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Synthesis and Application of Oxetanyl Peptides

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Presented by

Guido Patrick Möller

Dipl.-Chem., Westfälische Wilhelms-Universität Münster
Born August 14th 1987
Citizen of the Federal Republic of Germany

Accepted on the recommendation of

Prof. Dr. Erick M. Carreira, examiner
Prof. Dr. Karl-Heinz Altmann, co-examiner

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Publications & Presentations

Publications

K. Miyata, G. Möller, D. Schepmann, B. Wünsch

Pyridine Analogues of Spirocyclic σ_1-Receptor Ligands

Bioorg. Med. Chem. **2014**, *22*, 4277-4284

Presentations

14th Belgian Organic Synthesis Symposium

Poster presentation: "**Oxetayl Amino Acids as Peptidomimetics**"

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Poster presentation: "**Synthesis and Application of Oxetanyl Peptides**"

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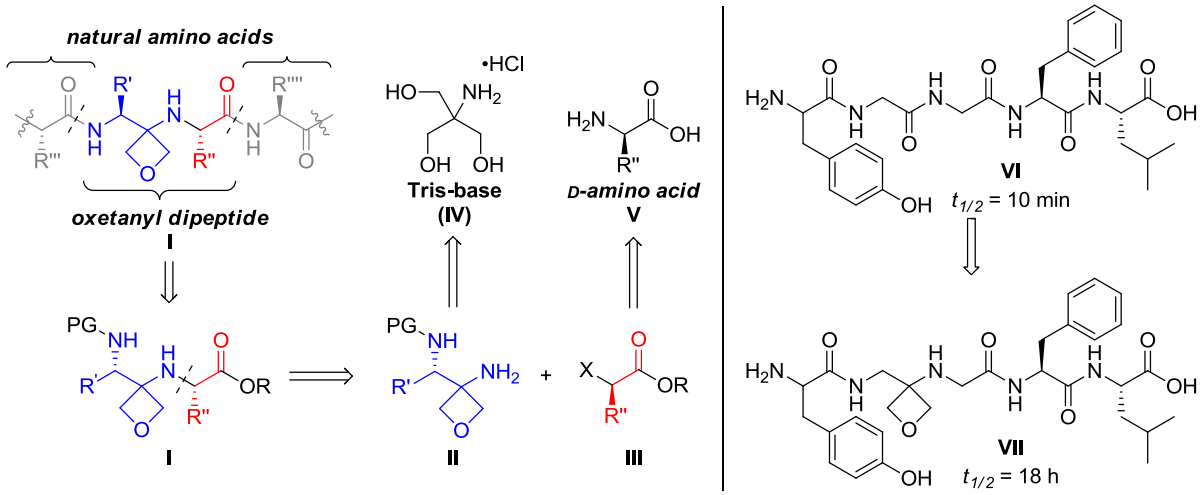
Table of Contents

Abstract

This work extends the concept of oxetanes as *gem*-dimethyl and carbonyl mimics in drug development to peptides. Naturally occurring pharmaceutically active peptides are invaluable lead structures for the design of pharmaceuticals. However, the use of peptides as drugs suffers from some inherent limitations such as low metabolic stability and bioavailability. Hence, we decided to design building blocks containing oxetanes that would significantly enhance the stability of the parent compound and at the same time retain or improve its biological activity.

In the first part of the project a variety of backbone-modified dipeptide building blocks **I** was prepared, where the peptidic amide bond is replaced by a 3-amino oxetane moiety. The synthetic strategy is designed to allow the modular assembly of **I** containing a diversity of side chains by alkylation of **II** with **III**. In turn, **II** and **III** were traced back to inexpensive, readily available starting materials, Tris-base (**IV**) and D-amino acids **V**, respectively (Scheme I).



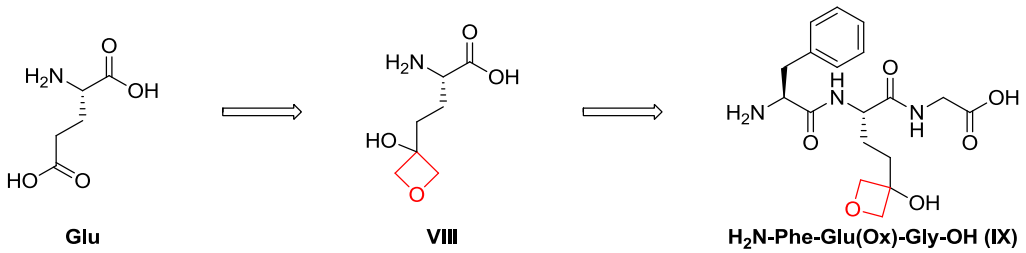
Scheme I Synthesis and Application of Oxetanyl Dipeptides I.

This approach relying on robust synthetic methods ensures the operationally simple formation of sufficient amounts of building blocks **I** for their incorporation into larger peptides. We chose the prominent endogenous neurotransmitter Leu-Enkephalin (**VI**) as our first target to evaluate the effect of

the oxetane modification on the properties of the parent peptide. In total, four analogues of **VI** were prepared. Indeed, the half-life time in human serum of the analogues was significantly increased to up to 18 h (for **VII**) compared to 10 min for the natural compound (Scheme I). Furthermore, two of the oxetanyl peptides still showed nanomolar affinity to the δ-opioid receptor. The most promising analog from the *in vitro* studies also showed analgesic activity in mice.

As a second target, we chose an inhibitor of the aggregation of α-synuclein. Fibrillation of α-synuclein is suspected to be the major cause of PARKINSON's disease. Also in this case, four oxetanyl analogues were prepared. Studies on their *in vitro* activity are ongoing.

The second part of the project aimed at the synthesis of side-chain modified oxetanyl amino acids. This time, the oxetane surrogate was used to modify the intrinsic properties of natural and unnatural amino acid side chains. On one hand, oxetanes were incorporated as gem-dimethyl replacements in hydrophobic amino acids to reduce their lipophilicity. On the other hand, the side-chain carbonyl groups in Asn, Gln, Asp and Glu were replaced by oxetanes to alter their electrostatic properties. Finally, an azetidine derivative of lysine was designed. In total, nine oxetanyl and azetidinyl amino acids were prepared employing well-established methodologies, i.e. asymmetric hydrogenation and ELLMAN auxiliary chemistry.



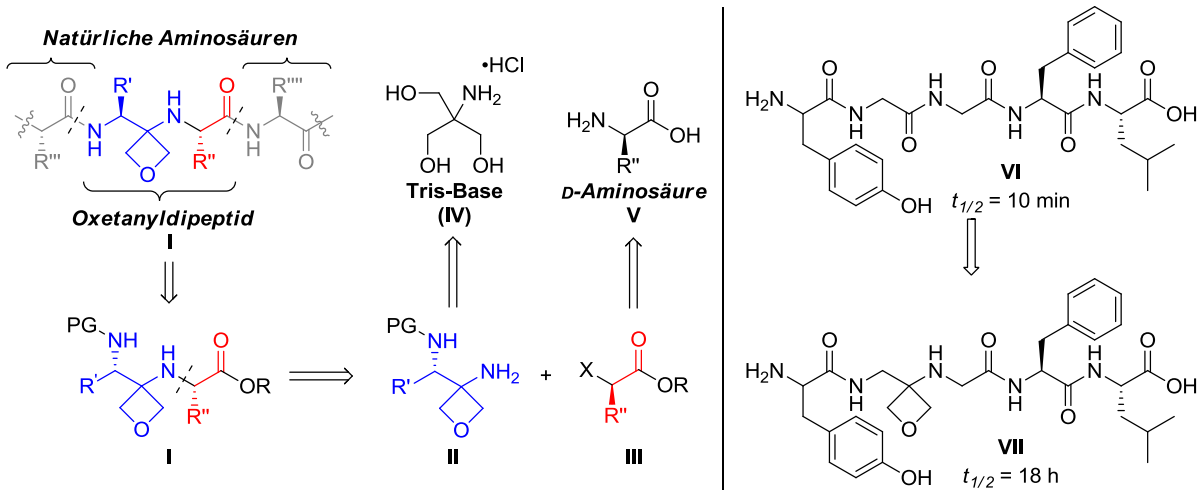
Scheme II Concept and Incorporation of VIII into IX.

Additionally, one of the novel oxetanyl amino acid building blocks (**VIII**) was incorporated into the anti-anaphylactic peptide FEG. Further studies to evaluate the activity of **IX** will be subject of future research (Scheme II).

Zusammenfassung

Diese Arbeit erweitert das Konzept, Oxetane als Ersatz für geminale Dimethyl- und Carbonylgruppen in der Wirkstoffentwicklung einzusetzen, auf Peptide. Natürlich vorkommende, pharmazeutisch aktive Peptide sind unersetzbare Leitstrukturen für das Design neuer Pharmazeutika. Jedoch sind Peptide aufgrund ihrer geringen metabolischen Stabilität und Bioverfügbarkeit nur bedingt als Wirkstoffe geeignet. Daher beschlossen wir, Oxetanbausteine zu entwickeln, die die Stabilität der ursprünglichen Verbindung erhöhen und zugleich ihre biologische Aktivität beibehalten oder verbessern.

Im ersten Teil des Projekts stellten wir eine Vielfalt Rückgrat-modifizierter Dipeptidbausteine **I** her, in denen die peptidische Amidbindung durch ein 3-Aminooxetan ersetzt ist. Die ausgewählte Synthesestrategie über die Alkylierung von **II** mit **III** erlaubte die modulare Synthese von **I** mit einer Vielzahl verschiedener Seitenketten. Die Bausteine **II** und **III** wiederum wurden auf die günstigen, kommerziell verfügbaren Startmaterialien Tris-Base (**IV**) und D-Aminosäuren **V** zurückgeführt (Schema I).



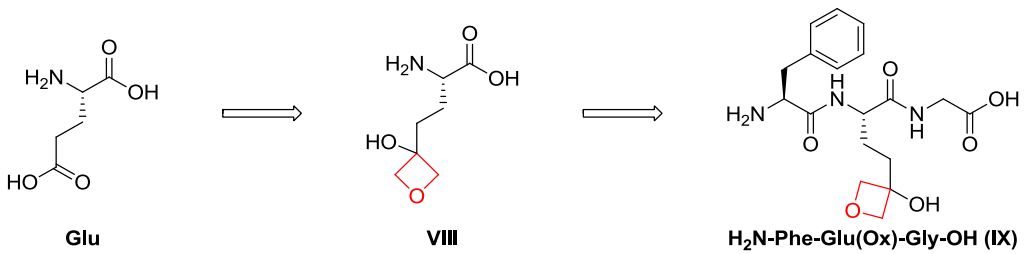
Schema I Synthese und Anwendung von Oxetanyldipeptiden I.

Der auf robusten synthetischen Methoden basierende Zugang zu **I** stellt die Verfügbarkeit ausreichender Mengen für die Herstellung grösserer Peptide

sicher. Als erste Anwendung, zur Bestimmung des Effekts vom Einbau von Oxetanen auf die Eigenschaften des ursprünglichen Peptids, wählten wir den bekannten endogenen Neurotransmitter Leu-Enkephalin (**VI**). Insgesamt wurden vier Analoga von **VI** hergestellt. Die Halbwertszeit in humanem Serum erhöht sich durch die Verwendung von Oxetanylpeptiden von 10 min für die natürliche Verbindung (**VI**) auf bis zu 18 h für **VII**. Zudem haben zwei der Analoga eine nanomolare Bindungsaffinität zum δ-Opioidrezeptor. Die vielversprechendste Verbindung aus den *in vitro* Studien zeigte außerdem analgetische Aktivität in Mäusen.

Als zweite Zielverbindung wählten wir einen Inhibitor der Aggregation von α-Synuclein. Die Fibrillation von α-Synuclein wird als einer der Hauptgründe für die PARKINSON'SCHE Krankheit angesehen. Auch hier wurden vier Analoga des natürlichen Peptids hergestellt. Studien zu ihrer *in vitro* Aktivität sind geplant.

Der zweite Teil des Projekts befasste sich mit der Synthese von Seitenketten-modifizierten Oxetanylaminosäuren. Diesmal sollten durch die Verwendung von Oxetanen die intrinsischen Eigenschaften von Seitenketten natürlicher und unnatürlicher Aminosäuren verändert werden. Einerseits wurde Oxetane anstelle von geminalen Dimethylgruppen eingesetzt, um die Lipophilie hydrophober Aminosäuren zu mildern. Andererseits, wurden die Carbonylgruppen in den Seitenketten von Asn, Gln, Asp und Glu durch Oxetane ersetzt, um deren elektrostatische Eigenschaften zu verändern. Schließlich wurde ein Azetidinderivat von Lysin entwickelt.



Schema II Konzept und Einbau von VIII in IX.

Insgesamt wurden neun Oxetanyl- und Azetidinylaminosäuren durch die Verwendung etablierter Methoden, d.h. asymmetrischer Hydrierung und ELLMAN Auxiliarchemie, hergestellt. Weiterhin wurde einer der neuen Oxetanylbausteine **VIII** in das anti-anaphylaktische Peptid FEG eingebaut. Weitere Studien zur Aktivität von **IX** sind noch im Gange.

List of Abbreviations

Ac	Acetyl
ADME	Absorption, distribution, metabolism, excretion
API	Active pharmatheutical ingredient
aq.	Aqueous
Ar	Aryl
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
BOM	Benzyloxymethyl
Bu	Butyl
Cbz	Benzyloxycarbonyl
cod	1,5-Cyclooctadiene
Cy	Cyclohexyl
d.r.	Diastereomeric ratio
Da	Dalton
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-(Dimethylamino)-pyridine
DMBA	1,3-Dimethylbarbituric acid
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EA	Ethyl acetate
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric Excess
EMEA	European Medicines Agency
eq	Stoichiometric Equivalents
ESI	Electrospray ionization
Et	Ethyl
EWG	Electron withdrawing group
FDA	Federal Drug Administration

Fmoc	Fluorenylmethoxycarbonyl
gem	Germinal
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]-pyridinium 3-oxid hexafluorophosphate
HBSS	Hanks' balanced salt solution
hex	Hexanes
HMDS	Hexamethyldisilazane, Bis(trimethylsilyl)amine
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
i.v.	Intravenous
IR	Infrared spectroscopy
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
log *P*	Logarithm of the 1-octanol/water partition coefficient
M	Molecular weight
M	Molar, mol/L
m.p.	Melting point
MALDI	Matrix-assisted laser desorption/ionization
Me	Methyl
Ms	Mesyl, Methanesulfonyl
MW	Microwave
NMM	*N*-Methylmorpholine
NMR	Nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PG	Protecting group
Ph	Phenyl
Pht	Phthaloyl
PMB	*para*-Methoxybenzyl
Pr	Propyl
PS	Polystyrene
PTFE	Polytetrafluoroethylene
R_t	Retention time
sat.	Saturated
SEM	Standard error of the mean

SFC	Supercritical fluid chromatography
Su	Succinimide
TBAI	Tetra-*n*-butylammonium iodide
Teoc	2-Trimethylsilylethyloxycarbonyl
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
ThT	Thioflavin T
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMG	1,1,3,3-Tetramethylguanidine
TMS	Trimethylsilyl
Troc	2,2,2-Trichloroethyloxycarbonyl
Ts	Tosyl, 4-Methylbenzenesulfonyl
UV	Ultraviolet

1

Introduction

1.1 Peptides in Drug Discovery

Drug development has gone through tremendous advancements to provide cure to more and more diseases, ever since.[1] Methodologies in this field of research such as clinical trials and the design of active pharmaceutical ingredients (APIs) from natural leads seem self-evident today.[2] However, considering the early development of small molecule therapeutics, e.g. Aspirin, tools in drug discovery have undergone an immense improvement. The way from using willow bark as a remedy for pain, reported as early as 1534 BC in Egypt to the discovery of acetyl salicylic acid as the optimized drug by Hoffmann in 1897[2,3] was mainly characterized by serendipity, where today modern structure activity relationship studies (SAR studies) and the understanding of activity at the molecular level along with computational and combinatorial chemistry pave the way for drug discovery. However, the aging of society, medical advancement and a number of incurable diseases create an ever-pressing need for the development of new highly potent therapeutics.

1.1.1 Paradigm Shift

Until very recently, drug discovery in industry focused on the development of small molecule APIs.[1] About twenty new therapeutics of this class were approved by the FDA per year between 1980 and 2011.[1,4] The development of small molecule drugs often begins with the screening of millions of different lead compounds against a certain pharmaceutically relevant target.[5,6] These libraries consist both of a collection of natural products[7] as well as a diverse set of chemical intermediates from industry and academia.[8] The most promising lead structure then undergoes an intensive SAR screen which eventually leads to the discovery of a highly potent pharmaceutical.[9,10] The structural refinement today is also regularly assisted by computational methods. In some cases, even the de novo generation of a lead structure can be achieved *in silico*.[11] Small molecule drugs were long perceived as the most promising class of therapeutics. The ease of deduction from natural products, the chemically diverse synthetic

methodologies available and the low cost of production made their development suitable in a competitive industrial setting.[12,13] The well-established procedures for process development additionally allow the large scale production of these compounds. Furthermore, small molecules are most of the time metabolically robust, hence applicable to oral administration, and show high membrane permeability.[1]

Based on their observations on small molecule drugs, Lipinski *et* al.[14] formulated the "rule of five" to define properties of an orally active small molecule drug. Further refinements and additions of and to these have then been made by GHOSE *et* al.[15] and VEBER *et* al.[16] LIPINSKI defined a molecule as drug-like if it had "sufficiently acceptable ADME properties and sufficiently acceptable toxicity properties to survive through the completion of human Phase I trials".[17] A summary of the original rules and the additions is provided in Table 1.

Table 1 The Rule of Five and Extensions thereof.

LIPINSKI	- No more than FIVE *H*-bond donors - No more than 2 x FIVE *H*-bond acceptors - A molecular weight < FIVE hundred Da - A partition coefficient log *P* < FIVE
GHOSE	- Partition coefficient -0.4 < log *P* < 5.6 - Molar refractivity: 40 < *A* < 130 - Molecular weight: 180 < *M* < 500 - Number of atoms: 20 < n_{Atoms} < 70 - Polar surface Area < 140 Å^2
VEBER	- 10 or fewer rotatable bonds - Polar surface area ≤ 140 Å^2

Despite the advances in small molecule drug discovery outlined above, the costs for the development of a new marketed pharmaceutical rise constantly. Today, following stricter regulatory rules focusing more and more on safety rather than potency is a major component of the drug discovery process.[1,13] The costs for the development of a single marketed API hence rose to around 1.3 billion dollar

today of which about 70% arise from failure.[18-20] About 35% of the developed compounds get dismissed in Phase I clinical trials due to toxicology issues, 63% of the remaining don't survive Phase II because of little potency and in Phase III another 45% are abandoned. Finally, 23% of the remaining structures don't pass the regulatory process at the FDA or EMEA.[13,21] In view of the decreasing number of marketed small molecule drugs the need for the development of new tools in drug discovery and new classes of therapeutics becomes obvious.

Indeed, the field of drug discovery has recently been expanded to much larger molecular scaffolds, so called biologics. Among them are mainly antibodies or recombinant proteins that exceed a molecular weight of 5000 Da. At first sight antibodies seem to be ideal drug candidates as they can specifically bind to the corresponding antigen, i.e. another protein, carbohydrate, lipid, etc. However, early attempts to use antibodies isolated from mice as therapeutics were not very successful. Indeed, antibodies from other species can themselves be an antigen in the human organism and hence trigger an immune response.[22] Only, when it was possible to modify antibodies to make them similar or identical to human antibodies this class of compounds could be used as drugs.[23-25] Today, antibodies themselves or conjugated to cytokines and small molecule drugs are used in for the treatment of a number of diseases. This class of compounds is considered a valuable addition in the tool box of the pharmaceutical industry.[1] Biologics often have much higher target specificity than small molecules and hence reduced side effects. Additionally, they can target protein-protein interfaces (PPIs) that because of their large surface area cannot be easily addressed by small molecules.[26] Another advantage of biologics is their metabolites which mostly are natural amino acids and other endogenous substances with low or no toxicity. However, as mentioned above, biologics tend to have a larger immunogenicity than small molecule drugs. Additionally, due to the high molecular mass, the potency per mass unit is rather low. Combined with the high production costs of biologics this poses another major drawback of this class of compounds.[27] Furthermore, violating all "rule of five" parameters, biologics have a negligible

oral availability which makes injection the only possible administration method. Orally available drugs are largely preferred by the pharmaceutical industry to improve the patient acceptance of a product.[13] Nevertheless, the potency of some biologics have easily outperformed this obstacle and become blockbuster drugs. Despite the uncountable number of degradation mechanism for proteins operative in any organism, some antibodies can survive up to weeks after single administration.[1] Apart from recombinantly prepared human insulin, e.g. the monoclonal antibodies ADALIMUMAB against rheumatoid arthritis and TRASTUZUMAB against breast cancer are between the top selling injectable biologics.[28]

Up to this point, drug discovery only took place at molecular weights under 500 Da or above 5000 Da. The gap between these two limits was considered as not desirable for the use as pharmaceuticals.[1] Compounds in this range would violate the "rule of five", hence not be orally available. Furthermore, they were predicted not to be drug-like in the traditional sense and also not outbalance this drawback by their intrinsic selectivity (Figure 1).

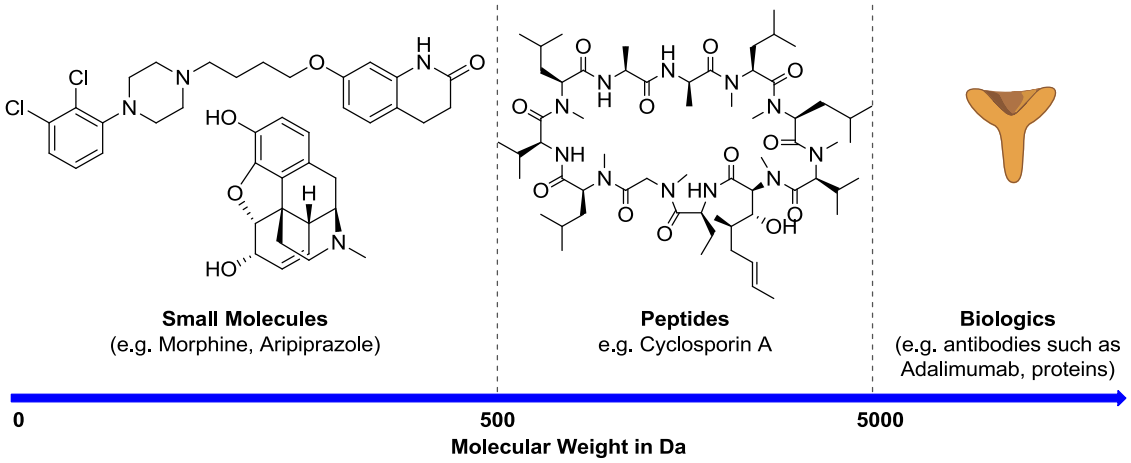


Figure 1 Classes of Potential APIs by Molecular Weight.

Since all medium sized peptides between five and 50 amino acids fall into this class of compounds, they were for a long time neglected in the drug discovery process. Additionally, the pharmacokinetic profile of peptides is rather undesirable. Most small peptides have poor oral availability, poor membrane

permeability, low metabolic stability in plasma and the digestive system as well as high hepatic and renal clearance.[29-32] Furthermore, the cost of production of peptides is higher than for the synthesis of small molecules although still not as high as for the expression of biologics.[27] Robust methods exist for the chemical synthesis of peptides.[33] However, they mostly rely on the reaction between protected amino acids mediated by coupling reagents. The protection and deprotection of amino acids as well as the coupling reagents[34] are major cost factors in the production of these compounds. Despite all these drawbacks for the use of peptides as drugs, peptide therapeutics have advanced to a new class of highly potent APIs.

1.1.2 Definition of Peptides and Peptidomimetics

The term "peptide" or more specifically "small peptide" usually refers to compounds assembled from 50 amino acid monomers or less.[1] In general, peptides are hetero-polymers of head-to-tail connected amino acids.[35] The monomers are enantiopure and have (*S*)-absolute configuration in all proteinogenic amino acids except for cysteine (*R*) and glycine (no chiral center). The amino acids are connected by amide bonds. Both the amide backbone and the side-chains can be engaged in ligand-target interactions *via H*-bonds, van-der-Waals forces, salt bridges, dipolar interactions. Furthermore, peptides can adopt a secondary structure which is defined as the folding of the amide backbone triggered by *H*-bonding interactions of the peptide backbone or hydrophobic/hydrophilic separation of the side-chains in polar media.

The term "peptidomimetic" can be broadly defined as ligand that has the same structure-activity relationship as a peptide for the same target.[36] In this work, peptidomimetics are more closely defined as compounds that have been designed by the replacement of defined elements of the original peptide structure with synthetic building blocks, thereby conserving all other features of the parent structure.[35] For example, single amide bonds could be replaced while conserving the rest of the backbone and the side chains or the complete backbone

could be exchanged for a different organic scaffold displaying the amino acid side chains.

1.1.3 Challenges and Opportunities

The era of peptide drugs has seen a major boost in 2012 when six therapeutics of this class were approved and marketed in a single year.[37] But how could peptides with all their unfavorable pharmacokinetic properties become one of the most important research areas in drug discovery? Therapeutic peptides are similar to small molecule drugs often derived from natural products. Nature has designed a vast number of different proteins each optimized to its specific function by evolution. Natural peptides and proteins are highly potent and selective pharmaceutically active substances. This makes these natural products ideal lead structures for drug discovery. Animal poisons which are designed to be fast acting[38] and stable as well as neurotransmitters like Leu-Enkephalin[39] which are designed to be rapidly degraded after exhibiting their effect can serve as natural starting points for the development of peptide drugs. A potential peptide pharmaceutically active agent would then be the smallest still active sequence of a potent natural protein. This approach uses the evolutionary optimization of nature to affect a certain target to short cut the tedious lead screening process. Still as for small molecule research also in the case of peptides, chemical and furthermore genetic and recombinant libraries can be used for high-throughput screening.[40]

The infinite sources for peptide lead structures however still cannot compensate insufficient ADME parameters.[41] Hence, only modern synthetic chemistry was able to make a drug out of a peptide. Until today, numerous modifications of peptides to improve their pharmacokinetic profile have been developed and reported.

The most straightforward approach is the design of primary structure mimics that use mimics to replace the peptide bond and hence protect it from proteolytic

degradation. Between these peptide bond isosteres are e.g. traditional depsipeptides, thiodepsipeptids, aza-peptides, alkenes, fluoroalkenes and reduced amide bonds[42-44] as well as more modern variants such as triazoles[45] or as outlined in this work amino-oxetanes.[46,47] These modifications allow producing peptide mimics that are more stable towards enzymatic degradation processes. Different primary structure mimics include side-chain modified amino acids. This class of building blocks allows fine tuning the interactions of a given peptide with the target and also increasing the bioavailability and possibly even membrane permeability.

A class of more abstract peptidomimetics includes surface[48] and secondary structure mimics.[49,50] In these cases, a robust and easily synthesized organic backbone is designed which allows the display of a diverse set of amino acid side-chains at various exit vectors. This second concept sees the original peptide backbone as not more than a string of atoms that carries the side chains that in turn build the relevantly functionalized surface for PPIs.

A third class of drug-like peptides leaves the constitution of the lead peptide intact. The modifications in these cases are introduced by a different stereo-chemistry or cyclization of the linear peptide to disturb the recognition of the amide bond motif by proteases.[51]

This work will focus only on primary structure mimics which rely on the assembly by peptide coupling chemistry. However, all classes of peptidomimetics open the door for the creation of new intellectual property. Furthermore, only the availability of a diverse set of opportunities for modification allows a comprehensive screening of SAR and relevant conformations. Backbone primary structure mimics as well as surface and secondary structure mimics and side-chain modified amino acids are hence valuable building blocks for the pharmaceutical industry. Especially in the cases of backbone primary structure mimics and side-chain modified amino acids that are compatible with solid phase peptide synthesis (SPPS)[52-54], rapid formation of

a diverse library of peptides for SAR studies is possible. Furthermore, the technique of SPPS has advanced and can be used for the fully automated production for medium scale (> 5 kg) of peptide samples.[27,55] Compared to recombinant methods for the formation of biologics, SPPS is more productive. Due to the easy separation from side products because of the use of solid resins products of extremely high purity can be obtained that easily withstand ever-increasing regulatory environments and are a valuable contribution to safe drugs.

Because of the building block nature, peptides can easily be modified in single positions. This might even open the door for the long lived dream of personalized medicine. Together with recently developed genetic tools that allow predicting interpatient variations of potency, therapeutic peptides could be a milestone in the development of personalized drugs.[56,57]

An often neglected advantage of peptides over small molecule drugs is their metabolism. Despite peptides are rapidly degraded their metabolites are amino acids and hence exhibit low or no toxicity. Additionally, the well-defined degradation pathway prevents the accumulation of the peptide drug in tissue and organs and even makes the design of peptide pro-drugs possible.[29]

Compared to biologics, peptide drugs are less immunogenic than their higher mass homologues. Additionally, the activity per mass unit is higher compared to biologics at a lower production cost. This is also attributed to a higher tissue penetration depth of peptides compared to larger entities.[58] Finally, small peptides have often longer storage life-times than antibodies and proteins.[29]

Up to this point, chemical modifications for the improvement of the pharmacokinetic profile of peptides as drugs have been described. In addition to chemistry which tries to take counter-measures against a certain degradation pathway different, approaches which circumvent the site of metabolic attack have been designed. Traditionally, the digestive degradation pathway is avoided

by subcutaneous, intramuscular or intravenous injection.[59,60] This administration method will always be superior in emergency medicine, where rapid action of the drug of choice is required. However, these procedures may cause discomfort to the patient and thereby reduce the product acceptance on the market. However, newly applied administration methods for peptide drugs *via* the mucosal route (e.g. nasal sprays), the oral route with drug release systems and penetration enhancers[61,62] or transdermally with patches have revolutionized the use of peptides as drugs.

In summary the interdisciplinary combination of novel chemical modifications, peptide synthesis process development and the design of administration techniques has opened the door for therapeutic peptides. Especially in view of strict regulatory rules and a competitive pharmaceutical market,[20] this new class of pharmaceuticals has become an invaluable addition to the toolbox of drug discovery. Today, peptide drugs for a number of indications have been developed and marketed including allergy, cardiovascular diseases, diabetes, immunity diseases, oncology and infective diseases.

1.1.4 Marketed Peptides

Peptides and Biologics are currently holding a 10% share of the pharmaceutical market worth > 40 billion US-$ per year which is expected to continue growing in the future. A large diversity of peptide drugs has been marketed already. This chapter is not meant to give a comprehensive overview over peptide therapeutics but rather features three recently marketed examples.

The selective proteasome inhibitor CARFILZOMIB (**1**) with anti-cancer activity was approved 2012 under the trade name KYPROLIS by the FDA. It is indicated for the treatment of patients with multiple myeloma who have failed to respond to other therapies already.[63] CARFILZOMIB (**1**) is derived from the naturally occurring peptide EPOXOMICIN (**2**) which displays strong anti-inflammatory activity (Figure 2).[64]

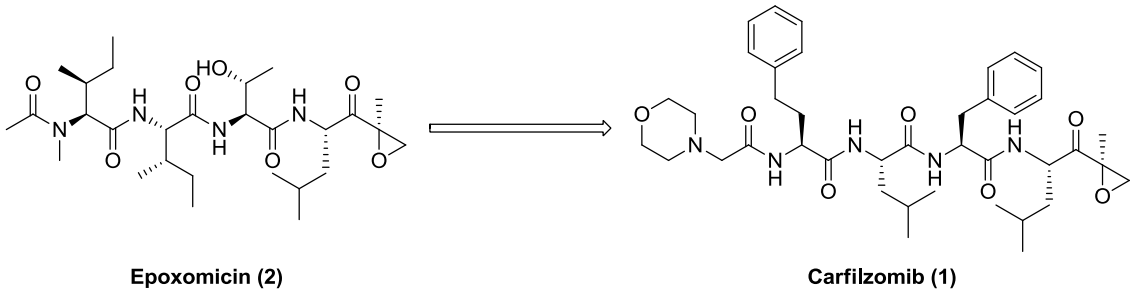


Figure 2 Epoxomicin (2) and Carfilzomib (1).

CARFILZOMIB (**1**) is an excellent example, how a pharmaceutically active natural peptide can be evolved to a potent drug. Extensive studies on the mechanism of action of EPOXOMICIN (**2**) revealed, that the terminal epoxy ketone moiety is essential for its function. Double nucleophilic attack of the *N*-terminal threonine of the proteasome residue first on the ketone part and then on the epoxide forms a morpholine ring and shuts down its active site. Proteasome over protease activity is believed to stem from the position of the active site in the protein respectively. *N*-terminal active sites are typically not observed in common proteases. Conserving the epoxy ketone feature and carefully optimizing the remaining amino acid residues finally furnished the anti-cancer drug **1**.[65]

As a second example BOCEPREVIR (**3**), a protease inhibitor for the treatment of hepatitis C virus genotype I caused hepatitis was chosen because of its unique structural elements (Figure 3). Compound **3** does not contain a single natural amino acid and was specifically designed as a drug. It was approved by the FDA in 2011 and marketed under the trade name VICTRELIS.[66]

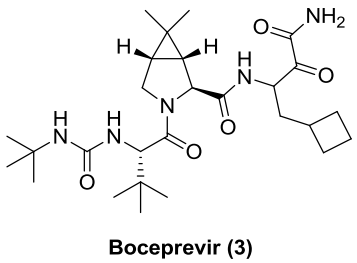


Figure 3 Boceprevir (3).

The conceptual idea was to identify an artificial peptide which would mimic the endogenous substrates of the targeted proteases to block their binding sites. Through screening an undecapeptide was originally identified which could then be truncated by further SAR studies and optimization of single amino acid residues by the analysis of X-Ray crystal structures. The most important structural element of **3** is the α-ketoamide which acts as a serine trap to deactivate the protease active site. The rather unusual bicyclic proline derivative was introduced as a consequence of identified conformational requirements from X-Ray crystal structures.[66]

Another related protease inhibitor for hepatitis C treatment is TELAPREVIR (**4**) (Figure 4).[67]

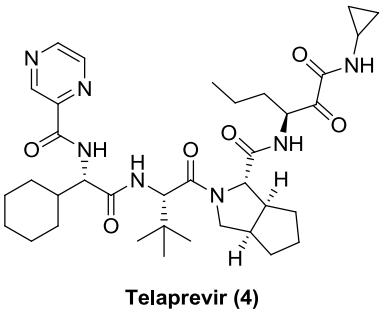


Figure 4 Telaprevir (4).

Similar to BOCEPREVIR (**3**) it contains only unnatural amino acids and the important α-ketoamide functionality as a serine trap. Furthermore, it also features a bicyclic proline derivative separated from the ketone by a hydrophobic amino acid and finally the *tert*-leucine (Tle) residue. In contrast to **3**, TELAPREVIR (**4**) contains an additional *N*-terminal hydrophobic amino acid residue and is *N*-terminally capped by a pyrazine amide. TELAPREVIR (**4**) has been found to be especially effective for the treatment of a previously treated chronic hepatitis C infection.[68,69] In combination with BOCEPREVIR (**3**) it provided a powerful toolbox for the treatment of this disease.[70,71]

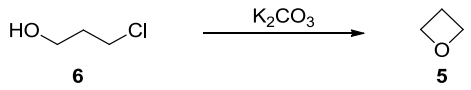
1.2 Oxetanes

Oxetane containing compounds have become an important addition to the synthetic tool box of medicinal chemistry. The unique properties of this four-membered heterocycle along with its surprising chemical and metabolic stability make it a promising moiety in SAR screening.

1.2.1 *De Novo* Synthesis

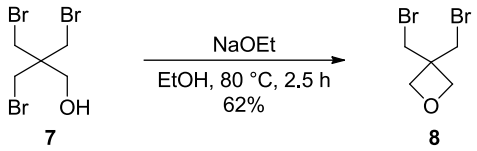
Along with the increasing use of oxetanes in medicinal chemistry, new synthetic methods have been developed for their synthesis. This chapter focusses on the most commonly employed synthetic routes to oxetanes rather than giving a comprehensive review.

The most traditional and obvious way to synthesize oxetanes is probably Williamson's ether synthesis. The first preparation of parent oxetane **5** was achieved by Reboul in 1878 from 3-chloropropanol (**6**).[72]



Scheme 1 First Synthesis of 5 from 6.

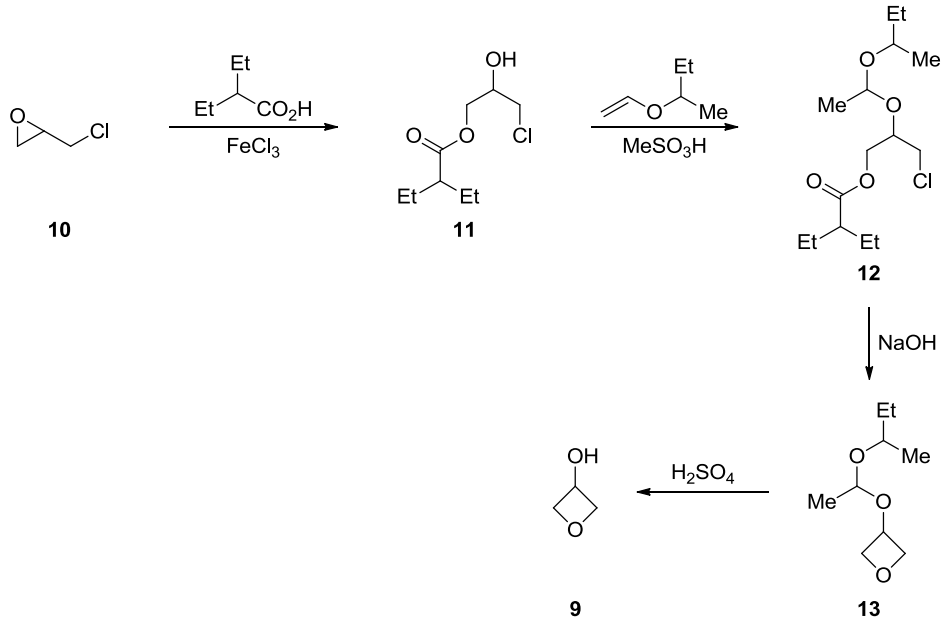
Additionally, treatment of the flame retardant tribromide **7** with base results in the clean formation of **8** (Scheme 2).[73,74]



Scheme 2 Synthesis of Oxetane 8 from Tribromide 7.[74]

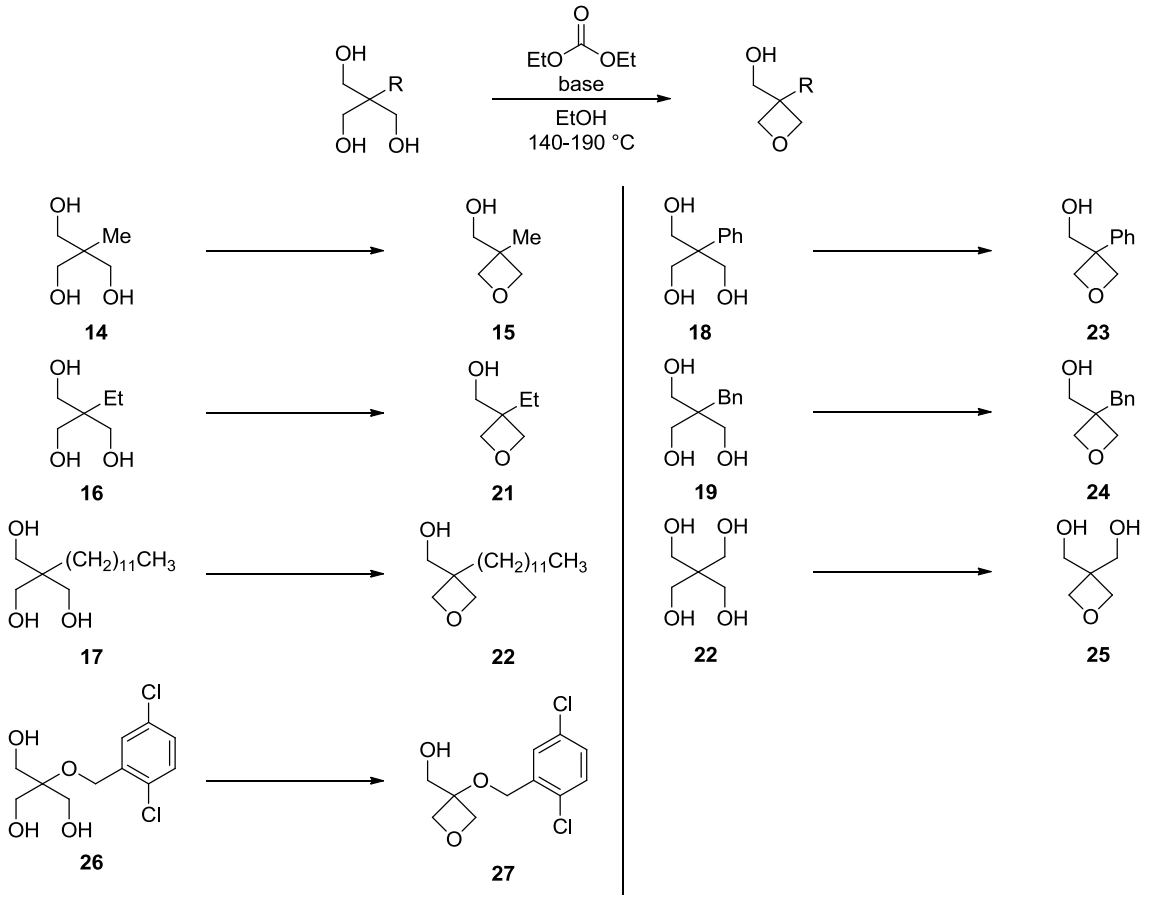
Furthermore, Syngenta developed the large scale synthesis of oxetane-3-ol (**9**) from epichlorohydrin (**10**) using the concept of the work of BAUM *et al*.[75,76] Nucleophilic opening of **10** led to alcohol **11** which was subsequently protected as acetal **12**. Ring closure occurred upon treatment of **12** with base. Finally the

resulting acetal **13** can be cleaved by treatment under acidic conditions to release oxetane-3-ol (**9**) (Scheme 3).



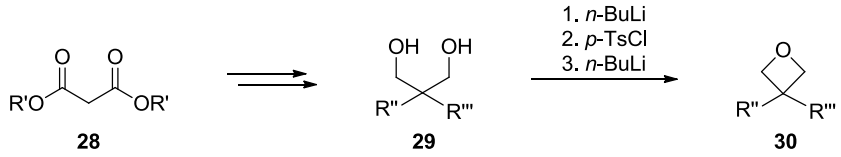
Scheme 3 Large Scale Synthesis of Oxentane-3-ol (9).

Another approach for the synthesis of more complex oxetanes starts from diols or triols. Already 1957 PATTISON reported the transformation of triol **14** to oxetane **15** in the presence of diethyl carbonate and potassium hydroxide in ethanol.[77] This procedure relies on the formation of the cyclic carbonate and subsequent intramolecular substitution. More examples of the conversion of triols **16**-**20** with different alkyl, benzyl or aryl substituents to oxetanes **21**-**25** by using this method were published later.[78-81]Furthermore, few examples with heteroatom substituents namely ethers like the reaction of **26** to **27** are precedent in the patent literature (Scheme 4).[82]



Scheme 4 Synthesis of Oxetanes from Triols with Diethyl Carbonate.

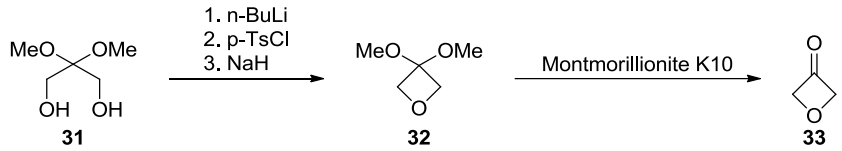
The second approach to oxetanes is the ring closure from diols by activation of one of the hydroxyl groups and subsequent intramolecular nucleophilic substitution. The diols themselves can often be traced back to malonates **28**. The most common procedure for this process is treatment of the diol **29** with one equivalent of *n*-BuLi followed by *p*-toluenesulfonyl chloride and again one equivalent of *n*-BuLi. The formation of numerous oxetanes **30** using this method has been reported by the group of JACOBSEN (Scheme 5).[83] Later, BOYD and DAVIES extended this concept to mono-silyl-protected triols.[84]



Scheme 5 Synthesis of Oxetanes 30 from Malonates 28.

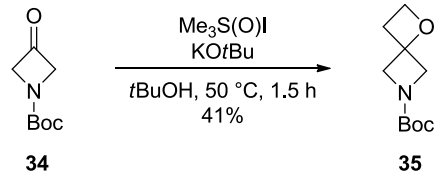
Additionally, the ring closure of diols **29** to oxetanes **30** can be achieved under MITSUNOBU conditions in the presence of a zinc salt.[85] A less prominent way for the activation of diols is the use of Diethoxytriphenylphosphorane.[86]

Finally, one of the most important procedures for the preparation of an oxetane using this approach is the ringclosure of diol **31** to ketal **32** which can in turn be converted to oxetane-3-one (**33**) (Scheme 6). Ketone **33** is one of the most commonly used commercial starting materials for the introduction of oxetanes into more complex molecular scaffolds.[87]



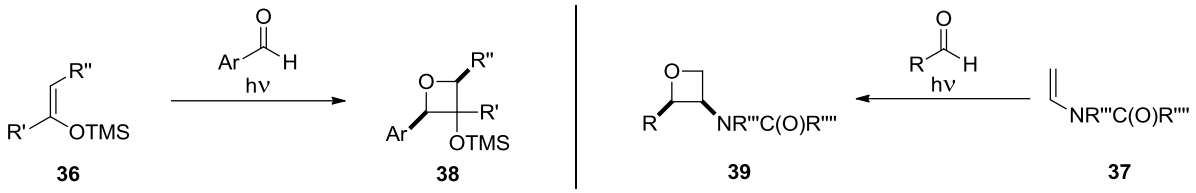
Scheme 6 Synthesis of Oxetane-3-one (33) by WUITSCHIK *et al.*[87]

Further classical methods include the preparation of oxetanes from carbonyl compounds, as represented by sulfur ylide chemistry or the PATERNÒ-BÜCHI reaction. The former method was used in a double Corey-Chaykovsky reaction from our group that features the conversion azetidine-3-one **34** into spirocycle **35** (Scheme 7).[88-90]



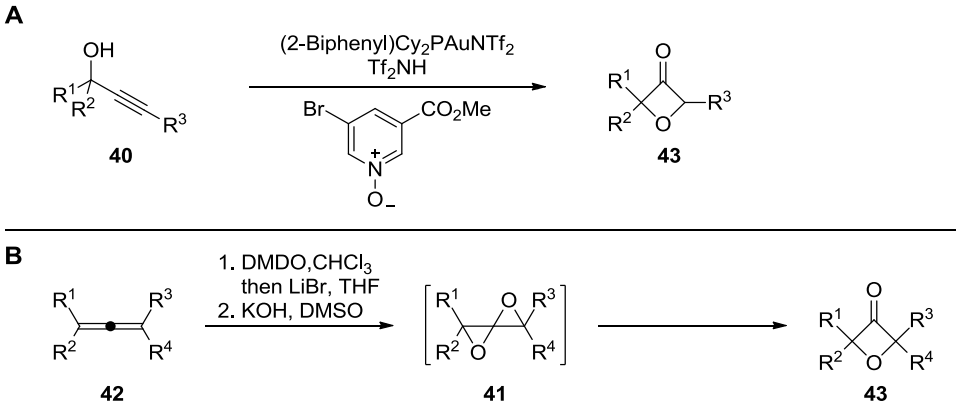
Scheme 7 Synthesis of Spirocycle 35 from 34.

A recent example of the PATERNÒ-BÜCHI approach for the synthesis of oxetanes is the reaction of silyl enol ethers **36** or enamines **37** with aldehydes to the corresponding functionalized oxetanes **38** and **39**.[91]



Scheme 8 Oxetane Synthesis by Bach.[91]

Two more modern methods for the preparation of oxetanes include ZHANG's work on the gold catalyzed cyclization of propargyl alcohols **40** (Scheme 9A)[92] and WILLIAMS' work on spirodiepoxides **41** derived from allenes **42** (Scheme 9B)[93]. Both of these approaches furnish oxetanones **43** which allow for further functionalization.



Scheme 9 Modern Methods for the Synthesis of Oxetanes.

1.2.2 Properties

Oxetanes are four-membered strained heterocycles which have received significant attention in medicinal chemistry for their unique properties which can improve key parameters of an underlying molecular scaffold. Looking at carbocycles, it becomes obvious that four-membered ring systems experience a large amount of ring strain which is comparable to that of cyclopropanes. For example, the ring strain of a 1,1-dimethyl-substituted cyclopropane has been calculated to be 26 kcal/mol compared to the ring strain for a 1,1-dimethyl-substituted cyclobutane of 24.1 kcal/mol.[94] However, oxetanes and cyclobutanes cannot be compared in all of their properties. The puckered conformation of unsubstituted cyclobutane for example is significantly different from the flat

structure of unsubstituted oxetane.[95] Only when substituents are attached to the oxetane core which exhibit eclipsing interactions, puckered compounds are obtained (for examples see crystal structures in this thesis).

Another main feature of oxetanes is the exposed oxygen lone pair which can be engaged in strong *H*-bonding interactions. Actually, between small ring size cyclic ethers, oxetanes show the highest hydrogen-bond strength. This can be generally explained by the fact, that with decreasing ring size, the bond angles within the ring become smaller, increasing the exposure of the oxygen lone pair. However, when the ring size is reduced to epoxides, a significant change of hybridization for the oxygen lone pairs occurs towards more s-character and hence less ability to participate in *H*-bonds.[96-98]

Several other general geometric parameters of oxetanes have been reported in the literature: The molecular volume of oxetane was determined to 61.4 cm^3/mol[99] and is hence comparable to the molecular volume of a *gem*-dimethyl group (75 cm^3/mol).[100] The C^3-O distance in an oxetane was found to be 2.1 Å in an oxetane obtained from averaging a set of published crystal structures.[101] This is 1.75 times longer than the C=O distance of the carbonyl bond (1.2 Å) (Figure 5).

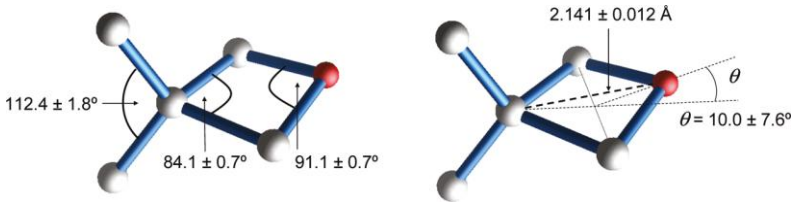


Figure 5 Average Structure of Oxetanes (adapted from Wuitschik *et al.*).[101]

As shown in earlier work from our group, the introduction of an oxetane unit into a pharmaceutically relevant structure can have favorable effects. Studies conducted by WUITSCHIK *et al.* showed that the oxetane can be perceived as an addition of bulk without adding lipophilicity, i.e. a liponeutral *gem*-dimethyl surrogate.[102] Furthermore, the solubility and metabolic stability can be potentially improved by this substitution.[101] Additionally, the oxetane moiety can

be regarded as an electron withdrawing group as demonstrated in a set of model compounds.[87] Finally, the exit vectors of the lone pairs of an oxetane and its *H*-bonding ability are similar to the values for a carbonyl group. Hence, oxetanes have been suggested as less electrophilic bioisosteres of carbonyl groups. However, the increase in lipophilic bulk by the introduction of two extra methylene units and the C-O distance as described above constitute the major structural differences between these two groups. Another striking difference between these moieties comes to light when looking at the conformational bias that is introduced on a linear system by their introduction. In the case of a carbonyl group, the aliphatic chain adopts an in-plane syn-alignment whereas in contrast in the case of an oxetane a gauche-alignment is favored.[101]

In summary, oxetanes have interesting intrinsic properties that make them potentially suitable as mimics of carbonyl or *gem*-dimethyl groups. First applications of this concept will be described in chapter 1.2.4.[101,103]

1.2.3 Building Blocks for Medicinal Chemistry

During the last ten years, a variety of oxetane containing spirocycles has been developed in our group. First, a diverse set of molecules **44**-**50** containing diverse sizes of nitrogen heterocycles was prepared (Figure 6).[102]

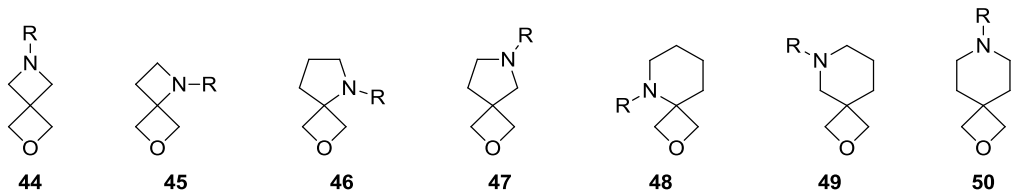


Figure 6 First Generation Oxetane Containing Spirocycles.

The availability of these building blocks allows the simple incorporation of the oxetane unit in more complex molecular scaffolds. The following spirocycle generations included another angular spirocycle **51** and the highly functionalized systems **52** and **53** (Figure 7).[88,104]

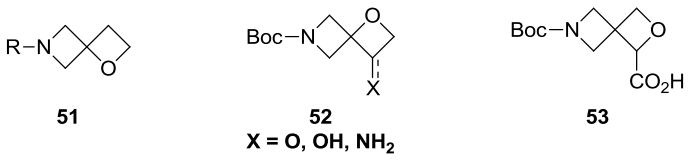
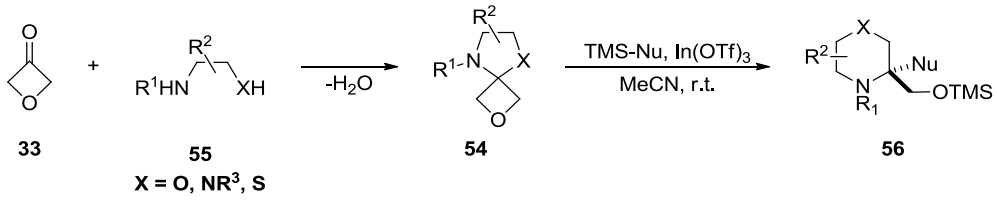


Figure 7 Second Generation Oxetane Containing Spirocycles.

Furthermore, the physicochemical and pharmacokinetic properties of the obtained spirocycles were extensively studied. In this context it was shown that the spiro[3.3]heptane systems may be perceived as metabolically robust isosters of (iso)morpholines.[88,102,104,105]

Additionally, the synthesis of surprisingly stable 4,5-spirocylces **54** from oxetane-3-one (**33**) and β-heteroatom-substituted amino compounds **55** and their application in the formation of highly substituted morpholines **56** were described recently (Scheme 10).[106]

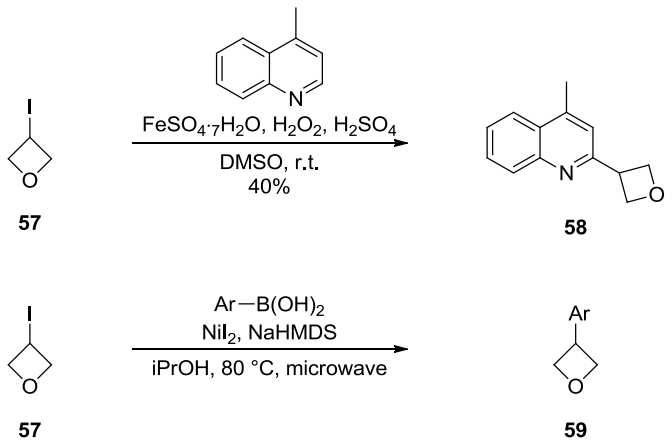


Scheme 10 Synthesis of Six-membered Heterocycles from Oxetane-3-one (33).

Finally, the synthesis of backbone-modified oxetanyl dipeptides was reported.[107,108] For a detailed discussion of these building blocks see chapter 2.

In addition to the work on oxetane-containing spirocycles carried out in our group, several other studies on building blocks containing oxetanes have been published.

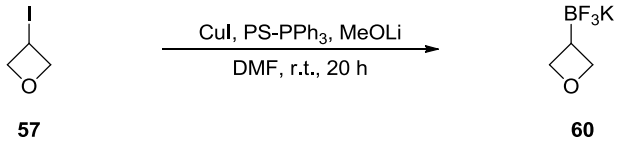
For example, DUNCTON *et al.* demonstrated the use of 3-iodooxetane (**57**) in MINISCI reactions and nickel catalyzed SUZUKI cross-couplings for the synthesis of (hetero)aryloxetanes **58** and **59** (Scheme 11).[109,110]



Scheme 11 Application of 3-Iodooxetane (57) in Cross-Coupling Reactions.

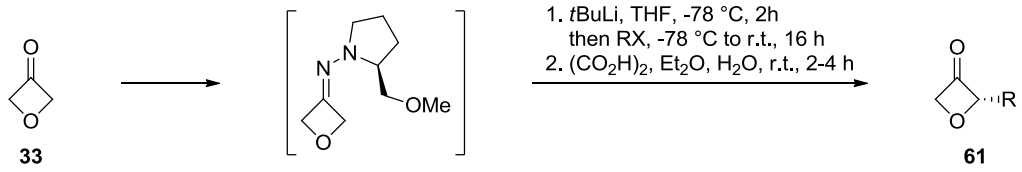
Iodide **57** has also been used in as an alkylating agent for the incorporation of the oxetane moiety in SAR studies.[111,112]

The group of MOLANDER reported the conversion of **57** to the corresponding potassium trifluoroborate **60** (Scheme 12).[113]



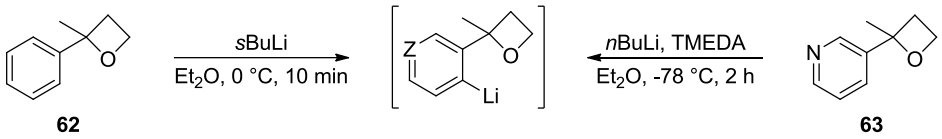
Scheme 12 Synthesis of Building Block 60.

Furthermore, GEDEN *et al.* reported the synthesis of 2-substituted oxetane-3-one building blocks **61** by the alkylation of **33** (Scheme 13).[114]



Scheme 13 Formation of Oxetane-3-ones 61 by Alkylation.

Finally, oxetane building blocks were also used as directing groups in the lithiation of 2-aryl- **62** and 2-pyridyl-oxetanes **63** (Scheme 14).[115,116]



62 63

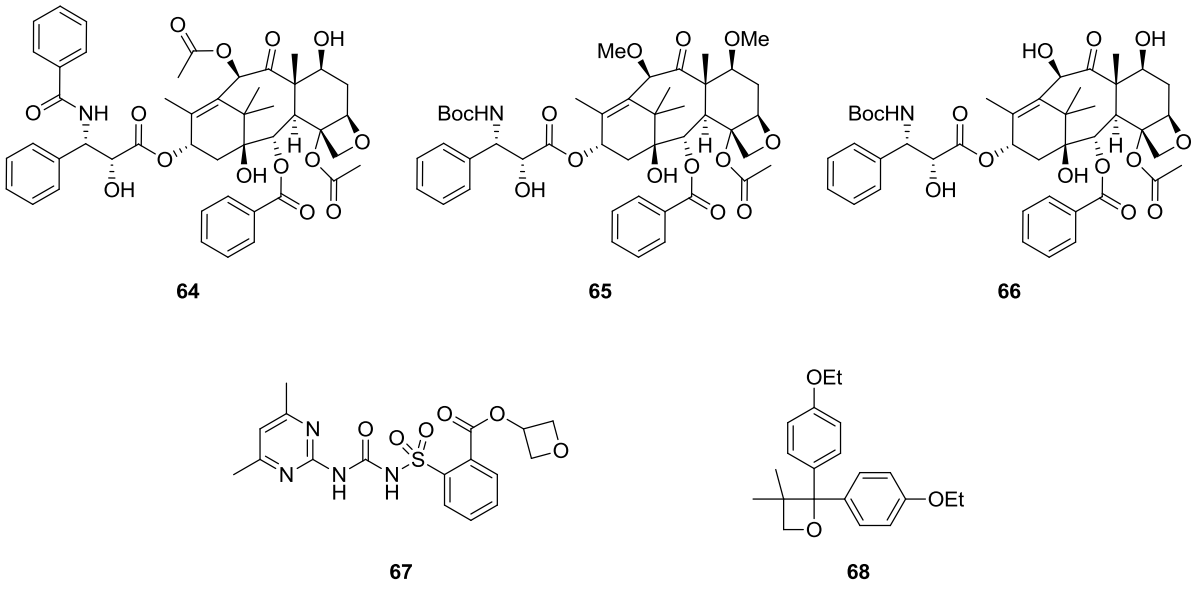
Scheme 14 Lithiation of 62 and 63.

This chapter only covers selected examples from the journal literature. Many more building blocks have been developed in the pharmaceutical industry and are represented in the patent literature.

A large variety of oxetane containing building blocks for medicinal chemistry is nowadays available from several commercial suppliers.

1.2.4 Applications

Up to this point only a few active pharmaceutical ingredients containing the oxetane moiety have been marketed. Certainly, PACLITAXEL (**64**) marketed as TAXOL and ABRAXANE as well as its close analogues CABAZITAXEL (**65**) and DOCETAXEL (**66**) are valuable cytostatic therapeutics.[117,118]



64 65 66

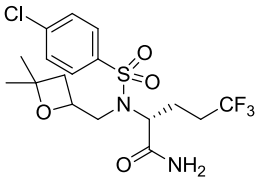
67 68

Figure 8 Oxetane Containing Pharmaceuticals and Agrochemicals.

More oxetane containing active substances can be found for agrochemical applications. Both the herbicide OXASULFURON (**67**) and the insecticide EDO (**68**)

contain the oxetane motif. EDO was developed as a more active and at the same time less persistant replacement for DDT (Figure 8).[119]

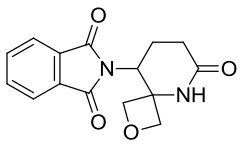
Numerous other reports of oxetane-containing compounds in the context of pharmaceutical development can be found in the literature. For example, arylsulfonamide **69** was developed as a metabolically stable γ-secretase inhibitor.[120] Furthermore, the oxetane moiety was used in several SAR screens, e.g. for the optimization of γ-secretase modulators[111,121] or nonstructural protein 5A inhibitors[122].



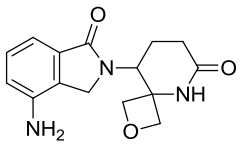
69

Figure 9 γ-Secretase Inhibitor 69.

Finally, our group reported the synthesis and metabolic stability of the oxetane analogues of Thalidomide **70** and Lenalidomide **71**.[123]



70



71

Figure 10 Oxetane Analogues of Thalidomide (70) and Lenalidomide (71).

2

Backbone-Modified Oxetanyl Peptides

2.1 Conceptual Framework[124]

Naturally occurring peptides are specifically designed to fulfill one or several biological functions. They are tailored from the twenty natural amino acids to perfectly match and selectively interact with a binding pocket of their target protein. Since the synthetic construction of these amide-linked heteropolymers is well-established and operationally simple,[33,34] peptides provide a valuable starting point as lead compounds or active agents in medicinal chemistry.[1,125] Small-molecule drug discovery often relies on the high-throughput screening of millions of compounds from synthetic and natural libraries to find a lead structure for further SAR evaluation and optimization. Contrarily, peptide drugs could immediately be derived from the corresponding endogenous peptidic ligand for the desired target.

However, the use of peptides as active pharmaceutical ingredients is limited by several factors: First and most importantly, peptides are labile to a number of enzymatic degradation processes. Predominantly, hydrolysis of the amide bonds by proteases often leads to rapid degradation and hence inactivation of the potential drug. Secondly, poor bioavailability[126,127] and a limited distribution profile, e.g. blood-brain-barrier permeability[128], reduce the utility of peptide pharmaceuticals. This is also manifested in the violation of the "rule of five" as defined by LIPINSKI *et al.*[14] and refined by GHOSE and coworkers.[15]

Hence, the synthetic modification of peptides to peptidomimetics provides a valuable tool to overcome these intrinsic obstacles.[129,130] As outlined in chapter 1.1, numerous approaches to peptide mimics have been described before. However, the variety of backbone modifications that resemble accurate and robust isosteres of the amide bond is still limited. As described in chapter 1.2.4, we have previously suggested that the incorporation of oxetanes into druglike scaffolds could improve their pharmacokinetic properties. We have shown that oxetanes can be perceived as chemically and metabolically robust isosters for

carbonyl groups such as esters, imides and ketones.[87,101,103] These reported applications were limited to small molecules.[102,123]

Herein, we expand the concept of oxetanes as building blocks for drug discovery to their use as carbonyl mimics in peptidic amide bonds. We envisioned the introduction of a 3-aminooxetane moiety to resemble the peptide bond. In contrast to traditional primary structure mimics such as esters, thioester, alkenes, fluoroalkenes,[47] triazoles[45,131,132] and reduced amide bonds,[42] the 3-aminooxetane preserves the unique *H*-bond donor/*H*-bond acceptor properties of the naturally occurring amide which are essential for the assembly of stable secondary structures (Figure 11). Furthermore, the oxetane unit would protect the replaced peptide bond from proteolysis and eventually also protect neighboring cleavage sites by hampering the recognition of the peptide motif by proteases.

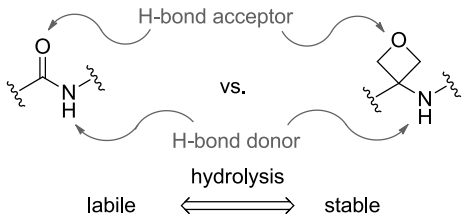


Figure 11 Oxetanes Resemble the Unique *H*-bond donor/*H*-bond Acceptor Dual Function of the Amide Bond.

Additionally, the 3-aminooxetane bioisostere converts the flat sp^2-carbonyl group into an sp^3-center, thereby closely resembling the exit vectors of the oxygen lone pairs and the *N*-*H* bond.

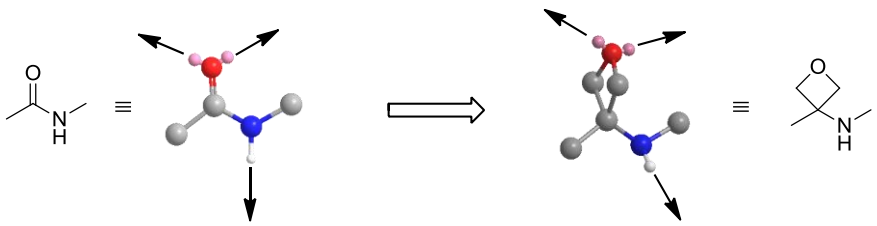


Figure 12 Estimated Exit Vectors for a Natural Amide Bond and a 3-Aminooxetane.

However, the introduction of an oxetane also leads to a strong conformational bias on the chain it is attached to, forcing it from an in plane syn-arrangement in

the carbonyl case into a gauche alignment as described by WUITSCHIK *et al*.[101] The introduction of this modification could hence expand the conformational space and flexibility of the parent peptide to better adopt a given binding pocket by induced fit. It might also be perceived as a tetrahedral intermediate mimic resembling the transitions state in enzyme catalyzed amide hydrolysis in the context of protease inhibitors.[133] As described before (chapter 1.2.2) the major structural differences are the increased C-O distance by the four-membered ring in an oxetane and the thereby introduced lipophilic bulk compared to a carbonyl group.[101]

2.2 Synthetic Strategy

We decided to design our synthetic approach to oxetanyl peptidomimetics to preserve the building block nature of peptides. This would enable us to construct oxetanyl building blocks which could then be used in standard peptide couplings (Figure 13). Hence, we pursued the stereoselective synthesis of oxetanyl dipeptides.

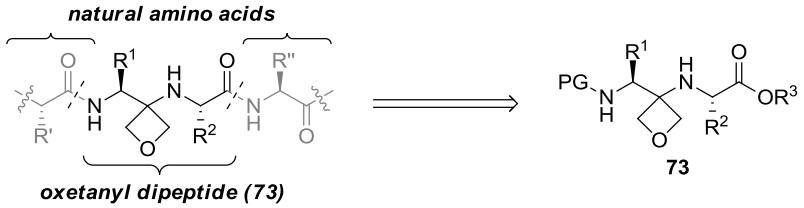
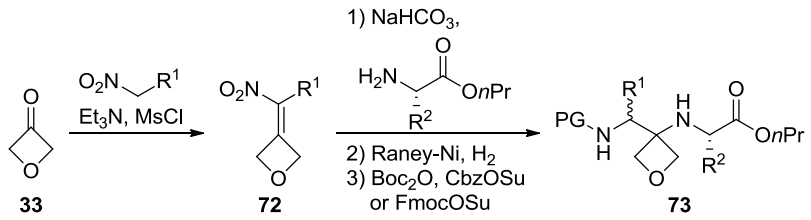


Figure 13 Disconnection of Peptides to Oxetanyl Dipeptides.

The first generation of backbone-modified oxetanyl dipeptides was independently synthesized both in our group[107] and by POWELL *et al.*[108] The strategy used therein relies on the MICHAEL addition of protected amino acids to nitro olefins (**72**) derived from oxetane-3-one (**33**) to yield oxetanyl dipeptides (**73**).

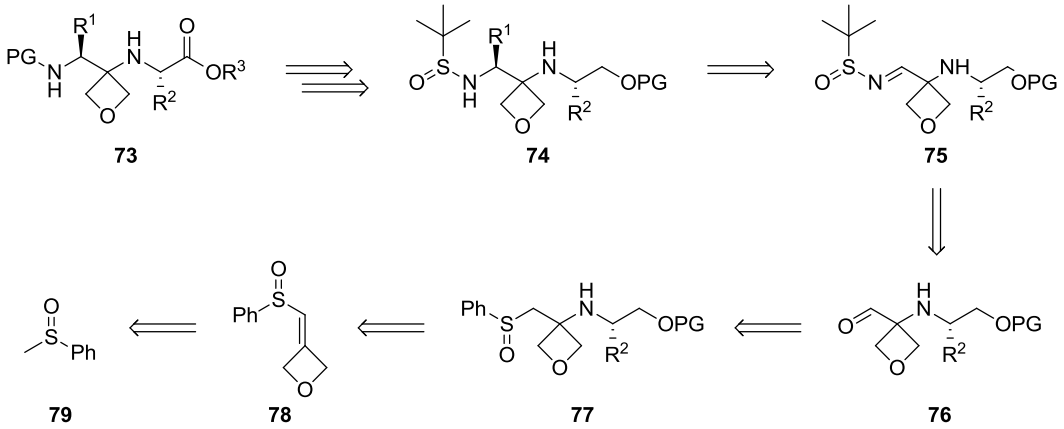


Scheme 15 Synthesis of Oxetanyl Dipeptides by CARREIRA and Coworkers.[107]

The major advantage of this synthetic route is the rapid assembly of various building blocks in less than five steps. However, only one of the two stereocenters in the dipeptide can be set from the natural amino acid. Hence, when functionalized nitro olefins ($R^1 \neq H$) are used, a 1:1 mixture of enantio- or diastereomers is obtained. This is highly undesirable for pharmaceutical applications, as an important feature of peptides for the interaction with biological interfaces is their defined stereochemistry. In summary, the approach displayed in Scheme 15 is highly advantageous for H_2N-Gly-^{Ox}AA-OH dipeptides but limited when two side-chains need to be displayed.

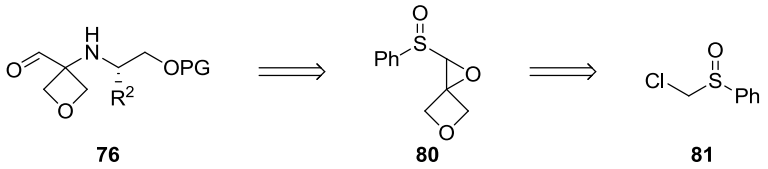
2.2.1 PUMMERER Approach to Oxetanyl Dipeptides

First, we envisioned a conceptionally similar strategy to the oxetanyl dipeptides as for the nitro olefins above. Oxetanyl peptide **73** could be traced back to the addition product **74** of an organometal to ELLMAN imine **75**.[134,135] This in turn could come from aldehyde **76** which would result from a PUMMERER rearrangement of adduct **77**. In analogy to the nitro olefin approach, **77** would come from the conjugate addition of a protected aminoalcohol to the condensation product **78** of oxetane-3-one (**33**) with (methylsulfinyl)benzene (**79**) (Scheme 16).



Scheme 16 Retrosynthetic Analysis with PUMMERER Rearrangement.

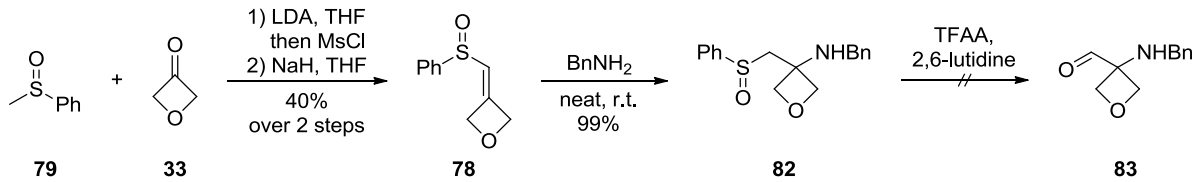
Alternatively, aldehyde **76** could be obtained from sulfinyl oxirane **80** by epoxide opening with a protected amino alcohol and subsequent rearrangement. **80** in turn could be obtained from the addition of α–chloro (methylsulfinyl)benzene (**81**) to oxetane-3-one (**33**) and subsequent ring-closure.



Scheme 17 Retrosynthetic Analysis Starting from α–Chloro (methylsulfinyl)benzene (81).

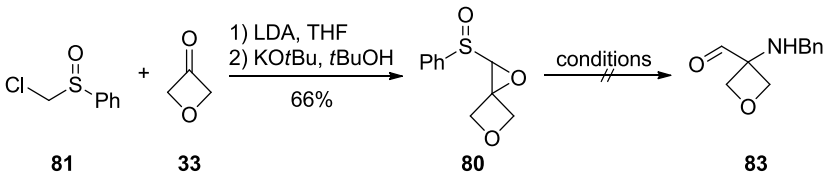
Unfortunately, both strategies outlined in this chapter did not lead to the desired oxetanyl dipeptides:

Starting from oxetane-3-one (**33**) and (methylsulfinyl)benzene (**79**), **78** was obtained in 40% yield over two steps. Subsequent conjugate addition of benzylamine as a model amine led to the desired product **82** in 99% yield. However, PUMMERER rearrangement on crude **82** to **83** did not proceed as planned. Under the reported conditions (TFAA, pyridine or 2,6-lutidine),[136] only decomposition of the starting material was observed (Scheme 18).



Scheme 18 Synthetic Approach to Oxetanyl Dipeptides 73 *via* Pummerer Rearrangement.

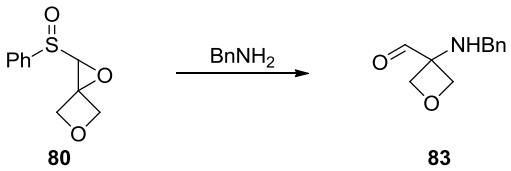
Starting from α–chloro (methylsulfinyl)benzene (**81**) and oxetane-3-one (**33**) the corresponding sulfinyl oxirane **80** was obtained by addition of **81** with LDA and subsequent ring closure with KO*t*Bu in *t*BuOH in 66% yield over two steps.



Scheme 19 Synthetic Approach to Oxetanyl Dipeptides 73 *via* Epoxide Opening.

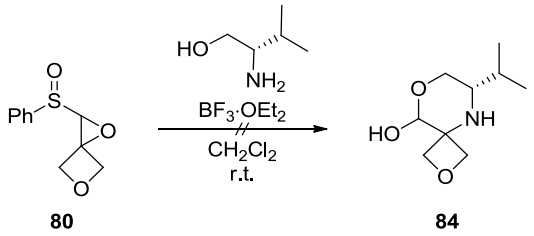
Unfortunately, epoxide opening with benzylamine did not proceed under the reported conditions[137,138] but only led to decomposition of the starting material or no reaction (Table 2).

Table 2 Screening of Conditions for Epoxide Opening.



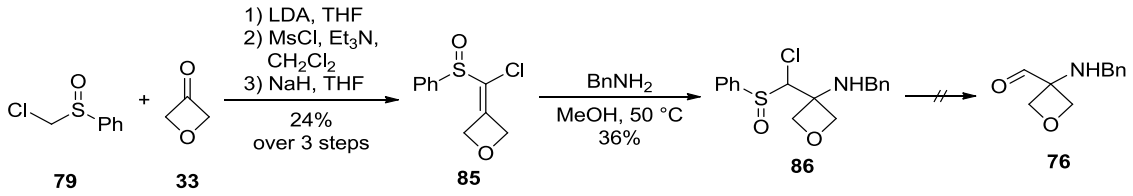
#	Additive	Solvent	Temperature	Result
1	--	--	70 °C	decomposition of **80**
2	*p*TsOH	CH_2Cl_2	r.t.	decomposition of **80**
3	$Cu(OTf)_2$	CH_2Cl_2	r.t.	no reaction
4	$BF_3 \cdot OEt_2$	CH_2Cl_2	r.t.	no reaction

Furthermore, (*S*)-valinol was tried as a nucleophile for the epoxide opening on **80** as possible lactol formation to **84** could help to stabilize the product aldehyde (Scheme 20).



Scheme 20 Attempted Epoxide Opening with (*S*)-Valinol.

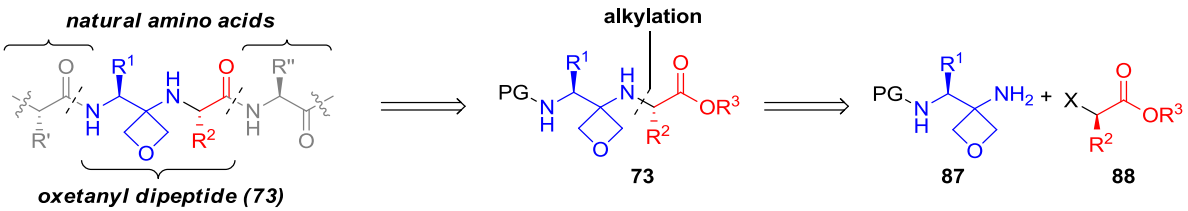
Additionally, vinylogous sulfoxide **85** was synthesized in 37% over two steps by addition of **81** to **33** and subsequent elimination with MsCl and Et_3N. Also in this case conjugate addition of benzylamine proceeded smoothly to give **86** in 36% yield. However, again the rearrangement[139] to the corresponding aldehyde **83** could not be effected under the reported conditions.



Scheme 21 Synthetic Approach to Aldehyde 76.

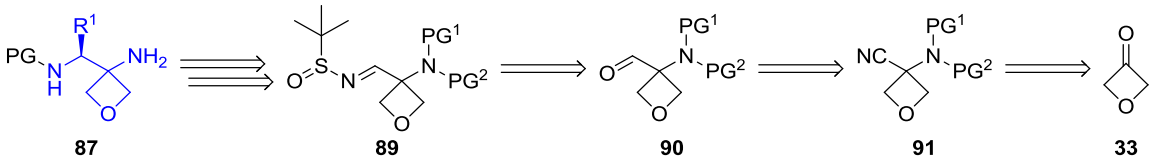
2.2.2 Alkylation Approach to Oxetanyl Dipeptides

After the first approach to **73** was not productive, we decided to base our second strategy even more on the assembly of individual building blocks. Hence, we envisioned to construct the desired oxetanyl dipeptides **73** from two monomeric building blocks by alkylation of a 3-aminooxetane **87** with an amino acid derived electrophile **88**. This would provide a highly versatile approach to **73** where both enantiomers of the diamines **87** and the alkylating agents **88** respectively could be used to construct all four possible diastereomers of **73**. This would allow to expand the concept of oxetanyl peptides to other approaches of peptidomimicry such as retro-inverso peptide.[140]



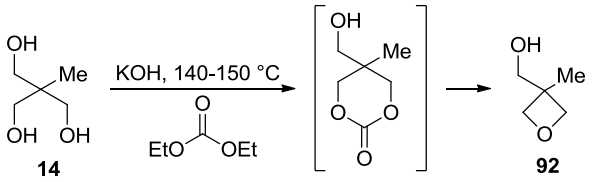
Scheme 22 Retrosynthesis of 73 by Alkylation.

For the diamine building blocks **87** we decided to again resort to organometal additions to ELLMAN imine **89**. The aldehyde precursor **90** in turn could be synthesized by reduction of nitrile **91** which itself would result from a STRECKER reaction of oxetane-3-one (**33**) with a suitably protected amine. This approach traces the desired building blocks **87** back to one common intermediate, **89**. It therefore provides a large synthetic flexibility to easily access oxetanyl dipeptides **73** decorated with a large variety of natural and unnatural amino acid side chains by the addition of the corresponding organometal reagents.



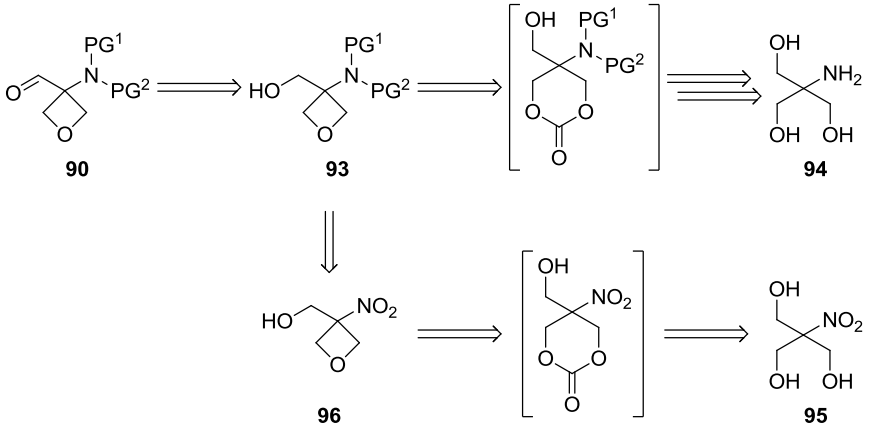
Scheme 23 Retrosynthetic Analysis of 87 *via* STRECKER Reaction.

The retrosynthetic strategy starting from oxetane-3-one (**33**) with a STRECKER reaction (Scheme 23) would give fast access to small amounts of **87** for the proof of concept of our alkylation strategy. However, we realized that for a convenient and operationally simple preparation of satisfying amounts of oxetanyl dipeptides **87** the use of cyanide reagents on large scale could be problematic. Also oxetane-3-one (**33**) is a rather expensive starting material. Hence, we were intrigued by the reported cyclization of triols such as **14** *via* their carbonates to the corresponding oxetanes as first reported by PATTISON in 1957 (Scheme 24).[77] **92** is readily used for the protection of carboxylic acids as their ortho esters as reported by COREY *et al.*[141] and the synthesis of polymers.[142]



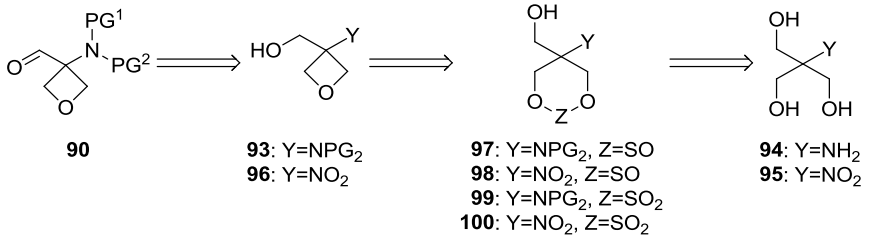
Scheme 24 Synthesis of 92 *via* the Corresponding Carbonate.[77]

Using this strategy would trace aldehyde **90** back to alcohol **93** and hence to triol **94,** also known as Tris-base. **94** and especially its HCl salt are widely used as buffer reagents in biochemistry and are therefore exceptionally cheap. The same holds true for their synthetic nitro precursor **95** which is commercially accessed from nitromethane and formaldehyde. Therefore, **95** could also be a starting point for the synthesis of **93** *via* **96** (Scheme 25).



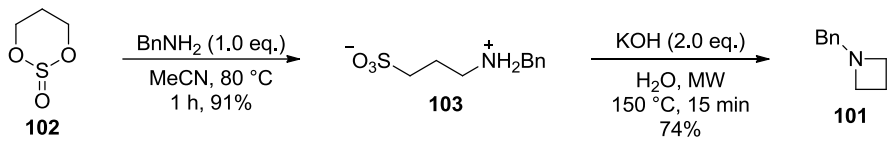
Scheme 25 Retrosynthesis of 93 from Tris-base (94) or 95 *via* the Carbonates.

Additionally, we envisioned not only the use of the carbonates as cyclization precursors but also considered the corresponding sulfites **97** and **98** as well as sulfates **99** and **100** (Scheme 26).



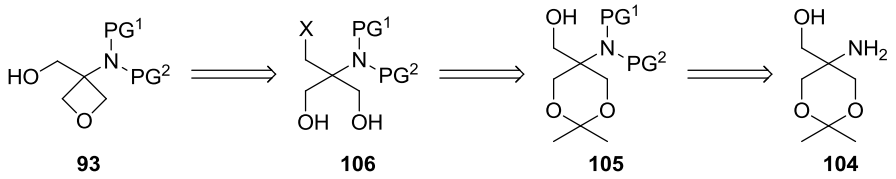
Scheme 26 Retrosynthesis of 93 from Tris-base (94) or 95 *via* the Sulfites and Sulfates.

The nucleophilic attack of cyclic sulfites and sulfates to give the corresponding substituted linear alcohols has been reported before.[143-145] However, the described transformations mostly rely on a large excess of a strong nucleophile. Very recently though, BURKETT *et al.*[146] described the formation of azetidines such as **101** from **102** *via* **103** by heating to 150 °C in a microwave with one equivalent of alkyl amine (Scheme 27).



Scheme 27 Azetidine formation from cyclic sulfite by BURKETT.

Being aware, that not many cases of these cyclizations are precedented in the literature, we also identified acetal **104** which had been synthesized before from Tris-base·HCl as a possible starting point for the synthesis of alcohol **93**. This would require double protection of the amine to give **105**, followed by activation of the alcohol and acetal cleavage to **106** to set the stage for cyclization by intramolecular displacement (Scheme 28).

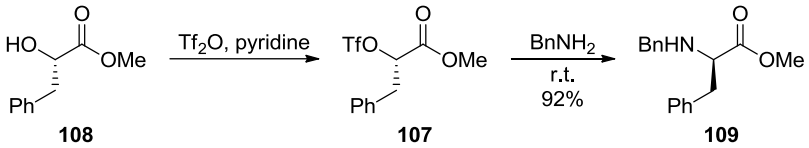


Scheme 28 Retrosynthesis of 93 from Acetal 104.

The latter three synthetic routes for the construction of the diamine building blocks **87** all rely on the use of readily available cheap starting materials that would enable us to access considerable quantities of the desired building blocks **73**. This is essential for the use of **73** in the construction of larger peptides and their pharmacological evaluation.

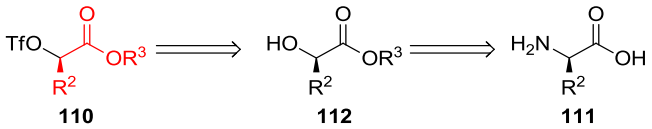
The second set of starting materials for the alkylation to **73** is a variety of alkylating agents **88**. EFFENBERGER *et al.*[147,148] and others[149] showed that the displacement of triflates such as **107** derived from **108** with an amine proceeds

exclusively in an SN2 fashion to yield one enantiomer of **109** with inversion (Scheme 29). Contrarily, tosylates, mesylates, bromo or chloro acids either show a considerably reduced reactivity or lead to racemization of the stereocenter.



Scheme 29 Enantiospecific Synthesis of 109 by EFFENBERGER.

We hence decided, that triflates **110** would be the ideal choice for our synthesis. Those could also easily be accessed from the corresponding D-amino acids **111** *via* the corresponding hydroxy acids **112** (Scheme 30).



Scheme 30 Retrosynthesis of Triflates 110.

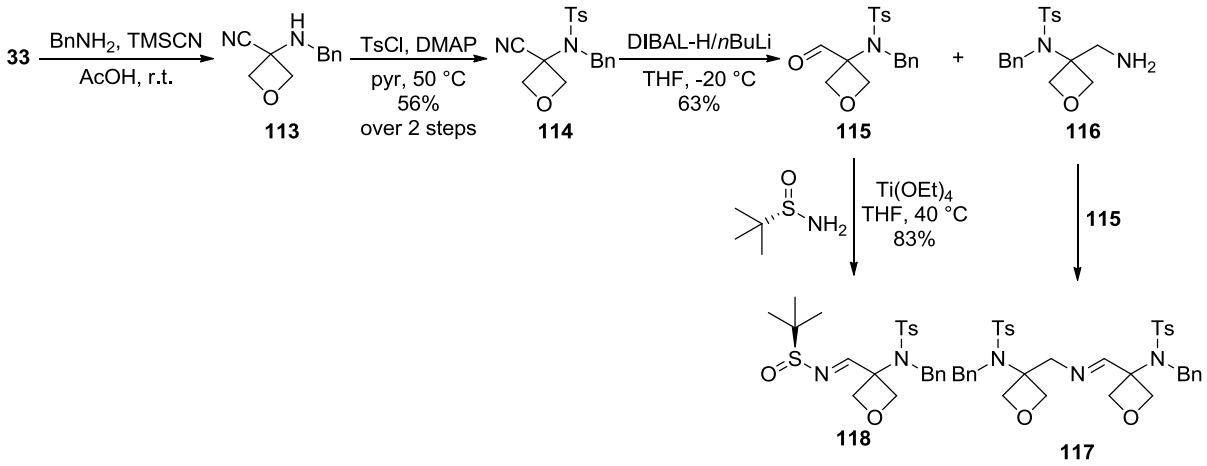
With both sets of building blocks, amines **87** and alkylating agents **88**, i.e. triflates **110**, the stage would be set for the assembly of a large diversity of oxetanyl dipeptides **73**.

2.3 Building Block Synthesis

2.3.1 Synthesis of Diamine Building Blocks 87

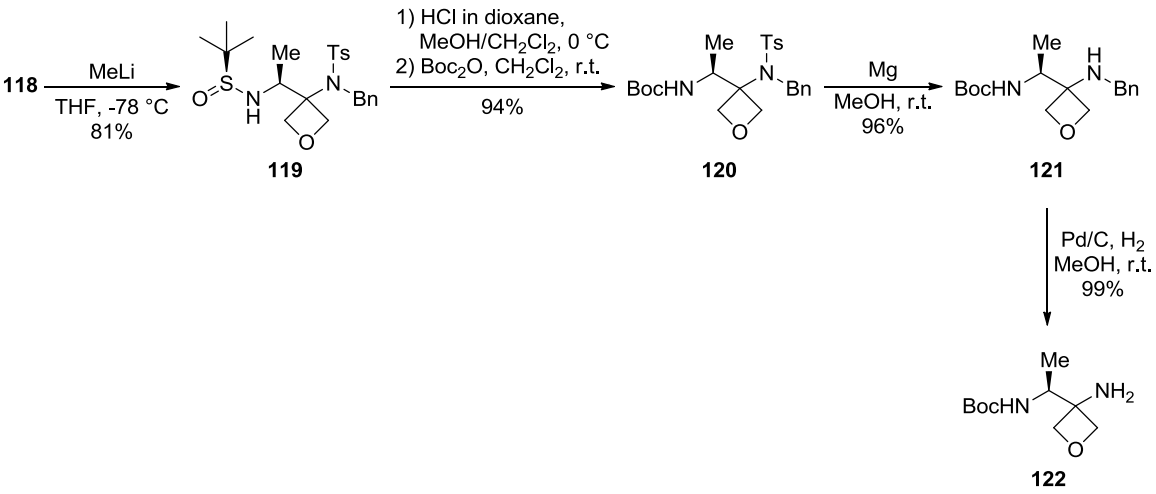
Before starting our attempts to synthesize **87,** we realized that we would have to double protect the amine in the 3-position of the oxetane for the planned organometal addition to the ELLMAN imine **89**. In the first approach to the synthesis of **87** *via* the STRECKER reaction of oxetane-3-one (**33**) we chose to use benzyl and tosyl as protecting groups to obtain a fully protected non basic amine. Hence, **33** was reacted with benzyl amine and TMS-CN in acetic acid. The obtained aminonitrile **113** reported previously[92] was immediately protected with TsCl in the presence of DMAP in pyridine to yield **114** in 56% yield over two

steps. Subsequent reduction of the nitrile **114** to the corresponding aldehyde **115** with DIBAL-H proved to be challenging: In the reaction some overreduced amine **116** was always produced which would immediately react to give imine **117** that in turn only slowly hydrolysed during column chromatography on silica and made the separation difficult. By using a 1:1 complex of *n*BuLi and DIBAL-H for the reduction of **114** the amount of **117** could be significantly reduced to yield **115** in an acceptable yield of 63%. Imine formation by condensation of **115** with the ELLMAN auxiliary in the presence of $Ti(OEt)_4$ cleanly furnished **118** in 74% yield (Scheme 31). In this first approach, the (*S*)-enantiomer of the auxiliary was used.



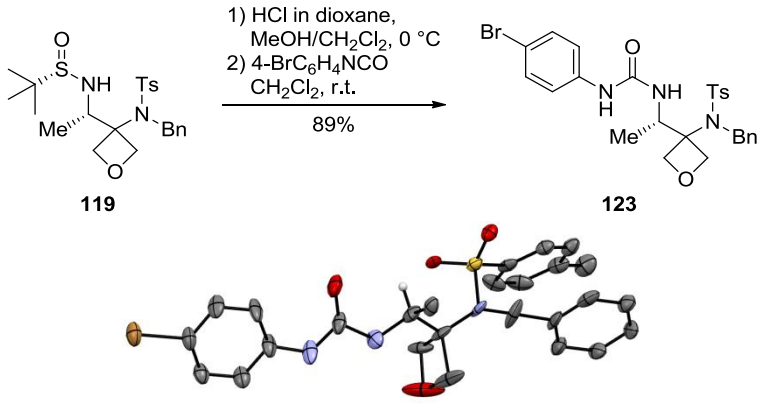
Scheme 31 Synthesis of 118 from 33 *via* Strecker Reaction.

After the planned key intermediate **118** for the synthesis of **87** was obtained, the addition of MeLi was pursued. Treatment of **118** with one equivalent of MeLi smoothly yielded the corresponding adduct **119** in 81% yield as the major diastereomer (d.r.=20:1). Subsequent removal of the auxiliary with anhydrous HCl in MeOH followed by Boc-protection furnished intermediate **120** in 94% yield. The free 3-aminooxetane ready for alkylation was then obtained by Ts-deprotection with magnesium in methanol to **121** (96% yield) followed by hydrogenolysis of the benzyl group to give **122** in 99% yield (Scheme 32).



Scheme 32 Synthesis of Diamine 122 from Imine 118.

The absolute configuration was confirmed as (*S*) by X-Ray crystal structure analysis of *p*-Br-phenyl urea derivative **123**. Again, the auxiliary was removed from adduct **119** and the intermediate amine was this time treated with *p*-Br-phenyl isocyanate to yield **123** in 89% (Scheme 33).

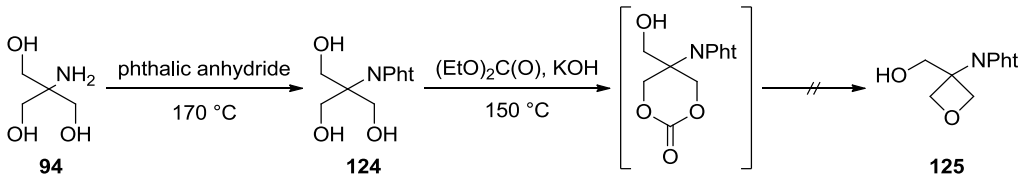


Scheme 33 Synthesis of Urea 123 from Adduct 119, ORTEP-plot of the X-Ray Crystal Structure of 123 (ellipsoids are drawn at 50% probability, hydrogen atoms, except at the *C*-stereocenter are omitted for clarity).

The first route to **118** starting from oxetane-3-one (**33**) provided us with enough material to establish the route to the first diamine **122**. However, this synthetic strategy was limited to small quantities due to the use of cyanide reagents and the laborious purification of **115**.

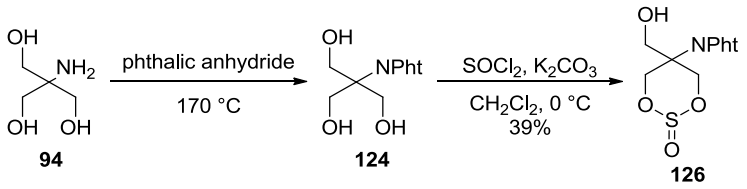
Hence, we next moved to an approach relying on the carbonate and sulfite/sulfate chemistry outlined in chapter 2.2.2 starting from Tris-base (**94**).

Again we decided to fully protect the amine to prevent interference of the nucleophilic amine and aziridine formation. This time, the phthalimide protecting group was used. A mixture of Tris-base (**94**) and phthalic anhydride was heated to 170 °C for 1 h until gas evolution ceased. After cooling to r.t. and extraction of the solids with acetone **124** was obtained as an extremely hygroscopic wax. The crude material was immediately subjected to the literature conditions[77] for carbonate formation and pyrolysis to the corresponding oxetane **125**. However, only decomposition of the starting material was observed (Scheme 34).



Scheme 34 Cyclization of 94 *via* the Carbonate.

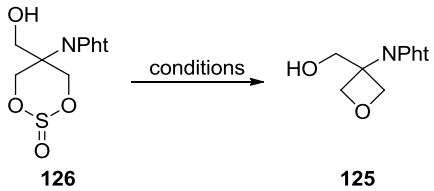
Crude **124** was also treated with thionyl chloride in the presence of K_2CO_3 in CH_2Cl_2 at 0 °C to obtain the cyclic sulfite **126** in 49% yield (Scheme 35).



Scheme 35 Synthesis of Cyclic Sulfite 126.

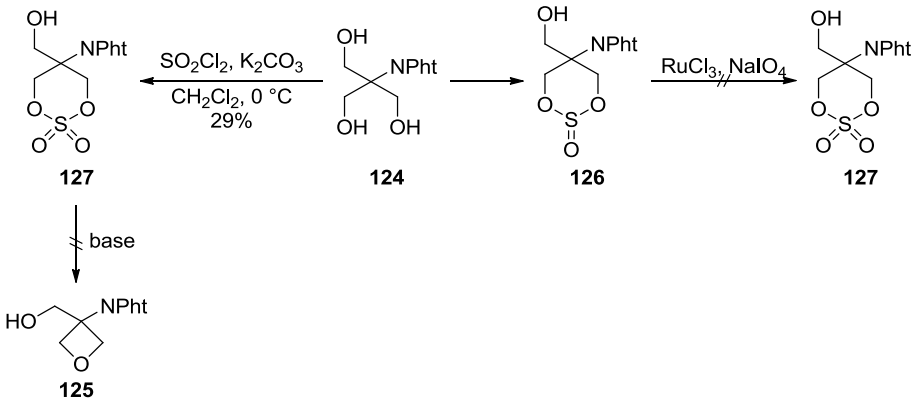
Unfortunately, conversion of **126** to the desired oxetane **125** was not productive under various conditions but led only to decomposition of the starting material or unidentified side products (Table 3).

Table 3 Attempts to the Ring Closure of 126 to 125.



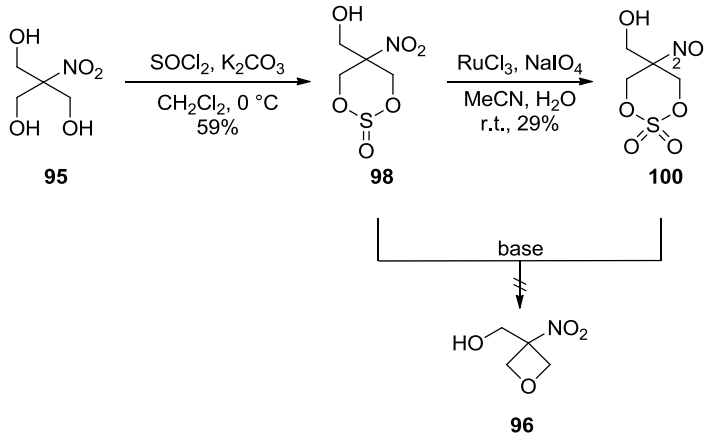
#	Base	Additive	Solvent	Temperature	Result
1	NaH	--	THF	70 °C	no reaction
2	*n*BuLi	--	THF	-78 °C	Unidentified adduct containing *n*Bu
3	K_2CO_3	--	DMF	r.t.	no reaction
4	K_2CO_3	--	DMF	80 °C	decomposition of **126**
5	--	NaI	MeCN	85 °C	no reaction

Since using the cyclic sulfite **126** as the starting material for the synthesis of **125** did not lead to the desired product, the cyclic sulfate **127** was synthezised. However, oxidation of **126** under frequently used conditions[150] with $RuCl_3$ and $NaIO_4$ did not lead to the desired product, but effected decomposition of the starting material. Only when crude **124** was directly treated with sulfuryl chloride, sulfate **127** could be obtained in moderate 29% yield. Unfortunately, treatment of crude **127** with base only led to decomposition of the starting material (Scheme 36).



Scheme 36 Synthesis of Sulfate 127 and Attempted Ringclosure to 125.

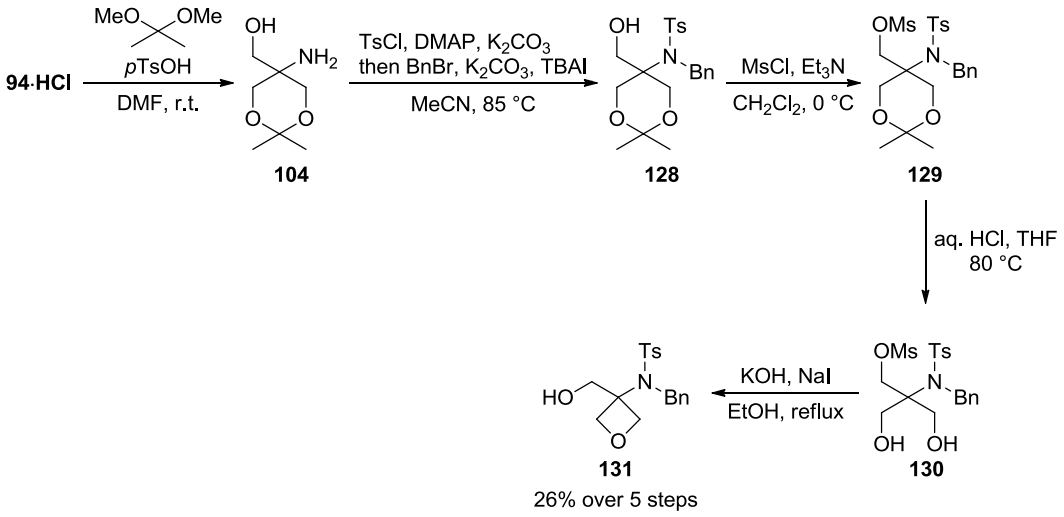
Next we turned our attention to the cyclization of triol **95** *via* the corresponding cyclic sulfite **98** and sulfate **100**. Treatment of **95** with thionyl chloride in the presence of K_2CO_3 in CH_2Cl_2 yielded **98** in 59%. Oxidation of **98** with $RuCl_3$ and $NaIO_4$ in MeCN/water in turn furnished **100** in 29% yield. Again cyclization of **98** to the corresponding oxetane **96** under basic conditions did not proceed but always led to rapid decomposition of the starting material (Scheme 37).



Scheme 37 Synthesis of Sulfate 98 and 100 and Attempted Ringclosure to 96.

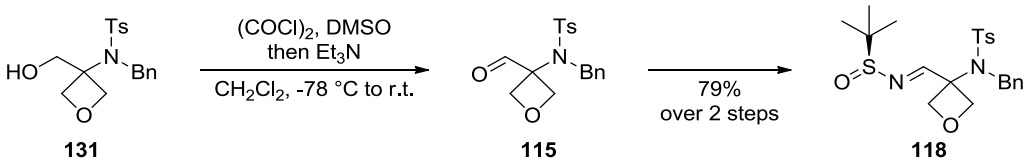
Hence, the route to imine **89** *via* cyclic intermediates such as carbonates, sulfites and sulfates of **94** and **95** was abandoned.

As mentioned in chapter 2.2.2, the dimethyl acetal **104** of Tris-base (**94**) was also identified as a starting point for the synthesis of imine **89**. Following the retrosynthetic outline, **104** was successfully prepared from **94** following a literature procedure.[151] The amine of **104** was then protected with tosyl and subsequently benzyl in a one pot procedure using K_2CO_3 in MeCN in presence of DMAP and TBAI respectively. Obtained crude **128** isolated by filtration and removal of the solvent was then subjected to MsCl and Et_3N to obtain **129**. Treatment of the crude material with aqueous HCl in THF furnished activated diol **130**. Again crude **130** was subjected to cyclization conditions with KOH and NaI in EtOH to rapidly form desired oxetanyl amino alcohol **131** in 26% overall yield in five steps from **94**. The synthesis of **131** was performed to provide >10 g of the desired product without chromatographic purification (Scheme 38).



Scheme 38 Synthesis of Aminoalcohol 131.

SWERN oxidation of **131** followed by condensation with the (*S*)-ELLMAN auxiliary under identical conditions as before cleanly yielded **118** in 79% over two steps (Scheme 39).

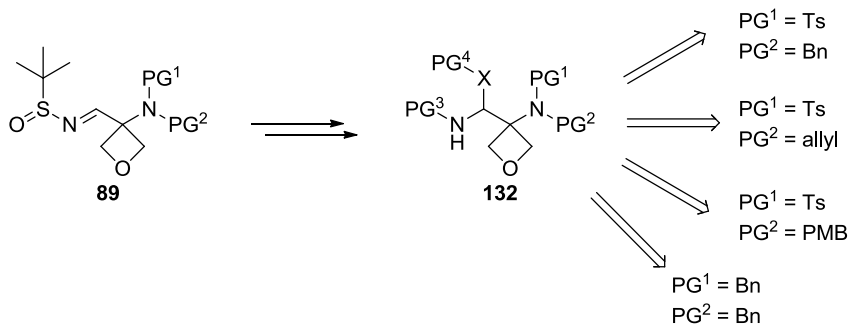


Scheme 39 Synthesis of 118 from 131.

This strategy provided us with rapid excess to considerable quantities of key intermediate imine **118** which was essential for the success of the oxetanyl peptide project. Consequently, the other enantiomer **ent-118** could be obtained by condensation with the opposite enantiomer of the ELLMAN auxiliary.

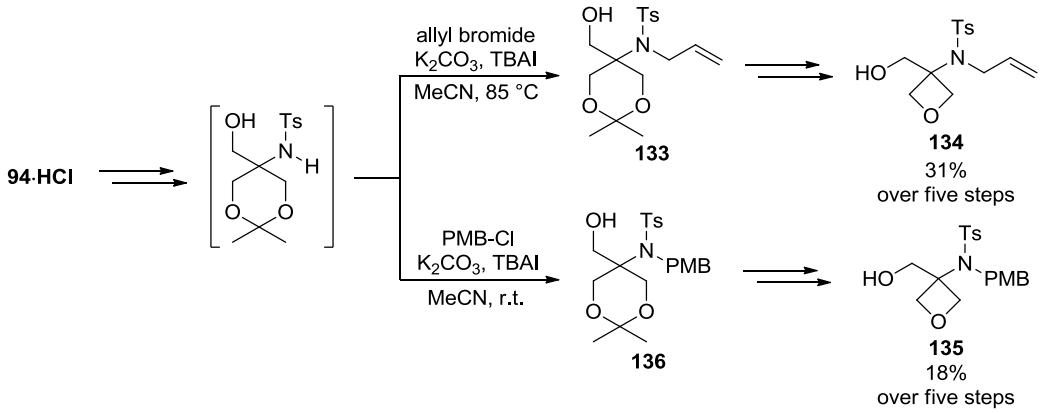
Different side chain functionalities (X) and different peptide coupling strategies (e.g. Boc/Bn, Fmoc/Alkyl, Cbz/Alkyl) require a diverse orthogonal protecting group pattern (PG^3/PG^4) on the building blocks used. We therefore quickly realized that the synthesis of diamines **132** with a variety of side chains and protecting group patterns would inevitably require a choice of protecting groups on imine **89**. So far only the Ts/Bn (**118**) combination was considered. We decided to keep the tosyl group (PG^1) as it proved to be essential for the

subsequent alkylation and consequently changed PG^2 from benzyl to allyl and *p*-methoxy benzyl (PMB) respectively (Scheme 40).



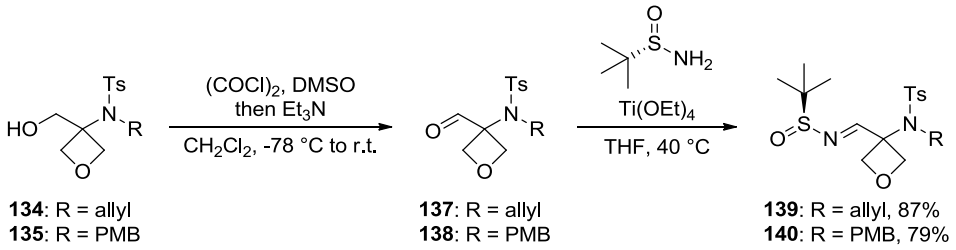
Scheme 40 Protecting Group Strategies for Diamines 132

This could easily be achieved by a slight variation of the sequence in Scheme 38. After tosylation, in the case of the allyl protecting group, simply allyl bromide was used instead of benzyl bromide. The one pot double protection to **133** proved to be equally effective and further elaboration furnished the corresponding aminoalcohol **134** in 31% over five steps from **94**·HCl. Now introducing one chromatographic purification after the oxetane formation also enabled us to conveniently produce >10 g of **134**. The PMB group was introduced using the same strategy now with PMB-Cl in the second protection step to yield **135** *via* intermediate **136** in five steps and 18% overall yield from **94**·HCl (Scheme 41).



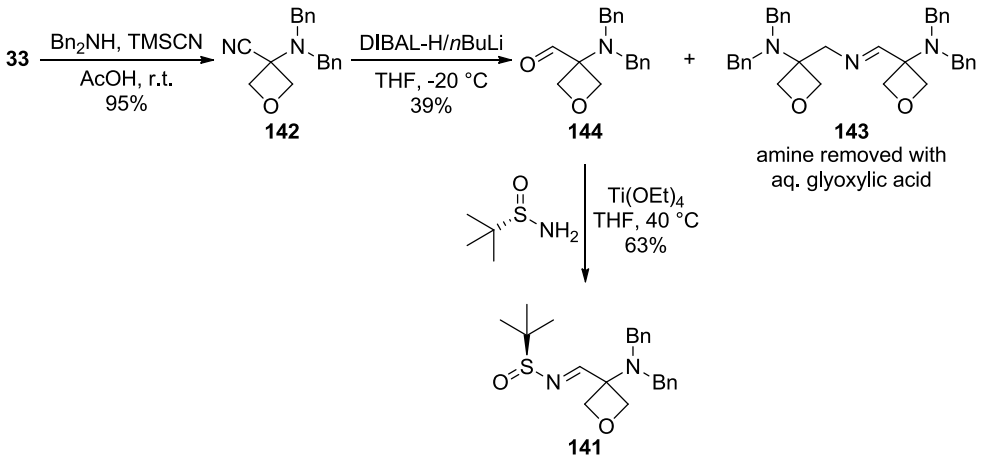
Scheme 41 Synthesis of Aminoalcohols 134 and 135.

After SWERN oxidation of aminoalcohols **134** and **135** to aldehydes **137** and **138** and condensation with the ELLMAN auxiliary the corresponding imines **139** and **140** were obtained in 87% and 79% yield over two steps respectively (Scheme 42).



Scheme 42 Synthesis of Imines 139 and 140.

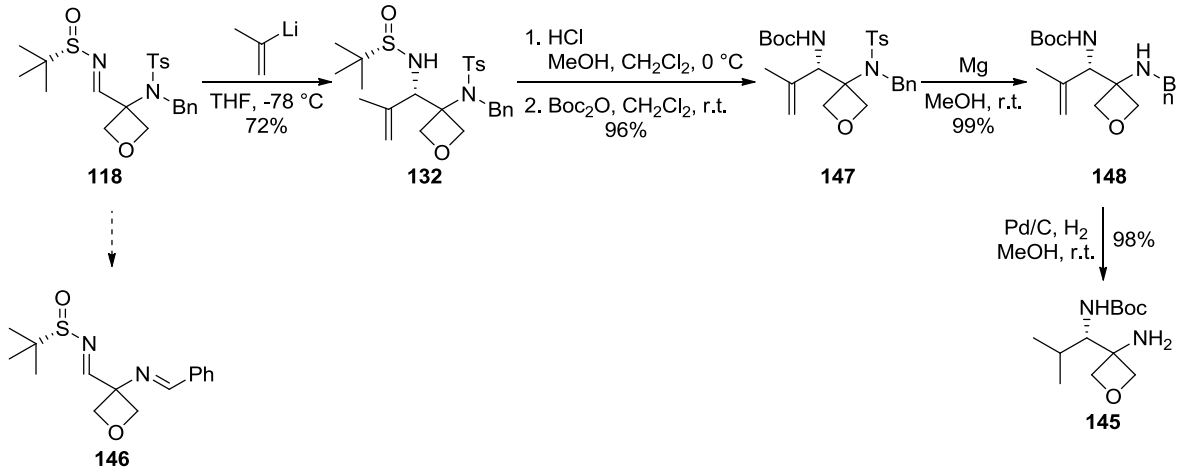
Furthermore, we envisioned that a fourth protecting group pattern in the form of dibenzyl protected imine **141** would be a valuable starting point since some side chain protecting group patterns might not tolerate the rather forcing magnesium in methanol deprotection conditions for the tosyl group. As mentioned above, the tosyl group after the first protection of **104** was shown to be essential for subsequent alkylation. Hence, the dibenzyl protecting group pattern could not be achieved using the previous route from Scheme 38. We again had to resort to STRECKER chemistry this time starting from oxetane-3-one (**33**) and dibenzylamine. The corresponding nitrile **142** was obtained in 95% yield. Reduction to the aldehyde was again challenging because of the formation of byproduct imine **143**. This time though, the byproduct could be conveniently hydrolysed by aqueous extraction with glyoxylic acid to liberate aldehyde **144** and remove the overreduced amine before chromatographic purification. The aldehyde **144** was obtained using the DIBAL-H/*n*-BuLi complex in 39% yield. Imine formation yielded **141** in 63% (Scheme 43).



Scheme 43 Synthesis of imine 141.

In summary, four key intermediate imines were prepared with Ts/Bn (**118**), Ts/allyl (**139**), Ts/PMB (**140**) and Bn/Bn (**141**) protecting group patterns. This would enable us to synthesize a variety of diamines **87** with several orthogonal protecting groups.

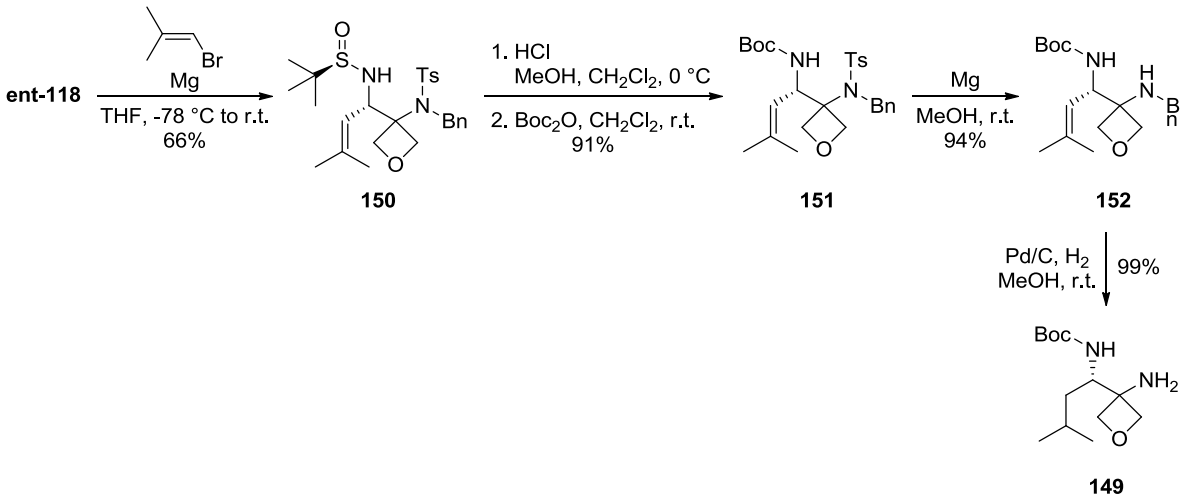
We now turned our attention to the synthesis of a number of oxetanyl diamines **87** *via* the addition of a suitable organometallic reagent to imines **89**. The synthesis of Boc-^{Ox}Ala-NH$_2$ (**122**) *via* MeLi addition to **118** is already described above. Next, we tried to approach the synthesis of Boc-^{Ox}Val-NH$_2$ (**145**) using an identical strategy. However, treatment of **118** with *i*PrLi or *i*PrMgBr did not lead to the desired adduct **132**, but mainly furnished a byproduct containing a second imine functionality by ^{1}H-NMR, presumably **146** by elimination of the tosyl group. We therefore decided to use 2-bromo propene as the side-chain precursor. Addition of the corresponding vinyl lithium reagent to **118** in THF yielded **132** in 72%. Removal of the ELLMAN auxiliary and reprotection with Boc$_2$O furnished **147** in 96%. Subsequent detosylation to **148** and removal of the benzyl group as well as reduction of the alkene by hydrogenation led to diamine **145** in 97% yield over two steps.



Scheme 44 Synthesis of Boc-^{Ox}Val-NH$_2$ (145).

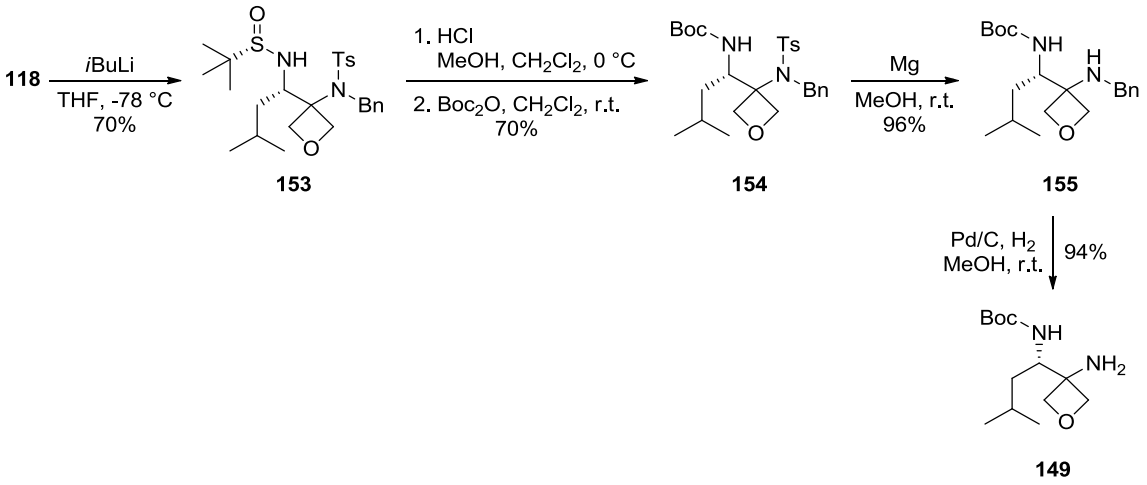
The absolute configuration of **145** was assigned in analogy to Boc-^{Ox}Ala-NH$_2$ (**122**) and Boc-^{Ox}Leu-NH$_2$ (**149**, *vide infra*).

Using the same approach, addition of the GRIGNARD reagent derived from 1-bromo-2-methyl-prop-1-ene to imine **ent-118** furnished adduct **150** in 66% as a precursor for the synthesis of Boc-^{Ox}Leu-NH$_2$ (**149**). This time, the desired (*S*)-configuration of the α-stereocenter was obtained from the (*R*)-imine **ent-118**. In analogy to the synthesis of **145**, the same deprotection and Boc-protection to **151**, tosyl deprotection to **152** and hydrogenation strategy delivered the desired diamine **149** in 85% overall yield from adduct **150**.



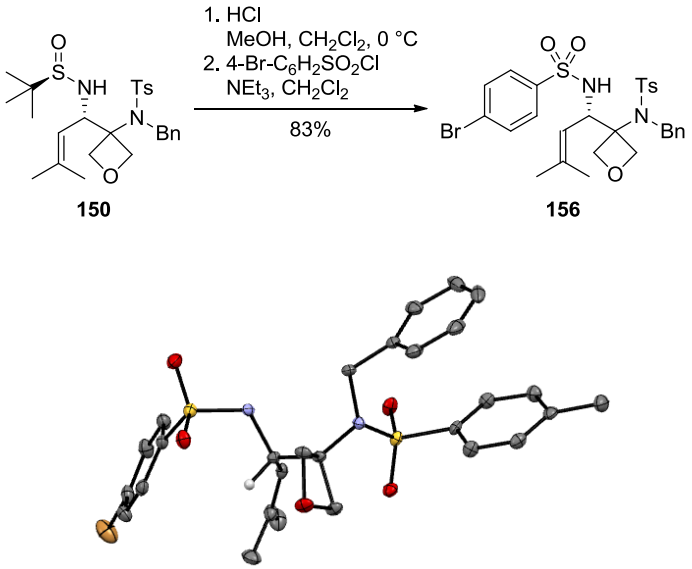
Scheme 45 First Generation Synthesis of Boc-OxLeu-NH2 (149).

We later realized that in this case the addition of isobutyl lithium to **118** does not lead to elimination as observed before but cleanly furnishes adduct **153** in 70% yield. Further elaboration *via* **154** and **155** efficiently led to **149** in 63% yield over three steps (Scheme 46). Identity of the absolute configuration was confirmed by comparison of the optical rotation to the data obtained from the synthesis of **149** *via* the vinyl magnesium bromide route.



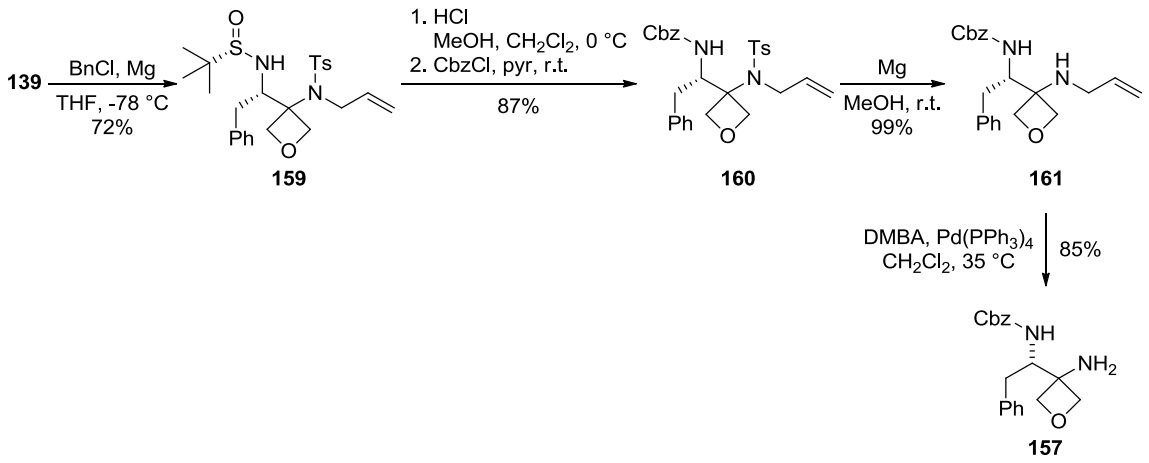
Scheme 46 Second Generation Synthesis of Boc-^{Ox}Leu-NH$_2$ (149).

The absolute configuration of **149** was assigned as (*S*) by X-Ray crystal structure analysis of derivative **156** obtained in two steps in 83% yield from **150** (Scheme 47).



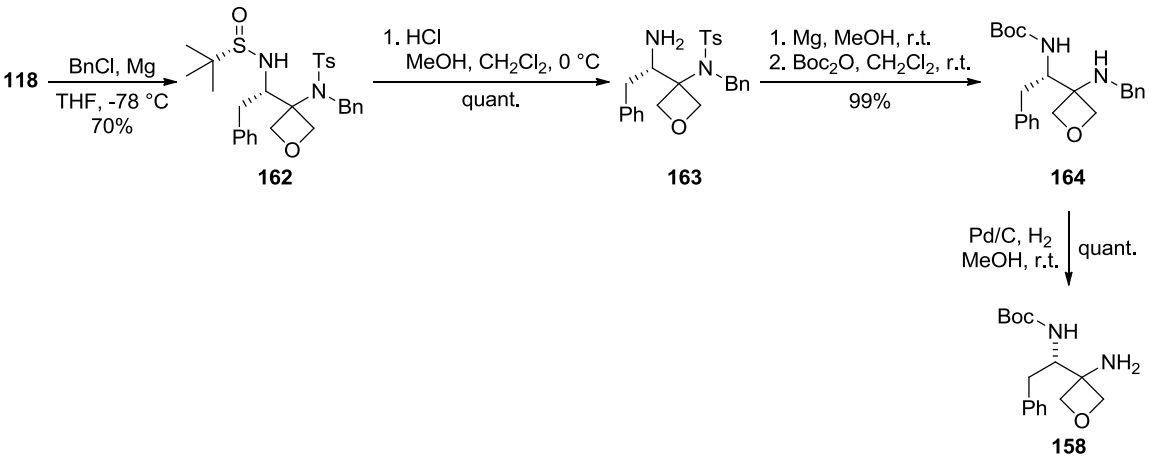
Scheme 47 Synthesis of Sulfonamide 156 from Adduct 150, ORTEP-plot of the X-Ray Crystal Structure of 156 (ellipsoids are drawn at 50% probability, hydrogen atoms, except at the C-stereocenter are omitted for clarity).

Next the synthesis of Cbz-^{Ox}Phe-NH_2 (**157**) and Boc-^{Ox}Phe-NH_2 (**158**) was pursued from imines **139** and **118** respectively. In order to introduce the Cbz-protecting group, the allyl protected imine **139** had to be used to ensure orthogonal deprotection. Addition of benzyl magnesium chloride to imine **139** yielded adduct **159** as a 4:1 mixture of diastereomers. The (*S*,*S*)-isomer was isolated in 72% by recrystallization. The auxiliary was subsequently removed under the conditions described above. This time the intermediate amine was treated with Cbz-Cl in pyridine to obtain derivative **160** in 87% yield. Detosylation with magnesium in methanol yielded allyl amine **161** in 99%. Finally, the allyl protecting group was removed with dimethyl barbituric acid in the presence of catalytic $Pd(PPh_3)_4$ to produce **157** in 85% yield (Scheme 48).



Scheme 48 Synthesis of Cbz-^{Ox}Phe-NH$_2$ (157).

In analogy to the synthesis of Boc-^{Ox}Leu-NH$_2$ (**149**), Boc-^{Ox}Phe-NH$_2$ (**158**) was obtained by the addition of benzyl magnesium chloride to imine **118**. The desired (*S*,*S*)-diastereomer of adduct **162** was again isolated by recrystallization in 70% yield. Removal of the auxiliary and protection of crude amine **163** led to the corresponding Boc derivative. However, the obtained material was inseparable from byproducts remaining from the auxiliary. Hence, the free amine **163** was isolated. Then, first the tosyl group was removed to ensure solubility before reprotection with Boc to yield **164** in 99% over two steps. Final cleavage of the benzyl group by hydrogenation quantitatively provided diamine **158** (Scheme 49).



Scheme 49 Synthesis of Boc-^{Ox}Phe-NH$_2$ (158).

The absolute configuration of **158** was determined as (*S*) by X-Ray crystal structure analysis of intermediate **162** (Figure 14).

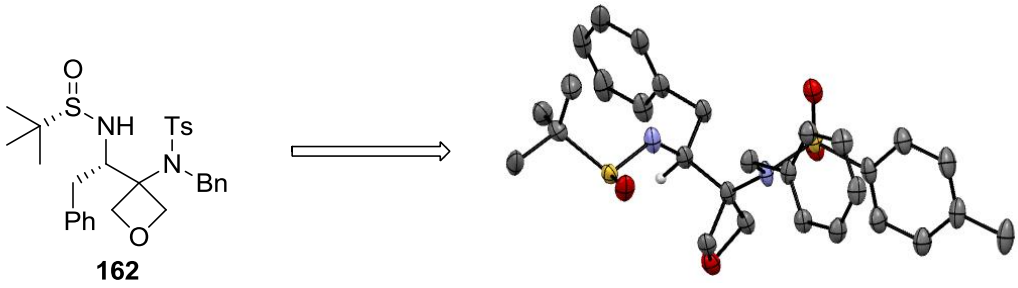
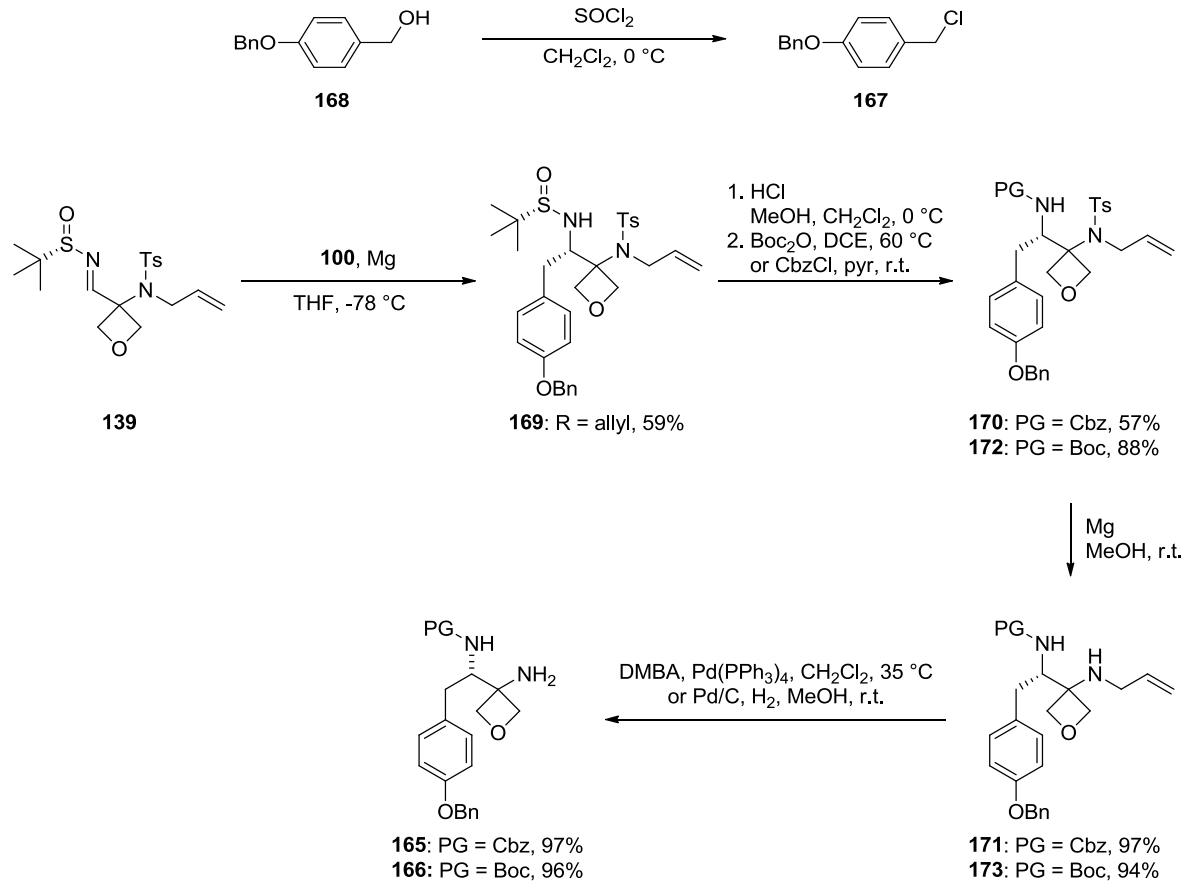


Figure 14 ORTEP-plot of the X-Ray Crystal Structure of 162 (ellipsoids are drawn at 50% probability, hydrogen atoms, except at the *C*-stereocenter, and disorder are omitted for clarity).

Also, both Cbz-^{Ox}Tyr(OBn)-NH_2 (**165**) and Boc-^{Ox}Tyr(OBn)-NH_2 (**166**) were successfully synthesized starting from imine **139**. The Cbz and benzyl protecting groups in **165** are intentionally not orthogonal to be able to deprotect a peptide carrying an *N*-terminal tyrosine in one step. First, side-chain precursor **167** was prepared from commercial alcohol **168** as reported before.[152] Addition of the corresponding benzyl magnesium chloride to **139** furnished adduct (*S*,*S*)-**169** in 59% yield. Again auxiliary cleavage and Cbz-protection to **170**, cleavage of the tosyl group to **171** and finally removal of the allyl group yielded **165** in 54% over three steps (Scheme 50).

Similarly, Boc-^{Ox}Tyr(OBn)-NH_2 (**166**) was also synthesized from adduct **169**. Further elaboration of **169** as described above *via* intermediates **172** and **173** led to diamine **166** in 79% over three steps (Scheme 50).



Scheme 50 Synthesis of Cbz-^{Ox}Tyr (OBn)-NH$_2$ (165) and Boc-^{Ox}Tyr (OBn)-NH$_2$ (166).

The absolute configuration of **165** and **166** was determined by comparison of the ^{1}H-NMR shifts of the benzylic protons of **169** to data obtained from **162** and **159**. The respective (S,S)- and (S,R)-diastereomers have significantly different characteristic signals that can be used for the assignment of the stereochemistry(Figure 15).

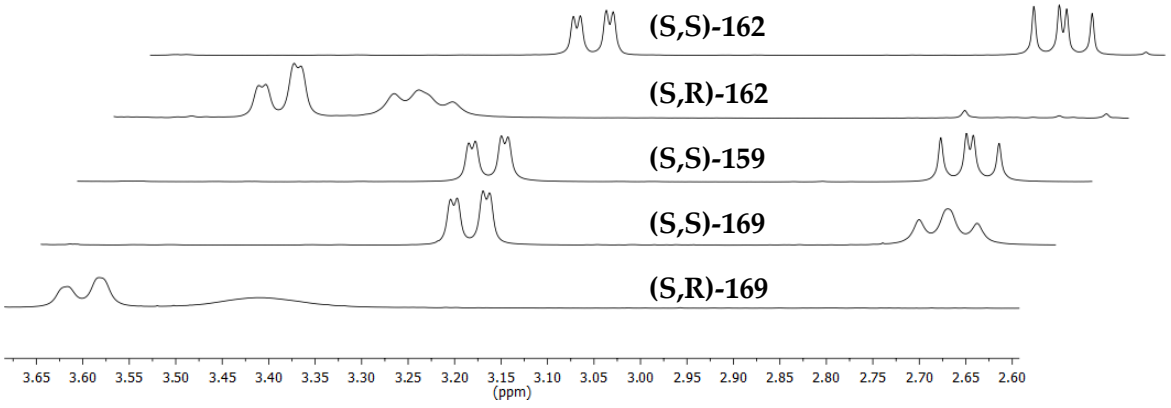
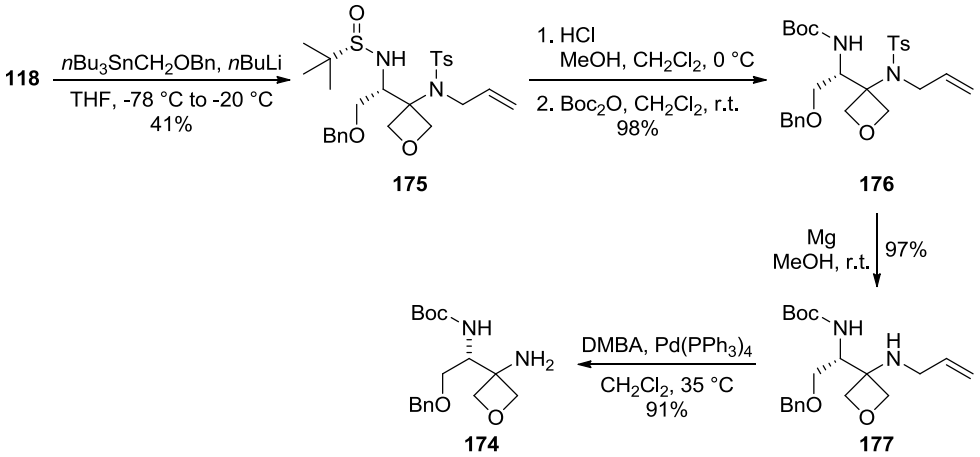


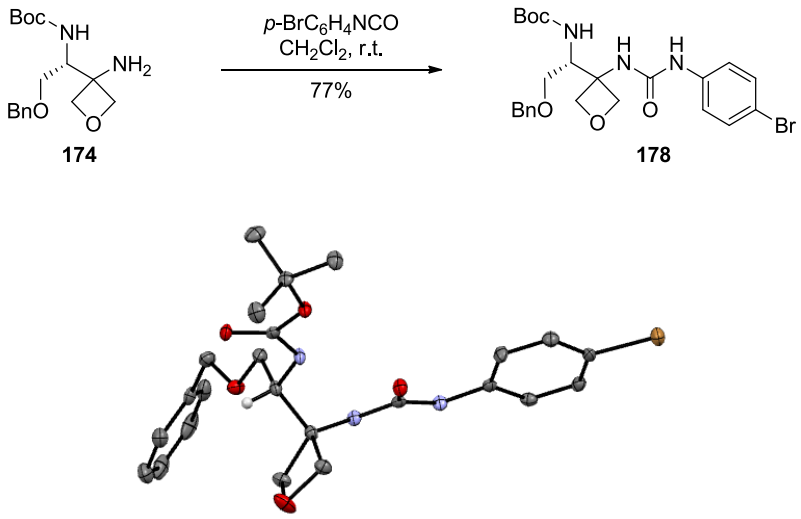
Figure 15 Determination of Absolute Configuration of 169 by ^{1}H-NMR Analysis.

As another hydroxyl functionalized amino acid surrogate, Boc-^{Ox}Ser(OBn)-NH_2 (**174**) was synthesized starting from imine **139**. First, the direct addition of the GRIGNARD reagent prepared from BOM-Cl was attempted, but did not lead to the desired product. Hence, the corresponding organotin reagent was prepared by deprotonation of tributyltin hydride with LDA and subsequent substitution with BOM-Cl. Transmetallation to the corresponding organolithium species and addition to **139** then yielded intermediate **175** in 41% yield. Following the same sequence with auxiliary removal and Boc-protection to **176**, detosylation to **177** and finally cleavage of the allyl protecting group furnished **174** in 79% yield over three steps (Scheme 51).



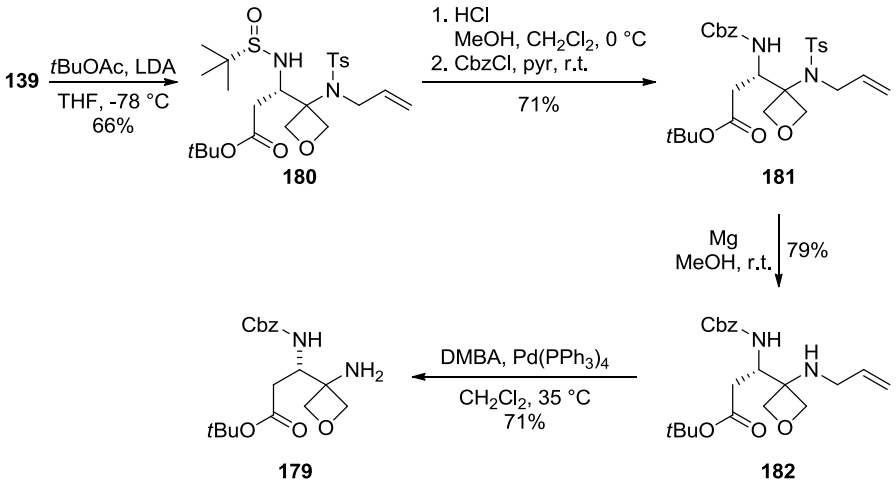
Scheme 51 Synthesis of Cbz-^{Ox}Ser (OBn)-NH_2 (174).

The absolute configuration of **174** was determined as (*R*) by X-Ray crystal structure analysis of urea **178** which was obtained from **172** by treatment with *p*-Br-phenyl isocyanate in 77% yield (Scheme 52).



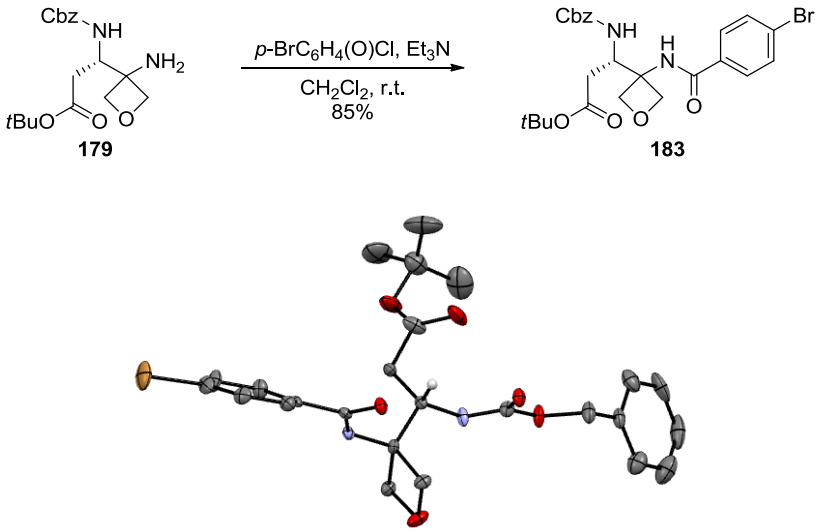
Scheme 52 Synthesis of Urea 178 from Diamine 174, ORTEP-plot of the X-Ray Crystal Structure of 178 (ellipsoids are drawn at 50% probability, hydrogen atoms, except at the *C*-stereocenter are omitted for clarity).

Introducing another side-chain functionality, Cbz-^{Ox}Asp(OtBu)-NH_2 (**179**) was prepared from imine **139**. Addition of the lithium enolate of *t*BuOAc provided adduct **180** as a 10:1 mixture of diastereomers. The (*S*,*S*)-isomer was isolated by repeated column chromatography in 66% yield. In analogy to the syntheses above, **179** was prepared in 40% yield over three more steps *via* intermediates **181** and **182** (Scheme 53).



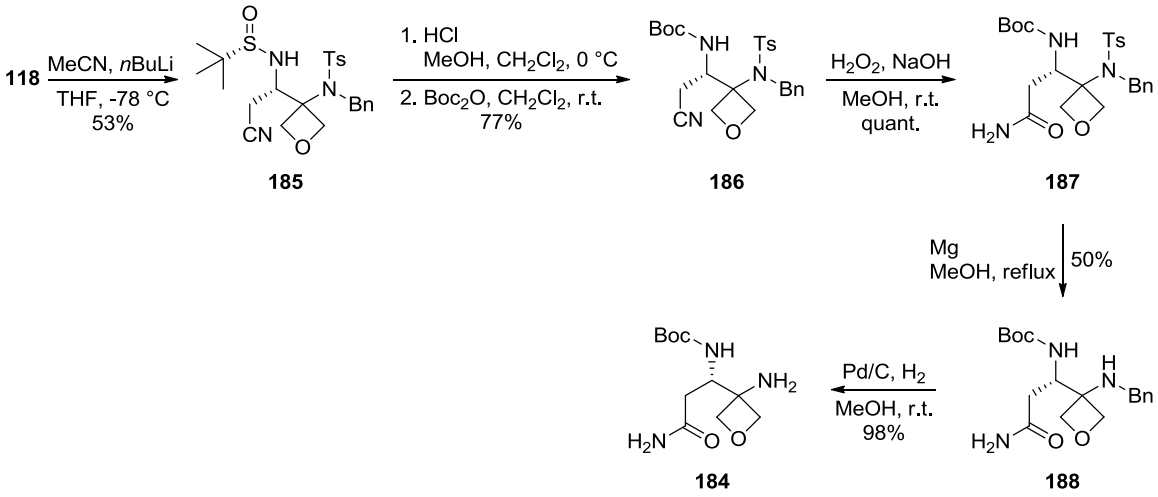
Scheme 53 Synthesis of Cbz-^{Ox}Asp (O*t*Bu)-NH_2 (179).

The absolute configuration of **179** was determined as (*S*) by X-Ray crystal structure analysis of amide **183** which was obtained from **179** with *p*-Br-benzoyl chloride in the presence of triethylamine in 85% yield (Scheme 54).



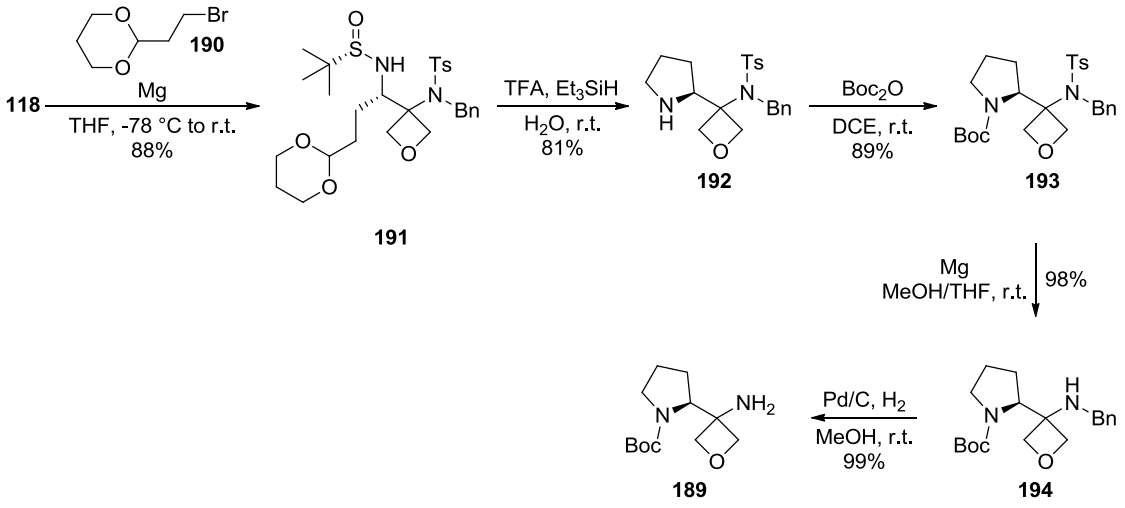
Scheme 54 Synthesis of Amide 183 from Diamine 179, ORTEP-plot of the X-Ray Crystal Structure of 178 (ellipsoids are drawn at 50% probability, hydrogen atoms, except at the *C*-stereocenter, and disorder of *t*Bu are omitted for clarity).

Additionally, Boc-^{Ox}Asn(NH_2)-NH_2 (**184**) was prepared from imine **118**. Side-chain protection was avoided because we assumed that the alkylation to a dipeptide **73** would proceed in the presence of the primary amide. Deprotonation of acetonitrile with *n*BuLi and subsequent addition to **118** provided adduct **185** as a 2:1 mixture of diastereomers. The major isomer was isolated by recrystallization in 53% yield. Removal of the auxiliary and Boc-protection yielded intermediate **186** in 77%. Hydrolysis of the nitrile to the corresponding primary amide with hydrogen peroxide provided **187** in quantitative yield. Cleavage of the tosyl group then led to **188** in 50% yield. Due to the poor solubility of **188** the crude material was immediately hydrogenated to obtain diamine **184** in 98% yield (Scheme 55).



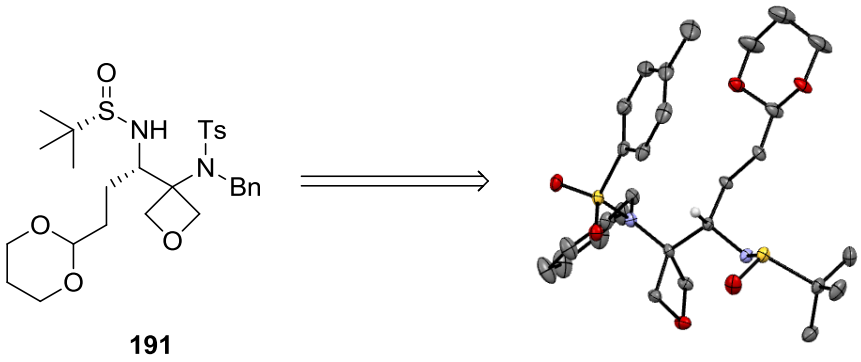
Scheme 55 Synthesis of Boc-^{Ox}Asn (NH_2)-NH_2 (184).

Finally, Boc-^{Ox}Pro-NH_2 (**189**) was obtained starting from imine **118**. Addition of the acetal protected GRIGNARD reagent derived from **190** to **118** yielded compound **191** in 88%. Subsequent treatment with TFA and triethyl silane affected both removal of the auxiliary and the acetal as well as formation of pyrrolidine **192** by reductive amination. Subsequent Boc-protection to **193**, tosyl deprotection to **194** and benzyl deprotection delivered the desired diamine **189** in 70% overall yield from adduct **191** (Scheme 56).



Scheme 56 Synthesis of Boc-^{Ox}Pro-NH_2 (189).

The absolute configuration of **189** was determined as (*S*) by X-Ray crystal structure analysis of intermediate **191** (Figure 16).

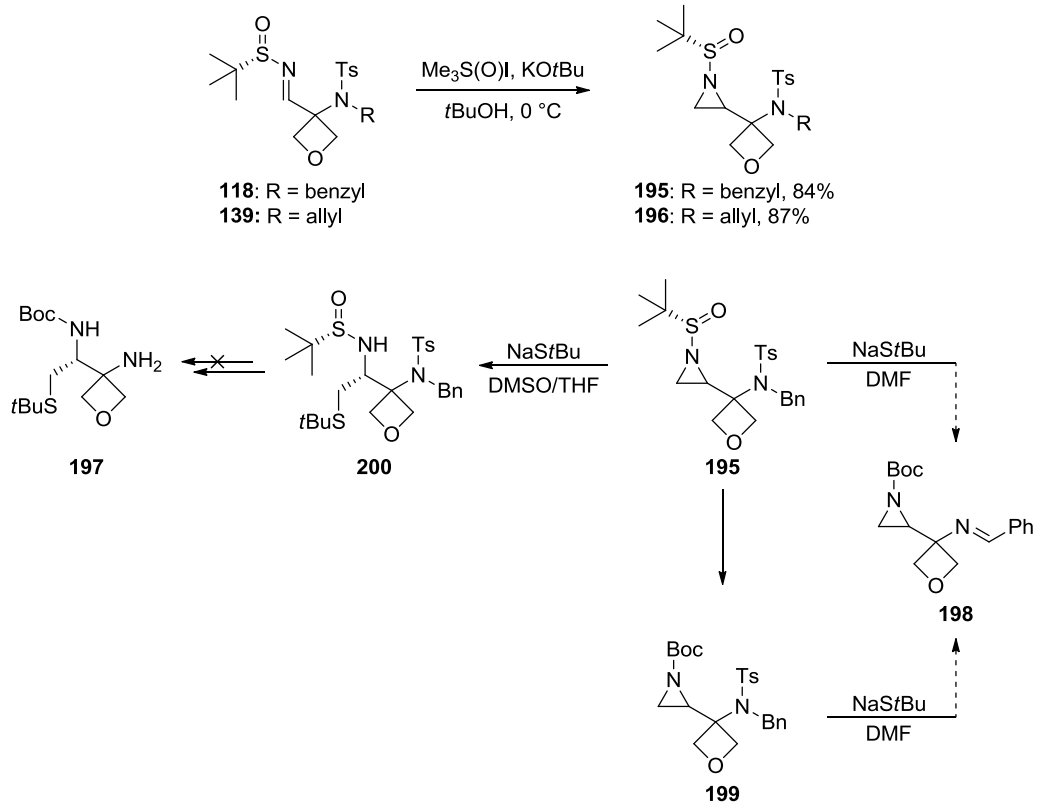


191

Figure 16 ORTEP-plot of the X-Ray Crystal Structure of 191 (ellipsoids are drawn at 50% probability, hydrogen atoms, except at the *C*-stereocenter, and disorder of the acetal are omitted for clarity).

Furthermore, imine **118** and **139** were transformed to the corresponding aziridines **195** and **196** in 84% and 87% by treatment with trimethylsulfoxonium iodide and KO*t*Bu in *t*BuOH. Unfortunately, the products were obtained in about 1:1 mixtures of diastereomers. In the case of **195** the two diastereomers could be separated by laborious repetitive column chromatography. The isomers of **196** were inseparable at this stage. With those two aziridines in hand we hoped to be able to access several functionalized side-chain containing diamines. First, the synthesis of Boc-^{Ox}Cys(S*t*Bu)-NH_2 (**197**) by opening the aziridine with a sulfur nucleophile was pursued. Treatment of **195** with sodium *t*butyl thiolate in DMF mainly led to side products presumably from the elimination of the tosyl group to the corresponding imine **198** and only provided traces of the desired ring opened product as determined by ^{1}H-NMR. Hence, the ELLMAN auxiliary was removed from **195** and the amine was reprotected with Boc to give **199** in quantitative yield. Treatment of **199** with sodium *t*butyl thiolate in DMF also mainly resulted in the formation of side products as observed above. Only when the solvent mixture was changed to THF/DMSO, the auxiliary containing intermediate **195** could successfully be converted into the desired thioether **200** in 67% yield. Subseqent removal of the auxiliary, protection with Boc and detosylation proceeded smoothly. However, in the final deprotection of the benzyl group complete conversion to **197** could never be observed and the

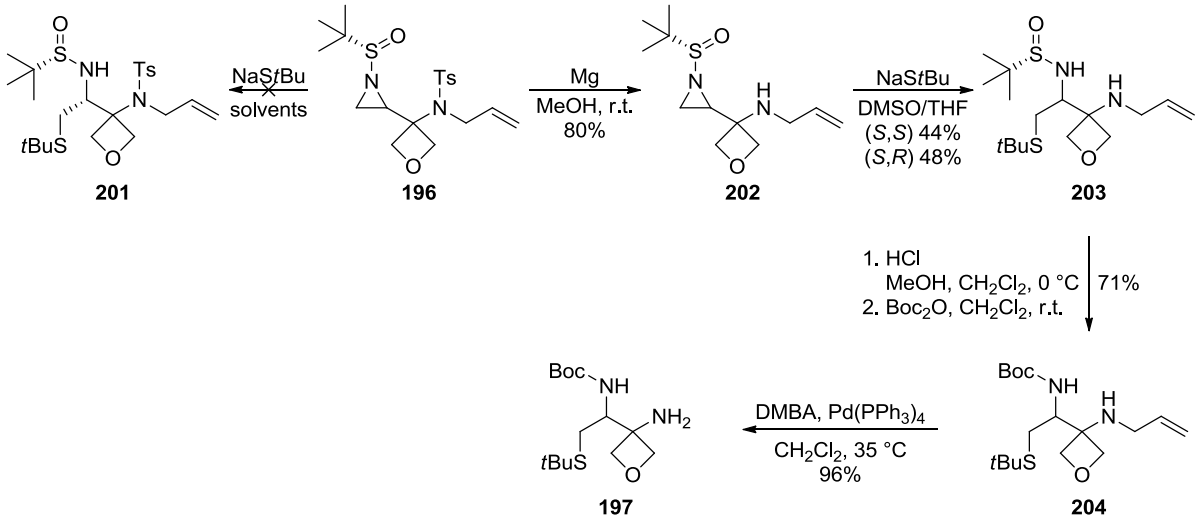
desired product was inseparable from a complex mixture of side products formed (Scheme 57).



Scheme 57 Attempted Synthesis of 197 from Aziridine 195.

Therefore, we decided to use allyl protected aziridine **196** for the synthesis of the cysteine building block **197**. Upon treatment of the mixture of diastereomers of **196** with sodium *t*butyl thiolate in various solvents, the desired product **201** was never isolated. Instead a mixture of products presumably containing an isomerized allyl group was isolated. We reasoned that the presence of the tosyl group could accelerate the isomerization process and hence decided to remove this protecting group directly from **196** to give **202** in 80% yield again as an inseparable mixture of diastereomers. Subsequent treatment of **202** with the thiolate reagent in THF/DMSO finally furnished the desired thioether **203** as a separable mixture of the two diastereomers (*S*,*S*)-**203** and (*S*,*R*)-**203** in 44% and 48% yield respectively. Subsequent removal of the auxiliary and protection with Boc to **204** as well as cleavage of the allyl group provided diamines (*S*)-**197** and (*R*)-**197** in 68% yield each, over two steps. In this case, the (*R*)-enantiomer

corresponds to the natural configuration because of the priority of sulfur in the CAHN-INGOLD-PRELOG system.



Scheme 58 Attempted Synthesis of 197 from Aziridine 196.

The absolute configuration of **197** was assigned by X-Ray crystal structure analysis.

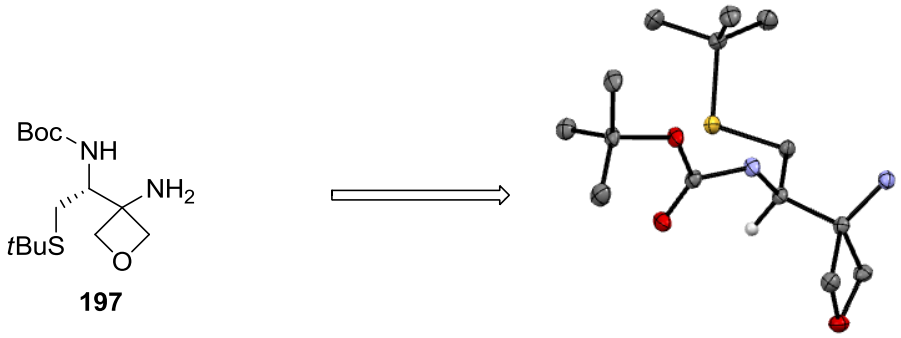
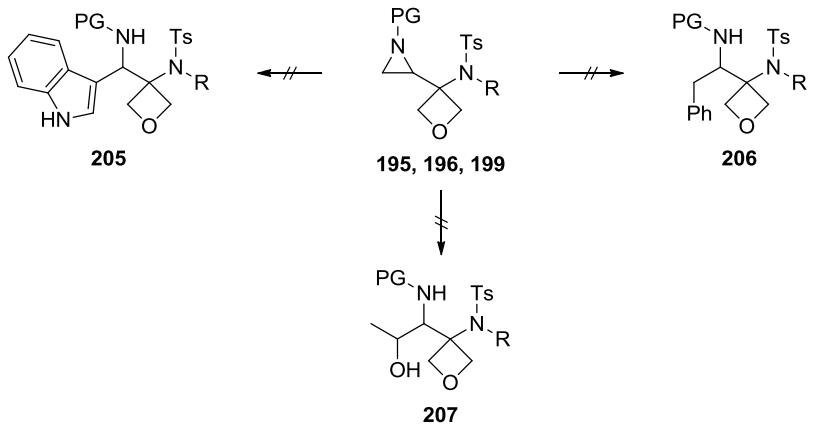


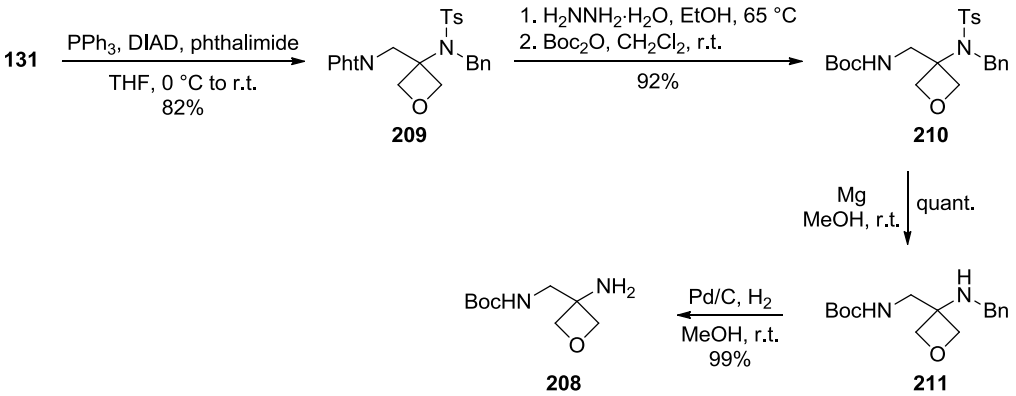
Figure 17 ORTEP-plot of the X-Ray Crystal Structure of 197 (ellipsoids are drawn at 50% probability, hydrogen atoms, except at the *C*-stereocenter, are omitted for clarity).

Additionally, ring opening of the aziridines was attempted under several other previously described conditions including reactions with indole[153,154],[153,154] treatment with PhMgBr in the presence of Cu(I)[155] and AGGARWALS boronic ester chemistry.[156] Unfortunately, the corresponding ring opened products **205**, **206** and **207** were never observed (Scheme 59).



Scheme 59 Attempts to Open Aziridines 195, 196 or 199.

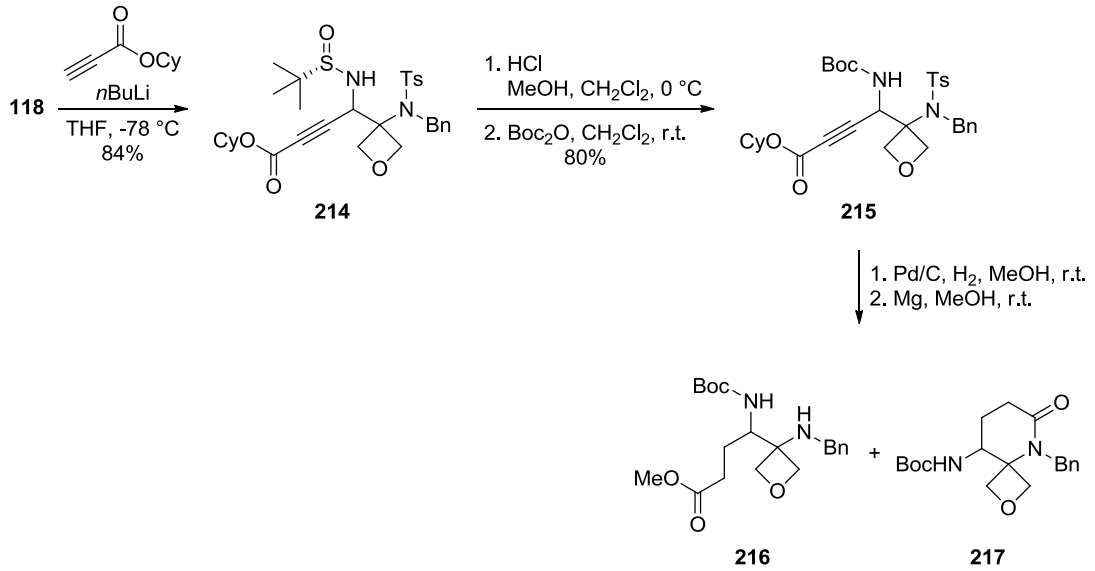
Last, we successfully synthesized Boc-^{Ox}Gly-NH$_2$ (**208**) from aminoalcohol **131**. This building block would give ^{Ox}Gly-AA dipeptides *via* the alkylation approach. It completes the toolbox of this synthetic strategy although the corresponding oxetanyl dipeptides can also be obtained by the addition of amino acids to the corresponding nitro olefin (see chapter 2.2). MITSUNOBU reaction with phthalimide on **131** yielded protected diamine **209** in 82%. After deprotection with hydrazine and protection with Boc **210** was obtained. Further cleavage of the tosyl group to **211** and final removal of the benzyl group provided **208** in 91% yield over three steps (Scheme 60).



Scheme 60 Synthesis of 208 from Aminoalcohol 131.

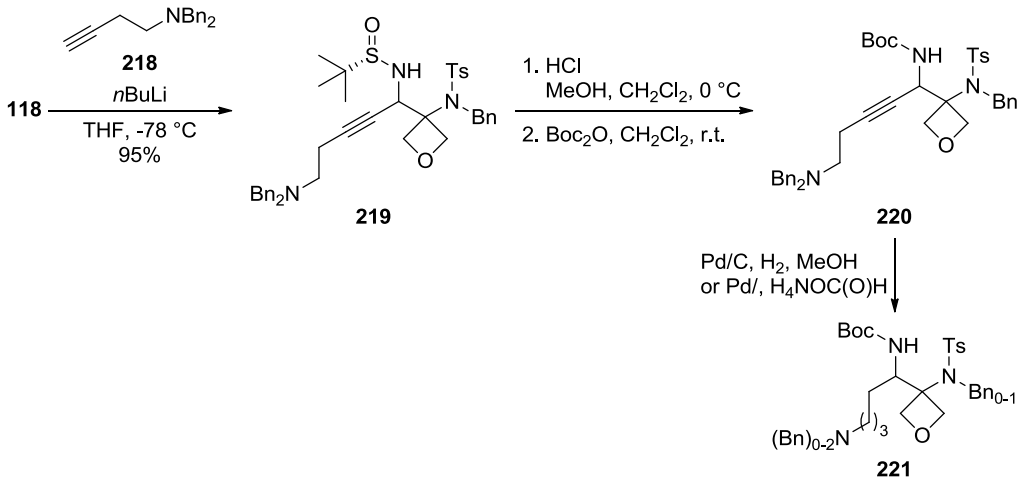
In addition to the building blocks synthesized as described above, the formation of Boc-^{Ox}Glu(OCy)-NH$_2$ (**212**) and Boc-^{Ox}Lys(NHCbz)-NH$_2$ (**213**) was attempted starting from imine **118**.

For the production of **212** deprotonated cyclohexyl propiolate was added to **118** to yield **214** and finally **215** in 67% after removal of the auxiliary and protection with Boc. However, after hydrogenation of the triple bond, tosyl deprotection gave a complex mixture of products, probably containing the corresponding methyl ester **216** and cyclized intermediate **217** as judged by crude ^{1}H-NMR (Scheme 61).



Scheme 61 Failed Synthesis of 212.

For the synthesis of **213** deprotonated alkyne **218** was added to imine **118** to give adduct **219** in 95% yield as a separable mixture of diastereomers. Unfortunately, after removal of the auxiliary and Boc protection to **220**, hydrogenation of the triple bond and cleavage of the two side-chain benzyl groups did not furnish the product containing the reduced side-chain. Instead a mixture of partially hydrogenated intermediates **221** was identified by LC-MS (Scheme 62).



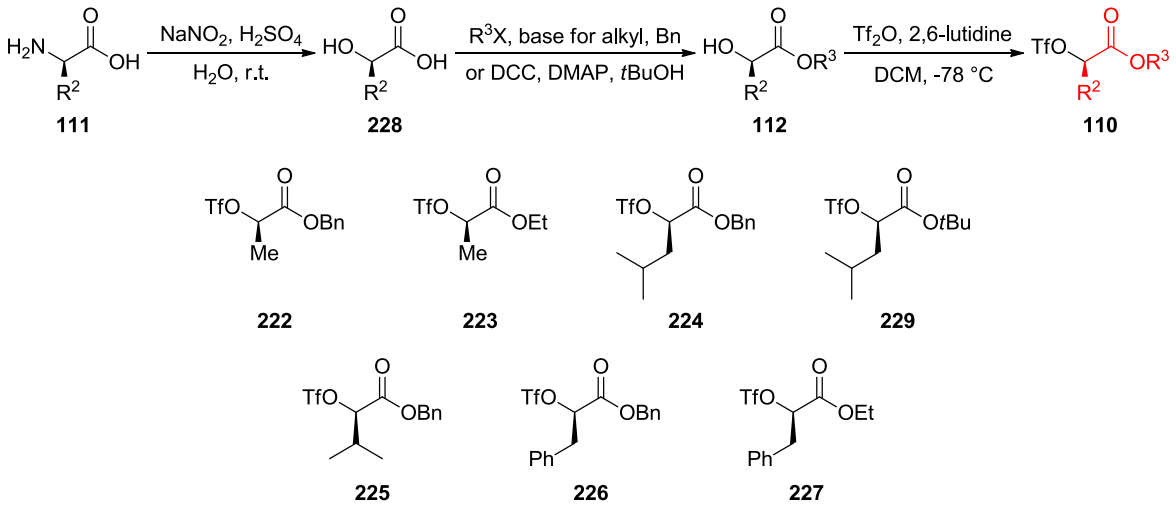
Scheme 62 Failed Synthesis of 213.

2.3.2 Synthesis of Triflates 110

With a diverse set of diamines in hand the first collection of building blocks for the alkylations was complete. Next, we turned our attention to the synthesis of a number of triflates **110**.

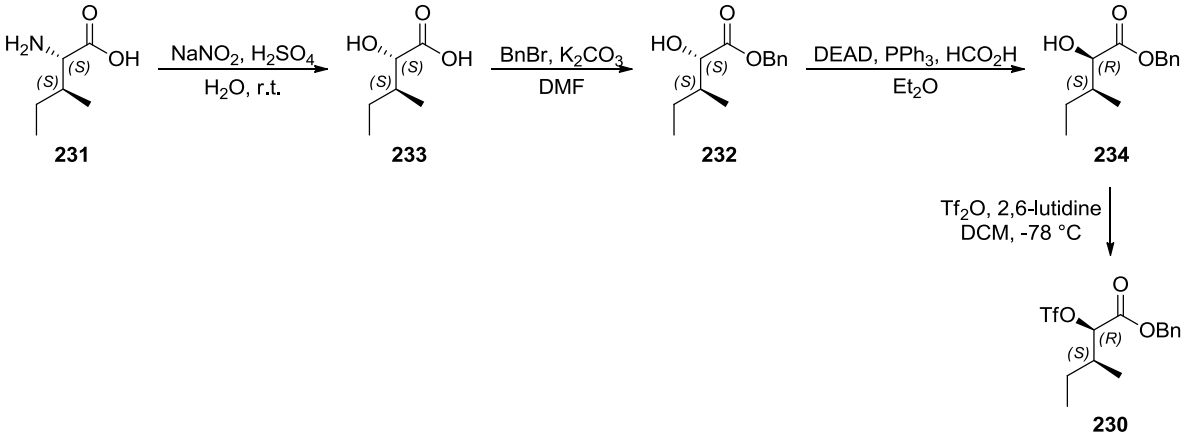
First, we focused our efforts on (*R*)-triflates **110** bearing only hydrocarbon side chains R^2 to reproduce the natural configuration in the corresponding dipeptides **73**. The protecting groups on the ester were chosen as *n*alkyl, benzyl and *t*butyl for the Cbz/alkyl, Boc/Bn and Fmoc/*t*butyl peptide coupling strategies respectively.

Starting from the corresponding commercially available D-amino acids **111**, TfO-^{D}Ala-OBn (**222**)[157], TfO-^{D}Ala-OEt (**223**)[158], TfO-^{D}Leu-OBn (**224**), TfO-^{D}Val-OBn (**225**)[157], TfO-^{D}Phe-OBn (**226**)[157], TfO-^{D}Phe-OEt (**227**)[158] were synthesized *via* the hydroxy acids **228** and hydroxyl esters **112** following literature procedures. For the synthesis of TfO-^{D}Leu-O*t*Bu (**229**)[159], the corresponding hydroxyacid was converted into its acetate to ensure *t*butyl ester formation under STEGLICH conditions. Removal of the acetate then led to the corresponding hydroxyester which was successfully transformed into triflate ester **229** (Scheme 63).



Scheme 63 Synthesis of Triflates with Hydrocarbon Side-Chains 222-227.

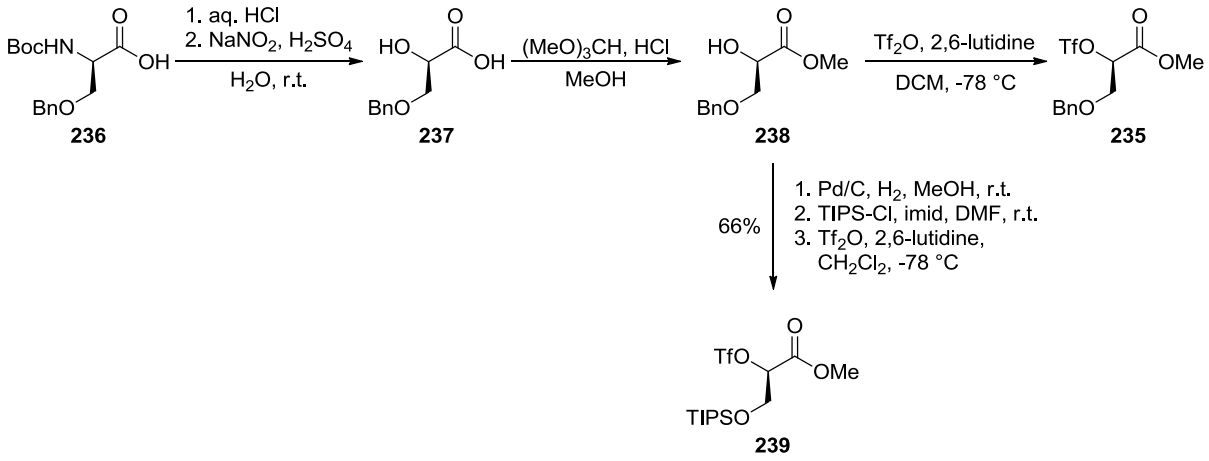
Addtitionally, the triflate **230** corresponding to isoleucine was synthesized. In this case, the side chain contains an additional stereocenter that is not inverted in the alkylation step to the dipeptides **73**. Hence, expensive D-ALLO-Isoleucine would have to be the precursor for the hydroxyacid synthesis. We therefore decided to start our synthesis from cheaper L-Isoleucine (**231**). After obtaining hydroxyester **232** *via* hydroxyacid **233** the alcohol was epimerized by MITSUNOBU inversion to give **234**. Finally, TfO-^{D,ALLO}Ile-OBn (**230**) was provided ready for alkylation (Scheme 64).[160]



Scheme 64 Synthesis of 230 from L-Isoleucine (231).

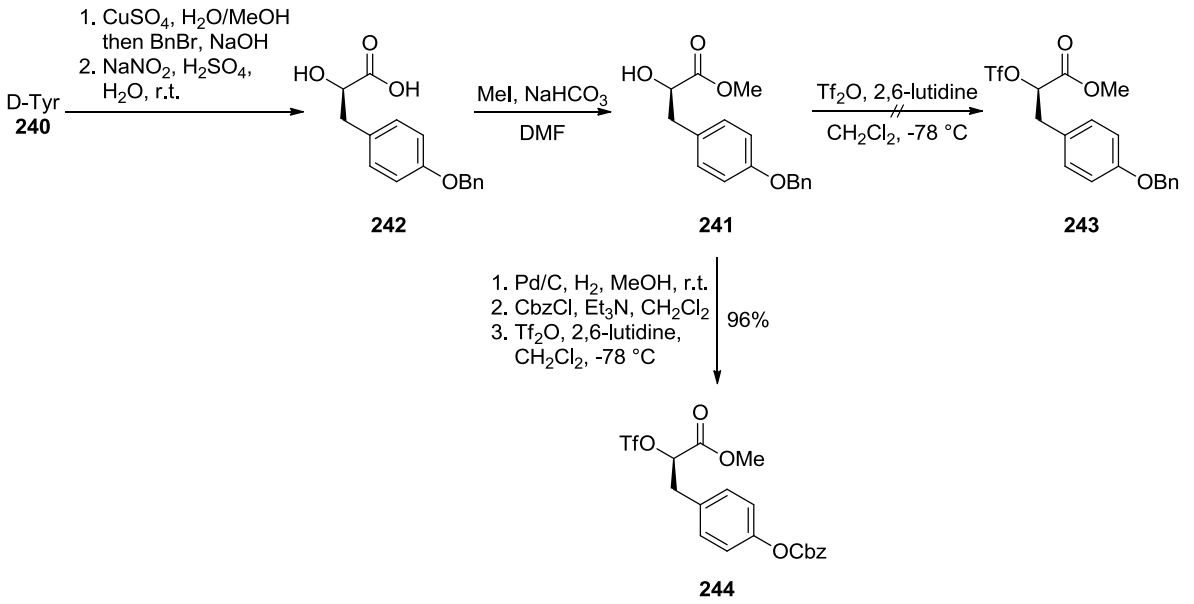
Next, we turned our attention to the synthesis of triflate esters **110** that carry a hydroxyl group in the side chain. First, we successfully obtained TfO-^{D}Ser(OBn)-

OMe (**235**) from BocNH-^{D}Ser(OBn)-OH (**236**) *via* hydroxyacid **237** and hydroxyester **238**.[161] We also decided to introduce a different protecting group for the side chain. Hence, the benzyl group was cleaved from **238** and the primary alcohol was TIPS-protected to give **239** in 35% yield after treatment with triflic anhydride (Scheme 65).



Scheme 65 Synthesis of Triflate Esters 235 and 239.

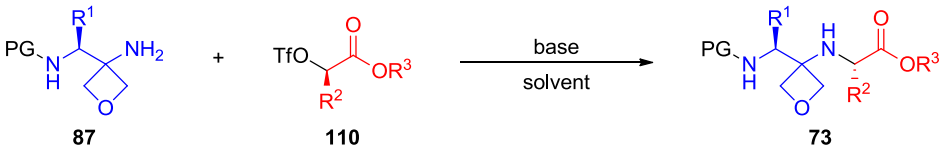
Secondly, we pursued the synthesis of a triflate analog of tyrosine. We again envisioned benzyl as the protecting group for the side chain. Hence, we started by protecting D-tyrosine (**240**) *via* its copper(II) complex.[162] The obtained amino acid derivative was then converted into the corresponding hydroxyester **241**[163] *via* hydroxyacid **242**. Finally, **241** was treated with triflic anhydride in the presence of 2,6-lutidine. Unfortunately the resulting TfO-^{D}Tyr(OBn)-OMe (**243**) was not stable to aqueous work-up and chromatographic purification probably due to elimination of the triflate group. Hence, the benzyl protecting group was removed from **241** by hydrogenation and the resulting phenol[164] was protected with Cbz and could then be successfully converted to TfO-^{D}Tyr(OCbz)-OMe (**244**) in 96% yield (Scheme 66).



Scheme 66 Synthesis of Triflate Ester 244.

2.3.3 Synthesis of Oxetanyl Dipeptides 73

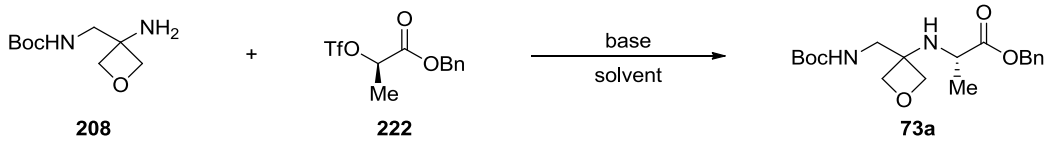
With both sets of building blocks, diamines **87** and triflates **110** in hand, we next focused on the alkylation to produce a variety of oxetanyl dipeptides **73** (Scheme 67).



Scheme 67 Synthesis of Oxetanyl Dipeptides 73.

We found that literature procedures often use chlorinated solvents such as CH_2Cl_2 or DCE and 2,6-lutidine as the base for these transformations.[147,165] However, with our substrates the reaction was extremely slow under these conditions. We hence screened a variety of solvents and bases to ensure the clean and diastereoselective formation of **73**. We first used the reaction between BocNH-^{Ox}Gly-NH_2 (**208**) and TfO-^{D}Ala-OBn (**222**) for our screening for a fast and clean reaction (Table 4).

Table 4 Optimization of Alkylation with Amine 208 and Triflate 222.

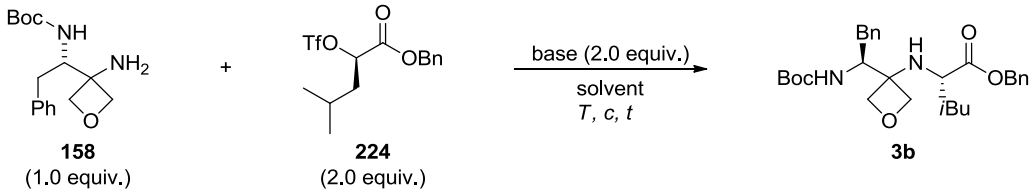


208 **222** **73a**

Entry	Base	Solvent	*T*	*c*	*t*	Yield
1	K_2CO_3	MeCN	r.t.	0.40 M	12 h	77%
2	DIPEA	MeCN	r.t.	0.40 M	24 h	78%
3	$NaHCO_3$	MeCN	r.t.	0.40 M	5 h	slow conversion
4	NaOAc	MeCN	r.t.	0.40 M	5 h	slow conversion
5	Na_2HPO_4	MeCN	r.t.	0.40 M	5 h	slow conversion
6	K_2CO_3	acetone	r.t.	0.40 M	19 h	mixture of products
7	K_2CO_3	EtOAc	r.t.	0.40 M	2 h	mixture of products
8	K_2CO_3	dioxane	r.t.	0.40 M	2 h	39%
9	K_2CO_3	THF	r.t.	0.40 M	2 h	68%
10	K_2CO_3	CH_2Cl_2	r.t.	0.40 M	5 h	slow conversion
11	K_2CO_3	DMF	r.t.	0.40 M	2 h	no product formed
12	K_2CO_3	DME	r.t.	0.40 M	2 h	no reaction
13	K_2CO_3, Bu_4NHSO_4 (0.2 equiv.)	MeCN	r.t.	0.40 M	2 h	69%

Up to this point the use of DIPEA or potassium carbonate in acetonitrile seemed promising (entries 1 & 2). We then moved to the BocNH-^{Ox}Phe-NH_2 (**158**)/TfO-^{D}Leu-OBn (**224**) system to ensure diastereoselectivity (Table 5).

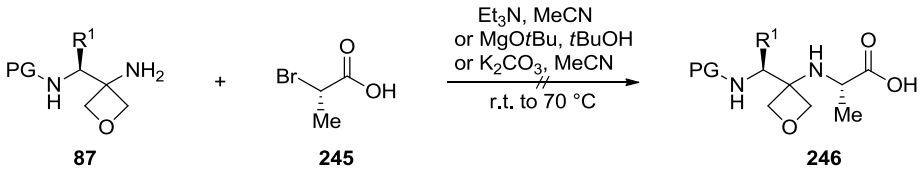
Table 5 Optimization of Alkylation with Amine 158 and Triflate 224.



Entry	Base	Solvent	*T*	*c*	*t*	Yield
1	DIPEA (2.2 equiv.)	MeCN	30 °C	0.40 M	24 h	62%
2	DIPEA	MeCN	r.t.	0.50 M	24 h	57%
3	DIPEA	MeCN	r.t.	0.27 M	38 h	55%
4	DIPEA	CH_2Cl_2	r.t.	0.27 M	113 h	29% incomplete conversion
5	K_2CO_3	MeCN	r.t.	0.40 M	14 h	61% mixture of diastereomers
6	proton sponge	MeCN	r.t.	0.4 M	19 h	56%
7	Et_3N	MeCN	r.t.	0.40 M	22 h	50% incomplete conversion
8	DBU	MeCN	r.t.	0.40 M	20 h	no product formed

We concluded that in our case the combination of acetonitrile as the solvent and DIPEA gives the best results (entry 1).

We also tried to use commercial bromoacids such as **245** as the alkylating agent to give dipeptide **246**, but no reaction was observed in these cases (Scheme 68).



Scheme 68 Attempted Use of Bromoacid 245 as the Alkylating Agent.

We then synthesized a variety of oxetanyl dipeptides **73** with diverse protecting group patterns, e.g. Boc/Bn (e.g. entries 1-6), Cbz/*n*Alkyl (entry 14) and

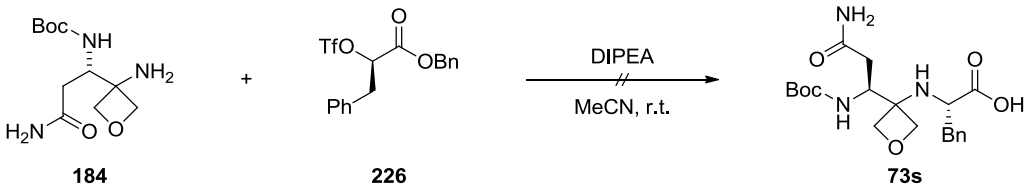
Cbz/*t*butyl (entry 11) as shown in Table 6. In the case of glycine derived alkylating agents we decided to use commercially available bromoacetates instead of the triflates.

Table 6 Synthesis of a Variety of Oxetanyl Dipetides 73.

Entry	Amine	PG	X	R^1	R^2	R^3	Product	Yield/%
1	**208**	Boc	Br	H	H	Bn	**73c**	75
2	**208**	Boc	OTf	H	Bn	Bn	**73d**	87
3	**145**	Boc	OTf	*i*Pr	Me	Bn	**73e**	79
4	**158**	Boc	OTf	Bn	*i*Bu	Bn	**73b**	62
5[b]	**158**	Boc	OTf	Bn	2-(*S*)-*sec*-Bu	Bn	**73f**	40
6	**158**	Boc	OTf	Bn	Bn	Bn	**73g**	67
7	**166**	Boc	Br	$CH_2(C_6H_4)$-4-OBn	H	Me	**73h**	87
8[b]	**122**	Boc	OTf	Me	*i*Pr	Bn	**73i**	56
9	**149**	Boc	OTf	*i*Bu	$CH_2(C_6H_4)$-4-OCbz	Me	**73j**	73
10	**179**	Cbz	Br	CH_2CO_2tBu	H	Bn	**73k**	90
11	**157**	Cbz	Br	Bn	H	*t*Bu	**73l**	98
12	**157**	Cbz	OTf	Bn	*i*Bu	Bn	**73m**	52
13	**157**	Cbz	OTf	Bn	*i*Bu	*t*Bu	**73n**	50
14	**165**	Cbz	Br	$CH_2(C_6H_4)$-4-OBn	H	Me	**73o**	72
15	**189**	Boc	OTf	"Pro"	Bn	Et	**73p**	60
16	**189**	Boc	Br	"Pro"	H	Bn	**73q**	87
17	**197**	Boc	OTf	CH_2StBu	Bn	Bn	**73r**	39

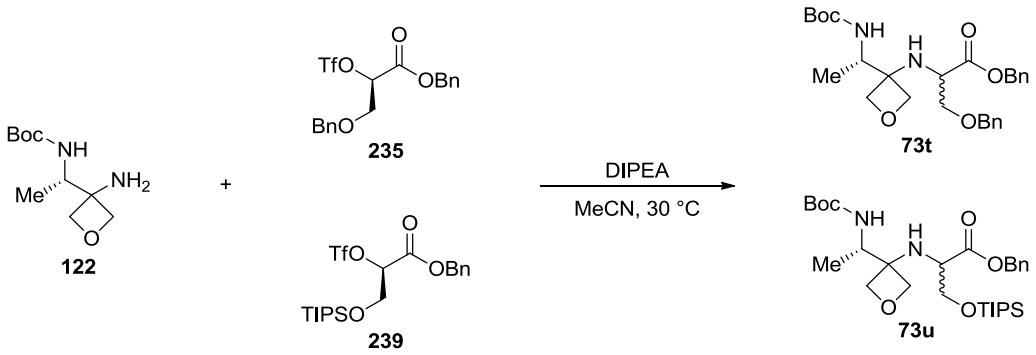
[a]Example conditions: oxetane (1.0 equiv.), triflate (2.0 equiv.), DIPEA (2.2 equiv.), [b] 60 °C

Unfortunately, the reaction of BocNH-^{Ox}Asn(NH_2)-NH_2 (**184**) as the diamine with TfO-^{D}Phe-OBn (**226**) did not furnish the desired dipeptide **73s** but led to a complex mixture of unidentified products (Scheme 69). This might be due to reactions of the unprotected primary amide with the triflate.



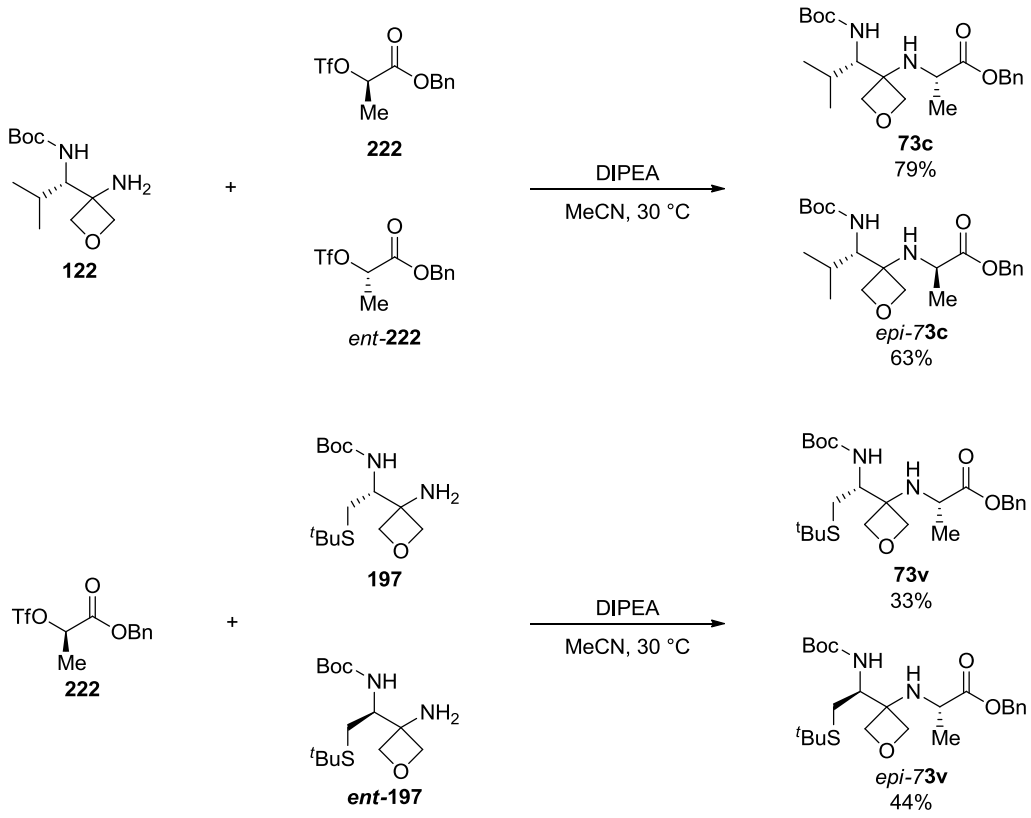
Scheme 69 Failed Synthesis of 73s from Amine 184.

When TfO-^{D}Ser(OBn)-OMe (**235**) was used as the alkylating agent in the reaction with diamine **122** the product **73t** was formed as a 3:1 mixture of diastereomers. We reasoned that this might due to an anchimeric effect of the ether oxygen in the side chain. Hence, the TIPS-protected triflate **239** was used. Unfortunately, also in this case the product **73u** was formed as a 3:1 mixture of diastereomers.



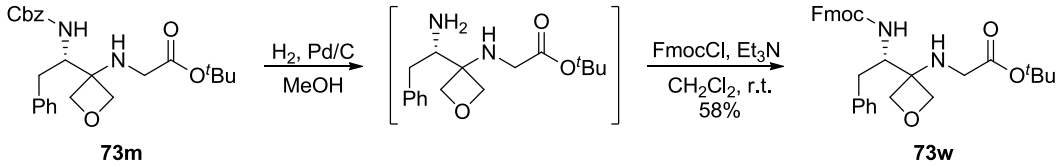
Scheme 70 Use of Serine Derived Triflates 235 and 239.

Additionally, we showcased the versatility of our synthetic building block approach to furnish all possible four diastereomers of the oxetanyl dipeptide and hence opening the door to use oxetanyl peptides in combination with other peptidomimetic approaches such as D-amino acids and retro-inverso peptides. We hence synthesized two diastereomers of BocNH-^{Ox}Ala-Ala-OBn (**73c**) using either enantiomer of the triflate **222** and two diastereomers of BocNH-^{Ox}Cys(S*t*Bu)-Ala-OBn (**73v**) using either enantiomer of the diamine **197**.



Scheme 71 Sythesis of Diastereomers of 73c and 73v.

Finally, we changed the protecting group on dipeptide **73l** from Cbz to Fmoc to yield **73w** in 58%. This would enable us to utilize Fmoc/*t*butyl solid phase peptide synthesis with our building blocks (Scheme 72).



Scheme 72 Synthesis of Fmoc-protected Dipeptide 73w.

First structural insight for oxetanyl peptides could be obtained from the X-Ray crystal structure of BocNH-^{Ox}Gly-Phe-OBn (**73d**). When compared to the closest natural dipeptide H_2N-Gly-Phe-OH of which the X-Ray crystal structure is known, a striking difference is observed in the overall 3D-structure. In the natural dipeptide, the atoms N^{α}, C^{α}, C(O), $N^{\alpha'}$, $C^{\alpha'}$, and $C^{\beta'}$ are all in plane with torsional angles close to 180° (ϕ_1=162°, ϕ_2=179°, ϕ_3=179°). In contrast, in the oxetanyl dipeptide **73d** only the [C^{Ox}, $N^{\alpha'}$; $C^{\alpha'}$, $C^{\beta'}$] plane is conserved with a

torsional angle of ϕ_3=176°. This can be attributed to a smaller (C^{α}, C^{Ox}, $N^{\alpha'}$) angle of ψ_1=111° in **73d** compared with the (C^{α}, C(O), $N^{\alpha'}$) angle in the natural dipeptide of ψ_1=116° and the increased steric repulsion from the extra two carbon atoms of the oxetane moiety. The conformational bias introduced by the oxetane has previously been investigated by WUITSCHIK *et al.*[101] and is confirmed by our findings. The twisted conformation of **73d** furthermore leads to a reduced C^{α}-$C^{\alpha'}$ distance of 3.0 Å compared to 3.8 Å in the natural compound (Figure 18).

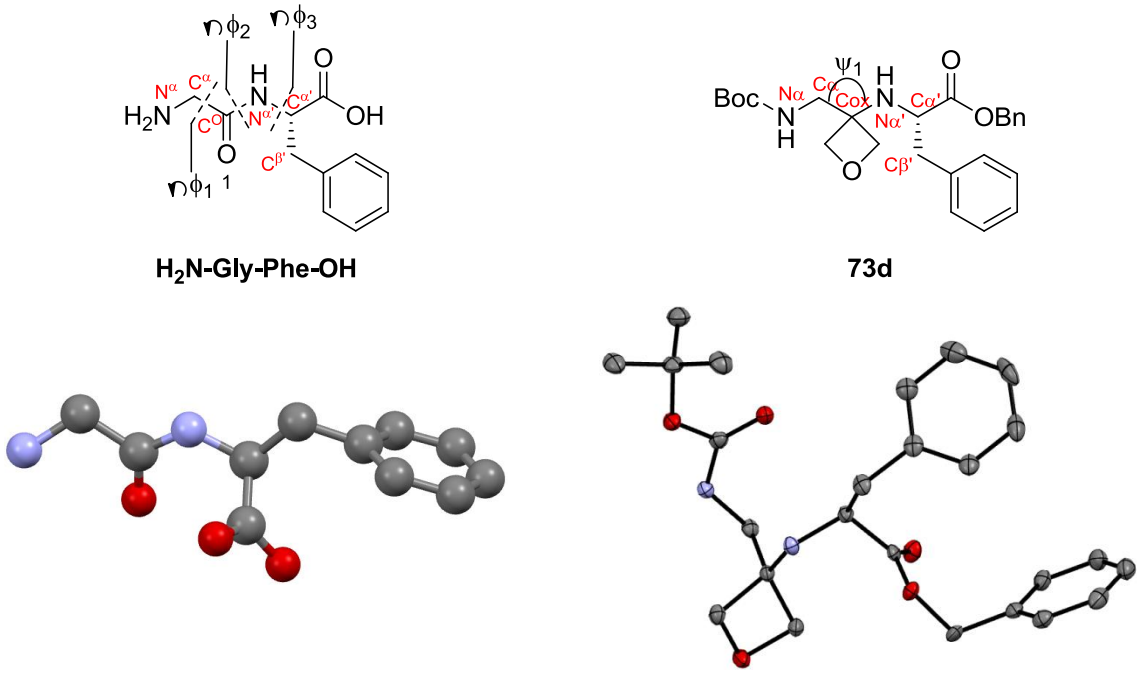


Figure 18 Comparison of X-Ray Crystal Structures of 73d and H_2N-Gly-Phe-OH.

2.4 Incorporation of Building Blocks 73 into Larger Peptides

With a diverse toolbox of oxetanyl dipeptides **73** in hand we decided to synthesize larger oxetane containing peptides to evaluate our peptidomimetics. We postulated that the incorporation of an oxetane as a replacement for a carbonyl group in the backbone of a peptide would lead to an enhanced hydrolytic stability thereby conserving biological activity.

2.4.1 Synthesis of Leu-Enkephalin Analogues

As a first example for a bioactive peptide we wanted to test our concept of oxetanyl peptidomimetics on, we chose the prominent endogenous opioid neurotransmitter Leu-Enkephalin (**247a**).

Leu-Enkephalin (**247a**) is a pentapeptide with the sequence H_2N-Tyr-Gly-Gly-Phe-Leu-OH and has a strong analgesic effect by binding to the δ- and μ-opioid receptors with nanomolar affinity.[39] We decided to synthesize four oxetanyl analogues **247b-e** where a different carbonyl is displaced by an oxetane in every peptidomimetic (Figure 19). This would enable us to thoroughly study the pharamcological effect of this bioisosteric substitution relative to its position in the sequence.

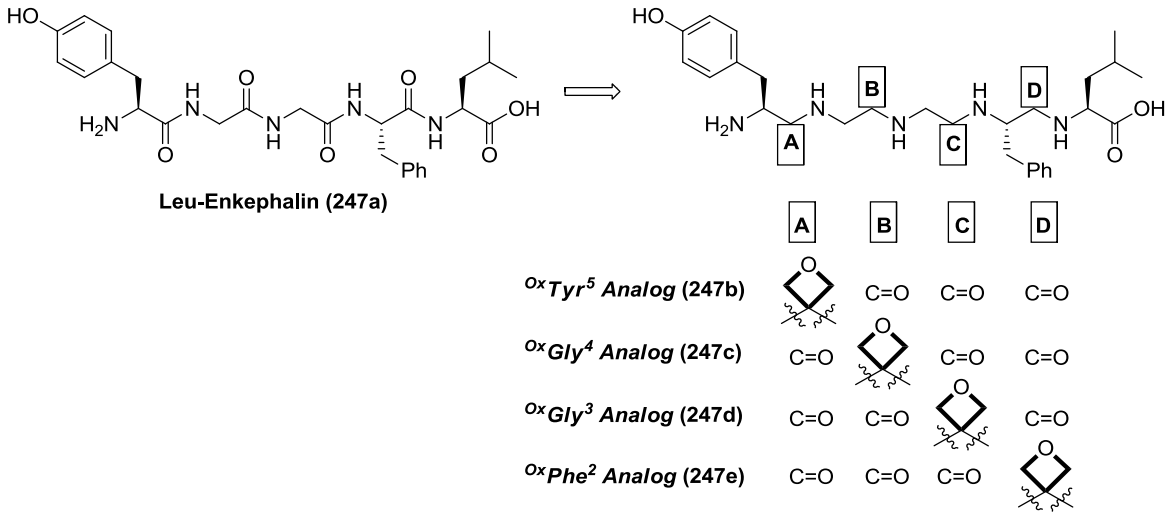
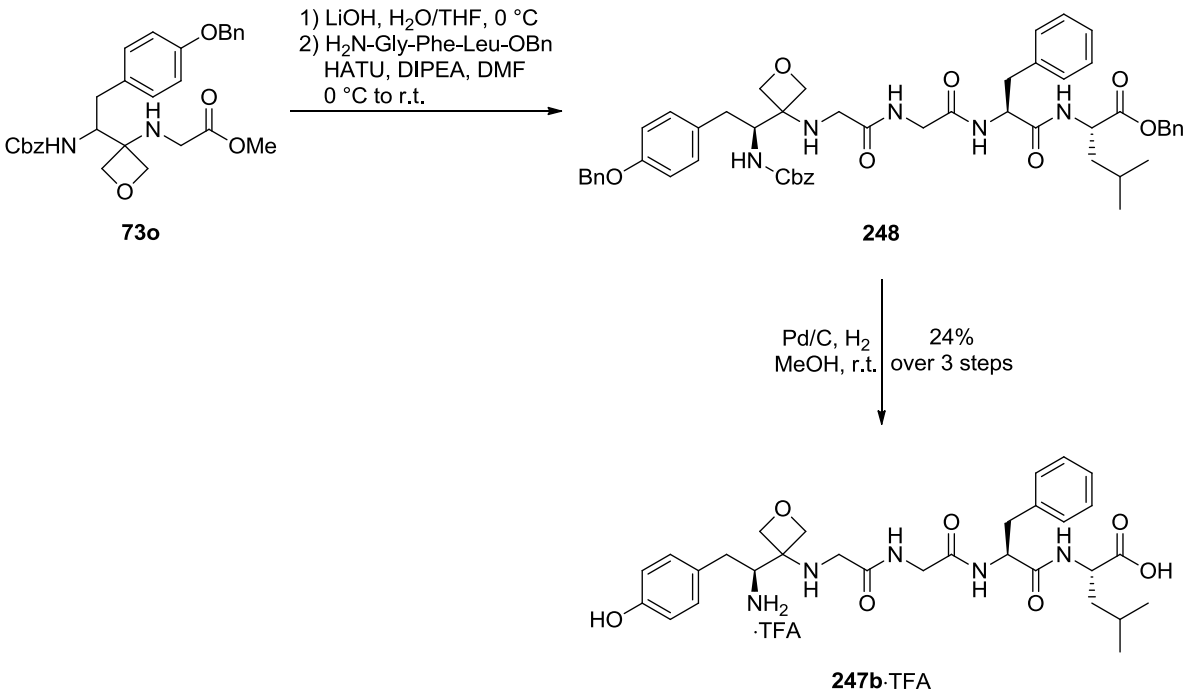


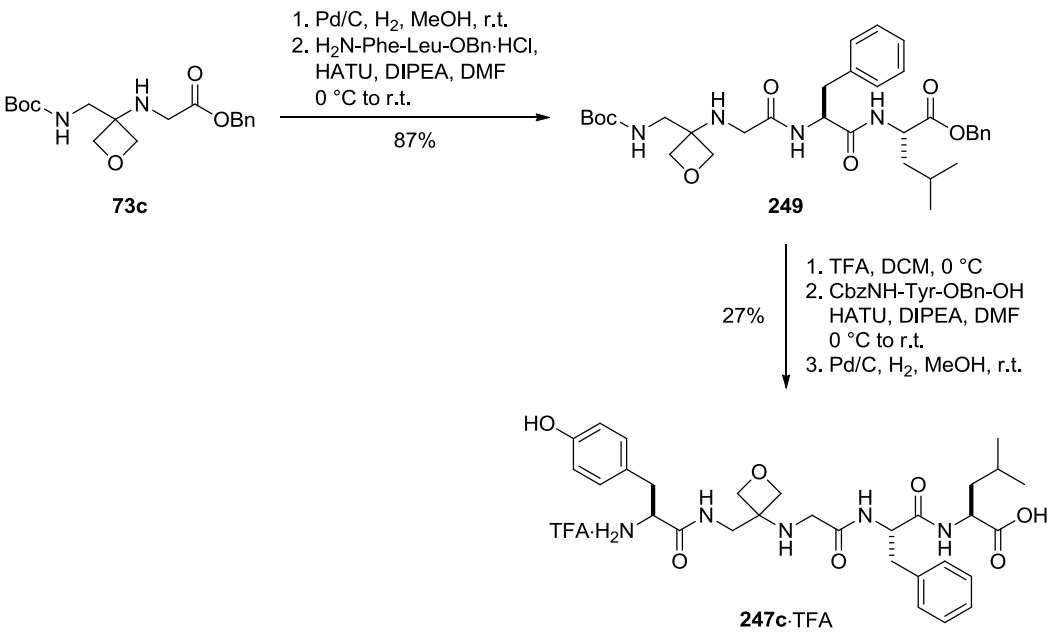
Figure 19 Leu-Enkephalin (247a) and Oxetanyl Analogues 247b-d.

We started our efforts with the synthesis of ^{Ox}Tyr analog **247b**. We envisioned final deprotection of the peptide by hydrogenation of benzyl ethers and esters as well Cbz groups. Hence we used CbzNH-^{Ox}Tyr(OBn)-Gly-OMe (**73o**) as the oxetanyl building block. HATU mediated coupling with the natural *C*-terminal tripeptide[166] cleanly provided fully protected intermediate **248** which was converted into the the free peptide **247b**. The desired product **247b** was obtained as its TFA-salt after purification by preparative HPLC in 24% from **73o** (Scheme 73).



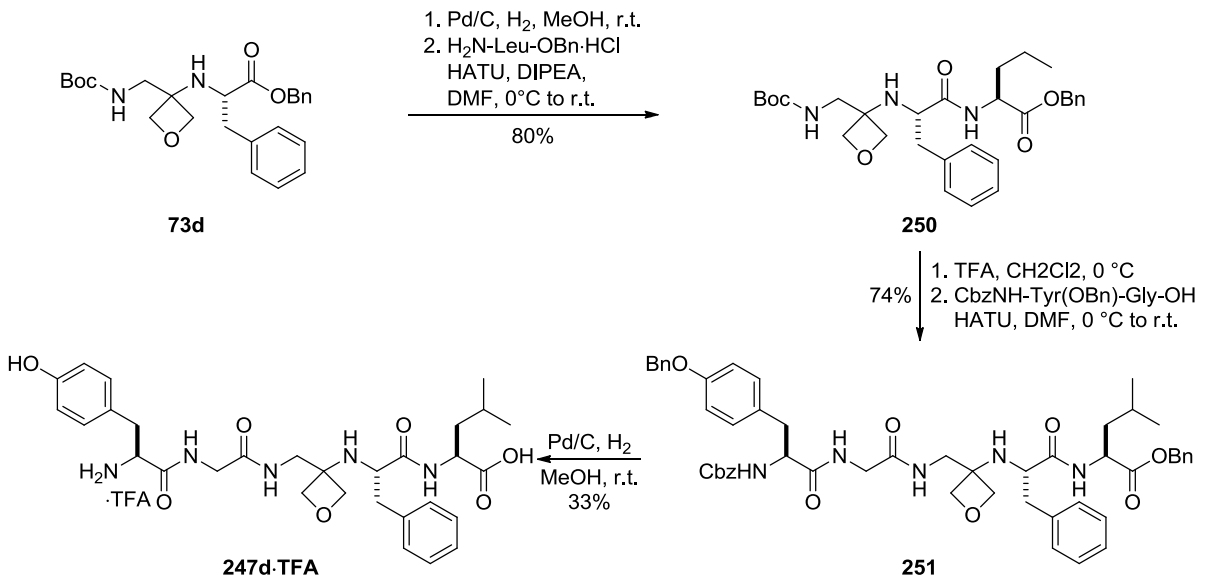
Scheme 73 Synthesis of 247b.

Next we turned our attention to the synthesis of the ^{Ox}Gly^{4} analog **247c**. This time BocNH-^{Ox}Gly-Gly-OBn **73c** was the oxetanyl building block of choice. We realized that *N*-terminal deprotection of the oxetanyl dipeptides could lead to oxetanyl ketopiperazine formation.[167] Therefore, we decided to couple into the *C*-terminal direction with the natural dipeptide H$_2$N-Phe-Leu-OBn.[168] The corresponding tetrapeptide **249** was obtained in 87% yield and was then coupled with CbzNH-Tyr(OBn)-OH to give the fully protected pentapeptide. The desired product **247c** was again obtained as the corresponding TFA-salt after global deprotection by hydrogenolysis and subsequent purification by preparative HPLC in 27% yield from **249** (Scheme 74).



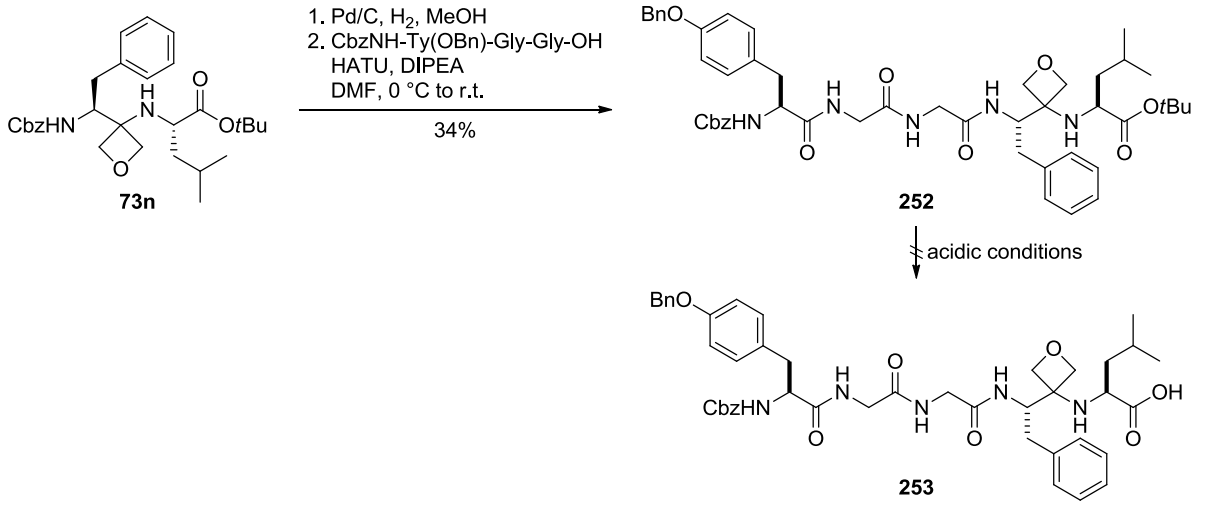
Scheme 74 Synthesis of 247c

The third analog **247d** with the $^{Ox}Gly^{3}$ modification was synthesized starting from oxetanyl dipeptide **73d**. Again, first the C-terminal coupling was performed this time with H_2N-Leu-OBn to give tripeptide **250** in 80% yield. Subsequently, the *N*-terminal dipeptide CbzNH-Tyr(OBn)-Gly-OH[169] was attached to yield the fully protected pentapeptide **251** in 74% yield. Finally, global deprotection was achieved by hydrogenation and the desired product **247d**·TFA was isolated in 33% yield after purification by preparative HPLC.



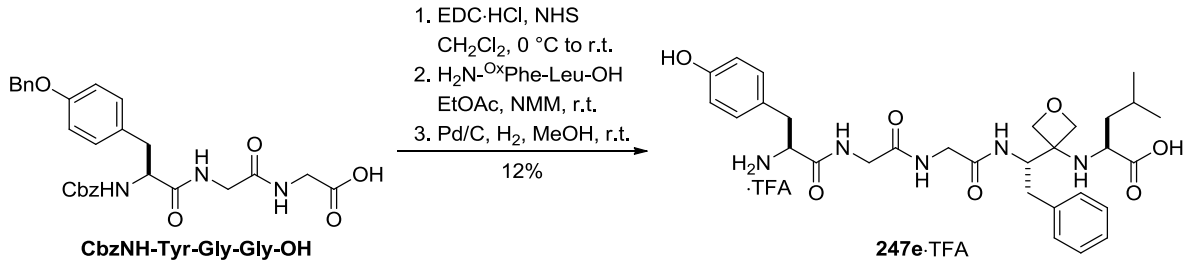
Scheme 75 Synthesis of 247d.

We then pursued the synthesis of the last Leu-Enkephalin analog **247e** carrying the ^{Ox}Phe^{2} modification. We first envisioned the use oxetanyl dipeptide **73n** containing a *t*-butyl ester to avoid diketopiperazine formation upon deprotection of the Cbz-group. Indeed, fully protected pentapeptide **252** was obtained by coupling with the corresponding *N*-terminal tripeptide CbzNH-Tyr(OBn)-Gly-Gly-OH.[170] Unfortunately, deprotection of the *t*-butyl ester to give **253** under acidic conditions only led to the decompostition of the starting material.



Scheme 76 Fist Generation Approach to 247e.

Hence, we chose a different peptide coupling strategy based on an NHS-ester mediated coupling between the CbzNH-Tyr(OBn)-Gly-Gly-OH[170] fragment and the unprotected oxetanyl dipeptide originating from **73m**. Finally, the desired product **247e**·TFA could be obtained in 12% yield over three steps after purification by preparative HPLC.



Scheme 77 Synthesis of 247e.

2.4.2 Serum Stability of Leu-Enkephalin Analogues 247a-e

We postulated that the introduction of oxetanes as bioisosters for carbonyl groups in the backbone of peptides could improve their metabolic profile and especially protect them against hydrolysis by proteases. A valuable indicator for the metabolic stability of a pharmaceutical is the stability in blood serum. Leu-Enkephalin **247a** is rapidly degraded in human serum with a half-life time of about 12 min.[171] The mechanism of its hydrolysis has been extensively studied before.[172,173] Leu-Enkephalin (**247a**) contains to major cleavage sites: The Tyr^5-Gly^4 bond is most labile to proteolytic cleavage. The Gly^3-Phe^2 site is also readily cleaved by proteases although the rate of hydrolysis is much slower at this position. We hence expected that the half-life times in human serum of the synthesized analogues **247b-e** could be a valuable measure for the ability of the oxetane to prevent proteolysis at the substituted site and also protect neighboring amide bonds. Many procedures for plasma and serum stability assays have been developed. We chose to use a slightly modified protocol recently published by ROCHON *et al*.[174] Therein, the peptide sample is dissolved in glucose-containing HBSS buffer and then mixed with the same volume of preincubated commercial human serum at 37 °C. The mixture is then kept at this

temperature for different times. After treatment with MeOH to precipitate all active proteins and centrifugation, the supernatant is analyzed by analytical HPLC for the remaining peptide content (Figure 20).

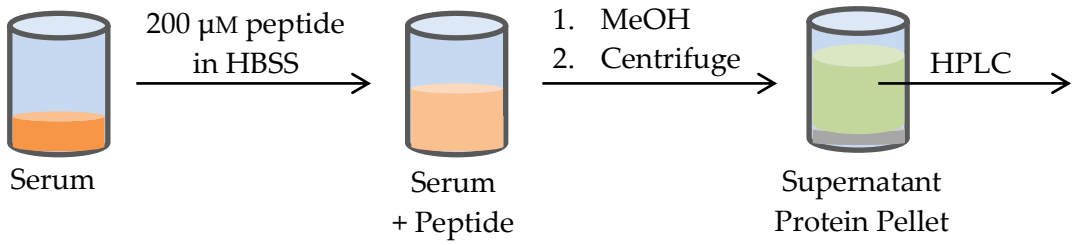


Figure 20 Serum Stability Assay.

Before starting the measurements in serum, we first ensured the detection of the natural Leu-Enkephalin (**247a**) and oxetanyl peptide **247c** by recording a concentration row.

Starting at the initial concentration in the assay of 33.3 µM, we were able to detect both compounds at least down to a 32-fold dilution to 0.52 µM. We also confirmed, that the area under the curve is a valid and reproducible, directly proportional measure of the peptide concentration (Figure 21).

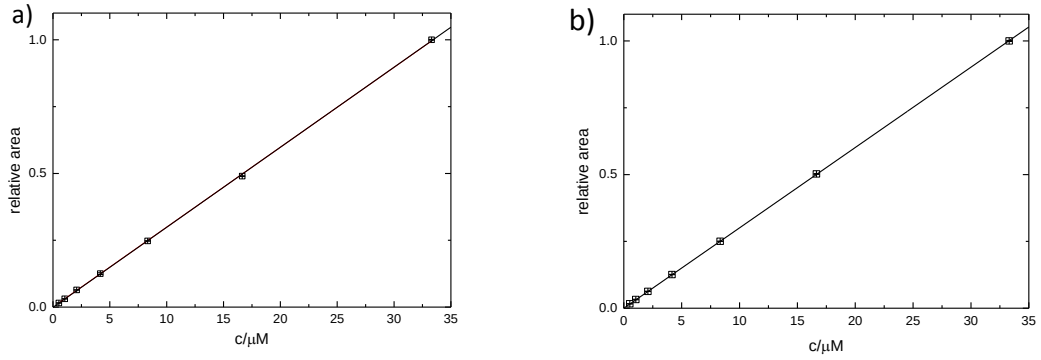


Figure 21 Area under the Curve Relative to the Value at the Starting Concentration against Concentration is Displayed: a) 247a, b) 247c (n=3, mean±σ).

Next, the natural peptide **247a** and the oxetanyl analogues **247b-e** were incubated in human serum for up to one hour. The remaining peptide concentration was determined by analytical HPLC at eight time points for **247a**

and **247d-e** as well as at two time points for **247b-c**. The area under the curve of the peak corresponding to the peptide was determined and compared to the concentration at *t*=0 (Figure 22).

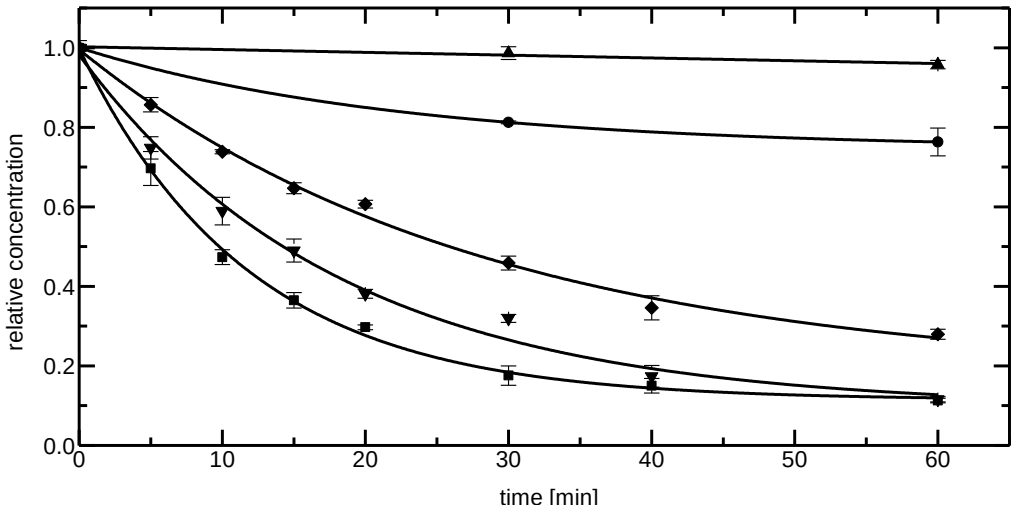


Figure 22 Stability of Leu-Enkephalin (247a, ■) and its Analogues (247b, ●; 247c, ▲; 247d, ▼; 247e, ◆) in Human Serum during 1 h. Relative concentration as mean±SEM against time is displayed.[175]

We found that natural Leu-Enkephalin (**247a**) is readily degraded in human serum with a half-life time of about ≈10 min as previously published.[171] The ^{Ox}Gly^{3} analog **247d** shows a similar although slightly increased half-life time of ≈15 min. This can be reasoned by the hydrolytic stability of the otherwise labile Gly^{3}-Phe^{2} site due to the oxetane substitution. ^{Ox}Phe^{2} analog **247e** is even more stable towards degradation with a significantly increased half-life time of ≈26 min. This suggests that the *C*-terminal substitution at the Phe^{2}-Leu^{1} site disturbs the recognition of the peptide by proteases to some extent. However, oxetane analogues **247b** and **247c** show increased half-life times and are not significantly degraded over the course of one hour. The remarkable stability of **247b** can easily be explained by the protection of the most labile Tyr^{5}-Gly^{4} cleavage site by the oxetane substitution. The resistance of **247c** can again only be explained by an interference of the oxetane in the recognition process by proteases. In **247c** the oxetane substitution is located in between the two main cleavage sites of Leu-Enkephalin (**247a**) and might protect both of them due to

steric or conformational reasons. We were intrigued by the highly increased stability of **247b** and **247c** although fully aware, that infinite stability is not at all a favorable property for any bioactive molecule. We therefore extended our studies on the serum stability to the time span of 24 h (Figure 23).

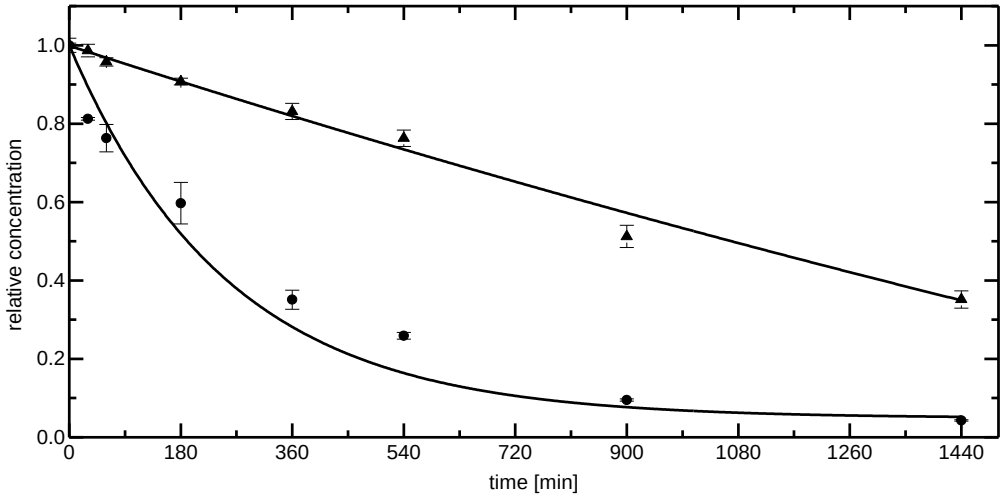


Figure 23 Stability of Oxetnayl Analogues (247b, ●; 247c, ▲) in Human Serum during 24 h. Relative concentration as mean±SEM against time is displayed.[176]

Indeed, also analogues **247b** and **247c** are slowly degraded in human serum with estimated half-life times of ≈3.2 h and ≈18 h respectively.

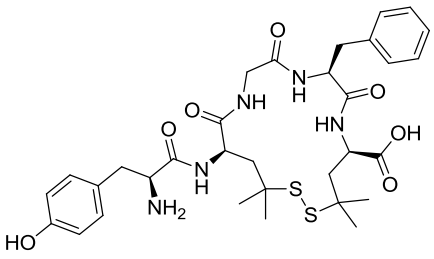
In summary, the introduction of oxetanes as a replacement for backbone carbonyl groups in peptides can be used to significantly increase the stability of the parent compounds. Careful choice of the site of substitution can be a valuable tool to tune the metabolic stability of a peptide drug and hence overcome its intrinsically insufficient pharmacokinetic profile.

2.4.3 Binding Affinity of Leu-Enkephalin Analogues 247a-e[177]

Up to this point, we showed that oxetanyl peptidomimetics can be used to increase the metabolic stability of the parent peptide. We reasoned that this might partially be due to a steric or conformational constraint introduced with the oxetane that hampers the recognition of the peptide by proteases. We hence asked the question if the oxetane mimics would still exhibit the same biological

activity as the parent compound. Leu-Enkephalin (**247a**) has a strong analgesic effect by binding at the μ- and δ-opioid receptors (μ<δ). The binding constant for the δ-opioid receptor was reported before as K_i = 8.05 nM[39] and K_i = 4 nM[178] depending on the assay conditions.

Therefore, we decided to study the binding affinity of oxetanyl peptides **247b-e** at the δ-opioid receptor with a radioligand binding assay. For the assay used in this study, the membrane fraction from homogenized rat brains was isolated. The protein content was then determined by the method developed by BRADFORD[179] and STOSCHECK[180]. The obtained solubilized membrane proteins including the δ-opioid receptor were subsequently incubated with the ligand peptide sample and the specific radioligand [^{3}H]-DPDPE (**254**), a Leu-Enkephalin mimic (Figure 24).



254

Figure 24 The Structure of DPDPE.

After rapid filtration and drying, a solid scintillator was melted onto the obtained filtermat. The radioactivity corresponding to the receptor-bound radioligand was measured with a scintillation analyzer. The peptide sample competes against the radioligand for receptor binding. Hence, the amount of remaining radioligand is an indirect measure of the bound tested ligand. The IC_{50}-value for each compound was determined by a logistic fit of the scintillation against concentration plot and subsequently converted into K_i values with the equation of CHENG and PRUSOFF[181].

First, the assay was carried out in the presence of phenylmethane-sulfonylfluoride (PMSF), a non-selective serine-protease inhibitor to prevent the

degradation of the samples and the radioligand. Under these conditions, analogues **247d** and **247e** showed a nanomolar binding affinity towards the δ-opioid receptor. Unfortunately, the value for natural Leu-Enkephalin (**247a**) could not be determined. This was attributed to a rapid degradation by proteolysis of the peptide in the rat brain preparation. RAYNOR *et al.*[178] reported the use of a mixture of additives including protease inhibitors to successfully measure the binding affinity of **247a** in a similar assay. We hence repeated our experiment in the presence of a commercial protease inhibitor cocktail (SIGMAFAST®, Sigma-Aldrich Biochemicals). Under these modified conditions the value for **247a** was determined as K_i = 9.2±2.3 nM, which is consistent with previously reported literature values mentioned above.[39,178] Analog **247e** shows a similar binding affinity of K_i = 43±9 nM. Also, analog **247d** still binds with a remarkable K_i = 157±15 nM. However, oxetanyl peptdes **247b** and **247c** do not show any affinity towards the δ-opioid receptor up to a concentration of 1 µM (Table 7).

Table 7 Binding Affinities of 247a-e.

Entry	Compound	K_i/nM[a] only PMSF	K_i/nM[b] with SIGMAFAST®
1	**247a**	> 1000	9.2±2.3
2	**247b**	> 1000	> 1000
3	**247c**	> 1000	> 1000
4	**247d**	176	157±15
5	**247e**	57	43±9

a n=1, b n=3, mean±SEM

In summary, oxetanyl peptides **247d** and **247e** still bind to the δ-opioid receptor with a similar affinity as the parent natural Leu-Enkephalin (**247a**). Even when the natural compound **247a** is readily degraded by proteases in the absence of a protease inhibitor, **247d** and **247e** still show the same binding affinity. These two analogues were the least stable in human serum but they still seem to resist the different metabolic degradation profile in rat brain. This is another indicator, that

the introduction of oxetanes can be a valuable tool to suppress proteolytic cleavage of peptide drugs and at the same time retain their pharmacological profile.

YAMAZAKI *et al.* suggested, that opioid peptides can be divided into a messaging sequence consisting of the *N*-terminal tetrapeptide and an address position consisting of the *C*-terminal residue. Furthermore, the messaging sequence contains two pharmacophoric residues (P) at each end and a two amino acid spacer (S) in between (Figure 25).

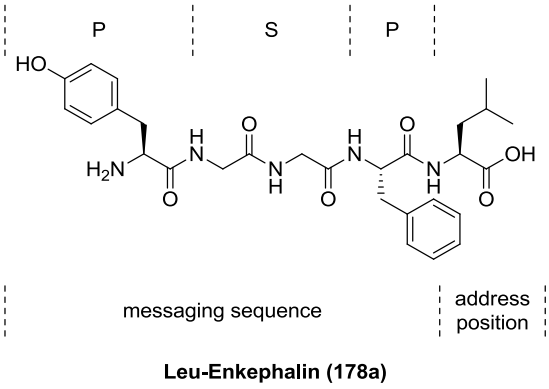


Figure 25 Pharmacophore Analysis of 247a.

The results 54 in Table 7 suggest that an oxetane substitution is possible both between the spacer and the second pharmacophoric residue of the messaging sequence (**247d**) as well as at the amide bond between the messaging sequence and the address position (**247e**) emphasizing its value as a carbonyl bioisostere.

2.4.4 *In vitro* Activity of Leu-Enkephalin Analogues 247a-e[182]

We showed that two of the synthesized oxetanyl peptides (**247d** and **247e**) still bind to the δ-opioid receptor with nanomolar affinities. However, an indication that their agonistic activity is also retained is still missing. We therefore decided to conduct a commercially available β-Arrestin 2 recruitment assay on cells overexpressing the δ-opioid receptor.

In the classical model of G-protein coupled receptor (GPCR) function, after activation of the receptor by a ligand, G-proteins are responsible for intracellular

signaling. The recruitment of β-Arrestin for example controls desensitization by internalization of the receptor. In the assay setup developed by DiscoveRx and marketed as PathHunter™ assays, the GPCR of interest is attached to a low-affinity peptide, called ProLink™ derived from the *N*-terminal sequence of β-galactosidase from *E. coli*. Additionally, β-Arrestin is connected to an ω-deletion mutant of β-galactosidase.[183] Upon recruitment of the modified β-arrestin, β-galactosidase can reconstitute in an enzyme fragment complementation reaction. The use of a low-affinity derivative of β-galactosidase on the GPCR side is important to make sure, that the reconstitution is triggered only by activation of the receptor and subsequent reversible recruitment of β-Arrestin and hence the close proximity of the second β-galactosidase fragment and not by a high intrinsic binding affinity. The recombination of both β-galactosidase fragments after β-Arrestin recruitment leads to the construction of a holoenzyme that is able to hydrolyze a given substrate into a luminescent probe which can be detected with a plate reader (Figure 26).[184,185] This assay concept ensures that only the receptor-specific agonistic action at the overexpressed modified δ-opioid receptor is measured.

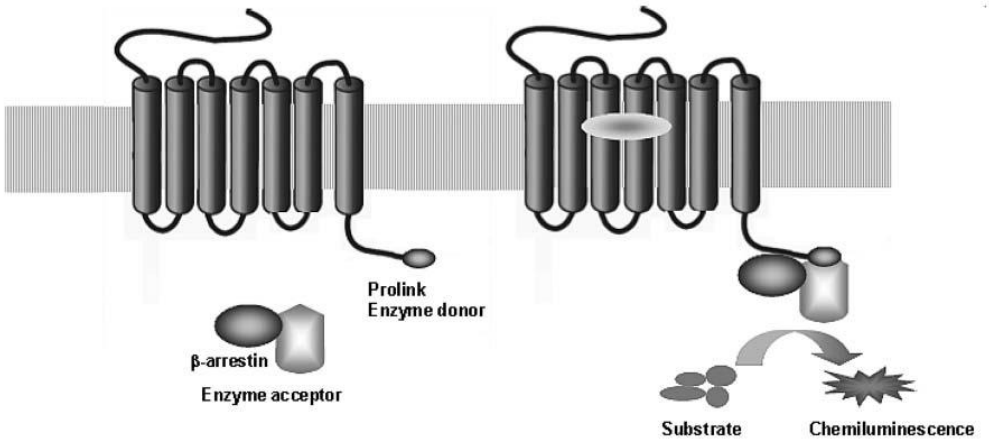
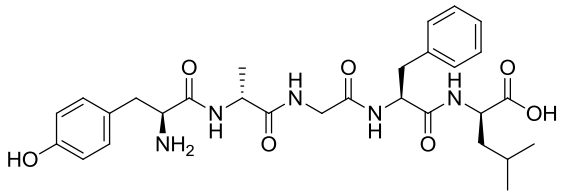


Figure 26 Principle of β-Arrestin Recruitment Assay, adopted from Van der Lee *et al.*[184]

The agonistic activity of peptidomimetics **247b-e** as well as of the natural compound **247a** was determined under standard assay conditions as provided

by DiscoveRx. In this case, DADLE (**255**), another Leu-Enkephalin analogue, was used as the positive control (Figure 27).



255

Figure 27 The Structure of DADLE.

The obtained values of luminescence were plotted against concentration and evaluated by a logistic fit (Figure 28). Natural Leu-Enkephalin (**247a**) showed an IC_{50} = 19.7±2.82nm which is consistent with previously reported values.[186,187] However, between the oxetanyl analogues, only **247b** and **247e** showed an agonistic activity at concentrations up to 1 mM. Somewhat in line with the results from the affinity assay (K_i = 43±9 nM) described above (chapter 2.4.3), **247e** showed a significant $IC_{50} \approx 5.6$ µM. Contrarily, **247d** which also showed a nanomolar affinity (K_i = 157±15 nM), did not exhibit any effect in the activity assay. Here, only **247b** showed a weak IC50 ≈ 54 µM outside the range of the affinity assay.

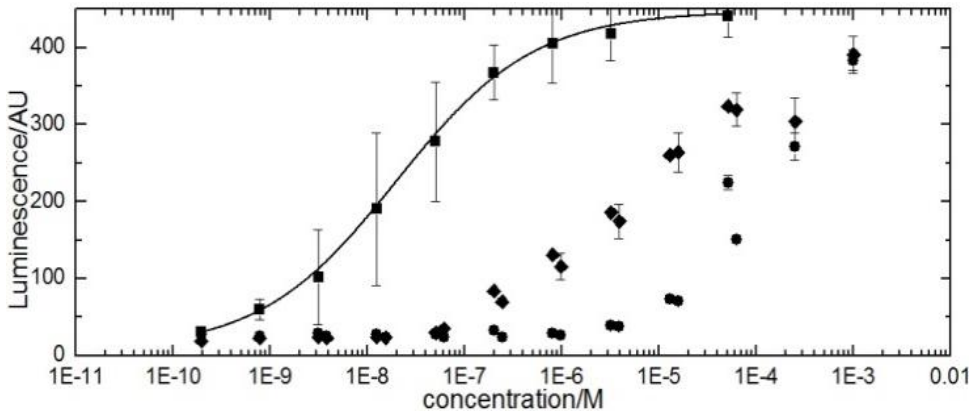


Figure 28 Activity of Leu-Enkephalin (247a ■) and its Analogues (247b (●),247e (◆)) at the δ-Opioid Receptor Measured by β-Arrestin Assay. (n=2, measured in triplicates, data shown as mean ± SD)

These striking differences between the data obtained in the affinity and the activity assay can be explained by a different mode of action of the oxetanyl

analogues compared to **247a**. Since the activity of **247c** and **247d** is significantly lower than their affinity towards the δ-opioid receptor, we suggest that they are a full and partial antagonist respectively. This would indicate, that the incorporation of an oxetane can also be used to fine tune the mode of action of a peptide drug. Especially in the field of pain release and morphine analogs, partial and full antagonists have been subject of extensive research to reduce the abuse potential of these drugs by overriding the analgesic effect at high doses.[188-191] Further studies to confirm the mode of action of these peptidomimetics will be conducted in the near future.

2.4.5 *In vivo* Activity of Oxetanyl Peptidomimetic 247e[192]

From the affinity and activity studies outlined above (chapters 2.4.3 to 2.4.4) we concluded, that ^{Ox}Phe^{2} analog **247e** can bind most efficiently and exhibit the highest agonistic effect at the δ-opioid receptor. We therefore decided, to test this compound in an *in vivo* setting. We chose the hotplate test to measure the analgesic effect of **247e** in mice. This assay was originally developed by EDDY and LEIMBACH in 1952.[193] The setup is very simple: A hotplate is heated to a stable temperature between 50 °C and 60 °C. Then the mouse is placed on the plate and the time until typical symptoms of pain are observed is measured. EDDY and LEIMBACH showed in an experiment with 2000 mice, that the response time is normally distributed. They measured a mean interval of $t = 9.51 \pm 1.02$ s.[193] Later CASARRUBEA *et al.* carefully described the different behavioral symptoms of rats in the hot plate test.[194]

In our assay, we chose *i.v.* administration into the tail vein of the respective sample to correlate the results to serum stability. We compared the analgesic effect of **247e** to the values obtained for the natural peptide **247a**, the strong analgesic agent morphine as a positive control and the buffer vehicle as a negative control.

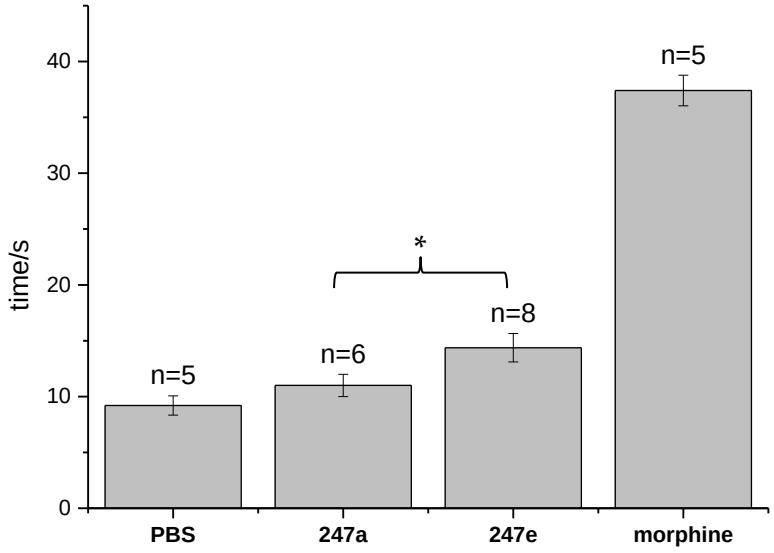


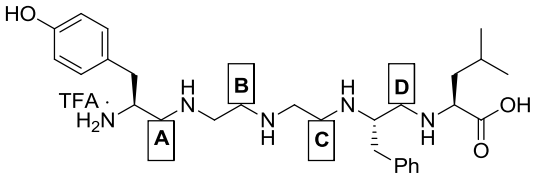
Figure 29 Hotplate Test, Time is Displayed as Mean±SEM (n=number of mice, c = 12.5 mg/kg for 247a and 247e, c = 10.0 mg/kg for morphine, * p < 0.05).

Indeed, administration of oxetanyl peptide **247e** leads to a significantly increased residence time (t =14 s) on the hot plate compared to **247a** (t = 11 s) as evaluated by a t-test. **247a** does not show any measurable effect under these conditions compared to the negative control (t = 9.2 s) which can again be attributed to a rapid proteolytic degradation. The value obtained for the negative control is consistent with previously reported data.[195]

2.4.6 Summary of Pharmacological Properties of 247a-e

In this work, Leu-Enkephalin (**247a**) and oxetanyl analogues **247b-e** have been extensively studied. First, their metabolic stability in human serum was determined. Natural Leu-Enkephalin (**247a**) showed a half-life time of 11 min whereas the half-life time for **247b-e** was increased to up to 18 h. Furthermore the binding affinity at the δ-opioid receptor was determined. The results indicate that analogues **247d** and **247e** still exhibit nanomolar binding affinities. Additionally, the agonistic activity at the δ-opioid receptor was measured in a cellular luminescence assay. We observed that only **247e** showed a considerable micromolar activity. We attributed the clear discrepancy between the results from the affinity and those from the activity assay to a modified mode of action

of the oxetanyl analogues and speculated that they might be partial or full antagonists. Nevertheless, the analgesic potential of **247e** was evaluated by a hotplate test in mice. The in vivo experiment showed that **247e** in contrast to **247a** shows a mild analgesic effect after *i.v.* administration indicating that it is active in the brain and not rapidly degraded in the blood stream. All pharmacological data obtained is summarized in Figure 30.

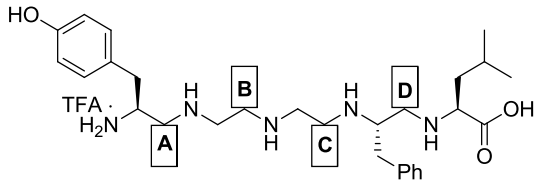


	A	B	C	D	Serum Half-life	δ-Affinity K_i/nM	δ–Agonist IC_{50}/μM	Hot Plate Test
***Leu-enkephalin* (247a)**	C=O	C=O	C=O	C=O	≈ 10 min	9.2	0.020	11 s
***Tyr*^{5}*(Ox) Analog* (247b)**		C=O	C=O	C=O	≈ 3.2 hrs	>1000	54	
***Gly*^{4}*(Ox) Analog* (247c)**	C=O		C=O	C=O	≈ 18 hrs	>1000	>1000	
***Gly*^{3}*(Ox) Analog* (247d)**	C=O	C=O		C=O	≈ 15 min	157	>1000	
***Phe*^{2}*(Ox) Analog* (247e)**	C=O	C=O	C=O		≈ 26 min	43	5.6	14 s

Figure 30 Summary of Pharmacological Data of 247a-e.

A comprehensive comparison of our Leu-Enkephalin analogues **247b-e** to previously reported mimics is difficult in view of the vast number of publications in this area. However, most of the studies do not focus on amide bond surrogates, but are rather based on inversion of the stereocenters (e.g. DADLE), side-chain to side-chain cyclizations (e.g. DPDPE) or side-chain to *C*-terminus cyclization[196] and side-chain modifications.[174,197,198] Comparably few studies concentrated on the systematic substitution of each amide bond with an amide bond surrogate. In this chapter we will focus our comparison on two recently published studies with *E*-alkenes (**256a-d**)[199], esters (**257a-d**) and *N*-methyl amides (**258a-d**)[174](Table 8). Earlier reports of similar systematic substitutions can e.g. be found from the groups of Houghten[200], Von Voigtlander[201], Belleau[202] and Liskamp[203].

Table 8 Comparison with other Leu-Enkephalin Mimics.



Entry		A[b]	B[b]	C[b]	D[b]	δ-Affinity Ki/nm	Serum Half-Life[a]
1	**256a**	⟋⟍				13.1	
2	**256b**		⟋⟍			761	
3	**256c**			⟋⟍		587	
4	**256d**				⟋⟍	196	
5	**257a**	C(O)O				150	
6	**257b**		C(O)O			303	
7	**257c**			C(O)O		34	
8	**257d**				C(O)O	11.9	72%
9	**258a**	C(O)NMe				1190	
10	**258b**		C(O)NMe			>5000	
11	**258c**			C(O)NMe		533	
12	**258d**				C(O)NMe	12.6	230%

a In % compared to the half-life time of **247a** in the respective study, b empty box = regular amide bond.

A substitution of the *N*-terminal peptide bond with an alkene (**256a**) leads to the retention of binding affinity at the δ-opioid receptor compared to **247a**. However, the same substitution leads to a significant decrease in affinity at all other positions. In contrast, in our mimics **247b-e** an oxetane substitution at the *N*-terminal two amide bonds was not tolerated and only substitution at the C-terminal two amide bonds still led to peptidomimetics with a nanomolar binding affinity. A similar result is obtained, when an ester is used as the amide bond surrogate. Like in our case oxetanyl peptides **247d** and **247e**, depsipeptides **257c** and **257d** still bind to the δ-opioid receptor. This suggests that the *H*-bond acceptor property is essential for the binding event in this position and the increased steric bulk is tolerated in the oxetane case. In the *N*-methyl amide series **258a-d**, only compound **247d** carrying the substitution in the *C*-terminal

position still binds to the δ-opioid receptor in the low nanomolar range. Furthermore, compound **258d** shows an increased metabolic stability in contrast to depsipeptide **257d** which is even more readily degraded than the natural peptide **247a**. This can be explained by the low hydrolytic stability of esters compared to amides. However, three of our four oxetanyl analogues (**247b**, **247c** and **247e**) even outperform the *N*-methyl amide derivative **258d** with half-life times increased by up to ≈11000%. This again shows that the 3-aminooxetane is a valuable building block in the toolbox of peptidomimicry as it closely resembles the steric and electronic features of the natural amide bond and increases the metabolic stability of the parent peptide.

2.4.7 Synthesis of α-Synuclein Inhibitors

As a second target we chose an inhibitor of the aggregation of α-Synuclein, a 140 amino acid containing protein with a weight of 14.5 kDa. It is one of the most abundant proteins in intracerebral tissue including human brains.[204,205] Aggregated α-Synuclein is the major component of inclusion bodies, so called Lewy bodies that have been found in the dopaminergic neurons of patients who suffered from *Morbus* Parkinson.[206,207] Hence, the aggregation process itself and the fibrilar aggregates deposited on nerve cells are a symptom or even one of the causes of this disease. Pharmaceutical agents targeting this process or the dissolution of these aggregates have been subject of intensive research.[208-210] Rather than on targeting a specific receptor, research on α-Synuclein is based on influencing protein-protein interactions (PPIs).[211,212] We envisioned the area of PPI inhibitors to be an ideal setting for oxetanyl peptides. We suggested that the conformational and steric bias induced by the oxetane could turn an aggregation-prone peptide into an inhibitor of the same.

Recently, the group of IM[213,214] developed a short peptidic inhibitor of α-Synuclein derived from a twelve residue hydrophobic stretch of the full protein which was shown to be essential for its aggregation.[215] We decided to incorporate the oxetane moiety into this already optimized hexapeptide with the sequence H_2N-

Pro-Gly-Val-Thr-Ala-Val-NH_2/OH (**259a**). Based on the optimization studies by IM, we reasoned that a substitution at the hydrophobic *N*- and *C*-terminal positions would be most promising. We therefore planned the synthesis of the ^{Ox}Pro^6 (**259b**), ^{Ox}Gly^5 (**259c**) and ^{Ox}Val^1 (**259d**) analogues (Figure 31).

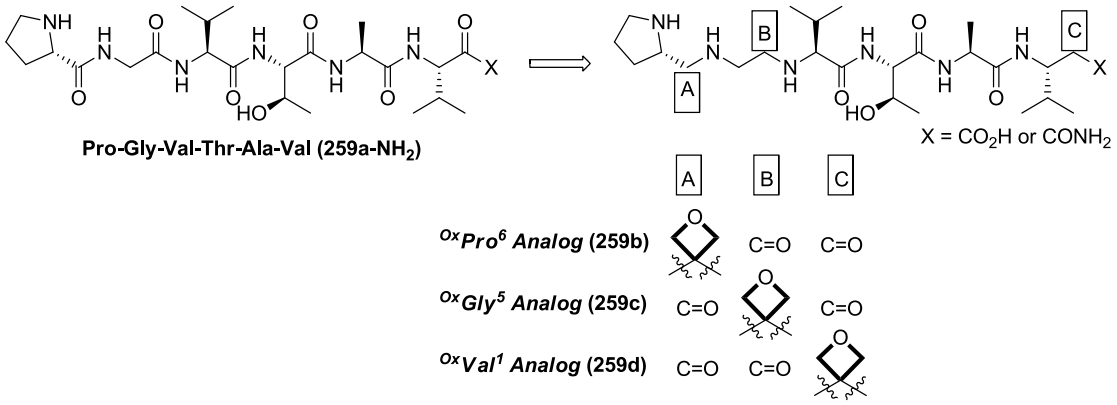
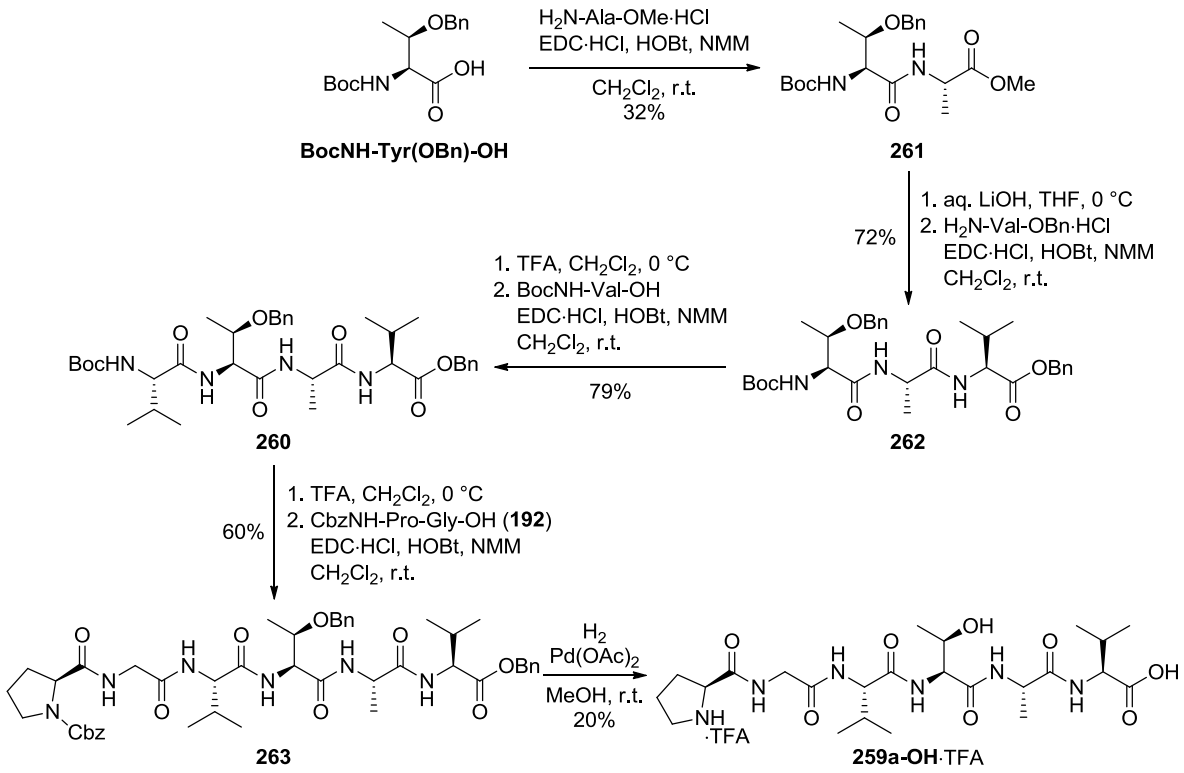


Figure 31 Planned Oxetanyl Modifications of 259.

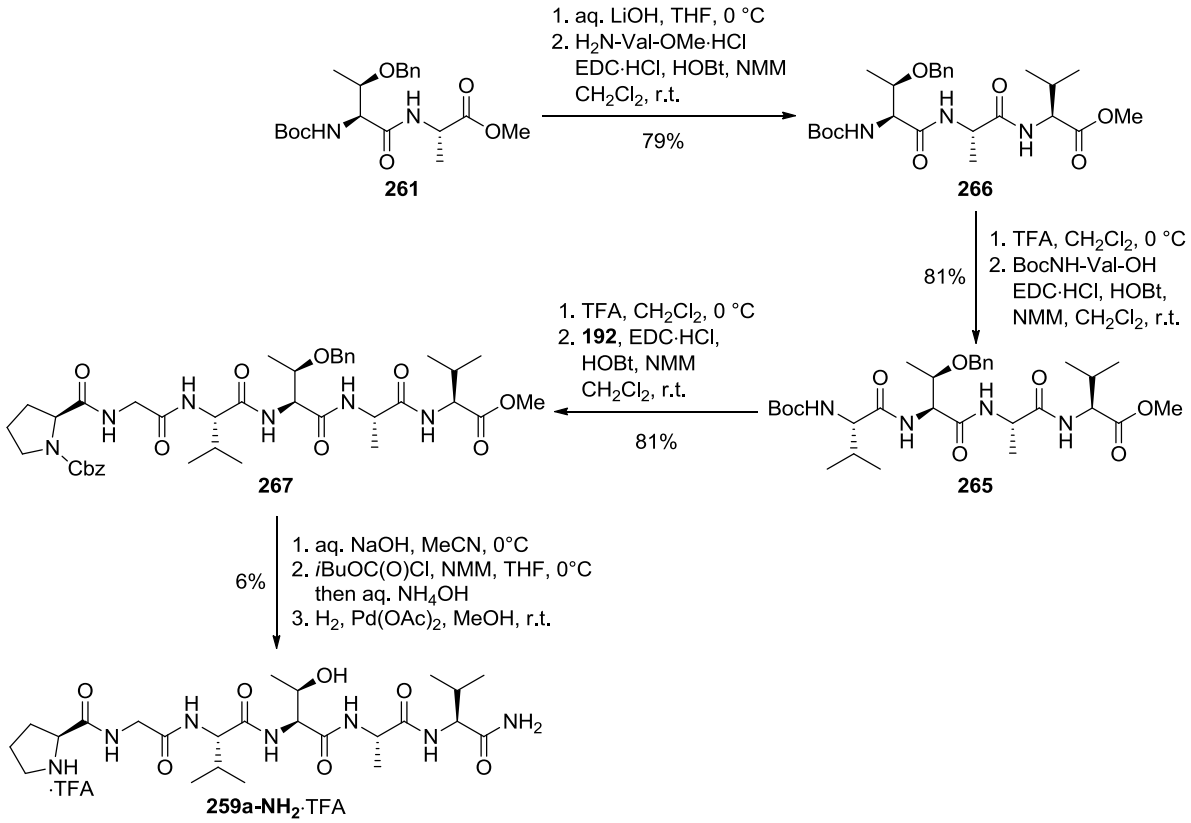
We first pursued the synthesis of the natural peptide acid **259a-OH** and amide **259a-NH2**. Again we resorted to a strategy with Cbz, benzyl ether and benzyl ester as protecting groups to enable final global deprotection by hydrogenation. We started our synthetic efforts from commercial BocNH-Tyr(OBn)-OH. In the case of **259a-OH**, standard peptide couplings mediated by EDC·HCl led to tetrapeptide BocNH-Val-Thr(OBn)-Ala-Val-OBn **260** *via* dipeptide **261** and tripeptide **262**. In parallel CbzNH-Pro-Gly-OH (**263**) was synthezised from commercial CbzNH-Pro-OH and H_2N-Gly-OMe.[216] Final coupling between the free acid and amine derived from **263** and **260** respectively led to fully protected hexapeptide **264**. Unfortunately, global deprotection by hydrogenation in the presence of catalytic amounts of palladium on charcoal proceeded slowly and resulted in a complex mixture of products. Only, when stoichiometric amounts of palladium acetate were used the desired product **259a-OH** could be obtained as its TFA salt after purification by preparative HPLC (Scheme 78).



Scheme 78 Synthesis of 259a-OH.

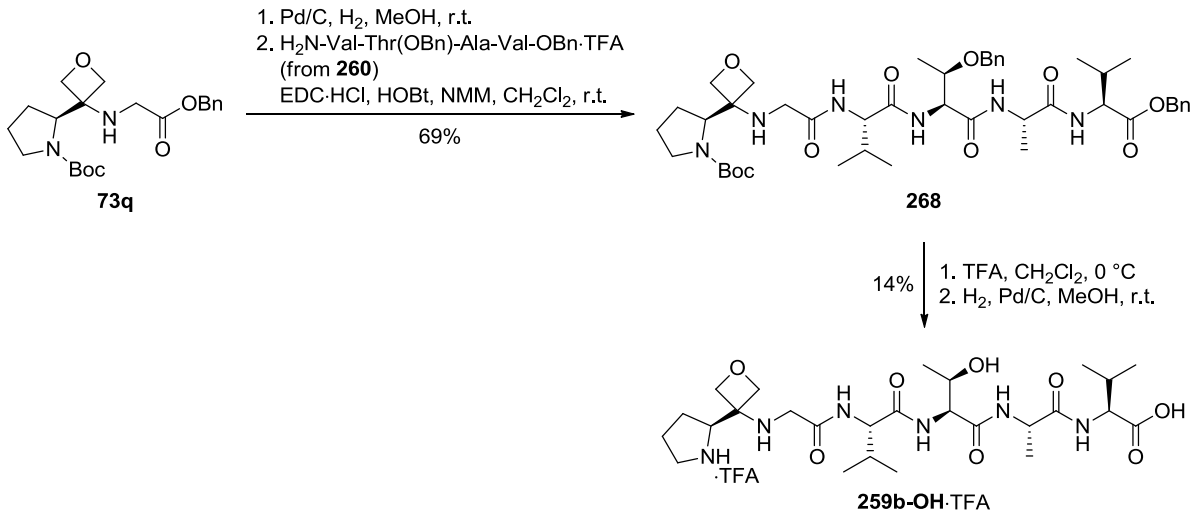
For the synthesis of **259a-NH2** essentially the same route was used. Again BocNH-Tyr(OBn)-OH was elaborated to tetrapeptide **265**, which now carried a methyl ester in the *C*-terminal position, *via* **266**. Peptide coupling with **263** furnished fully protected hexapeptide **267**. We first tried to convert the *C*-terminal methyl ester into the corresponding amide by simple aminolysis with ammonia in MeOH or water. However, we only observed decomposition of the starting material or products still containing the methyl ester, but missing the benzyl ether or Cbz-group as identified by LC-MS. Even preceding deprotection of the Cbz-group and the benzyl ester by hydrogenation did not lead to desired product in the aminolysis. Finally, the *C*-terminal primary amide was introduced by ester hydrolysis and subsequent treatment of the acid with isobutyl chloroformate to give the mixed anhydride followed by aminolysis with aqueous ammonia. Final deprotection of the crude material under hydrogenative conditions led to **259a**-NH2. The obtained material was found to be insoluble in all solvents except for DMSO and water and precipitated from the reaction mixture in the deprotection step as a colorless gel. Hence, only minimal amounts

of the TFA salt of **259a-NH2** accounting to no more than 6% yield could be obtained after purification by preparative HPLC (Scheme 79).



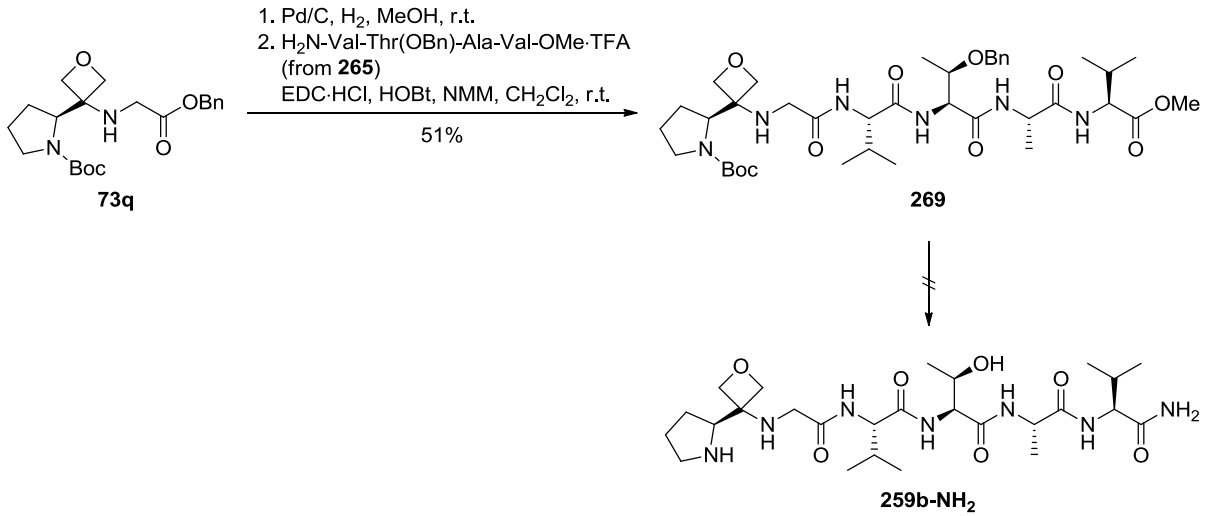
Scheme 79 Synthesis of 259a-NH2.

We now turned our attention to the synthesis of the oxetanyl analogues **259b-d**. We decided to use a similar route for the synthesis of $^{Ox}Pro^{6}$ analogues **259b-OH** and **259b-NH2** as for **259a-OH** and **259aNH2** starting from previously obtained tetrapeptides **260** and **265** respectively. Coupling of the free acid corresponding to oxetanyl dipeptide BocNH-Ox-Pro-Gly-OBn (**73q**) and free amine derived from **260** led to fully protected oxetanyl hexapeptide **268**. Boc-deprotection under standard TFA conditions and subsequent hydrogenolytic cleavage of the benzyl ether and ester then furnished the desired product **259b-OH** after purification by preparative HPLC. This time catalytic amounts of palladium on carbon were sufficient to achieve deprotection of **268** (Scheme 80).



Scheme 80 Synthesis of 259b-OH.

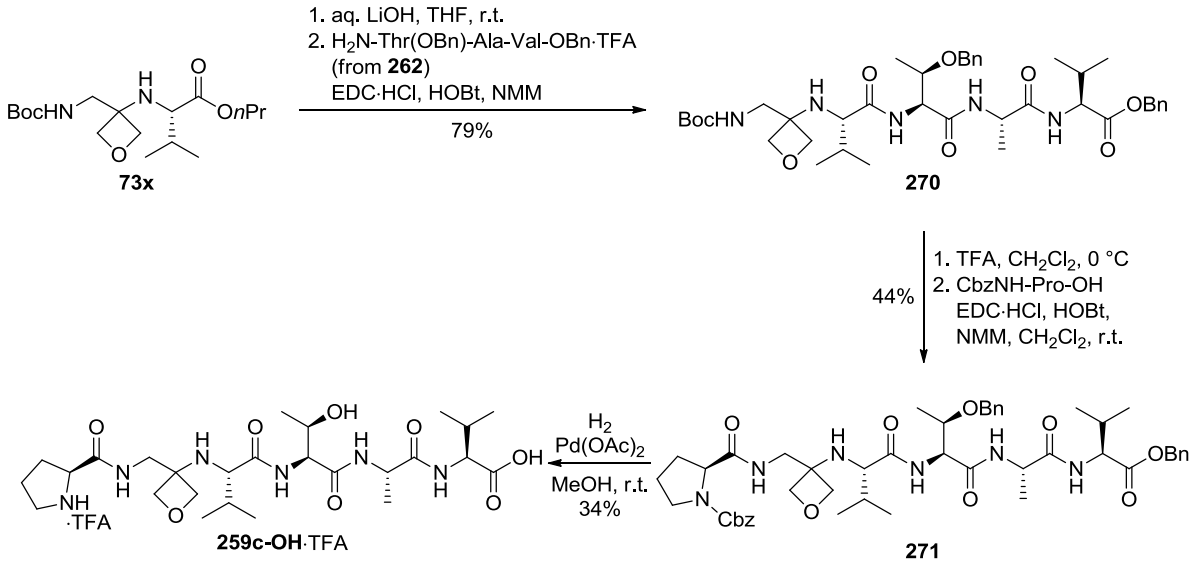
Starting from tetrapeptide methyl ester **265** and dipeptide mimic **73q**, fully protected hexapeptide **269** was obtained. However all attempts to convert the methyl ester **269** into the corresponding primary amide **259b-NH2**, including the treatment with anhydrous ammonia in MeOH, aqueous ammonium hydroxide, magnesium nitride in MeOH[217] and aminolysis of the corresponding mixed anhydride or acid chloride either led to no reaction or decomposition of the starting material (Scheme 81).



Scheme 81 Attempted Synthesis of 259b-NH2.

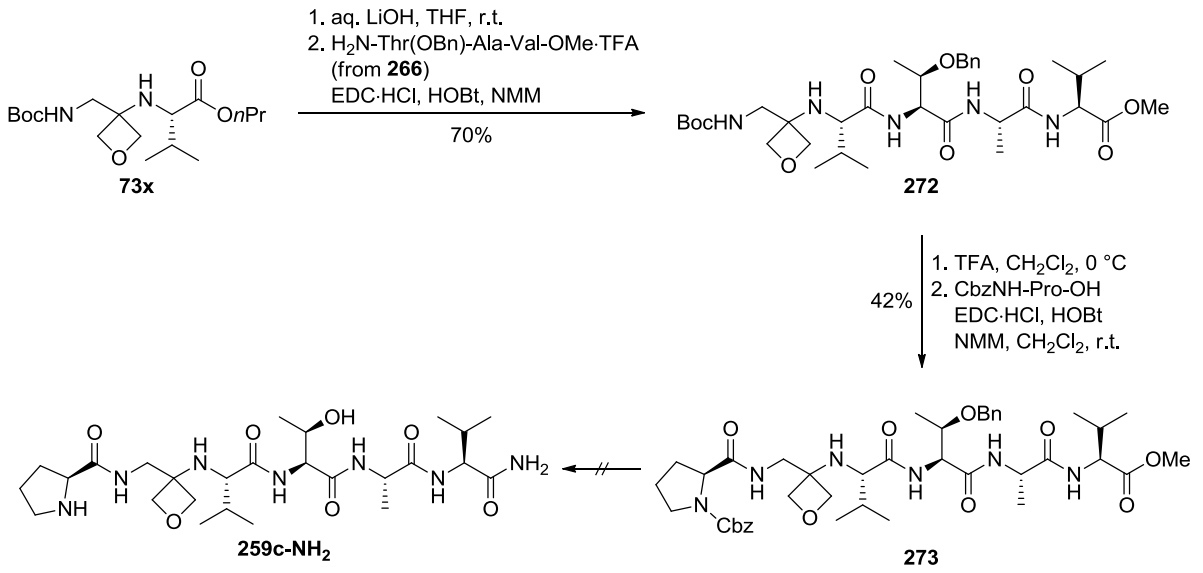
The synthesis of ^{Ox}Gly^{5} analogues **259c-OH** and **259c-NH2** was pursued starting from preciously obtained tripeptides **262** and **266** respectively. On the route to **259c-OH**, the free acid corresponding to previously reported oxetanyl dipeptide

73x was coupled to the free amine derived from **262** to give oxetanyl pentapeptide **270**. Fully protected hexapeptide **271** was then obtained by *N*-terminal deprotection of **270** with TFA and EDC·HCl mediated reaction with CbzNH-Pro-OH. Final global deprotection was again achieved by hydrogenation in the presence of stoichiometric amounts of palladium acetate. The desired product **259c-OH** was isolated as the corresponding TFA salt by preparative HPLC (Scheme 82).



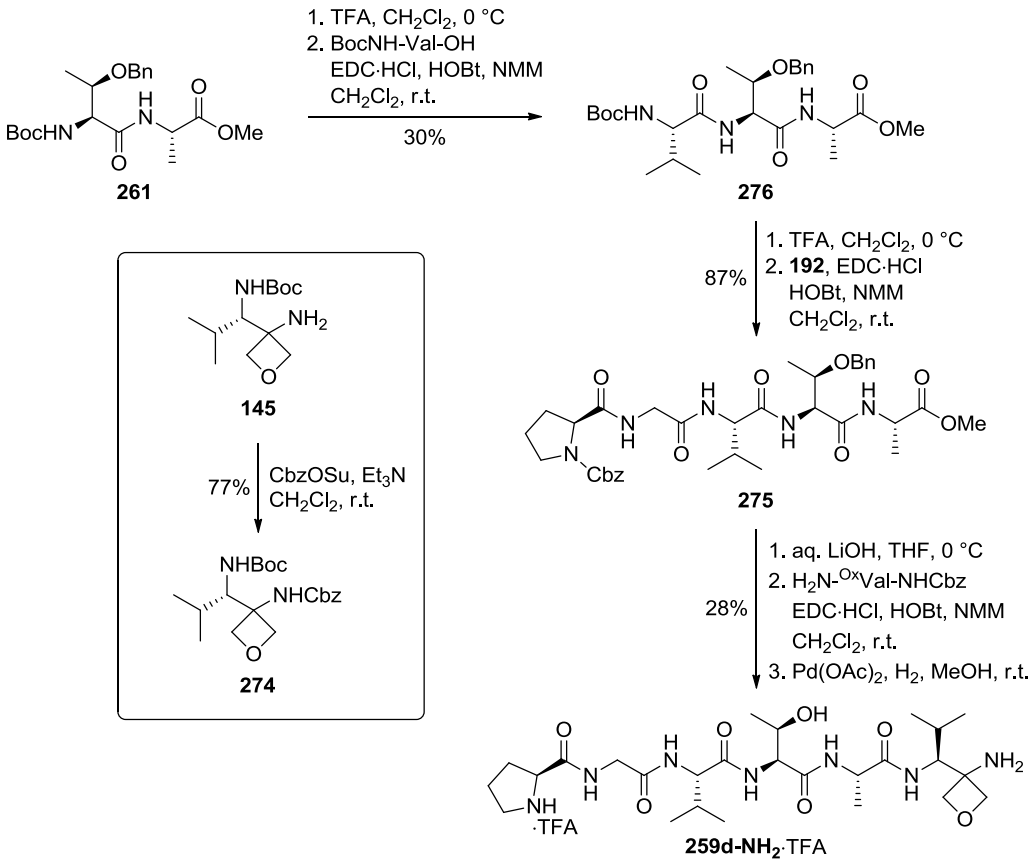
Scheme 82 Synthesis of 259c-OH.

Similarily, oxetanyl pentapetide methyl ester **272** was obtained from tripeptide **266** and oxetanyl dipeptide **73x**. Coupling with CbzNH-Pro-OH then led to hexapeptide methyl ester **273**. However, again all attempts to convert **273** into the desired product **259c-NH2** failed (Scheme 83).



Scheme 83 Attempted Synthesis of 259c-NH_2.

Last, we turned our attention to the synthesis of ^{Ox}Val^{1} analog **259d**. We identified previously obtained (chapter 2.3.1) diamine **145** as the suitable oxetanyl building block. To enable global deprotection by hydrogenation, **145** was Cbz-protected at the amine in the 3-position of the oxetane to give **274**. In parallel, pentapeptide methyl ester **275** was obtained by EDC·HCl mediated peptide couplings starting again from BocNH-Thr(OBn)-OH *via* **276**. The free amine derived from **274** after Boc-deprotection was then coupled to the free acid obtained from **275** to furnish oxetanyl hexapeptide. The crude material was directly submitted to hydrogenation conditions for global deprotection to yield the desired product **259d** which was then isolated as its TFA salt by preparative HPLC (Scheme 84).



Scheme 84 Synthesis of 259d-NH2.

In summary, both the natural peptide acid **259a-OH** and the natural peptide amide **259a-NH2** as well as oxetanyl analogues with ^{Ox}Pro^{6} (**259b-OH**), ^{Ox}Gly^{5} (**259c-OH**) and ^{Ox}Val^{1} (**259d**) substitutions were synthesized. This diverse set of natural peptides and peptidomimetics will enable us to extensively study the effect of an oxetane substitution on PPIs depending on its position in the peptide backbone.

2.4.8 Planned Activity Studies[218]

As mentioned previously (chapter 2.4.7), the toxicity of α-Synuclein is attributed to the aggregation process and the resulting fibrillar aggregates of this protein. We therefore decided to monitor the amount of α-Synuclein aggregates in the presence of an excess of the previously studied peptidic inhibitor **259a**[213,214] and our oxetanyl analogues **259b-d**. α-Synuclein aggregation kinetics are often studied with the help of the fluorescent dye thioflavin T (ThT).[219,220] ThT

selectively binds to structures with high β-sheet content like amyloidogenic fibrils. This is accompanied by a strong red shift of its emission spectrum which allows simple monitoring of the aggregation process. Recently, CAMPIONI *et al.* published a study on the aggregation of α-Synuclein and its dependency on the presence of an air-water interface.[221] They also disclosed a procedure to produce purely monomeric α-Synuclein to accurately study the aggregation process in the absence of preformed oligomers or protofibrills. Their work also includes a detailed description of plate reader assay setup suitable for our purposes. This facilitates the monitoring process over prolonged time span and only requires minimal amounts of protein as the same volume is monitored continuously without the need to withdraw a sample.

As already described by the group of IM[213,214], we planned to incubate a five-fold molar excess of the synthetic peptides **259a-d** with α-Synuclein in aqueous buffer under physiological conditions (37 °C, pH 7.4) and use the fluorescence readout to monitor the amount of formed amyloidogenic fibrils.

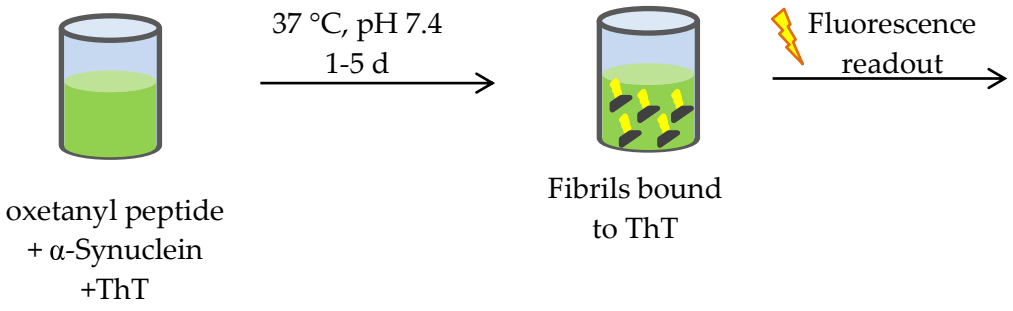


Figure 32 Principle of Fluorescence Assay for α-Synuclein Aggregation.

This would give us a detailed picture of effect of an oxetane substitution on the inhibitory potency of **259a** relative to its position in the peptide backbone.

3

Side Chain-Modified Oxetanyl Peptides

3.1 Conceptual Framework

In chapter 2 we reported the use of 3-aminooxetanes as amide bond mimics in peptides and showed that this new class of peptidomimetics can in principle be a valuable tool for the development of peptide drugs. The peptide backbone is needed for the construction of secondary and tertiary peptide structures through *H*-bonding and can also interact with a potential binding pocket.

However, the interactions between side-chain residues also play a crucial role in protein folding and protein-protein interactions (PPIs):[222] The hydrophobic effect is a major determinant of secondary structure formation. Furthermore, hydrophobic and electrostatic interactions of side-chain residues account for up to 80% of the interactions at protein-protein interfaces.[222,223] Hence, the incorporation of amino acids carrying a vast variety of side-chain residues into potential pharmaceutical agents has become a common process in drug discovery.[222] Along with the twenty proteinogenic amino acids, also "non-natural" amino acids have been synthesized and used.[224]

However, the exploitation of favorable hydrophobic interactions by the incorporation of corresponding natural and non-natural amino acids such as valine, leucine, isoleucine, *tert*-leucine[225] or neopentyl glycine[226] introduces a large portion of hydrophobic surface area which might have a negative effect on other parameters such as solubility and bioavailability. Similarly, the use of functionalized side chain residues as in asparagine, aspartic acid, glutamine or glutamic acid to enforce electrostatic interactions at the same time potentially creates new sites for metabolic degradation.

Therefore, we decided to design and synthesize a new set of side-chain modified amino acids that use the concept of oxetanes as isosters for gem-dimethyl and carbonyl group to improve key pharmacokinetic properties of the parent structures.

3.1.1 Oxetanes as Surrogates for *gem*-Dimethyl Groups in Amino Acids

Gem-dimethyl groups have frequently been used in drug discovery to introduce hydrophobic bulk or to shield sensitive functional groups and methylene units from metabolic attack. We have previously suggested that linking *gem*-dimethyl groups with an oxygen bridge to oxetanes can be beneficial to reduce their hydrophobicity.[87,101] Because of the similar molecular volume of an oxetane[99] and a *gem*-dimethyl group[100] we concluded that oxetanes can be perceived as less hydrophobic isosters of *gem*-dimethyl groups (Figure 33).[101]

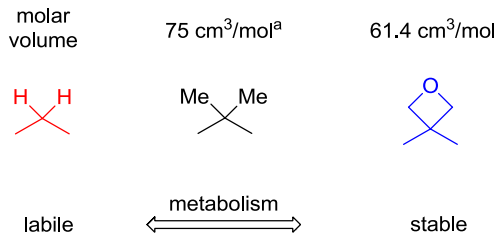


Figure 33 Comparison *gem*-Dimethyl vs. Oxetane (a molar volume of propane).

Especially when looking at the interaction between a ligand and a protein binding pocket, one could argue that due to the hydrophilic peptide backbone, every hydrophobic pocket might still have hydrophilic spots. The combination of hydrophobic and hydrophilic surface patches could be ideally addressed with the oxetane unit. We hence decided to synthesize the oxetanyl analogues of L-valine (Val(Ox), **277**), L-leucine (Leu(Ox), **278**), L-*tert*-leucine (Tle(Ox), **279**) and L-neopentyl glycine (Neo(Ox), **280**) (Figure 34).

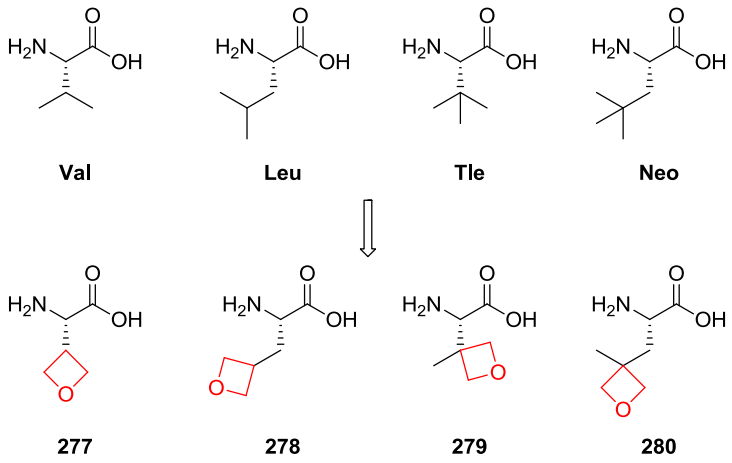


Figure 34 Substitution of *gem*-Dimethyl Groups with Oxetanes

3.1.2 Oxetanes as Surrogates for Carbonyl Groups in Amino Acids

Four of the 20 proteinogenic amino acids contain carbonyl groups in their side chain residues. Asparagine and its homologue glutamine carry primary amide functionalities which are uncharged and can participate in *H*-bonding and other electrostatic interactions. As outlined in chapter 2 we showed that 3-aminooxetanes can serve as amide bond mimics. Following this concept, we decided to replace the primary amide moieties in asparagine and glutamine accordingly to give oxetanyl analogues Asn(Ox) (**281**) and Gln(Ox) (**282**). This would lead to amino acid derivatives that are potentially more stable towards metabolic degradation through deamidation.[227-229] Mimics **281** and **282** also contain a mildly basic amine which could participate in salt bridges and furthermore increase the overall solubility of a pharmaceutical agent (Figure 35).

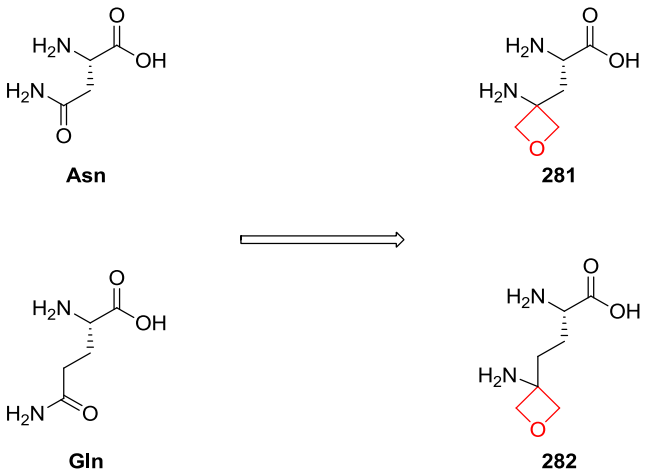


Figure 35 Substitution of Amides with Oxetanes in Asn and Gln.

On the other hand, aspartic and glutamic acid, contain carboxylic acids in their side-chains which can be charged under physiological conditions and participate in salt bridges. Again, we decided to prepare the corresponding 3-hydroxyoxetane containing mimics Asp(Ox) (**283**) and Glu(Ox) (**284**). We suggest that derivatives **283** and **284** are more stable towards enzymatic degradation.[230,231] Furthermore, this modification provides uncharged alternatives to the natural amino acids (Figure 36).

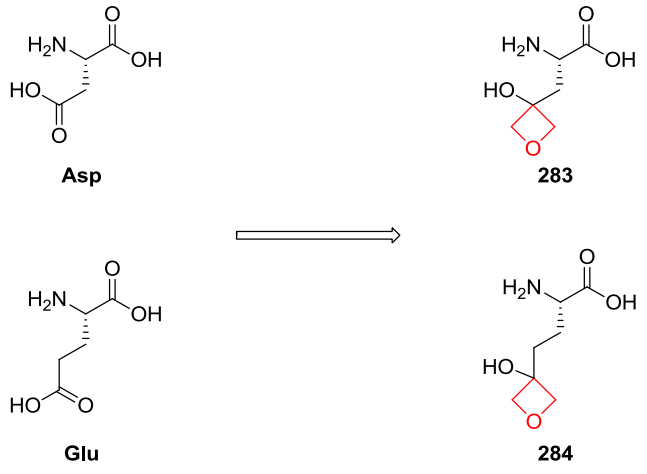


Figure 36 Substitution of Carboxylic Acids with Oxetanes in Asp and Glu.

3.1.3 Azetidine as a Side Chain-Modification

Finally, we were inspired by the earlier work in the group on azetidine containing spirocycles such as homospiropiperidine (2-azaspiro[3.3]heptane,

285)[105] to use an azetidine to modifiy the lysine ε-amine. We hence envisioned the synthesis of Lys(Az) (**286**) to provide a building block with enhanced basicity and steric accessibility of the ε-amine compared to conventional alkylated lysine analogues (Figure 37).

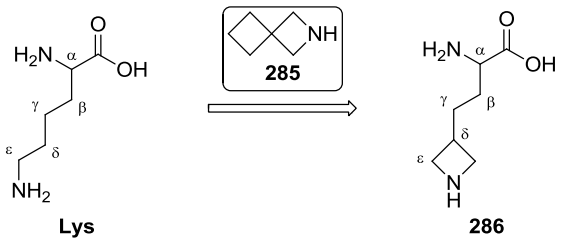


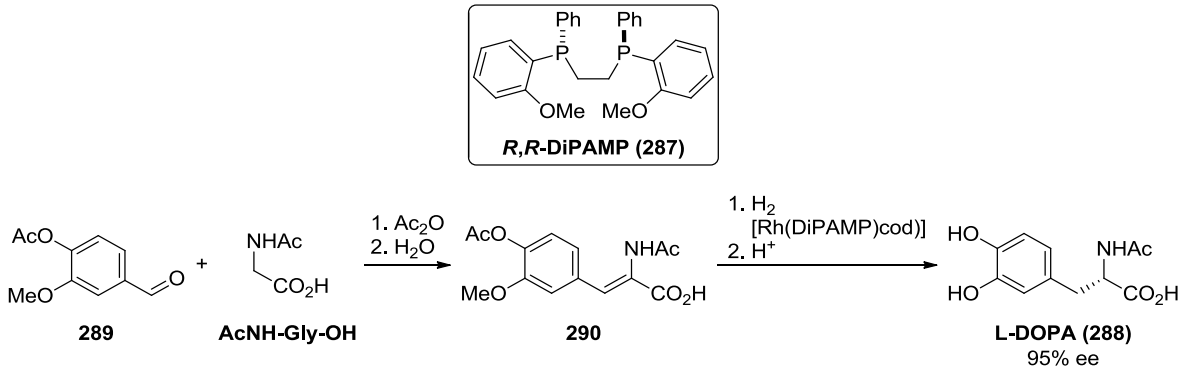
Figure 37 Conceptual Idea for Lys(Az) (286).

3.2 Synthetic Strategy

Our envisioned strategy towards the synthesis of side-chain modified oxetanyl amino acids is based on ELLMAN auxiliary chemistry and asymmetric hydrogenation, two well-established asymmetric methodologies. These would enable us to individually access both enantiomers of the desired products **277**-**284** and **286**. This would open the door for the use of the oxetane concept in combination with other peptidomimetic approaches like retro-inverso peptides.

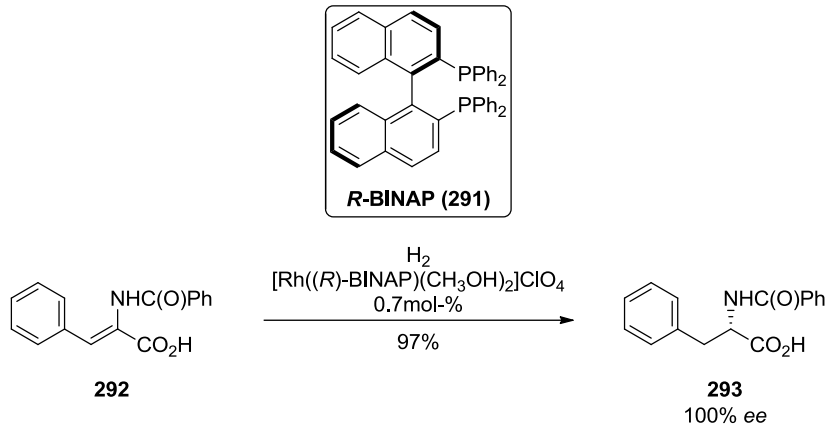
3.2.1 Synthesis of Side Chain-Modified Amino-Acids *via* Asymmetric Hydrogenation

WILKINSON's landmark discovery[232] of a soluble well-defined homogenous catalyst [$Rh(PPh_3)_3Cl$][233] for olefin hydrogenations opened the door for the development of asymmetric hydrogenations. First developments of chiral variants of Rh(I) catalyst were reported by KNOWLES[234,235], HORNER[236,237] and KAGAN[238]. These already included the enantioselective reduction of α,β-didehydro amino acids. KNOWLES[239] and coworkers also reported the first industrial use of asymmetric hydrogenation. The development and appllication of the bidentate, "chiral at phosphorous" ligand DiPAMP (**287**) furnished the MONSANTO process for the large scale production of L-DOPA (**288**) from **289** and acetyl glycine *via* intermediate **290** (Scheme 85).[240-242]



Scheme 85 The MONSANTO Process for the Production of L-DOPA.

Additionally, NOYORI reported another variant of the asymmetric hydrogenation of α,β-didehydro amino acids catalyzed by a combination of BINAP (**291**) with rhodium (e.g. the transformation of **292** to **293**, Scheme 86).[243,244]



Scheme 86 NOYORI's Asymmetric Hydrogenation of Benzamide 292.

Furthermore, the phospholane based ligands DuPhos (**294**) and BPE (**295**) were developed by BURK at DuPont (Figure 38).[245-248] The corresponding rhodium complexes were shown to tolerate a large substrate scope of dehydroamino acids and especially *E*/*Z*-mixtures thereof without a decrease in enantioselectivity.

Figure 38 Me-DuPhos (294) and Me-BPE (295).

The mechanism of rhodium catalyzed asymmetric hydrogenations was thoroughly studied by Halpern and Brown.[249-251]

Up to this point, all research efforts were focused on rhodium based systems with bidentate phosphine ligands. However, the extension of this concept to a broad range of substrates proved difficult since the reaction requires a suitable directing group. Later, after initial studies, NOYORI expanded the field to ruthenium based variants using a BINAP-Ru complex to overcome this limitation.[252,253]

Finally in 2000, the application of monodentate phosphorous based ligands in rhodium catalyzed asymmetric hydrogenation reactions was reported by several groups. Indeed, the newly developed catalytic systems were able to challenge or outperform the long preferred bidentate ligands. ORPEN and PRINGLE described the use of phosphonite **296**[254], REETZ[255,256] reported the application of phosphites **297** and FERINGA[257-260] published the use of the phosphoramidite ligand **298** (Figure 39). The main advantage of these ligands is their availability from inexpensive and readily available chiral starting materials which obviates the need for tedious resolution.

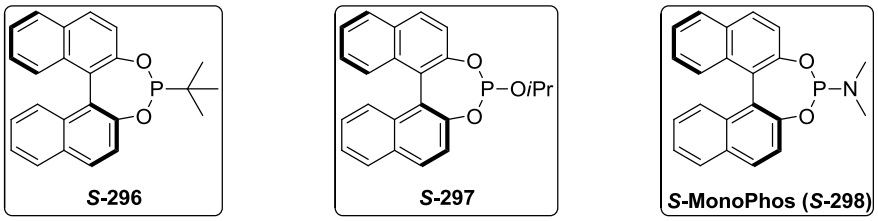
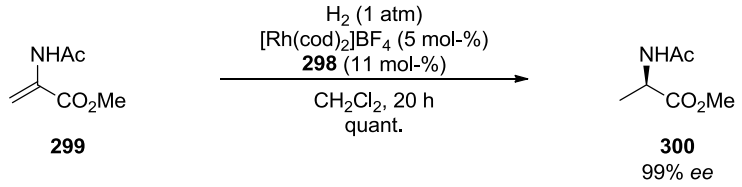


Figure 39 Monodentate Ligands 296, 297 and 298.

To date asymmetric hydrogenation reactions are one of the most extensively studied classes of asymmetric methodologies. A vast number of chiral ligand and metal combinations has been reported.[261-265]

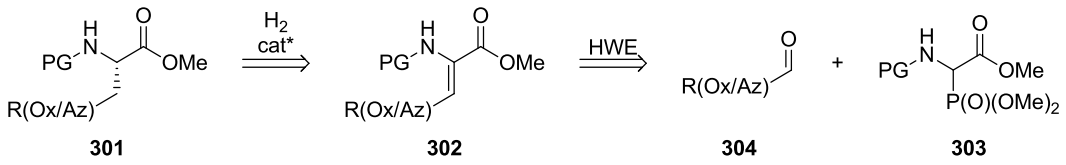
We were especially intrigued by FERINGA's MonoPhos (**298**), rhodium(I) system because of the broad substrate scope for the transformation α,β-didehydro amino acids (e.g. **299**) to the corresponding amino acids (e.g. **300**) in high enantiomeric

purity and the operationally simple procedure, i.e. room temperature and atmospheric pressure (Scheme 87).[257]



Scheme 87 Asymmetric Hydrogenation by FERINGA.

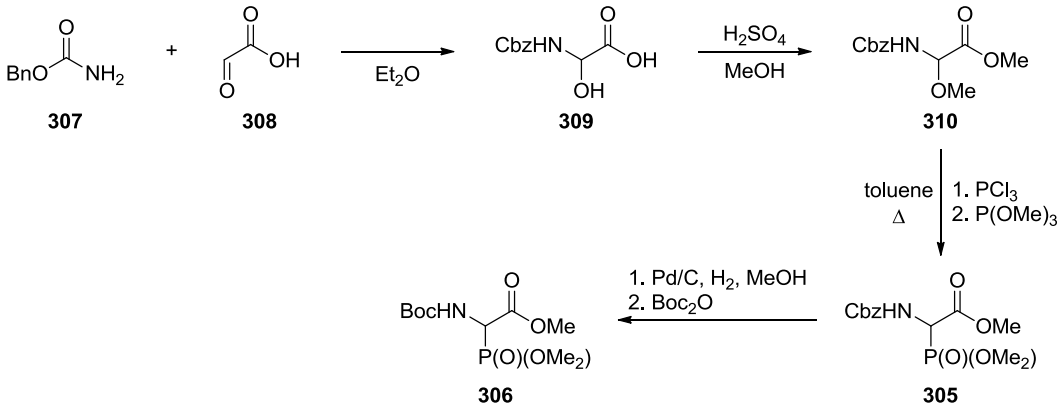
However, FERINGA's reports only include the use of acetamide protected amino acid precursors. We doubted that deprotection of the Ac group from the corresponding amino acids in the presence of an oxetane would be feasible. Also, we envisioned a strategy using protecting groups commonly tolerated in standard peptide coupling protocols such as Boc or Cbz. Some reports where these protecting groups have been used under similar conditions are precedented in the literature.[266] Hence, we decided to apply the MonoPhos-Rh system for the synthesis protected derivatives **301** of oxetanyl and azetidinyl amino acids **277**, **280**-**284** and **286** from the corresponding enamides **302**. These in turn would come from the HORNER-WADSWORTH-EMMONS reaction of a suitable glycine phosphonate ester **303** with an oxetanyl or azetidinyl aldehyde **304** (Scheme 88). When using DBU or TMG as the base in these reactions, exclusively the *Z*-isomers of the condensation products are usually obtained.



Scheme 88 Retrosythesis of Protected Amino Acids 301.

The synthesis of the Cbz- and Boc-protected reagents **305** and **306** had been reported previously. Compound **305** was prepared by addition of benzyl carbamate (**307**) to glyoxylic acid **308** to give **309**, subsequent treatment with sulfuric acid in methanol to furnish ester **310** and finally reaction with phosphorous trichloride and trimethyl phosphite.[267] Boc-protected derivative **306**

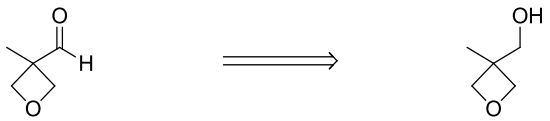
was then obtained by deprotection under hydrogenation conditions and reprotection with Boc_2O (Scheme 89).[268]



307 **308** **309** **310** **306** **305**

Scheme 89 Reported Syntheses of Reagents 305 and 306.

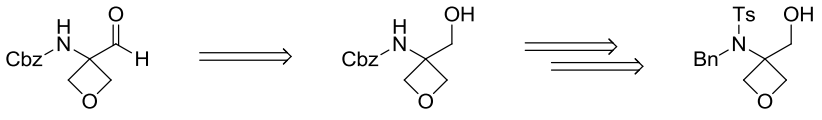
For the synthesis of Val(Ox) (**277**) commercially available oxetane-3-one (**33**) could be used as the carbonyl compound in the HWE reaction. The side-chain for Neo(Ox) (**280**) in turn would come from commercially available alcohol **15** by oxidation to aldehyde **311** (Scheme 90).[83]



311 **15**

Scheme 90 Planned Synthesis of 311.

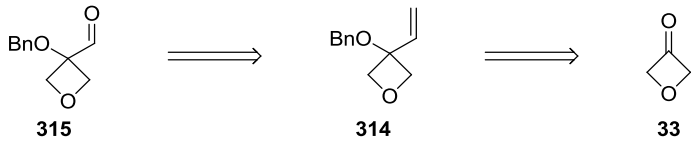
The synthesis of Asn(Ox) (**281**) could start from previously synthesized aminoalcohol **131** by deprotection of the tosyl and benzyl groups, subsequent reprotection with a common peptide protecting group, e.g. Cbz, to **312** and oxidation to the required aldehyde **313** (Scheme 91).



313 **312** **131**

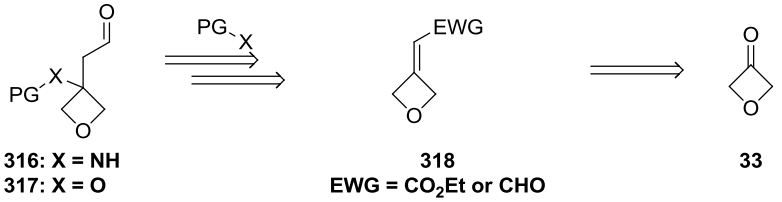
Scheme 91 Planned Synthesis of Aldehyde 313.

Addition of vinyl magnesium bromide to oxetane-3-one (**33**) followed by protection of the resulting alcohol as its benzyl ether **314** and ozonolysis would lead to aldehyde **315** resembling the side chain of Asp(Ox) (**283**) (Scheme 92).



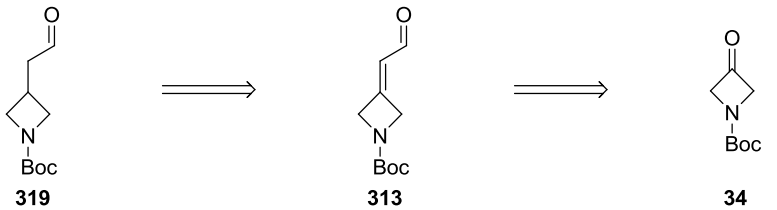
Scheme 92 Planned Synthesis of Aldehyde 315.

Aldehydes **316** and **317** corresponding to the side chains of Gln(Ox) (**282**) and Glu(Ox) (**284**) could be directly derived from oxetane-3-one (**33**) by homologation to **318** *via* a WITTIG reaction and subsequent conjugate addition of the appropriate heteroatom nucleophile (Scheme 93).



Scheme 93 Planned Synthesis of Aldehydes 316 and 317.

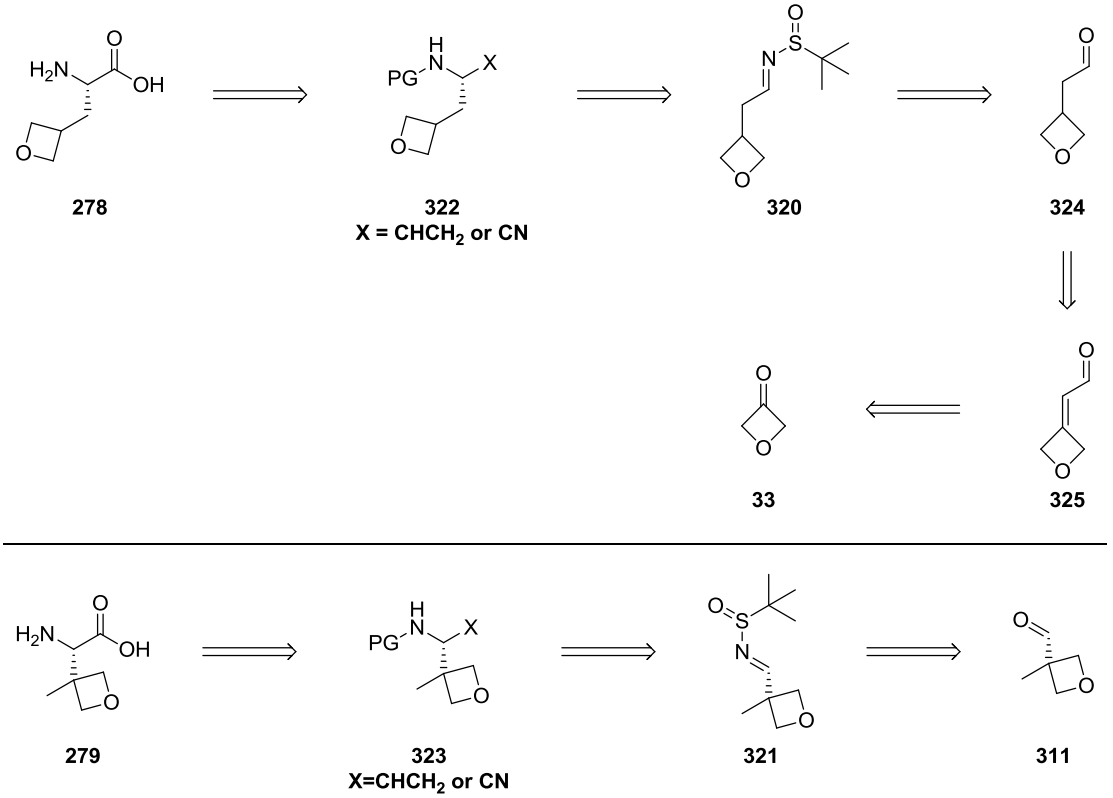
Finally, aldehyde **319** for the synthesis of Lys(Az) (**286**) could come from boc-azetidine-3-one (**34**) *via* WITTIG reaction with (triphenylphosphoranylidene)-acetaldehyde to **313** and subsequent reduction (Scheme 94).



Scheme 94 Planned Synthesis of Aldehyde 319.

3.2.2 Synthesis of Side Chain-Modified Amino-Acids *via* ELLMAN Imines

The synthesis of the remaining two side-chain modified oxetanyl amino acids Leu(Ox) (**278**) and Tle(Ox) (**279**) was again planned based on the well-established chemistry of ELLMAN imines. In these cases the synthesis could not be pursued using the asymmetric hydrogenation approach outlined above because of the difficult preparation of the carbonyl component for the HWE reaction (**278**) or the quaternary β-carbon (**279**).



Scheme 95 Retrosynthesis of 278 and 279.

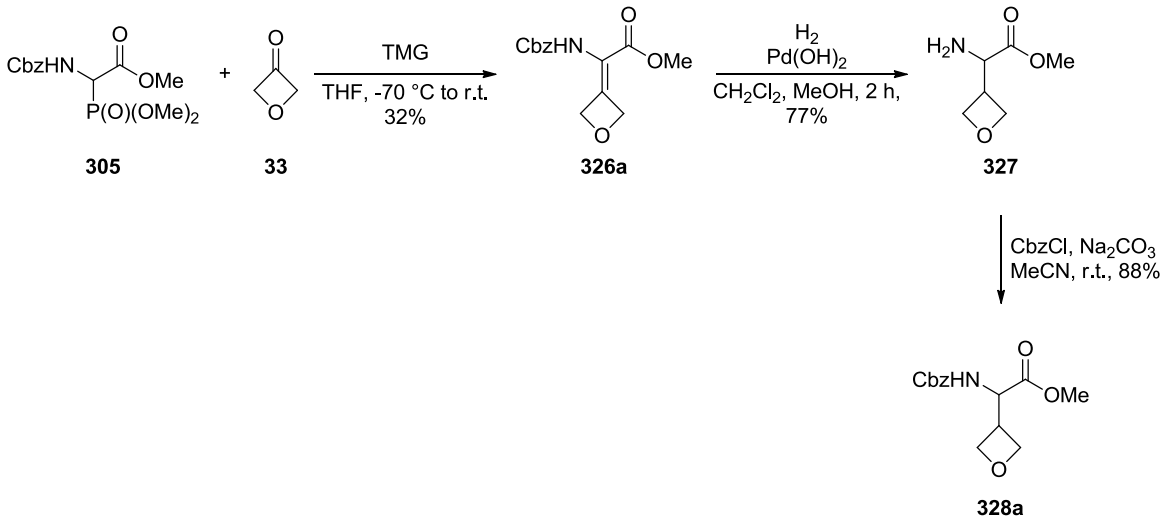
Hence, we decided to trace building blocks **278** and **279** back to the corresponding ELLMAN imine precursors **320** and **321** by the addition of cyanide or vinyl magnesium bromide to **322** and **323** as carboxylic acid synthons and subsequent hydrolysis or ozonolysis. Imines **320** and **321** in turn would originate from aldehydes **324** and **311** (previously described in chapter 3.2.1).[83] Finally, aldehyde **324** could be derived from oxetane-3-one (**33**) by WITTIG homologation to **325** and subsequent reduction (Scheme 95).

3.3 Building Block Synthesis

Up to now, we designed two synthetic routes to the desired building blocks **277**-**284** and **286**. These would allow us to synthesize both enantiomers of the desired building blocks. Furthermore, the hydrogenation approach is known to be scalable and would hence be ideal for the preparation of larger quantities of oxetanyl amino acids.

3.3.1 Synthesis of Val(Ox) (277)

We first attempted the synthesis of Val(Ox) (**277**). This building block was previously prepared as a racemate by a similar approach. The two enantiomers were then later resolved. Oxetane-3-one (**33**) was first reacted with **305** to the corresponding Cbz-protected dehydroamino acid **326a**. Hydogenation with Pearlman's catalyst then led to deprotection of the amine and reduction of the double bond to furnish **327**. MOLDES *et al.*[269] reported the resolution of **327** by crystallization of the tartrate salt, while WAKENHUT *et al.*[122] first reprotected the amine with Cbz to give **328a** and then used chiral HPLC (Scheme 96).

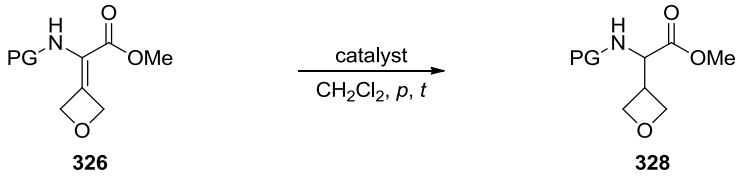


Scheme 96 Synthesis of 328 by MOLDES and WAKENHUT.

We decided to subject precursor **326a** directly to FERINGA's hydrogenation conditions using $[Rh(cod)_2BF_4]$ and *R*-MonoPhos (*R*-**298**) to obtain enantioenriched **328a** without the need for chiral resolution (Table 9).[257]

Unfortunately, no conversion to **328a** was observed even under elevated pressure (entries 1 and 6). This can be attributed to the fully substituted double bond which lies outside of the substrate scope of this hydrogenation method. Still, we decided to screen several protecting groups. We prepared Boc-, Troc, methyl carbamate and acetamide protected derivatives **326b-e**. However, Boc-, Troc-, and methyl carbamate protected substrates **326b-d** did not react either (**326b** and **326d**) or were decomposed (**326c**) under these conditions (entries 2-4 and 7). Only acetamide **326e** reacted with a conversion similar to the catalyst loading at 1 atm and 10 atm H_2 over 72 h (entries 5 and 8). We then examined catalyst system to [Rh(BPE)(cod)]OTf and indeed methyl carbamate **326d** was slowly converted to the desired product in 5 d at 10 atm H_2 (entry 9). Surprisingly, now also Boc-protected substrate **326b** showed an enhanced reactivity and was converted into Val(Ox) derivative **328b** in 99% yield after 1 d at 10 atm H_2 (entry 10). However, Cbz-, Troc- and acetamide protected substrates **326a**, **326c** and **326e** could still not be converted into the desired products under the optimized conditions (Table 9).

Table 9 Hydrogenation Conditions for 326.

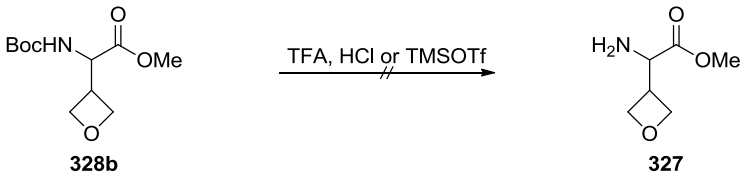


326 **328**

Entry	**257**	PG	Catalyst	*p*	*t*	Yield
1	**a**	Cbz	$[Rh(cod)_2]BF_4$ (5 mol-%) MonoPhos (11 mol-%)	1 atm	3 d	No conversion
2	**b**	Boc	$[Rh(cod)_2]BF_4$ (5 mol-%) MonoPhos (11 mol-%)	1 atm	1 d	No conversion
3	**c**	Troc	$[Rh(cod)_2]BF_4$ (5 mol-%) MonoPhos (11 mol-%)	1 atm	1 d	Decomposition
4	**d**	MeOC(O)	$[Rh(cod)_2]BF_4$ (5 mol-%) MonoPhos (11 mol-%)	1 atm	3 d	No conversion
5	**e**	MeC(O)	$[Rh(cod)_2]BF_4$ (5 mol-%) MonoPhos (11 mol-%)	1 atm	3 d	5%[a]
6	**a**	Cbz	$[Rh(cod)_2]BF_4$ (5 mol-%) MonoPhos (11 mol-%)	10 atm	3 d	No conversion
7	**d**	MeOC(O)	$[Rh(cod)_2]BF_4$ (5 mol-%) MonoPhos (11 mol-%)	10 atm	3 d	No conversion
8	**e**	MeC(O)	$[Rh(cod)_2]BF_4$ (5 mol-%) MonoPhos (11 mol-%)	10 atm	3 d	5%[a]
9	**d**	MeOC(O)	[Rh(BPE)(cod)]OTf (2 mol-%)	10 atm	5 d	90% (61%)[b]
10	**b**	Boc	[Rh(BPE)(cod)]OTf (2 mol-%)	10 atm	1 d	99%
11	**a**	Cbz	[Rh(BPE)(cod)]OTf (2 mol-%)	10 atm	3 d	No conversion
12	**c**	Troc	[Rh(BPE)(cod)]OTf (2 mol-%)	10 atm	1 d	Decomposition
13	**d**	MeC(O)	[Rh(BPE)(cod)]OTf (2 mol-%)	10 atm	3 d	2%[a]

a yield by ^{1}H-NMR, b yield by ^{1}H-NMR (isolated yield)

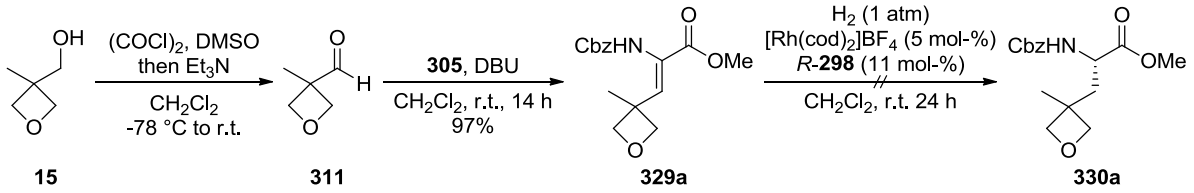
In order to determine the optical purity of obtained **328b** we next tried to deprotect the Boc-group to obtain amine **327**. Unfortunately, treatment under acidic conditions always led to fast decomposition of the starting material. Any further elaboration of this route was abandoned (Scheme 97).



Scheme 97 Attempted Deprotection of 328b.

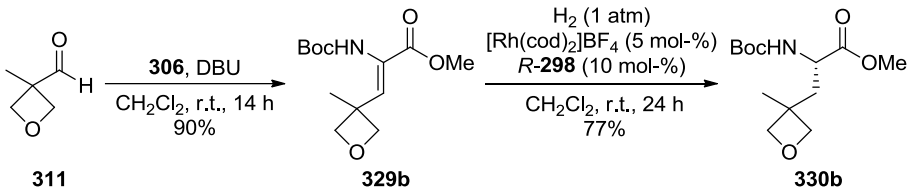
3.3.2 Synthesis of Neo(Ox) (280)

Next we turned our attention to the synthesis of Neo(Ox) (**280**). First, aldehyde **311** was obtained from commercially available alcohol **15**. We noticed, that **311** tends to decompose in its neat form and hence directly used the crude dichloromethane solution obtained from the SWERN oxidation. Reaction with Cbz-protected HWE reagent **305** furnished dehydroamino acid **329a** in 97% yield over two steps. With DBU as the base, only the *Z*-diastereomer of the enamine was obtained. Unfortunately, also in this case, asymmetric hydrogenation under FERINGA's conditions to **330a** was unsuccessful (Scheme 98).



Scheme 98 Attempted Synthesis of 330a.

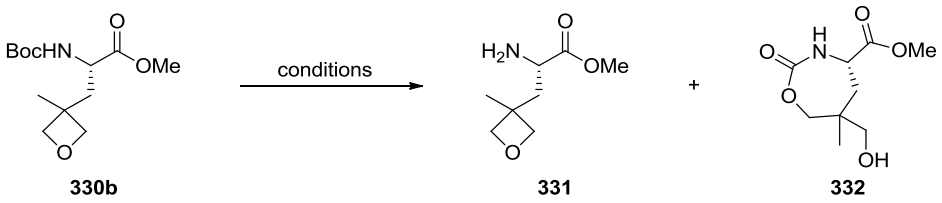
Hence, the protecting group was changed to Boc. Again, aldehyde **311** was used in an HWE reaction this time using reagent **306** to yield **329b** in 90%. As for dehydro Val(Ox) derivative **326b**, this protecting group pattern showed much higher reactivity and the reduced product could be obtained in 77% yield under standard conditions with *R*-**298** (Scheme 99).



Scheme 99 Synthesis of BocNH-Neo(Ox)-OMe 330a.

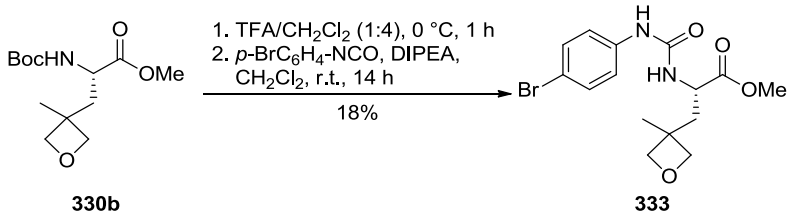
Again, deprotection proved difficult and only traces of the desired amine **331** were observed under various conditions (entries 3 and 4, Table 10). A major side-product observed in several cases was suggested to be seven membered ring **332** by crude ^{1}H-NMR which results from activation of the oxetane and subsequent attack of the Boc-carbonyl oxygen.

Table 10 Screening of Conditions for the Deprotection of 330a.



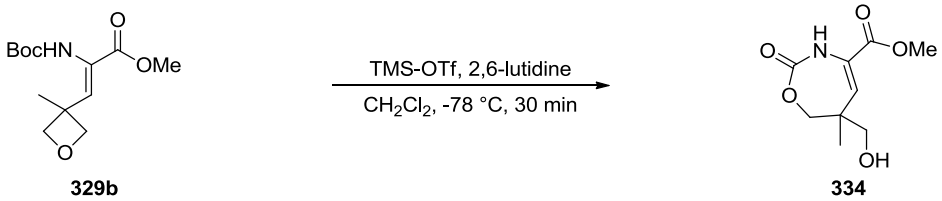
Entry	Reagent	Solvent	Temp.	Result
1	*p*TsOH·H_2O	MeCN	r.t.	Formation of **332**
2	Aq. HCl	THF	0 °C	Formation of **332**
3	TFA	CH_2Cl_2	0 °C	Traces of **331**, mainly **332**
4	TFA, thioanisole	CH_2Cl_2	0 °C	Traces of **331**, mainly **332**
5	$(NH_4)_2[Ce(NO_3)_6]$	MeCN	r.t.	Formation of **332**
6	HCl in dioxane	EtOAc	r.t.	Formation of **332**
7	NaI	Acetone	60 °C	No reaction
8	H_3PO_4	MeCN	0 °C	No reaction

However, small amounts of urea **333** could be obtained after deprotection with TFA and subsequent treatment with *p*-bromophenyl isocyanate for the determination of the enantiomeric excess. (Scheme 100).



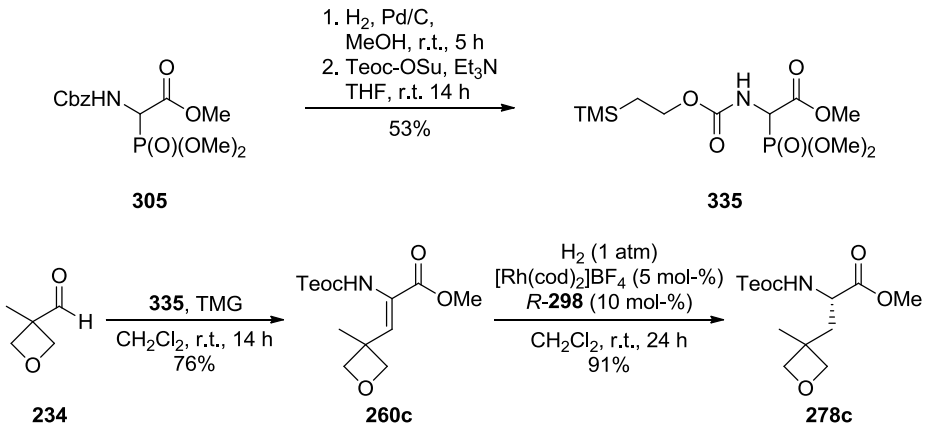
Scheme 100 Preparation of Urea 333 from 330b.

Deprotection of the Boc-group from hydrogenation precursor **329b** was also attempted but only led to rapid formation of **334** by the same mechanism (Scheme 101). **334** was isolated and identified by NMR.



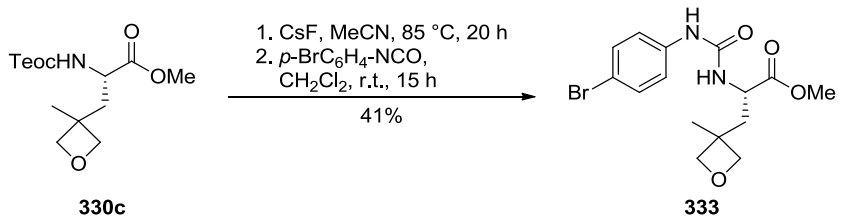
Scheme 101 Formation of Side-Product 334.

We again decided to change the protecting group, this time to Teoc. First, HWE reagent **335** was prepared from **305** by hydrogenation to remove the Cbz group and subsequent reprotection with Teoc-OSu. After reaction of **335** with aldehyde **311** protected dehydroamino acid **329c** was isolated. This time *E*/*Z*-mixtures were obtained with DBU as the base in the HWE reaction. The use of tetramethyl guanidine (TMG) however, only furnished the Z-isomer in 76% yield. Finally, asymmetric hydrogenation with $[Rh(cod)_2]BF_4$ and *R*-MonoPhos (*R*-**298**) at atmospheric pressure cleanly furnished TeocNH-Neo(Ox)-OMe (**330c**) in 91% yield (Scheme 102).[257]



Scheme 102 Synthesis of TeocNH-Neo(Ox)-OMe (330c).

Subsequent deprotection of the Teoc-group could be achieved by treatment with cesium fluoride in acetonitrile. The free amine was directly reacted with *p*-bromophenyl isocyanate to obtain urea **333** (Scheme 103). The corresponding racemic sample was obtained by hydrogenation of **329c** in the presence of palladium on carbon.



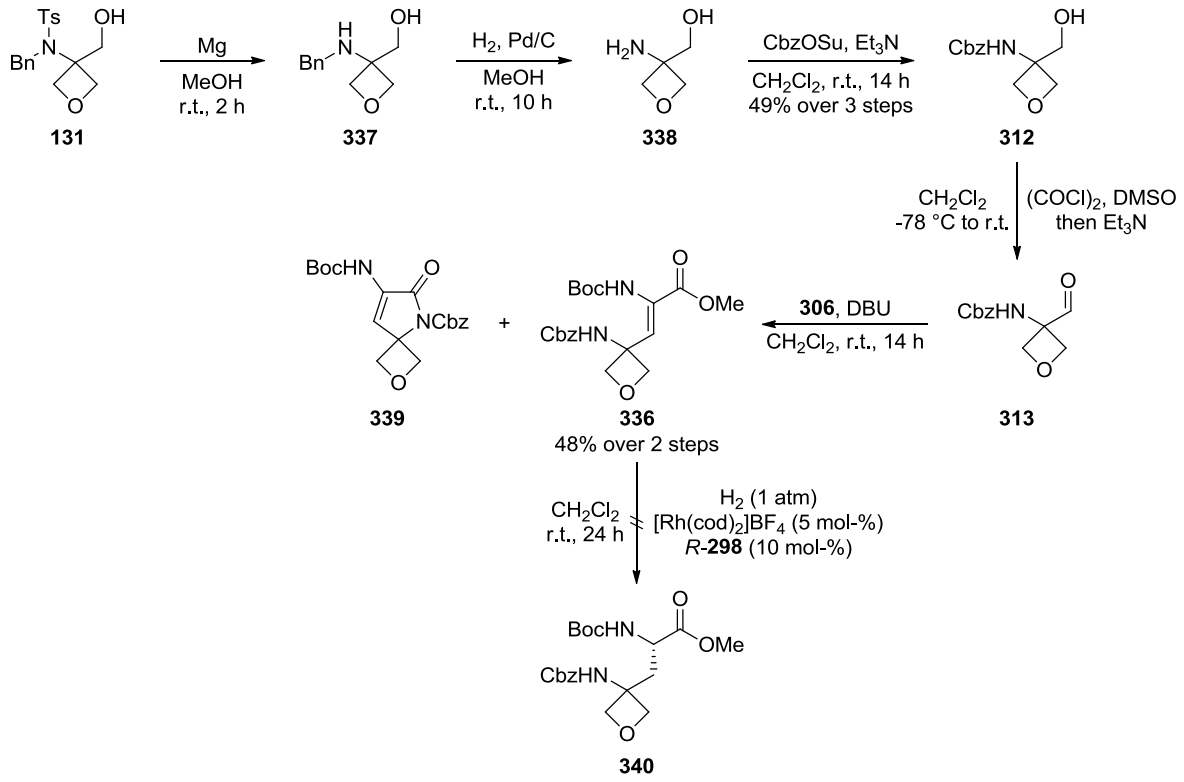
Scheme 103 Synthesis of Urea 333 from 330c.

Optical purity of **333** from the asymmetric hydrogenation of the Teoc- and Boc-protected precursors **329b** and **329c** was determined by chiral analytical HPLC to >98% and 84% *ee* respectively. Absolute configuration was assigned in analogy to Glu(Ox) and Lys(Az) (*vide infra*, chapters 3.3.5 and 3.3.7)

3.3.3 Synthesis of Asn(Ox) (281)

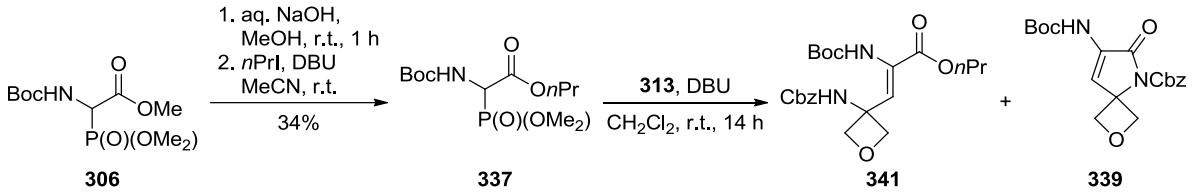
Up to this point, the oxetanyl side-chains incorporated were otherwise unfunctionalized. With the synthesis of Asn(Ox) (**281**) we first attempted the asymmetric hydrogenation in the presence another protected amine. We again chose the Boc/Alkyl profile for the backbone protection and this time Cbz for the

side-chain amine. Corresponding dehydroamino acid **336** was obtained starting from previously synthesized Ts- and benzyl protected alcohol **131** (chapter 2.3.1). Deprotection of the tosyl group to **337** and the benzyl group to **338** and reprotection of the free amino alcohol with Cbz led to **312** in 49% yield over three steps. Unfortunately, SWERN oxidation and subsequent reaction of crude aldehyde **313** with HWE reagent **306** furnished a mixture of products containing significant amounts of lactam **339** along with desired *Z*-isomer of **336**. Enamine **336** was nonetheless isolated in 48% yield. However, hydrogenation of **336** with $[Rh(cod)_2]BF_4$ and *R*-MonoPhos (*R*-**298**) did not effect the conversion of **336** to the desired Asn(Ox) derivative **340** (Scheme 104).



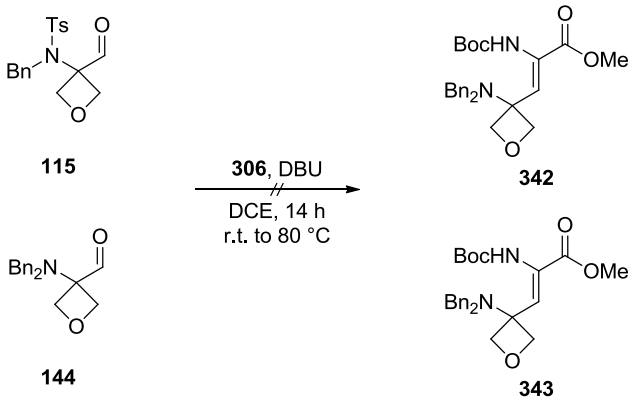
Scheme 104 Attempted Synthesis of BocNH-Asn(NHCbz, Ox)-OMe 340.

To suppress formation of undesired lactam **339**, reagent **306** was converted into its *n*-propyl ester **337**. Regrettably, the ratio of **339** to the desired condensation product **341** did not change compared to using the methyl ester (Scheme 105).



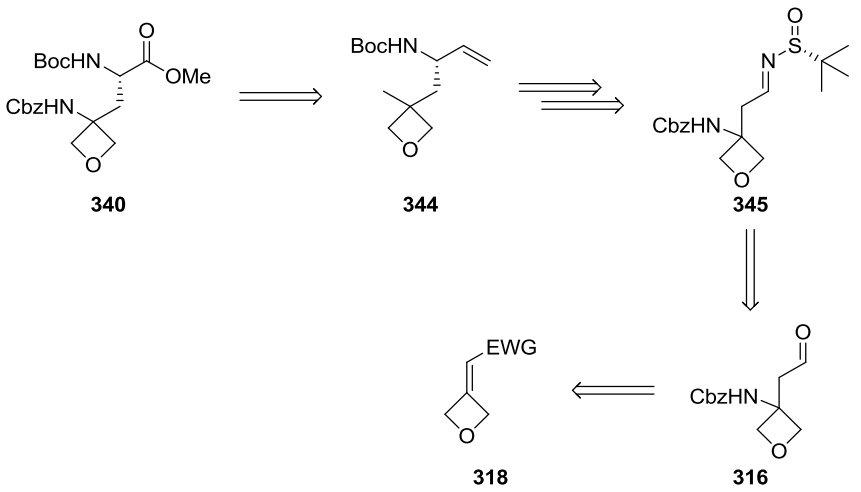
Scheme 105 Attempted Synthesis of 331.

We then attempted to directly use previously synthesized fully protected amino aldehydes **115** and **144** in the HWE reaction with **306** to enamines **342** and **343**. No reaction probably due to steric effects was observed in these cases even at elevated temperatures (Scheme 106).



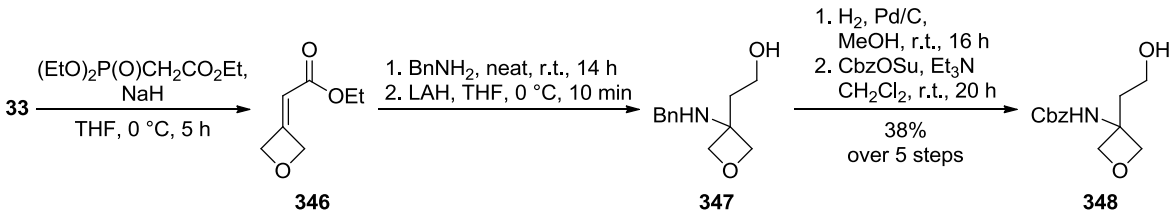
Scheme 106 Attempted Synthesis of Enamines 342 and 343.

Therefore, we decided to abandon the hydrogenation strategy for the synthesis of Asn(Ox) (**281**). Instead, we decided to turn our attention to the ELLMAN route outlined in chapter 0. This would in this case trace BocNH-Asn(NHCbz, Ox)-OMe (**340**) back to allyl amine **344**. Precursor **344** in turn would come from imine **345** and ultimately originate from aldehyde **316**. In chapter 3.2.1, we suggested **316** could be obtained by the 1,4-addition of a suitable nucleophile to **318**.



Scheme 107 Retrosynthesis for Second Generation Route to 340.

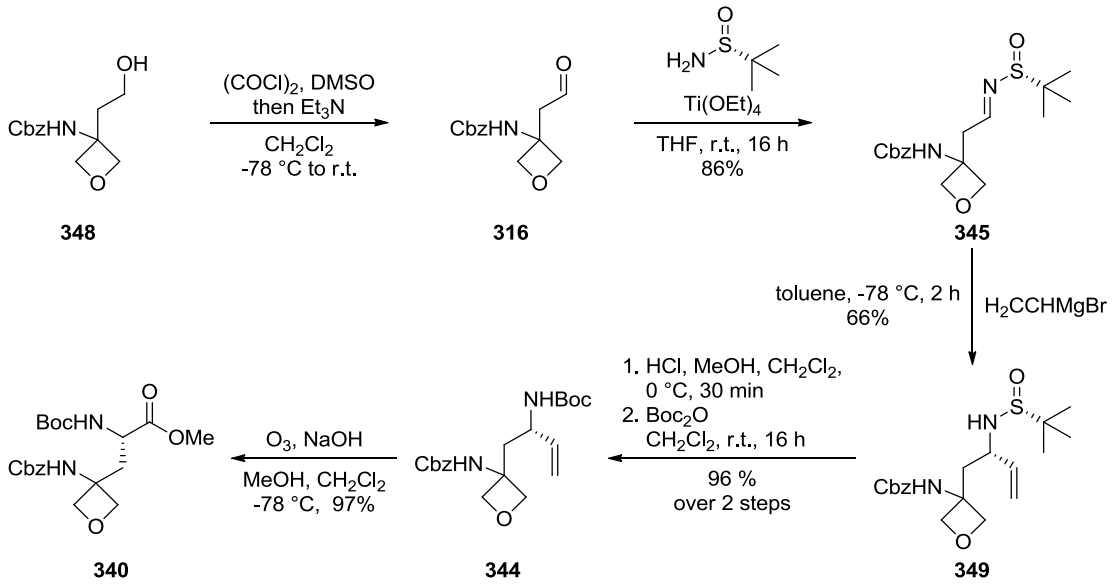
We started our synthetic efforts from oxetane-3-one (**33**) by a HWE reaction to previously reported unsaturated ester **346**.[101] MICHAEL acceptor **346** was then reacted with benzyl amine to the 1,4-addition product, followed by LAH reduction to the corresponding amino alcohol **347**. Subsequent hydrogenation of crude **347** and reprotection of the free amine with Cbz cleanly furnished **348** in 38% yield over five steps (Scheme 108).



Scheme 108 Synthesis of Aminoalcohol 348.

SWERN oxidation of alcohol **348** to aldehyde **316** and subsequent condensation with the (*R*)-ELLMAN auxiliary led to imine **345** in 86% over two steps. Again, the crude aldehyde solution from the oxidation step was used to reduce decomposition of **316**. Addition of vinyl magnesium bromide to **345** furnished allylamine **349** in 66% yield as a single diastereomer. Removal of the auxiliary and reprotection of the amine intermediate with Boc then yielded amino acid precursor **344** in 96%. Finally, allylamine **344** was converted into the corresponding methyl ester by ozonolysis under MARSHALL's conditions[270] to

yield BocNH-Asn(NHCbz, Ox)-OMe (**340**) in 97%. Oxidation of the allyl amine to the corresponding acid was also attempted with MnO_4 or $RuCl_3$ and $NaIO_4$.[271] In these cases, only traces of the desired product could be detected along with rapid decomposition of the starting material.

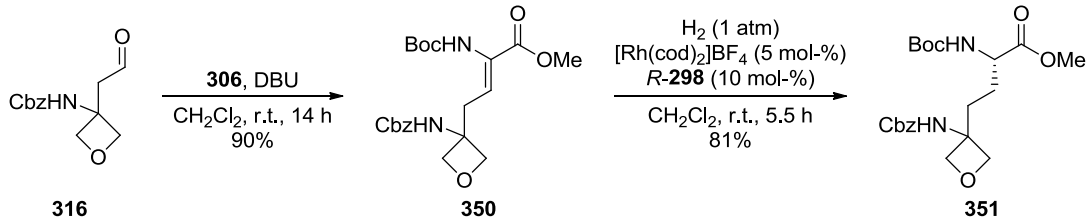


Scheme 109 Second Generation Synthesis of 340.

Absolute configuration of the α-stereocenter was assigned in analogy to Tle(Ox) (*vide infra*, chapter 3.3.8).

3.3.4 Synthesis of Gln(Ox) (282)

The synthesis of Gln(Ox) (**282**) was started from previously obtained aldehyde **316**. HWE reaction with **306** led to dehydroamino acid **350** in 83% yield. Subsequent, asymmetric hydrogenation cleanly delivered the desired derivative BocNH-Gln(NHCbz, Ox)-OMe (**351**) in 81% yield.[257]

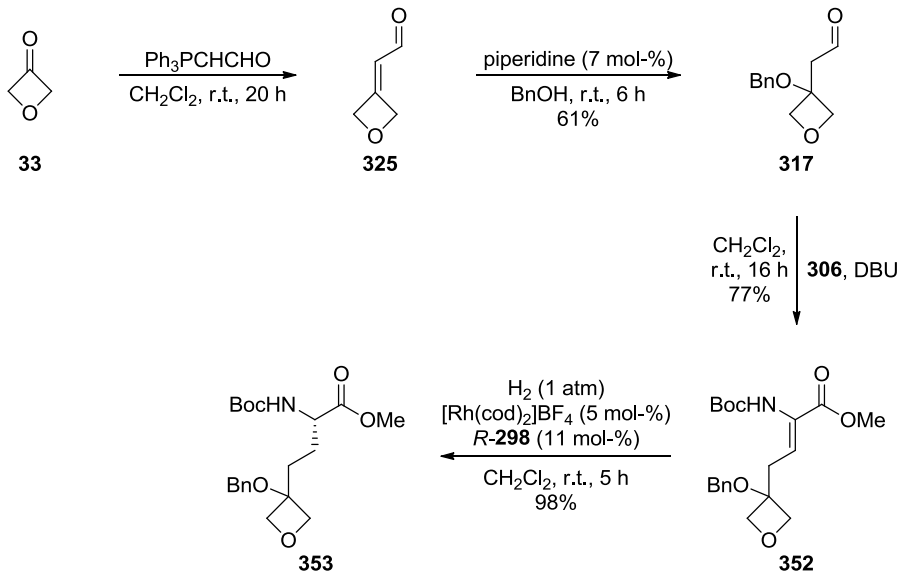


Scheme 110 Synthesis of BocNH-Gln(NHCbz, Ox)-OMe (351).

A racemic sample of **351** was obtained by using racemic ligand in the hydrogenation step. Enantiomeric excess was directly determined by chiral SFC of **351** to >98% *ee*.

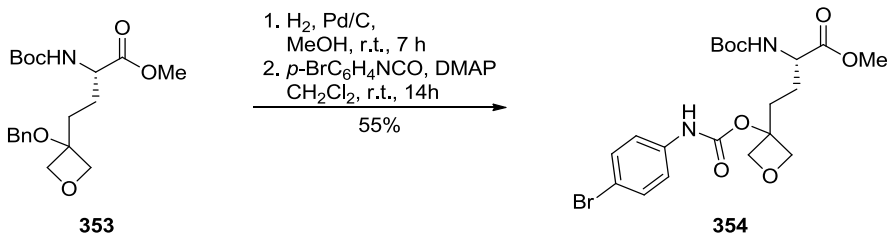
3.3.5 Synthesis of Glu(Ox) (284)

Similarly to the approach used for the synthesis of aldehyde **316** we started our synthetic efforts towards Glu(Ox) (**284**) from oxetane-3-one (**33**). Wittig reaction with (Triphenylphosphoranylidene)acetaldehyde yielded previously described unsaturated aldehyde **325**.[87] Subsequent 1,4-addition of benzylalcohol then furnished the required side chain aldehyde for Glu(Ox) **317** in 61% yield. The use of 7 mol-% piperidine as the catalyst proved to give the best yield in this step. HWE reaction with Boc-protected reagent **306** cleanly led to the *Z*-isomer of dehydroamino acid **352** in 77% yield. Finally, asymmetric hydrogenation with the Rh-MonoPhos system yielded the desired fully protected building block BocNH-Glu(OBn, Ox)-OMe (**353**) in 98% and 98% *ee* (Scheme 111).[257]



Scheme 111 Synthesis of BocNH-Glu(OBn, Ox)-OMe (353).

Furthermore, **352** was derivatized to carbamate **354** by hydrogenation to remove the side-chain protecting group followed by treatment with *p*-bromophenyl isocyanate (Scheme 112).



Scheme 112 Derivatization of 353 to Carbamate 354.

The absolute configuration of **354** was determined by single crystal X-Ray structure analysis as (*S*) (Figure 40). This is consistent with FERINGA's reports where (*R*)-MonoPhos ((*R*)-**298**) under the same conditions affords the (*S*)-enantiomers of acetamide protected amino acids.

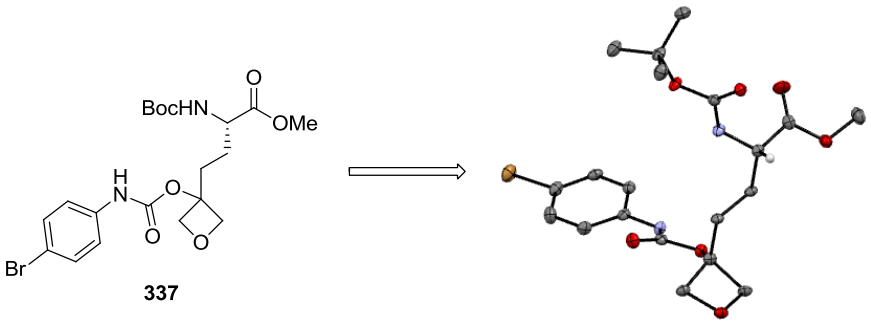
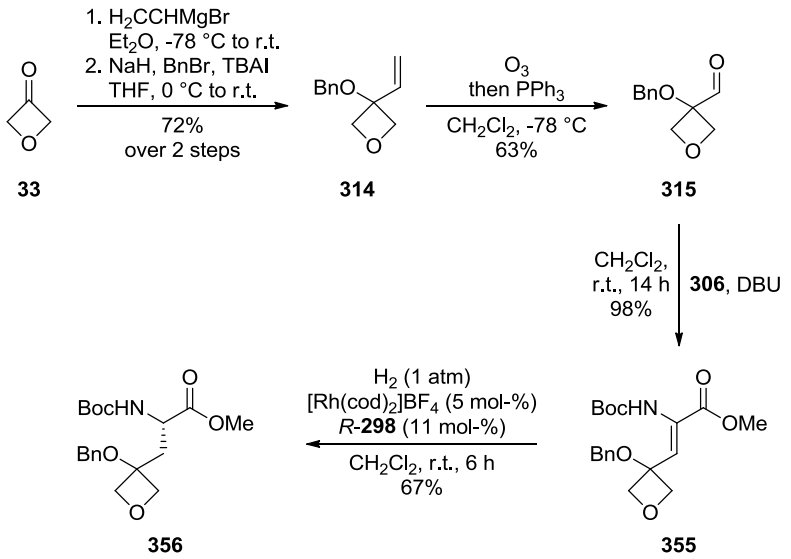


Figure 40 ORTEP-plot of the X-Ray Crystal Structure of 354 (ellipsoids are drawn at 50% probability, hydrogen atoms, except at the *C*-stereocenter, are omitted for clarity).

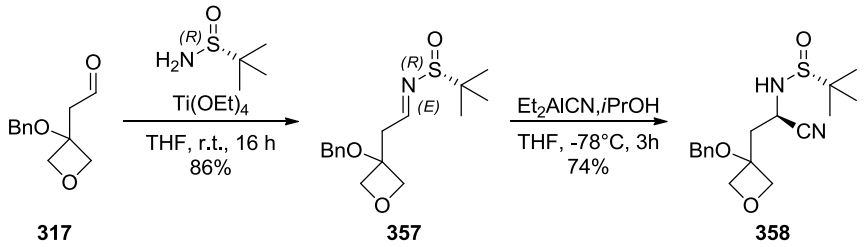
3.3.6 Synthesis of Asp(Ox) (283)

Next, we turned our attention to the synthesis of the Asp(Ox) (**283**) building block. Also in this case, we decided to start from oxetane-3-one (**33**). Addition of vinylmagnesium bromide and subsequent protection of the free alcohol with benzyl bromide delivered allyl alcohol **314** in 72% over two steps. Ozonolysis followed by reductive work-up cleanly furnished aldehyde **315** in 63% yield. HWE reaction with the Boc-protected reagent **306** gave dehydroamino acid **355** in 98% yield. Finally, asymmetric hydrogenation under the pevious conditions gave building block BocNH-Asp(OBn, Ox)-OMe (**356**) in 67% yield and >98% *ee* (Scheme 113).



Scheme 113 Synthesis of BocNH-Asp(OBn, Ox)-OMe (356).

Additionally, we investigated if previously synthesized aldehyde **317** could also be used for the synthesis of **356**. Condesation with the (*R*)-enantiomer of the ELLMAN auxiliary furnished imine **357** in 80% yield. We then decided to use cyanide as the precursor for the carboxylic acid in Asp(Ox) (**283**). The addition with ethylaluminum cyanoisopropoxide, generated from diethylaluminum cyanide and isopropanol,[272] cleanly provided adduct **358** as a single diastereomer in 74% yield (Scheme 114).



Scheme 114 Synthesis of Adduct 358 from Aldehyde 317.

The absolute configuration of **358** was determined by X-Ray crystal structure analysis as the undesired (*R,R*)-diastereomer (Figure 41).

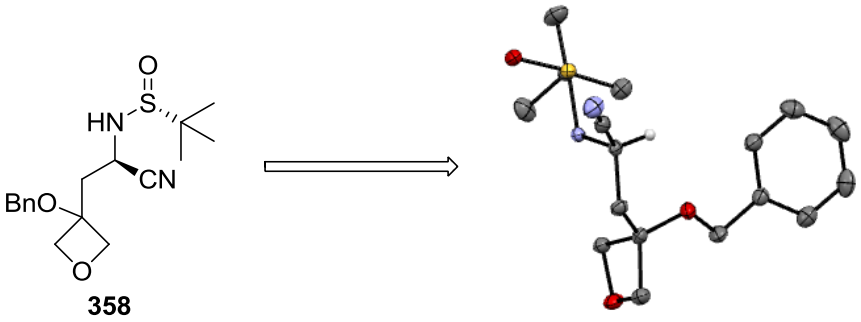
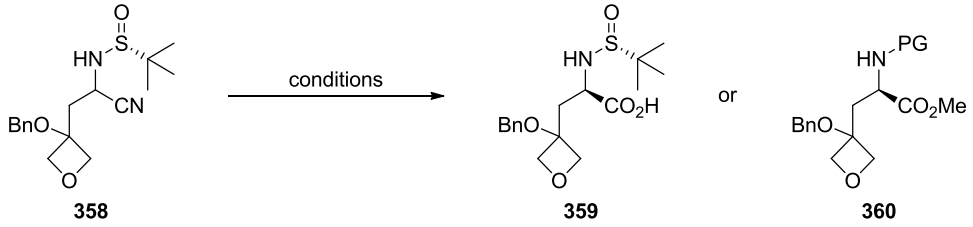


Figure 41 ORTEP-plot of the X-Ray Crystal Structure of 358 (ellipsoids are drawn at 50% probability, hydrogen atoms, except at the *C*-stereocenter, are omitted for clarity).

However, hydrolysis of the nitrile to the corresponding acid **359** or, under PINNER conditions, ester **360** was unsuccessful under a variety of conditions (Table 11).

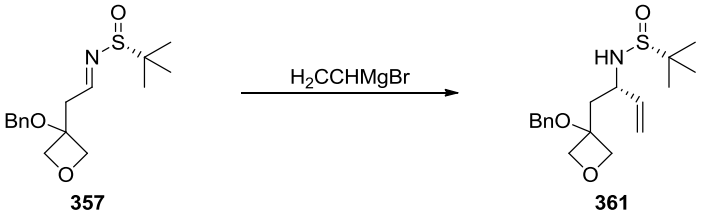
Table 11 Screening of Conditions for the Hydrolysis of 358.



Entry	Reagent	Solvent	Temp.	Result
1	H_2SO_4	water	60 °C	No reaction
2	AcCl	MeOH	0 °C	Complex Mixture
3	HCl	MeOH	0 °C	Complex Mixture
4	HCl	water	Reflux	Complex Mixture
5	Na_2O_2	water	90 °C	Complex Mixture

Hence, we again resorted to vinylmagnesium bromide as the carboxylic acid synthon. In this case diastereomeric mixtures of adduct **361** were observed. The use of toluene as the solvent at -78 °C finally provided **361** in a 2:1 separable mixture of diastereomers in 47% combined yield (Table 12).

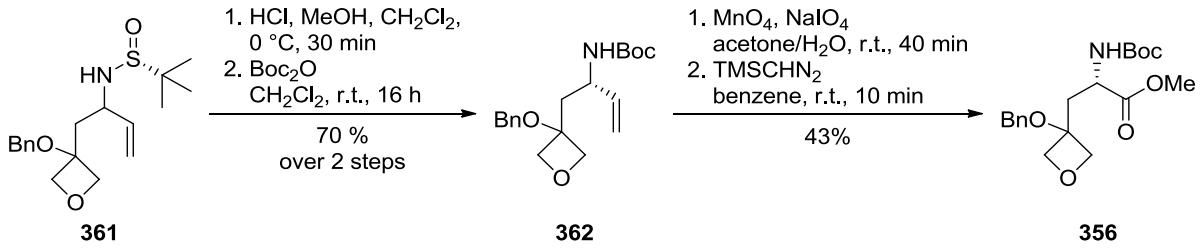
Table 12 Optimization of the Synthesis. of 361.



Entry	Solvent	Temp.	Time	Result
1	THF	-78 °C to 0 °C	30 min	10% yield
2	Et_2O	-78 °C	1 h	Low conversion
3	CH_2Cl_2	-78°C	20 min	Slow conversion, d.r. 2:1
4	Toluene	-78 °C.	10 min	88% (47%)[a] yield, d.r. 2:1
5	Toluene	reflux	5 min	No product formed

a yield (combined yield of separated diastereomers)

The major diastereomer of **361** was isolated by repetitive column chromatography and further elaborated to Boc-protected allyl amine **362** in 70% yield. Final oxidation to the corresponding amino acid was carried out with MnO_4 in the presence of $NaIO_4$. The desired product **356** was isolated in 43% yield after treatment with TMS-diazomethane (Scheme 115).

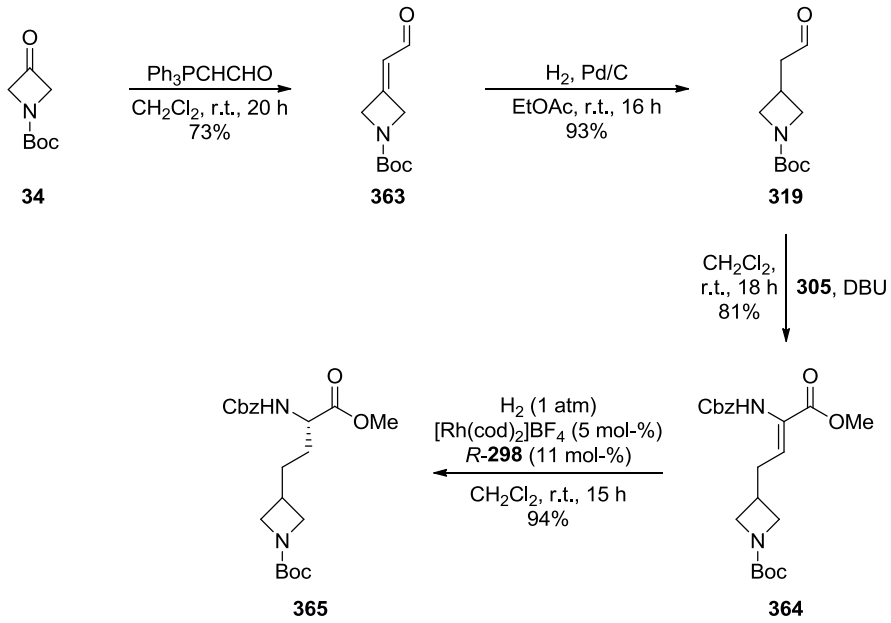


Scheme 115 Second Generation Synthesis of 356.

Since the much higher yielding and shorter route *via* the asymmetric hydrogenation was already established, the final oxidation step was not further optimized, e.g. by ozonolysis.

3.3.7 Synthesis of Lys(Az) (286)

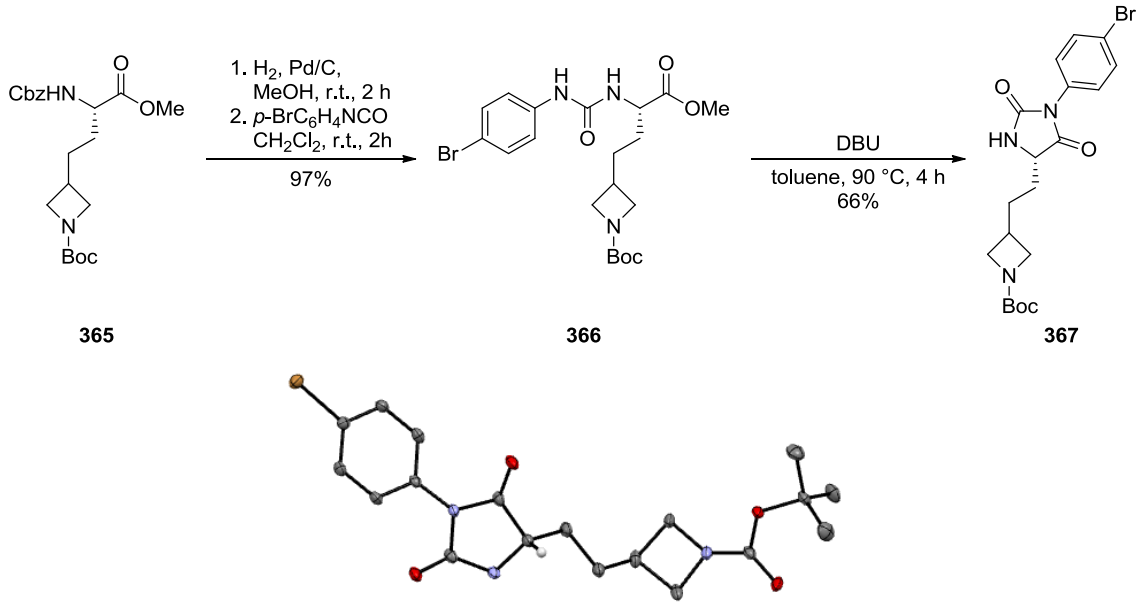
The last amino acid synthesis which was pursued *via* the asymmetric hydrogenation route aimed at azetidinyl amino acid Lys(Az) (**286**). In analogy to the synthesis of unsaturated aldehyde **325**, corresponding **363** was obtained from the reaction of Boc-azetidine-3-one (**34**) with (triphenylphosphoranylidene)-acetaldehyde in 73% yield as previously reported.[88] Hydrogenolysis in EtOAc in the presence of palladium on charcoal provided **319** in 93% yield. The use of methanol as the solvent in this step led to lower yields of **319**. Subsequently, dehydroamino acid **364** was obtained by HWE reaction with Cbz-protected glycine synthon **305** in 81% yield. Finally, asymmetric hydrogenation yielded fully protected amino acid CbzNH-Lys(NBoc, Az)-OMe (**365**) in 94% and 98% *ee*. As expected from previous hydrogenation attempts (chapter 3.3.1), the Cbz-group proved unreactive under these conditions (Scheme 116).



Scheme 116 Synthesis of CbzNH-Lys(NBoc, Az)-OMe (365).

In order to determine the absolute configuration of **365**, derivative **366** was obtained by Cbz-deprotection and subsequent treatment of the free amine with *p*-bromophenyl isocyanate. Upon crystallization, urea **366** cyclized to hydantoin **367** which was separately synthesized and characterized by treatment of **366**

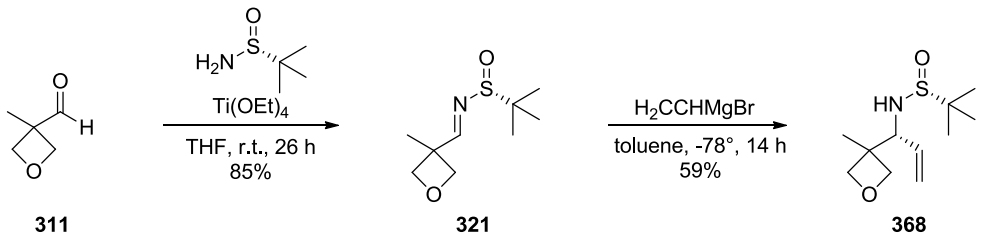
with DBU. Absolute configuration was determined by single crystal X-Ray structure analysis of hydantoin **367** (Scheme 117).



Scheme 117 Synthesis of Hydantoin 367 and ORTEP-plot of the X-Ray Crystal Structure of 367 (ellipsoids are drawn at 50% probability, hydrogen atoms, except at the *C*-stereocenter, are omitted for clarity).

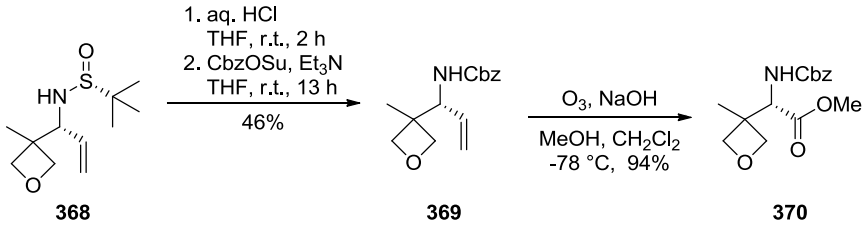
3.3.8 Synthesis of Tle(Ox) (278)

Finally, we turned our attention to Tle(Ox) (**278**) and Leu(Ox) (**279**) whose synthesis we had originally envisioned *via* the ELLMAN approach outlined in chapter 0. First, we pursued the synthesis of **278** from previously described aldehyde **311** (chapter 3.3.2). Imine **321** was obtained after condensation of **311** with the (*R*)-ELLMAN auxiliary in 85% yield. Subsequently, vinylmagnesium bromide was added to **321** to obtain allyl amine **368** (Scheme 118). Again, the GRIGNARD addition furnished a mixture of diastereomers of **368**. The highest d.r. (2:1) and yield could be obtained by using toluene as the solvent and running the reaction at -78 °C. The major diastereomer of **368** was isolated in 59% yield by repetitive column chromatography and then further elaborated to Tle(Ox) (**278**) derivative **370** (Scheme 119).



Scheme 118 Synthesis of Adduct 368.

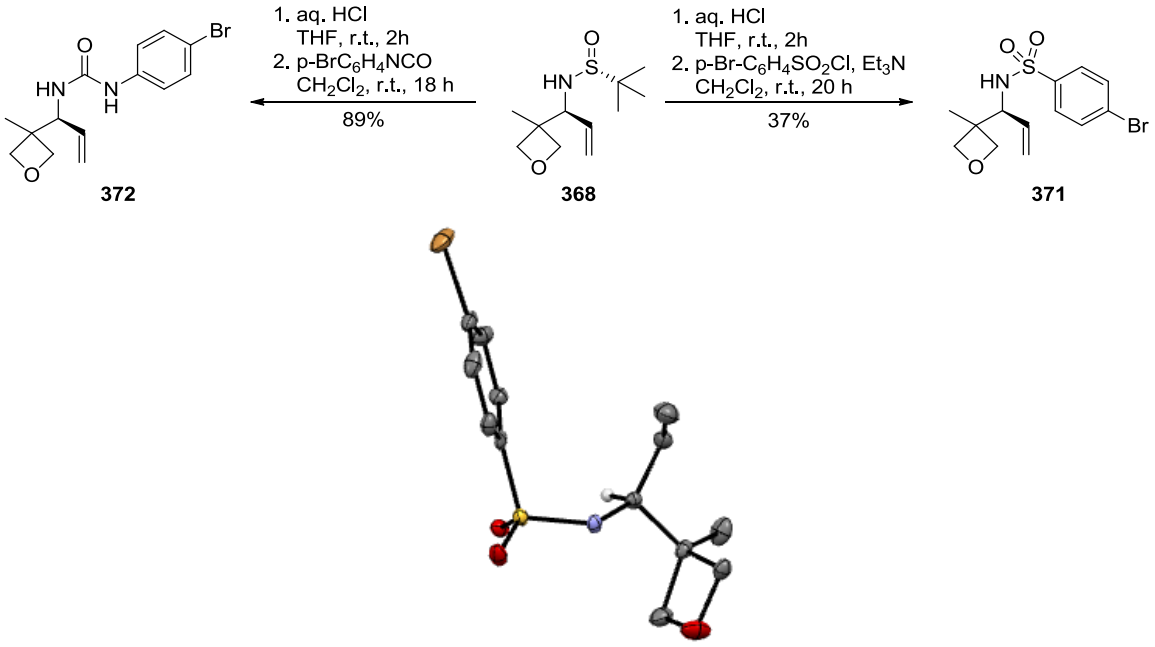
In the next step, the auxiliary had to be exchanged for a suitable protecting group for further transformations. In this case, we chose Cbz as the protecting group to complete the common Cbz/alkyl pattern and at the same time avoid problems originating from nucleophilic attack of the Boc-carbonyl oxygen upon deprotection. However, the conditions used up to this point, treatment of **368** with anhydrous HCl in methanol/CH_2Cl_2 at 0 °C followed by aqueous work-up, did not furnish the desired product, but led to decomposition of the starting material. Only when a combination of two molar aqueous HCl and THF was used at room temperature, **368** could cleanly be deprotected and **369** was obtained in 46% yield after treatment with CbzOSu. Final oxidation of the double bond to the corresponding methyl ester by ozonolysis under MARSHALL's conditions provided fully protected CbzNH-Tle(Ox)-OMe (**370**) in 94% yield (Scheme 119). Oxidation of allyl amine **369** in the presence of OsO_4 and oxone or $RuCl_3$ with $NaIO_4$ and subsequent treatment with TMS-diazomethane again gave inferior results (63% yield for Ru) (Scheme 119).[271]



Scheme 119 Synthesis of CbzNH-Tle(Ox)-OMe (370).

Furthermore, derivatives **371** and **372** were obtained from the minor diastereomer of **368** after removal of the auxiliary and reaction with *p*-bromobenzenesulfonyl chloride or *p*-bromophenyl isocyanate in 37% and 89%

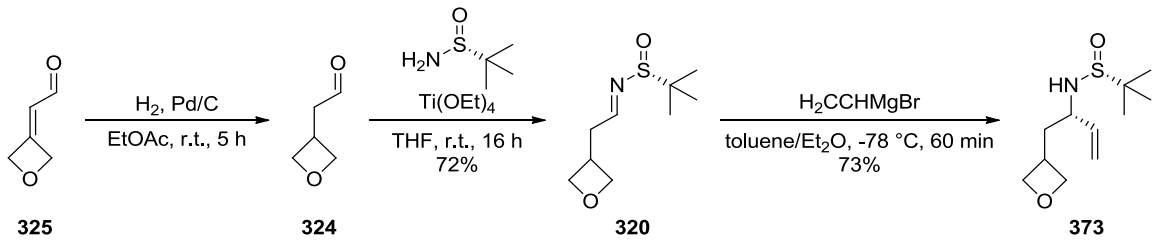
yield respectively. The absolute configuration of **371** was determined to (*S*) which would correspond to the (*R*)-enantiomer of **370** since the priorities according to the CIP-nomenclature of the substituents at the chiral center change in the final oxidation step (Scheme 120). This leads to the conclusion, that the major diastereomer in the addition step has (*R,R*)-Configuration and hence desired (*S*)-**370** was obtained as described above (Scheme 119).



Scheme 120 Synthesis of Derivatives 371 and 372 and ORTEP-plot of the X-Ray Crystal Structure of 371 (ellipsoids are drawn at 50% probability, hydrogen atoms, except at the *C*-stereocenter, are omitted for clarity).

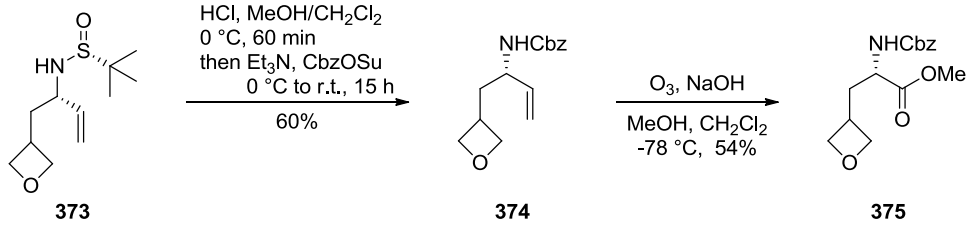
3.3.9 Synthesis of Leu(Ox) (279)

Finally, we turned our attention to the synthesis of Leu(Ox) (**279**). Using the same strategy as for the synthesis of aldehyde **319** (chapter 3.3.7), aldehyde **324** was obtained from **325** by hydrogenation in the presence of palladium on carbon in ethyl acetate. Condensation of crude aldehyde **324** with the (*R*)-enantiomer of the ELLMAN auxiliary furnished imine **320** in 72% yield over two steps. Reaction with vinylmagnesium bromide then afforded allyl amine **373** in 73% yield as a single diastereomer (Scheme 121).



Scheme 121 Synthesis of Adduct 373.

Also in this case, removal of the auxiliary under acidic conditions was difficult. Both our standard procedure with anhydrous HCl followed by aqueous work-up and the new method with aqueous HCl, which had been successful for Tle(Ox) precursor **368**, led to decomposition of **373**. Only, when the reaction mixture from using anhydrous HCl in methanol/CH_2Cl_2 at 0 °C was directly treated with triethylamine and CbzOSu, Cbz-protected derivative **374** could be isolated in 60% yield. Finally, oxidation of **374** under MARSHALL's conditions yielded the desired building block CbzNH-Leu(Ox)-OMe (**375**) in 54% (Scheme 122). However, all intermediates of this route are highly sensitive to acidic conditions which might limit the use of **375** as a robust building block in medicinal chemistry.

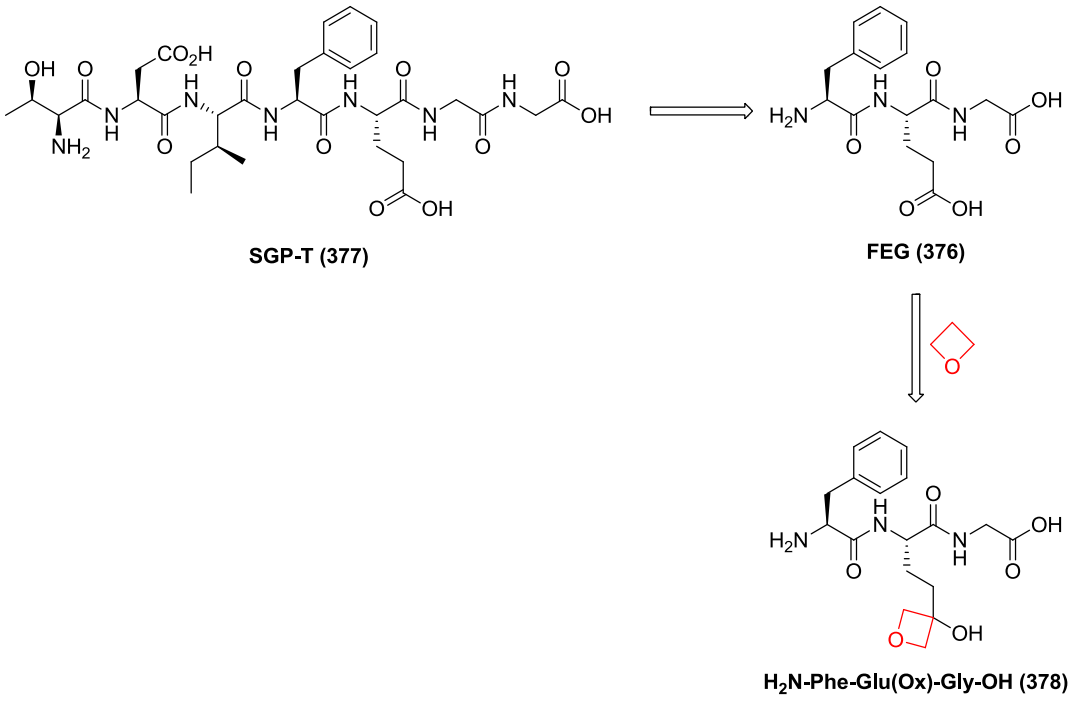


Scheme 122 Synthesis of CbzNH-Leu(Ox)-OMe (375).

Absolute configuration was assigned in analogy to Tle(Ox) derivative **371** (chapter 3.3.8).

3.4 Incorporation of Glu(Ox) (284) into Submandibular Gland Tripeptide Phe-Glu-Gly (376)

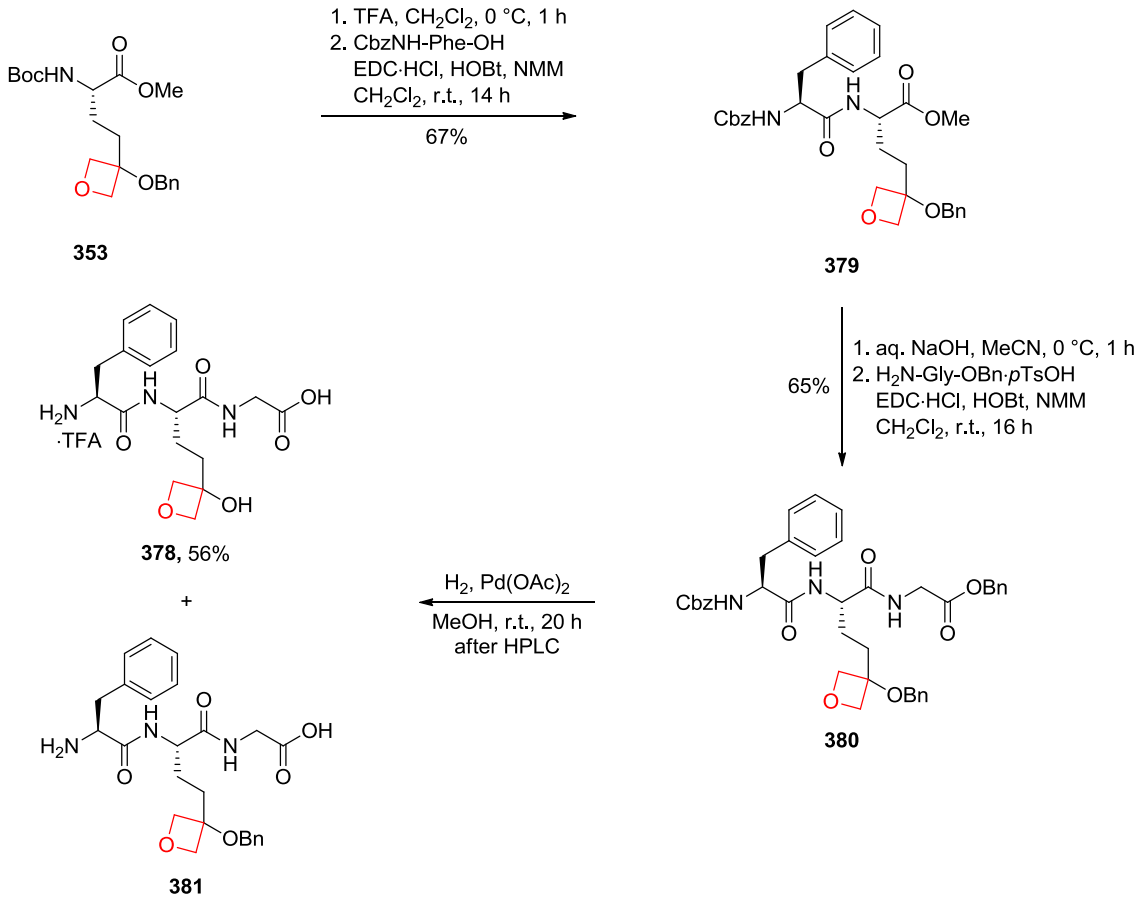
Up to this point, the envisioned building blocks **277**-**284** and **286** were synthesized (chapter 3.3) and therefore made available for the incorporation into larger bioactive peptides. We chose Submandibular Gland Tripeptide H_2N-Phe-Glu-Gly-OH (**376**)[273] as a first target for the evaluation of our oxetanyl amino acids in pharmacological settings. Tripeptide **376** is derived from the C-terminal region of submandibular gland peptide-T (SGP-T, **377**, H_2N-Thr-Asp-Ile-Phe-Glu-Gly-Gly-OH). Natural heptapeptide **377** is an endogenous inhibitor of hypotensive response to endotoxic and anaphylactic shock.[274,275] The truncated version **376** has been shown to be a potent anti-anaphylactic agent, as well.[273] Extensive structure-activity studies using a rat model[276] have been carried out to elucidate the mode of action of **376**.[273,277] Especially salt bridges, stabilizing the conformation of **376** have been under debate.[277] Hence, we decided to synthesize derivative H_2N-Phe-Glu(Ox)-Gly-OH (**378**) to test the effect of the substitution of the side-chain carboxylic acid by a 3-hydroxy oxetane unit (Scheme 123).



Scheme 123 Conceptual Idea for the Synthesis of 378.

3.4.1 Synthesis

The synthesis of H_2N-Phe-Glu(Ox)-Gly-OH was achieved from BocNH-Glu(OBn, Ox)-OMe (**353**) using standard EDC mediated peptide couplings. First, building block **353** was deprotected at the N-terminus and coupled to CbzNH-Phe-OH to yield fully protected dipeptide **379** in 67%. After *C*-terminal deprotection of **379** and reaction with H_2N-Gly-OBn, tripeptide **380** was obtained in 65% yield. Final deprotection of **380** to the desired free oxetanyl peptide **378** was achieved by hydrogenation and furnished **378** as its TFA salt in 56% yield after purification by preparative HPLC. The main side product in the last step was partially deprotected derivative **381** which in principle could be resubjected to the hydrogenation conditions (Scheme 124).



Scheme 124 Synthesis of H_2N-Phe-Glu(Ox)-Gly-OH (378).

3.4.2 Planned Biological Studies

The inhibition of intestinal anaphylaxis can be evaluated both *ex* and *in vivo*. The first method would involve the sensitization of rats to ovalbumin assisted by the administration of pertussis toxin.[274,278] The terminal ileum would then be excised and the isometric force generated by its treatment with ovalbumin relative to the response to urecholin, a cholinergic agonist, determined. The obtained data is a measure for anaphylaxis in the control sample. Finally, the isolated tissue would be incubated with tripeptides **378** and **376**. Subsequent stimulation with ovalbumin would again be tested and compared to the values for the control sample.[274,277]

Secondly, intestinal anaphylaxis can be studied by a complex procedure involving several surgical implantations of probes in rats. This would then allow monitoring the reaction of the ileum after the administration of ovalbumin to correspondingly sensitized rats.[273,279] Another *in vivo* rat model for intestinal anaphylaxis uses the accumulation of ^{125}I-labled bovine serum albumin in the intestinal tissue after challenging with sensitizing agent.[276] For our conceptual studies, investigations will be limited to the *ex vivo* method outlined above.

4

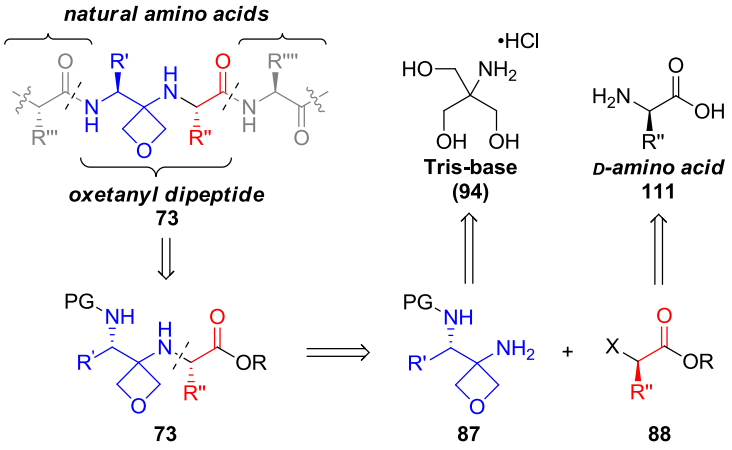
Conclusion & Outlook

4.1 Backbone-Modified Oxetanyl Peptides

We envision oxetanyl peptides, a new class of primary structure peptidomimetics, to be used as a valuable tool for the development of peptide based active pharmaceutical agents. Their enhanced metabolic stability along with retention of pharmacological activity makes them ideal candidates for drug development.

In chapter 2 of this work, a novel approach for the stereopure synthesis of backbone-modified oxetanyl peptides was elaborated. Our synthetic strategy is based on the synthesis of dipeptide building blocks **73** where the central amide bond is substituted with a 3-aminooxetane unit. The obtained dipeptide units can then be incorporated into larger peptides by standard peptide coupling.

The synthesis of a variety of stereopure oxetanyl dipeptides **73** was achieved *via* the alkylation of 3-amino oxetanes **87** with bromo acetates or triflate esters **88**. This modular approach not only allows the assembly of a large collection of different building blocks **73** but also makes all diastereomers of **73** available by appropriate choice of **87** and **88** (Scheme 125). This enables one to combine the oxetane concept with other peptidomimetic approaches such as retro-inverso peptides.



Scheme 125 Overview Dipeptide Synthesis an Incorporation.

Furthermore, both the 3-amino oxetanes **87** and the alkylating agents **88** were traced back to inexpensive and commercially available starting materials, Tris-base (**94**) and D-amino acids **111** respectively (Scheme 125). This inspired the development of a diverse collection of amines **87** and triflates **88** and provided access to sufficient amounts of material for the synthesis of larger oxetanyl peptides (Figure 42).

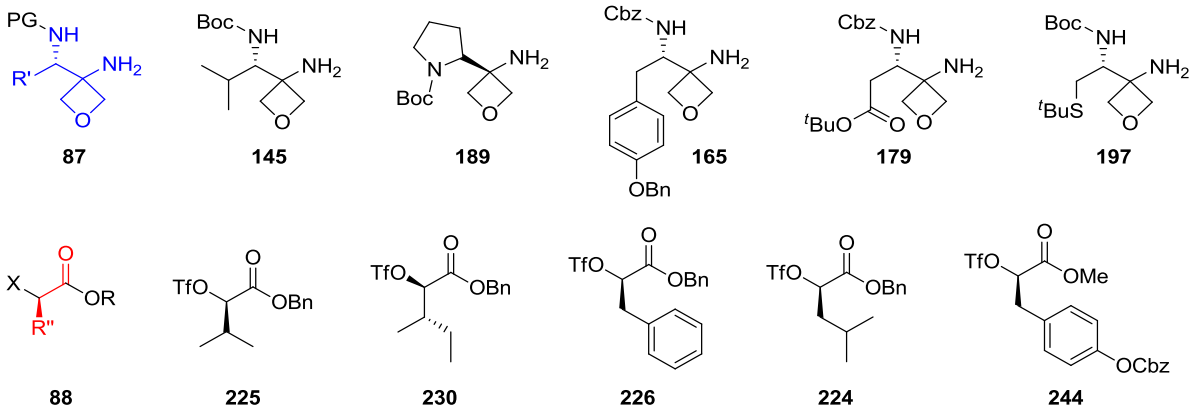
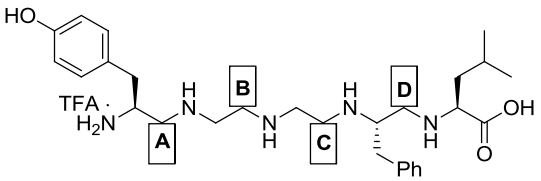


Figure 42 Selected Examples of Amines 87 and Triflates 88.

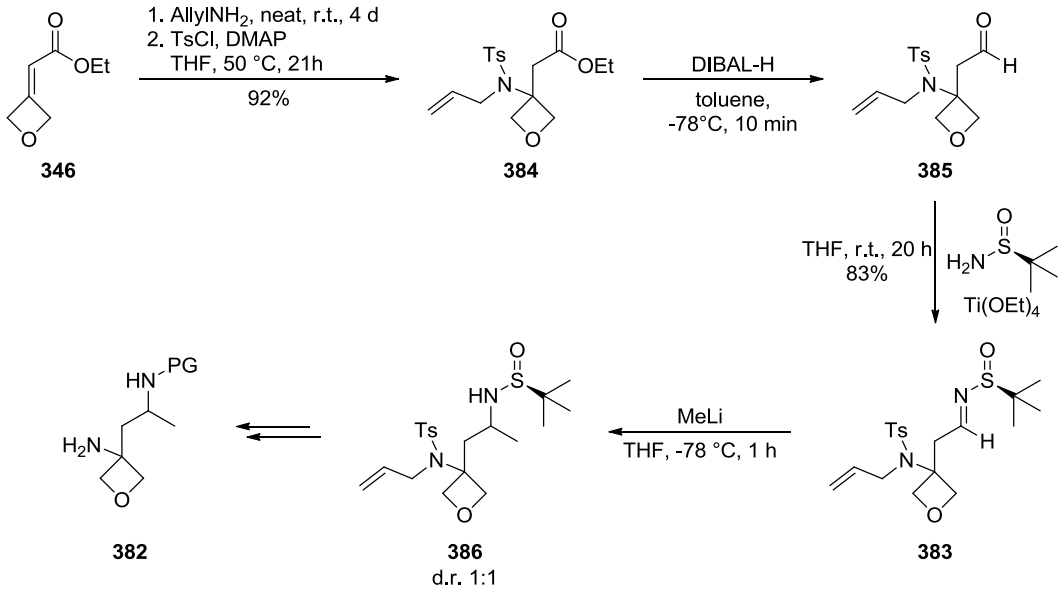
Finally, we have incorporated our newly designed building blocks **73** into two pharmaceutically active peptides. The first target was the prominent endogenous neurotransmitter Leu-Enkephalin (**247a**). Four analogues **247b-e**, each containing one oxetane substitution, were synthesized and evaluated for their metabolic stability as well as affinity and activity at the δ-opioid receptor. Furthermore, the *in vivo* activity of the most promising candidate (**247e**) was determined. We have shown that the incorporation of a 3-amino oxetane can significantly increase the half-life time of a peptide in human serum. Two (**247d** and **247e**) of obtained oxetanyl analogues still bind to the δ-opioid receptor with a nanomolar affinity. However, the agonistic activity is largely reduced; only compound **247e** is still active in the low micromolar range. Oxetanyl peptide **247e** still shows a significant analgesic activity in mice in a hot-plate test (Figure 43).



	A	B	C	D	Serum Half-life	δ-Affinity K_i/nM	δ–Agonist IC_{50}/μM	Hot Plate Test
***Leu-enkephalin* (247a)**	C=O	C=O	C=O	C=O	≈ 10 min	9.2	0.020	11 s
***Tyr*^{5}*(Ox) Analog* (247b)**		C=O	C=O	C=O	≈ 3.2 hrs	>1000	54	
***Gly*^{4}*(Ox) Analog* (247c)**	C=O		C=O	C=O	≈ 18 hrs	>1000	>1000	
***Gly*^{3}*(Ox) Analog* (247d)**	C=O	C=O		C=O	≈ 15 min	157	>1000	
***Phe*^{2}*(Ox) Analog* (247e)**	C=O	C=O	C=O		≈ 26 min	43	5.6	14 s

Figure 43 Summary of Results for Leu-Enkephalin Mimics 247b-e.

Secondly, four analogues of an inhibitor of the aggregation of α-Synuclein were synthesized. Fibrillation of α-Synuclein is suspected to be the major cause of PARKINSON's disease. Studies on their activity against the formation of α-Synuclein fibrils and their ability to redissolve amyloidogenic aggregates are ongoing.

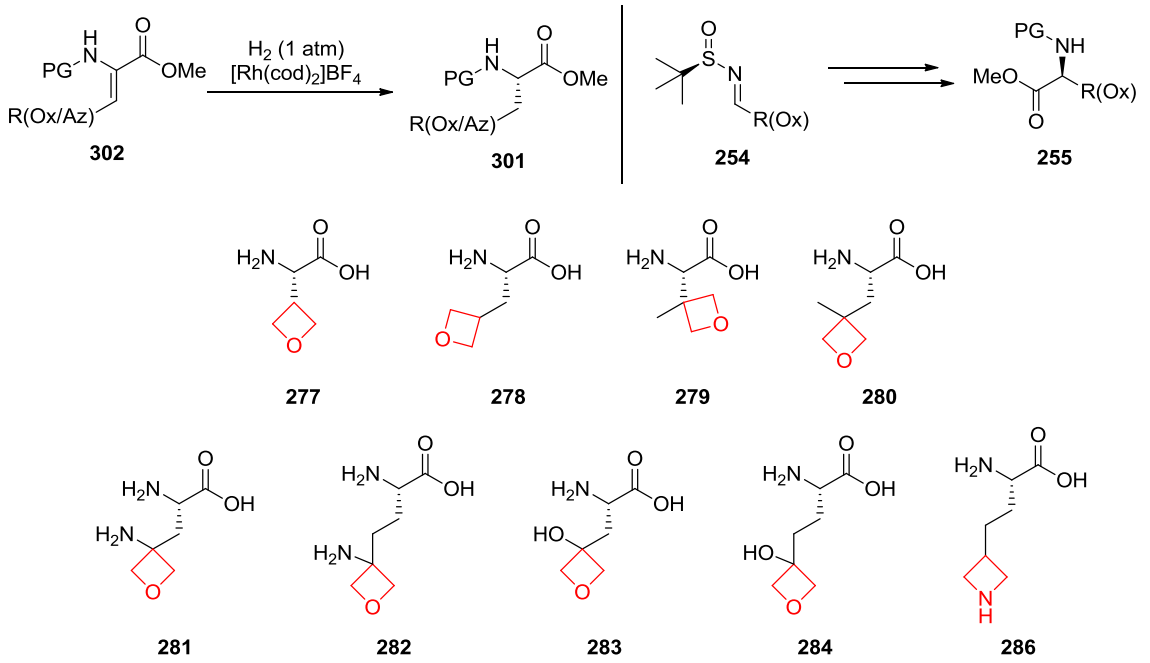


Scheme 126 Preliminary Studies towards the Synthesis of Oxetanyl β-Peptides.

In extension to this work, the concept of oxetanyl peptides could be applied to the synthesis of backbone-modified β-peptides or mixed α/β-peptides. Relying on the alkylation approach outlined above would necessitate the synthesis of the corresponding amine building blocks **382**. Preliminary studies showed that the key intermediate imine **383** can be derived from unsaturated ester (**346**) *via* ester **384** and aldehyde **385** in four steps and 76% overall yield. However, methyllithium addition to **383** to obtain adduct **386** so far only furnished inseparable 1:1 mixtures of diastereomers (Scheme 126). Further studies to optimize this step and towards the design of suitable alkylating agents will be subject of future research.

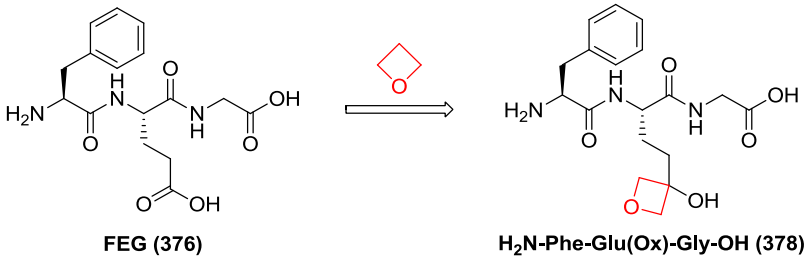
4.2 Side Chain-Modified Oxetanyl Peptides

Following the concept of oxetanes as surrogates for *gem*-dimethyl and carbonyl groups, several side-chain modified amino acids were envisioned as valuable building blocks in peptide synthesis. *Gem*-dimethyl groups are often used in medicinal chemistry to block metabolically labile sites. Mimicking gem-dimethyl groups with oxetanes could ameliorate the lipophilicity of these moieties. Hence, a variety of oxetane analogues of amino acids containing *gem*-dimethyl groups in their side chain (**277**-**280**) was synthesized to provide surrogates with improved lipophilicity profile. Furthermore, using the oxetane as a carbonyl mimic in amino acid side chains, significantly alters their electrostatic properties. Converting amides to mildly basic oxetanyl amines (**281**-**282**) and carboxylic acids to oxetanyl alcohols (**283**-**284**) led to novel building blocks that can engage in different intermolecular interactions thereby containing the typical exit vectors of the parent compounds. Finally, also Lys(Az) (**286**) was synthesized. Two strategies based on well-established methodologies, asymmetric hydrogenation and ELLMAN auxiliary chemistry, were employed for the preparation of the desired building blocks. This approach in principle also allows the preparation of either enantiomer of the building blocks (chapter 3.2).



Scheme 127 Summary of Synthesized Oxetanyl Amino Acids.

Additionally, we decided to incorporate the newly obtained oxetanyl amino acids into a bioactive peptide. We chose truncated submandibular glad peptide FEG as a suitable target. Especially the salt bridges originating from the side-chain carboxylic acid have been subject of SAR studies. Hence, the incorporation of the Glu(Ox) (**284**) building block could provide valuable insight into the function of the anti-anaphylactic agent FEG (Scheme 128). The synthesis of H_2N-Phe-Glu(Ox)-Gly-OH (**378**) was achieved by standard EDC mediated peptide couplings.



Scheme 128 Transition from FEG 376 to Oxetanyl Peptide 378.

Studies on the pharmacokinetic profile and the pharmaceutical cativity of **378** will be subject of future research.

5

Experimental Part

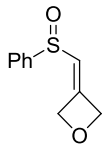
5.1 General Methods

Unless otherwise stated, all **REAGENTS** were purchased from commercial suppliers and used without further purification. Triethylamine and pyridine were distilled from potassium hydroxide under an atmosphere of dry nitrogen; *N*,*N*-Diisopropylethylamine was distilled from sodium hydride under an atmosphere of dry nitrogen. All non-aqueous **REACTIONS** were conducted under dry nitrogen atmosphere in reagent grade solvents and monitored by thin layer chromatography (TLC) on Merck silica gel 60 F254 TLC glass plates unless noted otherwise. Visualization was accomplished by irradiation with UV light at 254 nm and/or ceric ammonium molybdate, potassium permanganate or ninhydrin stain. Flash column chromatography was performed on Fluka silica gel (pore size 60 Å, 230-400 mesh particle size) at 0.3 bar pressure. ^{1}H, ^{19}F and ^{13}C **NMR SPECTRA** were recorded on VARIAN Mercury (300 MHz), BRUKER DRX (400 MHz), BRUKER Avance (400 MHz) spectrometers in the solvents indicated. Proton chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$ δ 7.26 ppm, Methanol-d^4 δ 3.31 ppm, Acetonitrile-d^3 δ 1.94 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br = broad signal), coupling constant(s) (J/Hz) and integration. ^{13}C NMR spectra were recorded with broadband ^{1}H-decoupling and are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$, δ 77.16 ppm, Methanol-d^4 δ 49.00 ppm, Acetonitrile-d^3 δ 118.26 ppm). Yields are reported for compounds as shown in the NMR spectra without correction for purity. **INFRARED SPECTRA (IR)** were recorded on a Perkin Elmer Varian 800 FT-IR Spectrophotometer and are wavenumbers of absorption (ν/cm^{-1}). **MASS SPECTROMETRIC MEASUREMENTS (MS)** were performed as high resolution ESI measurements on a Bruker maXis ESI-Q-TOF or as high resolution MALDI measurements on a Varian IonSpec Ultima – MALDI-FT ICR by the mass spectrometry service of the Laboratorium für Organische Chemie at the ETH

Zurich. **MELTING POINTS** were measured on a on a Büchi B-540 melting point apparatus using open glass capillaries and are uncorrected. **X-RAY CHRYSTALLOGRAPHIC DATA** was collected by Dr. Nils Trapp and Dr. Bernd Schweizer of the Laboratorium für Organische Chemie at the ETH Zürich. **OPTICAL ROTATIONS (α_D)** were measured with a Jasco P-2000 Polarimeter, 10 cm, 1.5 mL cell. **ENANTIOMERIC EXCESS (*ee*)** was determined by chiral analytical HPLC on a Waters e2695, 2998 or by chiral analytical supercritical fluid chromatography (SFC) on a Jasco2080Plus system.

5.2 Experimental Procedures to Chapter 2

3-((Phenylsulfinyl)methylene)oxetane (**78**)



To a solution of diisopropylamine (0.40 mL, 2.8 mmol, 1.3 eq) in THF (8.9 mL) at -78 °C was added *n*-BuLi (1.6 M in hexanes, 1.5 mL, 2.4 mmol, 1.1 eq). The mixture was stirred for 15 min. (Methylsulfinyl)benzene (300 mg, 2.1 mmol, 1.0 eq) in THF (0.89 mL) was added and the mixture was stirred for 30 min. A solution of oxetan-3-one (0.15 mL, 2.4 mmol, 1.1 eq) in THF (0.89 mL) was added and the solution was allowed to slowly warm up to r.t. for 1.5 h before cooling back to -78 °C and adding Ms-Cl (250 µl, 3.2 mmol, 1.5 eq). After stirring for 30 min at that temperature and 1 h at r.t. the reaction was quenched with sat. aq. NH_4Cl solution (20 mL). The aq. layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The crude product was filtered through a plug of silica (hex:EtOAc = 1:2) and used in the next step without further purification.

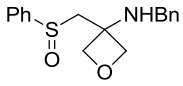
To a solution of crude 3-((phenylsulfinyl)methyl)oxetan-3-yl methanesulfonate (0.32 g, 1.1 mmol, 1.0 eq) in THF (4.3 mL) at 0 °C was added sodium hydride (60% in mineral oil, 0.065 g, 1.6 mmol). The mixture was allowed to warm to r.t. and further stirred for 3 h., The reaction was quenched by the addition of sat. aq. NH_4Cl solution (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The crude product was purified by FC on silica (EtOAc) to yield the title compound **78** (0.17 g, 0.86 mmol, 40% over two steps) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.68 – 7.50 (m, 5H), 6.00 – 5.94 (m, 1H), 5.74 – 5.63 (m, 1H), 5.63 – 5.53 (m, 1H), 5.37 – 5.22 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.0, 143.5, 131.1, 130.2, 129.7, 123.3, 79.2, 79.0 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{10}H_{11}O_2S$ $[M+H]^+$ 195.0474, found, 195.0475.

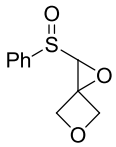
N-benzyl-3-((phenylsulfinyl)methyl)oxetan-3-amine (**82**)



A mixture of benzylamine (30 µL, 0.270 mmol, 1.05 eq) and **78** (50 mg, 0.257 mmol, 1.00 eq) was stirred neat at r.t. for 2.5 d. The mixture solidified to a colorless solid which was identified as **82** (77 mg, 0.255 mmol, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.69 – 7.28 (m, 10H), 4.75 (d, *J* = 7.0 Hz, 1H), 4.73 – 4.63 (m, 2H), 4.42 (d, *J* = 6.8 Hz, 1H), 4.01 – 3.84 (m, 2H), 3.50 (d, *J* = 12.9 Hz, 1H), 3.19 (d, *J* = 12.9 Hz, 1H) ppm.

2-(Phenylsulfinyl)-1,5-dioxaspiro[2.3]hexane (**80**)



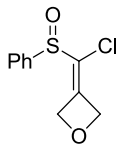
To a solution of diisopropylamine (265 µl, 1.86 mmol, 1.30 eq) in THF (6.0 mL) at -78 °C was added *n*-BuLi (1.6 M in hexanes, 0.98 mL, 1.58 mmol, 1.10 eq). The mixture was stirred for 15 min. ((Chloromethyl)sulfinyl)benzene (250 mg, 1.43 mmol, 1.00 eq) in THF (0.60 mL) was added and the mixture was stirred for 15 min. A solution of oxetan-3-one (100 µl, 1.58 mmol, 1.10 eq) in THF (0.60 mL) was added and the solution was stirred for 20 min before quenching with sat. aq. NH_4Cl solution (5 mL). The aq. layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The crude product (colorless oil was used in the next step without further purification.

To a solution of the crude product from the previous step (332 mg, 1.35 mmol, 1.00 eq) in *t*BuOH (9.0 mL) was added KO*t*Bu (227 mg, 2.02 mmol, 1.50 eq) at r.t. The mixture was stirred for 12.5 h before sat. aq. NH_4Cl solution (5 mL) was added. The aq. layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined org. layers were dried over Na_2SO_4. The crude product was purified by FC on silica (hex:EtOAc = 1:1) to yield **80** (198 mg, 0.943 mmol, 66% over two steps) as a colorless wax.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.79 – 7.45 (m, 5H), 5.41 (dd, *J* = 9.1, 1.5 Hz, 1H), 5.23 – 5.05 (m, 1H), 5.02 – 4.83 (m, 2H), 3.90 (s, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 132.2, 129.9, 124.7, 77.5, 71.6 ppm.

3-(Chloro(phenylsulfinyl)methylene)oxetane (**85**)



To a solution of diisopropylamine (320 µl, 2.23 mmol, 1.30 eq) in THF (7.2 mL) at -78 °C was added *n*-BuLi (1.6 M in hexanes, 1.18 mL, 1.89 mmol, 1.10 eq). The mixture was stirred for 15 min. ((chloromethyl)sulfinyl)benzene (300 mg, 1.72 mmol, 1.00 eq) in THF (0.72 mL) was added and the mixture was stirred for 15 min. A solution of oxetan-3-one (120 µl, 1.89 mmol, 1.10 eq) in THF (0.72 mL) was added and the solution was stirred for 20 min before quenching with sat. aq. NH_4Cl solution (5 mL). The aq. layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The crude product was directly used in the next step without further purification.

To a solution of the crude product (0.324 g, 1.31 mmol, 1.00 eq) in CH_2Cl_2 (10.5 mL) at 0 °C was added triethylamine (0.37 ml, 2.63 mmol, 2.00 eq). Then Ms-Cl (0.31 ml, 3.94 mmol, 3.00 eq) was added slowly. The mixture was stirred for 2 h. The mixture was diluted with aq. citric acid (5%, 20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The crude product was directly used in the next step without further purification.

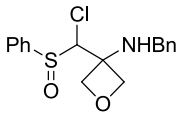
To a solution of the crude product (0.425 g, 1.31 mmol, 1.00 eq) in THF (5.2 mL) at 0 °C was added sodium hydride (60% in mineral oil, 0.262 g, 6.54 mmol, 5.00 eq). The mixture was stirred at 0 °C for 3 h before sat. aq. NH_4Cl solution (20 mL) was carefully added. The mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined org. layers were dried over Na_2SO_4 and concentrated.

The crude product was purified by FC on silica (hex:EA=1:1) to yield **85** (122 mg, 0.533 mmol, 24% over three steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 – 7.46 (m, 5H), 4.96 (d, J = 12.8 Hz, 1H), 4.75 (d, J = 12.8 Hz, 1H), 4.58 (d, J = 15.2 Hz, 1H), 4.50 (d, J = 15.1 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.1, 140.2, 135.9, 131.7, 129.4, 124.9, 63.0, 59.9 ppm.

N-benzyl-3-(chloro(phenylsulfinyl)methyl)oxetan-3-amine (**86**)



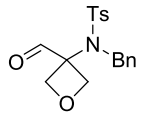
To a solution of **85** (80 mg, 0.350 mmol, 1.00 eq) in MeOH (3.5 mL) was added benzylamine (115 µl, 1.05 mmol, 3.00 eq). The mixture was stirred at 50 °C for 3.5 h. The solvent was removed under reduced pressure and the residue was purified by FC on silica (hex:EA=2:1) to yield **86** (105 mg, 0.313 mmol, 89%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 – 7.31 (m, 10H), 4.83 (s, 1H), 4.81 – 4.71 (m, 2H), 4.66 (d, J = 7.4 Hz, 1H), 4.46 (d, J = 7.4 Hz, 1H), 4.12 (d, J = 13.5 Hz, 1H), 4.03 (d, J = 13.5 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 141.5, 139.8, 132.0, 129.3, 128.8, 128.0, 127.5, 125.0, 83.7, 78.0, 77.8, 64.7, 47.3 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{17}H_{19}Cl_1N_1O_2S$ $[M+H]^+$ 336.0820, found, 336.0817.

N-benzyl-N-(3-formyloxetan-3-yl)-4-methylbenzenesulfonamide (**103**)

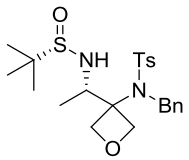


To a solution of DIBAL-H (1.0 M solution in hexane, 3.00 mL, 3.00 mmol, 1.88 eq) in Et_2O (2.63 mL) was added BuLi (1.6 M solution in hexane, 1.88 mL, 3.0 mmol, 1.88 eq) dropwise at 0 °C. After complete addition, the mixture was allowed to stir for 15 min at 0 °C, giving a 0.4 M solution of the ate-complex.

(4.0 mL 1.60 mmol, 1.00 eq) of this solution was added rapidly to a solution of **113** (548 mg, 1.60 mmol, 1.00 eq) in THF (3.2 mL) at -20 °C within 1 min. After complete addition the mixture was stirred for further 5 min at -20 °C, then the reaction was quenched with H_2O and 1 M $KHSO_4$ was added until pH = 4. The mixture was stirred vigorously for 45 min until formation of two clear layers. The layers were separated and the aqueous layer was extracted with EA (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to dryness. The residue was purified by FC on SiO_2 (hexane:EA = 2:1) to yield **115** (346 mg, 1.00 mmol, 63%) as a colorless solid.

For Analytical Data *vide infra.*

N-benzyl-*N*-(3-((*S*)-1-((*S*)-1,1-dimethylethylsulfinamido)ethyl)oxetan-3-yl)-4-methylbenzenesulfonamide (**119**)[280]



Methyl lithium (1.6 M in Et_2O, 1.67 mL, 2.67 mmol, 1.20 eq) was slowly added dropwise to a solution of **118** (1.00 g, 2.23 mmol, 1.00 eq) in THF (15 mL) at -78 °C. The mixture was stirred at -78 °C for 10 min, before the reaction was quenched with saturated aqueous $NaHCO_3$-solution. The mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (4 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by FC on silica gel (CH_2Cl_2:EA = 1:1) to afford *N*-benzyl-*N*-(3-((*S*)-1-((*S*)-1,1-dimethylethylsulfinamido)ethyl)oxetan-3-yl)-4-methylbenzenesulfonamide (**119**, 796 mg, 1.71 mmol, 77%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 8.2 Hz, 2H), 7.23–7.17 (m, 5H), 7.15–7.10 (m, 2H), 5.04–4.77 (m, 2H), 4.59–4.53 (m, 1H), 4.53–4.44 (m, 2H), 4.33 (s, 2H), 3.97 (qd, *J* = 6.6, 3.4 Hz, 1H), 2.38 (s, 3H), 1.39 (d, *J* = 6.6 Hz, 3H), 1.23 (s, 9H) ppm.

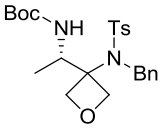
^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.9, 137.8, 135.6, 129.8, 128.7, 128.2, 128.0, 127.6, 76.8, 76.8, 66.3, 55.9, 53.9, 51.0, 22.8, 21.6, 16.8 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{23}H_{33}N_2O_4S_2$ $[M+H]^+$ 465.1876, found 465.1880.

IR (neat): ν [cm^{-1}] = 3285, 2962, 2893, 1598, 1455, 1327, 1152, 1054, 984, 874, 814.

$[\alpha]^{20}_D$ = +69.3 (c = 0.86, $CHCl_3$).

(*S*)-*tert*-butyl (1-(3-(*N*-benzyl-4-methylphenylsulfonamido)oxetan-3-yl)ethyl)carbamate (**120**)[280]



To a solution of **119** (740 mg, 1.59 mmol, 1.00 eq) in CH_2Cl_2:MeOH (16.0 mL, 1:1) was added HCl (4 M in dioxane, 1.59 mL, 6.37 mmol, 4.00 eq) at 0 °C. The mixture was stirred at this temperature for 30 min and was then quenched with saturated aqueous $NaHCO_3$-solution until pH > 7. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to dryness.

The residue was dissolved in CH_2Cl_2 (8.0 mL) and di-*tert*-butyl dicarbonate (417 mg, 1.91 mmol, 1.20 eq) was added at room temperature. The mixture was stirred for 16 h and then concentrated to about 20% of its volume. Purification by FC on silica gel (hex:EA = 2:1) to afford **120** (688 mg, 1.49 mmol, 94%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 8.3 Hz, 2H), 7.23–7.12 (m, 5H), 7.12–7.04 (m, 2H), 5.20 (d, *J* = 9.2 Hz, 1H), 5.06–4.87 (m, 1H), 4.82–4.65 (m, 1H), 4.55 (d, *J* = 7.3 Hz, 1H), 4.46–4.30 (m, 2H), 4.30–4.14 (m, 2H), 2.37 (s, 3H), 1.48 (s, 9H), 1.39 (d, *J* = 6.8 Hz, 3H).

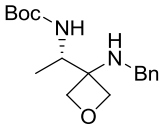
^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.7, 143.5, 138.4, 135.8, 129.6, 128.6, 128.3, 127.8, 127.4, 79.6, 77.0, 76.7, 66.5, 50.4, 49.2, 28.5, 21.6, 16.6 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{24}H_{32}N_2O_5S_5Na$ $[M+Na]^+$ 483.1924, found 483.1924.

IR (neat): ν [cm^{-1}] = 3283, 1704, 1536, 1455, 1340, 1253, 1152, 1084, 1057, 980, 912, 868, 811, 728, 699, 660, 586, 552, 536.

[α]$^{20}_D$ = +1.0 (c = 0.85, $CHCl_3$).

m.p. = 175 °C



(*S*)-*tert*-Butyl (1-(3-(benzylamino)oxetan-3-yl)ethyl)carbamate (**121**)[280]

To a suspension of **120** (688 mg, 1.49 mmol, 1.00 e) in MeOH:THF (15.0 mL, 14:1) were added magnesium turnings (363 mg, 14.9 mmol, 10.0 eq) and the mixture was stirred for 4 h at ambient temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl-solution and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by FC on silica gel (hex:EA = 1:1) to afford **121** (458 mg, 1.43 mmol, 96%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.32 (m, 4H), 7.30–7.25 (m, 1H), 4.99–4.89 (m, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 7.1 Hz, 1H), 4.52 (d, *J* = 7.1 Hz, 1H), 4.48 (d, *J* = 6.8 Hz, 1H), 4.19–4.14 (m, 1H), 3.99–3.92 (m, 2H), 1.55 (br, 1H), 1.46 (s, 9H), 1.17 (d, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.9, 140.3, 128.7, 128.1, 127.4, 79.7, 78.2, 77.4, 63.3, 50.0, 47.4, 28.5, 15.2 ppm.

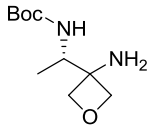
HRMS (ESI+): *m*/*z* calcd. for $C_{17}H_{26}N_2O_3Na$ $[M+Na]^+$ 329.1836, found 329.1832.

IR (neat): ν [cm^{-1}] = 3330, 3284, 2972, 2881, 1701, 1542, 1481, 1454, 1365, 1250, 1163, 1079, 1026, 963, 859.

[α]$^{21}_{D}$ = –8.3 (c = 1.08, $CHCl_3$).

m.p. = 98 °C

(*S*)-*tert*-Butyl (1-(3-aminooxetan-3-yl)ethyl)carbamate (**122**)[280]



To a solution of **121** (430 mg, 1.40 mmol, 1.00 eq) in MeOH (9.5 mL) was added Pd-C (10% Pd, 74.7 mg, 0.070 mmol, 5.00 mol-%) and the mixture was stirred under an atmosphere of H_2 (balloon) for 3.5 h. The mixture was filtered over Celite® and washed with EA and MeOH and the volatiles were removed under reduced pressure to afford **122** (303 mg, 1.40 mmol, 100%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.88 (br, 1H), 4.59 (d, *J* = 6.7 Hz, 1H), 4.53 (d, *J* = 6.5 Hz, 1H), 4.31 (d, *J* = 6.4 Hz, 2H), 4.17–4.06 (m, 1H), 1.65 (s, 2H), 1.44 (s, 9H), 1.09 (d, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.8, 83.0, 82.4, 79.5, 59.1, 50.9, 28.5, 14.9 ppm.

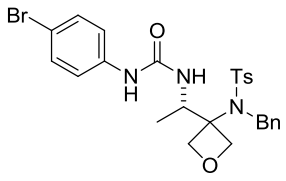
HRMS (ESI+): *m*/*z* calcd. for $C_{10}H_{21}N_2O_3$ $[M+H]^+$ 217.1547, found 217.1541.

IR (neat): ν [cm^{-1}] = 3297, 2972, 2880, 1703, 1532, 1365, 1249, 1160, 1057, 962, 860.

[α]$^{23}_{D}$ = –3.8 (c = 0.72, $CHCl_3$).

m.p. = 100 °C

(*S*)-*N*-benzyl-*N*-(3-(1-(3-(4-bromophenyl)ureido)ethyl)oxetan-3-yl)-4-methylbenzenesulfonamide (**123**)



HCl (4 M in dioxane, 92 µl, 0.367 mmol, 5.00 eq) was added to a solution of **119** (34.1 mg, 0.073 mmol, 1.00 eq) in CH_2Cl_2 (350 µl) and MeOH (350 µl) at 0 °C and the mixture was

stirred for 30 min. After completion, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure.

The residue was dissolved in CH_2Cl_2 (700 µl) and 1-bromo-4-isocyanatobenzene (16.0 mg, 0.081 mmol, 1.10 eq) was added at 0 °C. The mixture was stirred at room temperature for 1 h and then directly submitted to FC on silica gel (hex:EA = 1:1) to give **123** (36.6 mg, 0.066 mmol, 89%) as a colorless solid. Crystallization from CH_2Cl_2:MeOH afforded crystals suitable for x-ray crystal structure analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69–7.56 (m, 2H), 7.32–7.23 (m, 4H), 7.23–7.09 (m, 5H), 7.08–6.92 (m, 3H), 5.71 (d, *J* = 9.5 Hz, 1H), 5.12 (br, 1H), 4.78–4.61 (m, 2H), 4.60–4.31 (m, 2H), 4.24 (d, *J* = 15.7 Hz, 1H), 4.03 (br, 1H), 2.41 (s, 3H), 1.47 (d, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.13, 143.99, 138.38, 138.06, 135.08, 131.77, 129.81, 128.78, 128.62, 128.12, 127.39, 121.12, 115.31, 77.39, 76.48, 66.71, 49.89, 47.55, 21.65, 16.90.

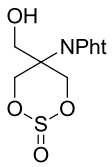
HRMS (ESI+): *m*/*z* calcd. for $C_{26}H_{29}BrN_3O_4S$ $[M+H]^+$ 558.1057, found 558.1055.

IR (neat): ν [cm^{-1}] = 3611, 3301, 2959, 2891, 1678, 1601, 1591, 1545, 1489, 132, 1320, 1305, 1153, 989, 830, 812, 674, 559, 541.

$[\alpha]^{24}_D$ = +9.0 (c = 0.66, $CHCl_3$).

m.p. = 134-136 °C (CH_2Cl_2:MeOH).

2-(5-(Hydroxymethyl)-2-oxido-1,3,2-dioxathian-5-yl)isoindoline-1,3-dione (**126**)



A mixture of phthalic anhydride (5.56 g, 37.5 mmol, 1.00 eq) and Tris-base (5.00 g, 41.3 mmol, 1.10 eq) was heated to 170 °C until gas evolution stopped. To the hot melt was added sand (10 g) and the mixture was allowed to cool to r.t. The sinter cake was grinded down with a hammer and the resulting powder was refluxed in acetone (100 mL) for 3 h. The solution was filtered hot and the filtrate was concentrated. The crude product was used in the next step without further purification.

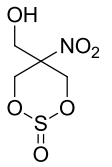
To a solution of the crude material (0.688 g, 2.74 mmol, 1.00 eq) in MeCN (27 mL) at 0 °C was added K_2CO_3 (1.89 g, 13.7 mmol, 5.00 eq) followed by $SOCl_2$ (0.300 ml, 4.11 mmol, 1.50 eq). The mixture was stirred at 0 °C for 45 min and then quenched by the addition of a few drops of MeOH. All volatiles were removed and the residue was purified by FC on silica (CH_2Cl_2:MeOH = 20:1) to yield **126** (320 mg, 1.08 mmol, 39%) as a colorless wax.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 – 7.53 (m, 4H), 5.26 – 5.11 (m, 2H), 4.82 – 4.60 (m, 2H), 3.69 – 3.47 (m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.7, 134.3, 131.5, 123.0, 61.3, 58.4, 58.3 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{12}H_{12}N_1O_6S$ $[M+H]^+$ 298.0380, found, 298.0381.

5-(Hydroxymethyl)-5-nitro-1,3,2-dioxathiane 2-oxide (**98**)

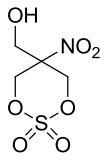


To a solution of 2-(hydroxymethyl)-2-nitropropane-1,3-diol (1.03 g, 6.84 mmol, 1.00 eq) in MeCN (68 mL) at 0 °C was added K_2CO_3 (4.73 g, 34.2 mmol, 5.00 eq) followed by $SOCl_2$ (0.50 ml, 6.84 mmol, 1.00 eq). The mixture was stirred at 0 °C for 45 min. TLC analysis still indicated the presence of starting material and $SOCl_2$ (0.20 mL, 2.74mmol, 0.40 eq) was added. The mixture was stirred for 1.5 h, concentrated and filtered over a pad of silica (CH_2Cl_2:MeOH = 20:1) to yield **98** (790 mg, 4.01 mmol, 59%) as a colorless wax.

^{1}H NMR (400 MHz, DMSO) δ = 5.69 (br s, 1H), 5.09 – 4.85 (m, 2H), 4.77 – 4.55 (m, 2H), 3.77 (s, 2H) ppm.

^{13}C NMR (101 MHz, DMSO) δ = 88.0, 62.4, 58.2 ppm.

5-(Hydroxymethyl)-5-nitro-1,3,2-dioxathiane 2,2-dioxide (**100**)

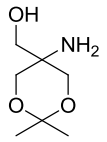


To a solution of **98** (410 mg, 2.08 mmol, 1.00 eq) in MeCN (5.8 mL) were added $NaIO_4$ (623 mg, 2.91 mmol, 1.40 eq) followed by a solution of $RuCl_3 \cdot H_2O$ (4.3 mg, 0.021 mmol, 1.00 mol-%) in water (1.2 mL). The mixture was stirred at r.t. for 1 h. The mixture was diluted with water (10 mL) and extracted with EA (3 x 30 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in a minimal amount of CH_2Cl_2 and the desired product **100** (120 mg, 0.610 mmol, 29%) was isolated as a colorless wax by trituration with hexanes.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.39 (br s, 1H), 5.26 – 5.14 (m, 2H), 4.97 – 4.85 (m, 2H), 3.74 (s, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 85.2, 73.2, 61.9 ppm.

(5-amino-2,2-dimethyl-1,3-dioxan-5-yl)methanol (**104**)

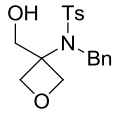


To a suspension of 2-amino-2-(hydroxymethyl)propane-1,3-diol·HCl (50 g, 320 mmol, 1.0 eq) in DMF (64 mL) were added 2,2-dimethoxypropane (58 mL, 480 mmol, 1.5 eq) and *p*-toluenesulfonic acid monohydrate (3.0 g, 16 mmol, 0.05 eq). The mixture was stirred for 20 h at room temperature. The solvent was removed under reduced pressure. To the residue was added EA (500 mL) and triethylamine (48 mL, 350 mmol, 1.09 eq). The mixture was stirred for 30 min. The colorless precipitate was filtered, washed with EA (200 mL) and discarded. The filtrate was concentrated and dried *in*

vacuo. Upon the addition of Et_2O (300 mL) a colorless solid precipitated which was filtered, washed with Et2O (50 mL) and dried in vacuo to yield (5-amino-2,2-dimethyl-1,3-dioxan-5-yl)methanol (38 g, 240 mmol, 74%) as a colorless solid.

The analytical data obtained was in accordance with the values previously reported.[151]

N-benzyl-*N*-(3-(hydroxymethyl)oxetan-3-yl)-4-methylbenzenesulfonamide (**131**)



To a solution of **104** (14 g, 84 mmol, 1.0 eq) in acetonitrile (84 mL) were added 4-toluenesulfonyl chloride (16 g, 86 mmol, 1.0 eq), potassium carbonate (23 g, 170 mmol, 2.0 eq) and DMAP (0.21 g, 1.7 mmol, 0.02 eq). The mixture was heated under reflux for 2 h. To the refluxing solution were added potassium carbonate (12 g, 84 mmol, 1.0 eq), TBAI (0.31 g, 0.84 mmol, 0.01 eq) and dropwise benzyl bromide (13 mL, 110 mmol, 1.3 eq). The suspension was heated under reflux for 3 h. TLC analysis still showed the presence of 1. Benzyl bromide (3.0 mL, 25 mmol, 0.3 eq) was added and the suspension was refluxed for 1 h. After cooling to room temperature the suspension was filtered over celite® with EA (100 mL) and the filtrate was concentrated.

The colorless oily residue was redissolved in CH_2Cl_2 (84 mL). To this solution were added Et_3N (18 ml, 130 mmol, 1.5 eq) and dropwise (*via* syringe pump 20 mL/h) methanesulfonyl chloride (9.8 ml, 130 mmol, 1.5 eq) at 0 °C and the cloudy mixture was stirred for 30 min at this temperature. The reaction was checked for completion by NMR of a small sample. To the suspension was added water (1 mL) before removing all volatiles.

The semisolid light yellow residue was redissolved in THF (84 mL) and aqueous HCl (2 N, 84 mL) and the biphasic mixture was heated at 80 °C for 1.5 h. After cooling to room temperature, the mixture was diluted with water (50 mL) and

extracted with EA (3 x 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (150 mL), dried over Na_2SO_4 and concentrated.

The oily light yellow residue was redissolved in EtOH (560 mL) and to the solution were added potassium hydroxide (5.7 g, 100 mmol, 1.2 eq) and sodium iodide (0.63 g, 4.2 mmol, 0.05 eq). The mixture was heated to reflux for 1 h. After 10 min a colourless precipitate formed. After cooling to room temperature, the solvent was removed under reduced pressure. The crude product was slurried in EA (200 mL) and filtered over a pad of silica with EA (200 mL). The filtrate was concentrated to yield a light yellow semi-solid, that was suspended in Et_2O (70 mL) and filtered. The filtercake was dried in vacuo to yield the desired product *N*-benzyl-*N*-(3-(hydroxymethyl)oxetan-3-yl)-4-methylbenzenesulfonamide (11 g, 32 mmol, 38%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (d, *J* = 8.3 Hz, 2H), 7.27 – 7.13 (m, 7H), 4.81 (d, *J* = 7.3 Hz, 2H), 4.40 (s, 2H), 4.34 (d, *J* = 7.3 Hz, 2H), 4.18 (d, *J* = 5.8 Hz, 2H), 2.40 (s, 3H), 2.29 – 2.15 (m, 1H).

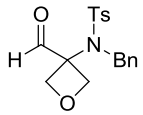
^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.0, 137.5, 136.6, 129.8, 128.7, 127.8, 127.7, 77.3, 66.6, 63.9, 50.6, 21.7 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{18}H_{22}N_1O_4S$ $[M+H]^+$ 348.1264, found, 348.1268.

IR (neat): ν [cm^{-1}] = 3404, 2925, 2884, 1599, 1496, 1456, 1403, 1377, 1345, 1319, 1308, 1292, 1271, 1238, 1211, 1170, 1149, 1089, 1080, 1056, 1028, 1015, 889, 841, 810, 784, 757, 698.

m.p. 131 °C.

N-benzyl-*N*-(3-formyloxetan-3-yl)-4-methylbenzenesulfonamide (**115**)



To a solution of oxalyl chloride (3.1 mL, 35 mmol, 1.2 eq) in CH_2Cl_2 (72 mL) was slowly added dimethyl sulfoxide (5.0 mL, 70 mmol, 2.2 eq) in CH_2Cl_2 (14 mL) at -78 °C (*via* syringe pump 30 mL/h). After stirring for 15 min **131** (11 g, 32 mmol) in CH_2Cl_2 (72 mL) was added slowly (*via* syringe pump 80 mL/h). After stirring for 0.5 h, Et_3N (13 mL, 96 mmol, 3.0 eq) was added. The mixture was stirred for 30 min, warmed to room temperature and stirred for 10 min before quenching with saturated aqueous NH_4Cl solution (150 mL). The mixture was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to yield *N*-benzyl-*N*-(3-formyloxetan-3-yl)-4-methylbenzenesulfonamide (11 g, 32 mmol, 100%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.72 (s, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.16 (m, 5H), 4.76 (d, *J* = 7.5 Hz, 2H), 4.52 (d, *J* = 7.6 Hz, 2H), 4.48 (s, 2H), 2.44 (s, 3H).

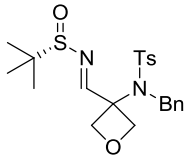
^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.6, 144.2, 137.5, 135.1, 129.9, 128.9, 128.6, 128.2, 127.2, 77.2, 74.2, 67.5, 50.3, 21.6 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{18}H_{20}N_2O_4S$ $[M+H]^+$ 346.1108, found, 346.1106.

IR (neat): ν [cm^{-1}] = 2948, 2831, 2324, 2168, 2052, 1980, 1730, 1596, 1497, 1456, 1447, 1400, 1382, 1358, 1332, 1303, 1292, 1270, 1235, 1205, 1188, 1155, 1126, 1090, 1059, 1025, 1013, 994, 965, 945.

m.p. 124 °C

(*S*,*E*)-*N*-benzyl-*N*-(3-(((*tert*-butylsulfinyl)imino)methyl)oxetan-3-yl)-4-methylbenzenesulfonamide (**118**)



To a solution of **115** (3.0 g, 8.7 mmol, 1.0 eq) and (*S*)-2-methylpropane-2-sulfinamide (1.6 g, 13 mmol, 1.5 eq) in THF

(43 mL) was added tetraethoxytitanium (3.6 mL, 17 mmol, 2.0 eq) and the mixture was stirred at 40 °C for 17 h. The reaction was poured into saturated aqueous NaCl solution (150 mL) under vigorous stirring. The solid was filtered over celite® and washed with EA (100 mL). The layers of the filtrate were separated and the aqueous layer was extracted with EA (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC on silica (hexane:EA=1:1) to yield (*S*,*E*)-*N*-benzyl-*N*-(3-(((*tert*-butylsulfinyl)imino)methyl)oxetan-3-yl)-4-methylbenzenesulfonamide (3.2 g, 7.2 mmol, 83%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.34 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.29 – 7.22 (m, 5H), 7.18 – 7.13 (m, 2H), 4.96 (d, *J* = 6.7 Hz, 1H), 4.89 (d, *J* = 6.7 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.54 (d, *J* = 15.8 Hz, 1H), 4.44 (d, *J* = 7.1 Hz, 1H), 4.28 (d, *J* = 15.8 Hz, 1H), 2.43 (s, 3H), 1.27 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.0, 144.1, 138.0, 135.6, 129.9, 128.9, 128.4, 128.3, 127.5, 77.2, 65.9, 58.0, 50.8, 22.6, 21.7 ppm.

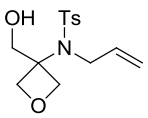
HRMS (ESI+): *m*/*z* calcd. for $C_{22}H_{29}N_2O_4S_2$ $[M+H]^+$ 449.1563, found, 449.1556.

IR (neat): ν [cm^{-1}] = 2956, 2881, 1618, 1597, 1495, 1419, 1339, 1323, 1157, 1127, 1091, 1064, 1027, 982, 920, 814, 732, 700.

m.p. 103 °C

[α]$^{25}_D$ +100.7 (*c* 0.860, $CHCl_3$)

N-allyl-*N*-(3-(hydroxymethyl)oxetan-3-yl)-4-methylbenzenesulfonamide (**134**)



To a solution of **104** (20 g, 120 mmol, 1.0 eq) in acetonitrile (120 mL) were added 4-toluenesulfonyl chloride (24 g, 120 mmol, 1.0 eq), potassium carbonate (33 g, 240 mmol, 2.0 eq) and DMAP (0.30 g, 2.4 mmol, 0.02 eq). The mixture was heated under reflux for 2 h.

To the refluxing solution were added potassium carbonate (17 g, 120 mmol, 1.0 eq), TBAI (2.2 g, 6.0 mmol, 0.05 eq) and dropwise allyl bromide (13 ml, 150 mmol, 1.25 eq). The suspension was heated under reflux for 3 h. After cooling to room temperature, the suspension was filtered over celite® with EA (100 mL) and the filtrate was concentrated.

The colorless oily residue was redissolved in CH_2Cl_2 (120 mL). To this solution were added triethylamine (25 mL, 180 mmol, 1.5 eq) and dropwise methanesulfonyl chloride (14 ml, 180 mmol, 1.5 eq) at 0 °C. The mixture was stirred for 35 min at this temperature. The reaction was checked for completion by NMR of a small sample. To the suspension was added water (2 mL) before removing all volatiles.

The semisolid light yellow residue was redissolved in THF (120 mL) and aqueous HCl (2 N, 120 mL) and the biphasic solution was heated at 80 °C for 2 h. The mixture was diluted with water (100 mL) and extracted with EA (4 x 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (100 mL), dried over Na_2SO_4 and concentrated.

The oily light yellow residue was redissolved in EtOH (800 mL) and to the solution were added potassium hydroxide (8.1 g, 150 mmol, 1.2 eq) and sodium iodide (0.91 g, 6.0 mmol, 0.05 eq). The mixture was heated to reflux for 30 min. After 10 min a colorless precipitate formed. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude product was slurried in EA (300 mL) and filtered over a pad of silica with EA (100 mL). The filtrate was concentrated to yield a light yellow oil which was purified by FC on silica (hex:EA=2:1) to yield *N*-allyl-*N*-(3-(hydroxymethyl)oxetan-3-yl)-4-methylbenzenesulfonamide (12 g, 42 mmol, 35%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 5.65 (ddt, *J* = 17.3, 10.2, 6.1 Hz, 1H), 5.15 – 5.05 (m, 1H), 5.07 – 4.99 (m, 1H), 4.90

(d, *J* = 7.2 Hz, 2H), 4.40 (d, *J* = 7.3 Hz, 2H), 4.23 (d, *J* = 6.0 Hz, 2H), 3.80 (dt, *J* = 7.1, 1.5 Hz, 2H), 2.28 – 2.19 (s, 3H), 2.23 (m, 1H).

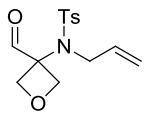
^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.2, 137.6, 134.6, 129.9, 127.8, 118.1, 77.2, 66.6, 63.7, 49.6, 21.7 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{14}H_{20}NO_4S$ $[M+H]^+$ 298.1108, found, 298.1107.

IR (neat): ν [cm^{-1}] = 3406, 2885, 1560, 1496, 1456, 1403, 1375, 1319, 1308, 1292, 1271, 1238, 1169, 1149, 1089, 1056, 1028, 968, 956, 945, 927, 889, 841, 810, 784, 756, 698, 671, 653, 587, 552.

m.p. 94 °C

N-allyl-*N*-(3-formyloxetan-3-yl)-4-methylbenzenesulfonamide (**137**)



To a solution of oxalyl chloride (4.0 mL, 46 mmol, 1.1 eq) in CH_2Cl_2 (94 mL) was slowly added dimethyl sulfoxide (6.5 mL, 91 mmol, 2.2 eq) in CH_2Cl_2 (19 mL) at -78 °C. After stirring for 15 min **134** (12 g, 42 mmol, 1.0 eq) in CH_2Cl_2 (94 mL) was added slowly. After stirring for 30 min triethylamine (17 mL, 120 mmol, 3.0 eq) was added. The mixture was stirred for 30 min, warmed to room temperature and stirred for another 10 min before quenching with saturated aqueous NH_4Cl solution (100 mL). The mixture was extracted with CH_2Cl_2 (3 x 100 mL), dried over Na_2SO_4 and concentrated under to yield *N*-allyl-*N*-(3-formyloxetan-3-yl)-4-methylbenzenesulfonamide (12 g, 41 mmol, 98%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.94 (s, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 5.80 – 5.64 (m, 1H), 5.17 – 5.11 (m, 2H), 5.12 – 5.05 (m, 1H), 4.89 – 4.84 (m, 2H), 4.71 – 4.66 (m, 2H), 3.87 (d, *J* = 6.5 Hz, 2H), 2.44 (s, 3H).

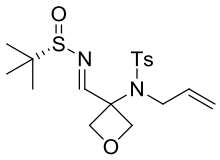
^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.5, 144.4, 137.4, 133.1, 130.1, 127.4, 120.1, 74.7, 67.7, 49.3, 21.7 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{14}H_{18}NO_4S$ $[M+H]^+$ 296.0951, found, 296.0952.

IR (neat): ν [cm^{-1}] = 3085, 2981, 2949, 2882, 2106, 1917, 1732, 1638, 1597, 1495, 1452, 1421, 1397, 1326, 1305, 1291, 1239, 1195, 1152, 1119, 1089, 1063, 1028, 1016, 992, 949, 916, 889, 808, 788, 705.

m.p. 73 °C

(*S*,*E*)-*N*-allyl-*N*-(3-(((tert-butylsulfinyl)imino)methyl)oxetan-3-yl)-4-methylbenzenesulfonamide (**139**)



To a solution of **137** (3.0 g, 10 mmol, 1.0 eq) and (*S*)-2-methylpropane-2-sulfinamide (1.8 g, 15 mmol, 1.5 eq) in THF (51 mL) was added tetraethoxytitanium (4.3 mL, 20 mmol, 2.0 eq) and the mixture was stirred at 40 °C for 17 h. The reaction was poured into saturated aqueous NaCl solution (150 mL) under vigorous stirring. The solid was filtered over celite® and washed with EA (100 mL). The layers of the filtrate were separated and the aqueous layer was extracted with EA (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC on silica (hex:EA=1:1) to yield (*S*,*E*)-*N*-allyl-*N*-(3-(((tert-butylsulfinyl)imino)methyl)oxetan-3-yl)-4-methylbenzenesulfonamide(3.1 g, 7.8 mmol, 77%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.69 (ddt, *J* = 16.9, 10.0, 6.3 Hz, 1H), 5.19 – 4.97 (m, 4H), 4.76 (d, *J* = 6.9 Hz, 1H), 4.58 (d, *J* = 6.0 Hz, 1H), 4.01 – 3.69 (m, 2H), 2.44 (s, 3H), 1.27 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.4, 144.2, 138.0, 133.7, 130.0, 127.5, 119.2, 65.7, 58.0, 49.8, 22.6, 21.7 ppm.

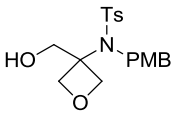
HRMS (ESI+): *m*/*z* calcd. for $C_{18}H_{27}N_2O_4S_2$ $[M+H]^+$ 399.1407, found, 399.1409.

IR (neat): ν [cm^{-1}] = 2959, 2885, 1620, 1598, 1494, 1475, 1456, 1420, 1402, 1338, 1306, 1253, 1185, 1159, 1088, 1049, 1015, 984, 924, 869, 846, 815, 753, 708, 662, 601, 572, 550, 518, 496.

m.p. 103 °C

[α]^{27}$_D$ +122.1 (*c* 1.55, $CHCl_3$)

N-(3-(hydroxymethyl)oxetan-3-yl)-*N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide (**135**)



To a solution of **104** (5 g, 30.1 mmol, 1.00 eq) in MeCN (30.1 mL) were added Ts-Cl (5.85 g, 30.7 mmol, 1.02 eq), K_2CO_3 (8.32 g, 60.2 mmol, 2.00 eq) and DMAP (0.074 g, 0.602 mmol, 2.00 mol-%). The mixture was heated under reflux for 2 h.

The suspension was cooled to 50 °C and (4.16 g, 30.1 mmol) and K_2CO_3, dropwise 1-(chloromethyl)-4-methoxybenzene (4.51 mL, 33.1 mmol, 1.10 eq) as well as TBAI (0.556 g, 1.50 mmol, 5.00 mol-%) were added. The suspension was kept at this temperature for 13 h. After cooling to room temperature, the suspension was filtered over celite® with EA (100 mL) and the filtrate was concentrated.

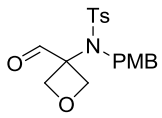
The colourless oily residue was redissolved in DCM (12 mL). To this solution were added Et_3N (6.29 mL, 45.1 mmol, 1.50 eq) and dropwise (*via* syringe pump 20 mL/h) Ms-Cl (3.52 mL, 45.1 mmol, 1.50 eq) at 0 °C and the mixture was stirred for 30 min. Completion was checked by taking NMR of a small sample. To the suspension was added water (1 mL) before removing all volatiles.

The semisolid light yellow residue was redissolved in THF (12 mL) and 2 N HCl (12 mL) and the biphasic solution was heated at 80 °C for 1.5 h. The mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ solution (150 mL), dried over Na_2SO_4 and concentrated.

The oily light yellow residue was redissolved in EtOH (200 mL) and to the solution were added KOH (2.026 g, 36.1 mmol, 1.20 eq) and NaI (0.225 g, 1.50 mmol, 5.00 mol-%). The mixture was heated to reflux. After 10 min a colorless precipitate formed. The mixture was further refluxed for 1 h before it was cooled to r.t. The solvent was removed under reduced pressure. The crude product was slurried in EtOAc and filtered over a pad of silica. The filtrate was concentrated to yield a light yellow oil, that was purified by FC on silica (EA:hex = 1:1) to yield **135** (3.283 g, 8.70 mmol, 29%) as a colorless wax.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.35 (s, 7.62 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 2H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.68 (d, *J* = 8.3 Hz, 2H), 4.74 (d, *J* = 6.8 Hz, 2H), 4.26 (d, *J* = 6.9 Hz, 4H), 4.07 (d, *J* = 5.6 Hz, 2H), 3.71 (s, 3H), 2.36 (s, 3H) ppm.

N-(3-formyloxetan-3-yl)-*N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide (**138**)



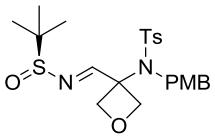
To a solution of oxalyl chloride (0.837 ml, 9.57 mmol, 1.10 eq) in CH_2Cl_2 (19.8 mL) was slowly added DMSO (1.36 mL, 19.1 mmol, 2.20 eq) in CH_2Cl_2 (3.95 mL) at -78 °C. After stirring for 15 min **135** (3.28 g, 8.70 mmol, 1.00 eq) in CH_2Cl_2 (19.8 mL) was added slowly. After stirring for 0.5 h Et_3N (3.64 ml, 26.1 mmol, 3.00 eq) was added. The mixture was stirred for 30 min, warmed to r.t. and stirred for 10 min before quenching with sat. aq. NH_4Cl solution (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL), dried over Na_2SO4 and concentrated under reduced pressure to yield **138** (3.19 g, 8.50 mmol, 98%) as a colorless wax.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.66 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.9 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 4.82 – 4.74 (m, 2H), 4.52 (d, *J* = 7.6 Hz, 2H), 4.43 (s, 2H), 3.77 (s, 3H), 2.45 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.0, 159.9, 144.3, 137.9, 130.1, 129.9, 127.2, 126.8, 114.4, 74.4, 67.4, 55.4, 49.9, 21.7 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{19}H_{21}N_1Na_1O_5S_1$ $[M+H]^+$ 398.1033, found, 398.1028.

(*S*,*E*)-*N*-(3-(((*tert*-butylsulfinyl)imino)methyl)oxetan-3-yl)-*N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide (**140**)

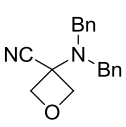


To a solution of **138** (2.36 g, 6.29 mmol, 1.00 eq) and (*S*)-2-methylpropane-2-sulfinamide (1.14 g, 9.44 mmol, 1.50 eq) in THF (31.5 mL) was added tetraethoxytitanium (2.64 mL, 12.6 mmol, 2.00 eq) and the mixture was stirred at 40 °C for 16 h. The reaction was poured into sat. aq. NaCl solution (150 mL) under vigorous stirring. The solid was filtered off over celite® and washed with EA (100 mL). The layers were separated and the aqueous layer was extracted with EA (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on SiO_2 (hex:EA = 1:1). The desired product **140** (2.43 g, 5.07 mmol, 81%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (s, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.04 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 4.93 (d, *J* = 6.7 Hz, 1H), 4.86 (d, *J* = 6.7 Hz, 1H), 4.68 – 4.64 (m, 1H), 4.45 (d, *J* = 15.5 Hz, 1H), 4.42 – 4.39 (m, 1H), 4.22 (d, *J* = 15.4 Hz, 1H), 3.76 (s, 3H), 2.42 (s, 3H), 1.25 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.1, 159.7, 143.9, 138.1, 129.9, 129.8, 127.4, 127.3, 114.2, 77.2, 65.7, 57.9, 55.4, 50.2, 22.5, 21.7 ppm.

3-(dibenzylamino)oxetane-3-carbonitrile (**142**)



To a solution of **33** (0.446 mL, 6.94 mmol, 1.00 eq) in AcOH (6.94 mL) at r.t. in a water bath was sequentially added dibenzylamine (5.34 ml,

27.8 mmol, 4.00 eq) and TMS-CN (1.86 mL, 13.9 mmol, 2.00 eq). The reaction was stirred for 11.5 h. The reaction mixture was carefully transferred into sat aq. $NaHCO_3$ solution (100 mL) with water (50 mL). The pH was adjusted to 8-9 with K_2CO_3 (solid). The aqueous emulsion was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by FC on silica (hex:EtOAc = 8:1) to yield **142** (1.83 g, 6.57 mmol, 95%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 – 7.27 (m, 10H), 4.34 (d, *J* = 6.9 Hz, 2H), 4.30 (d, *J* = 6.9 Hz, 2H), 3.52 (s, 4H).

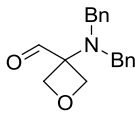
^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.8, 129.3, 128.8, 128.2, 117.9, 78.5, 60.9, 55.7 ppm.

HRMS (ESI+): *m/z* calcd. for $C_{18}H_{19}N_2O_1$ $[M+H]^+$ 279.1492, found, 279.1494.

IR (neat): ν [cm^{-1}] =2877, 2850, 1450, 1381, 1255, 1142, 985, 929, 754, 698.

m.p. 68 °C

3-(dibenzylamino)oxetane-3-carbaldehyde (**144**)



To a solution of DIBAL-H (1.0 M in hexane, 5.00 mL, 6.00 mmol, 1.50) in Et_2O (5.26 mL) was added *n*-BuLi (1.6 M solution in hexanes 3.66 mL, 6.00 mmol, 1.50 eq) dropwise at 0 °C. After complete addition, the mixture was allowed to stir for 15 min at 0 °C, giving a 0.45 M solution of the ate-complex.

This solution was then added dropwise to a solution of **142** (1.11 g, 4.00 mmol, 1.00 eq) in THF (8 mL) at -20 °C over 5 min. The mixture was stirred for 40 min before water (20 mL) and glyoxylic acid (50% in H_2O, 2.21 mL, 20.0 mmol, 5.00 eq) were added. The biphasic mixture was stirred for 15 min, extracted with EA (3 x 40 mL). The combined org. layers were washed with brine, dried over

Na_2SO_4 and concentrated. The residue was purified by FC on silica (hex:EA = 4:1) to yield **144** (0.439 g, 1.56 mmol, 39%) as a crystalline colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.14 (s, 1H), 7.40 – 7.13 (m, 10H), 4.53 (d, J = 7.0 Hz, 2H), 4.43 (d, J = 7.0 Hz, 2H), 3.84 (s, 4H) ppm.

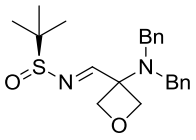
^{13}C NMR (101 MHz, $CDCl_3$) δ = 201.9, 138.6, 128.9, 128.6, 127.7, 75.1, 70.5, 54.0 ppm.

HRMS (ESI+): m/z calcd. for $C_{18}H_{19}N_1Na_1O_2$ $[M+Na]^+$ 304.1308, found, 304.1307.

IR (neat): ν [cm^{-1}] = 3027, 2947, 2866, 1722, 1493, 1454, 1363, 1186, 978, 958, 827, 753, 744.

m.p. 82 °C

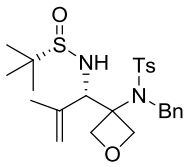
(*S*,*E*)-*N*-((3-(dibenzylamino)oxetan-3-yl)methylene)-2-methylpropane-2-sulfinamide (**141**)



A solution of **144** (0.234 g, 0.832 mmol, 1.00 eq) in THF (4.16 mL) was treated with (*S*)-2-methylpropane-2-sulfinamide (0.151 g, 1.25 mmol, 1.50 eq) and tetraethoxytitanium (0.349 mL, 1.66 mmol, 2.00 eq). After striing at r.t. for 14 h, the reaction was poured into sat. aq. NaCl solution (50 mL) under vigorous stirring. The solid was filtered off over celite® and washed with EA (50 mL). The layers were separated and the aqueous layer was extracted with EA (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC on silica (hex:EA = 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.52 (s, 1H), 7.37 – 7.22 (m, 10H), 4.55 (t, J = 5.6 Hz, 2H), 4.46 (d, J = 6.1 Hz, 1H), 4.35 (d, J = 6.2 Hz, 1H), 3.70 (s, 3H), 1.31 (s, 9H) ppm.

N-Benzyl-*N*-(3-((*S*)-1-((*S*)-1,1-dimethylethylsulfinamido)-2-methylallyl)oxetan-3-yl)-4-methylbenzenesulfonamide (**132**)[280]



To a solution of 2-bromoprop-1-ene (405 mg, 3.34 mmol, 1.50 eq) in THF (6.0 mL) was added *t*BuLi (1.9 M in pentane, 3.52 mL, 6.69 mmol, 3.00 eq) dropwise at –78 °C. After complete addition, the mixture was stirred at –78 °C for 1 h.

The yellow solution was transferred dropwise to a solution of **118** (1.00 g, 2.23 mmol, 1.00 eq) in THF (12.5 mL) at –78 °C. During the addition, the reaction was monitored by TLC. After complete consumption of the imine, addition was stopped (ca. 80% of the solution added) and the reaction was quenched with saturated aqueous NH_4Cl-solution and warmed to ambient temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by FC on silica gel (hex:EA = 1:1) to afford **132** (782 mg, 1.59 mmol, 72%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 (d, *J* = 7.9 Hz, 2H), 7.25–7.14 (m, 5H), 7.13–7.02 (m, 2H), 5.18–5.06 (m, 2H), 5.06–4.96 (m, 1H), 4.96–4.75 (m, 2H), 4.68 (d, *J* = 7.5 Hz, 1H), 4.57–4.35 (m, 2H), 4.35–4.19 (m, 2H), 2.38 (s, 3H), 1.92 (s, 3H), 1.30 (s, 9H) ppm.

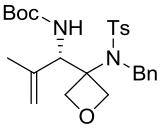
^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.0, 142.0, 137.5, 134.8, 129.8, 128.7, 128.7, 128.2, 127.9, 119.5, 76.7, 76.5, 66.2, 64.0, 56.0, 50.7, 23.0, 21.6, 19.0 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{25}H_{35}N_2O_4S_2$ $[M+H]^+$ 491.2033, found 491.2038.

IR (neat): ν [cm^{-1}] = 3275, 2960, 1641, 1598, 1496, 1455, 1364, 1329, 1305, 1268, 1225, 1152, 1089, 1066, 1011, 984, 940, 910, 876, 814, 779, 752, 731, 700, 665, 591.

$[\alpha]^{23}_D$ = +97.6 (c = 0.80, $CHCl_3$).

(*S*)-*tert*-Butyl (1-(3-(*N*-benzyl-4-methylphenylsulfonamido)oxetan-3-yl)-2-methylallyl)carbamate (**147**)[280]



To a solution of **132** (782 mg, 1.59 mmol, 1.00 eq) in CH_2Cl_2 (8.0 mL) and MeOH (8.0 mL) was added HCl (4 M in dioxane, 1.99 mL, 7.97 mmol, 5.00 eq) at 0 °C and the mixture was stirred at this temperature for 2.5 h. After complete conversion of the starting material, the reaction was quenched with saturated aqueous $NaHCO_3$-solution and extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was redissolved in toluene and the solution was evaporated to dryness again. The residue was dried under high vacuum. This procedure was repeated, until a constant weight was obtained.

The residue was dissolved in CH_2Cl_2 (5.0 mL) and a solution of di-*tert*-butyl dicarbonate (522 mg, 2.39 mmol, 1.50 eq) in CH_2Cl_2 (3.0 mL) was added. The mixture was stirred at room temperature for 12 h, before the solvent was removed under reduced pressure. The residue was purified by FC on silica gel (hex:EA = 3:1) to afford **147** (743 mg, 1.53 mmol, 96%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (d, *J* = 8.3 Hz, 2H), 7.22–7.09 (m, 5H), 7.08–7.01 (m, 2H), 5.88 (d, *J* = 8.2 Hz, 1H), 5.22–4.93 (m, 3H), 4.83–4.58 (m, 3H), 4.52–4.35 (m, 2H), 4.29 (d, *J* = 16.4 Hz, 1H), 2.38 (s, 3H), 1.94 (s, 3H), 1.49 (s, 9H) ppm.

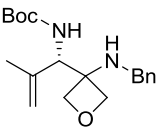
^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.6, 143.6, 142.3, 138.5, 135.4, 129.6, 128.6, 128.5, 127.9, 127.5, 116.9, 79.8, 77.4, 76.9, 66.34, 59.37, 50.56, 28.59, 21.59, 20.13 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{26}H_{34}N_2O_5SNa$ $[M+Na]^+$ 509.2081, found 509.2086.

IR (neat): ν [cm^{-1}] = 2976, 1693, 1598, 1496, 1455, 1365, 1332, 1243, 1153, 1116, 1090, 1058, 1028, 997, 951, 916, 855, 812, 784, 733, 697, 664, 602, 557, 542, 458.

$[\alpha]^{24}_D$ = –9.0 (c = 1.01, $CHCl_3$).

(*S*)-tert-Butyl (1-(3-(benzylamino)oxetan-3-yl)-2-methylallyl)carbamate (**148**)[280]



Magnesium turnings (367 mg, 15.1 mmol, 10.0 eq) were added to a solution of **147** (734 mg, 1.51 mmol, 1.00 eq) in MeOH (13.5 mL) and THF (1.5 mL). The mixture was vigorously stirred at room temperature for 3 h. The reaction was quenched by addition of saturated aqueous NH_4Cl-solution and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and after evaporation of the solvent **148**, (494 mg, 1.49 mmol, 99%) was obtained as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.31 (m, 4H), 7.31–7.26 (m, 1H), 5.21 (d, *J* = 9.1 Hz, 1H), 5.03–4.88 (m, 2H), 4.80 (d, *J* = 7.0 Hz, 1H), 4.75 (d, *J* = 7.0 Hz, 1H), 4.72–4.57 (m, 3H), 4.11 (s, 2H), 1.71 (s, 3H), 1.46 (m, 10H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.8, 141.9, 140.4, 128.7, 127.9, 127.3, 114.1, 79.8, 78.9, 77.6, 62.3, 60.5, 46.7, 28.5, 21.4 ppm.

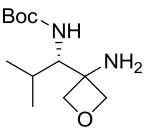
HRMS (ESI+): *m*/*z* calcd. for $C_{19}H_{28}N_2O_3Na$ $[M+Na]^+$ 355.1992, found 355.1987.

IR (neat): ν [cm^{-1}] = 3289, 2972, 2889, 1704, 1646, 1543, 1484, 1454, 1393, 1366, 1315, 1251, 1163, 1094, 1048, 1015, 972, 908, 883, 852, 744, 699, 587, 537.

$[\alpha]^{24}_D$ = –8.6 (c = 0.95, $CHCl_3$).

m.p. = 90 °C

(*S*)-tert-Butyl (1-(3-aminooxetan-3-yl)-2-methylpropyl)carbamate (**145**)[280]



To a solution of **148** (494 mg, 1.49 mmol, 1.00 eq) in MeOH (15.0 mL) was added Pd-C (10% Pd, 158 mg, 0.149 mmol, 10.0 mol-%) and the mixture was stirred under an atmosphere of H_2 (balloon) for 13 h.

Then, the mixture was filtered over celite®, the filter cake was washed with EA, and the filtrate was concentrated to dryness to afford **145** (356 mg, 1.46 mmol, 98%) as a colorless foam.

^{1}H NMR (400 MHz, Methanol-d4) δ = 4.94–4.86 (m, 2H), 4.79 (d, J = 7.9 Hz, 1H), 4.56–4.50 (m, 2H), 3.83 (d, J = 7.3 Hz, 1H), 1.94 (sept, J = 6.8 Hz, 1H), 1.47 (s, 9H), 0.94–0.89 (m, 6H) ppm.

^{13}C NMR (101 MHz, Methanol-d4) δ = 158.8, 81.1, 78.4, 77.7, 62.2, 59.1, 29.4, 28.6, 20.3, 18.3 ppm.

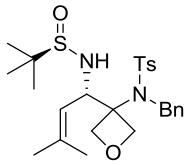
HRMS (ESI+): m/z calcd. for $C_{12}H_{25}N_2O_3$ $[M+H]^+$ 245.1860, found 245.1853.

IR (neat): ν [cm^{-1}] = 3288, 2966, 2878, 2051, 1710, 1599, 1515, 1482, 1392, 1366, 1289, 1244, 1165, 1043, 1019, 981, 872, 850, 782, 631.

$[\alpha]^{24}_D$ = –53.7 (c = 0.71, $CHCl_3$).

m.p. = 147 °C

N-benzyl-*N*-(3-((*S*)-1-((*R*)-1,1-dimethylethylsulfinamido)-3-methylbut-2-en-1-yl)oxetan-3-yl)-4-methylbenzenesulfonamide (**150**)[280]



Magnesium turnings (194 mg, 7.98 mmol, 6.00 eq) were stirred with a crystal of I_2 for 15 min and were then layered with a minimum amount of THF. 1-Bromo-2-methylprop-1-ene (719 mg, 5.32 mmol, 4.00 eq) and THF (10.0 mL) were added alternately to keep the exothermic reaction at slight reflux. After complete addition, the mixture was refluxed for 3 h in an oil bath and then cooled to room temperature.

The freshly prepared GRIGNARD solution was added dropwise to a solution of ent-**118** (597 mg, 1.33 mmol, 1.00 eq) in THF (5.00 mL) at -78 °C. The mixture was allowed to slowly warm to room temperature together with the cooling bath overnight. Saturated aqueous NH_4Cl solution and H_2O were added and the

layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by FC on silica gel (hex:EA = 1:2 to 100% EA) to afford **150** (441 mg, 0.875 mmol, 66%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, J = 8.2 Hz, 2H), 7.24–7.09 (m, 7H), 5.58 (d, J = 9.8 Hz, 1H), 5.14–4.73 (m, 2H), 4.73–4.50 (m, 2H), 4.50–4.19 (m, 3H), 4.00–3.73 (m, 1H), 2.35 (s, 3H), 1.84 (s, 3H), 1.73 (s, 3H), 1.24 (s, 9H) ppm.

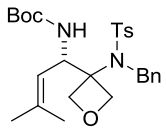
^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.7, 139.0, 138.0, 136.2, 129.6, 128.6, 127.8, 127.7, 127.5, 121.0, 75.8, 66.8, 58.1, 56.5, 51.1, 26.4, 22.8, 21.5, 18.9 ppm.

HRMS (ESI+): m/z calcd. for $C_{26}H_{36}N_2O_4S_2Na$ $[M+Na]^+$ 527.2009, found 527.2007.

IR (neat): ν [cm^{-1}] = 2959, 1599, 1496, 1454, 1332, 1230, 1152, 1114, 1055, 989, 916, 854, 811, 751, 699, 665, 599, 559, 542.

$[\alpha]^{22}_D$ = –32.8 (c = 1.24, $CHCl_3$).

(*S*)-*tert*-butyl (1-(3-(*N*-benzyl-4-methylphenylsulfonamido)oxetan-3-yl)-3-methylbut-2-en-1-yl)carbamate (**151**)[280]



HCl (4 M in dioxane, 1.10 mL, 4.31 mmol, 5.00 eq) was added to a solution of **150** (435 mg, 0.86 mmol, 1.00 eq) in CH_2Cl_2 (4.50 mL) and MeOH (4.50 mL) at 0 °C and the mixture was stirred at this temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure.

The oily residue was thoroughly dried under high vacuum and then dissolved CH_2Cl_2 (2.50 mL). A solution of di-*tert*-butyl dicarbonate (282 mg, 1.29 mmol, 1.50 eq) in CH_2Cl_2 (2.00 mL) was added and the resulting mixture was stirred at

room temperature for 3 h. The mixture was concentrated to about 10% and purified directly by FC in silica to yield **151** (392 mg, 0.783 mmol, 91%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, J = 7.9 Hz, 2H), 7.20–7.09 (m, 5H), 7.09–7.01 (m, 2H), 5.43 (d, J = 9.7 Hz, 1H), 5.29–5.09 (m, 1H), 5.06–4.85 (m, 2H), 4.84–4.65 (m, 1H), 4.58 (d, J = 7.4 Hz, 1H), 4.45–4.28 (m, 2H), 4.28–4.08 (m, 1H), 2.37 (s, 3H), 1.80 (s, 3H), 1.76 (s, 3H), 1.49 (s, 9H) ppm.

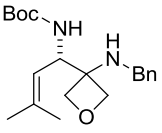
^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.6, 143.4, 138.6, 137.8, 135.7, 129.5, 128.5, 128.4, 127.8, 127.5, 121.0, 79.6, 77.1, 76.7, 66.4, 51.9, 50.6, 28.6, 26.2, 21.6, 18.9 ppm.

HRMS (ESI+): m/z calcd. for $C_{27}H_{37}N_2O_5S$ $[M+H]^+$ 501.2418, found 501.2413.

IR (neat): ν [cm^{-1}] = 3368, 2979, 1699, 1527, 1497, 1451, 1332, 1323, 1311, 1291, 1262, 1248, 1170, 1146, 1115, 1047, 997, 877, 786, 685, 648, 564.

$[\alpha]^{22}_D$ = –1.6 (c = 1.15, $CHCl_3$).

(*S*)-*tert*-butyl (1-(3-(benzylamino)oxetan-3-yl)-3-methylbut-2-en-1-yl)carbamate (**152**)[280]



Magnesium turnings (191 mg, 7.85 mmol, 10.0 eq) were added to a solution of **151** (393 mg, 0.785 mmol, 1.00 eq) in MeOH (7.00 mL) and THF (0.70 mL) and the mixture was vigorously stirred at room temperature for 3 h. Saturated aqueous NH_4Cl solution was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to dryness. The residue was purified by FC on silica gel (hex:EA = 2:1) to afford **152** (256 mg, 0.738 mmol, 94%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42–7.30 (m, 4H), 7.30–7.24 (m, 1H), 5.15–5.03 (m, 1H), 4.95 (d, J = 8.5 Hz, 1H), 4.77 (dd, J = 8.9, 8.9 Hz, 1H), 4.70–4.60 (m, 2H), 4.51

(d, *J* = 6.9 Hz, 1H), 4.43 (d, *J* = 6.9 Hz, 1H), 4.00 (d, *J* = 12.9 Hz, 1H), 3.95 (d, *J* = 12.9 Hz, 1H), 1.82 (d, *J* = 1.4 Hz, 3H), 1.75 (d, *J* = 1.4 Hz, 3H), 1.57 (br, 1H), 1.45 (s, 9H) ppm.

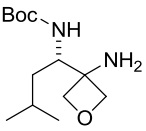
^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.9, 140.5, 138.6, 128.7, 128.1, 127.3, 120.6, 79.7, 78.0, 77.1, 63.5, 52.7, 47.3, 28.5, 26.2, 18.9 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{20}H_{30}N_2O_3Na$ $[M+Na]^+$ 369.2149, found 369.2143.

IR (neat): ν [cm^{-1}] = 2887, 1704, 1529, 1484, 1453, 1365, 1249, 1167, 1045, 1027, 1006, 965, 911, 747, 701, 487.

$[\alpha]^{20}_D$ = +9.9 (c = 1.13, $CHCl_3$).
m.p. = 113 °C.

(*S*)-*tert*-butyl (1-(3-aminooxetan-3-yl)-3-methylbutyl)carbamate (**149**)[280]



Pd-C (10% Pd, 78.0 mg, 0.074 mmol, 10.0 mol-%) was added to a solution of **152** (255 mg, 0.736 mmol, 1.00 eq) in MeOH (7.50 mL) and the mixture was stirred under an atmosphere of H_2 (balloon) for 2 h. The mixture was filtered over celite®, washed with EA, and the filtrate was concentrated to dryness to afford **149** (189 mg, 0.732 mmol, 99%) as a colorless foam.

^{1}H NMR (400 MHz, Methanol-d4) δ = 4.59 (d, *J* = 6.2 Hz, 1H), 4.46 (d, *J* = 6.4 Hz, 1H), 4.42–4.28 (m, 2H), 4.03 (dd, *J* = 11.7, 2.5 Hz, 1H), 1.73–1.57 (m, 1H), 1.44 (s, 9H), 1.40–1.25 (m, 1H), 1.20–1.07 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 6H) ppm.

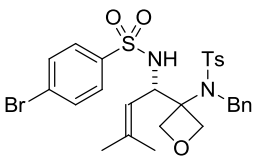
^{13}C NMR (101 MHz, Methanol-d4) δ = 158.7, 83.0, 82.6, 80.1, 60.5, 54.8, 38.8, 28.7, 26.2, 24.1, 21.8 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{13}H_{27}N_2O_3$ $[M+H]^+$ 259.2016, found 259.2018.

IR (neat): ν [cm^{-1}] = 3321, 2957, 2870, 1699, 1526, 1391, 1366, 1331, 1252, 1172, 1112, 1053, 976, 915, 873, 842.

[α]$^{20}_{D}$ = –43.2 (c = 0.75, $CHCl_3$).

(*S*)-*N*-benzyl-*N*-(3-(1-(4-bromophenylsulfonamido)-3-methylbut-2-en-1-yl)oxetan-3-yl)-4-methylbenzenesulfonamide (**156**)[280]



HCl (4 M in dioxane, 160 µL, 0.641 mmol, 5.00 eq) was added to a solution of **150** (64.7 mg, 0.128 mmol, 1.00 eq) in MeOH (650 µL) and CH_2Cl_2 (650 µL) at 0 °C and the mixture was stirred at this temperature for 30 min. Saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to dryness. The residue was dissolved in CH_2Cl_2 (650 µL) and triethyl amine (35.7 µl, 0.256 mmol, 2.00 eq), 4-bromobenzene-1-sulfonyl chloride (49.1 mg, 0.192 mmol, 1.50 eq), and DMAP (1.57 mg, 0.013 mmol, 10.0 mol-%) were added. After stirring at room temperature for 4 h, the mixture was directly purified by FC on silica gel (hexane:EA = 2:1) to afford **156** (65.7 mg, 0.106 mmol, 83%) as a colorless solid. Recrystallization from CH_2Cl_2/Et_2O gave crystals suitable for x-ray crystal structure analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74–7.66 (m, 2H), 7.66–7.60 (m, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.22–7.11 (m, 5H), 7.09–7.00 (m, 2H), 5.79 (d, *J* = 6.8 Hz, 1H), 5.06–4.96 (m, 1H), 4.95–4.72 (m, 2H), 4.72–4.53 (m, 1H), 4.53–4.34 (m, 2H), 4.34–4.10 (m, 2H), 2.38 (s, 3H), 1.51 (d, *J* = 1.3 Hz, 3H), 1.47 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.1, 140.9, 138.9, 137.4, 135.2, 132.0, 129.7, 129.0, 128.8, 128.3, 128.0, 127.8, 127.3, 120.0, 76.6, 76.1, 65.9, 56.6, 51.1, 25.9, 21.6, 18.6 ppm.

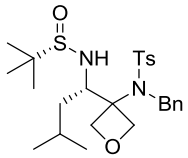
HRMS (ESI+): *m*/*z* calcd. for $C_{28}H_{31}BrN_2O_5S_2Na$ $[M+Na]^+$ 641.0750, found 641.0758.

IR (neat): ν [cm^{-1}] = 3192, 2928, 2883, 1576, 1448, 1340, 1325, 1278, 1228, 1173, 1157, 1089, 1050, 1010, 941, 742, 698, 674, 612, 560, 538.

[α]$^{24}_{D}$ = –38.8 (c = 0.39, $CHCl_3$).

m.p. = 201-202 °C (CH_2Cl_2).

N-benzyl-*N*-(3-((*S*)-1-((*S*)-1,1-dimethylethylsulfinamido)-3-methylbutyl)oxetan-3-yl)-4-methyl-benzenesulfonamide (**153**)



To a solution of **118** (1.5 g, 3.3 mmol, 1.0 eq) in THF (33 mL) at -78 °C was dropwise added isobutyllithium (1.7 M in heptane, 2.3 mL, 3.7 mmol, 1.5 eq). The mixture was stirred for 5 min at this temperature and then quenched with saturated aqueous NH_4Cl (30 mL) solution. The organic layer was separated and the aqueous layer was extracted with EA (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC on silica (hex:EA=2:1 to 1:1) to yield **153** (1.2 g, 2.3 mmol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 – 7.58 (m, 2H), 7.25 – 7.08 (m, 7H), 5.01 (br s, 1H), 4.92 – 4.64 (m, 3H), 4.59 (d, *J* = 6.5 Hz, 1H), 4.38 (d, *J* = 4.3 Hz, 2H), 3.86 – 3.75 (m, 1H), 2.38 (s, 3H), 1.78 (dtt, *J* = 13.2, 6.6, 3.0 Hz, 1H), 1.66 – 1.55 (m, 1H), 1.43 (t, *J* = 11.8 Hz, 1H), 1.23 (s, 9H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.79 (d, *J* = 6.5 Hz, 3H).

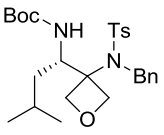
^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.8, 138.2, 135.9, 129.8, 128.8, 128.5, 127.9, 127.6, 77.6, 77.2, 66.6, 58.9, 56.7, 51.5, 41.1, 24.4, 24.3, 23.2, 21.6, 21.0 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{26}H_{39}N_2O_4S_2$ $[M+H]^+$ 507.2346, found, 507.2350.

IR (neat): ν [cm^{-1}] = 3284, 2957, 2927, 2870, 1598, 1496, 1456, 1416, 1389, 1366, 1336, 1305, 1230, 1154, 1091, 1067, 1027, 986, 939, 912, 881, 813, 754, 700, 666, 602, 546, 458.

[α]$^{24}_{D}$ +51.1 (*c* 1.07, $CHCl_3$)

(*S*)-tert-butyl (1-(3-(*N*-benzyl-4-methylphenylsulfonamido)oxetan-3-yl)-3-methylbutyl)carbamate (**154**)



To a solution of **153** (1.1 g, 2.3 mmol, 1.0 eq) in CH_2Cl_2/MeOH (1/1, 22 mL) was added at 0 °C HCl (4 M in dioxane, 2.8 ml, 11 mmol, 5.0 eq). The mixture was stirred for 1.5 h at this temperature. The oily residue was redissolved in CH_2Cl_2 (11 mL) and Boc_2O (0.78 ml, 3.4 mmol, 1.5 eq) was added. The solution was stirred at room temperature for 20 h and then concentrated. The residual solid was suspended in Et_2O (20 mL) and filtered. The filtercake was washed with Et_2O (2 x 10 mL) and dried *in vacuo* to yield **154** (790 mg, 1.6 mmol, 70%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, J = 8.2 Hz, 2H), 7.21 – 7.06 (m, 7H), 4.95 (br s, 1H), 4.83 (d, J = 10.1 Hz, 1H), 4.72 (br s, 1H), 4.56 (d, J = 7.2 Hz, 1H), 4.46 (d, J = 16.0 Hz, 1H), 4.36 – 4.14 (m, 3H), 2.37 (s, 3H), 1.79 – 1.62 (m, 3H), 1.48 (s, 9H), 0.99 (d, J = 6.3 Hz, 3H), 0.95 (d, J = 6.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.3, 143.4, 138.9, 135.9, 129.6, 128.6, 128.5, 127.8, 127.4, 79.6, 77.3, 67.0, 51.9, 50.4, 39.3, 28.6, 25.3, 24.2, 21.6 ppm.

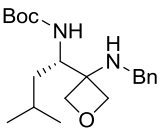
HRMS (ESI+): m/z calcd. for $C_{27}H_{39}N_2O_5S$ $[M+H]^+$ 503.2574, found, 503.2580.

IR (neat): ν [cm^{-1}] = 3385, 2958, 1701, 1599, 1512, 1497, 1455, 1390, 1366, 1334, 1253, 1156, 1104, 1090, 1056, 995, 918, 875, 844, 812, 755, 700, 668, 603, 562, 544.

***[α]*^{24}$_D$** -18.6 (*c* 0.79, $CHCl_3$)

m.p. 189 °C.

(*S*)-*tert*-butyl (1-(3-(benzylamino)oxetan-3-yl)-3-methylbutyl)carbamate (**155**)



To a suspension of **154** (0.69 g, 1.4 mmol, 1.0 eq) in MeOH (14 mL) were added magnesium turnings (0.33 g, 14 mmol, 10 eq). The mixture was at room temperature for 2 h. TLC still indicated the presence of starting material. Magnesium turnings (0.33 g, 14 mmol, 10 eq) were added and the mixture was stirred for another 2 h. The reaction was quenched with aqueous saturated NH_4Cl solution (20 mL) and extracted with EA (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to yield **155** (0.46 g, 1.3 mmol, 96%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 – 7.27 (m, 5H), 4.82 – 4.35 (m, 5H), 4.20 – 4.11 (m, 1H), 4.04 – 3.91 (m, 2H), 1.84 – 1.62 (m, 1H), 1.45 (s, 9H), 1.31 – 1.22 (m, 2H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.2, 140.2, 128.6, 128.1, 127.2, 79.4, 78.0, 77.6, 63.7, 52.4, 47.2, 38.9, 28.4, 25.0, 23.9, 21.7 ppm.

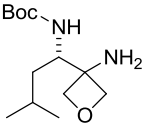
HRMS (ESI+): *m*/*z* calcd. for $C_{20}H_{33}N_2O_3$ $[M+H]^+$ 349.2486, found, 349.2487.

IR (neat): ν [cm^{-1}] = 3332, 2957, 2871, 1705, 1496, 1470, 1454, 1391, 1366, 1249, 1169, 1116, 1056, 1028, 981, 842, 738, 700.

***[α]*^{24}D** -85.9 (*c* 0.74, $CHCl_3$)

m.p. 126 °C.

(*S*)-tert-butyl (1-(3-aminooxetan-3-yl)-3-methylbutyl)carbamate (**149**)



To a mixture of Pd-C (10% Pd, 136 mg, 0.128 mmol, 10 mol%) and **155** was added MeOH (12.8 mL) and the mixture was stirred under an atmosphere of H2 (balloon) for 2 h. The mixture was filtered over Celite®, washed with MeOH and the filtrate was concentrated to dryness to afford **149** (312 mg, 0.732 mmol, 94%) as a colorless foam.

^{1}H NMR (400 MHz, Methanol-d4) δ = 4.59 (d, J = 6.2 Hz, 1H), 4.46 (d, J = 6.4 Hz, 1H), 4.42–4.28 (m, 2H), 4.03 (dd, J = 11.7, 2.5 Hz, 1H), 1.73–1.57 (m, 1H), 1.44 (s, 9H), 1.40–1.25 (m, 1H), 1.20–1.07 (m, 1H), 0.96 (d, J = 6.5 Hz, 6H) ppm.

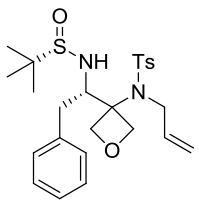
^{13}C NMR (101 MHz, Methanol-d4) δ = 158.7, 83.0, 82.6, 80.1, 60.5, 54.8, 38.8, 28.7, 26.2, 24.1, 21.8 ppm.

HRMS (ESI+): m/z calcd. for $C_{13}H_{27}N_2O_3$ $[M+H]^+$ 259.2016, found 259.2018.

IR (neat): ν [cm^{-1}] = 3321, 2957, 2870, 1699, 1526, 1391, 1366, 1331, 1252, 1172, 1112, 1053, 976, 915, 873, 842.

$[\alpha]^{20}_D$ = –43.2 (c = 0.75, $CHCl_3$).

N-allyl-*N*-(3-((*S*)-1-((*S*)-1,1-dimethylethylsulfinamido)-2-phenylethyl)oxetan-3-yl)-4-methylbenzene-sulfonamide (**159**)



Benzyl magnesium chloride was prepared from magnesium turnings (490 mg, 20 mmol, 8.0 eq) and benzyl chloride (1.2 mL, 10 mmol, 4.0 eq) in Et_2O (13 mL). After complete addition the mixture was refluxed for 3 h to give a brown suspension. The supernatant solution was added dropwise over 1 h to a solution of **139** (1.0 g, 2.5 mmol, 1.0 eq) in CH_2Cl_2 (13 mL) at -78 °C. The mixture was stirred at this temperature for 2 h and then warmed to room temperature over 12 h. The reaction was quenched by the addition of water (20 mL) and saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness, to leave a light yellow solid (d.r. 4:1). The crude product was recrystallized from hex/EA (2/1, 50 mL) to yield **159** (890 mg, 1.8 mmol, 72%) as a single diastereomer as a colorless powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.28 – 7.13 (m, 5H), 5.81 (ddt, J = 16.5, 10.2, 6.1 Hz, 1H), 5.33 – 5.06 (m, 2H), 5.04 –

4.89 (m, 2H), 4.69 (ddd, *J* = 14.5, 7.2, 1.8 Hz, 2H), 4.56 (br s, 1H), 4.21 (ddd, *J* = 10.5, 6.9, 3.1 Hz, 1H), 3.80 (d, *J* = 6.0 Hz, 2H), 3.24 (dd, *J* = 14.1, 3.1 Hz, 1H), 2.72 (dd, *J* = 14.1, 11.0 Hz, 1H), 2.42 (s, 3H), 0.91 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.2, 138.4, 137.9, 134.9, 130.1, 123.0, 128.5, 127.7, 126.6, 119.3, 77.4, 76.8, 66.4, 62.6, 56.3, 50.4, 38.2, 22.7, 21.7 ppm.

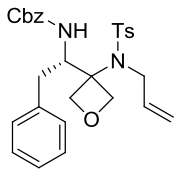
HRMS (ESI+): *m*/*z* calcd. for $C_{25}H_{35}N_2O_4S_2$ $[M+H]^+$ 491.2033, found, 491.2037.

IR (neat): ν [cm^{-1}] =3281, 2960, 2925, 1599, 1496, 1456, 1420, 1341, 1233, 1154, 1090, 1064, 992, 923, 886, 814, 748, 700, 665, 617, 581, 548, 463.

***[α]*^{24}D** +15.3 (*c* 0.80, $CHCl_3$)

m.p. 157 °C

(*S*)-benzyl (1-(3-(*N*-allyl-4-methylphenylsulfonamido)oxetan-3-yl)-2-phenylethyl)carbamate



To a solution of **159** (0.28 g, 0.56 mmol, 1.0 eq) in CH_2Cl_2/MeOH (5.6 mL) was added at 0 °C HCl (4 M in dioxane, 0.70 mL, 2.8 mmol, 5.0 eq). The mixture was stirred for 2 h at this temperature. Saturated aqueous $NaHCO_3$ solution (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The oily residue was redissolved in pyridine (2.8 mL) and Cbz-Cl (0.16 ml, 1.12 mmol, 2.0 eq) was added. The mixture was stirred at room temperature for 24 h. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with DCM (3 x 40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residual oil was evaporated from cyclohexane (3 x 40 mL) to remove remaining pyridine. The residue was purified by FC on silica (hex:EA=2:1) to yield **160** (250 mg, 0.49 mmol, 87%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (d, J = 8.2 Hz, 2H), 7.46 – 7.04 (m, 7H), 5.84 – 5.66 (m, 1H), 5.24 – 4.85 (m, 7H), 4.80 – 4.41 (m, 3H), 4.01 – 3.65 (m, 2H), 3.39 (dd, J = 14.4, 3.4 Hz, 1H), 2.86 (dd, J = 14.3, 11.4 Hz, 1H), 2.45 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.7, 144.0, 138.3, 137.9, 136.7, 134.6, 130.0, 129.3, 128.6, 128.5, 128.0, 127.8, 127.6, 126.7, 118.9, 77.0, 76.7, 66.7, 66.6, 56.2, 49.8, 36.2, 21.7 ppm.

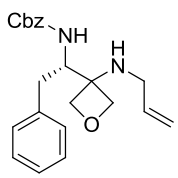
HRMS (ESI+): m/z calcd. for $C_{29}H_{33}N_2O_5S$ $[M+H]^+$ 521.2105, found, 521.2113.

IR (neat): ν [cm^{-1}] = 3334, 3031, 2925, 1720, 1599, 1536, 1496, 1454, 1331, 1250, 1154, 1089, 1058, 990, 923, 850, 814, 748, 699, 665, 581, 548.

[α]^{25}$_D$ -28.1 (c 0.84, $CHCl_3$)

m.p. 164 °C

(*S*)-benzyl (1-(3-(allylamino)oxetan-3-yl)-2-phenylethyl)carbamate (**161**)



To a suspension of **160** (900 mg, 1.7 mmol, 1.0 eq) in MeOH (17 mL) were added magnesium turnings (420 mg, 17 mmol, 10 eq). The mixture was sonicated for 10 min at room temperature and then further stirred at this temperature for 2 h. TLC still indicated the presence of starting material. Magnesium turnings (420 mg, 17 mmol, 10 eq) were added. The mixture was stirred for another 2 h. The reaction was quenched with aqueous saturated NH_4Cl solution (20 mL) and extracted with EA (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by FC on silica (hex:EA=2:1 to 1:1). The desired product **161** (0.625 g, 1.7 mmol, 99 % yield) was obtained as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 – 7.05 (m, 10H), 5.95 (ddt, J = 16.3, 10.9, 5.7 Hz, 1H), 5.29 – 4.97 (m, 5H), 4.62 – 4.24 (m, 5H), 4.80 – 4.41 (m, 3H), 3.47 (d, J = 5.8 Hz, 2H), 2.82 (ddd, J = 61.6, 14.1, 6.8 Hz, 2H).

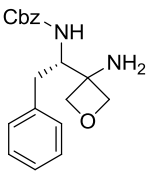
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.4, 137.7, 136.8, 136.6, 129.2, 128.8, 128.7, 128.2, 128.1, 126.9, 116.2, 78.5, 77.7, 66.9, 63.1, 56.8, 45.7, 36.1 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{22}H_{26}N_2O_3$ $[M+H]^+$ 367.2016, found, 367.2016.

IR (neat): ν [cm^{-1}] = 3323, 2924, 2876, 2854, 1695, 1644, 1604, 1539, 1496, 1454, 1418, 1332, 1244, 1134, 1028, 979, 918, 844, 738, 697, 578, 531, 462.

[α]^{25}$_D$ -9.78 (*c* 0.84, $CHCl_3$).

(*S*)-benzyl (1-(3-aminooxetan-3-yl)-2-phenylethyl)carbamate (**157**)



To a solution of **161** (0.63 g, 1.7 mmol, 1.0 eq) and 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (0.80 g, 5.1 mmol, 3.0 eq) in CH_2Cl_2 (17 mL) was added $Pd(Ph_3P)_4$ (0.099 g, 0.085 mmol, 5.0 mol-%) and the mixture was degassed by passing a stream on N_2 through the solution. Then, the reaction was heated to 35 °C for 4 h. After cooling to room temperature, the mixture was poured into saturated aqueous $NaHCO_3$ solution (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and evaporatd to dryness. The residue was purified by FC on silica (EA:MeOH=97:3) to yield **157** (0.470 g, 1.44 mmol, 85%) as a light yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.14 (m, 10H), 5.17 (br s, 1H), 5.04 (q, *J* = 12.3 Hz, 2H), 4.60 (d, *J* = 6.9 Hz, 1H), 4.48 – 4.35 (m, 1H), 4.27 (dd, *J* = 22.4, 6.8 Hz, 2H), 2.84 – 2.62 (m, 2H), 1.65 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.3, 137.6, 136.6, 129.1, 128.8, 128.6, 128.2, 128.1, 127.0, 83.1, 83.0, 66.9, 59.0, 57.4, 36.5 ppm.

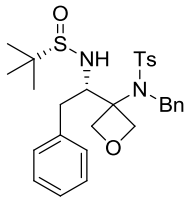
HRMS (ESI+): *m*/*z* calcd. for $C_{19}H_{23}N_2O_3$ $[M+H]^+$ 327.1703, found, 327.1704.

IR (neat): ν [cm^{-1}] = 3312, 3030, 2953, 2870, 1701, 1605, 1538, 1497, 1455, 1335, 1252, 1138, 1080, 1054, 1028, 975, 903, 840, 746, 698, 534, 461.

[α]$^{25}_{D}$ -23.9 (*c* 0.79, $CHCl_3$)

m.p. 119 °C

N-benzyl-*N*-(3-((*S*)-1-((*S*)-1,1-dimethylethylsulfinamido)-2-phenylethyl)oxetan-3-yl)-4-methylbenzenesulfonamide (**162**)[280]



Magnesium turnings (867 mg, 35.7 mmol, 8.00 eq) were stirred with a crystal of I_2 for 15 min and were then layered with a minimum amount of Et_2O. Benzyl chloride (2.26 g, 17.8 mmol, 4.00 eq) and Et_2O (22.0 mL) were added alternately to keep the exothermic reaction at slight reflux. After complete addition, the mixture was refluxed for 1 h in an oil bath and then cooled to room temperature.

The freshly prepared benzylmagnesium chloride solution was added to a solution of **118** (2.00 g, 4.46 mmol, 1.00 eq) in CH_2Cl_2 (22.0 mL) at -78 °C over the course of 1 h. The reaction was allowed to slowly warm to room temperature over night and was then quenched with saturated aqueous NH_4Cl-solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to dryness. The residue was recrystallized from MeOH to afford **162** (1.20 g, 2.22 mmol, 50%) as colorless needles.

The mother liquor was concentrated to dryness and the residue was purified by FC on silica gel (hex:EA 1:1 to 100% EA) to afford a second crop of **162** (494 mg, 0.91 mmol, 20%) as a colorless solid.

Combined yield: 1.69 g (3.13 mmol, 70%).

Recrystallization from MeOH gave crystals suitable for x-ray crystal structure analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (d, *J* = 8.3 Hz, 2H), 7.41–7.24 (m, 7H), 7.18 (m, 3H), 7.02–6.79 (m, 2H), 5.26–4.99 (m, 1H), 4.83 (m, 2H), 4.78–4.47 (m, 3H), 4.43–4.17 (m, 1H), 4.08–3.84 (m, 1H), 3.22 (dd, *J* = 14.1, 3.2 Hz, 1H), 2.71 (dd, *J* = 12.5, 12.5 Hz, 1H), 2.42 (s, 3H), 0.88 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.0, 138.4, 138.3, 136.2, 130.0, 129.9, 129.0, 128.7, 128.2, 128.1, 127.4, 126.4, 77.3, 76.4, 66.2, 61.6, 56.1, 51.4, 37.9, 22.7, 21.6 ppm.

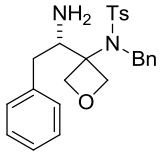
HRMS (ESI+): *m*/*z* calcd. for $C_{29}H_{36}N_2O_4S_2Na$ $[M+Na]^+$ 563.2009, found 563.2012.

IR (neat): ν [cm^{-1}] = 3284, 2881, 2286, 1981, 1599, 1494, 1453, 1417, 1323, 1308, 1147, 1088, 1063, 938, 898, 808, 756, 696, 679.

$[\alpha]^{25}_D$ = +31.6 (c = 0.86, $CHCl_3$).

m.p. = 217-218 °C (MeOH, dec.).

(*S*)-*N*-(3-(1-amino-2-phenylethyl)oxetan-3-yl)-*N*-benzyl-4-methylbenzenesulfonamide (**163**)[280]



To a solution of **162** (1.69 g, 3.13 mmol, 1.00 eq) in MeOH (15.5 mL) and CH_2Cl_2 (15.5 mL) was added HCl (4 M in dioxane, 3.91 mL, 15.6 mmol, 5.00 eq) at 0 °C and the mixture was stirred at this temperature for 45 min. The reaction was quenched saturated aqueous $NaHCO_3$-solution and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 30 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by FC on silica gel (hex:EA = 1:1 to 100% EA) to afford **163** (1.36 g, 3.13 mmol, quant.) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63 (d, *J* = 8.2 Hz, 2H), 7.38–7.30 (m, 2H), 7.29–7.20 (m, 3H), 7.20–7.10 (m, 7H), 5.21–4.98 (m, 1H), 4.98–4.83 (m, 1H), 4.72 (d, *J* = 7.2 Hz, 1H), 4.66 (d, *J* = 7.1 Hz, 1H), 4.50 (s, 2H), 3.79 (dd, *J* = 11.3, 2.5 Hz, 1H),

3.39 (d, *J* = 13.6 Hz, 1H), 2.59 (dd, *J* = 13.6, 11.2 Hz, 1H), 2.34 (s, 3H), 1.17 (br, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.7, 138.9, 137.7, 137.1, 129.6, 129.3, 128.8, 128.5, 127.8, 127.3, 127.2, 126.7, 77.5, 75.8, 67.7, 56.6, 51.4, 38.2, 21.5 ppm.

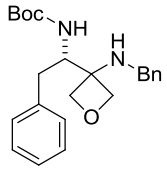
HRMS (ESI+): *m*/*z* calcd. for $C_{25}H_{29}N_2O_3S$ $[M+H]^+$ 437.1893, found 437.1891.

IR (neat): ν [cm^{-1}] = 2878, 1600, 1494, 1452, 1322, 1309, 1272, 1231, 1148, 1125, 1089, 1039, 1003, 962, 940, 899, 861, 810, 789, 757, 745, 704, 697, 678, 648, 608, 575.

$[\alpha]^{23}_D$ = –9.1 (c = 1.11, $CHCl_3$).

m.p. = 150 °C.

(*S*)-*tert*-butyl (1-(3-(benzylamino)oxetan-3-yl)-2-phenylethyl)carbamate (**164**)[280]



To a suspension of **163** (1.36 g, 3.12 mmol, 1.00 eq) in MeOH (28.3 mL) and THF (2.83 mL) were added magnesium turnings (757 mg, 31.2 mmol, 10.0 eq) and the mixture was stirred in a room temperature water bath for 3 h. The reaction was quenched with saturated aqueous NH_4Cl-solution and extracted with CH_2Cl_2 (4 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude diamine as a colorless wax.

The crude product was dissolved in CH_2Cl_2 (25.5 mL) and a solution of di-*tert*-butyl dicarbonate (714 mg, 3.27 mmol, 1.10 eq) in CH_2Cl_2 (5.50 mL) was added at 0 °C. The mixture was stirred at 0 °C for 1 h and at room temperature for 12 h. The solvent was removed in vacuo and the residue was purified by FC on silica gel (hex:EA = 2:1) to afford **164** (1.18 g, 3.08 mmol, 99%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42–7.34 (m, 4H), 7.33–7.26 (m, 3H), 7.25–7.16 (m, 3H), 4.87 (d, *J* = 9.4 Hz, 1H), 4.76–4.51 (m, 2H), 4.47 (d, *J* = 7.2 Hz, 1H), 4.44–4.22 (m, 2H), 4.00 (s, 2H), 3.04–2.53 (m, 2H), 1.60 (s, 1H), 1.37 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.9, 140.3, 138.0, 129.3, 128.7, 128.7, 128.2, 127.4, 126.7, 79.7, 78.5, 78.0, 63.4, 55.5, 47.4, 36.2, 28.4 ppm.

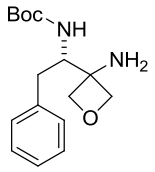
HRMS (ESI+): *m*/*z* calcd. for $C_{23}H_{31}N_2O_3$ $[M+H]^+$ 338.2329, found 338.2326.

IR (neat): ν [cm^{-1}] = 3332, 3028, 2965, 2884, 1716, 1534, 1495, 1453, 1392, 1365, 1246, 1164, 1062, 1020, 964, 928, 904, 849, 735, 698, 536, 491.

$[\alpha]^{26}_D$ = +3.7 (c = 0.77, $CHCl_3$).

m.p. = 108 °C

(*S*)-*tert*-Butyl (1-(3-aminooxetan-3-yl)-2-phenylethyl)carbamate (**158**)[280]



Pd-C (10 wt-% Pd, 164 mg, 0.15 mmol, 5.00 mol-%) was added to a solution of **164** (1.18 g, 3.08 mmol, 1.00 eq) in MeOH (30.0 mL) and the mixture was stirred under an atmosphere of H_2 (balloon) for 3 h. Then, the mixture was filtered over Celite®, the filter cake was washed with EA, and the filtrate was concentrated to dryness to afford **158** (841 mg, 2.88 mmol, 93%) as a colorless solid.

^{1}H NMR (400 MHz, Methanol-d4) δ = 7.32–7.25 (m, 4H), 7.23–7.16 (m, 1H), 4.70 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 7.1 Hz, 1H), 4.50 (d, *J* = 6.9 Hz, 1H), 4.47 (d, *J* = 7.1 Hz, 1H), 4.19 (dd, *J* = 11.2, 3.6 Hz, 1H), 2.94 (dd, *J* = 13.9, 3.8 Hz, 1H), 2.66 (dd, *J* = 13.9, 11.2 Hz, 1H), 1.29 (s, 9H) ppm.

^{13}C NMR (101 MHz, Methanol-d4) δ = 158.4, 139.3, 130.3, 129.4, 127.5, 80.8, 80.4, 80.3, 60.7, 57.5, 35.8, 28.6 ppm.

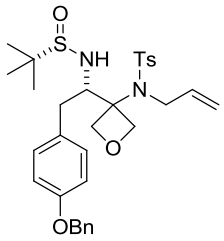
HRMS (ESI+): *m*/*z* calcd. for $C_{16}H_{25}N_2O_3$ $[M+H]^+$ 293.1860, found 293.1863.

IR (neat): ν [cm^{-1}] = 3319, 2976, 2870, 1698, 1604, 1522, 1496, 1455, 1391, 1366, 1335, 1250, 1170, 1079, 1051, 1017, 975, 845, 748, 700, 532.

$[\alpha]^{22}_D$ = -18.1 (*c* 0.50, $CHCl_3$).

m.p. = 135 °C.

N-allyl-*N*-(3-((*S*)-2-(4-(benzyloxy)phenyl)-1-((*S*)-1,1-dimethylethylsulfinamido)ethyl)oxetan-3-yl)-4-methylbenzenesulfonamide (**169**)



Magnesium turnings (244 mg, 10.0 mmol, 4.00 eq) were stirred with a crystal of I_2 and covered with a minimum amount of THF, before THF (12.5 mL) and a solution of 1-(benzyloxy)-4-(chloromethyl)benzene (1.75 g, 7.53 mmol, 3.00 eq) in THF (4.18 mL) were added alternately dropwise. After complete addition, the mixture was stirred at room temperature for 1 h.

The freshly prepared GRIGNARD solution was added dropwise over 30 min to a solution of **139** (1.00 g, 2.51 mmol, 1.00 eq) in THF (8.40 mL) at -78 °C. The reaction was allowed to warm to ambient temperature together with cooling bath overnight. Saturated aqueous NH_4Cl-solution was added, the layers were separated and the aqueous layer was extracted with EA (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by FC on silica gel (hexane:EA = 1:1 to 1:2 to 100% EA) to afford **169** (887 mg, 1.49 mmol, 59%) as colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86–7.78 (m, 2H), 7.47–7.27 (m, 7H), 7.16–7.07 (m, 2H), 6.94–6.86 (m, 2H), 5.91–5.76 (m, 1H), 5.21 (d, *J* = 17.4 Hz, 1H), 5.15 (d, *J* = 10.2 Hz, 1H), 5.07 (s, 2H), 4.97 (dd, *J* = 17.2, 7.1 Hz, 2H), 4.73 (d, *J* = 7.4 Hz, 1H), 4.70 (d, *J* = 6.9 Hz, 1H), 4.66–4.54 (m, 1H), 4.18 (ddd, *J* = 10.4, 6.7, 3.1 Hz, 1H), 3.83 (d, *J* = 6.2 Hz, 2H), 3.21 (dd, *J* = 14.2, 3.1 Hz, 1H), 2.70 (dd, *J* = 14.2, 10.9 Hz, 1H), 2.46 (s, 3H), 0.97 (s, 9H) ppm.

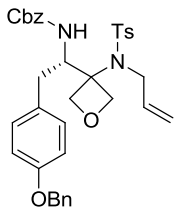
^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.5, 144.1, 137.9, 137.2, 134.8, 130.9, 130.7, 130.1, 128.7, 128.0, 127.6, 127.5, 119.2, 115.0, 77.4, 76.8, 70.1, 66.4, 62.5, 56.3, 50.4, 37.3, 22.8, 21.7 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{32}H_{41}N_2O_5S_2$ $[M+H]^+$ 597.2451, found 597.2451.

IR (neat): ν [cm^{-1}] = 3280, 3032, 2958, 1611, 1585, 1511, 1455, 1419, 1389, 1335, 1304, 1236, 1152, 1089, 1060, 1014, 918, 892, 860, 813, 737, 696, 663, 593, 566, 547, 511.

$[\alpha]^{23}_D$ = +4.7 (c = 0.94, $CHCl_3$).

(*S*)-benzyl (1-(3-(*N*-allyl-4-methylphenylsulfonamido)oxetan-3-yl)-2-(4-(benzyloxy)phenyl)ethyl)carba-mate (**170**)



To a solution of **169** (0.77 g, 1.29 mmol, 1.0 eq) in CH_2Cl_2/MeOH (1/1, 13 mL) was added at 0 °C HCl (4 M in dioxane, 1.29 mL, 5.14 mmol, 5.0 eq). The mixture was stirred for 1.5 h at this temperature. Saturated aqueous $NaHCO_3$ solution (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The oily residue was redissolved in pyridine (6.4 mL) and Cbz-Cl (0.22 ml, 1.54 mmol, 1.2 eq) was added. The mixture was stirred at room temperature for 14 h. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with DCM (3 x 40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residual oil was evaporated from cyclohexane (3 x 40 mL) to remove remaining pyridine. The residue was purified by FC on silica (hex:EA=2:1) to yield **170** (459 mg, 0.73 mmol, 57%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (d, *J* = 8.3 Hz, 2H), 7.47 – 7.27 (m, 9H), 7.20 – 7.10 (m, 4H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.74 (ddt, *J* = 16.6, 10.2, 6.2 Hz, 1H), 5.25 – 4.86 (m, 9H), 4.69 – 4.39 (m, 3H), 3.90 – 3.65 (m, 2H), 3.32 (dd, *J* = 14.5, 3.4 Hz, 1H), 2.80 (dd, *J* = 14.4, 11.1 Hz, 1H), 2.45 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.67, 156.72, 143.96, 138.32, 137.27, 136.79, 134.59, 130.24, 130.22, 130.01, 128.72, 128.53, 128.08, 128.00, 127.75, 127.65, 127.55, 118.88, 114.99, 70.13, 66.72, 66.59, 56.35, 49.83, 35.28, 21.69 ppm.

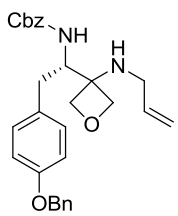
HRMS (ESI+): *m*/*z* calcd. for $C_{36}H_{39}N_2O_6S$ $[M+H]^+$ 627.2523, found, 527.2518.

IR (neat): ν [cm^{-1}] =3327, 2970, 1721, 1611, 1512, 1455, 1332, 1240, 1154, 1090, 1051, 1027, 920, 853, 816, 741, 697, 664, 574, 549, 485, 465.

[α]^{23}D -21.8 (*c* 0.32, $CHCl_3$)

m.p. 114 °C

(*S*)-benzyl (1-(3-(allylamino)oxetan-3-yl)-2-(4-(benzyloxy)phenyl)ethyl)carbamate (**171**)



To a solution of **170** (345 mg, 0.56 mmol, 1.0 eq) in MeOH (5.5 mL) were added magnesium turnings (134 mg, 5.5 mmol, 10 eq). The mixture was sonicated for 10 min at room temperature and then further stirred at this temperature for 3 h. The reaction was quenched with aqueous saturated NH_4Cl solution (20 mL) and extracted with EA (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by FC on silica (hex:EA=2:1 to 1:1). The desired product **171** (0.252 g, 0.55 mmol, 97 % yield) was obtained as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 – 7.26 (m, 10H), 7.11 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.02 – 5.86 (m, 1H), 5.24 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.17 – 4.97 (m, 6H), 4.55 – 4.27 (m, 5H), 3.46 (d, *J* = 5.8 Hz, 2H), 2.87 – 2.63 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.8, 137.1, 136.8, 130.2, 128.7, 128.7jj, 128.3, 128.1, 127.6, 116.2, 115.2, 78.5, 77.7, 70.2, 66.9, 63.0, 56.9, 45.7, 35.3 ppm.

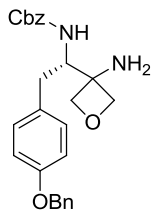
HRMS (ESI+): *m*/*z* calcd. for $C_{29}H_{33}N_2O_4$ $[M+H]^+$ 473.2435, found, 473.2436.

IR (neat): ν [cm^{-1}] =3326, 3033, 2952, 2876, 1715, 1611, 1584, 1511, 1454, 1242, 1177, 1111, 1027, 981, 917, 821, 738, 697, 541.

***[α]*^{23}D** -9.8 (*c* 0.53, $CHCl_3$).

m.p. 119 °C.

(*S*)-benzyl (1-(3-aminooxetan-3-yl)-2-(4-(benzyloxy)phenyl)ethyl)carbamate (**165**)



To a solution of **171** (0.175 g, 0.37 mmol, 1.0 eq) and 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (0.173 g, 1.11 mmol, 3.0 eq) in CH_2Cl_2 (3.7 mL) was added $Pd(Ph_3P)_4$ (21.4 mg, 0.019 mmol, 5.0 mol-%) and the mixture was degassed by passing a stream on N_2 through the solution. Then, the reaction was heated to 35 °C for 4 h. After cooling to room temperature, the mixture was poured into saturated aqueous $NaHCO_3$ solution (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The residue was purified by FC on silica (100% EA) to yield **165** (0.155 g, 1.44 mmol, 97%) as a light yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 – 7.27 (m, 10H), 7.11 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 5.23 – 4.98 (m, 5H), 4.60 (d, *J* = 6.8 Hz, 1H), 4.42– 4.20 (m, 3H), 1.65 (s, 2H), 4.07 (d, *J* = 6.9 Hz, 1H), 2.85 – 2.62 (m, 1H), 1.73 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.9, 137.1, 130.1, 128.7, 128.7, 128.1, 127.6, 115.2, 83.1, 83.1, 70.2, 66.9, 59.0, 57.4, 35.6 ppm.

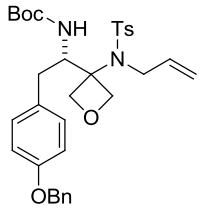
HRMS (ESI+): *m*/*z* calcd. for $C_{26}H_{29}N_2O_4$ $[M+H]^+$ 433.2122, found, 433.2124.

IR (neat): ν [cm^{-1}] = 3322, 3033, 2951, 2869, 1699, 1611, 1584, 1511, 1554, 1381, 1242, 1177, 1111, 1026, 976, 911, 822, 738, 696, 612, 543.

***[α]*^{23}D** -21.7 (*c* 0.52, $CHCl_3$).

m.p. 120 °C.

(*S*)-tert-butyl (1-(3-(*N*-allyl-4-methylphenylsulfonamido)oxetan-3-yl)-2-(4-(benzyloxy)phenyl)ethyl)carbamate (**172**)[280]



To a solution of **169** (880 mg, 1.48 mmol, 1.00 eq) in CH_2Cl_2 (7.40 mL) and MeOH (7.40 mL) was added HCl (4 M in dioxane, 1.48 mL, 5.90 mmol, 4.00 eq) at 0 °C and the mixture was stirred at this temperature for 60 min. The reaction was quenched with saturated aqueous $NaHCO_3$-solution and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was passed over short pad of silica gel (hex:EA = 1:2) and the product containing fractions were combined and evaporated to dryness.

The residual oil was dissolved in 1,2-dichloroethane (11.1 mL) and a solution of di-*tert*-butyl dicarbonate (483 mg, 2.21 mmol, 1.50 eq) in 1,2-dichloroethane (3.70 mL) was added. The mixture was heated to 60 °C for 12 h and after cooling to room temperature, the solvent was evaporated and the residue was purified by FC on silica gel (hexane:EA = 2:1) to afford **172** (770 mg, 1.30 mmol, 88%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (d, *J* = 8.2 Hz, 2H), 7.47–7.41 (m, 2H), 7.41–7.35 (m, 2H), 7.35–7.29 (m, 3H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.96–6.87 (m, 2H), 5.85–5.69 (m, 1H), 5.18 (d, *J* = 17.2 Hz, 1H), 5.09 (d, *J* = 10.3 Hz, 1H), 5.04 (s, 2H), 5.03–4.91 (m, 2H), 4.87 (d, *J* = 9.8 Hz, 1H), 4.64 (d, *J* = 7.2 Hz, 1H), 4.54–4.37 (m, 2H), 3.83 (dd, *J* = 16.6, 6.0 Hz, 1H), 3.72 (dd, *J* = 16.6, 6.7 Hz, 1H), 3.29 (dd, *J* = 14.4, 3.4 Hz, 1H), 2.76 (dd, *J* = 14.4, 11.2 Hz, 1H), 2.44 (s, 3H), 1.30 (s, 9H) ppm.

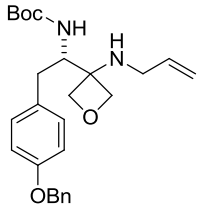
^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.6, 156.1, 143.8, 138.4, 137.3, 134.7, 130.5, 130.3, 130.0, 128.7, 128.0, 127.5, 127.5, 118.7, 114.9, 79.5, 77.2, 76.6, 70.2, 66.6, 55.6, 49.8, 35.3, 28.3, 21.7 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{33}H_{41}N_2O_6S$ $[M+H]^+$ 593.2680, found 593.2680.

IR (neat): ν [cm^{-1}] = 2975, 1698, 1611, 1511, 1454, 1390, 1365, 1328, 1239, 1153, 1089, 1044, 1017, 990, 921, 887, 858, 812, 776, 737, 696, 662, 599, 569, 547.

$[\alpha]^{23}_D$ = –19.8 (c = 0.98, $CHCl_3$).

(*S*)-*tert*-butyl (1-(3-(allylamino)oxetan-3-yl)-2-(4-(benzyloxy)phenyl)ethyl)-carbamate (**173**)[280]



Magnesium turnings (313 mg, 12.87 mmol, 10.0 eq) were added to a solution of **172** (763 mg, 1.29 mmol, 1.00 eq) in MeOH (11.5 mL) and THF (1.15 mL) and the mixture was stirred in a room temperature water bath for 3 h. The reaction was quenched with saturated aqueous NH_4Cl-solution. The mixture was extracted with CH_2Cl_2 (4 x 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford **173** (529 mg, 1.21 mmol, 94%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49–7.33 (m, 4H), 7.36–7.27 (m, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.04–5.89 (m, 1H), 5.32–5.21 (m, 1H), 5.19–5.09 (m, 1H), 5.04 (s, 2H), 4.86 (d, *J* = 9.5 Hz, 1H), 4.67–4.45 (m, 2H), 4.42 (d, *J* = 7.2 Hz, 1H), 4.32 (d, *J* = 6.9 Hz, 1H), 4.30–4.13 (m, 1H), 3.46 (d, *J* = 5.7 Hz, 2H), 2.91–2.52 (m, 2H), 1.64 – 1.19 (m, 10H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.7, 155.9, 137.2, 136.9, 130.2, 130.2, 128.7, 128.0, 127.5, 116.1, 115.1, 79.6, 78.5, 77.9, 70.2, 63.1, 55.8, 45.7, 35.2, 28.4 ppm.

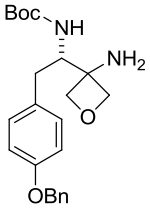
HRMS (ESI+): *m*/*z* calcd. for $C_{26}H_{35}N_2O_4$ $[M+H]^+$ 439.2591, found 439.2597.

IR (neat): ν [cm^{-1}] = 3316, 2972, 2885, 1711, 1510, 1455, 1442, 1365, 1334, 1241, 1175, 1071, 1044, 1023, 1007, 968, 913, 861, 813, 776, 737, 694, 535.

[α]$^{23}_{D}$ = –2.0 (c = 0.98, $CHCl_3$).

m.p. = 126 °C

(*S*)-tert-butyl (1-(3-aminooxetan-3-yl)-2-(4-(benzyloxy)phenyl)ethyl)carbamate (**166**)[280]



$Pd(Ph_3P)_4$ (68.5 mg, 0.059 mmol, 5.00 mol-%) was added to a solution of **173** (520 mg, 1.19 mmol, 1.00 eq) and 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (555 mg, 3.56 mmol, 3.00 eq) in CH_2Cl_2 (12.0 mL) and the mixture was degassed by passing a stream on N_2 through the solution. The reaction was heated to 35 °C for 6 h. After cooling to room temperature, the mixture was poured into saturated aqueous $NaHCO_3$-solution and extracted with CH_2Cl_2 (4 x 25 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The residue was purified by FC on silica gel (CH_2Cl_2:MeOH = 20:1). **166** (454 mg, 1.14 mmol, 96%) was obtained as a pale orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52–7.28 (m, 5H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.04 (s, 2H), 4.86 (d, *J* = 9.3 Hz, 1H), 4.59 (d, *J* = 6.9 Hz, 1H), 4.44–3.99 (m, 4H), 2.85–2.50 (m, 2H), 1.68 (s, 2H), 1.37 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.8, 155.8, 137.1, 130.1, 130.1, 128.7, 128.1, 127.6, 115.2, 83.2, 83.1, 79.5, 70.2, 59.0, 56.8, 35.6, 28.4 ppm.

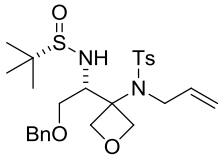
HRMS (ESI+): *m*/*z* calcd. for $C_{23}H_{31}N_2O_4$ $[M+H]^+$ 399.2278, found 399.2285.

IR (neat): ν [cm^{-1}] = 3381, 2928, 2866, 1683, 1612, 1511, 1468, 1455, 1444, 1387, 1366, 1336, 1240, 1174, 1024, 975, 939, 920, 861, 832, 811, 775, 738, 724, 695, 640, 615, 557, 516.

[α]^{24}D = –21.7 (c = 0.86, $CHCl_3$).

m.p. = 170 °C.

N-allyl-*N*-(3-((*R*)-2-(benzyloxy)-1-((*S*)-1,1-dimethylethylsulfinamido)ethyl)-oxetan-3-yl)-4-methylbenzenesulfonamide (**175**)[280]



To a solution of ((benzyloxy)methyl)tributylstannane (1.76 g, 4.29 mmol, 1.80 eq) in THF (8.00 mL) was added *n*-BuLi (1.6 M in hexanes, 2.53 mL, 4.05 mmol, 1.70 eq) dropwise at -78 °C. The yellowish mixture was stirred at -78 °C for 30 min, before transferred dropwise to a solution of **139** (950 mg, 2.38 mmol, 1.00 eq) in THF (8.00 mL) at -78 °C. After complete addition, the reaction was stirred at -78 °C for 1 h and then slowly warmed to -20 °C over the course of 3 h. Saturated aqueous NH_4Cl-solution was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 x 25 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by FC on silica gel (hexane:EA = 1:1 to 1:2) yielded **175** (510 mg, 0.979 mmol, 41%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81–7.71 (m, 2H), 7.36–7.28 (m, 5H), 7.28–7.24 (m, 2H), 5.65–5.47 (m, 1H), 5.06–4.87 (m, 5H), 4.81 (d, *J* = 7.3 Hz, 1H), 4.73 (d, *J* = 6.9 Hz, 1H), 4.51 (d, *J* = 11.7 Hz, 1H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.31–4.20 (m, 1H), 3.91–3.77 (m, 2H), 3.76–3.59 (m, 2H), 2.44 (s, 3H), 1.25 (s, 9H) ppm.

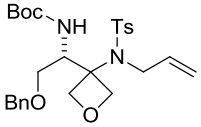
^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.2, 137.6, 137.5, 134.6, 129.9, 128.6, 128.0, 128.0, 127.8, 117.89, 77.9, 77.2, 73.6, 71.3, 66.0, 59.0, 56.3, 49.4, 22.9, 21.7 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{26}H_{37}N_2O_5S_2$ $[M+H]^+$ 521.2138, found 521.2131.

IR (neat): ν [cm^{-1}] = 3280, 2960, 2895, 2048, 1989, 1598, 1454, 1329, 1149, 1068, 988, 920, 878, 814, 699, 664.

[α]^{25}D = +49.3 (c = 0.50, $CHCl_3$).

(*R*)-tert-butyl (1-(3-(*N*-allyl-4-methylphenylsulfonamido)oxetan-3-yl)-2-(benzyloxy)ethyl)carbamate (**176**)[280]



HCl (4 M in dioxane, 1.22 mL, 4.86 mmol, 5.00 eq) was added to a solution of **175** (506 mg, 0.972 mmol, 1.00 eq) in CH_2Cl_2 (4.90 mL) and MeOH (4.90 mL) at 0 °C and the mixture was stirred at this temperature for 1 h. Saturated aqueous $NaHCO_3$-solution was added and the mixture was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure.

The obtained oil was dissolved in CH_2Cl_2 (3.70 mL) and a solution of di-*tert*-butyl dicarbonate (318 mg, 1.46 mmol, 1.50 eq) in CH_2Cl_2 (1.20 mL) was added. The mixture was stirred at room temperature for 90 min. After evaporation of the solvent, the residue was purified by FC on silica gel (hexane:EA = 3:1) to afford **176** (446 mg, 0.863 mmol, 89%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 8.2 Hz, 2H), 7.37–7.27 (m, 5H), 7.26–7.21 (m, 2H), 5.72–5.50 (m, 2H), 5.12–4.87 (m, 4H), 4.72 (d, *J* = 7.2 Hz, 1H), 4.67 (d, *J* = 7.6 Hz, 1H), 4.60–4.36 (m, 3H), 3.84 (dd, *J* = 17.4, 5.4 Hz, 1H), 3.75–3.45 (m, 3H), 2.43 (s, 3H), 1.48 (s, 9H) ppm.

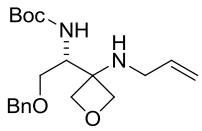
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.1, 143.8, 138.0, 137.6, 134.8, 129.8, 128.6, 128.0, 127.9, 127.8, 117.7, 80.0, 79.2, 75.4, 73.5, 70.0, 66.4, 53.0, 49.0, 28.5, 21.7 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{27}H_{36}N_2O_6SNa$ $[M+Na]^+$ 539.2186, found 539.2172.

IR (neat): ν [cm^{-1}] = 2978, 2051, 1705, 1497, 1326, 1247, 1154, 1089, 990, 921, 814, 740, 699, 660.

[α]^{23}D = +20.2 (c = 0.69, $CHCl_3$).

(*R*)-tert-butyl (1-(3-(allylamino)oxetan-3-yl)-2-(benzyloxy)ethyl)carbamate (**177**)[280]



Magnesium turnings (209 mg, 8.61 mmol, 10.0 eq) were added to a solution of **176** (445 mg, 0.861 mmol, 1.00 eq) in MeOH (8.50 mL) and the mixture was vigorously stirred at room temperature for 2.5 h. Saturated aqueous NH_4Cl-solution was added and the mixture was extracted with CH_2Cl_2 (4 x 15 mL). The combined organic layers were dried over $MgSO_4$ and after removal of the volatiles, **177** (304 mg, 0.839 mmol, 97%) was obtained as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40–7.28 (m, 3H), 7.28–7.23 (m, 2H), 6.00–5.84 (m, 1H), 5.32 (d, *J* = 9.1 Hz, 1H), 5.24–5.14 (m, 1H), 5.12–5.02 (m, 1H), 4.65 (d, *J* = 6.9 Hz, 1H), 4.59 (d, *J* = 7.2 Hz, 1H), 4.56–4.49 (m, 2H), 4.47 (s, 2H), 4.27–4.06 (m, 1H), 3.73 (dd, *J* = 9.9, 3.3 Hz, 1H), 3.55 (dd, *J* = 9.8, 4.9 Hz, 1H), 3.48–3.36 (m, 2H), 1.85 (br, 1H), 1.45 (s, 9H) ppm.

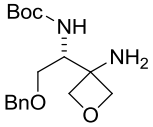
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.0, 137.8, 137.0, 128.6, 128.0, 127.6, 115.7, 79.8, 78.6, 77.4, 73.6, 69.1, 62.9, 53.5, 45.5, 28.5 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{20}H_{31}N_2O_4$ $[M+H]^+$ 363.2278, found 363.2280.

IR (neat): ν [cm^{-1}] = 3333, 2976, 2876, 1707, 1494, 1454, 1364, 1246, 1166, 1103, 980, 917, 735, 698.

$[\alpha]^{25}_D$ = +39.4 (c = 0.72, $CHCl_3$).

(*R*)-tert-butyl (1-(3-aminooxetan-3-yl)-2-(benzyloxy)ethyl)carbamate (**174**)[280]



$Pd(Ph_3P)_4$ (49.4 mg, 0.043 mmol, 5.00 mol-%) was added to a solution of **177** (310 mg, 0.855 mmol, 1.00 eq) and 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (401 mg, 2.57 mmol, 3.00 eq) in CH_2Cl_2 (8.50 mL) and the mixture was degassed by passing a stream on N_2 through the

solution. Then, the reaction was heated to 35 °C for 13 h. After cooling to room temperature, the mixture was poured into saturated aqueous $NaHCO_3$-solution and extracted with CH_2Cl_2 (4 x 25 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The residue was purified by FC on deactivated silica gel (CH_2Cl_2:MeOH = 30:1) and **174** (251 mg, 0.777 mmol, 91%) was obtained as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41–7.24 (m, 5H), 5.28 (d, *J* = 9.7 Hz, 1H), 4.69 (d, *J* = 6.7 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.49 (s, 2H), 4.32 (d, *J* = 6.7 Hz, 1H), 4.27 (d, *J* = 6.8 Hz, 1H), 4.24–4.13 (m, 1H), 3.72 (dd, *J* = 9.9, 3.8 Hz, 1H), 3.52 (dd, *J* = 9.9, 5.6 Hz, 1H), 1.82 (br, 2H), 1.45 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.88, 137.76, 128.57, 127.94, 127.60, 83.93, 82.74, 79.60, 73.54, 69.29, 58.70, 53.86, 28.44 ppm.

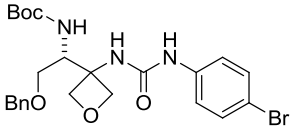
HRMS (ESI+): *m*/*z* calcd. for $C_{17}H_{27}N_2O_4$ $[M+H]^+$ 323.1965, found 323.1968.

IR (neat): ν [cm^{-1}] = 3263, 2979, 2885, 2360, 2341, 1699, 1548, 1394, 1364, 1276, 1166, 1107, 1024, 958, 817, 743, 699.

$[\alpha]^{25}_D$ = +33.6 (c = 0.73, $CHCl_3$).

m.p. = 104-105 °C (CH_2Cl_2).

(*R*)-*tert*-butyl (2-(benzyloxy)-1-(3-(3-(4-bromophenyl)ureido)oxetan-3-yl)ethyl)carbamate (**178**)[280]



To a solution of **174** (53.4 mg, 0.166 mmol, 1.00 eq) in CH_2Cl_2 (1.60 mL) was added 1-bromo-4-isocyanatobenzene (36.1 mg, 0.182 mmol, 1.10 eq) at 0 °C and the mixture was stirred at this temperature for 4 h. The mixture was directly submitted to FC on silica gel (hexane:EA = 2:3) to afford **178** (66.5 mg, 0.128 mmol, 77%) as a colorless

solid. Crystallization from CH_2Cl_2:hexane gave crystals suitable for x-ray crystal structure analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45–7.31 (m, 5H), 7.30–7.23 (m, 2H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.22 (br, 1H), 6.05 (d, *J* = 8.2 Hz, 1H), 5.14 (br, 1H), 4.74 (s, 2H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.58–4.40 (m, 3H), 4.33 (d, *J* = 11.9 Hz, 1H), 3.74 (dd, *J* = 9.4, 4.5 Hz, 1H), 3.53–3.33 (m, 1H), 1.44 (s, 9H) ppm.

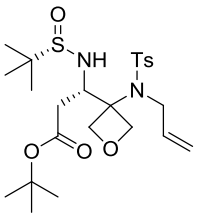
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.23, 154.84, 137.99, 137.33, 132.24, 128.89, 128.40, 128.25, 121.84, 116.56, 80.68, 79.96, 78.02, 73.37, 69.11, 59.02, 54.69, 28.52 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{24}H_{31}BrN_3O_5$ $[M+H]^+$ 520.1442, found 520.1438.

IR (neat): ν [cm^{-1}] = 3382, 3331, 3256, 2982, 2888, 2861, 1689, 1659, 1599, 1543, 1516, 1487, 1395, 1332, 1306, 1271, 1230, 1162, 1096, 1075, 821, 751, 654.

$[\alpha]^{24}_D$ = +25.2 (c = 0.59, $CHCl_3$).
m.p. = 192-193 °C (CH_2Cl_2:hex).

Tert-butyl 3-(3-(*N*-allyl-4-methylphenylsulfonamido)oxetan-3-yl)-3-((*S*)-1,1-dimethylethyl-sulfinamido)propanoate (**180**)



To a solution of diisopropylamine (0.97 mL, 6.8 mmol, 2.7 eq) in THF (13 mL) at -78 °C was added *n*-BuLi (3.9 mL, 6.3 mmol, 2.5 eq). The mixture was stirred for 30 min before adding *tert*-butyl acetate (0.92 mL, 6.8 mmol, 2.7 eq). After stirring for 30 min **139** (1.0 g, 2.5 mmol, 1.0 eq) in THF (13 mL) was added. The light yellow solution was stirred for additional 10 min before quenching with saturated aqueous NH_4Cl solution (25 mL). The mixture was extracted with EA (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product (d.r. 10:1) was purified by FC on silica (hex:EA:MeOH = 1:1:1%) to yield **180** (0.85 g, 1.6 mmol, 66%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 8.4 Hz, 2H), 7.45 – 7.30 (m, 2H), 5.87 – 5.62 (m, 1H), 5.28 – 5.08 (m, 2H), 5.00 – 4.84 (m, 2H), 4.72 – 4.56 (m, 3H), 4.42 (ddd, *J* = 10.0, 7.4, 2.8 Hz, 1H), 3.80 (d, *J* = 6.2 Hz, 1H), 2.85 (dd, *J* = 16.1, 2.9 Hz, 1H), 2.56 (dd, *J* = 16.1, 9.9 Hz, 1H), 2.45 (s, 3H), 1.47 (s, 9H), 1.22 (s, 9H).

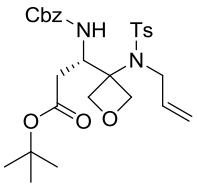
^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.5, 144.2, 137.8, 134.4, 130.1, 127.6, 119.5, 81.3, 77.2, 76.6, 65.8, 58.1, 56.6, 50.2, 39.1, 28.3, 23.0, 21.7 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{24}H_{39}N_2O_6S_2$ $[M+H]^+$ 515.2244, found, 515.2250.

IR (neat): ν [cm^{-1}] = 2978, 2926, 1730, 1393, 1342, 1367, 1154, 1067, 663, 650.

[α]^{26}D +36.9 (*c* 0.55, $CHCl_3$)

(*S*)-*Tert*-butyl 3-(3-(*N*-allyl-4-methylphenylsulfonamido)oxetan-3-yl)-3-(((benzyloxy)carbonyl)amino)-propanoate (**181**)



To a solution of **180** (0.66 g, 1.3 mmol, 1.0 eq) in CH_2Cl_2/MeOH (1/1, 13 mL) at 0 °C was added HCl (4 M in dioxane, 1.6 mL, 6.4 mmol, 5.0 eq). The mixture was stirred for 2 h at this temperature. Saturated aqueous $NaHCO_3$ solution (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was redissolved in pyridine (6.4 mL) and Cbz-Cl (0.28 ml, 1.9 mmol, 1.5 eq) was added. The mixture was stirred at room temperature for 22 h. concentrated. The crude mixture was concentrated and purified by FC on silica (hex:EA=2:1) to yield **181** (0.50 g, 0.91 mmol, 71% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 8.3 Hz, 2H), 7.44 – 7.28 (m, 7H), 5.79 – 5.62 (m, 1H), 5.52 (d, *J* = 9.7 Hz, 1H), 5.29 – 5.12 (m, 2H), 5.08 (d, *J* = 12.1 Hz, 2H), 4.98 – 4.86 (m, 2H), 4.81 – 4.68 (m, 1H), 4.50 (dd, *J* = 40.6, 7.3 Hz, 2H), 3.74 (ddd, *J* = 57.8, 16.5, 6.3 Hz, 2H), 2.90 (dd, *J* = 15.6, 3.8 Hz, 1H), 2.61 (dd, *J* = 15.6, 9.6 Hz, 1H), 2.44 (s, 3H), 1.41 (s, 3H).

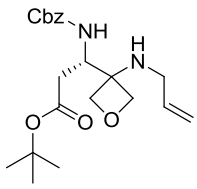
^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.5, 156.6, 143.9, 138.3, 136.6, 134.3, 130.0, 128.6, 128.2, 127.4, 119.1, 81.5, 77.4, 77.1, 76.1, 67.1, 66.2, 51.9, 49.7, 37.0, 28.1, 21.7 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{28}H_{36}N_2NaO_7S$ $[M+Na]^+$ 567.2135, found, 567.2132.

IR (neat): ν [cm^{-1}] = 3338, 2978, 1725, 1598, 1535, 1333, 1304, 1245, 1155, 1090, 597, 550.

[α]^{26}D +1.76 (*c* 0.80, $CHCl_3$)

(*S*)-*Tert*-butyl 3-(3-(allylamino)oxetan-3-yl)-3-(((benzyloxy)carbonyl)amino)propanoate (**182**)



To a solution of **181** (440 mg, 0.81 mmol, 1.0 eq) in MeOH (8.1 mL) were added magnesium turnings (200 mg, 8.1 mmol, 10 eq). The mixture was stirred for 2 h at room temperature. TLC still indicated the presence of starting material. Magnesium turnings (98 mg, 4.0 mmol, 5.0 eq) were added and the mixture was stirred for 4.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (40 mL). The mixture was extracted with CH_2Cl_2 (4 x 20 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The crude material was purified by FC on silica (hex:EA=2:1) to yield **182** (250 mg, 0.64 mmol, 79%) as a colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.28 (m, 5H), 5.91 (ddt, *J* = 17.0, 10.2, 5.7 Hz, 1H), 5.51 (br s, 1H), 5.24 (d, *J* = 18.1 Hz, 1H), 5.16 – 5.07 (m, 3H), 4.61 – 4.43 (m, 5H), 3.41 (d, *J* = 5.6 Hz, 2H), 2.52 (dd, *J* = 14.9, 4.9 Hz, 1H), 2.35 (dd, *J* = 15.0, 7.8 Hz, 1H), 1.41 (s, 9H).

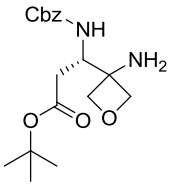
^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.9, 156.4, 136.7, 136.4, 128.7, 128.3, 128.3, 116.1, 81.5, 77.8, 77.6, 77.4, 67.2, 63.3, 52.4, 45.8, 36.4, 28.1 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{21}H_{31}N_2O_5$ $[M+H]^+$ 391.2227, found, 391.2220.

IR (neat): ν [cm^{-1}] =3321, 2977, 2879, 1721, 1537, 1498, 1456, 1367, 1244, 1155, 1043, 1027, 918, 844, 739, 697.

$[\alpha]^{26}_{D}$ +1.05 (*c* 0.66, $CHCl_3$)

(*S*)-*Tert*-butyl 3-(3-aminooxetan-3-yl)-3-(((benzyloxy)carbonyl)amino)propanoate (**179**)



To a solution of **182** (220 mg, 0.57 mmol, 1.0 eq) and 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (270 mg, 1.70 mmol, 3.0 eq) in CH_2Cl_2 (5.7 mL) was added $Pd(Ph_3P)_4$ (33 mg, 0.028 mmol, 5.0 mol-%) and the mixture was degassed by passing a stream on N_2 through the solution. Then, the reaction was heated to 35 °C for 7 h. After cooling to room temperature, the mixture was poured into saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The residue was purified by FC on silica (DCM:MeOH=15:1) to yield **179** (140 mg, 0.41 mmol, 71%) as an off-white powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.28 (m, 5H), 5.45 (d, *J* = 8.6 Hz, 1H), 5.16 – 5.03 (m, 2H), 4.62 (dd, *J* = 29.4, 6.7 Hz, 2H), 4.46 (dt, *J* = 9.3, 6.7 Hz, 1H), 4.28 (dd, *J* = 14.3, 6.8 Hz, 2H), 2.51 – 2.29 (m, 2H), 1.69 (s, 2H), 1.41 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.6, 156.3, 136.4, 128.7, 128.3, 128.3, 82.7, 82.5, 81.6, 67.1, 59.2, 53.4, 36.6, 28.1 ppm.

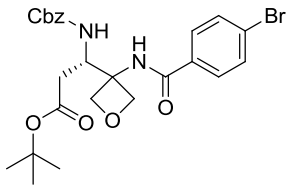
HRMS (ESI+): *m*/*z* calcd. for $C_{18}H_{26}N_2NaO_5$ $[M+Na]^+$ 373.1734, found, 373.1729.

IR (neat): ν [cm^{-1}] = 3312, 2925, 2855, 1715, 1534, 1456, 1482, 1456, 1368, 1337, 1245, 1156, 1049, 1028, 976, 839, 740, 698.

$[\alpha]^{25}_{D}$ -5.44 (*c* 0.72, $CHCl_3$).

m.p. 91 °C.

(*S*)-*Tert*-butyl 3-(((benzyloxy)carbonyl)amino)-3-(3-(4-bromobenzamido)oxetan-3-yl)propanoate (**183**)



To a solution of **179** (10 mg, 0.029 mmol, 1.0 eq) and triethylamine (6.0 µl, 0.043 mmol, 1.5 eq) in CH_2Cl_2 (0.29 mL) was added 4-bromobenzoyl chloride (6.3 mg, 0.029 mmol, 1.0 eq). The mixture was stirred for 1 h. The solvent was removed under reduced pressure and the crude material was purified by FC on silica (hex:EA=1:1) to yield **183** (13 mg, 0.024 mmol, 85%) as an off-white crystalline solid. Recrystallization from methanol provided single crystals suitable for X-Ray structure analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 – 7.55 (m, 4H), 7.41 – 7.31 (m, 5H), 6.42 (d, *J* = 8.1 Hz, 1H), 5.13 (s, 1H), 4.94 (d, *J* = 7.2 Hz, 1H), 4.84 – 4.65 (m, 3H), 4.58 (d, *J* = 7.2 Hz, 1H), 2.80 (dd, *J* = 14.6, 6.2 Hz, 1H), 2.49 (dd, *J* = 14.5, 8.1 Hz, 1H), 1.45 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.2, 167.1, 156.5, 136.4, 132.3, 132.2, 128.9, 128.7, 128.3, 128.3, 127.2, 82.2, 79.6, 77.7, 67.1, 60.1, 54.7, 37.4, 28.1 ppm.

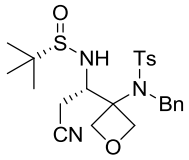
HRMS (ESI+): *m*/*z* calcd. for $C_{25}H_{30}BrN_2O_6$ $[M+H]^+$ 533.1282, found, 533.1290.

IR (neat): ν [cm^{-1}] = 3312, 2977, 2975, 1726, 1642, 1590, 1531, 1482, 1456, 1393, 1367, 1256, 1157, 1071, 1044, 1012, 976, 909, 871, 843, 756, 698, 464.

[α]^{26}D -42.0 (*c* 0.27, $CHCl_3$).

m.p. 201 °C.

N-benzyl-*N*-(3-(2-cyano-1-((S)-1,1-dimethylethylsulfinamido)ethyl)oxetan-3-yl)-4-methylbenzenesulfonamide (**185**)



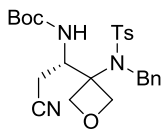
To a solution of MeCN (0.093 ml, 1.78 mmol, 4.00 eq) in THF (2.23 mL) at -78 °C was added *n*-BuLi (1.6 M in hexanes, 0.836 mL, 1.34 mmol, 3.00 eq). The mixture was stirred for 30 min before adding **118** (0.200 g, 0.446 mmol, 1.00 eq) in THF (2.23 mL). The light yellow solution was stirred for 15 min before quenching with aq. sat. NH_4Cl solution (20 mL). The mixture was extracted with EA (3 x 25 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC on silica (DCM:hex:acetone = 3:1:0.3→3:1:0.5) to yield **185** (120 mg, 0.245 mmol, 55%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 7.9 Hz, 2H), 7.35 – 7.21 (m, 7H), 5.16 – 4.79 (m, 3H), 4.77 – 4.70 (m, 1H), 4.66 – 4.57 (m, 2H), 4.24 – 4.01 (m, 1H), 2.83 – 2.62 (m, 2H), 2.43 (s, 3H), 1.26 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.5, 137.7, 135.2, 130.2, 129.3, 128.9, 128.5, 127.3, 117.7, 76.8, 75.2, 64.6, 56.9, 56.0, 50.9, 23.0, 22.0, 21.7 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{24}H_{31}N_3Na_1O_4S_2$ $[M+Na]^+$ 512.1648, found, 512.1653.

Tert-butyl (1-(3-(*N*-benzyl-4-methylphenylsulfonamido)oxetan-3-yl)-2-cyanoethyl)carbamate (**186**)



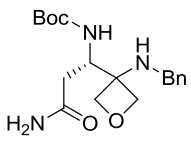
To a solution of **185** in CH_2Cl_2 (4.78 mL)/ MeOH (4.78 mL) at 0 °C was added HCl (4 M in dioxane, 1.20 mL, 4.78 mmol, 5.00 eq). The mixture was stirred for 1 h. Sat. aq. NaHCO3 solution (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was redissolved in CH_2Cl_2 (0.3 mL) and Boc_2O (333 µl, 1.43 mmol, 1.50 eq) was added. The mixture was stirred at 50 °C for 2 d. The crude mixture was purified by FC on silica (hex:EA = 2:1) to yield **186** (401 mg, 0.826 mmol, 86%) as a colorless foam

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (d, *J* = 8.3 Hz, 2H), 7.24 – 7.18 (m, 5H), 7.15 – 7.06 (m, 2H), 5.43 (d, *J* = 8.9 Hz, 1H), 5.06 – 4.71 (m, 2H), 4.64 – 4.56 (m, 1H), 4.53 – 4.22 (m, 4H), 3.07 – 2.80 (m, 2H), 2.40 (s, 3H), 1.49 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.6, 144.2, 137.6, 135.3, 129.9, 128.9, 128.3, 128.2, 127.5, 117.7, 80.9, 77.2, 75.9, 65.8, 50.5, 28.4, 21.7, 19.9 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{25}H_{31}N_3Na_1O_5S_1$ $[M+Na]^+$ 508.1877, found, 508.1875.

tert-butyl (3-amino-1-(3-(benzylamino)oxetan-3-yl)-3-oxopropyl)carbamate (**188**)



To a suspension of **186** (415 mg, 0.855 mmol, 1.00 eq) in MeOH (12 mL)/1 M NaOH (2.40 mL) at 50 °C was added drop wise H_2O_2 (1.75 mL, 17.1 mmol, 20.0 eq). The mixture was stirred for 2 h. After cooling to r.t.. the reaction was quenched by the careful addition of sat. aq. sodium thiosulfate solution. The aq. mixture was extracted with EtOAc (6 x 60 mL). The combined organic layers were dried over Na_2SO_4 and concentrated.

To a solution of the crude material in MeOH (15.1 mL) at reflux were added magnesium turnings (208 mg, 8.54 mmol, 10.0 eq). The mixture was stirred for 1 h, before another portion of magnesium turnings (208 mg, 8.54 mmol, 10.0 eq) were added. The mixture was stirred for 1 h. Sat. aq. NH_4Cl solution (40 mL) was added and the mixture was extracted with EA (4 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC on silica (CH_2Cl_2:MeOH = 15:1) to yield **188** (149 mg, 0.426 mmol, 50%) as a colorless solid.

^{1}H NMR (400 MHz, MeOH) δ = 7.37 – 7.27 (m, 5H), 6.27 (s, 1H), 5.62 (d, *J* = 7.7 Hz, 1H), 5.39 (s, 1H), 4.69 (d, *J* = 7.0 Hz, 1H), 4.61 – 4.51 (m, 3H), 4.41 – 4.30 (m, 1H), 3.93 (s, 1H), 2.51 (d, *J* = 5.2 Hz, 2H), 1.46 (s, 9H) ppm.

^{13}C NMR (101 MHz, MeOH) δ = 173.4, 156.6, 140.1, 128.8, 128.1, 127.5, 80.4, 78.1, 77.7, 63.7, 51.6, 47.4, 36.9, 28.5 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{18}H_{27}N_3Na_1O_4$ $[M+Na]^+$ 372.1894, found, 372.1892.

Tert-butyl (3-amino-1-(3-aminooxetan-3-yl)-3-oxopropyl)carbamate (**184**)

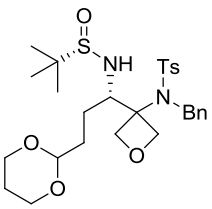
To a mixture of **188** (126 mg, 0.361 mmol, 1.00 eq) and Pd-C (10 wt-% Pd, 38.4 mg, 0.036 mmol, 10.0 mol-%) was added under N_2 MeOH (3.61 mL). The mixture was stirred with a H_2 balloon for 3.5 h. Pd-C (10 wt-% Pd, 19.2 mg, 0.018 mmol, 5.00 mol-%) was added and the mixture was stirred with a H_2 balloon for 3.5 h. The mixture was filtered through a syringe filter (PTFE) with MeOH (5 mL). The solvent was removed under reduced pressure to yield **184** (92 mg, 0.355 mmol, 98% yield) as a colorless solid.

^{1}H NMR (400 MHz, MeOH) δ = 4.61 (d, *J* = 6.3 Hz, 1H), 4.57 (d, *J* = 6.5 Hz, 1H), 4.42 (dd, *J* = 9.4, 4.7 Hz, 1H), 4.39 – 4.34 (m, 2H), 2.41 – 2.25 (m, 2H), 1.43 (s, 9H) ppm.

^{13}C NMR (101 MHz, MeOH) δ = 176.0, 158.2, 82.8, 82.6, 80.4, 60.4, 54.5, 36.9, 28.7 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{11}H_{21}N_3Na_1O_4$ $[M+Na]^+$ 282.1424, found, 282.1424.

N-Benzyl-N-(3-((S)-1-((S)-1,1-dimethylethylsulfinamido)-3-(1,3-dioxan-2-yl)propyl)oxetan-3-yl)-4-methylbenzenesulfonamide (**191**)[280]



Magnesium turnings (780 mg, 32.1 mmol, 9.00 eq) were stirred with a crystal of I_2 for 15 min and were then layered with a minimum amount of THF. 2-(2-bromoethyl)-1,3-dioxane (1.46 ml, 10.7 mmol, 3.00 eq) and THF (20.0 mL) were added alternately to keep the temperature of the exothermic reaction between 35-45 °C.

After complete addition, the mixture was allowed to stir for 2 h at ambient temperature.

The freshly prepared GRIGNARD solution was added dropwise to a solution of **118** (1.60 g, 3.57 mmol, 1.00 eq) in THF (16.0 mL) at –78 °C over the course of 40 min (ca. 0.5 mL/min). The mixture was slowly warmed to ambient temperature together with the cooling bath overnight (12 h). After careful addition of saturated aqueous $NaHCO_3$-solution, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 30 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified by FC on silica gel (100% EA) to afford **191** (1.78 g, 3.15 mmol, 88%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (d, J = 8.2 Hz, 2H), 7.25–7.14 (m, 7H), 5.01 (br, 1H), 4.94–4.76 (m, 1H), 4.73–4.58 (m, 2H), 4.57–4.40 (m, 2H), 4.32 (d, J = 16.2 Hz, 1H), 4.17–4.03 (m, 2H), 3.84–3.71 (m, 3H), 3.69 (br, 1H), 2.38 (s, 3H), 2.15–1.99 (m, 1H), 1.92–1.72 (m, 2H), 1.70–1.53 (m, 2H), 1.51–1.37 (m, 1H), 1.37–1.30 (m, 1H), 1.24 (s, 9H) ppm.

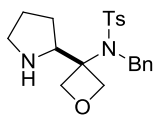
^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.8, 138.2, 136.0, 129.8, 128.7, 128.2, 127.9, 127.5, 102.1, 77.9, 77.0, 67.0, 66.4, 60.7, 56.7, 51.5, 32.3, 26.5, 26.0, 23.2, 21.6 ppm.

HRMS (ESI+): m/z calcd. for $C_{28}H_{41}N_2O_6S_2$ $[M+H]^+$ 565.2401, found 565.2385.

IR (neat): ν [cm^{-1}] = 3277, 2961, 2862, 1599, 1456, 1339, 1142, 1091, 1064, 1002, 918, 814.

$[\alpha]^{26}_D$ = +42.0 (c = 1.00, $CHCl_3$).

(*S*)-*N*-Benzyl-4-methyl-*N*-(3-(pyrrolidin-2-yl)oxetan-3-yl)benzenesulfonamide (**192**)[280]



A solution of **191** (1.73 g, 3.07 mmol, 1.00 eq) in a mixture of TFA (29.2 mL) and H_2O (1.53 mL) was stirred at room temperature for 20 min during which time the reaction turned pale brown. Then, triethylsilane (4.90 mL, 30.7 mmol, 10.0 eq) was added and stirring was continued for 24 h. The TFA was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 and treated with saturated aqueous $NaHCO_3$-solution until the mixture was basic. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure, and the residue was purified by FC on silica gel (CH_2Cl_2:MeOH:NEt_3 = 400:20:1) to afford **192** (955 mg, 2.47 mmol, 81%) as a beige solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60–7.54 (m, 2H), 7.18–7.06 (m, 7H), 5.02 (d, *J* = 7.2 Hz, 1H), 4.75 (d, *J* = 7.1 Hz, 1H), 4.58 (d, *J* = 7.2 Hz, 1H), 4.51 (d, *J* = 7.1 Hz, 1H), 4.44 (s, 2H), 4.07 (dd, *J* = 8.1, 8.1 Hz, 1H), 3.08–2.96 (m, 2H), 2.33 (s, 3H), 2.15–1.97 (m, 2H), 1.96–1.86 (m, 1H), 1.84–1.74 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.7, 137.5, 136.9, 129.5, 128.4, 127.8, 127.2, 127.1, 78.7, 76.0, 66.3, 62.8, 50.7, 47.3, 27.1, 25.9, 21.5 ppm.

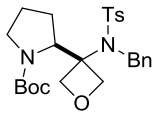
HRMS (ESI+): *m*/*z* calcd. for $C_{21}H_{27}N_2O_3S$ $[M+H]^+$ 387.1737, found 387.1735.

IR (neat): ν [cm^{-1}] = 2951, 2883, 1675, 1496, 1460, 1416, 1379, 1316, 1304, 1263, 1234, 1206, 1148, 1120, 1089, 1042, 1021, 999, 979, 950, 917, 885, 832, 808, 744, 702, 669, 657, 599, 656.

$[\alpha]^{25}_D$ = +22.2 (c = 0.87, $CHCl_3$).

m.p. = 119 °C

(*S*)-tert-Butyl 2-(3-(*N*-benzyl-4-methylphenylsulfonamido)oxetan-3-yl)pyrrolidine-1-carboxylate (**193**)[280]



To a solution of **192** (880 mg, 2.28 mmol, 1.00 eq) in CH_2Cl_2 (15 mL) was added a solution of di-*tert*-butyl dicarbonate (745 mg, 3.42 mmol, 1.50 eq) in CH_2Cl_2 (8.0 mL) and the mixture was stirred at room temperature for 14 h. The solvent was removed under reduced pressure and the residue was purified by FC on silica gel (hex:EA = 2:1) to afford **193** (989 mg, 2.03 mmol, 89%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 (d, J = 8.3 Hz, 2H), 7.20–7.05 (m, 7H), 5.11–4.56 (m, 5H), 4.56–4.42 (m, 1H), 4.42–4.25 (m, 1H), 3.89–3.53 (m, 1H), 3.53–3.34 (m, 1H), 2.49–2.20 (m, 4H), 2.10–1.79 (m, 3H), 1.48 (s, 9H) ppm.

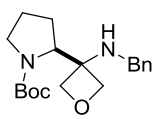
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.5, 143.3, 138.6, 136.5, 129.4, 128.3, 128.1, 127.5, 127.4, 80.1, 78.3, 77.4, 69.6, 60.9, 50.6, 48.3, 28.6, 28.0, 24.7, 21.5 ppm.

HRMS (ESI+): m/z calcd. for $C_{26}H_{35}N_2O_5S$ $[M+H]^+$ 487.2261, found 487.2267.

IR (neat): ν [cm^{-1}] = 2974, 1687, 1599, 1496, 1478, 1455, 1365, 1337, 1283, 1255, 1154, 1118, 1090, 1007, 921, 868, 813, 751, 698, 665, 586.

$[\alpha]^{25}_D$ = –29.8 (c = 0.82, $CHCl_3$).

(*S*)-tert-butyl 2-(3-(benzylamino)oxetan-3-yl)pyrrolidine-1-carboxylate (**194**)[280]



Magnesium turnings (522 mg, 24.3 mmol, 11.3 eq) were added to a solution of **193** (1.05 g, 2.15 mmol, 1.00 eq) in MeOH (21.5 mL) and the mixture was stirred in a room temperature water bath for 2.5 h. The reaction was quenched by addition of saturated aqueous NH_4Cl-solution and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over

$MgSO_4$ and after evaporation of the solvent **194** (698 mg, 2.10 mmol, 98%) was obtained as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (d, *J* = 7.4 Hz, 2H), 7.33 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.25 (t, *J* = 7.1 Hz, 1H), 4.91 (d, *J* = 7.1 Hz, 1H), 4.65 (d, *J* = 7.1 Hz, 1H), 4.59 (d, *J* = 7.1 Hz, 1H), 4.52 (d, *J* = 7.1 Hz, 1H), 4.24 (dd, *J* = 8.1, 4.7 Hz, 1H), 4.07 (s, 2H), 3.63 (br, 1H), 3.34–3.23 (m, 1H), 2.09–1.85 (m, 2H), 1.84–1.70 (m, 2H), 1.67 (s, 1H), 1.46 (s, 9H) ppm.

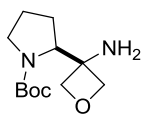
^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.7, 141.3, 128.6, 127.9, 127.0, 79.9, 77.8, 64.9, 62.1, 48.7, 47.0, 28.6, 27.5, 24.4 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{19}H_{29}N_2O_3$ $[M+H]^+$ 333.2173, found 333.2168.

IR (neat): ν [cm^{-1}] = 2972, 2875, 1689, 1478, 1454, 1387, 1364, 1281, 1251, 1160, 1100, 1028, 980, 955, 914, 846, 773, 734, 699.

$[\alpha]^{25}_D$ = –76.5 (c = 0.73, $CHCl_3$).

(*S*)-tert-butyl 2-(3-aminooxetan-3-yl)pyrrolidine-1-carboxylate (**189**)[280]



Pd-C (10% Pd, 112 mg, 0.11 mmol, 5.00 mol-%) was added to a solution of **194** (698 mg, 2.10 mmol, 1.00 eq) in MeOH (21.0 mL) and the mixture was stirred under an atmosphere of H_2 (balloon) for 24 h. Then, the mixture was filtered over Celite®, the filter cake was washed with EA, and the filtrate was concentrated to dryness to afford **189** (504 mg, 2.08 mmol, 99%) as a colorless wax.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.00 (d, *J* = 6.7 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.31–4.19 (m, 2H), 4.14 (dd, *J* = 8.1, 5.8 Hz, 1H), 3.61 (br, 1H), 3.33–3.21 (m, 1H), 2.10–1.97 (m, 1H), 1.97–1.84 (m, 1H), 1.80 (br, 2H), 1.77–1.59 (m, 2H), 1.45 (s, 9H) ppm.

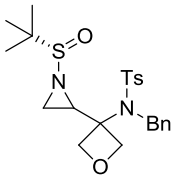
^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.5, 86.4, 81.0, 77.4, 62.5, 60.4, 48.7, 28.6, 27.6, 24.2 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{12}H_{23}N_2O_3$ $[M+H]^+$ 243.1703, found 243.1699.

IR (neat): ν [cm^{-1}] = 2972, 2873, 1687, 1479, 1456, 1389, 1365, 1283, 1249, 1161, 1104, 1045, 976, 949, 915, 844, 773, 590, 548, 462.

$[\alpha]^{25}_D$ = –71.2 (c = 0.72, $CHCl_3$).

N-benzyl-*N*-(3-(1-((*S*)-tert-butylsulfinyl)aziridin-2-yl)oxetan-3-yl)-4-methylbenzenesulfonamide (**195**)



To a suspension of trimethylsulfoxoniumiodide (0.245 g, 1.12 mmol, 2.50 eq) in THF (4.46 mL) was added KO*t*Bu (0.125 g, 1.12 mmol, 2.50 eq) at r.t. The mixture was heated to reflux for 2 h. After cooling to 0 °C **118** (0.200 g, 0.446 mmol, 1.00 eq) was added. The mixture was stirred for 2 h, quenched with water and extracted with CH_2Cl_2 (3 x 20 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC on silica (hex:EA = 1:1) to give **195** (0.173 g, 0.374 mmol, 84%) as a mixture of diastereomers. Samples of the pure diastereomers could be obtained by repeated FC on silica (CH_2Cl_2:acetone = 8:1).

Less polar diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (d, *J* = 8.2 Hz, 2H), 7.23 – 7.07 (m, 7H), 4.88 (d, *J* = 7.0 Hz, 1H), 4.69 (d, *J* = 7.0 Hz, 1H), 4.47 – 4.29 (m, 4H), 3.12 (dd, *J* = 6.9, 4.3 Hz, 1H), 2.39 (s, 4H), 2.25 (d, *J* = 7.0 Hz, 1H), 1.32 (s, 9H) ppm.

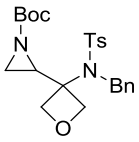
^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.8, 137.9, 135.9, 129.7, 128.6, 128.4, 128.0, 127.7, 77.2, 76.0, 62.8, 57.3, 50.1, 36.4, 29.9, 22.3, 21.6 ppm.

More polar diasteromer

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 8.4 Hz, 2H), 7.24 – 7.04 (m, 7H), 4.94 (d, *J* = 6.9 Hz, 1H), 4.59 (d, *J* = 6.9 Hz, 1H), 4.49 (d, *J* = 15.8 Hz, 1H), 4.41 (d, *J* = 6.9 Hz, 1H), 4.23 – 4.13 (m, 2H), 2.81 – 2.70 (m, 2H), 2.40 (s, 3H), 2.09 (d, *J* = 3.7 Hz, 1H), 1.26 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.9, 137.9, 136.0, 129.7, 128.7, 128.3, 128.0, 127.7, 77.1, 75.5, 62.6, 57.6, 50.1, 35.5, 22.9, 21.7 ppm.

Tert-butyl 2-(3-(N-benzyl-4-methylphenylsulfonamido)oxetan-3-yl)aziridine-1-carboxylate (**199**)

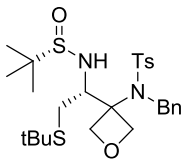


To a solution of **195** (200 mg, 0.432 mmol, 1.00 eq) (less polar diastereomer) in MeOH (2.2 mL)/CH_2Cl_2 (2.2 mL) was added at 0 °C HCl (4 M in dioxane, 540 µl, 2.16 mmol, 5.00 eq). The mixture was stirred for 1 h before quenching with sat. aq. $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. To the residue was added a solution of Boc_2O (151 µl, 0.648 mmol, 1.50 eq) in CH_2Cl_2 (2.2 mL). The mixture was stirred for 12 h. The solvent was removed under reduced pressure. The residue was purified by FC on silica (hex:EA = 4:1) to yield **199** (158 mg, 0.345 mmol, 80% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58 (d, *J* = 8.4 Hz, 2H), 7.22 – 7.06 (m, 7H), 4.98 (d, *J* = 7.1 Hz, 1H), 4.60 (d, *J* = 15.7 Hz, 1H), 4.48 – 4.38 (m, 2H), 4.30 (d, *J* = 15.7 Hz, 1H), 4.13 (d, *J* = 6.9 Hz, 1H), 3.08 (dd, *J* = 6.5, 3.6 Hz, 1H), 2.44 (d, *J* = 6.5 Hz, 1H), 2.38 (s, 3H), 2.30 (d, *J* = 3.7 Hz, 1H), 1.51 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.9, 143.7, 138.1, 136.0, 129.6, 128.6, 128.5, 127.9, 127.6, 82.1, 77.1, 74.7, 62.7, 49.7, 40.3, 28.0, 27.7, 21.6 ppm.

N-benzyl-*N*-(3-(2-(tert-butylthio)-1-(1,1-dimethylethylsulfinamido)ethyl)oxetan-3-yl)-4-methylbenzenesulfonamide (**200**)

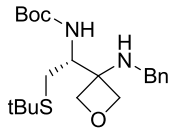


To a solution of **195** (488 mg, 1.055 mmol, 1.00 eq) (mixture of diastereomers) in THF (9.59 mL) and DMSO (0.96 mL) was added *tert*-butanethiol sodium salt (329 mg, 2.64 mmol, 2.50 eq). The mixture was stirred for 19 h. To the mixture was added water (20 mL). The mixture was extracted with EA (3 x 30 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The crude product was purified by FC on silica (DCM:acetone = 9:1) to yield the desired product **200** as two diastereomers. Combined yield: 389 mg, 0.704 mmol, 67%, colorless oils

More polar diasteromer

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (d, *J* = 8.4 Hz, 2H), 7.23 – 7.09 (m, 7H), 5.07 – 4.71 (m, 4H), 4.53 (d, *J* = 2.4 Hz, 2H), 4.13 – 3.96 (m, 1H), 3.09 – 2.77 (m, 2H), 2.38 (s, 3H), 1.34 (s, 9H), 1.28 (s, 9H) ppm.

Tert-butyl (1-(3-(benzylamino)oxetan-3-yl)-2-(tert-butylthio)ethyl)carbamate (**386**)



To a solution of **195** (198 mg, 0.358 mmol, 1.00 eq) in CH_2Cl_2 (1.8 mL)/ MeOH (1.8 mL) at 0 °C was added HCl (4 M in dioxane, 448 µL, 1.79 mmol, 5.00 eq). The mixture was stirred for 3.25 h. Sat. aq. NaHCO3 solution was added and the mixture was extracted with DCM (3 x 50 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was redissolved in DCE (1.8 mL) and Boc_2O (125 µL, 0.537 mmol, 1.50 eq) was added. The mixture was stirred at 50 °C for 15 h. The crude mixture was purified by FC on silica (hex:EA = 3:1) to yield tert-butyl (1-(3-(N-benzyl-4-methylphenylsulfonamido)oxetan-3-yl)-2-(tert-butylthio)ethyl)carbamate (143 mg, 0.261 mmol, 73%).

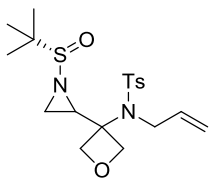
To a suspension of this material (140 mg, 0.255 mmol, 1.00 eq) in MeOH (2.32 mL)/THF (0.23 mL) was added magnesium turnings (62.0 mg, 2.55 mmol, 10.0 eq). The mixture was sonicated for 10 min and then stirred at r.t. for 50 min. The mixture became a clear solution after 10 min. The magnesium was consumed and the reaction not complete. Magnesium turnings (62.0 mg, 2.55 mmol, 10.0 eq) were added and the mixture was stirred for 2 h. As the reaction was still not complete, magnesium turnings (62.0 mg, 2.55 mmol, 10.0 eq) were added. The mixture was stirred for 3 h before quenching with NH_4Cl (20 mL). The mixture was extracted with EA (3 x 30 mL). The combined org layers were dried over Na_2SO_4 and concentrated to yield **386** (97 mg, 0.246 mmol, 96%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 – 7.17 (m, 5H), 5.16 (d, J = 9.6 Hz, 1H), 4.73 – 4.62 (m, 3H), 4.53 (d, J = 7.3 Hz, 1H), 4.36 – 4.22 (m, 1H), 4.02 (s, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.0, 140.2, 128.7, 128.1, 127.3, 79.9, 78.3, 78.0, 63.7, 53.5, 47.3, 42.7, 30.9, 29.0, 28.5, 28.4, 28.4 ppm.

HRMS (ESI+): m/z calcd. for $C_{21}H_{35}N_2O_3S_1$ $[M+H]^+$ 395.2363, found 395.2365.

N-allyl-*N*-(3-(1-((*S*)-tert-butylsulfinyl)aziridin-2-yl)oxetan-3-yl)-4-methylbenzenesulfonamide (**196**)



To a suspension of trimethylsulfoxoniumiodide (2.8 g, 13 mmol, 2.5 eq) in THF (50 mL) was added KO^{t}Bu (1.4 g, 13 mmol, 2.5 eq) at room temperature. The mixture was heated to reflux for 3 h. After cooling to 0 °C, **139** (2.0 g, 5.0 mmol) was added and the mixture was stirred for 1 h at this temperature before quenching with water (50 mL) and extracting with CH_2Cl_2 (3 x 40 mL).The combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by

FC on silica (hex:EA=1:1) to give **196** (1.8 g, 4.4 mmol, 87%, d.r. 1:1.3) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 – 7.73 (m, 4H), 7.34 – 7.30 (m, 4H), 5.72 – 5.51 (m, 2H), 5.17 – 4.98 (m, 4H), 4.98 – 4.78 (m, 4H), 4.59 – 4.27 (m, 4H), 3.91 – 3.65 (m, 4H), 3.16 (dd, *J* = 6.9, 4.2 Hz, 1H), 2.82 – 2.74 (m, 2H), 2.52 (dd, *J* = 4.3, 0.9 Hz, 1H), 2.43 (s, 6H), 2.30 (dd, *J* = 7.0, 0.9 Hz, 1H), 2.23 (d, *J* = 3.6 Hz, 1H), 1.32 (s, 10H), 1.25 (s, 8H).*

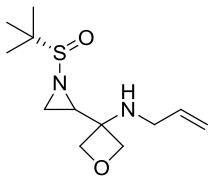
^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.1, 144.0, 137.9, 134.3, 134.3, 129.9, 129.9, 127.7, 127.7, 118.7, 118.5, 77.2, 77.0, 76.9, 76.0, 75.4, 62.4, 62.3, 57.6, 57.2, 49.3, 49.2, 36.4, 35.8, 30.1, 29.8, 22.8, 22.2, 22.1, 21.7 ppm.*

*reported as a mixture of diastereomers (d.r. 1:1.3)

HRMS (ESI+): *m/z* calcd. for $C_{19}H_{29}N_2O_4S_2$ $[M+H]^+$ 413.1563, found, 413.1565.

IR (neat): ν [cm^{-1}] = 2957, 2925, 1642, 1598, 1495, 1475, 1457, 1421, 1392, 1362, 1327, 1305, 1224, 1184, 1154, 1084, 1026, 1016, 988, 920, 879, 857, 814, 770, 707, 695, 661, 642, 589, 547.

N-allyl-3-(1-(tert-butylsulfinyl)aziridin-2-yl)oxetan-3-amine (**202**)



To a solution of **196** (1.8 g, 4.4 mmol, 1.0 eq) in MeOH (44 mL) were added magnesium turnings (2.1 g, 87 mmol, 10 eq). The mixture was sonicated for 5 min at room temperature before stirring at this temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution (100 mL) and extracted with EA (3 x 100 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure to yield **202** (0.90 g, 3.5 mmol, 80%, d.r. 1:1.3) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.99 – 5.85 (m, 2H), 5.23 (dt, *J* = 17.2, 1.6 Hz, 2H), 5.15 – 5.07 (m, 2H), 4.64 (d, *J* = 6.5 Hz, 1H), 4.59 – 4.40 (m, 7H), 3.43 (tt, *J* = 4.0, 1.6 Hz, 2H), 3.38 – 3.29 (m, 2H), 3.06 (dd, *J* = 7.1, 4.3 Hz, 2H), 2.74 (dd, *J* = 6.8, 0.7 Hz, 1H), 2.45 – 2.34 (m, 1H), 2.24 (d, *J* = 4.3 Hz, 1H), 2.16 (d, *J* = 7.1 Hz, 1H), 2.00 (dd, *J* = 4.1, 0.7 Hz, 1H), 1.25 (s, 19H).*

^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.6, 136.4, 116.6, 116.2, 78.7, 78.4, 78.3, 78.1, 59.7, 59.3, 57.6, 56.8, 46.4, 45.6, 35.7, 34.8, 26.9, 22.9, 22.4, 21.5 ppm.*

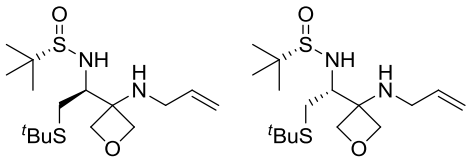
*reported as a mixture of diastereomers (d.r. 1:1.3)

HRMS (ESI+): *m*/*z* calcd. for $C_{12}H_{23}N_2O_2S$ $[M+H]^+$ 259.1475, found, 259.1474.

IR (neat): ν [cm^{-1}] = 3303, 2956, 2872, 1671, 1645, 1475, 1458, 1419, 1391, 1363, 1225, 1176, 1072, 979, 919, 825, 793, 701, 646, 595, 560, 455.

(*S*)-*N*-((S)-1-(3-(allylamino)oxetan-3-yl)-2-(tert-butylthio)ethyl)-2-methylpropane-2-sulfinamide **23a**

(*S*)-*N*-((*R*)-1-(3-(allylamino)oxetan-3-yl)-2-(tert-butylthio)ethyl)-2-methylpropane-2-sulfinamide **203**



To a solution of **202** (870 mg, 3.4 mmol, 1.0 eq) in THF/DMSO (10/1, 34 mL) was added *tert*-butanethiol sodium salt (1.0 g, 8.4 mmol, 2.5 eq). The suspension was stirred at room temperature for 16.5 h. The reaction mixture was treated with water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by FC on silica (DCM:acetone=4:1 to 1:1) to yield (*S*)-*N*-((S)-1-(3-(allylamino)oxetan-3-yl)-2-(tert-butylthio)ethyl)-2-methylpropane-2-sulfinamide (520 mg, 1.5 mmol, 44 %) and (*S*)-*N*-((*R*)-1-(3-(allylamino)oxetan-3-yl)-2-(tert-butylthio)ethyl)-2-methylpropane-2-sulfinamide (560 mg, 1.6 mmol, 48 %) as colorless oils.

(*S*)-*N*-((S)-1-(3-(allylamino)oxetan-3-yl)-2-(tert-butylthio)ethyl)-2-methylpropane-2-sulfinamide

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.96 (ddt, *J* = 17.1, 10.2, 5.6 Hz, 1H), 5.26 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.12 (dq, *J* = 10.3, 1.5 Hz, 1H), 4.65 (dd, *J* = 15.1, 7.1 Hz, 2H), 4.52 (dd, *J* = 23.5, 7.1 Hz, 2H), 4.18 (d, *J* = 7.7 Hz, 1H), 3.83 (ddd, *J* = 7.7, 6.2, 5.5 Hz, 1H), 3.47 (d, *J* = 5.6 Hz, 2H), 3.07 (dd, *J* = 12.7, 5.5 Hz, 1H), 2.80 (dd, *J* = 12.7, 6.3 Hz, 1H), 1.32 (s, 9H), 1.25 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.0, 115.9, 78.4, 78.3, 63.7, 59.3, 56.6, 45.6, 43.3, 31.0, 30.9, 22.9 ppm.

IR (neat): ν [cm^{-1}] = 3248, 2960, 2872, 1671, 1460, 1391, 1365, 1164, 1054, 982, 917, 594.

[α]$^{26}_D$ +59.1 (*c* 0.65, $CHCl_3$)

(*S*)-*N*-((*R*)-1-(3-(allylamino)oxetan-3-yl)-2-(tert-butylthio)ethyl)-2-methylpropane-2-sulfinamide

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.94 (ddt, *J* = 16.4, 10.7, 5.5 Hz, 1H), 5.26 (d, *J* = 17.3 Hz, 1H), 5.12 (d, *J* = 10.2 Hz, 1H), 4.76 (d, *J* = 7.5 Hz, 1H), 4.67 – 4.59 (m, 3H), 4.18 (d, *J* = 6.6 Hz, 1H), 3.79 (dd, *J* = 13.9, 5.0 Hz, 1H), 3.46 (qd, *J* = 13.4, 12.7, 4.8 Hz, 2H), 2.73 (qd, *J* = 12.6, 6.1 Hz, 2H), 1.31 (s, 9H), 1.24 (s, 9H).

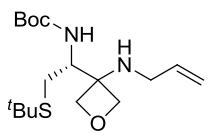
^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.9, 116.1, 79.2, 77.5, 63.4, 60.9, 56.6, 45.6, 42.8, 31.0, 30.7, 22.9 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{16}H_{33}N_2O_2S_2$ $[M+H]^+$ 349.1978, found, 349.1976.

IR (neat): ν [cm^{-1}] = 3289, 3080, 2960, 2927, 2869, 2324, 2112, 1981, 1667, 1645, 1472, 1460, 1418, 1391, 1364, 1265, 1217, 1163, 1044, 980, 916, 824, 794, 753, 690, 598, 555.

[α]$^{25}_D$ +12.6 (*c* 0.77, $CHCl_3$)

Tert-butyl (1-(3-(allylamino)oxetan-3-yl)-2-(tert-butylthio)ethyl)carbamate (**204**)



To a solution of (*S*,*R*)-**203** (0.55 g, 1.6 mmol, 1.0 eq) in CH_2Cl_2/MeOH (1/1, 18 mL) was added at 0 °C HCl (4 M in dioxane, 2.0 ml, 7.9 mmol, 5.0 eq). The mixture was stirred at this temperature for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated.

The resulting light yellow oil was dissolved in CH_2Cl_2 (7.89 mL) and Boc_2O (0.40 mL, 1.7 mmol, 1.1 eq) was added at 0 °C. The mixture was allowed to warm to room temperature and was then stirred for 3 d. The reaction mixture was concentrated and purified by FC on silica (hex:EA=2:1) to yield the (*R*)-**204** (0.386 g, 1.120 mmol, 71%) as a colorless wax.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.22 – 5.70 (m, 1H), 5.26 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.12 (dq, *J* = 10.3, 1.3 Hz, 1H), 5.08 (br s, 1H), 4.63 – 4.56 (m, 3H), 4.46 (d, *J* = 7.1 Hz, 1H), 4.21 (q, *J* = 7.4, 6.3 Hz, 1H), 3.51 – 3.42 (m, 2H), 2.83 – 2.65 (m, 2H), 1.46 (s, 9H), 1.31 (s, 9H)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.0, 136.9, 116.0, 79.9, 78.3, 78.0, 63.5, 53.6, 45.7, 42.8, 30.9, 29.0, 28.5 ppm.

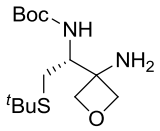
HRMS (ESI+): *m*/*z* calcd. for $C_{17}H_{33}N_2O_3S$ $[M+H]^+$ 345.2206, found, 345.2209.

IR (neat): ν [cm^{-1}] = 3322, 2967, 1710, 1493, 1460, 1392, 1366, 1250, 1167, 1045, 982, 918, 776.

$[\alpha]^{26}_D$ +8.52 (*c* 0.64, $CHCl_3$)

The other enantiomer of **204** was prepared using the same procedure.

Tert-butyl (1-(3-aminooxetan-3-yl)-2-(tert-butylthio)ethyl)carbamate (**197**)



To a solution of (*R*)-**204** (390 mg, 1.1 mmol, 1.0 eq) and 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (530 mg, 3.4 mmol, 3.0 eq) in CH_2Cl_2 (12 mL) was added $Pd(Ph_3P)_4$ (65 mg, 0.056 mmol, 5.0 mol-%) and the mixture was degassed by passing a stream on N_2 through the solution. Then, the reaction was heated to 35 °C for 3.5 h. After cooling to room temperature, the mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The residue was purified by FC on silica (100% EA) to yield (*R*)-**197** (330 mg, 1.1 mmol, 96%) as a colorless crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.07 (s, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.28 (d, *J* = 6.8 Hz, 1H), 4.25 – 4.13 (m, 3H), 2.84 – 2.56 (m, 2H), 1.73 (s, 2H), 1.43 (s, 9H), 1.30 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.8, 83.7, 82.6, 79.7, 59.4, 54.4, 42.8, 30.9, 29.0, 28.5 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{14}H_{28}N_2NaO_3S$ $[M+Na]^+$ 327.1713, found, 327.1714.

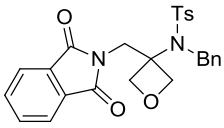
IR (neat): ν [cm^{-1}] = 3308, 2963, 2928, 2868, 1705, 1518, 1460, 1391, 1365, 1337, 1248, 1166, 1048, 1012, 977, 867, 833, 778, 721, 594.

***[α]*$^{26}_D$** +21.0 (*c* 0.70, $CHCl_3$)

m.p. 120 °C

The other enantiomer of **197** was prepared using the same procedure.

N-benzyl-*N*-(3-((1,3-dioxoisoindolin-2-yl)methyl)oxetan-3-yl)-4-methylbenzenesulfonamide (**209**)[280]



To a solution of **131** (1.00 g, 2.88 mmol, 1.00 eq) in THF (20.5 mL) were added phthalimide (593 mg, 4.03 mmol, 1.40 eq) and triphenylphosphine (981 mg, 3.74 mmol, 1.30 eq). The mixture was stirred at room temperature for 5 min and then cooled to 0 °C. Subsequently, DIAD (728 mL, 3.74 mmol, 1.30 eq) was added drop wise over 10 min. After complete addition, the mixture was stirred at 0 °C for 2 h and then at ambient temperature for 21 h. After evaporation of the solvent, the residue was submitted to FC on silica gel (hex:EA = 2:1). The product containing fractions were combined, evaporated to dryness, and the residue was triturated with MeOH to remove the diisopropyl hydrazine-1,2-dicarboxylate byproduct. The solid was filtered off, washed with MeOH and dried in vacuo to afford **209** (1.13 g, 2.37 mmol, 82%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94–7.87 (m, 2H), 7.78–7.69 (m, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.22–7.12 (m, 5H), 7.12–7.03 (m, 2H), 4.77 (d, *J* = 7.0 Hz, 2H), 4.58 (d, *J* = 7.2 Hz, 2H), 4.43 (s, 2H), 4.37 (s, 2H), 2.38 (s, 3H) ppm.

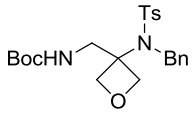
^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.0, 143.7, 138.2, 135.6, 134.3, 132.2, 129.6, 128.7, 128.1, 127.5, 127.5, 123.7, 78.5, 64.1, 49.7, 41.2, 21.6 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{26}H_{25}N_2O_5S$ $[M+H]^+$ 477.1479, found 477.1480.

IR (neat): ν [cm^{-1}] = 2890, 1714, 1426, 1400, 1371, 1352, 1329, 1154, 1090, 1071, 982, 947, 930, 901, 807, 771, 752, 723, 715, 700, 669, 645, 564, 542, 531.

m.p. = 166 °C

Tert-butyl ((3-(*N*-benzyl-4-methylphenylsulfonamido)oxetan-3-yl)methyl)-carbamate (**210**)[280]



To a suspension of **209** (1.10 g, 2.31 mmol, 1.0 eq) in EtOH (11.5 mL) was added hydrazine hydrate (578 mg, 11.5 mmol, 5.00 eq) and the mixture was heated to 65 °C. After 10 min, the solid had dissolved completely and before after 30 min, a white precipitate started to form again. After stirring fat 65 °C for 2 h, the mixture was cooled to ambient temperature and diluted with CH_2Cl_2 (10 mL). The solid was filtered off and washed with CH_2Cl_2. The combined filtrates were concentrated under reduced pressure. The residue was dissolved up in CH_2Cl_2 and insolubles were filtered off again and washed with CH_2Cl_2. The combined filtrates were washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure to leave an orange oil.

The oil was dissolved in CH_2Cl_2 (8.50 mL) and a solution of di-*tert*-butyl dicarbonate (756 mg, 3.46 mmol, 1.50 eq) in CH_2Cl_2 (2.90 mL) was added and the mixture was stirred at room temperature for 45 min. The solvent was removed under reduced pressure and the residue was purifed by FC on silica gel (hex:EA = 2:1) to afford **210** (953 mg, 2.13 mmol, 92%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (d, J = 8.3 Hz, 2H), 7.24–7.13 (m, 5H), 7.13–7.03 (m, 2H), 5.17 (br, 1H), 4.78 (d, J = 7.0 Hz, 2H), 4.35 (d, J = 7.4 Hz, 2H), 4.32 (s, 2H), 3.82 (d, J = 6.3 Hz, 2H), 2.38 (s, 3H), 1.46 (s, 9H) ppm.

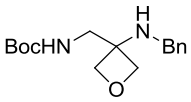
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.5, 143.9, 137.8, 135.9, 129.7, 128.6, 128.1, 127.9, 127.6, 79.8, 78.1, 63.7, 50.0, 45.2, 28.5, 21.6 ppm.

HRMS (ESI+): m/z calcd. for $C_{23}H_{30}N_2O_5SNa$ $[M+Na]^+$ 469.1768, found 469.1765.

IR (neat): ν [cm^{-1}] = 3305, 1975, 1709, 1536, 1326, 1304, 1271, 1251, 1144, 1091, 997, 975, 925, 903, 862, 811, 783, 755, 700, 669, 580, 560, 540.

m.p. = 127 °C.

Tert-butyl ((3-(benzylamino)oxetan-3-yl)methyl)carbamate (**211**)[280]



Magnesium turnings (513 mg, 21.1 mmol, 10.0 eq) were added to a solution of **210** (942 mg, 2.11 mmol, 1.00 eq) in MeOH (19.0 mL) and THF (1.90 mL). The mixture was stirred in a room temperature water bath for 6 h. The reaction was quenched with saturated aqueous NH_4Cl-solution and extracted with CH_2Cl_2 (4 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to obtain **211** (615 mg, 2.10 mmol, quant.) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45–7.31 (m, 4H), 7.31–7.26 (m, 1H), 4.92 (br, 1H), 4.51 (d, J = 6.7 Hz, 2H), 4.41 (d, J = 6.7 Hz, 2H), 3.76 (s, 2H), 3.58 (d, J = 5.4 Hz, 2H), 1.74 (br, 1H), 1.46 (s, 9H) ppm.

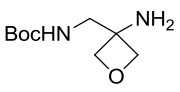
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.5, 139.8, 128.8, 128.2, 127.5, 79.9, 79.7, 60.0, 47.3, 44.3, 28.5 ppm.

HRMS (ESI+): m/z calcd. for $C_{16}H_{25}N_2O_3$ $[M+H]^+$ 293.1860, found 293.1859.

IR (neat): ν [cm^{-1}] = 3322, 2950, 2872, 1702, 1543, 1451, 1368, 1248, 1159, 996, 975, 956, 839, 766, 736, 704, 590, 510.

m.p. = 108 °C.

Tert-butyl ((3-aminooxetan-3-yl)methyl)carbamate (**208**)[280]



Pd-C (10% Pd, 111 mg, 0.10 mmol, 5.00 mol-%) was added to a solution of **211** (609 mg, 2.08 mmol, 1.00 eq) in MeOH (20.8 mL) and the mixture was stirred under an atmosphere of H_2 (balloon) for 9 h. Then, more Pd-C (10% Pd, 111 mg, 0.10 mmol, 5.00 mol-%) was added and stirring was

continued overnight (13 h) under an atmophere of H_2 (balloon). The mixture was filtered over Celite®, washed with EA and the filtrate was concentrated to dryness to afford **208** (421 mg, 2.05 mmol, 99%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.96 (br, 1H), 4.48 (d, J = 6.5 Hz, 2H), 4.39 (d, J = 6.4 Hz, 2H), 3.44 (d, J = 6.0 Hz, 2H), 1.65 (s, 2H), 1.44 (s, 9H) ppm.

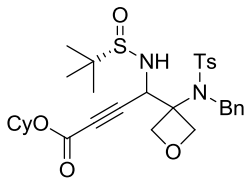
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.6, 82.8, 79.8, 56.6, 47.2, 28.5 ppm.

HRMS (ESI+): m/z calcd. for $C_9H_{19}N_2O_3$ $[M+H]^+$ 203.1390, found 203.1385.

IR (neat): ν [cm^{-1}] = 3317, 2975, 2945, 2873, 2360, 1700, 1548, 1392, 1365, 1269, 1253, 1163, 1006, 962, 908, 861, 826, 668.

m.p. = 76-78 °C (CH_2Cl_2).

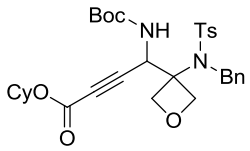
Cyclohexyl 4-(3-(N-benzyl-4-methylphenylsulfonamido)oxetan-3-yl)-4-((*S*)-1,1-dimethylethylsulfinamido)but-2-ynoate (**214**)



To a solution of cyclohexyl propiolate (0.210 g, 1.380 mmol, 2.00 eq) in THF (3.45 mL) at -78 °C was added *n*-BuLi (1.6 M in hexanes, 0.819 mL, 1.31 mmol, 1.90 eq) drop wise. The mixture was stirred for 60 min before adding **118** (0.309 g, 0.690 mmol, 1.00 eq) in THF (3.45 mL). The light yellow solution was stirred for 15 min before quenching cold with aq. sat. NH_4Cl solution (25 mL). The mixture was extracted with EA (3 x 25 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC on silica (hex:EA = 1:1) to yield **214** (0.348 g, 0.579 mmol, 84%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63 – 7.52 (m, 2H), 7.23 – 7.07 (m, 7H), 5.04 (d, J = 3.4 Hz, 1H), 4.96 (d, J = 7.7 Hz, 1H), 4.90 – 4.79 (m, 2H), 4.70 (d, J = 3.5 Hz, 1H), 4.62 – 4.50 (m, 4H), 2.39 (s, 3H), 1.94 – 1.83 (m, 2H), 1.81 – 1.68 (m, 2H), 1.61 – 1.34 (m, 7H), 1.31 (s, 9H) ppm.

Cyclohexyl 4-(3-(*N*-benzyl-4-methylphenylsulfonamido)oxetan-3-yl)-4-((tert-butoxycarbonyl)amino)but-2-ynoate (**215**)



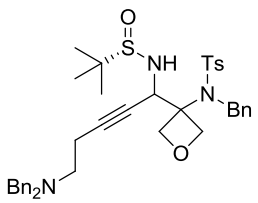
To a solution of **214** (0.319 g, 0.531 mmol, 1.00 eq) in CH_2Cl_2 (2.65 mL)/MeOH (2.65 mL) at 0 °C was added HCl (4 M in dioxane, 0.664 mL, 2.65 mmol, 5.00 eq). The mixture was stirred for 2 h. Sat. aq. $NaHCO_3$ solution (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was redissolved in CH_2Cl_2 (0.3 mL) and Boc_2O (0.185 ml, 0.796 mmol, 1.50 eq) was added. The mixture was stirred at r.t. for21 h. The crude mixture was purified by FC on silica (hex:EA = 3:1) to yield **215** (0.253 g, 0.424 mmol, 80%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 8.0 Hz, 2H), 7.26 – 7.12 (m, 7H), 5.58 (d, *J* = 9.5 Hz, 1H), 5.45 (d, *J* = 9.3 Hz, 1H), 5.06 – 4.95 (m, 1H), 4.95 – 4.75 (m, 2H), 4.74 – 4.53 (m, 2H), 4.47 (d, *J* = 7.4 Hz, 1H), 4.32 (d, *J* = 16.6 Hz, 1H), 2.41 (s, 3H), 1.96 – 1.84 (m, 2H), 1.83 – 1.69 (m, 2H), 1.53 (s, 9H), 1.49 – 1.24 (m, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.1, 152.4, 143.9, 137.5, 136.1, 129.7, 128.7, 127.8, 127.8, 83.3, 81.0, 77.7, 76.8, 76.4, 75.3, 65.6, 50.8, 46.9, 31.5, 31.5, 28.4, 27.5, 25.3, 23.8, 21.6 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{32}H_{44}N_3O_7S_1$ $[M+H]^+$ 614.2894, found 614.2896.

N-benzyl-*N*-(3-(5-(dibenzylamino)-1-((*S*)-1,1-dimethylethylsulfinamido)pent-2-yn-1-yl)oxetan-3-yl)-4-methylbenzenesulfonamide (**219**)



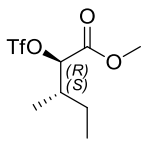
To a solution of *N*,*N*-dibenzylbut-3-yn-1-amine (0.126 g, 0.505 mmol, 2.00 eq) in THF (1.26 mL) at -78 °C was added *n*-BuLi (1.6 M in hexanes, 0.300 mL, 0.480 mmol, 1.90 eq) drop wise. The mixture was stirred for 60 min before adding **118** (0.113 g, 0.253 mmol, 1.00 eq) in THF (1.26 mL). The light yellow solution was

stirred for 5 min before quenching cold with aq. sat. NH_4Cl solution (20 mL). The mixture was extracted with EA (3 x 25 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC on silica (hex:EA = 1:1) to yield **219** (0.167 g, 0.239 mmol, 95%) as a mixture of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 – 7.07 (m, 19H), 4.96 – 4.79 (m, 3H), 4.68 – 4.57 (m, 2H), 4.50 – 4.36 (m, 2H), 3.64 (s, 4H), 2.69 (t, *J* = 7.4 Hz, 2H), 2.47 – 2.40 (m, 2H), 2.40 – 2.36 (m, 3H), 1.28 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.8, 143.7, 139.4, 139.3, 137.5, 136.7, 136.0, 129.5, 129.5, 128.7, 128.7, 128.5, 128.4, 128.4, 128.3, 128.3, 127.8, 127.7, 127.6, 127.5, 127.3, 127.0, 127.0, 87.6, 77.2, 76.4, 66.6, 65.9, 58.1, 58.1, 56.9, 56.2, 52.0, 51.8, 51.8, 51.1, 51.0, 22.7, 21.5, 21.5, 17.5, 17.4 ppm.

(2*R*,3*S*)-benzyl 3-methyl-2-(((trifluoromethyl)sulfonyl)oxy)pentanoate (**230**)



To a solution of **234** (788 mg, 3.55 mmol, 1.00 eq.) in CH_2Cl_2 (11.8 mL) was added 2,6-lutidine (495 µl, 4.25 mmol, 1.20 eq.) at -78 °C, followed by dropwise addition of triflic anhydride (719 µl, 4.25 mmol, 1.20 eq.). The resulting mixture was stirred at -78 °C for 30 min. The cooling bath was removed and the mixture was allowed to warm to r.t. before H_2O (10 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil was purified by FC on silica (hexane:EA 10:1) to yield **230** (1.19 g, 3.37 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46-7.36 (m, 5H), 5.30 (d, *J* = 3.2 Hz, 2H), 5.15 (d, *J* = 3.1 Hz, 1H), 2.19 – 2.08 (m, 1H), 1.58 – 1.47 (m, 1H), 1.43 – 1.30 (m, 1H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.0, 134.4, 128.9, 128.7, 128.7, 118.44 (q, J = 319.5 Hz), 86.5, 68.2, 37.8, 25.5, 13.4, 11.4 ppm.

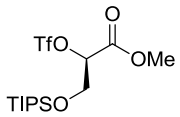
^{19}F NMR (282 MHz, $CDCl_3$) δ = -74.68 ppm.

HRMS (ESI+): m/z calcd. for $C_{14}H_{17}F_3NaO_5S$ $[M+Na]^+$ 377.0641, found, 377.0645.

IR (neat): ν [cm^{-1}] = 3037, 2973, 2942, 2884, 1763, 1499, 1457, 1417, 1389, 1337, 1282, 1243, 1204, 1145, 1094, 946, 914, 860, 786, 753, 698, 626, 501, 478.

[α]^{21}D 31.4 (c 0.65, $CHCl_3$)

(*R*)-methyl 2-(((trifluoromethyl)sulfonyl)oxy)-3-((triisopropylsilyl)oxy)-propanoate (**239**)

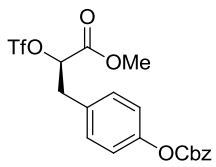


To a solution of (*R*)-methyl 2-hydroxy-3-((triisopropylsilyl)oxy)propanoate (101 mg, 0.365 mmol, 1.00 eq) in CH_2Cl_2 (0.5 mL) was added 2,6-lutidine (51.1 µl, 0.438 mmol, 1.20 eq) at -78 °C, followed by drop wise addition of Tf_2O (74.1 µl, 0.438 mmol, 1.20 eq) over 10 min. The resulting mixture was stirred at -78 °C for 30 min. The cooling bath was removed and the mixture was allowed to warm to r.t. before H_2O (10 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil was purified by FC on SiO_2 (hexane:EA = 4:1) to yield **239** (100 mg, 0.245 mmol, 67%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.20 (dd, J = 5.5, 3.0 Hz, 1H), 4.24 – 4.09 (m, 2H), 3.85 (s, 3H), 1.09 – 0.99 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.8, 123.4, 120.2, 117.0, 113.9, 84.2, 63.4, 53.4, 17.8, 11.9 ppm.

(*R*)-methyl 3-(4-(((benzyloxy)carbonyl)oxy)phenyl)-2-(((trifluoromethyl)-sulfonyl)oxy)propanoate (**244**)



To a solution of (*R*)-methyl 2-hydroxy-3-(4-hydroxyphenyl)propanoate[281] (67 mg, 0.34 mmol, 1.0 eq.) in CH_2Cl_2 (3.4 mL) was added Et_3N (47.6 µl, 0.34 mmol, 1.0 eq.) followed by dropwise Cbz-Cl (48.7 µl, 0.34 mmol, 1.0 eq.). The mixture was stirred for 3 h before quenching with water/1 M $NaHSO_4$ (1:1, 20 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined org. layers were dried over Na_2SO_4 and concentrated to yield (*R*)-methyl 3-(4-(((benzyloxy)carbonyl)oxy)phenyl)-2-hydroxypropanoate (110 mg, 0.333 mmol, 98%). The crude product was used in the next step without further purification.

To a solution of (*R*)-methyl 3-(4-(((benzyloxy)carbonyl)oxy)phenyl)-2-hydroxypropanoate (240 mg, 0.71 mmol, 1.0 eq) in CH_2Cl_2 (0.95 mL) was added 2,6-lutidine (99 µl, 0.85 mmol, 1.2 eq) at -78 °C, followed by dropwise addition of Tf_2O (0.14 mL, 0.85 mmol, 1.2 eq) over 10 min. The resulting mixture was stirred at this temperature for further 10 min before water (10 mL) was added. After warming to room temperature, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by FC on silica (hex:EA=6:1) to yield **244** (0.28 g, 0.60 mmol, 84%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 – 7.34 (m, 5H), 7.27 – 7.13 (m, 4H), 5.27 (s, 2H), 5.24 (dd, *J* = 8.4, 4.2 Hz, 1H), 3.83 (s, 3H), 3.35 (dd, *J* = 14.7, 4.2 Hz, 1H), 3.22 (dd, *J* = 14.7, 8.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.0, 153.5, 151.0, 134.8, 131.3, 130.7, 129.0, 128.9, 128.7, 121.6, 118.36 (q, J = 319.8 Hz), 83.6, 70.6, 53.5, 37.7 ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ = -75.05 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{19}H_{21}F_3NO_8S$ $[M+NH_4]^+$ 480.0934, found, 480.0934.

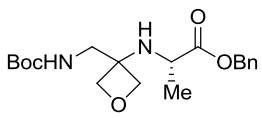
IR (neat): ν [cm^{-1}] = 3441, 3026, 2925, 1732, 1610, 1511, 1495, 1437, 1227, 1176, 1029, 830, 751, 670, 640, 519.

$[\alpha]^{26}_{D}$ -43.1 (*c* 0.70, $CHCl_3$)

General Procedure for the Synthesis of Dipeptide Building Blocks **73** (GP 1):

To a solution of the triflate or bromide (2.0 eq) in acetonitrile (0.40 M-0.5 M) were added at room temperature diisopropylethylamine (2.0 eq) and the diamine building block (1.0 eq). The mixture was stirred at 30 °C-60 °C for 1 d-5 d. The reaction mixture was then directly purified by FC on silica.

(*S*)-benzyl 2-((3-(((tert-butoxycarbonyl)amino)methyl)oxetan-3-yl)amino)propanoate (**73a**)



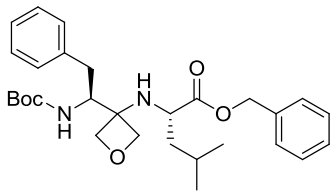
73a was prepared as a colorless oil (57 mg, 0.156 mmol, 78%) according GP 1 using **222** (137 mg, 0.440 mmol, 2.20 eq), diisopropylethylamine (77 µL, 0.440 mmol, 2.20 eq), **208** (40 mg, 0.200 mmol, 1.00 eq) and acetonitrile (0.50 mL). The reaction time was 28 h at 30 °C. The crude mixture was purified by FC on silica (hex:EA = 2:1→1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 – 7.31 (m, 5H), 5.17 (s, 2H), 4.96 (s, 1H), 4.44 (d, *J* = 6.5 Hz, 1H), 4.37 (d, *J* = 6.7 Hz, 1H), 4.31 (d, *J* = 6.6 Hz, 1H), 4.26 (d, *J* = 6.4 Hz, 1H), 3.66 – 3.36 (m, 3H), 1.48 (s, 9H), 1.35 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.3, 135.4, 128.8, 128.7, 128.6, 80.1, 80.0, 67.2, 59.6, 51.2, 44.7, 28.5, 20.8 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{19}H_{29}N_2O_5$ $[M+H]^+$ 365.2071, found, 365.2076.

(S)-benzyl 2-((3-((S)-1-((tert-butoxycarbonyl)amino)-2-phenylethyl)oxetan-3-yl)amino)-4-methylpentanoate (**73b**)[280]



The compound was prepared from **158** (58.5 mg, 0.200 mmol, 1.00 eq) and **224** (142 mg, 0.400 mmol, 2.00 eq) following GP 1. After stirring for 24 h at 30 °C, the mixture was purified by FC on silica gel (hex:EA = 3:1) to afford **73b** (62.0 mg, 0.125 mmol, 62%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45–7.30 (m, 5H), 7.31–7.16 (m, 5H), 4.96 (d, *J* = 9.0 Hz, 1H), 5.20 (d, *J* = 12.1 Hz, 1H), 5.16 (d, *J* = 12.1 Hz, 1H), 4.45–4.21 (m, 4H), 4.17 (d, *J* = 7.0 Hz, 1H), 3.82–3.64 (m, 1H), 2.95–2.80 (m, 1H), 2.81–2.57 (m, 1H), 1.97–1.81 (br, 1H), 1.83–1.68 (m, 1H), 1.65–1.53 (m, 1H), 1.50–1.41 (m, 1H), 1.36 (s, 9H), 1.01–0.90 (m, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.9, 156.0, 138.1, 135.6, 129.4, 128.7, 128.6, 128.6, 126.7, 79.6, 79.2, 79.2, 67.1, 63.0, 56.7, 54.5, 44.1, 36.0, 28.4, 25.0, 23.1, 22.4 ppm.

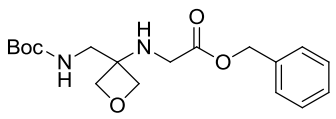
HRMS (ESI+): *m*/*z* calcd. for $C_{29}H_{41}N_2O_5$ $[M+H]^+$ 497.3010, found 497.3013.

IR (neat): ν [cm^{-1}] = 3315, 2957, 2929, 2872, 2398, 1741, 1712, 1546, 1510, 1454, 1366, 1266, 1247, 1162, 1064, 1008, 964, 742, 698.

$[\alpha]^{25}_D$ = –20.7 (c = 0.51, $CHCl_3$).

m.p. = 134-135 °C (hexane).

Benzyl 2-((3-(((tert-butoxycarbonyl)amino)methyl)oxetan-3-yl)amino)acetate (**73c**)[280]



The compound was prepared from **208** (48.9 mg, 0.200 mmol, 1.00 eq) and benzyl 2-bromoacetate (125 mg,

0.400 mmol, 2.00 eq) following GP 1. After stirring for 24 h at 30 °C, the mixture was purified by FC on silica gel (hex:EA = 3:1) to afford **73c** (64.6 mg, 0.159 mmol, 79%) as a colorless wax.

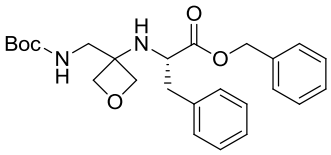
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 – 7.31 (m, 5H), 5.18 (s, 2H), 4.98 (br s, 1H), 4.45 (d, *J* = 6.7 Hz, 2H), 4.37 (d, *J* = 6.8 Hz, 2H), 3.54 – 3.39 (m, 4H), 2.09 (br s, 1H), 1.44 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.40, 156.44, 135.35, 128.83, 128.74, 128.61, 79.74, 79.35, 77.36, 67.23, 59.73, 44.87, 44.68, 28.50 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{18}H_{26}N_2NaO_5$ $[M+H]^+$ 373.1734, found 373.1733.

IR (neat): ν [cm^{-1}] = 3333, 2975, 2873, 1739, 1705, 1499, 1391, 1365, 1247, 1165, 974, 732, 697.

(*S*)-benzyl 2-((3-(((tert-butoxycarbonyl)amino)methyl)oxetan-3-yl)amino)-3-phenylpropanoate (**73d**)[280]



The compound was prepared from **208** (60.0 mg, 0.297 mmol, 1.00 eq) and **226** (230 mg, 0.593 mmol, 2.00 eq) following GP 1. After stirring for 22 h at r.t., the mixture was purified by FC on silica gel (hex:EA = 2:1) to afford **73d** (113 mg, 0.257 mmol, 87%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40–7.33 (m, 3H), 7.31–7.20 (m, 5H), 7.16 (d, *J* = 7.0 Hz, 2H), 5.13 (d, *J* = 12.1 Hz, 1H), 5.09 (d, *J* = 12.0 Hz, 1H), 4.63–4.42 (m, 1H), 4.28–4.19 (m, 2H), 4.16 (d, *J* = 6.7 Hz, 1H), 4.09 (d, *J* = 6.5 Hz, 1H), 3.55 (dd, *J* = 8.6, 5.4 Hz, 1H), 3.43–3.29 (m, 2H), 3.00 (dd, *J* = 13.4, 5.4 Hz, 1H), 2.77 (dd, *J* = 13.4, 8.6 Hz, 1H), 2.08 (s, 1H), 1.43 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.3, 156.3, 137.1, 135.2, 129.4, 128.8, 128.7, 128.7, 128.7, 127.2, 80.0, 79.5, 79.4, 67.3, 59.5, 57.4, 44.4, 40.8, 28.5 ppm.

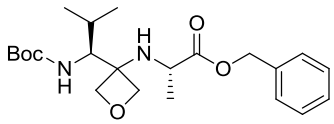
HRMS (ESI+): *m*/*z* calcd. for $C_{25}H_{33}N_2O_5$ $[M+H]^+$ 441.2384, found 441.2387.

IR (neat): ν [cm^{-1}] = 3315, 2957, 2929, 2872, 2398, 1741, 1712, 1546, 153428, 3314, 2979, 1718, 1700, 1509, 1364, 1269, 1246, 1231, 1161, 1055, 996, 983, 966, 944, 860, 756, 698.

[α]$^{24}_D$ = –3.9 (c = 0.59, $CHCl_3$).

m.p. = 109-110 °C (hexane).

(*S*)-benzyl 2-((3-((*S*)-1-((tert-butoxycarbonyl)amino)-2-methylpropyl)oxetan-3-yl)amino)propanoate (**73e**)[280]



The compound was prepared from **145** (48.9 mg, 0.200 mmol, 1.00 eq) and **222** (125 mg, 0.400 mmol, 2.00 eq) following GP 1. After stirring for 24 h at 30 °C, the mixture was purified by FC on silica gel (hex:EA = 3:1) to afford **73e** (64.6 mg, 0.159 mmol, 79%) as a colorless wax.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43–7.29 (m, 5H), 5.18 (s, 2H), 4.90 (d, *J* = 10.1 Hz, 1H), 4.60 (d, *J* = 7.0 Hz, 1H), 4.54 (d, *J* = 7.5 Hz, 1H), 4.37 (d, *J* = 6.9 Hz, 1H), 4.28 (d, *J* = 7.5 Hz, 1H), 3.90 (q, *J* = 7.0 Hz, 1H), 3.78 (dd, *J* = 10.2, 7.4 Hz, 1H), 1.84 (sept, *J* = 6.9 Hz, 1H), 1.61 (br, 1H), 1.45 (s, 9H), 1.38 (d, *J* = 7.0 Hz, 3H), 0.97–0.78 (m, 6H) ppm.

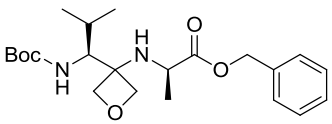
^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.6, 156.6, 135.7, 128.8, 128.6, 128.4, 80.4, 79.4, 79.3, 67.1, 63.6, 60.1, 51.3, 29.8, 28.5, 21.5, 20.3, 18.8 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{22}H_{35}N_2O_5$ $[M+H]^+$ 407.2540, found 407.2536.

IR (neat): ν [cm^{-1}] = 3330, 2964, 2876, 2360, 2341, 1732, 1707, 1498, 1456, 1391, 1366, 1247, 1172, 986, 736, 699.

[α]$^{20}_D$ = –27.2 (c = 0.57, $CHCl_3$).

(*R*)-benzyl 2-((3-((*S*)-1-((tert-butoxycarbonyl)amino)-2-methylpropyl)oxetan-3-yl)amino)propanoate (**epi-73e**)[280]



The compound was prepared from **145** (48.9 mg, 0.200 mmol, 1.00 eq) and **ent-222** (125 mg, 0.400 mmol, 2.00 eq) following GP 1. After stirring for 24 h at 30 °C, the mixture was purified by FC on silica gel (hex:EA = 3:1) to afford **epi-73e** (51.5 mg, 0.127 mmol, 63%) as a colorless wax.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46–7.28 (m, 5H), 5.22 (d, *J* = 12.2 Hz, 1H), 5.16 (d, *J* = 12.3 Hz, 1H), 4.78 (d, *J* = 10.1 Hz, 1H), 4.57 (d, *J* = 7.4 Hz, 1H), 4.52 (d, *J* = 7.4 Hz, 1H), 4.35 (d, *J* = 7.3 Hz, 1H), 4.25 (d, *J* = 7.5 Hz, 1H), 4.04 (q, *J* = 7.2 Hz, 1H), 3.79 (dd, *J* = 9.7, 9.7 Hz, 1H), 2.20 (s, 1H), 1.77–1.61 (m, 1H), 1.43 (s, 9H), 1.37 (d, J = 7.1 Hz, 3H), 0.96 (d, J = 6.5 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H) ppm.

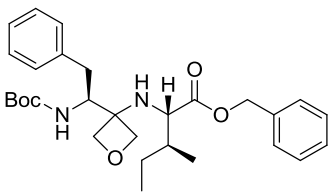
^{13}C NMR (101 MHz, $CDCl_3$) δ = 177.4, 156.3, 135.6, 128.8, 128.6, 128.4, 79.7, 79.3, 79.3, 67.3, 63.6, 61.4, 50.5, 30.7, 28.5, 22.3, 20.1, 19.7 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{22}H_{35}N_2O_5$ $[M+H]^+$ 407.2540, found 407.2541.

IR (neat): ν [cm^{-1}] = 3340, 2964, 2878, 2359, 1731, 1706, 1497, 1455, 1391, 1366, 1248, 1172, 985, 752, 699.

$[\alpha]^{22}_D$ = 24.6 (*c* = 0.53, $CHCl_3$).

(2*S*,3*S*)-benzyl 2-((3-((*S*)-1-((tert-butoxycarbonyl)amino)-2-phenylethyl)oxetan-3-yl)amino)-3-methylpentanoate (**73f**)[280]



To a solution of **158** (58.5 mg, 0.20 mmol, 1.00 eq) in MeCN (0.40 mL) were added N,N,-diisoproylethylamine (103 mg, 140 µL, 0.80 mmol, 1.00 eq) and **230** (283 mg, 0.80 mmol, 4.00 eq) and the mixture was heated to 50 °C for 96 h. After cooling to room temperature, the mixture was purified by FC on

silica gel (hex:EA = 3:1) to afford **73f** (39.4 mg, 0.079 mmol, 40%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50–7.31 (m, 5H), 7.31–7.14 (m, 5H), 5.22 (d, *J* = 12.1 Hz, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 4.90 (d, *J* = 9.0 Hz, 1H), 4.53–4.23 (m, 4H), 4.20 (d, *J* = 7.0 Hz, 1H), 3.73–3.47 (m, 1H), 3.02–2.82 (m, 1H), 2.82–2.60 (m, 1H), 2.13–1.86 (m, 1H), 1.86–1.71 (m, 1H), 1.59–1.43 (m, 1H), 1.36 (s, 9H), 1.22–1.06 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.3, 156.0, 138.2, 135.6, 129.4, 128.7, 128.7, 128.6, 128.6, 126.6, 79.6, 79.2, 79.0, 67.1, 63.1, 60.5, 57.0, 39.6, 36.0, 28.4, 25.2, 16.1, 11.9 ppm.

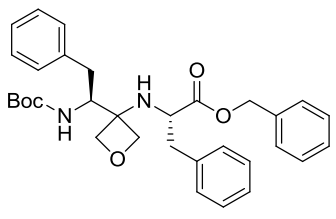
HRMS (ESI+): *m*/*z* calcd. for $C_{29}H_{40}N_2O_5Na$ $[M+Na]^+$ 519.2829, found 519.2827.

IR (neat): ν [cm^{-1}] = 3333, 2962, 2885, 1736, 1716, 1539, 1500, 1454, 1251, 1164, 1147, 968, 739, 700.

$[\alpha]^{24}_D$ = –21.4 (c = 0.97, $CHCl_3$).

m.p. = 114-115 °C (hexane).

(*S*)-benzyl 2-((3-((*S*)-1-((tert-butoxycarbonyl)amino)-2-phenylethyl)oxetan-3-yl)amino)-3-phenylpropanoate (**73g**)[280]



The compound was prepared from **158** (58.5 mg, 0.20 mmol, 1.0 eq) and **226** (155 mg, 0.40 mmol, 2.0 eq) following GP 1. After stirring for 24 h at 30 °C, the mixture was purified by FC on silica gel (hex:EA = 3:1) to afford **73g** (71.2 mg, 0.134 mmol, 67%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49–7.27 (m, 8H), 7.24 (d, *J* = 6.5 Hz, 2H), 7.17 (d, *J* = 6.6 Hz, 3H), 6.97 (d, *J* = 7.0 Hz, 2H), 5.19 (s, 2H), 4.98 (d, *J* = 9.1 Hz, 1H), 4.32 (d, *J* = 7.6 Hz, 1H), 4.27–4.09 (m, 2H), 4.07–3.93 (m, 1H), 3.93–3.73 (m, 2H), 3.17

(dd, *J* = 13.4, 4.8 Hz, 1H), 2.82 (dd, *J* = 13.4, 9.1 Hz, 1H), 2.73–2.28 (m, 2H), 1.92 (br, 1H), 1.37 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.6, 155.9, 138.0, 137.2, 135.4, 129.6, 129.1, 128.8, 128.8, 128.7, 128.7, 128.5, 127.2, 126.5, 79.5, 79.3, 78.6, 67.3, 62.5, 57.6, 57.3, 40.8, 36.1, 28.4 ppm.

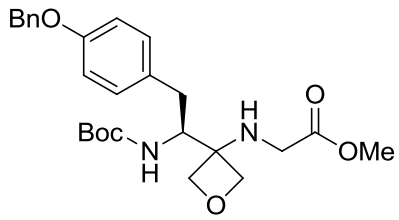
HRMS (ESI+): *m*/*z* calcd. for $C_{32}H_{39}N_2O_5$ $[M+H]^+$ 531.2853, found 531.2858.

IR (neat): ν [cm^{-1}] = 3339, 2972, 1712, 1496, 1455, 1366, 1248, 1169, 980, 751, 699.

[α]$^{22}_D$ = -20.3 (*c* = 0.56, $CHCl_3$).

m.p. = 128 °C

(S)-methyl 2-((3-(2-(4-(benzyloxy)phenyl)-1-((tert-butoxycarbonyl)amino)ethyl)oxetan-3-yl)amino)acetate (**73h**)



The compound was prepared from **166** (50.0 mg, 0.125 mmol, 1.00 eq) and methyl 2-bromoacetate (38.4 mg, 0.251 mmol, 2.00 eq) following GP 1. After stirring for 7 d at room temperature, the mixture was purified by FC on silica gel (hex:EA = 2:3) to afford **73h** (51.1 mg, 0.109 mmol, 87%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.4 7.35 (m, 4H), 7.35–7.29 (m, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.95–6.85 (m, 2H), 5.03 (s, 2H), 4.89 (d, *J* = 9.3 Hz, 1H), 4.56–4.36 (m, 2H), 4.37–4.12 (m, 3H), 3.79 (s, 3H), 3.78–3.59 (m, 2H), 2.84–2.64 (m, 2H), 2.04 (br, 1H), 1.37 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.28, 157.76, 155.89, 137.17, 130.22, 130.03, 128.69, 128.05, 127.57, 115.12, 79.64, 78.56, 77.81, 70.18, 62.79, 56.56, 52.40, 44.74, 35.36, 28.42 ppm.

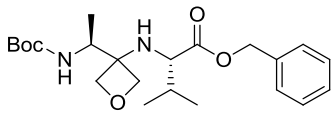
HRMS (ESI+): *m*/*z* calcd. for $C_{26}H_{35}N_2O_6$ $[M+H]^+$ 471.2490, found 471.2490.

IR (neat): ν [cm^{-1}] = 3332, 2956, 2360, 2341, 1742, 1705, 1614, 1512, 1455, 1439, 1364, 1242, 1219, 1173, 967, 741, 696.

[α]$^{24}_D$ = –4.5 (c = 0.83, $CHCl_3$).

m.p. = 96-98 °C (CH_2Cl_2).

(S)-benzyl 2-((3-((S)-1-((tert-butoxycarbonyl)amino)ethyl)oxetan-3-yl)amino)-3-methylbutanoate (**73i**)[280]



To a solution of **122** (43.3 mg, 0.20 mmol, 1.00 eq) in MeCN (0.40 mL) were added N,N,-diisoproylethylamine (103 mg, 140 µL, 0.80 mmol, 4.00 eq) and **225** (272 mg, 0.80 mmol, 4.00 eq) and the mixture was heated to 50 °C for 48 h. After cooling to room temperature, the mixture was purified by FC on silica gel (hex:EA = 3:1) to afford **73i** (**40**, 45.2 mg, 0.111 mmol, 56%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45–7.23 (m, 5H), 5.19 (d, *J* = 12.1 Hz, 1H), 5.16 (d, *J* = 12.1 Hz, 1H), 4.92 (d, *J* = 8.7 Hz, 1H), 4.47–4.36 (m, 2H), 4.34 (d, *J* = 6.9 Hz, 1H), 4.30 (d, *J* = 7.2 Hz, 1H), 4.13–3.98 (m, 1H), 3.46 (d, *J* = 5.3 Hz, 1H), 2.06–1.94 (m, 1H), 1.94–1.80 (br, 1H), 1.46 (s, 9H), 1.15 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.2, 156.0, 135.6, 128.8, 128.7, 128.6, 79.6, 78.9, 78.5, 67.1, 62.9, 61.2, 50.9, 32.4, 28.5, 19.6, 18.1, 15.2 ppm.

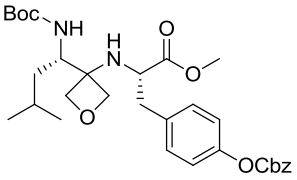
HRMS (ESI+): *m*/*z* calcd. for $C_{22}H_{35}N_2O_5$ $[M+H]^+$ 407.2540, found 407.2543.

IR (neat): ν [cm^{-1}] = 3353, 2964, 2878, 2398, 1713, 1552, 1504, 1457, 1366, 1254, 1238, 1166, 1077, 1062, 972, 699.

[α]$^{24}_D$ = –22.6 (c = 0.55, $CHCl_3$).

m.p. = 80-82 °C (CH_2Cl_2).

(*S*)-methyl 3-(4-(((benzyloxy)carbonyl)oxy)phenyl)-2-((3-((*S*)-1-((tert-butoxycarbonyl)amino)-3-methylbutyl)oxetan-3-yl)amino)propanoate (**73j**)



73j was prepared as a colorless oil (83 mg, 0.15 mmol, 73%) according to GP 1 using **244** (185 mg, 0.40 mmol, 2.0 eq), diisopropylethylamine (70 µL, 0.40 mmol, 2.0 eq), **149** (52 mg, 0.20 mmol, 1.0 eq) and acetonitrile (0.50 mL). The reaction time was 48 h at 30 °C. The crude mixture was purified by FC on silica (hex:EA=6:1 to 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 – 7.34 (m, 5H), 7.25 – 7.07 (m, 4H), 5.26 (s, 2H), 4.63 (d, *J* = 9.4 Hz, 1H), 4.50 – 4.39 (m, 1H), 4.31 – 4.17 (m, 1H), 4.08 (d, *J* = 6.9 Hz, 1H), 4.05 – 3.95 (m, 1H), 4.84 – 3.76 (m, 1H), 3.71 (s, 3H), 3.18 – 2.71 (m, 2H), 1.98 (br s, 1H), 1.65 – 1.53 (m, 1H), 1.43 (s, 9H), 1.18 – 0.98 (m, 2H), 0.89 (t, *J* = 7.0 Hz, 6H).

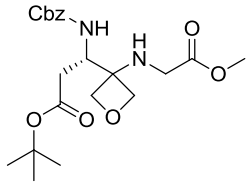
^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.9, 156.1, 153.5, 150.1, 135.1, 134.8, 130.5, 128.8, 128.7, 128.5, 120.9, 79.1, 78.2, 71.1, 70.64, 63.1, 57.4, 53.3, 52.3, 40.4, 38.9, 28.4, 24.9, 23.7, 21.6 ppm.

HRMS (ESI+): *m*/z calcd. for $C_{31}H_{43}N_2O_8$ $[M+H]^+$ 571.3014, found, 571.3011.

IR (neat): ν [cm^{-1}] = 3337, 3035, 2956, 2872, 1762, 1738, 1709, 1606, 1508, 1456, 1380, 1367, 1329, 1235, 1216, 1201, 1167, 1109, 1082, 1046, 1018, 1003, 848, 752, 697, 529.

[α]^{27}$_D$ -23.1 (*c* 0.87, $CHCl_3$)

(*S*)-*tert*-butyl 3-(((benzyloxy)carbonyl)amino)-3-(3-((2-methoxy-2-oxoethyl)amino)oxetan-3-yl)propanoate (**73k**)



73k was prepared as a colorless oil (76 mg, 0.18 mmol, 90%) according to GP 1 using methyl 2-bromoacetate (61 mg, 0.40 mmol, 2.0 eq), diisopropylethylamine (70 µL, 0.40 mmol, 2.0 eq), **179** (70 mg, 0.20 mmol, 1.0 eq) and acetonitrile (0.40 mL). The reaction time was 24 h at 30 °C. The crude mixture was purified by FC on silica (hex:EA=1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.28 (m, 5H), 5.55 (d, *J* = 9.1 Hz, 1H), 5.19 – 5.02 (m, 2H), 4.58 (d, *J* = 7.4 Hz, 1H), 4.51 – 4.39 (m, 4H), 3.75 (s, 3H), 3.61 (d, *J* = 3.3 Hz, 2H), 2.50 (dd, J = 15.0, 5.2 Hz, 1H), 2.37 (dd, *J* = 15.0, 7.7 Hz, 1H), 1.40 (s, 9H).

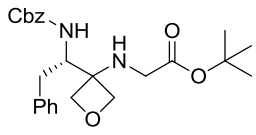
^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.0, 170.7, 156.4, 136.4, 128.7, 128.3, 128.3, 81.6, 77.8, 77.7, 67.2, 63.1, 52.8, 52.4, 44.8, 36.2, 28.1 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{21}H_{30}N_2NaO_7$ $[M+Na]^+$ 445.1945, found, 445.1951.

IR (neat): ν [cm^{-1}] = 3334, 2956, 1726, 1537, 1456, 1438, 1393, 1368, 1241, 1157, 1048, 1028, 983, 846, 740, 699, 496.

[α]$^{27}_D$ -0.88 (*c* 0.63, $CHCl_3$)

(*S*)-*tert*-butyl 2-((3-(1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)oxetan-3-yl)amino)acetate (**73l**)



73l was prepared as a colorless oil (86 mg, 0.20 mmol, 98%) according to GP 1 using *tert*-butyl 2-bromoacetate (78 mg, 0.40 mmol, 2.0 eq), diisopropylethylamine (70 µL, 0.40 mmol,

2.0 eq), **157** (65 mg, 0.20 mmol, 1.0 eq) and acetonitrile (0.50 mL). The reaction time was 48 h at 30 °C. The crude mixture was purified by FC on silica (hex:EA=3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.17 (m, 10H), 5.22 (d, J = 9.1 Hz, 1H), 5.03 (d, J = 13.2 Hz, 2H), 4.51 – 4.36 (m, 3H), 3.68 – 3.49 (m, 2H), 2.96 – 2.66 (m, 2H), 1.50 (s, 9H).

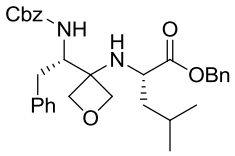
^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.1, 156.4, 137.6, 136.6, 129.2, 128.7, 128.6, 128.2, 128.0, 126.9, 82.1, 78.7, 77.8, 66.9, 62.8, 57.7, 45.7, 36.3, 28.2 ppm.

HRMS (ESI+): m/z calcd. for $C_{25}H_{33}N_2O_5$ $[M+H]^+$ 441.2384, found, 441.2382.

IR (neat): ν [cm^{-1}] =3331, 2928, 2877, 1725, 1537, 1497, 1455, 1394, 1368, 1333, 1242, 1156, 1067, 1028, 981, 843, 773, 747, 698, 603.

***[α]*^{26}D** -11.4 (c 0.58, $CHCl_3$)

(*S*)-benzyl 2-((3-((*S*)-1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)oxetan-3-yl)amino)-4-methylpentanoate (**73m**)



73m was prepared as a colorless oil (55 mg, 0.10 mmol, 52%) according to GP 1 using **224** (142 mg, 0.40 mmol, 2.0 eq), diisopropylethylamine (70 µL, 0.40 mmol, 2.0 eq), **157** (65 mg, 0.20 mmol, 1.0 eq) and acetonitrile (0.50 mL). The reaction time was 48 h at 30 °C. The crude mixture was purified by FC on silica (hex:EA = 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 – 7.01 (m, 15H), 5.33 (d, J = 8.8 Hz, 1H), 5.22 – 4.96 (m, 4H), 4.46 – 4.22 (m, 4H), 4.15 (d, J = 7.1 Hz, 1H), 3.79 – 3.67 (m, 1H), 2.93 – 2.73 (m, 1H), 1.81 – 1.68 (m, 1H), 1.64 – 1.52 (m, 1H), 1.50 – 1.38 (m, 1H), 0.94 (dd, J = 6.6, 5.1 Hz, 6H).

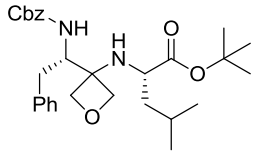
^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.9, 156.6, 137.8, 135.0, 129.3, 128.8, 128.8, 128.7, 128.6, 128.6, 128.6, 128.1, 128.0, 126.8, 79.3, 79.1, 67.2, 66.8, 62.9, 57.7, 54.6, 44.0, 36.0, 29.8, 25.0, 23.1, 22.3 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{32}H_{39}N_2O_5$ $[M+H]^+$ 531.2853, found, 531.2850.

IR (neat): ν [cm^{-1}] = 3337, 3064, 3032, 2958, 2872, 1996, 1729, 1497, 1455, 1369, 1333, 1242, 1168, 1028, 981, 742, 698, 605, 457.

***[α]*^{23}D** -14.9 (*c* 0.65, $CHCl_3$).

(*S*)-*tert*-butyl 2-((3-((*S*)-1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)oxetan-3-yl)amino)-4-methylpentanoate (**73n**)



73n was prepared as a colorless wax (50 mg, 0.20 mmol, 50%) according to GP 1 using **229** (70 mg, 0.40 mmol, 1.1 eq), diisopropylethylamine (40 µL, 0.22 mmol, 1.1 eq), **157** (65 mg, 0.20 mmol, 1.0 eq) and acetonitrile (0.50 mL). After 2.5 d again **229** (70 mg, 0.40 mmol, 1.1 eq) and diisopropylethylamine (40 µL, 0.22 mmol, 1.1 eq) were added. The total reaction time was 3.5 d at 30 °C. The crude mixture was purified by FC on silica (hex:EA=2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 – 7.18 (m, 10H), 5.44 (d, *J* = 9.1 Hz, 1H), 5.13 – 4.99 (m, 2H), 4.53 – 4.35 (m, 3H), 4.29 (d, *J* = 7.0 Hz, 1H), 4.17 (d, *J* = 7.0 Hz, 1H), 3.61 – 3.50 (m, 1H), 2.95 – 2.75 (m, 2H), 1.87 – 1.70 (m, 2H), 1.59 – 1.34 (m, 11H), 1.01 – 0.93 (m, 6H).

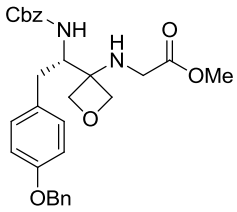
^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.6, 156.6, 137.9, 136.8, 129.3, 128.6, 128.6, 128.1, 127.9, 126.8, 81.6, 79.5, 79.3, 66.7, 62.9, 57.8, 55.2, 44.1, 36.1, 28.1, 25.0, 23.1, 22.4 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{29}H_{41}N_2O_5$ $[M+H]^+$ 497.3010, found, 497.3002.

IR (neat): ν [cm^{-1}] = 3332, 3064, 3031, 2957, 2928, 2871, 1724, 1605, 1537, 1497, 1455, 1393, 1368, 1331, 1243, 1151, 1083, 1064, 1029, 983, 921, 844, 774, 742, 698, 606, 533, 469.

[α]^{27}$_D$ -29.1 (*c* 0.53, $CHCl_3$).

(*S*)-methyl 2-((3-(1-(((benzyloxy)carbonyl)amino)-2-(4-(benzyloxy)phenyl)ethyl)oxetan-3-yl)amino)acetate (**73o**)



73o was prepared as a colorless solid (73 mg, 0.15 mmol, 72%) according to GP 1 using methyl 2-bromoacetate (38 µL, 0.40 mmol, 2.0 eq), diisopropylethylamine (70 µL, 0.40 mmol, 2.0 eq), **165** (65 mg, 0.20 mmol, 1.0 eq) and acetonitrile (0.50 mL). The reaction time was 48 h at 30 °C. The crude mixture was purified by FC on silica (hex:EA = 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 – 7.26 (m, 10H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.18 (d, *J* = 8.8 Hz, 1H), 5.09 – 4.98 (m, 4H), 4.51 – 4.34 (m, 3H), 4.28 – 4.18 (m, 2H), 3.85 – 3.56 (m, 5H), 2.77 (d, *J* = 6.6, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.3, 157.9, 137.1, 136.6, 130.2, 128.7, 128.7, 128.2, 128.1, 128.1, 127.6, 115.2, 78.6, 77.8, 70.2, 66.9, 62.7, 52.5, 44.7, 35.4 ppm.

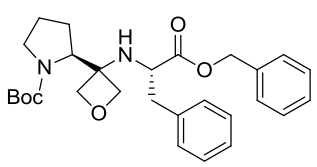
HRMS (ESI+): *m*/*z* calcd. for $C_{29}H_{33}N_2O_6$ $[M+H]^+$ 505.2333, found, 505.2329.

IR (neat): ν [cm^{-1}] = 3336, 3033, 2954, 1718, 1608, 1512, 1455, 1367, 1241, 1178, 1027, 981, 822, 740, 698, 553, 508, 458.

[α]^{24}$_D$ -10.6 (*c* 0.53, $CHCl_3$).

m.p. 111 °C.

(*S*)-tert-butyl 2-(3-(((*S*)-1-(benzyloxy)-1-oxo-3-phenylpropan-2-yl)amino)oxetan-3-yl)pyrrolidine-1-carboxylate (**73p**)[280]



The compound was prepared from **189** (48.5 mg, 0.200 mmol, 1.00 eq) and **226** (155 mg, 0.400 mmol, 2.00 eq) following GP 1. After stirring for 24 h at 30 °C, the mixture was purified by FC on deactivated silica gel (hex:EA = 4:1) and subsequently by FC on silica gel (hex:EA = 3:1) to afford **73p** (57.6 mg, 0.120 mmol, 60%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41–7.27 (m, 5H), 7.25–7.14 (m, 5H), 5.14 (s, 2H), 4.94–4.64 (m, 1H), 4.35 (d, *J* = 7.4 Hz, 1H), 4.28–4.12 (m, 1H), 4.12–3.93 (m, 2H), 3.79 (d, *J* = 7.4 Hz, 1H), 3.74–3.45 (m, 1H), 3.38–3.19 (m, 1H), 3.04 (dd, *J* = 13.1, 4.9 Hz, 1H), 2.78 (dd, *J* = 13.1, 8.7 Hz, 1H), 2.28 (s, 1H), 1.93–1.74 (m, 2H), 1.74–1.55 (m, 1H), 1.43 (m, 10H) ppm.

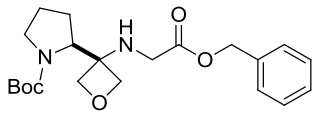
^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.9, 155.3, 138.1, 135.7, 129.9, 128.7, 128.5, 128.5, 128.2, 126.7, 81.6, 80.4, 78.3, 67.1, 64.2, 63.0, 57.0, 48.8, 42.1, 28.6, 27.3, 24.1 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{28}H_{37}N_2O_5$ $[M+H]^+$ 481.2697, found 481.2698.

IR (neat): ν [cm^{-1}] = 2975, 2874, 2360, 2341, 1732, 1693, 1496, 1478, 1455, 1391, 1366, 1256, 1165, 1118, 978, 913, 734, 700.

$[\alpha]^{25}_D$ = –52.4 (c = 0.99, $CHCl_3$).

(S)-tert-butyl 2-(3-((2-(benzyloxy)-2-oxoethyl)amino)oxetan-3-yl)pyrrolidine-1-carboxylate (**73q**)[280]



The compound was prepared from **189** (137 mg, 0.565 mmol, 1.00 eq) and benzyl 2-bromoacetate (194 mg, 0.848 mmol, 1.50 eq) following GP 1. After stirring for 60 h at room temperature, the mixture was purified by FC on silica gel (hex:EA = 3:2) to afford **73q** (191 mg, 0.490 mmol, 87%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43–7.28 (m, 5H), 5.19 (s, 2H), 4.97–4.78 (m, 1H), 4.59 (d, *J* = 7.3 Hz, 1H), 4.40 (d, *J* = 7.3 Hz, 1H), 4.35 (d, *J* = 7.3 Hz, 1H), 4.15 (dd, *J* = 8.4, 4.9 Hz, 1H), 3.79 (d, *J* = 17.6 Hz, 1H), 3.71 (d, *J* = 17.7 Hz, 1H), 3.67–3.51 (m, 1H), 3.36–3.22 (m, 1H), 2.18–1.79 (m, 3H), 1.79–1.63 (m, 2H), 1.45 (s, 9H) ppm.

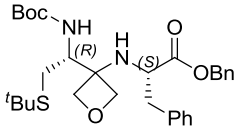
^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.8, 155.6, 135.7, 128.7, 128.5, 128.4, 79.9, 79.9, 77.8, 66.9, 64.4, 62.2, 48.7, 45.0, 28.6, 27.4, 24.3 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{21}H_{30}N_2O_5Na$ $[M+Na]^+$ 413.2047, found 413.2048.

IR (neat): ν [cm^{-1}] = 2975, 2877, 2360, 2341, 1742, ,1689, 1456, 1391, 1365, 1254, 1163, 979, 699, 633.

$[\alpha]^{24}_D$ = –58.0 (c = 0.78, $CHCl_3$).

(*S*)-benzyl 2-((3-((*R*)-1-((tert-butoxycarbonyl)amino)-2-(tert-butylthio)ethyl)-oxetan-3-yl)amino)-3-phenylpropanoate (**73r**)



73r was prepared as a colorless oil (54 mg, 0.099 mmol, 50%) according to GP 1 using **226** (155 mg, 0.400 mmol, 2.00 eq), diisopropylethylamine (70 µL, 0.40 mmol, 2.0 eq), **197** (61 mg, 0.20 mmol, 1.0 eq) and acetonitrile (0.50 mL). The reaction time was 48 h at 30 °C. The crude mixture was purified by FC on silica (hex:EA = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 – 7.11 (m, 10H), 5.21 – 5.04 (m, 3H), 4.48 (d, *J* = 7.4 Hz, 1H), 4.38 (d, *J* = 7.2 Hz, 1H), 4.20 (d, *J* = 7.5 Hz, 1H), 4.14 – 4.04 (m, 1H), 4.01 (d, J = 7.2 Hz, 1H), 3.97 (dd, J = 8.5, 5.3 Hz, 1H), 3.20 – 3.00 (m, 2H), 2.83 (dd, J = 13.3, 8.4 Hz, 1H), 2.53 (ddd, J = 53.7, 12.9, 6.6 Hz, 2H), 1.45 (s, 9H), 1.27 (s, 9H).

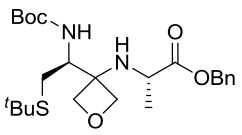
^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.4, 156.0, 137.1, 135.5, 129.7, 128.8, 128.7, 128.6, 128.6, 127.1, 79.7, 79.1, 78.9, 67.3, 63.1, 57.7, 54.8, 46.0, 42.6, 40.9, 30.9, 28.5 ppm.

HRMS (MALDI): *m*/*z* calcd. for $C_{30}H_{43}N_2O_5S$ $[M+H]^+$ 543.2887, found, 543.2875.

IR (neat): ν [cm^{-1}] = 3334, 3088, 3064, 3031, 2962, 2929, 1712, 1497, 1455, 1391, 1365, 1333, 1266, 1250, 1214, 1165, 1113, 980, 698..

[α]$^{24}_D$ -15.1 (*c* 1.85, $CHCl_3$).

(*S*)-benzyl 2-((3-((*S*)-1-((*tert*-butoxycarbonyl)amino)-2-(*tert*-butylthio)ethyl)oxetan-3-yl)amino)propa-noate (***epi*-73v**)



***epi*-73v** was prepared as a colorless wax (41 mg, 0.088 mmol, 44%) according to GP 1 using **222** (130 mg, 0.40 mmol, 2.0 eq), diisopropylethylamine (70 µL, 0.40 mmol, 2.0 eq), ***ent*-197** (61 mg, 0.20 mmol, 1.0 eq) and acetonitrile (0.50 mL). The reaction time was 48 h at 30 °C. The crude mixture was purified by FC on silica (hex:EA = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.32 (m, 5H), 5.18 (d, *J* = 3.8 Hz, 2H), 5.03 (br s, 1H), 4.52 (d, *J* = 7.3 Hz, 2H), 4.41 (d, *J* = 7.4 Hz, 1H), 4.33 (d, *J* = 7.4 Hz, 1H), 4.23 – 4.17 (m, 1H), 3.89 (q, *J* = 7.0 Hz, 1H), 2.79 – 2.62 (m, 2H), 2.27 (br s, 1H), 1.46 (s, 9H), 1.37 (d, *J* = 7.0 Hz, 6H), 1.31 (s, 9H).

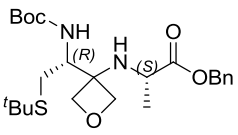
^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.5, 155.9, 135.6, 128.8, 128.6, 128.4, 78.8, 67.2, 63.4, 54.6, 51.2, 42.8, 30.9, 28.8, 28.5, 21.9 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{24}H_{39}N_2O_5S$ $[M+H]^+$ 467.2574, found, 467.2574.

IR (neat): ν [cm^{-1}] = 3337, 3034, 2972, 2930, 2878, 1734, 1713, 1498, 1456, 1391, 1366, 1328, 1250, 1213, 1166, 1047, 1029, 1009, 980, 913, 867, 838, 752, 698, 603, 460.

$[\alpha]_D^{27}$ -16.7 (*c* 0.59, $CHCl_3$)

(*S*)-benzyl 2-((3-((*S*)-1-((*tert*-butoxycarbonyl)amino)-2-(*tert*-butylthio)ethyl)oxetan-3-yl)amino)propa-noate (**73v**)



73v was prepared as a colorless wax (31 mg, 0.066 mmol, 33%) according to GP 1 using **222** (130 mg, 0.40 mmol, 2.0 eq), diisopropylethylamine (70 µL, 0.40 mmol, 2.0 eq), **197** (61 mg, 0.20 mmol, 1.0 eq) and acetonitrile (0.50 mL). The reaction time was 66 h at 30 °C. The crude mixture was purified by FC on silica (hex:EA = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42-7.32 (m, 5H), 5.27 – 5.15 (m, 3H), 4.60 (d, *J* = 7.1 Hz, 1H), 4.54 (d, *J* = 7.5 Hz, 1H), 4.42 (d, *J* = 7.1 Hz, 1H), 4.33 (d, *J* = 7.5 Hz, 1H), 4.25 – 4.13 (m, 1H), 3.84 (q, *J* = 7.0 Hz, 1H), 2.85 – 2.65 (m, 2H), 1.49 (s, 9H), 1.41 (d, *J* = 7.0 Hz, 3H), 1.34 (s, 9H).

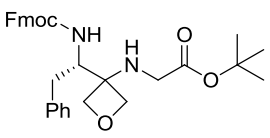
^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.3, 155.9, 135.5, 128.6, 128.4, 128.3, 79.1, 78.9, 67.0, 63.1, 54.5, 51.4, 42.6, 30.8, 28.4, 21.0 ppm.

HRMS (MALDI): *m*/*z* calcd. for $C_{24}H_{39}N_2O_5S$ $[M+H]^+$ 467.2574, found, 467.2576.

IR (neat): ν [cm^{-1}] = 3334, 3088, 3064, 3031, 2962, 2929, 1712, 1497, 1455, 1365, 1266, 1250, 1213, 1164, 980, 749, 698.

$[\alpha]_D^{22}$ –2.10 (*c* 0.25, $CHCl_3$).

(*S*)-tert-butyl 2-((3-(1-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-phenylethyl)oxetan-3-yl)amino)acetate (**73w**)



To a mixture of **73m** (71 mg, 0.16 mmol, 1.0 eq.) and Pd/C (8.58 mg, 8.06 µmol) under N_2 was added MeOH (1.6 mL). The suspension was stirred under H_2 (balloon) for 3.5 h, filtered through a syringe filter (5 mL MeOH). The filtrate was concentrated. The residue was redissolved in DCM and triethylamine and Fmoc-Cl were added. After stirring for 14 h, the mixture was concentrated and purified by FC on silica (hex:EA = 2:1) to yield the title compound **73w** (49 mg, 0.093 mmol, 58%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 7.5 Hz, 1H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 5.26 (d, *J* = 9.1 Hz, 1H), 4.50 – 4.08 (m, 10H), 3.70 – 3.53 (m, 2H), 2.93 – 2.75 (m, 2H), 1.52 (s, 9H).

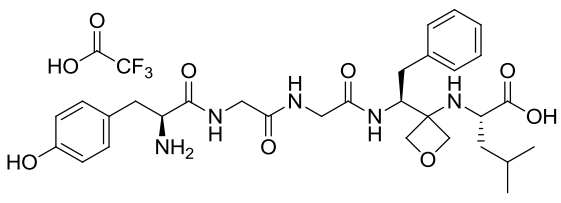
^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.3, 156.4, 143.9, 141.5, 137.6, 129.2, 128.8, 127.8, 127.2, 126.9, 125.2, 120.1, 82.1, 78.6, 77.9, 66.8, 62.8, 57.6, 47.4, 45.7, 36.2, 28.3 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{32}H_{37}N_2O_5$ $[M+H]^+$ 529.2697, found, 529.2697.

IR (neat): ν [cm^{-1}] = 3329, 3065, 2927, 1725, 1605, 1537, 1496, 1478, 1451, 1394, 1368, 1331, 1243, 1156, 1082, 1033, 980, 842, 758, 741, 701, 667, 621, 572, 537.

***[α]*^{26}D** -12.7 (*c* 0.39, $CHCl_3$).

(*S*)-2-((3-((*S*)-1-(2-(2-((*S*)-2-amino-3-(4-hydroxyphenyl)propanamido)acetamido)acetamido)-2-phenylethyl)oxetan-3-yl)amino)-4-methylpentanoic acid, TFA (**247e**)



To a solution of 1-hydroxypyrrolidine-2,5-dione (11 mg, 0.098 mmol, 1.3 eq.) and (S)-5-(4-(benzyloxy)benzyl)-3,6,9-

trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oic acid (40 mg, 0.077 mmol, 1.0 eq.)[282] in THF (0.4 mL) at 0 °C was added EDC·HCl (19 mg, 0.098 mmol, 1.3 eq.) suspended in CH_2Cl_2 (0.4 mL). The mixture was stirred at r.t. for 18 h. The reaction was quenched with sat. aq. NH_4Cl solution (10 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give crude (*S*)-2,5-dioxopyrrolidin-1-yl 5-(4-(benzyloxy)benzyl)-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oate which was used in the next step without further purification.

To a mixture of **73m** (31 mg, 0.058 mmol, 1.0 eq.) and Pd/C (6.2 mg, 5.8 μmol, 10 mol-% Pd) was added MeOH (0.6 mL). The mixture was stirred under H_2 (balloon) for 30 min. N-methylmorpholine (0.013 ml, 0.117 mmol, 2.0 eq) was added and the mixture was stirred under H_2 (balloon) for another 30 min. The suspension was filtered over celite. The filtrate was concentrated to give crude (S)-2-((3-((S)-1-amino-2-phenylethyl)oxetan-3-yl)amino)-4-methylpentanoic acid containing N-methylmorpholine.

To a solution of (*S*)-2,5-dioxopyrrolidin-1-yl 5-(4-(benzyloxy)benzyl)-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oate (36 mg, 0.059 mmol, 1.0 eq.) and (S)-2-((3-((S)-1-amino-2-phenylethyl)oxetan-3-yl)amino)-4-methylpentanoic acid (18 mg, 0.059 mmol, 1.0 eq) in EtOAc (0.6 mL) was added N-methylmorpholine (0.013 mL, 0.12 mmol, 2.0 eq.). The mixture was stirred for 20 h before the addition of aqueous $NaHSO_4$ solution (1 M, 20 mL). The mixture was extracted with EtOAc(3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give crude (*S*)-2-((3-((5*S*,14*S*)-5-(4-(benzyloxy)benzyl)-3,6,9,12-tetraoxo-1,15-diphenyl-2-oxa-4,7,10,13-tetraazapentadecan-14-yl)oxetan-3-yl)amino)-4-methylpentanoic acid as a colorless powder and was used in the next step without further purification.

To a mixture of (*S*)-2-((3-((5*S*,14*S*)-5-(4-(benzyloxy)benzyl)-3,6,9,12-tetraoxo-1,15-diphenyl-2-oxa-4,7,10,13-tetraazapentadecan-14-yl)oxetan-3-yl)amino)-4-methylpentanoic acid (47 mg, 0.058 mmol, 1.0 eq) and Pd/C (6.2 mg, 5.8 μmol,

10 mol-% Pd) was added MeOH/DCM (4/1, 1.5 mL). The mixture was stirred under H_2 (balloon) for 5 h. The suspension was filtered over celite. The filtrate was concentrated and the residue was purified by preparative HPLC (Waters 2545, 2767, Reprosil Gold 120 C18, 5 µm, 125 x 20 mm, 0.1 % TFA in MeCN/H2O, 20:80 to 90:10, 26.5 mL/min, R_t=8.9 min) to give **247e**·TFA (5 mg, 7.2 µmol, 12% over 3 steps).

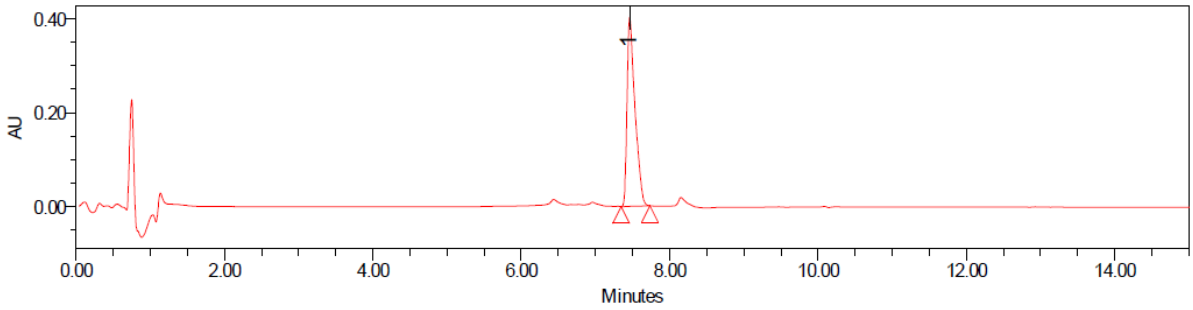
^{1}H NMR (600 MHz, MeOD) δ = 7.29 – 7.25 (m, 4H), 7.23 – 7.16 (m, 1H), 7.10 (d, J = 8.5 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 4.64 (dd, J = 10.3, 4.1 Hz, 1H), 4.58 – 4.51 (m, 3H), 4.40 (d, J = 7.4 Hz, 1H), 4.09 – 3.96 (m, 3H), 3.87 (d, J = 16.7 Hz, 1H), 3.82 – 3.76 (m, 2H), 3.71 (d, J = 16.7 Hz, 1H), 3.13 (dd, J = 14.2, 6.6 Hz, 1H), 3.04 (dd, J = 14.2, 4.2 Hz, 1H), 2.95 (dd, J = 14.1, 8.0 Hz, 1H), 2.77 (dd, J = 14.1, 10.3 Hz, 1H), 1.94 – 1.87 (m, 1H), 1.69 – 1.62 (m, 1H), 1.57 – 1.51 (m, 1H), 1.01 (d, J = 6.7 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H)

^{13}C NMR (150 MHz, MeOD) δ = 179.1, 171.7, 171.4, 170.5, 162.7, 158.3, 139.5, 131.6, 131.5, 130.2, 129.5, 127.6, 126.0, 116.8, 79.1, 79.1, 64.7, 56.4, 56.1, 55.9, 44.2, 43.3, 37.7, 35.7, 26.1, 23.2, 22.7.

HRMS (ESI+): m/z calcd. for $C_{30}H_{42}N_5O_7$ $[M+H]^+$ 584.3079, found, 584.3079.

IR (neat): ν [cm^{-1}] = 3290, 2960, 1673, 1518, 1455, 1203, 1139, 839, 801, 723.

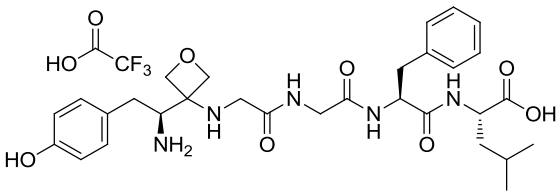
Analytical HPLC



Waters e2695, 2998, 0.1% TFA in acetonitrile/water, 0-2 min 90% water, 2-12 min linear gradient to 10% water, 12-15 min linear gradient to 90% water, Reprosil-Gold 2.0x120 mm, C18, 3 µm

Retention time: 7.46 min.

(*S*)-2-((*S*)-2-(2-(2-((3-((*S*)-1-amino-2-(4-hydroxyphenyl)ethyl)oxetan-3-yl)amino)acetamido)acetamido)-3-phenylpropanamido)-4-methylpentanoic acid, TFA (**247b**)



To a solution of **73o** (58 mg, 0.12 mmol, 1.0 eq.) in THF (1.1 mL) at 0 °C was added aqueous LiOH solution (1 M, 0.58 mL, 0.58 mmol, 5.0 eq.) The mixture was stirred for 30 min before quenching with saturated aqueous $NaHCO_3$ solution (20 mL). The mixture was extracted with EtOAc(3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give crude (*S*)-2-((3-(1-(((benzyloxy)carbonyl)amino)-2-(4-(benzyloxy)phenyl)ethyl)oxetan-3-yl)amino)acetic acid (52 mg) which was used in the next step without further purification.

To a solution of (*S*)-2-((3-(1-(((benzyloxy)carbonyl)amino)-2-(4-(benzyloxy)phenyl)ethyl)oxetan-3-yl)amino)acetic acid (52 mg, 0.11 mmol, 1.0 eq) in DMF (0.66 mL) were sequentially added DIPEA (74 μL, 0.42 mmol, 4 eq.), (*S*)-benzyl 2-((*S*)-2-(2-aminoacetamido)-3-phenylpropanamido)-4-methylpentanoate, TFA (114 mg, 0.21 mmol, 2.0 eq.)[166] and HATU (44 mg, 0.12 mmol, 1.1 eq.) at 0 °C. The mixture was stirred at 0 °C for 2 h and at r.t. for 14 h. The mixture was filtered through a pad of silica (EtOAc:hexane = 2:1). The residue was lyophilized twice from benzene (30 mL) to give crude (*S*)-benzyl 2-((*S*)-2-(2-(2-((3-((*S*)-1-(((benzyloxy)carbonyl)amino)-2-(4-(benzyloxy)phenyl)ethyl)oxetan-3-yl)amino)acetamido)acetamido)-3-phenylpropanamido)-4-methylpentanoate as a colorless foam (61 mg) which was used in the next step without further purification.

To a mixture of (*S*)-benzyl 2-((*S*)-2-(2-(2-((3-((*S*)-1-(((benzyloxy)carbonyl)amino)-2-(4-(benzyloxy)phenyl)ethyl)oxetan-3-yl)amino)acetamido)acetamido)-3-phenylpropanamido)-4-methylpentanoate (51 mg, 0.057 mmol, 1.0 eq) and Pd/C (6.0 mg, 5.7 µmol, 10 mol-% Pd) was added MeOH (1.1 mL). The mixture was stirred under H_2 (balloon) for 3 h. The suspension was filtered over celite. The filtrate was concentrated and the residue was purified by preparative HPLC (Waters 2545, 2767, Reprosil Gold 120 C18, 5 µm, 125 x 20 mm, 0.1 % TFA in MeCN/H2O, 20:80 to 90:10, 20.0 mL/min, R_t=14.4 min) to give **247b** (20 mg, 29 µmol, 24% over 3 steps).

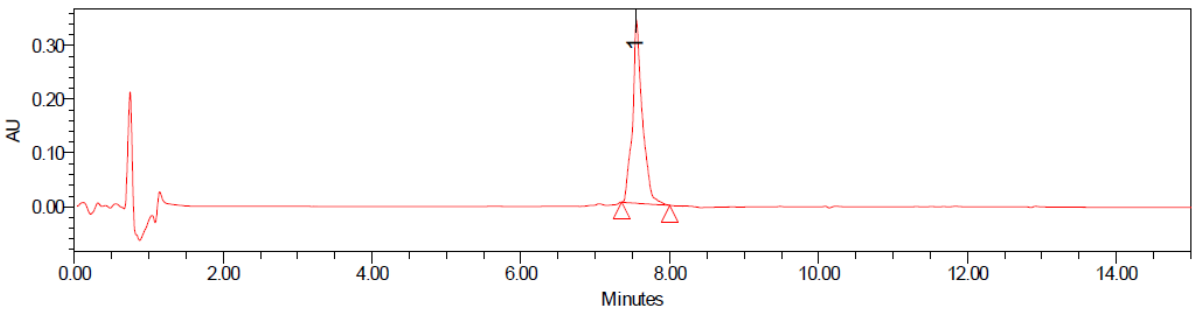
^{1}H NMR (600 MHz, MeOD) δ = 7.29 – 7.22 (m, 5H), 7.17 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 4.77 – 4.59 (m, 2H), 4.47 – 4.39 (m, 3H), 3.92 – 3.80 (m, 3H), 3.67 – 3.52 (m, 2H), 3.23 – 3.16 (m, 1H), 3.11 (dd, J = 14.6, 5.1 Hz, 1H), 2.91 – 2.80 (m, 2H), 1.75 – 1.61 (m, 3H), 0.95 (d, J = 6.3 Hz, 3H), 0.90 (d, J = 6.3 Hz, 3H).

^{13}C NMR (150 MHz, MeOD) δ = 175.6, 175.3, 173.5, 171.3, 158.2, 138.3, 131.3, 130.4, 130.4, 129.5, 129.4, 127.8, 127.2, 117.0, 117.0, 78.5, 77.6, 62.6, 58.6, 55.8, 52.2, 46.5, 42.9, 41.6, 39.0, 34.1, 26.0, 26.0, 23.4, 23.4, 21.9.

HRMS (ESI+): *m/z* calcd. for $C_{30}H_{42}N_5O_7$ $[M+H]^+$ 584.3079, found, 584.3073.

IR (neat): ν [cm^{-1}] = 3289, 2961, 1668, 1518, 1441, 1278, 1202, 1142, 946, 838, 800, 723.

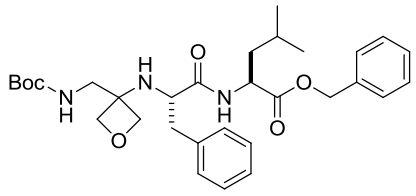
Analytical HPLC



Waters e2695, 2998, 0.1% TFA in acetonitrile/water, 0-2 min 90% water, 2-12 min linear gradient to 10% water, 12-15 min linear gradient to 90% water, Reprosil-Gold 2.0x120 mm, C18, 3 µm

Retention time: 7.56 min.

(*S*)-benzyl 2-((*S*)-2-((3-(((tert-butoxycarbonyl)amino)methyl)oxetan-3-yl)amino)-3-phenylpropanamido)-4-methylpentanoate (**250**)[280]



To a solution of **73d** (187 mg, 0.424 mmol, 1.00 eq) in MeOH (5.66 mL) and EtOAc (2.83 mL) was added Pd/C (22.6 mg, 0.021 mmol, 5 mol-% Pd) and the mixture was stirred under an atmosphere of H_2 (balloon) for 1 h. The catalyst was filtered off over a sintered glass fritt covered with a filter paper and the solid was washed with MeOH/H_2O and EtOAc until the product had completely dissolved. The combined layers were concentrated to dryness to give crude (S)-2-((3-(((tert-butoxycarbonyl)amino)methyl)oxetan-3-yl)amino)-3-phenylpropanoic acid (149 mg, 0.425 mmol, quant.) as a colorless solid which was used in the next step without further purification.

To a solution of(*S*)-2-((3-(((tert-butoxycarbonyl)amino)methyl)oxetan-3-yl)amino)-3-phenylpropanoic acid (149 mg, 0.425 mmol, 1.0 eq) in DMF (2.12 mL) at 0 °C were added DIPEA (208 µl, 1.19 mmol, 2.80 eq.), then (*S*)-benzyl 2-amino-4-methylpentanoate hydrochloride (132 mg, 0.510 mmol, 1.20 eq.), and then HATU (194 mg, 0.510 mmol, 1.20 eq) and the mixture was stirred at 0 °C for 2 h and then warmed to r.t. over night. After stirring at r.t. for 18 h, the mixture was poured into saturated $NaHCO_3$ solution and extracted with DCM (4 x 10 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated to dryness. The residue was purified by FC on SiO_2 (hexane:EA 1:1) to yield **250** (187 mg, 0.338 mmol, 80%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 9.0 Hz, 1H), 7.39 – 7.30 (m, 7H), 7.29 – 7.20 (m, 3H), 5.21 – 5.09 (m, 2H), 5.03 (d, J = 5.8 Hz, 1H), 4.68 (td, J = 9.2, 4.8 Hz, 1H), 4.15 (d, J = 6.9 Hz, 2H), 4.10 (d, J = 6.8 Hz, 1H), 4.05 (d, J = 6.9 Hz, 1H), 3.53 (dd, J = 9.5, 3.8 Hz, 1H), 3.40 (dd, J = 14.4, 6.9 Hz, 1H), 3.26 (dd, J = 14.2, 5.5 Hz, 2H), 2.67 (dd, J = 13.7, 9.5 Hz, 1H), 1.88 (s, 1H), 1.74 – 1.62 (m, 1H), 1.61 – 1.51 (m, 2H), 1.43 (s, 9H), 0.93 (t, J = 6.6 Hz, 6H).

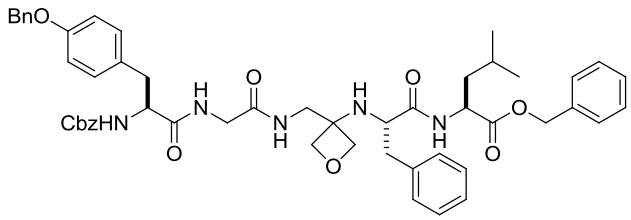
^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.1, 173.2, 156.8, 137.1, 135.4, 129.3, 129.1, 128.8, 128.7, 128.5, 127.5, 79.6, 78.8, 78.3, 67.4, 60.5, 59.0, 50.5, 45.8, 41.5, 40.3, 28.5, 25.0, 23.1, 21.8.

HRMS (ESI+): m/z calcd. for $C_{31}H_{44}N_3O_6$ $[M+H]^+$ 554.3225, found, 554.3230.

IR (neat): ν [cm^{-1}] = 3323, 2959, 2872, 1708, 1660, 1505, 1247, 1166, 974, 748, 698.

[α]^{20}$_D$ -40.6 (c 1.00, $CHCl_3$).

(*S*)-benzyl 2-((*S*)-2-((3-((*S*)-5-(4-(benzyloxy)benzyl)-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazaundecan-11-yl)oxetan-3-yl)amino)-3-phenylpropanamido)-4-methylpentanoate (**251**)[280]



To a solution of **250** (183 mg, 0.331 mmol, 1.00 eq.) in CH_2Cl_2 (2.98 mL) was added TFA (0.33 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min at r.t. for 4 h. Then, toluene (3 mL) was added and the mixture was evaporated to dryness. The residue was taken up in toluene and again evaporated to dryness. The residue was dissolved in Et_2O and again evaporated to dryness to leave a yellow foam, which was dried in vacuo for 1 h and directly used in the next step without further purification.

To a solution of (*S*)-benzyl 2-((*S*)-2-((3-(aminomethyl)oxetan-3-yl)amino)-3-phenylpropanamido)-4-methylpentanoate 2,2,2-trifluoroacetate (188 mg,

0.331 mmol, 1.00 eq.) in DMF (2.07 mL) at 0 °C were added DIPEA (174 µl, 0.994 mmol, 3.00 eq.), then (*S*)-2-(2-(((benzyloxy)carbonyl)amino)-3-(4-(benzyloxy)phenyl)propanamido)acetic acid (199 mg, 0.431 mmol, 1.30 eq.)[169], and HATU (164 mg, 0.431 mmol, 1.30 eq.) and the mixture was stirred at 0 °C for 2 h and at r.t. for 21 h. The mixture was poured into sat. $NaHCO_3$ solution and extracted with DCM (3 x 10 mL) and EA (2 x 10 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated to dryness. The residue was purified by CC on SiO_2 (EA:MeOH 50:1) to yield **251** as a colorless oil (220 mg, 0.245 mmol, 74%).

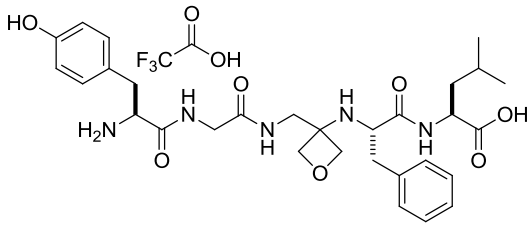
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 9.2 Hz, 1H), 7.42 – 7.17 (m, 20H), 7.04 (d, *J* = 8.6 Hz, 4H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.36 (d, *J* = 6.6 Hz, 1H), 5.13 (q, *J* = 12.2 Hz, 2H), 5.04 – 4.96 (m, 4H), 4.77 (td, *J* = 9.3, 4.6 Hz, 1H), 4.24 (dd, *J* = 21.9, 6.8 Hz, 2H), 4.13 – 3.91 (m, 4H), 3.79 (dd, *J* = 17.1, 5.2 Hz, 1H), 3.60 – 3.42 (m, 3H), 3.25 (dd, *J* = 13.7, 3.7 Hz, 1H), 3.05 (dd, *J* = 14.0, 6.3 Hz, 1H), 2.93 (dd, *J* = 14.0, 7.7 Hz, 1H), 2.65 (dd, *J* = 13.7, 9.6 Hz, 1H), 1.82 (s, 2H), 1.66 – 1.47 (m, 2H), 0.93 (d, *J* = 6.0 Hz, 3H), 0.88 (d, *J* = 5.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.6, 174.1, 171.5, 169.6, 158.0, 156.4, 136.9, 136.8, 135.7, 134.9, 130.4, 130.2, 129.2, 129.1, 129.0, 129.0, 128.7, 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 128.2, 128.2, 128.0, 128.0, 127.9, 127.5, 127.5, 127.4, 115.1, 70.0, 67.7, 67.2, 60.5, 59.2, 56.9, 50.3, 44.3, 42.8, 41.6, 40.4, 37.1, 24.9, 23.0, 21.7.

HRMS (ESI+): *m*/*z* calcd. for $C_{52}H_{60}N_5O_9$ $[M+H]^+$ 898.4386, found, 898.4388.

[α]$^{25}_D$ –8.90 (*c* 1.35, $CHCl_3$).

(S)-2-((S)-2-((3-((2-((S)-2-amino-3-(4-hydroxyphenyl)propanamido)acetamido)methyl)oxetan-3-yl)amino)-3-phenylpropanamido)-4-methylpentanoic acid (**247d**)[280]



To a solution of **251** (87 mg, 0.097 mmol, 1.0 eq.) in MeOH (4.8 mL) was added Pd/C (21 mg, 0.019 mmol, 20 mol-% Pd) and the mixture was stirred under an atmosphere of H_2 (balloon) for 1 h. The catalyst was filtered off over celite. The filtrate was concentrated to dryness to give crude **247d** which was purified by preparative HPLC (Waters 2545, 2767, Reprosil Gold 120 C18, 5 µm, 125 x 20 mm, 0.1 % TFA in MeCN/H2O, 20:80 to 90:10, 20.0 mL/min, R_t=12.9 min) to yield **247d**·TFA as the as a yellowish solid (22 mg, 0.031 mmol, 33%).

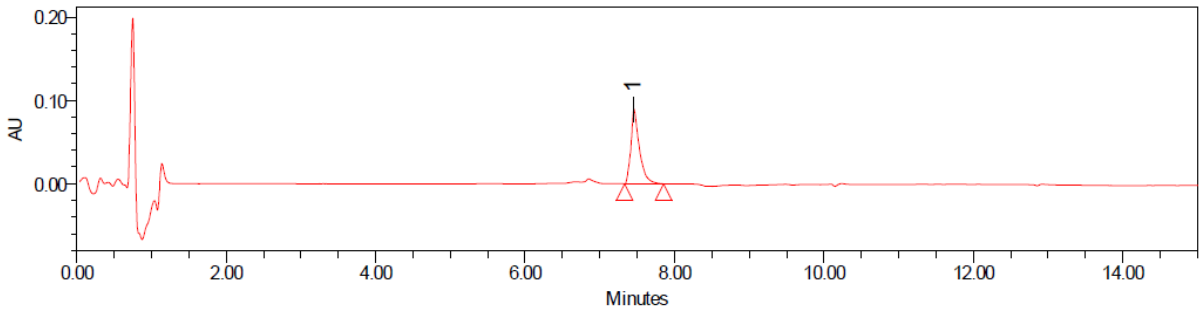
^{1}H NMR (600 MHz, MeOD) δ = 7.35 – 7.29 (m, 3H), 7.27 – 7.23 (m, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 4.45 (dd, *J* = 7.9, 6.8 Hz, 1H), 4.28 (dd, *J* = 6.8, 3.9 Hz, 1H), 4.20 (d, *J* = 6.8 Hz, 1H), 4.14 (d, *J* = 6.9 Hz, 1H), 4.05 (dd, *J* = 8.0, 6.5 Hz, 1H), 3.95 (d, *J* = 16.7 Hz, 1H), 3.72 (d, *J* = 16.7 Hz, 1H), 3.69 – 3.63 (m, 2H), 3.46 (d, *J* = 14.2 Hz, 1H), 3.18 – 3.09 (m, 2H), 2.96 (dd, *J* = 14.2, 8.0 Hz, 1H), 2.75 (dd, *J* = 13.6, 9.0 Hz, 1H), 1.68 – 1.59 (m, 3H), 0.95 (d, *J* = 6.3 Hz, 3H), 0.92 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (150 MHz, MeOD) δ = 177.6, 176.6, 175.7, 171.7, 170.5, 162.9, 162.6, 158.4, 158.3, 138.6, 138.6, 131.7, 131.6, 130.7, 130.6, 129.8, 128.2, 126.0, 116.9, 79.9, 79.7, 61.6, 60.0, 56.2, 52.0, 44.6, 43.3, 41.7, 41.2, 37.7, 26.1, 23.4, 21.8 ppm.

HRMS (MALDI): *m*/*z* calcd. for $C_{30}H_{41}N_5NaO_7$ $[M+Na]^+$ 606.2898, found, 606.2899.

IR (neat): ν [cm^{-1}] = 2964, 1673, 1518, 1201, 1141, 839, 800, 723.

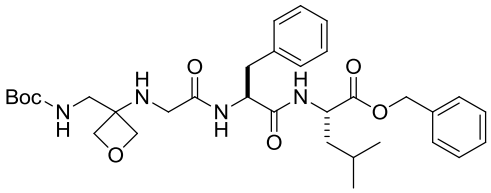
Analytical HPLC



Waters e2695, 2998, 0.1% TFA in acetonitrile/water, 0-2 min 90% water, 2-12 min linear gradient to 10% water, 12-15 min linear gradient to 90% water, Reprosil-Gold 2.0x120 mm, C18, 3 µm

Retention time: 7.46 min.

2-((S)-2-(2-((3-(((tert-butoxycarbonyl)amino)methyl)oxetan-3-yl)amino)acetamido)-3-phenylpropanamido)-4-methylpentanoate (**249**)[280]



To a solution of benzyl **73c** (82.9 mg, 0.237 mmol, 1.00 eq.) in MeOH (2.37 mL) was added Pd/C (12.6 mg, 0.012 mmol, 5.00 mol-% Pd) and the mixture was stirred under an atmophere of H_2 for 1 h at r.t. After complete consumption of the starting material, the mixture was filtered over Celite and washed with EA, MeOH and DCM. The filtrate was concentrated to yield 2-((3-(((tert-butoxycarbonyl)amino)methyl)oxetan-3-yl)amino)acetic acid (59 mg) as a colorless solid which was used in the next step without further purification.

To a solution of (*S*)-benzyl 2-((*S*)-2-amino-3-phenylpropanamido)-4-methylpentanoate hydrochloride (101 mg, 0.249 mmol, 1.10 eq.)[168] in DMF (0.47 mL) at 0 °C were added DIPEA (58.0 µl, 0.332 mmol, 2.80 eq.), then 2-((3-(((tert-butoxycarbonyl)amino)methyl)oxetan-3-yl)amino)acetic acid (35.4 mg, 0.142 mmol, 1.00 eq.), and then HATU (54.1 mg, 0.142 mmol, 1.20 eq.) and the mixture was stirred at 0 °C for 2 h and then at r.t. for 18 h. The mixture was

poured into sat. $NaHCO_3$ solution and extracted with EA (4 x 10 mL). The combined organic fractions were washed with brine, dried over $MgSO_4$ and concentrated to dryness. The residue was purified by CC on SiO_2 (EA:MeOH 50:1) to yield **249** (120 mg, 0.196 mmol, 87%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.30 (m, 5H), 7.27 – 7.15 (m, 5H), 6.54 (d, *J* = 7.9 Hz, 1H), 5.13 (s, 3H), 4.73 – 4.62 (m, 1H), 4.56 (td, *J* = 8.3, 5.2 Hz, 1H), 4.38 – 4.28 (m, 2H), 4.26 (s, 2H), 3.45 – 3.32 (m, 2H), 3.30 (s, 2H), 3.15 – 2.99 (m, 2H), 2.06 (s, 1H), 1.62 – 1.49 (m, 3H), 1.45 (s, 9H), 0.88 – 0.81 (m, 6H).

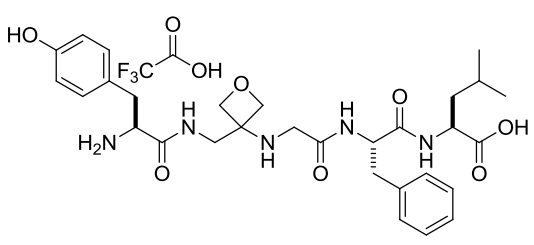
^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.4, 171.9, 170.8, 156.7, 136.5, 135.4, 129.3, 128.8, 128.7, 128.6, 128.4, 127.2, 80.0, 78.4, 67.2, 60.5, 54.2, 51.2, 46.2, 45.4, 41.2, 38.0, 28.5, 24.9, 22.8, 22.0.

HRMS (ESI+): *m*/*z* calcd. for $C_{33}H_{46}N_4NaO_7$ $[M+H]^+$ 633.3259, found, 633.3260.

IR (neat): ν [cm^{-1}] = 3317, 2961, 2878, 1660, 1652, 1519, 1504, 1251, 1164, 973, 841, 741, 690.

[α]$^{20}_D$ –17.8 (*c* 0.95, $CHCl_3$).

(*S*)-2-((*S*)-2-(2-((3-(((*S*)-2-amino-3-(4-hydroxyphenyl)propanamido)methyl)oxetan-3-yl)amino)acetamido)-3-phenylpropanamido)-4-methylpentanoic acid (**247c**)[280]



To a solution of **249** (107 mg, 0.177 mmol, 1.00 eq.) in CH_2Cl_2 (1.59 mL) was added TFA (0.18 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and at r.t. for 4 h. Then, toluene (3 mL) was added and the mixture was evaporated to dryness. The residue was taken up in toluene and again evaporated to dryness. The residue was dissolved in Et_2O and again

evaporated to dryness to leave a yellow foam (crude (S)-benzyl 2-((S)-2-(2-((3-(aminomethyl)oxetan-3-yl)amino)acetamido)-3-phenylpropanamido)-4-methylpentanoate 2,2,2-trifluoroacetate, which was dried *in vacuo* for 1 h and directly used in the next step without further purification.

To a solution of (*S*)-benzyl 2-((*S*)-2-(2-((3-(aminomethyl)oxetan-3-yl)amino)acetamido)-3-phenylpropanamido)-4-methylpentanoate 2,2,2-trifluoroacetate (110 mg, 0.176 mmol, 1.00 eq.) in DMF (0.88 mL) at 0 °C were added DIPEA (92 µl, 0.528 mmol, 3.00 eq.), then (*S*)-2-(((benzyloxy)carbonyl)amino)-3-(4-(benzyloxy)phenyl)propanoic acid (93 mg, 0.229 mmol, 1.30 eq.), and HATU (87 mg, 0.229 mmol, 1.30 eq.) and the mixture was stirred at 0 °C for 2 h and at r.t. for 21 h. The mixture was poured into sat. $NaHCO_3$ solution and extracted with DCM (5 x 10 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated to dryness. The residue was passed over a plug of silica (EA:MeOH 50:1). The product was used in the next step without further purification.

To a solution of (*S*)-2-((*S*)-2-(2-((3-(((*S*)-2-amino-3-(4-hydroxyphenyl)propanamido)methyl)oxetan-3-yl)amino)acetamido)-3-phenylpropanamido)-4-methylpentanoic acid (50 mg, 0.056 mmol, 1.0 eq.) in MeOH (3 mL) was added Pd/C (12 mg, 0.011 mmol, 20 mol-% Pd) and the mixture was stirred under an atmosphere of H_2 (balloon) for 1 h. The catalyst was filtered off over celite. The filtrate was concentrated to dryness to give crude (*S*)-2-((*S*)-2-(2-((3-(((*S*)-2-amino-3-(4-hydroxyphenyl)propanamido)methyl)oxetan-3-yl)amino)acetamido)-3-phenylpropanamido)-4-methylpentanoic acid which was purified by preparative HPLC (Waters 2545, 2767, Reprosil Gold 120 C18, 5 µm, 125 x 20 mm, 0.1 % TFA in MeCN/H2O, 20:80 to 90:10, 20.0 mL/min, R_t=14.4 min) to yield the title compound as the as a colorless solid (27 mg, 0.047 mmol, 27% over two steps).

^{1}H NMR (500 MHz, MeOD) δ = 7.30 – 7.25 (m, 4H), 7.23 – 7.18 (m, 1H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 4.76 (dd, *J* = 9.0, 4.9 Hz, 1H), 4.48 – 4.38 (m,

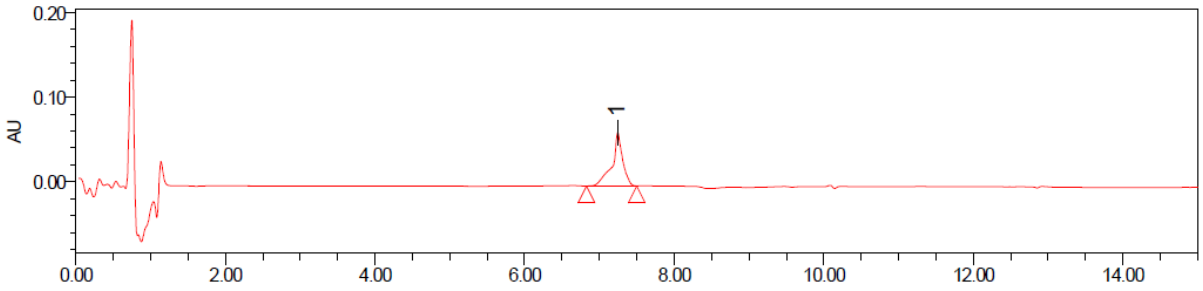
3H), 4.35 (dd, *J* = 7.2, 2.5 Hz, 2H), 3.99 (dd, *J* = 8.2, 6.7 Hz, 1H), 3.62 (d, *J* = 14.4 Hz, 1H), 3.50 (d, *J* = 14.2 Hz, 2H), 3.42 (d, *J* = 16.6 Hz, 1H), 3.23 (dd, *J* = 14.1, 4.9 Hz, 1H), 3.11 (dd, *J* = 14.1, 6.7 Hz, 1H), 2.99-2.89 (m, 2H), 1.76 – 1.62 (m, 3H), 0.96 (d, *J* = 6.3 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, MeOD) δ = 175.6, 173.6, 170.9, 170.9, 158.3, 138.0, 131.5, 130.5, 129.5, 127.9, 126.0, 116.9, 78.4, 61.9, 56.1, 55.3, 52.2, 46.1, 43.7, 41.6, 39.2, 37.8, 26.0, 23.4.

HRMS (ESI+): *m*/*z* calcd. for $C_{30}H_{42}N_5O_7$ $[M+H]^+$ 584.3079, found, 584.3083.

IR (neat): ν [cm^{-1}] = 3259, 3087, 2962, 1669, 1615, 1518, 1441, 1278, 1200, 1143, 1089, 946, 842, 800, 723, 702, 663, 559.

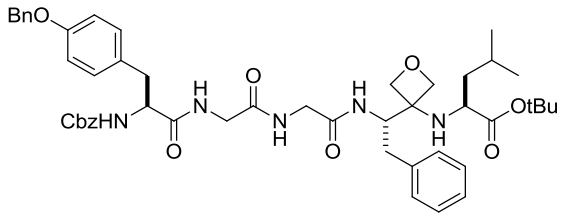
Analytical HPLC



Waters e2695, 2998, 0.1% TFA in acetonitrile/water, 0-2 min 90% water, 2-12 min linear gradient to 10% water, 12-15 min linear gradient to 90% water, Reprosil-Gold 2.0x120 mm, C18, 3 µm

Retention time: 7.25 min.

(S)-tert-butyl 2-((3-((5S,14S)-5-(4-(benzyloxy)benzyl)-3,6,9,12-tetraoxo-1,15-diphenyl-2-oxa-4,7,10,13-tetraazapentadecan-14-yl)oxetan-3-yl)amino)-4-methylpentanoate (**252**)



To a solution of (S)-tert-butyl 2-((3-((S)-1-amino-2-phenylethyl)oxetan-3-yl)amino)-4-methylpentanoate (0.037 g, 0.102 mmol, 1.00 eq) in DMF (340 µL) were sequentially added DIPEA (27 µL, 0.155 mmol, 1.50eq), (S)-5-(4-(benzyloxy)benzyl)-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oic acid (0.058 g, 0.112 mmol, 1.10 eq), HATU (0.043 g, 0.112 mmol, 1.10 eq) at 0 °C. The mixture was stirred at 0 °C for 1 h and at r.t. for 3 h. The mixture was purified by FC on SiO2 (EA) to yield **252** (30 mg, 0.035 mmol, 34%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 – 6.98 (m, 20H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.89 – 5.77 (m, 1H), 5.13 – 4.97 (m, 4H), 4.84 – 4.73 (m, 1H), 4.40 (d, *J* = 7.3 Hz, 1H), 4.35 – 4.24 (m, 3H), 4.21 – 4.03 (m, 2H), 3.87 – 3.62 (m, 4H), 3.14 – 2.75 (m, 4H), 1.90 – 1.72 (m, 3H), 1.61 – 1.37 (m, 13H), 1.00 (dd, *J* = 8.4, 6.6 Hz, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 177.9, 172.6, 168.9, 158.0, 156.8, 137.9, 136.8, 135.7, 130.1, 129.2, 128.6, 128.6, 128.5, 128.3, 128.1, 127.8, 127.5, 126.6, 115.2, 81.9, 79.2, 70.0, 67.4, 62.7, 57.3, 56.0, 54.8, 53.4, 44.0, 43.5, 43.0, 36.9, 35.7, 29.7, 27.9, 25.0, 23.0, 22.2 ppm.

HRMS (MALDI): *m*/*z* calcd. for $C_{49}H_{61}N_5Na_1O_9$ $[M+Na]^+$ 886.4361, found, 866.4361.

IR (neat): ν [cm^{-1}] = 3311, 2930, 1717, 1653, 1612, 1512, 1454, 1368, 1333, 1241, 1177, 1151, 1027, 982, 843.

[α]$^{25}_{D}$ +5.80 (*c* 0.90, $CHCl_3$, Hg, λ = 365 nm).

Peptide Stability in Human Serum

Materials

Human Serum from human male AB plasma was purchased from Sigma Aldrich (H4522-20mL, Lot# SLBC8756V) and used as received. HBSS buffer (137mM NaCl, 5.37 mM KCl, 0.44mM KH_2PO_4, 5.55 mM glucose, 0.34 mM Na_2HPO_4, 4.17 mM $NaHCO_3$, pH 7.4) was prepared in nanopure water (Thermo Scientific, Barnstead GenPure). Fmoc-Leucine was purchased from Bachem and used as received. MeOH was purchased from Merck (LiChrosolv®) and used as received.

Method

Human serum (30 µL) was incubated at 37 °C for 15 min under slight agitation (300 rpm) before adding the analyst peptide solution (30 µL, 200 µM in HBSS) to give a final peptide concentration of 100 µM. The mixture was vortexed to ensure complete mixing. The sample was then incubated at 37 °C under slight agitation (300 rpm) for the time specified before adding MeOH (120 µL). The suspension was centrifuged (4 °C, 15 min, 13000 rpm). To a sample of the supernatant (155 µL) were added MeOH (2.5 µL) and Fmoc-Leucine (2.5 µL, 1 mM in MeOH). The sample was vortexed and analyzed by HPLC (Waters e2695, 2998, 0.1% TFA in acetonitrile/water, 0-2 min 90% water, 2-12 min linear gradient to 10% water, 12-15 min linear gradient to 90% water, Reprosil-Gold 2.0x120 mm, C18, 3 µm). From the chromatogram at 223 nm a baseline was subtracted to compensate for the acetonitrile absorption that was recorded at least every six samples. The peak corresponding to the analyzed peptide was integrated and the relative area in respect to the measurement at 0 min was recorded. Each measurement was triplicated.

Radioligand Affinity Assay[283]

Materials

The rat brains for the δ-opioid receptor binding assay were commercially available (Harlan-Winkelmann, Borchen, Germany). Homogenizers: Elvehjem Potter (B. Braun Biotech International, Melsungen, Germany) and Soniprep 150, MSE, London, UK). Centrifuges: Cooling centrifuge model Rotina 35R (Hettich, Tuttlingen, Germany) and High-speed cooling centrifuge model Sorvall RC-5C plus (Thermo Fisher Scientific, Langenselbold, Germany). Multiplates: standard 96-well multiplates (Diagonal, Muenster, Germany). Shaker: self-made device with adjustable temperature and tumbling speed (scientific workshop of the institute). Harvester: MicroBeta FilterMate-96 Harvester. Filter: Printed Filtermat Typ A and B. Scintillator: Meltilex (Typ A or B) solid state scintillator. Scintillation analyzer: MicroBeta Trilux (all Perkin Elmer LAS, Rodgau-Jügesheim, Germany).

Preparation of membrane homogenates from rat brain

5 rat brains (species: Sprague Dawley rats) were homogenized with the potter (500-800 rpm, 10 up-and-down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200 x g for 10 min at 4 °C. The supernatant was separated and centrifuged at 23500 x g for 20 min at 4 °C. The pellet was resuspended in 5-6 volumes of buffer (50 mM TRIS, pH 7.4) and centrifuged again at 23500 x g (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in 5-6 volumes of buffer and frozen (−80 °C) in 1.5 mL portions containing about 1.5 mg protein/mL.

Protein determination

The protein concentration was determined by the method of Bradford, modified by Stoscheck.[179,180] The Bradford solution was prepared by dissolving 5 mg of Coomassie Brilliant Blue G 250 in 2.5 mL of EtOH (95 %, v/v). 10 mL deionized

H_2O and 5 mL phosphoric acid (85%, m/v) were added to this solution, the mixture was stirred and filled to a total volume of 50.0 mL with deionized water. The calibration was carried out using bovine serum albumin as a standard in 9 concentrations (0.1, 0.2, 0.4, 0.6, 0.8, 1.0, 1.5, 2.0 and 4.0 mg/mL). In a 96-well standard multiplate, 10 µL of the calibration solution or 10 µL of the membrane receptor preparation were mixed with 190 µL of the Bradford solution, respectively. After 5 min, the UV absorption of the protein-dye complex at λ = 595 nm was measured with a platereader (Tecan Genios, Tecan, Crailsheim, Germany).

General procedures for the binding assays

The test compound solutions were prepared by dissolving approximately 10 µmol (usually 2-4 mg) of test compound in DMSO so that a 10 mM stock solution was obtained. To obtain the required test solutions for the assay, the DMSO stock solution was diluted with the respective assay buffer. The filtermats were presoaked in 0.5% aqueous polyethylenimine solution for 2 h at room temperature before use. All binding experiments were carried out in duplicates in the 96-well multiplates. The concentrations given are the final concentration in the assay. Generally, the assays were performed by addition of 50 µL of the respective assay buffer, 50 µL test compound solution in various concentrations (10^{-5}, 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9} and 10^{-10} mol/L), 50 µL of corresponding radioligand solution and 50 µL of the respective receptor preparation into each well of the multiplate (total volume 200 µL). The receptor preparation was always added last. During the incubation, the multiplates were shaken at a speed of 500-600 rpm at the specified temperature. Unless otherwise noted, the assays were terminated after 120 min by rapid filtration using the harvester. During the filtration each well was washed five times with 300 µL of water. Subsequently, the filtermats were dried at 95 °C. The solid scintillator was melted on the dried filtermats at a temperature of 95 °C for 5 min. After solidifying of the scintillator at room temperature, the trapped radioactivity in the filtermats was measured

with the scintillation analyzer. Each position on the filtermat corresponding to one well of the multiplate was measured for 5 min with the [^{3}H]-counting protocol. The overall counting efficiency was 20%. The IC50-values were calculated with the program GraphPad Prism® 3.0 (GraphPad Software, San Diego, CA, USA) by non-linear regression analysis. Subsequently, the IC50 values were transformed into K_i-values using the equation of Cheng and Prusoff[181]. The Ki-values are given as mean value ± SEM from three independent experiments.

δ opioid receptor

The assay was performed with the radioligand [^{3}H]-DPDPE (69 Ci/mmol, Amersham). The thawed rat membrane preparation (about 75 µg of the protein) was incubated with various concentrations of test compounds, 3 nM [^{3}H]-DPDPE, and TRIS-$MgCl_2$-buffer (50 mM, 8 mM $MgCl_2$, pH 7.4) supplemented with SIGMAFAST® protease inhibitor mix (Sigma Aldrich Biochemicals, Hamburg, Germany; 1 tablet dissolved in 100 mL of buffer) at 37 °C. The non-specific binding was determined with 10 µM unlabeled Morphine. The K_d-value of DPDPE is 0.65 nM.

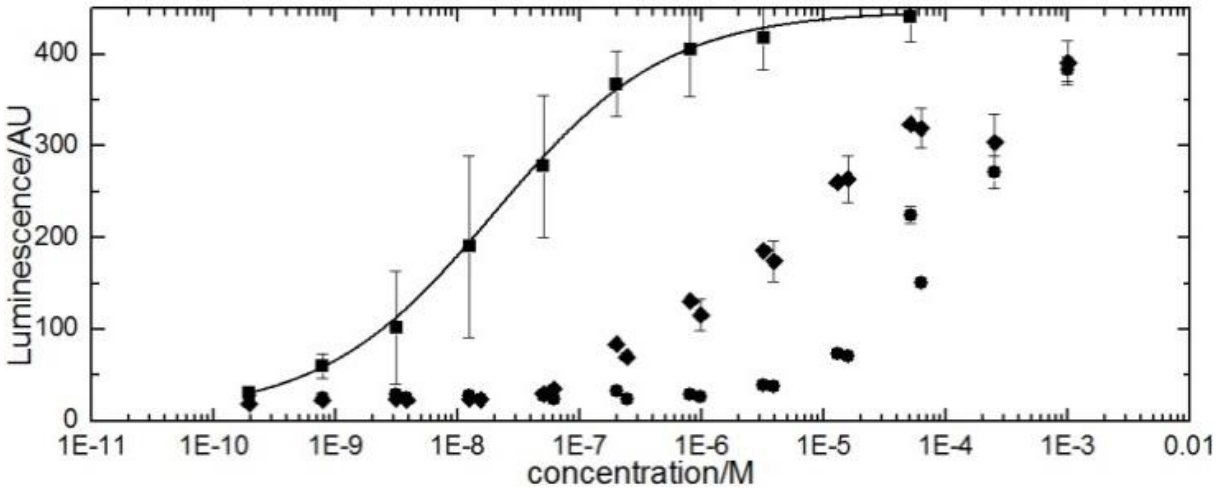
Compound	**K_i/nM (n=3), mean±SEM**
2a	9.2±2.3
2b	>1000
2c	>1000
2d	157±15
2e	43±9
Morphine	2.5±0.5
Naloxone	2.4±0.5
Naltrindole	14.7±4.3

β-Arrestin GPCR Assay[284]

Method:

Biological activity was measured using the PathHunter® eXpress OPRD1 CHO-K1 β-Arrestin GPCR Assay (DiscoverX #93-0400E2CP2M). Compounds were diluted in commercial HBSS and their activity measured according to protocol. Luminescence read-out was performed on a Synergy Mx plate reader (Biotek).

Results



Activity of Leu-Enkephalin and its analogues at the δ-Opioid receptor measured by β-Arrestin Assay. Leu-Enkephaline (**2a** ■) as well as oxetane derivatives **2b** (●) and **2e** (◆) show a dose-dependent response. (n=2, measured in triplicates, data shown as mean ± SD)

Data processing

For **2a**, EC_{50} was calculated by a logistic fit of the data points.

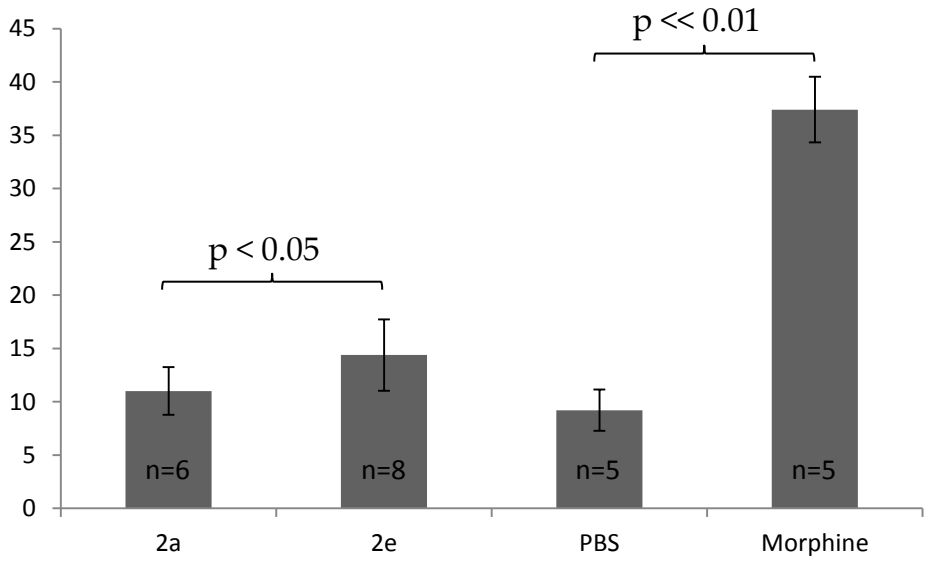
For **2b** and **2e**, the logistic fit did not fully converge because of missing top plateau values and EC50 values could only be estimated.

Hot Plate Test[285]

Method:

The analgesic activity of natural Leu-Enkephalin and **2e** was determined by a hot plate test on adult male C57B6/N mice (Charles River, Germany) weighing 33-38 g. Prior to the experiment the animals were housed in groups (n=5) in a temperature and humidity controlled environment with *ad libitum* food and water availability. The compounds were dissolved in sterile PBS (Gibco, Life technologies) at a concentration of 1 mg/mL. 6-8 mice per condition were administered 12.5 mg/kg intravenously 10 min before the hot plate test. Morphine (10 mg/kg) was used as the positive control. Each mouse was placed on an electrically heated hot plate surface (54±1 °C) surrounded by a plexiglas cylinder. The time until the mouse started to lick its hind paws or to jump with all four feet was recorded. The animal was removed from the hot plate, if it did not respond within 45 s in order to avoid tissue damage. All data are expressed as mean±SEM.[193]

Results:



Conditions: The mice were placed on the hot plate (54±1 °C) 10 min after i.v. injection of **2a** and **2e** (12.5 mg/kg). The times the mice spent on the plate before licking their hind paws or jumping with all four feet were measured and are depicted as mean±SEM (*n*=number of animals).

General Procedure for Peptide Coupling (GP 2):

The corresponding acid (1.0-1.1 eq) and the corresponding amine (1.0-1.1 eq) were suspended CH_2Cl_2 (0.1 M). To the mixture were added *N*-methylmorpholine (3.0-6.0 eq), EDC·HCl (1.0-1.1 eq) and HOBt (1.0-1.1 eq). The resulting light yellow solution was stirred at r.t for (14-20 h). The reaction was quenched with sat. aq. NH_4Cl (reaction volume) and extracted with CH_2Cl_2 (3 x reaction volume). The crude product was purified by FC on silica (hex:EA) or trituration with hex:Et_2O (1:1)

NaOH/MeCN - General Procedure for Ester Deprotection (GP 3):

To a solution of the corresponding acid (1.0 eq) in MeCN (0.1 M) at 0 °C was added aq. NaOH (0.25 M, 5.0 eq). The mixture was stirred until the starting material was consumed as judged by TLC. The mixture was diluted with aq. $NaHSO_4$ solution (1 M, reaction volume) and extracted with EA (3 x reaction volume)

LiOH/THF - General Procedure for Ester Deprotection (GP 4):

To a solution of the corresponding acid (1.0 eq) in THF (0.1 M) at 0 °C was added aq. LiOH (1 M, 5.0 eq). The mixture was stirred until the starting material was consumed as judged by TLC. The mixture was diluted with aq. $NaHSO_4$ solution

(1 M, reaction volume) and extracted with EA (3 x reaction volume). The crude product was used in the coupling step without further purification.

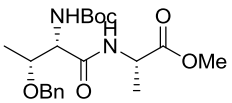
General Procedure for Boc Deprotection (GP 5):

The substrate was dissolved in CH_2Cl_2/TFA (4:1, 0.1 M) and stirred at 0 °C until the starting material was consumed as judged by TLC. To the mixture was then added toluene (1/10 of the reaction volume) and all volatiles were removed. The residue was azeotropically dried with toluene (3 x 1/10 of the reaction volume). If the substrate was sensitive to concentrated acid, the reaction mixture was transferred into sat. aq. $NaHCO_3$ solution (five reaction volumes) and extracted with EA (3 x five reaction volumes). The crude product was used in the coupling step without further purification.

General Procedure for Bn-ester deprotection (GP 6):

To a mixture of the substrate (1.0 eq) and Pd/C (10 wt-% Pd, 10 mol-% Pd) was added MeOH (0.1 M). The suspension was stirred under an atm of H_2 until the starting material was consumed as judged by TLC.

BocNH-Thr(Bn)-Ala-OMe (**261**)



Following GP 2 using BocNH-Thr(Bn)-OH (19.6 g, 41.1 mmol, 1.1 eq), H_2N-Ala-OMe·HCl (3.86 g, 37.4 mmol, 1.0 eq), *N*-methylmorpholine (12.3 mL, 112 mmol, 3.0 eq), EDC·HCl (7.17 g, 37.4 mmol, 1.0 eq) and HOBt (5.73 g, 37.4 mmol, 1.0 eq) the title compound was obtained after FC on silica (hex:EA=2:1) as a colorless foam (4.77 g, 12.1 mmol, 32%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.28 (m, 5H), 7.15 (br s), 5.49 (br s, 1H), 4.68 – 4.52 (m, 3H), 4.33 – 4.25 (m, 1H), 4.22 – 4.12 (m, 1H), 3.72 (s, 3H), 1.46 (s, 9H), 1.36 (d, *J* = 7.2 Hz, 3H), 1.22 (d, *J* = 6.4 Hz, 3H) ppm.

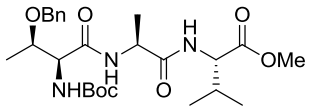
^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.1, 169.7, 155.9, 138.1, 128.5, 127.9, 127.8, 80.2, 75.0, 71.6, 57.6, 52.5, 48.3, 28.4, 18.4, 15.3 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{20}H_{31}N_2O_6$ $[M+H]^+$ 395.2177, found, 395.2177.

IR (neat): ν [cm^{-1}] = 3331, 3292, 2977, 1751, 1689, 1647, 1526, 1164, 1054, 696.

$[\alpha]^{23}_D$ + 21.1 (*c* = 1.51, $CHCl_3$)

BocNH-Thr(Bn)-Ala-Val-OMe (**266**)



First, crude BocNH-Thr(Bn)-Ala-OH was obtained from **261** (1.00 g, 2.54 mmol, 1.00 eq) and aq. LiOH (12.7 mL) in THF (25.4 mL) following GP 4.

Following GP 2 using crude BocNH-Thr(Bn)-Ala-OH (0.966 g, 2.54 mmol, 1.0 eq), H_2N-Val-OMe·HCl (0.468 g, 2.79 mmol, 1.1 eq), *N*-methylmorpholine (1.12 mL, 10.2 mmol, 4.0 eq), EDC·HCl (0.487 g, 2.54 mmol, 1.0 eq) and HOBt (0.389 g, 2.54 mmol, 1.0 eq) the title compound **266** was obtained after FC on silica (hex:EA=2:1) as a colorless foam (0.995 g, 2.02 mmol, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.29 (m, 5H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 8.7 Hz, 1H), 5.46 (d, *J* = 7.2 Hz, 1H), 4.68 – 4.46 (m, 4H), 4.34 – 4.19 (m, 2H), 3.75 (s, 3H), 2.22 – 2.08 (m, 1H), 1.47 (s, 9H), 1.35 (d, *J* = 7.0 Hz, 3H), 1.22 (d, *J* = 6.4 Hz, 3H), 0.92 (t, *J* = 7.0 Hz, 6H) ppm.

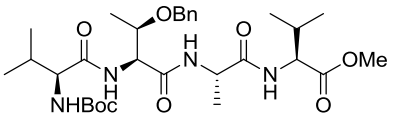
^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.2, 171.8, 170.3, 155.9, 138.0, 128.6, 128.0, 127.8, 80.4, 74.9, 71.8, 58.1, 57.4, 52.3, 49.2, 31.2, 28.4, 19.1, 17.9, 17.9, 15.7 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{25}H_{40}N_3O_7$ $[M+H]^+$ 494.2861, found, 494.2856.

IR (neat): ν [cm^{-1}] = 3294, 2973, 1692, 1642, 1530, 1165, 697.

***[α]*^{23}D** – 7.27 (*c* = 0.935, $CHCl_3$)

BocNH-Val-Thr(Bn)-Ala-Val-OMe (**265**)



First, crude H_2N-Thr(Bn)-Ala-Val-OMe·TFA was obtained from **266** (0.936 g, 1.90 mmol, 1.00) and isolated by azeotropic evaporation following GP 5.

Following GP 2 using BocNH-Val-OH (0.453 g, 2.09 mmol, 1.1 eq), crude H_2N-Thr(Bn)-Ala-Val-OMe·TFA (0.962 g, 1.90 mmol, 1.0 eq), *N*-methylmorpholine (0.83 mL, 7.58 mmol, 4.0 eq), EDC·HCl (0.400 g, 2.09 mmol, 1.1 eq) and HOBt (0.319 g, 2.09 mmol, 1.1 eq) the title compound **265** was obtained after FC on silica (hex:EA=1:1→EA) as a colorless foam (0.915 g, 1.54 mmol, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (d, *J* = 8.0 Hz, 1H), 7.36 – 7.2i6 (m, 5H), 6.99 (dd, *J* = 8.6, 3.4 Hz, 2H), 5.01 (d, *J* = 5.2 Hz, 1H), 4.68 – 4.58 (m, 2H), 4.53 – 4.44 (m, 3H), 4.37 – 4.29 (m, 1H), 3.95 (t, *J* = 4.9 Hz, 1H), 3.74 (s, 3H), 2.32 – 2.12 (m, 2H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.36 (s, 9H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.98 – 0.92 (dd, *J* = 6.9, 3.1 Hz, 9H) ppm.

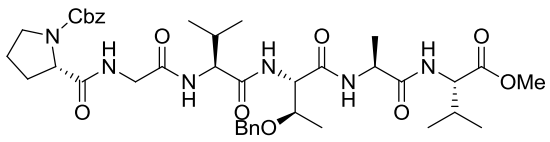
^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.2, 172.1, 172.0, 170.0, 156.7, 137.9, 128.5, 128.0, 127.8, 81.0, 74.1, 71.8, 61.1, 57.7, 57.6, 52.1, 49.2, 31.1, 30.2, 28.3, 19.6, 19.1, 18.1, 17.7, 17.6, 16.6 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{30}H_{49}N_4O_8$ $[M+H]^+$ 593.3545, found, 593.3544.

IR (neat): ν [cm^{-1}] = 3273, 2968, 1689, 1636, 1520, 1164.

***[α]*^{23}D** – 16.0 (*c* = 0.770, $CHCl_3$)

CbzNH-Pro-Gly-Val-Thr(Bn)-Ala-Val-OMe (**267**)



First, crude H_2N-Val-Thr(Bn)-Ala-Val-OMe·TFA was obtained from **265** (0.500 g, 0.844 mmol, 1.00 eq) anjd isolated by azeotropic evaporation following GP 5.

Following GP 2 using Cbz-Pro-Gly-OH (0.284 g, 0.928 mmol, 1.1 eq), crude H_2N-Val-Thr(Bn)-Ala-Val-OMe·TFA (0.416 g, 0.844 mmol, 1.0 eq), *N*-methylmorpholine (0.46 mL, 4.22 mmol, 5.0 eq), EDC·HCl (0.178 g, 0.928 mmol, 1.1 eq) and HOBt (0.142 g, 0.928 mmol, 1.1 eq) the title compound **267** was obtained after FC on silica (EA) as a colorless foam (0.535 g, 0.685 mmol, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 – 7.50 (m, 4H), 7.37 – 7.16 (m, 10H), 5.20 – 4.79 (m, 4H), 4.62 – 4.42 (m, 3H), 4.31 – 4.15 (m, 2H), 3.91 – 3.38 (m, 7H), 2.27 – 1.75 (m, 6H), 1.43 – 1.27 (m, 3H), 1.22 – 1.06 (m, 3H), 0.98 – 0.77 (m, 12H) ppm.

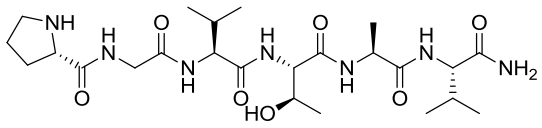
^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.8, 172.2, 171.8, 170.0, 169.0, 155.4, 138.3, 136.3, 128.5, 128.1, 127.9, 127.5, 127.4, 126.9, 75.4, 71.8, 66.9, 65.9, 60.7, 60.0, 57.7, 57.2, 52.2, 48.8, 47.2, 43.3, 31.4, 31.1, 30.0, 24.7, 19.4, 19.1, 19.0, 18.8, 18.0, 16.4 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{40}H_{57}N_6O_{10}$ $[M+H]^+$ 781.4131, found, 781.4126.

IR (neat): ν [cm^{-1}] = 3280, 2967, 1632, 1535.

***[α]*^{23}D** + 31.0 (*c* = 0.770, $CHCl_3$)

H_2N-Pro-Gly-Val-Thr(OH)-Ala-Val-NH_2 (**259a ·NH_2**)



First, crude CbzNH-Pro-Gly-Val-Thr(Bn)-Ala-Val-OH was obtained from **267** (164 mg, 0.214 mmol, 1.00 eq) and aq. NaOH (4.3 mL) in MeCN (2.1 mL) following GP 3.

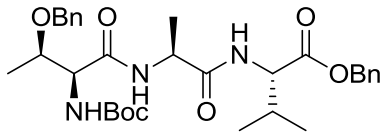
To a solution of the obtained crude acid in THF (2.1 mL) at 0 °C were sequentially added isobutyl chloroformate (56 µL, 0.428 mmol, 2.00 eq), *N*-methylmorpholine (71 µL, 0.642 mmol, 3.00 eq). The mixture was stirred for 1 h before conc. ammonium hydroxide (3.33 mL, 21.4 mmol, 100 eq) was added. The mixture was allowed to warm to r.t. and stirred overnight. The reaction mixture was acidified with aq. $NaHSO_4$ solution (1 M, 50 mL) and extracted with EA (3 x 50 mL). The suspended colorless powder was isolated with the org. layer and concentrated. Crude NMR in DMSO suggested that Cbz-deprotection already occurred at this stage. The crude product (34 mg, 0.054 mmol, 1.00 eq) and $Pd(OAc)_2$ (12 mg, 0.054 mmol, 1.00 eq) were suspended in MeOH (5.38 mL). The mixture was stirred under an atm of H_2 for 24 h. The crude mixture was filtered through a syringe filter (PTFE) with MeOH/H_2O (1:1, 100 mL) and the filtrate was concentrated. The crude product was purified by preparative HPLC (Waters 2545, 2767, Reprosil Gold 120 C18, 5 µm, 125 x 20 mm, 0.1 % TFA in MeCN/H_2O, 90:10, 26.5 mL/min) to yield the title compound as the as a colorless foam (1.8 mg, 3.32 µmol, 6.2%)

^{1}H NMR (600 MHz, DMSO) δ = 7.84 (t, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.30 (s, 1H), 7.23 (s, 1H), 7.04 (s, 1H), 6.90 (s, 1H), 6.52 (s, 1H), 4.88 (d, *J* = 5.5 Hz, 1H), 4.34 – 4.29 (m, 1H), 4.25 – 4.17 (m, 2H), 4.13 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.10 – 4.04 (m, 1H), 4.02 – 3.94 (m, 1H), 3.73 – 3.57 (m, 2H), 3.46 – 3.39 (m, 1H), 3.28 – 3.21 (m, 1H), 2.07 – 1.77 (m, 6H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 6.3 Hz, 3H), 0.88 – 0.77 (m, 12H) ppm.

^{13}C NMR (151 MHz, DMSO) δ = 174.6, 172.8, 172.8, 171.9, 171.2, 170.3, 169.6, 66.4, 59.5, 58.2, 57.8, 57.4, 57.4, 48.4, 48.4, 46.0, 43.6, 30.4, 30.3, 30.3, 29.8, 23.9, 19.6, 19.3, 18.1, 18.0, 17.9, 17.9 ppm.

HRMS (MALDI): *m*/*z* calcd. for $C_{24}H_{44}N_7O_7$ $[M+H]^+$ 542.3297, found, 542.3297.

BocNH-Thr(Bn)-Ala-Val-OBn (**262**)



First, crude BocNH-Thr(Bn)-Ala-OH was obtained from **261** (0.860 g, 2.18 mmol, 1.00 eq) and aq. LiOH (10.9 mL, 5.00 eq) in THF (21.8 mL) following GP 4.

Following GP 2 using crude BocNH-Thr(Bn)-Ala-OH (0.829 g, 2.18 mmol, 1.0 eq), H_2N-Val-OBn·HCl (0.910 g, 2.40 mmol, 1.1 eq), *N*-methylmorpholine (0.95 mL, 8.72 mmol, 4.0 eq), EDC·HCl (0.418 g, 2.18 mmol, 1.0 eq) and HOBt (0.334 g, 2.18 mmol, 1.0 eq) the title compound **262** was obtained after FC on silica (hex:EA=2:1) as a colorless foam (0.894 g, 1.57 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.27 (m, 10H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 1H), 5.44 (d, *J* = 7.3 Hz, 1H), 5.26 – 5.08 (m, 2H), 4.66 – 4.47 (m, 4H), 4.29 – 4.16 (m, 2H), 2.20 – 2.10 (m, 1H), 1.45 (s, 9H), 1.32 (d, *J* = 7.0 Hz, 3H), 1.18 (d, *J* = 6.4 Hz, 3H), 0.86 (dd, *J* = 14.1, 6.9 Hz, 6H) ppm.

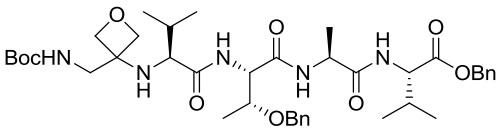
^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.8, 171.6, 170.3, 155.9, 138.0, 135.5, 128.7, 128.6, 128.6, 128.5, 128.0, 127.8, 80.4, 74.9, 71.7, 67.1, 58.1, 57.4, 49.2, 31.2, 28.4, 19.1, 18.0, 17.8, 15.7 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{31}H_{44}N_3O_7$ $[M+H]^+$ 570.3174, found, 570.3168.

IR (neat): ν [cm^{-1}] = 3307, 2973, 1718, 1644, 1520, 1165, 737.

***[α]*^{23}D** – 12.5 (*c* = 0.820, $CHCl_3$)

BocNH-^{Ox}Gly-Val-Thr(Bn)-Ala-Val-OBn (**270**)[280]



First, crude BocNH-^{Ox}Gly-Val-OH was obtained from BocNH-OxGly-Val-O*n*Pr[107] (30 mg, 0.087 mmol, 1.00 eq) and aq. LiOH (1.70 mL, 20.0 eq) in MeOH (0.5 mL) following GP 4.

Also, crude H_2N-Thr(Bn)-Ala-Val-OBn·TFA was obtained from **262** (99 mg, 0.174 mmol, 1.00 eq) and isolated by azeotropic evaporation following GP 5.

Following GP 2 using crude BocNH-^{Ox}Gly-Val-OH (26 mg, 0.087 mmol, 1.0 eq), crude H_2N-Thr(Bn)-Ala-Val-Bn·TFA (0.102 g, 0.174 mmol, 2.0 eq), *N*-methylmorpholine (48 µL, 0.435 mmol, 5.0 eq), EDC·HCl (33 mg, 0.174 mmol, 2.0 eq) and HOBt (27 mg, 0.174 mmol, 2.0 eq) the title compound was obtained after FC on silica (hex:EA=2:1) as a colorless foam (52 mg, 0.069 mmol, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 7.1 Hz, 1H), 7.40 – 7.27 (m, 10H), 7.16 (d, *J* = 7.7 Hz, 1H), 6.62 (d, *J* = 8.7 Hz, 1H), 5.46 (d, *J* = 6.3 Hz, 1H), 5.23 – 5.06 (m, 2H), 4.74 – 4.56 (m, 3H), 4.58 – 4.43 (m, 3H), 4.40 – 4.26 (m, 3H), 4.04 – 3.94 (m, 1H), 3.67 – 3.56 (m, 1H), 3.35 (dd, *J* = 14.1, 4.8 Hz, 1H), 3.24 (d, *J* = 4.5 Hz, 1H), 2.19 – 2.06 (m, 2H), 1.29 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.92 – 0.81 (m, 9H) ppm.

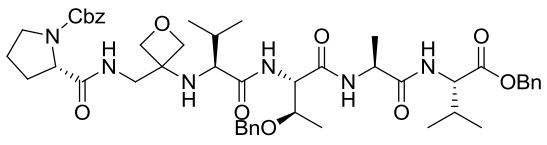
^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.0, 171.8, 171.7, 169.4, 157.1, 137.8, 135.4, 128.7, 128.6, 128.6, 128.5, 128.1, 127.9, 79.2, 78.7, 74.6, 71.7, 67.2, 62.3, 60.7, 57.4, 55.5, 49.2, 46.1, 34.1, 31.9, 31.3, 25.7, 25.1, 19.8, 19.0, 18.3, 17.8, 15.2 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{40}H_{60}N_5O_9$ $[M+H]^+$ 754.4386, found, 754.4379.

IR (neat): ν [cm^{-1}] = 3290, 2967, 1631, 1528, 1166, 976, 752.

***[α]*^{23}$_D$ –** 76.3 (*c* = 0.250, $CHCl_3$)

CbzNH-Pro-^{Ox}Gly-Val-Thr(Bn)-Ala-Val-OBn (**271**)



First, crude H_2N-^{Ox}Gly-Val-Thr(Bn)-Ala-Val-OBn was obtained from **270** (71 mg, 0.094 mmol, 1.00 eq) and isolated by aq. extraction following GP 5.

Following GP 2 using Cbz-Pro-OH (52 mg, 0.210 mmol, 2.0 eq), crude H_2N-^{Ox}Gly-Val-Thr(Bn)-Ala-Val-OMe (69 mg, 0.105 mmol, 1.0 eq), *N*-methylmorpholine (58 µL, 0.525 mmol, 5.0 eq), EDC·HCl (40 mg, 0.210 mmol, 2.0 eq) and HOBt (32 g, 0.210 mmol, 2.0 eq) the title compound was obtained after FC on silica (EA) as a colorless foam (41 mg, 0.046 mmol, 44%).

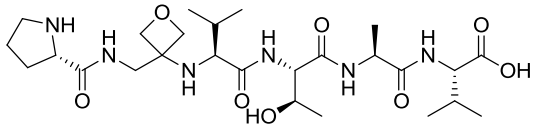
^{1}H NMR, ^{13}C NMR, COSY, HSQC, HMBC data are only displayed in the spectra parts due to high number of rotamers.

HRMS (ESI+): *m*/*z* calcd. for $C_{48}H_{64}N_6O_{10}$ $[M+H]^+$ 885.4757, found, 885.4752.

IR (neat): ν [cm^{-1}] = 3299, 2964, 2875, 1639, 1539, 1195, 977.

$[\alpha]^{23}_D$ – 27.0 (*c* = 0.220, $CHCl_3$)

H_2N-Pro-^{Ox}Gly-Val-Thr(OH)-Ala-Val-OH (**259c ·OH**)



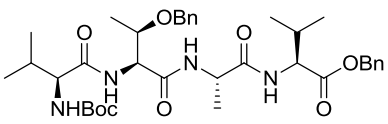
271 (29 mg, 0.033 mmol, 1.00 eq) and $Pd(OAc)_2$ (3.7 mg, 0.016 mmol, 0.50 eq) were suspended in MeOH (1.0 mL). The mixture was stirred under an atm of H_2 for 24 h. The crude mixture was filtered through a syringe filter (PTFE) with MeOH (25 mL) and the filtrate was concentrated. The crude product was purified by preparative HPLC (Waters 2545, 2767, Reprosil Gold 120 C18, 5 µm, 125 x 20 mm, 0.1 % TFA in MeCN/H_2O, 90:10, 26.5 mL/min) to yield the title compound **259c** as the as a colorless foam (6.4 mg, 11 µmol, 34%)

^{1}H NMR (400 MHz, Methanol) δ = 4.69 – 4.63 (m, 1H), 4.54 – 4.34 (m, 6H), 4.29 – 4.16 (m, 2H), 3.88 (d, *J* = 14.3 Hz, 1H), 3.61 (d, *J* = 14.3 Hz, 1H), 3.57 – 3.50 (m, 1H), 3.46 – 3.33 (m, 2H), 2.49 – 2.39 (m, 1H), 2.25 – 2.00 (m, 5H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.21 (d, J = 6.4 Hz, 3H), 1.08 – 0.97 (m, 12H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.2, 174.7, 172.0, 171.1, 170.1, 79.2, 78.7, 68.8, 63.7, 62.4, 61.4, 59.4, 59.2, 50.5, 47.4, 45.3, 33.0, 31.5, 31.0, 25.1, 20.2, 19.6, 19.5, 18.7, 18.6, 18.2 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{26}H_{47}N_6O_8$ $[M+H]^+$ 571.3450, found, 571.3451.

BocNH-Val-Thr(Bn)-Ala-Val-OBn (**260**)



First, crude H_2N-Thr(Bn)-Ala-Val-OBn·TFA was obtained from **262** (0.500 g, 0.878 mmol, 1.00 eq) and isolated by azeotropic evaporation following GP 5.

Following GP 2 using BocNH-Val-OH (0.210 g, 0.965 mmol, 1.1 eq), crude H_2N-Thr(Bn)-Ala-Val-OBn·TFA (0.512 g, 0.877 mmol, 1.0 eq), *N*-methylmorpholine (0.39 mL, 3.51 mmol, 4.0 eq), EDC·HCl (0.185 g, 0.97 mmol, 1.1 eq) and HOBt (0.148 g, 0.97 mmol, 1.1 eq) the title compound **260** was obtained after FC on silica (hex:EA=1:1→EA) as a colorless foam (0.465 g, 0.70 mmol, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 1H), 7.41 – 7.27 (m, 10H), 7.05 – 6.94 (m, 2H), 5.26 – 5.11 (m, 2H), 5.00 (d, *J* = 5.2 Hz, 1H), 4.69 – 4.41 (m, 5H), 4.36 – 4.28 (m, 1H), 3.95 (t, *J* = 4.9 Hz, 1H), 2.31 – 2.16 (m, 2H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.36 (s, 9H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 6.7 Hz, 6H) ppm.

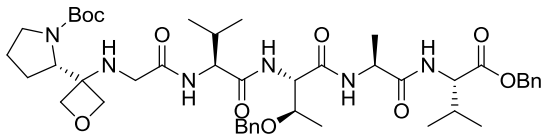
^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.1, 171.9, 171.6, 169.9, 156.7, 138.0, 135.8, 128.6, 128.5, 128.4, 128.3, 128.0, 127.8, 80.9, 74.1, 71.8, 66.9, 61.1, 57.7, 57.5, 49.2, 31.1, 30.2, 28.3, 19.6, 19.1, 17.9, 17.7, 16.6 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{36}H_{53}N_4O_8$ $[M+H]^+$ 669.3858, found, 669.3851.

IR (neat): ν [cm^{-1}] = 3279, 2934, 1637, 1530, 1168, 739.

$[\alpha]^{23}_D$ – 15.6 (*c* = 1.08, $CHCl_3$)

CbzNH-^{Ox}Pro-Gly-Val-Thr(Bn)-Ala-Val-OBn (**268**)



First, crude H_2N-Val-Thr(Bn)-Ala-Val-OBn·TFA was obtained from **260** (62 mg, 0.098 mmol, 1.00 eq) and isolated by azeotropic evaporation following GP 5.

Also, crude BocNH-^{Ox}Pro-Gly-OH was obtained from **73q** (50 mg, 0.128 mmol, 1.00 eq) and Pd/C (14 mg, 0.013 mmol, 10 mol-%) in MeOH (1.2 mL) following GP 6.

Following GP 2 using BocNH-^{Ox}Pro-Gly-OH (27 mg, 0.089 mmol, 1.0 eq), crude H_2N-Val-Thr(Bn)-Ala-Val-OBn·TFA (67 mg, 0.098 mmol, 1.1 eq), *N*-methylmorpholine (0.49 µL, 0.445 mmol, 5.0 eq), EDC·HCl (19 mg, 0.098 mmol, 1.1 eq) and HOBt (15 mg, 0.098 mmol, 1.1 eq) the title compound **268** was obtained after FC on silica (EA) as a colorless foam (52 mg, 0.061 mmol, 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.30 (m, 10H), 5.27 – 5.10 (m, 2H), 4.90 (d, *J* = 7.4 Hz, 1H), 4.72 – 4.65 (m, 2H), 4.60 – 4.52 (m, 4H), 4.44 (t, *J* = 6.6 Hz, 1H), 4.38 (d, *J* = 7.4 Hz, 1H), 4.32 (d, *J* = 7.4 Hz, 1H), 4.20 (dd, *J* = 8.4, 5.3 Hz, 1H), 4.17 – 4.09 (m, 1H), 3.69 (d, *J* = 17.8 Hz, 1H), 3.45 (d, *J* = 17.7 Hz, 1H), 3.37 – 3.29 (m, 1H), 2.27 – 2.05 (m, 3H), 2.02 – 1.90 (m, 1H), 1.89 – 1.77 (m, 1H), 1.76 – 1.65 (m, 1H), 1.48 (s, 9H), 1.37 (d, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.97 (dd, *J* = 16.6, 6.8 Hz, 6H), 0.88 (dd, *J* = 9.7, 6.8 Hz, 6H) ppm.

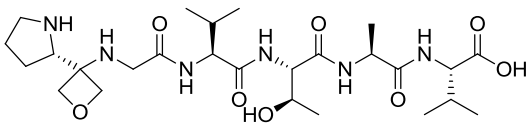
^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.1, 171.5, 171.2, 169.3, 137.9, 135.5, 128.5, 128.5, 128.3, 128.3, 127.9, 127.7, 80.3, 74.2, 71.4, 66.9, 64.3, 62.1, 58.5, 57.4, 56.6, 49.0, 48.7, 45.9, 38.6, 31.0, 28.5, 19.4, 19.0, 18.2, 17.8, 17.8, 15.6 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{45}H_{67}N_6O_{10}$ $[M+H]^+$ 851.4913, found, 851.4906.

IR (neat): ν [cm^{-1}] = 3287, 2969, 1690, 1636, 1536, 1391, 1163, 848, 752.

***[α]*^{23}D - 123** (*c* = 0.21, $CHCl_3$)

H_2N-^{Ox}Pro-Gly-Val-Thr(OH)-Ala-Val-OH (**259b ·OH**)



First, crude H_2N-^{Ox}Pro-GlyVal-Thr(Bn)-Ala-Val-OBn was obtained from **268** (33 mg, 0.039 mmol, 1.00 eq) and isolated by aq. extraction following GP 5.

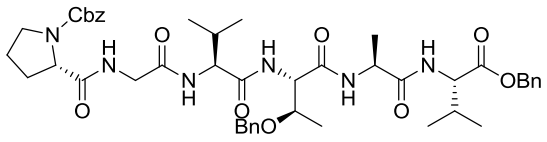
Crude H_2N-^{Ox}Pro-GlyVal-Thr(Bn)-Ala-Val-OBn (29 mg, 0.039 mmol, 1.00 eq) and Pd/C (10-wt% Pd, 8.2 mg, 0.007 mmol, 20 mol-%) were suspended in MeOH (0.8 mL). The mixture was stirred under an atm of H_2 for 26 h. The crude mixture was filtered through a syringe filter (PTFE) with MeOH (9 mL) and the filtrate was concentrated. The crude product was purified by preparative HPLC (Waters 2545, 2767, Reprosil Gold 120 C18, 5 µm, 125 x 20 mm, 0.1 % TFA in MeCN/H_2O, 90:10, 26.5 mL/min) to yield the title compound as the as a colorless foam (3.0 mg, 5.3 µmol, 14%)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.62 – 4.54 (m, 4H), 4.48 (q, *J* = 7.1 Hz, 1H), 4.41 (d, *J* = 4.3 Hz, 1H), 4.31 (d, *J* = 5.7 Hz, 1H), 4.29 (d, *J* = 7.1 Hz, 1H), 4.21 (t, *J* = 8.4 Hz, 1H), 4.17 (dd, *J* = 6.4, 4.3 Hz, 1H), 3.91 (d, *J* = 17.6 Hz, 1H), 3.72 (d, *J* = 17.6 Hz, 1H), 3.55 – 3.49 (m, 1H), 3.43 – 3.38 (m, 2H), 2.39 – 2.28 (m, 1H), 2.20 – 1.92 (m, 5H), 1.40 (d, *J* = 7.1 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.04 – 0.96 (m, 12H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.1, 175.0, 174.5, 173.6, 171.7, 79.3, 78.5, 70.5, 68.5, 61.3, 60.8, 59.6, 59.1, 50.3, 46.3, 31.7, 26.7, 24.7, 19.9, 19.8, 19.6, 18.6, 18.4, 18.3 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{26}H_{47}N_6O_8$ $[M+H]^+$ 571.3450, found, 571.3450.

CbzNH-Pro-Gly-Val-Thr(Bn)-Ala-Val-OBn (**264**)



First, crude H_2N-Val-Thr(Bn)-Ala-Val-OBn·TFA was obtained from **260** (230 mg, 0.344 mmol, 1.00 eq) and isolated by azeotropic evaporation following GP 5.

Also, crude CbzNH-Pro-Gly-OH was obtained from CbzNH-Pro-Gly-OMe (121 mg, 0.378 mmol, 1.00 eq) and aq. NaOH (0.25 M, 7.56 mL, 1.89 mmol, 5.00 eq) in ACN (3.8 mL) following GP 3.[216]

Following GP 2 using CbzNH-Pro-Gly-OH (116 mg, 0.378 mmol, 1.1 eq), crude H_2N-Val-Thr(Bn)-Ala-Val-OBn·TFA (196 mg, 0.344 mmol, 1.0 eq), *N*-methylmorpholine (151 µL, 1.38 mmol, 4.0 eq), EDC·HCl (73 mg, 0.378 mmol, 1.1 eq) and HOBt (58 mg, 0.378 mmol, 1.1 eq) the title compound was obtained after FC on silica (EA) as a colorless foam (178 mg, 0.208 mmol, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 – 7.78 (m, 1H), 7.56 (d, *J* = 9.5 Hz, 2H), 7.37 – 7.22 (m, 15H), 7.17 – 7.11 (m, 2H), 5.23 – 5.08 (m, 3H), 4.86 – 4.67 (m, 3H), 4.59 – 4.42 (m, 3H), 4.40 – 4.26 (m, 3H), 4.22 – 4.14 (m, 1H), 2.23 – 2.06 (m, 4H), 1.91 – 1.72 (m, 2H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.92 – 0.84 (m, 9H), 0.79 (d, *J* = 6.6 Hz, 3H) ppm.

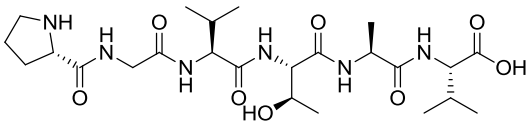
^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.9, 172.8, 172.0, 171.4, 170.3, 169.2, 155.7, 138.3, 136.2, 135.4, 128.8, 128.7, 128.5, 128.3, 128.0, 127.7, 127.5, 126.7, 75.4, 71.9, 67.2, 67.1, 60.9, 57.8, 57.4, 49.1, 47.4, 43.5, 31.2, 30.0, 24.9, 19.3, 19.1, 19.0, 17.9, 16.5. ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{46}H_{61}N_6O_{10}$ $[M+H]^+$ 857.4444, found, 857.4438.

IR (neat): ν [cm^{-1}] = 3277, 2935, 1707, 1694, 1631, 1530, 1413, 1354, 1211, 1092, 750.

$[\alpha]^{23}_D$ + 34.6 (*c* = 0.555, $CHCl_3$)

H_2N-Pro-Gly-Val-Thr(OH)-Ala-Val-OH (**259a**·**OH**)



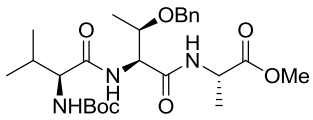
264 (80 mg, 0.093 mmol, 1.00 eq) and $Pd(OAc)_2$ (21 mg, 0.093 mmol, 1.00 eq) were suspended in MeOH (3.1 mL). The mixture was stirred under an atm of H_2 for 24 h. The crude mixture was filtered through a syringe filter (PTFE) with MeOH (25 mL) and the filtrate was concentrated. The crude product was purified by preparative HPLC (Waters 2545, 2767, Reprosil Gold 120 C18, 5 µm, 125 x 20 mm, 0.1 % TFA in MeCN/H_2O, 90:10, 26.5 mL/min) to yield the title compound as the as a colorless foam (10.3 mg, 19 µmol, 20%)

^{1}H NMR (600 MHz, Methanol) δ = 4.44 (q, *J* = 7.1 Hz, 1H), 4.40 (d, *J* = 4.3 Hz, 1H), 4.31 (dd, *J* = 8.6, 6.5 Hz, 1H), 4.26 (dd, *J* = 9.2, 6.1 Hz, 2H), 4.18 – 4.14 (m, 1H), 3.99 (q, *J* = 16.3 Hz, 2H), 3.42 – 3.37 (m, 1H), 3.34 – 3.31 (m, 1H), 2.46 – 2.38 (m, 1H), 2.21 – 2.00 (m, 5H), 1.37 (d, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 6.4 Hz, 3H), 0.97 (dd, *J* = 9.3, 6.8 Hz, 12H) ppm.

^{13}C NMR (151 MHz, Methanol) δ = 175.0, 174.6, 173.7, 171.8, 171.3, 170.5, 68.5, 61.2, 60.6, 59.6, 59.2, 50.4, 47.5, 43.6, 31.7, 31.6, 30.9, 25.1, 19.8, 19.8, 19.6, 18.5, 18.4, 18.2 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{24}H_{43}N_6O_8$ $[M+H]^+$ 543.3137, found, 543.3132.

BocNH-Val-Thr(Bn)-Ala- OMe (**276**)



First, crude H_2N-Thr(Bn)-Ala-OMe·TFA was obtained from **261** (2.01 g, 5.10 mmol, 1.00 eq) and isolated by azeotropic evaporation following GP 5.

Following GP 2 using crude H_2N-Thr(Bn)-Ala-OMe·TFA (2.08 g, 5.10 mmol, 1.0 eq), BocNH-Val-OH (1.22 g, 5.61 mmol, 1.1 eq), *N*-methylmorpholine (2.24 mL, 20.4 mmol, 4.0 eq), EDC·HCl (1.08 g, 5.61 mmol, 1.1 eq) and HOBt (0.858 g, 5.61 mmol, 1.1 eq) the title compound **276** was obtained after FC on silica (hex:EA=1:1) as a colorless glass (0.745 g, 1.51 mmol, 30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 – 7.19 (m, 6H), 6.92 (d, *J* = 7.1 Hz, 1H), 5.06 (d, *J* = 7.8 Hz, 1H), 4.69 – 4.47 (m, 4H), 4.23 – 4.12 (m, 1H), 4.05 – 3.95 (m, 1H), 2.27 – 2.06 (m, 1H), 1.38 (s, 9H), 1.34 (d, *J* = 7.3 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H) ppm.

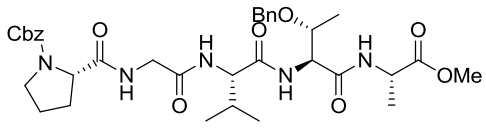
^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.8, 171.7, 169.2, 156.1, 138.0, 128.5, 127.9, 127.8, 80.2, 74.2, 71.6, 60.3, 56.3, 52.4, 52.3, 48.3, 30.7, 28.3, 19.4, 17.9, 17.6, 15.4 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{25}H_{40}N_3O_7$ $[M+H]^+$ 494.2861, found, 494.2861.

IR (neat): ν [cm^{-1}] = 3282, 2934, 1745, 1690, 1641, 1548, 1520, 1166, 742.

***[α]*^{23}D** + 1.36 (*c* = 0.795, $CHCl_3$)

CbzNH-Pro-Gly-Val-Thr(Bn)-Ala-OMe (**275**)



First, crude H_2N-Val-Thr(Bn)-Ala- OMe·TFA was obtained from **276** (0.350 g, 0.709 mmol, 1.00 eq) and isolated by azeotropic evaporation following GP 5.

Also, crude CbzNH-Pro-Gly-OH was obtained from CbzNH-Pro-Gly-OMe (273 mg, 0.851 mmol, 1.00 eq) and aq. NaOH (0.25 M, 17.0 mL, 4.26 mmol, 5.00 eq) in MeCN (8.5 mL) following GP 3.

Following GP 2 using Cbz-Pro-Gly-OH (0.261 g, 0.851 mmol, 1.2 eq), crude H_2N-Val-Thr(Bn)-Ala-OMe·TFA (0.360 g, 0.709 mmol, 1.0 eq), *N*-methylmorpholine (0.39 mL, 3.55 mmol, 5.0 eq), EDC·HCl (0.163 g, 0.851 mmol, 1.2 eq) and HOBt (0.130 g, 0.851 mmol, 1.2 eq) the title compound was obtained after trituration with hex:Et_2O (1:1, 50 mL) as a col[219]orless foam (0.420 g, 0.709 mmol, 87%).

^{1}H NMR (400 MHz, Methanol) δ = 7.45 – 7.16 (m, 10H), 5.18 – 5.03 (m, 2H), 4.62 – 4.40 (m, 4H), 4.37 – 4.19 (m, 1H), 4.17 – 4.06 (m, 1H), 3.96 (d, *J* = 16.9 Hz, 1H), 3.78 (d, *J* = 17.0 Hz, 1H), 3.66 (s, 3H), 3.62 – 3.37 (m, 2H), 2.32 – 1.78 (m, 6H), 1.40 (d, *J* = 7.3 Hz, 3H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.04 – 0.83 (m, 6H) ppm.

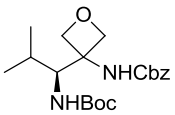
^{13}C NMR (101 MHz, Methanol) δ = 175.7, 174.3, 174.0, 172.0, 171.7, 139.8, 138.0, 129.6, 129.3, 129.1, 128.9, 128.6, 128.5, 76.7, 72.6, 68.3, 62.3, 61.4, 58.8, 52.7, 43.9, 31.7, 31.1, 25.5, 19.7, 19.3, 17.6, 17.0 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{35}H_{48}N_5O_9$ $[M+H]^+$ 682.3447, found, 682.3440.

IR (neat): ν [cm^{-1}] = 3285, 2966, 1747, 1709, 1636, 1541, 1416, 1356, 1210, 1118, 746.

***[α]*^{23}D** + 25.3 (*c* = 0.785, $CHCl_3$)

BocNH-^{Ox}Val-NHCbz (**274**)



To a solution of **145** (100 mg, 0.409 mmol, 1.00 eq) in CH_2Cl_2 (2.0 mL) were added benzyl (2,5-dioxopyrrolidin-1-yl) carbonate (153 mg, 0.614 mmol, 1.50 eq) and Et_3N (86 µL, 0.614 mmol, 1.50 eq). The mixture was stirred for 20 h at r.t. and directly purified by FC on silica (hex:EA=3:1) to yield **274** as a colorless oil (120 mg, 0.317 mmol, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 – 7.30 (m, 5H), 5.88 (d, *J* = 10.0 Hz, 1H), 5.47 (s, 1H), 5.17 – 5.04 (m, 2H), 4.75 – 4.66 (m, 2H), 4.57 (d, *J* = 7.0 Hz, 1H), 4.40 (d, *J* = 7.0 Hz, 1H), 3.97 (t, *J* = 9.4 Hz, 1H), 1.76 – 1.64 (m, 1H), 1.45 (s, 9H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H) ppm.

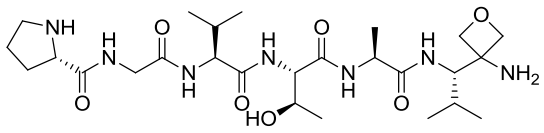
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.6, 156.1, 135.9, 128.8, 128.6, 128.3, 81.3, 79.3, 67.4, 60.9, 60.5, 30.6, 28.5, 20.1, 19.1 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{20}H_{30}N_2NaO_5$ $[M+H]^+$ 401.2047, found, 401.2041.

IR (neat): ν [cm^{-1}] = 3325, 2968, 1696, 1515, 1391, 1367, 1245, 1168, 1054, 989, 742.

***[α]*^{23}D** – 55.7 (*c* = 0.755, $CHCl_3$)

H_2N-Pro-Gly-Val-Thr(Bn)-Ala-^{Ox}Val-NH_2 (**259d ·NH_2**)



First, crude H_2N-^{Ox}Val-NHCbz was obtained from **274** (51 mg, 0.135 mmol, 1.00 eq) and isolated by aq. extraction following GP 5.

Also, crude CbzNH-Pro-Gly-Val-Thr(Bn)-Ala-OH was obtained from **275** (110 mg, 0.162 mmol, 1.00 eq) and aq. LiOH (1 M, 0.81 mL, 0.810 mmol, 5.00 eq) in THF (1.6 mL) following GP 4.

Following GP 2 using crude CbzNH-Pro-Gly-Val-Thr(Bn)-Ala-OH (108 mg, 0.162 mmol, 1.2 eq), crude H_2N-^{Ox}Val-NHCbz (38 mg, 0.135 mmol, 1.0 eq), *N*-methylmorpholine (0.10 mL, 0.95 mmol, 7.0 eq), EDC·HCl (0.031 g, 0.162 mmol, 1.2 eq) and HOBt (0.025 g, 0.162 mmol, 1.2 eq) the crude fully protected peptide was obtained as an off-white amorphous solid (50 mg, 0.054 mmol, 40%). In this case the product was isolated by trituration with hexanes (50 mL) of the residue obtained from aq. extraction.

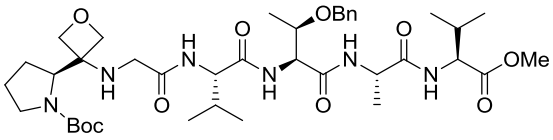
The crude material (10 mg, 11 μmol, 1.00 eq) and $Pd(OAc)_2$ (2.4 mg, 11 μmol, 1.00 eq) were suspended in MeOH (1.1 mL). The mixture was stirred under an atm of H_2 for 24 h. The crude mixture was filtered through a syringe filter (PTFE) with MeOH (25 mL) and the filtrate was concentrated. The crude product was pruified by preparative HPLC (Waters 2545, 2767, Reprosil Gold 120 C18, 5 μm, 125 x 20 mm, 0.1 % TFA in MeCN/H_2O, 90:10, 26.5 mL/min) to yield the title compound as the as a colorless foam (1.7 mg, 3.0 μmol, 28%)

HSQC is provided with the spectra.

^{1}H NMR (400 MHz, Methanol) δ = 4.51 (dd, *J* = 17.5, 8.2 Hz, 2H), 4.32 – 4.22 (m, 5H), 4.17 (dd, *J* = 6.4, 5.2 Hz, 1H), 4.07 – 4.05 (m, 1H), 3.99 (d, *J* = 6.8 Hz, 1H), 3.66 – 3.58 (m, 1H), 3.30 – 3.23 (m, 1H), 2.30 – 2.06 (m, 4H), 1.99 – 1.89 (m, 1H), 1.85 – 1.71 (m, 1H), 1.41 (d, *J* = 7.3 Hz, 3H), 1.26 (d, *J* = 6.4 Hz, 3H), 1.08 (dd, *J* = 13.5, 6.8 Hz, 6H), 0.94 (dd, *J* = 16.5, 6.7 Hz, 6H) ppm.

HRMS (MALDI): *m*/*z* calcd. for $C_{26}H_{48}N_7O_7$ $[M+H]^+$ 570.3610, found, 570.3609.

BocNH-^{Ox}Pro-Gly-Val-Thr(Bn)-Ala-Val-OMe (**269**)

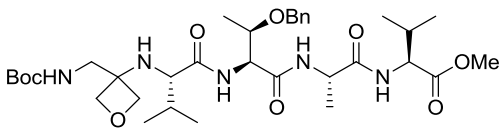


A mixture of BocNH-^{Ox}Pro-Gly-OH (38 mg, 0.172 mmol, 1.00 eq), TFA·H_2N-Val-Thr(Bn)-Ala-Val-OMe (69 mg, 0.139 mmol, 1.10 eq), *N*-methylmorpholine (0.056 mL, 0.506 mmol, 4.00eq), HOBT (0.021 g, 0.139 mmol, 1.10 eq) and EDC (0.027 g, 0.139 mmol, 1.10 eq) in CH_2Cl_2 (1.27 mL) was stirred at r.t. for 20 h. The reaction was quenched with aq. sat. NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The crude product was purified by FC on silica (hex:EA = 2:1) to yield the desired product **269** (0.050 g, 0.065 mmol, 51%) as a colorless glass.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 – 7.79 (m, 1H), 7.79 – 7.62 (m, 1H), 7.44 – 7.19 (m, 8H), 4.94 – 4.81 (m, 2H), 4.72 – 4.63 (m, 3H), 4.61 – 4.55 (m, 2H), 4.47 (dd, *J* = 8.6, 5.3 Hz, 1H), 4.39 (d, *J* = 7.3 Hz, 1H), 4.34 (d, *J* = 7.4 Hz, 1H), 4.20 (dd, *J* = 8.4, 5.2 Hz, 1H), 3.98 (dt, *J* = 4.2, 2.2 Hz, 1H), 3.77 – 3.67 (m, 5H), 3.50 (d, *J* = 17.7 Hz, 1H), 3.34 (dt, *J* = 11.0, 7.0 Hz, 1H), 2.17 – 2.04 (m, 4H), 1.98 (dt, *J* = 12.9, 6.6 Hz, 1H), 1.87 – 1.78 (m, 1H), 1.76 – 1.66 (m, 1H), 1.47 (s, 9H), 1.36 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 6.4 Hz, 3H), 0.94 (dd, *J* = 14.3, 6.8 Hz, 6H), 0.87 (t, *J* = 6.8 Hz, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.8, 172.5, 172.4, 172.3, 171.3, 169.1, 138.1, 128.5, 128.5, 127.9, 127.8, 127.7, 80.4, 77.0, 74.5, 71.4, 64.4, 62.3, 57.9, 57.5, 56.2, 52.2, 48.8, 45.9, 31.7, 31.0, 28.6, 28.4, 24.4, 19.4, 19.0, 18.9, 18.1, 18.0, 15.2 ppm.

BocNH-^{Ox}Gly-Val-Thr(Bn)-Ala-Val-OMe (**272**)

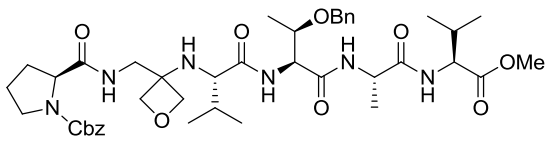


A mixture of TFA·H_2N-Thr(Bn)-Ala-Val-OMe (94 mg, 0.186 mmol, 1.10 eq), BocNH-^{Ox}Gly-Val-OH (51 mg, 0.169 mmol, 1.00 eq), N-methylmorpholine (74.2 µL, 0.675 mmol, 4.00 eq), HOBT (25.8 mg, 0.169 mmol, 1.00 eq) and EDC (32.3 mg, 0.169 mmol, 1.00 eq) in CH_2Cl_2 (1.7 mL) was stirred at r.t. for 20 h. The reaction was quenched with aq. sat. NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The crude product was purified by FC on silica (hex:EA = 2:1) to yield **272** (0.111 g, 0.164 mmol, 97%) as a colorless glass.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 – 7.68 (m, 1H), 7.43 – 7.27 (m, 5H), 7.11 (d, *J* = 7.7 Hz, 1H), 6.53 (d, *J* = 8.7 Hz, 1H), 5.46 (s, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.67 – 4.58 (m, 2H), 4.55 – 4.42 (m, 3H), 4.40 – 4.28 (m, 3H), 4.07 – 3.95 (m, 1H), 3.64 (dd, *J* = 14.2, 7.4 Hz, 1H), 3.36 (dd, *J* = 14.2, 4.8 Hz, 1H), 3.26 – 3.20 (m, 1H), 2.19 – 2.05 (m, 2H), 1.43 (s, 9H), 1.31 (d, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.93 – 0.87 (m, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.8, 172.2, 171.6, 169.2, 137.7, 128.6, 128.0, 127.8, 79.1, 78.6, 74.4, 71.7, 62.3, 57.2, 55.3, 52.2, 49.2, 31.8, 31.2, 28.4, 19.7, 18.9, 18.1, 17.9, 17.7, 15.0 ppm.

CbzNH-Pro-^{Ox}Gly-Val-Thr(Bn)-Ala-Val-OMe (**273**)



A mixture of TFA·H_2N-^{Ox}Gly-Val-Thr(Bn)-Ala-Val-OMe (29 mg, 0.050 mmol, 1.00 eq), CbzNH-Pro-OH (25 mg, 0.100 mmol, 2.00 eq), N-methylmorpholine (27 µL, 0.250 mmol, 5.00 eq), HOBT (15 mg, 0.100 mmol, 2.00 eq) and EDC (19 mg, 0.100 mmol, 2.00 eq) in CH_2Cl_2 (0.5 mL) was stirred at r.t. for 22 h. The reaction was quenched with aq. sat. NH_4Cl solution (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The crude product was purified by FC on silica (CH_2Cl_2:MeOH = 9:1) to yield **273** (0.038 g, 0.047 mmol, 94%) as a colorless glass.

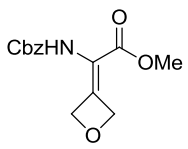
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.29 (m, 10H), 5.19 – 5.05 (m, 2H), 4.81 – 4.10 (m, 10H), 4.05 – 3.84 (m, 2H), 3.73 (s, 3H), 3.64 – 2.97 (m, 4H), 2.21 – 1.80 (m, 6H), 1.35 – 1.28 (m, 3H), 1.20 – 1.11 (m, 3H), 1.01 – 0.97 (m, 3H), 0.96 – 0.86 (m, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.5, 173.4, 172.3, 171.8, 169.8, 155.5, 137.8, 136.7, 128.6, 128.6, 128.1, 127.9, 127.9, 127.8, 79.1, 74.9, 71.7, 67.1, 63.3, 60.6, 57.4, 55.5, 52.3, 49.3, 47.1, 44.9, 32.1, 31.2, 29.8, 28.5, 24.8, 19.8, 19.0, 18.5, 18.3, 18.0, 15.1 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{42}H_{61}N_6O_{10}$ $[M+H]^+$ 809.444, found, 809.4447.

5.3 Experimental Procedures to Chapter 3

Methyl 2-(((benzyloxy)carbonyl)amino)-2-(oxetan-3-ylidene)acetate (**326a**)



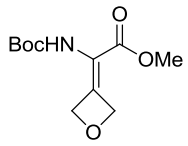
To a solution of **305** (506 mg, 1.526 mmol, 1.10 eq) in CH_2Cl_2 (2.5 mL) at r.t. was added DBU (220 µl, 1.46 mmol, 1.05 eq). The mixture was stirred for 10 min. **33** (89 µl, 1.39 mmol, 1.00 eq) was added. The mixture was stirred for 17.5 h. The crude mixture was purified by FC on silica (hex:EtOAc = 1:1) to yield **326a** (330 mg, 1.19 mmol, 86%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 – 7.29 (m, 5H), 6.78 (s, 1H), 5.50 – 5.35 (m, 4H), 5.11 (s, 2H), 3.79 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.7, 152.9, 139.9, 135.8, 128.8, 128.6, 128.4, 116.0, 78.8, 78.8, 67.6, 52.9 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{14}H_{15}N_1Na_1O_5$ $[M+Na]^+$ 300.0842, found, 300.0839.

Methyl 2-((tert-butoxycarbonyl)amino)-2-(oxetan-3-ylidene)acetate (**326b**)



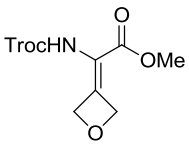
To a solution of **306** (517 mg, 1.74 mmol, 1.10 eq) in CH_2Cl_2 (15.8 mL) at r.t. was added DBU (250 µl, 1.66 mmol, 1.05 eq). The mixture was stirred for 10 min. **33** (102 µl, 1.58 mmol, 1.00 eq) was added. The mixture was stirred for 16.5 h. The crude mixture was purified by FC on silica (hex:EtOAc = 1:1) to yield **326b** (278 mg, 1.14 mmol, 72%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.53 (s, 1H), 5.45 – 5.34 (m, 4H), 3.78 (s, 3H), 1.43 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.9, 152.0, 139.0, 116.2, 80.8, 78.8, 78.7, 52.6, 28.1 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{11}H_{17}N_1Na_1O_5$ $[M+Na]^+$ 266.0999, found, 266.0997.

Methyl 2-(oxetan-3-ylidene)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)acetate (**326c**)

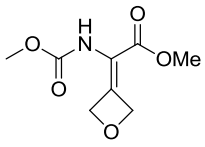


To a solution of methyl 2-amino-2-(dimethoxyphosphoryl)acetate (119 mg, 0.604 mmol, 1.50 eq) in CH_2Cl_2 (1.51 mL) was added Et_3N (107 µl, 0.765 mmol, 1.90 eq) followed by dropwise trichloroethyl chloroformate (94 µl, 0.684 mmol, 1.70eq) at r.t. The mixture was stirred for 30 min at r.t. CH_2Cl_2 (2.52 mL) and DBU (176 µl, 1.167 mmol, 2.90 eq) were added and the mixture was stirred for 10 min before **33** (25.9 µL, 0.402 mmol, 1.00 eq) was added slowly. The crude mixture was purified by FC on silica (hex:EtOAc = 1:1) to yield **326c** (88 mg, 0.276 mmol, 69%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.97 (s, 1H), 5.48 – 5.38 (m, 4H), 4.73 (s, 2H), 3.83 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.6, 115.6, 95.2, 78.8, 78.6, 76.4, 74.9, 53.1 ppm.

Methyl 2-((methoxycarbonyl)amino)-2-(oxetan-3-ylidene)acetate (**326d**)



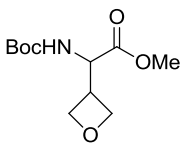
To a solution of methyl 2-(dimethoxyphosphoryl)-2-((methoxycarbonyl)amino)acetate (340 mg, 1.33 mmol, 1.10 eq) in CH_2Cl_2 (12.1 mL) at r.t. was added DBU (192 µL, 1.27 mmol, 1.05 eq). The mixture was stirred for 10 min. **33** (78 µL, 1.21 mmol, 1.00 eq) was added. The mixture was stirred for 16.5 h. The crude mixture was filtered over a pad of silica with EtOAc (80 mL). The solvent was removed under reduced pressure yielding **326d** (0.240 g, 1.19 mmol, 98%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.71 (s, 1H), 5.49 – 5.31 (m, 4H), 3.79 (s, 3H), 3.69 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.8, 153.6, 139.8, 116.1, 78.8, 78.8, 52.9, 52.8 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_8H_{11}N_1Na_1O_5$ $[M+Na]^+$ 224.0529, found, 224.0533.

Methyl 2-((tert-butoxycarbonyl)amino)-2-(oxetan-3-yl)acetate **(328b)**



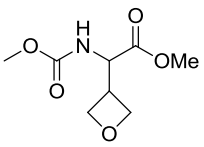
A mixture of Rh(BPE)(cod)triflate (1.0 mg, 1.64 μmol, 2.00 mol-%) and **326b** (20 mg, 0.082 mmol, 1.00 eq) in MeOH (0.66 mL) was stirred under 10 atm of H_2 for 36 h. The mixture was passed over a silica plug with EtOAc (20 mL) to remove the catalyst and the filtrate was concentrated to leave **328b** (20 mg, 0.082 mmol, 99%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.22 (d, *J* = 9.1 Hz, 1H), 4.79 – 4.48 (m, 4H), 3.72 (s, 3H), 1.44 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.8, 155.8, 73.8, 73.4, 54.6, 52.7, 37.7, 28.4 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{11}H_{20}N_1O_5$ $[M+H]^+$ 246.1336, found, 246.1341.

Methyl 2-((methoxycarbonyl)amino)-2-(oxetan-3-yl)acetate **(328d)**



A mixture of Rh(BPE)(cod)triflate (0.5 mg, 0.81 μmol, 2.00 mol-%) and **326d** (8.1 mg, 0.040 mmol, 1.00 eq) in MeOH (0.16 mL) was stirred under 10 atm of H_2 for 60 h. The mixture was purified by CC on silica (CH_2Cl_2:acetone = 9:1) to yield **328d** (5 mg, 0.025 mmol, 61%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.35 (d, *J* = 8.7 Hz, 1H), 4.80 – 4.52 (m, 5H), 3.74 (s, 3H), 3.71 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.5, 157.1, 73.7, 73.4, 55.1, 52.8, 37.8 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_8H_{14}N_1O_5$ $[M+H]^+$ 204.0866, found, 204.0868.

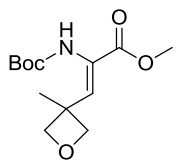
(*Z*)-Methyl 2-(((benzyloxy)carbonyl)amino)-3-(3-methyloxetan-3-yl)acrylate (**329a**)

To a solution of **305** (310 mg, 0.936 mmol, 1.10 eq) in CH_2Cl_2 (2.00 mL) at r.t. was added DBU (0.136 mL, 0.905 mmol, 1.05 eq). The mixture was stirred for 10 min. 3-methyloxetane-3-carbaldehyde (125 mg, 0.624 mmol, 1.00 eq) in CH_2Cl_2 (2.00 mL) was added. The mixture was stirred for 17.5 h. The crude mixture was purified by FC on silica (hex:EtOAc = 1:1) to yield **329a** (185 mg, 0.606 mmol, 97%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.40 – 7.28 (m, 5H), 6.62 (s, 1H), 6.40 (s, 1H), 5.12 (s, 2H), 4.75 (d, *J* = 5.6 Hz, 2H), 4.35 (d, *J* = 5.3 Hz, 2H), 3.75 (s, 3H), 1.59 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.8, 154.3, 138.3, 135.6, 128.4, 128.3, 128.1, 124.7, 81.7, 67.7, 52.8, 41.0, 24.2 ppm.

(*Z*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(3-methyloxetan-3-yl)acrylate (**329b**)



To a solution of methyl **306** (1.00 g, 3.36 mmol, 1.00 eq) in CH_2Cl_2 (51 mL) at r.t. was added DBU (0.56 mL, 3.70 mmol, 1.10 eq). The mixture was stirred for 10 min. 3-methyl-oxetane-3-carbaldehyde (1.97 g, 34 wt% solution in CH_2Cl_2, 6.73 mmol, 2.00 eq) was added. The mixture was stirred for 16 h. The crude mixture was filtered over a pad of silica with EA (50 mL) and concentrated under reduced pressure. The crude product was purified by FC on silica (hex:EtOAc = 2:1) yielding **329b** (0.82 g, 3.02 mmol, 90 %) as a viscous colorless oil that solidified upon standing.

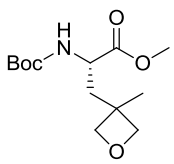
^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.54 (s, 1H), 6.02 (s, 1H), 4.79 (d, *J* = 5.8 Hz, 2H), 4.39 (d, *J* = 5.8 Hz, 2H), 3.79 (s, 3H), 1.62 (s, 3H), 1.45 (s, 9H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ = 165.6, 153.7, 136.9, 124.9, 81.8, 81.1, 52.7, 41.0, 28.3, 24.2 ppm.

HRMS (ESI+): m/z calcd. for $C_{13}H_{21}NNaO_5$ $[M+Na]^+$ 294.1312, found, 294.1312.

IR (neat): ν [cm^{-1}] = 3220, 2962, 2883, 1718, 1342, 1277, 1160, 977, 960, 829.

(*S*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(3-methyloxetan-3-yl)propanoate (**330b**)



To a solution of $[Rh(COD)_2]BF_4$ (3.7 mg, 9.2 μmol, 0.05 eq) and (*R*)-MonoPhos (6.6 mg, 18 μmol, 0.10 equiv.) in CH_2Cl_2 (1.15 mL) under nitrogen was added a solution of **329b** (50.0 mg, 180 μmol, 1.00 equiv.) in CH_2Cl_2 (3.46 mL). The flask was equipped with a hydrogen ballon for 4.5 h and the solution was concentrated under reduced pressure. The residue was purified by FC on silica (hex:EA = 1:1) yielding **330b** (24.1 mg, 88.0 mmol, 48 %) as a colorless oil.

^{1}H NMR (400 MHz, CDCl3) δ = 5.04 (d, *J* = 8.3 Hz, 1H), 4.49 (d, *J* = 5.8 Hz, 1H), 4.39 (d, *J* = 5.8 Hz, 1H), 4.34 (m, 1H), 4.29 – 4.24 (m, 2H), 3.70 (s, 3H), 2.12 – 1.93 (m, 2H), 1.44 (s, 3H), 1.40 (s, 9H) ppm.

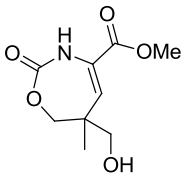
^{13}C NMR (101 MHz, CDCl3) δ = 173.4, 155.2, 83.1, 80.2, 52.5, 50.9, 41.7, 38.3, 28.4, 22.8.

HRMS (ESI+): m/z calcd. for $C_{13}H_{23}NNaO_5$ $[M+Na]^+$ 296.1468, found, 296.1464.

IR (neat): ν [cm^{-1}] = 3335, 2968, 2871, 1746, 1713, 1521, 1367, 1251, 1166, 978.

[α]^{23}D **-** 3.40 (*c* = 0.260, $CHCl_3$)

Methyl 6-(hydroxymethyl)-2-oxo-2,3,6,7-tetrahydro-1,3-oxazepine-4-carboxylate (**334**)

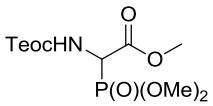


A solution of **329b** (150 mg, 0.553 mmol, 1.00 eq) in CH_2Cl_2 (4.42 mL) and TFA (1.11 mL) was stirred at 0 °C for 3 h. The mixture was poured into sat. aq. $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined org. layers were dried over Na_2SO_4 and concentrated to yield **334** (50 mg, 0.249 mmol, 45%).

^{1}H NMR (400 MHz, CDCl3) δ = 7.35 (s, 1H), 6.12 (s, 1H), 4.34 (dd, *J* = 12.0, 1.2 Hz, 1H), 4.11 (dd, *J* = 12.0, 0.8 Hz, 1H), 3.84 (s, 3H), 3.66 (d, *J* = 10.9 Hz, 1H), 3.54 (d, *J* = 10.9 Hz, 1H), 1.87 (s, 1H), 1.13 (s, 3H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 163.7, 156.3, 125.3, 123.1, 72.2, 67.3, 53.6, 42.6, 20.2 ppm

Methyl 2-(dimethoxyphosphoryl)-2-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)acetate (**335**)



To a mixture of methyl **305** (3.16 g, 9.54 mmol, 1.00 eq) and palladium on carbon (10 wt-% Pd, 0.508 g, 0.477 mmol, 5.00 mol-%) under N_2 was added MeOH (31.8 mL). The flask was equipped with a hydrogen ballon for 5 h. The mixture was filtered over a pad of celite with MeOH (100 mL). The filtrate was concentrated. THF (30 mL), Et_3N (1.99 ml, 14.3 mmol, 1.50 eq) and 2,5-dioxopyrrolidin-1-yl (2-(trimethylsilyl)ethyl) carbonate (2.72 g, 10.5 mmol, 1.10 eq) were added and the mixture was stirred for 14 h. The mixture was concentrated and purified by FC on silica (EA:hex=2:1→EA) to yield **335** (1.72 g, 5.02 mmol, 53 %) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.50 – 5.45 (m, 1H), 4.89 (dd, *J* = 22.6, 9.3 Hz, 1H), 4.19 – 4.11 (m, 2H), 3.83 – 3.76 (m, 9H), 1.14 – 0.74 (m, 2H), 0.00 (s, 9H) ppm.

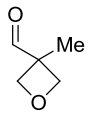
^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.4, 156.0 (d, *J* = 8.1 Hz), 64.4, 54.2 (d, *J* = 6.4 Hz), 54.1 (d, *J* = 6.8 Hz), 53.4 , 52.0 (d, *J* = 148.4 Hz), 17.7, -1.44 ppm.

^{31}P NMR (162 MHz, $CDCl_3$) δ = 18.6 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{11}H_{25}NO_7PSi$ $[M+H]^+$ 342.1132, found, 342.1130.

IR (neat): ν [cm^{-1}] = 2955, 1748, 1715, 1522, 1311, 1248, 1212, 1179, 1029, 859, 834, 776, 695.

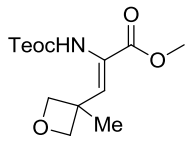
3-Methyloxetane-3-carbaldehyde (**311**)



To a solution of oxalyl chloride (3.77 mL, 43.1 mmol, 1.10 eq) in CH_2Cl_2 (89.9 mL) was slowly added DMSO (6.11 mL, 86.0 mmol, 2.20 eq) in CH_2Cl_2 (18.0 mL) at -78 °C. After stirring for 15 min (3-methyloxetan-3-yl)methanol (3.91 mL, 39.2 mmol, 1.00 eq) in CH_2Cl_2 (89.9 mL) was added slowly. After stirring for 0.5 h Et_3N (16.4 mL, 117 mmol, 3.00 eq) was added. The mixture was stirred for 30 min, warmed to r.t. and stirred for 10 min before quenching with sat. aq. NH_4Cl solution (150 mL). The mixture was extracted with CH_2Cl_2 (3 x 70 mL), dried over Na_2SO_4 and concentrated to a volume of about 5 mL to yield 3-methyloxetane-3-carbaldehyde (2.67 g, 26.7 mmol, 68 %) as a colorless solution (26.4 wt-% by ^{1}H NMR with 1,4-dinitrobenzene as the internal standard) in CH_2Cl_2.

Analytical data was in accordance with those reported in the literature.[83]

(*Z*)-Methyl 3-(3-methyloxetan-3-yl)-2-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)acrylate (**329c**)



To a solution of **335** (0.258 g, 0.756 mmol, 1.00 eq) in CH_2Cl_2 (12.60 mL) at r.t. was added 1,1,3,3-tetramethylguanidine (0.104 mL, 0.831 mmol, 1.10 eq). The mixture was stirred for 10 min. 3-methyloxetane-3-carbaldehyde (0.303 g, 0.907 mmol, 1.20 eq) was added. The mixture was stirred for 28 h. The crude mixture was concentrated and purified by FC on silica (hex:EA = 4:1 → hex:EA = 1:1) to yield **329c** (0.180 g, 0.571 mmol, 76 %) as a very viscous colorless oil.

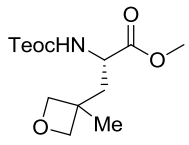
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.60 (s, 1H), 6.10 (s, 1H), 4.78 (d, *J* = 5.8 Hz, 2H), 4.40 (d, *J* = 5.8 Hz, 2H), 4.17 (d, *J* = 17.2 Hz, 2H), 3.80 (s, 3H), 1.62 (s, 3H), 1.14 – 0.92 (m, 2H), 0.04 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.4, 154.9, 137.7, 128.5, 81.8, 64.4, 52.8, 41.0, 24.2, 17.8, -1.3. ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{14}H_{25}NNaO_5Si$ $[M+Na]^+$ 338.1394, found, 338.1393.

IR (neat): ν [cm^{-1}] = 3279, 2954, 2875, 1717, 1502, 1437, 1248, 1233, 1051, 979, 835, 858.

(*S*)-Methyl 3-(3-methyloxetan-3-yl)-2-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)propanoate (**330c**)



To a mixture of $[Rh(COD)_2]BF_4$ (6.8 mg, 0.017 mmol, 5.00 mol-%), (*R*)-MonoPhos (12.1 mg, 0.034 mmol, 10.0 mol-%) under a H_2 atmosphere was added was added a solution of **329c** (106 mg, 0.336 mmol, 1.00 eq) in CH_2Cl_2 (8.00 mL). The reaction mixture was stirred at r.t. under H_2 (balloon) for 19 h. The crude mixture was concentrated and purified by FC on silica (hex:EA = 2:1) to yield **330c** (93.0 mg, 0.293 mmol, 91 %) as a colorless oil

A racemic sample was obtained by hydrogenation with palladium on charcoal (5.00 mol-%) as a catalyst in MeOH.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.03 (d, *J* = 9.1 Hz, 1H), 4.50 (d, *J* = 5.9 Hz, 1H), 4.45 – 4.35 (m, 2H), 4.29 (dd, *J* = 5.8, 2.6 Hz, 2H), 4.19 – 4.09 (m, 2H), 3.73 (s, 3H), 2.15 – 1.94 (m, 2H), 1.46 (s, 3H), 1.04 – 0.86 (m, 9H) ppm.

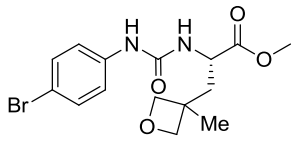
^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.3, 156.2, 83.2, 83.1, 63.8, 52.6, 51.3, 41.6, 38.4, 22.8, 17.8, -1.4 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{14}H_{27}NNaO_5Si$ $[M+Na]^+$ 340.1551, found, 340.1558.

IR (neat): ν [cm^{-1}] = 3322, 2955, 2871, 1747, 1719, 1530, 1249, 1211, 1058, 979, 859, 837.

***[α]*^{23}D -** 3.44 (*c* = 0.545, $CHCl_3$)

(*S*)-methyl 2-(3-(4-bromophenyl)ureido)-3-(3-methyloxetan-3-yl)propanoate (**333**)



a) From Teoc-protected amino acid

To a solution of **330c** (38.0 mg, 0.120 mmol, 1.00 eq) in acetonitrile (0.48 mL) was added CsF (54.5 mg, 0.359 mmol, 3.00 eq). The mixture was stirred at 80 °C for 20 h diluted with sat. aq. NaHCO3 solution (5 mL) and extracted with EA (3 x 15 mL). The combined org. layers were dried over Na2SO4 and concentrated.

The residue was redissolved in CH2Cl2 (1.0 mL) and to the solution was added 1-bromo-4-isocyanatobenzene (28.4 mg, 0.144 mmol, 1.20 eq). The mixture was stirred for 15 h and then directly purified by preparative TLC (EA:hex=2:1) to yield **333** (18.0 mg, 0.048 mmol, 41 %) as a colorless foam.

b) From Boc-protected amino acid

A solution of **330b** (24.1 mg, 0.09 mmol, 1.00 equiv.) in CH_2Cl_2 (0.71 mL)/TFA (0.18 mL) was stirred at 0 °C until starting material was fully consumed. To the solution was added toluene (1 mL) and all volatiles were removed. The residue was evaporated from toluene (2 x 1 mL).

The residue was dissolved in CH_2Cl_2 (0.88 mL) and 1-bromo-4-isocyanatobenzene (19.2 mg, 0.10 mmol, 1.10 equiv.) and *N*-ethyl-*N*-isopropyl-propan-2-amine (0.08 mL, 0.44 mmol, 5.00 equiv.) were added. The mixture was stirred at r.t. overnight. The solution was concentrated under reduced pressure and the residue was purified by preparative TLC yielding **333** (6.0 mg, 0.016 mmol, 18 %) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 – 7.36 (m, 2H), 7.22 – 7.17 (m, 2H), 7.12 – 7.04 (m, 1H), 5.62 – 5.52 (m, 1H), 4.69 – 4.57 (m, 1H), 4.58 – 4.50 (m, 1H), 4.49 – 4.41 (m, 1H), 4.38 (dd, *J* = 5.8, 3.8 Hz, 2H), 3.77 (s, 3H), 2.21 – 2.01 (m, 2H), 1.50 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.5, 154.8, 137.3, 132.1, 121.8, 116.3, 83.1, 83.0, 52.7, 50.4, 41.4, 38.4, 22.6 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{15}H_{20}BrN_2O_4$ $[M+H]^+$ 371.0601, found, 371.0599.

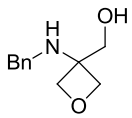
IR (neat): ν [cm^{-1}] = 3338, 2926, 2867, 1743, 1657, 1592, 1545, 1489, 1306, 1210, 978, 827.

***[α]*^{23}D** + 3.19 (*c* = 0.150, $CHCl_3$)

HPLC (derivative from 330c) Daicel Chiralcel OD-R, 55 % H_2O, 45 % ACN, 0.4 mL/min, 27 °C, 223 nm, 84 % *ee* (t_R (major) = 32.8 min, t_R (minor) = 30.6 min).

HPLC (derivative from 330b) Daicel Chiralcel OD-R, 55 % H_2O, 45 % ACN, 0.4 mL/min, 27 °C, 223 nm, >98 % *ee* (t_R (major) = 23.2 min, t_R (minor) = 21.8 min).

(3-(Benzylamino)oxetan-3-yl)methanol (**337**)



To a solution of **131** (2.00 g, 5.76 mmol, 1.00 equiv.) in MeOH (58 mL) were added magnesium turnings (1.40 g, 57.6 mmol, 10.0 equiv.). The mixture was stirred at r.t. for 2h until all magnesium had dissolved. TLC (EA) still indicated remaining starting material. Magnesium turnings (0.70 g, 28.8 mmol, 5.00 equiv.) were added, stirred for another 2 h. TLC (EA) indicated full conversion. The reaction mixture was diluted with EA (50 mL) and sat. aq. NH4Cl solution (50 mL) and water (20 mL) were added. The mixture was stirred until all solids had dissolved and was then extracted with EA (3 x 50 mL). The combined organic layers were dried over Na2SO4 and concentrated. The crude residue was purified by FC on silica (100% EA) to yield (3-(benzylamino)oxetan-3-yl)methanol (0.651 g, 3.37 mmol, 59%) as a colorless wax.

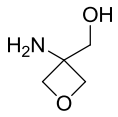
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.27 (m, 5H), 4.57 (d, J = 7.0 Hz, 2H), 4.42 (d, J = 7.0 Hz, 2H), 3.89 (s, 2H), 3.78 (s, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.8, 128.8, 128.1, 127.6, 79.2, 64.3, 60.9, 47.2 ppm.

HRMS (ESI+): m/z calcd. for $C_{11}H_{16}N_1O_2$ $[M+H]^+$ 194.1176, found, 194.1175.

IR (neat): ν [cm^{-1}] = 3356, 2944, 2872, 1453, 1045, 968, 737, 698.

(3-aminooxetan-3-yl)methanol (**338**)



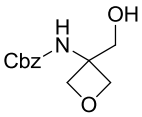
To a mixture of **337** (0.651 g, 3.37 mmol, 1.00 equiv.) and palladium on carbon (0.179 g, 10 wt-%, 0.168 mmol, 5 mol-%) under an atmosphere of N_2 was added MeOH (34 mL). The resulting suspension was stirred under H_2 (balloon) for 18 h. The mixture was filtered through a pad of celite with MeOH (50 mL) and the filtrate was concentrated to yield (3-aminooxetan-3-yl)methanol (0.343 g, 3.33 mmol, 99%) as a colorless solid.

^{1}H NMR (400 MHz, MeOH) δ = 4.57 – 4.38 (m, 4H), 3.70 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 82.2, 67.3, 57.7 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_4H_{10}N_1O_2$ $[M+H]^+$ 104.0706, found, 104.0708.

Benzyl (3-(hydroxymethyl)oxetan-3-yl)carbamate (**312**)



To a solution of **338** (0.095 g, 0.921 mmol, 1.00 eq) in CH_2Cl_2 (9.21 ml) was added benzyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.253 g, 1.01 mmol, 1.10 eq) followed by Et_3N (0.257 ml, 1.843 mmol, 2.00 eq). The mixture was stirred for 15 h. TLC showed almost no conversion. DMAP (0.034 g, 0.276 mmol, 30.0 mol-%) was added and the mixture was stirred for 50 min. The colorless solution was concentrated and the residue was purified by FC on silica (hex:EA=1:1) to yield **312** (0.151 g, 0.636 mmol, 69%) as a colorless oil.

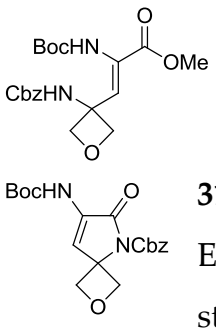
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 – 7.29 (m, 5H), 5.44 (s, 1H), 5.09 (s, 2H), 4.70 (d, *J* = 6.6 Hz, 2H), 4.52 (d, *J* = 6.1 Hz, 2H), 4.01 (s, 2H), 2.65 (s, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.5, 136.0, 128.8, 128.5, 128.4, 78.2, 67.2, 65.7, 57.2 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{12}H_{15}N_1Na_1O_4$ $[M+Na]^+$ 260.0893, found, 260.0894.

IR (neat): ν [cm^{-1}] = 3370, 2934, 2889, 1696, 1509, 1455, 1237, 1045, 740.

(*Z*)-methyl 3-(3-(((benzyloxy)carbonyl)amino)oxetan-3-yl)-2-((*tert*-butoxycarbonyl)amino)acrylate (**336**)



To a solution of oxalyl chloride (0.116 mL, 1.33 mmol, 1.10 eq) in CH_2Cl_2 (5.50 mL) was slowly added DMSO (0.189 ml, 2.66 mmol, 2.20 eq) in CH_2Cl_2 (1.10 mL) at -78 °C. After stirring for 15 min **312** in CH_2Cl_2 (5.50 mL) was added slowly. After stirring for 0.5 h Et_3N (0.506 ml, 3.63 mmol, 3.00 eq) was added. The mixture was stirred for 30 min, warmed to r.t. and stirred for 10 min before quenching with sat. aq. NH_4Cl solution (150 mL). The mixture was extracted with CH_2Cl_2 (3 x 70 mL), washed with water (50 mL) dried over Na_2SO_4 and concentrated. The crude product was used in the next step without further purification.

To a solution of **306** (0.300 g, 1.01 mmol, 1.00 eq) in CH_2Cl_2 (5.04 mL) at r.t. was added DBU (0.152 ml, 1.01 mmol, 1.00 eq). The mixture was stirred for 10 min. benzyl (3-formyloxetan-3-yl)carbamate (0.285 g, 1.21 mmol, 1.20 eq) in CH_2Cl_2 (5.04 mL) was added.The mixture was stirred for 14 h. The crude mixture was concentrated und purified by FC on silica (hex:EA = 2:1) yielding **336** (0.198 g, 0.487 mmol, 48.3%) as a colorless oil and **339** (0.110 g, 0.294 mmol, 29%) as a colorless solid.

336:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.23 (m, 5H), 5.98 (s, 1H), 5.03 (s, 2H), 4.72 (s, 4H), 3.76 (s, 3H), 1.37 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.2, 155.3, 153.7, 136.2, 128.6, 128.3, 128.2, 126.5, 81.6, 79.6, 66.9, 55.8, 53.0, 28.1 ppm.

HRMS (ESI+): *m*/*z* calcd. for $C_{20}H_{26}N_2Na_1O_7$ $[M+Na]^+$ 429.1632, found, 429.1629.

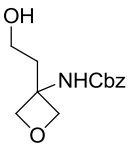
IR (neat): ν [cm^{-1}] = 2926, 1699, 1511, 1354, 1265, 1245, 1155, 1052, 965, 758, 697.

339:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 – 7.30 (m, 5H), 6.85 (s, 1H), 5.45 (s, 2H), 5.33 (d, J = 6.4 Hz, 2H), 4.74 (d, J = 6.4 Hz, 2H), 1.50 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.1, 152.2, 150.4, 135.0, 128.8, 128.7, 128.4, 121.8, 82.2, 77.4, 68.6, 64.4, 28.2 ppm.

Benzyl (3-(2-hydroxyethyl)oxetan-3-yl)carbamate (**348**)



346 (3.36 g, 23.6 mmol, 1.00 eq) and benzylamine (2.58 mL, 23.6 mmol, 1.00 eq) were mixed neat and stirred at r.t. for 14 h. The crude product was used in the next step without further purification.

To a suspension of LAH (1.72 g, 45.3 mmol, 1.92 eq) in THF (89 mL) at 0 °C was drop wise added a solution of crude ethyl 2-(3-(benzylamino)oxetan-3-yl)acetate (5.89 g, 23.6 mmol, 1.00 eq) in THF (30 mL). The mixture was further stirred for 10min at 0 °C. To the mixture was added a half-sat. aq. solution of Rochelle's salt (50 mL). The emulsion was stirred for 30 min. The layers were separated and the aq. layer was extracted with EA (2 x 50 mL). The combined org. layers were dried over Na_2SO_4 and concentrated to yield crude **347**.

To a mixture of crude **347** (4.90 g, 23.6 mmol, 1.00 eq) and palladium on carbon (1.26 g, 1.18 mmol, 5.00 mol-%) under N_2 was added MeOH (118 mL). The mixture was purged with H_2 (balloon) and stirred under H_2 for 16 h. The mixture was filtered through a pad of celite with EA (100 mL) and the filtrate was concentrated. To the filtrate were added CH_2Cl_2 (50 mL), Et_3N (6.59 ml, 47.3 mmol, 2.00 eq) and benzyl (2,5-dioxopyrrolidin-1-yl) carbonate (5.89 g, 23.6 mmol, 1.00 eq). The mixture was stirred for 20 h, concentrated and directly purified by FC on silica (hex:EA = 1:1) to yield **348** (3.11 g, 12.4 mmol, 52 %) as a colorless oil.

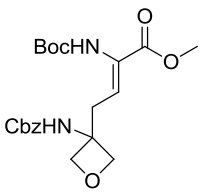
^{1}H NMR (400 MHz, CDCl3) δ = 7.43 – 7.33 (m, 5H), 5.52 (br s, 1H), 5.14 (s, 2H), 4.85 (d, *J* = 6.5 Hz, 2H), 4.60 (d, *J* = 6.5 Hz, 2H), 3.81 (t, *J* = 5.6 Hz, 2H), 2.26 (t, *J* = 5.6 Hz, 2H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 155.4, 136.1, 128.6, 128.3, 128.2, 81.0, 66.9, 59.0, 55.9, 38.6 ppm.

HRMS (ESI+): m/z calcd. for $C_{13}H_{17}NNaO_4$ $[M+Na]^+$ 274.1050, found, 274.1052.

IR (neat): ν [cm^{-1}] = 3313, 2954, 2883, 1694, 1523, 1267, 1058, 971, 737, 696.

(*Z*)-methyl 4-(3-(((benzyloxy)carbonyl)amino)oxetan-3-yl)-2-((*tert*-butoxycarbonyl)amino)but-2-enoate (**350**)



To a solution of oxalyl chloride (434 µl, 4.96 mmol, 1.20 eq) in CH_2Cl_2 (18.8 mL) was slowly added DMSO (646 µl, 9.10 mmol, 2.20 eq) in CH_2Cl_2 (3.7 mL) at -78 °C. After stirring for 15 min benzyl (3-(2-hydroxyethyl)oxetan-3-yl)carbamate (1.04 g, 4.13 mmol, 1.00 eq) in CH_2Cl_2 (18.8 mL) was added slowly. After stirring for 0.5 h Et_3N (1.73 mLl, 12.4 mmol, 3.00 eq) was added. The mixture was stirred for 30 min, warmed to r.t. and stirred for 10 min before quenching with sat. aq. NH_4Cl solution (150 ml). The mixture was extracted with DCM (3 x 70 mL), dried over Na_2SO_4 and concentrated und red. pressure to a volume of about 5 mL to yield crude benzyl (3-(2-oxoethyl)oxetan-3-yl)carbamate (0.942 g, 3.78 mmol, 91 %) as a light yellow solution (13.7 wt-% by NMR with 1,4-dinitrobenzene as internal standard) in CH_2Cl_2.

To a solution of **306** (0.600 g, 2.02 mmol, 1.10 eq) in CH_2Cl_2 (18.3 mL) at r.t. was added DBU (0.304 mL, 2.02 mmol, 1.10 eq). The mixture was stirred for 10 min. Crude benzyl (3-(2-oxoethyl)oxetan-3-yl)carbamate (13.7 wt-% in CH_2Cl_2, 3.34 g, 1.83 mmol, 1.00 eq) was added. The mixture was stirred for 14 h. The crude

mixture was concentrated and purified by FC on silica (hex:EA = 2:1) yielding **350** (0.640 g, 1.52 mmol, 83 %) as a colorless foam.

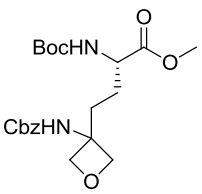
^{1}H NMR (400 MHz, CDCl3) δ = 7.38 – 7.28 (m, 5H), 6.17 (s, 1H), 6.00 (br s, 1H), 5.11 (s, 2H), 5.00 (br s, 2H), 4.46 (d, *J* = 6.2 Hz, 2H), 3.78 (s, 3H), 2.94 (d, *J* = 7.5 Hz, 2H), 1.47 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 164.9, 155.1, 153.6, 136.5, 132.4, 129.4, 128.6, 128.2, 128.1, 81.4, 80.0, 66.6, 55.7, 52.7, 36.0, 28.3 ppm.

HRMS (ESI+): m/z calcd. for $C_{21}H_{28}N_2NaO_7$ $[M+Na]^+$ 443.1789, found, 443.1787.

IR (neat): ν [cm^{-1}] = 2961, 2882, 1701, 1500, 1250, 1157, 1048, 1027, 976, 738.

(*S*)-methyl 4-(3-(((benzyloxy)carbonyl)amino)oxetan-3-yl)-2-((*tert*-butoxycarbonyl)amino)butanoate (**351**)



To a mixture of $[Rh(COD)_2]BF_4$ (9.8 mg, 0.024 mmol, 5.00 mol-%) (*R*)-MonoPhos (17.4 mg, 0.048 mmol, 10.0 mol-%) under an atmosphere of H_2 was added **350** (203 mg, 0.483 mmol, 1.00 eq) in CH_2Cl_2 (12.1 mL). The reaction mixture was stirred at r.t. 5.5 h. The solvent was removed under red. pressure and the residue was purified by FC on silica (EA:hex = 1:2) to yield **351** (0.166 g, 0.393 mmol, 81 %) as a colorless foam.

^{1}H NMR (400 MHz, CDCl3) δ = 7.42 – 7.32 (m, 5H), 5.24 (br s, 1H), 5.17 – 5.08 (m, 3H), 4.77 – 4.66 (m, 2H), 4.48 – 4.41 (m, 2H), 4.38 – 4.27 (m, 1H), 3.76 (s, 3H), 2.19 – 1.99 (m, 2H), 1.93 – 1.79 (m, 1H), 1.72 – 1.62 (m, 1H), 1.47 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 172.8, 155.5, 154.7, 136.2, 128.8, 128.4, 128.3, 80.5, 80.3, 67.0, 56.2, 53.2, 52.6, 31.7, 28.4, 27.2 ppm.

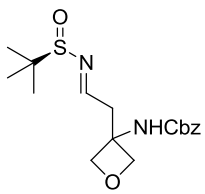
HRMS (ESI+): m/z calcd. for $C_{21}H_{30}N_2NaO_7$ $[M+Na]^+$ 445.1945, found, 445.1946.

IR (neat): ν [cm^{-1}] = 2966, 1710, 1510, 1259, 1162, 1051, 1028, 979, 741.

***[α]*^{23}D** - 0.421 (*c* = 0.435, $CHCl_3$)

SFC Daicel Chiralpak IB, 95 % CO_2, 5.0 % MeOH, 2.0 mL/min, 25 °C, 208 nm, >98 % *ee* (t_R (major) = 16.5 min, t_R (minor) = 15.1 min).

(*R*,*E*)-benzyl (3-(2-((tert-butylsulfinyl)imino)ethyl)oxetan-3-yl)carbamate (**345**)



To a solution of benzyl (3-(2-oxoethyl)oxetan-3-yl)carbamate in CH_2Cl_2 (13.7 wt-%, 3.25 g, 1.78 mmol, 1.00 eq) in THF (8.9 mL) were added (*R*)-2-methylpropane-2-sulfinamide (0.238 g, 1.96 mmol, 1.10 eq) and tetraethoxytitanium (0.746 mL, 3.56 mmol, 2.00 eq). The mixture was stirred at r.t. for 16 h and then poured into sat. aq. NaCl solution (100 mL). The resulting suspension was filtered over celite with EA (100 mL). The layers were separated and the aq. layer was extracted with EA (2 x 100 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC on silica (hex:EA = 2:1) to yield **345** (0.537 g, 1.52 mmol, 86%) as a colorless wax.

^{1}H NMR (400 MHz, CDCl3) δ 8.05 (t, *J* = 3.3 Hz, 1H), 7.40 – 7.29 (m, 5H), 5.54 (s, 1H), 5.15 – 4.97 (m, 2H), 4.75 (dd, *J* = 19.4, 6.9 Hz, 2H), 4.61 – 4.50 (m, 2H), 3.44 – 3.24 (m, 2H), 1.15 (s, 9H) ppm.

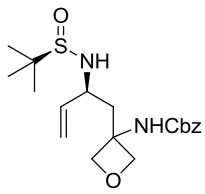
^{13}C NMR (101 MHz, CDCl3) δ = 165.7, 154.7, 136.1, 128.7, 128.5, 128.3, 80.7, 80.6, 67.0, 57.1, 54.8, 41.7, 22.5 ppm.

HRMS (ESI+): m/z calcd. for $C_{17}H_{24}N_2NaO_4S$ $[M+Na]^+$ 375.1349, found, 375.1346.

IR (neat): ν [cm^{-1}] = 2960, 1715, 1623, 1524, 1265, 1075, 980.

***[α]*^{23}D** -126 (*c* = 0.77, $CHCl_3$)

Benzyl (3-((*S*)-2-((*R*)-1,1-dimethylethylsulfinamido)but-3-en-1-yl)oxetan-3-yl)carbamate (**349**)



To a solution of **345** (287 mg, 0.814 mmol, 1.00 eq) in toluene (10.9 mL) was added vinylmagnesium bromide (2.03 mL, 2.04 mmol, 2.50 eq) at -78 °C. The mixture was stirred for 60 min. TLC still indicated the presence of starting material. Vinylmagnesium bromide (1.22 mL, 1.22 mmol, 1.50 eq) was added and the mixture was stirred for 60 min before sat. aq. NH_4Cl solution (30 mL) was added. The mixture was extracted with EA (3 x 30 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC on silica (hex:EA = 1:2) to yield **349** (0.203 g, 0.534 mmol, 66 %) as a colorless oil.

^{1}H NMR (400 MHz, CDCl3) δ 7.41 – 7.29 (m, 5H), 6.67 (s, 1H), 5.75 (ddd, *J* = 16.6, 10.3, 5.8 Hz, 1H), 5.25 – 5.08 (m, 4H), 4.72 (dd, *J* = 13.0, 6.8 Hz, 2H), 4.51 (dd, *J* = 31.3, 6.8 Hz, 2H), 4.01 – 3.91 (m, 1H), 3.30 (d, *J* = 6.6 Hz, 1H), 2.48 – 2.41 (m, 1H), 2.35 – 2.23 (m, 1H), 1.18 (s, 9H) ppm.

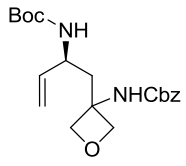
^{13}C NMR (101 MHz, CDCl3) δ = 154.7, 139.4, 136.5, 128.7, 128.3, 128.3, 115.9, 82.4, 80.6, 66.7, 56.0, 55.7, 55.4, 41.5, 22.8 ppm.

HRMS (ESI+): m/z calcd. for $C_{19}H_{29}N_2O_4S$ $[M+H]^+$ 381.1843, found, 381.1849.

IR (neat): ν [cm^{-1}] = 2957, 2880, 1711, 1523, 1264, 1226, 1046, 983, 925, 741.

***[α]*^{23}D** – 55.6 (*c* = 0.90, $CHCl_3$)

(*S*)-Benzyl (3-(2-Boc-aminobut-3-en-1-yl)oxetan-3-yl)carbamate (**344**)



To a solution of **349** (154 mg, 0.405 mmol, 1.00 eq) in CH_2Cl_2 (2.0 mL)/MeOH (2.0mL) at 0 °C was added HCl in dioxane (4 M, 506 µL, 2.02 mmol, 5.00 eq). The mixture was stirred at that temperature for 30 min. The reaction was quenched with sat. aq. $NaHCO_3$

solution (20 mL) and extracted with CH_2Cl_2 (4 x 20 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in CH_2Cl_2 (2.0 mL) and Boc_2O (141 µL, 0.607 mmol, 1.50 eq) was added. The mixture was stirred for 16 h. The crude solution was purified by FC on silica (hex:EA = 3:1) to yield the title compound **344** (147 mg, 0.390 mmol, 96 %) as a colorless oil.

^{1}H NMR (400 MHz, CDCl3) δ 7.43 – 7.28 (m, 5H), 6.34 (s, 1H), 5.79 (ddd, *J* = 16.3, 10.3, 5.1 Hz, 1H), 5.22 – 5.02 (m, 4H), 4.93 – 4.84 (m, 1H), 4.63 – 4.45 (m, 4H), 4.31 – 4.18 (m, 1H), 2.33 (d, *J* = 14.2 Hz, 1H), 2.09 (dd, *J* = 14.2, 11.0 Hz, 1H), 1.41 (s, 9H) ppm.

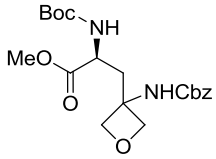
^{13}C NMR (101 MHz, CDCl3) δ = 155.9, 155.0, 138.2, 136.6, 128.6, 128.2, 128.1, 115.2, 81.4, 80.4, 80.3, 66.6, 55.4, 49.1, 40.3, 28.5 ppm.

HRMS (ESI+): m/z calcd. for $C_{20}H_{28}N_2NaO_5$ $[M+Na]^+$ 399.1890, found, 399.1892.

IR (neat): ν [cm^{-1}] = 2975, 1692, 1512, 1254, 1167, 1070, 982, 920.

[α]^{23}D + 0.83 (*c* = 0.87, $CHCl_3$)

(*S*)-methyl 3-(3-(((benzyloxy)carbonyl)amino)oxetan-3-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate (**340**)



To a solution of **344** (0.105 g, 0.279 mmol, 1.00 eq) in CH_2Cl_2 (10.5 mL)/MeOH (3.5 mL) at -78 °C was added NaOH in MeOH (2.5 M, 0.558 mL, 1.40 mmol, 5.00 eq). Ozonized oxygen was bubbled through the mixture until the color of the solution turned to blue. Nitrogen was bubbled through the blue solution until the color faded completely before sat. aq. NH_4Cl solution (10 mL) and water (10 mL) were added and the solution was allowed to warm to r.t. Sodium thiosulfate (200 mg) was added, the layers were separated and the aq. layer was extracted with CH_2Cl_2 (2 x 20 mL).

The combined org. layers were dried over Na_2SO_4 and concentrated to yield **340** (0.091 g, 0.223 mmol, 80 %) as a colorless oil.

^{1}H NMR (400 MHz, CDCl3) δ 7.40 – 7.32 (m, 5H), 6.26 (s, 1H), 5.33 (d, *J* = 7.8 Hz, 1H), 5.15 – 5.07 (m, 2H), 4.87 (d, *J* = 7.0 Hz, 1H), 4.58 – 4.49 (m, 3H), 4.36 (t, *J* = 8.4 Hz, 1H), 3.74 (s, 3H), 2.63 – 2.54 (m, 1H), 2.23 (dd, *J* = 14.1, 10.9 Hz, 1H), 1.40 (s, 9H) ppm.

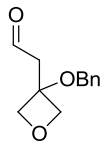
^{13}C NMR (101 MHz, CDCl3) δ = 172.7, 155.9, 154.9, 128.9, 128.7, 128.3, 128.2, 81.1, 80.9, 80.2, 66.8, 55.4, 52.9, 50.7, 38.7, 28.4 ppm.

HRMS (ESI+): m/z calcd. for $C_{20}H_{28}N_2NaO_7$ $[M+Na]^+$ 431.1789, found, 431.1788.

IR (neat): ν [cm^{-1}] = 2964, 1699, 1505, 1366, 1252, 1163, 1062, 981, 752, 698.

***[α]*^{23}D** + 10.8 (*c* = 1.77, $CHCl_3$)

2-(3-(benzyloxy)oxetan-3-yl)acetaldehyde (**317**)



Phenylmethanol (5.28 mL, 50.8 mmol, 6.50 eq) and **325** (0.766 g, 7.81 mmol, 1.00 eq) and piperidine (0.054 mL, 0.55 mmol, 0.07 eq) were mixed neat and stirred for 6 h. The mixture was directly purified by FC on silica (hex:EA=2:1) to yield **317** (0.975 g, 4.73 mmol, 60.5 % yield) as a colorless oil.

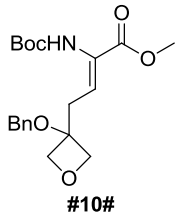
^{1}H NMR (400 MHz, CDCl3) δ = 9.80 (t, *J* = 2.2 Hz, 1H), 7.39 – 7.28 (m, 5H), 4.93 (d, *J* = 7.9 Hz, 2H), 4.62 (s, 2H), 4.58 (d, *J* = 7.9 Hz, 2H), 3.25 – 2.85 (m, 2H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 199.4, 137.6, 128.7, 128.1, 127.5, 80.2, 66.4, 48.9 ppm.

HRMS (ESI+): m/z calcd. for $C_{12}H_{18}NO_3$ $[M+H]^+$ 224.1281, found, 224.1280.

IR (neat): ν [cm^{-1}] = 2950, 2877, 1721, 1251, 1135, 1047, 1027, 973, 737, 697.

(*Z*)-Methyl 4-(3-(benzyloxy)oxetan-3-yl)-2-((*tert*-butoxycarbonyl)amino)but-2-enoate (**352**)



#10#

To a solution of **306** (0.438 g, 1.47 mmol, 1.10 eq) in CH_2Cl_2 (13.4 mL) at r.t. was added DBU (0.222 ml, 1.47 mmol, 1.10 eq). The mixture was stirred for 10 min. **317** (0.276 g, 1.34 mmol, 1.00 eq) was added. The mixture was stirred for 16 h. The crude mixture was concentrated and purified by FC on silica (hex:EA = 1:1) yielding **352** (0.388 g, 1.03 mmol, 77 %) as a very viscous light yellow oil.

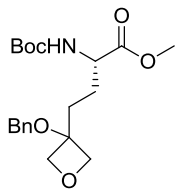
^{1}H NMR (400 MHz, CDCl3) δ = 7.43 – 7.28 (m, 5H), 6.59 (t, *J* = 7.0 Hz, 3H), 6.28 (br s, 1H), 4.78 (d, *J* = 7.0 Hz, 2H), 4.51 (s, 2H), 4.44 (d, *J* = 7.4 Hz, 2H), 3.78 (s, 3H), 2.94 (d, *J* = 6.9 Hz, 2H), 1.48 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 165.1, 153.2, 138.0, 128.7, 128.5, 128.0, 127.6, 81.0, 80.3, 78.3, 66.0, 52.6, 34.3, 28.4 ppm.

HRMS (ESI+): m/z calcd. for $C_{20}H_{27}NNaO_6$ $[M+Na]^+$ 400.1731, found, 400.1733.

IR (neat): ν [cm^{-1}] = 3319, 2953, 2877, 1715, 1495, 1367, 1243, 1157, 975, 1026, 738, 698.

(*S*)-Methyl 4-(3-(benzyloxy)oxetan-3-yl)-2-((*tert*-butoxycarbonyl)amino)butanoate (**353**)



To a solution of $[Rh(COD)_2]BF_4$ (11.5 mg, 0.028 mmol, 5.00 mol-%), (*R*)-MonoPhos (20.3 mg, 0.056 mmol, 10.0 mol-%) in CH_2Cl_2 (3.53 mL) was added a solution of **352** (213 mg, 0.564 mmol, 1.00 eq) in CH_2Cl_2 (10.6 mL). The reaction mixture was stirred at r.t.

under H_2 (balloon) for 5 h. The mixture was concentrated and purified by FC on silcia (hex:EA = 2:1) to yield methyl **353** (210 mg, 0.553 mmol, 98 %) as a colorless oil.

^{1}H NMR (400 MHz, CDCl3) δ = 7.39 – 7.27 (m, 5H), 5.11 (d, *J* = 8.3 Hz, 1H), 4.74 (d, *J* = 6.7 Hz, 2H), 4.44 (d, *J* = 3.9 Hz, 2H), 4.43 – 4.31 (m, 3H), 3.75 (s, 3H), 2.16 – 1.86 (m, 3H), 1.77 – 1.63 (m, 1H), 1.45 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 172.9, 155.4, 137.9, 128.5, 127.8, 127.4, 80.2, 80.2, 78.5, 65.4, 53.2, 52.4, 30.4, 28.3, 28.3, 26.3 ppm.

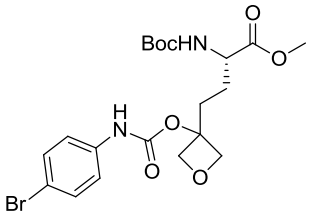
HRMS (ESI+): m/z calcd. for $C_{20}H_{29}NNaO_6$ $[M+Na]^+$ 402.1887, found, 402.1886.

IR (neat): ν [cm^{-1}] = 3342, 2953, 2875, 1744, 1714, 1454, 1367, 1164, 1055, 1027, 977, 739.

[α]^{23}D **+** 15.2 (*c* = 0.655, $CHCl_3$)

SFC Daicel Chiralpak IB, 98 % CO_2, 2.0 % MeOH, 2.0 mL/min, 25 °C, 208 nm, >98 % *ee* (t_R (major) = 13.4 min, t_R (minor) = 14.2 min).

(*S*)-Methyl 4-(3-(((4-bromophenyl)carbamoyl)oxy)oxetan-3-yl)-2-((*tert*-butoxycarbonyl)amino)butanoate (**354**)



To a mixture of palladium on carbon (10 wt-%, 16.3 mg, 0.015 mmol, 10.0 mol-%) and **353** (58.0 mg, 0.153 mmol, 1.00 eq) under N_2 was added MeOH (1.53 mL). The mixture was stirred under H_2 (balloon) for 7 h. The suspension was filtered through a syringe filter (PTFE) with EA (5 mL) and the filtrate was concentrated.

To a solution of crude methyl 2-((*tert*-butoxycarbonyl)amino)-4-(3-hydroxyoxetan-3-yl)butanoate (44.2 mg, 0.152 mmol, 1.00 eq) in CH_2Cl_2 (0.61 mL) were added DMAP (1.9 mg, 0.015 mmol, 10.0 mol-%) and 1-bromo-4-

isocyanatobenzene (60.2 mg, 0.304 mmol, 2.00 eq). The mixture was stirred for 14 h. The mixture was purified by FC on silica (hex:EA = 2:1) to yield **354** (41.0m g, 0.084 mmol, 55 %) as a colorless solid.

^{1}H NMR (400 MHz, CDCl3) δ = 7.44 – 7.40 (m, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.85 (s, 1H), 5.09 (d, *J* = 8.1 Hz, 1H), 4.82 (t, *J* = 7.0 Hz, 2H), 4.52 (t, *J* = 6.3 Hz, 2H), 4.40 – 4.33 (m, 1H), 3.73 (s, 3H), 2.32 – 2.15 (m, 2H), 2.03 – 1.89 (m, 1H), 1.80 – 1.68 (m, 1H), 1.42 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 172.8, 155.5, 151.4, 136.7, 132.2, 120.4, 80.4, 79.6, 53.2, 52.7, 30.2, 29.9, 28.4, 26.6 ppm.

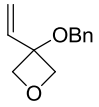
HRMS (ESI+): m/z calcd. for $C_{20}H_{28}BrN_2O_7$ $[M+H]^+$ 487.1074, 489.1057, found, 487.1070, 489.1053.

IR (neat): ν [cm^{-1}] = 2967, 1723, 1532, 1398, 1210, 1163, 1052, 827, 759.

***[α]*^{23}D** + 6.33 (*c* = 0.430, $CHCl_3$)

X-Ray: single crystals were grown by diffusion of hexanes into a substrate solution in acetone. Absolute configuration was determined as (*S*).

3-(benzyloxy)-3-vinyloxetane (**314**)



To a solution of **33** (0.893 ml, 13.9 mmol, 1.00 eq) in Et_2O (69 mL) at -78 °C was added vinylmagnesium bromide in diethyl ether (15.3 mL, 15.26 mmol, 1.10 eq). The mixture was allowed to warm to r.t. over night. Sat. aq. NH_4Cl solution (60 mL) was added. The layers were separated and the aq. layer was extracted with Et_2O (2 x 30 mL). The combined org. layers were dried over Na_2SO_4 and concentrated to about 1 mL.

This solution (3-vinyloxetan-3-ol (1.39 g, 13.9 mmol, 1.00 eq)) was diluted with THF (139 mL). To this solution at 0 °C was portion wise added NaH (0.610 g, 15.3 mmol, 1.10 eq). The mixture was stirred for 1 h before the addition of benzyl

bromide (1.98 mL, 16.7 mmol, 1.2 eq) and TBAI (0.512 g, 1.39 mmol, 0.10 eq). The resulting slurry was allowed to warm to r.t. over night. The mixture was poured into water (100 mL) and extracted with EA (3 x 100 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The crude product was purified by FC on silica (hex:EA = 9:1) to yield **314** (1.90 g, 9.98 mmol, 72 %) over two steps as a light yellow oil.

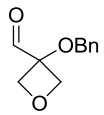
^{1}H NMR (400 MHz, CDCl3) δ = 7.49 – 7.28 (m, 5H), 6.11 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.64 – 5.34 (m, 2H), 4.78 (d, *J* = 7.1 Hz, 2H), 4.62 (d, *J* = 7.3 Hz, 2H), 4.39 (s, 2H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 138.1, 137.1, 128.6, 127.9, 127.7, 117.3, 80.2, 79.5 ppm.

HRMS (EI+): m/z calcd. for $C_{12}H_{14}O_2$ $[M]^+$ 190.0994, found, 190.0989.

IR (neat): ν [cm^{-1}] = 2949, 2879, 1719, 1454, 1275, 1173, 1026, 977, 751, 714.

3-(benzyloxy)oxetane-3-carbaldehyde (**315**)



Through a solution of **314** (1.17 g, 6.15 mmol, 1.00 eq) in CH_2Cl_2 (123 mL) at -78 °C was passed ozonized oxygen until the solution turned blue. A stream of nitrogen was passed through the solution until the solution was colorless again. Triphenylphosphine (4.84 g, 18.5 mmol, 3.00 eq) was added and the mixture was allowed to warm to r.t. The mixture was stirred for 2 h and then washed with aq. 1M sodium thiosulfate solution (50 mL). The org. layer was dried over Na_2SO_4 and concentrated. The crude product was purified by FC on silica (hex:EA = 1:1) to yield **315** (0.741 g, 3.86 mmol, 63%) as a colorless oil.

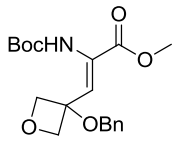
^{1}H NMR (400 MHz, CDCl3) δ = 9.84 (s, 1H), 7.55 – 7.26 (m, 5H), 4.77 (s, 4H), 4.58 (s, 2H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 199.0, 136.8, 128.8, 128.5, 128.0, 82.8, 75.7, 68.4 ppm.

HRMS (EI+): m/z calcd. for $C_{11}H_{12}NO_3$ $[M]^+$ 192.0786, found, 192.0781.

IR (neat): ν [cm^{-1}] = 2950, 2880, 1730, 1454, 1185, 1026, 976, 736, 697.

(*Z*)-Methyl 3-(3-(benzyloxy)oxetan-3-yl)-2-((*tert*-butoxycarbonyl)amino)acrylate (**355**)



To a solution of **306** (0.598 g, 2.01 mmol, 1.10 eq) in CH_2Cl_2 (18.3 mL) at r.t. was added DBU (0.303 ml, 2.01 mmol, 1.10 eq). The mixture was stirred for 10 min. 3-(benzyloxy)oxetane-3-carbaldehyde (0.352 g, 1.83 mmol, 1.00 eq) was added. The mixture was stirred for 14 h. The crude mixture was concentrated und purified by FC on silica (hex:EA = 4:1) yielding **355** (0.650 g, 1.79 mmol, 98 %) as a colorless oil.

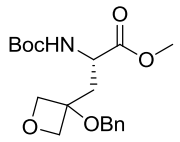
^{1}H NMR (400 MHz, CDCl3) δ = 7.42 – 7.32 (m, 5H), 6.69 (s, 1H), 6.43 (s, 1H), 4.93 (d, *J* = 7.8 Hz, 1H), 4.70 (d, *J* = 7.6 Hz, 1H), 4.38 (s, 2H), 3.87 (s, 3H), 1.41 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 164.7, 152.3, 137.2, 128.5, 128.1, 128.0, 127.6, 124.2, 81.4, 81.3, 77.9, 67.0, 52.7, 28.0 ppm.

HRMS (ESI+): m/z calcd. for $C_{19}H_{25}NNaO_6$ $[M+Na]^+$ 386.1574, found, 386.1575.

IR (neat): ν [cm^{-1}] = 2976, 2878, 1717, 1455, 1367, 1252, 1153, 1025, 983, 739.

Methyl 3-(3-(benzyloxy)oxetan-3-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate (**356**)



To a mixture of $[Rh(COD)_2]BF_4$ (6.8 mg, 0.017 mmol, 5.00 mol-%) and (*R*)-MonoPhos (12.0 mg, 0.033 mmol, 10.0 mol-%) und H_2 atmosphere was added a solution of **355** (121 mg, 0.333 mmol, 1.00 eq) in CH_2Cl_2 (8.32 mL). The reaction mixture was stirred at r.t. under H_2 (balloon) for 6 h, concentrated and purified by FC on silica (hex:EtOAc = 2:1) to yield **356** (0.082 g, 0.224 mmol, 67 %) as a colorless oil.

^{1}H NMR (400 MHz, CDCl3) δ = 7.46 – 7.24 (m, 5H), 5.30 (s, 1H), 4.88 – 4.78 (m, 3H), 4.66 (s, 3H), 4.54 (dd, *J* = 7.5, 0.8 Hz, 2H), 4.48 – 4.41 (m, 1H), 3.60 (s, 3H), 1.42 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 172.7, 155.2, 137.8, 128.5, 127.8, 127.6, 80.0, 79.8, 79.6, 78.9, 65.8, 52.3, 50.3, 37.5, 28.3 ppm.

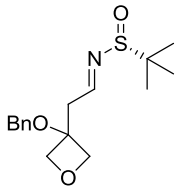
HRMS (ESI+): m/z calcd. for $C_{19}H_{27}NNaO_6$ $[M+Na]^+$ 388.1731, found, 388.1734.

IR (neat): ν [cm^{-1}] = 2965, 1715, 1366, 1249, 1165, 1054, 981, 845, 740.

[α]^{23}D – 6.27 (*c* = 0.650, $CHCl_3$)

SFC Daicel Chiralcel OJ-H, 95 % CO_2, 5.0 %MeOH, 2.0 mL/min, 25 °C, 211 nm, >98 % *ee*, (t_R (major) = 4.39 min, t_R (minor) = 5.01 min).

(*R*,*E*)-*N*-(2-(3-(benzyloxy)oxetan-3-yl)ethylidene)-2-methylpropane-2-sulfinamide (**357**)



To a solution of **317** (0.975 g, 4.73 mmol, 1.00 eq) in THF (23.6 mL) were added (*R*)-2-methylpropane-2-sulfinamide (0.630 g, 5.20 mmol, 1.10 eq) and tetraethoxytitanium (1.98 mL, 9.46 mmol, 2.00 eq). The mixture was stirred at r.t. for 16 h. The mixture was quenched with sat. aq. NaCl solution (50 mL), filtered through a pad of celite and

extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated- The residue was purified by FC on silica (hex:EtOAc = 2:1 → EtOAc) to yield **357** (1.17 g, 3.79 mmol, 80%) as a colorless oil.

^{1}H NMR (400 MHz, CDCl3) δ = 8.10 (t, *J* = 5.0 Hz, 1H), 7.38 – 7.27 (m, 5H), 4.85 (dd, *J* = 7.0, 4.3 Hz, 2H), 4.63 – 4.52 (m, 4H), 3.27 – 3.19 (m, 2H), 1.17 (s, 9H) ppm.

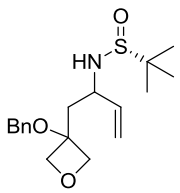
^{13}C NMR (101 MHz, CDCl3) δ = 164.9, 137.6, 128.6, 128.0, 127.5, 80.2, 78.0, 66.1, 57.0, 41.5, 22.5 ppm.

HRMS (ESI+): m/z calcd. for $C_{16}H_{23}NaO_3S$ $[M+Na]^+$ 332.1291, found, 332.1297.

IR (neat): ν [cm^{-1}] = 2955, 2874, 1622, 1455, 1364, 1082, 978.

[α]^{23}D – 182 (*c* = 0.570, $CHCl_3$)

(*R*)-*N*-(1-(3-(benzyloxy)oxetan-3-yl)but-3-en-2-yl)-2-methylpropane-2-sulfinamide (**361**)



To a solution of **357** (490 mg, 1.58 mmol, 1.00 eq) in toluene (32 mL) at -78 °C was added vinylmagnesium bromide (4.75 mL, 4.75 mmol, 3.00 eq). The mixture was stirred at r.t. for 60 min. To the solution was added sat. aq. $NaHCO_3$ solution (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC on silica (EtOAc) to yield **361** (0.160 g, 0.474 mmol, 29.9 % yield) as a colorless oil.

Less polar diastereomer:

^{1}H NMR (400 MHz, CDCl3) δ = 7.43 – 7.25 (m, 5H), 5.78 – 5.65 (m, 1H), 5.38 – 5.22 (m, 1H), 5.24 – 5.13 (m, 1H), 4.92 – 4.84 (m, 2H), 4.75 (d, *J* = 11.3 Hz, 1H), 4.67 (d, *J* = 11.3 Hz, 1H), 4.61 (dd, *J* = 7.5, 0.6 Hz, 1H), 4.46 – 4.38 (m, 1H), 4.23 (d, *J* = 3.3 Hz, 1H), 4.15 – 4.03 (m, 1H), 2.34 – 2.23 (m, 2H), 1.04 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 138.4, 137.5, 128.6, 127.9, 127.6, 117.2, 80.1, 79.9, 79.5, 65.8, 55.1, 54.6, 42.3, 22.5 ppm.

HRMS (ESI+): m/z calcd. for $C_{18}H_{28}N_1O_3S$ $[M+H]^+$ 338.1784, found, 338.1789.

IR (neat): ν [cm^{-1}] = 2952, 2873, 1455, 1056, 981, 736.

$[\alpha]^{22}_D$ – 62.5 (*c* = 0.605, $CHCl_3$)

More polar diastereomer:

^{1}H NMR (400 MHz, CDCl3) δ = 7.42 – 7.27 (m, 5H), 5.90 (ddd, *J* = 17.1, 10.3, 7.5 Hz, 1H), 5.35 – 5.22 (m, 1H), 5.16 (d, *J* = 10.3 Hz, 1H), 4.81 (dt, *J* = 7.2, 0.8 Hz, 1H), 4.75 (dt, *J* = 7.2, 0.9 Hz, 1H), 4.65 (d, *J* = 11.3 Hz, 1H), 4.60 – 4.49 (m, 3H), 4.09 – 3.99 (m, 1H), 3.44 (d, *J* = 6.7 Hz, 1H), 2.46 – 2.36 (m, 1H), 2.24 – 2.14 (m, 1H), 1.14 (s, 9H) ppm.

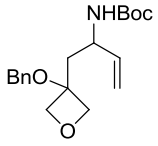
^{13}C NMR (101 MHz, CDCl3) δ = 139.2, 137.9, 128.6, 127.9, 127.6, 117.2, 80.7, 80.7, 78.9, 65.6, 55.8, 55.7, 41.1, 22.6 ppm.

HRMS (ESI+): m/z calcd. for $C_{18}H_{28}N_1O_3S$ $[M+H]^+$ 338.1784, found, 338.1781.

IR (neat): ν [cm^{-1}] = 2950, 2871, 1420, 1050, 979, 920, 734.

$[\alpha]^{22}_D$ – 33.3 (*c* = 1.90, $CHCl_3$)

Tert-butyl (1-(3-(benzyloxy)oxetan-3-yl)but-3-en-2-yl)carbamate (**362**)



To a solution of **361** (150 mg, 0.444 mmol, 1.00 eq) in CH_2Cl_2 (2.22 mL)/MeOH (2.22 mL) at 0 °C was added HCl (4 M in dioxane, 556 µL, 2.22 mmol, 5.00 eq). The mixture was stirred at that temperature for 45 min. The reaction was quenched with sat. aq. $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (4 x 20 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was redissolved in CH_2Cl_2 (2 mL) and Boc_2O (155 µL, 0.667 mmol, 1.50 eq) was added. The mixture

was stirred for 13 h. The crude solution was purified by FC on silica (hex:EA = 3:1) to yield**362** (103 mg, 0.309 mmol, 70%) as a colorless oil.

^{1}H NMR (400 MHz, CDCl3) δ = 7.46 – 7.27 (m, 4H), 5.79 (ddd, *J* = 16.7, 10.3, 6.0 Hz, 1H), 5.19 (d, *J* = 17.2 Hz, 1H), 5.08 (d, *J* = 10.3 Hz, 1H), 4.94 (s, 1H), 4.79 (t, *J* = 7.2 Hz, 2H), 4.69 (d, *J* = 11.2 Hz, 1H), 4.61 (d, *J* = 11.2 Hz, 1H), 4.55 (dd, *J* = 14.1, 7.3 Hz, 2H), 4.41 – 4.33 (m, 1H), 2.37 – 2.14 (m, 2H), 1.42 (s, 9H) ppm.

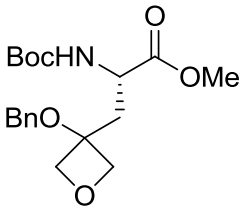
^{13}C NMR (101 MHz, CDCl3) δ = 155.18, 138.28, 138.07, 128.66, 127.88, 127.66, 115.15, 80.59, 80.42, 79.35, 65.75, 50.13, 40.28, 28.54 ppm.

HRMS (ESI+): m/z calcd. for $C_{19}H_{27}N_1Na_1O_4$ $[M+Na]^+$ 356.1832, found, 356.1832.

IR (neat): ν [cm^{-1}] = 2976, 1702, 1509, 1366, 1246, 1167, 979.

$[\alpha]^{22}_D$ – 2.36 (*c* = 0.665, $CHCl_3$)

Methyl 3-(3-(benzyloxy)oxetan-3-yl)-2-((tert-butoxycarbonyl)amino)propanoate (**356**)

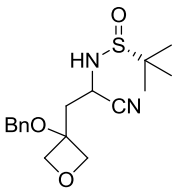


To a solution of **362** (38 mg, 0.114 mmol, 1.00 eq) in acetone (2.53 mL)/water (1.27 mL) were added $NaIO_4$ (122 mg, 0.570 mmol, 5.00 mL), $KMnO_4$ (12.6 mg, 0.080 mmol, 0.70 eq) and $NaHCO_3$ (9.57 mg, 0.114 mmol, 1.00 eq). The mixture was stirred at r.t. 40 min before diluting with EtOAc (10 mL) and 1 M $NaHSO_4$ (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was redissolved in benzene (1 mL) and treated with TMS-Diazomethane (2.00 M in Et_2O, 114 µL, 0.228 mmol, 2.00 eq). After stirring for 10 min AcOH (0.1 mL) was added. The solution was poured into $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined org. layers were dried over Na_2SO_4 and concentrated.

The crude product was purified by FC on silica (hex:EA=2:1) to yield **356** (18 mg, 0.049 mmol, 43%) as a colorless oil.

For analytical data see above.

(R)-N-((R)-2-(3-(benzyloxy)oxetan-3-yl)-1-cyanoethyl)-2-methylpropane-2-sulfinamide (**358**)



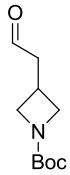
To a solution of diethylaluminium cyanide (1 M in toluene, 3.79 mL, 3.79 mmol, 1.50 eq) in THF (3.0 mL) was added 2-propanol (604 µL, 7.83 mmol, 3.10 eq). The mixture was stirred at r.t. for 15 min. This solution was then added to a solution of **357** (782 mg, 2.53 mmol, 1.00 eq) in THF (7.08 mL) at -78 °C. After stirring for 15 min the mixture was warmed to r.t. and stirred for 2 h. After cooling to -78 °C again sat. aq. $NaHCO_3$ solution (10 mL) was added. A solution of Rochelles salt (50 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined org layers were dried over Na_2SO^4. The solvent was removed under red pressure. On addition of hexanes:ether (1:2, 20 mL), **358** (0.650 g, 1.932 mmol, 76%) precipitated and was collected by filtration.

^{1}H NMR (400 MHz, CDCl3) δ 7.43 – 7.29 (m, 5H), 4.95 (dd, *J* = 7.8, 2.7 Hz, 2H), 4.76 (d, *J* = 1.2 Hz, 2H), 4.69 – 4.63 (m, 2H), 4.41 – 4.31 (m, 2H), 2.67 – 2.48 (m, 2H), 1.13 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 137.4, 128.8, 128.2, 127.7, 119.1, 79.4, 79.3, 78.5, 66.3, 57.1, 42.2, 40.9, 22.5 ppm.

HRMS (ESI+): m/z calcd. for $C_{17}H_{25}N_2O_3S$ $[M+H]^+$ 337.1580, found, 337.1579.

Tert-butyl 3-(2-oxoethyl)azetidine-1-carboxylate (**319**)



To a solution of **363** (1.06 g, 5.39 mmol, 1.00 eq)[88] in EA (26.9 mL) was added palladium on charcoal (0.115 g, 0.108 mmol, 2.00 mol-%). The mixture was stirred under a H_2 atmosphere for 16 h. The crude mixture was filtered through a pad of celite with EA (100 mL). The solvent was removed under red. pressure to yield **319** (1.00 g, 5.02 mmol, 93 %).

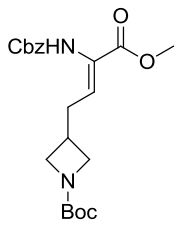
^{1}H NMR (400 MHz, CDCl3) δ = 9.76 (s, 1H), 4.15 – 4.08 (m, 2H), 3.55 (dd, *J* = 8.8, 5.4 Hz, 2H), 2.97 – 2.85 (m, 1H), 2.83 – 2.79 (m, 2H), 1.42 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 200.2, 156.4, 79.6, 54.9, 48.5, 28.5, 23.1 ppm.

HRMS (ESI+): m/z calcd. for $C_{10}H_{17}NNaO_3$ $[M+Na]^+$ 222.1101, found, 222.1102.

IR (neat): ν [cm^{-1}] = 2974, 2884, 1694, 1394, 1365, 1138, 1070, 859, 772, 560.

(*Z*)-*Tert*-butyl 3-(3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobut-2-en-1-yl)azetidine-1-carboxylate (**364**)



To a solution of **305** (1.77 g, 5.36 mmol, 1.10 eq) in CH_2Cl_2 (32.5 mL) at r.t. was added DBU (770 µL, 5.11 mmol, 1.10 eq). The mixture was stirred for 10 min. **319** (970 mg, 4.87 mmol, 1.00 eq) in CH_2Cl_2 (16.2 mL) was added. The mixture was stirred for 17.5 h. The mixture was concentrated to one third of its initial volume and purified by FC on silica (hex:EA = 2:1) to yield **364** (1.60 g, 3.96 mmol, 81 %) as a very viscous colorless oil.

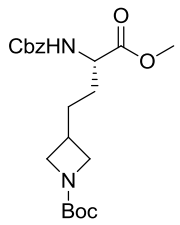
^{1}H NMR (400 MHz, CDCl3) δ = 7.42 – 7.29 (m, 5H), 6.48 (t, *J* = 7.2 Hz, 1H), 6.33 (s, 1H), 5.15 (s, 2H), 4.01 (t, *J* = 8.3 Hz, 2H), 3.76 (s, 3H), 3.56 (dd, *J* = 8.6, 5.2 Hz, 2H), 2.68 – 2.56 (m, 1H), 2.49 (t, *J* = 7.4 Hz, 2H), 1.43 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 164.9, 156.4, 154.0, 136.0, 133.2, 128.7, 128.5, 128.4, 79.5, 67.7, 54.3, 52.7, 33.3, 28.5, 27.7 ppm.

HRMS (ESI+): m/z calcd. for $C_{21}H_{28}N_2NaO_6$ $[M+Na]^+$ 427.1840, found, 427.1838.

IR (neat): ν [cm^{-1}] = 2968, 2882, 1694, 1400, 1366, 1223, 1140, 1045, 1028, 752, 771.

(*S*)-*Tert*-butyl 3-(3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutyl)azetidine-1-carboxylate (**365**)



To a mixture of $[Rh(COD)_2]BF_4$ (25.6 mg, 0.063 mmol, 5.00 mol-%) (*R*)-MonoPhos (45.3 mg, 0.126 mmol, 10.0 mol-%) under an atmosphere of H_2 was added **364** (510 mg, 1.26 mmol, 1.00 eq) in CH_2Cl_2 (31.5 mL). The reaction mixture was stirred at r.t. for 15 h. The solvent was removed under red. Pressure and the residues was purified by FC on silica (EA:hex = 1:2) to yield **365** (484 mg, 1.19 mmol, 94 %) as a light yellow oil.

^{1}H NMR (400 MHz, CDCl3) δ = 7.43 – 7.28 (m, 5H), 5.36 (d, *J* = 8.2 Hz, 1H), 5.10 (s, 2H), 4.43 – 4.31 (m, 1H), 3.97 (t, *J* = 8.3 Hz, 2H), 3.74 (s, 3H), 3.61 – 3.37 (m, 2H), 2.57 – 2.33 (m, 1H), 1.84 – 1.72 (m, 1H), 1.67 – 1.51 (m, 3H), 1.42 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 172.7, 156.4, 155.9, 136.3, 128.7, 128.4, 128.3, 79.4, 67.2, 54.5, 53.7, 52.6, 30.2, 30.0, 28.5, 28.4 ppm.

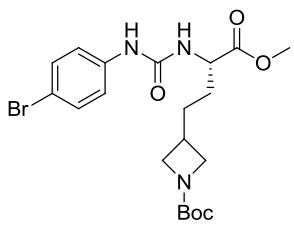
HRMS (ESI+): m/z calcd. for $C_{21}H_{30}N_2NaO_6$ $[M+Na]^+$ 429.1996, found, 429.1995.

IR (neat): ν [cm^{-1}] = 2957, 2879, 1698, 1406, 1213, 1141, 1028, 774, 741.

***[α]*^{23}D** + 13.7 (*c* = 1.12, $CHCl_3$)

SFC Daicel Chiralpak IA, 90 % CO_2, 10 % MeOH, 2.5 mL/min, 25 °C, 208 nm, 98 % *ee* (t_R (major) = 5.97 min, t_R (minor) = 5.63 min).

Tert-butyl 3-(3-(3-(4-bromophenyl)ureido)-4-methoxy-4-oxobutyl)azetidine-1-carboxylate (**366**)



To a mixture of palladium on carbon (10 wt-%, 12.0 mg, 0.012 mmol, 0.05 eq) and **365** under N_2 was added MeOH (2.3 mL). The mixture was stirred under H_2 (balloon) for 2 h. The suspension was filtered through a syringe filter with EA (10 mL) and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (4 mL) and 1-bromo-4-isocyanatobenzene (0.050 g, 0.254 mmol, 1.10 eq) was added. The solution was stirred for 2 h and then directly purified by FC on silica (hex:EA = 1:1 →EA) to yield **366** (105 mg, 0.223 mmol, 97 %) as a colorless foam.

^{1}H NMR (400 MHz, CDCl3) δ = 7.50 (s, 1H), 7.37 – 7.32 (m, 2H), 7.26 – 7.22 (m, 2H), 4.57 – 4.48 (m, 1H), 4.00 (t, *J* = 8.4 Hz, 2H), 3.73 (s, 3H), 3.54 – 3.47 (m, 2H), 2.52 – 2.42 (m, 1H), 1.81 – 1.72 (m, 2H), 1.69 – 1.50 (m, 2H), 1.44 (s, 9H) ppm.

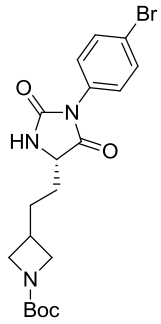
^{13}C NMR (101 MHz, CDCl3) δ = 173.6, 156.7, 155.0, 138.1, 131.9, 121.0, 115.4, 79.9, 54.2, 52.5, 52.5, 30.1, 30.1, 28.4, 28.3 ppm.

HRMS (ESI+): m/z calcd. for $C_{20}H_{28}BrN_3NaO_5$ $[M+Na]^+$ 492.1105, 494.1087, found, 492.1104, 494.1085.

IR (neat): ν [cm^{-1}] = 2958, 2879, 1743, 1654, 1699, 1545, 1489, 1396, 1206, 1154, 826, 756.

[α]^{23}$_D$ **+** 19.6 (*c* = 0.620, $CHCl_3$)

Tert-butyl 3-(2-(1-(4-bromophenyl)-2,5-dioxoimidazolidin-4-yl)ethyl)azetidine-1-carboxylate (**367**)



A solution of **366** (96.0 mg, 0.204 mmol, 1.00 eq) and DBU (0.046 ml, 0.306 mmol, 1.50 eq) in toluene (2.0 mL) was stirred at 90 °C for 4 h. The solvent was removed and the residue was purified by FC on silica (hex:EA = 1:2) to yield **367** (59.0 mg, 0.135 mmol, 66 %) as a colorless solid.

^{1}H NMR (400 MHz, CDCl3) δ = 7.65 – 7.60 (m, 2H), 7.37 – 7.32 (m, 2H), 4.26 – 4.18 (m, 1H), 4.05 (t, *J* = 8.3 Hz, 2H), 3.62 – 3.54 (m, 2H), 2.59 – 2.49 (m, 1H), 1.96 – 1.67 (m, 4H), 1.46 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 172.3, 156.5, 156.0, 132.4, 130.5, 127.6, 122.2, 79.7, 56.8, 53.7, 29.4, 29.3, 28.6, 28.5 ppm.

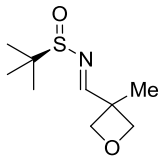
HRMS (ESI+): m/z calcd. for $C_{19}H_{24}BrN_3NaO_4$ $[M+Na]^+$ 460.0842, 462.0824, found, 460.0842, 462.0824.

IR (neat): ν [cm^{-1}] = 2969, 2879, 1718, 1492, 1408, 1146, 752, 726, 639.

***[α]^{23}D* - 0.490** (*c* = 0.535, $CHCl_3$)

X-Ray: Single crystals were obtained by diffusion of hexanes into a solution of the substrate in EA. Absolute configuration was determined as (*S*).

(*R*,*E*)-2-methyl-N-((3-methyloxetan-3-yl)methylene)propane-2-sulfinamide (**321**)



To a solution of (*R*)-2-methylpropane-2-sulfinamide (0.798 g, 6.58 mmol, 1.00 eq) in THF (32.9 mL) was added 3-methyloxetane-3-carbaldehyde solution in CH_2Cl_2 (26 wt-%, 2.79 g, 7.24 mmol, 1.10 eq) followed by tetraethoxytitanium (2.75 mL, 13.2 mmol, 2.00 eq). The mixture was stirred for 26 h and then poured into sat. aq. NaCl solution (100 mL). The resulting suspension was filtered over celite with EA (100 mL).

The layers were separated and the aq. layer was extracted with EA (2 x 100 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC on silica (hex:EA = 1:1) to yield **321** (1.14 g, 5.58 mmol, 85 %) as a colorless wax.

^{1}H NMR (400 MHz, CDCl3) δ = 8.18 (s, 1H), 4.86 (d, *J* = 5.9 Hz, 1H), 4.79 (d, *J* = 5.9 Hz, 1H), 4.49 (dd, *J* = 6.0, 2.7 Hz, 2H), 1.54 (s, 3H), 1.19 (s, 9H) ppm.

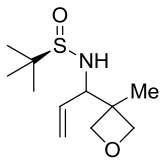
^{13}C NMR (101 MHz, CDCl3) δ = 169.8, 79.7, 79.4, 57.1, 44.9, 22.4, 21.3 ppm.

HRMS (ESI+): m/z calcd. for $C_9H_{18}NO_2S$ $[M+H]^+$ 204.1053, found, 204.1058.

IR (neat): ν [cm^{-1}] = 2963, 2872, 1620, 1088, 985, 836.

***[α]*^{23}D** – 252 (*c* = 0.93, $CHCl_3$)

(*R*)-2-methyl-N-(1-(3-methyloxetan-3-yl)allyl)propane-2-sulfinamide (**368**)



To a solution of **321** (1.51 g, 7.43 mmol, 1.00 eq) in toluene (74.3 mL) at -78 °C was added vinylmagnesium bromide in THF (1 M, 11.2 mL, 11.2 mmol, 1.50 eq). The mixture was stirred for 90 min. Still, starting material was detected by TLC. Hence, vinylmagnesium bromide in THF (1 M, 2.23 mL, 2.23 mmol, 0.30 eq) was added and the mixture was stirred for 90 min before sat. aq. NH_4Cl solution (30 mL) was added. The layers were separated and the aq. layer was extracted with EA (2 x 50 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC on silica (Ø 3.5 cm, *h* 40 cm, *V* 15 mL, DCM:acetone = 6:1 (100 fractions), 4:1 (40 fractions), 2:1 (30 fractions) to 1:1 (30 fractions)) to yield the desired product in two diastereomers: a) the minor, less polar diastereomer (*R*)-2-methyl-N-((*S*)-1-(3-methyloxetan-3-yl)allyl)propane-2-sulfinamide (0.441 g, 1.91 mmol, 26 %) and b) the major, more polar diastereomer (*R*)-2-methyl-N-((*R*)-1-(3-methyloxetan-3-yl)allyl)propane-2-sulfinamide (1.02 g, 4.41 mmol, 59%) as colorless oils.

(*R*)-2-methyl-N-((*S*)-1-(3-methyloxetan-3-yl)allyl)propane-2-sulfinamide

^{1}H NMR (400 MHz, CDCl3) δ = 5.74 (ddd, *J* = 17.1, 10.4, 6.7 Hz, 1H), 5.45 – 5.23 (m, 2H), 4.60 (d, *J* = 6.0 Hz, 1H), 4.51 (d, *J* = 6.1 Hz, 1H), 4.29 (dd, *J* = 12.9, 6.1 Hz, 2H), 4.19 – 4.13 (m, 1H), 3.21 (d, *J* = 8.0 Hz, 1H), 1.28 (s, 3H), 1.21 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 135.1, 119.0, 81.3, 80.1, 64.9, 56.6, 43.0, 22.8, 19.2 ppm.

HRMS (ESI+): m/z calcd. for $C_{11}H_{22}NO_2S$ $[M+H]^+$ 232.1366, found, 232.1371.

IR (neat): ν [cm^{-1}] = 2963, 2872, 1620, 1088, 985, 836.

[α]^{23}D – 252 (*c* = 0.93, $CHCl_3$)

(*R*)-2-methyl-N-((*R*)-1-(3-methyloxetan-3-yl)allyl)propane-2-sulfinamide

^{1}H NMR (400 MHz, CDCl3) δ = 5.61 (ddd, *J* = 17.0, 10.2, 7.4 Hz, 1H), 5.39 – 5.24 (m, 2H), 4.63 (d, *J* = 6.2 Hz, 1H), 4.53 (d, *J* = 6.4 Hz, 1H), 4.37 (dd, *J* = 11.4, 6.3 Hz, 2H), 4.12 – 4.07 (m, 1H), 3.48 (d, *J* = 4.5 Hz, 1H), 1.29 (s, 3H), 1.23 (s, 9H) ppm.

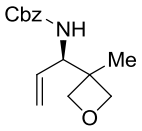
^{13}C NMR (101 MHz, CDCl3) δ = 134.6, 119.4, 80.3, 80.0, 63.3, 56.0, 42.9, 22.8, 19.9 ppm.

HRMS (ESI+): m/z calcd. for $C_{11}H_{22}NO_2S$ $[M+H]^+$ 232.1366, found, 232.1362.

IR (neat): ν [cm^{-1}] = 2961, 2870, 1457, 1387, 1363, 1061, 979, 595.

[α]^{23}D – 102 (*c* = 0.76, $CHCl_3$)

(*R*)-benzyl (1-(3-methyloxetan-3-yl)allyl)carbamate (**369**)



To a solution of (*R*)-2-methyl-N-((*R*)-1-(3-methyloxetan-3-yl)allyl)propane-2-sulfinamide (329 mg, 1.42 mmol, 1.00 eq) in THF (14.2 mL) was added aq. HCl (2 M, 3.56 mL, 7.11 mmol, 5.00 eq). The mixture was vigorously stirred at r.t. for 2 h and then poured into sat. aq. $NaHCO_3$ solution (20 mL). The aq. layer was extracted with CH2Cl2 (4 x 20 mL). The combined org. layers were dried over Na_2SO_4 and concentrated.

The residue was dissolved in THF (7.1 mL) and benzyl (2,5-dioxopyrrolidin-1-yl) carbonate (886 mg, 3.56 mmol, 2.50 eq) as well as Et_3N (496 µL, 3.56 mmol, 2.50 eq) were added. The mixture was stirred for 13 h and directly purified by FC on silica (hex:EA = 3:1) to yield **369** (171 mg, 0.654 mmol, 46 %) as a colorless oil.

^{1}H NMR (300 MHz, CDCl3) δ = 7.42 – 7.29 (m, 5H), 5.69 (ddd, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.31 – 5.20 (m, 2H), 5.12 (s, 2H), 4.96 (s, 1H), 4.61 – 4.51 (m, 3H), 4.32 (dd, *J* = 6.2, 2.4 Hz, 2H), 1.27 (s, 3H) ppm.

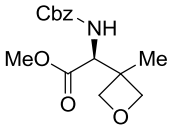
^{13}C NMR (101 MHz, CDCl3) δ = 156.3, 136.4, 133.9, 128.7, 128.4, 128.3, 117.5, 80.2, 80.0, 67.2, 58.5, 42.4, 20.1 ppm.

HRMS (ESI+): m/z calcd. for $C_{15}H_{20}NO_3$ $[M+H]^+$ 262.1438, found, 262.1436.

IR (neat): ν [cm^{-1}] = 2964, 2875, 1708, 1532, 1239, 1074, 977, 739.

***[α]*^{23}D** + 31.7 (*c* = 0.50, $CHCl_3$)

(*S*)-Methyl 2-(((benzyloxy)carbonyl)amino)-2-(3-methyloxetan-3-yl)acetate (**370**)



To a solution of benzyl (1-(3-methyloxetan-3-yl)allyl)carbamate (0.0400 g, 0.153 mmol, 1.00 eq) in CH_2Cl_2 (5.7 mL)/MeOH (1.9 mL) at -78 °C was added NaOH in MeOH (2.5 M, 0.306 mL, 0.765 mmol, 5.00 eq). Ozonized oxygen was bubbled through the mixture until the color of the solution turned to blue. Nitrogen was bubbled through the blue solution

until the color faded completely before sat. aq. NH_4Cl solution (10 mL) and water (10 mL) were added and the solution was allowed to warm to r.t. Sodium thiosulfate (200 mg) was added, the layers were separated and the aq. layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined org. layers were dried over Na_2SO_4 and concentrated to yield **370** (0.0423 g, 0.143 mmol, 94 %) as a colorless wax.

^{1}H NMR (600 MHz, CDCl3) δ = 7.44 – 7.29 (m, 5H), 5.38 (d, *J* = 9.0 Hz, 1H), 5.12 (s, 2H), 4.86 – 4.72 (m, 3H), 4.30 (d, *J* = 6.4 Hz, 1H), 4.23 (d, *J* = 6.4 Hz, 1H), 3.73 (s, 3H), 1.28 (s, 3H) ppm.

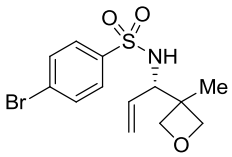
^{13}C NMR (151 MHz, CDCl3) δ = 171.2, 156.5, 136.1, 128.8, 128.5, 128.4, 80.1, 79.8, 67.6, 58.9, 52.7, 42.3, 19.8 ppm.

HRMS (ESI+): m/z calcd. for $C_{15}H_{20}NO_5$ $[M+H]^+$ 294.1336, found, 294.1336.

IR (neat): ν [cm^{-1}] = 2959, 2880, 1721, 1532, 1250, 1218, 1050, 978, 860, 741.

[α]$_D^{23}$ + 30.9 (*c* = 0.40, $CHCl_3$)

(*S*)-4-bromo-*N*-(1-(3-methyloxetan-3-yl)allyl)benzenesulfonamide (**371**)



To a solution of (*R*)-2-methyl-N-((*S*)-1-(3-methyloxetan-3-yl)allyl)propane-2-sulfinamide (59 mg, 0.255 mmol, 1.00 eq) in THF (2.55 mL) was added aq. HCl (2 M, 0.638 mL, 1.28 mmol, 5.00 eq). The mixture was vigorously stirred at r.t. for 2 h and then poured into sat. aq. $NaHCO_3$ solution (20 mL). The aq. layer was extracted with CH_2Cl_2 (4 x 20 mL). The combined org. layers were dried over Na2SO4 and concentrated.

The residue was dissolved in CH_2Cl_2 (1.0 mL) and 4-bromobenzene-1-sulfonyl chloride (98 mg, 0.383 mmol, 1.50 eq) as well as Et3N (89 µL, 0.638 mmol,

2.50 eq) were added. The mixture was stirred for 20 h and directly purified by FC on silica (hex:EA = 2:1) to yield **371** (33 mg, 0.095 mmol, 37 %) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.69 (m, 2H), 7.65 – 7.58 (m, 2H), 5.44 (ddd, *J* = 17.2, 10.4, 7.0 Hz, 1H), 5.12 (d, *J* = 9.1 Hz, 1H), 5.06 – 4.89 (m, 2H), 4.50 (d, *J* = 6.3 Hz, 1H), 4.43 (d, *J* = 6.3 Hz, 1H), 4.29 (dd, *J* = 6.3, 3.2 Hz, 2H), 4.20 – 4.10 (m, 1H), 1.23 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.8, 132.7, 132.4, 128.9, 127.8, 118.8, 80.2, 79.6, 61.9, 42.7, 19.4 ppm.

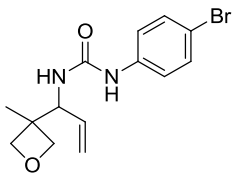
HRMS (ESI+): m/z calcd. for $C_{13}H_{17}BrNO_3S$ $[M+H]^+$ 346.0107, 348.0087, found, 346.0103, 348.0084.

IR (neat): ν [cm^{-1}] = 2966, 2878, 1576, 1336, 1161, 1068, 927, 825, 741.

***[α]*^{23}D** + 46.5 (*c* = 0.56, $CHCl_3$)

X-Ray: Single crystals were obtained by diffusion of hexanes into a solution of the substrate in EA. Absolute configuration was determined as (*S*).

1-(4-bromophenyl)-3-(1-(3-methyloxetan-3-yl)allyl)urea (**372**)



To a solution of (*R*)-2-methyl-N-((*S*)-1-(3-methyloxetan-3-yl)allyl)propane-2-sulfinamide (40 mg, 0.173 mmol, 1.00 eq) in THF (1.73 mL) was added aq. HCl (2 M, 0.432 mL, 0.864 mmol, 5.00 eq). The mixture was vigorously stirred at r.t. for 2 h and then poured into sat. aq. $NaHCO_3$ solution (20 mL). The aq. layer was extracted with CH_2Cl_2 (4 x 20 mL). The combined org. layers were dried over Na2SO4 and concentrated.

The residue was dissolved in CH_2Cl_2 (1.0 mL) and 1-bromo-4-isocyanatobenzene (38 mg, 0.190 mmol, 1.10 eq) as well as Et3N (60 µL, 0.432 mmol, 2.50 eq) were added. The mixture was stirred for 2 h and directly purified by FC on silica (hex:EA = 1:1) to yield **372** (50 mg, 0.154 mmol, 89 %) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.10 (s, 1H), 5.74 (ddd, *J* = 16.7, 10.4, 6.1 Hz, 1H), 5.54 (d, *J* = 8.6 Hz, 1H), 5.38 – 5.23 (m, 2H), 4.69 – 4.55 (m, 3H), 4.40 (dd, *J* = 9.1, 6.3 Hz, 2H), 1.32 (s, 3H) ppm.

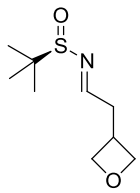
^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.3, 137.7, 134.3, 132.1, 121.8, 117.7, 116.2, 80.1, 79.5, 57.3, 42.4, 20.8 ppm.

HRMS (ESI+): m/z calcd. for $C_{14}H_{18}BrN_2O_2$ $[M+H]^+$ 325.0546, 325.0546, found, 346.0103, 348.0084.

IR (neat): ν [cm^{-1}] = 2955, 1653, 1592, 1489, 1229, 983, 824.

[α]^{22}D – 52.4 (*c* = 0.255, $CHCl_3$)

(*R*,*E*)-2-methyl-N-(2-(oxetan-3-yl)ethylidene)propane-2-sulfinamide (**320**)



To a mixture of **325** (1.01 g, 10.3 mmol, 1.00 eq) and palladium on carbon (0.547 g, 0.514 mmol, 5.00 mol-%) under N_2 was added EA (34.3 mL). The suspension was stirred under H_2 (balloon) for 5 h. The mixture was then filtered through a pad of celite with EA (50 mL) yielding crude 2-(oxetan-3-yl)acetaldehyde (0.865 g, 8.64 mmol, 84 %) as a colorless oil

To a solution of crude 2-(oxetan-3-yl)acetaldehyde (346 mg, 3.46 mmol, 1.00 eq) in THF (17.3 mL) were added (*R*)-2-methylpropane-2-sulfinamide (461 mg, 3.80 mmol, 1.10 eq) and tetraethoxytitanium (1.45 mL, 6.91 mmol, 2.00 eq). The mixture was stirred at r.t. for 16 h. The mixture was poured into sat. aq. NaCl solution (50 mL) and immediately filtered over a pad of celite with EA (50 mL). The layers of the filtrate were separated and the aq. layer was extracted with EA (3 x 50 mL). The combined org. layers were dried over Na2SO4 and concentrated. The residue was purified by FC on silica (hex:EA = 1:1→EA) to yield **320** (593 mg, 2.92 mmol, 72 %) as a colorless oil

^{1}H NMR (400 MHz, CDCl3) δ = 8.05 (t, *J* = 3.5 Hz, 1H), 4.89 – 4.82 (m, 2H), 4.46 – 4.38 (m, 2H), 3.49 – 3.33 (m, 1H), 2.93 (dd, *J* = 7.6, 3.5 Hz, 2H), 1.15 (s, 9H) ppm.

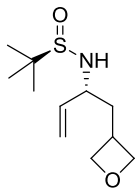
^{13}C NMR (101 MHz, CDCl3) δ = 166.6, 77.0, 76.7, 56.6, 39.8, 31.6, 22.3 ppm.

HRMS (ESI+): m/z calcd. for $C_9H_{18}NO_2S$ $[M+H]^+$ 204.1053, found, 204.1048.

IR (neat): ν [cm^{-1}] = 2962, 2869, 1622, 1364, 1085, 976, 858.

***[α]*^{23}D** - 244 (*c* = 0.66, $CHCl_3$)

(*R*)-2-methyl-*N*-((*S*)-1-(oxetan-3-yl)but-3-en-2-yl)propane-2-sulfinamide (**373**)



To a solution of **320** (365 mg, 1.80 mmol, 1.00 eq) in toluene (35.9 mL) at -78 °C was added vinylmagnesium bromide in THF (1 M, 2.7 mL, 2.69 mmol, 1.50 eq). The mixture was stirred at -78 °C for 60 min. Sat. aq. $NaHCO_3$ solution (10 mL) was added and the mixture was warmed to r.t. The layers were separated and the aq. layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC on silica (EA) to yield **373** (305 mg, 1.32 mmol, 73 %) as a colorless oil.

^{1}H NMR (400 MHz, CDCl3) δ = 5.77 (ddd, *J* = 17.5, 10.3, 7.3 Hz, 1H), 5.28 – 5.11 (m, 2H), 4.80 – 4.69 (m, 2H), 4.46 – 4.36 (m, 2H), 3.73 – 3.62 (m, 1H), 3.18 – 3.09 (m, 1H), 3.06 (d, *J* = 6.0 Hz, 1H), 2.12 – 2.03 (m, 1H), 1.98 – 1.88 (m, 1H), 1.21 (s, 9H) ppm.

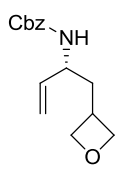
^{13}C NMR (101 MHz, CDCl3) δ = 139.1, 117.2, 77.8, 77.7, 57.5, 55.9, 39.4, 32.4, 22.7 ppm.

HRMS (ESI+): m/z calcd. for $C_{11}H_{22}NO_2S$ $[M+Na]^+$ 232.1366, found, 232.1367.

IR (neat): ν [cm^{-1}] = 2959, 2867, 1363, 1056, 977.

***[α]*^{23}D** – 87.2 (*c* = 0.58, $CHCl_3$)

(*S*)-benzyl (1-(oxetan-3-yl)but-3-en-2-yl)carbamate (**374**)



To a solution of **373** (195 mg, 0.843 mmol, 1.00 eq) in CH_2Cl_2 (4.2mL)/MeOH (4.2 mL) at 0 °C was added HCl in dioxane (4 M, 527 µL, 2.11 mmol, 2.5 eq). The mixture was stirred for 60 min before Et_3N (587 µL, 4.21 mmol, 5.00 eq) and benzyl (2,5-dioxopyrrolidin-1-yl) carbonate (315 mg, 1.26 mmol, 1.50 eq) were added. The mixture was allowed to warm to r.t. and stirred for 15 h. The mixture was directly purified by FC on silica (hex:EA = 2:1) to yield **374** (132 mg, 0.505 mmol, 60 %) as a colorless oil.

^{1}H NMR (400 MHz, CDCl3) δ = 7.42 – 7.29 (m, 5H), 5.71 (ddd, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.21 – 5.04 (m, 4H), 4.80 – 4.69 (m, 2H), 4.63 (s, 1H), 4.40 (t, J = 6.2 Hz, 2H), 4.18 – 4.06 (m, 1H), 3.16 – 3.04 (m, 1H), 2.01 – 1.83 (m, 2H) ppm.

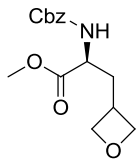
^{13}C NMR (101 MHz, CDCl3) δ = 155.8, 137.9, 136.5, 128.7, 128.4, 128.3, 115.6, 77.7, 77.5, 67.0, 52.2, 39.4, 32.6 ppm.

HRMS (ESI+): m/z calcd. for $C_{15}H_{20}NO_3$ $[M+H]^+$ 262.1438, found, 262.1437.

IR (neat): ν [cm^{-1}] = 2958, 2873, 1701, 1532, 1248, 1068, 974, 739.

[α]^{23}D – 3.93 (*c* = 0.56, $CHCl_3$)

(*S*)-Methyl 2-(((benzyloxy)carbonyl)amino)-3-(oxetan-3-yl)propanoate (**375**)



To a solution of **374** (0.0700 g, 0.268 mmol, 1.00 eq) in CH_2Cl_2 (5.7 mL)/MeOH (1.9 mL) at -78 °C was added NaOH in MeOH (2.5 M, 0.536 ml, 1.34 mmol, 5.00 eq). Ozonized oxygen was bubbled through the mixture until the color of the solution turned to blue. Nitrogen was bubbled through the blue solution until the color faded completely before sat. aq. NH_4Cl solution (10 mL) and water (10 mL) were added and the solution was allowed to warm to r.t. Sodium thiosulfate (200 mg) were added, the layers were separated and the aq. layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined org.

layers were dried over Na_2SO_4 and concentrated to yield **375** (0.0422 g, 0.143 mmol, 54 %) as a colorless oil.

^{1}H NMR (400 MHz, CDCl3) δ = 7.40 – 7.30 (m, 5H), 5.30 (d, *J* = 8.2 Hz, 1H), 5.10 (s, 2H), 4.80 – 4.68 (m, 2H), 4.42 – 4.29 (m, 3H), 3.75 (s, 3H), 3.18 – 3.05 (m, 1H), 2.32 – 2.21 (m, 1H), 2.11 – 1.96 (m, 1H) ppm.

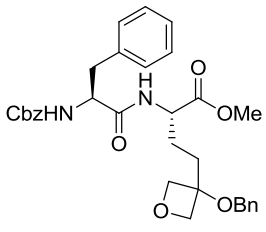
^{13}C NMR (101 MHz, CDCl3) δ = 172.5, 155.8, 136.2, 128.7, 128.5, 128.3, 77.3, 77.1, 67.3, 52.7, 52.6, 37.0, 32.2 ppm.

HRMS (ESI+): m/z calcd. for $C_{15}H_{20}NO_5$ $[M+H]^+$ 294.1336, found, 294.1334.

IR (neat): ν [cm^{-1}] = 2957, 1720, 1531, 1441, 1216, 1060, 975, 699.

[α]^{23}D – 9.96 (*c* = 0.50, $CHCl_3$)

(*S*)-methyl 2-((*S*)-2-(((benzyloxy)carbonyl)amino)-3-phenylpropanamido)-4-(3-(benzyloxy)oxetan-3-yl)butanoate (**379**)



First, crude H_2N-Glu(Ox, OBn)-OMe was obtained from **353** (56 mg, 0.145 mmol, 1.00 eq) and isolated by azeotropic destillation following GP 5.

Following GP 2 using crude H_2N-Glu(Ox, OBn)-OMe (40.5 mg, 0.145 mmol, 1.00 eq), CbzNH-Phe-OH (65.1 mg, 0.218 mmol, 1.50 eq), *N*-methylmorpholine (0.096 mL, 0.870 mmol, 6.00 eq), EDC·HCl (0.042 g, 0.218 mmol, 1.5 eq) and HOBt (0.033 g, 0.218 mmol, 1.5 eq) **379** (55 mg, 0.067 mmol, 67%) was obtained as a colorless wax.

^{1}H NMR (400 MHz, CDCl3) δ = 7.53 – 7.26 (m, 15H), 6.43 (d, *J* = 7.6 Hz, 1H), 5.34 (d, *J* = 7.9 Hz, 1H), 5.20 – 5.05 (m, 2H), 4.86 – 4.71 (m, 2H), 4.64 (td, *J* = 7.3, 4.7 Hz, 1H), 4.56 – 4.34 (m, 5H), 3.78 (s, 3H), 3.15 (qd, *J* = 13.8, 6.8 Hz, 2H), 2.08 – 1.63 (m, 4H) ppm.

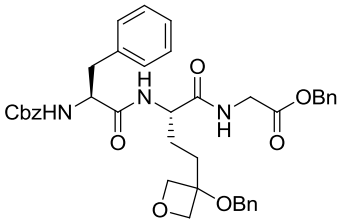
^{13}C NMR (101 MHz, CDCl3) δ = 172.0, 170.8, 156.0, 138.0, 136.3, 136.2, 129.4, 128.9, 128.7, 128.4, 128.2, 127.9, 127.5, 127.3, 80.2, 78.6, 67.3, 65.5, 56.4, 52.7, 52.2, 38.3, 30.3, 26.1 ppm.

HRMS (ESI+): m/z calcd. for $C_{32}H_{37}N_2O_7$ $[M+H]^+$ 561.2595, found, 561.2585.

IR (neat): ν [cm^{-1}] = 2951, 1669, 1533, 1454, 1214, 1052, 977, 742.

***[α]*^{24}D** + 1.14 (*c* = 0.46, $CHCl_3$)

(5*S*,8*S*)-benzyl 5-benzyl-8-(2-(3-(benzyloxy)oxetan-3-yl)ethyl)-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oate (**380**)



First, crude CbzNH-Phe-Glu(Ox, OBn)-OH was obtained from **379** (40 mg, 0.071 mmol, 1.00 eq) following GP 3.

Following GP 2 using crude CbzNH-Phe-Glu(Ox, OBn)-OH (39 mg, 0.071 mmol, 1.00 eq), TsOH·H_2N-Gly-OBn (36 mg, 0.107 mmol, 1.50 eq), *N*-methylmorpholine (0.043 mL, 0.426 mmol, 6.00 eq), EDC·HCl (0.015 g, 0.078 mmol, 1.1 eq) and HOBt (0.012 g, 0.078 mmol, 1.1 eq) **380** (32 mg, 0.046 mmol, 65%) was obtained as a colorless wax.

^{1}H NMR (400 MHz, CDCl3) δ = 7.39 – 7.11 (m, 20H), 6.60 – 6.46 (m, 2H), 5.33 – 5.22 (m, 1H), 5.16 (s, 2H), 5.04 (d, *J* = 3.6 Hz, 2H), 4.72 (t, *J* = 6.5 Hz, 2H), 4.52 – 4.43 (m, 2H), 4.42 – 4.31 (m, 3H), 3.94 (d, *J* = 5.6 Hz, 2H), 3.04 (d, *J* = 6.9 Hz, 2H), 2.02 – 1.70 (m, 4H) ppm.

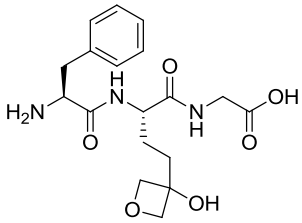
^{13}C NMR (101 MHz, CDCl3) δ = 171.0, 170.9, 169.3, 153.8, 138.0, 136.0, 135.2, 129.2, 128.8, 128.7, 128.6, 128.6, 128.6, 128.4, 128.3, 128.1, 127.8, 127.5, 127.2, 80.0, 79.8, 78.9, 67.3, 67.2, 65.5, 56.5, 52.6, 41.2, 38.1, 30.7, 25.8 ppm.

HRMS (ESI+): m/z calcd. for $C_{40}H_{44}N_3O_8$ $[M+H]^+$ 694.3123, found, 694.3117.

IR (neat): ν [cm^{-1}] = 2948, 1646, 1536, 1455, 1203, 743.

$[\alpha]^{24}_{D}$ – 4.81 (*c* = 0.38, $CHCl_3$)

2-((*S*)-2-((*S*)-2-amino-3-phenylpropanamido)-4-(3-hydroxyoxetan-3-yl)butanamido)acetic acid (**378**)



To a solution of **380** (24 mg, 0.035 mmol, 1.00 eq) in MeOH (1.7 mL) was added palladium(II) acetate (7.8 mg, 0.035 mmol, 1.00 eq). The mixture was stirred under H_2 (balloon) for 20 h. The suspension was filtered through a syringe filter (PTFE) and the filtrate was concentrated. The crude product was purified by preparative HPLC to yield **378** (7.4 mg, 0.020 mmol, 56%) as a colorless foam.

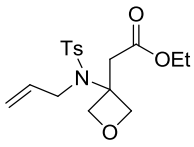
^{1}H NMR (400 MHz, CDCl3) δ = 7.43 – 7.25 (m, 5H), 4.55 (dd, *J* = 6.5, 1.4 Hz, 2H), 4.51 – 4.43 (m, 3H), 4.15 (ddd, *J* = 7.2, 5.6, 1.5 Hz, 1H), 4.04 – 3.93 (m, 0H), 3.91 – 3.81 (m, 0H), 3.27 (d, *J* = 5.8 Hz, 1H), 3.03 (ddd, *J* = 14.3, 8.5, 1.4 Hz, 1H), 1.99 – 1.71 (m, 4H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 173.5, 172.5, 169.5, 135.6, 130.5, 130.2, 128.9, 84.7, 84.7, 74.4, 55.6, 54.6, 41.7, 38.6, 34.7, 27.5 ppm.

HRMS (ESI+): m/z calcd. for $C_{18}H_{26}N_3O_6$ $[M+H]^+$ 380.1816, found, 380.1819.

5.4 Experimental Procedures to Chapter 4

Ethyl 2-(3-(N-allyl-4-methylphenylsulfonamido)oxetan-3-yl)acetate (**384**)



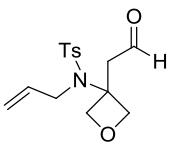
A mixture of **346** (2.25 g, 15.83 mol, 1.00 eq) and allyl amine (1.19 mL, 15.83 mmol, 1.00 eq) was stirred for 4 d at r.t.

The resulting light yellow oil was dissolved in pyridine and to the solution were added Ts-Cl (3.32 g, 17.39 mmol, 1.10 eq) and DMAP (97 mg, 0.79 mmol, 5.00 mol-%). The mixture was stirred at 50 °C for 26 h. After cooling to r.t. the dark brown suspension was poured into 1 M $NaHSO_4$ solution (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC on silica (hex:EA = 2:1) to yield **3** (5.14 g, 14.54 mmol, 92%) as a colorless oil.

^{1}H NMR (400 MHz, CDCl3) δ = 7.72 (d, *J* = 8.4 Hz, 2H), 7.33 – 7.27 (m, 2H), 5.86 – 5.74 (m, 1H), 5.24 – 5.07 (m, 2H), 5.03 – 4.96 (m, 2H), 4.56 – 4.47 (m, 2H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.84 – 3.76 (m, 2H), 3.23 (s, 2H), 2.42 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 170.5, 143.8, 138.0, 135.2, 129.8, 127.7, 117.9, 117.9, 79.6, 61.4, 61.0, 49.7, 41.7, 21.6, 14.2 ppm.

N-allyl-4-methyl-*N*-(3-(2-oxoethyl)oxetan-3-yl)benzenesulfonamide (**385**)

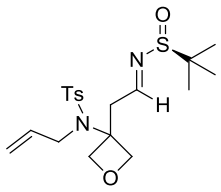


To a solution of **384** (0.611 g, 1.729 mmol, 1.00 eq) in toluene (17.3 mL) at -78 °C was added dropwise DIBAL-H (1.2 M in toluene, 1.59 mL, 1.90 mmol, 1.10 eq). The mixture was stirred for 10 min before MeOH (5 mL) was added. To the solution was added sat aq Rochelle salt solution (20 mL) and the mixture was stirred for 30 min at r.t. The layers were separated and the aq. layer was extracted with EA (2 x 30 mL). The combined org. layers were dried over Na_2SO_4 and concentrated. The crude material was used in the next step without any further purification

^{1}H NMR (400 MHz, CDCl3) δ = 9.83 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.77 – 5.62 (m, 1H), 5.22 – 5.06 (m, 2H), 5.00 (d, *J* = 7.3 Hz, 2H), 4.41 (d, *J* = 7.5 Hz, 2H), 3.78 (d, *J* = 6.0 Hz, 2H), 3.32 (s, 2H), 2.43 (s, 3H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 199.1, 143.9, 137.2, 134.2, 129.6, 127.3, 118.2, 79.3, 77.2, 60.5, 50.0, 49.1, 21.4 ppm.

(*S*,*E*)-N-allyl-N-(3-(2-((tert-butylsulfinyl)imino)ethyl)oxetan-3-yl)-4-methylbenzenesulfonamide (**383**)



To a solution of **384** (0.527 g, 1.703 mmol, 1.00 mmol) in THF (8.5 mL) were added (*S*)-2-methylpropane-2-sulfinamide (0.227 g, 1.87 mmol, 1.00 eq) and tetraethoxytitanium (0.713 mL, 3.41 mmol, 2.00 eq). The mixture was stirred at r.t. for 14 h. The mixture was quenched with aq. NaCl, filtered through a pad of celite and extracted with EtOAc. The combined org. layers were dried over Na_2SO_4 and concentrated. The residue was purified by FC on silica (hex:EtOAc = 1:1) to yield **2** (0.585 g, 1.42 mmol, 83%) over 2 steps as a colorless oil.

^{1}H NMR (400 MHz, CDCl3) δ = 8.15 (t, *J* = 5.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 3H), 5.73 – 5.63 (m, 1H), 5.19 – 5.04 (m, 2H), 5.01 – 4.92 (m, 2H), 4.42 (d, *J* = 7.3 Hz, 2H), 3.78 – 3.65 (m, 2H), 3.37 (t, *J* = 5.1 Hz, 2H), 2.43 (s, 3H), 1.20 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl3) δ = 199.1, 143.9, 137.2, 134.2, 129.6, 127.3, 118.2, 79.3, 77.2, 60.5, 50.0, 49.1, 21.4 ppm.

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7

Appendix

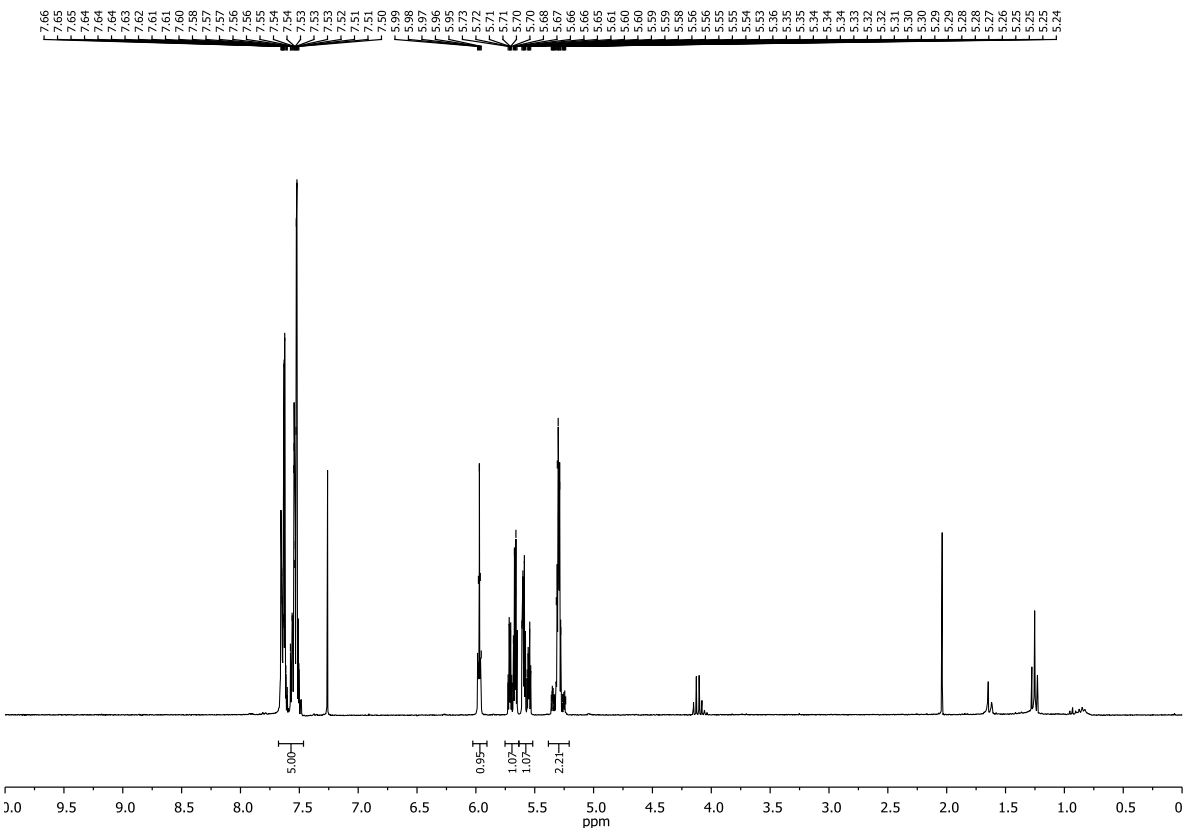


Figure 44 ^{1}H-NMR Spectrum of 78.

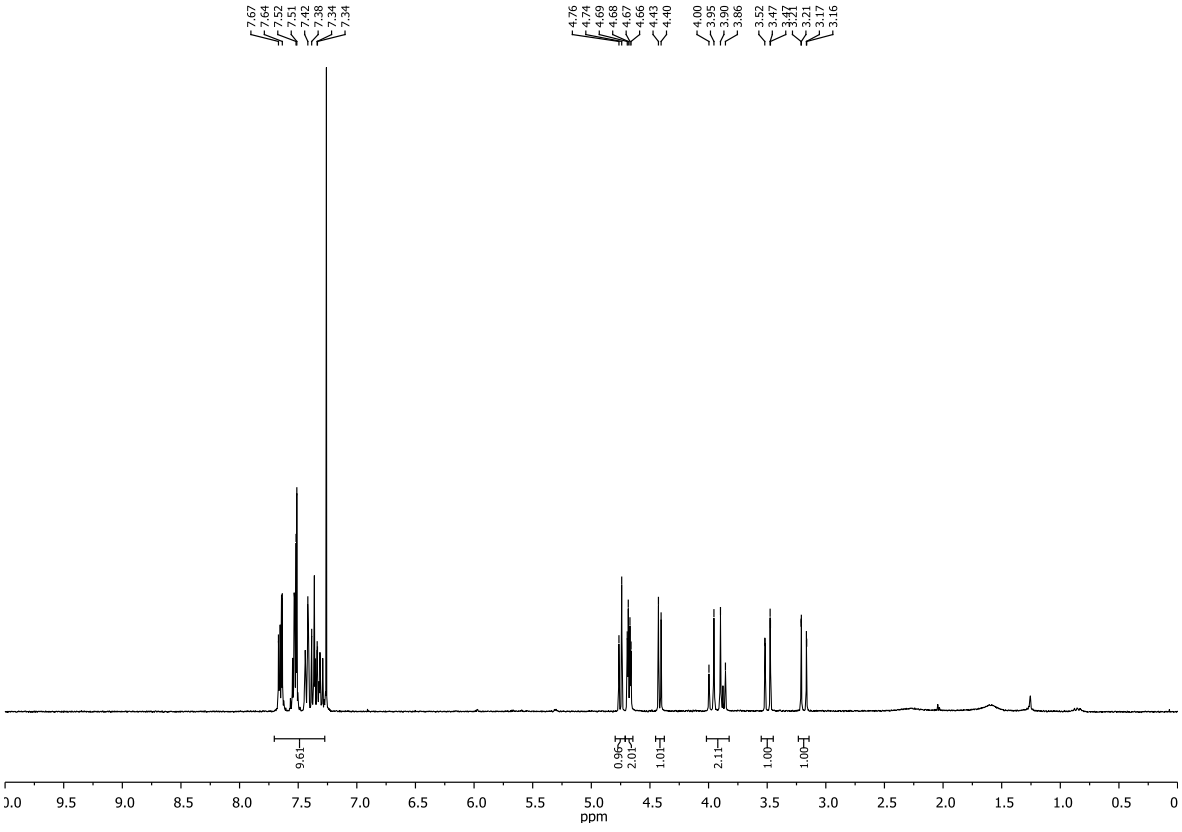


Figure 45 ^{1}H-NMR Spectrum of 82.

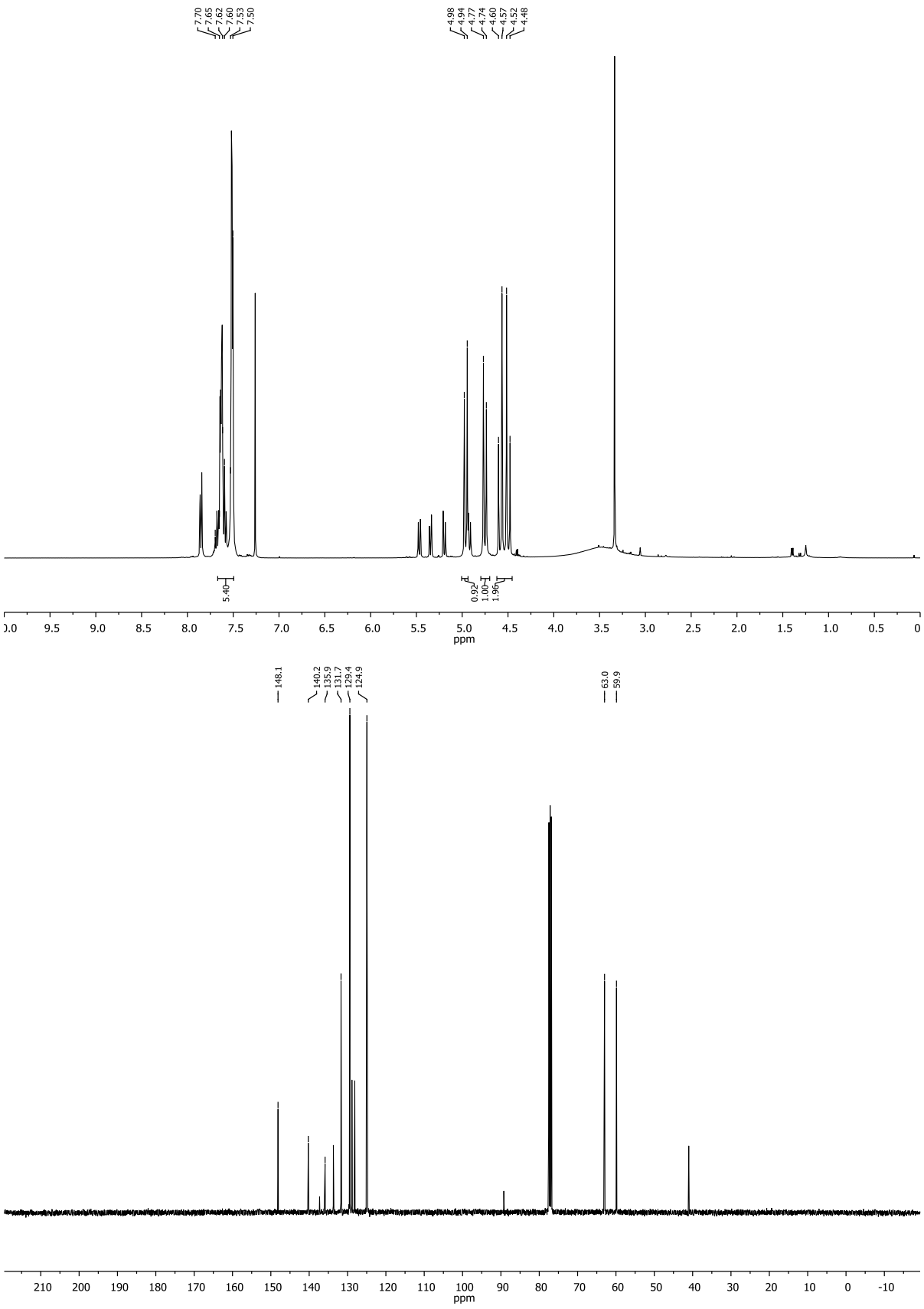


Figure 46 ^{1}H- and ^{13}C-NMR Spectra of 85

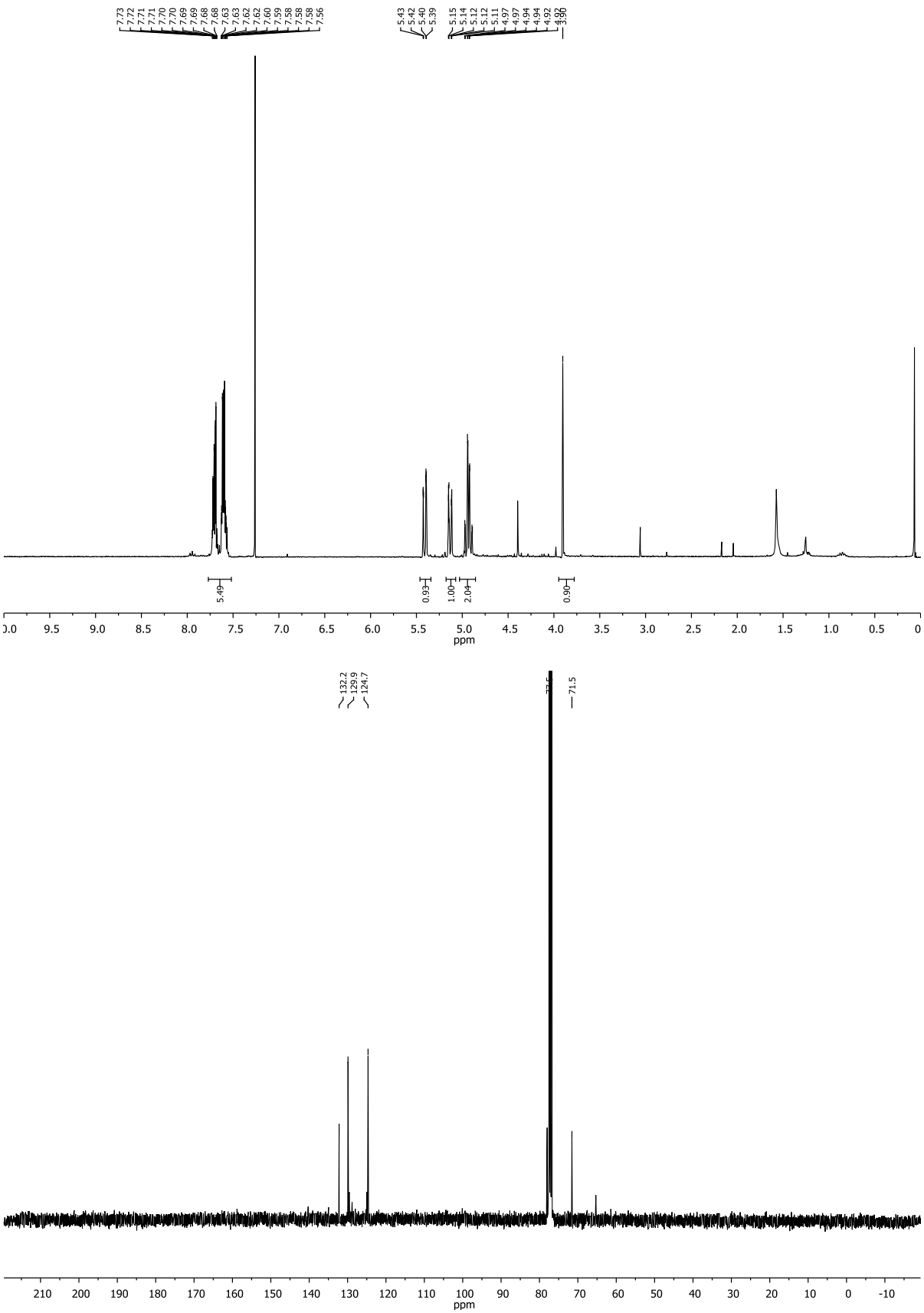


Figure 47 ^{1}H- and ^{13}C-NMR Spectra of 80.

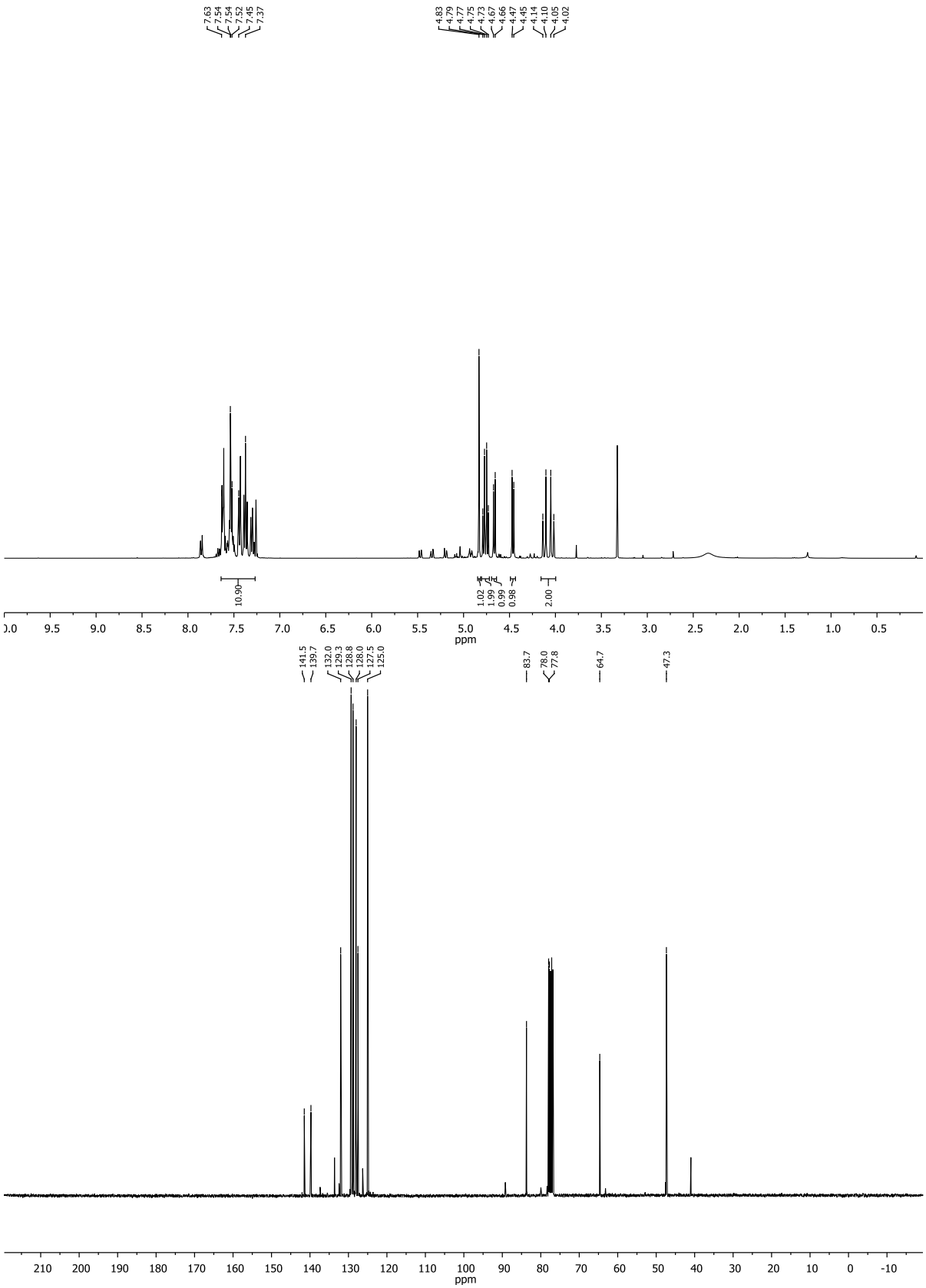


Figure 48 ^{1}H- and ^{13}C-NMR Spectra of 86.

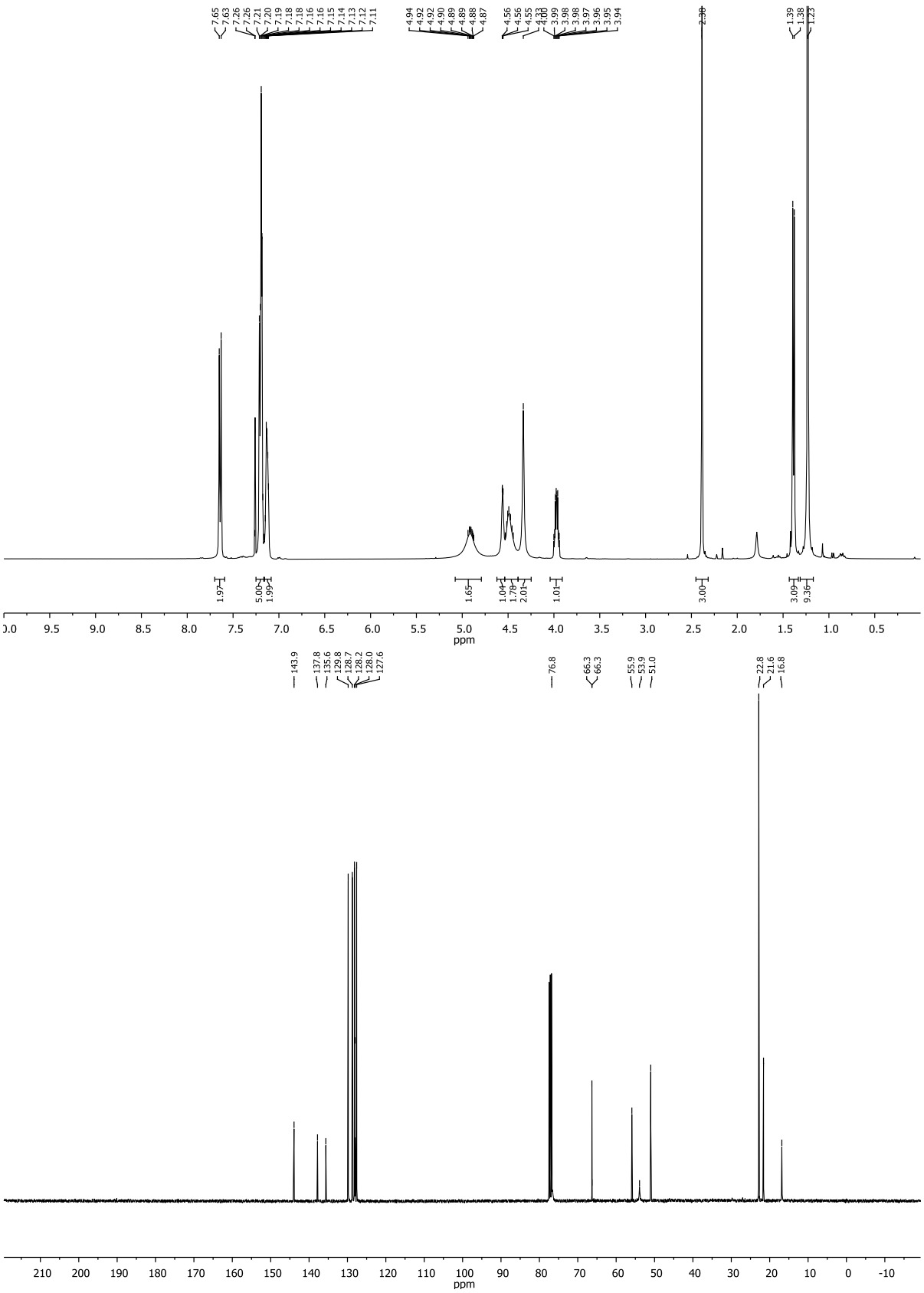


Figure 49 ^{1}H- and ^{13}C-NMR Spectra of 119.

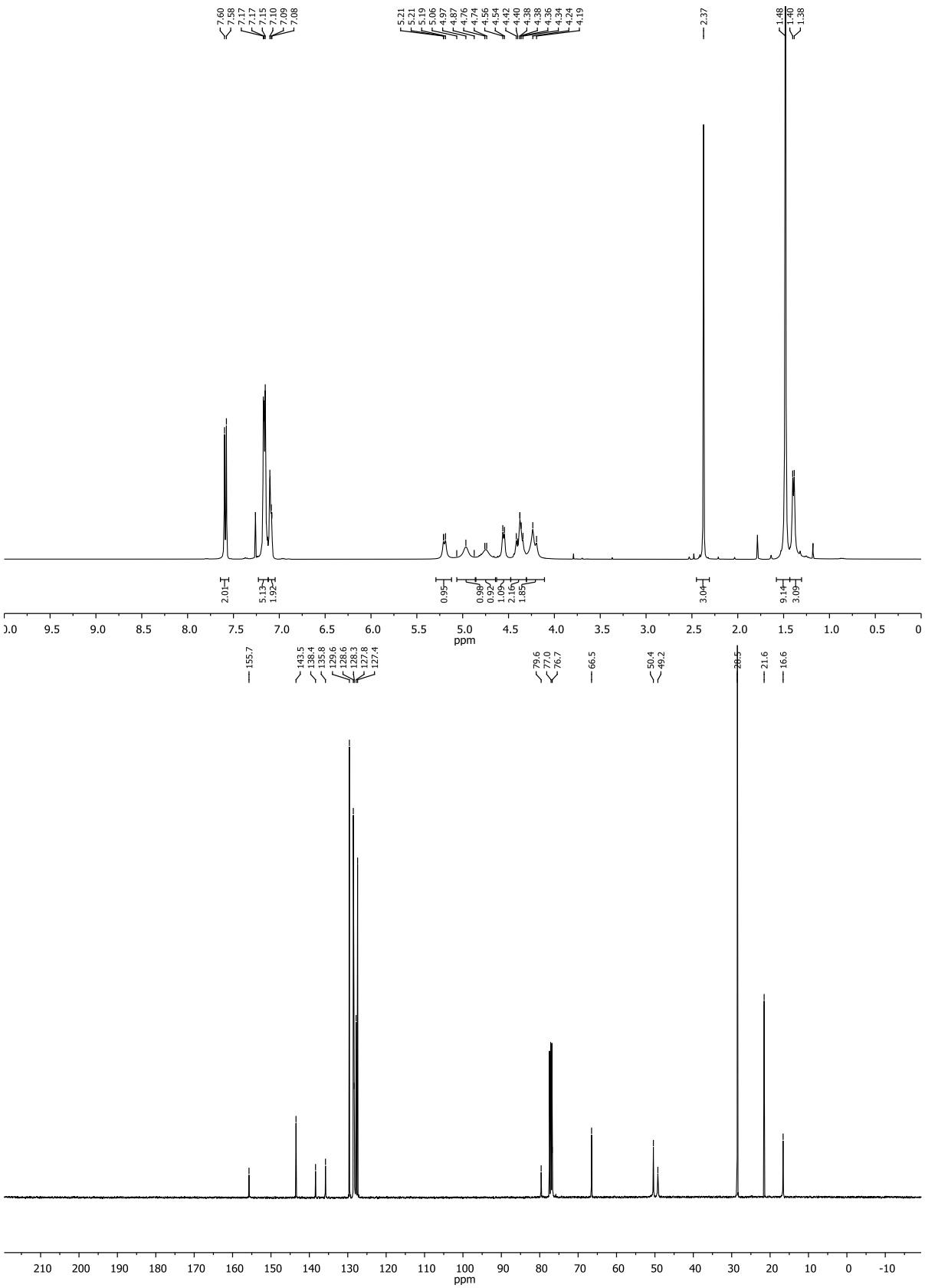


Figure 50 ^{1}H- and ^{13}C-NMR Spectra of 120.

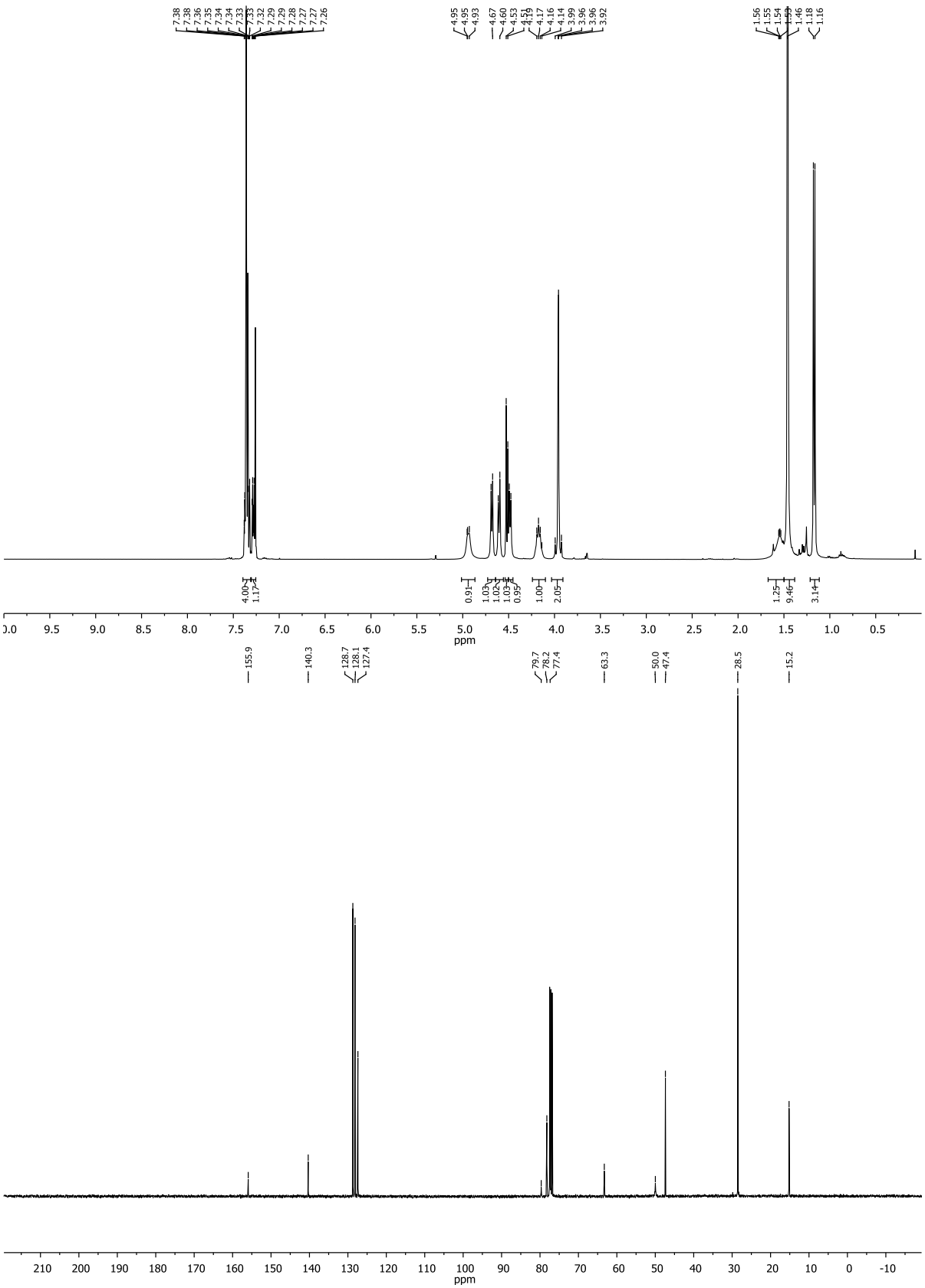


Figure 51 ^{1}H- and ^{13}C-NMR Spectra of 121.

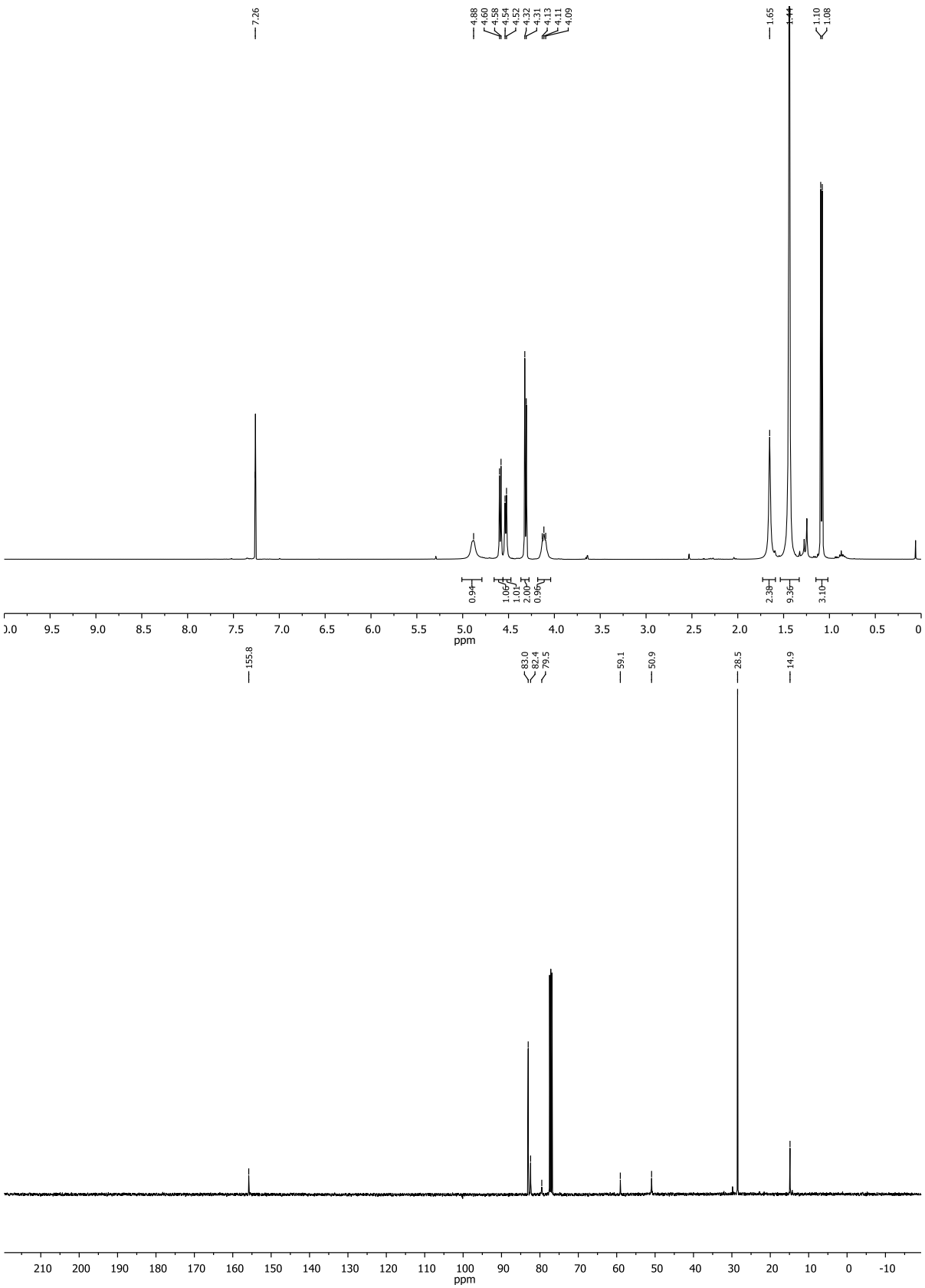


Figure 52 ^{1}H- and Spectra of ^{13}C-NMR 122.

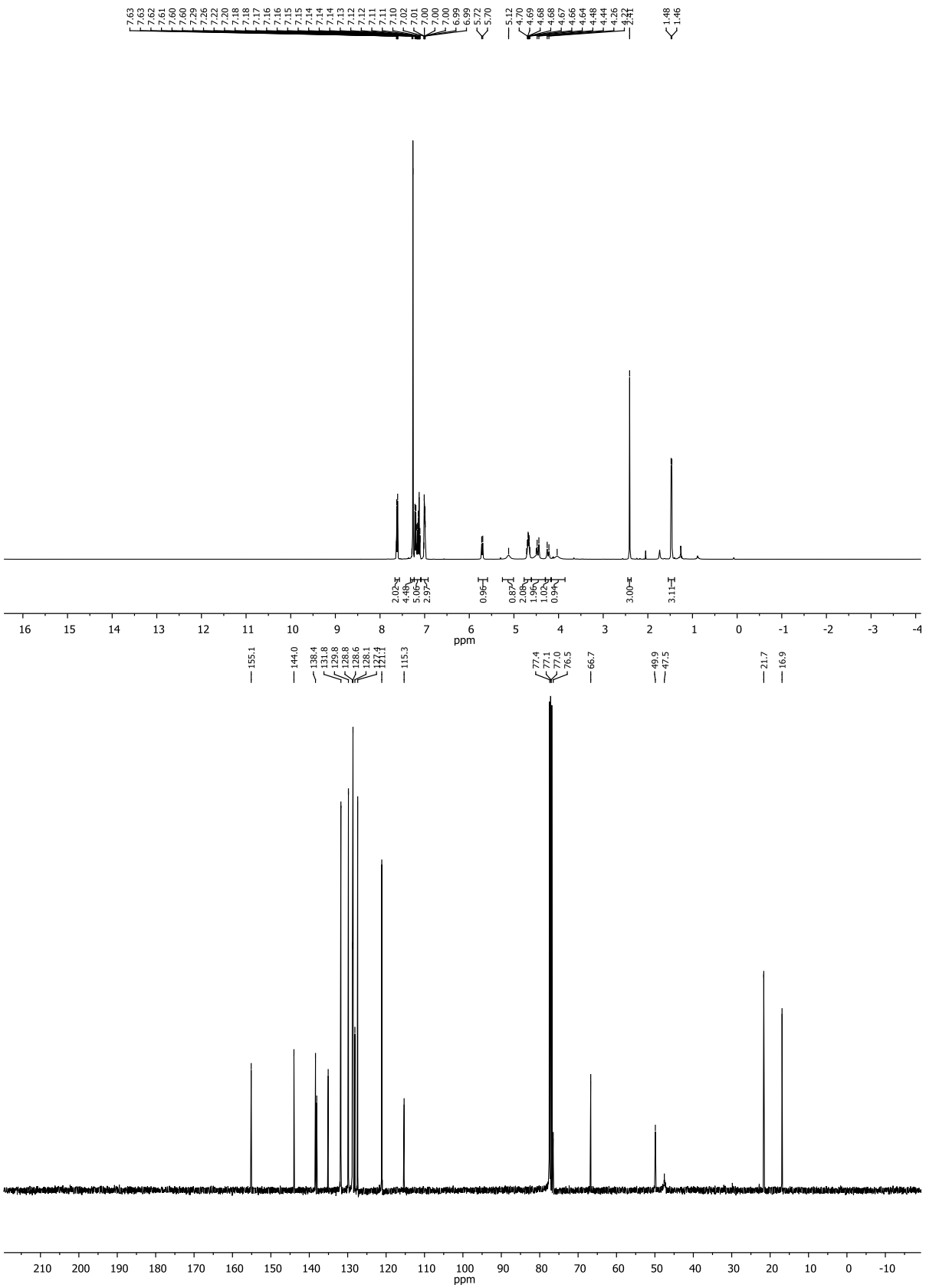


Figure 53 ^{1}H- and Spectra of ^{13}C-NMR 123.

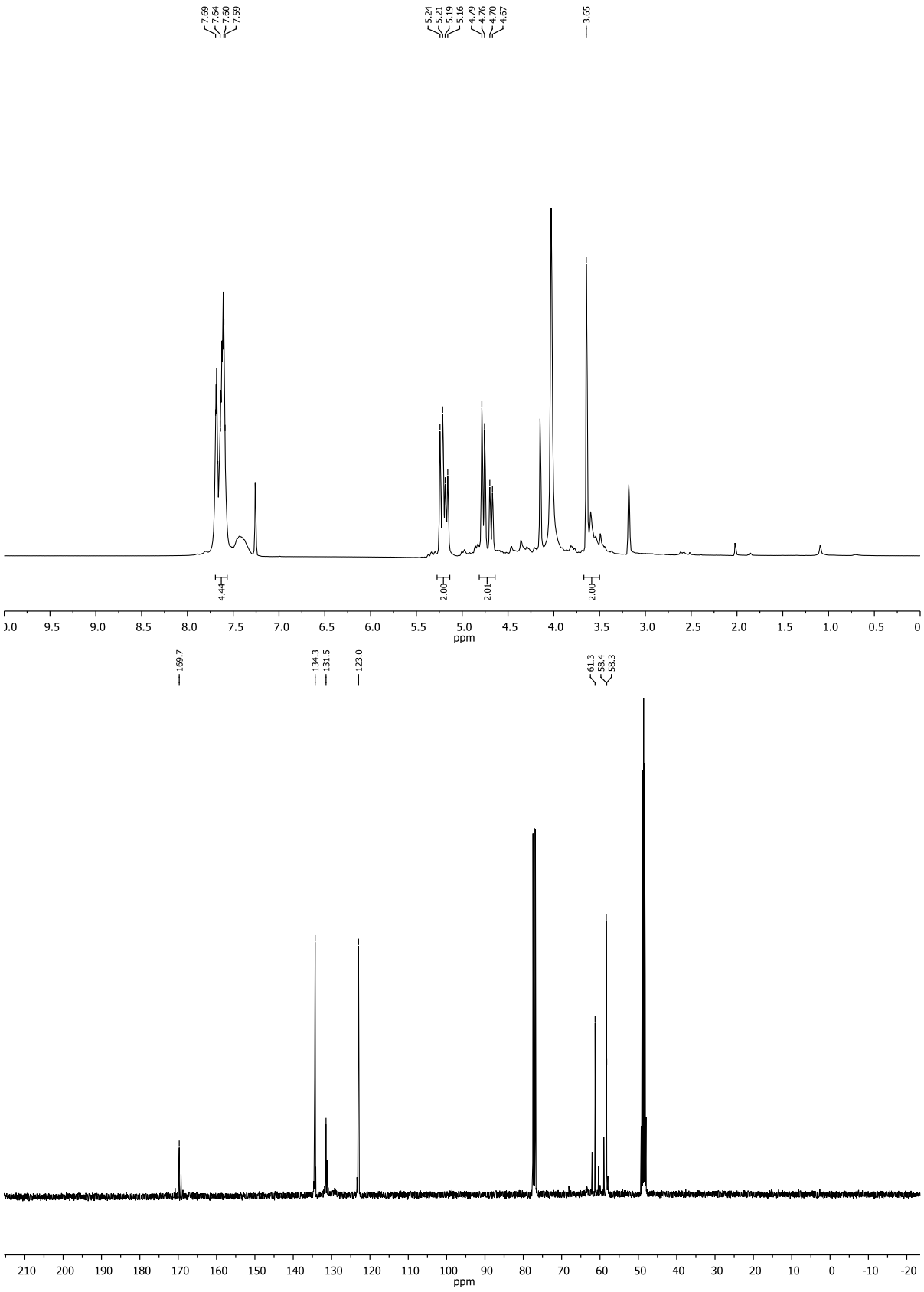


Figure 54 ^{1}H- and ^{13}C-NMR Spectra of 126.

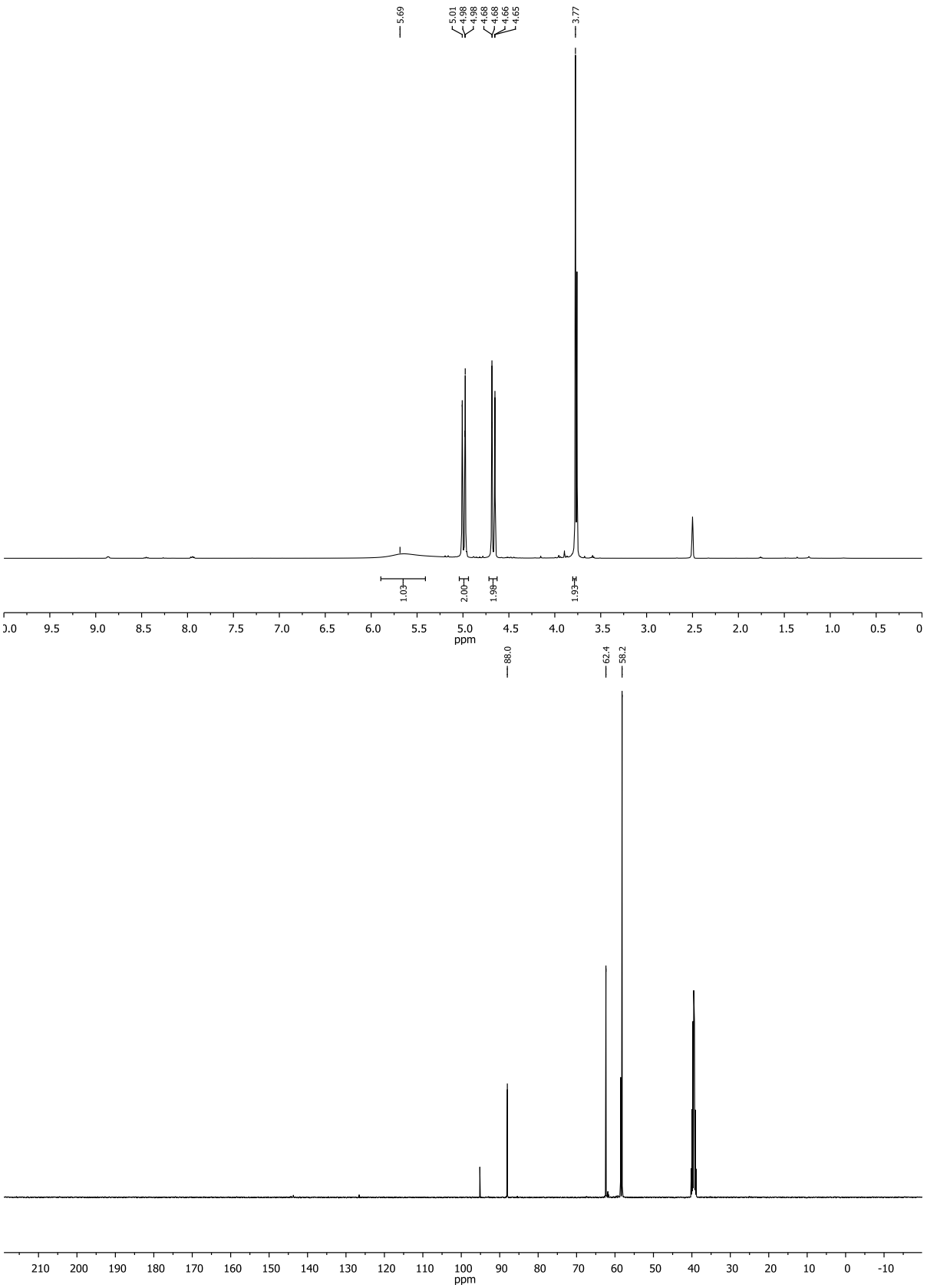


Figure 55 ^{1}H- and ^{13}C-NMR Spectra of 98.

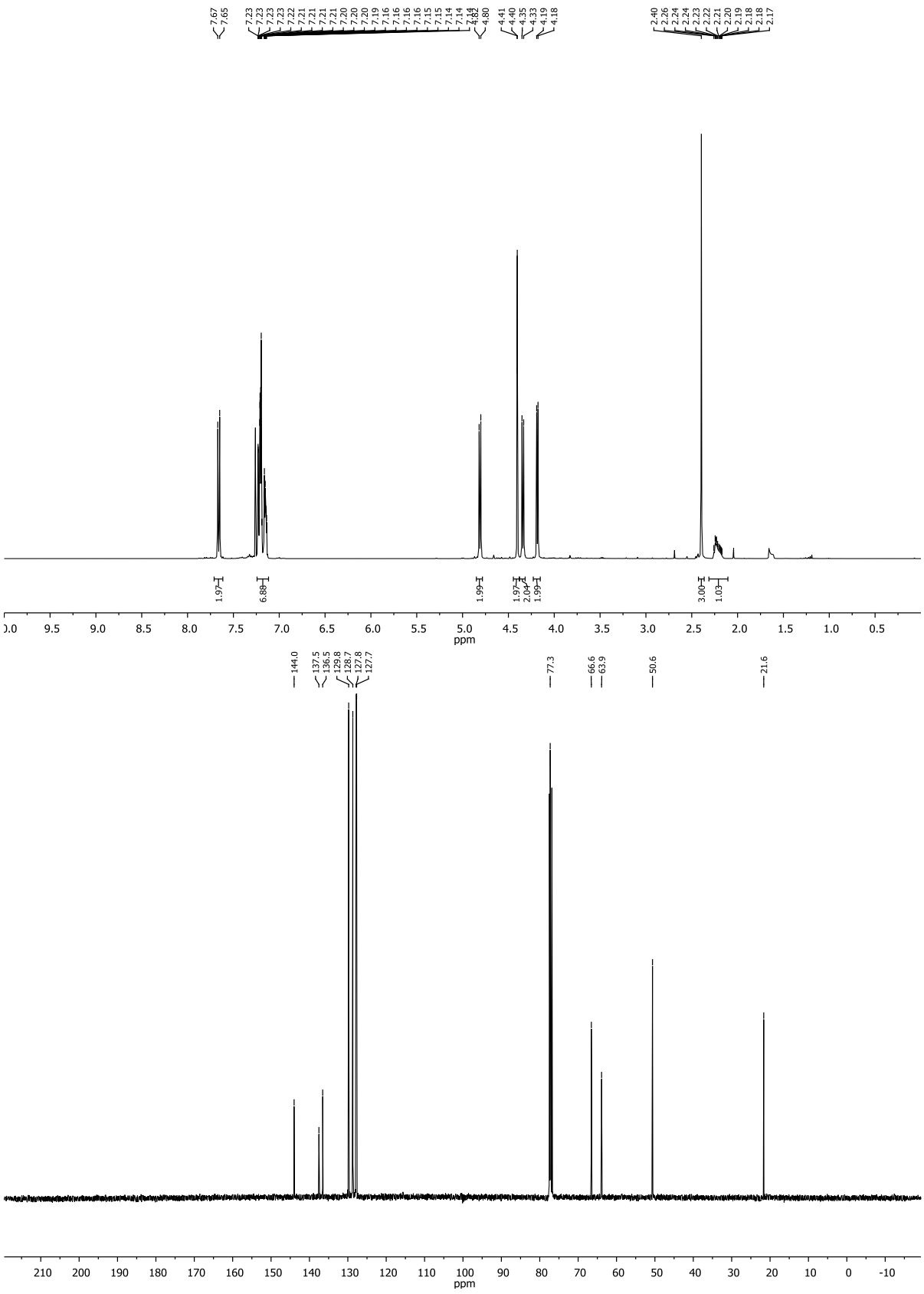


Figure 56 ^{1}H- and ^{13}C-NMR Spectra of 131.

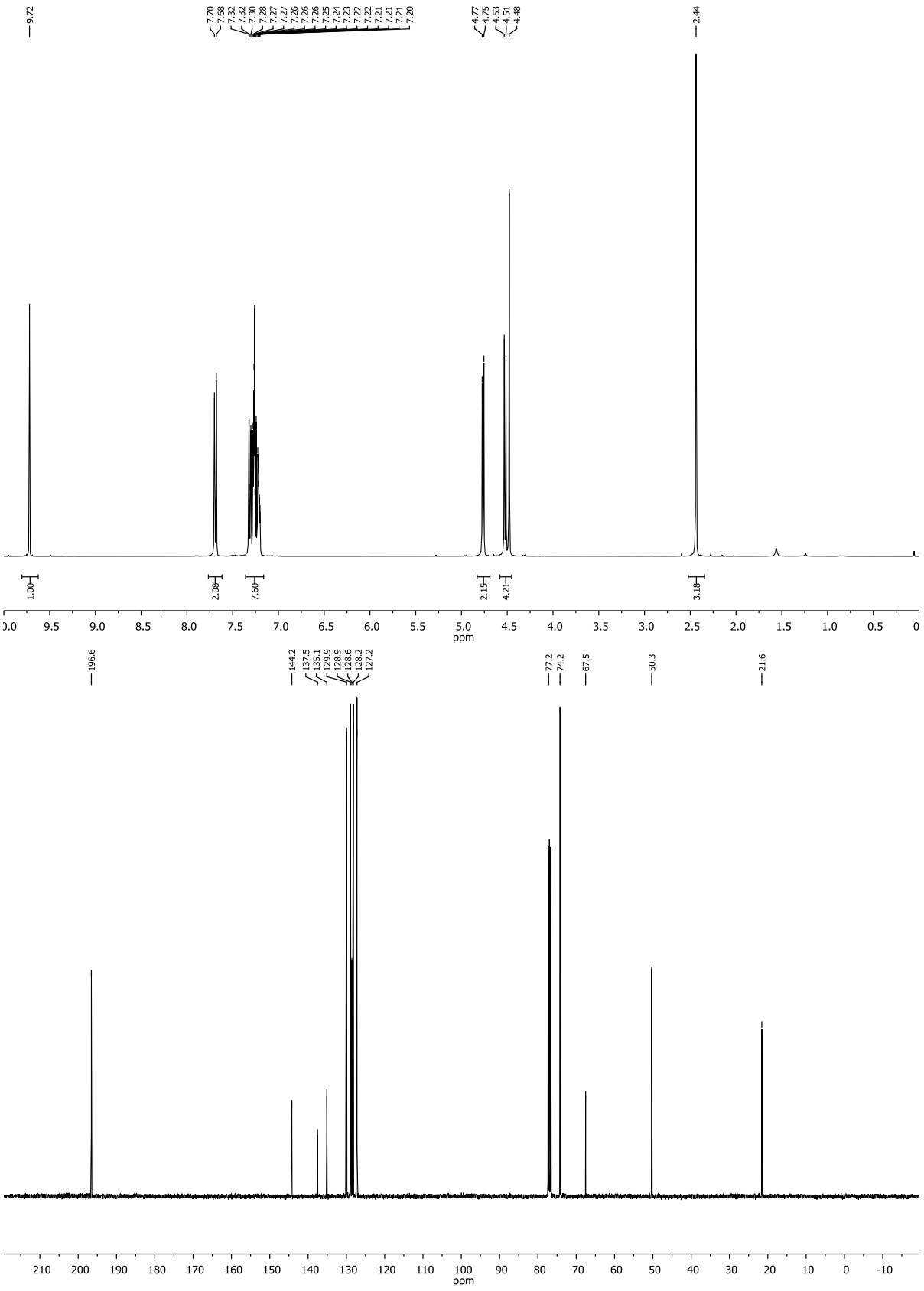


Figure 57 ^{1}H- and ^{13}C-NMR Spectra of 115.

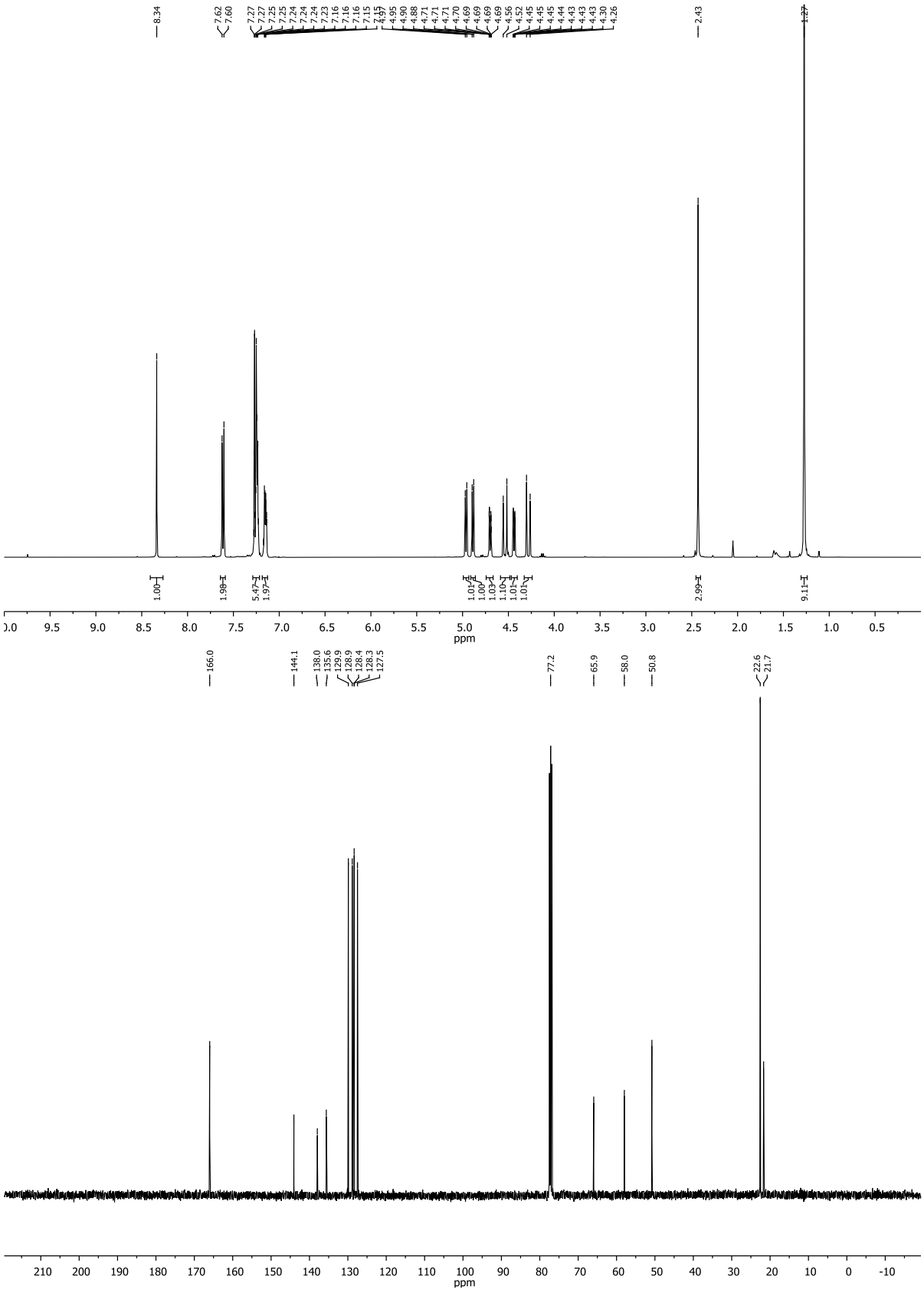


Figure 58 ^{1}H- and ^{13}C-NMR Spectra of 118.

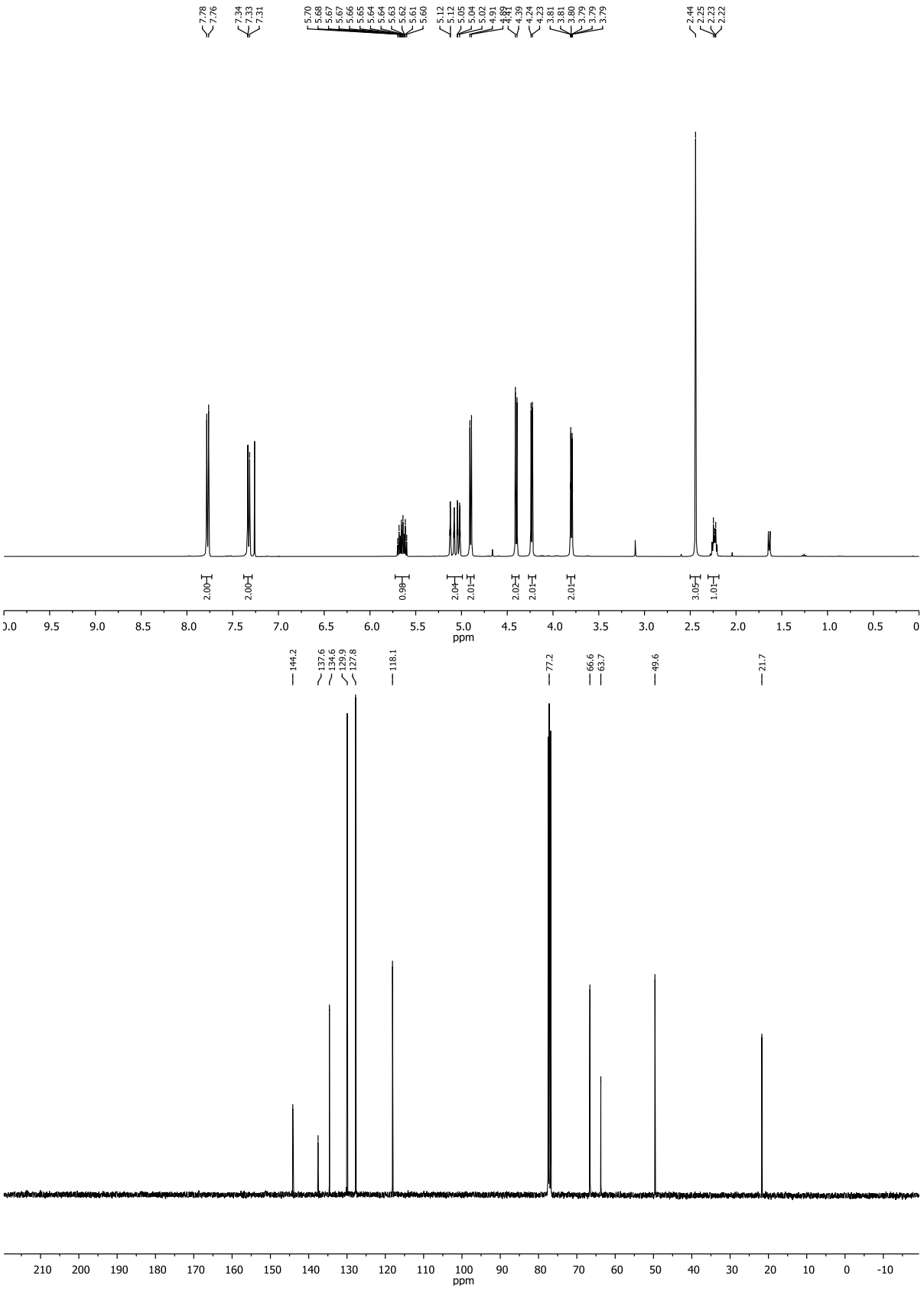


Figure 59 ^{1}H- and ^{13}C-NMR Spectra of 134.

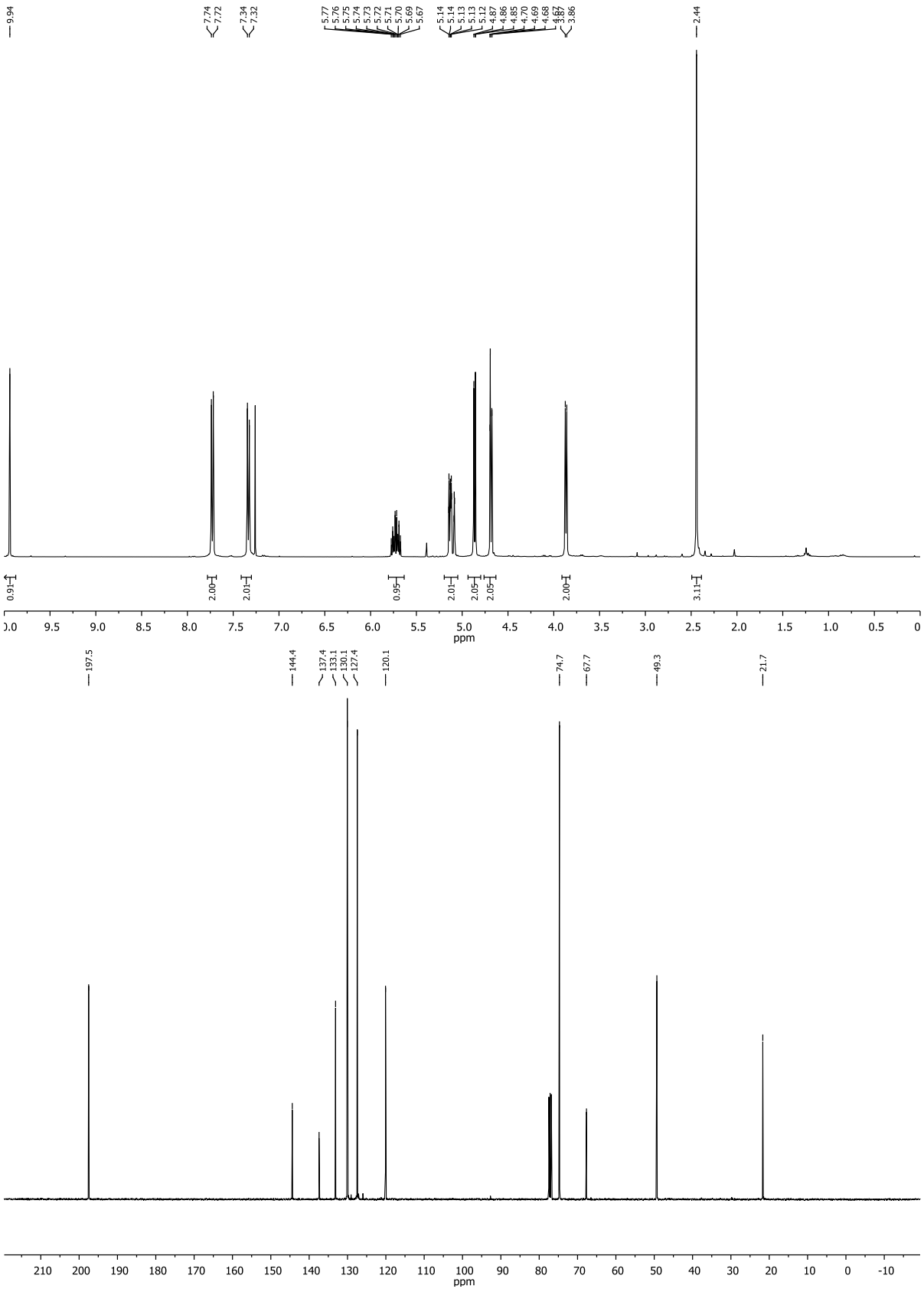


Figure 60 ^{1}H- and ^{13}C-NMR Spectra of 137.

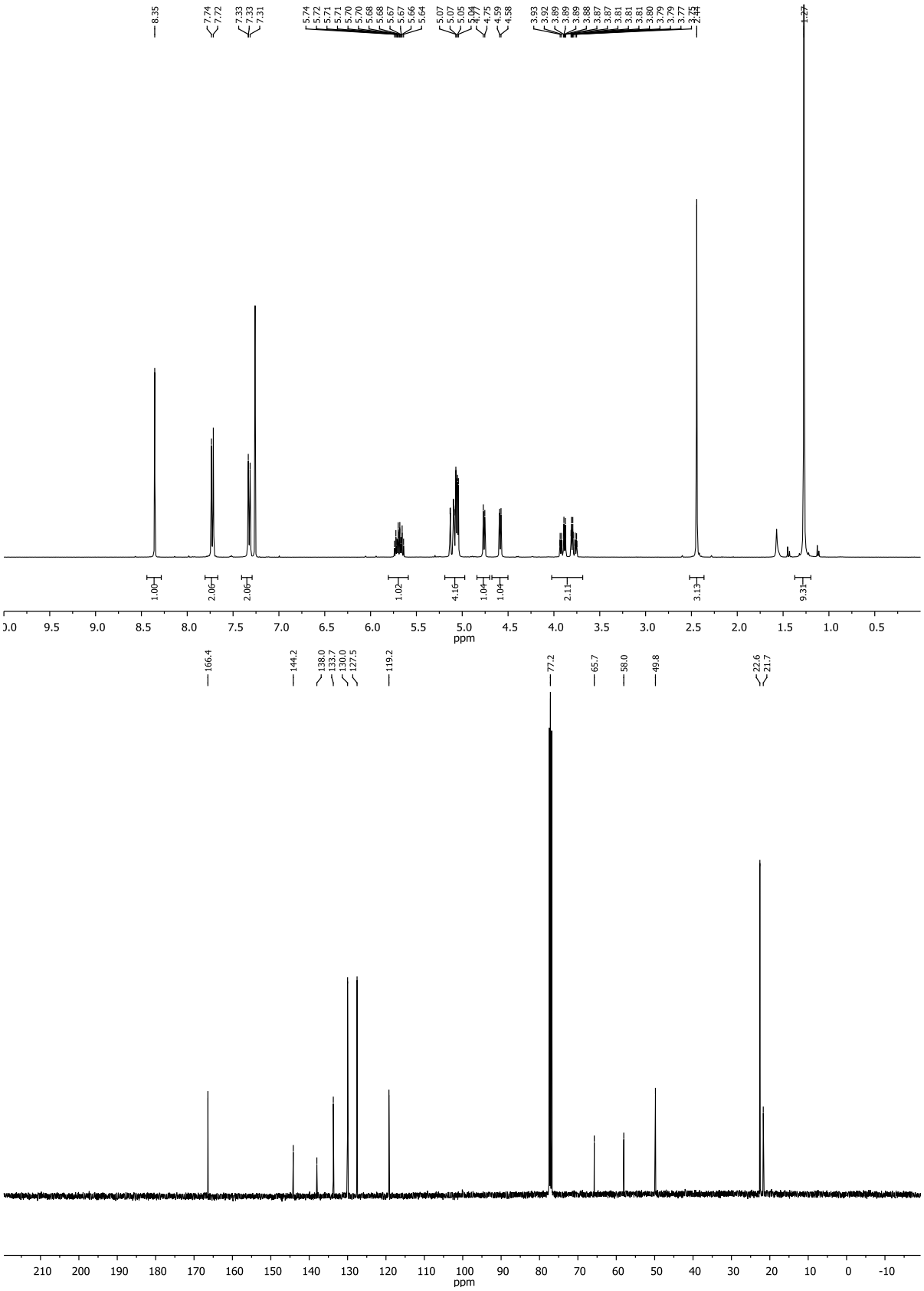


Figure 61 ^{1}H- and ^{13}C-NMR Spectra of 139.

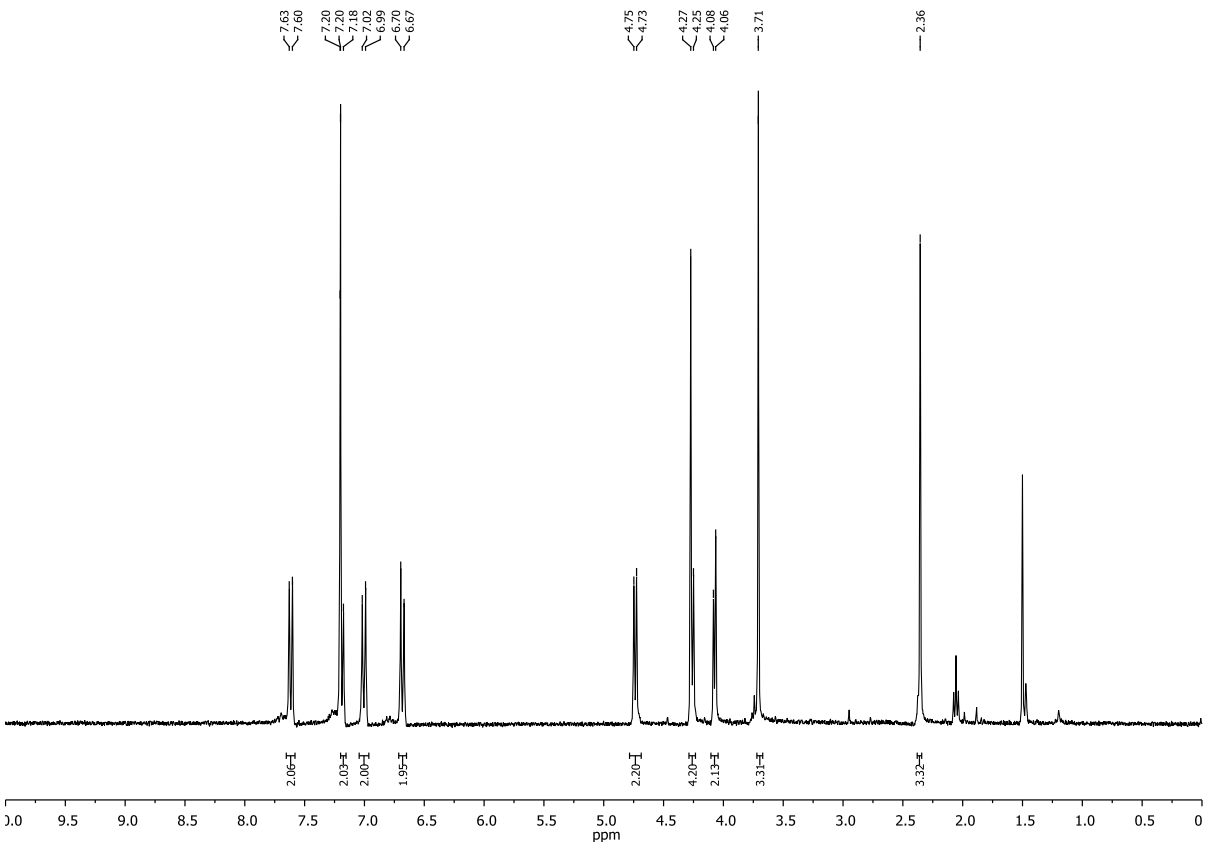


Figure 62 ^{1}H-NMR Spectrum of 135.

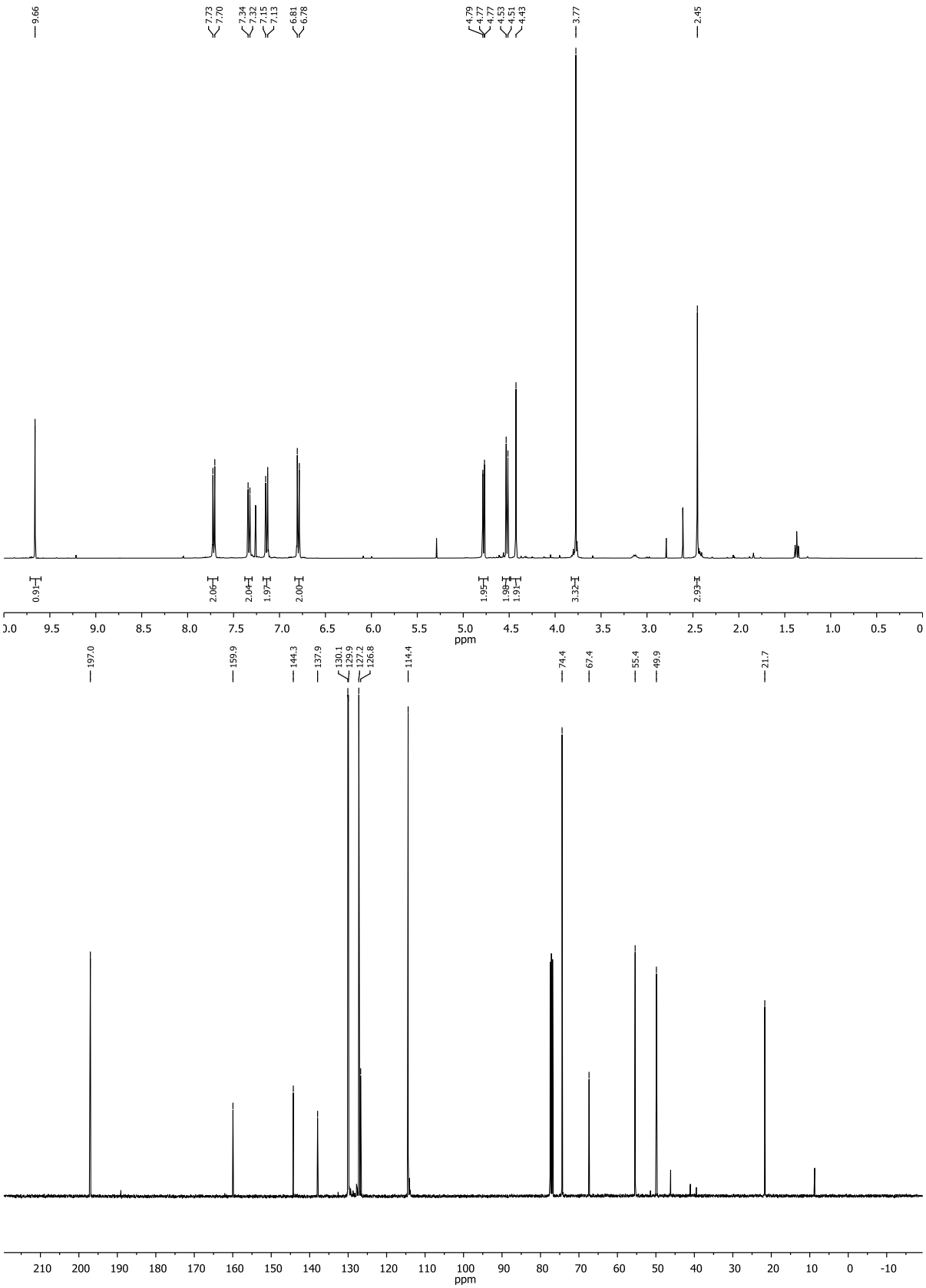


Figure 63 ^{1}H- and ^{13}C-NMR Spectra of 138.

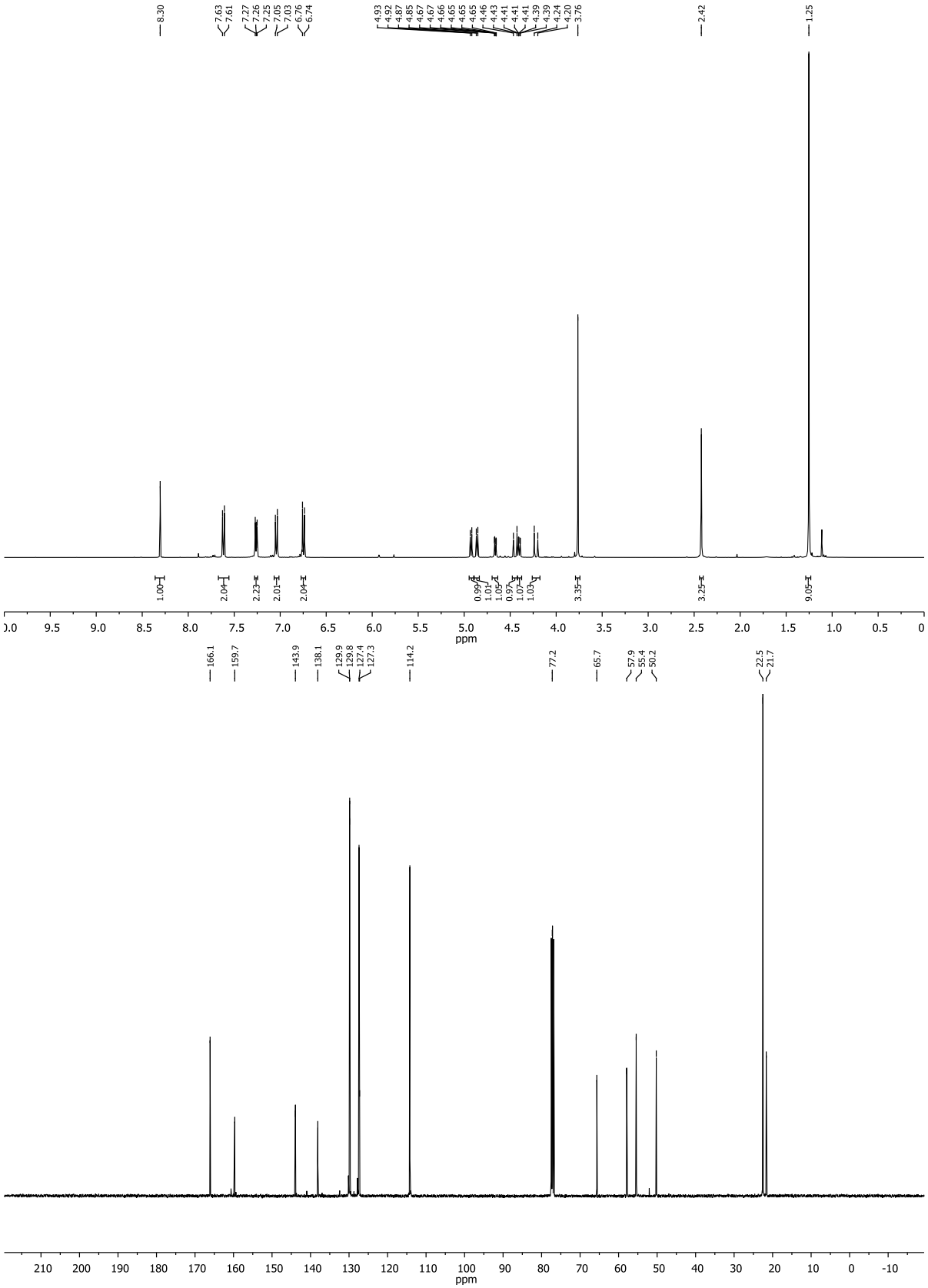


Figure 64 ^{1}H- and ^{13}C-NMR Spectra of 140.

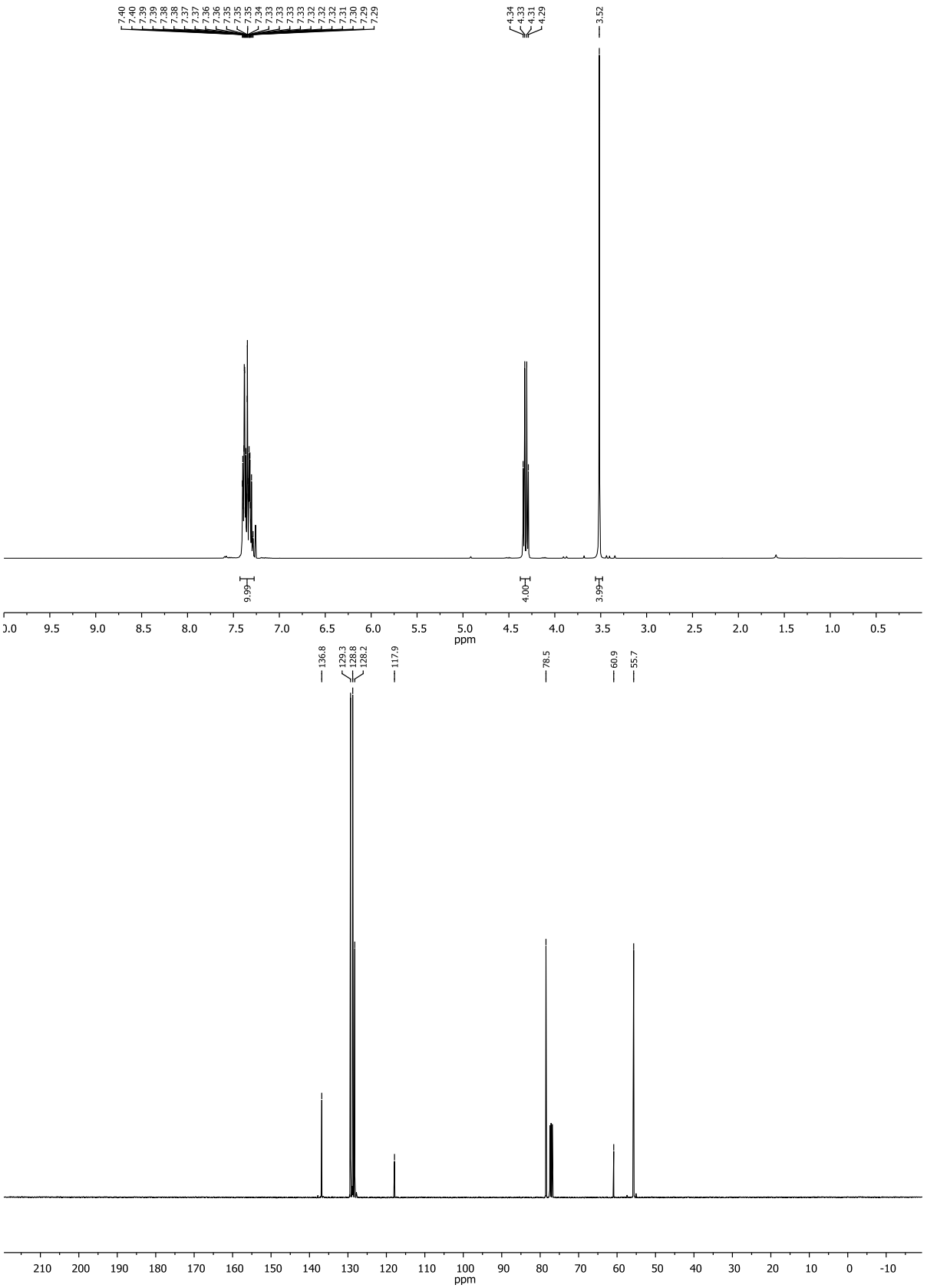


Figure 65 ^{1}H- and ^{13}C-NMR Spectra of 142.

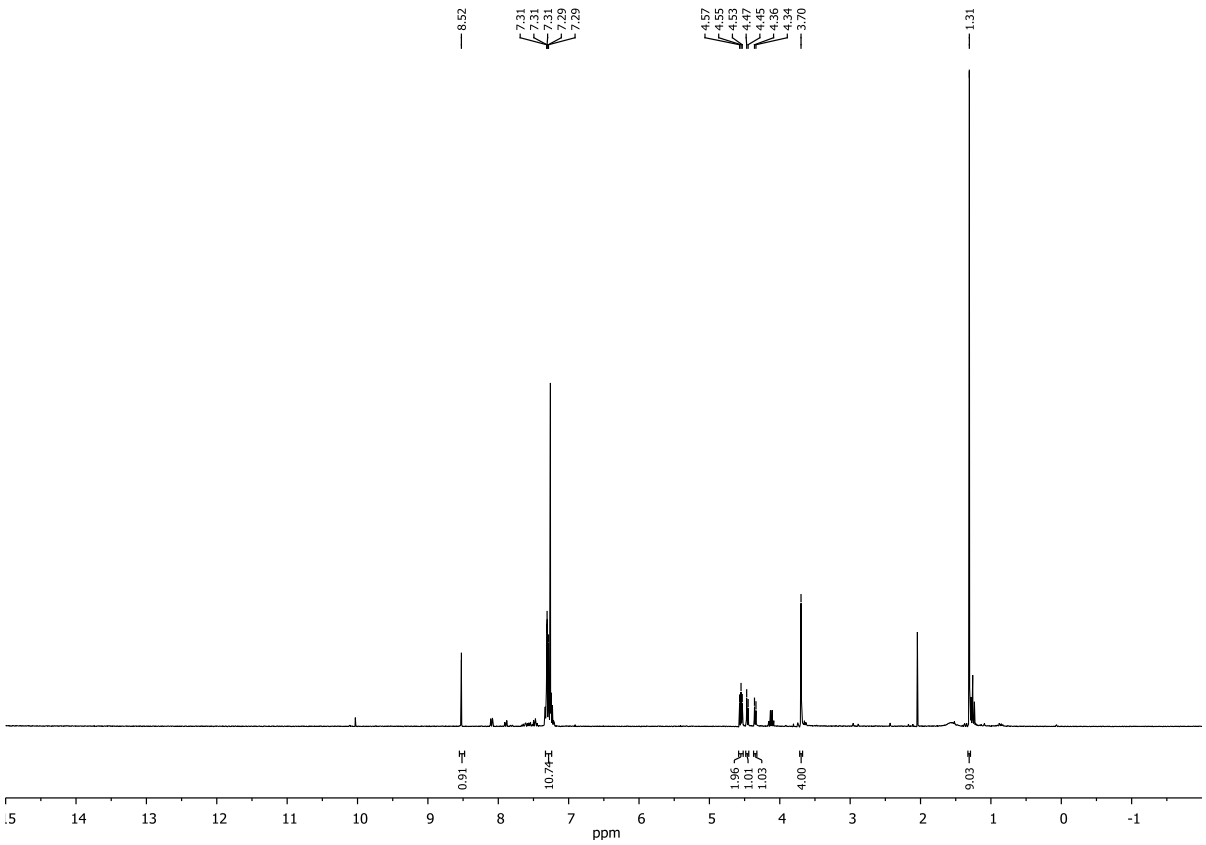


Figure 66 ^{1}H-NMR Spectrum of 141.

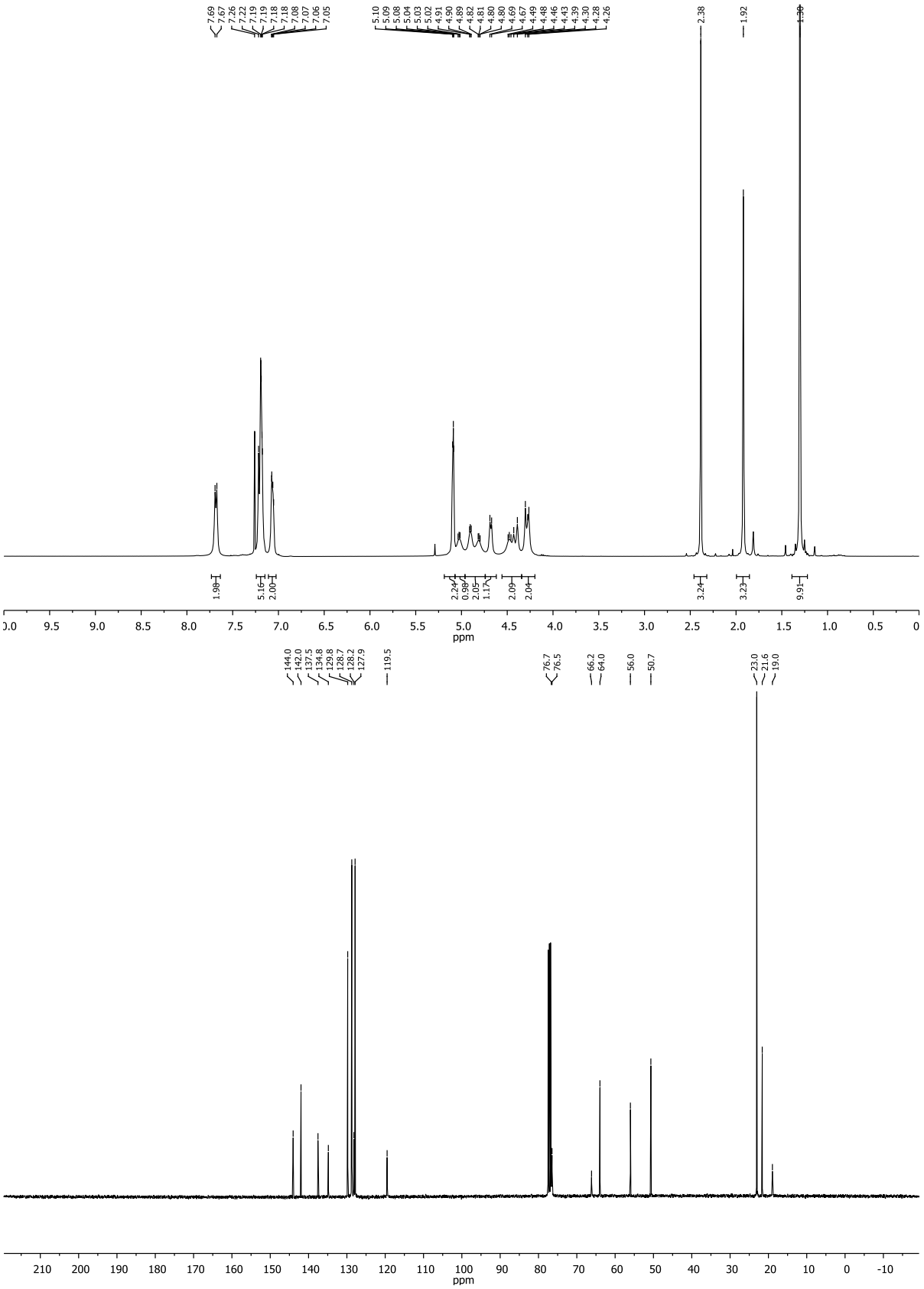


Figure 67 ^{1}H- and ^{13}C-NMR Spectra of 132.

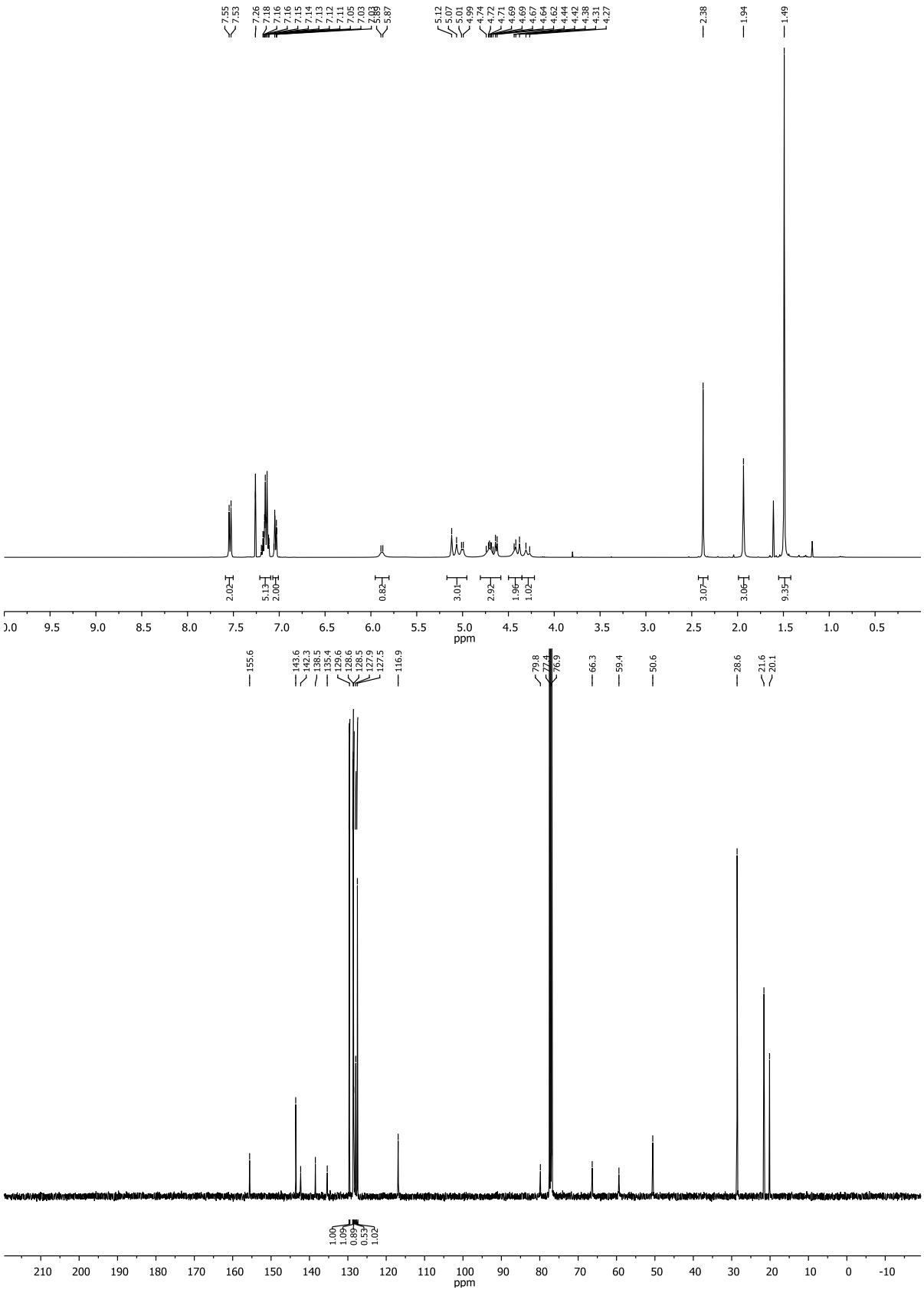


Figure 68 ^{1}H- and ^{13}C-NMR Spectra of 147.

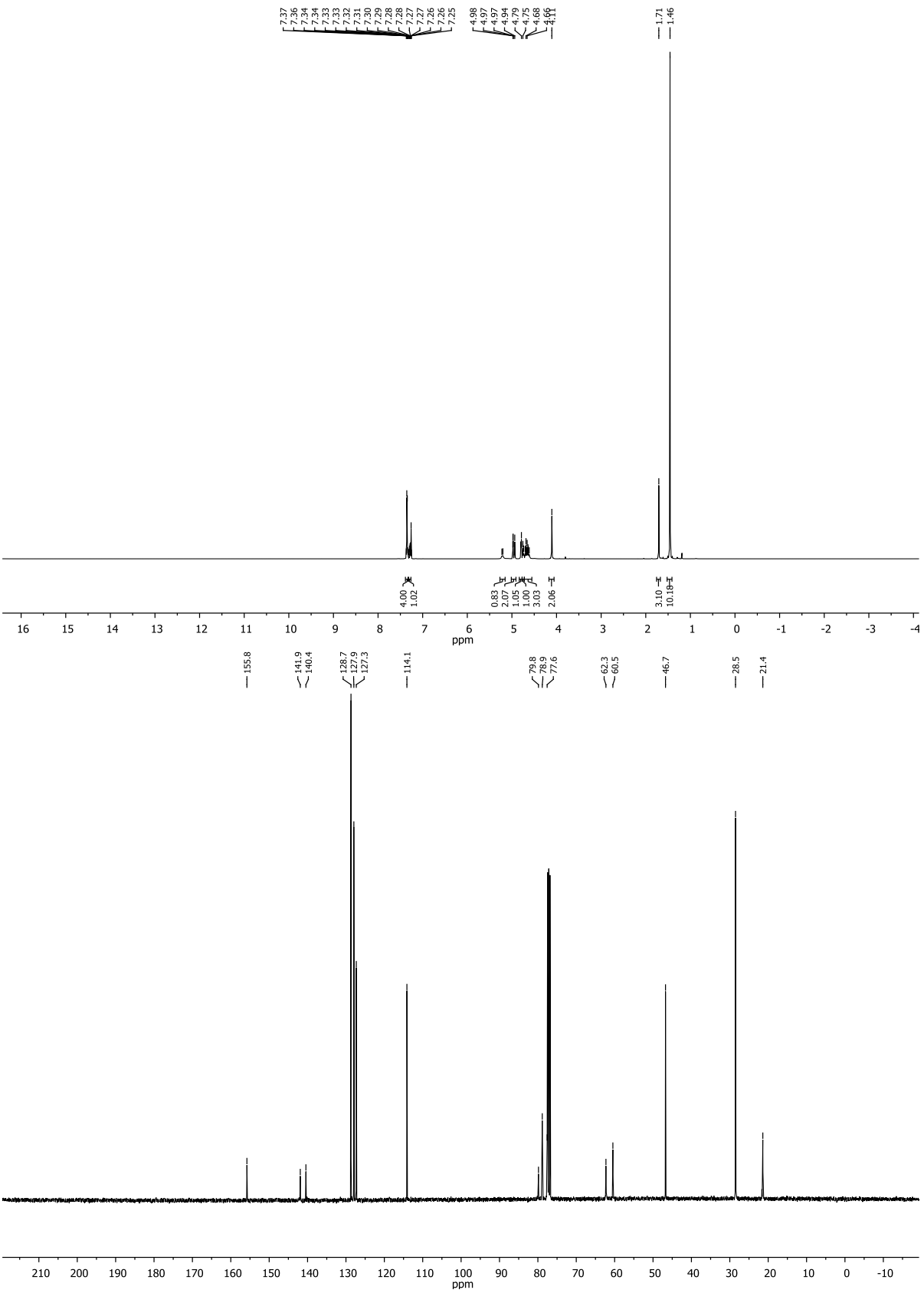


Figure 69 ^{1}H- and ^{13}C-NMR Spectra of 148.

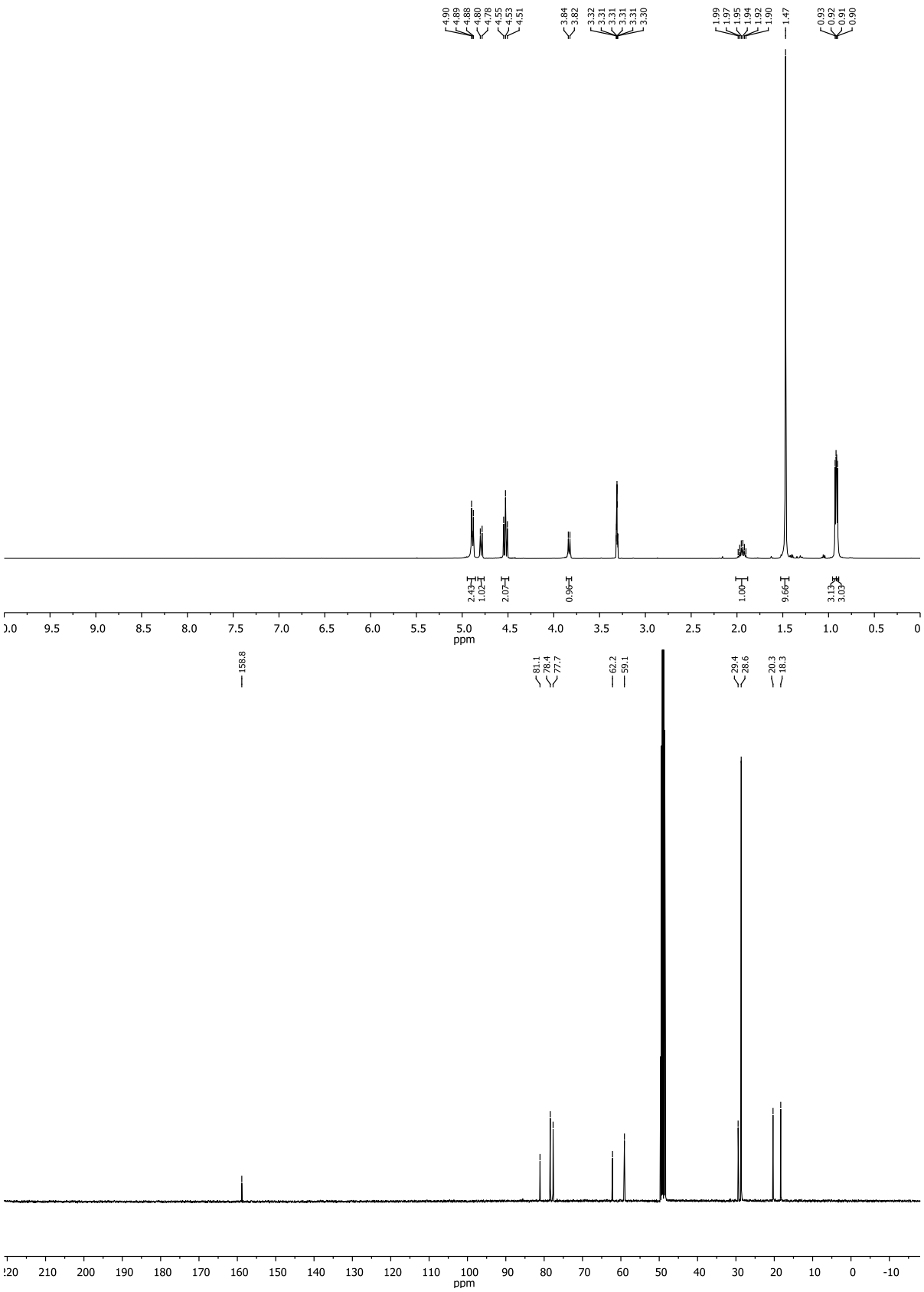


Figure 70 ^{1}H- and ^{13}C-NMR Spectra of 145.

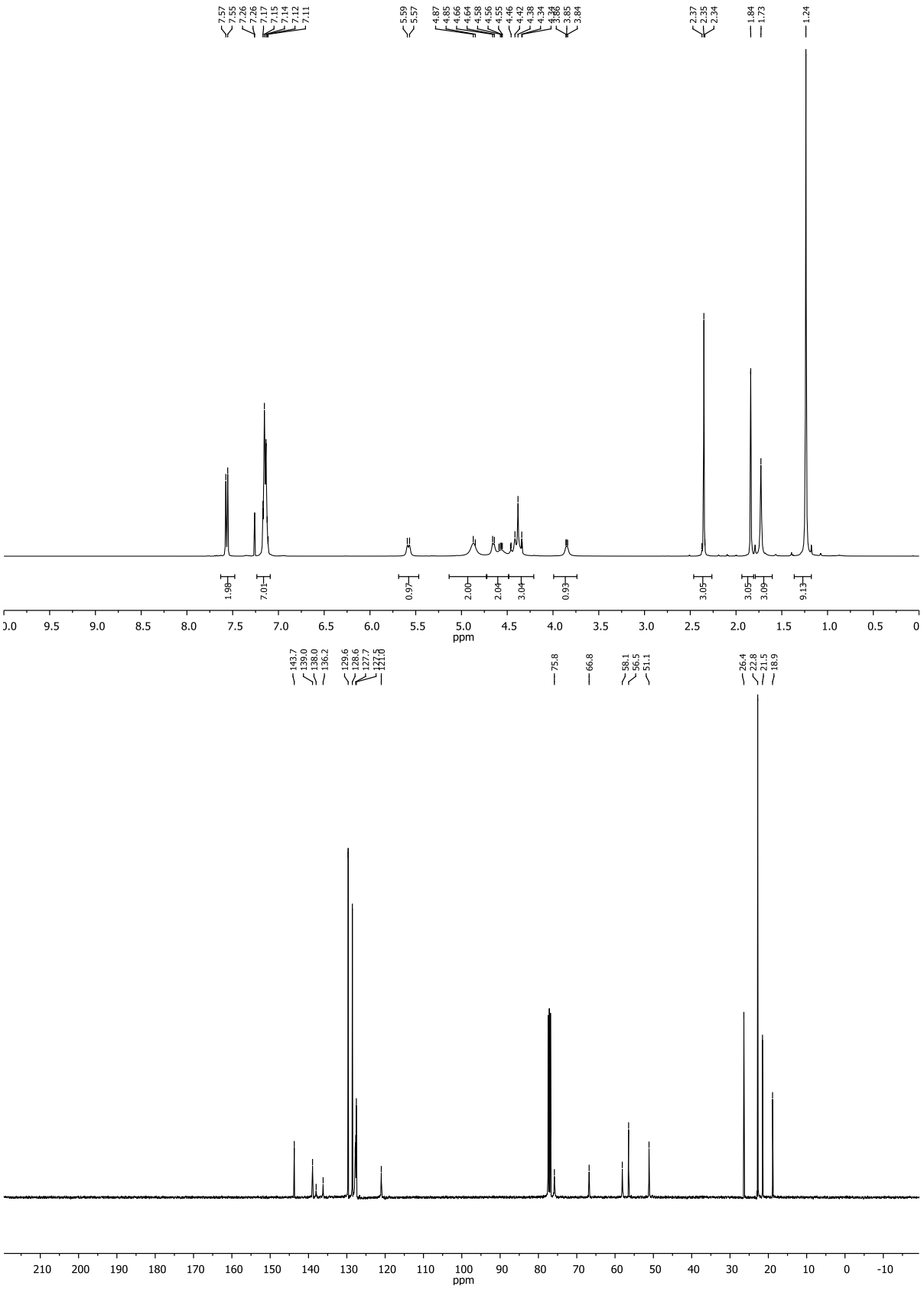


Figure 71 ^{1}H- and ^{13}C-NMR Spectra of 150.

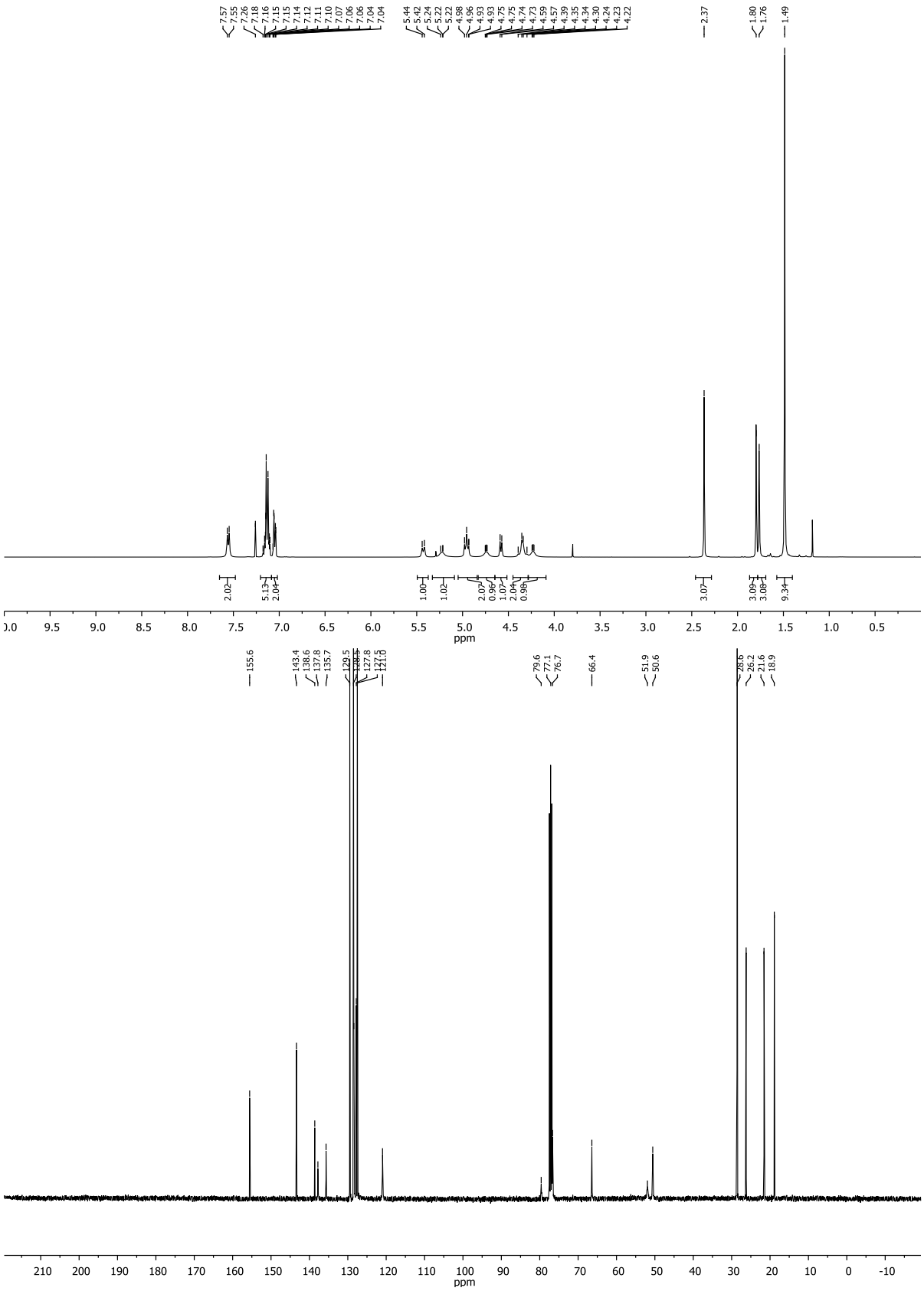


Figure 72 ^{1}H- and ^{13}C-NMR Spectra of 151.

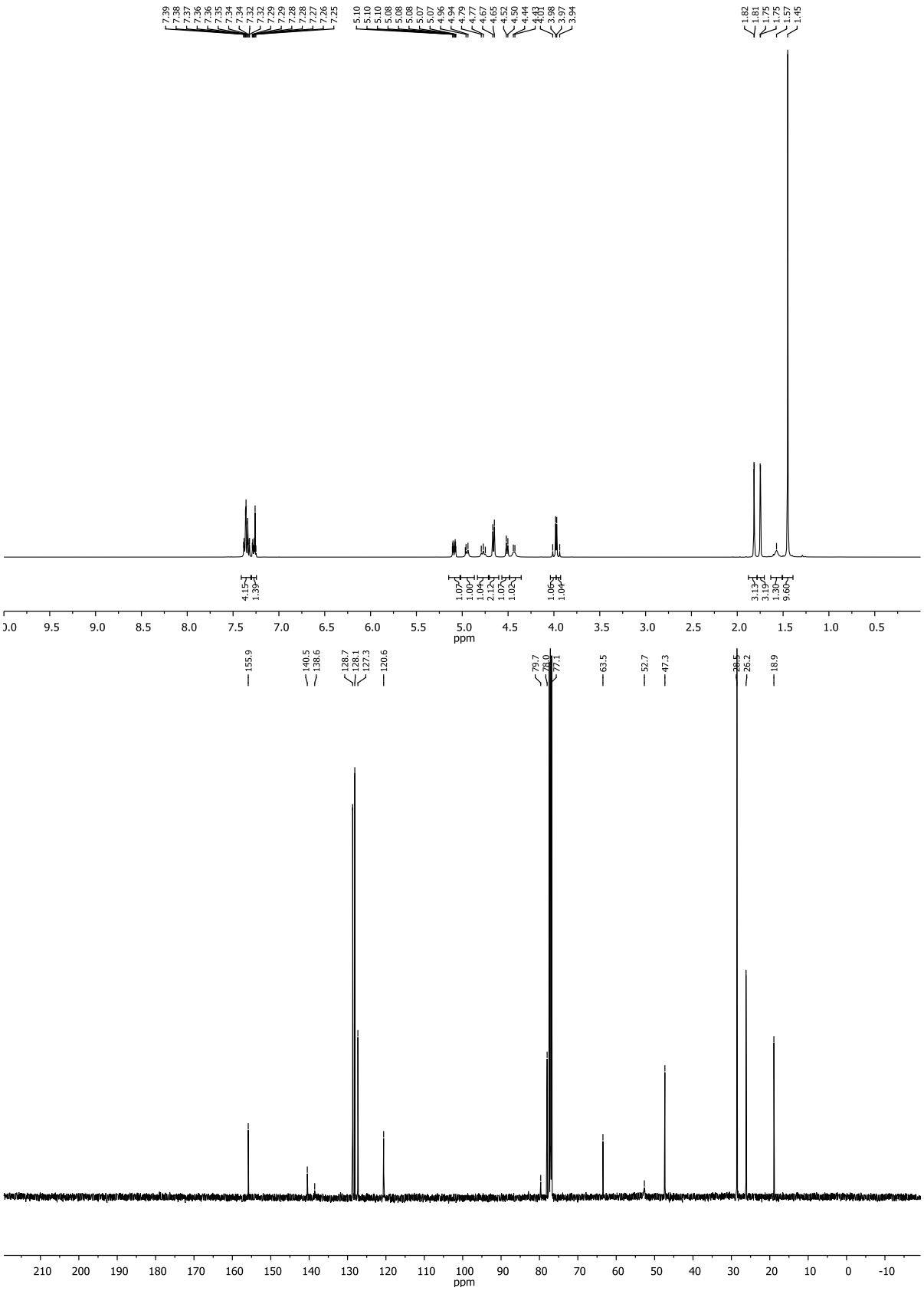


Figure 73 ^{1}H- and ^{13}C-NMR Spectra of 152.

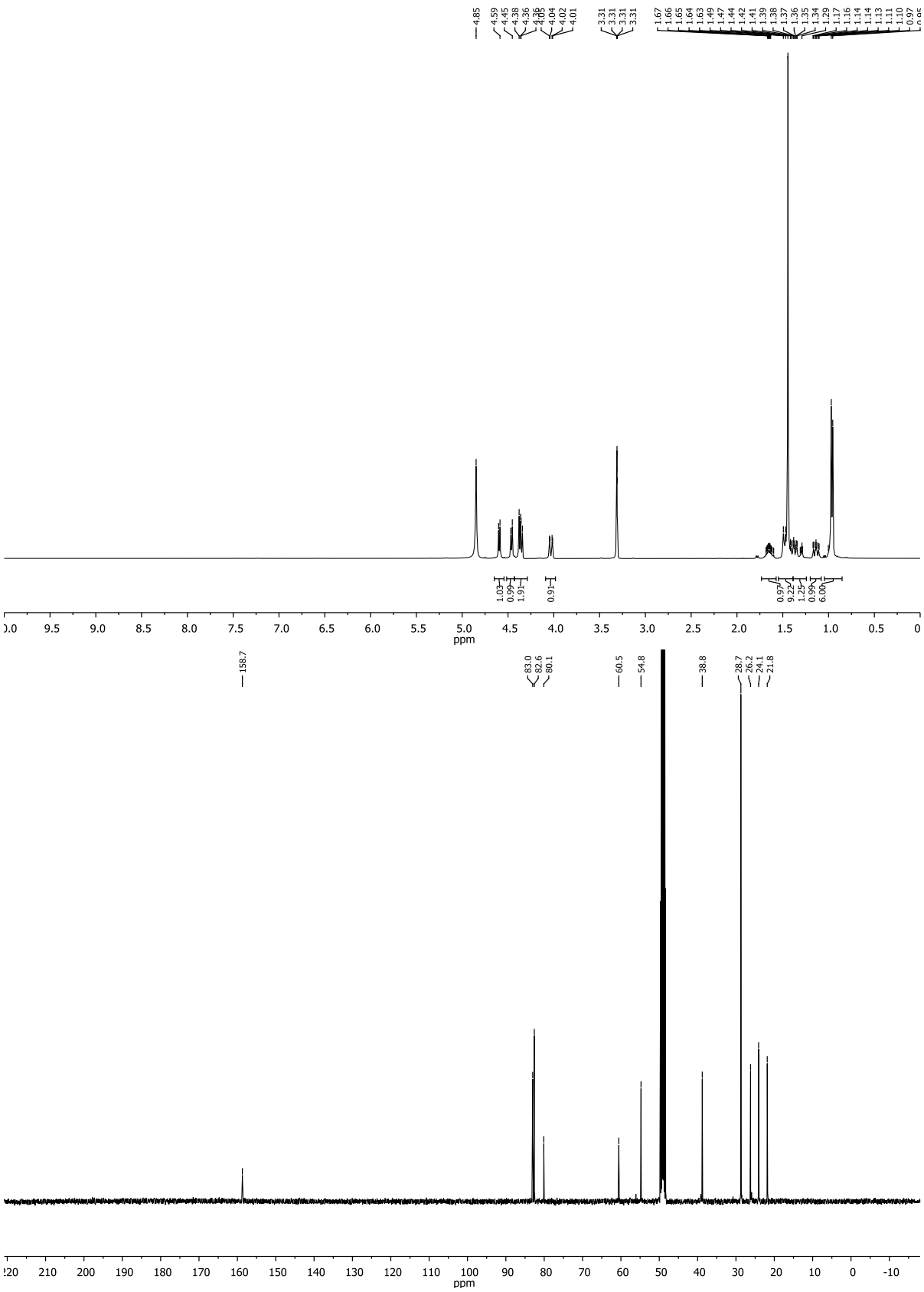


Figure 74 ^{1}H- and ^{13}C-NMR Spectra of 149.

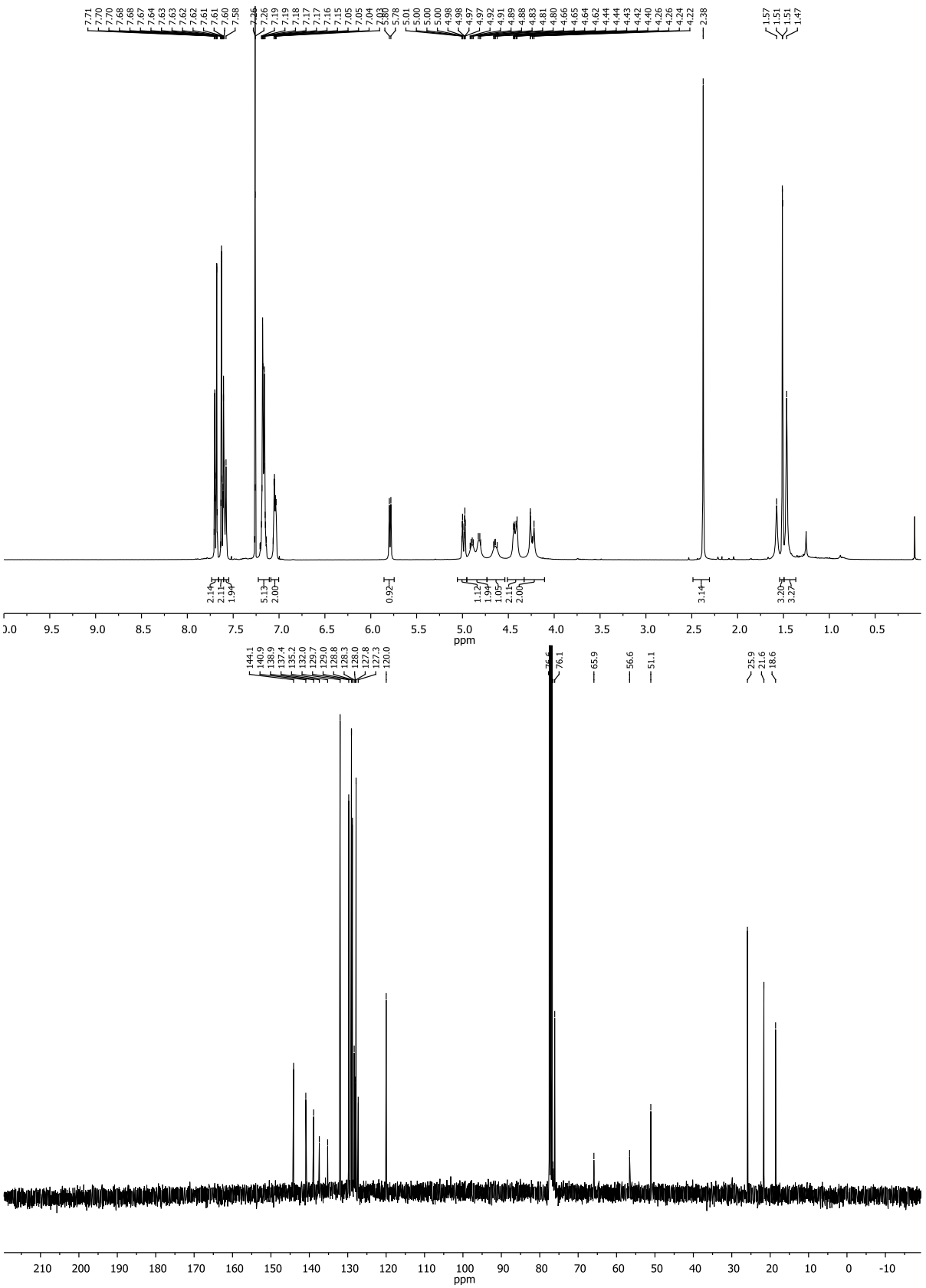


Figure 75 ^{1}H- and ^{13}C-NMR Spectra of 156.

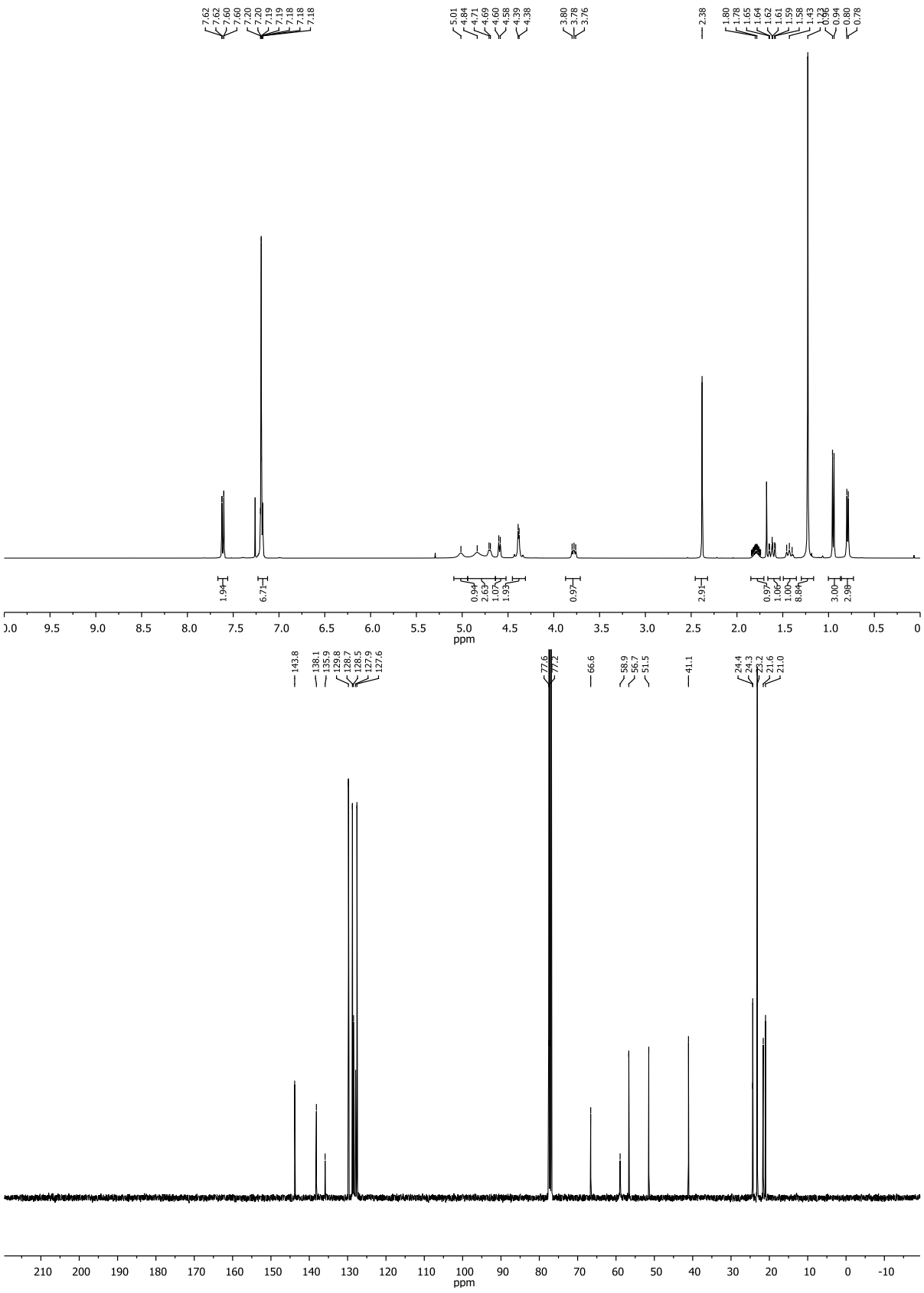


Figure 76 ^{1}H- and ^{13}C-NMR Spectra of 153.

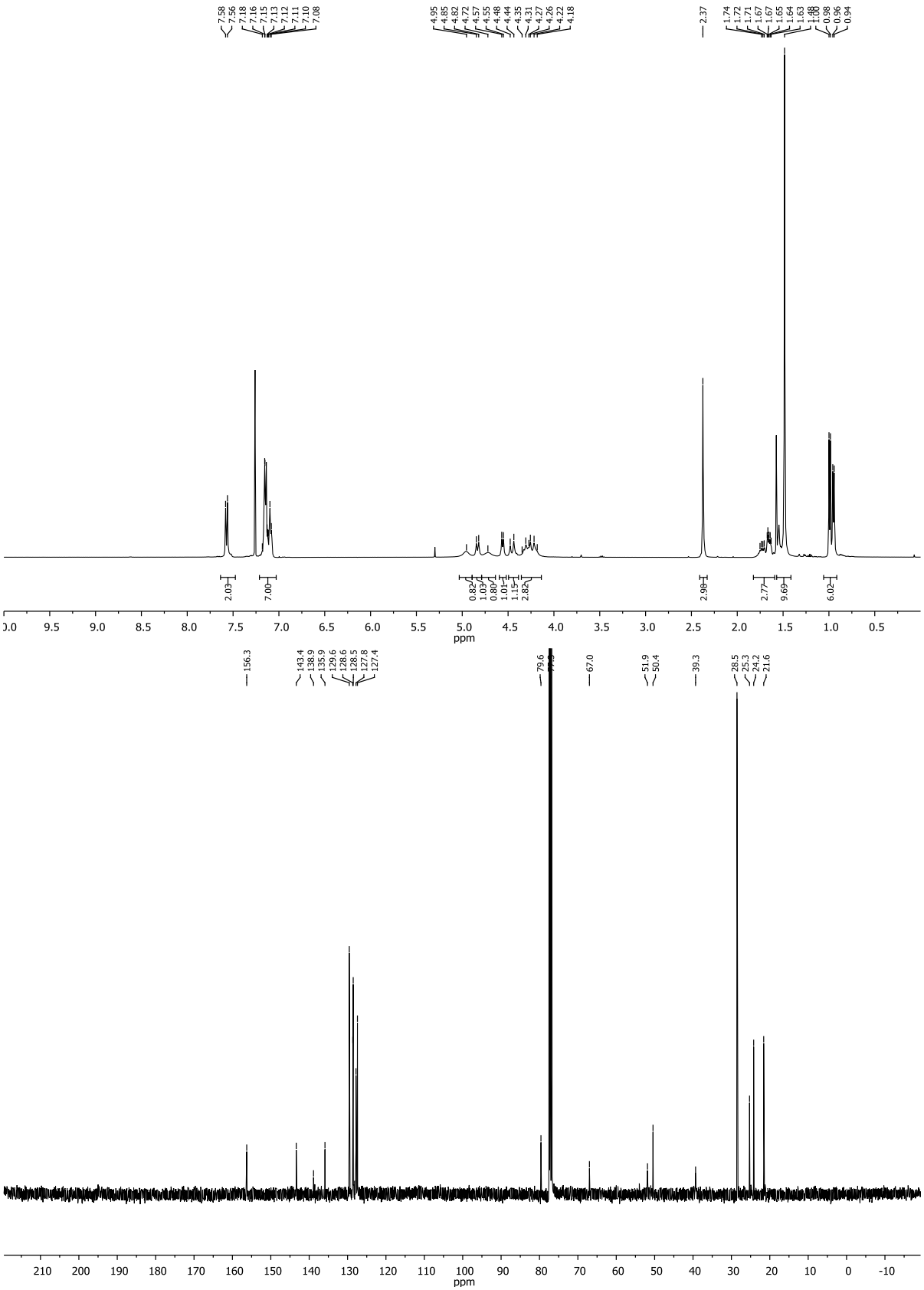


Figure 77 ^{1}H- and ^{13}C-NMR Spectra of 154.

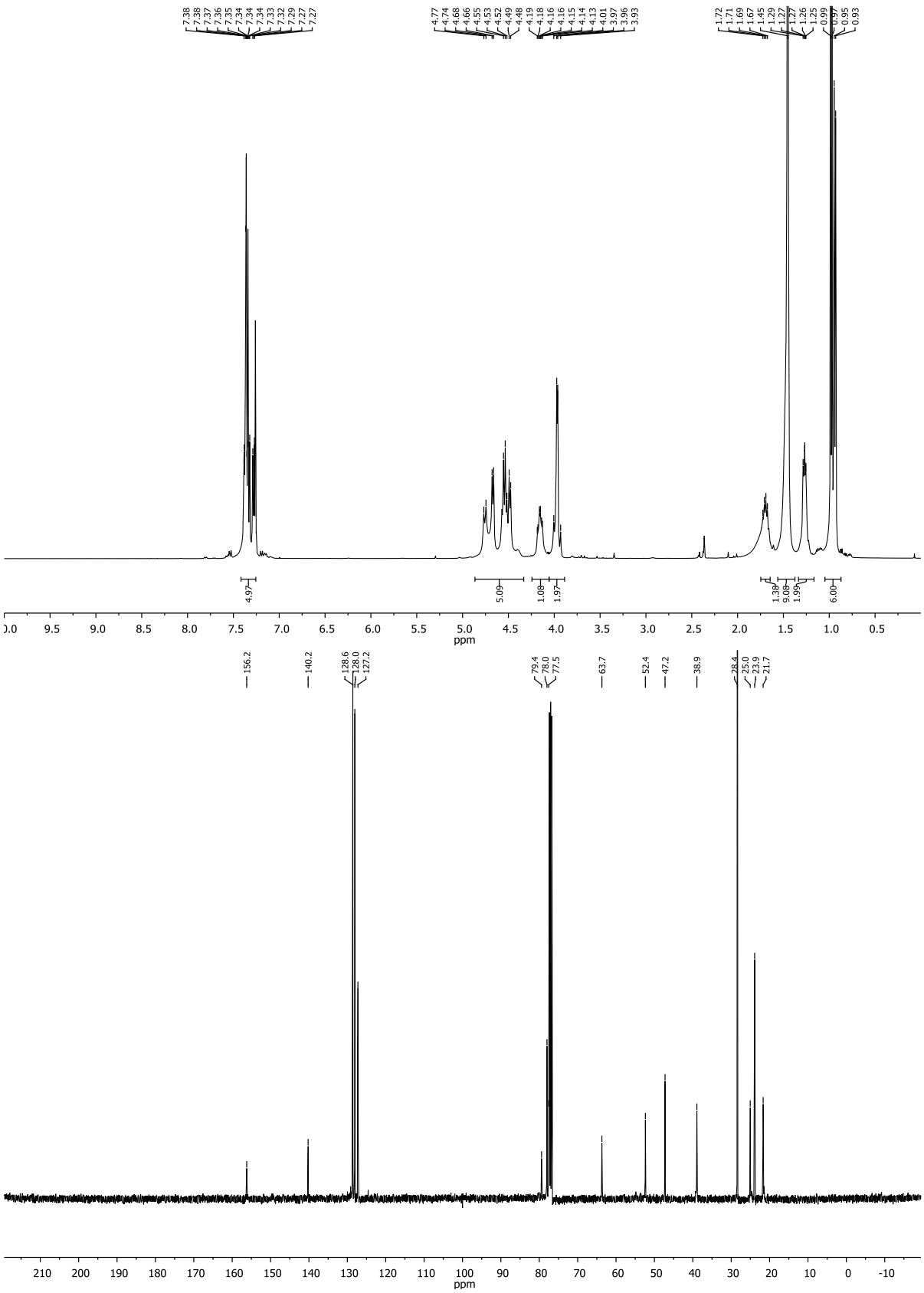


Figure 78 ^{1}H- and ^{13}C-NMR Spectra of 155.

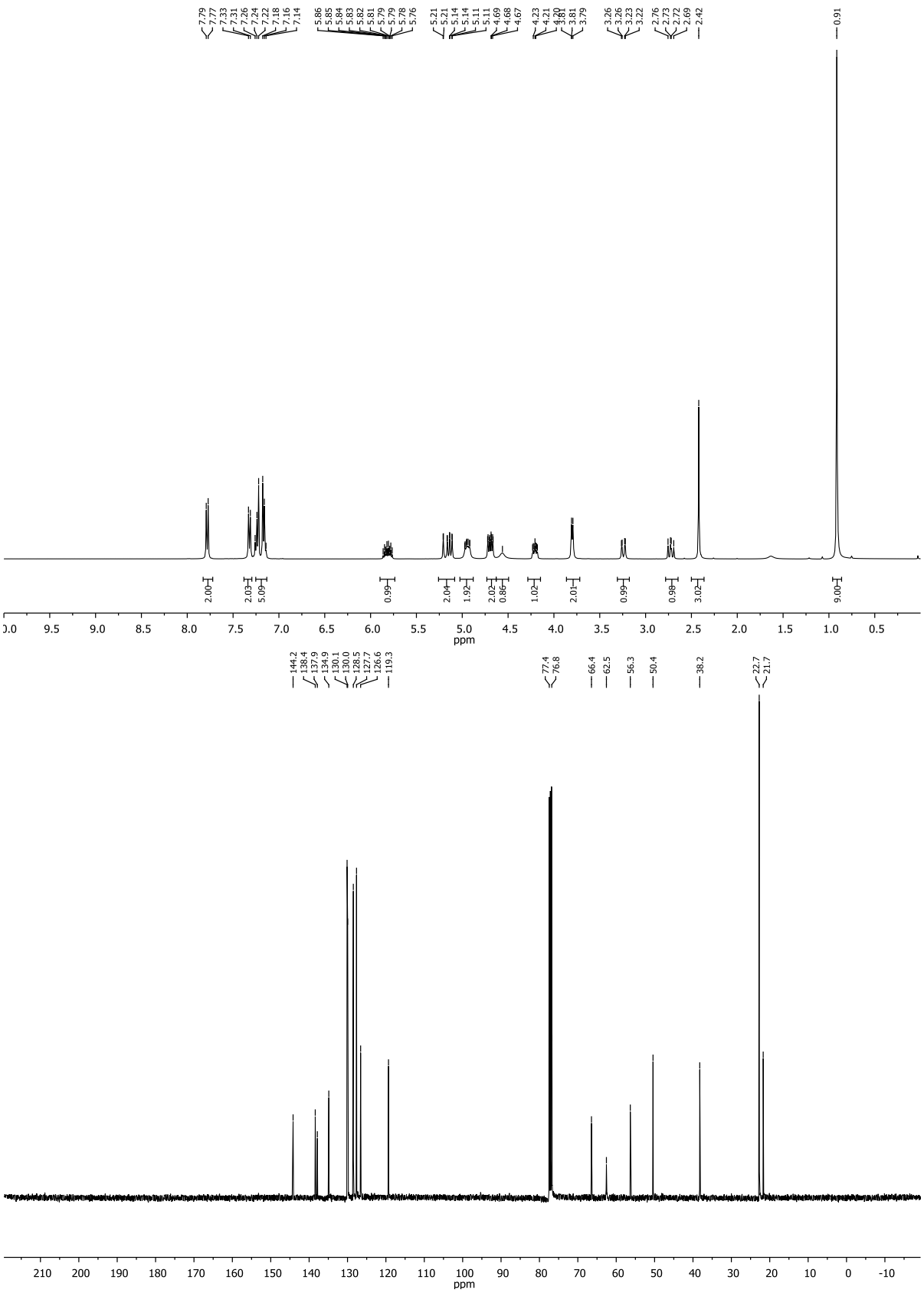


Figure 79 ^{1}H- and ^{13}C-NMR Spectra of 159.

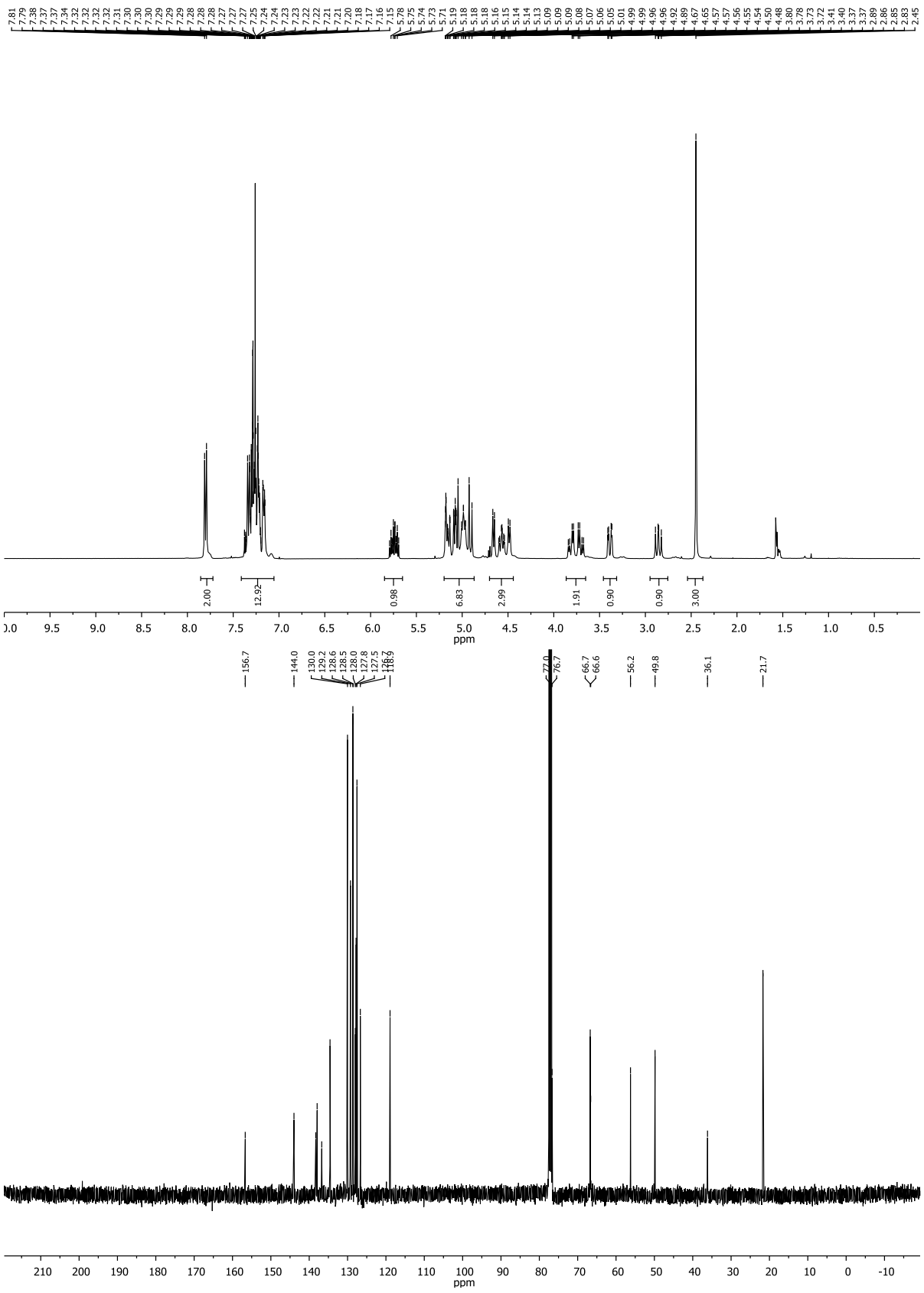


Figure 80 ^{1}H- and ^{13}C-NMR Spectra of 160.

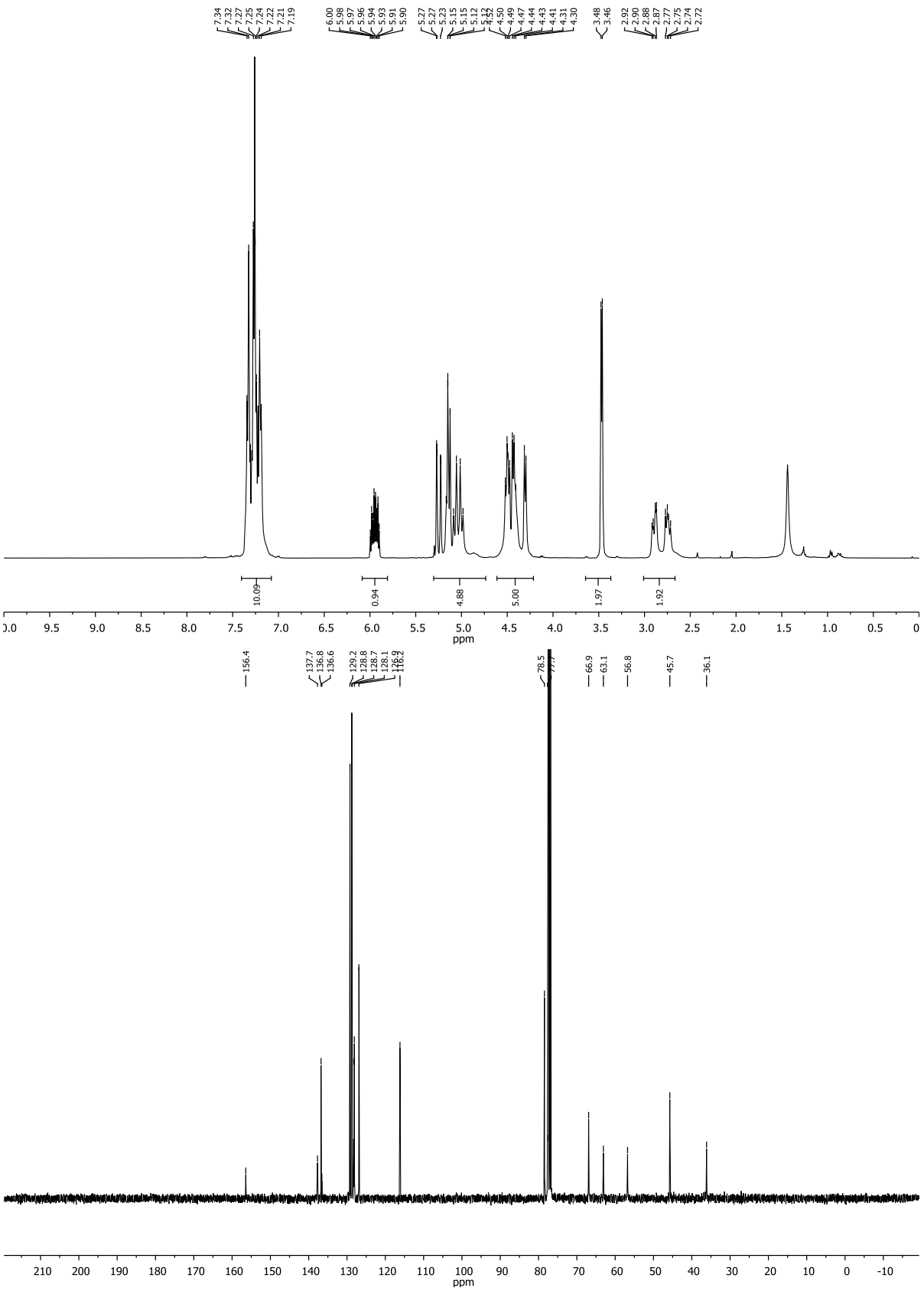


Figure 81 ^{1}H- and ^{13}C-NMR Spectra of 161.

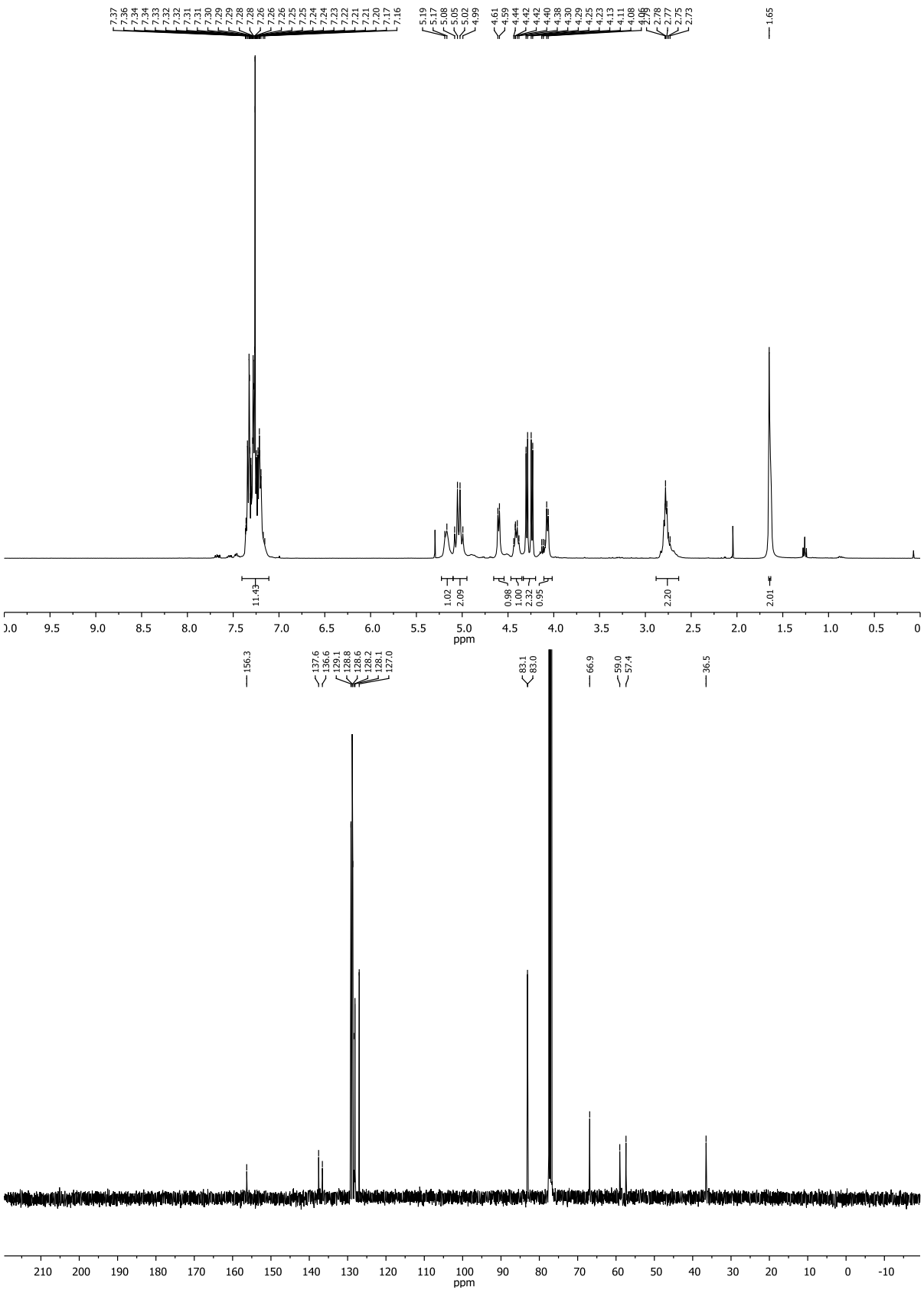


Figure 82 ^{1}H- and ^{13}C-NMR Spectra of 157.

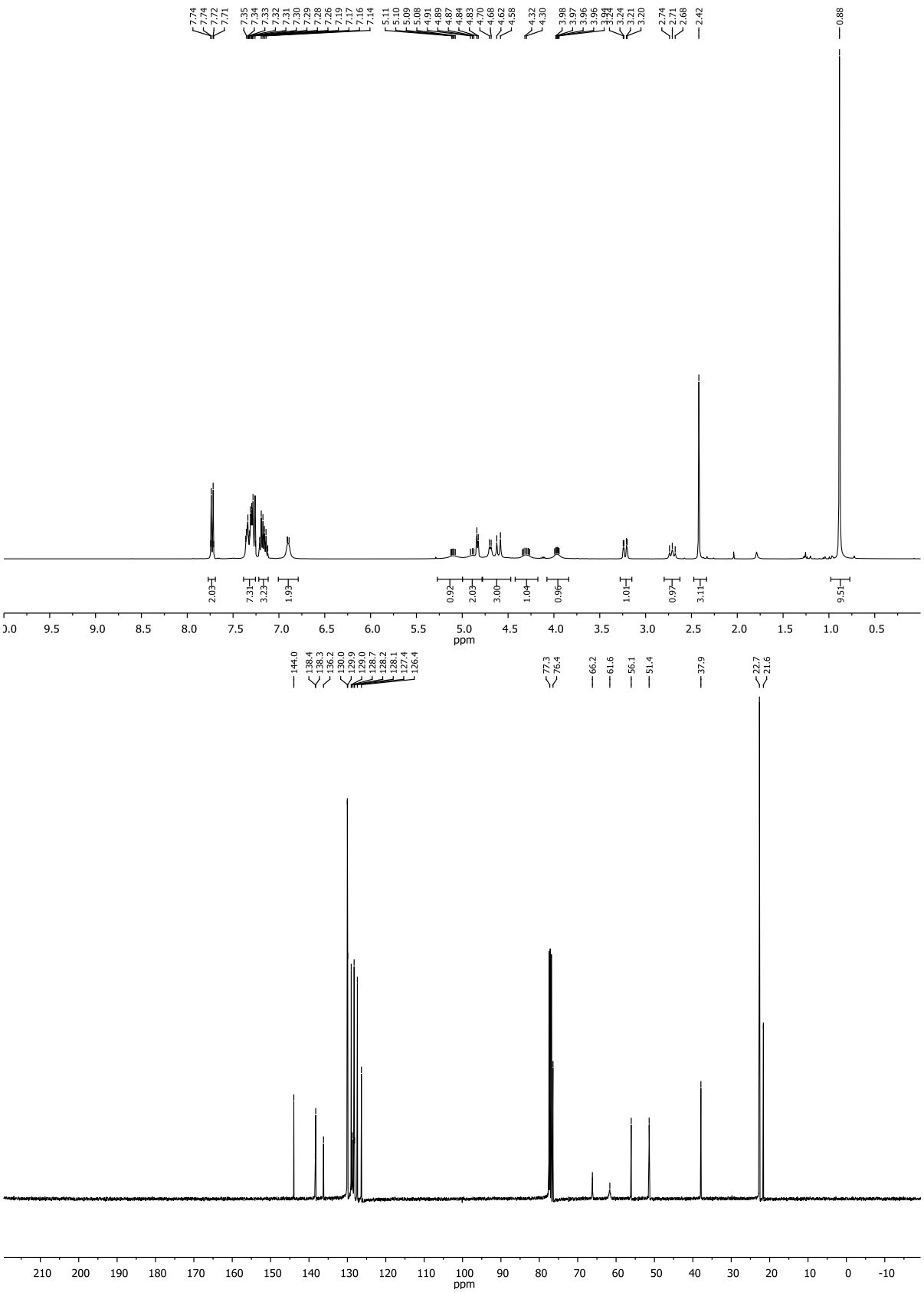


Figure 83 ^{1}H- and ^{13}C-NMR Spectra of 162.

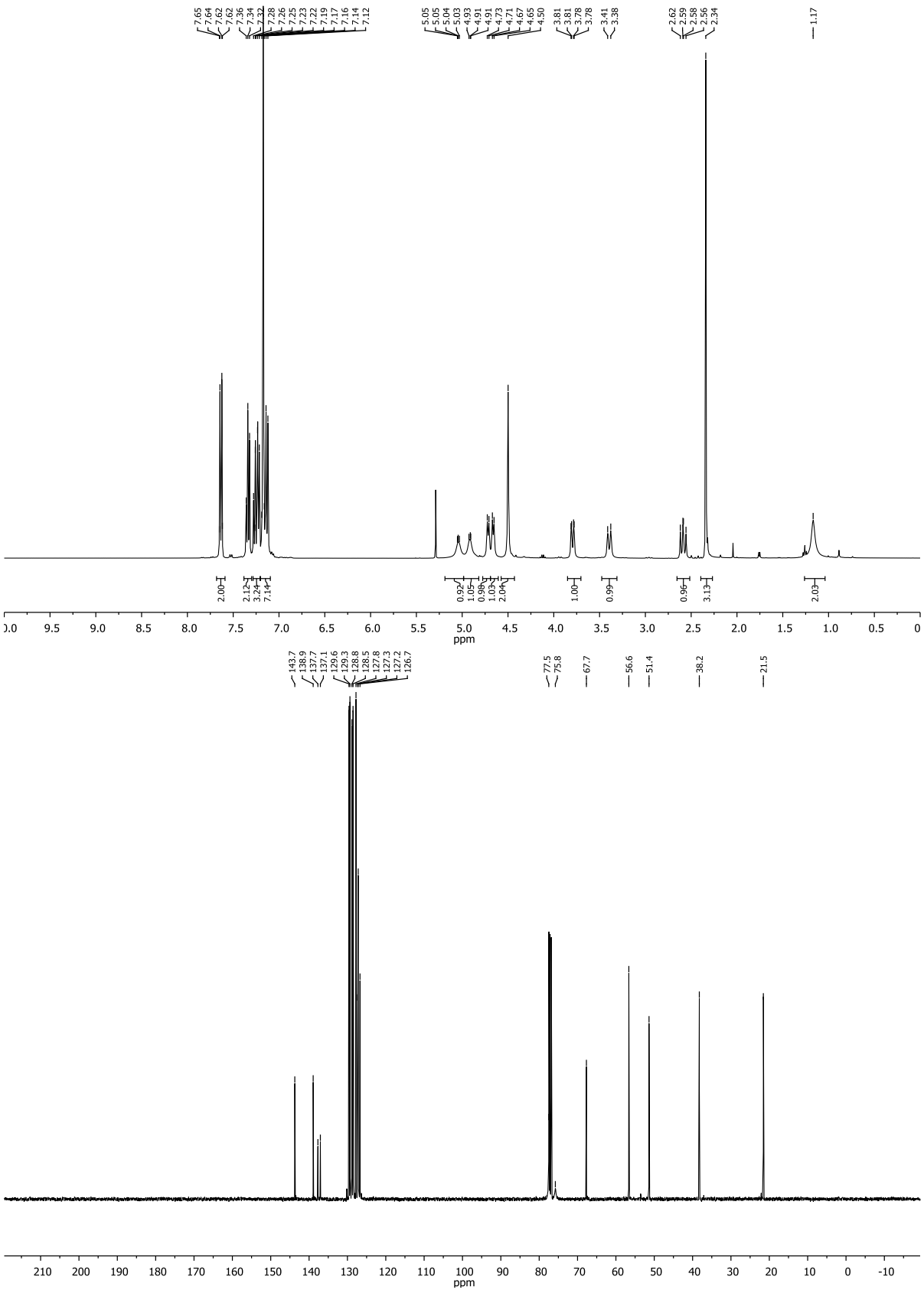


Figure 84 ^{1}H- and ^{13}C-NMR Spectra of 163.

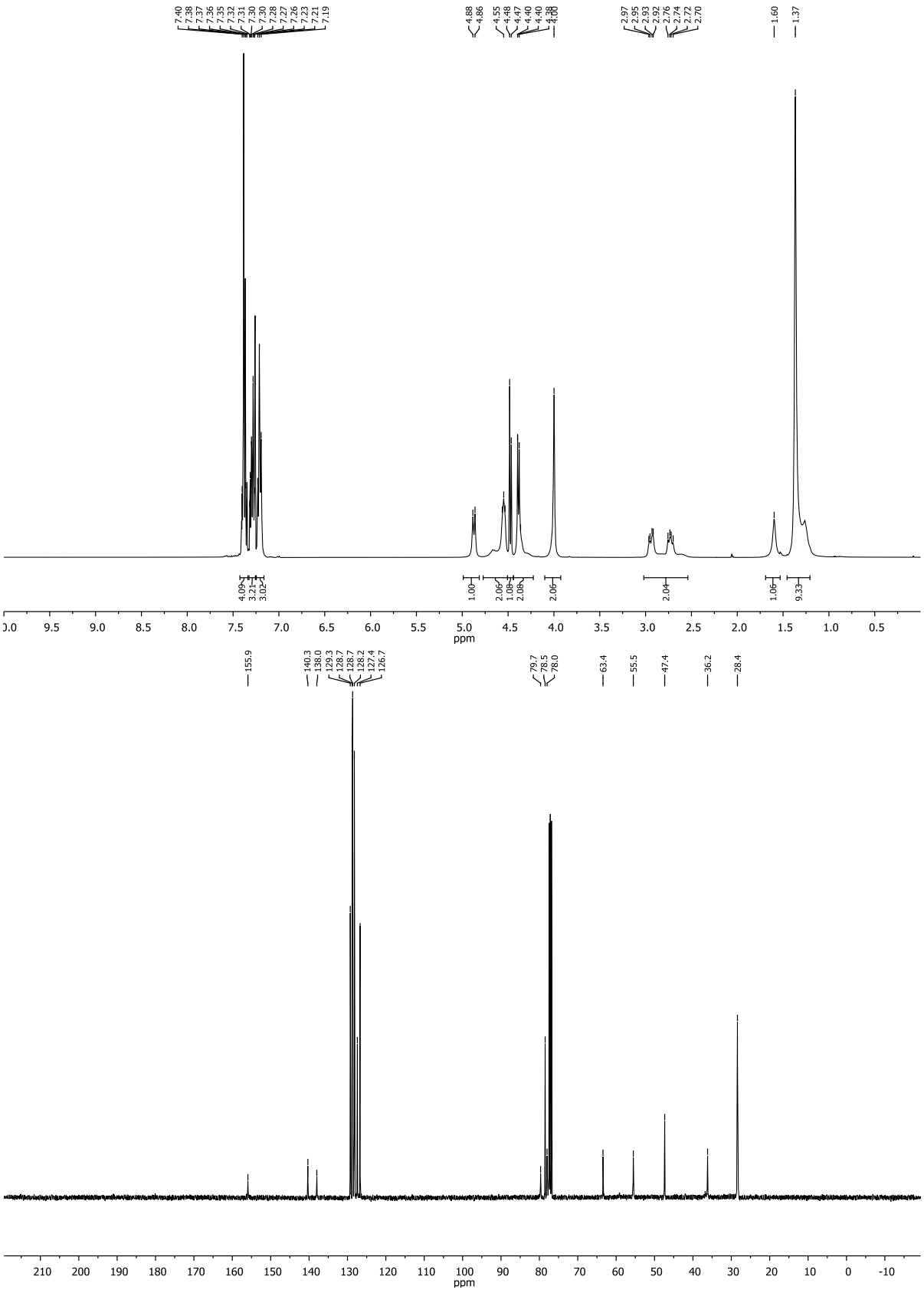


Figure 85 ^{1}H- and ^{13}C-NMR Spectra of 164.

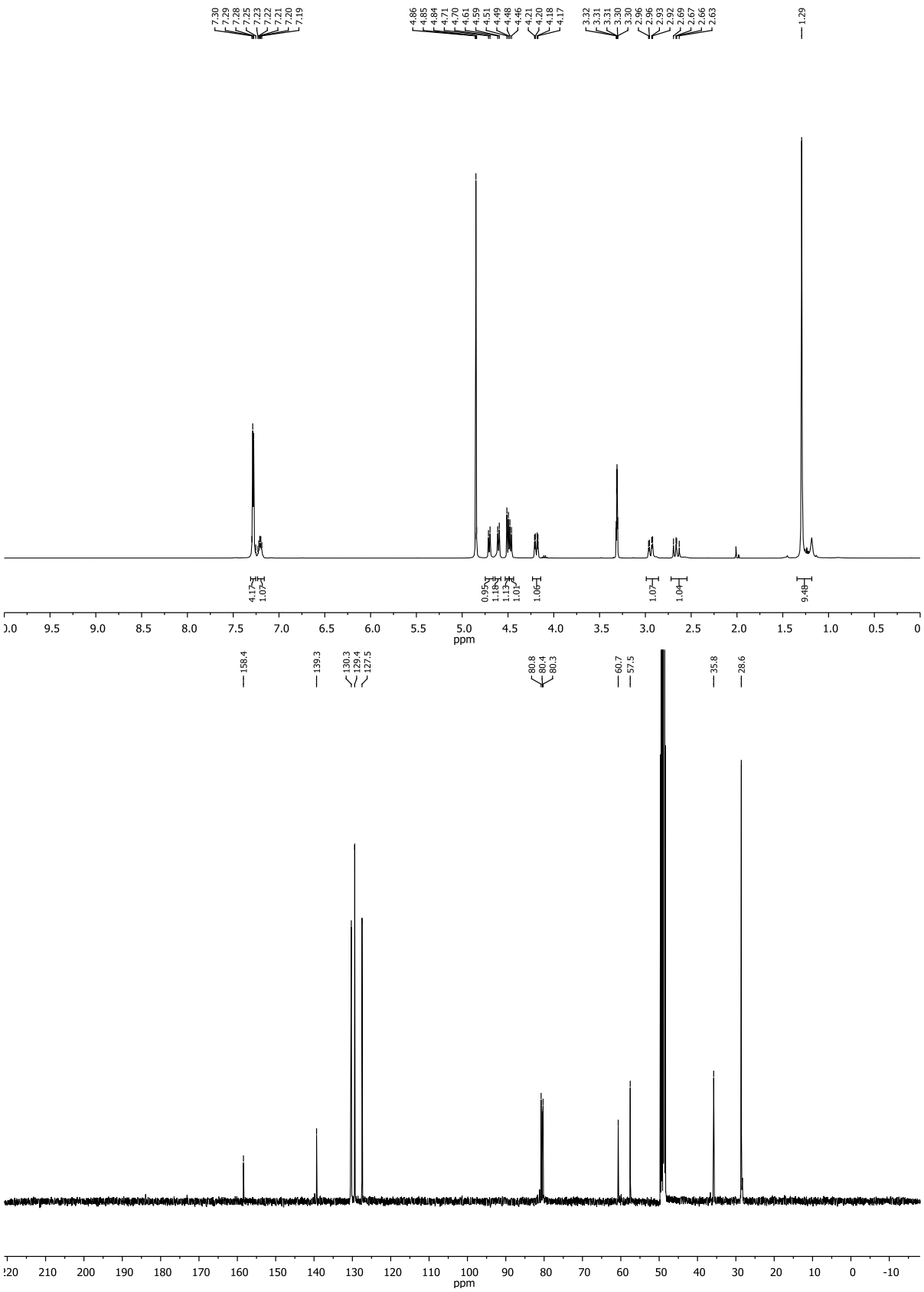


Figure 86 ^{1}H- and ^{13}C-NMR Spectra of 158.

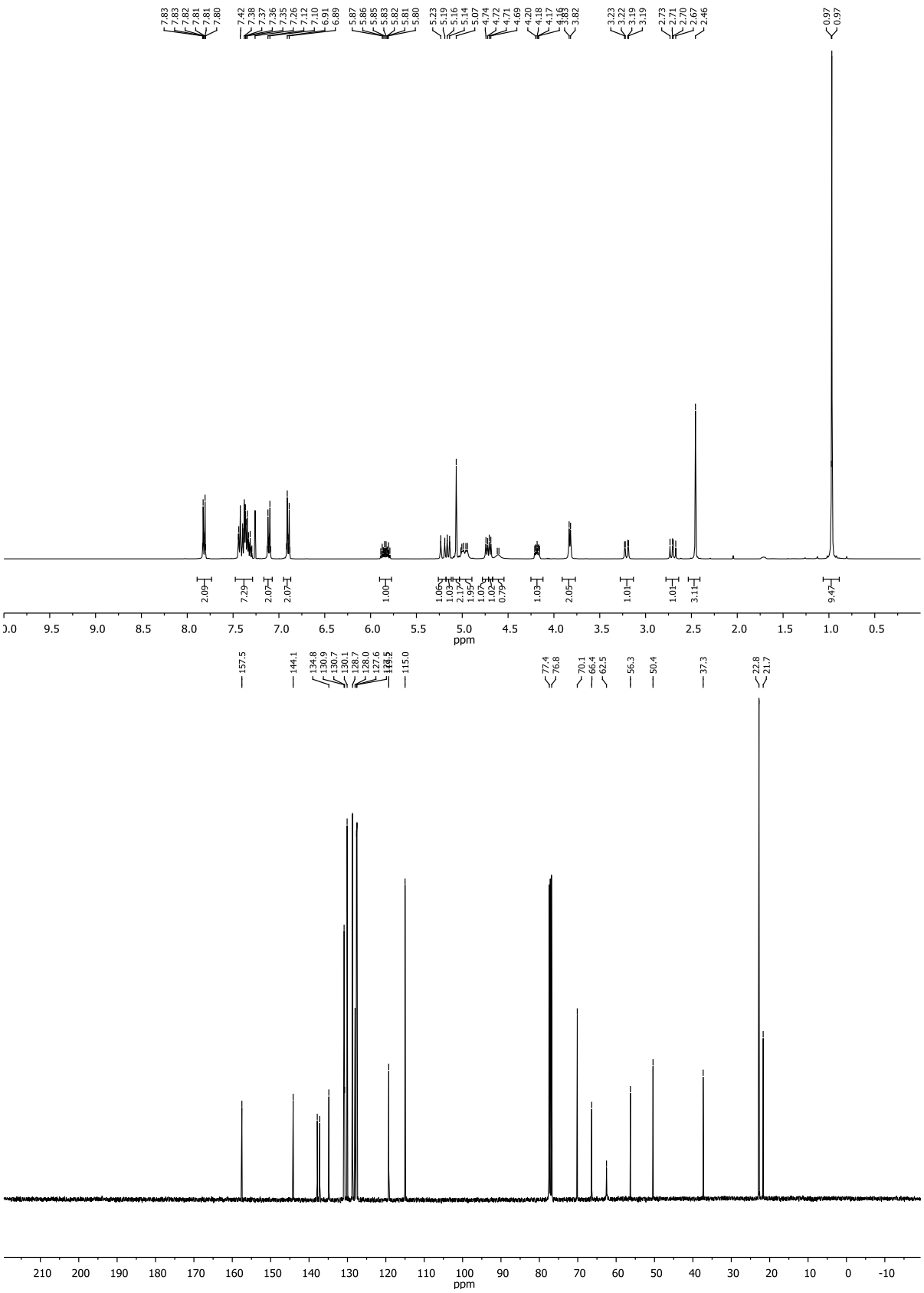


Figure 87 ^{1}H- and ^{13}C-NMR Spectra of 169.

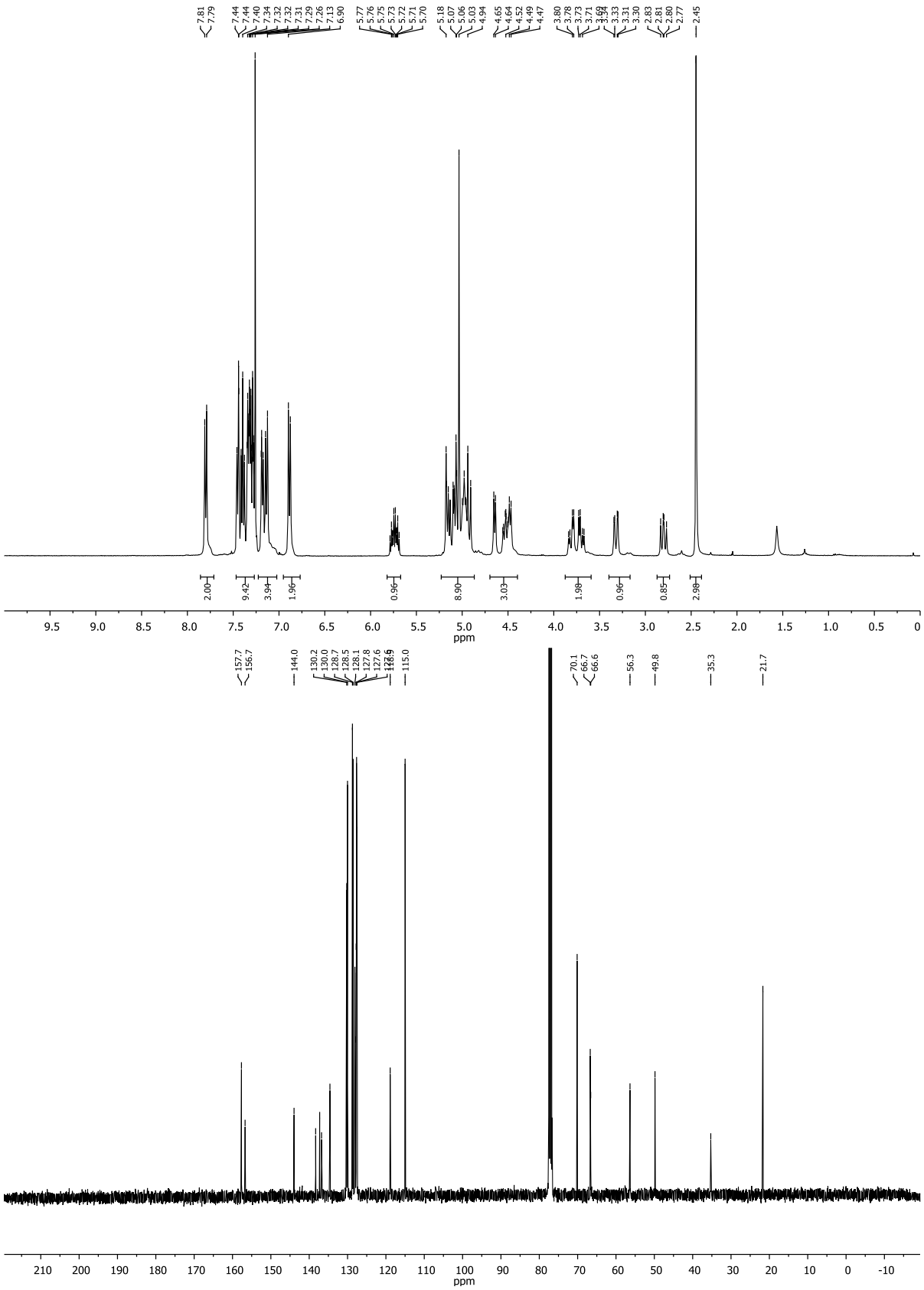


Figure 88 ^{1}H- and ^{13}C-NMR Spectra of 170.

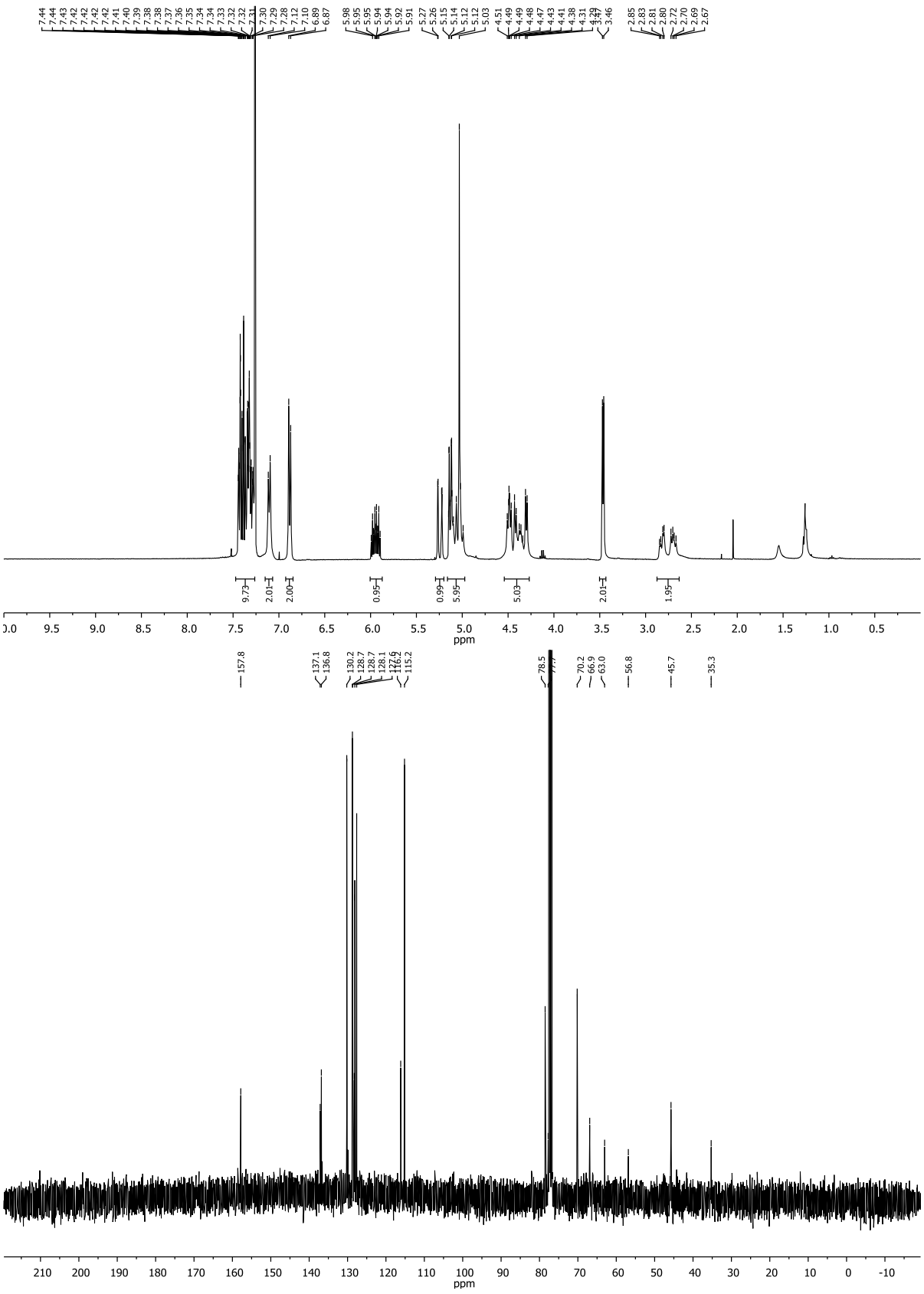


Figure 89 ^{1}H- and ^{13}C-NMR Spectra of 171.

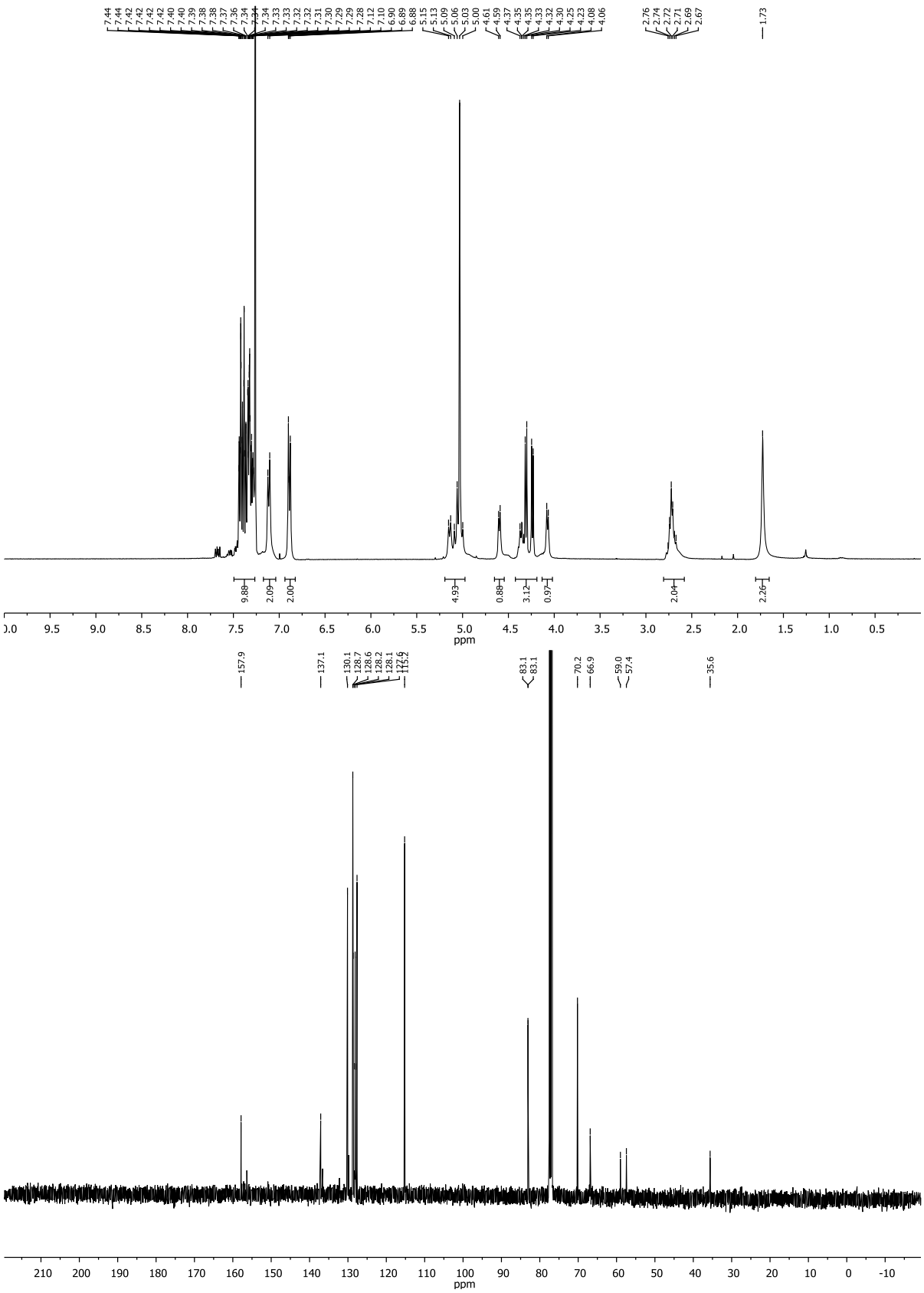


Figure 90 ^{1}H- and ^{13}C-NMR Spectra of 165.

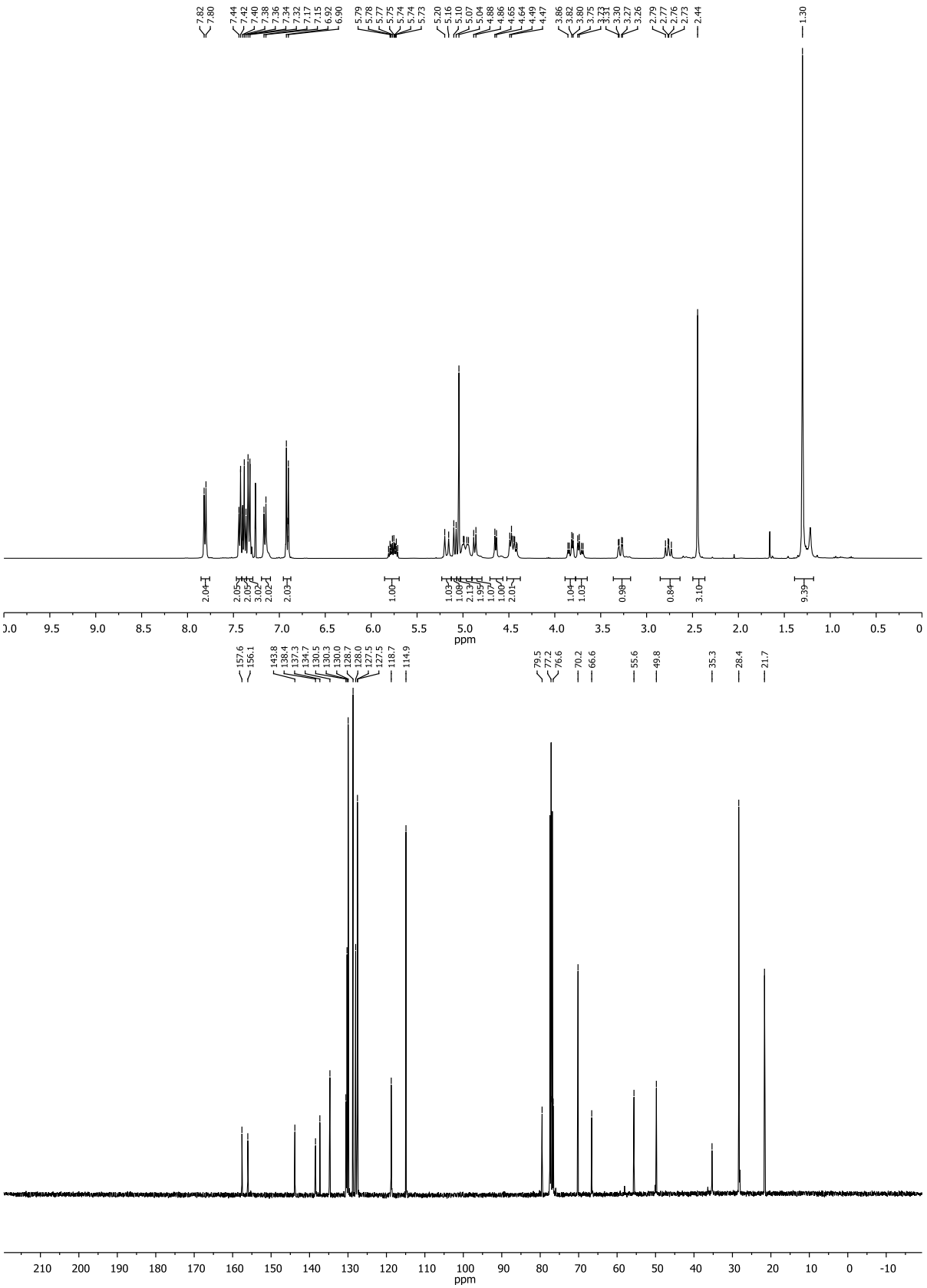


Figure 91 ^{1}H- and ^{13}C-NMR Spectra of 172.

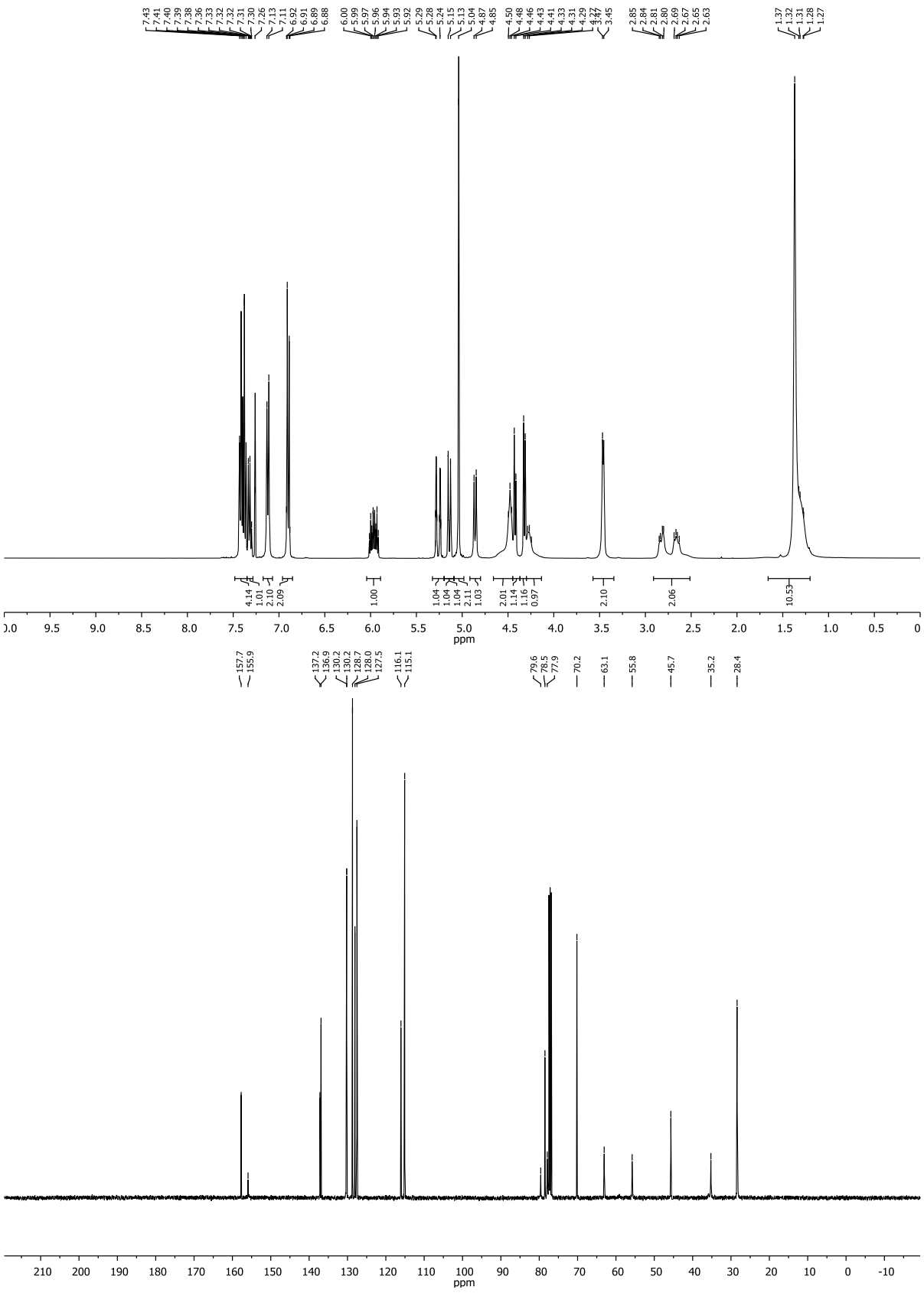


Figure 92 ^{1}H- and ^{13}C-NMR Spectra of 173.

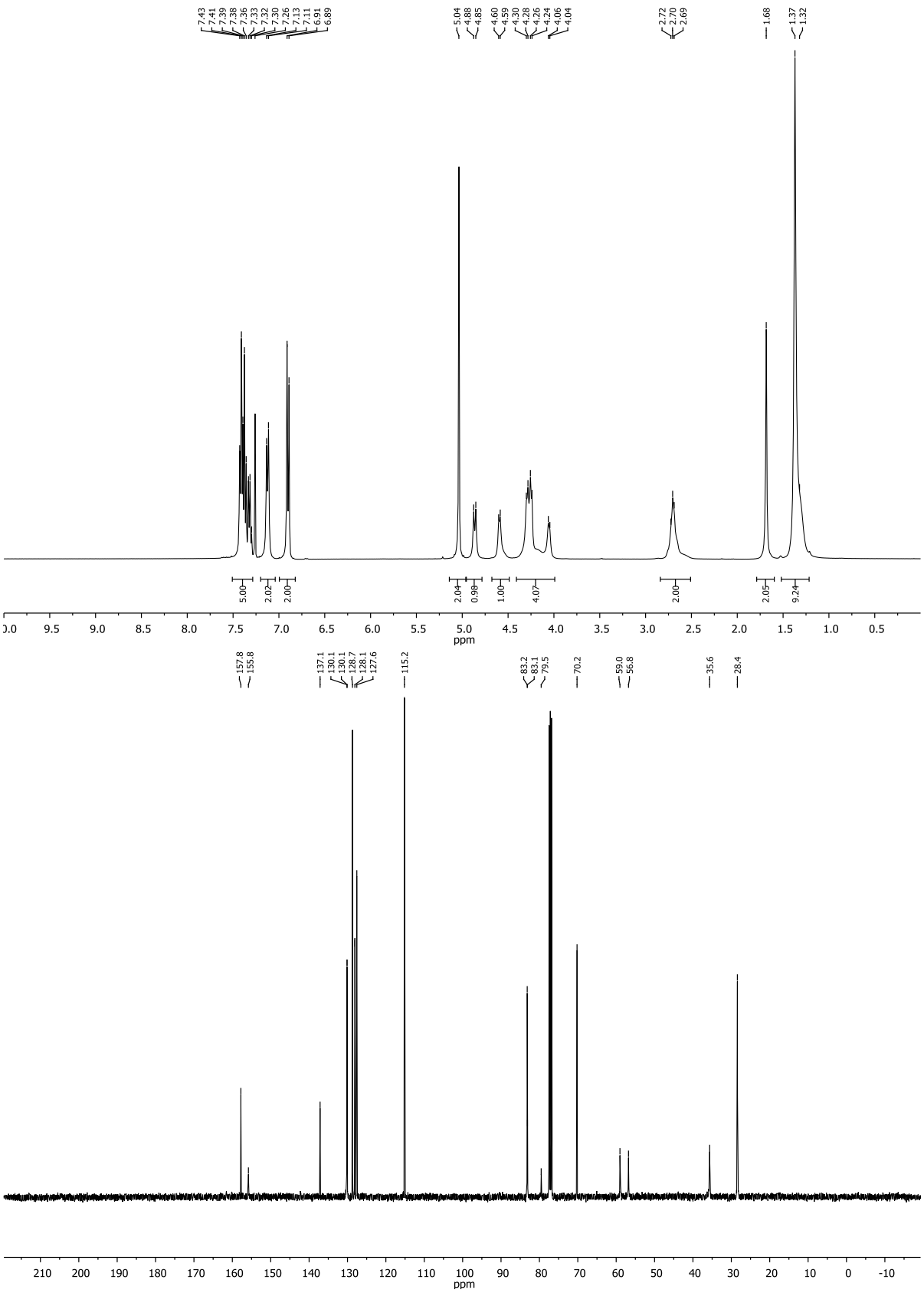


Figure 93 ^{1}H- and ^{13}C-NMR Spectra of 166.

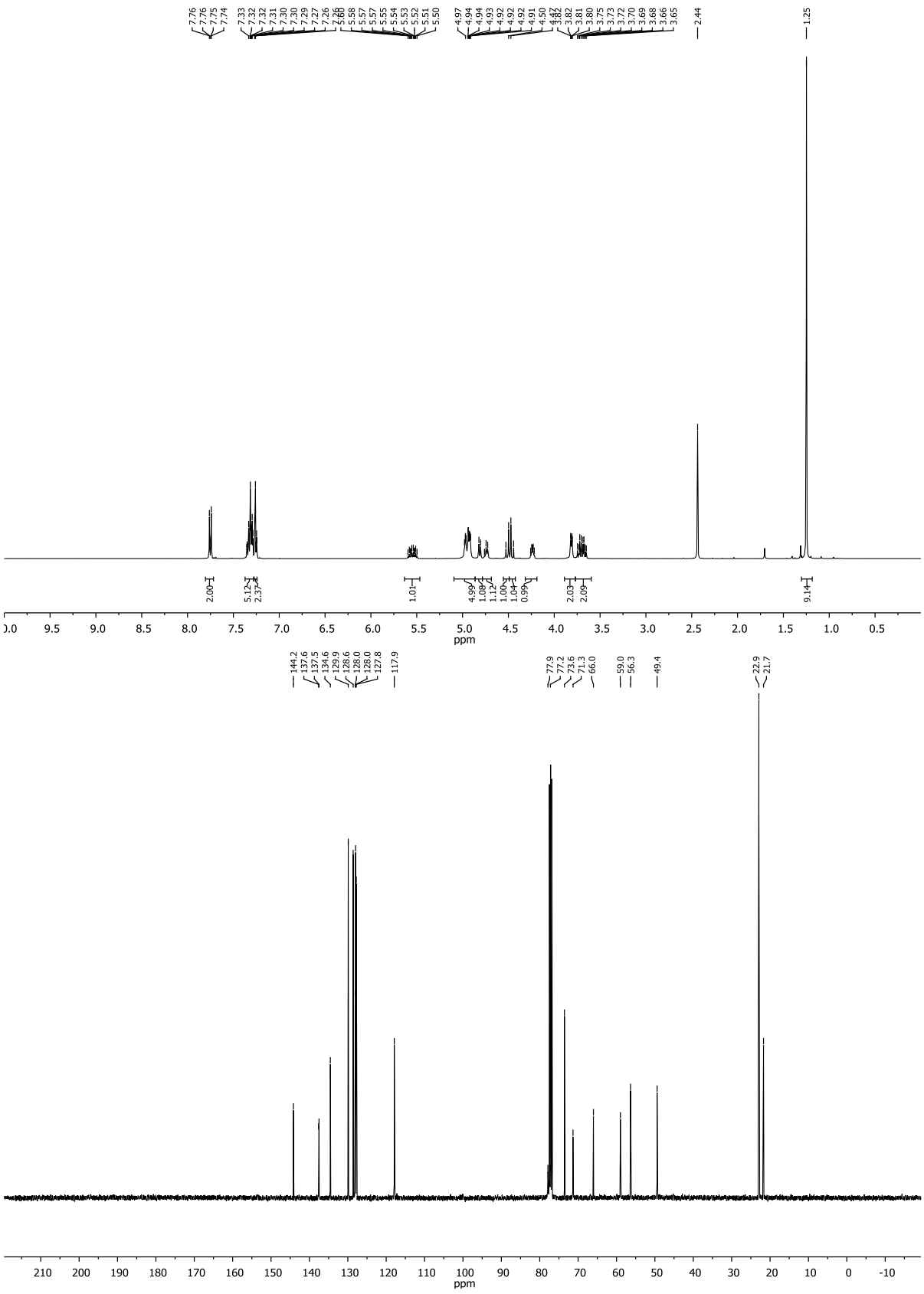


Figure 94 ^{1}H- and ^{13}C-NMR Spectra of 175.

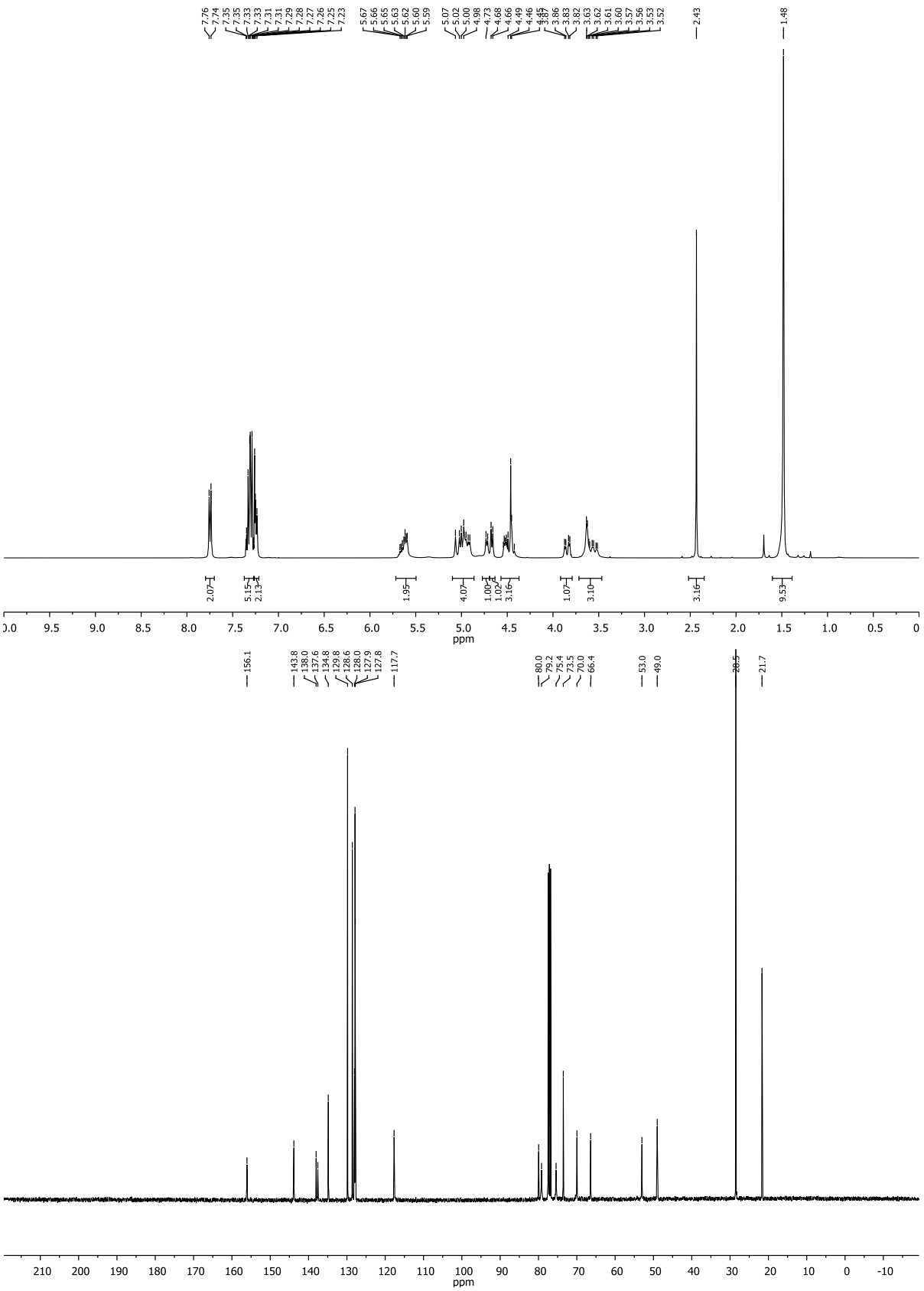


Figure 95 ^{1}H- and ^{13}C-NMR Spectra of 176.

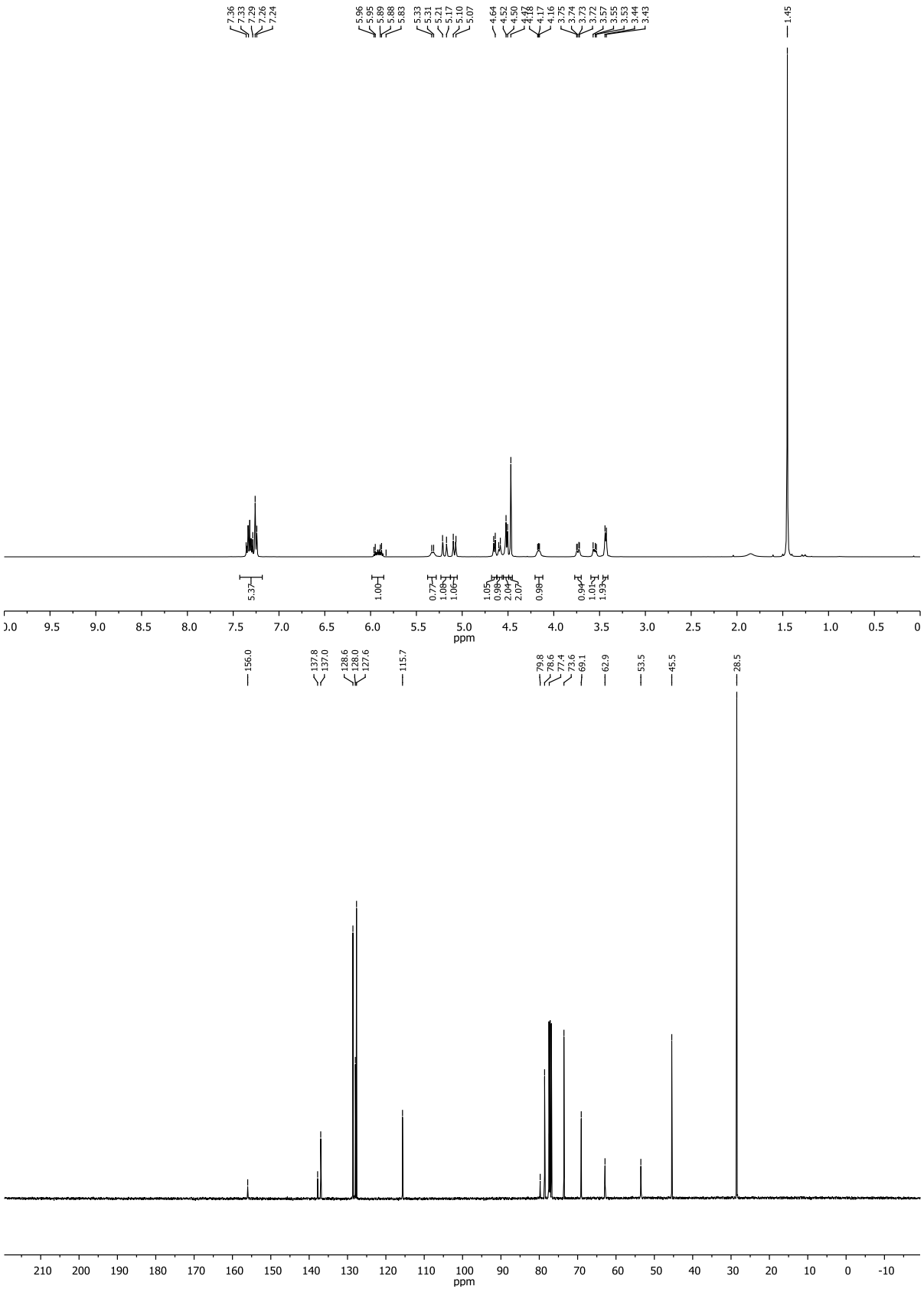


Figure 96 ^{1}H- and ^{13}C-NMR Spectra of 177.

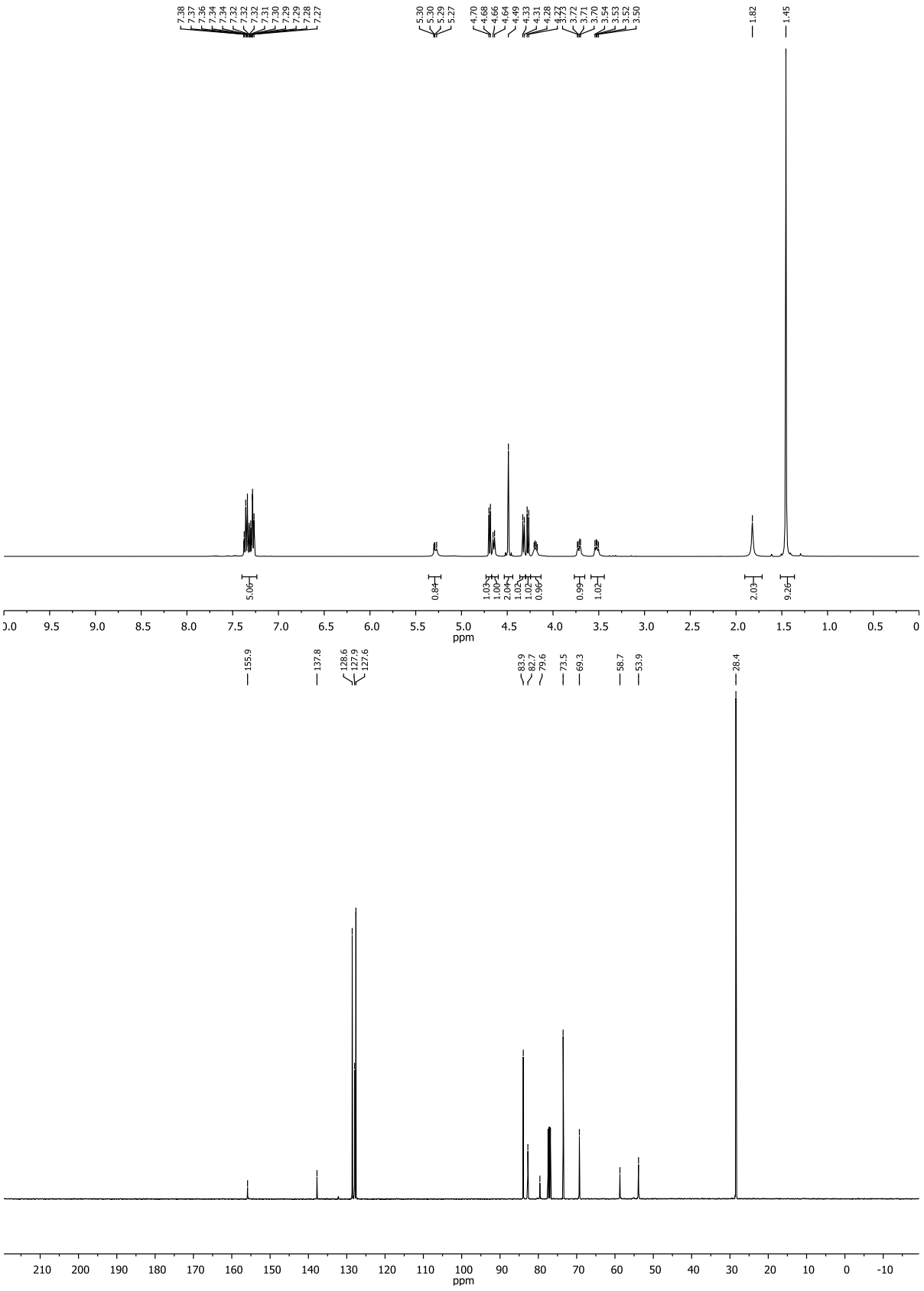


Figure 97 ^{1}H- and ^{13}C-NMR Spectra of 174.

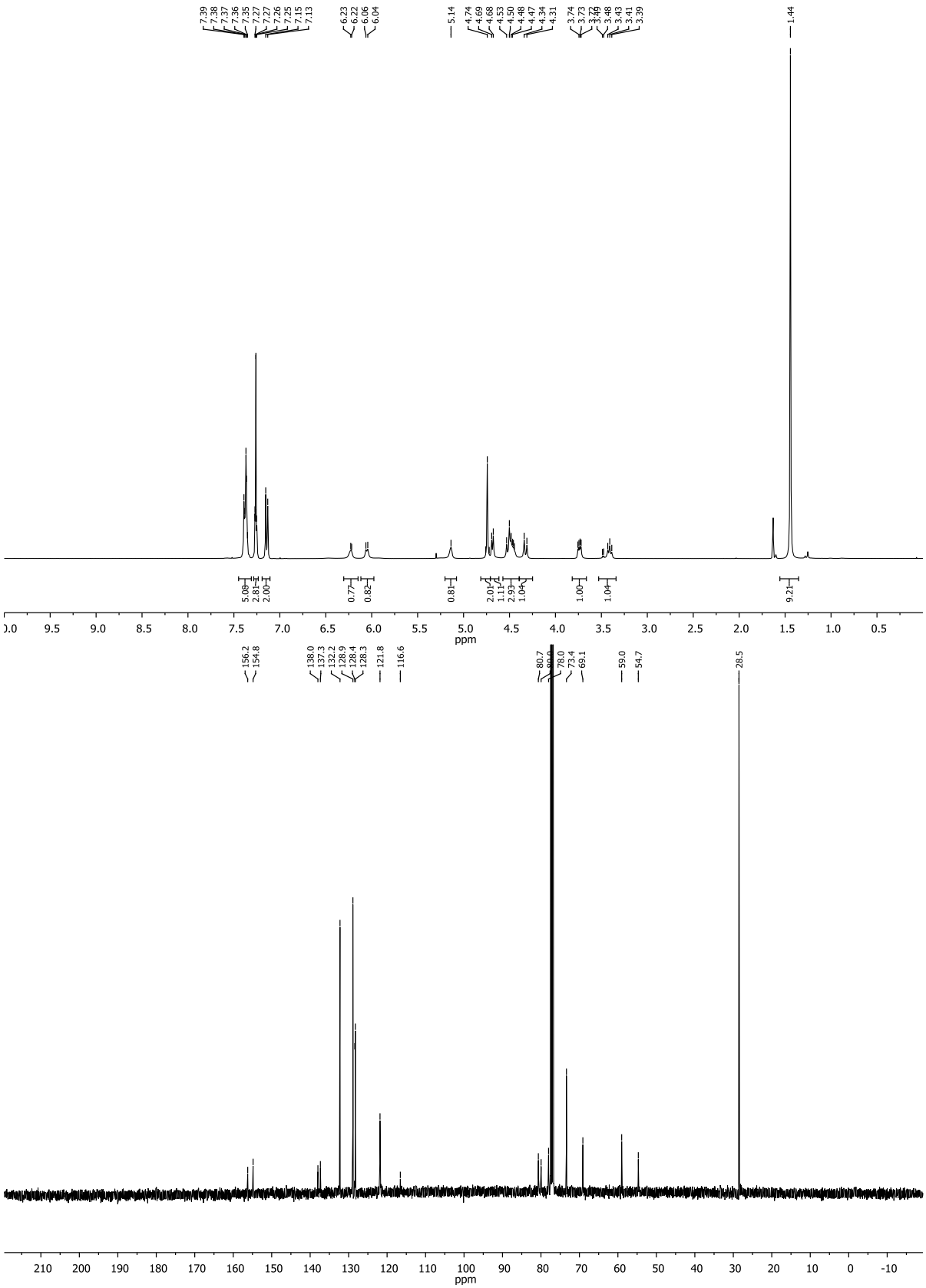


Figure 98 ^{1}H- and ^{13}C-NMR Spectra of 178.

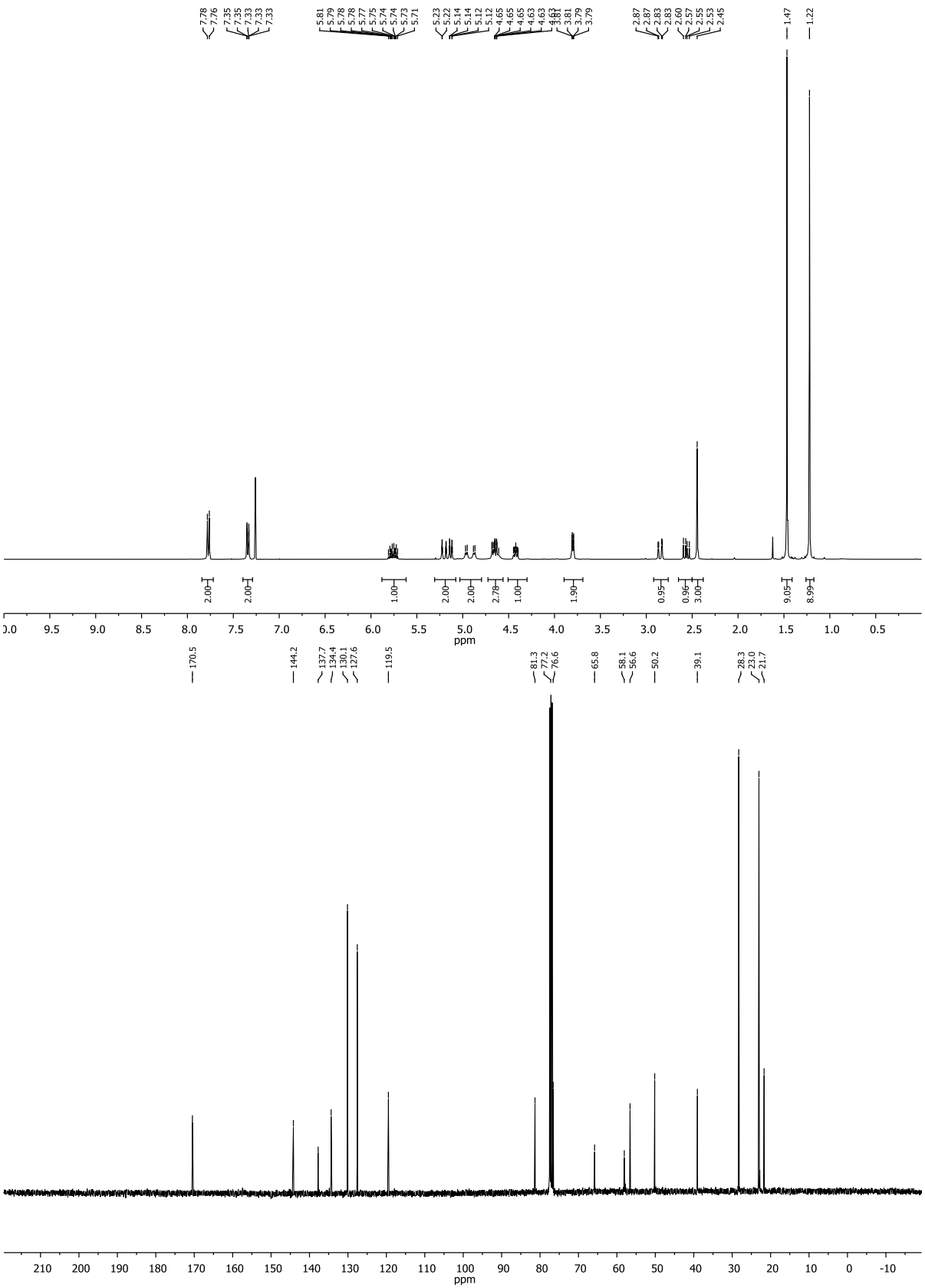


Figure 99 ^{1}H- and ^{13}C-NMR Spectra of 180.

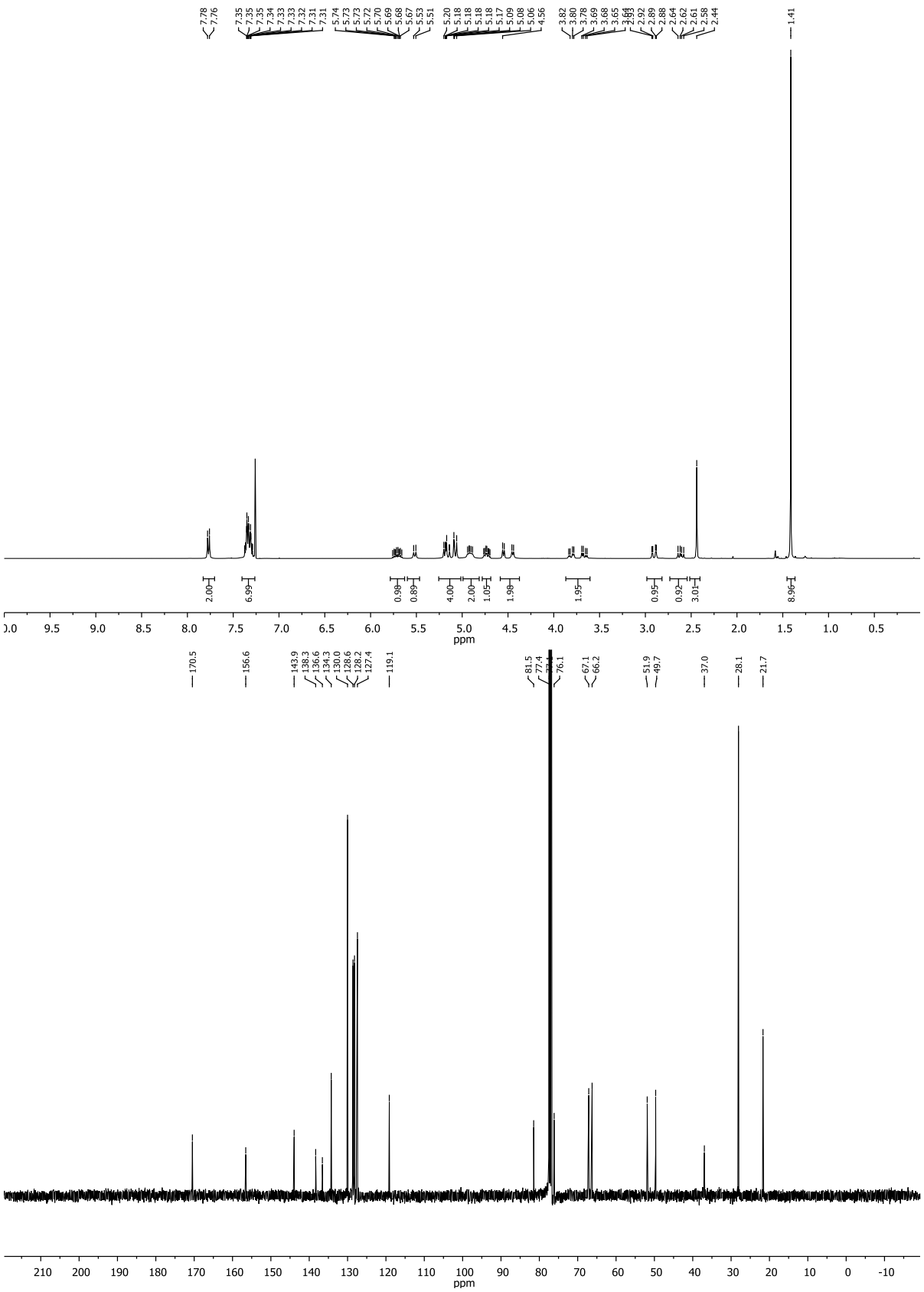


Figure 100 ^{1}H- and ^{13}C-NMR Spectra of 181.

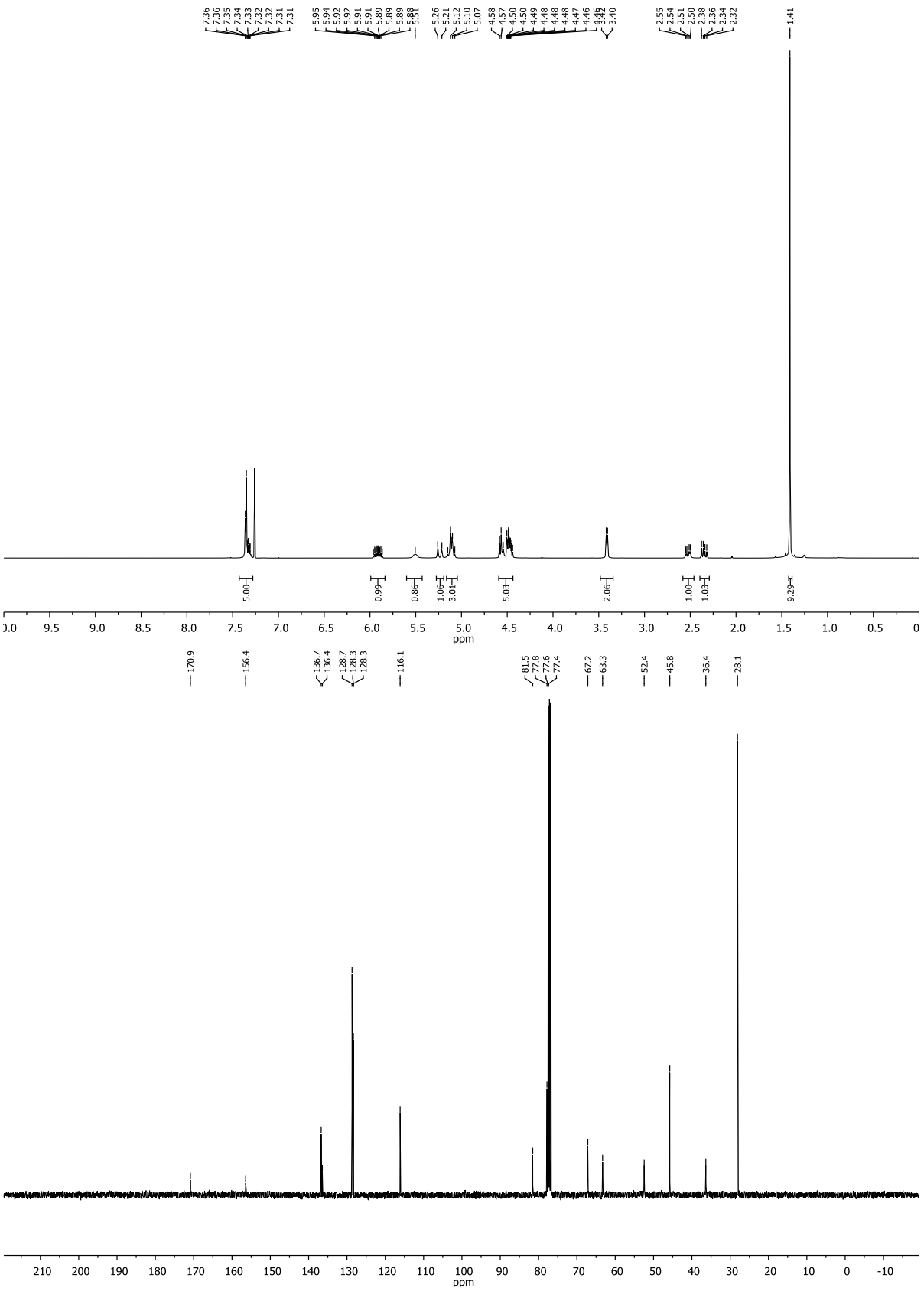


Figure 101 ^{1}H- and ^{13}C-NMR Spectra of 182.

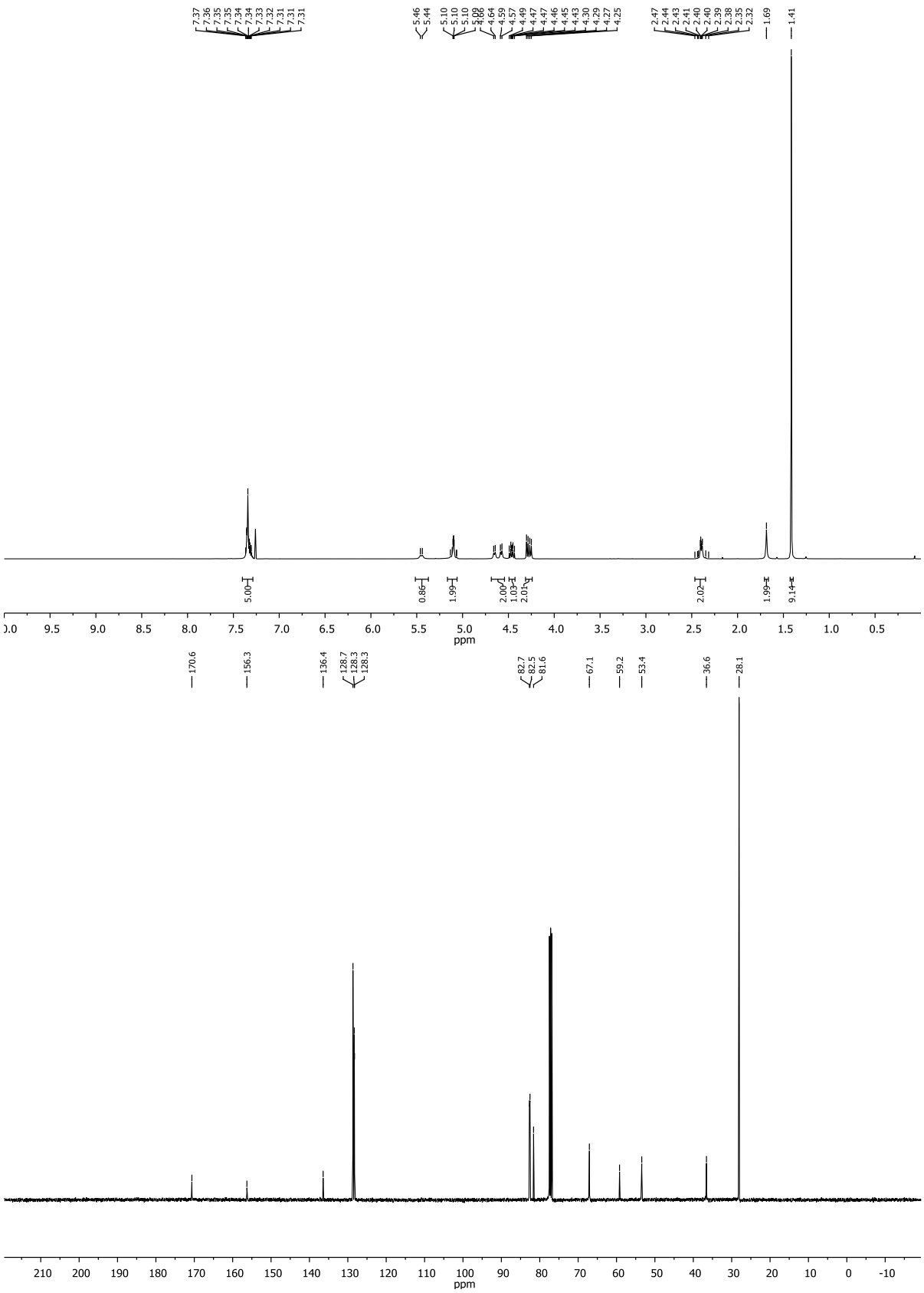


Figure 102 ^{1}H- and ^{13}C-NMR Spectra of 179.

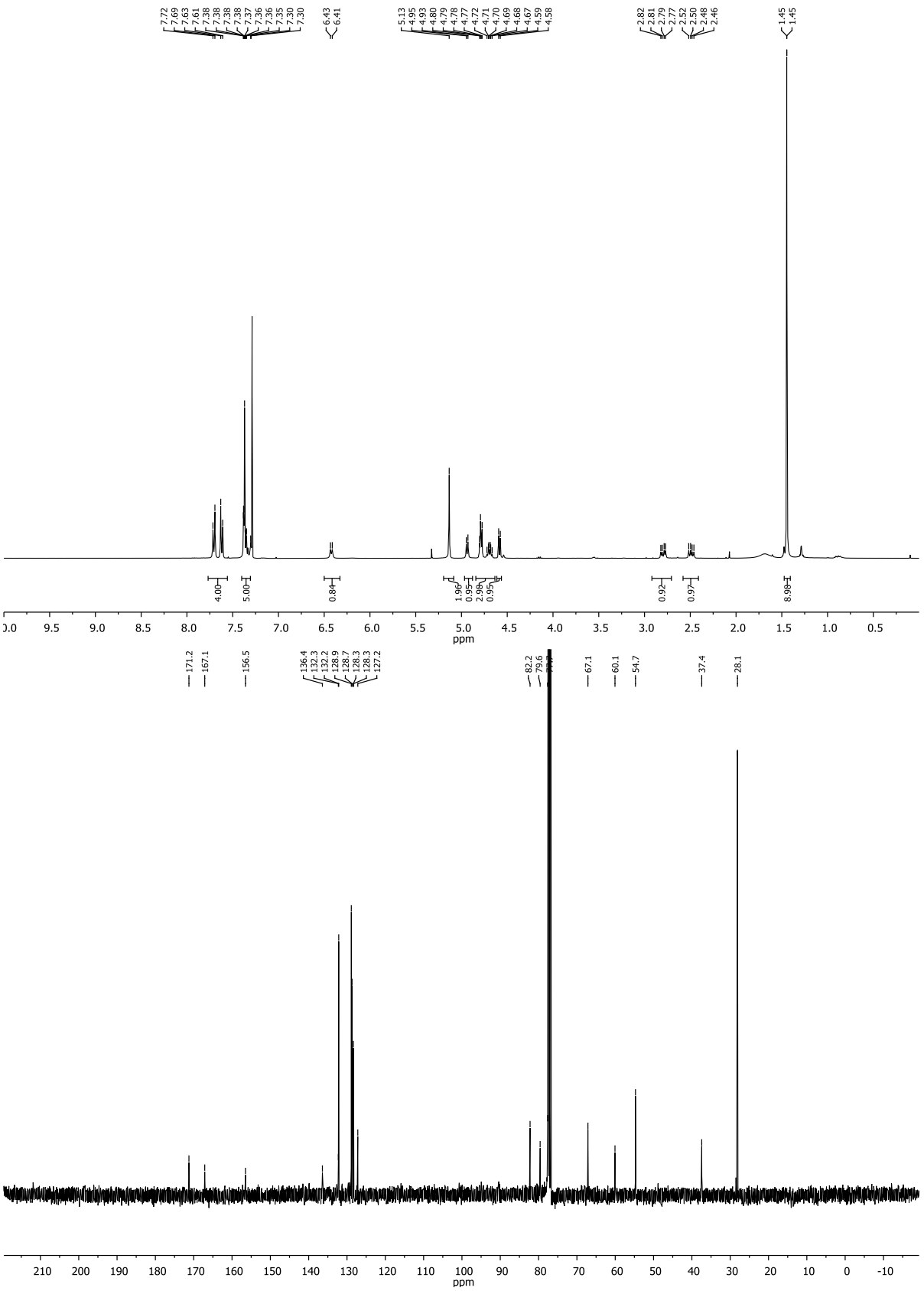


Figure 103 ^{1}H- and ^{13}C-NMR Spectra of 183.

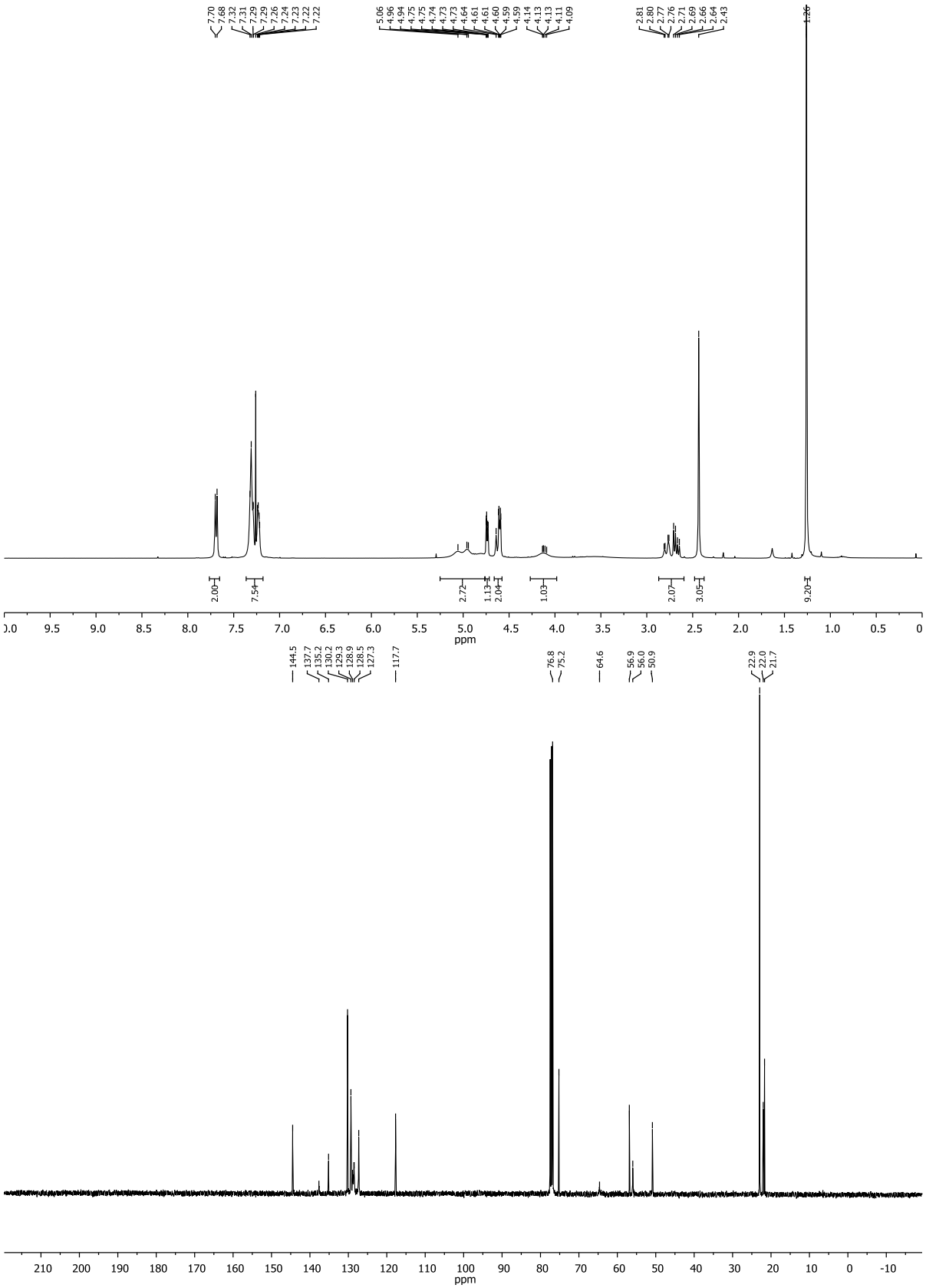


Figure 104 ^{1}H- and ^{13}C-NMR Spectra of 185.

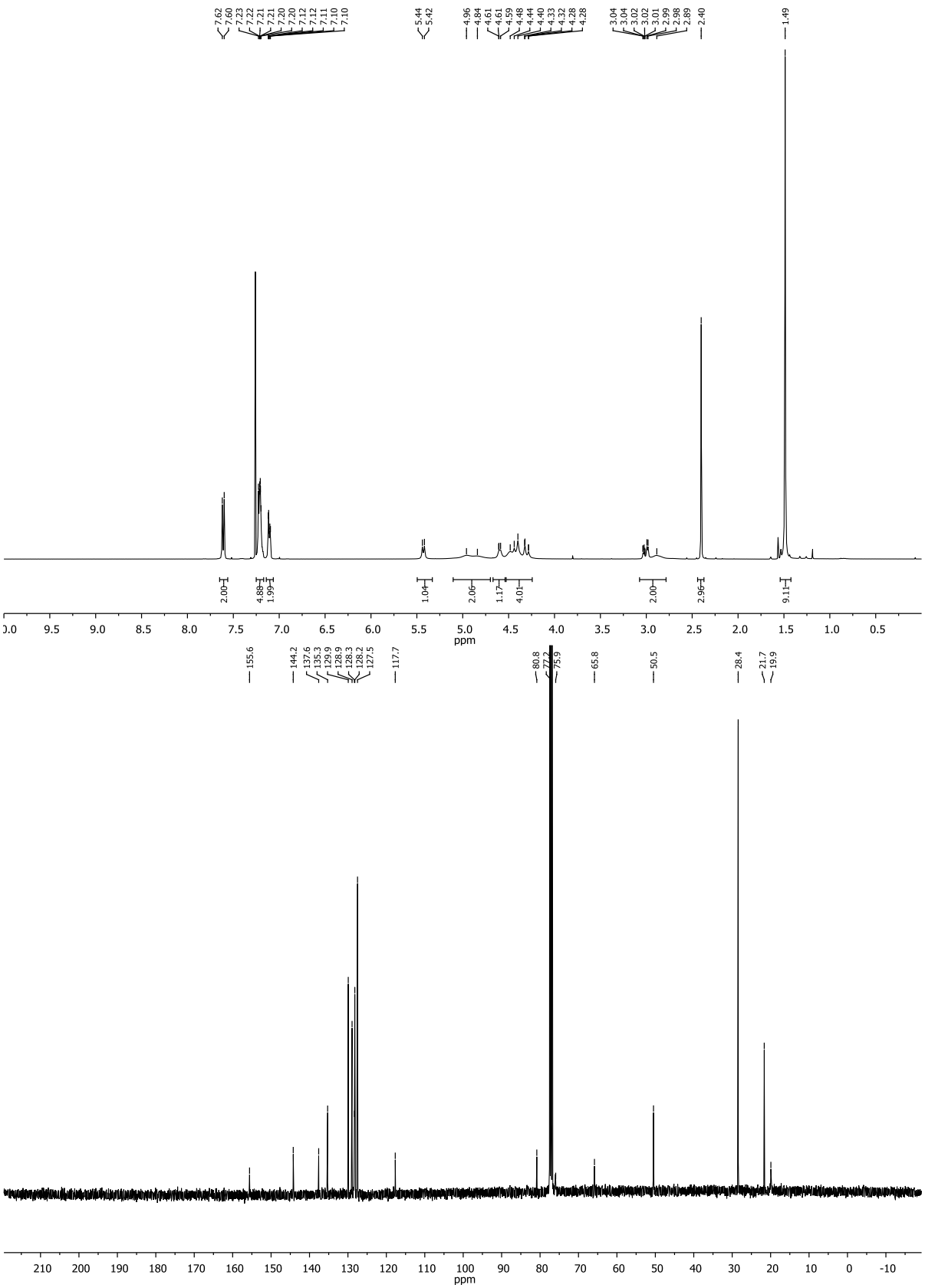


Figure 105 ^{1}H- and ^{13}C-NMR Spectra of 186.

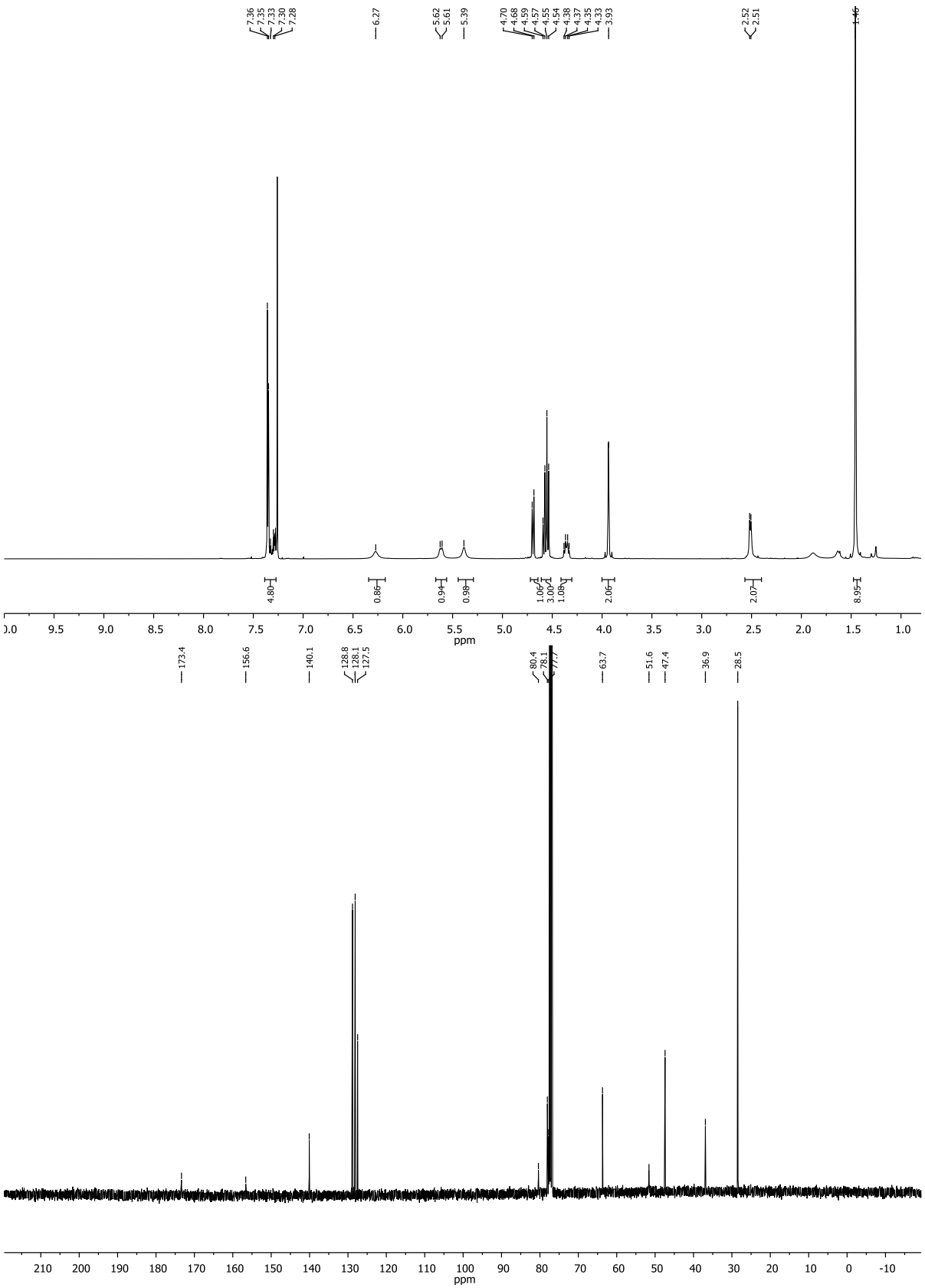


Figure 106 ^{1}H- and ^{13}C-NMR Spectra of 188.

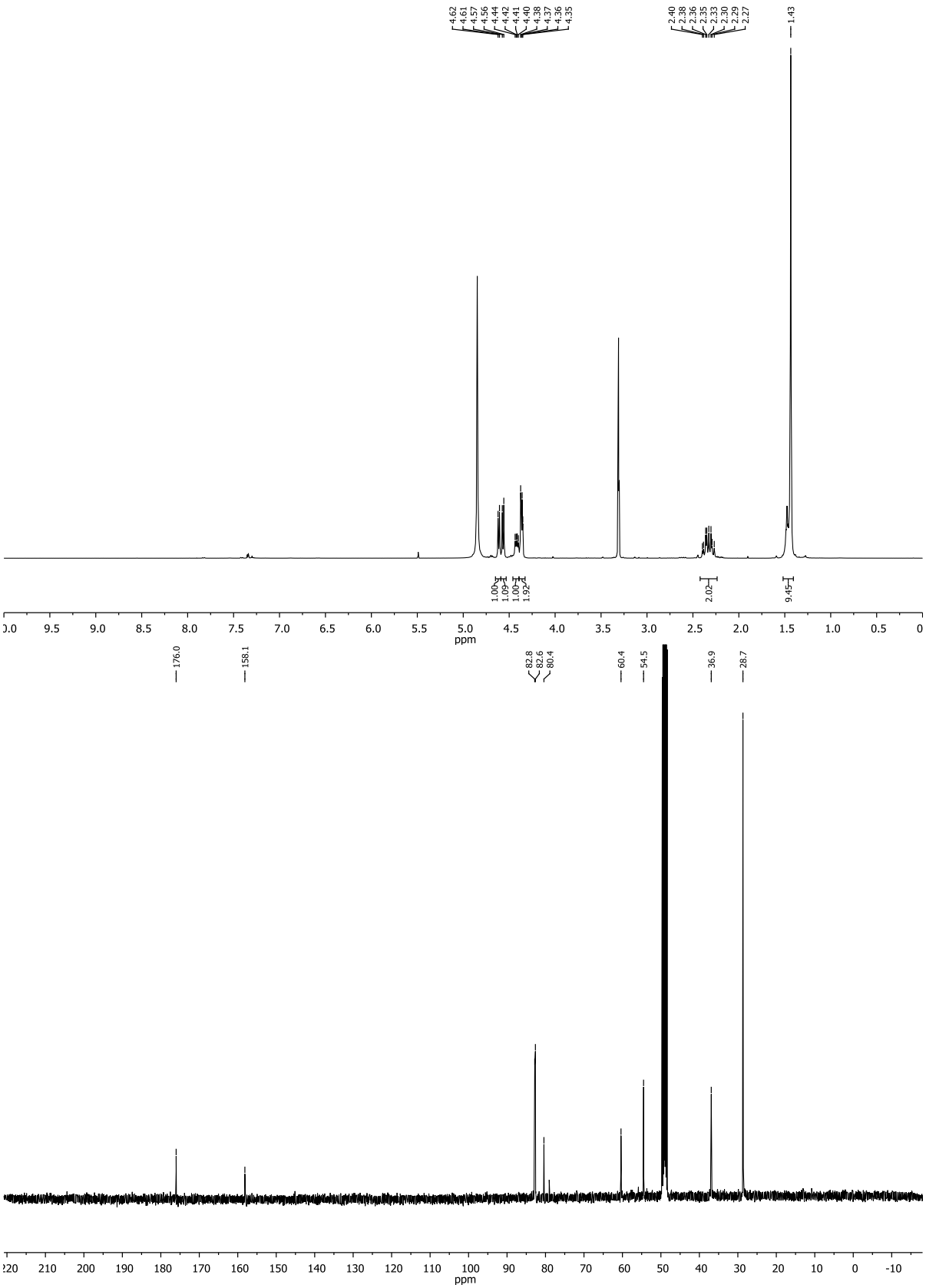


Figure 107 ^{1}H- and ^{13}C-NMR Spectra of 184.

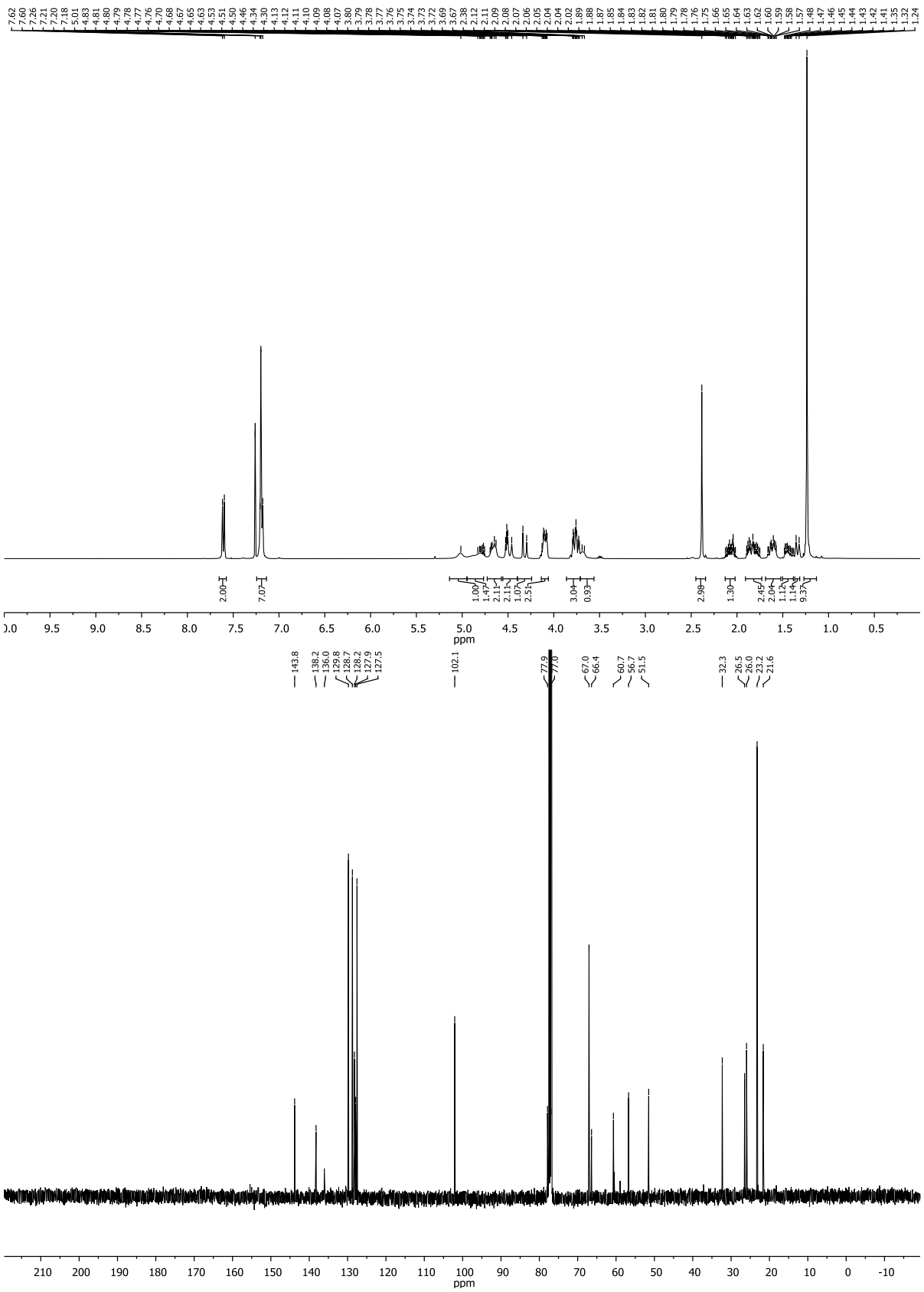


Figure 108 ^{1}H- and ^{13}C-NMR Spectra of 191.

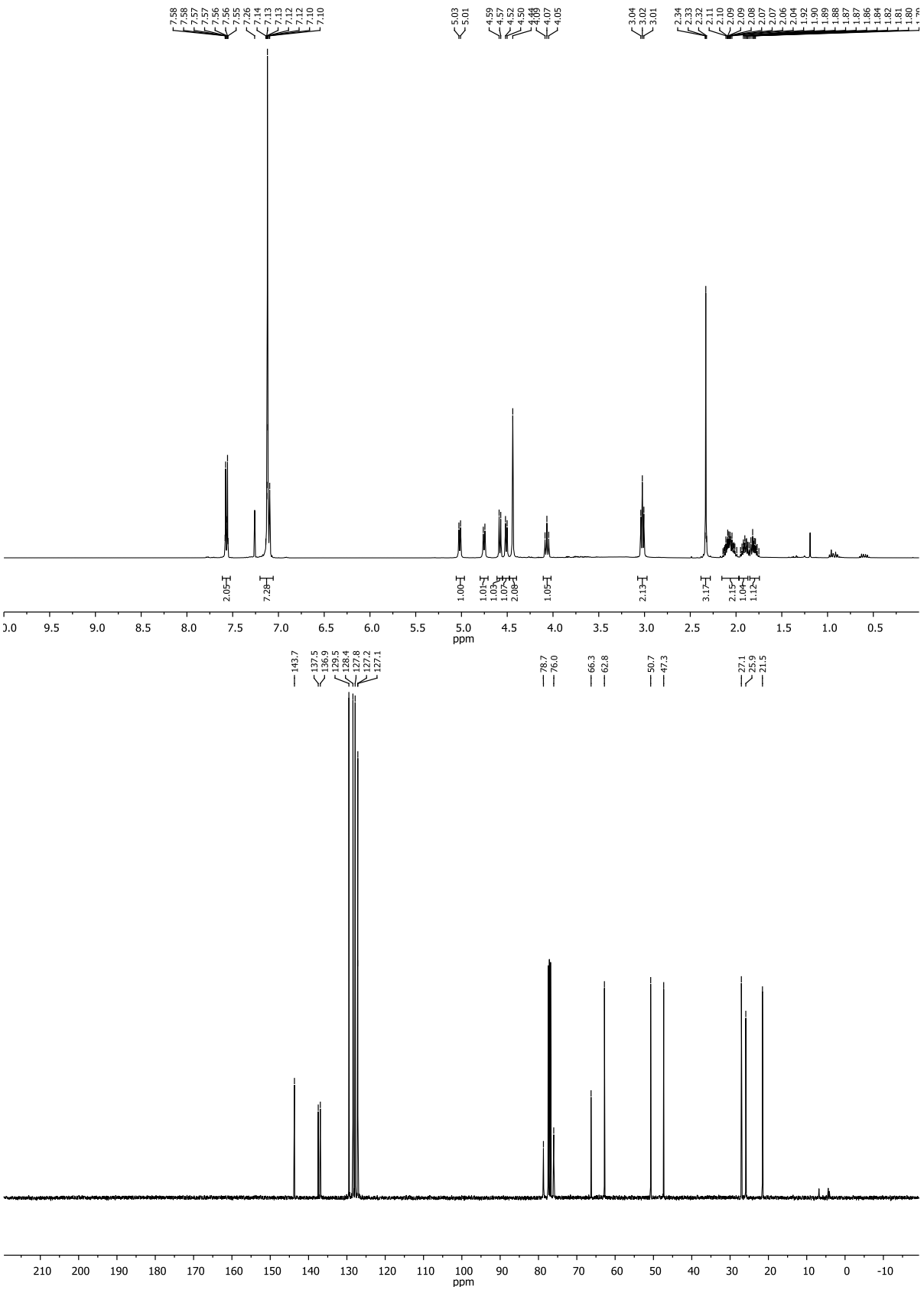


Figure 109 ^{1}H- and ^{13}C-NMR Spectra of 192.

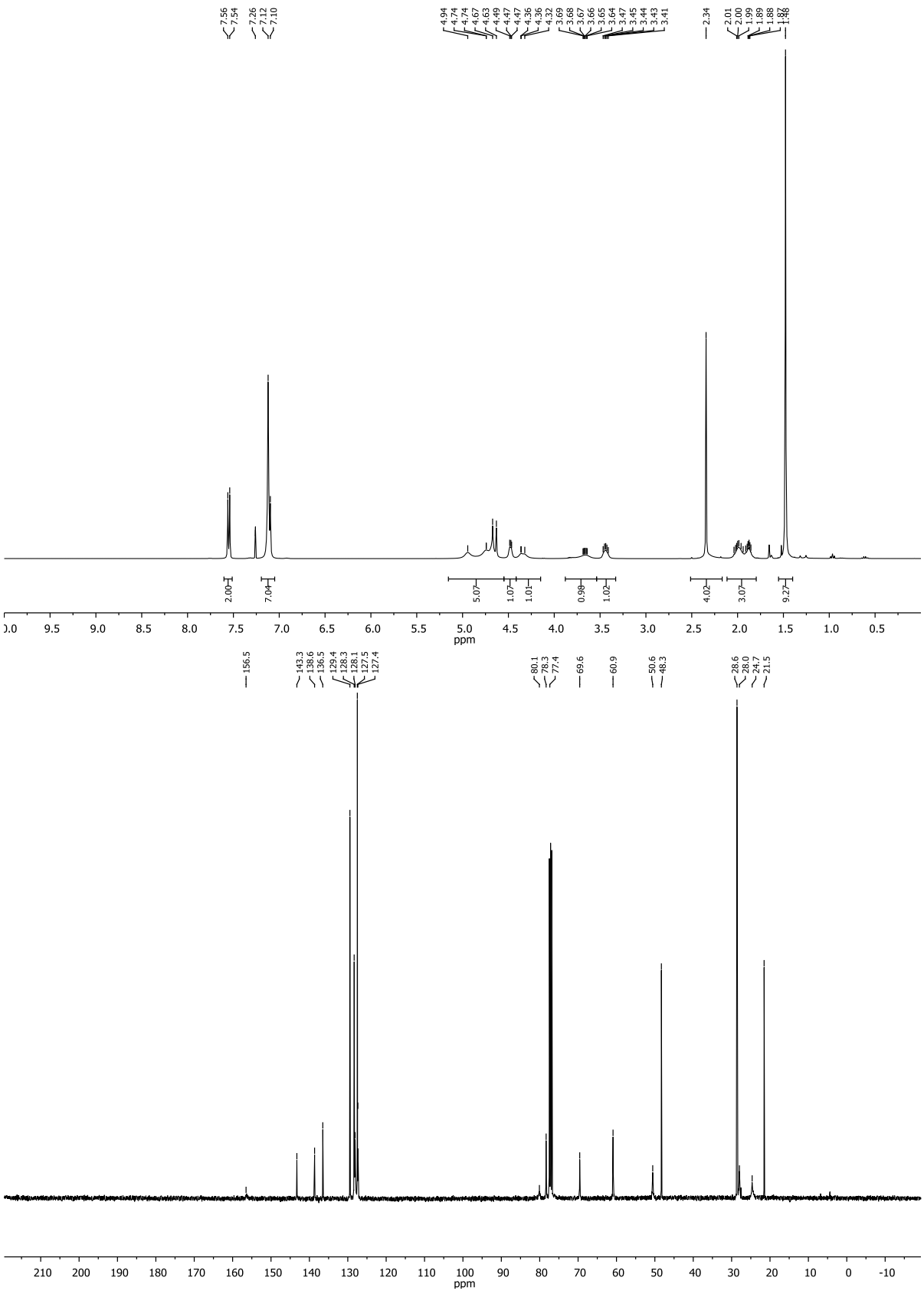


Figure 110 ^{1}H- and ^{13}C-NMR Spectra of 193.

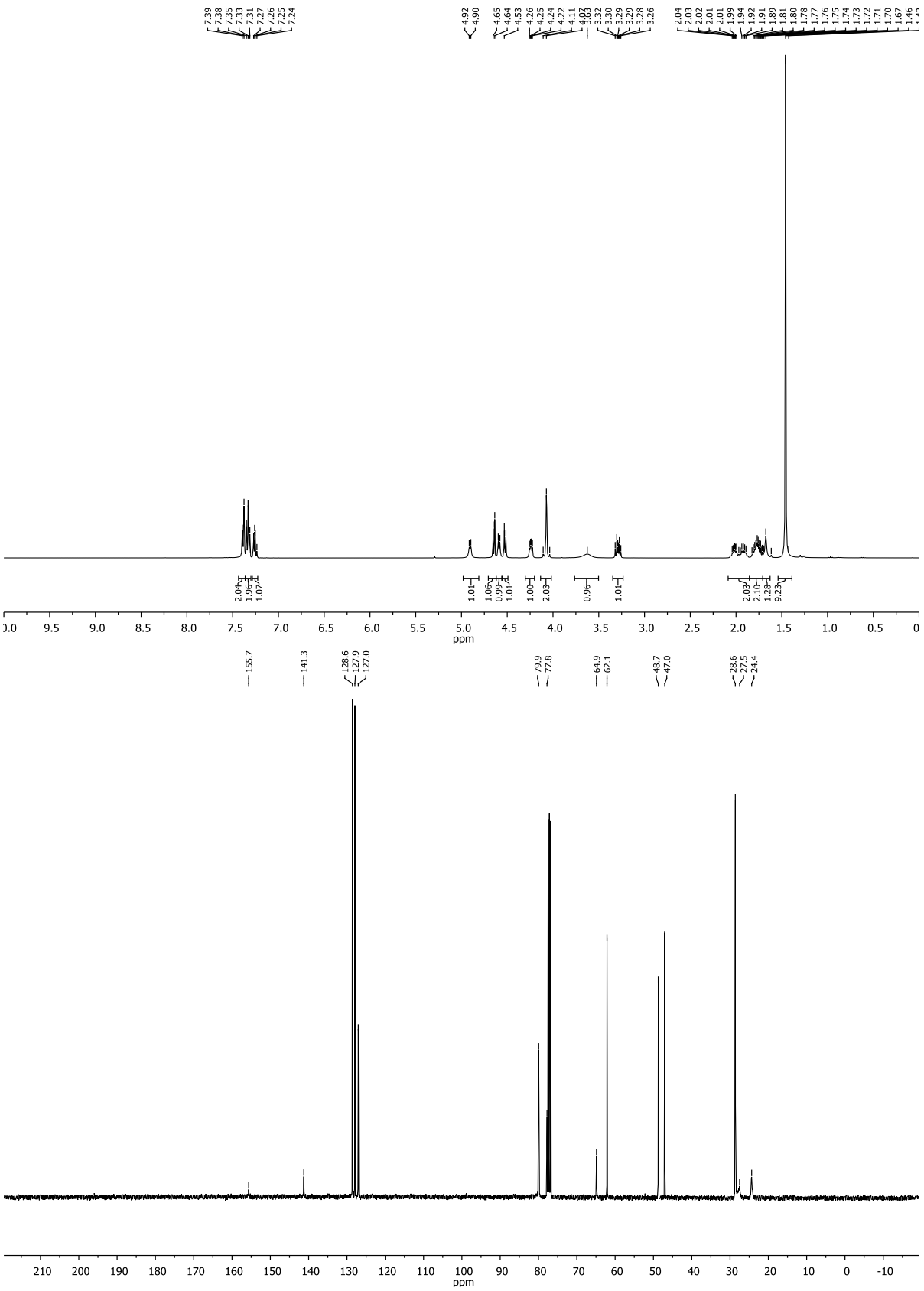


Figure 111 ^{1}H- and ^{13}C-NMR Spectra of 194.

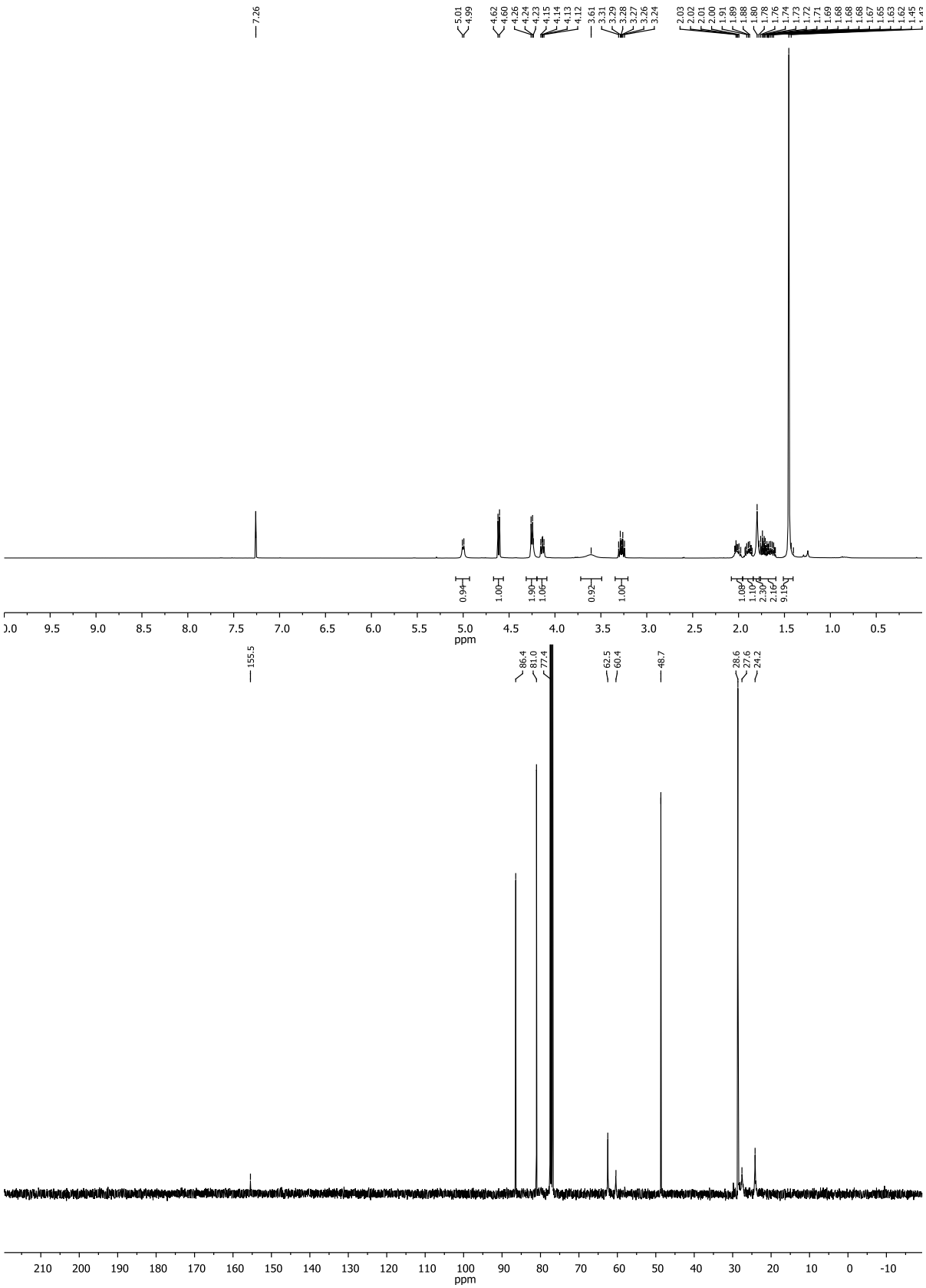


Figure 112 ^{1}H- and ^{13}C-NMR Spectra of 189.

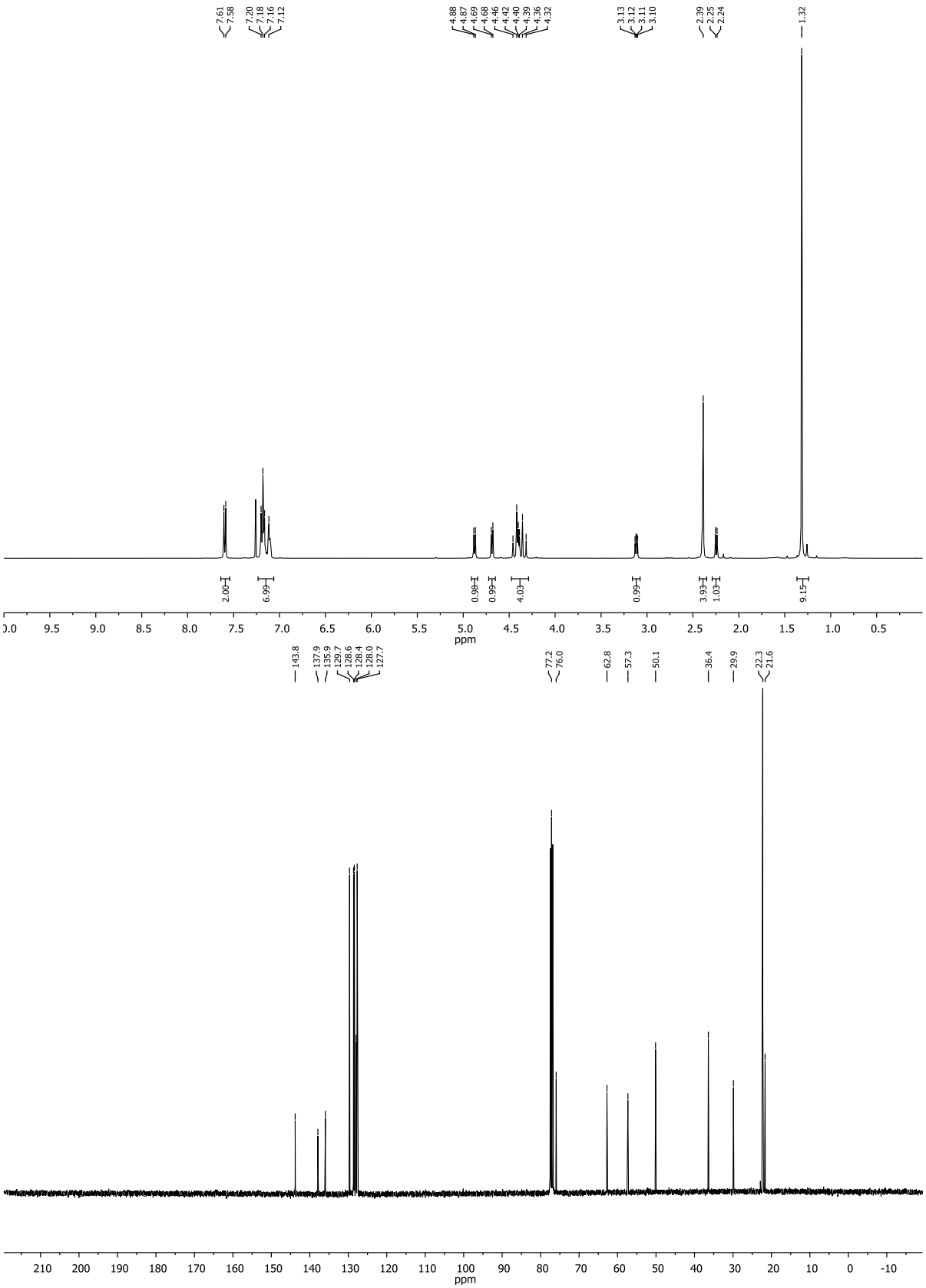


Figure 113 ^{1}H- and ^{13}C-NMR Spectra of the less polar diastereomer of 195.

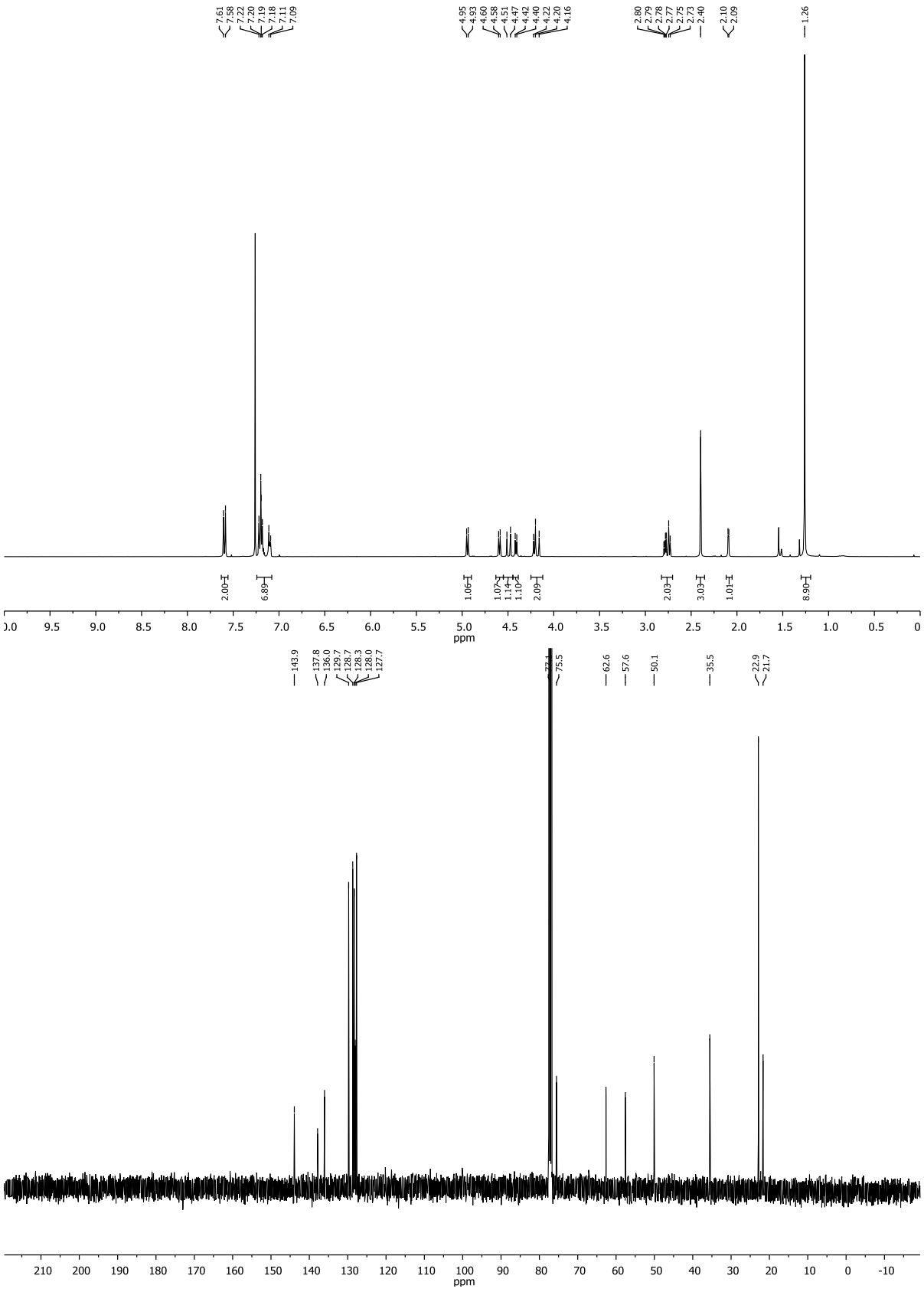


Figure 114 ^{1}H- and ^{13}C-NMR Spectra of the more polar diastereomer of 195.

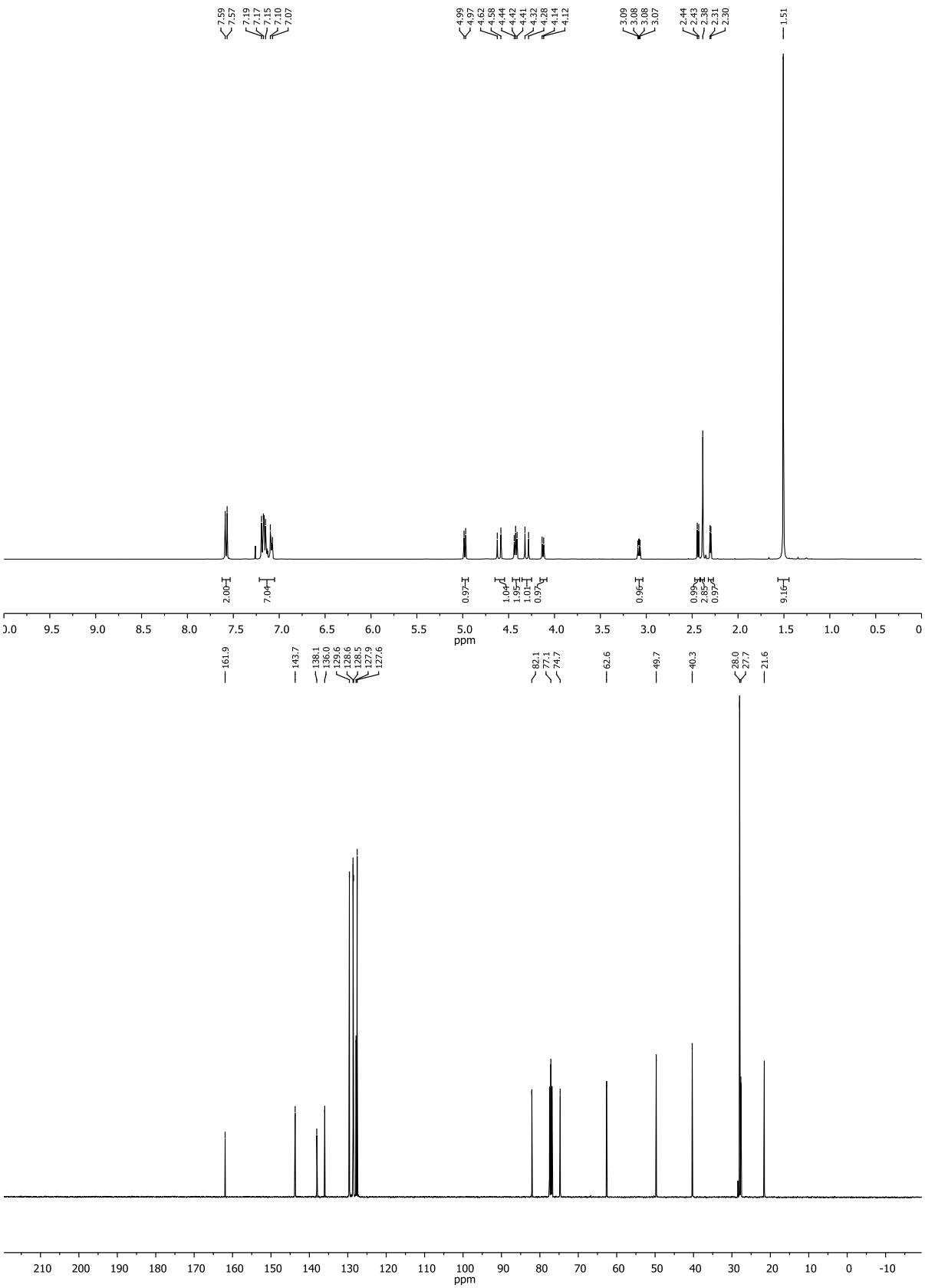


Figure 115 ^{1}H- and ^{13}C-NMR Spectra of 199.

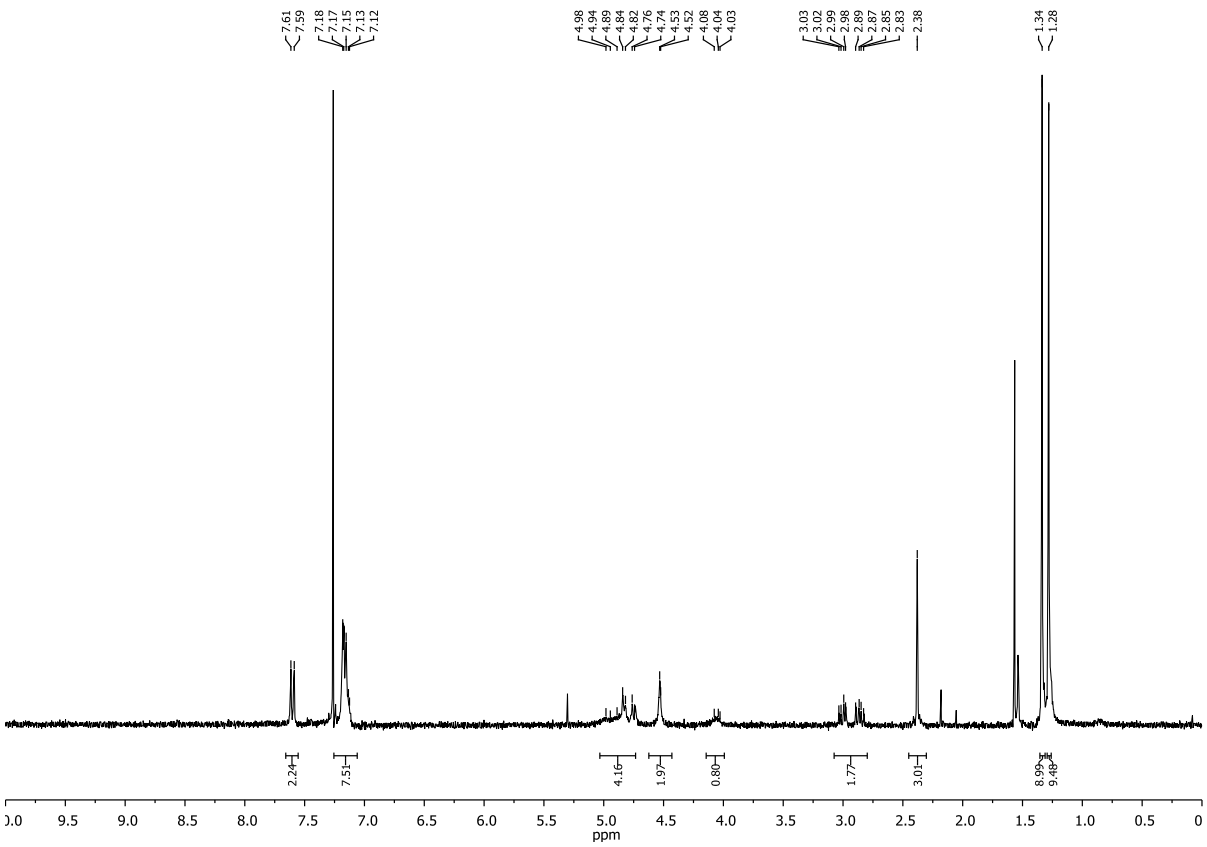


Figure 116 ^{1}H-NMR Spectrum of 200.

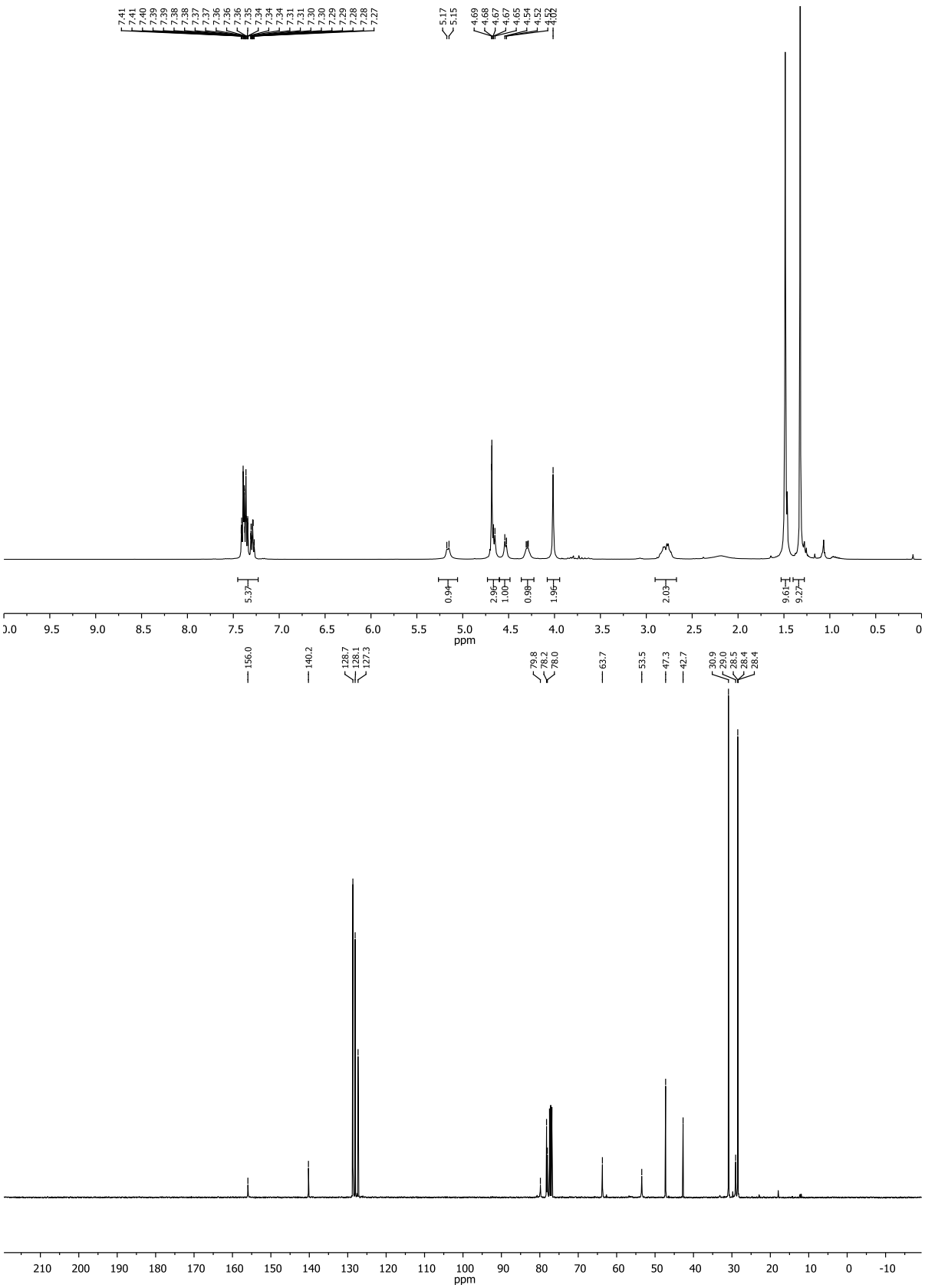


Figure 117 ^{1}H- and ^{13}C-NMR Spectra of 386.

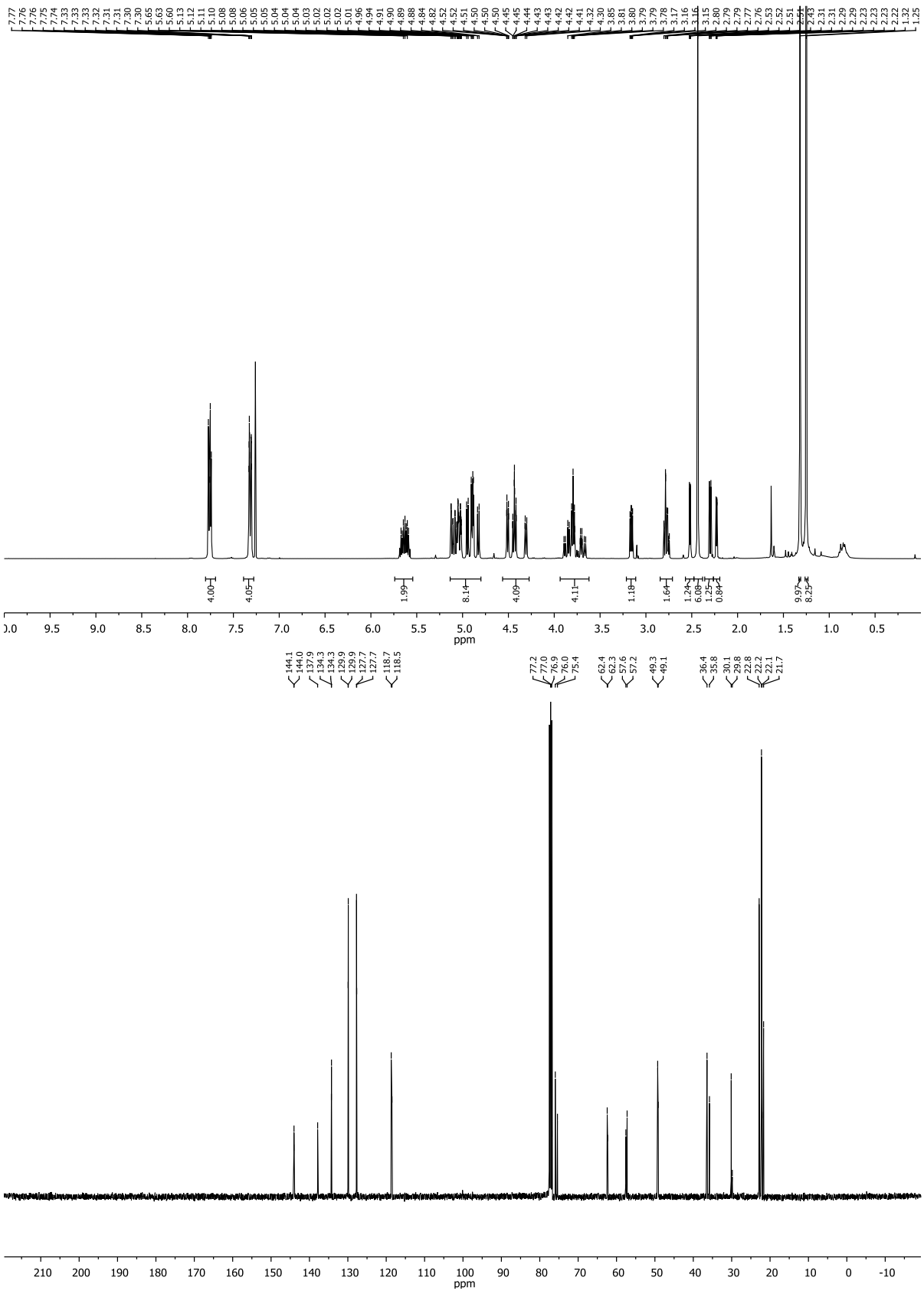


Figure 118 ^{1}H- and ^{13}C-NMR Spectra of 196.

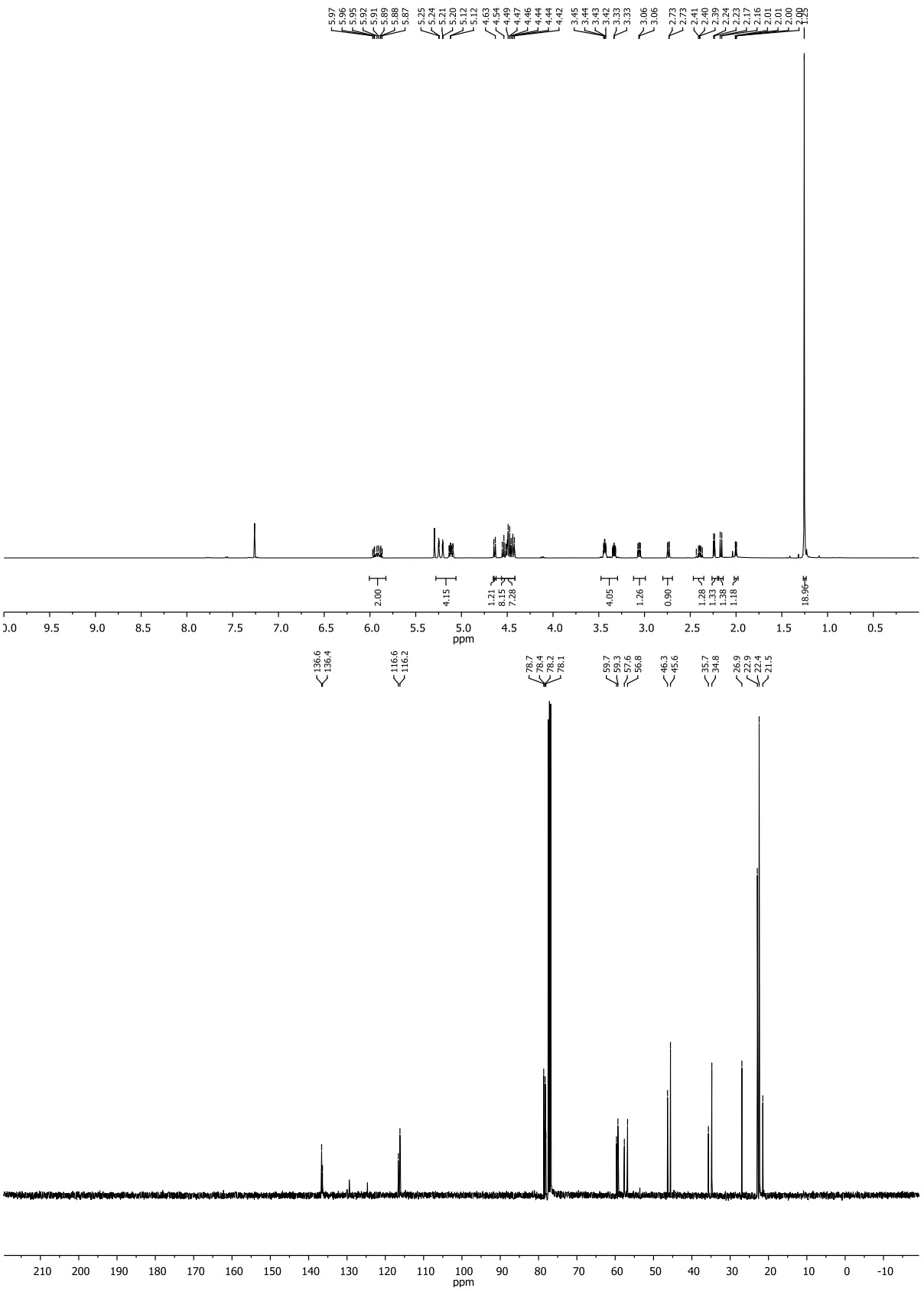


Figure 119 ^{1}H- and ^{13}C-NMR Spectra of 202.

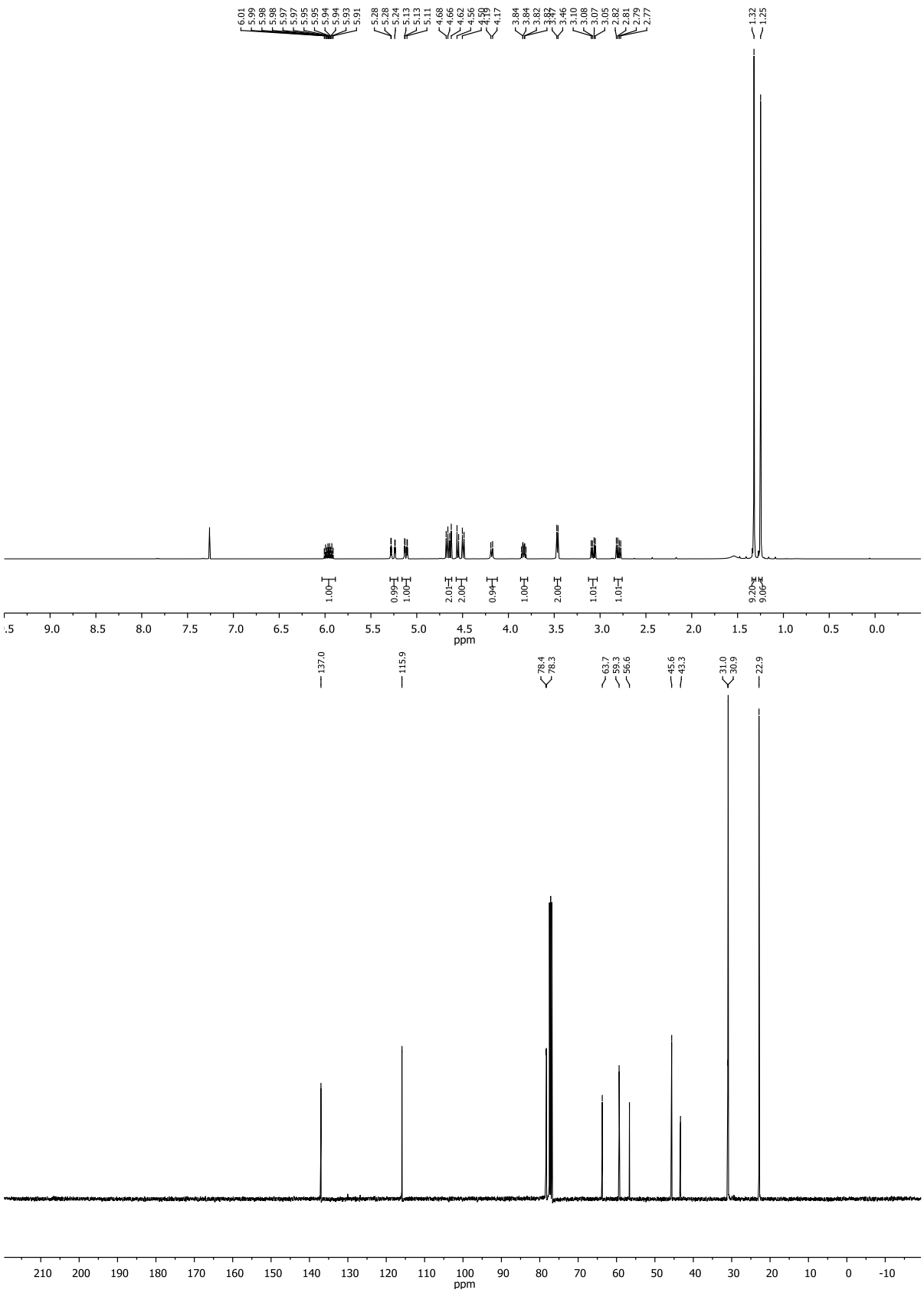


Figure 120 ^{1}H- and ^{13}C-NMR Spectra of the less polar diastereomer of 203.

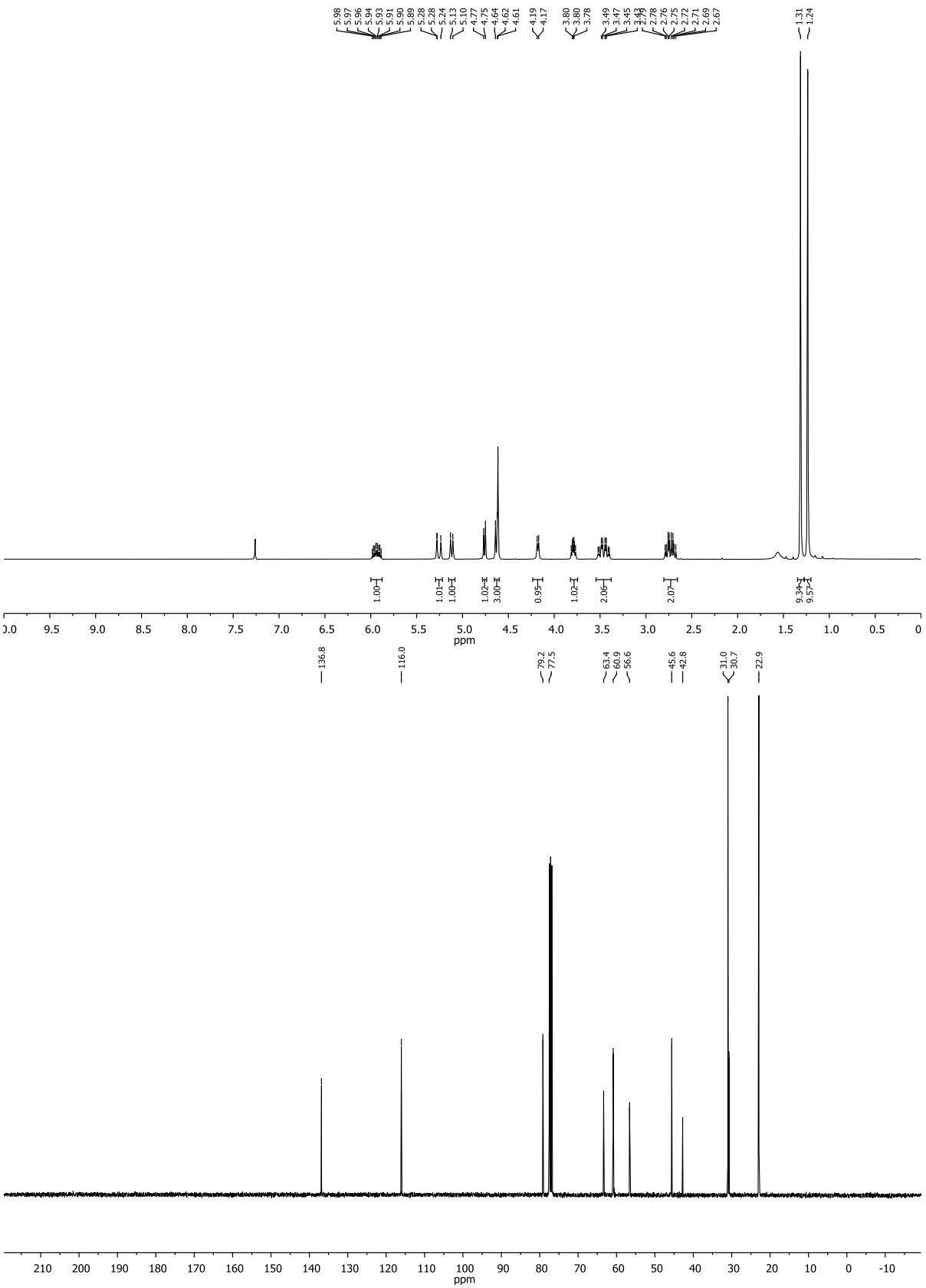


Figure 121 ^{1}H- and ^{13}C-NMR Spectra of the more polar diastereomer of 203.

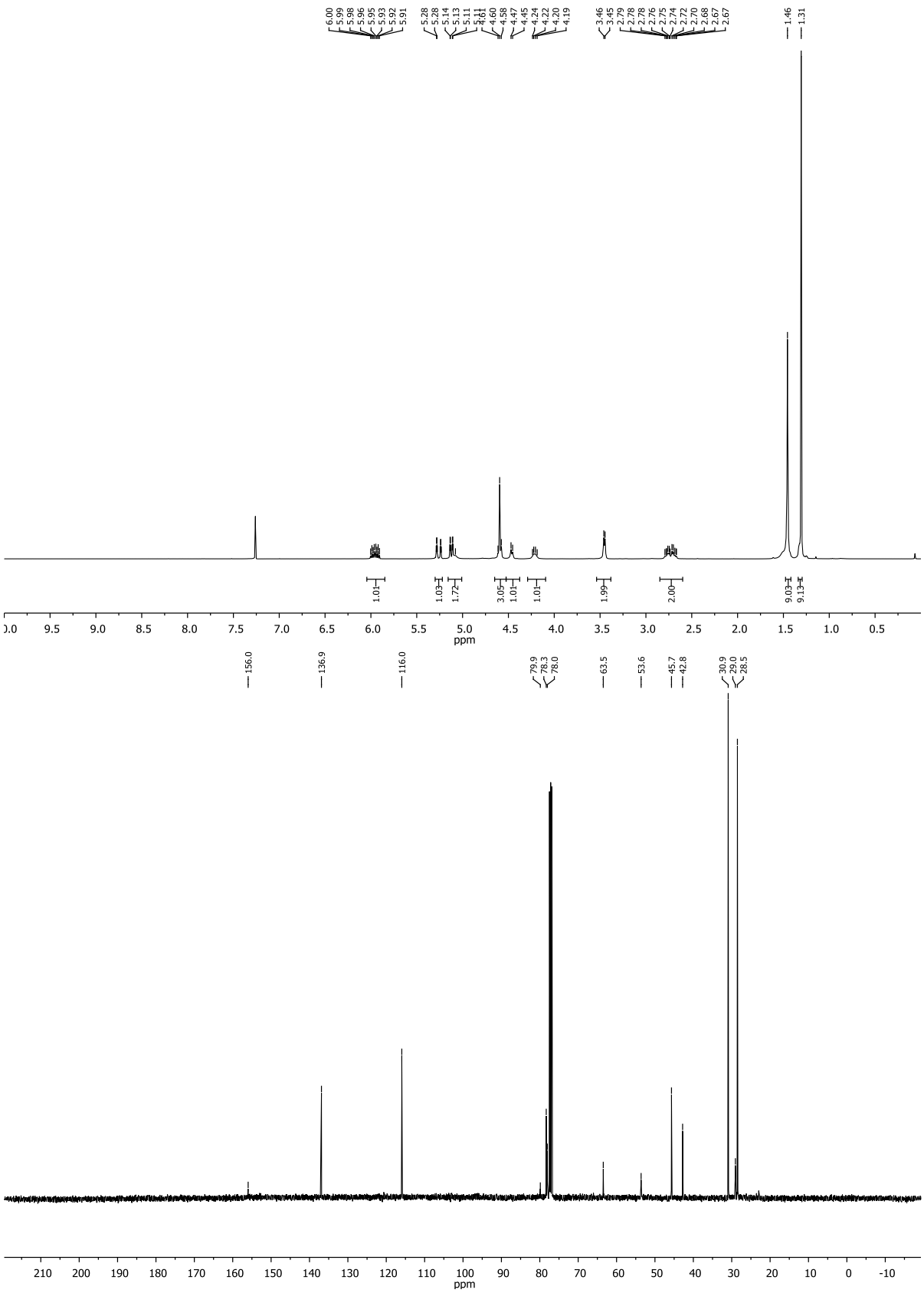


Figure 122 ^{1}H- and ^{13}C-NMR Spectra of 204.

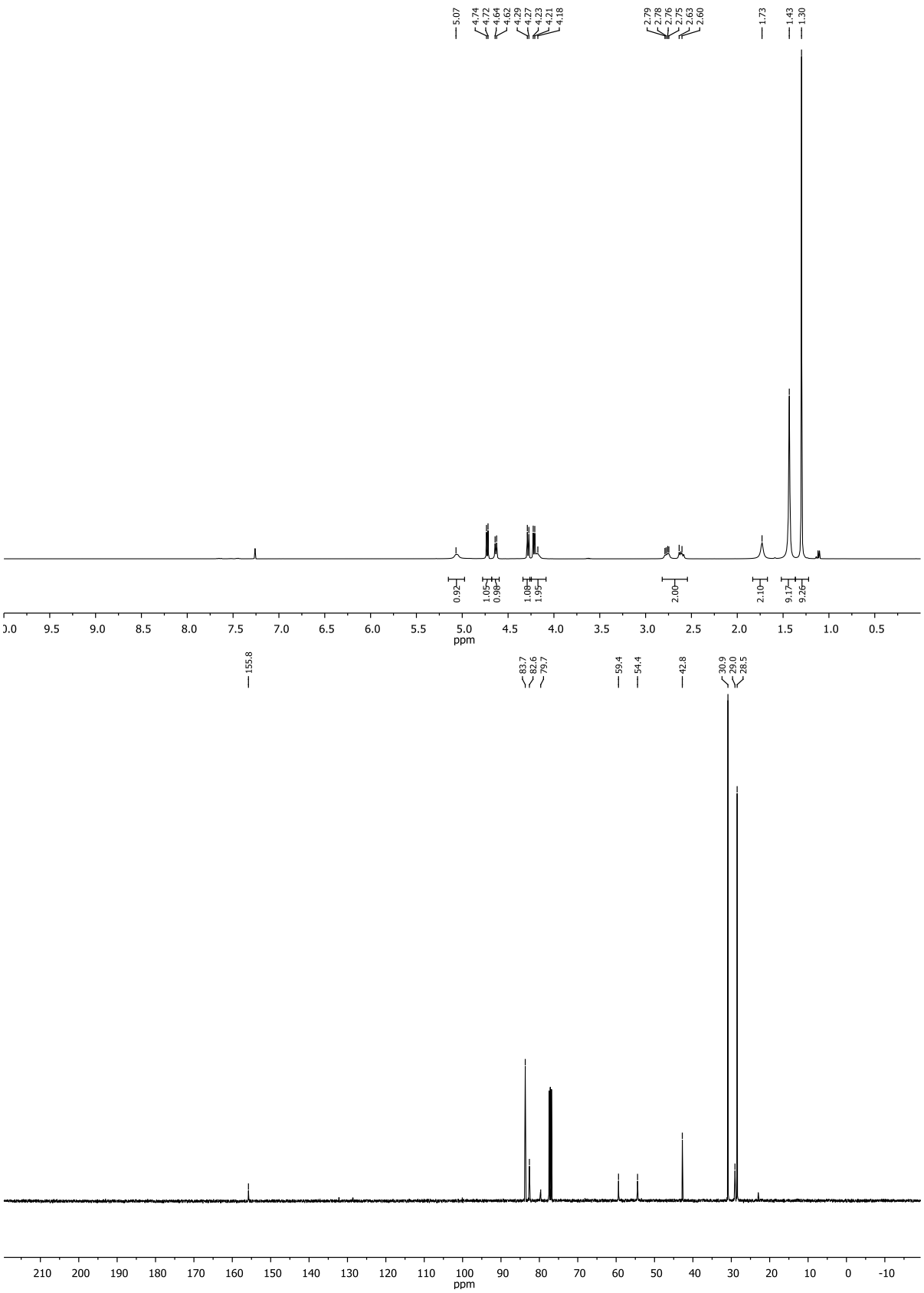


Figure 123 ^{1}H- and ^{13}C-NMR Spectra of 197.

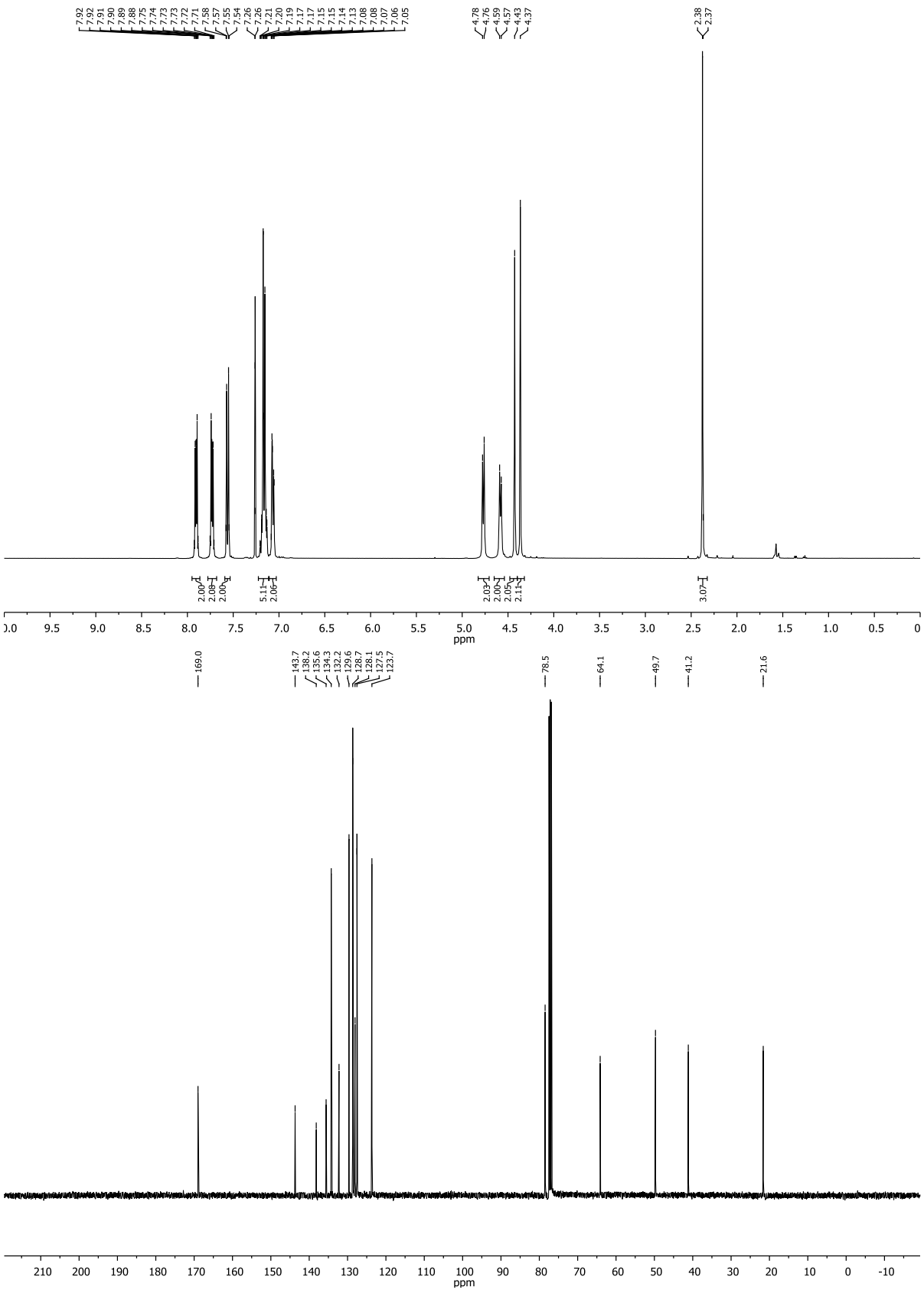


Figure 124 ^{1}H- and ^{13}C-NMR Spectra of 209.

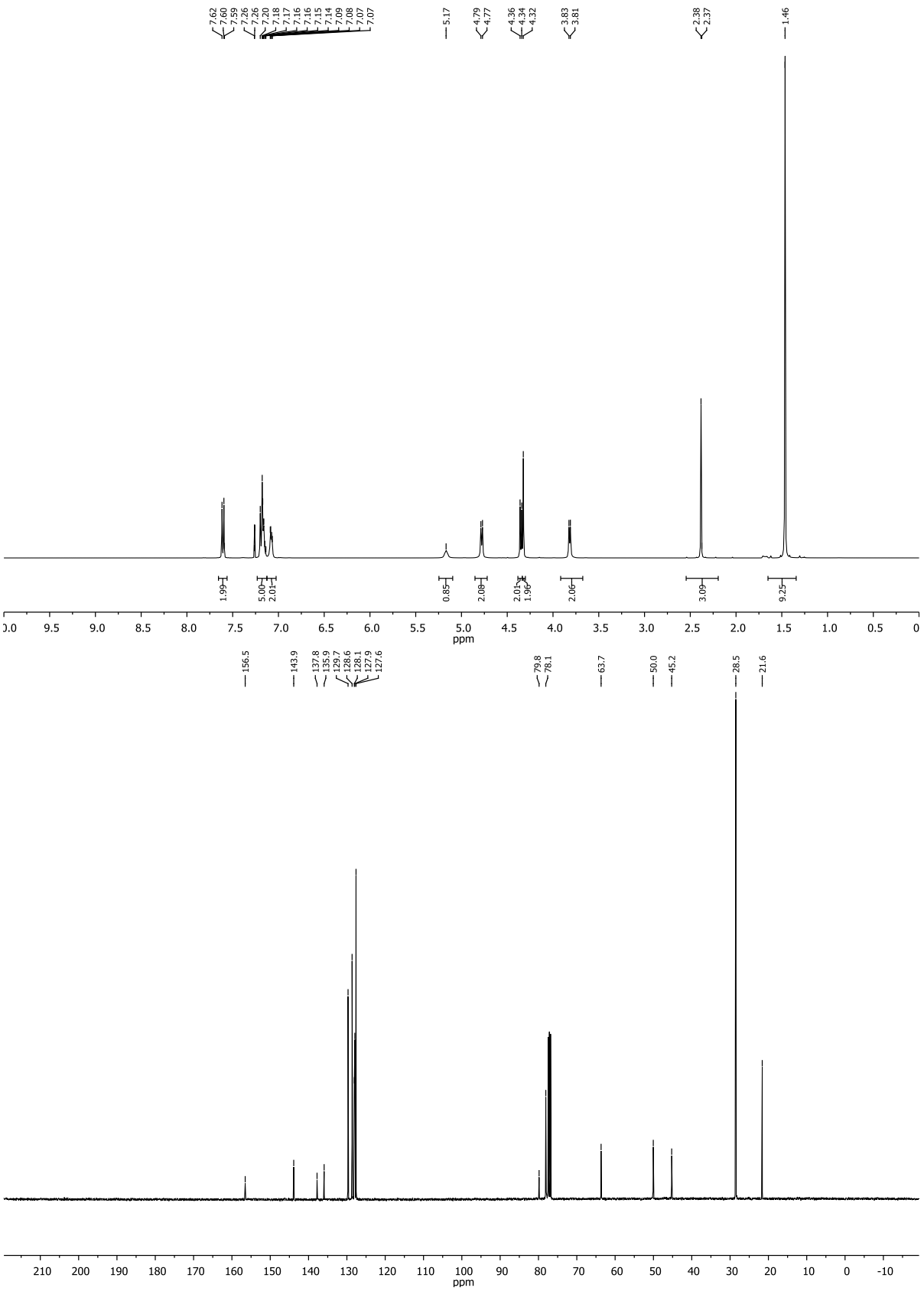


Figure 125 ^{1}H- and ^{13}C-NMR Spectra of 210.

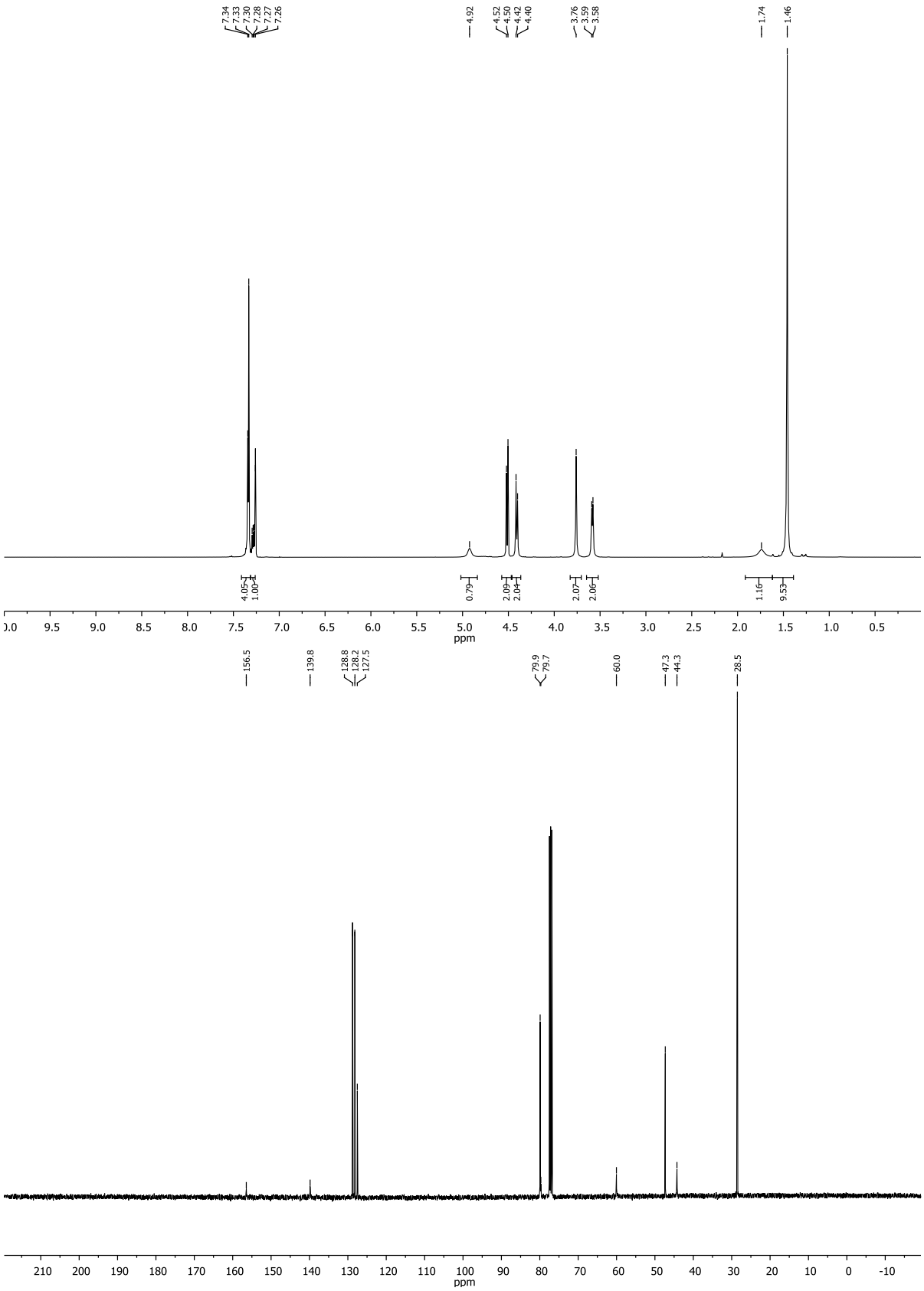


Figure 126 ^{1}H- and ^{13}C-NMR Spectra of 211.

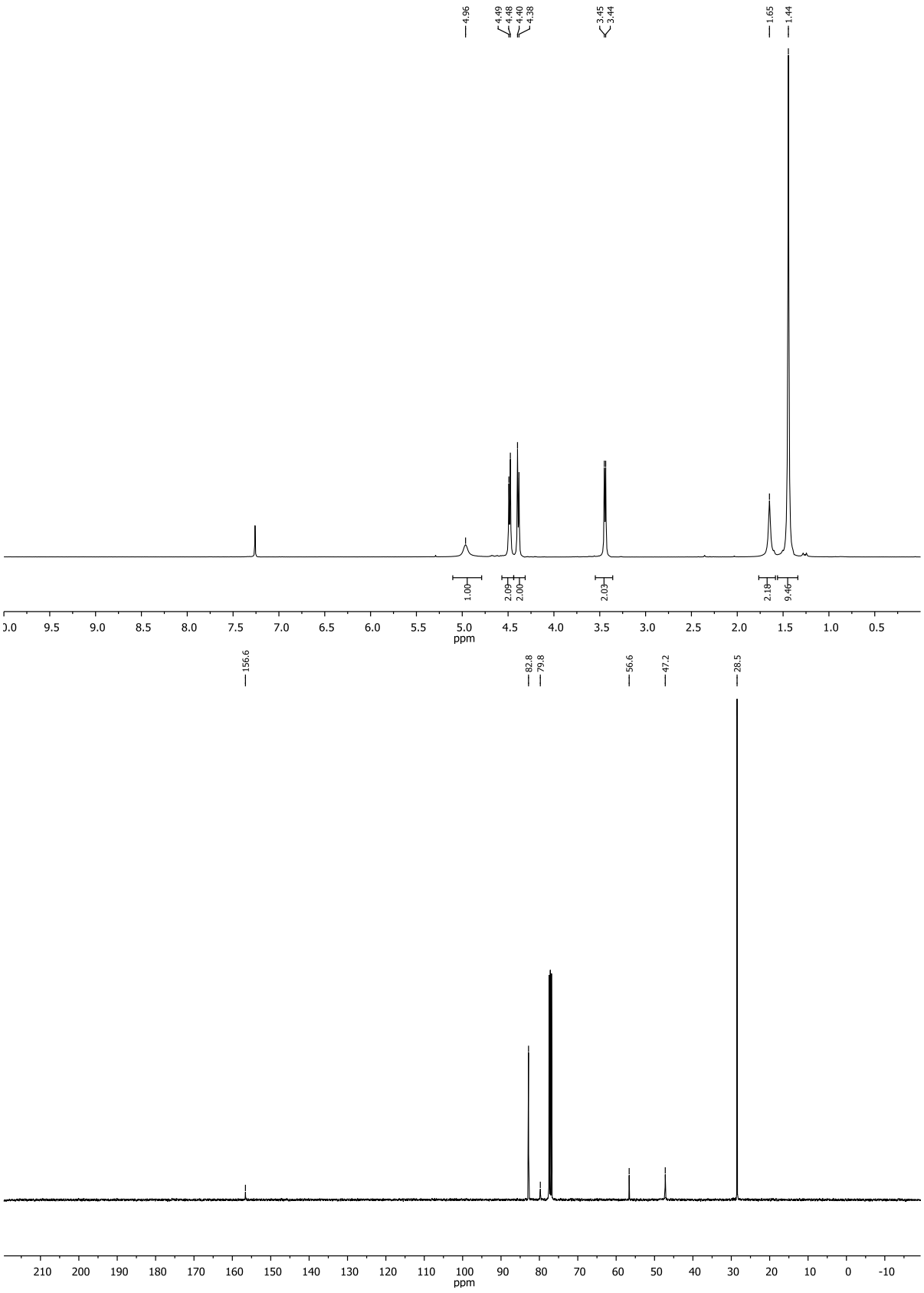


Figure 127 ^{1}H- and ^{13}C-NMR Spectra of 208.

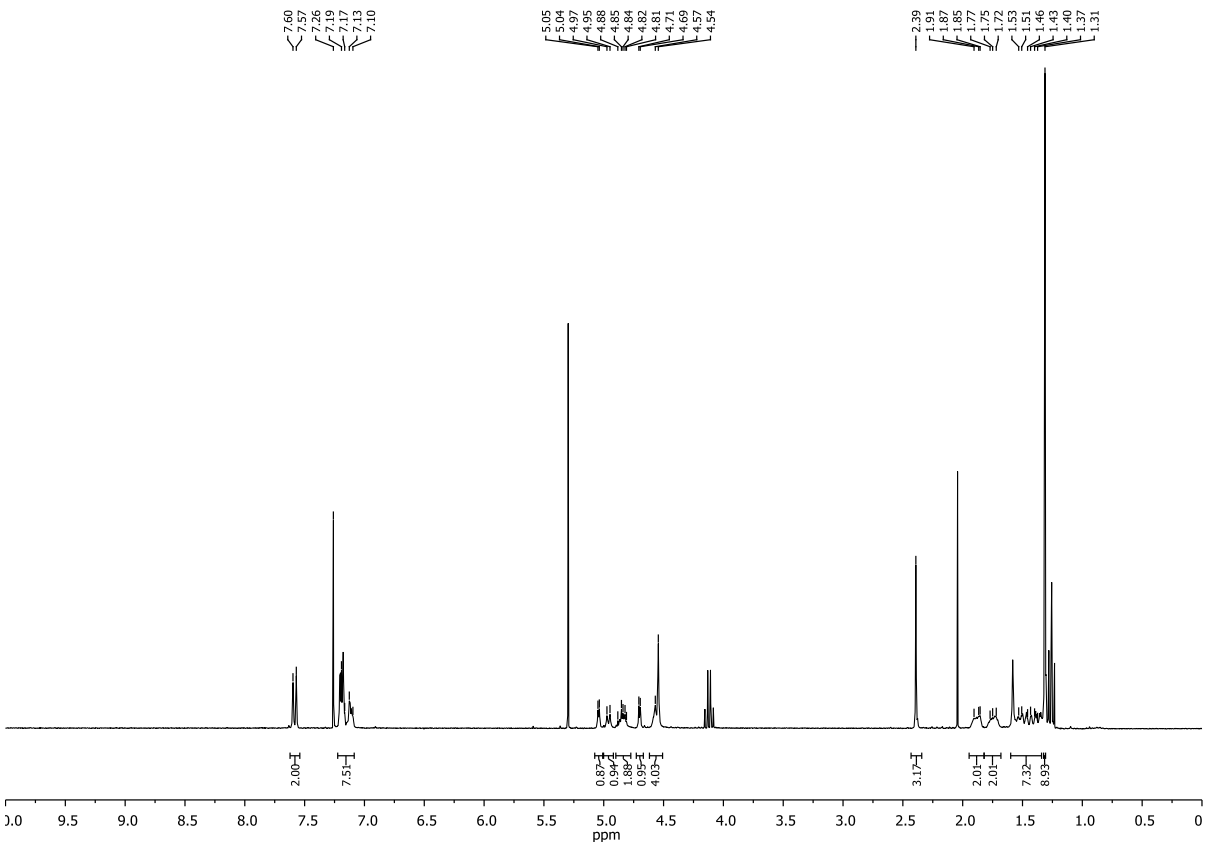


Figure 128 ^{1}H- NMR Spectrum of 214.

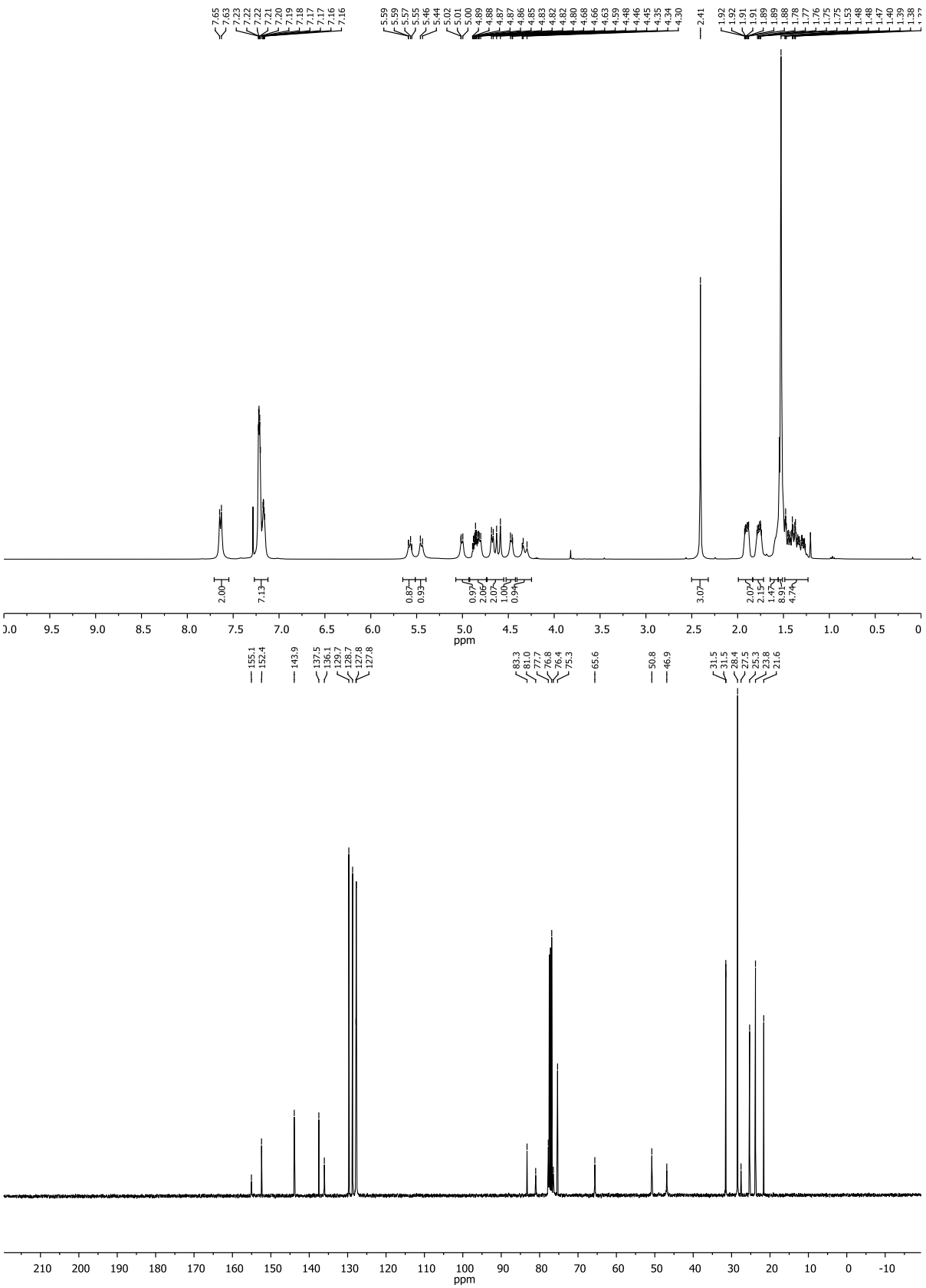


Figure 129 ^{1}H- and ^{13}C-NMR Spectra of 215.

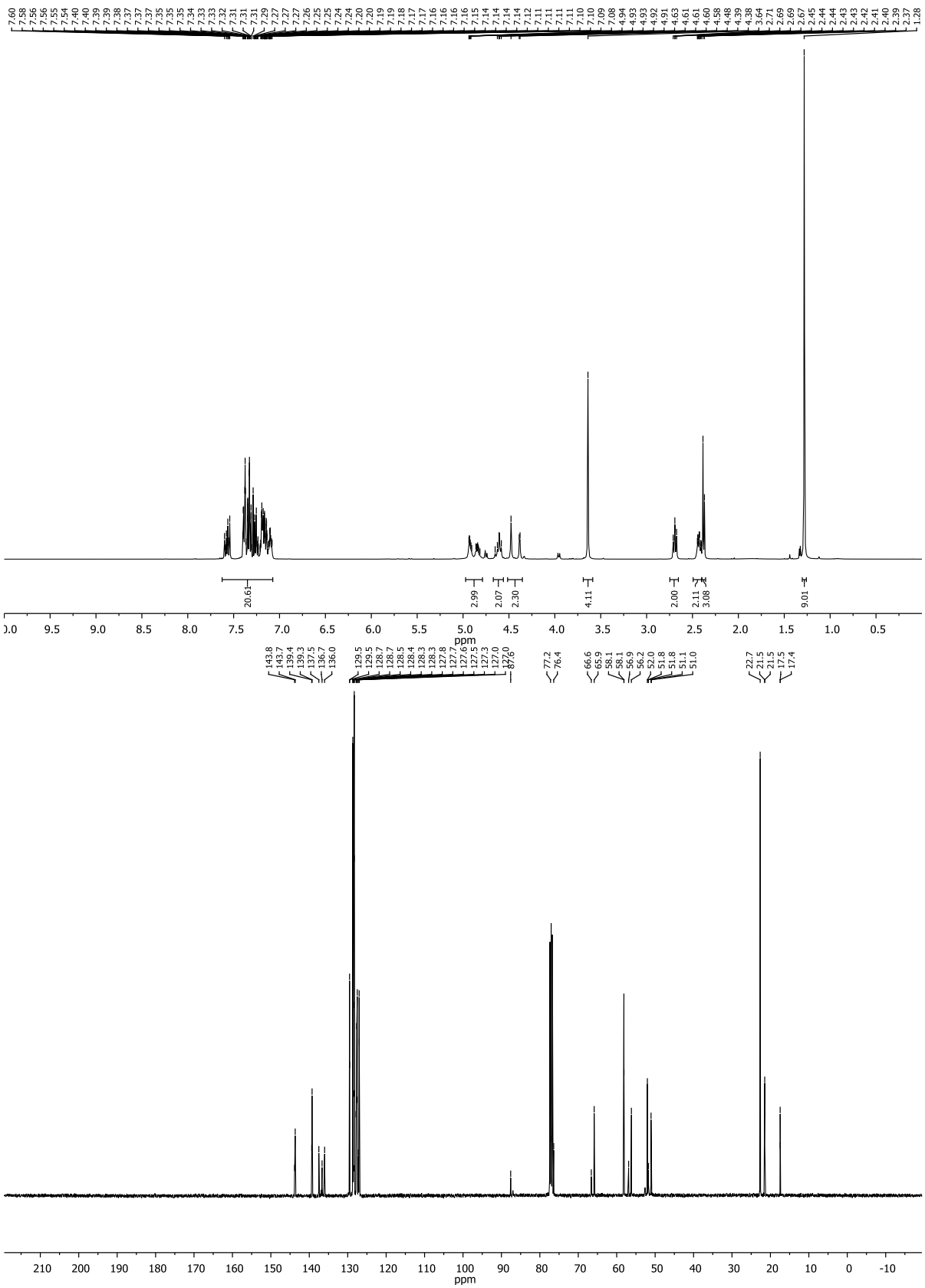
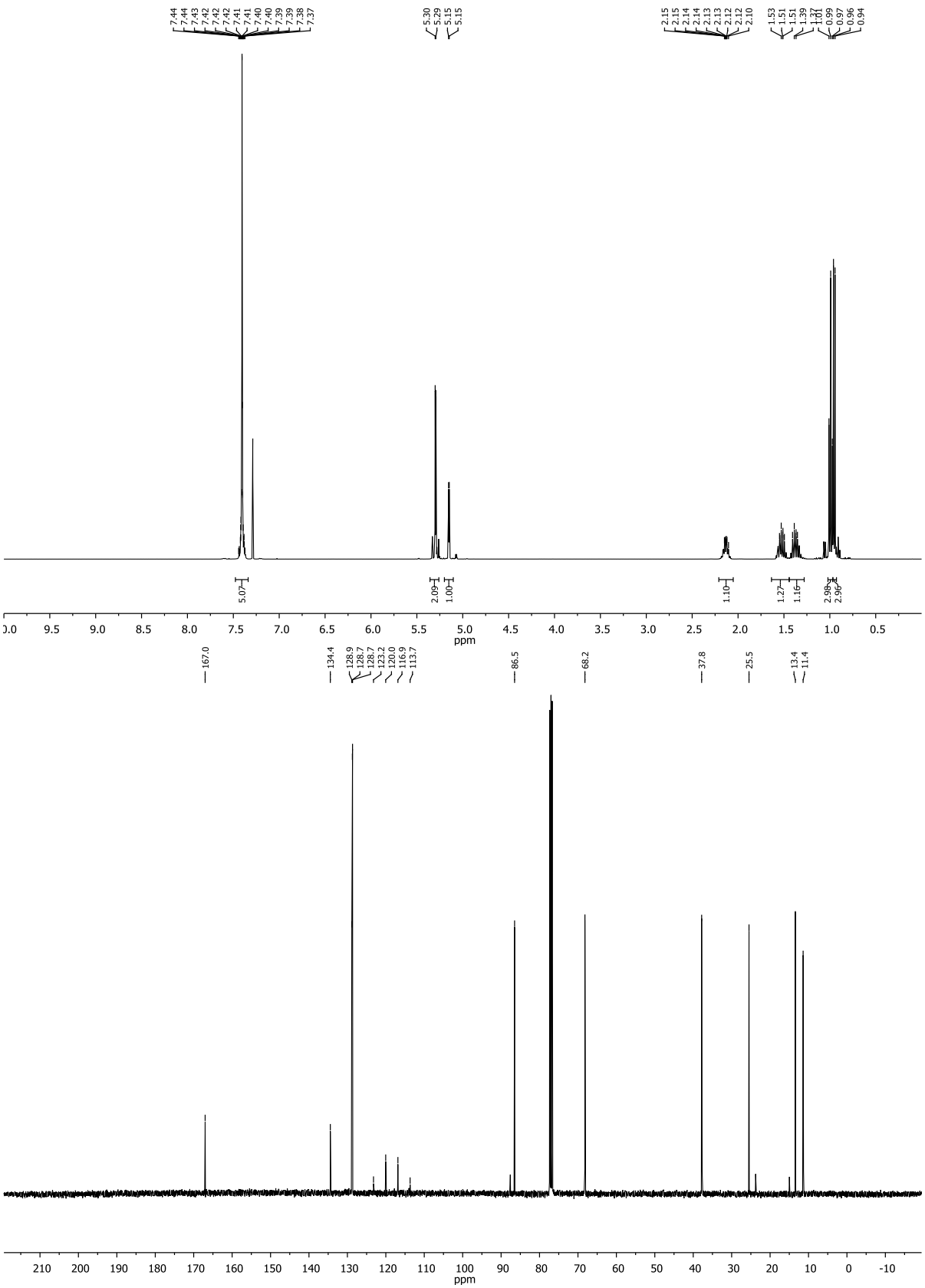


Figure 130 ^{1}H- and ^{13}C-NMR Spectra of 219.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2.14
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2.13
2.12
2.12
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1.00
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ppm

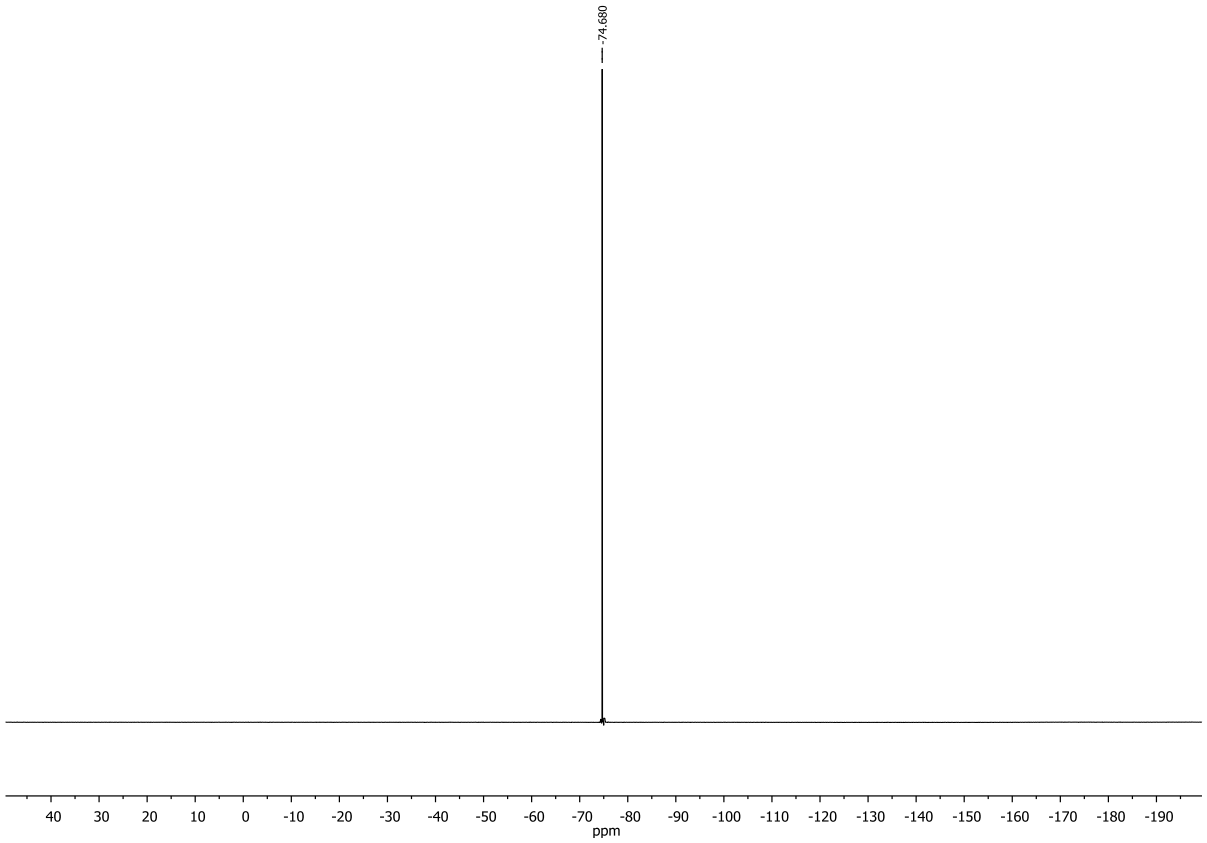


Figure 131 ^{1}H-, ^{13}C- and ^{19}F-NMR Spectra of 230.

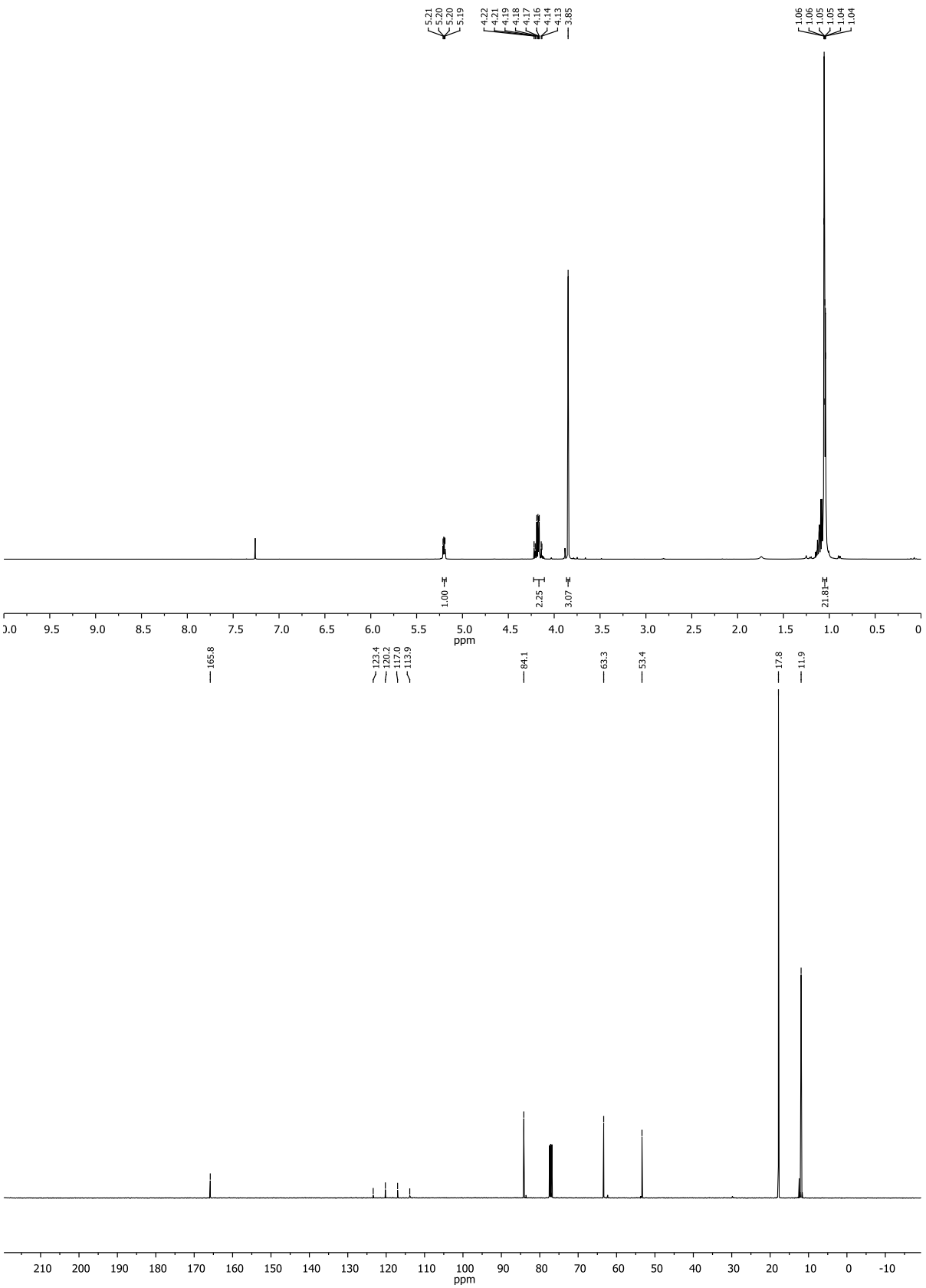
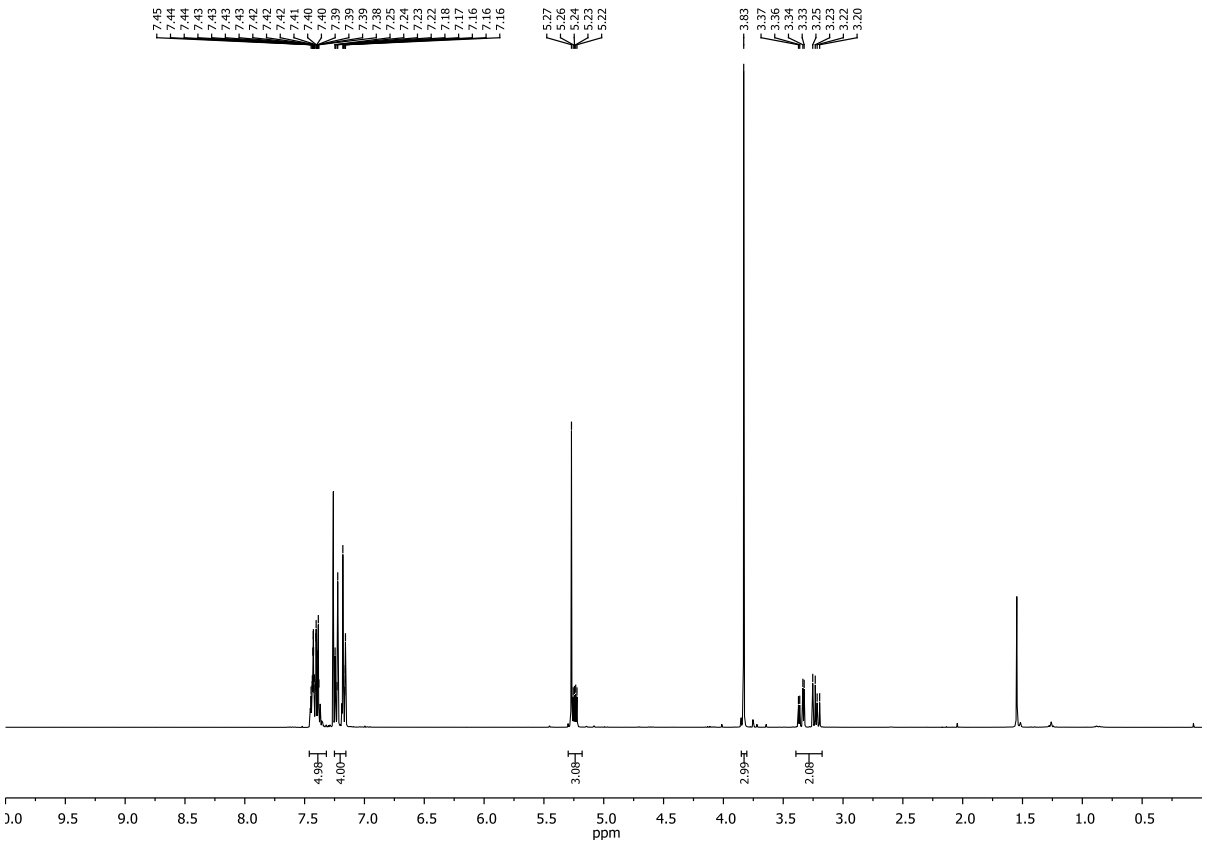


Figure 132 ^{1}H- and ^{13}C-NMR Spectra of 239.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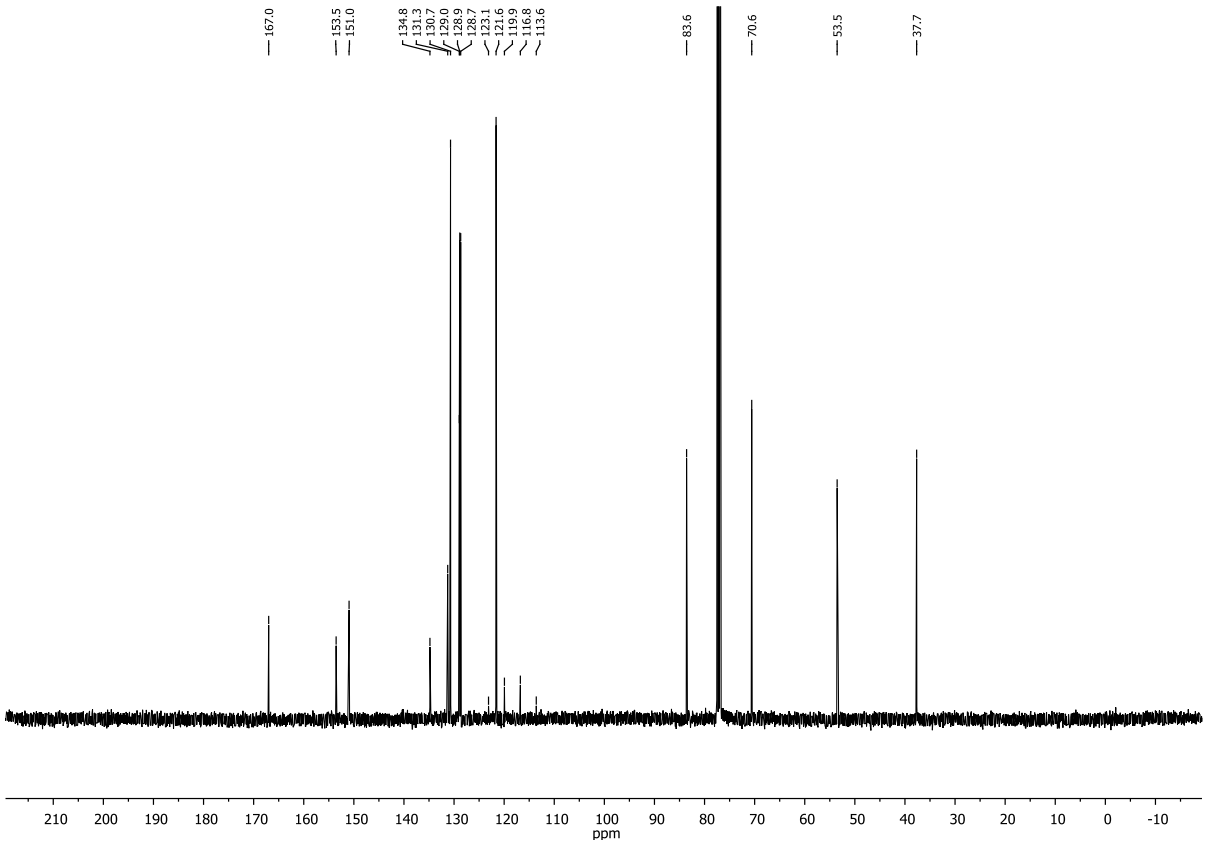
ppm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113.6
83.6
70.6
53.5
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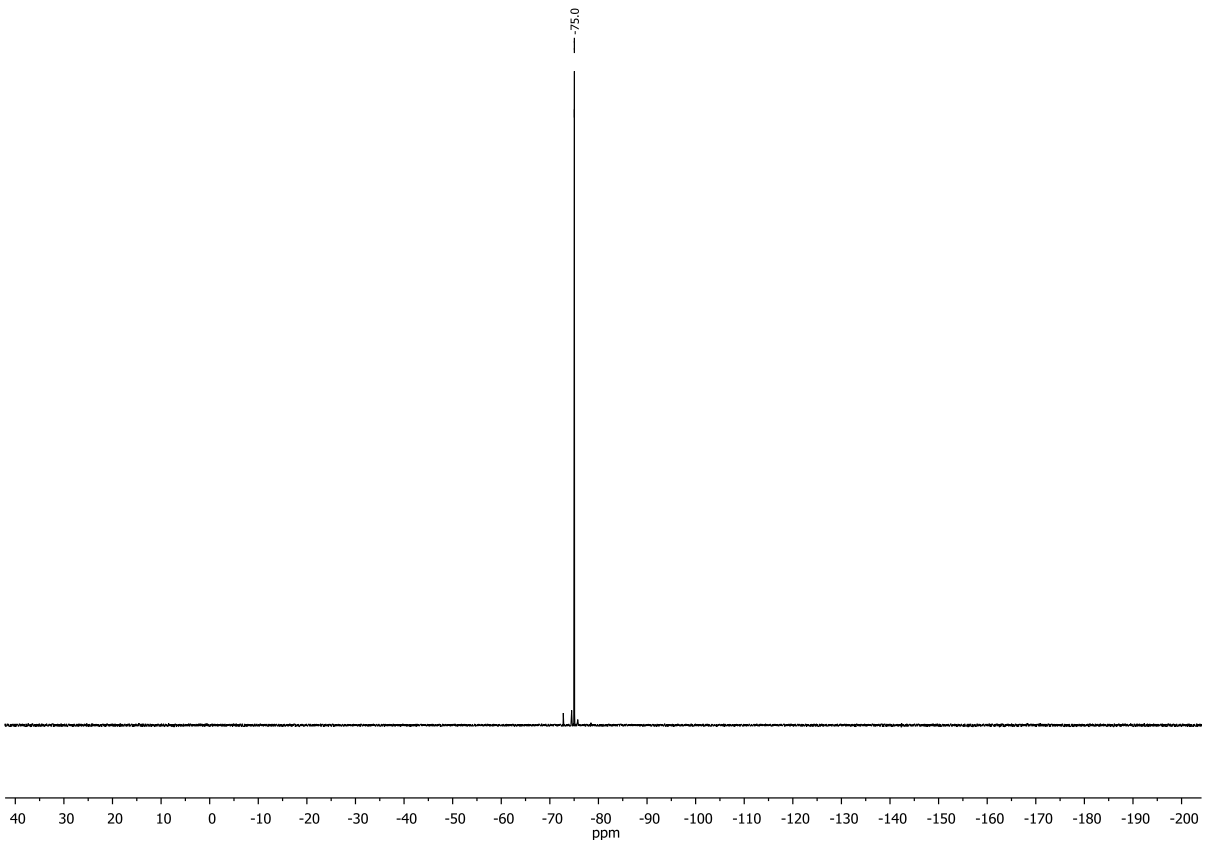


Figure 133 ^{1}H-, ^{13}C- and ^{19}F-NMR Spectra of 244.

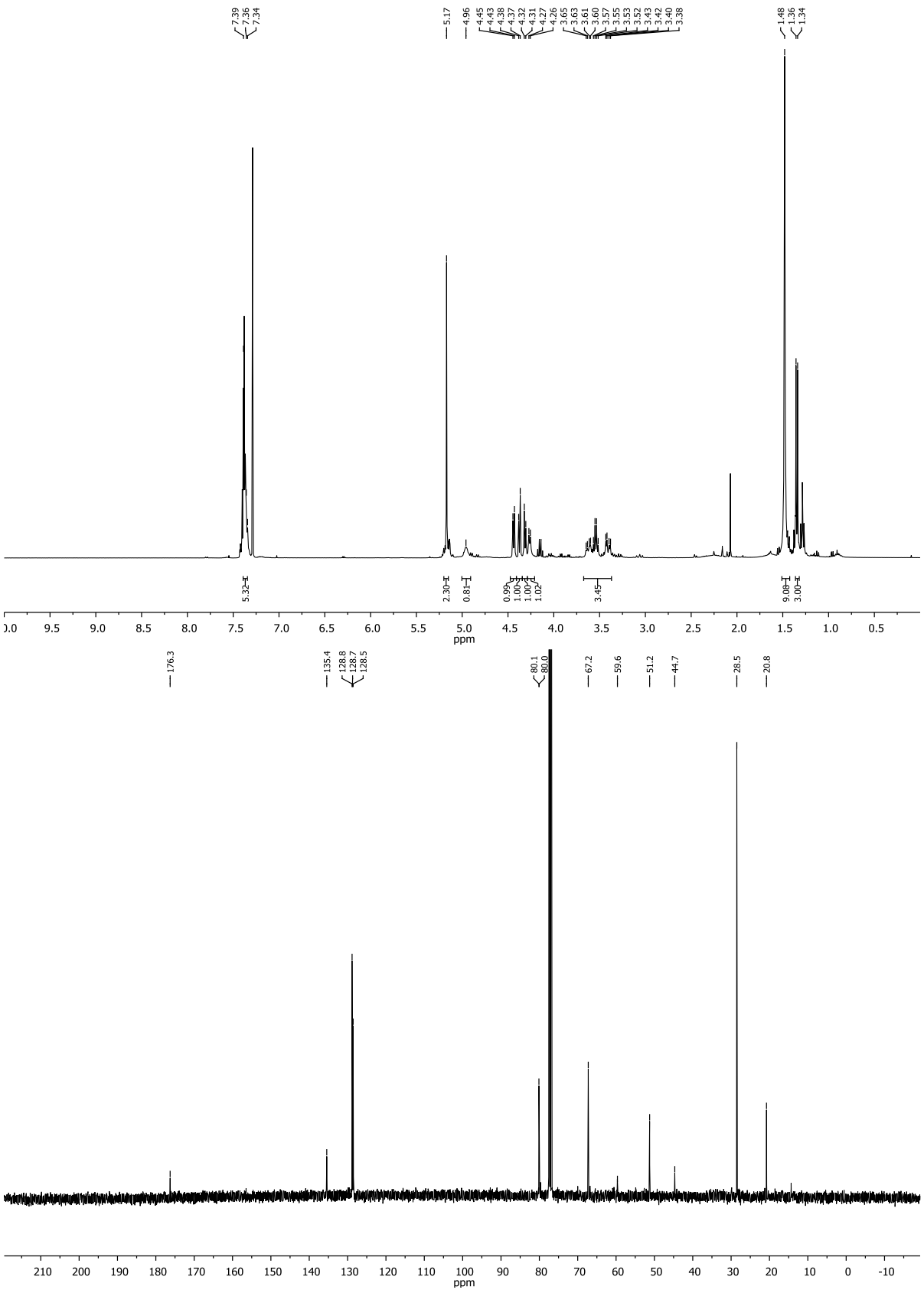


Figure 134 ^{1}H- and ^{13}C-NMR Spectra of 73a.

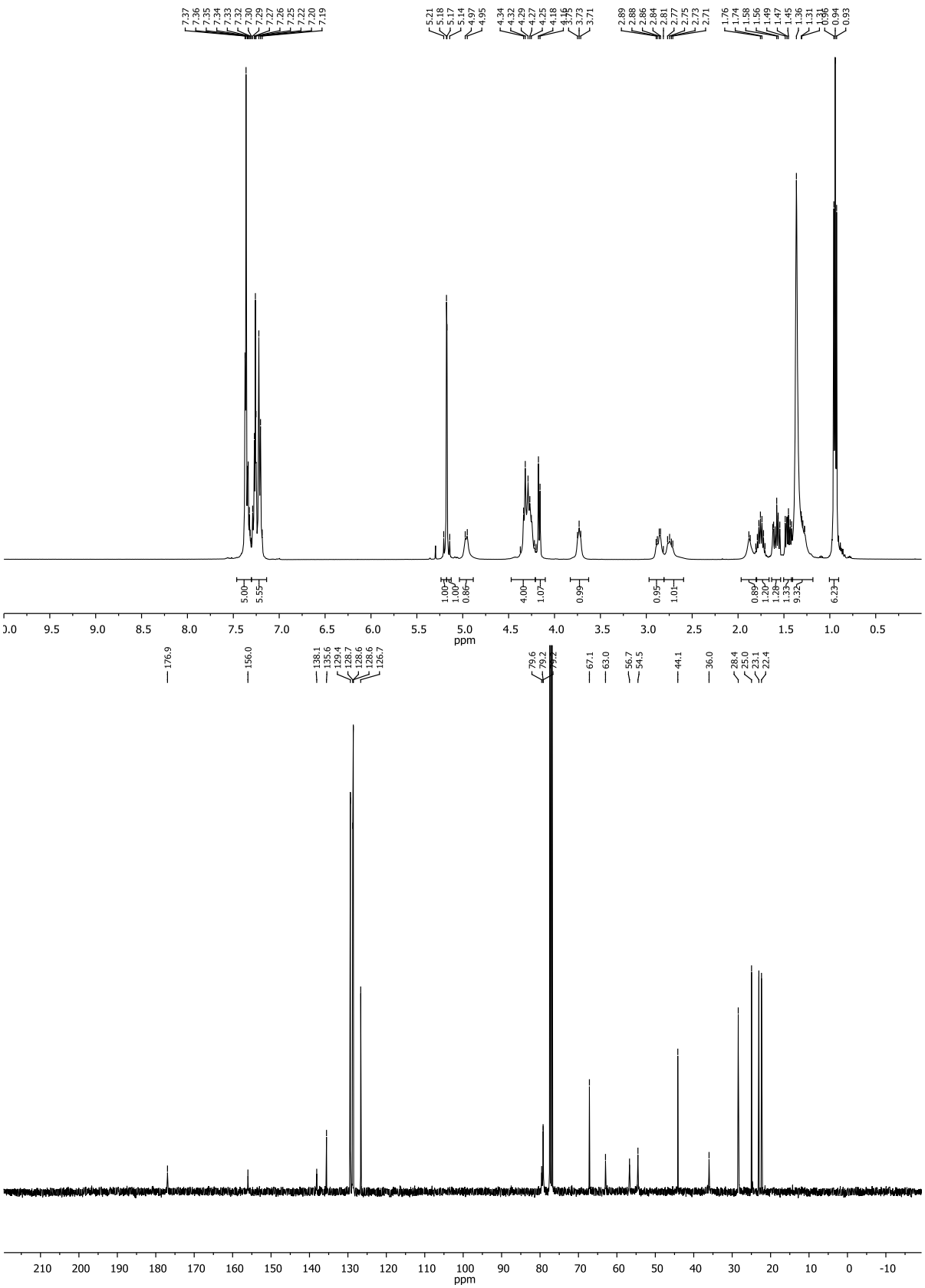


Figure 135 ^{1}H- and ^{13}C-NMR Spectra of 73b.

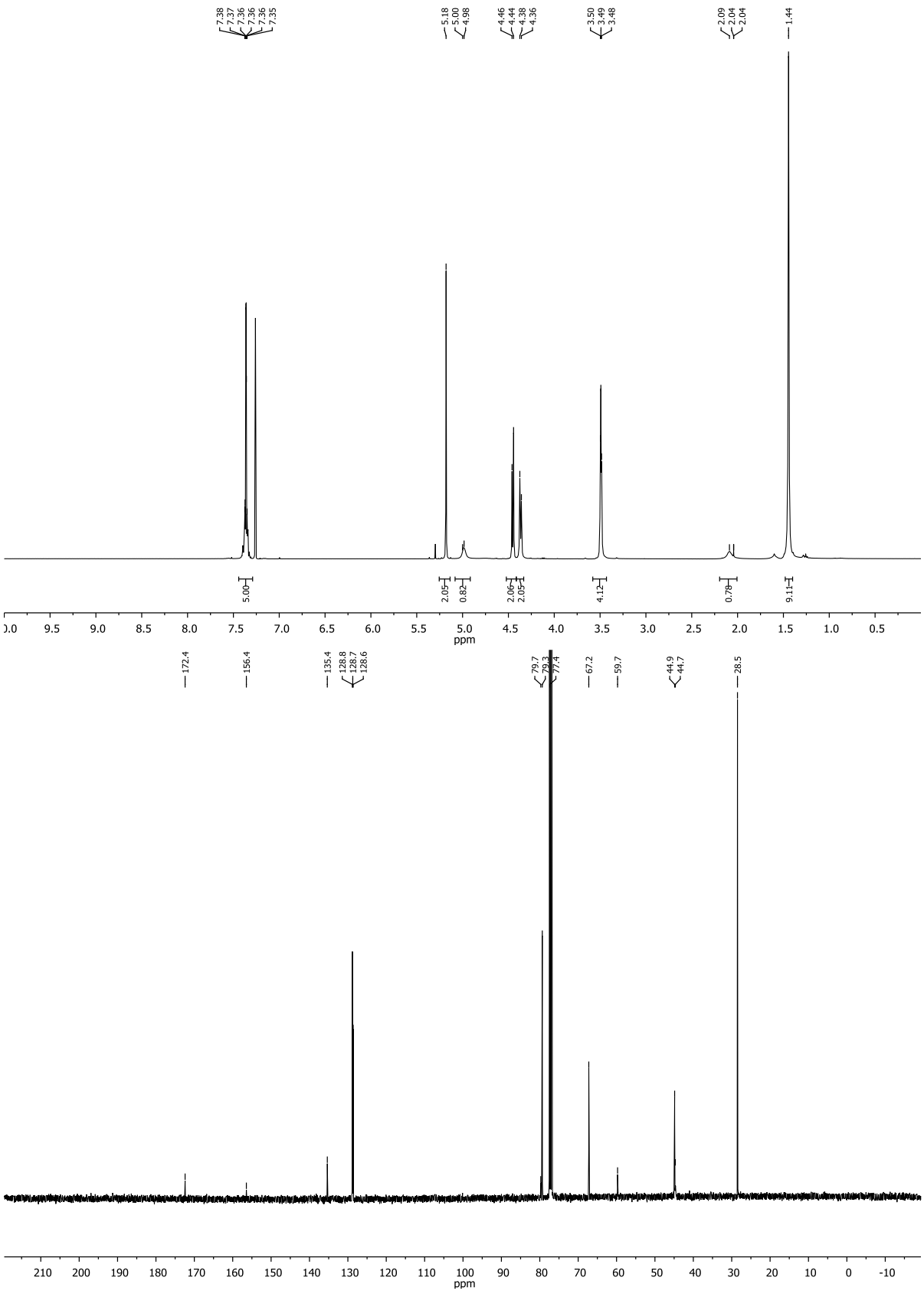


Figure 136 ^{1}H- and ^{13}C-NMR Spectra of 73c.

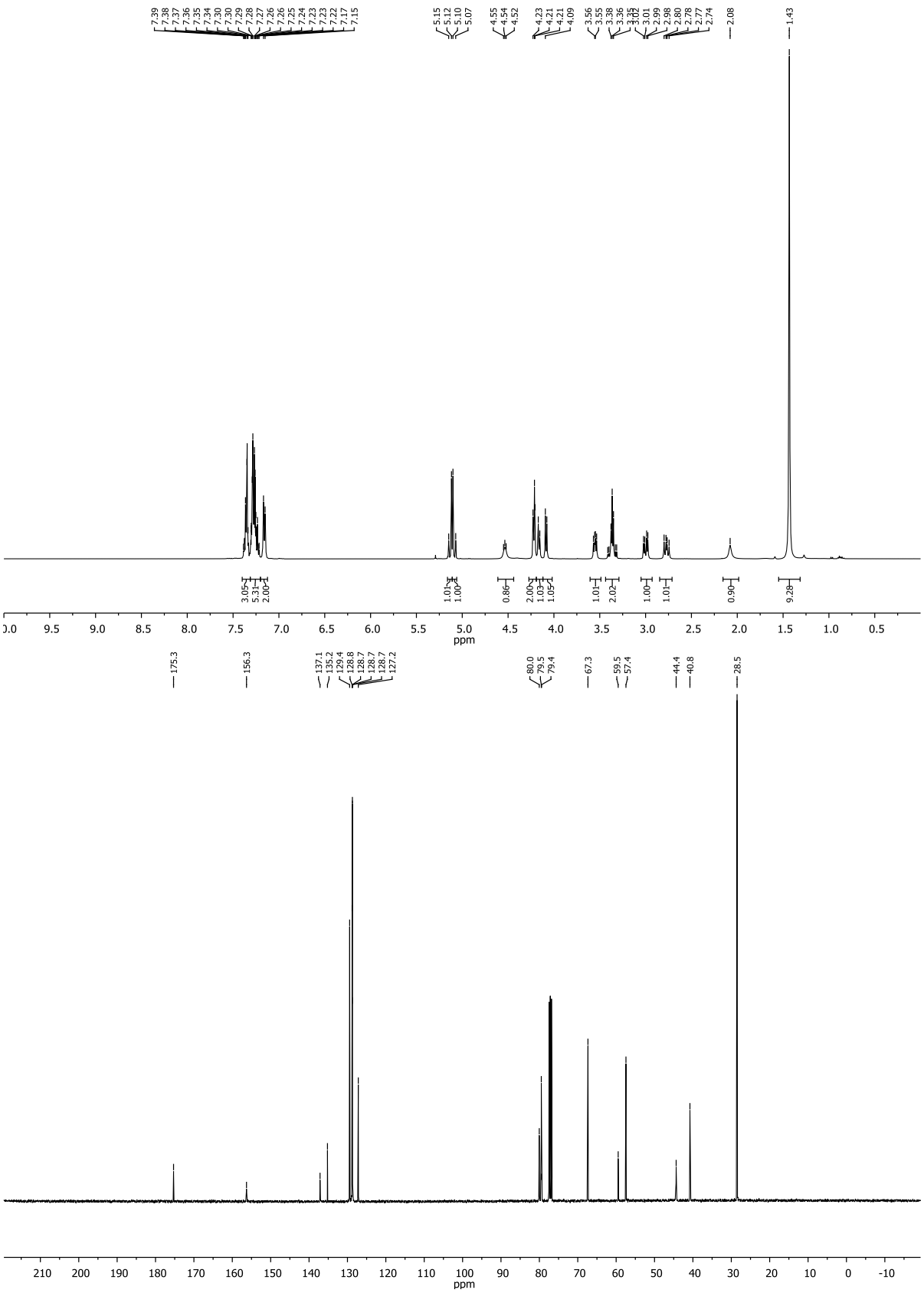


Figure 137 ^{1}H- and ^{13}C-NMR Spectra of 73d.

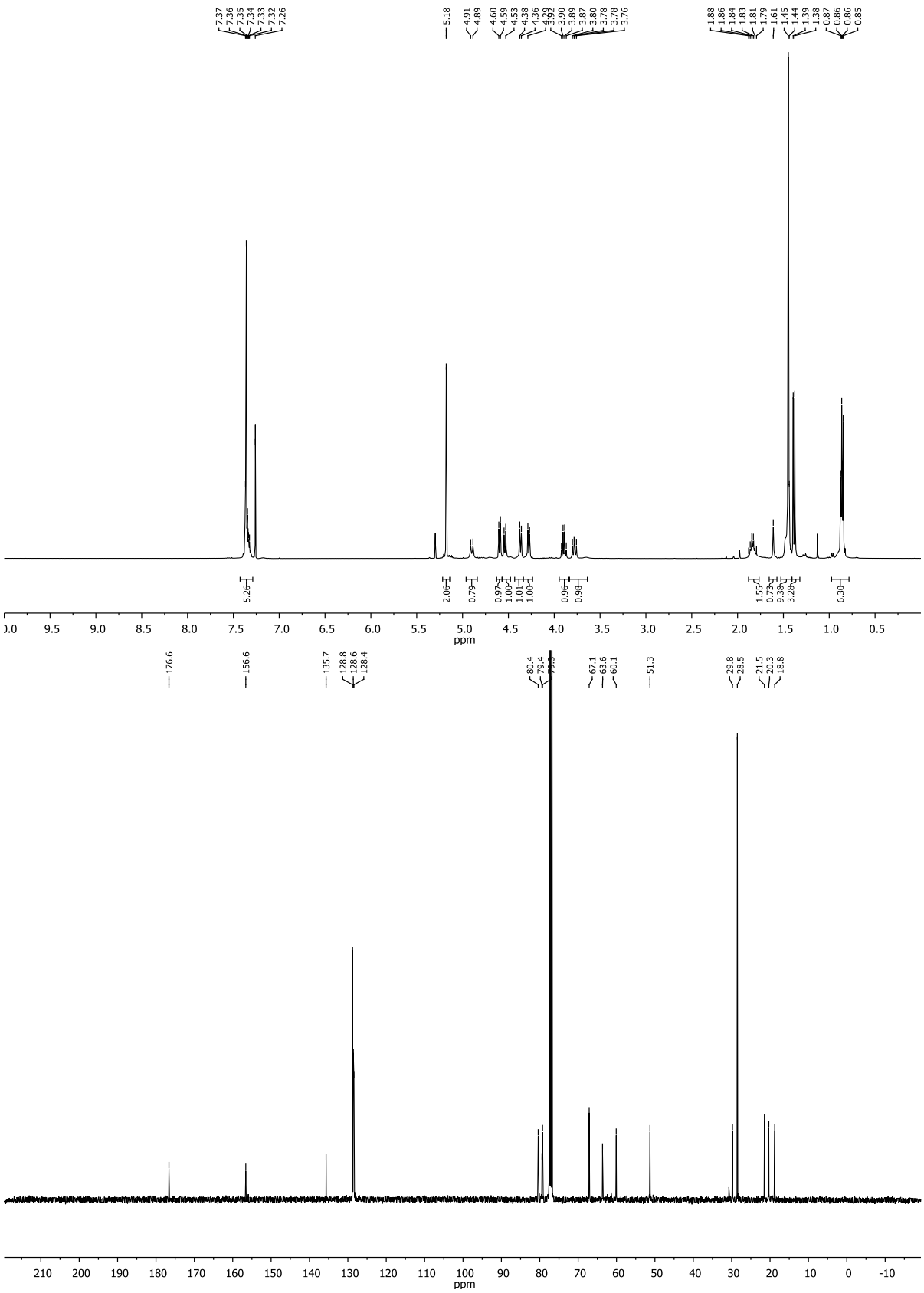


Figure 138 ^{1}H- and ^{13}C-NMR Spectra of 73e.

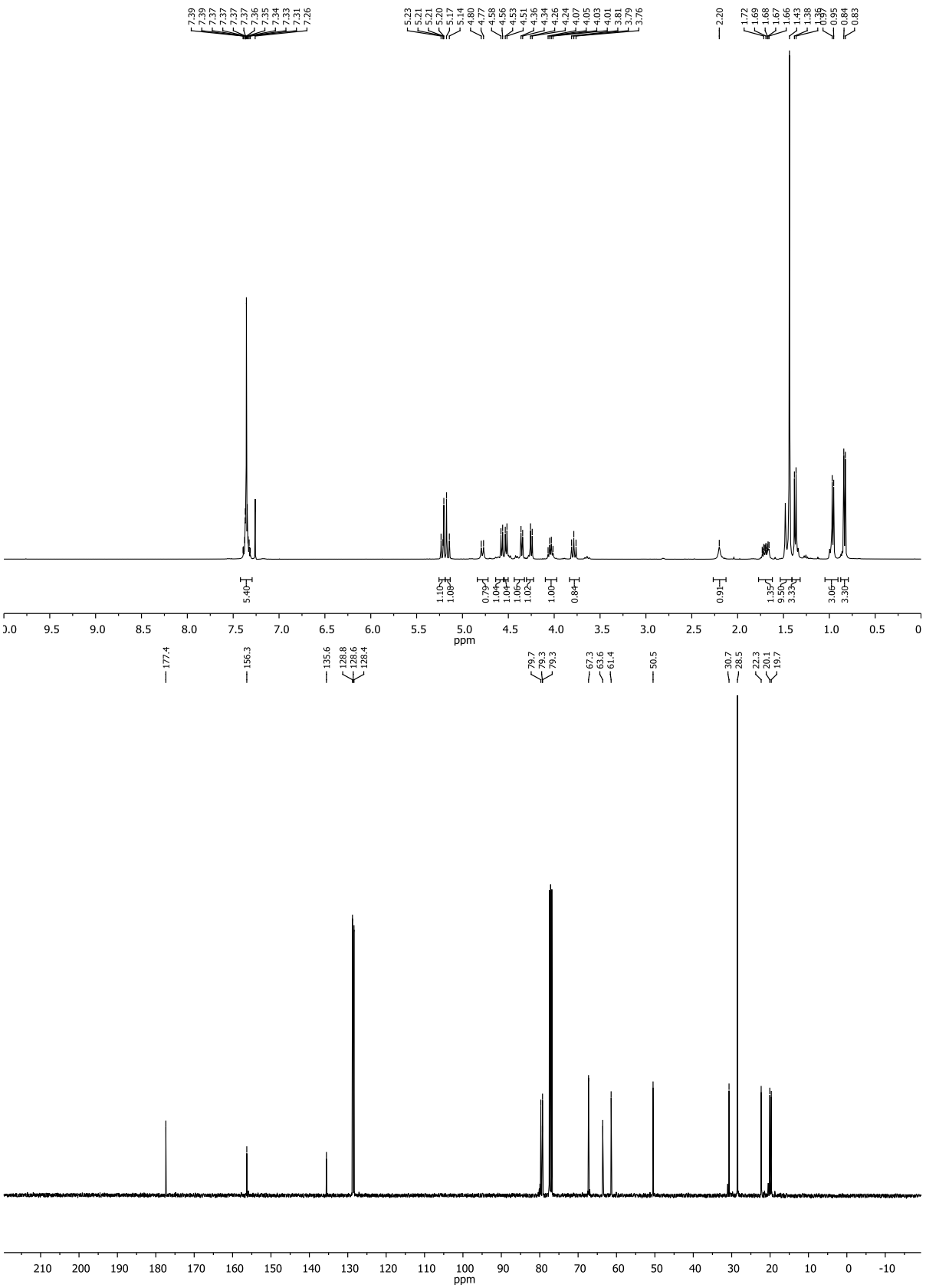


Figure 139 ^{1}H- and ^{13}C-NMR Spectra of epi-73e.

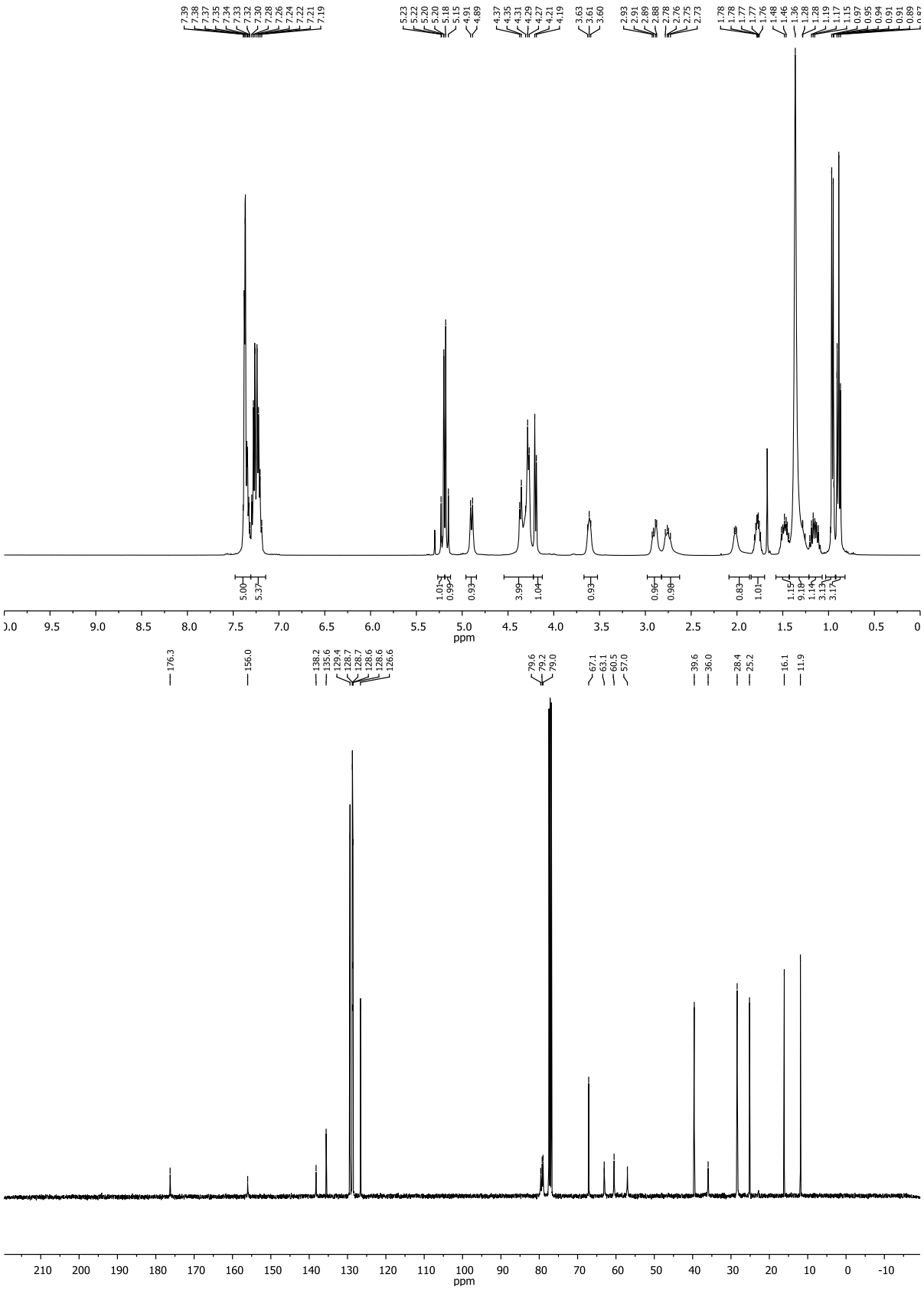


Figure 140 ^{1}H- and ^{13}C-NMR Spectra of 73f.

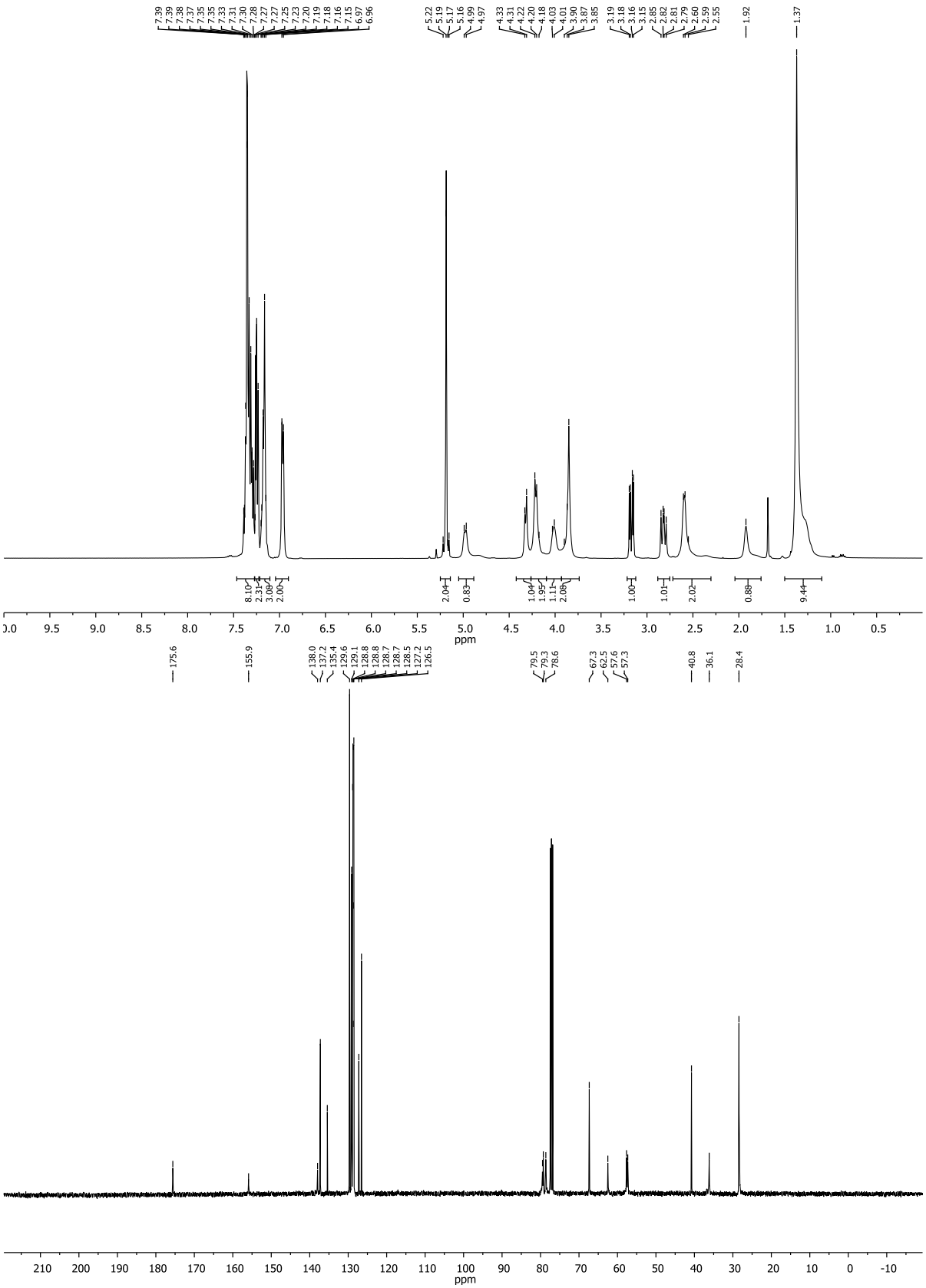


Figure 141 ^{1}H- and ^{13}C-NMR Spectra of 73g.

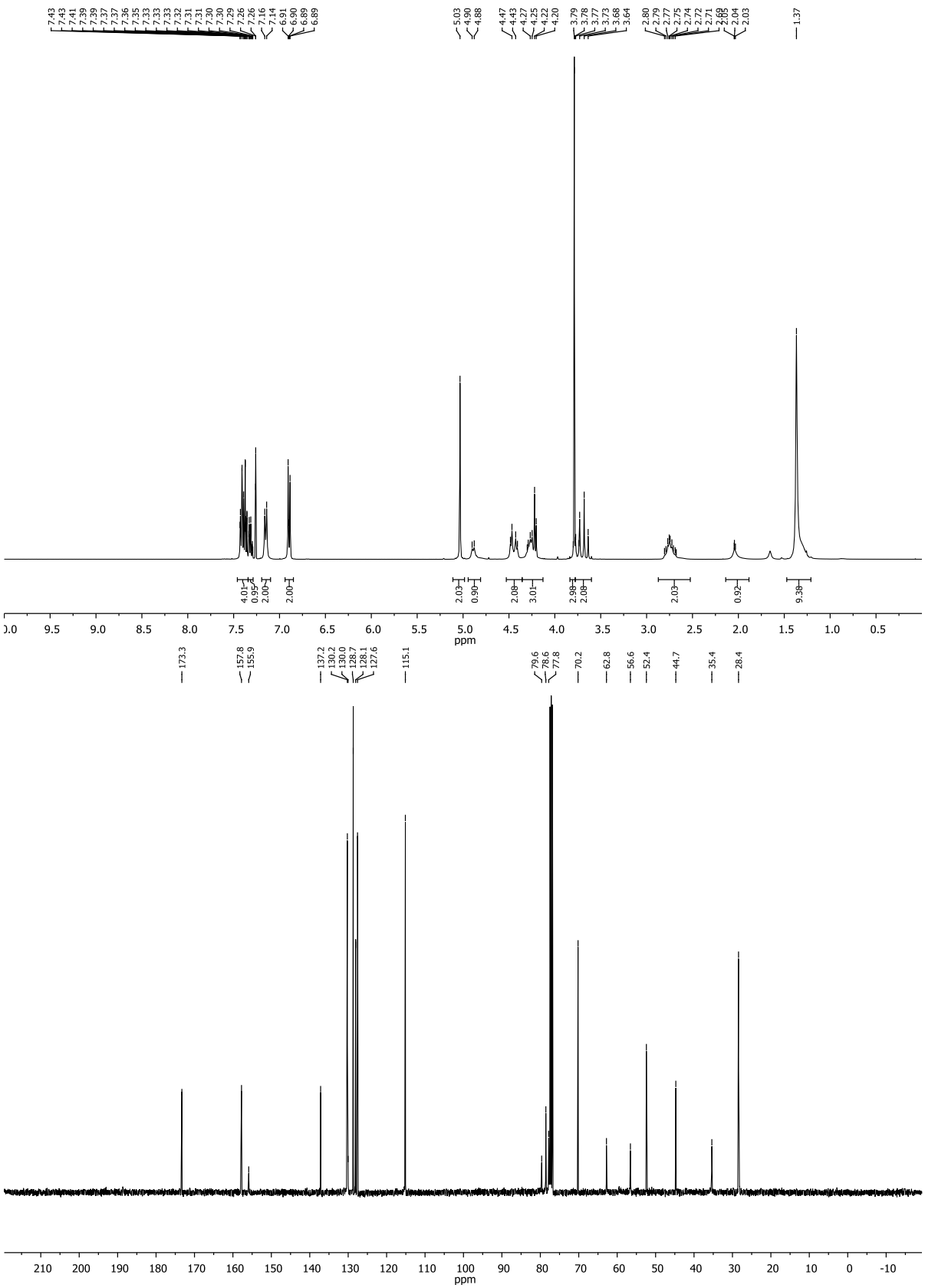


Figure 142 ^{1}H- and ^{13}C-NMR Spectra of 73h.

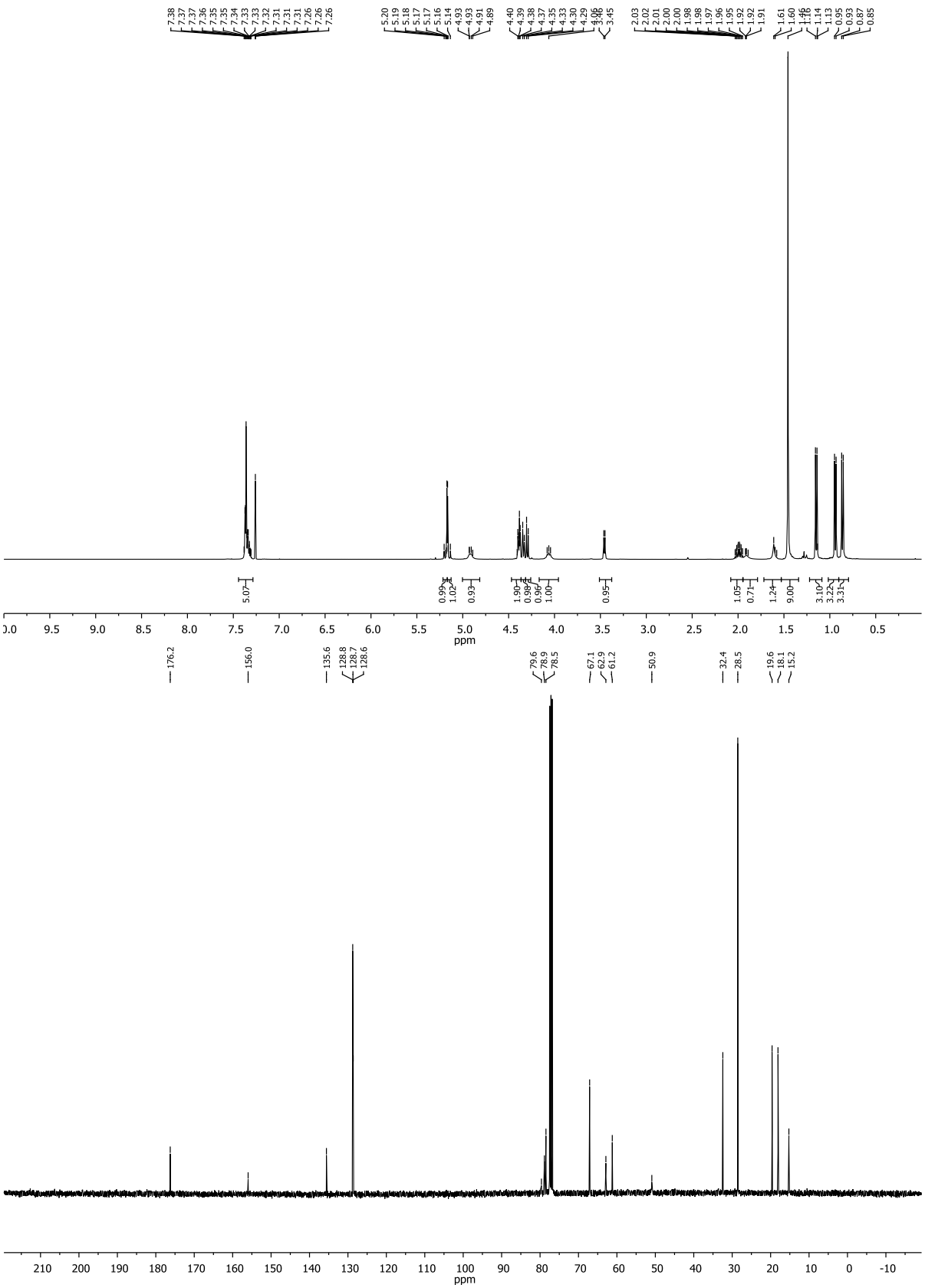


Figure 143 ^{1}H- and ^{13}C-NMR Spectra of 73i.

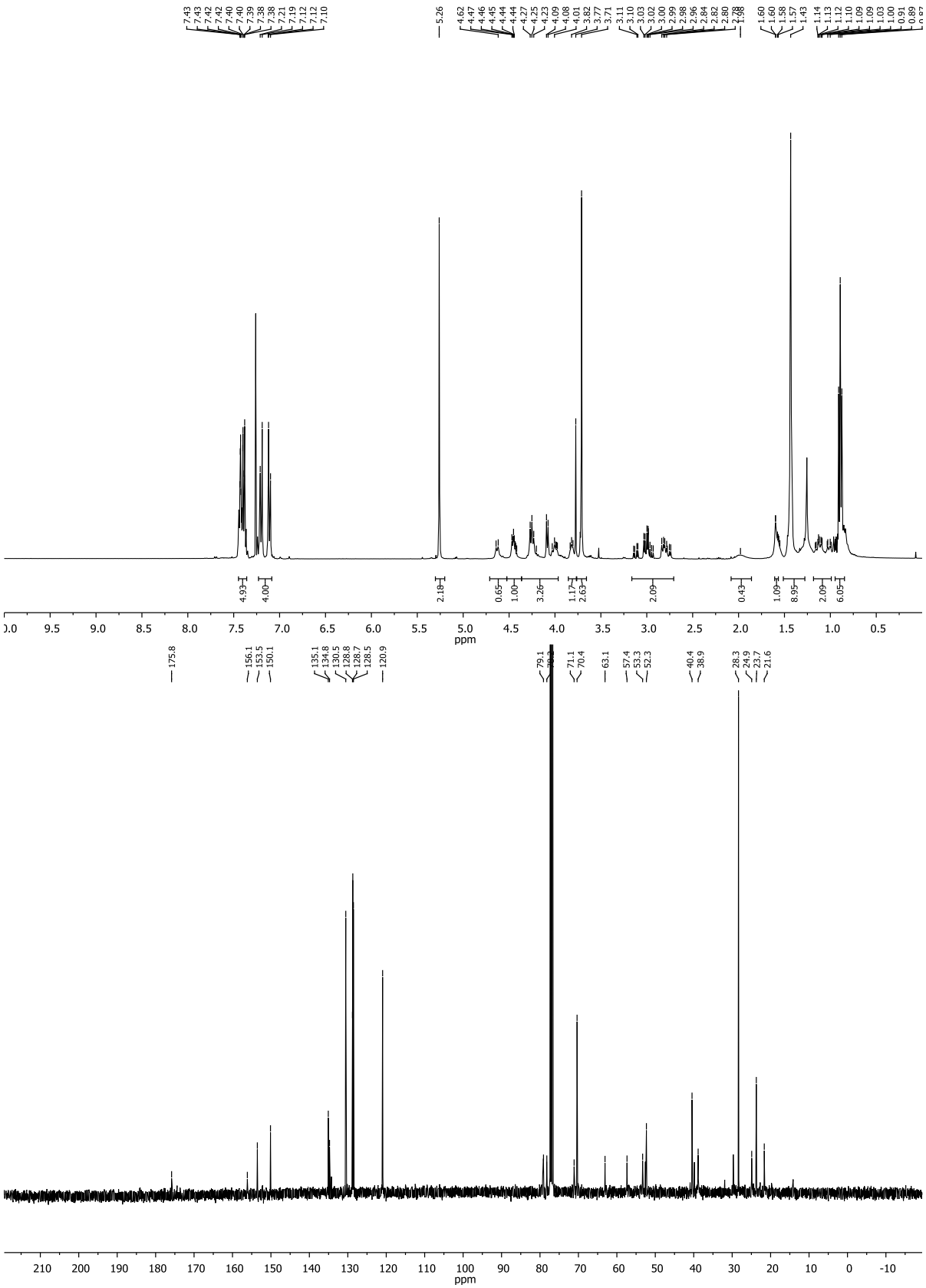


Figure 144 ^{1}H- and ^{13}C-NMR Spectra of 73j.

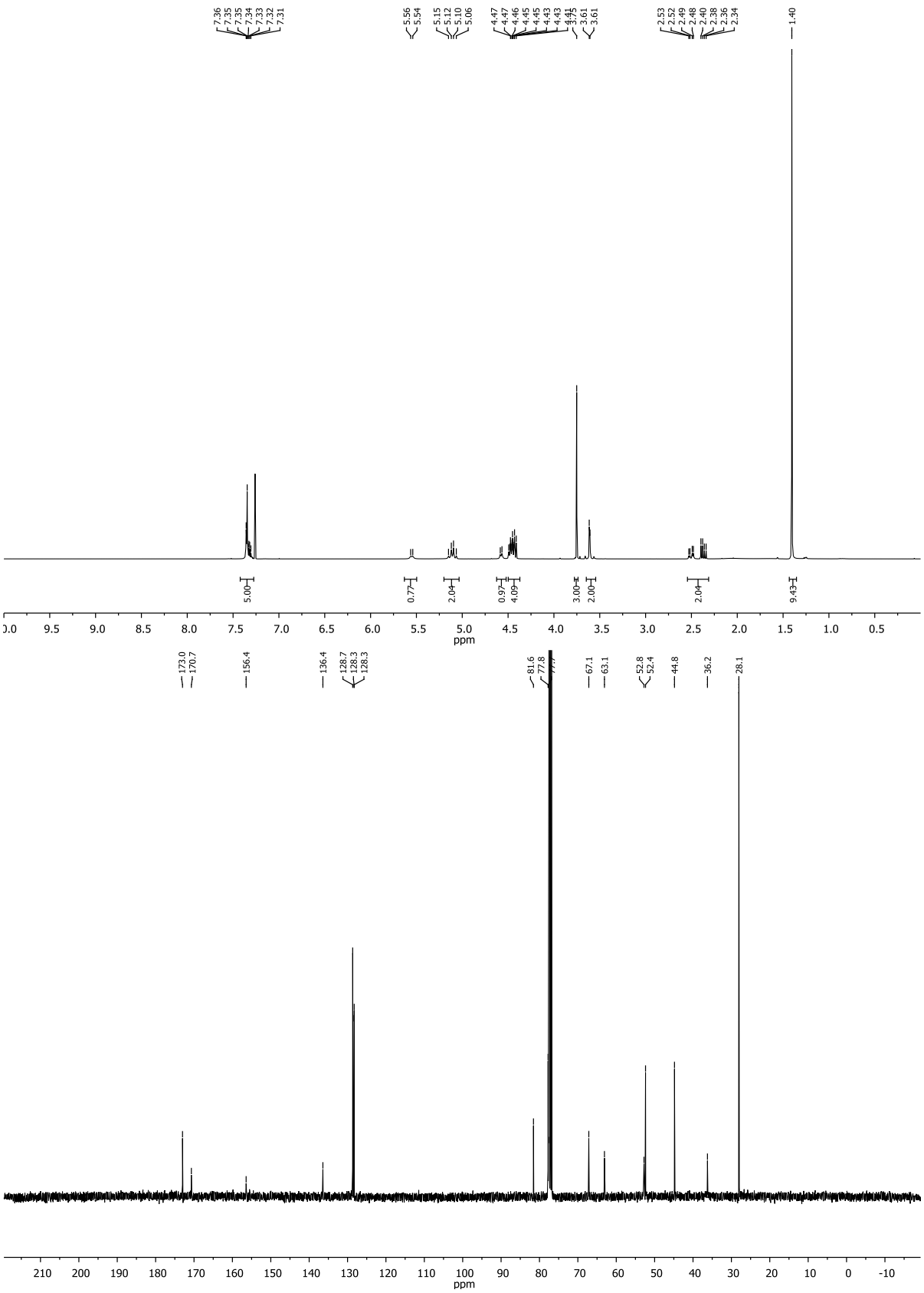


Figure 145 ^{1}H- and ^{13}C-NMR Spectra of 73k.

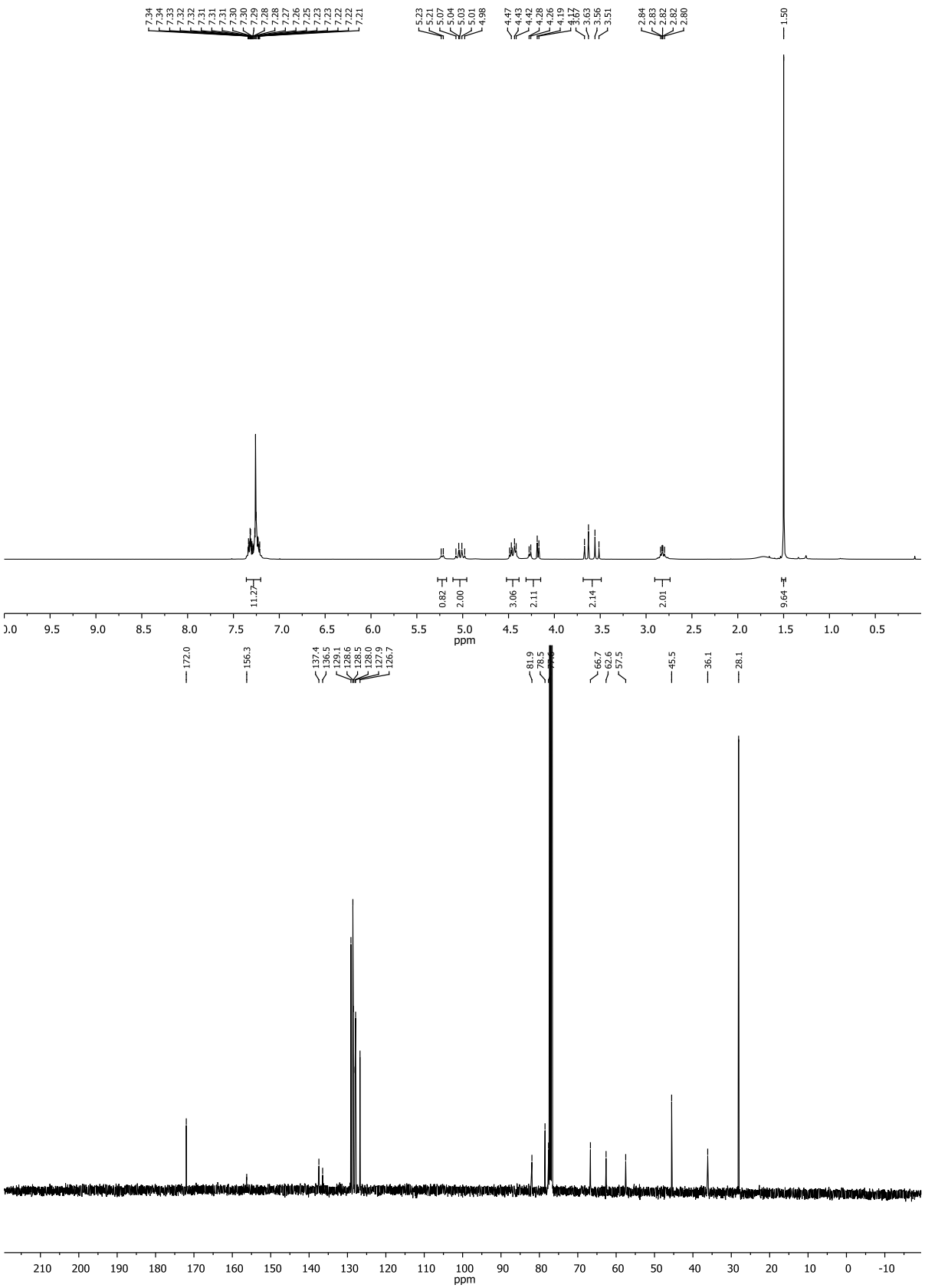


Figure 146 ^{1}H- and ^{13}C-NMR Spectra of 73l.

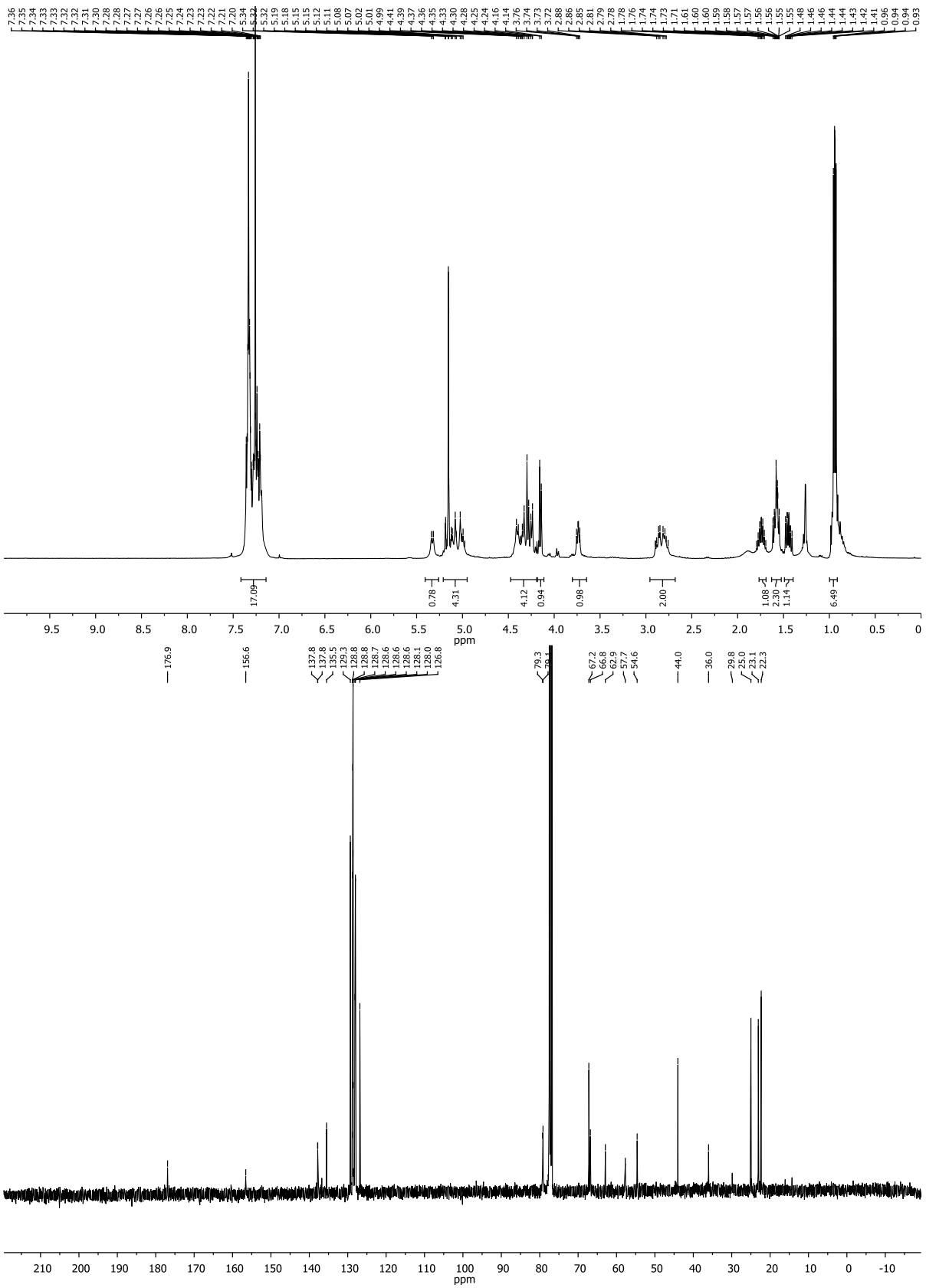


Figure 147 ^{1}H- and ^{13}C-NMR Spectra of 73m.

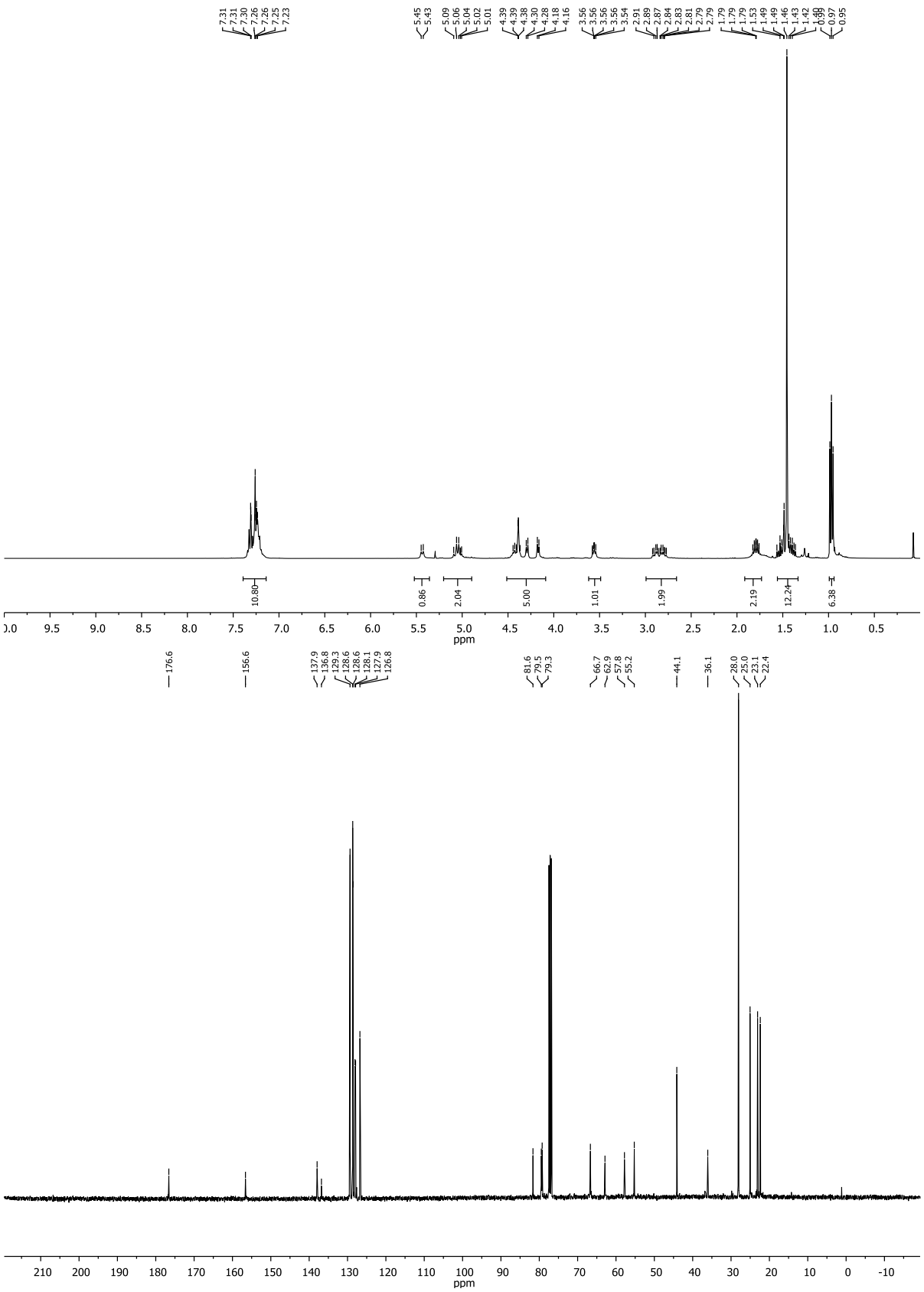


Figure 148 ^{1}H- and ^{13}C-NMR Spectra of 73n.

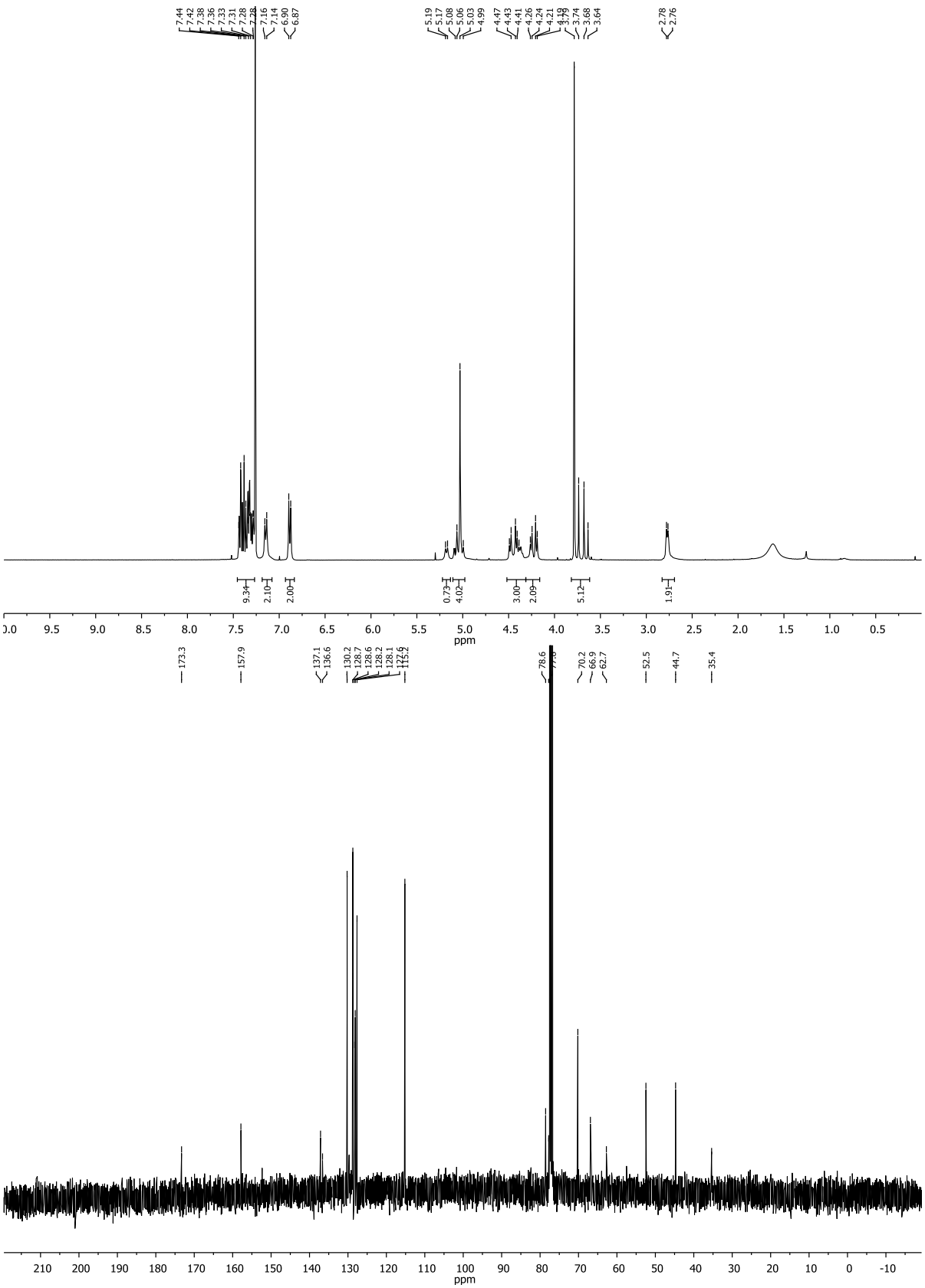


Figure 149 ^{1}H- and ^{13}C-NMR Spectra of 73o.

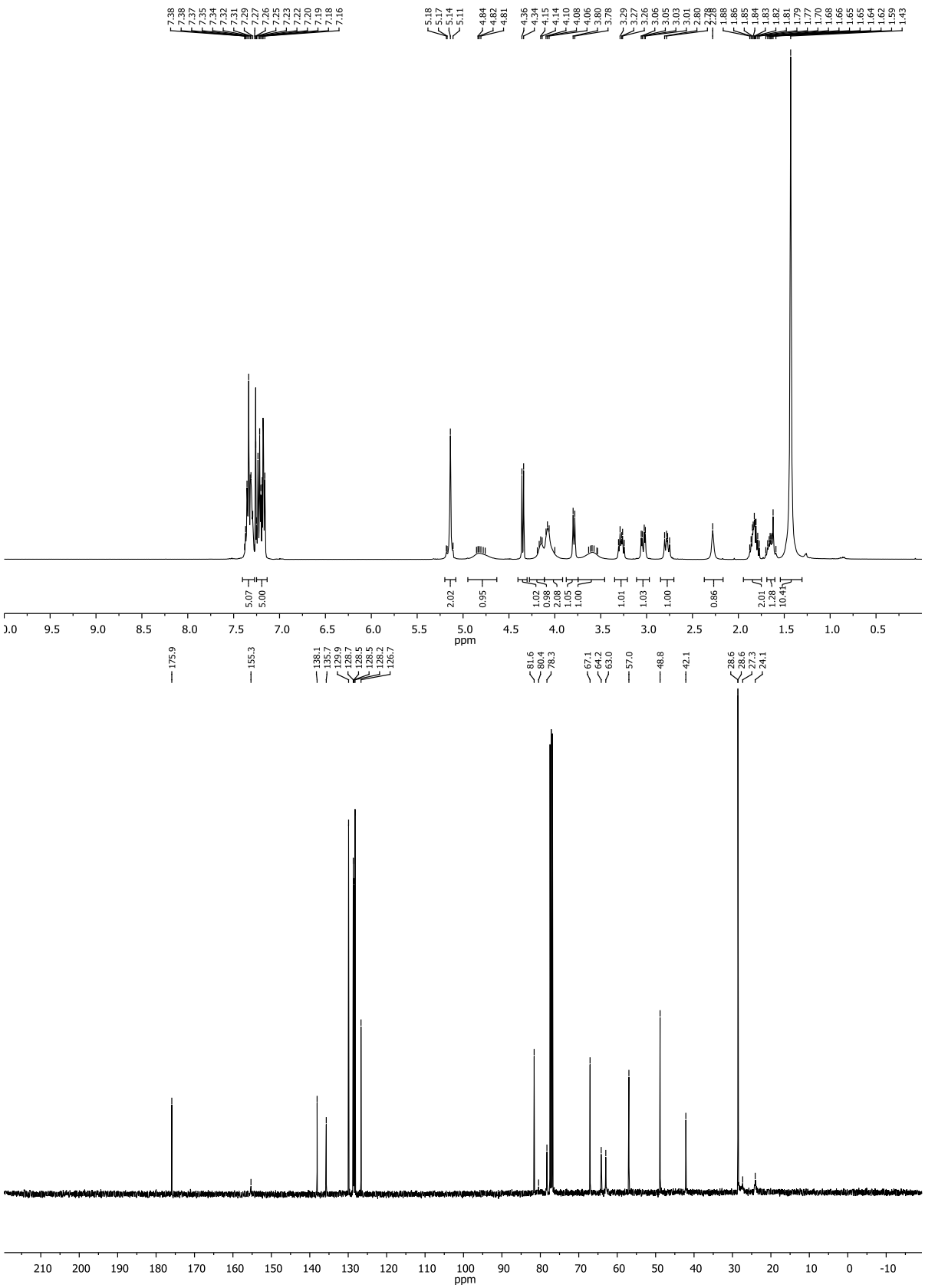


Figure 150 ^{1}H- and ^{13}C-NMR Spectra of 73p.

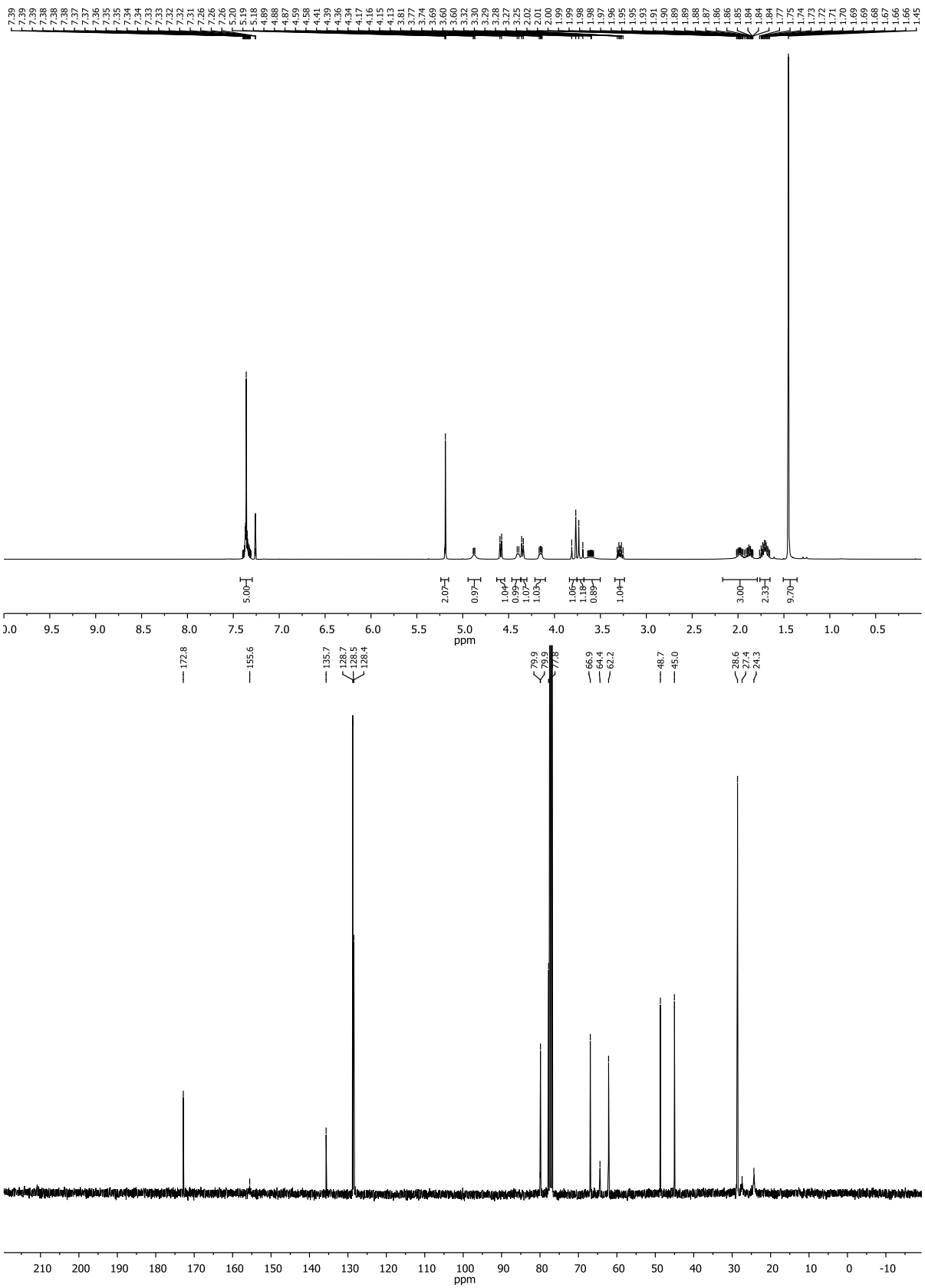


Figure 151 ^{1}H- and ^{13}C-NMR Spectra of 73q.

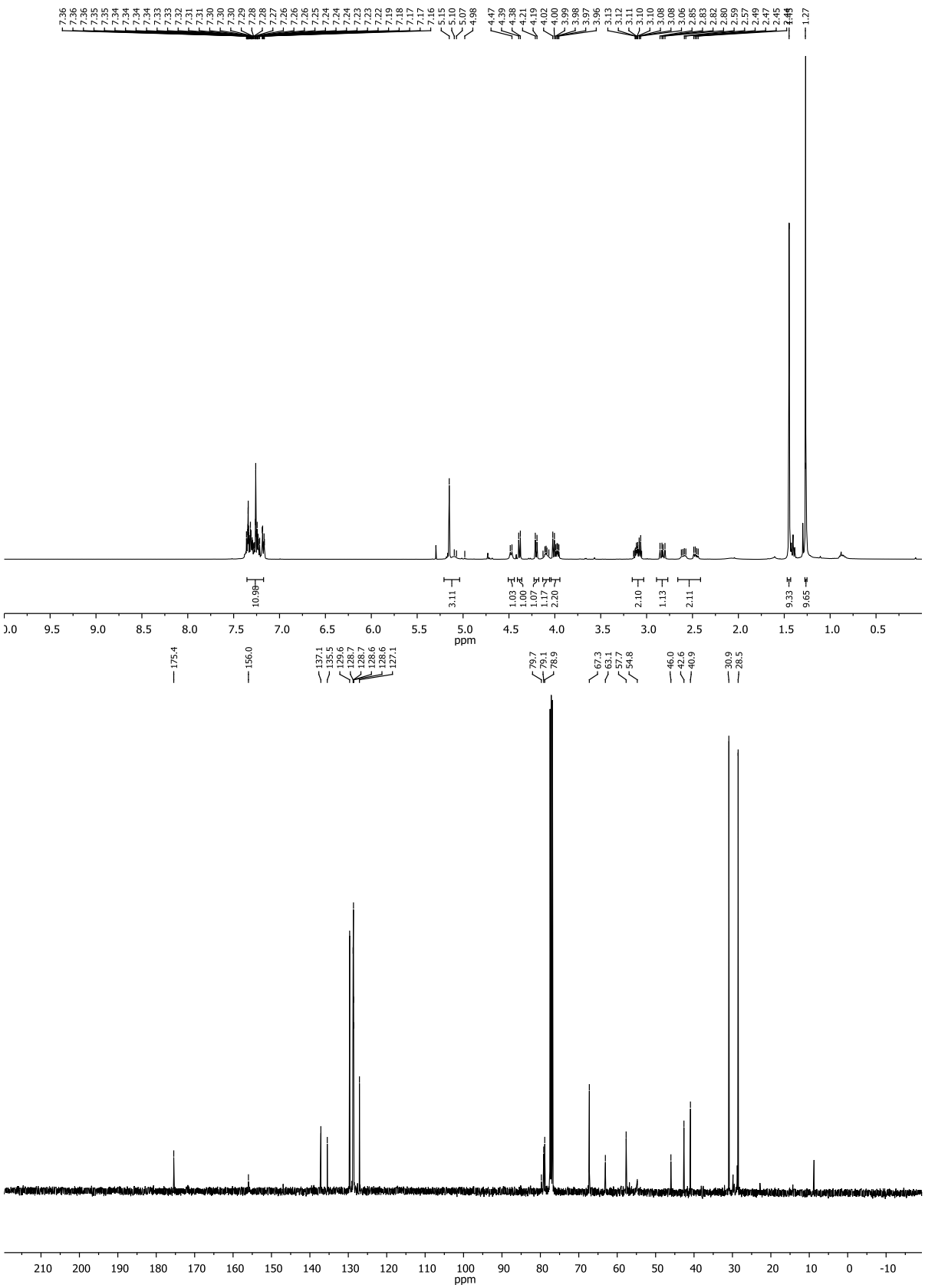


Figure 152 ^{1}H- and ^{13}C-NMR Spectra of 73r.

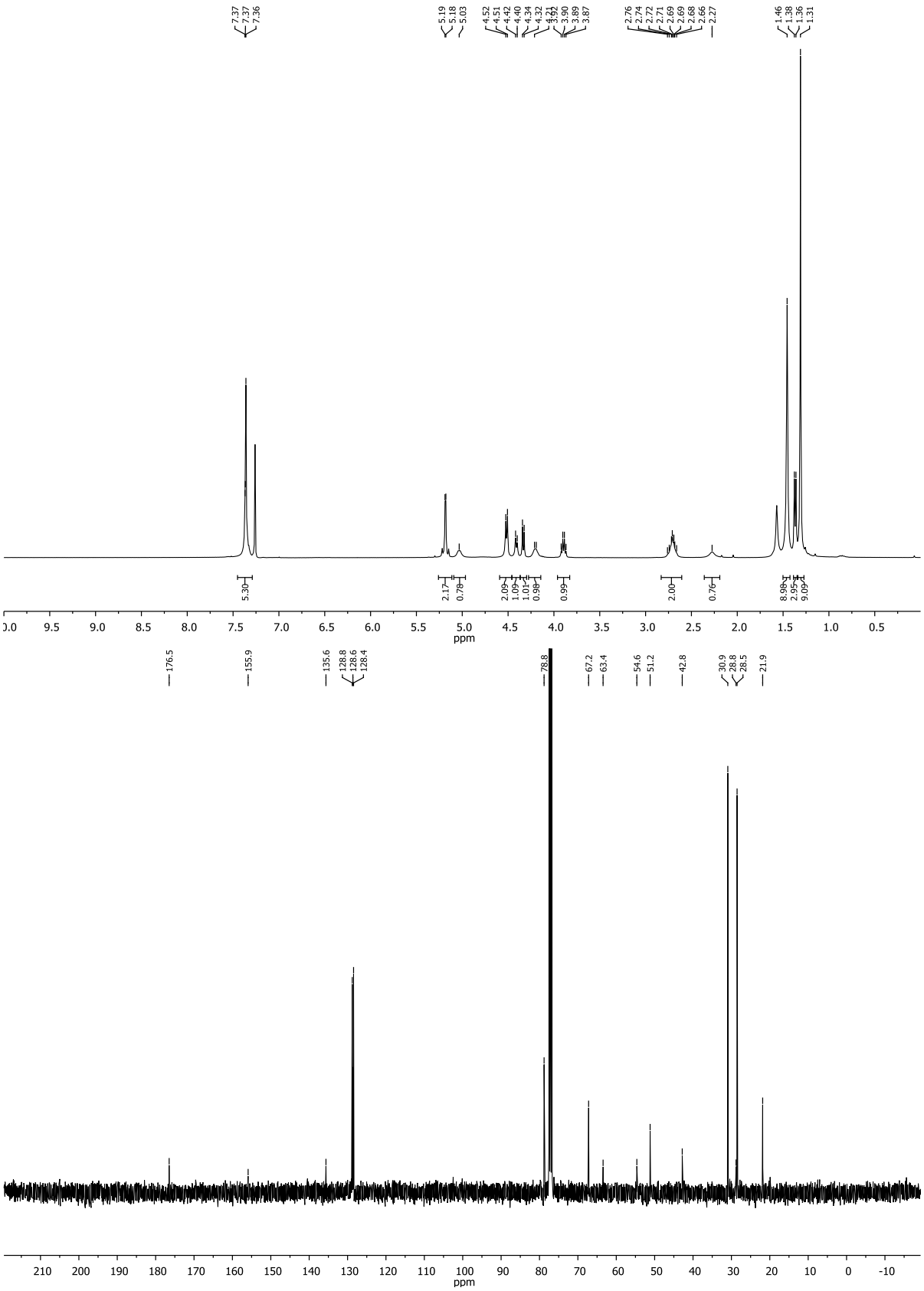


Figure 153 ^{1}H- and ^{13}C-NMR Spectra of *epi*-73v.

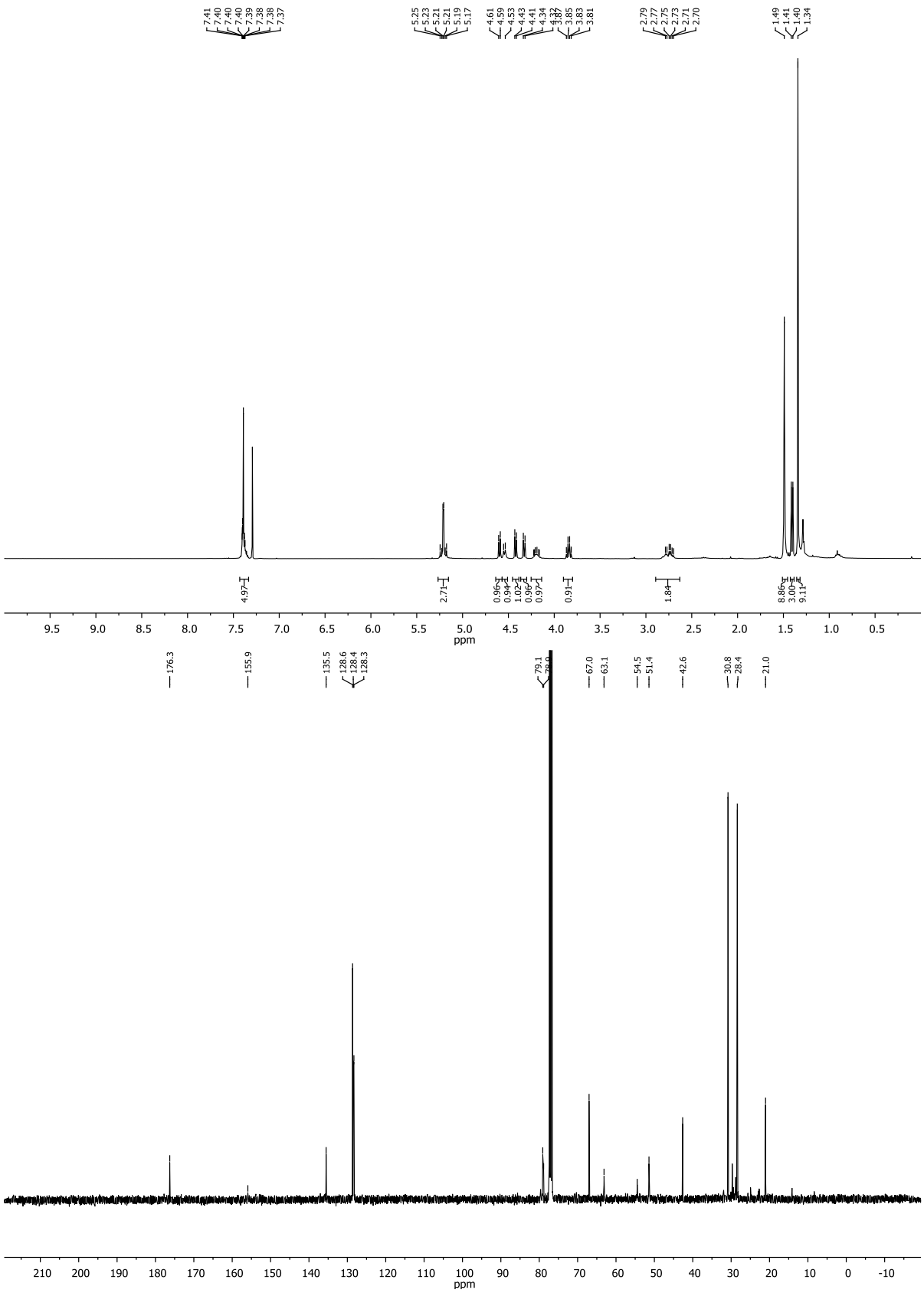


Figure 154 ^{1}H- and ^{13}C-NMR Spectra of 73v.

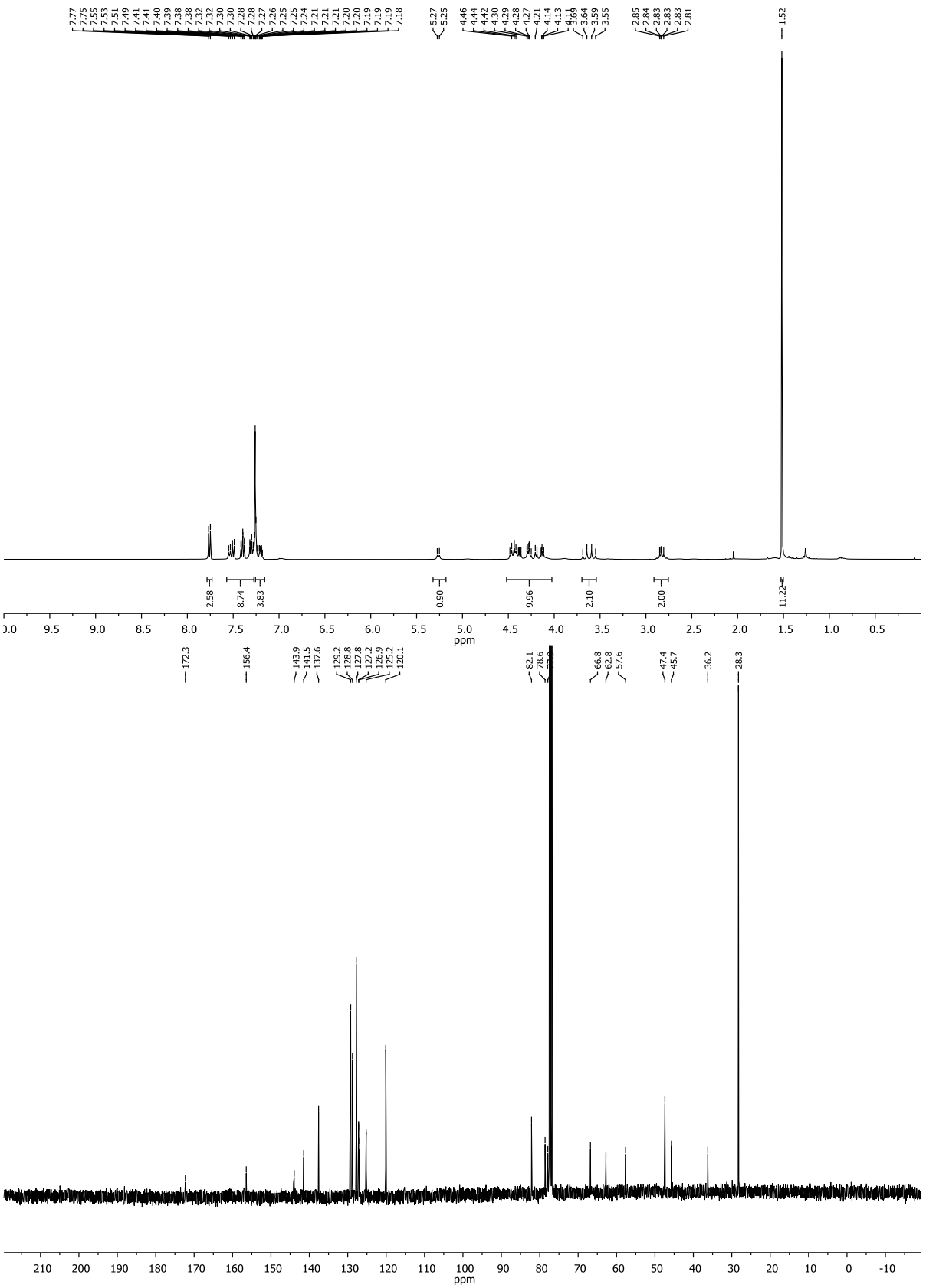


Figure 155 ^{1}H- and ^{13}C-NMR Spectra of 73w.

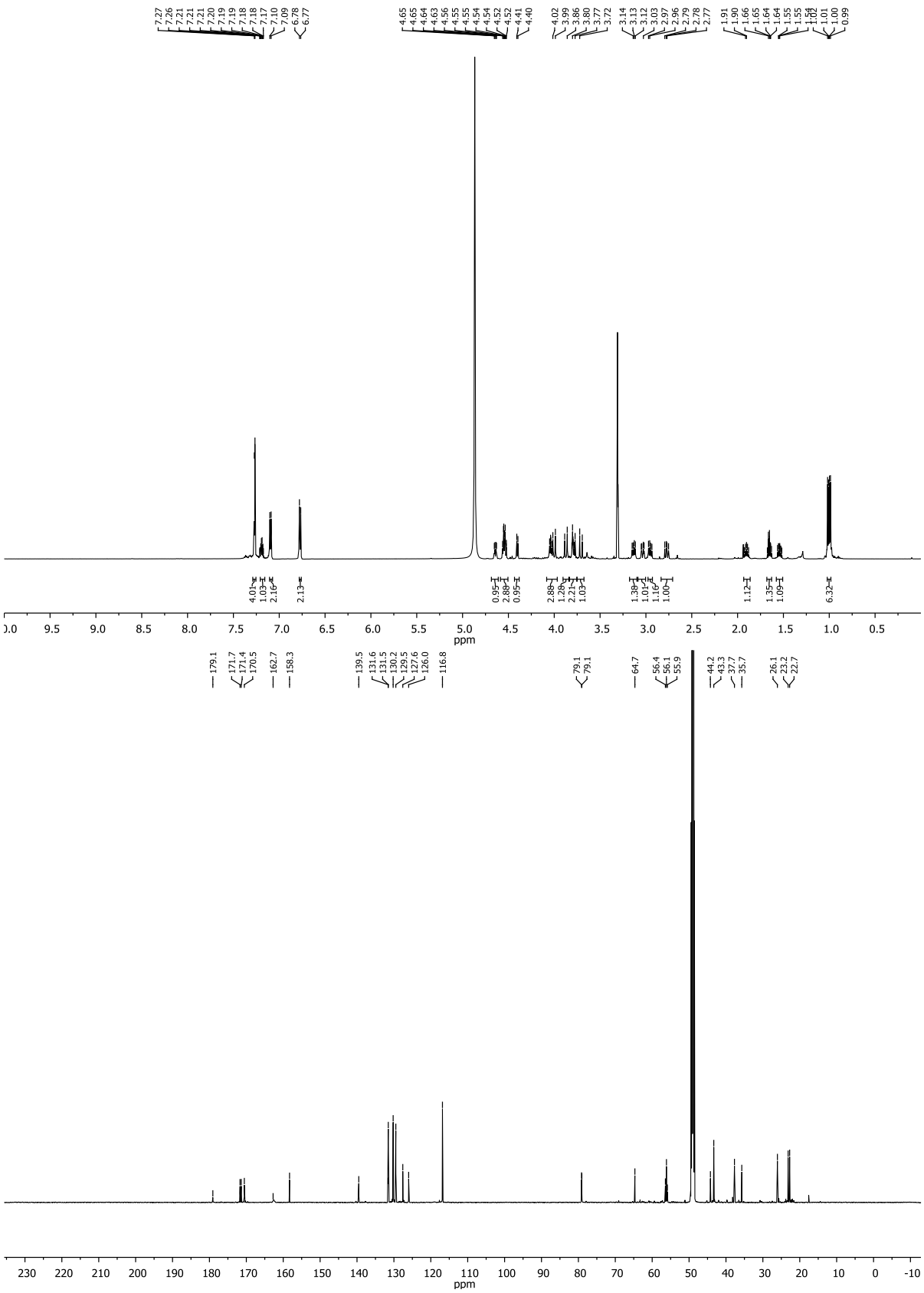
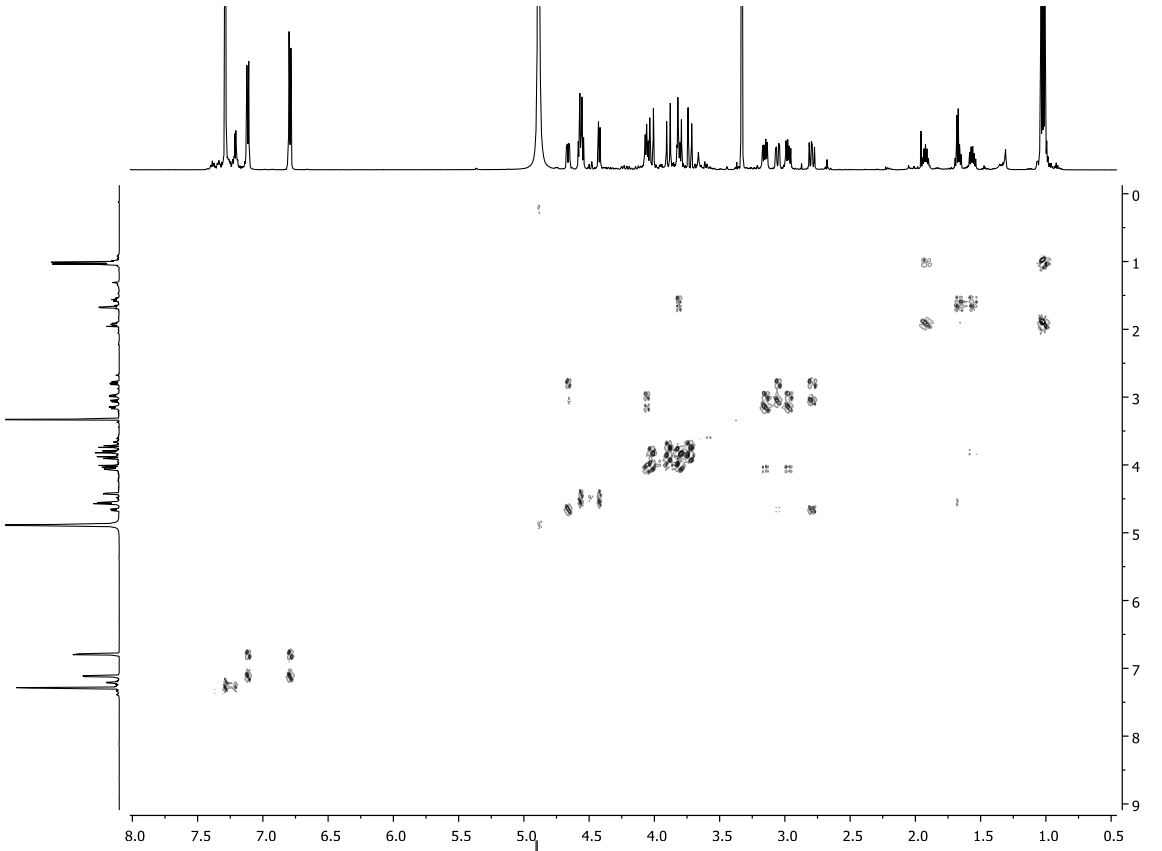


Figure 156 ^{1}H- and ^{13}C-NMR Spectra of 247e.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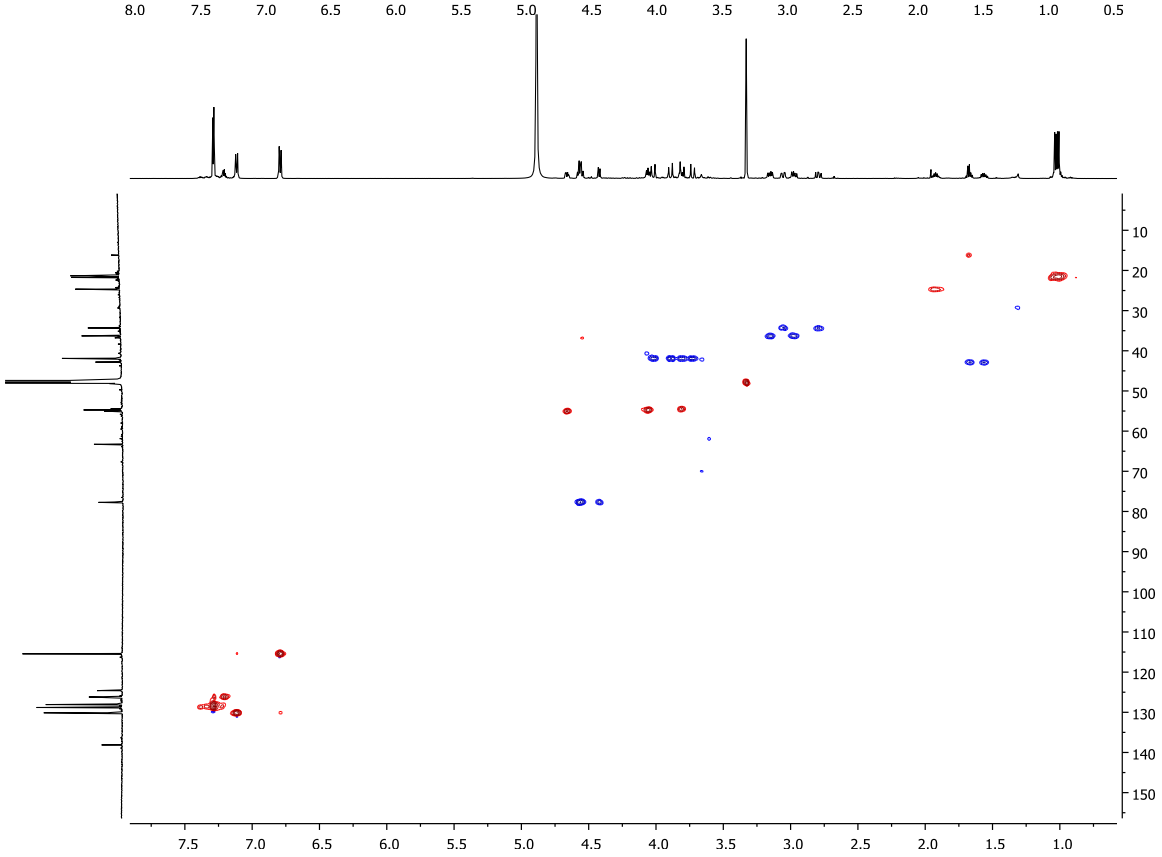
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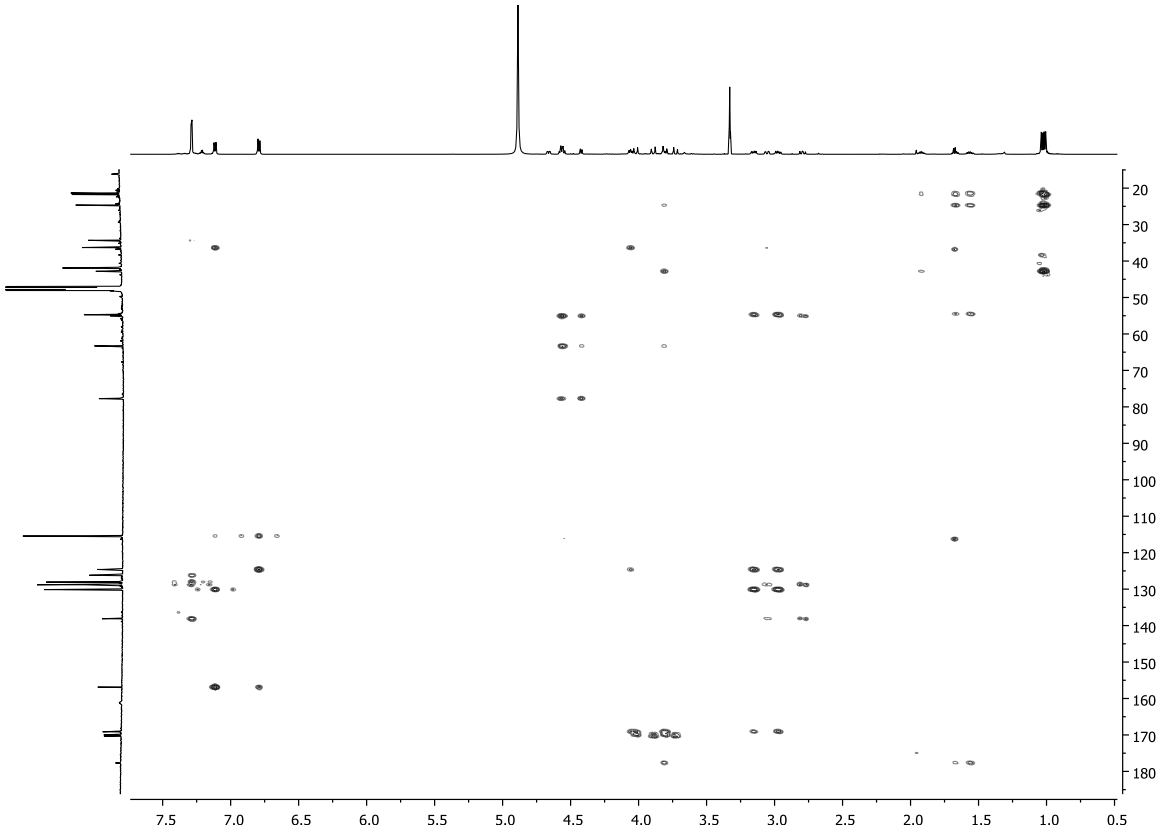


Figure 157 COSY, HSQC, HMBC Spectra of 247e.

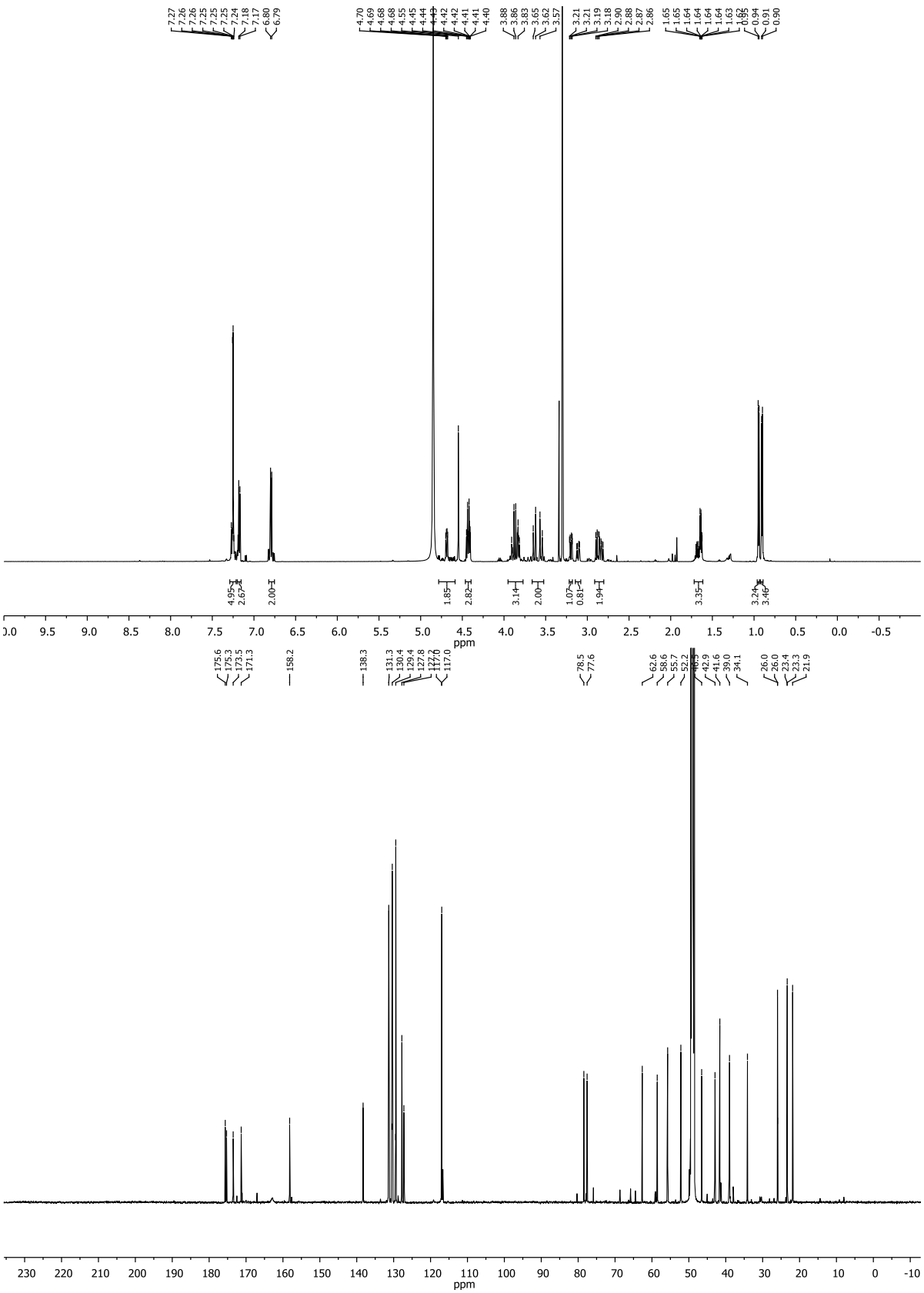
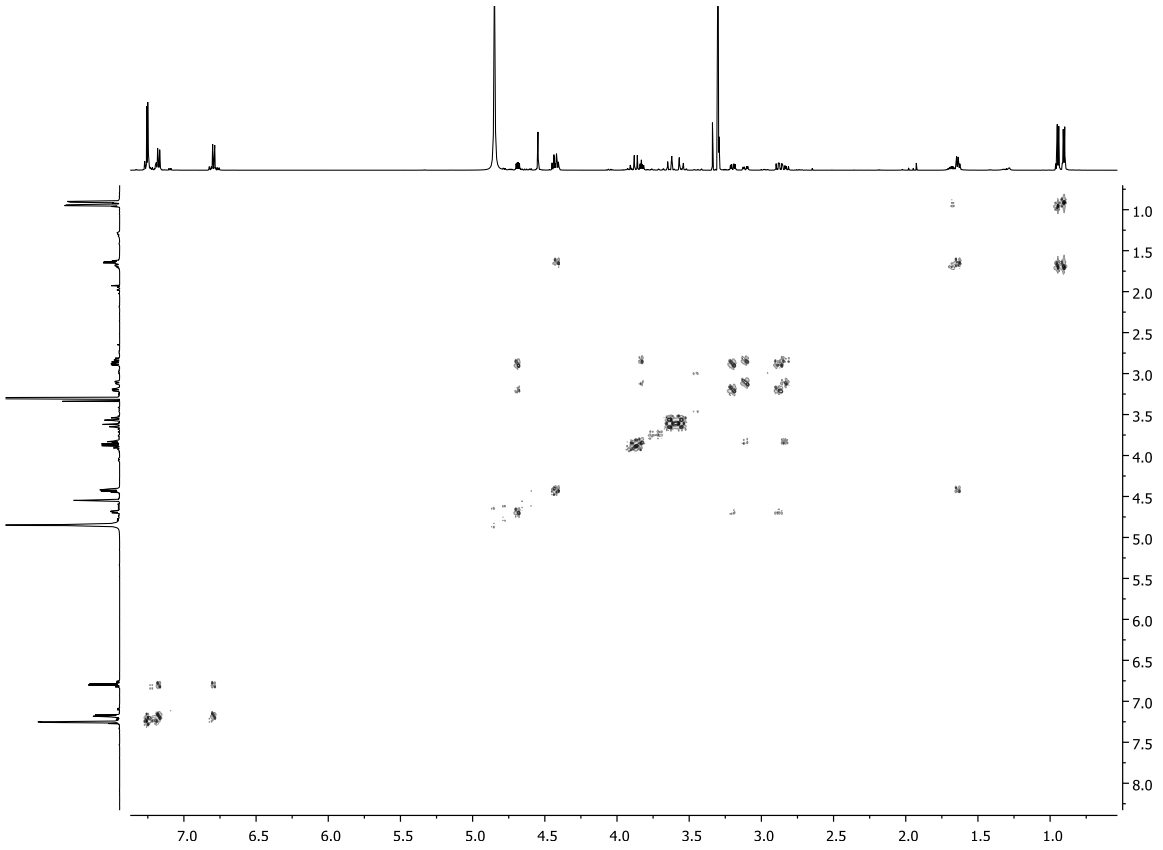


Figure 158 ^{1}H- and ^{13}C-NMR Spectra of 247b.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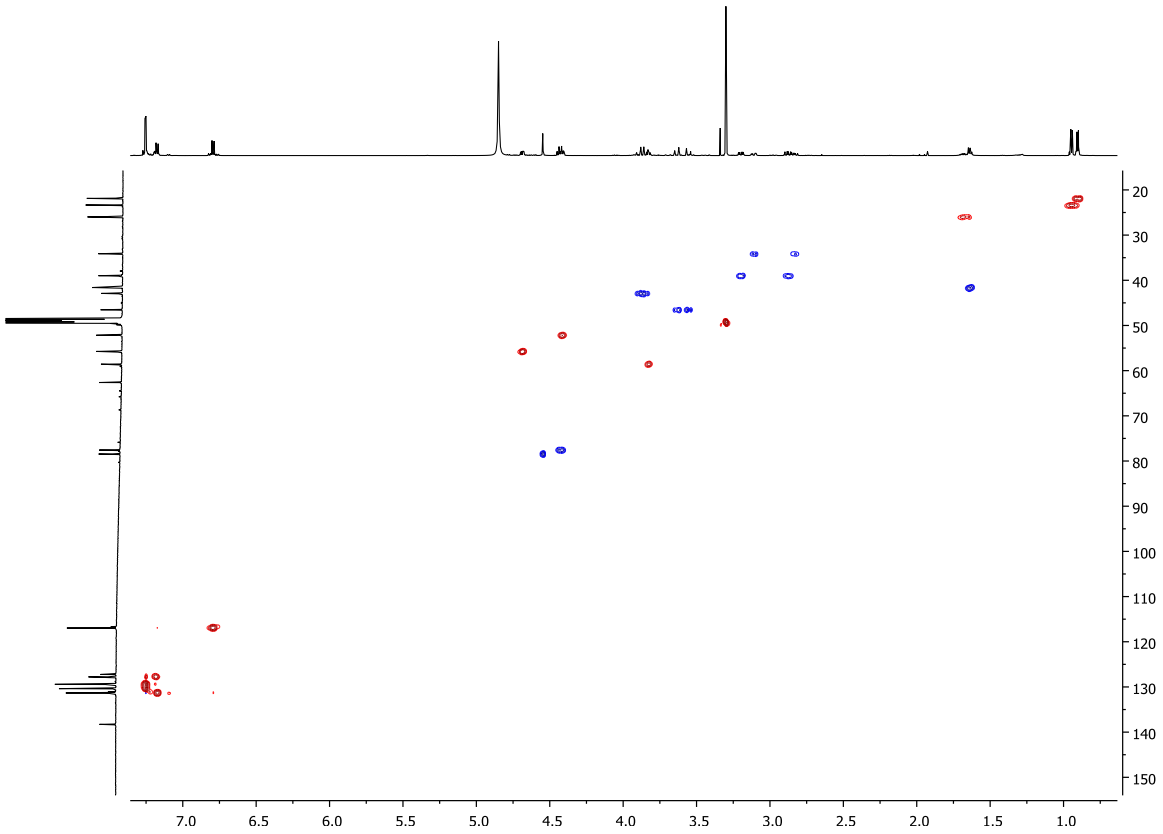
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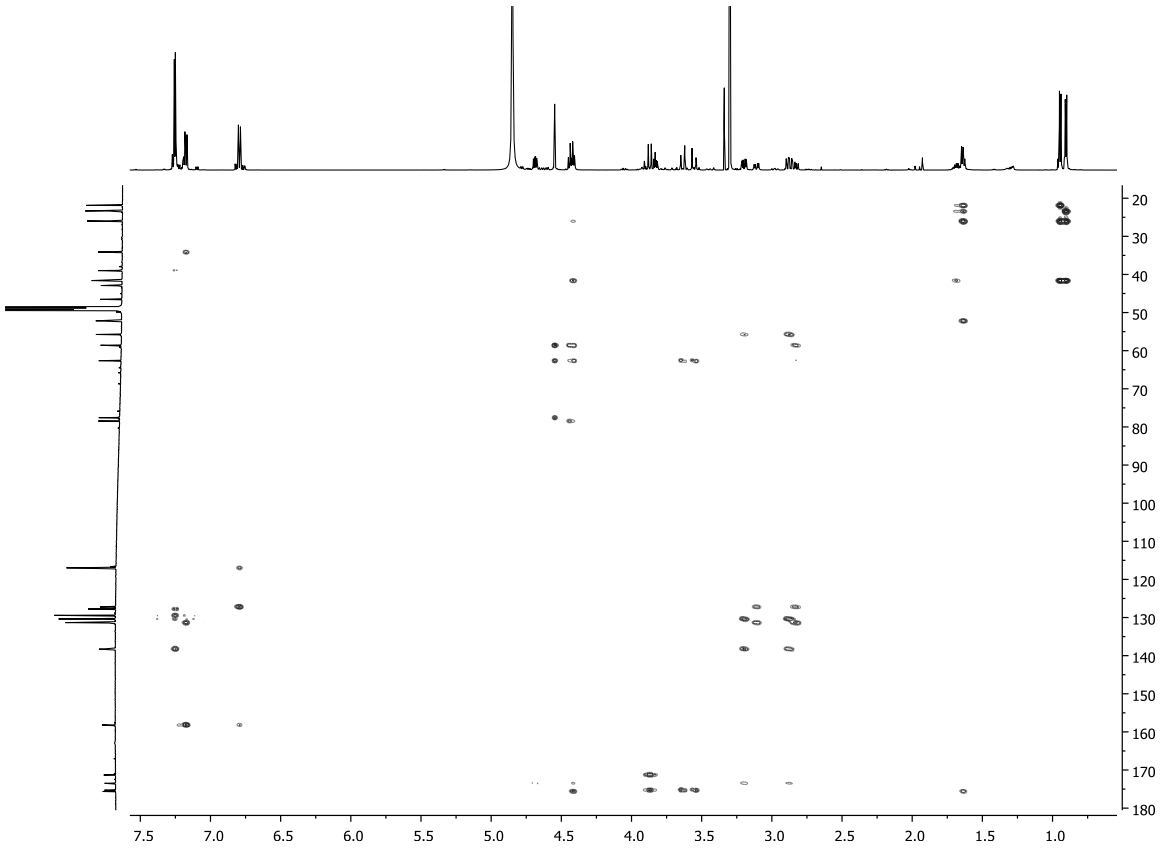


Figure 159 COSY, HSQC, HMBC Spectra of 247b.

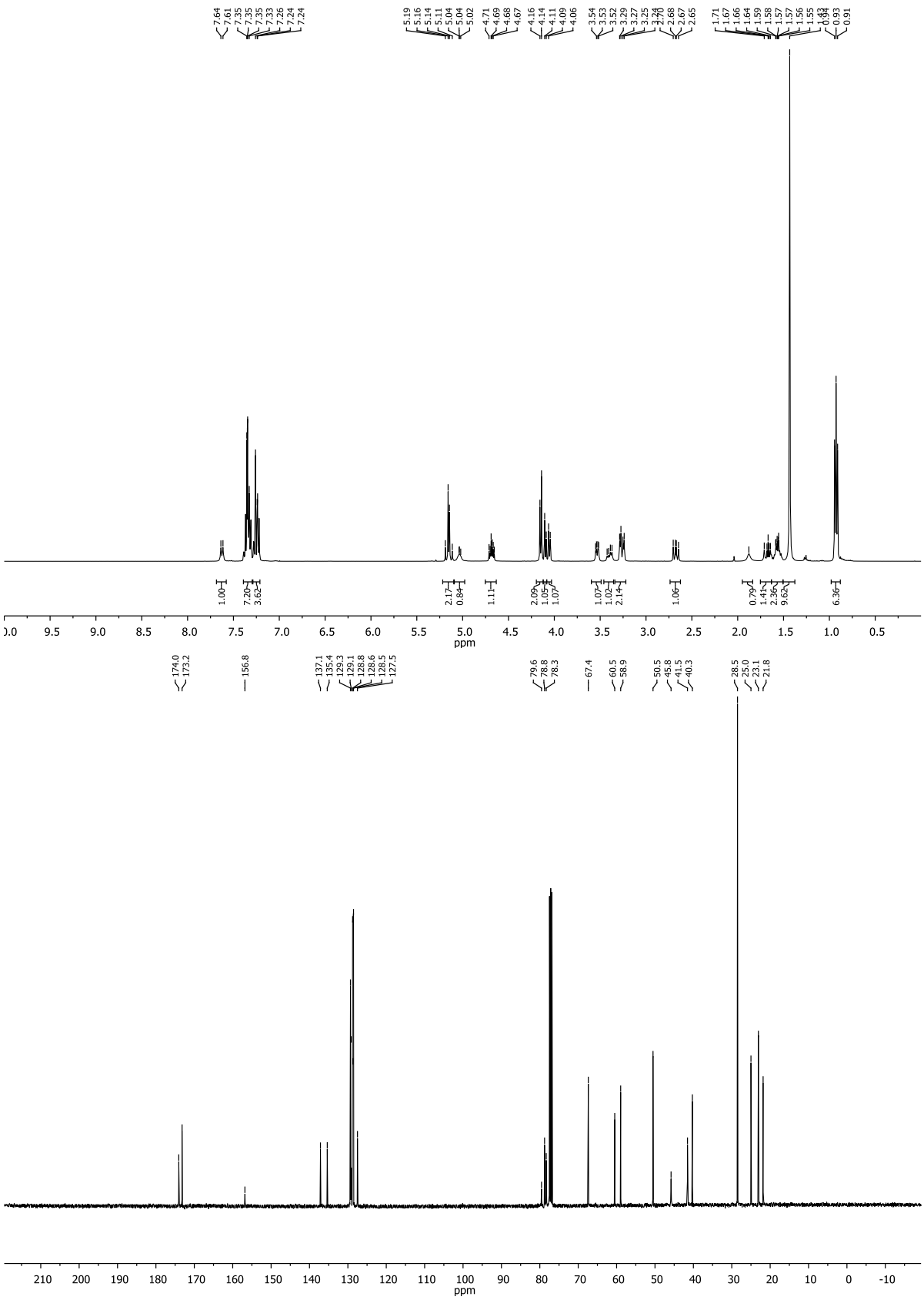


Figure 160 ^{1}H- and ^{13}C-NMR Spectra of 250.

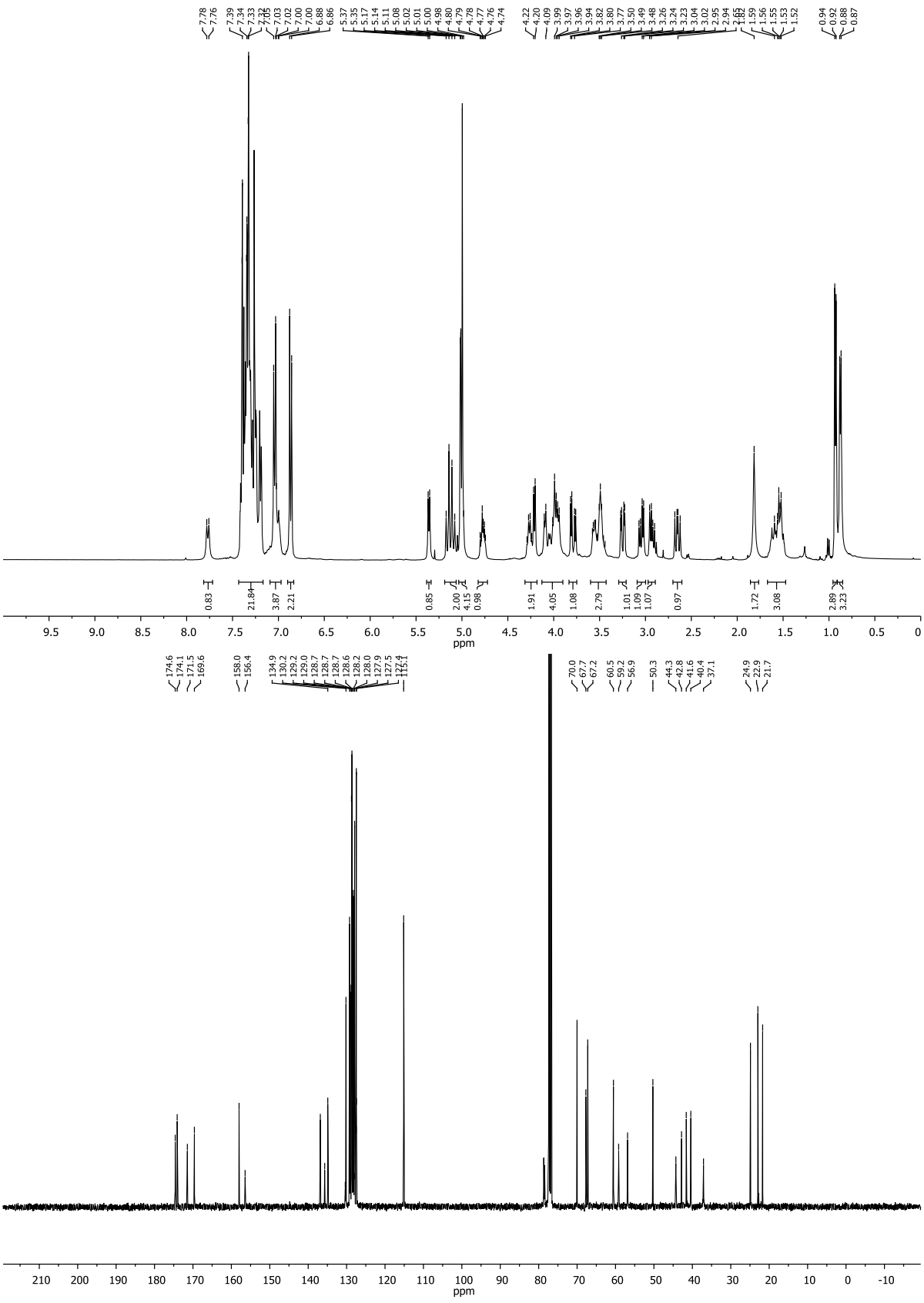


Figure 161 ^{1}H- and ^{13}C-NMR Spectra of 251.

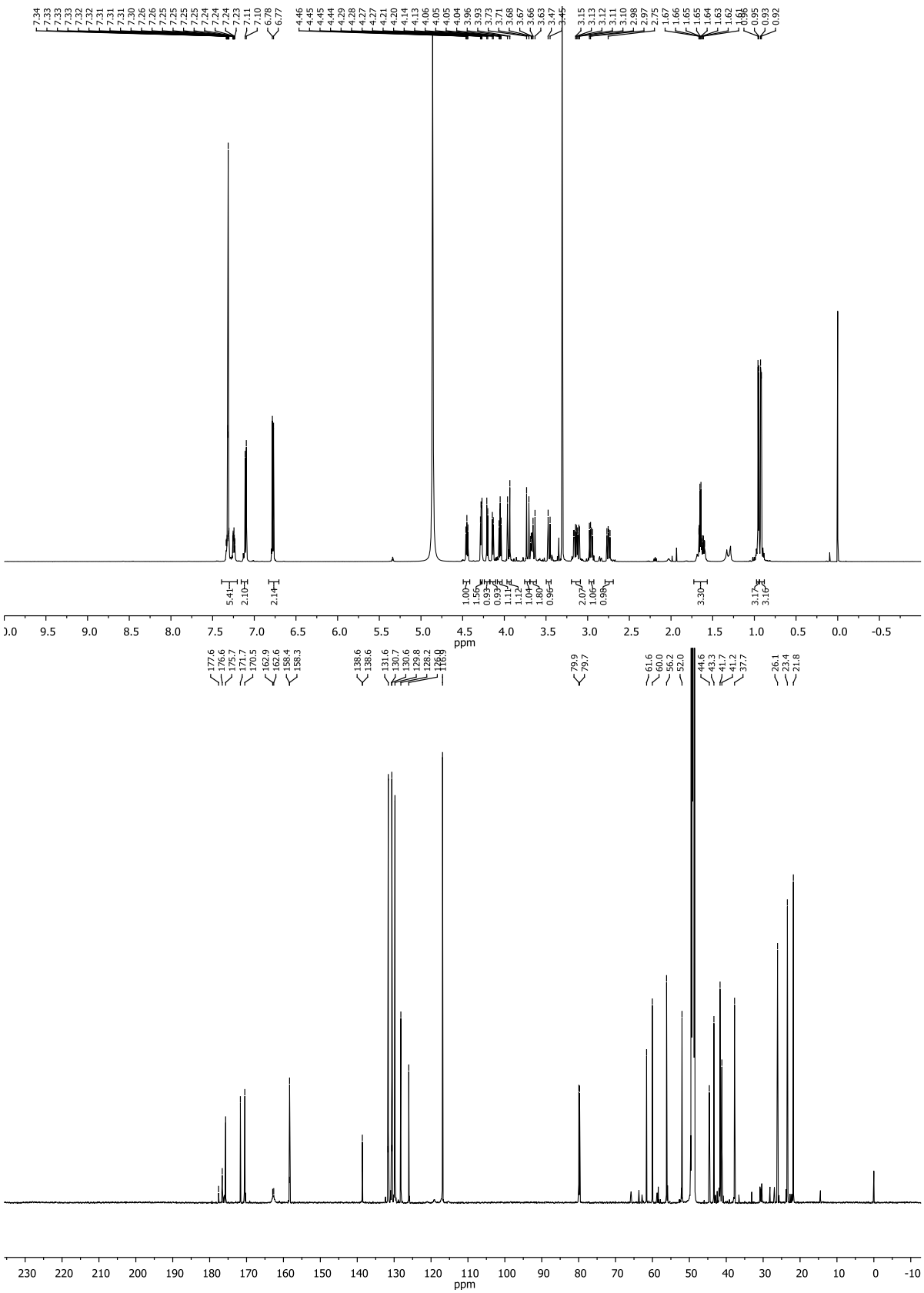
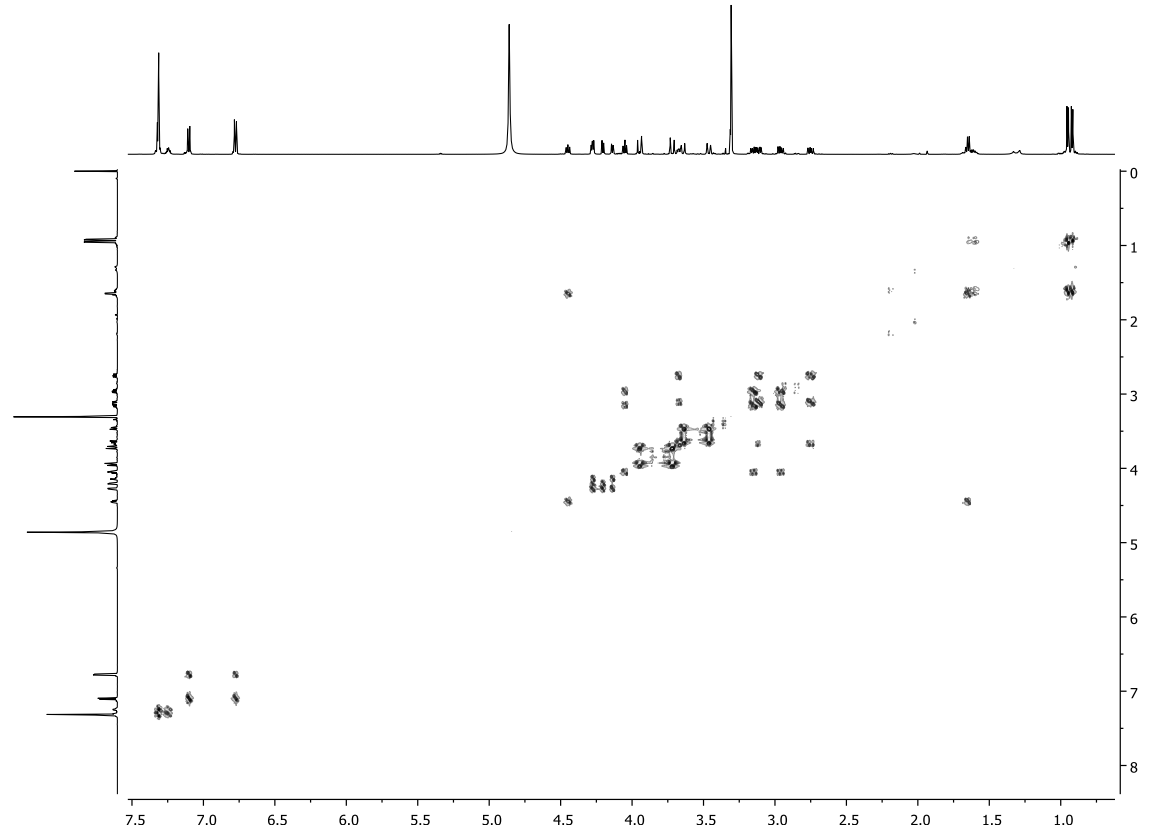


Figure 162 ^{1}H- and ^{13}C-NMR Spectra of 247d.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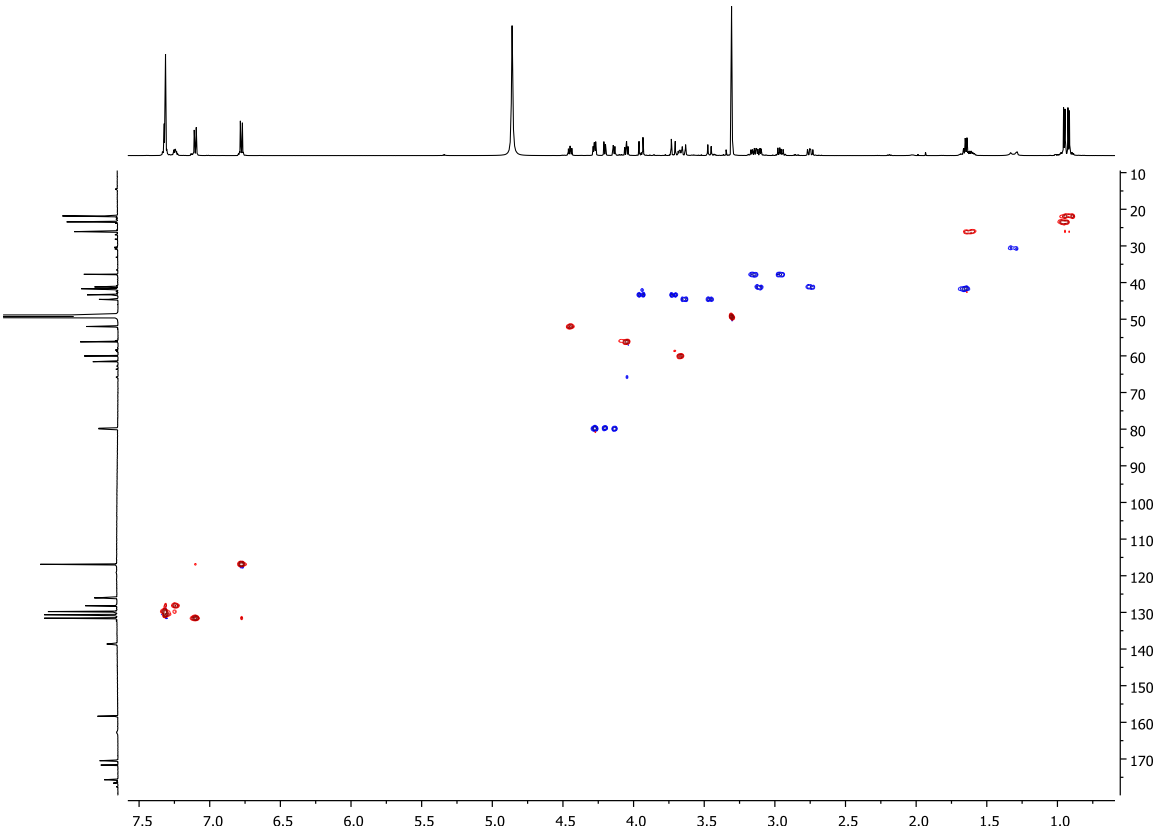
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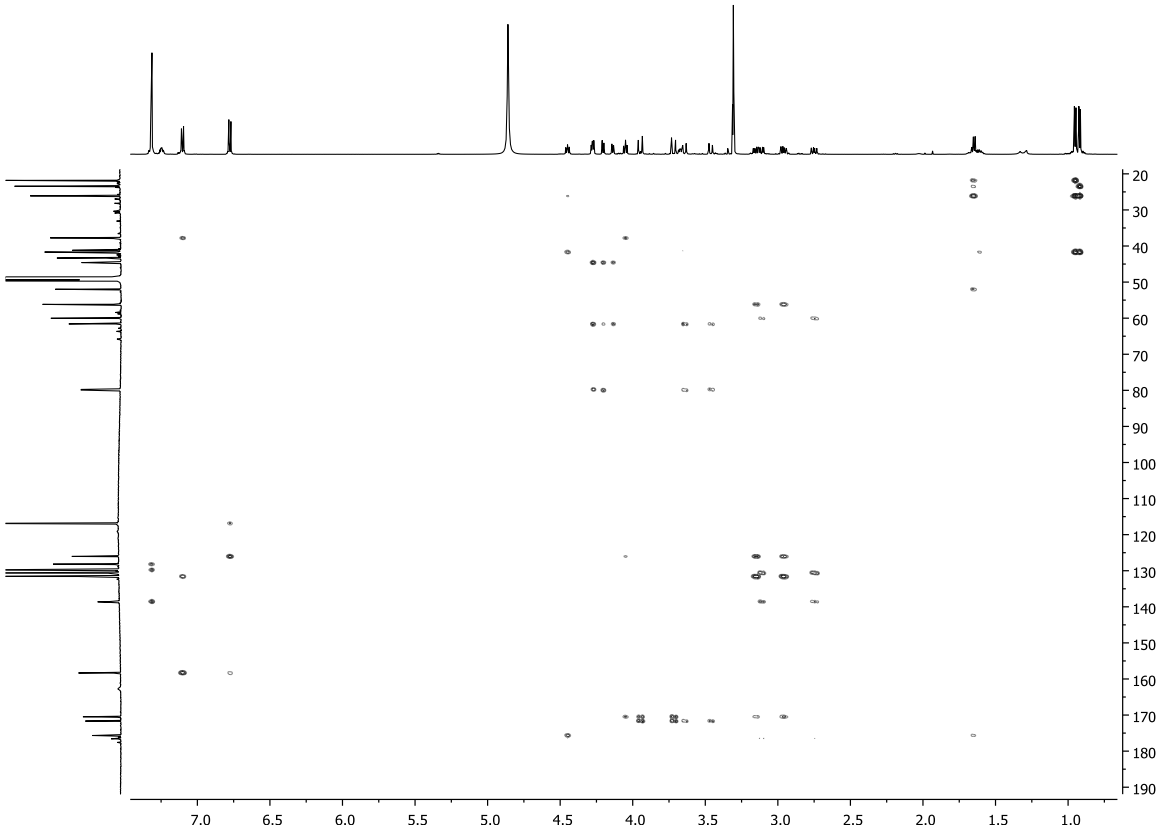


Figure 163 COSY, HSQC, HMBC Spectra of 247d.

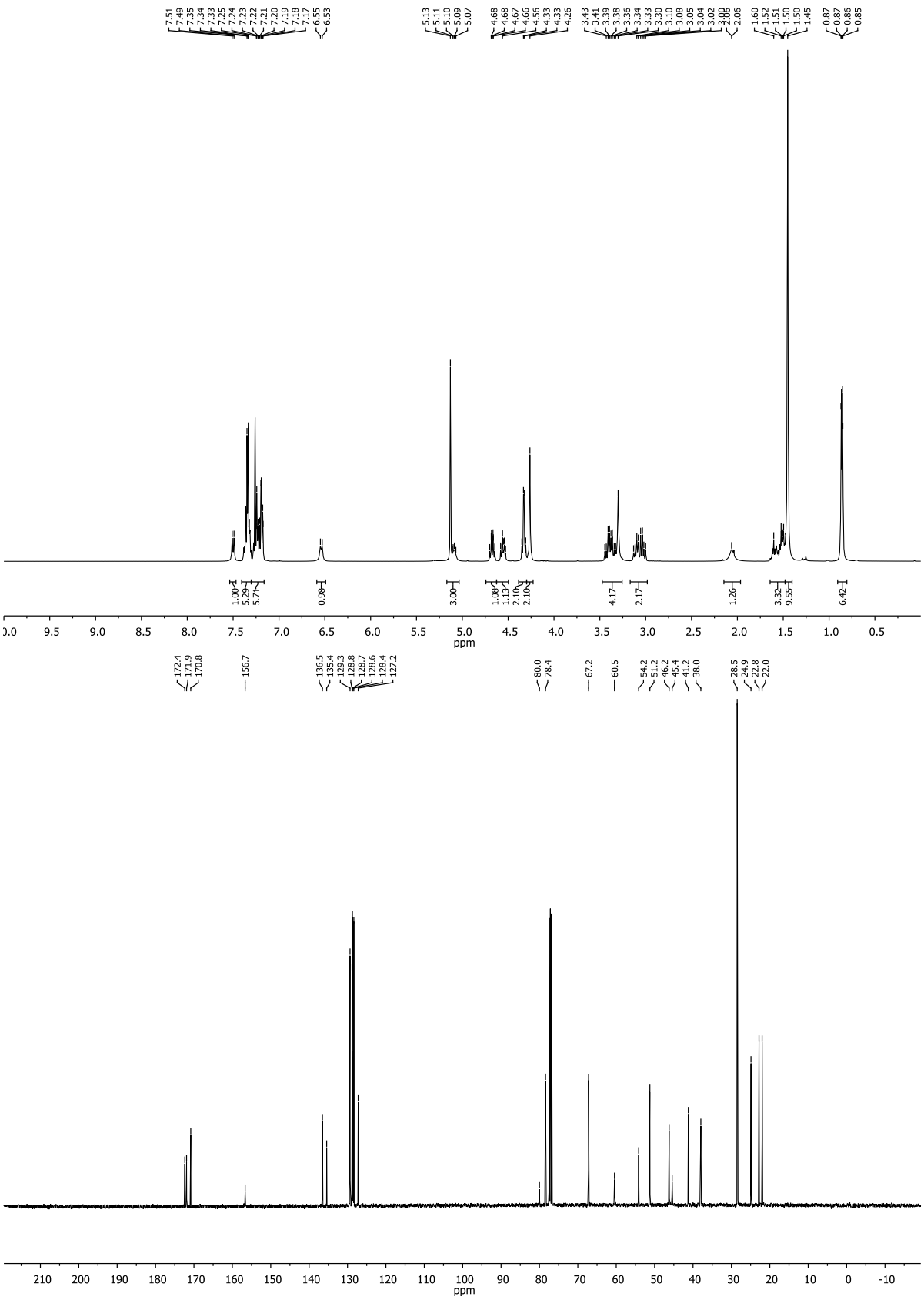


Figure 164 ^{1}H- and ^{13}C-NMR Spectra of 249.

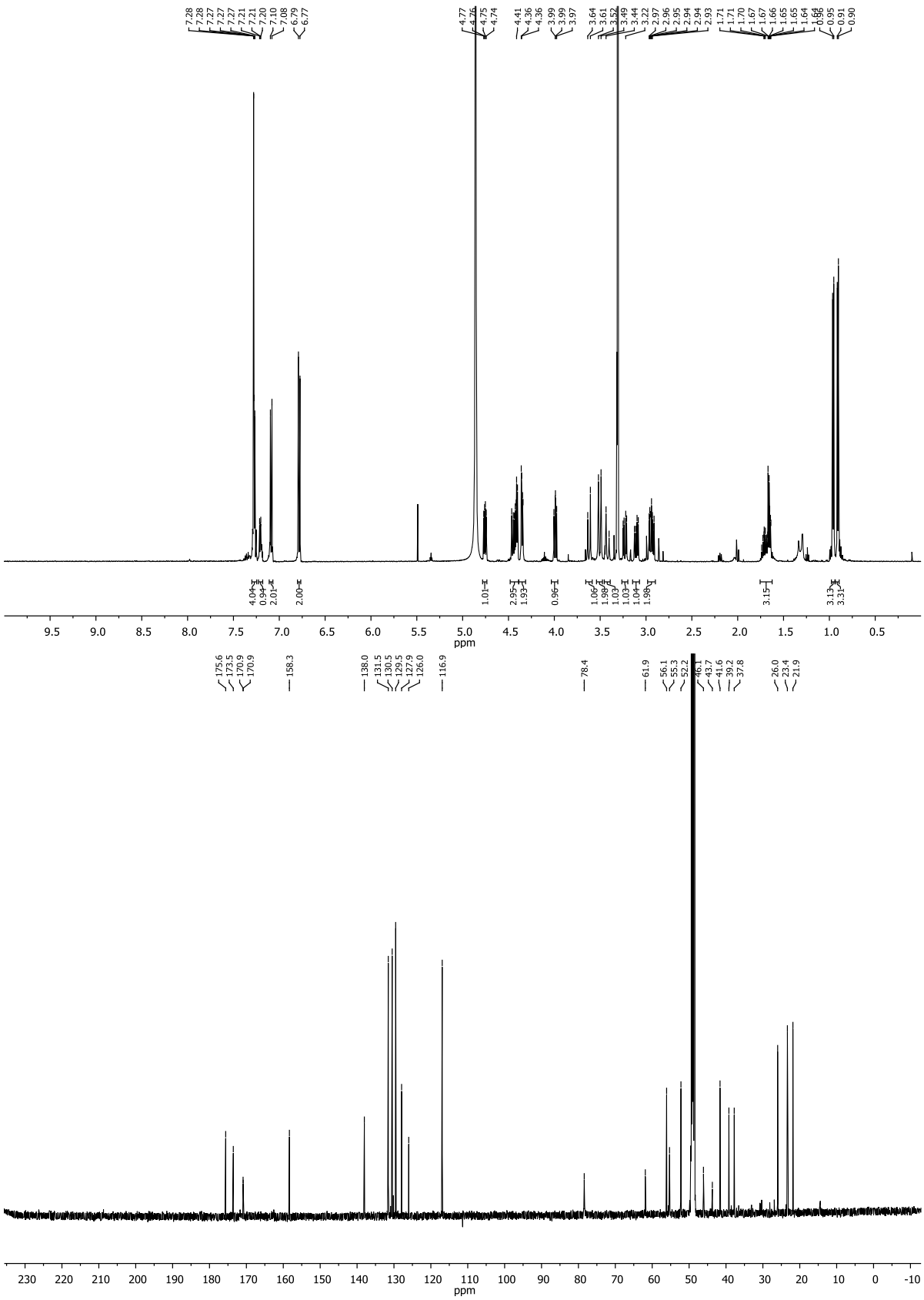
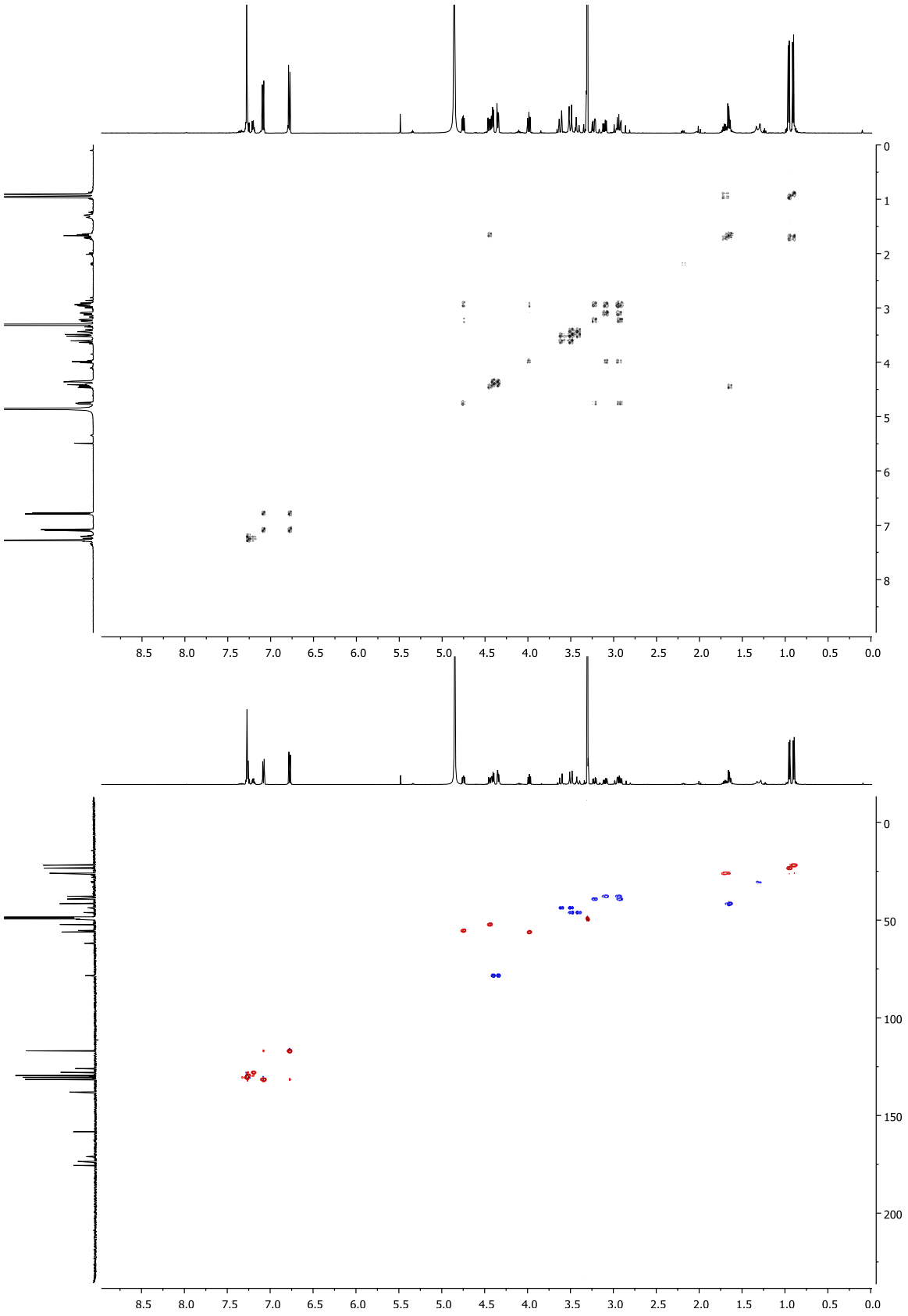


Figure 165 ^{1}H- and ^{13}C-NMR Spectra of 247c.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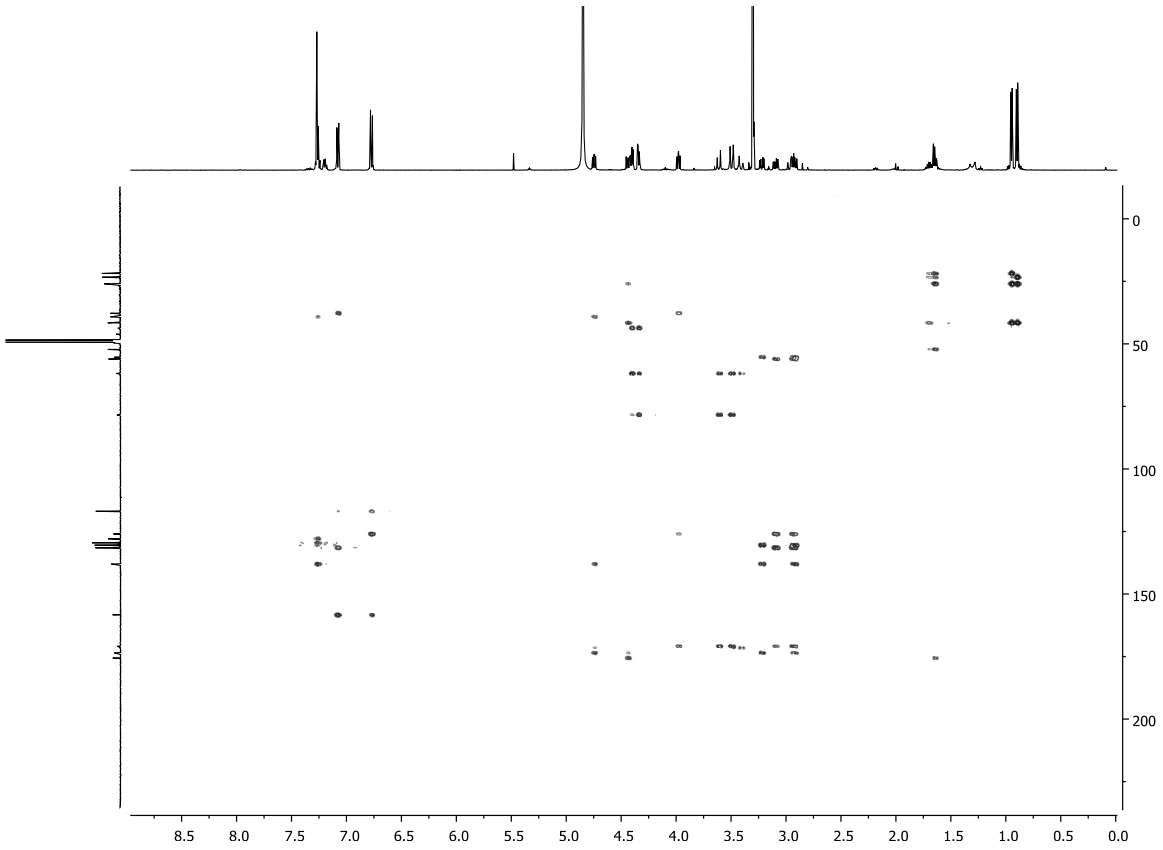


Figure 166 COSY, HSQC, HMBC Spectra of 247c.

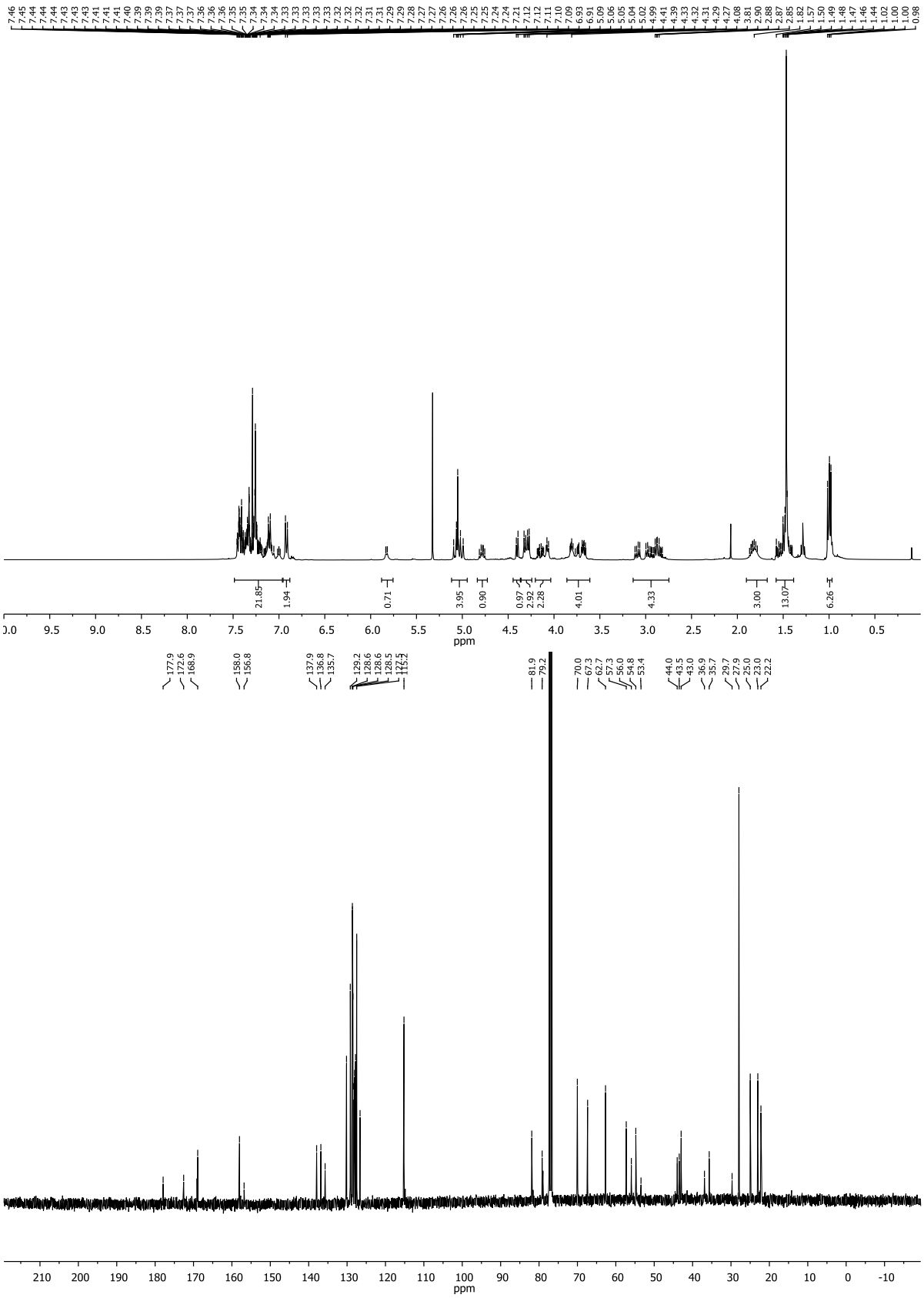


Figure 167 ^{1}H- and ^{13}C-NMR Spectra of 252.

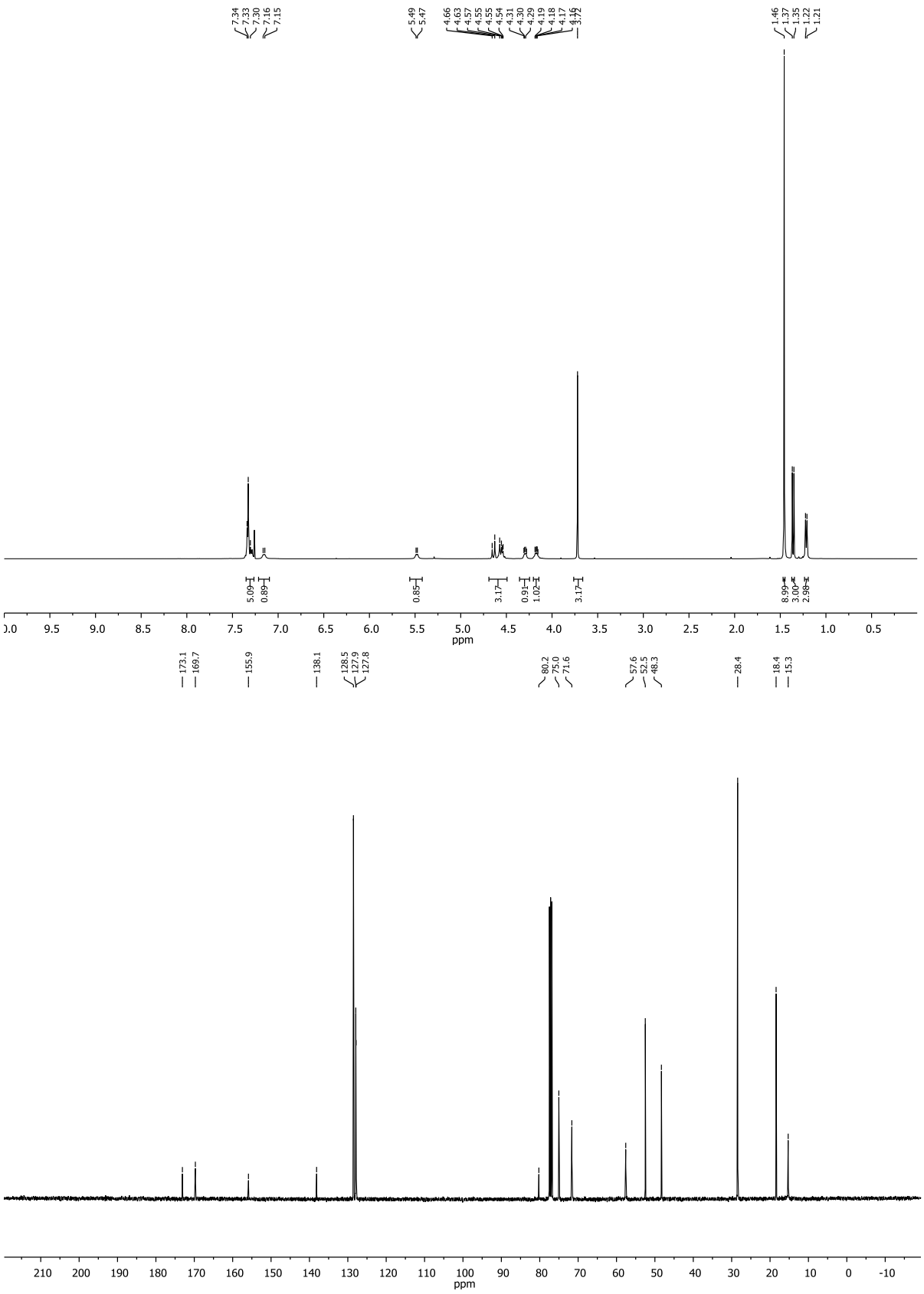


Figure 168 ^{1}H- and ^{13}C-NMR Spectra of 261.

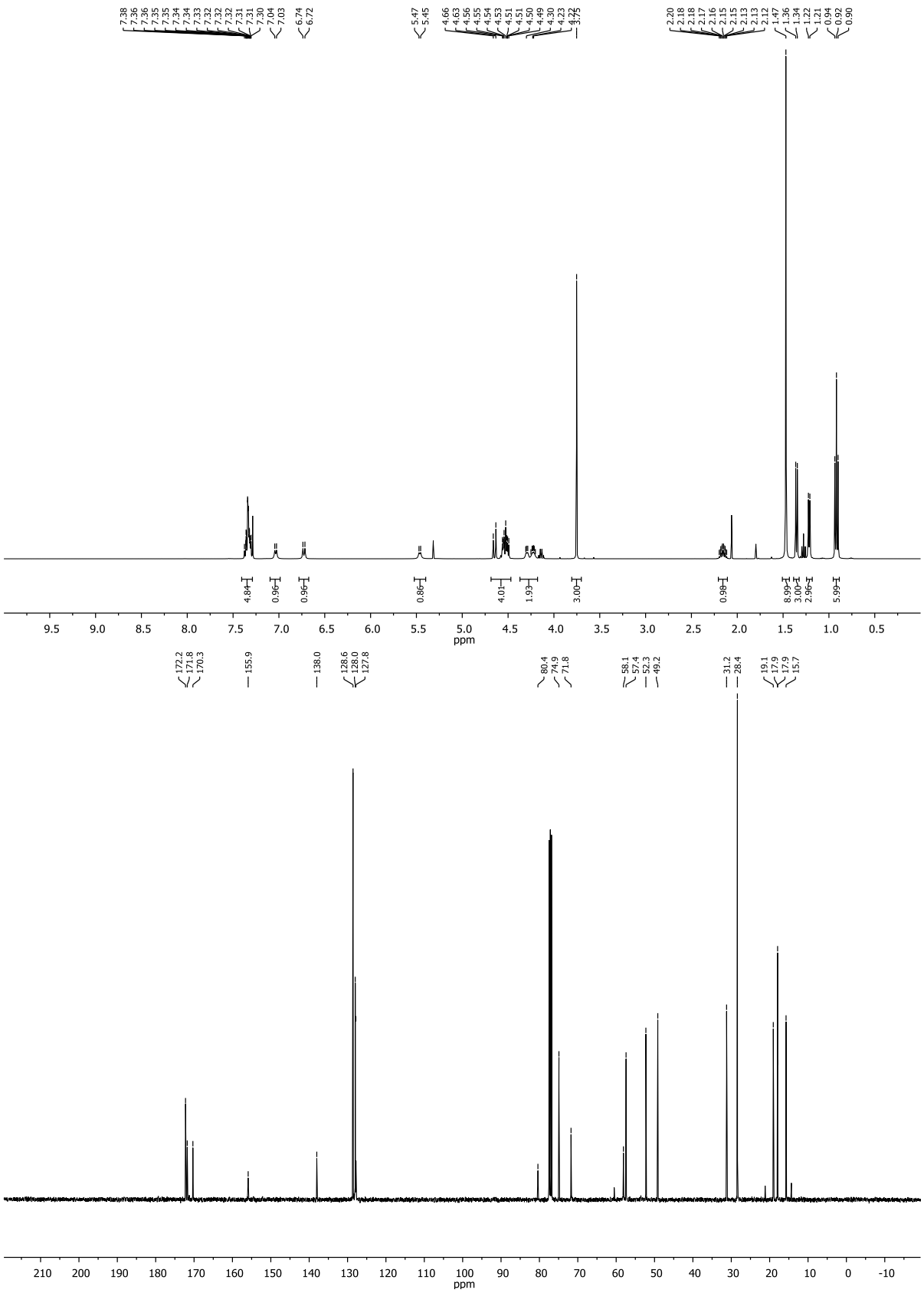


Figure 169 ^{1}H- and ^{13}C-NMR Spectra of 266.

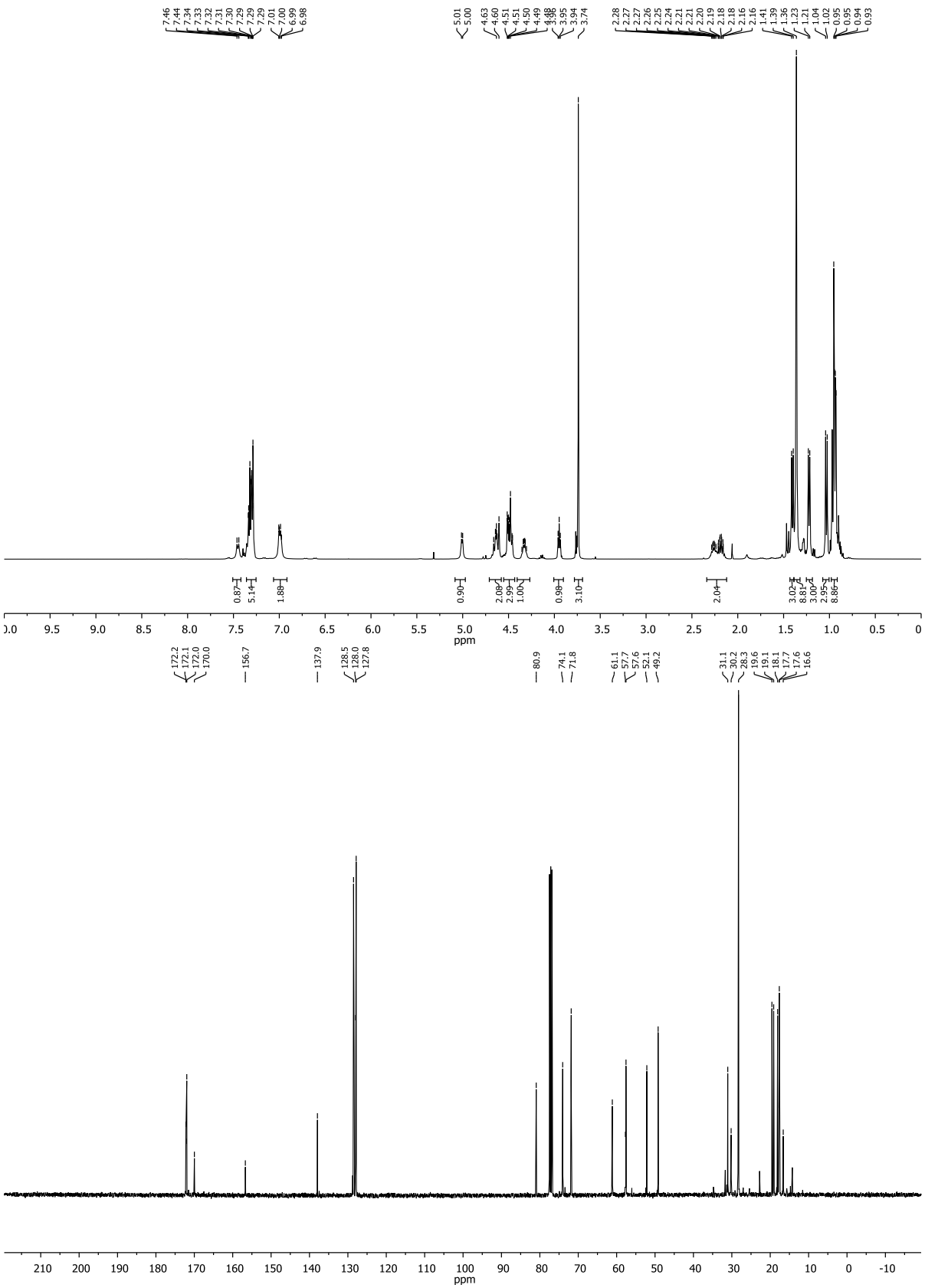


Figure 170 ^{1}H- and ^{13}C-NMR Spectra of 265.

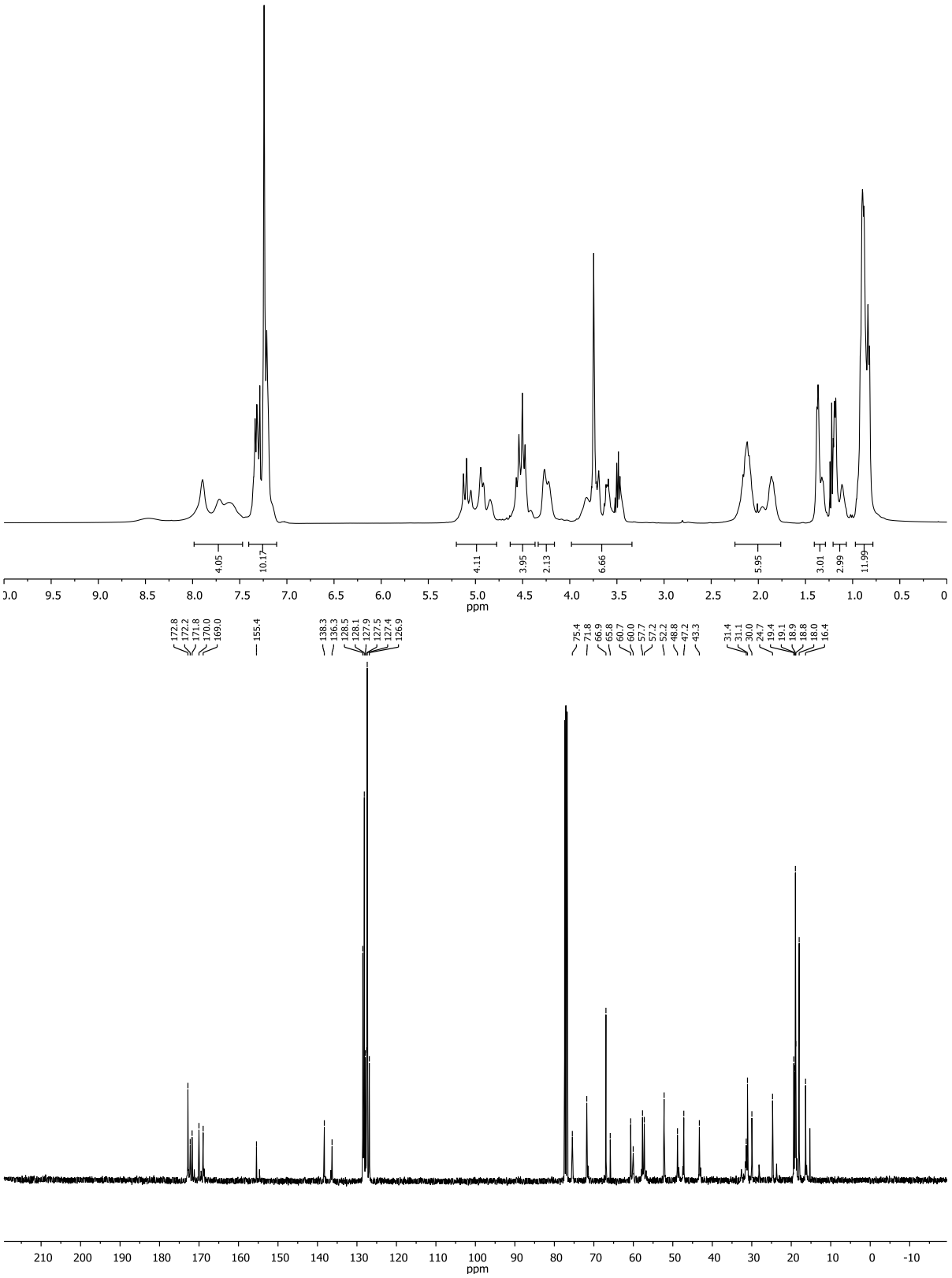


Figure 171 ^{1}H- and ^{13}C-NMR Spectra of 267.

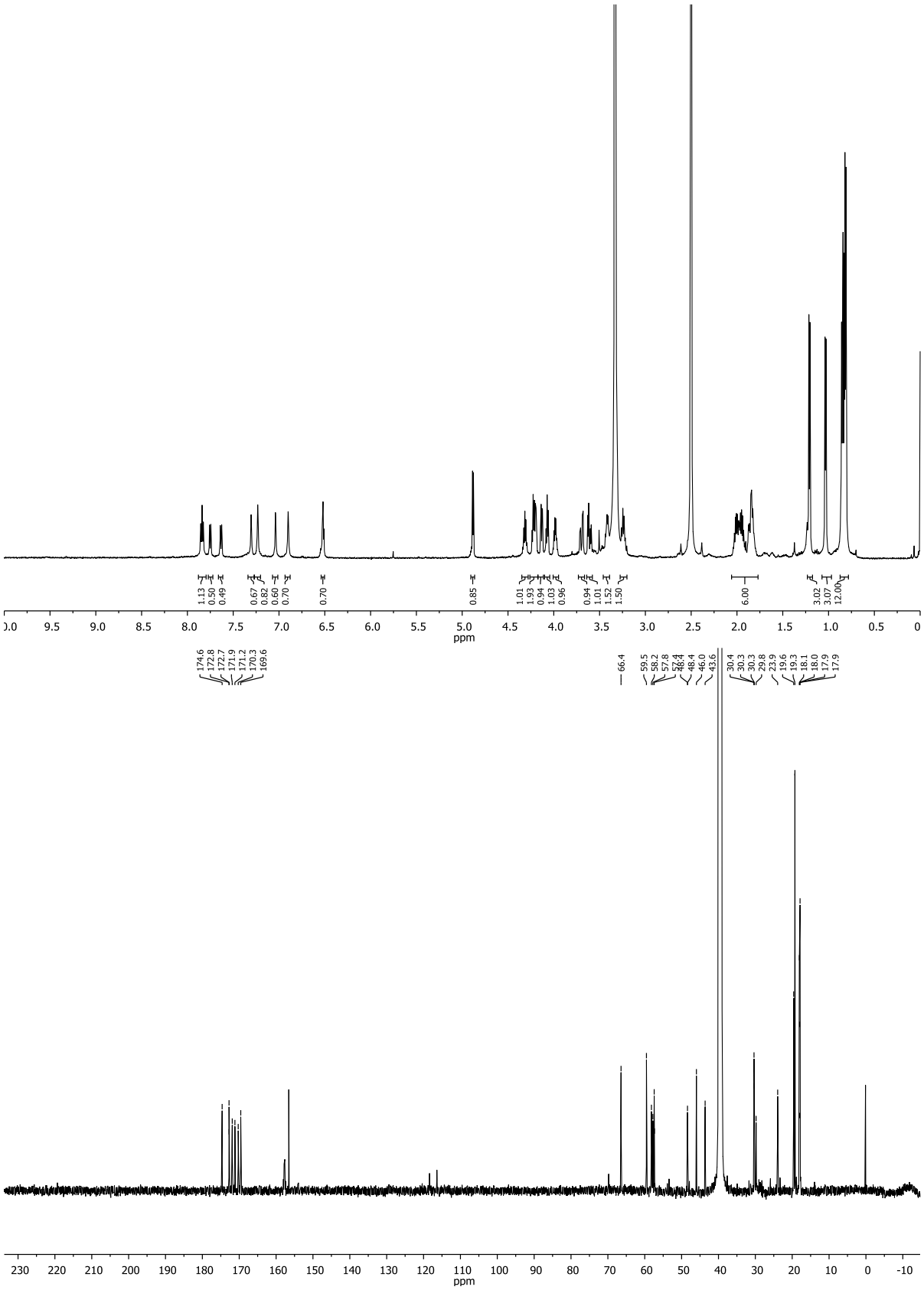


Figure 172 ^{1}H- and ^{13}C-NMR Spectra of 259a ·NH$_2$.

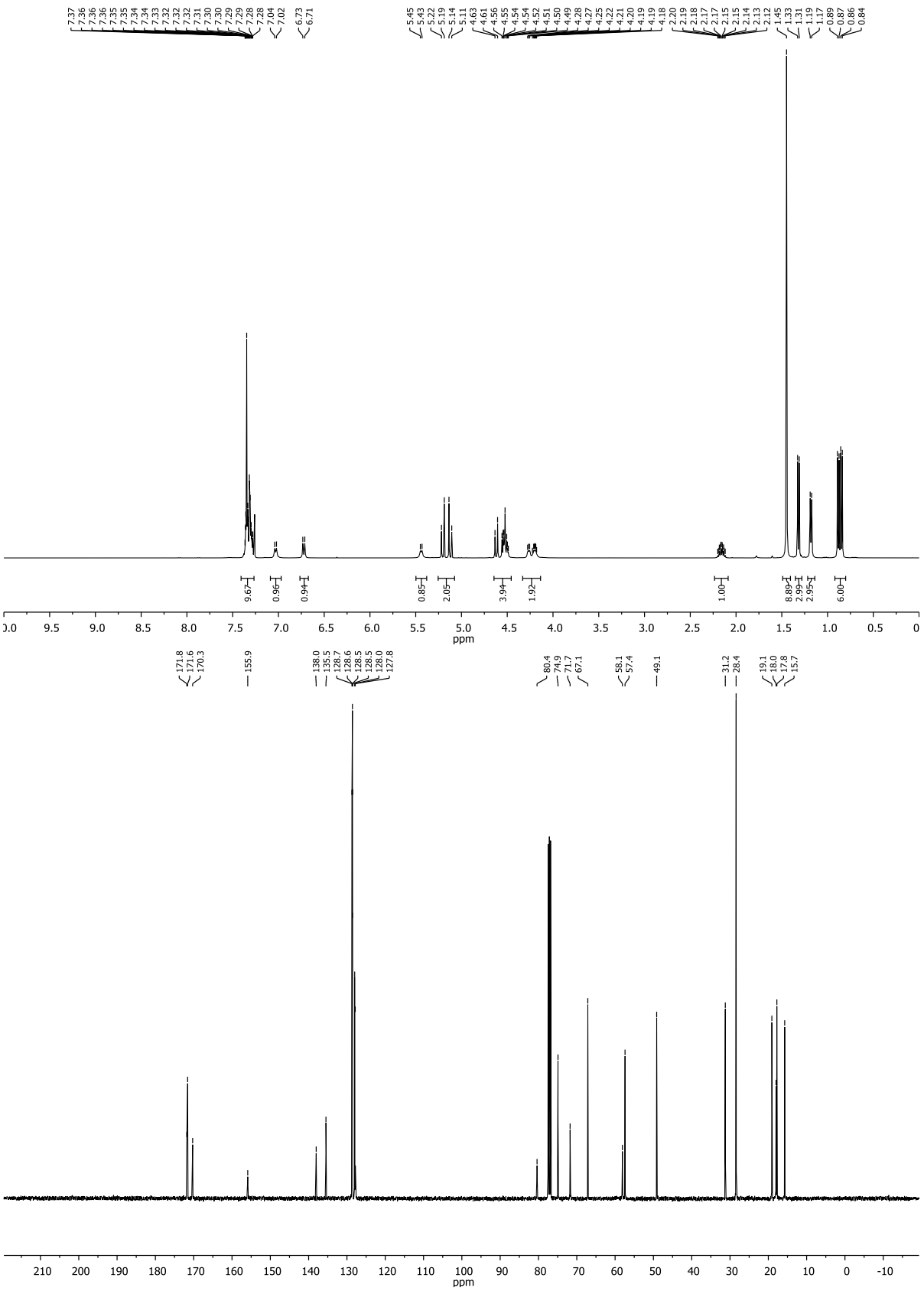


Figure 173 ^{1}H- and ^{13}C-NMR Spectra of 262.

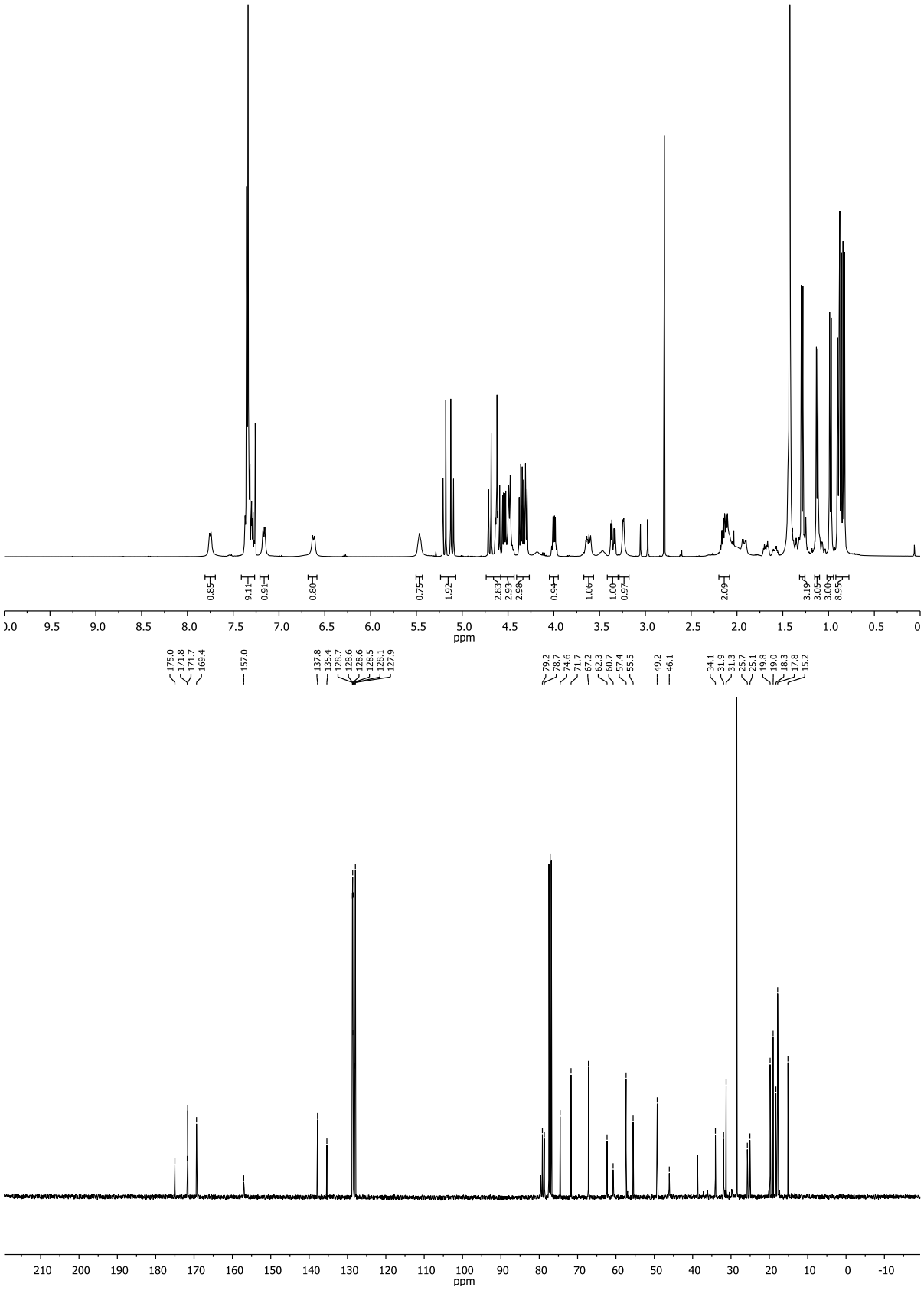


Figure 174 ^{1}H- and ^{13}C-NMR Spectra of 270.

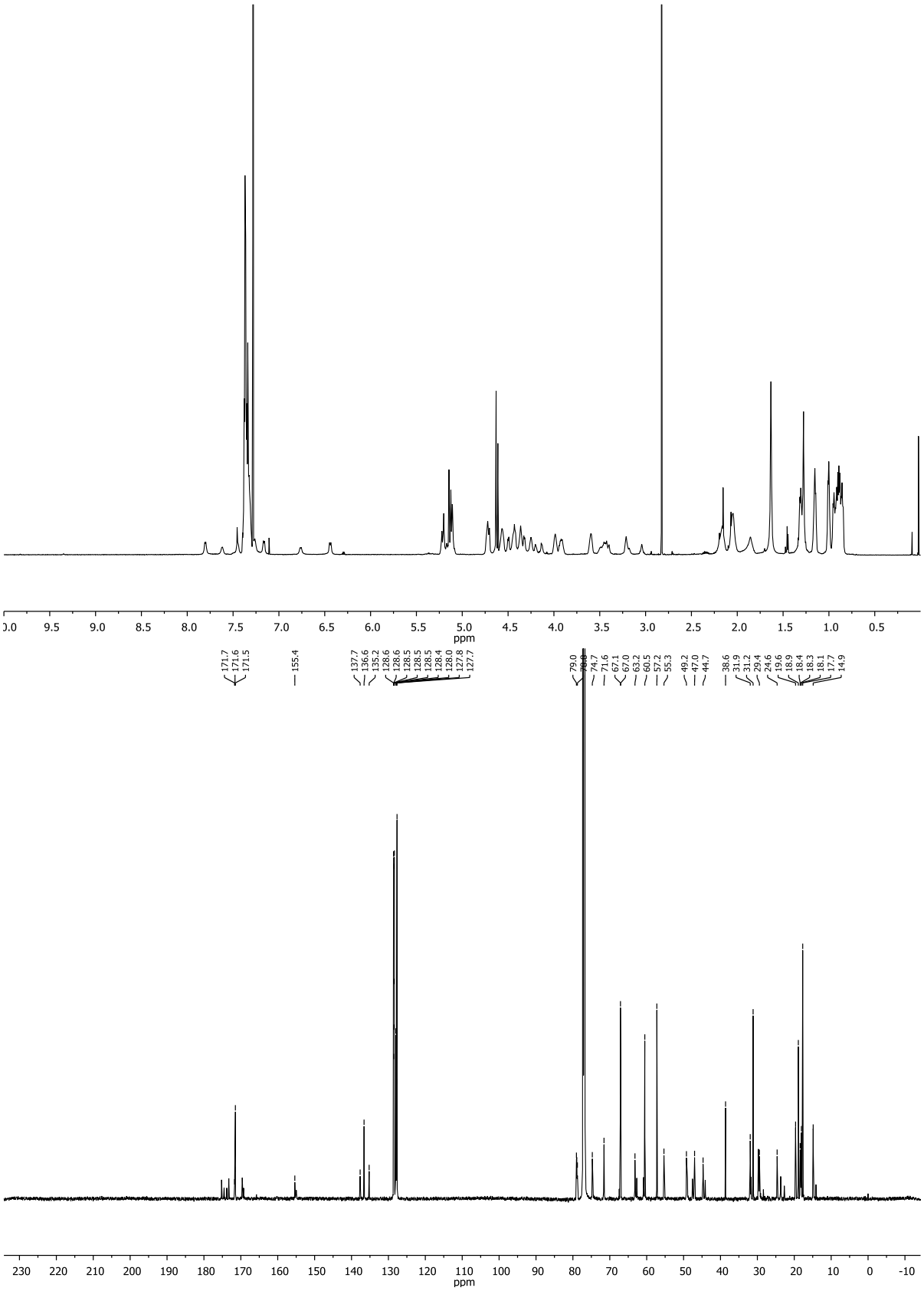


Figure 175 ^{1}H- and ^{13}C-NMR Spectra of 271.

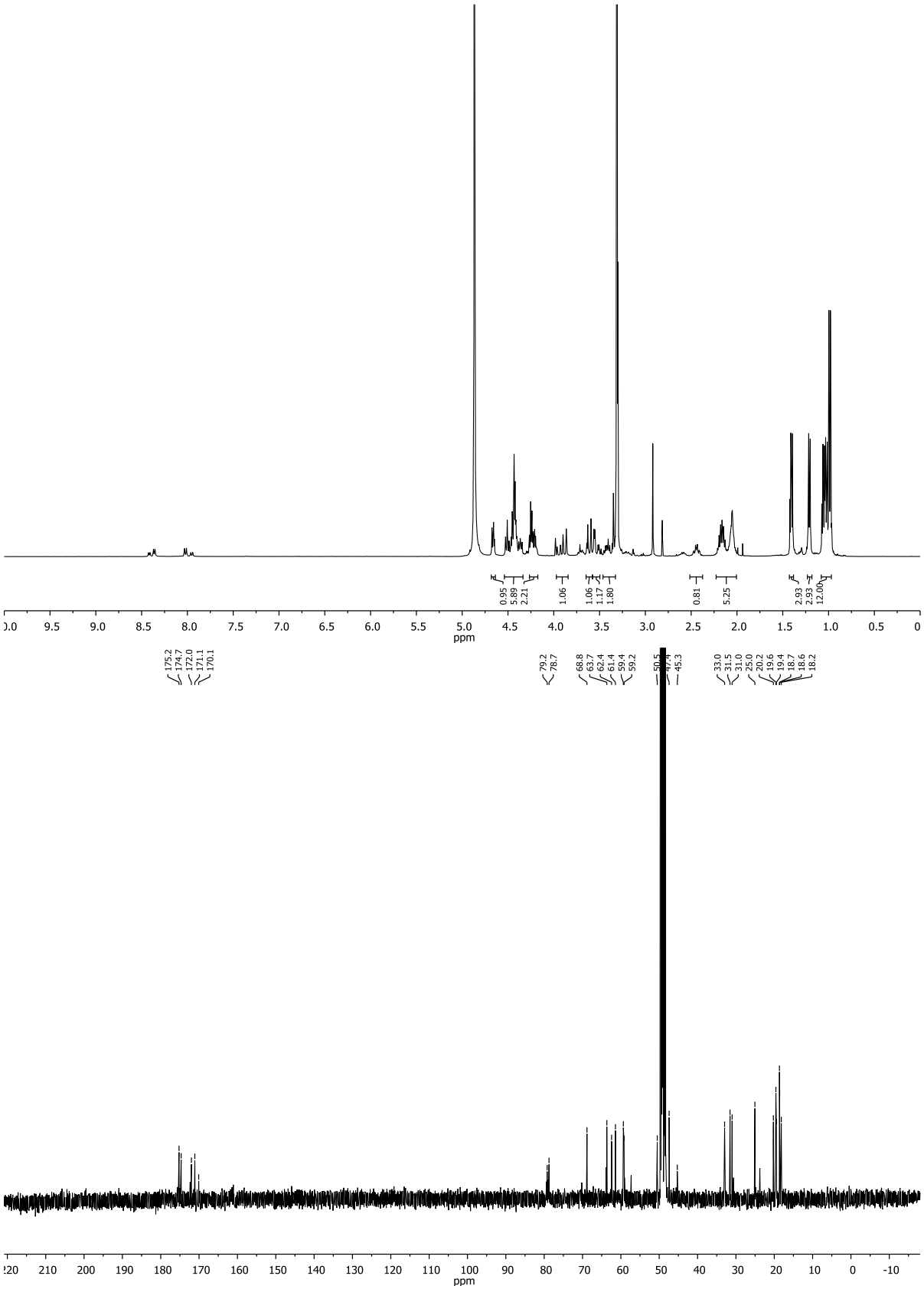


Figure 176 ^{1}H- and ^{13}C-NMR Spectra of 259c -OH.

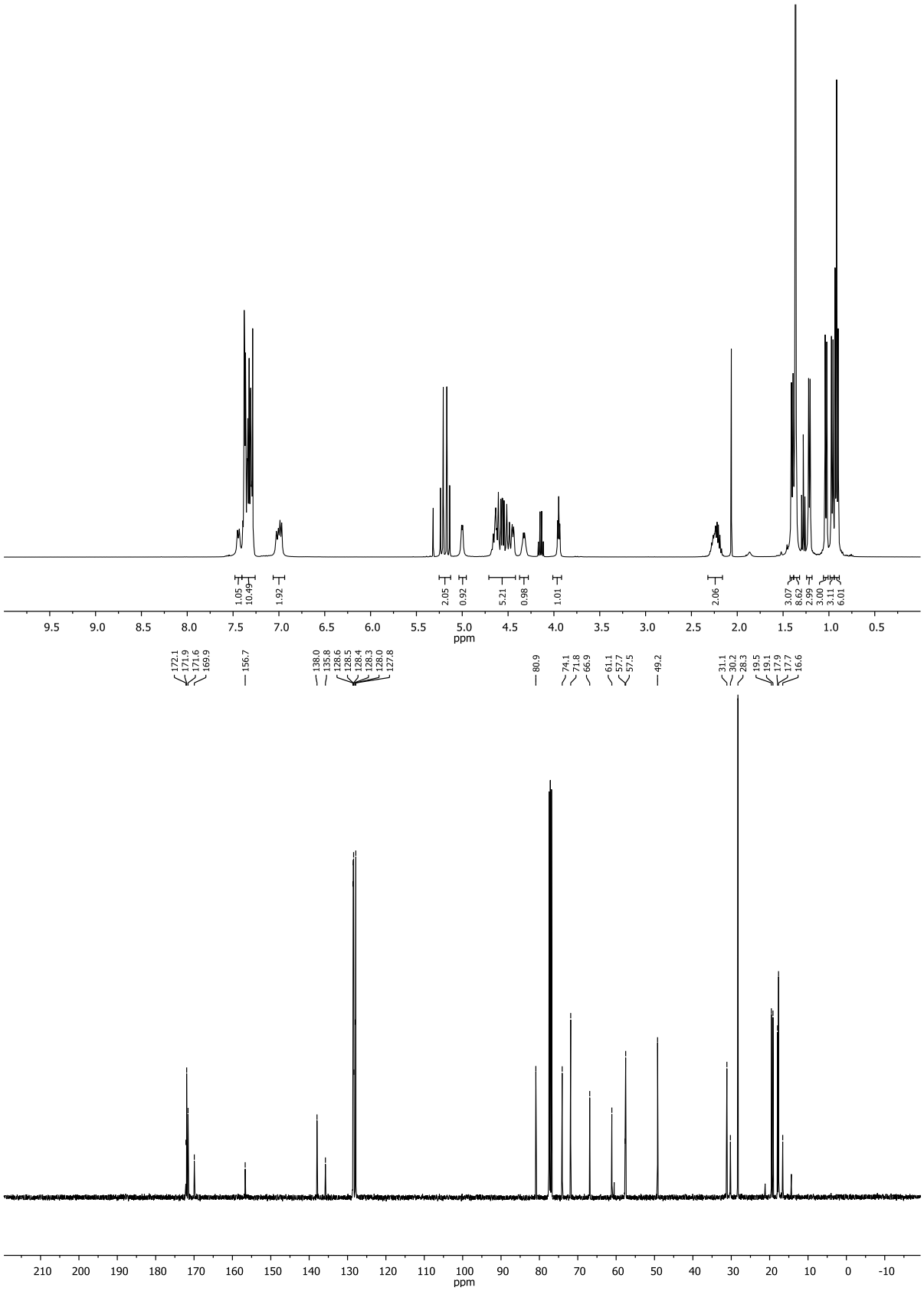


Figure 177 ^{1}H- and ^{13}C-NMR Spectra of 260.

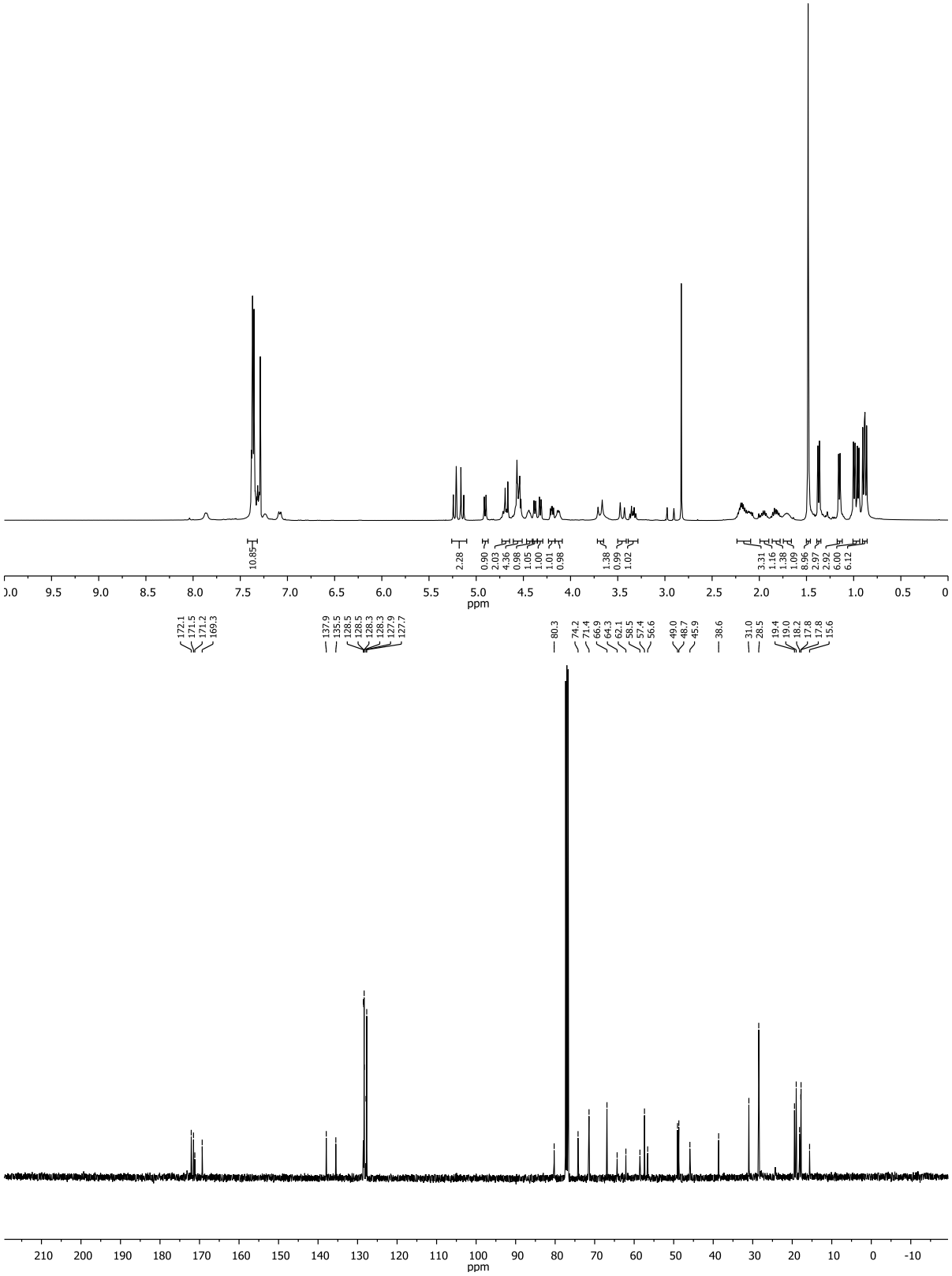


Figure 178 ^{1}H- and ^{13}C-NMR Spectra of 268.

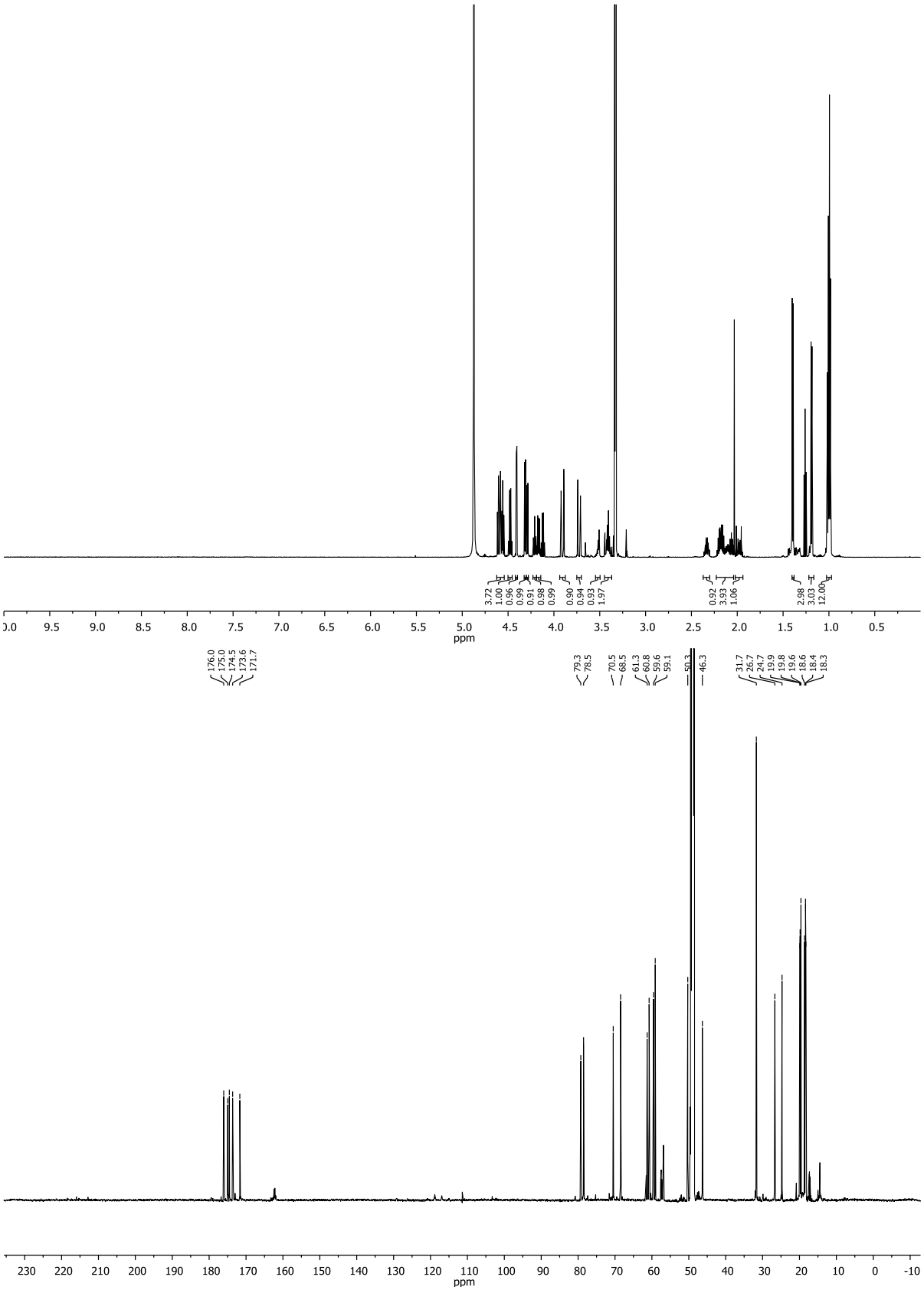


Figure 179 ^{1}H- and ^{13}C-NMR Spectra of 259b ·OH.

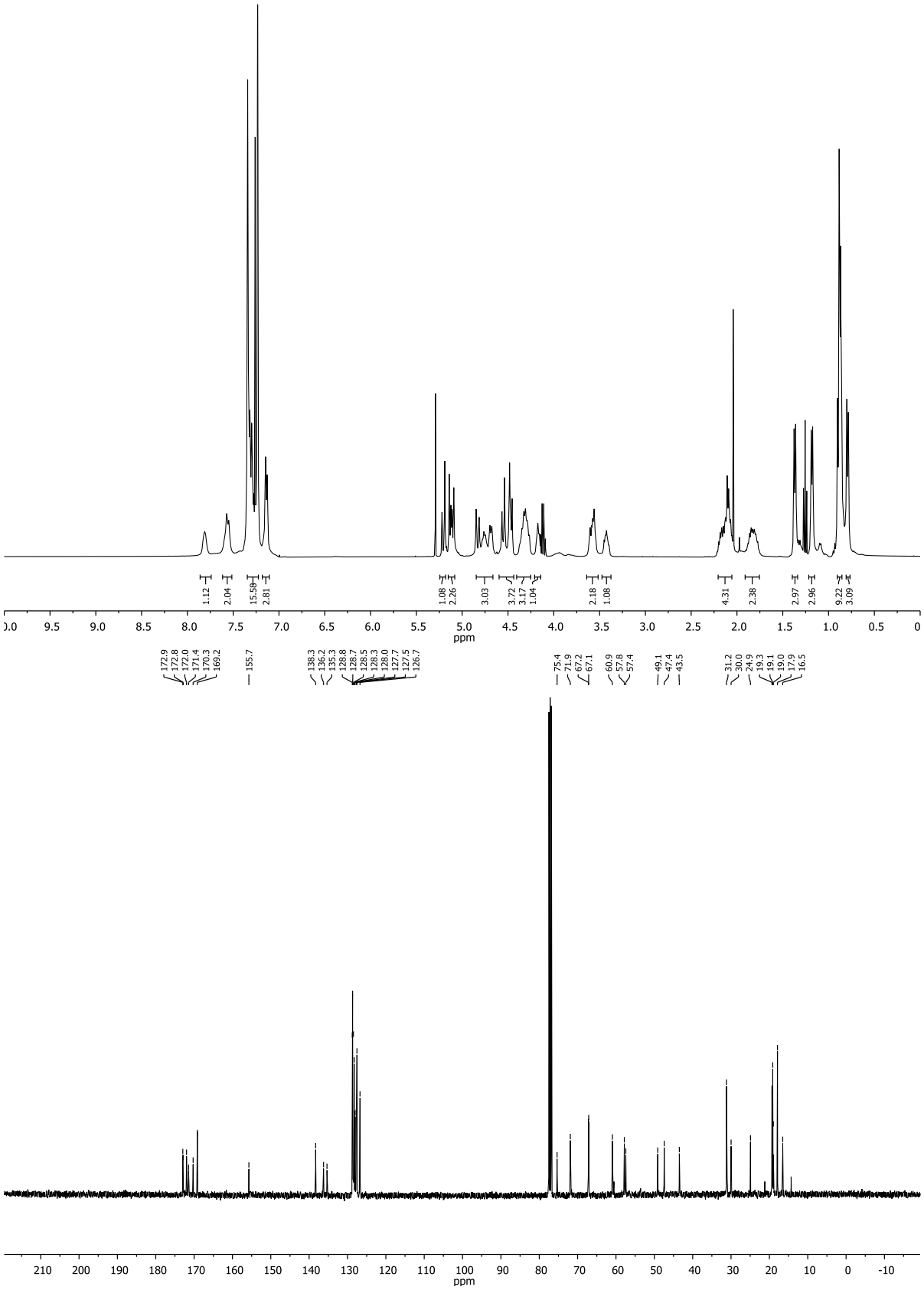


Figure 180 ^{1}H- and ^{13}C-NMR Spectra of 264.

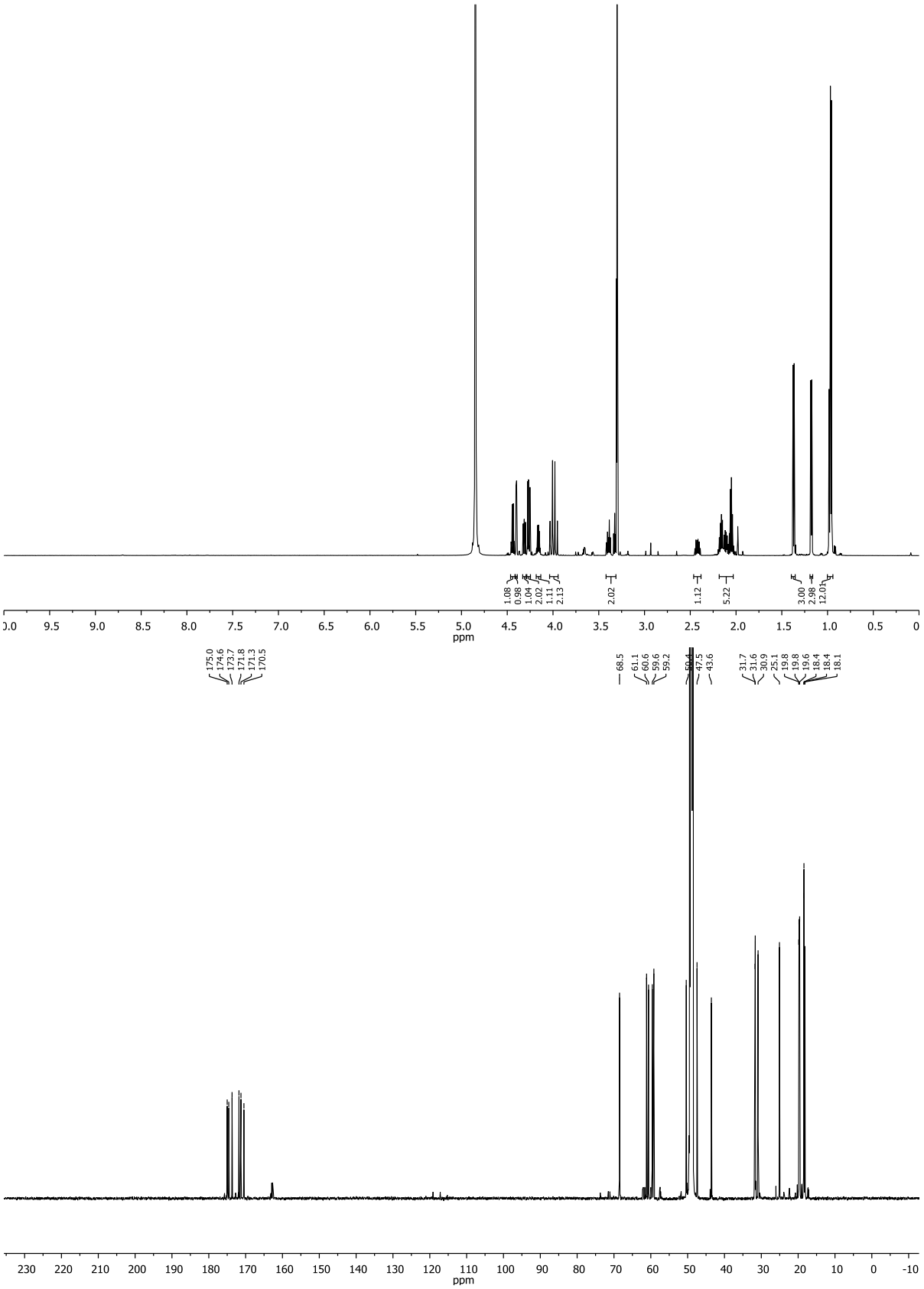


Figure 181 ^{1}H- and ^{13}C-NMR Spectra of 259a·OH.

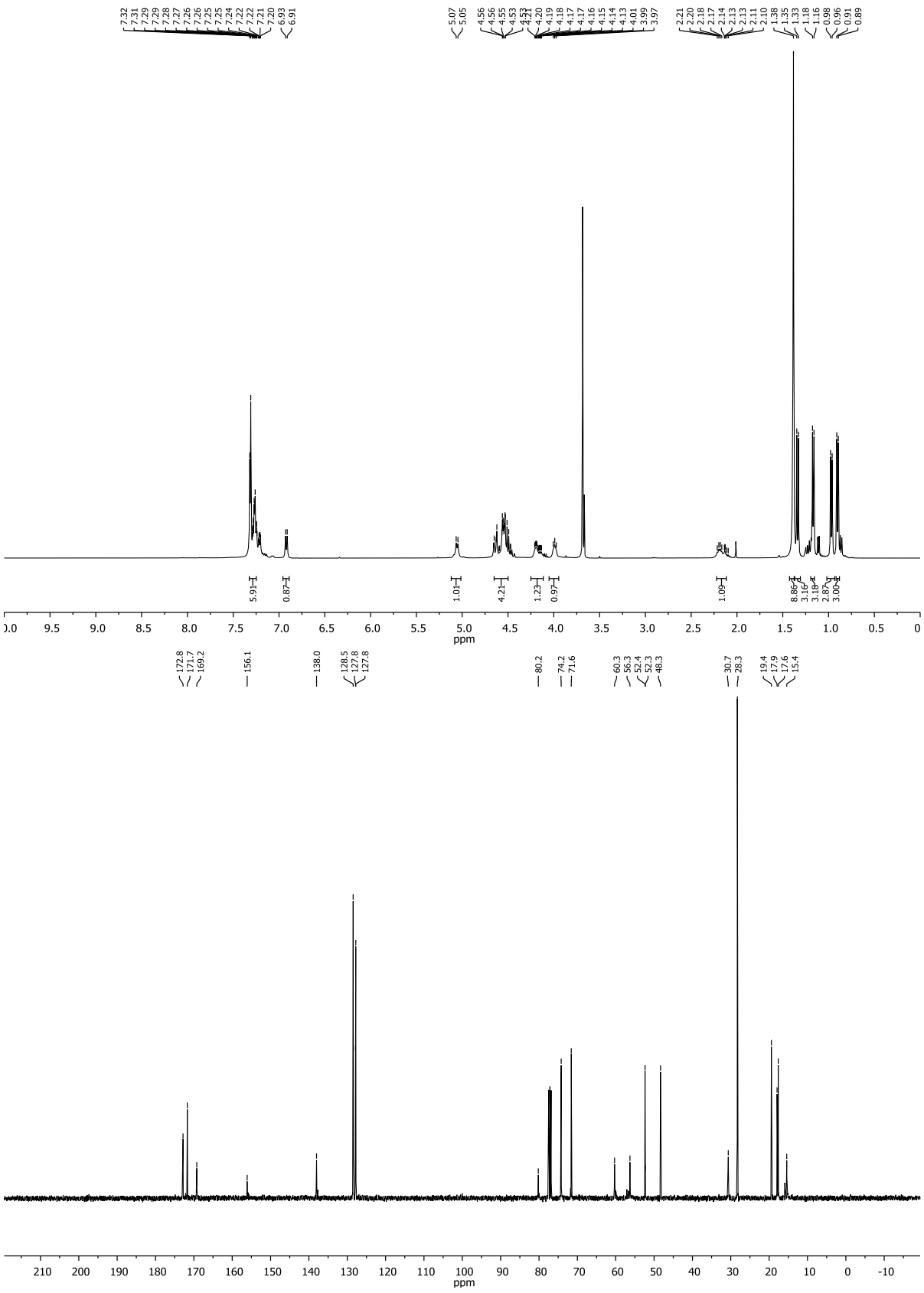


Figure 182 ^{1}H- and ^{13}C-NMR Spectra of 276.

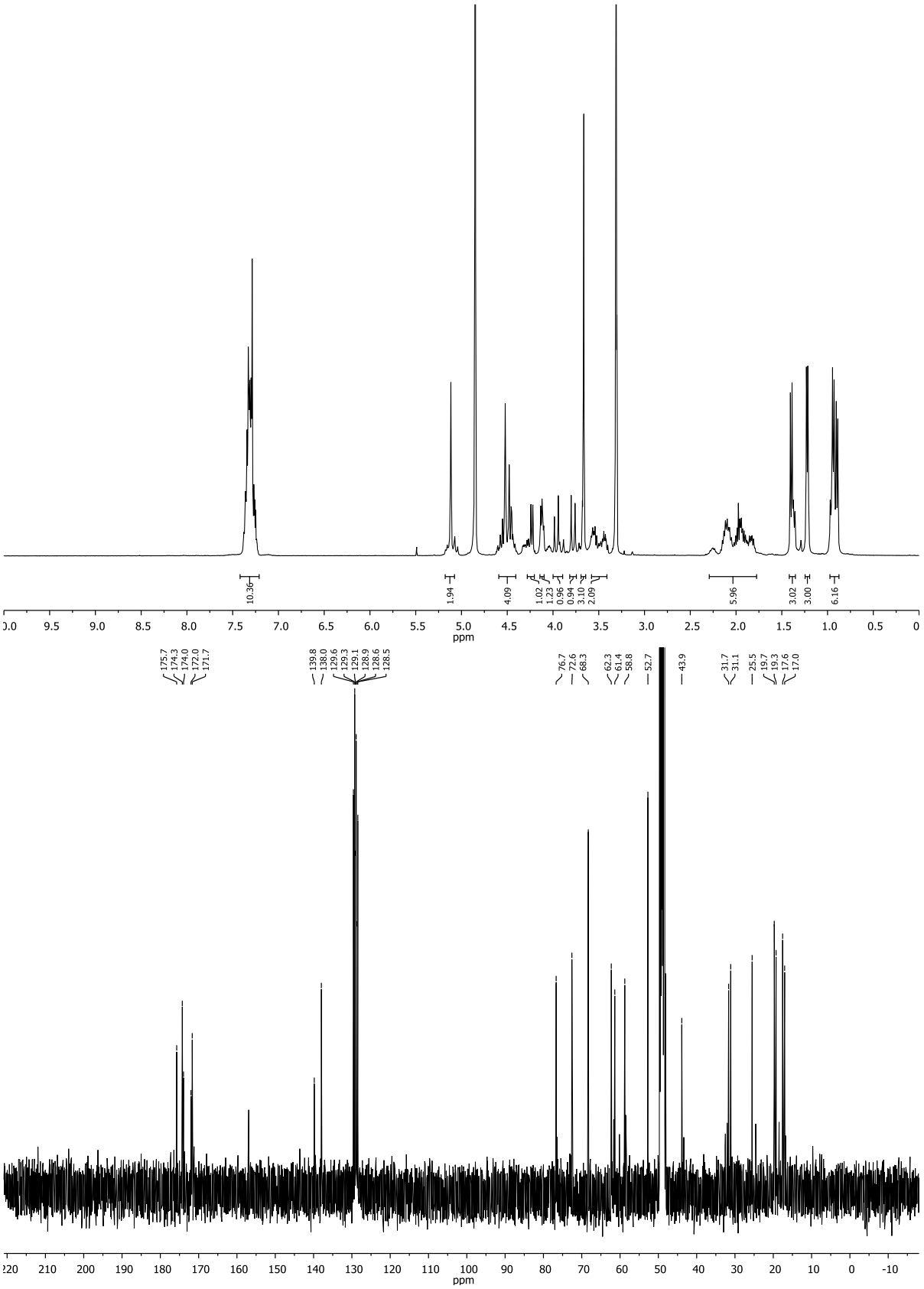


Figure 183 ^{1}H- and ^{13}C-NMR Spectra of 275.

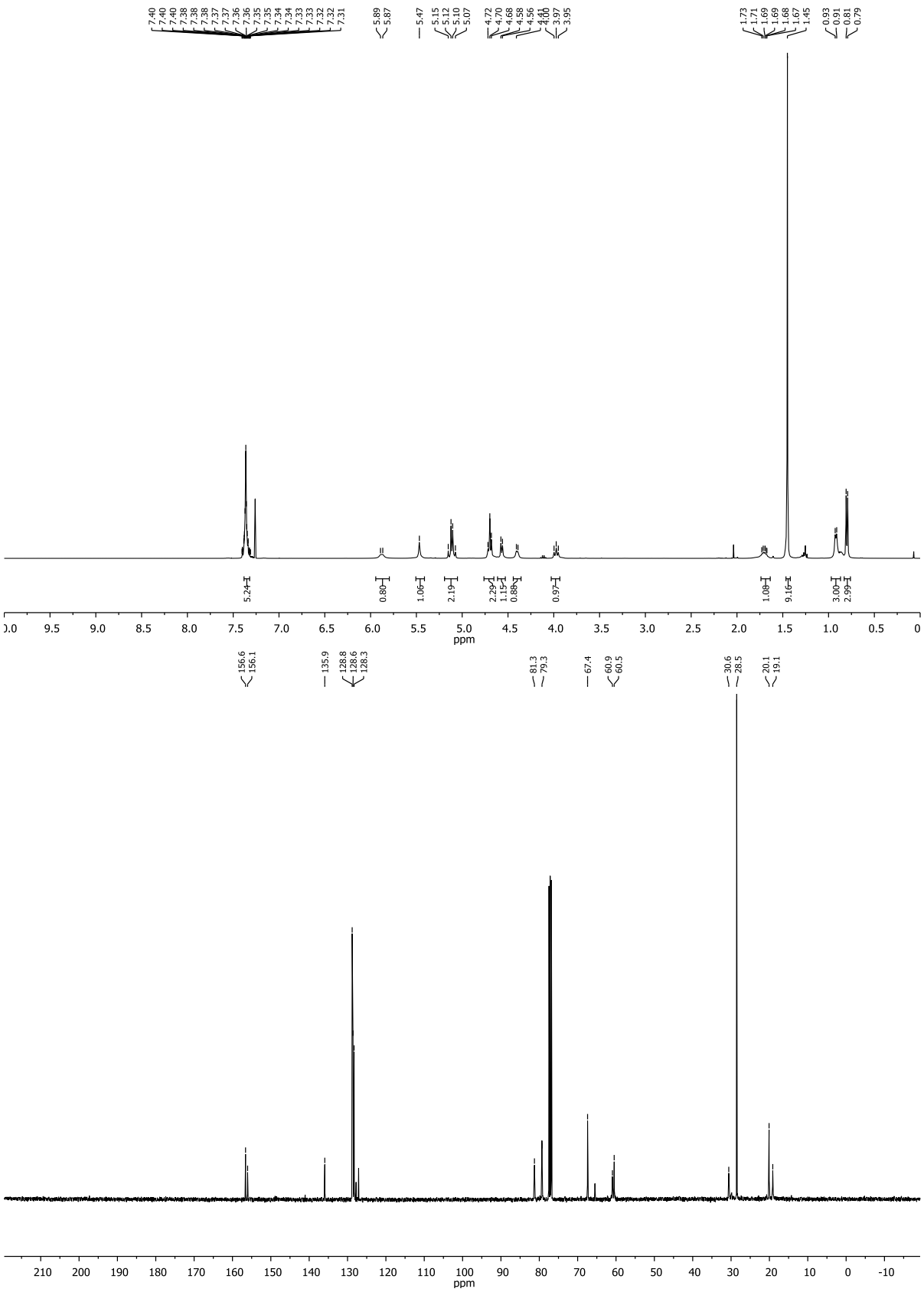


Figure 184 ^{1}H- and ^{13}C-NMR Spectra of 274.

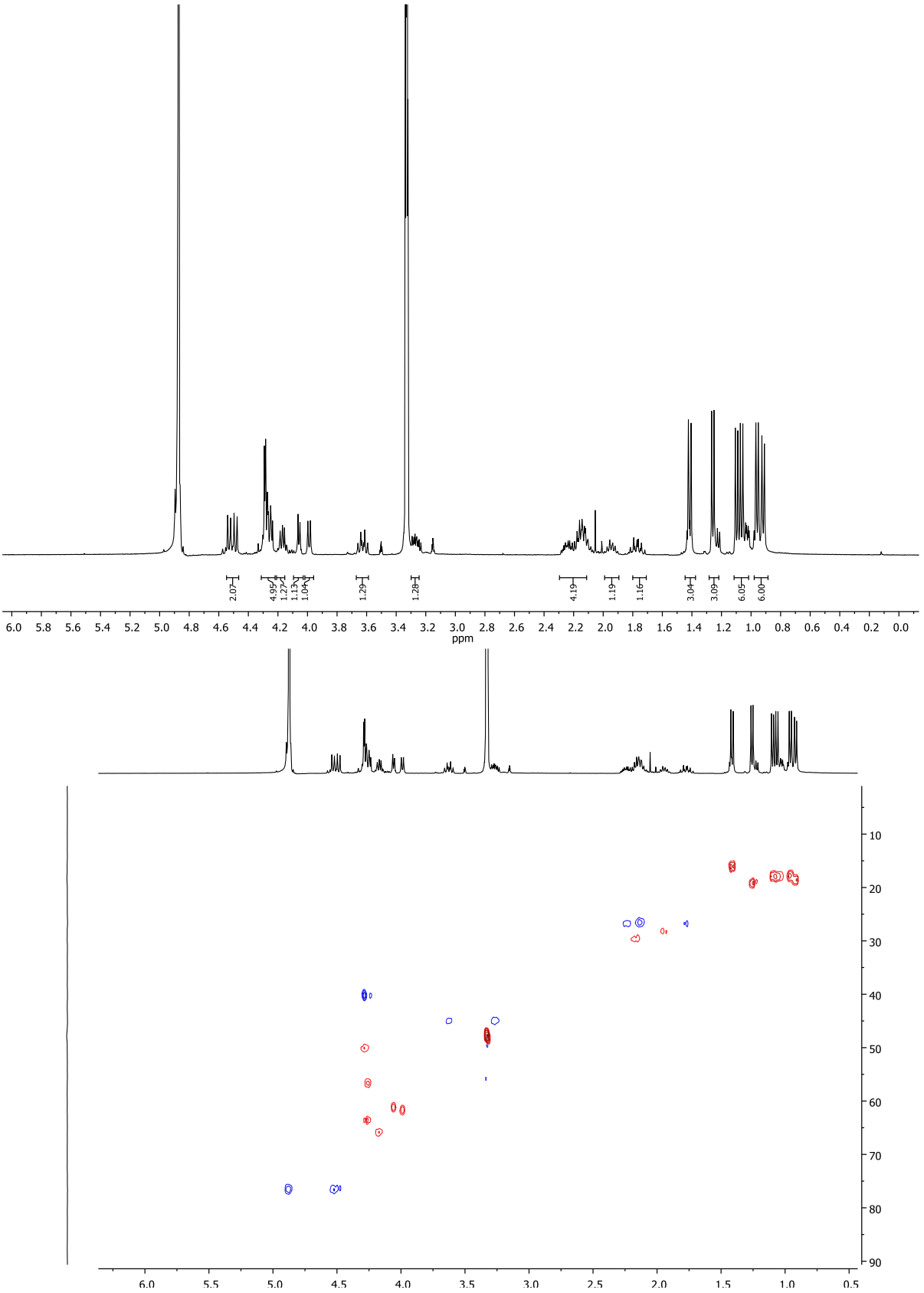


Figure 185 ^{1}H- and HSQC-NMR Spectra of 259d·NH$_2$.

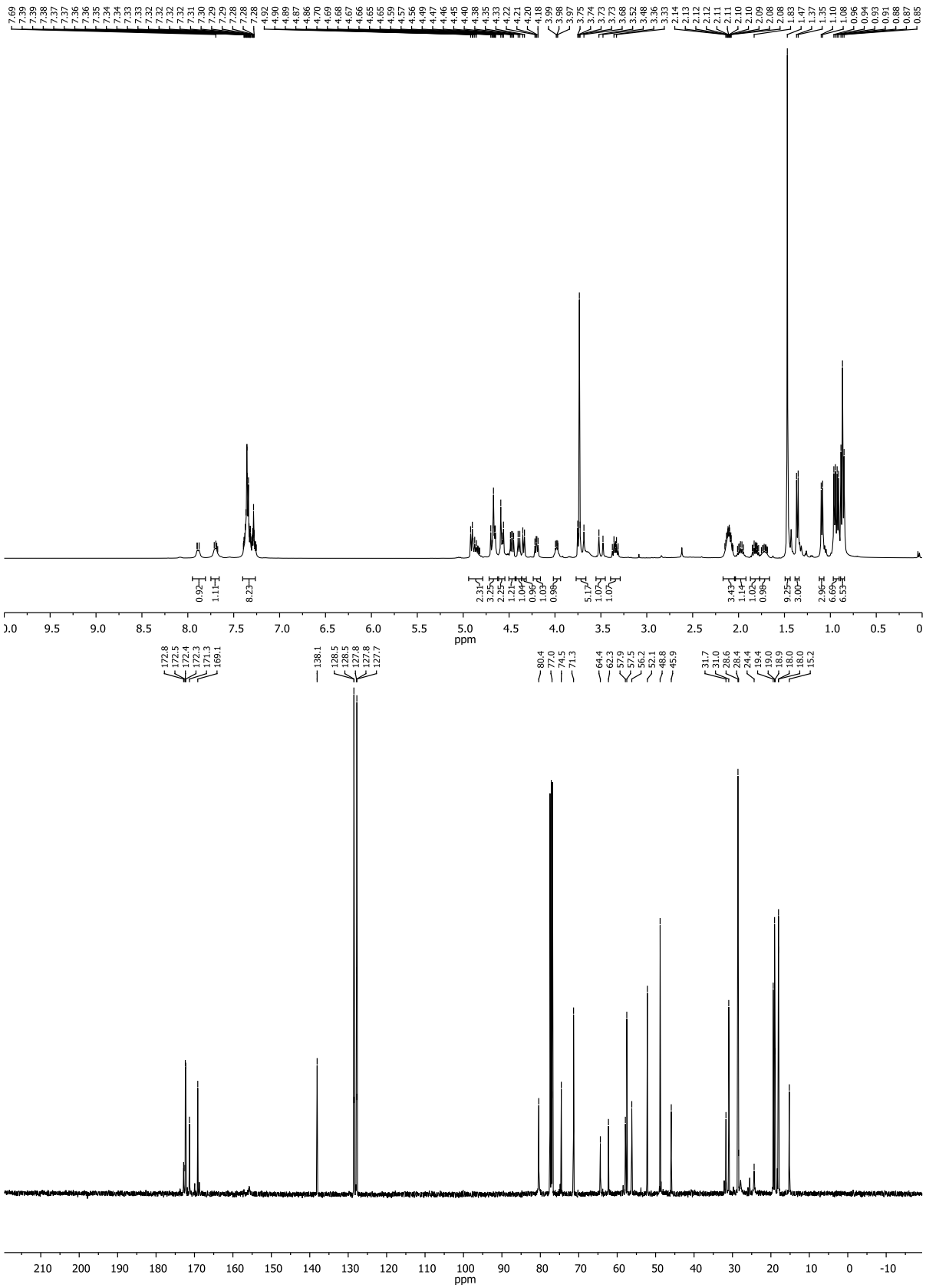


Figure 186 ^{1}H- and ^{13}C-NMR Spectra of 269.

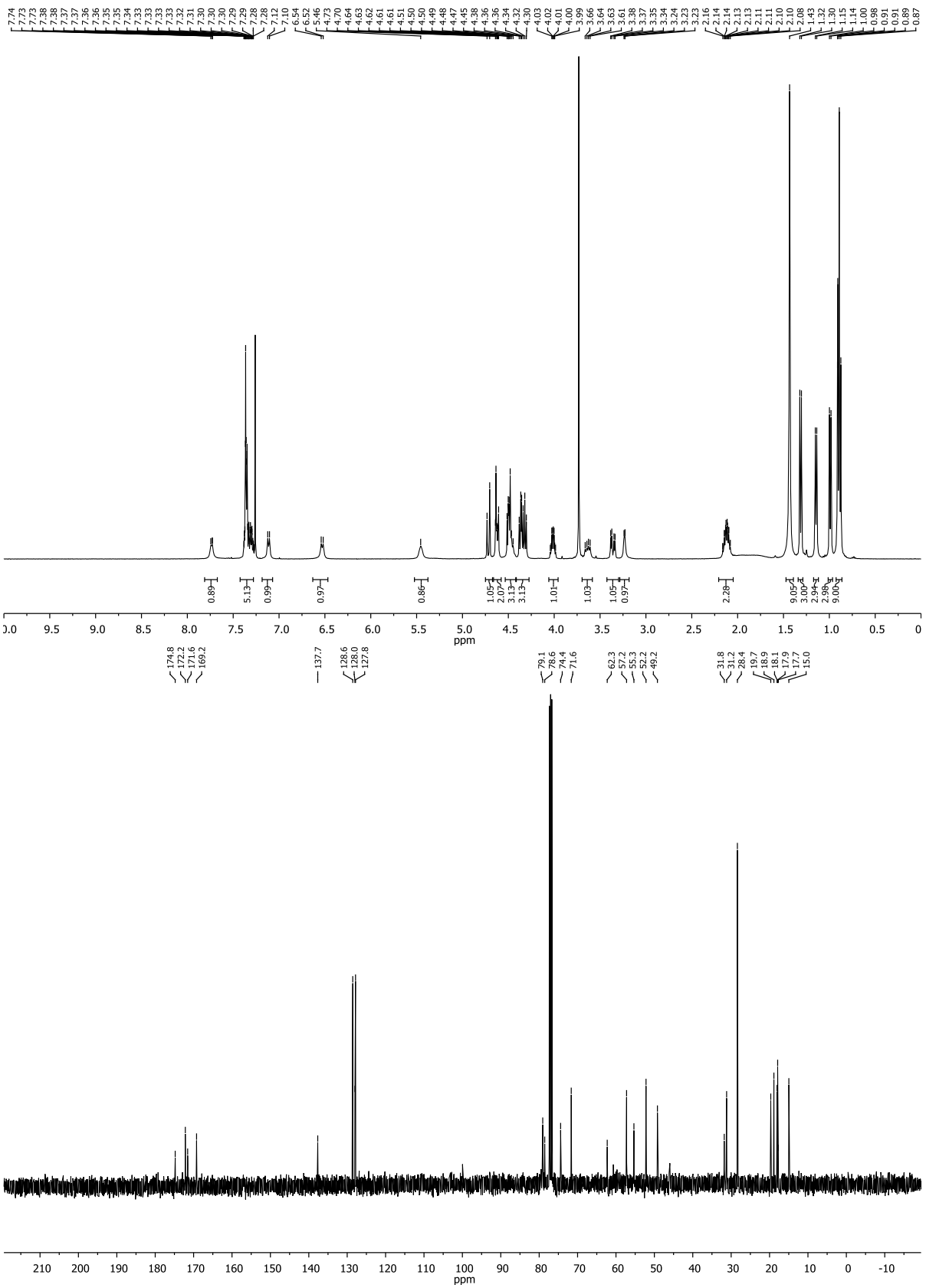


Figure 187 ^{1}H- and ^{13}C-NMR Spectra of 272.

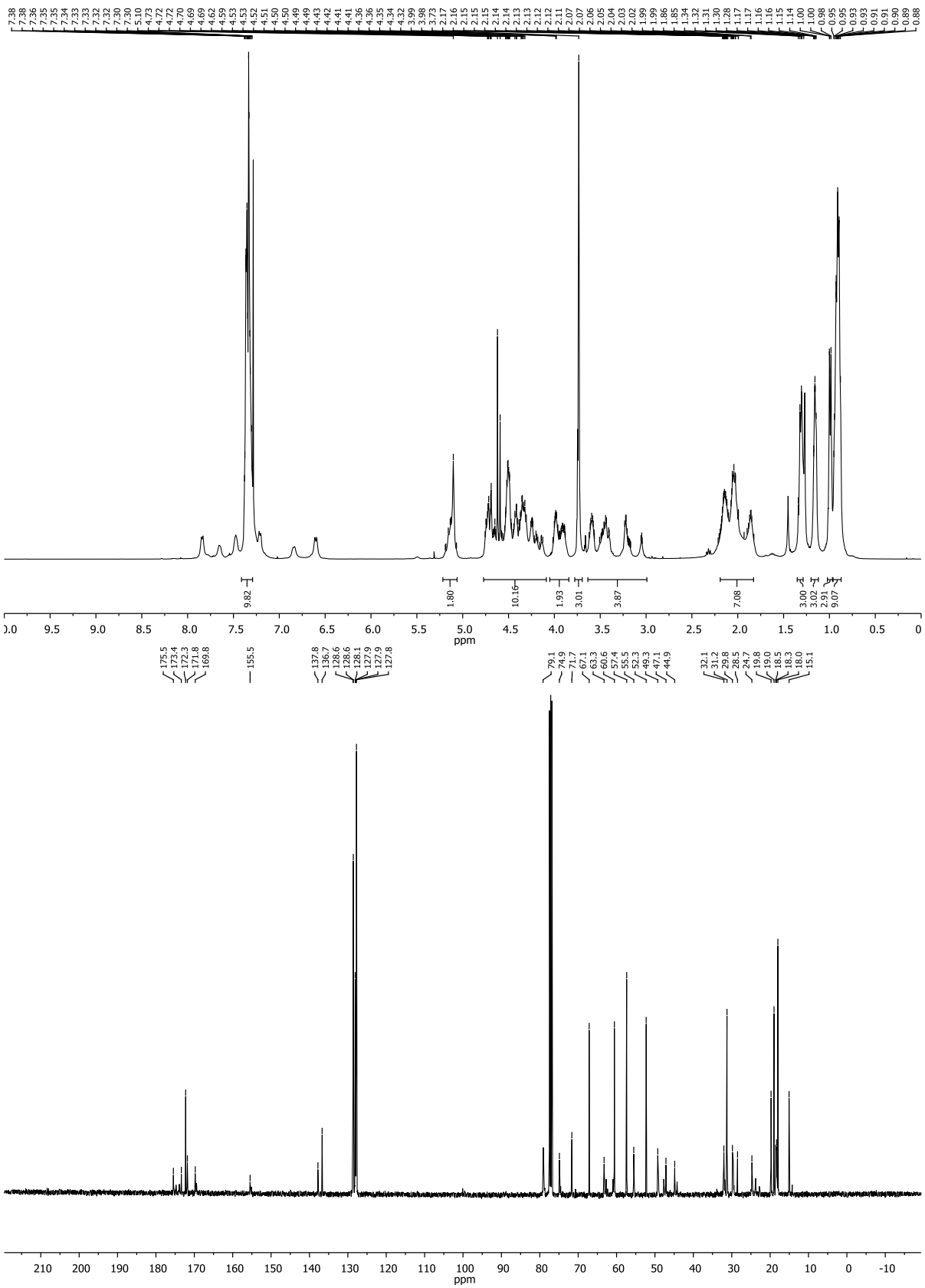


Figure 188 ^{1}H- and ^{13}C-NMR Spectra of 273.

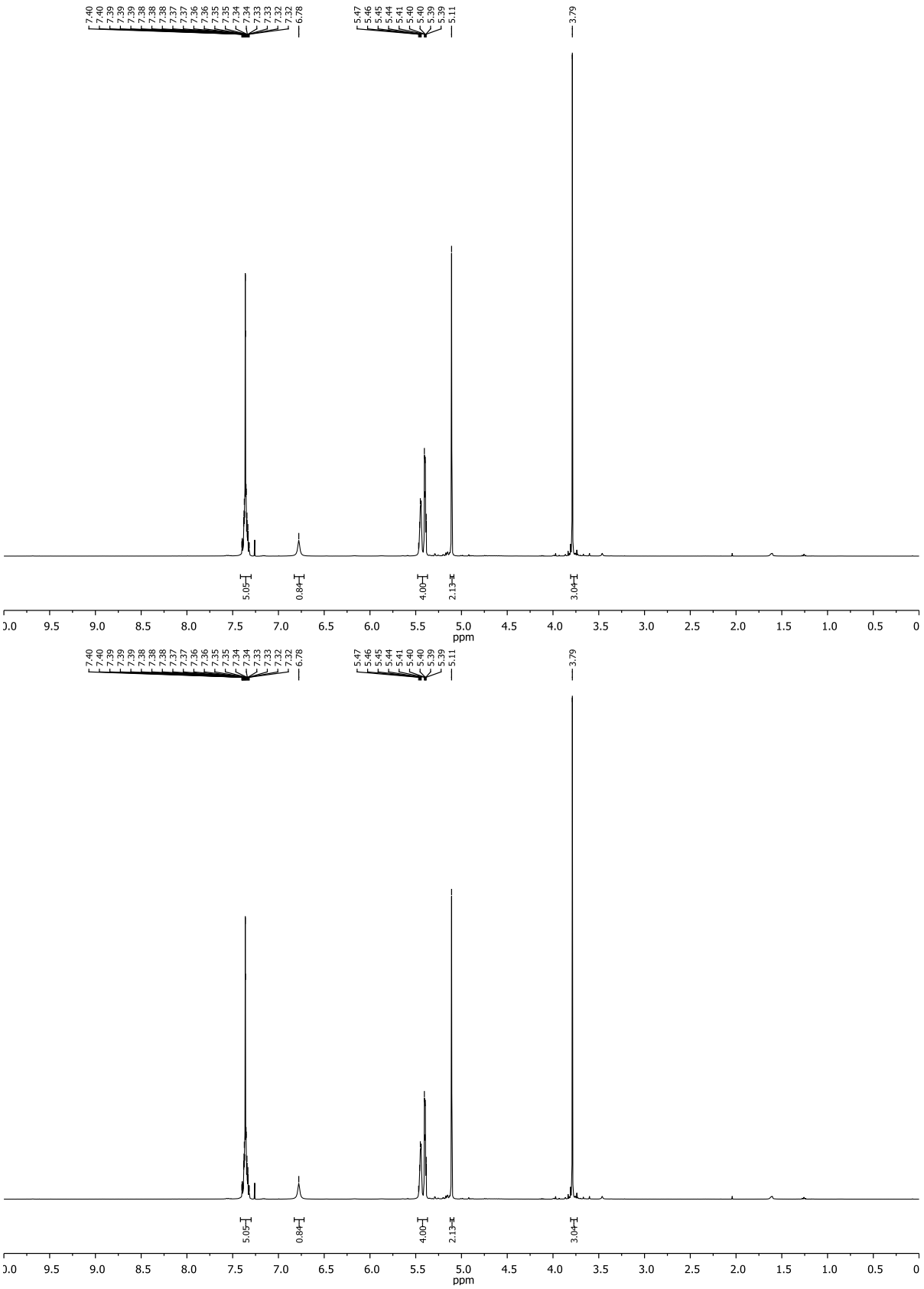


Figure 189 ^{1}H- and ^{13}C-NMR Spectra of 326a.

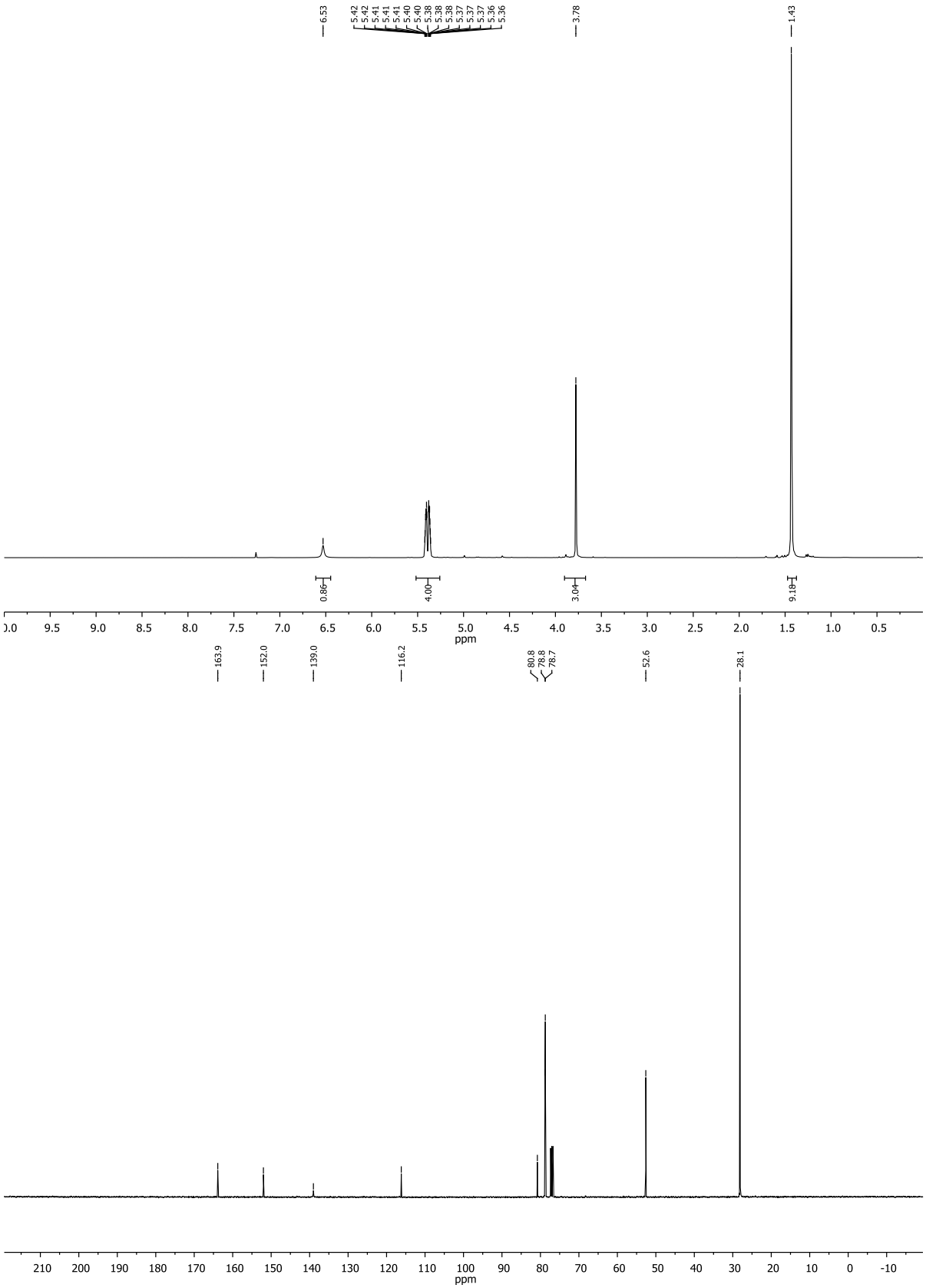


Figure 190 ^{1}H- and ^{13}C-NMR Spectra of 326b.

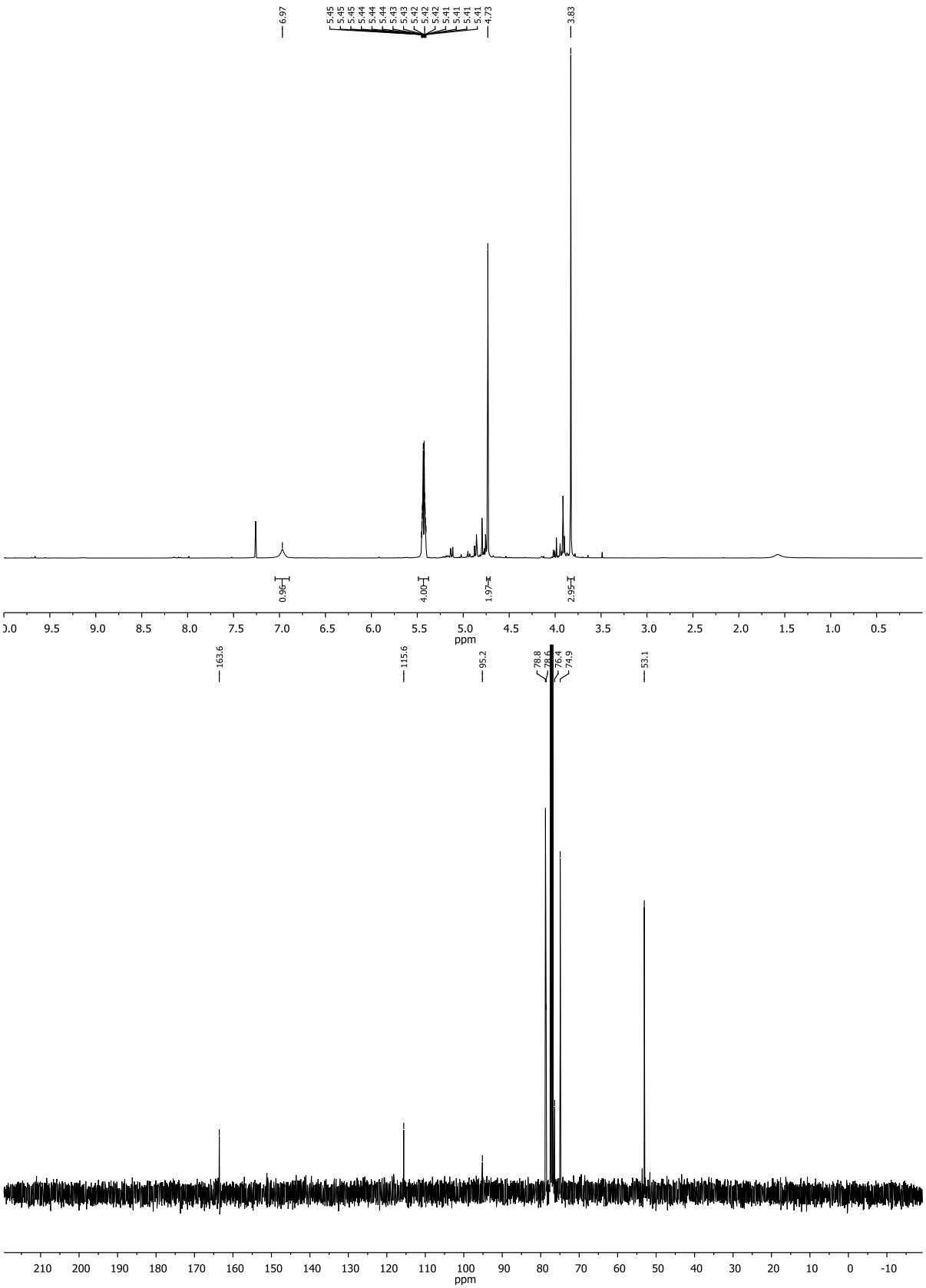


Figure 191 ^{1}H- and ^{13}C-NMR Spectra of 326c.

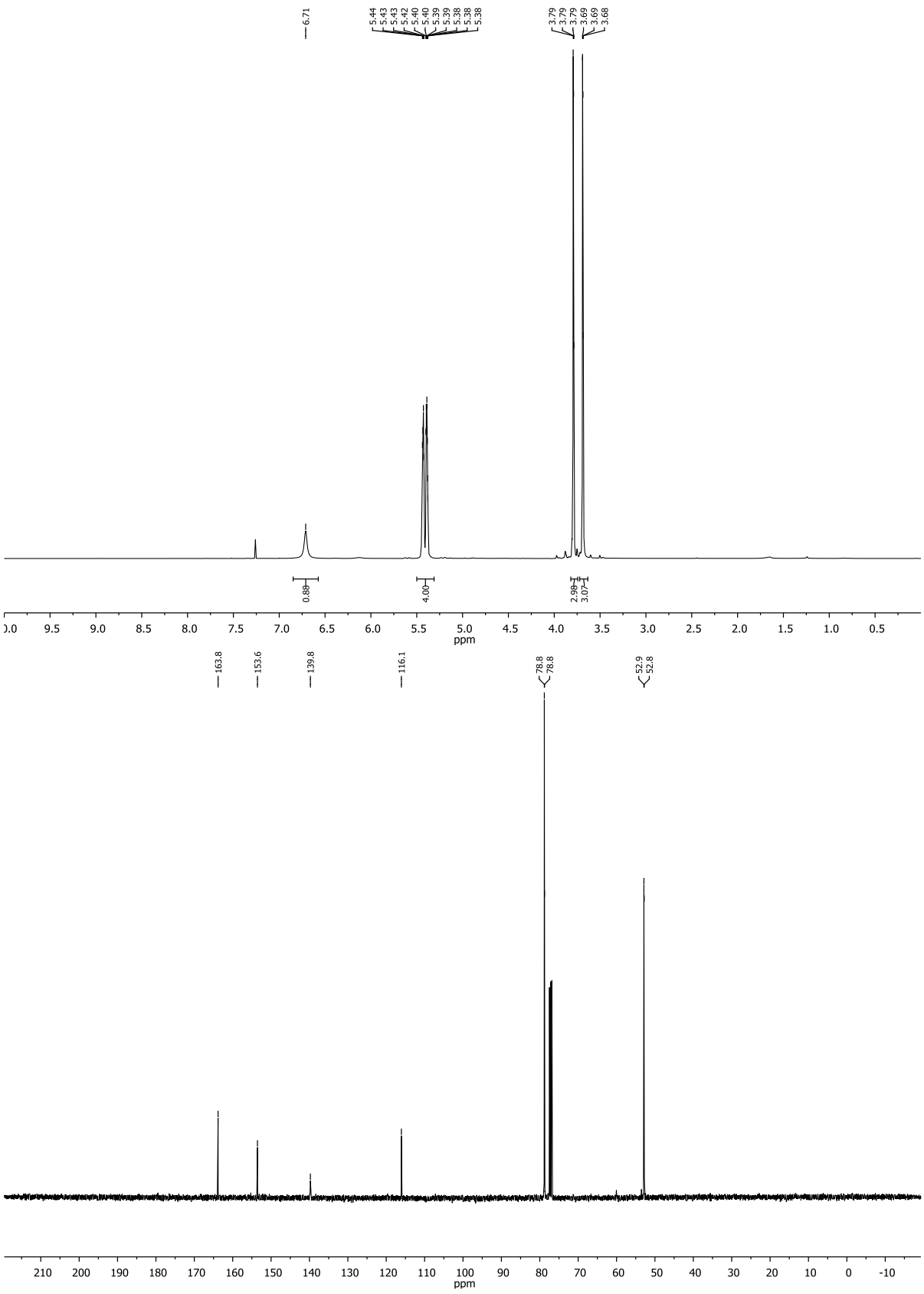


Figure 192 ^{1}H- and ^{13}C-NMR Spectra of 326d.

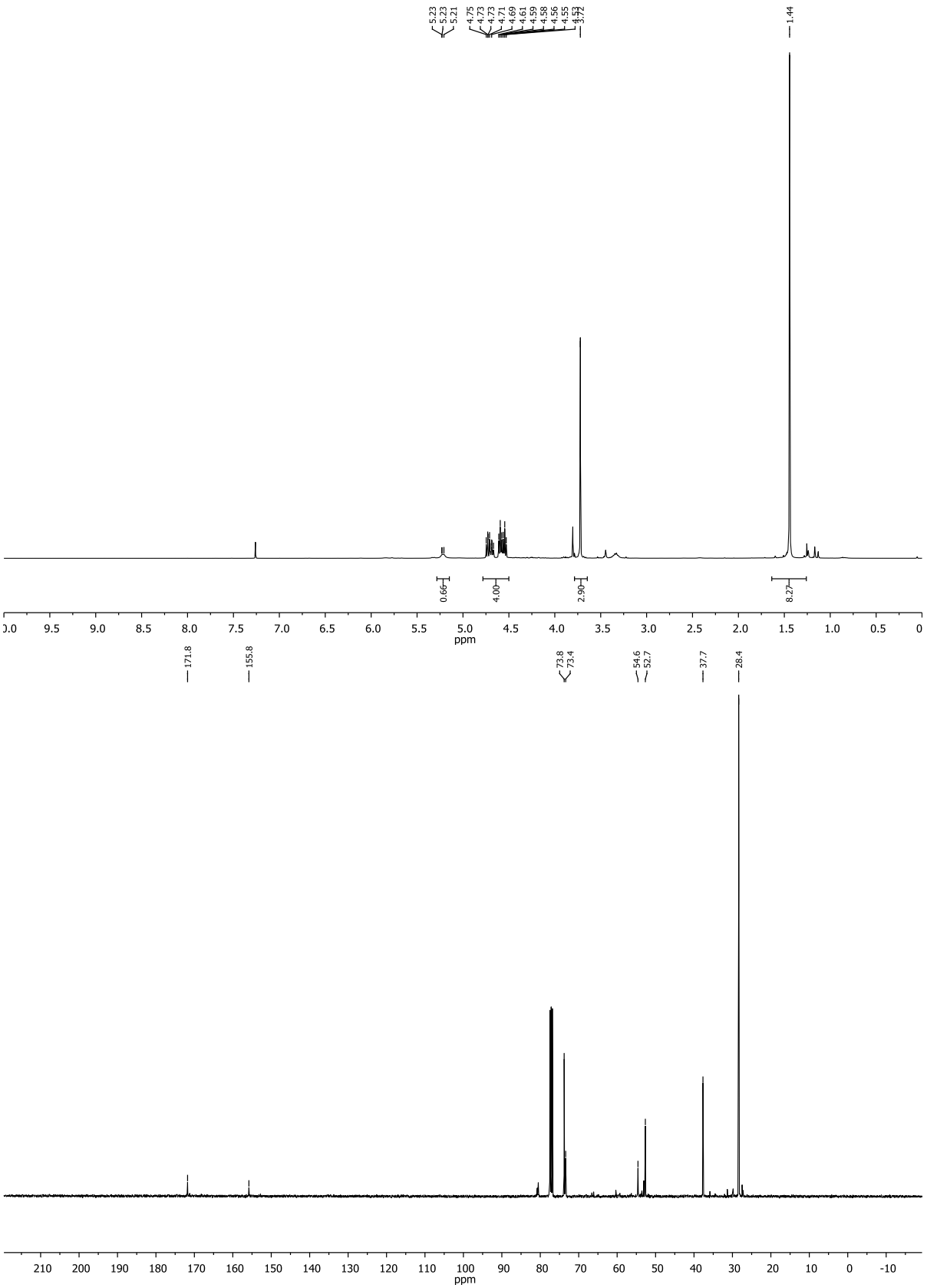


Figure 193 ^{1}H- and ^{13}C-NMR Spectra of 328b.

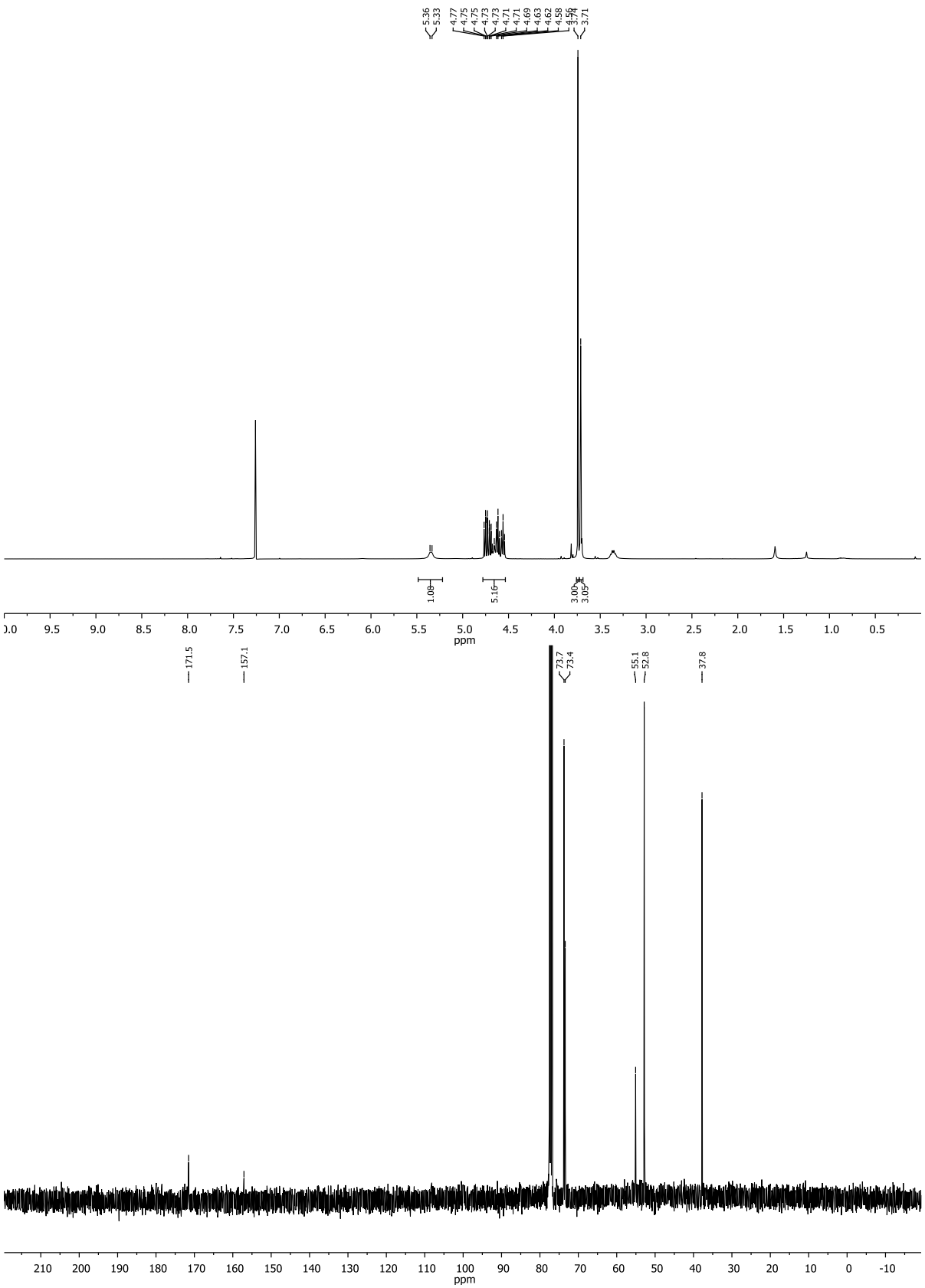


Figure 194 ^{1}H- and ^{13}C-NMR Spectra of 328d.

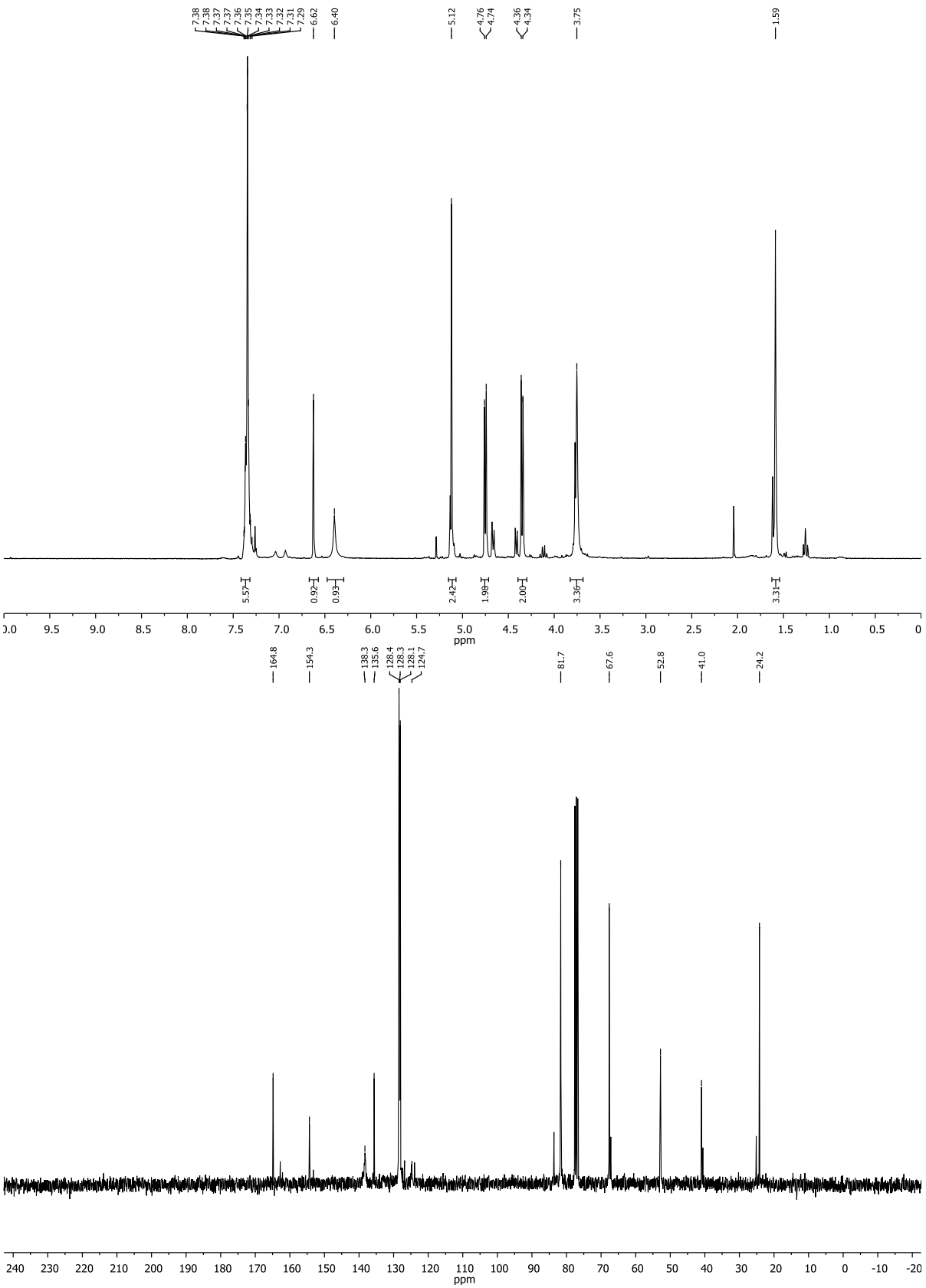


Figure 195 ^{1}H- and ^{13}C-NMR Spectra of 329a.

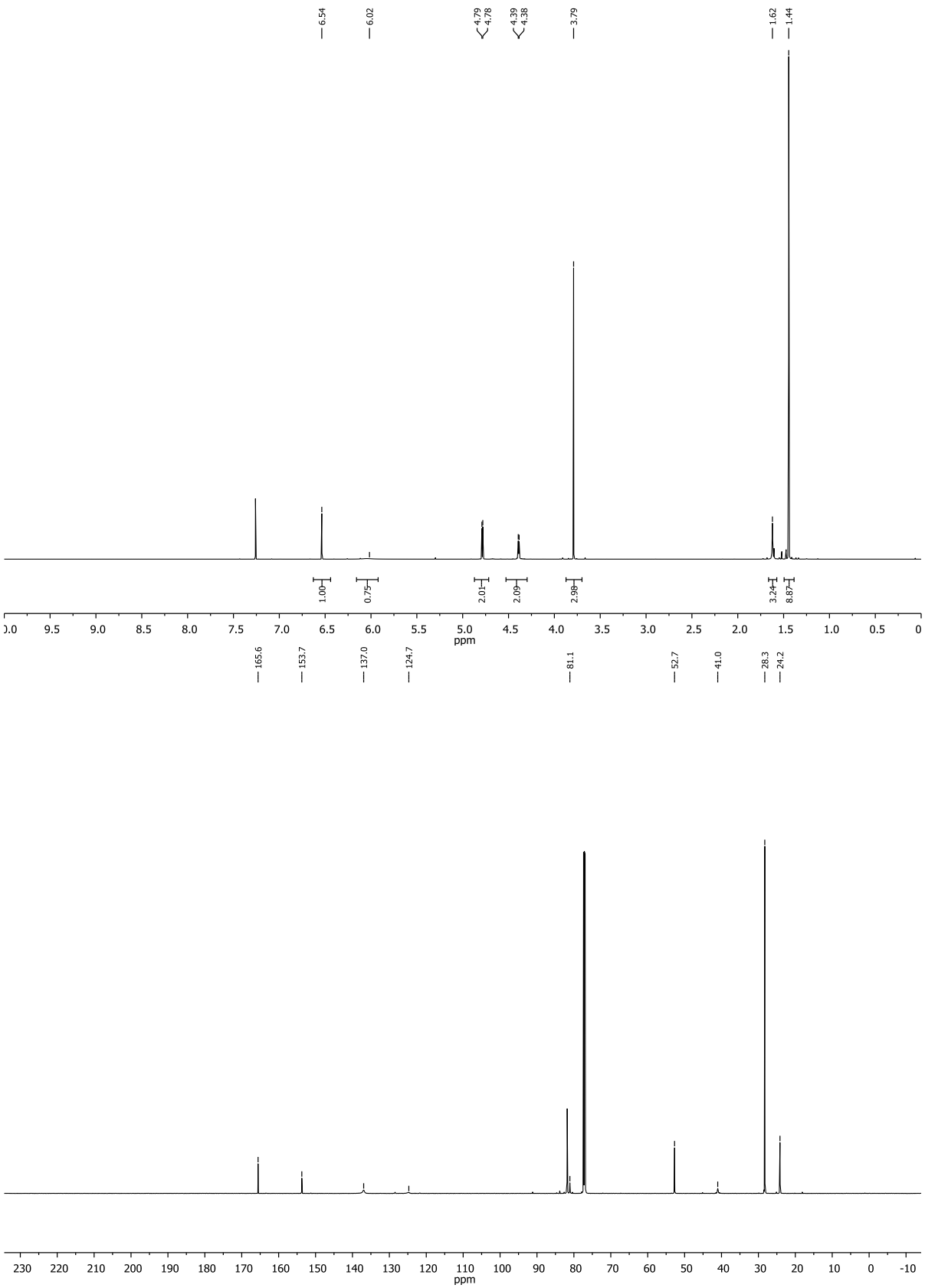


Figure 196 ^{1}H- and ^{13}C-NMR Spectra of 329b.

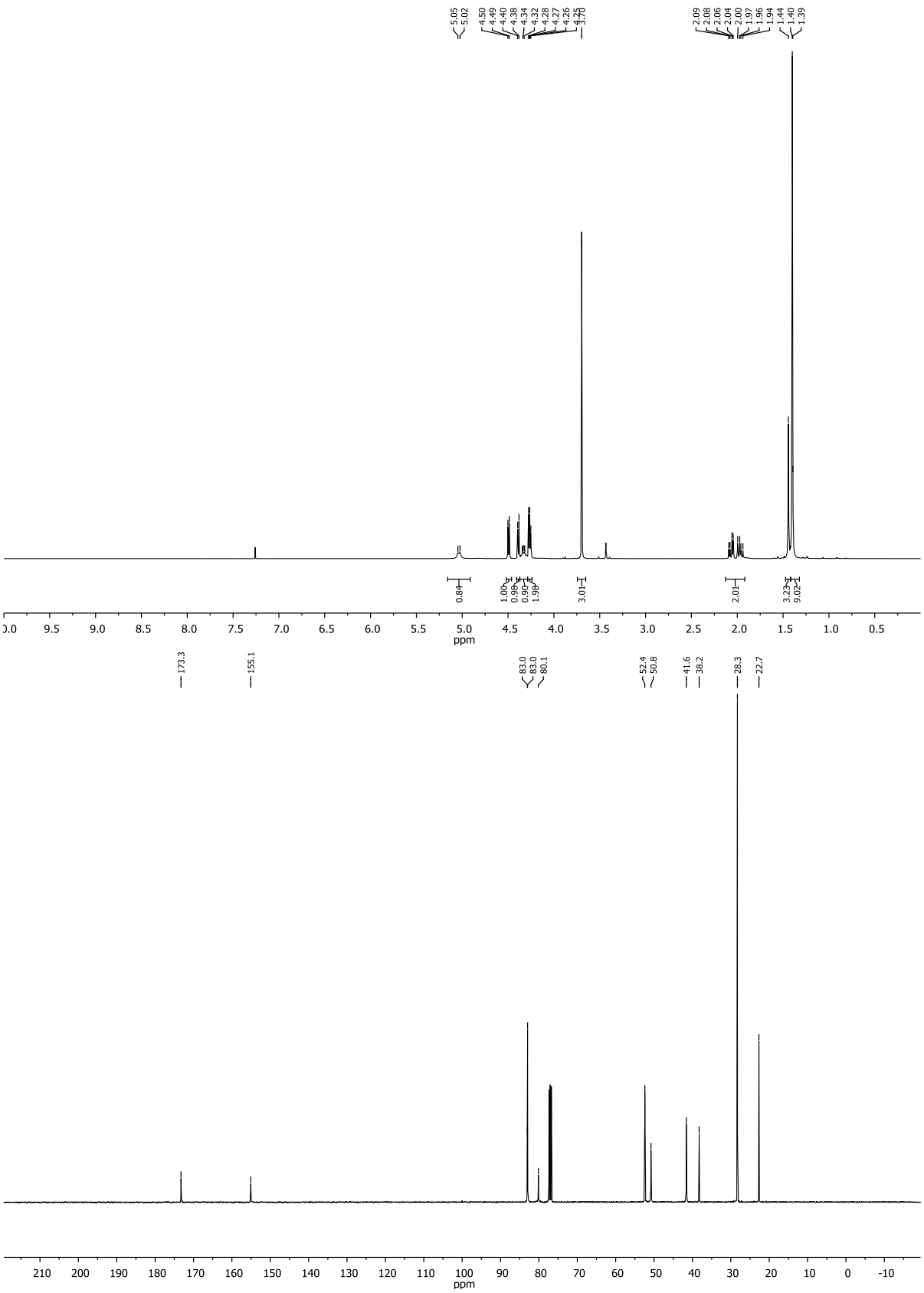


Figure 197 ^{1}H- and ^{13}C-NMR Spectra of 330b.

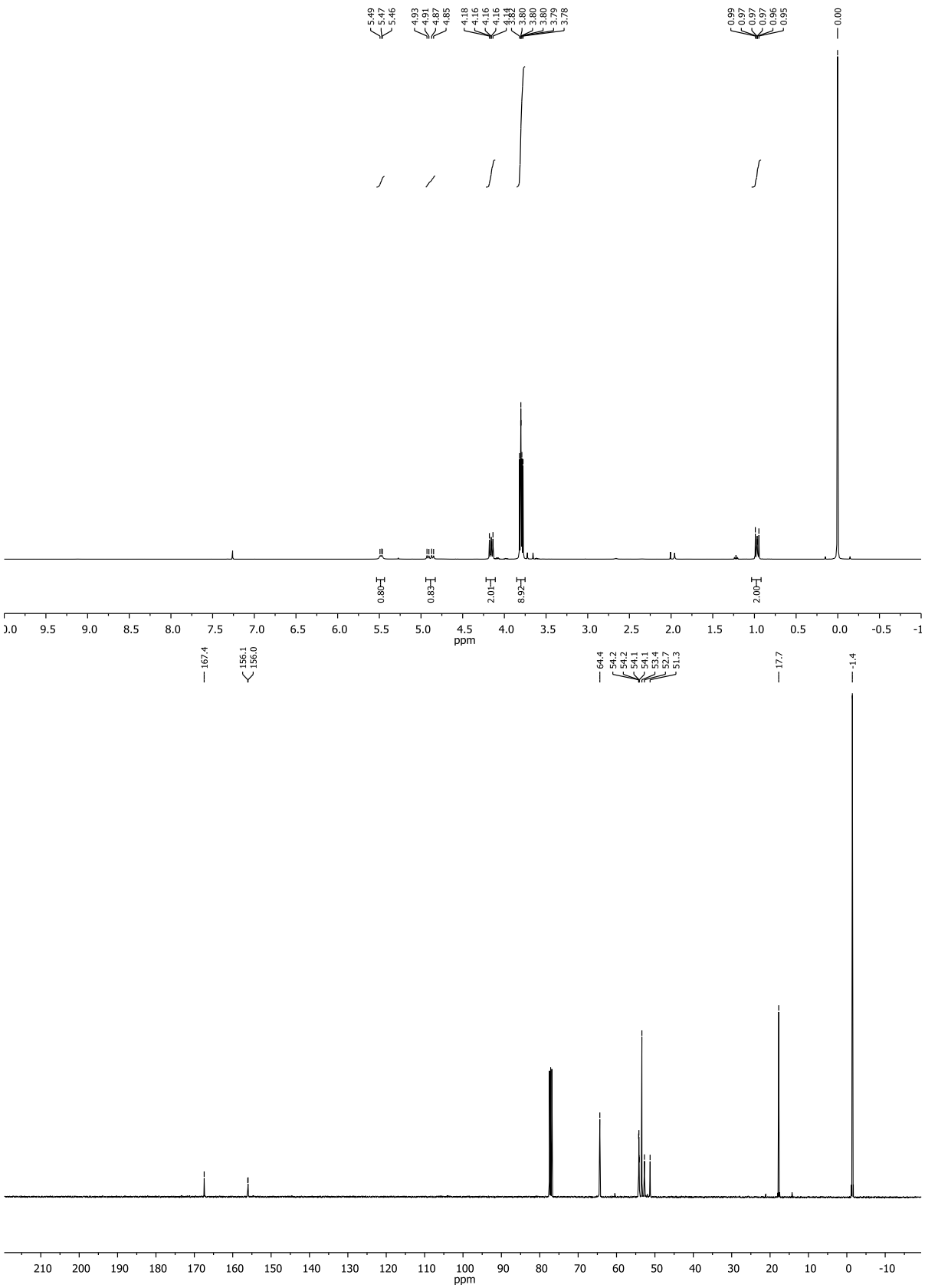


Figure 198 ^{1}H- and ^{13}C-NMR Spectra of 335.

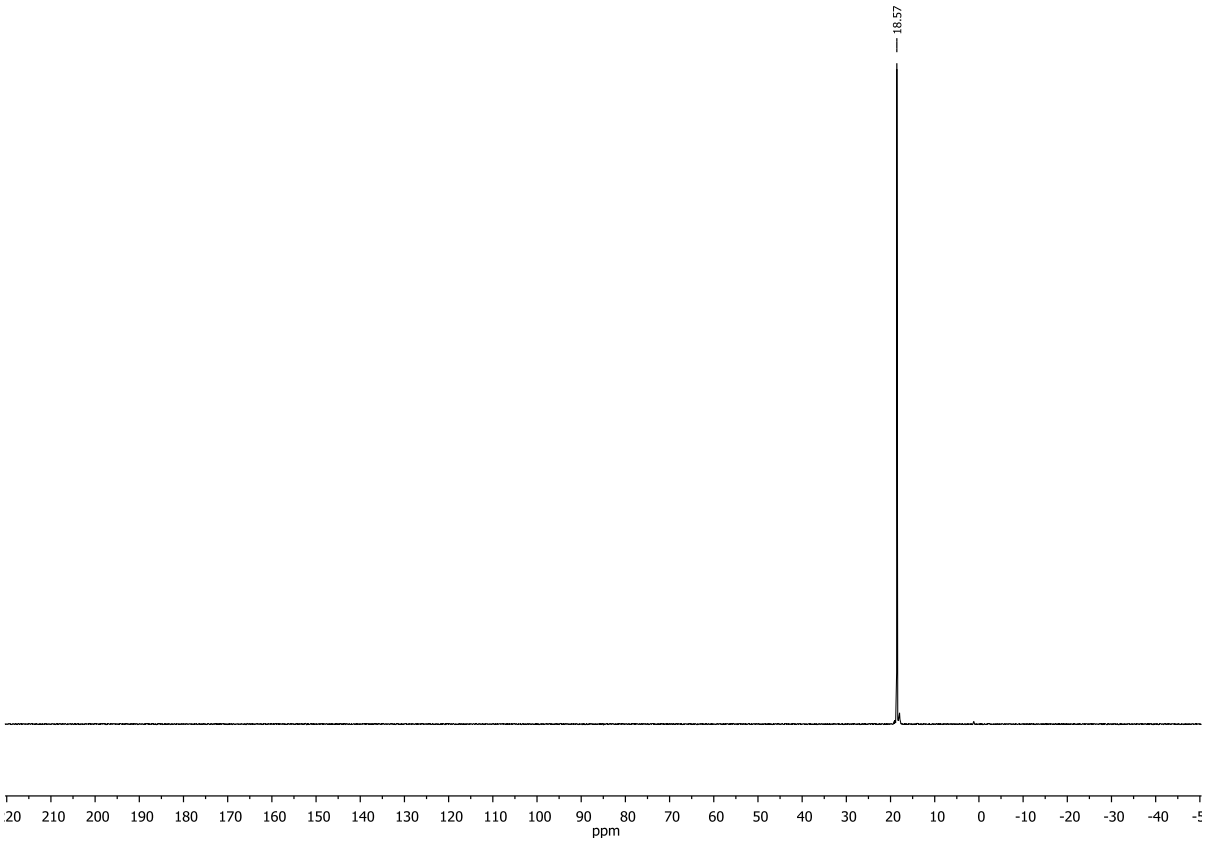


Figure 199 ^{31}P-NMR Spectrum of 335.

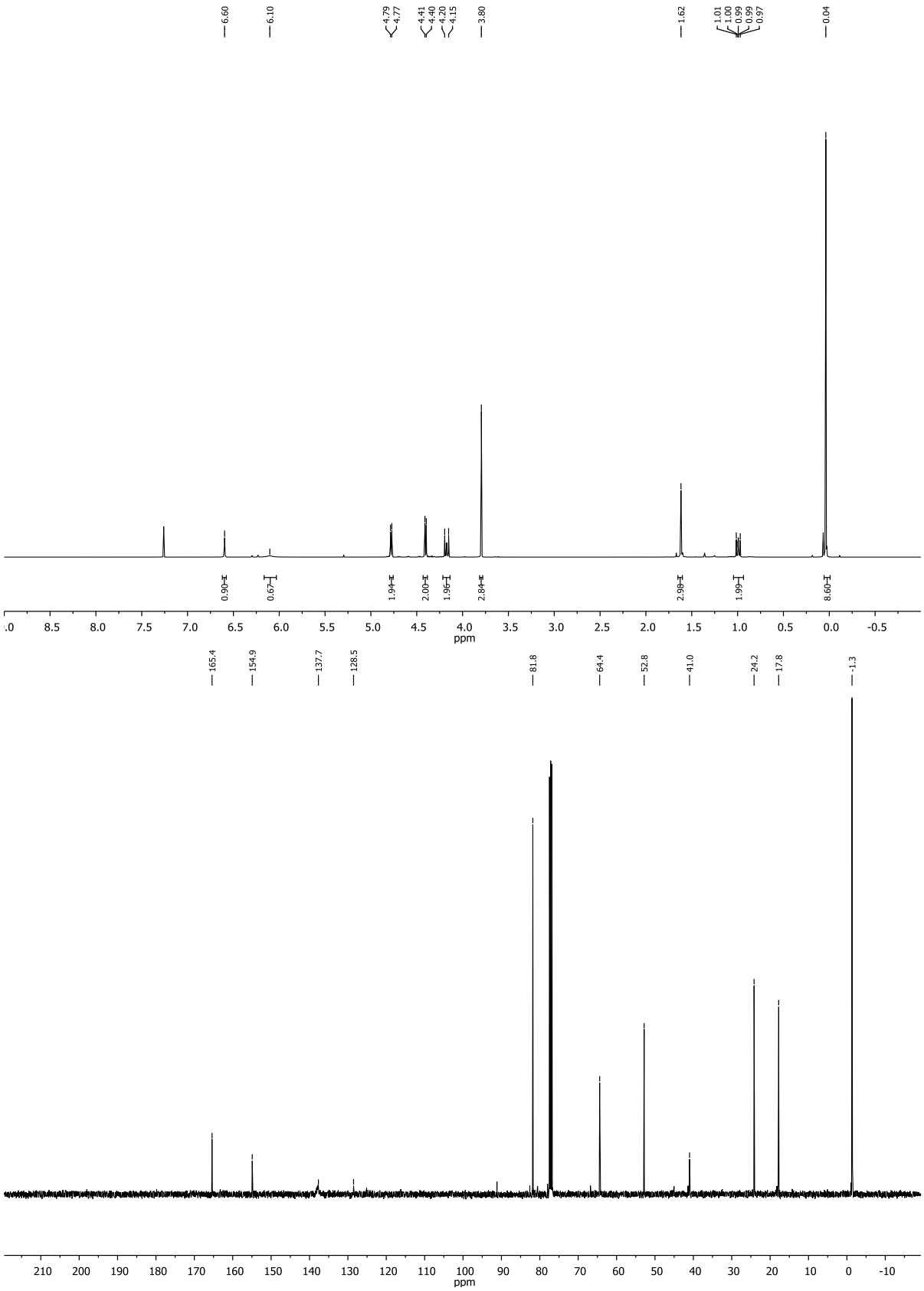


Figure 200 ^{1}H- and ^{13}C-NMR Spectra of 329c.

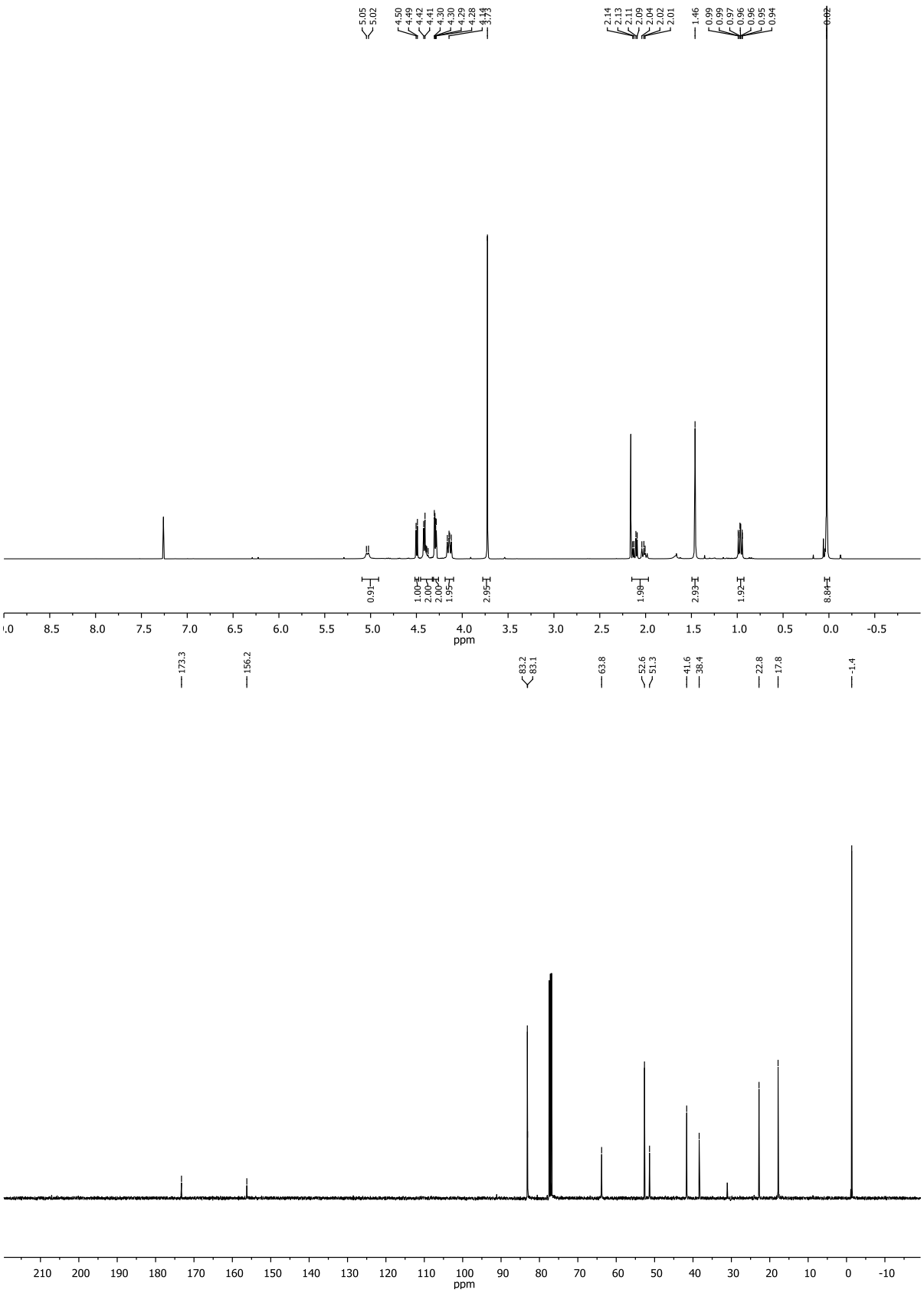


Figure 201 ^{1}H- and ^{13}C-NMR Spectra of 330c.

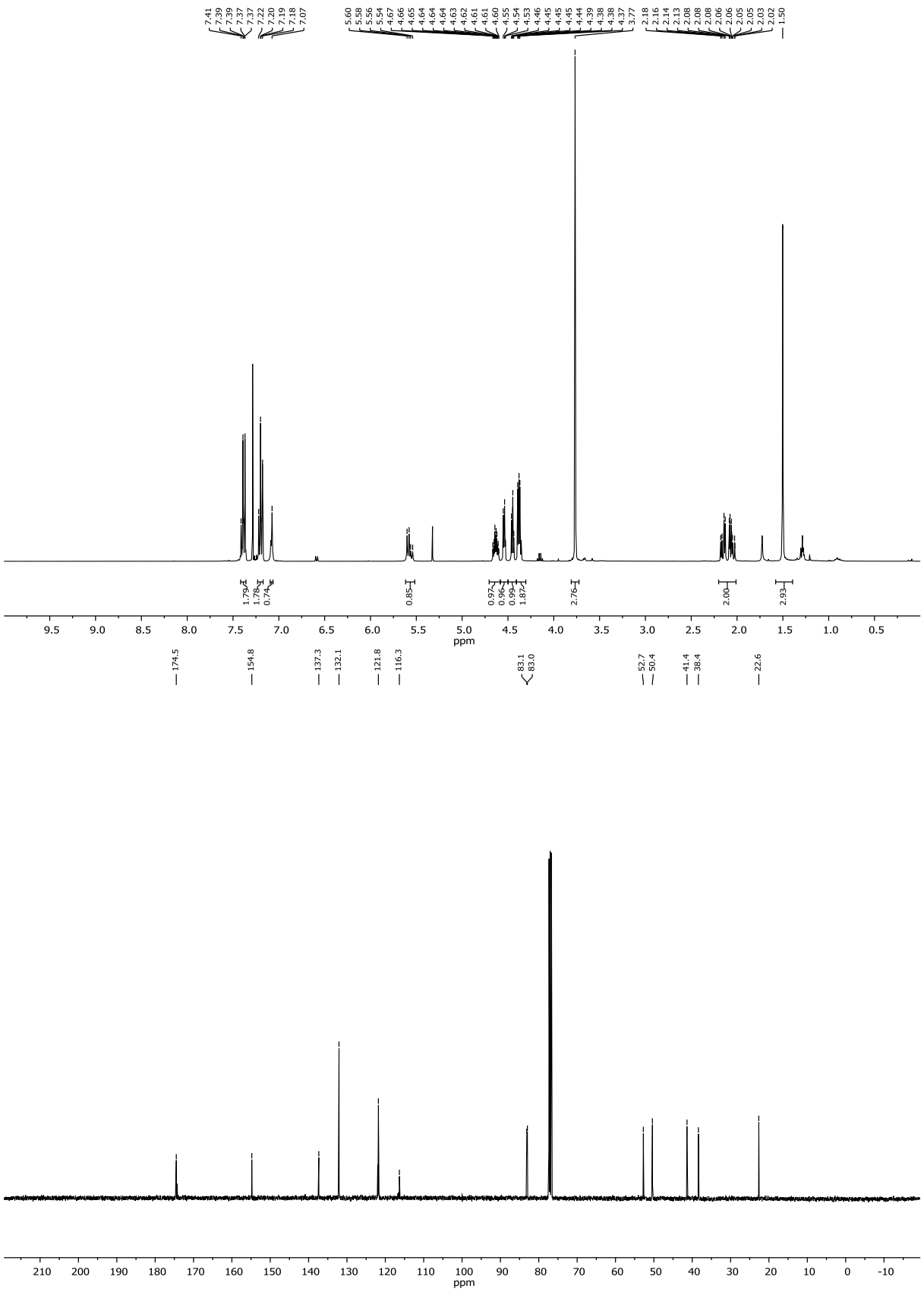


Figure 202 ^{1}H- and ^{13}C-NMR Spectra of 333.

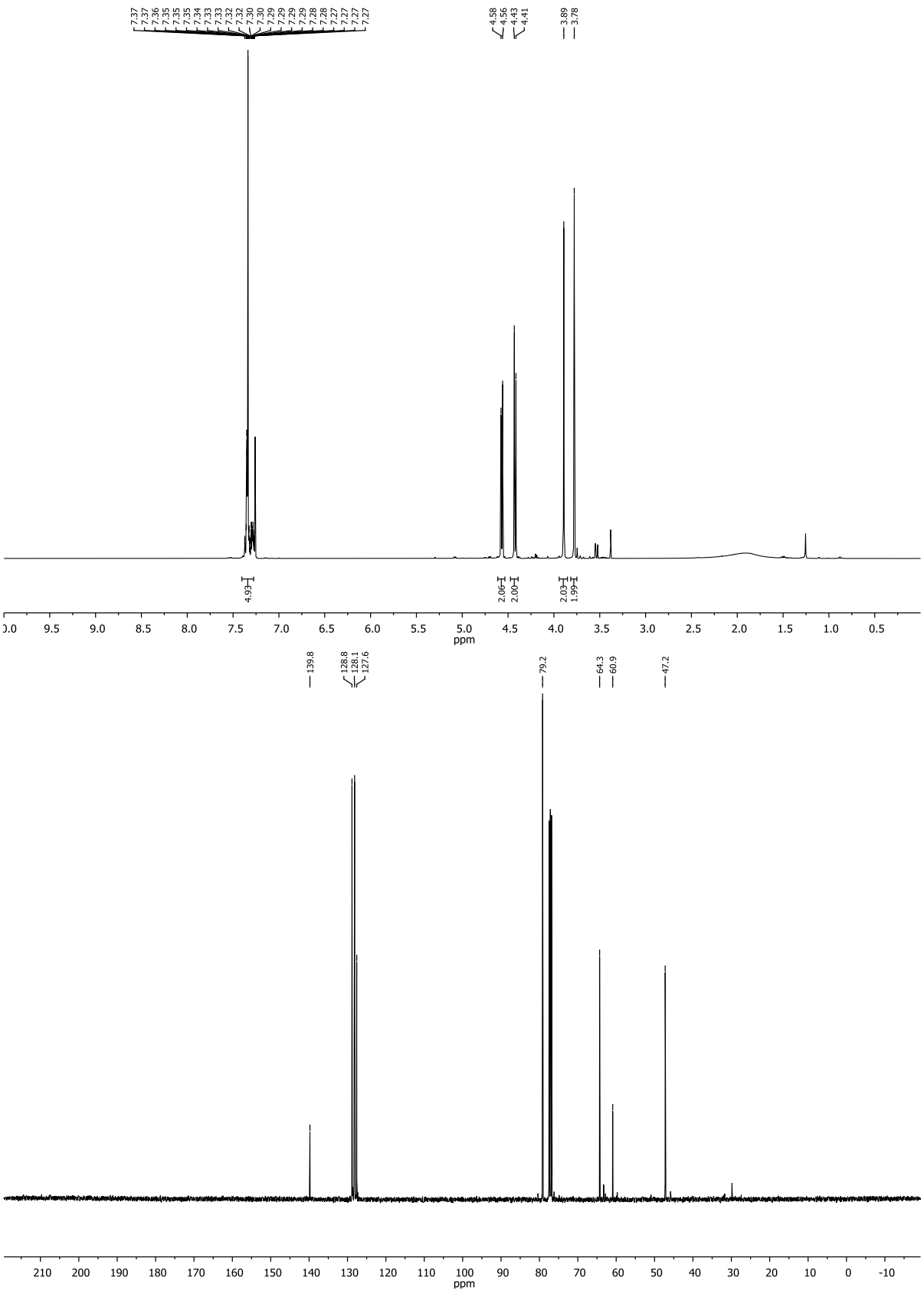


Figure 203 ^{1}H- and ^{13}C-NMR Spectra of 337.

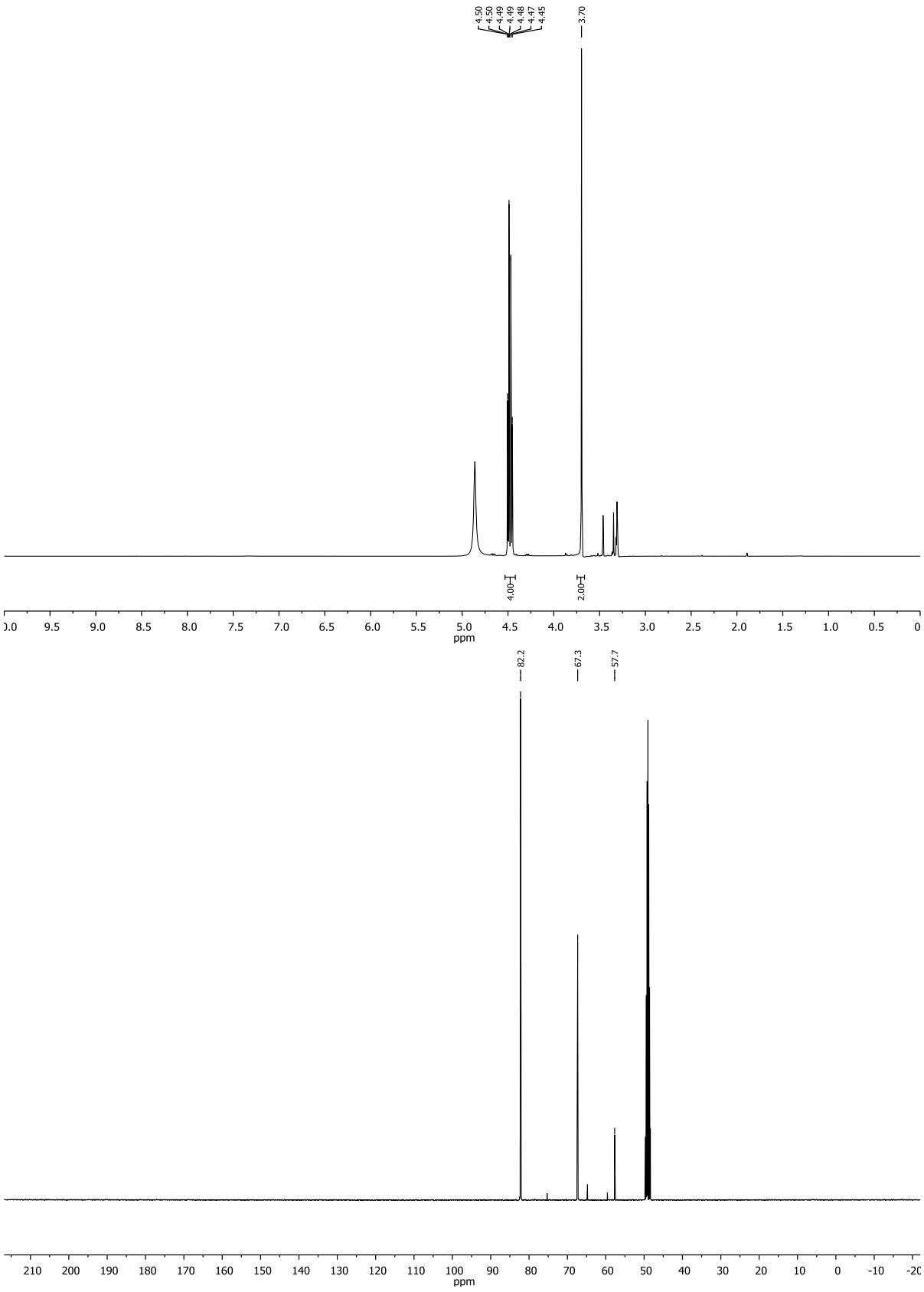


Figure 204 ^{1}H- and ^{13}C-NMR Spectra of 338.

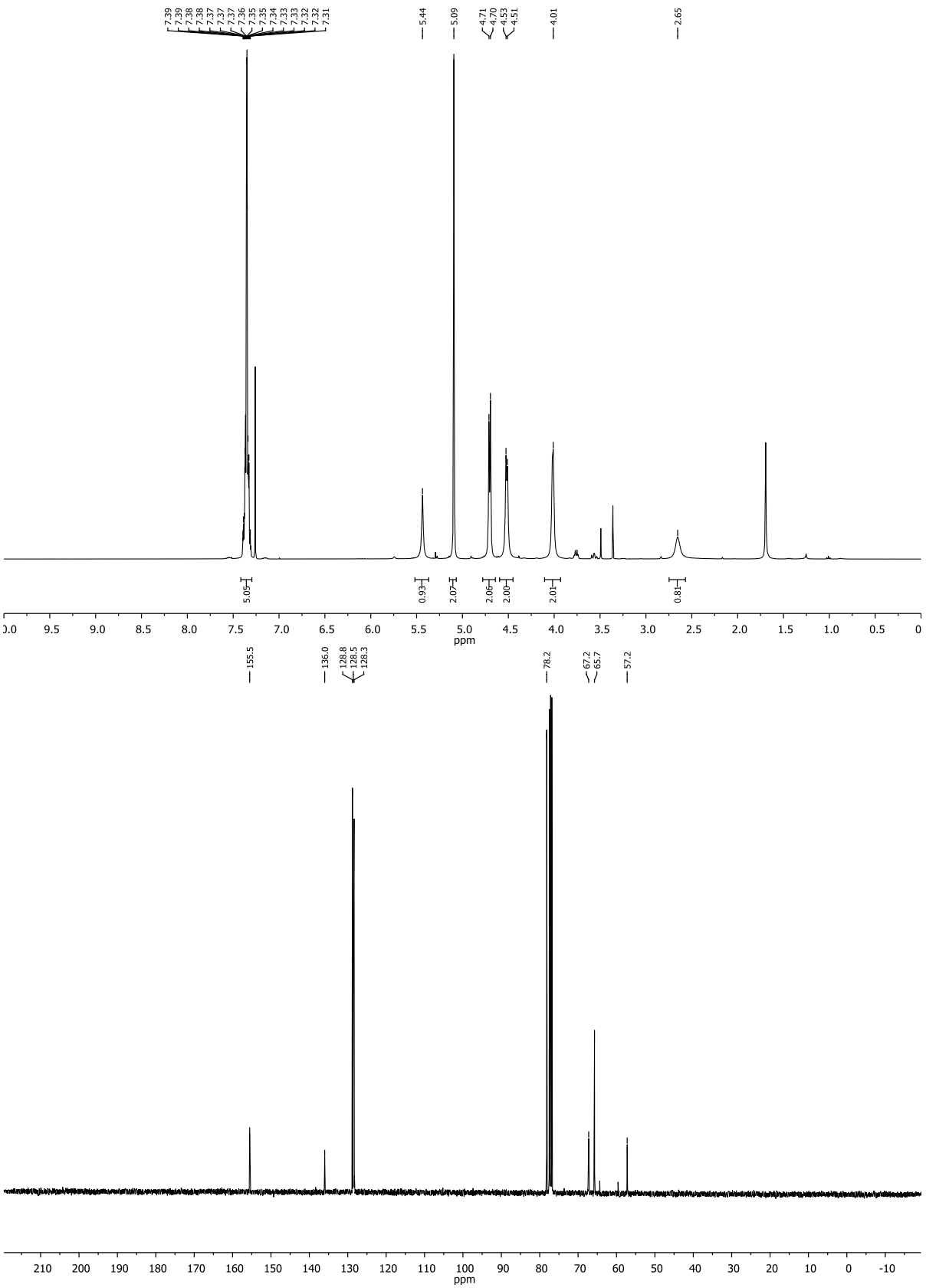


Figure 205 ^{1}H- and ^{13}C-NMR Spectra of 312.

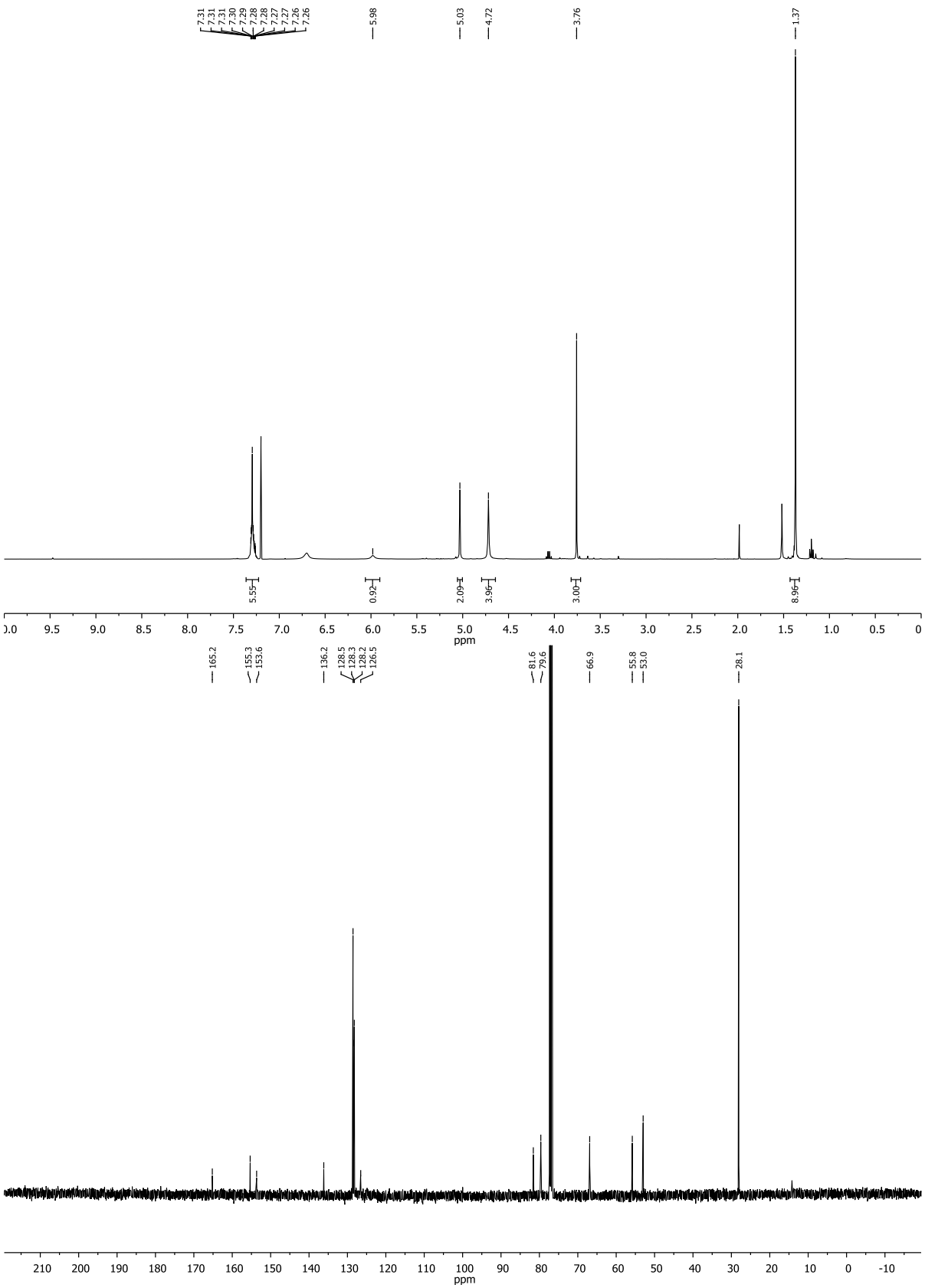


Figure 206 ^{1}H- and ^{13}C-NMR Spectra of 336.

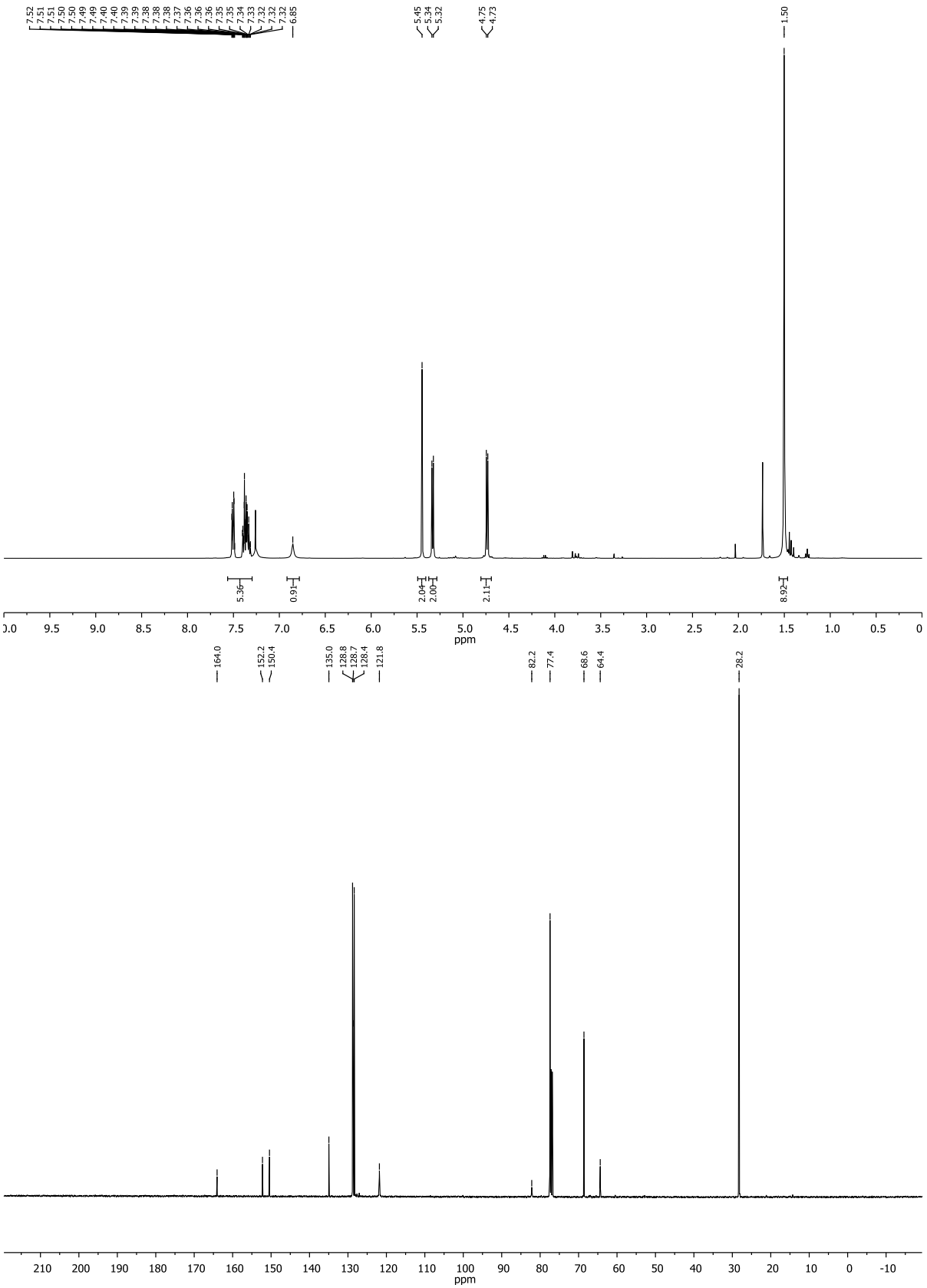


Figure 207 ^{1}H- and ^{13}C-NMR Spectra of 339.

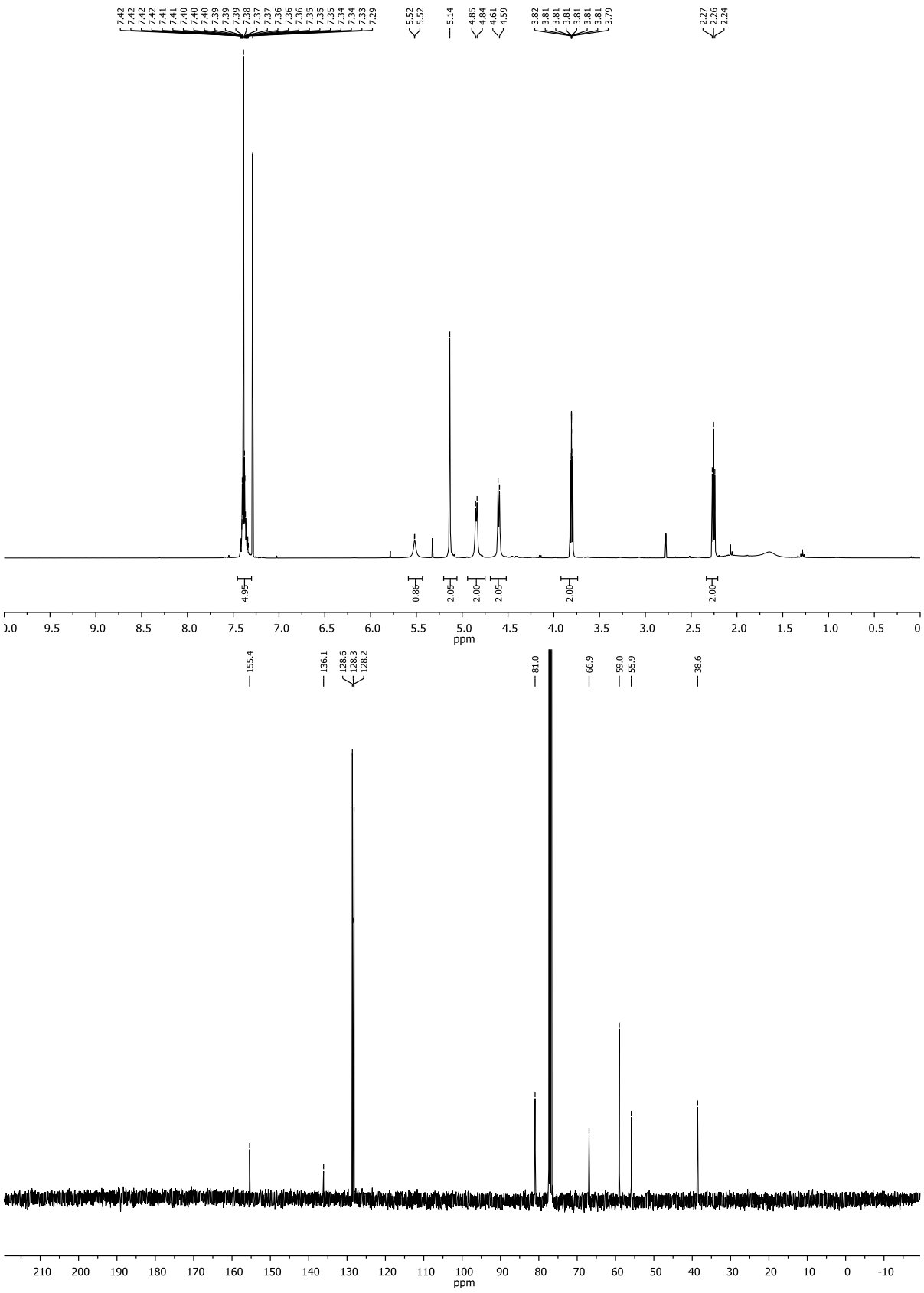


Figure 208 ^{1}H- and ^{13}C-NMR Spectra of 348.

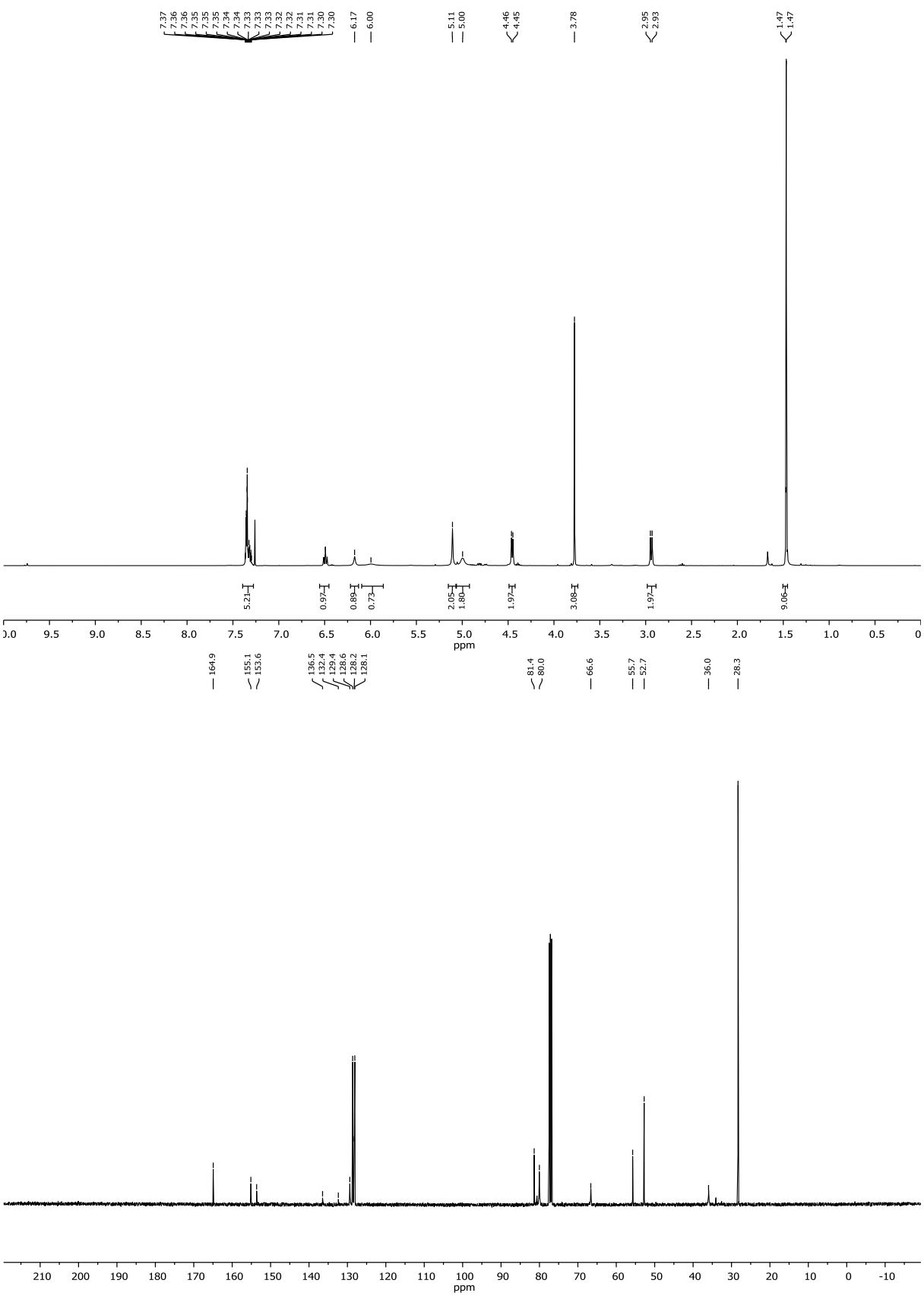


Figure 209 ^{1}H- and ^{13}C-NMR Spectra of 350.

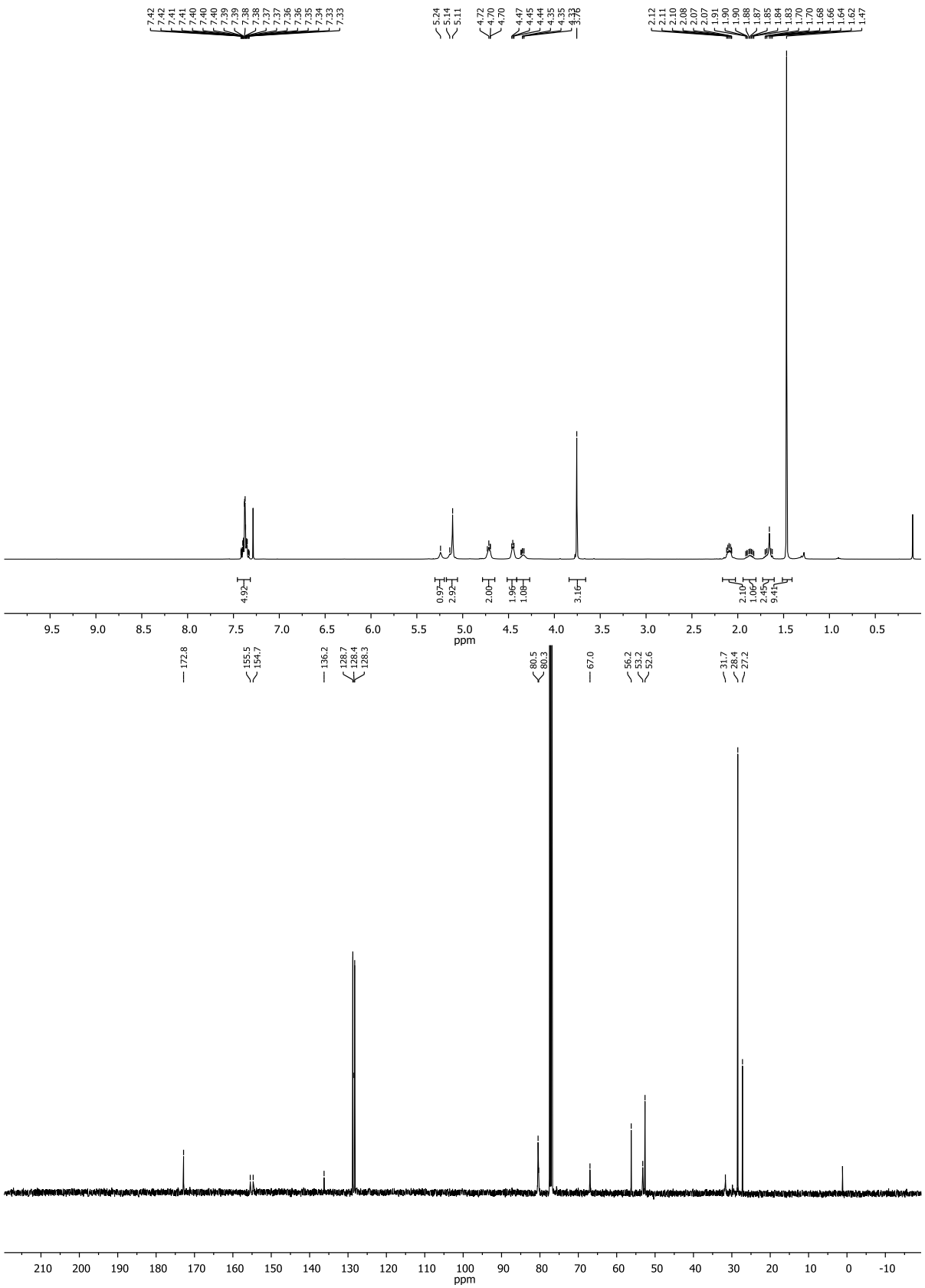


Figure 210 ^{1}H- and ^{13}C-NMR Spectra of 351.

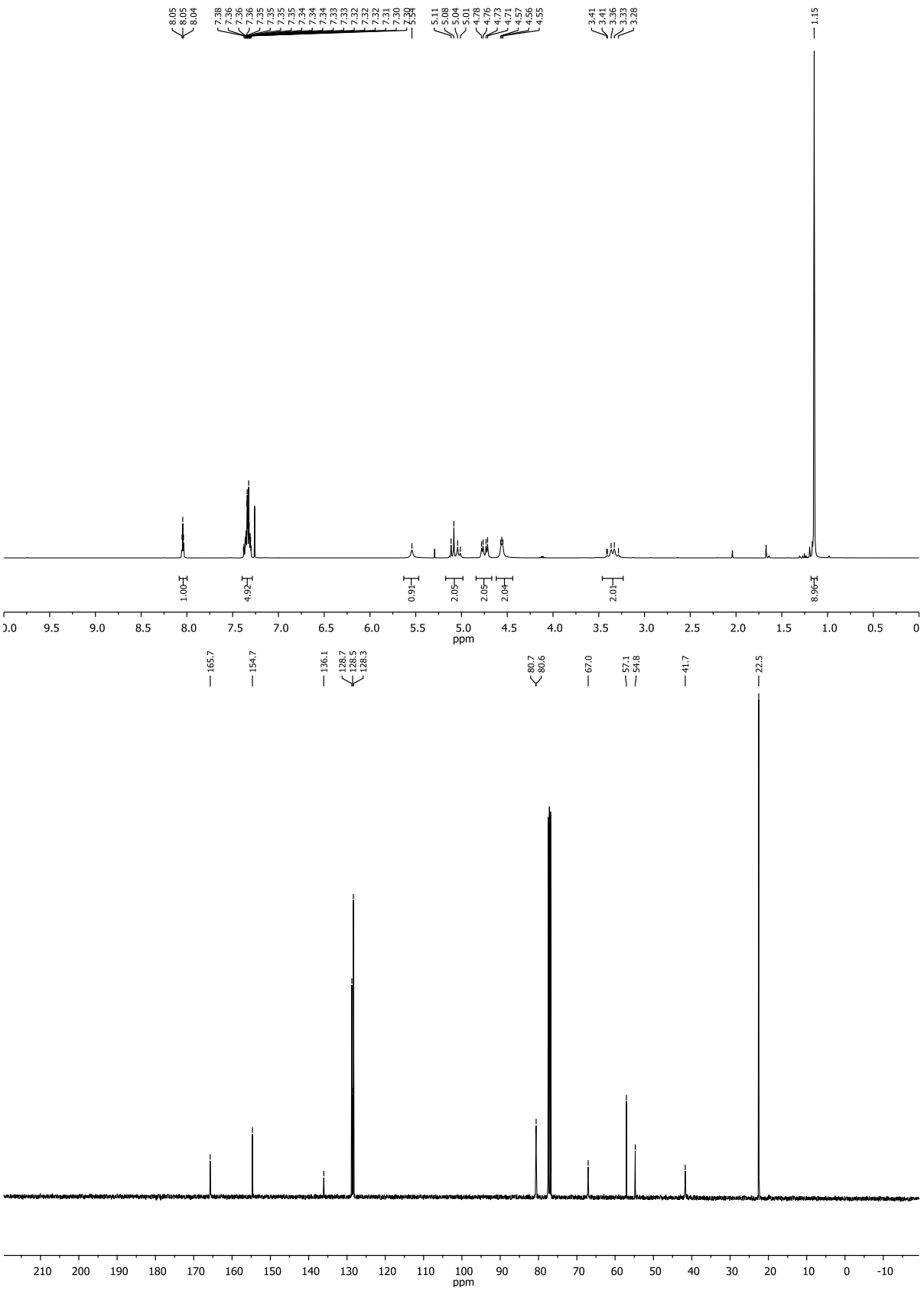


Figure 211 ^{1}H- and ^{13}C-NMR Spectra of 345.

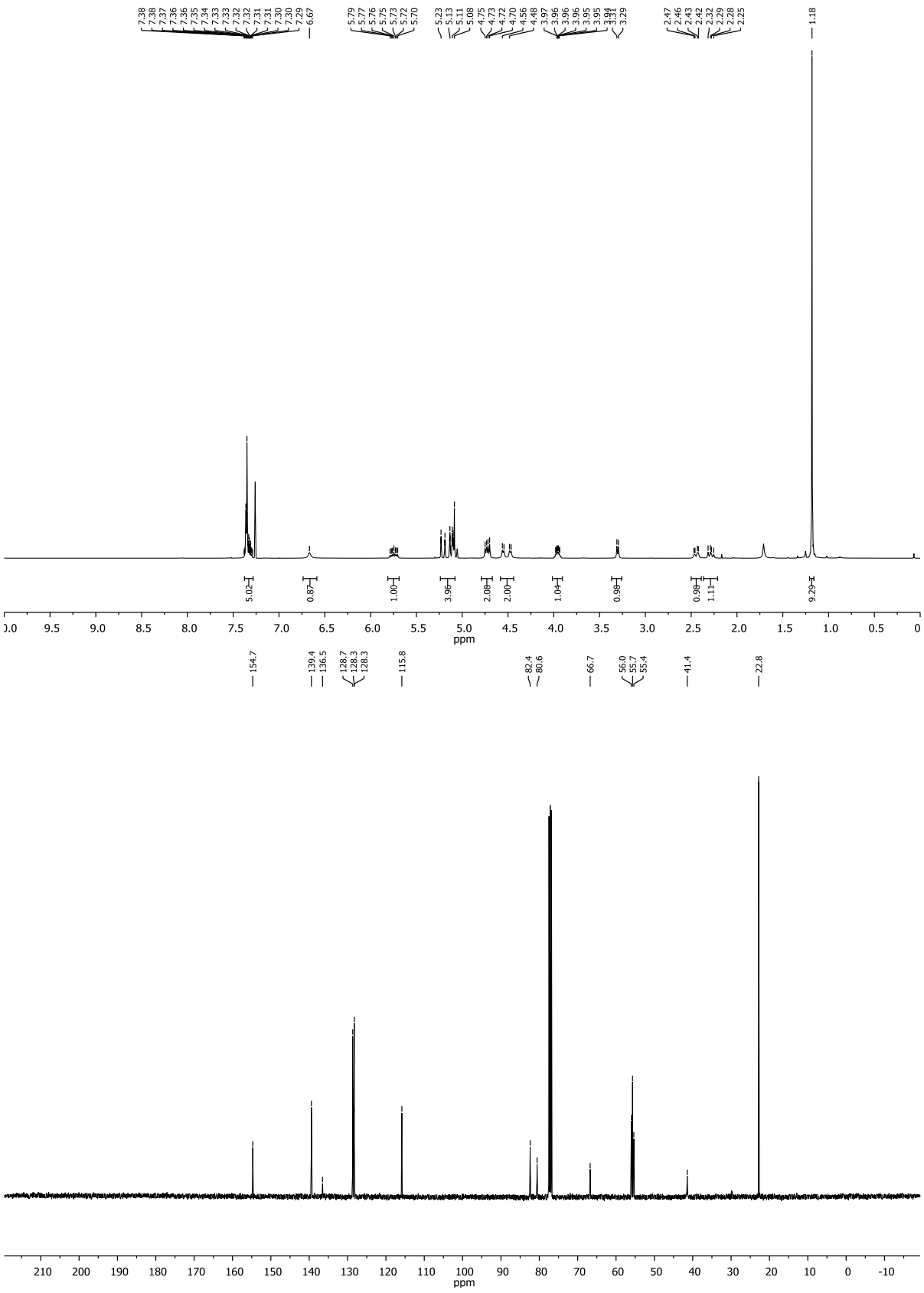


Figure 212 ^{1}H- and ^{13}C-NMR Spectra of 349.

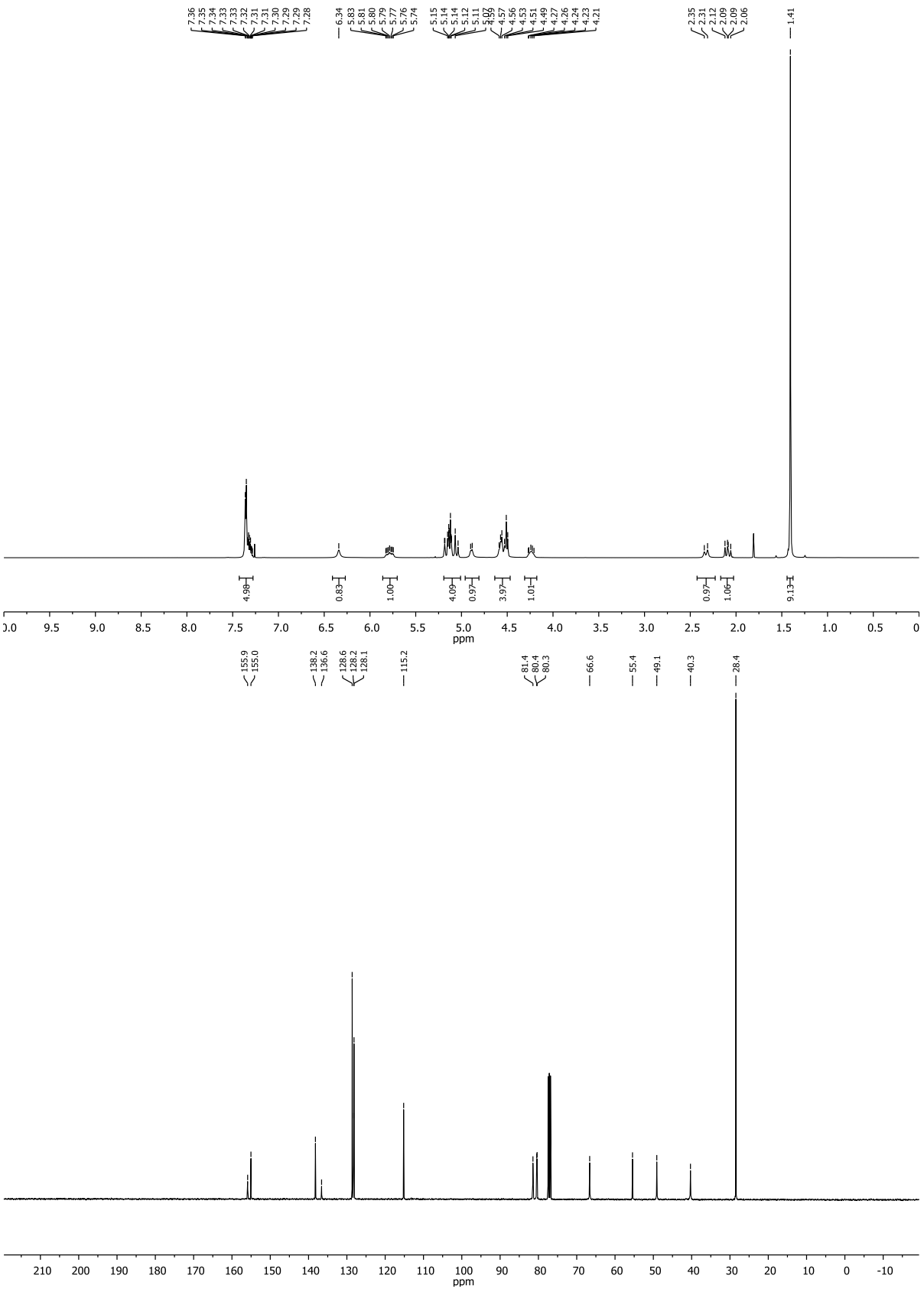


Figure 213 ^{1}H- and ^{13}C-NMR Spectra of 344.

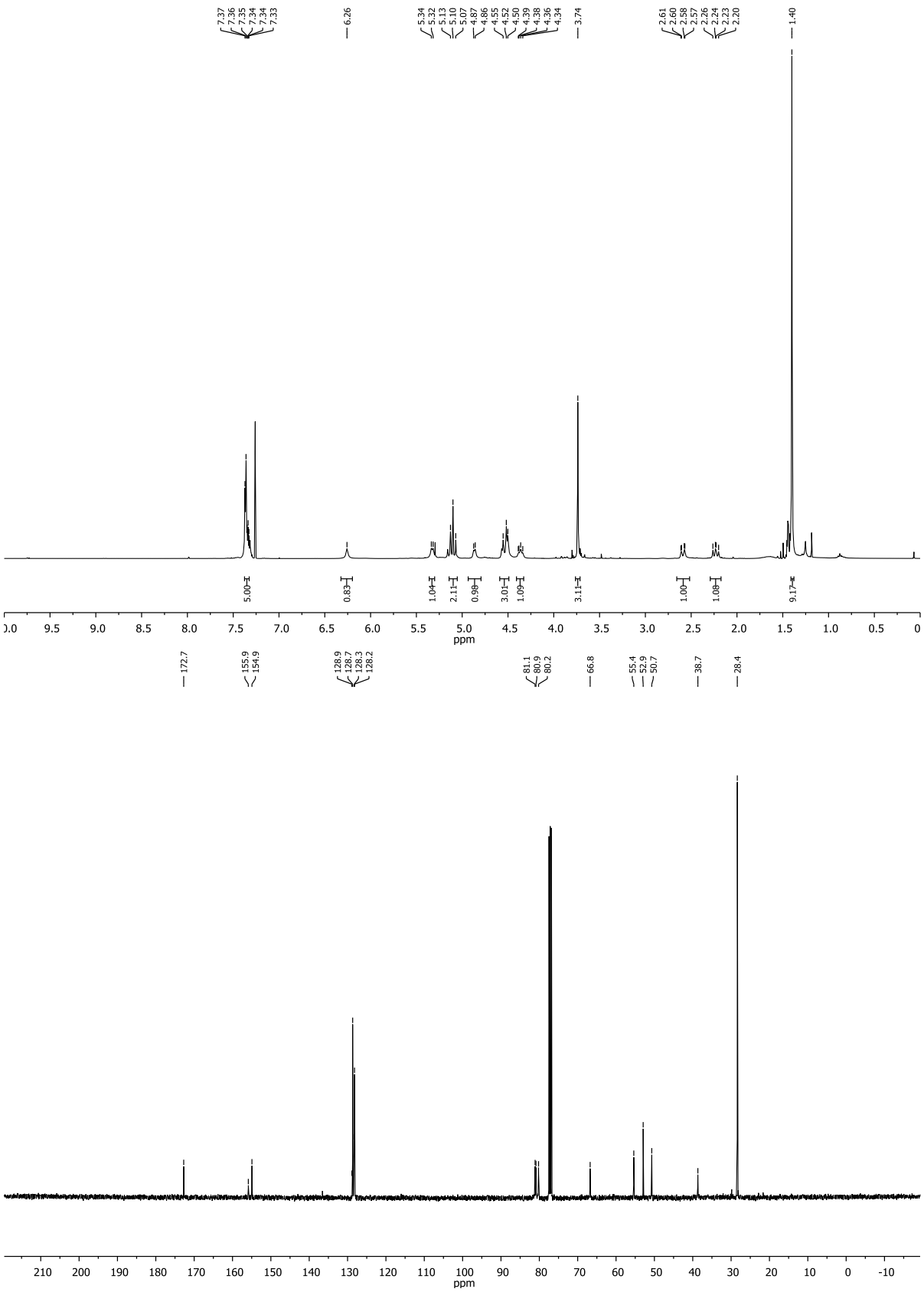


Figure 214 ^{1}H- and ^{13}C-NMR Spectra of 340.

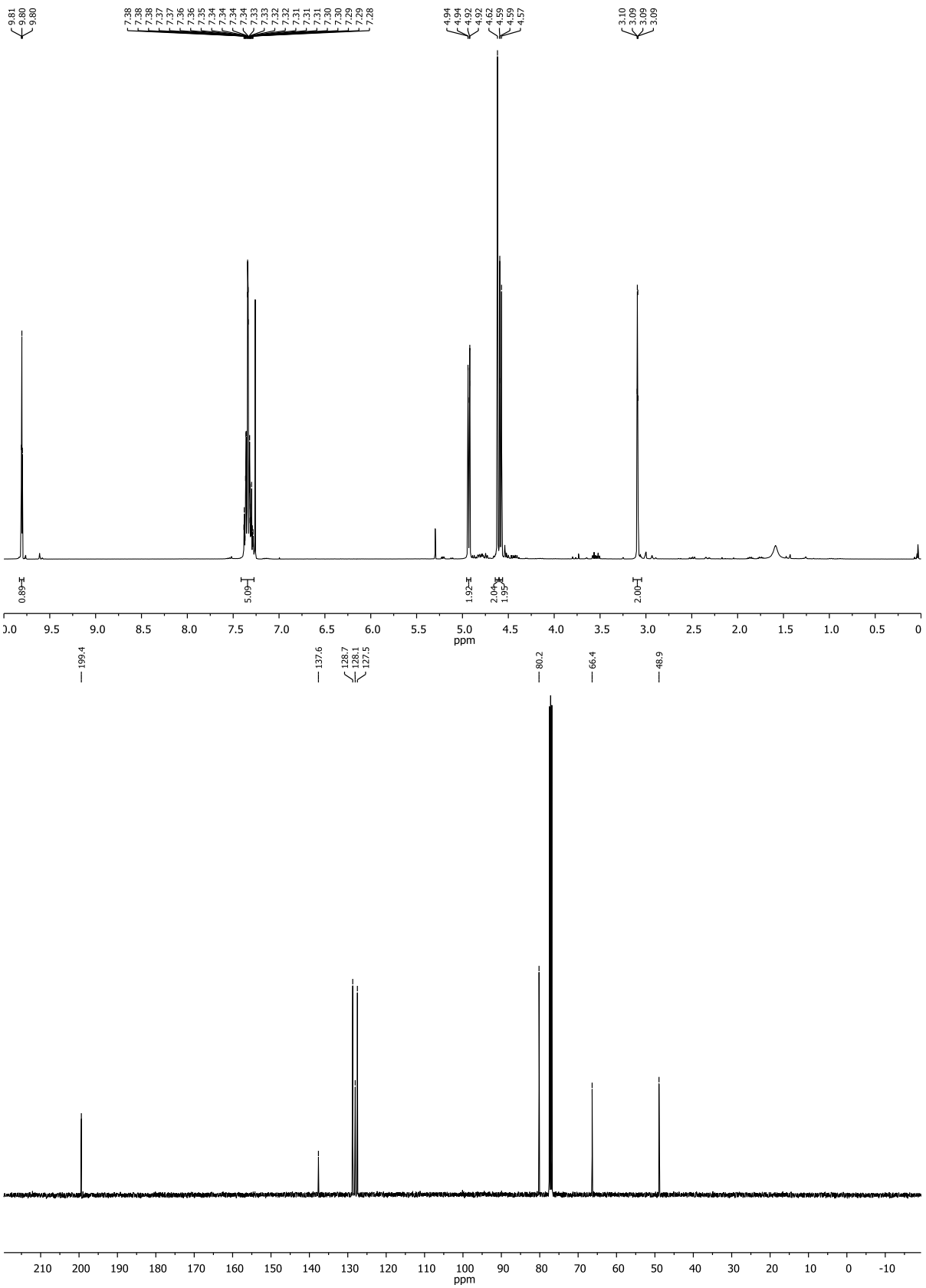


Figure 215 ^{1}H- and ^{13}C-NMR Spectra of 317.

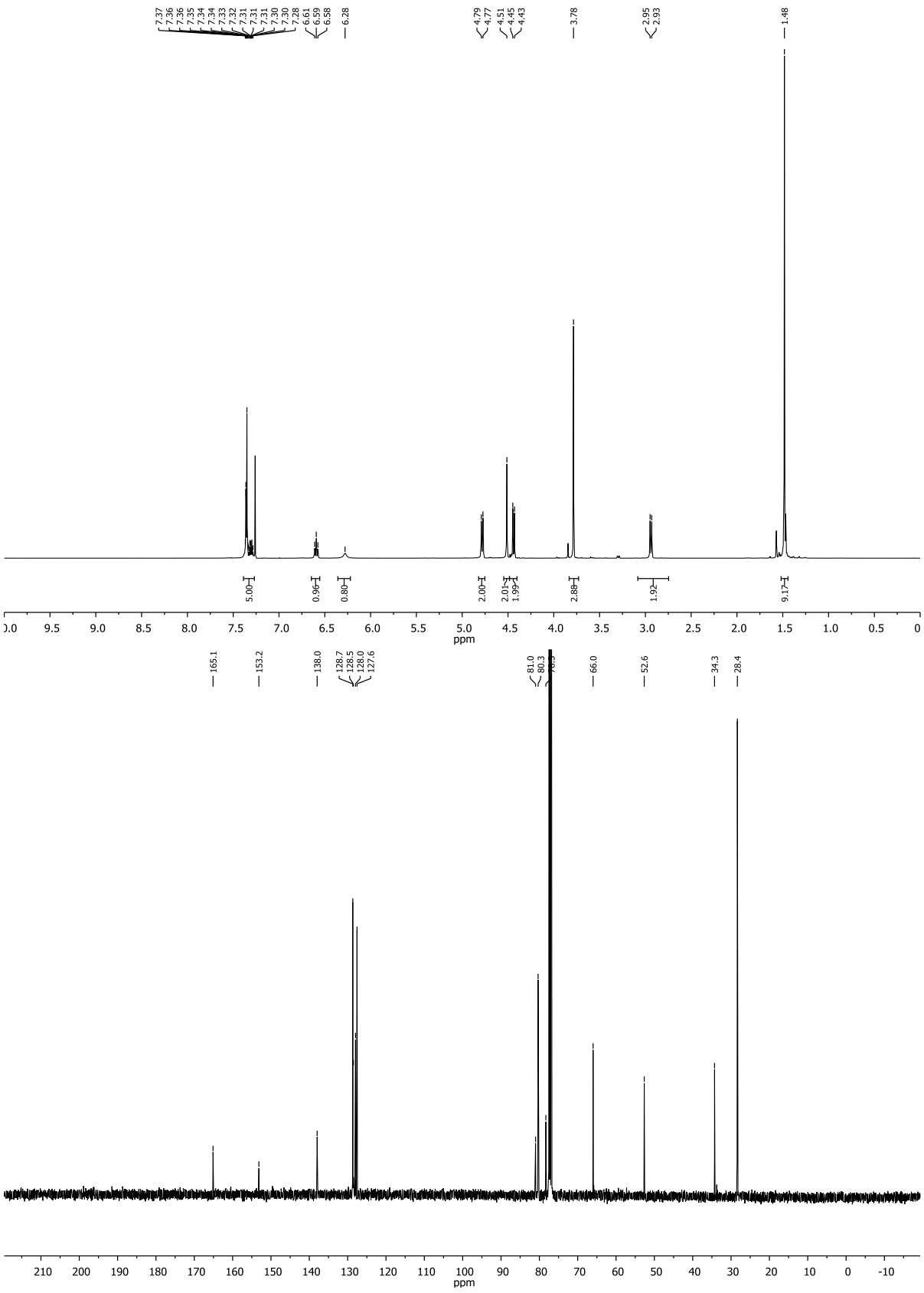


Figure 216 ^{1}H- and ^{13}C-NMR Spectra of 352.

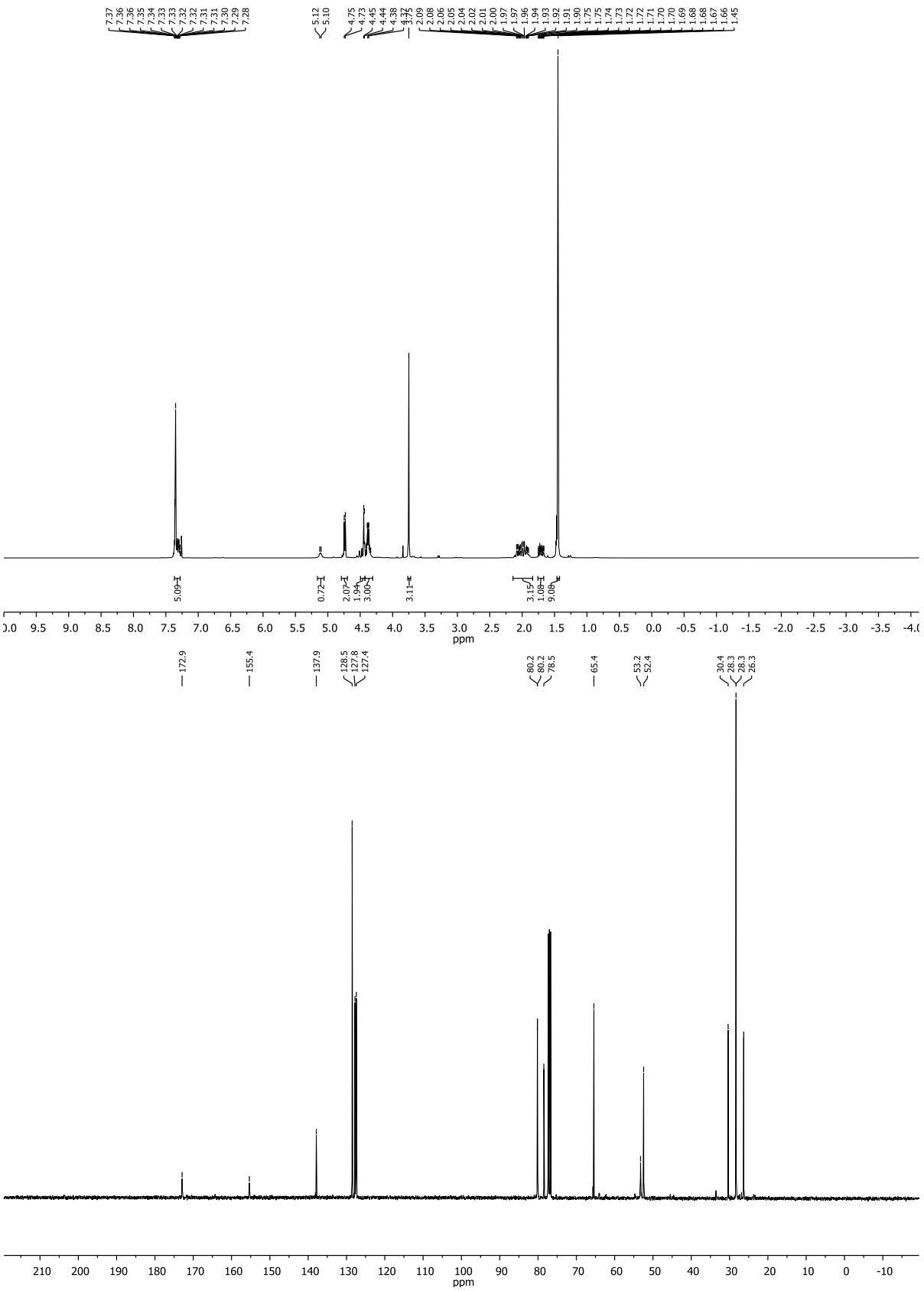


Figure 217 ^{1}H- and ^{13}C-NMR Spectra of 353.

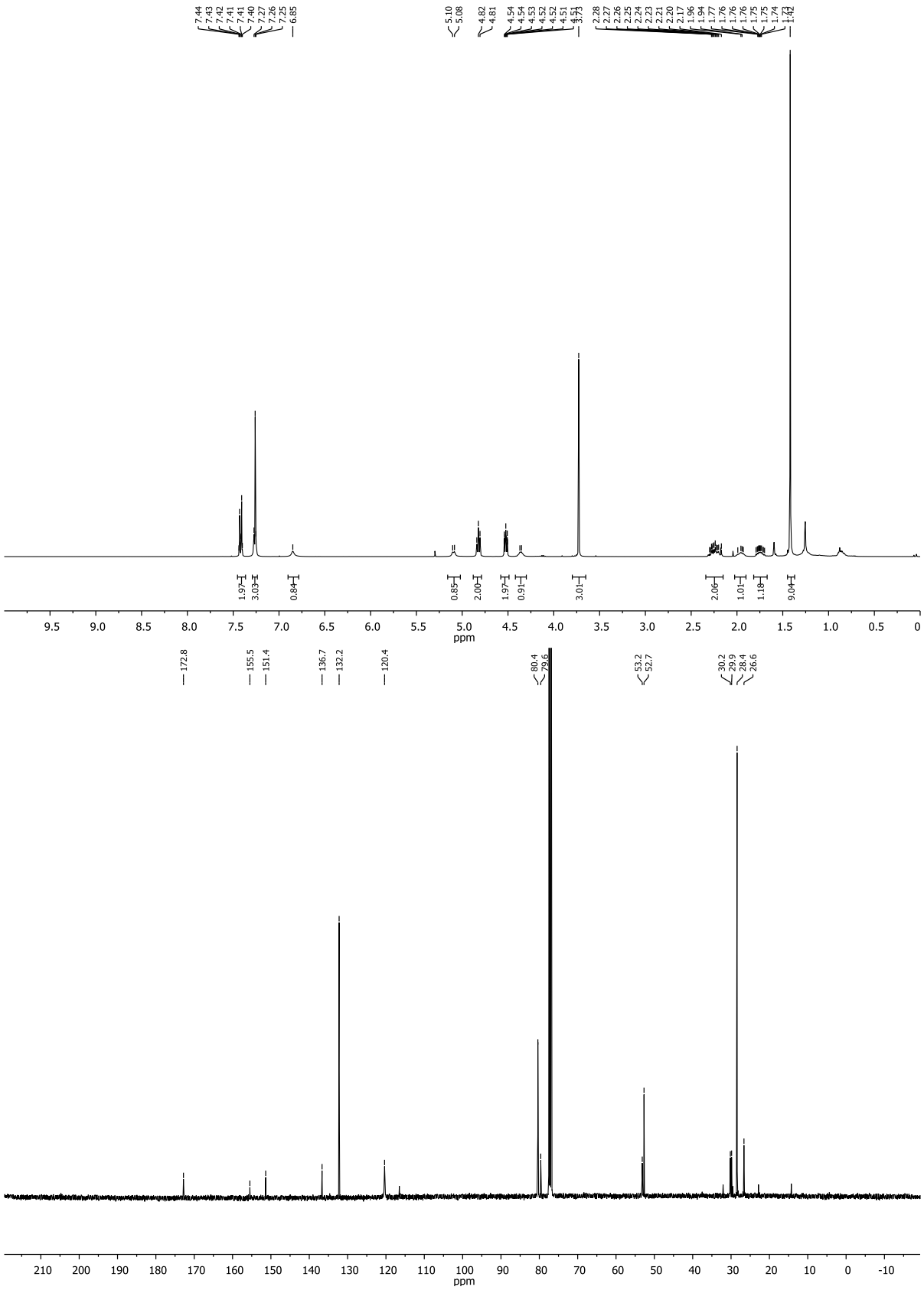


Figure 218 ^{1}H- and ^{13}C-NMR Spectra of 354.

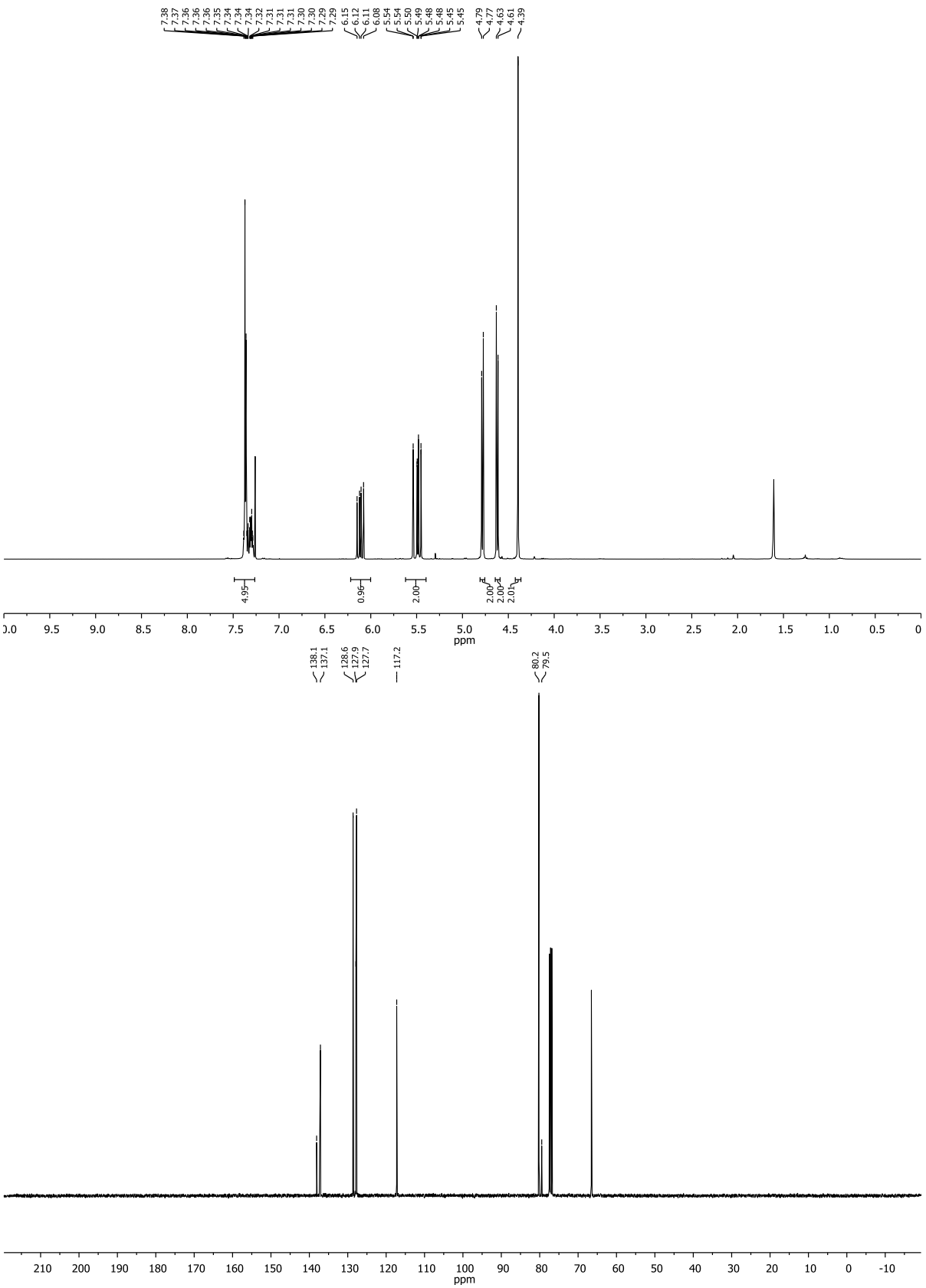


Figure 219 ^{1}H- and ^{13}C-NMR Spectra of 314.

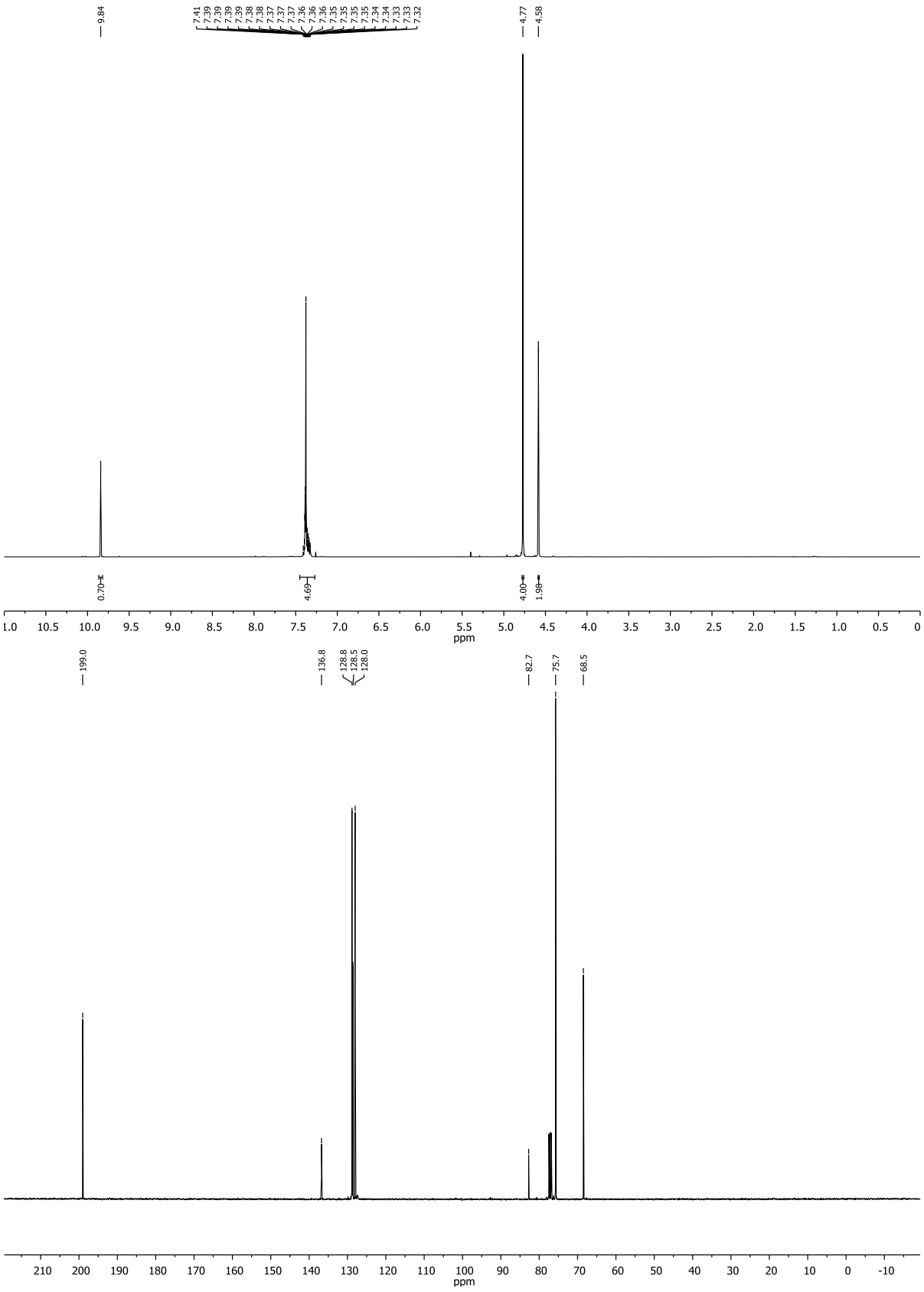


Figure 220 ^{1}H- and ^{13}C-NMR Spectra of 315.

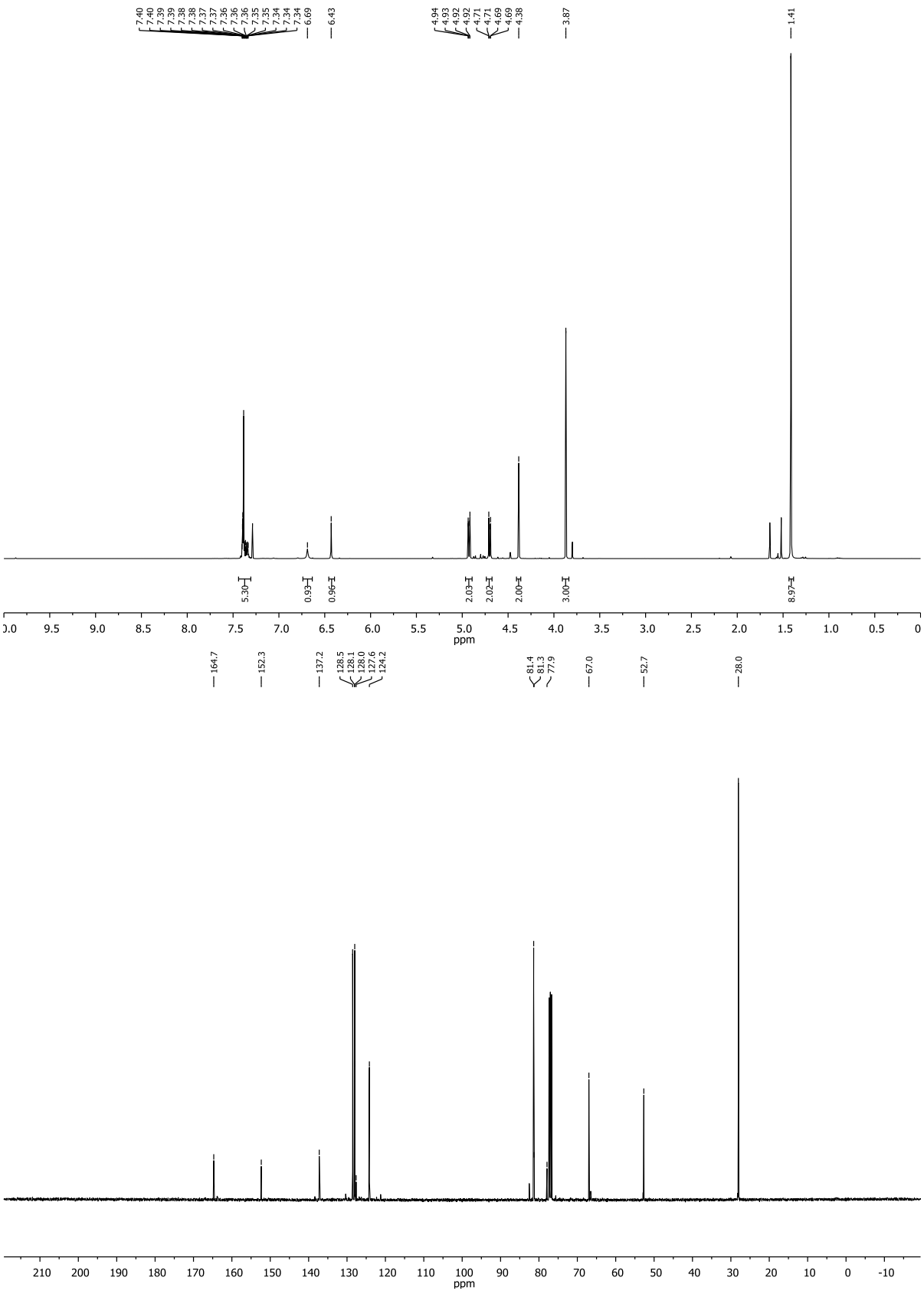


Figure 221 ^{1}H- and ^{13}C-NMR Spectra of 355.

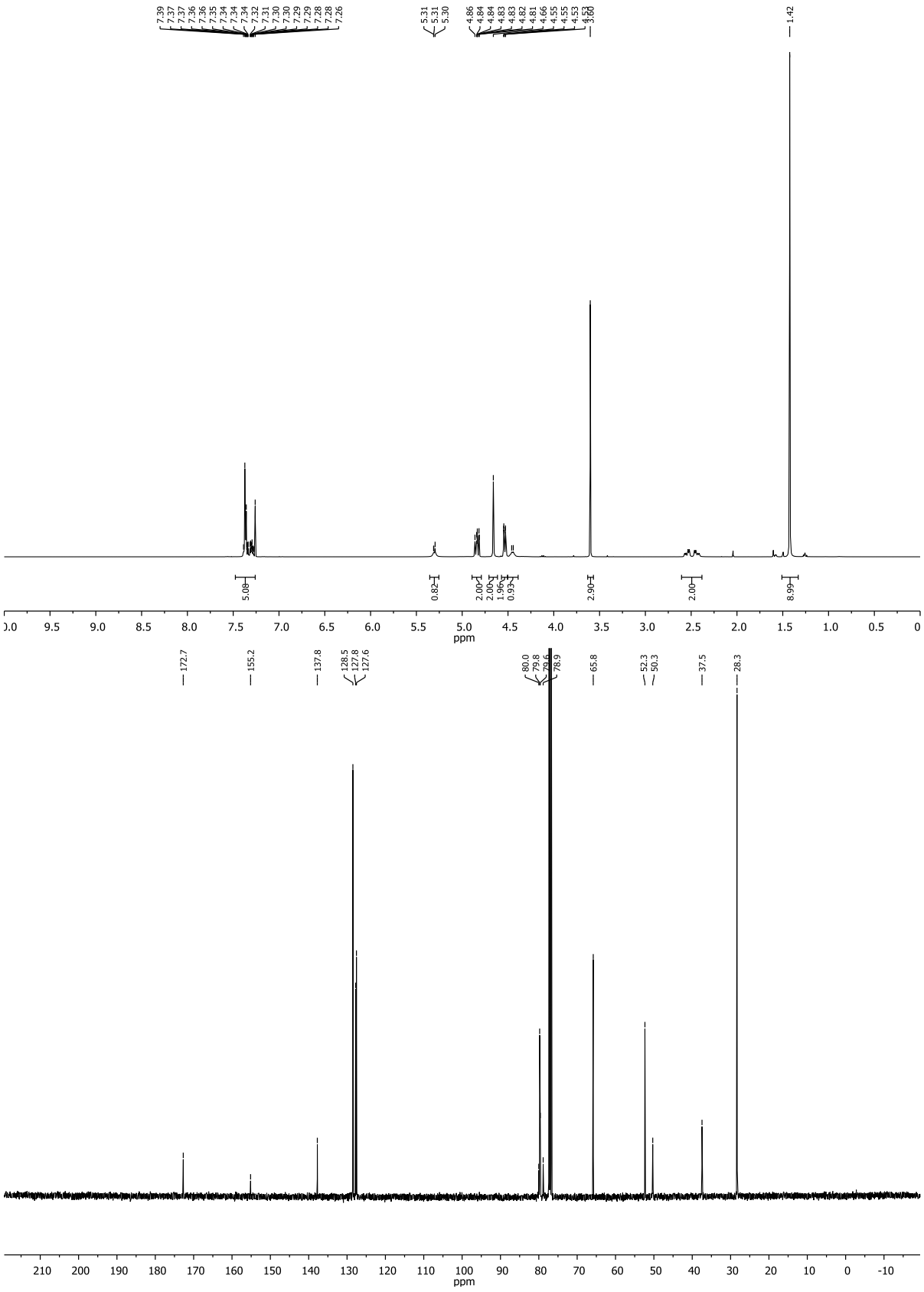


Figure 222 ^{1}H- and ^{13}C-NMR Spectra of 356.

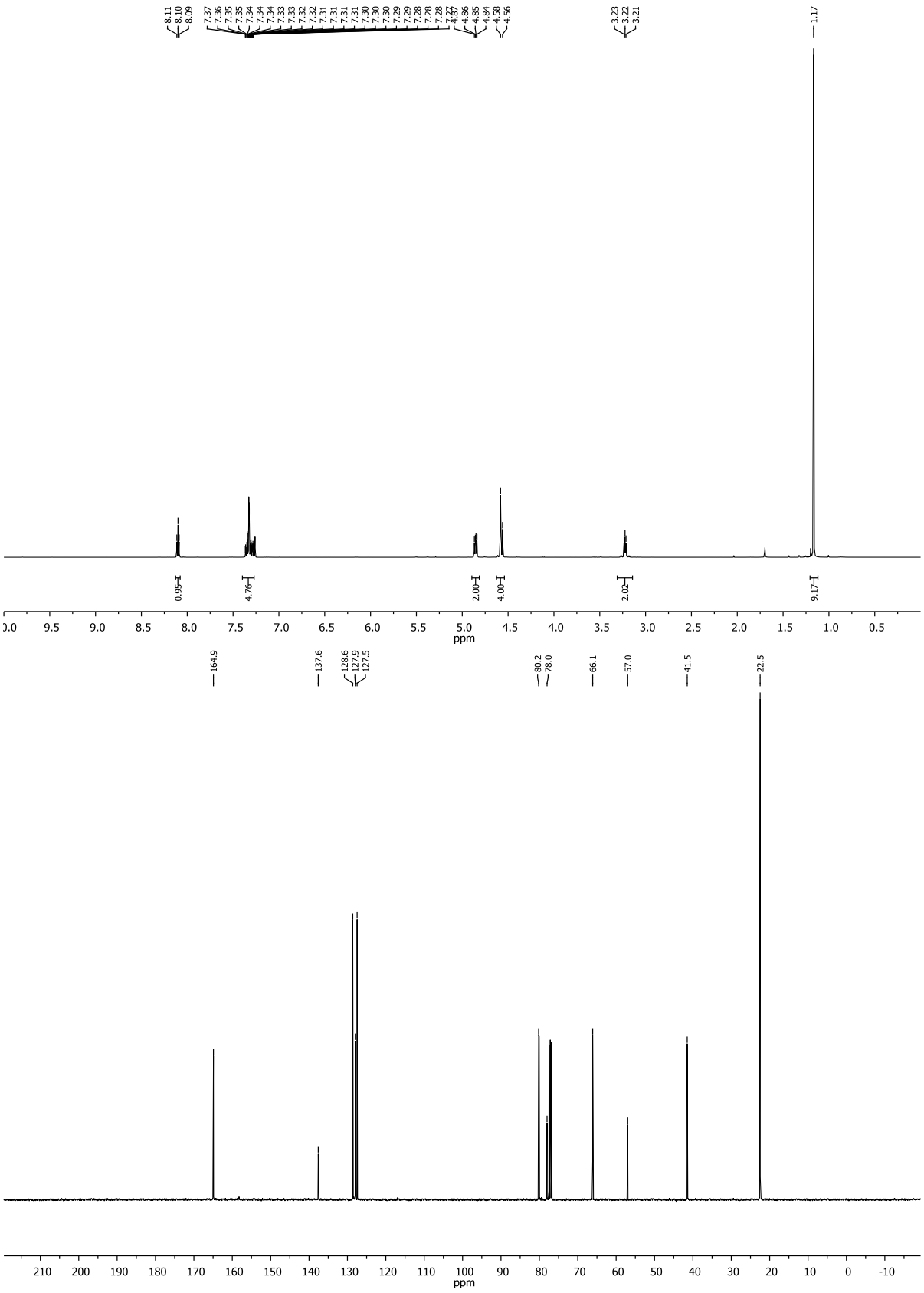


Figure 223 ^{1}H- and ^{13}C-NMR Spectra of 357.

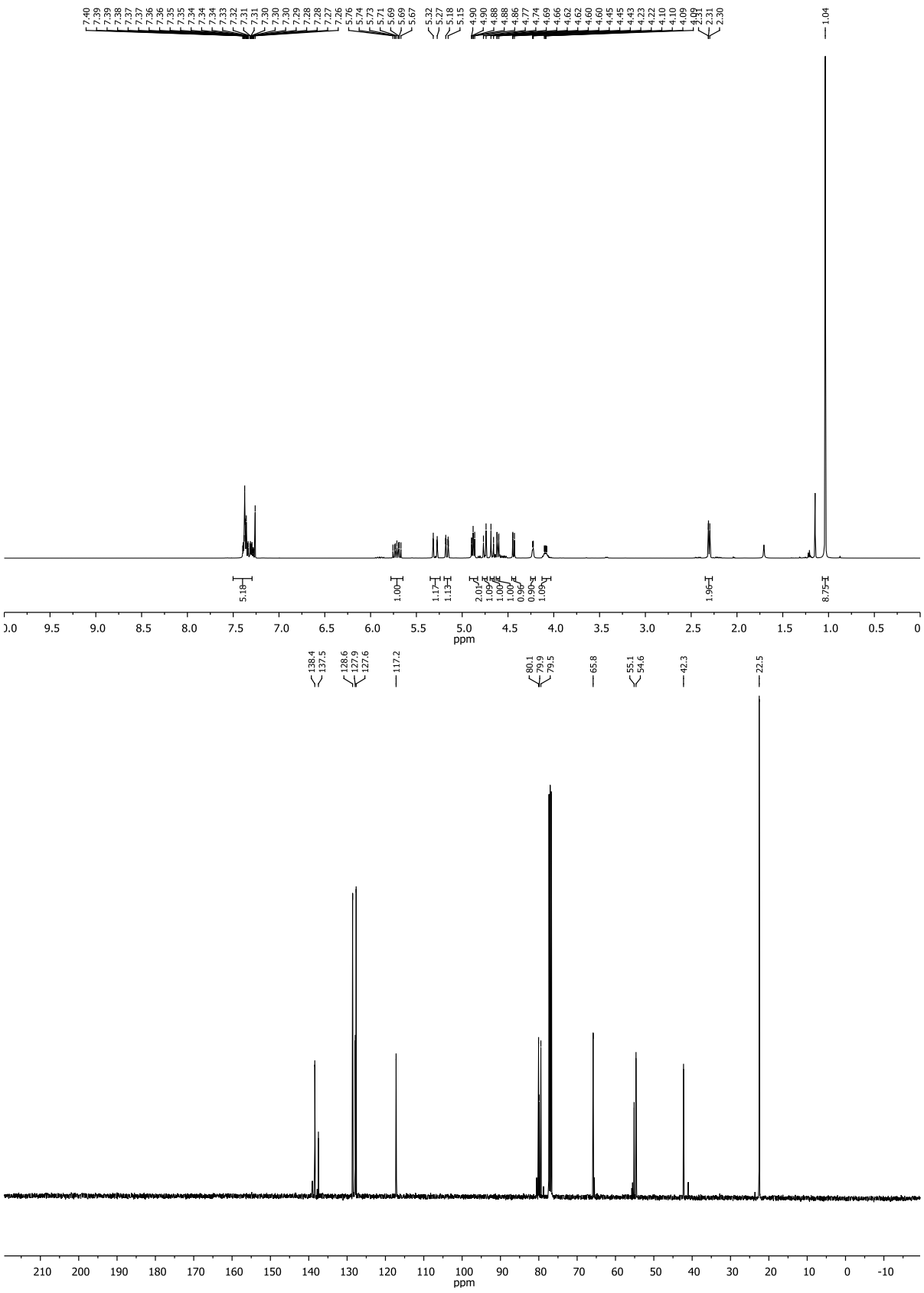


Figure 224 ^{1}H- and ^{13}C-NMR Spectra of the less polar diastereomer of 361.

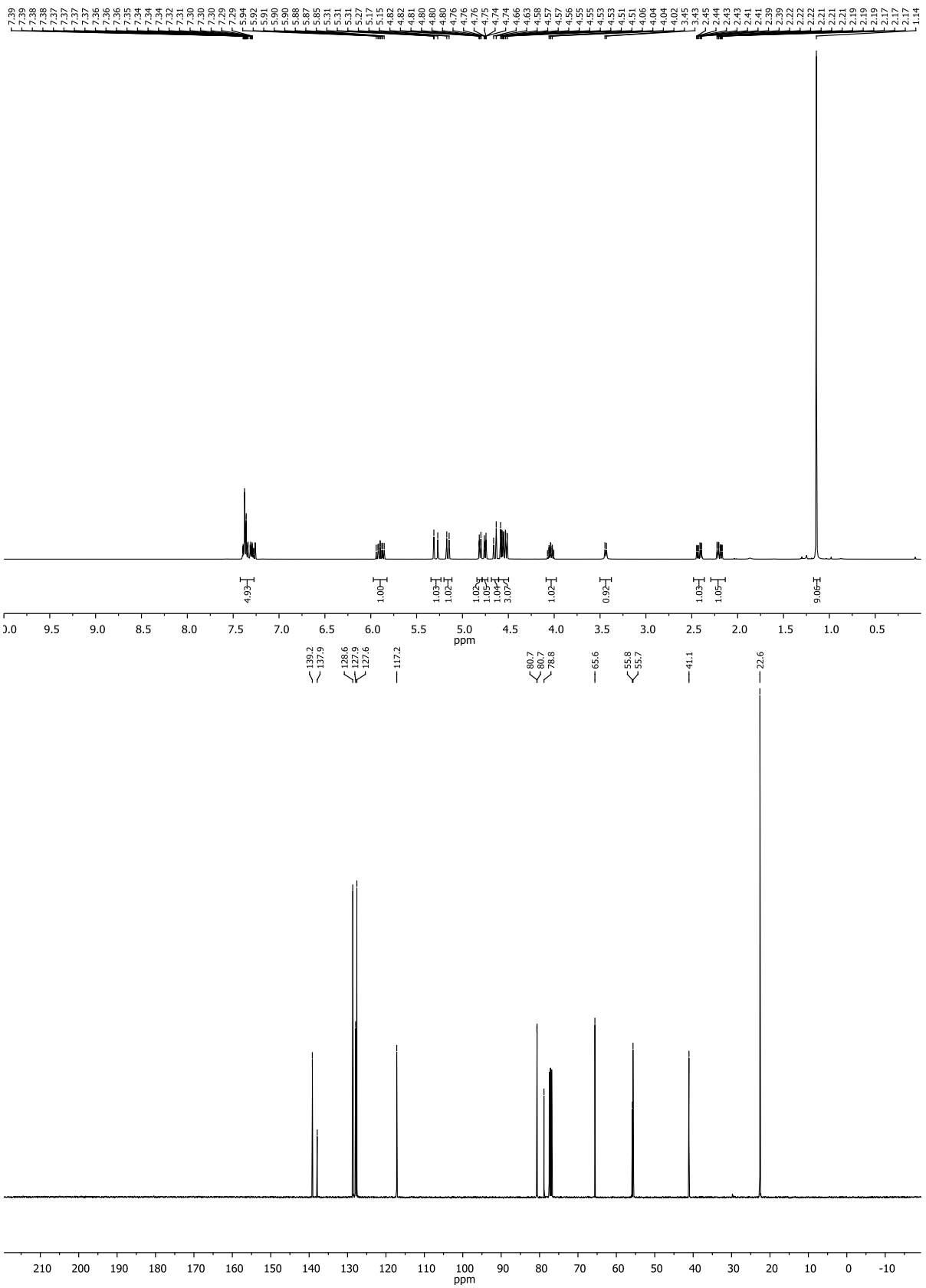


Figure 225 ^{1}H- and ^{13}C-NMR Spectra of the more polar diastereomer of 361.

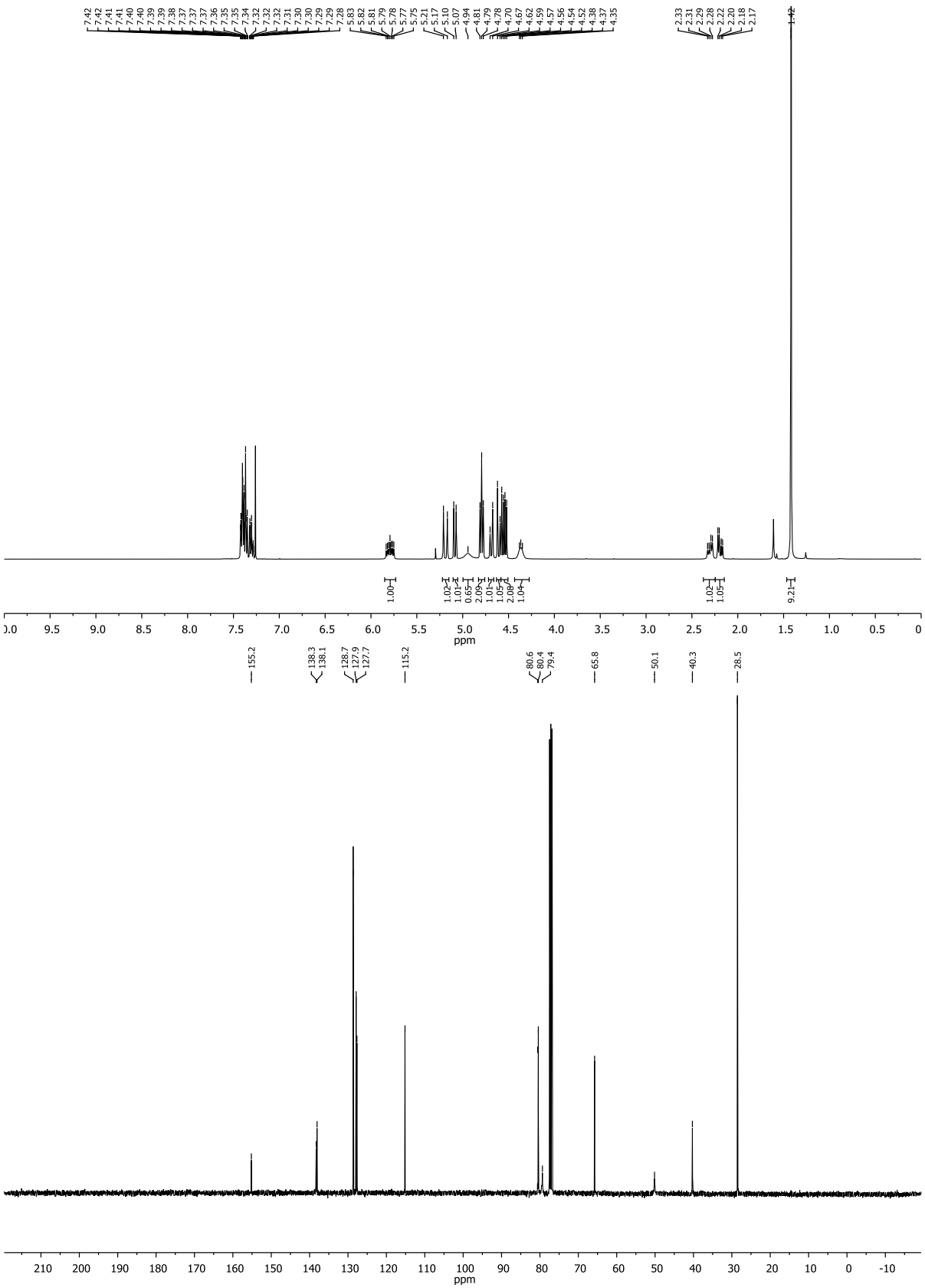


Figure 226 ^{1}H- and ^{13}C-NMR Spectra of 362.

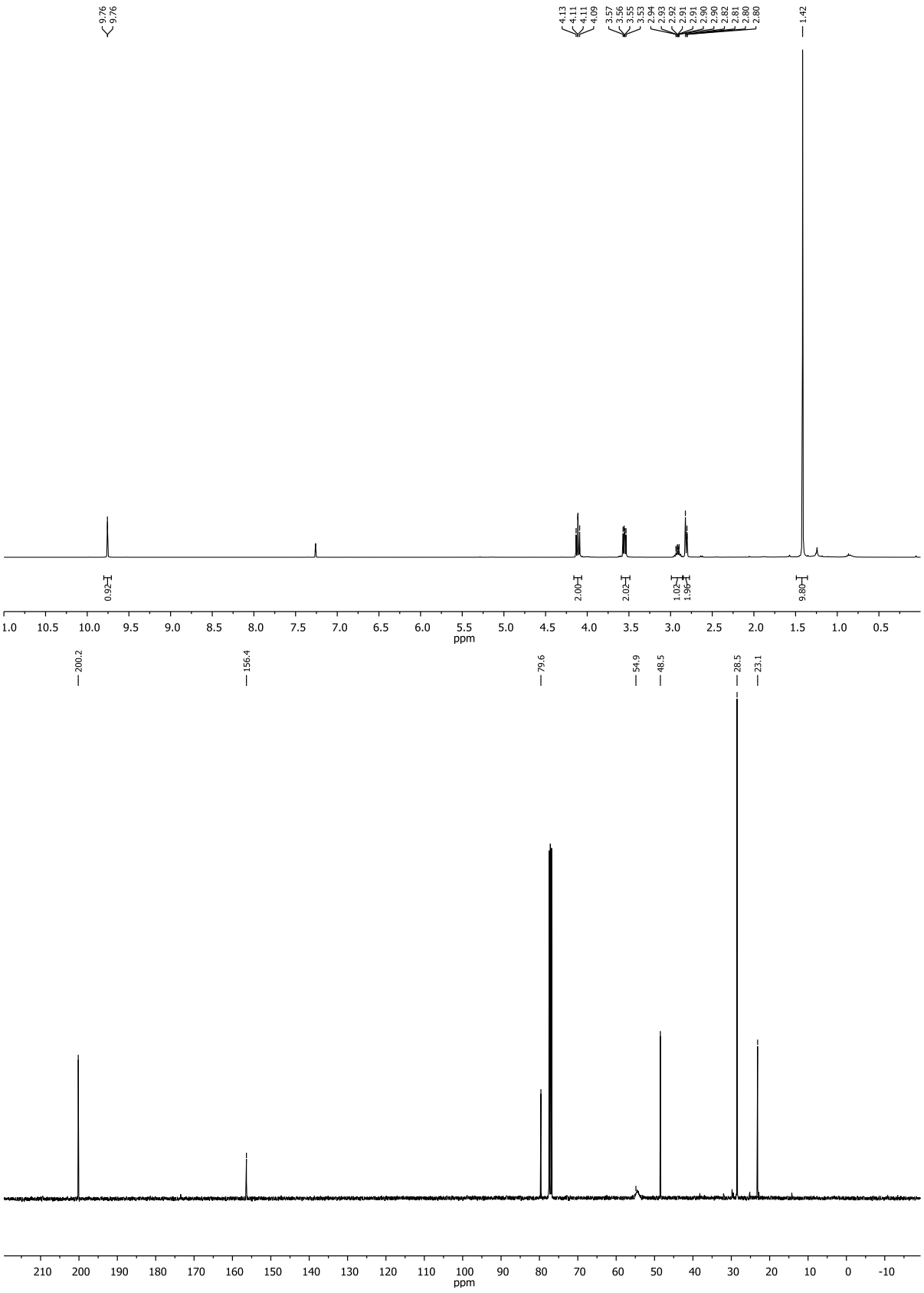


Figure 227 ^{1}H- and ^{13}C-NMR Spectra of 319.

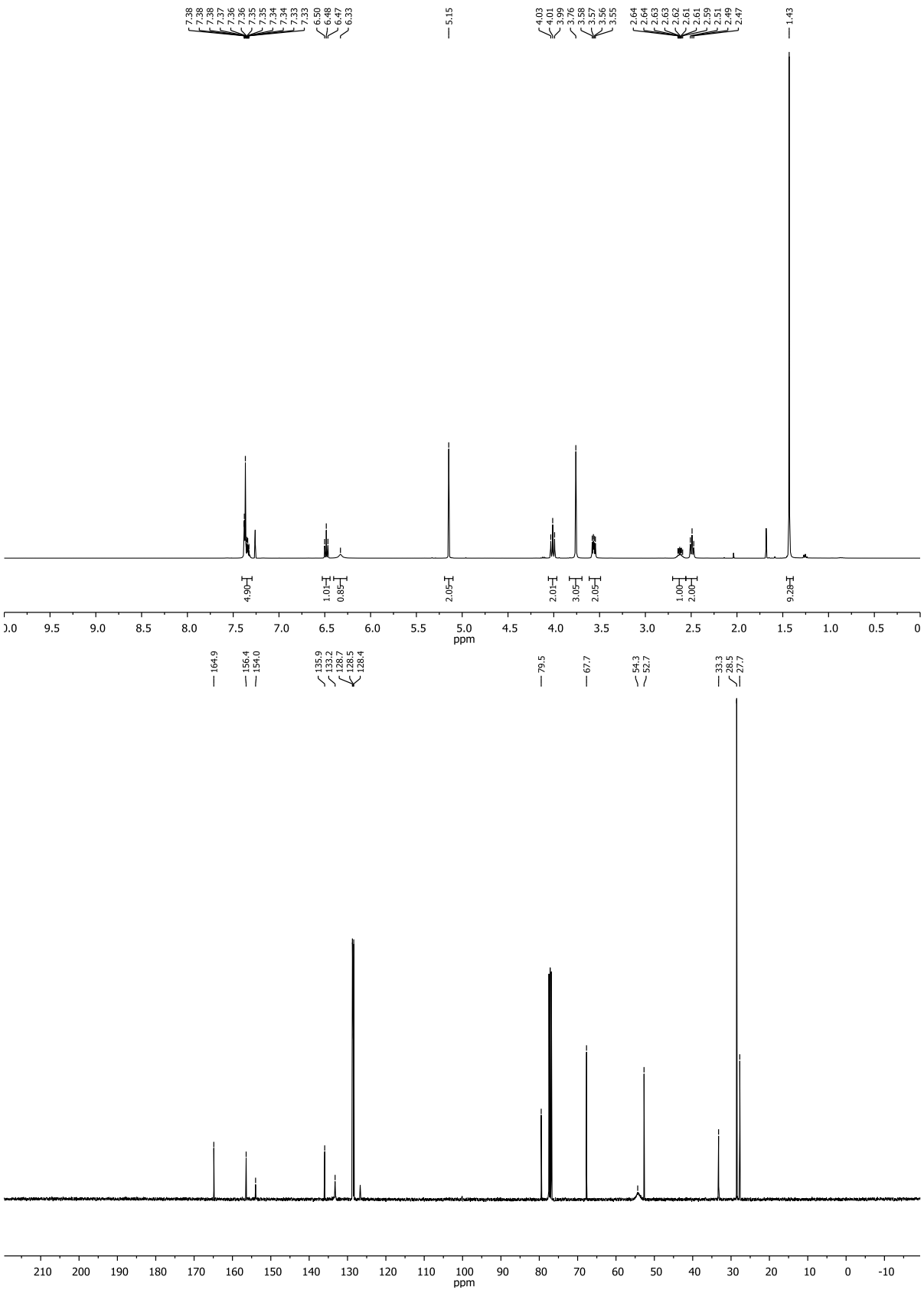


Figure 228 ^{1}H- and ^{13}C-NMR Spectra of 364.

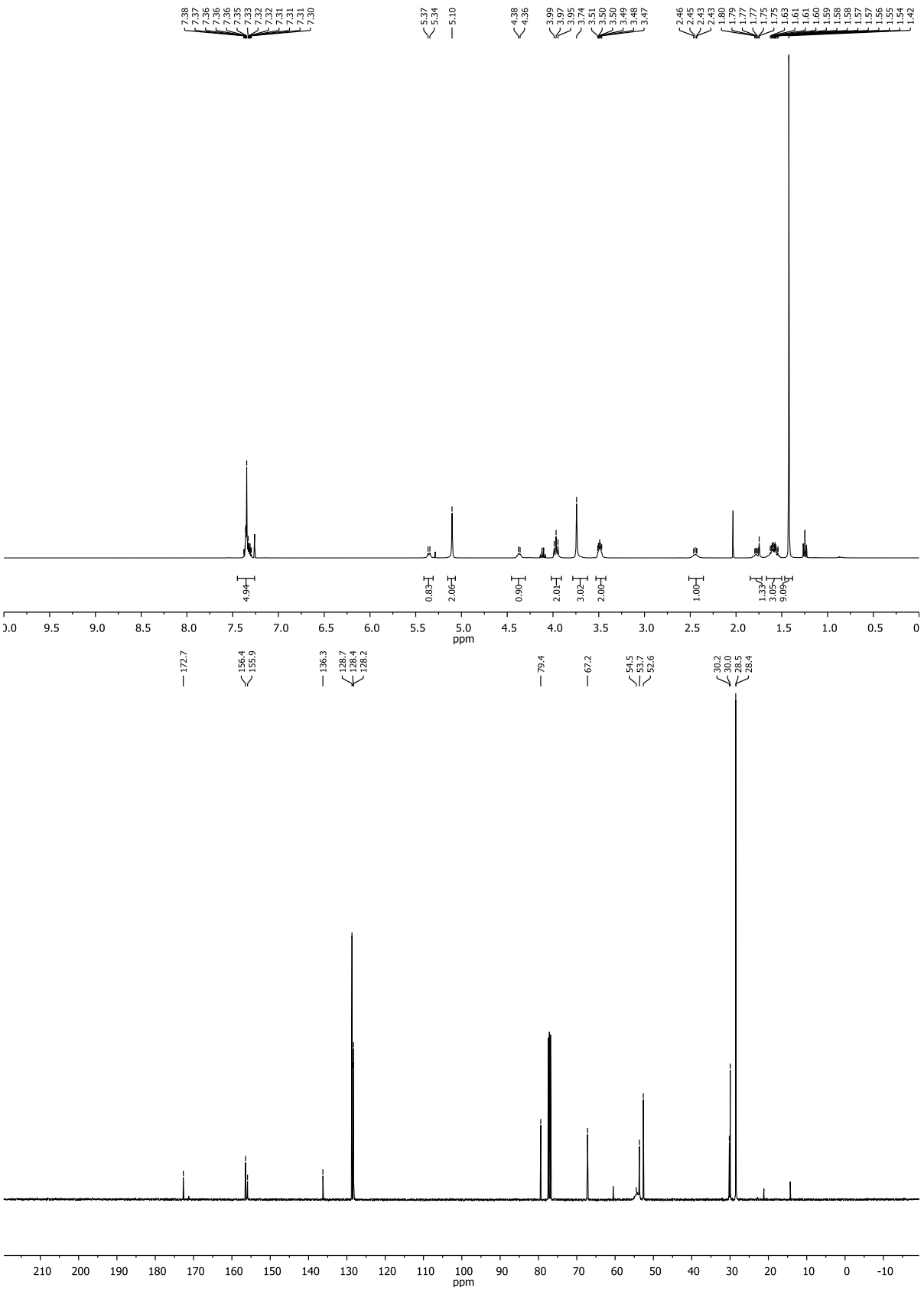


Figure 229 ^{1}H- and ^{13}C-NMR Spectra of 365.

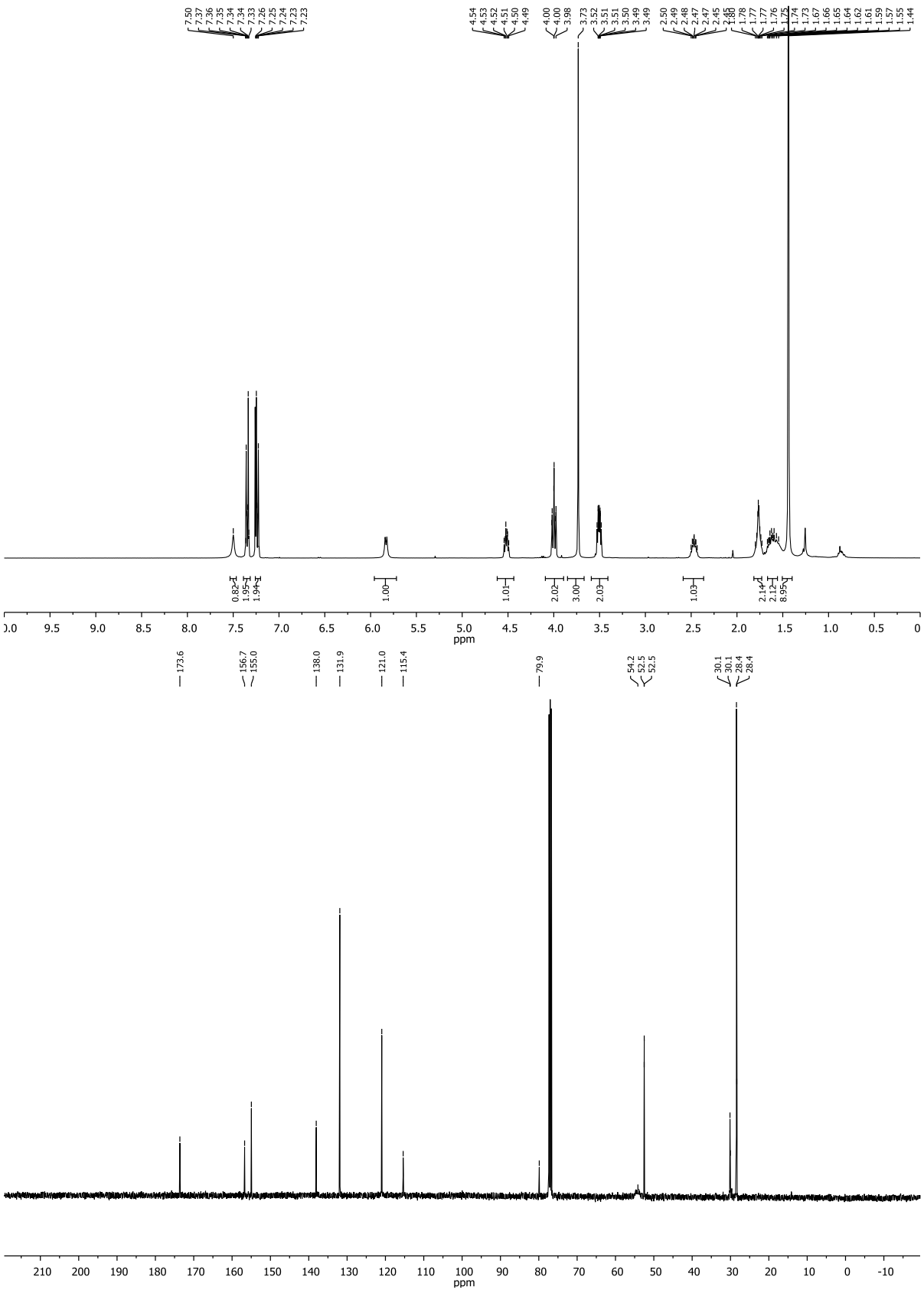


Figure 230 ^{1}H- and ^{13}C-NMR Spectra of 366.

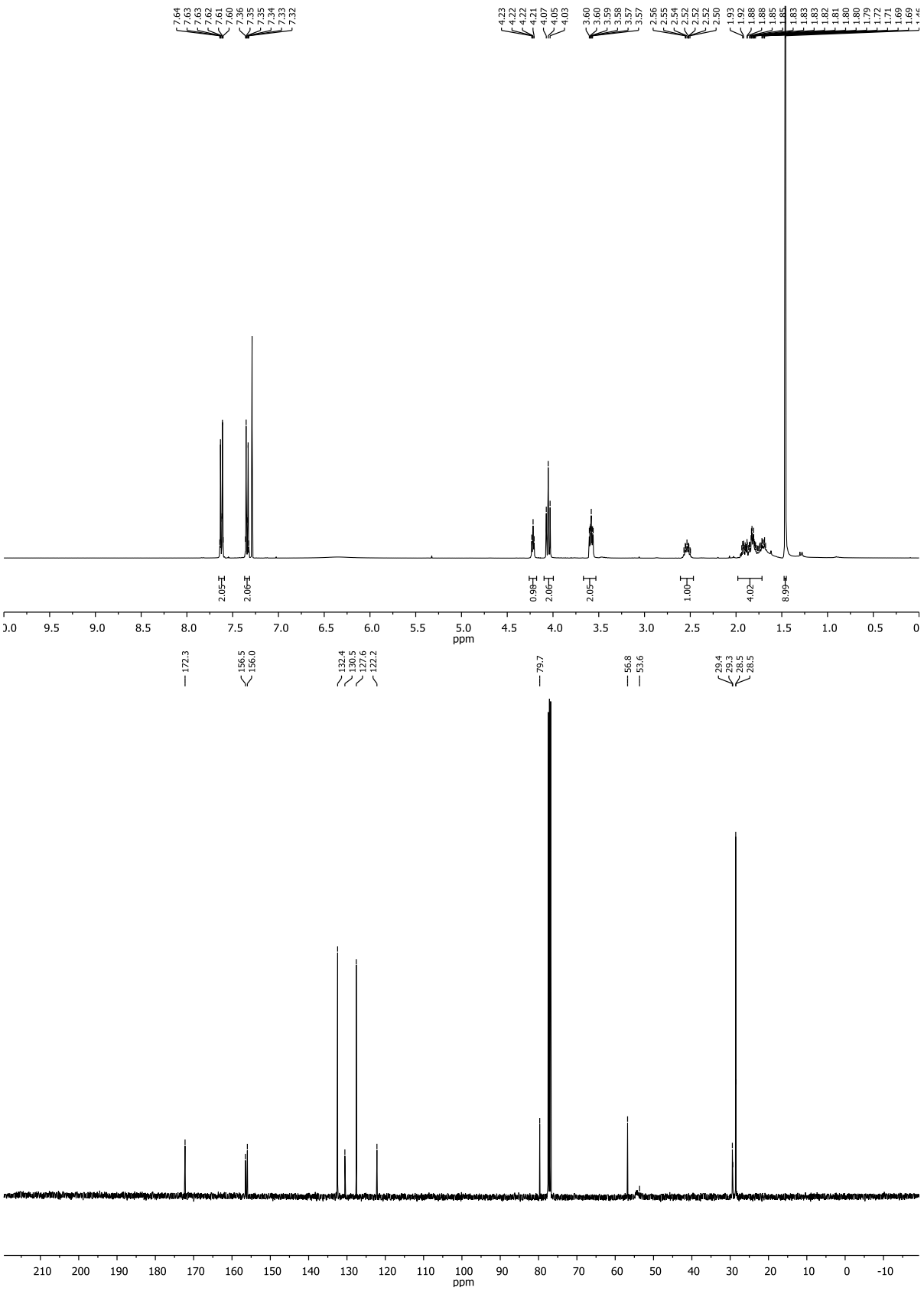


Figure 231 ^{1}H- and ^{13}C-NMR Spectra of 367.

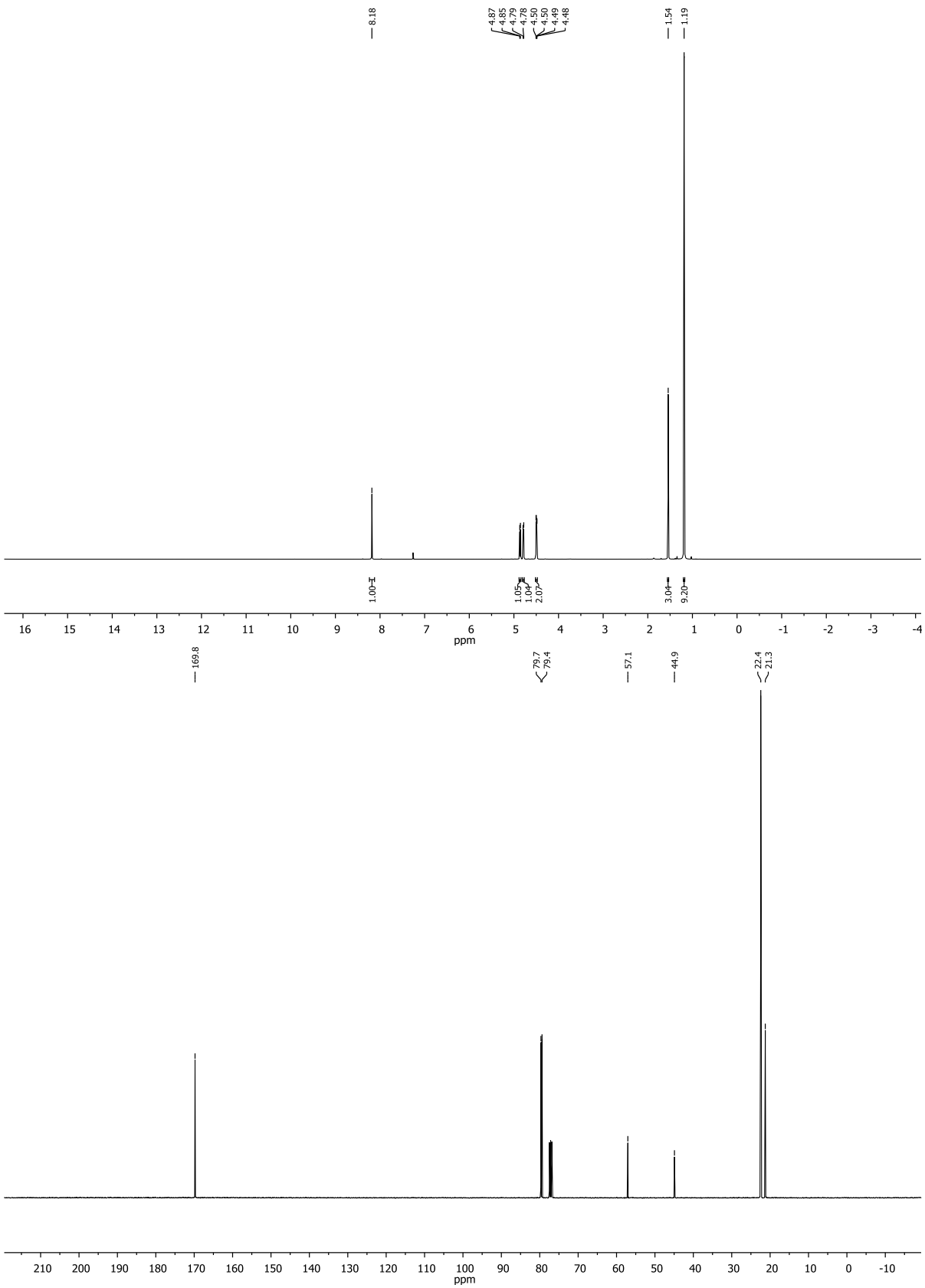


Figure 232 ^{1}H- and ^{13}C-NMR Spectra of 321.

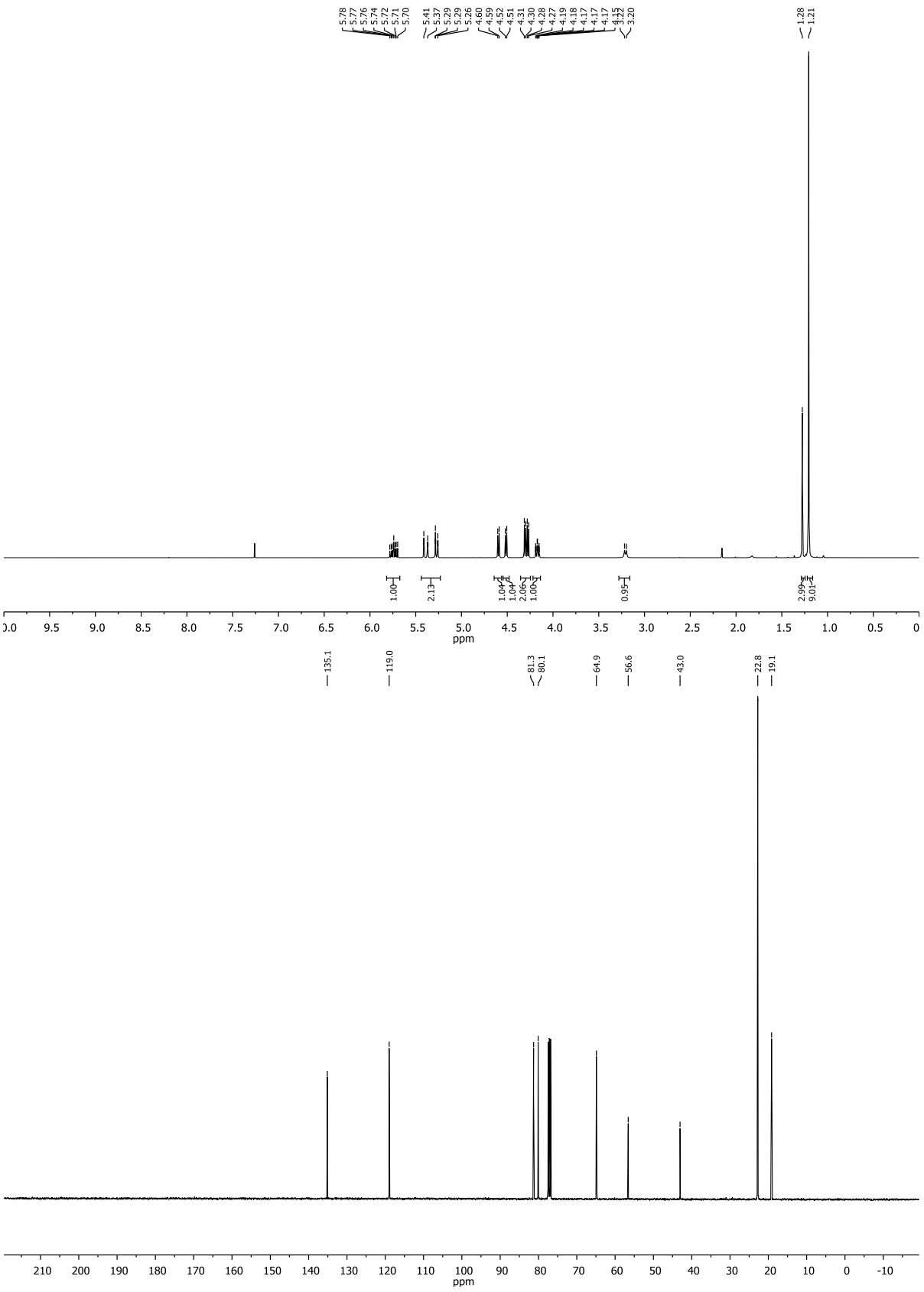


Figure 233 ^{1}H- and ^{13}C-NMR Spectra of the minor diastereomer of 368.

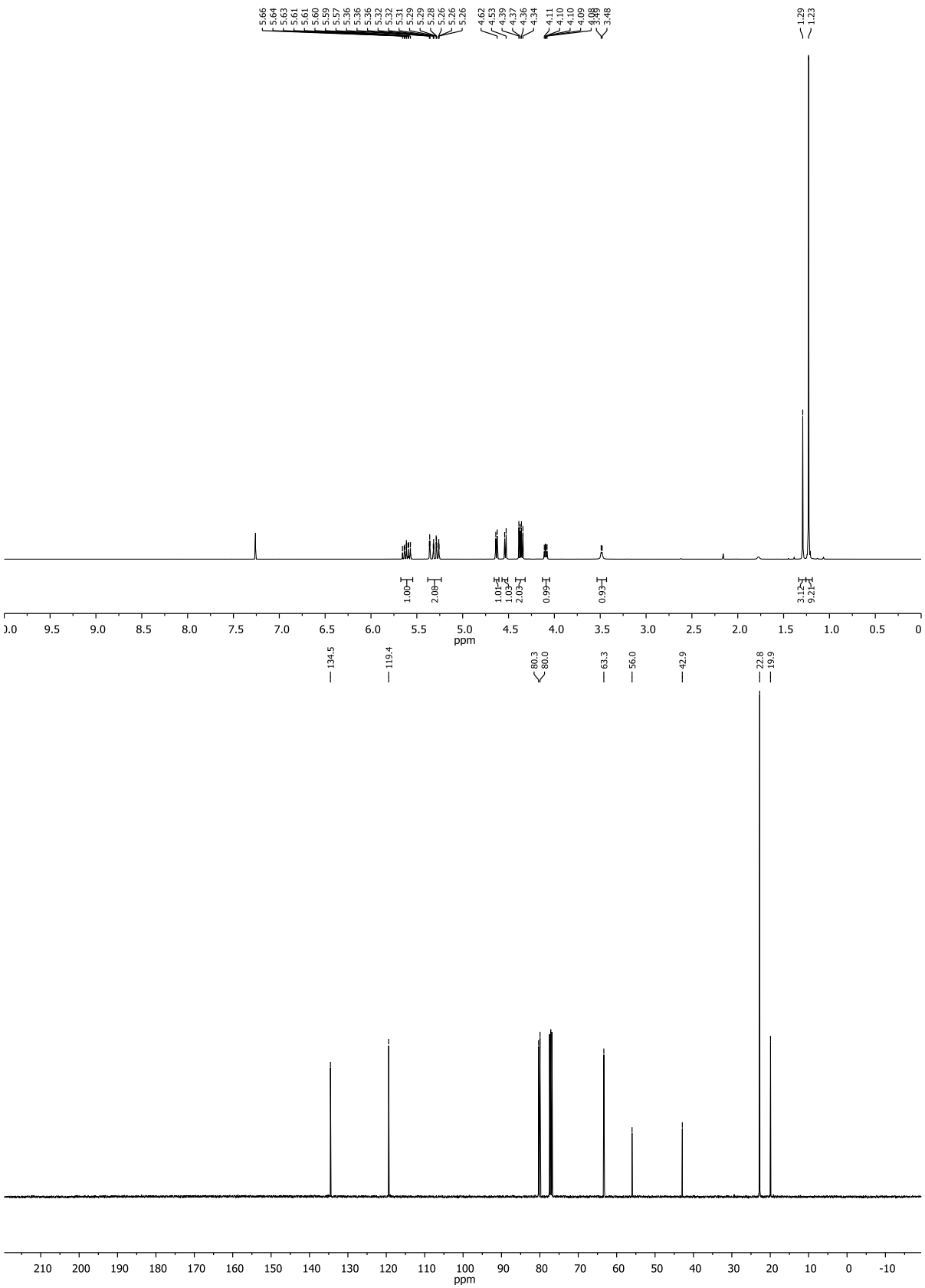


Figure 234 ^{1}H- and ^{13}C-NMR Spectra of the major diastereomer of 368.

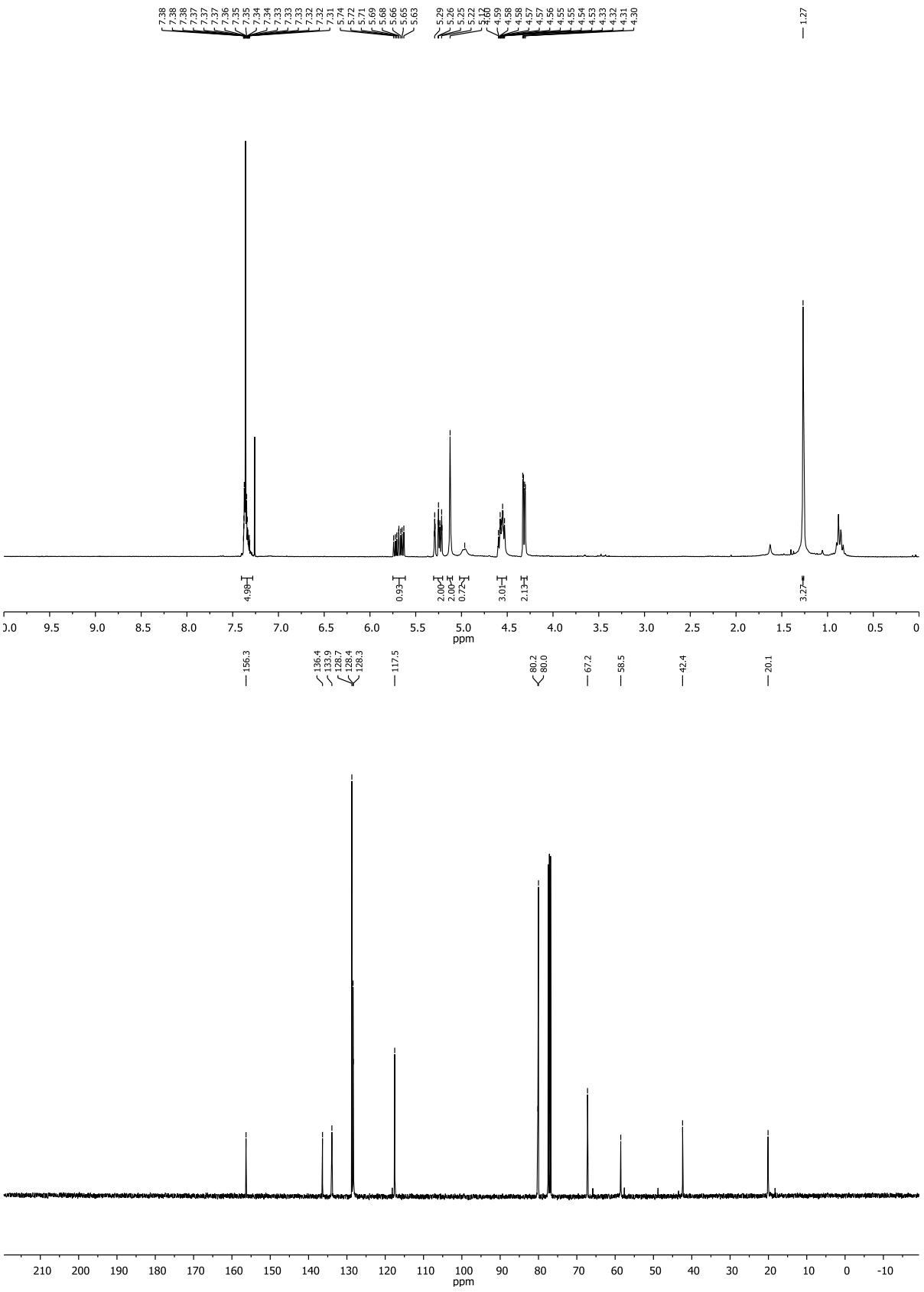


Figure 235 ^{1}H- and ^{13}C-NMR Spectra of 369.

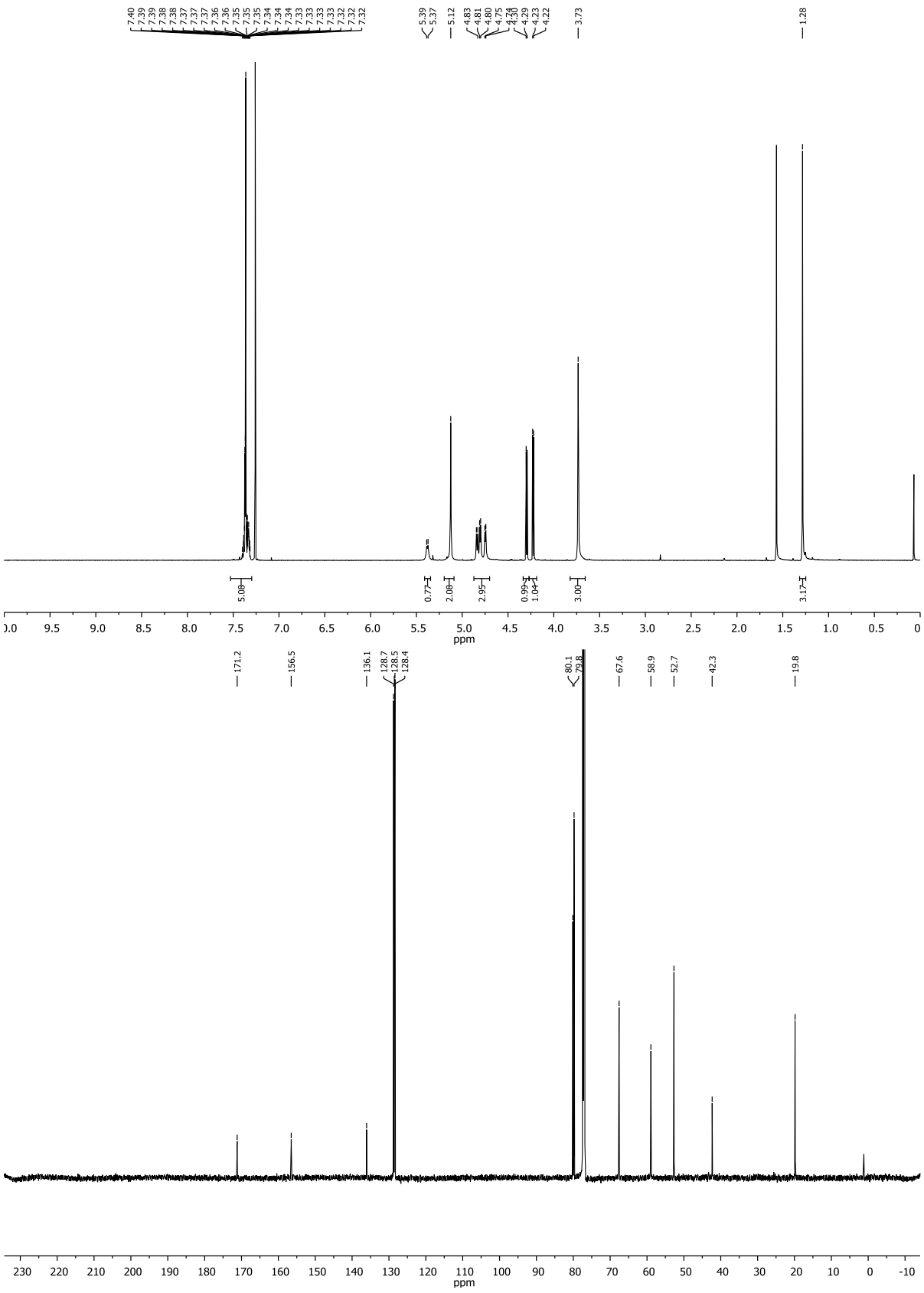


Figure 236 ^{1}H- and ^{13}C-NMR Spectra of 370.

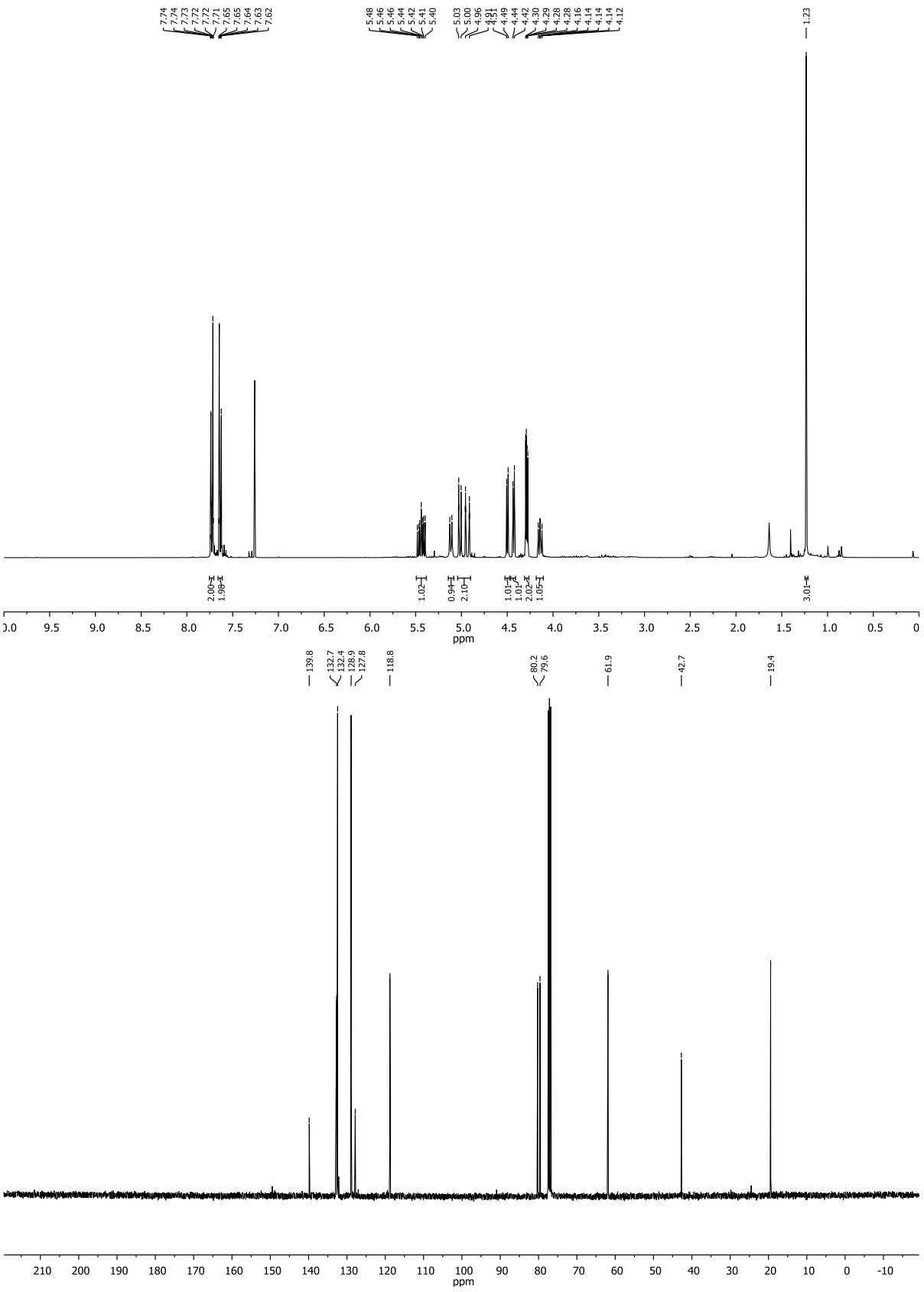


Figure 237 ^{1}H- and ^{13}C-NMR Spectra of 371.

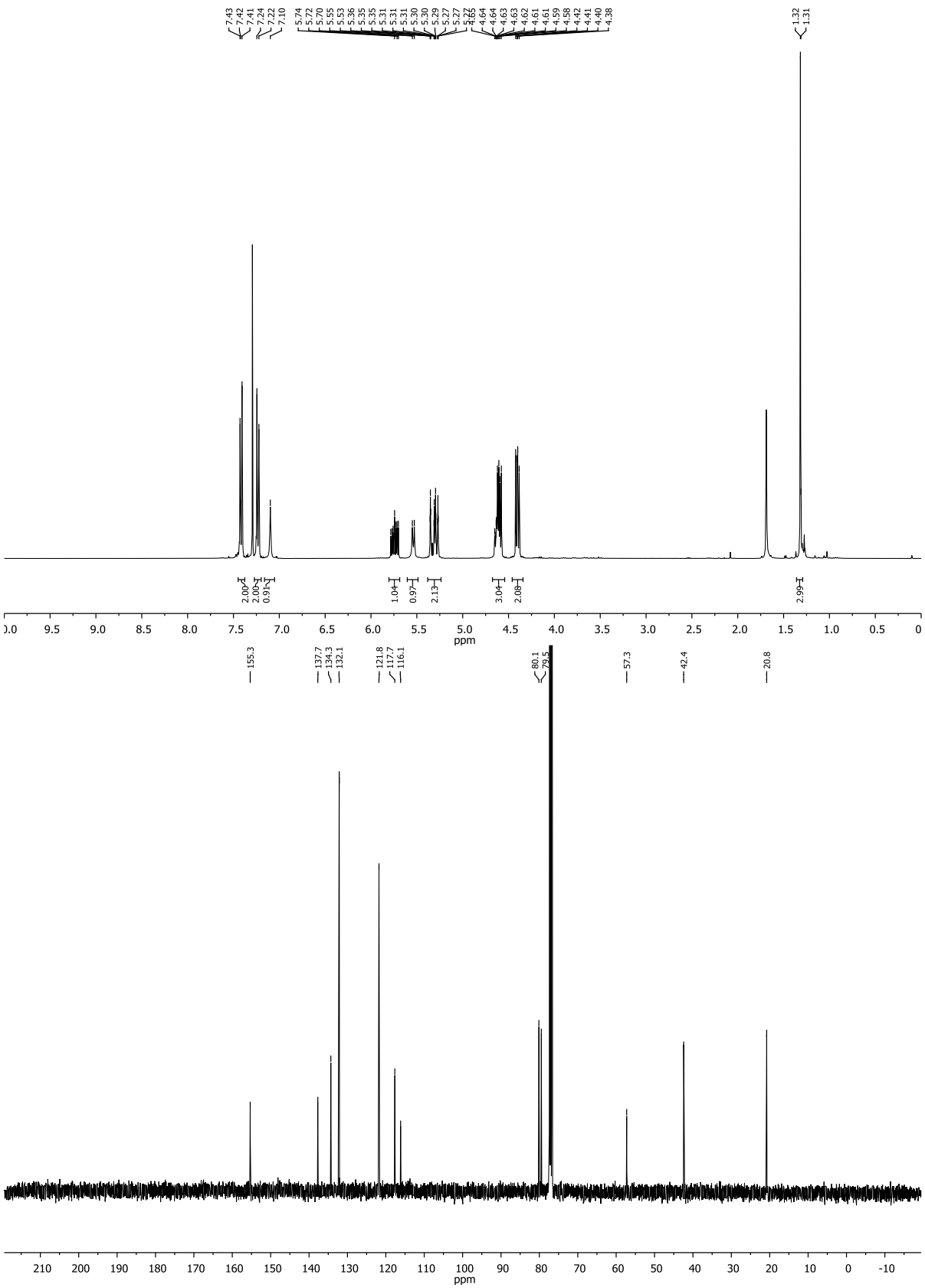


Figure 238 ^{1}H- and ^{13}C-NMR Spectra of 372.

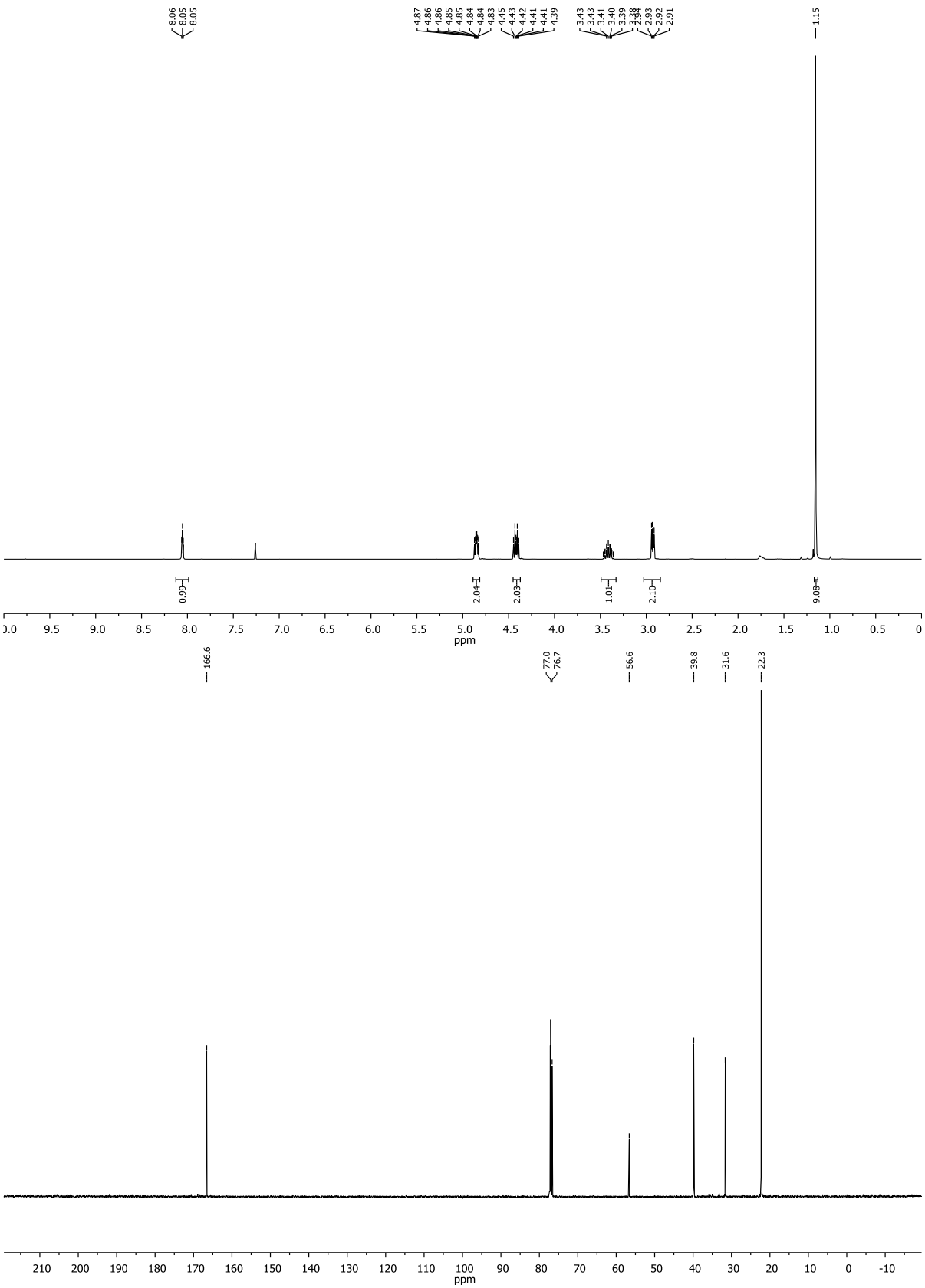


Figure 239 ^{1}H- and ^{13}C-NMR Spectra of 320.

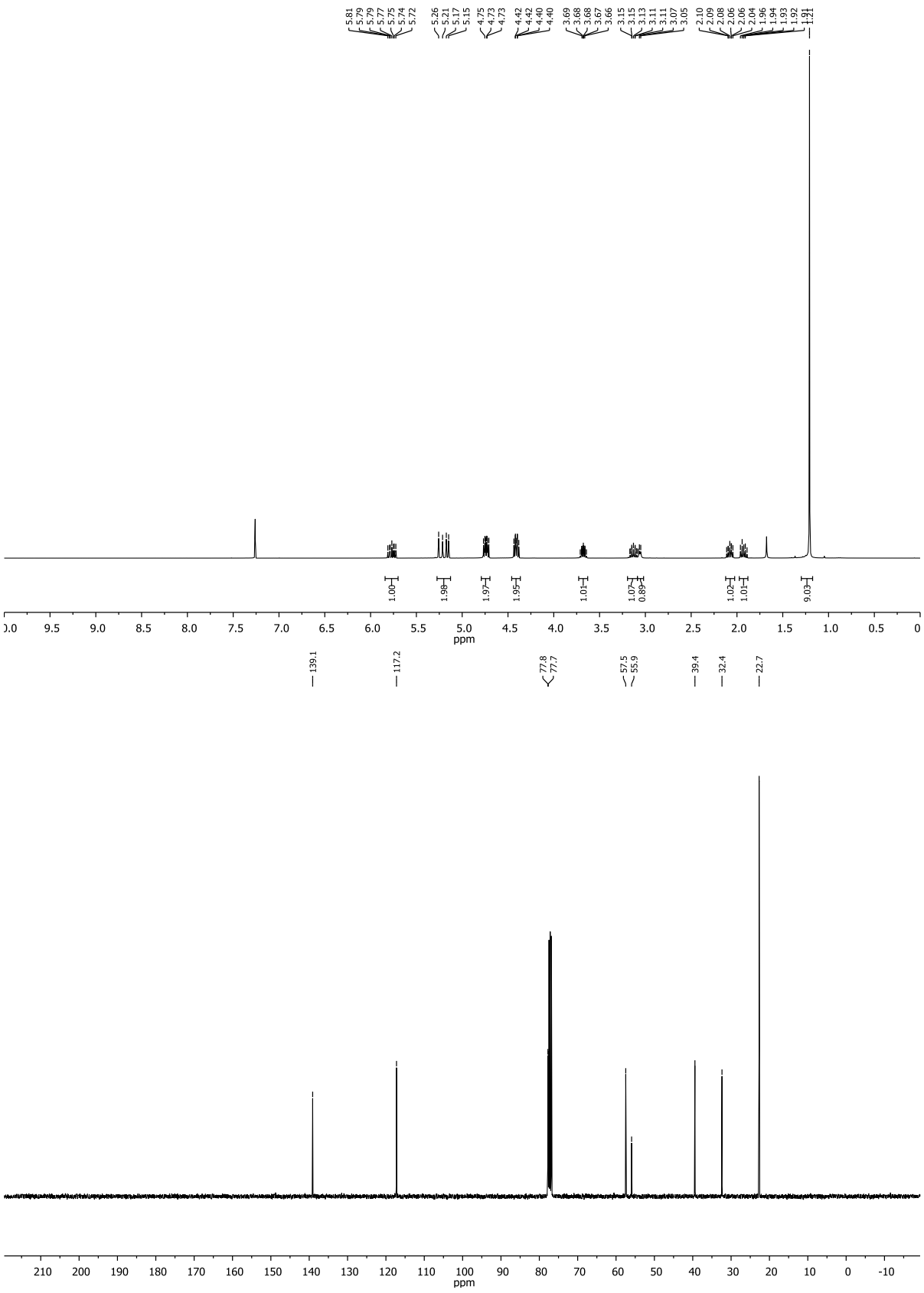


Figure 240 ^{1}H- and ^{13}C-NMR Spectra of 373.

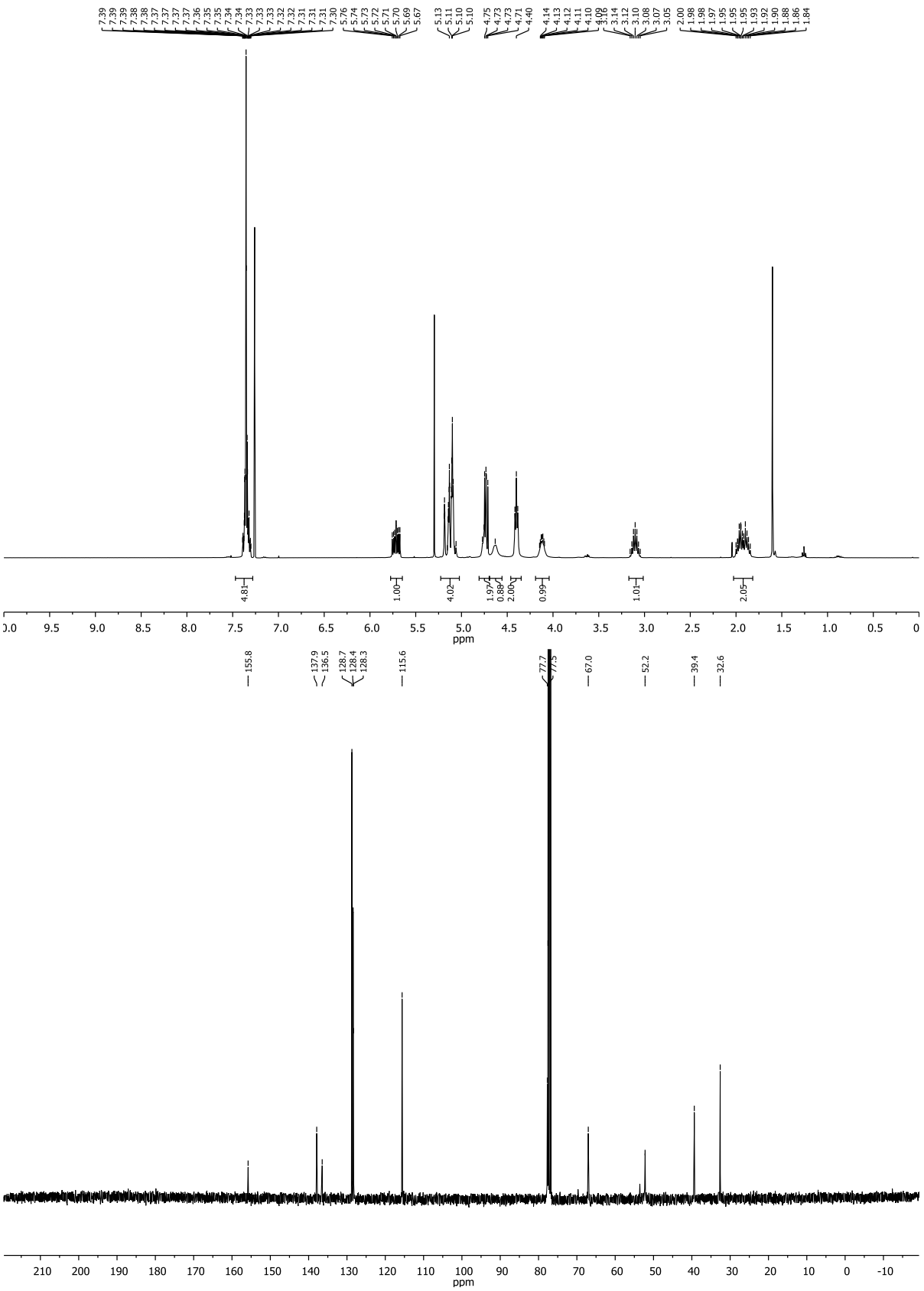


Figure 241 ^{1}H- and ^{13}C-NMR Spectra of 374.

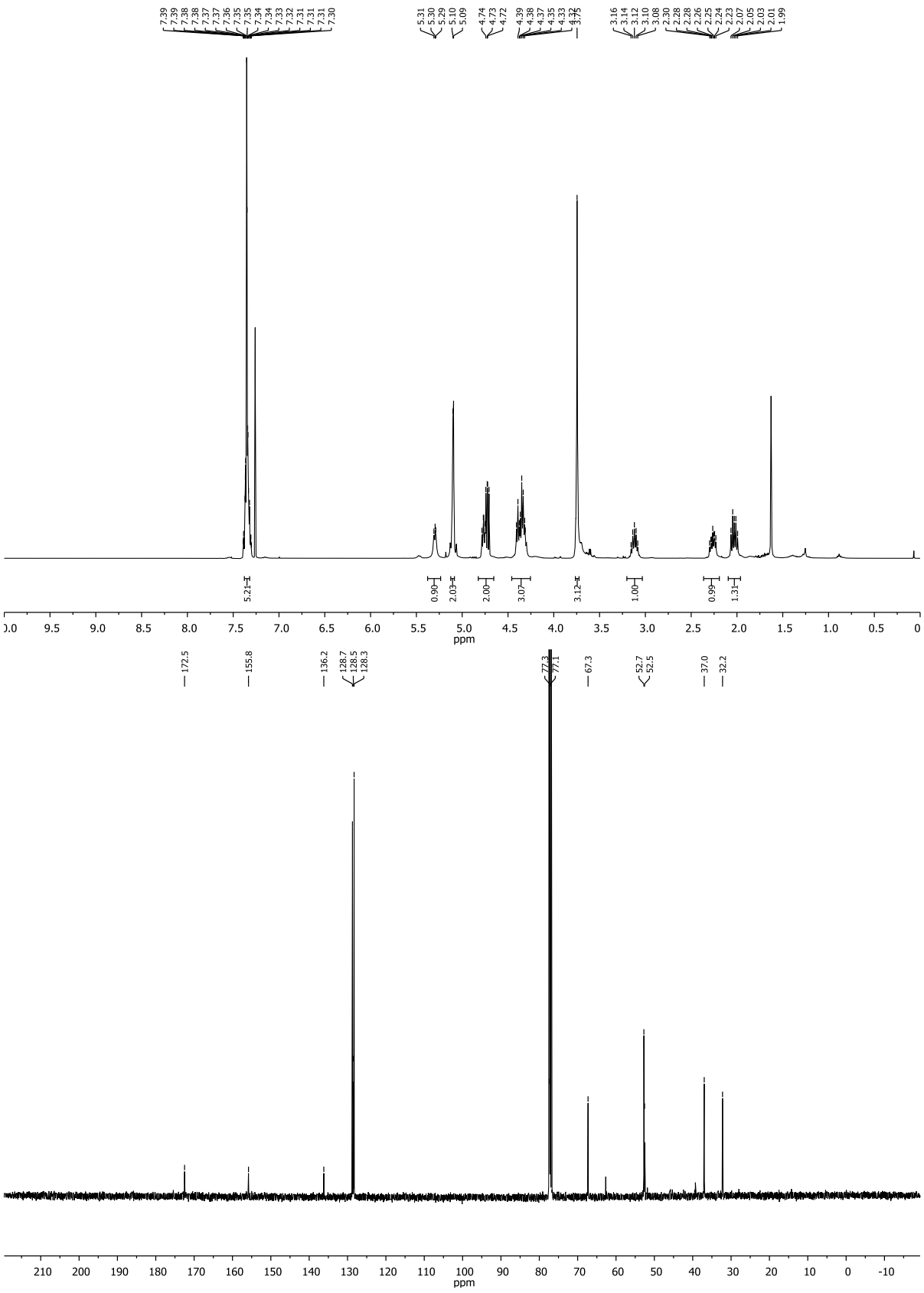


Figure 242 ^{1}H- and ^{13}C-NMR Spectra of 375.

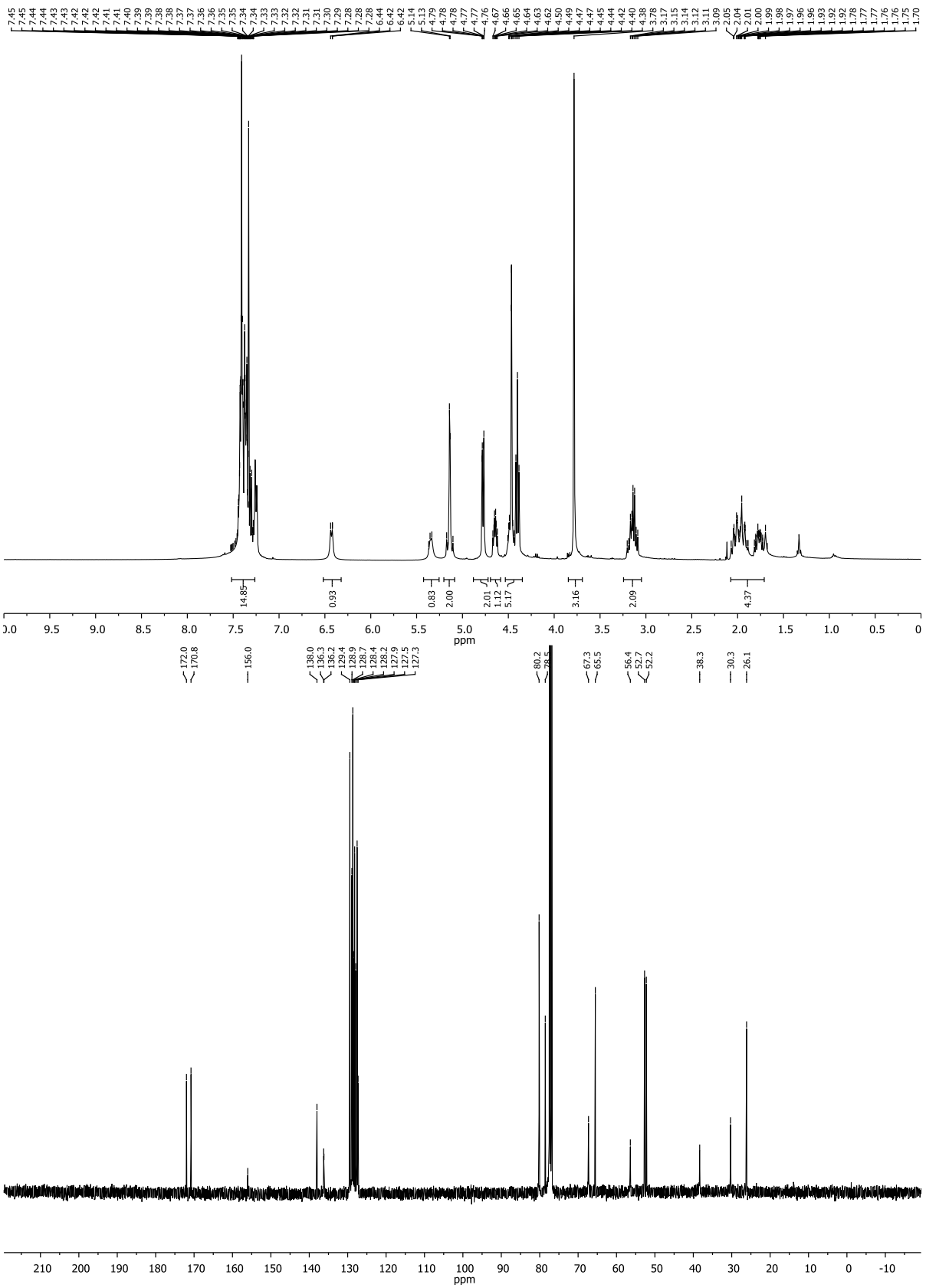


Figure 243 ^{1}H- and ^{13}C-NMR Spectra of 379.

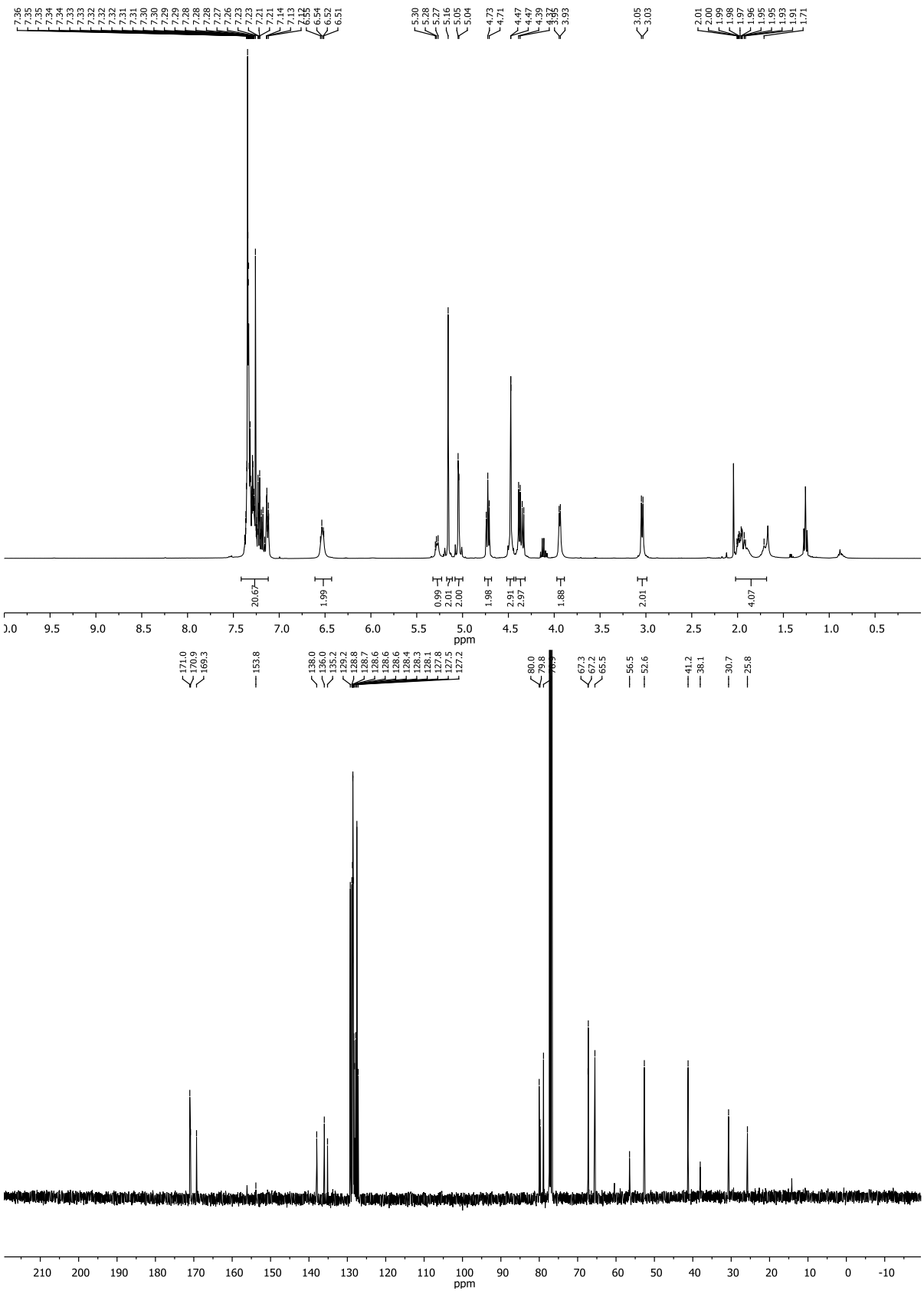


Figure 244 ^{1}H- and ^{13}C-NMR Spectra of 380.

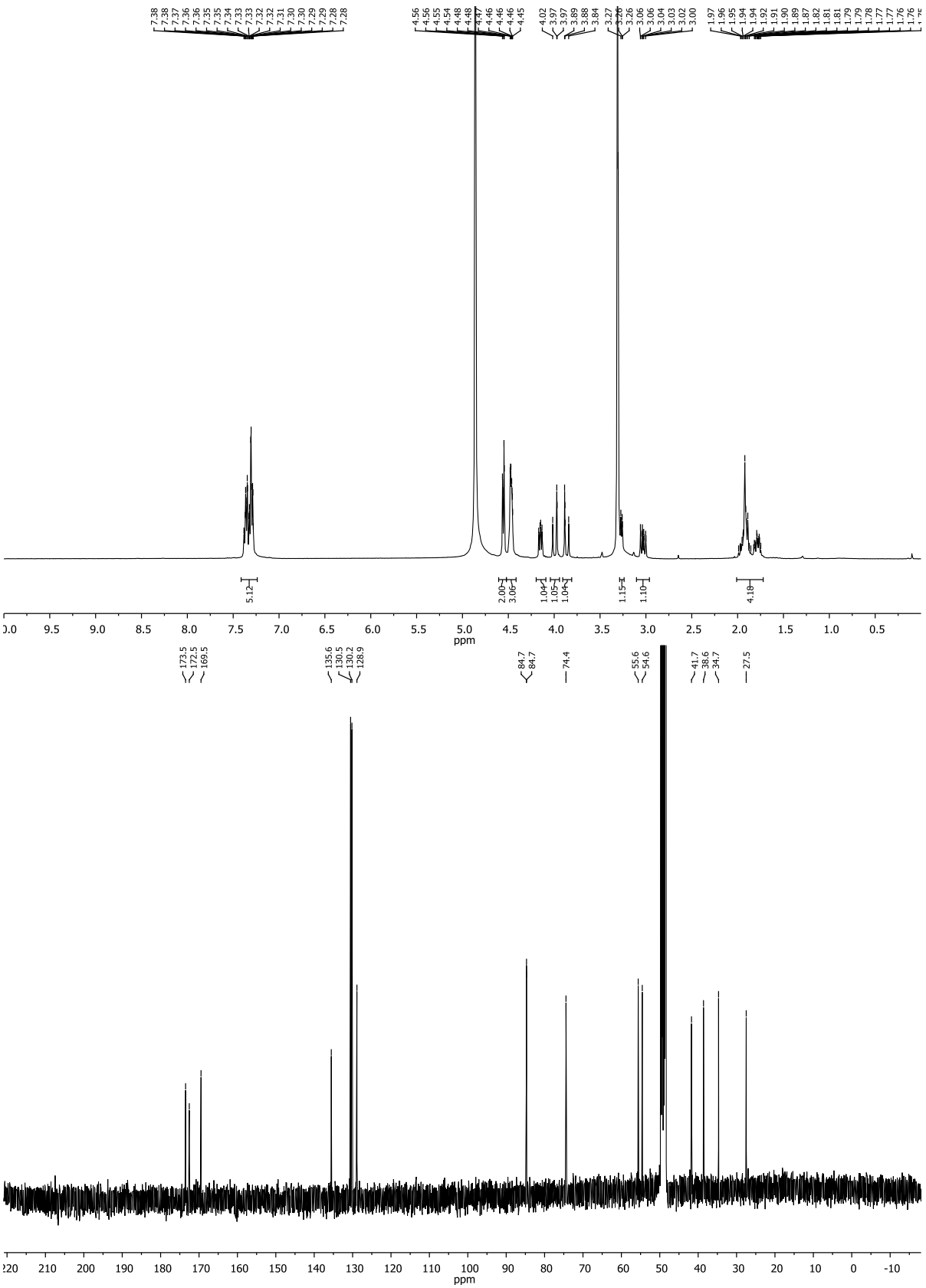


Figure 245 ^{1}H- and ^{13}C-NMR Spectra of 378.

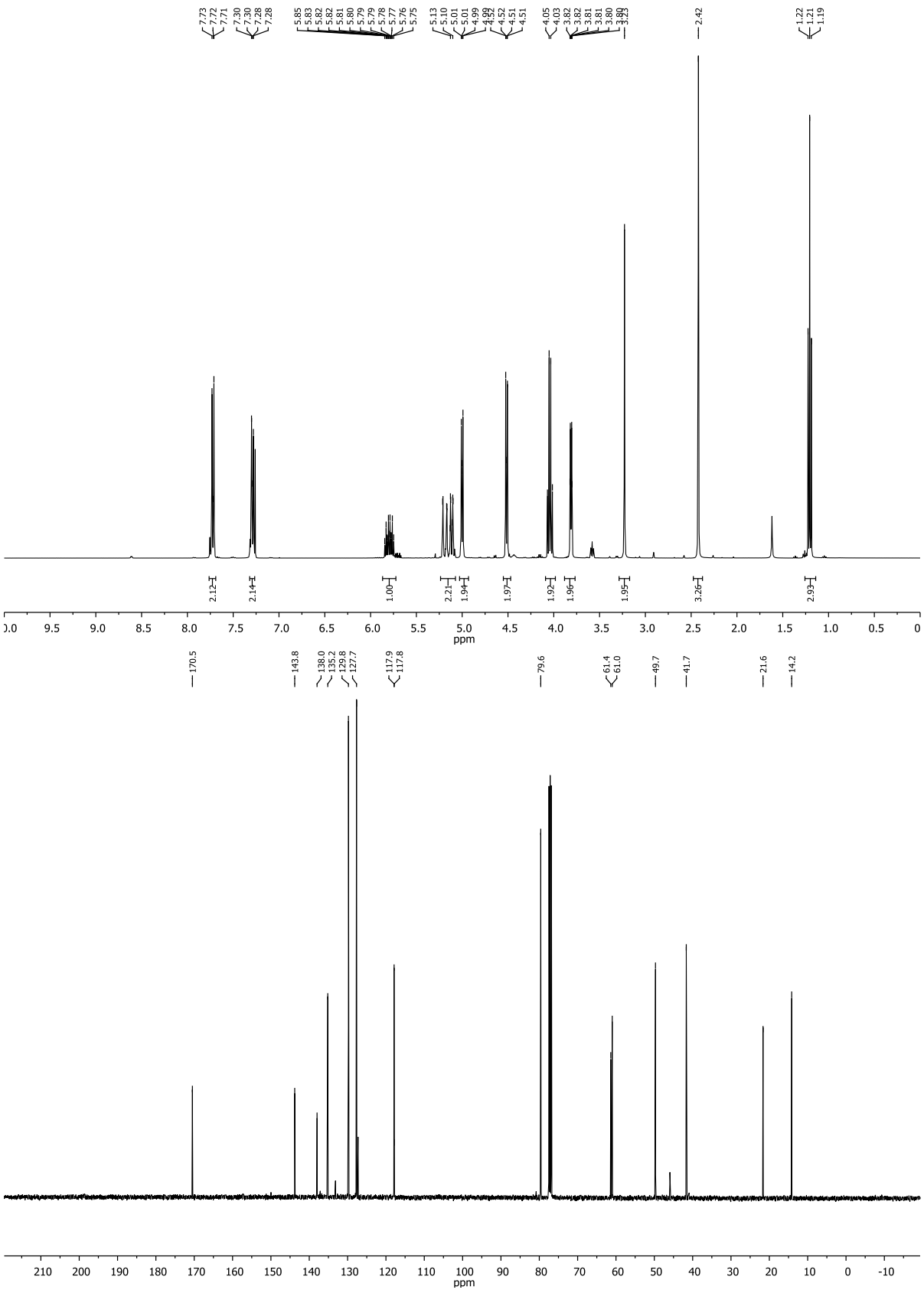


Figure 246 ^{1}H- and ^{13}C-NMR Spectra of 3.

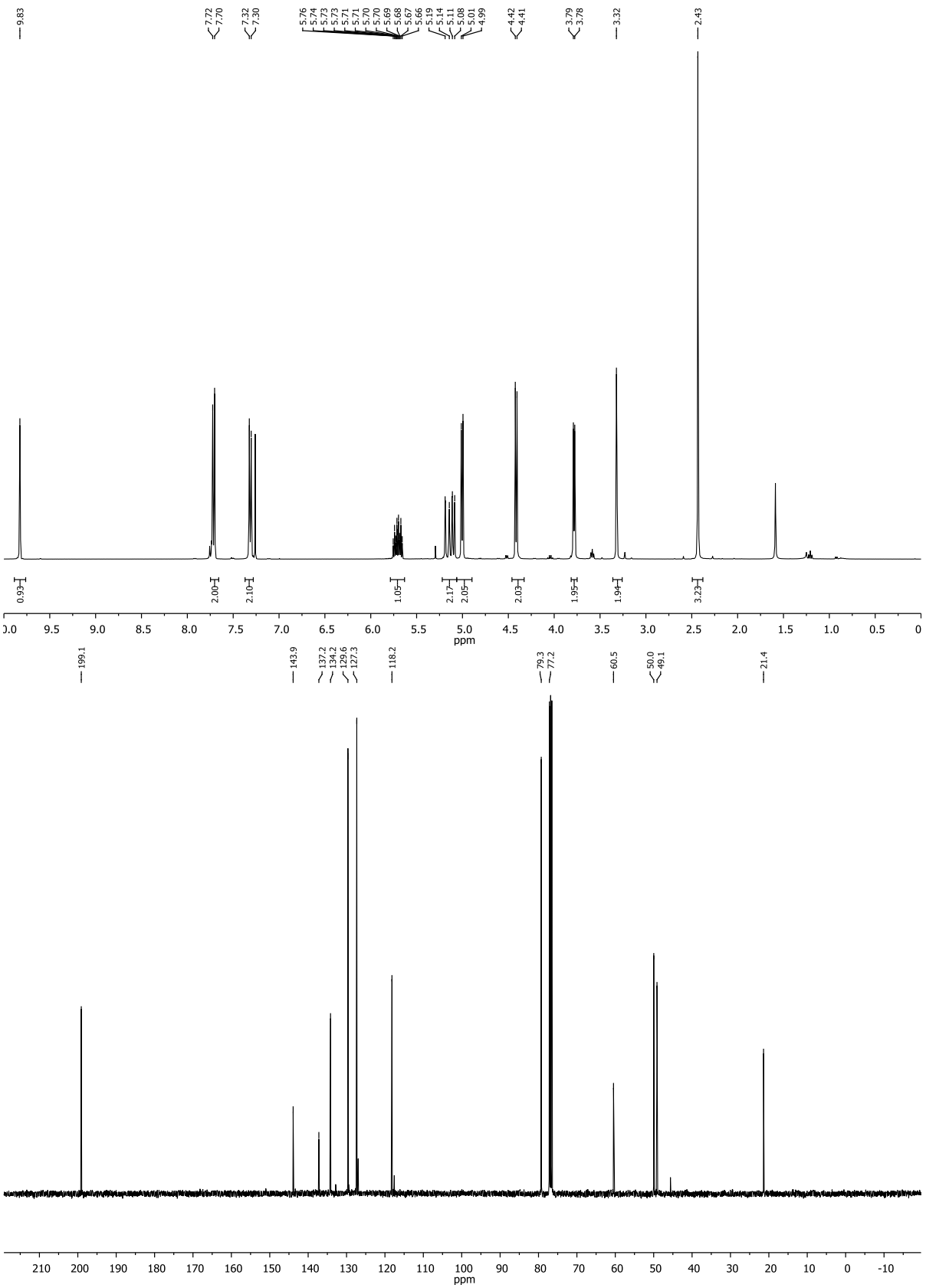


Figure 247 ^{1}H- and ^{13}C-NMR Spectra of 4.

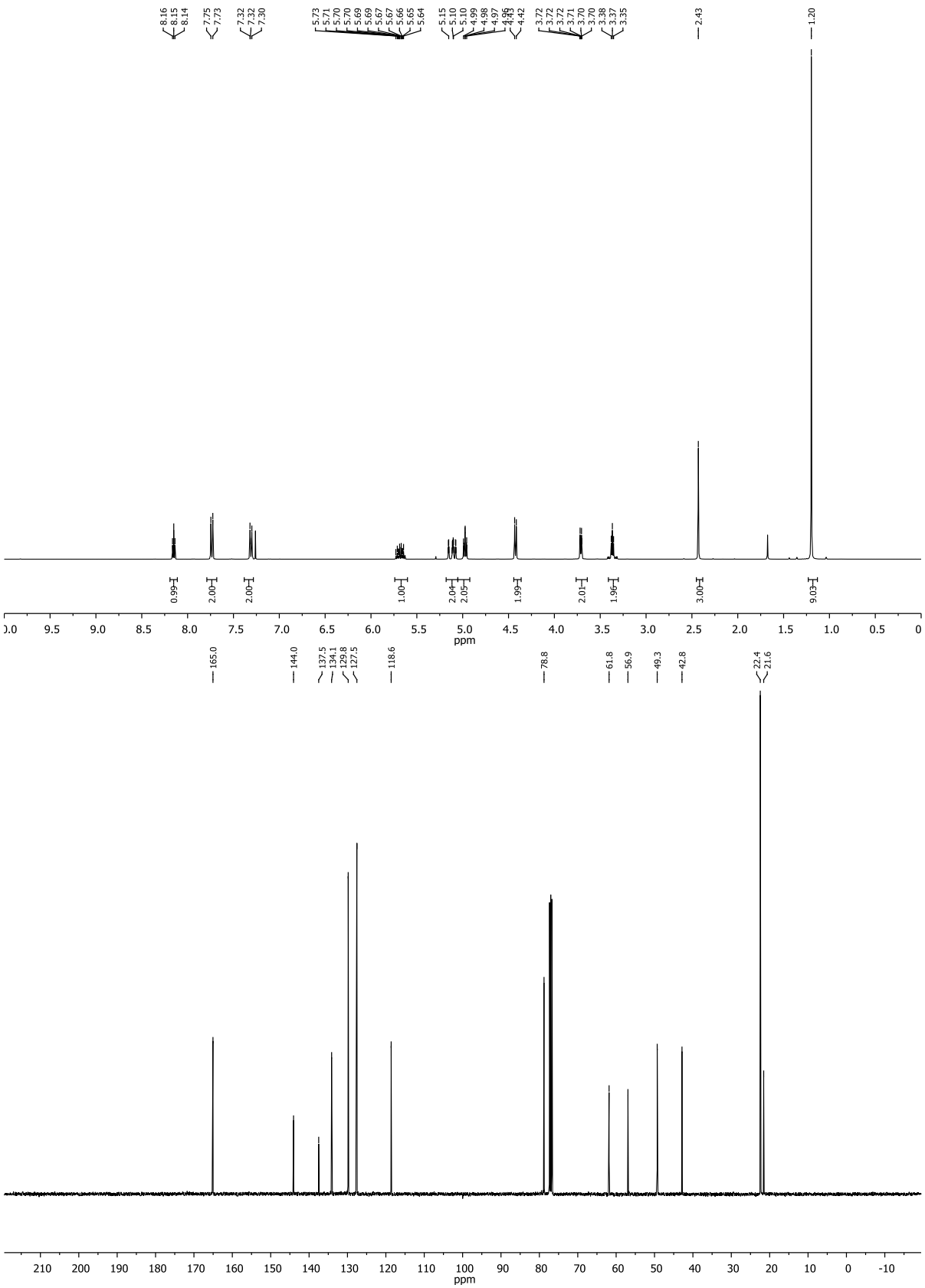
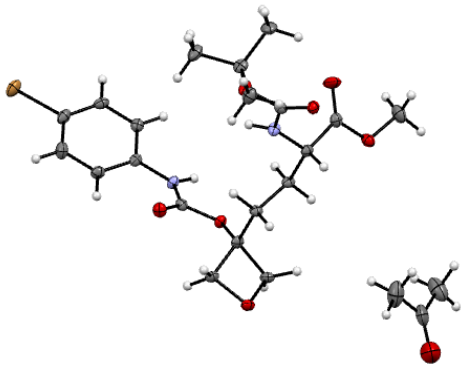


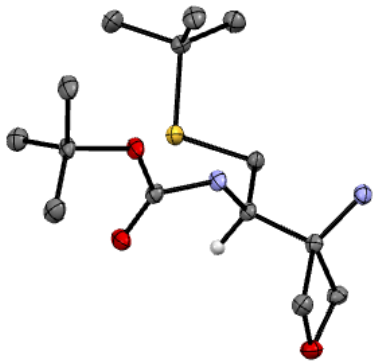
Figure 248 ^{1}H- and ^{13}C-NMR Spectra of 2.

Table 13 Crystal Data and Structure Refinement for 354.



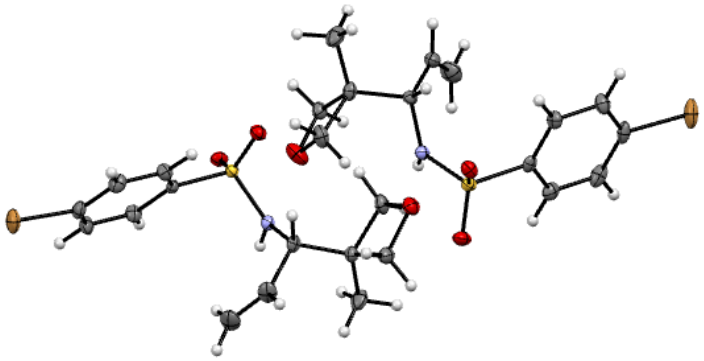
Empirical formula	$C_{43}H_{60}Br_2N_4O_{15}$
Formula weight	1032.77
Temperature/K	100.0(2)
Crystal system	orthorhombic
Space group	$P2_12_12$
a/Å	16.7915(18)
b/Å	24.133(3)
c/Å	5.9888(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2426.8(4)
Z	2
ϱ_{calc}g/cm^3	1.413
μ/mm^{-1}	1.739
F(000)	1072.0
Crystal size/mm^3	0.2 × 0.19 × 0.015
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.852 to 54.902
Index ranges	-21 ≤ h ≤ 21, -29 ≤ k ≤ 31, -7 ≤ l ≤ 7
Reflections collected	19771
Independent reflections	5538 [R_{int} = 0.0446, R_{sigma} = 0.0677]
Data/restraints/parameters	5538/306/301
Goodness-of-fit on F^2	1.014
Final R indexes [I>=2σ (I)]	R_1 = 0.0356, wR_2 = 0.0680
Final R indexes [all data]	R_1 = 0.0487, wR_2 = 0.0711
Largest diff. peak/hole / e Å^{-3}	0.71/-0.46
Flack parameter	0.023(5)

Table 14 Crystal Data and Structure Refinement for 197.



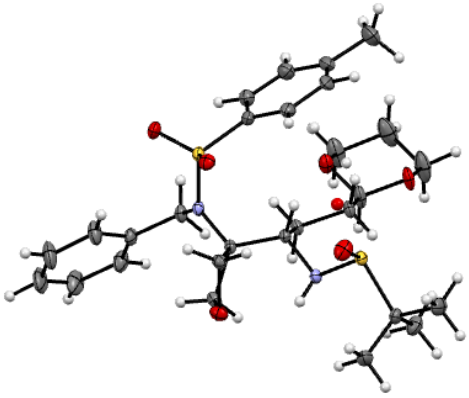
Empirical formula	$C_{14}H_{28}N_2O_3S$
Formula weight	304.44
Temperature/K	99.99
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	5.4302(4)
b/Å	15.9643(12)
c/Å	19.0144(14)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1648.3(2)
Z	4
ρ_{calc}mg/mm^3	1.227
m/mm^{-1}	0.206
F(000)	664.0
Crystal size/mm^3	0.26 × 0.26 × 0.2
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	4.284 to 54.96°
Index ranges	-7 ≤ h ≤ 6, -20 ≤ k ≤ 20, -24 ≤ l ≤ 24
Reflections collected	53403
Independent reflections	3758[R(int) = 0.0267]
Data/restraints/parameters	3758/2/195
Goodness-of-fit on F^2	1.097
Final R indexes [I>=2σ (I)]	R_1 = 0.0268, wR_2 = 0.0723
Final R indexes [all data]	R_1 = 0.0284, wR_2 = 0.0747
Largest diff. peak/hole / e Å^{-3}	0.38/-0.19
Flack parameter	0.002(9)

Table 15 Crystal Data and Structure Refinement for 371.



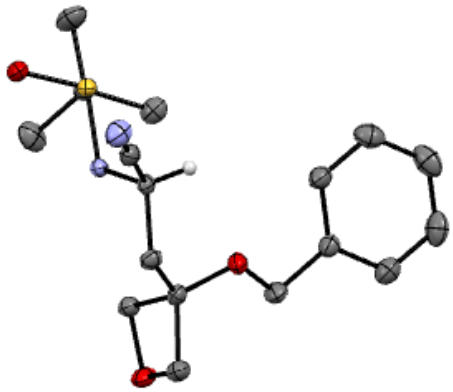
Empirical formula	$C_{13}H_{16}BrNO_3S$
Formula weight	346.24
Temperature/K	100.0(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	10.4172(17)
b/Å	14.184(3)
c/Å	11.086(2)
α/°	90
β/°	117.479(5)
γ/°	90
Volume/Å^3	1453.2(4)
Z	4
ρ_{calc}g/cm^3	1.583
μ/mm^{-1}	2.975
F(000)	704.0
Crystal size/mm^3	0.35 × 0.32 × 0.28
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.442 to 56.116
Index ranges	-13 ≤ h ≤ 13, -18 ≤ k ≤ 18, -14 ≤ l ≤ 14
Reflections collected	73078
Independent reflections	6979 [R_{int} = 0.0349, R_{sigma} = 0.0277]
Data/restraints/parameters	6979/387/351
Goodness-of-fit on F^2	1.054
Final R indexes [I>=2σ (I)]	R_1 = 0.0201, wR_2 = 0.0498
Final R indexes [all data]	R_1 = 0.0221, wR_2 = 0.0502
Largest diff. peak/hole / e Å^{-3}	0.49/-0.34
Flack parameter	0.0153(19)

Table 16 Crystal Data and Structure Refinement for 191.



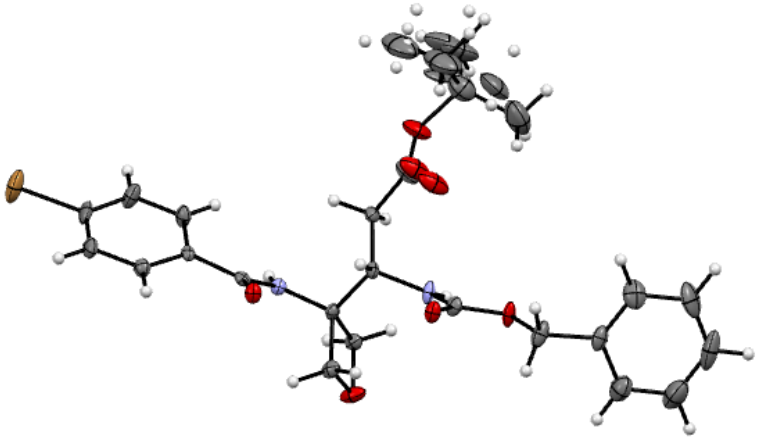
Empirical formula	$C_{28}H_{40}N_2O_6S_2$
Formula weight	564.74
Temperature/K	99.99
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	12.2783(9)
b/Å	12.6553(9)
c/Å	18.7589(16)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2914.9(4)
Z	4
ϱ_{calc}mg/mm^3	1.287
m/mm^{-1}	0.226
F(000)	1208.0
Crystal size/mm^3	0.36 × 0.16 × 0.05
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	4.622 to 55.93°
Index ranges	-16 ≤ h ≤ 16, -16 ≤ k ≤ 16, -24 ≤ l ≤ 24
Reflections collected	49982
Independent reflections	6995[R(int) = 0.0440]
Data/restraints/parameters	6995/1/356
Goodness-of-fit on F^2	1.041
Final R indexes [I>=2σ (I)]	R_1 = 0.0332, wR_2 = 0.0789
Final R indexes [all data]	R_1 = 0.0387, wR_2 = 0.0817
Largest diff. peak/hole / e Å^{-3}	0.59/-0.24
Flack parameter	0.009(18)

Table 17 Crystal Data and Structure Refinement for 358.



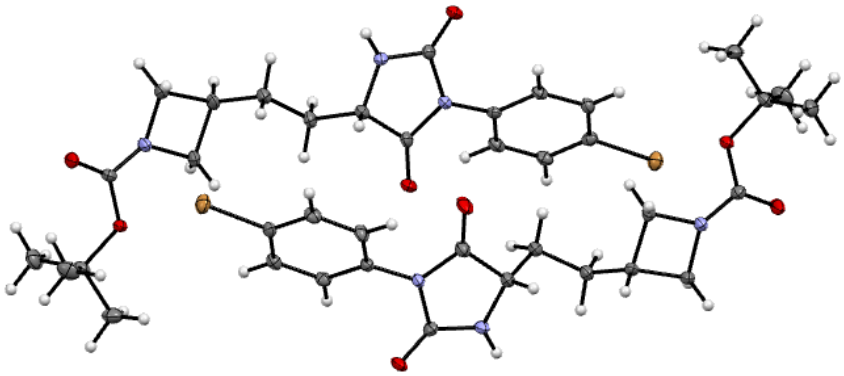
Empirical formula	$C_{17}H_{24}N_2O_3S$
Formula weight	336.44
Temperature/K	100(2)
Crystal system	Monoclinic
Space group	P2(1)
a/Å	9.6369(4)
b/Å	7.0655(3)
c/Å	13.1139(6)
α/°	90
β/°	98.278(2)
γ/°	90
Volume/Å^3	883.62(7)
Z	2
ϱ_{calc}mg/mm^3	1.265
m/mm^{-1}	0.199
F(000)	360
Crystal size/mm^3	0.52 × 0.35 × 0.15
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	1.57 to 27.90°
Index ranges	-12 ≤ h ≤ 12, -8 ≤ k ≤ 9, -16 ≤ l ≤ 17
Reflections collected	7052
Independent reflections	3847 [R(int) = 0.0292]
Data/restraints/parameters	3847/1/303
Goodness-of-fit on F^2	1.391
Final R indexes [I>=2σ (I)]	R_1 = 0.0337, wR_2 = 0.0822
Final R indexes [all data]	R_1 = 0.0413, wR_2 = 0.0872
Largest diff. peak/hole / e Å^{-3}	0.427/-0.286

Table 18 Crystal Data and Structure Refinement for 183.



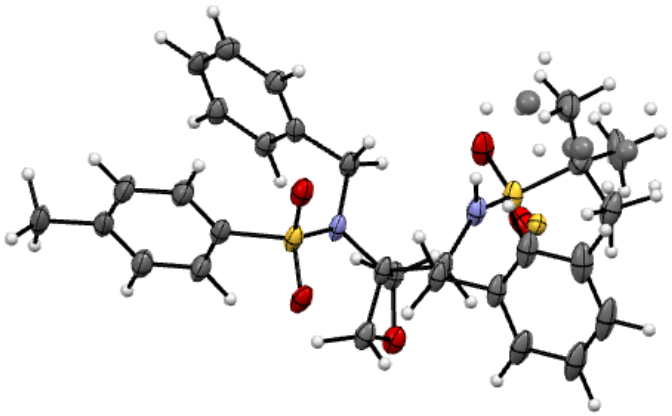
Empirical formula	$C_{25}H_{29}N_2O_6Br$
Formula weight	533.41
Temperature/K	99.99
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	10.0435(12)
b/Å	10.7709(14)
c/Å	24.399(3)
α/°	90.00
β/°	90.00
γ/°	90.00
Volume/Å^3	2639.4(6)
Z	4
ϱ_{calc}mg/mm^3	1.342
m/mm^{-1}	1.597
F(000)	1104.0
Crystal size/mm^3	0.16 × 0.05 × 0.015
2Θ range for data collection	4.14 to 55.12°
Index ranges	-13 ≤ h ≤ 13, -13 ≤ k ≤ 14, -31 ≤ l ≤ 31
Reflections collected	19149
Independent reflections	6080[R(int) = 0.0749]
Data/restraints/parameters	6080/168/341
Goodness-of-fit on F^2	0.951
Final R indexes [I>=2σ (I)]	R_1 = 0.0476, wR_2 = 0.0825
Final R indexes [all data]	R_1 = 0.0896, wR_2 = 0.0930
Largest diff. peak/hole / e Å^{-3}	0.57/-0.40
Flack parameter	0.013(9)

Table 19 Crystal Data and Structure Refinement for 367.



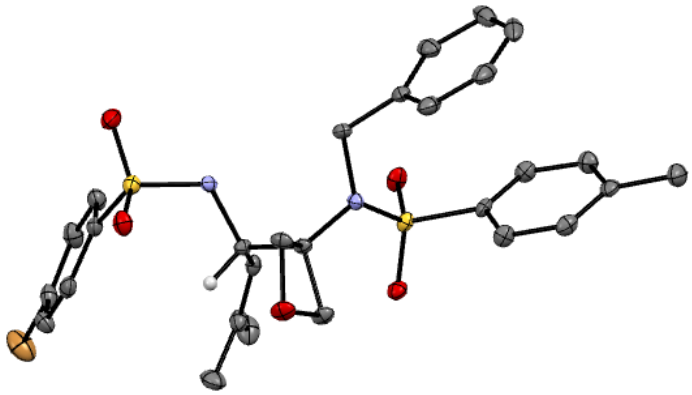
Empirical formula	$C_{19}H_{24}BrN_3O_4$
Formula weight	438.32
Temperature/K	99.99
Crystal system	monoclinic
Space group	$P2_1$
a/Å	6.1826(6)
b/Å	15.7445(14)
c/Å	20.4012(19)
α/°	90
β/°	90.697(2)
γ/°	90
Volume/Å^3	1985.7(3)
Z	4
ρ_{calc}g/cm^3	1.466
μ/mm^{-1}	2.099
F(000)	904.0
Crystal size/mm^3	0.26 × 0.09 × 0.07
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.268 to 59.522
Index ranges	-8 ≤ h ≤ 8, -21 ≤ k ≤ 21, -28 ≤ l ≤ 28
Reflections collected	80713
Independent reflections	11284 [R_{int} = 0.0332, R_{sigma} = 0.0296]
Data/restraints/parameters	11284/1/499
Goodness-of-fit on F^2	1.039
Final R indexes [I>=2σ (I)]	R_1 = 0.0223, wR_2 = 0.0536
Final R indexes [all data]	R_1 = 0.0257, wR_2 = 0.0544
Largest diff. peak/hole / e Å^{-3}	0.44/-0.34
Flack parameter	0.0100(19)

Table 20 Crystal Data and Structure Refinement for 162.



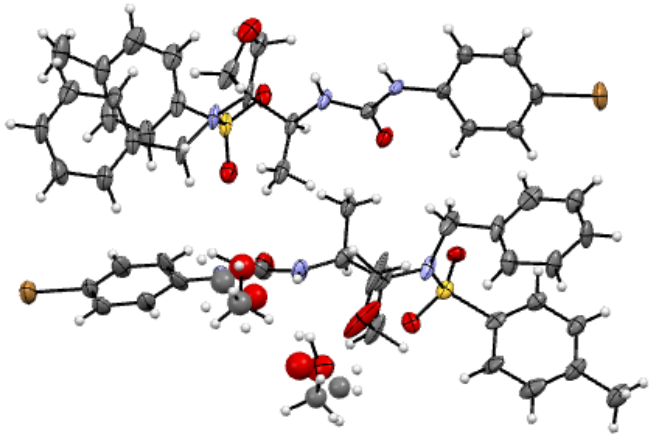
Empirical formula	$C_{29}H_{36}N_2O_4S_2$
Formula weight	540.72
Temperature/K	100(2)
Crystal system	monoclinic
Space group	C_2
a/Å	19.1057(11)
b/Å	6.4391(4)
c/Å	23.2138(13)
α/°	90
β/°	106.124(4)
γ/°	90
Volume/Å^3	2730.6(3)
Z	4
ϱ_{calc}mg/cm^3	1.315
μ/mm^{-1}	2.070
F(000)	1152
Crystal size/mm^3	0.02 × 0.01 × 0.01
Radiation	Cu (λ = 1.54178)
2Θ range for data collection/°	4.69 to 64.90
Index ranges	-19 ≤ h ≤ 22, -7 ≤ k ≤ 7, -27 ≤ l ≤ 25
Reflections collected	5774
Independent reflections	3193 [R_{int} = 0.0379]
Data/restraints/parameters	3193/7/376
Goodness-of-fit on F^2	1.113
Final R indexes [I>=2σ (I)]	R_1 = 0.0356, wR_2 = 0.0884
Final R indexes [all data]	R_1 = 0.0410, wR_2 = 0.0919
Largest diff. peak/hole / e Å^{-3}	0.185/-0.281

Table 21 Crystal Data and Structure Refinement for 156.



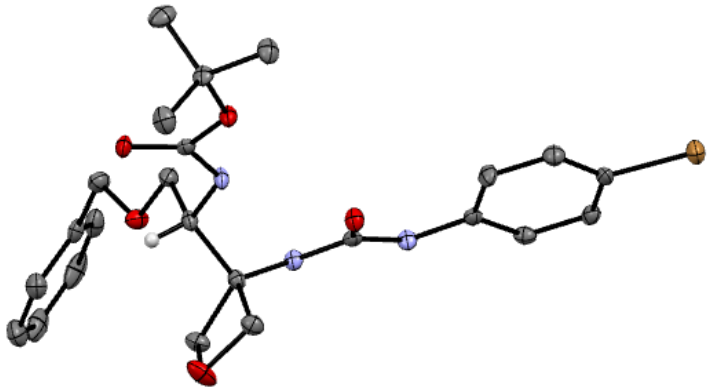
Empirical formula	$C_{28}H_{32}BrN_2O_5S_2$
Formula weight	620.59
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	13.3441(6)
b/Å	6.3849(2)
c/Å	16.1360(7)
α/°	90
β/°	95.366(2)
γ/°	90
Volume/Å^3	1368.77(10)
Z	2
ϱ_{calc}mg/cm^3	1.506
μ/mm^{-1}	1.696
F(000)	642
Crystal size/mm^3	0.32 × 0.06 × 0.03
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	1.90 to 27.55
Index ranges	-17 ≤ h ≤ 17, -7 ≤ k ≤ 8, -20 ≤ l ≤ 20
Reflections collected	21825
Independent reflections	6125 [R_{int} = 0.0264]
Data/restraints/parameters	6125/1/346
Goodness-of-fit on F^2	0.970
Final R indexes [I>=2σ (I)]	R_1 = 0.0257, wR_2 = 0.0607
Final R indexes [all data]	R_1 = 0.0310, wR_2 = 0.0621
Largest diff. peak/hole / e Å^{-3}	0.386/-0.490

Table 22 Crystal Data and Structure Refinement for 123.



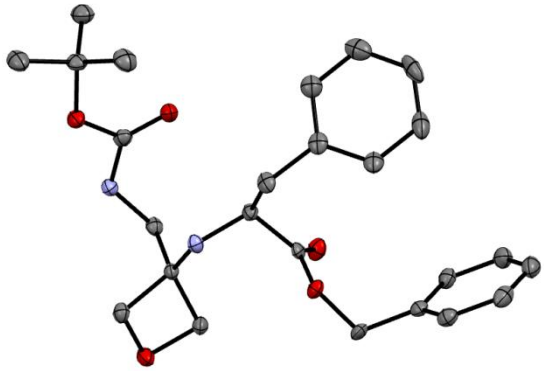
Empirical formula	$C_{27}H_{32}BrN_3O_5S$
Formula weight	590.53
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	7.2768(5)
b/Å	38.457(3)
c/Å	10.1623(9)
α/°	90
β/°	109.743(3)
γ/°	90
Volume/Å^3	2676.7(4)
Z	4
ρ_{calc}mg/cm^3	1.465
μ/mm^{-1}	1.656
F(000)	1224
Crystal size/mm^3	0.16 × 0.12 × 0.02
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	2.12 to 27.63
Index ranges	-9 ≤ h ≤ 9, -50 ≤ k ≤ 49, -11 ≤ l ≤ 13
Reflections collected	29888
Independent reflections	12198 [R_{int} = 0.0859]
Data/restraints/parameters	12198/5/676
Goodness-of-fit on F^2	0.934
Final R indexes [I>=2σ (I)]	R_1 = 0.0627, wR_2 = 0.1067
Final R indexes [all data]	R_1 = 0.1456, wR_2 = 0.1317
Largest diff. peak/hole / e Å^{-3}	0.698/-0.466

Table 23 Crystal Data and Structure Refinement for 178.



Empirical formula	$C_{24}H_{30}BrN_3O_5$
Formula weight	520.42
Temperature/K	100(2)
Crystal system	Orthorombic
Space group	$P2_12_12_1$
a/Å	9.6689(5)
b/Å	13.7338(7)
c/Å	17.9303(11)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2381.0(2)
Z	4
ϱ_{calc}mg/cm^3	1.452
μ/mm^{-1}	1.767
F(000)	1080
Crystal size/mm^3	0.44 × 0.28 × 0.15
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	2.27 to 27.65
Index ranges	-11 ≤ h ≤ 12, -17 ≤ k ≤ 16, -23 ≤ l ≤ 23
Reflections collected	39635
Independent reflections	5530 [R_{int} = 0.0297]
Data/restraints/parameters	5530/0/418
Goodness-of-fit on F^2	1.010
Final R indexes [I>=2σ (I)]	R_1 = 0.0202, wR_2 = 0.0457
Final R indexes [all data]	R_1 = 0.0229, wR_2 = 0.0463
Largest diff. peak/hole / e Å^{-3}	0.371/-0.198

Table 24 Crystal Data and Structure Refinement for 73d.



Empirical formula	$C_{25}H_{32}N_2O_5$
Formula weight	440.52
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1$
a/Å	12.737(9)
b/Å	5.931(4)
c/Å	15.911(10)
α/°	90
β/°	104.930(14)
γ/°	90
Volume/Å^3	1161.4(14)
Z	2
ϱ_{calc}mg/mm^3	1.260
m/mm^{-1}	0.088
F(000)	472.0
Crystal size/mm^3	0.28 × 0.04 × 0.01
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	4.742 to 50.132°
Index ranges	-13 ≤ h ≤ 15, -7 ≤ k ≤ 6, -18 ≤ l ≤ 18
Reflections collected	5255
Independent reflections	3917[R(int) = 0.0397]
Data/restraints/parameters	3917/1/298
Goodness-of-fit on F^2	1.014
Final R indexes [I>=2σ (I)]	R_1 = 0.0465, wR_2 = 0.0839
Final R indexes [all data]	R_1 = 0.0749, wR_2 = 0.0937
Largest diff. peak/hole / e Å^{-3}	0.18/-0.17
Flack parameter	-2.0(10)

Curriculum Vitae

Born August 14th 1987 in Düsseldorf, Germany

1997-2006	Carl-Friedrich von Weizsäcker-Gymnasium, Ratingen, Germany
2003-2004	Lancing College, Lancing, West Sussex, Great Britain
2006	Abitur
2006-2011	Studies in Chemistry (Diplom), WWU Münster, Germany
10/2010-03/2011	Diplomarbeit in the group of Prof. Dr. Bernhard Wünsch, Institute for Pharmaceutical and Medicinal Chemistry, WWU Münster, Germany Title: "*Synthese spirocyclischer σ1-Rezeptorliganden mit Pyridinstruktur*"
03/2010-05/2010	Internship in the Discovery Chemistry division, Hoffmann-La Roche AG, Basel, Switzerland
03/2011	Diplom-Chemiker
07/2011-06/2015	Doctoral Studies in the group of Prof. Erick M. Carreira, ETH Zurich, Switzerland Title: "*Synthesis and Application of Oxetanyl Peptides*"

Scholarships

2007-2011	Scholarship of the "Studienstiftung des deutschen Volkes e.V."

During my doctoral studies, I was once teaching assistant for an introductory-level organic chemistry laboratory course and supervised one exchange student, two undergraduate students during research projects as well as an apprentice in the first year.