Development of a Total Synthesis of Myxovalargin A and Derivatives

–

Investigations on Transformations with Polymer-Supported Bisazidoiodate (I)

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für meine Eltern

Zusammenfassung

Teresa Kösel

Entwicklung einer Totalsynthese von Myxovalargin A und Derivaten
-
Organochemische Untersuchungen zu polymergebundenem Bisazidoiodat (I)

Schlagwörter: Myxovalargin A, Naturstoffsynthese, Peptidantibiotika, Festphasen-Peptidsynthese, polymergebundenes Iodazid, Photochemie, selektive Oxidation von sekundären Alkoholen, Azidierung von Phenolen und Ketonen

Der erste Teil der vorliegenden Dissertation befasst sich mit der chemischen Totalsynthese des peptidischen Naturstoffs Myxovalargin A, der aus einem Kulturüberstand des Myxobakterienstamms *Myxococcus fulvus*, Mx f65, isoliert wurde und bereits im Jahr 1981 erstmals namentliche Erwähnung fand. Es zeigt antibiotische Aktivität gegen eine Vielzahl von GRAM-positiven und GRAM-negativen Bakterien. Die damals mittels Fütterungsexperimenten postulierte Aminosäuresequenz mit entsprechenden Konfigurationen steht jedoch im Gegensatz zu den Ergebnissen einer neuerdings durchgeführten Genclusteranalyse. Aus diesem Grund wurden in dieser Arbeit beide Varianten des Myxovalargins mittels einer Kombination aus Fest- und Flüssigphasenpeptidchemie synthetisiert. Massenspektrometrische Vergleiche der beiden synthetisierten Myxovalargine mit dem aus dem bakteriellen Überstand isolierten Naturprodukt bestätigten zweifelsfrei die durch die Genclusteranalyse postulierte Stereochemie. Darüber hinaus wurde ein synthetischer Zugang zu strukturell vereinfachten Myxovalargin-Derivaten untersucht.

Der zweite Teil dieser Dissertation beschäftigt sich mit organochemischen Untersuchungen zum polymergebundenen Bisazidoiodat (I), das die gleichen chemischen Eigenschaften wie Iodazid besitzt, jedoch nicht dessen explosiven Charakter. Von besonderer Bedeutung ist hier die photochemisch-induzierte homolytische Spaltung des Iodazids, wodurch Azidradikale freigesetzt werden, die die Grundlage für eine chemoselektive Oxidation von sekundären Alkoholen in Präsenz von primären Alkoholen legen. Darüber hinaus wurde eine neue Reaktivität von Iodazid gegenüber Phenolen und Ketonen erforscht, wobei die zwischenzeitliche Bildung des Hypoiodits den Schlüsselschritt in der oxidativen Azidierung von Phenolen und Ketonen darstellt.

Abstract

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Keywords: Myxovalargin A, natural product synthesis, peptide antibiotics, solid-phase peptide synthesis, polymer-bound iodoazide, photochemistry, selective oxidation of secondary alcohols, azidation of phenols and ketones

The first part of this dissertation deals with the chemical total synthesis of peptide natural product Myxovalargin A, which was isolated from a culture supernatant of the myxobacterial strain *Myxococcus fulvus*, Mx f65, and first mentioned by name as early as 1981. It exhibits antibiotic activity against a wide range of GRAM-positive and GRAM-negative bacteria. However, the amino acid sequence with corresponding configurations obtained from feeding experiments at that time contrasts with the results of a recent gene cluster analysis. For this reason, both variants of myxovalargin were synthesized in this work by a combination of solid-phase and liquid-phase peptide chemistry. Mass spectrometric comparisons of the two synthesized myxovalargins with the natural product isolated from the bacterial supernatant confirmed unequivocally the stereochemistry postulated by the gene cluster analysis. Moreover, a synthetic approach for structurally simplified myxovalargin derivatives was investigated.

The second part of this dissertation deals with chemical studies on polymer-bound bisazidoiodate (I), which exhibits the same chemical properties as iodoazide, but not its explosive character. Of particular importance here is the photochemically induced homolytic cleavage of iodine azide to release azide radicals, which provide the reactive species for the chemoselective oxidation of secondary alcohols in the presence of primary alcohols. In addition, a new reactivity of iodine azide toward phenols and ketones was explored, with the intermediate formation of hypoiodite being the key step in the oxidative azidation of phenols and ketones.

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Abbreviations and Preliminary Remarks

List of Abbreviations

$[\alpha]^t_D$	specific optical rotation values
A-domain	adenylation domain
Ac	acetyl
Ala	alanine
Alloc	allyloxycarbonyl
APCI	chemical ionization at atmospheric pressure
Arg	arginine
BDE	bond dissociation energy
Bkd	branched chain ketoacid dehydrogenase
Boc	*tert*-butyloxycarbonyl
c	concentration
C-domain	condensation domain
cat.	catalytic
CoA	coenzyme A
COSY	correlation spectroscopy
Cryo-EM	cryogenic electron microscopy
δ	chemical shift
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIC	diisopropylcarbodiimide
DIPEA	*N,N*-diisopropylethylamine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMP	DESS-MARTIN-periodinane
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
d.r.	diastereomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
E-domain	epimerization domain

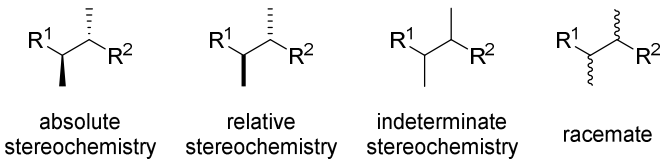
ee	enantiomeric excess
equiv.	equivalents
ESI	electrospray ionization
Et	ethyl
et al.	*et alii,* and others
EtOAc	ethyl acetate
FA	formic acid
FAB mass	fast atom bombardment (mass spectrometry)
FDA	Food and Drug Administration
Fmoc	fluorenylmethoxycarbonyl
fr.	fraction
GCMS	gas chromatography mass spectrometry
h	hours
HATU	(1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate
HIPS	Helmholtz Institute for Pharmaceutical Research Saarland
HMBC	heteronuclear multiple-bond correlation spectroscopy
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
Hz	hertz
HZI	Helmholtz Centre for Infection Research
IBCF	isobutyl chloroformate
IBX	2-iodoxybenzoic acid
IR	infrared
*i*Val	isovaleric
J	coupling constant (NMR)
LCMS	liquid chromatography mass spectrometry
LD value	lethal dose value

Lit.	literature
Me	methyl
MeOH	methanol
MeCN	acetonitrile
MIC	minimum inhibitory concentration
min	minutes
MT-domain	methyltransferase domain
NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NP	normal-phase
NRP	non-ribosomal peptide
NRPS	non-ribosomal peptide synthetase
OPA	*ortho*-phthaldehyde
Oxyma	ethyl cyanohydroxyiminoacetate
o2s	over two steps
PABA	*para*-aminobenzoic acid
Pbf	2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl
PCP	peptide carrier protein
PE	petroleum ether
Ph	phenyl
PIDA	(diacetoxyiodo)benzene
PIFA	[bis(trifluoroacetoxy)iodo]benzene
ppm	parts per million (NMR)
PyAOP	(7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
quant.	quantitative
QTOF	quadrupole time-of-flight (mass spectrometry)
R	residue
rac	racemate

R_f	retardation factor
RNA	ribonucleic acid
RP	reversed-phase
rt	room temperature
sat.	saturated
sec	seconds
SM	starting material
SPPS	solid-phase peptide synthesis
t	time
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
Teoc	2-(trimethylsilyl)ethoxycarbonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
T_M	melting point
TMS	trimethylsilyl
t_R	retention time
*t*RNA	transfer ribonucleic acid
Tyr	tyrosine
UPLC	ultra high performance liquid chromatography
UV	ultraviolet
Val	valine
WHO	World Health Organization
WP	wide pore

Preliminary Remarks

Stereochemistry is represented in this work as follows: Wedged bonds represent absolute stereochemistry, while bars indicate relative stereochemistry. In addition, single bonds refer to undefined stereochemistry and wavy bonds are used for racemates.



The type of atom numbering used in part to assign NMR signals in the experimental section does not follow IUPAC rules.

Parts of the research of this work have already been published:

[1] Photochemical Transformations with Iodine Azide after Release from an Ion-Exchange Resin, T. Kösel, G. Schulz, G. Dräger, A. Kirschning, *Angew. Chem. Int. Ed.* **2020**, *59*, 12376-12380; *Angew. Chem.* **2020**, *132*, 12475-12479.

[2] Oxidative azidations of phenols and ketones using iodine azide after release from an ion exchange resin, T. Kösel, G. Dräger, A. Kirschning, *Org. Biomol. Chem.* **2021**, *19*, 2907-2911.

Topic A: Development of a Total Synthesis of Myxovalargin A and Derivatives

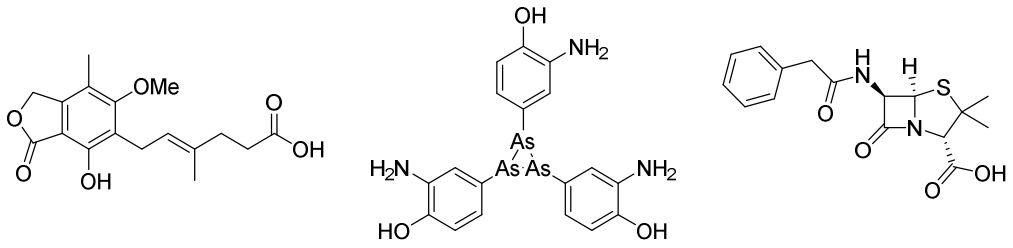
A1 Introduction

A1.1 Antibiotics for the Treatment of Infectious Diseases

For many years, infectious diseases were the leading cause of human mortality. However, since the discovery of antibiotics, the associated death rate has declined significantly.[1]

In 1893, the Italian microbiologist and physician B. GOSIO reported mycophenolic acid (**1**, Figure 1) being isolated from *Penicillium glaucum* during his studies on pellagra.[2] At that time, it was known to be effective against *Bacillus anthracis*, later antiviral, antifungal and antitumor properties were reported as well.[3] Thus, this was the first described antibiotic from a natural source.[4]

In the first decade of the 20th century, P. EHRLICH was introduced to cell staining of bacteria and started to work on organoarsenic compounds being potent against some bacterial strains.[4] In 1910, the first synthetically produced antibiotic was already approved as a drug. Thus, arsphenamine (**2**, Figure 1), later known as Salvarsan, was synthesized by A. BERTHEIM in the laboratories of P. EHRLICH which provided the basic structure for the treatment of syphilis.[5,6]



1 mycophenolic acid **2** arsphenamine (Salvarsan) **3** penicillin G

Figure 1: Some of the first antibiotics – mycophenolic acid (**1**), arsphenamine (**2**) and penicillin G (**3**).

In 1928, the golden age of antibiotics began, when A. FLEMING discovered that his *Staphylococcus aureus* colony was contaminated with a fungus (*P. chrysogenum*). Such *Staphylococci* in close proximity to the fungus underwent lysis whereas more distant bacteria were not affected. FLEMING concluded that the fungus must have produced a substance that was potent against bacteria and thus investigated penicillin G (**3**, Figure 1).[7] After World War II, penicillin was increasingly used to treat bacterial infections in the general population and became the first member of β-lactam antibiotics.[4]

[1] R. I. Aminov, *Front. Microbiol.* **2010**, *1*, 1-7.
[2] B. Gosio, *G. Accad. Med. Torino* **1893**, *61*, 464-487.
[3] J. E. Silverman Kitchin, M. K. Pomeranz, G. Pak, K. Washenik, J. L. Shupack, *J. Am. Acad. Dermatol.* **1997**, *37*, 445-449.
[4] K. Nicolaou, S. Rigol, *J Antibiot.* **2018**, *71*, 153-184.
[5] P. Ehrlich, A. Bertheim, *Berichte der Dtsch. Chem. Gesellschaft* **1912**, *45*, 756-766.
[6] K. J. Williams, *J. R. Soc. Med.* **2009**, *102*, 343-348.
[7] A. Fleming, *Br. J. Exp. Pathol.* **1929**, *10*, 226-236.

This milestone marked the beginning of research and development of numerous classes of antibiotics. The decades between 1950 and 1970 were the golden years for the discovery of novel antibiotic classes.[1] With the increasing development of resistance, it is becoming more and more important to discover new active substances.

A1.2 Antibiotic Resistance

According to WHO, antibiotic resistance is one of the "biggest threats" to our global health today.[8]

In general, an antibiotic is selectively directed against a bacterial target that occurs in this form only in prokaryotic cells or in a derived form in eukaryotic ones. In this way, antibiotics usually have few side effects. These targets include the bacterial cell membrane, DNA and RNA syntheses, protein and cell wall syntheses and the folic acid (Vitamin B9) metabolism (Figure 2).[9] Examples for antibiotics include β-lactams, which inhibit the formation of the bacterial cell wall. Eukaryotes are not affected, since their cells do not consist of cell walls.

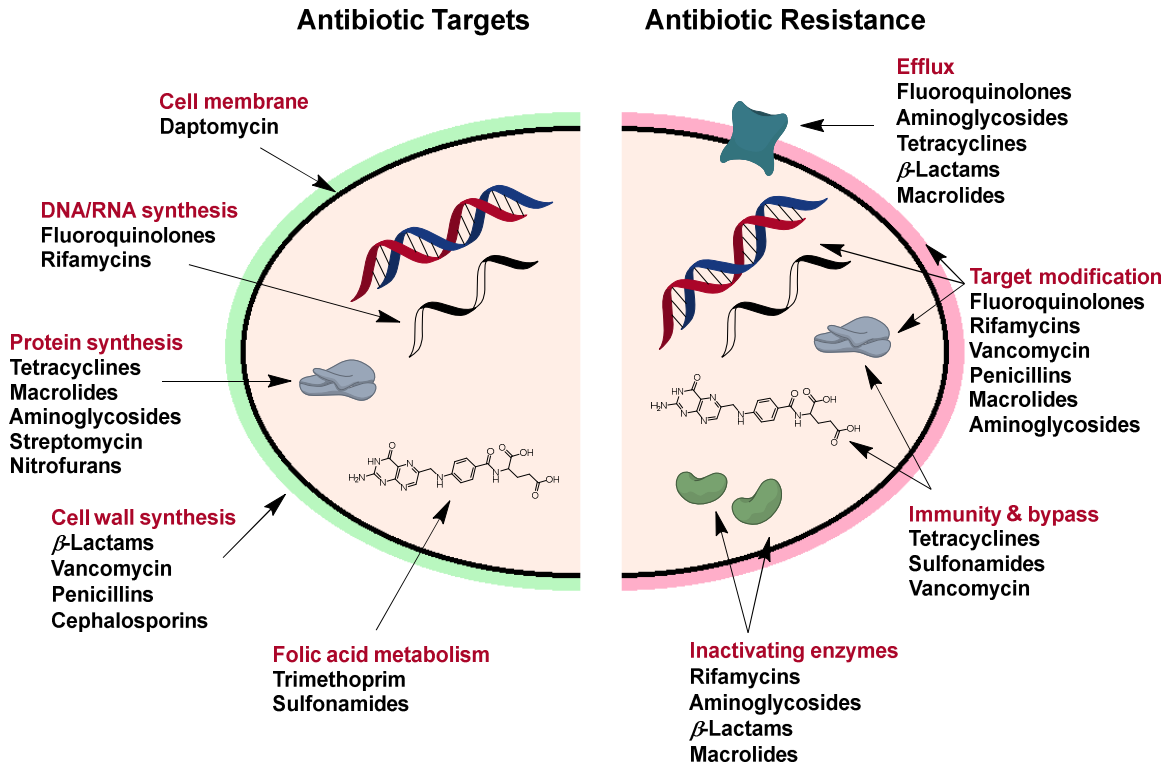
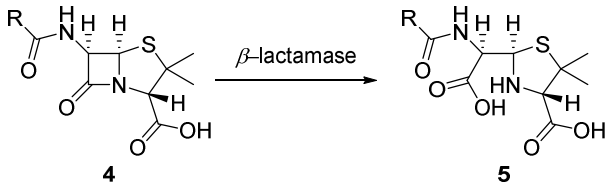


Figure 2: Antibiotic target sites and mechanisms of resistance with some popular antibiotics as respective examples.[9]

[8] https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance; accessed: 11.01.2022, 4.20 pm.
[9] G. D. Wright, *BMC Biology* **2010**, *8*, 123.

Antibiotic resistance now arises through four main mechanisms: *efflux* meaning that the antibiotic is pumped outwards the cell; *target modification* by enzymes or mutation; *immunity and bypass* where the antibiotic is prevented from reaching the target by binding to a protein and *inactivating enzymes* which modify antibiotics in order to inhibit their impact (Figure 2).[9] An example of the latter is the inhibition of *β*-lactam antibiotics **4** (e.g. penicillin) by *β*-lactamases (Scheme 1). Here, the enzyme catalyzes the hydrolytic opening of the lactam ring, which is necessary for antibiotic action. Moreover, the irreversible binding of the ring opening products to endogenous proteins can trigger allergic reactions.[10]



Scheme 1: Hydrolytic inactivation of *β*-lactam antibiotic **4** (e.g. penicillin) by *β*-lactamases.

The genes for resistance traits can be shared between bacteria of different taxonomic groups through mobile genetic elements such as naked DNA, plasmids, bacteriophages, or transposons (horizontal gene transfer).[11] Due to the growing selection pressure from increased administration of antibiotics, resistance formation is the conclusive evolutionary response of bacteria.[9] Treatment of an increasing number of infections, such as tuberculosis, pneumonia, and blood poisoning becomes harder and sometimes impossible as currently existing antibiotics become less effective.[8]

But what can humans do to stop this process as there is currently no way to hinder bacteria from forming a resistance mechanism? First, the amount of antibiotic usage should be reduced, this includes the use in food animals and agriculture. Secondly, global surveillance of resistance frequency would simplify choices of treatment and thirdly, isolating hospitalized patients with resistant bacteria would prevent their spreading.[11] Nevertheless, antibiotic research remains indispensable. The discovery of penicillin demonstrated the importance of natural products in the development of new drugs. Compared to synthetic drugs, the natural product class of antibiotics is characterized by considerable structural complexity.[12] Therefore, it is not surprising that some research institutions are focusing on natural products in their antibiotic research.

[10] B. Schäfer: *Naturstoffe in der chemischen Industrie*, Spektrum Akademischer Verlag, Germany, **2007**, 196-197.
[11] S. B. Levy, B. Marshall, *Nat. Med.* **2004**, *10*, S122-S129.
[12] S. E. Rossiter, M. H. Fletcher, W. M. Wuest, *Chem. Rev*. **2017**, *117*, 12415-12474.

A1.3 Myxobacteria – Producers of Powerful Natural Products

Microorganisms produce a variety of secondary metabolites.[13] These are compounds that are produced by organisms only in certain dangerous situations or for intercellular communication and are then often released into the environment. In many cases, however, their effects and benefits are completely unknown but open up a wide range of possible effective compounds for the treatment of diseases.[14]

Myxobacteria belong to one class of these microorganisms and were first mentioned by THAXTER *et al*. in 1892.[15] They are GRAM-negative bacteria and possess the largest bacterial genome known to date with over 14 million base pairs which offer many secondary metabolite clusters.[16,17] Myxobacteria belong to the δ-proteobacteria and are obligate, aerobic rods. They are measuring between 0.7-1.0 μm in width and have a length of 3-12 μm.[18] A distinctive feature of myxobacteria is that they are able to form fruiting bodies in the presence of nutrient deficiency, which is more commonly known from eukaryotic myxomycetes or fungi.[17] Myxobacteria move by gliding or creeping. They have been found in all climate zones (incl. the Antarctic), and at all altitudes. They occur in soils, on bark, dung and in decaying plant material and have been found in fresh water or marine sediments as well. But they especially prefer warm partial shade and humid tropical and subtropical habitats.[18]

Together with the actinomycetes, they now are part of the largest group of natural product producers.[19] Over the last 30 years, more than 100 secondary metabolites with over 500 analogs from more than 7500 myxobacterial strains were reported.[20] The majority of isolated, biologically active myxobacterial products act against bacteria or fungi.[17] But anticancer, antimalarial, immunosuppressive, antioxidative and cytotoxic compounds have been found as well. Many of them are derivatives of polyketide synthases (PKSs) and non-ribosomal peptide synthetases (NRPSs) or belong to the terpene class of natural products.[20,21]

[13] A. L. Demain, *Appl. Microbiol. Biotechnol*. **1999**, *52*, 455-463.
[14] P. M. Dewick, *Medicinal Natural Products – A Biosynthetic Approach,* 3rd edition; John Wiley and Sons, Chichester **2009**, 7.
[15] R. Thaxter, *Botanical Gazette* **1892**, *17*, 389-406.
[16] K. Han, Z. F. Li, R. Peng, L. P. Zhu, T. Zhou, L. G. Wang, S. G. Li, X. B. Zhang, W. Hu, Z. H. Wu, N. Qin, Y. Z. Li, *Sci. Rep.* **2013**, *2101*, 1-7.
[17] K. Gerth, S. Pradella, O. Perlova, S. Beyer, R. Müller, *J. Biotechnol*. **2003**, *106*, 233-253.
[18] H. Reichenbach, G. Höfle, *Biotech. Adv*. **1993**, *11*, 219-277.
[19] M. Nett, G. M. König, *Nat. Prod. Rep*. **2007**, *24*, 1245-1261.
[20] J. Hermann, A. A. Fayad, R. Müller, *Nat. Prod. Rep*. **2017**, *34*, 135-160.
[21] M. A. Bhat, A. K. Mishra, M. A. Bhat, M. I. Banday, O. Bashir, I. A. Rather, S. Rahman, A. A. Shah, A. T. Jan, *Pharmaceutics* **2021**, *13*, 1265-1296.

Figure 3 illustrates some examples of pharmaceutically active compounds with myxobacterial origin. Thuggacin A (**6**, Figure 3) was isolated from the myxobacterium S*orangium cellulosum* and proved to be active against *Mycobacterium tuberculosis*. This is a promising finding in the wake of increasing resistance to conventional antibiotics used to treat tuberculosis.[22] Another very prominent myxobacterial agent is epothilone B (**7**) isolated from *Sorangium cellulosum* as well. It possesses tubulin-binding properties and its semisynthetic derivative ixabepilone was approved by the FDA in 2007 for the treatment of breast cancer.[23] In 2014, a new class of antibiotic compounds from *Cystobacter* sp., Cb v34, was described and they were called cystobactamids. They are characterized by some unique features like a linkage of the PABA building blocks through a *β*-methoxyasparagine moiety in cystobactamid **8**. They are described to strongly inhibit bacterial gyrase.[20,24] Formylindol derivative indiacen B (**9**) was isolated from *Sandaracinus amylolyticus*. It is active against some GRAM-positive and -negative bacteria and fungi and thus offers interesting possibilities for pharmaceutical compounds.[25]

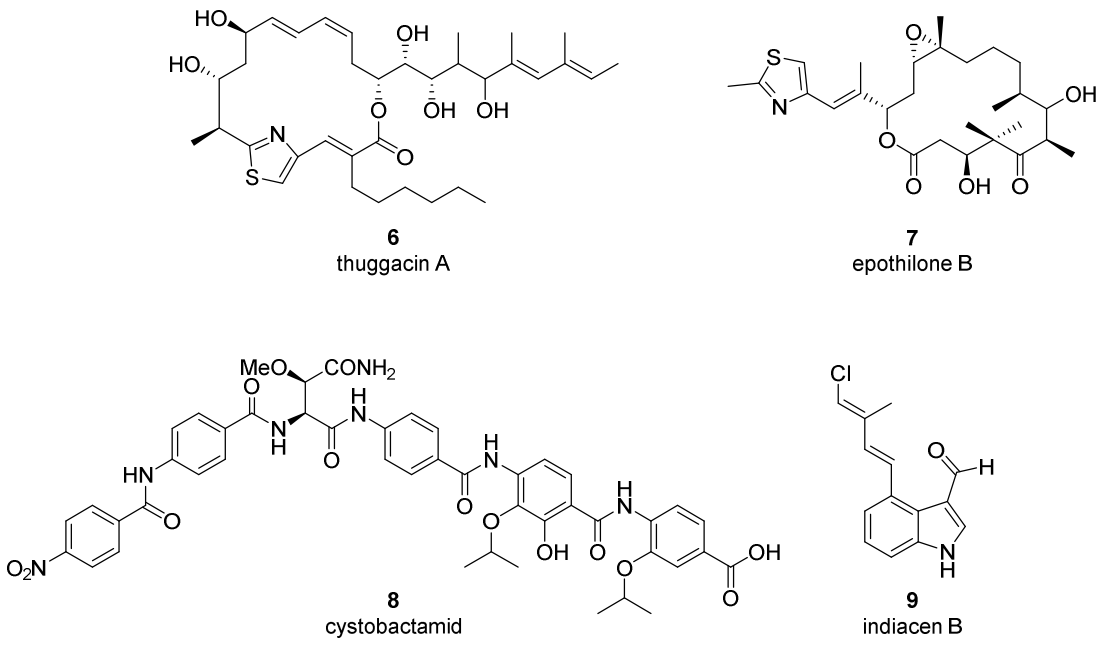


Figure 3: A selection of myxobacterial natural products.

[22] H. Steinmetz, H. Irschik, B. Kunze, H. Reichenbach, G. Höfle, R. Jansen, *Chem. Eur. J.* **2007**,*13*, 5822-5832.
[23] K.-H. Altmann, G. Höfle, R. Müller, J. Mulzer and K. Prantz, *The Epothilones: An Outstanding Family of Anti-Tumor Agents*, Springer, Vienna, **2009**, vol. 90.
[24] S. Baumann, J. Herrmann, R. Raju, H. Steinmetz, K. I. Mohr, S. Hüttel, K. Harmrolfs, M. Stadler, R. Müller, *Angew. Chem., Int. Ed.* **2014**, *53*, 14605-14609.
[25] H. Steinmetz, K. I. Mohr, W. Zander, R. Jansen, K. Gerth and R. Müller, *J. Nat. Prod.* **2012**, *75*, 1803-1805.

A1.4 Myxovalargin A – a Polypeptide with Antibiotic Properties

Another class of myxobacterial natural products are the myxovalargins, which originate from the myxobacterial strain *Myxococcus fulvus*, strain Mx f65, being isolated in 1969 from a soil sample collected in the Kaiserstuhl mountains.[26] Myxovalargins were first mentioned by name in 1981.[27] In an antibiotic screening program conducted by the *Gesellschaft für biotechnologische Forschung (GBF) Braunschweig,* Germany, now Helmholtz Centre for Infection Research (HZI), culture supernatant from *Myxococcus fulvus*, Mx f65, showed biological activity against a variety of GRAM-positive and GRAM-negative bacteria. Subsequently, within the framework of a large-scale fermentation, myxovalargins A, B, C, and D were eventually isolated and described in more detail in 1983.[26] Structurally, they are linear, long peptides and are characterized as colorless amorphous powders with a molecular weight between 1500 and 1700.[27,26] The dominant compound, myxovalargin A (**10**, Figure 4), hereinafter referred to only as myxovalargin, was then particularly studied.

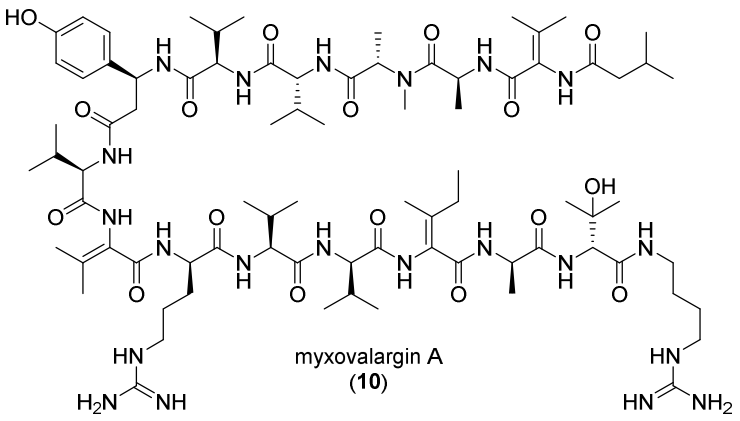


Figure 4: Chemical structure of myxovalargin A (**10**).

A1.4.1 Structural Elucidation of Myxovalargin A

Initial attempts to elucidate the structure were described as early as 1981 and 1983. At that time, ^{1}H- and ^{13}C-NMR spectra as well as quantitative amino acid analysis of hydrolysates revealed that myxovalargin (**10**) contains the amino acids valine, alanine, and arginine in a 5:2:1 ratio. Moreover, several unusual amino acids and building blocks such as *N*-methylalanine, *β*-hydroxyvaline, agmatine, 3-methylbutyric acid, *α,β*-dehydrovaline, and *α,β* -dehydroleucine could be dectected. The *C*-terminus of the molecule carries an agmatine and the *N*-terminus contains the 3-methylbutyric acid.[26,27] FAB mass spectrometry with positive ions was also used to determine the molecular formula $C_{81}H_{139}N_{21}O_{17}$. However, the amino acid sequence could not be determined by

[26] H. Irschik, K. Gerth, T. Kemmer, H. Steinmetz, H. Reichenbach, *J. Antibiot.* **1983**, *36*, 6-12.

[27] T. Kemmer, S. Santoso, H. Steinmetz, H. Irschik, L. Witte, G. Höfle, *Int. Conf. Chem. Biotechnol. Biol. Act. Nat. Prod., 1st* **1981**, *3*, 285-289.

either NMR or MS analysis. Also, cleavage of the molecule by proteolytic enzymes or partial acidic hydrolysis failed to give useful information. For this reason, STEINMETZ *et al.* were forced to perform selective chemical degradation reactions and dansylation steps. Using EDMAN degradation, preparative HPLC and TLC, MS and NMR analyses, the sequence was finally determined. Next, the absolute configuration of the amino acids had to be identified. This was done from the total hydrolysis mixture by derivatization with *ortho*-phthalaldehyde (OPA) and 3-mercapto-2-methyl butanol followed by column chromatography on RP-18 silica gel. The L-configuration of *N*-Me-Ala was determined by chiral gas chromatography. According to STEINMETZ, the sequence starting from the *N*-terminus is finally as follows: 3-methylbutyric acid, *α,β*-dehydrovaline, L-alanine, *N*-methyl-L-alanine, D-valine, D-valine, *(S)-β*-tyrosine, **L-valine**, *α,β*-dehydrovaline, D-arginine, **D-valine**, D-valine, *(E)*-dehydroisoleucine, D-alanine, D-3-hydroxyvaline and agmatine.[28] The myxovalargin derivative that features this sequence is referred to below as myxovalargin-L,D.

A few years later, studies on the biosynthesis of myxovalargin (**10**) were carried out at Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), leading to contradictory results. It was found that according to the biosynthesis, the valine in position 7 should be D-valine instead of L-valine and the valine in position 10 should be L- instead of D-valine. If these investigations were correct, the published structure would have to be revised. To resolve this inconsistency, the genetic information was verified by re-sequencing and southern-blotting, yielding the same result. Subsequently, an independent experiment was performed for sequence analysis: precursor feeding approach coupled with mass spectrometry. These results also unambiguously supported the new stereochemistry, so consequently, the correct sequence seems to be the following: 3-methylbutyric acid, *α,β*-dehydrovaline, L-alanine, *N*-methyl-L-alanine, D-valine, D-valine, *(S)-β*-tyrosine, **D-valine**, *α,β*-dehydrovaline, D-arginine, **L-valine**, D-valine, *(E)*-dehydroisoleucine, D-alanine, D-3-hydroxyvaline and agmatine.[29,30] Accordingly, the myxovalargin derivative that exhibits this sequence is referred to herein as myxovalargin-D,L.

[28] H. Steinmetz, H. Irschik, H. Reichenbach, *Sixth USSR-FRG Symposium on Chemistry on Peptides and Proteins,* Hamburg **1987**, printed in *Chemistry of Peptides and Proteins, Vol. 4*, ed. W. Voelter, Atempto Verlag Tübingen **1989**, 13-18.

[29] U. Scheid, unpublished doctoral dissertation, Universität des Saarlandes, Saarbrücken, **2021**.

[30] U. Scheid, J. Herrmann, R. Müller, *et al.*, unpublished manuscript, HIPS, Universität des Saarlandes, Saarbrücken, **2022**.

A1.4.2 Biological Profile of Myxovalargin A

After the isolation of myxovalargin, studies on its biological activity were carried out and described by IRSCHIK as early as 1983. At that time, myxovalargin was found to be effective against a wide range of bacteria, with minimum inhibitory concentrations (MICs) ranging from 0.3 to 5.0 μg/mL for GRAM-positive bacteria and from 6 to 100 μg/mL for GRAM-negative bacteria. Contrary, no effects were observed against fungi and yeasts. In addition, myxovalargin exhibits toxicity to mice: the LD_{50} value (subcutaneously) is 10 mg/kg and the LD_{100} value is 30 mg/kg.[26]

Almost three decades later, scientists from HIPS have re-examined the biological profile of myxovalargin and found interesting results. Inhibitory activity against *M. tuberculosis* was found as well as spontaneous resistant mutants of *M. tuberculosis* at 10-fold MIC. In addition, myxovalargin was confirmed to have effective antibiotic activity against a number of GRAM-positive bacteria and moderate activity against GRAM-negative pathogens such as an efflux-deficient strain of *Escherichia coli* or bovine respiratory pathogens *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilas somni*. In addition, myxovalargin also prevents the growth of mastitis-causing pathogens *Staphylococcus aureus* and *Streptococcus uberis* (Table 1).[30]

Table 1: Minimum inhibitory concentrations (MICs) of myxovalargin A.[30]

bacterial strain	MIC (μg/mL)
Staphylococcus aureus	1 - 2
Streptococcus uberis	0.25 - 2
Micrococcus luteus	1
Escherichia coli	32
Pseudomonas aeruginosa	16 - 32
Mycobacterium tuberculosis	0.2 - 3.4
Mannheimia haemolytica	20
Pasteurella multocida	10
Histophilas somni	8
Enterococcus faecium	0.5

As early as 1983 and 1985, publications concerning the mechanism of action of myxovalargin were published by REICHENBACH, IRSCHIK *et al*. At that time, experiments with *S. aureus* and *B. subtilis* showed that the antibiotic effect of myxovalargin was based on the inhibition of bacterial protein biosynthesis. At concentrations of less than 1 μg/mL, myxovalargin was able to abruptly stop protein biosynthesis, whereas the synthesis of RNA, DNA, and other cell wall components was not affected until 15 minutes later. At this point, the inhibition of protein biosynthesis was attributed to an interaction of the antibiotic with aminoacyl-*t*RNA at the A site of the ribosome. However, at

higher concentrations, RNA synthesis was also immediately interrupted, suggesting an alternative mechanism of action.[26,31]

New research results confirm these observations. The ribosome was identified as the molecular target based on sequencing of resistant mutants. In addition, the results of cryo-EM structural analysis indicate that translation is stopped at a late stage of translation initiation, as myxovalargin binds within the exit tunnel resulting in complete closure.[30]

Inhibition of eukaryotic translation was not observed, but myxovalargin has an unspecific membrane effect at concentrations above 18 μg/mL that damages both eukaryotic cells and human erythrocytes. Although good results were obtained in a mouse model of *Pasteurella multocida* sepsis, severe intoxication was observed after one week application in the more difficult mouse model of acute *M. tuberculosis* infection.[30,31]

A1.4.3 Biosynthesis of Myxovalargin A

In nature, myxovalargin is produced by the myxobacterium *Myxococcus fulvus* in a non-ribosomal protein biosynthesis by a non-ribosomal peptide synthetase (NRPS).[29] NRPSs are large multienzyme complexes capable of producing large peptides from single amino acids. The 20 proteinogenic amino acids form the starting building blocks for the biosynthesis of non-ribosomal peptides (NRPs) and are complemented by other building blocks produced in specific biosynthetic pathways. NRP biosynthesis usually proceeds in three phases: building block assembly, NRPS-mediated peptide assembly and post-NRPS modification and decoration. The NRPS is characterized by a modular arrangement of its enzymes, which are specialized for chain extension or modification as well as for passing the growing peptide to the following module.[32]

The biosynthesis of myxovalargin is depicted in Schemes 2-4 and was described by U. SCHEID in his doctoral thesis from HIPS.[29] He conducted his studies on the *Myxococcus fulvus* strain MCy6431. The genetic sequence responsible for myxovalargin biosynthesis can be divided into five genes (mxv A-E) that encode the fourteen modules of NRPS, while in the upstream part there are another six genes (mxv F-K) that encode additional proteins being also required for myxovalargin production (Scheme 2). With 58 kbp, the myxovalargin biosynthetic gene cluster is one of the largest NRPS gene clusters described to date.[29]

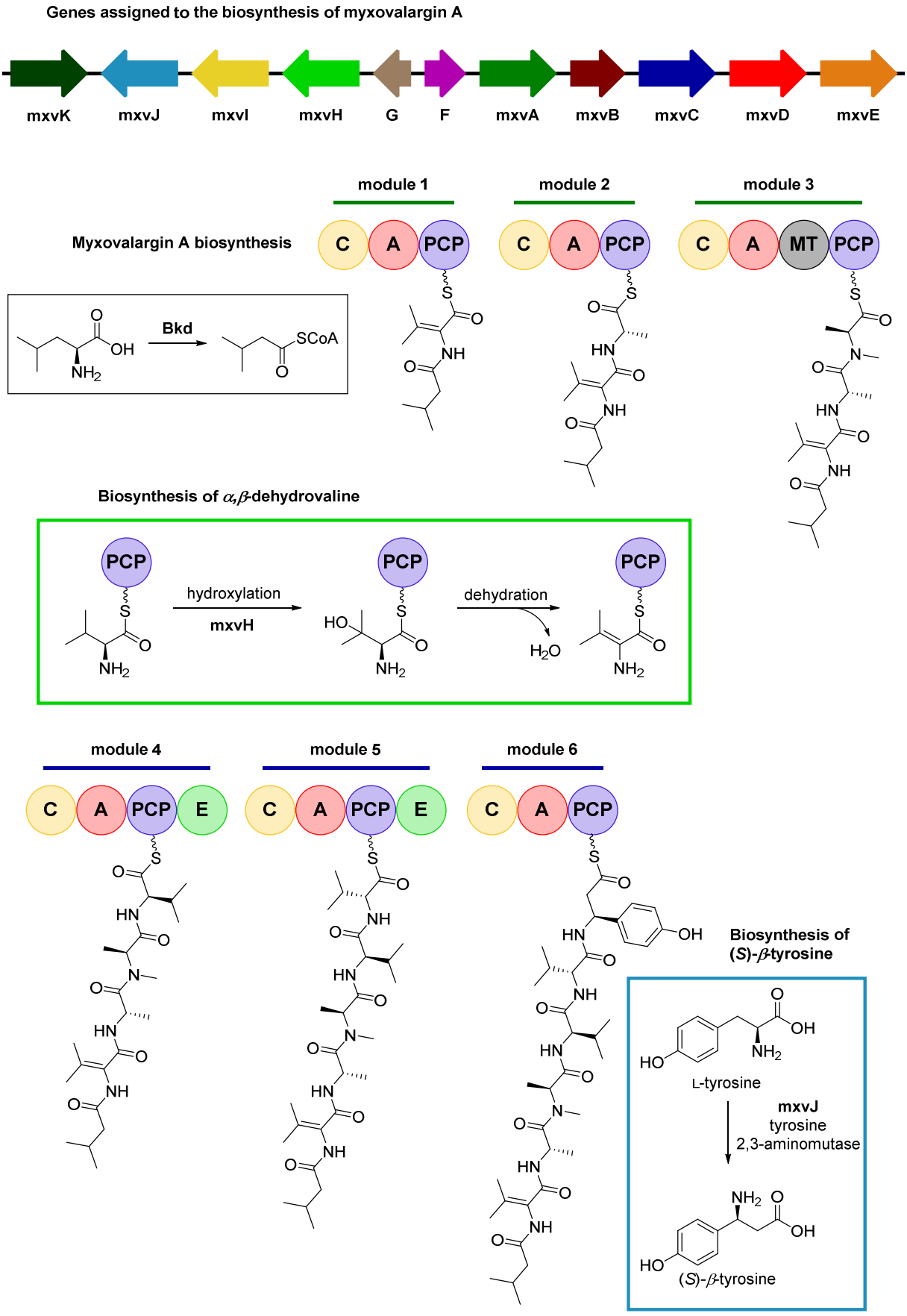
[31] H. Irschik, H. Reichenbach, *J. Antibiot.* **1985**, *38*, 1237-1245.
[32] R. D. Süssmuth, A. Mainz, *Angew. Chem. Int. Ed.* **2017**, *56*, 3770-3821.

The fourteen modules of the NRPS assembly line are located on mxvA (modules 1-3), C (modules 4-9), D (modules 10-13) and E (module 14) being in linear order. Module 1 (Scheme 2) consists of a condensation (C-) domain, an adenylation (A-) domain and a peptide carrier protein (PCP). The synthesis starts with isovaleryl-CoA generated from leucine by the branched chain ketoacid dehydrogenase (Bkd).[30] The A-domain chooses and activates the amino acids to an adenylate and the C-domain performs amide bond formation by which the peptide is transferred from one PCP to the next PCP under covalent thioester formation. In this way, the peptide grows.

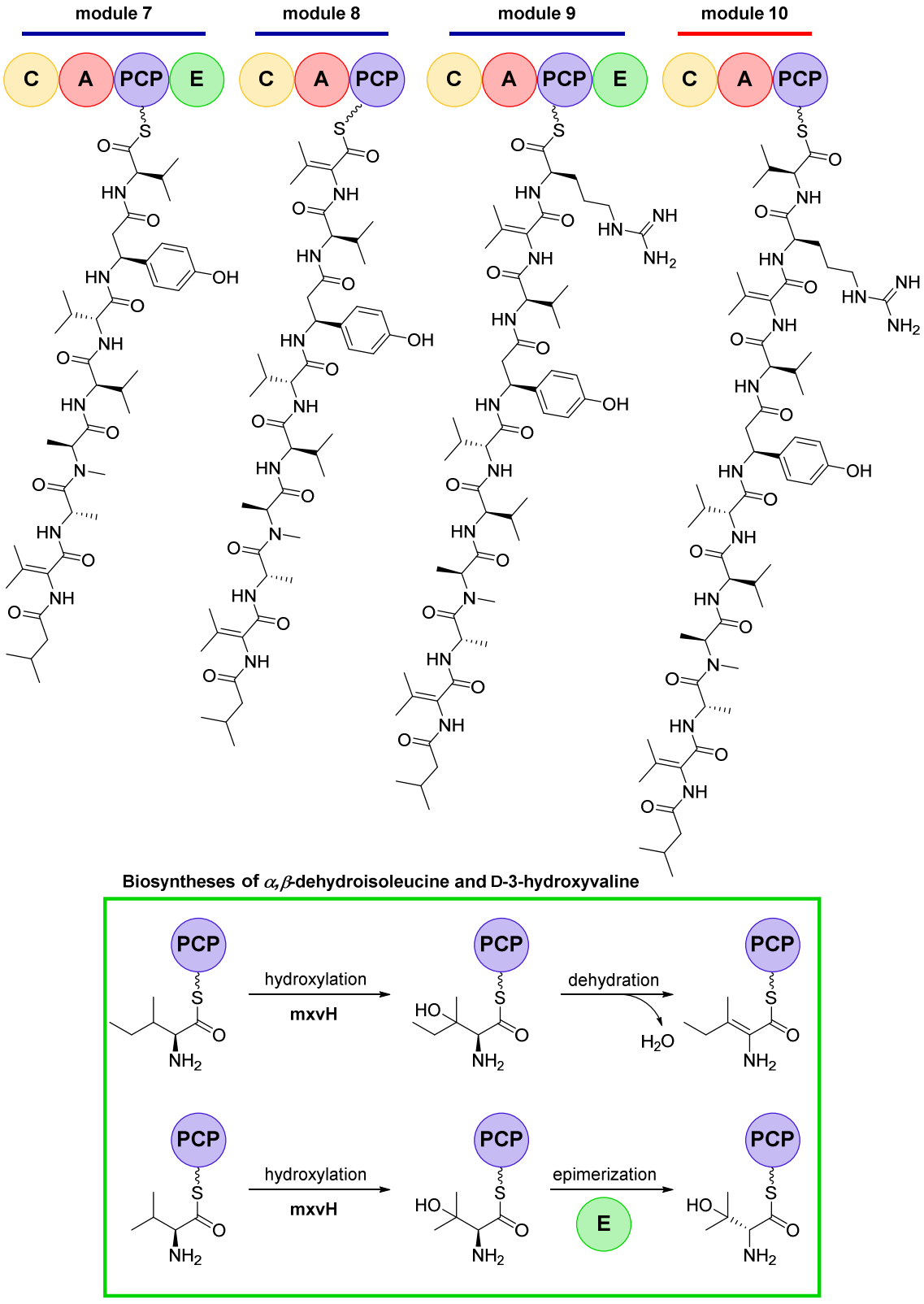
A special feature is the synthesis of dehydrovaline. It is assumed that mxvH encodes for the enzyme responsible for the *β*-hydroxylation of valine. Subsequent dehydration then yields the *α,β*-dehydrovaline.[29]

The next peculiarity is found on module 3, which contains a methyltransferase (MT-) domain catalyzing the *N*-methylation of the corresponding alanine. Epimerization (E-) domains are responsible for converting L- to D-amino acids as is the case for valines in modules 4 and 5, for example. Module 6 is responsible for the binding of *β*-tyrosine, which is catalyzed from L-tyrosine by a tyrosine 2,3-aminomutase encoded on mxvJ. An E-domain was found in module 7, indicating that the valine has an *(R)*-configuration and not an *(S)*-configuration as previously assumed. In contrast, module 10 lacks the E-domain, so this position is L-valine. Module 12 (Figure 4) incorporates dehydroisoleucine, which is first hydroxylated (mxvH) and then dehydrogenated, as already described for dehydrovaline (Figure 3).

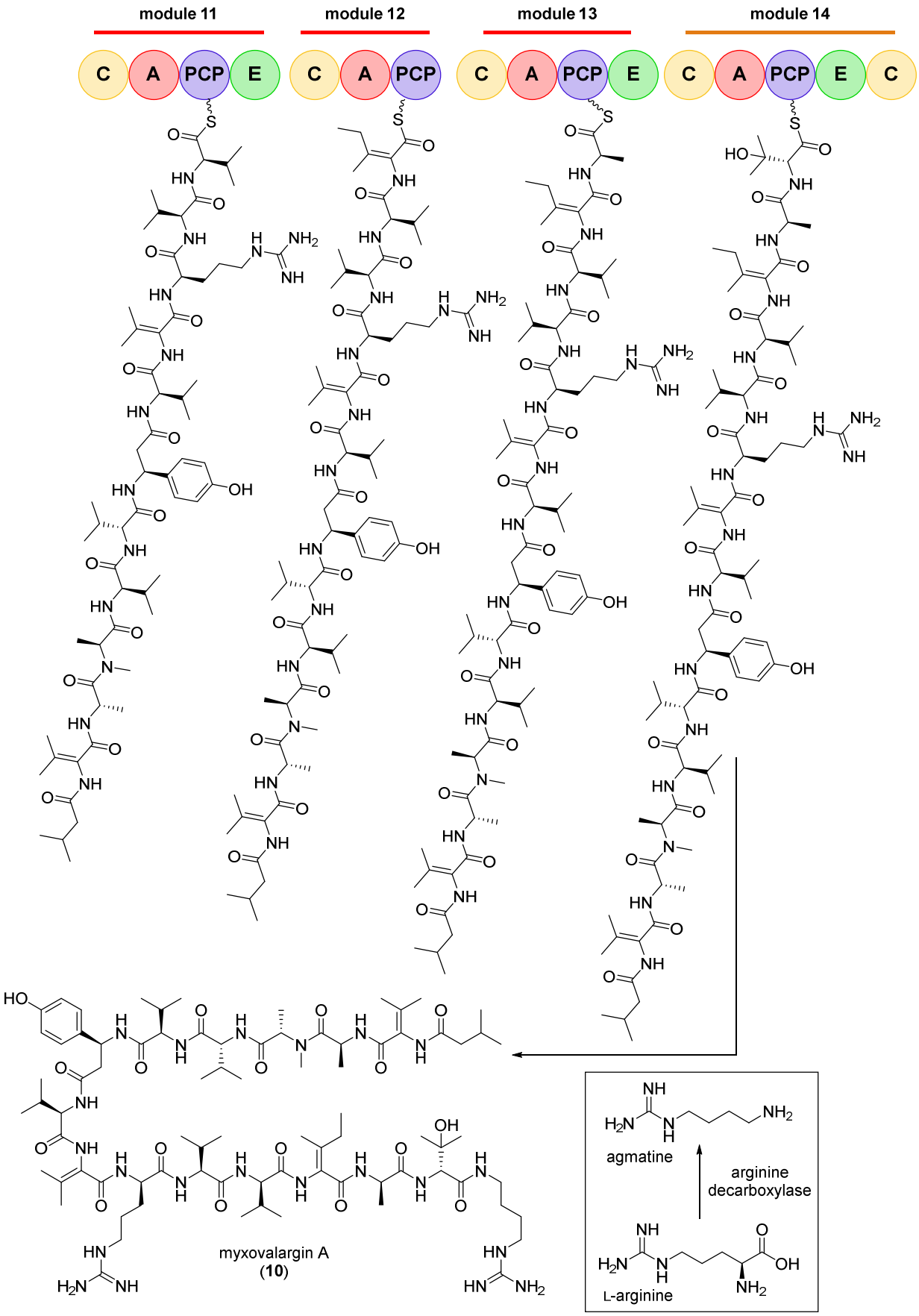
In module 14 (Figure 4), D-3-hydroxyvaline is incorporated. Interestingly, L-valine is first hydroxylated (mxvH) and then epimerized by an E-domain (Figure 3). The last C-domain of module 14 is thought to catalyze the condensation of free agmatine with the polypeptide chain to give the complete myxovalargin-D,L (**10**). Agmatine is here produced from arginine via decarboxylation by the arginine decarboxylase.[29]



Scheme 2: Myxovalargin biosynthesis. The NRPS assembly line consists of 14 modules located on mxvA, C, D and E. C = condensation domain, A = adenylation domain, PCP = peptide carrier protein, MT = methyl transferase, E = epimerization domain.[29]



Scheme 3: Myxovalargin biosynthesis. C = condensation domain, A = adenylation domain, PCP = peptide carrier protein, MT = methyl transferase, E = epimerization domain.[29]



Scheme 4: Myxovalargin biosynthesis and final condensation of the polypeptide chain with agmatine. C = condensation domain, A = adenylation domain, PCP = peptide carrier protein, MT = methyl transferase, E = epimerization domain.[29]

A1.5 Preliminary Studies on the Total Synthesis of Myxovalargin A

The chemical total synthesis of myxovalargin is of fundamental importance for two reasons. First, the revised stereochemistry of valines at positions 7 and 10 could be definitively demonstrated, and second, a total synthesis approach offers the chance to obtain less cytotoxic derivatives, which would make an enormous contribution to antibiotic research in view of increasing resistances, especially against tuberculosis. Some preliminary work on the total synthesis of the incorrectly published myxovalargin-L,D (**11**, Figure 5) by F. GILLE and M. SIEBKE already exists.

A1.5.1 Preliminary Work by Dr. Franziska Gille

The first investigations into a total synthetic approach to myxovalargin-L,D (**11**) began in 2011 with GILLE's master thesis[33] and her doctoral dissertation[34] based on it. This also resulted in a publication[35] dealing with the synthesis of *α,β*-unsaturated amino acids under GOLDBERG conditions.

GILLE subdivided myxovalargin-L,D (**11**) into four different large fragments A-D, which were synthesized separately and subsequently linked (Figure 5). It was considered that sensitive structural elements such as *α,β*-dehydroamino acids, the *β*-hydroxytyrosine, and the guanidine moieties should be introduced as late as possible.[34]

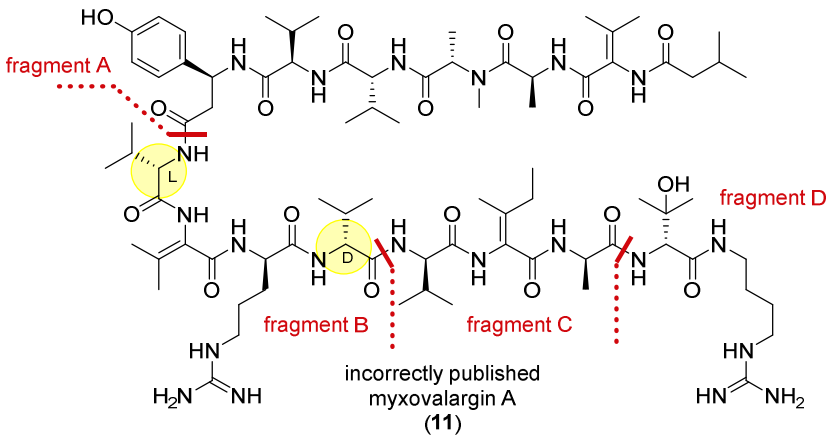
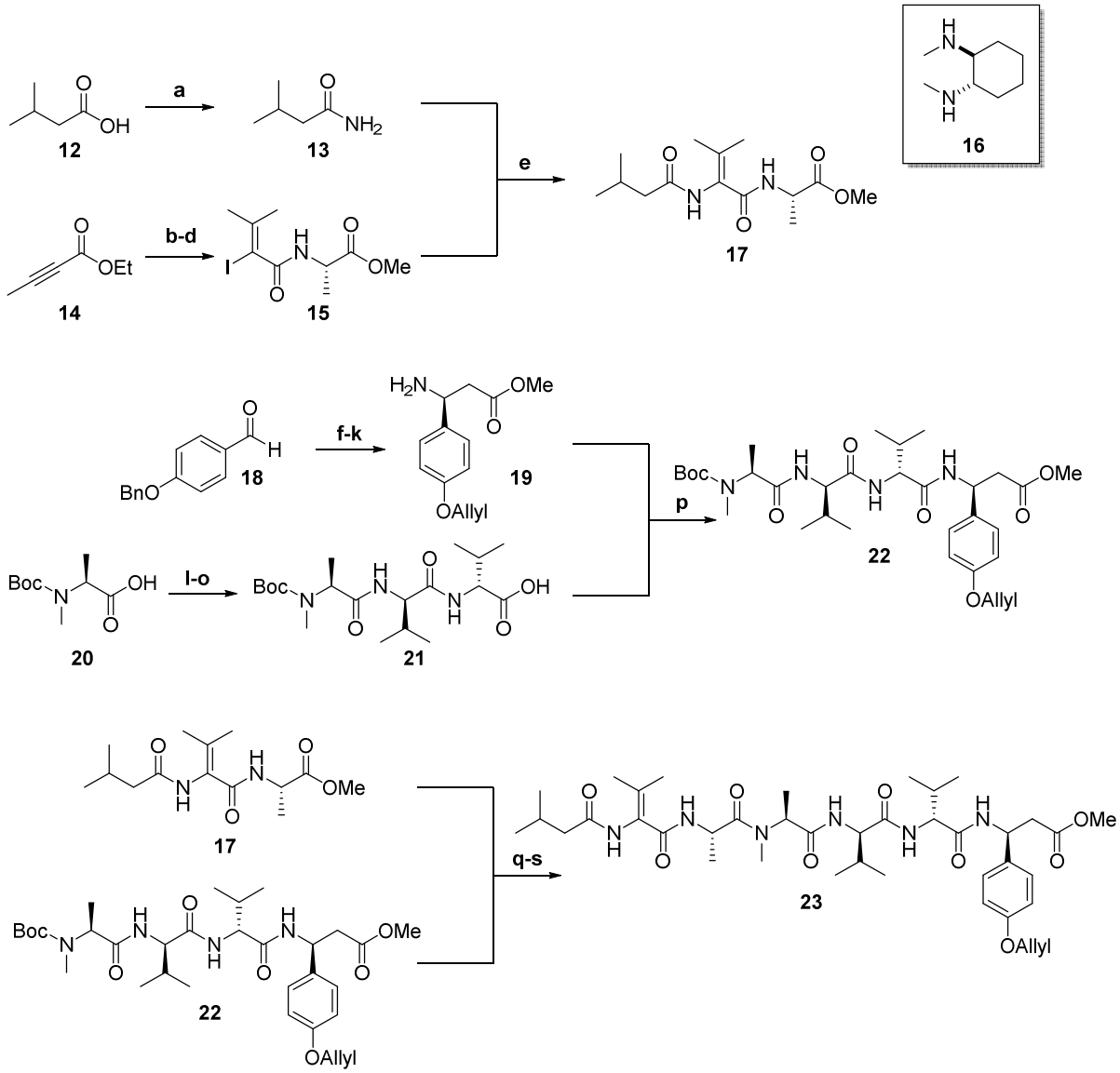


Figure 5: Stereochemistry of the incorrectly published myxovalargin (**11**).

GILLE began with the synthesis of fragment A (**23**), which was also split into two smaller peptides **17** and **22**. Methyl ester **17** was obtained in moderate yield by copper-catalyzed cross-coupling[35] of amide **13** with vinyl iodide **15** after extensive optimization studies. The synthesis of amide **13** was carried out in one step starting from corresponding acid **12**. The required vinyl

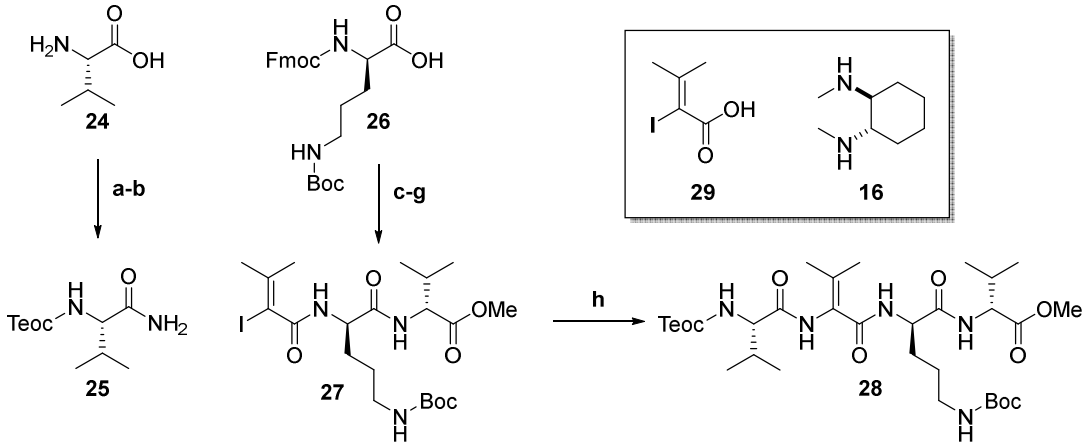
[33] F. Gille, master thesis, Leibniz Universität Hannover, Hannover, **2012**.
[34] F. Gille, doctoral dissertation, Leibniz Universität Hannover, Hannover **2015**.
[35] F. Gille, A. Kirschning, *Beistein J. Chem.* **2016**, *12*, 564-570.

iodide **15** was prepared in a three-step synthesis from commercially available alkyne ester **14**. In parallel, tetrapeptide **22** was prepared in five steps starting from Boc-*N*-Me-L-alanine (**20**) and tyrosine derivative **19**, which itself was synthesized from benzaldehyde **17** in six steps. Finally, the synthesis of the *N*-acylated fragment A **23** was completed in a peptide coupling and deprotection cascade starting from peptides **17** and **22** (Scheme 5).[34]



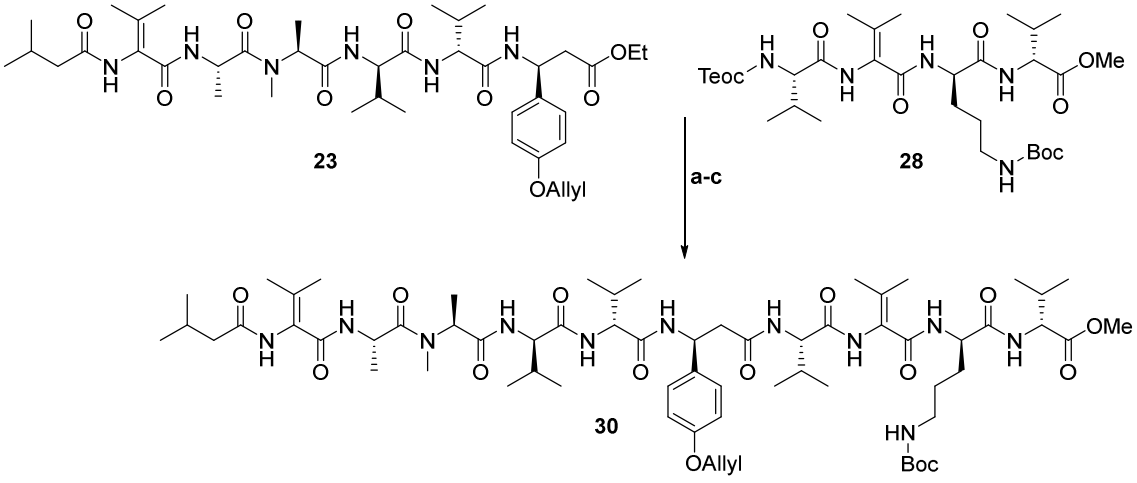
Scheme 5: Preliminary studies on the synthesis of fragment A (**23**): a) NMM, IBCF, DME, 0 °C, 15 min, then aq. NH_3-solution (25%), 0 °C → rt, 16 h, 70%; b) CuI, MeLi (1.6M in Et_2O), THF, -10 °C, 30 min, then **14** in THF, -78 °C, 2.5 h, then I_2 in THF, -78 °C, 30 min; c) LiOH, H_2O, EtOH, 60 °C, 3.5 h, 86% o2s; d) L-Ala-OMe·HCl, PyAOP, HOAt, DIPEA, DMF, 0 °C → rt, 23 h, 86%; e) **16**, CuI, K_2CO_3, 1,4-dioxane, 50 °C, 22 h, 35%; f) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, rt, 18 h, 84%, *E*-isomer; g) *N*-benzyl-phenylethylamine, *n*-Buli (2.5M in hexane), THF, -78 °C, 12.5 h, 97%, *d.r.* > 10:1; h) Pd/C (10%), H_2, CH_3OH, rt, 3 d; i) Boc_2O, THF, rt, 15 h, 78% o2s; j) AllylBr, K_2CO_3, TBAI, acetone, 50 °C, 21 h, 92%; k) TFA, CH_2Cl_2, 0 °C, 3 h, quant.; l) D-Val-OMe·HCl, EDC·HCl, HOBt, DIPEA, CH_2Cl_2, 0 °C → rt, 16 h, quant.; m) LiOH (1M), THF, 0 °C → rt, 20 h; n) D-Val-OMe·HCl, EDC·HCl, HOBt, DIPEA, CH_2Cl_2, 0 °C → rt, 20 h, 99% o2s; o) LiOH (1M), THF, 0 °C → rt, 16 h; p) **19**, PyAOP, HOAt, DIPEA, DMF, 0 °C → rt, 26 h, 74% o2s; q) LiOH (1M), THF, 0 °C → rt, 20 h; r) TMSI, CH_2Cl_2, rt, 10 min, quant.; s) EDC·HCl, HOAt, $NaHCO_3$, CH_2Cl_2/DMF (1:1), 0 °C → rt, 77% o2s.[34]

Fragment B-L,D (**28**) was synthesized from Teoc-protected valine **25** and vinyl iodide **27** under optimized copper-catalyzed GOLDBERG cross-coupling conditions (Scheme 6). A particular challenge here was to establish a suitable protecting group strategy. Boc- or Teoc-protected valines in combination with Boc- or Cbz-protected vinyl iodides gave the best results, allowing yields of up to 50%. Here, amide **25** was prepared in two steps starting from L-valine (**24**), while the synthesis of the vinyl iodide **27** involved five steps starting from acid **26**.[34]



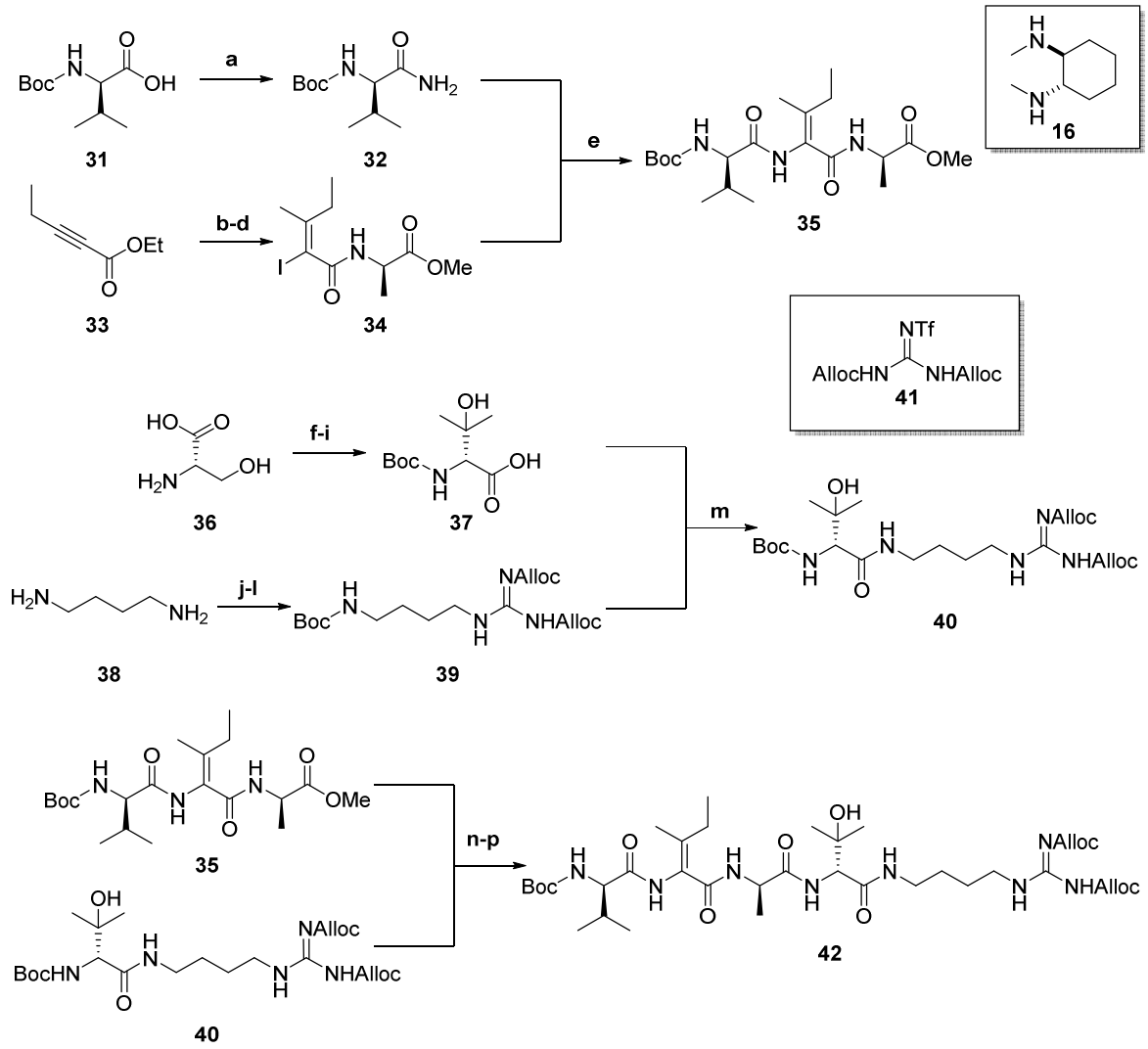
Scheme 6: Preliminary studies on the synthesis of fragment B-L,D (**28**): a) TeocOSu, Et_3N, 1,4-dioxane/H_2O (1:1), rt, 15 h; b) NMM, IBCF, DME, 0 °C, 20 min, then aq. NH_3-solution (25%), 0 °C → rt, 23 h, quant. o2s; c) $TMSCHN_2$ (2M in Et_2O), toluene, CH_3OH, 0 °C → rt, quant.; d) $(NH_2CH_2CH_2)_3N$, CH_2Cl_2, 0 °C → rt, 3 h, 92%; e) acid **29**, PyAOP, HOAt, DIPEA, DMF, 0 °C → rt, 22 h, 86%; f) LiOH (1M), THF, 0 °C → rt, 16 h; g) D-Val-OMe·HCl, PyAOP, HOAt, DIPEA, DMF, 0 °C → rt, 23 h, 87% o2s; h) CuI, K_2CO_3, **16**, 70 °C, 18 h, 47%.[34]

Based on the preliminary work, fragment A (**23**) was coupled with tetrapeptide **28** (fragment B-L,D) to form the *N*-acylated decapeptide **30** in a three-step synthesis (Scheme 7).[34]



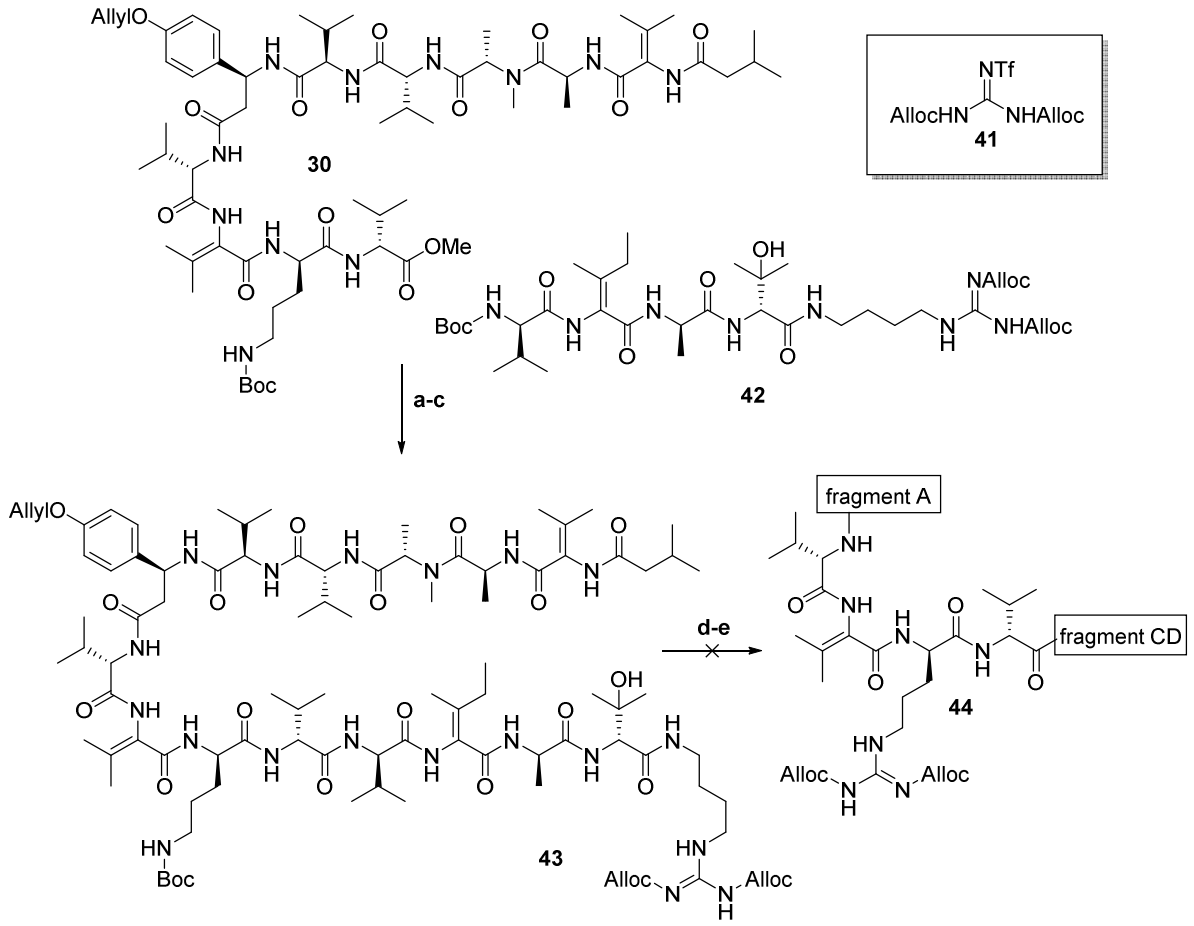
Scheme 7: Preliminary studies on the synthesis of fragment AB-L,D (**30**): a) **23**, LiOH (1M), THF, 0 °C → rt, 22 h, 80%; b) **28**, TBAF (1M in THF), THF, rt, 20 h, quant.; c) HOAt, PyAOP, DIPEA, DMF, 0 °C → rt, 20 h, 46%.[34]

Furthermore, fragments C (**35**) and D (**40**) were synthesized (Scheme 8). Fragment C (**35**) was also formed by the copper-catalyzed cross-coupling of amide **32** with vinyl iodide **34**, which itself was prepared in three steps starting from the commercially available ester **33**. Acid **31** was converted into amide **32** in one step. For the synthesis of fragment D (**40**), GILLE first prepared the nonproteinogenic amino acid Boc-D-*β*-hydroxyvaline (**37**) in a four-step synthetic sequence starting from L-serine (**36**). By amidination of a primary amino function, agmatine **39** could be obtained starting from 1,4-diaminobutane (**38**). Subsequent coupling of acid **37** with amine **39** finally led to fragment D (**40**). The subsequent linkage of the two fragments C (**35**) and D (**40**) occurred in a good yield of 58% to give peptide DE (**42**) over three steps.[34]



Scheme 8: Preliminary studies on the synthesis of fragment CD (**42**): a) NMM, IBCF, DME, 0 °C, 15 min, then aq. NH_3-solution (25%), 0 °C → rt, 20 h, quant.; b) CuI, MeLi (1.6M in Et_2O), THF, 0 °C, 30 min, then **33** in THF, -78 °C, 3 h, then I_2 in THF, - 78 °C, 15 min; c) LiOH, H_2O/EtOH (7.5:1), 60 °C, 22.5 h, 86% o2s; d) D-Ala-OMe·HCl, PyAOP, HOAt, DIPEA, DMF, 0 °C → rt, 22 h, 58%; e) CuI, K_2CO_3, **16**, 1,4-dioxane, 70 °C, 20 h, 48%; f) $SOCl_2$, CH_3OH, 0 °C → rt, 14 h; g) Boc_2O, Et_3N, CH_2Cl_2, 0 °C → rt, 16 h, quant. o2s; h) CH_3MgBr (3M in Et_2O), Et_2O, -78 °C → rt, 2 h, 93%; i) TEMPO, NaClO, $NaClO_2$, CH_3CN, phosphate buffer pH 7, 35 °C, 24 h, 90%; j) Boc_2O, 1,4-dioxane, rt, 20 h, 89%; k) **41**, Et_3N, CH_2Cl_2, rt, 16 h, 95%; l) TFA, CH_2Cl_2, 0 °C, 2.5 h, quant.; m) EDC·HCl, HOBt, DIPEA, CH_2Cl_2, 0 °C → rt, 24 h, 74%; n) **35**, LiOH (1M), THF, 0 °C → rt, 22 h; o) **40**, TMSI, CH_2Cl_2, rt, 15 min; p) PyAOP, HOAt, DIPEA, DMF, 0 °C → rt, 25 h, 58% o3s.[34]

Starting from the large peptide fragments, the myxovalargin backbone **43** was now to be obtained (Scheme 9). For this purpose, fragments AB-L,D (**30**) and CD (**42**) were linked in three steps to form oligopeptide **43** in a 60% yield. This should be followed by the introduction of the guanidine functionality into the ornithine side chain to complete the peptide backbone **44**. However, the amidination failed under the chosen conditions, which GILLE had already been able to apply successfully in the synthesis of fragments B (**28**) and D (**40**). She then attempted to incorporate the guanidine at an earlier point in the synthesis, with attempts at the *N*-acylated decapeptide **30**, but unfortunately this also failed. Likewise, the aid of another amidination reagent (*N,N*-bis(*tert*-butoxycarbonyl)-*N*''-trifluoromethanesulfonylguanidine) did not work. Based on these results, it became apparent that the introduction of a guanidine functionality might prove difficult, and GILLE had to terminate her work at this stage.[34]

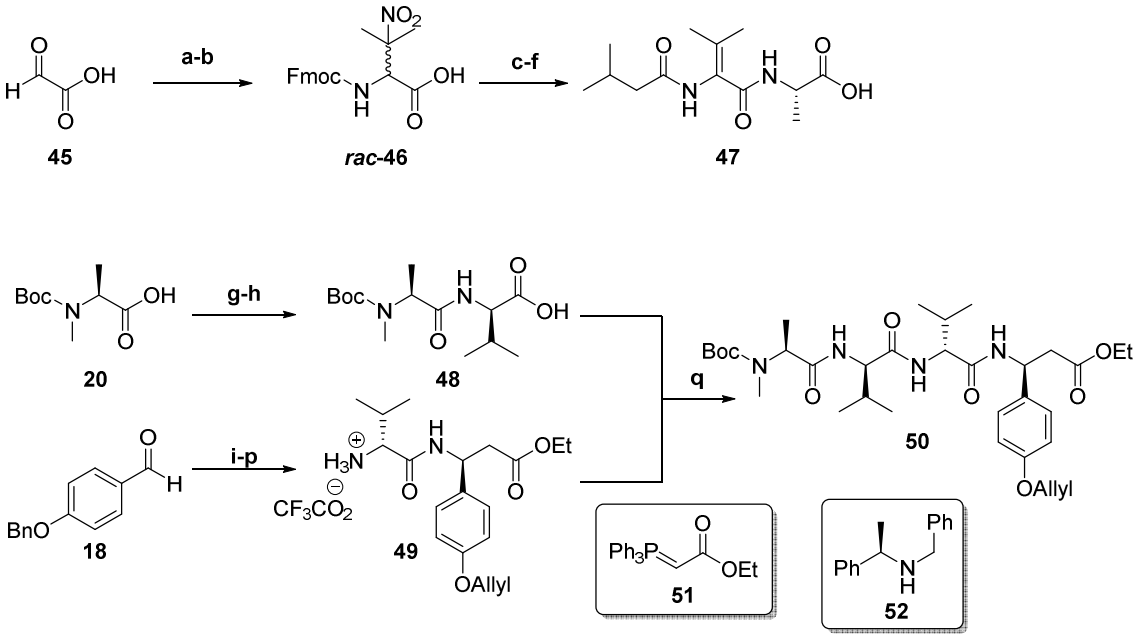


Scheme 9: Preliminary studies on the synthesis of myxovalargin-L,D scaffold **44**: a) **30**, LiOH (1M), THF, 0 °C → rt, 22 h; b) **42**, TMSI, CH_2Cl_2, rt, 10 min; c) HATU, HOAt, DIPEA, DMF, 0 °C → rt, 25 h, 60% o3s; d) TMSI, CH_2Cl_2, rt, 10 min; e) **41**, DIPEA, CH_2Cl_2, rt, 20 h.[34]

A1.5.2 Preliminary Work by Dr. Maik Siebke

After GILLE'S departure, SIEBKE took over the work on the total synthesis of myxovalargin as part of his doctoral studies.[36] For this purpose, further material of fragments A (**23**), B-L,D (**28**), C (**35**) and D (**40**) was needed, implying an upscaling of the corresponding syntheses. In addition, fragment B-L,D (**28**) with the incorrectly published stereochemistry at the valine functionalities was to be prepared along with the correct configuration (fragment B-D,L (**63**)).

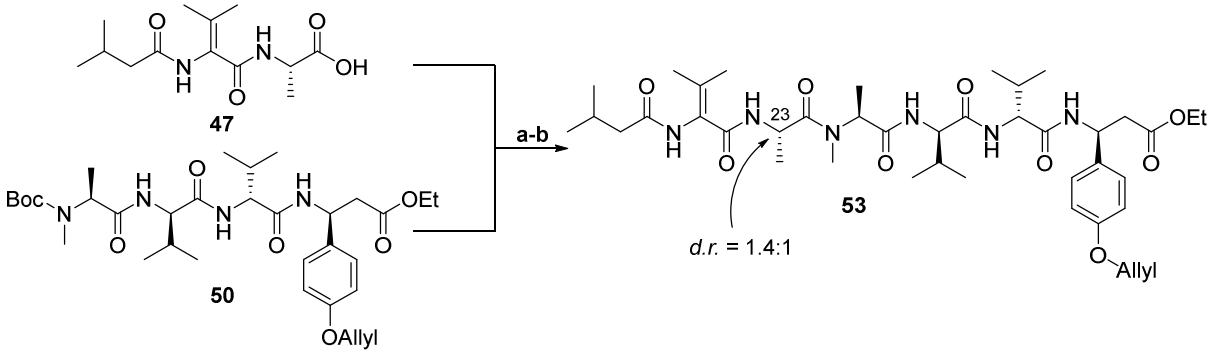
In the course of this upscaling process, the syntheses of fragments A and B were rearranged, since the already established GOLDBERG reaction for the assembly of dehydroamino acids proved to be inefficient due to the limited batch size. Thus, SIEBKE was also able to obtain these fragments via an elimination strategy of 3-NO_2 amino acids, which in the case of fragment A was enabled by saponification of nitrovaline **46** to give acid **47** (Scheme 10). Furthermore, the synthesis of fragment **50** was modified because a late coupling of the β-tyrosine from GILLE'S work was not reproducible. Thus, L-valine was already coupled to β-tyrosine to give ester **49** before the latter could form tetrapeptide **50** when coupled with acid **48**.[36]



Scheme 10: Preliminary studies on the synthesis of fragments **47** and **50**: a) 2-NO_2-propane, NH_3 (conc., 25%), KOH, H_2O, 2 h, 54%; b) FmocCl, Na_2CO_3, 1,4-dioxane, H_2O, 0 °C, 6 h, 72%; c) EDC·HCl, HOAt, $NaHCO_3$, L-Ala-OMe·HCl, 0 °C → rt, 18 h, 97%; d) Me_2NH, DMF, rt, 4 h; e) $(iVal)_2O$, Et_3N, CH_2Cl_2, -78 °C → rt, 18 h, 54% o2s; f) LiOH (1M), H_2O, THF, 0 °C → rt, 14 h, 85%; g) D-Val-OMe·HCl, EDC·HCl, HOBt, DIPEA, CH_2Cl_2, 0 °C → rt, 16 h, 82%; h) LiOH, THF, H_2O, 0 ° C → rt, 20 h, quant.; i) **51**, CH_2Cl_2, rt, 24 h, quant., *E/Z* > 20:1; j) **52**, *n*-BuLi, THF, -78 °C, 30 min, then ester, -78 °C, 4 h, 49%, *d.r.* > 10:1; k) $Pd(OH)_2$/C, H_2 (1 bar), AcOH, toluene, MeOH, rt, 3 d, 97%; l) HCl (conc., 37%), Et_3N, Boc_2O, MeOH, 0 °C → rt, 16 h, 83%; m) AllylBr, TBAI, K_2CO_3, acetone, 50 °C, 24 h, 97%; n) HCl, 1,4-dioxane, 0 °C → rt, 2 h, quant.; o) EDC·HCl, Oxyma, DIPEA, CH_2Cl_2, 0 °C → rt, 20 h, 93%; p) TFA, CH_2Cl_2, 0 °C, 2 h, quant.; q) HOBt, EDC·HCl, DIPEA, CH_2Cl_2, 0 °C → rt, 16 h, 90%, *d.r.* > 10:1.[36]

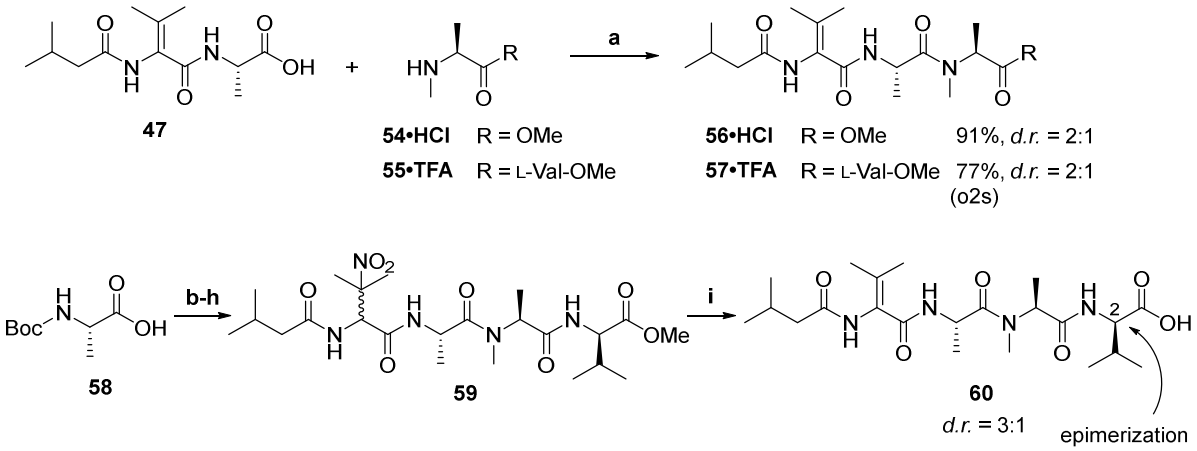
[36] M. Siebke, doctoral dissertation, Leibniz Universität Hannover, Hannover **2021**.

At this stage, the coupling of peptides **47** and **50** to fragment A (**53**) should occur (Scheme 11). However, the coupling conditions tested by SIEBKE resulted in epimerization of the alanine stereocenter at position 23. Since complete loss of stereocenter integrity at the end of the overall synthesis would no longer have provided sufficient evidence of the myxovalargin structure, the synthesis was rearranged at this point.[36]



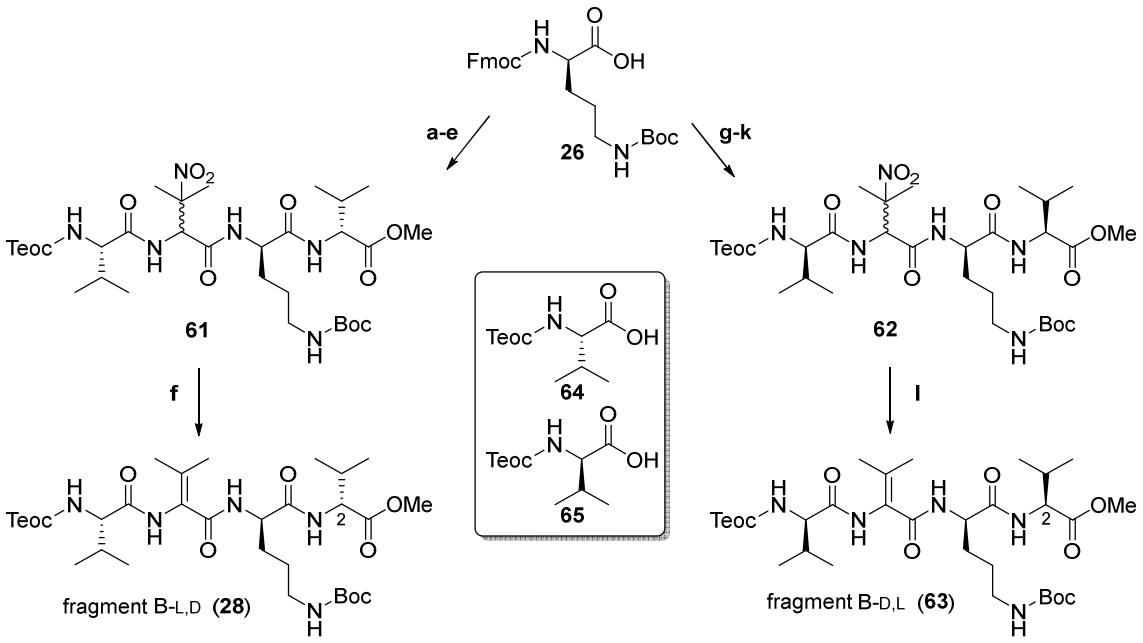
Scheme 11: Preliminary studies on the synthesis of fragment A (**53**): a) TFA, CH_2Cl_2, 0 °C, 2 h; b) HOAt, EDC·HCl, $NaHCO_3$, CH_2Cl_2/DMF (1:1), -15 °C → rt, 49%, *d.r.* = 1.4:1.[36]

Since sequential coupling of acid **47** with *N*-Me-Ala derivatives **54** and **55** also did not yield sufficient diastereoselectivity, an alternative route was sought for the entire fragment A, with the problematic Ala-*N*-Me-Ala coupling chosen as starting point (Scheme 12). Saponification of fragment **59** also led to epimerization at position 2 of acid **60**, revealing that valine methyl esters exhibit a general risk of epimerization in the endgame.[36]



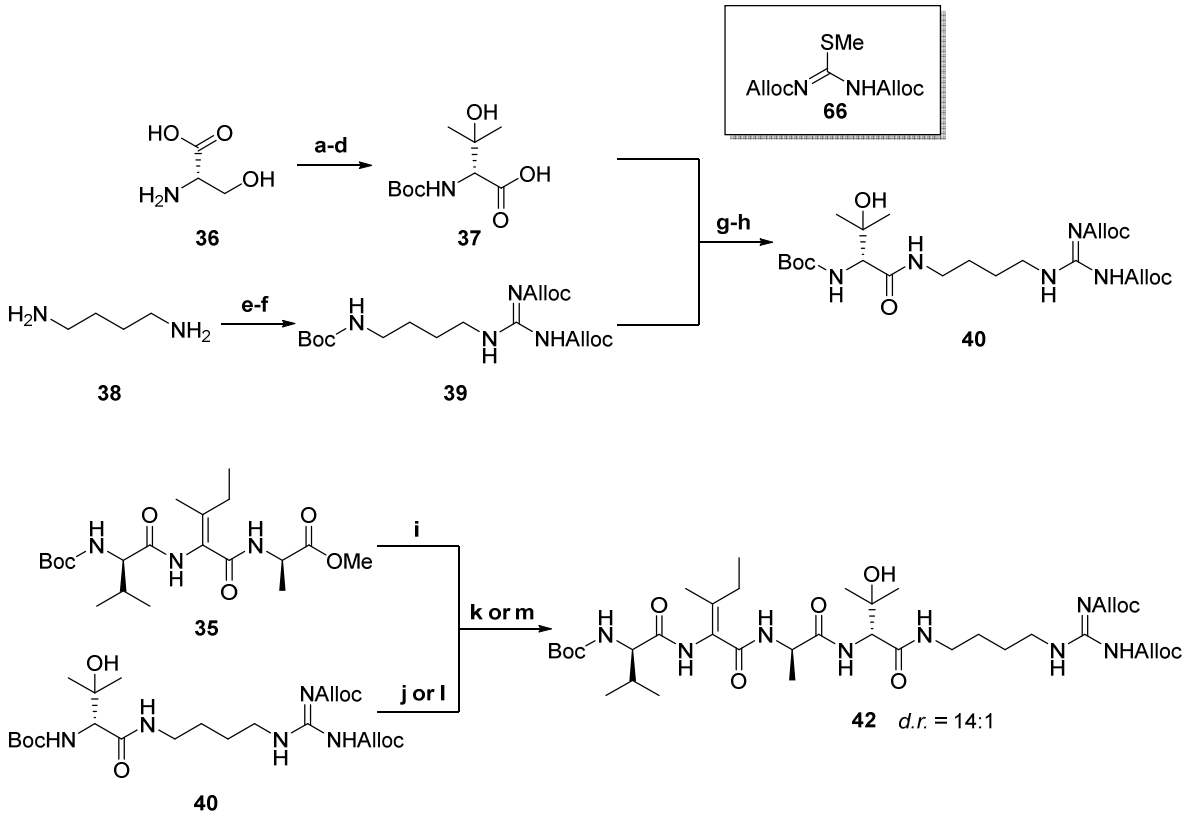
Scheme 12: Alternative approaches to the tetrapeptide **60**: a) EDC·HCl, HOAt, $NaHCO_3$, MeCN/DMF (5:1), -15 °C → rt, 16 h; b) *H*-L-MeAla-OMe·HCl, EDC·HCl, HOAt, $NaHCO_3$, CH_2Cl_2/DMF (5:1), -15 °C → rt, 20 h, quant.; c) LiOH, H_2O/THF, 0 °C → rt, 20 h; d) *H*-D-Val-OMe·HCl, EDC·HCl, HOBt, DIPEA, CH_2Cl_2, 0 °C → rt, 20 h, 89% o2s; e) TFA, CH_2Cl_2, 0 °C, 2 h; f) **46**, EDC·HCl, HOAt, $NaHCO_3$, 0 °C → rt, 20 h, 90% o2s, *d.r.* = 2:1; g) Me_2NH, DMF, rt, 2 h; h) (*i*Val)$_2$O, 2,6-lutidine, CH_2Cl_2, -78 °C → rt, 20 h, quant. o2s, *d.r.* = 2:1, i) LiOH, THF/H_2O, 0 °C → rt, 20 h.[36]

The synthesis conditions to fragments B-L,D (**28**) and B-D,L (**63**) were overall adopted from GILLE (Scheme 13). However, SIEBKE found that methyl ester cleavage of fragments **61** and **62** led to loss of the Teoc protecting groups as well as epimerization of the stereocenters at position 2. He finally succeeded in elimination by using the amine base TBD.[36]



Scheme 13: Preliminary studies on the syntheses of fragments B-L,D (**28**) and B-D,L (**63**): a) *H*-D-Val-OMe·HCl, EDC·HCl, HOAt, $NaHCO_3$, CH_2Cl_2, 0 °C → rt, 16 h, 93%; b) $(H_2NCH_2CH_2)_3N$, CH_2Cl_2, 0 °C → rt, 3 h; c) **46**, EDC·HCl, HOAt, $NaHCO_3$, CH_2Cl_2/DMF (5:1), 0 °C → rt, 16 h, 75% o2s, *d.r.* = 1:1; d) Me_2NH, DMF, rt, 4 h; e) **64**, EDC·HCl, HOAt, CH_2Cl_2/DMF (5:1), 0 °C → rt, 16 h, 76% o2s, *d.r.* = 1:1; f) TBD, CH_2Cl_2, -78 °C → rt, 20 h, 69%, *d.r.*>15:1; g) EDC·HCl, HOAt, $NaHCO_3$, CH_2Cl_2/DMF (5:1), 0 °C → rt, 16 h, 98%; h) $(H_2NCH_2CH_2)_3N$, CH_2Cl_2, 0 °C → rt, 4 h, 99%; i) **46**, EDC·HCl, HOAt, $NaHCO_3$, CH_2Cl_2/DMF (5:1), 0 °C → rt, 18 h, 86%, *d.r.* = 1.5:1; j) Me_2NH, DMF, rt, 6 h; k) **65**, EDC·HCl, HOAt, $NaHCO_3$, CH_2Cl_2/DMF (5:1), 0 °C → rt, 20 h, 79% o2s, *d.r.* = 3:1; l) TBD, CH_2Cl_2, -78 °C → rt, 20 h, 62%, *d.r.* > 15:1.[36]

Finally, the coupling of fragments C (**35**) and D (**40**) followed (Scheme 14). Fragment C (**35**) was successfully synthesized by SIEBKE using GILLE'S route. However, in the synthesis of fragment D (**40**), the preparation of the guanidination reagent could not be reproduced, so the reagent was replaced by Alloc-protected methylisothiourea **66**. The subsequent coupling of acid **35** and amine **40** according to GILLE'S conditions could not be reproduced without epimerization and was therefore optimized by SIEBKE. It finally succeeded under alternative coupling conditions with a yield of 60% and a diastereoisomeric ratio of 14:1.[36]



Scheme 14: Preliminary studies on the synthesis of fragment CD (**42**): a) $SOCl_2$, CH_3OH, 0 °C → rt, 20 h; b) Boc_2O, Et_3N, CH_2Cl_2, 0 °C → rt, 16 h, 68% o2s; c) CH_3MgBr (3M in Et_2O), Et_2O, -78 °C → rt, 2 h, 95%; d) TEMPO, NaClO, $NaClO_2$, CH_3CN, phosphate buffer pH 7, 35 °C, 48 h, 81%; e) Boc_2O, 1,4-dioxane, rt, 20 h, 95%; f) **66**, Et_3N, CH_2Cl_2, rt, 72 h, 93%; g) TMSI, CH_2Cl_2, rt, 5 min; h) **37**, EDC·HCl, Oxyma, $NaHCO_3$, CH_2Cl_2/DMF (6:1), 0 °C → rt, 20 h, 71%; i) LiOH, H_2O, THF, 0 °C → rt, 20 h, quant.; j) TMSI, CH_2Cl_2, rt, 10 min; k) PyAOP, HOAt, DIPEA, DMF, 0 °C → rt, 18 h, 62% o2s, *d.r.* = 1:1; l) TFA, CH_2Cl_2, 0 °C, 2 h; m) EDC·HCl, HOAt, $NaHCO_3$, MeCN/DMF (1:1), -15 °C → rt, 20 h, 60% o2s, *d.r.* = 14:1.[36]

Through SIEBKE'S work, it became clear that some protecting groups severely complicate the endgame. In particular, valine methyl esters proved to be problematic, as they tend to epimerize easily. For this reason, the syntheses of certain fragments would have to be altered again, which SIEBKE was unable to do due to time constraints.[36]

A2 Project Aims

The aim of this work is to finalize the total synthesis of myxovalargin A (**10**), building on the dissertations of GILLE and SIEBKE. For this, two syntheses are to be fullfilled (Figure 6). First, the synthesis of myxovalargin-D,L (**10**) with the correct stereochemistry of the valines in positions 7 (D-valine) and 10 (L-valine) is to be carried out; second, the synthesis of the incorrectly published myxovalargin-L,D (**11**) with the incorrect stereochemistry (7: L-valine; 10: D-valine). Through these two total syntheses, a final verification of the configuration derived from the gene cluster analysis should be obtained.

On this basis, synthetic studies should be carried out on possible derivatives of myxovalargin-D,L (**10**), aiming at those which can be represented by a simplified synthesis. In this context, particular attention should be paid to *β*-tyrosine, which is difficult to prepare and could well be replaced by *α*-L-tyrosine. Another starting point for simplifying the structure are the dehydroamino acids, which could be replaced by their corresponding natural representatives valine and isoleucine. Simplified syntheses should yield a sufficiently large amount of the respective derivatives for subsequent biological studies. Desirable would be those with the same good antibiotic properties (e.g., against *M. tuberculosis*) but with lower cytotoxicity. This would be of enormous importance to combat increasing resistances.

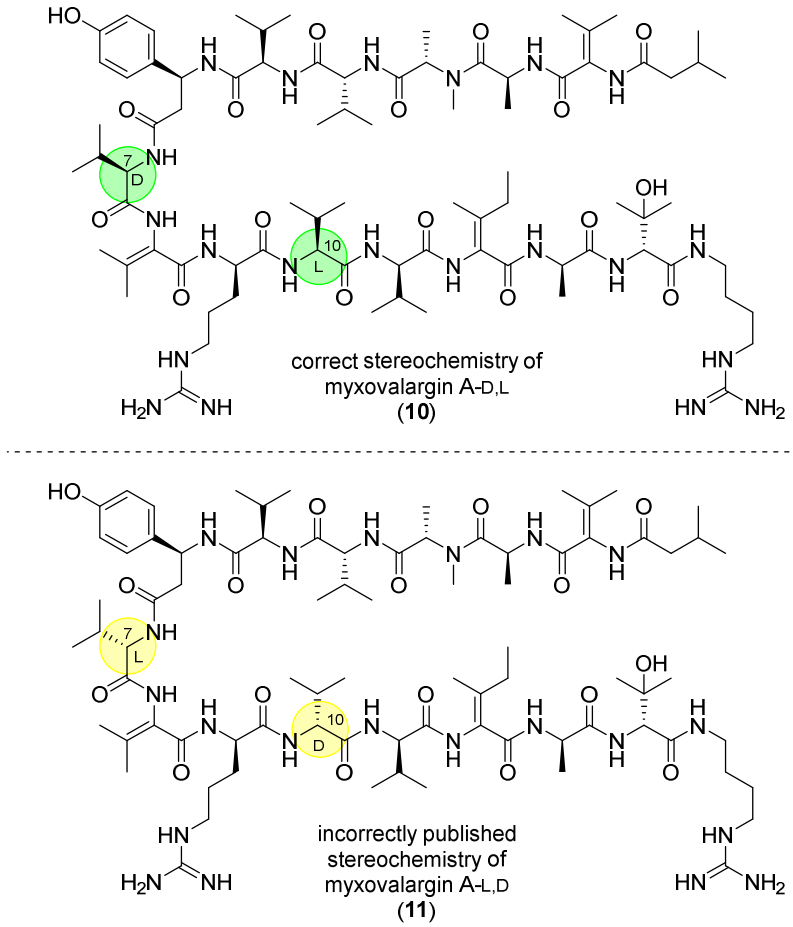


Figure 6: Stereochemistry of myxovalargins (**10**) and (**11**) to be synthesized.

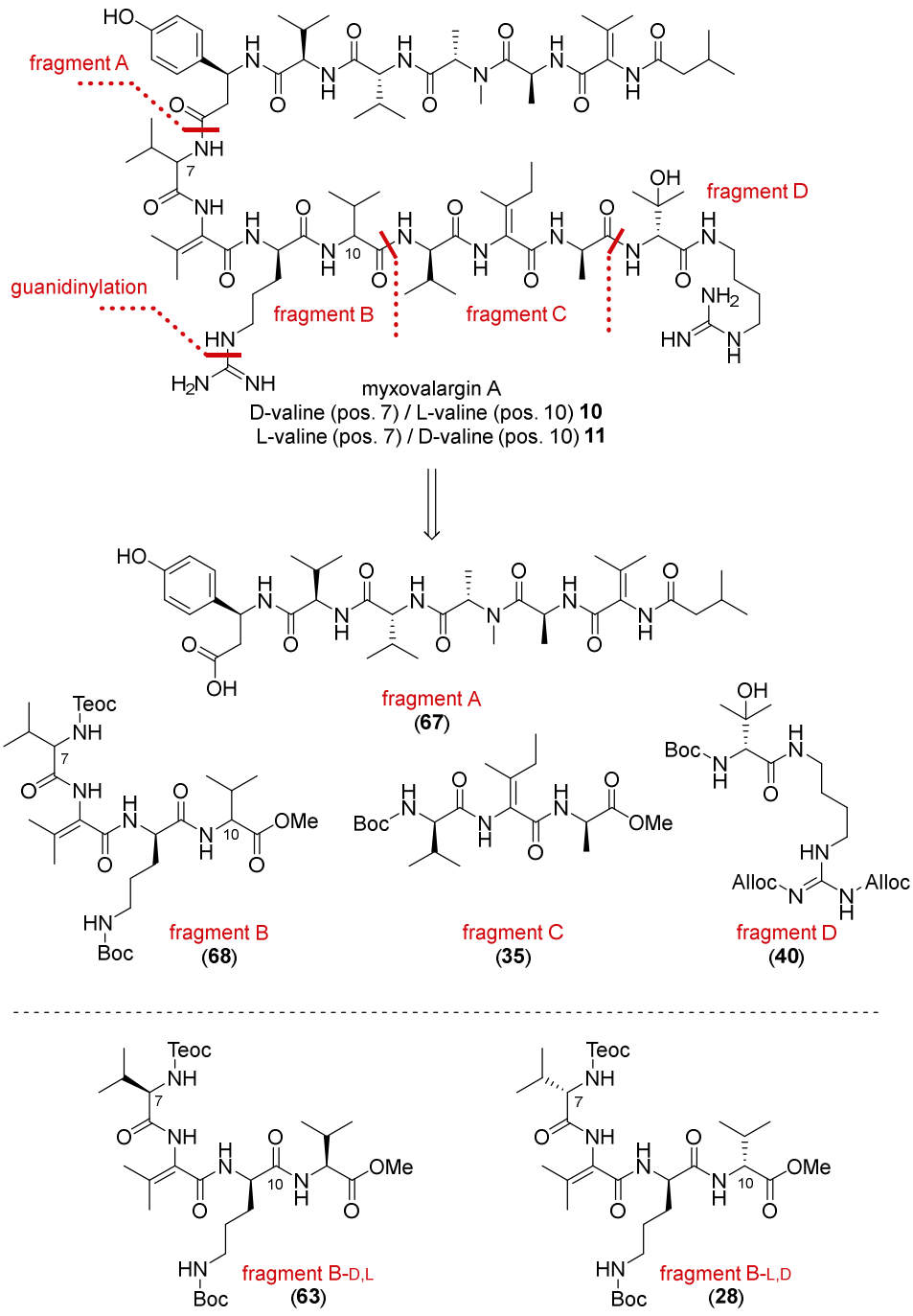
A3 Results and Discussion

A3.1 Retrosynthetic Analysis

As mentioned in Section A1.4.1, the stereochemistry of the two valine units at positions 7 and 10 derived from EDMAN degradation was incorrectly determined. For this reason, both myxovalargin derivatives **10** and **11** are to be prepared in order to obtain unambiguous structural evidence. However, since this does not change the basic synthetic strategy, both derivatives can be analyzed retrosynthetically in the same manner.

Following the retrosyntheses of GILLE[34] and SIEBKE[36], the oligopeptide is dissected into four smaller fragments, designated A-D from the *N*-terminus to the *C*-terminus (Scheme 15). At this point, it should be noted that SIEBKE once again divided fragment A (**67**) into two parts and termed it fragment AB, but this is no longer advantageous for this work due to a change in fragment A's synthesis strategy. The two myxovalargin derivatives become accessible by employing the stereochemically distinct configurational isomers B-D,L (**63**) and B-L,D (**28**). All fragments A-D are to be constructed individually and subsequently linked together by peptide couplings. As described by GILLE and SIEBKE, the guanidine function of the ornithine side chain will be introduced later. The finalization of the molecule should occur in the end by a global deprotection of all Allyl and Alloc groups.

As can be deduced from the studies of GILLE and SIEBKE (see chapter A1.5), there is a particular need for optimization in the synthesis of fragment A (**67**) and the late stage coupling and guanidinylation conditions.[34,36] Further details are described in the respective chapters.

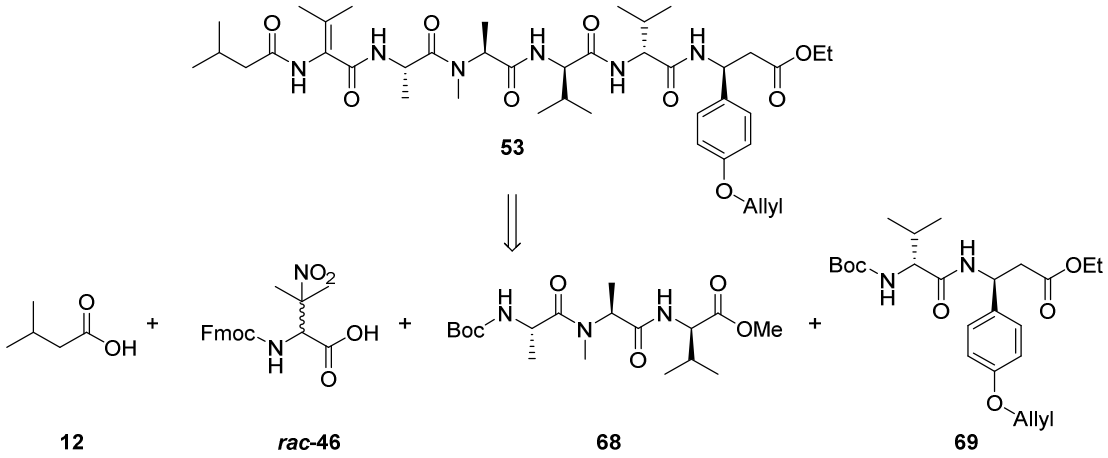


Scheme 15: Retrosynthetic analysis towards the total synthesis of myxovalargins **10** and **11**.

A3.2 Studies towards the Synthesis of Fragment A

A3.2.1 Boc/OMe Route to Fragment A

As described in Section A1.5, SIEBKE'S studies revealed difficulties in the coupling of *N*-methyl alanine. To circumvent the problem of possible epimerizations, SIEBKE attempted to prepare fragment A (**53**) in an alternative route (Scheme 16). Following BOGER'S approach[37], the new synthesis envisaged the coupling of the two alanine moieties and subsequent coupling with D-valine methyl ester to give tripeptide **68**. This is followed by coupling with nitrovaline ***rac*-46** and isovaleric acid (**12**) and subsequent nitro elimination. The tetrapeptide obtained in this way is then to be coupled with dipeptide **69**.[36] Since SIEBKE was not able to finish the synthesis due to time constraints, the studies in the present work began with a replication and optimization of SIEBKE'S new approach to fragment A (**53**).



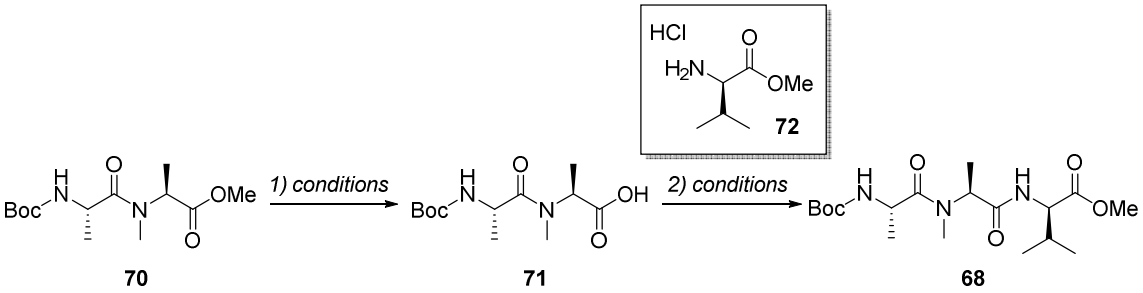
Scheme 16: Retrosynthetic approach to fragment A (**53**).

The synthesis of fragment A (**53**) started with a screening of different coupling conditions and reagents, starting with alanine dipeptide **70** from SIEBKE'S stock (Table 2). This reaction was carried out in two steps. After saponification of methyl ester **70** with LiOH, peptide coupling of acid **71** with valine methyl ester hydrochloride (**72**) was studied under different coupling conditions. For example, after fast addition of a LiOH solution followed by usage of EDC·HCl and HOBt/DIPEA or HOAt/$NaHCO_3$, respectively, only a *d.r.* of 1:1 was obtained (Entries 1-2), which could be significantly improved by dropwise addition of $LiOH_{(aq)}$ and usage of 6-Cl-HOBt (Entries 4-5). The best result was obtained by dropwise addition of LiOH (1M in H_2O) with subsequent employment of EDC·HCl, HOBt, and DIPEA in dichloromethane, which led to a quantitative conversion and a

[37] a) D. L. Boger, H. Keim, B. Oberhauser, E. P. Schreiner, C. A. Foster, *J. Am. Chem. Soc.* **1999**, *121*, 6197-6205. b) Y. Chen, M. Bilban, C. A. Foster, D. L. Boger, *J. Am. Chem. Soc.* **2002**, *124*, 5431-5440.

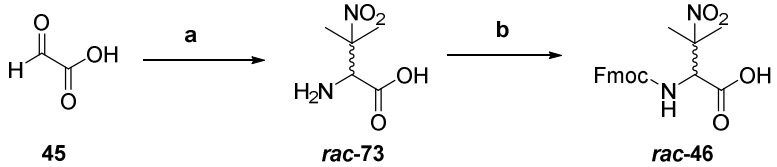
diastereomeric ratio of 12:1 in small scale and gave the tripeptide **68** with 58% and a diastereomeric ratio of 16:1 in large scale (Table 2, Entries 3, 6).

Table 2: Screening table for the optimization of the reactions towards tripeptide **68** (*referred to second conditions).



entry	scale (mg)*	1) conditions	2) conditions	yield o2s	*d.r.*
1	153	fast addition of LiOH (1M in H_2O), THF, 0 °C → rt, 22 h	**72**, EDC·HCl, HOBt, DIPEA, CH_2Cl_2, 0 °C → rt, 18 h	67%	1:1
2	161	fast addition of LiOH (1M in H_2O), THF, 0 °C → rt, 22 h	**72**, EDC·HCl, HOAt, $NaHCO_3$, CH_2Cl_2, -15 °C → rt, 18 h	73%	1:1
3	**44.7**	**dropwise** addition of LiOH (1M in H_2O), THF, 0 °C → rt, 16 h	**72**, EDC·HCl, **HOBt**, **DIPEA**, CH_2Cl_2, 0 °C → rt, 16 h	**quant.**	**12:1**
4	133	dropwise addition of LiOH (1M in H_2O), THF, 0 °C → rt, 17 h	**72**, EDC·HCl, HOAt, $NaHCO_3$, CH_2Cl_2, -15 °C → rt, 18 h	78%	2:1
5	63.4	dropwise addition of LiOH (1M in H_2O), THF, 0 °C → rt, 17 h	**72**, EDC·HCl, 6-Cl HOBt, DIPEA, CH_2Cl_2, 0 °C → rt, 16 h	65%	10:1
6	**3134**	**dropwise** addition of LiOH (1M in H_2O), THF, 0 °C → rt, 17 h	**72**, EDC·HCl, **HOBt**, **DIPEA**, CH_2Cl_2, 0 °C → rt, 17 h	**58%**	**16:1**

Next, 3-nitrovaline (***rac*-73**) had to be prepared from acid **45** (Scheme 17). This was accomplished by a racemic synthesis following the prescription of COGHLAN[38], which had also already been successfully carried out by SIEBKE.[36] Subsequent Fmoc-protection according to the standard protocol gave Fmoc-3-nitrovaline ***rac*-46** in good yield.

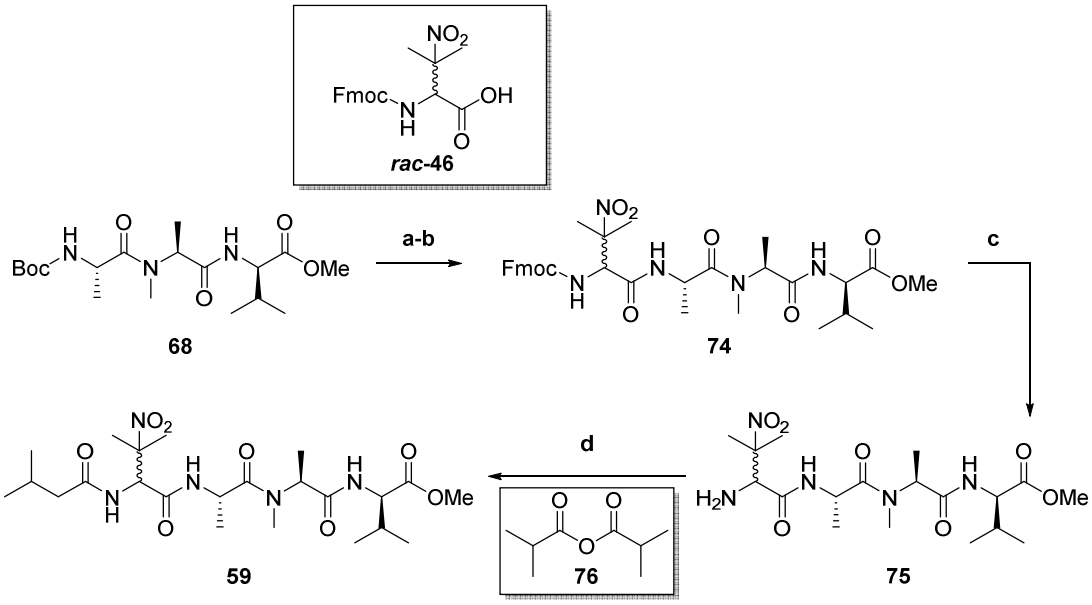


Scheme 17: Synthesis towards Fmoc-protected 3-nitrovaline (***rac*-46**): a) 2-NO_2-Propan, NH_3 (conc., 25%), KOH, H_2O, 18 h, 34%; b) Fmoc-Cl, Na_2CO_3, 1,4-dioxane, 0 °C → rt, 7 h, 62%.

This was followed by Boc-deprotection of peptide **68** with TFA in dichloromethane at 0 °C, and EDC·HCl/HOAt/$NaHCO_3$ mediated peptide coupling with nitrovaline ***rac*-46** which gave complete

[38] P. A. Coghlan, C. J. Easton, *J. Chem. Soc., Perkin Trans. 1,* **1999**, 2659-2660.

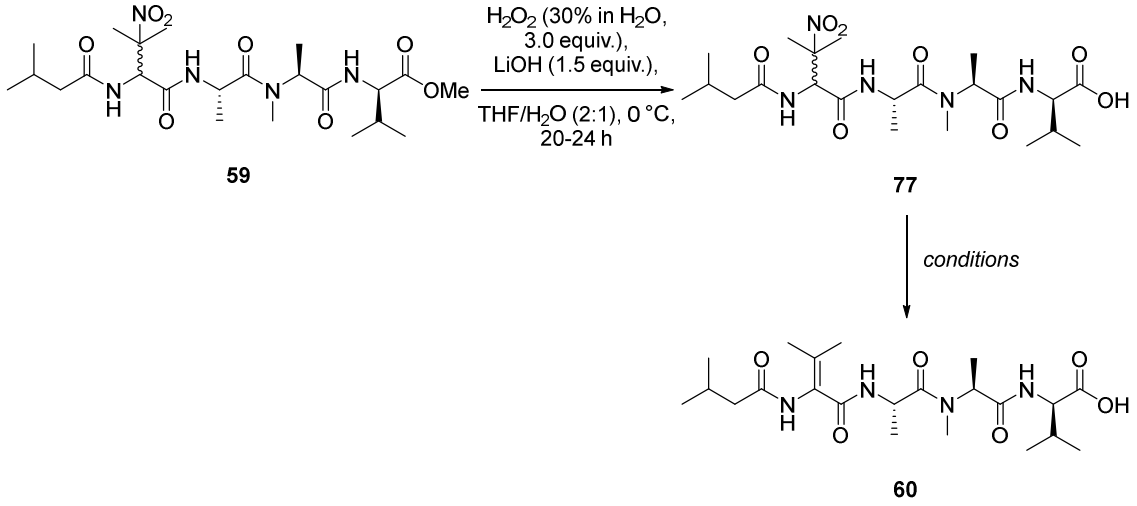
conversion to nitro compound **74**. Subsequent Fmoc-deprotection with dimethylamine in DMF and coupling with isovaleric anhydride (**76**) afforded peptide **59** in a 65% yield and a diastereomeric ratio of 2.5:1 (Scheme 18).



Scheme 18: Synthesis towards tetrapeptide **59**: a) TFA, CH_2Cl_2, 0 °C, 2.5 h; b) ***rac*-46**, EDC·HCl, HOAt, $NaHCO_3$, CH_2Cl_2, 0 °C → rt, 16 h, quant. *d.r.* = 3:1; c) Me_2NH (40% wt in H_2O), DMF, rt, 2.5 h; d) **76**, 2,6-lutidine, CH_2Cl_2, -78 °C → rt, 56% o2s, *d.r.* = 2.5:1.

Next, saponification of methyl ester **59** and subsequent nitro elimination should follow (Table 3). These transformations were envisaged in a two-step manner in direct succession. Saponification was conducted overnight with H_2O_2 (30% in H_2O) and LiOH in a 2:1 solution of THF/H_2O at 0 °C and proceeded smoothly. Nitro-elimination was performed immediately afterwards by using LiOH in H_2O at 0 °C. The smallest scale (26.8 mg) yielded the best result (41% yield, *d.r.* = 8:1, Entry 1). When extending the reaction scale to 90.1 mg and 110 mg (Entries 2-3), the yield increased to 60% but the diastereomeric ratio was lowered to 6:1. Smaller scales enabled work-up and purification by addition of AcOH and direct transfer to a reversed-phase column chromatography system (BÜCHI). If the scale was increased to more than 500 mg, product and salt eluted together, even if similar workup and purification techniques as well as solvent evaporation were performed prior to column chromatographic purification. In addition, high amounts of salts seem to promote a decomposition of the product during final solvent evaporation (Entries 4-5).

Table 3: Evaluation of different conditions for saponification of methyl ester **59** and subsequent nitro-elimination of acid **77**.

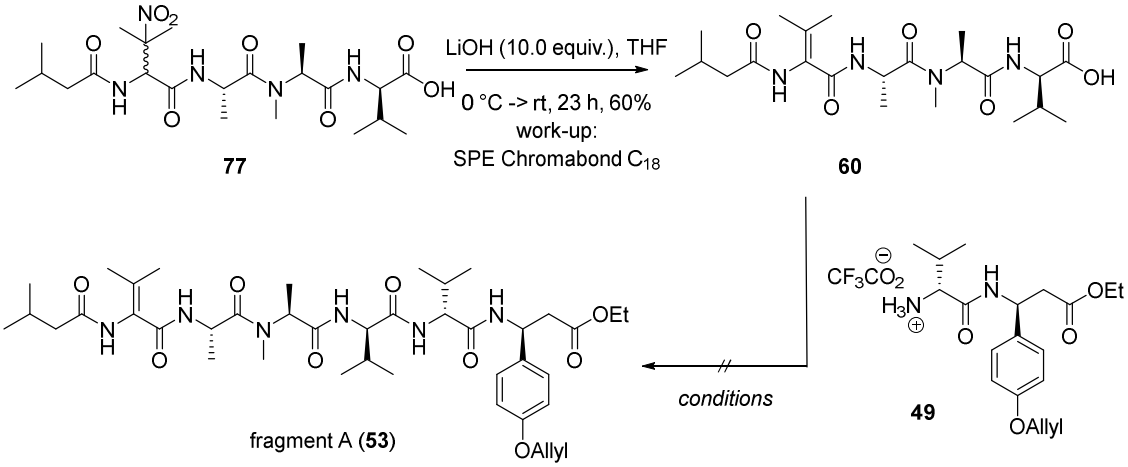


59 **77** **60**

entry	scale (mg)	conditions	work-up	yield o2s	*d.r.*
1	26.8	LiOH in H_2O (10 equiv.), THF, 0 °C, 18 h	addition of AcOH, RP BÜCHI, solvent evaporation	41%	8:1
2	90.1	LiOH in H_2O (10 equiv.), THF, 0 °C, 17 h	addition of AcOH, RP BÜCHI, solvent evaporation	46%	6:1
3	110	LiOH in H_2O (10 equiv.), THF, 0 °C, 23 h	addition of AcOH, RP BÜCHI, solvent evaporation	60%	6:1
4	661	LiOH in H_2O (10 equiv.), THF, 0 °C, 22 h	addition of AcOH, RP BÜCHI, solvent evaporation	no conversion	
5	562	LiOH in H_2O (10 equiv.), THF, 0 °C, 22 h, LiOH (7.0 equiv.), 4 h	addition of AcOH, some THF evaporated, RP BÜCHI, solvent evaporation	no conversion	

To prevent simultaneous elution of product and salt, SPE columns were subsequently tested (Table 4), and it was found that at least 50% of the product could be desalted in one purification step. The other 50% continued to elute along with the salt. Several runs yielded desalted material (160 mg) that was used to study the final coupling conditions to fragment A (**53**) with tyrosine derivative **49**. However, unfortunately, all these reactions failed. The use of HOAt/$NaHCO_3$ conditions (Entry 1) gave a different compound, while HOBt/DIPEA (Entry 2), Oxyma/DIPEA (Entry 3) and Oxyma/$NaHCO_3$ (Entry 4) conditions resulted in no coupling.

Table 4: Attempted peptide coupling towards the synthesis of fragment A (**53**).

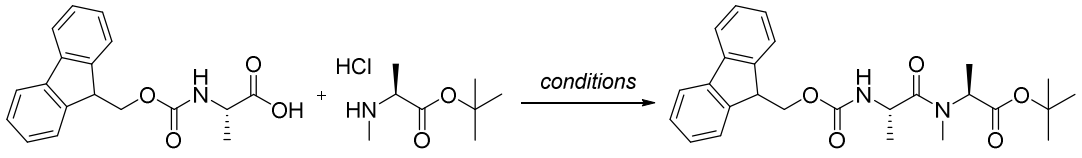


entry	conditions	result
1	HOAt (1.7 equiv.), EDC·HCl (1.7 equiv.), $NaHCO_3$ (5.0 equiv.), CH_2Cl_2/DMF (6:1), -78 °C → rt, 22 h	decomposition
2	HOBt (1.5 equiv.), EDC·HCl (1.3 equiv.), DIPEA (3.0 equiv.), CH_2Cl_2/DMF (1:1), -78 °C → rt, 24 h	no conversion
3	Oxyma Pure (1.5 equiv.), EDC·HCl (1.5 equiv.), DIPEA (1.5 equiv.), CH_2Cl_2/DMF (1:1), -78 °C → rt, 24 h	no conversion
4	Oxyma Pure (1.5 equiv.), EDC·HCl (1.5 equiv.), $NaHCO_3$ (5.0 equiv.), CH_2Cl_2/DMF (1:1), -78 °C → rt, 24 h	no conversion

A3.2.2 Fmoc/*tert*-Butyl Route to Fragment A

Due to a lack of acid **60**, the condition screening was terminated at this point. To prevent isomerization by valine methyl esters, a new route to fragment A (**53**) was envisaged by modifying the protecting group strategy (Fmoc instead of Boc) and employing *tert*-butyl instead of methyl esters. For this purpose, an evaluation of coupling conditions and coupling reagents for the challenging alanine coupling was performed (Table 5). Peptide coupling of Fmoc-protected alanine **78** with valine *tert*-butyl ester hydrochloride **79** was studied using HOAt/$NaHCO_3$ and Oxyma/DIPEA systems. Comparing the two conditions on a 240 mg scale, Oxyma resulted in better yields (62%, Entries 1-2). When scaled up to 2.39 g, the previously efficient BÜCHI purification conditions no longer resulted in satisfactory separation. Consequently, four different BÜCHI conditions were tested, with reversed-phase chromatography giving the best purification (Entry 3). Finally, Oxyma conditions and a reversed-phase BÜCHI chromatography purification technique led to dipeptide **80** in a 74% yield (*d.r.* = 8:1) for a 1.67 g scale (Entry 4).

Table 5: Peptide coupling of Fmoc-protected alanine **78** with valine *tert*-butyl ester hydrochloride **79**.



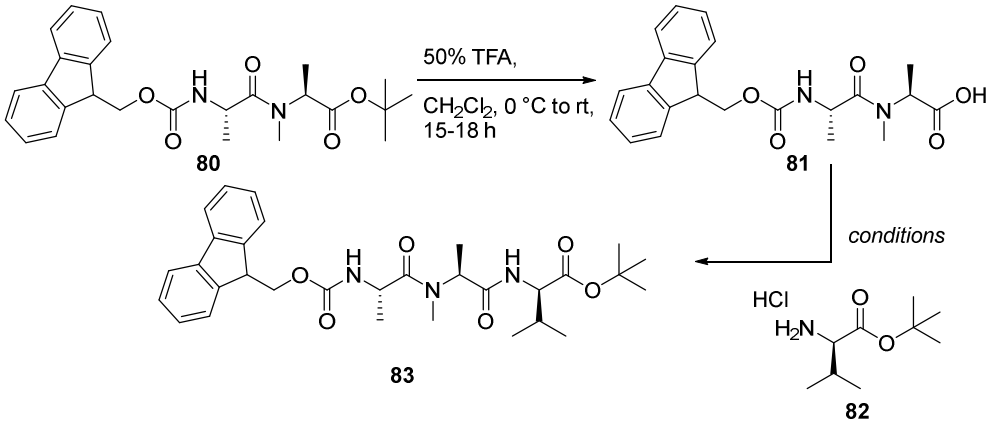
78 **79** **80**

entry	scale (g)	conditions	work-up	yield (%)
1	0.24	HOAt (1.6 equiv.), EDC·HCl (1.6 equiv.), $NaHCO_3$ (5.0 equiv.), CH_2Cl_2/DMF (5:1), -15 °C → rt, 24 h	extraction with EtOAc and 1M HCl-, $NaHCO_3$-, NaCl-solution, BÜCHI 0-3% MeOH in CH_2Cl_2	49
2	0.24	Oxyma Pure (2.0 equiv.), EDC·HCl (1.6 equiv.), DIPEA (3.5 equiv.), CH_2Cl_2/DMF (5:1), -15 °C → rt, 24 h	extraction with EtOAc, NaCl-solution, BÜCHI 0-3% MeOH in CH_2Cl_2	62
3	2.39	Oxyma Pure (2.0 equiv.), EDC·HCl (1.6 equiv.), DIPEA (3.5 equiv.), CH_2Cl_2/DMF (5:1), -15 °C → rt, 24 h	extraction with EtOAc, NaCl-solution, 1) BÜCHI 0 – 3% MeOH in CH_2Cl_2, 2) BÜCHI 0.5 – 3% MeOH/ CH_2Cl_2, 3) BÜCHI 0 – 40% EtOAc in PE, 4) BÜCHI RP 0-100% MeOH in H_2O (still not perfectly purified)	32
4	1.67	Oxyma Pure (2.0 equiv.), EDC·HCl (1.6 equiv.), DIPEA (3.5 equiv.), CH_2Cl_2/DMF (5:1), -15 °C → rt, 23 h	extraction with EtOAc, NaCl-solution, BÜCHI RP 0-100% MeOH in H_2O	**74**

Next, *t*Bu-ester cleavage of peptide **80** with 50% TFA gave rise of acid **81** being subsequently coupled with valine **82** (Table 6). The Oxyma/DIPEA conditions chosen for this purpose were only applicable to small scales (21.8 mg, Entry 1). When increasing the reaction scale to 273 mg, the conditions did not yield the desired product (Entry 2). For this reason, coupling conditions were changed to the HOBt/DIPEA system (Entry 3), which also slightly improved the yield at larger scales and gave tripeptide **83** in a yield of 32% with a diastereomeric ratio of 15:1.

Unfortunately, the new route proved to be more challenging than expected. Firstly, it was characterized by miserable yields, and secondly, large-scale purification caused problems. For this reason, a new approach to the synthesis of fragment A (**53**) was investigated, which led into the field of solid-phase synthesis.

Table 6: Saponification of peptide **80** with subsequent coupling of valine derivative **82**.



entry	scale (mg)	conditions	yield o2s
1	21.8	**82**, Oxyma Pure (2.0 equiv.), EDC·HCl (1.6 equiv.), DIPEA (3.5 equiv.), CH_2Cl_2/DMF (5:1), -15 °C → rt, 23 h	23%
2	273	**82**, Oxyma Pure (2.0 equiv.), EDC·HCl (1.6 equiv.), DIPEA (3.5 equiv.), CH_2Cl_2/DMF (5:1), -15 °C → rt, 23 h	no conversion
3	685	**82**, HOBt (1.5 equiv.), EDC·HCl (1.3 equiv.), DIPEA (3.0 equiv.), CH_2Cl_2, 0 °C → rt, 17 h	**32%** *d.r.* = 15:1

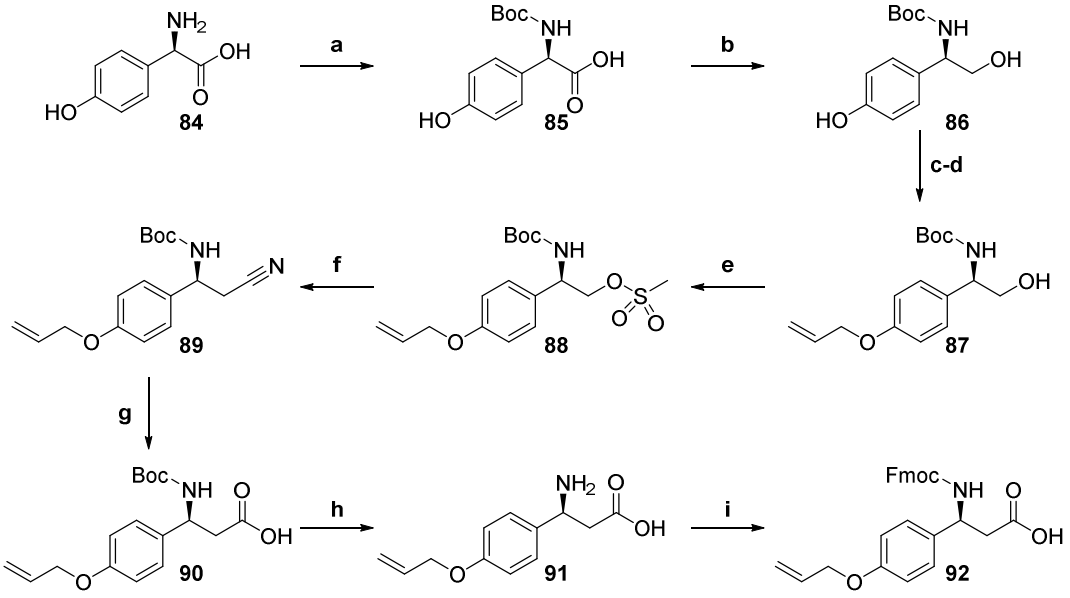
A3.2.3 Solid-Phase Route to Fragment A

Due to the difficulties in obtaining enantioselective access to fragment A (**53**), studies were conducted in the field of solid-phase peptide synthesis (SPPS). As early as 1963, BRUCE MERRIFIELD published the synthesis of a tetrapeptide on a solid resin and thus laid the foundation for SPPS. He received the Nobel Prize in 1984.[39] This technique is distinguished by several advantages over conventional liquid-phase reaction control. A large number of reactions can be carried out in a single reaction vessel. After each coupling step, reagents and byproducts can be easily filtered off. This allows reagents to be used in excess, resulting in shorter reaction times and consequently less isomerization. Also, purifications after each reaction step are simplified. Over the years, improved and automated procedures for SPPS have been developed and a variety of large peptides could be synthesized in this way.[40] One example is the complex peptide Yaku'amide B, which is characterized by structural similarity to myxovalargin.[41]

[39] B. Merrifield, *Angew. Chem. Int. Ed. Engl*. **1985**, *24*, 799-810.
[40] V. Mäde, S. Els-Heindl, A. G. Beck-Sickinger, *Beilstein J. Org. Chem*. **2014**, *10*, 1197-1212.
[41] H. Itoh, K. Miura, K. Kamiya, T. Yamashita, M. Inoue, *Angew. Chem. Int. Ed*. **2020**, *59*, 4564-4571.

A collaboration with DR. ANNA-LUISA WARNKE and PROF. DR. OLIVER PLETTENBURG from the Institute for Medicinal Chemistry (Helmholtz Munich) provided the opportunity to gain access to a Liberty Blue™ Automated Microwave Peptide Synthesizer from CEM. The great advantage of microwave-assisted peptide synthesis in many cases is that even sterically hindered amino acids become accessible. In addition, reaction time can be reduced significantly and side reactions such as racemization become controllable.[42] In the case of *N*-methyl alanine, it appears to be a highly promising method.

Encouraged by these reports, protected *β*-tyrosine **92** had to be synthesized (Scheme 19). This was performed in a nine-step synthesis following a protocol by T. SEEDORF. Starting with amine **84**, Boc-protection was followed by reduction of acid **85** with BH_3 in THF to give primary alcohol **86**. Subsequent Allyl-protection of the phenol group gave alcohol **87** in 17% over three steps. This was followed by activation of the primary alcohol as mesylate **88** and subsequent substitution by sodium cyanide to afford nitrile **89** in two steps with a yield of 58%. Basic hydrolysis of the nitrile function gave acid **90** in 49% yield. Finally, switching the protecting groups from Boc to Fmoc led to the final *β*-tyrosine derivative **92**.



Scheme 19: Synthesis towards protected *β*-tyrosine derivative **92**: a) $NaHCO_3$, Boc_2O, 1,4-dioxane/H_2O (1:1), 0 °C → rt, 18 h, 77%; b) BH_3 in THF, THF, 0 °C, 16 h; c) NaOH (0.5M), MeOH, rt, 1.5 h; d) allyl bromide, DMF, 0 °C, 18 h, 17% o3s; e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h; f) NaCN, DMSO, 40 °C, 17 h, 58% o2s; g) NaOH (2M in H_2O), EtOH, 90 °C, 5 h, 49%; h) TFA, CH_2Cl_2, 0 °C, 20 h; i) Fmoc-Cl, Na_2CO_3 (20% sol.), 1,4-dioxane, 0 °C → rt, 20 h, 97% o2s.

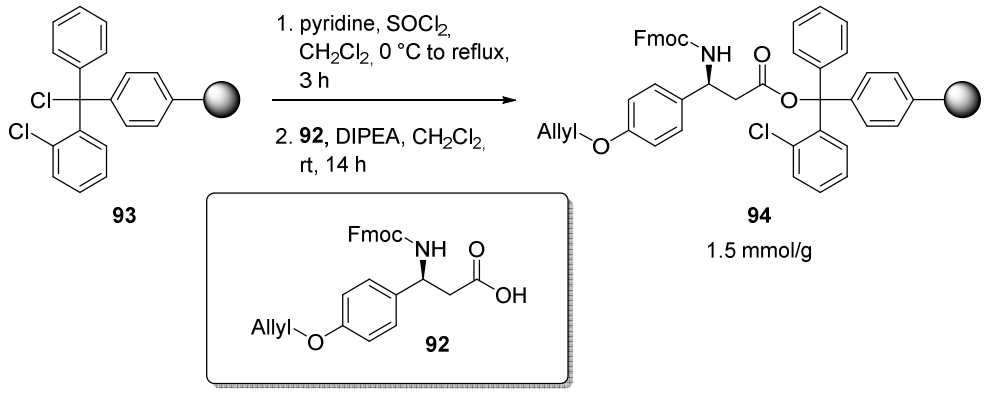
[42] G. S. Vanier, *Microwave-Assisted Solid-Phase Peptide Synthesis Based on the Fmoc Protecting Group Strategy (CEM).* In: K. J. Jensen, P. T. Shelton, S. L. Pedersen (eds) P*eptide Synthesis and Applications.* Methods in Molecular Biology (Methods and Protocols), vol. 1047. Humana Press, Totowa, NJ, **2013**, 235-249.

However, further optimization for the final purification of acid **92** was required (Table 7). Column chromatographic purification using a normal phase BÜCHI system gave yields between 41% and 46% on both smaller (Entry 1) and larger scales (Entry 2). Changing the purification conditions to simply washing the product with H_2O and petroleum ether (Entry 3) significantly increased the yield to 97% in two steps without loss of purity.

Table 7: Purification of protected *β*-tyrosine derivative **92**.

entry	scale (g)	purification	yield o2s (%)
1	0.63	BÜCHI MeOH/CH_2Cl_2	46
2	1.97	BÜCHI MeOH/CH_2Cl_2	41
3	1.97	washed with H_2O and PE	**97**

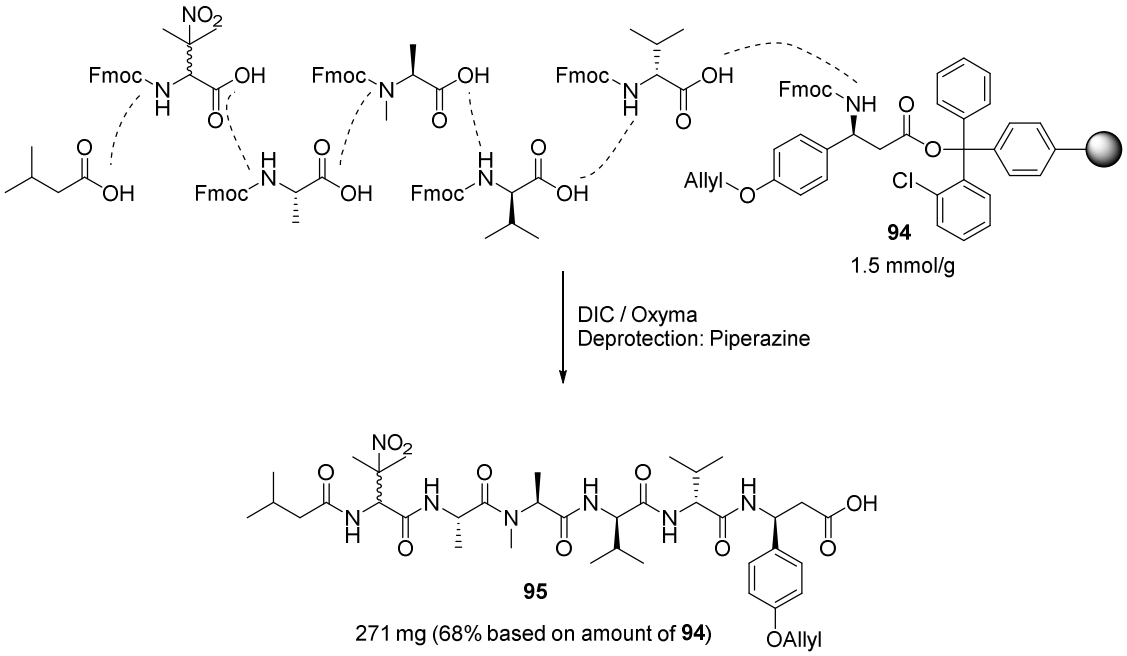
Once the original amino acid **92** was obtained, it was necessary to consider which resin was most suitable for synthesis. Since the peptide synthesizer is a microwave-assisted device, 2-chlorotrityl chloride resin **93** was chosen. TSELIOS showed that this resin, in combination with microwave-assisted reaction control, significantly accelerated peptide synthesis while racemization remained low.[43] Furthermore, the question arose as to whether the initial loading of the resin should be done prior to solid-phase synthesis or left to the synthesizer. However, since a large excess of acid **92** would have been required to load the resin on the synthesizer, given the complex, nine-steps synthesis, the first option was chosen, i.e., the chlorotrityl chloride resin **93** was activated with $SOCl_2$ and then pre-loaded with acid **92** to give resin **94** being passed to the apparatus. The weight gain confirmed a loading of 1.5 mmol/g (Scheme 20).



Scheme 20: Pre-loading of resin **93** with *β*-tyrosine derivative **92**.

[43] M. Ieronymaki, M. E. Androutsou, A. Pantelia, I. Friligou, M. Crisp, K. High, K. Penkman, D. Gatos, T. Tselios, *Biopolymers (Peptide Science),* **2015**, *104*, 506-514.

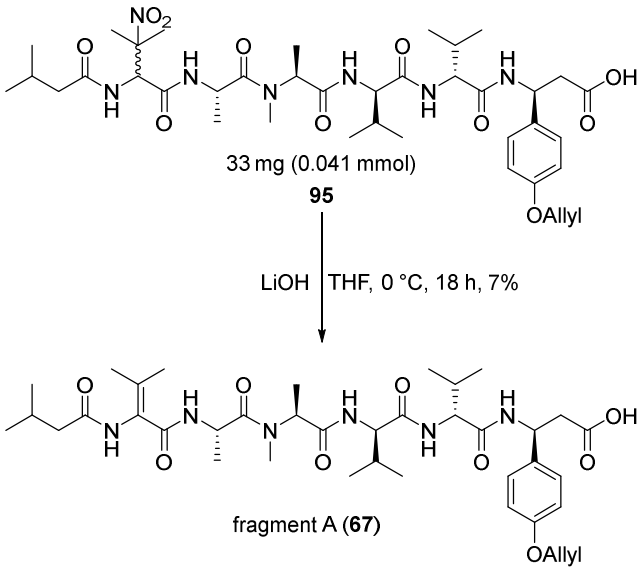
With all building blocks in hand, fragment A precursor **95** was prepared according to the general procedure for the synthesis of peptides with the automated microwave peptide synthesizer in an 0.5 mmol scale (Scheme 21).[44] Polymer-bound *β*-tyrosine derivative **94**, Fmoc-D-Val-OH, Fmoc-*N*-Me-Ala-OH, Fmoc-Ala-OH, amino-3-methyl-3-nitrobutanoic acid and isovaleric acid were employed. Piperazine was chosen for Fmoc-deprotection, DIC as activator and Oxyma as coupling reagent. After complete synthesis, the peptide was purified by BÜCHI reversed-phase chromatography to yield 271 mg of fragment A precursor **95** which equals a 68% yield based on the amount of polymer-bound amino acid **94**.



Scheme 21: SPPS of fragment A precursor **95**.

A subsequent nitro-elimination with LiOH (Scheme 22) and purification by BÜCHI reversed-phase chromatography gave purified fragment A (**67**) with a diastereomeric ratio of 3:1 (determined by QTOF). The diastereomers were separated by preparative HPLC and the main diastereomer was isolated and fully characterized.

[44] The synthesis was performed with the assistance of Dr. ANNA-LUISA WARNKE and TIM SEEDORF on the peptide synthesizer of Prof. Dr. OLIVER PLETTENBURG'S research group.

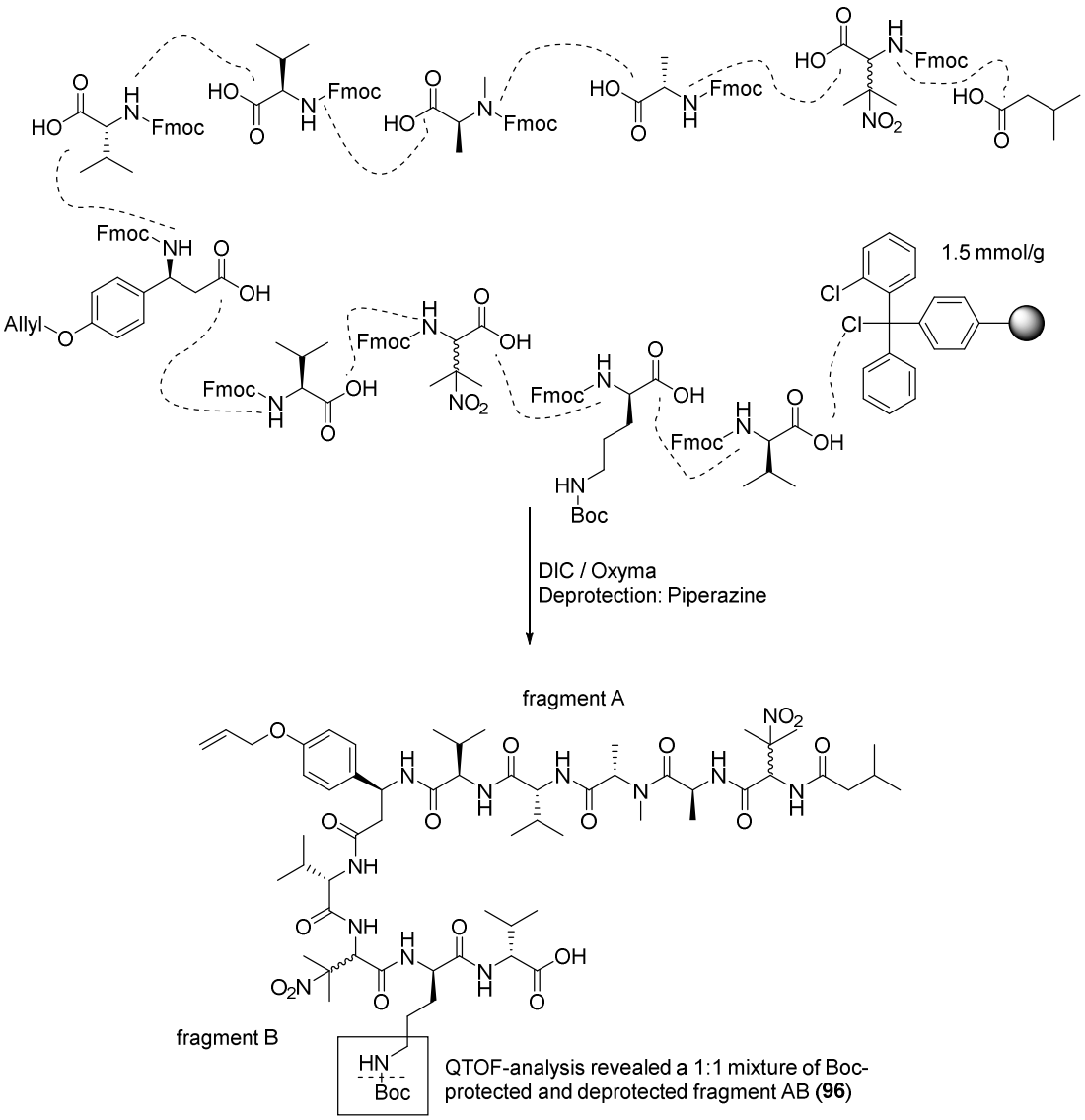


Scheme 22: Nitro-elimination to fragment A (**67**).

A3.3 Studies towards the Synthesis of Fragment AB

A3.3.1 Solid-Phase Route to Fragment AB-L,D

Encouraged by this result, it was assumed that fragment AB (**96**) could be synthesized in a similar manner (Scheme 23). The studies in this regard were first performed on fragment AB-L,D, which was expected to provide the incorrect stereochemistry for myxovalargin-L,D (**11**, see Chapter A2). This time, the first amino acid (D-valine) was automatically loaded onto the resin in the synthesizer, and the crude material was then purified by preparative HPLC. In this way, 21 mg of the purified fragment AB-L,D (**96**) was isolated, and the correct mass was detected by LCMC analysis. However, a more accurate measurement using QTOF revealed a 1:1 mixture of Boc-protected and deprotected compound. The deprotection of Boc was probably caused by the use of 1% TFA in CH_2Cl_2 during cleavage from the resin after synthesis.



Scheme 23: SPPS towards fragment AB-L,D (**96**).

To prevent Boc-deprotection during cleavage, three different approaches were tested for the synthesis of fragment AB-L,D (**96**) using the automated peptide synthesizer (Figure 7). An initial approach envisaged the coupling of fragment A precursor **95** with the first two amino acids of fragment B (D-valine + nitrovaline) and the introduction of the arginine residue at a later stage, but in this case, it was not possible to obtain any product **97**. The second attempt involved the substitution with Pbf-protected arginine for Boc-protected ornithine to avoid the problem of deprotection during cleavage. Unfortunately, this attempt also failed. The final approach was to resynthesize fragment AB-L,D (**96**). This time, formic acid was used for its cleavage, resulting in a very low yield of 16%, however, the correct mass was detected by LCMS analysis. Therefore, this approach proved to be the most promising method, and the cleavage was repeated using a mixture

of dichloromethane and hexafluoroisopropanol instead of formic acid. GRELL described a 4:1 mixture of dichloromethane and hexafluoroisopropanol as an effective and rapid reagent with only low racemization potential during cleavage of peptides from 2-chlorotrityl chloride resins.[45] Although this route increased the yield to 26%, the diastereomeric ratio (*d.r.* = 2:1) after subsequent nitro-elimination proved to be far from satisfactory.

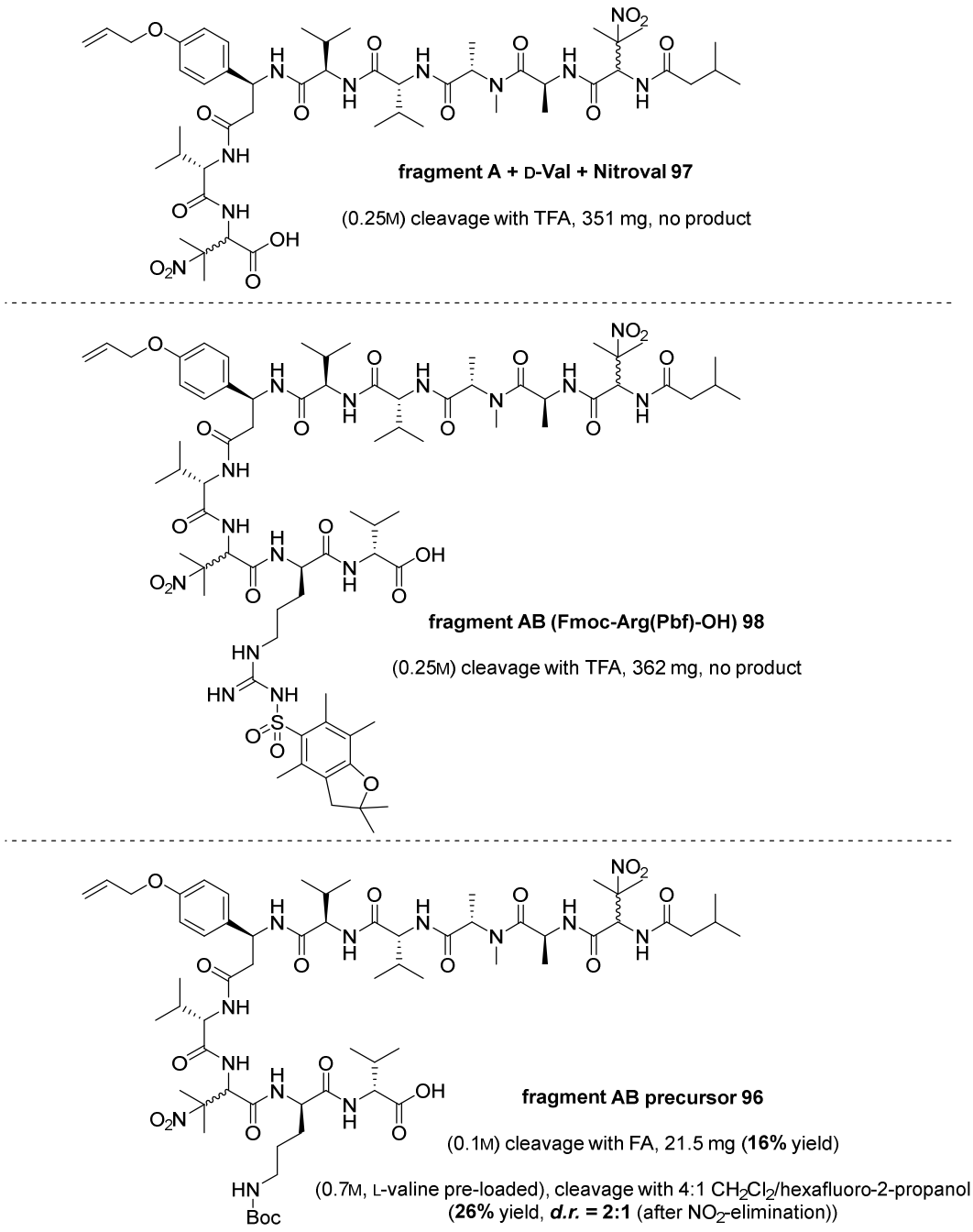


Figure 7: Different approaches towards fragment AB-L,D precursor **96**.

[45] R. Bollhagen, M. Schmiedberger, K. Barlos, E. Grell, *J. Chem. Soc., Chem. Commun*. **1994**, *22*, 2559-2560.

A3.3.2 Alternative Route to Fragment AB-D,L

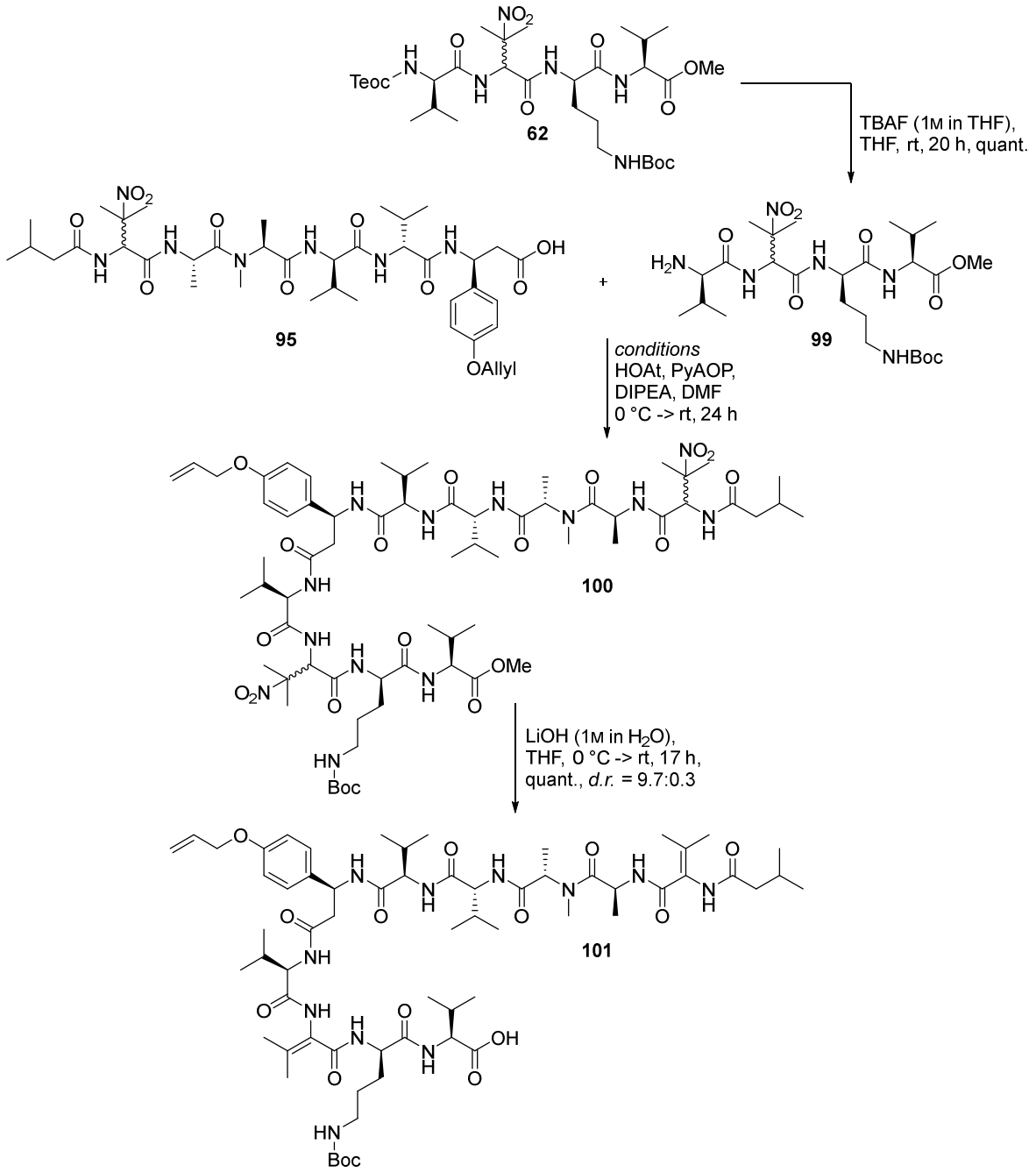
Since the automated solid-phase peptide synthesis did not provide a satisfactory result for the synthesis of fragment AB-L,D (**96**), only fragment A (**95**) was prepared in this way and then coupled to deprotected fragment B-D,L (**99**) under normal liquid-phase conditions (Table 8).

The synthesis of protected fragment B-D,L (**62**) did not require any further optimization, so that this compound could be obtained from SIEBKE'S stock, who had already prepared it in sufficient quantities.[36] It was deprotected with TBAF following the protocol of GILLE[34] and free amine **99** was obtained in quantitative yield.

Subsequently, an optimization of the reaction conditions for the coupling of fragments A and B was desired. For this purpose, the HOAt, PyAOP and DIPEA coupling system was investigated as basis, following GILLE'S work. Under the conditions she used, with 1.1 equivalents of coupling reagents and DIPEA respectively, only an 18% yield was obtained after 17 hours (Entry 1). A slight increase in the amount of coupling reagents and base already led to an improved yield of 24% (Entry 2). However, a further increase did not lead to any significant change, but apparently to a more pronounced decomposition of fragment A (**95**), which could only be reisolated in 48% (Entry 3). Next, it was investigated whether using a larger amount of fragment B-D,L (**100**) would change the yield; and indeed, it increased to 71% (Entry 4). Finally, a longer reaction time was tested, but with a stirring time of 36 hours, the yield dropped again to 25% (Entry 5). The purification of these larger fragments was remarkably successful on the BÜCHI automated column chromatography apparatus using wide pore reversed-phase C18 columns.

Subsequently, mutual nitro-elimination and saponification of the methyl ester were performed on the large precursor of fragment AB-D,L (**100**) anticipating that this would yield a better diastereomeric ratio than SIEBKE'S attempts on the smaller fragment A (**53**). And indeed, elimination with LiOH succeeded in quantitative yield with a diastereomeric ratio of 9.7:0.3 determined upon QTOF measurement.

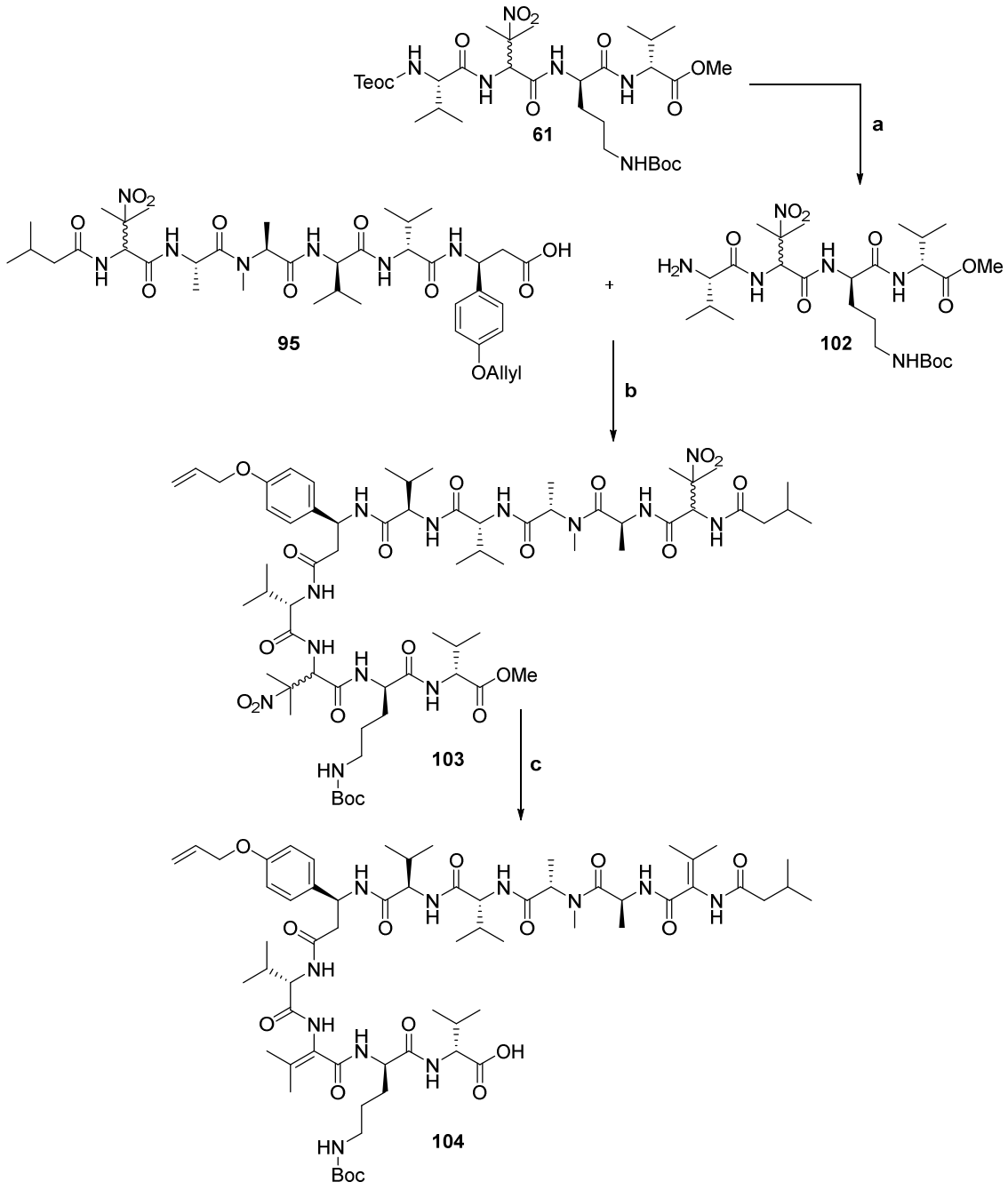
Table 8: Coupling conditions towards the synthesis of fragment AB-D,L (**101**).



entry	n (A) (mmol)	m (A) (mg)	B (equiv.)	HOAt (equiv.)	PyAOP (equiv.)	DIPEA (equiv.)	yield (%)	A reisol. (%)
1	0.14	112	1.1	1.1.	1.1	4.6	18	52
2	0.14	110	1.2	1.5	3.0	5.0	24	57
3	0.08	63	1.5	4.0	7.0	5.0	25	48
4	**0.10**	**79**	**2.16**	**2.2**	**3.0**	**5.0**	**71**	**20**
5 (36 h)	0.09	76	2.2	2.2	3.0	5.0	25	55

A3.3.3 Synthetic Route to Fragment AB-L,D

In a corresponding way, the synthesis of fragment AB-L,D (**104**) with the incorrectly published stereochemistry was carried out (Scheme 24). For this purpose, the optimized conditions were used, and the protected fragment C (**61**) obtained from SIEBKE'S stock was quantitatively deprotected by TBAF. Subsequently, the coupling of fragment A (**95**) produced by the peptide synthesizer with deprotected fragment B (**102**) was performed. For this, the optimized HOAt/PyAOP/DIPEA conditions were employed and gave peptide **103** in a slightly lower yield of 47% compared to the first epimer. Finally, nitro-elimination yielded fragment AB-L,D (**104**).



Scheme 24: Synthesis towards fragment AB-L,D (**104**): a) TBAF (1M in THF), THF, rt, 20 h, quant.; b) HOAt (2.2 equiv.), PyAOP (3.0 equiv.), DIPEA (5.0 equiv.), DMF, 0 °C → rt, 24 h, 46%; c) LiOH (1M in H_2O), THF, 0 °C → rt, 17 h, 76%.

The improved diastereoselectivity of the latter approach is highlighted in the ^{1}H-NMR spectra of the products from both synthetic routes towards fragment AB-L,D (**104**). Figure 8 shows these two spectra obtained after final nitro-elimination and saponification. The top spectrum depicts the product resulting from the coupling of fragment A (**95**) prepared in the synthesizer with fragment B-L,D (**99**) from the SIEBKE stock carried out in liquid-phase. The bottom part shows the spectrum of fragment AB-L,D (**104**) completely prepared by the automated peptide synthesizer with subsequent liquid-phase saponification and nitro-elimination. The signal for the NMe group is labeled in each case. It clearly shows that epimerization occurs to a greater extent in the synthesizer and supports the approach of synthesizing fragment AB by preparing fragment A under solid-phase conditions and then coupling to fragment B under liquid-phase conditions.

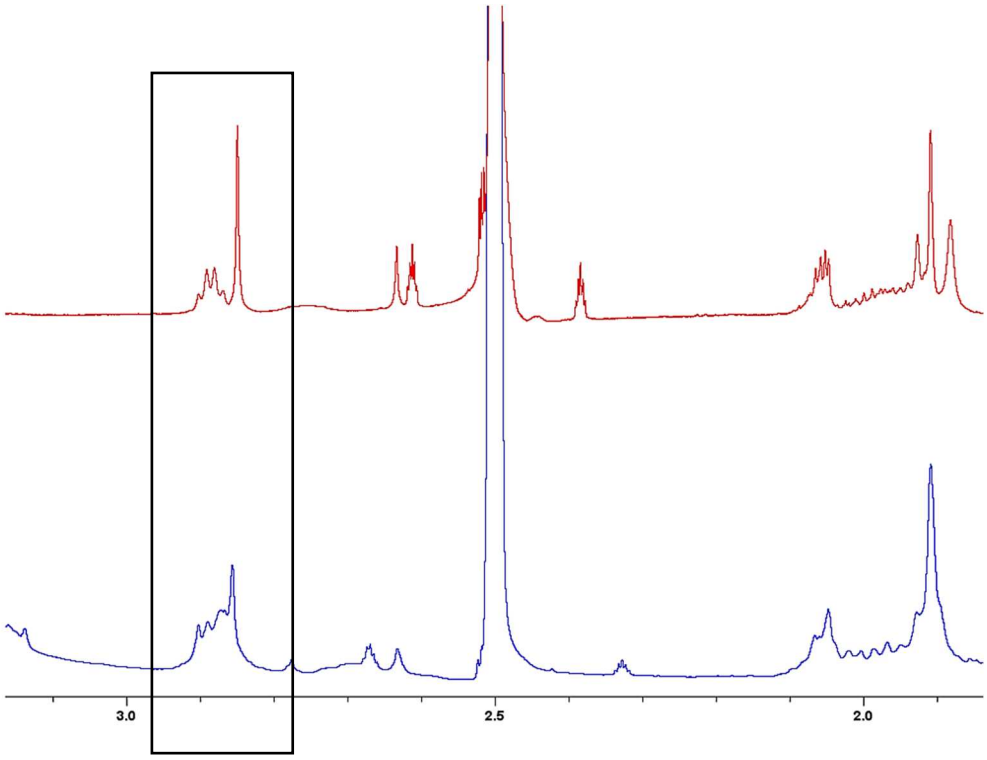
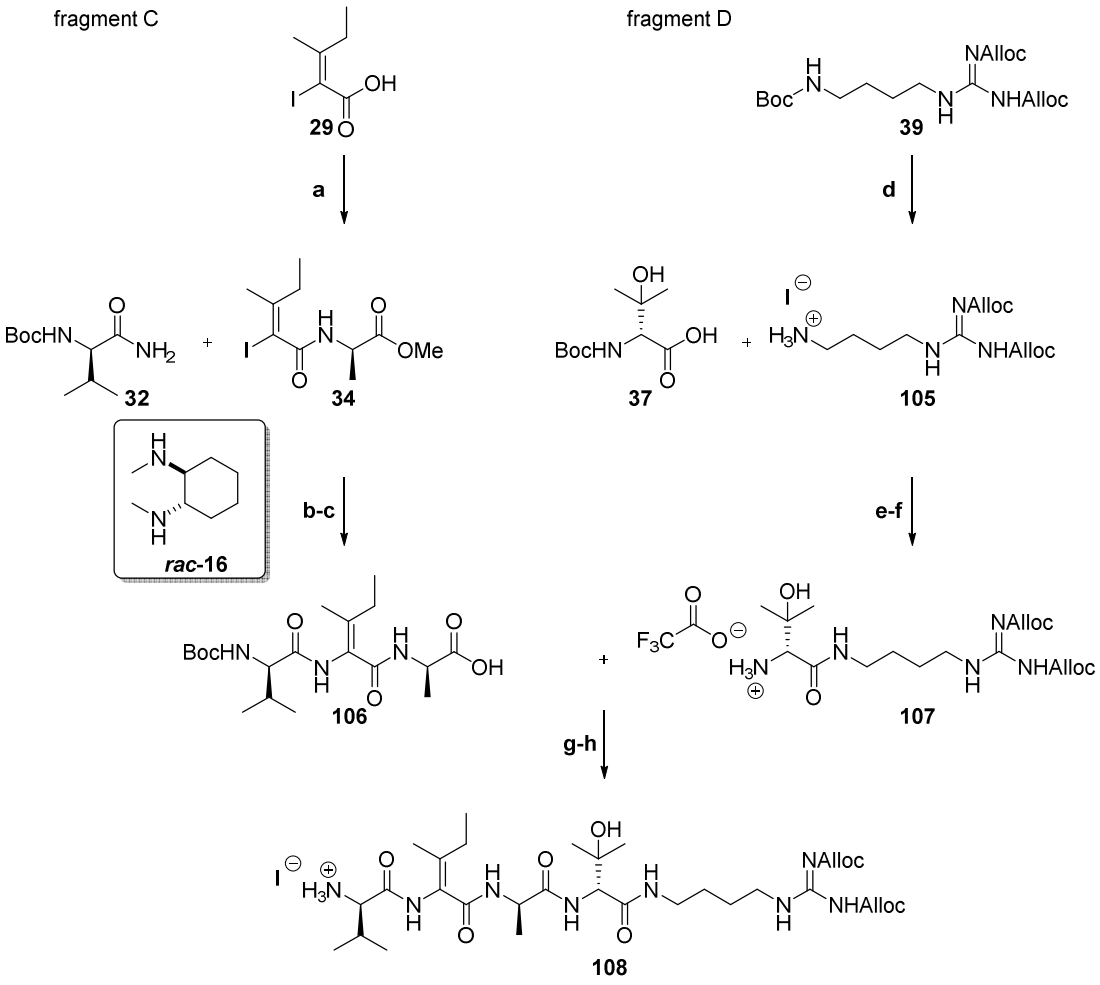


Figure 8: Comparison of a section of the ^{1}H-NMR spectra of fragment AB-L,D (**104**) obtained with the automated peptide synthesizer (bottom, in blue) and that obtained with classical liquid-phase synthesis (top, in red). The signal from the NMe group is highlighted, showing the better diastereomeric ratio in the upper spectrum.

A3.4 Synthesis of Fragment CD

The syntheses of fragments C (**106**) and D (**107**) were carried out analogously to the routes of GILLE and SIEBKE (Scheme 25).[34,36] Since SIEBKE had already carried out extensive optimization experiments and had nevertheless declared GILLE'S route to be the most favorable, further optimization of the synthesis of fragment CD (**108**) was dispensed with in this work. Since the two predecessors had already produced sufficient material of the four building blocks **29**, **32**, **37** and **39**, it was only required to perform the coupling and deprotection reactions on a sufficient scale which were reproducible in good yields. At this point, special reference should be made to the GOLDBERG reaction optimized by GILLE[35], which gave satisfactory yields only on a small scale of about 100 mg. Nevertheless, the parallel synthesis provided sufficient material. The final coupling of fragments C (**106**) and D (**107**) was performed with EDC·HCl and HOAt and proceeded in excellent yield. Finally, subsequent TMSI-assisted Boc-deprotection provided the free amine DE **108** for coupling with fragment AB.

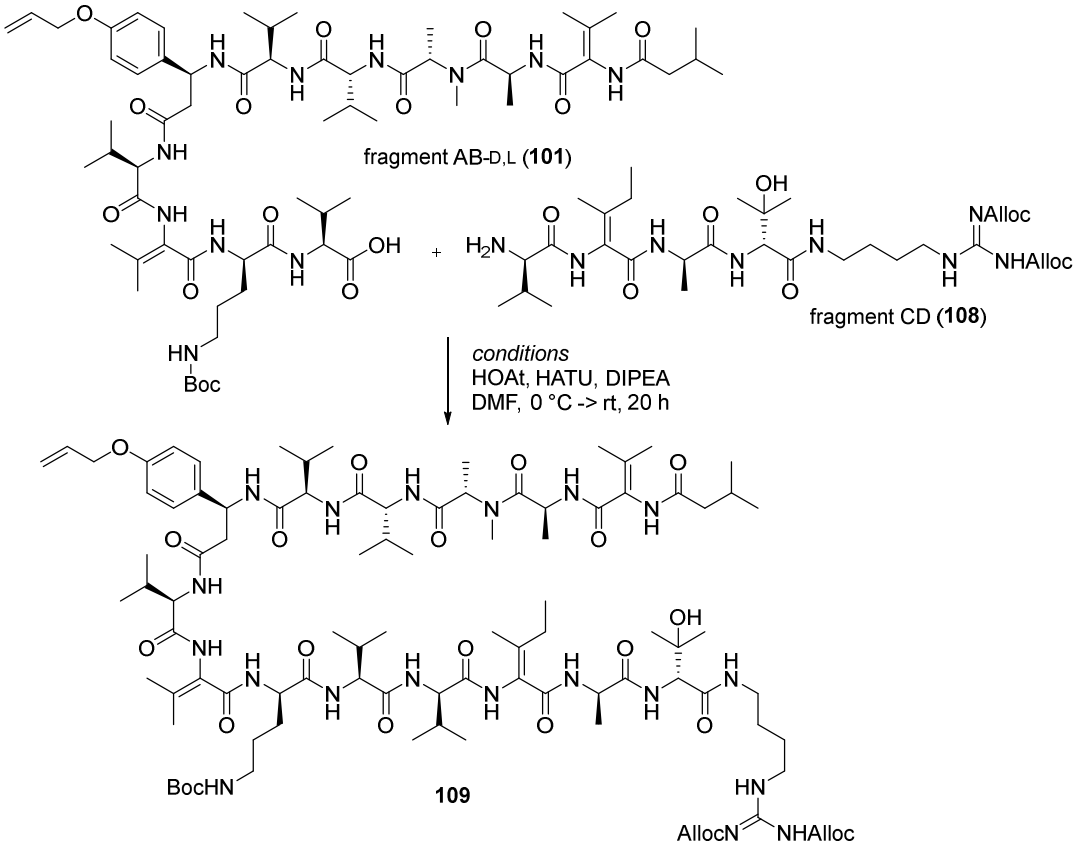


Scheme 25: Synthesis of fragment CD (**108**): a) D-Ala-OMe·HCl, PyAOP, HOAt, DIPEA, DMF, 0 °C → rt, 22 h, 76%; b) CuI, ***rac*-16**, K_2CO_3, 1,4-dioxane (degassed), 70 °C, 18 h, 72%; c) LiOH (1M in H_2O), THF, 0 °C → rt, 21 h, 98%; d) TMSI, CH_2Cl_2, rt, 4 h, quant.; e) EDC·HCl, Oxyma, $NaHCO_3$, CH_2Cl_2/DMF (6:1), 0 °C → rt, 17 h, 43%; f) TFA, 0 °C, 2 h, quant.; g) EDC·HCl, HOAt, MeCN, DMF, -15 °C, 10 min, $NaHCO_3$, rt, 20 h, 67%, *d.r.* > 15:1; h) TMSI, CH_2Cl_2, rt, 10 min, quant.

A3.5 Studies towards the Endgame of Myxovalargin A

A3.5.1 Synthesis of Myxovalargin-D,L

With the required fragments AB-D,L (**101**) and CD (**108**) in hand, the final coupling to the myxovalargin-D,L backbone **109** was now investigated (Scheme 26). Following GILLE'S conditions,[34] a screening of different conditions was performed for the HOAt/HATU/DIPEA system (Table 9). A moderate yield of 55% was initially obtained on a small scale with 1.2 to 1.5 equivalents of fragment CD (**108**) and coupling reagents, respectively, and 5.0 equivalents of DIPEA (Entry 1). By slightly increasing the amount of coupling reagents while maintaining constant amounts of fragment CD (**108**) and DIPEA resulted in a significant decrease of the yield to 11% with 63% of fragment AB-D,L (**101**) being recovered (Entry 2). Reducing the quantity of base did not improve the yield either (Entry 3). Only a molar increase of fragment CD (**108**) to 3.2 equiv. while maintaining 2.5 equiv. of coupling reagents led to an improvement of yield again to 55%, that could also be maintained on a larger scale (Entry 4). Finally, due to the successful coupling of fragment AB-D,L (**101**), HATU was replaced by PyAOP, but this did not lead to any detectable conversion (Entry 5). Since the starting material was gradually running low, the screening was stopped at this point and the moderate yield of 55% under HATU conditions described in Entry 4 was accepted for this late stage coupling reaction.



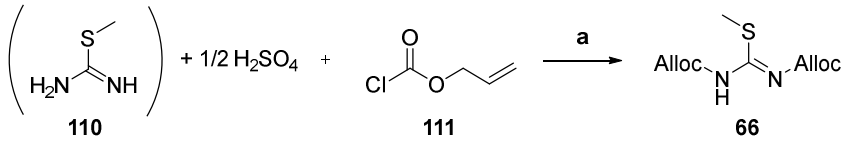
Scheme 26: Final coupling reaction towards the synthesis of the myxovalargin-D,L backbone **109**.

Table 9: Conditions for the coupling of fragment AB-D,L (**101**) with fragment CD (**108**).

entry	n (AB) (mmol)	m (AB) (mg)	CD (equiv.)	HOAt (equiv.)	HATU/PyAOP (equiv.)	DIPEA (equiv.)	yield (%)	AB reisol. (%)
1	0.004	4.60	1.2	1.5	HATU: 1.5	5.0	**55**	-
2	0.023	30.0	1.2	2.0	HATU: 2.5	5.0	11	63
3	3x0.012	3x14.6	1.2	2.0	HATU: 2.0	4.5	15	48
4	0.040	50.0	3.2	2.5	HATU: 2.5	5.0	**55**	-
5	0.017	21.0	1.5	2.0	PyAOP: 2.5	4.5	no conversion	-

With the myxovalargin-D,L backbone **109** in hand, the next step was to establish conditions for Boc-deprotection and subsequent guanidinylation reactions. For this, the smaller fragment B-L,D (**28**) was chosen, which had already been synthesized by SIEBKE and was still available in larger quantities (Table 10).[36] It was ideally suited as a test molecule due to the identical chemical environment of the arginine side chain. The already established LEWIS acid trimethylsilyl iodide (TMSI) was chosen for Boc-deprotection because it had shown promising results in previous work.[34,36] It is ideally suited for the removal of nitrogen protecting groups, such as Boc and Alloc. Depending on the reaction time selected, chemoselectivity can be achieved. For example, deprotection of Boc occurs within a few minutes, while all other protecting groups present in the molecule remain inviolate. Another advantage of this reagent is its ease of workup. No extraction is required after the reaction, which is of enormous importance, especially for the very large, polar peptide chains in late-stage synthesis. Thus, the reaction can be stopped simply by adding methanol. The solvent is then removed under reduced pressure, and the desired product is obtained as a salt.[46] The results of employing TMSI in the proof-of-concept study monitored by mass spectrometry were consistent with these expectations and thus already provided the deprotection reagent for the subsequent reaction on myxovalargin-D,L backbone **109**.

The next step was to establish conditions for the guanidinylation. Therefore Alloc-protected methylisothiourea **66**, which had already been successfully employed by SIEBKE for the synthesis of fragment D, was prepared starting from commercially available *(S)*-methylisothiourea sulfate (**110**) in 56% yield (Scheme 27).[36]

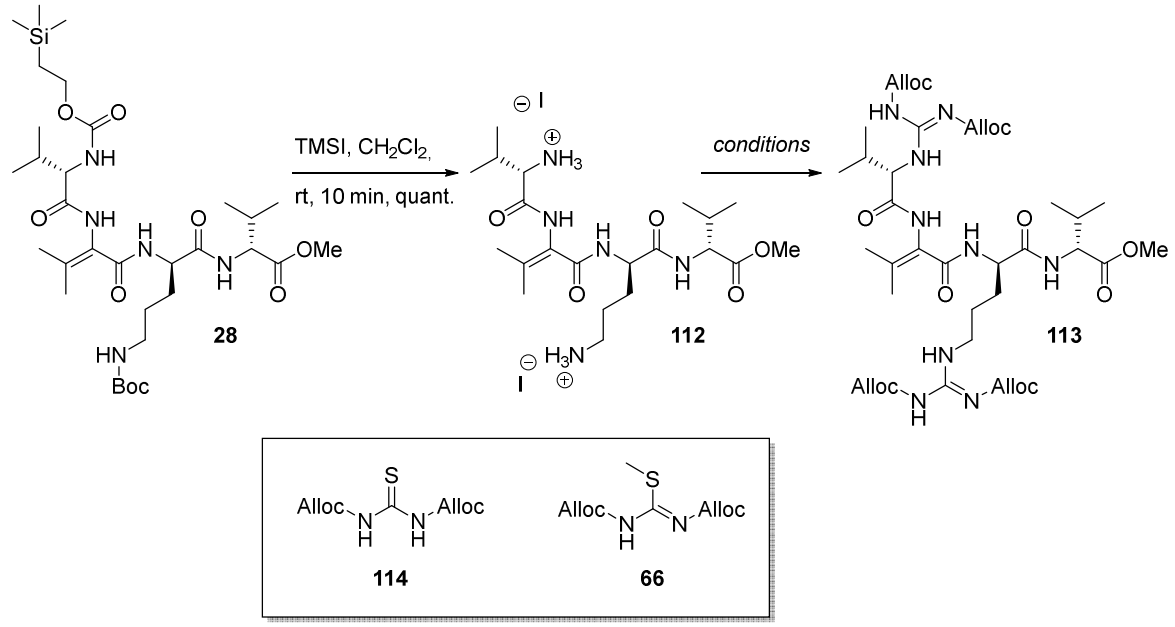


Scheme 27: Synthesis of Alloc-protected methylisothiourea **66**: a) 10% $NaHCO_{3(aq)}$, $NaOH_{(aq)}$, rt, 20 h, 56%.

[46] a) R. S. Lott, V. S. Chauhan, C. H. Stammer, *J. Chem. Soc., Chem. Commun*. **1979**, *11*, 495-496; b) G. A. Olah, S. C. Narang, *Tetrahedron* **1982**, *38*, 2225-2277.

Two promising approaches were chosen for guanidinylation conditions (Table 10). First, guanidinylation was tested with *N,N'*-di-Alloc-thiourea **114** in the presence of mercuric chloride. QIAN described these conditions in his case using di-Boc-thiourea as an efficient method for guanidinylation of sterically or electronically deactivated amines.[47] However, these conditions did not lead to any conversion with fragment B-L,D (**28**, Entry 1). The second approach involved guanidinylation in a manner similar to that established by GILLE and SIEBKE on fragment D.[34,36] For this purpose, Alloc-protected methylisothiourea **66** was used in combination with triethylamine, and since the Teoc protecting group proved not to be stable under these conditions, a di-guanidinylation occurred instead (Entry 2). However, since Teoc protecting groups are not present in the myxovalargin backbone, this effect is negligible. Based on these results, the already established guanidinylation method proved to be the method of choice and was used in the following.

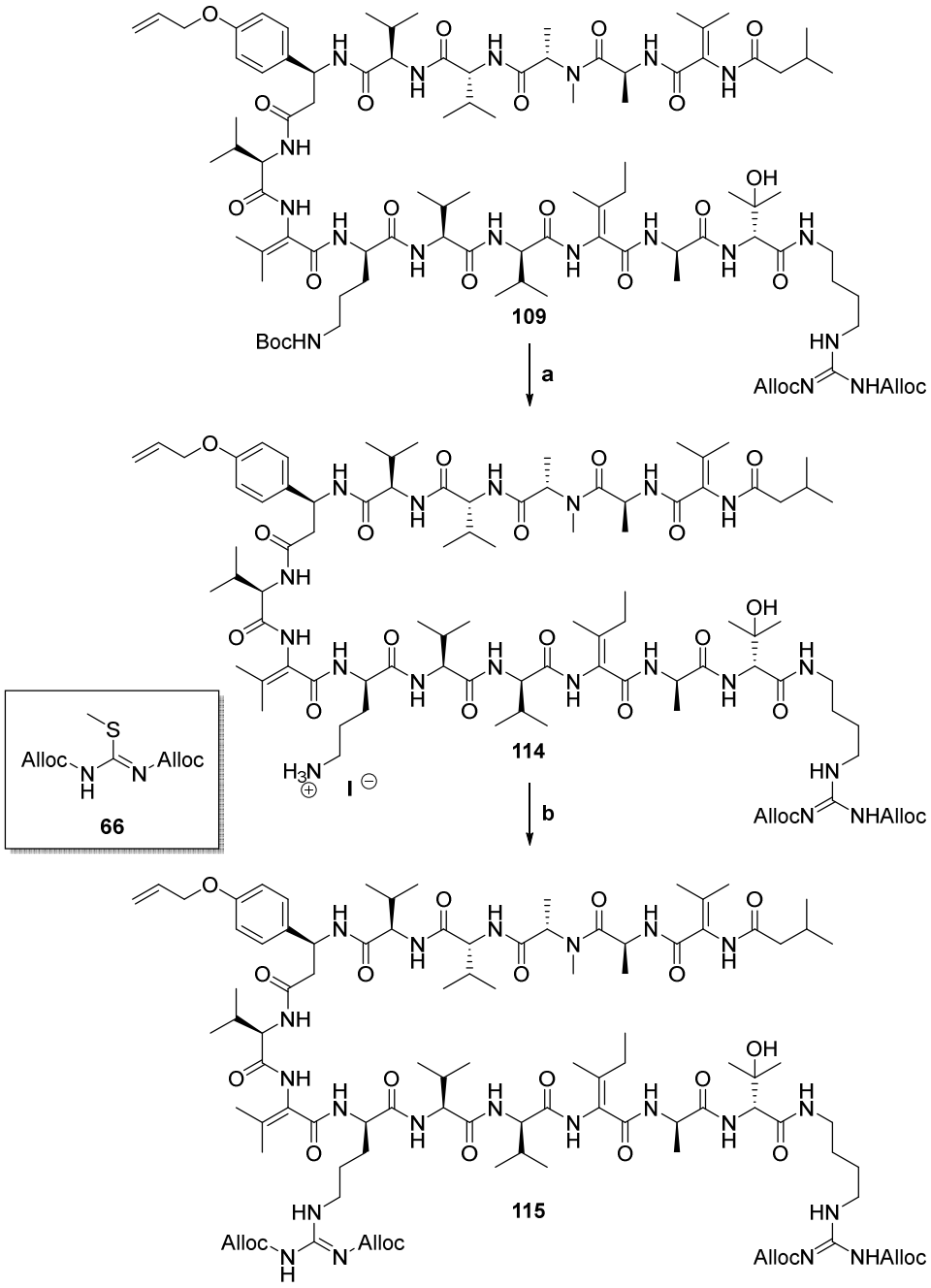
Table 10: Proof-of-concept study on guanidinylation conditions performed on fragment B-L,D (**28**).



entry	conditions	result
1	**114**, Et_3N, $HgCl_2$, DMF, 0 °C → rt, 12 h	no conversion
2	**66**, Et_3N, THF, rt, 12 h	Teoc deprotection resulted in dual guanidated product **113**

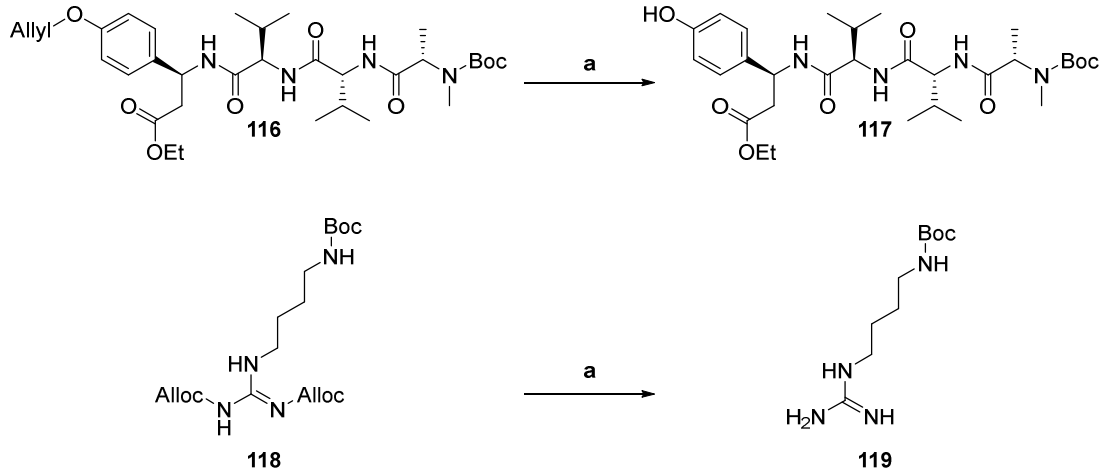
[47] K. S. Kim, L. Qian, *Tetrahedron Lett*. **1993**, *34*, 6766-7680.

The conditions established in this manner were subsequently applied to the myxovalargin-D,L backbone **109** (Scheme 28). TMSI-assisted Boc-deprotection followed by guanidinylation with Alloc-protected methyl isothiourea gave protected myxovalargin-D,L (**115**) in a 29% yield over two steps.



Scheme 28: Boc-deprotection and subsequent guanidinylation towards protected myxovalargin-D,L (**115**): a) TMSI, CH_2Cl_2, rt, 10 min; b) **66**, Et_3N, THF, rt, 12 h, quant.

Next, a proof-of-concept study was conducted in search of suitable global deprotection conditions (Scheme 29). For this purpose, both a short peptide sequence **116** from fragment A containing the Allyl-protected *β*-tyrosine and the Alloc-protected agmatine derivative **118** from fragment B were used as test compounds. Deprotection was carried out using the catalyst palladium-tetrakis(triphenylphosphine) in combination with phenylsilane.[48] The latter serves as a reductive scavenger and is required to capture the reactive, cationic Pd-allyl complexes and to regenerate the Pd(0) catalyst. Mass spectrometric studies of the two test reactions showed complete deprotection in both cases, whereupon these conditions were applied to myxovalargin.

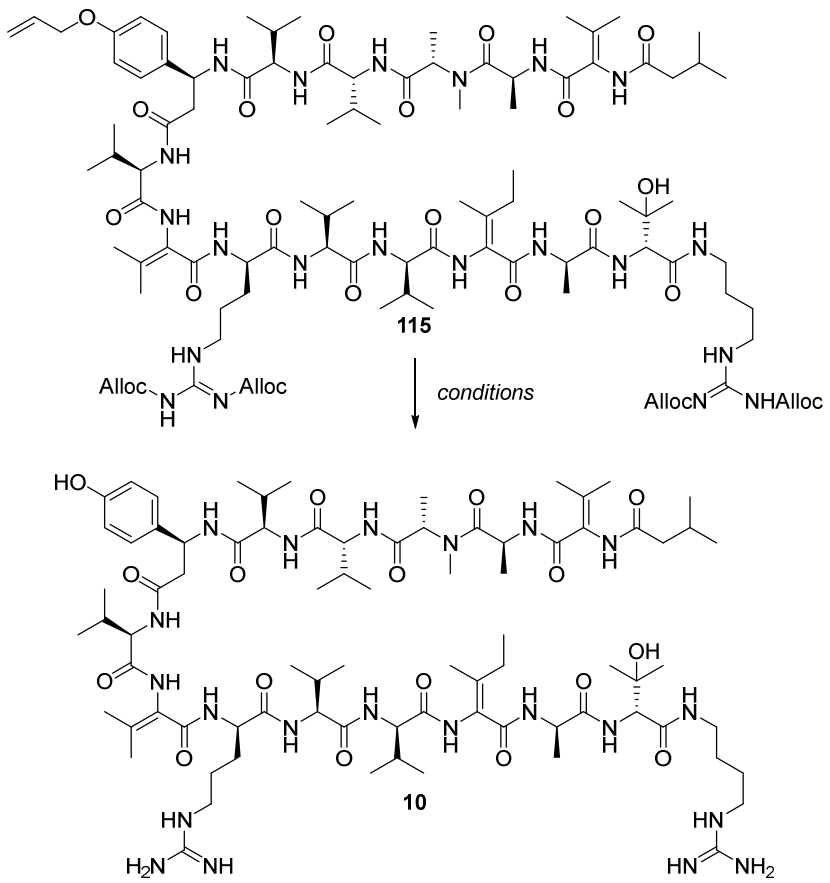


Scheme 29 Proof-of-concept study on Allyl- and Alloc-deprotection conditions performed on tetrapeptide **116** and agmatine derivative **118**: a) $PhSiH_3$ (2.00 equiv.), $Pd(PPh_3)_4$ (0.02 equiv.), CH_2Cl_2, rt, 17 h.

Encouraged by these results, the same conditions for global Allyl and Alloc-deprotection were applied to myxovalargin-D,L backbone **115**. Several purification steps using reversed-phase column chromatography and semipreparative HPLC resulted in about 1 mg of myxovalargin-D,L (**10**), corresponding to a yield of about 33% (Table 11). However, a completely pure NMR could not be obtained despite all these purification steps. Investigations using high-resolution mass spectrometry revealed the reason for this: first, it was demonstrated that the synthetic myxovalargin-D,L (**10**) and the compound isolated from the bacterial culture supernatant were the same molecules with identical stereochemistry.

[48] M. Dessolin, M.-G. Guillerez, N. Thieriet, F. Guibé, A. Loffet, *Tetrahedron Lett*. **1995**, *36*, 5741-5744.

Table 11: Global deprotection towards myxovalargin-D,L (**10**).



entry	conditions	result
1	$PhSiH_3$ (6.0 equiv.), $Pd(PPh_3)_4$ (0.2 equiv.), CH_2Cl_2, rt, 2 h	**~33%** + impurity
2	aniline (6.0 equiv.), $Pd(PPh_3)_4$ (0.2 equiv.), THF, rt, 2 h	traces

Figure 9 shows the chromatograms of the two myxovalargins-D,L. The chromatogram of the synthetic product is depicted in the middle, while that of the natural myxovalargin is displayed at the bottom. It is obvious that both compounds have the same retention time. Thus, in agreement with the gene cluster analysis, it was again shown that the originally published configuration needs to be corrected to D-valine at position 7 and L-valine at position 10 (see Section A1.4). In addition, the upper part of Figure 9 displays a chromatogram corresponding to a molecule with a mass *m/z* 830 (doubly ionized) and, accordingly, 1658 u. This is a mass with 18 u less compared to the myxovalargin with 1676 u. The retention time of the compound is very similar to that of the myxovalargin; indeed, the peaks overlap. This indicates that the compound is a very similar peptide. The mass, for example, would suggest a peptide in which the tertiary alcohol was eliminated at the hydroxyvaline, but neither MS nor NMR analyses allow a clear conclusion here. However, since the two compounds already elute almost simultaneously at the QTOF, it was not possible to separate them by HPLC. Therefore, global deprotection with the last milligram was tested a second time by

using aniline as scavenger, since this gave very good results in the group's cystobactamid project,[49] whereas myxovalargin could only be obtained in traces. Since the material did not suffice for further optimization, the synthesis of myxovalargin was completed with the result that, despite a minor impurity, the stereochemistry determined by gene cluster analysis could be confirmed beyond doubt.

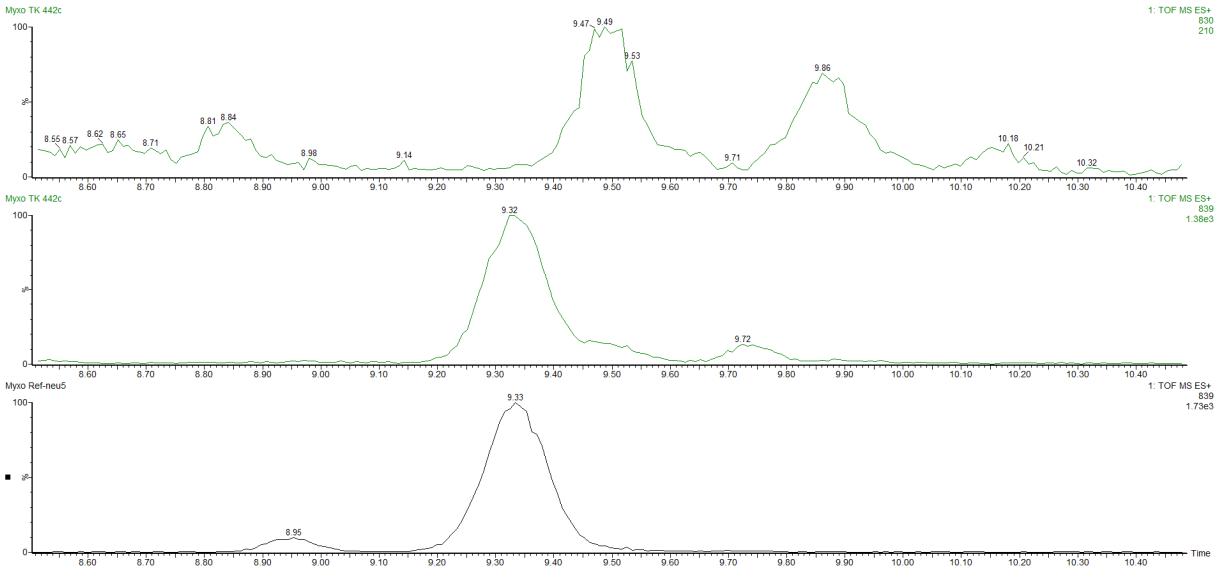
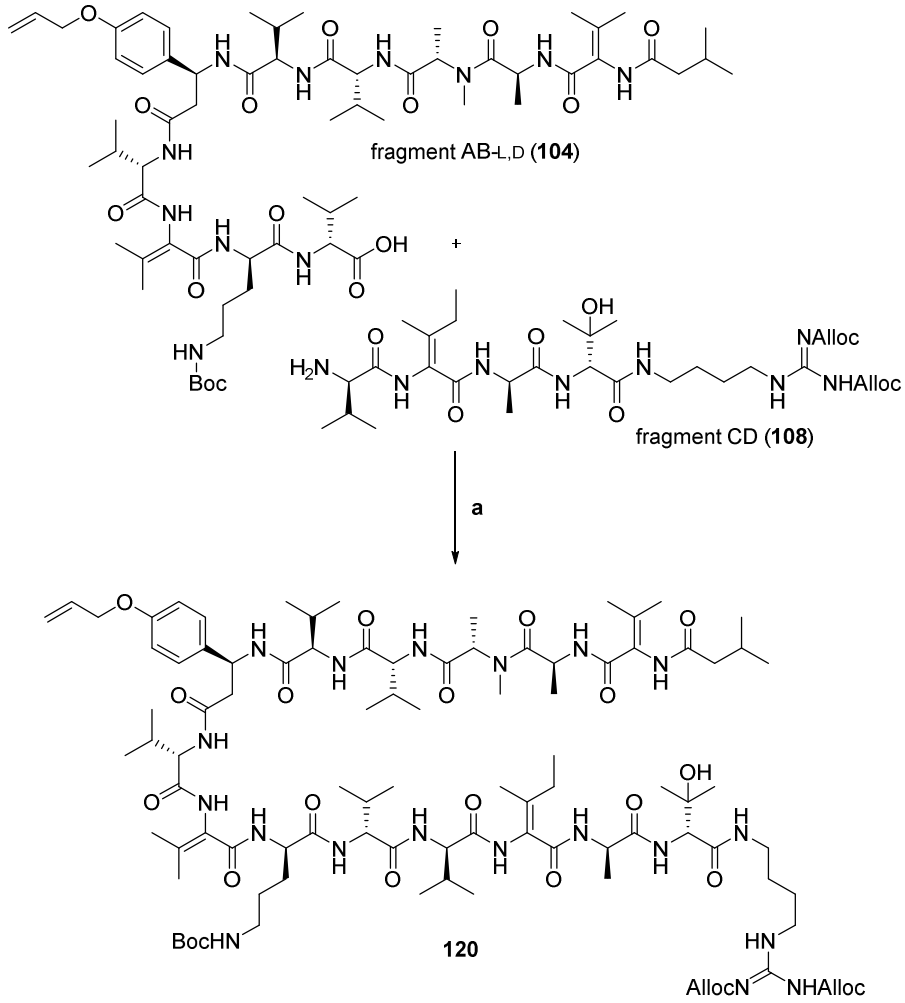


Figure 9: Mass spectrometric comparison of the synthesized (middle) with myxovalargin-D,L (**10**) isolated from the supernatant of a bacterial culture (bottom). This chromatogram shows the same stereochemistry of the two molecules. The upper part shows a chromatogram of an impurity with a similar retention time.

A3.5.2 Synthesis of incorrectly published Myxovalargin-L,D

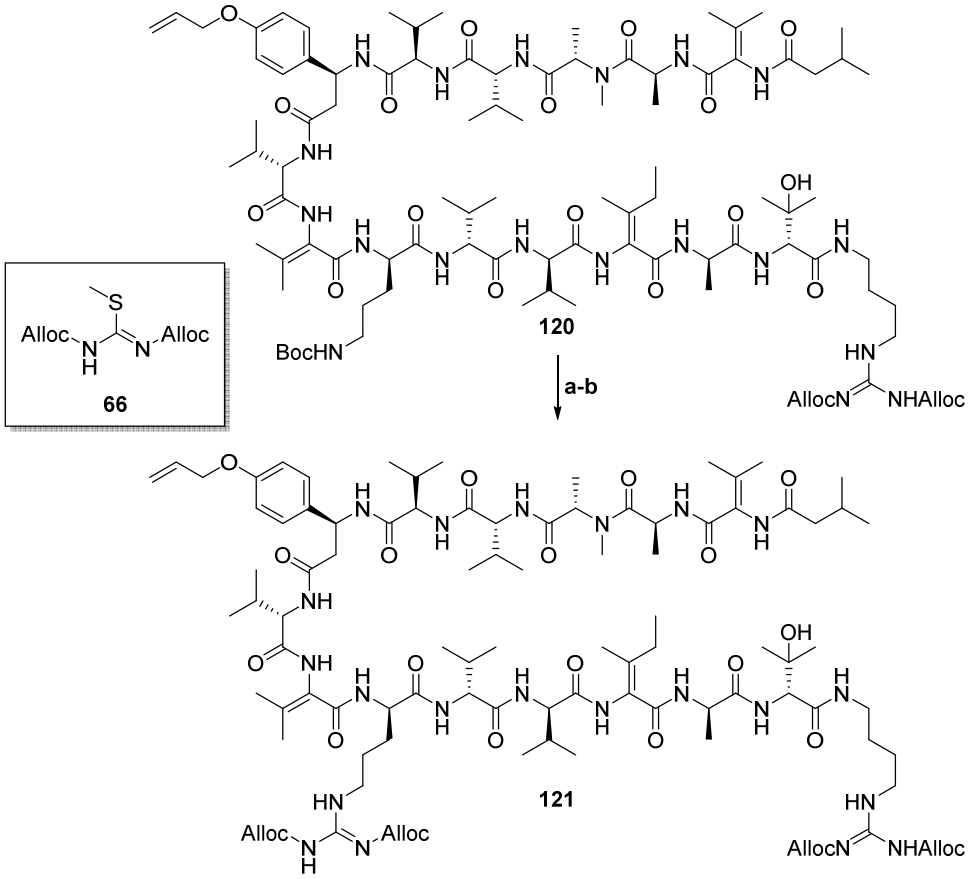
For an ultimate structural proof, myxovalargin-L,D (**11**) should also be prepared with the incorrectly published stereochemistry containing L-valine at position 7 and D-valine at position 10. For this purpose, the coupling of fragment AB-L,D (**104**) with fragment DE (**108**) was performed under the already established conditions. Thus, using HOAt, HATU, and DIPEA, the myxovalargin-L,D backbone **120** was obtained in 58% yield (Scheme 30).

[49] T. Planke, doctoral dissertation, Leibniz Universität Hannover, Hannover **2019**.



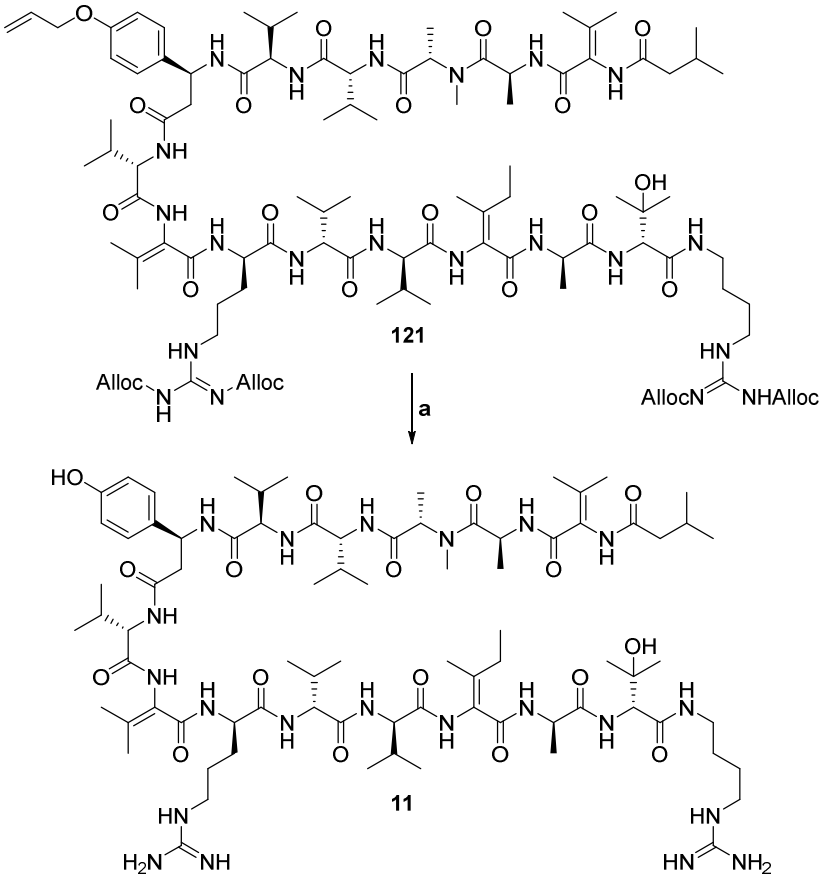
Scheme 30: Coupling of fragments AB-L,D (**104**) and CD (**108**) towards the incorrectly published myxovalargin-L,D backbone (**120**): a) HOAt (2.5 equiv.), HATU (2.5 equiv.), DIPEA (5.0 equiv.), DMF, 0 °C → rt, 20 h, 58%.

With the myxovalargin-L,D backbone **120** in hand, Boc-deprotection and subsequent guanidinylation were to be performed (Scheme 31). For this purpose, deprotection was repeated with already established conditions using LEWIS acid trimethylsilyl iodide (TMSI) in dichloromethane. For guanidinylation, Alloc-protected methylisothiourea **66** and triethylamine were employed in an established manner. Thus, the myxovalargin-L,D precursor **121** was obtained within two steps in 41% yield.



Scheme 31: Boc-deprotection and subsequent guanidinylation towards protected myxovalargin-L,D (**121**): a) TMSI, CH_2Cl_2, rt, 10 min; b) **66**, Et_3N, THF, rt, 12 h, 41% o2s.

Since late-stage coupling yields are not particularly good, it was not possible to re-optimize the global deprotection conditions at this point. Therefore, deprotection was performed as previously described with $Pd(PPh_3)_4$ and phenylsilane anticipating that a shorter reaction time would not cause elimination (Scheme 32). Re-examination with high-resolution mass spectrometry showed that the second synthetically prepared myxovalargin-L,D (**11**) and the compound isolated from the bacterial culture supernatant were not the same molecules. Figure 10 shows the chromatograms of the two myxovalargins. The central chromatogram shows the synthetic product **11** while that of the natural myxovalargin-D,L (**10**) is displayed at the bottom, revealing that the two retention times show significant differences (9.55 and 9.28 min). Noteworthy, the high-resolution masses are identical. Thus, in agreement with the gene cluster analysis and the results of the first synthesis, it was again demonstrated that the originally published configuration with L-valine in position 7 and D-valine in position 10 was incorrect (see Section A1.4).



Scheme 32: Global deprotection towards the incorrectly published myxovalargin-L,D (**11**): $PhSiH_3$ (6.0 equiv.), $Pd(PPh_3)_4$ (0.2 equiv.), CH_2Cl_2, rt, 30 min, 61% (1:1 mixture of myxovalargin-L,D (**11**) and fragment with *m/z* +2).

It should also be noted that while no mass peak with a mass of 830 was found, an impurity with a mass of *m/z* 840 (doubly ionized) was detected, belonging to a compound with a mass of 1678 u, which would thus be 2 u heavier than myxovalargin. It is apparent that the retention times of myxovalargin-L,D (**11**) and the compound *m/z* 840 are identical, suggesting that this is a markedly similar molecule, possibly one with one less double bond. However, neither NMR nor MS analysis permit a more definite conclusion. Nevertheless, it could be proven again that the originally published stereochemistry needs to be revised.

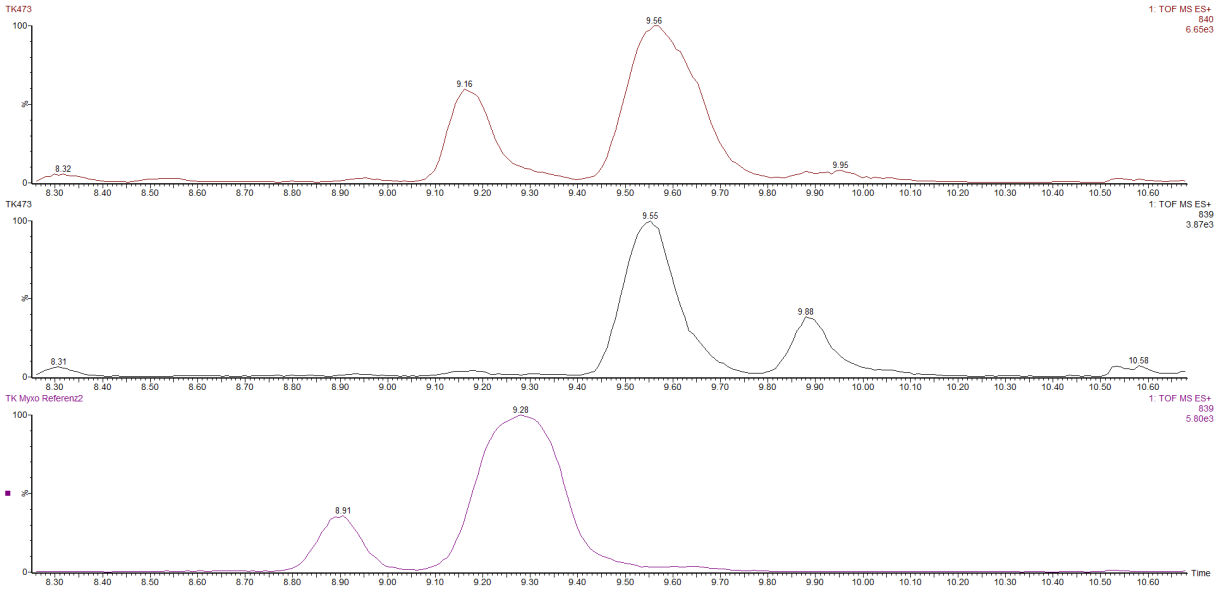


Figure 10: Mass spectrometric comparison of the synthesized, incorrectly published myxovalargin-L,D (**11**, middle) with myxovalargin-D,L (**10**) isolated from the supernatant of a bacterial culture (bottom). This chromatogram shows that structurally they are not the same molecule. It is concluded that the stereochemistry differs. The upper part shows a structural similar compound of myxovalargin-L,D.

A3.6 Synthetic Studies towards Derivatives of Myxovalargin

Since a possible access to myxovalargin was found, simplified derivatives should now be synthesized. For this purpose, the amino acids that were difficult to prepare, such as dehydroamino acids and β-tyrosine, were to be replaced by their natural representatives valine and isoleucine in both configurations, respectively, and α-L-tyrosine (Figure 11). In addition, late guanidinylation was to be partially omitted. The aim was to investigate the influence of these amino acids on cytotoxicity in the hope of obtaining a compound with the same antibiotic properties but with lower toxicity.

To this end, the syntheses of the individual derivatized building blocks is described below. The aim of this work was the synthesis of derivatives from the individual fragments according to the modular principle, following the two syntheses described before.

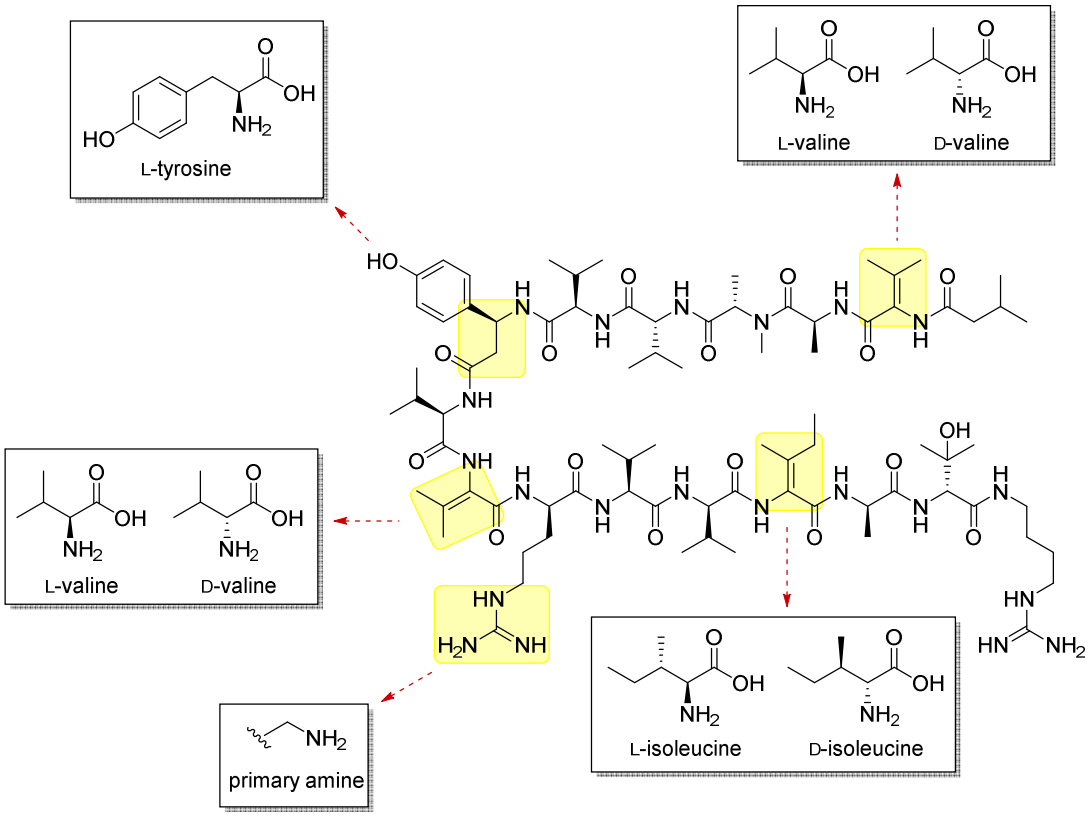


Figure 11: For derivatization of myxovalargin, amino acids that were difficult to prepare, such as dehydroamino acids and *β*-tyrosine, were to be replaced by their natural representatives.

A3.6.1 Studies on the Synthesis of an alternative Fragment A

First, a slightly modified fragment A-*α*-Tyr (**122**) should be prepared containing the natural *α*-L-tyrosine instead of the previously employed *β*-tyrosine. Dehydrovaline should initially be retained in this fragment (Figure12).

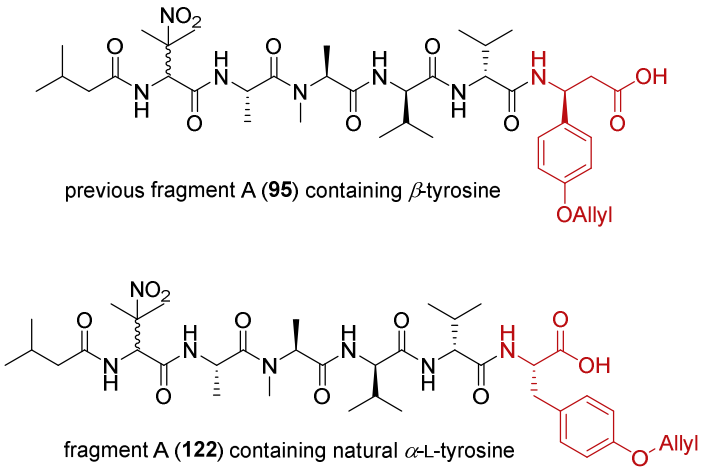
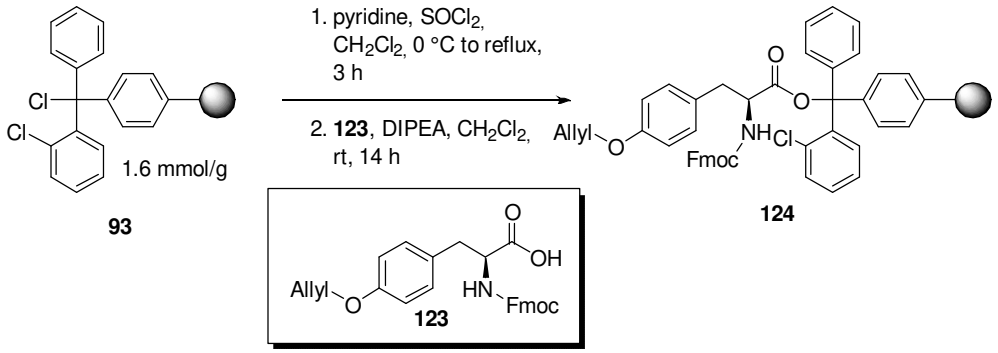


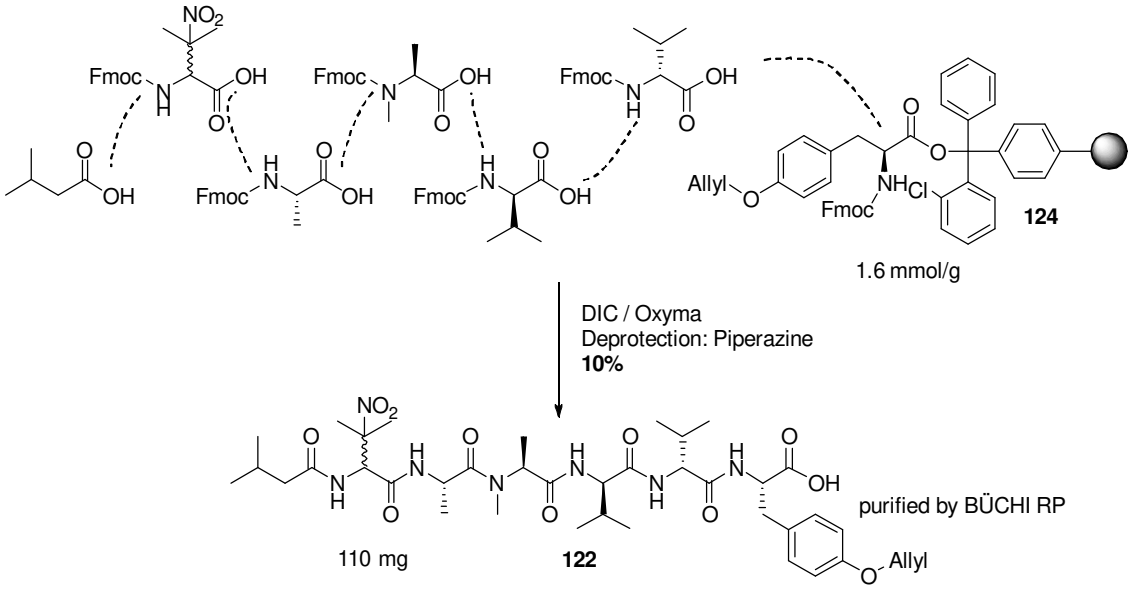
Figure 12: Comparison of *α*- and *β*-tyrosine-containing A-fragments **95** and **122**.

Following the solid-phase peptide synthesis of fragment A (**95**, see section A3.3.3), the corresponding fragment A-α-Tyr (**122**) with the natural α-L-tyrosine **123** instead of β-tyrosine was now to be prepared by the automated peptide synthesizer.[50] For this purpose, the 2-chlorotrityl chloride resin **93** was pre-loaded with the commercially available Allyl- and Fmoc-protected α-L-tyrosine **84** as before (Scheme 33).



Scheme 33: Pre-loading of protected α-L-tyrosine **123** on 2-chlorotrityl chloride resin (**93**).

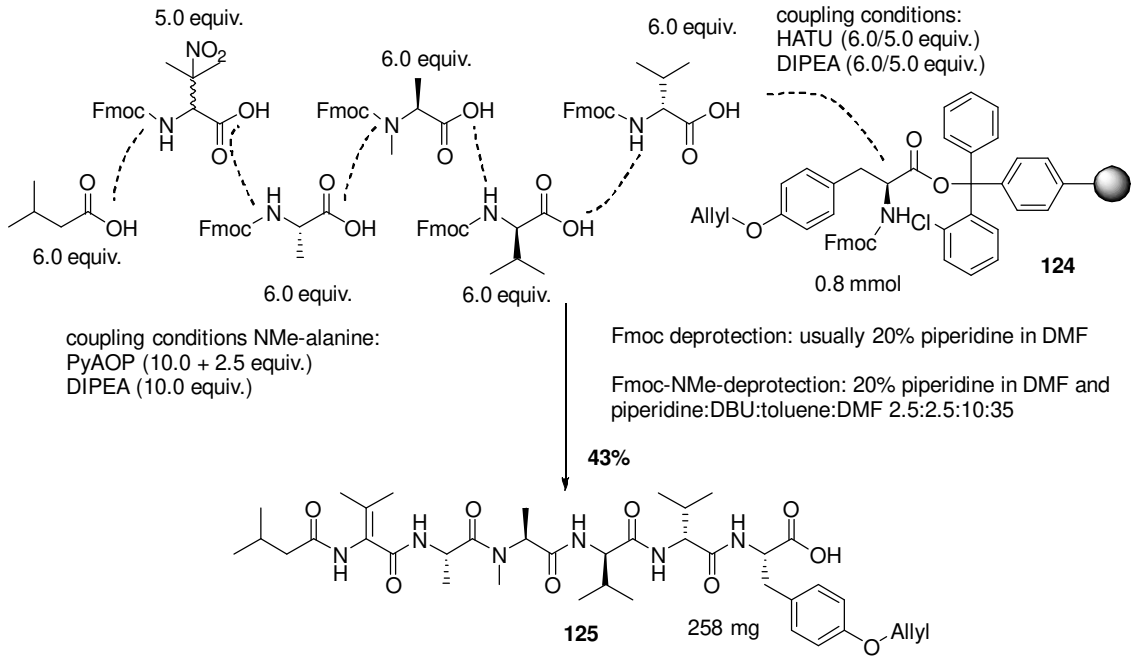
As previously described, the microwave-assisted automated peptide synthesizer was now loaded with the required amino acids and the pre-loaded resin **124** (Scheme 34). The peptide synthesis was performed with DIC/Oxyma and piperazine as Fmoc-deprotection agent. Subsequent purification by reversed-phase column chromatography yielded only 110 mg corresponding to a very low yield of 10%. As it turned out later, this was due to an internal defect in the device.



Scheme 34: Solid-phase synthesis of α-L-tyrosine containing fragment A-α-Tyr (**122**) by the automated peptide synthesizer.

[50] The synthesis was performed with the assistance of Dr. MAIK SIEBKE and bachelor student MIKAIL ÖZBASI (as part of his bachelor thesis) on the peptide synthesizer of Prof. Dr. OLIVER PLETTENBURG'S research group.

However, due to time constraints, it was not possible to wait several months for fragment A-*α*-Tyr (**122**), so an alternative solid-phase method was chosen for the synthesis (Scheme 35). This time, the couplings were performed manually in the classical manner using a vortexer-based setup under the guidance of DR. HAYDN BALL from the PLETTENBURG group. Since the couplings did not proceed under microwave irradiation, HATU and DIPEA were chosen for the couplings instead of Oxyma. For the difficult *N*-methyl coupling, PyAOP was used according to a protocol from GIRALT.[51] The respective amino acid, coupling reagent, and DIPEA were premixed before being added to the resin. In the case of nitrovaline, cleavage of the nitro group was observed during this step, which might have been avoided by cooling of the mixture. However, since this was rather conducive to further synthesis, it had no consequence. After subsequent purification, 258 mg of nitro-eliminated fragment A-*α*-Tyr (**125**) could finally be isolated, corresponding to a yield of 43%.



Scheme 35: Manually performed solid-phase synthesis for derivatization of fragment A-*α*-Tyr (**125**).

[51] M. Teixidó, F. Albericio, E. Giralt, *J. Peptide Res.* **2005**, *65*, 153-166.

A3.6.2 Studies on the Syntheses of Derivatives of Fragment B

Next, derivatives of fragment B-D,L (**63**) were to be prepared. For this purpose, the dehydrovaline was replaced by L- or D-valine, respectively (Figure 13).

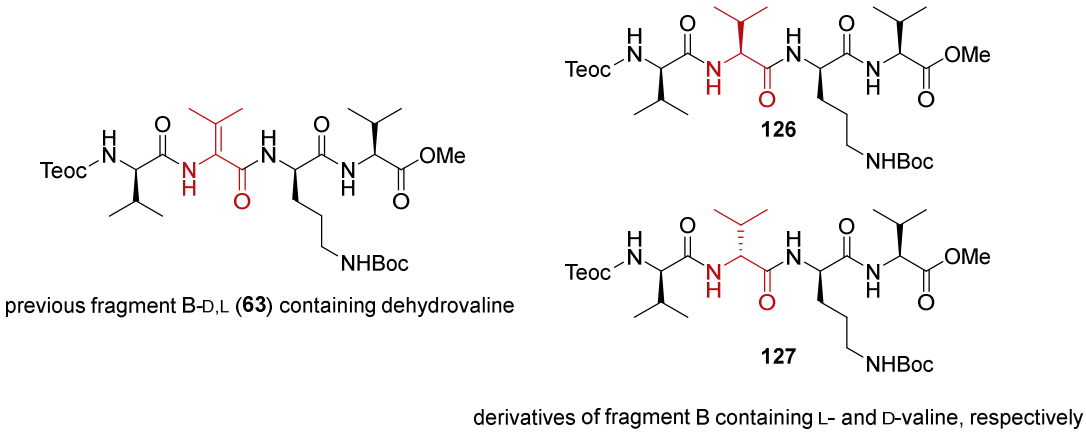
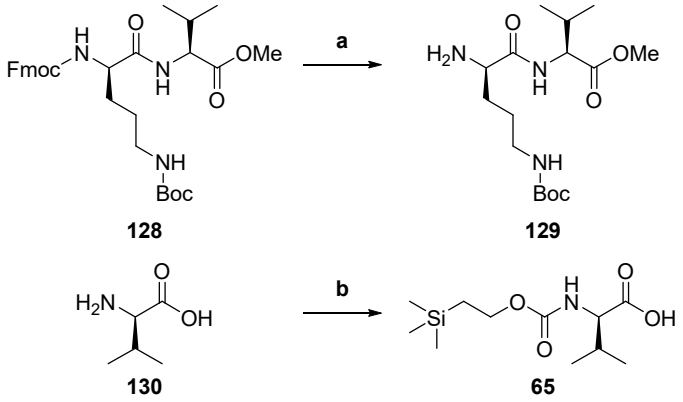


Figure 13: Comparison of different valine-containing fragments B.

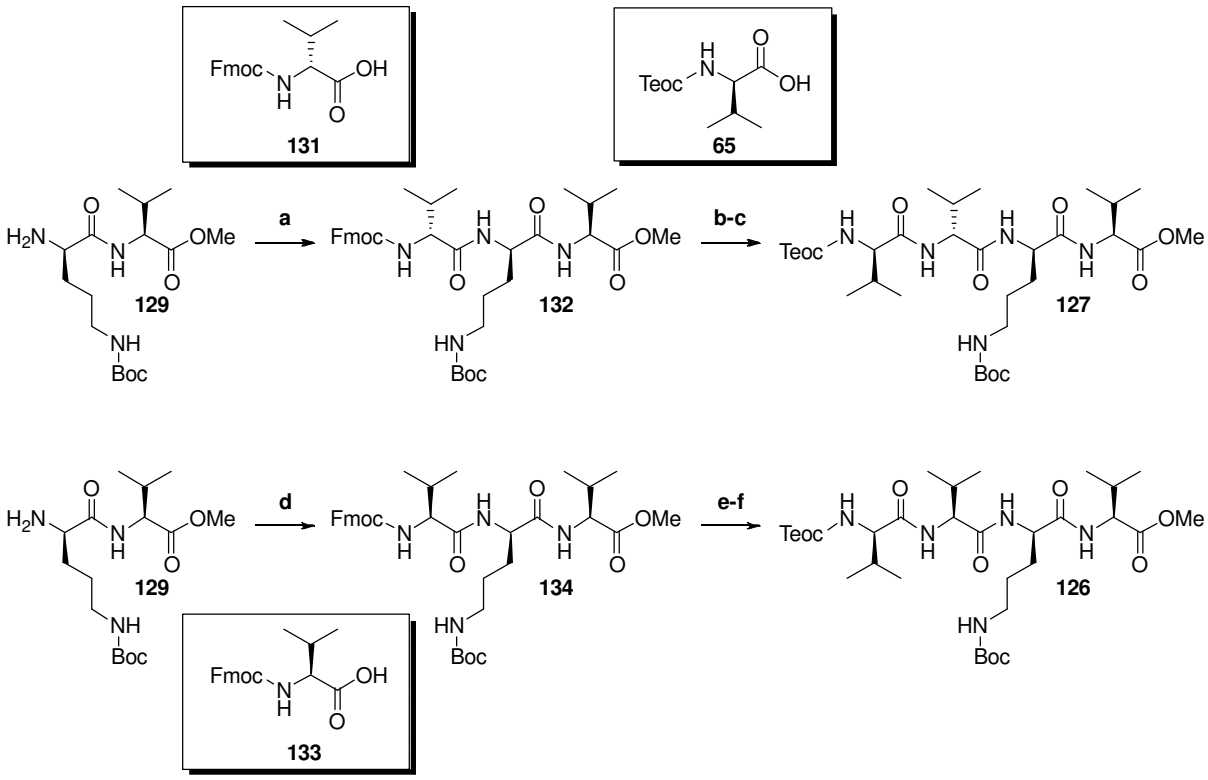
For this purpose, however, two building blocks first had to be synthesized as part of some preliminary work (Scheme 36). First, Fmoc-deprotection was performed on the starting building block, dipeptide **128** from the SIEBKE stock, according to the conditions of GILLE and SIEBKE. By using tris(2-amino-ethyl)amine, free amine **129** was obtained in quantitative yield. In addition, D-valine (**130**) was protected with TeocOSu in 89% yield for use in subsequent syntheses.[34,36]



Scheme 36: Fmoc-deprotection of dipeptide **128** and synthesis of Teoc-protected D-valine (**65**): a) tris(2-amino-ethyl)amine, CH_2Cl_2, 0 °C → rt, 19 h, 99%; b) TeocOSu, Et_3N, H_2O/1.4-dioxane (1:1), rt, 16 h, 89%.

With the appropriate building blocks in hand, the two tetrapeptides **127** and **126** were smoothly prepared following the synthesis of the original fragment B.[34,36] For this purpose, the free amine **129** was first coupled with Fmoc-protected D- (**131**) or L-valine (**133**) to form the respective tripeptides **132** and **134** (Scheme 37). Yields between 32% (**132**) and 48% (**134**) were obtained with HOBt, EDC·HCl, and DIPEA, respectively. Subsequent quantitative Fmoc-deprotection and final coupling

with Teoc-protected D-valine **65** using the HOAt/EDC/DIPEA system provided tetrapeptides **127** (59%) and **126** (78%) thereby resulting in two new derivatives of fragment B.



Scheme 37: Synthesis of fragment B's derivatives **127** and **126**: a) **131**, HOBt, EDC·HCl, DIPEA, CH_2Cl_2, 0 °C → rt, 22 h, 32%; b) Me_2NH, DMF, rt, quant.; c) **65**, HOAt, EDC·HCl, DIPEA, CH_2Cl_2, DMF, 0 °C → rt, 59%; d) **133**, HOBt, EDC·HCl, DIPEA, CH_2Cl_2, 0 °C → rt, 22 h, 48%; e) Me_2NH, DMF, rt, quant.; f) **65**, HOAt, EDC·HCl, DIPEA, CH_2Cl_2, DMF, 0 °C → rt, 78%.

A3.6.3 Studies on the Synthesis of an alternative Fragment C

Subsequently, for a derivatization of fragment C (**106**), dehydroisoleucine was to be replaced by the corresponding natural isoleucine (Figure 14). For cost reasons, only L-isoleucine was used initially.

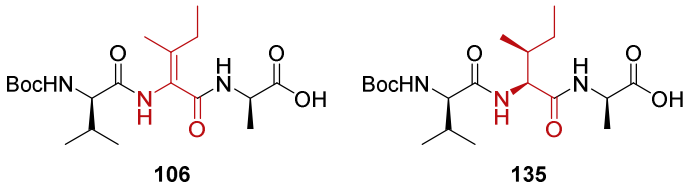
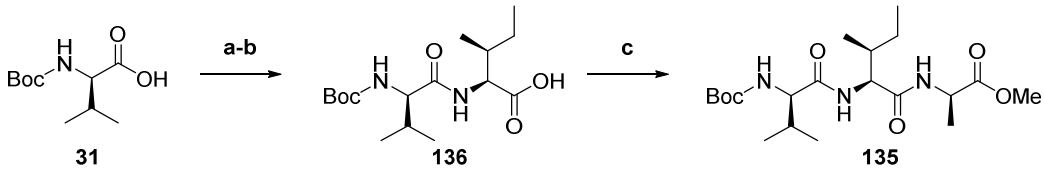


Figure 14: Potential derivative **135** of fragment C (**106**).

For this purpose, starting from Boc-protected D-valine (**31**) and L-isoleucine methyl ester hydrochloride, HOBt/EDC·HCl based peptide coupling was carried out following SIEBKE'S and GILLE'S syntheses of fragment D. Subsequent saponification gave dipeptide **136** in 78% yield over

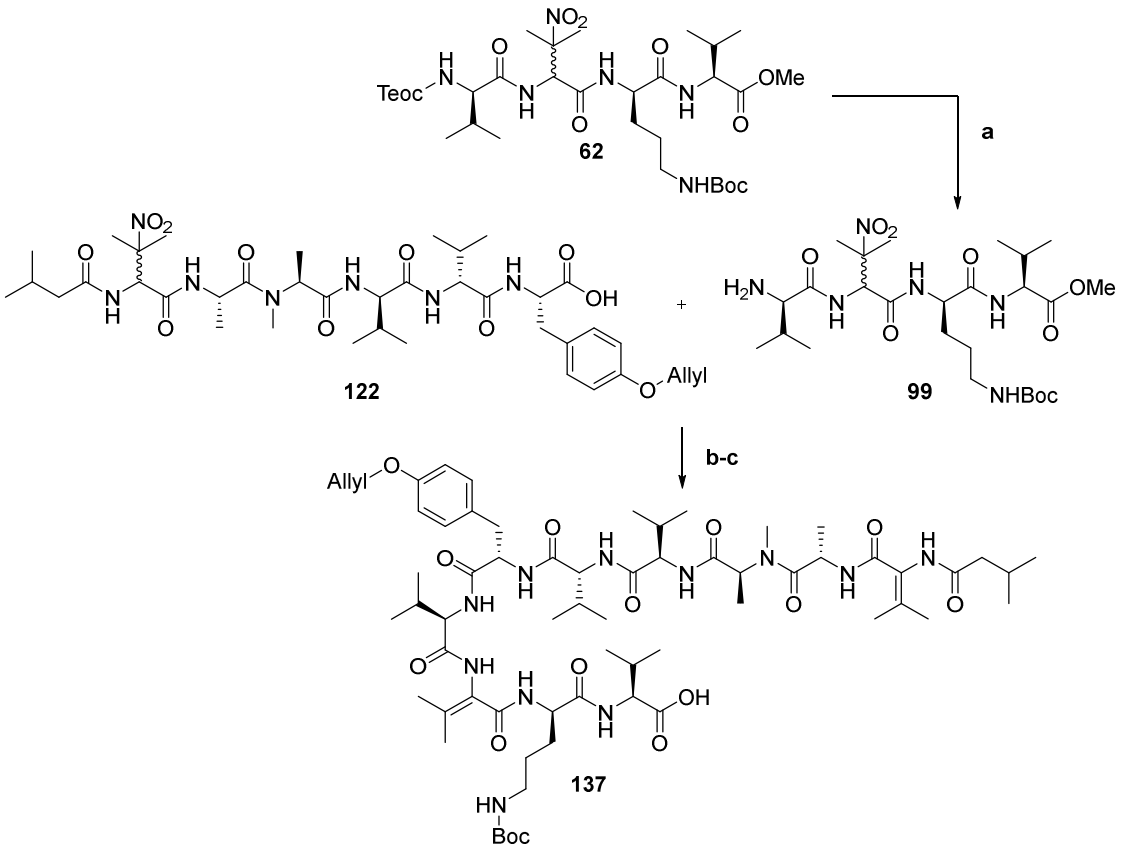
two steps. Coupling with D-alanine methyl ester hydrochloride thereafter afforded modified fragment C (**135**) in 84% yield (Scheme 38).



Scheme 38: Synthesis of L-isoleucine containing fragment C (**135**): a) L-isoleucine methyl ester hydrochloride, HOBt, EDC·HCl, DIPEA, CH_2Cl_2, 0 °C → rt, 20 h, 78%; b) LiOH (1M in H_2O), THF, 0 °C, 18 h, quant.; c) D-alanine methyl ester hydrochloride, HOBt, EDC·HCl, DIPEA, CH_2Cl_2, 0 °C → rt, 4 d, 84%.

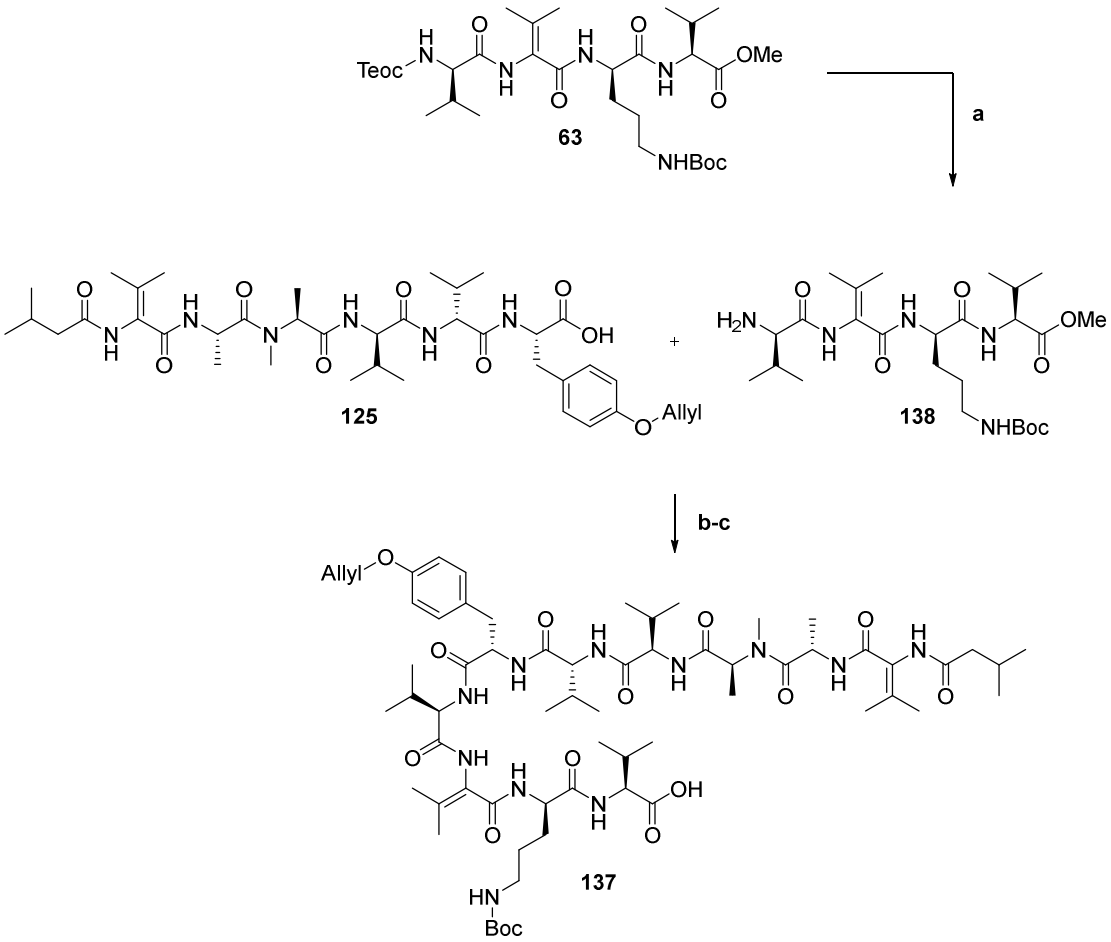
A3.6.4 Studies on the Synthesis of an alternative Fragment AB

The first derivative to be prepared was one in which only fragment A was exchanged. For this purpose, the derivatized fragment A-*α*-Tyr (**122**) from the peptide synthesizer was coupled with the original, deprotected fragment B-D,L (**99**). Subsequent saponification and nitro-elimination provided derivatized fragment AB-*α*-Tyr (**137**) in 20% yield over two steps (Scheme 39).



Scheme 39: Synthesis of fragment AB-*α*-Tyr (**137**): a) TBAF (1M in THF), THF, rt, 20 h, 64%; b) HOAt, PyAOP, DIPEA, DMF, 0 °C → rt, 24 h, 20%; c) LiOH (1M), THF, 0 °C → rt, quant.

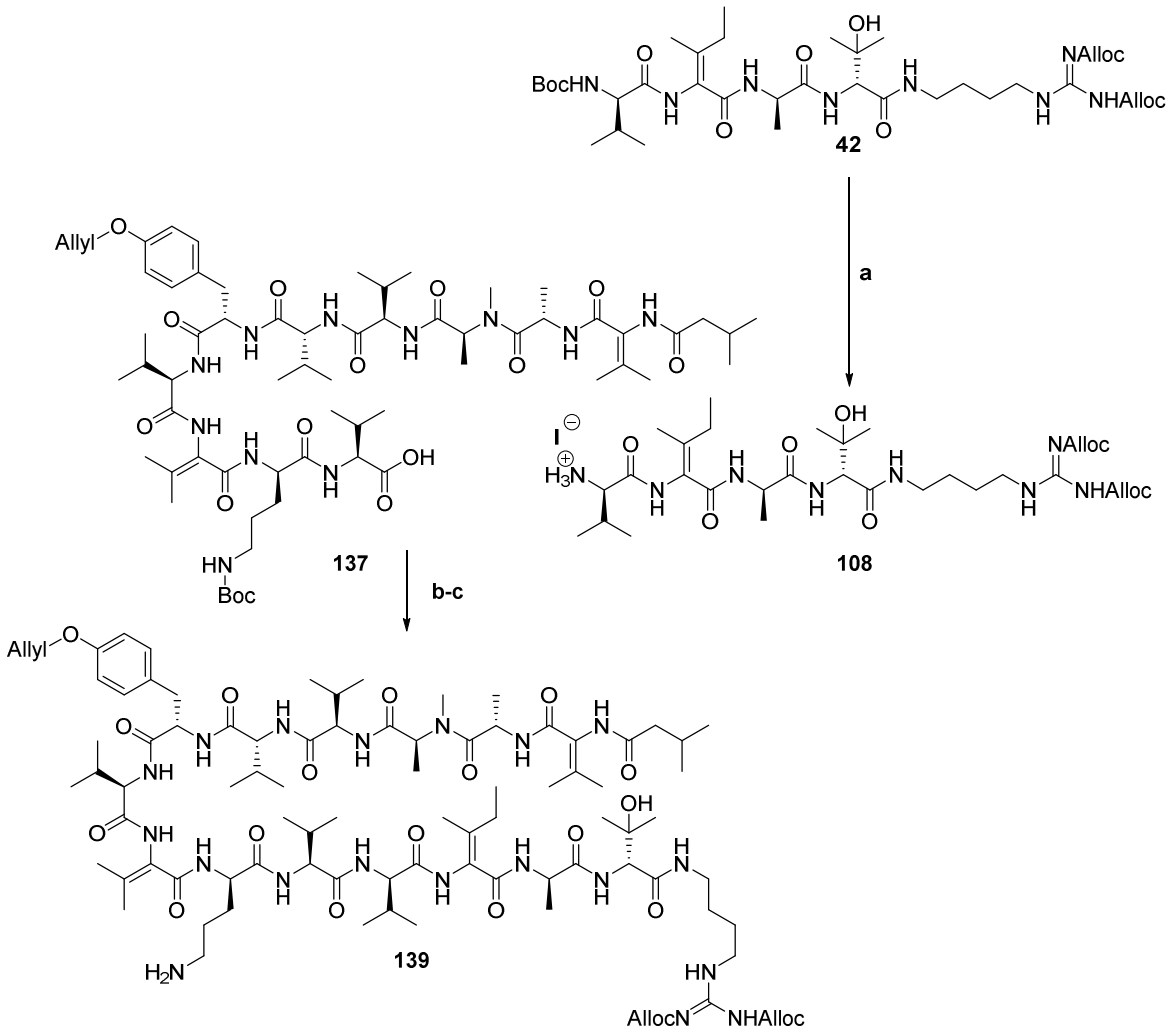
Fragment A-α-Tyr **125** obtained from manual solid-phase synthesis was converted in the same way. Here, fragment B-D,L (**63**) from SIEBKE'S stock was employed, which already contained dehydrovaline instead of nitrovaline. Interestingly, Teoc-deprotection of tetrapeptide **63** gave a much better yield compared to the corresponding compound **62** with nitrovaline. Finally, coupling and saponification yielded the derivatized fragment AB-α-Tyr (**137**) once again (Scheme 40).



Scheme 40: Alternative synthesis of fragment AB-α-Tyr (**137**): a) TBAF (1M in THF), THF, rt, 20 h, quant.; b) HOAt, PyAOP, DIPEA, DMF, 0 °C → rt, 24 h, 53%; c) LiOH (1M), THF, 0 °C → rt, 24%.

A3.6.5 Studies on the Synthesis towards a Derivative of Myxovalargin

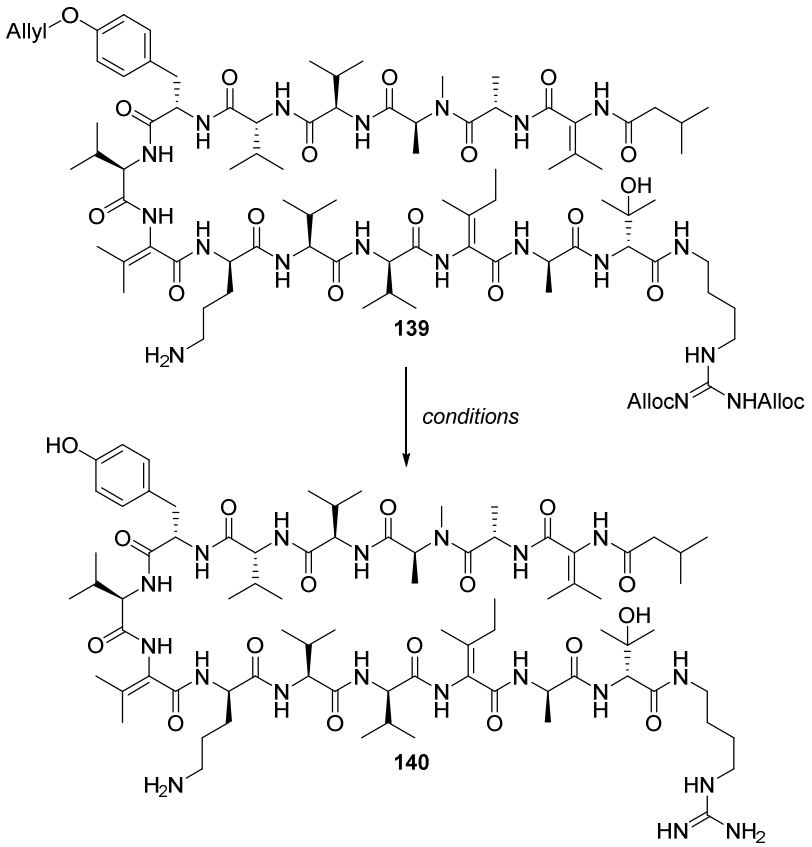
With fragment AB-α-Tyr (**137**) in hand, synthesis of the large peptide backbone **139** was now addressed (Scheme 41). As previously described, fragment AB-α-Tyr (**137**) was coupled to the original Boc-protected fragment DE (**108**) under HOAt/HATU/DIPEA conditions, and subsequent TMSI-mediated Boc-deprotection yielded the myxovalargin-α-Tyr backbone **139** in 17% yield over two steps.



Scheme 41: Fragment coupling towards protected myxovalargin-*α*-Tyr **139**: a) TMSI, CH_2Cl_2, rt, 10 min, quant.; b) HOAt, HATU, DIPEA, DMF, 0 °C → rt, 17 h, 17%; c) TMSI, CH_2Cl_2, 10 min, rt, quant.

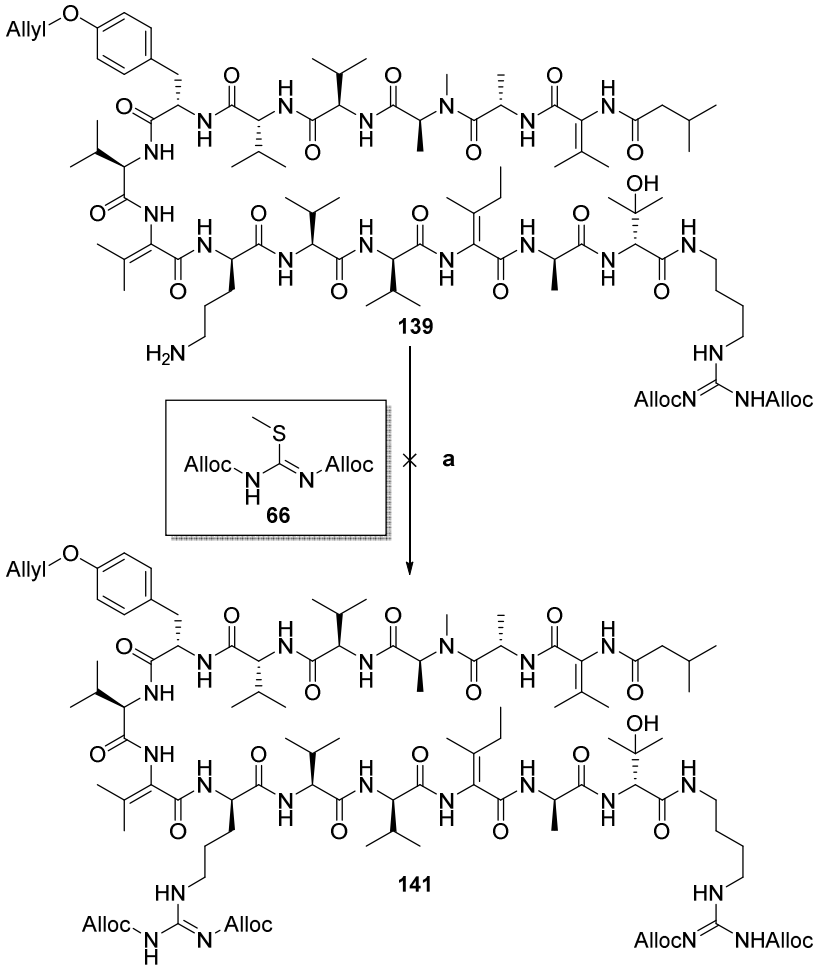
Subsequently, different global Allyl- and Alloc-deprotection conditions were investigated (Table 12). Since the global deprotection conditions in the previous two myxovalargin syntheses led to byproducts, this time the studies were carried out with 2.0 equiv. phenylsilane and 0.2 equiv. $Pd(PPh_3)_4$ (Entry 1); however, no conversion was observed. The use of six equivalents of phenylsilane and an extended reaction time also resulted in no deprotection, allowing the starting material to be completely reisolated (Entry 2). Subsequently, K_2CO_3/MeOH were employed again as scavenger. This resulted in a yield of 38%, but a more accurate mass spectrometric analysis after only 30 minutes revealed a diastereomer mixture of 1.0:0.9:0.8. (Entry 3) Since it could not be determined which compound represented the desired one, a new experiment used aniline as scavenger. Irritatingly, a diastereomer mixture of 0.9:1.0:0.8 was detected here after only 30 minutes (Entry 4). Since this also contradicted the results under Entry 3 and no more starting material was available, it was decided to terminate the investigations on this derivative.

Table 12: Screening of conditions for global deprotection towards *α*-Tyr derivative **140**.



entry	conditions	result
1	$PhSiH_3$ (2.0 equiv.), $Pd(PPh_3)_4$ (0.2 equiv.), CH_2Cl_2, rt, 2 h	no conversion
2	$PhSiH_3$ (6.0 equiv.), $Pd(PPh_3)_4$ (0.2 equiv.), CH_2Cl_2, rt, 2-20 h	no conversion
3	K_2CO_3 (6.0 equiv.), $Pd(PPh_3)_4$ (0.2 equiv.), MeOH, rt, 30 min	**38%**, *d.r.* = 1.0:0.9:0.8
4	aniline (3.3 equiv.), $Pd(PPh_3)_4$ (0.2 equiv.), THF, rt, 30 min	traces, *d.r.* = 0.9:1.0:0.8

Nevertheless, as a last attempt, guanidinylation of *α*-Tyr derivative **139** was sought, since it was assumed that racemization might be related to the free amine, as this was the only significant difference from the two previously synthesized myxovalargins, in which side products appeared but no epimerization of the stereocenters was detectable. Thus, under the already established conditions using methylisothiourea and triethylamine in THF, derivative **141** was to be prepared (Scheme 42). However, this only led to decomposition of the *α*-Tyr derivative backbone **139**. Since the derivatization thus proved to be much more complex and time-consuming than originally assumed, this derivatization approach was discontinued at this point for economic reasons.



Scheme 42: Attempted guanidinylation of *α*-Tyr derivative backbone **139**: a) **66**, Et_3N, THF, rt, 12 h, no conversion.

A4 Conclusions and Future Work

The aim of this work was to complete the total synthesis of myxovalargin commenced by GILLE[34] and SIEBKE[36] in order to obtain a final structural proof. This was required as the originally published configurations of valines at positions 7 and 10 of the myxovalargin backbone differed from recent findings based on a gene cluster analysis performed at HIPS. For this purpose, the two myxovalargins **10** and **11** depicted in Figure 15 were to be prepared and subsequently compared to the natural product obtained from the bacterial culture supernatant during a large-scale fermentation.

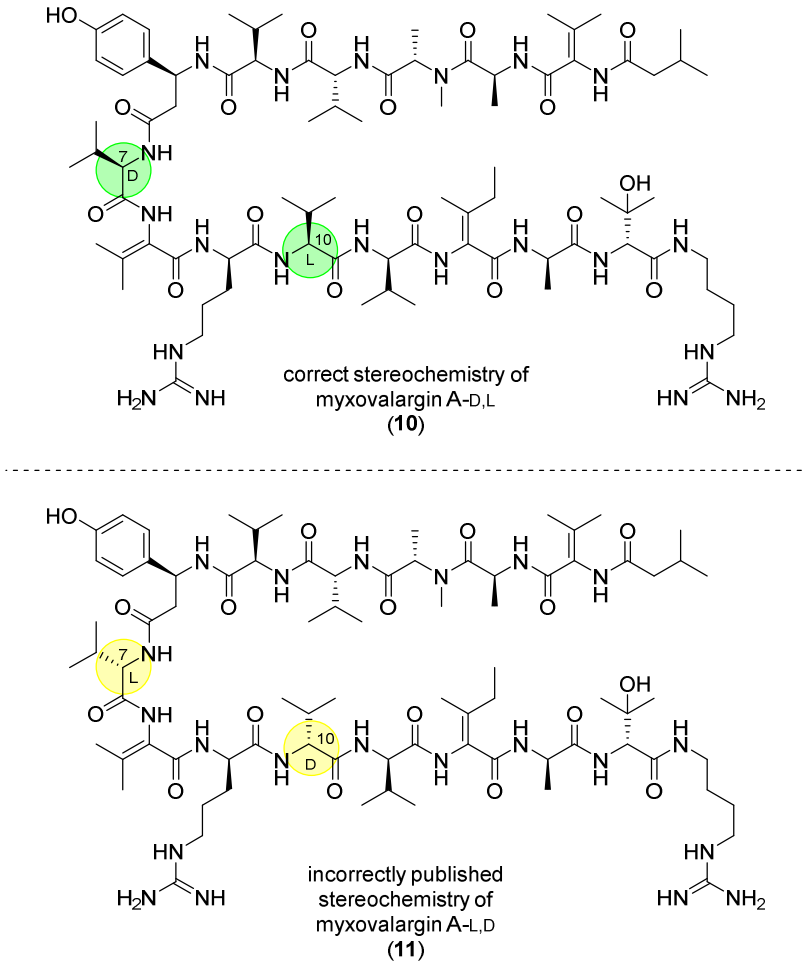
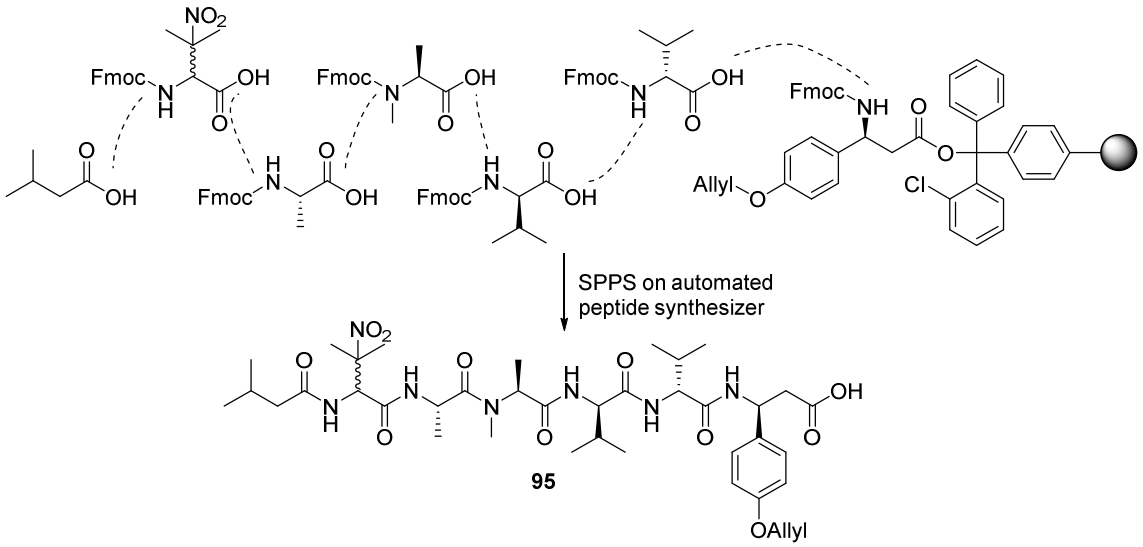


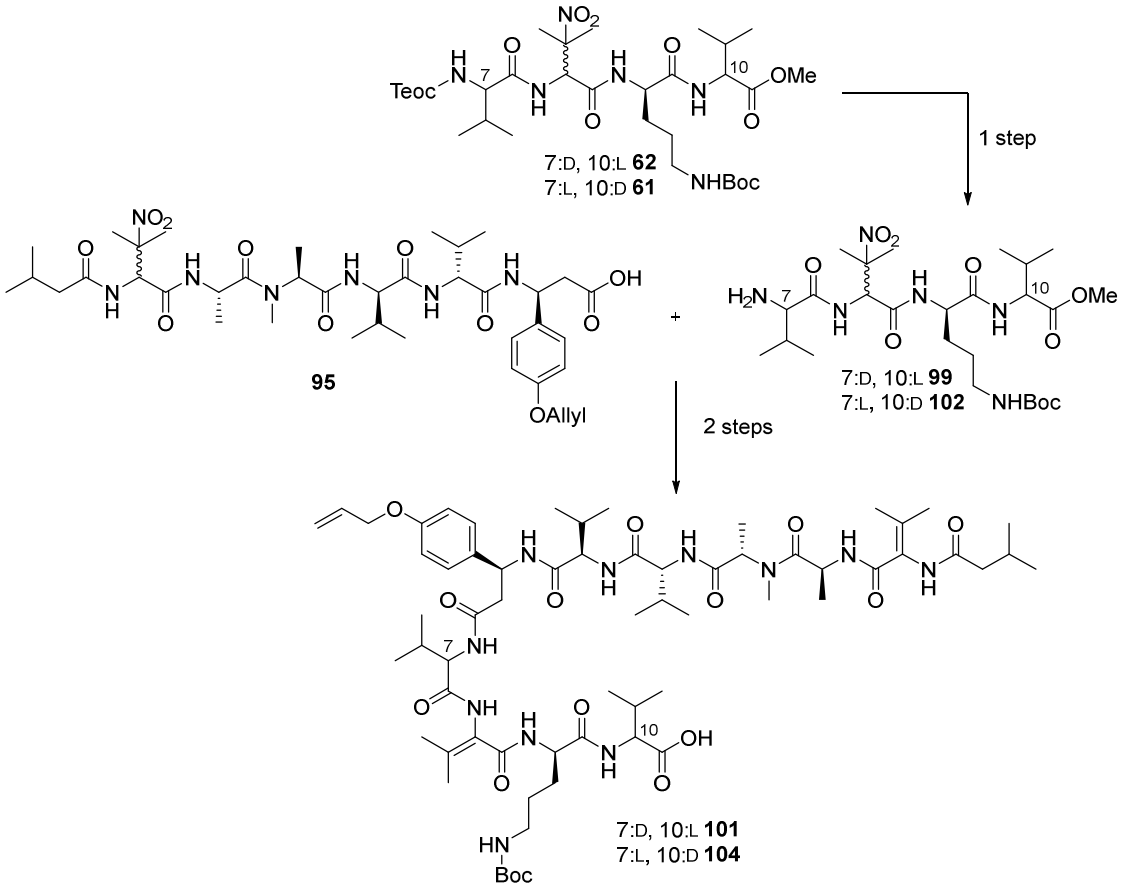
Figure 15: Structures of the two myxovalargins **10** and **11** to be prepared.

As part of this effort, the synthesis of fragment A (**95**) was switched to solid-phase synthesis due to strong epimerization in solution-phase, which was excellently achieved using an automated peptide synthesizer (Scheme 43).



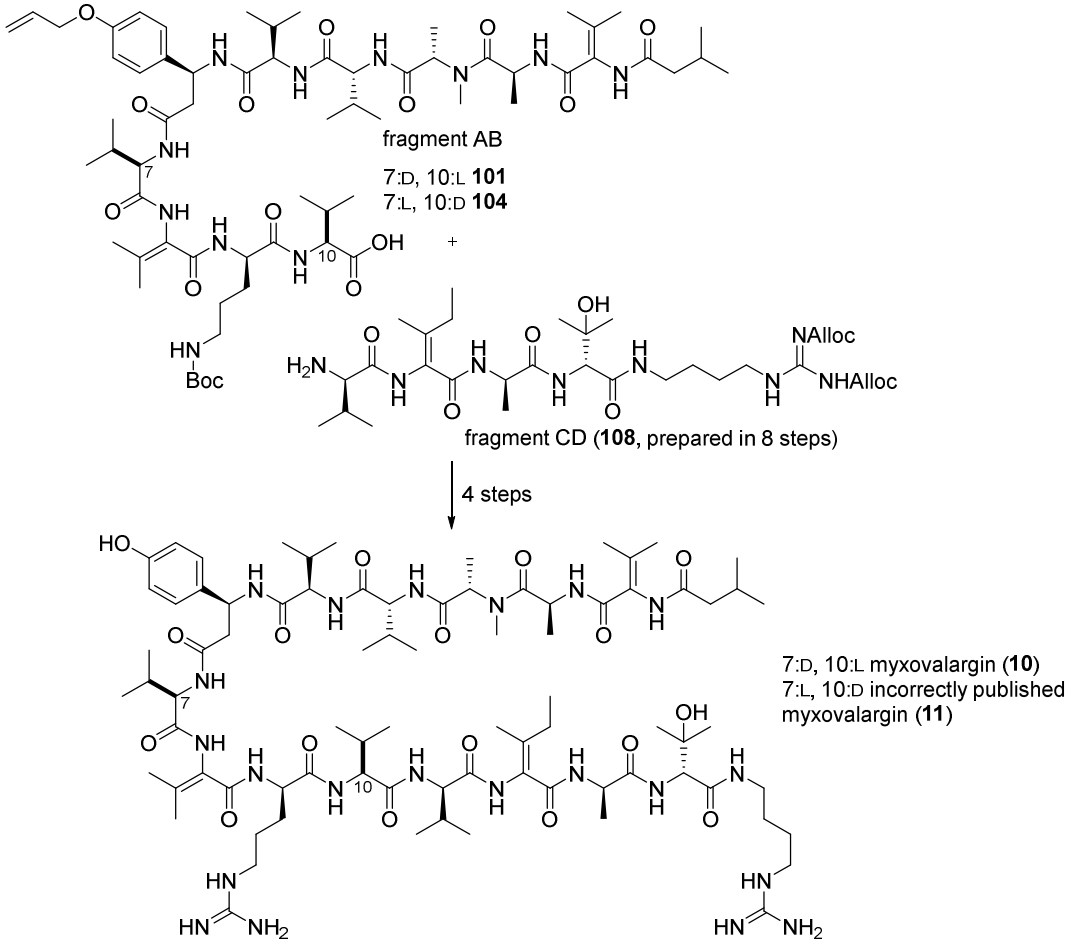
Scheme 43: Solid-phase synthesis of fragment A (**95**).

Subsequent coupling of fragments A (**95**) and B (syntheses of the latter had already been sufficiently optimized by GILLE[34] and SIEBKE[36]), and simultaneous nitro-elimination and saponification yielded peptides **101** and **104** via two steps. This could be realized for the preparations of both desired AB-backbones (Scheme 44).



Scheme 44: Synthesis of both fragments AB (**101**) and (**104**).

Subsequent linkage of both fragments AB-D,L (**101**) and AB-L,D (**104**) with CD (**108**), which synthesis itself involved eight steps, yielded the two myxovalargins **10** and **11** in four steps each (Scheme 45). Mass spectrometric studies revealed impurities in both cases that were not separable by preparative HPLC, but HRMS comparison of the two synthesized myxovalargins with the natural product isolated from the bacterial supernatant revealed without doubt the same stereochemistry in the case of the first synthesized myxovalargin-D,L (**10**). Thus, the two total syntheses performed in this work confirmed the stereochemistry determined from the gene cluster analysis (D-valine in position 7 and L-valine in position 10) and with this result the project could be successfully completed after a total of eleven years.



Scheme 45: Syntheses towards the two myxovalargins **10** and **11**.

In addition, simplified derivatives should now be synthesized to obtain a compound with the same antibiotic properties but lower toxicity. To this end, in a first approach, the synthetically complex *β*-tyrosine was replaced by its natural representative *α*-L-tyrosine in fragment A-*β*-Tyr (**125**). In addition, the late guanidinylation was to be partially omitted. However, since both global deprotection and guanidinylation proved to be problematic, this approach was discarded again.

Future work envisions further studies on the derivatization of myxovalargin-D,L (**10**). Since it has proven difficult to obtain derivatives with sufficient purity for biological testing by total synthesis, future focus will be on modifying the natural product isolated from the bacterial supernatant. This offers several targets that could be modified, such as the guanidine side chains or free alcohols of tyrosine or hydroxyvaline.

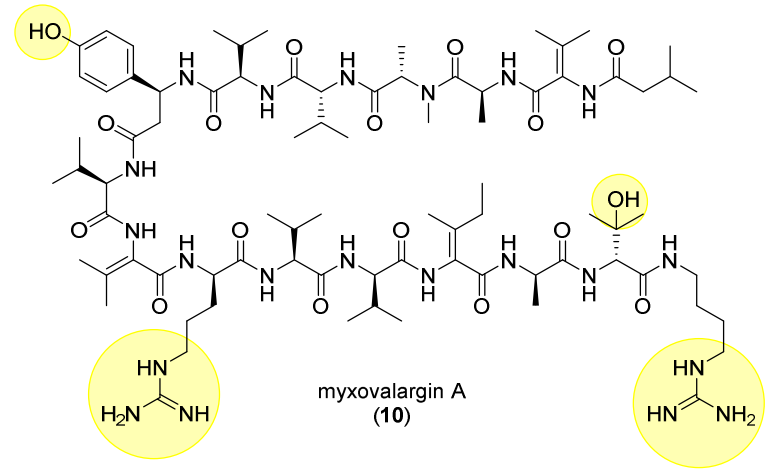
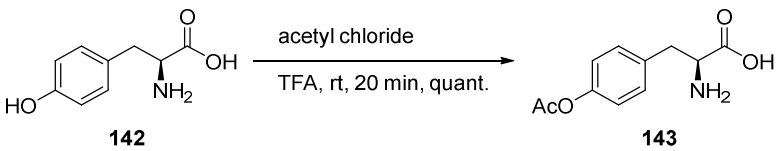


Figure 16: Potential targets for late-stage modification of myxovalargin-D,L (**10**).

Since many *O*- and *N*-alkylations or acetylations require the use of harsh reaction conditions or high temperatures, finding particularly mild conditions poses a major challenge. Selective reaction control would also be advantageous, since protection and deprotection reactions should be avoided as much as possible, as was observed in the total syntheses described in this report. Initial studies on the selective *O*-acetylation of tyrosine (**142**) have already been successfully carried out. For example, following a procedure by COLETTI-PREVIERO[52], the tyrosine-*O* (**142**) could be selectively acetylated with acetyl chloride in dry trifluoroacetic acid, while the free amino groups remained unaffected (Scheme 46). However, it remains to be seen how a large peptide will respond to these conditions, which could be investigated in future work.



142 **143**

Scheme 46: *O*-Selective acetylation of L-tyrosine (**142**).

[52] A. Previero, L. G. Barry, M.-A. Coletti-Previero, *Biochim. Biophys. Acta* **1972**, *263*, 7-13.

Topic B: Investigations on Transformations with Polymer-Supported Bisazidoiodate (I)

B1 Introduction

B1.1 The Chemistry of Hypervalent Iodine Compounds

In the last decades of the previous century, hypervalent iodine reagents were increasingly used in the field of organic synthesis. The great advantage of these compounds is that they exhibit similar reactivity to heavy metals, e.g., mercury (II), lead (IV) or thallium (III), but are much safer, milder and more environmentally friendly.[53] Hypervalent iodine compounds were first presented to the public by WILLGERODT as early as 1886.[54] Today, more than 130 years later, they are used as efficient reagents for oxidations, halogenations, aminations, rearrangements, C-C bond forming, and transition metal catalyzed reactions in both solution- and solid-phase synthesis.[55]

The general term "hypervalent iodine compounds" for molecules with iodine in higher oxidation states is derived from the three-center-four-electron bond (3c-4e), in which the 5*p* orbital of the iodine atom overlaps with the orbitals of the two ligands (X-I-X). This strongly polarized hypervalent bond is weak and therefore responsible for the particular reactivity of these compounds. Most of them contain iodine in the oxidation states (V) and (III) named as λ^5- and λ^3-iodanes, respectively (Figure 17). Pentavalent iodine derivatives are characterized by a square bipyramidal geometry. Two 3c-4e bonds connect all four electronegative ligands X to iodine whereas organic substituent R is linked by a regular covalent bond. In contrast, trivalent iodine compounds have a trigonal-bipyramidal structure. Their bonding orbital is occupied by two electrons from iodine's nonhybridized 5*p* orbital and one electron of each ligand X resulting in a highly polarized hypervalent bond which is longer and weaker compared to a covalent bond. This explains the high electrophilic reactivity of hypervalent iodine compounds used in the synthesis of complex organic compounds, which are described further in the following chapters.[55,56]

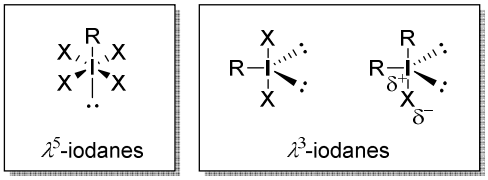
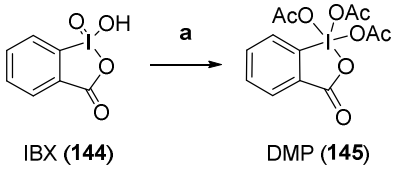


Figure 17: Typical structures of λ^5- and λ^3-iodanes.[55]

[53] H. Tohma, Y. Kita, *Adv. Synth. Catal*. **2004**, *346*, 111-124.
[54] C. Willgerodt, *J. Prakt. Chem*. **1886**, *33*, 154-160.
[55] A. Yoshimura, V. V. Zhdankin, *Chem. Rev*. **2016**, *116*, 3328-3435.
[56] V. V. Zhdankin, *J. Org. Chem*. **2011**, *76*, 1185-1197.

B1.2 Organoiodine (V) Reagents

Pentavalent iodine compounds represent an important class in the field of hypervalent iodine chemistry. In addition to iodylarenes ($ArIO_2$) the two cyclic iodine (V) oxidizing reagents 2-iodoxybenzoic acid (IBX, **144**) and DESS-MARTIN-periodinane (DMP, **145**) along with their analogues are of particular importance (Scheme 47).[57]



Scheme 47: Conversion of 2-iodoxybenzoic acid (IBX) to DESS-MARTIN periodinane (DMP): a) Ac_2O, AcOH, 100 °C, 93%.[63]

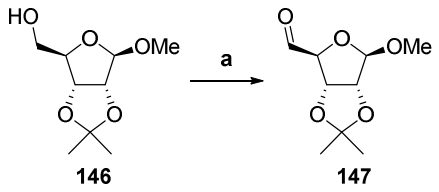
B1.2.1 2-Iodobenzoic Acid and its Analogues

For the first time, IBX was prepared in 1893 by HARTMAN and MAYER through the oxidation of 2-iodobenzoic acid with potassium bromate in aqueous solution of sulfuric acid.[58] In 1999, SANTAGOSTINO described a safer procedure for its preparation by using Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) for the oxidation of 2-iodobenzoic acid in water at 70 -75 °C. But even the bromate-free IBX samples are still dangerous. As SANTAGOSTINO noted, pure IBX explodes at 233 °C.[59] In addition, with the exception of DMSO and MeCN, IBX is insoluble in most organic solvents.[56] But what makes it such a successful reagent despite these drawbacks?

It is a particularly selective oxidant for the oxidation of alcohols to the corresponding carbonyl compounds, even if various other functional groups, such as amines, thioethers or double bonds, are also present in the molecule. Thus, primary alcohols are converted to the corresponding aldehydes and secondary alcohols to the corresponding ketones at room temperature without overoxidation. Chiral primary alcohols can also be oxidized in an appropriate manner without epimerization, as has been achieved, for example, for ribosyl alcohol **146**, which could be stereoselectively converted to the corresponding aldehyde **147**, an important intermediate in the synthesis of the core structures of the antibiotics polyoxin and nikkomycin (Scheme 48).[60] Over the years, IBX has been used in numerous syntheses, analogs have been prepared, solvents and

[57] U. Ladziata, V. V. Zhdankin, *Arkivoc*, **2006**, *ix*, 26-58.
[58] C. Hartman, V. Mayer, *Chem. Ber.* **1893**, *26*, 1727-1732.
[59] M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537-4538.
[60] J. D. More, N. S. Finney, *Synlett* **2003**, *9*, 1307-1310.

temperatures have been optimized, reviews were written[61], and even polymer-bound IBX[62] has been used, highlighting its great utility.[56]



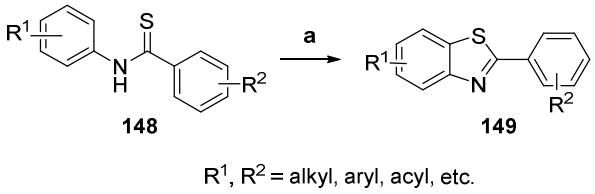
146 **147**

Scheme 48: Oxidation towards ribosyl aldehyde **147** by IBX: a) IBX, MeCN, 80 °C, 75 min, 93%.[60]

B1.2.2 DESS-MARTIN Periodinane (DMP)

In 1983, D. B. DESS and J. C. MARTIN described in a short communication how they were able to convert IBX with acetic anhydride at 100 °C to a triacetate, which they termed periodinane. This also proved to be a simple and valuable oxidizing agent for the conversion of primary alcohols to their corresponding aldehydes and secondary alcohols to ketones.[63] Within a very short time, it was widely utilized in synthetic chemistry under the name DESS-MARTIN-Periodinane (DMP) in a variety of total syntheses. The original communication became one of the most cited articles ever published in *The Journal of Organic Chemistry*. For the oxidation of alcohols containing sensitive functional groups such as amines, sulfides, or phosphine oxides, DMP is particularly preferred because of its mild reaction conditions and high chemoselectivity. Therefore, it is employed in numerous total syntheses of biologically important natural products, cardiovascular and anticancer drugs.[56] For example, the oxidation of *N*-protected *β*-amino alcohols with DMP to the corresponding aldehydes occurs with 99% *ee* and excellent yield, while the same oxidation under SWERN conditions achieves only 50-68% *ee*.[64] Recently, DMP has also been used as a reagent in a number of other synthetically useful oxidative transformations, such as the one-pot oxidative allylation of MORITA-BAYLIS-HILLMAN adducts with allyltrimethylsilanes promoted by DMP/$BF_3 \cdot OEt_2$,[65] or the synthesis of 2-substituted benzothiazoles by oxidative cyclization of thioformanilides **148** (Scheme 49).[66]

[61] V. Satam, A. Harad, R. Rajule, H. Pati, *Tetrahedron* **2010**, *66*, 7659-7706.
[62] M. Mülbaier, A. Giannis, *Angew. Chem. Int. Ed.* **2001**, *40*, 4393-4394.
[63] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155-4156.
[64] A. G. Myers, B. Zhong, M. Movassaghi, D. W. Kung, B. A. Lanman, S. Kwon, *Tetrahedron Lett.* **2000**, *41*, 1359-1362.
[65] J. S. Yadav, B. V. S. Reddy, A. P. Singh, A. K. Basak, *Synthesis* **2008**, *3*, 469-473.
[66] D. S. Bose, M. Idrees, *J. Org. Chem.* **2006**, *71*, 8261-8263.



Scheme 49: Cyclization of thioformanilides by using DMP: a) DMP, CH_2Cl_2, rt, 15 min, 85-95%.[66]

B1.3 Organioiodine (III) Reagents

There are various classes of trivalent iodine compounds, such as iodosylarenes, iodohalides, acyloxy- and sulfonyloxyaryliodanes, mono- and diamidoiodanes, iodonium salts, ylides, imides, and heterocyclic iodine (III) compounds (Figure 18). In particular, the aryl substituents are characterized by high stability and are widely used in organic synthesis.[55] Since it would be too far-reaching at this point to review all classes in detail, the remarks will concentrate on a few of particular importance for this work.

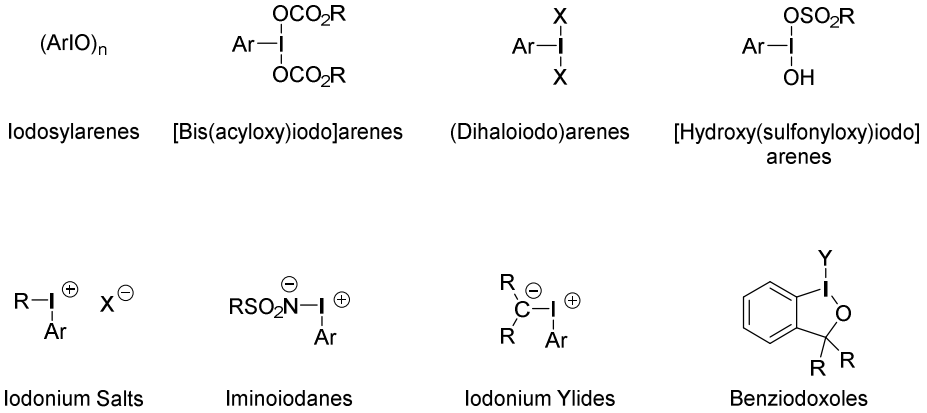


Figure 18: Main classes of iodine (III) reagents.[55]

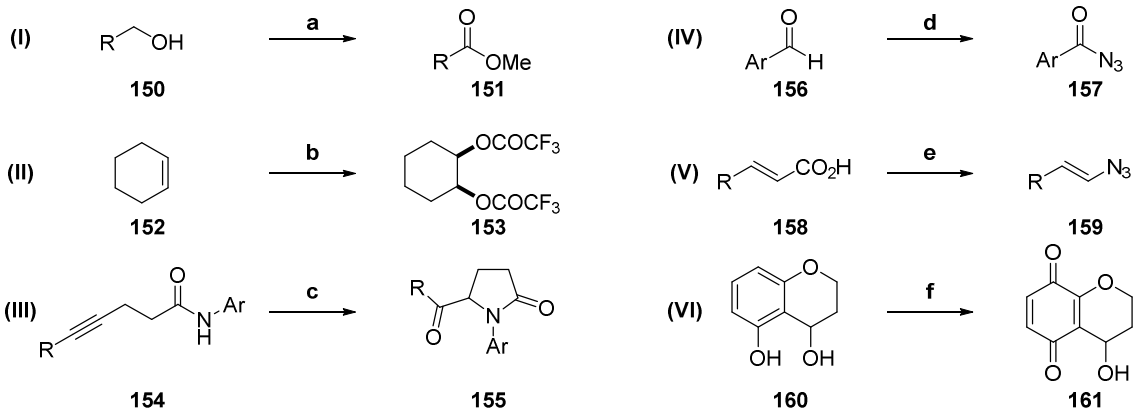
B1.3.1 [Bis(acyloxy)iodo]arenes

The [bis(acyloxy)iodo]arenes ($ArI(O_2CR)_2$) are among the most important representatives of the hypervalent iodine (III) compounds. In particular, the two most common compounds (diacetoxyiodo)benzene (PIDA)[67] and [bis(trifluoroacetoxy)iodo]benzene (PIFA) should be mentioned here, which are even commercially available and, among other applications, are often used as oxidizing agents. There are two general methods for preparing [bis(acyloxy)iodo]arenes.

[67] A. Kirschning, *J. Prakt. Chem.* **1998**, *340*, 184-186.

First, they can be made by oxidation of an aryl iodide in the presence of a carboxylic acid or by a ligand exchange reaction of an available (diacetoxyiodo)arene with a carboxylic acid.[55]

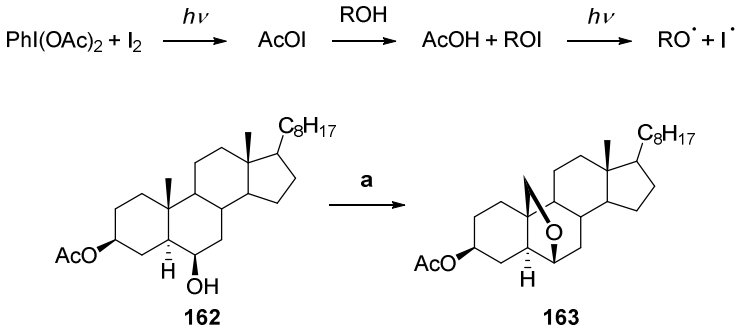
[Bis(acyloxy)iodo]arenes are characterized by a wide range of applications (Scheme 50). Thus, they are most commonly used as oxidizing agents. For example, the oxidation of aldehydes or primary alcohols **150** by treatment with $PhI(OAc)_2 \cdot I_2$ in a methanol solution gives methyl ester **151** in high yields (Scheme 50, I).[68,69] In addition, [bis(acyloxy)iodo]arenes are excellent reagents for oxidative transformations of alkenes. For example, treatment of cyclohexene (**152**) with PIFA under refluxing conditions leads to *cis*-1,2-bis(trifluoroacetate) (**153**) in high yield (Scheme 50, II).[70] Another interesting application is the synthesis of heterocycles by the PIFA-induced oxidative cationic cyclization reaction. One example is the conversion of alkynylamides **154** in TFA to pyrrolidinones **155** (Scheme 50, III).[71] In addition, aldehydes **156** can be converted to aroylazides **157** with PIDA and sodium azide in good yields (Scheme 50, IV). This reaction presumably proceeds by an initial *in situ* formation of (diazidoiodo)benzenes.[72] Another useful reaction is the direct decarboxylative azidation of *α,β*-unsaturated carboxylic acids **158** with PIFA and sodium azide in the presence of Et_3NBr which acts as phase transfer reagent. In this way, vinyl azides **159** are obtained in good yields (Scheme 50, V). This approach can also be adopted for the synthesis of acyl azides.[73] Moreover, PIDA can be employed in the oxidation of e.g., weakly acidic phenols **160** to quinones **161** (Scheme 50, VI).[74]



Scheme 50: A selection of applications of PIDA and PIFA: a) $PhI(OAc)_2$, I_2, MeOH, rt, 2-5 h, 82-92%; b) $PhI(OCOCF_3)_2$, CH_2Cl_2, reflux, 36 h, 95%; c) $PhI(OCOCF_3)_2$, CF_3CH_2OH, 0 °C, 1-3 h, 33-77%; d) $PhI(OAc)_2$, NaN_3, CH_2Cl_2, rt, 1-2 h, 43-92%; e) $PhI(OCOCF_3)_2$, NaN_3, Et_4NBr, CH_2Cl_2, rt, 0.5-3 h, 70-88%; f) PIDA, MeCN/H_2O 2:1, rt, 15 min, 69%.[55,67]

[68] N. N. Karade, G. B. Tiwari, D. B. Huple, *Synlett* **2005**, *360*, 2039-2042.
[69] N. N. Karade, V. H. Budhewar, A. N. Katkar, G. B. Tiwari, *Arkivoc* **2006**, *xi*, 162-167.
[70] M. Çelik, C. Alp, B. Coşkun, M. S. Gültekin, M. Balci, *Tetrahedron Lett*. **2006**, *47*, 3659-3663.
[71] I. Tellitu, S. Serna, M. T. Herrero, I. Moreno, E. Domínguez, R. SanMartin, *J. Org. Chem*. **2007**, *72*, 1526-1529.
[72] D.-J. Chen, Z.-C. Chen, *Tetrahedron Lett.* **2000**, *41*, 7361-7363.
[73] V. N. Telvekar, B. S. Takale, H. M. Bachhav, *Tetrahedron Lett*. **2009**, *50*, 5056-5058.
[74] C. Sate B, J. A. Valderrama, R. Tapia, F. Farifia, M. C. Paredes, *Synth. Commun*. **1992**, *22*, 955-960.

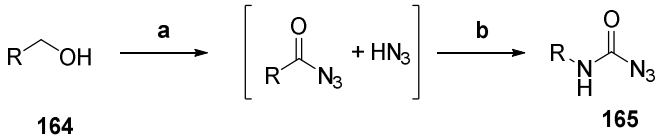
In addition, alcohols can be photochemically converted to alkoxy radicals in the presence of PIDA and iodine.[67] In this way, cyclizations or fragmentations can occur, as shown in Scheme 51 for the steroidal compound **162**.[75]



Scheme 51: Photochemical activation of alcohols using PIDA: a) PIDA, I_2, *hν*, 90%.

B1.3.2 Hypervalent Iodine Halides

Hypervalent iodine halides are generally characterized by high thermal stability, which turns them into useful reagents in organic synthesis. Inorganic iodine halides include (dichloroiodo)arenes, which are mainly used as chlorinating reagents, and (dichloroiodo)benzene, $PhICl_2$, which can be prepared by chlorination of iodobenzene with chlorine in dichloromethane or chloroform.[76] (Dichloroiodo)benzene can be used as an oxidizing agent. Of particular interest is the CURTIUS rearrangement that occurs upon oxidation of the primary alcohol **164** with $PhICl_2$-NaN_3 to give carbamoyl azide **165** (Scheme 52).[77]



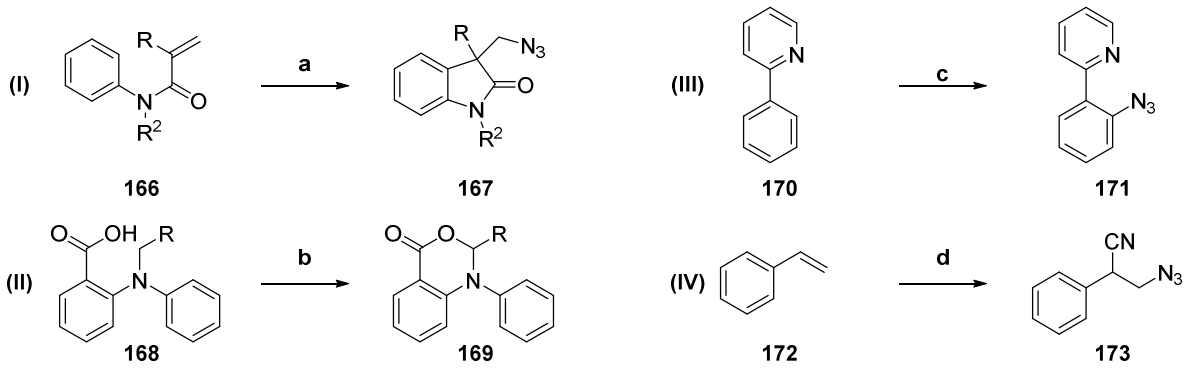
Scheme 52: CURTIUS rearrangement of alcohol **164**: a) $PhICl_2$, NaN_3, EtOAc, 0 °C, 24 h, then b) 80 °C, 8 h, 72-93%.

B1.3.3 Aryliodine (III) Compounds with Azido Ligands

Nitrogen ligand-containing aryl iodine (III) compounds generally have low thermal stability and are more sensitive to moisture. For this reason, they may be less represented in organic synthesis than those with I-O bonds. Nevertheless, they are of great synthetic value. Particular attention should focus on the acyclic hypervalent iodine derivatives with azido ligands, $PhI(N_3)OAc$ and

[75] P. de Armas, J. I. Concepcion, C. G. Francisco, R. Hernandez, J. A. Salazar, E. Suarez, *J. Chem. Soc., Perkin Trans. 1*, **1989**, 405-411.
[76] H. J. Lucas, E. R. Kennedy, *Org. Synth. Coll. Vol. III*, Wiley, New York, **1955**, 482.
[77] X.-Q. Li, X.-F. Zhao, C. Zhang, *Synthesis* **2008**, *16*, 2589-2593.

$PhI(N_3)_2$, which are involved in many azidation reactions. Azidoiodanes are usually prepared *in situ* from a hypervalent iodine reagent and a source of azide anions as they readily decompose to iodobenzene and dinitrogen at -25 °C to 0 °C. They play an important role in allylic azidations, mono or vicinal diazidations of alkenes, benzyl or alkylazidations, *α*-azidations of carbonyl compounds or C-H azidations of aldehydes, and oxidative decarboxylative azidations of *α,β*-unsaturated carboxylic acids.[55] Scheme 53 shows an example of how ANTONCHICK converts alkenes **166** at room temperature via radical cascade reactions of C-N and C-C bond formations to 2-oxindoles **167** under metal-free conditions (Scheme 53, I).[78] Another example is the intramolecular C-O bond formation of *N,N*-diaryl tertiary amines **168** through a $PhI(OAc)_2$-NaN_3 system mediated oxygenation (Scheme 53, II).[79] In addition, metal-catalyzed azidations are also relevant. For example, LI *et al.* reported the rhodium (III) catalyzed C-H azidation of arenes **170** with azdoiodanes **171** generated *in situ* (Scheme 53, III).[80] Another example is the copper-catalyzed MARKOVNIKOV-style intermolecular azidocyanation of aryl alkenes **172** to *α*-azido-propanenitriles **173** (Scheme 53, IV).[81]

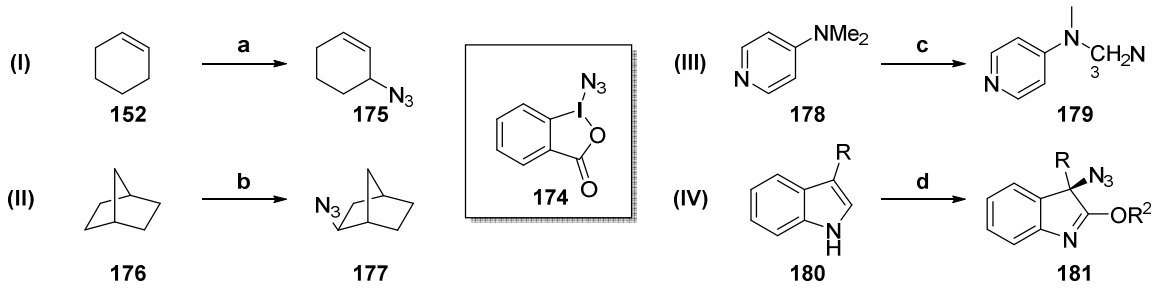


Scheme 53: A selection of applications of aryliodide (III) compounds with azido ligands: a) $PhI(OCOCF_3)_2$, $TMSN_3$, CH_2Cl_2, rt, 1 h, 50-90%; b) $PhI(OAc)_2$, NaN_3, CH_2Cl_2, rt, 1 h, 42-91%; c) i) $PhI(OAc)_2$, $TsOH{\cdot}H_2O$, $[\{RhCp{\cdot}Cl_2\}_2]$, acetone, 15 min, ii) NaN_3, 50 °C, 16 h, 52-89%; d) $PhI(OAc)_2$, $TMSN_3$, TMSCN, $Cu(TFA)_2$, MeOH, rt, 10 min, 32-84%.[55]

However, probably the best known cyclic iodine (III) azidation reagent is the ZHDANKIN reagent (1-azido-1,2-benziodoxol-3(1*H*)-one, **174**), which was first described in 1996.[82] It is certainly the most commonly used representative from the class of azidobenziodoxoles, which are thermally stable, less explosive and storable. It can be prepared in good yields by reacting appropriate benziodoxoles with trimethylsilyl azide or sodium azide.[55] With this reagent, the direct azidation of many organic substrates such as alkenes **152** (Scheme 54, I), branched hydrocarbons **176**

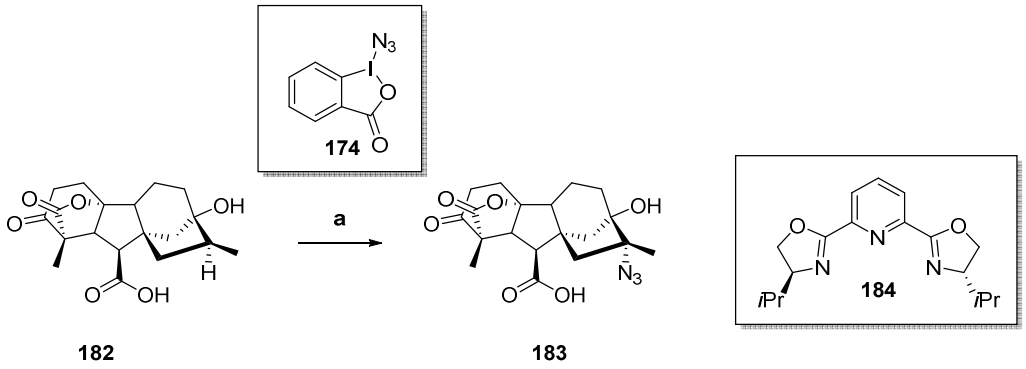
[78] K. Matcha, R. Narayan, A. P. Antonchick, *Angew. Chem., Int. Ed.* **2013**, *52*, 7985-7989.
[79] N. Zhang, R. Cheng, D. Zhang-Negrerie, Y. Du, K. Zhao, *J. Org. Chem.* **2014**, *79*, 10581-10587.
[80] F. Xie, Z. Qi, X. Li, *Angew. Chem., Int. Ed.* **2013**, *52*, 11862-11866.
[81] L. Xu, X.-Q. Mou, Z.-M. Chen, S.-H. Wang, *Chem. Commun.* **2014**, *50*, 10676-10679.
[82] V. V. Zhdankin, A. P. Krasutsky, C. J. Kuehl, A. J. Simonsen, J. K. Woodward, B. Mismash, J. T. Bolz, *J. Am. Chem. Soc.* **1996**, *118*, 5192-5197.

(Scheme 54, II) or anilines **178** (Scheme 54, III) could be achieved.[82] Over the years, other applications have been added, such as copper-catalyzed oxoazidations and alkoxyazidations of indoles **180** with azidobenziodoxol (Scheme 54, IV).[83]



Scheme 54: Applications of the ZHDANKIN reagent: a) **174**, $ClCH_2CH_2Cl$, benzoyl peroxide (cat.), reflux, 3 h, 23%; b) **174**, benzoyl peroxide, PhCl, 100-105 °C, 3-4 h, 45%; c) **174**, CH_2Cl_2, reflux, 0.5 h, 90%; d) **174**, $Cu(acac)_2$, R^2OH, 60 °C, 1.5 h, 47-77%.[82,83]

In addition, HARTWIG'S group has described an iron catalyst-mediated selective tertiary C-H azidation reaction that can also be used to perform late-stage azidations on complex molecules. Azido groups are easily converted into a variety of other nitrogen-containing compounds (Scheme 55).[84]



Scheme 55: Fe-catalyzed late-stage C-H bond azidation: a) **174**, $Fe(OAc)_2$, **184**, MeCN, 50 °C, 75%.

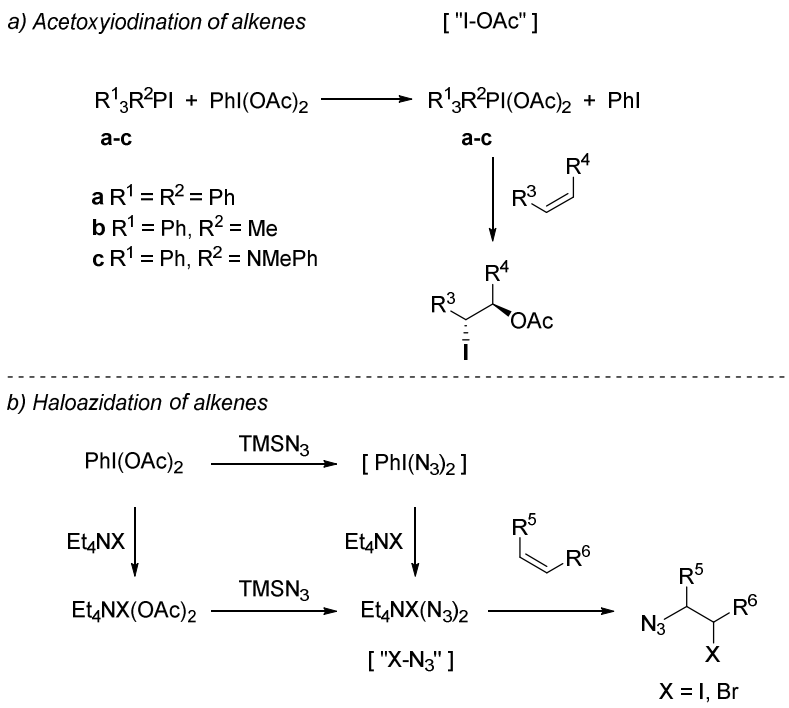
B1.4 Iodate (I) Anions

B1.4.1 Ligand Transfer from Iodine (III) Reagents to Halides in Solution-Phase

Of very special interest to this work is a class of electrophilic iodonium reagents prepared by iodine (III)-mediated oxidation of ammonium or phosphonium iodide.[85,86,87] PIDA and PIFA are

[83] H. Yin, T. Wang, N. Jiao, *Org. Lett.* **2014**, *16*, 2302-2305.
[84] A. Sharma, J. F. Hartwig, *Nature* **2015**, *517*, 600-604.
[85] A. Kirschning, C. Plumeier, L. Rose, *Chem. Commun*. **1998**, 33-34.
[86] A. Kirschning, Md. A. Hashem, H. Monenschein, L. Rose, K.-U. Schöning, *J. Org. Chem*. **1999**, *64*, 6522-6526.
[87] Md. A. Hashem, A. Jung, M. Ries, A. Kirschning, *Synlett*, **1998**, *2*, 195-197.

likewise employed for this purpose. The resulting acylated iodate (I) complexes can be further diversified by ligand exchange with silylated nucleophiles such as $TMSN_3$ to form the corresponding -ate (I) anions. As early as 1998 and 1999, several of such phosphonium and ammonium salts of diacetoxyiodate (I) anions and ammonium salts of haloazides were described in the KIRSCHNING group, which can be used to perform 1,2-acetoxyiodinations and 1,2-azidoiodinations of alkenes. Prior to this time, acetoxyiodinations were rarely used and required KIO_3 in glacial AcOH at 60 °C[88] or heavy metal salts in the presence of I_2.[89] Iodine (I) compound *N*-iodosuccinimide (NIS) with AcOH at 60 °C[90] was also employed. Since HASSNER'S pioneering work,[91] haloazidations also gained increasing importance. However, since iodine azide, prepared from sodium azide and iodine chloride, was very explosive, handling proved problematic. The phosphonium and ammonium salts of diacetoxyiodate (I) and the ammonium salts of bis(azido)iodate behave chemically like the corresponding acetyl hypoiodites and iodine azides, respectively, without their harsh properties. In addition to the corresponding iodine compounds, these salts were also prepared from ammonium bromide, yielding bromate (I) anions (Scheme 56).[85,86]

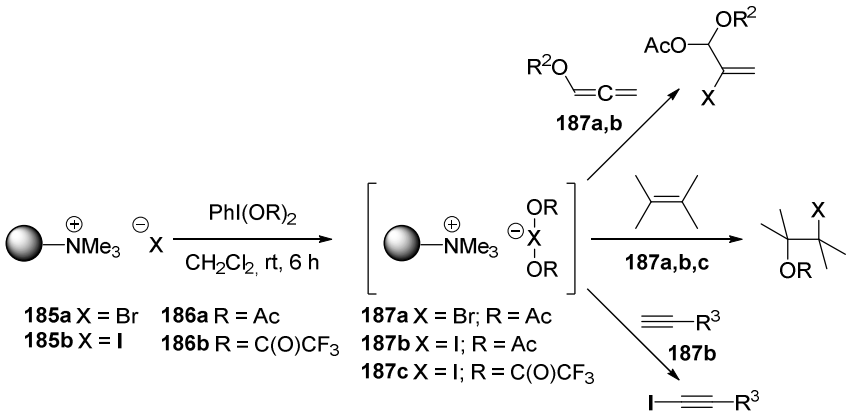


Scheme 56: Iodine (III)-promoted oxidation of halide anions and subsequent 1,2-addition to alkenes.

[88] L. Mangoni, M. Adinolfi, G. Barone, M. Parrilli, *Tetrahedron Lett*., **1973**, 4485-4486.
[89] L. Birckenbach, J. Goubeau, E. Berninger, *Ber. Dtsch. Chem. Ges*. **1932**, *65*, 1339.
[90] M. Adinolfi, M. Parrilli, G. Barone, G. Laonigro, L. Mangoni, *Tetrahedron Lett*., **1976**, 3661-3662.
[91] F. W. Fowler, A. Hassner, L. A. Levy, *J. Am. Chem. Soc*. **1967**, *89*, 2077-2082.

B1.4.2 Polymer-supported Acetoxy Haloate (I) Anions

Based on these haloate salts, several polymer-bound electrophilic reagents were reported in the KIRSCHING group as well. The advantage of polymer-bound reagents and solid-phase chemistry is the simplicity of reaction control and workup, since the reagents can be easily filtered off on completion of the reaction. For this reason, they can be used in excess, resulting in shorter reaction times. These reagents are prepared by iodine (III) mediated ligand transfer followed by oxidation of polystyrene-supported halides **185a** and **185b** (Scheme 57). In this way, bromide **185a** is converted with PIDA to form polymer **187a**, while electrophilic reagents **187b** and **187c** are generated from iodide **185b** by treatment with PIDA and PIFA, respectively. It was found that these reagents can be utilized to convert alkenes to α-haloacetates, while their employment on alkoxyallenes leads to vinyl iodides. In contrast, terminal alkynes are converted to the corresponding 1-iodo alkynes.[92]

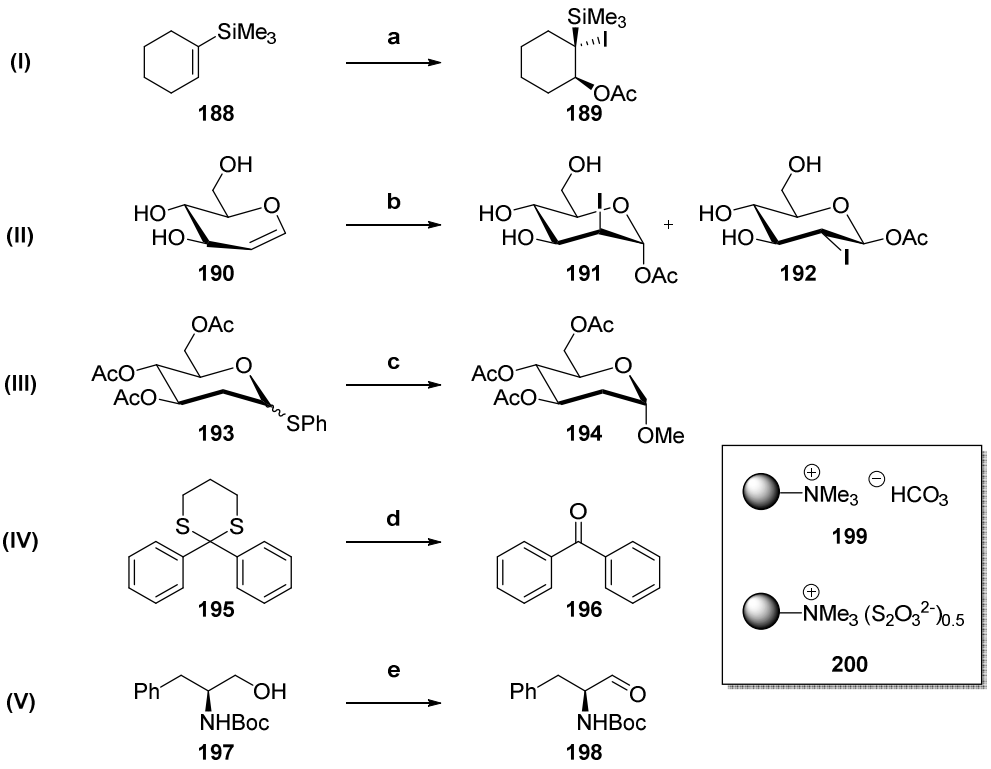


Scheme 57: Reactions of alkenes, alkynes and alkoxyallenes with polymer-supported electrophilic reagents.[92]

Thus, these reagents have been used for a variety of transformations. In addition to those involving alkenes, alkynes[92] and glycals,[93,94] these include the haloacetoxylation of allyl and vinyl silanes[95] or the activation of thioglycosides[96] and dithioacetals[97] or, as in the case of bromide **187a**, its employment as a co-oxidant for TEMPO-mediated oxidations. Some examples are given in Scheme 58.[98,99]

[92] H. Monenschein, G. Sourkouni-Argirusi, K. M. Schubothe, T. O'Hare, A. Kirschning, *Org. Lett*. **1999**, *13*, 2101-2104.
[93] A. Kirschning, M. Jesberger, H. Monenschein, *Tetrahedron Lett*. **1999**, *40*, 8999-9002.
[94] A. Kirschning, M. Jesberger, A. Schönberger, *Org. Lett*. **2001**, *23*, 3623-3626.
[95] S. Domann, G Sourkouni-Argirusi, N. Merayo, A. Schönberger, A. Kirschning, *Molecules*, **2001**, *6*, 61-66.
[96] J. Jaunzems, G. Sourkouni-Argirusi, M. Jesberger, A. Kirschning, *Tetrahedron Lett*. **2003**, *44*, 637-639.
[97] S. Luiken, A. Kirschning, *J. Org. Chem*. **2008**, *73*, 2018-2020.
[98] M. Brünjes, G Sourkouni-Argirusi, A. Kirschning, *Adv. Synth. Catal*. **2003**, *345*, 635-642.
[99] K. Kloth, M. Brünjes, E. Kunst, T. Jöge, F. Gallier, A. Adibekian, A. Kirschning, *Adv. Synth. Catal*. **2005**, 347, 1423-1434.

Thus, an 1,2-addition by resin **187b** to vinylsilane **188** occurs, resulting in iodoacetylated compound **189** (Scheme 58, I).[95] In addition, the completely unprotected glycal **190** was found to undergo 1,2-cohalogenation with polymer-assisted reagent **187b**, giving pyranosyl acetates **191** and **192** in 71% yield (Scheme 58, II).[93] Furthermore, thioglycoside **193** was converted to the glycosidation product **194** by polymer **187c** in the presence of MeOH (Scheme 58, III).[96] As an example of polymer-assisted hydrolysis of dithioacetals, dithiane **195** is shown. The resin **187c** is used as electrophilic activating agent. In addition to the desired carbonyl compound **196**, TFA and 1,2-dithiolane-1,1-dioxide are also released, which can be removed with scavenger resins **199** and **200** (Scheme 58, IV).[97] Finally, an example of TEMPO-mediated oxidation of α-amino alcohols is given in which the polymer-bound bromate (I) complex **187a** serves as a co-oxidant and provides aldehyde **198** (Scheme 58, V).[98]

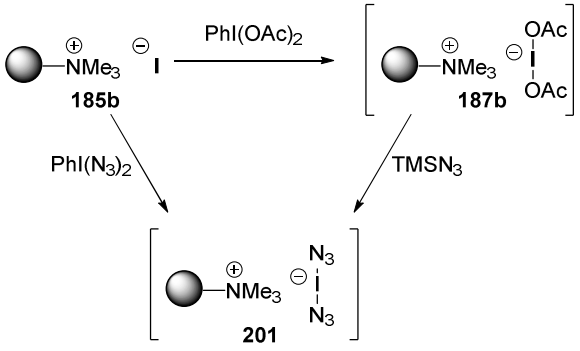


Scheme 58: Selected transformations with polymer-supported electrophilic reagents: a) **187b**, CH_2Cl_2, rt, 5 h, 76%;[95] b) **187b**, MeCN, rt, 12 h, 71%, 2.5:1;[93] c) **187c**, MeOH, CH_2Cl_2, rt, 4 h, 95%, α/β = 4:1;[96] d) **187c**, **199**, **200**, MeCN/H_2O (20:1), rt, 1 h, 94%;[97] e) **187a**, CH_2Cl_2, rt, 2 h, TEMPO (cat.), 99%.[98]

B1.4.3 Polymer-supported Diazidoiodate (I)

Continuing the work on ligand transfer from hypervalent iodine (III) reagents to halides in solution, the KIRSCHNING group developed a polymer-bound bisazidoiodate (I) **201** reagent that behaves like iodine azide. There are two routes by which it can be prepared (Scheme 59). First, it is possible to convert (diacetoxyiodoso)benzene with polymer-bound iodide **185b** in dichloromethane at room

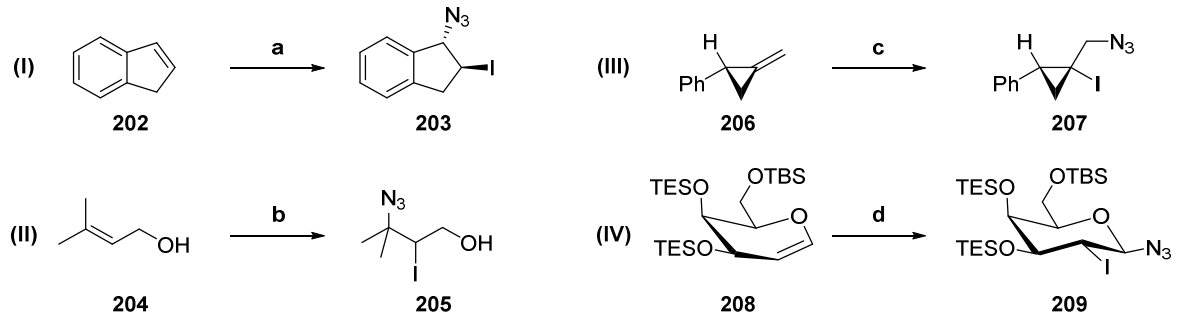
temperature giving polymer-bound di(acetyloxy)iodate (I) **187b** described above, which eventually leads to the desired reagent by reaction with trimethylsilyl azide. Alternatively, polymer-bound bisazidoiodate (I) **201** can be obtained by direct azide transfer through the reaction of polymer-bound iodide **185b** with (diazidoiodoso)benzene. However, in this case, efficient azide transfer was interfered by trimethylsilyl acetate in solution, since $PhI(N_3)_2$ had to be previously generated *in situ* by reaction of PIDA with $TMSN_3$. Therefore, the first route of preparation was considered more efficient. The main advantage of this reagent is the absence of any explosive character, which is always a major hazard with iodine azide.[100]



Scheme 59: Preparation of polymer-bound bis(azido)iodate (I) **201**.[100]

Since the pioneering work of HASSNER *et al.,* iodoazidation of alkenes has been used to introduce nitrogen functionalities into carbon frameworks.[91] Polymer-bound iodine azide **201** can be used to perform 1,2-iodoazidations of alkenes under mild conditions with the formation of the *anti*-addition products (Scheme 60), while the lack of any explosive character of this polymer-bound iodine azide **201** renders this a safe iodoazidation method. The regioselectivity of 1,2-addition is determined by the stability of the intermediate carbenium ion after electrophilic attack and usually leads to the MARKOVNIKOV addition products.[100] Thus, sensitive *β*-iodine azides **203** were obtained in good yields after filtration and removal of the solvent (Scheme 60, I). Free hydroxy groups in allyl and homoallyl positions **204** were also tolerated under the conditions used (Scheme 60, II), and addition to methylenecyclopropane **206** also proceeded under strict regio- and stereocontrol (Scheme 60, III). Glycal **208** functionalization was likewise possible (Scheme 60, IV).[93,100]

[100] A. Kirschning, H. Monenschein, C. Schmeck, *Angew. Chem. Int. Ed*. **1999**, *38*, 2594-2596; *Angew. Chem.* **1999**, *111*, 2720-2722.

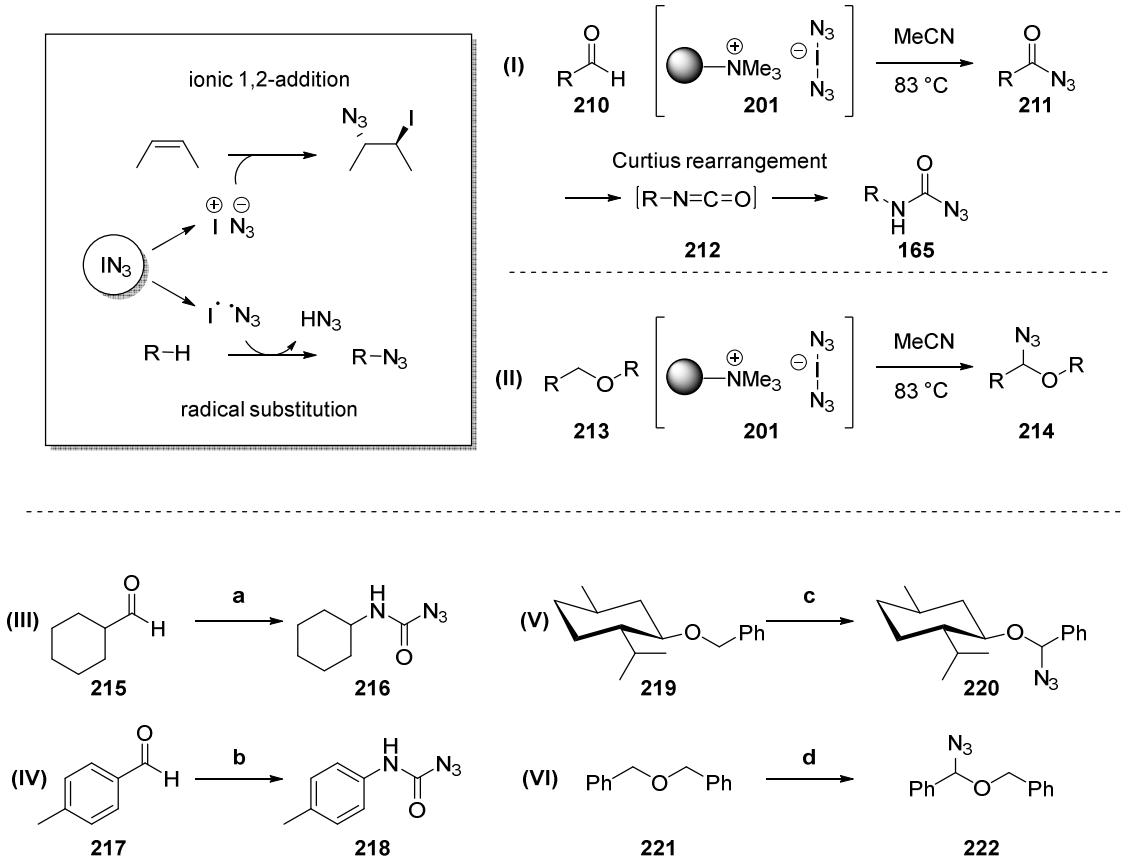


Scheme 60: Iodoazidation of alkenes with polymer-supported iodine azide **201**: a) **201**, CH_2Cl_2, 20 h, 78%; b) **201**, CH_2Cl_2, 1.5 d, 98%; c) **201**, CH_2Cl_2, 2 d, 48%; d) **201**, CH_2Cl_2, 12 h, 82%.[100]

In addition to the ionic properties of the polymer-bound diazidoiodate (I) anion **201** mentioned above, radical azidations have also been described by BOLS *et al.*[101] The azido group is a highly functional group in organic synthesis and can be converted to free amines or undergo photochemical or cycloaddition reactions. For example, aldehydes **210** can be converted to carbamoyl azides **165** (Scheme 61, I) and benzyl ethers **213** to azido ethers **214** (Scheme 61, II) by treatment with polymer-bound iodoazide **201** at 83 °C in MeCN. Typically, the reactions were carried out by heating the substrate for four hours under reflux with four equivalents of polymer **201** in acetonitrile. The yields for the conversion of aldehydes to carbamoyl azides ranged between 87 and 96% (Scheme 61, III-IV), while the yields for the conversion of benzyl ethers to azidobenzyl ethers were slightly lower with 57-66% (Scheme 61, V-VI).[101] It can be assumed that polymer **201** acts by slow release of IN_3. The reaction with aldehydes proceeds in a way that acyl azide **211** is formed first. At high temperatures, a CURTIUS rearrangement gives isocyanates **212**, which with azides yield the corresponding carbamoyl azides **165**. Such carbamoyl azides, which can also be prepared classically with $PhI(OAc)_2$ or IN_3, can be converted, for example, into amines, carbamates or ureas.[102]

Homolysis of iodine azide bonds can be carried out at high temperatures, and the azide radicals released in this process are the driving force not only for the transformations with aldehydes, but also for the substitution of enol ethers leading to the corresponding azidoethers (Scheme 61).[103] With knowledge of all these reactions, the foundation for the work presented here has been laid.

[101] L. G. Marinescu, C. M. Pedersen, M. Bols, *Tetrahedron* **2005**, *61*, 123-127.
[102] L. Marinescu, J. Thinggaard, Ib B. Thomsen, M. Bols, *J. Org. Chem.* **2003**, *68*, 9453-9455.
[103] C. M. Pedersen, L. G. Marinescu, M. Bols, *Org. Biomol. Chem.* **2005**, *3*, 816-822.



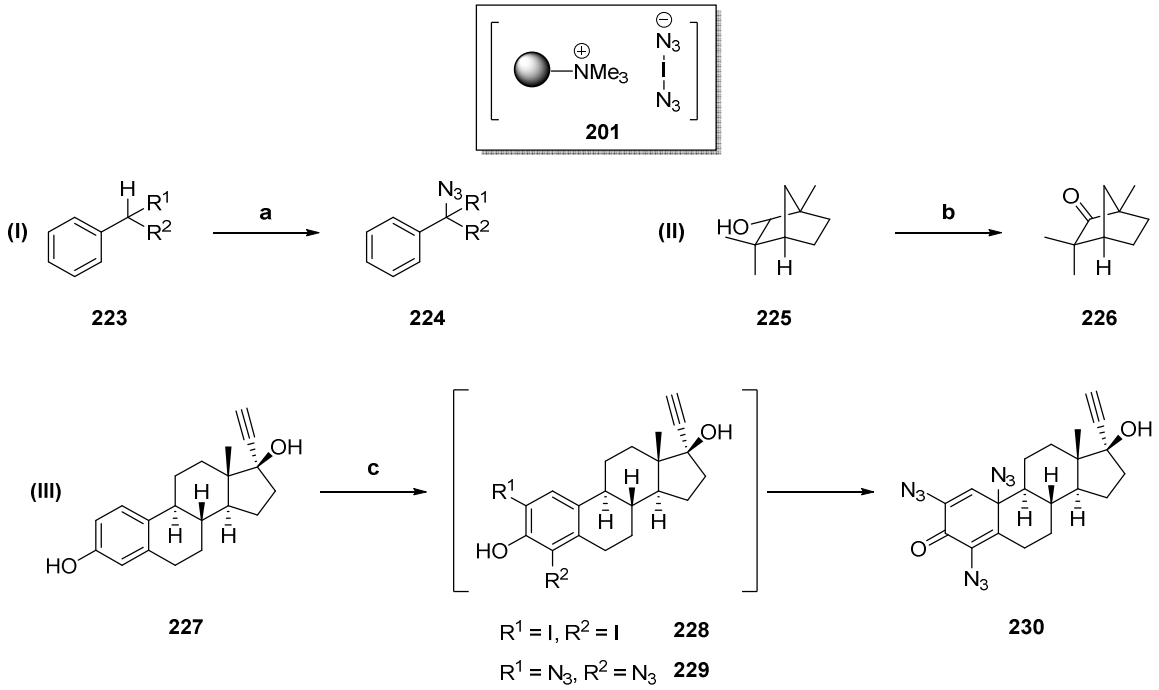
Scheme 61: Radical azidation using polymer-supported diazidoiodate (I) **201**. Aldehydes are converted to acyl azides and benzyl ethers to azido ethers: a) **201**, MeCN, 83 °C, 4 h, 96%; b) **201**, MeCN, 83 °C 4 h, 96%; c) **201**, MeCN, 83 °C 4 h, 60%; d) **201**, MeCN, 83 °C 4 h, 64%.[101]

B2 Project Aims

Based on the described insights of KIRSCHNING and BOLS, the utility of polymer-bound bisazidoiodate (I) for C-H functionalization on terpenes has already been tested as part of a master thesis.[104] For this purpose, conversion of different substrates with polymer **201** under various reaction conditions was investigated (thermal conditions, irradiation, photoredox catalysis). In that proof-of-concept study, the substitution of enol ethers described by BOLS was found to proceed not only at 83 °C but also at room temperature under irradiation with UV light at 356 nm, as well as radical substitution in the benzylic position in general (Scheme 62, I). Moreover, oxidative properties of the polymer-bound bisazidoiodate (I) **201** were found. Thus, in an experiment on the radical azidation of fenchyl alcohol (**225**), it was observed that instead of azidation, oxidation of the alcohol **225** occurred. This happened both at 83 °C and upon irradiation with UV light (Scheme 62, II). In another series of experiments, in which the polymer-bound iodine azide **201** was stirred with ethinylestradiol (**227**) at room temperature and in the absence of light, another

[104] T. Kösel, master thesis, Leibniz Universität Hannover, Hannover, **2018**.

unexpected discovery was made. Thus, the formation of three estradiol derivatives **228**-**230** was detected, with initial studies revealing that formation begins with diiodide **228** and leads to trisazido adduct **230** via bisazido adduct **229** as an intermediate (Scheme 62, III).



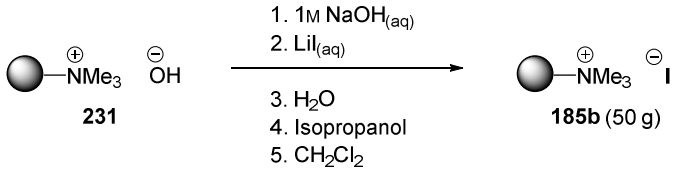
Scheme 62: Conversions of different substrates with polymer **201** under various reaction conditions: a) 201, degassed MeCN, hν (365 nm), rt or 83 °C, 16 h, 18-90%; b) **201**, degassed MeCN, hν (365 nm), rt or 83 °C, 24 h, 75%-quant.; c) **201**, MeCN, rt, 14 h, 95%.

Due to time constraints, these new discoveries could not be investigated in the master thesis in a satisfactory manner and will be further explored in the present work. Therefore, the aim of this second part of the thesis is firstly to gain further insight into the oxidative properties of bisazidoiodate (I) **201** and secondly to examine the azidations in more detail. For this purpose, the substrate scope will be extended, and the reaction mechanisms will be investigated, including different activation conditions, such as irradiation or higher temperatures.

B3 Results and Discussion

B3.1 Preparation of Functionalized Resins

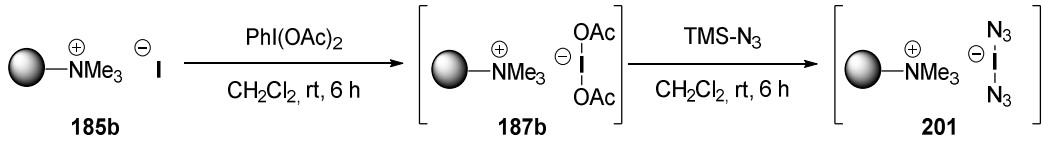
First, polymer-bound iodide **185b** was prepared by ion exchange from commercial brownish polymer-bound hydroxide **231** (Amberlyst® A26 resin from ABCR), which has a quaternary ammonium countergroup and a theoretical loading of 4.2 mmol/g hydroxide (Scheme 63). Ion exchange was performed by first rinsing resin **231** with 1M $NaOH_{(aq)}$ for reactivation to ensure complete hydroxide loading, followed by a second rinse with saturated LiI solution. Lithium iodide was chosen because lithium has a high charge density and promotes anion exchange according to the HSAB principle. The resin was then washed with distilled water to remove excess ions, followed by a rinse with isopropyl alcohol to remove water, and finally with dichloromethane as it easily evaporates and was the solvent of choice for the following reactions. The light pink resin **185b** can be prepared in 50 g scale and is stable for several months after drying *in vacuo* when stored at -15 °C in the dark under argon atmosphere.[104]



Scheme 63: Preparation of polymer-bound iodide **185b**.

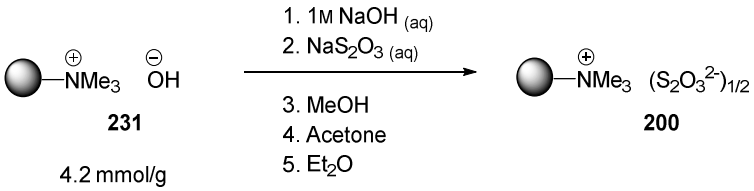
Based on previous experience of the KIRSCHNING group with polymer-bound iodine (I) **185b**, the effective iodide loading of the final resin is assumed to be half the original loading of the commercial resin in hydroxide form (4.2 mmol hydroxide per gram resin). This means that all data on the equivalents of polymer-bound iodide species in this work are based on the maximum practical loading of 2.1 mmol iodide per gram resin, which is consistent with the gravimetrically determined loading of some samples.

On this basis, reaction of polystyrene-bound iodide **185b** with (diacetoxy)-iodobenzene in the absence of light in dichloromethane at room temperature gave the pale-yellow polymer-bound di(acetyloxy)iodate (I) **187b**. This reaction was carried out according to the literature.[100] Resin **187b** can also be prepared in a 50 g scale. Subsequent treatment of polystyrene-bound di(acetyloxy)iodate (I) **187b** with trimethylsilyl azide gave resin **201** according to the experimental procedure described hereinbefore.[100] The polymer-bound iodine azide **201** exhibits an orange color and can also be prepared in a 50 g scale. It behaves chemically like iodine azide without its explosive character and, after drying *in vacuo*, can be stored at -15 °C for several months under argon atmosphere (Scheme 64).[104]



Scheme 64: Preparation of polymer-bound bisazidoiodate (I) **201**.

Moreover, thiosulfate ion exchange resin **200** was prepared from the commercial brownish polymer-bound hydroxide **231** (Amberlyst® A26 resin from ABCR) with a theoretical loading of 4.2 mmol/g hydroxide. Ion exchange was performed by sequentially rinsing resin **231** with 1M $NaOH_{(aq)}$ to ensure complete loading, followed by a saturated $Na_2S_2O_3$ solution. The resin was then rinsed with methanol to remove excess water and salts followed by acetone to remove methanol, and finally with diethyl ether as it evaporates easily (Scheme 65). The light pink resin **200** can be prepared in a 50 g scale and stored under argon atmosphere at -15 °C in the dark for several weeks. A thiosulfate ion exchange resin was added for reductive workup of reactions and removal of byproducts such as iodine and IN_3. In this way, the need for hydrolytic workup is circumvented.



Scheme 65: Preparation of polymer-bound thiosulfate **200**.

B3.2 Thermally Induced Oxidations

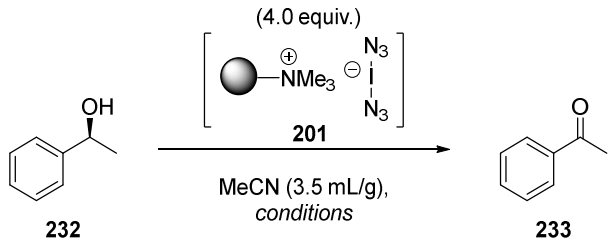
B3.2.1 Oxidation of Secondary Alcohols at 60 °C

In previous studies on the chemistry of haloate (I) complexes on polymer supports, diazidoiodate (I) **201** was found to possess oxidizing properties.[104] To investigate this further, various primary and secondary alcohols were selected as test substrates for oxidations with reagent **201** as oxidant.

First, the oxidation of secondary alcohols was roughly tested using 1-phenylethanol (**232**) as a first model substrate. In this experimental protocol, the amount of resin **201** was kept constant and dry acetonitrile was used as solvent following previous research.[104] When the reaction was carried out at room temperature, formation of only traces of ketone **233** were observed, regardless of whether the reaction mixture was shaken or stirred (Table 13, Entries 1-2). By raising the temperature to 83 °C, acetophenone (**233**) was obtained in a good yield of 70% (Entry 3). When heating more mildly at 60 °C, the yield was increased to 90% after 20 h (Entry 4).

With these primary data at hand, a more detailed optimization of the reaction conditions was to be carried out in the following.

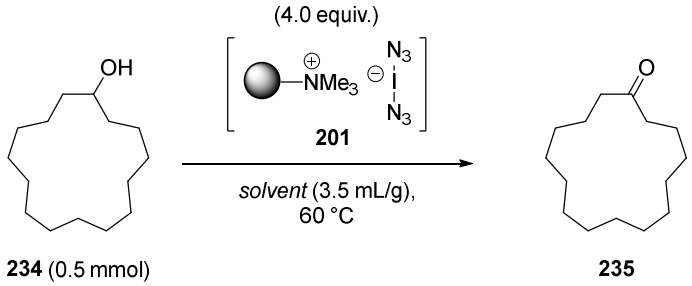
Table 13: Oxidation of 1-phenylethanol (**232**) using polymer-supported diazidoiodate (I) **201**.



entry	scale (mmol)	time	conditions	232	233
1	1.2	3 h	dry MeCN, rt, shaking	98%	2%
2	1.2	18 h	dry MeCN, rt, stirring	98%	2%
3	1.2	5 h	dry MeCN, 83 °C, stirring	-	70%
4	**0.6**	**20 h**	**dry MeCN, 60 °C, stirring**	**-**	**90%**

Encouraged by these results, a screening of different dry solvents was performed in the reaction of polymer-supported diazidoiodate (I) **201** with cyclopentadecanol (**234**) as test substrate. Toluene and cyclohexane were selected as examples of nonpolar solvents, tetrahydrofuran, ethyl acetate, acetonitrile, and *tert*-butyl acetate as polar aprotic solvents, and 2-propanol and methanol as polar protic solvents (Table 14). Reactions were carried out in a RADLEYS carousel and stopped either at complete conversion detected by TLC or after six days, and the ratio of alcohol **234** to ketone **235** was measured by NMR analysis. The best result was obtained with acetonitrile (Entry 1), followed by ethyl acetate (Entry 2). The use of 2-propanol as solvent did not lead to a sufficient conversion (Entry 8); possibly the solvent itself was oxidized.

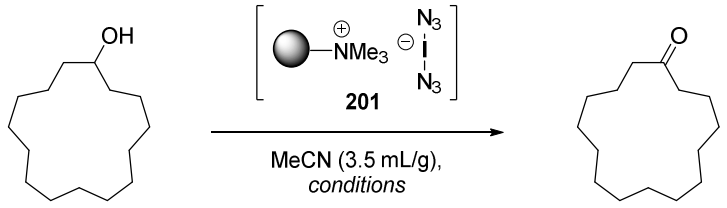
Table 14: Solvent screen for the oxidation of cyclopentadecanol (**234**) using polymer-supported diazidoiodate(I) **201**.



entry	solvent	time	ratio 234:235	entry	solvent	time	ratio 234:235
1	**acetonitrile**	**20 h**	**0:1**	**5**	cyclohexane	6 d	0.4:1
2	ethyl acetate	39 h	0:1	**6**	tetrahydrofuran	6 d	5.2:1
3	methanol	5 d	0.9:1	**7**	*tert*-butyl acetate	6 d	0.2:1
4	toluene	6 d	0.4:1	**8**	2-propanol	6 d	20:1

In view of these results, it was investigated whether a difference in conversion or purity of the oxidized species was obtained when dry or degassed acetonitrile was used at different temperatures (Table 15). But in fact, the use of dry acetonitrile as solvent at 60 °C resulted in complete conversion providing the purest product **235** (Entry 2). Interestingly, irradiation with a wavelength of 365 nm as an energy source at room temperature gave cyclopentadecanone (**235**) in 85% yield, which could indicate that a radical mechanism was also operating.

Table 15: Condition screen for the oxidation of cyclopentadecanol (**234**) using polymer-supported diazidoiodate (I) **201**.

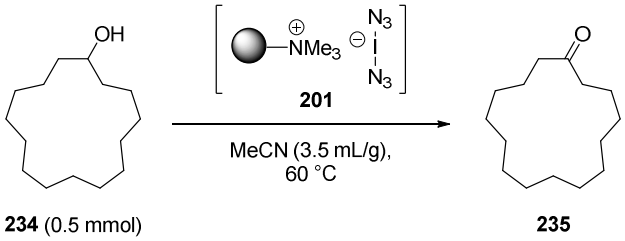


234 **235**

entry	scale (mmol)	equiv. (201)	time	conditions	234	235
1	0.5	4.0	7 h	dry MeCN, 83 °C	2%	96%
2	**0.5**	**4.0**	**24 h**	**dry MeCN, 60 °C**	**-**	**quant.**
3	0.5	4.0	24 h	dry MeCN, 40 °C	7%	92%
4	0.33	6.0	14 h	degassed MeCN, 83 °C	9%	90%
5	0.33	6.0	14 h	degassed MeCN, 60 °C	1%	98%
6	0.33	6.0	14 h	degassed MeCN, 40 °C	1%	65%
7	0.33	6.0	16 h	dry MeCN, h*v* (365 nm), rt	-	85%

To determine the optimum amount of resin **201** as oxidant, an equivalent screening was performed using 2.0 to 6.0 equivalents of reagent **201** (Table 16). Reactions were terminated when complete conversion of alcohol **434** was observed and judged by TLC. When 2.0 or 3.0 equivalents of resin **201** were used, the reactions lasted four days and yielded only 75-85% (Entries 1-2). Performing the oxidations with 5.0 and 6.0 equiv. of diazidoiodate (I) **201** resulted in faster conversion but lower purity. Thus, the already established protocol using 4.0 equiv. gave the best result with quantitative conversion to pure ketone **235**.

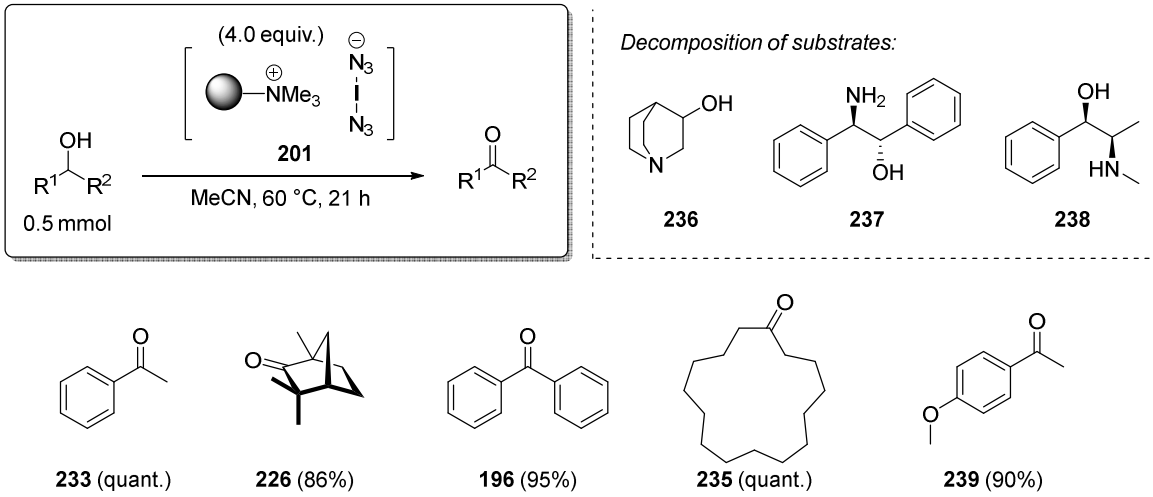
Table 16: Equivalent screen for the oxidation of cyclopentadecanol (**234**) using polymer-supported diazidoiodate (I) **201**.



234 (0.5 mmol) **235**

entry	equiv. (201)	time	yield
1	2.0	4 d	85%
2	3.0	4 d	75%
3	**4.0**	**20 h**	**quant.**
4	5.0	20 h	90%
5	6.0	20 h	90%

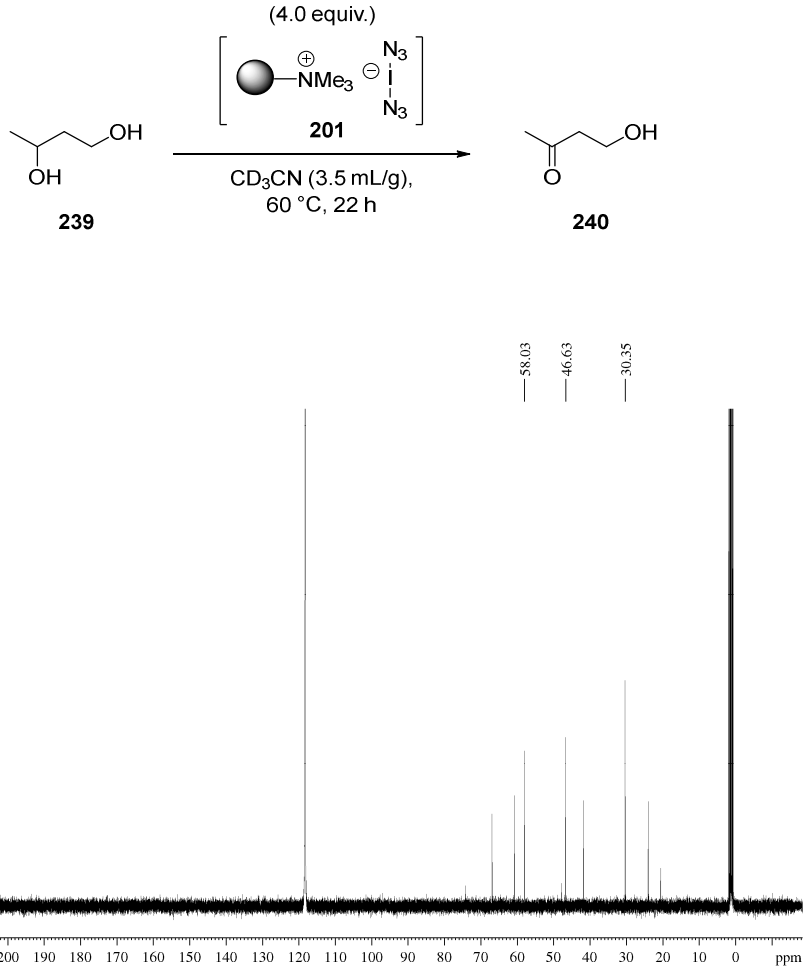
Considering these factors, it can be concluded that the optimal settings for the oxidation of secondary alcohols comprise stirring 4.0 equiv. of resin **201** in dry acetonitrile at a temperature of 60 °C in an overnight reaction (16-24 hours). Under these conditions, oxidation of various secondary alcohols was performed (Scheme 66). Thus, in addition to cyclopentadecanol and 1-phenylethanol, diphenylmethanol, fenchyl alcohol and 1-(4-methoxyphenol)ethanol could be oxidized to the corresponding ketones **235**, **233**, **196**, **226** and **239** in very good yields ranging from 86% to quantitative conversions. Interestingly, alcohols **236**, **237** and **238**, containing nitrogen functionalities, decomposed under these reaction conditions.



Scheme 66: Oxidations of secondary alcohols under thermal conditions.

B3.2.2 Chemoselective Oxidation of Diols at 60 °C

With this in mind, diols containing both a primary and a secondary hydroxyl group were selected as more complex substrates for a chemoselectivity study. The purpose was to determine whether only the secondary alcohol function was oxidized under the optimized oxidation conditions described above. The first substrate tested was the volatile butane-1,3-diol (**239**) in deuterated acetonitrile as solvent (Scheme 67). Such a procedure has the advantage that NMR spectra can be measured directly from the crude reaction mixture. The resulting ^{13}C-NMR spectrum clearly shows a mixture of diol **239** and ketone **240** with the associated chemical shift of the carbonyl carbon at 209.35 ppm (cf. Lit.:[105] ^{13}C δ ($CDCl_3$): 209.5 ppm), indicating that only oxidation of the secondary alcohol has occurred and no oxidation of the primary alcohol function, whose carbonyl carbon would expectedly have a chemical shift of 198.6 ppm ($CDCl_3$) according to the literature.[106]



Scheme 67: ^{13}C-NMR analysis shows selective oxidation of secondary alcohol using polymer-bound bisazidoiodate (I) **201**.

[105] F. Li, N. Wang, L. Lu, G. Zhu, *J. Org. Chem.* **2015**, *80*, 3538-3546.
[106] T. Nakano, T. Terada, Y. Ishii, M. Ogawa, *Synthesis* **1986**, *9*, 774-776.

Based on this observation, the oxidation of further diols was investigated (Table 17). For this purpose, diols **293-242** served as test compounds and the previously described thiosulfate resin **200** was used for workup. It became apparent that the best results for diol oxidation were likewise obtained with 4.0 equiv. of polymer **201** at 60 °C in acetonitrile, as already described for the oxidation of secondary alcohols. Under these conditions, the oxidation of diol **239** was first reexamined. Since no complete conversion was observed after 22 hours, the reaction was repeated in deuterated solvent and its progress was followed by ^{13}C-NMR analysis. However, some starting material could still be observed after five days (Entry 1). At a temperature of 83 °C, the presence of ketone **240** could no longer be detected, only diol **239** and traces of a new, unknown compound were found (Entry 2). Diol **241** was also oxidized to the corresponding ketone with remarkable chemoselectivity, although without complete conversion. Neither an increase in resin **201** equivalents nor an increase in temperature resulted in a significant difference (Entries 3-5). Interestingly, oxidation of diol **242** was not possible at all. Increasing the temperature to 83 °C or using 8.0 equivalents of polymer **201** (Entries 6-8) had no effect. A possible reason for this could be the 1,2-distance between the hydroxyl groups in contrast to the 1,3-relationship in diols **239** and **241**.

In addition, acetal **243** was chosen as another test substrate with an 1,2-distance between alcohol functions. In this case, 17 equivalents of resin **201** were used to provide a particularly large excess of oxidant to be tested, since oxidation of diol **239** was not completed after a reaction time of five days when only 4.0 equivalents of resin **201** were used. Unfortunately, even after 38 hours, the crude NMR spectrum showed mainly starting material and traces of a ketone that decomposed before further purification and characterization were possible (Entry 9). For this reason, it was decided to connect TBS-protection immediately after the oxidation step and to reduce the amount of resin **201**, since the high excess could be a reason for the decomposition (Entries 10-11). When only five equivalents of resin **201** were employed, the crude NMR showed only the protected diol **243** (Entry 10), and even with 10 equivalents of resin **201**, starting material **243** remained after three days with the crude NMR spectrum showing a second compound which again decomposed before purification and characterization were possible (Entry 11).

Since the previous test substrates tended to decompose, pyranol **244** was chosen as further diol for oxidation of the secondary alcohol functionalities because it also exhibited an 1,3-distance of alcohol functionalities. The amount of resin **201**, reaction time, and temperature were identical to the previous reaction approaches for the oxidation of acetal **243**, and unfortunately, so were the reaction results. All three reaction conditions gave only trace amounts of new compounds which decomposed before further analysis was possible, and no complete conversion of pyranol **244** was

observed (Entries 12-14). Only the application of five equivalents of polymer **201** showed traces of a ketone in the crude NMR material (Entry 13).

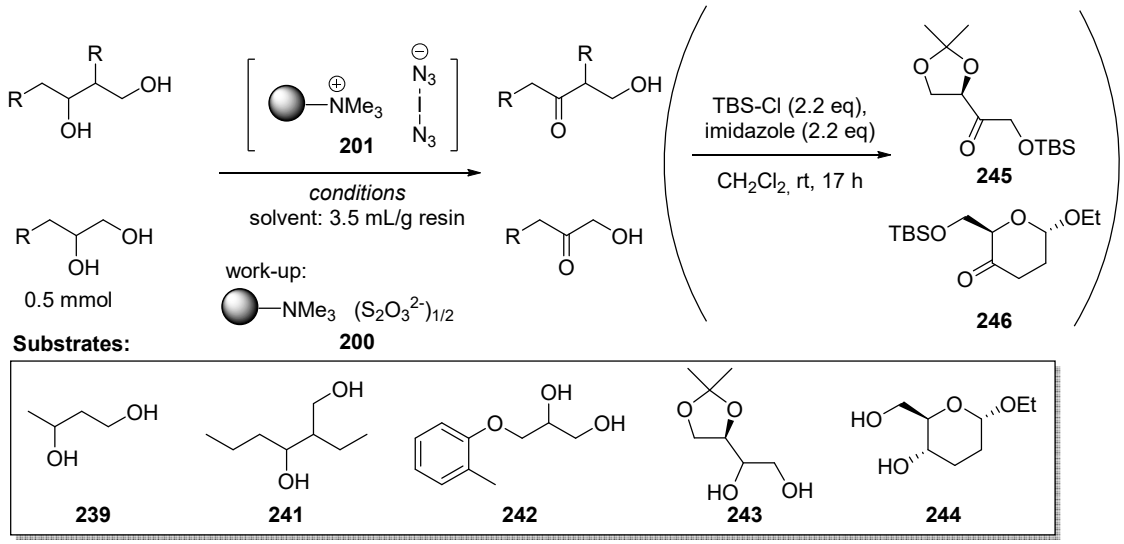
To avoid decomposition during the oxidation of diols **243** and **244**, both reactions were tested in deuterated acetonitrile as solvent. The idea was to perform a NMR measurement directly from the crude reaction mixture, as a proof-of-concept study based on the model oxidation of diol **239**.

When studying the oxidation of diol **243** in CD_3CN and using 14 equivalents of resin **201**, the crude NMR spectrum taken after 40 hours only revealed the starting material **243** and an onset of decomposition (Entry 15), while the NMR spectrum after 4.5 days indicated complete decomposition (Entry 16). Using 5.0 equivalents of resin **201**, NMR spectra after 17 hours revealed only diol **243** and after 44 hours traces of a new compound which was not a carbonyl compound, as the low field chemical shift in the ^{13}C-NMR spectrum appeared at 154 ppm (Entries 17-18). Only under irradiation conditions (365 nm) a new peak appeared at 207 ppm, which could belong to a ketone (Entry 19). Unfortunately, the characterization of this new compound was not possible due to the small amount of material.

Oxidation of pyranol **244** in deuterated acetonitrile showed a similar trend to the previous reactions. Using 14 equivalents of resin **201**, the crude NMR after 40 hours showed mainly the starting material **244** and traces of a new compound that was not a carbonyl compound, as the highest chemical shift in the ^{13}C-NMR spectrum appeared at 154 ppm (Entry 20). Decomposition was observed in the NMR measurement after 4.5 days (Entry 21). When 5.0 equiv. of resin **201** were employed, the ^{13}C-NMR spectrum still indicated pyranol **244** and traces of a new compound with the low field shift at 154 ppm (Entries 22-23). Using a photochemical activation mode (365 nm), a new signal appeared at 210 ppm in the ^{13}C-NMR that matched a keto group, but its characterization was not possible due to the small amount of material available (Entry 24).

Given these unsatisfactory results, further investigation of oxidation under photochemical conditions was carried out in the following.

Table 17: Thermal oxidations of diols using resin **201** (*yields calculated from NMR spectra of crude products).

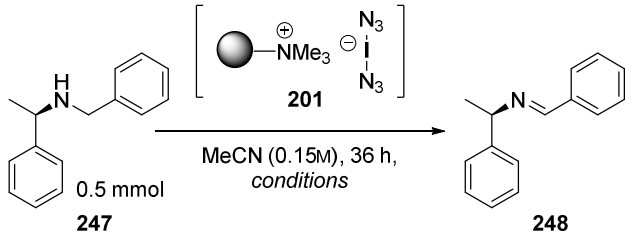


entry	SM	equiv. (201)	solvent	°C	time	TBS	result
1	**239**	4.00	$CDCl_3$	60	5 d	**-**	**ketone** + SM
2	**239**	4.00	$CDCl_3$	83	5 d	-	SM + traces of new compound (no ketone)
3	**241**	4.00	MeCN	60	2 d	**-**	**ketone** (75%)* + SM
4	**241**	4.00	MeCN	83	3 d	**-**	**ketone** (65%)*+ SM
5	**241**	5.00	MeCN	60	3 d	**-**	**ketone** (75%)*+ SM
6	**242**	3.00	MeCN	60	2 d	-	SM +traces of new compounds (no ketone)
7	**242**	4.00	MeCN	83	2 d	-	SM +traces new compounds (no ketone)
8	**242**	8.00	MeCN	60	3 d	-	SM +traces of new compounds (no ketone)
9	**243**	17.0	MeCN	60	38 h	-	SM and traces of ketone, decomposition before purification
10	**243**	5.00	MeCN	65	17 h	yes	protected SM
11	**243**	10.0	MeCN	60	3 d	yes	protected SM + fragments (^{13}C δ 153 ppm), decomposition before purification
12	**244**	17.0	MeCN	60	38 h	-	SM and new peaks (^{13}C δ 154 ppm), decomposition before purification
13	**244**	5.00	MeCN	65	17 h	yes	protected SM + traces of ketone, decomposition before purification
14	**244**	10.0	MeCN	60	3 d	yes	protected SM + new peaks (^{13}C δ 153 ppm), decomposition before purification
15	**243**	14.0	CD_3CN	63	40 h	-	SM, decomposition started
16	**243**	14.0	CD_3CN	63	5 d	-	decomposition
17	**243**	5.00	CD_3CN	60	17 h	-	only SM
18	**243**	5.00	CD_3CN	60	44 h	-	SM and new compound (^{13}C δ 154 ppm)
19	**243**	5.00	CD_3CN	rt, hν 365 nm	15 h	-	SM + traces of ketone
20	**244**	14.0	CD_3CN	63	40 h	-	crude NMR: SM + new peaks (^{13}C δ 154 ppm)
21	**244**	14.0	CD_3CN	63	5 d	-	crude NMR: decomposition
22	**244**	5.00	CD_3CN	60	17 h	-	SM + new peak (^{13}C δ 154 ppm)
23	**244**	5.00	CD_3CN	60	44 h	-	SM + new peaks (^{13}C δ 154 ppm)
24	**244**	5.00	CD_3CN	rt, hν 365 nm	15 h	-	SM + traces of ketone, not enough material for complete characterization

B3.2.3 Oxidation of Amines

In a proof-of-concept study, it was investigated whether amines could also serve as substrates for this type of oxidation protocol. And indeed, imines can be formed under the described conditions with polymer-bound iodoazide **201** (Table 18). The best result for the oxidation of (*R*)-*N*-benzyl-1-phenylethan-1-amine (**247**) was obtained using 4.0 equiv. of polymer **201** and at a temperature of 83 °C within 36 h (Entry 2). At 60 °C and under ultraviolet irradiation (365 nm), a yield of about 70% was obtained (Entries 1, 3). Column chromatographic purification was achieved by adding 1% triethylamine to the eluent.

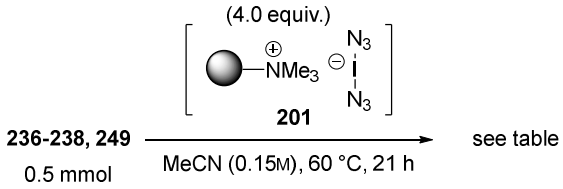
Table 18: Oxidation of amine **247** (*yields calculated based on crude ^{1}H-NMR spectra).

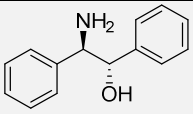
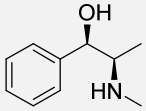
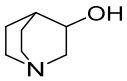
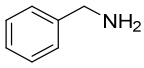
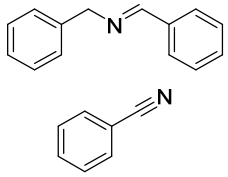


entry	conditions	result
1	4.0 equiv. of polymer **201**, 60 °C	70-80%*
2	4.0 equiv. of polymer **201**, 83 °C	quant.
3	4.0 equiv. of polymer **201**, hν (365 nm), rt	60-70%*

Subsequently, the scope of this oxidation process was extended to several substituted amines **236-239**, **249**, some of which also contained a hydroxyl group (Table 19). Surprisingly, all of these amines tend to decompose under the described conditions (4.0 equiv. of polymer **201**, 60 °C, 21 h; Entries 1-3). Using benzylamine (**249**) as substrate, a mixture of benzonitrile (**251**) and dimer **250** was formed (Entry 4). To examine whether decomposition of the amino alcohols accompanied the reaction or occurred during the workup process, these reactions were repeated in deuterated acetonitrile. Interestingly, the result was almost identical. Amines **237** and **238** decomposed again and amine **236** did not react at all. In summary, decomposition occurred during the reaction process. For this reason, the oxidation of amines with polymer-bound bisazidoiodate (I) **201** was not further assessed.

Table 19: Investigations on amine oxidations using resin **201** (*yields calculated from NMR spectra of crude products).



entry	substrate	result	entry	substrate	result
1	 **237**	decomposition	**3**	 **238**	decomposition
2	 **236**	decomposition	**4**	 **249**	 **250**:**251** (1:1)

B3.3 Photochemical Oxidation of Alcohols

Parts of this chapter B3.3 have already been published.[107]

Polymer-bound azidoiodate (I) **201** can also be considered as Hal-X species. HUANG *et al.*[108] determined the bond dissociation energy (BDE) for H-N_3 (**256**) to be 92.7 kcal/mol, indicating that the azide radical is a much stronger hydrogen atom abstractor than iodine or bromine radicals (BDE (H-I) = 71.3 kcal/mol, BDE (H-Br) = 86.5 kcal/mol).[109] The I-N_3 bond dissociation energy of azidoiodinans **174**, **253** and **254** show similar values to that of iodine azide (**256**) in the range of 29-35 kcal/mol (Figure 19). Although no photocatalytic reactions with iodine azide (**256**) have been published so far, it is assumed that this is only due to its explosive character.

[107] T. Kösel, G. Schulz, G. Dräger, A. Kirschning, *Angew. Chem. Int. Ed.* **2020**, *59*, 12376-12380; *Angew. Chem.* **2020**, *132*, 12475-12479.
[108] X. Huang, J. T. Groves, *ACS Catal.* **2016**, *6*, 751-759.
[109] (a) Y. R. Luo, *Comprehensive Handbook of Chemical Bond Energies*; CRC Press, Boca Raton, FL, **2007**; (b) W. R. Zheng, Z. C. Chen, W. X. Xu, *Chin. J. Chem. Phys.* **2013**, *26*, 541-548.

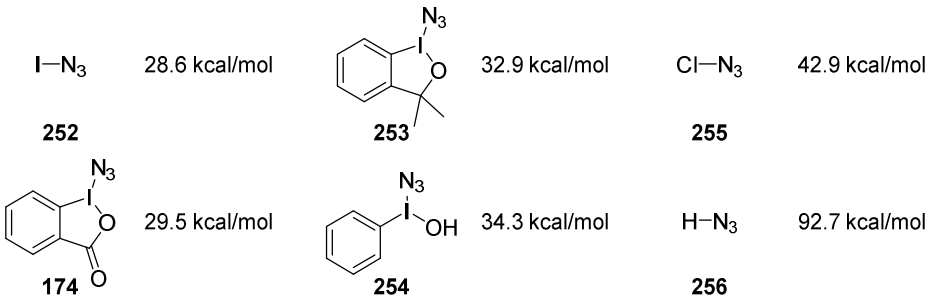


Figure 19: X-N_3 bond dissociation energies (BDE) of common organic iodine azides.

With this in mind, another approach for the oxidation of secondary alcohols was the use of blue LED irradiation as an energy source. For this purpose, a 3D-printed photoreactor with a diameter of 115 mm was designed and constructed by G. SCHULZ and A. STEPANYUK from the KIRSCHNING group. A 5 m long LED light bar with 60 LED/m (type 5050 RGB) was used as light source (12 W/m). A 120 mm PC fan was employed to cool the reactor to ambient temperature during the reaction. The color was set to blue (wavelengths 445 - 510 nm) and the reaction vessels could be integrated directly into the lid of the reactor (Figure 20).

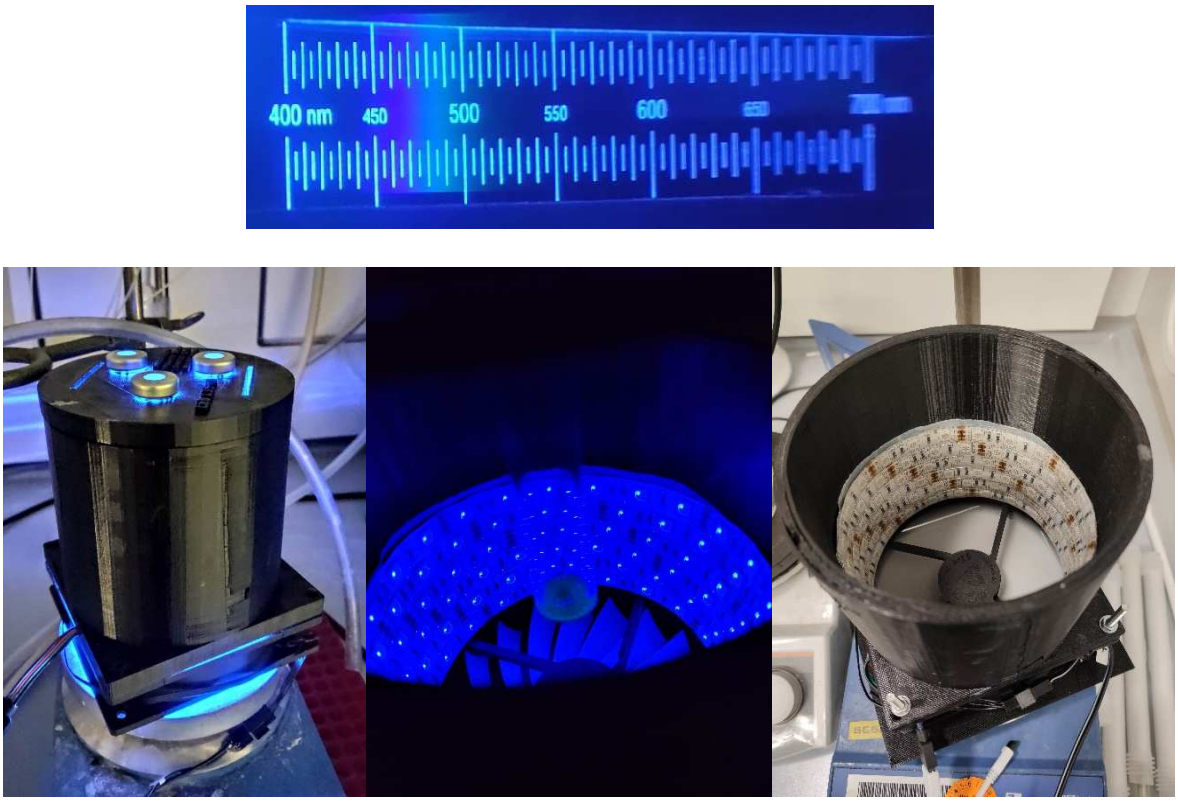
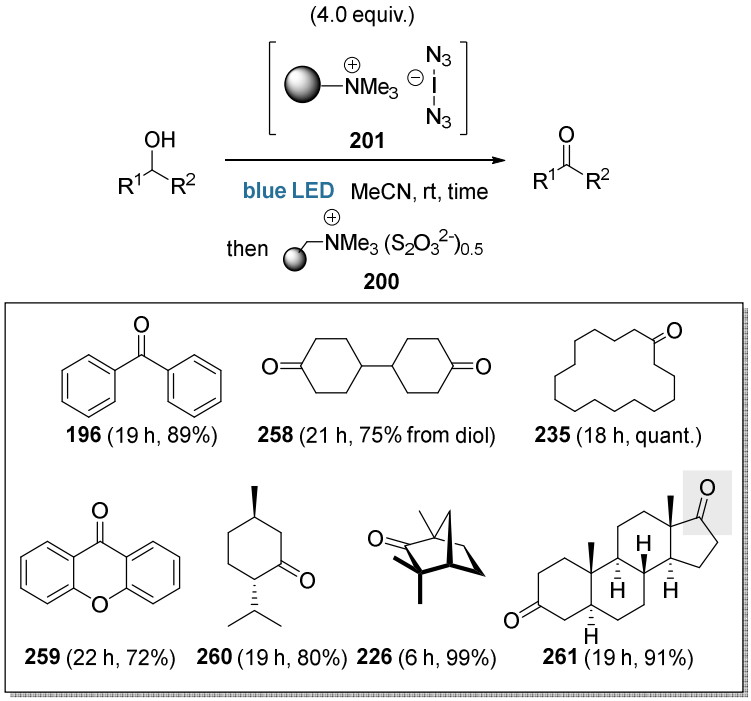


Figure 20: 3D-printed photoreactor. The color was set to blue (wavelengths 445 – 510 nm).[107]

B3.3.1 Photochemical Oxidation of Secondary Alcohols

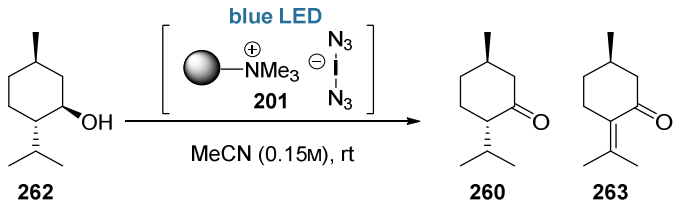
With this in mind, a more promising approach for the oxidation of secondary alcohols was to implement the photoreactor described above using blue LED light (445 – 510 nm) as energy source and 4.0 equiv. of resin **201** in acetonitrile at ambient temperature. With this method, secondary alcohols were oxidized to the corresponding ketones in excellent yields (72% - quant.) within six to 22 hours. It was irrelevant whether the alcohol was aromatic or aliphatic or if two alcohol functionalities coexisted (Scheme 68). For work-up, thiosulfate resin **200** was employed again, which easily removed excess iodine from the reaction mixture and could subsequently be simply filtered off.[107]



Scheme 68: Photochemical oxidation of secondary alcohols with resin **201** (grey mark refers to site of oxidation).[107]

Interestingly, while studying the oxidation of menthol (**262**), it was observed that pulegone (**263**) was synthesized as a byproduct in different ratios when the amount of resin **201** was varied (Table 20). Using 4.0 equivalents of resin **201**, 15% menthone (**260**) and 23% pulegone (**263**) were synthesized (Entry 1). When the amount of resin **201** was increased to 8.0 equiv. the yield of menthone (**260**) increased to 80% and the yield of pulegone (**263**) decreased to 20% (Entry 2), and when 10.0 equiv. of resin **201** were employed, menthone (**260**) was obtained in 98% yield, without pulegone (**263**) as a byproduct (Entry 3). Interestingly, quantitative conversion to menthone (**260**) was achieved when only 2.0 equiv. of resin **201** were applied (Entry 4).

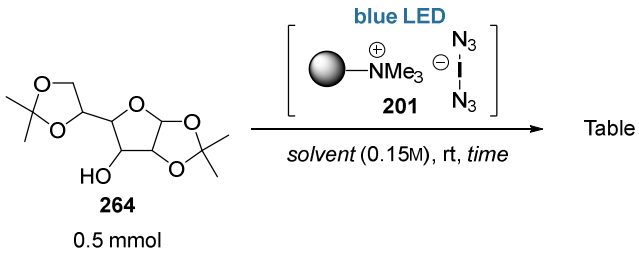
Table 20: Investigations into the photochemical oxidation of menthol (**262**) using blue LED light and resin **201**.



entry	equiv. (201)	time	ratio between menthone (260) and pulegone (263) (yield calculated by *GC or #NMR)
1	4.0	19 h	15:34*
2	8.0	22 h	80:20#
3	10.0	22 h	98:0#
4	**2.0**	4 d	quant:0#

Encouraged by these results, a more complex carbohydrate **264** was used as a secondary alcohol test substrate (Table 21). When deuterated acetonitrile was used as solvent, the crude NMR showed a mixture of many different compounds, indicating decomposition during the reaction process (Entry 1). It is assumed that polymer-bound iodine azide **201** reacts with furan rings, leading to decomposition. However, when THF and Et_2O were employed as solvents, the crude NMRs revealed only starting material, indicating that the assumed azide radicals react with the solvents (Entries 2-3).

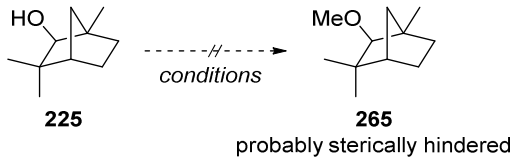
Table 21: Photochemical oxidation of carbohydrate **264** using polymer-bound iodine azide **201**.



entry	solvent	time	result
1	CD_3CN	19 h	crude NMR shows mixture of many different compounds
2	THF	20 h	crude NMR shows only SM
3	Et_2O	20 h	crude NMR shows only SM

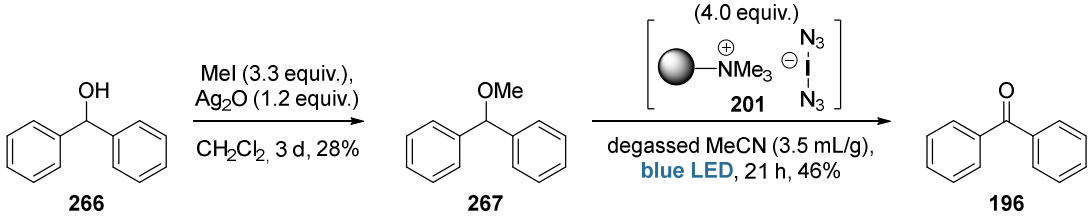
To demonstrate that alcohol oxidations proceed via a radical mechanism involving ketyl radicals, a methyl ether was to be prepared from a secondary alcohol which had previously been successfully oxidized. For this purpose, fenchyl alcohol (**225**) was mixed with MeI and Ag_2O or NaOH respectively (Table 22, Entries 1-2). However, methylation did not occur under either condition, indicating that the fenchyl alcohol was too sterically hindered.

Table 22: Anticipated methylation of fenchyl alcohol (**225**).



entry	conditions	result
1	MeI (3.3 equiv.), Ag_2O (1.2 equiv.), CH_2Cl_2	no conversion
2	MeI (3.3 equiv.), NaOH (1.2 equiv.), CH_2Cl_2	no conversion

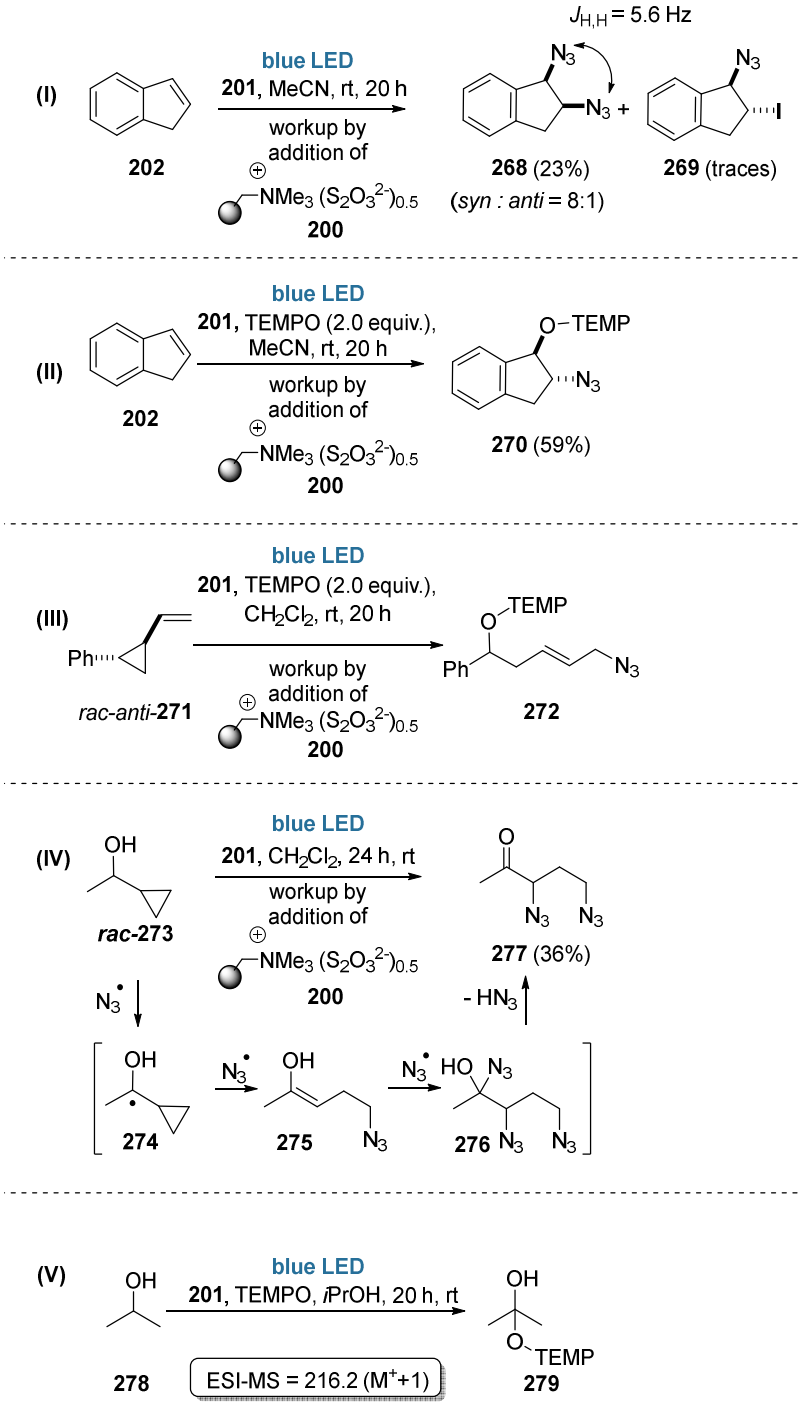
For this reason, the substrate was replaced by diphenylmethanol (**266**). Methylation with MeI and Ag_2O in CH_2Cl_2 gave methyl ether **267** in 28% yield (Scheme 69) which was subjected to the established conditions and the corresponding ketone **196** was isolated as the major product, indicating that the oxidation of alcohols occurs via ketyl radicals.[107]



Scheme 69: Photochemical oxidation of methyl ether **267**.

For further evidence of a radical mechanism, a series of experiments was carried out by G. SCHULZ. Firstly, indene (**202**) was exposed to polymer-bound iodine azide **201** under irradiation with blue LED light, giving the *syn*-bisazido adduct **268** (Scheme 70, I). As described in Section B1.4.3, the *anti*-azido iodination product **269** is formed under non-radical conditions, which is indicative of a radical mechanism. Further evidence for the presence of azide radicals was obtained by using TEMPO as a radical scavenger. Thus, the *anti*-1,2-adduct **270** of indene (**202**) was formed (Scheme 70, II). SCHULZ also performed a radical clock experiment under the established conditions. For this, vinylcyclopropane **271** was used as starting material and gave the ring-opened allyl azide **272** as clear evidence for an alkyl radical intermediate (Scheme 70, III). In addition, 1-cyclopropylethan-1-ol (**273**) was converted to bisazide **277** under the photochemical conditions, providing unequivocal evidence that ketyl radical **274** must have been formed as an intermediate (Scheme 70, IV). Finally, he performed detailed mass spectrometric studies (LC-ESI-MS) with the crude reaction mixture of the oxidation of isopropanol **278** in the presence of TEMPO. A signal was found at $m/z = 216.2$ ($M^+ + 1$) indicative of the TEMPO adduct **279** (Scheme 70, V). In conclusion, all these experiments provided evidence for the formation of azide and ketyl radicals

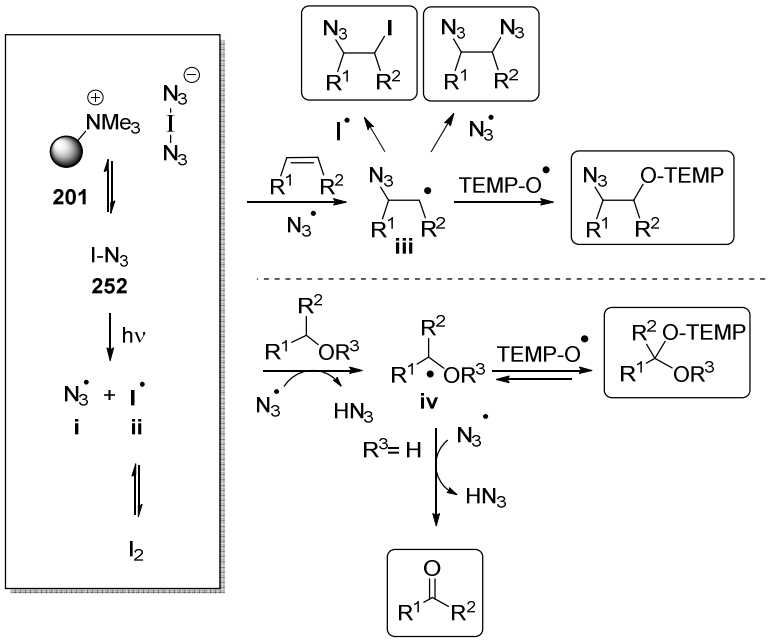
during the oxidation of secondary alcohols by polymer-bound iodine azide **201** under blue LED light irradiation.[107]



Scheme 70: Experiments (I-V) that provide evidence for azide and ketyl radical formation during alcohol formation performed by GÖRAN SCHULZ.[107]

Based on these results, the following radical mechanism can be proposed (Scheme 71): Polymer-bound bisazidoiodate (I) **201** gives rise to iodine azide (**252**), which is homolytically cleaved under photocatalytic conditions into an azide radical **i** and an iodine radical **ii**. The latter is able to recombine to I_2, which is not described for the azide radical. Instead, **i** can interact with alkenes,

and the newly formed alkene radical **iii** can be captured by iodine radicals, azide radicals or TEMPO. Moreover, the azide radical **i** can force C-H abstraction next to a C-O bond, leading to a ketyl radical **iv**. This can either be captured by TEMPO or form the corresponding ketone by attack of a second azide radical.[107]



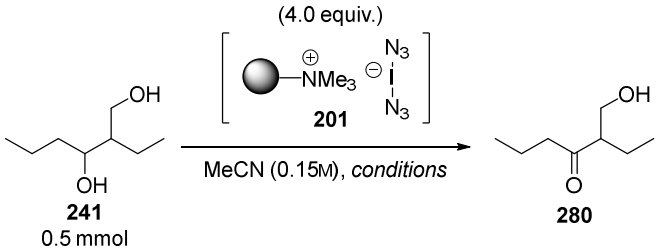
Scheme 71: Proposed mechanistic considerations for radical transformations.[107]

B3.3.2 Photochemical and Chemoselective Oxidation of Diols

Subsequently, the photochemical oxidation of diols was investigated (Table 23). For this purpose, different wavelengths were tested by employing blue and green LED light. 2-Ethylhexane-1,3-diol (**241**) was used as test substrate with 4.0 equiv. of polymer **201** in acetonitrile, and the reaction result was determined in ratios of starting material **241**, ketone **280**, and an unknown byproduct. When the reaction mixture was irradiated with blue LED light for 12 hours, an 1:1.5 mixture of ketone **280** and undesired byproduct was obtained (Entry 1). The amount of byproduct could be reduced by irradiating the mixture with green LED light for 20 hours (Entry 2). However, the best result was observed by irradiating with blue LED light for 5 hours (Entry 3). Only ketone **280** was synthesized selectively in 88% yield. When irradiated with green LED light for five hours, an 1:10 mixture of starting material **241** and ketone **280** was observed (Entry 4). As a blind experiment, diol **241** and polymer **201** were stirred in acetonitrile for 19 hours in the absence of light (Entry 5). In this case, a 22:1 mixture of diol **241** and ketone **280** was obtained. It was also investigated whether the use of 6.0 equiv. of resin **201** instead of 4.0 equiv. could improve the yield (Entry 6). Interestingly, this is not the case. The yield decreased from 88% with 4.0 equiv. to 60% with 6.0 equiv. of **201**.

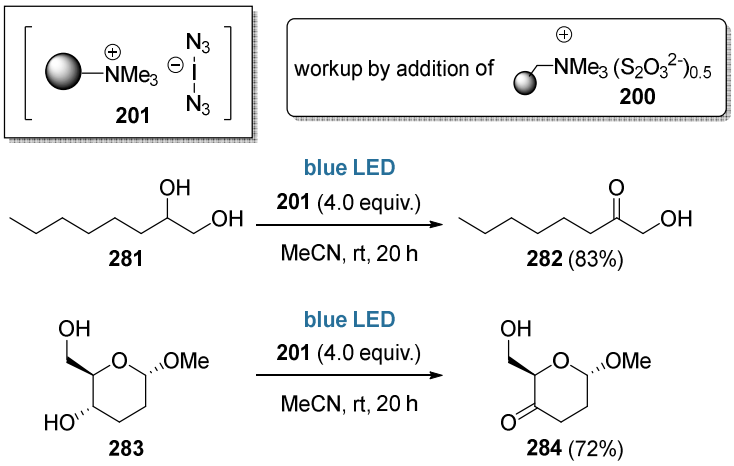
Also, as expected, irradiation of diol **241** with blue LED light without addition of reagent **201** did not lead to any conversion (Entry 7). This experiment was performed to prove that reagent **201** is responsible for the oxidation itself and that the irradiation only catalyzes this process.

Table 23: Photochemical oxidations of diols using polymer-bound iodine azide **201**.



entry	conditions	result (ratio of diol 241, ketone 280 and unknown byproduct)
1	4.00 equiv. (**201**), blue LED light, rt, 12 h	0:1:1.5
2	4.00 equiv. (**201**), green LED light, rt, 20 h	0:1:0.5
3	4.00 equiv. (**201**), **blue LED light, rt, 5 h**	**0:1(88%):0**
4	4.00 equiv. (**201**), green LED light, rt, 5 h	1:10:0
5	4.00 equiv. (**201**), exclusion of light, rt, 19 h	22:1:0
6	6.00 equiv. (**201**), blue LED light, rt, 18 h	0:1(60%):0
7	**0.00 equiv**. (**201**), blue LED light, rt, 18 h	**no conversion**

Using blue LED light as a promising activation method and 4.0 equivalents of resin **201**, two more diols **281** and **283** were oxidized (Scheme 72). In both cases, the secondary hydroxyl group was oxidized with remarkable chemoselectivity to form the hydroxy ketones **282** and **284**. The selective oxidation of the 2,3-deoxyglycoside **283**[110] to the corresponding uloside **284** is particularly noteworthy and synthetically useful due to the circumvention of protecting group chemistry, which is a typical feature of carbohydrate synthesis.[107]

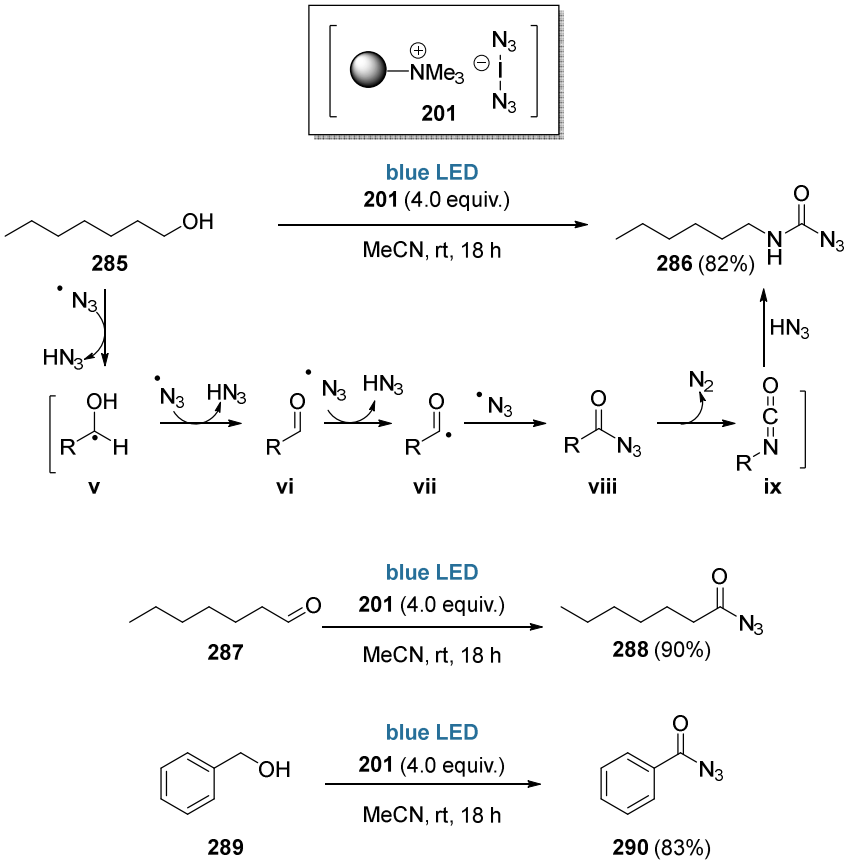


Scheme 72: Photochemical oxidation of diols using polymer-bound iodine azide **201**.[107]

[110] R. J. Ferrier, N. Prasad, *J. Chem. Soc. C,* **1969**, 570-575.

B3.3.3 Photochemical Oxidation of Primary Alcohols

Furthermore, primary alcohols were also oxidised by polymer-bound iodine azide **201** (Scheme 73). Compared to secondary alcohols being smoothly oxidised to the corresponding ketones within a few hours at room temperature, heptanol (**285**) reacted much slower. When **285** was exposed to polymer **201** under the typical photolytic conditions, hexylcarbamoyl azide (**268**) formed after 20 h. Mechanistically, it can be assumed that heptanal (**287**, **vi**) was formed first via ketyl radical **v** followed by H-abstraction and generation of an acyl radical **vii**. This is trapped by azide radical **i** to give acyl azide **viii**. Subsequently, a CURTIUS rearrangement would yield the corresponding isocyanate **ix** which finally reacts with HN_3 to give hexylcarbamoyl azide (**286**). Evidence for this sequence was collected, when heptanal (**287**) was exposed to polymer-bound iodine azide **201** under standard photolytic conditions. The acyl azide **288** was isolated in 90% yield. Obviously, CURTIUS rearrangement did not occur, nor did it when using benzyl alcohol (**289**). The number of equivalents of HX formed (X= I or N_3) is greater when starting from heptanol (**285**) compared to heptanal (**287**) promoting carbamoylazide **286** formation from acyl azide **viii**.[107]



Scheme 73: Photochemical oxidation of primary alcohols using polymer-bound iodine azide **201**.[107]

Moreover, the proposed mechanism was confirmed when an ^{1}H-NMR experiment was performed on the oxidation of heptanol (**285**) with iodine azide **201** under irradiation with blue LED light. NMR samples were taken at specific intervals and measured without further workup in deuterated acetonitrile after the solvent was evaporated. Figure 21 shows the spectra of heptanol (**285**), acyl azide **288**, and carbamoyl azide **286**, as well as the crude NMR spectra of the various samples. To characterize the individual compounds, the corresponding signals are highlighted in grey. Thus, the NH signal between 5.0 and 5.5 ppm and the CH_2 signal between 3.0 and 3.5 ppm are characteristic of carbamoyl azide **286**, the signal between 2.0 and 2.5 ppm shows the formation of the acyl azide **288** and the signal between 3.5 and 4.0 ppm shows the CH_2 group next to the alcohol functionality of **285**. In the low field area beyond 9.0 ppm, the proton of the aldehyde CO*H* characteristically appears. Interestingly, aldehyde **287** is formed as an intermediate after one hour and has disappeared completely after two days. After two hours, the formation of acyl azide **288** started and decreased in the last samples. The formation of carbamoyl azide **286** began to occur after two hours and after 30.5 hours heptanol (**285**) was completely converted. All these results support the previously described mechanism.

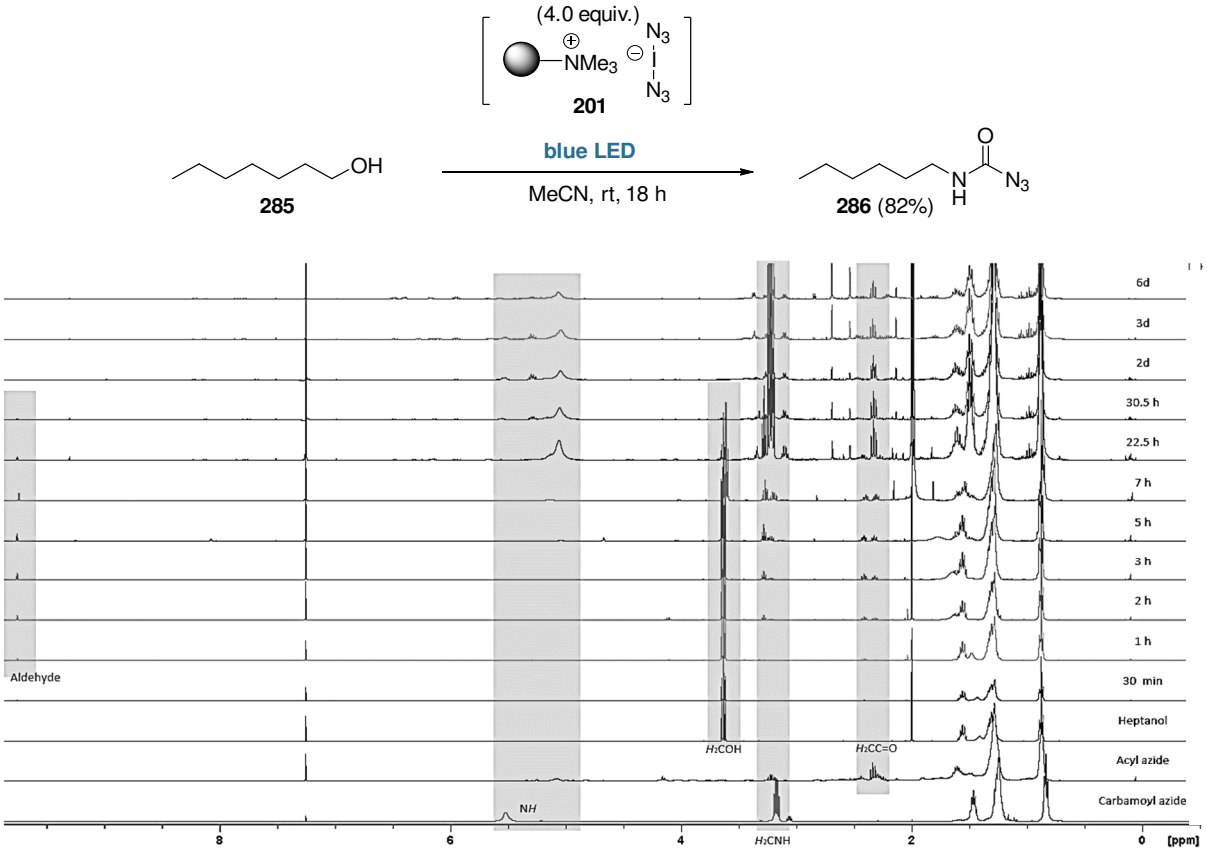
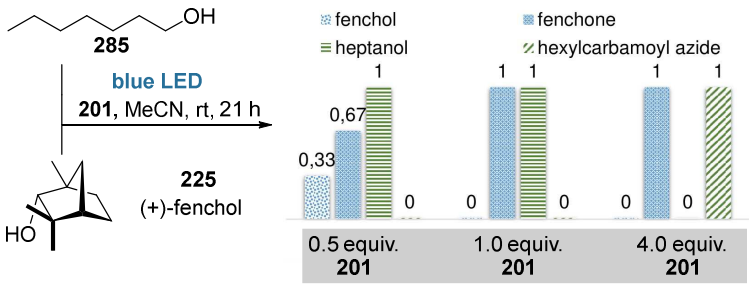


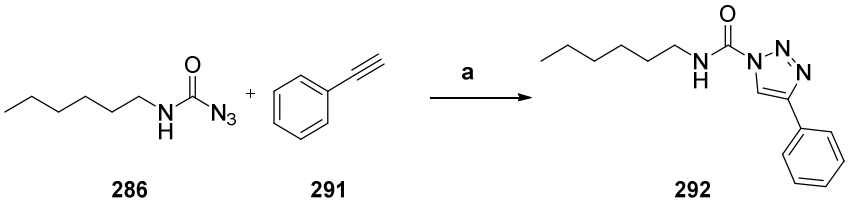
Figure 21: ^{1}H-NMR experiment: Photochemical oxidation of heptanol (**285**) using resin **201**. It shows the spectra of heptanol (**285**), acyl azide **288**, and carbamoyl azide **286**, as well as the raw NMR spectra of the various samples. To characterize the individual compounds, the corresponding signals are highlighted in grey.

The preference for the oxidation of secondary alcohols was clearly demonstrated in a competition experiment between (+)-fenchol (**225**) and heptanol (**285**) in the presence of various amounts of resin **201** with 21 h reaction time (Scheme 74). It was found that fenchol (**225**) was already oxidized when 0.5 equiv. of polymer **201** were used and the reaction was completed with the use of 1.0 equiv. of **201**. Whereas heptanol (**285**) showed no conversion using 1.0 equiv. yet; it required 4.0 equiv. of bisazidoiodate (I) **201** to form hexylcarbamoyl azide **286**.[107]



Scheme 74: Competition experiment between (+)-fenchol (**50**) and heptanol (**44**).[107]

With regard to carbamoyl azides, one convenient application is the possibility of their application in 1,3-dipolar cycloadditions. The resulting triazole ring is an important structure in drug and natural product chemistry. Using SHARPLESS conditions with $CuSO_4 \cdot 5H_2O$ and sodium ascorbate at ambient temperature, triazole **292** was synthesized in 76% yield starting from carbamoyl azide **286** and alkyne **291** (Scheme 75).[111]



Scheme 75: Click reaction of carbamoyl azide **286** and alkyne **291**: a) $CuSO_4 \cdot 5H_2O$ (1 mol%), sodium ascorbate (5 mol%), H_2O/*t*BuOH, 2:1, rt, 21 h, 76%.

B3.4 Iodination and Oxidative Azidation of Phenols

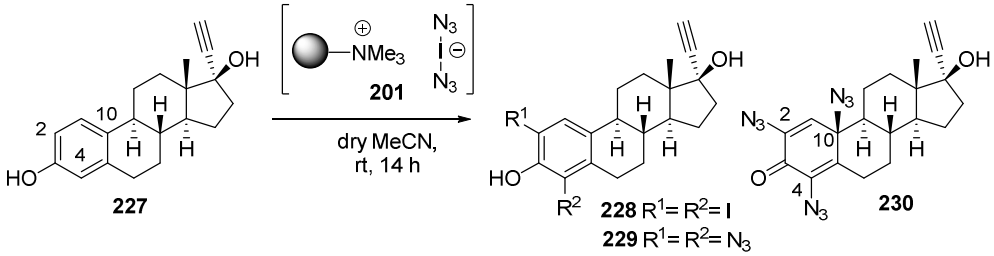
Parts of this chapter B3.4 have already been published.[112]

It was already established in the master thesis described above that ethinylestradiol (**227**) can be converted into the three estradiol derivatives **228**-**230** under treatment with polymer-supported bisazidoiodine (I) **201** at room temperature in dry acetonitrile (Table 24).[104] In this process, the

[111] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596-2599.
[112] T. Kösel, G. Dräger, A. Kirschning, *Org. Biomol. Chem.* **2021**, *19*, 2907-2911.

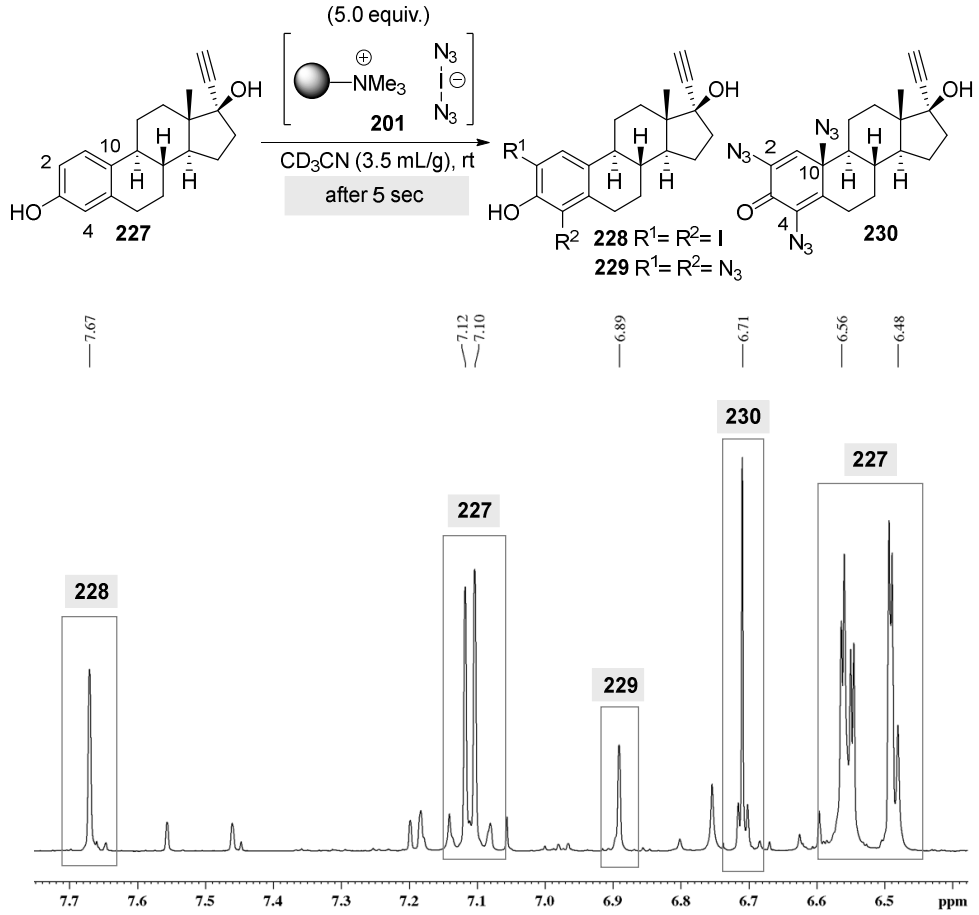
formation of dienone **230** with three azide groups appears to occur via the intermediates diiodide **228** and bisazido adduct **229**. In an initial experiment in which the amount of resin **201** was slowly increased, it was observed that when 1.0 and 2.0 equivalents of polymer **201** were used, respectively, diiodide **228** and diazide **229** were clearly detected (Entries 1-2). The percentage of triazido adduct **230** was steadily increasing along with the number of equivalents of resin **201**. With four equivalents of iodine azide **201**, only ethinylestradiol (**227**) and mainly product **230** were detected (Entry 3), and with five equivalents, the triazido adduct **230** could be isolated in 95% yield (Entry 4). However, this experiment did not provide more precise information on the time sequence of adduct formation.[104]

Table 24: Conversion of ethinylestradiol (**227**) using polymer-supported bisazidoiodine (I) **201**. [a]Ratios determined by ^{1}H-NMR spectroscopic analysis. [b]Isolated yield is given.[104]



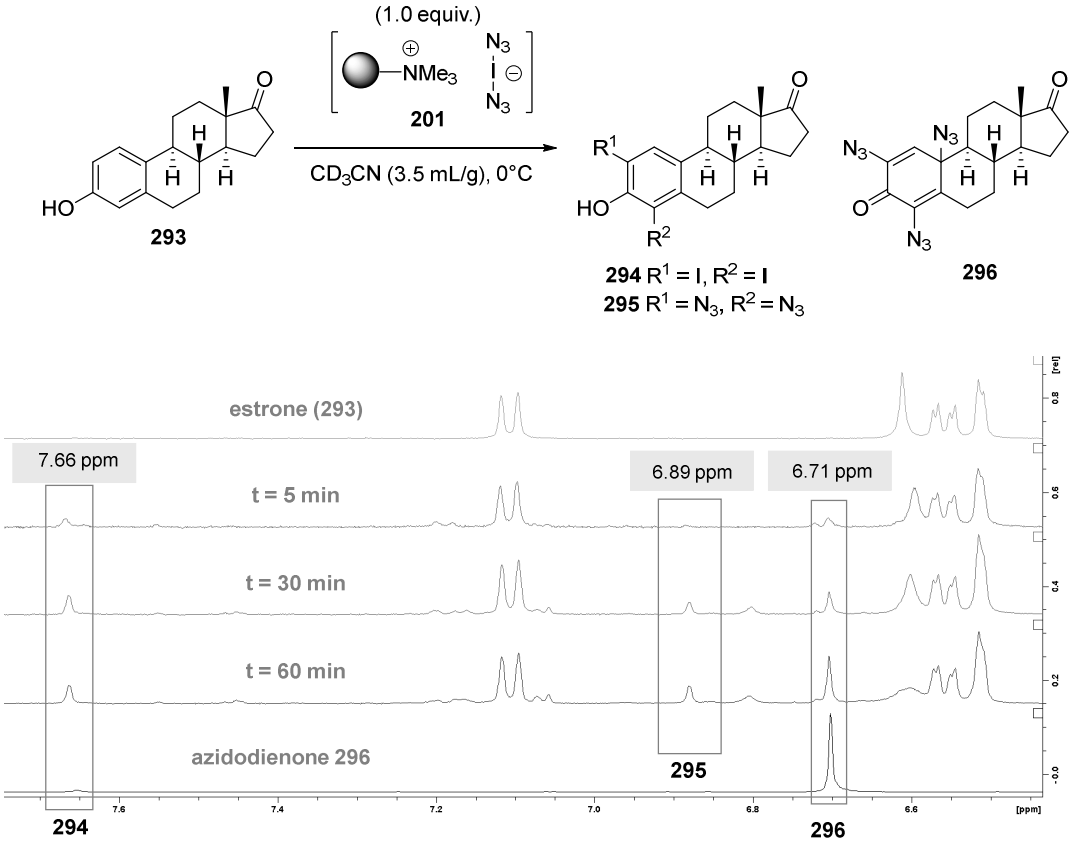
entry	equiv. (201)	227	228	229	230 in %[a]
1	1	64	14	4	17
2	2	29	21	5	45
3	4	10	-	-	90
4	5	-	-	-	95[b]

To obtain mechanistic information, an ^{1}H-NMR experiment was performed after converting ethinylestradiol (**227**) with five equivalents of **201** in deuterated acetonitrile at ambient temperature. Scheme 76 shows the ^{1}H-NMR spectrum of the sample recorded after a reaction time of only five seconds. Even after such a short time, the formation of diiodide **228** (δ = 7.67 ppm), bisazide **229** (δ = 6.89 ppm), and **230** (δ = 6.71 ppm) could be observed from the chemical shift of the proton in position 1 from the respective steroid derivative. All products **228-230** could be isolated and characterized. However, in order to obtain information about the chronology of the multistep process, it was necessary to modify the experiment.[112]



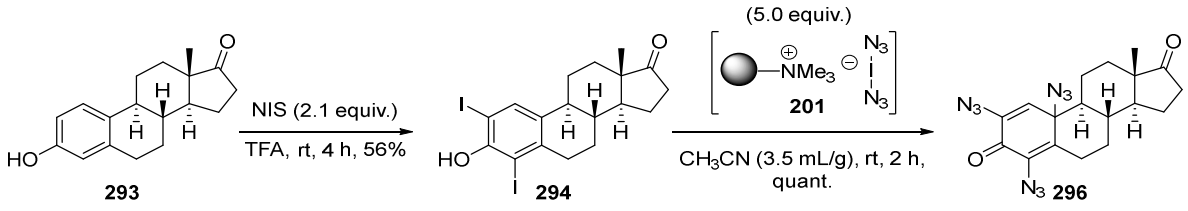
Scheme 76: Reaction monitoring of ethinylestradiol (**227**) with **201** by ^{1}H-NMR analysis. After five seconds, the corresponding H-1 signals from compounds **227**-**230** are clearly visible, as are the H-4 signals from **227** at 6.5 ppm. [112]

For this reason, the tracking of the reaction was repeated with estrone (**293**) as substrate. In the hope of gaining more clarity on the time course of iodide and azide formation, an attempt was made to slow down the reaction. For this purpose, only one equivalent of polymer-bound iodine azide **201** was employed, and the reaction was carried out at 0 °C in deuterated acetonitrile. Within an hour, several samples were taken and analyzed directly by ^{1}H-NMR spectroscopy, with the most informative NMR spectra shown in Scheme 77. This time, the chronology of the events and the formation of the diiodo and diazido adducts **294** and **295** could be revealed. After only five minutes, a strong signal was detected at δ = 7.66 ppm, characteristic of diiodide **294**. Subsequently, a signal at δ = 6.89 ppm appeared only after 30 minutes, which is indicative of the bisazido adduct **295**. These results suggest that diiodide **294** is most likely a precursor of bisazido adduct **295**, whereupon azidodienone **296** (δ = 6.71 ppm) is formed, showing a very clear peak in the NMR spectrum after only 60 minutes.[112]



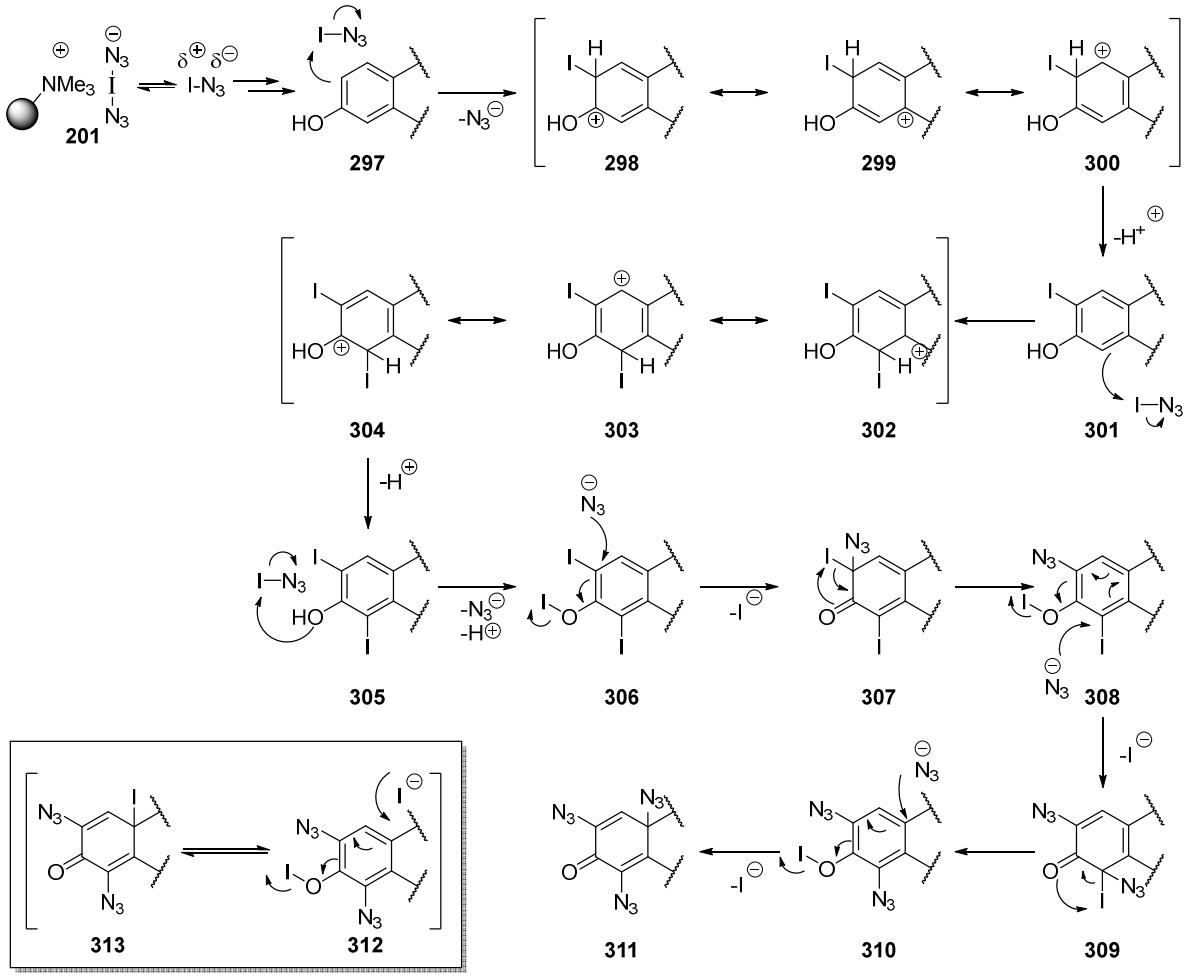
Scheme 77: Tracking of the reaction with estrone (**293**) as substrate and **201** by ^{1}H-NMR spectroscopic analysis. Samples were taken after indicated time. Bisazide **295** was not isolated, but the signal at δ = 6.89 ppm was assigned by comparison with the corresponding signal at δ = 6.89 ppm for bisazide **229**. Already after 5 min, diiodide **294** was formed followed by **295** revealing the timing of formation.[112]

To obtain a second proof that the formation of azidodienone **296** occurs via initial electrophilic iodination of the *ortho*-positions, diiodide **294** was prepared independently (Scheme 78). For this purpose, estrone (**293**) was converted to the corresponding diiodide **294** in 56% yield in a reaction with NIS and TFA. Adduct **294** was now exposed to bisazidoiodate (I) **201** under standard conditions to quantitatively afford azidodienone **296**.[112]



Scheme 78: Synthesis of azidodienone **296** starting from independently prepared diiodide **294**.[112]

These studies now allow the postulation of a mechanism in which the formation of azidodienone **311** occurs via initial building of diiodine **305**, followed by the formation of bisazido adduct **310** (Scheme 79). The first step is an electrophilic aromatic iodination by iodine azide in *ortho*-position to oxygen, giving rise to the arenium ion **298** and its resonance structures **299**-**300**. Proton abstraction and a second electrophilic aromatic substitution lead to the diiodinated compound **305**. The proposed activation of the phenolic position by iodine azide leads to the hypoiodite **306**. The subsequent nucleophilic addition of the azide results in the formation of dienone **307**, which after iodonium migration forms the new hypoiodite **308**. Aromatization is believed to be the driving force here. After two further azidations of compounds **308** and **310**, the latter facilitated by the strongly electrophilic character of dienone **310**, trisazido adduct **311** is finally formed. If iodide were to attack in the *para*-position of **312**, dienone **313** would be formed, which was not isolated, implying that this compound is energetically unfavorable.[104,112]



Scheme 79: Postulated mechanism for azidodienone formation.[104,112]

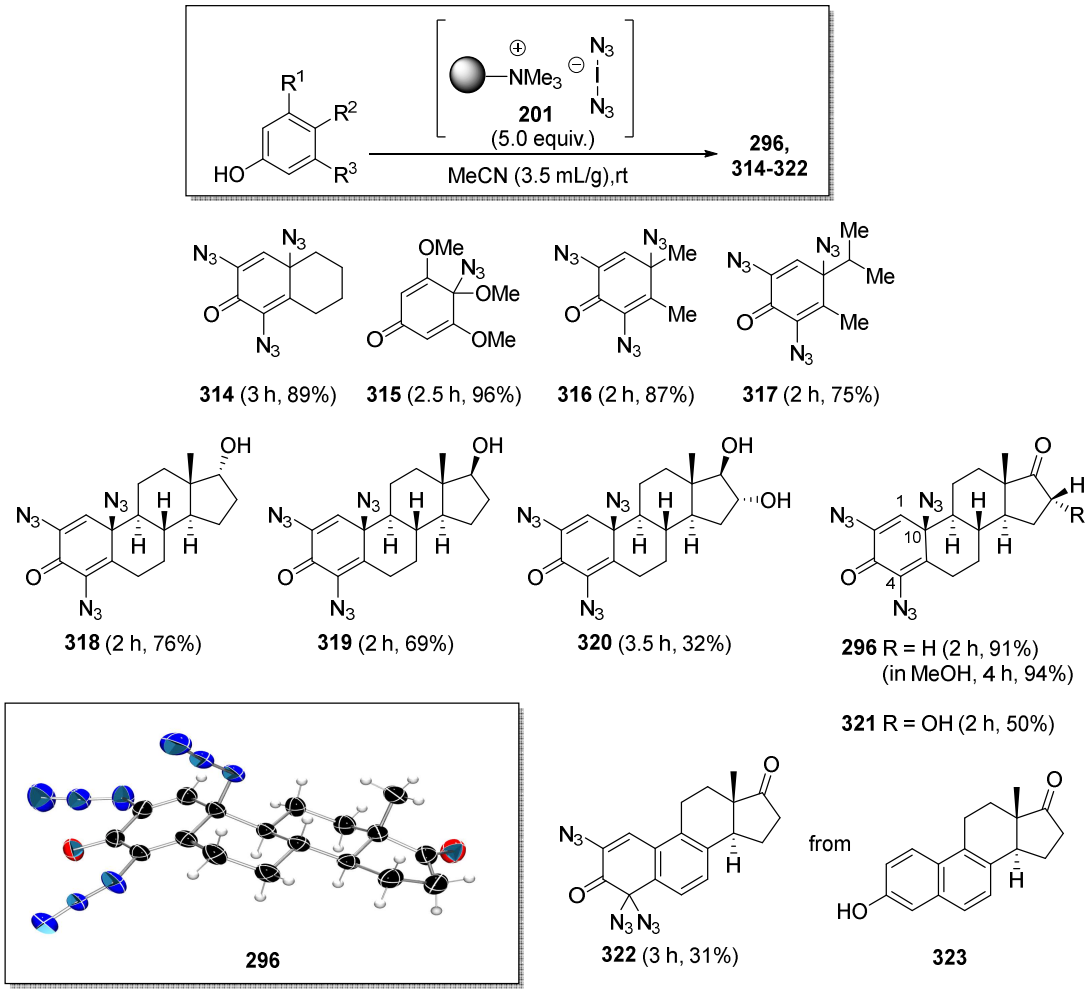
On the basis of these mechanistic insights, the substrate scope should now be investigated in more detail. For this purpose, various phenols and steroids were selected and exposed to five equivalents of polymer-bound iodine azide **201** in acetonitrile at ambient temperature (Scheme 80). The conversion of the majority of these phenols to azides **296**, **314** - **321** proceeded with excellent yields and required a reaction time between two and four hours. The lower yield of **320** might be due to the steroid being bound to the cation exchange resin.[112]

A brief investigation of solvent effects revealed that methanol could also be used, as previously described by OKAMOTO *et al.*, who performed *ortho*-iodinations of phenols with benzyl trimethylammonium dichloroiodate (I) in methanol.[113] He reported that the use of methanol was advantageous and postulated that the active reagent was methyl hypoiodite. This is consistent with the mechanism described here, which also features hypoiodite as reactive intermediate.[112]

The structure of the dienones and the stereochemistry of the newly formed stereocenter in position 10 were unequivocally confirmed by X-ray crystallographic analysis performed by G. DRÄGER. Based on the structural and stereochemical similarity, it is assumed that the other products **318**-**321** all possess *β*-oriented azide substituents at C-10 as determined for azidodienone **296**. ^{1}H-NMR analysis also revealed nearly identical chemical shifts for the H-1 of the various products **314, 316-321**, also suggesting identical stereochemistry of the azide at position 10. In addition, characterization of new azides was accompanied by IR spectroscopy, where a signal at about 2100 cm^{-1} was observed upon azide formation.[112]

Interestingly, there were two exceptions to the reaction results. For example, the reaction with an arene containing three methoxy groups gave *para*-substituted monoazidodienone **315** in a remarkable yield of 96%. Another unusual observation was made when polymer-bound iodine azide **201** was employed to equilenine (**323**), which was isolated for the first time from the urine of pregnant mares[114] and exhibited various biological activities. With this substrate, diazidation was observed at position 4 and no reaction at position 10, with the aromatic B ring remaining completely intact.[112]

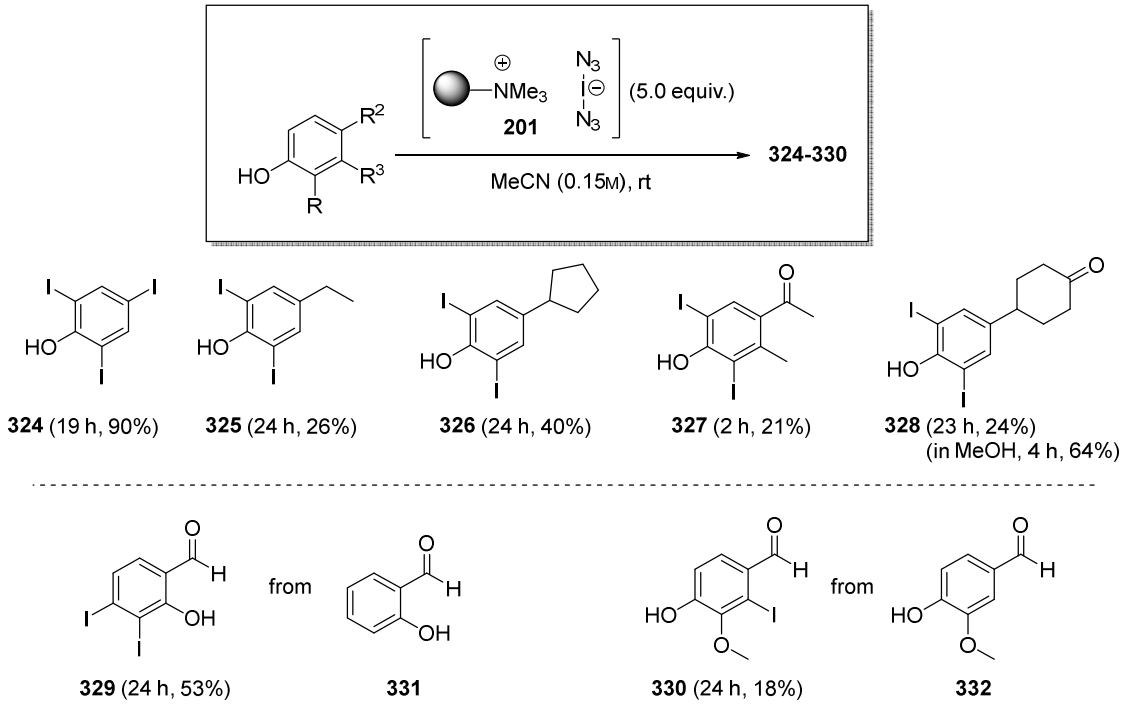
[113] S. Kajigaeshi, T. Kakinami, H. Yamasaki, S. Fujisaki, M. Kondo, T. Okamoto, *Chem. Lett*. **1987**, *16*, 2109-2112.
[114] a) A. Girard, G. Sandulesco, A. Fridenson, J. J. Rutgers, *C. R. Acad. Sci*. **1932**, *195*, 981; b) V. M. Dembitsky, N. Savidov, V. V. Poroikov, T. A. Gloriozova, A. B. Imbs, *Appl. Microbiol. Biotechnol*. **2018**, *102*, 4663-4674.



Scheme 80: Azidation of phenols by using polymer-bound bisazidoiodate (I) **201**. The configuration of C-10 in **318**-**321** is proposed based on X-ray crystallographic analysis of **321** (C = black, O = red, N = blue).[112]

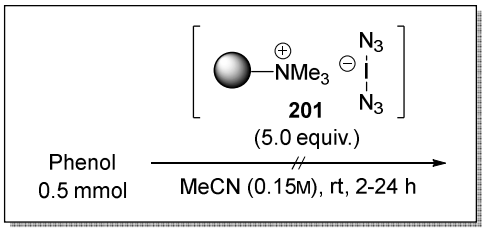
In addition, some phenols were observed where the reaction stopped under standard conditions already after electrophilic iodination of both *ortho*-positions (Scheme 81). Phenol **324** was iodinated in 90% yield, being by far the best result. All other iodinations proceeded with yields between 18% and 53%, although in the case of phenol **328** the yield could be increased from 24% to 64% when methanol was used as solvent instead of acetonitrile. Along with the strongly activating hydroxy substituent, phenols **325**, **326** and **328** also contain weakly activating alkyl substituents in the *para*-position, which have a weak +I effect that slightly increases electron density on the aromatic ring. However, this is similar for steroids. The only difference in phenols **325**, **326**, and **328** is that the electron-shifting property of the alkyl group in *meta*-position to the alcohol is omitted. However, this is not the case with phenol **327**; instead, here the keto group in *para*-position has withdrawing properties and is characterized by -M and -I effects. It turns out that the described triazidodienones are formed only when alkyl substituents with weakly activating properties, characterized by a +I effect, are present in the *meta*- and *para*-positions to the phenol substituent. Moreover, the *ortho*- and *meta*-iodination of phenol **331** is particularly noteworthy. The *ortho*-iodination can be

explained by the fact that the OH group has an *ortho*/*para* and the aldehyde substituent a *meta* directing effect, but this is in marked contrast to the iodination in *meta*-position to the phenol group. Equally unexpectedly, the monoiodinated phenol **330** formed with iodination in *meta*-position to the OH substituent, where it is strongly activating, since OH substituents are characterized by both a +M and a +I effect and are not normally masked by the mediate activating effect of a methoxy group, which has a +M effect but at the same time a -I effect. Nevertheless, phenol **330** was the only product isolated from this reaction in 18% yield. It is possible that side reactions occur whose products trap azide anions and thus suppress the substitution of iodides by azides.

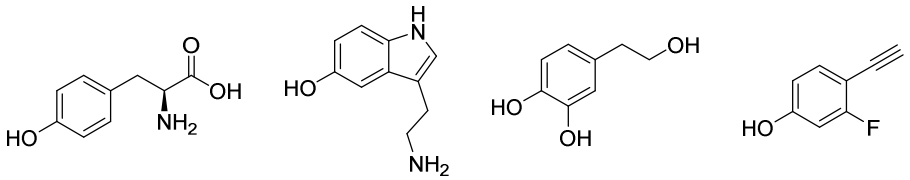


Scheme 81: Iodinations of some phenols using polymer-bound bisazidoiodate (I) **201**.

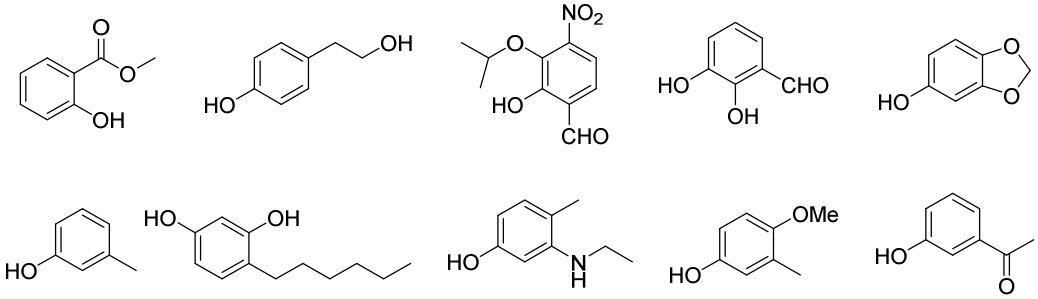
In addition, a variety of other phenols could not be iodinated or azidated under standard conditions using polymer-bound bisazidoiodate (I) **201** (Scheme 82). For some substrates with very polar side chains, such as serotonin, no product could be isolated at all, suggesting that they have been absorbed by the resin. For other phenols with more substituents, e.g., tyrosol, 4-hexylresorcinol, or methyl salicylates, crude NMR spectrometric analysis revealed a mixture of a broad range of fragments and compounds that could not be further separated. Whereas, alternatively, they were substrates that did not react at all, such as specially prepared Boc-protected serotonin. Therefore, in conclusion, especially steroids with a phenol A ring could be selectively converted into the corresponding azidodienones in excellent yields, whereas other phenols reacted very unpredictably. This indicates that not only the substituents influence the reactivity, but also the intramolecular structure and associated sterics of the A and B rings or alkyl groups control the reaction of iodine azide **201**.



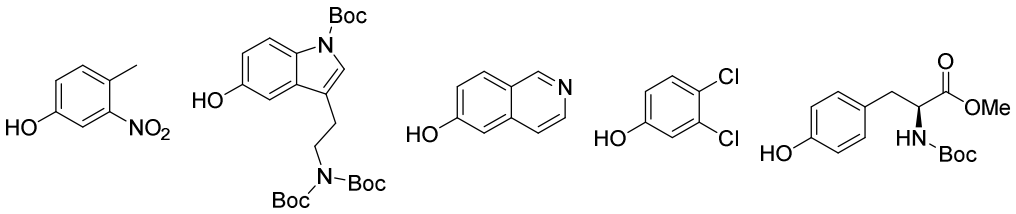
Presumably, addition of these substrates to resin **201** resulted in a loss of isolable compounds:



A crude NMR study directly from the reaction mixture with these substrates revealed the presence of a number of different compounds, which were not further separated:



These substrates were not observed to undergo significant transformation:

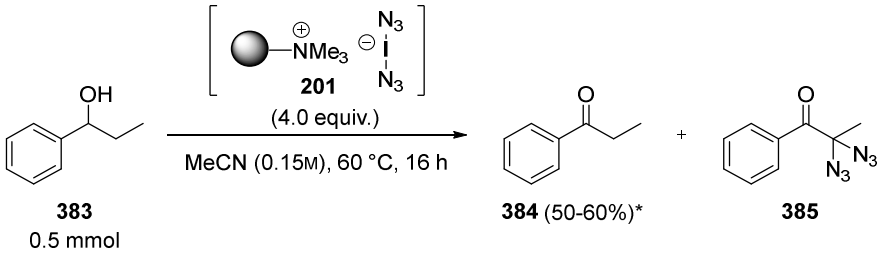


Scheme 82: Phenols, not reacting as expected.

B3.5 Azidation of Acylarenes

Parts of this chapter B3.5 have already been published.[112]

Interestingly, during the studies on the oxidation of secondary alcohols using polymer-bound bisazidoiodate (I) **201**, it was found that when 1-phenylpropanol (**383**) was employed in acetonitrile at 60 °C, a 1:1 mixture of propiophenone (**384**) and diazide **385** was formed after 16 hours (Scheme 83). This result is in accordance with the azidation reactions described above. First, the alcohol **383** was oxidized to the corresponding ketone **384**, followed by diazidation to give diazidated ketone **385**.

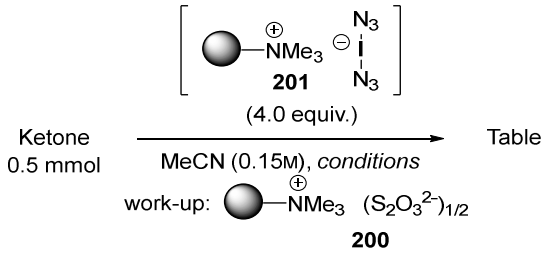


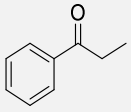
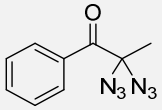
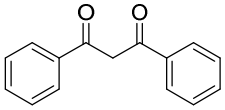
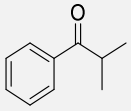
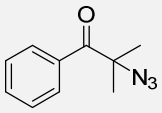
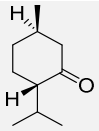
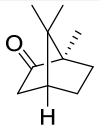
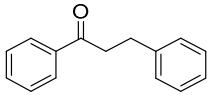
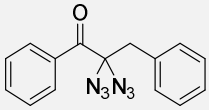
Scheme 83: Conversion of 1-phenylpropanol (**383**) using resin **201** (*yields determined by NMR analysis).

The azidation of ketones was eventually investigated in more detail. It was found that the azidation depended on the chemical nature of both substrates and the conditions applied, including the number of formal equivalents of functionalized polymer **201** (Table 25). Propiophenone (**384**) was chosen as the first test substrate as it had already been established for azidation reactions. Since the conversion did not proceed to completion in the previous reaction, the temperature was increased from 60 °C to 83 °C. The usage of 4.0 equivalents of polymer-bound bisazidoiodate (I) **201** was maintained. After a reaction time of four days, it was possible to isolate 95% of the diazidated ketone **385** (Entry 1). Interestingly, diketone **386** did not react at all under the identical conditions, even when a reaction time of seven days was employed (Entry 2). When 2-methyl-1-phenylpropan-1-one (**387**) was studied, it was found that best yields were achieved when the amount of reagent **201** was increased to 8.0 equivalents (Entries 3-4). When this reaction was instead carried out under microwave irradiation at 150 °C (Entry 5), a 50:1 ratio between starting material **387** and product **388** was obtained, while no azidation occurred under ultraviolet irradiation conditions (Entry 6). Remarkably, it was found that preferably aromatic ketones can be azidated. For aliphatic ketones such as menthone (**260**, Entry 7) or fenchone (**226**, Entry 8), no conversion occurred when 4.0 equivalents of polymer-bound iodine azide **201** were used at 83 °C. Instead, menthone (**260**) decomposed after 16 hours. A possible reason for this observation lies in the mesomeric properties of the aromatic ring.

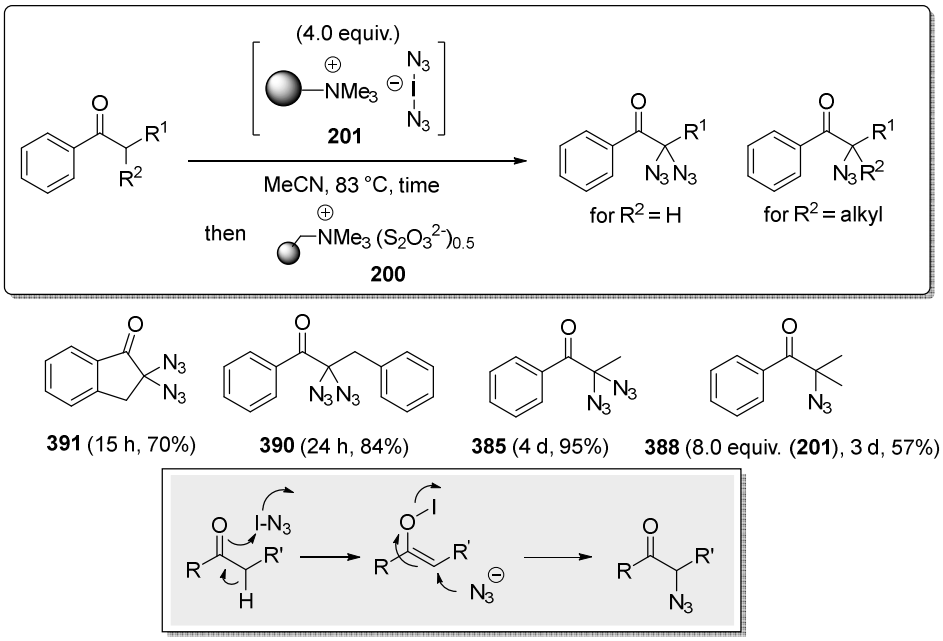
Alternatively, the use of blue LED irradiation at room temperature as an energy source for azidation was investigated in more detail. However, neither aliphatic nor aromatic ketones showed any reactivity under these conditions (Entries 9-12). Only when the amount of resin **201** was doubled to 8.0 equivalents the formation of trace amounts of diazide **390** could be detected after a reaction time of four days (Entry 11). In summary, heating to 83 °C and using 4.0 formal equivalents of polymer **201** provided the best reaction conditions for the azidation of aromatic ketones.

Table 25: Studies on the azidation of ketones using polymer-bound iodine azide **201**.



entry	substrate	equiv. (201)	conditions	time	result
1	 **384**	**4.0**	**83 °C**	**4 d**	 **385 (95%)**
2	 **386**	4.0	83 °C	16 h – 7 d	no conversion
3	 **387**	6.0	83 °C	16 h	 **388** **387:388** 8:1
4	**387**	8.0	83 °C	3 d	**388** (57%)
5	**387**	4.0	microwave, 150 °C	1 h	**387**:**388** 50:1
6	**384**	4.0	h*ν* (365 nm), rt	24 h	no conversion
7	 **260**	4.0	83 °C	16 h	no conversion
8	 **226**	4.0	83 °C	16 h	no conversion
9	**226**	4.0	blue LED, rt	19 h	no conversion
10	 **389**	4.0	degassed MeCN, blue LED, rt	3 d	no conversion
11	**389**	8.0	degassed MeCN, blue LED, rt	4 d	 **390** (traces)
12	**389**	4.0	blue LED, rt	24 h	no conversion

In summary, studies on the chemical properties of diazidoiodate (I) **201** showed that mono- and diazidations with aromatic ketones proceed best in acetonitrile at 83 °C (Scheme 84). After 15 h to 3 d, azidation was observed in α-position of the ketones. As before, thiosulfate ion exchange resin **200** was used for reductive workup and removal of byproducts such as iodine and IN_3. The yields of the azidated ketones obtained in this way ranged from 57% to 95%. Geminal bisazides offer the possibility to be directly converted into nitrogen-containing heterocycles such as tetrazoles or triazoles, which are of interest in pharmaceutical research.[115] Mechanistically, arylarenes behave similarly to phenols in the presence of iodine azide. Azidation could be initiated by hypoiodite formation, similar to that proposed in Scheme 79 for phenol oxidation and azidation.[112]

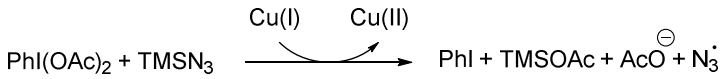


Scheme 84: Thermal azidation of acylarenes using polymer-bound iodine azide **201**.[112]

B3.6 Transition Metal Catalysis

Following the work of BUCHWALD *et al*. it was investigated whether the presence of Cu-catalysts could improve the yields of azidation and oxidation reactions. In his publication, he described the Cu (I)-catalyzed radical oxyfunctionalization of alkenes. In this process, the initial reaction between the Cu (I) catalyst and the radical source generates a Cu (II) species and a radical, which subsequently reacts with a substrate. For this purpose, PIDA was used as oxidant and trimethylsilylazide the precursor of the azidyl radical (Scheme 85).[116]

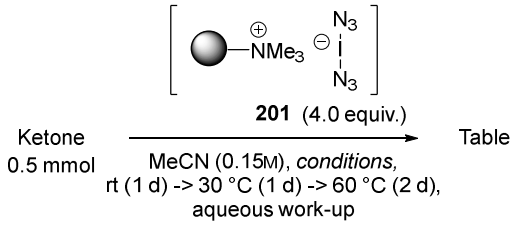
[115] I. E. Çelik, S. F. Kirsch, *Eur. J. Org. Chem*. **2021**, *107*, 53-63.
[116] R. Zhu, S. L. Buchwald, *J. Am. Chem. Soc*. **2015**, *137*, 8069-8077.

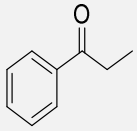
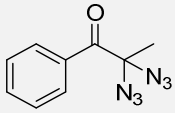
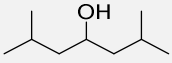


Scheme 85: Proposed mechanism of azide radical formation.[116]

For this reason, it was assumed that polymer-bound bisazidoiodate (I) **201** described within this work might react in a similar manner, and two different Cu (I) sources were investigated - CuI and $Cu(MeCN)_4PF_6$ (Table 26). CuI was used in three different concentrations at different temperatures (between ambient temperature and 60 °C) in the presence of polymer-bound iodoazide **201**. Unfortunately, however, no improvement was observed compared to the conditions without catalyst; only a mixture of ketone **384** and bisazide **385** was obtained (Entries 1-3). The same result was achieved with $Cu(MeCN)_4PF_6$ (Entries 4-6). Oxidation of alcohol **392** gave the corresponding ketone and a number of other compounds appearing in the crude ^{1}H-NMR spectrum, thus this reaction with copper (I) catalysis did not give any new or improved results either (Entry 7).

Table 26: Attempted Cu (I)-catalyzed radical functionalization.



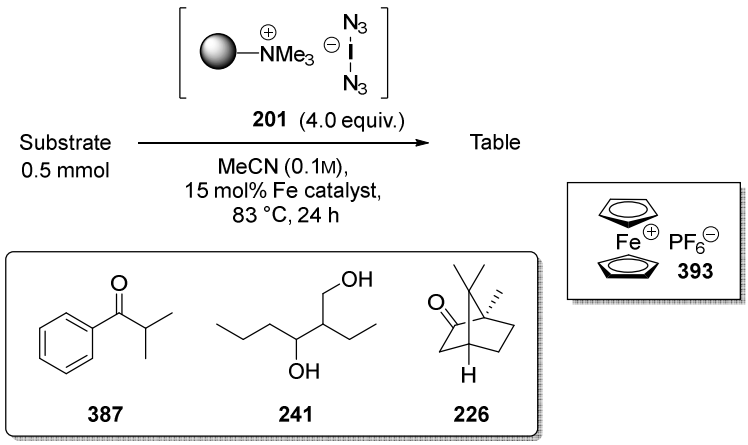
entry	substrate	Cu(I) source	result
1	 **384**	0.05 equiv. CuI	 **384**:**385** (1:1)
2	**384**	1.0 equiv. CuI	**384**:**385** (1:1)
3	**384**	2.2 equiv. CuI	**384**:**385** (1:1)
4	**384**	0.05 equiv. $Cu(MeCN)_4PF_6$	**384**:**385** (1:1)
5	**384**	1.0 equiv. $Cu(MeCN)_4PF_6$	**384**:**385** (1:1)
6	**384**	2.2 equiv. $Cu(MeCN)_4PF_6$	**384**:**385** (1:1)
7	 **392**	1.0 equiv. $Cu(MeCN)_4PF_6$	ketone + many unknown compounds

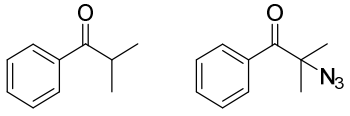
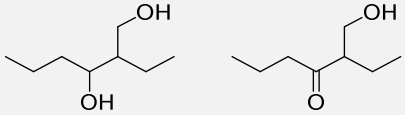
Since the application of copper catalysts did not show significant differences, three different iron catalysts were tested, based on the work of HARTWIG *et al*. He described iron-catalyzed late-stage azidations with the ZHDANKIN reagent.[117] Since polymer-bound iodazide **201** described here has

[117] A. Sharma, J. F. Hartwig, *Nature*, **2015**, *517*, 600-604.

similar properties to the ZHDANKIN reagent, it was therefore suspected that iron catalysis might also be beneficial in this context. The iron catalysts screened here were $Fe(acac)_3$, $FeCl_2$, and ferrocenium hexafluorophosphate (Table 27). The aromatic ketone 2-methyl-1-phenylpropan-1-one (**387**), 2-ethylhexane-1,3-diol (**241**), and aliphatic fenchone (**226**) were used as test substrates. Interestingly, $Fe(acac)_3$ appeared to inhibit the reactivity of polymer **201** in all cases (Entries 1, 3, 5), whereas $FeCl_2$ did not affect the yields described above (Entries 2, 4, 6). Fenchone (**226**) did not react under any of the conditions tested (Entries 5-6). Finally, Fe-catalyst **393** was used at various concentrations under the conditions described in Table 27, and interestingly, it also inhibited these transformations. The oxidation of diol **241** was strongly inhibited when 1.0 equiv. and 0.15 equiv. of the catalyst **393** were used (Entries 7-8). Fenchone (**226**) also did not react under typical azidation conditions, either with 1.0 equiv. of catalyst **393** or with 0.15 equiv. (Entry 9).

Table 27: Attempted iron-catalyzed functionalization.



entry	substrate	Fe catalyst	result
1	**387**	$Fe(acac)_3$	no conversion
2	**387**	$FeCl_2$	 **387**:**388** (5:1)
3	**241**	$Fe(acac)_3$	 **241**:**280** (50:1)
4	**241**	$FeCl_2$	**280** + different byproducts
5	**226**	$Fe(acac)_3$	no conversion
6	**226**	$FeCl_2$	no conversion
7	**241**	1.0 equiv. (**393**)	**241**:**280** (20:1)
8	**241**	0.15 equiv. (**393**)	no conversion
9	**226**	1.0 / 0.15 equiv. (**393**)	no conversion

B4 Conclusions and Future Work

In summary, this work has established new applications for polymer-bound diazidoiodate (I), which is a safe, non-explosive form of iodoazide that can be obtained from an ion-exchange resin, in this case Amberlyst A-26. This electrophilic iodonium reagent can be prepared by iodine (III)-mediated oxidation of the corresponding iodide form followed by ligand exchange with trimethylsilyl azide. It can be stored in the dark at -15 °C for several months.

A particular reactivity was observed upon irradiation with blue LED light. After the release of iodoazide from the polymer-bound bisazidiodate (I) anions, a series of radical reactions were observed, such as chemoselective oxidation of secondary alcohols in the presence of primary alcohols or azidation of aldehydes. With prolonged reaction time, carbamoyl azides could also be formed from primary alcohols by CURTIUS rearrangement. Oxidation of secondary alcohols was further observed at temperatures of 60 °C. The particular advantage of this method is the mild, selective oxidation of secondary alcohols in the presence of primary alcohols. Not many methods for selective oxidation of secondary alcohols are described in the literature. For example, there are certain cases where standard alcohol oxidants can preferentially oxidize secondary alcohols in the presence of primary ones when the substrates are favorable,[118] such as COREY-KIM oxidation,[119] TFAA-activated DMSO,[120] COLLINS reagent,[119] or PDC.[120] The FÉTIZON'S reagent should also be mentioned,[121] but it is very sensitive to steric hindrances.[122] *N*-Bromoacetamide is also mainly used for the oxidation of secondary alcohols of steroids.[123] In addition, STEVENS' oxidant has been described for secondary alcohols,[124] which can be oxidized with NaOCl-AcOH at below 5 °C, but these are harsh conditions that not all functional groups can tolerate, as are the oxidation possibilities with molecular chlorine or bromine.[125] Given these possibilities, the oxidation method with the polymer-bound azidoiodate (I) and blue LED light offers a mild and well-applicable alternative.

In addition, a new reactivity of iodoazide towards phenols and ketones was found. Thus, steroids and structurally similar phenols can be converted into the corresponding triple azidated dienones and acylarenes have been azidated. The main advantage of this method over many other azidation options is the non-explosive nature of iodine azide, which is due to its binding in the solid-phase.

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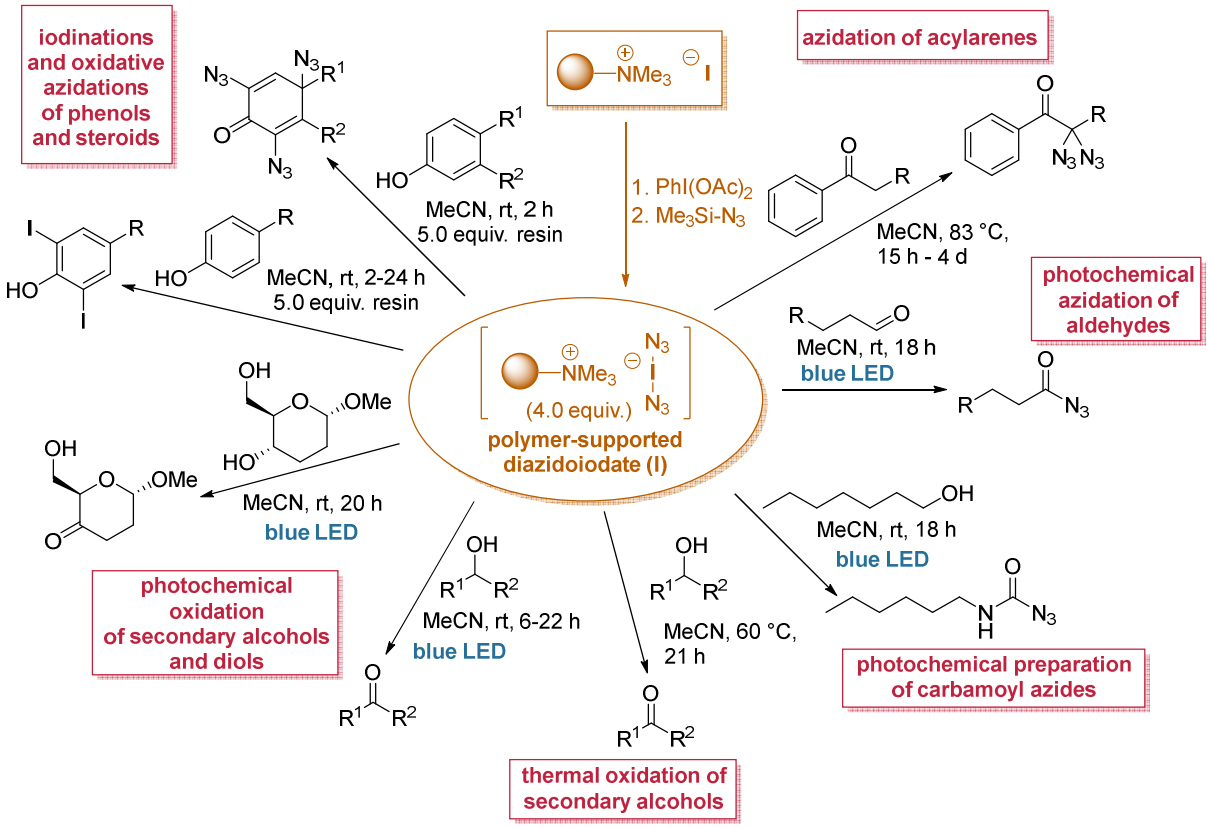
[118] G. Tojo, M. Fernández, *Selective Oxidations of Secondary Alcohols in Presence of Primary Alcohols.* In: *Oxidation of Alcohols to Aldehydes and Ketones. Basic Reactions in Organic Synthesis*; Springer, Boston, MA, **2006**.
[119] H. Tomioka, K. Takai, K. Oshima, H. Nozaki, *Tetrahedron Lett.* **1981**, *22*, 1605-1508.
[120] L. F. Tietze, S. Henke, C. Bärtels, Tetrahedron, **1988**, *44*, 7145-7153.
[121] M. Fétizon, M. Golfier, J.-M. Louis, *J. Chem. Soc. D,* **1969**, *19*, 1102-1102.
[122] M. J. Kurth, C. M. Yu, *J. Org. Chem*. **1985**, *50*, 1840-1845.
[123] H. Reich, T. Reichstein, *Helv. Chim. Acta* **1943**, *26*, 562-585.
[124] R. V. Stevens, K. T. Chapman, H. N. Weller*, J. Org. Chem.* **1980**, *45*, 2030-2032.
[125] M. Al Neirabeyeh, J.-C. Ziegler, B. Gross, P. Caubère, *Synthesis* **1976**, *12*, 811-813.

The configuration of the newly formed stereocenters in steroids was confirmed by X-ray crystallographic analysis. Mechanistically, the formation of hypoiodite intermediates is likely a key step in oxidative azidation reactions. However, phenols substituted only in *para*-position can be diiodinated mainly in *ortho*-position (Scheme 86).

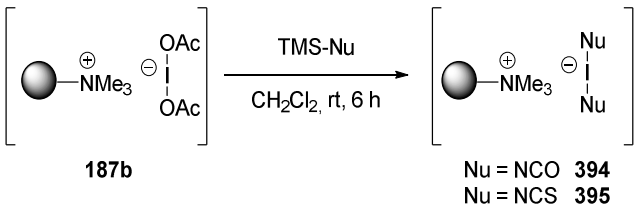
In addition, the oxidation of amines was investigated in a proof-of-concept study in which a secondary amine was oxidized to the corresponding imine, proving that oxidative transformations are in principle possible using the polymer-supported bisazidoiodates (I). However, when additional amines were employed, decomposition occurred in most cases, which was also observed to some extent in the oxidation of phenols. This would be a possible starting point for future investigations. On the one hand, the oxidation of amines should be studied in more detail, and on the other hand, studies on the use of polymer-bound iodoazide under milder conditions, such as at lower temperatures or by increasing the use of scavengers that could trap iodine or radicals, should be carried out.

Moreover, the combination of transition metal catalysts such as copper or iron catalysts with the polymer-bound iodine azide was investigated. No added value has been found here so far, but it cannot be ruled out that other reactivities may arise when other catalysts based on other metals are used.



Scheme 86: Summary of the chemistry established in this work with polymer-bound diazidoiodate (I). **201**

Furthermore, it is possible to generate polymer-bound bromate compounds instead of iodates, for example, or to bind other nucleophiles to the halogenates instead of azides, as has already been done in the past. In the future, these compounds could also be investigated with a view to their use in the field of C-H activation or late functionalization of complex compounds, as in the end of a total synthesis. It would be possible to introduce other functional groups instead of azides, and it would also be interesting to investigate if oxidative transformations of steroids are also possible with other groups such as isocyanates or isothiocyanates (Scheme 87). All in all, it can be summarized that a wide range of reactivities has already been uncovered for polymer-bound bisazidoiodate (I), but the chemistry of polymer-bound haloate (I) complexes still offers a whole range of possibilities that go far beyond this work.



Scheme 87: Derivatization of polymer-bound iodate (I) complexes.

Experimental

E1 General Experimental Considerations

Reagents and solvents: All non-aqueous reactions were carried out under an inert atmosphere (argon) with dried glassware, using standard techniques as described in the literature.[126] Anhydrous solvents (MeCN, CH_2Cl_2) were obtained from a MB solvent purification system (MBRAUN) or commercial solvents were used as supplied (from ACROS ORGANICS, ABCR, MERCK, TCI, ALFA AESAR). Petroleum ether (60 °C) and THF were distilled before application and triethylamine was dried over KOH and distilled as well. Commercial reagents were used as supplied. Deuterated solvents for NMR were received from DEUTERO.

Thin layer chromatography (TLC): Analytical thin-layer chromatography was performed on precoated aluminium-backed silica gel plates (ALUGRAM® Xtra SIL G/UV254 by MACHEREY-NAGEL) with a layer thickness of 0.2 mm. Visualization of the developed chromatogram was performed by UV absorbance (254 nm) and/or stained with aqueous potassium permanganate solution with subsequent heat treatment.

[126] G. P. J. Leonard, B. Lygo, G. Procter, *Praxis Der Organischen Chemie*, Wiley-VCH, **2008**.

Flash column chromatography: Flash column chromatography was performed using mesh silica by MACHEREY-NAGEL (grain size 40-63 μm), with the indicated solvent system according to the standard techniques. Alternatively, a BÜCHI purification system was applied containing two pump modules (C-605), a UV-Vis detector (C-630), a fraction collector (C-660) and the control unit C-620. The separation was performed with columns as indicated. The system was controlled via Sepacore® control software.

Nuclear magnetic resonance (NMR) spectroscopy: NMR spectra were recorded on a BRUKER Ultrashield 500 MHz with Avance-III HD console, an Ascend 400 MHz with Avance-III console, an Ascend 400 MHz with Avance-III HD console, an Ultrashield 400 MHz with Avance-I console and an Ascend 600 MHz with Avance Neo console.

Chemical shifts for ^{1}H-NMR spectra are recorded in parts per million from tetramethylsilane with the residual protic solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm, CD_3OD: δ 3.31 ppm, $(CD_3)_2SO$: δ 2.50 ppm, C_6D_6: δ 7.16 ppm, D_2O: δ 4.79 ppm, CD_3CN: δ 1.94 ppm).[127] Data are reported as follows: chemical shift (multiplicity [s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, quin = quintet, oct = octet and m = multiplet], coupling constant (in Hz), integration and assignment). All multiplet signals were quoted over a chemical shift range.

^{13}C-NMR spectra are recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.00 ppm, CD_3OD: δ 49.00 ppm, $(CD_3)_2SO$: δ 39.52 ppm, C_6D_6: δ 128.06 ppm, CD_3CN: δ 1.32 ppm, 118.26 ppm).[127] The multiplicities are corresponding to the non-decoupled spectra and are described as follows: p = primary, s = secondary, t = tertiary, q = quaternary.

Assignments of ^{1}H- and ^{13}C-spectra were based upon the analysis of δ- and J-values, as well as COSY, HMBC, HSQC and adequate experiments where appropriate.

Mass spectrometry (MS): High resolution mass spectrometry (HRMS) was measured with a Micromass LCT with lockspray source. The injection proceeded in loop-mode with a HPLC system by WATERS (Alliance 2695). Alternatively, mass spectra were recorded with a Acquity-UPLC system by WATERS in combination with a QTOF Premier mass spectrometer by WATERS in lockspray mode. The ionization happened by electrospray ionization (ESI) or by chemical ionization at atmospheric pressure (APCI). The calculated and found mass are reported.

[127] H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512-7515.

Gas chromatography (GCMS): Gas chromatograms were measured on the devices GC-17 and QP-500 by SHIMADZU (Duisburg) with an Optima-5-MS capillary column (0.25 mm, 0.30 mm, 0.32 mm, MACHEREY-NAGEL, Düren). The detection proceeded via flame ionization in combination with a mass spectrum HP 5973 Mass Selective Detector by HP.

High performance liquid chromatography (HPLC): Semi-preparative HPLC was performed using an Alliance 2695 HPLC-system by WATERS with a WATERS 996 diode array detector (λ = 200-350 nm) and a Nucleodur C18 HTec column (5 μm, 250 mm, Ø 8 mm) by MACHEREY-NAGEL. Mass detection was conducted with a WATERS Quattro micro API mass spectrometer in negative ionization mode.

Preparative HPLC was performed using a GILSON HPLC-system (pump 331/332) with additional MERCK HITACHI Split-Pump (L-6200A, UV-Vis detector L-4250) and a MACHEREY-NAGEL Nucleodur C18 ISIS column (5 μm, 250 mm, Ø 21 mm with guard cartridge, 40 mm, Ø 21 mm). Mass detection was conducted with a WATERS Micromass ZQ mass spectrometer in negative ionisation mode.

Operating conditions and retention times (t_R) are reported in the experimental details.

Infrared (IR) spectra: Infrared spectra (ν_{max}, FTIR) were recorded in reciprocal centimeters (cm^{-1}) as thin films or compressed solids on a SHIMADZU FT-IR Affinity-1S spectrometer.

Melting points: Melting points were determined on a SRS OptiMelt apparatus and are not corrected.

Optical Rotation: Specific optical rotation values $[\alpha]^t_D$ were measured in a quartz cuvette on a polarimeter 341 by PERKINELMER at a wavelength of 589 nm (D) and given temperature *t*. Concentrations *c* are given in g/100 mL solvent.

Freeze-pump-thaw-technique (fpt): Degassed solvents were prepared by the fpt technique. For this, the appropriate dry solvent was placed under an argon atmosphere in a SCHLENK flask being connected to the SCHLENK line. The solvent was frozen in the flask using liquid nitrogen. Then the stopcock was opened to vacuum and the atmosphere was evaporated for five minutes. The flask was sealed and thawed until the solvent melted using an acetone bath being replaced by the cooling bath in order to repeat these steps until a gas evolution at the solution was no longer seen. A minimum of three cycles was needed. Subsequently, the flask was filled with argon gas and sealed. The solvent was ready to use.

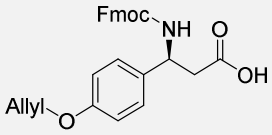
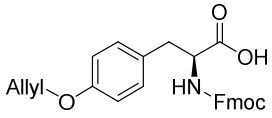
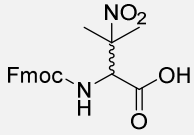
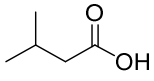
UV-lamp: Irradiation reactions were performed with a 365 nm high intensity UV lamp (100 Watt) by ANALYTIKJENA, an ENDRESS+HAUSER Company.

Peptide synthesizer: Peptides were synthesized with a LIBERTY BLUE™ Automated Microwave Peptide Synthesizer from CEM following a standard Fmoc-protocol (Table 28). A 2-chlorotrityl chloride resin (200-400 mesh, 1.50-1.90 mmol/g) from BACHEM was used. The appropriate reagents were prepared as stock solutions before they were added to the synthesizer. Standard couplings of Fmoc-protected amino acids (5.00 equiv. in regard to resin) were performed with DIC (5.00 equiv.) and OxymaPure (5.00 equiv.) in DMF. The corresponding Fmoc-deprotection was conducted with 10% piperazine (w/v) in EtOH:NMP (10:90, 5.00 equiv.). As required, the reaction mixture was irradiated with microwaves. The amino acids that were used are depicted in Table 29. The specific cleavages of the final peptides are described in the respective experimental.

Table 28 Overview of the settings used for the coupling as well as the deprotection.

	Temp. [°C]	Power [W]	Time [s]	ΔT [°C]
standard coupling	75	170	15	2
	90	30	110	1
deprotection	75	155	15	2
	90	30	50	1

Table 29: Natural amino acids used for solid-phase synthesis of peptides, orthogonally protected natural amino acids and unnatural (amino) acids.

(amino)acid	one-letter code	three-letter code	reagent
alanine	A	Ala	Fmoc-Ala-OH
arginine	R	Arg	Fmoc-Arg(Pbf)-OH
valine	V	Val	Fmoc-Val-OH
***N*-Me-alanine**	-	-	Fmoc-*N*-Me-Ala-OH
D-valine	v	D-Val	Fmoc-D-Val-OH
ornithine	-	-	Fmoc-Ornithine(Boc)-OH
(*R*)-3-(4-(allyloxy)phenyl)-3-aminopropanoic acid	-	-	
(*S*)-3-(4-(allyloxy)phenyl)-3-aminopropanoic acid	-	-	
amino-3-methyl-3-nitrobutanoic acid	-	-	
isovaleric acid	-	-	

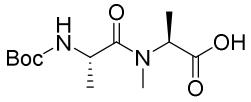
Photoreactor for photo-activated reactions

In a 3D printed photoreactor with a diameter of 115 mm, photo-activated reactions were carried out. As light source a 5.00 m LED light strip with 60.0 LED/m (type 5050 RGB) was employed (12.0 W/m). A 120 mm PC fan was used to cool the reactor to ambient temperature during the reaction. The color was set to blue (wavelengths 445 - 510 nm).

E2 Experimental Procedures – Topic A

E2.1 Boc/OMe Route to Fragment A

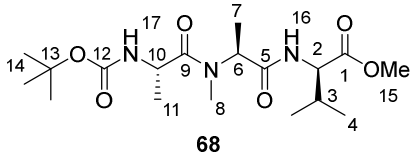
N-((*tert*-Butoxycarbonyl)-L-alanyl)-*N*-methyl-L-alanine (71)



71

To a solution of methyl *N*-((*tert*-butoxycarbonyl)-L-alanyl)-*N*-methyl-L-alaninate (52.7 mg, 183 μmol, 1.00 equiv.) in THF (1.83 mL, 0.1M) at 0 °C, LiOH (1M in H_2O, 76.8 mg, 1.83 mmol, 10.0 equiv.) was added and the reaction mixture was stirred for 16 h at room temperature. Then the reaction was terminated by addition of Et_2O (10.0 mL) and H_2O (10.0 mL), the aqueous layer was washed with Et_2O and the pH was adjusted to 0-1. Then the aqueous layer was extracted with EtOAc (4 x 10.0 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure, affording acid **71** as a colorless oil that was used in the next step without further purification.

Methyl *N*-((*tert*-butoxycarbonyl)-L-alanyl)-*N*-methyl- L-alanyl-D-valinate (68)



68

To a solution of *N*-((*tert*-butoxycarbonyl)-L-alanyl)-*N*-methyl-L-alanine (**71**, 44.7 mg, 160 μmol, 1.00 equiv.) and D-valine methyl ester hydrochloride (30.0 mg, 179 μmol, 1.10 equiv.) in CH_2Cl_2 (1.60 mL) at 0 °C, HOBt (86% wt, 36.8 mg, 240 μmol, 1.50 equiv.), EDC·HCl (38.3 mg, 200 μmol, 1.25 equiv.) and DIPEA (83.6 µL, 480 μmol, 3.00 equiv.) were added and the reaction mixture was stirred for 16 h at room temperature. The reaction was terminated by addition of 1M HCl solution (5.00 mL) and EtOAc (10.0 mL) and extracted with EtOAc (3x 10.0 mL). The combined organic extracts were washed with am 1M HCl solution (2x 10.0 mL), sat. $NaHCO_3$ solution (3x 10.0 mL) and brine (1x 10.0 mL), dried with $MgSO_4$ and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (NP-BÜCHI: solvent A: CH_2Cl_2, solvent B: 10% MeOH in CH_2Cl_2, 15x150 mm column, flow rate: 20 mL/min, 30 sec/fr., gradient: (t [min]/solvent B [%]): 0/0; 30/3,

t_R = 14.5 – 16.5 min) afforded peptide **68** (63.8 mg, 160 μmol, quant., *d.r.* = 12:1) as a colorless foam.

Rotamers: Minor:Major = 1.0:1.21. NMR-measurement at RT (major):

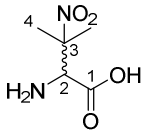
^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.94 (d, *J* = 8.3 Hz, 1H, *H*-16), 6.96 (d, *J* = 7.7 Hz, 1H, *H*-17), 5.07 (q, *J* = 7.1 Hz, 1H, *H*-6), 4.41 (quin, *J* = 7.1 Hz, 1H, *H*-10), 4.16 (dd, *J* = 8.2, 6.7 Hz, 1H, *H*-2), 3.63 (s, 3H, *H*-15), 2.91 (s, 3H, *H*-8), 2.06 (oct, *J* = 6.4 Hz, 1H, *H*-3), 1.36 (s, 9H, *H*-14), 1.25 (d, *J* = 7.8 Hz, 3H, *H*-7), 1.13 (d, *J* = 8.0 Hz, 3H, *H*-11), 0.85 (d, *J* = 7.2 Hz, 6H, *H*-4a/b).

NMR- measurement at RT (minor):

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.78 (d, *J* = 7.7 Hz, 1H, *H*-16), 7.35 (d, *J* = 6.0 Hz, 1H, *H*-17), 4.92 (q, *J* = 6.6 Hz, 1H, *H*-6), 4.55 (quin, *J* = 6.6 Hz, 1H, *H*-10), 4.19 (t, *J* = 5.1 Hz, 1H, *H*-2), 3.61 (s, 3H, *H*-15), 2.63 (s, 3H, *H*-8), 2.06 (oct, *J* = 6.5 Hz, 1H, *H*-3), 1.37 (s, 9H, *H*-14), 1.25 (d, *J* = 7.8 Hz, 3H, *H*-7), 1.13 (d, *J* = 7.6 Hz, 3H, *H*-11), 0.93 (d, *J* = 7.7 Hz, 3H, *H*-4a), 0.90 (d, *J* = 7.1 Hz, 3H, *H*-4b).

The analytical data are consistent with those reported in the literature.[36]

(D,L)-3-Nitrovaline (*rac*-73)



***rac*-73**

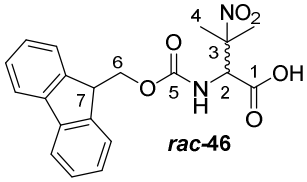
To a solution of KOH (14.1 g, 251 mmol, 2.20 equiv.) in H_2O (280 mL), 2-nitropropane (20.0 mL, 223 mmol, 1.95 equiv.), NH_3 (25% in H_2O, 150 mL, 930 μmol, 8.54 equiv.) and a solution of glyoxylic acid monohydrate (10.5 g, 114 mmol, 1.00 Äq) in H_2O (40.0 mL) were added. The mixture was stirred for 2 h at ambient temperature. Then, the reaction was terminated by adjusting the pH to 0 with conc. HCl whereby the solution changed to blue. The aqueous phase was washed with CH_2Cl_2 (3x) and the solvent was removed under reduced pressure. The residue was diluted in EtOH, filtered and the filtrate was concentrated to about half under reduced pressure, mixed in equal parts with Et_2O, filtered again and aniline (30.0 mL) was added to the filtrate until a turbidity of the solution appeared. The turbid solution was stored at 2-8 °C for 16 h. It was then filtered, the solid was washed with ethanol and dried under high vacuum for 16 h. Nitrovaline ***rac*-73** (6.35 g, 39.2 mmol, 34% yield) was obtained as a colorless solid.[128]

[128] This compound was prepared by the bachelor student M. ÖZBASI under supervision in the context of his bachelor thesis.

T_M: 140 °C; decomp. (Lit.[36]: 142°C); **^{1}H-NMR** (D_2O, 400 MHz): δ [ppm] 4.36 (s, 1H, *H*-2), 1.81 (s, 3H, *H*-4a), 1.77 (s, 3H, *H*-4b).

The analytical data are consistent with those reported in the literature.[36]

N-Fmoc-D,L-3-Nitrovaline (*rac*-46)



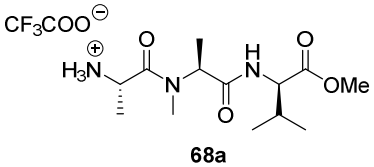
rac-46

To a suspension of D,L-3-nitrovaline ***rac*-73** (1.81 g, 11.2 mmol, 1.00 equiv.) in 1,4-dioxane (50.0 mL), a Na_2CO_3 solution (10%, 100 mL) was added. Then Fmoc-Cl (3.19 g, 12.3 mmol, 1.10 equiv.) dissolved in 1,4 dioxane (50.0 mL) was added via a dropping funnel at 0 °C over a period of 1 h. The reaction was stirred for 6 h at 0 °C. For terminating the reaction, water and Et_2O were added, the phases were separated, and the aqueous phase was washed with Et_2O (3x). Then, the pH of the aqueous phase was brought to pH = 0-1 by addition of semi-conc. HCl solution and the aqueous phase was extracted with EtOAc (3x). The combined organic phases were washed with a sat. NaCl solution, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Coevaporation with toluene (4x), MeOH (3x) and CH_2Cl_2 (2-4x) gave nitrovaline ***rac*-46** (2.67 g, 6.95 mmol, 62% yield) as a colorless solid.[129]

T_M: 56 °C, (Lit.[36]: 58-60°C); **^{1}H-NMR** (DMSO-d_6; 400 MHz): δ [ppm] 8.10 (d, J = 9.9 Hz, 1H, N*H*), 7.89 (d, J = 7.5 Hz, 2H, Ar-*H*), 7.74-7.73 (m, 2H, Ar-*H*), 7.42 (m, 2H, Ar-*H*), 7.33 (m, 2H, Ar-*H*), 4.98 (d, J = 9.9 Hz, 1H, *H*-2), 4.40 (dd, J = 10.6, 7.2 Hz, 1H, *H*-6a), 4.33 (dd, J = 10.6, 7.2 Hz, 1H, *H*-6b), 4.25 (t, J = 7.0 Hz, 1H, *H*-7), 1.58 (s, 3H, *H*-4a), 1.50 (s, 3H, *H*-4b).

The analytical data are consistent with those reported in the literature.[36]

(*S*)-1-(((*S*)-1-(((*R*)-1-Methoxy-3-methyl-1-oxobutan-2-yl)amino)-1-oxopropan-2-yl)-(methyl)amino)-1-oxopropan-2-aminium-2,2,2-trifluoroacetate (68a)

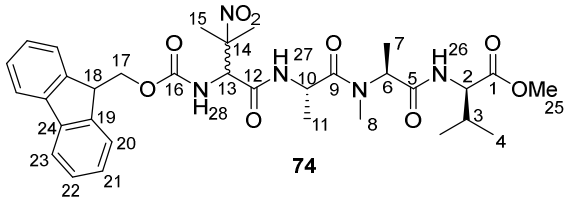


68a

To a solution of methyl *N*-((*tert*-butoxycarbonyl)-L-alanyl)-*N*-methyl-L -alanyl-D-valinate (**68**, 2.56 g, 6.63 mmol, 1.00 equiv.) in CH_2Cl_2 (66.3 mL) at 0 °C, TFA (25.5 mL, 332 mmol, 50.0 equiv.) was added and the reaction mixture was stirred for 3 h at 0 °C. Then the solvent was removed under reduced pressure, affording deprotected peptide **68a** as a colorless foam that was used in the next step without further purification.

[129] This compound was prepared by the bachelor student K. RÜTHER under supervision in the context of her bachelor studies.

Methyl *N*-((2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methyl-3-nitrobutanoyl)-L-alanyl)-*N*-methyl-L-alanyl-D-valinate (74)



74

To a solution of (*S*)-1-(((*S*)-1-(((*R*)-1-methoxy-3-methyl- 1-oxobutan- 2-yl)amino)- 1-oxopropan- 2-yl) (methyl)amino)- 1-oxopropan- 2-aminium- 2,2,2- trifluoroacetate (**68a**, 2.54 g, 6.63 mmol, 1.00 equiv.) and (*R,S*)-*N*-Fmoc-3-NO_2-valine (***rac*-46**, 3.82 g, 9.95 mmol, 1.50 equiv.) in CH_2Cl_2/DMF (5:1, 99.5 mL) at 0 °C, HOAt (1.49 g, 10.9 mmol, 1.65 equiv.), EDC·HCl (2.10 g, 10.9 mmol, 1.65 equiv.) and $NaHCO_3$ (4.18 g, 49.8 mmol, 5.00 equiv.) were added and the reaction mixture was stirred for 16 h at room temperature. The reaction was terminated by addition of 1M $KHSO_4$ solution (20.0 mL) and EtOAc (60.0 mL) and extracted with EtOAc (3x 50.0 mL). The combined organic extracts were washed with a $NaHCO_3$ solution (2x 50.0 mL) and brine (1x 50.0 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (NP-BÜCHI: solvent A: CH_2Cl_2, solvent B: 10% MeOH in CH_2Cl_2, 40x150 mm column, flow rate: 80 mL/min, 30 sec/fr., gradient: (t [min]/solvent B [%]): 0/7; 10/20; 15/30, t_R = 7.0-14.5 min) afforded peptide **74** (4.50 g, 6.89 mmol, quant., *d.r.* = 3:1) as a colorless foam.

Rotamers: Minor:Major = 1.0:4.0 NMR-measurement at RT (major):

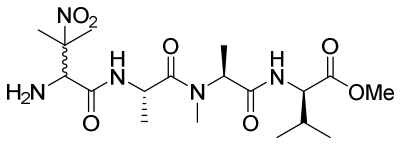
^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 8.58 (d, *J* = 6.1 Hz, 1H, *H*-27), 7.97 (d, *J* = 8.1 Hz, 1H, *H*-26), 7.89 – 7.87 (m, 2H, Ar-*H*), 7.76 – 7.70 (m, 2H, Ar-*H*), 7.43 – 7.39 (m, 2H, Ar-*H*), 7.34 – 7.30 (m, 2H, Ar-*H*), 5.12 – 4.94 (m, 1.7H, *H*-6, *H*-13), 4.79 – 4.71 (m, 0.6H, *H*-10), 4.47 – 4.09 (m, 4H, *H*-2, *H*-17, *H*-18), 3.63 (s, 2H, *H*-25), 2.94 (s, 1.3H, *H*-8_A), 2.68 (s, 0.6H, *H*-8_B), 1.71 – 1.66 (m, 2H, *H*-15), 1.59 – 1.54 (m, 2H, *H*-15), 1.52 – 1.48 (m, 2H, *H*-15), 1.32 – 1.20 (m, 6H, *H*-7, *H*-11), 0.93 – 0.82 (m, 6H, *H*-4a/b).

NMR- measurement at RT (minor):

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 8.79 (d, *J* = 5.0 Hz, 0.3H, *H*-27), 7.97 (d, *J* = 8.1 Hz, 1H, *H*-26), 7.89 – 7.87 (m, 2H, Ar-*H*), 7.76 – 7.70 (m, 2H, Ar-*H*), 7.43 – 7.39 (m, 2H, Ar-*H*), 7.34 – 7.30 (m, 2H, Ar-*H*), 4.91 – 4.71 (m, 0.3H, *H*-6, *H*-13), 4.70 – 4.62 (m, 0.4H, *H*-10), 4.47 – 4.09 (m, 4H, *H*-2, *H*-17, *H*-18), 3.61 (s, 1H, *H*-25), 2.90 (s, 0.7H, *H*-8_A), 2.72 (s, 0.6H, *H*-8_B), 1.71 – 1.66 (m, 2H, *H*-15), 1.59 – 1.54 (m, 2H, *H*-15), 1.52 – 1.48 (m, 2H, *H*-15), 1.32 – 1.20 (m, 6H, *H*-7, *H*-11), 0.93 – 0.82 (m, 6H, *H*-4a/b).

The analytical data are consistent with those reported in the literature.[36]

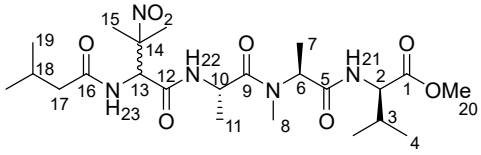
Methyl *N*-((2-amino-3-methyl-3-nitrobutanoyl)-L-alanyl)-*N*-methyl-L-alanyl-D-valinate (75)



75

To a solution of methyl *N*-((2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)- 3-methyl- 3-nitrobutanoyl)-L-alanyl)-*N*-methyl-L-alanyl-D-valinate (**74**, 1.10 g, 1.69 mmol, 1.00 equiv.) in DMF (16.9 mL) at room temperature, dimethylamine (40% wt in H_2O, 856 μL, 16.9 mmol, 10.0 equiv.) was added and the reaction mixture was stirred for 3 h. Then the solvent was removed under reduced pressure, affording deprotected peptide **75** as a colorless foam that was used in the next step without further purification.

Methyl *N*-methyl-*N*-((3-methyl-2-(3-methylbutanamido)-3-nitrobutanoyl)-L-alanyl)-L-alanyl-D-valinate (59)



59

To a solution of methyl *N*-((2-amino-3-methyl-3-nitrobutanoyl)- L-alanyl)- *N*-methyl- L-alanyl- D-valinate (**75**, 729 mg, 1.69 mmol, 1.00 equiv.) in CH_2Cl_2 (16.9 mL) at -78 °C, 2,6-lutidine (589 μL, 5.07 mmol, 3.00 equiv.) and isovaleric anhydride (**76**, 509 μL, 2.54 mmol, 1.50 equiv.) were added and the reaction mixture was stirred for 24 h at room temperature. The solution was terminated by addition of 1M HCl solution (15.0 mL) and EtOAc (20.0 mL) and extracted with EtOAc (3x 20.0 mL). The combined organic extracts were washed with an 1M HCl solution (2x 20.0 mL), $NaHCO_3$ solution (2x 20.0 mL) and brine (1x 20.0 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. Purification by two flash column chromatographies (NP-BÜCHI: solvent A: CH_2Cl_2, solvent B: 10% MeOH in CH_2Cl_2, 40x150 mm column, flow rate: 80 mL/min, 30 sec/fr., gradient: (t [min]/solvent B [%]): 0/7; 10/20; 15/30; 30/30, t_R = 12.5-17.5 min) and RP-BÜCHI: solvent A: H_2O + 0.1% FA, solvent B: MeOH + 0.1% FA, 40x150 mm column, flow rate: 60 mL/min, 30 sec/fr., gradient: (t [min]/solvent B [%]): 0/10; 2/10; 26/100; 30/100, t_R = 9.0 – 12.0 min) afforded peptide **59** (697 mg, 1.35 mmol, 56% yield o2s, *d.r.* = 2.5:1) as a colorless foam.

Rotamers: Minor:Major = 1.0:2.0 NMR-measurement at RT (major):

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 8.58 (d, *J* = 7.6 Hz, 0.25H, *H*-22), 8.52 (d, *J* = 6.5 Hz, 0.4H, *H*-22), 8.20 – 8.16 (m, 0.7H, *H*-23), 8.03 – 7.94 (m, 1.2H, *H*-21, *H*-23), 5.30 – 5.25 (m, 1H, *H*-13), 5.10 – 5.04 (m, 0.7H, *H*-6), 4.62 (quin, *J* = 6.5 Hz, 0.45H, *H*-10), 4.19 – 4.08 (m, 1H, *H*-2), 3.64 – 3.60 (m, 3H, *H*-20), 2.92 (s, 1.4H, *H*-8a), 2.88 (s, 0.7H, *H*-8b), 2.12 – 1.88 (m, 4H, *H*-3,

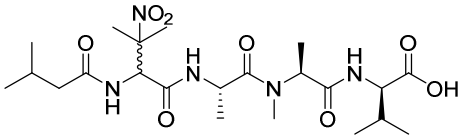
H-17, *H*-18), 1.68 – 1.63 (m, 2H, *H*-15a/b), 1.57 – 1.49 (m, 4H, *H*-15a/b), 1.30 – 1.17 (m, 6H, *H*-7, *H*-11), 0.90 – 0.81 (m, 12H, *H*-4a/b, *H*-19a/b).

NMR- measurement at RT (minor):

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 8.72 (d, J = 5.2 Hz, 0.2H, *H*-22), 8.44 (d, J = 5.4 Hz, 0.1H, *H*-22), 8.10 (d, J = 10.0 Hz, 0.1H, *H*-23), 8.20 – 8.16 (m, 0.7H, *H*-23), 8.03 – 7.94 (m, 1.2H, *H*-21), 5.30 – 5.25 (m, 1H, *H*-13), 4.89 – 4.81 (m, 0.3H, *H*-6), 4.77 – 4.69 (m, 0.55H, *H*-10a), 4.19 – 4.08 (m, 1H, *H*-2), 3.64 – 3.60 (m, 3H, *H*-20), 2.70 (s, 0.3H, *H*-8b), 2.66 (s, 0.6H, *H*-8a), 2.12 – 1.88 (m, 4H, *H*-3, *H*-17, *H*-18), 1.68 – 1.63 (m, 2H, *H*-15a/b), 1.57 – 1.49 (m, 4H, *H*-15a/b), 1.30 – 1.17 (m, 6H, *H*-7, *H*-11), 0.90 – 0.81 (m, 12H, *H*-4a/b, *H*-19a/b).

The analytical data are consistent with those reported in the literature.[36]

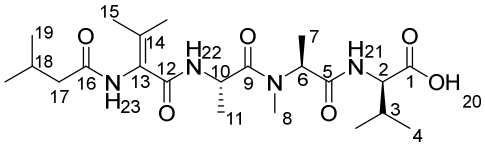
N-Methyl-*N*-((3-methyl-2-(3-methylbutanamido)-3-nitrobutanoyl)-L-alanyl)-L-alanyl-D-valine (77)



77

To a solution of methyl *N*-methyl-*N*-((3-methyl-2-(3-methylbutanamido)-3-nitrobutanoyl)-L-alanyl)-L-alanyl-D-valinate (**59**, 26.8 mg, 2.43 mmol, 1.00 equiv.) in THF/H_2O (2:1, 520 μL) at 0 °C, a solution of LiOH·H_2O (3.30 mg, 78.0 μmol, 1.50 equiv.) and H_2O_2 (4.80 μL, 156 μmol, 3.00 equiv.) in H_2O (39.0 μL) was added and the reaction mixture was stirred for 23 h. Then the reaction was terminated by addition of a sat. $Na_2S_2O_3$ solution (2.00 mL) and acetic acid (2.00 mL). Purification by flash column chromatography (RP-BÜCHI: solvent A: H_2O + 0.1% FA, solvent B: MeOH + 0.1% FA, 12x150 mm column, flow rate: 10 mL/min, 60 sec/fr., gradient: (t [min]/solvent B [%]): 0/10; 5/10; 50/100; 60/100, t_R = 24.0 – 34.0 min) afforded acid **77** as a colorless foam that was used in the next step without further purification.

N-Methyl-*N*-((3-methyl-2-(3-methylbutanamido)but-2-enoyl)-L-alanyl)-L-alanyl-D-valine (60)



60

To a solution of *N*-methyl-*N*-((3-methyl-2-(3-methylbutanamido)-3-nitrobutanoyl)-L-alanyl)-L-alanyl-D-valine (**77**, 14.1 mg, 28.0 μmol, 1.00 equiv.) in THF (280 μL) at 0 °C, a solution of LiOH (1M in H_2O, 11.8 mg, 281 μmol, 10.0 equiv.) was added and the reaction mixture was stirred for 18 h. Then the

reaction was terminated by addition of acetic acid (2.00 mL). Purification by flash column chromatography (RP-BÜCHI: solvent A: H_2O + 0.1% FA, solvent B: MeOH + 0.1% FA, 40x150 mm column, flow rate: 10 mL/min, 60 sec/fr., gradient: (t [min]/solvent B [%]): 0/10; 5/10; 50/100; 60/100, t_R = 21.0 – 32.0 min) afforded peptide **60** (9.70 mg, 21.0 μmol, 41% yield o2s, *d.r.* = 8:1) as a colorless foam.

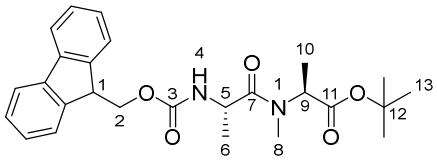
Measurement at rt, (ratio of rotamers (major:minor)=2:1, d.r.(x:y)=8:1):

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 8.92-8.88 (m, 1H, *H*-23), 8.02 – 7.91 (m, 0.6H, *H*-21 minor, *H*-22, minor), 7.79-7.59 (m, 1.4H, *H*-21 major, *H*-22 major), 5.10-5.05 (m, 0.5H, *H*-6x, major), 4.99-4.83 (m, 0.5H, *H*-6x minor, *H*-6b), 4.76-4.66 (m, 1H, *H*-10), 4.15-4.05 (m, 1H, *H*-2), 2.93-2.91 (m, 2H, *H*-8x major, *H*-8y major), 2.82 (s, 0.25H, *H*-8y minor), 2.67 (s, 0.75H, *H*-8x minor), 2.11-1.96 (m, 4H, *H*-3, *H*-17, *H*-18), 1.92-1.90 (m, 3H, *H*-15a), 1.65 (s, 3H, *H*-15b), 1.27-1.17 (m, 6H, *H*-7, *H*-11), 0.90-0.84 (m, 12H, *H*-4a/b, *H*-19a/b).

The analytical data are consistent with those reported in the literature.[36]

E2.2 Fmoc/*tert*-Butyl Route to Fragment A

***tert*-Butyl *N*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)-L-alanyl)-*N*-methyl-L-alaninate (80)**



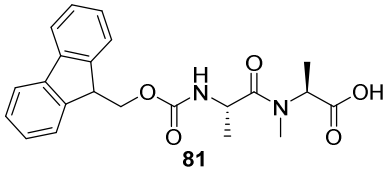
80

To a solution of (((9*H*-fluoren-9-yl)methoxy)carbonyl)-L-alanine (**78**, 1.67 g, 5.37 mmol, 1.05 equiv.) in CH_2Cl_2/DMF 5:1 (36.0 mL) at – 15 °C, Oxyma Pure (1.02 g, 7.16 mmol, 2.00 equiv.) and EDC·HCl (1.12 g, 5.84 mmol, 1.63 equiv.) were added. Then DIPEA (2.20 mL, 12.5 mmol, 3.50 equiv.) and *tert*-butyl methyl-L-alaninate hydrochloride (**79**, 700 mg, 3.58 mmol, 1.00 equiv.) were added and the reaction mixture was stirred for 22 h at room temperature. The reaction was terminated by addition of diluted NaCl solution (10.0 mL) and EtOAc (10.0 mL) and extracted with EtOAc (3x 10.0 mL). The combined organic extracts were washed with brine (3x 10.0 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 12x150 mm column, flow rate: 20.0 mL/min, 60 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 15/20; 30/50; t_R = 16.0 min) afforded peptide **80** (1.20 g, 2.65 mmol, 74% yield, *d.r.* = 8:1) as a colorless oil.

$[\alpha]_D^{25.2}$: - 57.0° (*c* 0.46, MeOH); **^{1}H-NMR** (DMSO-d_6, 400 MHz): δ [ppm] 7.89 (d, *J* = 7.4 Hz, 2H, Ar-*H*), 7.72 (t, *J* = 6.8 Hz, 2H, Ar-*H*), 7.59 – 7.52 (m, 1H, N*H*), 7.41 (t, *J* = 7.4 Hz, 2H, Ar-*H*), 7.32 (t, *J* = 7.2 Hz, 2H, Ar-*H*), 4.86 – 4.71 (m, 1H, *H*-9), 4.54 – 4.47 (m, 1H, *H*-5), 4.26 – 4.20 (m, 3H,

H-2), 2.91 – 2.62 (3x s, 3H, *H*-8), 1.37 (s, 9H, *H*-13), 1.25 – 1.17 (m, 6H, 2x *H*-6, *H*-10); **^{13}C-NMR** (DMSO-d_6, 100 MHz): δ [ppm] 172.5 (q, *C*-11), 170.4 (q, *C*-7), 155.6 (q, *C*-3), 143.9 (q, Ar-*C*), 143.8 (q, Ar-*C*), 140.7 (q, 2x Ar-*C*), 127.6 (t, 2x Ar-*C*), 127.0 (t, 2x Ar-*C*), 125.3 (t, Ar-*C*), 125.2 (t, Ar-*C*), 120.1 (t, 2x Ar-*C*), 80.5 (q, *C*-12), 65.6 (s, *C*-2), 52.9 (t, *C*-9), 2x 46.6 (s/t, *C*-1, *C*-5), 31.0 (p, *C*-8), 27.5 (p, 3x *C*-13, 16.8 (p, *C*-6), 13.8 (p, H_3CNCCH_3); **HRMS** (ESI) *m/z* calculated for $C_{26}H_{32}N_2O_5Na$ $[M+Na]^+$ 475.2209; found 475.2211.

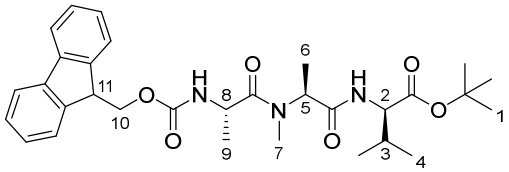
_N_-((((9_H_-Fluoren-9-yl)methoxy)carbonyl)-L-alanyl)-_N_-methyl-L-alanine (81)



81

To a solution of *tert*-butyl *N*-((((9*H*-fluoren-9-yl)methoxy) carbonyl)-L-alanyl)- *N*-methyl- L-alaninate (**80**, 783 mg, 1.73 mmol, 1.00 equiv.) in CH_2Cl_2 (17.3 mL) at 0 °C, TFA (6.62 mL, 86.5 mmol, 50.0 equiv.) was added and the reaction mixture was stirred for 18 h at room temperature. Then the solvent was removed under reduced pressure, affording deprotected peptide **81** as a colorless foam that was used in the next step without further purification.

***tert*-Butyl _N_-((((9_H_-fluoren-9-yl)methoxy)carbonyl)-L-alanyl)-_N_-methyl-L-alanyl-D-valinate (83)**



83

To a solution of *N*-((((9*H*-fluoren-9-yl)methoxy) carbonyl)-L-alanyl)-*N*-methyl-L-alanine (**81**, 685 mg, 1.73 mmol, 1.00 equiv.) and D-valine-*tert*-butylester hydrochloride (**82**, 399 mg, 1.90 mmol, 1.10 equiv.) in CH_2Cl_2 (17.3 mL) at 0 °C, HOBt (86% wt, 397.4 mg, 2.60 mmol, 1.50 equiv.), EDC·HCl (414 mg, 2.16 mmol, 1.25 equiv.) and DIPEA (904 µL, 5.19 mmol, 3.00 equiv.) were added and the reaction mixture was stirred for 18 h at room temperature. The reaction was terminated by addition of 1M HCl (5.00 mL) and EtOAc (10.0 mL) and extracted with EtOAc (3x 10.0 mL). The combined organic extracts were washed with an 1M HCl solution (2x 10.0 mL), $NaHCO_3$ solution (3x 10.0 mL) and brine (1x 10.0 mL), dried with $MgSO_4$ and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 80.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 15/20; 30/50; 45/80; t_R = 30.0 min) afforded peptide **83** (310 mg, 562 μmol, 32% yield, *d.r.* = 15:1) as a yellow foam.

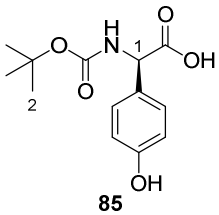
^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.93 – 7.61 (m, 6H, Ar-*H*, N*H*), 7.41 (t, *J* = 7.4 Hz, 2H, Ar-*H*), 7.32 (t, *J* = 7.2 Hz, 2H, Ar-*H*), 5.10 – 4.96 (m, 1H, *H*-5), 4.67 – 4.47 (m, 1H, *H*-8), 4.27 – 4.21 (m, 3H, *H*-10), 4.10 – 4.00 (m, 1H, *H*-2), 2.91 – 2.67 (s, 3H, *H*-7), 2.09 – 1.09 (m, 1H, *H*-3),

1.39 – 1.34 (m, 9H, *H*-1), 1.25 – 1.17 (m, 6H, *H*-6, *H*-9), 0.86 – 0.79 (m, 6H, *H*-4); **HRMS** (ESI) *m/z* calculated for $C_{31}H_{41}N_3O_6Na$ $[M+Na]^+$ 574.2893; found 574.2896.

Since the compound decomposed during high temperature ^{1}H-NMR measurement, no further spectra and optical rotation were measured.

E2.3 Solid-Phase Route to Fragment A

(*R*)-2-((*tert*-Butoxycarbonyl)amino)-2-(4-hydroxyphenyl) acetic acid (85)



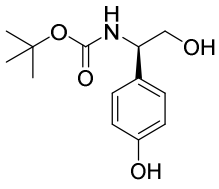
85

To a suspension of 4-hydroxy-D-phenylglycine (**84**, 27.9 g, 167 mmol, 1.00 equiv.) in dioxane/H_2O (1:1, 800 mL). $NaHCO_3$ (70.0 g, 833 mmol, 5.00 equiv.) was added before addition of Boc_2O (40.0 g, 183 mmol, 1.10 equiv.) at 0 °C. The suspension was warmed to room temperature and stirred for 20 h. The organic solvent was removed under reduced pressure. EtOAc and a 5M HCl solution were added. The organic phase was washed with a 5M HCl solution, H_2O and brine, dried over $MgSO_4$ and concentrated under reduced pressure to furnish carbamate **85** (34.5 g, 129 mmol, 77% yield) as colorless solid, which was used in the next step without further purification.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 12.57 (bs, 1H, COO*H*), 9.43 (bs, 1H, O*H*), 7.37 (d, *J* = 7.8 Hz, 1H, N*H*), 7.18 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 6.71 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.96 (d, *J* = 8.7 Hz, 1H, *H*-1), 1.38 (s, 9H, *H*-2).

The analytical data are consistent with those reported in the literature.[130,131]

***tert*-Butyl (*R*)-(2-hydroxy-1-(4-hydroxyphenyl)ethyl)carbamate (86)**



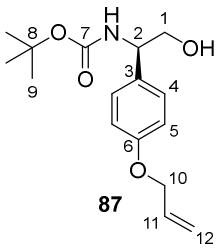
86

To a solution of acid **85** (33.4 g, 124 mmol, 1.00 equiv.) in THF (165 mL), BH_3 (0.9M in THF, 276 mL, 249 mmol, 2.00 equiv.) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 2 h before it was treated with H_2O and EtOAc and stirred at room temperature for 30 min. The aqueous phase was

[130] T. Seedorf, *unpublished results*, Leibniz Universität Hannover, **2022**.
[131] G. M. Salituro, C. A. Townsend, *J. Am. Chem. Soc*. **1990**, *112*, 760-770.

extracted with EtOAc. The combined organic phases were washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish diol **86** that was used in the next step without further purification.

tert-Butyl (*R*)-(1-(4-(allyloxy)phenyl)-2-hydroxyethyl)carbamate (87)



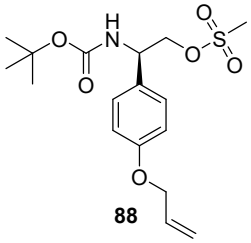
87

To a solution of phenol **86** (40.5 g, 160 mmol, 1.00 equiv.) in MeOH (130 mL), a NaOH solution (0.5M in H_2O, 320 mL, 160 mmol, 1.00 equiv.) was added. The solution was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in DMF (220 mL) before addition of allyl bromide (17.0 mL, 192 mmol, 1.20 equiv.) at 0 °C. The solution was stirred at room temperature for 24 h and subsequently concentrated under reduced pressure. The residue was purified by column chromatography (dry load, PE/EtOAc = 7:1, 5:1, 4:1, 3:1) to furnish primary alcohol **87** (5.86 g, 20.0 mmol, 17% yield o3s) as colorless solid.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.18 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 7.11 (d, *J* = 8.2 Hz, 1H, N*H*), 6.86 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 6.07 – 5.98 (m, 1H, *H*-11), 5.38 (dq, *J* = 1.9, 17.2 Hz, 1H, *H*-12), 5.24 (dq, *J* = 1.6, 10.5 Hz, 1H, *H*-12), 4.72 (t, *J* = 5.8 Hz, 1H, O*H*), 4.54 – 4.52 (m, 2H, *H*-10), 4.48 – 4.43 (m, 1H, *H*-2), 3.46-3.42 (m, 2H, *H*-1), 1.36 (s, 9H, *H*-9); **^{13}C-NMR** (DMSO-d_6, 100 MHz): δ [ppm] 157.0 (q, *C*-6), 155.1 (q, *C*-7), 134.0 (t, *C*-11), 133.9 (q, *C*-3), 127.9 (t, Ar-*C*), 117.3 (s, *C*-12), 114.2 (t, Ar-*C*), 77.6 (q, *C*-8), 68.1 (s, *C*-10), 64.9 (s, *C*-1), 56.1 (t, *C*-2), 28.3 (p, *C*-9).

The analytical data are consistent with those reported in the literature.[130]

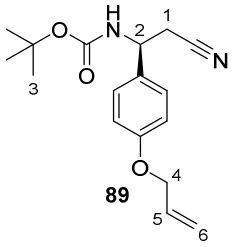
(*R*)-2-(4-(Allyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)ethyl methanesulfonate (88)



88

To a solution of alcohol **87** (46.9 g, 160 mmol, 1.00 equiv.) in CH_2Cl_2 (150 mL), Et_3N (4.19 mL, 29.9 mmol, 1.50 equiv.) was added. The solution was cooled to 0 °C and MsCl (2.34 mL, 29.8 mmol, 1.50 equiv.) was added. The mixture was stirred at 0 °C for 2 h before addition of a sat. NH_4Cl solution. The aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish crude product **88** as yellow solid, which was used in the next step without further purification.

***tert*-Butyl (*S*)-(1-(4-(allyloxy)phenyl)-2-cyanoethyl)carbamate (89)**

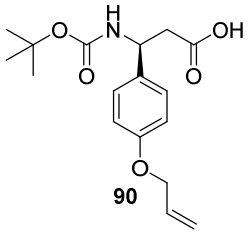


To a solution of mesylate **88** (160 mmol, 1.00 equiv.) in DMSO (150 mL), NaCN (2.94 g, 60.3 mmol, 3.00 equiv.) was added. The solution was stirred at 40 °C for 17 h before addition of H_2O. The aqueous phase was extracted with Et_2O (4x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (PE/EtOAc = 4:1, 2:1) to furnish nitrile **89** (3.52 g, 11.6 mmol, 58% yield o2s) as colorless solid.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 7.65 (d, J = 10.1 Hz, 1H, N*H*), 7.25 (d, J = 8.7 Hz, 2H, Ar-*H*), 6.91 (d, J = 8.7 Hz, 2H, Ar-*H*), 6.07 – 5.98 (m, 1H, *H*-5), 5.38 (dq, J = 1.8, 17.1 Hz, 1H, *H*-6), 5.24 (dq, J = 1.5, 10.5 Hz, 1H, *H*-6), 4.84 – 4.78 (m, 1H, *H*-2), 4.54 (dt, J = 5.2, 1.6 Hz, 2H, *H*-4), 2.94 – 2.78 (m, 2H, *H*-1), 1.37 (s, 9H, *H*-3).

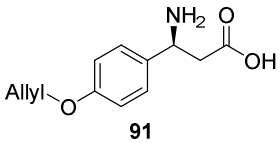
The analytical data are consistent with those reported in the literature.[130]

(*S*)-3-(4-(Allyloxy)phenyl)-3-((*tert*-butoxycarbonyl)amino)propanoic acid (90)



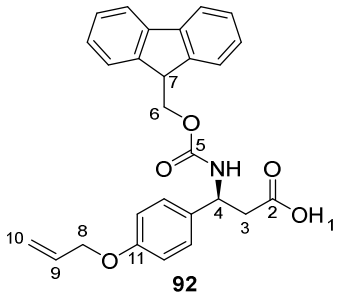
To a solution of nitrile **89** (3.52 g, 11.6 mmol, 1.00 equiv.) in EtOH (159 mL), NaOH (2M in H_2O, 57.1 mL, 116 mmol, 10.0 equiv.) was added. The solution was stirred at 90 °C for 5 h. After cooling down to room temperature, the solvent was removed under reduced pressure. The residue was acidified with a 2M HCl solution and extracted with EtOAc (4x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, concentrated under reduced pressure and to furnish carboxylic acid **90** (1.84 g, 5.74 mmol, 49% yield) as colorless solid that was used in the next without further purification.

(*S*)-3-(4-(Allyloxy)phenyl)-3-aminopropanoic acid (91)



To a solution of acid **90** (2.30 g, 7.15 mmol, 1.00 equiv.) in CH_2Cl_2 (55.0 mL) at 0 °C, TFA (27.4 mL, 358 mmol, 50.0 equiv.) was added and the reaction mixture was stirred for 15 h at 0 °C. Then the solvent was removed under reduced pressure, affording deprotected peptide **91** as a colorless foam that was used in the next step without further purification.

(*S*)-3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-(allyloxy)phenyl)propanoic acid (92)

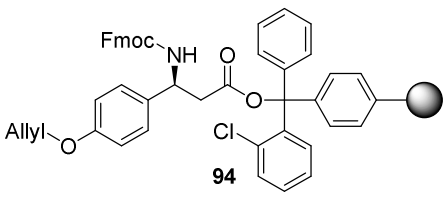


92

To a solution of acid **91** (1.58 g, 7.15 mmol, 1.00 equiv.) in 1,4-dioxane (71.5 mL) and 10% Na_2CO_3-solution (143 mL) at 0 °C, Fmoc-Cl (2.22 g, 8.57 mmol, 1.20 equiv.) in 1,4-dioxane (71.5 mL) was added over 10 min. The reaction mixture was stirred for 16 h at room temperature. Then the mixture was diluted with H_2O (20.0 mL) and the aqueous layer was washed with Et_2O (3x 40.0 mL) and the pH was adjusted to 1 with conc. HCl. Then the aqueous layer was extracted with EtOAc (3 x 20.0 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. Purification by washing the crude product with water and PE afforded acid **92** (3.08 g, 6.94 mmol, 97% yield o2s) as a colorless foam.

$[\alpha]_D^{27.4}$ = - 39.2° (*c* 0.38, MeOH); **^{1}H-NMR** (DMSO-d_6, 400 MHz): δ [ppm] 12.57 – 11.85 (bs, 1H, *H*-1), 7.89 – 7.85 (m, 3H, N*H,* Ar-*H*), 7.67 (d, *J* = 7.4 Hz, 2H, Ar-*H*), 7.43 – 7.21 (m, 6H, Ar-*H*), 6.89 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.08 – 5.98 (m, 1H, *H*-9), 5.41 – 5.36 (m, 1H, *H*-10), 5.26 – 5.23 (m, 1H, *H*-10), 4.92 – 4.86 (m, 1H, *H*-4), 4.54 (d, *J* = 5.2 Hz, 2H, *H*-6), 4.30 – 4.17 (m, 3H, *H*-7, *H*-8), 2.74 – 2.58 (m, 2H, *H*-3); **^{13}C-NMR** (DMSO-d_6, 100 MHz): δ [ppm] 171.8 (q, *C*-2), 157.2 (q, *C*-11), 155.3 (q, *C*-5), 143.9 (q, Ar-*C*), 143.8 (q, Ar-*C*), 140.7 (q, Ar-*C*), 135.0 (q, Ar-*C*), 133.8 (t, *C*-9), 127.6 (t, Ar-*C*), 127.5 (t, Ar-*C*), 127.1 (t, Ar-*C*), 127.0 (t, Ar-*C*), 125.2 (t, Ar-*C*), 125.1 (t, Ar-*C*), 120.1 (t, Ar-*C*), 117.4 (s, *C*-10), 114.4 (t, Ar-*C*), 68.1 (s, *C*-8), 65.3 (s, *C*-6), 51.0 (t, *C*-4), 46.7 (t, *C*-7), 41.1 (s, *C*-3); **HRMS** (ESI) *m/z* calculated for $C_{27}H_{25}NO_5Na$ [M+Na] 466.1630; found 466.1630.

Synthesis of Fragment A (67)



94

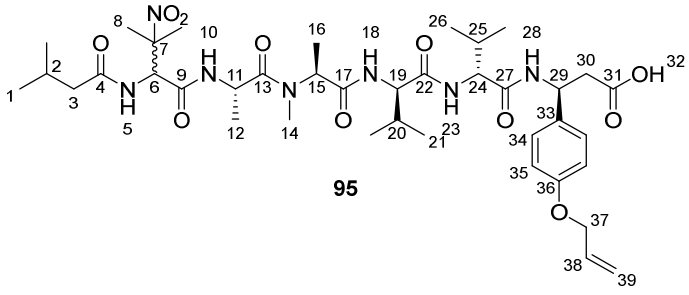
Activation of 2-chlorotrityl chloride resin

The 2-chlorotrityl chloride resin (**93**, 1.5 mmol/g, 2.10 g, 3.15 mmol, 1.00 equiv.) was suspended in CH_2Cl_2 (21.0 mL) at 0 °C. Then pyridine (609 μL, 7.56 mmol, 2.40 equiv.) and thionyl chloride (274 μL, 3.78 mmol, 1.20 equiv.) were added and the mixture was stirred under refluxing conditions. After 3 h the resin was filtered, washed with CH_2Cl_2 (6x) and dried *in vacuo*.

Loading of chlorotrityl resin

A mixture of acid **92** (1.68 g, 3.78 mmol, 1.20 equiv.) and DIPEA (2.74 mL, 15.8 mmol, 5.00 equiv.) in CH_2Cl_2 (21.0 mL) was added to the activated chlorotrityl resin. The suspension was stirred for 18 h at ambient temperature. Then the resin was filtered, washed with CH_2Cl_2/MeOH/DIPEA, CH_2Cl_2, DMF, and CH_2Cl_2 and dried *in vacuo* to give resin **94** in 3.10 g.

(3*S*,6*R*,9*R*,12*S*,15*S*)-3-(4-(Allyloxy)phenyl)-6,9-diisopropyl-12,13,15,22-tetramethyl-18-(2-nitropropan-2-yl)-5,8,11,14,17,20-hexaoxo-4,7,10,13,16,19-hexaazatricosanoic acid (95)



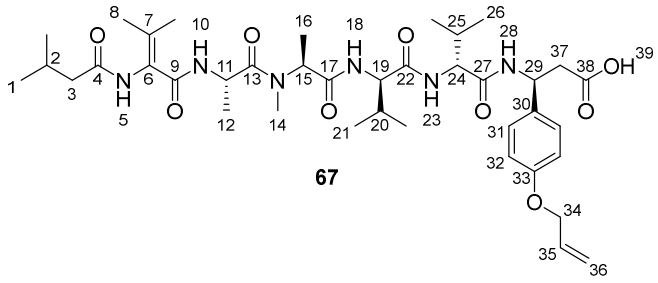
95

The title compound was prepared according to the general procedure for the synthesis of peptides using a Liberty Blue™ Automated Microwave Peptide Synthesizer from CEM in a 5x 0.50 mmol scale. Pre-loaded 2-chlorotrityl chloride resin **94** (5x 333 mg), Fmoc-D-Val-OH (3.12 g), Fmoc-*N*-Me-Ala-OH (1.50 g), Fmoc-Ala-OH (1.43 g), amino-3-methyl-3-nitrobutanoic acid (1.77 g) and isovaleric acid (470 mg) were used. After peptide synthesis was completed, the resin was transferred into a 20.0 mL syringe with filter. The solvent was removed under reduced pressure, and the resin was washed with DMF (3x 15.0 mL) and CH_2Cl_2 (3x 15.0 mL). The cleavage of the peptide from the resin was performed by adding 3.00 mL of 1% TFA in CH_2Cl_2 to the syringe vessel which was shaken for 2 min at room temperature. The liquid was filtered into a flask containing 3.00 mL of 10% pyridine in MeOH. The cleavage and filtration steps were repeated four more times. The combined filtrates were combined in a 500 mL round bottom flask and the solvent was removed under reduced pressure. The sequence was checked via LCMS. Purification by flash column chromatography (RP-BÜCHI, solvent A: water + 0.1% FA, solvent B: MeOH + 0.1% FA, 15x150 mm column, flow rate: 80.0 mL/min, 15 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/10; 3/10; 13/100; 15/100; t_R = 10.0 min) afforded fragment **95** (272 mg, 338 μmol, 68% yield) as a colorless foam.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 8.58 – 8.50 (m, 1H, *H*-10), 8.38 – 8.36 (m, 1H, *H*-28), 8.21 – 8.15 (m, 1H, *H*-5), 7.81 – 7.78 (m, 1H, *H*-18/*H*-23), 7.59 – 7.29 (m, 1H, *H*-18/*H*-23), 7.20 (d, *J* = 8.6 Hz, 2H, 2x *H*-34), 6.84 (d, *J* = 8.6 Hz, 2H, 2x *H*-35), 6.06 – 5.97 (m, 1H, *H*-38), 5.39 – 5.34 (m, 1H, *syn H*-39), 5.25 – 5.22 (m, 1H, *anti H*-39), 5.14 (q, *J* = 7.6 Hz, 1H, *H*-29), 5.07 – 5.01 (m, 1H, *H*-15), 4.73 – 4.56 (m, 1H, *H*CCH_3), 4.53 – 4.51 (m, 2H, *H*-37), 4.19 – 4.14 (m, 1H, *H*-19/

H-24), 4.09 (t, *J* = 8.3 Hz, 1H, (m, 1H, *H*-19/*H*-24), 3.17 – 2.81 (2s, 3H, *H*-14), 2.64 – 2.62 (m, 2H, *H*-30), 2.11 – 1.99 (m, 2H, *H*-3), 1.95 – 1.87 (m, 3H, *H*-2, *H*-20, *H*-25), 1.66 – 1.48 (m, 6H, *H*-8), 1.23 – 1.17 (m, 6H, *H*-12, *H*-16), 0.86 – 0.71 (m, 18H, *H*-1, *H*-21, *H*-26); **^{13}C-NMR** (DMSO-d_6, 100 MHz): δ [ppm] 172.0 (q, *C*-4), 171.9 (q, *C*=O), 171.7 (q, *C*=O), 170.9 (q, *C*=O), 170.8 (q, *C*=O), 170.6 (q, *C*=O), 169.7 (q, *C*=O), 157.1 (q, *C*-36), 134.3 (q, *C*-33), 133.8 (t, *C*-38), 127.6 (t, 2x *C*-34), 117.3 (s, *C*-39), 114.3 (t, 2x *C*-35), 89.0 (q, *C*-7), 68.1 (s, *C*-37), 57.9 (t, *C*-19/*C*-24), 57.3 (t, *C*-19/*C*-24), 56.8 (t, *C*-6), 51.5 (t, *C*-15), 48.6 (t, *C*-29), 45.6 (t, *C*-11), 44.2 (s, *C*-3), 40.7 (s, *C*-30), 30.4 (p, *C*-14), 30.2 (t, *C*-20/*C*-25), 25.7 (t, *C*-2), 25.6 (t, *C*-20/*C*-25), 23.6 – 22.3 (p, *C*-8), 23.3 (p, *C*-8), 22.3 (p, *C*-8), 22.2 (p, *C*-1/*C*-21/*C*-26), 22.1 (p, *C*-1/*C*-21/*C*-26), 22.0 (p, *C*-1/*C*-21/*C*-26), 21.6 (p, *C*-8), 19.2 (*C*-1/*C*-21/*C*-26), 19.1 (p, *C*-1/*C*-21/*C*-26), 18.3 (p, *C*-1/*C*-21/*C*-26), 18.2 (p, *C*-1/*C*-21/*C*-26), 17.9 (p, *C*-1/*C*-21/*C*-26), 16.5 (p, *C*-12), 14.5 (p, *C*-16); **HRMS** (ESI) *m/z* calculated for $C_{39}H_{62}N_7O_{11}$ $[M+H]^+$ 804.4507; found 804.4502.

Fragment A: (3*S*,6*R*,9*R*,12*S*,15*S*)-3-(4-(Allyloxy)phenyl)-6,9-diisopropyl-12,13,15,22-tetramethyl-,8,11,14,17,20-hexaoxo-18-(propan-2-ylidene)-4,7,10,13,16,19-hexaaza-tricosanoic acid (67)



67

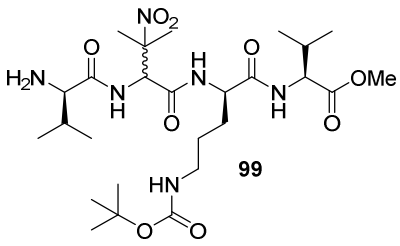
To a solution of fragment **95** (33.0 mg, 41.1 μmol, 1.00 equiv.) in THF (410 μL) at 0 °C, LiOH (1M in H_2O, 17.2 mg, 411 μmol, 10.0 equiv.) was added and the reaction mixture was stirred for 16 h at room temperature. Then the reaction was terminated by addition of acetic acid (47.0 μL). The solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI, solvent A: water + 0.1% FA, solvent B: MeOH; 12x150 mm column, flow rate: 10.0 mL/min, 60 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/10; 5/10; 45/100; 60/100; t_R = 36.0 min) and a second purification by preparative HPLC (solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, flow rate: 3.0 mL/min, gradient: (*t* [min]/solvent B [%]): 0/35; 60/50; t_R = 26.0 min) afforded fragment A (**67**, 2.30 mg, 3.00 μmol, 7% yield) as a colorless foam.

$[\alpha]_D^{23.5}$: - 31.7° (*c* 0.23, MeOH); **^{1}H-NMR** (DMSO-d_6, 500 MHz): δ [ppm] 12.58 – 11.47 (bs, 1H, *H*-39), 8.93 – 8.90 (m, 1H, *H*-5), 8.55 – 8.38 (m, 1H, *H*-28), 7.81 – 7.62 (m, 2H, 2x *H*N), 7.53 (d, *J* = 8.8 Hz, 1H, *H*-10), 7.20 (d, *J* = 8.7 Hz, 2H, 2x *H*-31), 6.83 (d, *J* = 8.7 Hz, 2H, 2x *H*-32), 6.05 – 5.98 (m, 1H, *H*-35), 5.38 – 5.34 (m, 1H, *anti H*-36), 5.24 – 5.22 (m, 1H, *syn H*-36), 5.13 – 5.09 (m,

1H, *H*-29), 5.00 (q, *J* = 7.1 Hz, 1H, *H*-15), 4.73 – 4.67 (m, 1H, *H*-11), 4.53 – 4.51 (m, 2H, *H*-34), 4.18 – 4.14 (m, 1H, *H*-19/*H*-24), 4.09 – 4.06 (m, 1H, *H*-19/*H*-24), 2.86 – 2.64 (2s, 3H, *H*-14), 2.60 – 2.58 (m, 2H, *H*-37), 2.09 – 2.05 (m, 2H, *H*-3), 2.03 – 2.00 (m, 1H, *H*-2), 1.96 – 1.91 (m, 5H, 2x *H*C(CH$_3$)$_2$ / 1x *H*-8), 1.65 (s, 3H, *H*-8), 1.21 – 1.20 (m, 3H, *H*-16), 1.18 – 1.17 (m, 3H, *H*-12), 0.89 (d, *J* = 6.5 Hz, 6H, *H*-1), 0.82 – 0.72 (m, 12H, *H*-21, *H*-26); **^{13}C-NMR** (DMSO-d$_6$, 125 MHz): δ [ppm] 172.1 (q, *C*-38), 172.0 (q, *C*=O), 170.9 (q, *C*=O), 170.8 (q, *C*=O), 170.6 (q, *C*-26), 169.6 (q, *C*=O), 164.5 (q, *C*=C, *C*=O), 160.9 (q, *C*-6), 157.0 (q, *C*-33), 134.3 (q, *C*-30), 133.8 (t, *C*-35), 127.6 (t, 2x *C*-31), 125.5 (q, *C*-7), 117.3 (s, *C*-36), 114.2 (t, 2x *C*-32), 68.1 (s, *C*-34), 58.1 (t, *C*-19/*C*-24), 57.5 (t, *C*-19/*C*-24), 51.7 (t, *C*-15), 48.7 (t, *C*-29), 45.1 (t, *C*-11), 44.3 (s, *C*-3), 41.0 (s, *C*-37), 30.4 (p, *C*-14), 30.3 (t, *C*-20/*C*-25), 25.5 (t, *C*-2), 22.4 (p, *C*-1), 20.7 (p, *C*-8), 20.1 (t, *C*-20/*C*-25), 19.2 (*C*H$_3$), 19.1 (p, *C*-21/*C*-26), 18.3 (p, *C*-21/*C*-26), 17.9 (p, 2x *C*-21/*C*-26), 17.4 (p, *C*-12), 14.4 (p, *C*-16); **HRMS** (ESI) *m/z* calculated for $C_{39}H_{61}N_6O_9$ $[M+H]^+$ 757.4422; found 757.4201.

E2.4 Syntheses of Fragments AB

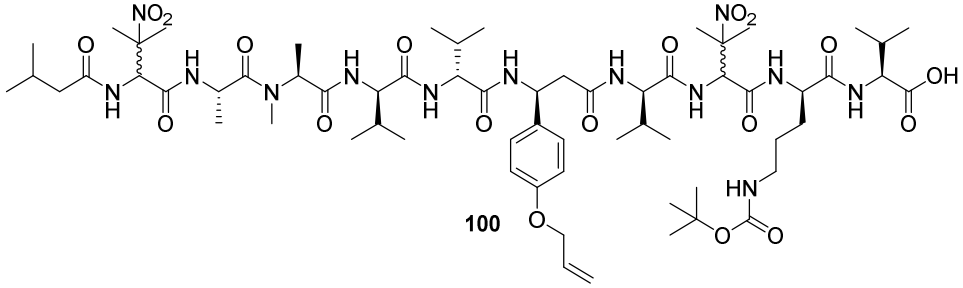
Fragment B-D,L: Methyl ((2*R*)-2-(2-((*R*)-2-amino-3-methylbutanamido)-3-methyl-3-nitrobutanamido)-5-((*tert*-butoxycarbonyl)-amino)pentanoyl)-L-valinate (99)



99

To a solution of Teoc-protected peptide **62** (575 mg, 785 μmol, 1.00 equiv.) in THF (15.7 mL), TBAF (1M in THF, 7.85 mL, 0.1M) was added and the reaction mixture was stirred for 15 h at ambient temperature. Then the solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI, solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, 12x150 mm column, flow rate: 10.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 5/0; 55/100; 60/100; t_R = 7.0 – 11.5 min) afforded fragment B-D,L (**99**, 487 mg, 575 μmol, quant.) as a colorless foam that was used in the next step without further purification.

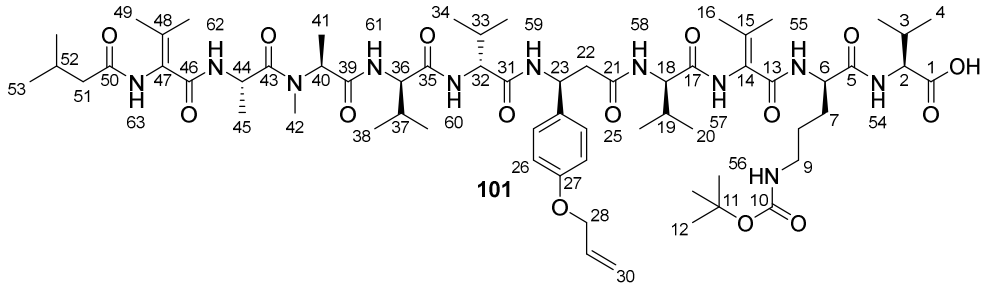
((2*R*)-2-(2-((2*R*)-2-((3*S*)-3-(4-(Allyloxy)phenyl)-3-((2*R*)-3-methyl-2-((2*R*)-3-methyl-2-((2*S*)-2-((2*S*)-*N*-methyl-2-(3-methyl-2-(3-methylbutanamido)-3-nitrobutanamido) propanamido)-propanamido)butanamido)butan-amido)propanamido)-3-methyl-butanamido)-3-methyl-3-nitrobutanamido)-5-((*tert*-butoxycarbonyl)amino)pentanoyl)-L-valine (100)



To a solution of fragment A (**95**, 78.7 mg, 97.9 μmol, 1.00 equiv.) and fragment B-D,L (**99**, 125 mg, 212 μmol, 2.16 equiv.) in DMF (1.00 mL) at 0 °C, HOAt (29.3 mg, 215 μmol, 2.20 equiv.), PyAOP (153 mg, 294 μmol, 3.00 equiv.) and DIPEA (85.3 µL, 490 μmol, 5.00 equiv.) were added and the reaction mixture was stirred for 23 h at ambient temperature under an argon atmosphere. The reaction was terminated by addition of MeOH (1.00 mL) and the solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI; solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, 4 g WP C18 column, flow rate: 10.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 24/95; 30/95; t_R = 22.0 – 27.0 min) afforded peptide **100** (95.2 mg, 69.0 μmol, 71% yield) as a colorless foam.

Due to the presence of diastereomers linked with the two nitro groups, peptide **100** was used in the next step without further purification or characterization.

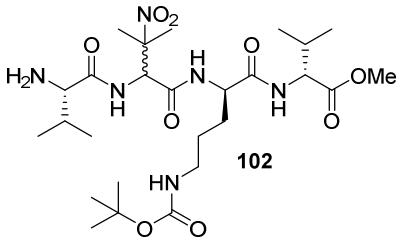
Fragment AB-D,L: ((*R*)-2-(2-((*R*)-2-((*S*)-3-(4-(Allyloxy)phenyl)-3-((*R*)-3-methyl-2-((*R*)-3-methyl-2-((*S*)-2-((*S*)-*N*-methyl-2-(3-methyl-2-(3-methylbutanamido)but-2-enamido)pro-panamido) propanamido)butanamido)butanamido)propan-amido)-3-methylbutan-amido)-3-methyl-but-2-enamido)-5-((*tert*-butoxycarbonyl)amino)pentanoyl)-L-valine (101)



To a solution of peptide **100** (27.3 mg, 20.0 μmol, 1.00 equiv.) in THF (500 μL), LiOH (1M in H_2O, 8.40 mg, 200 μmol, 10.0 equiv.) was added dropwise at 0 °C and the reaction mixture was stirred at ambient temperature. After 4 h, the reaction was terminated by addition of phosphate buffer solution (pH 7) and adjusted to pH 7. The solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI; solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, 4 g WP C18 column, flow rate: 10.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 25/95; 30/95; t_R = 14.0 – 20.5 min) afforded fragment AB-D,L (**101**, 25.6 mg, 20.0 μmol, quant., *d.r.* = 9.7:0.3) as a colorless foam.

$[\alpha]_D^{21.4}$: - 7.7° (*c* 0.3, DMSO-d_6); **^{1}H-NMR** (DMSO-d_6, 600 MHz): δ [ppm] 9.13 (s, 1H, *H*-57/*H*-63), 8.91 (s, 1H, *H*-57/*H*-63), 8.32 – 8.27 (m, 1H, N*H*), 7.92 – 7.88 (m, 2H, N*H*), 7.80 – 7.78 (m, 1H, N*H*), 7.63 – 7.61 (m, 1H, N*H*), 7.54 – 7.49 (m, 2H, N*H*), 7.20 (d, *J* = 7.9 Hz, 2H, *H*-25), 6.80 (d, *J* = 9.2 Hz, 2H, *H*-26), 6.71 (t, *J* = 5.6 Hz, 1H, *H*-56), 6.03 – 5.97 (m, 1H, *H*-29), 5.36 – 5.33 (m, 1H, *H*-30), 5.23 – 5.21 (m, 1H, *H*-30), 5.15 – 5.12 (m, 1H, *H*-23), 5.05 – 4.98 (m, 1H, *H*-40), 4.71 – 4.67 (m, 1H, *H*-44), 4.51 – 4.50 (m, 2H, *H*-28), 4.33 – 4.29 (m, 1H, *H*-6), 4.16 – 4.03 (m, 4H, *H*-2, *H*-18, *H*-32, *H*-36), 2.89 – 2.84 (m, 2H, *H*-9), 2.85 (s, 3H, *H*-42), 2.77 – 2.74 (m, 1H, *H*-22), 2.62 – 2.61 (m, 1H, *H*-19/*H*-33/*H*-37), 2.52 – 2.51 (m, 1H, *H*-22), 2.46 – 2.45 (m, 2H, *H*-19/*H*-33/*H*-37), 2.06 – 1.65 (m, 18H, *H*-3, *H*-7, *H*-16, *H*-49, *H*-51, *H*-52), 1.51 – 1.50 (m, 1H, *H*-7), 1.43 – 1.39 (m, 2H, *H*-8), 1.35 (s, 9H, *H*-12), 1.25 – 1.16 (m, 6H, *H*-41, *H*-45), 0.89 – 0.67 (m, 30H, *H*-4, *H*-20, *H*-34, *H*-38, *H*-53); **^{13}C-NMR** (DMSO-d_6, 150 MHz): δ [ppm] 172.9 (q, *C*=O), 172.1 (q, *C*=O), 171.7 (q, *C*=O), 171.0 (q, *C*=O), 170.9 (q, *C*=O), 170.8 (q, *C*=O), 170.6 (q, *C*=O), 169.7 (q, *C*=O), 164.9 (q, *C*=O), 164.5 (q, *C*=O), 163.2 (q, *C*=O), 157.1 (q, *C*-27), 155.6 (q, *C*-10), 134.4 (q, 2x *C*-14, *C*-47), 134.1 (q, *C*-24), 133.8 (t, *C*-29), 127.9 (t, 2x *C*-25), 125.5 (q, *C*-15/*C*-48), 125.1 (q, *C*-15/*C*-48), 117.2 (s, *C*-30), 114.1 (t, 2x *C*-26), 77.4 (q, *C*-11), 68.1 (s, *C*-28), 58.2 (t, *C*-2/*C*-18/*C*-32/*C*-36), 57.8 (t, *C*-2/*C*-18/*C*-32/*C*-36), 57.5 (t, *C*-2/*C*-18/*C*-32/*C*-36), 57.3 (t, *C*-2/*C*-18/*C*-32/*C*-36), 52.3 (t, *C*-6), 51.7 (t, *C*-40), 49.5 (t, *C*-23), 45.1 (t, *C*44), 44.2 (s, *C*-51), 41.8 (s, *C*-22), 40.0 (s, *C*-9), 30.4 (p, *C*-42), 30.3 (t, *C*-3/*C*-19/*C*-33/*C*-37), 30.1 (t, *C*-3/*C*-19/*C*-33/*C*-37), 30.0 (t, *C*-3/*C*-19/*C*-33/*C*-37), 29.9 (s, *C*-7), 29.6 (t, *C*-3/*C*-19/*C*-33/*C*-37), 28.3 (s, 3x *C*-12), 25.8 (s, *C*-8), 25.5 (t, *C*-52), 22.3 (p, 2x *C*-53), 20.7 (p, *C*-16/*C*-49), 20.7 (p, *C*-16/*C*-49), 20.3 (p, *C*-16/*C*-49), 20.1 (p, *C*-16/*C*-49), 19.2 (p, *C*-4/*C*-20/*C*-34/*C*-38), 19.2 (p, *C*-4/*C*-20/*C*-34/*C*-38), 19.1 (p, *C*-4/*C*-20/*C*-34/*C*-38), 19.1 (p, *C*-4/*C*-20/*C*-34/*C*-38), 18.9 (p, *C*-4/*C*-20/*C*-34/*C*-38), 18.4 (p, *C*-4/*C*-20/*C*-34/*C*-38), 18.3 (p, *C*-4/*C*-20/*C*-34/*C*-38), 18.2 (p, *C*-4/*C*-20/*C*-34/*C*-38), 17.4 (p, *C*-41/*C*-45), 14.4 (p, *C*-41/*C*-45); **HRMS** (ESI) *m/z* calculated for $C_{64}H_{104}N_{11}O_{15}$ $[M+H]^+$ 1266.7713; found 1266.7704.

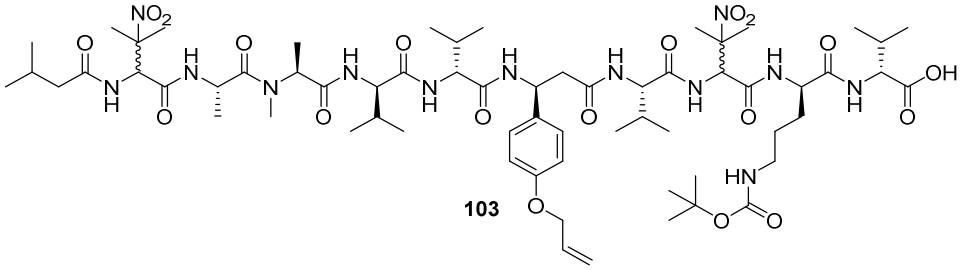
Fragment B-L,D: Methyl ((2*R*)-2-(2-((*S*)-2-amino-3-methylbutanamido)-3-methyl-3-nitrobutanamido)-5-((*tert*-butoxycarbonyl)amino)pentanoyl)-D-valinate (102)



102

To a solution of Teoc-protected peptide **61** (519 mg, 708 μmol, 1.00 equiv.) in THF (14.2 mL), TBAF (1M in THF, 7.10 mL, 0.1M) was added and the reaction mixture was stirred for 16 h at ambient temperature. Then the reaction was terminated by addition of MeOH (1.00 mL) and the solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI; solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, 4 g WP C18 column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 25/95; 30/95; t_R = 9.5 – 17.0 min) afforded fragment B-L,D (**102**, 416 mg, 707 μmol, quant.) as a colorless foam that was used in the next step without further purification and characterization.

((2*R*)-2-(2-((2*S*)-2-((3*S*)-3-(4-(Allyloxy)phenyl)-3-((2*R*)-3-methyl-2-((2*R*)-3-methyl-2-((2*S*)-2-((2*S*)-*N*-methyl-2-(3-methyl-2-(3-methylbutanamido)-3-nitrobutanamido) propan-amido)-propanamido)butanamido)butan-amido)propanamido)-3-methylbutanamido)-3-methyl-3-nitrobutanamido)-5-((*tert*-butoxycarbonyl)amino)pentanoyl)-D-valine (103)

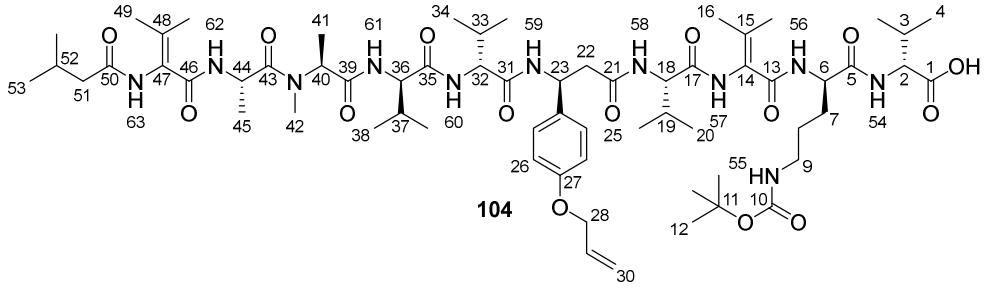


103

To a solution of fragment A (**95**, 116 mg, 144 μmol, 1.00 equiv.) and fragment B-L,D (**102**, 156 mg, 265 μmol, 1.80 equiv.) in two separate batches in DMF (1.60 mL) at 0 °C, HOAt (43.1 mg, 317 μmol, 2.20 equiv.), PyAOP (225 mg, 432 μmol, 3.00 equiv.) and DIPEA (125 μL, 720 μmol, 5.00 equiv.) were added and the reaction mixture was stirred for 16 h at ambient temperature. The reaction was terminated by addition of MeOH (1.00 mL), the batches were united and the solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI; solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, 40 g WP C18 column, flow rate: 30.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 2/0; 23/100; 30/100; t_R = 17 – 28 min) afforded peptide **103** (183 mg, 133 μmol, 46% yield) as a colorless foam

Due to the presence of diastereomers linked with the two nitro groups, peptide **103** was used in the next step without further characterization.

Fragment AB-L,D: ((*R*)-2-(2-((*S*)-2-((*S*)-3-(4-(Allyloxy)phenyl)-3-((*R*)-3-methyl-2-((*R*)-3-methyl-2-((*S*)-2-((*S*)-*N*-methyl-2-(3-methyl-2-(3-methylbutanamido)but-2-enamido)-propan-amido)propanamido)butanamido)butanamido)propan-amido)-3-methylbutan-amido)-3-methylbut-2-enamido)-5-((*tert*-butoxycarbonyl)amino)pentanoyl)-D-valine (104)



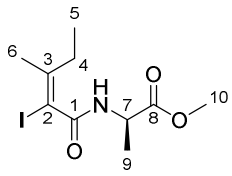
To a solution of peptide **103** (182 mg, 132 μmol, 1.00 equiv.) in THF (1.32 mL), LiOH (1M in H_2O, 55.6 mg, 1.32 mmol, 10.0 equiv.) was added dropwise at 0 °C and the reaction mixture was stirred at ambient temperature. After 17 h, the reaction was terminated by addition of phosphate buffer solution (pH 7) and adjusted to pH 7. The solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI; solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, 24 g WP C18 column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 3/0; 26/100; 30/100; t_R = 12.5 – 28.5 min) afforded fragment AB-L,D (**104**, 127 mg, 100 μmol, 76% yield, *d.r.* = 8.7:1.3) as a colorless foam.

$[\alpha]_D^{23.6}$: - 22.5° (*c* 0.4, DMSO-d_6); **^{1}H-NMR** (DMSO-d_6, 600 MHz): δ [ppm] 8.99 – 8.92 (m, 2H, *H*-57, *H*-63), 8.21 (s, 1H, N*H*), 7.78 – 7.51 (m, 6H, N*H*), 7.16 (d, *J* = 8.7 Hz, 2H, *H*-25), 6.79 (d, *J* = 8.8 Hz, 2H, *H*-26), 6.71 (t, *J* = 5.6 Hz, 1H, *H*-55), 6.03 – 5.98 (m, 1H, *H*-29), 5.37 – 5.34 (m, 1H, *H*-30), 5.24 – 5.22 (m, 1H, *H*-30), 5.13 – 5.11 (m, 1H, *H*-23), 5.02 – 5.01 (q, *J* = 7.1 Hz, 1H, *H*-40), 4.71 – 4.68 (m, 1H, *H*-44), 4.51 – 4.50 (m, 2H, *H*-28), 4.16 – 4.09 (m, 4H, *H*-2, *H*-6, *H*-18, *H*-32, *H*-36), 2.89 – 2.88 (m, 2H, *H*-9), 2.85 (s, 3H, *H*-42), 2.63 (m, 1H, *H*-22), 2.61 (m, 1H, *H*-19/*H*-33/*H*-37), 2.52 – 2.51 (m, 1H, *H*-22), 2.49 – 2.47 (m, 2H, *H*-19/*H*-33/*H*-37), 2.06 – 1.59 (m, 18H, *H*-3, *H*-7, *H*-16, *H*-49, *H*-51, *H*-52), 1.55 – 1.51 (m, 1H, *H*-7), 1.48 – 1.43 (m, 2H, *H*-8), 1.36 (s, 9H, *H*-12), 1.25 – 1.17 (m, 6H, *H*-41, *H*-45), 0.89 – 0.74 (m, 30H, *H*-4, *H*-20, *H*-34, *H*-38, *H*-53); **^{13}C-NMR** (DMSO-d_6, 150 MHz): δ [ppm] 172.1 (q, *C*=O), 172.0 (q, *C*=O), 171.5 (q, *C*=O), 171.4 (q, *C*=O), 170.9 (q, *C*=O), 170.8 (q, *C*=O), 170.6 (q, *C*=O), 169.9 (q, *C*=O), 164.9 (q, *C*=O), 164.5 (q, *C*=O), 163.2 (q, *C*=O), 156.8 (q, *C*-27), 155.5 (q, *C*-10), 134.6 (q, 2x *C*-14, *C*-47), 134.4 (q, *C*-24), 133.8 (t, *C*-29), 127.2 (t, 2x *C*-25), 125.5 (q, *C*-15/*C*-48), 124.9 (q, *C*-15/*C*-48), 117.2 (s, *C*-30), 114.1 (t, 2x *C*-26), 77.3 (q, *C*-11), 68.1 (s, *C*-28), 58.3 (t, *C*-2/*C*-18/*C*-32/*C*-36), 58.0 (t, *C*-2/*C*-18/*C*-32/*C*-36), 57.8 (t, *C*-2/*C*-18/*C*-32/*C*-36), 57.4 (t, *C*-2/*C*-18/*C*-32/*C*-36), 52.3 (t, *C*-6),

51.6 (t, *C*-40), 49.3 (t, *C*-23), 45.0 (t, *C*-44), 44.2 (s, *C*-51), 41.8 (s, *C*-22), 41.3 (s, *C*-9), 30.4 (p, *C*-42), 30.3 (s/t, *C*-3/*C*-7/*C*-19/*C*-33/*C*-37), 30.0 (s/t, *C*-3/*C*-7/*C*-19/*C*-33/*C*-37), 29.5 (s/t, *C*-3/*C*-7/*C*-19/*C*-33/*C*-37), 28.9 (s/t, *C*-3/*C*-7/*C*-19/*C*-33/*C*-37), 28.6 (s/t, *C*-3/*C*-7/*C*-19/*C*-33/*C*-37), 28.3 (s, 3x *C*-12), 25.5 (s/t, *C*-8/*C*-52), 25.5 (s/t, *C*-8/*C*-52), 22.3 (p, 2x *C*-53), 20.7 (p, *C*-16/*C*-49), 20.7 (p, *C*-16/*C*-49), 20.3 (p, *C*-16/*C*-49), 20.1 (p, *C*-16/*C*-49), 19.3 (p, *C*-4/*C*-20/*C*-34/*C*-38), 19.3 (p, *C*-4/*C*-20/*C*-34/*C*-38), 19.2 (p, *C*-4/*C*-20/*C*-34/*C*-38), 19.1 (p, *C*-4/*C*-20/*C*-34/*C*-38), 18.2 (p, *C*-4/*C*-20/*C*-34/*C*-38), 18.0 (p, *C*-4/*C*-20/*C*-34/*C*-38), 17.8 (p, *C*-4/*C*-20/*C*-34/*C*-38), 17.7 (p, *C*-4/*C*-20/*C*-34/*C*-38), 17.4 (p, *C*-41/*C*-45), 14.4 (p, *C*-41/*C*-45); **HRMS** (ESI) *m/z* calculated for $C_{64}H_{104}N_{11}O_{15}$ $[M+H]^+$ 1266.7715; found 1266.7713.

E2.5 Synthesis of Fragment CD

Methyl (*E*)-(2-iodo-3-methylpent-2-enoyl)-D-alaninate (34)



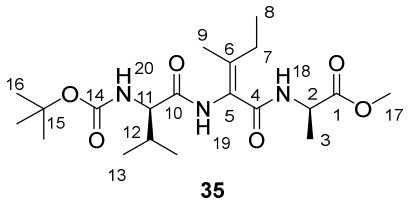
34

To a solution of D-alanine methylester hydrochloride (1.05 g, 7.52 mmol, 1.20 equiv.) in DMF (60.0 mL), HOAt (910 mg, 6.69 mmol, 1.10 equiv.), PyAOP (3.50 g, 6.71 mmol, 1.07 equiv.) and carboxylic acid (1.50 g, 6.25 mmol, 1.00 equiv.) dissolved in DMF (5.00 mL) were added. The solution was cooled to 0 °C and DIPEA (5.40 mL, 31.2 mmol, 5.00 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 20 h. Afterwards a sat. NH_4Cl solution and EtOAc were added. The aqueous phase was extracted with EtOAc (6x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc = 4:1) to give vinyliodide **34** (1.66 g, 5.11 mmol, 76% yield, *d.r.* > 15:1) as a colorless solid.[128]

T_M: 59-60 °C (Lit.: 58-60 °C)[34]; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ [ppm] 6.23 (d, J = 6.6 Hz, 1H, N*H*), 4.61 (quin, J = 7.3 Hz, 1H, *H*-7), 3.77 (s, 3H, *H*-10), 2.40 (q, J = 7.5 Hz, 2H, *H*-4), 1.98 (s, 3H, *H*-6), 1.44 (d, J = 7.3 Hz, 3H, *H*-9), 1.08 (t, J = 7.5 Hz, *H*-5); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 173.3 (q, *C*-8), 166.7 (q, *C*-1), 151.2 (q, *C*-3), 87.0 (q, *C*-2), 52.7 (p, *C*-10), 48.6 (t, *C*-7), 29.4 (p, *C*-4), 27.3 (s, *C*-9), 18.3 (p, *C*-6), 13.2 (p, *C*-5); **HRMS** (ESI) *m/z* calculated for $C_{10}H_{16}NO_3NaI$ $[M+Na]^+$ 348.0073; found 348.0062.

The analytical data are consistent with those reported in the literature.[34]

Methyl ((*E*)-2-((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-3-methylpent-2-enoyl)-D-alaninate (35)

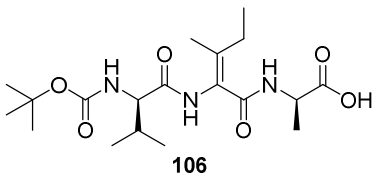


To a solution of vinyl iodide **34** (250 mg, 769 μmol, 2.00 equiv.) in degassed 1,2-dioxane (500 μL), in six separate batches, *tert*-butyl (*R*)-(1-amino-3-methyl-1-oxobutan-2-yl) carbamate (**32**, 83.3 mg, 385 μmol, 1.00 equiv.), K_2CO_3 (106 mg, 769 μmol, 2.00 equiv.), CuI (44.0 mg, 231 μmol, 0.60 equiv.) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (***rac*-16**, 250 μL, 1.59 mmol, 4.10 equiv.) were added. The mixture was stirred at 70 °C for 20 h. Afterwards a sat. NH_4Cl solution was added, and the mixture was diluted with EtOAc. The aqueous phase was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2/MeOH = 100:0, 100:1, 100:2) to furnish fragment C (**35**, 687 mg, 1.10 mmol, 72% {average yield over all six batches}) as a colorless solid.[128]

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 8.98 (s, 1H, *H*-19), 7.74 (d, *J* = 6.8 Hz, 1H, *H*-18), 6.85 (d, *J* = 7.7 Hz, 1H, *H*-20), 4.29 (p, *J* = 7.1 Hz, 1H, *H*-2), 3.77 (t, *J* = 7.5 Hz, 1H, *H*-11), 3.61 (s, 3H, *H*-17), 2.35 (q, *J* = 7.3 Hz, 2H, *H*-7), 1.95 (oct, *J* = 7.4 Hz, 1H, *H*-12), 1.66 (s, 3H, *H*-9), 1.37 (s, 9H, *H*-16), 1.26 (d, *J* = 7.2 Hz, 3H, *H*-3), 0.99 (t, *J* = 7.4 Hz, 3H, *H*-8), 0.89 (d, *J* = 6.8 Hz, 3H, *H*-13a), 0.86 (d, *J* = 6.8 Hz, 3H, *H*-13b); **HRMS** (ESI) *m/z* calculated for $C_{20}H_{35}N_3O_6Na$ $[M+Na]^+$ 590.2842; found 590.2833.

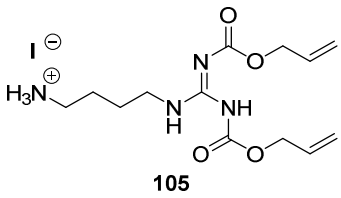
The analytical data are consistent with those reported in the literature.[35]

((*E*)-2-((*R*)-2-((*tert*-Butoxycarbonyl)amino)-3-methylbutanamido)-3-methylpent-2-enoyl)-D-alanine (106)



To a solution of methyl ester **35** (300 mg, 725 μmol, 1.00 equiv.) in THF (2.50 mL), LiOH (1M in H_2O, 2.50 mL, 747 mmol, 10.3 equiv.) was added dropwise at 0 °C. The reaction was stirred at room temperature for 20 h. H_2O and Et_2O were added, and the aqueous phase was washed with Et_2O (2x) and acidified with an 1M HCl solution and extracted with EtOAc (4x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish fragment C (**106**, 285 mg, 713 μmol, 98% yield), which was used in the next step without further purification.

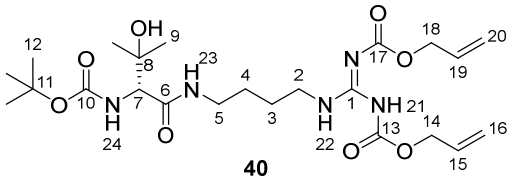
4-(2,3-Bis((allyloxy)carbonyl)guanidino)butan-1-aminium iodide (105)



105

To a solution of carbamate **39** (1.00 g, 2.51 mmol, 1.00 equiv.) in CH_2Cl_2 (25.0 mL), TMSI (290 μL, 2.76 mmol, 1.10 equiv.) was added dropwise. The solution was stirred at room temperature for 4 h. MeOH was added, and the solution was concentrated and coevaporated with CH_2Cl_2 (3x 5.00 mL) under reduced pressure. The crude iodide **105** was used in the next step without further purification.

(*N*-Boc-D-3-hydroxyvalyl)-*Nθ,Nθ'*-bisalloc-*Nα*-agmatide (40)



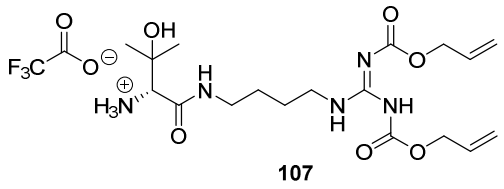
40

To a solution of *N*-Boc-3-hydroxy-D-valine (**37**, 532 mg, 2.28 mmol, 1.00 equiv.) and iodide **105** (1.00 g, 2.51 mmol, 1.10 equiv.) in CH_2Cl_2 (30.0 mL) and DMF (5.00 mL), Oxyma (486 mg, 3.42 mmol, 1.50 equiv.), EDC·HCl (546 mg, 2.85 mmol, 1.30 equiv.) and $NaHCO_3$ (957 mg, 11.4 mmol, 5.00 equiv.) were added at 0 °C and the reaction mixture was stirred at room temperature for 20 h. A solution of HCl (1M) and EtOAc were added, and the organic phase was washed with an 1M HCl solution (2x), a sat. $NaHCO_3$ solution (2x) and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (MeOH in CH_2Cl_2 = 0 → 1.5%) to give fragment D (**40**, 509 mg, 991 μmol, 43% yield) as colorless oil.[128]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 11.80 (s, 1H, *H*-21), 8.43 (t, *J* = 5.1 Hz, 1H, *H*-22), 6.71 (s, 1H, *H*-23), 6.02 – 5.85 (m, 2H, *H*-15, *H*-19), 5.55 (d, *J* = 8.6 Hz, 1H, *H*-24), 5.39 – 5.29 (m, 3H, H-16, *H*-20), 5.24 – 5.21 (m, 1H, *H*-20), 4.66 – 4.60 (m, 4H, *H*-14, *H*-18), 4.18 (s, 1H, O*H*), 3.84 (d, *J* = 9.1 Hz, 1H, *H*-7), 3.46 (q, *J* = 6.8 Hz, 2H, *H*-2), 3.31 (q, *J* = 6.0 Hz, 2H, *H*-5), 1.63 – 1.57 (m, 4H, *H*-3, *H*-4), 1.42 (s, 9H, *H*-12), 1.29 (s, 3H, *H*-9), 1.18 (s, 3H, *H*-9); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 172.5 (q, *C*-6), 163.2 (q, *C*-17), 156.4 (q, *C*-1/*C*-10), 156.1 (q, *C*-1/*C*-10), 153.9 (q, *C*-13), 132.9 (t, *C*-19), 131.0 (t, *C*-15), 119.7 (s, *C*-16), 118.2 (s, *C*-20), 80.4 (q, *C*-11), 71.8 (q, *C*-8), 67.3 (s, *C*-14), 66.6 (s, *C*-18), 60.0 (t, *C*-7), 40.8 (s, *C*-2), 38.9 (s, *C*-5), 28.4 (3C, p, *C*-12), 27.6 (p, *C*-9a), 26.5 (s, *C*-3/*C*-4), 26.4 (s, *C*-3/*C*-4), 25.5 (p, *C*-9b); **HRMS** (ESI): *m/z* calculated for $C_{23}H_{39}N_5O_8Na$ $[M+Na]^+$: 536.2696; found: 536.2689.

The analytical data are consistent with those reported in the literature.[35]

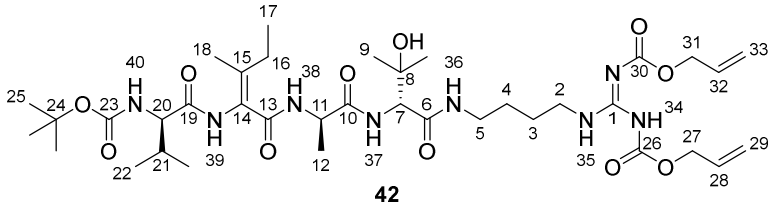
(*R*,*Z*)-7-(((Allyloxy)carbonyl)amino)-16-hydroxy-16-methyl-5,14-dioxo-4-oxa-6,8,13-triazaheptadeca-1,6-dien-15-aminium trifluoroacetate (107)



107

To a solution of carbamate **40** (509 mg, 991 μmol) in CH_2Cl_2 (9.99 mL), TFA (3.79 mL, 49.6 mmol, 50.0 equiv.) was added at 0 °C. The solution was stirred at 0 °C for 4 h. All volatiles were removed under reduced pressure and the residue was coevaporated with MeOH (2x, 0 mbar, rt) and CH_2Cl_2 (20 mbar, 40 °C). The crude product **107** was used in the next step without further purification.

Fragment CD (42)



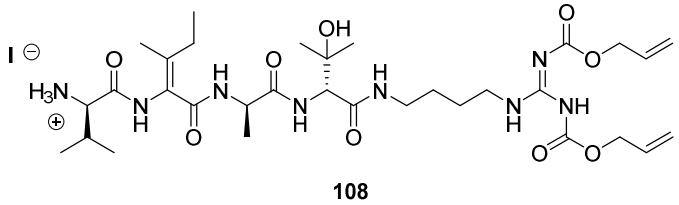
42

To a solution of acid **106** (201 mg, 503 μmol, 1.50 equiv.) and TFA salt **107** (139 mg, 335 μmol, 1.00 equiv.) in MeCN (3.00 mL) and DMF (1.50 mL), EDC·HCl (122 mg, 637 μmol, 1.90 equiv.) and HOAt (105 mg, 771 μmol, 2.30 equiv.) in DMF (3.00 mL) were added at -15 °C dropwise over 10 min. $NaHCO_3$ (197 mg, 2.35 mmol, 7.00 equiv.) was added and the mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with H_2O and MeOH. Purification by flash column chromatography (RP-BÜCHI: solvent A: water + 0.1% FA, solvent B: MeOH + 0.1% FA, 12x150 mm, 10 mL/min, 60 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/10; 5/10; 50/100; 60/100; t_R = 38 – 46 min) afforded fragment CD (**42**, 180 mg, 227 mmol, 67% yield) as colorless oil.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 11.57 (s, 1H, *H*-34), 9.27 (s, 1H, *H*-39), 8.37 (t, *J* = 5.0 Hz, 1H, *H*-35), 7.89 (d, *J* = 7.0 Hz, 1H, *H*-38), 7.79 – 7.71 (m, 2H, *H*-36, *H*-37), 6.77 (d, *J* = 7.1 Hz, 1H, *H*-40), 6.00 – 5.88 (m, 2H, H-28, *H*-32), 5.38 – 5.34 (m, 1H, *H*-29a), 5.30-5.25 (m, 2H, *H*-29b, *H*-33a), 5.19-5.16 (m, 1H, *H*-33b), 4.75 (s, 1H, O*H*), 4.67 – 4.66 (m, 2H, *H*-27), 4.50 – 4.48 (m, 2H, *H*-31), 4.30 (p, *J* = 7.2 Hz, 1H, *H*-11), 4.22 (d, *J* = 9.8 Hz, 1H, *H*-7), 3.86 (t, *J* = 7.3 Hz, 1H, *H*-20), 3.31-3.27 (m, 2H, *H*-2), 3.15 – 3.09 (m, 1H, *H*-5a), 3.06 – 2.95 (m, 1H, *H*-5b), 2.33 – 2.20 (m, 2H, *H*-16), 2.00 – 1.91 (m, 1H, *H*-21), 1.68 (s, 3H, *H*-18), 1.53 – 1.46 (m, 2H, *H*-3), 1.43 – 1.37 (m, 12H, *H*-4, *H*-25), 1.24 (d, *J* = 7.2 Hz, 3H, *H*-12), 1.11 – 1.09 (m, 6H, *H*-9), 0.99 (t, *J* = 7.5 Hz, 3H, *H*-17), 0.88 (d, *J* = 6.8 Hz, 6H, *H*-22).

The analytical data are consistent with those reported in the literature.[35]

Boc-deprotected fragment CD (108)

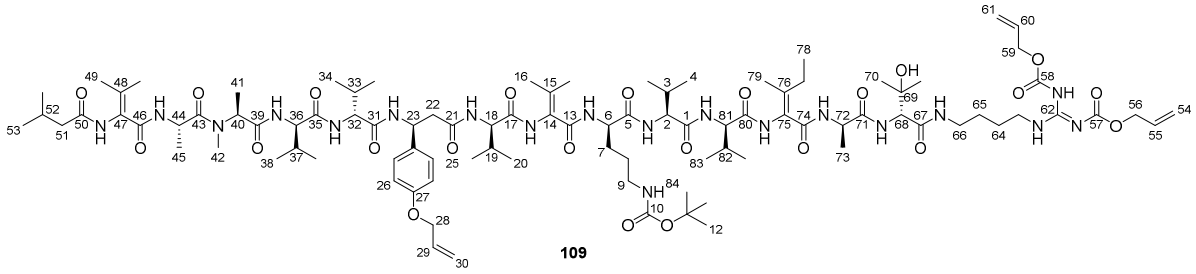


108

To a solution of carbamate **42** (306 mg, 386 μmol, 1.00 equiv.) in CH_2Cl_2 (3.86 mL), TMSI (105 μL, 771 μmol, 2.00 equiv.) was added dropwise. The reaction was stirred at room temperature for 1 h. MeOH was added, and the solution was concentrated and coevaporated with CH_2Cl_2 (3x 5.00 mL) under reduced pressure. The crude product was used in the next step without further purification

E2.6 Syntheses of Myxovalargins

Boc-protected fragment ABCD-D,L (109)



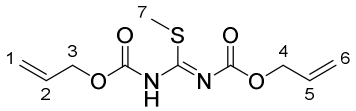
109

To a solution of fragment AB-D,L (**101**, 4.60 mg, 3.63 μmol, 1.00 equiv.) and fragment CD (**108**, 3.03 mg, 4.36 μmol, 1.20 equiv.) in DMF (500 μL) at 0 °C, HOAt (740 mg, 76.6 μmol, 1.50 equiv.), HATU (29.1 mg, 76.6 μmol, 2.50 equiv.) and DIPEA (26.7 μL, 5.45 μmol, 5.00 equiv.) were added and the reaction mixture was stirred for 17 h at ambient temperature. The reaction was terminated by addition of MeOH (1.00 mL) and the solvent was removed under reduced pressure. Purification by preparative HPLC (solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA; flow rate: 15.0 mL/min; gradient: (t [min]/solvent B [%]): 0/20; 80/100; 100/100; t_R = 19.0 – 22.0 min) afforded Boc-protected fragment ABCD-D,L (**109**, 3.90 mg, 2.00 μmol, 55% yield) as a rose foam.

$[\alpha]_D^{21.3}$: + 1.0° (c 0.1, DMSO-d_6); **^{1}H-NMR** (DMSO-d_6, 600 MHz): δ [ppm] 9.33 – 8.88 (m, 3H, N*H*), 8.51 – 8.32 (m, 2H, N*H*), 8.31 – 8.15 (m, 2H, N*H*), 8.12 – 8.04 (m, 1H, N*H*), 7.89 – 7.69 (m,

6H, N*H*), 7.62 – 7.60 (m, 2H, N*H*), 7.23 – 7.16 (m, 2H, *H*-25), 6.81 – 6.80 (d, *J* = 8.7 Hz, 2H, *H*-26), 6.72 – 6.66 (m, 1H, N*H*-84), 6.04 – 5.90 (m, 3H, *H*-29, *H*-55, *H*-60), 5.37 – 5.15 (m, 8H, *H*-23, *H*-30, *H*-54, *H*-61, O*H*), 5.14 – 5.01 (m, 1H, *H*-40), 4.71 – 4.66 (m, 3H, *H*-44, *H*-56, *H*-59), 4.50 – 4.49 (m, 4H, *H*-28, *H*-56, *H*-59), 4.37 – 4.12 (m, 10H, *H*-2, *H*-6, *H*-18, *H*-32, *H*-36, *H*-63, *H*-68, *H*-72, *H*-81), 3.17 – 2.99 (m, 2H, *H*-66), 2.93 – 2.73 (m, 5H, *H*-9, *H*-42), 2.72 – 2.63 (m, 1H, *H*-22), 2.54 – 2.51 (m, 6H, *H*-3, *H*-19, *H*-22, *H*-33, *H*-37, *H*-82), 2.30 – 2.24 (m, 2H, *H*-77), 2.07 – 1.60 (m, 18H, *H*-16, *H*-49, *H*-51, *H*-52, *H*-79), 1.51 – 1.49 (m, 3H, *H*-7, *H*-64), 1.41 – 1.39 (m, 4H, *H*-8, *H*-65), 1.35 (s, 9H, *H*-12), 1.23 – 1.16 (m, 9H, *H*-41, *H*-45, *H*-73), 1.10 – 1.05 (m, 6H, *H*-70), 0.96 – 0.96 (m, 3H, *H*-78), 0.89 – 0.73 (m, 36H, *H*-4, *H*-20, *H*-34, *H*-38, *H*-53, H-83); **^{13}C-NMR** (DMSO-d_6, 150 MHz): δ [ppm] 173.1 (q, *C*=O), 171.9 (q, *C*=O), 171.5 (q, *C*=O), 170.8 (q, *C*=O), 170.8 (q, *C*=O), 170.5 (q, *C*=O), 170.5 (q, *C*=O), 170.5 (q, *C*=O), 169.8 (q, *C*=O), 169.6 (q, *C*=O), 169.5 (q, *C*=O), 169.3 (q, *C*=O), 165.0 (q, *C*=O), 165. 0 (q, *C*=O), 164.9 (q, *C*=O), 162.9 (q, C-57/C-58), 156.9 (q, *C*-27), 155.5 (q, *C*-10), 155.0 (q, *C*-62), 152.5 (q, C-57/C-58), 134.3 (3x q, *C*-14, *C*-47, *C*-75), 134.1 (q, *C*-24), 133.7 (t, *C*-29/*C*-55/*C*-60), 133.5 (t, *C*-29/*C*-55/*C*-60), 131.8 (t, *C*-29/*C*-55/*C*-60), 127.5 (t, 2x *C*-25), 125.4 (q, *C*-15/*C*-48/*C*-76), 125.2 (q, *C*-15/*C*-48/*C*-76), 124.7 (q, *C*-15/*C*-48/*C*-76), 118.8 (s, *C*-30/*C*-54/*C*-61), 117.3 (s, *C*-30/*C*-54/*C*-61), 117.2 (s, *C*-30/*C*-54/*C*-61), 114.1 (t, 2x *C*-26), 77.3 (q, *C*-11), 70.9 (q, *C*-69), 68.0 (s, *C*-28), 66.4 (s, *C*-56/*C*-59), 65.4 (s, *C*-56/*C*-59), 59.9 (t, *C*-2/*C*-18/*C*-32/*C*-36/*C*-68/*C*-81), 59.8 (t, *C*-2/*C*-18/*C*-32/*C*-36/*C*-68/*C*-81), 58.3 (t, *C*-2/*C*-18/*C*-32/*C*-36/*C*-68/*C*-81), 57.6 (t, *C*-2/*C*-18/*C*-32/*C*-36/*C*-68/*C*-81), 57.6 (t, *C*-2/*C*-18/*C*-32/*C*-36/*C*-68/*C*-81), 57.4 (t, *C*-2/*C*-18/*C*-32/*C*-36/*C*-68/*C*-81), 52.5 (t, *C*-6/*C*-23/*C*-40/*C*-44/*C*-72), 51.6 (t, *C*-6/*C*-23/*C*-40/*C*-44/*C*-72), 49.4 (t, *C*-6/*C*-23/*C*-40/*C*-44/*C*-72), 48.8 (t, *C*-6/*C*-23/*C*-40/*C*-44/*C*-72), 45.0 (t, *C*-6/*C*-23/*C*-40/*C*-44/*C*-72), 44.2 (s, *C*-51), 41.7 (s, *C*-22), 40.1 (s, *C*-9 and *C*-63 beneath DMSO-signal), 38.1 (s, *C*-66), 30.7 (t, *C*-3/*C*-19/*C*-33/*C*-37/*C*-82), 30.4 (t, *C*-3/*C*-19/*C*-33/*C*-37/*C*-82), 30.3 (t, *C*-3/*C*-19/*C*-33/*C*-37/*C*-82), 30.1 (t, *C*-3/*C*-19/*C*-33/*C*-37/*C*-82), 29.6 (t, *C*-3/*C*-19/*C*-33/*C*-37/*C*-82 and s, *C*-7), 28.2 (s, 3x *C*-12), 27.3 (p, *C*-70), 26.2 (s, *C*-77), 26.1 (s, *C*-65), 26.0 (s, *C*-64), 25.8 (s, *C*-8), 25.5 (t, *C*-53), 22.3 (p, 2x *C*-53), 20.6 (p, *C*-16/*C*-49), 20.4 (p, *C*-16/*C*-49), 20.2 (p, *C*-16/*C*-49), 20.0 (p, *C*-16/*C*-49), 19.3 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 19.2 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 19.1 (2x p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 19.0 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 19.0 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 18.4 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 18.2 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 18.1 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 18.0 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 17.8 (p, *C*-41/*C*-45/*C*-73/*C*-79), 17.6 (p, *C*-41/*C*-45/*C*-73/*C*-79), 17.4 (p, *C*-41/*C*-45/*C*-73/*C*-79), 14.5 (p, *C*-41/*C*-45/*C*-73/*C*-79), 12.6 (p, *C*-78); **HRMS** (ESI) *m/z* calculated for $C_{96}H_{155}N_{19}O_{23}$ $[M+2H/2]^+$ 972.0850; found 972.0850.

N,N'-Bisalloc-*(S)*-methylisothiourea (66)



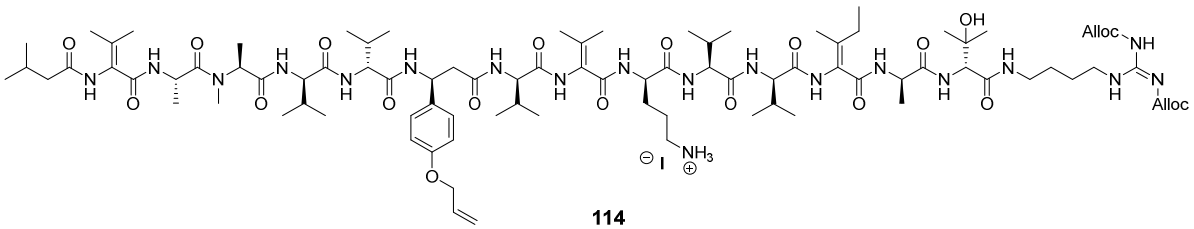
66

To a mixture of methyl carbamimidothioate (**110**, 5.00 g, 35.9 mmol, 1.00 equiv.) in a 10% solution of $NaHCO_3$ (50.0 mL) and NaOH solution (5M in H_2O, 7.20 mL, 1.00 equiv.), AllocCl (11.5 mL, 108 mmol, 3.00 equiv.) was added dropwise over a period of 5 min and the reaction mixture was stirred for 20 h at ambient temperature. The reaction was terminated by addition of H_2O and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with H_2O (1x) and brine (1x), dried with $MgSO_4$ and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: CH_2Cl_2; 15x150 mm column, flow rate: 80.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/15; 30/100; t_R = 3.0 – 12.5 min) afforded urea **66** (5.23 g, 20.2 mmol, 56% yield) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 11.83 (s, 1H, N*H*), 6.03 – 5.87 (m, 2H, *H*-2, *H*-5), 5.38 – 5.34 (m, 2H, *H*-1, *H*-6), 5.30 – 5.25 (m, 2H, *H*-1, *H*-6), 4.67 – 4.65 (m, 4H, *H*-3, *H*-4), 2.42 (s, 3H, *H*-7).

The analytical data are consistent with those reported in the literature.[36]

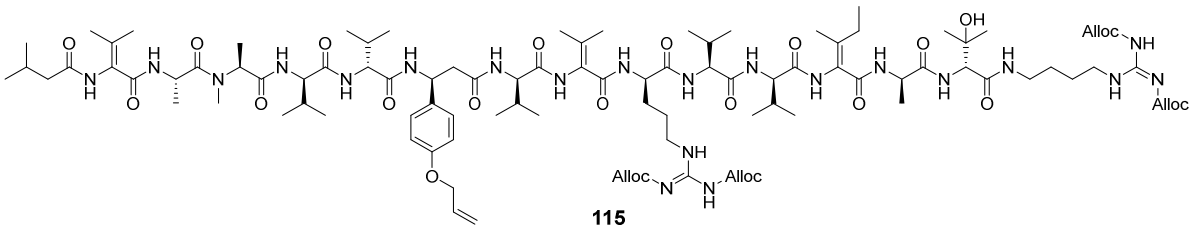
Boc-deprotected fragment ABCD-D,L (114)



114

To a solution of Boc-protected fragment ABCD-D,L (**109**, 20.0 mg, 10.3 μmol, 1.00 equiv.) in CH_2Cl_2 (650 μL), TMSI (7.00 μL, 51.5 μmol, 5.00 equiv.) was added and the reaction mixture was stirred for 1 h at ambient temperature. Then the solvent was removed under reduced pressure affording deprotected peptide **114** as a yellow foam that was used in the next step without further purification.

Guanidinylated fragment ABCD-D,L (115)

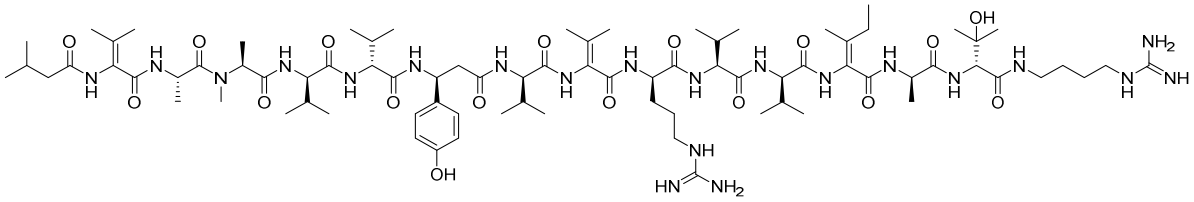


115

To a solution of Boc-deprotected fragment ABCD-D,L (**114**, 10.3 μmol, 1.00 equiv.) and *N,N'*-bisalloc-*(S)*-methylisothiourea (**66**, 10.6 mg, 41.2 μmol, 4.00 equiv.) in THF (700 μL) at 0 °C, Et_3N (7.10 µL, 51.5 μmol, 5.00 equiv.) was added dropwise and the reaction mixture was stirred for 16 h at ambient temperature under an argon atmosphere. The reaction was terminated by addition of H_2O (1.00 mL) and the solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI; solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, 4 g WP C18 column, flow rate: 10.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 22/95; 30/95; t_R = 17 – 33 min) afforded guanidinylated fragment ABCD-D,L (**115**, 21.1 mg, 10.3 μmol, quant.) as a colorless foam that was used in the next step without further purification.

HRMS (ESI) *m/z* calculated for $C_{100}H_{159}N_{21}O_{25}$ $[M+2H/2]^+$ 1027.0908; found 1027.0896.

Myxovalargin-D,L (10)

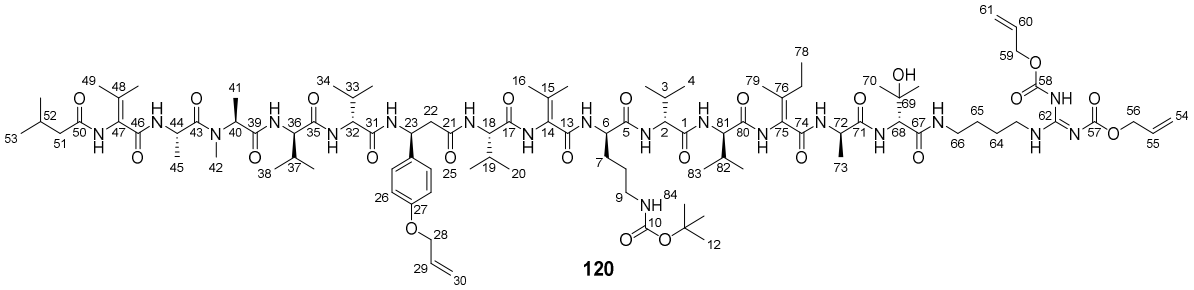


10

To a solution of guanidinylated fragment ABCD-D,L (**115**, 34.1 mg, 16.6 μmol, 1.00 equiv.) and phenylsilane (12.3 μL, 99.6 μmol, 6.00 equiv.) in CH_2Cl_2 (400 μL), $Pd(PPh_3)_4$ (3.8 mg, 3.3 μmol, 0.20 equiv.) was added and the reaction mixture was stirred for 2 h at ambient temperature. The reaction was terminated by addition of H_2O (500 μL) and MeOH (500 μL) and the solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI; solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, 12 g WP C18 column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 25/95; 30/95; t_R = 14.5 – 25.0 min) afforded myxovalargin-D,L (**10**, 31.4 mg, 18.7 μmol, 33% yield o3s) as a colorless foam.

^{1}H-NMR (DMSO-d_6, 600 MHz): δ [ppm] 9.31 – 8.92 (m, 1H, N*H*), 8.46 – 8.19 (m, 4H, N*H*), 7.80 – 7.27 (m, 16H, N*H*, Tyr-O*H*), 7.09 – 7.07 (m, 2H, Ar-*H*), 6.62 – 6.61 (m, 2H, Ar-*H*), 5.22 – 4.67 (m, 3H, NC*H*), 4.39 – 4.09 (m, 9H, NC*H*), 3.12 – 3.04 (m, 4H, NCH_3, CH_2, HCC*H*), 2.86 – 2.82 (m, 2H, NCH_3, CH_2, HCC*H*), 2.74 – 2.65 (m, 1H, NCH_3, CH_2, HCC*H*), 2.52 – 2.51 (m, 1H, CH_2, HCC*H,* CH_3), 2.29 – 2.28 (m, 2H, C*H*/CH_2/,CH_3), 2.04 – 1.96 (m, 2H, CH_2/CH_3), 1.96 – 1.93 (m, 4H, CH_2/CH_3), 1.90 (m, 8H, CH_2/CH_3), 1.67 – 1.54 (m, 13H, CH_2/CH_3), 1.44 – 1.38 (m, 4H, CH_2/CH_3), 1.21 – 1.16 (m, 11H, CH_2/CH_3), 1.11 – 1.09 (m, 6H, CH_3), 0.98 (m, 3H, H_2CCH_3), 0.86-– 0.78 (m, 36H, CH_3); **^{13}C-NMR** (DMSO-d_6, 600 MHz): δ [ppm] 174.2 (q, *C*=O), 172.0 (q, *C*=O), 171.9 (q, *C*=O), 170.9 (q, *C*=O), 170.8 (q, *C*=O), 170.7 (q, *C*=O), 170.5 (q, *C*=O), 169.9 (q, *C*=O), 169.7 (q, *C*=O), 166.6 (q, *C*=O), 166.4 (q, *C*=O), 157.1 (q, O*C*-Ar), 157.1 (q, *C*=N), 133.4 (q, *C*=C), 133.3 (q, *C*=C), 131.5 (q, *C*=C), 131.4 (q, *C*=C), 128.8 (q, *C*=C), 128.7 (q, *C*=C), 128.0 (q, *C*=C), 127.7 (q, *C*=C), 114.6 (q, *C*=C), 70.9 (q, HO*C*), 60.1 (t, N*C*H), 57.9 (t, N*C*H), 57.4 (t, N*C*H), 57.3 (t, N*C*H), 57.0 (t, N*C*H), 49.4 (t, N*C*H), 44.4 (t, N*C*H), 44.2 (t, N*C*H), 40.4 (t, N*C*H), 30.4 (s, *C*H_2), 29.1 (t, H_3C*C*H), 28.8 (t, H_3C*C*H), 28.7 (t, H_3C*C*H), 28.7 (t, H_3C*C*H), 28.6 (t/s, H_3C*C*H/*C*H_2), 27.4 (t/s, H_3C*C*H/*C*H_2), 26.3 (t/s, H_3C*C*H/*C*H_2), 26.1 (t/s, H_3C*C*H/*C*H_2), 25.8 (s, t/s, H_3C*C*H/*C*H_2), 25.1 (s/p, *C*H_2/*C*H_3), 22.3 (s/p, *C*H_2/*C*H_3), 20.3 (s/p, *C*H_2/*C*H_3), 19.2 (s/p, *C*H_2/*C*H_3), 19.2 (s/p, *C*H_2/*C*H_3), 19.1 (s/p, *C*H_2/*C*H_3), 18.4 (s/p, *C*H_2/*C*H_3), 18.0 (s/p, *C*H_2/*C*H_3), 17.5 (p, *C*H_3), 17.4 (p, *C*H_3), 17.0 (p, *C*H_3), 14.5 (p, *C*H_3), 12.7 (p, H_2C*C*H_3); **HRMS** (ESI) *m/z* calculated for $C_{181}H_{137}N_{21}O_{17}$ $[M+2H/2]^+$ 839.0329; found 839.0330.

Boc-protected fragment ABCD-L,D (120)



120

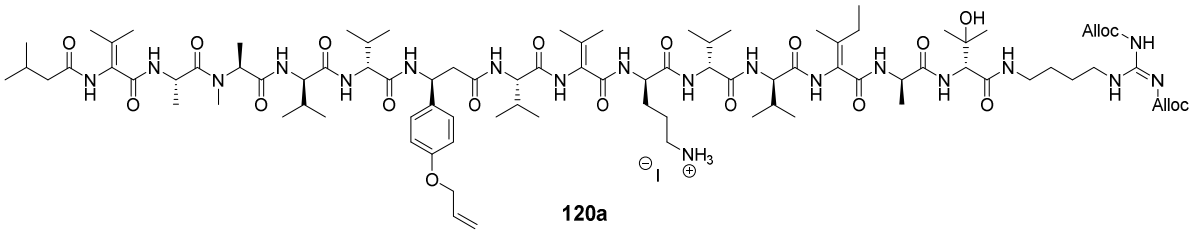
To a solution of fragment AB-L,D (**104**, 248 mg, 196 μmol, 1.00 equiv.) and fragment CD (**108**, 304 mg, 437 μmol, 2.23 equiv.) in DMF (2.00 mL) at 0 °C, HOAt (66.7 mg, 490 μmol, 2.50 equiv.), HATU (186 mg, 490 μmol, 2.50 equiv.) and DIPEA (170 µL, 980 μmol, 5.00 equiv.) were added and the reaction mixture was stirred for 17 h at ambient temperature. The reaction was terminated by addition of MeOH (1.00 mL) and the solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI; solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, 40 g WP C18 column, flow rate: 30.0 mL/min, 30 sec/fr., gradient:

(*t* [min]/solvent B [%]): 0/0; 2/0; 23/100; 30/100; t_R = 20.5 – 60.0 min) afforded Boc-protected fragment ABCD-L,D (**120**, 220 mg, 113 μmol, 58% yield) as a colorless foam.

$[\alpha]_D^{24.5}$: – 72.0° (*c* 0.1, DMSO-d_6); **^{1}H-NMR** (DMSO-d_6, 500 MHz): δ [ppm] 9.72 – 8.63 (m, 1H, N*H*), 8.99 (m, 1H, N*H*), 8.91 – 8.88 (m, 1H, N*H*), 8.35 (t, *J* = 5.5 Hz, 1H, N*H*), 8.27 – 8.26 (m, 1H, N*H*), 8.15 – 8.14 (m, 1H, N*H*), 7.86 – 7.47 (m, 10H, N*H*), 7.16 – 7.15 (d, *J* = 8.4 Hz, 2H, *H*-25), 6.82 – 6.80 (d, *J* = 8.7 Hz, 2H, *H*-26), 6.74 (t, *J* = 5.4 Hz, 1H, N*H*-84), 6.04 – 5.88 (m, 3H, *H*-29, *H*-55, *H*-60), 5.37 – 5.16 (m, 8H, *H*- 23, *H*-30, *H*-54, *H*-61, O*H*), 5.00 – 4.86 (m, 1H, *H*-40), 4.69 – 4.65 (m, 3H, *H*-44, *H*-56, *H*-59), 4.51 – 4.48 (m, 4H, *H*-28, *H*-56, *H*-59), 4.42 – 3.93 (m, 10H, *H*-2, *H*-6, *H*-18, *H*-32, *H*-36, *H*-63, *H*-68, *H*-72, *H*-81), 3.13 – 2.99 (m, 2H, *H*-66), 2.94 – 2.82 (m, 5H, *H*-9, *H*-42), 2.79 – 2.69 (m, 1H, *H*-22), 2.54 – 2.51 (m, 6H, *H*-3, *H*-19, *H*-22, *H*-33, *H*-37, *H*-82), 2.34 – 2.21 (m, 2H, *H*-77), 2.06 – 1.65 (m, 18H, *H*-16, *H*-49, *H*-51, *H*-52, *H*-79), 1.52 – 1.39 (m, 7H, *H*-7, *H*-8, *H*-64, *H*-65), 1.36 (s, 9H, *H*-12), 1.25 – 1.17 (m, 9H, *H*-41, *H*-45, *H*-73), 1.11 (m, 6H, *H*-70), 0.98 (t, *J* = 7.4 Hz, 3H, *H*-78), 0.93 – 0.72 (m, 36H, *H*-4, *H*-20, *H*-34, *H*-38, *H*-53, H-83); **^{13}C-NMR** (DMSO-d_6, 150 MHz): δ [ppm] 172.5 (q, *C*=O), 172.1 (q, *C*=O), 172.0 (q, *C*=O), 171.9 (q, *C*=O), 171.8 (q, *C*=O), 171.1 (q, *C*=O), 170.9 (q, *C*=O), 170.7 (q, *C*=O), 170.7 (q, *C*=O), 170.4 (q, *C*=O), 170.0 (q, *C*=O), 169.7 (q, *C*=O), 165.5 (q, *C*=O), 165. 2 (q, *C*=O), 164.5 (q, *C*=O), 162.9 (q, *C*-57/*C*-58), 156.9 (q, *C*-27), 155.5 (q, *C*-10), 155.0 (q, *C*-62), 152.5 (q, *C*-57/*C*-58), 134.6 (3x q, *C*-14, *C*-47, *C*-75), 134.1 (q, *C*-24), 133.7 (t, *C*-29/*C*-55/*C*-60), 133.5 (t, *C*-29/*C*-55/ *C*-60), 131.8 (t, *C*-29/*C*-55/*C*-60), 127.2 (t, 2x *C*-25), 125.5 (q, *C*-15/*C*-48/*C*-76), 124.6 (q, *C*-15/ *C*-48/*C*-76), 123.8 (q, *C*-15/*C*-48/*C*-76), 118.8 (s, *C*-30/*C*-54/*C*-61), 117.3 (s, *C*-30/*C*-54/*C*-61), 117.2 (s, *C*-30/*C*-54/*C*-61), 114.2 (t, 2x *C*-26), 77.3 (q, *C*-11), 70.9 (q, *C*-69), 68.0 (s, *C*-28), 66.4 (s, *C*-56/*C*-59), 65.4 (s, *C*-56/*C*-59), 60.2 (t, *C*-2/*C*-18/*C*-32/*C*-36/*C*-68/*C*-81), 59.7 (t, *C*-2/*C*-18/ *C*-32/*C*-36/*C*-68/*C*-81), 59.0 (t, *C*-2/*C*-18/*C*-32/*C*-36/*C*-68/*C*-81), 58.9 (t, *C*-2/*C*-18/*C*-32/*C*-36/ *C*-68/*C*-81), 58.3 (t, *C*-2/*C*-18/*C*-32/*C*-36/*C*-68/*C*-81), 57.6 (t, *C*-2/*C*-18/*C*-32/*C*-36/*C*-68/*C*-81), 53.9 (t, *C*-6/*C*-23/*C*-40/*C*-44/*C*-72), 51.9 (t, *C*-6/*C*-23/*C*-40/*C*-44/*C*-72), 49.2 (t, *C*-6/*C*-23/*C*-40/ *C*-44/*C*-72), 48.5 (t, *C*-6/*C*-23/*C*-40/*C*-44/*C*-72), 45.1 (t, *C*-6/*C*-23/*C*-40/*C*-44/*C*-72), 44.2 (s, *C*-51), 42.2 (s, *C*-22), 40.1 (s, *C*-9 and *C*-63 beneath DMSO-signal), 38.1 (s, *C*-66), 31.2 (t, *C*-3/*C*-19/*C*-33/*C*-37/*C*-82), 30.5 (t, *C*-3/*C*-19/*C*-33/*C*-37/*C*-82), 30.2 (t, *C*-3/*C*-19/*C*-33/*C*-37/ *C*-82), 30.1 (t, *C*-3/*C*-19/*C*-33/*C*-37/*C*-82), 29.4 (t, *C*-3/*C*-19/*C*-33/*C*-37/*C*-82 and s, *C*-7), 29.3 (t, *C*-3/*C*-19/*C*-33/*C*-37/*C*-82 and s, *C*-7), 28.2 (s, 3x *C*-12), 27.1 (p, *C*-70), 26.3 (s, *C*-77), 26.2 (s, *C*-65), 26.0 (s, *C*-64), 25.8 (s, *C*-8), 25.5 (t, *C*-53), 22.3 (p, *C*-53), 22.0 (p, *C*-53), 21.0 (p, *C*-16/*C*-49), 20.6 (p, *C*-16/*C*-49), 20.3 (p, *C*-16/*C*-49), 20.0 (p, *C*-16/*C*-49), 19.2 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 19.1 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 19.1 (2x p, *C*-4/*C*-20/*C*-34/ *C*-38/*C*-83), 18.9 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 18.9 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83),18.6 (p, *C*-4/

C-20/ *C*-34/*C*-38/*C*-8), 18.4 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 18.3 (p, *C*-4/*C*-20/*C*-34/ *C*-38/*C*-83), 18.2 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 18.0 (p, *C*-41/*C*-45/*C*-73/*C*-79), 17.6 (p, *C*-41/ *C*-45/*C*-73/ *C*-79), 17.3 (p, *C*-41/*C*-45/*C*-73/*C*-79), 14.3 (p, *C*-41/*C*-45/*C*-73/*C*-79), 12.6 (p, *C*-78); **HRMS** (ESI) *m/z* calculated for $C_{96}H_{156}N_{19}O_{23}$ $[M+H]^+$ 1943.1621; found 1943.1627.

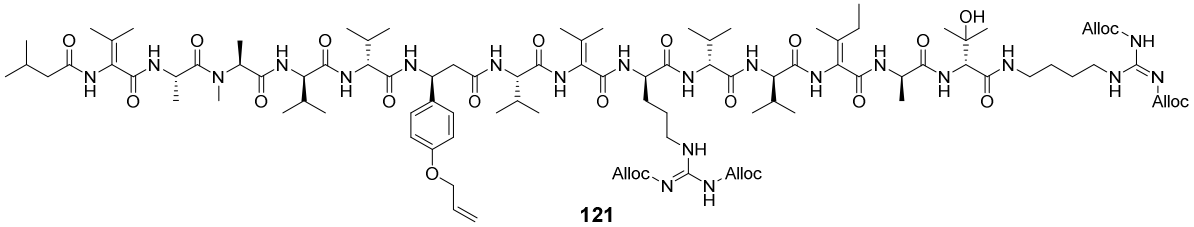
Boc-deprotected fragment ABCD-L,D (120a)



120a

To a solution of Boc-protected fragment ABCD-L,D (**120**, 60.0 mg, 30.9 μmol, 1.00 equiv.) in CH_2Cl_2 (500 μL), TMSI (13.0 μL, 92.6 μmol, 3.00 equiv.) was added and the reaction mixture was stirred for 1 h at ambient temperature. The reaction was terminated by addition of H_2O (500 μL) and MeOH (500 μL) and the solvent was removed under reduced pressure affording deprotected peptide **120a** as a yellow foam that was used in the next step without further purification.

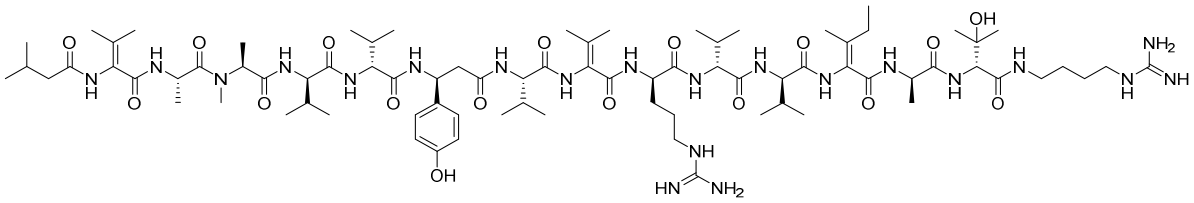
Guanidinylated fragment ABCD-L,D (121)



121

To a solution of Boc-deprotected fragment ABCD-L,D (**120a**, 30.9 μmol, 1.00 equiv.) and *N,N*'-bisalloc-*(S)*-methylisothiourea (**66**, 31.9 mg, 124 μmol, 4.00 equiv.) in THF (800 μL) at 0 °C, Et_3N (21.5 µL, 154.4 μmol, 5.00 equiv.) was added dropwise and the reaction mixture was stirred for 17 h at ambient temperature under an argon atmosphere. The reaction was terminated by addition of H_2O (1.00 mL) and MeOH (1.00 mL) and the solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI; solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, 12 g WP C18 column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 2/0; 23/100; 30/100; t_R = 20 – 60 min) afforded guanidinylated fragment ABCD-L,D (**121**, 26.1 mg, 12.7 μmol, 41% yield o2s) as a colorless foam that was used in the next step without further purification.

Myxovalargin-L,D (11)



11

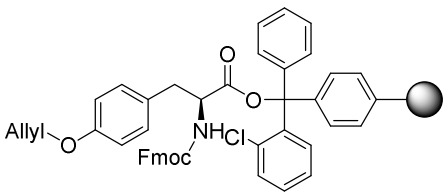
To a solution of guanidinylated fragment ABCD-L,D (**121**, 17.5 mg, 8.50 μmol, 1.00 equiv.) and phenylsilane (6.30 μL, 51.1 μmol, 6.00 equiv.) in CH_2Cl_2 (400 μL), $Pd(PPh_3)_4$ (2.00 mg, 1.70 μmol, 0.20 equiv.) was added and the reaction mixture was stirred for 2 h at ambient temperature under an argon atmosphere. The reaction was terminated by addition of H_2O (500 μL) and MeOH (500 μL) and the solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI; solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, 12 g WP C18 column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 5/0; 27/100; 30/100, t_R = 12.5 – 30.5 min) afforded myxovalargin-L,D (**11**, 8.70 mg, 5.20 μmol, 61% yield) as a colorless foam.

^{1}H-NMR (DMSO-d_6, 600 MHz): δ [ppm] 8.08 – 7.28 (m, 23H, N*H*, Tyr-O*H*), 7.22 – 7.18 (m, 2H, Ar-*H*), 6.65 – 6.62 (m, 2H, Ar-*H*), 5.72 – 5.61 (m, 1H, NC*H*), 5.41 – 5.35 (m, 1H, NC*H*), 5.29 – 5.10 (m, 2H, NC*H*), 5.06 – 4.63 (m, 1H, NC*H*), 4.52 – 4.36 (m, 1H, NC*H*), 4.28 – 3.90 (m, 5H, NC*H*), 3.51 – 3.50 (m, 10H, NCH_3, CH_2, HCC*H*), 3.14 – 3.06 (m, 2H, HCC*H*), 3.06 – 2.99 (m, 1H, HCC*H*), 2.54 – 2.51 (m, 3H, CH_2, HCC*H*), 2.28 – 2.17 (m, 1H, C*H*/CH_2), 2.02 – 1.97 (m, 12H, CH_2/CH_3), 1.80 – 1.59 (m, 9H, CH_2/CH_3), 1.48 – 1.41 (m, 4H, CH_2/CH_3), 1.29 – 1.27 (m, 11H, CH_2/CH_3), 1.15 – 1.09 (m, 6H, CH_3), 0.99 – 0.97 (m, 3H, H_2CCH_3), 0.89 – 0.75 (m, 36H, CH_3); **^{13}C-NMR** (DMSO-d_6, 150 MHz): δ [ppm] 174.7 (q, *C*=O), 174.3 (q, *C*=O), 174.0 (q, *C*=O), 173.9 (q, *C*=O), 173.4 (q, *C*=O), 173.3 (q, *C*=O), 173.2 (q, *C*=O), 172.7 (q, *C*=O), 172.0 (q, *C*=O), 170.9 (q, *C*=O), 170.1 (q, *C*=O), 169.9 (q, *C*=O), 169. 3 (q, *C*=O), 166.0 (q, *C*=O), 165.9 (q, *C*=O), 165.8 (q, *C*=O), 156.9 (q, O*C*-Ar), 156.8 (q, *C*=N), 131.3 (q, *C*=C), 129.8 (q, *C*=C), 128.1 (q, *C*=C), 127.9 (q, *C*=C), 127.2 (q, *C*=C), 126.8 (q, *C*=C), 126.5 (q, *C*=C), 124.2 (q, *C*=C), 123.7 (q, *C*=C), 72.4 (q, HO*C*), 72.3 (t, N*C*H), 69.8 (t, N*C*H), 67.3 (t, N*C*H), 67.2 (t, N*C*H), 62.8 (t, N*C*H), 60.3 (t, N*C*H), 60.2 (t, N*C*H), 52.2 (t, N*C*H), 49.3 (t, N*C*H), 48.9 (t, N*C*H), 48.8 (t, N*C*H), 47.8 (t, N*C*H), 45.9 (s, *C*H_2), 41.4 (s, *C*H_2), 40.1 (s, *C*H_2 beneath DMSO-signal), 35.1 (s, *C*H_2), 31.3 (t, H_3C*C*H), 29.1 (t, H_3C*C*H), 29.0 (t, H_3C*C*H), 28.8 (t, H_3C*C*H), 28.7 (t/s, H_3C*C*H/*C*H_2), 28.7 (t/s, H_3C*C*H/*C*H_2), 28.7 (t/s, H_3C*C*H/*C*H_2), 28.6 (t/s, H_3C*C*H/*C*H_2), 28.6 (s, t/s, H_3C*C*H/*C*H_2), 27.5 (s/p, *C*H_2/*C*H_3), 27.2 (s/p, *C*H_2/*C*H_3), 26.6 (s/p, *C*H_2/*C*H_3), 26.6 (s/p, *C*H_2/*C*H_3), 25.1 (s/p, *C*H_2/*C*H_3), 25.1 (s/p, *C*H_2/*C*H_3), 24.5 (s/p, *C*H_2/*C*H_3), 23.6 (s/p, *C*H_2/*C*H_3), 22.3 (p, *C*H_3), 22.1 (p, *C*H_3), 22.1 (p, *C*H_3),

20.1 (p, *C*H$_3$), 20.0 (p, *C*H$_3$), 20.0 (p, *C*H$_3$), 19.9 (p, *C*H$_3$), 19.9 (p, *C*H$_3$), 19.9 (p, *C*H$_3$), 19.2 (p, *C*H$_3$), 19.2 (p, *C*H$_3$), 19.1 (p, *C*H$_3$), 15.9 (p, *C*H$_3$), 14.0 (p, H$_2$C*C*H$_3$); **HRMS** (ESI) *m/z* calculated for $C_{181}H_{137}N_{21}O_{17}$ $[M+2H/2]^+$ 839.0329; found 839.0332.

E2.7 Syntheses of Derivatives

Synthesis of fragment A-*α*-Tyr (122)



124

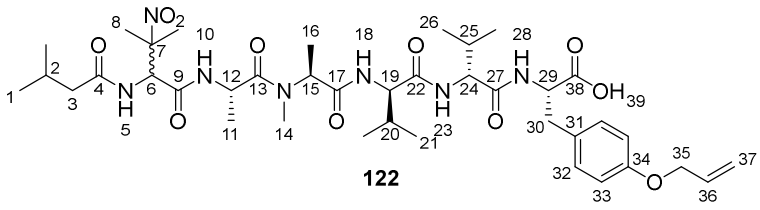
Activation of chlorotrityl resin

The 2-chlorotrityl chloride resin (**93**, 1.60 mmol/g, 2.10 g, 3.36 mmol, 1.00 equiv.) was suspended in CH_2Cl_2 (21.0 mL) at 0 °C. Then, pyridine (650 μL, 8.06 mmol, 2.40 equiv.) and thionyl chloride (292 μL, 4.03 mmol, 1.20 equiv.) were added and the mixture was stirred under refluxing conditions. After 3 h the resin was filtered, washed with CH_2Cl_2 (6x) and dried *in vacuo*.

Loading of chlorotrityl resin

A mixture of (*S*)-3-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-(allyloxy)phenyl)-propanoic acid (**123**, 1.79 g, 4.03 mmol, 1.20 equiv.) and DIPEA (2.92 mL, 16.8 mmol, 5.00 equiv.) in CH_2Cl_2 (21.0 mL) was added to the activated chlorotrityl resin. The suspension was stirred for 18 h at ambient temperature. Then, the resin was filtered, washed with CH_2Cl_2/MeOH/DIPEA, CH_2Cl_2, DMF, and CH_2Cl_2 and dried *in vacuo* to give 3.15 g of resin **124**.

(2*S*,5*R*,8*R*,11*S*,14*S*)-2-(4-(Allyloxy)benzyl)-5,8-diisopropyl-11,12,14,21-tetramethyl-17-(2-nitropropan-2-yl)-4,7,10,13,16,19-hexaoxo-3,6,9,12,15,18-hexaazadocosanoic acid (122)



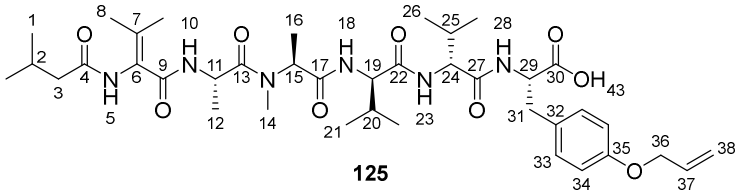
122

The title compound was prepared according to the general procedure for the synthesis of peptides with a Liberty Blue^{TM} Automated Microwave Peptide Synthesizer from CEM in a 3x0.5 mmol scale. Polymer-bound *α*-Tyr **124** (3x 313 mg), Fmoc-D-Val-OH (4.68 g), Fmoc-*N*-Me-Ala-OH (2.28 g), Fmoc-Ala-OH (2.18 g), amino-3-methyl-3-nitrobutanoic acid (2.69 g) and isovaleric acid (715 mg) were used. After peptide synthesis was completed, the resin was transferred into a 20.0 mL syringe with filter. The solvent was exhausted, and the resin was washed with DMF (3x 15.0 mL) and CH_2Cl_2 (3x 15.0 mL). The cleavage of the peptides was performed by adding of 1% TFA in CH_2Cl_2 (3.00 mL) to the syringe

vessel which was shaken for 2 min at room temperature. The liquid was filtered into a flask containing 10% pyridine in MeOH (3.00 mL). The cleavage and filtration steps were repeated four more times. All the filtrates were combined in a 500 mL round bottom flask and the solvent was removed under reduced pressure. The sequence was checked via LCMS. Purification by flash column chromatography (RP-BÜCHI, solvent A: water + FA, solvent B: MeCN + 0.1% FA; 40g WP column, flow rate: 30.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 25/100; 30/100; t_R = 19.0 – 28.5 min) afforded fragment A-α-Tyr (**122**, 111 mg, 138 μmol, 10% yield) as a colorless foam.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 8.58 – 8.50 (m, 1H, N*H*), 8.23 – 8.18 (m, 2H, N*H*), 7.70 – 7.67 (m, 1H, N*H*), 7.62 – 7.57 (m, 1H, N*H*), 7.12 (d, *J* = 8.6 Hz, 2H, *H*-33), 6.80 (d, *J* = 8.6 Hz, 2H, *H*-32), 6.04 – 5.97 (m, 1H, *H*-36), 5.38 – 5.33 (m, 1H, *H*-37), 5.27 – 5.24 (m, 1H, *H*CN), 5.24 – 5.21 (m, 1H, *H*-37), 5.08 – 5.03 (p, *J* = 7.1 Hz, 1H, *H*-29), 4.72 – 4.57 (m, 1H, *H*CN), 4.50 – 4.49 (d, *J* = 5.1 Hz, 2H, *H*-35), 4.38 – 4.34 (m, 1H, *H*CN), 4.19 – 4.16 (m, 2H, *H*CN), 3.02 – 2.98 (m, 1H, *H*-30), 2.88 – 2.85 (m, 3H, *H*-14), 2.77 – 2.72 (m, 1H, *H*-30), 2.11 – 1.89 (m, 4H, *H*-3, 2x *H*C$(CH_3)_2$), 1.82 – 1.75 (m, 1H, *H*C$(CH_3)_2$), 1.65 – 1.50 (m, 6H, *H*-8), 1.21 – 1.18 (m, 6H, 2x C*H*$_3$), 0.85 – 0.76 (m, 12H, C*H*$_3$), 0.61 – 0.58 (m, 6H, 3x HC(C*H*$_3$)$_2$); **^{13}C-NMR** (DMSO-d_6, 100 MHz): δ [ppm] 173.0 (q, *C*=O), 172.1 (q, *C*=O), 171.9 (q, *C*=O), 171.8 (q, *C*=O), 171.0 (q, *C*=O), 170.6 (q, *C*=O), 166.8 (q, *C*=O), 156.8 (q, *C*-34), 133.9 (t, *C*-36), 130.1 (q, t, *C*-31, *C*-32), 117.2 (s, *C*-30), 114.3 (q, *C*-33), 89.0 (q, *C*-7), 68.1 (s, *C*-35), 57.5 (t, N*C*H), 57.2 (t, N*C*H), 56.8 (t, N*C*H), 53.7 (t, N*C*H), 51.4 (t, N*C*H), 45.6 (t, N*C*H), 44.2 (s, *C*-3), 36.0 (s, *C*-30), 30.8 (p, *C*-14), 30.2 (t, H*C*$(CH_3)_2$), 30.2 (t, H*C*$(CH_3)_2$), 25.7 (t, H*C*$(CH_3)_2$), 23.7 (p, *C*H$_3$), 22.3 (p, *C*H$_3$), 22.1 (p, *C*H$_3$), 21.7 (p, *C*H$_3$), 19.3 (p, *C*H$_3$), 19.1 (p, *C*H$_3$), 18.0 (p, *C*H$_3$), 17.5 (p, *C*H$_3$), 17.1 (p, *C*H$_3$), 16.5 (p, *C*H$_3$), 14.6 (p, *C*H$_3$) ppm; **HRMS** (ESI) *m/z* calculated for $C_{39}H_{61}N_7O_{11}Na$ $[M+Na]^+$ 826.4327; found 826.4321.

(2*S*,5*R*,8*R*,11*S*,14*S*)-2-(4-(Allyloxy)benzyl)-5,8-diisopropyl-11,12,14,21-tetramethyl-4,7, 10,13,16,19-hexaoxo-17-(propan-2-ylidene)-3,6,9,12,15,18-hexaazadocosanoic acid (125)



125

In a fritted peptide synthesis vessel the tyrosine- loaded resin **124** (500 mg, 0.80 mmol) was swollen in CH_2Cl_2/DMF (1:1, 6.00 mL) for 10 min followed by three washing steps with DMF (6.00 mL). Then a solution of piperidine in DMF (10.0 mL, 20% v/v) was added and the mixture was vortexed for 3 min, pulled dry and vortexed a second time for 15 min with a freshly prepared solution of piperidine in DMF (10.0 mL, 20% v/v). Afterwards, the resin was washed with DMF (3x 6.00 mL).

In a second vessel, 9.60 mL of HATU stock solution in DMF (8.60 g in 50.0 mL) was added to Fmoc-D-valine (1.60 g, 4.80 mmol, 6.00 equiv.) and DIPEA (1.60 mL, 9.40 mmol, 12.0 equiv.). The mixture was then added to the resin and vortexed for 45 min followed by three washing steps with DMF. Then a solution of piperidine in DMF (10.0 mL, 20% v/v) was added and the mixture was vortexed for 3 min, pulled dry and vortexed a second time for 15 min with a freshly prepared solution of piperidine in DMF (10.0 mL, 20% v/v). Afterwards, the resin was washed with DMF (3x 6.00 mL).

In a separate vessel, 9.60 mL of HATU stock solution in DMF (8.60 g in 50.0 mL) was added to Fmoc-D-valine (1.60 g, 4.80 mmol, 6.00 equiv.) and DIPEA (1.60 mL, 9.40 mmol, 12.0 equiv.). The mixture was then added to the resin and vortexed for 45 min followed by three washing steps with DMF. Then a solution of piperidine in DMF (10.0 mL, 20% v/v) was added and the mixture was vortexed for 3 min, pulled dry and vortexed a second time for 15 min with a freshly prepared solution of piperidine in DMF (10.0 mL, 20% v/v). Afterwards, the resin was washed with DMF (3x 6.00 mL).

In a separate vessel, 9.60 mL of HATU stock solution in DMF (8.60 g in 50.0 mL) was added to Fmoc-*N*-Me-Ala-OH (1.60 g, 4.80 mmol, 6.00 equiv.) and DIPEA (1.60 mL, 9.40 mmol, 12.0 equiv.). The mixture was then added to the resin and vortexed for 45 min followed by three washing steps with DMF. Then a solution of piperidine in DMF (10.0 mL, 20% v/v) was added and the mixture was vortexed for 3 min, pulled dry and vortexed a second time for 15 min with a freshly prepared solution of piperidine in DMF (10.0 mL, 20% v/v). Next, a mixture of piperidine/DBU/toluene/DMF (2.5:2.5:10:35, 10.0 mL) was added and the mixture was vortexed for 5 min. The last step was repeated. Afterwards, the resin was washed with DMF (3x 6.00 mL).

In a separate vessel, PyAOP (4.50 g, 8.60 mmol, 10.8 equiv.) was added to Fmoc-Ala-OH (1.50 g, 4.80 mmol, 6.00 equiv.) in DMF (8.00 mL) and DIPEA (2.80 mL, 8.0 mmol, 20.0 equiv.). The mixture was then added to the resin and vortexed for 1 h. Then, PyAOP (1.10 g, 2.00 mmol, 2.50 equiv.) was added and the mixture was vortexed overnight followed by three washing steps with DMF. Then a solution of piperidine in DMF (10.0 mL, 20% v/v) was added and the mixture was vortexed for 3 min, pulled dry and vortexed a second time for 15 min with a freshly prepared solution of piperidine in DMF (10.0 mL, 20% v/v). Afterwards, the resin was washed with DMF (3x 6.00 mL).

In a separate vessel, 8.00 mL of HATU stock solution in DMF (8.60 g in 50.0 mL) was added to amino-3-methyl-3-nitrobutanoic acid (1.50 g, 4.00 mmol, 2.50 equiv.) and DIPEA (1.40 mL, 8.00 mmol, 10.0 equiv.). The mixture was then added to the resin and vortexed for 45 min followed by three washing steps with DMF. Then, a solution of piperidine in DMF (10.0 mL, 20% v/v) was added and the mixture was vortexed for 3 min, pulled dry and vortexed a second time for 15 min with a freshly prepared solution of piperidine in DMF (10.0 mL, 20% v/v). Afterwards, the resin was washed with DMF (3x 6.00 mL).

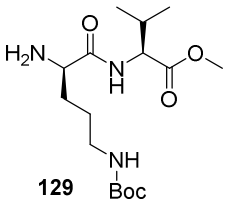
In a separate vessel, 9.60 mL of HATU stock solution in DMF (8.60 g in 50.0 mL) was added to 3-methylbutanoic acid (490 mg, 4.80 mmol, 6.00 equiv.) and DIPEA (1.60 mL, 9.40 mmol, 12.0 equiv.). The mixture was then added to the resin and vortexed for 45 min.

Afterwards, the resin was transferred into a 20.0 mL syringe with filter. The solvent was exhausted, and the resin was washed with DMF (3x 15.0 mL) and CH_2Cl_2 (3x 15.0 mL). The cleavage of the peptide was performed by adding 1% TFA in CH_2Cl_2 (3.00 mL) to the syringe vessel which was shaken for 2 min at room temperature. The liquid was filtered into a flask containing 10% pyridine in MeOH (3.00 mL). The cleavage and filtration steps were repeated four more times. All the filtrates were combined in a 500 mL round bottom flask and the solvent was removed under reduced pressure. The sequence was checked via LCMS. Purification by flash column chromatography (RP-BÜCHI, solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA; 40g WP column, flow rate: 30.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 25/100; 30/100; t_R = 14.5 – 20.5 min) afforded peptide **125** (258 mg, 341 μmol, 43% yield) as a colorless foam.

$[\alpha]_D^{23.2}$: - 45.0° (*c* 0.1; MeOH); **^{1}H-NMR** (DMSO-d_6, 400 MHz): δ [ppm] 8.90 – 8.89 (m, 1H, N*H*), 8.23 – 8.19 (m, 1H, N*H*), 7.92 – 7.57 (m, 3H, N*H*), 7.12 (d, *J* = 8.6 Hz, 2H, *H*-33), 6.80 (d, *J* = 8.6 Hz, 2H, *H*-34), 6.05 – 5.96 (m, 1H, *H*-37), 5.38 – 5.33 (m, 1H, *H*-38), 5.24 – 5.21 (m, 1H, *H*-38), 5.05 – 4.99 (m, 1H, NC*H*), 4.74 – 4.67 (m, 1H, NC*H*), 4.51 – 4.49 (d, *J* = 5.2 Hz, 2H, *H*-36),

4.39 – 4.34 (m, 1H, NC*H*), 4.20 – 4.16 (m, 2H, NC*H*), 3.02 – 2.65 (m, 7H, *H*-14, *H*-31, 2x*H*C(CH_3)$_2$), 2.06 – 1.65 (m, 9H, *H*-3, *H*-8, C-*H*), 1.27 – 1.16 (m, 6H, 2x CH_3), 0.90 – 0.76 (m, 12H, CH_3), 0.62 – 0.57 (m, 6H, 3x HC(CH_3)$_2$); **^{13}C-NMR** (DMSO-d_6, 100 MHz): δ [ppm] 173.0 (q, *C*=O), 172.1 (q, *C*=O), 170.9 (q, *C*=O), 170.6 (q, *C*=O), 170.0 (q, *C*=O), 164.5 (q, *C*=O), 163.1 (q, *C*=O), 156.8 (q, *C*-35), 134.4 (q, *C*-6), 133.9 (t, *C*-37), 130.1 (t, *C*-33), 125.5 (q, *C*-32), 117.2 (s, *C*-38), 114.3 (t, *C*-34), 68.1 (s, *C*-36), 57.6 (t, N*C*H), 57.2 (t, N*C*H), 53.7 (t, N*C*H), 51.6 (t, N*C*H), 45.1 (t, N*C*H), 44.3 (s, *C*-3), 35.9 (s, *C*-31), 30.7 (t, H*C*(CH_3)$_2$), 30.4 (p, *C*-14), 30.2 (t, H*C*(CH_3)$_2$), 25.5 (t, H*C*(CH_3)$_2$), 22.4 (p, *C*H_3), 20.7 (p, *C*H_3), 20.1 (p, *C*H_3), 21.7 (p, *C*H_3), 19.3 (p, *C*H_3), 19.1 (p, *C*H_3), 18.0 (p, *C*H_3), 17.5 (p, *C*H_3), 17.1 (p, *C*H_3), 17.4 (p, *C*H_3), 14.1 (p, *C*H_3); **HRMS** (ESI) *m/z* calculated for $C_{39}H_{60}N_6O_9Na$ $[M+Na]^+$ 779.4319; found 779.4310.

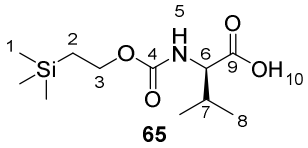
Methyl ((*R*)-2-amino-5-((*tert*-butoxycarbonyl)amino)pentanoyl)-L-valinate (129)



129

To a solution of Fmoc-protected amine **128** (1.60 g, 2.82 mmol, 1.00 equiv.) in CH_2Cl_2 (28.2 mL), tris(2-aminoethyl)amine (2.82 mL) was added at 0 °C. After stirring at room temperature for 19 h silica gel was added, and the suspension was concentrated under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH/Et_3N 98:1:1) to afford amine **129** (967 mg, 2.80 mmol, 99% yield) as a yellow oil, which was used in the next step without further purification.

Teoc-D-Val-OH (65)



65

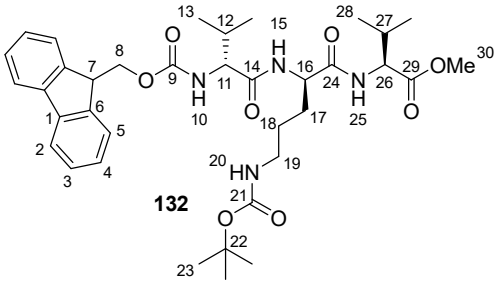
To a solution of D-valine (1.22 g, 10.4 mmol, 1.00 equiv.) in H_2O (10.0 mL), TeocOSu (3.00 g, 11.5 mmol, 1.10 equiv.) dissolved in 1,4-dioxane (10.0 mL) and Et_3N (1.58 g, 2.16 mL, 15.6 mmol, 1.50 equiv.) were added at ambient temperature and mixture was stirred for 16 h. The reaction was terminated by addition of an 1M $KHSO_4$ solution and EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic phases were washed with H_2O (4x), dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish acid **65** (2.42 g, 9.27 mmol, 89% yield) as a colorless oil.

$[\alpha]_D^{24.3}$: + 5.82° (*c* 1.03; MeOH), {Lit:[36] $[\alpha]_D^{26.6}$: + 6.9° (*c* 2.52; MeOH)}; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ [ppm] 9.18 (bs, 1H, *H*-10), 5.15 (d, *J* = 8.9 Hz, 1H, N*H*), 4.32 (dd, *J* = 8.8, 4.3 Hz, 1H, *H*-6), 4.17 (t, *J* = 8.5 Hz, 2H, *H*-3), 2.24 – 2.20 (m, 1H, *H*-7), 1.01 – 0.92 (m, 8H, *H*-2, *H*-8), 0.03 (s, 9H, *H*-1); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 177.1 (q, *C*-10), 156.9 (q, *C*-4), 63.8 (s/t,

C-3/*C*-6), 58.8 (s/t, *C*-3/*C*-6), 31.1 (t, *C*-7), 19.2 (s, *C*-2), 17.8 (p, *C*-8), 17.5 (p, *C*-8), -1.38 (p, *C*-1); **HRMS** (ESI) *m/z* calculated for $C_{11}H_{23}NO_4SiNa$ $[M+Na]^+$ 284.1294; found 284.1302.

The analytical data are consistent with those reported in the literature.[36]

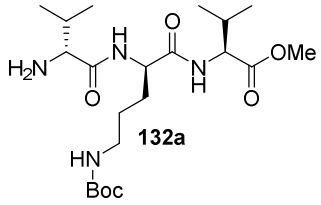
Methyl ((*R*)-2-((*R*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methyl-butan-amido)-5-((*tert*-butoxycarbonyl)amino)pentanoyl)-L-valinate (132)



To a solution of peptide **129** (596 mg, 1.73 mmol, 1.00 equiv.), Fmoc-D-Val-OH (644 mg, 1.90 mmol, 1.10 equiv.), HOBt (396 mg, 2.59 mmol, 1.50 equiv.) and EDC·HCl (413 mg, 2.16 mmol, 1.25 equiv.) in CH_2Cl_2 (17.3 mL) and DMF (4.00 mL), DIPEA (451 μL, 2.59 mmol, 1.50 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred at ambient temperature for 22 h. Then the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 100:0 → 95:5) to afford peptide **132** (373 mg, 559 μmol, 32% yield) as a colorless solid.

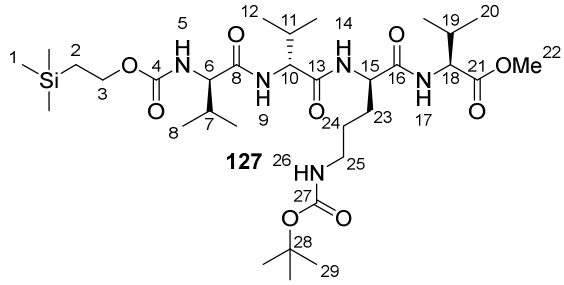
T_M: 185 – 190 °C; **$[\alpha]_D^{24.4}$:** + 22.9 ° (*c* 0.14; MeOH); **^{1}H-NMR** (DMSO-d_6, 400 MHz): δ [ppm] 8.20 (d, *J* = 8.4 Hz, 1H, N*H*), 7.90 – 7.88 (m, 3H, Ar-*H*/N*H*), 7.73 (t, *J* = 6.5 Hz, 2H, Ar-*H*), 7.46 – 7.39 (m, 3H, Ar-*H*/N*H*), 7.32 (t, *J* = 7.4 Hz, 2H, Ar-*H*), 6.76 (t, *J* = 6.2 Hz, 1H, N*H*), 4.47 – 4.41 (m, 1H, C*H*), 4.32 – 4.18 (m, 4H, *H*-8/C*H*), 3.90 – 3.86 (m, 1H, C*H*), 3.61 (s, 3H, *H*-30), 2.92 – 2.86 (m, 2H, *H*-19), 2.07 – 1.93 (m, 2H, *H*-12, *H*-27), 1.66 – 1.57 (m, 1H, CH_2), 1.53 – 1.44 (m, 1H, CH_2), 1.41 – 1.37 (m, 1H, CH_2), 1.34 (s, 9H, *H*-23), 1.23 – 1.18 (m, 1H, CH_2), 0.87 – 0.82 (m, 12H, *H*-13, *H*-28); **^{13}C-NMR** (DMSO-d_6, 100 MHz): δ [ppm] 171.9 (q, *C*=O), 171.8 (q, *C*=O), 170.9 (q, *C*=O), 156.1 (q, *C*=O), 155.5 (q, *C*=O), 143.9 (q, Ar-*C*), 143.8 (q, Ar-*C*), 140.7 (q, Ar-*C*), 140.7 (q, Ar-*C*), 127.6 (q, Ar-*C*), 127.1 (q, Ar-*C*), 125.3 (q, Ar-*C*), 120.1 (q, Ar-*C*), 77.3 (q, *C*-22), 65.7 (s, *C*-8), 60.3 (t, HN*C*H), 57.2 (t, HN*C*H), 51.9 (t, HN*C*H), 51.7 (p, *C*-30), 46.7 (t, *C*-7), 40.8 – 38.9 (s, *C*H_2 beneath DMSO-peak), l30.3 (t, H*C*CH_3), 30.1 (t, H*C*CH_3), 28.2 (p, *C*-23), 26.6 (s, *C*H_2), 25.9 (s, *C*H_2), 19.2 (p, *C*H_3), 18.9 (p, *C*H_3), 18.2 (p, *C*H_3), 18.1 (p, *C*H_3); **HRMS** (ESI) *m/z* calculated for $C_{36}H_{50}N_4O_8Na$ $[M+Na]^+$ 689.3526; found 689.3533.

Methyl ((*R*)-2-((*R*)-2-amino-3-methylbutanamido)-5-((*tert*-butoxycarbonyl)amino)-pentanoyl)-L-valinate (132a)



Fmoc-protected amine **132** (334 mg, 501 μmol, 1.00 equiv.) was dissolved in DMF (5.00 mL) and dimethylamine (40% in H_2O, 254 μL, 5.01 mmol, 10.0 equiv.) was added at ambient temperature. After stirring for 16 h the mixture was concentrated under reduced pressure. The residue was used in the next step without further purification.

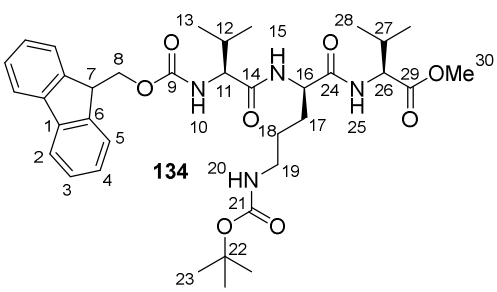
Methyl ((*R*)-5-((*tert*-butoxycarbonyl)amino)-2-((*R*)-3-methyl-2-((*R*)-3-methyl-2-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)butanamido)butanamido)pentanoyl)-L-valinate (127)



To a solution of peptide **132a** (501 μmol, 1.00 equiv.), *N*-Teoc-D-Val (**65**, 144 mg, 551 μmol, 1.10 equiv.), HOAt (85.2 mg, 626 μmol, 1.25 equiv.) and EDC·HCl (120 mg, 626 μmol, 1.25 equiv.) in CH_2Cl_2 (5.00 mL) and DMF (1.00 mL), DIPEA (436 μL, 2.51 mmol, 5.00 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred at ambient temperature for 22 h. Then the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 100:0 → 99:1) to afford peptide **127** (202 mg, 294 μmol, 59% yield) as a colorless foam.

$[\alpha]_D^{21.5}$: + 30.0° (*c* 0.16; MeOH); **^{1}H-NMR** (DMSO-d_6, 400 MHz): δ [ppm] 8.15 (d, *J* = 8.4 Hz, 1H, N*H*), 7.92 (d, *J* = 8.1 Hz, 1H, N*H*), 7.74 (d, *J* = 9.9 Hz, 1H, N*H*), 7.05 (d, *J* = 10.3 Hz, 1H, N*H*), 6.76 (t, *J* = 5.7 Hz, 2H, *H*-26), 4.42 – 4.37 (m, 1H, HNC*H*), 4.21 – 4.17 (m, 2H, HNC*H*), 4.08 – 3.86 (m, 3H, HNC*H*, *H*-3), 3.62 (s, 3H, *H*-22), 2.89 – 2.85 (m, 2H, *H*-25), 2.07 – 1.91 (m, 3H, 3x$(CH_3)_2$C*H*), 1.63 – 1.57 (m, 1H, CH_2), 1.52 – 1.42 (m, 1H, CH_2), 1.40 – 1.31 (m, 11H, *H*-29, CH_2), 0.93 (t, *J* = 8.4 Hz, 2H, *H*-2), 0.87 – 0.80 (m, 18H, CH_3), 0.02 (s, 9H, *H*-1); **^{13}C-NMR** (DMSO-d_6, 100 MHz): δ [ppm] 171.8 (q, *C*=O), 171.6 (q, *C*=O), 171.2 (q, *C*=O), 170.5 (q, *C*=O), 156.2 (q, *C*=O), 155.5 (q, *C*=O), 77.3 (q, *C*$(CH_3)_3$), 61.8 (s, *C*-3), 60.1 (t, HN*C*H), 57.5 (t, HN*C*H), 57.1 (t, HN*C*H), 51.9 (t, HN*C*H), 51.7 (p, *C*-22), 39.7 (s, *C*H_2 beneath DMSO-peak), 30.5 (t, H*C*CH_3), 30.2 (t, H*C*CH_3), 30.1 (t, H*C*CH_3), 29.9 (s, *C*H_2), 28.2 (p, *C*-29), 25.9 (s, *C*H_2), 22.1 (s, *C*-2), 19.2 (p, *C*H_3), 19.2 (p, *C*H_3), 19.0 (p, *C*H_3), 18.1 (p, *C*H_3), 18.1 (p, *C*H_3), 17.4 (p, *C*H_3), -1.4 (p, *C*-1); **HRMS** (ESI) *m/z* calculated for $C_{32}H_{61}N_5O_9SiNa$ $[M+Na]^+$ 710.4136; found 710.4134.

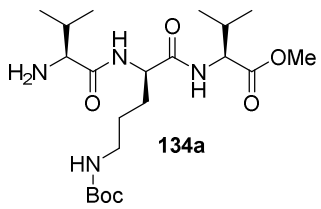
Methyl ((*R*)-2-((*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methyl-butanamido)-5-((*tert*-butoxycarbonyl)amino)pentanoyl)-L-valinate (134)



To a solution of peptide **129** (596 mg, 1.73 mmol, 1.00 equiv.), Fmoc-L-Val-OH (644 mg, 1.90 mmol, 1.10 equiv.), HOBt (396 mg, 2.59 mmol, 1.50 equiv.) and EDC·HCl (413 mg, 2.16 mmol, 1.25 equiv.) in CH_2Cl_2 (17.3 mL) and DMF (4.00 mL), DIPEA (451 μL, 2.59 mmol, 1.50 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred at ambient temperature for 22 h. Then, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 100:0 → 95:5) to furnish peptide **134** (555 mg, 832 μmol, 48% yield) as a colorless solid.

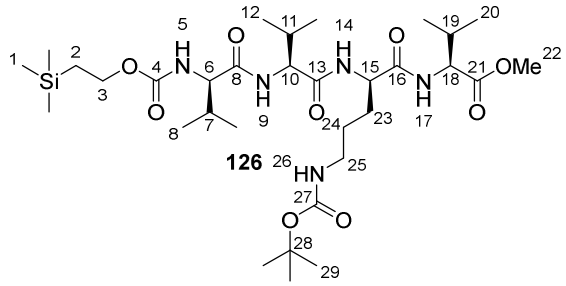
T_M: 145 – 150 °C; **$[\alpha]_D^{24.5}$:** - 9.05° (*c* 0.21; MeOH); **^{1}H-NMR** (DMSO-d_6, 400 MHz): δ [ppm] 8.18 (d, *J* = 8.1 Hz, 1H, N*H*), 8.01 (d, *J* = 8.4 Hz, 1H, N*H*), 7.89 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.73 (t, *J* = 8.9 Hz, 2H, Ar-*H*), 8.47 (d, *J* = 8.5 Hz, 1H, N*H*), 7.41 (t, *J* = 7.7 Hz, 2H, Ar-*H*), 7.32 (t, *J* = 7.5 Hz, 2H, Ar-*H*), 6.76 (t, *J* = 5.4 Hz, 1H, N*H*), 4.39 – 4.34 (m, 1H, C*H*), 4.30 – 4.14 (m, 4H, *H*-8/C*H*), 3.91 (t, *J* = 7.9 Hz, 1H, C*H*), 3.61 (s, 3H, *H*-30), 2.92 – 2.82 (m, 2H, *H*-19), 2.03 – 1.90 (m, 2H, 2x$(CH_3)_2$C*H*), 1.67 – 1.61 (m, 1H, CH_2), 1.53 – 1.41 (m, 2H, CH_2), 1.35 (s, 9H, *H*-23), 1.32 – 1.19 (m, 1H, CH_2), 0.88 – 0.80 (m, 12H, *H*-13, *H*-28); **^{13}C-NMR** (DMSO-d_6, 100 MHz): δ [ppm] 171.8 (q, *C*=O), 171.7 (q, *C*=O), 171.4 (q, *C*=O), 156.2 (q, *C*=O), 155.5 (q, *C*=O), 143.9 (q, Ar-*C*), 143.8 (q, Ar-*C*), 140.7 (q, Ar-*C*), 140.7 (q, Ar-*C*), 127.6 (q, Ar-*C*), 127.1 (q, Ar-*C*), 125.4 (q, Ar-*C*), 120.1 (q, Ar-*C*), 77.4 (q, *C*-22), 65.8 (s, *C*-8), 60.3 (t, HN*C*H), 57.2 (t, HN*C*H), 51.9 (t, HN*C*H), 51.7 (p, *C*-30), 46.6 (t, *C*-7), 40.8 – 38.9 (s, *C*H_2 beneath DMSO-peak), 30.2 (t, H*C*CH_3), 30.0 (t, H*C*CH_3), 29.8 (s, *C*H_2), 28.2 (p, *C*-23), 26.0 (s, *C*H_2), 19.2 (p, *C*H_3), 18.9 (p, *C*H_3), 18.4 (p, *C*H_3), 18.1 (p, *C*H_3); **HRMS** (ESI) *m/z* calculated for $C_{36}H_{50}N_4O_8Na$ $[M+Na]^+$ 689.3526; found 689.3541.

Methyl ((*R*)-2-((*S*)-2-amino-3-methylbutanamido)-5-((*tert*-butoxycarbonyl)amino)-pentanoyl)-L-valinate (134a)



Fmoc-protected amine **134** (531 mg, 796 μmol, 1.00 equiv.) was dissolved in DMF (8.00 mL) and dimethylamine (40% in H_2O, 403 μL, 7.96 mmol, 10.0 equiv.) was added at ambient temperature. After stirring for 16 h the mixture was concentrated under reduced pressure. The residue was used in the next step without further purification.

Methyl ((*R*)-5-((*tert*-butoxycarbonyl)amino)-2-((*S*)-3-methyl-2-((*R*)-3-methyl-2-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)butanamido)butanamido)pentanoyl)-L-valinate (126)

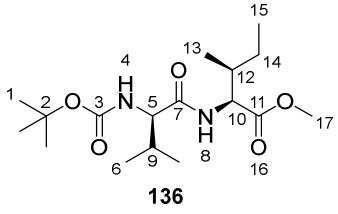


126

To a solution of peptide **134a** (796 μmol, 1.00 equiv.), *N*-Teoc-D-Val (**65**, 229 mg, 876 μmol, 1.10 equiv.), HOAt (135 mg, 995 μmol, 1.25 equiv.) and EDC·HCl (191 mg, 995 μmol, 1.25 equiv.) in CH_2Cl_2 (8.00 mL) and DMF (2.00 mL), DIPEA (693 μL, 3.98 mmol, 5.00 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred at ambient temperature for 22 h. Then, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 100:0 → 99:1) to afford peptide **126** (428 mg, 623 μmol, 78% yield) as a colorless foam.

$[\alpha]_D^{21.9}$: + 4.7° (*c* 0.15; MeOH); **^{1}H-NMR** (DMSO-d_6, 500 MHz): δ [ppm] 8.07 – 8.04 (m, 2H, N*H*), 7.91 (d, *J* = 8.3 Hz, 1H, N*H*), 6.84 (d, *J* = 8.8 Hz, 1H, N*H*), 6.75 (t, *J* = 5.6 Hz, 2H, *H*-26), 4.39 – 4.34 (m, 1H, HNC*H*), 4.20 – 4.16 (m, 2H, HNC*H*), 4.07 – 3.96 (m, 3H, HNC*H*, *H*-3), 3.62 (s, 3H, *H*-22), 2.91 – 2.82 (m, 2H, *H*-25), 2.03 – 1.92 (m, 3H, *H*-7, *H*-11, *H*-19), 1.66 – 1.59 (m, 1H, CH_2), 1.50 – 1.46 (m, 1H, CH_2), 1.40 – 1.32 (m, 11H, *H*-29, CH_2), 0.91 (t, *J* = 8.4 Hz, 2H, *H*-2), 0.84 – 0.80 (m, 18H, *H*-8, *H*-12, *H*-20), 0.01 (s, 9H, *H*-1); **^{13}C-NMR** (DMSO-d_6, 125 MHz): δ [ppm] 171.9 (q, *C*=O), 171.7 (q, *C*=O), 171.5 (q, *C*=O), 170.9 (q, *C*=O), 156.3 (q, *C*=O), 155.5 (q, *C*=O), 77.3 (q, *C*-28), 61.8 (s, *C*-3), 59.8 (t, HN*C*H), 57.8 (t, HN*C*H), 57.2 (t, HN*C*H), 51.9 (t, HN*C*H), 51.7 (p, *C*-22), 39.8 (s, *C*H_2 beneath DMSO-peak), 30.5 (t, H*C*CH_3), 30.3 (t, H*C*CH_3), 30.1 (t, H*C*CH_3), 29.0 (s, *C*H_2), 28.2 (p, *C*-29), 25.9 (s, *C*H_2), 22.1 (s, *C*-2), 19.3 (p, *C*H_3), 19.0 (p, *C*H_3), 18.1 (p, *C*H_3), 17.9 (p, *C*H_3), 17.9 (p, *C*H_3), 17.4 (p, *C*H_3), -1.5 (p, *C*-1); **HRMS** (ESI) *m/z* calculated for $C_{32}H_{61}N_5O_9SiNa$ $[M+Na]^+$ 710.4136; found 710.4123.

Methyl (*tert*-butoxycarbonyl)-D-valyl-L-alloisoleucinate (136)



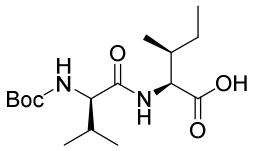
136

To a solution of *N*-Boc-Val-OH (3.50 g, 16.1 mmol, 1.00 equiv.), L-isoleucine methyl ester hydrochloride (3.22 g, 17.7 mmol, 1.10 equiv.), HOBt (3.70 g, 24.2 mmol, 1.50 equiv.) and EDC·HCl (3.86 g, 20.1 mmol, 1.25 equiv.) in CH_2Cl_2 (160 mL), DIPEA (4.20 mL, 24.2 mmol, 1.50 equiv.) was added dropwise over a period of 10 min at 0 °C. The reaction mixture was stirred at ambient temperature for 20 h.

Then, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 100:0 → 98:2 → 96:4 → 94:6) to afford peptide **136** (4.33 g, 12.6 mmol, 78% yield) as a colorless solid.

T_M: 148 – 150 °C; **$[\alpha]_D^{22.7}$:** - 6.9° (*c* 0.48; CH_2Cl_2); **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ [ppm] 6.45 (d, *J* = 6.9 Hz, 1H, N*H*), 5.09 (d, *J* = 8.3 Hz, 1H, N*H*), 4.56 (q, *J* = 4.5 Hz, 1H, HNC*H*), 3.90 (t, *J* = 7.4 Hz, 1H, HNC*H*), 3.71 (s, 3H, *H*-17), 2.10 – 2.07 (m, 1H, *H*CCH_3), 1.93 – 1.83 (m, 1H, *H*CCH_3), 1.42 (m, 10H, *H*-1, *H*-14), 1.20 – 1.22 (m, 1H, *H*-14), 0.95 – 0.87 (m, 12H, *H*-6, *H*-13, *H*-15); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 172.3 (q, *C*=O), 171.6 (q, *C*=O), 155.9 (q, *C*=O), 79.9 (q, *C*-2), 60.1 (t, HN*C*H), 56.5 (t, HN*C*H), 52.2 (p, *C*-17), 37.9 (t, H*C*CH_3), 30.8 (t, H*C*CH_3), 28.4 (p, *C*-1), 25.2 (s, *C*-14), 19.3 (p, *C*H_3), 18.0 (p, *C*H_3), 15.5 (p, *C*H_3), 11.6 (p, *C*-15); **HRMS** (ESI) *m/z* calculated for $C_{17}H_{32}N_2O_5Na$ $[M+Na]^+$ 367.2209; found 367.2209.

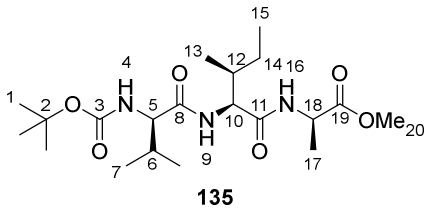
(*tert*-Butoxycarbonyl)-D-valyl-L-alloisoleucine (136a)



136a

Methyl ester **136** (4.30 g, 12.48 mmol, 1.00 equiv.) was dissolved in THF (125 mL) and LiOH (1M in H_2O, 125 mL, 125 mmol, 10.0 equiv.) was added dropwise at 0 °C. The reaction was stirred at room temperature for 18 h. H_2O and Et_2O were added, and the aqueous phase was washed with Et_2O (2x). Then the aqueous phase was acidified with an 1M HCl solution and extracted with EtOAc (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish acid **136a** (4.11 g, 12.45 mmol, quant.) as a colorless solid, which was used in the next step without further purification.

Methyl (*tert*-butoxycarbonyl)-D-valyl-L-alloisoleucyl-D-alaninate (135)



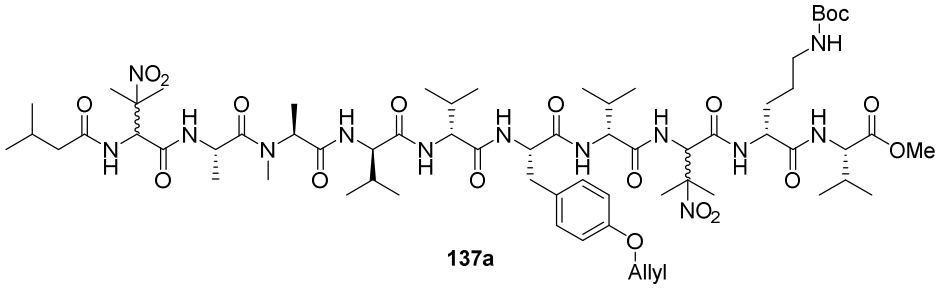
135

To a solution of peptide **136a** (4.54 g, 13.8 mmol, 1.00 equiv.), alanine methyl ester hydrochloride (2.11 g, 15.1 mmol, 1.10 equiv.), HOBt (3.16 g, 20.6 mmol, 1.50 equiv.) and EDC·HCl (3.30 g, 17.2 mmol, 1.25 equiv.) in CH_2Cl_2 (138 mL), DIPEA (3.60 mL, 20.6 mmol, 1.50 equiv.) was added dropwise over a period of 10 min at 0 °C. The reaction mixture was stirred at ambient temperature for 4 d. Then, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 100:0 → 98:2) and a second NP-BÜCHI column chromatography (solvent A: CH_2Cl_2, solvent B: MeOH, 40x150 mm column, flow rate: 80.0 mL/min, 30 sec/fr., gradient:

(*t* [min]/solvent B [%]): 0/0; 15/0; 15/100; 30/100; t_R = 4.0 – 30.0 min) afforded peptide **135** (4.81 g, 11.6 mmol, 84% yield) as a colorless solid.

T_M: 170 – 175 °C; **$[\alpha]_D^{21.8}$:** - 43.4° (*c* 1.10; CH_2Cl_2); **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ [ppm] 7.49 – 7.41 (m, 2H, N*H*), 5.67 (d, *J* = 9.4 Hz, 1H, N*H*), 4.50 (p, *J* = 7.2 Hz, 1H, *H*-18), 4.37 (t, *J* = 8.5 Hz, 1H, *H*-5/*H*-10), 4.04 (t, *J* = 8.1 Hz, 1H, *H*-5/*H*-10), 3.68 (s, 3H, *H*-20), 2.03 – 1.98 (m, 1H, *H*-6/*H*-12), 1.88 – 1.81 (m, 1H, *H*-6/*H*-12), 1.53 – 1.49 (m, 1H, *H*-14), 1.38 (m, 9H, *H*-1), 1.32 (d, *J* = 7.2 Hz, 3H, CH_3), 1.12 – 1.01 (m, 1H, *H*-14), 0.90 – 0.79 (m, 12H, CH_3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 173.2 (q, *C*=O), 172.3 (q, *C*=O), 171.2 (q, *C*=O), 156.0 (q, *C*=O), 79.4 (q, *C*-2), 60.1 (t, *C*-5/*C*-10), 57.7 (t, *C*-5/*C*-10), 52.3 (p, *C*-20), 48.0 (p, *C*-18), 36.9 (t, *C*-6/*C*-12), 30.9 (t, *C*-6/*C*-12), 28.4 (p, *C*-1), 25.0 (s, *C*-14), 19.3 (p, *C*H_3), 18.4 (p, *C*H_3), 17.8 (p, *C*H_3), 15.3 (p, *C*H_3), 11.2 (p, *C*-15); **HRMS** (ESI) *m/z* calculated for $C_{20}H_{37}N_3O_6Na$ $[M+Na]^+$ 438.2580; found 438.2592.

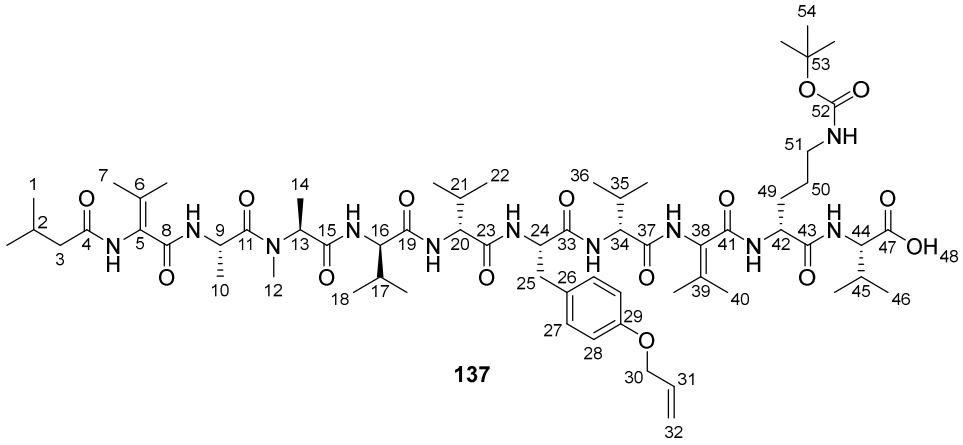
Methyl ((2*R*)-2-(2-((2*R*)-2-((2*S*)-3-(4-(allyloxy)phenyl)-2-((2*R*)-3-methyl-2-((2*R*)-3-methyl-2-((2*S*)-2-((2*S*)-*N*-methyl-2-(3-methyl-2-(3-methylbutanamido)-3-nitrobutan-amido)-propan-amido)propanamido)butanamido)butanamido)propanamido)-3-methyl-butanamido)-3-methyl-3-nitrobutanamido)-5-((*tert*-butoxycarbonyl)amino)pentanoyl)-L-valinate (137a)



137a

To a solution of fragment A-α-Tyr (**122**, 158 mg, 197 μmol, 1.00 equiv.) and fragment B-D,L (**99**, 255 mg, 432 μmol, 2.20 equiv.) in DMF (2.00 mL) at 0 °C, HOAt (58.8 mg, 432 μmol, 2.20 equiv.), PyAOP (308 mg, 591 μmol, 3.00 equiv.) and DIPEA (172 µL, 985 μmol, 5.00 equiv) were added and the reaction mixture was stirred for 20 h at ambient temperature. The reaction was terminated by addition of MeOH (1.00 mL) and the solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI, solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, 24 g WP C18 column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 25/100; 30/100; t_R = 18.0 – 22.5 min) afforded peptide **137a** (55.1 mg, 40.0 μmol, 20% yield) as a colorless foam.

((*R*)-2-(2-((*R*)-2-((*S*)-3-(4-(Allyloxy)phenyl)-2-((*R*)-3-methyl-2-((*R*)-3-methyl-2-((*S*)-2-((*S*)-*N*-methyl-2-(3-methyl-2-(3-methylbutanamido)but-2-enamido)propanamido)-propanamido)-butanamido)butanamido)propanamido)-3-methylbutanamido)-3-methylbut-2-enamido)-5-((*tert*-butoxycarbonyl)amino)pentanoyl)-L-valine (137)

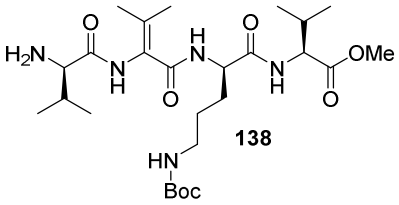


To a solution of peptide **137a** (55.1 mg, 40.0 μmol, 1.00 equiv.) in THF (800 μL), LiOH (1M in H_2O, 16.8 mg, 400 μmol, 10.0 equiv.) was added dropwise at 0 °C and the reaction mixture was stirred at ambient temperature. After 20 h, the reaction was terminated by addition of phosphate buffer solution (pH 7) and adjusted to pH 7. The solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI, solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, 24 g WP C18 column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/ solvent B [%]): 0/0; 25/100; 30/100; t_R = 15.5 – 25.5 min) afforded fragment AB-α-Tyr (**137**, 51.7 mg, 40.0 μmol, quant.) as a colorless foam.

$[\alpha]_D^{25.5}$: - 21.8° (*c* 1.6; DMSO-d_6); **^{1}H-NMR** (DMSO-d_6, 600 MHz): δ [ppm] 9.08 – 9.01 (m, 1H, *H*N), 8.91 – 8.89 (m, 1H, *H*N), 8.29 – 8.09 (m, 2H, *H*N), 7.91 – 7.80 (m, 2H, *H*N), 7.61 – 7.52 (m, 2H, *H*N), 7.14 (d, *J* = 8.6 Hz, 2H, *H*-27), 6.78 (d, *J* = 8.6 Hz, 2H, *H*-28), 6.71 (m, 1H, *H*N), 6.03 – 5.97 (m, 1H, *H*-31), 5.36 – 5.34 (m, 1H, *H*-32), 5.23 – 5.21 (m, 1H, *H*-32), 5.03 – 4.81 (m, 1H, NC*H*), 4.71 – 4.59 (m, 2H, NC*H*), 4.49 (d, *J* = 4.9 Hz, 2H, *H*-30), 4.36 – 4.34 (m, 1H, NC*H*), 4.17 – 4.07 (m, 4H, NC*H*), 2.93 – 2.50 (m, 10H, *H*-12, H_2C, *H*C(CH_3)$_2$), 2.08 – 1.90 (m, 12H, *H*-7, *H*-40), 1.79 – 1.50 (m, 8H, *H*C, CH_2), 1.40 – 1.36 (m, 11H, C*H*, *H*-54), 1.26 – 1.15 (m, 6H, *H*-10, *H*-14), 0.89 – 0.52 (m, 30H, CH_3); **^{13}C-NMR** (DMSO-d_6, 100 MHz): δ [ppm] 172.1 (q, *C*=O), 171.5 (q, *C*=O), 171.5 (q, *C*=O), 171.0 (q, *C*=O), 170.9 (q, *C*=O), 170.7 (q, *C*=O), 170.6 (q, *C*=O), 170.3 (q, *C*=O), 165.0 (q, *C*=O), 164.8 (q, *C*=O), 164.5 (q, *C*=O), 156.8 (q, *C*-29), 155.6 (q, *C*-52), 153.5 (q, *C*=C), 133.9 (t, *C*=C), 130.2 (t, *C*-27), 125.5 (q, *C*-25), 121.1 (q, *C*=C), 119.0 (q, *C*=C), 117.1 (s, *C*-30), 114.2 (t, *C*-28), 77.4 (q, *C*-53), 68.1 (s, *C*-30), 57.8 (t, N*C*H), 57.8 (t, N*C*H), 57.7 (t, N*C*H),

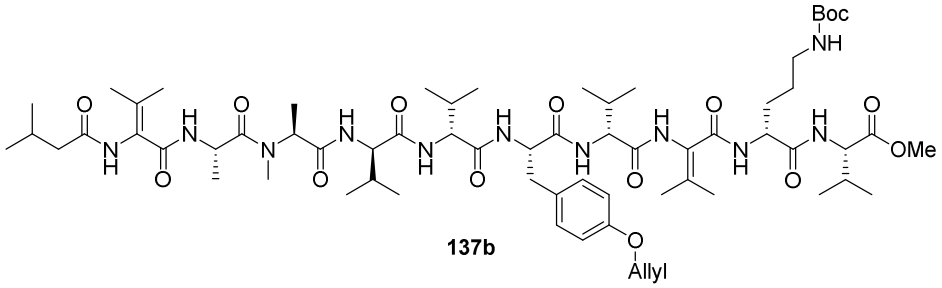
57.4 (t, N*C*H), 51.6 (t, N*C*H), 51.1 (t, N*C*H), 48,1 (t, N*C*H), 45.1 (t, N*C*H), 44.3 (s, *C*-3), 38.6 (s, H_2C), 36.6 (s, *C*-25), 30.4 (p, *C*-12), 30.3 (t, $HC(CH_3)_2$), 30.2 (t, $HC(CH_3)_2$), 30.2 (t, $HC(CH_3)_2$), 30.0 (t, $HC(CH_3)_2$), 29.8 (t, $HC(CH_3)_2$), 28.3 (s, *C*-54), 25.6 (p/s/t, *C*H/*C*H_2/*C*H_3), 25.5 (p/s/t, *C*H/*C*H_2/*C*H_3), 22.4 (p, *C*H_3), 20.7 (p, *C*H_3), 19.4 (p, *C*H_3), 19.3 (p, *C*H_3), 19.3 (p, *C*H_3), 19.1 (p, *C*H_3), 18.1 (p, *C*H_3), 18.0 (p, *C*H_3), 18.0 (p, *C*H_3), 17.7 (p, *C*H_3), 17.4 (p, *C*H_3), 14.5 (p, *C*H_3); **HRMS** (ESI) *m/z* calculated for $C_{64}H_{103}N_{11}O_{15}Na$ $[M+Na]^+$ 1288.7533; found 1288.7559.

Methyl ((*R*)-2-(2-((*R*)-2-amino-3-methylbutanamido)-3-methylbut-2-enamido)-5-((*tert*-butoxycarbonyl)amino)pentanoyl)-L-valinate (138)



To a solution peptide **63** (368 mg, 536 μmol, 1.00 equiv.) in THF (10.7 mL), TBAF (1M in THF, 5.40 mL, 0.1M) was added and the reaction mixture was stirred for 19 h at ambient temperature. Then the solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI, solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, 40 g WP C18 column, flow rate: 30.0 mL/min; 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 5/0; 25/80; t_R = 12.5 – 17.0 min) afforded fragment **183** as a colorless foam (290 mg, 536 μmol, quant.) that was used in the next step without further purification.

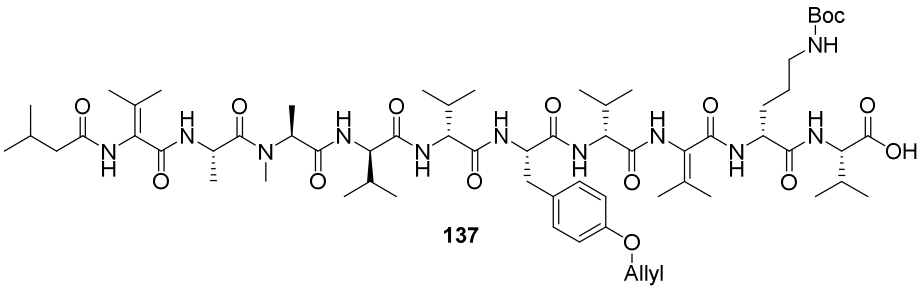
Methyl ((*R*)-2-(2-((*R*)-2-((*S*)-3-(4-(allyloxy)phenyl)-2-((*R*)-3-methyl-2-((*R*)-3-methyl-2-((*S*)-2-((*S*)-*N*-methyl-2-(3-methyl-2-(3-methylbutanamido)but-2-enamido)propan-amido)propan-amido)butanamido)butanamido)propanamido)-3-methylbutanamido)-3-methylbut-2-enamido)-5-((*tert*-butoxycarbonyl)amino)pentanoyl)-L-valinate (137b)



To a solution of fragment A-α-Tyr (**125**, 258 mg, 341 μmol, 1.00 equiv.) and fragment B-D,L (**138**, 290 mg, 536 μmol, 1.57 equiv.) in DMF (3.40 mL) at 0 °C, HOAt (102 mg, 750 μmol, 2.20 equiv.), PyAOP (533 mg, 1.02 mmol, 3.00 equiv.) and DIPEA (297 µL, 1.71 mmol, 5.00 equiv.) were added and the reaction mixture was stirred for 18 h at ambient temperature under an argon atmosphere. The reaction was terminated by addition of MeOH (1.00 mL) and the solvent was

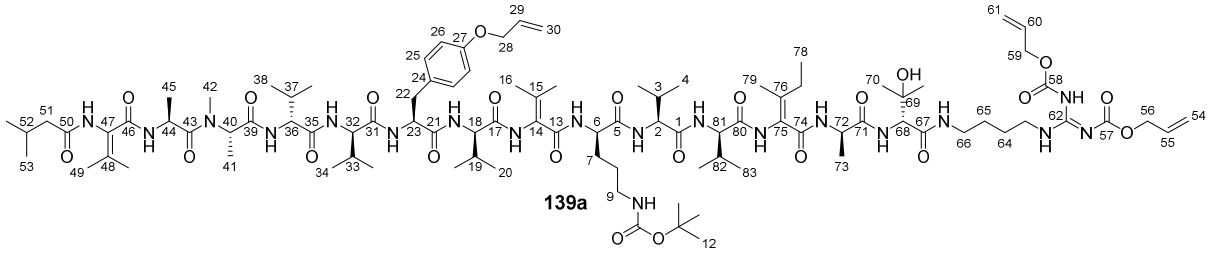
removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI; solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA; 40 g WP C18 column, flow rate: 30.0 mL/min; 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 2/0; 28/100; 30/100; t_R = 13.5 – 18.5 min) afforded peptide (**137b**, 232 mg, 181 μmol, 53% yield) as a colorless foam which was used in the next step without further purification.

((*R*)-2-(2-((*R*)-2-((*S*)-3-(4-(Allyloxy)phenyl)-2-((*R*)-3-methyl-2-((*R*)-3-methyl-2-((*S*)-2-((*S*)-*N*-methyl-2-(3-methyl-2-(3-methylbutanamido)but-2-enamido)propanamido)-propanamido)-butanamido)butanamido)propanamido)-3-methylbutanamido)-3-methylbut-2-enamido)-5-((*tert*-butoxycarbonyl)amino)pentanoyl)-L-valine (137)



To a solution of peptide **137b** (232 mg, 181 μmol, 1.00 equiv.) in THF (1.81 mL), LiOH (1M in H_2O, 75.9 mg, 1.81 mmol, 10.0 equiv.) was added dropwise at 0 °C and the reaction mixture was stirred at ambient temperature. After 3 h, the reaction was terminated by addition of phosphate buffer solution (pH 7) and adjusted to pH 7. The solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI; solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA; 40 g WP C18 column, flow rate: 30.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 2/0; 28/100; 30/100; t_R = 17.5 – 24.5 min) afforded peptide **137** (55.7 mg, 44.0 μmol, 24% yield) as a colorless foam which was used in the next step without further purification.

Protected fragment ABCD-α-Tyr (139a)

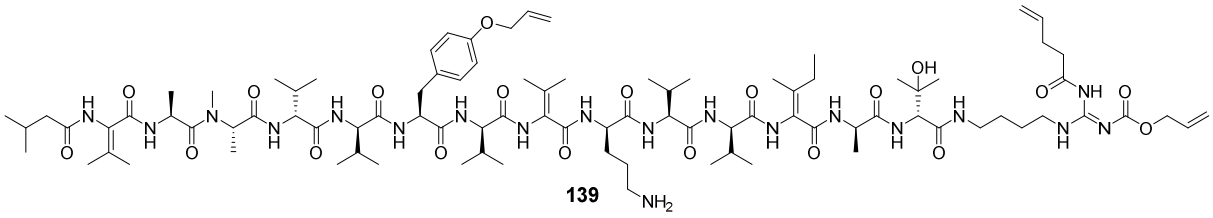


To a solution of fragment AB-α-Tyr (**137**, 107 mg, 84.8 μmol, 1.00 equiv.) and fragment CD (**108**, 268 mg, 386 μmol, 4.55 equiv.) in DMF (1.00 mL) at 0 °C, HOAt (28.9 mg, 212 μmol, 2.50 equiv.), HATU (80.6 mg, 212 μmol, 2.50 equiv.) and DIPEA (74.0 µL, 424 μmol, 5.00 equiv.) were added and the reaction mixture was stirred for 16 h at ambient temperature. The reaction was terminated by addition of MeOH (1.00 mL) and the solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI, solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, 40 g WP C18 column, flow rate: 30.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 2/0; 28/100; 30/100; t_R = 21.5 – 26.5 min) afforded peptide **139a** (27.6 mg, 14.2 μmol, 17% yield) as a colorless foam.

$[\alpha]_D^{28.4}$ = – 2.70° (*c* 0.3, DMSO-d_6); **^{1}H-NMR** (DMSO-d_6, 600 MHz): δ [ppm] 9.34 – 8.88 (m, 3H, N*H*), 8.15 – 8.05 (m, 3H, N*H*), 7.94 – 7.54 (m, 10H, N*H*), 7.15 (d, *J* = 8.3 Hz, 2H, *H*-25), 6.79 (d, *J* = 8.6 Hz, 2H, *H*-26), 6.69 – 6.65 (m, 1H, N*H*), 6.03 – 5.90 (m, 3H, *H*-29, *H*-55, *H*-60), 5.37 – 5.17 (m, 8H, *H*- 23, *H*-30, *H*-54, *H*-61, O*H*), 5.03 – 4.79 (m, 1H, *H*-40), 4.67 – 4.66 (m, 3H, *H*-44, *H*-56, *H*-59), 4.49 – 4.48 (m, 4H, *H*-28, *H*-56, *H*-59), 4.45 – 3.95 (m, 10H, *H*-2, *H*-6, *H*-18, *H*-32, *H*-36, *H*-63, *H*-68, *H*-72, *H*-81), 3.16 – 3.02 (m, 2H, *H*-66), 2.92 – 2.88 (m, 5H, *H*-9, *H*-42), 2.69 – 2.65 (m, 1H, *H*-22), 2.54 – 2.51 (m, 6H, *H*-3, *H*-19, *H*-22, *H*-33, *H*-37, *H*-82), 2.33 – 2.20 (m, 2H, *H*-77), 2.02 – 1.65 (m, 18H, *H*-16, *H*-49, *H*-51, *H*-52, *H*-79), 1.50 – 1.39 (m, 7H, *H*-7, *H*-8, *H*-64, *H*-65), 1.36 (s, 9H, *H*-12), 1.23 – 1.19 (m, 9H, *H*-41, *H*-45, *H*-73), 1.11 – 1.07 (m, 6H, *H*-70), 0.97 (t, *J* = 7.4 Hz, 3H, *H*-78), 0.89 – 0.50 (m, 36H, *H*-4, *H*-20, *H*-34, *H*-38, *H*-53, *H*-83); **^{13}C-NMR** (DMSO-d_6, 150 MHz): δ [ppm] 172.2 (q, *C*=O), 172.1 (q, *C*=O), 172.0 (q, *C*=O), 171.9 (q, *C*=O), 171.8 (q, *C*=O), 171.4 (q, *C*=O), 171.3 (q, *C*=O), 170.9 (q, *C*=O), 170.6 (q, *C*=O), 170.5 (q, *C*=O), 170.2 (q, *C*=O), 169.8 (q, *C*=O), 165.0 (q, *C*=O), 164.8 (q, *C*=O), 164.5 (q, *C*=O), 162.9 (q, *C*-57/*C*-58), 156.8 (q, *C*-27), 155.5 (q, *C*-10), 155.1 (q, *C*-62), 152.5 (q, *C*-57/*C*-58), 134.5 (3x q, *C*-14, *C*-47, *C*-75), 134.3 (q, *C*-24), 133.9 (t, *C*-29/*C*-55/*C*-60), 133.5 (t, *C*-29/*C*-55/*C*-60), 131.9 (t, *C*-29/*C*-55/*C*-60), 129.6 (t, 2x *C*-25), 125.5 (q, *C*-15/*C*-48/*C*-76), 125.0 (q, *C*-15/*C*-48/*C*-76), 124.8 (q, *C*-15/*C*-48/*C*-76), 118.8 (s, *C*-30/*C*-54/*C*-61), 117.3 (s, *C*-30/*C*-54/*C*-61), 117.1 (s, *C*-30/*C*-54/*C*-61), 114.2 (t, 2x *C*-26), 77.3 (q, *C*-11), 71.0 (q, *C*-69), 68.1 (s, *C*-28), 66.5 (s, *C*-56/*C*-59), 65.4 (s, *C*-56/*C*-59), 60.1 (t, *C*-2/*C*-18/*C*-32/*C*-36/*C*-68/*C*-81), 59.9 (t, *C*-2/*C*-18/*C*-32/*C*-36/*C*-68/*C*-81), 58.4 (t, *C*-2/*C*-18/*C*-32/*C*-36/*C*-68/*C*-81), 58.2 (t, *C*-2/*C*-18/*C*-32/*C*-36/*C*-68/*C*-81), 57.8 (t, *C*-2/*C*-18/*C*-32/*C*-36/*C*-68/*C*-81), 57.6 (t, *C*-2/*C*-18/*C*-32/*C*-36/*C*-68/*C*-81), 54.3 (t, *C*-6/*C*-23/*C*-40/*C*-44/*C*-72), 52.1 (t, *C*-6/*C*-23/*C*-40/*C*-44/*C*-72), 51.6 (t, *C*-6/*C*-23/*C*-40/*C*-44/*C*-72), 48.6 (t, *C*-6/*C*-23/*C*-40/*C*-44/*C*-72), 45.2 (t, *C*-6/*C*-23/*C*-40/*C*-44/*C*-72), 44.2 (s, *C*-51), 40.4 (s, *C*-22), 40.2 (s, *C*-9 and *C*-63 beneath DMSO-signal), 38.2 (s, *C*-66), 31.3 (t, *C*-3/*C*-19/*C*-33/*C*-37/*C*-82), 31.3 (t, *C*-3/*C*-19/*C*-33/*C*-37/*C*-82), 30.7 (t, *C*-3/*C*-19/*C*-33/*C*-37/*C*-82), 30.3 (t, *C*-3/*C*-19/*C*-33/*C*-37/*C*-82), 29.1 (t, *C*-3/*C*-19/*C*-33/*C*-37/*C*-82 and s, *C*-7), 28.8 (t, *C*-3/*C*-19/*C*-33/

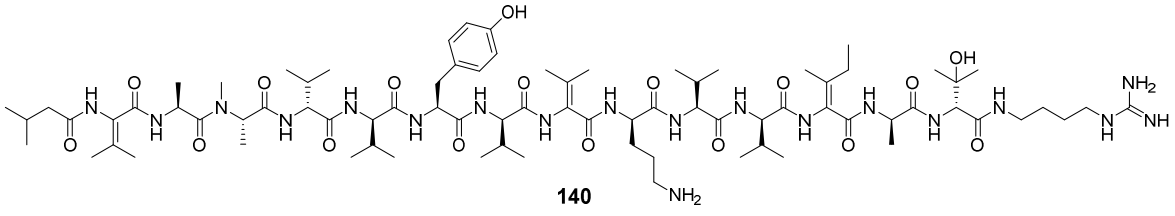
C-37/*C*-82 and s, *C*-7), 28.7 (s, 3x *C*-12), 28.2 (p, *C*-70), 27.3 (s, *C*-77), 26.6 (s, *C*-65), 26.3 (s, *C*-64), 26.1 (s, *C*-8), 25.9 (t, *C*-52), 25.5 (p, *C*-53), 25.1 (p, *C*-53), 22.3 (p, *C*-16/*C*-49), 22.1 (p, *C*-16/*C*-49), 20.7 (p, *C*-16/*C*-49), 20.4 (p, *C*-16/*C*-49), 20.3 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 20.1 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 19.3 (2x p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 19.3 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 19.2 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 19.1 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 19.0 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 18.9 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 18.4 (p, *C*-4/*C*-20/*C*-34/*C*-38/*C*-83), 18.3 (p, *C*-41/*C*-45/*C*-73/*C*-79), 18.1 (p, *C*-41/*C*-45/*C*-73/*C*-79), 17.5 (p, *C*-41/*C*-45/*C*-73/*C*-79), 13.9 (p, *C*-41/*C*-45/*C*-73/*C*-79), 12.6 (p, *C*-78); **HRMS** (ESI) *m/z* calculated for $C_{96}H_{155}N_{19}O_{23}Na$ $[M+Na]^+$ 1965.1441; found 1965.1470.

Fragment ABCD-*α*-Tyr (139)



To a solution of Boc-protected fragment ABCD-*α*-Tyr (**139a**, 18.7 mg, 9.60 μmol, 1.00 equiv.) in CH_2Cl_2 (500 μL), TMSI (2.60 μL, 19.2 μmol, 2.00 equiv.) was added and the reaction mixture was stirred for 1 h at ambient temperature under an argon atmosphere. Then the solvent was removed under reduced pressure affording deprotected peptide **139** as a yellow foam that was used in the next step without further purification.

Myxovalargin-*α*-Tyr (140)



To a solution of Boc-deprotected fragment ABCD-*α*-Tyr (**139**, 12.8 mg, 6.94 μmol, 1.00 equiv.) and $Pd(PPh_3)_4$ (1.60 mg, 1.40 μmol, 0.20 equiv.) in MeOH (500 μL), K_2CO_3 (5.75 mg, 41.6 μmol, 6.00 equiv.) was added and the reaction mixture was stirred for 2 h at ambient temperature under an argon atmosphere. The reaction was terminated by addition of H_2O (500 μL) and the solvent was removed under reduced pressure. Purification by flash column chromatography (RP-BÜCHI, solvent A:water + 0.1% FA, solvent B: MeCN + 0.1% FA, 24 g WP C18 column, flow rate:

20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 2/0; 28/100; 30/100; t_R = 12.5 – 19.5 min) afforded myxovalargin-*α*-Tyr (**140**, 5.90 mg, 3.60 *μ*mol, 38% yield o2s; *d.r.* = 0.8:2.8:2.7:0.4:2.3) as a colorless foam.

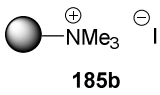
NMR measurement was performed with the diastereomer mixture:

^{1}H-NMR (DMSO-d_6, 600 MHz): *δ* [ppm] 9.30 – 8.94 (m, 2H, N*H*, Tyr-O*H*), 8.33 – 7.65 (m, 17H, N*H*, Tyr-O*H*), 7.02(d, *J* = 7.7 Hz, 2H, Ar-*H*), 6.60 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 5.02 – 4.90 (m, 1H, NC*H*/O*H*), 4.72 – 4.68 (m, 1H, NC*H*/O*H*), 4.57 (m, 1H, NC*H*/O*H*), 4.47 – 4.37 (m, 1H, NC*H*/O*H*), 4.33 – 4.16 (m, 8H, NC*H*/O*H*), 3.17 – 3.04 (m, 3H, CH_2), 2.93 – 2.79 (m, 3H, NCH_3), 2.72 – 2.64 (m, 2H, CH_2, HCC*H*), 2.54 (m, 8H, CH_2, HCC*H*), 2.28 (m, 2H, C*H*/CH_2/CH_3), 2.08 – 1.94 (m, 6H, C*H*/CH_2/CH_3), 1.90 – 1.89 (m, 6H, CH_2/CH_3), 1.67 – 1.65 (m, 8H, CH_2/CH_3), 1.44 (m, 6H, CH_2/CH_3), 1.23 – 1.16 (m, 10H, CH_2/CH_3), 1.11 – 1.06 (m, 6H, CH_3), 0.98 (t, *J* = 7.3Hz, 3H, H_2CCH_3), 0.88 – 0.56 (m, 36H, CH_3); **^{13}C-NMR** (DMSO-d_6, 150 MHz): *δ* [ppm] 172.1 (q, *C*=O), 172.0 (q, *C*=O), 171.7 (q, *C*=O), 171.6 (q, *C*=O), 171.5 (q, *C*=O), 171.0 (q, *C*=O), 170.9 (q, *C*=O), 170.8 (q, *C*=O), 170.6 (q, *C*=O), 170.5 (q, *C*=O), 170.0 (q, *C*=O), 169.9 (q, *C*=O), 165.0 (q, *C*=O), 164.8 (q, *C*=O), 164.5 (q, *C*=O), 157.2 (q, *C*=N), 155.8 (q, O*C*Ar), 130.0 (q, *C*=C), 129.9 (q, *C*=C), 129.6 (q, *C*=C), 127.6 (q, *C*=C), 125.5 (q, *C*=C), 125.4 (q, *C*=C), 124.2 (q, *C*=C), 114.8 (q, *C*=C), 114.7 (q, *C*=C), 70.9 (q, HO*C*), 64.6 (t, N*C*H), 60.3 (t, N*C*H), 60.1 (t, N*C*H), 58.2 (t, N*C*H), 57.8 (t, N*C*H), 57.7 (t, N*C*H), 57.5 (t, N*C*H), 57.3 (t, N*C*H), 54.5 (t, N*C*H), 52.1 (t, N*C*H), 51.7 (t, N*C*H), 45.1 (s, *C*H_2), 40.4 (s, *C*H_2), 40.3 (s, *C*H_2), 38.1 (s, *C*H_2), 37.5 (s, *C*H_2), 30.7 (t/p H_3C*C*H/N*C*H_3), 30.4 (t/p H_3C*C*H/N*C*H_3), 29.9 (t/p H_3C*C*H/N*C*H_3), 29.7 (t/p H_3C*C*H/N*C*H_3), 28.8 (t/s, t/p H_3C*C*H/N*C*H_3), 28.7 (t/p H_3C*C*H/N*C*H_3), 27.4 (t/s/p, *C*H/*C*H_2/*C*H_3), 26.3 (t/s/p, *C*H/*C*H_2/*C*H_3), 26.2 (t/s/p, *C*H/*C*H_2/*C*H_3), 26.0 (t/s/p, *C*H/*C*H_2/*C*H_3), 25.8 (t/s/p, *C*H/*C*H_2/*C*H_3), 25.5 (t/s/p, *C*H/*C*H_2/*C*H_3), 22.3 (s/p, *C*H_2/*C*H_3), 22.1 (s/p, *C*H_2/*C*H_3), 20.3 (p, *C*H_3), 20.1 (p, *C*H_3), 19.2 (p, *C*H_3), 19.1 (p, *C*H_3), 18.5 (p, *C*H_3), 18.3 (p, *C*H_3), 18.0 (p, *C*H_3), 18.0 (p, *C*H_3), 17.8 (p, *C*H_3), 17.5 (p, *C*H_3), 14.5 (p, *C*H_3), 12.7 (p, H_2C*C*H_3); **HRMS** (ESI) *m/z* calculated for $C_{80}H_{137}N_{19}O_{17}$ $[M+2H/2]^+$ 818.0220; found 818.0222.

E3 Experimental Procedures – Topic B

E3.1 Preparation of Functionalized Resins

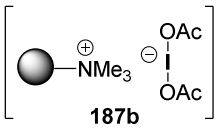
Synthesis of polymer 185b



185b

Polymer-bound hydroxide (Amberlyst® A26-resin from ABCR; 4.20 mmol/g hydroxide) was flushed successively with 1M NaOH (4.00 mL/g polymer), sat. LiI-solution (5.00 mL/g polymer), distilled water (4.00 mL/g polymer), isopropyl alcohol (4.00 mL/g polymer) and CH_2Cl_2 (4.00 mL/g polymer). Drying *in vacuo* afforded a light pink resin **185b**. It was prepared that way on a 50.0 g scale.[104]

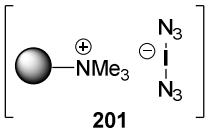
Synthesis of polymer 187b



187b

A suspension of polymer-bound iodide **185b** (4.20 mmol iodide per gram resin, 1.00 equiv.) and $PhI(OAc)_2$ (1.80 equiv.) was shaken in dry CH_2Cl_2 (3.00 mL/mmol iodide) at 665 rpm for 6 h at room temperature under an argon atmosphere. During this time, the reaction mixture was protected from light. The light yellow resin **187b** was filtered, washed with CH_2Cl_2 (30 mL/g resin) and dried *in vacuo*. Practically, the effective loading was found to be up to 2.1 mmol reagent per gram resin. It can be stored several months under an argon atmosphere at –15 °C in the dark without loss of activity.[104]

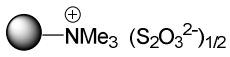
Synthesis of polymer 201



201

A suspension of polymer-bound iodide **187b** (4.20 mmol iodide per gram resin, 1.00 equiv.) and trimethylsilyl azide (2.60 equiv.) was shaken in dry CH_2Cl_2 (4.00 mL/mmol iodide) at 665 rpm for 6 h at room temperature under an argon atmosphere. During this time, the reaction mixture was protected from light. The orange-colored resin **201** was filtered, washed with CH_2Cl_2 (30.0 mL/g resin) and dried *in vacuo*. Practically, the effective loading was found to be up to 2.10 mmol reagent per gram resin. It can be stored several months under an argon atmosphere at –15 °C in the dark without loss of activity.[104]

Preparation of polymer-bound thiosulfate 200



200

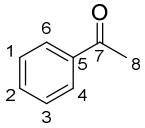
Polymer-bound hydroxide (Amberlyst® A26-resin from ABCR; 4.20 mmol/g hydroxide) was flushed successively with 1M NaOH (4.00 mL/g polymer), a sat. $Na_2S_2O_3$-solution (5.00 mL/g polymer), methanol (4.00 mL/g polymer), acetone (4.00 mL/g polymer) and Et_2O (4.00 mL/g polymer). Drying *in vacuo* afforded the light pink resin **200**. It was prepared on a 50.0 g scale.

E3.2 Oxidation Reactions

E3.2.1 Oxidation under thermal conditions – General procedure

A mixture of the alcohol/amine (0.50 mmol, 1.00 equiv.) and polymer-bound iodine azide **201** (952 mg, 2.10 mmol, 4.00 equiv.) was stirred in absolute MeCN (3.33 mL) at given temperature under an argon atmosphere. After full consumption of the starting material was monitored by TLC the reaction was terminated by filtration and the resin was washed with EtOAc and concentrated under reduced pressure.

Acetophenone (233)



233

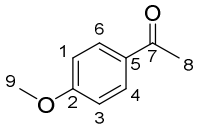
The title compound was prepared according to the general procedure with (*S*)-1-phenylethan-1-ol as starting material at 60 °C. After 16 h, the product was purified by flash column chromatography (PE/EtOAc = 4:1) affording acetophenone (**233**, 83.9 mg, 699 μmol, quant.) as a light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] 7.97 – 7.95 (m, 2H, *H*-6, *H*-4), 7.58 – 7.54 (m, 1H, *H*-2), 7.48 – 7.44 (m, 2H, *H*-1, *H*-3), 2.60 (s, 3H, *H*-8); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] 198.3 (s, *C*-7), 137.2 (s, *C*-5), 133.2 (d, *C*-2), 128.7 (d, 2C, *C*-1,3/6,4), 128.4 (d, 2C, *C*-1,3/6,4), 26.7 (q, 2C, *C*-8).

The analytical data are consistent with those reported in the literature.[132]

[132] K. Moriyama, M. Takemura, H. Togo, *Org. Lett.* **2012**, *14*, 2414-2417.

1-(4-Methoxyphenyl)ethan-1-one (239)



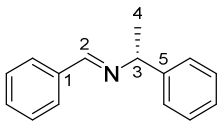
239

The title compound was prepared according to the general procedure with (*S*)-1-(4-methoxyphenyl)ethan-1-ol as starting material. After 16 h, the product was purified by flash column chromatography (PE/EtOAc = 4:1) affording 1-(4-methoxyphenyl)ethan-1-one (**239**, 94.6 mg, 602 μmol, 90% yield) as a light yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] 7.95 – 7.92 (m, 2H, *H*-4, *H*-6), 6.95 – 6.91 (m, 2H, *H*-1, *H*-3), 3.87 (s, 3H, *H*-9), 2.55 (s, 3H, *H*-8); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] 196.9 (s, *C*-7), 163.6 (s, *C*-2), 130.7 (d, *C*-4, *C*-6), 130.5 (s, *C*-5), 113.8 (d, *C*-1, *C*-3), 55.6 (q, *C*-9), 26.5 (q, *C*-8).

The analytical data are consistent with those reported in the literature.[133]

(*R,E*)-1-Phenyl-*N*-(1-phenylethyl)methanimine (248)



248

The title compound was prepared according to the general procedure with (*R*)-*N*-benzyl-1-phenylethan-1-amine as starting material at 83 °C. After 36 h, the product was purified using flash column chromatography (NP-BÜCHI, solvent A: 1% Et_3N in PE, solvent B: Et_2O, 15x150 mm column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 30/10; t_R = 3.0 min). The imine **248** (105 mg, 500 μmol, quant.) was obtained as a colorless foam.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.38 (s, 1H, *H*-2), 7.81 – 7.76 (m, 2H, Ar-*H*), 7.44 – 7.32 (m, 7H, Ar-*H*), 7.26 – 7.22 (m, 1H, Ar-*H*), 4.55 (q, *J* = 6.6 Hz, 1H, *H*-3), 1.60 (d, *J* = 6.6 Hz, 3H, *H*-4); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 159.6 (q, *C*-2), 145.3 (q, *C*-5), 136.6 (q, *C*-1), 130.7 (t, Ar-*C*), 128.7 (t, Ar-*C*), 128.6 (t, Ar-*C*), 128.4 (t, Ar-*C*), 126.9 (t, Ar-*C*), 126.8 (t, Ar-*C*), 69.9 (t, *C*-3), 25.0 (p, *C*-4).

The analytical data are in accordance with those reported in the literature.[134]

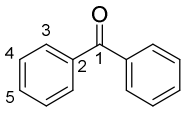
E3.2.2 Photochemical Oxidation of Alcohols – General procedure

A mixture of alcohol (0.50 mmol, 1.00 equiv.) and polymer-bound iodine azide **201** (952 mg, 2.00 mmol, 4.00 equiv.) was stirred under blue LED light in absolute MeCN (3.33 mL) at ambient temperature under an argon atmosphere. After full consumption of the starting material was

[133] D. J. Lippincott, P. J. Trejo-Soto, F. Gallou, B. H. Lipshutz, *Org. Lett.* **2018**, *20*, 5094-5097.
[134] T. Bosanac, C. S. Wilcox, *J. Am. Chem. Soc.* **2002**, *124*, 4194-4195.

monitored by TLC the reaction was terminated by filtration and the resin was washed with EtOAc. Polymer-bound thiosulfate **200** was added to the combined organic phases and the reaction mixture was stirred for 10 min until the solution was nearly colorless. This was filtered through a pad of cotton and concentrated under reduced pressure.

Benzophenone (196)



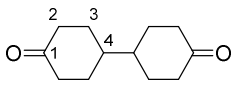
196

The title compound was prepared according to the general procedure using diphenylmethanol as starting material. After 19 h, the ketone **196** (80.9 mg, 444 μmol, 89% yield) was obtained as a colorless foam.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.82 – 7.80 (m, 4H, *H*-3), 7.61 – 7.56 (m, 2H, *H*-5), 7.50 – 7.46 (m, 4H, *H*-4); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 196.8 (q, *C*-1), 137.7 (q, *C*-2), 132.5 (t, Ar-*C*), 130.1 (t, Ar-*C*), 128.4 (t, Ar-*C*).

The analytical data are in accordance with those reported in the literature.[135]

[1,1'-Bi(cyclohexane)]-4,4'-dione (258)



258

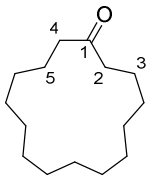
The title compound was prepared according to the general procedure with [1,1'-bi(cyclohexane)]-4,4'-diol as starting material. After 21 h, the product was purified using flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 10.0 mL/min, 30 sec/fr., PE/EtOAc = 3:7, t_R = 15.0 min). Diketone **258** (72.7 mg, 374 μmol, 75% yield) was obtained as a colorless foam.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 2.40 – 2.27 (m, 8H, *H*-2), 2.07 – 2.03 (m, 4H, *H*-3), 1.72 – 1.67 (m, 2H, *H*-4), 1.54 – 1.44 (m, 4H, *H*-3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 211.7 (q, 2C, *C*-1), 41.0 (t, 2C, *C*-4), 40.4 (s, 4C, C-2), 30.0 (s, 4C, *C*-3).

The analytical data are in accordance with those reported in the literature.[136]

[135] T. Huang, T. Chen, L.-B. Han, *J. Org. Chem.* **2018**, *83*, 2959-2965.
[136] Z.-W. Mei, T. Omote, M. Mansour, H. Kawafuchi, Y. Takaguchi, A. Jutand, S. Tsuboi, T. Inokuchi, *Tetrahedron* **2008**, *64*, 10761-10766.

Cyclopentadecanone (235)



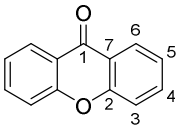
235

The title compound was prepared according to the general procedure with cyclopentadecanol as starting material. After 18 h, the product was purified using flash column chromatography (NP-BÜCHI, solvent A: CH_2Cl_2, solvent B: MeOH, 15x150 mm column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (t [min]/solvent B [%]): 0/0; 30/2; t_R = 2.0 min). Ketone **235** (112 mg, 497 μmol, quant.) was obtained as a colorless foam.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 2.39 (t, J = 6.7 Hz, 4H, *H*-2, *H*-4), 1.66 – 1.59 (m, 4H, *H*-3, *H*-5), 1.31 – 1.26 (br, 20H, C*H*$_2$); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 212.8 (q, *C*-1), 42.2 (s, *C*-2, *C*-4), 27.7, 26.9, 26.8, 26.5, 26.4, 23.6 (s, 12C, *C*H$_2$); **HRMS** (ESI) *m/z* calculated for $C_{15}H_{28}ONa$ $[M+Na]^+$ 247.2038; found 247.2039.

The analytical data are in accordance with those reported in the literature.[137]

9*H*-Xanthen-9-one (259)



259

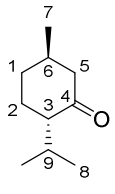
The title compound was prepared according to the general procedure with xanthydrol as starting material. After 22 h, the product was purified using flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 10.0 mL/min, 30 sec/fr., PE/EtOAc = 9:1, t_R = 7.0 min). The ketone **259** (70.4 mg, 360 μmol, 72% yield) was obtained as a colorless foam.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.35 (dd, J = 1.7, 7.9 Hz, 2H, Ar-*H*), 7.76 – 7.71 (m, 2H, Ar-*H*), 7.51 (dd, J = 0.9, 8.4 Hz, 2H, Ar-*H*), 7.41 – 7.37 (m, 2H, Ar-*H*); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 177.4 (q, *C*-1), 156.4 (q, 2C, *C*-2), 135.0 (t, 2C, *C*-4), 126.9 (t, 2C, *C*-6), 124.1 (t, 2C, *C*-5), 122.0 (q, 2C, *C*-7), 118.1 (t, 2C, *C*-3).

The analytical data are in accordance with those reported in the literature.[138]

[137] S. Bienz, M. Hesse, *Helv. Chim. Acta.* **1987**, *70*, 2146-2151.
[138] T. Ramani, P. Umadevi, K. L. Prasanth, B. Sreedhar, *Eur. J. Org. Chem.* **2013**, *2013*, 6021-6026.

(2*S*,5*R*)-2-Isopropyl-5-methylcyclohexan-1-one (360)



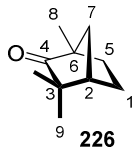
360

The title compound was prepared according to the general procedure except that 8.00 formal equiv. of polymer **201** were used. (1*R*,2*S*,5*R*)-(−)-Menthol served as starting material. After 19 h, the product was purified using preparative gas chromatography (*c* (crude sample) = 52 mg/mL; *T*-program: 90 °C – 30 °C / min – 150 °C – 8 °C / min – 220 °C – 45 °C / min – 280 °C – iso 4 min; t_R = 7.307) in order to obtain 2.00 mg of pure product for analytical investigations. The ketone **360** (61.8 mg, 401 μmol, 80% yield) was obtained as a colorless oil.

$[\alpha]_D^{28.6}$: - 19.6° (*c* 0.12, $CHCl_3$) {Lit.[139] $[\alpha]_D^{20}$: - 23.1° (*c* 5.18, $CHCl_3$)}; **^{1}H-NMR** ($CDCl_3$, 600 MHz): δ [ppm] 2.37 – 2.34 (m, 1H, *H*-5), 2.17 – 2.11 (m, 1H, *H*-5), 2.08 – 2.02 (m, 2H *H*-3, *H*-1/*H*-2), 2.00 – 1.96 (m, 1H, *H*-6), 1.92 – 1.83 (m, 2H, *H*-9, *H*-1/*H*-2), 1.40 – 1.32 (m, 2H, *H*-1/*H*-2), 1.01 (d, *J* = 6.4 Hz, 3H, *H*-7), 0.92 (d, *J* = 6.8 Hz, 3H, *H*-8), 0.86 (d, *J* = 6.8 Hz, 3H, *H*-8); **^{13}C-NMR** ($CDCl_3$, 150 MHz): δ [ppm] 212.6 (q, *C*-4), 56.1 (t, *C*-3), 51.0 (s, *C*-5), 35.6 (s, *C*-1), 34.1 (t, *C*-6), 28.0 (t, C-9), 26.1 (s, *C*-2), 22.4 (p, *C*-7), 21.4 (p, *C*-8), 18.9 (p, *C*-8).

The analytical data are in accordance with those reported in the literature.[139]

(1*R*,4*S*)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2-one (226)



226

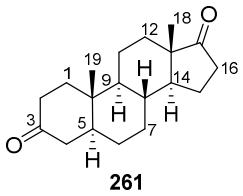
The title compound was prepared according to the general procedure with (1*R*)-*endo*-(+)-fenchyl alcohol as starting material. After 6 h, the product was purified using flash column chromatography (pentane/EtOAc = 1:0 → 1:1). Ketone **226** (75.1 mg, 494 μmol, 99% yield) was obtained as a colorless foam.

R_f = 0.65 (toluene/EtOAc = 9:1); **$[\alpha]_D^{24.3}$**: - 41.5° (*c* 3.0, acetone), {Lit.[140] $[\alpha]_D^{20}$: - 44° (*c* 1.0, hexane)}; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ [ppm] 2.14 – 2.13 (m, 1H, *H*-2), 1.81 – 1.79 (m, 1H, *H*-7), 1.79 – 1.67 (m, 2H, *H*-1), 1.59 – 1.55 (m, 1H, *H*-5), 1.54 – 1.51 (m, 1H, *H*-7), 1.42 – 1.34 (m, 1H, *H*-5), 1.14 (s, 3H, *H*-8), 1.03 (s, 6H, *H*-9); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 223.6 (q, *C*-4), 54.3 (q, *C*-6), 47.5 (q, *C*-3), 45.5 (t, *C*-2), 41.8 (s, *C*-7), 32.0 (s, *C*-5), 25.1 (s, *C*-1), 23.5 (p, *C*-9), 21.9 (p, *C*-9), 14.8 (p, *C*-8); **GCMS** (t_R = 9.350 min) *m/z* calculated for $C_{10}H_{16}O$ $[M]^+$ 152.1; found 152.0.

The analytical data are in accordance with those reported in the literature.[140]

[139] P. W. Moore, C. D. G. Read, P. V. Bernhardt, C. M. Williams, *Chemistry* **2018**, *24*, 4556–4561.
[140] E. Kolehmainen, K. Laihia, J. Korvola, R. Kauppinen, M. Pitkänen, B. Mannila, E. Mannila, *Magn. Reson. Chem.* **1990**, *28*, 812-816.

(5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-Dimethyltetradecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17(2*H*)-dione (261)



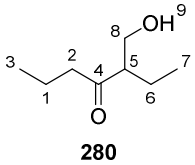
261

The title compound was prepared according to the general procedure with (5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*) - 17 - hydroxy - 10, 13 - dimethylhexadeca-hydro-3*H*-cyclopenta[*a*]phen-anthren-3-one as starting material. After 19 h, the product was then purified using flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 30/40, t_R = 14.0 min). Oxidation product **261** (132 mg, 457 μmol, 91% yield) was obtained as a colorless foam.

$[\alpha]_D^{28.6}$: + 111.3° (*c* 0.15, MeOH), {Lit.[141] $[\alpha]_D^{20}$: + 112.5° (*c* 0.2, EtOH)} **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ [ppm] 2.46 – 2.22 (m, 4H, *H*-2, *H*-4, *H*-16), 2.11 – 1.89 (m, 4H, *H*-1, *H*-2, *H*-9, *H*-15), 1.83 – 1.78 (m, 2H, *H*-16), 1.69 – 1.47 (m, 4H, *H*-5, *H*-8, *H*-11, *H*-15), 1.41 – 1.20 (m, 6H, *H*-1, *H*-6, *H*-7, *H*-14), 1.04 – 0.93 (m, 4H, *H*-12, *H*-18), 0.86 (s, 3H, *H*-19), 0.81 – 0.74 (m, 1H, *H*-12); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 221.0 (q, *C*-17), 211.7 (q, *C*-3), 54.0 (t, *C*-14), 51.3 (t, *C*-9), 47.8 (q, *C*-13), 46.7 (t, *C*-5), 44.7 (s, *C*-4), 38.5 (s, *C*-2), 38.2 (s, *C*-1), 35.9 (q, *C*-10), 35.9 (s, *C*-16), 35.0 (t, *C*-8), 31.6 (s, *C*-7), 30.6 (s, *C*-12), 28.7 (s, *C*-6), 21.9 (s, *C*-15), 20.8 (s, *C*-11), 13.9 (p, *C*-19), 11.5 (p, *C*-18).

The analytical data are in accordance with those reported in the literature.[141]

3-(Hydroxymethyl)heptan-4-one (280)



280

The title compound was prepared according to the general procedure with 2-ethylhexane-1,3-diol as starting material. After 20 h, the product was purified using flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 30/40; t_R = 13.0 min). Ketone **280** (63.3 mg, 439 μmol, 88% yield) was obtained as a colorless oil.

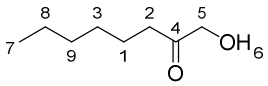
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 3.79 (dd, *J* = 11.0, 7.4 Hz, 1H, *H*-8), 3.69 (dd, *J* = 10.9, 4.2 Hz, 1H, *H*-8), 2.65 – 2.59 (m, 1H, *H*-5), 2.47 (t, *J* = 7.2 Hz, 2H, *H*-2), 2.01 (br, 1H, *H*-9), 1.69 – 1.49 (m, 4H, *H*-1, *H*-6), 0.94 – 0.89 (m, 6H, *H*-3, *H*-7); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm]

[141] a) Saifullah, Azizuddin, S. Khan, K. Ali, M. I. Choudhary, *Chem. Nat. Compd.* **2014**, *50*, 669-672; b) M. S. Yusubov, P. S. Postnikov, R. Y. Yusubova, A. Yoshimura, G. Jürjens, A. Kirschning, V. V. Zhdankin, *Adv. Synth. Catal.* **2017**, *359*, 3207-3216.

215.3 (q, *C*-4), 62.6 (s, *C*-8), 55.1 (t, *C*-5), 44.9 (s, *C*-2), 21.4 (s, *C*-7), 17.0 (s, *C*-1), 13.9 (p, *C*-3), 12.0 (p, *C*-7); **HRMS** (ESI) *m/z* calculated for $C_8H_{16}O_2Na$ $[M+Na]^+$ 167.1048; found 167.1046.

The analytical data are in accordance with those reported in the literature.[142]

1-Hydroxyoctan-2-one (282)



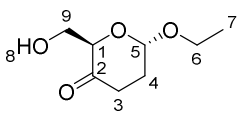
282

The title compound was prepared according to the general procedure with octane-1,2-diol as starting material. After 20 h, the product was purified using flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 30/50; t_R = 9.0 min). Ketone **282** (59.5 mg, 412 μmol, 83% yield) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 4.24 (s, 2H, *H*-5), 3.12 (br, 1H, *H*-6), 2.40 (t, *J* = 7.6 Hz, 2H, *H*-2), 1.64 – 1.59 (m, 2H, *H*-1), 1.30 – 1.28 (m, 6H, CH_2), 0.88 (t, *J* = 6.4 Hz, 3H, *H*-7); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 210.1 (q, *C*-4), 68.2 (s, *C*-5), 38.6 (s, *C*-2), 31.6 (s, *C*-9), 29.0 (s, *C*-3), 23.8 (s, *C*-1), 22.6 (s, *C*-8), 14.1 (p, *C*-7).

The analytical data are in accordance with those reported in the literature.[143]

(2*R*,6*S*)-6-Ethoxy-2-(hydroxymethyl)dihydro-2*H*-pyran-3(4*H*)-one (284)



284

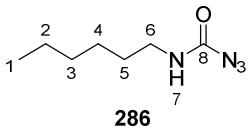
The title compound was prepared according to the general procedure with (2*R*,3*S*,6*S*)- 6-ethoxy- 2-(hydroxymethyl)tetrahydro- 2*H*-pyran- 3-ol. After 20 h, the product was purified using flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/40; 30/60; t_R = 7.0 min). Ketone **284** (62.9 mg, 361 μmol, 72% yield) was obtained as a colorless oil.

$[\alpha]_D^{23.8}$: + 78.2° (*c* 0.28, MeOH); **^{1}H-NMR** ($CDCl_3$, 600 MHz): δ [ppm] 5.07 (t, *J* = 4.3 Hz, 1H, *H*-5), 4.19 (t, *J* = 4.6 Hz, 1H, *H*-1), 3.93 – 3.84 (m, 2H, *H*-9), 3.83 – 3.78 (m, 1H, *H*-6), 3.61 – 3.54 (m, 1H, *H*-6), 2.64 – 2.58 (m, 1H, *H*-3), 2.48 – 2.42 (m, 1H, *H*-3), 2.32 – 2.25 (m, 1H, *H*-4), 2.06 – 2.00 (m, 1H, *H*-4), 1.26 – 1.25 (m, 3H, *H*-7); **^{13}C-NMR** ($CDCl_3$, 150 MHz): δ [ppm] 210.1 (q, *C*-2),

[142] C. Kuhakarn, K. Kittigowittana, M. Pohmakotr, V. Reutrakul, *Tetrahedron* **2005**, *61*, 8995-9000.
[143] J. M. William, M. Kuriyama, O. Onomura, *Adv. Synth. Catal.* **2014**, *356*, 934-940.

96.4 (t, *C*-5), 74.9 (t, *C*-1), 63.5 (s, *C*-6), 61.8 (s, *C*-9), 34.4 (s, *C*-3), 29.0 (s, *C*-4), 15.2 (p, *C*-7); **HRMS** (ESI) *m/z* calculated for $C_8H_{14}O4Na$ $[M+Na]^+$ 197.0790; found 197.0791.

Hexylcarbamoyl azide (286)



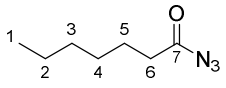
286

The title compound was prepared according to the general procedure with heptanol as starting material. After 21 h, the product was purified by flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 10.0 mL/min, 30 sec/fr., PE/EtOAc = 91:9, t_R = 8.0 min). Ketone **286** (62.9 mg, 361 μmol, 72% yield) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 5.10 (s, 1H, *H*-7), 3.23 (q, J = 6.8 Hz, 2H, *H*-6), 1.52 – 1.46 (m, 2H, *H*-5), 1.34 – 1.26 (m, 6H, 3xCH_2), 0.88 (t, 3H, *H*-1); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 156.5 (q, *C*-8), 41.3 (s, *C*-6), 31.5 (s, CH_2), 29.6 (s, CH_2), 26.5 (s, CH_2), 22.6 (s, CH_2), 14.1 (p, *C*-1); **IR** ν_{max} [cm^{-1}] 2137 $\nu(N_3)$; **HRMS** (ESI) *m/z* calculated for $C_7H_{14}N_4O$ $[M+H]^+$ 170.1168; found 170.1167.

The analytical data are in accordance with those reported in the literature.[144]

Heptanoyl azide (288)



288

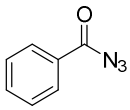
The title compound was prepared according to the general procedure using heptanal as starting material. After 18 h, the ketone **288** (69.8 mg, 450 μmol, 90% yield) was obtained as a yellow oil. Heptanoyl azide was found to be very unstable (being in accordance with hexanoyl azide which is reported in literature[145]), therefore only crude NMR- and IR-spectra are given.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 2.36 – 2.23 (m, 2H, *H*-6), 1.65 – 1.56 (m, 2H, *H*-5), 1.29 (m, 6H, 3xCH_2), 0.88 – 0.87 (m, 3H, *H*-1); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 179.1 (q, *C*-7), 34.0 (s, *C*-6), 31.6 (s, CH_2), 28.9 (s, CH_2), 24.8 (s, CH_2), 22.6 (s, CH_2), 14.1 (p, *C*-1); **IR** ν_{max} [cm^{-1}] 2137 $\nu(N_3)$; **GCMS** (t_R = 13.806 min) *m/z* calculated for $C_7H_{13}N_3O$ $[M-N_2]^+$ 127.1; found 127.1; $[M-N_3]^+$ 113.1; found 113.1; $[M-ON_3]^+$ 97.1; found 97.1

[144] X.-Q. Li, X.-F. Zhao, C. Zhang, *Synthesis* **2008**, *16*, 2589-2593.

[145] S. Azeez, P. Chaudhary, P. Sureshbabu, S. Sabiah, J. Kandasamy, *Org. Biomol. Chem.* **2018**, *16*, 8280-8285.

Benzoyl azide (290)



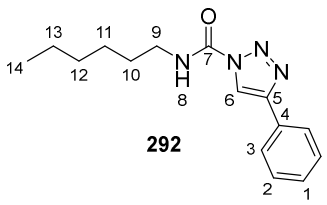
290

The title compound was prepared according to the general procedure with benzyl alcohol as starting material. After 48 h, the product was purified by flash column chromatography (NP-BÜCHI, solvent: PE, 15x150 mm column, flow rate: 10.0 mL/min, 30 sec/fr., t_R = 8.0 min). Ketone **290** (61.0 mg, 415 μmol, 83% yield) was afforded as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.04 – 8.02 (m, 2H, Ar-*H*), 7.64 – 7.60 (m, 2H, Ar-*H*), 7.48 – 7.44 (m, 2H, Ar-*H*); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 172.7 (q, *C*=O), 134.5 (t, Ar-*C*), 130.8 (q, Ar-*C*), 129.6 (t, Ar-*C*), 128.8 (t, Ar-*C*); **IR** ν_{max} [cm^{-1}] 2137 ν(N_3).

The analytical data are in accordance with those reported in the literature.[146]

***N*-Hexyl-4-phenyl-1*H*-1,2,3-triazole-1-carboxamide (292)**



292

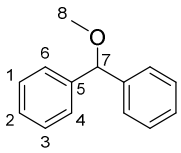
A mixture of hexylcarbamoyl azide (**286**, 45.7 mg, 268 μmol, 1.00 equiv.) and phenylacetylene (35.4 μL, 322 μmol, 1.20 equiv.) was stirred in a 1:1 mixture of *tert*-butyl alcohol and water (1.07 mL) at ambient temperature. Sodium ascorbate (26.8 μmol, 26.8 μL of freshly prepared 1M solution in H_2O, 0.10 equiv.) was added, followed by copper (II) sulfate pentahydrate (669 mg, 2.68 μmol, in 500 μL H_2O, 0.01 equiv.). After 20 h, the reaction was terminated by addition of H_2O and extracted with EtOAc (3x 5.00 mL). The combined organic extracts were washed with brine (1x 50.0 mL), dried with $MgSO_4$ and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 10.0 mL/min, 30 sec/fr., PE/EtOAc = 9:1, t_R = 10.0 min) afforded triazole **292** (55.5 mg, 204 μmol, 76% yield) as a colorless foam.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.47 (s, 1H, *H*-6), 7.89 – 7.86 (m, 2H, Ar-*H*), 7.48 – 7.44 (m, 2H, Ar-*H*), 7.40 – 7.36 (m, 1H, Ar-*H*), 3.54 – 3.49 (m, 2H, *H*-9), 1.69 (p, *J* = 7.3 Hz, 2H, *H*-10), 1.44 – 1.31 (m, 6H, 3xCH_2), 0.90 (t, *J* = 7.1 Hz, 3H, *H*-14); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 148.4 (q, *C-7*), 147.4 (t, *C*-6), 129.6 (q, Ar-*C*), 129.1 (t, 2C, Ar-*C*), 128.9 (q, Ar-*C*), 126.1 (t, 2C, Ar-*C*), 117.9 (q, *C*-5). 41.0 (s, *C*-9), 31.5 (s, CH_2), 29.5 (s, CH_2), 26.6 (s, CH_2), 22.7 (s, CH_2), 14.1 (p, *C*-14).

[146] A. G. Bakhoda, Q. Jiang, Y. M. Badiei, J. A. Bertke, T. R. Cundari, T. H. Warren, *Angew. Chem. Int. Ed.* **2019**, *58*, 3421-3425.

MS methods (ESI, EI, APCI, GC) were performed to collect mass data, but without success.

(Methoxymethylene)dibenzene (267)



267

To a mixture of diphenylmethanol (1.00 g, 5.40 mmol, 1.00 equiv.) and Ag_2O (1.50 g, 6.48 mmol, 1.20 equiv.) in CH_2Cl_2 (8.00 mL) at 0 °C, MeI (1.12 mL, 6.48 mmol, 3.30 equiv.) was added. After 67 h at ambient temperature, the reaction was terminated by filtering through Celite™. It was washed with excess CH_2Cl_2. The solvent was removed under reduced pressure. Purification by flash column chromatography (NP-BÜCHI, solvent: CH_2Cl_2, 15x150 mm column, flow rate: 10.0 mL/min, 30 sec/fr., t_R = 3.0 min) afforded dibenzene **267** (301 mg, 1.52 mmol, 28% yield) as a colorless foam.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.35 – 7.30 (m, 8H, Ar-*H*), 7.25 – 7.21 (m, 2H, Ar-*H*), 5.23 (s, 1H, *H*-7), 3.37 (s, 3H, *H*-8); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 142.2 (q, 2C, *C*-5), 128.5 (t, 2C, Ar-*C*), 127.6 (t, 2C, Ar-*C*), 127.0 (t, 2C, Ar-*C*), 85.6 (t, *C*-7), 57.1 (p, *C*-8).

The analytical data are in accordance with those reported in the literature.[147]

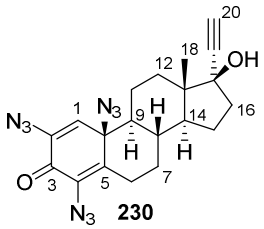
E3.3 Iodination and Oxidative Azidation of Phenols

E3.3.1 Azidation of Phenols – General procedure

A mixture of phenol (0.50 mmol, 1.00 equiv.) and polymer-bound iodine azide **201** (1.19 g, 2.50 mmol, 5.00 equiv.) was stirred in absolute MeCN (4.16 mL, 3.50 mL/g polymer) at ambient temperature under an argon atmosphere. After the full consumption of the starting material was monitored by TLC the reaction was terminated by filtration, the resin was washed with EtOAc and the combined filtrates were concentrated under reduced pressure.

[147] C. Wu, Z. Bao, X. Xu, J. Wang, *Org. Biomol. Chem*. **2019**, *17*, 5714-5724.

(8*S*,9*S*,13*S*,14*S*,17*R*)-2,4,10-Triazido-17-ethynyl-17-hydroxy-13-methyl-6,7,8,9,10,11, 12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one (230)



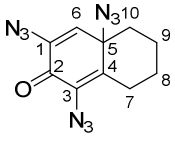
230

A mixture of ethinylestradiol (200 mg, 675 μmol, 1.00 equiv.) and polymer **201** (5.00 equiv. with respect to substrate) was stirred at 300 rpm under light protection in absolute MeCN (3.50 mL/g polymer) at room temperature under an argon atmosphere. After 60 h the reaction was terminated by filtration and the resin was washed with CH_2Cl_2 (3 x 20 mL/g polymer). The filtrate was washed a 5% sodium thiosulfate solution (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. Purification by flash column chromatography (NP-BÜCHI, solvent A: toluene, solvent B: EtOAc, 15x150 mm column, flow rate: 10.0 mL/min, 60 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/5; 30/25; t_R = 6.0 min) afforded dienone **230** (269 mg, 641 μmmol, 95% yield) as a brown oil.[104]

R_f = 0.26 (toluene/EtOAc = 9:1); $[\alpha]_D^{29.4}$: - 7.3° (*c* 0.12, CH_2Cl_2); **^{1}H-NMR** ($CDCl_3$, 600 MHz): δ [ppm] 6.57 (s, 1H, *H*-1), 3.10 – 3.07 (m, 1H, *H*-6), 2.53 (s, 1H, *H*-20), 2.31 – 2.26 (m, 1H, *H*-16), 2.23 – 2.18 (m, 12H, *H*-6), 2.02 – 1.97 (m, 1H, *H*-16), 1.94 – 1.90 (m, 1H, *H*-7), 1.82 – 1.77 (m, 2H, *H*-8/*H*-11/*H*-15), 1.75 – 1.63 (m, 4H, *H*-7/*H*-12/*H*-11/*H*-15), 1.46 – 1.41 (m, 1H, *H*-14), 1.39 – 1.34 (m, 1H, *H*-11/*H*-15), 1.20 – 1.16 (m, 1H, *H*-9), 1.05 – 0.98 (m, 1H, *H*-7), 0.91 (s, 3H, *H*-18); **^{13}C-NMR** ($CDCl_3$, 150 MHz): δ [ppm] 176.1 (q, *C*-3), 145.4 (q, *C*-5), 135.1 (q, *C*-2), 129.7 (q, *C*-4), 128.7 (t, *C*-1), 87.1 (q, *C*-19), 79.6 (q, *C*-17), 74.4 (t, *C*-20), 66.2 (q, *C*-10), 53.9 (t, *C*-9), 48.9 (t, *C*-14), 46.9 (q, *C*-13), 38.9 (s, *C*-16), 32.1 (s, *C*-12), 31.8 (s, *C*-7), 26.5 (s, *C*-6), 23.3 (s, *C*-11/*C*-15), 23.2 (s, *C*-11/*C*-15), 12.7 (p, *C*-18); **HRMS** (ESI) *m/z* calculated for $C_{20}H_{20}N_9O_2$ $[M-H]^-$ 418.1740; found 418.1744; **IR** ν_{max} [cm^{-1}] 2110, 2093 ν(N_3), 1661 ν(C=O), 1603, 1333, 1315, 1292, 1263, 1213, 1057, 735, 656.[104]

The analytical data are consistent with those reported in the literature.[104]

1,3,4*a*-Triazido-5,6,7,8-tetrahydronaphthalen-2(4*aH*)-one (314)



314

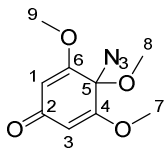
The title compound was prepared according to the general procedure using 5,6,7,8-tetrahydronaphthalen-2-ol as starting material. After 3 h, dienone **314** (120 mg, 444 μmol, 89% yield) was obtained as a yellow foam.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 6.26 (s, 1H, *H*-6), 3.04 (d, *J* = 13.8 Hz, 1H, *H*-7), 2.16 – 2.08 (m, 1H, *H*-7), 2.04 – 2.00 (m, 1H, *H*-10), 2.00 – 1.96 (m, 1H, *H*-8), 1.79 – 1.72 (m, 1H, *H*-9), 1.68 – 1.65 (m, 1H, *H*-9), 1.41 – 1.33 (m, 1H, *H*-10), 1.28 – 1.23 (m, 1H, *H*-8); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 176.7 (q, *C*-2), 143.9 (q, *C*-4), 134.7 (q, *C*-1), 130.0 (t, *C*-6), 129.8 (q, *C*-3),

63.2 (q, *C*-5), 38.7 (s, *C*-10), 26.6 (s, *C*-7), 26.3 (s, *C*-8), 20.7 (s, *C*-9); **IR** ν_{max} [cm^{-1}] 2941, 2862, 2091 $\nu(N_3)$, 1659 ν(C=O), 1605, 1435, 1339, 1325, 1310, 1202, 1167, 1136, 1078, 1051, 964, 939, 926, 895, 876, 781, 671, 650, 556, 528.

MS methods (ESI, EI, APCI, GC) were performed to collect mass data, but without success.

4-Azido-3,4,5-trimethoxycyclohexa-2,5-dien-1-one (315)

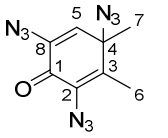


315

The title compound was prepared according to the general procedure using 3,4,5-trimethoxyphenol as starting material. After 2.5 h, dienone **315** (108 mg, 479 μmol, 96% yield) was obtained as a yellow foam.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 5.51 (s, 2H, *H*-1, *H*-3), 3.77 (s, 6H, *H*-7, *H*-9), 3.18 (s, 3H, *H*-8); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 185.5 (q, *C*-2), 165.3 (q, 2C, *C*-4, *C*-6), 103.2 (t, 2C, *C*-1, *C*-3), 85.2 (q, *C*-5), 56.5 (p, 2C, *C*-7, *C*-9), 53.0 (p, *C*-8); **ESI-MS** (ESI) *m/z* calculated for $C_9H_{11}N_3O_4Na$ $[M+Na]^+$ 248.0647; found 248.0644; **IR** ν_{max} [cm^{-1}] 2116 $\nu(N_3)$, 1663 ν(C=O), 1630, 1605, 1458, 1360, 1335, 1246, 1211, 1148, 1105, 1049, 1007, 912, 856, 727, 646, 627, 604, 554, 469.

2,4,6-Triazido-3,4-dimethylcyclohexa-2,5-dien-1-one (316)



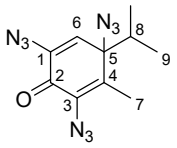
316

The title compound was prepared according to the general procedure using 3,4-dimethylphenol as starting material. After 2 h, dienone **316** (107 mg, 437 μmol, 87% yield) was obtained as a yellow foam.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 6.31 (s, 1H, *H*-5), 2.02 (s, 3H, *H*-6), 1.41 (s, 3H, *H*-7); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 176.2 (q, *C*-1), 141.8 (q, *C*-3), 134.2 (q, *C*-8), 131.6 (q, *C*-2), 130.5 (t, *C*-5), 63.2 (q, *C*-4), 25.0 (p, *C*-7), 14.3 (p, *C*-6); **IR** ν_{max} [cm^{-1}] 2114 $\nu(N_3)$, 1600-1700 ν(C=O), 1489, 1451, 1327, 1258, 1045, 928, 527, 467, 407.

Various MS methods (ESI, EI, APCI, GC) were performed to collect mass data, but without success.

2,4,6-Triazido-4-isopropyl-3-methylcyclohexa-2,5-dien-1-one (317)



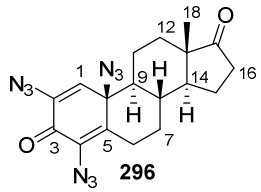
317

The title compound was prepared according to the general procedure with 3-methyl-4-isopropylphenol as starting material. After 2 h, the reaction was terminated. Purification by flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 18/0; 30/20; t_R = 5.0 - 6.0 min) afforded dienone **317** (103 mg, 375 μmol, 75% yield) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 6.32 (s, 1H, *H*-6), 2.08 (p, *J* = 6.9 Hz, 1H, *H*-8), 1.98 (s, 3H, *H*-7), 1.09 (d, 3H, *J* = 6.8 Hz, *H*-9), 0.65 (d, 3H, *J* = 6.9 Hz, *H*-9); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 176.3 (q, *C*-2), 142.1 (q, *C*-4), 136.5 (q, *C*-1), 132.9 (q, *C*-3), 126.0 (t, *C*-6), 70.5 (q, *C*-5), 35.4 (t, *C*-8), 17.3 (p, *C*-9), 16.8 (p, *C*-9), 14.0 (p, *C*-7), **IR** ν_{max} [cm^{-1}] 2968, 2112 $\nu(N_3)$, 1662 ν(C=O), 1645, 1602 ν(C=O), 1464, 1389, 1368, 1327, 1209, 1032, 941, 885, 739, 671, 532, 411.

Various MS methods (ESI, EI, APCI, GC) were performed to collect mass data, but without success.

(8*S*,9*S*,10*R*,13*S*,14*S*)-2,4,10-Triazido-13-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17(6*H*)-dione (296)



296

The title compound was prepared according to the general procedure with estrone as starting material. After 2 h, the reaction was terminated. Purification by flash column chromatography (NP-BÜCHI, solvent A: toluene, solvent B: EtOAc, 15x150 mm column, flow rate: 10.0 mL/min, 60 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/5; 30/25; t_R = 5.0 - 14.0 min) afforded dienone **296** (172 mg, 454 μmol, 91% yield) as a colorless solid.

T_M > 150 °C (decomposition); **$[\alpha]_D^{20.0}$**: + 88.3° (*c* 1.0, $CHCl_3$); **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ [ppm] 6.53 (s, 1H, *H*-1), 3.13 – 3.10 (m, 1H, *H*-6), 2.45 (dd, *J* = 19.4, 8.7 Hz, 1H, *H*-16), 2.22 (td, *J* = 13.7, 4.8 Hz, 1H, *H*-6), 2.14 – 2.00 (m, 2H, *H*-7/*H*-12, *H*-16), 1.96 – 1.89 (m, 2H, *H*-8, *H*-15), 1.85 – 1.79 (m, 2H, *H*-11, *H*-7/*H*-12), 1.77 – 1.72 (m, 1H, *H*-11), 1.62 – 1.51 (m, 1H, *H*-15), 1.25 – 1.13 (m, 3H, *H*-9, *H*-14/*H*-7/*H*-12), 1.10 – 1.00 (m, 1H, *H*-7/*H*-12), 0.90 (s, 3H, *H*-18); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 219.7 (q, *C*-17), 175.9 (q, *C*-3l), 144.7 (q, *C*-5), 135.1 (q, *C*-2), 129.8 (q, *C*-4), 128.2 (t, *C*-1), 66.0 (q, *C*-10), 53.9 (t, *C*-9), 49.7 (t, *C*-14), 47.6 (q, *C*-13), 35.6 (s, *C*-16), 35.1 (t, *C*-8), 30.9 (s, *C*-7/*C*-12), 30.8 (s, *C*-7/*C*-12), 26.3 (s, *C*-6), 22.6 (s, *C*-11), 21.9 (s, *C*-15), 13.7 (p, *C*-18); **IR** ν_{max} [cm^{-1}] 2943, 2116, 2095 $\nu(N_3)$, 1736, 1663 ν(C=O), 1603 ν(C=O), 1454, 1339, 1317, 1231, 1063, 1034, 1005, 905, 727, 648, 559.

The structure was unequivocally proven by X-ray crystal analysis. Various MS methods (ESI, EI, APCI, GC) were performed to collect mass data, but without success.

X-ray crystal structure analysis of 296

Determination of the relative configuration of compound **296** was confirmed by X-ray structure analysis using a BRUKER SMART X2S benchtop crystallographic system. The data are deposited at the Cambridge Crystallographic Data Center (CCDC 2049506).

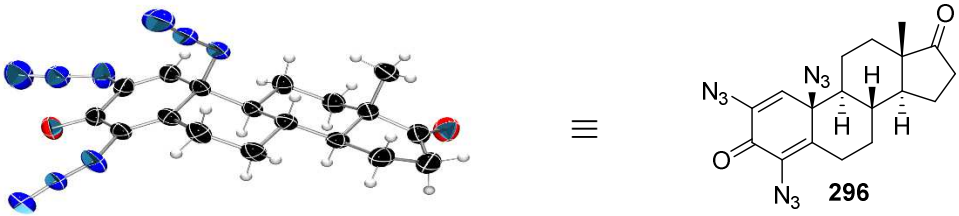


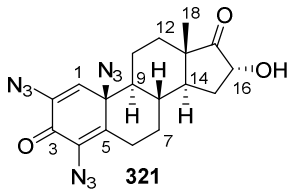
Table 30: Sample and crystal data for **296**.

Identification code	TK287b	
Chemical formula	$C_{18}H_{19}N_9O_2$	
Formula weight	393.42 g/mol	
Temperature	300(2) K	
Wavelength	0.71073 Å	
Crystal size	0.130 x 0.470 x 0.510 mm	
Crystal system	monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 6.7974(12) Å	α = 90°
	b = 13.920(2) Å	β = 91.655(6)°
	c = 9.9497(18) Å	γ = 90°
Volume	941.0(3) $Å^3$	
Z	2	
Density (calculated)	1.388 g/cm^3	
Absorption coefficient	0.098 mm^{-1}	
F(000)	412	

Table 31: Data collection and structure refinement for **296**.

Theta range for data collection	2.52 to 27.80°	
Index ranges	-8<=h<=8, -18<=k<=18, -13<=l<=12	
Reflections collected	21262	
Independent reflections	4350 [R(int) = 0.0843]	
Coverage of independent reflections	98.1%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.9870 and 0.9520	
Structure solution technique	direct methods	
Structure solution program	SHELXT 2014/5 (Sheldrick, 2014)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2018/3 (Sheldrick, 2018)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	4350 / 1 / 263	
Goodness-of-fit on F^2	0.866	
Final R indices	3248 data; I>2σ(I)	R1 = 0.0486, wR2 = 0.1241
	all data	R1 = 0.0730, wR2 = 0.1413
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.1000P)^2]$ where $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	1.0(10)	
Largest diff. peak and hole	0.238 and -0.179 eÅ^{-3}	
R.M.S. deviation from mean	0.040 eÅ^{-3}	

(8*S*,9*S*,10*R*,13*S*,14*S*,16*R*)-2,4,10-Triazido-16-hydroxy-13-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17(6*H*)-dione (321)

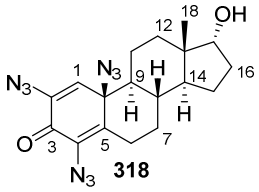


321

The title compound was prepared according to the general procedure using 16*α*-hydroxyestrone (19.2 μmol) as starting material. After 2 h, dienone **321** (3.90 mg, 9.50 μmol, 50% yield) was obtained as a yellow foam.

[*α*]$_D^{24.2}$: + 22.3° (*c* 0.39, $CDCl_3$); **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ [ppm] 6.52 (s, 1H, *H*-1), 4.38 (d, *J* = 8.1 Hz, 1H, *H*-16), 3.16 – 3.12 (m, 1H, *H*-6), 2.22 (td, *J* = 13.8, 5.1 Hz, 1H, *H*-6), 1.99 – 1.86 (m, 5H, *H*-7/*H*-8/*H*-12/*H*-15), 1.82 – 1.76 (m, 2H, *H*-11), 1.49 – 1.42 (m, 1H, *H*-14), 1.38 – 1.31 (m, 1H, *H*-7/*H*-12/*H*-15), 1.21 – 1.15 (m, 1H, *H*-9), 1.07 – 1.04 (m, 1H, *H*-7/*H*-12/*H*-15), 1.02 (s, 3H, *H*-18); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 218.2 (q, *C*-17), 176.0 (q, *C*-3), 144.2 (q, *C*-5), 135.4 (q, *C*-2), 130.1 (q, *C*-4), 127.8 (t, *C*-1), 71.2 (t, *C*-16), 66.0 (q, *C*-10), 53.8 (t, *C*-9), 47.6 (q, *C*-13), 46.8 (t, *C*-14), 35.1 (t, *C*-8), 30.8 (s, *C*-7/*C*-12/*C*-15), 30.7 (s, *C*-7/*C*-12/*C*-15), 30.6 (s, *C*-7/*C*-12/*C*-15), 26.2 (s, *C*-6), 22.2 (s, *C*-11), 14.1 (p, *C*-18); **HRMS** (ESI) *m/z* calculated for $C_{18}H_{18}N_9O_3$ $[M-H]^-$ 408.1533; found 408.1530; **IR** ν_{max} [cm^{-1}] 2114 $\nu(N_3)$, 1748, 1603 ν(C=O), 1339, 1315, 1009, 910, 731, 648, 552, 409.

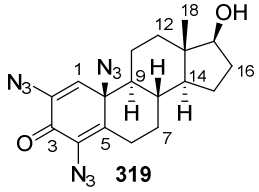
(8*S*,9*S*,13*S*,14*S*,17*R*)-2,4,10-Triazido-17-hydroxy-13-methyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one (318)



The title compound was prepared according to the general procedure using 17α-estradiol (0.30 mmol) as starting material. After 2 h, dienone **318** (90.0 mg, 228 μmol, 76% yield) was obtained as a yellow foam.

[α]$_D^{26.2}$: + 7.5° (*c* 1.6, MeOH); **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ [ppm] 6.57 (s, 1H, *H*-1), 3.75 (d, *J* = 5.7 Hz, 1H, *H*-17), 3.09 – 3.06 (m, 1H, *H*-6), 2.24 – 2.13 (m, 2H, *H*-6, *H*-16), 1.96 – 1.93 (m, 1H, *H*-16), 1.86 – 1.82 (m, 1H, *H*-11), 1.79 – 1.70 (m, 3H, *H*-8, *H*-11, *H*-15), 1.56 – 1.42 (m, 3H, *H*-7, *H*-12), 1.39 – 1.32 (m, 1H, *H*-14), 1.27 – 1.22 (m, 1H, *H*-15), 1.18 – 1.12 (m, 1H, *H*-9), 1.09 – 0.99 (m, 1H, *H*-7), 0.71 (s, 3H, *H*-18); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 176.1 (q, *C*-3), 145.5 (q, *C*-5), 134.9 (q, *C*-2), 129.6 (q, *C*-4), 128.7 (t, *C*-1), 79.6 (t, *C*-17), 66.3 (q, *C*-10), 54.0 (t, *C*-9), 47.3 (t, *C*-14), 45.4 (q, *C*-13), 35.8 (t, *C*-8), 32.6 (s, *C*-7/*C*-16), 32.5 (s, *C*-7/*C*-16), 30.8 (s, *C*-12), 26.7 (s, *C*-6), 24.9 (s, *C*-15), 22.9 (s, *C*-11), 16.9 (p, *C*-18); **HRMS** (ESI) *m/z* calculated for $C_{18}H_{21}N_9O_2Na$ $[M+Na]^+$ 418.1716; found 418.1728; **IR** ν_{max} [cm^{-1}] 2938, 2116 $\nu(N_3)$, 1663 ν(C=O), 1603, 1339, 1317, 1211, 934, 885, 419, 403.

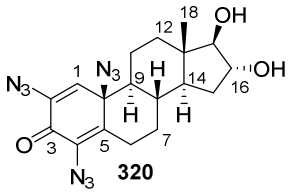
(8*S*,9*S*,13*S*,14*S*,17*S*)-2,4,10-Triazido-17-hydroxy-13-methyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one (319)



The title compound was prepared according to the general procedure using 17β-estradiol as starting material. After 3 h, the dienone **319** (136 mg, 343 μmol, 69% yield) was obtained as a yellow foam.

[α]$_D^{26.8}$: + 33.0° (*c* 0.8, MeOH); **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ [ppm] 6.55 (s, 1H, *H*-1), 3.59 (t, *J* = 8.4 Hz, 1H, *H*-17), 3.07 – 3.04 (m, 1H, *H*-6), 2.22 – 2.14 (m, 1H, *H*-6), 2.08 – 2.03 (m, 1H, *H*-16), 1.91 – 1.73 (m, 4H, *H*-7, *H*-8, *H*-11, *H*-12), 1.66 – 1.64 (m, 1H, *H*-11), 1.58 – 1.56 (m, 1H, *H*-15), 1.48 – 1.40 (m, 1H, *H*-16), 1.34 – 1.26 (m, 1H, *H*-15), 1.10 – 1.03 (m, 2H, *H*-9, *H*-12), 0.95 – 0.87 (m, 2H, *H*-7, *H*-14), 0.78 (s, 3H, *H*-18); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 176.0 (q, *C*-3), 145.5 (q, *C*-5), 134.9 (q, *C*-2), 129.5 (q, *C*-4), 128.7 (t, *C*-1), 81.3 (t, *C*-17), 66.2 (q, *C*-10), 54.2 (t, *C*-9), 49.5 (t, *C*-14), 43.1 (q, *C*-13), 36.0 (s, *C*-12), 35.6 (t, *C*-8), 31.7 (s, *C*-7), 30.4 (s, *C*-16), 26.5 (s, *C*-6), 23.5 (s, *C*-15), 23.0 (s, *C*-11), 11.0 (p, *C*-18); **HRMS** (ESI) *m/z* calculated for $C_{18}H_{20}N_9O_2$ $[M-H]^-$ 394.1740; found 394.1741; **IR** ν_{max} [cm^{-1}] 2943, 2112, 2093 $\nu(N_3)$, 1661 ν(C=O), 1601, 1333, 1314, 1263, 1213, 1055, 939, 895, 864, 735, 704, 656, 559, 656.

(8*S*,9*S*,13*S*,14*S*,16*R*,17*R*)-2,4,10-triazido-16,17-dihydroxy-13-methyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one (320)

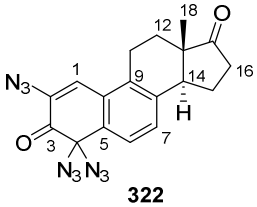


320

The title compound was prepared according to the general procedure using estriol (0.24 mmol) as starting material. After 3.5 h, dienone **320** (31.8 mg, 77.3 μmol, 32% yield) was obtained as a yellow foam.

[α]$_D^{24.2}$: + 22.2° (*c* 0.5, MeOH); **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ [ppm] 6.54 (s, 1H, *H*-1), 4.16 – 4.12 (m, 1H, *H*-16), 3.48 – 3.47 (m, 1H, *H*-17), 3.11 – 3.06 (m, 1H, *H*-6), 2.23 – 2.15 (m, 1H, *H*-6), 1.87 – 1.76 (m, 5H, *H*-7, *H*-8, *H*-11, *H*-12, *H*-15), 1.69 – 1.64 (m, 1H, *H*-11), 1.57 – 1.51 (m, 1H, *H*-15), 1.33 – 1.30 (m, 1H, *H*-14), 1.18 – 1.13 (m, 2H, *H*-9, *H*-12), 1.03 – 0.93 (m, 1H, *H*-7), 0.82 (s, 3H, *H*-18); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 176.1 (q, *C*-3), 145.1 (q, *C*-5), 135.2 (q, *C*-2), 129.8 (q, *C*-4), 128.4 (t, *C*-1), 89.5 (t, *C*-17), 78.5 (t, *C*-16), 66.2 (q, *C*-10), 54.1 (t, *C*-9), 47.4 (t, *C*-14), 43.8 (q, *C*-13), 35.9 (s, *C*-12), 35.1 (t, *C*-8), 34.1 (s, *C*-15), 31.6 (s, *C*-7), 26.5 (s, *C*-6), 22.7 (s, *C*-11), 12.2 (p, *C*-18); **HRMS** (ESI) *m/z* calculated for $C_{18}H_{20}N_9O_3$ $[M-H]^-$ 410.1689; found 410.1687; **IR** ν_{max} [cm^{-1}] 3337, 2936, 2122 $\nu(N_3)$, 1653 ν(C=O), 1339, 1213, 1061, 941, 883, 419.

(13*S*,14*S*)-2,4,4-triazido-13-methyl-11,12,13,14,15,16-hexahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17(4*H*)-dione (322)



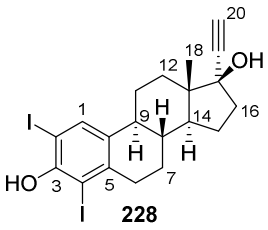
322

The title compound was prepared according to the general procedure using equilenin (93.9 μmol) as starting material. After 3 h, dienone **322** (11.4 mg, 29.3 μmol, 31% yield) was obtained as a yellow foam.

[α]$_D^{25.8}$: + 20.8° (*c* 0.4, EtOH); **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ [ppm] 8.47 (s, 1H, *H*-1), 7.57 (d, *J* = 19.4, 7.4 Hz, 1H, *H*-6), 7.30 (d, *J* = 7.4 Hz, 1H, *H*-7), 3.12 – 3.08 (m, 1H, *H*-11), 3.03 – 2.98 (m, 1H, *H*-14), 2.74 – 2.67 (m, 2H, *H*-11, *H*-16), 2.53 – 2.36 (m, 2H, *H*-15, *H*-16), 2.15 – 2.09 (m, 1H, *H*-12), 2.02 – 1.96 (m, 1H, *H*-15), 1.90 – 1.86 (m, 1H, *H*-12), 0.74 (s, 3H, *H*-18); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 218.4 (q, *C*-17), 186.96 (q, *C*-3), 150.3 (t, *C*-1), 141.5 (q, Ar-*C*), 135.4 (q, Ar-*C*), 135.3 (q, Ar-*C*), 132.7 (q, Ar-*C*), 128.3 (q, Ar-*C*), 128.2 (t, *C*-7), 126.1 (t, *C*-6), 96.1 (q, *C*-4), 46.8 (t, *C*-14), 46.7 (s, *C*-13), 36.4 (s, *C*-16), 28.7 (s, *C*-12), 23.9 (s, *C*-11), 21.5 (s, *C*-16), 13.8 (p, *C*-18); **IR** ν_{max} [cm^{-1}] 2922, 2104 $\nu(N_3)$, 1738, 1699 ν(C=O), 1460, 1406, 1346, 1069, 909, 731, 648, 552.

Various MS methods (ESI, EI, APCI, GC) were performed to collect mass data, but without success.

(8*R*,9*S*,13*S*,14*S*,17*R*)-17-Ethynyl-2,4-diiodo-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*α*]phenanthrene-3,17-diol (228)



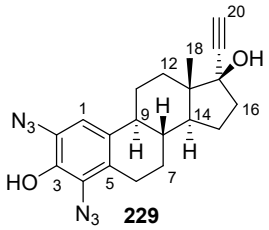
228

A mixture of ethinylestradiol (300 mg, 1.01 mmol, 1.00 equiv.) and polymer-bound iodine azide **201** (1.92 g, 4.04 mmol, 4.00 equiv.) was stirred at 805 rpm in dry and degassed MeCN (6.70 mL) at 83 °C. After 4 h the reaction was terminated by filtration and the resin was washed with CH_2Cl_2 (3 x 20.0 mL/g resin). The filtrate was washed with a 5% sodium thiosulfate solution (10.0 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. Purification by preparative HPLC (solvent A: water + 0.1% FA, solvent B: MeCN + 0.1% FA, flow rate: 15.0 mL/min, gradient: (*t* [min]/solvent B [%]): 0/5; 80/100; 100/100; t_R = 57.0 min) afforded diiodide **228** (221 mg, 404 μmol, 20% yield) as a brown oil.[104]

R_f = 0.38 (toluene/EtOAc = 9:1); $[\alpha]_D^{28.5}$: – 1.5 ° (*c* 0.2, CH_2Cl_2); **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ [ppm] 7.63 (s, 1H, *H*-1), 2.83 – 2.77 (m, 1H, *H*-6), 2.67 – 2.62 (m, 1H, *H*-6), 2.61 (s, 1H, *H*-20), 2.38 – 2.33 (m, 1H, *H*-16), 2.33 – 2.28 (m, 1H, *H*-11), 2.25 – 2.20 (m, 1H, *H*-9), 2.07 – 1.99 (m, 1H, *H*-16), 1.97 – 1.93 (m, 1H, *H*-7), 1.91 – 1.86 (m, 1H, *H*-12), 1.82 – 1.77 (m, 1H, *H*-15), 1.75 – 1.71 (m, 1H, *H*-12), 1.68 – 1.63 (m, 1H, *H*-14), 1.52 – 1.37 (m, 3H, *H*-8, *H*-11, *H*-15), 1.37 – 1.31 (m, 1H, *H*-7), 0.87 (s, 3H, *H*-18); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 151.4 (q, *C*-3), 140.9 (q, *C*-10), 136.6 (q, *C*-5), 136.0 (t, *C*-1), 92.2 (q, *C*-4), 87.4 (q, *C*-2), 79.9 (q, *C*-19), 78.4 (q, *C*-17), 74.4 (t, *C*-20), 49.3 (t, *C*-14), 47.1 (q, *C*-13), 43.6 (t, *C*-9), 39.1 (s, *C*-16), 38.5 (t, *C*-8), 37.3 (s, *C*-6), 32.7 (s, *C*-12), 28.1 (s, *C*-7), 26.8 (s, *C*-11), 22.9 (s, *C*-15), 12.7 (p, *C*-18); **HRMS** (ESI) *m/z* calculated for $C_{20}H_{21}I_2O_2$ $[M-H]^-$ 546.9631; found 546.9630.[104]

The analytical data are consistent with those reported in the literature.[104]

(8*R*,9*S*,13*S*,14*S*,17*R*)-2,4-Diazido-17-ethynyl-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*α*]phenanthrene-3,17-diol (229)



229

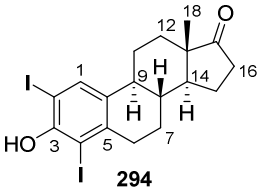
A mixture of ethinylestradiol (300 mg, 1.01 mmol, 1.00 equiv.) and polymer-bound iodine azide **201** (1.92 g, 4.04 mmol, 4.00 equiv.) was stirred at 805 rpm in dry and degassed MeCN (6.70 mL) at 83 °C under an argon atmosphere. After 4 h the reaction was terminated by filtration and the resin was washed with CH_2Cl_2 (3 x 20.0 mL/g resin). The filtrate was washed with a 5% sodium thiosulfate solution (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and purification by preparative HPLC (solvent A: water + 0.1% FA, solvent B:

MeCN + 0.1% FA; flow rate: 15.0 mL/min; gradient: (*t* [min]/solvent B [%]): 0/5; 80/100; 100/100; t_R = 62.0 min) afforded steroid **229** (138 mg, 364 μmol, 17% yield) as a brown oil.[104]

R_f = 0.34 (toluene/EtOAc = 9:1); $[\alpha]_D^{29.5}$: – 1.5 ° (*c* 0.13, CH_2Cl_2); **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ [ppm] 6.82 (s, 1H, *H*-1), 2.82 (dd, *J* = 17.9, 5.5 Hz, 1H, *H*-6), 2.60 (s, 1H, *H*-20), 2.58 – 2.51 (m, 1H, *H*-6), 2.38 – 2.28 (m, 2H, *H*-11, *H*-16), 2.21 – 2.15 (m, 1H, *H*-9), 2.07 – 1.99 (m, 1H, *H*-16), 1.94 – 1.91 (m, 1H, *H*-7), 1.91 – 1.87 (m, 1H, *H*-12), 1.81 – 1.73 (m, 1H, *H*-15), 1.73 – 1.68 (m, 1H, *H*-12), 1.68 – 1.64 (m, 1H, *H*-14), 1.52 – 1.40 (m, 3H, *H*-8, *H*-11, *H*-16), 1.35 – 1.30 (m, 1H, *H*-7), 0.88 (s, 3H, *H*-18); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 139.6 (q, *C*-3), 133.9 (q, *C*-10), 127.4 (q, *C*-5), 125.1 (q, *C*-4), 123.9 (q, *C*-2), 111.5 (t, *C*-1), 87.5 (q, *C*-19), 79.9 (q, *C*-17), 74.3 (t, *C*-20), 49.5 (t, *C*-14), 47.1 (q, *C*-13), 43.7 (t, *C*-9), 39.1 (s, *C*-16), 38.7 (t, *C*-8), 32.7 (s, *C*-12), 26.8 (s, *C*-7), 26.7 (s, *C*-11), 25.4 (s, *C*-6), 22.9 (s, *C*-15), 12.8 (p, *C*-18); **HRMS** (ESI) *m/z* calculated for $C_{20}H_{21}N_6O_2$ $[M-H]^-$ 377.1726; found 377.1723; **IR** ν_{max} [cm^{-1}] 2924, 2108 (N_3), 1490, 1325, 1261, 1051, 1020, 735, 702, 659.[104]

The analytical data are consistent with those reported in the literature.[104]

(8*R*,9*S*,13*S*,14*S*)-3-hydroxy-2,4-diiodo-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]-phenanthren-17-one (294)



294

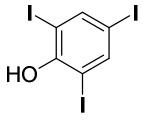
To a mixture of estrone (200 mg, 739 μmol, 1.00 equiv.) in TFA (10.0 mL), NIS (350 mg, 1.55 mmol, 2.10 equiv.) was added and the reaction was stirred at ambient temperature. After 4 h, the mixture was poured onto H_2O (100 mL) and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with a saturated solution of sodium thiosulfate and water and dried over $MgSO_4$. Purification by flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/10; 30/15; t_R = 3.5 - 11.0 min) afforded diiodide **294** (216 mg, 414 μmol, 56% yield) as a colorless solid.

T_M = 220 °C; $[\alpha]_D^{22.7}$: + 101.5° (*c* 0.4, CH_2Cl_2); **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ [ppm] 7.62 (s, 1H, *H*-1), 5.78 (s, 1H, O*H*), 2.89 – 2.83 (m, 1H, *H*-6), 2.72 – 2.63 (m, 1H, *H*-6), 2.55 – 2.48 (m, 1H, *H*-16), 2.38 – 2.34 (m, 1H, *H*-11), 2.30 – 2.21 (m, 1H, *H*-9), 2.20 – 2.13 (m, 1H, *H*-16), 2.11 – 2.05 (m, 2H, *H*-7, *H*-15), 1.98 – 1.94 (m, 1H, *H*-12), 1.66 – 1.60 (m, 1H, *H*-15), 1.52 – 1.47 (m, 4H, *H*-8, *H*-11, *H*-12, *H*-14), 1.43 – 1.36 (m, 1H, *H*-7), 0.90 (s, 3H, *H*-18); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 220.6 (q, *C*-17), 151.6 (q, *C*-3), 140.8 (q, *C*-5), 136.1 (t/q, *C*-1/*C*-10), 136.0 (t/q, *C*-1/*C*-10), 92.1 (q, *C*-4), 78.5 (q, *C*-2), 50.3 (t, *C*-14), 47.9 (q, *C*-13), 44.0 (t, *C*-9), 37.5 (t, *C*-8), 37.2 (s, *C*-6),

35.9 (s, *C*-16), 31.5 (s, *C*-12), 27.4 (s, *C*-7), 26.4 (s, *C*-11), 21.7 (s, *C*-15), 13.9 (p, *C*-18); **HRMS** (ESI) *m/z* calculated for $C_{18}H_{19}I_2O_2$ $[M-H]^-$ 520.9475; found 520.9473.

The analytical data are consistent with those reported in the literature.[148]

2,4,6-Triiodophenol (324)



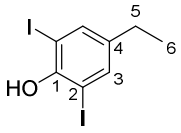
324

The title compound was prepared according to the general procedure with phenol (1.59 mmol) as starting material. After 18 h, triiodophenol **324** (675 mg, 143 μmol, 90% yield) was obtained as a brown solid.

R_f = 0.69 (toluene/EtOAc = 9:1); T_M: 148 °C (Lit.[149]: 152-159 °C); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ [ppm] 7.93 (s, 2H, Ar-*H*), 5.78 (s, 1H, O*H*); **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ [ppm] 153.9 (q, *C*-OH), 146.5 (t, *C*-H), 83.5 (q, *C*-I), 83.4 (q, *C*-I); **HRMS** (ESI) *m/z* calculated for $C_6H_2I_3O$ $[M-H]^-$ 470.7240; found 470.7240.

The analytical data are consistent with those reported in the literature.[149]

4-Ethyl-2,6-diiodophenol (325)



325

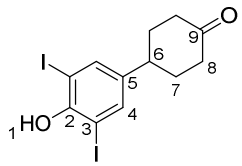
The title compound was prepared according to the general procedure using 4-ethylphenol as starting material. After 24 h, the reaction was terminated. Purification by flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/15; 30/15; t_R = 6.0 – 7.0 min) afforded diiodide **325** as a purple oil (48.3 mg, 129 μmol, 26% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ [ppm] 7.50 (s, 2H, *H*-3), 5.58 (s, 1H, O*H*), 2.52 (q, *J* = 7.6 Hz, 2H, *H*-5), 1.19 (t, *J* = 7.6 Hz, 3H, *H*-6); **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ [ppm] 151.6 (q, *C*-1), 140.5 (q, 2C, *C*-4), 138.7 (t, 2C, *C*-3), 82.2 (q, 2C, *C*-2), 27.2 (s, *C*-5), 15.7 (p, *C*-6); **HRMS** (ESI) *m/z* calculated for $C_8H_7{}^{127}I_2O$ $[M-H]^-$ 372.8586; found 372.8590.

The analytical data are consistent with those reported in the literature.[150]

[148] I. Bacsa, B. E. Herman, R. Jójárt, K. S. Herman, J. Wölfling, G. Schneider, M. Varga, C. Tömböly, T. L. Rižner, M. Szécsi, E. Mernyák, *J. Enzyme Inhib. Med. Chem*. **2018**, *33*, 1271-1282.
[149] Y. Satkar, L. F. Yera-Ledesma, N. Mali, D. Patil, P. Navarro-Santos, L. A. Segura-Quezada, P. I. Ramírez-Morales, C. R. Solorio-Alvarado, *J. Org. Chem.* **2019**, *84*, 4149-4164.
[150] W.-C. Yang, P. Dai, K. Luo, L. Wu, *Adv. Synth. Catal*. **2016**, *358*, 3184-3190.

4-(4-Hydroxy-3,5-diiodophenyl)cyclohexan-1-one (328)

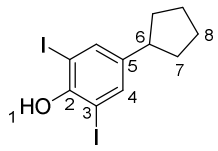


328

The title compound was prepared according to the general procedure using 4-(4-hydroxyphenyl)-cyclohexanone as starting material. After 23 h, the reaction was terminated. Purification by flash column chromatography (NP-BÜCHI, solvent A: toluene, solvent B: EtOAc, 15x150 mm column, flow rate: 10.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/5; 30/25; t_R = 12.0 – 16.5 min) afforded diiodide **328** (53.9 mg, 122 μmol, 24% yield) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ [ppm] 7.55 (s, 2H, *H*-4), 5.67 (s, 1H, *H*-1), 2.90 (tt, *J* = 3.4, 18.3 Hz, 1H, *H*-6), 2.50 – 2.46 (m, 4H, CH_2), 2.21 – 2.14 (m, 2H, CH_2), 1.91 – 1.78 (m, 2H, CH_2); **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ [ppm] 210.4 (q, *C*-9), 152.3 (q, *C*-2), 140.9 (q, *C*-5), 137.5 (t, 2C, *C*-4), 82.4 (q, 2C, *C*-3), 41.09 (s, 4C, *C*-8), 41.06 (t, *C*-6), 33.9 (s, 4C, *C*-7); **HRMS** (ESI) *m/z* calculated for $C_{12}H_{11}I_2O_2$ $[M-H]^-$ 440.8849; found 440.8836.

4-Cyclopentyl-2,6-diiodophenol (326)

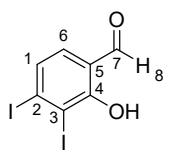


326

The title compound was prepared according to the general procedure using 4-cyclopentylphenol as starting material. After 23 h, the reaction was terminated. Purification by flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 30/15; t_R = 2.5 – 4.5 min) afforded diiodide **326** (80.8 mg, 195 μmol, 39% yield) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ [ppm] 7.52 (s, 2H, *H*-4), 5.58 (s, 1H, *H*-1), 2.88 – 2.80 (m, 1H, *H*-6), 2.05 – 2.98 (m, 2H, CH_2), 1.80 – 1.74 (m, 2H, CH_2), 1.68 – 1.63 (m, 2H, CH_2), 1.52 – 1.44 (m, 2H, CH_2); **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ [ppm] 151.6 (q, *C*-2), 142.9 (q, *C*-5), 138.0 (t, 2C, *C*-4), 82.2 (q, 2C, *C*-3), 44.4 (t, *C*-6), 34.7 (s, 2C, *C*H_2), 25.4 (s, 2C, *C*H_2); **HRMS** (ESI) *m/z* calculated for $C_{11}H_{11}I_2O$ $[M-H]^-$ 412.8899; found 412.8895.

2-Hydroxy-3,4-diiodobenzaldehyde (329)



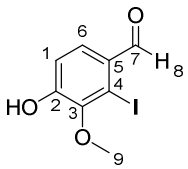
329

The title compound was prepared according to the general procedure using 4-cyclopentylphenol as starting material. After 24 h, the reaction was terminated. Purification by flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 20.0 mL/min, 30 sec/fr.,

PE/EtOAc = 9:1, t_R = 3.0 – 4.0 min) afforded diiodide **329** (99.8 mg, 270 μmol, 53% yield) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ [ppm] 11.72 (s, 1H, O*H*), 9.70 (s, 1H, *H*-8), 8.24 (d, *J* = 2.0 Hz, 1H, *H*-1), 7.83 (d, *J* = 2.1 Hz, 1H, *H*-6); **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ [ppm] 194.9 (q, *C*-7), 160.3 (q, *C*-4), 153.1 (t, *C*-1), 142.2 (t, *C*-6), 122.0 (q, *C*-5), 87.3 (q, *C*-3), 81.3 (q, *C*-2); **HRMS** (ESI) *m/z* calculated for $C_7H_3I_2O_2$ $[M-H]^-$ 372.8223; found 372.8230.

4-Hydroxy-2-iodo-3-methoxybenzaldehyde (330)

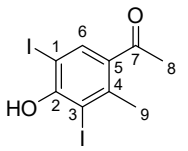


330

The title compound was prepared according to the general procedure using vanillin as starting material. After 3 h, the reaction was terminated. Purification by flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/10; 20/20; 30/20; t_R = 10.0 – 17.0 min) afforded iodide **330** (24.6 mg, 88.5 μmol, 18% yield) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ [ppm] 9.77 (s, 1H, *H*-8), 7.82 (d, *J* = 1.7 Hz, 1H, *H*-1/*H*-6), 7.38 (d, *J* = 1.7 Hz, 1H, *H*-1/*H*-6), 6.69 (br s, 1H, O*H*), 3.97 (s, 3H, *H*-9); **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ [ppm] 189.7 (q, *C*-7), 151.6 (q, *C*-2), 146.6 (q, *C*-3), 136.3 (t, *C*-1/*C*-6), 131.2 (q, *C*-5), 108.8 (t, *C*-1/*C*-6), 80.6 (q, *C*-4), 56.7 (p, *C*-9); **HRMS** (ESI) *m/z* calculated for $C_8H_6IO_3$ $[M-H]^-$ 276.9362; found 276.9353.

1-(4-Hydroxy-3,5-diiodo-2-methylphenyl)ethan-1-one (327)

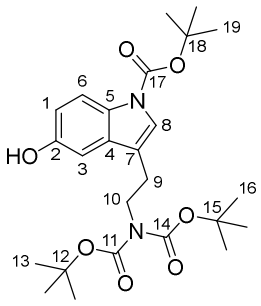


327

The title compound was prepared according to the general procedure using 4-hydroxy-2-methylacetophenon as starting material. After 2 h, iodide **327** (42.0 mg, 104 μmol, 21% yield) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ [ppm] 7.95 (s, 1H, *H*-6), 2.60 (s, 3H, CH_3), 2.54 (s, 3H, CH_3); **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ [ppm] 199.3 (q, *C*-7), 155.8 (q, *C*-2), 143.5 (q, *C*-4), 139.5 (t, *C*-6), 134.4 (q, *C*-5), 95.2 (q, 2C, *C*-1, *C*-3), 29.8 (p, *C*H_3), 27.3 (p, *C*H_3); **HRMS** (ESI) *m/z* calculated for $C_9H_7I_2O_2$ $[M-H]^-$ 400.8536; found 400.8521.

Boc-protected serotonin (396)



396

To a mixture of serotonin (100 mg, 567 μmol, 1.00 equiv.) in MeCN (5.67 mL), Boc_2O (433 mg, 1.99 mmol, 3.50 equiv.) and DMAP (208 mg, 1.70 mmol, 3.00 equiv.) were added and the reaction mixture was stirred for 24 h at ambient temperature. The reaction was terminated by addition of H_2O and extracted with EtOAc (3x). The combined organic extracts were washed with 1M HCl solution (1x) and brine (1x), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 12x150 mm column, flow rate: 20.0 mL/min, 30sec/fr., gradient: (*t* [min]/solvent B [%]): 0/10; 22/10; 22/20; 30/20; t_R = 8.50 – 13.5 min) afforded Boc-protected serotonin **396** (18.4 mg, 38.6 μmol, 7% yield) as a colorless oil.

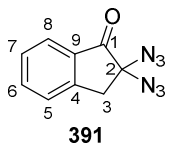
^{1}H-NMR ($CDCl_3$, 400 MHz) δ [ppm] 8.09 (m, 1H, *H*-1/*H*-6), 7.44 (s, 1H, *H*-8), 7.31 – 7.30 (m, 1H, *H*-1/*H*-6), 7.12 – 7.10 (m, 1H, *H*-3), 4.62 (br. s, 1H, O*H*), 3.44 – 3.43 (m, 2H, *H*-10), 2.86 (t, *J* = 6.5 Hz, 2H, *H*-9), 1.66 (s, 9H, *H*-13/*H*-16/*H*-19), 1.57 (s, 9H, *H*-13/*H*-16/*H*-19), 1.44 (s, 9H, *H*-13/*H*-16/*H*-19); **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ [ppm] 156.0 (q, *C*-2/*C*-11/*C*-15/*C*-17), 152.5 (q, *C*-2/*C*-11/*C*-15/*C*-17), 149.6 (q, *C*-2/*C*-11/*C*-15/*C*-17), 146.9 (q, *C*-2/*C*-11/*C*-15/*C*-17), 133.3 (q, *C*-4/*C*-5/*C*-7), 131.2 (q, *C*-4/*C*-5/*C*-7), 124.5 (t, *C*-8), 118.2 (t, *C*-3), 117.9 (q, *C*-4/*C*-5/*C*-7), 116.0 (t, *C*-1/*C*-6), 111.3 (t, *C*-1/*C*-6), 83.9 (q, *C*-12/*C*-15/*C*-18), 83.5 (q, *C*-12/*C*-15/*C*-18), 79.5 (q, *C*-12/*C*-15/*C*-18), 40.2 (s, *C*-10), 28.5 (p, *C*-13/*C*-16/*C*-19), 28.3 (p, *C*-13/*C*-16/*C*-19), 27.9 (p, *C*-13/*C*-16/*C*-19), 25.6 (s, *C*-9); **HRMS** (ESI) *m/z* calculated for $C_{25}H_{36}N_2O7Na$ $[M+Na]^+$ 499.2420; found 499.2413.

E3.4 Azidation of Acylarenes

General procedure

A mixture of the ketone (0.50 mmol, 1.00 equiv.) and polymer-bound iodine azide **201** (952 mg, 2.10 mmol, 4.00 equiv.) was stirred in absolute MeCN (3.33 mL) at 83 °C under an argon atmosphere. After full consumption of the starting material was monitored by TLC, the reaction was terminated by filtration and the resin was washed with EtOAc. Polymer-bound thiosulfate **200** was added to the combined organic phases and the reaction mixture was stirred for 10 min until the solution was nearly colorless. This was filtered through a pad of cotton and concentrated under reduced pressure.

2,2-Diazido-3,4-dihydroinden-1-one (391)



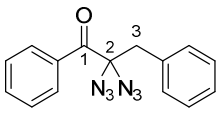
391

The title compound was prepared according to the general procedure with 1-indanone (1.51 mmol) as starting material. After 15 h, diazide **391** (227 mg, 106 μmol, 70% yield) was obtained as a green oil.

R_f = 0.33 (PE/EtOAc = 9:1); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ [ppm] 7.86 – 7.84 (m, 1H, *H*-8), 7.73 – 7.68 (m, 1H, *H*-6), 7.49 – 7.42 (m, 2H, *H*-5, *H*-7), 3.30 (s, 2H, *H*-3); **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ [ppm] 194.9 (s, *C*-1), 149.3 (s, *C*-9), 137.2 (d, *C*-6), 132.1 (s, *C*-4), 128.9 (d, *C*-7), 126.7 (d, *C*-5), 126.0 (d, *C*-8), 80.4 (s, *C*-2), 39.6 (t, *C*-3); **IR** ν_{max} [cm^{-1}] 2099 $\nu(N_3)$.[104]

The analytical data are consistent with those reported in the literature.[151]

2,2-Diazido-1,3-diphenylpropan-1-one (390)



390

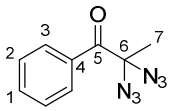
The title compound was prepared according to the general procedure with 1,3-diphenylpropan-1-one as starting material. After 23 h, the product was purified using flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (t [min]/solvent B [%]): 0/0; 30/10; t_R = 7.5 min). Azide **390** (123 mg, 420 μmol, 84% yield) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.04 – 8.01 (m, 2H, Ar-*H*), 7.63 – 7.59 (m, 1H, Ar-*H*), 7.50 – 7.45 (m, 2H, Ar-*H*), 7.31 – 7.28 (m, 3H, Ar-*H*), 7.21 – 7.18 (m, 2H, Ar-*H*), 3.41 (s, 2H, *H*-3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 193.1 (q, *C*-1), 133.9 (t, Ar-*C*), 133.7 (q, Ar-*C*), 132.5 (q, Ar-*C*), 130.8 (t, 2C, Ar-*C*), 130.3 (t, 2C, Ar-*C*), 128.7 (t, 2C, Ar-*C*), 128.6 (t, 2C, Ar-*C*), 128.1 (t, Ar-*C*), 85.8 (q, *C*-2), 43.2 (s, *C*-3).

The analytical data are consistent with those reported in the literature.[151]

[151] D. A. Kamble, P. U. Karabal, P. V. Chouthaiwale, A. Sudalai, *Tetraheron Lett*. **2012**, *53*, 4195-4198.

2,2-Diazido-1-phenylpropan-1-one (385)



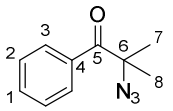
385

The title compound was prepared according to the general procedure with propiophenone as starting material. After 3 d, the product was purified using flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 30/10; t_R = 9.0 min). Diazide **385** (103 mg, 477 μmol, 95% yield) was obtained as a yellow liquid.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ [ppm] 8.13 – 8.11 (m, 2H, Ar-*H*), 7.63 – 7.59 (m, 1H, Ar-*H*), 7.50 – 7.46 (m, 2H, Ar-*H*), 1.86 (s, 3H, *H*-7); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 192.1 (q, *C*-5), 134.0 (q, *C*-4), 132.8 (t, 2C, Ar-*C*), 130.4 (t, 2C, Ar-*C*), 128.7 (t, *C*-1), 83.4 (q, *C*-6), 22.6 (p, *C*-7).

The analytical data are consistent with those reported in the literature.[151]

2-Azido-2-methyl-1-phenylpropan-1-one (388)



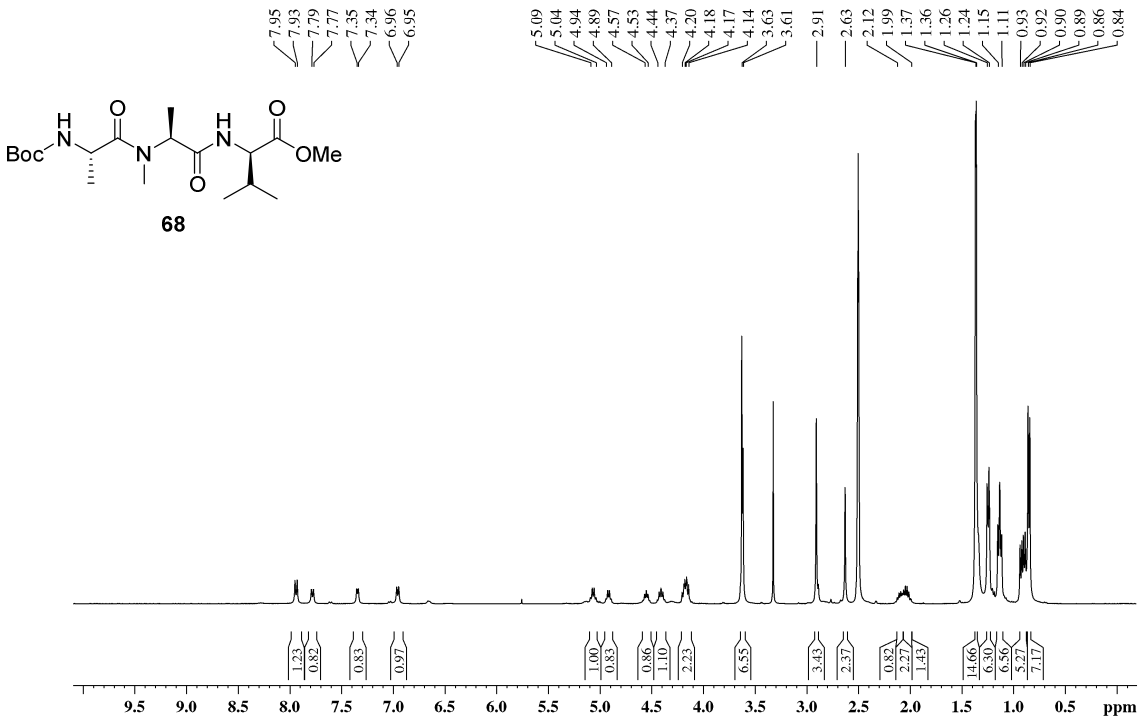
388

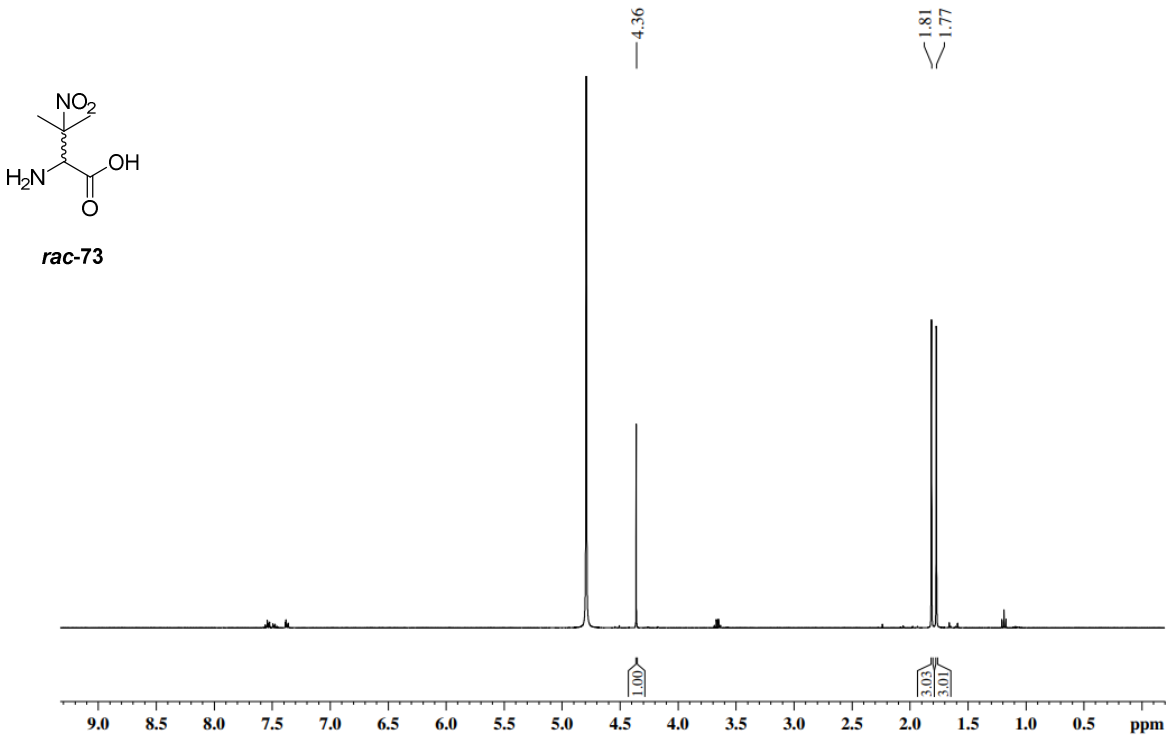
The title compound was prepared according to the general procedure except that 8.00 equiv. of polymer **201** and 6.66 mL MeCN were used. 2-Methyl-1-phenylpropan-1-one served as starting material. After 3 d, the product was purified using flash column chromatography (NP-BÜCHI, solvent A: PE, solvent B: EtOAc, 15x150 mm column, flow rate: 20.0 mL/min, 30 sec/fr., gradient: (*t* [min]/solvent B [%]): 0/0; 30/5; t_R = 10.5 min). Azide **388** (54.2 mg, 287 μmol, 57% yield) was obtained as a yellow oil.

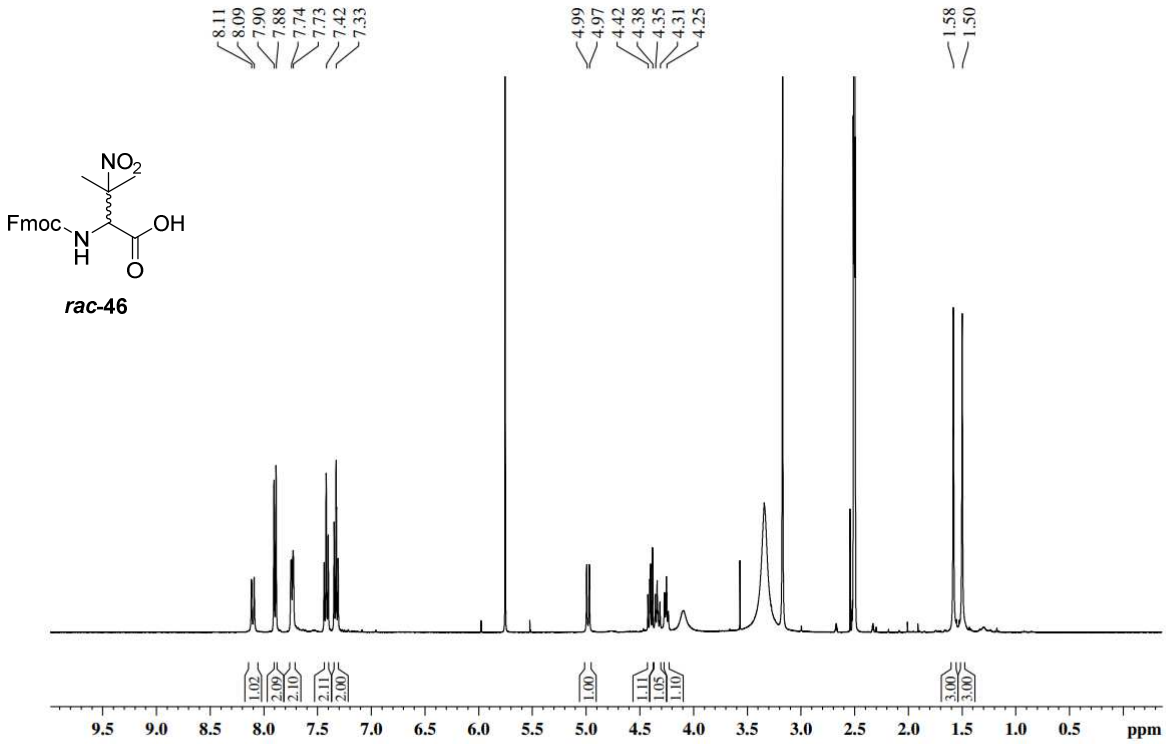
^{1}H-NMR ($CDCl_3$, 600 MHz): δ [ppm] 8.11 – 8.09 (m, 2H, Ar-*H*), 7.57 – 7.55 (m, 1H, Ar-*H*), 7.47 – 7.44 (m, 2H, Ar-*H*), 1.62 (s, 6H, *H*-7, *H*-8); **^{13}C-NMR** ($CDCl_3$, 150 MHz): δ [ppm] 199.6 (q, *C*-5), 134.7 (q, *C*-4), 133.0 (t, *C*-1), 129.9 (t, 2C, Ar-*C*), 128.5 (t, 2C, Ar-*C*), 67.7 (q, *C*-6), 25.1 (p, 2C, *C*-7, *C*-8).

The analytical data are consistent with those reported in the literature.[151]

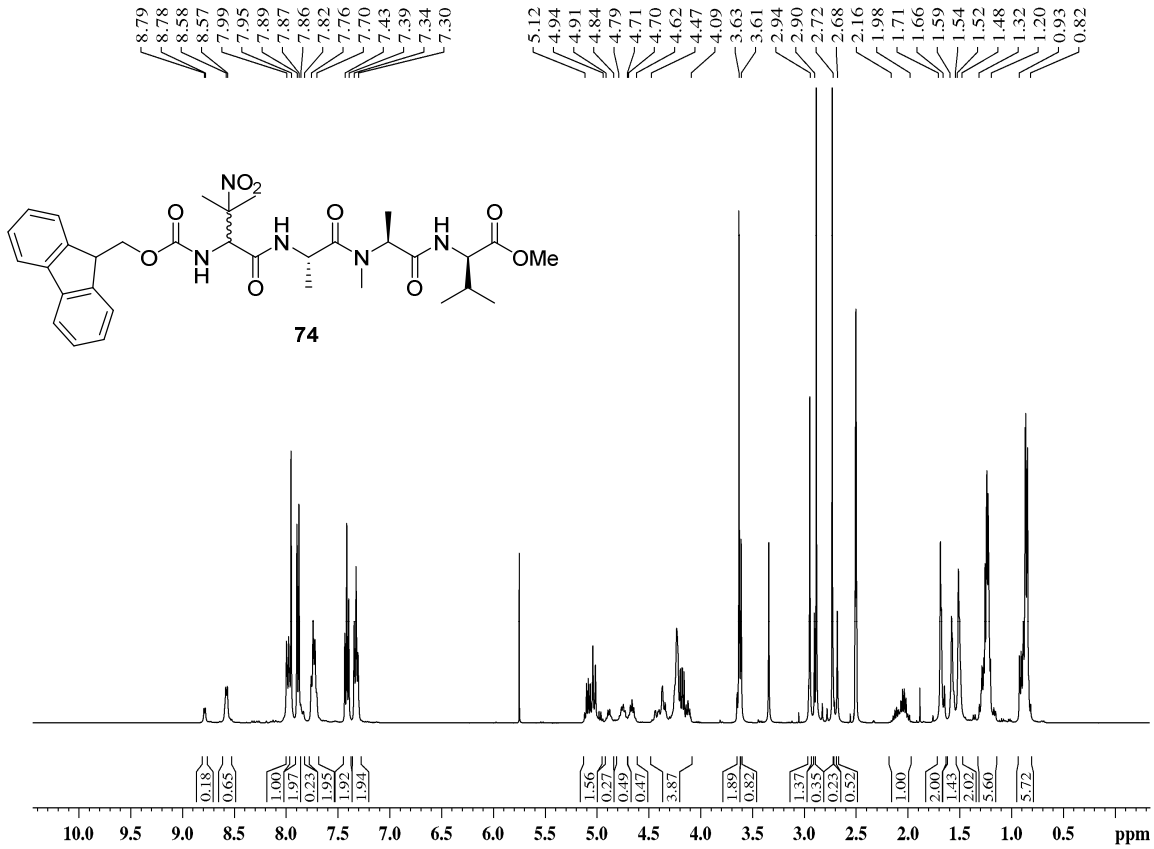
Attachments






8.11
8.09
7.90
7.88
7.74
7.73
7.42
7.33
4.99
4.97
4.42
4.38
4.35
4.31
4.25
1.58
1.50
NO2
Fmoc
N
H
OH
O
1.02
2.00
2.10
2.11
2.00
1.00
1.11
1.05
1.10
3.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

rac-**46**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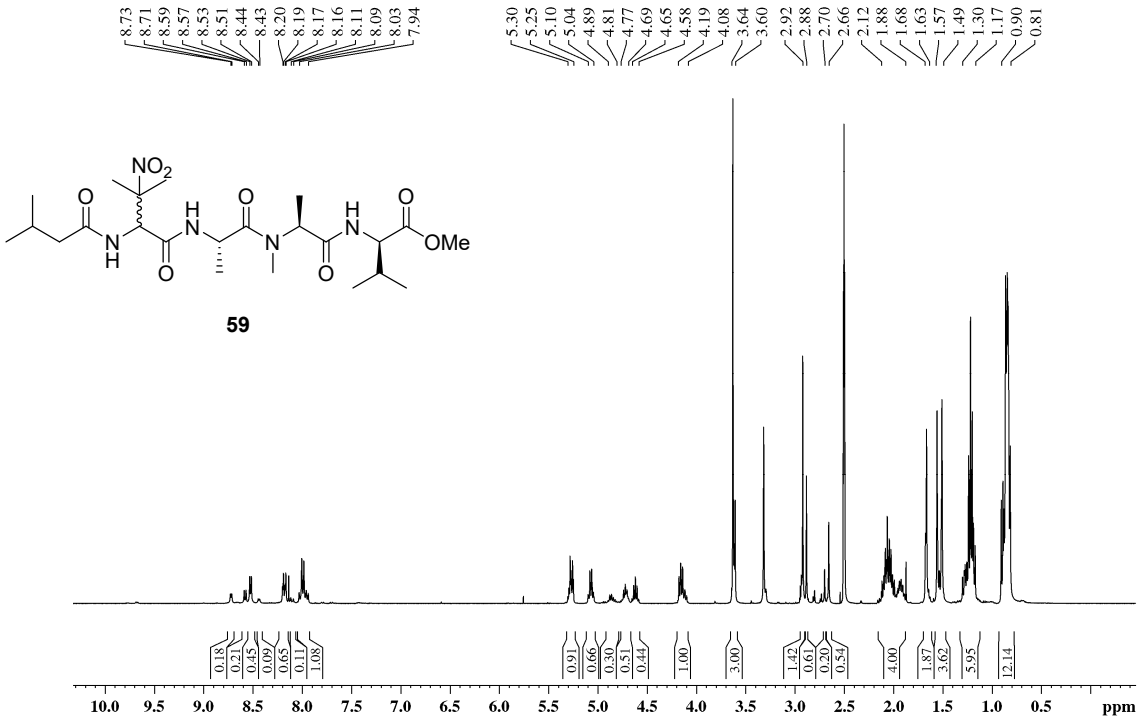
8.78
8.58
8.57
7.99
7.95
7.89
7.87
7.86
7.82
7.76
7.70
7.43
7.39
7.34
7.30
5.12
4.94
4.91
4.84
4.79
4.71
4.70
4.62
4.47
4.09
3.63
3.61
2.94
2.90
2.72
2.68
2.16
1.98
1.71
1.66
1.59
1.54
1.52
1.48
1.32
1.20
0.93
0.82
NO2
O
N
H
O
H
N
O
N
O
H
N
O
OMe
0.18
0.65
1.00
1.97
0.23
1.95
1.92
1.94
1.56
0.27
0.49
0.47
3.87
1.89
0.82
1.37
0.35
0.23
0.52
1.00
2.00
1.43
2.02
5.60
5.72
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

74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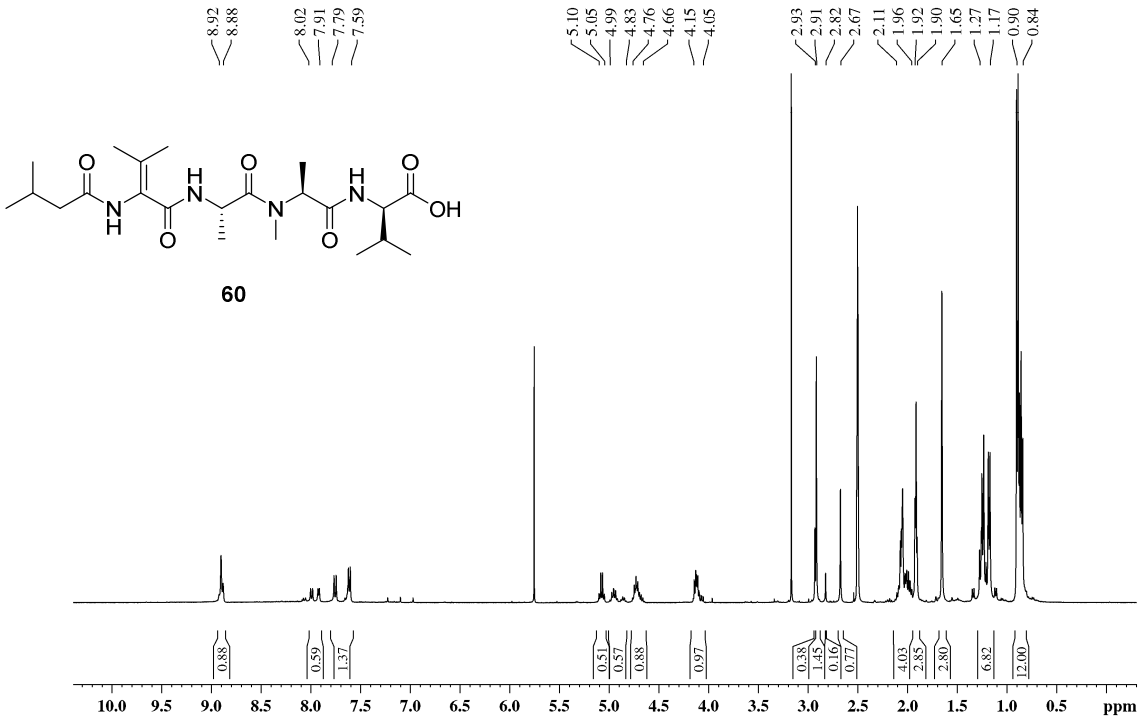
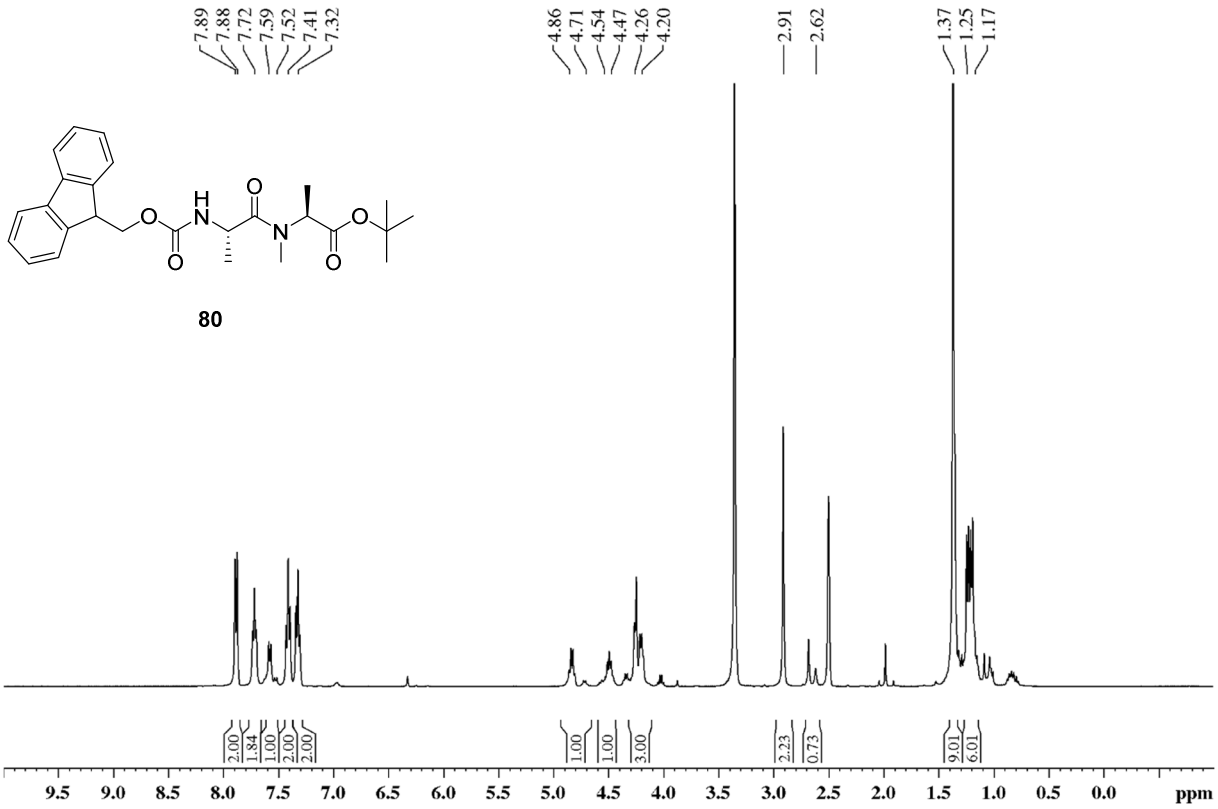
8.71
8.59
8.57
8.53
8.51
8.44
8.43
8.20
8.19
8.17
8.16
8.11
8.09
8.03
7.94
5.30
5.25
5.10
5.04
4.89
4.81
4.77
4.69
4.65
4.58
4.19
4.08
3.64
3.60
2.92
2.88
2.70
2.66
2.12
1.88
1.68
1.63
1.57
1.49
1.30
1.17
0.90
0.81
NO2
O
N
H
O
H
N
O
N
O
H
N
O
OMe
0.18
0.21
0.45
0.09
0.65
0.11
1.08
0.91
0.66
0.30
0.51
0.44
1.00
3.00
1.42
0.61
0.20
0.54
4.00
1.87
3.62
5.95
12.14
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

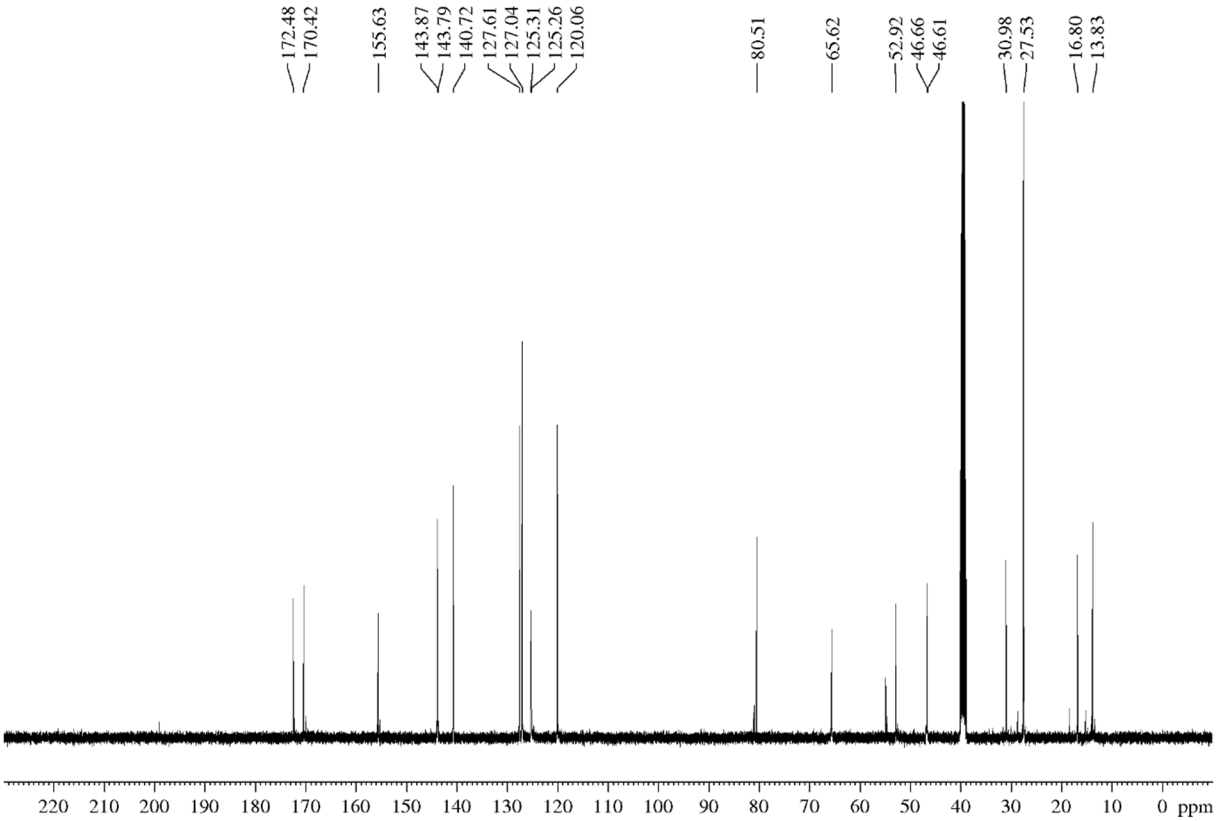
59

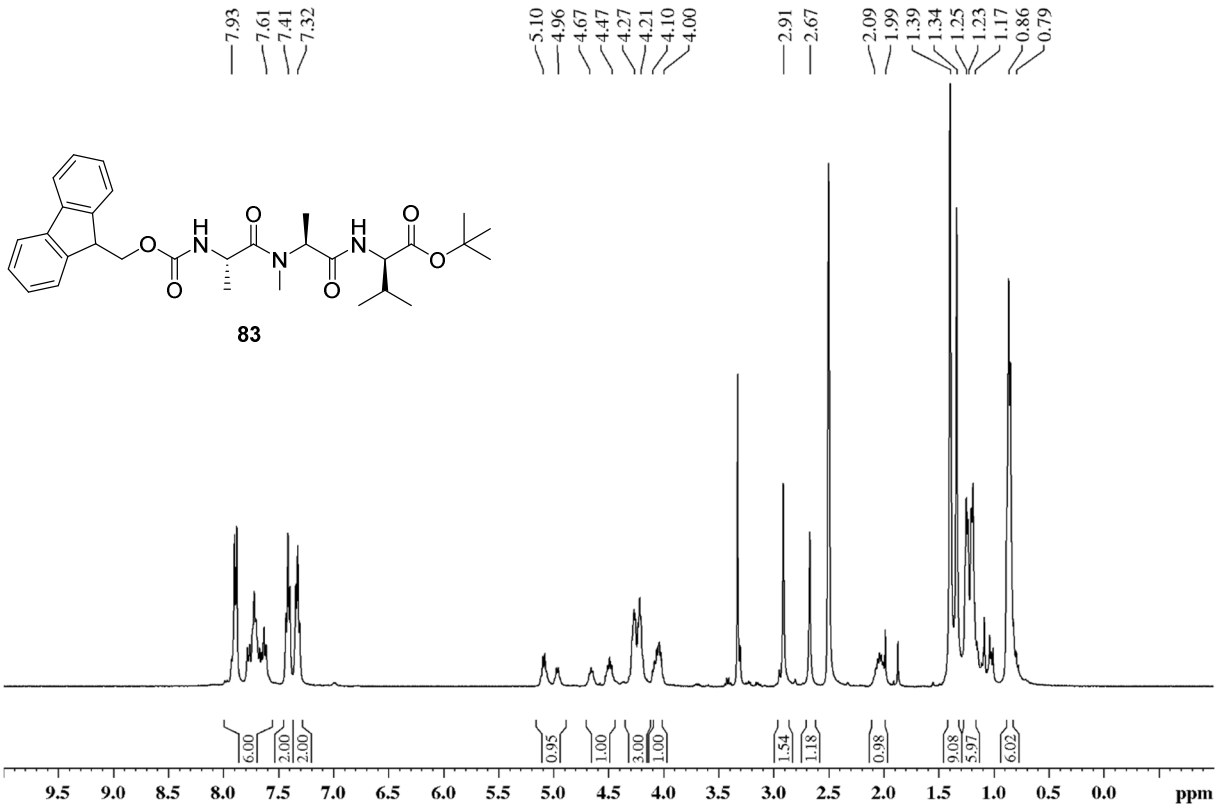

8.92
8.88
8.02
7.91
7.79
7.59
5.10
5.05
4.99
4.83
4.76
4.66
4.15
4.05
2.93
2.91
2.82
2.67
2.11
1.96
1.92
1.90
1.65
1.27
1.17
0.90
0.84
O
N
H
O
H
N
O
N
O
H
N
O
OH
0.88
0.59
1.37
0.51
0.57
0.88
0.97
0.38
1.45
0.16
0.77
4.03
2.85
2.80
6.82
12.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

60

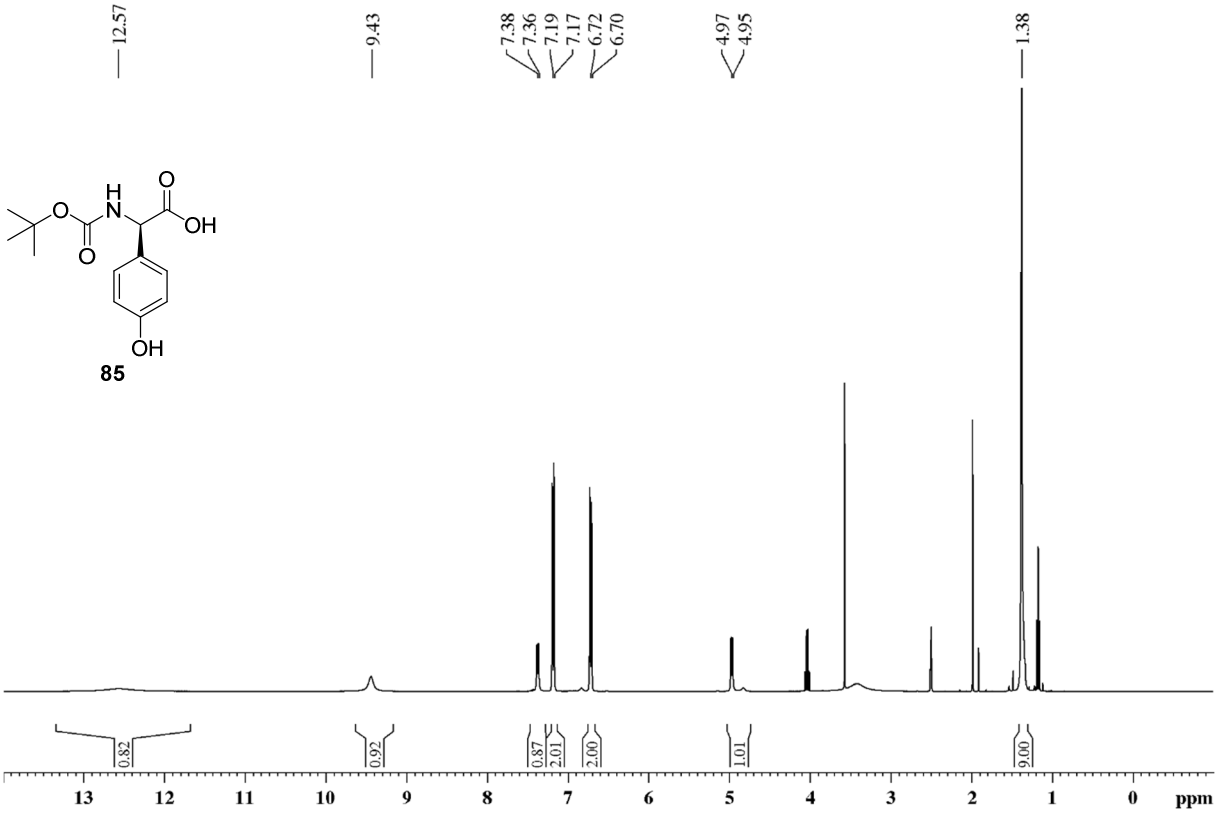

7.89
7.88
7.72
7.59
7.52
7.41
7.32
4.86
4.71
4.54
4.47
4.26
4.20
2.91
2.62
1.37
1.25
1.17
2.00
1.84
1.00
2.00
2.00
1.00
1.00
3.00
2.23
0.73
9.01
6.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

80


172.48
170.42
155.63
143.87
143.79
140.72
127.61
127.04
125.31
125.26
120.06
80.51
65.62
52.92
46.66
46.61
30.98
27.53
16.80
13.83
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.93
7.61
7.41
7.32
5.10
4.96
4.67
4.47
4.27
4.21
4.10
4.00
2.91
2.67
2.09
1.99
1.39
1.34
1.25
1.23
1.17
0.86
0.79
6.00
2.00
2.00
0.95
1.00
3.00
1.00
1.54
1.18
0.98
9.08
5.97
6.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

83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9.43
7.38
7.36
7.19
7.17
6.72
6.70
4.97
4.95
1.38
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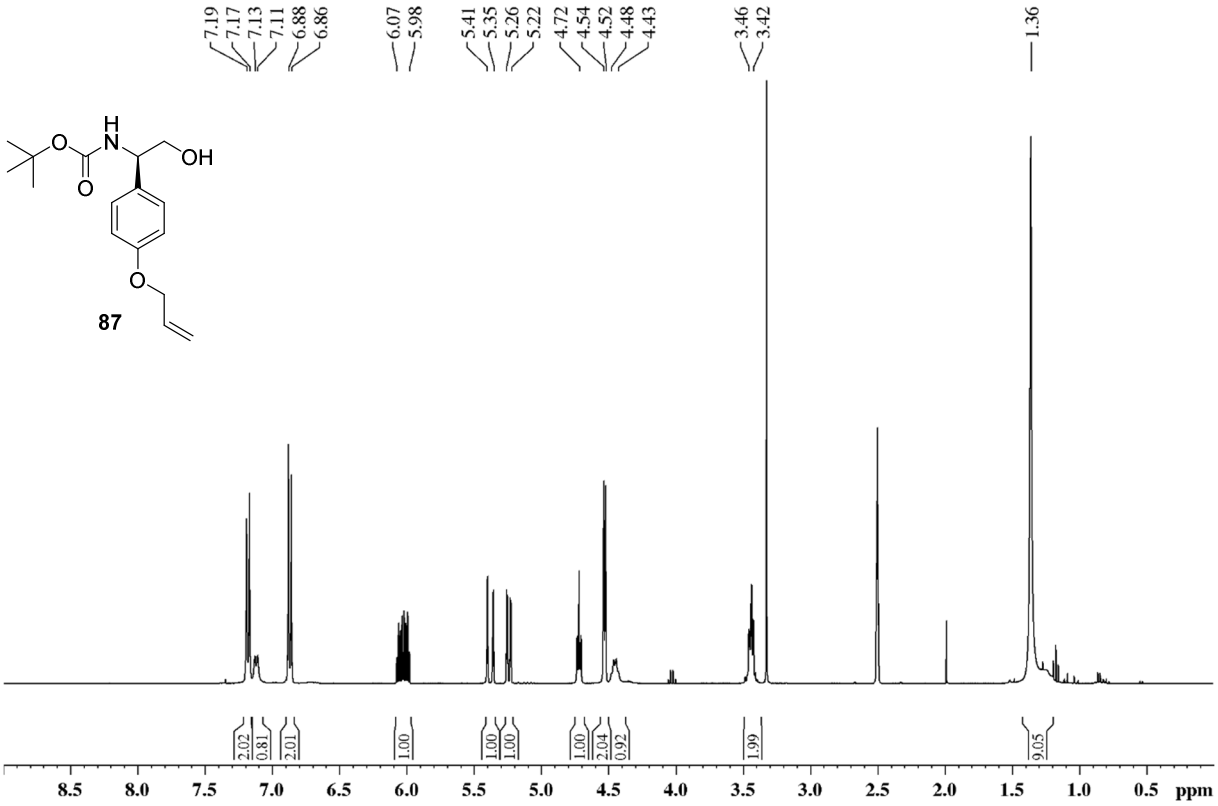
0.92
0.87
2.01
2.00
1.01
9.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0
ppm

85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7.17
7.13
7.11
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6.86
6.07
5.98
5.41
5.35
5.26
5.22
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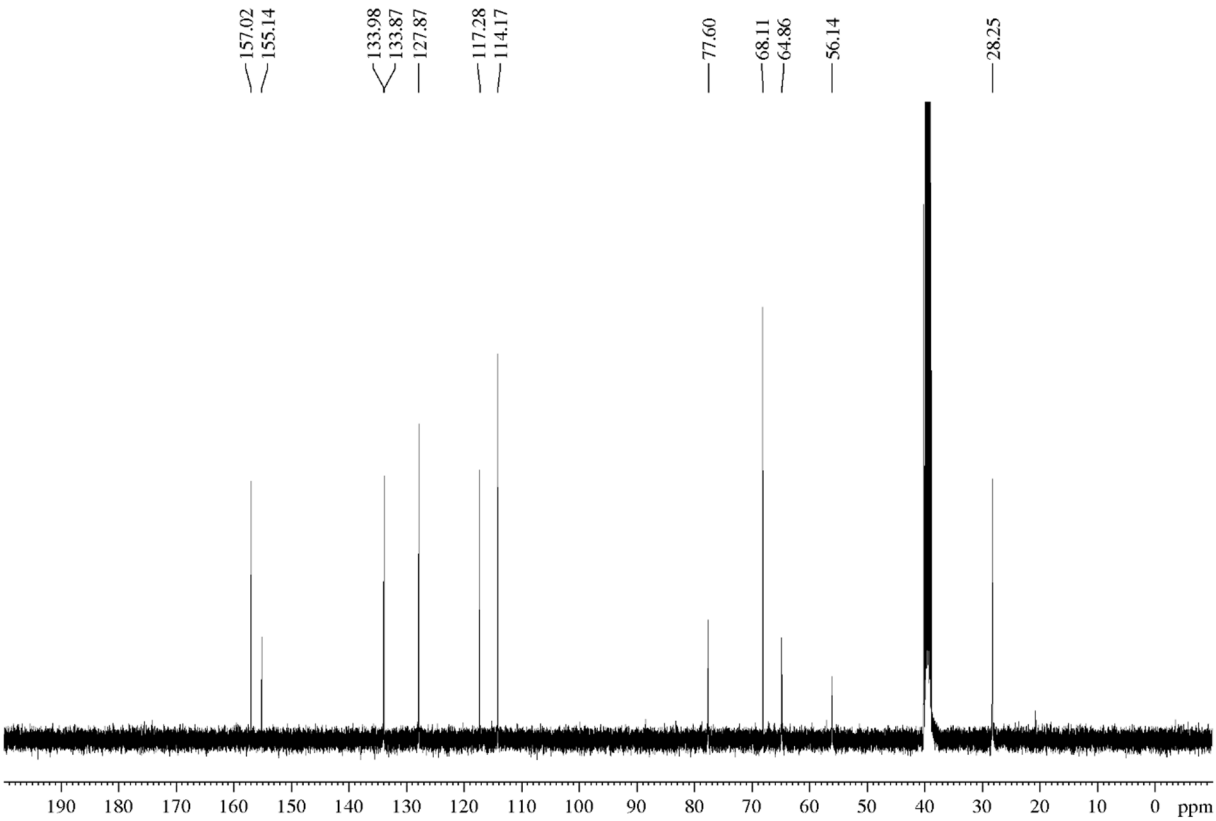
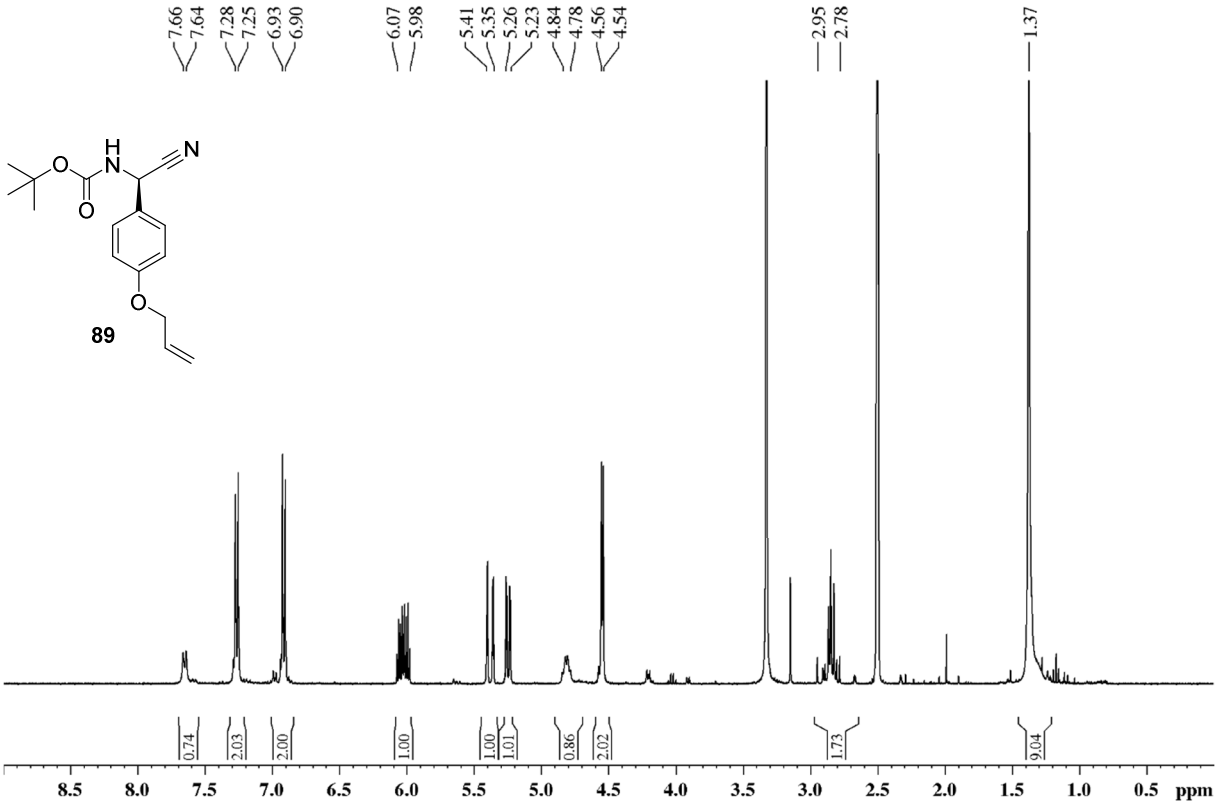
4.54
4.52
4.48
4.43
3.46
3.42
1.36
H
N
O
O
OH
O
87
2.02
0.81
2.01
1.00
1.00
1.00
1.00
2.04
0.92
1.99
9.05
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


157.02
155.14
133.98
133.87
127.87
117.28
114.17
77.60
68.11
64.86
56.14
28.25
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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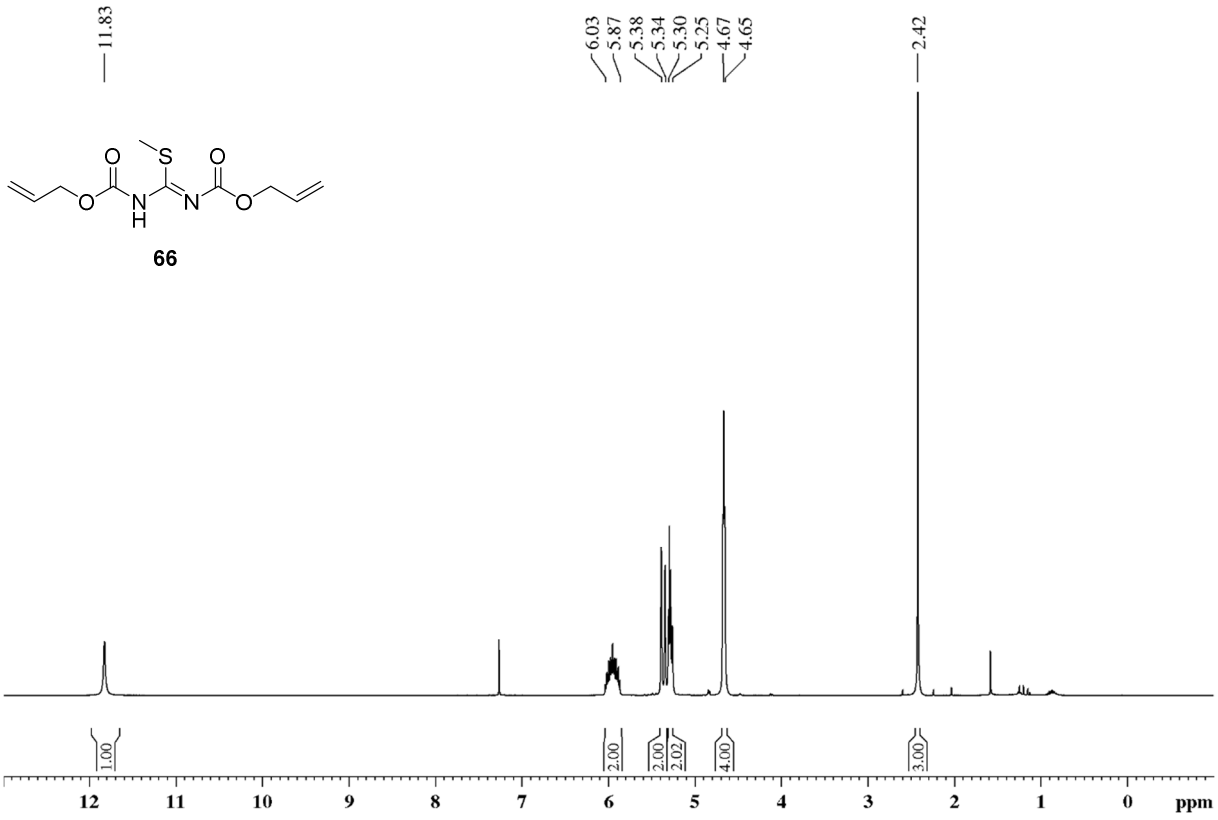
7.64
7.28
7.25
6.93
6.90
6.07
5.98
5.41
5.35
5.26
5.23
4.84
4.78
4.56
4.54
2.95
2.78
1.37
89
0.74
2.03
2.00
1.00
1.00
1.01
0.86
2.02
1.73
9.04
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm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4.67
4.65
2.42
66
1.00
2.00
2.00
2.02
4.00
3.00
12
11
10
9
8
7
6
5
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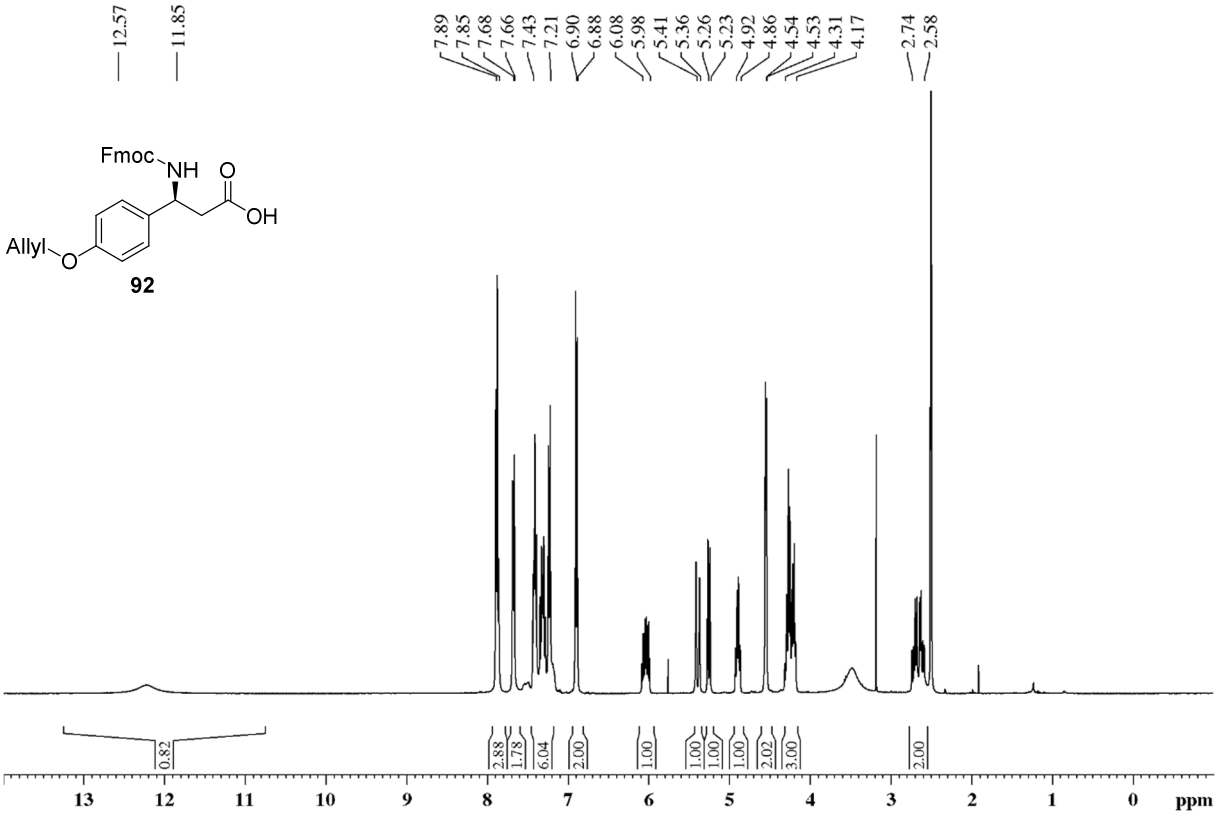
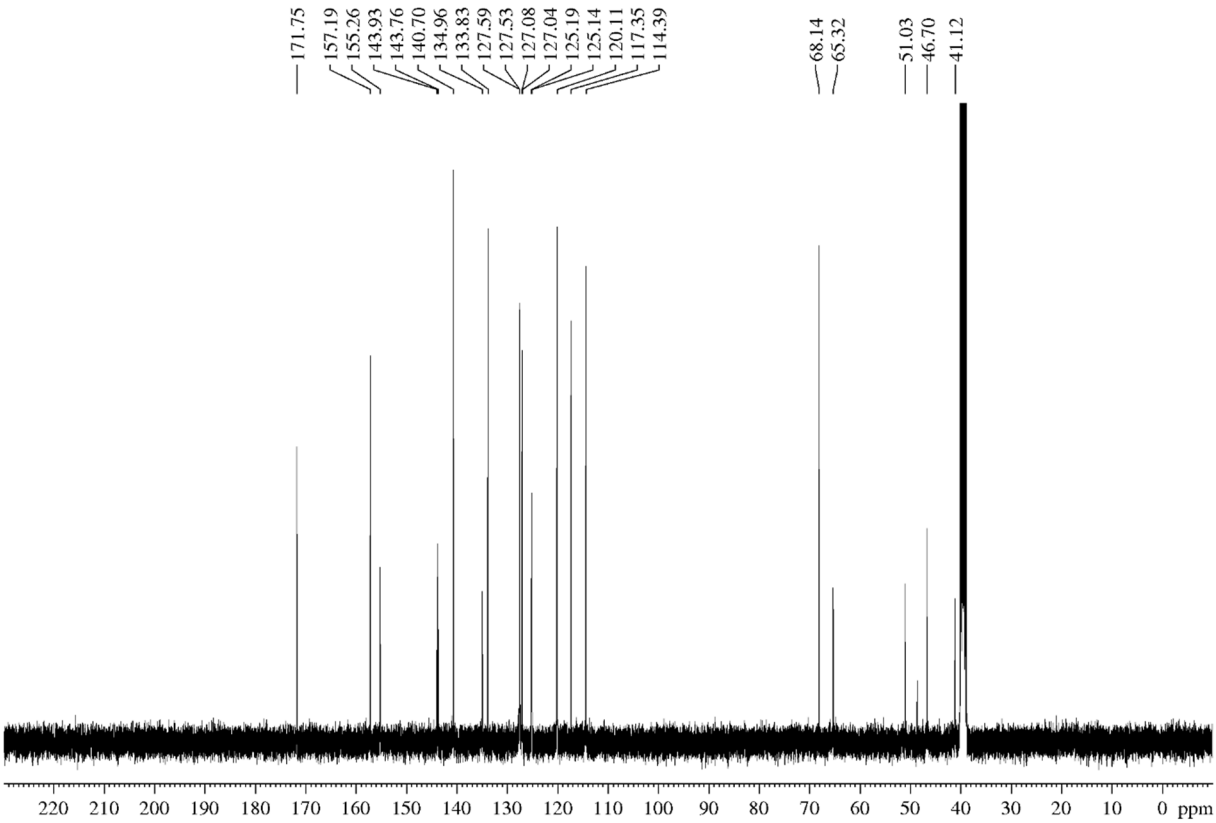
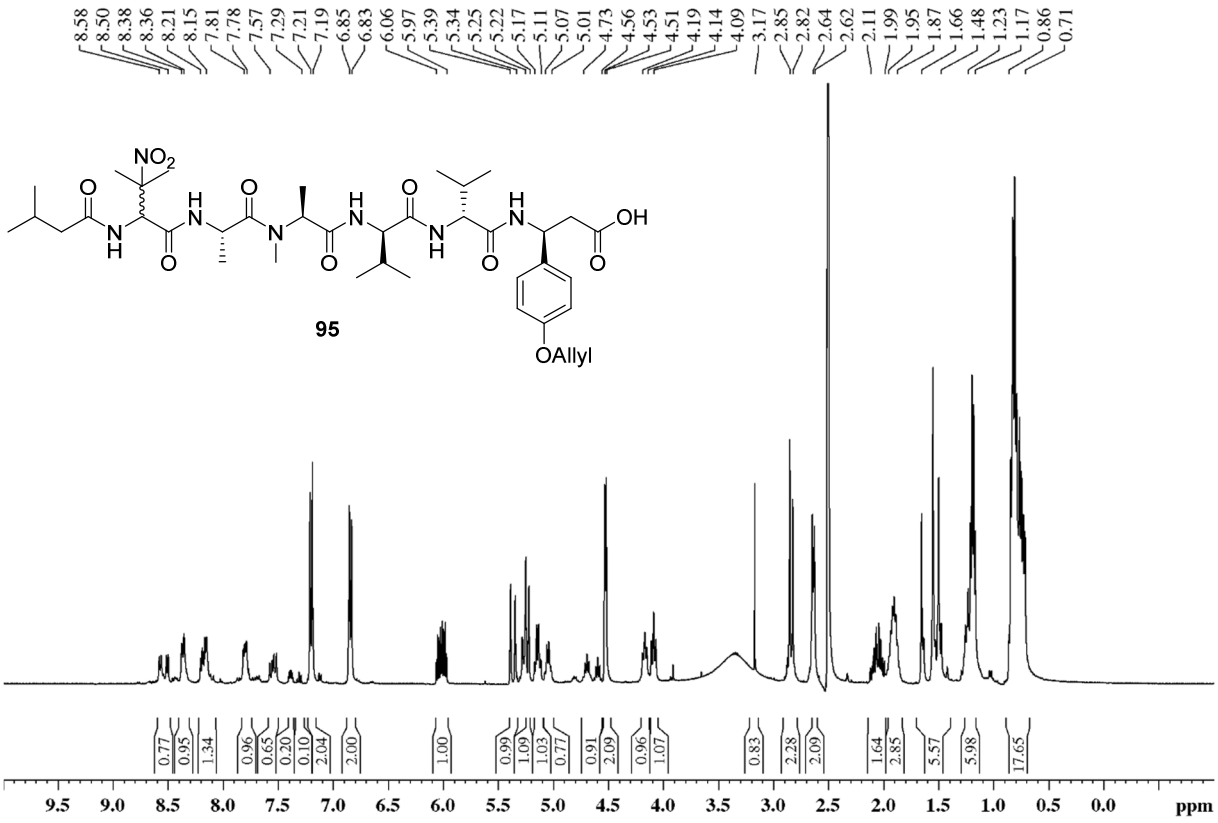
3
2
1
0
ppm


12.57
11.85
7.89
7.85
7.68
7.66
7.43
7.21
6.90
6.88
6.08
5.98
5.41
5.36
5.26
5.23
4.92
4.86
4.54
4.53
4.31
4.17
2.74
2.58
Fmoc
NH
O
OH
Allyl
O
92
0.82
2.88
1.78
6.04
2.00
1.00
1.00
1.00
1.00
2.02
3.00
2.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm


171.75
157.19
155.26
143.93
143.76
140.70
134.96
133.83
127.59
127.53
127.08
127.04
125.19
125.14
120.11
117.35
114.39
68.14
65.32
51.03
46.70
41.12
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


8.58
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8.36
8.21
8.15
7.81
7.78
7.57
7.29
7.21
7.19
6.85
6.83
6.06
5.97
5.39
5.34
5.25
5.22
5.17
5.11
5.07
5.01
4.73
4.56
4.53
4.51
4.19
4.14
4.09
3.17
2.85
2.82
2.64
2.62
2.11
1.99
1.95
1.87
1.66
1.48
1.23
1.17
0.86
0.71
NO2
OH
OAllyl
95
0.77
0.95
1.34
0.96
0.65
0.20
0.10
2.04
2.00
1.00
0.99
1.09
1.03
0.77
0.91
2.09
0.96
1.07
0.83
2.28
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1.64
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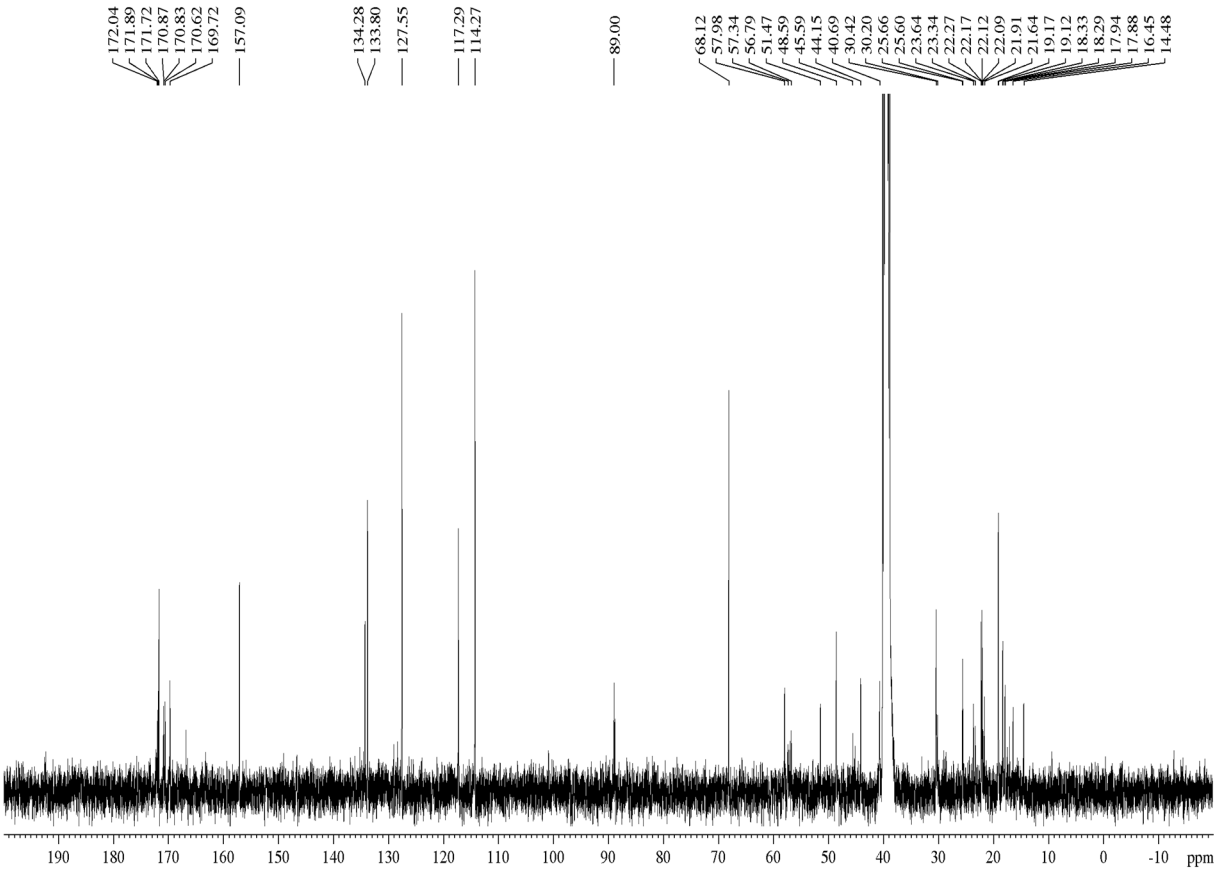
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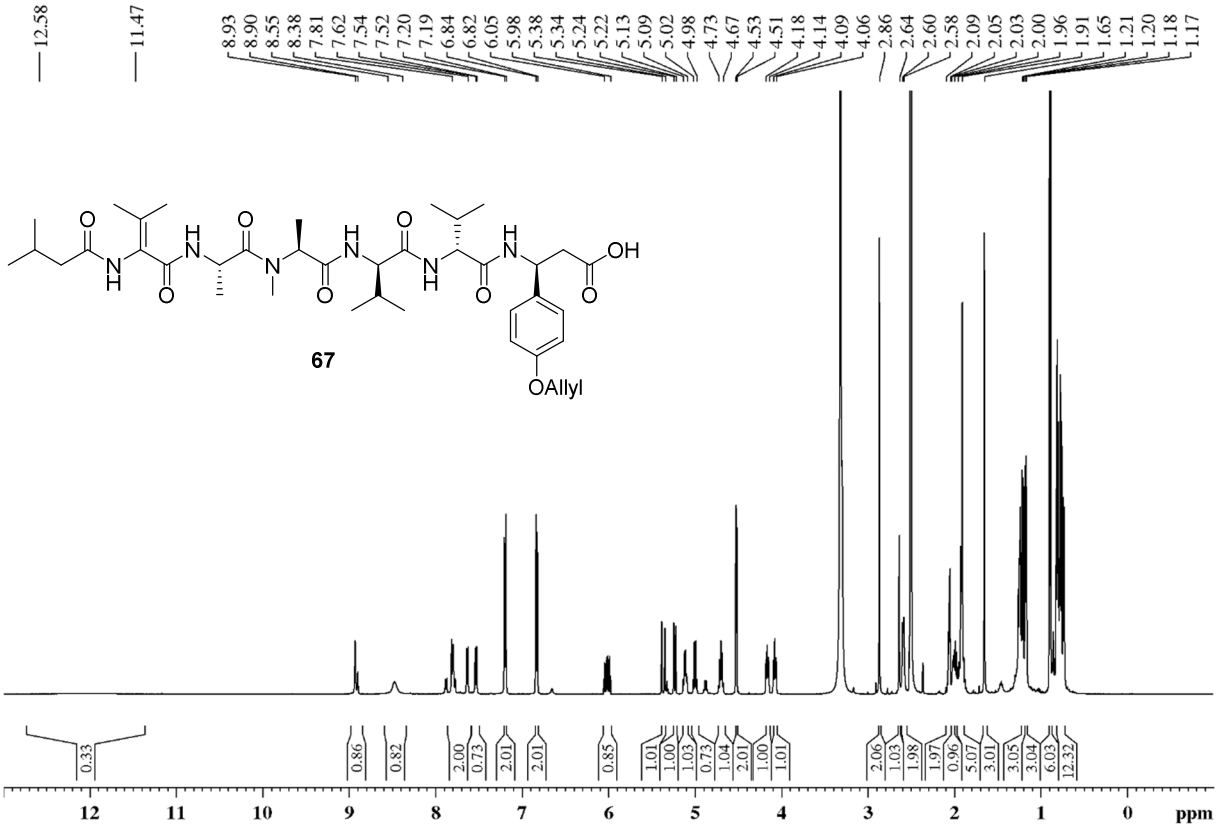
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4.09
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2.05
2.03
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1.91
1.65
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OH
OAllyl
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3.01
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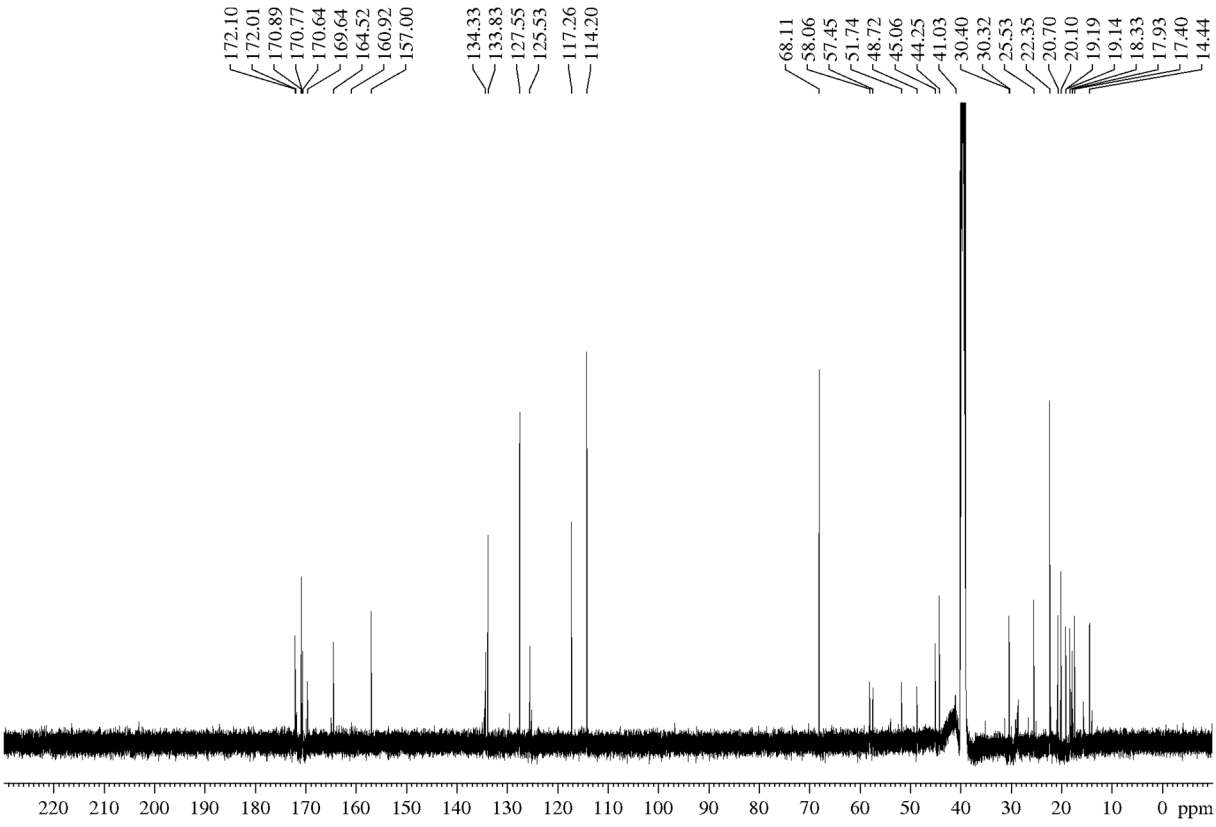
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57.45
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48.72
45.06
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25.53
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20.10
19.19
19.14
18.33
17.93
17.40
14.44
220
210
200
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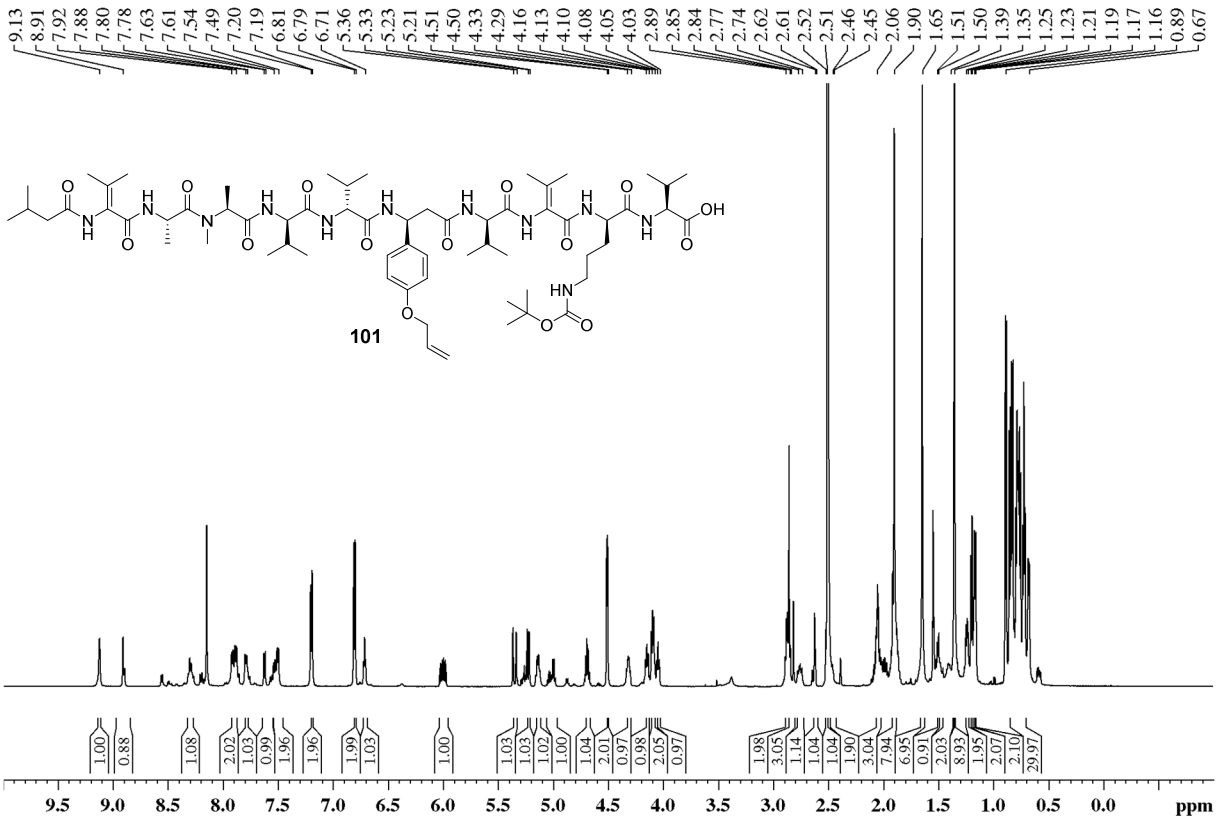
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5.23
5.21
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4.29
4.16
4.13
4.10
4.08
4.05
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2.89
2.85
2.84
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2.74
2.62
2.61
2.52
2.51
2.46
2.45
2.06
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1.00
1.03
1.03
1.02
1.00
1.04
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0.98
2.05
0.97
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1.04
1.90
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2.10
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7.0
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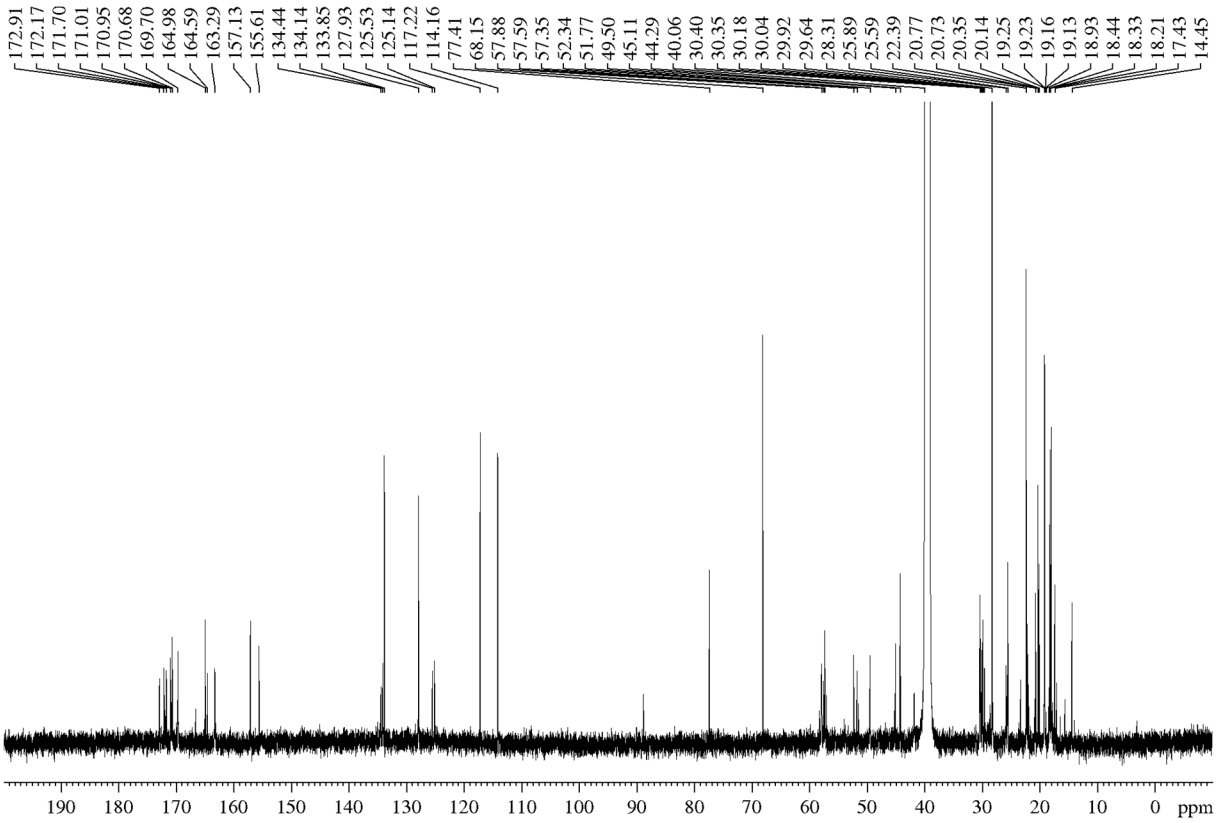
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133.85
127.93
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125.14
117.22
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68.15
57.88
57.59
57.35
52.34
51.77
49.50
45.11
44.29
40.06
30.40
30.35
30.18
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25.59
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20.73
20.35
20.14
19.25
19.23
19.16
19.13
18.93
18.44
18.33
18.21
17.43
14.45
190
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150
140
130
120
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60
50
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20
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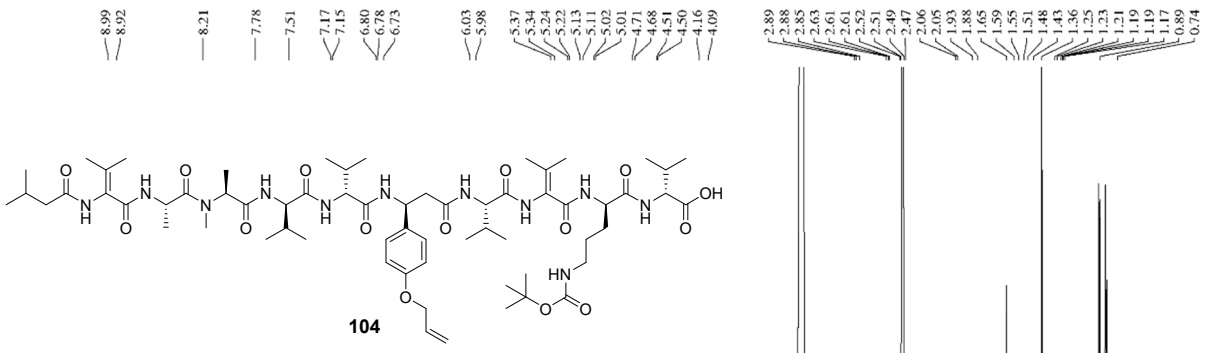
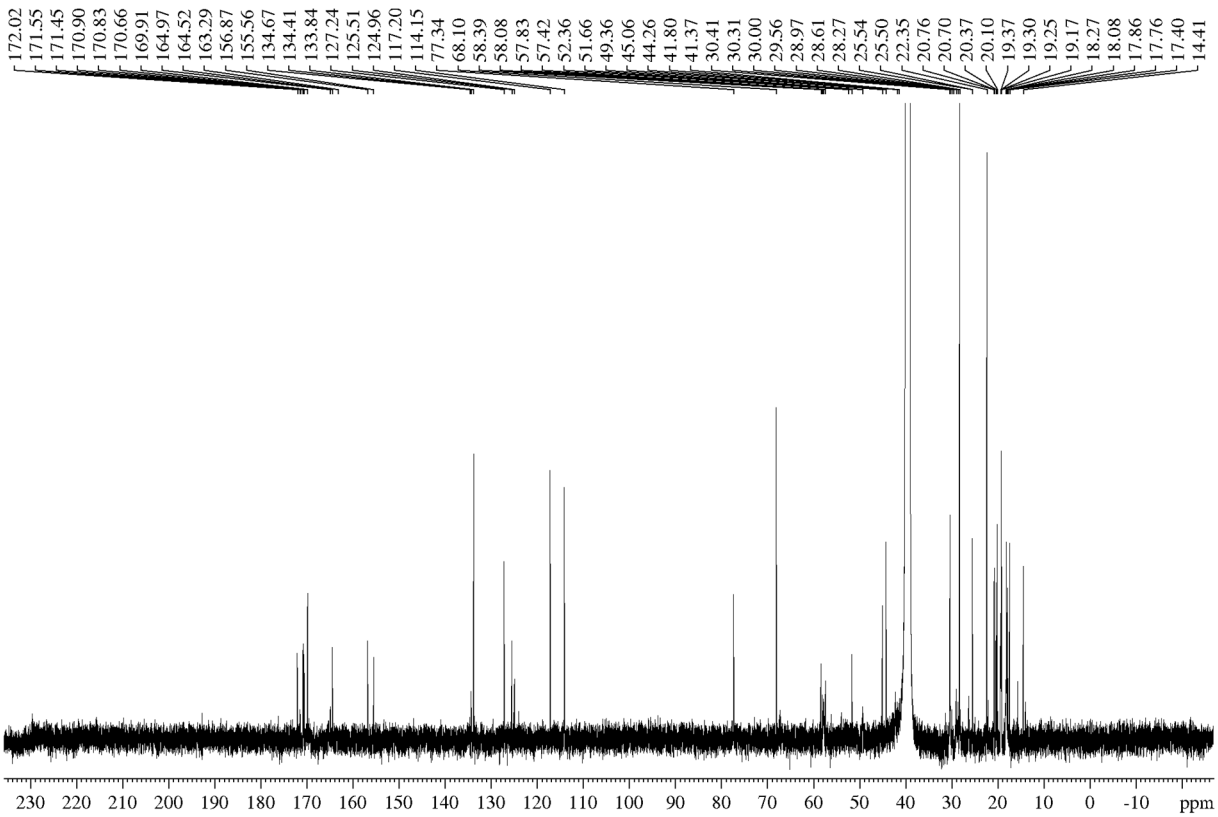
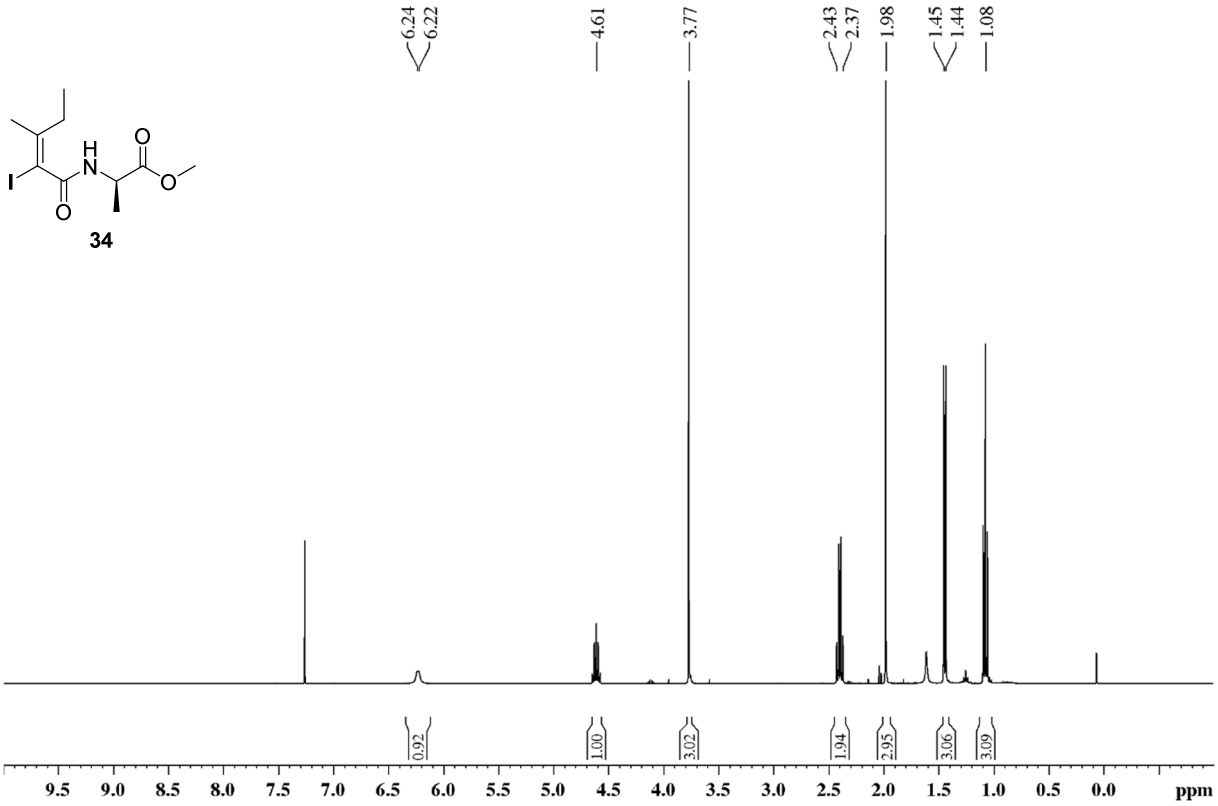


104

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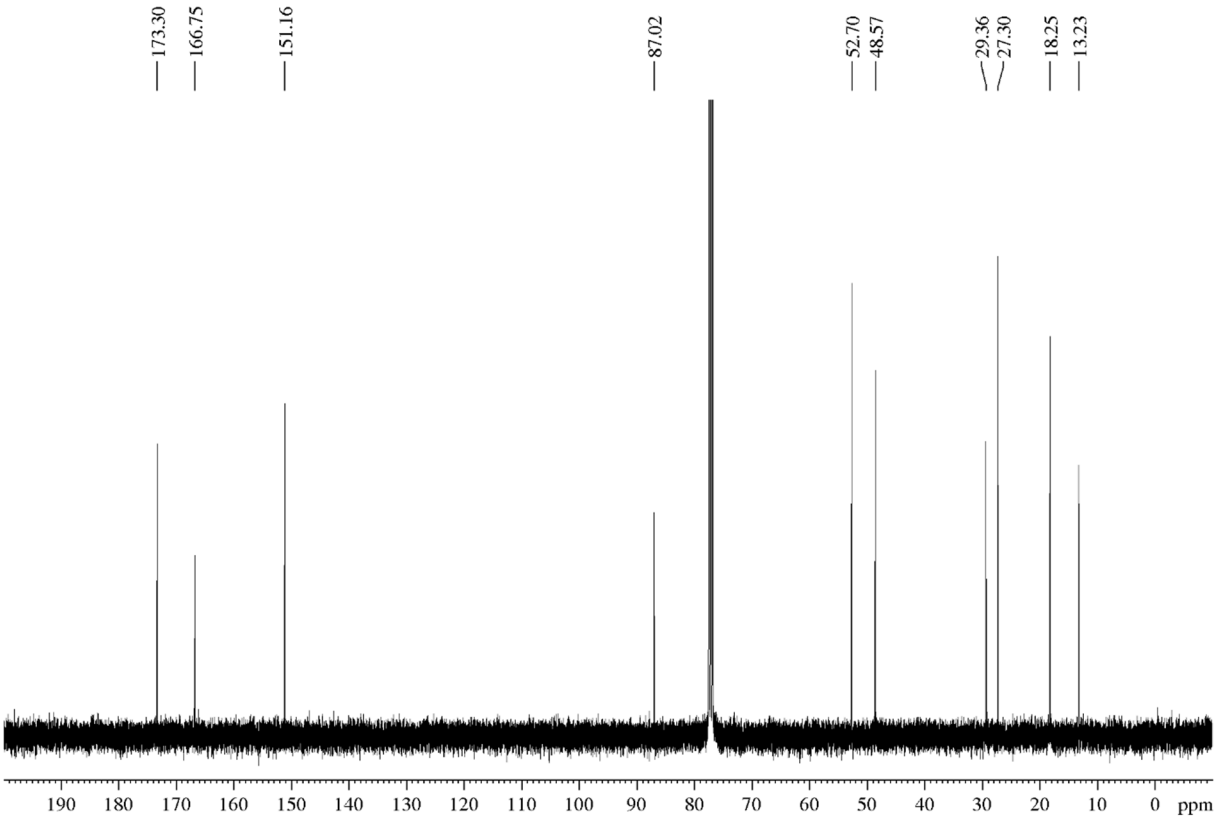
1.44
1.08
0.92
1.00
3.02
1.94
2.95
3.06
3.09
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

34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166.75
151.16
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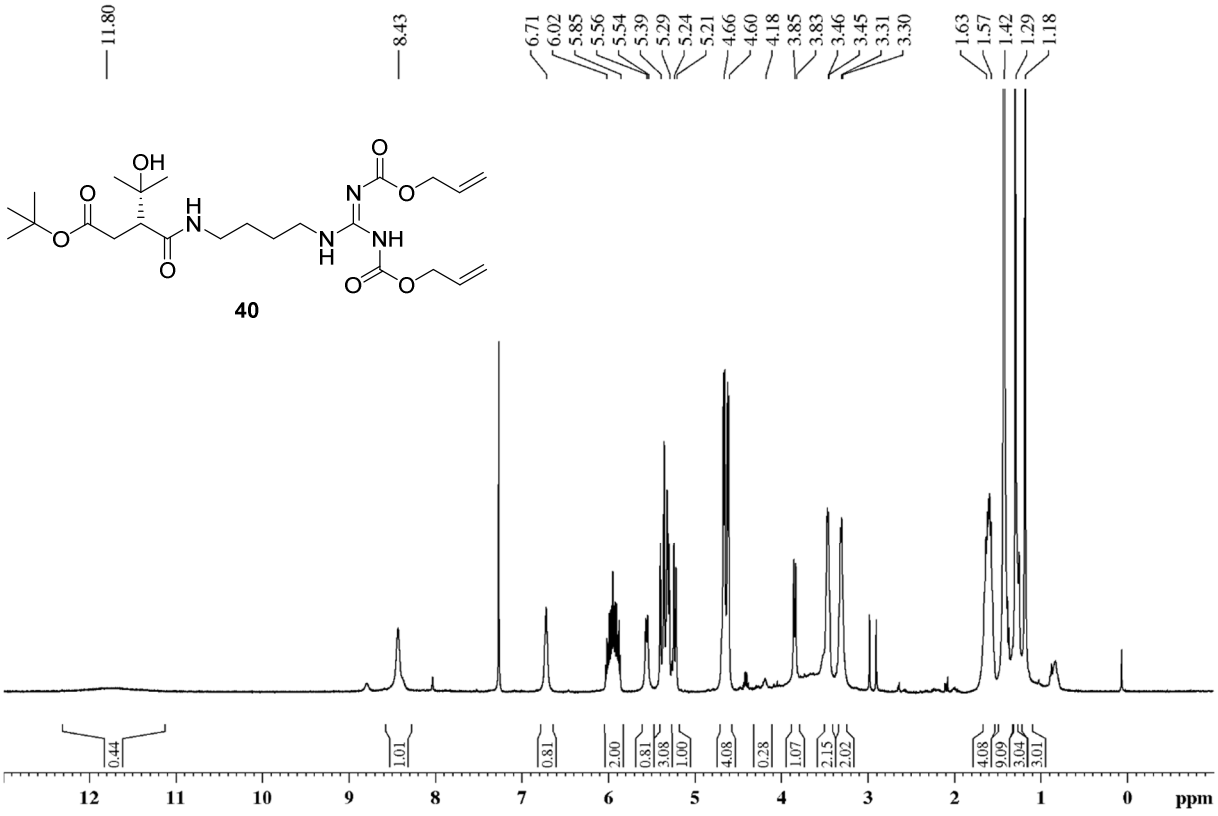
48.57
29.36
27.30
18.25
13.23
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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4.18
3.85
3.83
3.46
3.45
3.31
3.30
1.63
1.57
1.42
1.29
1.18
OH
O
O
H
N
O
N
O
N
H
NH
O
O
40
0.44
1.01
0.81
2.00
0.81
3.08
1.00
4.08
0.28
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2.15
2.02
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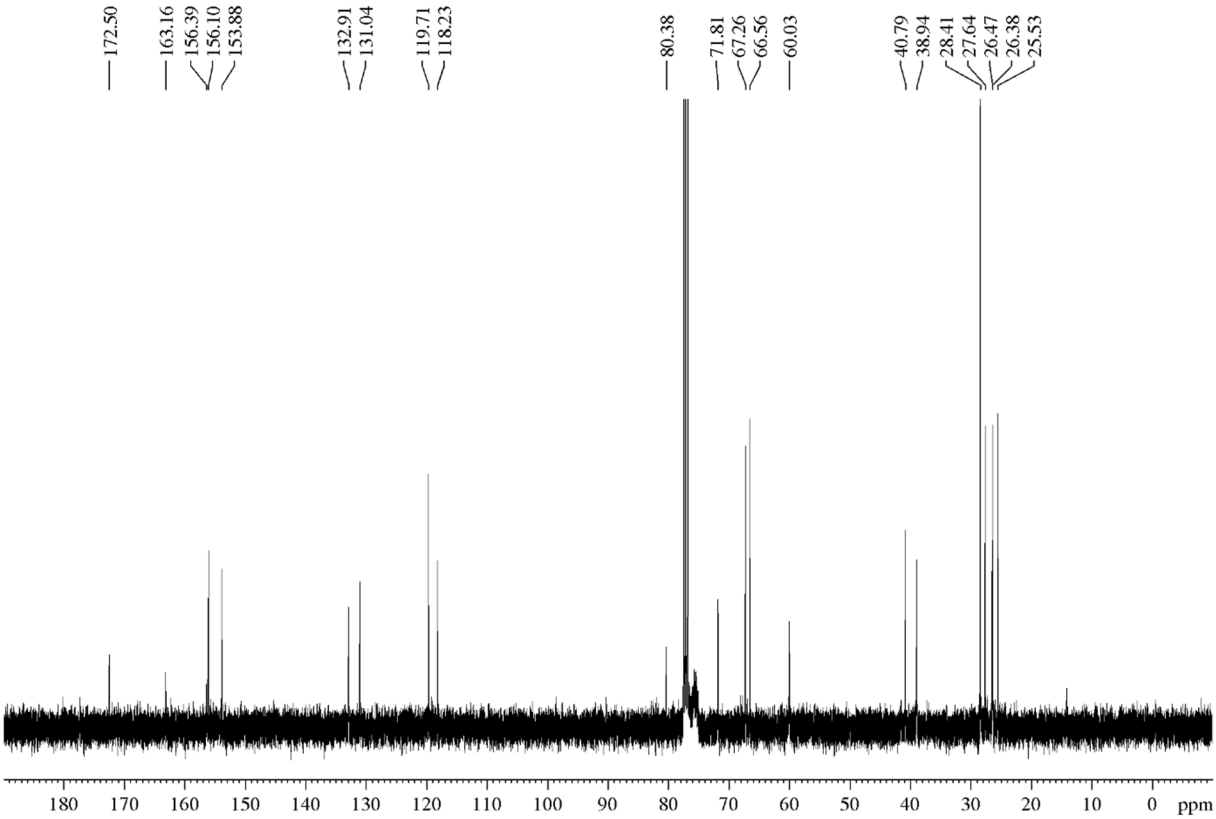
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119.71
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80.38
71.81
67.26
66.56
60.03
40.79
38.94
28.41
27.64
26.47
26.38
25.53
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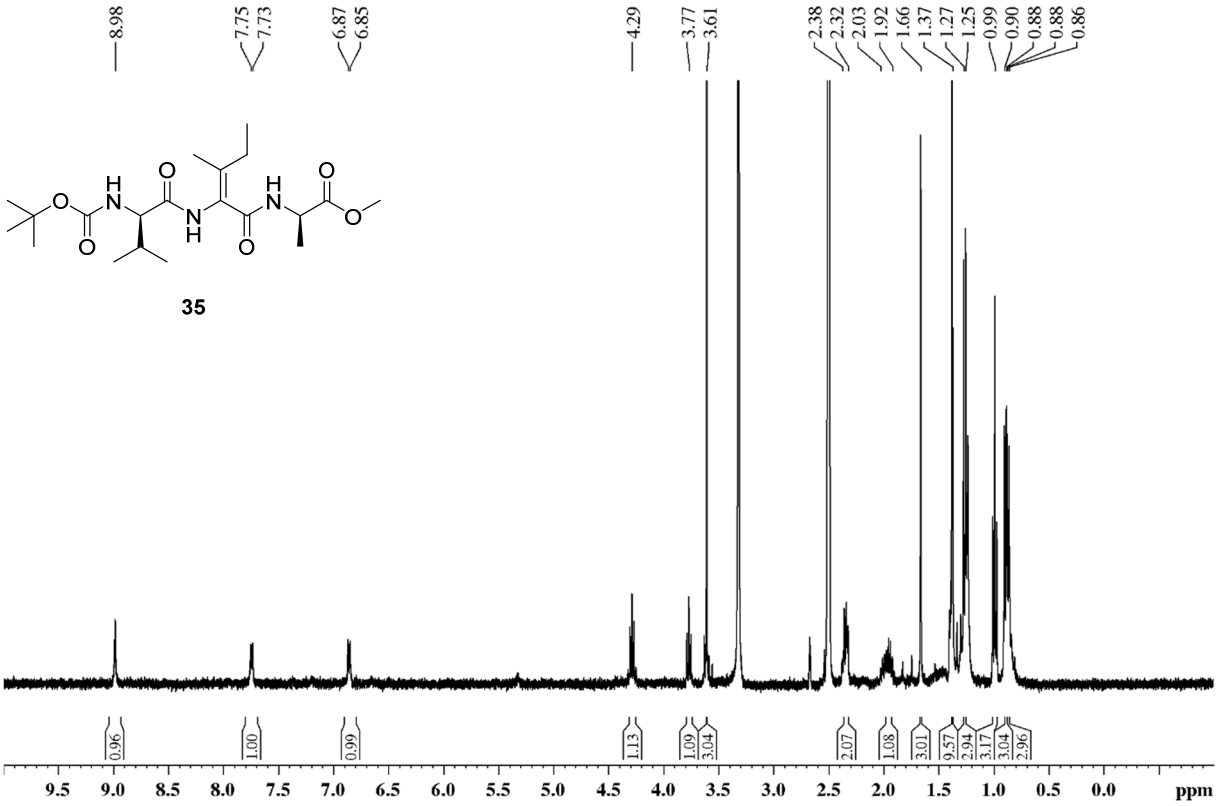
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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1.37
1.27
1.25
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0.88
0.88
0.86
0.96
1.00
0.99
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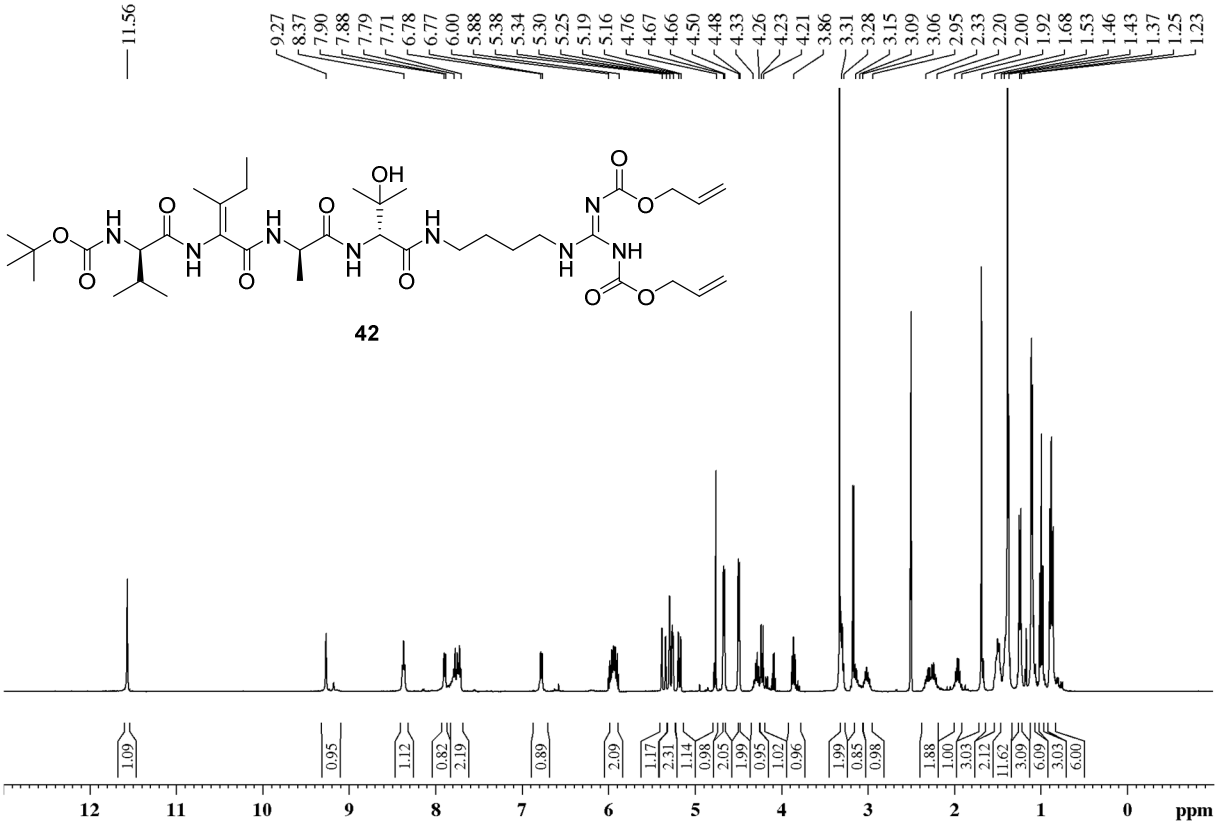
3.04
2.96
ppm

35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5.25
5.19
5.16
4.76
4.67
4.66
4.50
4.48
4.33
4.26
4.23
4.21
3.86
3.31
3.28
3.15
3.09
3.06
2.95
2.33
2.20
2.00
1.92
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1.53
1.46
1.43
1.37
1.25
1.23
1.09
0.95
1.12
0.82
2.19
0.89
2.09
1.17
2.31
1.14
0.98
2.05
1.99
0.95
1.02
0.96
1.99
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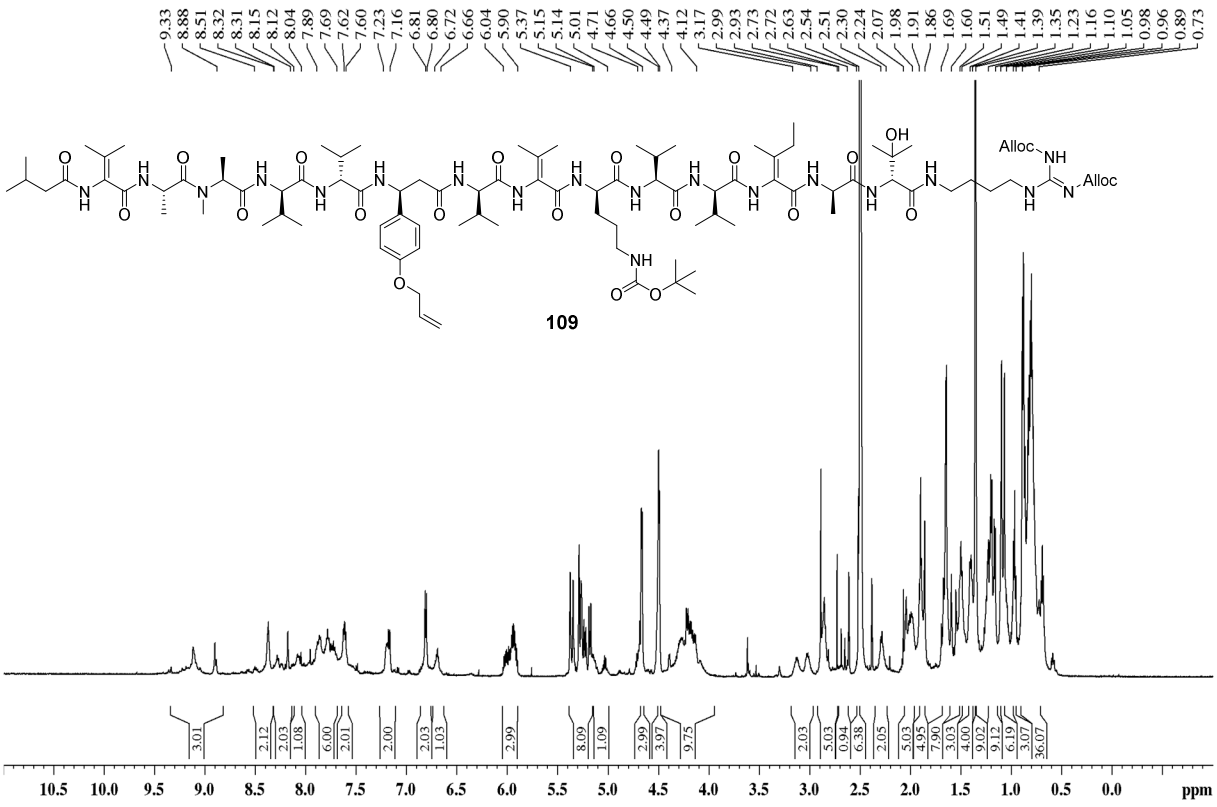
1.88
1.00
3.03
2.12
11.62
3.09
3.03
6.00
ppm

42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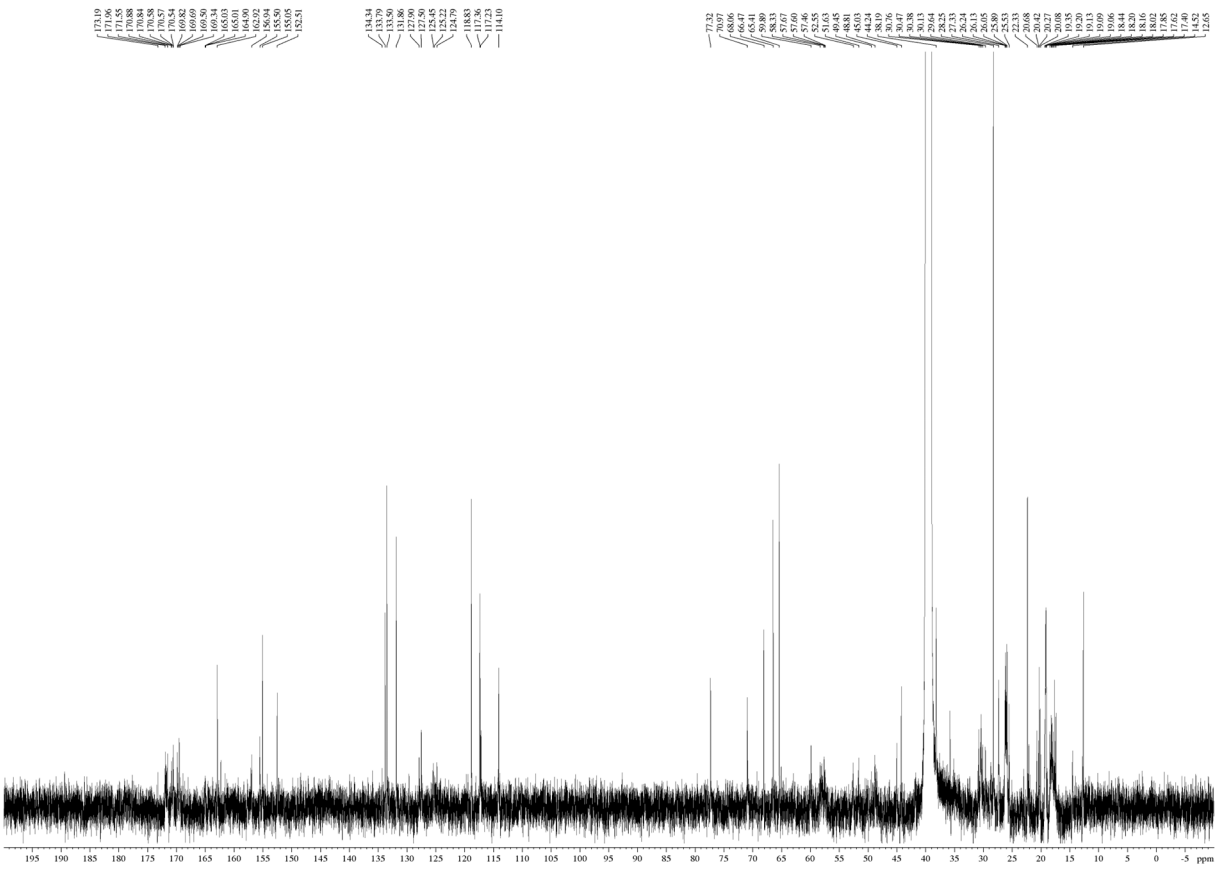
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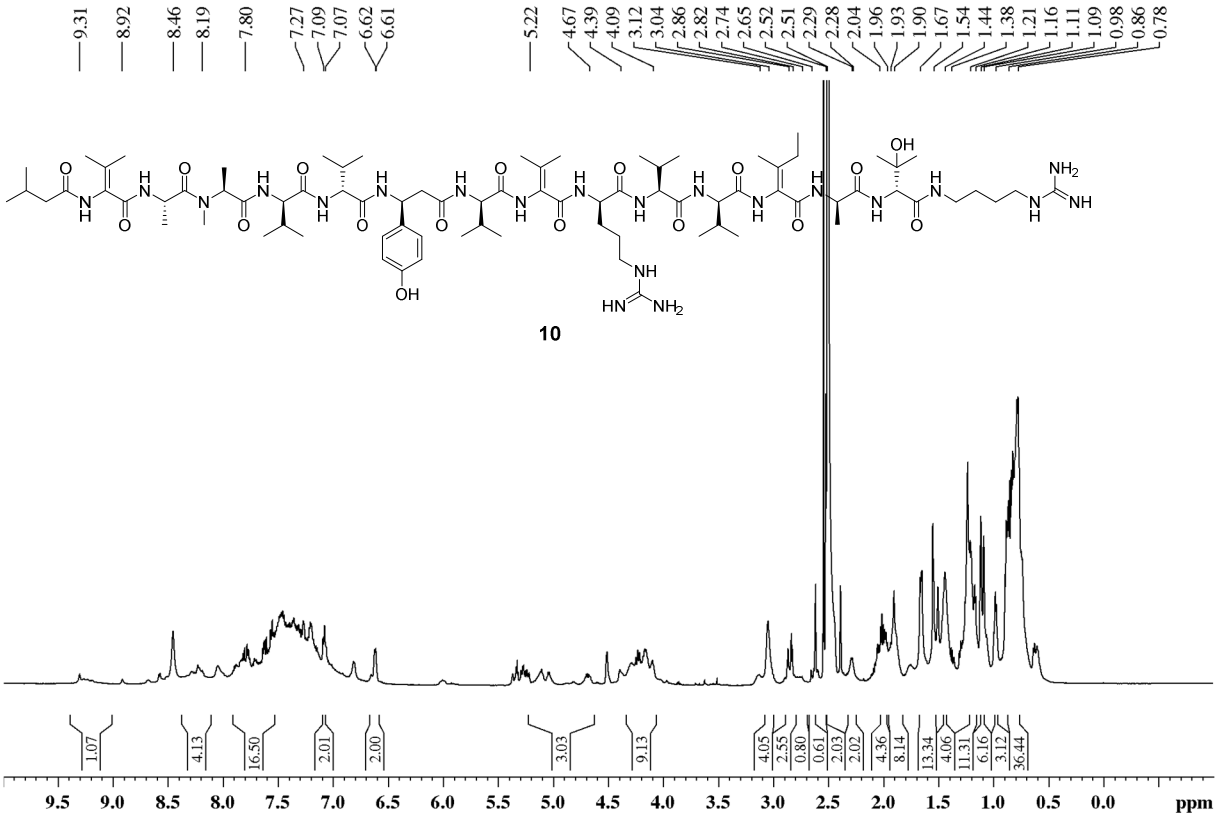
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6.61
5.22
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4.39
4.09
3.12
3.04
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2.74
2.65
2.52
2.51
2.29
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2.04
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1.44
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0.86
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1.07
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2.00
3.03
9.13
4.05
2.55
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13.34
4.06
11.31
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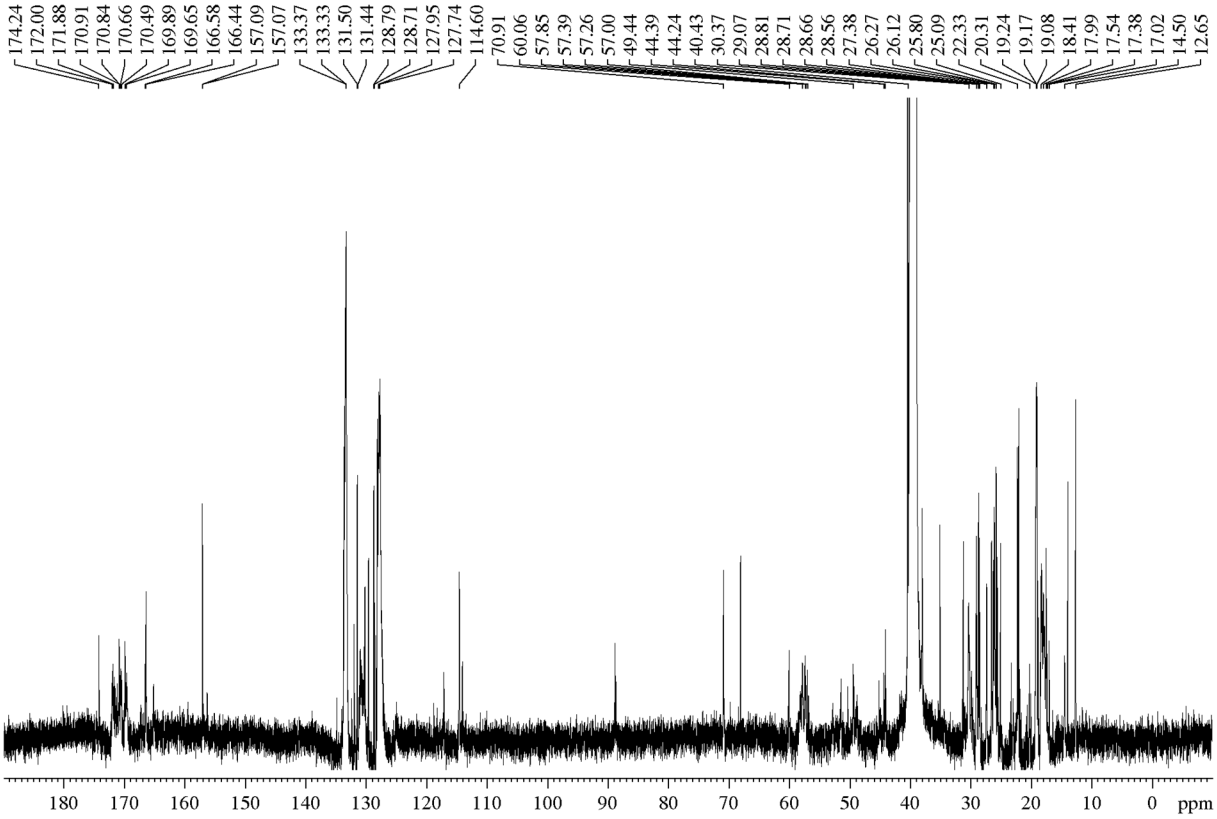
3.12
36.44
ppm

10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157.07
133.37
133.33
131.50
131.44
128.79
128.71
127.95
127.74
114.60
70.91
60.06
57.85
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57.26
57.00
49.44
44.39
44.24
40.43
30.37
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28.56
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26.12
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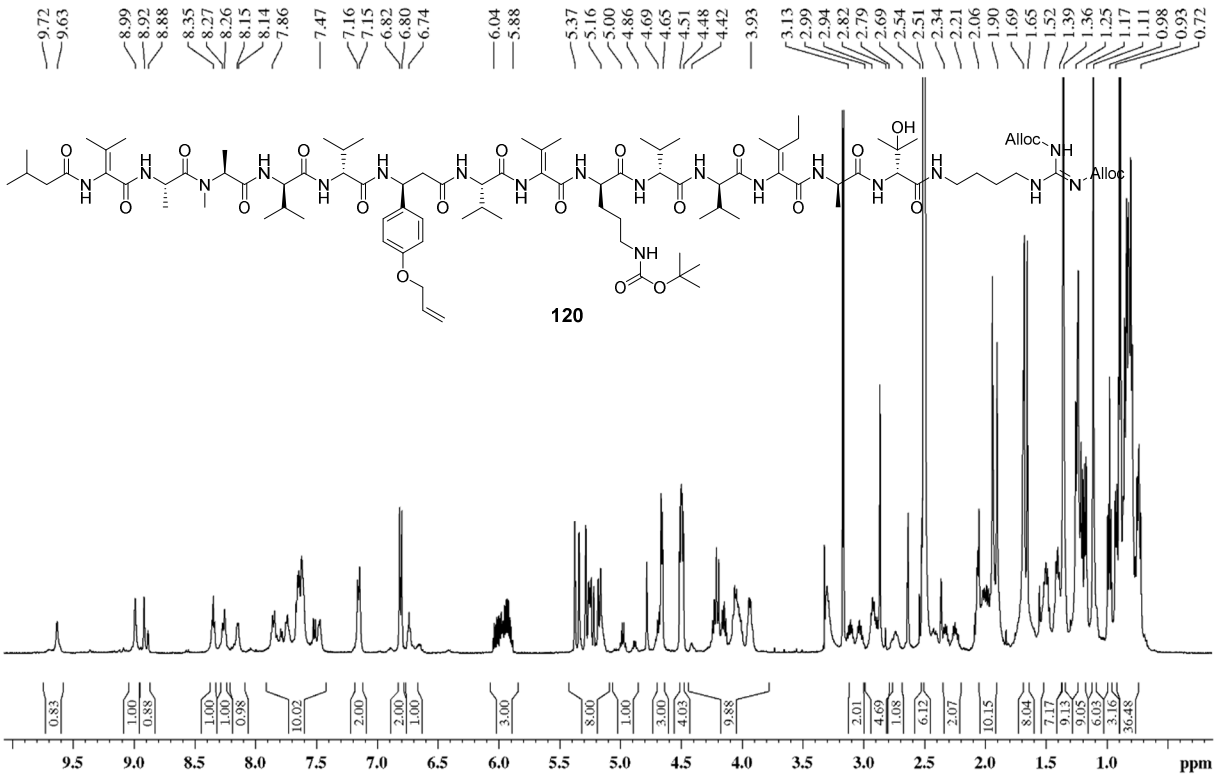
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6.80
6.74
6.04
5.88
5.37
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5.00
4.86
4.69
4.65
4.51
4.48
4.42
3.93
3.13
2.99
2.94
2.82
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OH
Alloc
NH
Alloc
NH
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1.08
6.12
2.07
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7.17
9.13
9.05
6.03
3.16
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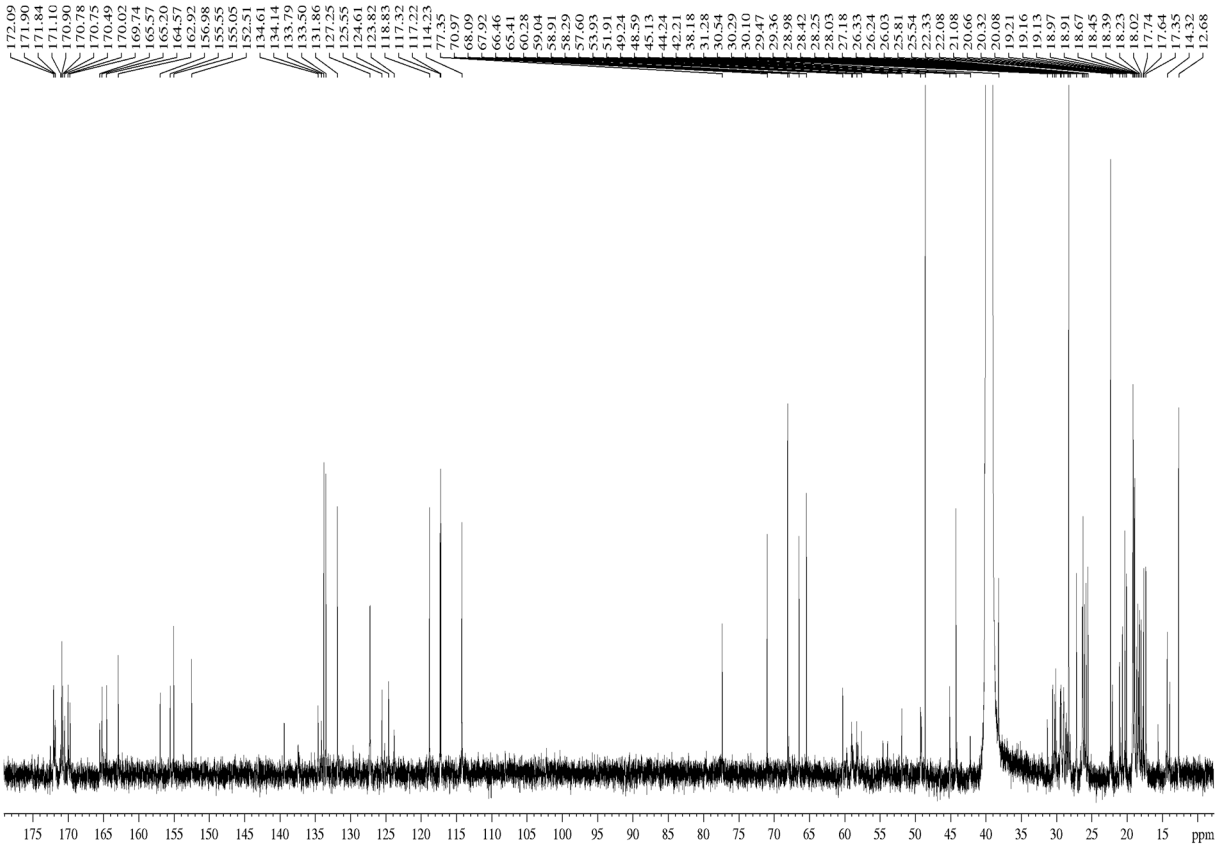
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155.05
152.51
134.61
134.14
133.79
133.50
131.86
127.25
125.55
124.61
123.82
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117.22
114.23
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20.08
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18.23
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160
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130
125
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115
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25
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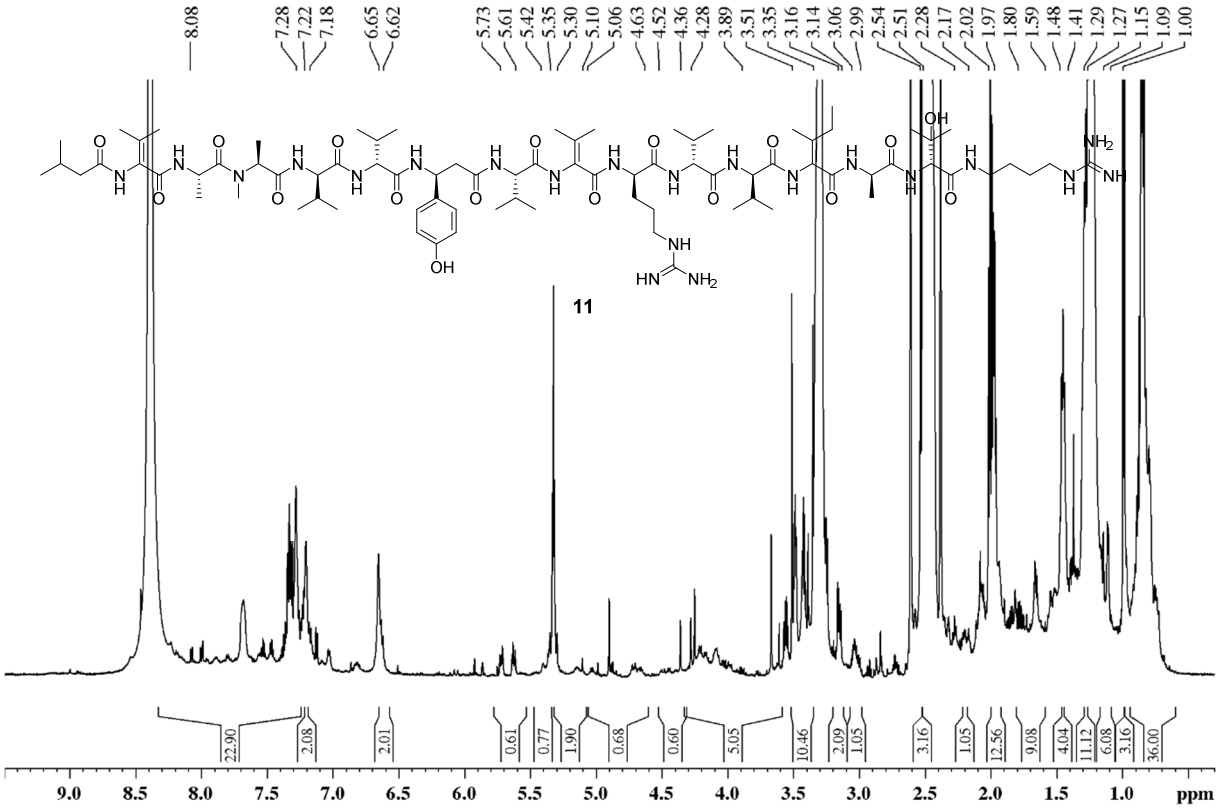
15
ppm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4.63
4.52
4.36
4.28
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3.51
3.35
3.16
3.14
3.06
2.99
2.54
2.51
2.28
2.17
2.02
1.97
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1.00
11
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10.46
2.09
1.05
3.16
1.05
12.56
9.08
4.04
11.12
6.08
3.16
36.00
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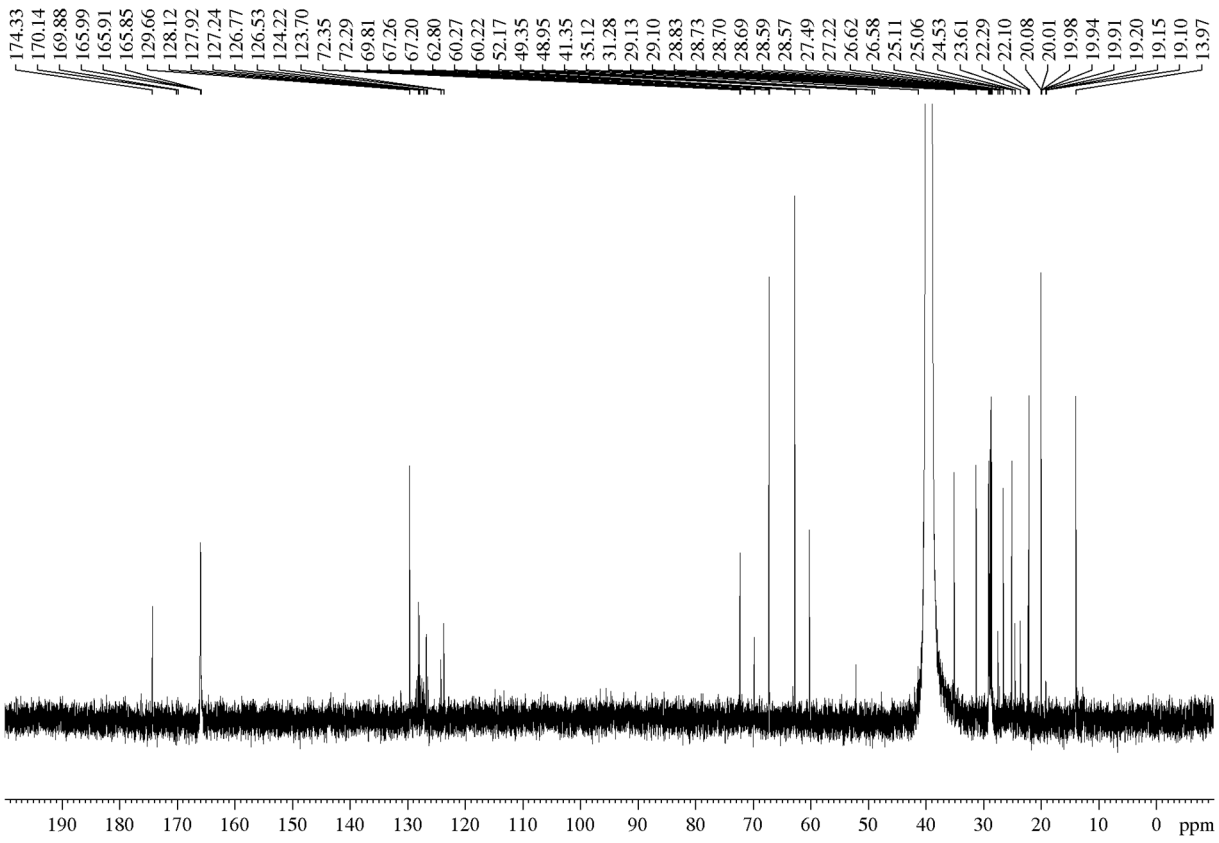
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124.22
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20.08
20.01
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19.94
19.91
19.20
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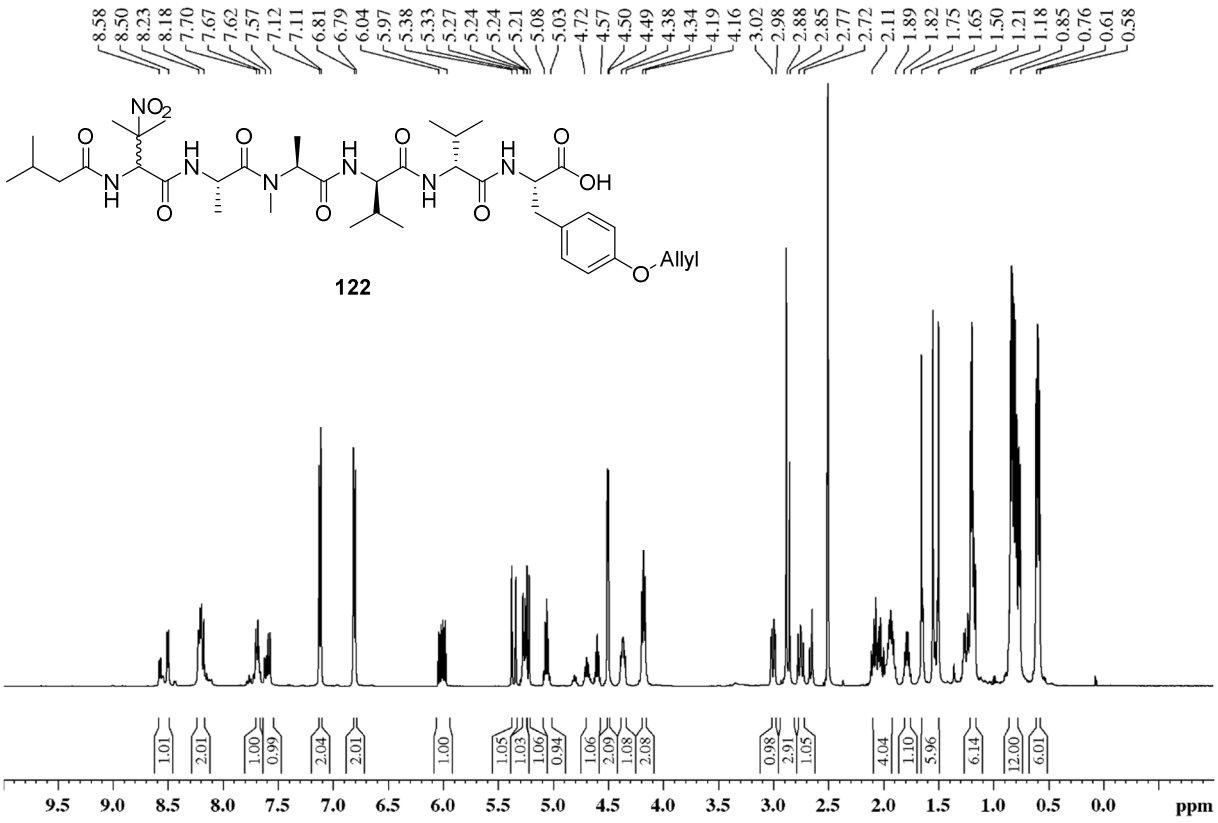
19.10
13.97
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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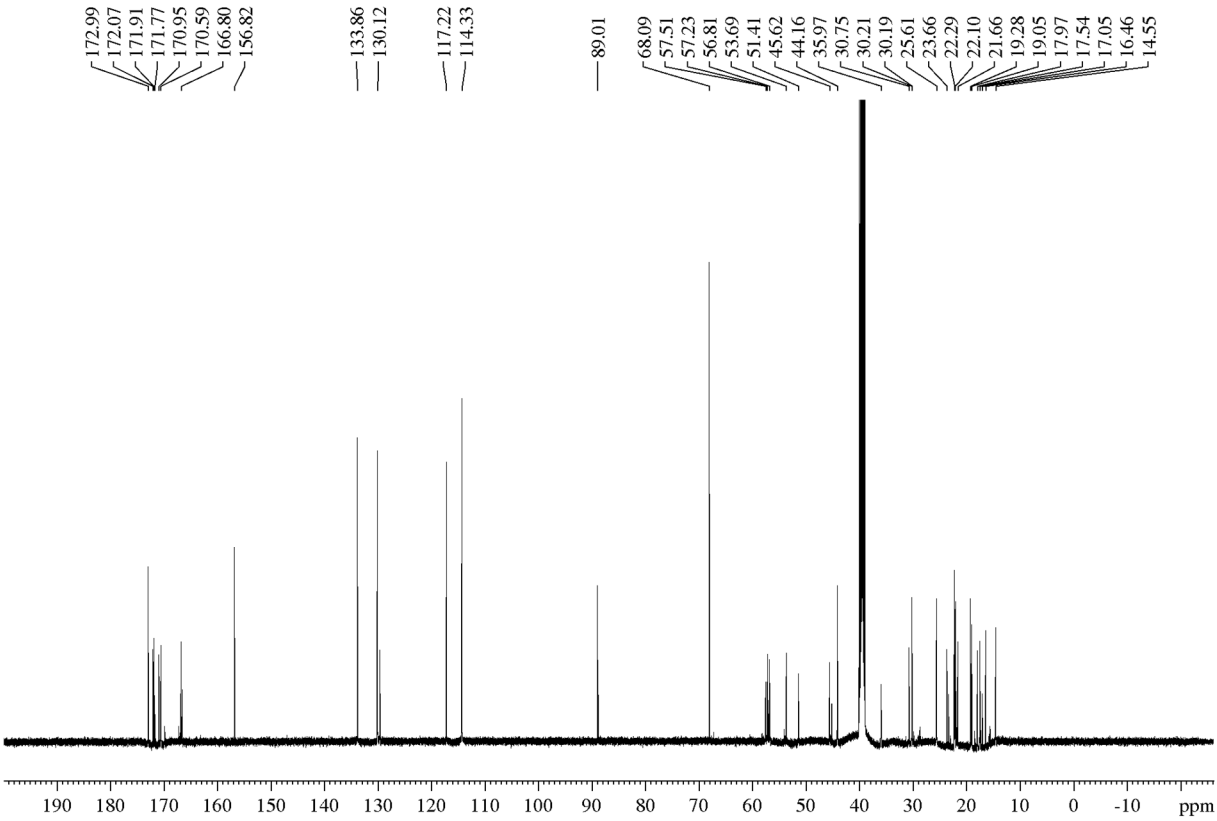
7.11
6.81
6.79
6.04
5.97
5.38
5.33
5.27
5.24
5.24
5.21
5.08
5.03
4.72
4.57
4.50
4.49
4.38
4.34
4.19
4.16
3.02
2.98
2.88
2.85
2.77
2.72
2.11
1.89
1.82
1.75
1.65
1.50
1.21
1.18
0.85
0.76
0.61
0.58
NO2
OH
Allyl
122
1.01
2.01
1.00
0.99
2.04
2.01
1.00
1.05
1.03
1.06
0.94
1.06
2.09
1.08
2.08
0.98
2.91
1.05
4.04
1.10
5.96
6.14
12.00
6.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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117.22
114.33
89.01
68.09
57.51
57.23
56.81
53.69
51.41
45.62
44.16
35.97
30.75
30.21
30.19
25.61
23.66
22.29
22.10
21.66
19.28
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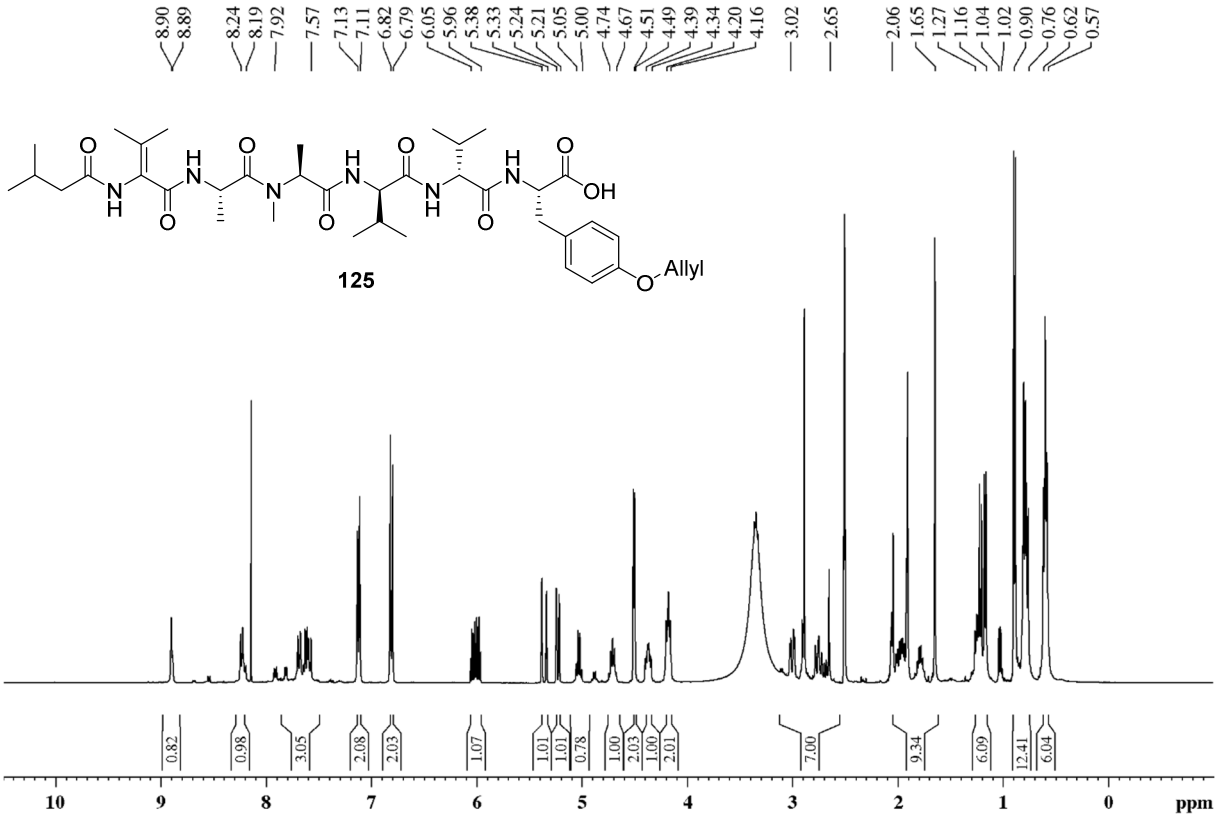
17.54
17.05
16.46
14.55
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm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5.38
5.33
5.24
5.21
5.05
5.00
4.74
4.67
4.51
4.49
4.39
4.34
4.20
4.16
3.02
2.65
2.06
1.65
1.27
1.16
1.04
1.02
0.90
0.76
0.62
0.57
125
Allyl
0.82
0.98
3.05
2.08
2.03
1.07
1.01
1.01
0.78
1.00
2.03
1.00
2.01
7.00
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12.41
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10
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8
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6
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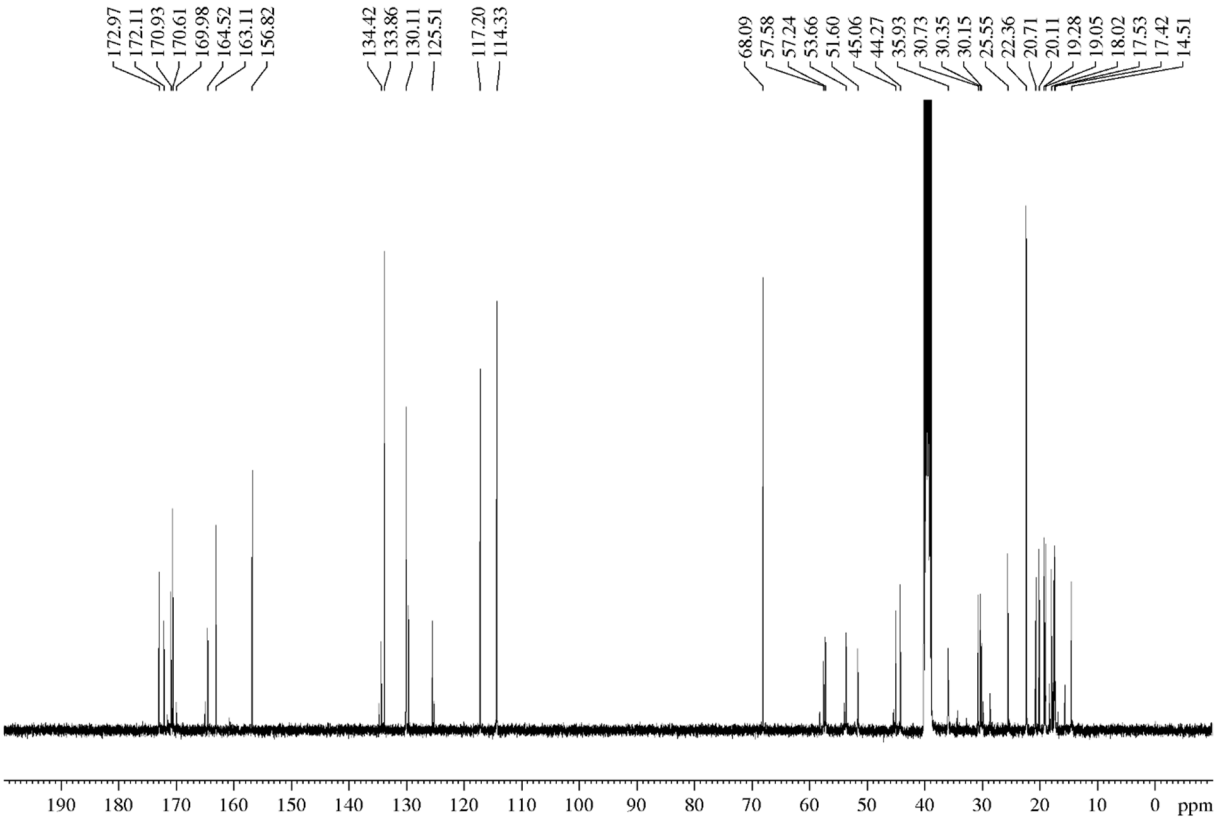
3
2
1
0
ppm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125.51
117.20
114.33
68.09
57.58
57.24
53.66
51.60
45.06
44.27
35.93
30.73
30.35
30.15
25.55
22.36
20.71
20.11
19.28
19.05
18.02
17.53
17.42
14.51
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180
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150
140
130
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20
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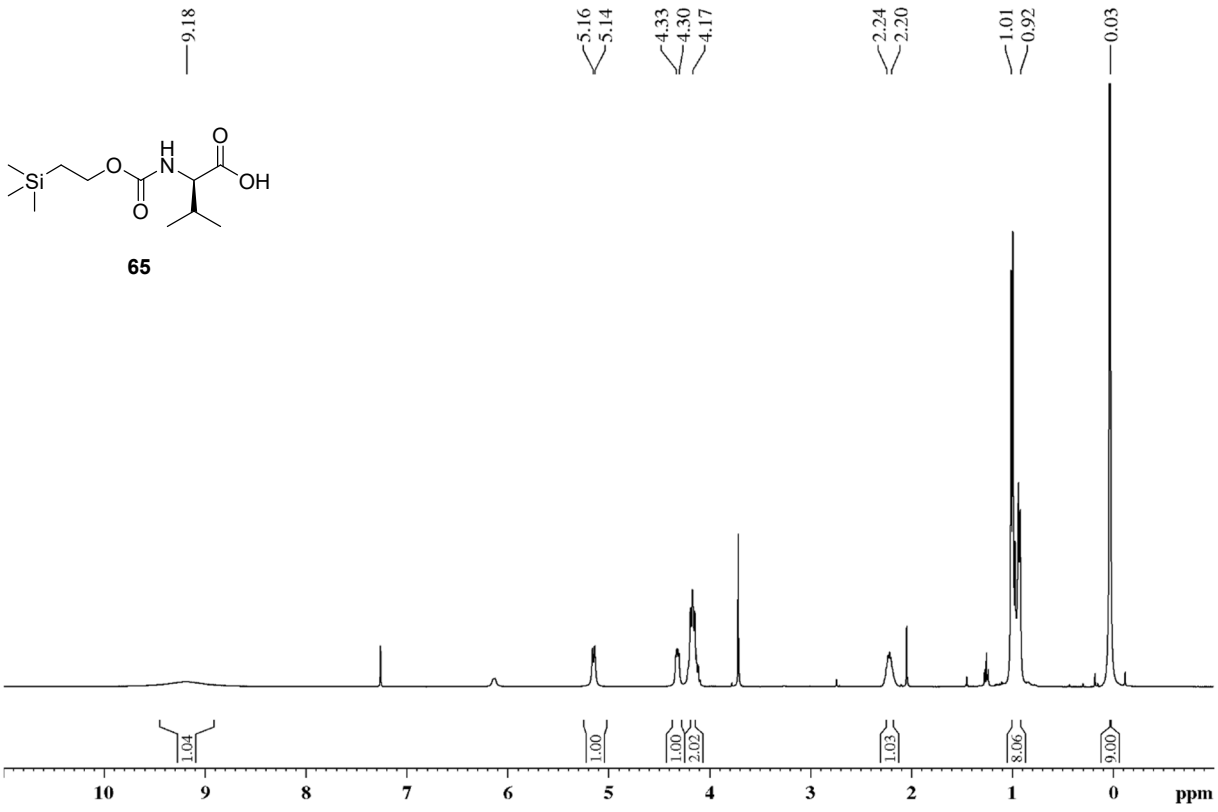
ppm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5.16
5.14
4.33
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4.17
2.24
2.20
1.01
0.92
0.03
1.04
1.00
1.00
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8.06
9.00
10
9
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7
6
5
4
3
2
1
0
ppm

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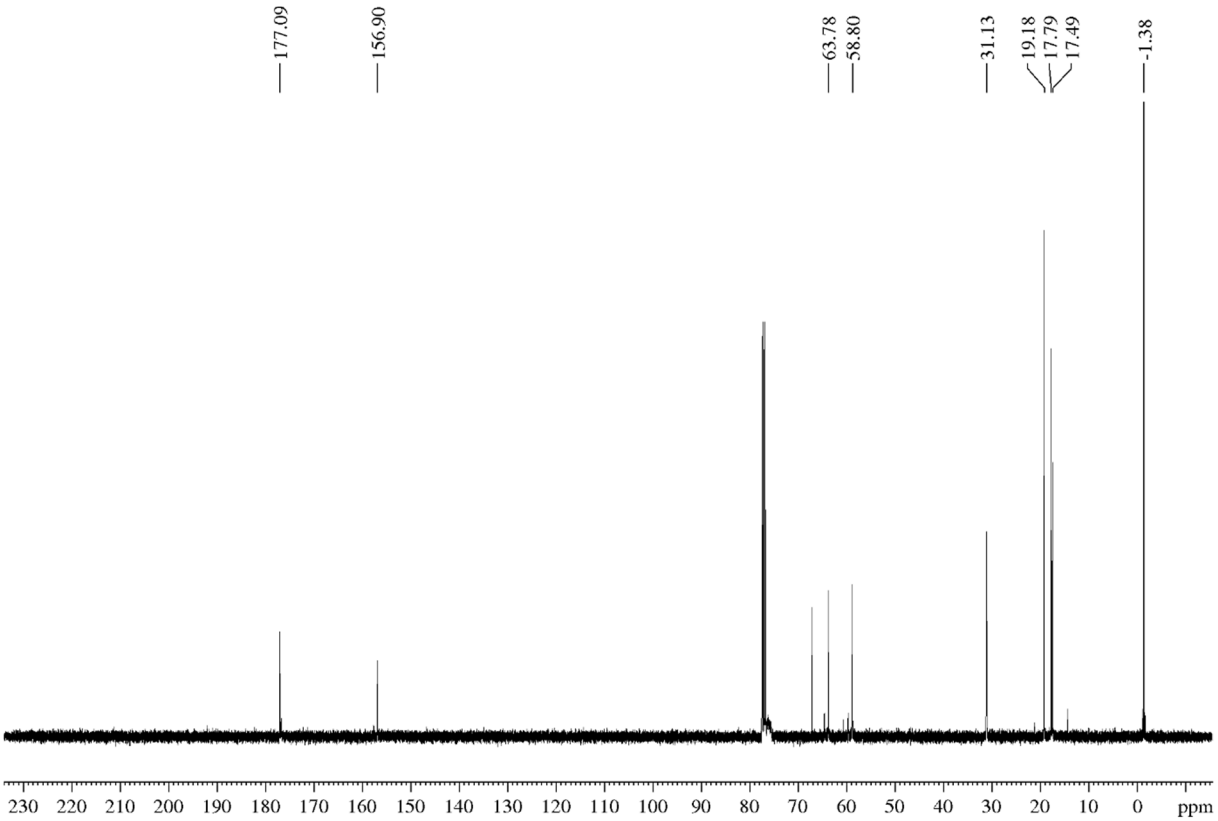
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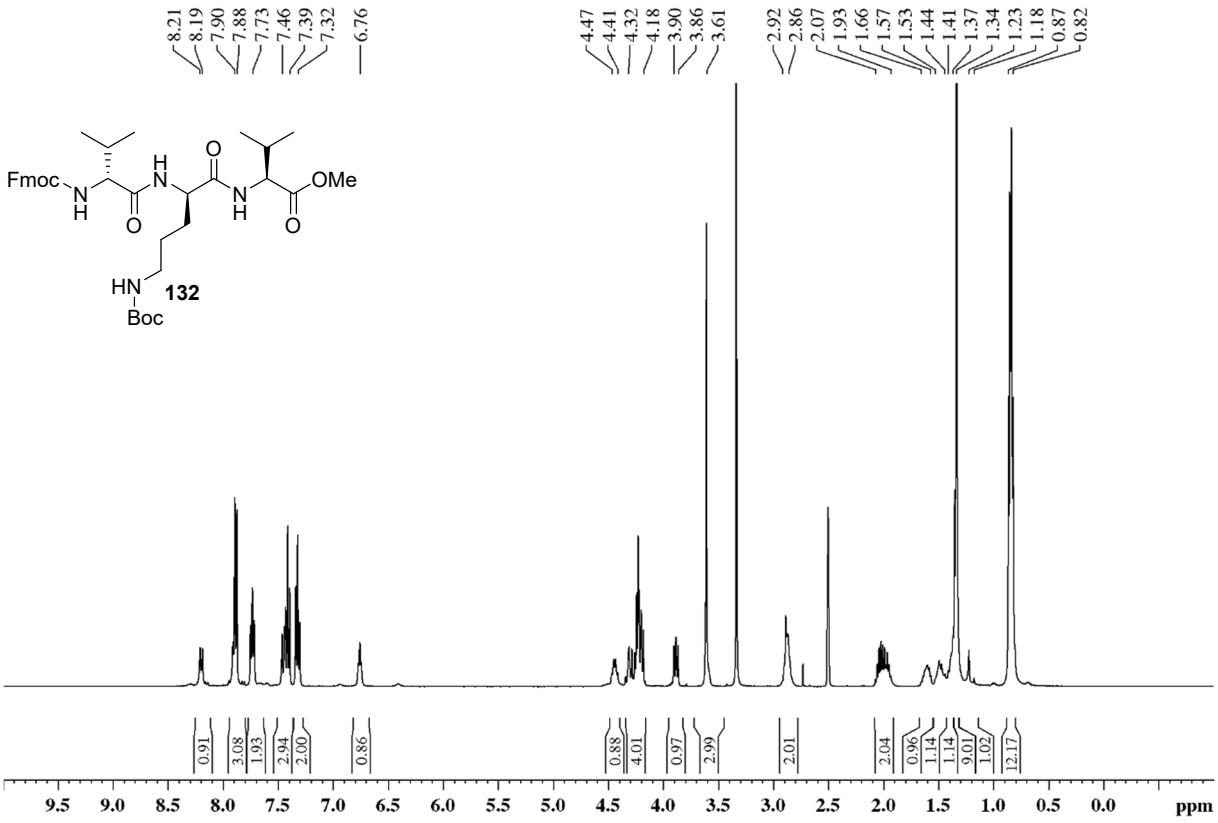
156.90
63.78
58.80
31.13
19.18
17.79
17.49
-1.38
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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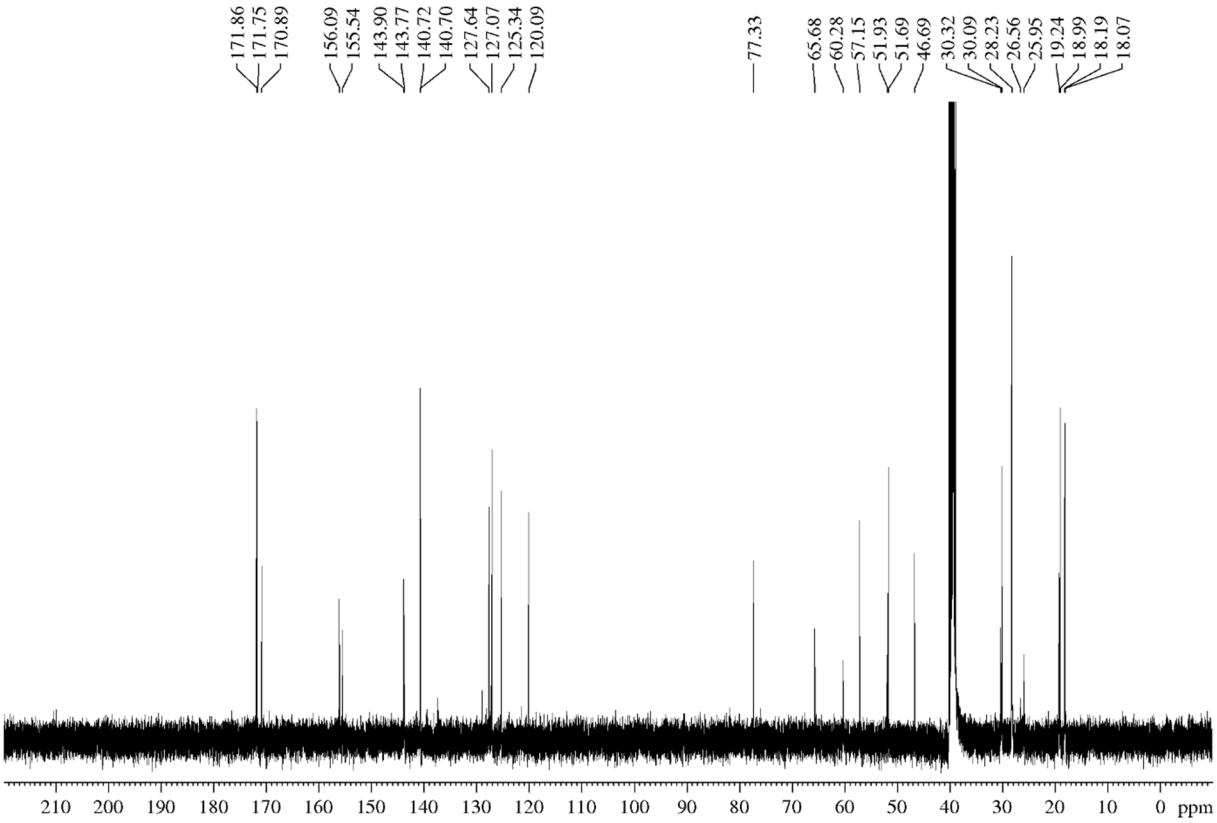
8.19
7.90
7.88
7.73
7.46
7.39
7.32
6.76
4.47
4.41
4.32
4.18
3.90
3.86
3.61
2.92
2.86
2.07
1.93
1.66
1.57
1.53
1.44
1.41
1.37
1.34
1.23
1.18
0.87
0.82
Fmoc
N
H
O
H
N
O
N
H
O
OMe
HN
Boc
132
0.91
3.08
1.93
2.94
2.00
0.86
0.88
4.01
0.97
2.99
2.01
2.04
0.96
1.14
1.14
9.01
1.02
12.17
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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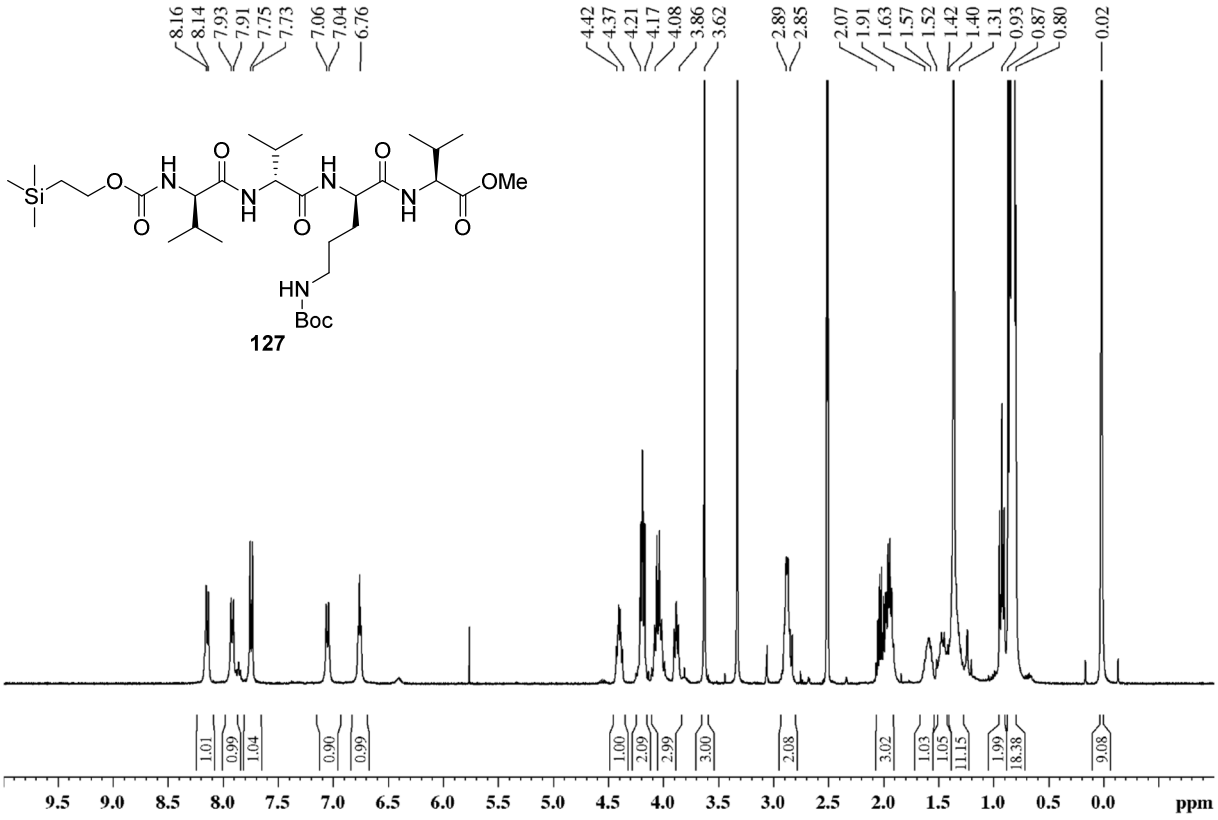
127.64
127.07
125.34
120.09
77.33
65.68
60.28
57.15
51.93
51.69
46.69
30.32
30.09
28.23
26.56
25.95
19.24
18.99
18.19
18.07
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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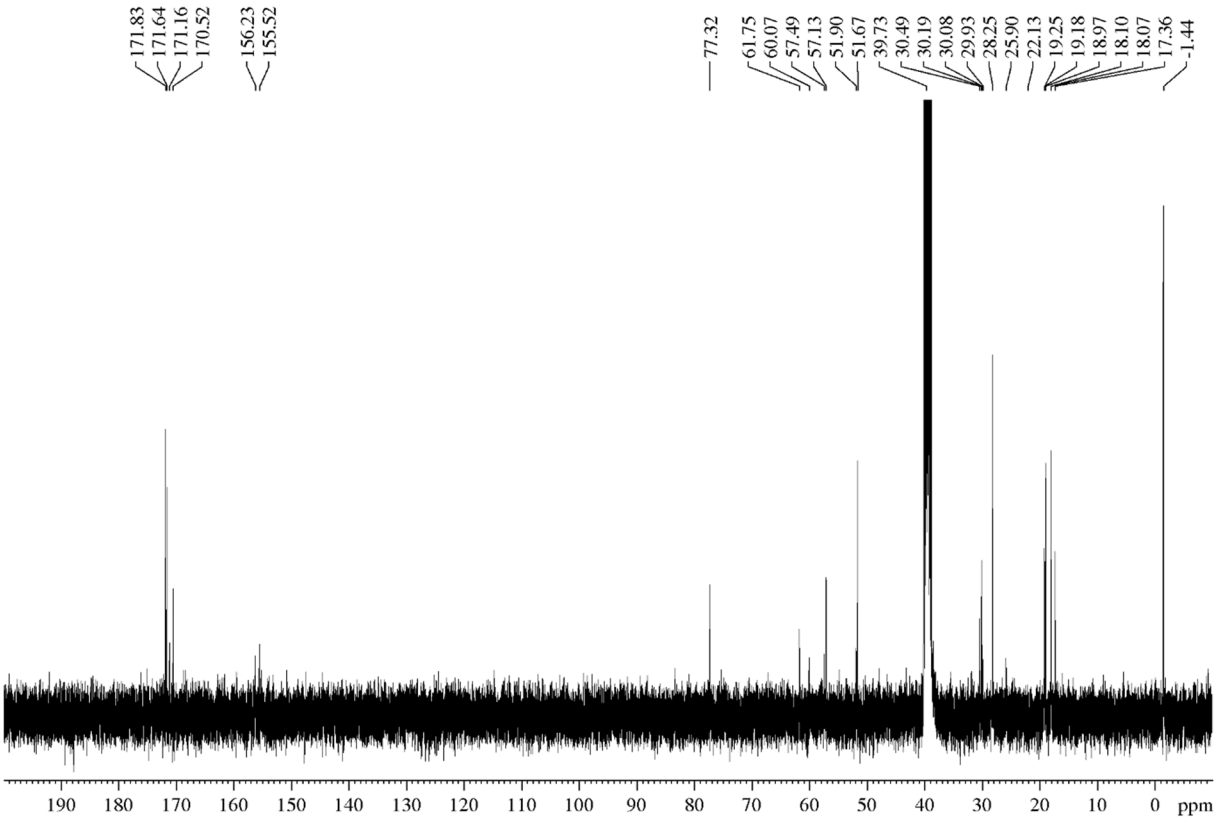
8.14
7.93
7.91
7.75
7.73
7.06
7.04
6.76
4.42
4.37
4.21
4.17
4.08
3.86
3.62
2.89
2.85
2.07
1.91
1.63
1.57
1.52
1.42
1.40
1.31
0.93
0.87
0.80
0.02
Si
O
H
N
O
O
N
H
O
H
N
O
N
H
O
OMe
HN
Boc
127
1.01
0.99
1.04
0.90
0.99
1.00
2.09
2.99
3.00
2.08
3.02
1.03
1.05
11.15
1.99
18.38
9.08
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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51.90
51.67
39.73
30.49
30.19
30.08
29.93
28.25
25.90
22.13
19.25
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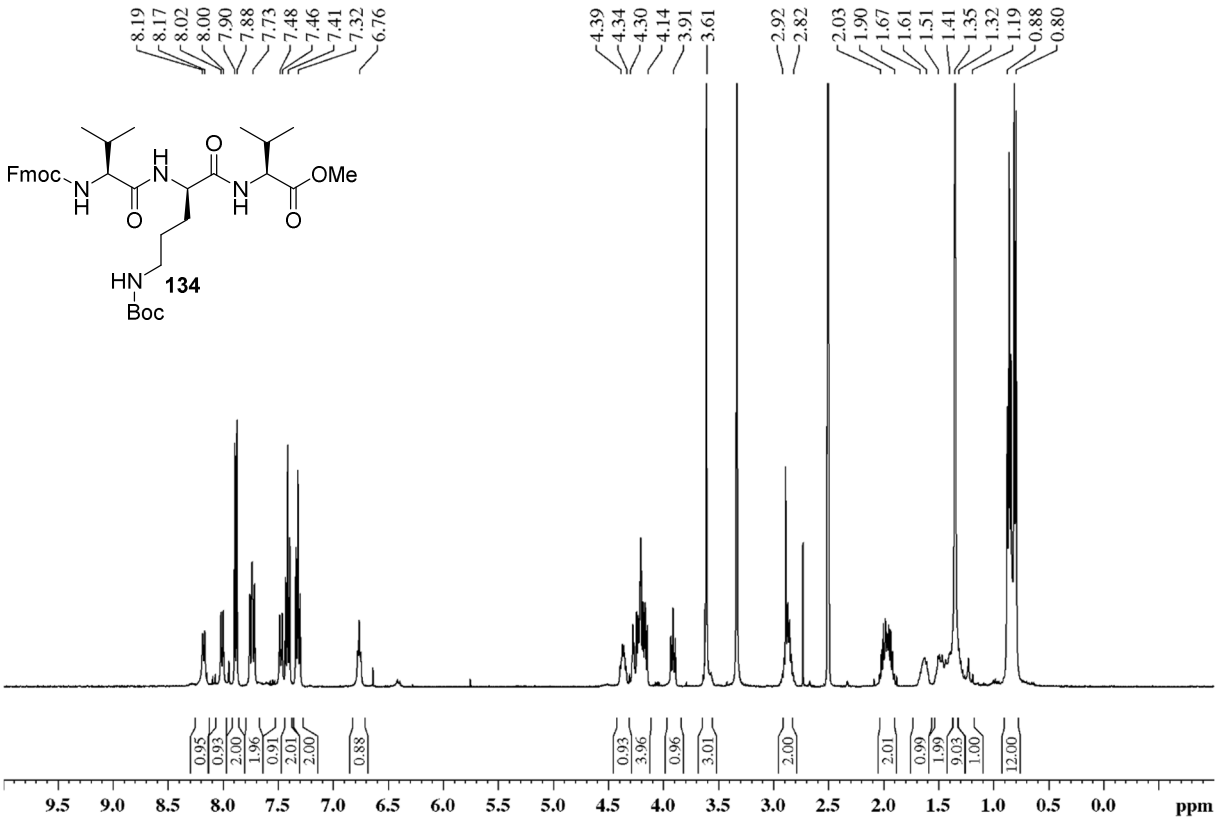
18.97
18.10
18.07
17.36
-1.44
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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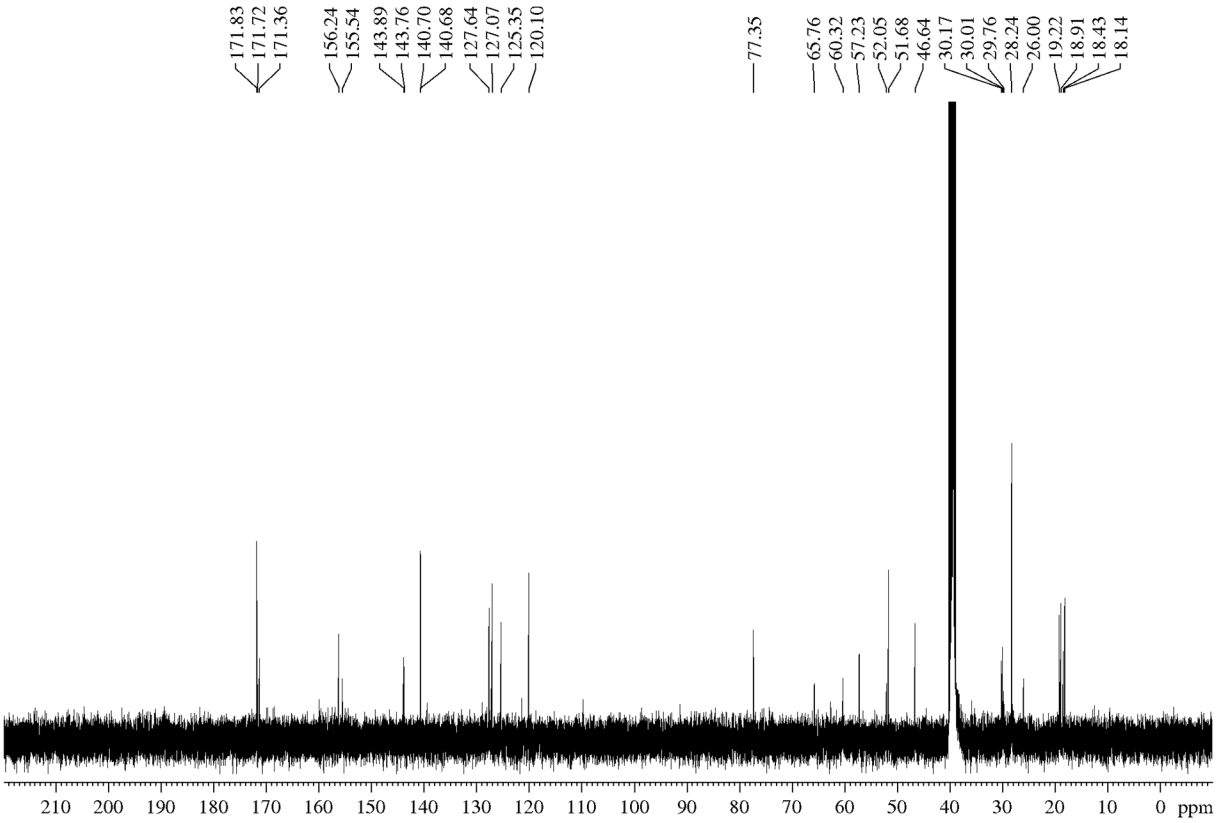
7.48
7.46
7.41
7.32
6.76
4.39
4.34
4.30
4.14
3.91
3.61
2.92
2.82
2.03
1.90
1.67
1.61
1.51
1.41
1.35
1.32
1.19
0.88
0.80
Fmoc
N
H
O
H
N
O
N
H
O
OMe
HN
Boc
134
0.95
0.93
2.00
1.96
0.91
2.01
2.00
0.88
0.93
3.96
0.96
3.01
2.00
2.01
0.99
1.99
9.03
1.00
12.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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143.76
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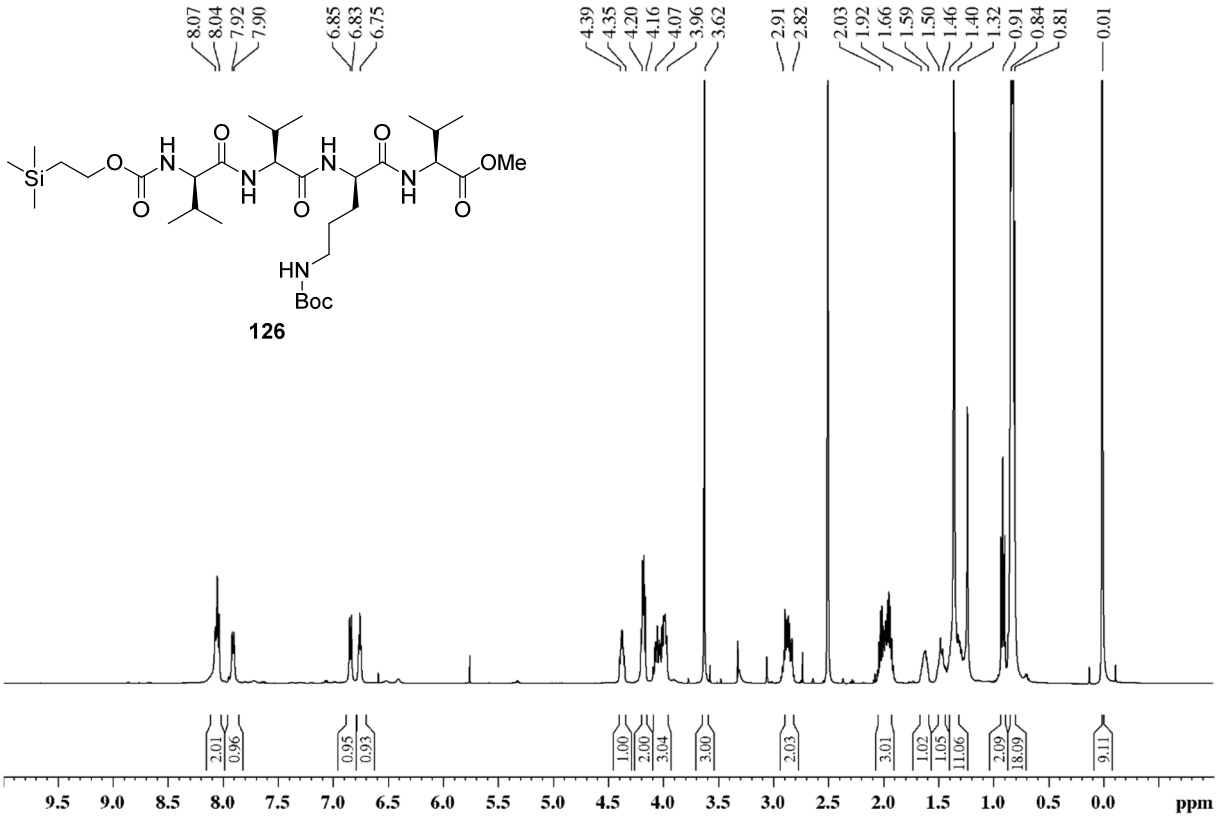
140.68
127.64
127.07
125.35
120.10
77.35
65.76
60.32
57.23
52.05
51.68
46.64
30.17
30.01
29.76
28.24
26.00
19.22
18.91
18.43
18.14
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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8.04
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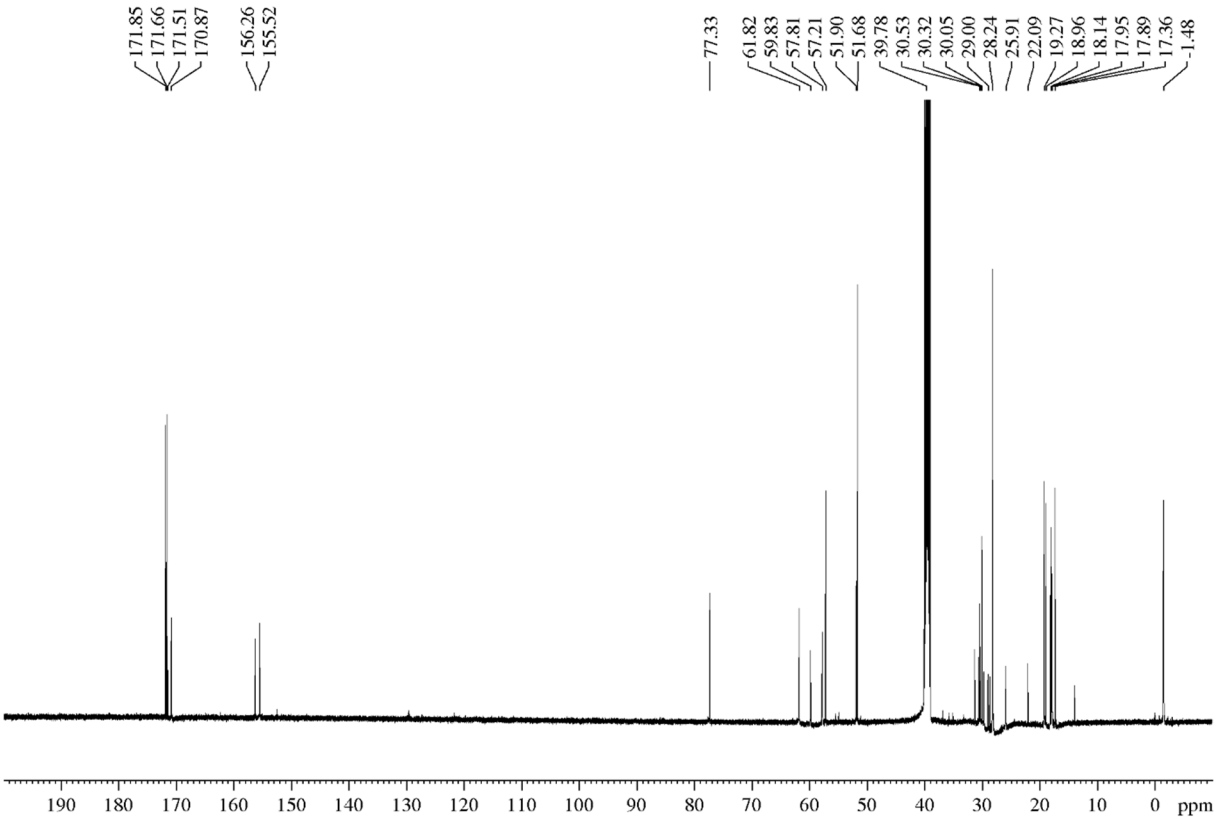
6.75
4.39
4.35
4.20
4.16
4.07
3.96
3.62
2.91
2.82
2.03
1.92
1.66
1.59
1.50
1.46
1.40
1.32
0.91
0.84
0.81
0.01
Si
O
H
N
O
O
N
H
O
H
N
O
N
H
O
OMe
HN
Boc
126
2.01
0.96
0.95
0.93
1.00
2.00
3.04
3.00
2.03
3.01
1.02
1.05
11.06
2.09
18.09
9.11
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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57.21
51.90
51.68
39.78
30.53
30.32
30.05
29.00
28.24
25.91
22.09
19.27
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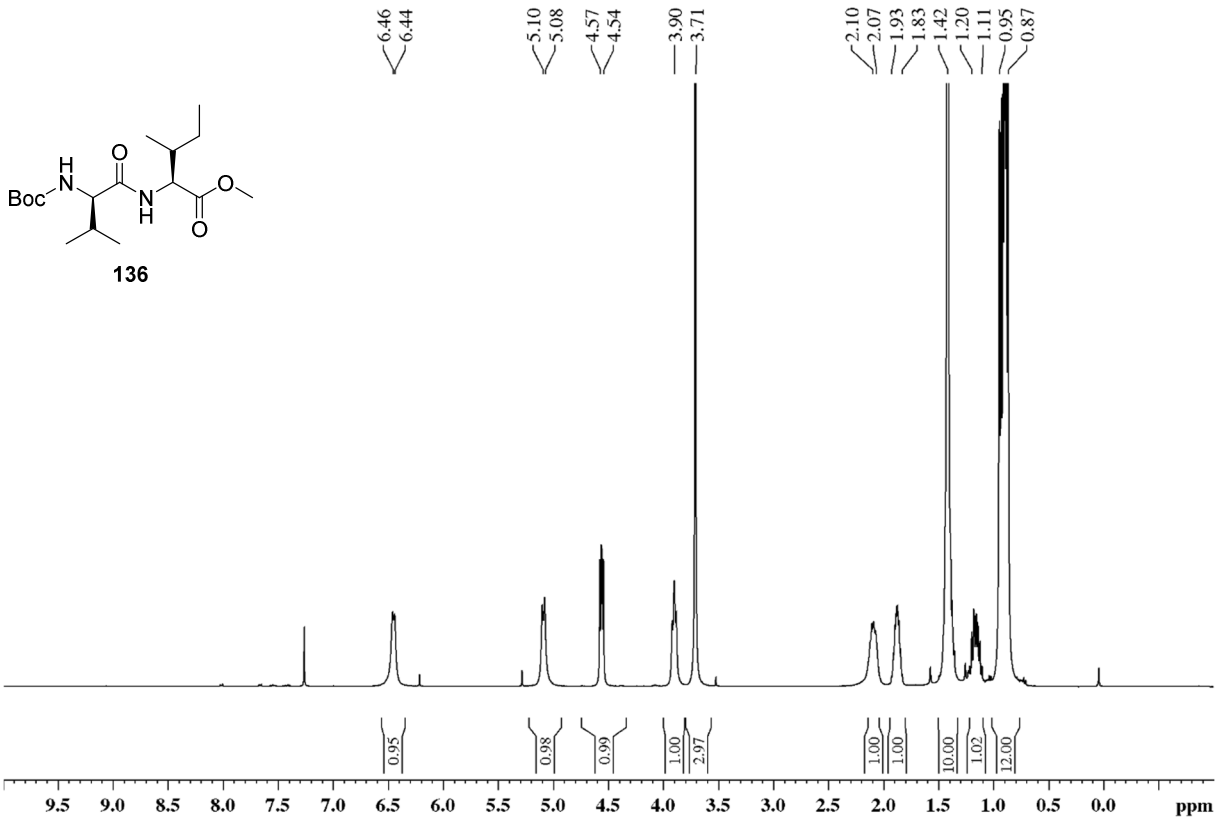
18.14
17.95
17.89
17.36
-1.48
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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4.54
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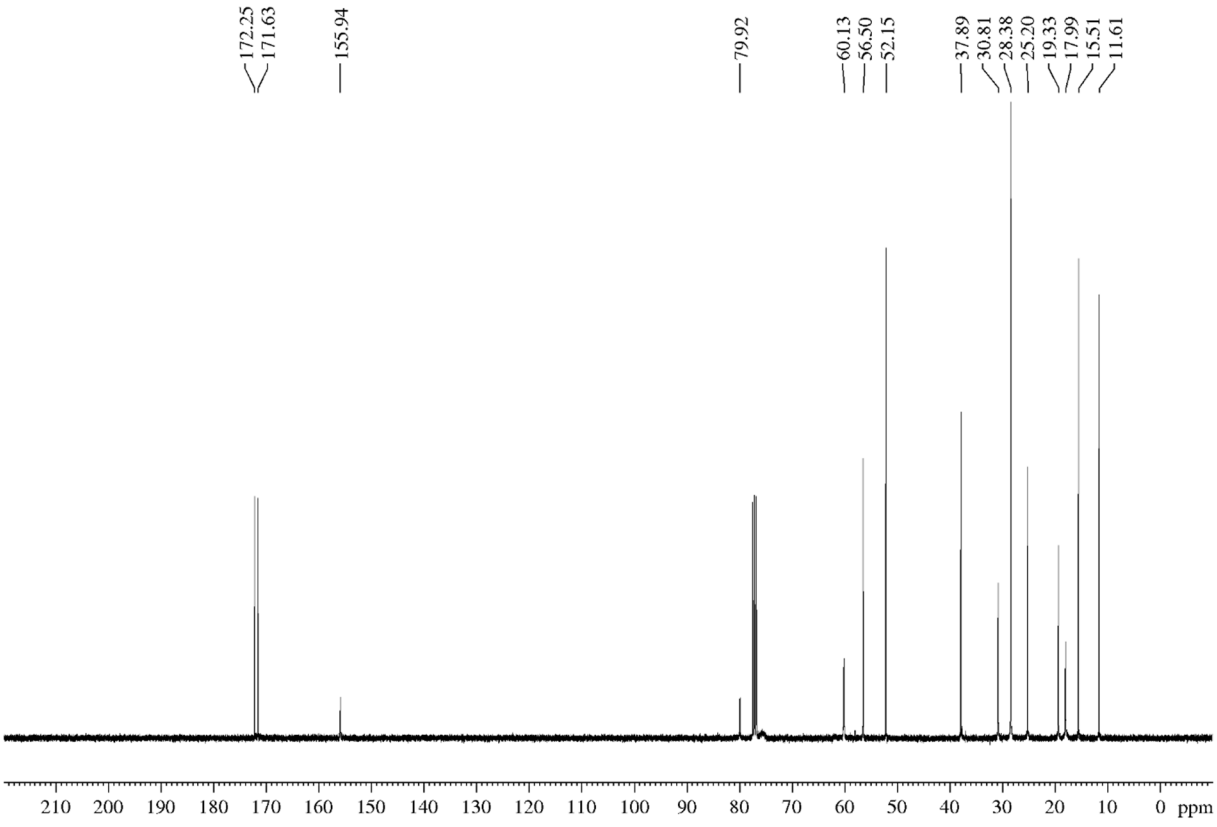
3.71
2.10
2.07
1.93
1.83
1.42
1.20
1.11
0.95
0.87
0.95
0.98
0.99
1.00
2.97
1.00
1.00
10.00
1.02
12.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm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37.89
30.81
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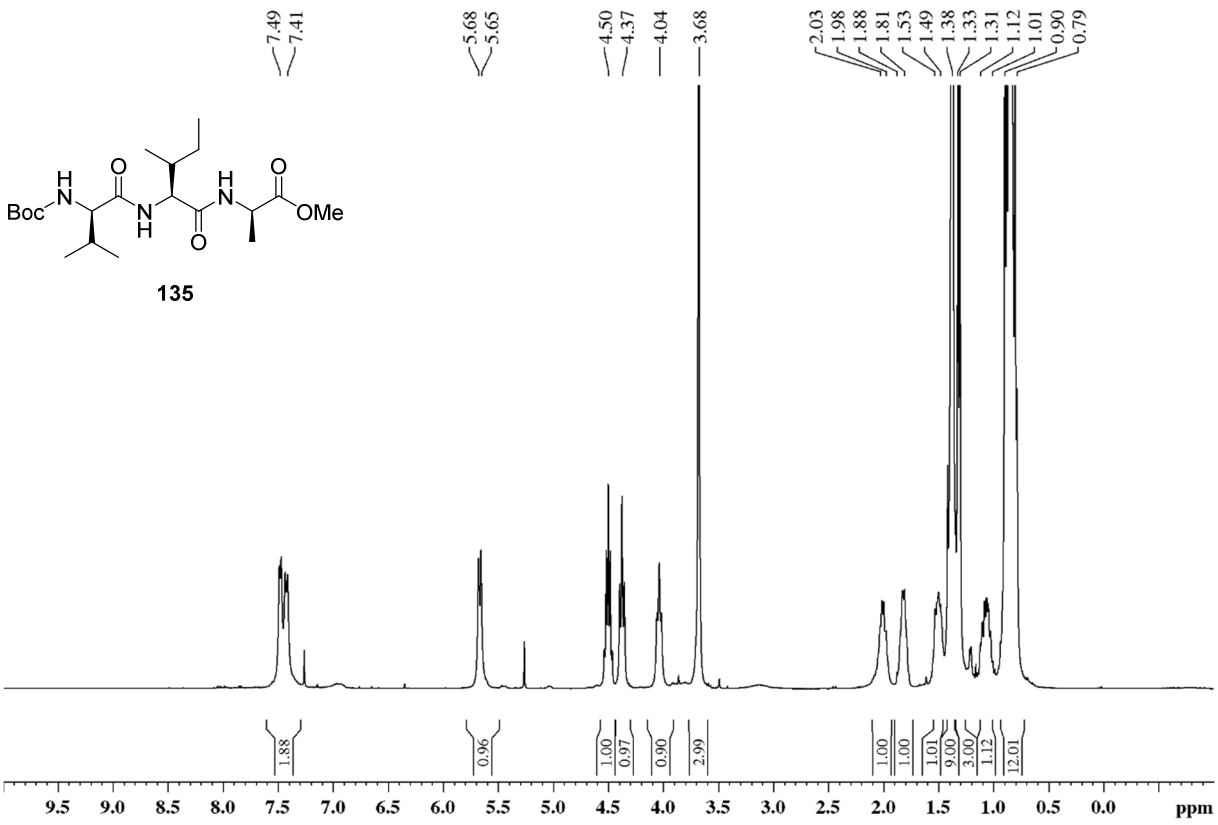
25.20
19.33
17.99
15.51
11.61
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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1.81
1.53
1.49
1.38
1.33
1.31
1.12
1.01
0.90
0.79
Boc
OMe
135
1.88
0.96
1.00
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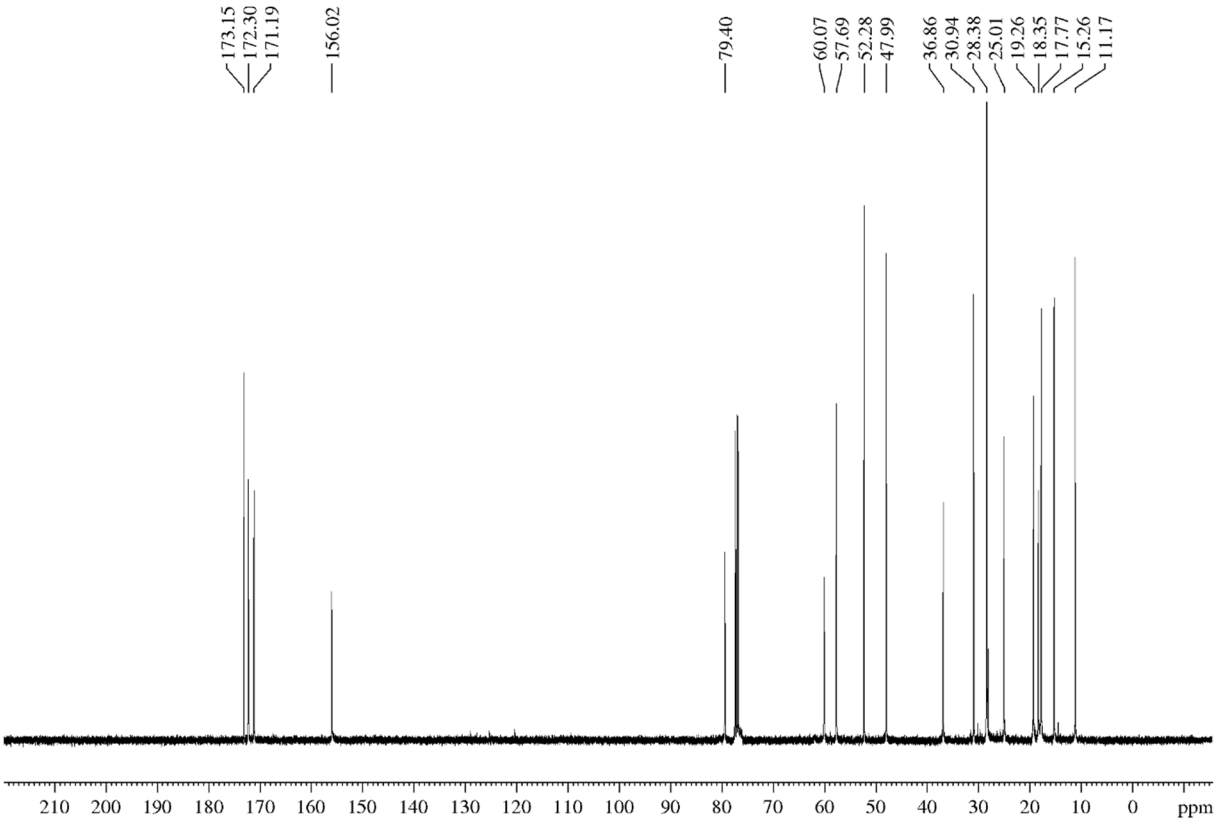
0.90
2.99
1.00
1.00
1.01
9.00
3.00
1.12
12.01
ppm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18.35
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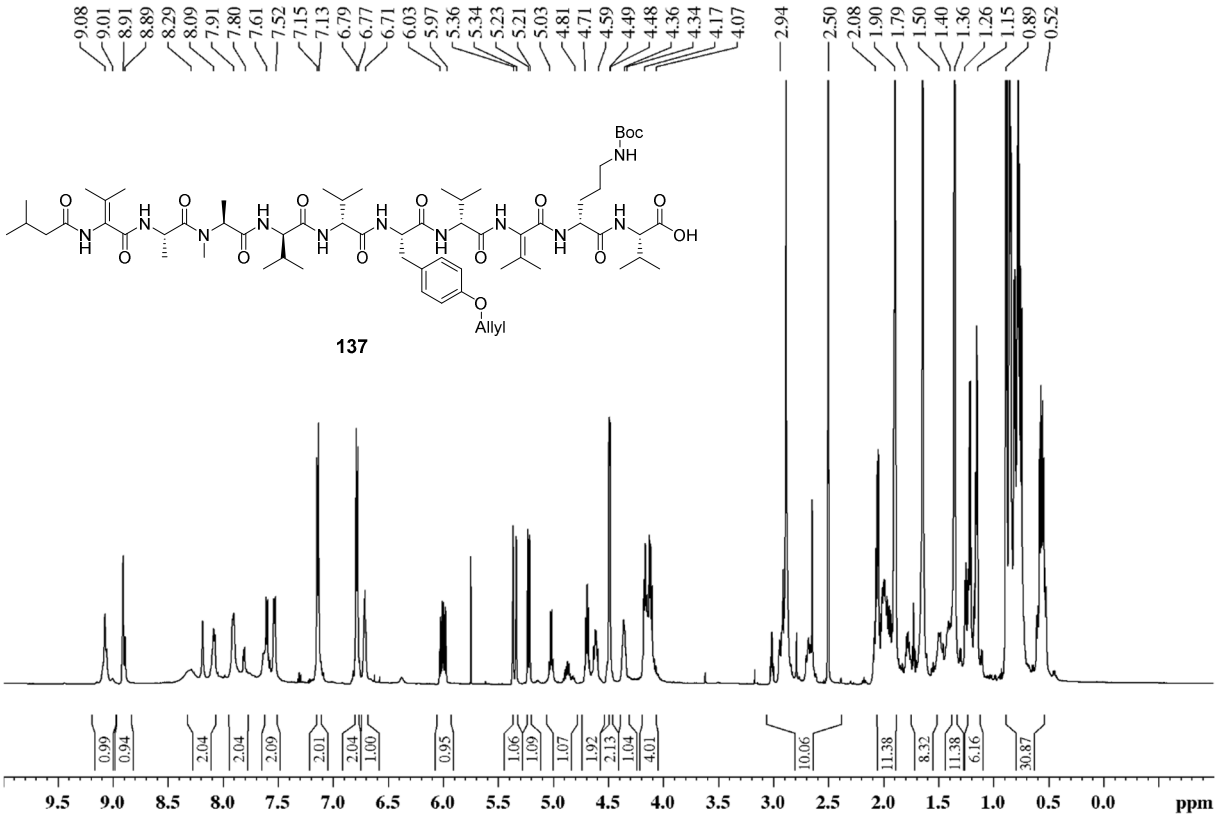
11.17
ppm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6.79
6.77
6.71
6.03
5.97
5.36
5.34
5.23
5.21
5.03
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4.71
4.59
4.49
4.48
4.36
4.34
4.17
4.07
2.94
2.50
2.08
1.90
1.79
1.50
1.40
1.36
1.26
1.15
0.89
0.52
Boc
NH
OH
O
Allyl
137
0.99
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2.04
2.04
2.09
2.01
2.04
1.00
0.95
1.06
1.09
1.07
1.92
2.13
1.04
4.01
10.06
11.38
8.32
11.38
6.16
30.87
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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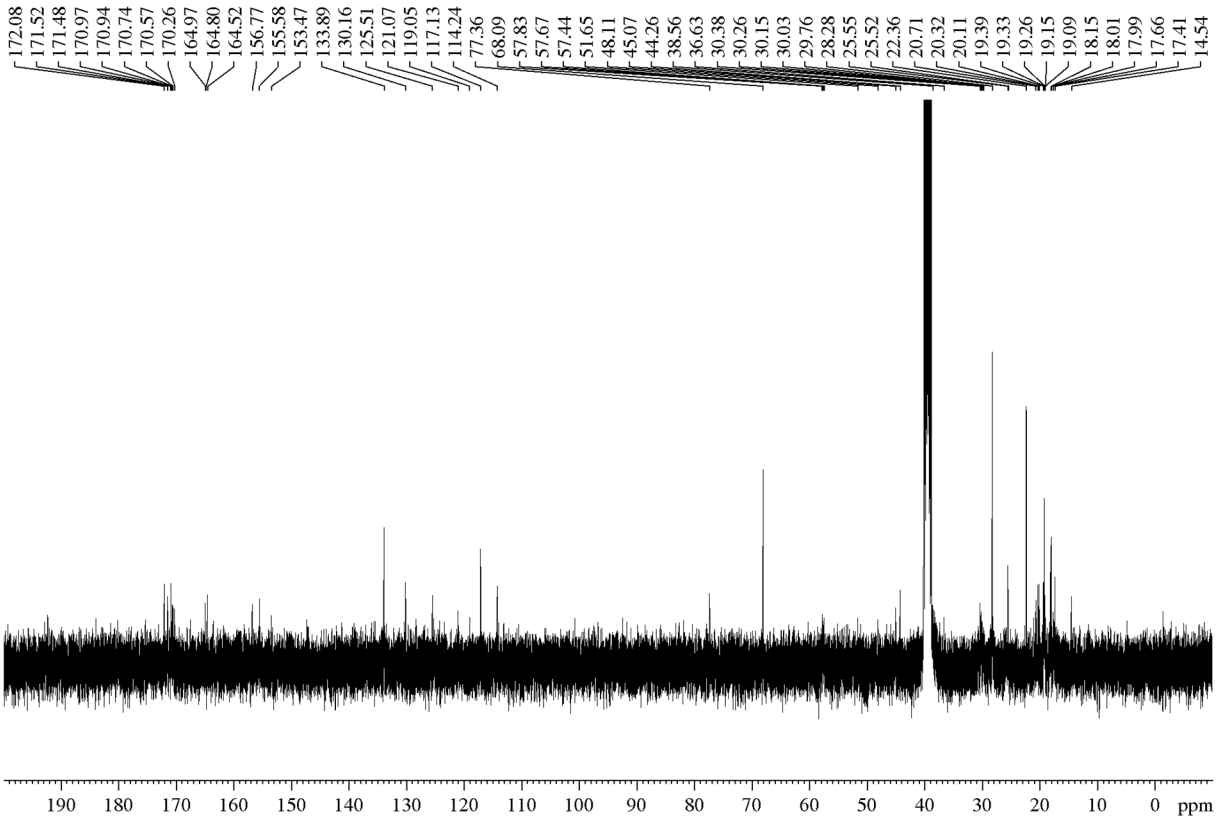
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153.47
133.89
130.16
125.51
121.07
119.05
117.13
114.24
77.36
68.09
57.83
57.67
57.44
51.65
48.11
45.07
44.26
38.56
36.63
30.38
30.26
30.15
30.03
29.76
28.28
25.55
25.52
22.36
20.71
20.32
20.11
19.39
19.33
19.26
19.15
19.09
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18.01
17.99
17.66
17.41
14.54
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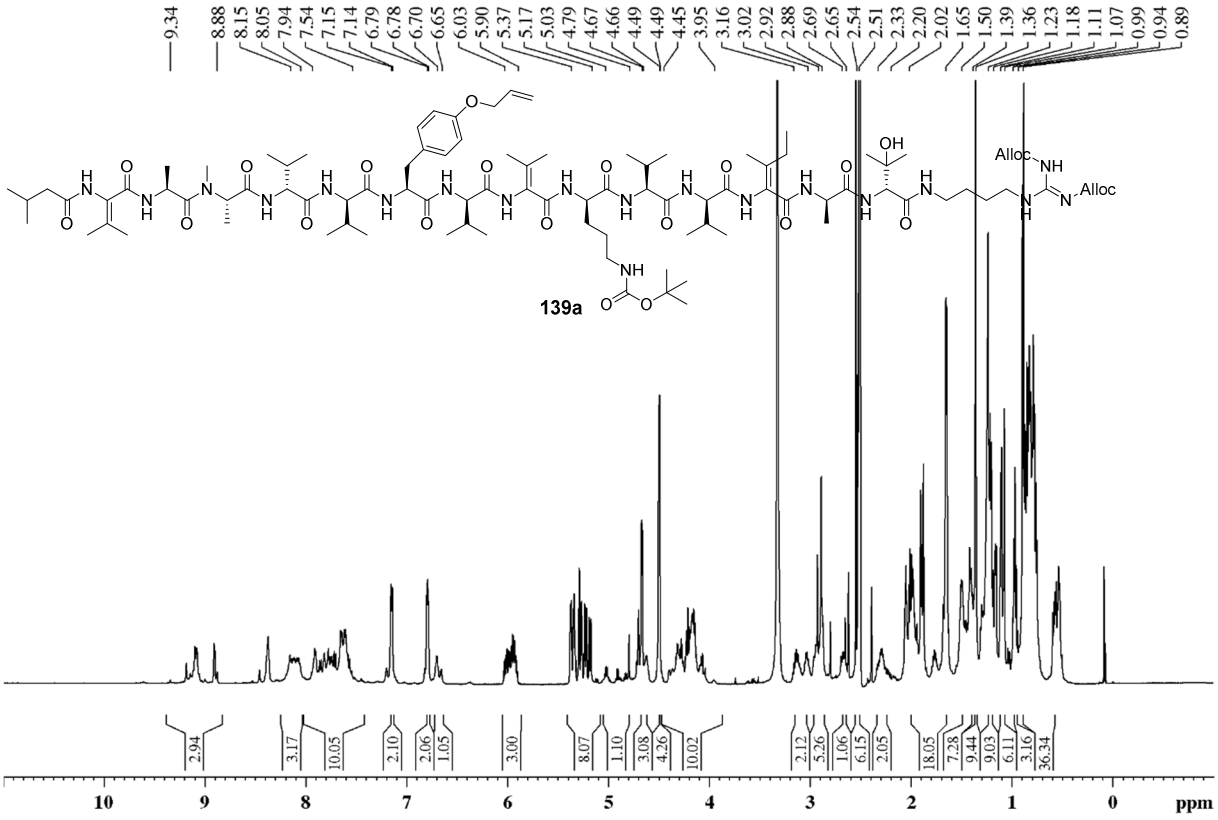
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6.03
5.90
5.37
5.17
5.03
4.79
4.67
4.66
4.49
4.49
4.45
3.95
3.16
3.02
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2.88
2.69
2.65
2.54
2.51
2.33
2.20
2.02
1.65
1.50
1.39
1.36
1.23
1.18
1.11
1.07
0.99
0.94
0.89
OH
Alloc
NH
Alloc
NH
139a
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10.05
2.10
2.06
1.05
3.00
8.07
1.10
3.08
4.26
10.02
2.12
5.26
1.06
6.15
2.05
18.05
7.28
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6
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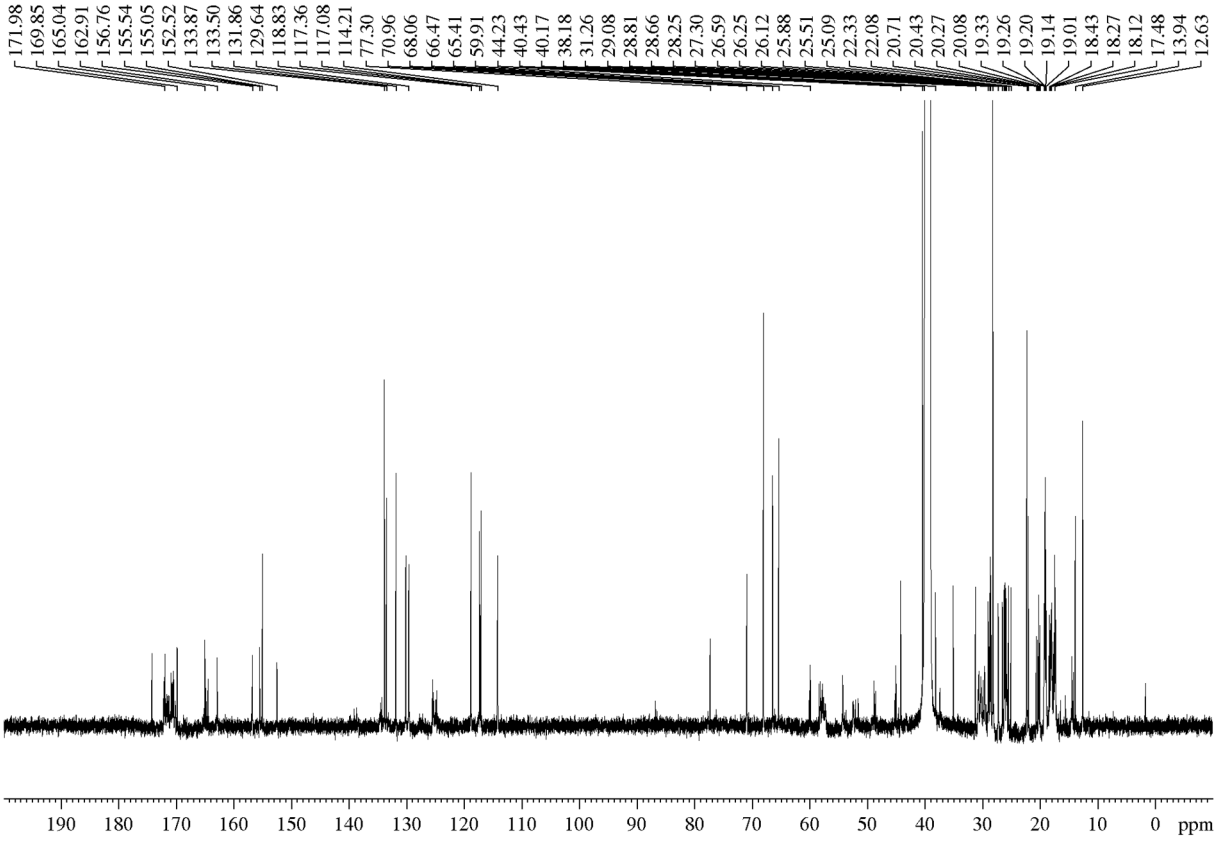
0
ppm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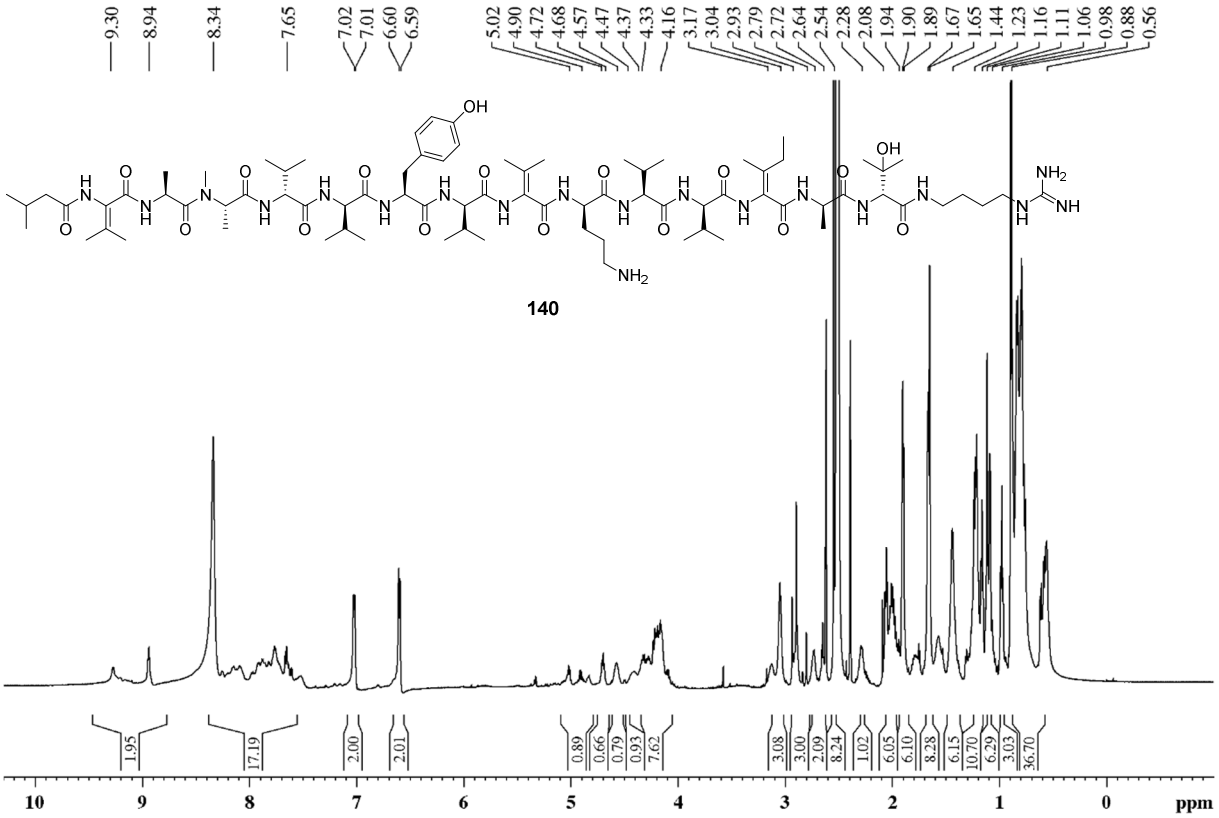
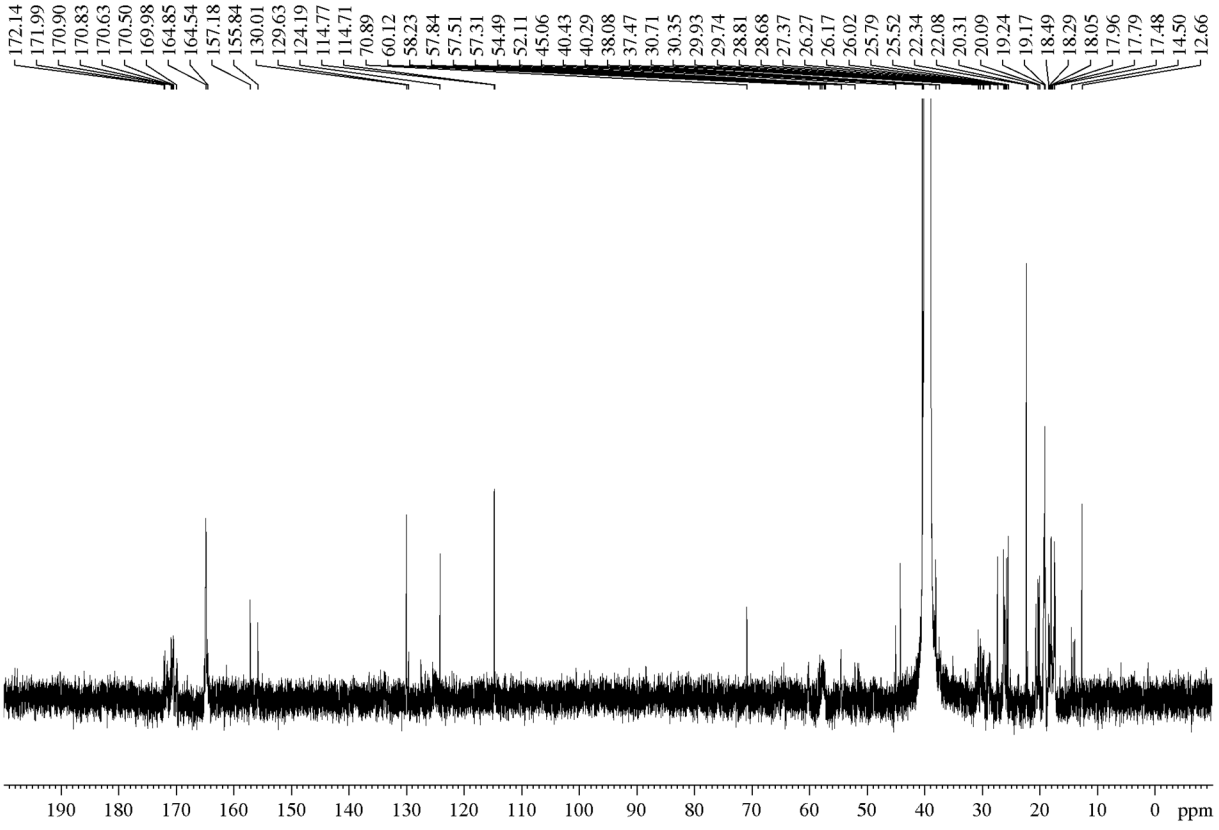
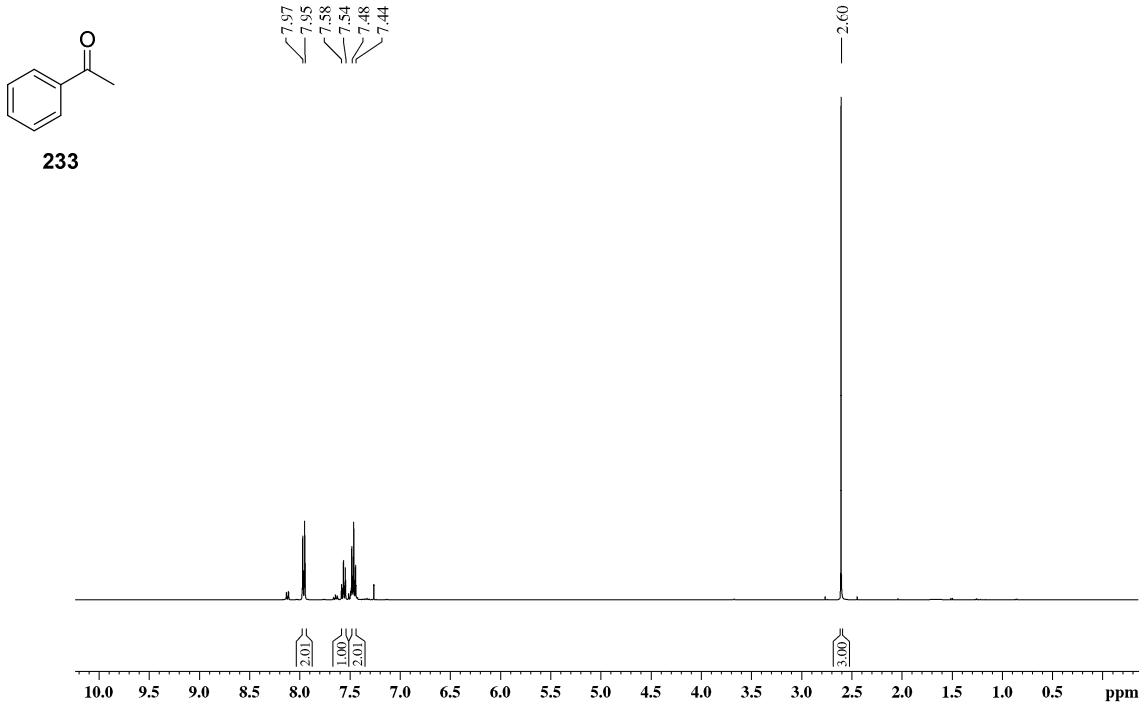
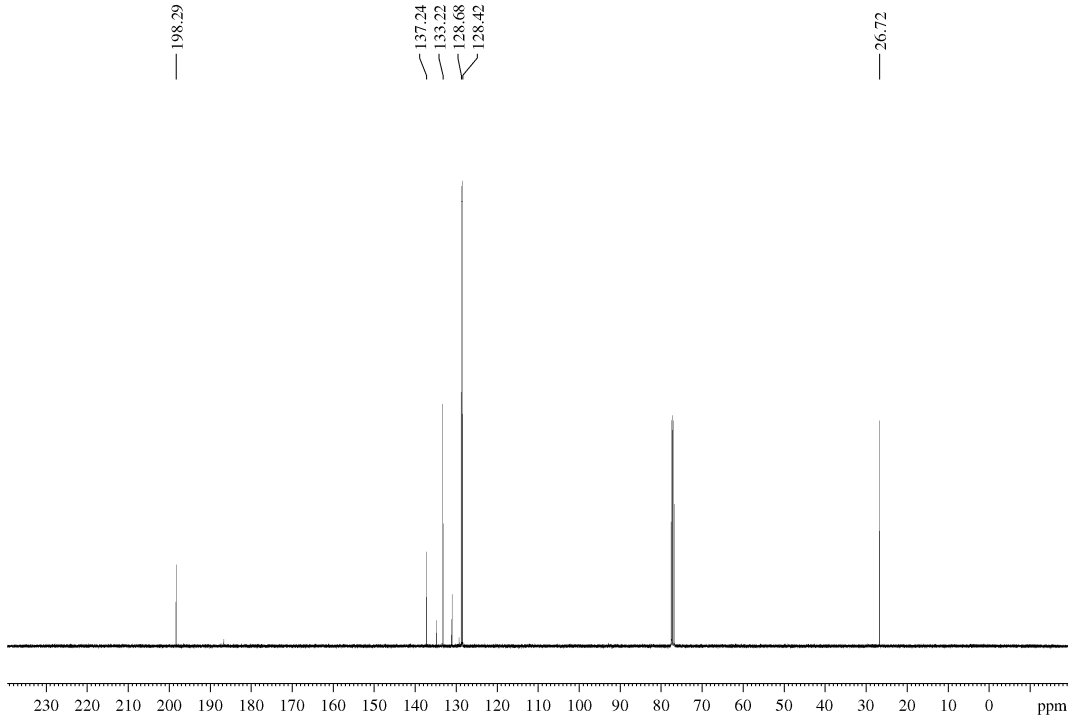
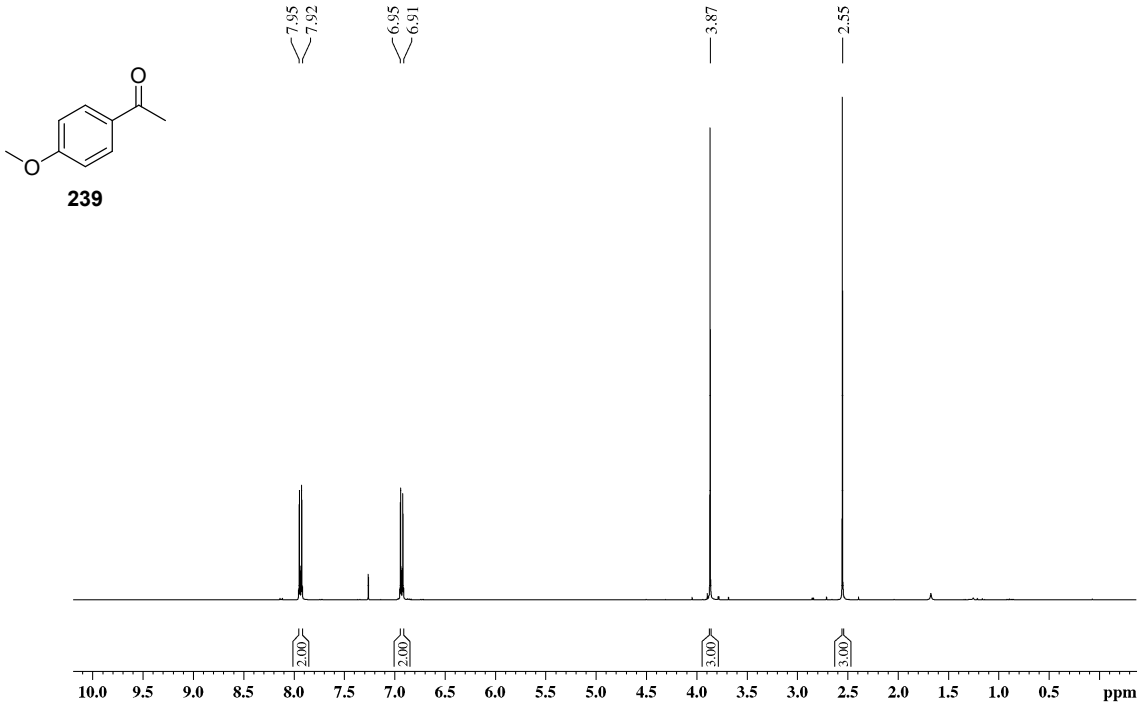
131.86
129.64
118.83
117.36
117.08
114.21
77.30
70.96
68.06
66.47
65.41
59.91
44.23
40.43
40.17
38.18
31.26
29.08
28.81
28.66
28.25
27.30
26.59
26.25
26.12
25.88
25.51
25.09
22.33
22.08
20.71
20.43
20.27
20.08
19.33
19.26
19.20
19.14
19.01
18.43
18.27
18.12
17.48
13.94
12.63
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


9.30
8.94
8.34
7.65
7.02
7.01
6.60
6.59
5.02
4.90
4.72
4.68
4.57
4.47
4.37
4.33
4.16
3.17
3.04
2.93
2.79
2.72
2.64
2.54
2.28
2.08
1.94
1.90
1.89
1.67
1.65
1.44
1.23
1.16
1.11
1.06
0.98
0.88
0.56
OH
NH2
NH
NH2
140
1.95
17.19
2.00
2.01
0.89
0.66
0.79
0.93
7.62
3.08
3.00
2.09
8.24
1.02
6.05
6.10
8.28
6.15
10.70
6.29
3.03
36.70
10
9
8
7
6
5
4
3
2
1
0
ppm

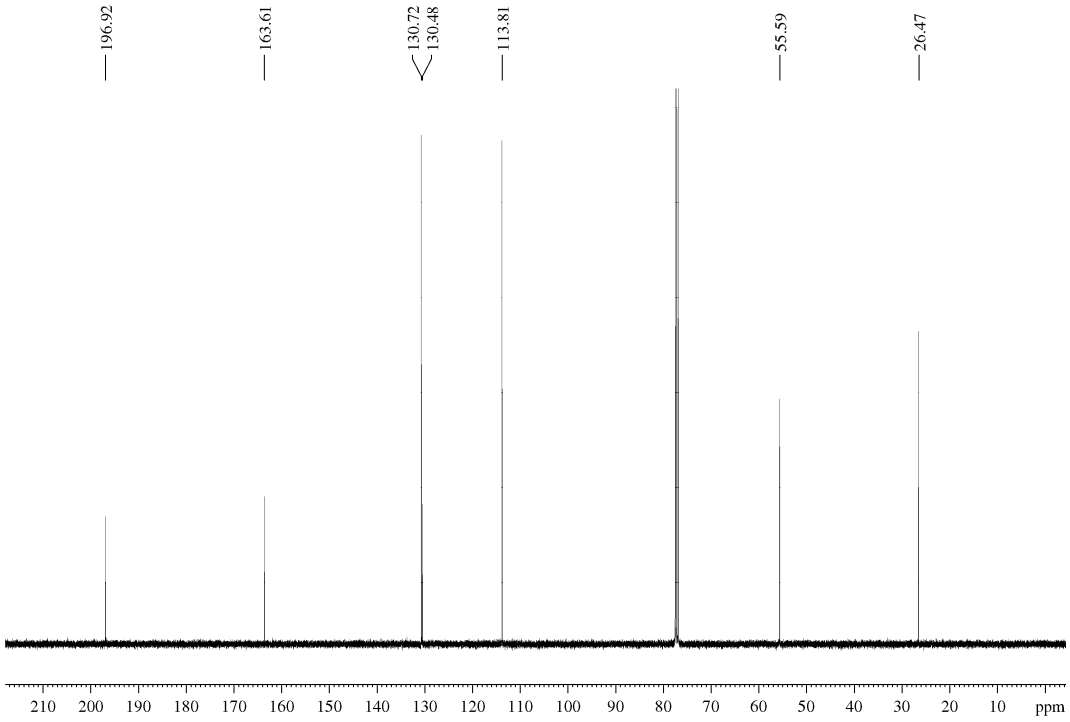

172.14
171.99
170.90
170.83
170.63
170.50
169.98
164.85
164.54
157.18
155.84
130.01
129.63
124.19
114.77
114.71
70.89
60.12
58.23
57.84
57.51
57.31
54.49
52.11
45.06
40.43
40.29
38.08
37.47
30.71
30.35
29.93
29.74
28.81
28.68
27.37
26.27
26.17
26.02
25.79
25.52
22.34
22.08
20.31
20.09
19.24
19.17
18.49
18.29
18.05
17.96
17.79
17.48
14.50
12.66
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

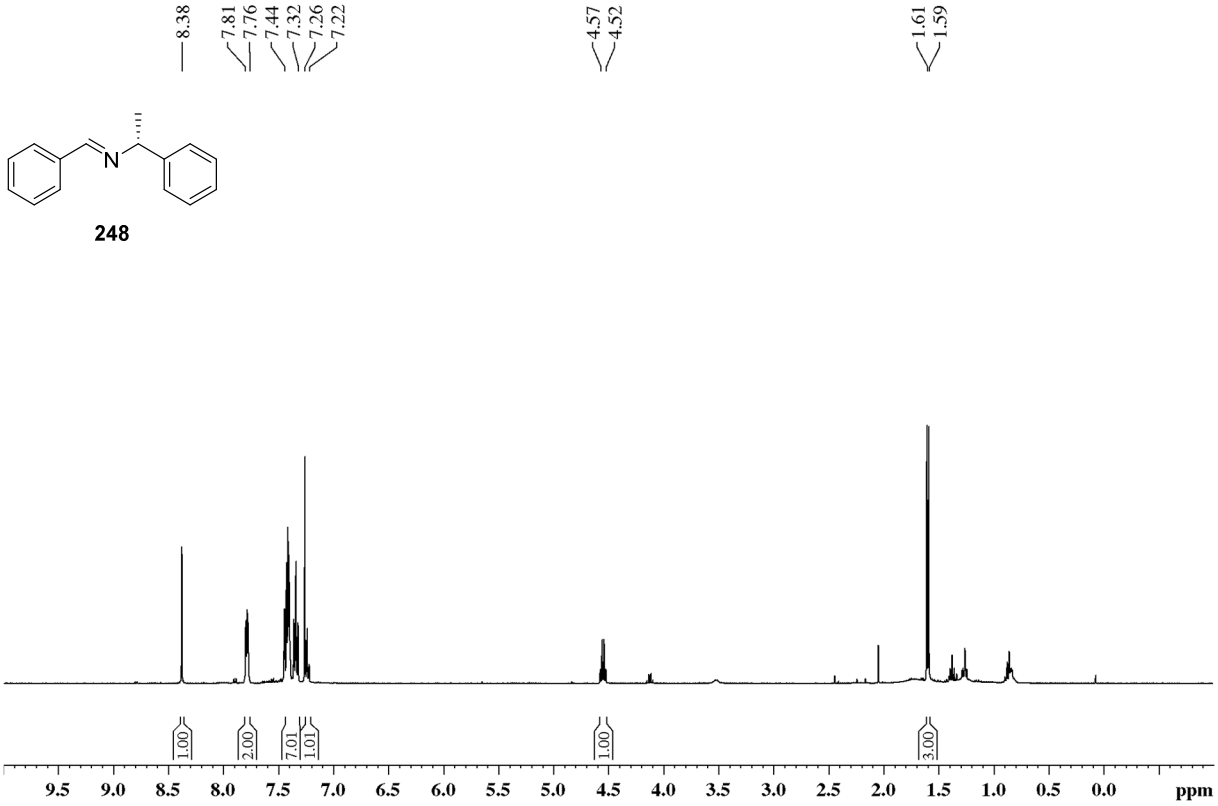

O
233
7.97
7.95
7.58
7.54
7.48
7.44
2.60
2.01
1.00
2.01
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

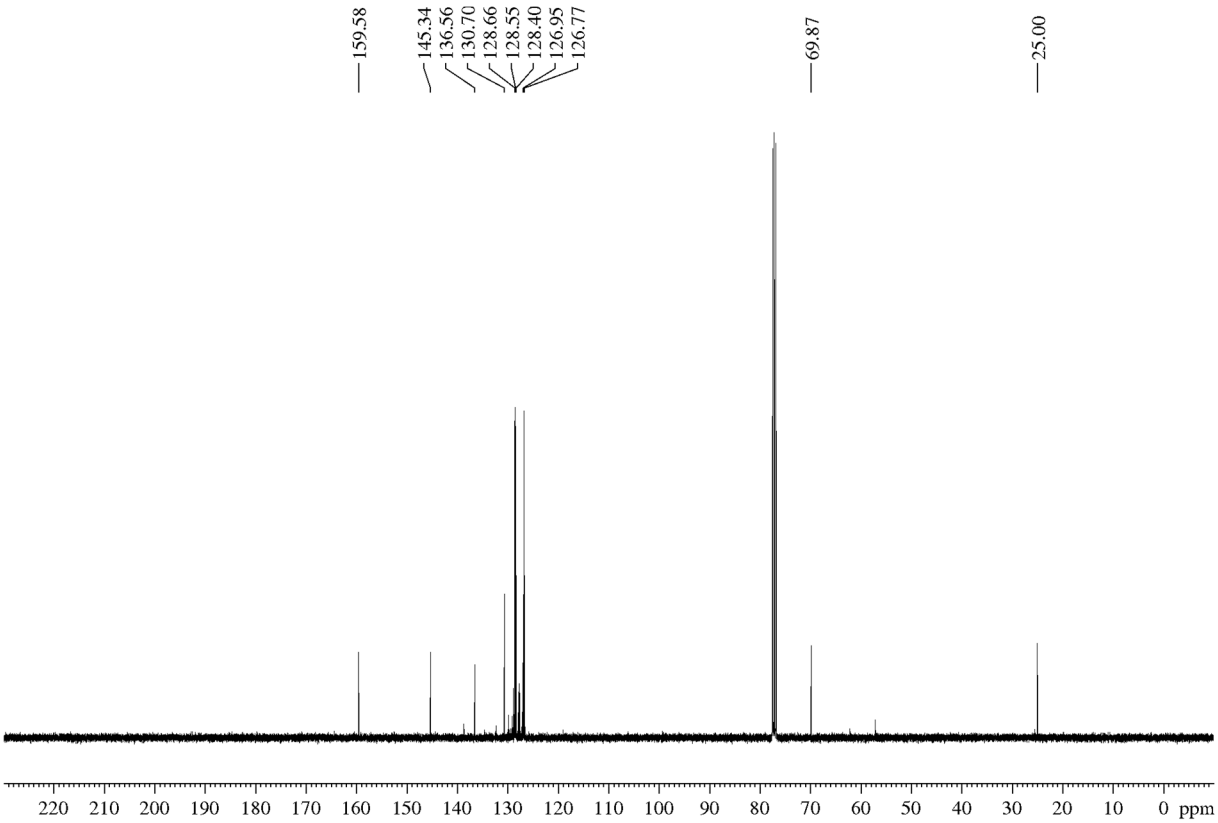

198.29
137.24
133.22
128.68
128.42
26.72
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

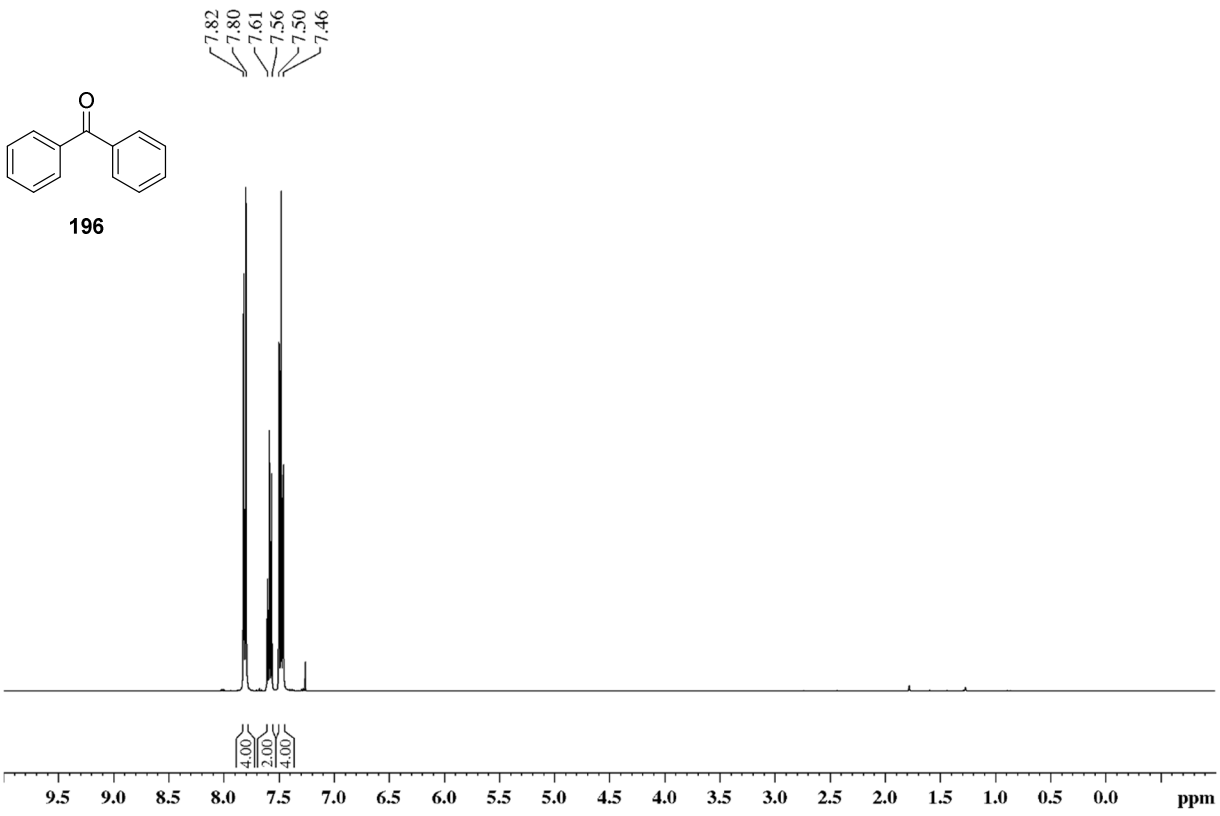

7.95
7.92
6.95
6.91
3.87
2.55
2.00
2.00
3.00
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

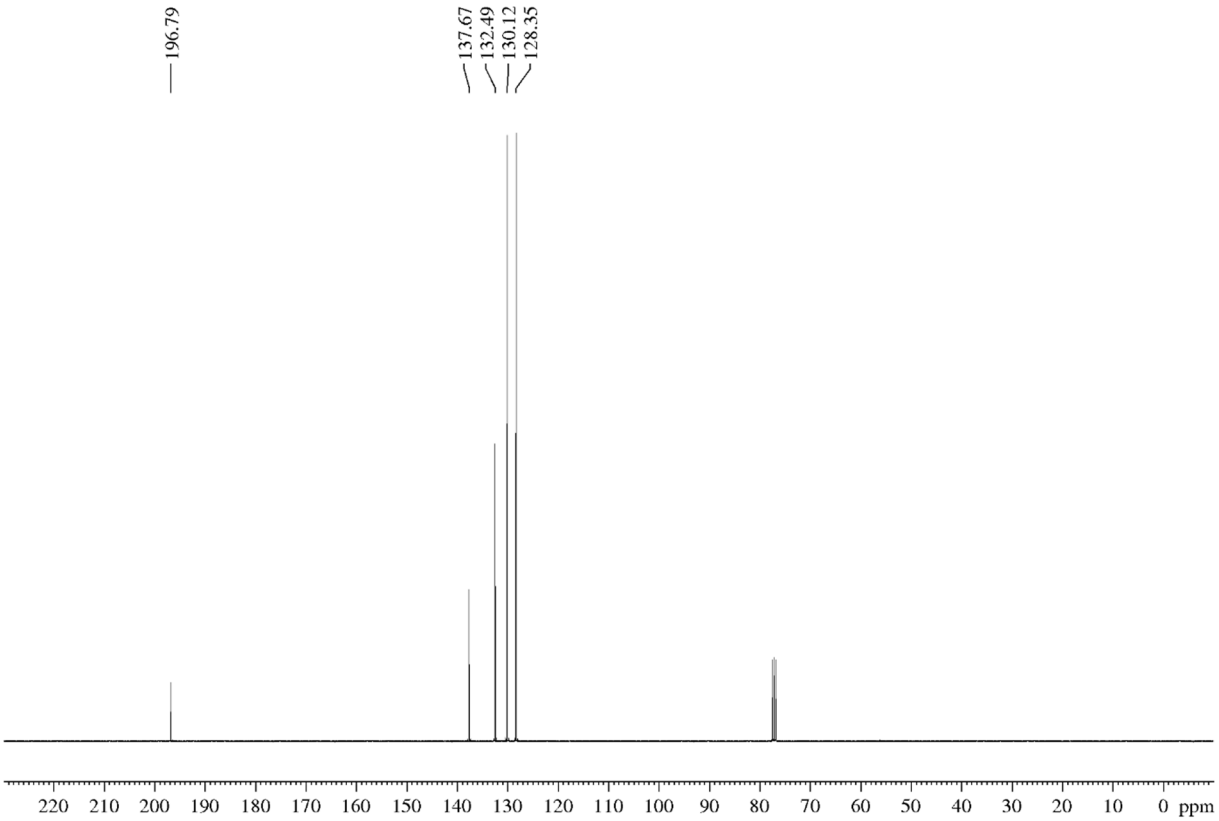
239

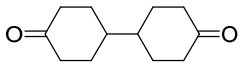

196.92
163.61
130.72
130.48
113.81
55.59
26.47
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


8.38
7.81
7.76
7.44
7.32
7.26
7.22
4.57
4.52
1.61
1.59
N
248
1.00
2.00
7.01
1.01
1.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


159.58
145.34
136.56
130.70
128.66
128.55
128.40
126.95
126.77
69.87
25.00
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

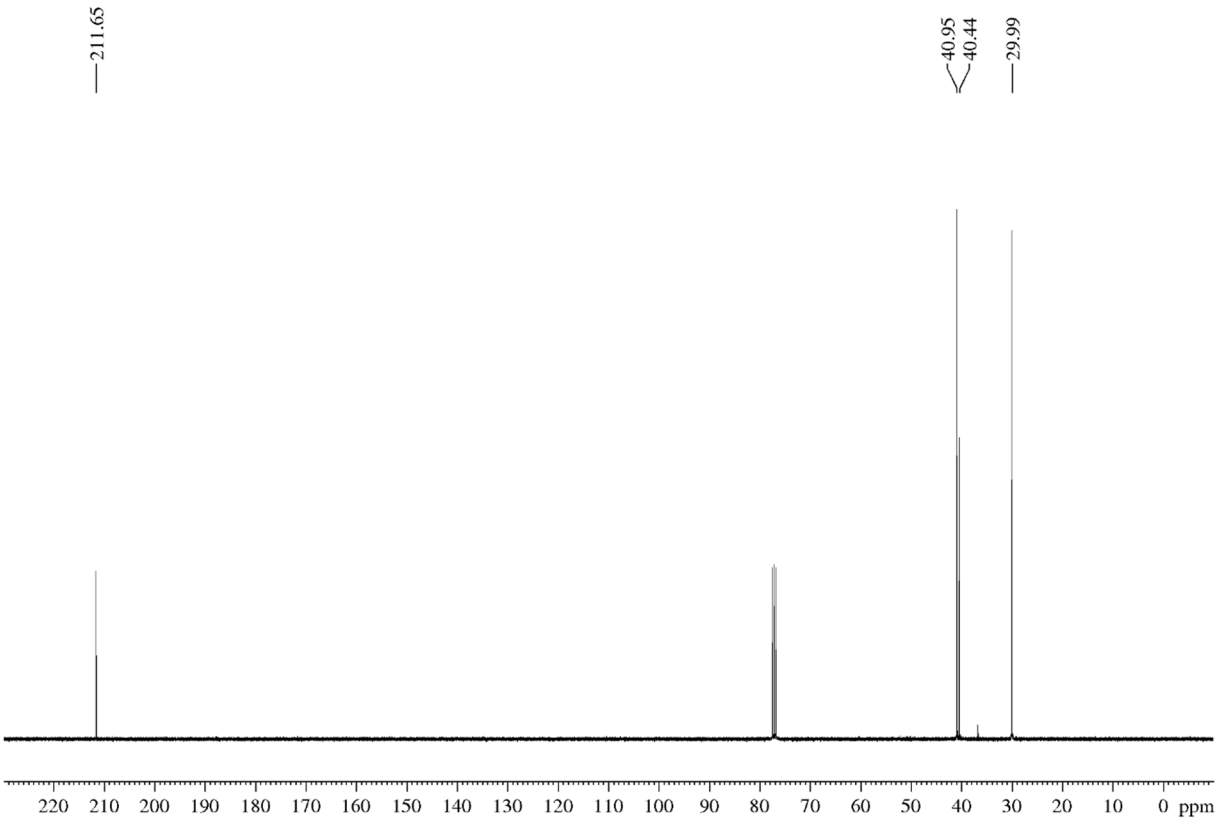

7.82
7.80
7.61
7.56
7.50
7.46
O
196
4.00
2.00
4.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

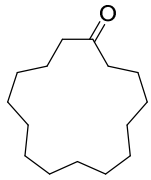

196.79
137.67
132.49
130.12
128.35
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



258

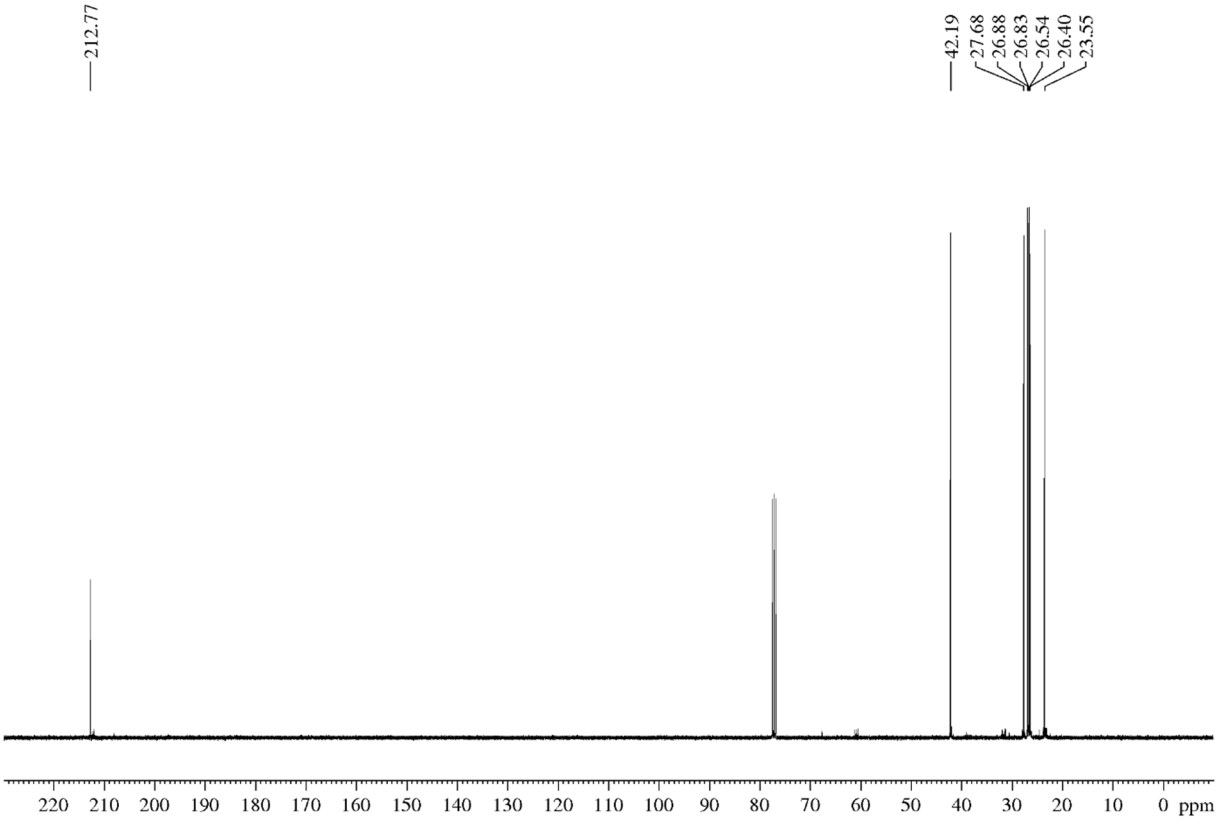
2.40
2.27
2.07
2.03
1.72
1.67
1.54
1.44
8.00
4.00
2.00
4.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

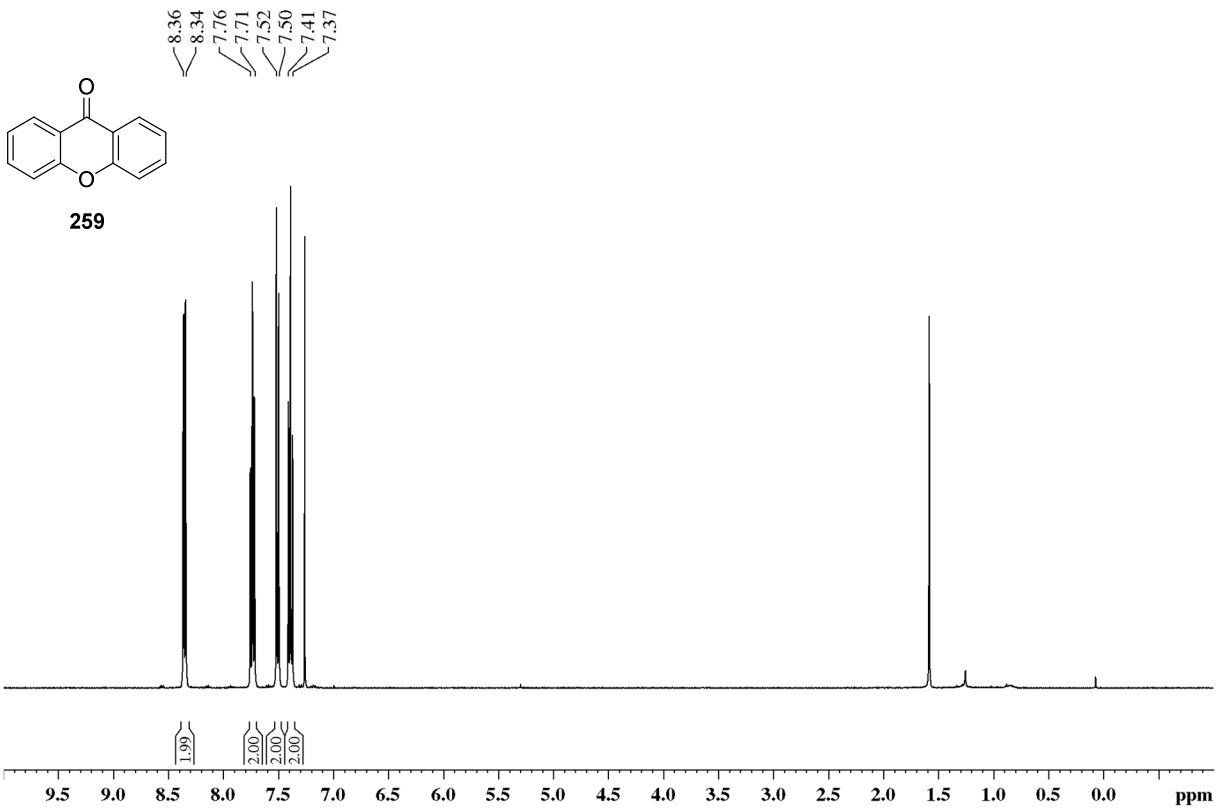

211.65
40.95
40.44
29.99
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

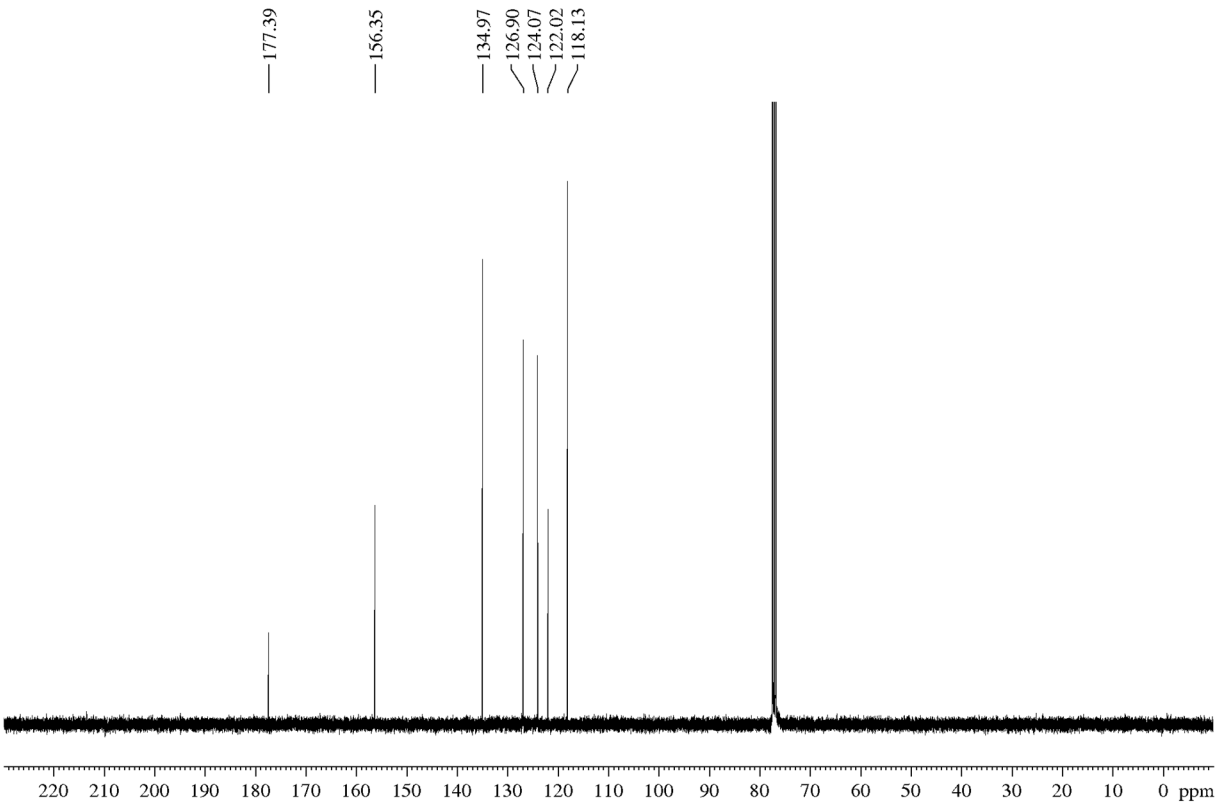


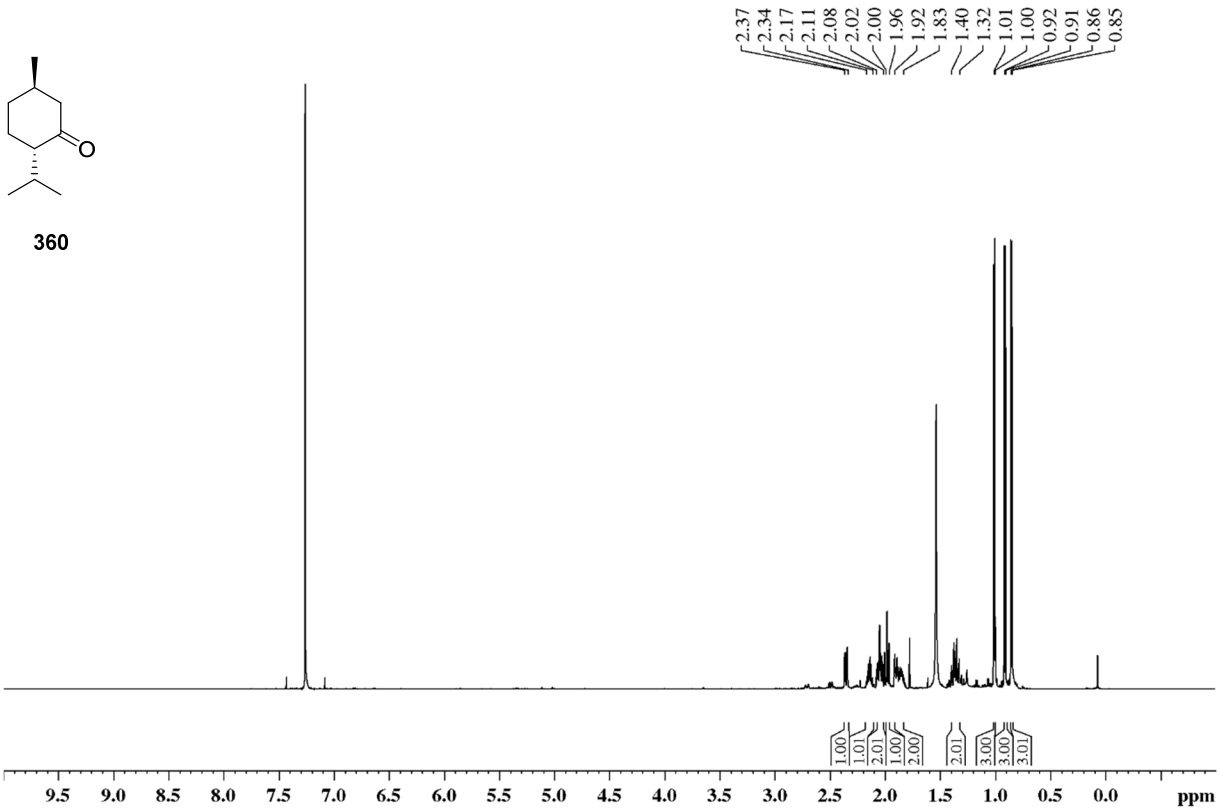
235

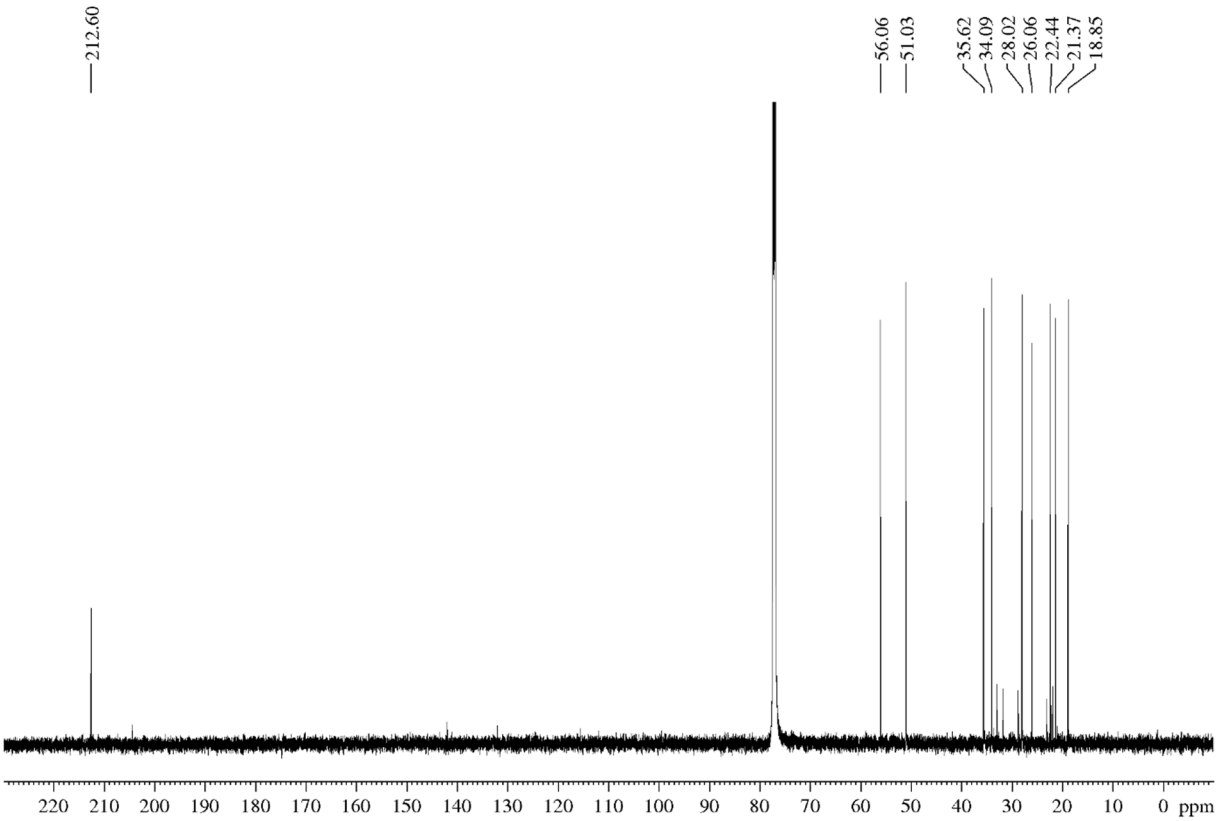
2.39
1.66
1.59
1.31
1.26
4.00
4.00
20.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

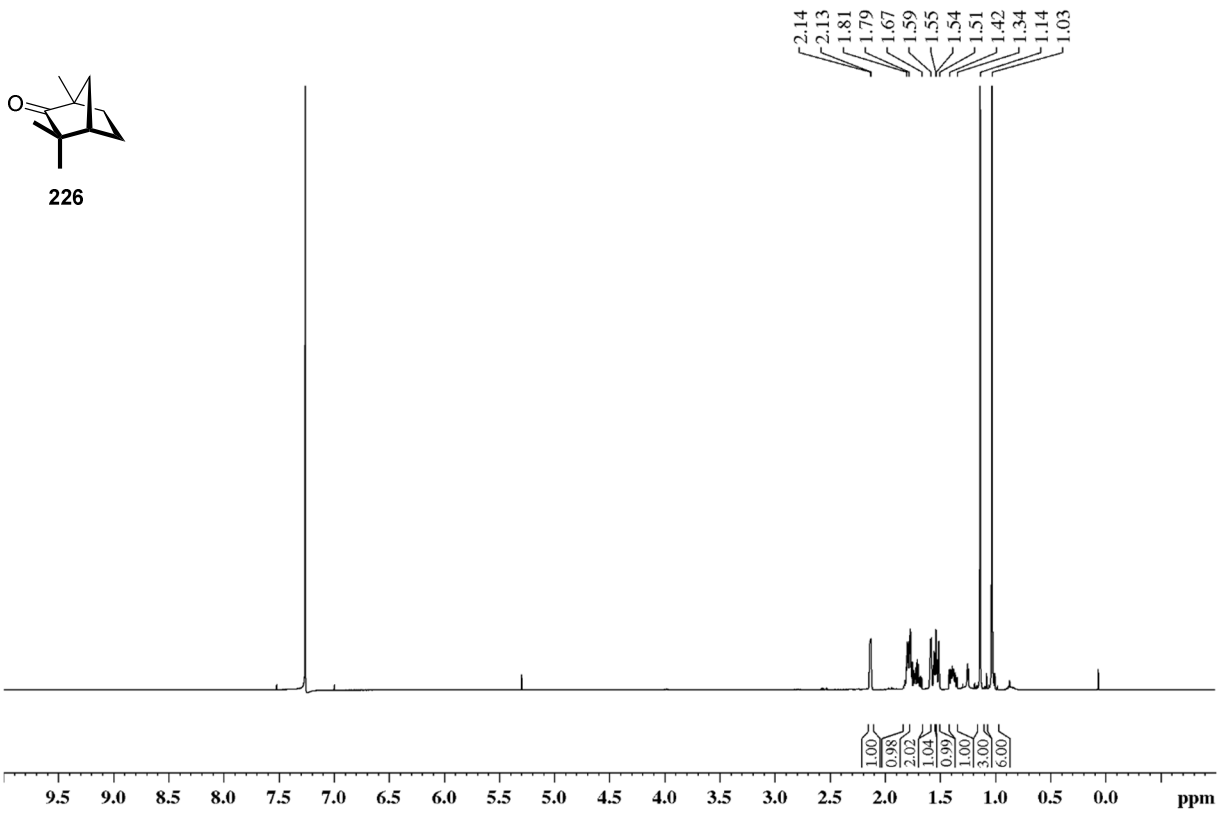

212.77
42.19
27.68
26.88
26.83
26.54
26.40
23.55
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

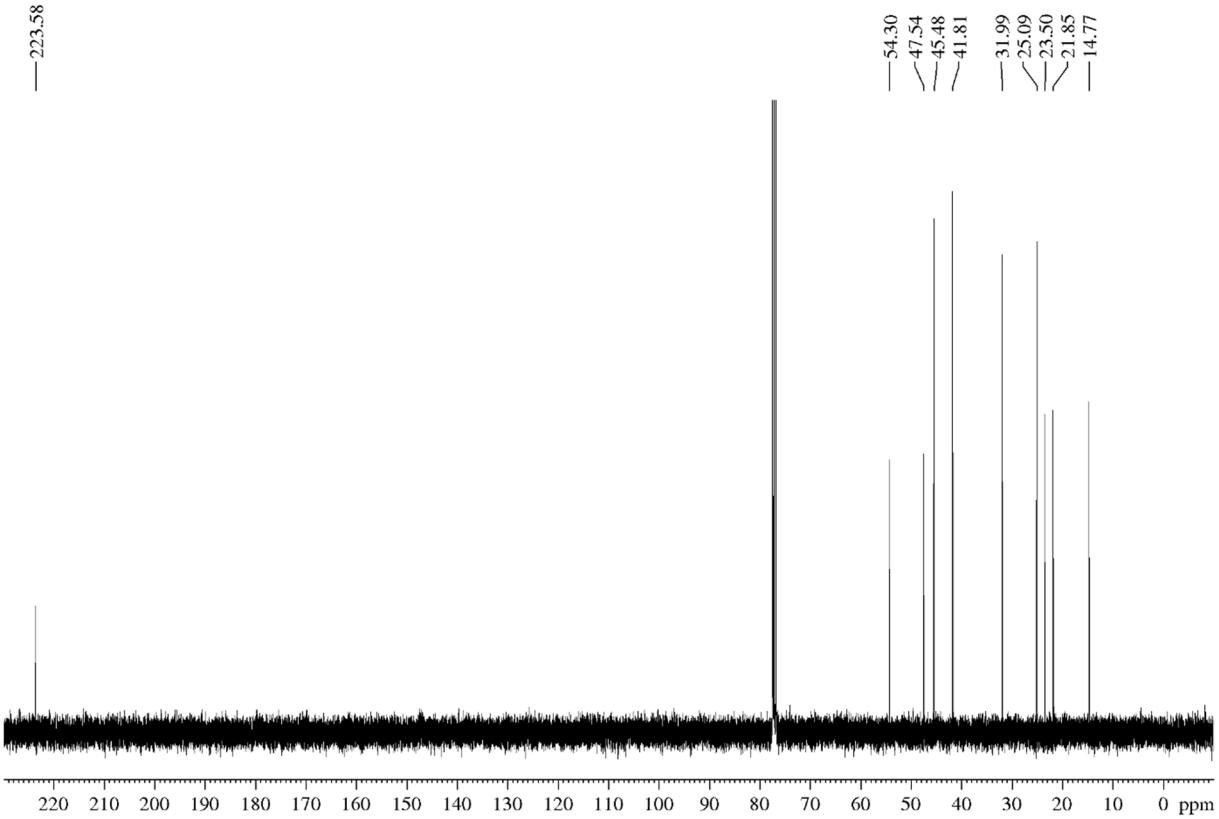

8.36
8.34
7.76
7.71
7.52
7.50
7.41
7.37
O
O
259
1.99
2.00
2.00
2.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

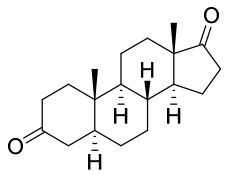

177.39
156.35
134.97
126.90
124.07
122.02
118.13
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


2.37
2.34
2.17
2.11
2.08
2.02
2.00
1.96
1.92
1.83
1.40
1.32
1.01
1.00
0.92
0.91
0.86
0.85
O
360
1.00
1.01
2.01
1.00
2.00
2.01
3.00
3.00
3.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


212.60
56.06
51.03
35.62
34.09
28.02
26.06
22.44
21.37
18.85
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

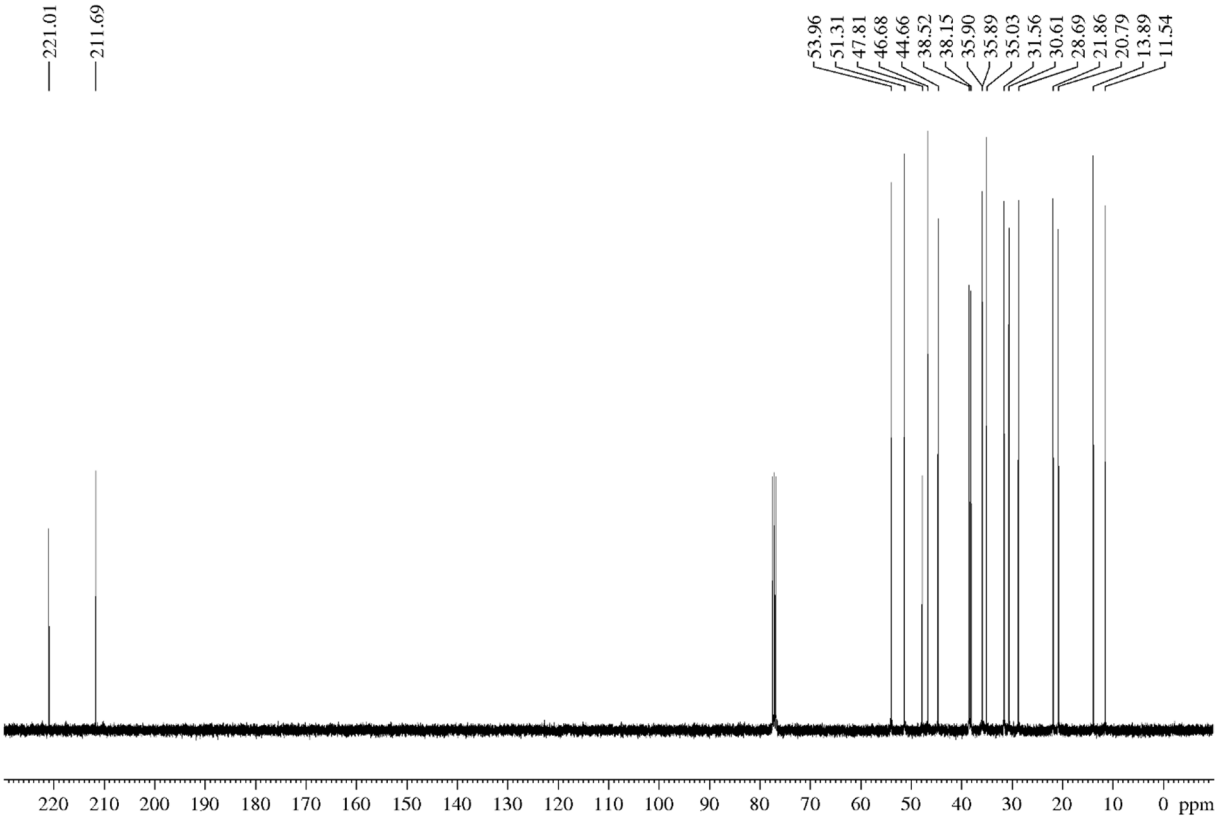

226
2.14
2.13
1.81
1.79
1.67
1.59
1.55
1.54
1.51
1.42
1.34
1.14
1.03
1.00
0.98
2.02
1.04
0.99
1.00
3.00
6.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

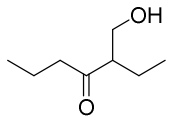

223.58
54.30
47.54
45.48
41.81
31.99
25.09
23.50
21.85
14.77
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



261

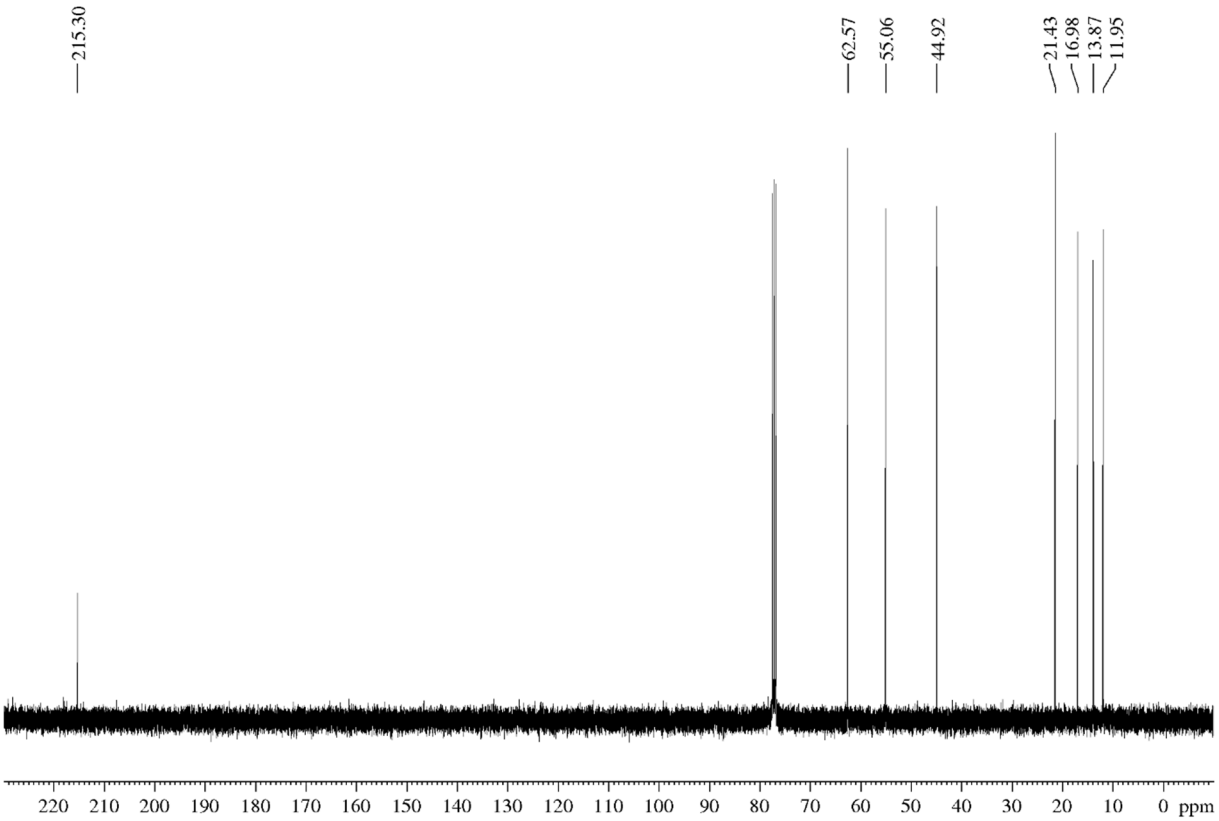
2.46
2.22
2.11
1.89
1.83
1.78
1.69
1.47
1.41
1.20
1.04
0.93
0.86
0.81
0.74
4.02
4.02
1.99
4.04
6.05
4.00
3.00
1.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

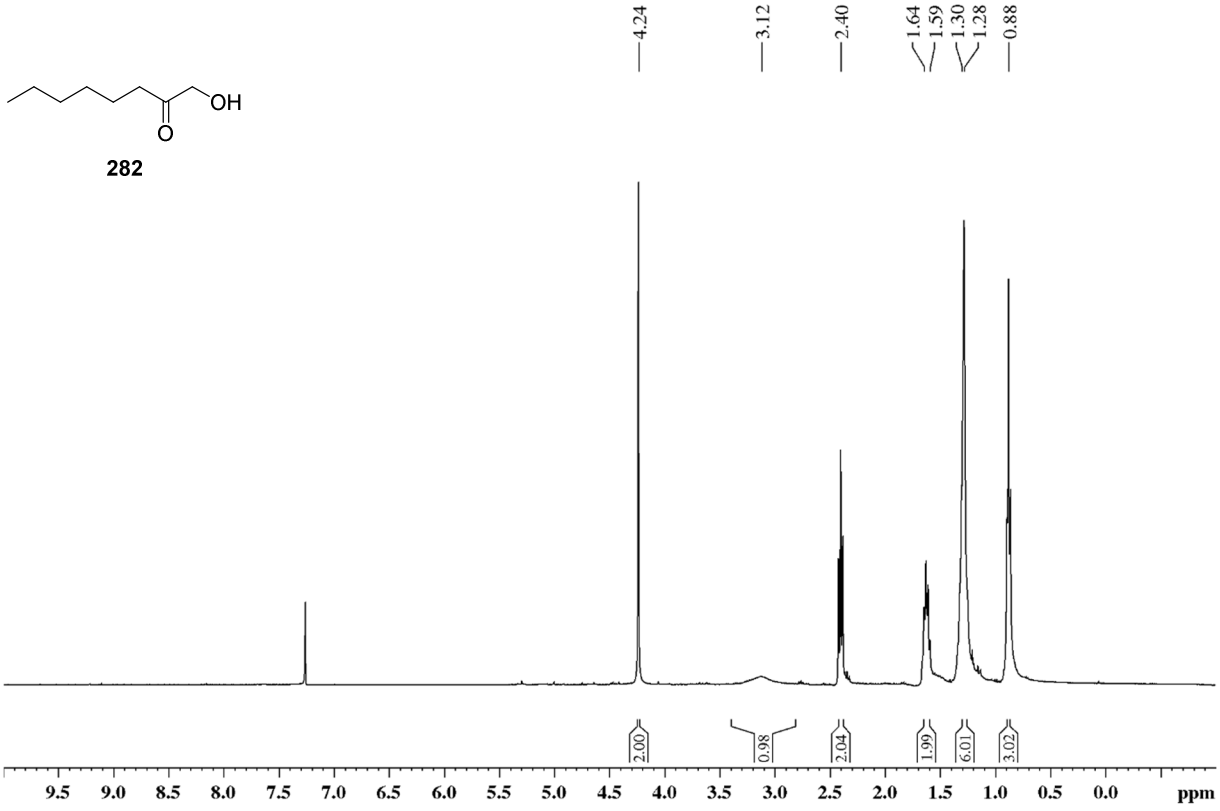

221.01
211.69
53.96
51.31
47.81
46.68
44.66
38.52
38.15
35.90
35.89
35.03
31.56
30.61
28.69
21.86
20.79
13.89
11.54
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

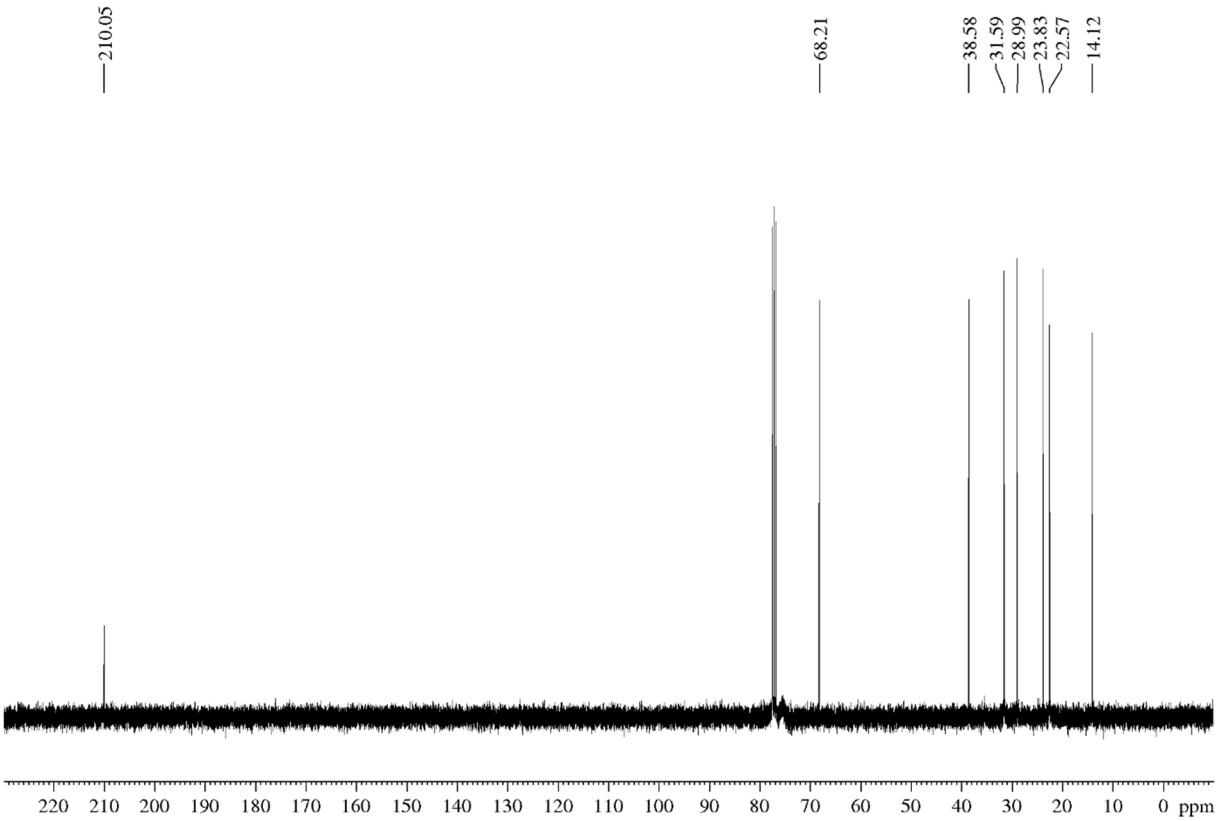

OH
O

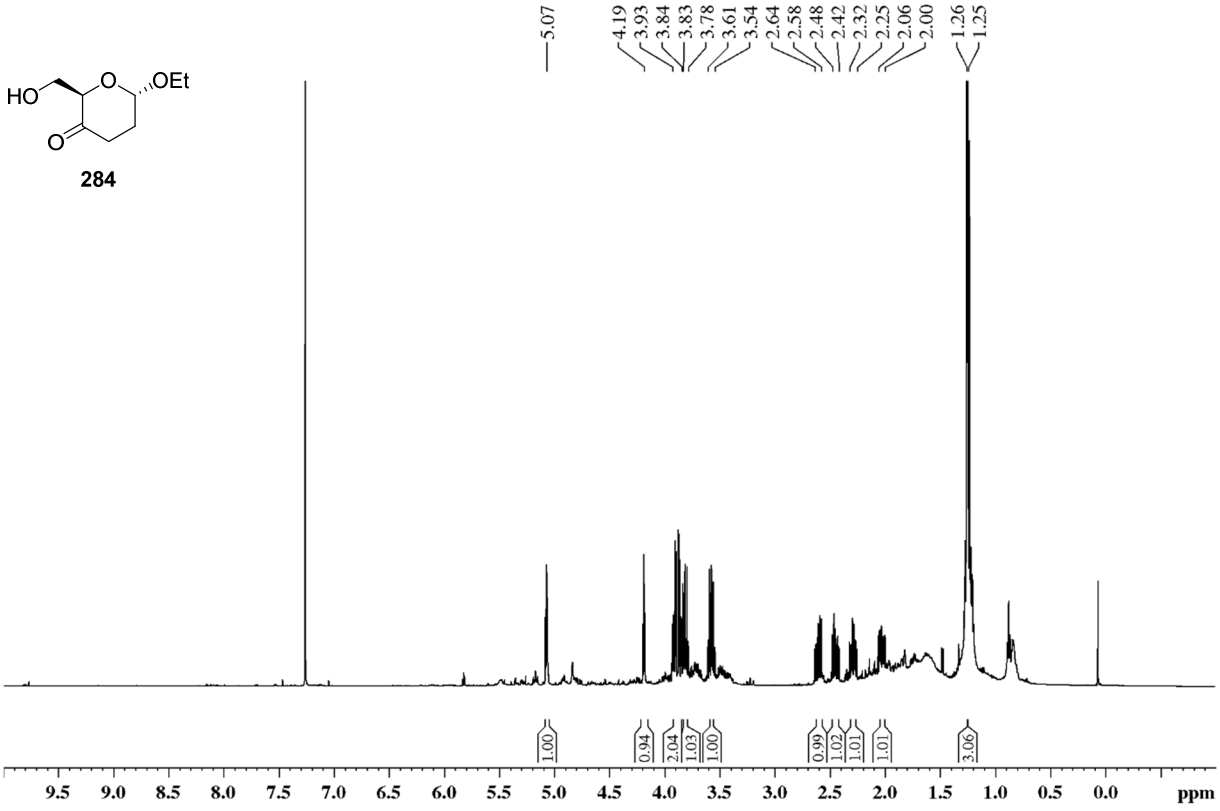
280

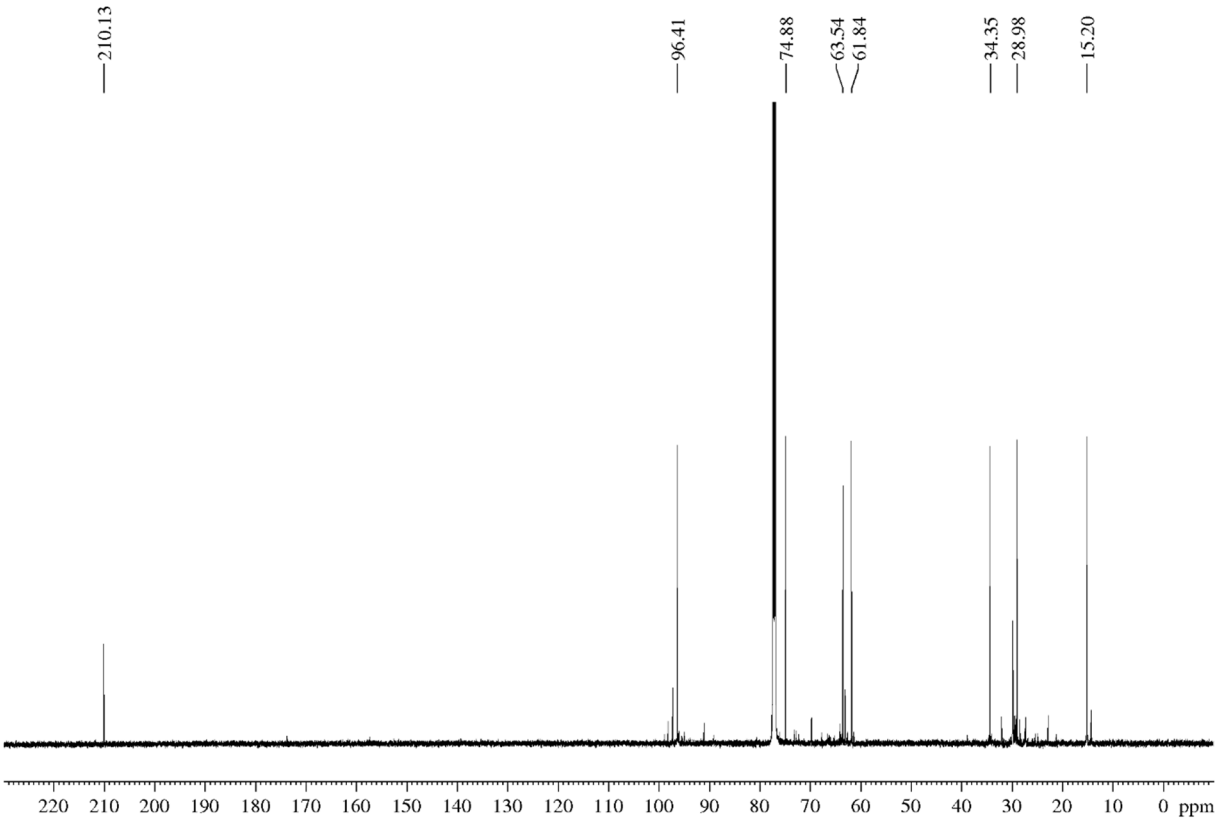
3.81
3.76
3.71
3.67
2.65
2.59
2.47
2.01
1.69
1.49
0.94
0.89
0.99
0.99
1.00
2.00
1.00
4.03
6.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

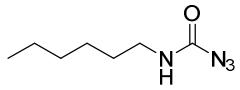

215.30
62.57
55.06
44.92
21.43
16.98
13.87
11.95
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


OH
O
282
4.24
3.12
2.40
1.64
1.59
1.30
1.28
0.88
2.00
0.98
2.04
1.99
6.01
3.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


210.05
68.21
38.58
31.59
28.99
23.83
22.57
14.12
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

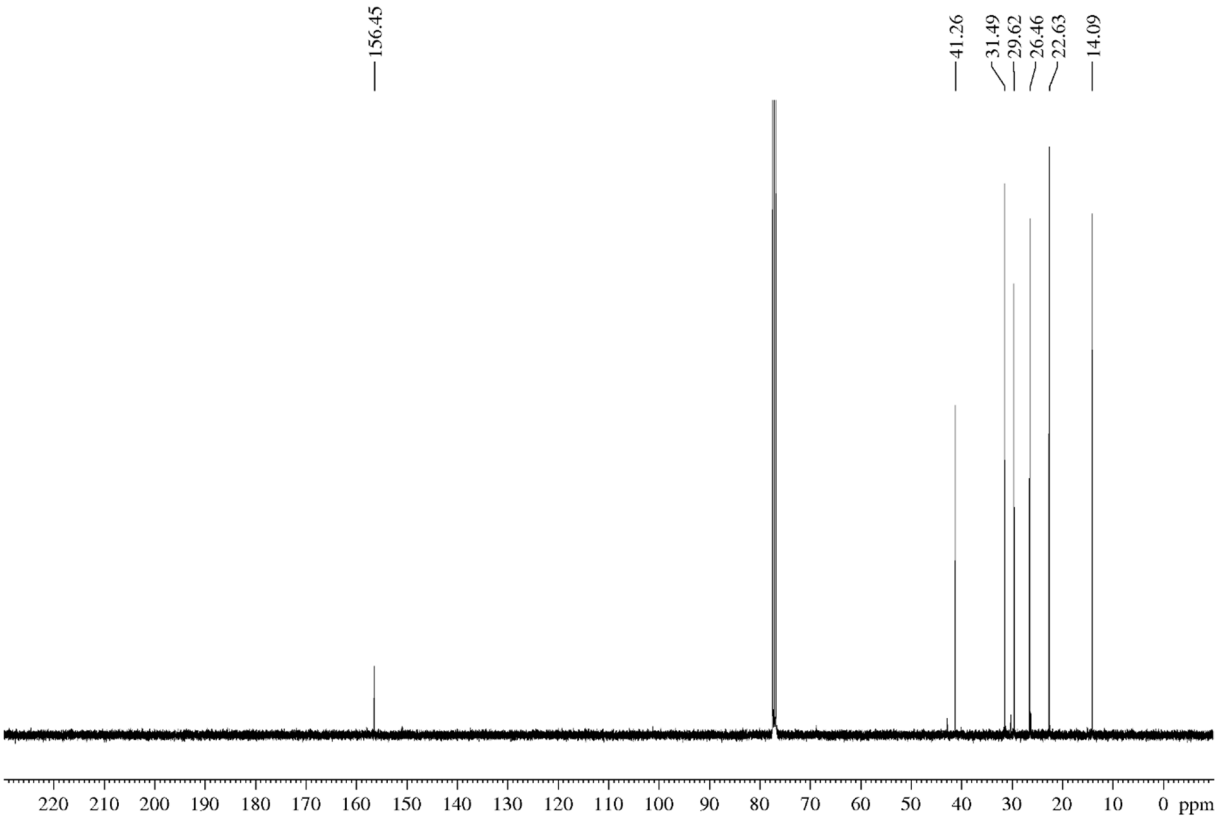

HO
O
OEt
O
284
5.07
4.19
3.93
3.84
3.83
3.78
3.61
3.54
2.64
2.58
2.48
2.42
2.32
2.25
2.06
2.00
1.26
1.25
1.00
0.94
2.04
1.03
1.00
0.99
1.02
1.01
1.01
3.06
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

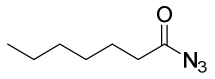

210.13
96.41
74.88
63.54
61.84
34.35
28.98
15.20
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



286

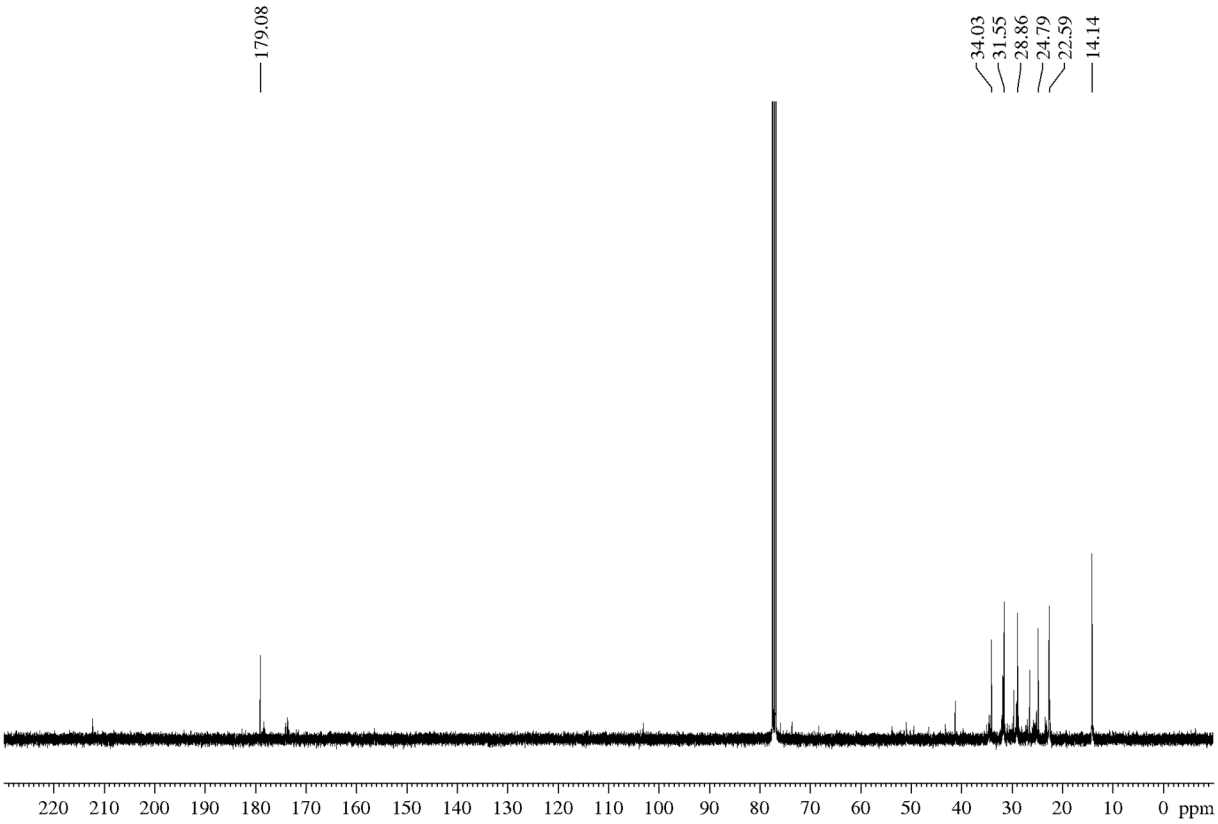
5.10
3.25
3.20
1.52
1.46
1.34
1.26
0.88
1.00
2.00
2.02
5.99
2.99
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

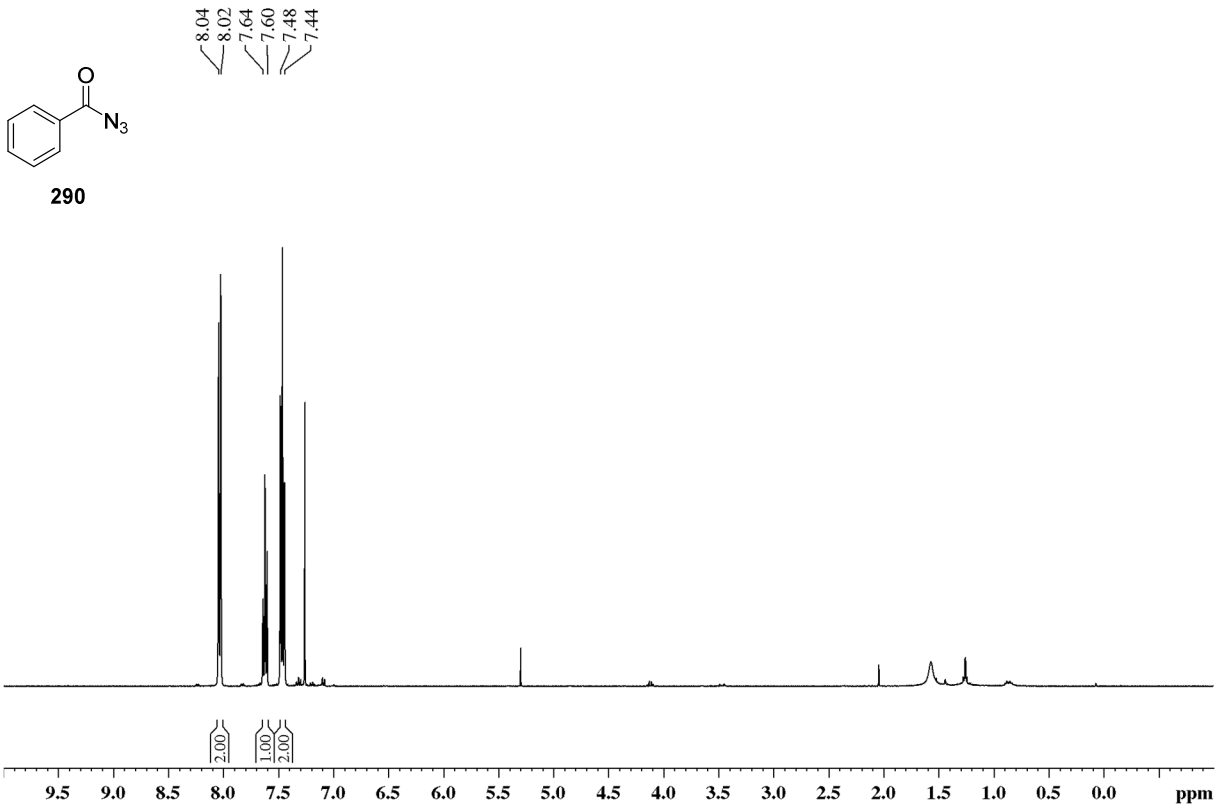

156.45
41.26
31.49
29.62
26.46
22.63
14.09
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

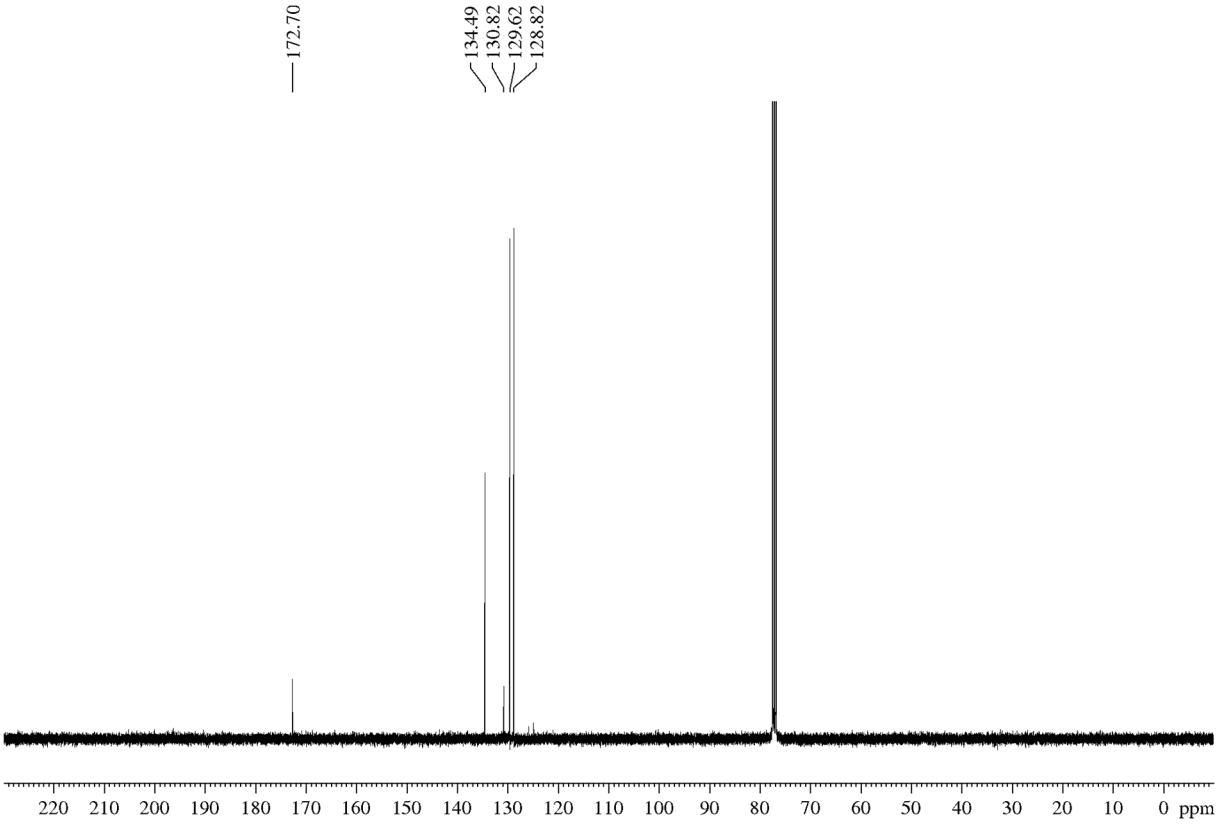


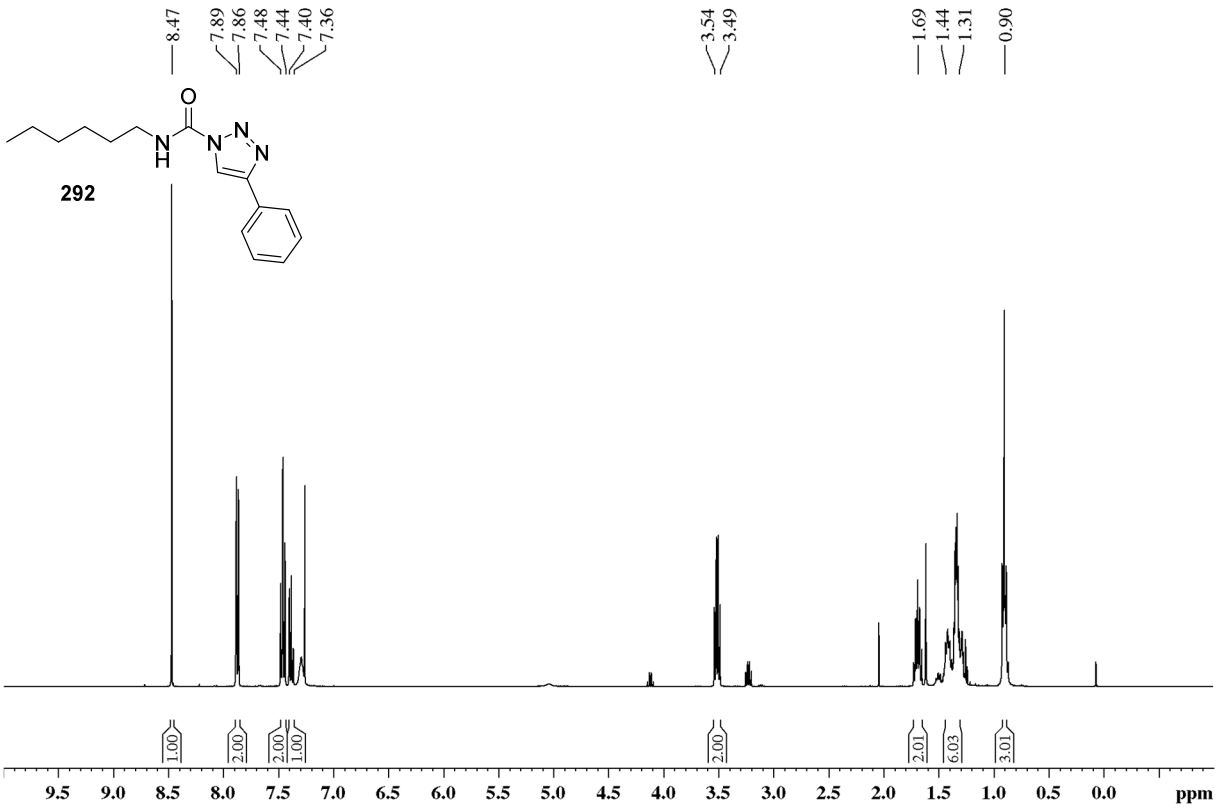
288

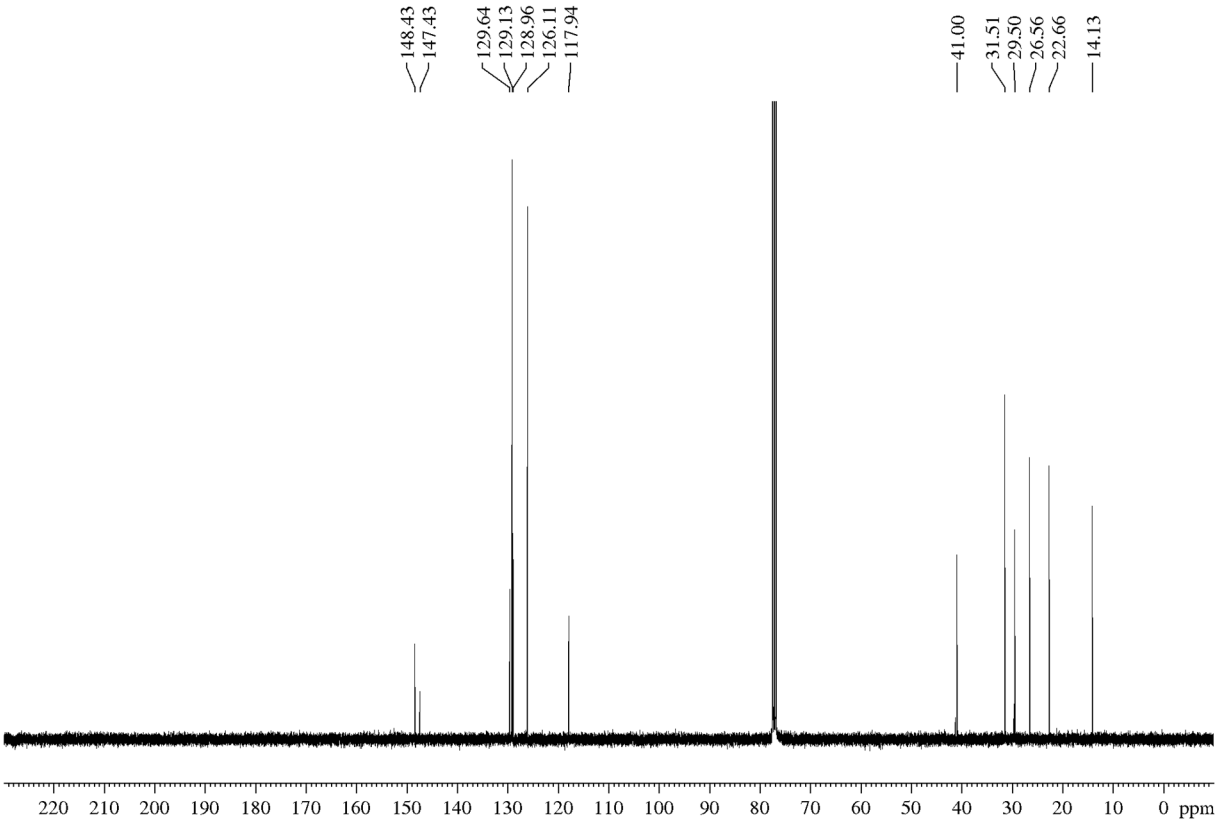
2.36
2.23
1.65
1.56
1.29
0.88
0.87
2.00
2.11
6.15
3.10
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

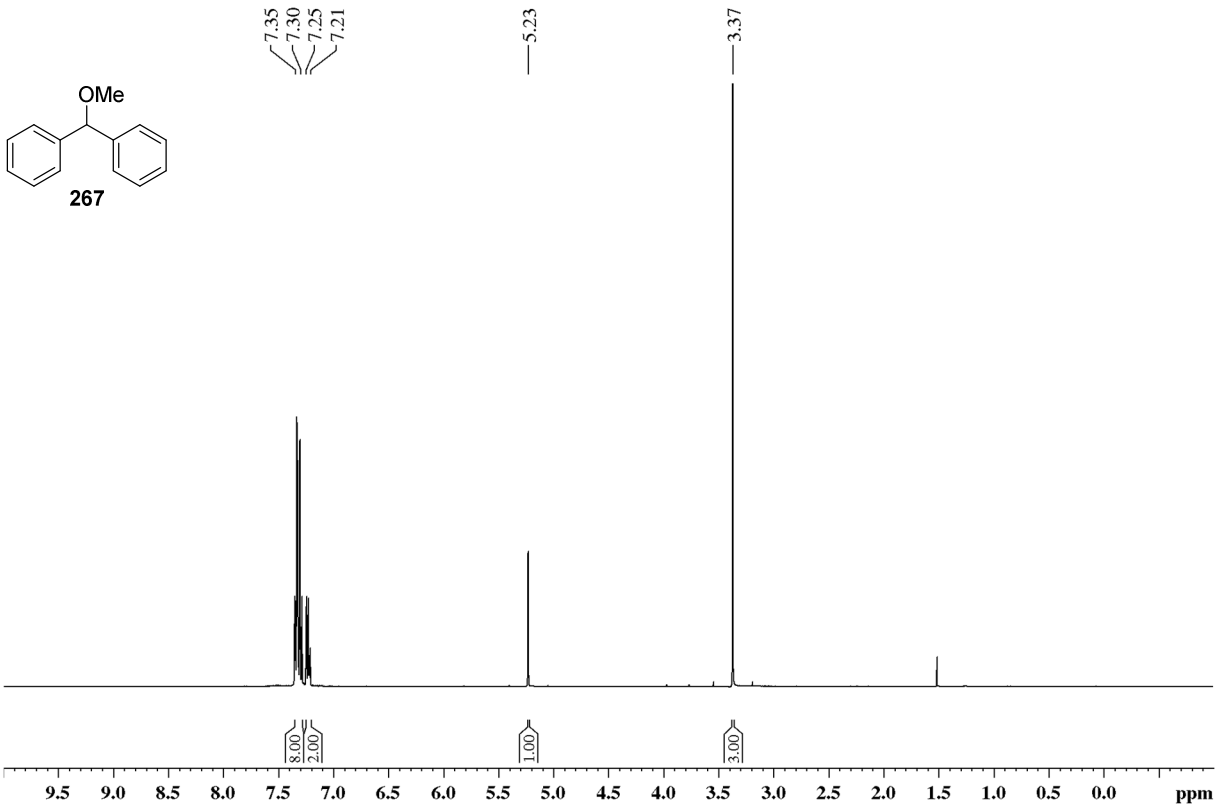

179.08
34.03
31.55
28.86
24.79
22.59
14.14
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

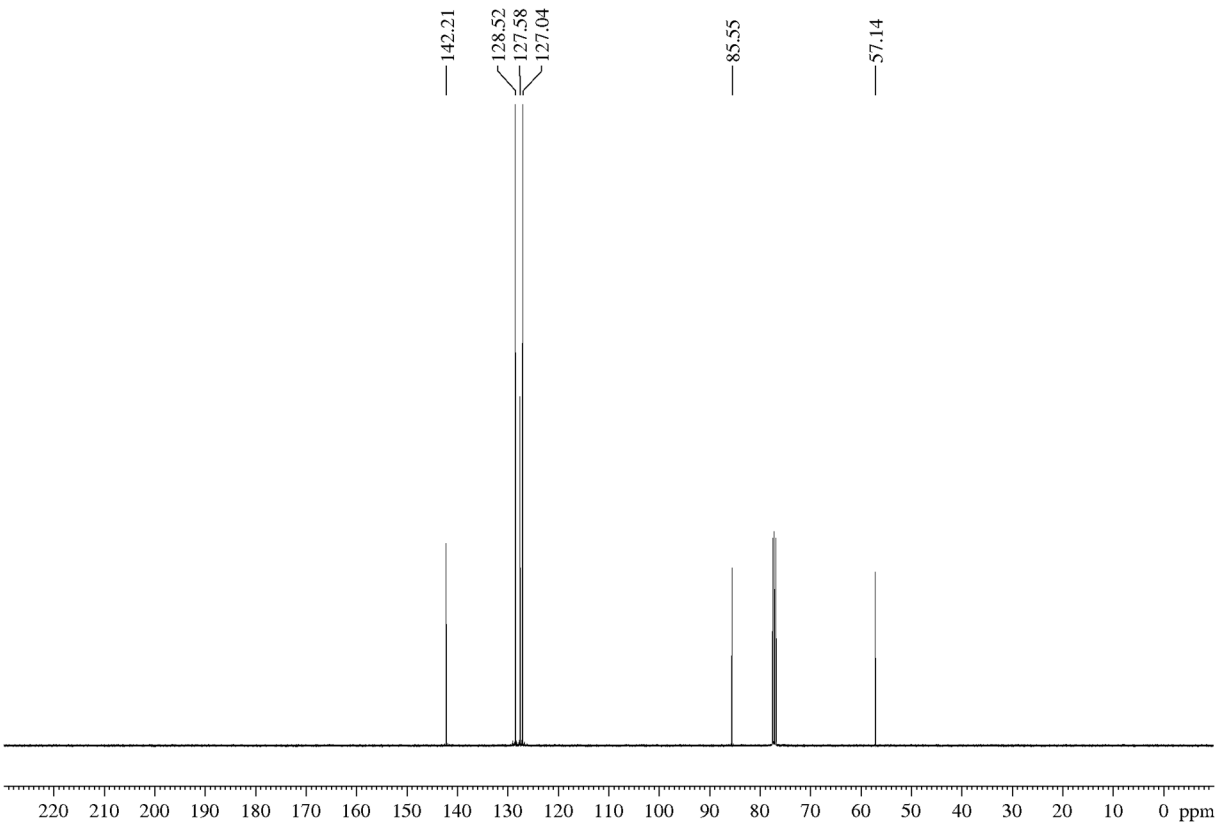

8.04
8.02
7.64
7.60
7.48
7.44
O
N3
290
2.00
1.00
2.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

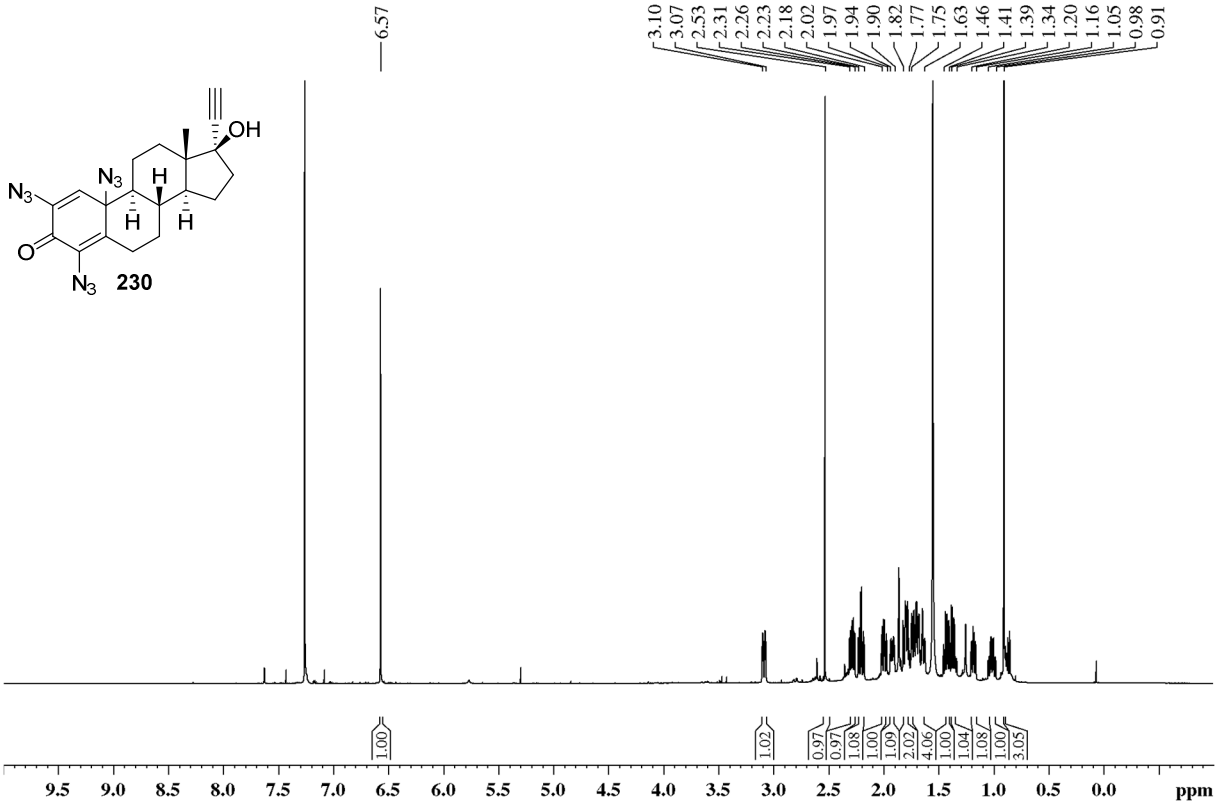

172.70
134.49
130.82
129.62
128.82
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

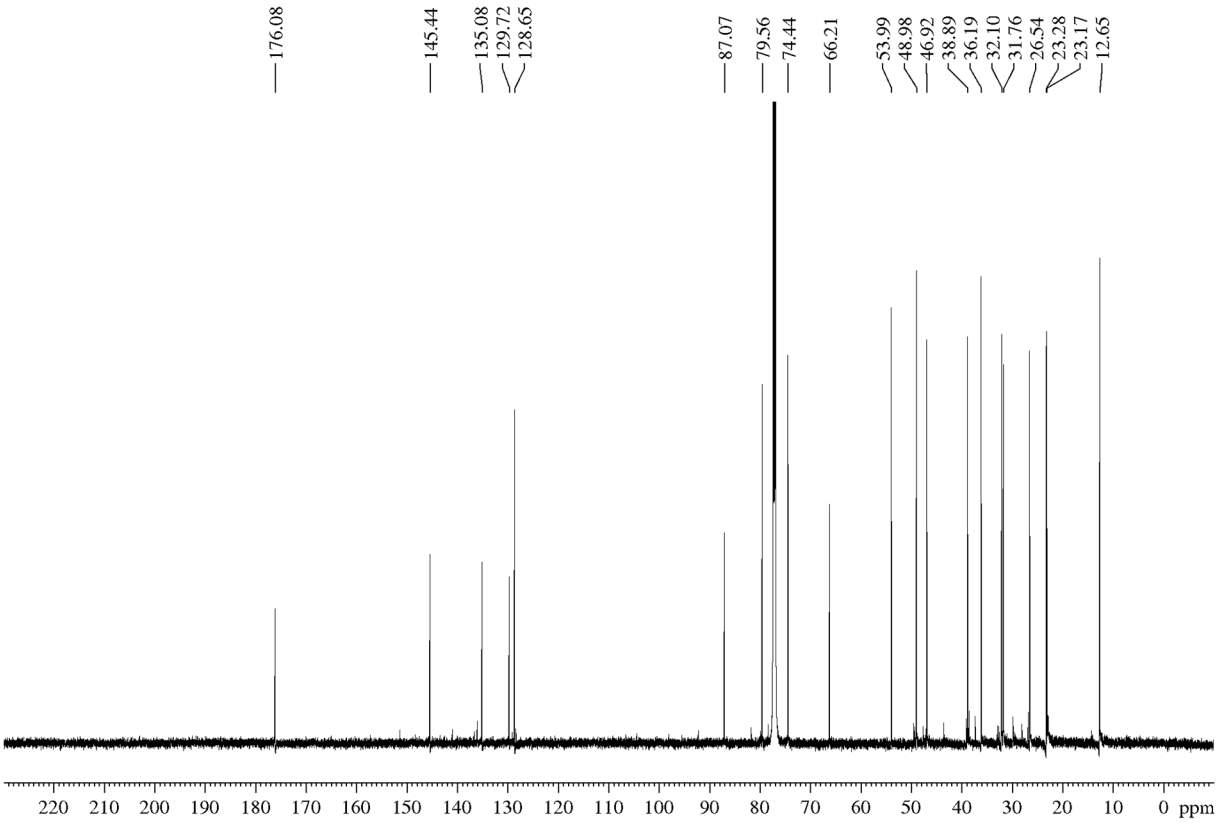

8.47
7.89
7.86
7.48
7.44
7.40
7.36
3.54
3.49
1.69
1.44
1.31
0.90
292
1.00
2.00
2.00
1.00
2.00
2.01
6.03
3.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

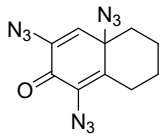

148.43
147.43
129.64
129.13
128.96
126.11
117.94
41.00
31.51
29.50
26.56
22.66
14.13
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.35
7.30
7.25
7.21
5.23
3.37
OMe
267
8.00
2.00
1.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


142.21
128.52
127.58
127.04
85.55
57.14
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

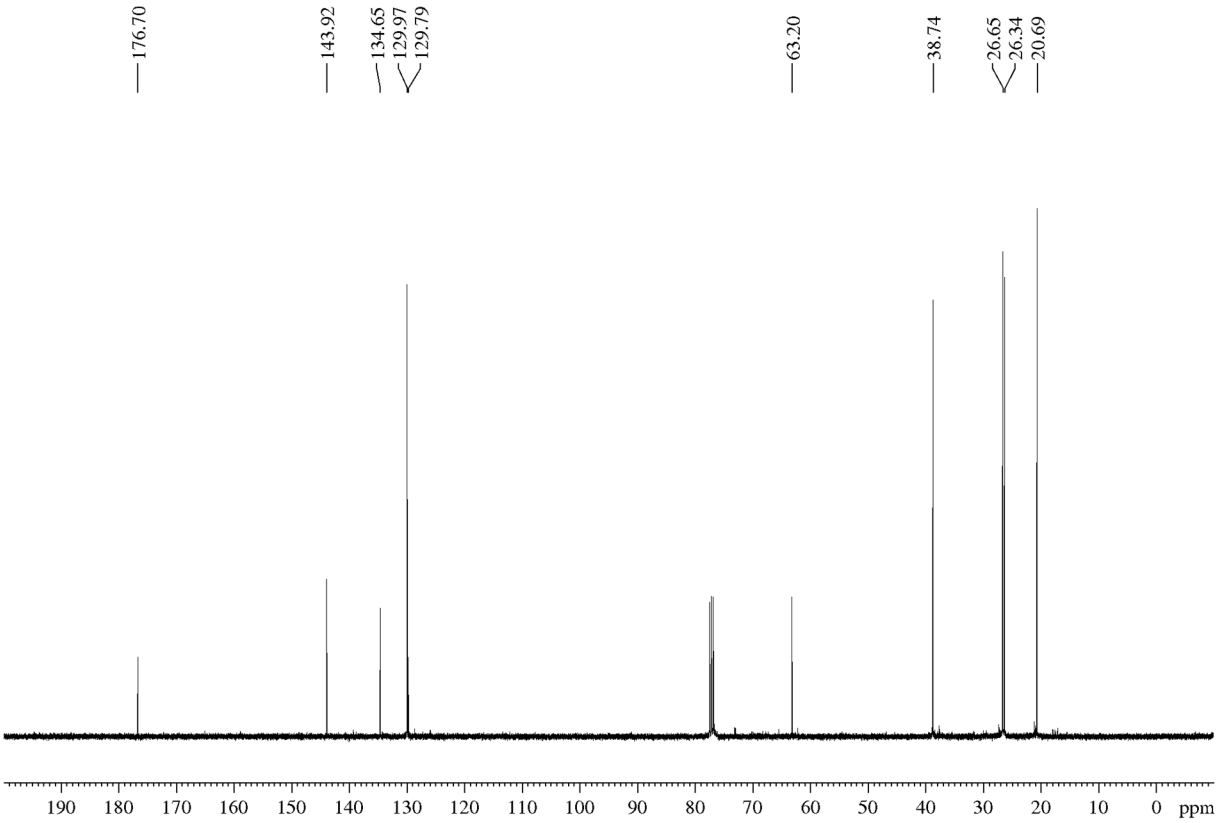

6.57
3.10
3.07
2.53
2.31
2.26
2.23
2.18
2.02
1.97
1.94
1.90
1.82
1.77
1.75
1.63
1.46
1.41
1.39
1.34
1.20
1.16
1.05
0.98
0.91
OH
N3
N3
H
H
H
O
N3
230
1.00
1.02
0.97
0.97
1.08
1.00
1.09
2.02
4.06
1.00
1.04
1.08
1.00
3.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

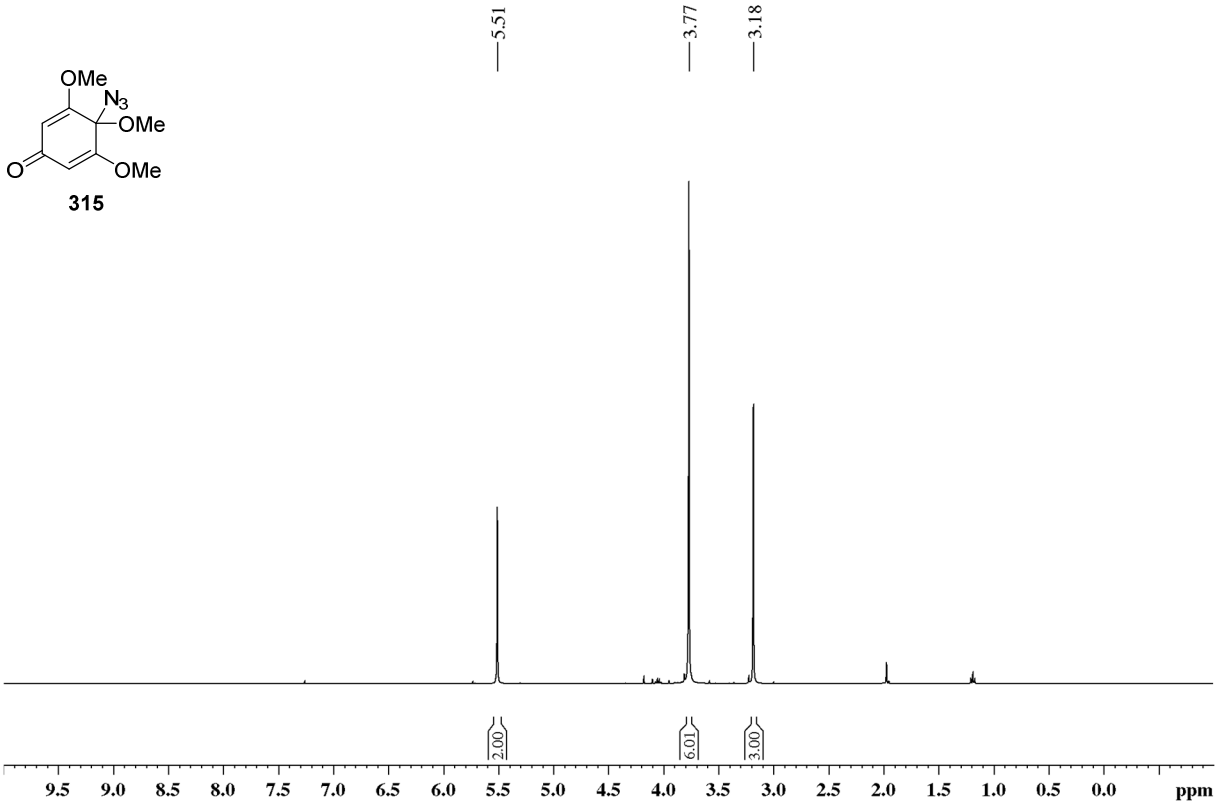

176.08
145.44
135.08
129.72
128.65
87.07
79.56
74.44
66.21
53.99
48.98
46.92
38.89
36.19
32.10
31.76
26.54
23.28
23.17
12.65
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

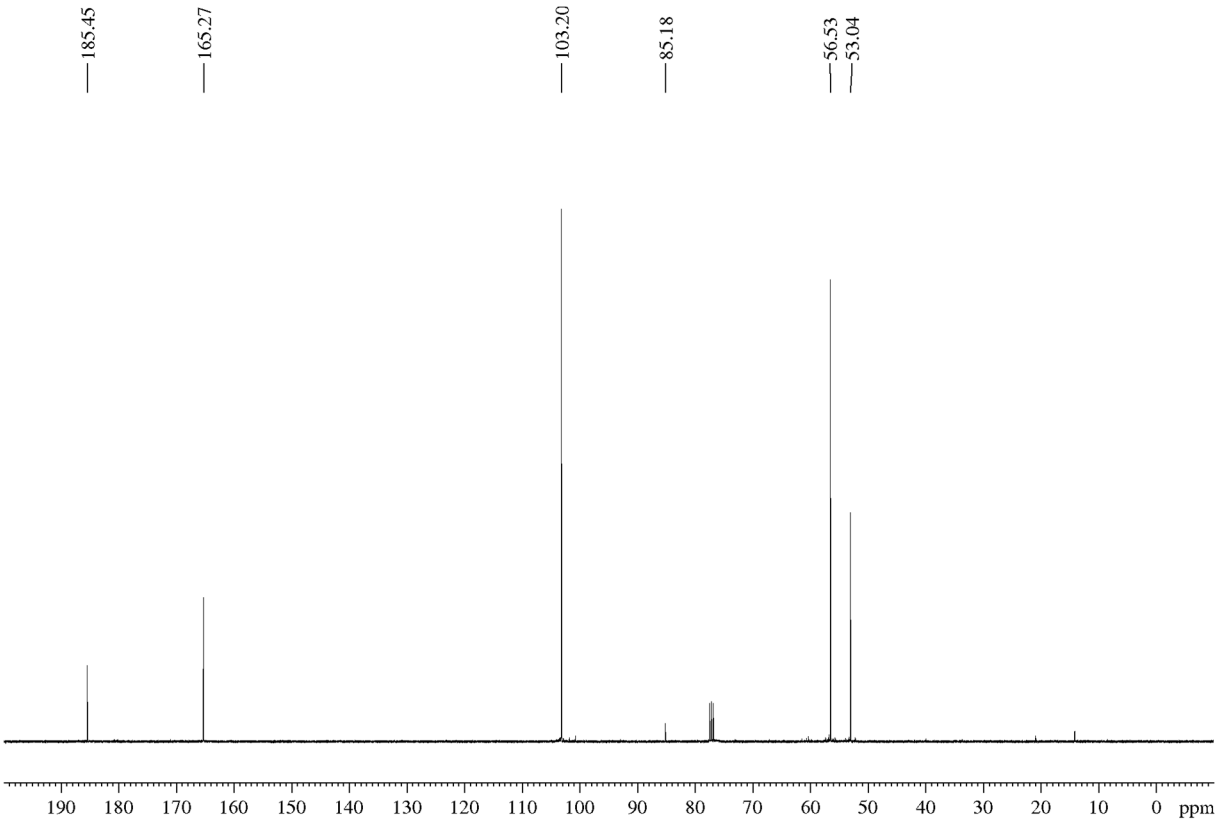

N3
N3
O
N3

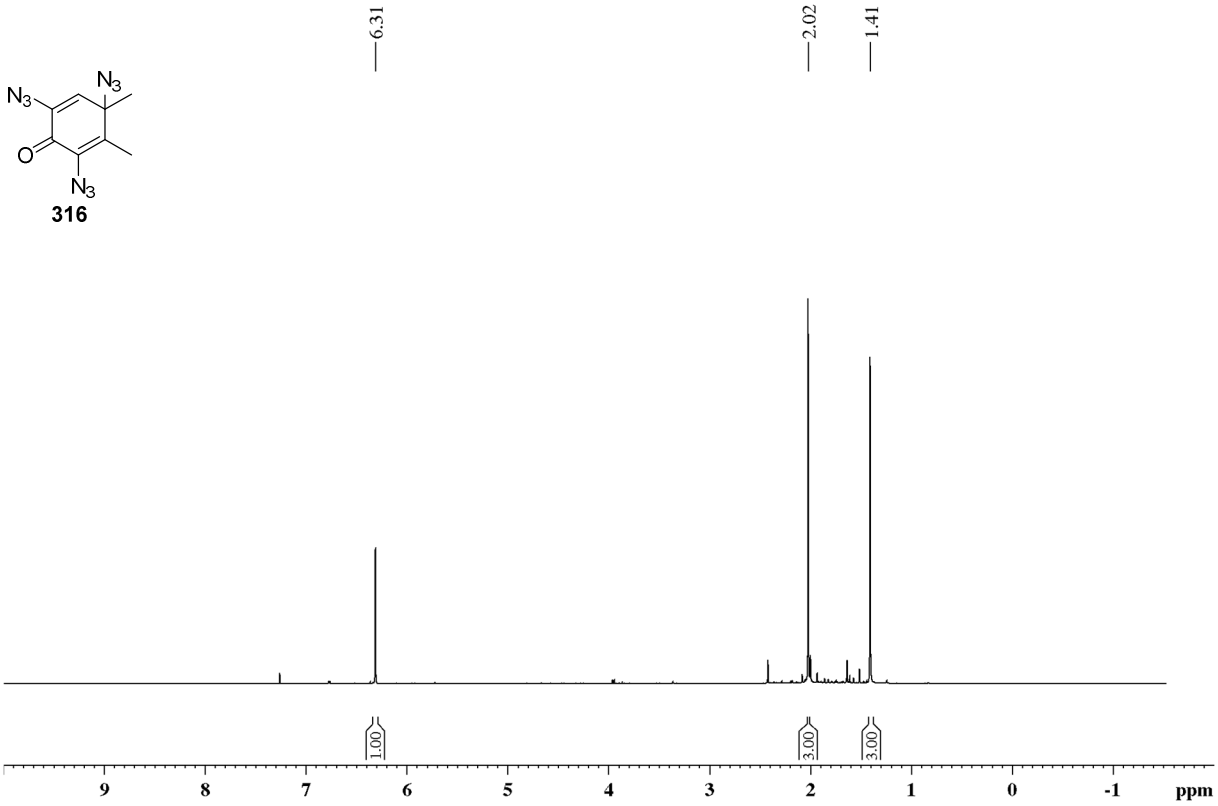
314

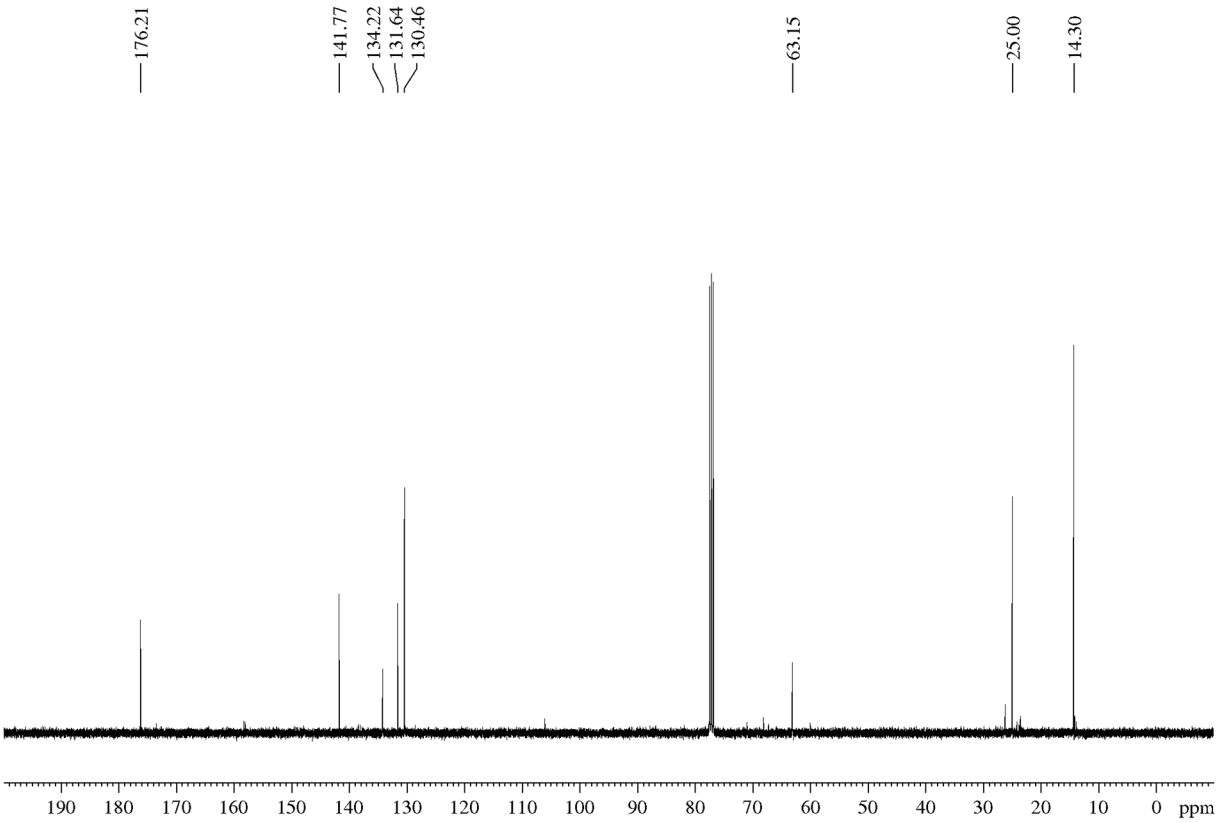
6.26
3.05
3.02
2.16
2.08
2.04
2.00
1.96
1.79
1.72
1.68
1.65
1.41
1.33
1.28
1.23
1.00
1.00
1.06
1.04
1.05
1.05
1.02
1.02
1.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

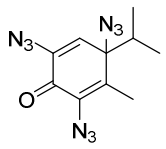

176.70
143.92
134.65
129.97
129.79
63.20
38.74
26.65
26.34
20.69
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


OMe
N3
OMe
O
OMe
315
5.51
3.77
3.18
2.00
6.01
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


185.45
165.27
103.20
85.18
56.53
53.04
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

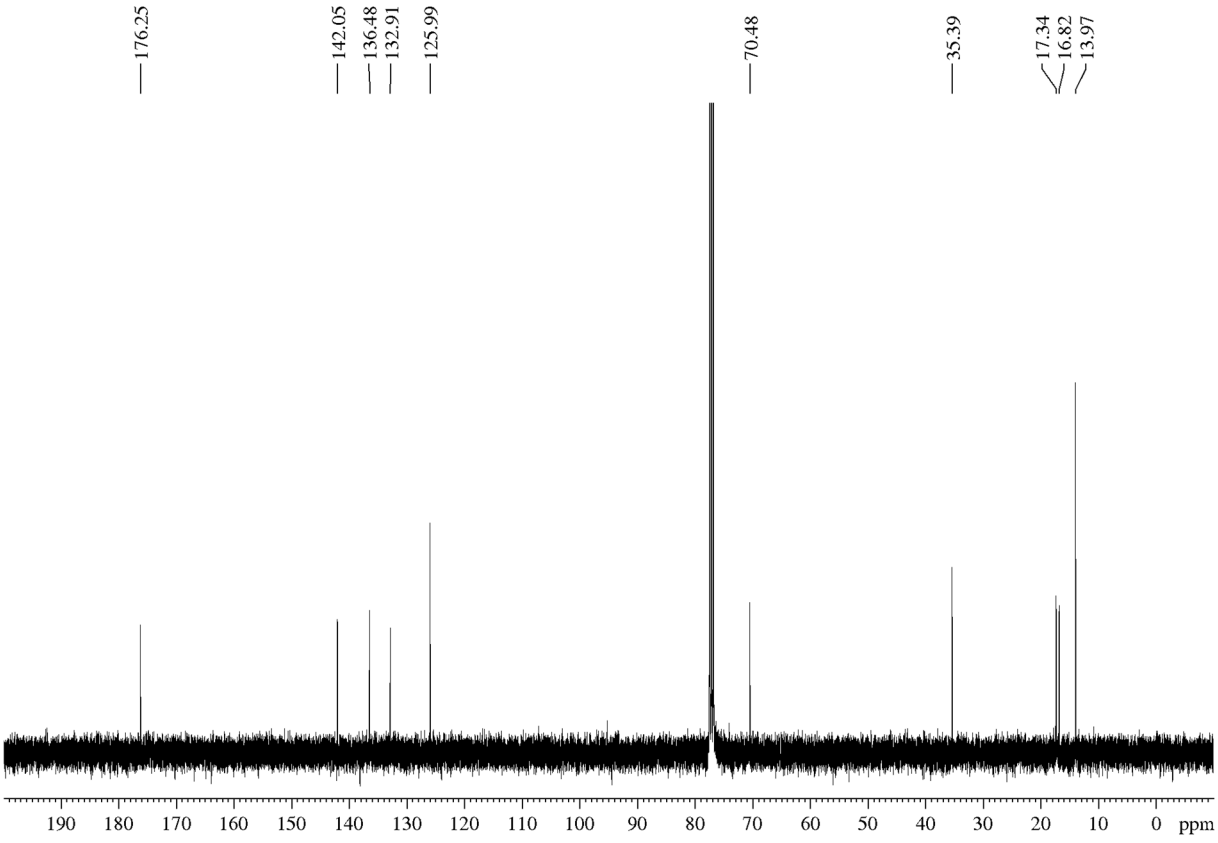

6.31
2.02
1.41
N3
N3
O
N3
316
1.00
3.00
3.00
9
8
7
6
5
4
3
2
1
0
-1
ppm

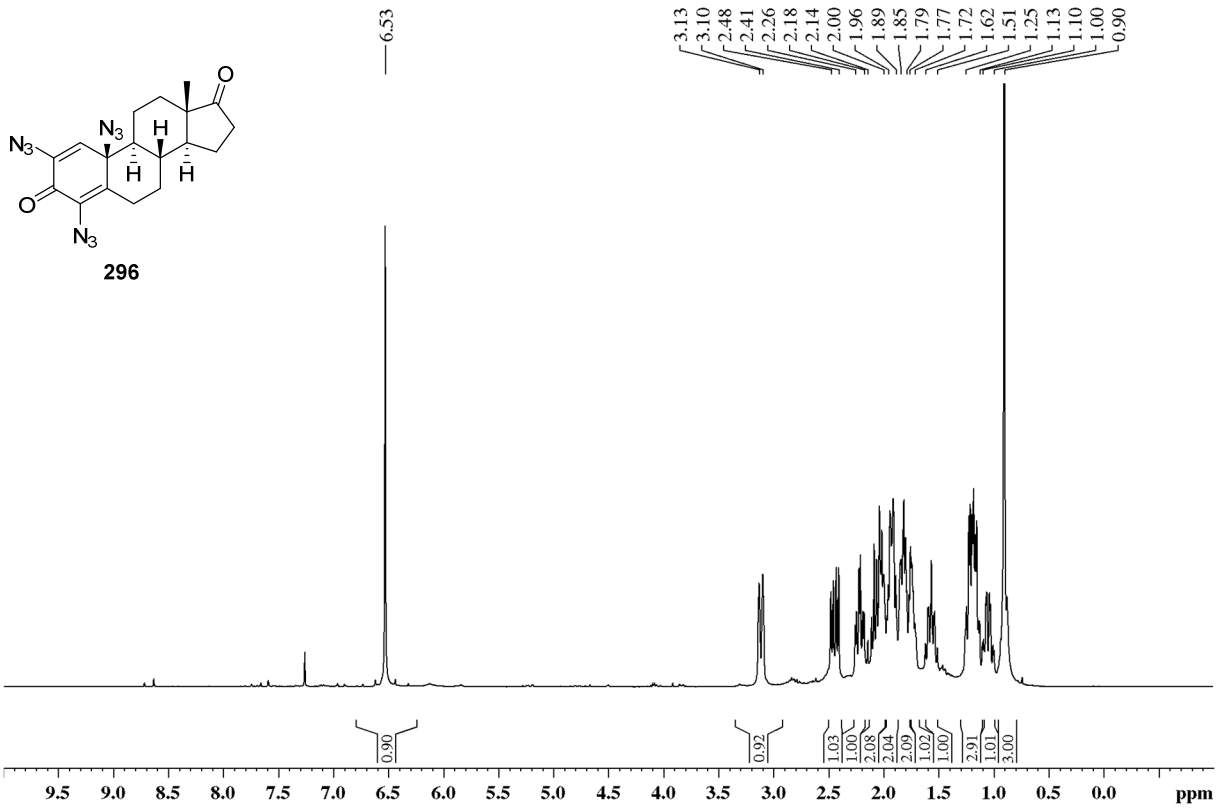

176.21
141.77
134.22
131.64
130.46
63.15
25.00
14.30
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


N3
N3
O
N3

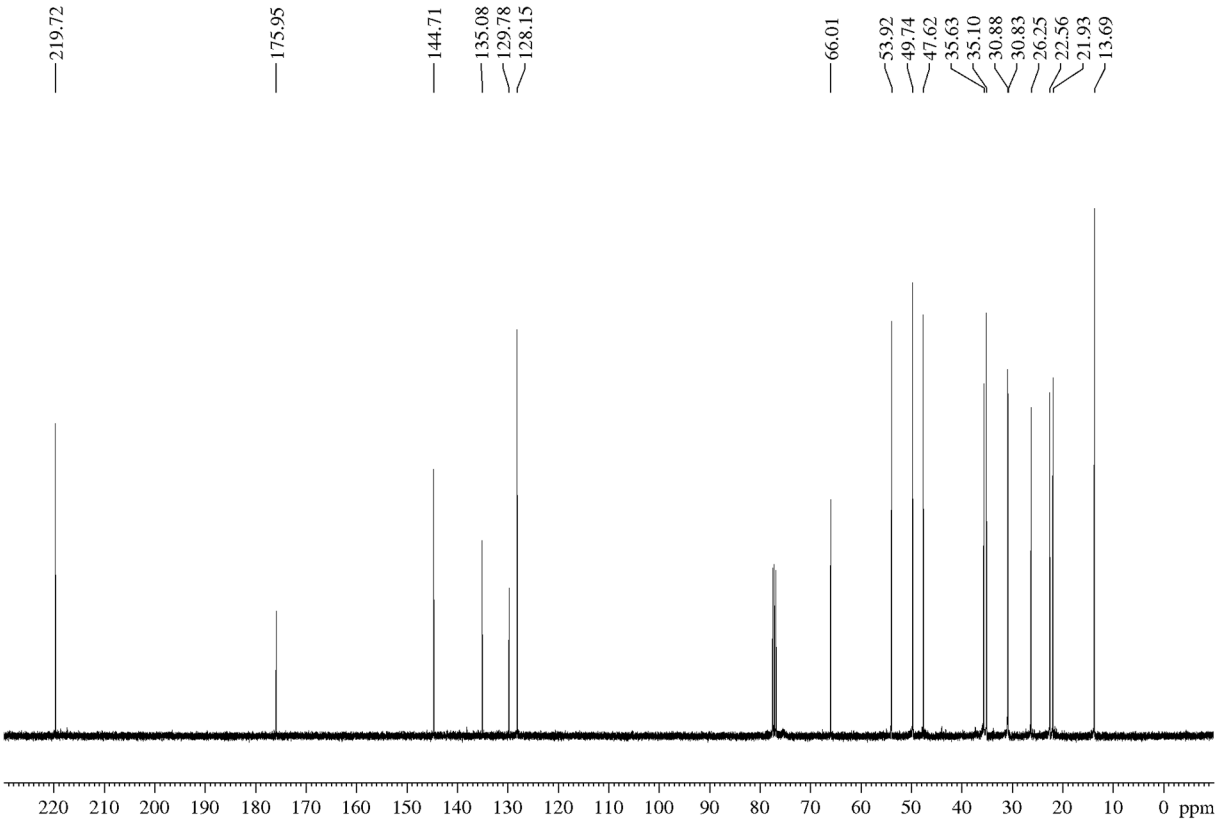
317

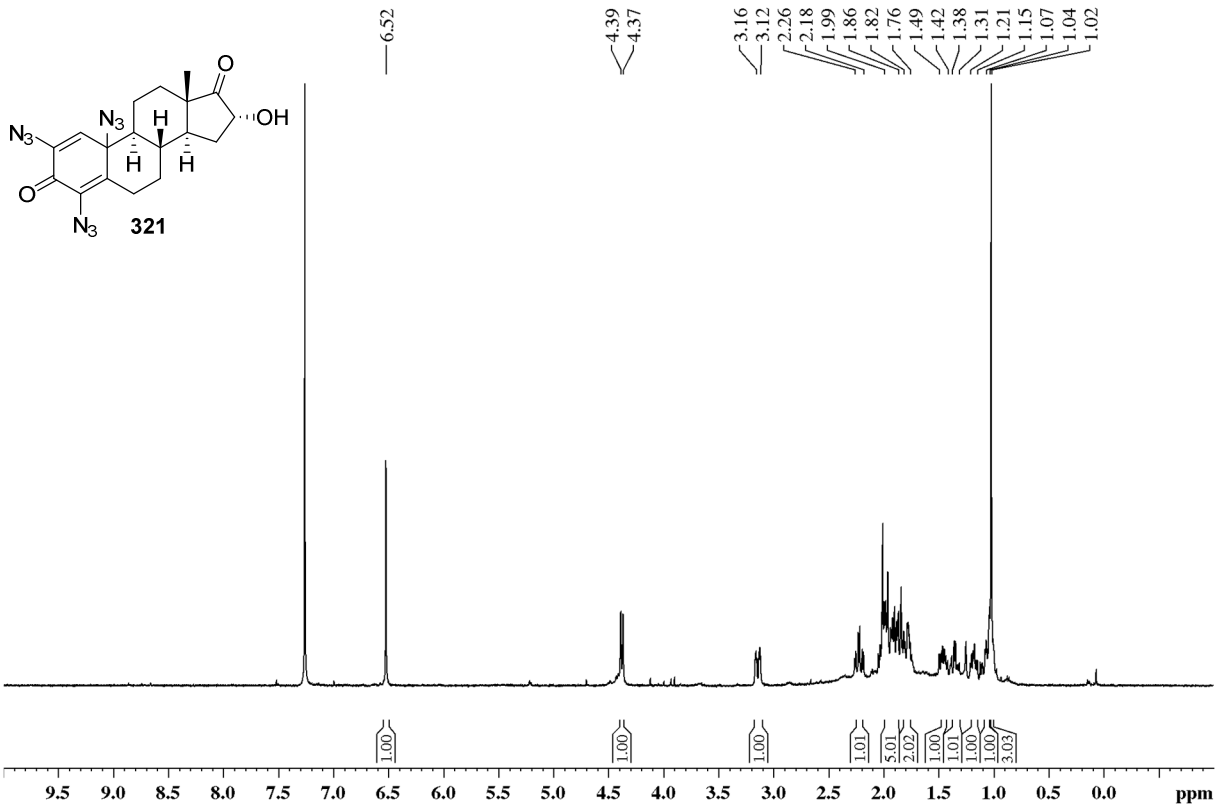
6.32
2.08
1.98
1.09
1.08
0.65
0.64
1.00
1.00
3.00
3.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

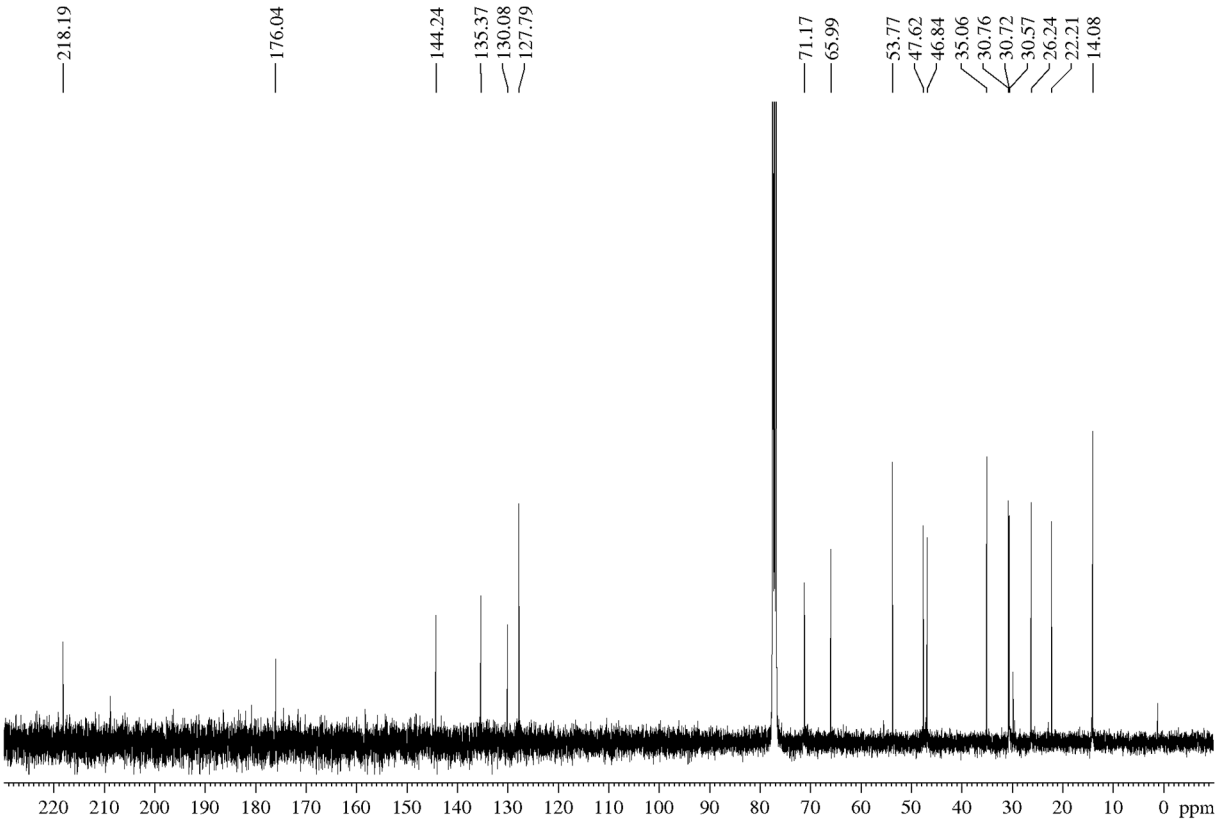

176.25
142.05
136.48
132.91
125.99
70.48
35.39
17.34
16.82
13.97
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

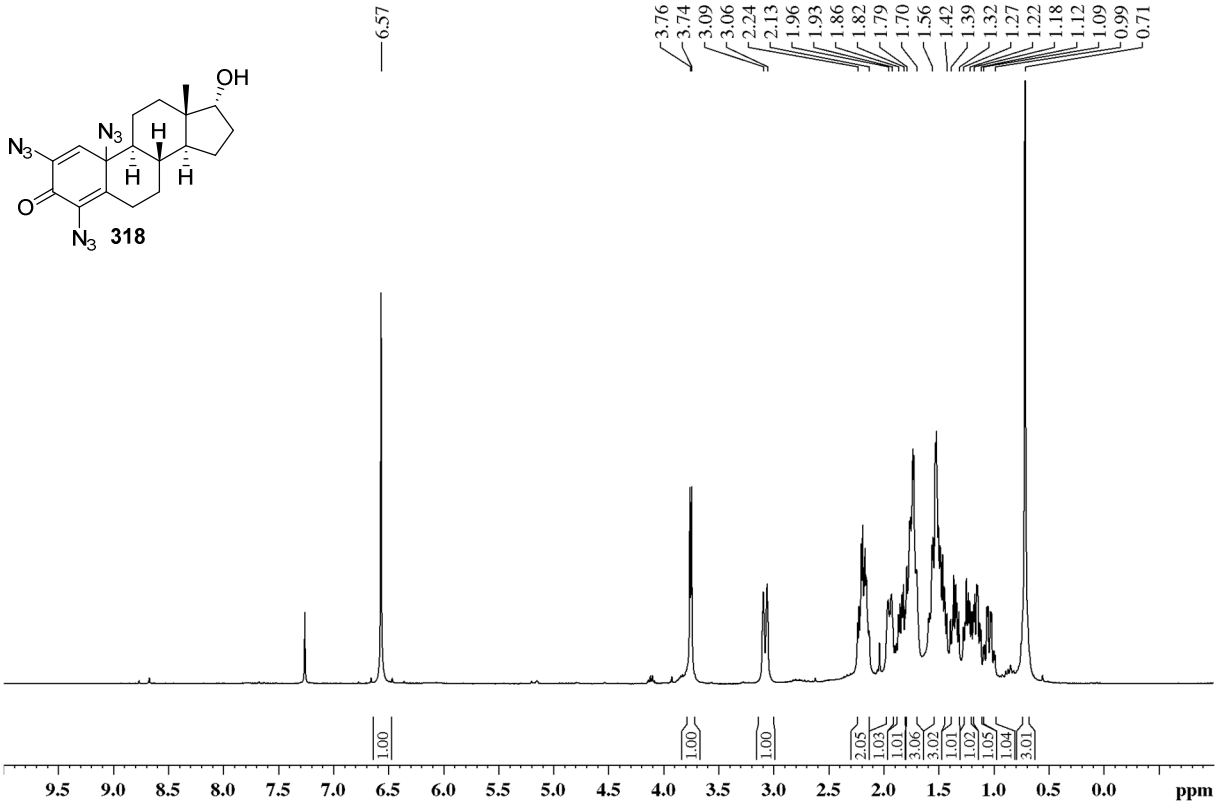

6.53
3.13
3.10
2.48
2.41
2.26
2.18
2.14
2.00
1.96
1.89
1.85
1.79
1.77
1.72
1.62
1.51
1.25
1.13
1.10
1.00
0.90
0.90
0.92
1.03
1.00
2.08
2.04
2.09
1.02
1.00
2.91
1.01
3.00
ppm

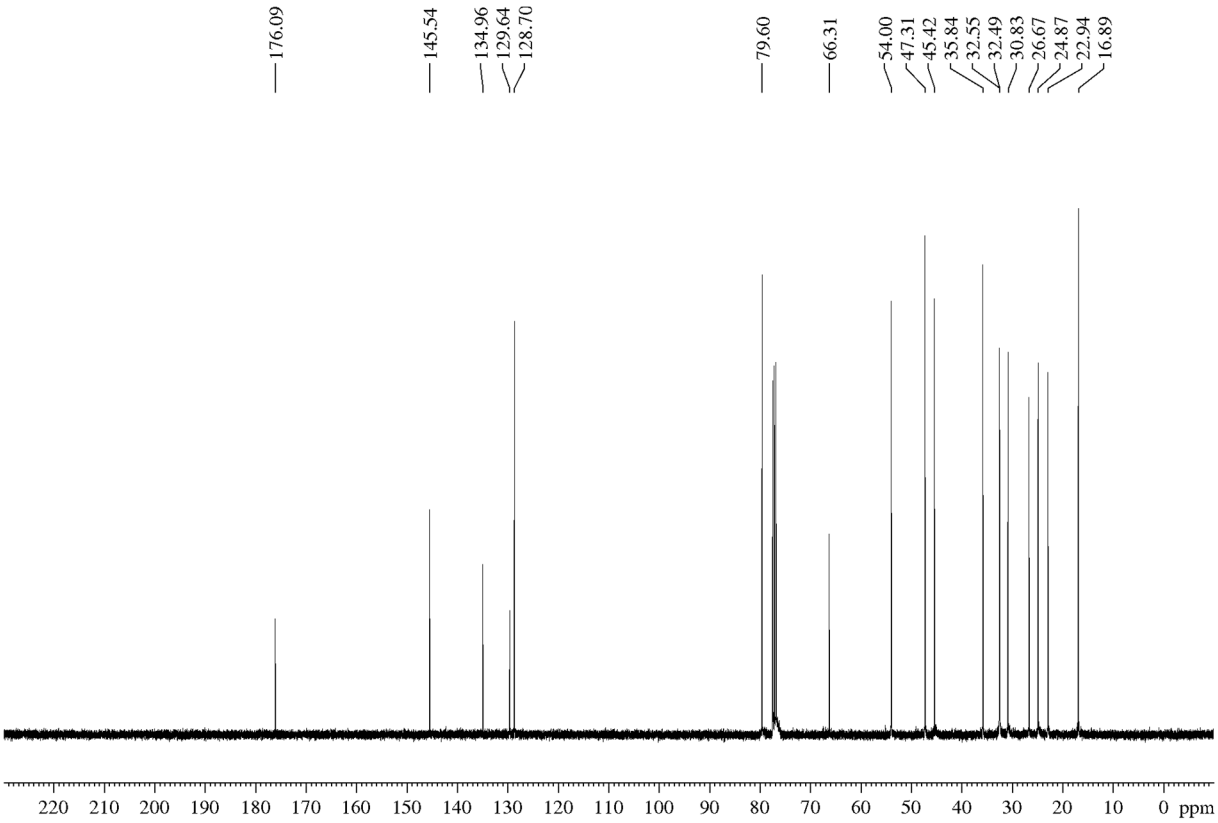
296

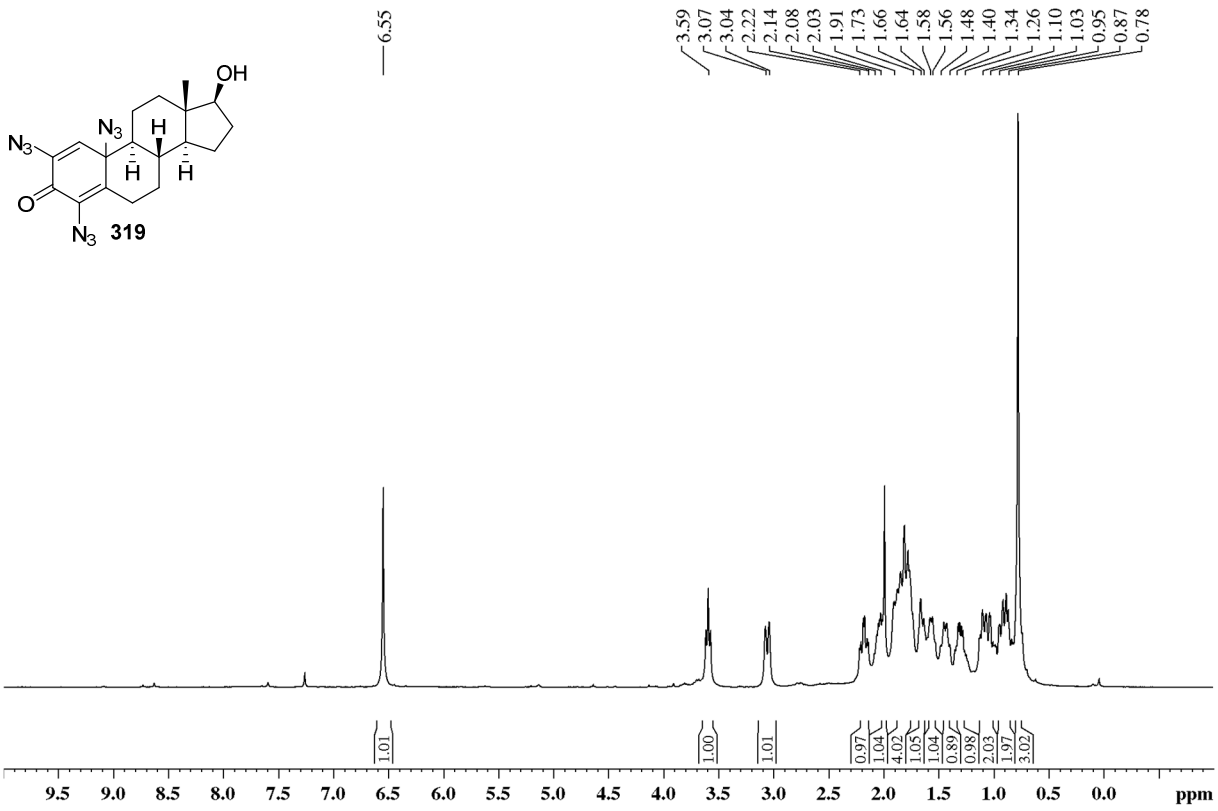

219.72
175.95
144.71
135.08
129.78
128.15
66.01
53.92
49.74
47.62
35.63
35.10
30.88
30.83
26.25
22.56
21.93
13.69
ppm

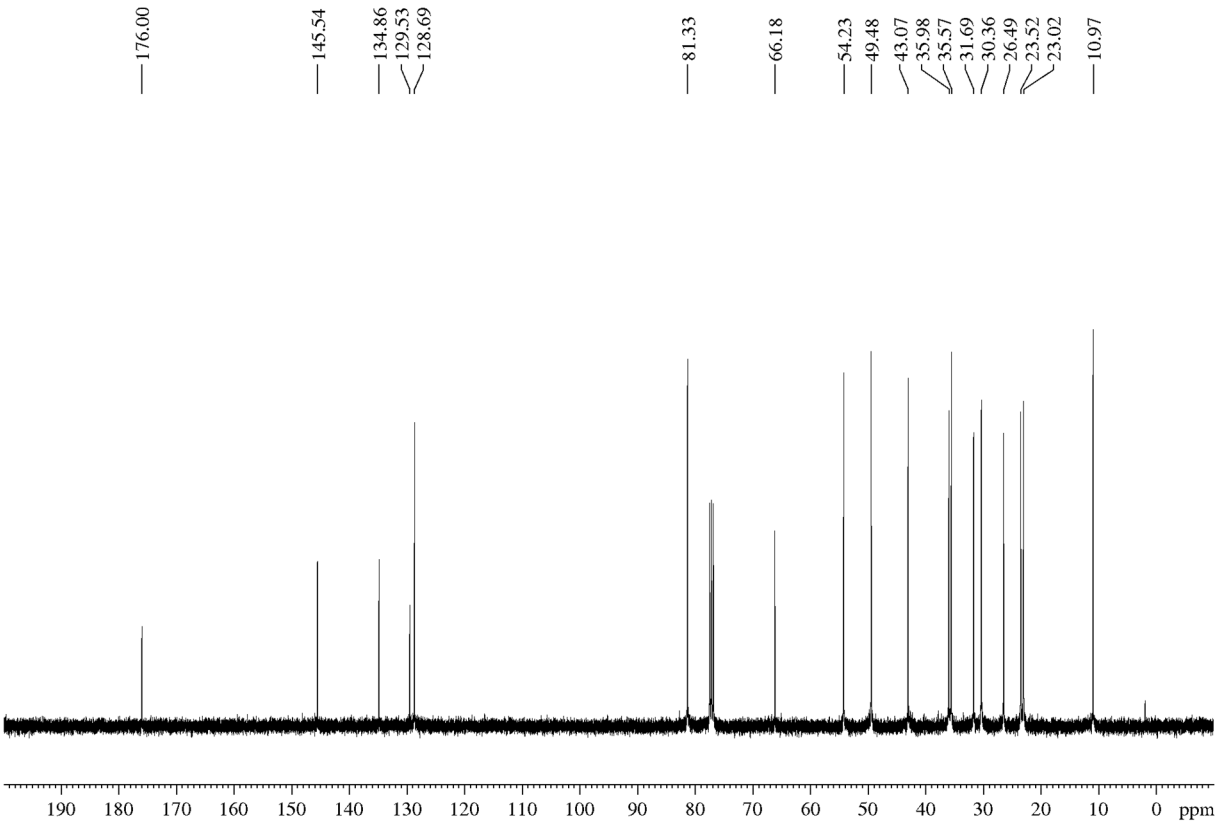

6.52
4.39
4.37
3.16
3.12
2.26
2.18
1.99
1.86
1.82
1.76
1.49
1.42
1.38
1.31
1.21
1.15
1.07
1.04
1.02
1.00
1.00
1.00
1.01
5.01
2.02
1.00
1.01
1.00
1.00
3.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

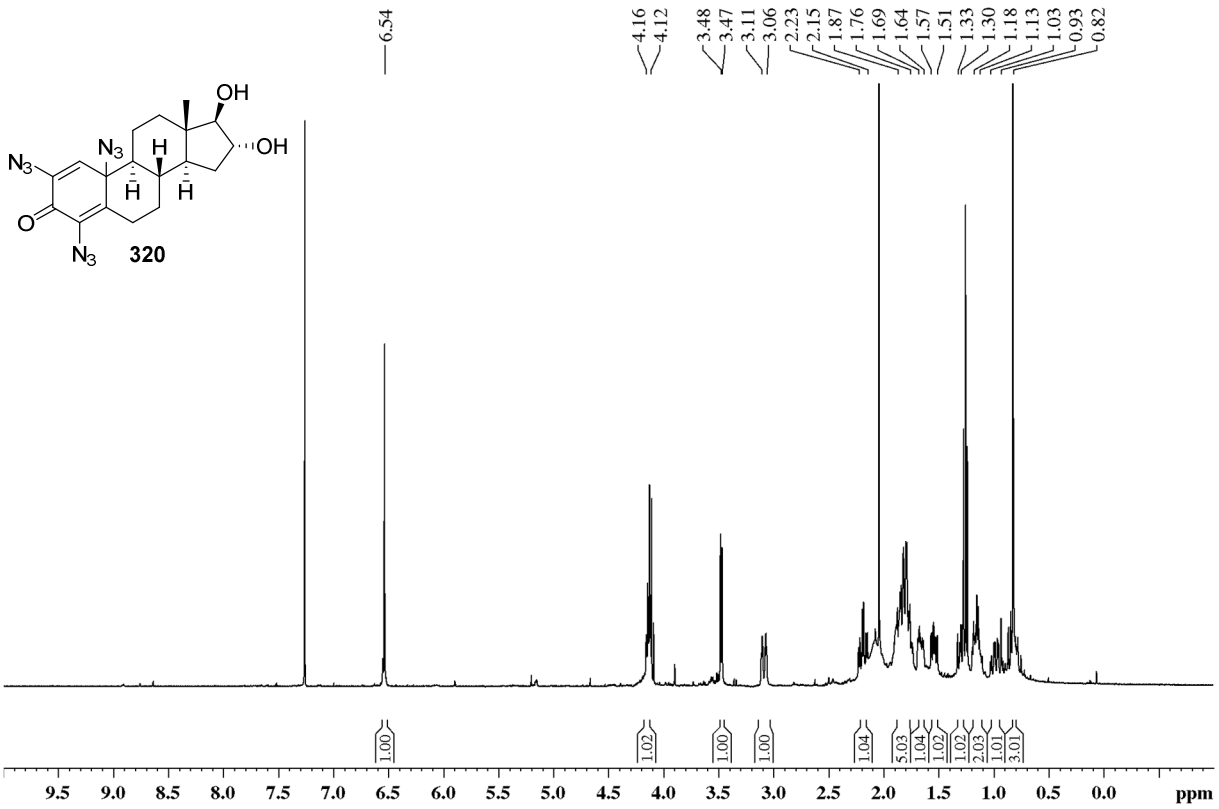

218.19
176.04
144.24
135.37
130.08
127.79
71.17
65.99
53.77
47.62
46.84
35.06
30.76
30.72
30.57
26.24
22.21
14.08
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

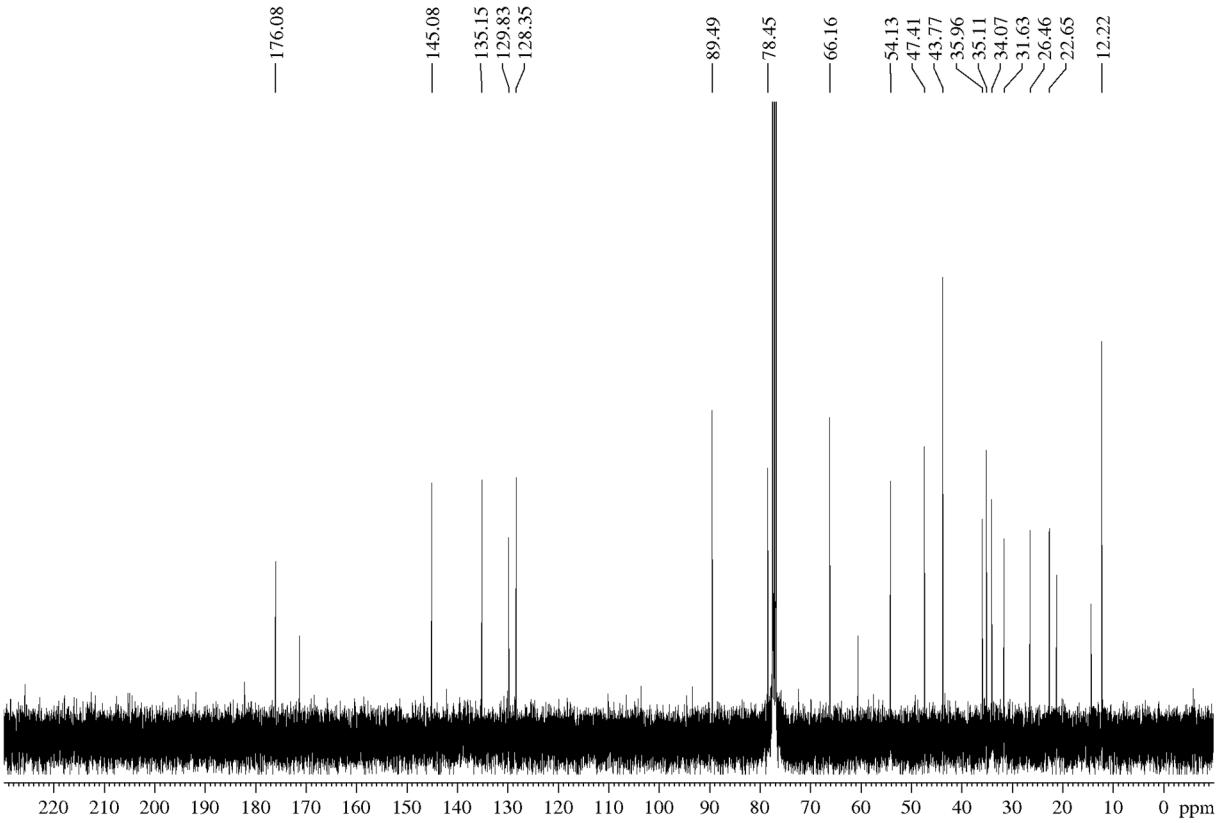

OH
N3
N3
H
H
H
O
N3
318
6.57
3.76
3.74
3.09
3.06
2.24
2.13
1.96
1.93
1.86
1.82
1.79
1.70
1.56
1.42
1.39
1.32
1.27
1.22
1.18
1.12
1.09
0.99
0.71
1.00
1.00
1.00
2.05
1.03
1.01
3.06
3.02
1.01
1.02
1.05
1.04
3.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

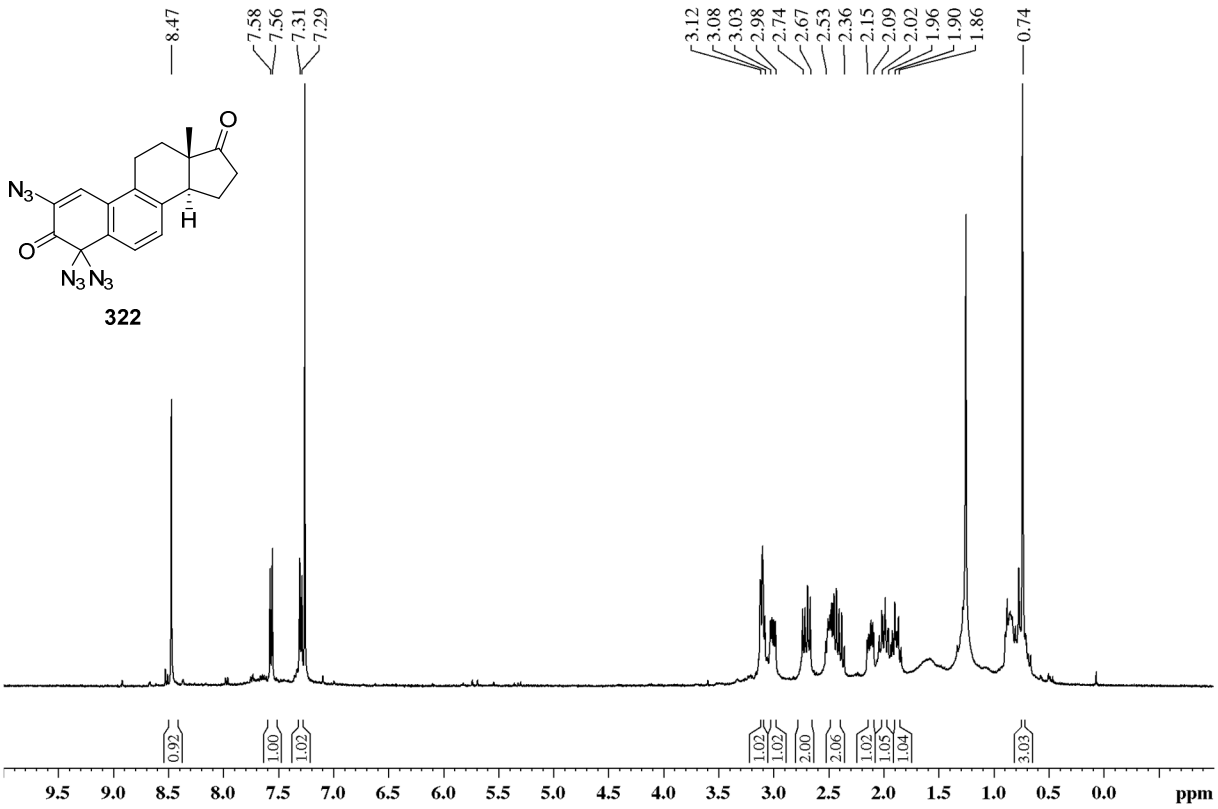

176.09
145.54
134.96
129.64
128.70
79.60
66.31
54.00
47.31
45.42
35.84
32.55
32.49
30.83
26.67
24.87
22.94
16.89
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

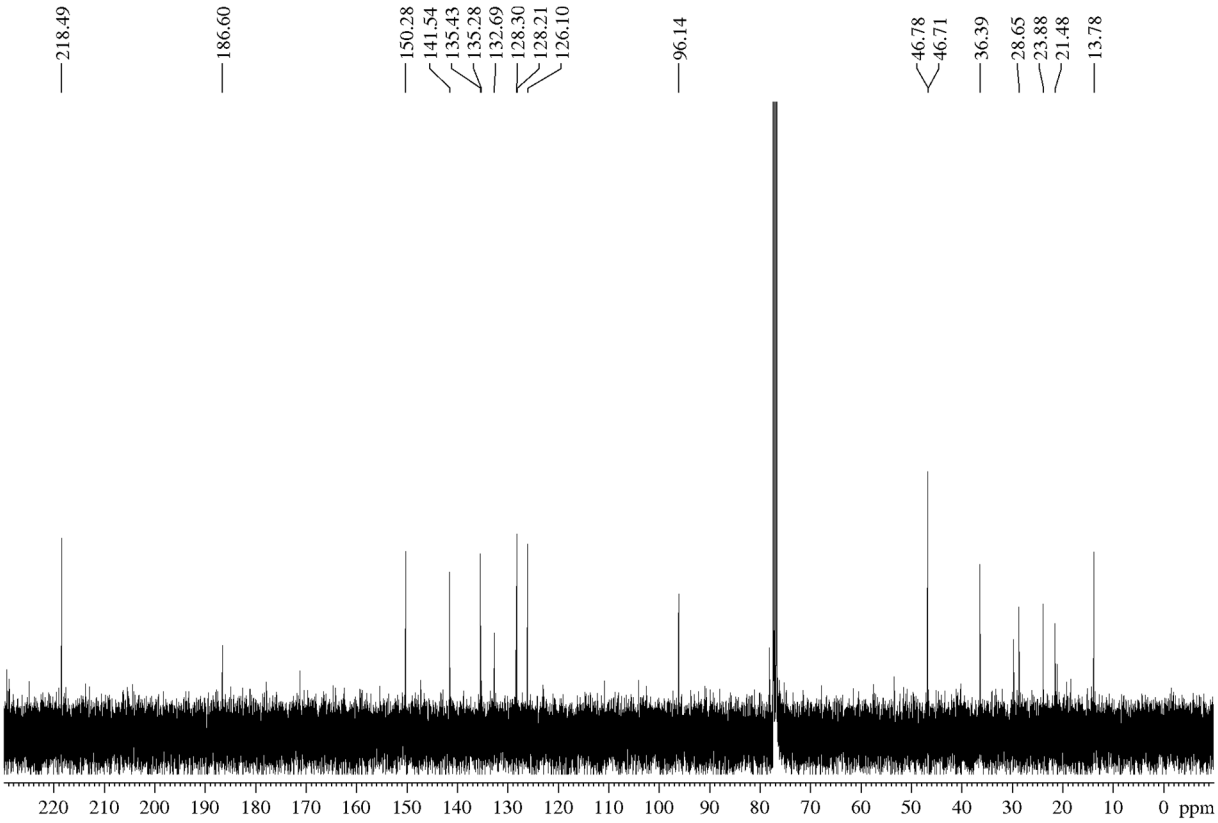

OH
N3
N3
H
H
H
O
N3
319
6.55
3.59
3.07
3.04
2.22
2.14
2.08
2.03
1.91
1.73
1.66
1.64
1.58
1.56
1.48
1.40
1.34
1.26
1.10
1.03
0.95
0.87
0.78
1.01
1.00
1.01
0.97
1.04
4.02
1.05
1.04
0.89
0.98
2.03
1.97
3.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

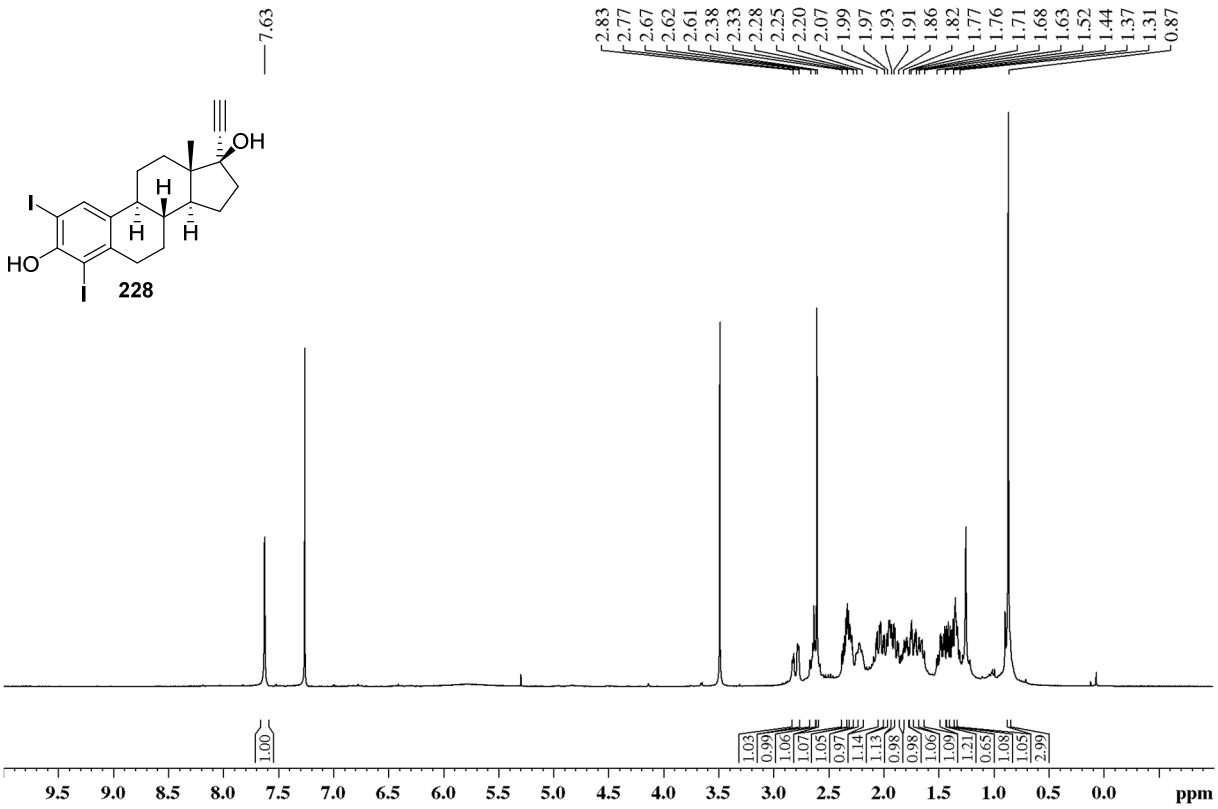

176.00
145.54
134.86
129.53
128.69
81.33
66.18
54.23
49.48
43.07
35.98
35.57
31.69
30.36
26.49
23.52
23.02
10.97
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


6.54
4.16
4.12
3.48
3.47
3.11
3.06
2.23
2.15
1.87
1.76
1.69
1.64
1.57
1.51
1.33
1.30
1.18
1.13
1.03
0.93
0.82
OH
N3
H
OH
N3
H
H
O
N3
320
1.00
1.02
1.00
1.00
1.04
5.03
1.04
1.02
1.02
2.03
1.01
3.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


176.08
145.08
135.15
129.83
128.35
89.49
78.45
66.16
54.13
47.41
43.77
35.96
35.11
34.07
31.63
26.46
22.65
12.22
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


8.47
7.58
7.56
7.31
7.29
3.12
3.08
3.03
2.98
2.74
2.67
2.53
2.36
2.15
2.09
2.02
1.96
1.90
1.86
0.74
O
N3
H
O
N3 N3
322
0.92
1.00
1.02
1.02
1.02
2.00
2.06
1.02
1.05
1.04
3.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


218.49
186.60
150.28
141.54
135.43
135.28
132.69
128.30
128.21
126.10
96.14
46.78
46.71
36.39
28.65
23.88
21.48
13.78
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.63
2.83
2.77
2.67
2.62
2.61
2.38
2.33
2.28
2.25
2.20
2.07
1.99
1.97
1.93
1.91
1.86
1.82
1.77
1.76
1.71
1.68
1.63
1.52
1.44
1.37
1.31
0.87
OH
H
H
H
I
HO
I
228
1.00
1.03
0.99
1.06
1.07
1.05
0.97
1.14
1.13
0.98
0.98
1.06
1.09
1.21
0.65
1.08
1.05
2.99
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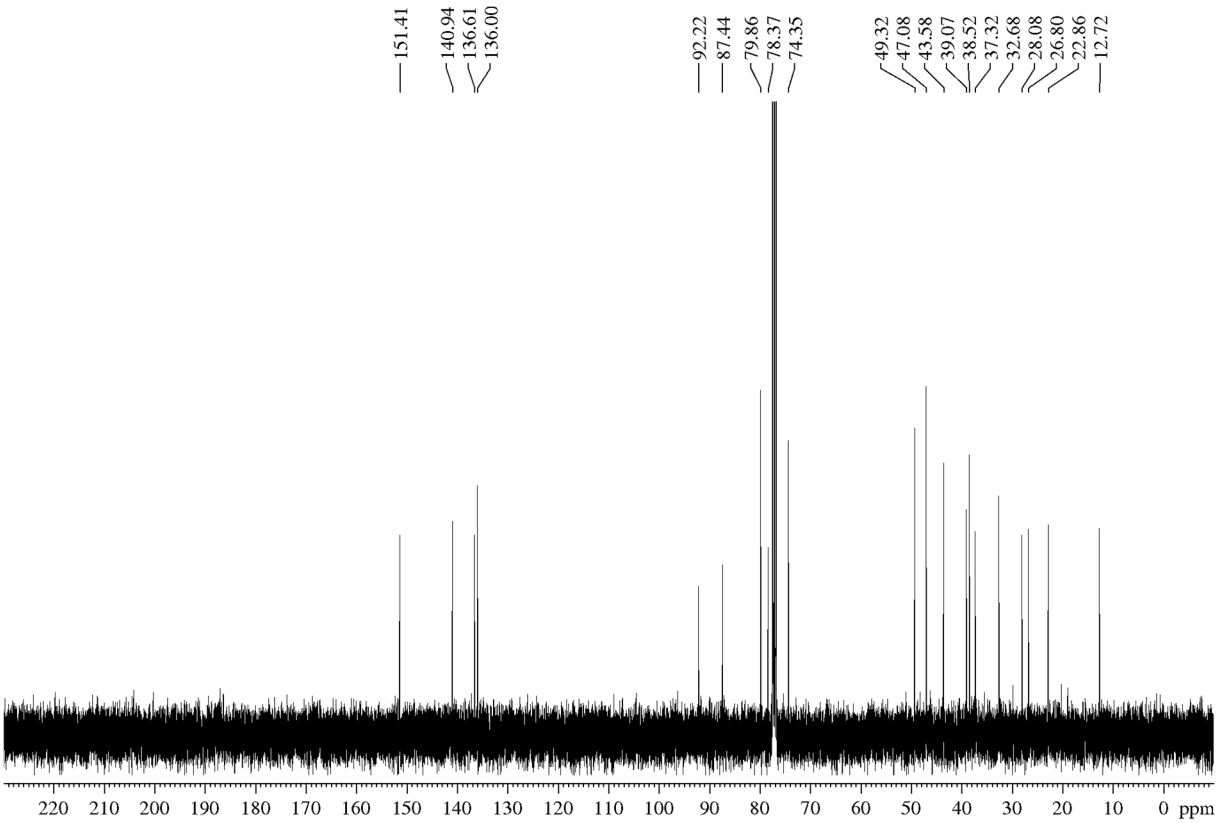
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79.86
78.37
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47.08
43.58
39.07
38.52
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32.68
28.08
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22.86
12.72
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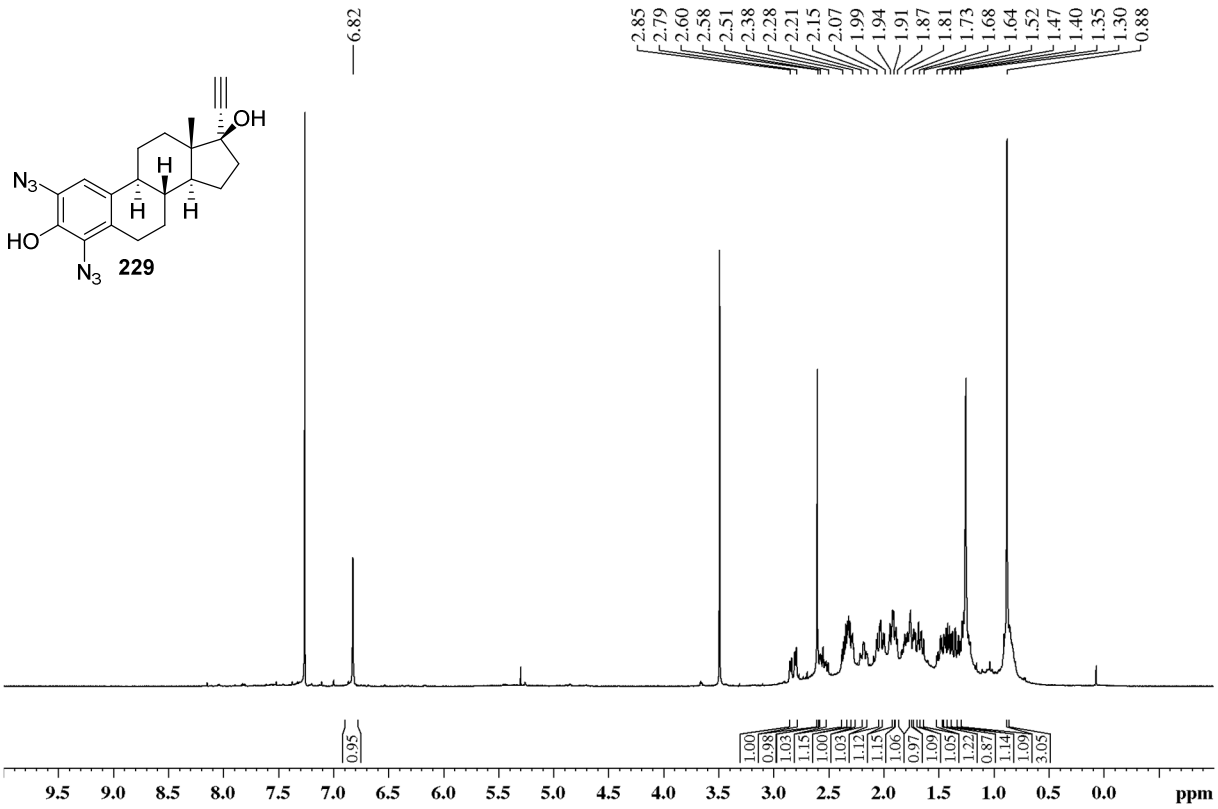
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2.79
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2.58
2.51
2.38
2.28
2.21
2.15
2.07
1.99
1.94
1.91
1.87
1.81
1.73
1.68
1.64
1.52
1.47
1.40
1.35
1.30
0.88
OH
N3
H
H
H
HO
N3
229
0.95
1.00
0.98
1.03
1.15
1.00
1.03
1.12
1.15
1.06
0.97
1.09
1.05
1.22
0.87
1.14
1.09
3.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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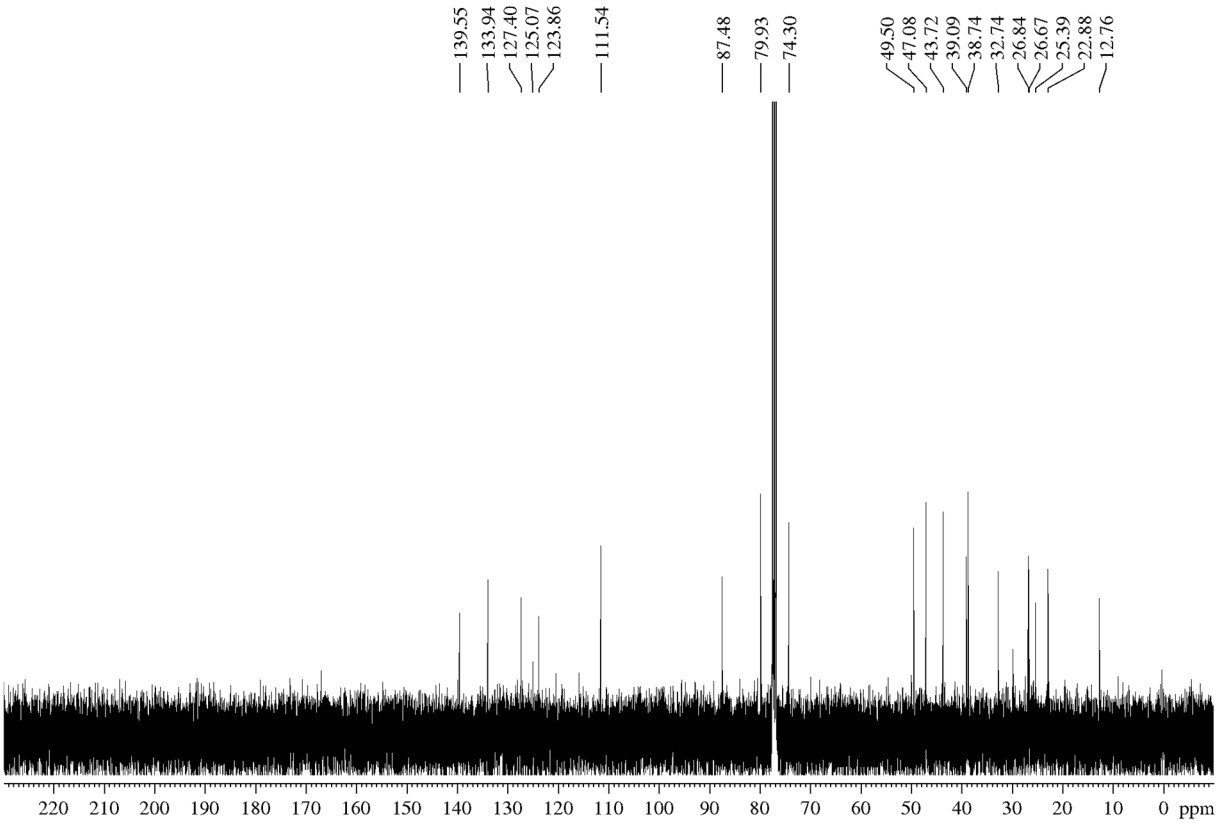
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79.93
74.30
49.50
47.08
43.72
39.09
38.74
32.74
26.84
26.67
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22.88
12.76
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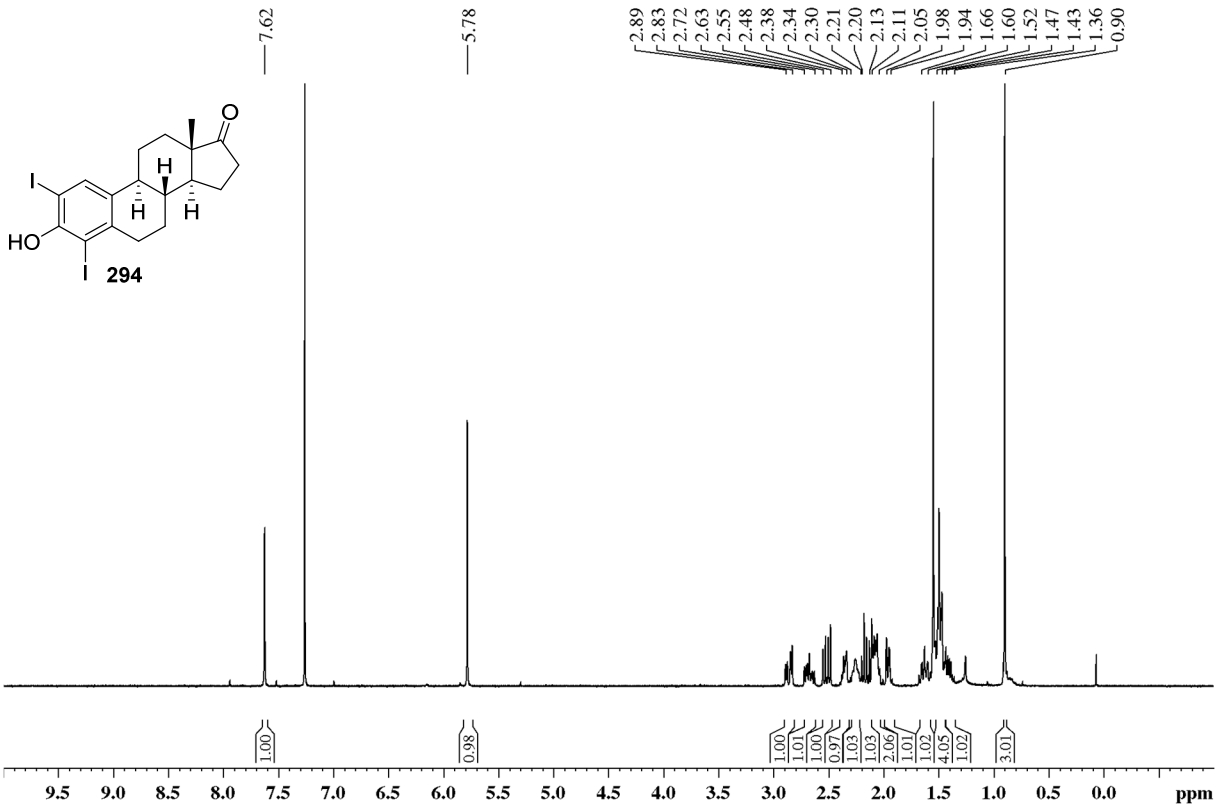
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2.89
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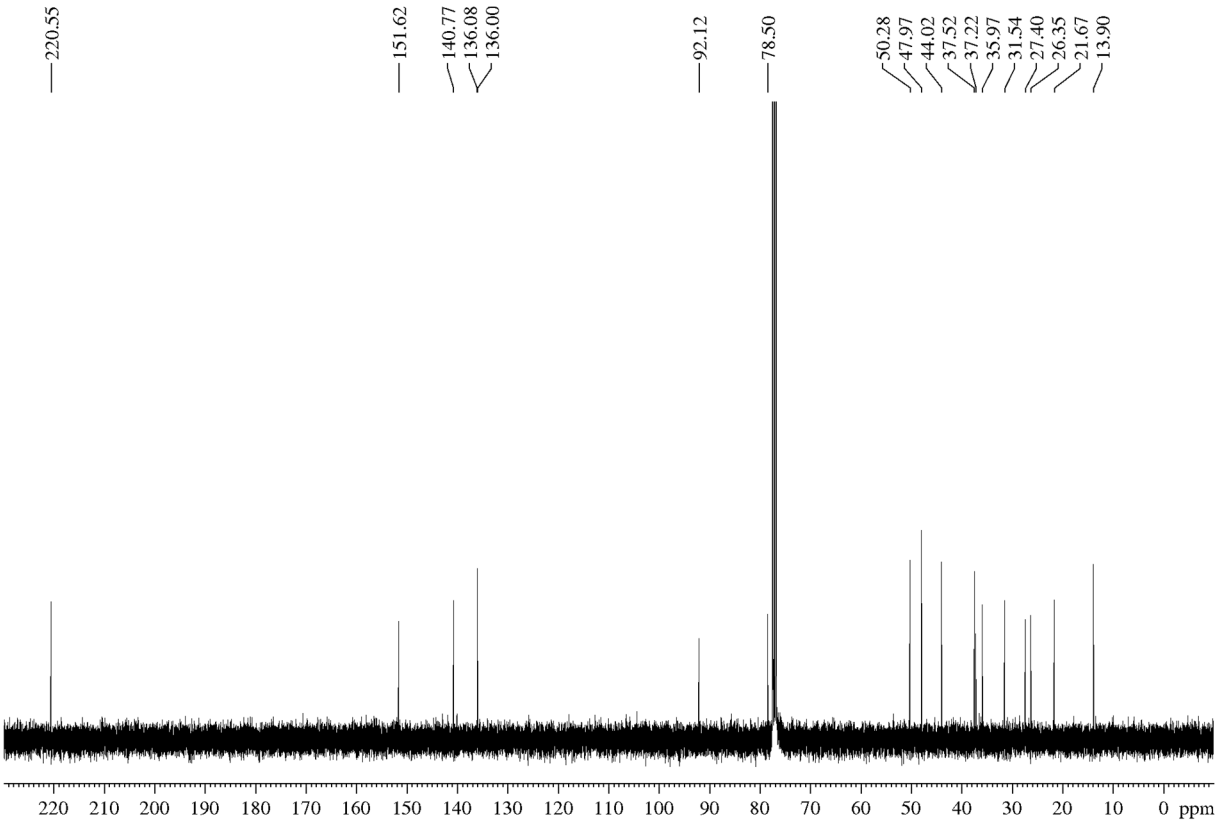
2.55
2.48
2.38
2.34
2.30
2.21
2.20
2.13
2.11
2.05
1.98
1.94
1.66
1.60
1.52
1.47
1.43
1.36
0.90
O
H
I
H
H
HO
I
294
1.00
0.98
1.00
1.01
1.00
0.97
1.03
1.03
2.06
1.01
1.02
4.05
1.02
3.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm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140.77
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136.00
92.12
78.50
50.28
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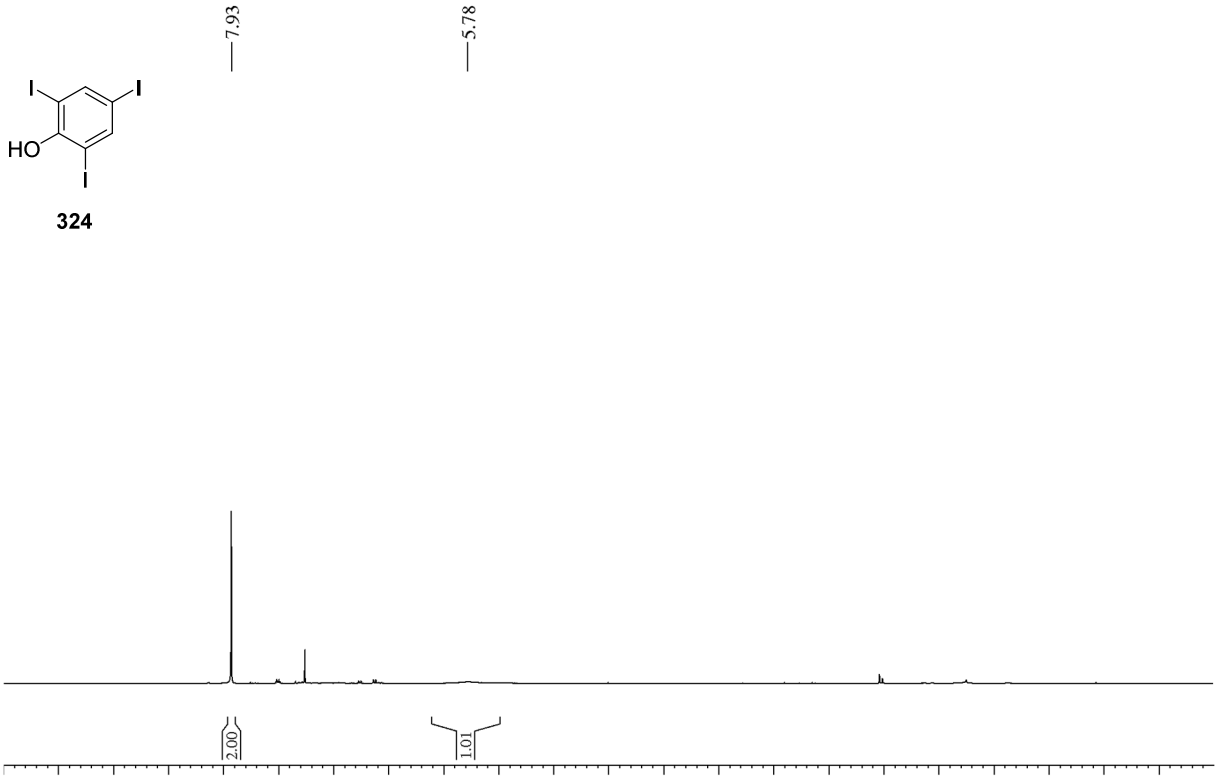
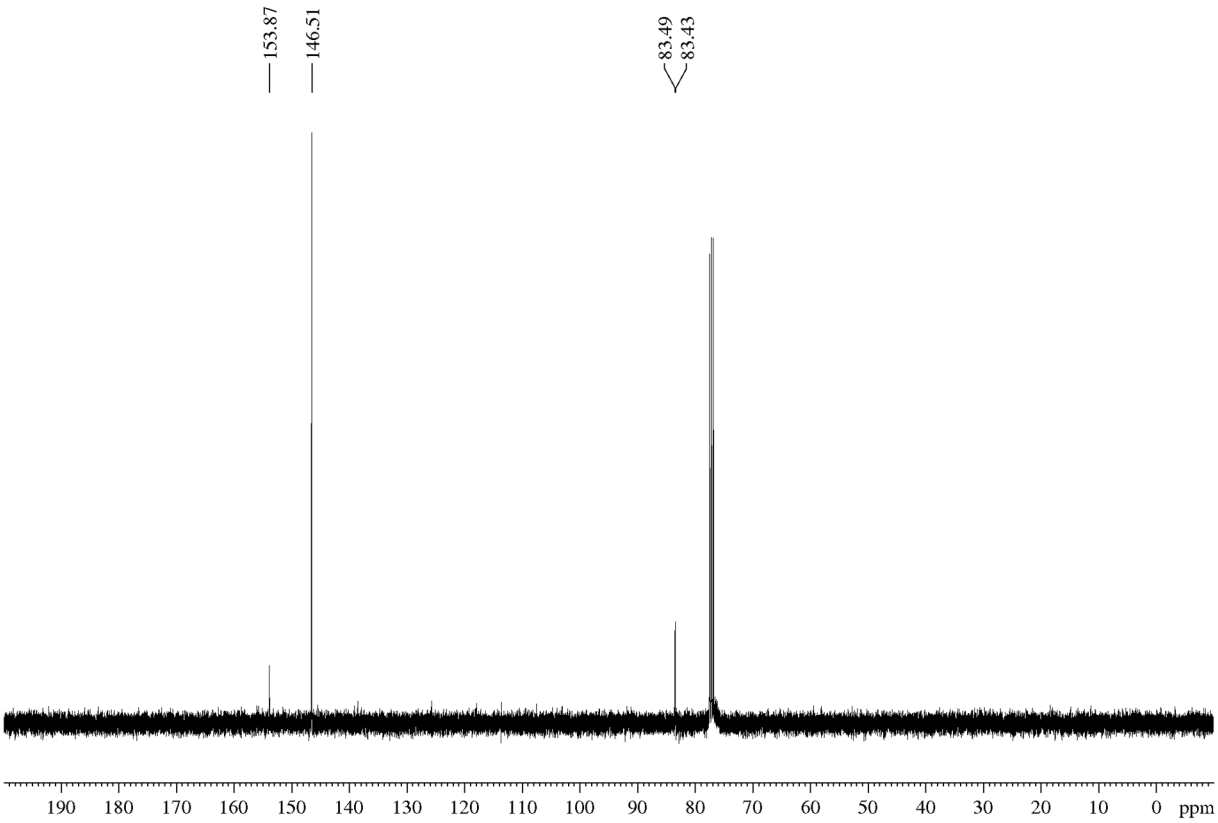
44.02
37.52
37.22
35.97
31.54
27.40
26.35
21.67
13.90
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.93
5.78
I
I
HO
I
2.00
1.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

324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146.51
83.49
83.43
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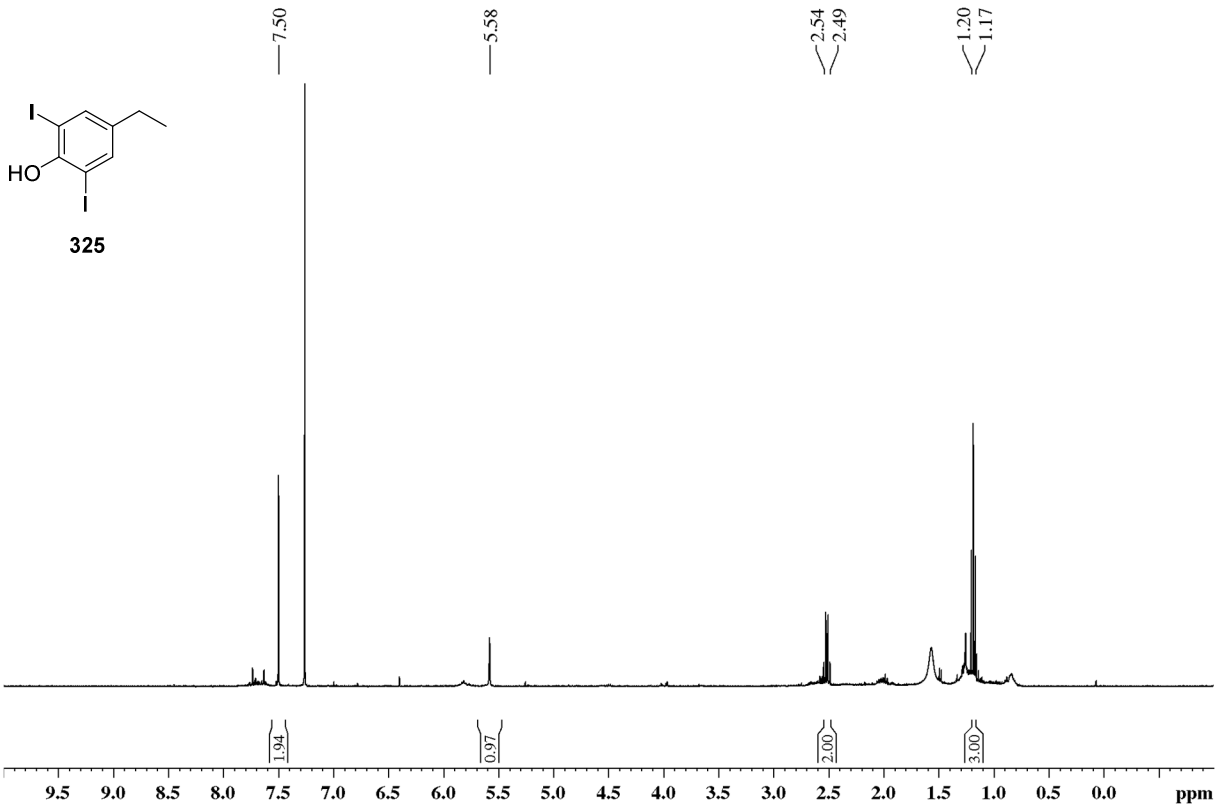
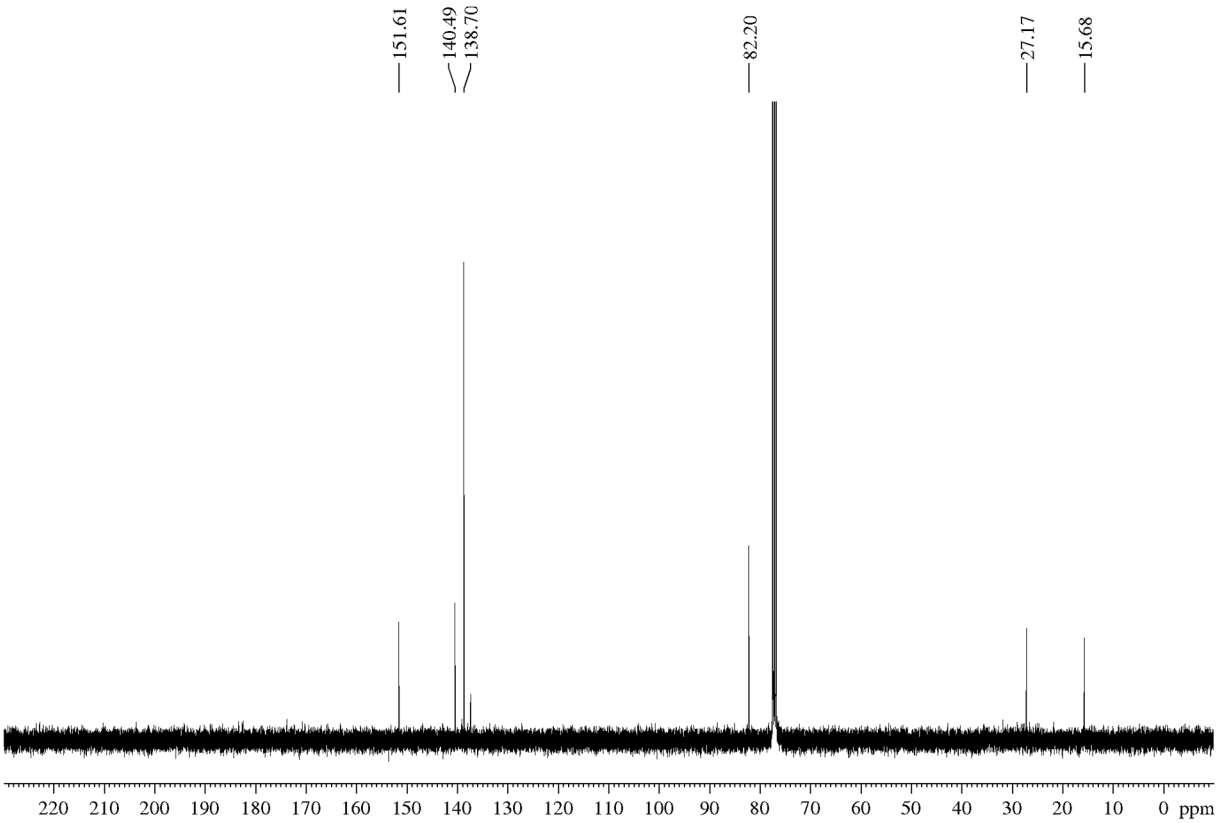

7.50
5.58
2.54
2.49
1.20
1.17
I
HO
I
325
1.94
0.97
2.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


151.61
140.49
138.70
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27.17
15.68
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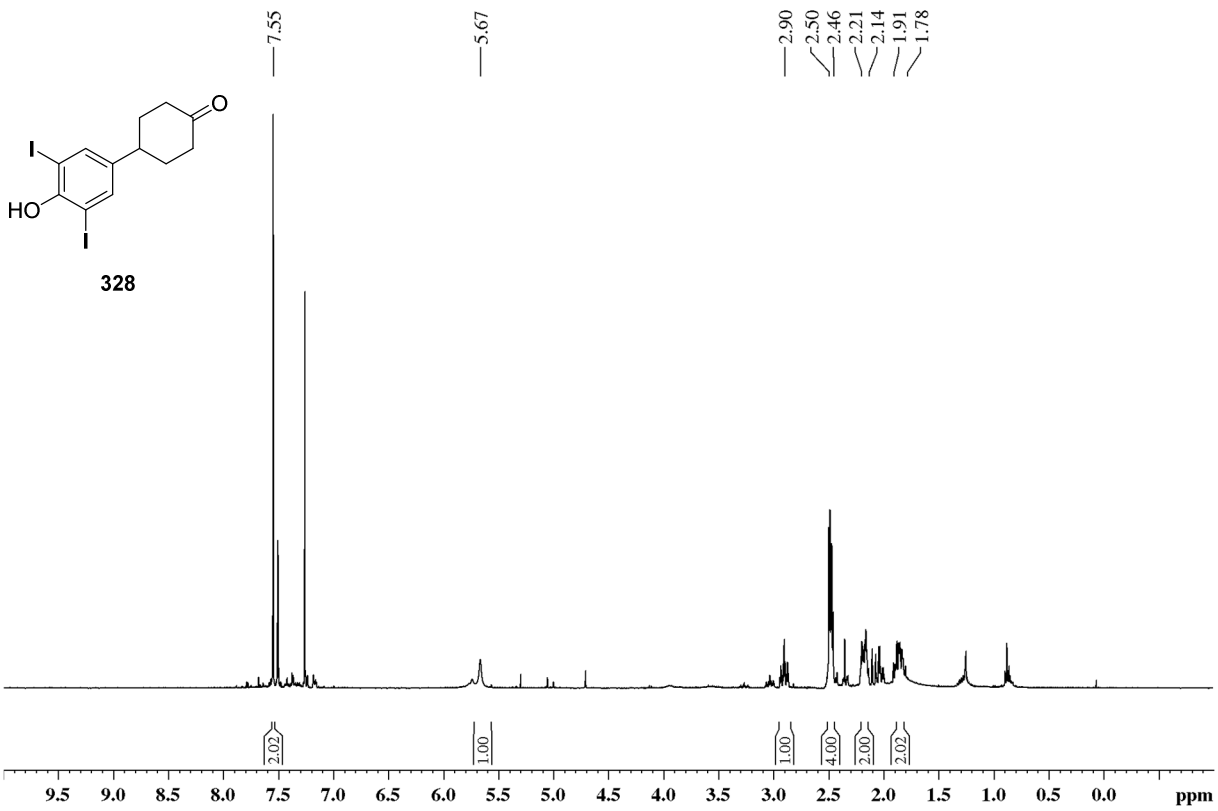
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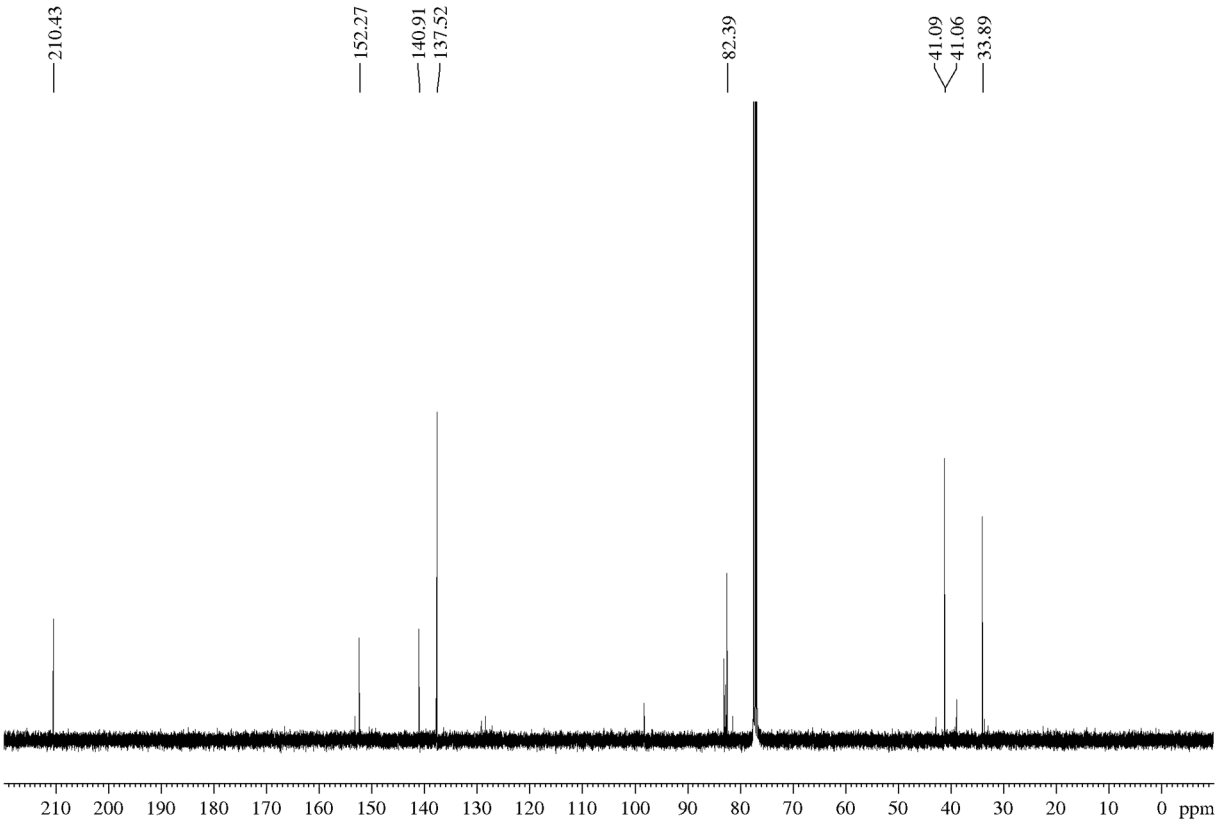
5.67
2.90
2.50
2.46
2.21
2.14
1.91
1.78
O
I
HO
I
328
2.02
1.00
1.00
4.00
2.00
2.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm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82.39
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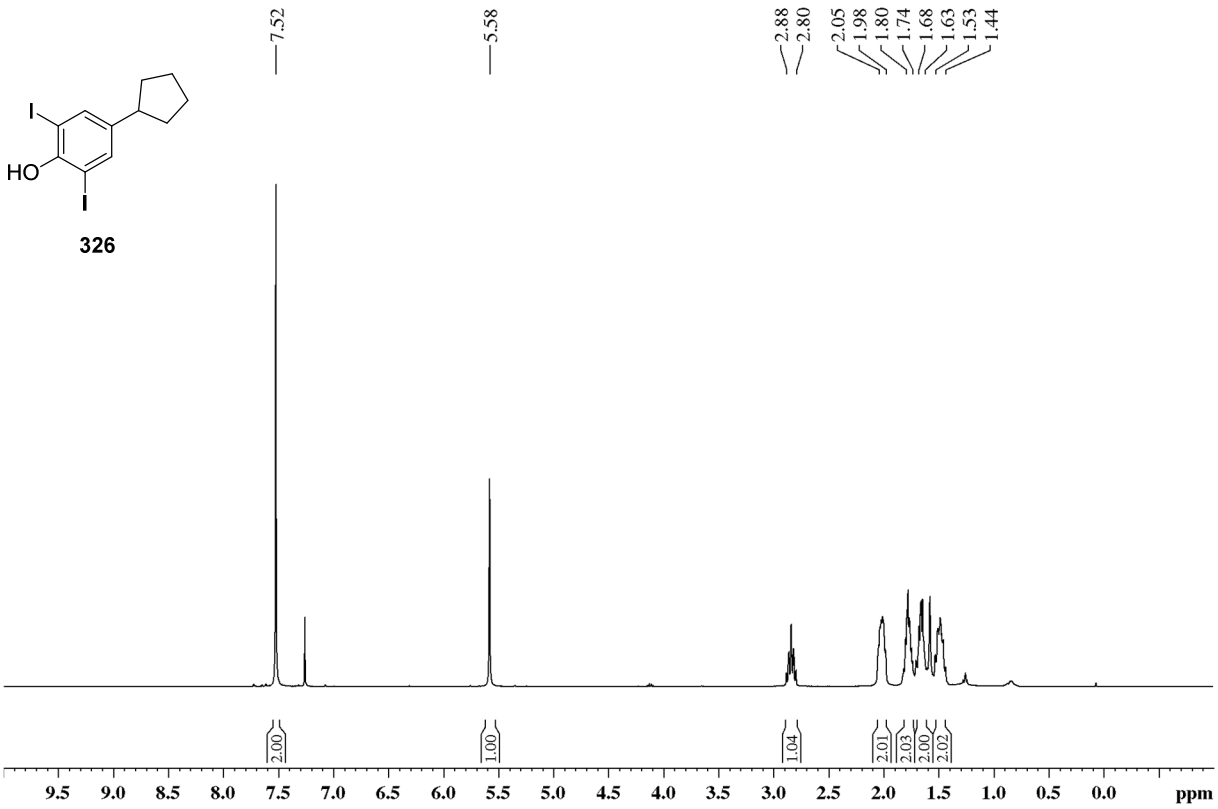
41.06
33.89
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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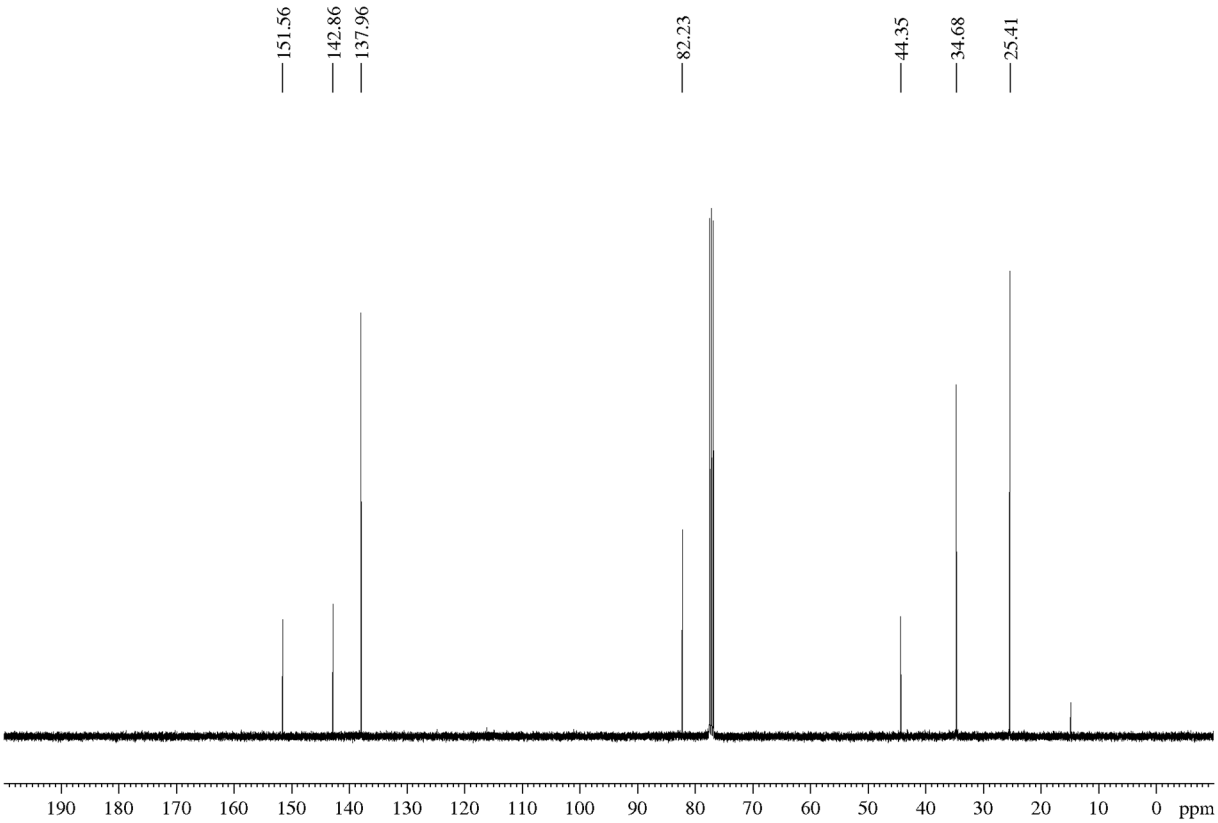
5.58
2.88
2.80
2.05
1.98
1.80
1.74
1.68
1.63
1.53
1.44
I
HO
I
326
2.00
1.00
1.04
2.01
2.03
2.00
2.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm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137.96
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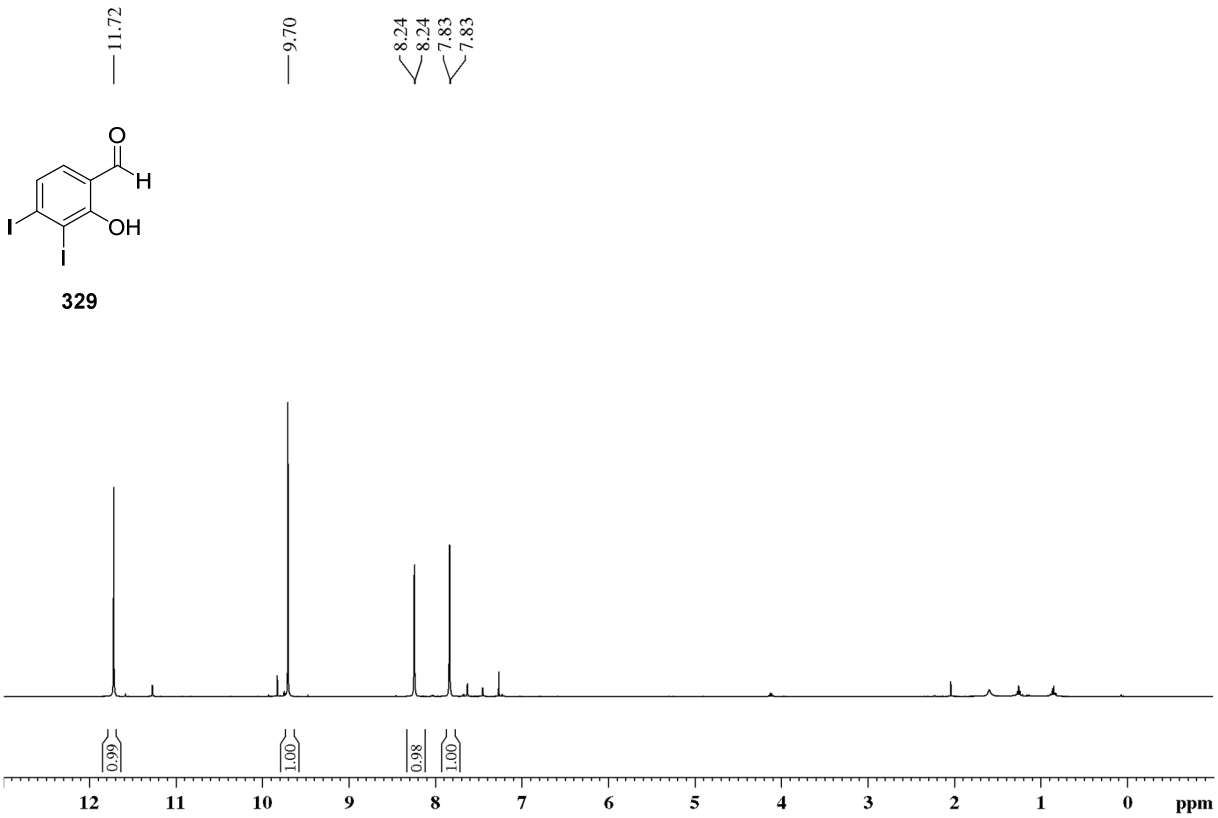
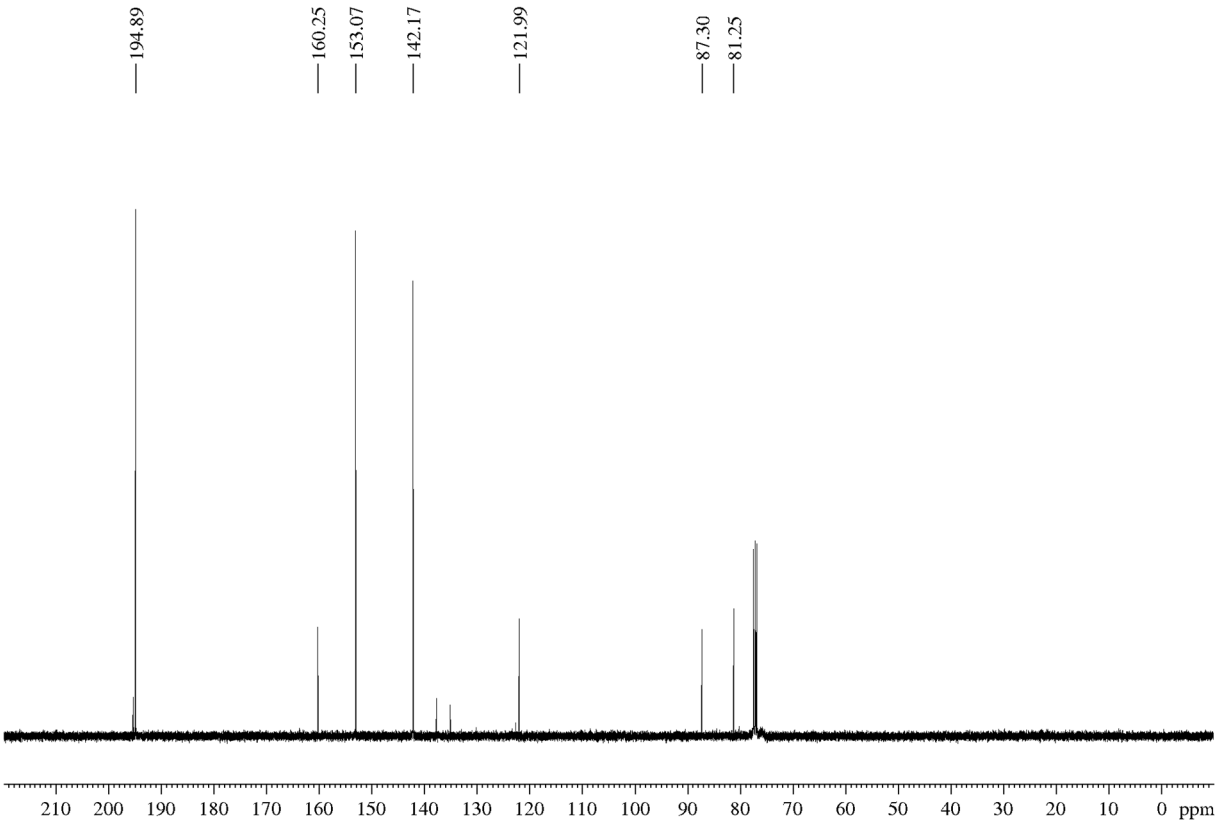
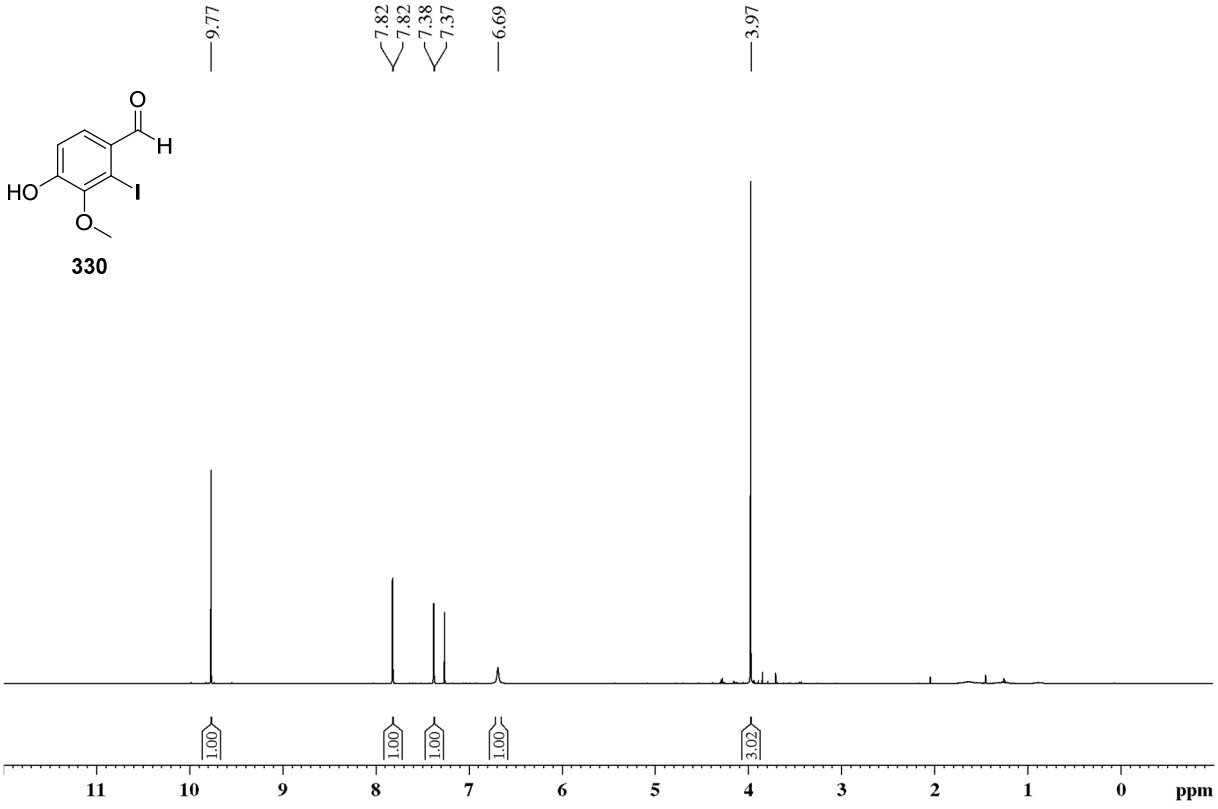
34.68
25.41
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


11.72
9.70
8.24
8.24
7.83
7.83
O
H
I
OH
I
0.99
1.00
0.98
1.00
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

329


194.89
160.25
153.07
142.17
121.99
87.30
81.25
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm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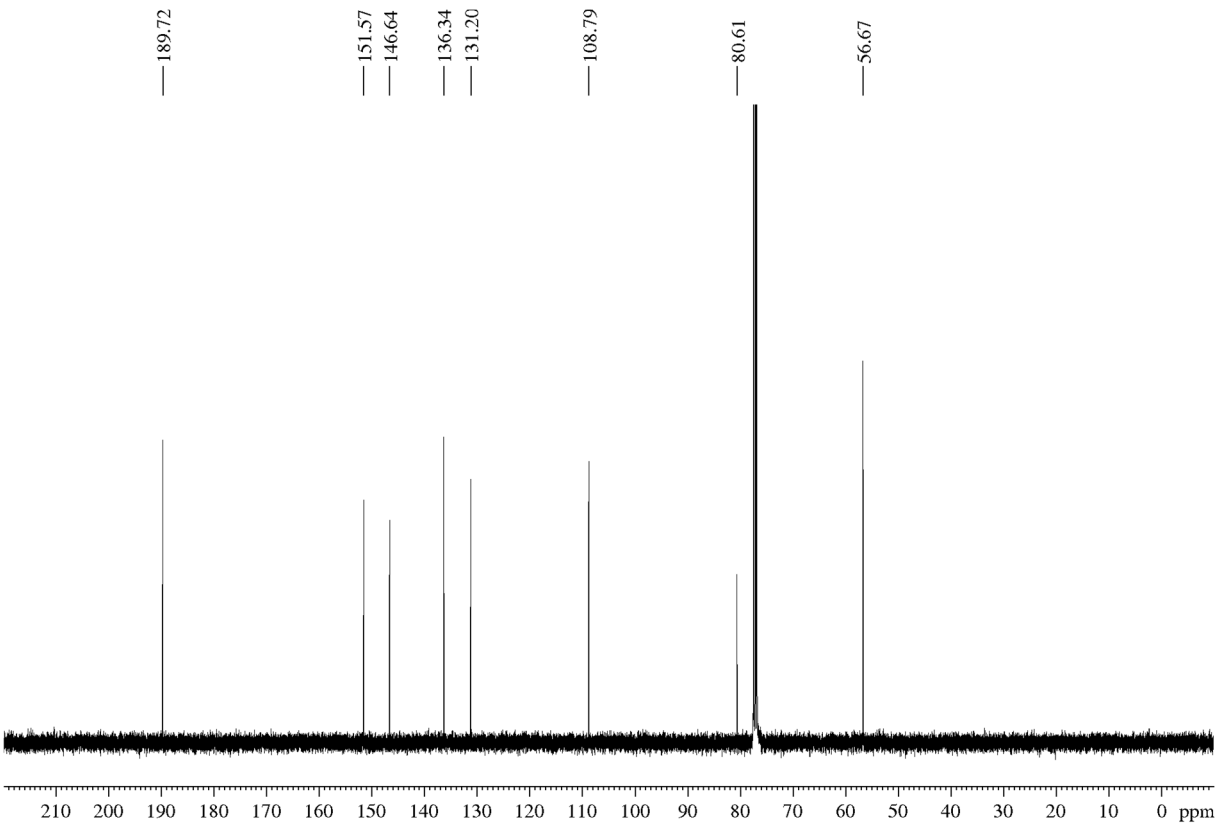
7.82
7.38
7.37
6.69
3.97
O
H
HO
I
O
330
1.00
1.00
1.00
1.00
3.02
11
10
9
8
7
6
5
4
3
2
1
0
ppm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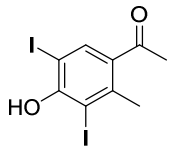
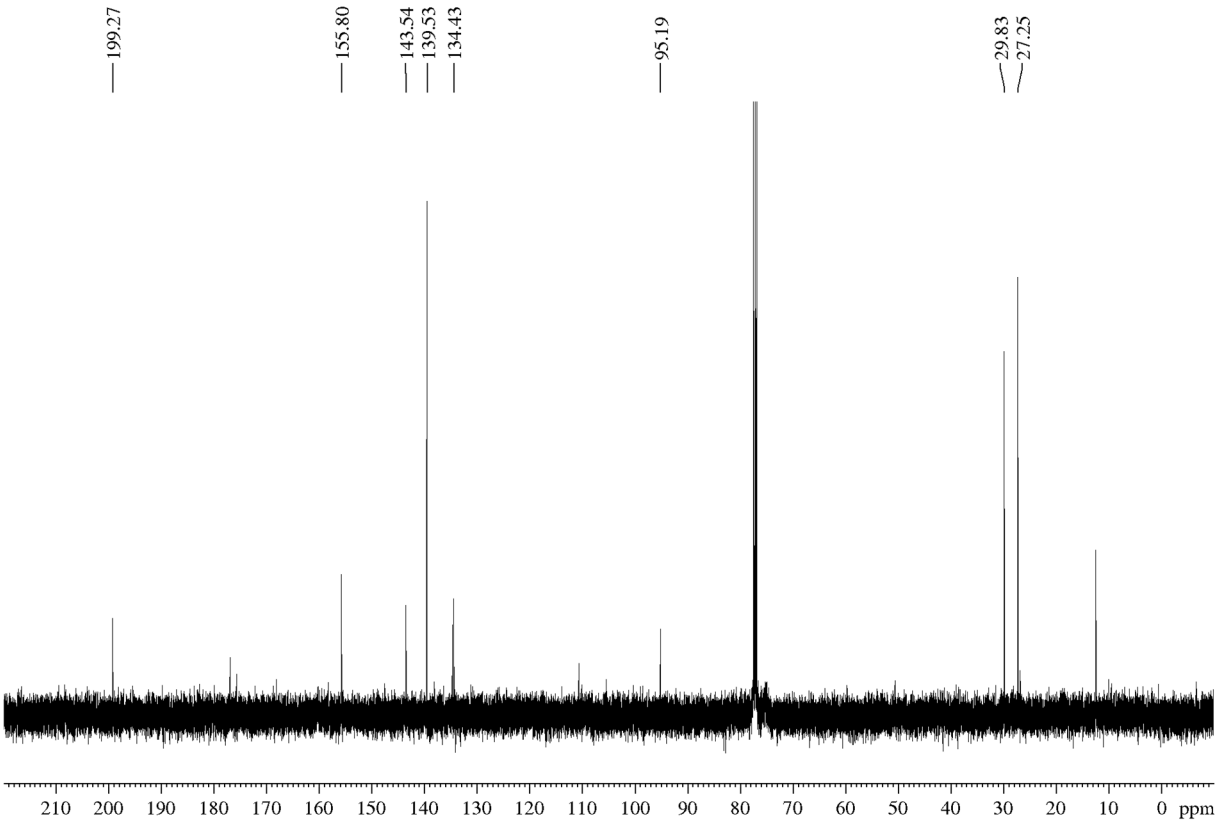
108.79
80.61
56.67
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm


O
I
HO
I

327

7.95
2.60
2.54
1.00
2.99
3.02
11
10
9
8
7
6
5
4
3
2
1
0
ppm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143.54
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134.43
95.19
29.83
27.25
210
200
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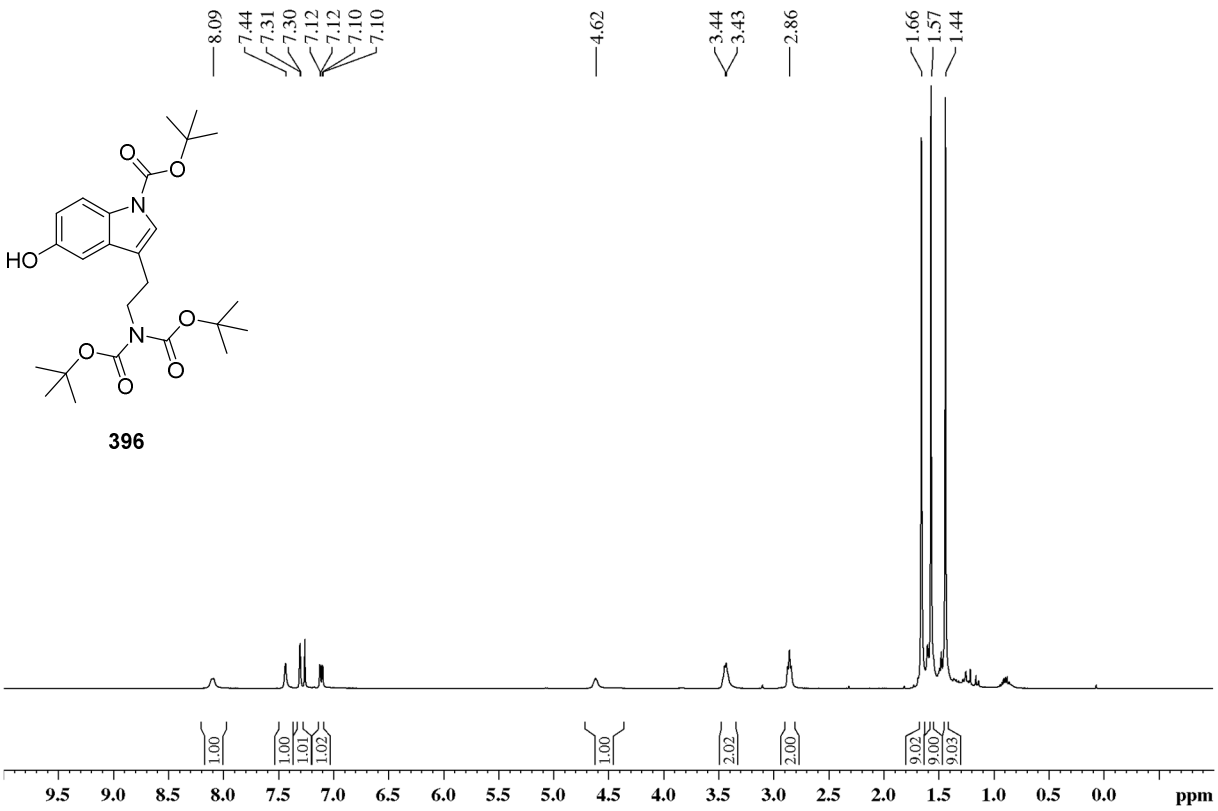
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm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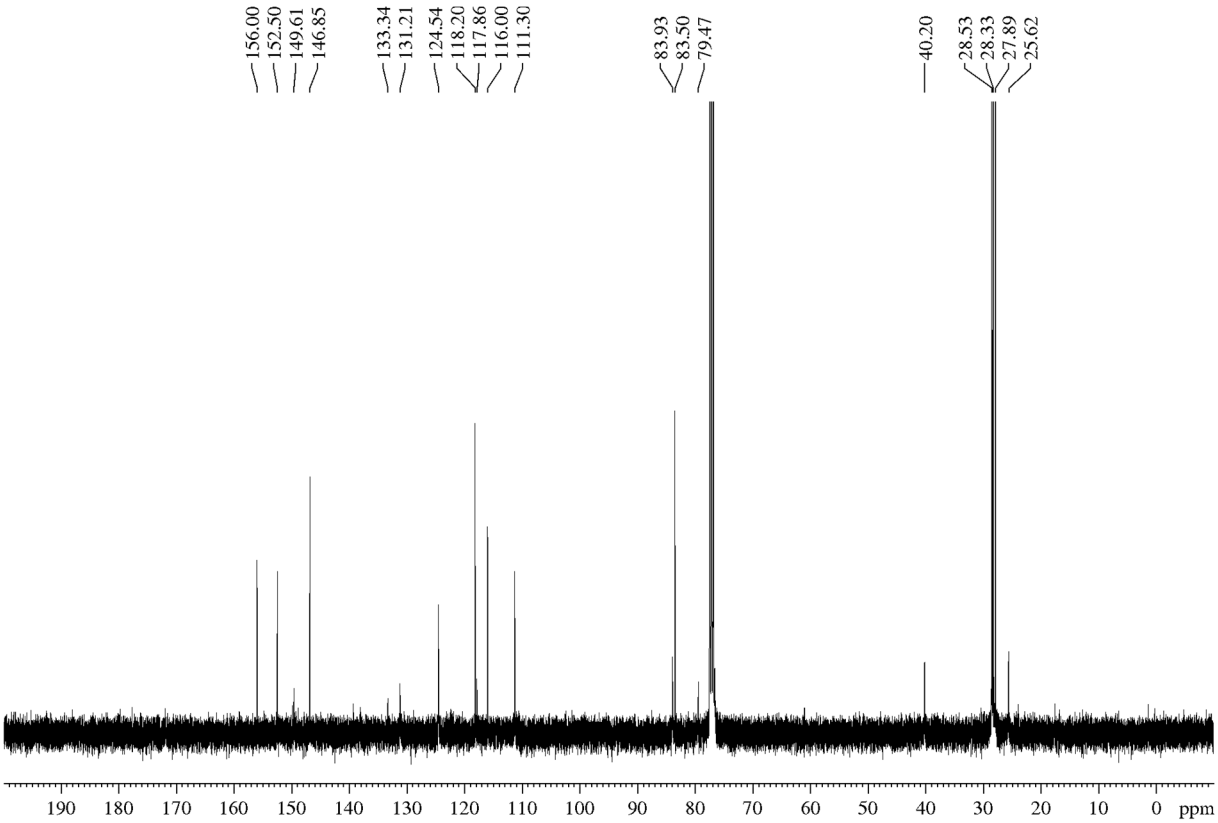
7.31
7.30
7.12
7.12
7.10
7.10
4.62
3.44
3.43
2.86
1.66
1.57
1.44
HO
O
O
N
O
O
N
O
O
O
O
1.00
1.00
1.01
1.02
1.00
2.02
2.00
9.02
9.00
9.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

396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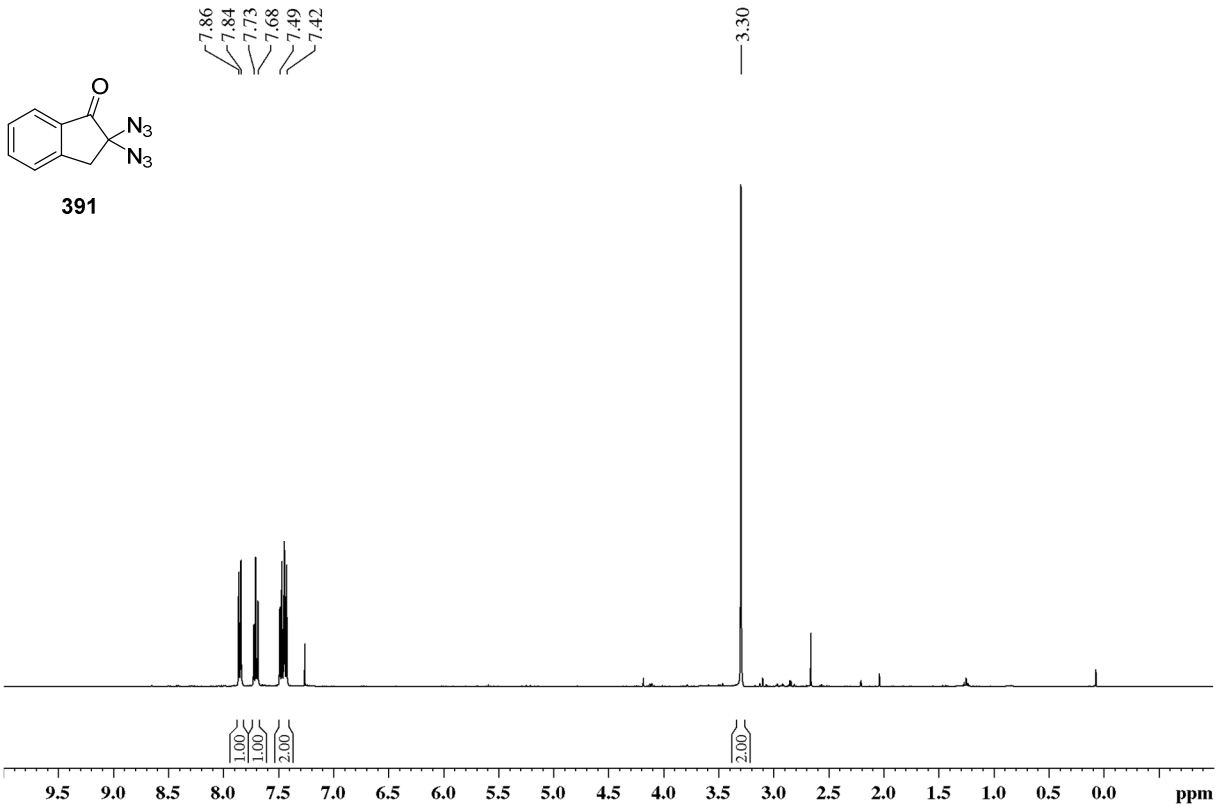
152.50
149.61
146.85
133.34
131.21
124.54
118.20
117.86
116.00
111.30
83.93
83.50
79.47
40.20
28.53
28.33
27.89
25.62
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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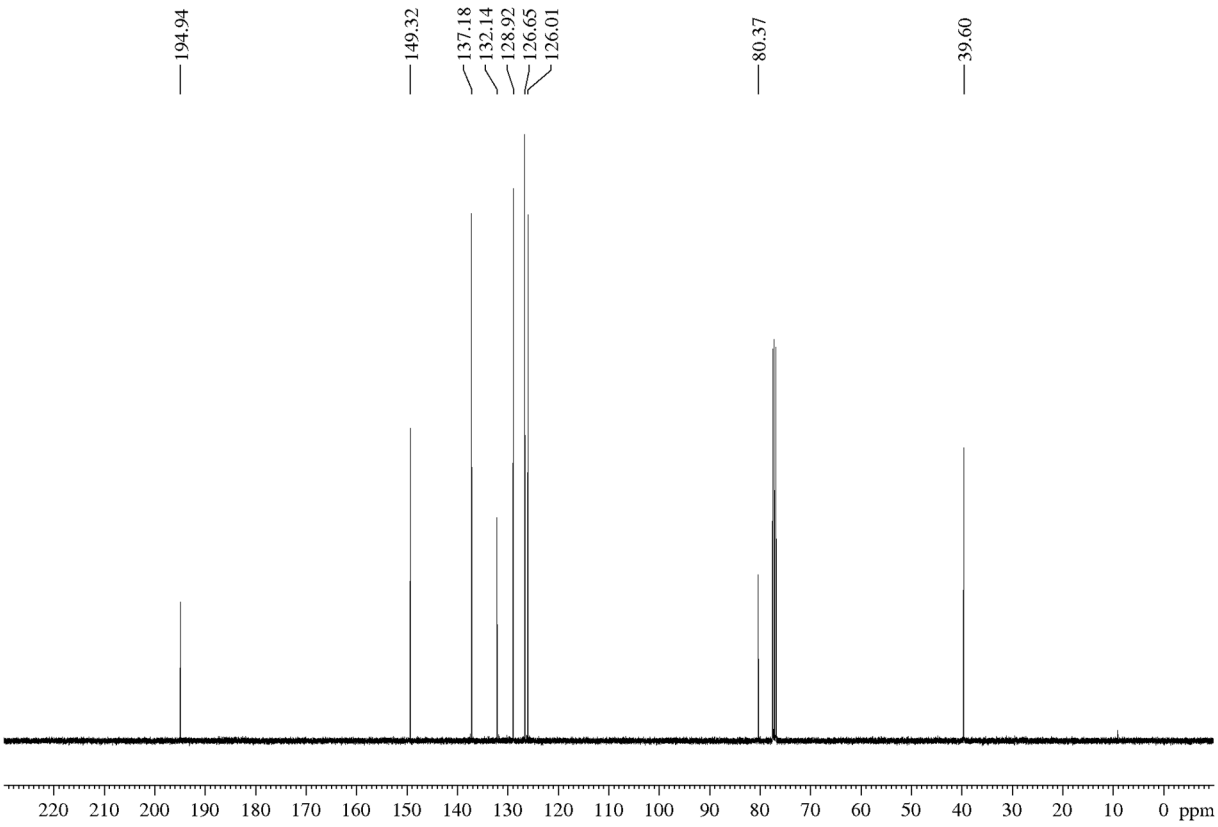
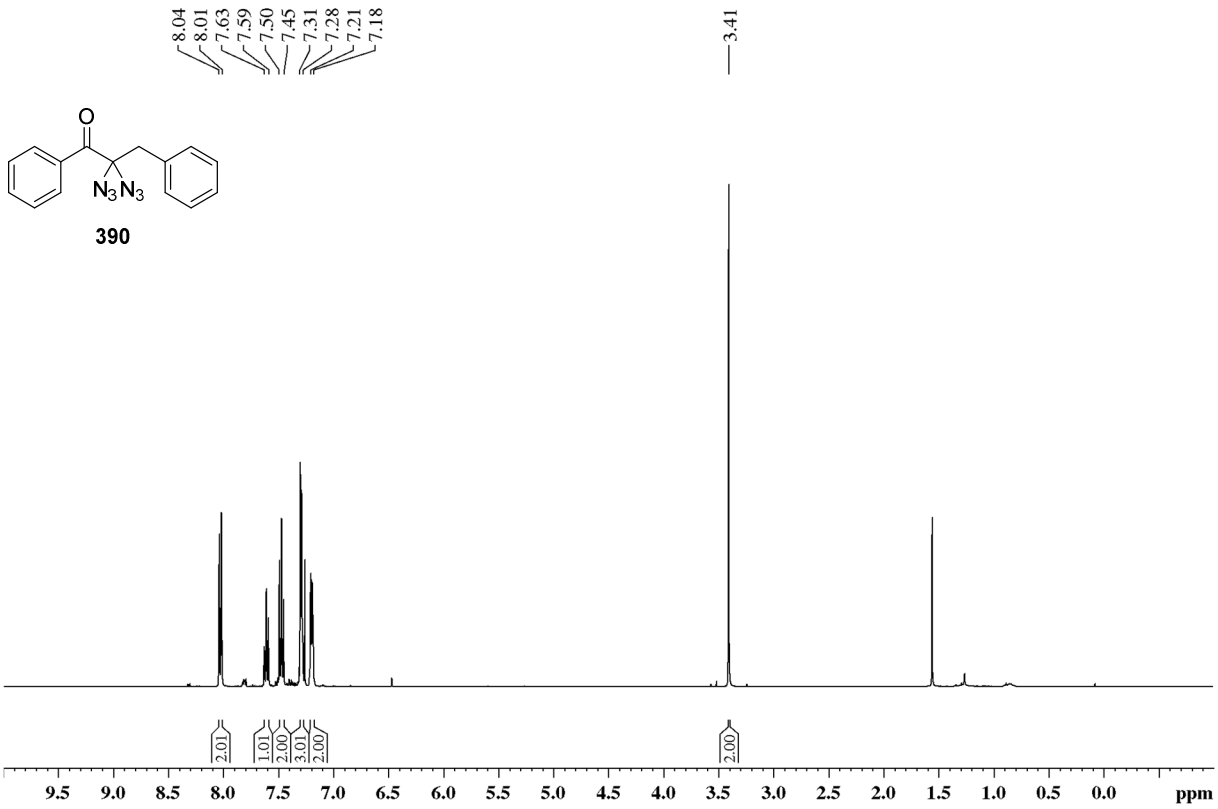
7.73
7.68
7.49
7.42
3.30
O
N3
N3
391
1.00
1.00
2.00
2.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


194.94
149.32
137.18
132.14
128.92
126.65
126.01
80.37
39.60
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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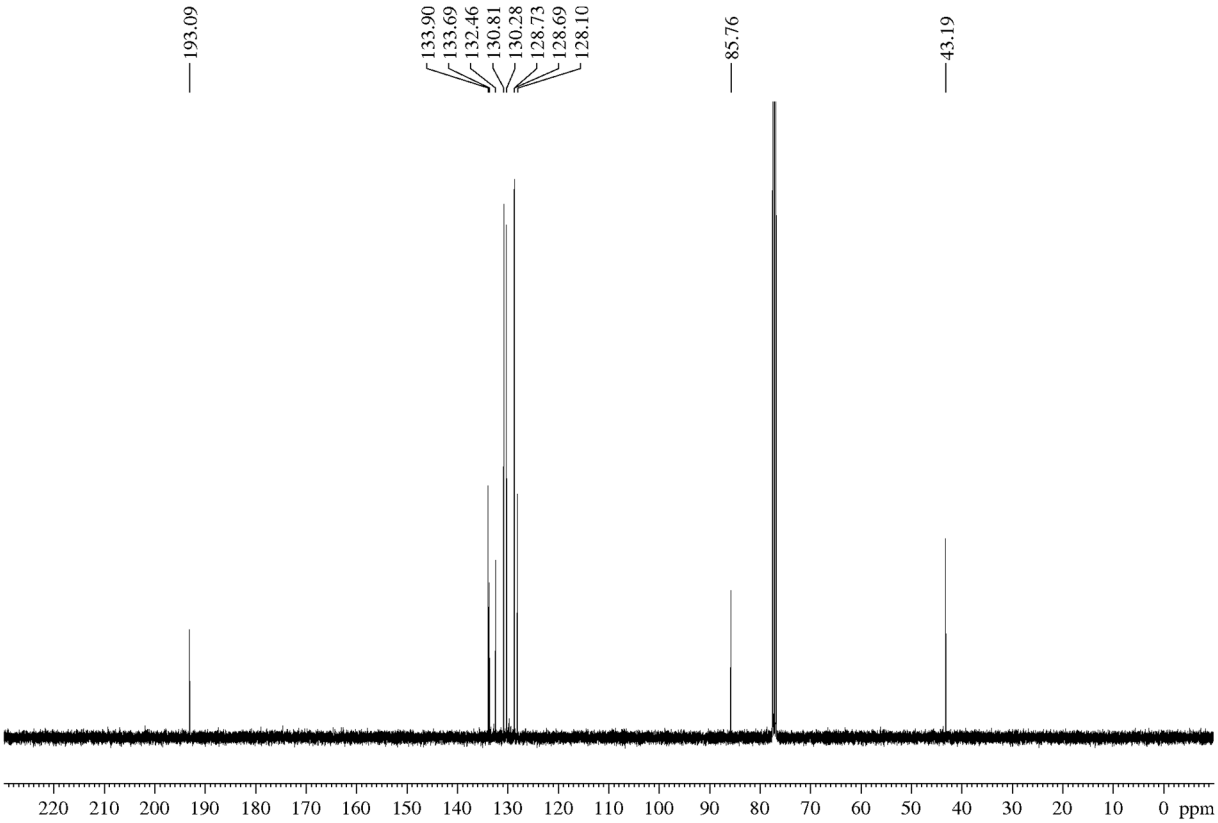
8.01
7.63
7.59
7.50
7.45
7.31
7.28
7.21
7.18
3.41
O
N3N3
390
2.01
1.01
2.00
3.01
2.00
2.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


193.09
133.90
133.69
132.46
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130.28
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128.69
128.10
85.76
43.19
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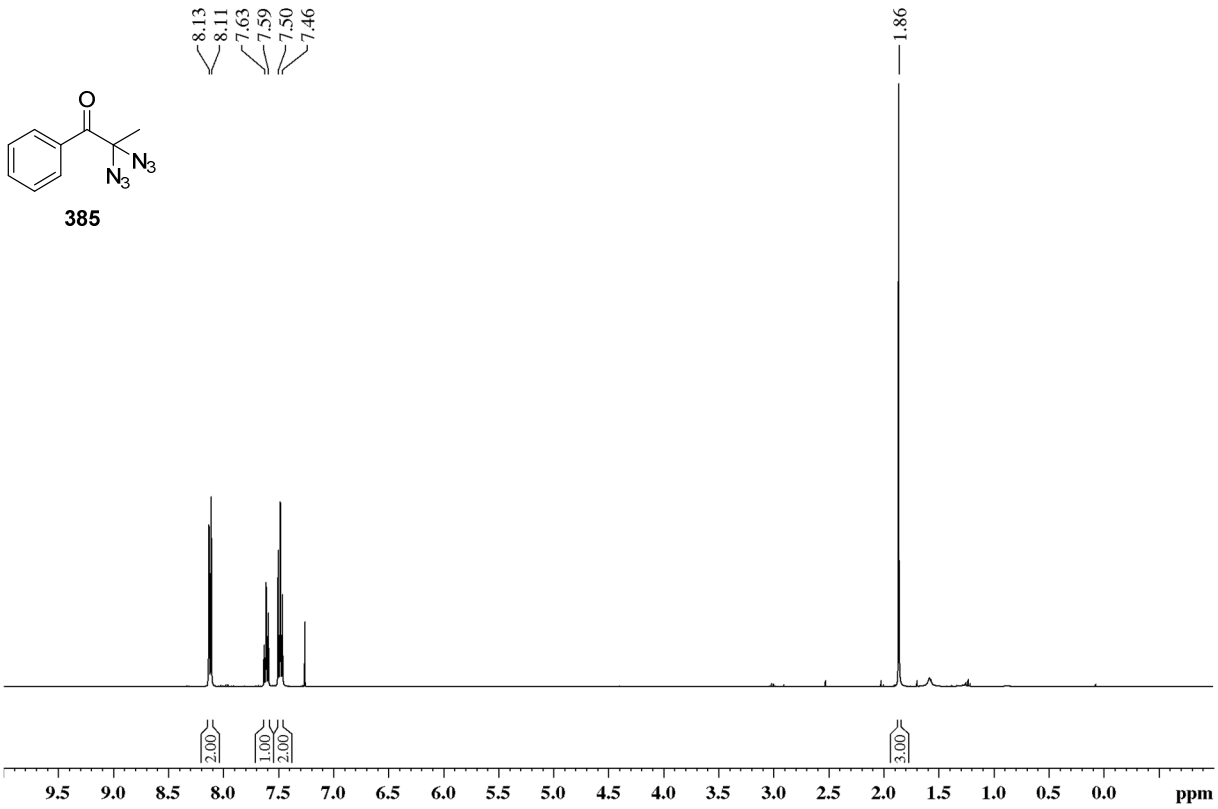
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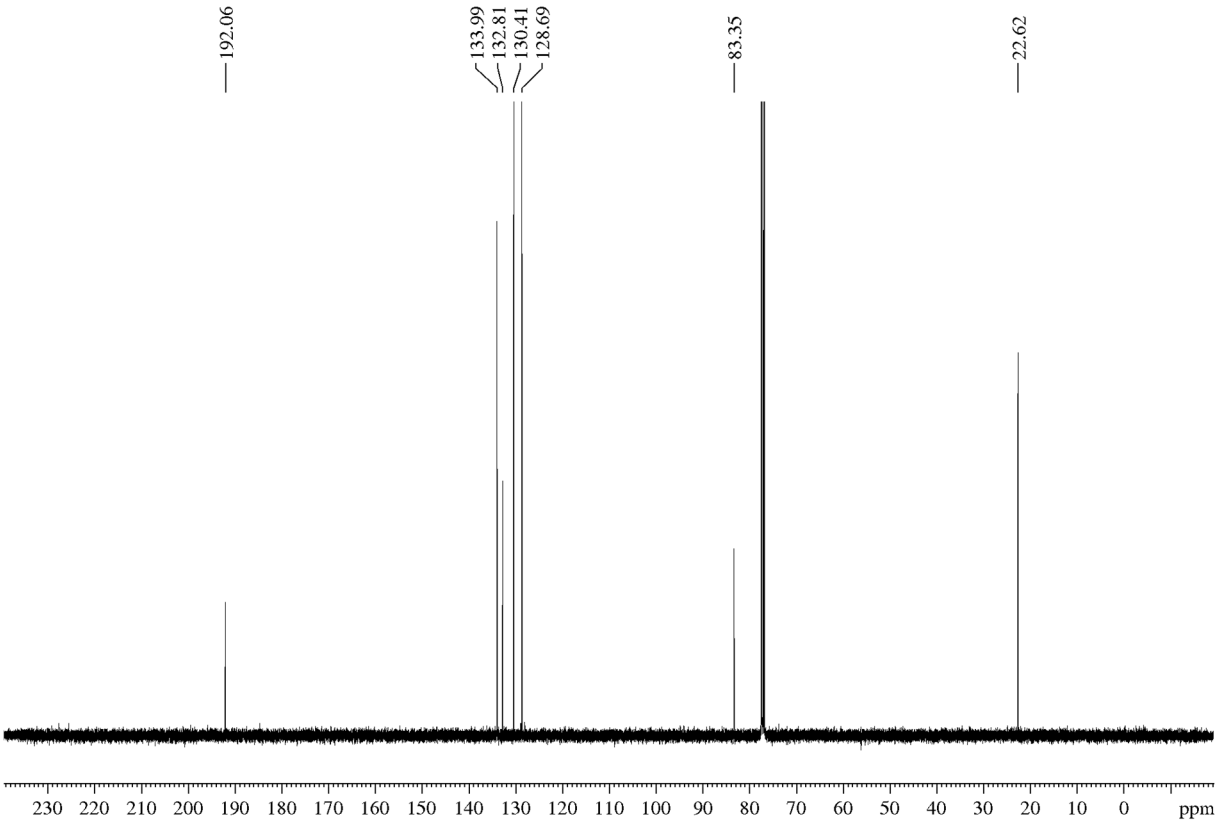
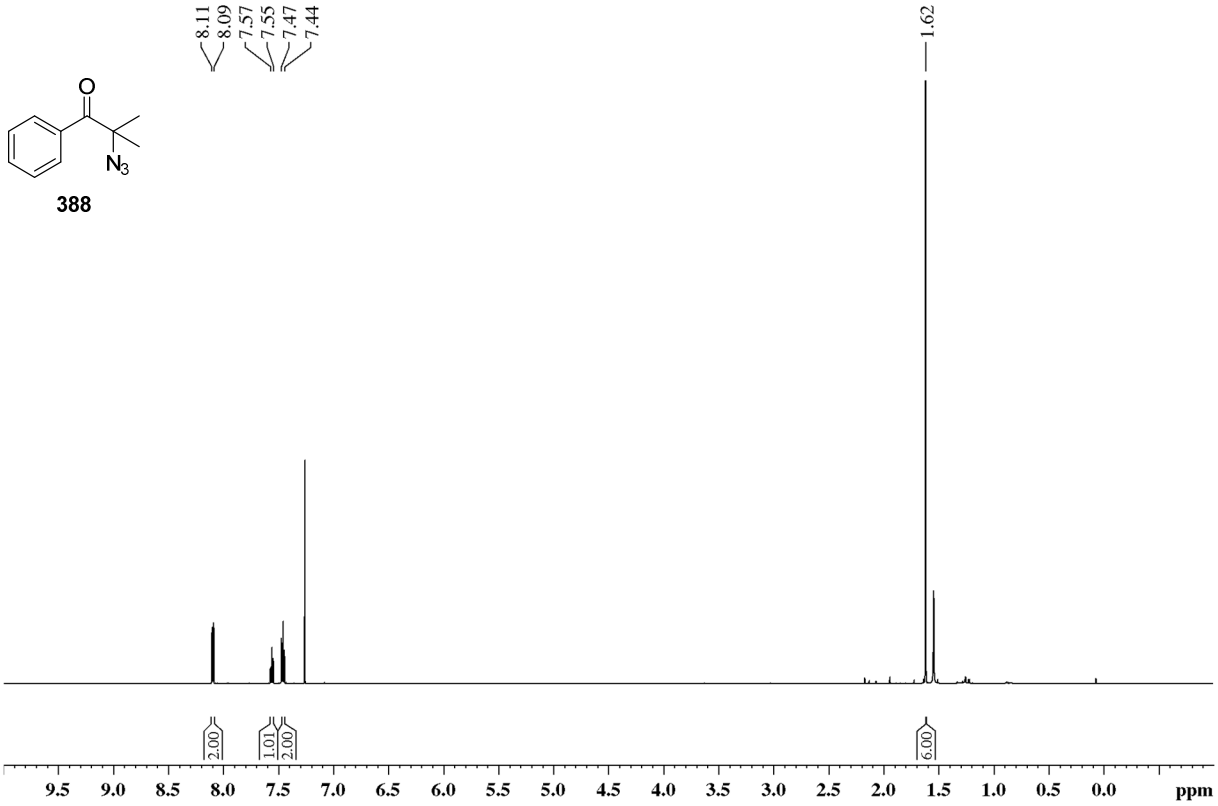
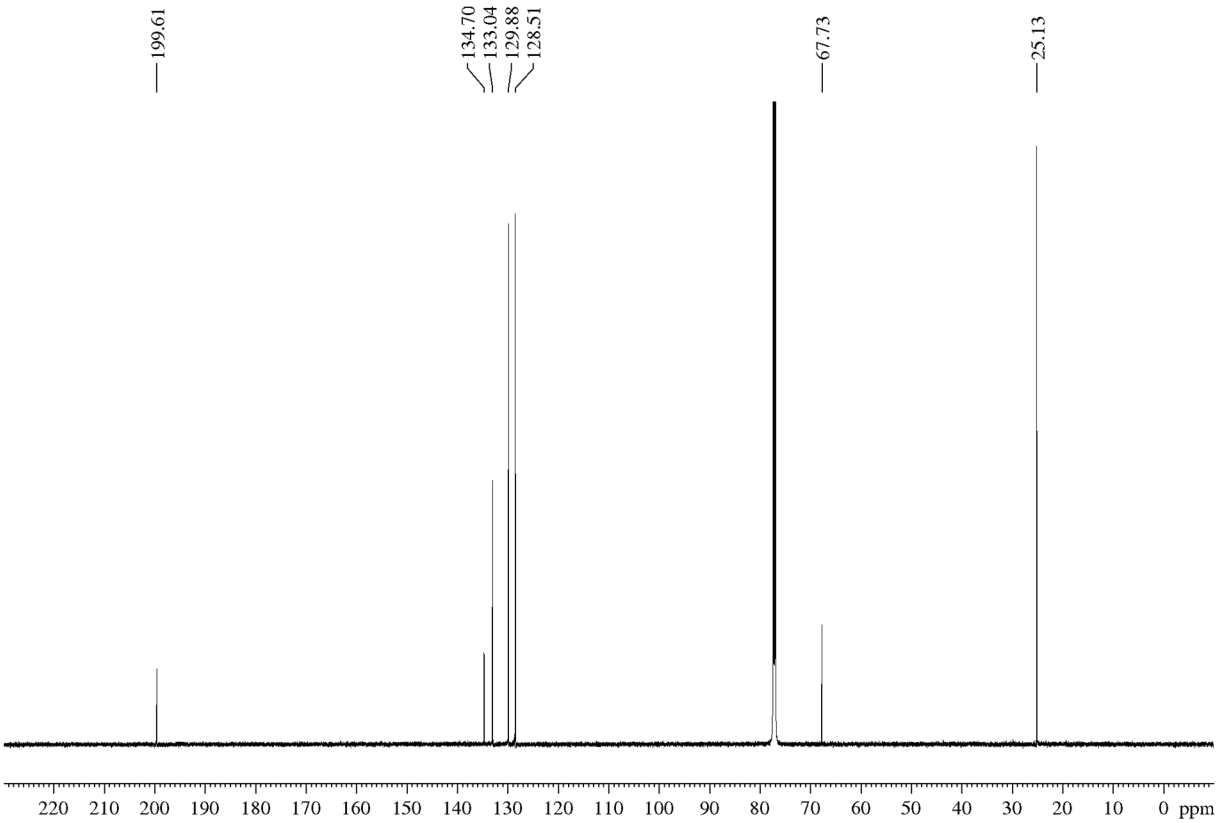
8.11
7.63
7.59
7.50
7.46
1.86
O
N3
N3
385
2.00
1.00
2.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


192.06
133.99
132.81
130.41
128.69
83.35
22.62
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


8.11
8.09
7.57
7.55
7.47
7.44
1.62
O
N3
388
2.00
1.01
2.00
6.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


199.61
134.70
133.04
129.88
128.51
67.73
25.13
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

Danksagung

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Curriculum Vitae and List of Scientific Publications

Personal Data

Name: Teresa Kösel

Date and place of birth: 12.01.1995 in Hannover, Germany

Nationality: German

Academic Background

12/2018 – 06/2022 **Leibniz Universität Hannover (LUH), Doctoral Studies in Organic Chemistry**
Hannover, Germany

- Institute of Organic Chemistry, research group of Prof. Dr. Andreas Kirschning
- Scholarship: Lindemann Scholarship from the Dr. Heinz Lindemann Foundation
- Doctoral thesis topic: "Development of a Total Synthesis of Myxovalargin A and Derivatives – Investigations on Transformations with Polymer-Supported Bisazidoiodate (I)"

09/2017 – 03/2018 **Imperial College London, Research Stay**
London, England

- Department of Chemistry, research group of Prof. Alan Armstrong
- Scholarship: Erasmus+
- Research topic: „Studies Towards the Synthesis of CDK2 Inhibitors"

10/2016 – 11/2018 **LUH, M. Sc. in Medicinal and Natural Product Chemistry**
Hannover, Germany

- Laboratory practical course in the field of medicinal chemistry in cooperation with Helmholtz Zentrum München
- Master thesis: "Radical Substitutions on Terpenes by Homolytic Activation of Haloate(I)-Complexes" in the research group of Prof. Dr. Andreas Kirschning

10/2013 – 08/2016 **LUH and Medizinische Hochschule Hannover (MHH), B. Sc. in Biochemistry**
Hannover, Germany

- Student assistant at MHH - supervision of the biochemistry practical course for medical students
- Bachelor thesis: „Zur Synthese von Rickiol E3: Upscailing und Optimierung" in the research group of Prof. Dr. Markus Kalesse

06/2013 Hannah-Arendt-Gymnasium Barsinghausen, Germany **– Abitur**

Poster Presentation

- European Symposium of Organic Chemistry (ESOC), Austria, Vienna, **2019**.

Scientific Publications

[1] Multiparameter kinetic analysis for covalent fragment optimization using quantitative irreversible tethering (qIT), G. B. Craven, D. P. Affron, T. Kösel, T. L. M. Wong, Z. H. Jukes, C.-T. Liu, R. M. L. Morgan, A. Armstrong, D. J. Mann, *ChemBioChem* **2020**, *21*, 3417 –3422.

[2] Photochemical Transformations with Iodine Azide after Release from an Ion-Exchange Resin, T. Kösel, G. Schulz, G. Dräger, A. Kirschning, *Angew. Chem. Int. Ed*. **2020**, *59*, 12376-12380; *Angew. Chem.* **2020**, *132*, 12475-12479.

[3] Oxidative azidations of phenols and ketones using iodine azide after release from an ion exchange resin, T. Kösel, G. Dräger, A. Kirschning, *Org. Biomol. Chem*. **2021**, *19*, 2907-2911.