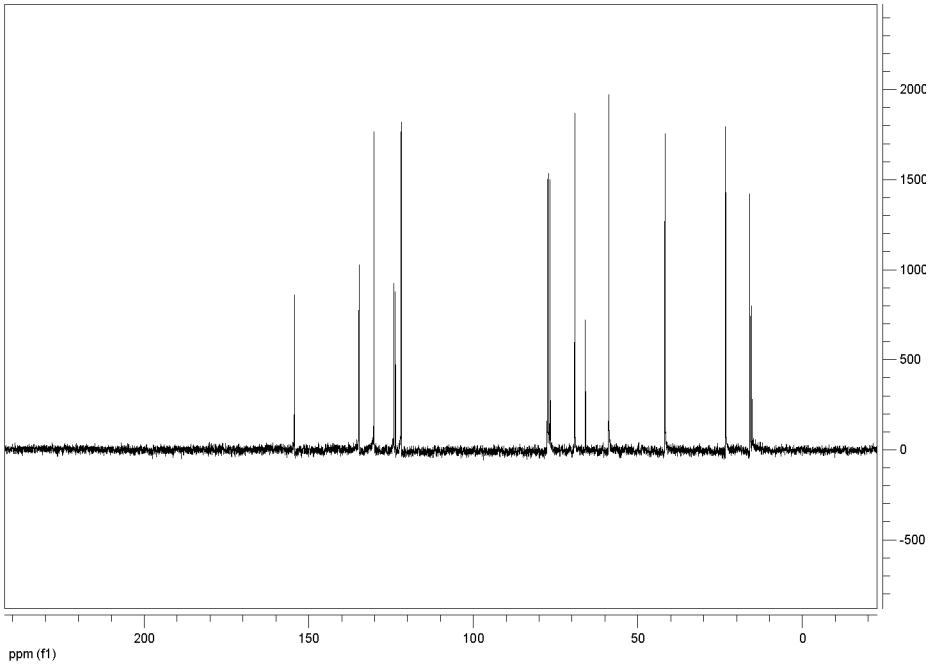

350
300
250
200
150
100
500
0
-500
10.0
5.0
0.0
ppm (f1)

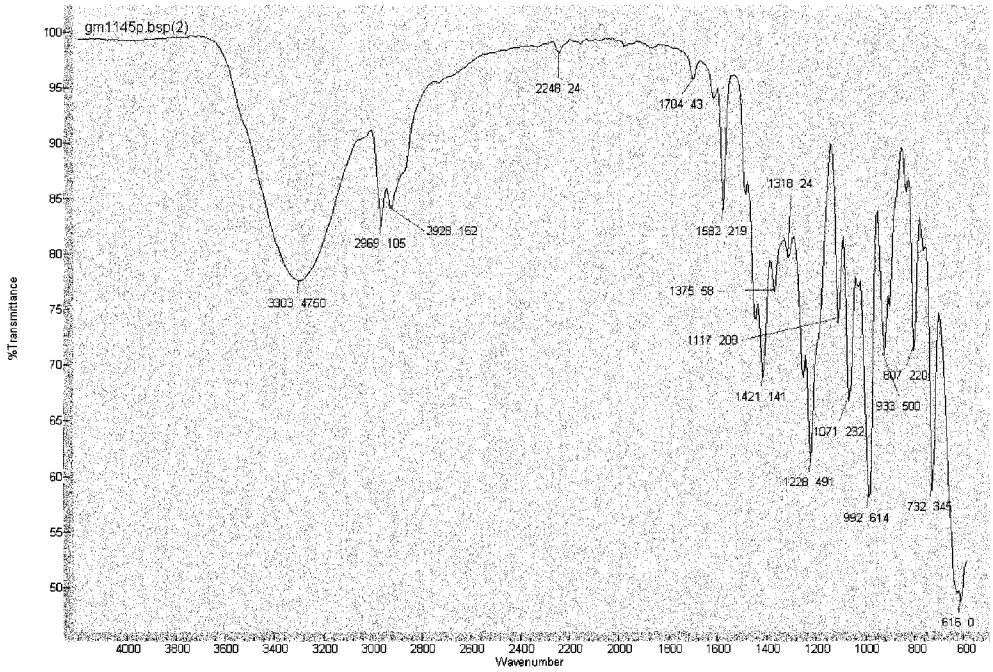

200
150
100
500
0
200
150
100
50
0
ppm (f1)

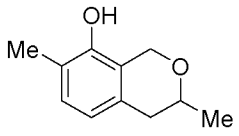

OH
OH
Me
O
Me

419

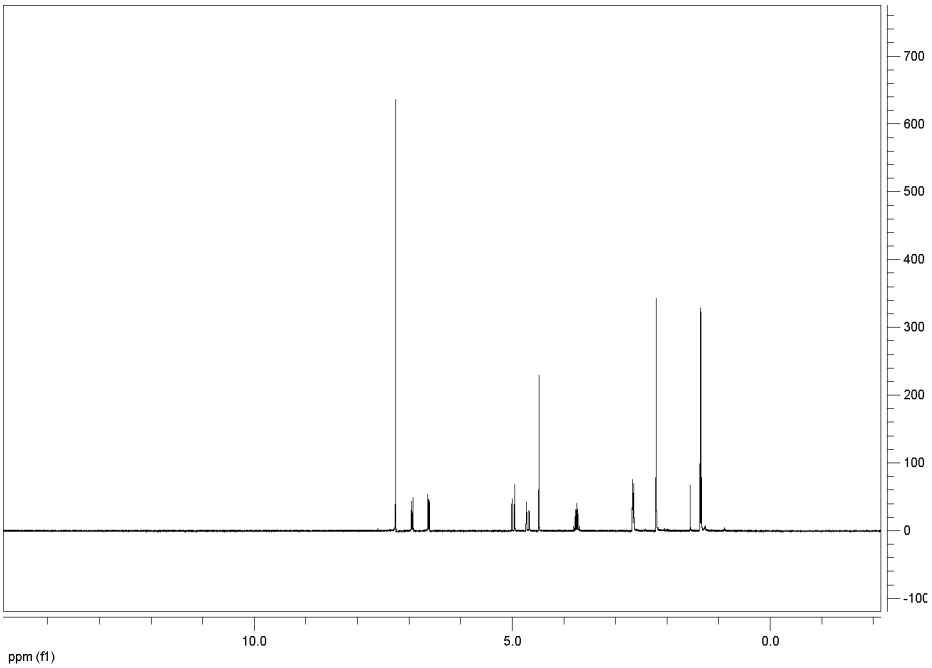

500
400
300
200
100
0
10.0
5.0
0.0
ppm (f1)

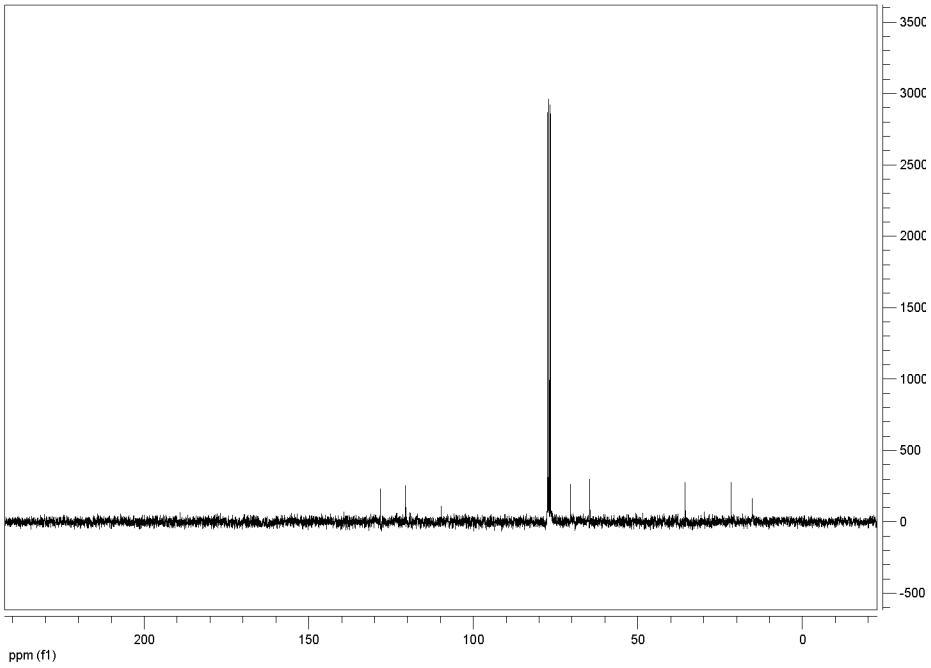

2000
1500
1000
500
0
-500
200
150
100
50
0
ppm (f1)

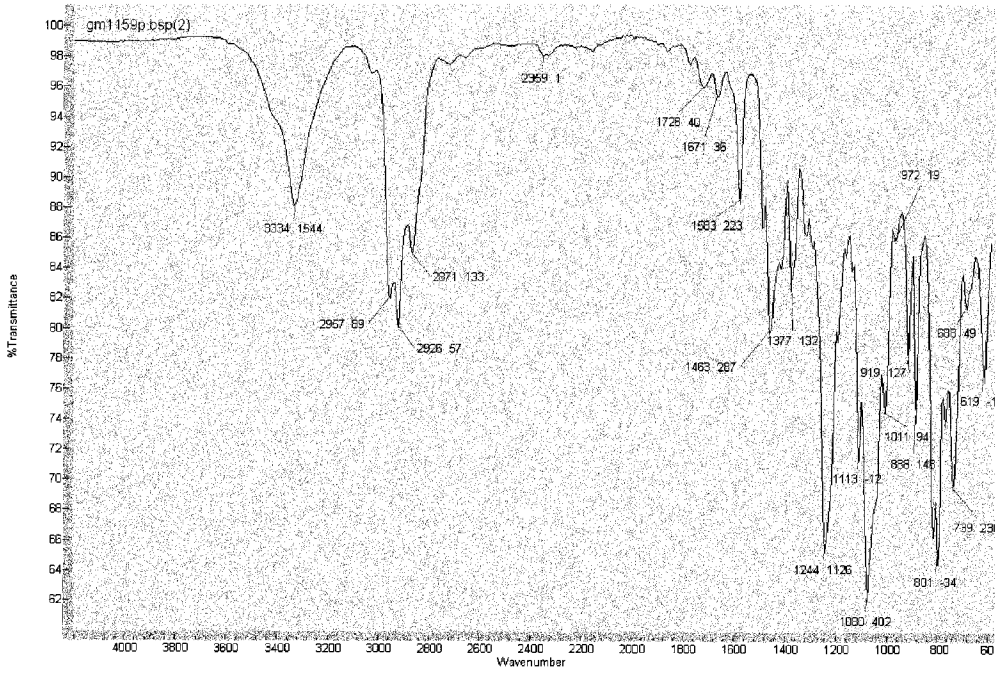

gm1145p.bsp(2)
%Transmittance
Wavenumber
3303 4750
2969 105
2928 162
2248 24
1704 43
1582 219
1375 58
1318 24
1117 209
1421 141
1228 491
1071 232
992 614
933 500
807 220
732 345
615 0

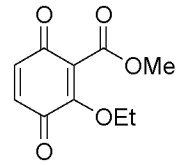

OH
Me
O
Me

420

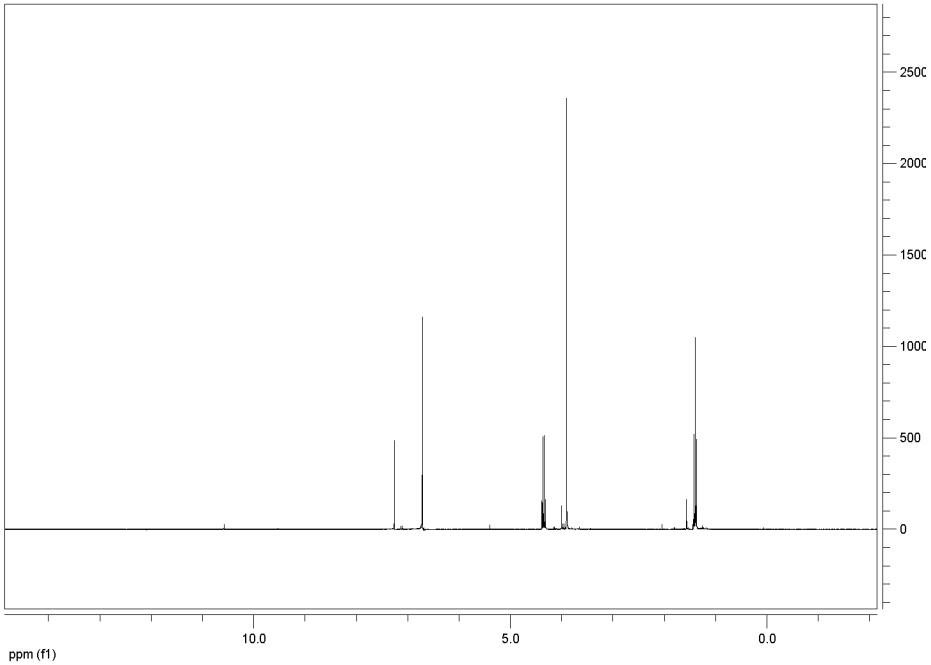

ppm (f1)

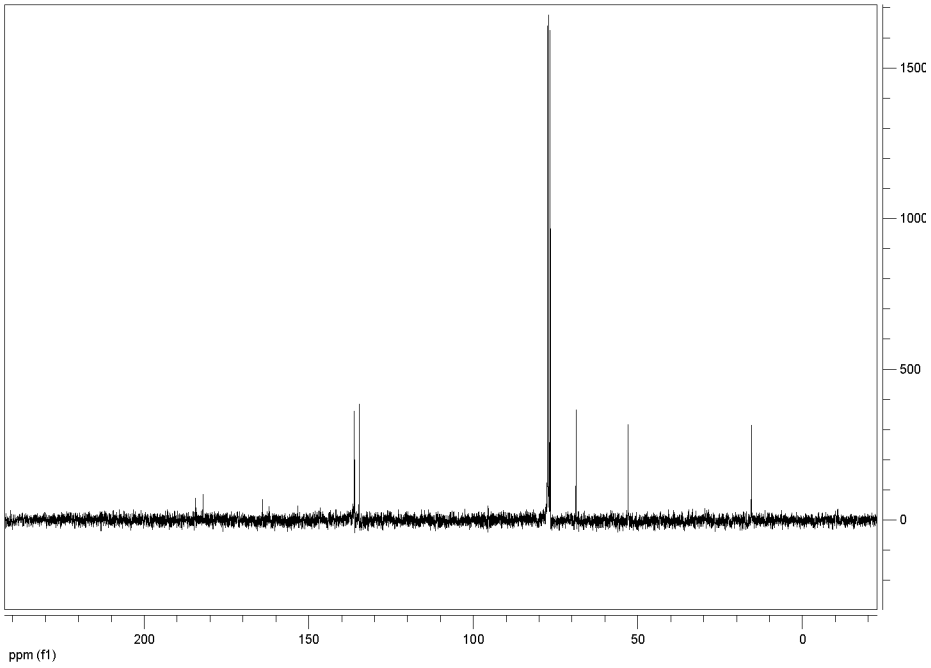

3500
3000
2500
2000
1500
1000
500
0
-500
200
150
100
50
0
ppm (f1)

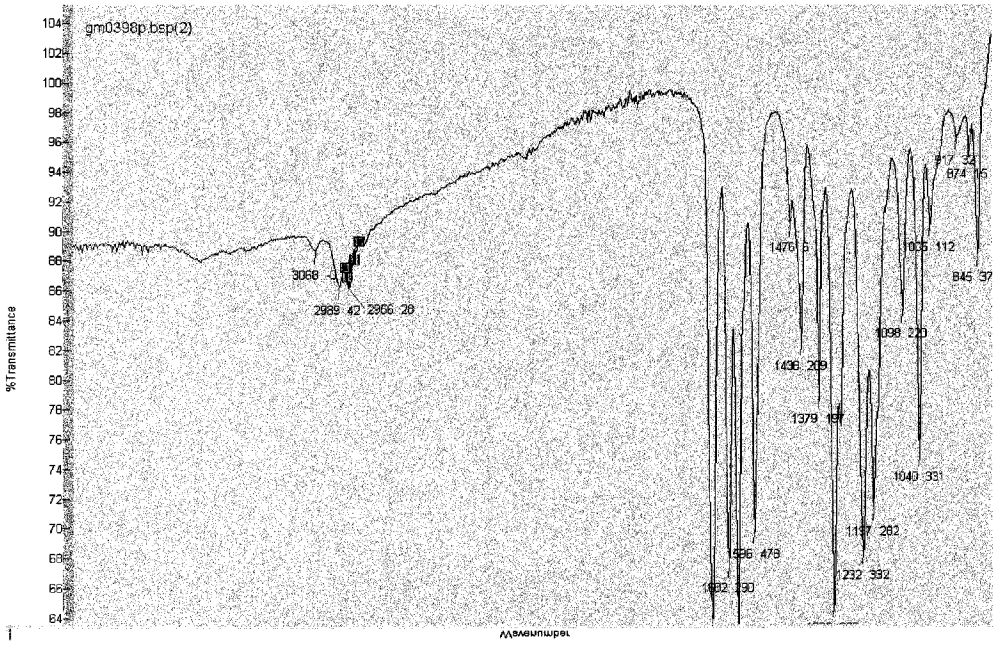

gm1159p.bsp(2)
%Transmittance
Wavenumber
3334 1544
2957 69
2926 57
2871 133
2359 1
1728 40
1671 36
1583 223
1463 267
1377 132
1244 1126
1113 72
1080 402
1011 94
972 19
919 127
838 148
801 34
739 23
635 49
619
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
60

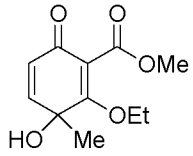

O
O
OMe
OEt
O

422

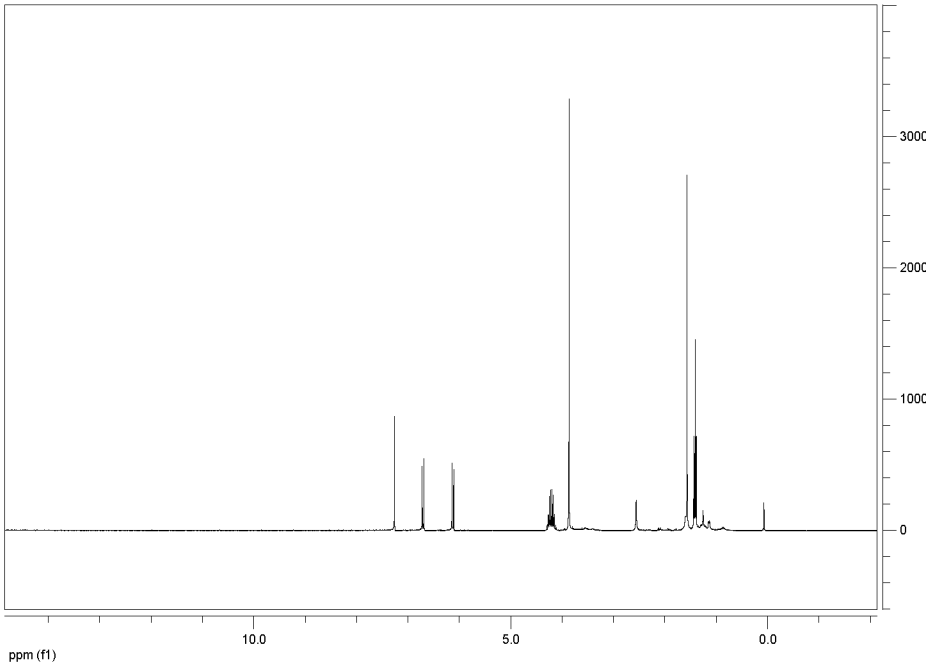

2500
2000
1500
1000
500
0
10.0
5.0
0.0
ppm (f1)

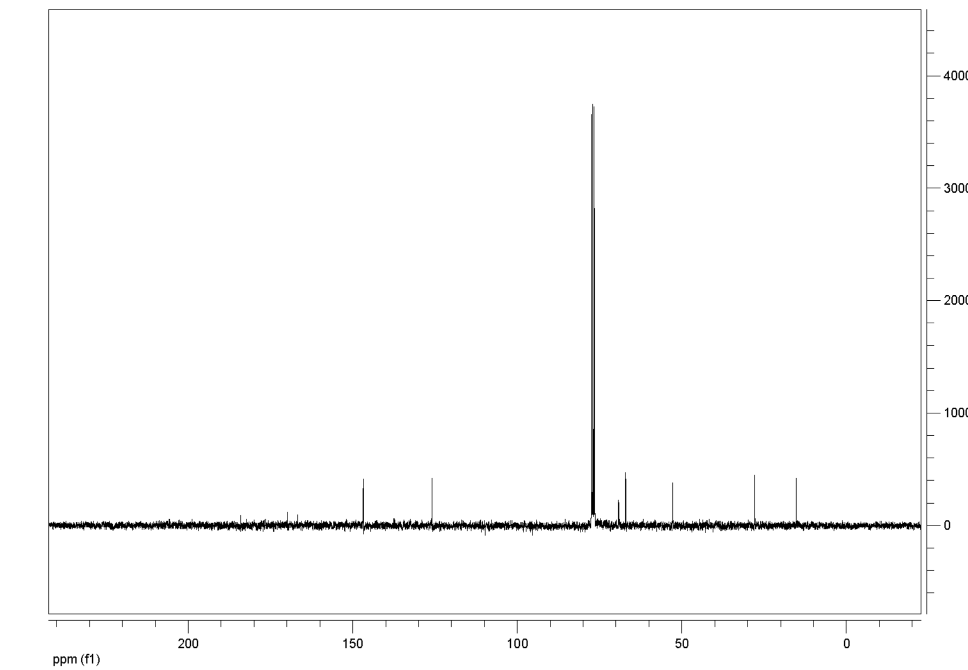

1500
1000
500
0
200
150
100
50
0
ppm (f1)

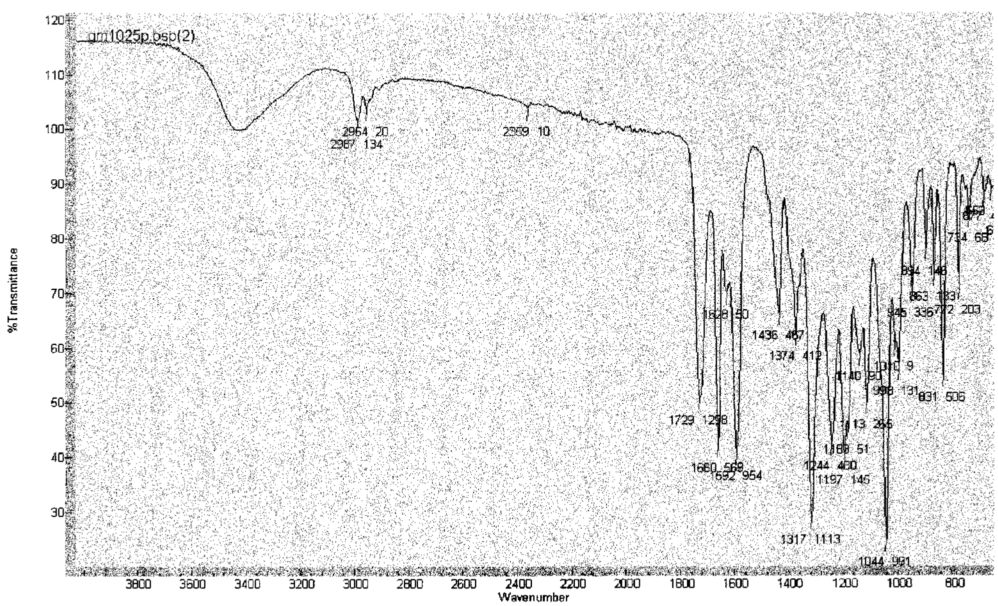

gm0398p.bsp(2)
%Transmittance
3068
2989 42
2906 28
1476 8
1439 209
1379 197
1232 332
1137 282
1098 220
1040 331
1005 112
996 478
982 230
874 95
845 37

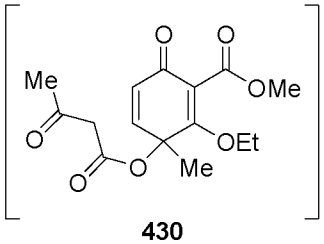

O
O
OMe
OEt
HO
Me

423

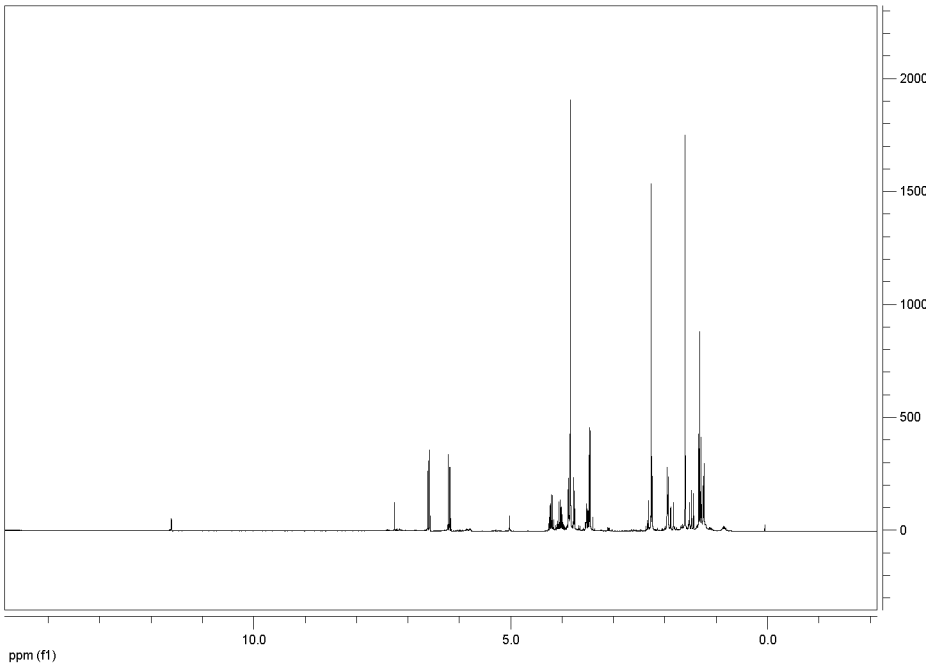

3000
2000
1000
0
10.0
5.0
0.0
ppm (f1)

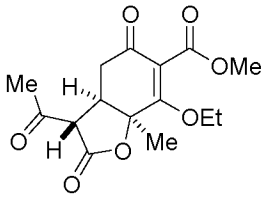

ppm (f1)
200
150
100
50
0
3000
2000
0


gm1025p.bsp(2)
%Transmittance
Wavenumber
1729
1436
1374
1317
1113
1244
1197

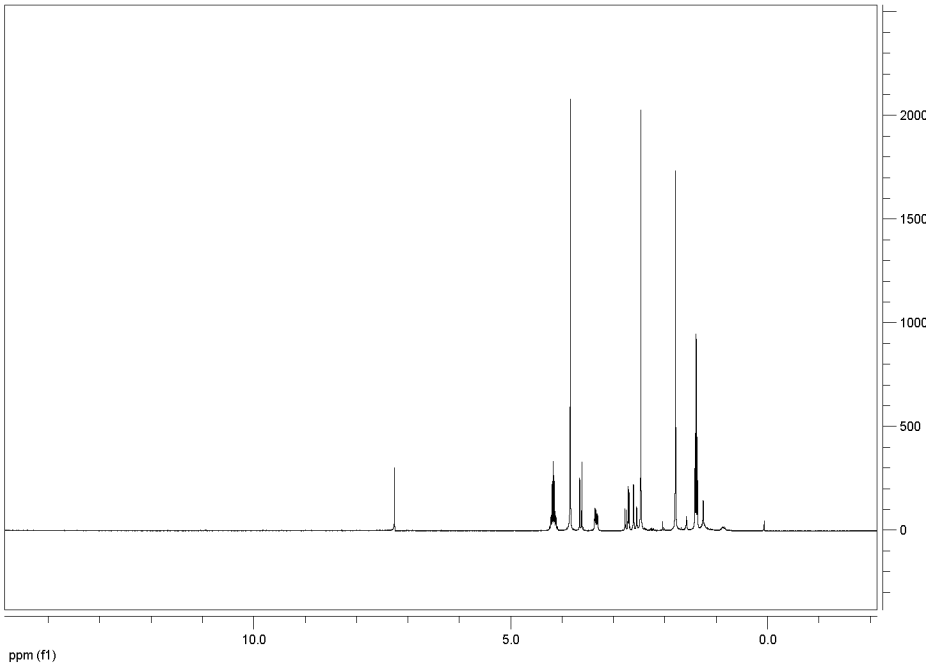

Me
O
O
O
O
O
OMe
OEt
Me

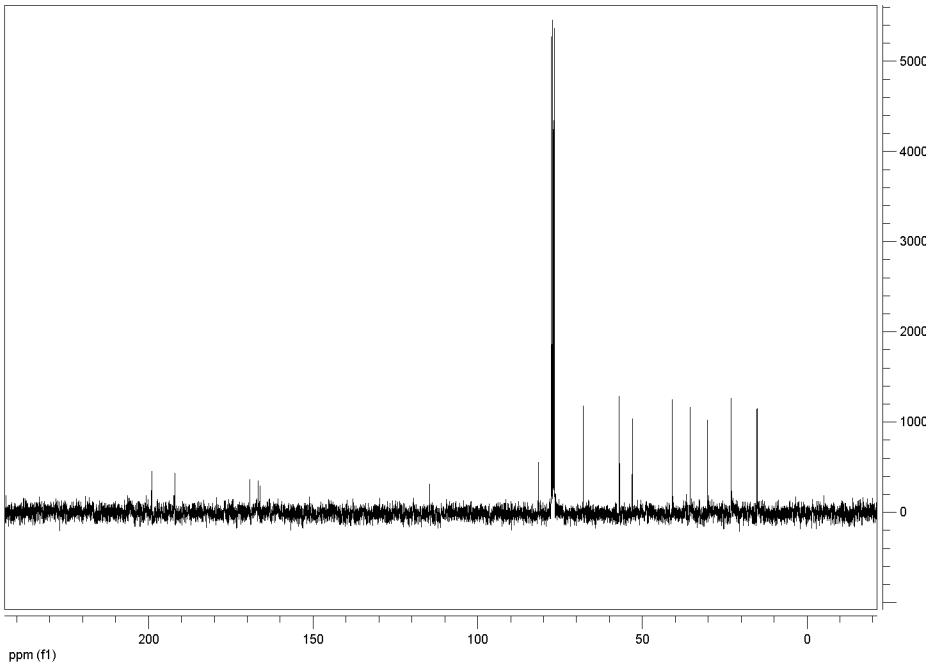
430

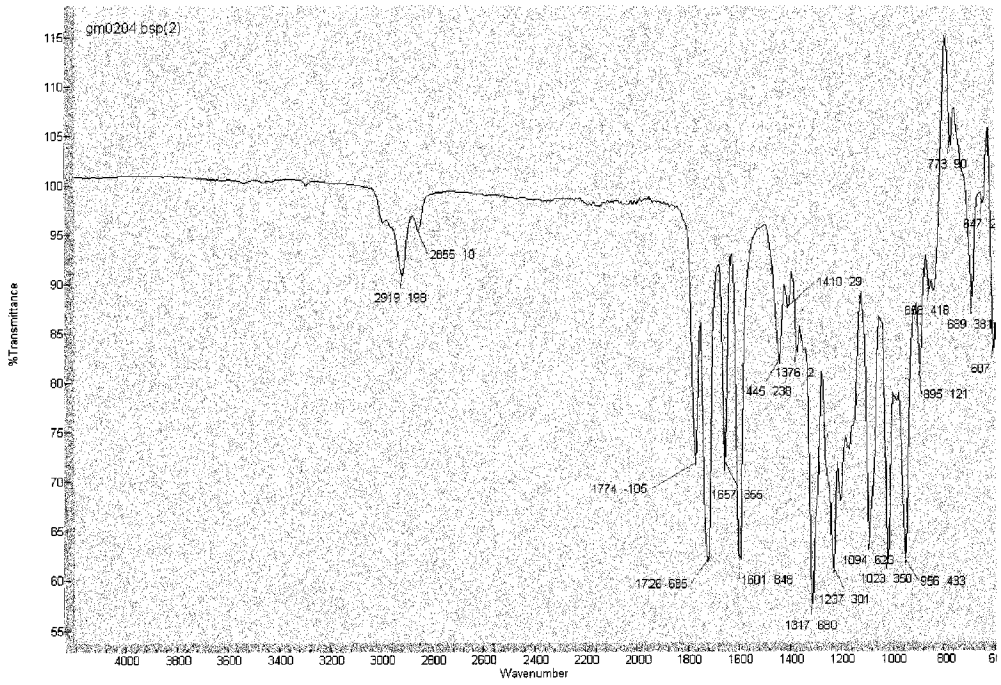

2000
1500
1000
500
0
10.0
5.0
0.0
ppm (f1)

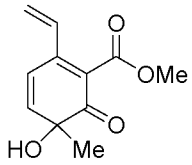

O
O
OMe
Me
H
OEt
O
H
O
Me
O

431

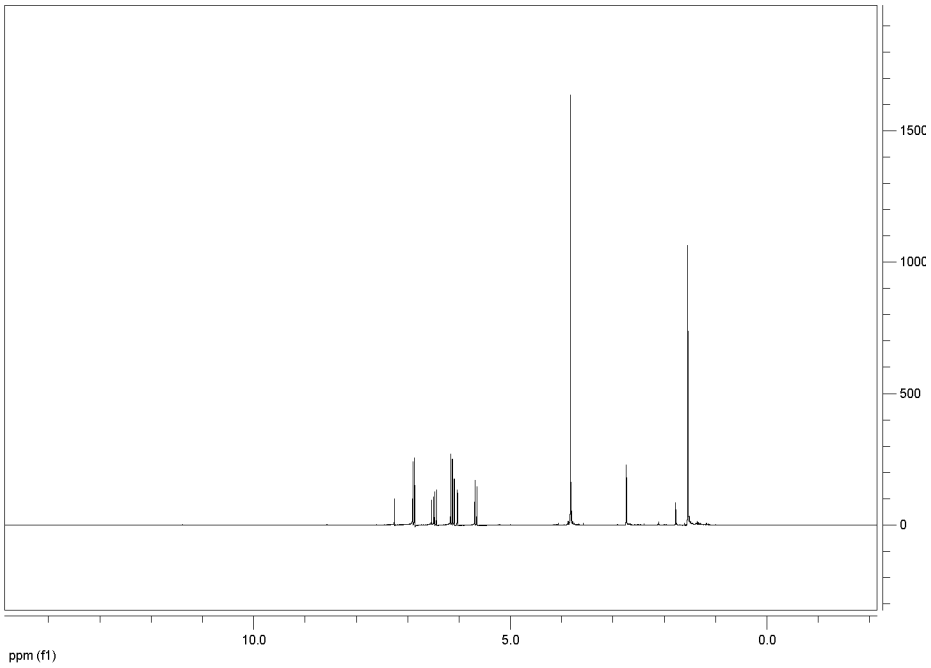

2000
1500
1000
500
0
10.0
5.0
0.0
ppm (f1)

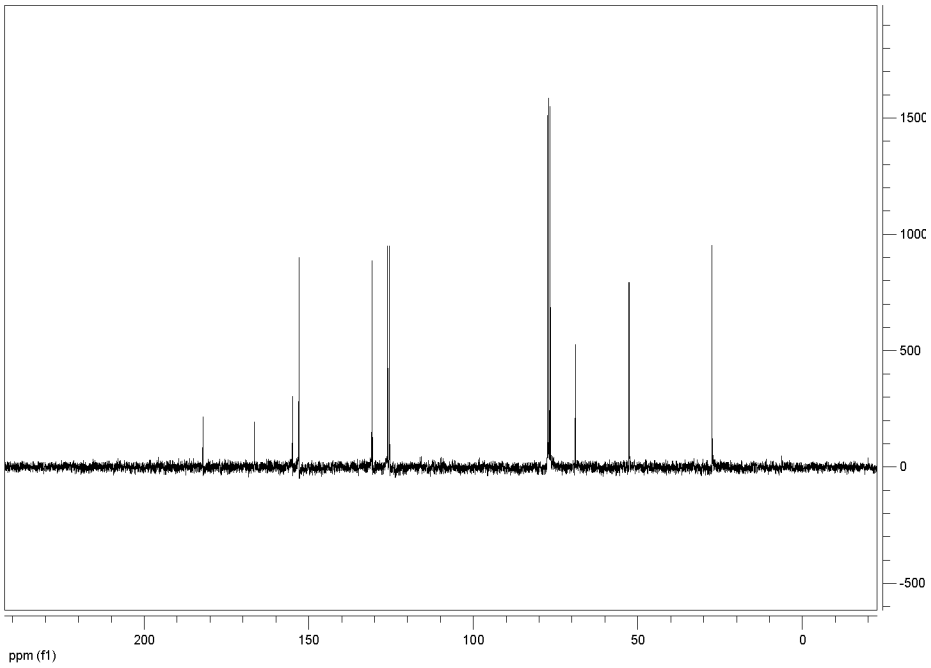

5000
4000
3000
2000
1000
0
200
150
100
50
0
ppm (f1)

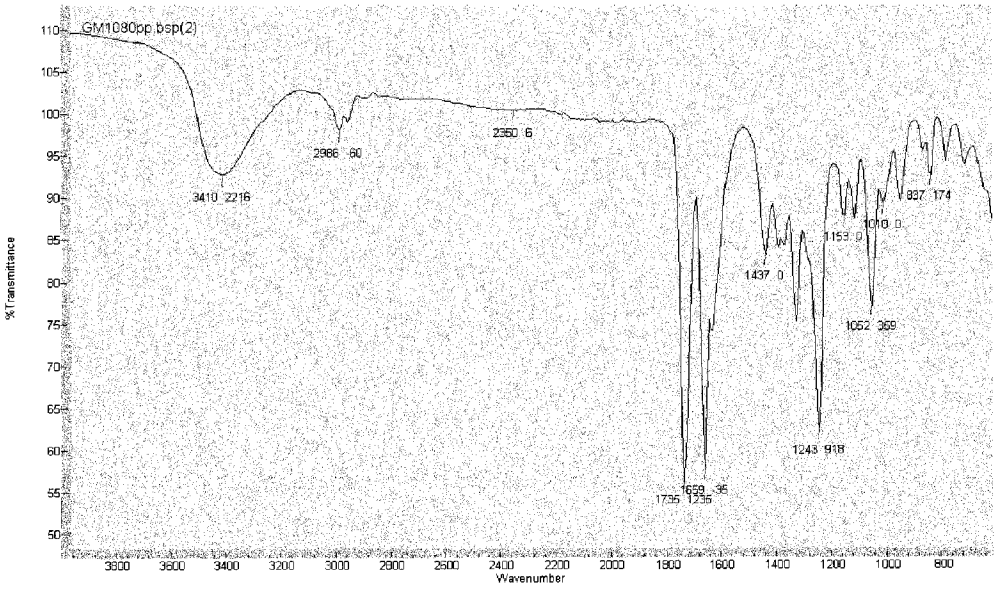

gm0204.bsp(2)
%Transmittance
Wavenumber
2919.188
2855.10
1774.106
1726.685
1657.356
1601.846
1445.238
1410.29
1376.2
1317.680
1237.301
1094.623
1023.350
956.433
995.121
773.90
607

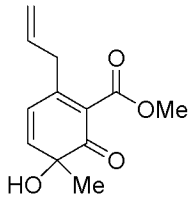

O
OMe
O
HO
Me

434

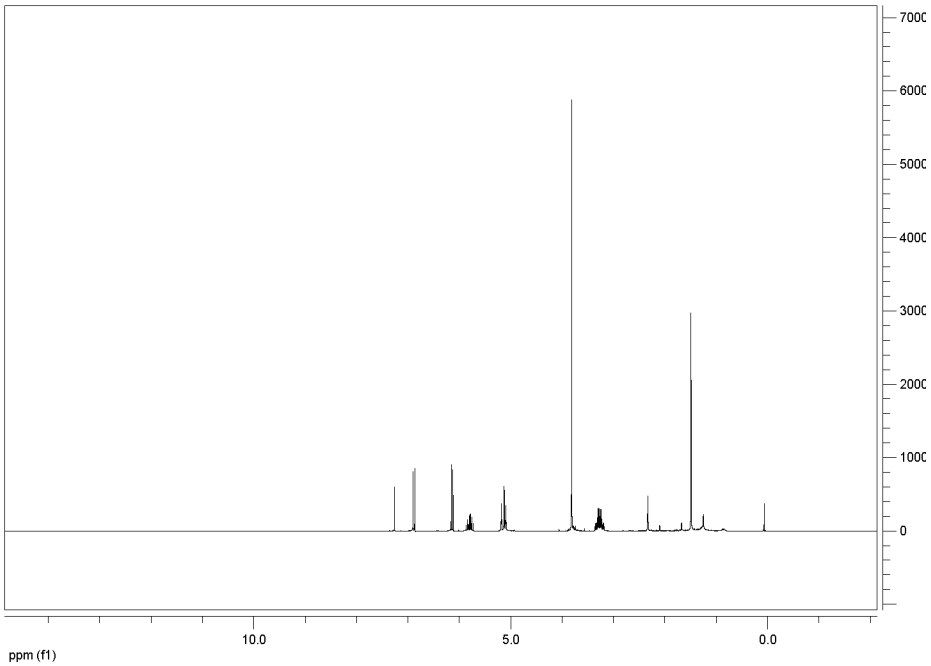

10.0
5.0
0.0
ppm (f1)

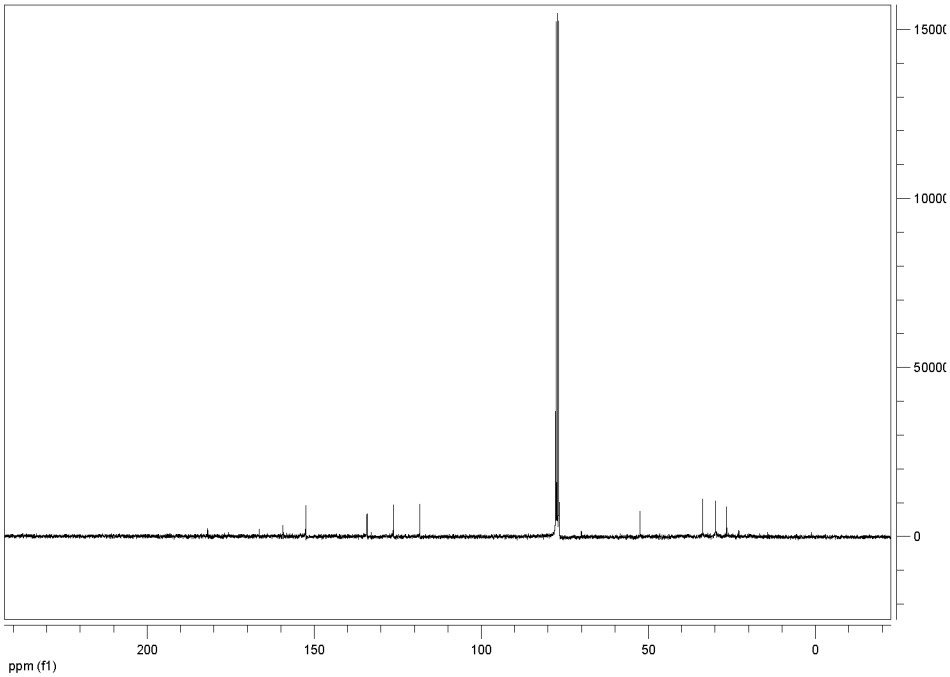

1500
1000
500
0
-500
200
150
100
50
0
ppm (f1)

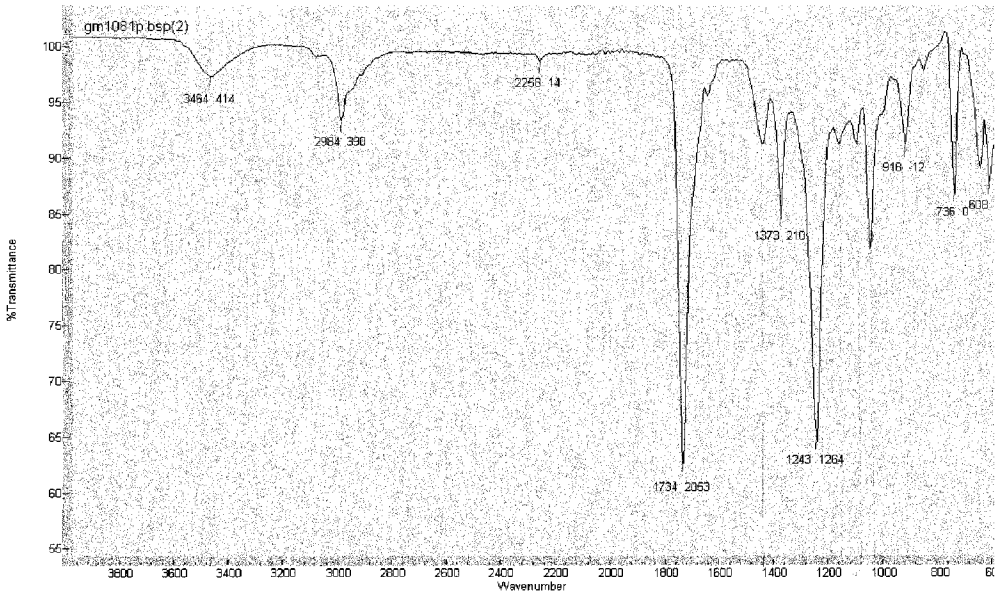

GM1080pp.bsp(2)
%Transmittance
Wavenumber
3410.2216
2986.60
2360.6
1659.35
1735.1236
1437.0
1243.918
1153.0
1052.369
1010.0
887.174

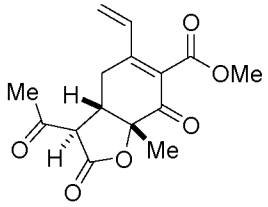

O
OMe
O
HO
Me

435

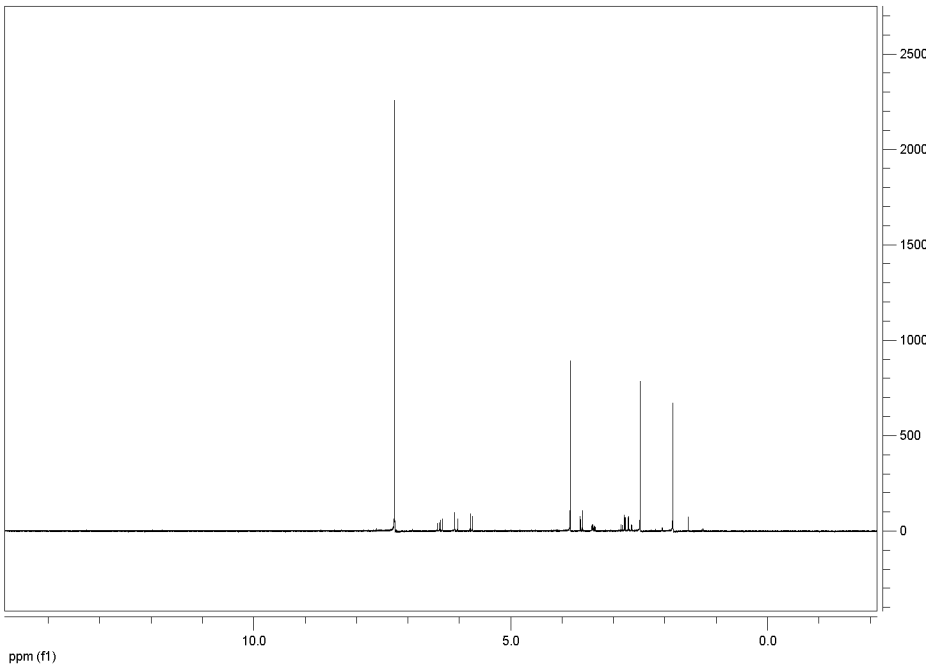

7000
6000
5000
4000
3000
2000
1000
0
10.0
5.0
0.0
ppm (f1)

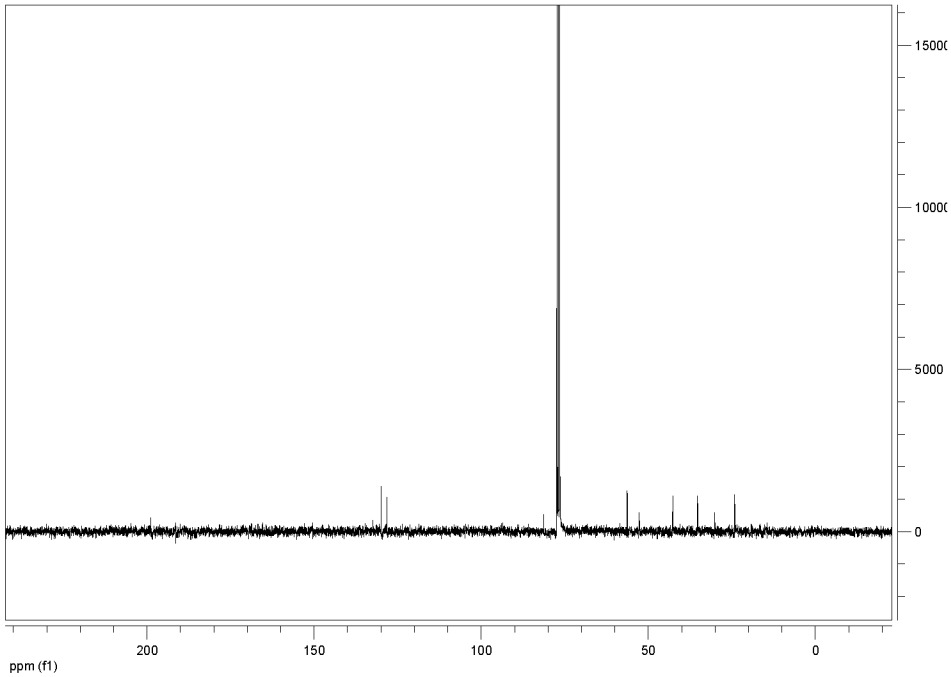

15000
10000
5000
0
200
150
100
50
0
ppm (f1)

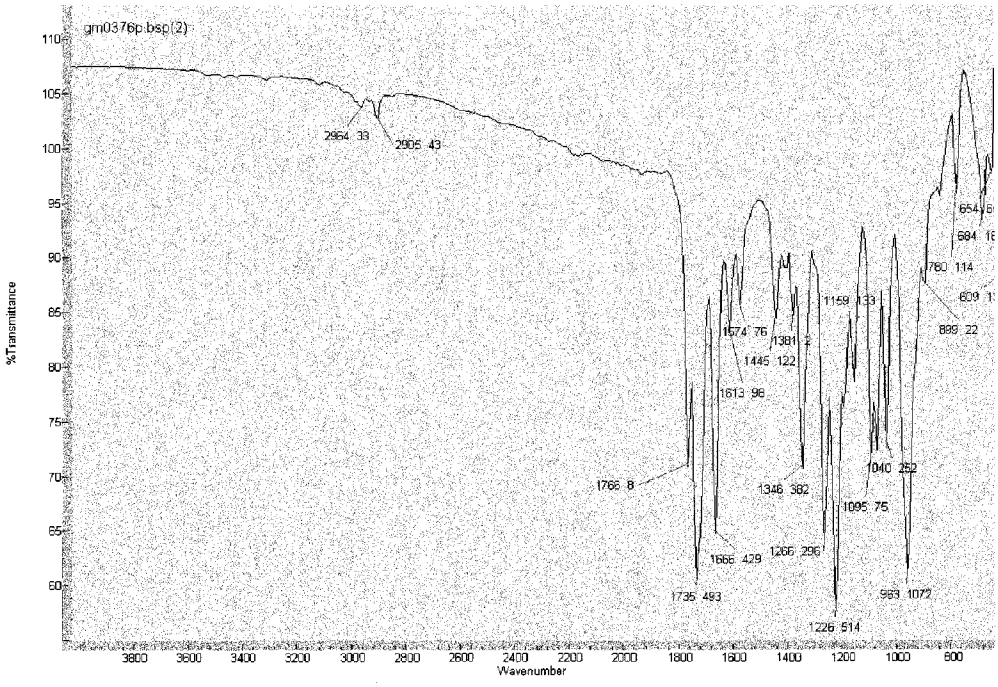

gm1081p.bsp(2)
%Transmittance
Wavenumber
3454.41
2984.39
2258.14
1734.20
1373.21
1243.12
1264.
918.12
736.0
608

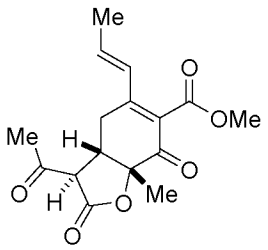

Me
H
O
OMe
O
O
H
O
Me
O

437

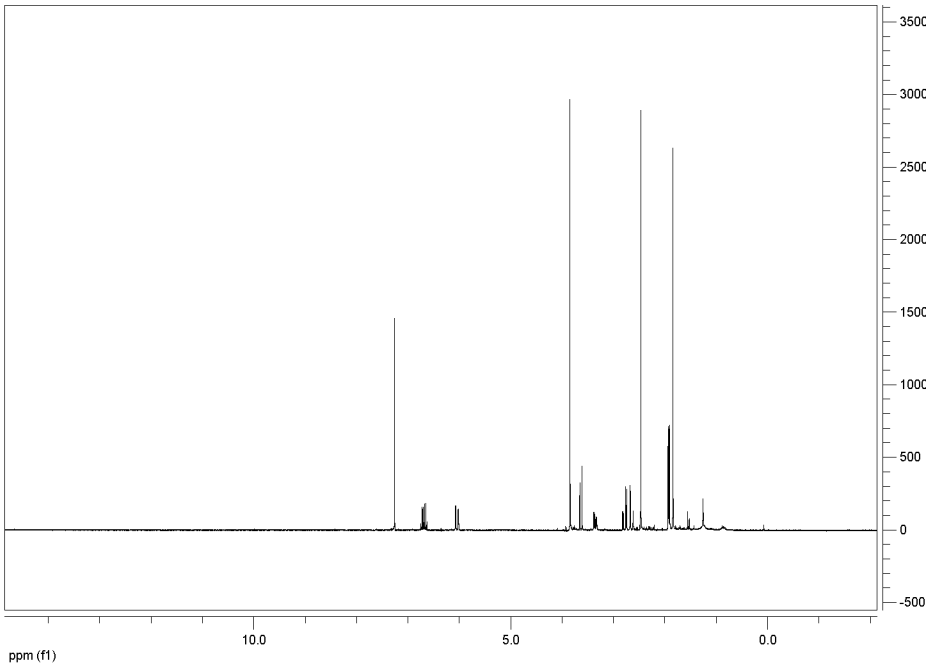

2500
2000
1500
1000
500
0
10.0
5.0
0.0
ppm (f1)

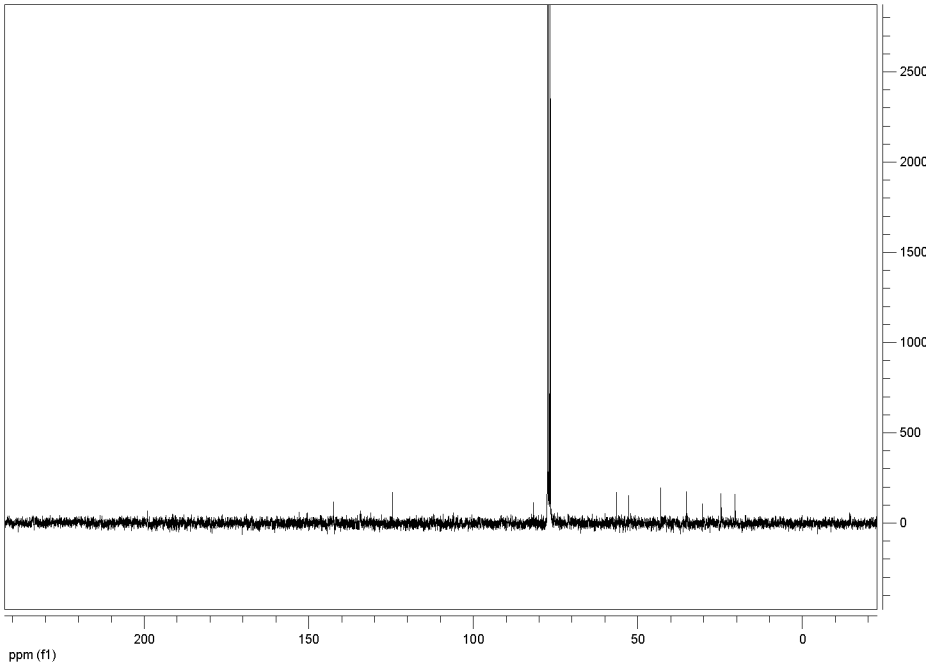

15000
10000
5000
0
200
150
100
50
0
ppm (f1)

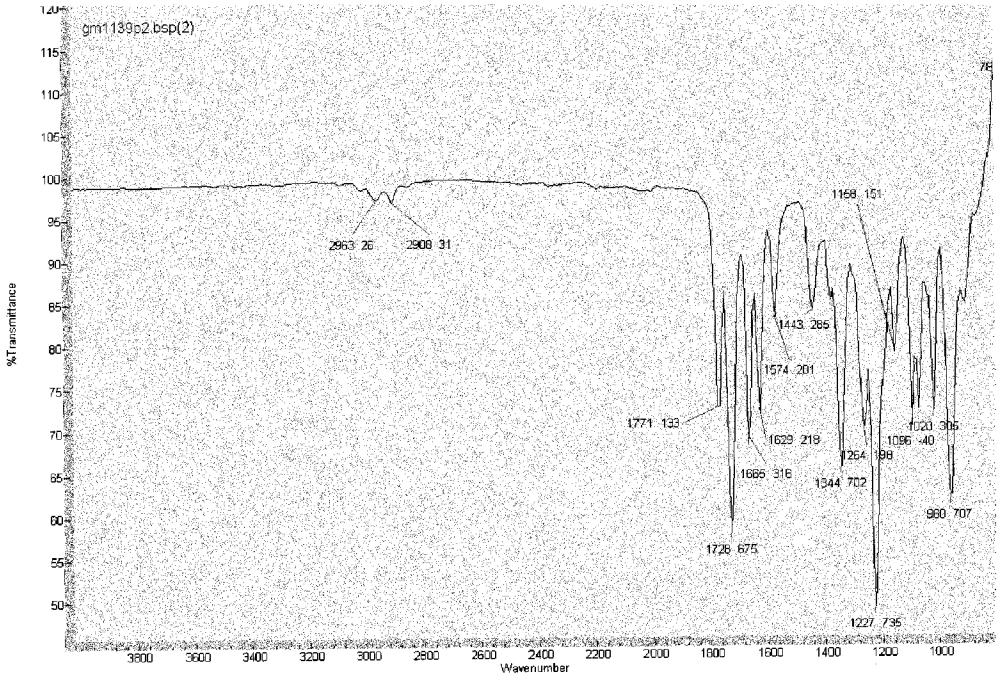

gm0376p.bsp (2)
%Transmittance
Wavenumber
2964.33
2905.43
1766.8
1735.493
1666.429
1613.98
1574.76
1445.122
1381.2
1348.382
1266.296
1226.514
1159.133
1095.75
1040.252
983.1072
899.22
760.114
654.6
684.18
809.1
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800

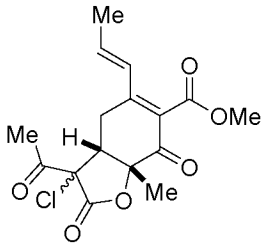

Me
O
OMe
Me
H
O
O
H
O
Me
O

438

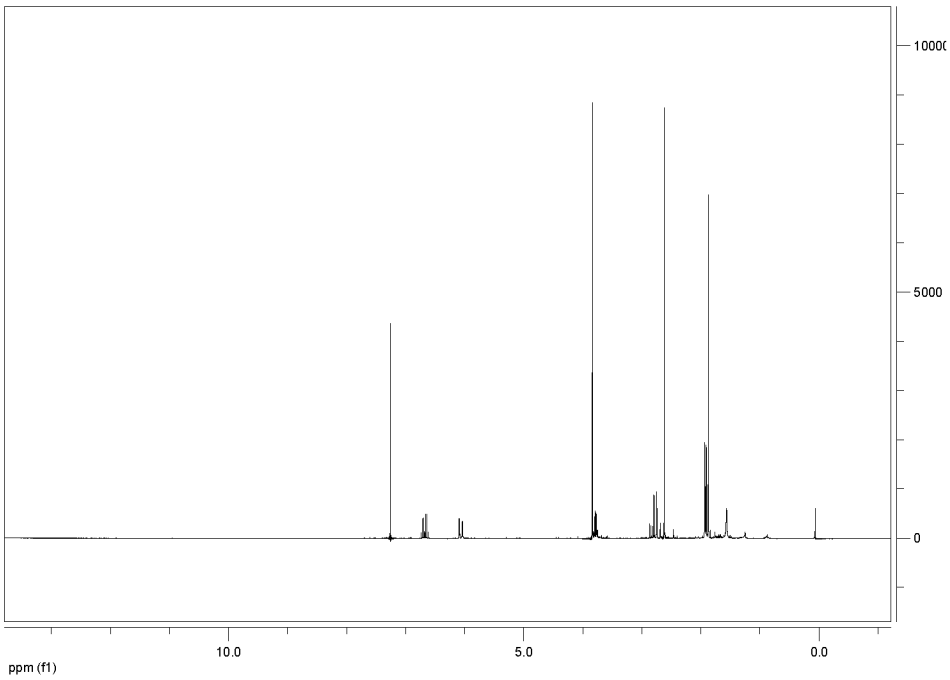

3500
3000
2500
2000
1500
1000
500
0
-500
10.0
5.0
0.0
ppm (f1)

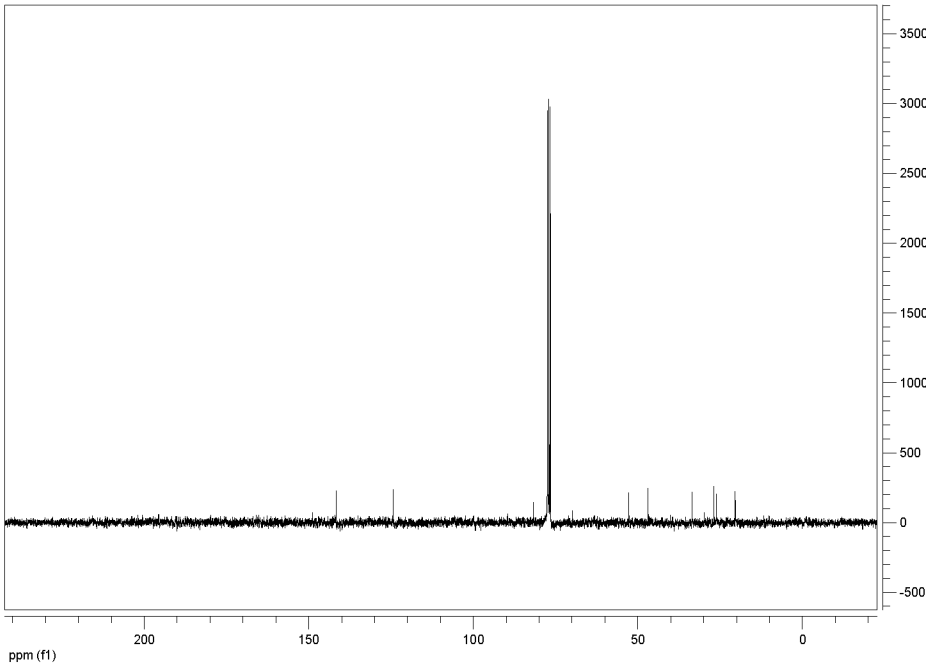

2500
2000
1500
1000
500
0
200
150
100
50
0
ppm (f1)

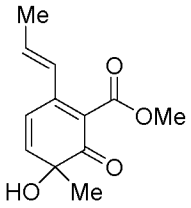

gm1139p2.bsp(2)
%Transmittance
Wavenumber
2963 26
2908 31
1771 133
1728 675
1685 316
1629 218
1574 201
1443 285
1344 702
1264 198
1227 735
1158 151
1096 40
1020 305
980 707


Me
O
OMe
Me
H
O
O
Cl
O
Me
O

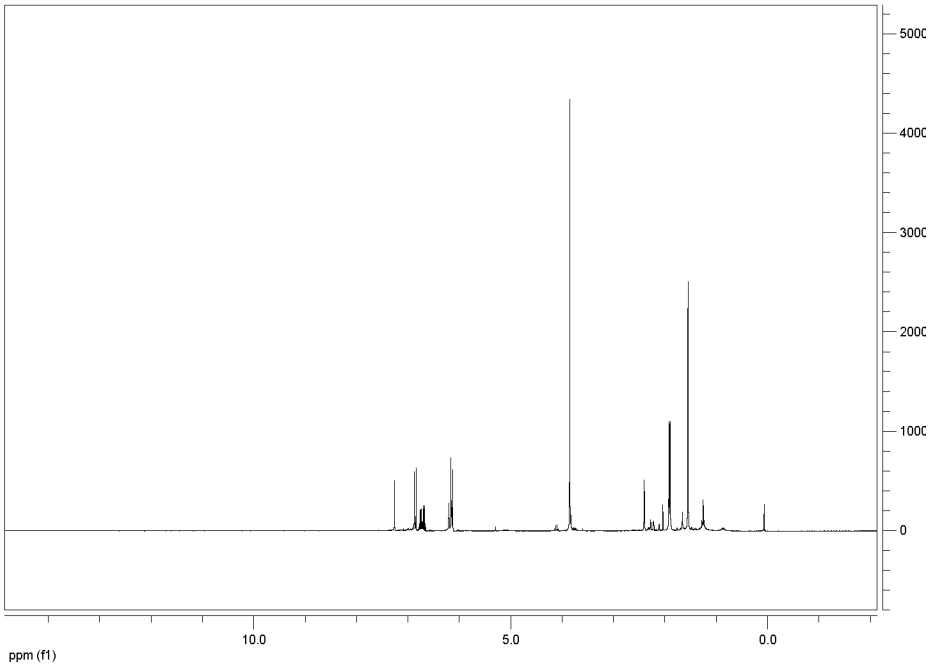
444


10000
5000
0
10.0
5.0
0.0
ppm (f1)


3500
3000
2500
2000
1500
1000
500
0
-500
200
150
100
50
0
ppm (f1)


Me
O
OMe
O
HO
Me

452


5000
4000
3000
2000
1000
0
10.0
5.0
0.0
ppm (f1)