Synthese neuer Tetracyclin-Abkömmlinge und weiterer bioaktiver, naturstoff-basierter Derivate

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I wish I could tell you that it gets better.
But… it doesn't. <u>You</u> get better!

[Joan Rivers]

Abstract

Keywords: total synthesis • natural products • tetracyclines • Diels–Alder reactions • 1,3-dipolar cycloadditions • α-ketol rearrangement • antibiotics • non-antimicrobials

Ever since the isolation of its first members in the late 1940s, the tetracycline class of natural products has been greatly enriched, with the production of chemically modified or semisynthetic compounds contributing significantly to the total number. With his 1953 preparation of (–)-tetracycline by hydrogenolysis of chlortetracycline, Lloyd Conover was not only the first to ever describe a chemically modified tetracycline, but his unprecedented discovery also proved that synthetically modified natural product-derived compounds could exhibit biological activity.
Since this breakthrough in the field, several semisynthetic tetracyclines have entered the market, and the practice of elaborating older compounds into novel active derivatives has gained increased popularity. Following this motivation, this work aimed at the total synthetic preparation of five atypical tetracycline-related natural products: *demethylpremithramycinone* and *premithramycinone*, both identified in 1998 as precursors of the biosynthesis of aureolic acids; *chromocyclin*, the aglycon of the 1968 isolated streptomyces metabolite chromocylclomycin along with its *C*4-empimer *epi-chromocyclin*; and *carbamidochelocardin*, a potent chelocardin-derived antibiotic compound prepared in 2015 through biosynthetic engineering.

Following a convergent approach, the construction of the naphthacene core of the proposed targets was envisioned to proceed *via* an unprecedented *Diels–Alder reaction with furan key step* between variously decorated decalin-enones (eastern fragments) and *in-situ* generated isobenzofurans (western fragments). The chosen strategy would allow for high tunability of the two fragments, fulfilling the premise of synthesizing the targeted tetracyclines *via* a common pathway. An additional asset of the proposed protocol is represented by the quick and facile installation of the (*S*)-configured *C*12a-positioned alcohol *via* a *late-stage hydroxylation*, followed by an *α-ketol rearrangement*.
At first, the required western and eastern fragments for accessing demethylpremithramycinone, premithramycinone, chromocyclin, and *epi*-chromocyclin, as well as the western fragment of carbamidochelocardin, were successfully prepared, and the total synthesis of demethylpremithramycinone was pursuit. By employing a Diels–Alder reaction with furan, the naphthacene core of the target was successfully constructed from a *C*8a-deoxy eastern fragment. The installation of the *C*12a-positioned tertiary alcohol with the desired configuration in the previously prepared product resulted in the formation of an advanced precursor, which was finally subjected to the global deprotection strategy. The targeted natural product was ultimately isolated as a dimedone enamine (14 steps; 2,2%-yield), with the conversion of the functionality towards the desired methyl ketone repeatedly failing to set in. Nevertheless, the viability of the global approach was confirmed, with the proposed strategy allowing for the preparation of novel tetracycline-derived compounds, three of which were subjected to biological evaluation. With respect to carbamidochelocardin, since the preparation of a suitable eastern fragment couldn't be completed, the route leading to its preparation was ultimately abandoned.

Despite the uncompleted preparation of the originally envisioned targets, the strategy elaborated for their synthesis managed to prove its potential on account of three fulfilled premises:
I) by providing convenient access to structurally diverse eastern fragments *via* a divergent approach;
II) by a facile construction of the naphthacene core along with the required decorations; and
III) by the ability to generate both (*R*)- and (*S*)- configured tertiary alcohols at the *C*12a-position starting from deoxy-precursors.

Kurzzusammenfassung

Schlagwörter: Totalsynthese • Naturstoffe • Tetracycline • Diels–Alder-Reaktionen • 1,3-dipolare Cycloadditionen • α-Ketol-Umlagerung • Antibiotika • nicht-antimikrobielle Wirkstoffe

Seit der Isolierung der ersten Tetracycline in den späten 1940er Jahren wurde diese Naturstoffklasse stark erweitert, wobei die Herstellung chemisch modifizierter oder halbsynthetischer Verbindungen einen wesentlichen Beitrag zur Gesamtzahl leistet. Mit seiner 1953 erfolgten Herstellung von (–)-Tetracyclin durch die Hydrogenolyse von Chlortetracyclin war Lloyd Conover nicht nur der erste, der ein chemisch modifiziertes Tetracyclin beschrieb, sondern seine beispiellose Entdeckung bewies auch, dass synthetisch modifizierte, aus Naturstoff gewonnene Verbindungen biologische Aktivität aufweisen können. Seit diesem Durchbruch sind mehrere halbsynthetische Tetracycline auf den Markt gekommen, und die Praxis der Umwandlung älterer Verbindungen in neue aktive Derivate hat an Bedeutung gewonnen. Aus dieser Motivation heraus zielte diese Arbeit auf die synthetische Herstellung von fünf atypischen Tetracyclin-Abkömmlingen ab: *Demethyl-premithramycinon* und *Premithramycinon*, die beide 1998 als Vorläufer der Biosynthese von Aureolsäuren identifiziert wurden; *Chromocyclin*, das Aglykon des 1968 isolierten Streptomyces-Metaboliten Chromocylclomycin zusammen mit seinem *C*4-Empimer *epi-Chromocyclin*; und *Carbamidochelocardin*, eine wirksame, von Chelocardin abgeleitete antibiotische Verbindung, die 2015 durch *biosynthetic engineering* hergestellt wurde.

Einem konvergenten Ansatz folgend sollte die Konstruktion des Naphthacen-Gerüsts der Zielmoleküle über einen *Diels–Alder-Reaktion-mit-Furan-Schlüsselschritt* zwischen unterschiedlich dekorierten Decalin-Enonen (Ostfragmente) und *in-situ* erzeugten Isobenzofuranen (Westfragmente) erfolgen. Dabei sollte die gewählte Strategie eine hohe Derivatisierung der beiden Fragmente ermöglichen und somit die Prämisse erfüllen, die gewünschten Tetracycline über einen gemeinsamen Weg zu synthetisieren. Ein weiterer Vorteil der vorgeschlagenen Route stellt die schnelle und einfache Installation des (*S*)-konfigurierten Alkohols in *C*12a-Position über eine *direkte Hydroxylierung*, gefolgt von einer *α-Ketol-Umlagerung* dar.

Zunächst wurden die erforderlichen West- und Ostfragmente für den Zugang zu Demethylpremithramycinon, Premithramycinon, Chromocyclin und *epi*-Chromocyclin sowie das Westfragment von Carbamidochelocardin erfolgreich hergestellt, und die Synthese von Demethylpremithramycinon angestrebt. Dabei wurde das Naphthacen-Gerüst des Zielmoleküls erfolgreich durch eine Diels–Alder-Reaktion mit Furan aufgebaut. Der Einbau des tertiären Alkohols in der *C*12a-Position mit der gewünschten Konfiguration führte dann zur Bildung eines fortgeschrittenen Vorläufers, der schließlich der globalen Entschützungsstrategie unterzogen wurde. Das angestrebte Molekül wurde schließlich in Form eines Dimedon-Enamins isoliert (14 Stufen, 2,2% Ausbeute), wobei die Umwandlung der Funktionalität in das gewünschte Methylketon wiederholt ausblieb. Dennoch wurde die Durchführbarkeit des globalen Ansatzes bestätigt, wobei die vorgeschlagene Strategie die Herstellung neuartiger Tetracyclin-Abkömmlinge ermöglichte, von denen Drei einer biologischen Evaluation unterzogen wurden. Im Falle von Carbamidochelocardin konnte die Herstellung eines geeigneten Ostfragments nicht abgeschlossen werden, sodass die Synthese aufgegeben wurde. Trotzdem konnte die für ihre Synthese ausgearbeitete Strategie ihr Potenzial aufgrund folgender Prämissen unter Beweis stellen:
I) durch einen schnellen Zugang zu strukturell vielfältigen Ostfragmenten; II) durch eine einfache Konstruktion des Naphthacen-Gerüsts; und III) durch die Fähigkeit, sowohl (*R*)- als auch (*S*)-konfigurierte tertiäre Alkohole an der *C*12a-Position darzustellen.

Preface

The experimental work covered in this thesis was conducted at the Institute of Organic Chemistry of the Gottfried Wilhelm Leibniz University Hannover, Germany, under the supervision of Prof. Dr. Markus Kalesse, from August 2019 to May 2023.

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Morwenna, if hell means to endlessly work on aromats… you're coming with me, Pal!

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Abbreviation and acronym index

~	*approximately*
Δ	*reflux*
µg	*microgram*
µl	*microliter*
Ø	*diameter*
1D-(*spectrum*)	*one-dimensional*
2D-(*spectrum*)	*two-dimensional*
A. baumannii	*Acinetobacter baumannii*
A. eutrophus	*Aligacenes eutrophus*
AcOH/ AcO-	*acetic acid/ acetate*
ACP	*acyl carrier protein*
Ag_2CO_3	*silver carbonate*
Ag_2O	*silver oxide*
AIBN	*2,2'-azobis(2-methylpropionitrile)*
AMR	*antimicrobial resistance*
approx.	*approximately*
aq.	*aqueous*
Ar	*argon*
arom.	*aromatization*
atm.	*atmosphere/ atmospheric (pressure)*
ATP	*adenosintriphosphat*
B. subtilis	*Bacillus subtilis (hay bacillus)*
$B(OH)_3$	*boric acid*
BBr_3	*boron tribromide*
BCl_3	*boron trichloride*
$BF_3{\cdot}OEt_2$	*boron trifluoride diethyl etherate*
BHT	*2,6-di-tert-butyl-4-methylphenol*
Bn-	*benzyl group*
BnBr	*benzyl bromide*
BnOH	*benzyl alcohol*
Boc_2O	*di-tert-butyl dicarbonate*
Br_2/ Br-	*bromine/ bromide*
brsm	*based on recovered starting material*
$(Bu_3Sn)_2O$	*bis(tributyltin) oxide*
^{13}C(-*shifts*)	*carbon-13*
C_5H_6	*cyclopentadiene*
C_6D_6	*deuterated benzene [($^2H_6$)benzene]*
C_6H_6	*benzene*
$CaCl_2$	*calcium chloride*
CbzCl	*benzyl carbonochloridate*
$CDCl_3$	*deuterated chloroform [($^2H_3$)chloroform]*
CDI	*di(1H-imidazol-1-yl)methanone*
CD_3CN	*deuterated acetonitrile [($^2H_3$)acetonitrile]*
CD_3OD	*deuterated methanol [($^2H_4$)methanol]*
$CeCl_3$	*cerium(III) chloride*
CF_3-	*trifluoromethyl group*
ChdM I and II	*chelocardin methyltransferases*
ChdN	*chelocardin aminotransferases*
ChdO I and II	*chelocardin oxygenases*

ChdPKS	*chelocardin minimal type II polyketide synthase*
ChdQ I and II	*chelocardin aromatase/ cyclases*
ChdT	*chelocardin ketoreductase*
ChdX	*chelocardin aromatase/ cyclase*
ChdY	*chelocardin aromatase/ cyclase*
$CHCl_3$	*chloroform*
CH_2Cl_2	*dichloromethane*
$(CH_2OH)_2$	*ethylene glycol*
CH_3CHO	*acetaldehyde*
CH_3I	*iodomethane*
$Cl\text{-}CON(Me)_2$	*dimethylcarbamoyl chloride*
$Cl\text{-}CO_2Me$	*methyl carbonochloridate*
$Cl\text{-}CO_2{}^{i}Pr$	*isopropyl carbonochloridate*
Cl_2/ Cl-	*chlorine/ chloride*
CmmG	*chromomycin glycosyltransferase*
CmmM II	*chromomycin methyltransferase*
CmmO IV	*chromomycin oxygenase*
$(COCl)_2$	*oxalyl dichloride*
CO_2	*carbon dioxide*
$(CO_2Me)_2$	*dimethyl oxalate*
COSY	*correlation spectroscopy*
COVID-19	*coronavirus disease*
CrO_3	*chromium trioxide*
Cs_2CO_3	*cesium carbonate*
$CuCl_2$	*copper(II) chloride*
CuCN	*copper(I) cyanide*
*C*xy	*carbon atom xy*
cycloadd.	*cycloaddition*
d.r.	*diastereomeric ratio*
DBU-HOAc	*1,8-diazabicyclo[5.4.0]undec-7-ene, acetic acid adduct*
DDQ	*4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile*
DEAD	*diethyl diazenedicarboxylate*
deoxy-	*deoxygenated*
DIBAl-H	*diisobutylaluminium hydride*
DIPEA	*N-ethyl-N-(propan-2-yl)propan-2-amine*
DMAP	*N,N-dimethylpyridin-4-amine*
DMDO	*3,3-dimethyldioxirane*
DME	*1,2-dimethoxyethane*
DMF	*N,N-dimethylformamide*
DMSO	*(methanesulfinyl)methane*
(*E*)-*isomer*	*entgegen (ger.; opposite)*
E. coli	*Eschericihia coli*
E. faecium	*Enterococcus faecium*
ee	*enantiomeric excess*
epi	*epimeric*
equiv.	*equivalent(s)*
et al.	*lat. and others*
EtOAc	*ethyl acetate*
EtOH	*ethanol*
EtSNa	*sodium ethanethiolate*
Et_2O	*ethoxyethane (diethyl ether)*
F^-	*fluoride*
fig.	*figure*
g	*gram*

GmbH	*Gesellschaft mit beschränkter Haftung (ger. type of legal entity)*
GPa	*gigapascal*
h	*hour(s)*
hν	*photons*
^{1}H(-*shifts*)	*proton*
H-	*hydrogen atom*
H_2	*dihydrogen*
H[BF_4]	*tetrafluoroboric acid*
HBr	*hydrogen bromide*
HBr-HOAc	*hydrogen bromide (acetic acid solution)*
HCl	*hydrochloric acid*
HC(O)$CO_2{}^t$Bu	*tert-butyl 2-oxoacetate*
HCO_2H	*formic acid*
H_2CO	*formaldehyde*
HF	*hydrofluoric acid*
HMBC	*heteronuclear multiple-bond correlation*
HN^iPr_2	*N-(propan-2-yl)propan-2-amine (diisopropylamine)*
$HNMe_2$	*dimethylamine*
HO_2-	*hydroperoxide group*
H_2O/ HO-	*water/ hydroxy group*
H_2O_2	*hydrogen peroxide*
H_3O^+/ H^+	*oxonium*
H_3PO_4	*orthophosphoric acid*
HR-ESI-MS	*high resolution-electrospray ionization-mass spectrometry*
HSQC	*heteronuclear single-quantum correlation*
H_2SO_4	*sulfuric acid*
Hz	*hertz*
i.e.	*id est (lat. it is)*
I_2	*iodine*
IBX	*1-hydroxy-1λ^5,2-benziodoxole-1,3-dione*
IMDAF	*intramolecular Diels–Alder [reaction] with furan*
intram.	*intramolecular*
^{i}PrMgCl	*isopropylmagnesium chloride*
^{i}PrOH	*isopropanol*
K. pneumoniae	*Klebsiella pneumoniae*
$KClO_3$	*potassium chlorate*
KCN	*potassium cyanide*
K_2CO_3	*potassium carbonate*
KH	*potassium hydride*
$KHCO_3$	*potassium hydrogencarbonate*
KHMDS	*potassium 1,1,1-trimethyl-N-(trimethylsilyl)silanaminide*
KOH	*potassium hydroxide*
l	*liter*
LAH; $LiAlH_4$	*lithium tetrahydridoaluminate(III)*
LDA	*lithium N-(propan-2-yl)propan-2-aminide*
Li[Al(OtBu)$_3$H]	*lithium tri(tert-butoxy)aluminum hydride*
LiCl	*lithium chloride*
LiO^{t}Bu	*lithium tert-butoxide*
LiOTf	*lithium trifluoromethanesulfonate*
lit.	*literature*
LUMO	*lowest unoccupied molecular orbital*
m-	*meta*-
M	*molar*

m.p.	*melting point*
m/z	*mass-to-charge ratio*
Me-	*methyl group*
MeCN	*acetonitrile*
MeI	*iodomethane*
MeLi	*methyllithium*
MEMCl	*1-(chlormethoxy)-2-methoxyethane*
MeMgBr/ MeMgI	*methylmagnesium bromide/ methylmagnesium iodide*
MeO-	*methoxy group*
MeOH	*methanol*
Me_2SO_4	*dimethyl sulfate*
mg	*milligram*
$Mg(OMe)_2$	*magnesium methoxide*
MHz	*megahertz*
MIC	*minimum inhibitory concentration*
min	*minute(s)*
ml	*milliliter*
MMPP	*magnesium bis(2-carbonoperoxoylbenzoate)*
MnO_2	*manganese(IV) oxide*
mol	*mole*
MOMBr	*bromo(methoxy)methane*
MsCl	*methanesulfonyl chloride*
MTBE	*2-methoxy-2-methylpropane*
MtmG	*mithramycin glycosyltransferase*
MtmL	*mithramycin acyl-CoA ligase*
MtmM I and II	*mithramycin methyltransferase*
MtmO II and IV	*mithramycin oxygenases*
MtmPKS	*mithramycin minimal type II polyketide synthase*
MtmQ	*mithramycin aromatase*
MtmT I and II	*mithramycin ketoreductases*
MtmX	*mithramycin cyclase*
MtmY	*mithramycin cyclase*
MTPAO-	*α-methoxy-α-(trifluoromethyl)phenylacetate*
n	*normal*
N	*nitrogen atom*
N_3-	*azido group*
$NaBH_4$	*sodium tetrahydridoborate*
NaH	*sodium hydride*
$NaHCO_3$	*sodium hydrogencarbonate*
NaHMDS	*sodium 1,1,1-trimethyl-N-(trimethylsilyl)silanaminide*
NaH_2PO_4	*sodium dihydrogen phosphate*
NaI	*sodium iodide*
$NaIO_4$	*sodium periodate*
NaN_3	*sodium azide*
$NaNO_2$	*sodium nitrite*
NaOH	*sodium hydroxide*
NBS	*1-bromopyrrolidine-2,5-dione*
NBSH	*2-nitrobenzenesulfonylhydrazide*
^{n}BuLi	*normal-butyllithium*
NCS	*1-chloropyrrolidine-2,5-dione*
NEt_3	*triethylamine*
$NHBoc_2$	*di-tert-butyl 2-imidodicarbonate*
NHC	*N-heterocyclic carbenes*

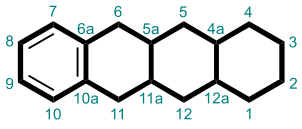
$NHEt_2$	*N-ethylethanamine*
NH_2-OH·HCl	*hydroxylamine hydrochloride*
NH_3/ NH_2-	*ammonia/ amino group*
$[NH_4]HCO_2$	*ammonium formate*
$[Ni(acac)_2]$	*nickel(II) bis(acetylacetonate)*
NMR	*nuclear magnetic resonance*
NO_2^-/ NO_2-	*nitrite / nitro group*
NOE	*nuclear Overhauser effect*
NPG_2-	*fully protected amino group*
o-	*ortho-*
O_2/ *O*-	*oxygen/ oxygen atom*
O_3	*ozone*
OsO_4	*osmium tetraoxide*
OxyD	*oxytetracycline amidotransferase*
p-	*para-*
P. aeruginosa	*Pseudomonas aeruginosa*
$Pb(OAc)_4$	*lead(IV) acetate*
$Pb_2(OH)(OAc)_3$	*basic lead(II) acetate*
PCl_5	*phosphorus pentachloride*
$[Pd(allyl)Cl]_2$	*allylpalladium(II) chloride dimer*
Pd-black	*coarse, sponge-like form of elemental palladium*
$PdCl_2$	*palladium(II) chloride*
$[Pd(dppf)Cl_2]$	*[1,1'-bis(diphenylphosphino)ferrocene]-palladium(II) dichloride*
PE	*petroleum ether*
PG	*protection group*
Ph-	*phenyl*
$PhI(OTFA)_2$	*(bis(trifluoroacetoxy)iodo)benzene*
$PhMe_2Si$-	*dimethyl(phenyl)silyl group*
PhS-	*phenyl sulfide group*
phthN-	*phthalimide functionality*
Ph_2O	*diphenyl ether*
Ph_2PLi	*lithium diphenylphosphide*
PPh_3	*triphenylphosphine*
ppm	*parts per million*
pre-*xy*	*precursor of compound xy*
prim.	*primarily*
proton-sponge®	*N^1,N^1,N^8,N^8-tetramethylnaphthalene-1,8-diamine*
(*Amano lipase*) PS	*phosphatidylserine*
psi	*pounds per square inch*
PtO_2	*platinum(IV) oxide*
*p*TSA	*4-methylbenzene-1-sulfonic acid*
py	*pyridine*
quant.	*quantitative*
(*R*)-	*rectus (lat.; right)*
Ra-Ni	*Raney nickel, sponge-like form of elemental nickel*
rac-*xy*	*racemic compound xy*
rearr.	*rearrangement*
R_f	*retardation factor*
RP-HPLC	*reversed-phase high performance liquid chromatography*
R_3Si-	*tri(alkyl)silyl group*
R_3SiCl	*chlorotri(alkyl)silane*
rt	*room temperature*
s	*sec*

(*S*)-	*sinister (lat.; left)*
S. aureus	*Staphylococcus aureus*
S. rimosus	*Streptomyces rimosus*
SAM	*S-adenosyl methionine*
^{s}BuLi	*sec-butyllithium*
S_EAr	*electrophilic aromatic substitution*
SET	*single electron transfer*
SiO_2	*silicon dioxide*
SmI_2	*samarium(II) iodide*
S_N2	*nucleophilic substitution*
$SOCl_2$	*thionyl chloride*
subseq.	*subsequent*
subst.	*substituted*
t	*tertiary*
tab.	*table*
TBAF	*N,N,N-tributylbutan-1-aminium fluoride*
TBS-	*tert-butyldimethylsilyl group*
TBSCl	*tert-butyl(chloro)di(methyl)silane*
TBSOTf	*trimethylsilyl trifluoromethanesulfonate*
^{t}BuLi	*tert-butyllithium*
$^{t}BuNO_2$	*tert-butyl nitrite*
TESCl	*chlor(triethyl)silan*
TFA	*trifluoroacetic acid*
THF	*tetrahydrofuran*
TIPS-	*tri(isopropyl)silyl group*
TMEDA	*N,N,N′,N′-tetramethylethane-1,2-diamine*
TMS-	*tri(methyl)silyl group*
TMS-CHN_2	*(trimethylsilyl)diazomethane*
TMSCl	*chlor(trimethyl)silan*
TMSCN	*trimethylsilyl cyanide*
TMSOMs	*trimethylsilyl methanesulfonate*
TPP	*5,10,15,20-tetraphenyl-21H,23H-porphyrin*
TS	*transition state*
UV	*ultraviolet*
(v/v)	*volume by volume*
var.	*various/ variously*
WHO	*World Health Organization*
wt%	*weight-percentage*
(*Z*)-*isomer*	*zusammen (ger.; together)*
$ZnBr_2$	*zinc bromide*
$ZnCl_2$	*zinc chloride*

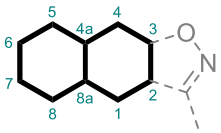
The acronyms used to describe the multiplicity of NMR-signals are given in chapter 6.1.

General remarks

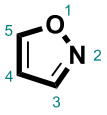
The numbering of the atoms of the naphthacene core, the decalin core, and isoxazole was carried out in accordance with the following scheme:



naphthacene core



decalin core



isoxazole

The configuration of the compounds was described as follows:

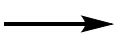
absolute configuration

relative configuration

undefined configuration

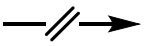
used to highlight epimerization

Chemical modifications were marked in schemes by using the following arrows:

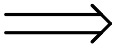


general reaction arrow

planned transformation



unsuccesaful transformation



retrosynthetic arrow

1 Introduction

"Wuhan Municipal Health Commission, China, reported a cluster of cases of pneumonia in Wuhan [...]. A novel coronavirus was eventually identified."

With this first account from December 31, 2019, begins the WHO timeline of the progress and evolution of the COVID-19 pandemic of 2020-2021. As more cases emerged, China publicly shared the genetic sequence of COVID-19 on January 19, 2020. One day later, the first reported case outside of China emerged in Thailand.[1] What followed was a two-year pandemic of unprecedented dimensions, for which global authorities were largely unprepared. The aftermath of the pandemic sparked the re-emergence of a much older debate in the scientific community: antimicrobial resistance (AMR)– the so-called "silent pandemic".[2] With the global rise of AMR, which poses a major threat to global health, food security, and development, and the declining effectiveness of classical antibiotics in treating infections such as pneumonia, tuberculosis, or gonorrhea, the need for novel antibiotics with improved properties is more justified than ever before.[3]

Soon after the discovery of the first members– aureomycin (**I**; 1948, from *Streptomyces aureofaciens*) and terramycin (**II**; 1949, from *Streptomyces rimosus*),[4] the tetracycline family of natural products quickly became one of the most prescribed classes of antimicrobial drugs.[5] Their use ranges from the treatment of pathologies of bacterial origin, including both Gram-positive and Gram-negative bacteria, to those caused by atypical organisms such as chlamydiae, mycoplasmas, and rickettsiae, or protozoan parasites.[4,6]

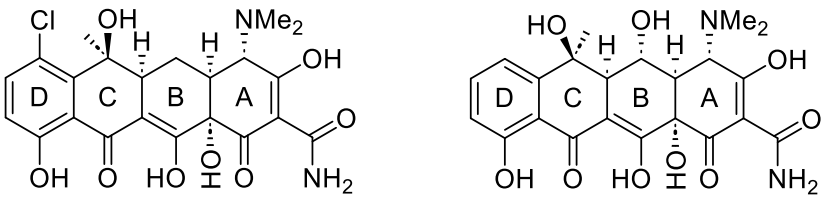


Fig. 1.1: Structures of chlortetracycline (**I**) and oxytetracycline (**II**).

Quick to recognize the tremendous potential of these compounds, Cyanamid was the first to market a tetracycline-based antibiotic (aureomycin; **I**) on December 1, 1948, with Pfizer's terramycin (**II**) following shortly thereafter in 1950. Three years later, in 1953, Lloyd Conover was the first to successfully prepare a chemically modified tetracycline– (–)-tetracycline, by the hydrogenolytic dehalogenation of chlortetracycline. This unprecedented discovery proved that chemically modified natural product derivatives could also exhibit biological activity, with the tetracycline synthetically prepared by Conover being just as potent as the parent compound.[7]
Conover's 7-dechloro-tetracycline has been available by prescription since 1953.[8] Ever since this breakthrough in the field, the tetracycline class of natural products has been significantly enriched, with the production of chemically modified or semisynthetic compounds, many of which have entered the market, contributing significantly to the total number.[9] Furthermore, the practice of elaborating older compounds into novel active derivatives has become increasingly popular– as will be shown in the following chapters.[10]

2 Tetracyclines in nature, medicine, and chemistry

Given the complexity and breadth of the field, a detailed discussion of all the advances and particularities of the tetracycline class of antibiotics would be beyond the scope of this work. Therefore, in the following chapter 2.1, several biological and medicinal particularities of six compounds of interest will be briefly discussed. These compounds include the future natural product targets: demethylpremithramycinone (**X**), premithramycinone (**XI**), chromocyclin (**III**), and *epi*-chromocyclin (**V**), as well as the chelocardin (**XVIII**)-derived carbamidochelocardin (**XXVIII**).

Furthermore, chapter 2.2 summarizes the representative advances made towards the total synthetic preparation of various tetracycline targets over the past decades, the analysis of which is fundamental prior to the elaboration of a novel synthetic approach.

2.1 Tetracyclines: isolation and bioactive properties

Originally discovered in 1953 in several actinomycetes such as *Streptomyces argilaeus*, the anti-tumoral and antimicrobial properties of aureolic acid (mithramycin; **XIII** in **scheme 2.1.2**), an FDA-approved RNA synthesis inhibitor used in the treatment of testicular cancer, have been well documented long before its structure was elucidated and its biosynthesis determined.[11-13] Initial studies conducted by Miyamoto et al. in 1964 led to the discovery of chromomycinone as the aglycone of chromomycin A_3 (**XIV**).[14] Four years later, Berlin et al. determined the presence of the annulated 6/6/6-tricycle in all aureolic acid-derived natural products known to that date. Thus, the close relationship between the compounds was first established.[13] Furthermore, with their 1968 isolation of chromocylclomycin (**IV**), a streptomyces metabolite, Berlin et al. were able to identify the only chromocyclin (**III**)-bearing natural product known to date,[15] the absolute configuration of the aglycone being unambiguously assigned by the authors in 1973.[16] In addition to their unprecedented discovery, the aglycone of chromocyclin (**III**) was found to bear a (*R*)-configured methyl ether decoration at the *C*4-position, a novelty for both aureolic acids as well as tetracyclines. Furthermore, the compound was found to equilibrate upon treatment with bases, forming its *C*4-epimer–*epi*-chromocyclin (**V**).[16] Since this phenomenon is well documented for tetracyclines, with epimerization being observed even under mild, neutral conditions,[17] it leaves room for speculation as to whether the (*R*)-configured ether is actually present in the natural product or formed during the extraction- and characterization steps.

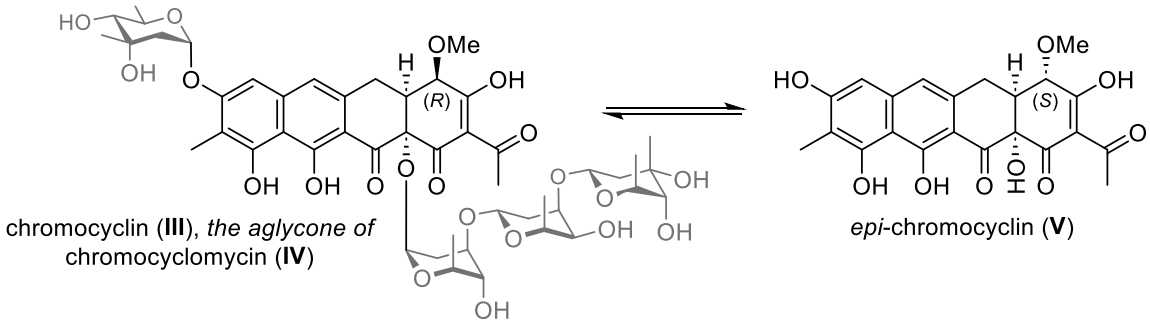
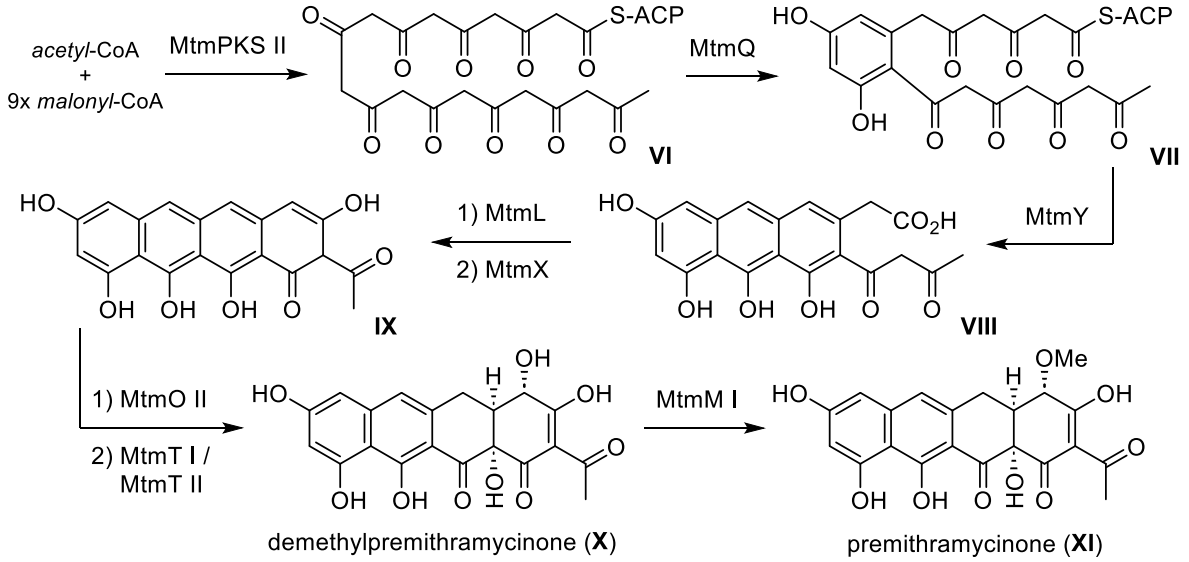


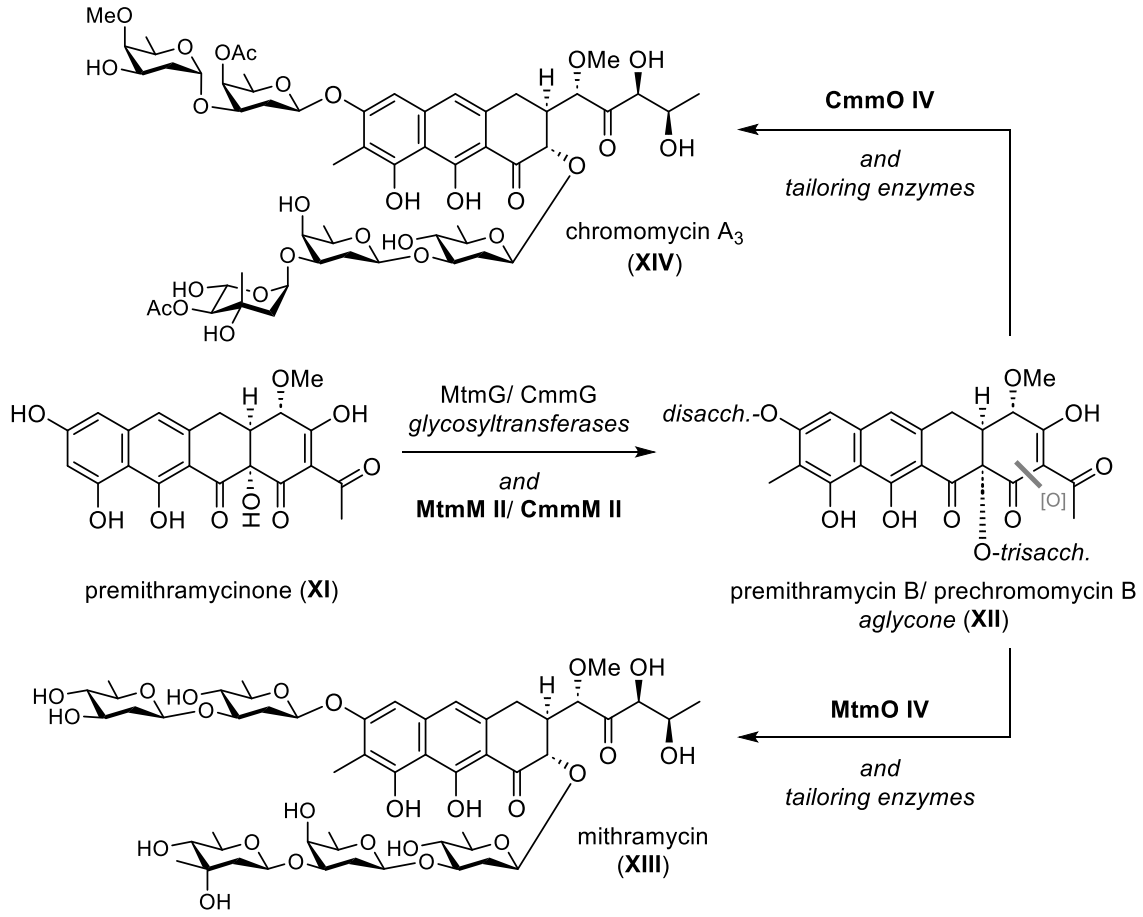
Fig. 2.1.1: Structures of chromocylclomycin (**IV**) and *epi*-chromocyclin (**V**).

Although Berlin et al. provided valuable contributions with their structure elucidation of the aureolic acids and efforts towards establishing their biosynthetic path, a major break-through in the field came in 1998 from Rohr et al., who were able to isolate and characterize two tetracyclic intermediates of the pathway: demethylpremithramycinone (**X**) and premithramycinone (**XI**).[18] With their discovery, the authors were able to prove that the isolated precursors were biosynthetically related to the tetracycline family of natural products, their subsequent efforts eventually leading to a full understanding of the biosynthetic pathway.[11,18-24] Relevant steps from the biosynthesis of demethylpremithramycinone (**X**) and premithramycinone (**XI**) are highlighted in **scheme 2.1.1**.



Scheme 2.1.1: Aureolic acid biosynthesis I: the formation of demethylpremithramycinone (**X**) and premithramycinone (**XI**), as the first isolable products of the pathway.

The biosynthesis of premithramycinone (**XI**) starts with the initial formation of a linear decaketide (**VI**) by the mithramycin-polyketide synthase MtmPKS type II,[25] which undergoes partial cyclization promoted by the cyclase/ aromatase MtmQ to form product **VII**. The constructed aromatic ring represents the D-ring of the future tetracycline system. Under the action of the cyclase MtmY the annulated B/C-ring systems of the final teracycle are formed (generation of **VIII**). The last required cyclization (construction of the A-ring; formation of **IX**) is carried out by the cyclase MtmX, the transformation being subsequent to an initial adenylation step, mediated by MtmL. Final tailoring is catalyzed by the oxygenases MtmO II and MtmT I/ MtmT II-complexes to furnish the first isolable tetracycline-related intermediate of the pathway– demethylpremithramycinone (**X**).[11] An additional step, catalyzed by methyltransferase MtmM I, finally gives premithramycinone (**XI**) by mediating the methylation of the secondary alcohol at the *C*4-position and thus furnishing the second stable intermediate of the pathway.[23] In addition, the MtmM I-related methyltransferases MtmM II and CmmM II were found to be involved in the final *C*-*C*-bond formation of the pathway and thus in the generation of the characteristic architecture of *epi*-chromocyclin (**V**).[19,23] By enabling the methylation of the *C*9-position, the enzymes furnish the advanced biosynthetic intermediates premithramycin B and prechromomycin B, with their common aglycone **XII** being shown in **scheme 2.1.2**.

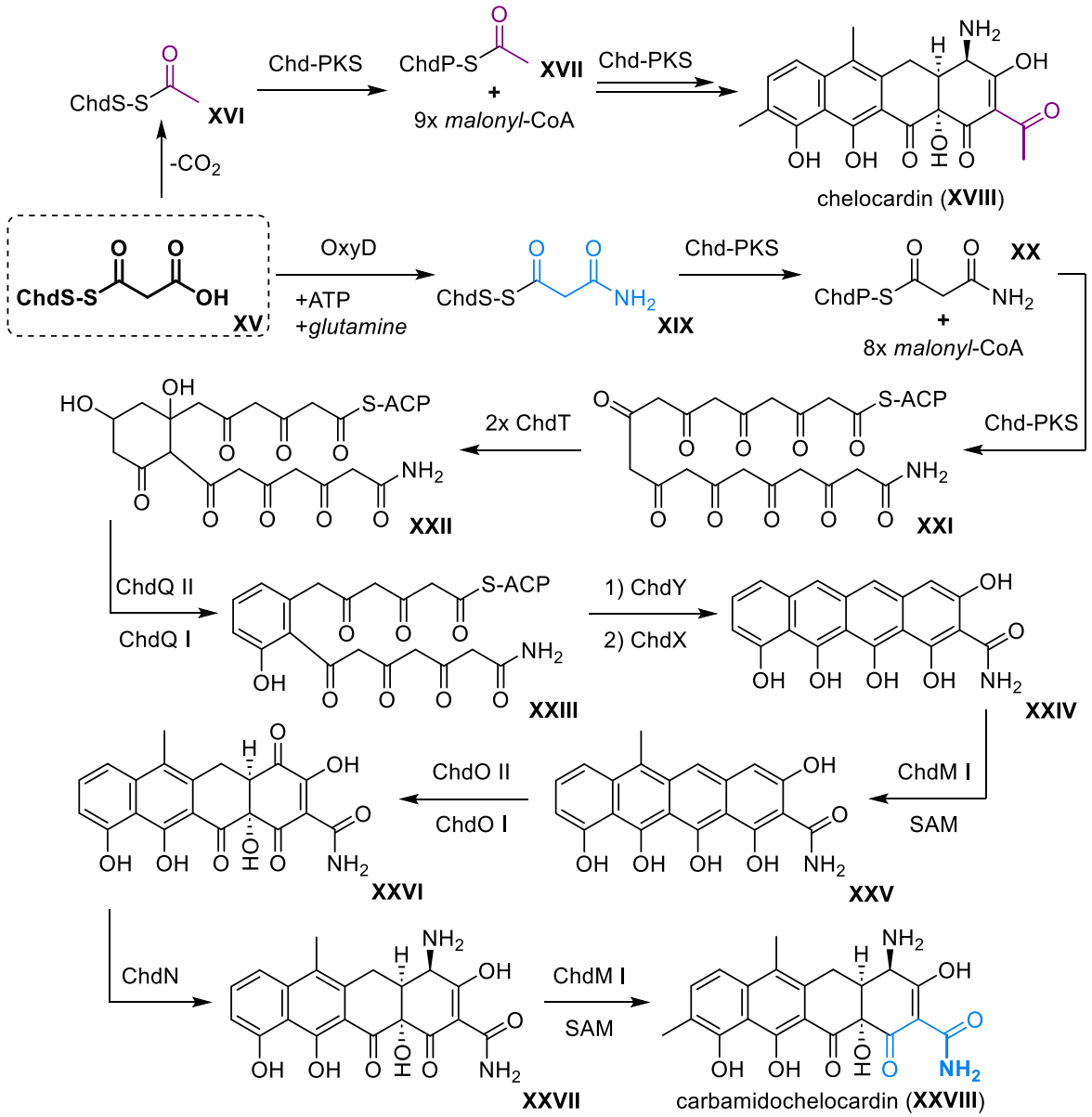


Scheme 2.1.2: Aureolic acid biosynthesis II: a Bayer-Villiger oxidative rearrangement furnishes the characteristic tricyclic core of chromomycin A_3 (**XIV**) and mithramycin (**XIII**).

In 2005, Gibson and Rohr provided an in-depth overview of the key termination step of the mithramycin (**XIII**) biosynthesis in *Streptomyces agillaceus*– a Bayer-Villiger oxidation induced by the oxygenase MtmO IV.[19,21] Similar findings were made by Bosserman and Rohr in 2011 while analyzing the formation of chromomycin A_3 (**IV**) in *Streptomyces griseus*, with the Bayer-Villiger oxidative rearrangement being reasserted as the key termination step of the sequence.[20] In both instances, the glycosylated, bioactive[22] tricyclic products were found to originate from the *epi*-chromocyclin-derived precursors premithramycin B and prechromomycin B, the characteristic glycoside moieties being installed prior to oxidation.

Even though omitted from the discussions, the presence of the complex sugar moieties in the final natural products was found to be decisive in the origin of bioactivity.[26] By not bearing any (oligo-)saccharide components, the premithramycinones **X** and **XI** were found to lack any antimicrobial properties; premithramycinone (**XI**), however, reportedly shows mild antitumor activity against various cancer cell lines, such as lung (A549) and breast (MDA-MB 231) carcinomas.[27]

Carbamidochelocardin (**XXVIII**), prepared through biosynthetic engineering in 2015 by the groups of R. Müller and H. Petković, represents the fruition of a broad inter-institutional effort to establish new antibiotic leads with enhanced properties within the tetracycline family, thus contributing to the global effort of combating increased antibiotic resistances.[10] By inserting specific gene clusters from *Streptomyces rimosus* (an oxytetracycline-producing bacterium) into *Amycolatopsis sulphurea*, the "classical" chelocardin (**XVIII**) biosynthetic pathway was altered to produce the aimed architecture of **XXVIII**. A simplified overview of the initiation steps in the biosynthetic pathway of amidochelocardin (**XVIII**) as well as the complete path for accessing amidochelocardin (**XXVIII**) is shown in **scheme 2.1.3**.



Scheme 2.1.3: The biosynthesis of carbamidochelocardin (**XXVIII**).[10,28]

With respect to chelocardin (**XVIII**), the biosynthetic initiation steps are similar to those of the aureolic acids (**scheme 2.1.1**). Thus, after the decarboxylation of malonate **XV** yields the acylated precursor **XVI**, a PKS-mediated cascade leads to the formation of the tetracyclic natural product.[10] For the bioengineered derivative **XXVIII**, however, the non-native amidotransferase OxyD from *S. rimosus* ensures the conversion of the common malonate precursor **XV** *via* a transamination step

towards malonamate **XIX**. This transformation represents the key feature of the modified pathway, with **XIX** carrying the distinctive *C*2-amido-functionality of carbamidochelocardin (**XXVIII**). Further elaborations are induced by the type II minimal polyketide synthase Chd-PKS genes, with the initiation step being represented by the formation of the linear decaketide **XXI** (**scheme 2.1.3**).[10,28] By undergoing several cyclization steps, product **XXI** is finally converted to tetracyclic product **XXIV** under the action of the ketoreductase ChdT (formation of precursor **XXII**) and the aromatases/cyclases ChdQ I, ChdQ II, ChdY and ChdX. Once the construction of the undecorated, fully aromatized naphthacene core is completed, the methylation of the *C*6-position is induced by the methyltransferase ChdM I, with the enzyme also inducing the methylation of the *C*9-position in the last step of the pathway. Finally, the characteristic decorations of the A/B-ring system were found to be introduced during the termination steps by the oxygenases ChdO II and ChdO I, with the (*R*)-configured amine moiety at *C*4 being generated by the aminotransferase ChdN.[28]

Isolated in 1962 from *Nocardia sulphurea*,[29] the atypical tetracycline-related natural product chelocardin (**XVIII**) was found to exhibit antibiotic properties against clinically relevant Gram-negative and Gram-positive pathogens,[30] having a concentration-dependent dual mechanism of action. In 2016, Stepanek et al. found that chelocardin (**XVIII**) inhibits protein biosynthesis when administered at low concentrations, while high doses of the drug result in cell membrane damage, the compound's dual mechanism of action representing an attractive asset.[31] Furthermore, chelocardin (**XVIII**) was successfully used in the 1970s in treating urinary tract infections during a small Phase II clinical study, with little to no adverse-affects reported by the test-subjects.[10] In spite of the reported promising results, the natural product was never marketed as a drug, with the interest in the compound rapidly dropping in the following years. With the rise of the global burden of bacterial antimicrobial resistances,[32] however, old targets began to redraw the attention of the scientific community in the quest to find novel lead compounds. Amidochelocardin (**XXVIII**) quickly emerged as an interesting lead, showing remarkable antibacterial activity against the pathogens of the ESKAPE panel[1] and combating resistances previously shown to chelocardin.[32]

Four years after the first preparation of the lead, Lukežič et al. biosynthetically produced in 2019 a series of amidochelocardin-derived tetracyclines, with activities against Gram-positive and Gram-negative indicator strains lower than those of the parent compound.[33] Furthermore, the (amido)chelocardin-derived array of bioactive compounds was enriched later in 2019 with the first production of semisynthetic derivatives.[30] In analogy to the previous study, the newly produced compounds, even though exhibiting antimicrobial properties against the ESKAPE panel, failed to show any notable activity in comparison to the leads chelocardin (**XVIII**) and amidochelocardin (**XXVIII**).[30] Nevertheless, the studies conducted have partially led to the determination of several pharmacophores of the lead structure. These include the aromatized C-ring, the *C*9-methyl group, and the presence of the primary amine at *C*4.[30,32] Interestingly, the *C*4-epimers of chelocardin and *N*,*N*-dimethyl-*epi*-amidochelocardin were found to be less effective than their parent compounds, highlighting the importance of the (*R*)-configuration of the *C*4-amine in achieving enhanced antimicrobial activity. By taking this crucial aspect into consideration, and especially since an irrefutable determination of the absolute configuration of carbamidochelocardin (**XXVIII**) has never been provided by the isolators, a stereocontrolled total synthetic preparation of the compound is most certainly justified.

[1] *E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and various *Enterobacter* species.

2.2 Tetracyclines in total synthesis

Considering the important role played by the tetracycline family of natural products in the context of combating bacterial pathologies, it is not surprising that numerous efforts have been made in the past decades to chemically synthesize and modify them. With the recognition of the bioactive potential of the compounds in the late 1940s, many efforts to prepare the natural products by total synthesis followed rapidly in the following years. With the completion of early strategies, the outcomes contributed primarily to the unambiguous structural assignment of the compounds, not to mention the enrichment of knowledge in the field of organic chemistry. With more recent reports, however, feasible pathways towards the preparation of fully synthetic drugs with improved properties were enabled.[34] Thus, with the constant need for drug discovery and optimization, especially in the context of resistance formation, synthetic efforts to provide quick and easy access to compounds with enhanced antimicrobial properties are not only justified but highly welcomed.

The following chapter summarizes the total syntheses of tetracycline natural products and derivatives thereof over the past decades, focusing on two aspects: I) the construction of the characteristic naphthacene backbone, and II) the generation of the challenging *C*12a-positioned tertiary alcohol (where applicable). Approaches aimed at the preparation of biosynthetically closely related type II polyketides (**fig. 2.2.1**), such as the anthracyclinone antibiotic aranciamycinon **XXIX**,[35] the unusual hexacyclic metabolite A-74528 (**XXX**),[36] or (+)-olivin (**XXXI**)– the aglycon of olivomycin A (an aureolic acid),[37] will be excluded from the discussion, even though the approaches envisioned for their preparation often rely on already established or inspire novel methodologies for accessing tetracycline targets. Furthermore, since only successfully completed total syntheses were selected to represent the advances made in the field over time, the efforts conducted by Barton et al.,[38] who followed the Dieckmann-approach established by Muxfeldt for the generation of the tetracycline backbone (*chapter 2.2.3*), or the macrocyclic approach proposed by Evans,[39] will not be discussed. By relying heavily on the methodologies implemented by Myers for the generation and derivatization of various tetracycline targets (*chapter 2.2.5.2*), Nicolaou's total synthesis of viridicatumtoxin B (**XXXII**), published in 2013, will also be omitted from the discussion.[40]

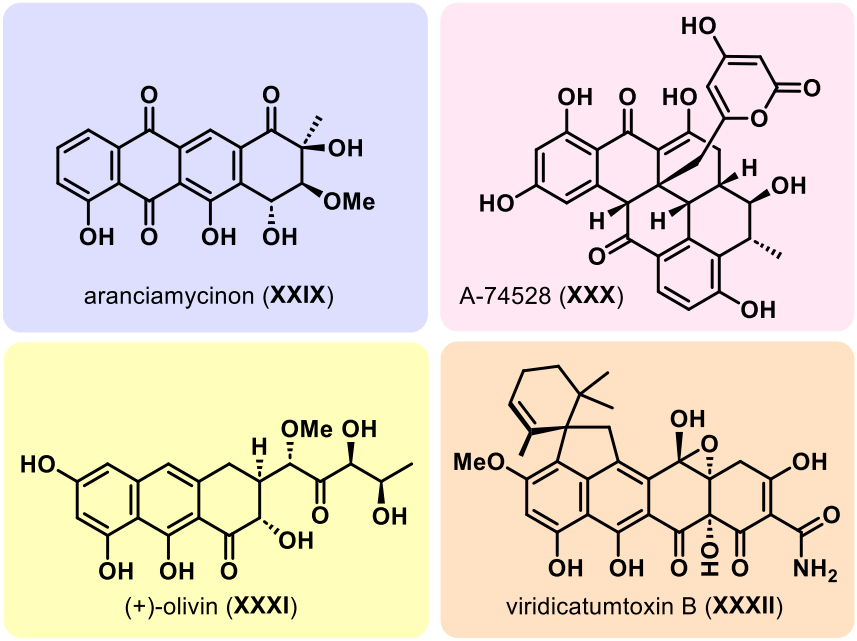
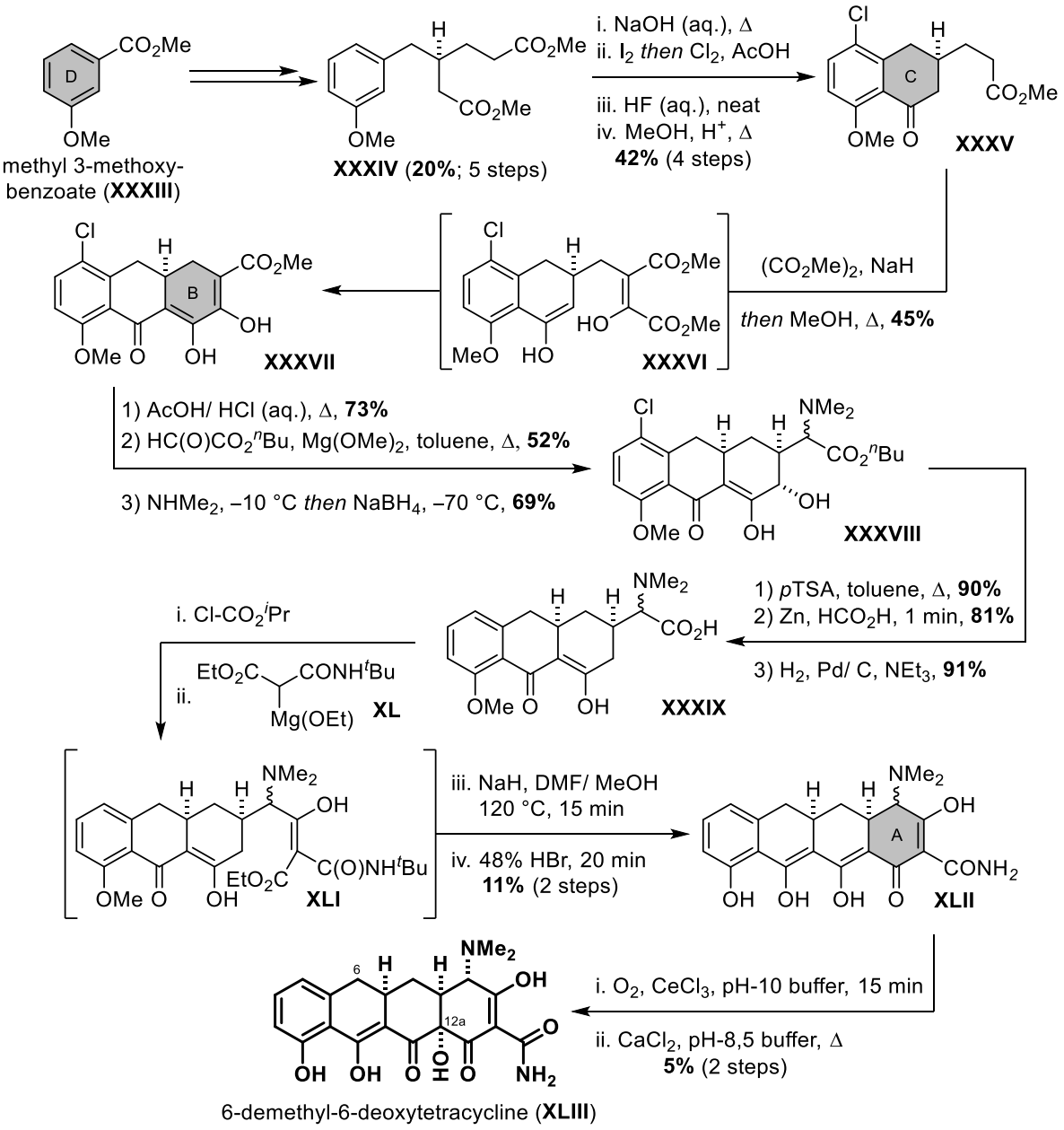


Fig. 2.2.1: Structures of the tetracycline-related type II polyketide natural products aranciamycinon (**XXIX**), A-74528 (**XXX**), (+)-olivin (**XXXI**) and viridicatumtoxin B (**XXXII**).

2.2.1 Woodward's 1962 synthesis of (±)-6-demethyl-6-deoxytetracycline

The first account of a total synthetic preparation of a tetracycline-derived target comes from the group of R. Woodward with their 1962 completed synthesis of (±)-6-demethyl-6-deoxytetracycline (**XLIII**).[41,42] Envisioning a linear approach (**scheme 2.2.1**), the group was able to access target **XLIII** in 25 steps, the product being obtained with a ~0,002% yield.
Starting with methyl 3-methoxy-benzoate (**XXXIII**), which is already bearing the future D-ring of the tetracycline core, the compound was elaborated in five steps to precursor **XXXIV**, thus setting the stage for the formation of the C-ring. By saponification of the ester moieties of **XXXIV** and chlorination of the *para*-position (in respect to the MeO-group) of the phenyl moiety, the C ring was constructed in a regioselective fashion by an intramolecular condensation, mediated by aqueous HF. Precursor **XXXV** was thus obtained with a 42% yield (four steps).



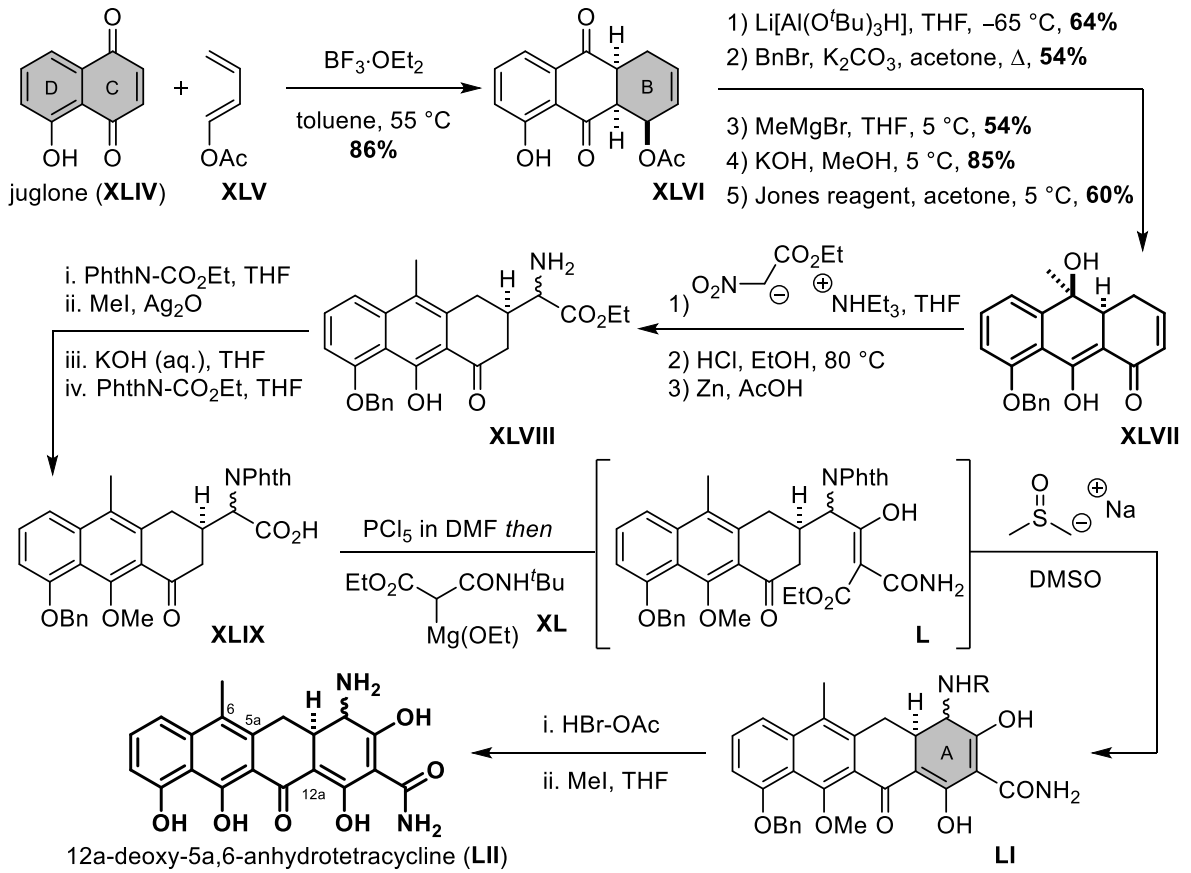
Scheme 2.2.1: Woodward's linear D/C/B/A-approach for accessing (±)-6-demethyl-6-deoxytetracycline (**XLIII**).[41]

Following the preparation of product **XXXV**, the formation of the B-ring was completed in an additional step *via* an intermolecular condensation with dimethyl oxalate (formation of **XXXVII**). With the addition of MeOH to the reaction system, an otherwise kinetically favored intramolecular condensation was suppressed, thus allowing the smooth formation of tricyclic ketone **XXXVII** and further advancement of the synthesis towards the targeted tetracycline **XLIII**. Further derivatizations included the homologation of the carboxylate-side chain by decarboxylation, and subsequent Aldol condensation, as well as the generation of the dimethylamine moiety at the future *C*4-position (formation of **XXXVIII**). The sequence exclusively afforded the thermodynamically more favored diastereomer, in which the carboxyamino side chain assumes an equatorial position. The reduction of the ketone towards the corresponding secondary alcohol also proceeded in a stereoselective fashion. The newly generated functionality, along with the chloro-functionality at the aryl moiety, was then cleaved to give tricycle **XXXIX**, the precursor of a final condensation step. Upon activation of the carboxy-moiety, precursor **XXXIX** was treated with Grignard reagent **XL**, leading to the exclusive formation of the labile malonamate **XLI**. Since isolation of the precursor was not possible due to stability concerns, malonamate **XLI** was briefly treated with NaH, the process affording the characteristic naphthacene core of the target compound with a rather unsatisfactory yield of 11% (two steps; based on product **XLII**). The absolute configuration of the dimethylamine moiety at *C*4, as drawn, was only postulated by Woodward to be consistent with that of naturally occurring tetracyclines, without providing experimental evidences. Nevertheless, the hydroxy functionality at *C*12a was successfully introduced in a final step *via* oxidation of the deoxy-compound **XLII**, with a stereochemical readjustment of the *C*4-position being required due to the partial epimerization of the compound. Since Woodward only succeeded to synthesize a tetracycline-derived compound and not a natural product, it is not surprising that other approaches followed in later years. Furthermore, the unsatisfactory overall yield and the length of Woodward's approach justify the need for alternative synthetic approaches.

2.2.2 Shemyakin’s 1967 synthesis of (±)-12a-deoxy-5a,6-anhydrotetracycline

Five years after Woodward’s breakthrough, in 1967, M. Shemyakin proposed an alternative path for accessing tetracycline-related compounds by successfully completing the total synthesis of (±)-12a-deoxy-5a,6-anhydrotetracycline (**LII**).[43] And while the final stages of the proposed strategy (construction of the A-ring; **scheme 2.2.2**) rely heavily on the protocol implemented by Woodward, the authors were nevertheless able to provide a quicker access to the initial D/C/B-ring system (formation of **XLVI**) by employing a Diels−Alder reaction between juglone (**XLIV**) and 1-acetoxy-1,3-butadiene (**XLV**).[44] The prepared material **XLVI** was then smoothly converted further to tricycle **XLVII**. Thus, the preparation of “Woodward’s ketone” **XLVII** was completed in six linear steps with a combined yield of 8%. Inexplicably, despite the successful generation of the characteristic decorations of tetracycline natural products at *C*6, the dehydration of the position was pursued after the required carboxyamino side chain was introduced *via* a Henry reaction (formation of **XLVIII**).

Ultimately, with the preparation of phthalimide **XLIX** completed, the stage was set for the construction of the A-ring and the end-game strategy, which were conducted in accordance with Woodward’s approach. The followed strategy ultimately led to the formation of the targeted anhydrotetracycline **LII**. Since the authors did not provide any yields for the elaborations of tricycle **XLVII** towards the final product **LII**, a comparison of the approach with that originally proposed by Woodward is not possible.



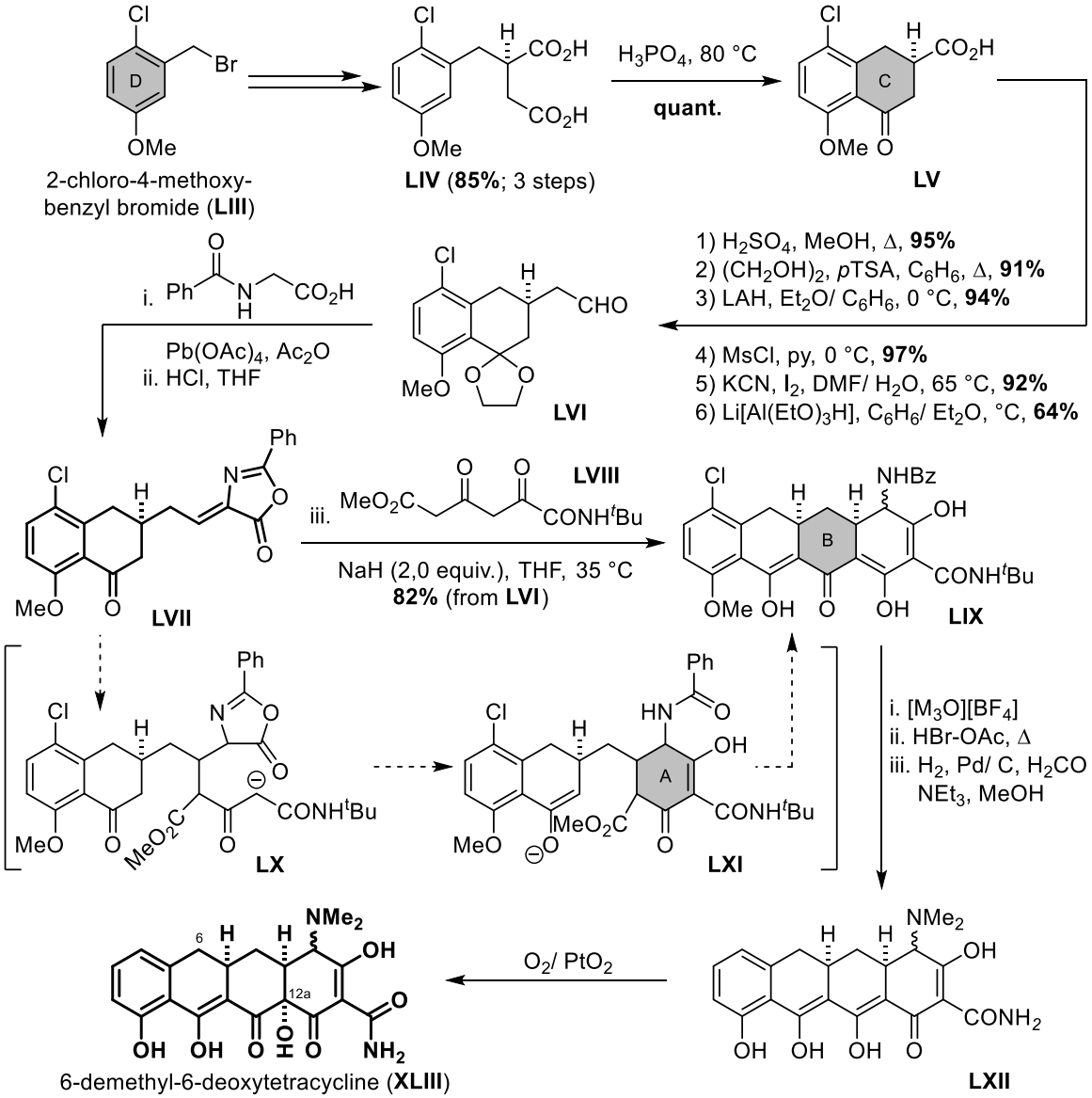
Scheme 2.2.2: Shemyakin's linear DC/B/A-approach for accessing (±)-12a-deoxy-5a,6-anhydrotetracycline (**LII**).[43]

2.2.3 Muxfeldt's approaches towards 6-demethyl-6-deoxytetracycline (1965) and (±)-terramycin (1968)

Through his initial attempt, H. Muxfeld was able to present in 1965 (just three years after Woodward's first accomplishment in the field) an alternative way of accessing 6-demethyl-6-deoxytetracycline (**XLIII**).[45] By employing a linear D/C/AB-strategy (**scheme 2.2.3**), Muxfeldt was able to synthesize target **XLIII** in just 15 steps by adapting a 1962 elaborated strategy.[46]

Starting with precursor **LIII**, bearing the D-ring of the future tetracycline, the compound was elaborated in four steps to bicycle **LV** with a combined yield of 83%. Once the generation of the C-ring was completed, ketone **LV** was further elaborated to aldehyde **LVI**. The transformations involved the formation of the acetonide moiety as a masking strategy for the keto-functionality as well as the homologation of the carboxylic acid side chain to the corresponding aldehyde moiety. The five-step sequence afforded **LVI** with a 46% yield, thus setting the stage for further elaborations.

In order to establish the A/B-ring system of the target, the authors envisioned an elaborate cyclization cascade, which first required the successful formation of the phenyl-oxazolone-bearing precursor **LVII**. This crucial intermediate was then subjected to cyclization conditions. Using only one equivalent of base (NaH), the cyclization cascade, consisting of an initial condensation with hippuric acid **LVIII**, first led to the formation of the A-ring. The generation of the B-ring, and thus the smooth construction of the epimeric tetracyclic product **LIX** followed from intermediary compound **LXI**, with the transformation requiring an additional base-equivalent.



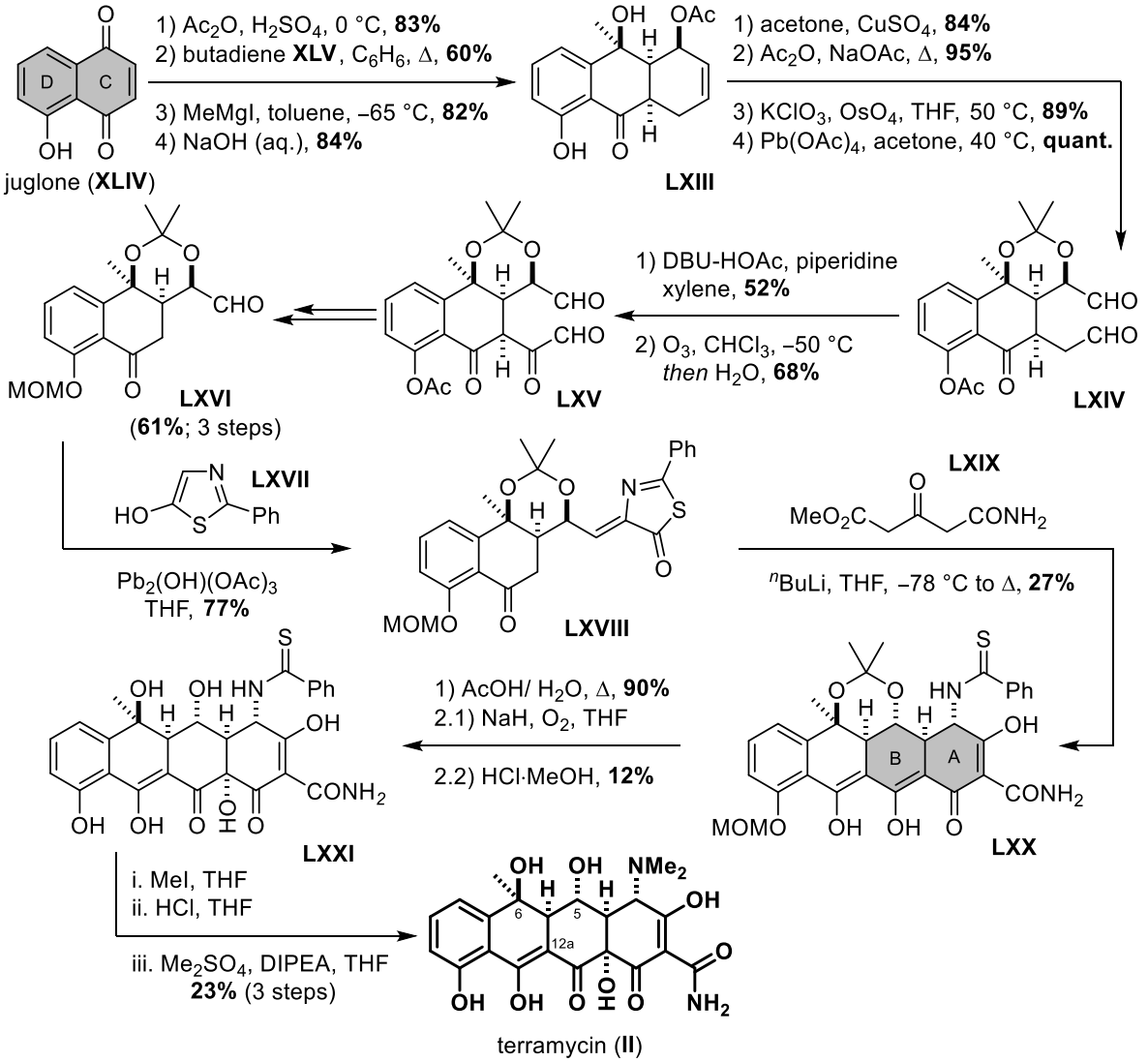
Scheme 2.2.3: Muxfeldt's approach towards 6-demethyl-6-deoxytetracycline (**LII**) *via* a linear D/C/AB-ring-construction strategy.[45]

With the successful construction of the naphthacene core (generation of **LIX**), the authors were able to conduct the final transformations to complete their synthesis of 6-demethyl-6-deoxytetracycline (**XLIII**). Thus, starting from precursor **LIX**, the *N*-benzyl group was removed with Meerwein's salt, and the phenol ether and amide moieties were dealkylated. In an additional hydrogenation step, the chloro-functionality was cleaved concomitantly with the alkylation of the secondary amine. For this sequence the authors failed to mention the obtained yields. Nevertheless, a PtO_2-catalyzed oxidation of the *C*12a-position finally gave the targeted product **XLIII**.[47]

Although his early strategy was successful in providing access to tetracycline scaffolds of lower complexity, Muxfeldt's great breakthrough to the field came three years later with the first total synthesis of the naturally occurring tetracycline (±)-terramycin (**II**).[48] By combining the assets of their first strategy, with Shemyakin's approach of constructing the D/C-ring system (**scheme 2.2.2**), Muxfeldt successfully completed the total synthesis of (±)-terramycin (**II**) in 22 linear steps (**scheme 2.2.4**) with a combined yield of 0,06%.[49]

Strating from juglone (**XLIV**), the D/C-ring system was elaborated over 13 steps to aldehyde **LXVI**, a precursor suitable for the already established strategy of simultaneously constructing the A/B-rings.

These derivatizations primarily included the brief construction of an early B-ring *via* a [4+2]-cycloaddition between juglone (**XLIV**) and acetoxy-butadiene **XLV**, along with its degradation to obtain aldehyde **LXVI**. In contrast to Shemyakin's approach, by not using BF_3 as a Lewis acid and masking the phenol group as an acetate, the Diels–Alder reaction employed by the authors proceeded with opposite regioselectivity to that described previously, conveniently allowing the formation of a *C*5, *C*6-dioxygenated precursor. The obtained product was further elaborated to tricycle **LXIII**. The *C*6-positioned methyl group was conveniently introduced after the cycloaddition by a stereospecific Grignard addition, with the sequence successfully fulfilling the premise of constructing a tetracycline target bearing the natural functionalities at *C*6 early in the synthesis. Further on, the 1,3-diol motif of **LXIII** was masked as an acetonide and the synthesis pursued towards aldehyde **LXVI**. The 13-step sequence gave tricyclic product **LXVI** with a combine yield of 5%.



Scheme 2.2.4: Muxfeldt's first total synthesis of a tetracycline natural product, (±)-terramycin (**II**), *via* a linear DC/AB-approach.[48]

In analogy to the previous encounter, Muxfeldt envisioned a similar cyclization approach for the simultaneous construction of the A/B-ring system. However, in contrast to his initial strategy, which led to the formation of product **LIX** as a mixture of epimers, the previously used phenyl-oxazolone ring was replaced by a thiazolone analogue **LXVII**. With the performed alteration, the authors were still unable to achieve any stereocontrol for the formation of the *C*4- and *C*4a-positions. However, due

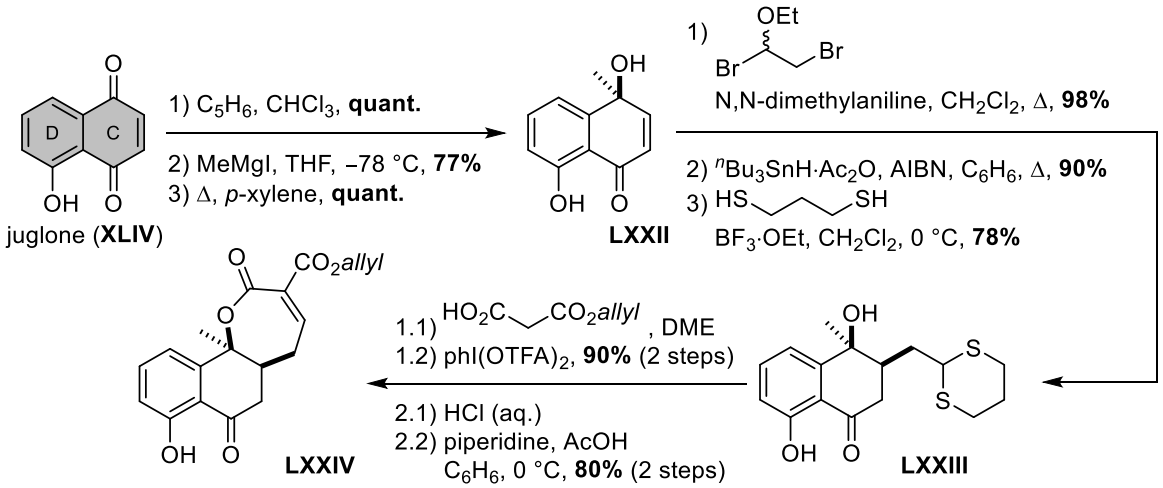
to the presence of a thio-moiety in the compound, the cyclization product could be readily crystalized to give diastereomerically pure pentacycle **LXX**.

A final noteworthy transformation of the approach is represented by the generation of the *C*12a-positioned tertiary alcohol by the method originally described by Woodward (*chapter 2.2.1*), which proceeded with a highly unsatisfactory yield of 12%. Despite their elegant approach of addressing the naphthacene core, Muxfeldt et al. failed to provide reliable access to the large-scale production of tetracycline natural products and derivatives thereof on account of two shortcomings: I) by failing to control the generation of *C*4- and *C*4a-stereocenters, and II) by not providing a superior alternative to the *C*12a-oxidation; this issue remained to be solved decades later with Tatsuta's entry to the field (*chapter 2.2.5.1*). Nevertheless, the route developed by Muxfeldt was successfully used to synthesize several tetracycline analogues in quantities suitable for clinical trials.[50]

2.2.4 Stork's 1996 synthesis of (±)-12a-deoxytetracycline

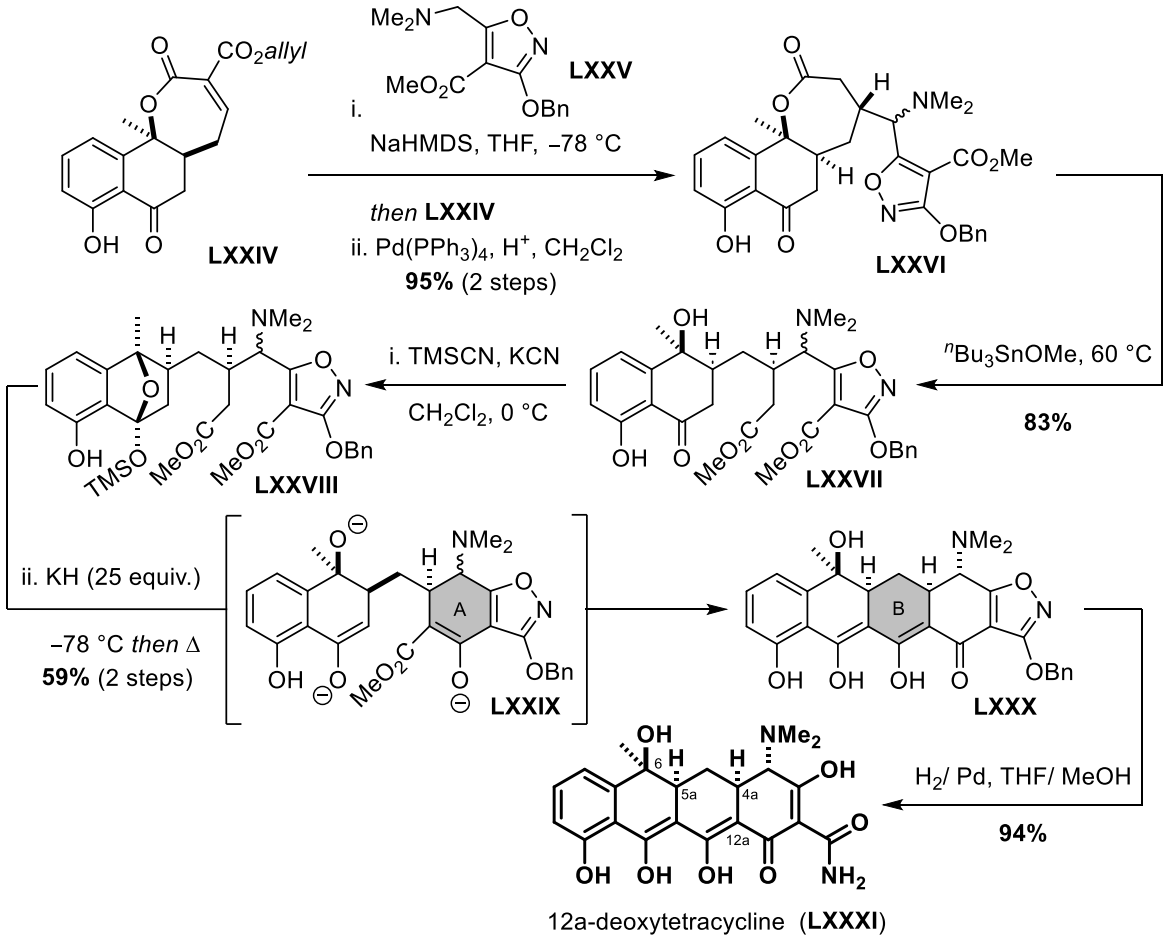
Up until Myers et al. first presented their approach towards the total synthesis of tetracycline-derived compounds in 2005 (*chapter 2.2.5.2*), the strategy developed by G. Stork in 1996 represented the most effective way to access the characteristic core of the natural products.[50] By proposing a linear stereocontrolled DC/AB-strategy, the authors were able to elegantly address the construction of their target (±)-12a-deoxytetracycline (**LXXXI**) in only 16 steps, with a combined yield of 17%.[51] Furthermore, the use of isoxazole motifs as masking agents for the A-ring functionalities made Stork a trailblazer in the field of tetracycline total synthesis, with his strategy still being employed in modern-day approaches.[36,40]

Starting, like Shemyakin, with juglone (**XLIV**) as the D/C-ring precursor, the first step of Stork's total synthesis was represented by an *exo*-selective Diels–Alder reaction with cyclopentadiene (**scheme 2.2.5**). Upon formation, the bridged tricyclic product was treated with MeMgI, and the enone moiety was regenerated *via* a *retro*-Diels–Adler reaction to furnish precursor **LXXII**. With the installation of the *C*6-functionalities completed, the authors used the newly generated stereocenter to further elaborate the structure toward their target **LXXXI**. Thus, derivatization of enone **LXXII**, which primarily required the installation of the *C*5a-positioned side chain, along with its elaboration towards tricycle **LXXIV**, was successfully conducted in seven steps with a remarkable yield of 50%.



Scheme 2.2.5: Stork's DC/AB-approach for accessing (±)-12a-deoxytetracycline (**LXXXI**): Construction of the advanced precursor **LXXIV**.[51]

In a further step, the coupling between enone **LXXIV** and the crucial isoxazole-derived **LXXV** was achieved *via* a diastereoselective Michael-addition, with the subsequent removal of the carboxy-moiety at the future *C*12a-position leading to the formation of the epimeric ketone **LXXVI** (**scheme 2.2.6**). Up to this point, and despite the formation of *C*4-epimers, the authors were able to successfully generate the *C*4a-, *C*5a- and *C*6-centers in a stereocontrolled manner. The cleavage of the ε-caprolactone moiety of **LXXVI** was performed in an additional step under mild conditions to give the advanced precursor **LXXVII**, which was further elaborated to give intermediary compound **LXXVIII** as the precursor of the final cyclization step. By treating **LXXVIII** with a large excess of base (25 equiv.), a Dieckmann cyclization-cascade was triggered, which successfully led to the simultaneous construction of the A/B-ring system of the target molecule. Pentacycle **LXXX** was thus obtained as a mixture of separable *C*4-epimers.



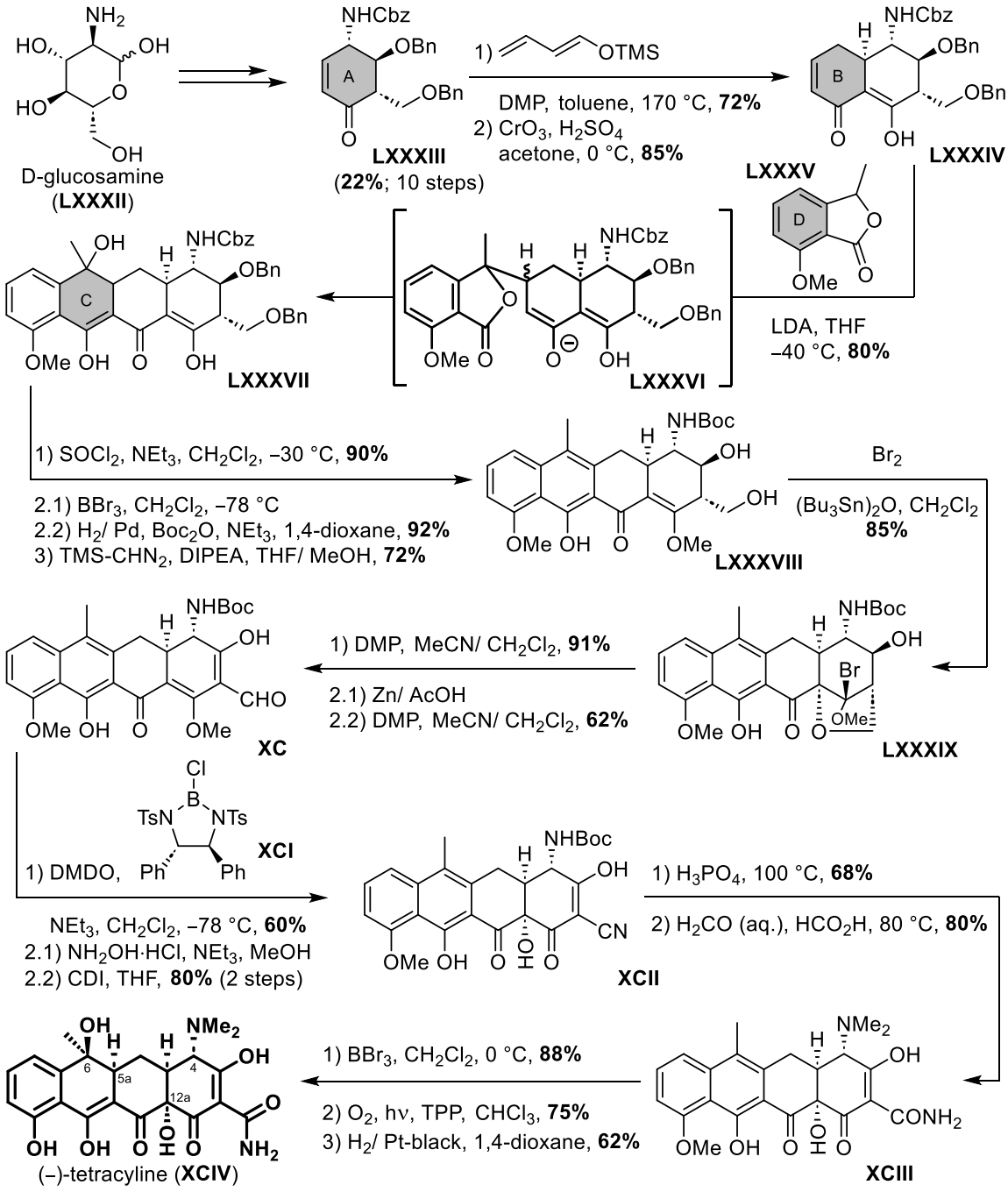
Scheme 2.2.6: Stork's DC/AB-approach for accessing (±)-12a-deoxytetracycline (**LXXXI**): Elaboration of precursor **LXXIV** and end-game strategy.[51]

Lastly, the scission of the heterocycle moiety under hydrogenation conditions elegantly yielded the target tetracycline **LXXXI**, thus concluding Stork's contribution to the field. Unfortunately, further elaboration of the compound towards a *C*12a-hydroxylated product was found to be impractical, with this long-standing problem remaining to be solved four years later by Tatsuta's approach.

2.2.5 The Michael–Dieckmann approach

2.2.5.1 Tatsuta's first stereoselective synthesis of (–)-tetracycline (2000)

At the turn of the century, in 2000, nearly forty years after Woodward first proposed his total synthetic strategy of addressing tetracycline-related compounds (*chapter 2.2.1*), the first stereoselective synthesis of (–)-tetracycline (**XCIV**) was finally completed by K. Tatsuta.[52]
Envisioning a convergent approach for completing the task, Tatsuta's take on the total synthesis of a tetracycline member is highlighted in **scheme 2.2.7**, with the sequence beginning with the ten-step derivatization of the chiron D-glucosamine (**LXXXII**) towards enantiomerically pure enone **LXXXIII**.

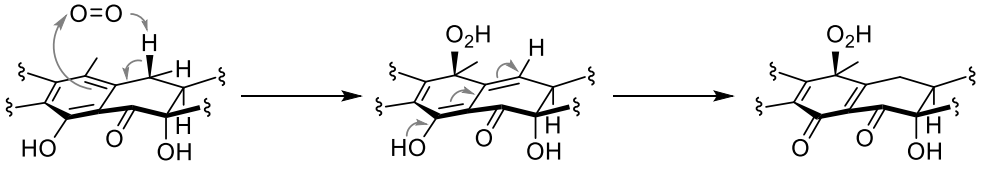


Scheme 2.2.7: Tatsuta's stereoselective synthesis of (–)-tetracycline (**XCIV**) *via* a convergent A/B+D→C-approach.[52]

Having completed the preparation of enone **LXXXII**, bearing the future A-ring of the tetracycline target **XCIV**, its skeleton was conveniently further elaborated towards decalin **LXXXIV**– the product of a Diels–Alder reaction. The thus obtained A/B-ring-bearing product was then subjected, along with phthalide **LXXXV** (the future D-ring), to cyclization conditions, with the employed Michael–Dieckmann approach conveniently furnishing the desired naphthacene architecture in one step with a remarkable 80% yield. Product **LXXXVII** was thus obtained as a mixture of diastereomers, with the authors failing to provide further comments on the observed outcome. Nevertheless, by readily aromatizing the newly formed C-ring during the preparation of precursor **LXXXVIII**, the issue was corrected, the required decorations at *C*6 remaining to be adjusted later in the synthesis.

Failing to recognize the value of Stork's approach of masking 1,3-diekto-functionalities as isoxazoles, the further adjustment of the A-ring decorations of precursor **LXXXVIII** was achieved by a rather unusual detour, a direct oxidation of the two alcohols at *C*2 and *C*3, failing to provide the authors with the desired outcome. The successful preparation of oxidation product **XC** set the stage for an unprecedented, stereoselective hydroxylation of the *C*12a-position. By employing DMDO as an oxidizer and diazaborolidine **XCI** as a chiral auxiliary, the introduction of the tertiary alcohol moiety at *C*12a was remarkably achieved with a 60% yield, and the obtained product further derivatized to tetracycline-precursor **XCIII**.

The last notable transformation of Tatsuta's approach is represented by the highly successful derivatization of the *C*6-position to selectively install the desired quaternary alcohol moiety. By employing a 1986-established protocol, the authors were able to successfully introduce the highly challenging group *via* a stereoselective oxidation, with a formal ene mechanism (**scheme 2.2.8**) underlying this process.[53] Furthermore, due to the presence of the dimethylamine moiety at *C*4, shielding the lower side of the molecule, the reaction proceeded from the less hindered *re*-side, yielding a (*S*)-configured hydroperoxide. The reduction of the reactive functionality was achieved in the final step by employing noble metal-catalyzed hydrogenation conditions, with the two-step sequence proceeding with a combined yield of 47%.



Scheme 2.2.8: Simplified mechanism of the $^1O_2$-oxydation of the *C*6-position in Tatsuta's strategy of preparing (–)-tetracycline (**LXII**).[53]

Finally, with these last successful modifications complete, the stereocontrolled total synthesis of (–)-tetracycline (**XCIV**) was concluded. Despite the length of their strategy (34 steps and 0,002% overall yield), Tatsuta provided with his concise construction of the naphthacene core a major contribution to the field of tetracycline total synthesis. Together with Stork's contribution (*chapter 2.2.4*), Tatsuta's tandem Michael–Dieckmann protocol represents the foundation of numerous modern-day strategies for accessing tetracycline natural products and derivatives thereof, with A. Myers beautifully combining the assets of both strategies for the elaboration of his approach, as will be shown below.

2.2.5.2 Myers's tetracycline syntheses

In terms of recent contributions to the field of tetracycline total synthesis, the efforts brought by the Myers laboratory in the past two decades (beginning in 2005) represent a major turning point. Drawing heavily on previous advances, primarily those of Stork (*chapter 2.2.4*) and Tatsuta (*chapter 2.2.5.1*), Myers and his collaborators were successful in combining the assets of both strategies, thus providing a rapid and stereoselective access to variously substituted tetracycline targets with crucial bioactive properties.[50] A generalized overview of the convergent skeleton construction strategy is highlighted in **fig. 2.2.2**.[54] In analogy to Stork's 1996 protocol for accessing (±)-12a-deoxytetracyline (**LXXXI**; *chapter 2.2.4*), Myers also implemented, for the protection of the polar functionalities at the A-ring, the isoxazole masking-strategy.[51] In all cases, the heterocycle moiety of the advanced precursors **XCIX** remained to be cleaved during the end-game of the synthesis by the use of Pd-black under an H_2-atmosphere.[50,55-57] In addition to the unveiling of the isoxazole, a hydrolytic cleavage of the TBS-ether at *C*12a by the use of aqueous HF was also required during the global deprotection step. Ultimately, the advanced precursor **XCIX**, bearing the characteristic tetracycline core with all the required decorations, were traced back to fragments **C** (i.e., the *eastern fragments*) and **CI** (i.e., the *western fragments*), whose coupling proceeded through a tandem Michael–Dieckmann cascade. This strategy was elaborated in accordance with the protocol implemented by Tatsuta et al. for their 2000-completed stereoselective synthesis of (–)-tetracycline (**XCIV**; *chapter 2.2.5.1*). However, in contrast to Tatsuta's use of phthalides (**LXXXV**) as western fragments, Myers utilized *ortho*-toluate anions **CI**, thus eliminating the need for *C*6-derivatization upon fragment coupling.[50]

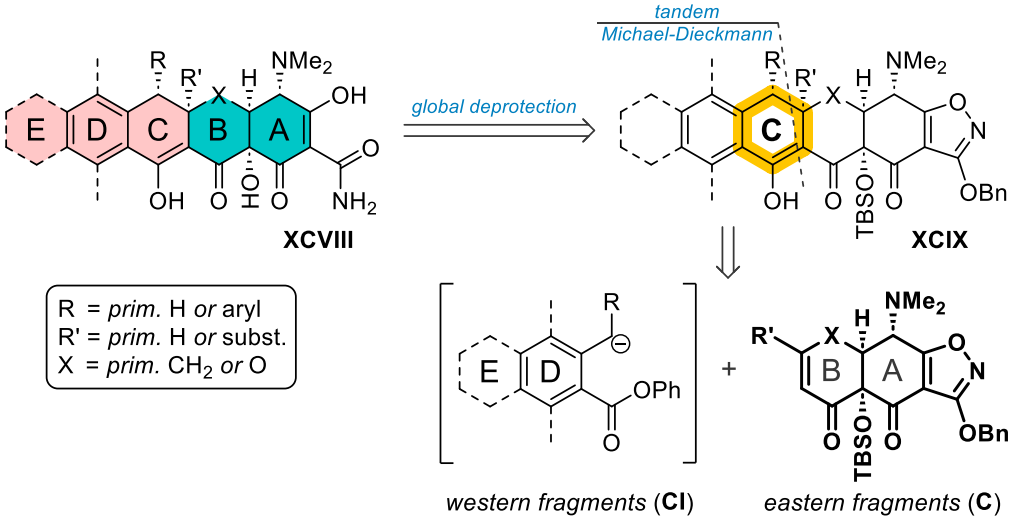


Fig. 2.2.2: Myers's generalized retrosynthetic approach for accessing variously decorated tetracycline targets. The characteristic naphthacene skeleton was addressed through a convergent A/B+D(E)→C-approach *via* a tandem Michael–Dieckmann-cascade.[50,57-59]

With the implementation of the convergent approach, Myers was quick to recognize the tremendous potential of fragment tunability, successfully providing, in several stages, access to numerous panels of variously decorated tetracycline derivatives. The generalized structure **XCVIII** in **fig. 2.2.2** highlights the structural diversity of the synthesized compounds. Furthermore, starting from crucial decalin-enone **CVI** (**scheme 2.2.9**), Myers was able to elegantly access, in 2005, through his convergent strategy, (–)-tetracycline (**XCIV**) in just six steps and 14% yield (**fig. 2.2.3**).[56] Exceptionally, the construction of the naphthacene core in the synthesis of (–)-tetracycline (**XCIV**)

proceeded *via* a Diels–Alder reaction between eastern fragment **CIV** and an *in-situ* formed *ortho*-quinone dimethide **CIII**. This account represents the only known example of a successful naphthacene core-construction *via* a [4+2]-cycloaddition protocol in the context of tetracycline total synthesis.

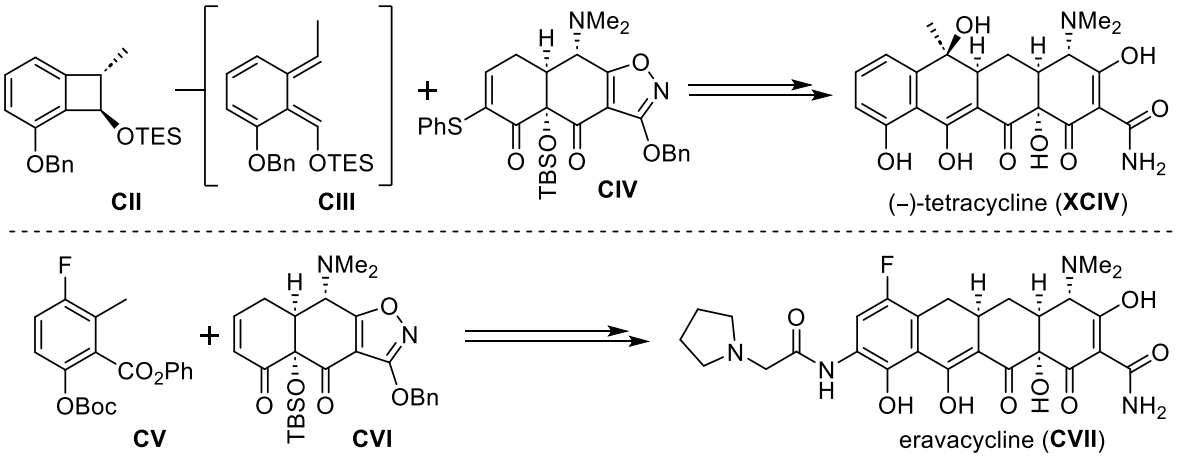
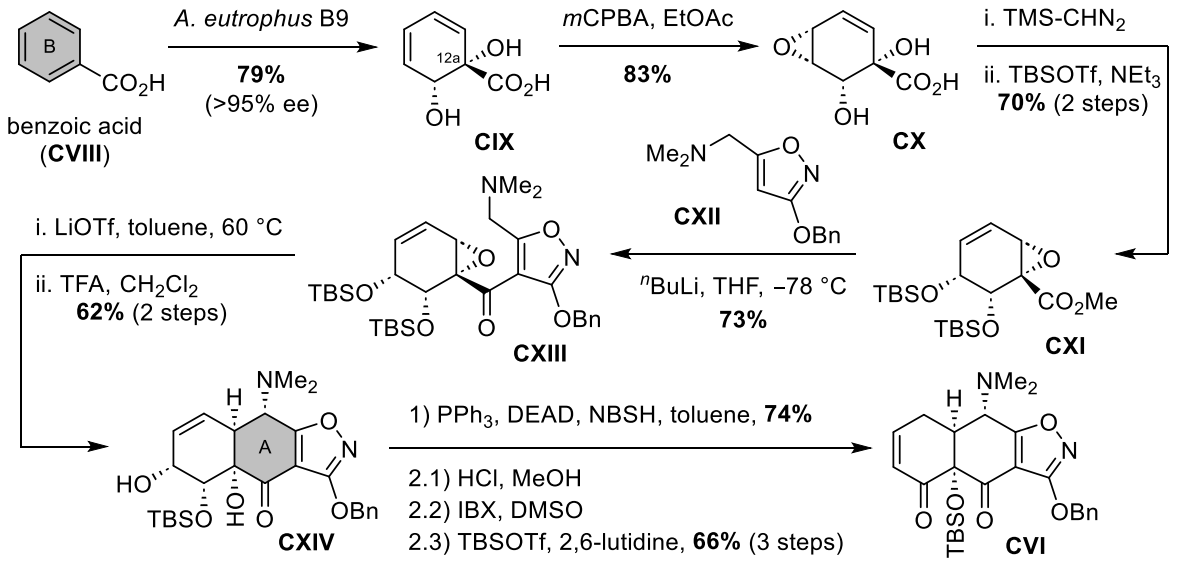


Fig. 2.2.3: Myers's key steps for accessing (–)-tetracycline (**XCIV**) and eravacycline (**CVII**), an FDA-approved injectable drug used to treat complicated intraabdominal infections.[34]

Another notable asset of Myers's approach is represented by the introduction of the challenging tertiary alcohol at the *C*12a-position (decalin's *C*8a) early in the synthesis. By derivatizing the less complex decalin eastern fragments (**C**) prior to the generation of the naphthacene core, the authors elegantly overcame this long-lasting challenge, with three approaches for accessing crucial fragment **CVI** being proposed over the past years.

The first proposed synthesis of enone **CVI** was achieved by Myers et al. in 2005 through a linear ten-step approach (**scheme 2.2.9**), starting with benzoic acid (**CVIII**) as a precursor for the future B-ring.[50] By successfully employing an enzymatic dihydroxylation of precursor **CVIII**, the authors were able to prepare product **CIX** in a stereocontrolled manner (79% yield and >95% ee). The newly generated stereocenters were then further used to direct the construction of additional functionalities, with product **CIX** being successfully elaborated into epoxy-ester **CXI** in three steps.

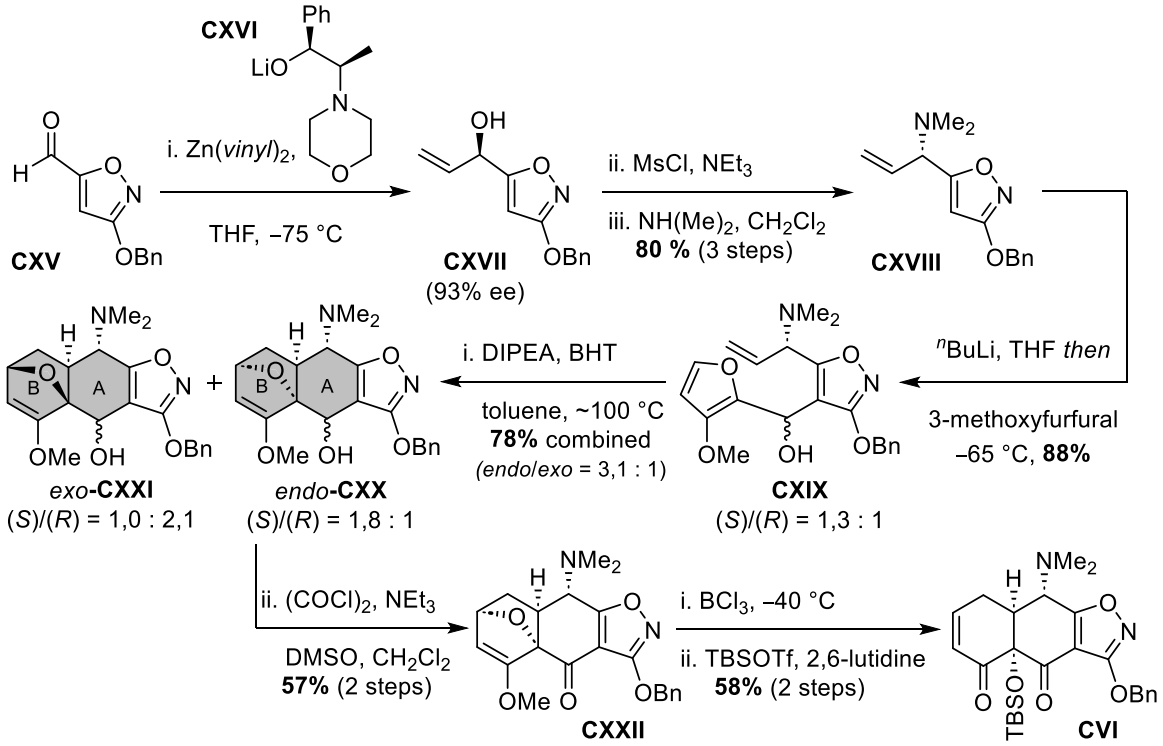


Scheme 2.2.9: First-generation synthesis of decalin-enone **CVI**.[50]

Further elaboration of epoxide **CXI** led to the formation of the advanced intermediate **CXIII**, the precursor of the key cyclization step. Thus, an initial intramolecular opening of the epoxide moiety by the dimethylamino-group triggered a base-assisted Sommelet-Hauser-type rearrangement, resulting in the simultaneous formation of both the A-ring as well as the crucial *C*12a-positioned tertiary alcohol. Product **CXIV** was finally converted to the targeted eastern fragment **CVI**, with the ten steps required for its preparation proceeding with a combined yield of ~14%.

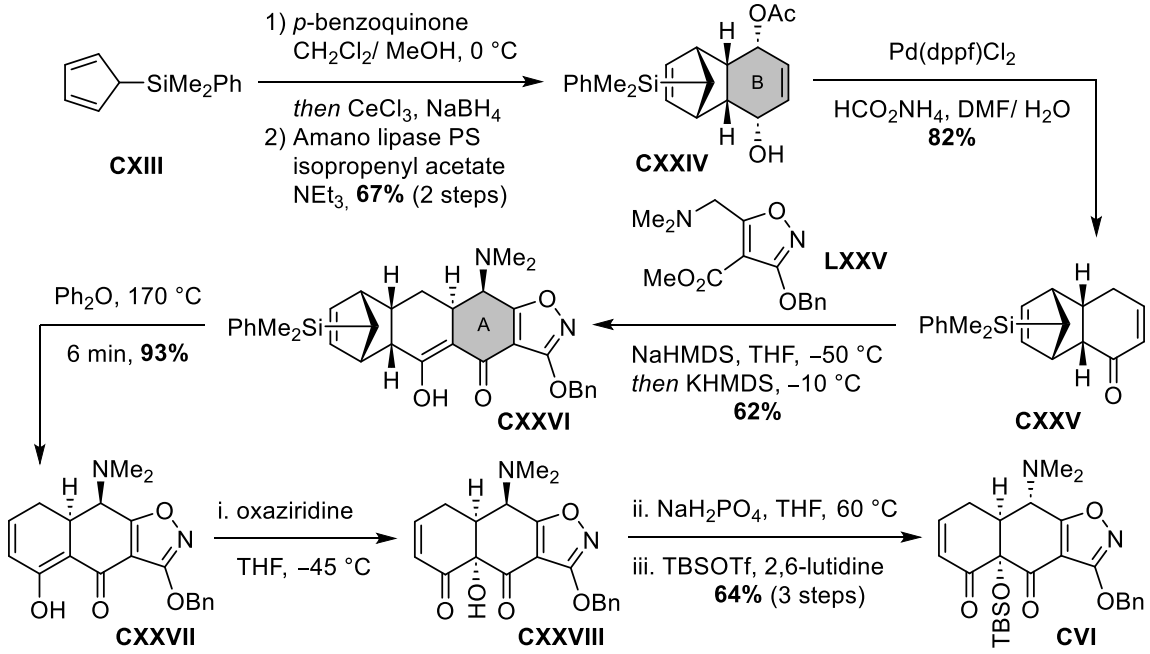
Despite the effective preparation of product **CVI** by the aforementioned means, Myers et al. proposed in 2007 their second, improved strategy for accessing the valuable building block (**scheme 2.2.10**). By employing an intramolecular Diels–Alder with furan protocol (IMDAF) for the construction of the decalin core, the authors were able to conveniently control both the simultaneous formation of the A/B-ring system as well as the configuration of the *C*12a-center.[60] Thus, upon coupling the enantiomerically pure isoxazole **CXVIII** (prepared in three steps from aldehyde **CXV**) with 3-methoxyfurfural, the resulting epimeric product **CXIC** was subjected to cyclization conditions. The implemented [4+2]-cycloaddition proceeded smoothly, yielding the *endo*- and *exo*-arranged products **CXX** and **CXXI**, respectively. The epimeric *endo*-product **CXX** was then subjected to a Swern oxidation, which provided the required functionality at *C*1, thus allowing the successful preparation of decalin **CVI** in two additional steps.

Since the elaboration of decalin **CXXI**, the *exo*-product of the IMDAF protocol, would have resulted in the formation of an undesired (*R*)-configured tertiary alcohol at the future *C*12a-position, its further derivatization was not carried out by the authors. A conformational correction by means of an α-ketol rearrangement could have potentially solved this issue and thus contributed to an increased overall yield. Nevertheless, Myers was able to complete his second approach towards fragment **CVI** with a slightly improved yield of 18%.



Scheme 2.2.10: Improved synthesis of decalin-enone **CVI** *via* an IMDAF protocol.[60]

In his last attempt to provide quicker access to decalin-enone **CVI**, Myers proposed a convergent strategy based on a Michael–Claisen key step (**scheme 2.2.11**).[55] Thus, after completing the synthesis of the B-ring (**CXXIV**) *via* an *endo*-selective Diels-Alder reaction between *para*-benzoquinone and cyclopentadiene-derived **CXIII**, a palladium-mediated rearrangement conveniently provided enone **CXXV**. The precursor was then subjected to cyclization conditions together with isoxazole **LXXV**: a repurposed derivative from Stork's approach (*chapter 2.2.4*). The tandem Michael–Claisen cascade employed by Myers resulted in the formation of the A-ring in a diastereoselective manner, with the presence of the bridged, temporary C-ring being solely responsible for the observed outcome. Despite the formation of an architecture bearing an undesired (*R*)-configured amine at *C*4, product **CXXI** was further elaborated towards the aimed target. The transformations included a *retro*-Diels–Alder reaction to unveil the enone moiety of the final product as well as the generation of the *C*8a-positioned alcohol (later becoming the *C*12a position). In a penultimate step, the undesired configuration of the *C*4 position was successfully epimerized to give the (*S*)-configured dimethylamine moiety, with the protection of the free alcohol at *C*8a representing the final step of the modified approach. Starting from silylated cyclopentadiene **CXIII**, Myers's eight-step, third-generation approach managed to provide enone **CVI** with a 20% yield.

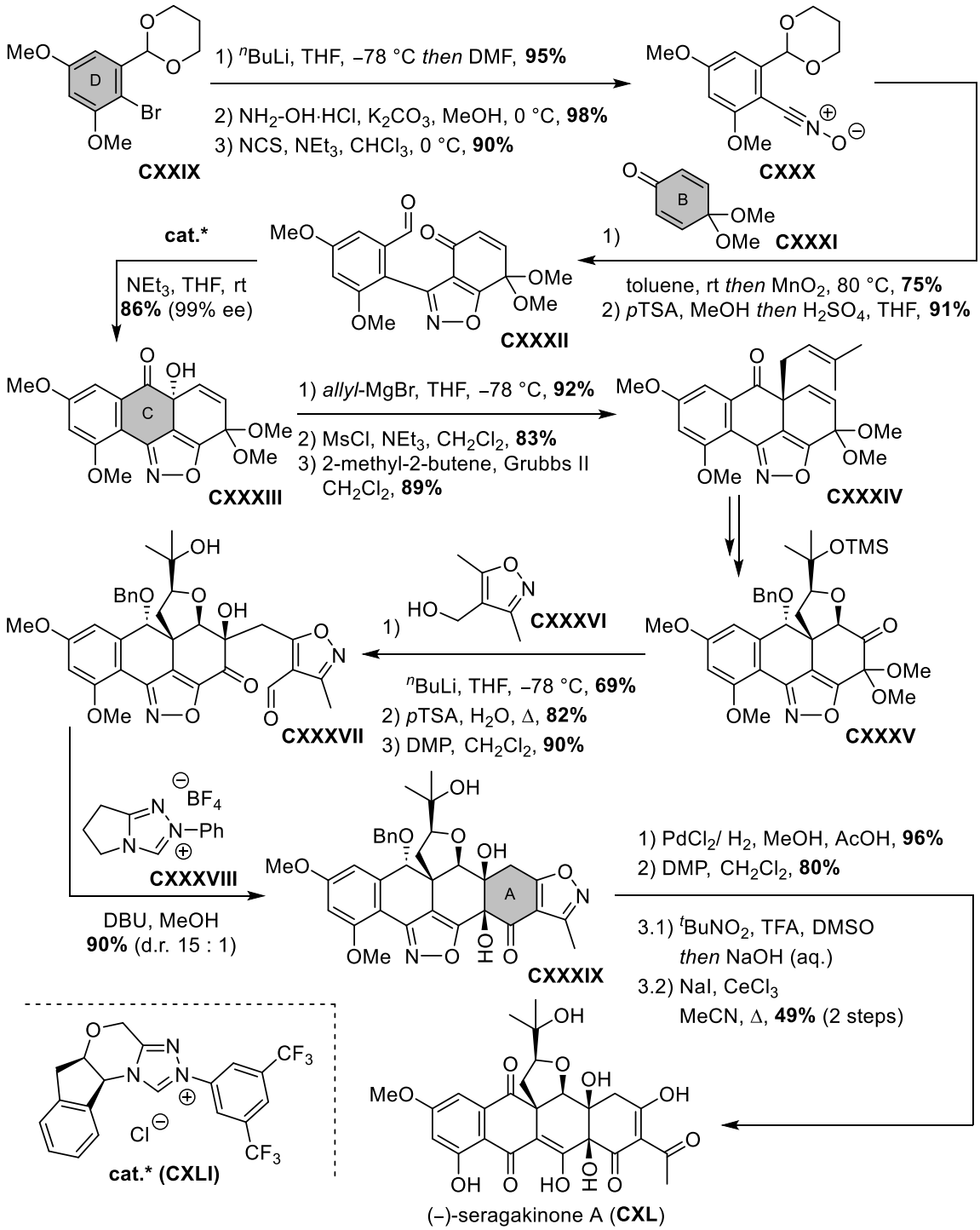


Scheme 2.2.11: Third generation synthesis of decalin-enone **CVI** *via* a tandem Michael–Claisen approach.[55]

2.2.6 Suzuki's benzoin approach towards (–)-seragakinone A (2011)

The final entry in the series of representative total syntheses of tetracycline-related compounds is marked by K. Suzuki's 2011 preparation of (–)-seragakinone A.[61] Based on one of their earlier reports,[62] the protocol envisioned by the authors for addressing their targeted natural product **CXL** consisted of a stereoselective benzoin reaction for the construction of the C-ring and a formal Aldol–benzoin cascade for the generation of the A-ring. The latter strategy strongly resembles the aforementioned Michael–Dieckmann approach elaborated by Tatsuta (*chapter 2.2.5.1*). Furthermore, to protect the 1,3-diketone motifs of the target, Suzuki also implemented Stork's isoxazole strategy.

Starting with building block **CXXIX**, bearing the D-ring of the targeted natural product, isolable nitril oxide **CXXX** was prepared in three straight-forward steps and subjected to an intermolecular 1,3-dipolar addition (**scheme 2.2.12**). The coupling of the highly reactive dipole **CXXX** with a benzoquinone-derived **CXXXI** *via* a [3+2]-cycloaddition readily furnished the advanced precursor **CXXXII**, setting the stage for a first benzoin reaction. By employing the NHC-precursor **CXXXVIII** as a chiral catalyst, the authors were able to construct the C-ring with a high yield of 86% *via* an unprecedented stereoselective intramolecular benzoin cyclization. Further, side-chain-specific elaborations and derivatizations led to the formation of the pentacycle **CXXXV**.



Scheme 2.2.12: Suzuki's synthesis of the antimicrobial natural product (–)-seregakinone A (**CXL**) *via* a stereoselective benzoin key step.[61]

The A-ring construction *via* a formal Aldol step was immediately followed by an additional benzoin reaction, catalyzed by the NHC-precursor **CXXXVIII**. The highly complex four-step sequence led to the construction of the naphthacene-bearing product **CXXXIX** with a combined yield of 46% and excellent diastereoselectivity (d.r. 15:1). The last steps of the synthesis, consisting primarily of the removal of protective groups, such as the cleavage of the isoxazole moieties, finally afforded the natural product target **CXL**.

With the implementation of an unprecedented strategy, Suzuki et al. successfully completed the total synthesis of (–)-seregakinone A (**CXL**) in 26 linear steps, with a global yield of 2,3%. Furthermore, the developed protocol represents a powerful example of an alternative strategy for addressing highly complex tetracycline targets.

3 Aim of the thesis

Previously, several particularities of the tetracycline family of natural products were discussed, emphasizing the importance of perpetual development and optimization of both old and new members of this drug class as part of the general effort of combating antibiotic resistance (*chapter 2.1*). Despite the broad medicinal relevance of the topic, this work will further focus solely on the exploration of synthetic aspects of tetracycline chemistry. By implementing a strategy with enhanced assets compared to known approaches (*chapter 2.2*), the preparation of two valuable tetracycline-related aureolic acid biosynthetic precursors– demethylpremithramycinone (**1**) and premithramycinone (**2**), both shown in **fig. 3.1**, is aimed *via* a common total synthetic route (**fig. 3.2**). The reassurance of the absolute configuration of the targeted compounds, as well as enabling the synthesis of novel, potentially bioactive derivatives, represent additional focus points of the global aim. In addition, due to their close structural relationship to the two originally aimed premithramycinones, the synthesis of *epi*-chromocyclin (**3**), alongside its *C*4-epimer chromocyclin (**4**), is also envisioned *via* the common path. Lastly, the total synthesis of carbamidochelocardin (**5**), a chelocardin (**6**)-derived tetracycline with promising antibiotic properties,[10] is also aimed at, thus contributing to previous efforts to validate the absolute configuration of the compound.

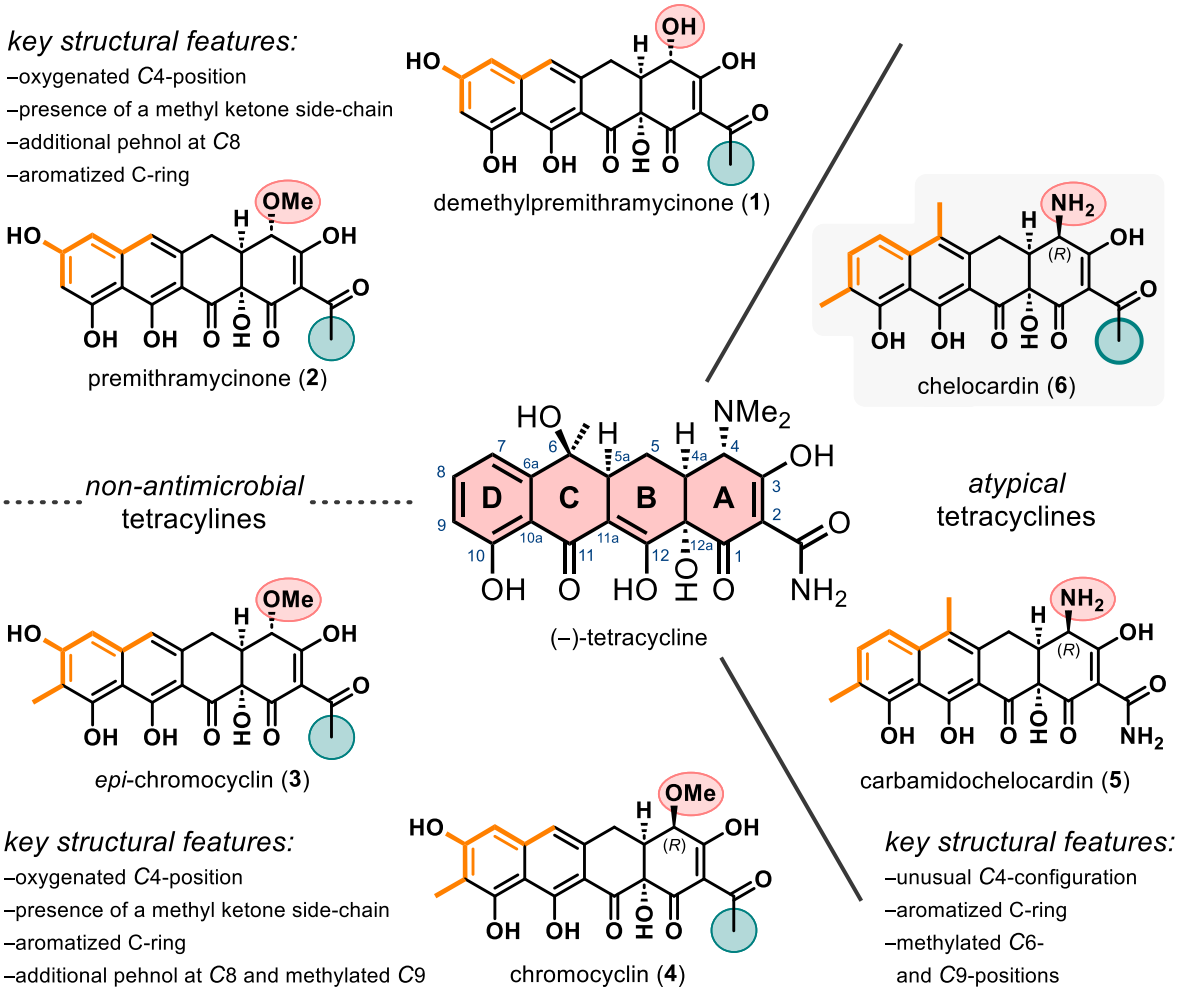


Fig. 3.1: The structures of the five tetracycline targets, depicted next to the parent compound (–)-*tetracycline*. Carbamidochelocardin (**5**) is shown alongside chelocardin (**6**), with the naturally occurring tetracycline not being part of the synthetically aimed targets, however.

Given the close structural relationship of the compounds (*chapter 2.1*), the synthesis of the aimed natural product targets shown in **fig. 3.1** is envisioned *via* a common strategy. Inspired by previously reported total syntheses of tetracycline natural products and derivatives thereof, such as those reported by K. Tatsuta,[52] A. G. Myers,[50,63] and G. Stork,[51] the chosen common stereoselective, convergent strategy for accessing the aimed targets relies on both established protocols as well as original approaches for overcoming long-known challenges. While the majority of the published tetracycline syntheses of the past two decades mainly rely on Michael–Dickman cyclizations for accessing the characteristic tetracyclic skeleton (*chapter 2.2.5*),[50-52] a Diels–Alder reaction with furan was envisioned in this instance as the key transformation, with several additional assets of the route being highlighted in **fig. 3.2**.

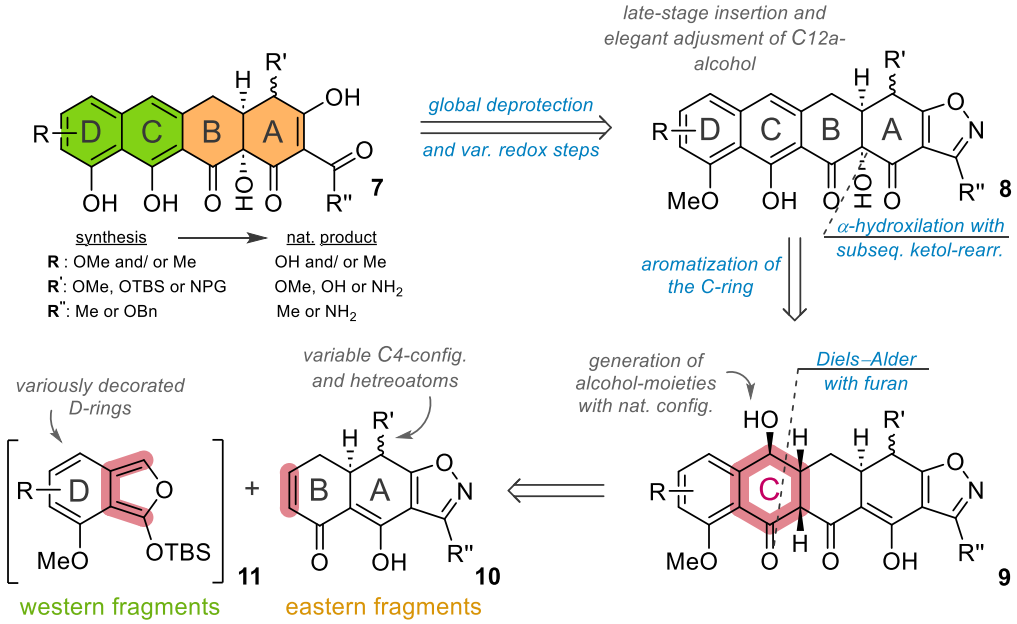


Fig. 3.2: Generalized retrosynthetic approach for accessing the targeted tetracycline natural products shown in **fig. 3.1**. The napthacene core is constructed *via* a Diels–Alder rection with furan between *in-situ* generated isobenzofurans **11** (i.e., the *western fragments*) and variously decorated decalin-enones **10** (i.e., the *eastern fragments*).

By using the strategy implemented by Stork in 1978 of utilizing isoxazoles as masking agents for 1,3-diketone functionalities,[64] the final decorations of the A-ring of the aimed natural products (**7**) arise from the hydrogenolytic cleavage of the isoxazole motif of **8**. Further, specific removals of additional protective groups, such as silyl- and methyl-ethers, required for the protection of alcohol and phenol functionalities are also to be cleaved during this final stage. Envisioning a late-stage derivatization of the *C*12a-position, the tertiary alcohol can be traced back to a direct α-hydroxylation of an aromatized precursor **9**. By typically employing bulky peroxides, this transformation is expected to yield the naturally (*S*)-configured alcohol in the cases of chromocyclin (**4**) and carbamido-chelocardin (**5**). On the other hand, for the preparation of the two premithramycinones **1** and **2**, as well as *epi*-chromocylin (**3**), the reaction is expected to yield an undesired, (*R*)-configured *C*12a-alcohol due to steric hinderance exerted by *C*4-positioned functionalities.

In order to overcome this potential impediment, an α-ketol-type rearrangement is envisioned for correcting the configuration of the *C*12a-alcohol. Nevertheless, the ability to generate both (*R*)- and (*S*)- configured tertiary alcohols at *C*12a represents an additional, noteworthy asset of the envisioned strategy in the context of accessing new tetracycline-derived compounds with bioactive potential.

Furthermore, since the advanced precursor **8** can be traced back to an architecture lacking the tertiary hydroxy-functionality, the preparation of *C*12a-deoxy-compounds is also enabled by the strategy.

Alternatively, by following the protocols proposed by Meyers et al. (*chapter 2.2.5.2*),[50,55] an early-stage derivatization strategy relying on the use of suitable *C*8a-hydroxylated eastern fragments can also be envisioned for accessing the aimed targets.

Finally, the advanced tetracyclines can be traced back to a reaction precursor **9**– the product of a [4+2]-cycloaddition between decalin-enones **10** and *in-situ* generated isobenzofurans **11**. By choosing the shown convergent approach, a high tunability of fragments **10** and **11** is enabled, fulfilling the premise of synthesizing the targeted tetracyclines *via* a common path.

4 Results and discussions

The following chapter comprises the synthetic efforts towards the aimed tetracycline targets shown previously in **fig. 3.1**. Regarding the close structural relationship of the compounds, and common synthetic approach envisioned for their preparation, the discussions concerning the synthesis of the aimed targets were grouped in three subchapters. Starting the discussion with the two aureolic acid biosynthetic precursors demethylpremithramycinone (**1**) and premithramycinone (**2**), the preparation of the *C*9-methylated homologue *epi*-chromocyclin (**3**) is also included in chapter 4.1, the synthesis of the three compounds relying on the use of common building blocks. Furthermore, since most synthetic efforts were originally directed towards the preparation of demethylpremithramycinone (**1**), the discussion of the strategies employed for the synthesis of this compound is mandatory in the introductory part of the chapter, providing valuable information and insights for future approaches. Following the extensive presentation of the efforts and strategies directed towards the total synthesis of tetracyclines **1**, **2** and **3**, chapter 4.2 provides insights on the efforts made in accessing the tetracycline-related natural product chromocyclin (**4**), with the (*R*)-configured *C*4-alcohol demanding a slightly modified approach compared to those employed for the previous targets. Lastly, initial trials aiming at the total synthesis of carbamidochelocardin (**5**) are presented under chapter 4.3, with two strategies for accessing the compound being proposed and investigated.

4.1 The premithramycinones and *epi*-chromocyclin

4.1.1 Retrosynthetic analysis

Reiterating the convergent retrosynthetic strategy shown in chapter 3, **fig. 4.1.1** highlights important disconnections for accessing the aimed tetracycline targets:

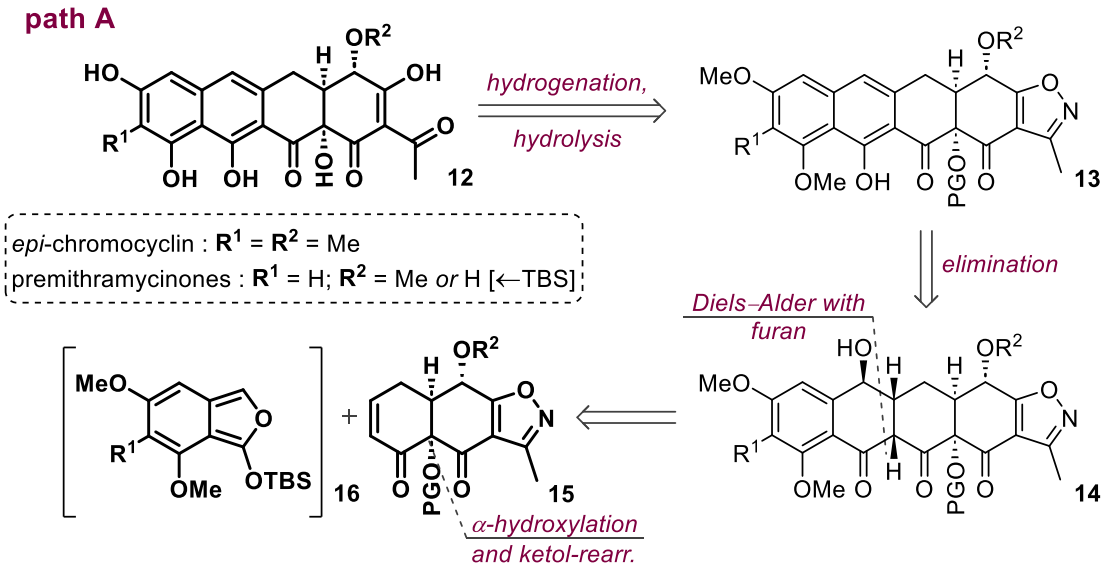


Fig. 4.1.1: Retrosynthetic disconnections for the construction of the tetracycline core (**path A**) in the common syntheses of demethylpremithramycinone (**1**: $R^1 = R^2 = H$ [←TBS]), premithramycinone (**2**: $R^1 = H$; $R^2 = Me$) and *epi*-chromocyclin (**3**: $R^1 = R^2 = Me$). The (*S*)-configured *C*12-alcohol is introduced prior to the [4+2]-cycloaddition in decalin **15**.

As it was highlighted in the previous discussion of the retrosynthetic strategy (*chapter 3*), the masked polar functionalities of the tetracycline backbone are to be released from an advanced pentacyclic precursor **13** during the final steps of the synthesis– the end-game. These transformations include the hydrogenolytic cleavage of the isoxazole motif, releasing the masked methyl ketone at the A-ring as well as the cleavage of the aryl-methyl-ethers at the D-ring, and the silyl ether at *C*4.
Further on, the aromatization of the C-ring of **13** conveniently arises from an elimination reaction from precursor **14**, the product of an *endo*-selective [4+2]-cycloaddition between an isobenzofuran **16**, formed *in-situ* from a corresponding phthalide (such as **20**) and decalin-enone **15**.
Contrary to the retrosynthetic approach discussed in chapter 3, which primarily envisioned a late-stage generation and adjustment of the tertiary alcohol at *C*12a, an initial early-stage functionalization strategy in which the alcohol moiety is introduced in the eastern fragment **15** prior to fragment-coupling was first proposed and exploited. This early-stage protocol (**path A**; shown in **fig. 4.1.1**) was inspired by various strategies proposed previously by Myers et al.,[50,55] with the generation of a suitable precursor **15** conveniently relying on a *C*8a-deoxy precursor **19**, one of the two key building blocks of **path B**– the late-stage *C*12a-derivatization strategy (**fig. 4.1.2**). The use of a common precursor conveniently bridges the two strategies together, allowing for alterations and adaptations at various stages of the synthesis.

Regarding **path B**, the aimed natural product targets demethylpremithramycinone (**1**), premithramycinone (**2**) and *epi*-chromocyclin (**3**) can be accessed, in analogy to **path A**, from an advanced pentacyclic intermediate **17** by following the global deprotection strategy described previously. In contrast to the early-stage derivatization strategy, however, through **path B**, the *C*12a-hydroxy functionality of the advanced intermediate **17** (a **13**-analogon) is to be generated prior to deprotection from deoxy-precursor **18**.

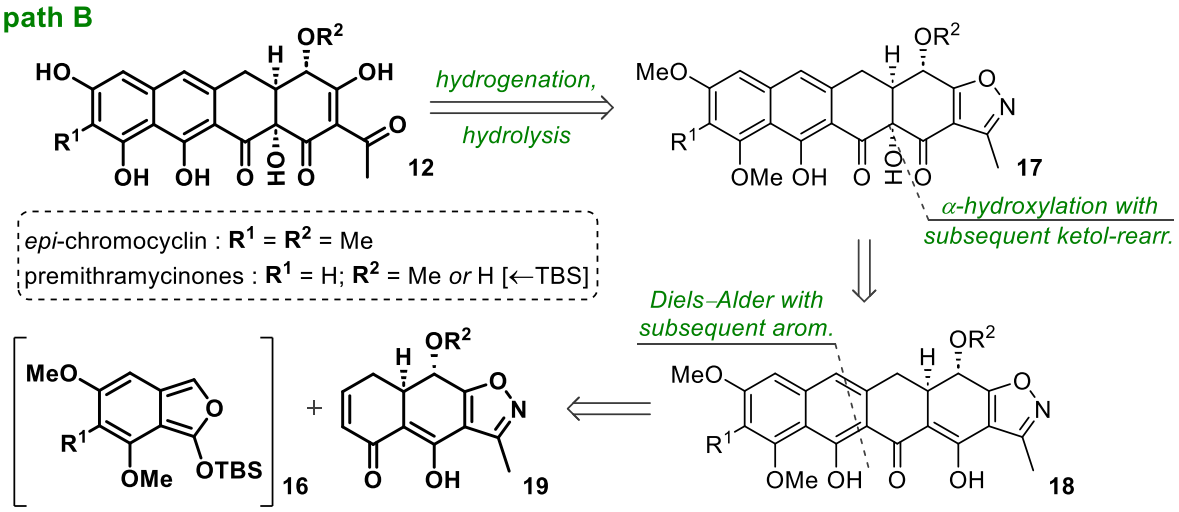


Fig. 4.1.2: Retrosynthetic disconnections for the construction of the naphthacene core (**path B**) in the syntheses of demethylpremithramycinone (**1**: $R^1 = R^2 = H$[←TBS]), premithramycinone (**2**: $R^1 = H$; $R^2 = Me$) and *epi*-chromocyclin (**3**: $R^1 = R^2 = Me$). In contrast to the previously proposed strategy, this route utilizes an *C*8a-deoxygenated eastern fragment **19**, with the generation of the tertiary alcohol moiety at *C*12a occurring in the late stages of the synthesis, prior to the global deprotection step.

Lastly, the generation of the characteristic tetracycline backbone of the targets can be traced back to a [4+2]-cycloaddition between an isobenzofuran **16** and a less advanced decalin precursor **19**, with the strategies aiming at their preparation being shown in **fig. 4.1.3**.

Starting with the retrosynthetic analysis of the less complex fragment required for the key [4+2]-cycloaddition step, the common strategy envisioned for the preparation of the highly reactive, *in-situ* formed isobenzofurans **16** is depicted in the upper part of **fig. 4.1.3**. Being formed directly *via* deprotonation and subsequent trapping of the formed enolates as silyl ethers, dienes **16** can be traced back to the highly stable phthalides **20**. By employing an intramolecular acylation reaction, phthalides **20** arise from the highly decorated aromatic precursors **21**, which can be easily accessed *via* bromination, followed by a simple carbonylation for the instalment of the carbamate moiety from the readily available benzyl alcohols **22**.

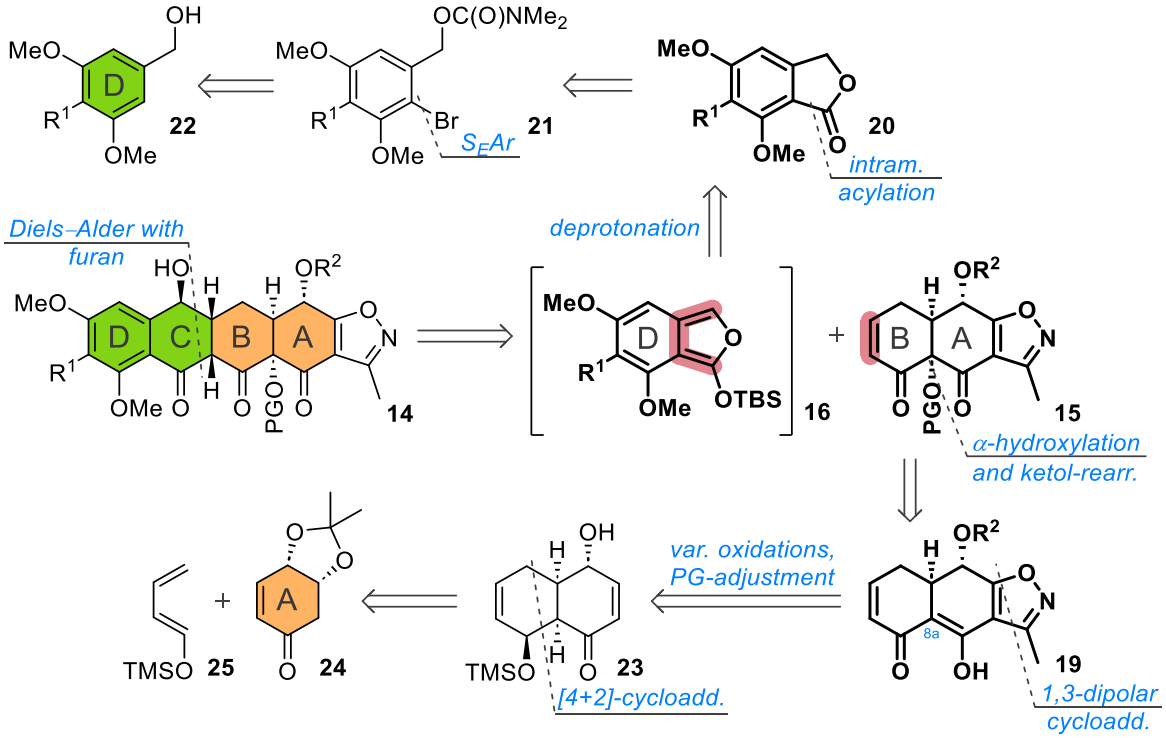


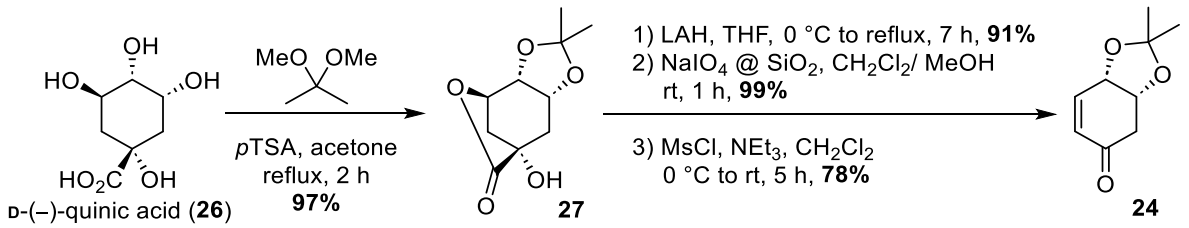
Fig. 4.1.3: Retrosynthetic considerations for accessing isobenzofurans **16**, and decalins **15** and **19** as suitable precursors in the envisioned Diels–Alder reaction with furan for the construction of the tetracycline skeleton. While **16** is generated *in-situ* from phthalide **20**, a building block accessed easily from commercially available benzyl alcohols **22**, the syntheses of decalins **15** and **19** demand slightly more elaborate approaches.

Finally, ketol **15**, required for the early-stage strategy, can be traced back to decalin **19**, a direct hydroxylation, followed by an α-ketol rearrangement being envisioned for its preparation. Originally proposed by Stork et al. in 1996,[51] the strategy of masking 1,3-diketo-functionalities at the tetracycline A-ring as isoxazoles rapidly gained popularity in the field of total synthesis of tetracycline natural products (*chapter 2.2.4*), the conveniency of the method leading to its implementation for this work. And while most of the reported protocols rely on the use of highly functionalized isoxazole building blocks, with the decalin skeleton being constructed *via* tandem Michael–Dieckmann type reactions around the heterocycle,[51,55] this work envisions an intermolecular 1,3-dipolar cycloaddition protocol for the generation of the isoxazole motif, with the transformation allowing for an elegant installation of the targeted architecture. Thus, the *C*8a-deoxy precursor **19** can be traced back to decalin **23**, the product of a Diels–Alder reaction between the literature-known enone **24** (conveniently accessed in four steps from D-(–)-quinic acid **26**)[65-67] and silyloxybutadiene **25**. The proposed [4+2]-cyclization strategy was inspired by the protocol employed by Tatsuta for the first total synthesis of (–)-tetracycline (*chapter 2.2.5.1*).[52]

4.1.2 Demethylpremithramycinone– path A

Beginning with the efforts directed towards accessing demethylpremithramycinone (**1**), the following chapter summarizes the protocols implemented for the preparation of the targeted compound *via* **path A**, providing an in-depth discussion on the utilized strategies and synthetic methodologies. An accurate description of the experiments as well as an extensive analysis of the isolated products are provided in chapter 6. **Path A**, through which the targeted tetracycline natural products are envisioned to be accessed *via* an early-stage generation of the challenging tertiary alcohol moiety at *C*12a, was proposed in accordance with known approaches,[55] with its initial exploitation providing valuable knowledge for future strategies and potential adaptations. Furthermore, while heavily relying on eastern fragment **41**, **path A** depends on the preparation of the *C*8a-deoxy building block **32**, with the derivatization of its *C*8a-position (later becoming the *C*12a-position in the tetracycline backbone), resulting in the formation of ketol **35** in two steps. In the eventuality that the envisioned protocol would not yield the desired outcome, *C*8a-deoxy precursor **32** could be used in the context of **path B**– the late-stage derivatization of the naphthacene backbone, the versatile use of the building blocks representing a strong asset of the proposed global approach.

As it was mentioned in the introductory part of the chapter, the envisioned linear, stereocontrolled preparation of enone **41** begins with four literature-known steps from the readily available D-(−)-quinic acid, a chiron with long-known applications in total syntheses of natural products.[63] The path leading to enone **24** is shown in **scheme 4.1.1**.



Scheme 4.1.1: Literature-known steps for accessing enone **24** from D-(−)-quinic acid (**26**).

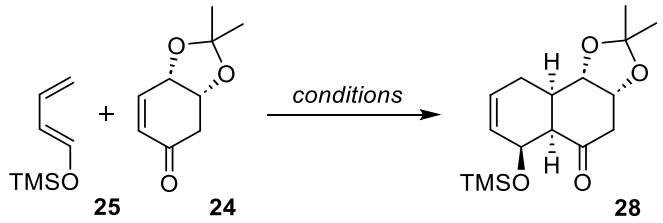
In the presence of 2,2-dimethoxypropane and catalytic amounts of *para*-toluenesulfonic acid, the *cis*-diol motif of D-(−)-quinic acid (**26**) was converted to the corresponding acetal, which serves as a protective group for future elaborations. Furthermore, under the given mildly acidic conditions, an esterification reaction conveniently allowed for the installation of a bridged, intramolecular ester in addition to the acetalization process. The synthesis of **27** was conducted in accordance with the protocol described by Kawashima et al., with the obtained yield of **97%** slightly exceeding the one originally reported by the authors.[65]

Further on, the three-step sequence used in the preparation of **24** relied on a LAH-mediated reduction of the previously installed ester to the corresponding primary alcohol, with the generated 1,2-diol being conveniently cleaved to the corresponding ketone in the second step *via* a periodate cleavage. Lastly, an elimination afforded enone **24**, the precursor of an initial Diels−Alder reaction. For the preparation of the target, literature-known methodologies[2] were employed, with a combined yield of **70%** being recorded and a single purification step being required to give the aimed building block on a multigram scale.

[2] Trost et al. (LAH-reduction),[66] Wang et al. (periodate cleavage)[67] and Kawashima et al. (elimination).[65]

With the successful preparation of enone **24** completed, the synthesis of **28**, the first decalin precursor of the route, was accomplished through a [4+2]-cycloaddition step between enone **24** and silyloxybutadiene **25**. For this, diene **25** was synthesized from crotonaldehyde in accordance with a protocol adapted after Böse et al.,[68] with the reaction successfully giving the aimed product in a moderate yield (**46%**). Upon the successful preparation of both diene **25** and enone **24**, the synthetic efforts were directed towards the preparation of the Diels–Alder cycloaddition product **28**, with several trials being conducted in order to establish suitable reaction conditions. Based on the implemented protocols, the trials shown in **tab. 1** can be divided into two categories: I) reactions performed at elevated temperatures (entries **I.** to **III.**), and II) reactions performed under high pressure (entries **IV.** and **V.**).

Tab. 1: [4+2]-cycloaddition between enone **24** and silyloxybutadiene **25** leading to the construction of decalin **28**: screenings for suitable conditions.



25 **24** **28**

entry	diene	solvent	conditions	time	outcome
I.	up to 3,0 equiv.	toluene (0,1 to 1,0M)	95 °C to 160 °C [69-71]	up to 48 h	mainly decomposition; **28** isolated in negligible yields (< **14%**)
II.	up to 3,0 equiv.	toluene (0,6M) *or* CH_2Cl_2 (0,1M)	–10 °C to 60 °C; with *or* without $ZnCl_2$ (1,5 equiv.) *or* $ZnBr_2$ (1,5 equiv.)	up to 72 h	no conversion
III.	up to 3,0 equiv.	toluene (0,1 to 1,0M)	95 °C to 160 °C [69]; with $ZnCl_2$ (1,5 equiv.) *or* $ZnBr_2$ (1,5 equiv.) [35,72]	up to 2 h	decomposition
IV.	up to 3,2 equiv.	CH_2Cl_2 (1,7M)	1,5 GPa; room temperature	up to 24 h	**28** (28-60%)
V.	up to 3,0 equiv.	THF (3,0 to 6,0M)	1,1 to 1,5 GPa; room temperature	up to 72 h	**28** (50-72%)

Aiming at a strategy analogous to the one proposed by Tatsuta et al.,[52,73] the preparation of decalin **28** was initially attempted by reacting enone **24** with diene **25** at high temperatures for prolonged times (entry **I.** in the optimization table). After these preliminary conditions only managed to give bicyclic product **28** in very poor yields, with elevated temperatures mainly leading to the decomposition of the starting materials, new strategies had to be screened in order to ensure smooth access to the desired building block.

Furthermore, the addition of electron scavengers, such as BHT, failed to improve the reaction outcome, the presence of the additives in the reaction matrix further contributing to the already difficult isolation of the product.

The use of various zinc salts as Lewis-acids was also exploited in accordance with existing literature,[35,72] with entries **II.** and **III.** of **tab.1** summarizing the investigated conditions and the reaction outcomes. As it is clearly shown, the strategy of LUMO-lowering[74] also failed to give the desired outcome, the treatment of the reaction with either anhydrous $ZnCl_2$, or anhydrous $ZnBr_2$ leading to no conversion when the reaction was performed at low or mild temperatures (entry **II.**). Elevated temperatures, on the other hand, led to a rapid decomposition of the starting materials (entry **III.**).

By exposing concentrated solutions of the two starting materials **24** and **25** in CH_2Cl_2 to pressures up to 1,5 GPa, conditions not unprecedented in the context of Diels–Alder reactions,[75,76] the formation of decalin **28** was initially observed in moderate yields of up to **60%** (entry **IV.**). Further optimizations of the reaction parameters, such as an increase in pressure and prolonged reaction times, ultimately gave diastereomerically pure product **28** in high yields (entry **V.**).[3] The formation of any additional reaction products was not observed.

Following the successful establishment of reliable reaction conditions, an extensive analysis of the isolated product was required, with its outcome leading to the irrefutable assignment of its structure to that of the desired decalin **28**. Relying on common NMR-experiments, the combination of both 1D- and 2D-spectra confidently allowed the assignment of the product architecture, with the spatial arrangement being confirmed by means of NOE-analysis. Representative NOE-contacts are highlighted in **fig. 4.1.4**. Furthermore, since decalin **28** was conveniently found to be the sole product of the Diels–Alder reaction, a brief mechanistic insight into its formation is also schematically highlighted in **fig. 4.1.4**, providing a rationale for the observed stereochemical outcome.

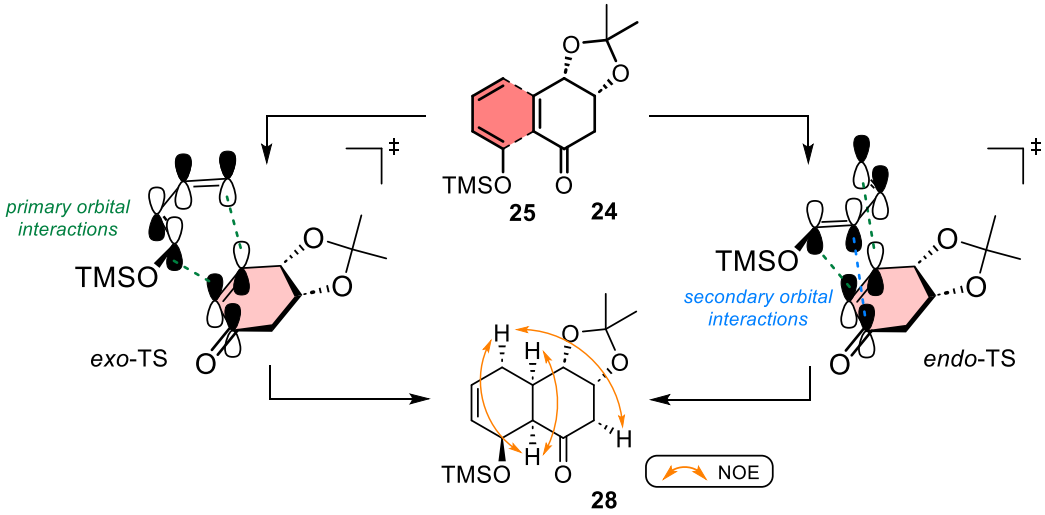


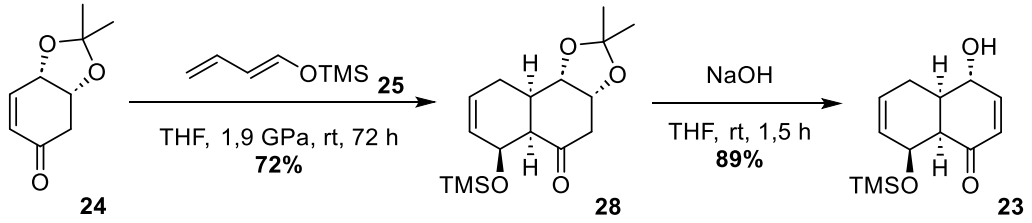
Fig. 4.1.4: Mechanistic considerations for the [4+2]-cycloaddition leading to the formation of decalin **28**, alongside representative NOE-contacts.

Proceeding *via* a concerted, stereospecific path, the Diels–Alder reaction represents a powerful tool for accessing variously decorated six-membered rings, its relevance for synthetic applications being constantly reasserted over the years. Furthermore, the ability to generate new stereogenic centers without relying on the use of chiral auxiliaries, or catalysts represents an additional asset of the reaction.[77]

[3] Entry **V.** indicates the highest recorded yield for the transformation. After several repetitions, however, a stable yield of **69%** was recorded.

For the formation of bicyclic product **28**, the employed [4+2]-cycloaddition between diene **25** and dienophile **24** resulted in the generation of three new stereocenters, the stereochemical outcome being solely driven by the architecture of enone **24**, with the paths leading to the formation of the product being shown in **fig. 4.1.4**. Located in the immediate proximity of the enone moiety, the bulky, acetal-protected *syn*-diol-functionality of **24** allows for the cycloaddition reaction to proceed only from one side, the process, regardless of *endo*- or *exo*-selective, leading to the formation of a single diastereomer. Nevertheless, the hypothetical transition states (TS) of both an *exo*- and *endo*-selective proceeding of the reaction are shown in **fig. 4.1.4**, the mechanistic considerations being in accordance with experimental observations.

Following the cycloaddition reaction, enone **28** was converted in one step *via* an elimination reaction to decalin **23** (**scheme 4.1.2**), a suitable substrate for an intermolecular 1,3-dipolar cycloaddition. Since the previously inserted acetal moiety serves as a leaving group in the elimination reaction, an additional deprotection step could be conveniently omitted.

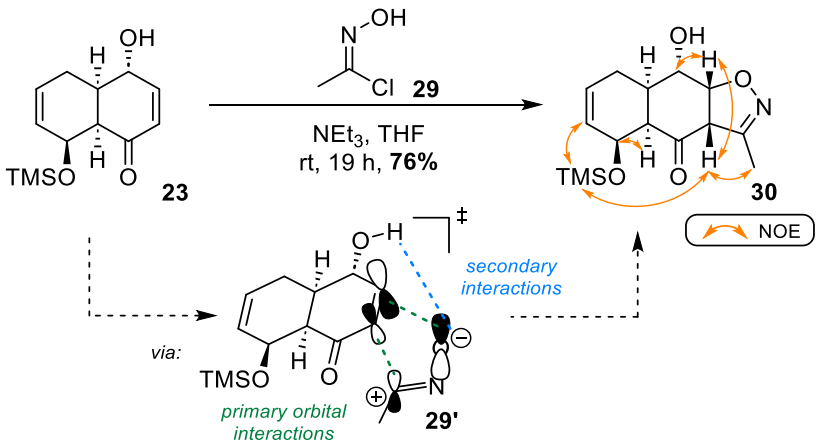


Scheme 4.1.2: A Diels–Alder reaction conveniently provides access to complex decalin **28**, which, upon treatment with aqueous base, affords enone **23**, a suitable precursor of an intermolecular 1,3-dipolar cycloaddition.

For the generation of the isoxazole motif as a 1,3-diktone equivalent at the future tetracycline A-ring, a Huisgen 1,3-dipolar cycloaddition with *in-situ* generated nitrile oxide (from **29**; **scheme 4.1.3**) was chosen in disregard of other protocols. By avoiding laborious multi-step syntheses of functionalized isoxazoles prior to the construction of the decalin moiety,[40,50,51,55] or the generation *via* complicated intramolecular cycloadditions,[62,78] the adaptation of this long-known and well-established strategy represents an elegant shortcut and a strong asset of the proposed route.
Despite strong indications that the generation of unstable chloro oximes as precursors to nitrile oxides could be detrimental for a successful reaction outcome,[79] a two-step protocol was nevertheless regarded for the [3+2]-cycloaddition step. For this, chloro oxime **29** was initially synthesized in accordance with the protocol described by Brown et al.[80] by treating an acetaldoxime-solution with NCS, with the use of DMF as a solvent inconveniently demanding an aqueous work-up step prior to the [3+2]-cycloaddition.[4] Furthermore, an additional drawback of the method was represented by the need to isolate concentrated solutions of **29**, since their spontaneous, violent decomposition was often encountered throughout synthesis. Therefore, an approach originally proposed by Hyls et al.[78] was adapted, becoming the method of choice for preparing reagent **29**. By performing the synthesis in CH_2Cl_2, a solvent compatible with the cycloaddition step, the freshly prepared reagent could be directly used for the following transformation, making the need for an aqueous work-up as well as the handling of potentially explosive precursors fully obsolete. The presence of *N*-hydroxysuccinimide in the reaction matrix was not found to influence the outcome of the cycloaddition step in any way.

[4] A full description of the reaction conditions is provided in chapter 6.2.1.5.1.

With a reliable protocol for accessing chloro oxime **29** established, the envisioned [3+2]-cycloaddition with precursor **23** as the dipolarophile proceeded smoothly in the presence of NEt_3 as a base.[81] Isoxazoline-bearing tricycle **30** was thus isolated as the sole product, the reaction proceeding with a yield of **76%**. The formation of any undesired regio- or diastereomers was not observed.



Scheme 4.1.3: An intermolecular [3+2]-cycloaddition between enone **23** and an *in-situ* generated nitrile oxide (**29**→**29'**) affords the isoxazoline motif of tricyclic precursor **30**.

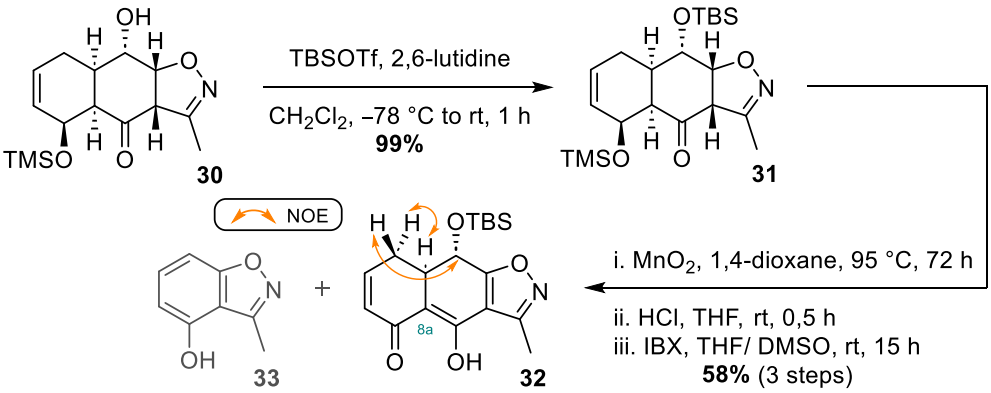
Proceeding in a concerted manner, the stereospecific 1,3-dipolar cycloaddition is an orbital symmetry-driven process, the outcome of which depends on both steric and electronic factors.[80] Therefore, the reaction often proceeds with the formation of product-mixtures, with experimentally observed regio- and diastereoselectivities being at times in contradiction with theoretic predictions (based on frontier orbital theory).[82]

Highlighted in **scheme 4.1.3** are the interactions that underly the formation of tricycle **30**, the product of a [3+2]-cycloaddition between enone **23** (i.e., the dipolarophile) and the *in-situ* generated acetonitrile oxide **29'**– an ambiphilic dipole. In analogy to the observations made by Adembri et al.[83] during their preparation of several isoxazolines *via* a regio- and diastereoselective 1,3-dipolar cycloaddition between nitril oxides and 2-cyclopenten-1-ones, the secondary alcohol at *C*4 is considered to play a crucial role in the stereochemical outcome of the reactions. Favoring the approach of the 1,3-dipole from the convex back-side through polar, secondary interactions (hydrogen bond formation), the *C*4-alcohol moiety ensures a strong diastereofacial selectivity in the formation of a concave-convex-arranged reaction product **30**. Furthermore, by tethering the dipole, the *C*4-alcohol is considered to play a crucial role in ensuring the regioselective proceeding of the process. And while the diastereoselectivity of the process is not of particular interest for future transformations, since the newly generated stereocenters are being annulled in the upcoming aromatization step, the selective formation of a single product ensures the smooth proceeding of the synthesis.

In order to generate the envisioned isoxazole motif from the corresponding isoxazoline, an additional oxidation step had to be performed. Since the required conditions for this step might have led to an undesired oxidation of the secondary alcohol at *C*4, the protection of the group was required. Initially, the TBS-protection of alcohol **30** was performed by using TBSCl as a silylation agent, alongside DMAP, and imidazole as a base. However, the protocol shown in **scheme 4.1.4** was found to be superior in giving precursor **31**, thus setting the stage for the isoxazoline oxidation.

While several oxidative aromatization methods for the preparation of isoxazoles from the corresponding isoxazolines are reported in literature, many relying on reagents such as DDQ[84] or I_2,[85] the use of MnO_2 as an oxidant seems to predominate in most instances, the advantages of the reagent being represented by its low toxicity as well as the eased handling of both reaction set- and

work-up.[5] By following a protocol described by Takikawa et al.,[86] the generation of the targeted aromatic heterocycle was conveniently achieved from precursor **31** by using MnO_2 as an oxidizer (**scheme 4.1.4**). The obtained reaction product was then quickly converted further towards the *C*8a-deoxy eastern fragment **32**.[6]



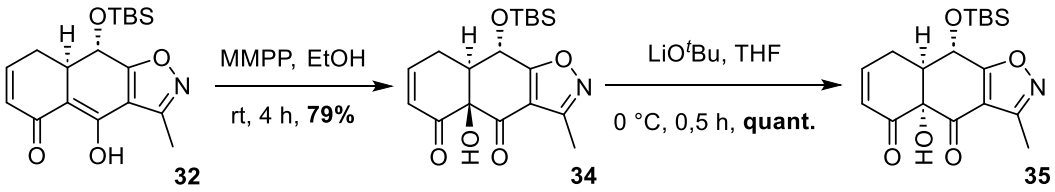
Scheme 4.1.4: Formation of the *C*8a-deoxy product **32**– a valuable precursor in both paths envisioned for accessing demethylpremithramycinone (**1**).

*C*8a-deoxy enone **32**– the first valuable precursor in the synthesis of dimethylpremithramycinone (**1**), was finally prepared in two straight-forward steps by following the sequence depicted in **scheme 4.1.4** (steps ii. and iii.). While the TMS-protection group was selectively cleaved under mild, acidic conditions, a subsequent IBX-mediated oxidation of the allylic alcohol allowed the installation of the enone moiety. The three-step process proceeded with a combined yield of **58%**, the drawback being represented by the aromatization of the isoxazoline moiety.
Thus, fragment **32** was prepared from D-(–)-quinic acid on a multigram scale over eleven linear steps, with the combined yield of the seven original steps employed for its synthesis lying at **28%**.

In the end, the generation of ketol **35**– the crucial building block of **path A**, was achieved in two steps, starting from the *C*8a-deoxy-precursor **32** (**scheme 4.1.5**). For the construction of the highly functionalized precursor, bearing the characteristic decorations of the A/B-ring systems of the future tetracycline natural product target **1**, the *C*8a-positioned tertiary alcohol was introduced *via* a direct α-hydroxylation approach (formation of **34**). By employing a protocol relying on the use of MMPP as a mild oxidizer to the detriment of other methods, such as those described by Nicolaou (use of DMDO with a catalytic amount of $[Ni(acac)_2]$),[40] Kummer (use of Davis' oxaziridine),[55] Morimitsu (IBX),[87] or Elkin (*m*CPBA),[88] diastereomerically pure ketol **34** could be easily accessed from vinylogous acid **32**. The obtained yield of **79%** represents an unprecedented achievement, with similar transformations performed in the context of tetracycline total syntheses on substrates similar to enone **32**, proceeding with notably poorer outcomes.[55,88,89]

[5] Based on result-counts generated by common chemistry-database search engines.

[6] While the proposed sequence gave reliable results in most instances, at times, an isoxazoline-bearing reaction product **64** (*chapter 4.1.4*; **scheme 4.1.11**) was also isolated alongside enone **32**. Aromatization trials of **64** were attempted by the already described means or by performing the oxidation under milder conditions in chlorobenzene at 80 °C. Isoxazole **33** was obtained instead of the desired product **32**, with an elimination-*retro*–Diels–Alder path presumably underlying its formation.



Scheme 4.1.5: Two-step synthesis of ketol **35** from deoxy-precursor **32**. An α-ketol rearrangement furnishes the desired (*S*)-configuration of the newly introduced tertiary alcohol.

Relying on mechanistic considerations[7] and in accordance with experimental observations made by the Nicolaou- and Myers-laboratories during their efforts to access various tetracyclines and derivatives thereof,[40,55] the newly constructed stereocenter at *C*8a is postulated to bear an undesired (*R*)-configuration; an additional equilibration step is required for its stereochemical adjustment.

Originally reported in 1895 by the dutch chemists L. de Bruyn and A. Ekenstein,[90] the α-ketol rearrangement (also known as the acyloin rearrangement) is defined as a concerted [1,2]-alkyl shift induced primarily in tertiary ketols either by bases, Brønsted- and Lewis-acids or heat.[91,92] Despite its long history and versatile applicability, the ketol-rearrangement remains largely unused for synthetic purposes, with recently developed methodologies partly failing to highlight the true potential of the reaction.[93,94] Nevertheless, the ketol rearrangement has found, over time, some applications in the field of steroid synthesis, being, in analogy to metabolic processes, employed primarily as D-ring expansion-strategies (D-homoannulation) in 17-hydroxy-20-keto steroids.[95-97] In this case, however, a base-catalyzed α-ketol rearrangement[98] was employed for the adjustment of the *C*8a stereocenter, with the underlying mechanism of the process being highlighted in **fig. 4.1.5**.

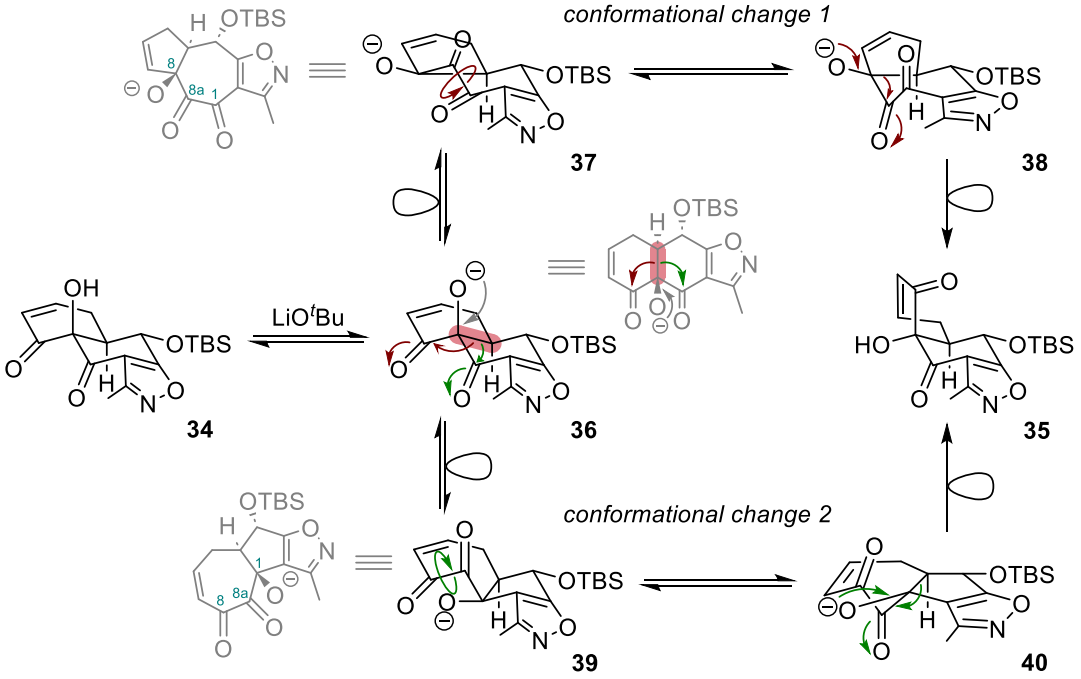


Fig. 4.1.5: Proposed mechanism underlying the formation of ketol **35** *via* an α-ketol rearrangement.

[7] By employing the bulky peroxy acid MMPP for the hydroxylation, the introduction of the new functionality at *C*8a is expected to proceed antiperiplanar to the sterically demanding (*S*)-configured silyloxy moiety at *C*4.

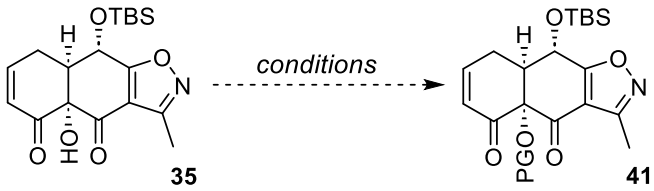
Under the action of catalytic amounts of LiO^{t}Bu, an α-ketol rearrangement can be triggered in **34** by first deprotonating the tertiary alcohol to form the corresponding alkoxide-species **36**. The alkoxide then readily rearranges to give either intermediate **37**, bearing an annulated 5/7/5-tricyclic skeleton or species **39**, bearing a 7/5/5-tricyclic architecture. Both paths are considered equally plausible. Through a careful conformational analysis of intermediates **37** and **39**, the highly unfavored dipole repulsions caused by the *syn*-oriented oxygen atoms at *C*1 and *C*8 become evident. In order to minimize these interactions, a conformational change sets it, with intermediates **38** and **40**, in which the oxygen atoms are now *anti*-oriented, arising from the process. The structural adjustment represents the driving force of the reaction, being also responsible for its irreversible character.[99] In addition, a second, irreversible ketol rearrangement refurnishes the initial decalin skeleton, with product **35**, bearing the desired, otherwise thermodynamically less-favored, *cis*-decalin motif, being obtained with a remarkable yield.

In lieu of crystallographic data, a proper crystallization of the material not being achieved in the course of the experimental work, NMR-spectroscopic data were used for an accurate structure-determination instead. While the recorded chemical shifts of both products **34** and **35** differ only slightly, a strong indication of the successful outcome of the reaction lies in the chemical shifts of the *C*8a-atoms. Recorded at 75,4 ppm ($CDCl_3$; a full signal-assignment is given in chapter 6.2.1.8), the *C*8a-atom of ketol **34** experiences a low-field shift after performing the rearrangement towards **35**, with the newly recorded value for *C*8a lying at 79,6 ppm ($CDCl_3$; full data-set in chapter 6.2.1.8). These observations were found to be largely in accordance with the experimental data provided by the literature.[55]

Considering the outcome of the analyses performed for both ketols **34** and **35**, the results being comparable with those provided by trustworthy sources, the synthesis towards eastern fragment **41** was pursued *via* the initially envisioned path, with a successful total synthetic preparation of the targeted tetracycline **1** remaining to establish the validity of the assumptions regarding the configuration of the two epimers.

In order to access an eastern fragment **41** suitable for the Diels–Alder key step, the alcohol moiety of the previously formed ketol **35** had to be masked with a suitable protection group, its presence doubtlessly perturbing the smooth proceeding of the reaction. For this, several trials with various silylation agents were carried out, with their outcome being summarized in **tab. 2**.

Tab. 2: Screenings for suitable protective groups in the synthesis of eastern fragment **41**.



entry	reagent(s)	solvent	temperature	time	outcome
I.	TMSCl/ imidazole/ DMAP	CH_2Cl_2	0 °C to 45 °C	18 h	no conversion
II.	TBSOTf/ 2,6-lutidine	CH_2Cl_2	–78 °C	1 h	decomposition
III.	MOMBr/ DIPEA[100]	CH_2Cl_2	0 °C to 45 °C	15 h	no conversion
IV.	MEMCl/ NaH	THF	0 °C to 65 °C	4 h	no conversion

As it is clearly indicated by the first entry in the table, the utilized conditions for the envisioned TMS-protection failed to give any outcome; the use of DMAP and elevated temperatures, along with

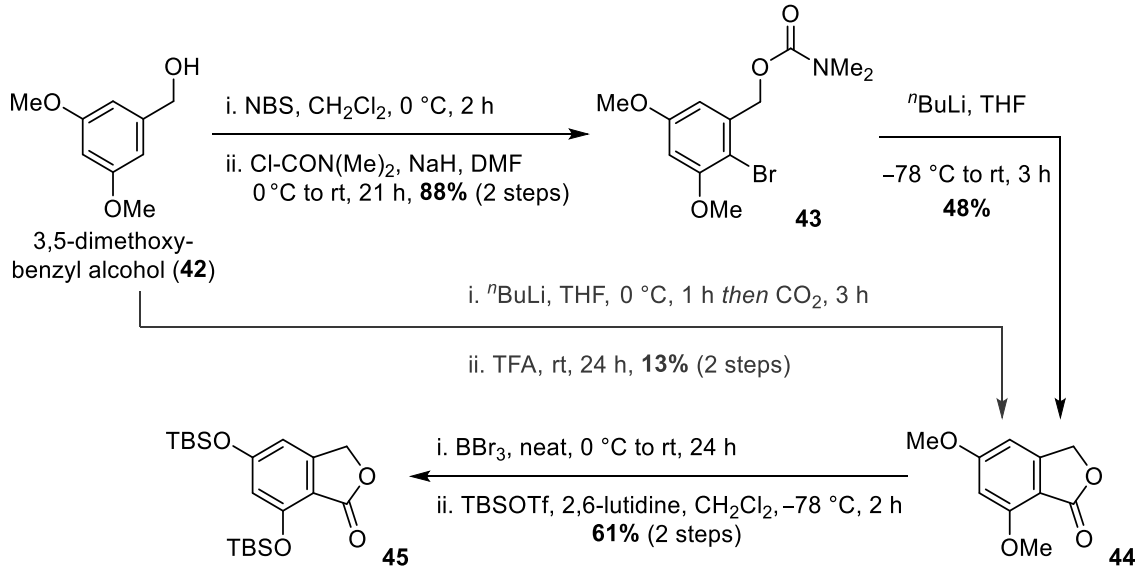
prolonged reaction times failed to contribute to a successful product formation. As a result, the more reactive TBSOTf was considered for derivatizing the *C*8a-alcohol (entry **II.**). The use of the highly reactive reagent led, however, to the decomposition of the starting material. Lastly, two more trials to protect the tertiary alcohol were conducted, with the used reagents and conditions highlighted under entries **III.** and **IV.**.

After the derivatization attempts to form the corresponding acetals also failed to yield favorable results, as the sterically demanding TBSO-functionality at *C*4 was presumably prohibiting the introduction of another bulky group into the system, the underlying route (**path A**) was abandoned. Thus, the way was pawed for the secondly proposed approach– the late-stage derivatization strategy. Nevertheless, by exploring the possibility of generating decalin **41**– an advanced precursor bearing the entirety of the decorations present at the tetracyclines A- and B-rings early on, valuable information for future syntheses could be collected, especially regarding the generation and manipulation of the challenging tertiary alcohol functionality.

4.1.3 Demethylpremithramycinone – path B

After the previously described path of accessing enone **41** failed to provide the desired outcome, **path B** was considered for accessing the targeted tetracycline natural product **1**, with a thorough discussion of the retrosynthesis being provided under chapter 4.1.1.
By planning to access the hydroxy-functionality at tetracyclines *C*12a-position later in the synthesis, **path B** conveniently relies on deoxy-enone **32** as the eastern fragment, with the previously exploited methodologies for the insertion and adjustment of the tertiary alcohol being highly relevant for the completion of the task.

With the synthesis of the eastern fragment **32** accomplished, the remaining task prior to the envisioned Diels–Alder reaction with furan was represented by the generation of phthalide **44** (i.e., the western fragment). By following a straight-forward approach and employing both original and literature-known strategies, the synthesis of the target was completed in accordance with the path shown in **scheme 4.1.6**. An initial protocol, originally proposed by Clarke et al.,[101] which failed to provide reliable access to **44**, is also shown alongside the successful strategy.



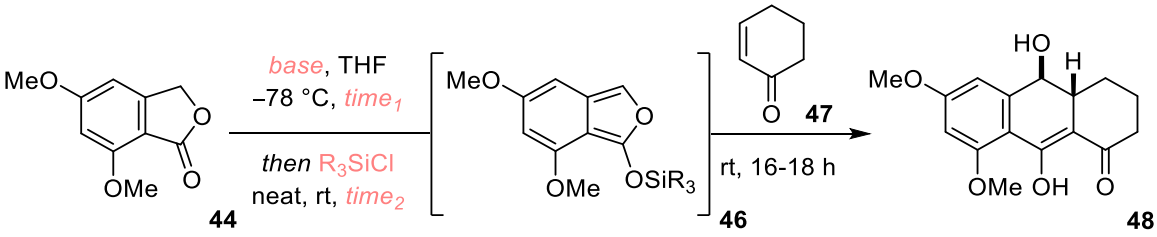
Scheme 4.1.6: Synthesis of phthalides **44** and **45** from 3,5-dimthoxybenzyl alcohol (**42**).

Attempting to reproduce the results published by Clarke et al.,[101] an initial batch of roughly 8,0 mmol of alcohol **42** was converted in accordance with the described procedures, giving product **44** in a very poor yield (**13%**). A scale-up attempt (approx. 30 mmol **42**) resulted in the exclusive formation of the undesired 4-substituted acid with a **54%** yield. Slight modifications of the approach, consisting mainly of using LiCl as an additive,[34] and/ or enhanced electrophiles such as methyl chloroformate or (*N*,*N*)-dimethylcarbamoyl chloride, also failed to give any satisfactory results. Therefore, a second approach was envisioned for accessing the target.

By also relying on the use of 3,5-dimethoxybenzyl alcohol (**42**) as a starting material, phthalide **44** was conveniently prepared in three linear steps with an overall yield of **42%**. In contrast to the previously investigated strategy, the second approach highlighted in **scheme 4.1.6** relies on a Li-base-mediated intramolecular acylation of known precursor **43** (synthesis adapted after Yamagami et al.[102]). In order to facilitate the lithiation step, the *ortho*-position of benzyl alcohol **42** was first brominated (following the protocol reported by Wright et al.[103]) prior to the generation of the carbamate moiety. While the installed carbamate smoothly allowed for the successful generation of phthalide **44**, the methyl carbonate counterpart failed to undergo cyclization when subjected to similar reaction conditions. In this instance, the reaction led to the formation of a complex product mixture, which was not further analyzed. Furthermore, the use of the stronger ^{t}BuLi as a base in the generation of product **44** did not manage to provide a higher yield than by using ^{n}BuLi. Lastly, in the eventuality of an unsuccessful cleavage of the methyl ether protection groups during the last phase of the synthesis, the Me-ether functionalities were cleaved by using BBr_3 and exchanged with the slightly more labile TBS-groups. Phthalide **45** was thus obtained in two steps with a moderate yield (**61%**).

After successfully completing the synthesis of both fragments **32** (i.e., the *eastern fragment*) and **44** (i.e., the *western fragment*), the synthetic focus was directed towards the coupling of the two building blocks. With most of the recently published tetracycline total syntheses relying on a Michael–Dieckmann cascade for addressing the naphthacene core (*chapter 2.2.5*), a Diels–Alder reaction with furan was envisioned in this instance for constructing the aimed tetracycline backbone, the transformation representing the key step of the envisioned strategy.
Despite never being successfully implemented for the construction of tetracycline natural products, the proposed Diels–Alder reaction with furan cannot be considered fully unprecedented in the given context. After successfully implementing the aforementioned transformation in their 1995 published total synthesis of dynemicin A,[104,105] a late account from the Myers laboratory describes the potential use of the reaction for the construction of tetracycline architectures during an initial screening trial.[54] However, being confronted with poor yields and selectivities for the investigated model reaction, the group quickly abandoned the strategy, shifting their focus towards the optimization of the now well-known Michael–Dieckmann approach.[55] Nevertheless, the construction of the targeted tetracycline natural products shown in chapter 3 was pursued *via* the Diels–Alder path, with the cycloaddition reaction aiming at the coupling of enone **32** with an *in-situ* generated isobenzofuran **46**. Herein, a reliable generation and immediate conversion of the highly reactive furan species were of crucial importance. Thus, the derivatization and handling of phthalide **44** was initially proposed in agreement with Gaich et al.[106] And while the authors reported a high degree of stability for a TIPS-protected isobenzofuran intermediate bearing similar structural features to **46**,[106] the isolation of such an architecture has proven impossible in this instance. Furthermore, since the generation of enone **32** has proven to be quite laborious, a model reaction was formulated and several conditions were screened before performing the reaction with the actual fragments. For this, commercially available 2-cyclohexen-1-one (**47**) was chosen as a dienophile and reacted with phthalide **44**, which was previously prepared on a multigram scale. The results of the screenings are summarized in **tab. 3**.

Tab. 3: Diels–Alder reaction with furan between phthalide **44** and 2-cyclohexen-1-one (**47**) as a model-substrate: screenings for suitable conditions. 1,1 equiv. of phthalide **44** were used.



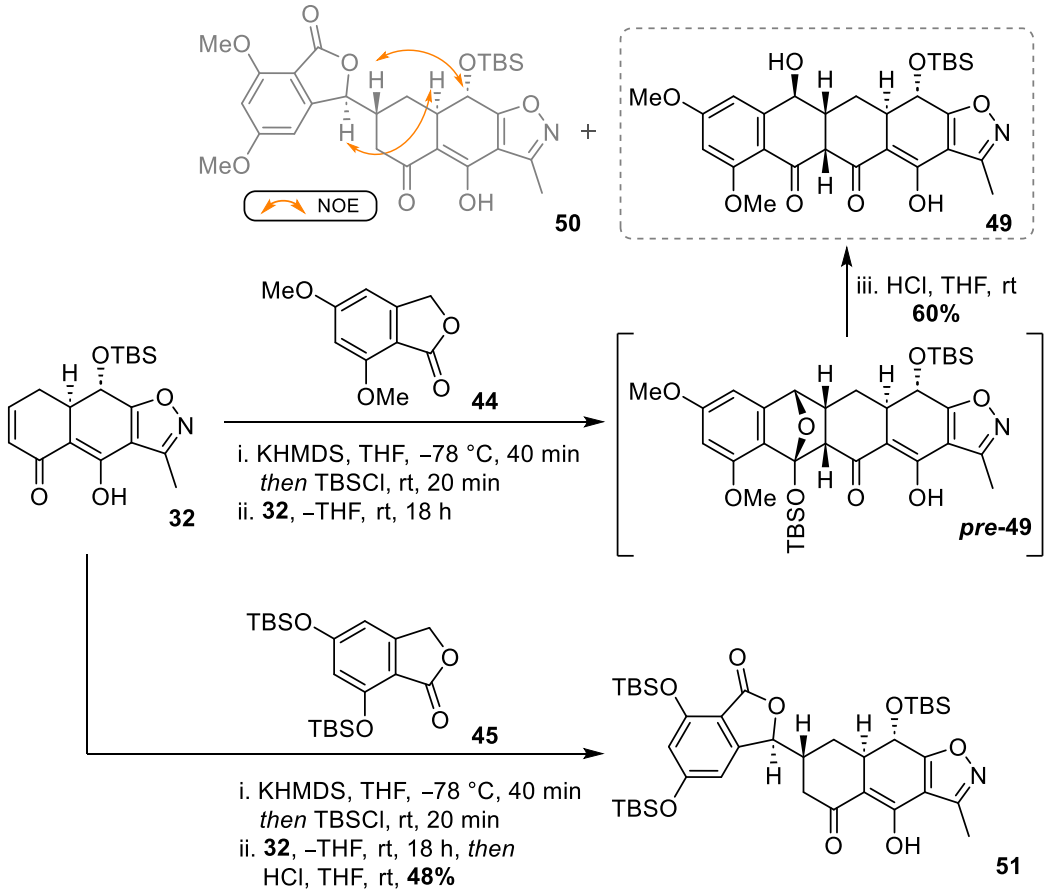
entry	base	time$_1$ [min.]	R$_3$SiCl	time$_2$ [min.]	conc.	outcome
Ia.	^{i}Pr$_2$NH (0,55 equiv.) and MeLi (2,80 equiv.)	50	TMSCl (1,40 equiv.)	30	0,7M	*Michael-addition* (**45%**)
Ib.	^{i}Pr$_2$NH (0,55 equiv.) and MeLi (2,80 equiv.)	50	TBSCl (1,40 equiv.)	30	0,7M	**no reaction**
Ic.	^{i}Pr$_2$NH (0,55 equiv.) and MeLi (2,80 equiv.)	50	TESCl (1,40 equiv.)	30	0,7M	**48** (traces)
II.	NaHMDS (1,30-1,70 equiv.)	30	TBSCl (up to 1,70 equiv.)	20	>2,0 M	**no conversion**
IIIa.	KHMDS (1,70 equiv.)	40	TMSCl (1,70 equiv.)	20	>2,0 M	**no conversion**
IIIb.	KHMDS (1,90 equiv.)	40	TBSCl (1,80 equiv.)	20	>2,0 M	**48** (**48%**)

The main focus points during the screening trials fell mainly on two aspects: I) an efficient deprotonation of phthalide **44** and II) trapping the generated enolate with various silyl-protection groups. The later precaution was considered, since, according to Tobia and Rickborn, the direct use of highly labile lithium-enolates in the context of cycloadditions is associated with low yields and the potential formation of undesirable side products.[107] By establishing proper conditions for the generation of furan **46**, the cycloaddition step towards tricycle **48** was expected to proceed in an *endo*-selective fashion.[106,108] Therefore, the entries presented in **tab. 3** can be grouped into two distinctive categories in accordance with I) and II). Firstly, attempts relying on the use of LDA[107,109,110] as a base for the deprotonation of **44** are highlighted under **Ia.-Ic.**, the protocol being primarily inspired by the one utilized by Roush et al. in their stereoselective total synthesis of (+)-olivin, the aglycon of olivomycin A– an aureolic acid.[37] In contrast to the methodology proposed by the authors, the generated highly reactive litihiated species was trapped in this instance with various silylating agents. While the use of the bulky TESCl (entry **Ic.**) and TBSCl (entry **Ib.**) failed to provide any outcome, the use of TMSCl only managed to promote the Michael-addition between **46-TMS** and enone **47** (product structure in analogy to **50** and **51**; **scheme 4.1.7**), with the desired [4+2]-cycloaddition failing to set in, presumably due to an insufficient concentration of the reaction medium (see further).

Lastly, several trials relying on the use of HMDS-bases were considered and investigated. By adapting the conditions implemented by Gaich et al. for their *endo*-selective Diels–Alder reaction with furan,[106] deprotonation of phthalide **44** was initially attempted by using NaHMDS as a base and TBSCl as a trapping agent (entry **II.**). The conditions, however, failed in providing the desired outcome. By changing the base for the stronger KHMDS, a successful outcome was achieved in combination with TBSCl as a trapping agent (entry **IIIb.**), with TMSCl (entry **iiia.**) failing to promote the reaction.

At this point, it is mandatory to highlight the importance of ensuring a concentrated reaction medium while performing the cycloaddition step, the formation of a Michael-addition product (structure in analogy to **50** and **51**) being otherwise encountered.[8] Furthermore, the complete removal of the solvent (THF) from the deprotonation step prior to cycloaddition has represented a drawback, with the intended transformation failing to set in. Performing the Diels–Alder reaction under concentrated conditions in CH_2Cl_2 also failed to yield the desired outcome, a slow decomposition of the two reaction partners being observed instead.

By subjecting phthalide **44** and enone **32** to the previously established conditions, the first precursor of the route bearing the characteristic naphthacene core (**49**; **scheme 4.1.7**) could be successfully prepared.



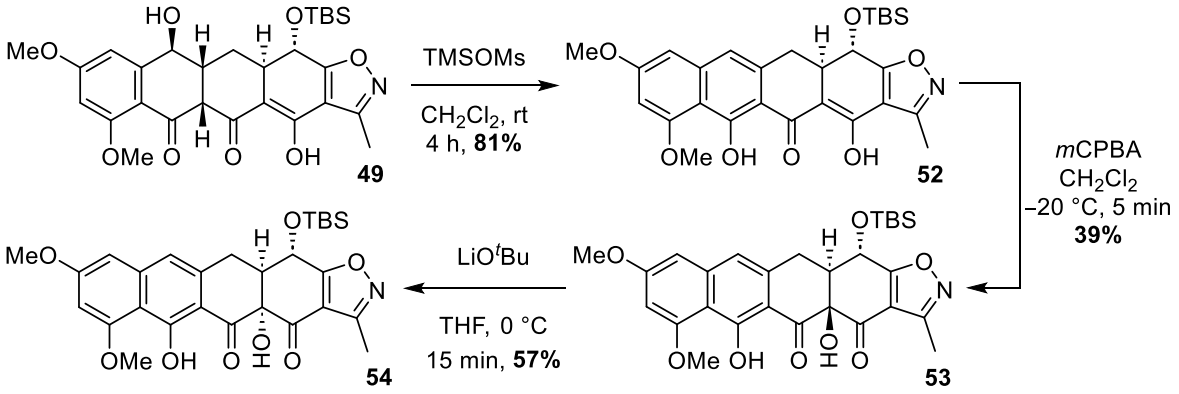
Scheme 4.1.7: A Diels–Alder reaction with furan between enone **32** and phthalide **44** conveniently furnished the highly functionalized tetracycline core of demethylpremithramycinone (**1**).

[8] Initially, the protocol used for the Diels–Alder reaction required an inert filtration of the *in-situ* prepared diene **46-TBS**. However, over time, this step was omitted without affecting the outcome of the reaction. It is also important to emphasize that the addition of the enone must be performed prior to the concentration step.

In spite of recent accounts,[106] the isolation and characterization of cycloaddition product **pre-49** was not attempted due to stability concerns. Therefore, in order to maintain the integrity of the newly constructed architecture by preventing unspecific degradations from setting in, the isolated product was quickly converted to precursor **49** under the action of dilute acid. Thus, diastereomerically pure pentacycle **49** was obtained in most instances as the sole reaction product. The formation of the 1,4-addition product **50** (traces) was observed on several occasions, presumably as a result of an insufficient concentration of the reaction or the decomposition of product **pre-49**. Moreover, due to stability concerns, the structure of product **49** was ascertained by means of 1D- and 2D-NMR-analyses, with lengthy NOE-spectra not being measured. Nevertheless, the structure of **49** was postulated in accordance with the theoretically expected outcome of an *endo*-selective Diels–Alder reaction and in analogy to published observations.[106-108] Extensive analyses performed on more stable architectures, like those of **65** (**scheme 4.1.12**) and **76** (**scheme 4.1.18**), also support this premise.

Since the generation of a *di*-TBS-protected phthalide **45** was successfully completed previously, a [4+2]-cycloaddition was performed with enone **32** by the established means, with the reaction yielding in this instance only the 1,4-addition product **51**. A conversion of the isolated material towards the corresponding pentacycle by treating it with KHMDS failed to provide any outcome at all.[55] Screenings of suitable bases or reaction conditions were not further investigated.

With the preparation of precursor **49** completed, a series of linear transformations (**scheme 4.1.8**) had to be carried out to provide access to the targeted tetracycline natural product **1**.
At first, the aromatization of the C-ring was achieved *via* an elimination reaction by adapting a protocol published by Roush et al.[37] The employed transformation proceeded smoothly in giving the advanced reaction intermediate **52** with an **81%** yield.



Scheme 4.1.8: Synthesis of the advanced intermediate **54** in the late-stage derivatization strategy of accessing demethylpremithramycinone (**1**). Starting from precursor **49**, the tertiary alcohol at *C*12a is generated and adjusted in analogy to previously established protocols.

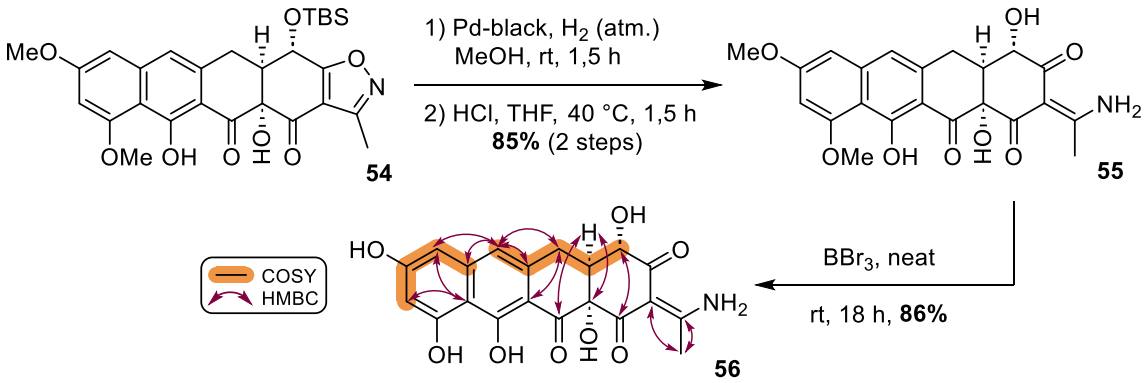
In contrast to **path A** (*chapter 4.1.2*), the late-stage derivatization strategy of generating and adjusting the tertiary alcohol at *C*12a was carried out from the deoxy-compound **52** by the means shown in **scheme 4.1.5**. Therefore, the synthesis of ketol **53** was originally aimed at *via* a direct hydroxylation with MMPP. However, while the synthesis of ketol **34** (**scheme 4.1.5**) proceeded smoothly by this means, the advanced ketol **53** could only be obtained after treating precursor **52** with *m*CPBA, the very short reaction-time being crucial in achieving reproducible results. Thus, the α-hydroxylation of **52** was successfully completed with a moderate yield of **39%**, with the outcome being comparable with previously reported ones for similar architectures.[88] Furthermore, ketol **53** could be purified only by means of RP-HPLC; any other chromatographic method would lead to its decomposition.

In addition to the protocols relying on MMPP and *m*CPBA, the conversion of vinylogues acid **52** towards ketol **53** was also attempted by treating the educt with a mixture of H_2O_2 and K_2CO_3, with the conditions failing to yield a favorable outcome.

Nevertheless, the presumably undesired configuration of the *C*12a-alcohol of ketol **53** was inverted as initially envisioned *via* an α-ketol rearrangement, with the conditions established previously in the synthesis of decalin **35** (**scheme 4.1.5**) being exploited for completing this task.

The conversion of the more demanding tetracycline-derived **53** proceeded, in contrast to decalin **35**, only with a moderate yield of **57%**. Furthermore, since the transformation only requires the use of a catalytic amount of LiO^{t}Bu, the presence of the acidic phenol at *C*11 demanded the use of an increased amount of base (1,3 equiv.) in order to initiate the rearrangement. In analogy to compounds **34** and **35** (**scheme 4.1.5**), an accurate and irrefutable determination of the absolute configuration of ketols **53** and **54** has proven to be difficult by spectrometric and spectroscopic means. Nevertheless, the observed low-field shift of the *C*12a-signal after performing the rearrangement[9] reinforced the assumptions made previously (*chapter 4.1.2*) towards the absolute configuration of the two ketols, with the completion of the synthesis remaining to ultimately prove these beliefs.

Lastly, after successfully generating the required decorations at the tetracycline core, the global deprotection of the previously installed protective groups was attempted by following the path shown in **scheme 4.1.5**. In accordance with numerous accounts reported in the literature (see further), the isoxazole moiety of **54** was conveniently cleaved under hydrogenation conditions with Pd-black, with the mild conditions ensuring a smooth cleavage of the heterocycle. The obtained product was then subjected to acid-hydrolysis, with the used conditions supposedly ensuring both the cleavage of the silyl group as well as the hydrolysis of the previously generated enamine functionality to the corresponding ketone. Unfortunately, while the protocol has proven to be successful in achieving the cleavage of the TBS-group, the conversion of the enamine functionality at *C*2 to the corresponding methyl ketone failed to set in (forming product **55**), thus initiating a lengthy quest to establish proper conditions for achieving this transformation. Since this elaborate investigation did not lead to a successful outcome and in order to maintain a clear overview of the route towards the targeted natural product, the trials for achieving the required enamine-hydrolysis were summarized in **tab. 5** and will be discussed later in this chapter.[10]



Scheme 4.1.9: Global deprotection strategy in the synthesis of demethylpremithramycinone (**1**). While the hydrogenolytic cleavage of isoxazole **54** was successful, the resulted enamine **55** failed to undergo hydrolysis to the corresponding methyl ketone functionality.

[9] 79,8 ppm for **54**, from an initial 76,3 ppm for **53**; spectra recorded in $CDCl_3$; peak-listings under *6.2.3*.

[10] The order in which the hydrogenation of the isoxazole and the hydrolysis of the TBS-ether are performed is obsolete. By following the indicated order, however, products with higher purity could be obtained.

Since numerous trials of accessing the methyl ketone functionality failed to give the desired outcome, the cleavage of the methyl-ethers at *C*8 and *C*10 was carried out with the obtained product **55**. After an initial demethylation trial with BBr_3 in CH_2Cl_2 [111] failed to give the desired outcome, a series of protocols were investigated in order to find suitable conditions for completing the transformation. Since the advanced tetracycline precursor **55** was too valuable, and the prepared amounts were highly limited, phthalide **44** was used instead for the screening trials.

Methyl-ether cleavage of **44** was initially attempted with BCl_3 in accordance with the protocols described by Carvaho et al.[70] and Génot et al.[71], with the methods failing in removing the protection groups. Further unsuccessful attempts relied on the use of either EtSNa[112-115] or Ph_2PLi[116,117] as dealkylating agents. However, these methods also led in most instances to a rapid degradation of the substrate. Attempts in accordance with the protocol described by Cao et al.[118], who proposed the use of $BF_3{\cdot}OEt_2$, alongside NaI for achieving the *O*-demethylation of various substrates, including alkyl ethers, also remained unsuccessful.

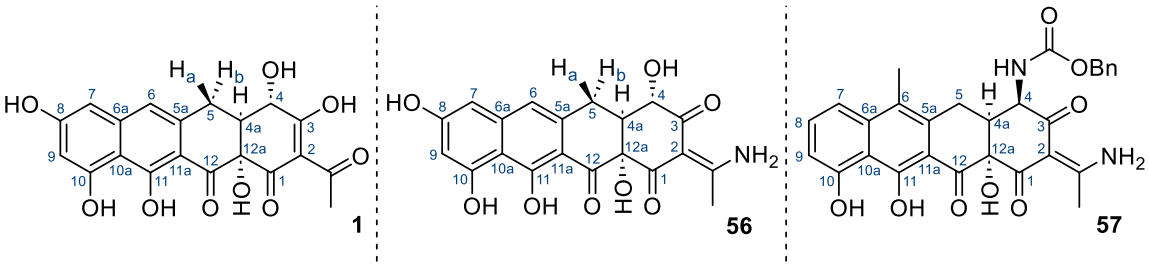
Finally, after slight adjustments were carried out, the initially performed BBr_3-protocol managed to successfully provide *O*-demethylation of **44**, with the adaptations mainly consisting of elevating the amount of reagent used (approx. 8,0 equiv./ MeO-group) and dissolving the starting material directly in the reagent-solution. Changes in temperature did not seem to affect the outcome of the reaction.

With the proper conditions established, the preparation of dimedone enamine **56** was successfully accomplished from precursor **55** with an **86%** yield. The isolated product also failed to undergo hydrolysis towards the desired methyl ketone.

Thus, the synthesis of **56**, the enamine-analogue of demethylpremithramycinone (**1**), was successfully completed by the envisioned late derivatization strategy (**path B**), with the eight steps required for its preparation from the two fragments **32** and **44** proceeding with a combined yield of **8%**. And while the architecture of product **56** lacks the methyl ketone side chain at *C*2, most of the recorded ^{1}H- and ^{13}C-shifts seem to be in accordance with those reported for the natural product (**tab. 4.1** and **4.2**),[16] this observation validating the previously made assumptions concerning the outcome of the ketol-rearrangement required for the stereo adjustment of the *C*12a-positioned alcohol.

Tab. 4.1: ^{1}H-NMR shifts of naturally occurring demethylpremithramycinone (**1**; 400 MHz, CD_3OD)[18] and synthetic dimedone enamine **56** (400 MHz, CD_3OD).

atom	1: δ [ppm]	56: δ [ppm]	atom	1: δ [ppm]	56: δ [ppm]
CH_3	2,65 (s)	2,57 (s)	**5-Hb**	3,46 (br. d, *J* = 16 Hz)	3,47 (dd, *J* = 16,7, 4,4 Hz)
4	4,00 (br. d,*J* = 11 Hz)	3,98 (d, *J* = 11,7 Hz)	**6**	6,89 (s)	6,88 (s)
4a	2,50 (m)	2,49–2,54 (m)	**7**	6,52 (d, *J* = 2 Hz)	6,51 (d, *J* = 2,1 Hz)
5-Ha	3,19 (br. d, *J* = 16 Hz)	3,23 (m)	**9**	6,33 (d, *J* = 2 Hz)	6,32 (d, *J* = 2,1 Hz)



Scheme 4.1.10: Structures of demethylpremithramycinone (**1**), dimedone enamine **56** and 2'-amino-*N*-carbobenzoxychelocardin (**57**) with the characteristic *C*-atom-labeling.

Tab. 4.2: ^{13}C-NMR shifts of naturally occurring demethylpremithramycinone (**1**) (100,6 MHz, CD_3OD)[18] and dimedone enamine **56** (151,0 MHz, CD_3OD), along with representative ^{13}C-shifts of 2'-amino-*N*-carbobenzoxychelocardin (**57**)[11] (CD_3OD).[119]

atom	1: δ [ppm]	56: δ [ppm]	57: δ [ppm]	atom	1: δ [ppm]	56: δ [ppm]
CH_3	30,7	24,3	23,8	6a	143,3	143,3
C=O / C–NH_2	203,6	177,8	174,7	7	103,6	103,3
1	196,7	197,1	190,0	8	163,9	163,6
2	111,6	105,5	105,0	9	102,8	102,5
3	167,4	193,7	192,1	10	161,0	161,2
4	70,0	71,8	-	10a	108,1	108,1
4a	46,6	46,2	-	11	163,8	167,5
5	26,7	27,0	-	11a	107,9	108,3
5a	135,5	135,9	-	12	197,6	198,5
6	119,0	118,6	-	**12a**	78,9	78,2

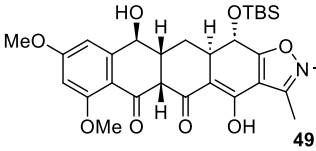
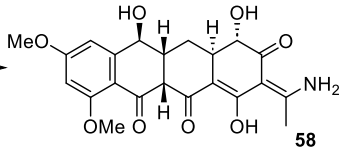
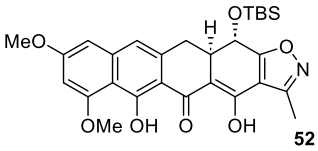
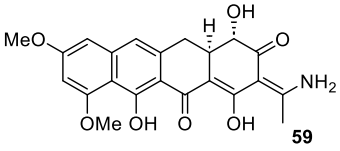
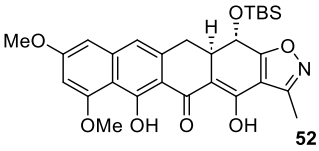
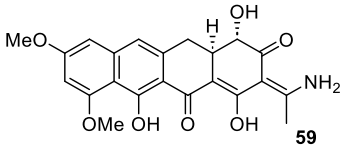
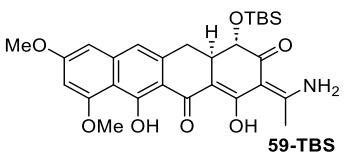
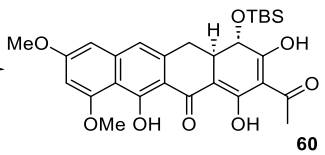
Considering the structural differences between natural product **1** and enamine **56**, a perfect NMR signal overlap cannot be expected, yet the comparison of the recorded shifts (**tab. 4.1** and **4.2**) provides strong evidence for the successful generation of the aimed naphthacene skeleton, along with its characteristic decorations. While the ^{1}H-signals of **56** seem to correspond to those reported by Rohr et al. (with the omission of the polar protons),[18] the *C*-atoms in the south-east region of the molecule (*C*1-3 and 12a) unsurprisingly differ significantly from those of the natural product. Nevertheless, upon accurately assigning all signals to the corresponding atoms, the representative shifts were also compared, in addition to the natural product **1**, with those reported by Chu et al. (**tab. 4.2**)[119] for synthetic 2'-amino-*N*-carbobenzoxychelocardin (**57**; **scheme 4.1.10**). The strong overlap of the recorded ^{13}C-NMR shifts with those reported by the authors for the south-eastern region of dimedone enamine **57** further supports the observations made during this work.

In spite of the numerous trials directed towards its preparation, the originally targeted natural product **1** could not be accessed during the time span of this work, with the synthetic efforts being ultimately halted. **Table 5** comprises various strategies for accessing the desired methyl ketone functionality at *C*2 both directly from various isoxazole-bearing tetracycline precursors (entries **III. a.-c.**, **IV.** and **V. b.-c.**), as well as attempts to hydrolyze isolable dimedone enamines upon hydrogenolytic cleavage of the corresponding isoxazole motifs. In most instances, these attempts were performed in accordance with reported protocols, relying primarily on the use of either acids (entries **I.**, **II.**, **V. a.**, **VI. a.**), base (entry **VI. c.**), or, in some instances, various NO_2^--sources (entries **III. d.** and **VI. b.**). While the trials relying on the use of base or nitrite almost always led to a rapid degradation of the used substrates, most of the trials performed under the action of variously concentrated mineral or organic acids failed to give any outcome at all, with the cleavage of the TBS-ether being recorded on several occasions instead. The addition of $CuCl_2$ to the reaction mixtures also failed to provide a favorable outcome.[120]

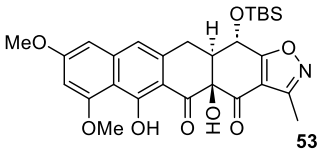
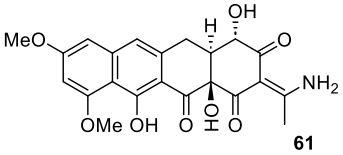
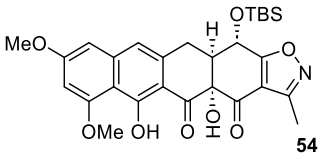
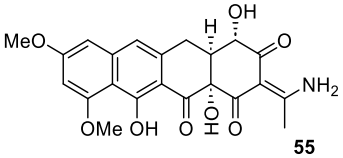
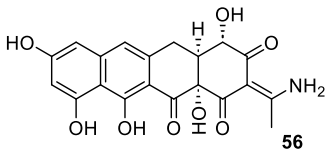
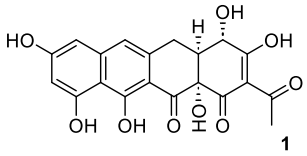
Reductive conditions, such as those summarized under entries **III. b.** (partly using nascent hydrogen for the cleavage of the heterocycles), **III. c.**, and **IV.** (relying on a SET-protocol initiated by SmI_2), even though largely successful in achieving the scission of various isoxazole motifs, have also proven to be unsuccessful in generating the desired methyl ketone at the A-ring, with the isolated materials bearing the enamine functionality instead.

[11] The spectrometer frequency was not reported by the authors.
Only the characteristic shifts of the southeast region of the molecule were reported.

Tab. 5: Screenings for suitable conditions for the *C*2-methyl ketone generation.

entry	substrate	conditions	outcome
I.	 **49**	*i. Pd-black/ H_2, MeOH, rt, 1,5 h* [20] ii. HCl (conc.), MeOH, 50 °C >**75%**; 2 steps	 **58**
II.	 **52**	*i. Pd-black/ H_2, MeOH, rt, 1,5 h* ii. see below	 **59**
	ii. HCl (up to 12M), MeOH *or* THF *or* neat, up to 90 °C, up to 18 h [121] **<86%** (2 steps)		
	ii. AcOH (20 equiv.), MeCN, rt, up to 18 h (no yield determination)		
	ii. oxalic acid (10 wt%, 20 equiv.) EtOH, rt, up to 18 h [122] (no yield determination)		
	ii. $CuCl_2$ (1,5 equiv.), MeCN, rt, 18 h [120] **59-TBS** (no yield determination)		
III.	 **52**	see below	 **59**
a.	Ra-Ni/ H_2, $B(OH)_3$ (5,0 equiv.) *or* HCl (1M), MeOH, rt, 1 h [123,124] **decomposition**		
	Pd-black/ H_2, $B(OH)_3$ (5,0 equiv.) *or* HCl (1M), THF, rt, 1 h **59** and **59-TBS** (>**90%**)		
	Pd-black/ H_2, $CuCl_2$ (1,5 equiv.), THF, rt, 1 h **no reaction**		
b.	Zn-dust, AcOH (1M-solution), rt, 18 h [125] **59-TBS** (>**90%**; with traces of **59**)		
	Zn-dust, HCl (1M), THF, rt, 18 h **59-TBS** (>**90%**; with traces of **59**)		
	Fe-dust, NH_4Cl (4,0 equiv.), THF, rt, 18 h [126] **59-TBS** (<**90%**; with traces of **59**)		
	[Mo(cht)$(CO)_3$] (0,5 equiv.), HCl (1M, 1,5 equiv.), THF/ H_2O 70 °C, 18 h,[127-129] primary decomposition and **59-TBS** (traces)		
	Al-dust, $CuCl_2$-solution (1M), rt, 2 h [129] **no conversion**		
c.	O_3, CH_2Cl_2/ MeOH, −78 °C, 10 min **decomposition**		
	SmI_2, THF, −78 °C, 20 min [130] **decomposition**		
d.	 **59-TBS**	^{t}BuNO$_2$ (3,0 equiv.), DMSO *then* TFA (5,0 equiv.) [108] 0 °C, 2 h **decomposition**	 **60**

Tab. 5: Screenings for suitable conditions for the *C*2-methyl ketone generation. (*continuation*)

entry	substrate	conditions	outcome
IV.	 **53**	SmI_2, THF, –78 °C, 20 min **primarily decomposition** (**73** in traces)	 **61**
V.	 **54**	see below	 **55**
a.	*i. Pd-black/ H_2, MeOH, rt, 1,5 h* ii. HCl (up to 6,0M), THF, *or* neat, up to 90 °C and 6 h up to **85%** (2 steps)		
b.	Pd-black/ H_2, $B(OH)_3$ (5,0 equiv.), THF, rt, 1 h **55-TBS** and **55** (traces) (no yield determination)		
c.	O_3, CH_2Cl_2/ MeOH, –78 °C, 10 min **unclear outcome** (southeastern region unassignable *via* NMR-analysis)		
VI.	 **56**	see below	 **1**
a.	*p*TSA (210 equiv.), MeOH, rt, 72 h **no reaction**		
b.	$NaNO_2$ (3,0 equiv.), HCl (1M, 5,0 equiv.), MeCN, -20 °C, 20 min **decomposition**		
c.	Cs_2CO_3, MeOH/ THF/ H_2O, 65 °C, 1 h [131] **decomposition**		

Ozonolysis (entry **III. c.**) of the isoxazole-bearing precursor **52** was also attempted in close analogy to the method proposed by Kozikowski et al. of accessing β-hydroxyketones *via* the cleavage of isoxazolines.[132] However, despite the promising premise, decomposition was observed shortly after the material was exposed to the mentioned conditions, with the fast degradation of the vinylogues acid being presumably responsible for the unsuccessful outcome of the reaction.[133] When subjected to ozonolytic conditions, precursor **54** (entry **V. c.**), lacking the vinylogous acid motif, underwent full conversion; the structure of the isolated material remained, however, unelucidated. While the newly synthesized compound bore some of the characteristic features of the tetracycline core, an accurate assignment of the ^{1}H- and ^{13}C-NMR-signals of the southeast region of the molecule was not possible. Furthermore, spectrometric analyses have also proven futile in providing clarity on the issue, with the recorded mass clearly indicating the presence of a nitrogen atom in the molecule. Considering the unclear outcome, the strategy was eventually abandoned.

After failing to generate the required methyl ketone functionality of the targeted tetracycline natural product **1**, the late-stage derivatization strategy was ultimately abandoned and a last adaptation of the path pursued (**path B'**; *chapter 4.1.4*). Nevertheless, the exploration of this strategy undoubtedly provided valuable insights for future efforts to access tetracycline natural products, with the successful late-stage generation of the *C*12a-positioned alcohol representing one of its key assets.

4.1.4 Demethylpremithramycinone – path B'

Finally, the last subchapter concerning the total synthesis of demethylpremithramycinone (**1**) comprises the efforts made by following a slightly modified approach to that presented previously in chapter 4.1.3. The underlying retrosynthetic strategy is highlighted in **fig. 4.1.6**.
In contrast to the previously explored path, **path B'** relies on the use of an isoxazoline motif to mask the diketone functionality at the A-ring. Thus, an additional *C*3-alcohol oxidation would be required in order to furnish the required structural feature of natural product **1** from an advanced precursor **62**. Tetracycline **62** can be traced back to a pentacyclic isoxazoline-bearing precursor **63**, with the reductive cleavage of the heterocycle unveiling the β-hydroxy ketone motif at the A-ring.[134,135]

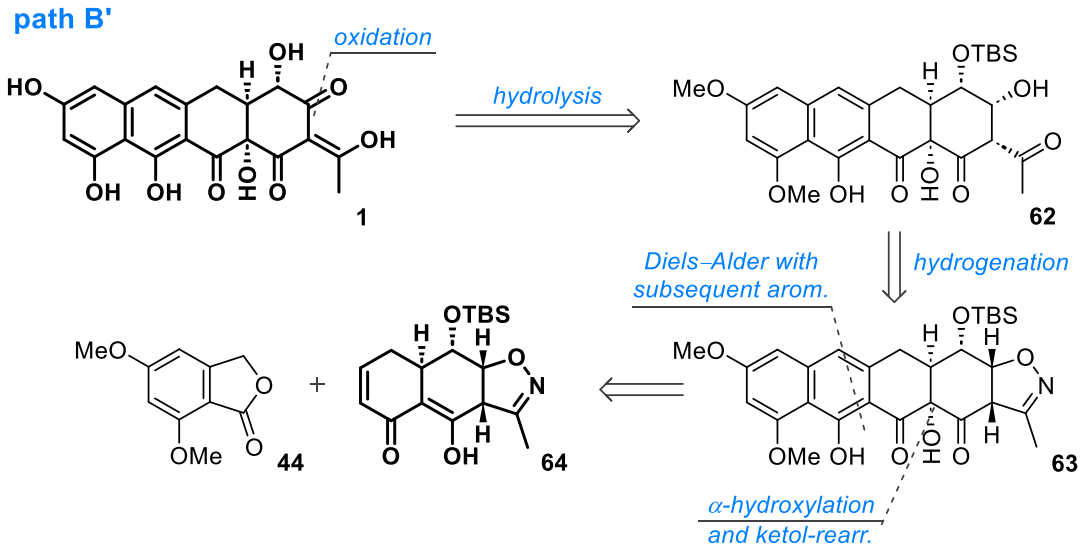
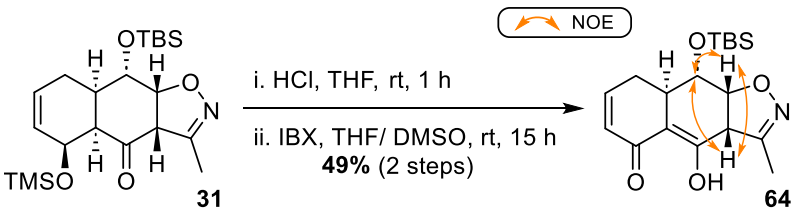


Fig. 4.1.6: Modified route for the accessing demethylpremithramycinone (**1**). In order to overcome previously encountered difficulties (i.e., the unsuccessful enamine hydrolysis), the modified enone **64** was implemented for the construction of the naphthacene core.

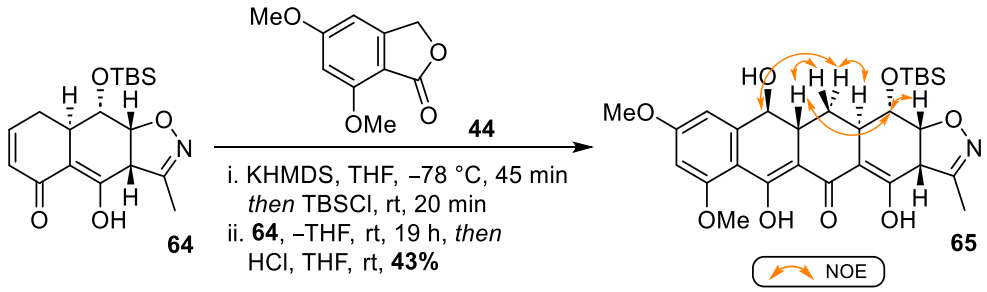
In analogy to the previously explored path, the modified approach also relies on a late-stage derivatization of the *C*12a-position, with the generation of the tertiary alcohol of precursor **63** being envisioned in accordance with already established protocols (*chapter 4.1.3*). Furthermore, the generation of the characteristic architecture of the natural product is also envisioned to proceed in analogy to the previous strategy *via* a Diels–Alder reaction with furan between phthalide **44** and enone **64**– an easily accessible precursor from decalin **31** (**scheme 4.1.11**).



Scheme 4.1.11: Two-step synthesis of enone **64** from the already prepared precursor **31**.

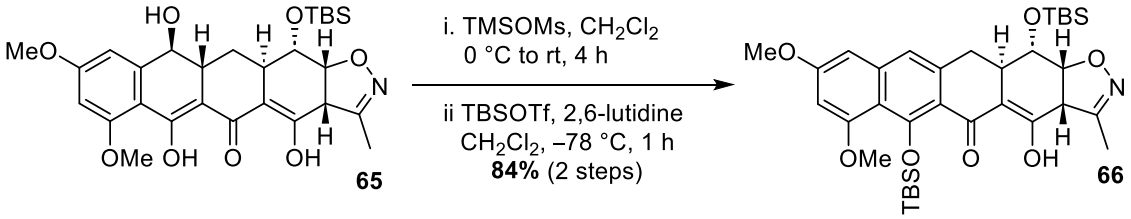
By omitting the isoxazoline aromatization prior to silyl ether cleavage and oxidation of the thus resulting allylic alcohol to the corresponding enone, *C*8a-deoxy eastern fragment **64** was conveniently prepared in two steps from decalin precursor **31**. The sequence proceeded smoothly, with a satisfactory

yield of **49%**. The newly prepared enone **64** conveniently underwent [4+2]-cycloaddition with phthalide **44** under previously explored conditions (**scheme 4.1.12**).



Scheme 4.1.12: Construction of the first tetracycline precursor in the modified path towards demethylpremithramycinone (**1**). Pentacycle **65** was isolated as the sole reaction product of an *endo*-selective Diels–Alder reaction with furan between enone **64** and phthalide **44**.

While the determination of the absolute configuration of the previously prepared homologue **49** (**scheme 4.1.7**) could not be performed due to stability concerns, the structure of cycloaddition product **65** could be accurately determined by means of NOE-analysis. By establishing the absolute configuration of the newly generated stereocenters, the *endo*-selective proceeding of the reaction could be irrefutably proven. Upon successfully generating the characteristic tetracycline skeleton *via* the [4+2]-cycloaddition, the synthesis was pursued in agreement with the previously established protocols (**scheme 4.1.13**).

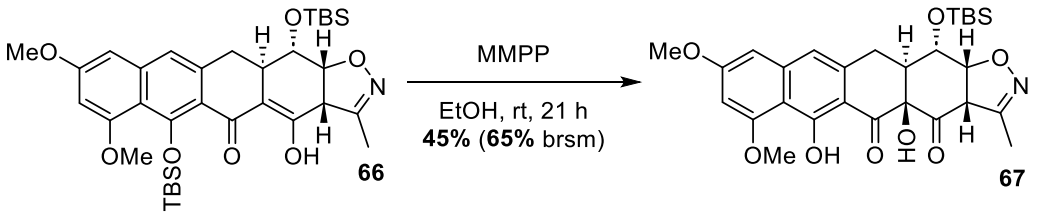


Scheme 4.1.13: C-ring-aromatization of pentacycle **65** during the synthesis of demethylpremithramycinone (**1**)

At first, the aromatization of the C-ring was carried out *via* a TMSOMs-assisted elimination in precursor **65**; the transformation was expected to proceed similarly to that reported in chapter 4.1.3 (**scheme 4.1.13**). Spectrometric analysis[12] of the crude determined, however, that the obtained product was lacking the silyl-protection group, possibly due to an acidification of the reaction mixture through methanesulfonic acid. A previously unanticipated reprotection step had to be therefore carried out with the obtained aromatized material, *di*-TBS-protected precursor **66**, being thus obtained in two steps with an excellent yield of **84%**.

Proceeding towards the newly envisioned *end-game* strategy, the final derivatization of the tetracycline architecture– the generation of the alcohol at *C*12a, was attempted by following the conditions highlighted in **scheme 4.1.14**. Interestingly, while the synthesis of precursor **53** was achieved by oxidizing **52** with *m*CPBA, the protocol failed to give the expected outcome when applied to the synthesis of **67**. In this instance, the conditions led to a rapid decomposition of the starting material. Therefore, the insertion of the OH-functionality was achieved instead through an MMPP-oxidation, the reaction proceeding with a **45%** yield.

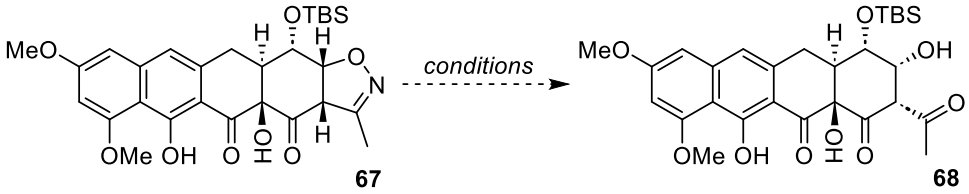
[12] HR-ESI-MS; m/z = 548,2075 for $[C_{28}H_{35}NO_7SiNa]^+$,
found m/z = 434,1214 ($[C_{22}H_{21}NO_7Na]^+$; calc. m/z = 434,1210)



Scheme 4.1.14: An MMPP-mediated oxidation conveniently allows for the installation of the *C*12a-alcohol in tetracycline precursor **66**.

With the installation of the *C*12a-alcohol successfully completed, initial trials towards the cleavage of the isoxazole moiety were carried out with the obtained product **67**, with the results being summarized in **tab. 6**. Since ketol **67** was initially produced in small amounts, in order to determine the viability of the newly proposed strategy, the cleavage of the heterocycle was attempted prior to the stereoadjustment of the newly introduced tertiary alcohol.

Tab. 6: Isoxazoline-cleavage attempts in the modified approach towards demethylpremithramycinone (**1**).[13]

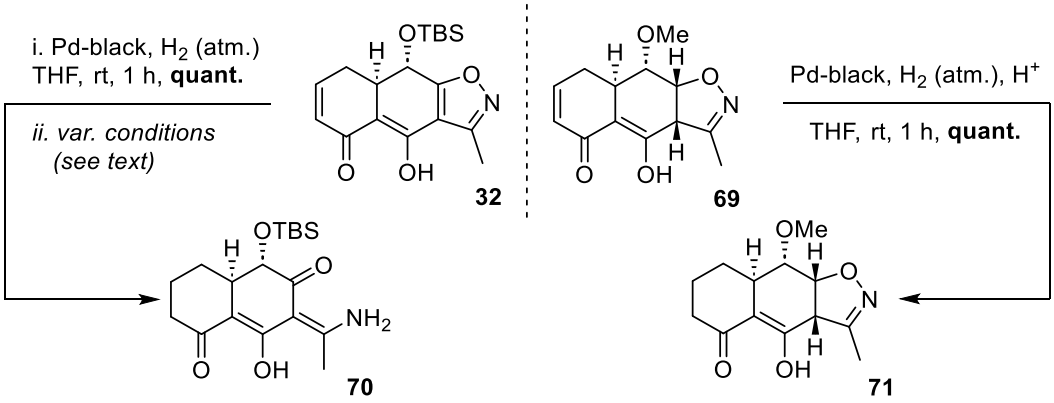


entry	conditions	outcome
I.	Pd-black/ H_2, $B(OH)_3$ (1,5 equiv.) MeOH, rt, 1,5 h	no conversion
II.	Ra-Ni/ H_2, $B(OH)_3$ (1,5 equiv.) MeOH, rt, 1 h	no conversion
III.	O_3, CH_2Cl_2/ MeOH –78 °C, 10 min	decomposition
IV.	SmI_2, THF, –78 °C, 20 min	decomposition

Inspired by previous accounts (see previous trials in chapter 4.1.3), the unveiling of the isoxazoline moiety of **67** was first attempted *via* hydrogenation conditions. After initial runs with either Pd-black or Ra-Ni failed to give any outcome at all (trials not included in the table), two acid-assisted[136,137] hydrogenation protocols (entries **I.** and **II.**) were attempted in accordance with Muri and Carreira.[124] In both instances, the starting material failed to undergo ring-opening.
Additionally attempted cleavage trials relied on ozonolytic conditions (entry **III.**) and a SmI_2-promoted protocol (entry **IV.**), with both methods failing to yield tetracyclic product **68**.
Despite previous successes of accessing β-hydroxyketones *via* the ozonolytic cleavage of various isoxazolines reported by Kozikowski et al.,[132,138] intermediate **67** failed to undergo the aimed transformation, the decomposition of the material being observed instead. A rapid degradation of the starting material was also encountered while attempting the SmI_2-protocol proposed by Bode and Carreira for the reduction of isoxazolines.[130]

[13] Highlighted in the **tab. 6** are only the trials relying on the use of precursor **67**. Additional attempts at cleaving the isoxazoline motif in variously decorated tetracycline architectures were conducted externally, with their outcomes also remaining unsuccessful.

Ultimately, considering the numerous unsuccessful trials of generating the methyl ketone functionality at the *C*2-position, including through the modified late-stage derivatization path, the proposed strategy of accessing demethylpremithramycinone (**1**) was abandoned. Nevertheless, an isoxazole-/ isoxazoline-hydrogenation study (**scheme 4.1.15**) was conducted briefly with decalins **32** (synthesis of **1**; *chapter 4.1.1*) and **69** (synthesis of **2**; *chapter 4.1.5*) to ascertain the possibility of achieving the cleavage of the heterocycles at an earlier stage in the synthesis.



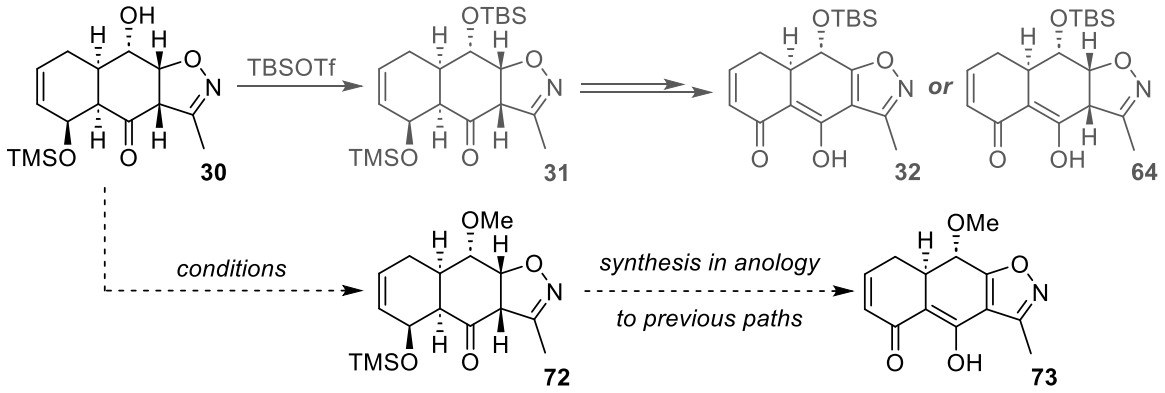
Scheme 4.1.15: Hydrogenations of the *C*8a-deoxy eastern fragments **32** and **69** (*chapter 4.1.5*). While the isoxazole moiety leads upon hydrogenation to the formation of a non-hydrolysable enamine, the isoxazoline-bearing counterpart failed to undergo N-O-bond cleavage.

When subjected to similar reductive conditions (hydrogenolytic cleavage with Pd-black), the trials shown in **scheme 4.1.15** were found to lead to very different outcomes. In addition to the commonly observed reduction of the enone moiety to the corresponding saturated ketone, isoxazole-bearing decalin **32** unsurprisingly underwent ring-scission, leading to the formation of enamine **70**. The integrity of the isoxazoline motif of **69** remained unaffected under the applied reaction conditions; further trials with the isolated product or with educt **69** were not conducted.
The hydrolysis of the isolated enamine **70** was, however, further attempted by subjecting it to several of the previously explored protocols (**tab. 5**; *chapter 4.1.3*).
By treating **70** with variously concentrated mineral acids under conditions similar to those shown before, only the cleavage of the TBS-ether could be observed, with the enamine functionality failing to undergo hydrolysis towards the corresponding methyl ketone. Furthermore, the treatment of ethereal solutions of the compound with dilute aqueous bases, such as NaOH (2M), also failed to provide any outcome, even at elevated temperatures and/ or prolonged reaction times.
In addition to the aforementioned protocols, trials relying on the use of various NO_2^--sources were conducted in accordance with entry **VI. b.** of **tab. 5** (generation of HNO_2 from $NaNO_2$ and aq. HCl) or the protocol described by Takada et al. (use of $^tBuNO_2$ in combination with TFA).[61] In both instances, a rapid decomposition of the starting material was encountered.

Lastly, even though unsuccessful in providing an alternative path for the synthesis of the targeted tetracycline natural products, the studies shown in **scheme 4.1.15** illustrate excellently the shortcomings of the attempted strategies. On one hand, by relying on isoxazoles for masking the functionalities at the A-ring, the completion of **path B** couldn't be achieved as envisioned due to an unsuccessful hydrolysis of the enamine functionality (resulted from the hydrogenolytic scission of the heterocycle). On the other hand, the modified **path B'**, through which the methyl ketone functionality at *C*2 was envisioned to be released from an isoxazoline motif, was abandoned due to the unsuccessful cleavage of the heterocycle.

4.1.5 Premithramycinone

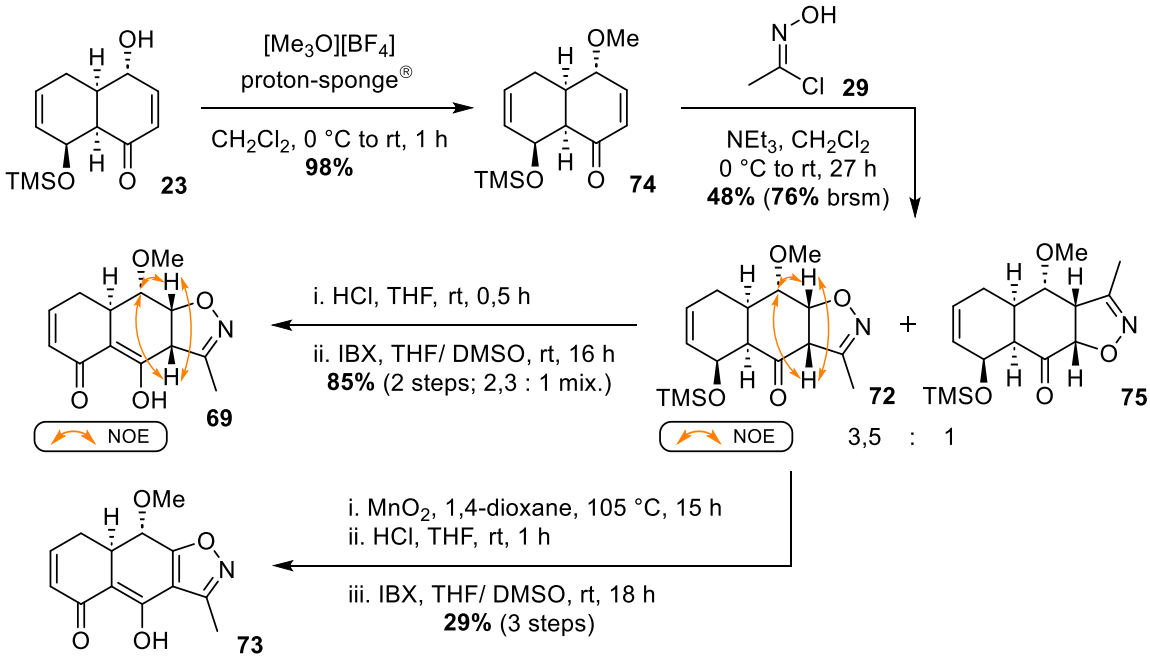
The following subchapter summarizes the synthetic efforts directed towards the preparation of premithramycinone (**2**; **scheme 4.1.18**) *via* the common total synthetic path presented in chapter 4.1.1, with the route heavily depending on previously gained insights from the attempted total syntheses of demethylpremithramycinone (**1**). Since the syntheses of the two natural products **1** and **2** were not performed in chronological order, the originally envisioned strategy for accessing premithramycinone (**2**) was partially carried out in accordance with the paths originally exploited for the preparation of natural product target **1** (*chapters 4.1.2* to *4.1.4*). In this instance, the construction of the characteristic tetracyclic core was also envisioned to proceed *via* a Diels–Alder reaction with furan between phthalide **44** (diene) and a methylated decalin-enone **73**.
Given the close similarity of *C*8a-deoxy enone **73** to the silylated counterpart **32** (both shown in **scheme 4.1.16**), its synthesis was originally envisioned in analogy to the preparation of **31**, starting from precursor **30** (*chapter 4.1.2*).



Scheme 4.1.16: Attempted synthesis of decalin-enone **73**– the methylated analogue of eastern fragment **32**, in the proposed total synthetic path for accessing premithramycinone (**2**).

For the preparation of precursor **72**, several methylation attempts were conducted in accordance with known protocols. These trials included deprotonation of alcohol **30** with various bases, such as K_2CO_3,[139] KH,[140] NaH,[141,142] Ag_2CO_3 or ^{n}BuLi,[143] followed by the treatment of the generated alkoxide with methyl electrophiles, such as MeI[140,143] or Me_2SO_4.[139,141,142] Unfortunately, all protocols failed to afford the desired product, with most trials leading to the decomposition of the starting material. Unconventional methods, such as the protocol described by Aoyama et al.,[144] which enables the methylation of alcohols with TMS-CHN_2 in the presence of aq. $H[BF_4]$, were also attempted, failing, however, to provide a favorable outcome. A trial with Meerwein's salt[145] managed to give methylated product **72** nevertheless, the poor outcome of the reaction (**5%** yield; conditions described in *chapter 6.3.1.2*) made the protocol impractical.

After the direct methylation attempts of secondary alcohol **30** failed to give any desirable outcome, the derivatization of allylic alcohol **23**– the precursor of the 1,3-dipolar cycloaddition in the synthesis of tricycle **32**, was attempted in accordance with the conditions proposed by Nakamura et al.[145] By treating decalin **23** with Meerwein's salt in the presence of proton-sponge® (**scheme 4.1.17**), the methylation of the *C*4-positioned secondary alcohol was successfully achieved at last, with the obtained yield of **98%** allowing for the smooth proceeding of the synthesis.
With the preparation of methyl ether **74** completed, the installation of the isoxazoline moiety was pursued in accordance with the previously employed strategy (*chapter 4.1.2*), the outcome of the reaction being highlighted as well in **scheme 4.1.17**.



Scheme 4.1.17: Preparation of *C*8a-deoxy decalin-enone **73** in the total synthesis of premithramycinone (**2**).

By exposing decalin **74** to the cycloaddition conditions established previously in the synthesis of tricycle **30** (*chapter 4.1.2*), the synthesis of the isoxazoline-bearing precursor **72** could be successfully completed. In contrast to the originally performed [3+2]-cycloaddition, which proceeded with an increased yield of **76%**, giving **30** as the single reaction product, the transformation highlighted in **scheme 4.1.17** resulted in the formation of a mixture of partially inseparable regioisomers. Product **72** was therefore isolated alongside its undesired regioisomer **75** in a 3,5:1-ratio. While both products were found to bear a concave-convex-arranged architecture, the formation of regioisomers highlights the crucial role of the *C*4-positioned alcohol for a regioselective proceeding of the reaction: by not being tethered by the secondary alcohol (*chapter 4.1.2*), the *in-situ* generated, ambiphilic acetonitrile oxide (←**29**) is able to approach the dipolarophile in two different orientations, the preferred one nevertheless leading to the formation of the desired product **72**.

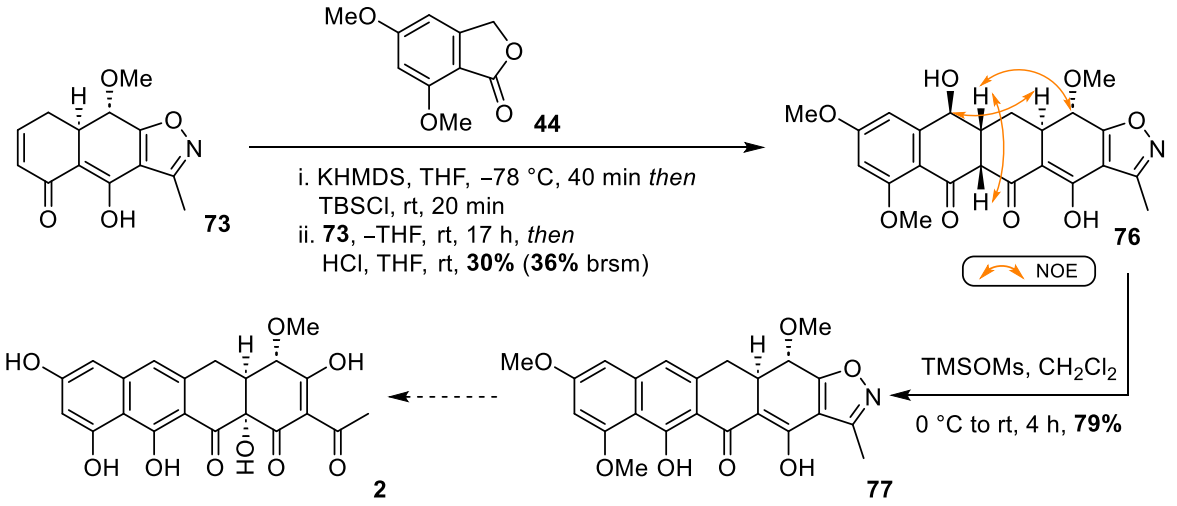
Despite the formation of regioisomers, the sequence towards eastern fragments **73** (**path B**) and **69** (**path B'**) was continued with the isolated mixture of products **72** and **75**, the further performed elaborations being in agreement with previously established protocols.

For the synthesis of isoxazoline-bearing precursor **69**, a two-step sequence was employed, consisting of an acid-mediated hydrolysis of the TMS-ether, followed by the oxidation of the resulted allylic alcohol to the corresponding enone. The transformations proceeded with an **85%** yield.

Inexplicably, by performing the two-step sequence, the ratio between the two isolated regioisomers was found to have dropped by approx. a third, with the separation of the products not being achieved by means of flash column chromatography. In spite of that, external results have shown that the construction of tetracyclines *via* [4+2]-cycloaddition is feasible with mixtures of regioisomers, the separation of the resulting products being successfully achieved by means of RP-HPLC.

On the other hand, by employing an additional step prior to the previous two-step sequence (aromatization of the isoxazoline to the corresponding isoxazole), *C*8a-deoxy eastern fragment **73** could be successfully isolated as the single reaction product, the recorded **29%** yield being based on pure educt **72**. Although the oxidation of the heterocycle was achieved by following the MnO_2-protocol, conversion of fragment **72** seemed to proceed with a lower yield than the original transformation, with attempts of utilizing DDQ[146] as an oxidant failing to provide any outcome at all.

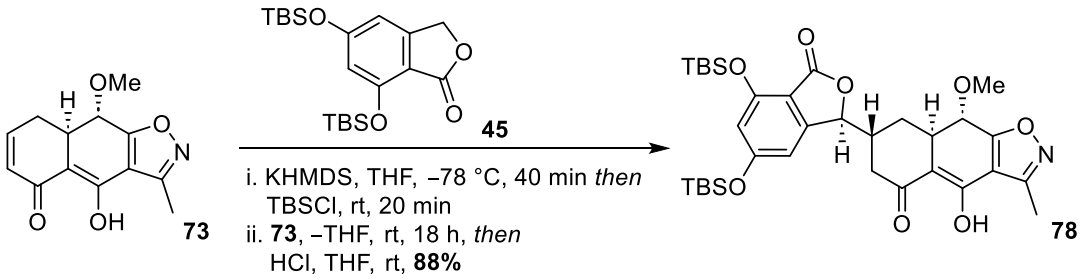
By the time the syntheses of the two fragments **69** and **73** were successfully completed, the attempts aiming at the total synthesis of demethylpremithramycinone (**1**) had already proven the impracticability of the strategy. Nevertheless, the coupling of enone **73** with phthalide **44** *via* the already explored Diels–Alder reaction with furan was carried out in order to further cement the applicability of the protocol for the construction of tetracycline architectures (**scheme 4.1.18**).



Scheme 4.1.18: Partially completed synthesis of premithramycinone (**2**) from enone **73** and the previously prepared phthalide **44**.

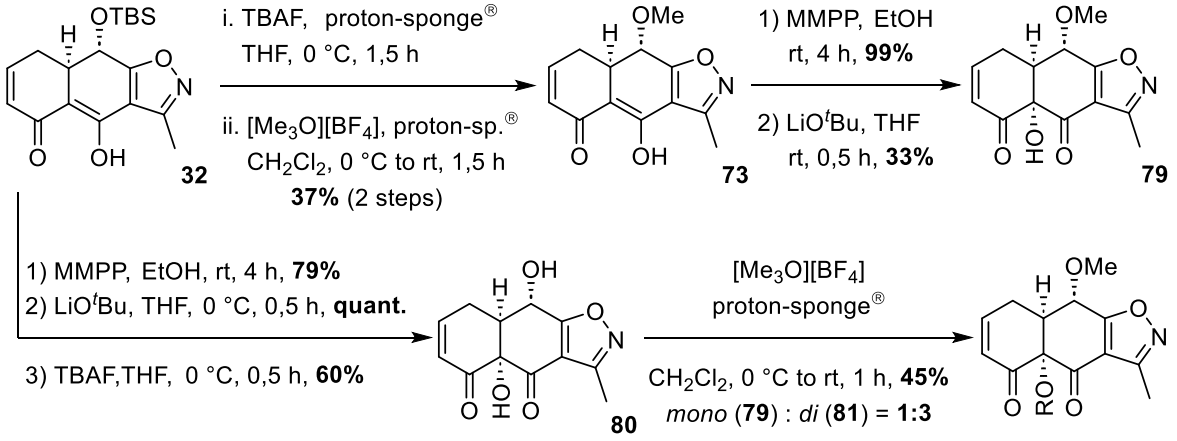
The [4+2]-cycloaddition of fragments **73** and **44** yielded, as anticipated, pentacycle **76**, with the NOE-assisted assignment of the absolute configuration of the product proving once more (*chapter 4.1.4*) the preference of the reaction towards the formation of an *endo*-arranged product. Lastly, by treating the secondary alcohol of **76** with TMSOMs, conditions previously explored during the syntheses of demethylpremithramycinone (**1**), the aromatization of the C-ring was conveniently achieved with a **79%** yield. Further derivatization trials were not conducted with the isolated tetracycline precursor **77**.

In addition to the [4+2]-cycloaddition shown in **scheme 4.1.18**, the coupling of eastern fragment **73** was also attempted with the modified phthalide **45** *via* a Diels–Alder reaction with furan (**scheme 4.1.19**). As in the case of the synthesis of demethylpremithramycinone (**1**; *chapter 4.1.3*), the envisioned cycloaddition reaction failed to set in, the exclusive formation of the conjugated addition product being observed instead. Since the construction of a suitable tetracycline precursor (**76**) was already achieved previously, the cyclization of the isolated material was not attempted.



Scheme 4.1.19: Alternative construction of the tetracycline core of premithramycinone (**2**) from intermediates **73** and a modified *di*-TBS-protected phthalide **45**. In this instance, the substrates failed to undergo [4+2]-cycloaddition, yielding the 1,4-addition product **78** instead.

Lastly, since during the exploration of the early-stage derivatization strategy of accessing the targeted natural products (**path A**), the *C*4-*O*-methylated fragment **73** was derivatized alongside the *C*8a-deoxy decalin **32**, the results of the performed studies will be briefly discussed in the upcoming section of the chapter (**scheme 4.1.20**). Along with the synthesis of ketol **79**, an alternative route for accessing precursor **73** directly from isoxazole-bearing decalin **32** is also highlighted in **scheme 4.1.20**.



Scheme 4.1.20: Alternative route for the preparation of eastern fragment **73** from tricyclic precursor **32** as well as the synthesis of ketol **79** in the early-stage derivatization strategy (**path A**) of accessing premithramycinone (**2**).

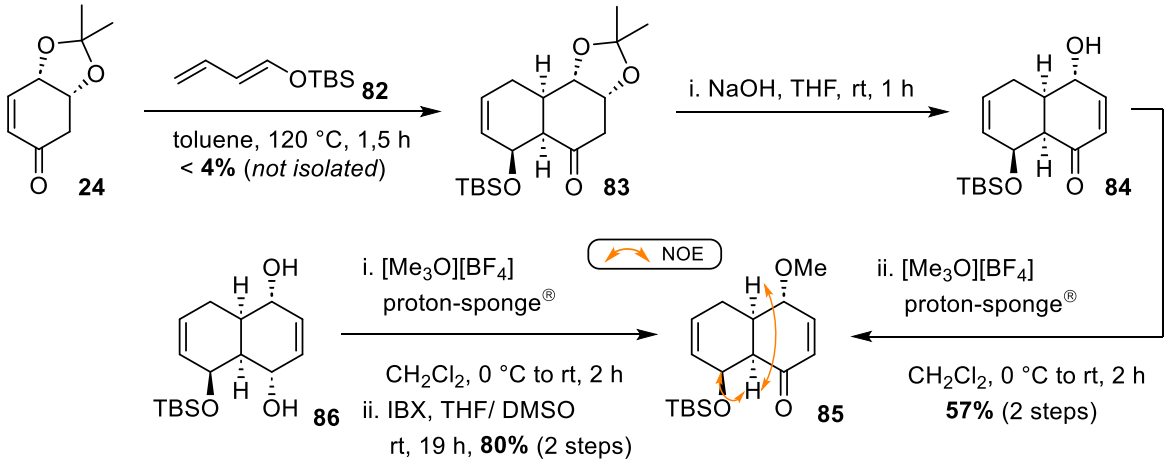
By cleaving the silyl-protection group of enone **32** with TBAF-reagent in the alternative protocol for accessing fragment **73**, the thus released secondary alcohol at *C*4 was methylated by already explored means. While the derivatization of the highly labile alcohol is expected to proceed smoothly (in analogy to the formation of **74**), its generation from silyl ether **32** represents the rate-limiting factor of the sequence. Furthermore, benzoisoxazole **33** (**scheme 4.1.4**) was often encountered as a decomposition product, its formation proceeding presumably *via* an elimination-*retro*-Diels–Alder path. Nevertheless, the proposed short-cut provided quick access to product **73**, thus conveniently bridging the paths for accessing the required *C*8a-deoxy eastern fragments in the syntheses of premithramycinones **1** and **2**.

In analogy to the path aiming at the synthesis of ketol **35** (*chapter 4.1.2*), the methylated analogue **79** could also be easily prepared in two steps. The α-ketol rearrangement required for the adjustment of the newly generated stereocenter at *C*8a interestingly proceeded in this instance with a lower yield (**33%**) than that recorded for the generation of ketol **35** (**quant.**). By performing 1D- and 2D-NMR analyses (*chapter 6.3.1.4.1*) of both ketol **79** and its *C*8a-epimer (structure not shown), a low-field shift of the ^{13}C-signal corresponding to the *C*8a-position was observed after performing the rearrangement reaction. This observation was in agreement with previous findings (*chapters 4.1.2* and *4.1.3*) and serves as proof for the successful outcome of the transformation.

While attempting the initial synthesis of ketol **79** by the previously shown means, a second strategy for its preparation was envisioned starting from TBS-protected ketol **35** (*chapter 4.1.2*). By treating **35** with TBAF-reagent, the cleavage of the silyl ether was successfully achieved, and diol **80** was thus generated with a satisfactory yield (**60%**). Considering the inaccessibility of the tertiary alcohol moiety of ketol **35** during the derivatization trials performed while exploring **path A**, the methylation of the secondary alcohol of diol **80** was considered to be favored in disregard to the congested tertiary alcohol at *C*8a, the process being believed to proceed in a chemoselective manner. However, the

methylation of diol **80** with Meerwein's salt led to the formation of a product-mixture consisting primarily of dimethylated ketol **81**, with the strategy being ultimately abandoned.

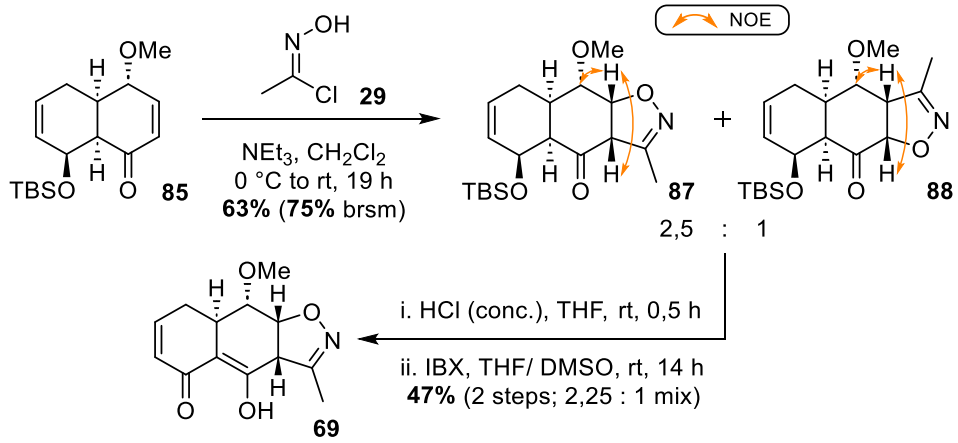
Before concluding the chapter dedicated to the efforts directed towards the preparation of premithramycinone (**2**), a last alternative for the preparation of the *C*8a-deoxy eastern fragment **69** will be further presented. In contrast to previous strategies (**scheme 4.1.17** and **scheme 4.1.20**), which relied on the use of advanced precursors from the synthesis of silyl ether **32**, the path highlighted in **scheme 4.1.21** goes as far back as the initially performed Diels–Alder reaction for accessing decalin **28**. By replacing the originally used TMS-oxybutadiene **25** with the more stable TBS-protected analogue **82**,[147] the [4+2]-cycloaddition reaction with enone **24**, envisioned for the construction of the decalin core, was performed under elevated temperatures and atmospheric pressure. In contrast to the high-pressure protocol employed for the synthesis of decalin **28**, the modified path of accessing precursor **83** led primarily to the unspecific decomposition of the starting materials. The taregted cycloaddition product was obtained only in trace amounts, its isolation from the complex reaction matrix being virtually impossible by means of flash column chromatography. Despite these drawbacks, however, the synthesis of compound **69** *via* the modified path was pursued with the obtained material by following the sequence depicted in **scheme 4.1.21**.



Scheme 4.1.21: Attempted alternative route for the preparation of isoxazoline **69**: While a path similar to that used for the preparation of decalin **23** (*chapter 4.1.2*) furnished precursor **85** only in very low yields, the repurposing of precursor **86** (*chapter 4.2*) has proven to be highly lucrative.

By following the path originally proposed for the preparation of decalin **32**, the Diels–Alder product **83** was further converted *via* a two-step sequence to enone **85**, a precursor suitable for the 1,3-dipolar cycloaddition. And while the newly explored strategy failed to prove its viability, the preparation of enone **85** could be conveniently achieved in two steps from an otherwise undesired intermediate **86**, originating from the route envisioned for accessing chromocyclin (**5**; **scheme 4.2.2**). Upon treating allyl diol **86** with Meerwein's salt, the regioselective conversion of the *C*4-positioned alcohol (*chapter 4.2*) to the corresponding methyl ether was achieved, with the remaining alcohol at *C*1 being oxidized in an additional step to the corresponding enone moiety. Thus, precursor **85** could be accessed in a reliable way, with the amounts of material produced *via* this approach allowing for further elaborations of the compound towards the aimed fragment **69** (**scheme 4.1.22**).

In order to establish the isoxazoline moiety of the targeted fragment (**scheme 4.1.22**), a 1,3-dipolar cycloaddition between chloro oxime **29** and decalin **85** was performed, with the transformation proceeding smoothly, giving tricyclic precursor **87** with a satisfactory yield of **63%**. Once more (**scheme 4.1.17**), the reaction led to the formation of an inseparable mixture of regioisomers **87** and **88**.



Scheme 4.1.22: A 1,3-dipolar cycloaddition step furnishes the isoxazoline-bearing precursor **87** along with its regioisomer **88**. Two more steps are required for the successful preparation of decalin **69** from tricycle **87**.

Lastly, the modified strategy for accessing isoxazoline-bearing decalin **69** was completed from decalin **87** (mixture with regioisomer **88**) in two steps. The sequence consisted of an acid-mediated hydrolysis of the TBS-ether group at *C*8, followed by the IBX-oxidation of the thus released allylic alcohol, and proceeded with a satisfactory yield of **47%**. Product **69** was isolated along with its regioisomer (not shown; structure in analogy to that of **88**), with the separation of the two compounds remaining to be completed at a later stage of the synthesis.

In conclusion, by employing the originally proposed strategy for accessing the aimed natural product target, premithramycinone (**2**), the synthesis of an advanced, *C*12a-deoxy tetracycline precursor **77** was successfully achieved. Given the repeatedly unsuccessful attempts of completing the total synthesis of demethylpremithramycinone (**1**) explored previously (*chapters 4.1.3* and *4.1.4*), the further elaboration of the prepared intermediate (**77**) towards **2** was not attempted. Nevertheless, its generation proved again the viability of the proposed strategy for addressing complex tetracycline architectures by the means of Diels–Alder reaction with furan.

While the [4+2]-cycloaddition step performed for the construction of the tetracycline core conveniently reutilized phthalide **44** as a diene, the dienophile– a slightly modified eastern fragment **32** (decalin **73**), had to be synthesized first. Four strategies were investigated for this task.

At first, the route utilized for the preparation of enone **32** was repurposed, with methyl-eastern fragment **73** being successfully prepared in five steps from precursor **23**. A combined yield of **22%** was obtained for this sequence (**scheme 4.1.17**). The direct conversion of enone **32** over two steps to fragment **73** (**scheme 4.1.20**) proceeded with a **37%** yield.

With a slight adaptation to the approach highlighted in **scheme 4.1.17**, isoxazoline-enone **69** was conveniently prepared in five steps from precursor **23**. By omitting the oxidation of the heterocycle, a yield increase was observed, the four-step sequence proceeding with a combined yield of **63%**. On the other hand, with the preparation of **69** *via* a modified Diels–Alder reaction (**scheme 4.1.21**), cycloaddition product **83** was isolated in very poor yields (**< 4%**).

In addition to the previously explored protocols, isoxazoline-bearing decalin-enone **69** could be conveniently accessed by repurposing an otherwise undesired decalin **86** from the strategy aiming at the total synthesis of *epi*-chromocyclin **4**. Thus, by following the protocols shown in **scheme 4.1.21** and **scheme 4.1.22**, fragment **69** was successfully prepared in five steps with a combined yield of **44%**.

The successful repurposing of precursors from the pathways for accessing both demethylpremithramycinone (**1**) and *epi*-chromocyclin (**2**) in the synthesis of premithramycinone (**3**) ultimately highlights the high tunability and versatility of the proposed global strategy.

4.1.6 *epi*-Chromocyclin

Since previous trials (*chapters 4.1.2* to *4.1.4*) led to unsatisfactory results, the total synthetic preparation of *epi*-chromocyclin (**3**), initially envisioned to proceed through the joined strategy for accessing natural product targets **1** and **2**, was not attempted. In this instance, the construction of the characteristic tetracycline core *via* the [4+2]-cycloaddition reaction would have relied on eastern fragment **73** and a methylated phthalide **89** (**fig. 4.1.7**).

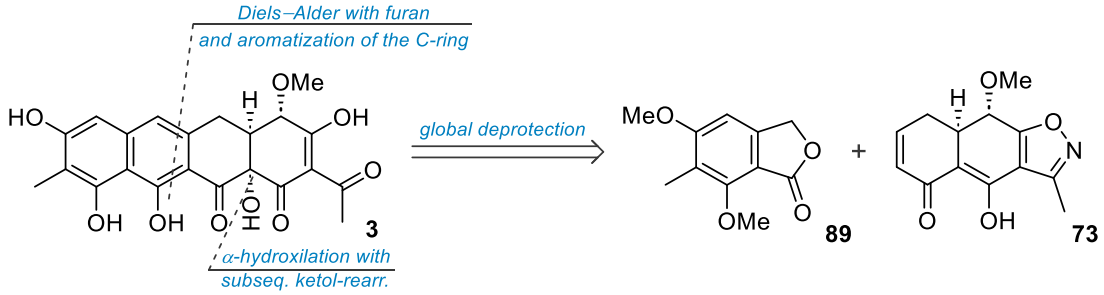
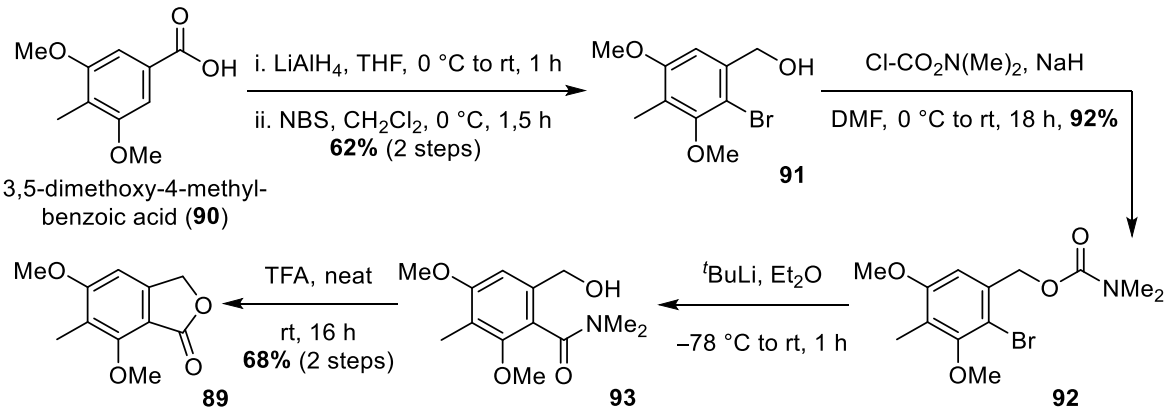


Fig. 4.1.7: Proposed retrosynthetic path for accessing *epi*-chromocyclin (**3**) *via* a [4+2]-cycloaddition key step between decalin-enone **73** and methyl-phthalide **89**.

While decalin-enone **73** was already successfully prepared by various means during the attempted synthesis of premithramycinone (**2**; *chapter 4.1.5*), the preparation of phthalide **89** (**scheme 4.1.23**) was envisioned in accordance with the route utilized for the preparation of its demethyl-analogue **44** (**scheme 4.1.6**).

Starting from the commercially available 3,5-dimethoxy-4-methyl-benzoic acid (**90**), the first step towards lactone **89** consisted of the reduction of the acid to the corresponding primary alcohol. While an effective DIBAl-H-reduction of **90** was already reported in literature,[148] a $LiAlH_4$-based protocol was preferred instead due to cost-saving reasons.[149] Nevertheless, the obtained benzyl alcohol was further converted in accordance with the originally proposed route for accessing lactone **44** (**scheme 4.1.6**). The performed follow-up transformations consisted of the *mono*-bromination of the aromatic core (formation of **91**), followed by the conversion of the alcohol moiety to the corresponding *N*,*N*-dimethylcarbamate (formation of **92**).



Scheme 4.1.23: Synthesis of methyl-phthalide **89** from 3,5-dimthoxy-4-methyl-benzoic acid (**90**) in analogy to the route utilized for phthalide **44** (**scheme 4.1.6**).

Lastly, after an initial trial with ^{n}BuLi failed to give the expected outcome, the formation of the lactone moiety of substrate **89** *via* an intramolecular carbonylation step was attempted with the use of ^{t}BuLi. Under the modified conditions, however, benzyl alcohol **93** was obtained instead of the aimed phthalide, its formation presumably originating from **89**, in which the lactone moiety was rapidly opened under the presence of Me_2N^- to form the corresponding amide functionality. Nevertheless, the methylated western fragment **89** was obtained from amide **93** *via* an intramolecular transesterification, with the two-step sequence employed for its conversion from precursor **92** proceeding conveniently with a combined yield of **68%**.

In spite of being slightly longer than the method proposed previously by Sargent (three steps; 70% yield),[149] the strategy highlighted in **scheme 4.1.23** proceeded smoothly over five steps, giving phthalide **89** with a combined yield of **39%**. Furthermore, the proposed strategy was able to prove its viability once more, providing a safe and efficient alternative to the aforementioned protocol, which relies on the use of stochiometric amounts of CuCN for the installation of the lactone moiety.[149]

4.2 Chromocyclin

The last discussion regarding an attempted total synthesis of one of the non-antimicrobial tetracycline natural products shown in **fig. 3.1** concerns the efforts directed towards the preparation of chromocyclin (**4**). Despite its close structural relationship to its previously addressed *C*4-epimer (*epi*-chromocyclin **3**; *chapter 4.1.6*), the discussion concerning the preparation of **4** is treated independently due to several alterations to the common path. And while the end-game strategy of the proposed route (**fig. 4.2.1**) was envisioned in analogy with those previously explored, with the path relying on the use of phthalide **89** (*chapter 4.1.6*) for the installation of the C/D-ring functionalities, a modified, *C*4-(*R*)-configured eastern fragment **94** is required for completing the synthesis.

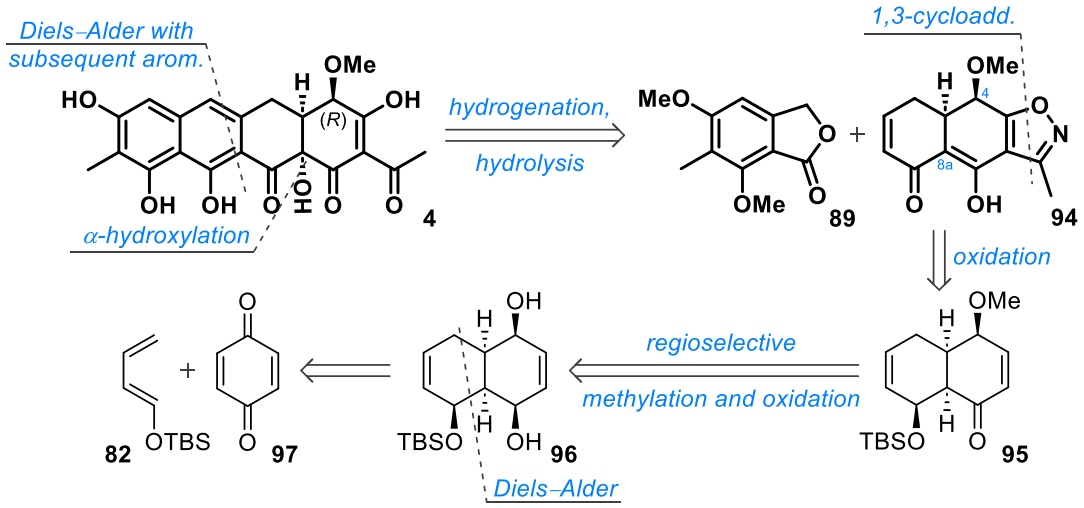


Fig. 4.2.1: Retrosynthetic considerations for accessing chromocyclin (**4**). The construction of the tetracycline backbone is once again envisioned to proceed *via* a Diels–Alder reaction with furan between *C*8a-deoxy eastern fragment **94** and the previously described phthalide **89**.

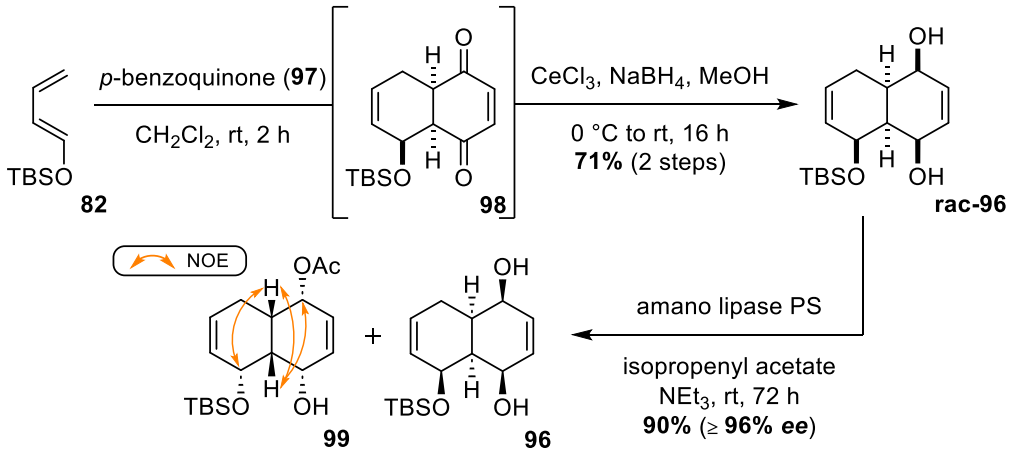
Being in agreement with the initially proposed common strategy of accessing the targeted natural products **1** - **5** (chapter 3), the construction of the characteristic core of chromocyclin (**4**) was also envisioned to proceed *via* a Diels–Alder reaction (**fig. 4.2.1**) between decalin-enone **94** (i.e., the *eastern fragment*) and an *in-situ* formed isobenzofuran, originating from methyl-phthalide **89** (i.e., the *western fragment*; preparation described in *4.1.6*). Additional functionalities of the target, primarily those at the A-ring, remain to be established in the final stages of the synthesis (late-stage derivatization; **path B**), in analogy with already explored methodologies (*chapter 4.1.3*).

While the *C*8a-deoxy eastern fragments required for the syntheses of targets **1** – **3** bore an (*S*)-configured ether moiety at *C*4, building block **94** possesses a (*R*)-arranged methyl ether instead. Therefore, since the stereoselective approaches utilized previously for the construction of the decalin architecture could not be implemented in this instance, a new approach, relying on well-established protocols, was required. Thus, the generation of the heterocycle moiety of **94** was envisioned to proceed *via* a 1,3-dipolar cycloaddition, the final building block being traced back to decalin **95**.

A two-step sequence consisting of a regioselective methylation followed by an alcohol oxidation allows precursor **95** to be traced back to allyl diol **96**, with the selectivity of the methylation being postulated to originate from the steric bulk exerted by the TBS-protection group at *C*8.

Lastly, decalin **96**, the product of a Diels–Alder reaction, can be traced back to two simple building blocks: *para*-benzoquinone (**97**) and siloxydiene **82** (*chapter 4.1.5*), a diastereoselective Luche reduction ensuring the formation of the alcohol moieties at *C*1 and *C*4.

By following the proposed retrosynthetic strategy of accessing **94** shown in **fig. 4.2.1**, the preparation of the first decalin precursor of the path is highlighted in **scheme 4.2.1**. As envisioned, the Diels–Alder reaction of siloxydiene **82** with *para*-benzoquinone (**97**) proceeded to give the highly labile decalin-dienone **98** (relative configuration shown), which was quickly converted upon formation *via* a Luche reduction to racemic decalin-diol **rac-96**. The sequence conveniently afforded the racemic product with a combined yield of **71%**. In contrast to the initially performed Diels–Alder reaction for generating precursors **28** (*chapter 4.1.2*) or **83** (*chapter 4.1.5*), the [4+2]-cycloaddition shown in **scheme 4.2.1** led to the formation of a racemate, with the previously recorded stereoselectivity induced by the acetonide motif of **24** not being provided in this instance. Therefore, upon pursuing the syntheses towards **94**, the chiral resolution of the isolated diol **rac-96** had to be performed.

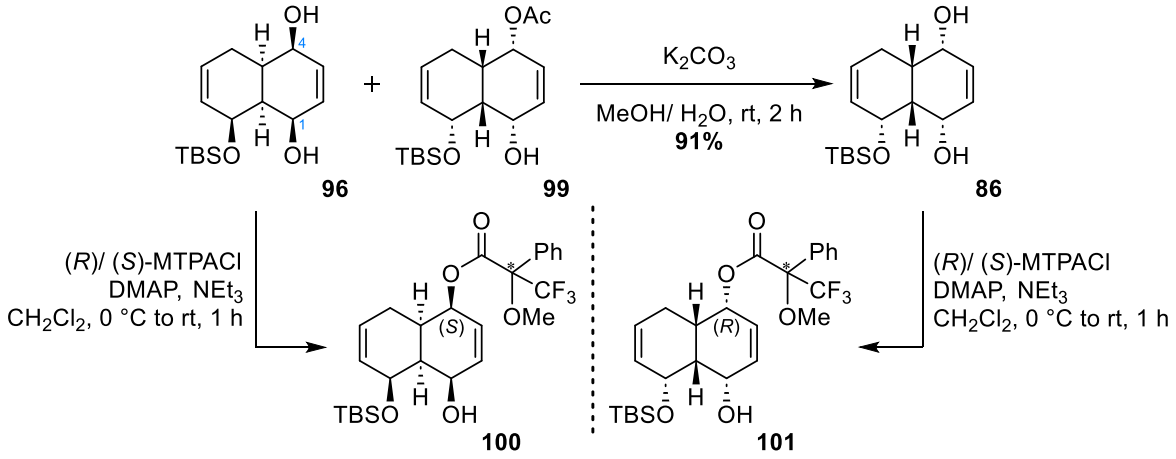


Scheme 4.2.1: An initial Diels–Alder reaction, followed by a Luche reduction furnish decalin-diol **96** in the synthesis of eastern fragment **94**.

Inspired by the protocol proposed by Sulikowski et al.,[150] the resolution of **rac-96** was effectively accomplished by using immobilized amano lipase PS. Enantiomerically pure diol **96** and acetate **99** were thus isolated as the products of the process. Since the determination of the relative configuration of **rac-96** was not possible due to spectral overlap, the accurate assessment of the structure *via* NMR-spectroscopy was first enabled with the formation of acetate **99**. And while the implemented methods gave irrefutable information about the relative arrangement of the product, the absolute configuration of the isolated compounds **96** and **99** had to be determined *via* the Mosher-ester method.[151] For this purpose, both products were treated independently with Mosher's acid chlorides, with acetate **99** failing, however, to undergo derivatization at the *C*1-position. This observation represented a first hint towards the validity of the initially made assumption regarding the inertness of the *C*1-alcohol towards derivatization. Nevertheless, the acetate was removed *via* alkaline hydrolysis before reapplying the previously attempted conditions. Thus, the generated diol **86** was subjected, along with its enantiomer **96**, to the aforementioned conformational analysis. The outcome of the study is schematically highlighted in **scheme 4.2.2**, with a thorough discussion of the method and its outcome given in chapter 6.4.1.3.

As a result of the performed analyses, the absolute configuration of the resolution products **96** and **99** was irrefutably determined, thus ensuring the smooth and accurate proceeding of future syntheses. Furthermore, the exclusive preference of the highly reactive chiral acid chlorides towards the *C*4-positioned alcohols of both compounds **96** and **86**, to the detriment of the *C*1-positioned one, became obvious during the investigation. As a result, the initially predicted inaccessibility of the *C*1-alcohol, ensured by the presence of the bulky TBS-ether at *C*8, was confirmed, and a regioselective proceeding of future transformations was therefore expected.

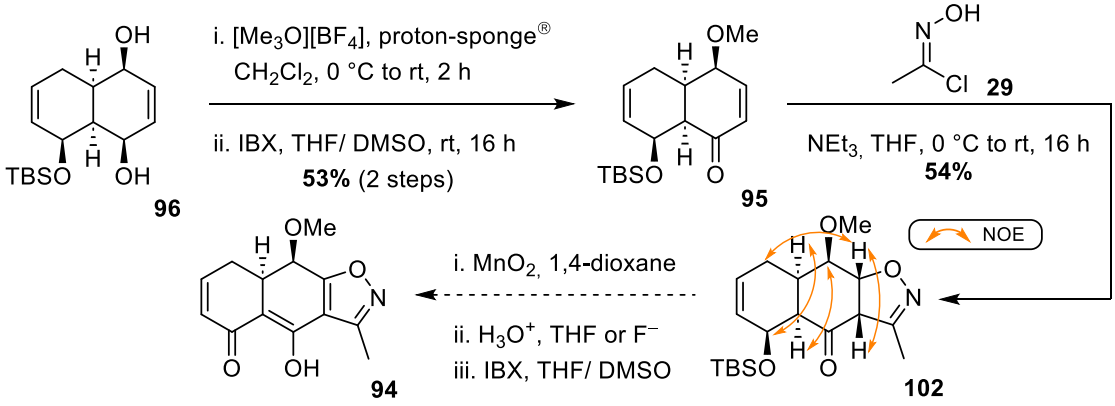
In addition to the support provided through the conformational study and the insight gained by the selective derivatization of the *C*4-alcohol, the generation of **86** also opened a previously unanticipated path for accessing decalin-enone **73** (**scheme 4.1.21**)– a valuable precursor in the synthesis of both premithramycinone (**2**) and *epi*-chromocyclin (**3**).



Scheme 4.2.2: Determination of the absolute configuration of diols **96** and **86** (originating from acetate **99**) from the chiral resolution step *via* the Mosher-ester method.

Proceeding in accordance with the strategy depicted in **fig. 4.2.1**, methylation of diol **96** was initially attempted with MeI and K_2CO_3, the conditions failing, however, to deliver the desired methyl ether functionality at *C*4. By applying the previously utilized Meerwein-protocol (*chapter 4.1.5*), the envisioned transformation proceeded nevertheless smoothly and in a regioselective fashion (**scheme 4.2.3**). The remaining allylic alcohol at *C*1 was then converted to the corresponding enone *via* an IBX-mediated oxidation. Enone **95** was thus successfully prepared in two steps with a moderate yield of **53%**. The formation of regioisomers was not encountered.

With the installation of the required functionalities completed, the construction of the isoxazoline core was pursued from enone **95** in accordance with previous accounts *(chapters 4.1.2* to *4.1.4*). By treating the bicyclic starting material with a freshly prepared solution of oxime **29** in the presence of NEt_3, the exclusive formation of a concave-convex-arranged product **102** was observed. While the conformation of the tricyclic product (NOE) was not surprising in the given context (*chapter 4.1.2*), the regioselective proceeding of the reaction, observed to occur otherwise only during the preparation of precursor **30** (**scheme 4.1.11**), seemed unusual nevertheless. Further investigations, aiming to provide a clear explanation behind this occurrence, were, however, not conducted.



Scheme 4.2.3: Partially completed route for accessing isoxazole-bearing fragment **94** from enantiomerically pure allyl diol **96** in the synthesis of chromocyclin (**4**).

Lastly, with the previously explored routes relying on the use of either isoxazole- or isoxazoline-bearing architectures failing to lead to a positive outcome (*chapters 4.1.3* and *4.1.4*), the cleavage of the heterocycles or elaborations of their degradation products remaining consistently unachievable, no further efforts were conducted towards synthesizing compound **94** or derivatives thereof. Ultimately, the route depicted in **scheme 4.2.3**, along with the global attempt to synthesize chromocyclin (**4**), were halted at this stage.

4.3 Carbamidochelocardin

Finally, the upcoming chapter comprises the efforts directed toward the total synthetic preparation of the unusual tetracycline carbamidochelocardin (**5**), a bioengineered, chelocardin (**6**)-derived compound with promising antibiotic properties (*chapter 2.1*). By following the strategy originally proposed for jointly addressing targets **1** – **4**, the completion of the total synthesis of amidochelocardin (**5**) was envisioned to proceed in agreement with **path B**– the late-stage derivatization approach (*chapter 4.1.1*). Valuable insights gained during the exploration of the attempted synthesis of demethylpremithramycinone (**1**) *via* this route (*chapter 4.1.3*) played a decisive role in the elaboration of the path addressing the natural product-derived target (**fig. 4.3.1**).
Thus, in analogy to previous strategies, the polar functionalities of target **5**, such as the phenol at *C*10, the primary amine at *C*4 and the decorations at the A-ring, were planned to be released during the end-game stage from an advanced precursor **103** *via* hydrolysis or hydrogenation, respectively. Since previous targets, bearing a methyl ketone functionality at *C*2, required the implementation of methyl-isoxazoles as masking agents, a modified approach for addressing the amide moiety of **5** was required. Therefore, the simultaneous generation of the *C*2-amide alongside the *C*3-enol is envisioned to originate from the unveiling of the benzylated hydroxy-isoxazole motif of ketol **103**. The proposed strategy was inspired by previous approaches implemented by Stork,[51] Myers,[50,55] Evans[39] and Nicolaou[40] for their syntheses of complex tetracycline natural products and derivatives thereof.

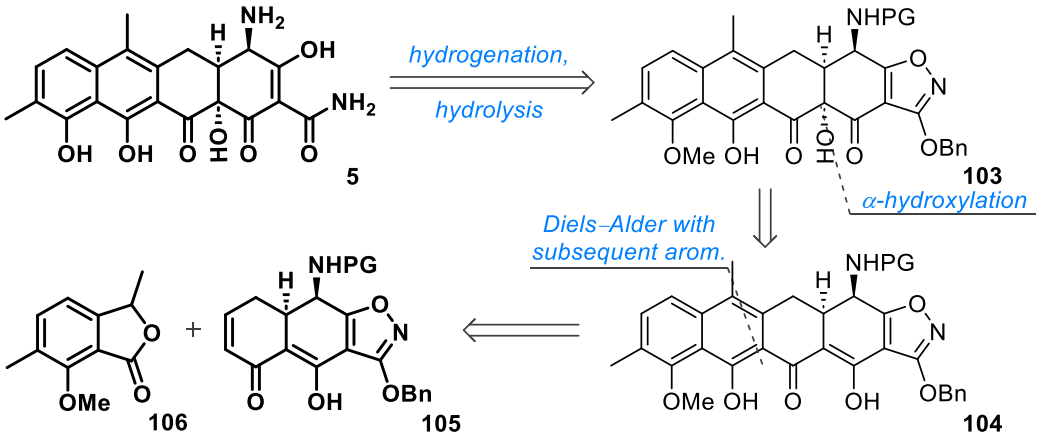


Fig. 4.3.1: Proposed retrosynthetic strategy for accessing carbamidochelocardin (**5**). Relying on a Diels–Alder reaction with furan between phthalide **106** and decalin-enone **105**, the construction of the characteristic tetracyclic core is aimed at in a convergent manner.

Further on, the generation of ketol **103**, bearing the representative (*S*)-configured tertiary alcohol at *C*12a, was envisioned to proceed in agreement with the strategy implemented for the synthesis of demethylpremithramycinone (**1**; **path B** in chapter 4.1.3) from vinylogous acid **104**.
Since the previously mentioned natural product target **1** bears an (*S*)-configured alcohol at *C*4, the derivatization of the *C*12a-position was immediately followed by an α-ketol rearrangement, with the transformation ensuring the correct adjustment of the newly generated stereocenter. By employing bulky peroxides, the derivatization of the *C*12a-position of **104** is expected to directly yield the required (*S*)-configured tertiary alcohol, the *si*-side attack being driven by the presence of the (*R*)-configured protected amine at *C*4, shielding the top face of the system.
Lastly, the formation of precursor **104** can be traced back to a Diels–Alder reaction with furan with subsequent aromatization. The [4+2]-cycloaddition is expected to proceed by already explored means (*chapter 4.1.3*) between phthalide **106** (the *western fragment*), bearing the D-ring functionalities, and

decalin-enone **105** (the *eastern fragment*), bearing the particularities of the A/B-ring system. The strategies envisioned for accessing the two fragments **106** and **105** are highlighted in **fig. 4.3.2**.

For the synthesis of the more complex decalin-enone **105**, two paths were proposed and exploited, their discussions being treated independently in the upcoming subchapters. The key focus point during the development of the proposed approaches was represented primarily by the installation of the isoxazole moiety. While the strategy of accessing **105** discussed in chapter 4.3.1 relied on the generation of the heterocycle *via* a [3+2]-cycloaddition between an advanced decalin precursor **109** and an *in situ* generated benzyloxynitrile oxide **110'**, the discussions summarized in chapter 4.3.2 concern the efforts made towards accessing the target *via* a Michael–Claisen approach between isoxazole **107** and an enone-bearing precursor **108**.

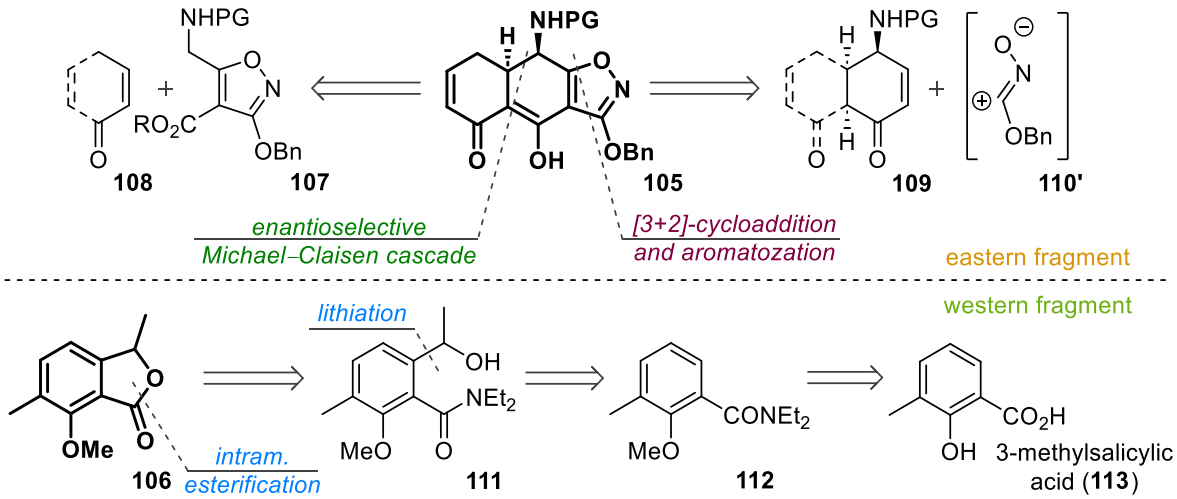
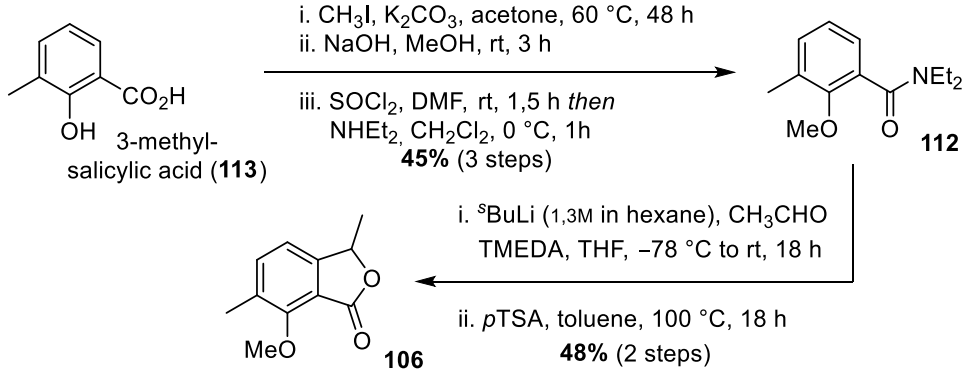


Fig. 4.3.2: Proposed retrosynthetic path for accessing western fragment **106** and eastern fragment **105**. While phthalide **106** can be conveniently traced back to the readily available 3-methylsalicylic acid (**112**), enone **105** demands a more laborious approach.

In contrast to decalin **105**, the synthesis of western fragment **106** requires a less laborious approach, with a linear sequence being envisioned for its preparation. Beginning with the lactone moiety, the functionality can be addressed by an intramolecular esterification of precursor **111**, in which the methylated benzyl alcohol functionality is introduced *via* a directed *ortho*-lithiation[152] from aryl amide **112**. Precursor **112** can be conveniently traced back to the commercially available 3-methylsalicylic acid (**113**), with three literature-known steps being required for its preparation.[153] The forward synthesis of phthalide **106** (i.e., the *western fragment*) is highlighted in **scheme 4.3.1**.



Scheme 4.3.1: Five-step synthesis of phthalide **106** from the readily available salicylic acid-derived precursor **112**.

By following the path proposed by Egan et al.,[153] the synthesis of precursor **112** was achieved in three steps from 3-methylsalicylic acid (**113**), with a combined yield of **45%**. At first, the phenol was methylated by using methyl iodide in the presence of K_2CO_3. Under these conditions, the conversion of the acid moiety to the corresponding methyl ester was also observed in addition to the desired formation of the aryl methyl ether. Nevertheless, the ester was cleaved under alkaline conditions in an additional step and the released acid was converted to the desired (*N*,*N*)-diethylamide functionality. In analogy to the path reported by Egan et al.,[153] the directed lithiation of aryl amide **112** with ^{s}BuLi, followed by the trapping of the generated organolithium species with acetaldehyde, resulted in the formation of benzyl alcohol **111** (shown in **fig. 4.3.2**). Finally, an acid-mediated intramolecular transesterification allowed for the installation of the lactone moiety, thus affording phthalide **106** in a moderate yield of **48%** (two steps).

4.3.1 Synthesis of decalin-enone **105** *via* [3+2]-cycloaddition

Proceeding in agreement with previously explored strategies of accessing decalin-enones with similar architectures to that of **105**, the installation of the isoxazole moiety, masking the polar functionalities at the tetracycline A-ring, was initially envisioned to proceed in a [3+2]-cycloaddition fashion between enone **114** (**fig. 4.3.3**) and an *in situ* generated benzyloxynitrile oxide **110'** (structure shown in **fig. 4.3.2**). Decalin **114**, bearing the (*R*)-configured Cbz-protected amine at *C*4, can be conveniently traced back to allyl diol **96**, a valuable precursor from the synthesis of chromocyclin (**4**). Therefore, the generation of the secondary amine moiety of **114** *via* a Tsuji–Trost reaction with NH_3 can be expected to proceed with both high regio- and diastereoselectivities (*chapters 4.1.5* and *4.2*). The remaining enone moiety at *C*1 can be conveniently traced back to the oxidation of the corresponding allyl alcohol.

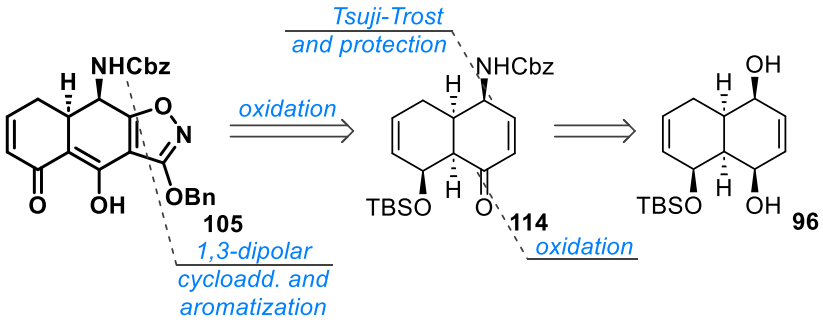
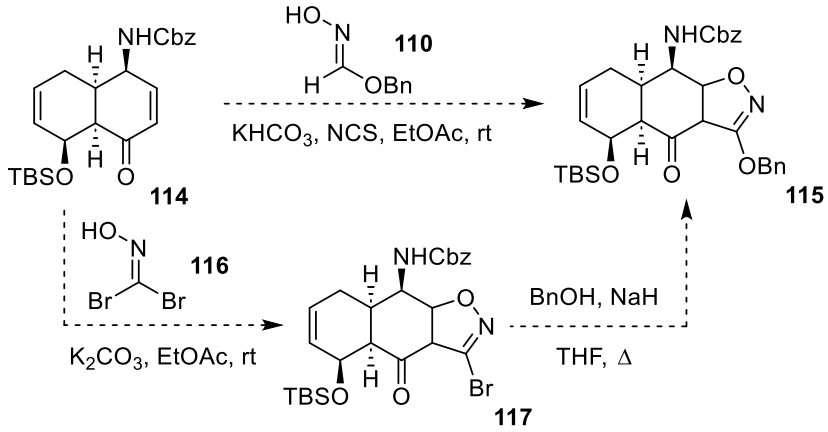


Fig. 4.3.3: First-generation strategy towards decalin-enone **105**. While the installation of the isoxazoline moiety is envisioned *via* a 1,3-dipolar cycloaddition, precursor **114** can be conveniently traced back to the already established decalin **96** (*chapter 4.2*).

Before attempting the forward synthesis of **105**, the feasibility of generating annulated benzyloxy-isoxazole architectures by the means proposed previously had to be ascertained. For this, two known approaches were taken into consideration, the strategies being highlighted in **scheme 4.3.2**. At first, a straight-forward approach utilized by Wzorek et al.[39] during their studies towards the total synthesis of tetracycline natural products was considered for the construction of the aimed heterocycle. By treating complex propargyl alcohol derivatives with benzyl formhydroxymate **110** under the conditions shown in **scheme 4.3.2**, the authors were able to successfully prepare a small array of highly functionalized isoxazoles, with their reported results serving as motivation for the upcoming investigations. In the given context, however, the proposed protocol would lead to the formation of an

isoxazoline-bearing precursor **115**, with an additional aromatization step required for accessing **105**. Nevertheless, inspired by the aforementioned observations, the synthesis of benzyl formhydroxymate **110** was attempted prior to the derivatization of allyl diol **96** by following the method established by El-Seedi et al.[154] First, tribenzyl orthoformate was prepared easily in accordance with the method described by Gil et al.[155] and subjected to the conditions reported by El-Seedi et al.[154] Unfortunately, by further converting the tribenzyl orthoformate towards **110**,[14] the aimed product could be isolated only with a poor yield of approx. **4%**, with repetitions or slight alterations of the method remaining unsuccessful in improving its outcome. Eventually, even though promising, the strategy of directly accessing the benzyloxy-isoxazoline scaffold of **115** *via* a dipolar cycloaddition between **114** and benzyloxynitrile oxide **110'** could not be further investigated, the impractical and highly laborious preparation of the required oxime **110** leading to its abandonment.



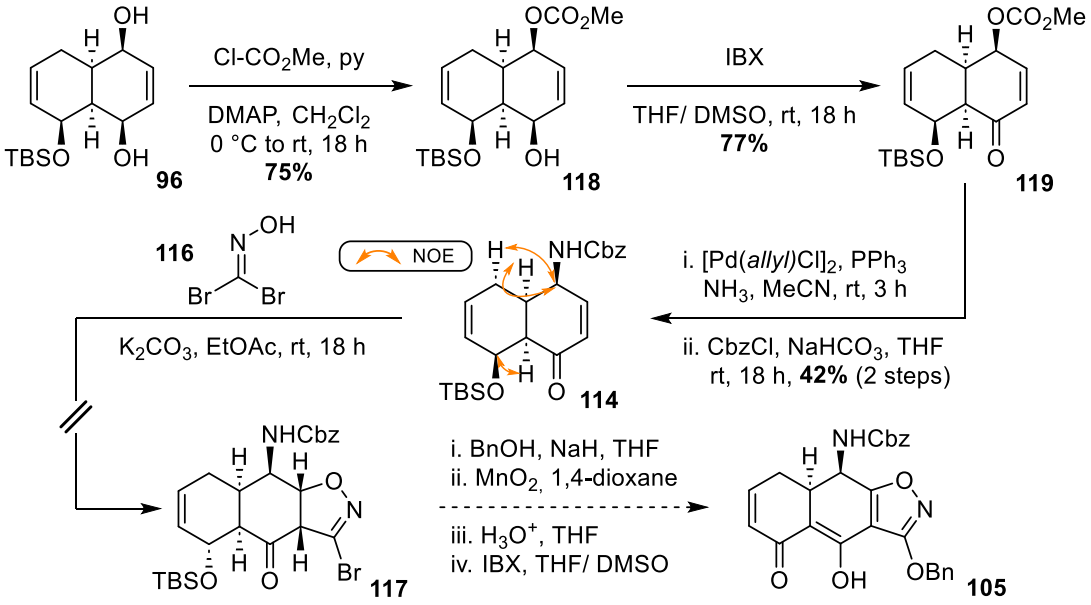
Scheme 4.3.2: Proposed strategies for accessing the isoxazole scaffold of **105**. While the protocol proposed by Wzorek et al.[39] was found to be unreliable, a path in accordance with the method reported by Umstead et al.[156] (formation of **117**) was considered instead.

For the second attempted strategy of establishing the isoxazole moiety of **115**, a protocol reported by Umstead et al. was considered.[156] In this instance, the 1,3-dipolar cycloaddition of bromonitrile oxide, generated *in-situ* from dibromoformaldoxime (**116**), between both electron-rich (substituted dihydrofurans) and electron-poor (substituted enones) olefins was proposed and investigated. Proceeding in a regiospecific fashion, several bromo-isoxazolines were successfully prepared by the authors, with the use of enone-bearing substrates leading to the formation of product architectures similar to that of **117** in satisfactory yields (62%).
Furthermore, by following the protocol reported by Tamborini et al.,[157] the required benzyloxy-isoxazoline scaffold of **115** could be easily accessed from **117** *via* an additional derivatization step. Therefore, with the promising premise of conveniently installing the benzyloxy-isoxazoline moiety *via* a [3+2]-cycloaddition, the synthesis of **105** was originally pursued in agreement with the path shown in **scheme 4.3.3**. Beginning with the previously prepared allyl diol **96** (*chapter 4.2*), the first step towards the preparation of **105** was represented by the regioselective conversion of the *C*4-alcohol to the corresponding methyl carbonate **118** (in analogy to the synthesis of **73** in **scheme 4.1.20** and **95** in **scheme 4.2.3**). Proceeding with a satisfactory yield (**75%**), the derivatization of the *C*4-position was

[14] A steady stream of H_2S (freshly prepared from Na_2S and conc. HCl-solution) was passed at room temperature through a mixture consisting of tribenzyl orthoformate and anhydrous $ZnCl_2$ for ten minutes. The cloudy mixture was then cooled to 0 °C and reacted with a NH_2OH-solution. By reproducing the scale reported by El-Seedi et al., 50 mmol of tribenzyl orthoformate were subjected to the mentioned conditions, with **110** being obtained in a 4,5% yield instead of 68%.[154]

required in order to generate a suitable leaving group for the upcoming Tsuji–Trost reaction.[158] The remaining alcohol at *C*1 was then oxidized with IBX to form enone **119**.

After successfully providing facile access to enone **119**, the stage was set for the installation of the (*R*)-configured *C*4-amine *via* a stereoselective Tsuji–Trost reaction. By performing the transformation in the presence of aqueous NH_3– a soft nucleophile, the installation of the *C*4-amine proceeded smoothly. However, given the high polarity of the newly generated compound **128** (shown in **scheme 4.3.5**), its purification and thus accurate determination of its absolute configuration have proven to be difficult. Therefore, the isolated material was immediately converted to carbamate **120**, the Cbz-protection step allowing for an eased handling and purification of the compound. Upon subjecting reaction product **120** to NMR-analysis, its absolute configuration could be irrefutably determined and the stereoconservative proceeding of the Tsuji–Trost reaction confirmed.[158]

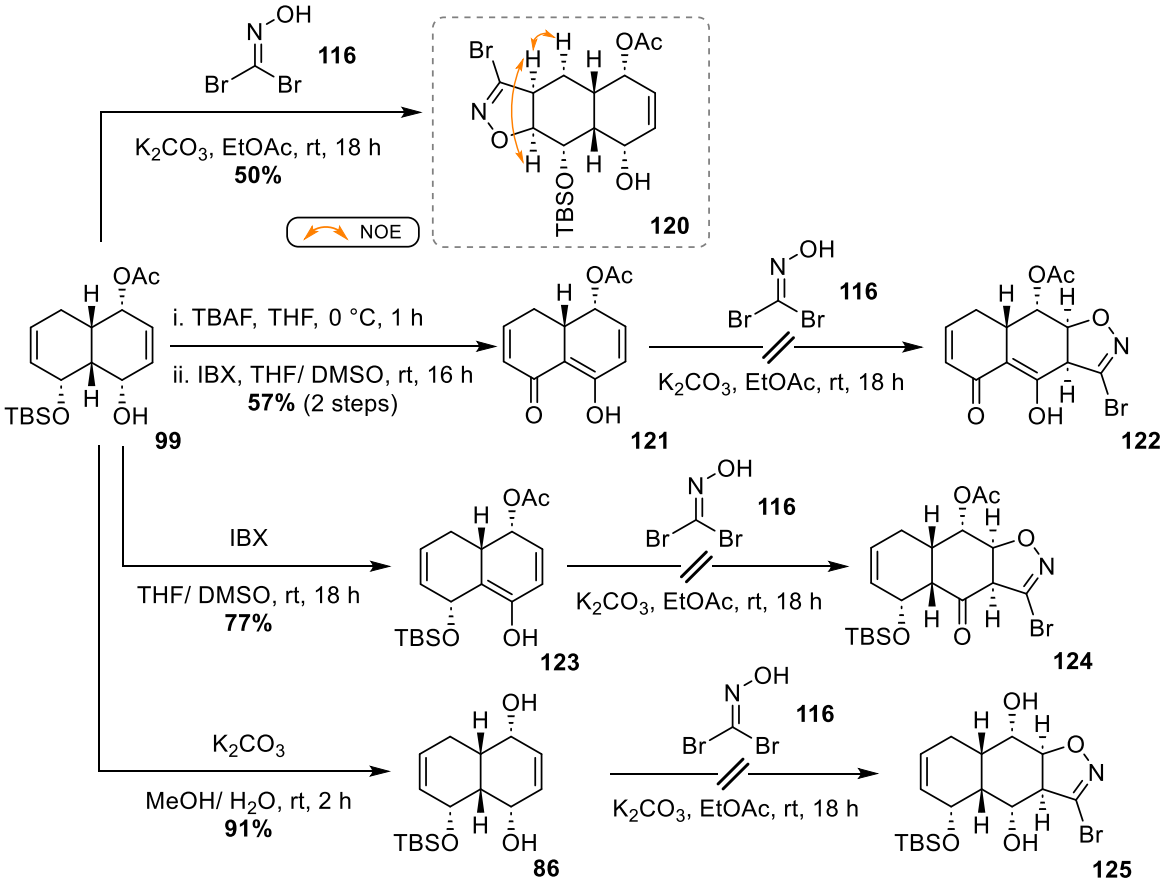


Scheme 4.3.3: Attempted preparation of eastern fragment **105** in the convergent synthesis of amidochelocardin (**5**). Starting from the previously prepared bicyclic intermediate **96**, the (*R*)-configured amino group at *C*4 is introduced *via* a stereoselective Tsuji–Trost reaction.

Lastly, a first trial towards the installation of the bromo-isoxazoline moiety was conducted with amide **114** by following the method proposed by Umstead et al.[156] Unfortunately, upon treating decalin-enone **114** with dibromoformaldoxime (**116**) under the conditions shown in **scheme 4.3.3**, the reaction failed to set in, with further trials and adaptations of the protocol also remaining unsuccessful in providing the desired outcome.

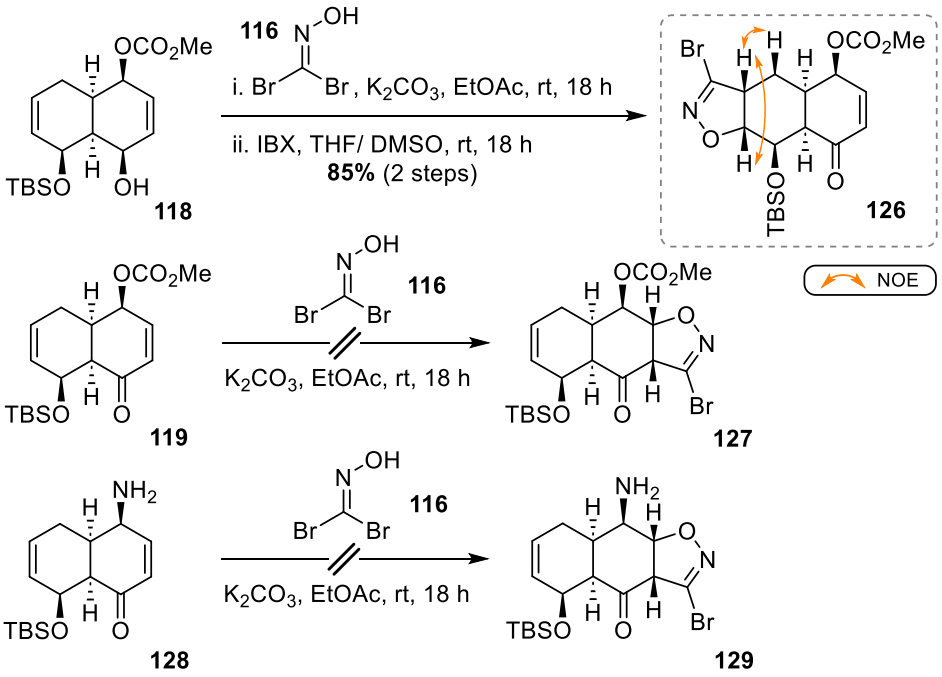
By replacing the originally used base (K_2CO_3) with NEt_3, thus ensuring a homogenous reaction medium, a rapid degradation of the reaction components was observed, even at temperatures below 0 °C. The repeatedly failed trials of accessing tricycle **117** from **114** ultimately led to the abandonment of the strategy. A lengthy quest for establishing suitable precursors for the dipolar cycloaddition within the proposed retrosynthesis was thus initiated, with the following sections comprising a series of attempted 1,3-dipolar cycloadditions between dibromoformaldoxime (**116**) and a wide array of potentially suitable decalin precursors (**scheme 4.3.4** and **scheme 4.3.5**). The utilized substrates originated either from the route depicted in **scheme 4.3.3** (i.e., the initially attempted preparation of fragment **105**) and the alternative route of accessing methylated decalin **85** in the total synthesis of premithramycinone (**2**; *chapter 4.1.5*). Acetate **99** originates alongside allyl diol **96** from the chiral resolution of **rac-96**, a valuable precursor in the attempted syntheses of chromocyclin (**4**).

Beginning with the attempted [3+2]-cycloadditions of dibromoformaldoxime (**116**) with acetate **99** and derivatives thereof, the results of the performed studies are summarized in **scheme 4.3.4**. Under the applied conditions, among the investigated candidates, only acetate **99** managed to undergo the desired transformation. Given the similar electronic properties of the two olefin moieties of **99**, the *in-situ* generated bromonitrile oxide (not shown; structure in analogy to **110'**) seemed to prefer the less congested olefin at *C*6-*C*7. Thus, the transformation exclusively yielded the concave-convex-arranged tricycle **120** as the sole reaction product, with the newly generated bromo-functionality conveniently pointing away from the bulky silyloxy group at *C*8. These observations were found to be in agreement with those reported by Umstead et al., who, upon treating allylic alcohols with dibromoformaldoxime (**116**), encountered the formation of regioisomers with architectures similar to that of **120**. [156] Furthermore, the studies summarized in **scheme 4.3.6** also seem to confirm the aforementioned observations.



Scheme 4.3.4 Overview of the trials performed towards finding a suitable precursor for the [3+2]-cycloaddition during the attempted synthesis of eastern fragment **105**.
Various substrates, originating from previously explored routes (*chapter 4.2*), as well as newly prepared derivatives thereof, were subjected to the conditions proposed by Umstead et al.[156]

In spite of bearing an undesired architecture, cycloaddition product **120** was nevertheless subjected, upon alcohol oxidation, to the conditions proposed by Tamborini et al. for generating benzyloxy-substituted isoxazolines from their corresponding bromo-derivatives.[157] Since the envisioned transformation failed to set in, the initial premise of addressing benzyloxy-isoxazolines by this strategy (**scheme 4.3.2**) could not be confirmed, with bromide **120** failing to undergo the aimed transformation. Nevertheless, several additional cycloaddition screenings (**scheme 4.3.5**) were conducted in order to ascertain the possibility of installing the isoxazoline moiety at an earlier stage in the synthesis.

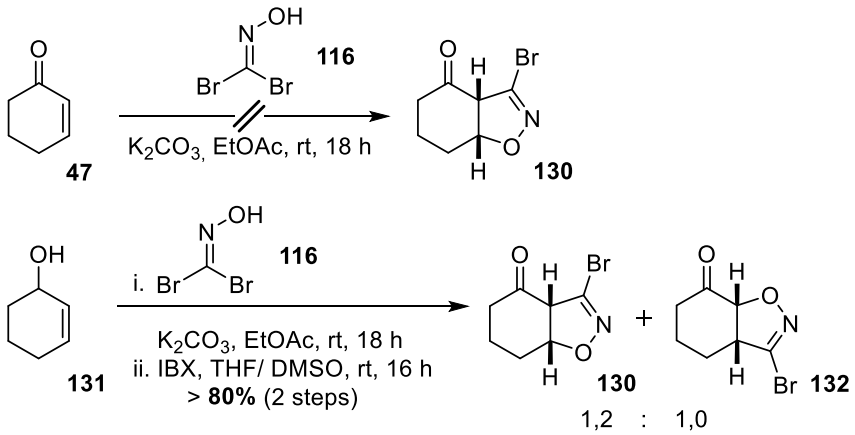


Scheme 4.3.5: Further attempts towards establishing suitable substrates for the [3+2]-cycloaddition within the originally proposed route of accessing eastern fragment **105**.

During a second trial of establishing suitable substrates for the envisioned 1,3-dipolar cycloaddition, a small panel consisting of precursors originating from the attempted synthesis of carbamate **117** was investigated. This included carbamate **118**, enone **119** and amine **128**. Precursor **118** was found to be the only substrate to successfully undergo cycloaddition with oxime **116**, with its architecture highly resembling that of acetate **99**. Upon oxidizing the obtained cycloaddition product with IBX, enone **126** was obtained and its structure determined by means of NMR-analysis, with the oxidation step easing the assignment of the recorded signals. Once more, the cycloaddition reaction proceeded smoothly in a diastereoselective manner, the obtained product bearing, in the given context, an unsuitable architecture for future derivatizations. Nevertheless, the conversion of the bromo-functionality at the isoxazoline core towards the much-required benzyloxy moiety was attempted by the previously addressed means, with the convex-concave-arranged product failing once more to undergo the envisioned transformation. This observation raised further suspicions regarding the feasibility of the proposed strategy.

Failing to ascertain a suitable target for the [3+2]-cycloaddition within the shown panels, the reactions with the dipole originating from dibromoformaldoxime (**116**) clearly leading to the exclusive formation of architectures that were not compatible with the originally envisioned strategy, the path depicted in **scheme 4.3.3** was ultimately halted. A last study was conducted, however, in order to further cement previous reasonings, with the outcome shown in **scheme 4.3.6**.

By subjecting both 2-cyclohexen-1-one (**47**) and 2-cylco-hexen-1-ol (**131**) to the already explored conditions, only allylic alcohol **131** managed to undergo cycloaddition with dibromoformaldoxime (**116**), enone **47**, unsurprisingly (see above), failing to show any reactivity at all. Since alcohol **131** was used as a racemate for this study, the reaction resulted in the formation of a complex, inseparable mixture of regio- and diastereomers.



Scheme 4.3.6: Cycloaddition-study: Treatment of 2-cyclohexen-1-one (**47**) and 2-cylco-hexen-1-ol (**131**) with dibromoformaldoxime (**116**). While enone **47** showed no reactivity, allylic alcohol **131** underwent the desired transformation, yielding a complex mixture of inseparable products.

By oxidizing the alcohol moiety of the obtained cycloaddition product to the corresponding ketone functionality, a mixture consisting primarily of products **130** and **132** was obtained, and a brief, joint characterization was performed. Based on the acquired data, a slight preference of the dipole towards the formation of **130**– the regioisomer where the newly introduced bromo-functionality is located in a 1,3-distance to the alcohol moiety, became obvious. This observation was found to be in disagreement with previous experimental observations; free allylic alcohols being found to play an active role in the regioselective proceeding of the reaction (*chapter 4.1.2*). Nevertheless, the unpredictability of the investigated [3+2]-cycloaddition was thus proven once more, thus further contributing to the need for establishing a new strategy for accessing eastern fragment **105**.

4.3.2 Synthesis of decalin-enone **105** *via* a Michael–Claisen cascade

In a second attempt to synthesize decalin-enone **105** as the *C*8a-deoxy eastern fragment in the proposed total synthetic path for addressing amidochelocardin (**5**; **fig. 4.3.1**), a strategy, successfully implemented by the Myers laboratories for accessing various tetracycline-derived compounds, was considered (**fig. 4.3.4**).[55] In contrast to the previously presented efforts of generating the isoxazole motif *via* a [3+2]-cycloaddition, the adapted approach utilizes a diastereoselective Michael–Claisen cascade for the construction of enone **105**, bearing the A/B-ring motif of the future tetracycline target **5**. The aimed isoxazole-bearing decalin can thus be traced back to the bridged pentacyclic intermediate **133**, its enone motif being released *via* a *retro*-Diels–Alder step. The isoxazole-bearing intermediate **133**, representing the product of the envisioned ciclization cascade, can be traced back to enone **134**– a chiral equivalent of cyclohexenone,[159,160] and isoxazole **135**, with the bridged architecture of enone **134** being solely responsible for the diastereoselective proceeding of the transformation.

While enone **134**, a literature-known compound, can be conveniently accessed by means of a Diels–Alder reaction between silylated cyclopentadiene **136** and *para*-benzoquinone **97**,[55] the preparation of isoxazole **135** demands, primarily for the installation of the desired *N*-bearing moieties, several alterations to already established approaches. Nevertheless, its generation can be traced back to benzyl alcohol **137**, a valuable building block in the synthesis of tetracycline natural products.[40,54]

Taking the high, versatile reactivity of amines into consideration and with regard to the entirety of the envisioned approach, two strategies were envisioned for the protection of the *C*4-amine functionality of eastern fragment **105**: (I) its masking as a N_3-group and (II) its *di*-Boc-protection, both strategies ensuring a high orthogonality for future transformations.

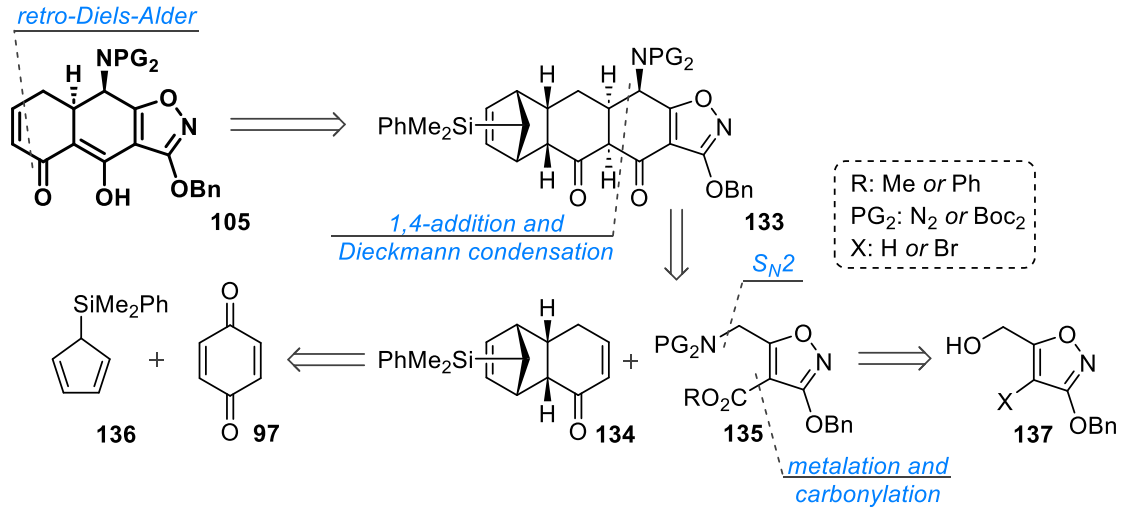
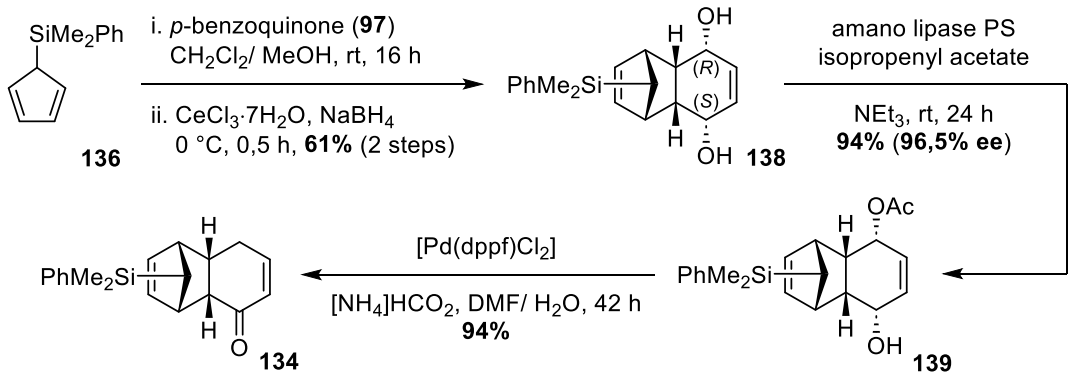


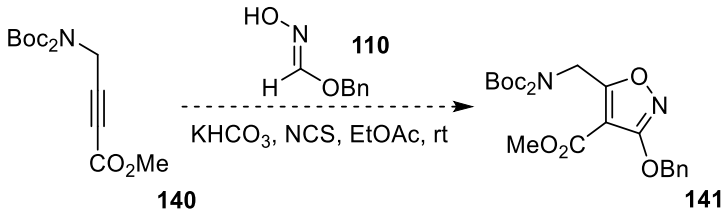
Fig. 4.3.4: Second-generation approach towards decalin-enone **105**. By employing a literature-inspired protocol consisting of a Michael–Claisen cascade between enone **134** and isoxazole **135**,[20] the construction of the decalin core of **105** is aimed in a convergent fashion.

Before addressing the attempts at synthesizing isoxazole **135**, the forward synthesis of enone **134** (**scheme 4.3.7**), accomplished in accordance with the path described by Kummer et al., will be briefly presented in the upcoming part.[55] At first, *meso*-diol **138**, bearing the B-ring of the future tetracycline skeleton, was constructed in two steps *via* an *endo*-selective Diels–Alder reaction between 1,4-benzoquinone (**97**) and the silylated cyclopentadiene **136**, followed by the Luche reduction of the carbonyl moieties. Since the product of the [4+2]-cycloaddition is C_2-symmetric and the 1,2-reduction proceeded in a diastereoselective fashion, *meso*-diol **138** was isolated as the sole reaction product with a moderate yield of **61%**. Further on, diol **138** was successfully desymmetrized in the presence of isopropenyl acetate under the catalytic action of amano lipase PS, the reaction exclusively providing acetate **139** with an excellent yield of **94%** and **96,5% ee**.
Lastly, a palladium-mediated stereospecific 1,4-hydrogen migration[161] gave the highly unstable (*chapter 6.5.3.3*) rearranged enone **134** with an excellent yield of **94%**.



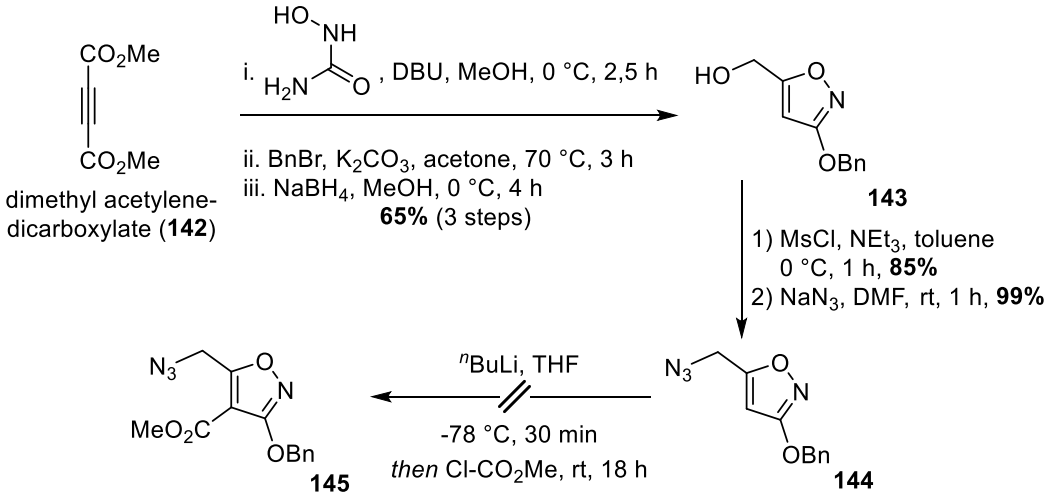
Scheme 4.3.7: Four-step synthesis of enone **134**, including an *endo*-selective Diels–Alder reaction between cyclopentadiene **136** and *para*-benzoquinone (**97**).[55]

With the synthesis of one of the two fragments required for the modified approach (**fig. 4.3.4**) towards eastern fragment **105** completed, the synthetic focus could be shifted towards the preparation of suitably decorated isoxazoles, bearing architectures similar to that of **135**. At first, a hypothetic synthetic approach towards building block **141** was envisioned to proceed in one step, in analogy with the previously proposed path of accessing precursor **115** (**scheme 4.3.2**). For this strategy, alkyne **140** would have been prepared in accordance with existing literature[162] and reacted with oxime **110** in a 1,3-dipolar cycloaddition-fashion (**scheme 4.3.8**).[154,163] However, since previous attempts at synthesizing oxime **110** repeatedly failed to yield reliable results, this initial strategy was never investigated, a path following the strategies exploited by Kummer et al. being preferred instead.[55]



Scheme 4.3.8: Hypothetic one-step strategy of accessing isoxazole **141** *via* a 1,3-dipolar cycloaddition between alkyne **140** and oxime **110**.

Following the path originally elaborated by the Myers laboratory, the crucial isoxazole building block **143** could be easily accessed *via* the three-step sequence highlighted in **scheme 4.3.9**.[55] By treating acetylene-dicarboxylate **142** with *N*-hydroxyurea in the presence of DBU, the isoxazole skeleton was constructed *via* a formal [3+2]-cycloaddition reaction.[164] Further derivatizations of the newly generated architecture consisted of the benzyl-protection of the phenol group, followed by the reduction of the *C*5-methyl ester to form the corresponding alcohol. Benzyl alcohol **143** was thus obtained with a moderate yield of **65%** on a multigram scale.



Scheme 4.3.9: Attempted synthesis of isoxazole building block **145**.

With the construction of precursor **143** completed, the synthesis of azide **145** was first attempted *via* the three-step sequence shown in **scheme 4.3.9**. By first mesylating benzyl alcohol **143**, the azide moiety of **144** was easily introduced through a substitution reaction, the two steps proceeding with a combined yield of **84%**. Unfortunately, the attempted introduction of the *C*4-ester moiety in precursor **144** remained unsuccessful. By treating azide **144** with a solution of ^{n}BuLi at –78 °C, the degradation of the starting material set in rapidly, making the addition of the chloroformate obsolete.

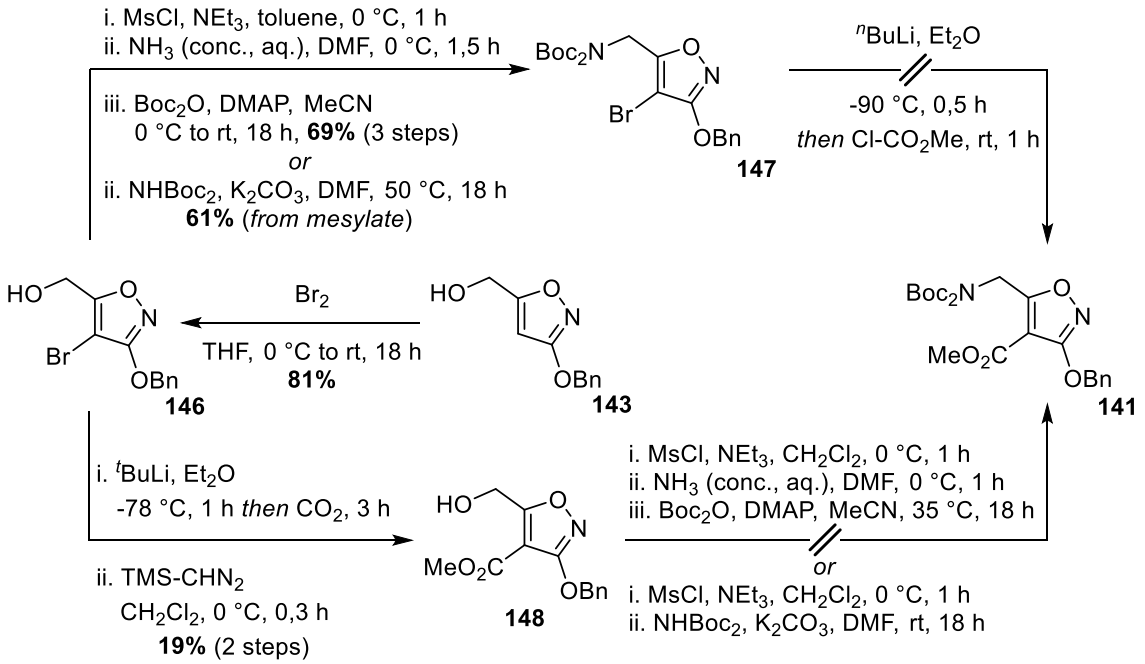
The decomposition path was not further investigated. Ultimately, the strategy aiming at the synthesis of **145**, by the means highlighted in **scheme 4.3.9**, was abandoned and a new strategy explored.

Considering the generally unstable nature of organoazides, their demanding handling and poor reaction predictability, an isoxazole target **141**, bearing a *di*-Boc-protected amino-functionality, was taken into consideration for the new strategy. Furthermore, in order to facilitate the installation of the methyl ester functionality at *C*4, the position was brominated by known means (**143→146)**,[165] with the desired functionality remaining to be generated through a lithiation/carbonylation step.[55] Starting from bromide **146**, two approaches towards **141** were proposed and investigated (**scheme 4.3.10**).

At first, the benzyl alcohol moiety of the starting material **146** was derivatized to generate the corresponding *di*-Boc-protected amine (→**147**), the last step towards **141** being represented in this instance by the installation of the carboxylate at *C*4.

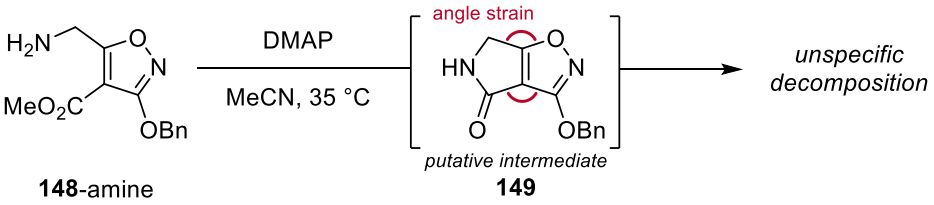
The conversion of alcohol **146** to bromide **147** proceeded smoothly, with two routes being successfully elaborated. By first mesylating the alcohol, the protected amino-group could be either generated *via* an amination-protection approach (**69%** yield over three steps) or by following an approach proposed by Oslund et al.[166] Through this protocol, the previously generated **146**-mesylate was directly converted to **147** by using $NHBoc_2$ in the presence of base (**61%** yield from mesylate). Despite the successful preparation of **147** however, the generation of the carboxylate moiety at *C*4 could not be achieved by the implemented strategy (**scheme 4.3.10**), the utilized conditions rapidly leading to an unspecific degradation of the starting material.

By following the second envisioned strategy of accessing precursor **141**, the brominated *C*4-position of isoxazole **146** was successfully derivatized (formation of methyl ester **148**) *via* a two-step sequence, the transformation proceeding, however, only with a poor yield of **19%**. Nevertheless, the synthesis towards isoxazole **141** was pursued with alcohol **148**, with the final step of the sequence, i.e., the installation of the *di*-Boc-protected amino-moiety, relying on the means already explored before.



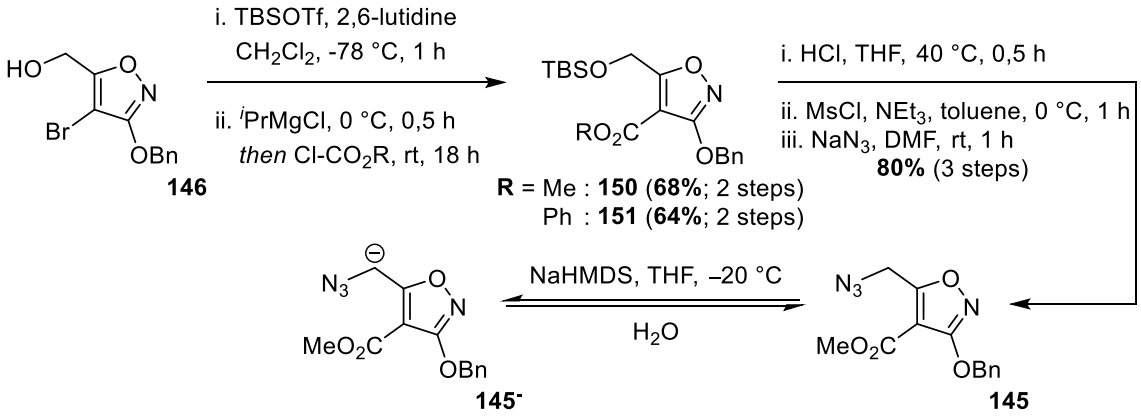
Scheme 4.3.10: Further attempts towards the generation of an isoxazole building block bearing an architecture similar to that of intermediate **135**. Through the modified approach, the synthesis of *di*-Boc-protected benzyl amine **141** was investigated *via* different protocols.

While the mesylation of the benzyl alcohol moiety managed to proceed smoothly, conveniently yielding the desired product, the further attempted derivatizations of the compound towards **141** failed to deliver the desired outcome. In the first instance, during the step-wise installation of the required functionalities, a slow decomposition of the utilized materials was observed upon the addition of DMAP to the reaction mixture. By lacking any chemoselectivity towards the activation of carboxylates and derivatives thereof, the presence of DMAP, required otherwise for a successful *di*-protection of the amino-group, is believed to have facilitated an intramolecular transesterification reaction (**scheme 4.3.11**), thus resulting in the generation of a highly labile bicycle **149**.[167,168] By experiencing a high angular strain at the annulation-positions,[131] the formed intermediary product **149** would rapidly undergo N-O-bond cleavage, the scission of the heterocycle being presumably responsible for further, unspecific decomposition of the material. Investigations into elucidating the decomposition path of aminated **148** were not conducted. Nevertheless, the *in-situ* formation of the strained intermediate **149** is also believed to have led to the decomposition of the material during the second attempted approach of protecting the amino-group *via* the direct strategy (use of $NHBoc_2$).
Considering the unreliability of the attempted methods, the strategy relying on the use of isoxazole **141** was ultimately abandoned, and the focus shifted back to the azide-bearing precursor **145**, with a last effort towards its preparation being conducted.



Scheme 4.3.11: Boc-protection of **148**-amine: formation of putative intermediate **149**.

Inspired by the strategy developed by Myers and Brubaker for converting *C*4-brominated isoxazoles (e.g., **146**) to the corresponding carboxylates using ^{i}PrMgCl, followed by treatment of the newly formed organomagnesium species with CO_2, the modified route towards azide **145** is shown in **scheme 4.3.12**.[60,165]



Scheme 4.3.12: Preparation of azide-bearing isoxazole **145** from benzyl alcohol **146** *via* a modified approach along with an initial stability trial.

In contrast to the preparation of **148** *via* the lithiation/ carbonylation protocol (**scheme 4.3.10**), the benzyl alcohol moiety of **146** was protected prior to *C*4-derivatization by converting it to the corresponding TBS-ether. The metalation of the isoxazole was then achieved in accordance with the

aforementioned strategy, whereby the trapping with chloroformates, as opposed to gaseous CO_2, conveniently led to the formation of esters **150** and **151**.[15]

Finally, azide **145** was successfully prepared in three steps, including the cleavage of the silyl ether, the mesylation of the thus released benzyl alcohol, and, lastly, an azidation reaction. The sequence gave product **145** with an **80%** yield, with a base-stability trial being conducted with the obtained material in order to ascertain its viable use for the envisioned Michael–Claisen step. For this purpose, the material was dissolved in dry THF and treated with a NaHMDS-solution (1M; THF) at –20 °C.[55] Upon completion of the addition of the base, a rapid degradation of the material was observed, the trial, along with the whole strategy, being thus abandoned.

By failing to generate a favorable outcome, both strategies presented in chapters 4.3.1 and 4.3.2 were ultimately abandoned, with the total synthesis of carbamidochelocardin (**5**) remaining to be achieved by other means. Nevertheless, the exploration of the proposed paths provides valuable insights for future attempts. Since the presented syntheses were conducted during the last part of the preparative work, a continuation of the synthetic efforts could not be conducted.

[15] The use of phenyl esters in disregard of their counterparts was described in the past to facilitate the condensation step during the coupling of isoxazoles with enone **134**.[58] With the implemented approach, the preparation of both phenyl and methyl esters was enabled.

5 Summary, conclusions, and outlook

Initiated in 2016 as part of an inter-institutional effort to discover new leads with enhanced antimicrobial properties within the tetracycline drug family, the total synthetic strategy addressed in chapter 3 was originally solely aiming at the preparation of the natural product-derived target carbamidochelocardin (**5**; **fig. 5.1.1**), with the validation of its absolute configuration representing the ultimate scope. Inevitably, the potential of accessing unprecedented, fully synthetic derivatives *via* total synthesis quickly became apparent, and the isolation of tetracyclic reaction precursors as well as the preparation of new tetracycline-derived compounds became an additional task. The tetracycline biosynthetically related non-antimicrobial natural products (**fig. 5.1.1**), demethylpremithramycinone (**1**), premithramycinone (**2**), *epi*-chromocyclin (**3**), and chromocyclin (**4**), were added to the target panel shortly thereafter, their accession also being aimed at by the means envisioned for the preparation of the originally proposed target. Given the slightly lower molecular complexity of these compounds, in contrast to that of amidochelocardin (**5**), as well as the potential of jointly accessing all targets in similar ways by repurposing advanced reaction intermediates, the synthetic advances previously presented in this work focused mainly on the preparation of the *C*4-oxygenated compounds **2** – **5** (*chapters 4.1* and *4.2*). The synthesis of carbamidochelocardin (**5**; *chapter 4.3*) was attempted during the later stages of the preparative work. Several trials were attempted towards the completion of the task, with the insights originating from the investigations provided by several researchers,[16] serving as the foundation for the proposed synthetic strategies.

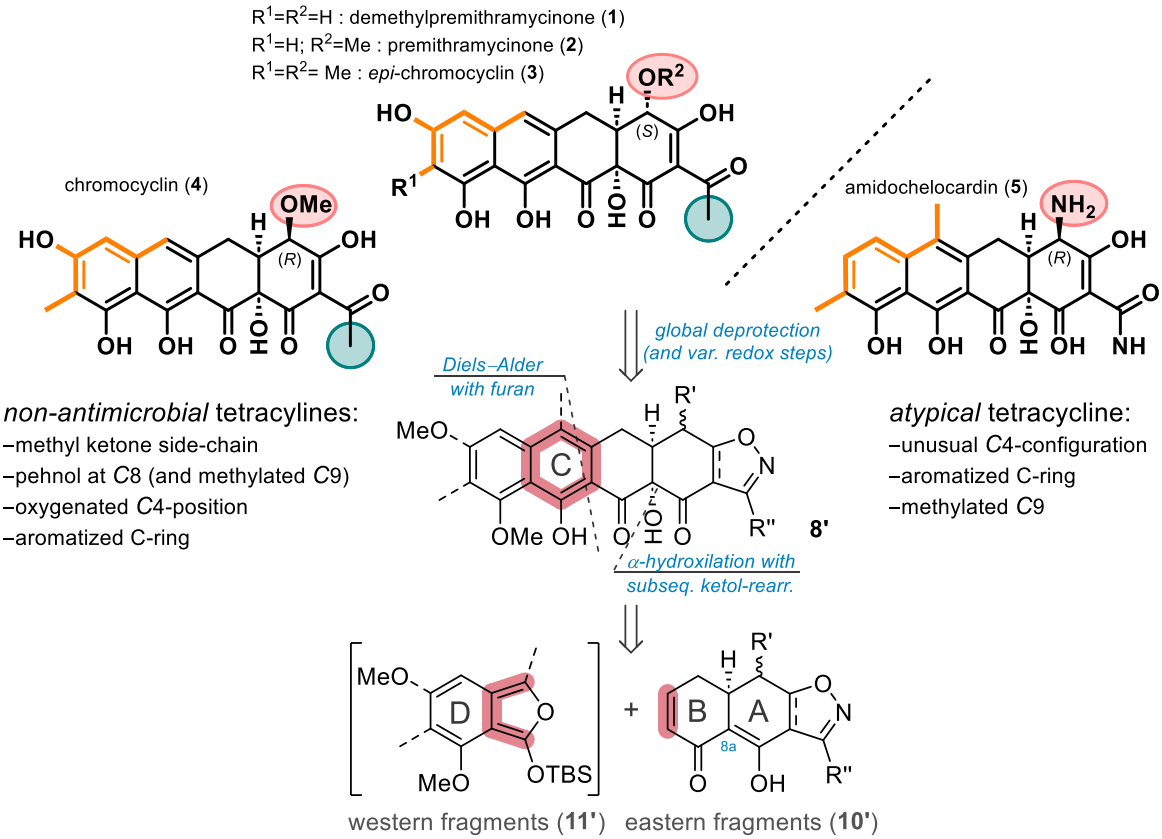


Fig. 5.1.1: The structures of the targeted tetracyclines **1** – **5**, depicted along the generalized retrosynthetic approach envisioned for their preparation.

[16] Unpublished results provided by U. Eggert, V. Wandelt, and A. Serraiocco.

Ultimately, the following chapter summarizes the successes and breakthroughs as well as the recurring difficulties encountered during the synthetic investigations. Since significant progress towards the synthesis of demethylpremithramycinone (**1**) was made during the preparative part of the work, the results of these advances will be summarized in chapter 5.1.2, leaving chapter 5.1.1 to address the advances made towards the preparation of the eastern fragments. The progress made towards the total synthesis of carbamidochelocardin (**5**) is discussed in chapter 5.2.
In addition, since a small panel of reaction precursors derived from the attempted total synthesis of demethylpremithramycinone (**1**) was externally evaluated to determine any potential antimicrobial activity, the results of these trials have also been included in chapter 5.1.2.

5.1 The premithramycinones and chromocyclins

Given the close structural relationship of the targets, their preparation often relying on building blocks of common origins and of similar complexity, the advances made towards the total syntheses of the two premithramycinones **1** and **2**, as well as those concerning *epi*-chromocyclin (**3**), alongside its *C*4-epimer chromocyclin (**4**), will be jointly addressed in the upcoming subchapters. The focus herein lies on the synthesis of the eastern fragments required for the envisioned [4+2]-cycloaddition step as well as the progress made towards accessing demethylpremithramycinone (**1**).
The preparation of the two phthalide-based western fragments **44** (*chapter 4.1.3*), required for the synthesis of premithramycinones **1** and **2**, and **89** (*chapter 4.1.6*), required for that of chromocyclins **3** and **4**, will be completely omitted from the discussions, their preparation proceeding in both instances smoothly from commercially available sources.

5.1.1 Divergent Synthesis of the eastern fragments

In order to fulfill the initial premise of addressing the natural product targets shown in **fig. 5.1.1** *via* a common route, a highly divergent approach towards the preparation of the eastern fragments, bearing most of the characteristic decorations of the future A/B-ring systems, had to be implemented prior to the construction of the naphthacene core. By following the retrosynthetic strategy discussed previously in the introductory part of chapter 4 and taking into consideration the structural differences of the targets, the construction of the two aureolic acid biosynthetic precursors demethyl-premithramycinone (**1**) and premithramycinone (**2**), as well as that of the *C*9-methylated homologue *epi*-chromocyclin (**3**), was found to rely on the use of eastern fragments of common origin. Chromocyclin (**4**) and amidochelocardin (**5**), both bearing an (*R*)-configured *C*4-center, demanded, on the other hand, a modified approach towards the preparation of their characteristic eastern fragments. For this purpose, a second route was envisioned, its proceeding *via* the formation of a racemic reaction intermediate (see further) conveniently bridging the two strategies, further contributing to the divergent nature of the global approach. Due to the more challenging nature of the strategy required for its preparation, the routes aiming at the synthesis of the eastern fragment required for the preparation of amidochelocardin (**5**) were summarized in chapter 5.2.

Beginning with the aureolic acid biosynthetic precursor demethylpremithramycinone (**1**), the initial considerations regarding its preparation led to the elaboration of two approaches: an early-stage derivatization strategy (i.e., **path A**; *chapter 4.1.2*), proposed in agreement with the advances made by the Myers laboratories (*chapter 2.2.5.2*), and a late-stage derivatization strategy (i.e., **path B**;

chapter 4.1.3). The difference between the two approaches lies in the generation of the *C*8a-positioned tertiary alcohol (later becoming the *C*12a-position of the tetracycline core). Conveniently, the exploration of the first mentioned strategy (**path A**) required the successful synthesis of *C*8a-deoxy product **32** (**fig. 5.1.2**)– the key building block for the late-stage derivatization strategy.

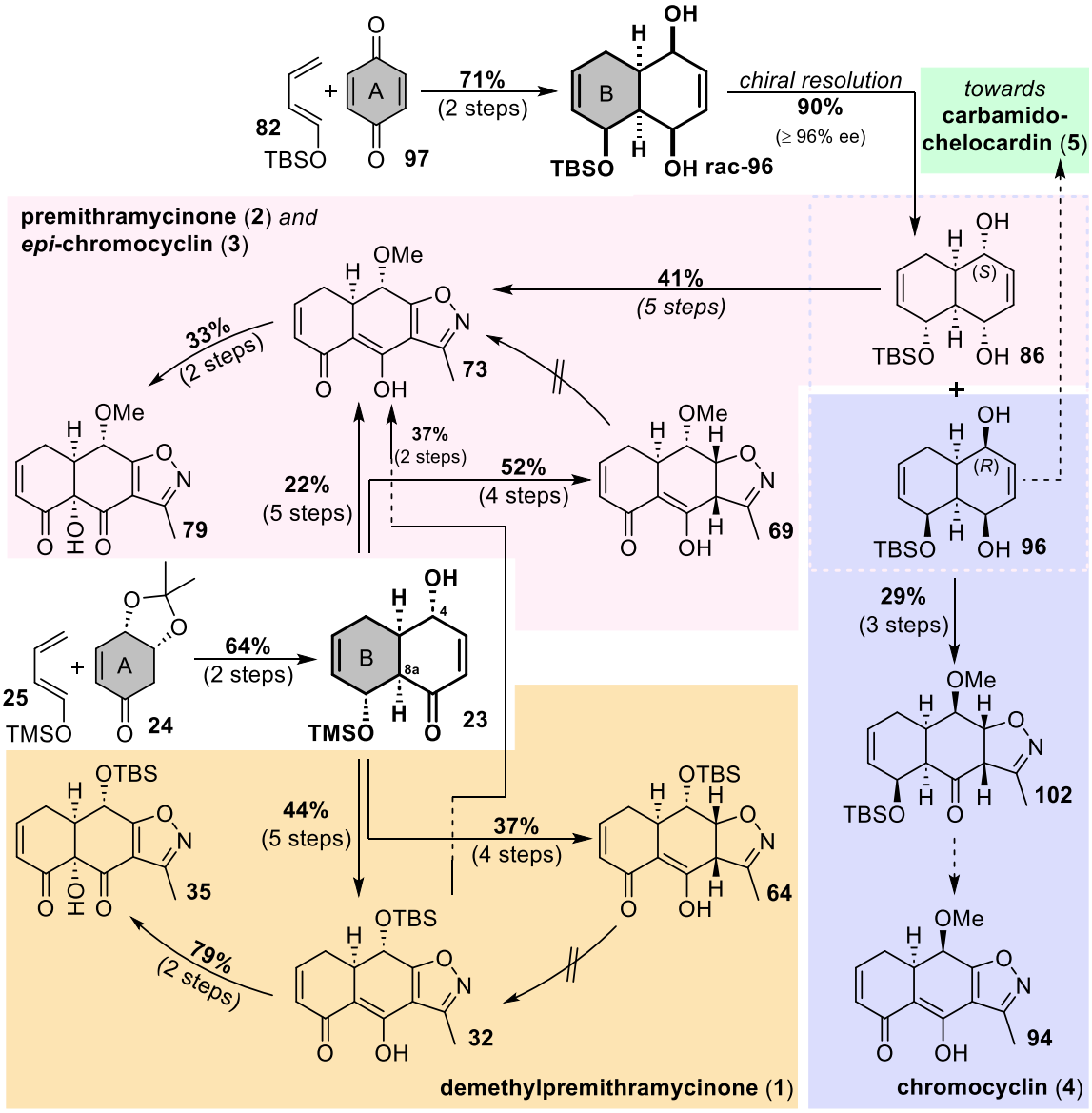


Fig. 5.1.2: Divergent approach towards the preparation of the eastern fragments required for accessing targets **1** – **4** *via* a Diels–Alder key step.

By following the path depicted in **fig. 5.1.2**, the multigram-scale production of the valuable *C*8a-deoxy eastern fragment **32** was successfully achieved from the privileged decalin-enone **23** in five steps with a satisfactory yield of **44%** (*chapter 4.1.2*). Key compound **23**, as the first A/B-ring bearing precursor of the synthesis, was prepared in two steps (**64%**), with the construction of its skeleton originating from an enantiospecific [4+2]-cycloaddition between silyloxybutadiene **25** and enone **24**, a literature-known compound derived from D-(–)-quinic acid.

With the synthesis of decalin-enone **32** completed, ketol **35** was readily accessed in two steps with a combined yield of **79%**. By employing the bulky oxidizing agent MMPP, the *C*8a-positioned alcohol was first generated with an undesired (*R*)-configuration. Nevertheless, the configurational adjustment of the center was elegantly achieved *via* an unprecedented (*chapter 2.2*) α-ketol rearrangement.

While exploring the path leading to the formation of compounds **32** and **35**, required in the synthesis of demethylpremithramycinone (**1**), the potential of repurposing enone **23** for accessing the fragments needed for the syntheses of premithramycinone (**2**) and *epi*-chromocyclin (**3**) became obvious. Thus, *C*8a-deoxy decalin-enone **73** was prepared by similar means to those established originally for enone **32**, a yield of **22%** being observed over five steps from precursor **23**. In contrast to previous encounters (synthesis of fragment **32**), the generation of the isoxazole moiety proceeded in this instance with a slightly lower yield and with the formation of regioisomers (ratio 3,5 : 1), with the factors underlying the observed proceeding of the transformation being discussed in chapters 4.1.2 and 4.1.5. Additionally, the direct conversion of silyl ether-bearing fragment **32** towards the methylated counterpart **73** was also possible, the two-step sequence proceeding with a **37%** yield. Further on, the generation and adjustment of the *C*8a-positioned tertiary alcohol of ketol **79** was also successfully accomplished by the previously explored means, the reaction proceeding in this instance with a **33%** yield. The rearrangement reaction represented in this instance the limiting factor.

In view of the repeatedly encountered problem of unsuccessful enamine hydrolysis during the hydrogenolytic cleavage of the isoxazole moiety (*chapter 4.1.3*), the isoxazoline-bearing fragments **64** and **69** (isolated along its regioisomer as an inseparable mixture) were synthesized from enone **23** as part of a later modification to the global approach (**path B'**; *chapter 4.1.4*). Attempts to aromatize the heterocyclic moieties of decalins **64** and **69** towards the eastern fragments **32** and **73**, respectively, repeatedly led to their degradation and the formation of undesired products (chapter 4.1.4).

By bearing an unusual (*R*)-configuration at the *C*4-center, the synthesis of the eastern fragment of chromocyclin **94** was targeted by following a modified approach to that of the previously discussed compounds (*chapter 4.2*). The envisioned strategy, relying on a Diels–Alder reaction between silyloxybutadiene **82** and *para*-benzoquinone (**97**) for the rapid construction of the A/B-ring system, is also highlighted in **fig. 5.1.2**. In contrast to the initially performed [4+2]-cycloaddition, which led to the formation of diastereomerically pure decalin **23**, the latter trial gave, upon Luche reduction, diol **96** as a racemate. Therefore, the chiral resolution of the isolated product **rac-96** was required, with the separation of the two enantiomers (**90%** and **>96% ee**) delightfully affording enantiomerically pure diol-precursor **96** and, upon saponification, precursor **86**. By further elaborating the *C*4-(*R*)-configured diol **96**, the advanced intermediate **102** from the synthesis of eastern fragment **94** was obtained over three steps with a combined yield of **29%**. Given the difficulties encountered while exploring the last stages of the total synthesis of demethylpremithramycinone (**1**; *chapters 4.1.3* and *4.1.4*), the unveiling of the methyl ketone functionality at the A-ring being virtually impossible by the attempted means, the efforts of accessing eastern fragment **94** were no longer pursued. Nevertheless, by establishing quick and reliable access to *C*4-(*R*)-configured decalins, the possibility of addressing carbamidochelocardin (**5**) from diol **96** became obvious. Enantiomerically pure diol **86**, on the other hand, bearing an (*S*)-configured secondary alcohol at *C*4, was successfully advanced in five linear steps with a combined yield of **41%** to decalin-enone **73**– the *C*8a-deoxy eastern fragment required for the synthesis of premithramycinone (**2**; *chapter 4.1.5*) and *epi*-chromocyclin (**3**; *chapter 4.1.6*). The elaboration of diol **86** towards eastern fragment **32**, even though plausible, was never attempted.

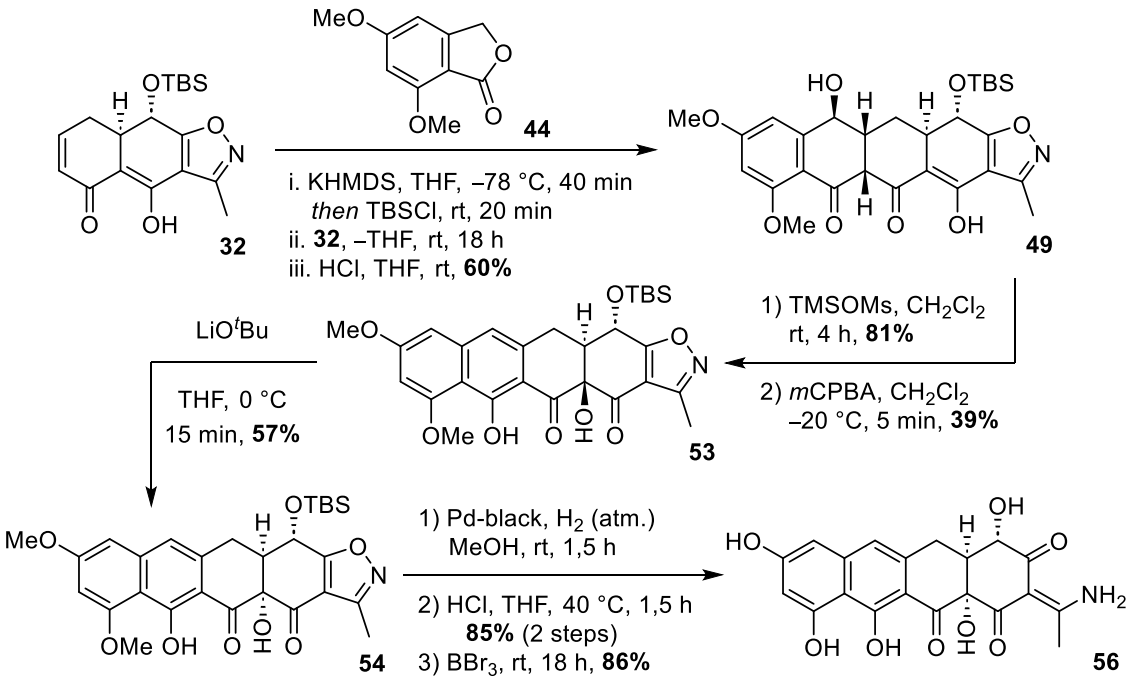
Finally, with the implementation of the approach shown in **fig. 5.1.2**, the elaborated strategies for accessing the eastern fragments of the targeted compounds were successfully bridged, and the initial premise of addressing the natural product shown in **fig. 5.1.1** *via* a common path ultimately fulfilled.

5.1.2 Advances towards demethylpremithramycinone

By providing reliable access to both western and eastern fragments by the previously reiterated means (*chapter 5.1.1*), the way was paved for future elaborations of the compounds towards the natural product targets. Since decalin-enones **32** and **35** were the first members of the panel to be synthesized, the total synthesis of demethylpremithramycinone (**1**) was first attempted in agreement with **path A**– the early-stage derivatization strategy (*chapter 4.1.2*). Inspired by the approach established by Myers et al. in 2005,[50,56] who utilized for the generation of various tetracycline targets fragments already containing the tertiary alcohol functionality at the A/B-ring junction, the preparation of tetracycline target **1** was attempted by using eastern fragment **35**.

Prior to forging the characteristic ring system, however, the protection of the *C*8a-positioned alcohol was unsuccessfully attempted by several means. With this path failing to prove its viability, the late-stage derivatization strategy, requiring the generation of the *C*12a-positioned alcohol to proceed prior to the global deprotection of the system, was considered instead. For this approach (**path B**; *chapter 4.1.3*), *C*8a-deoxy eastern fragment **32** was successfully reacted with phthalide **44** *via* an *endo*-selective Diels–Alder reaction, the transformation resulting in the formation of a highly decorated naphthacene precursor **49** with a satisfactory yield of **60%** (**scheme 5.1.1**). Pursuing the syntheses further towards the aureolic acid biosynthetic precursor **1**, the C-ring of pentacycle **49** was successfully aromatized in one step (**81%**), a small amount of the thus prepared *C*12a-deoxy-compound being deprotected (preparation of **152** described in chapter 6.2.3.4) and subjected along with two other tetracyclines to biological evaluation (*see further*; **tab. 7**).

Further on, with the aid of *m*CPBA, the introduction of the hydroxy-functionality at the *C*12a-position was successfully achieved, giving ketol **53** with a **39%** yield. Since the reaction afforded, as originally anticipated, an undesired (*R*)-configured *C*12a-alcohol due to steric hinderance exerted by the bulky *C*4-positioned TBSO-group, the configuration of the functionality was corrected *via* an α-ketol rearrangement (**57%**). The successful outcome of this key sequence represents a novel, viable solution to a long-lasting problem in the field (*chapter 2.2*).



Scheme 5.1.1: Seven-step approach towards the total synthesis of demethylpremithramycinone (**1**) by following the late-stage derivatization strategy.

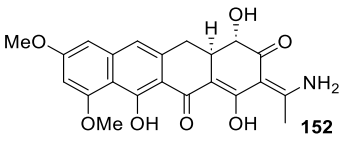
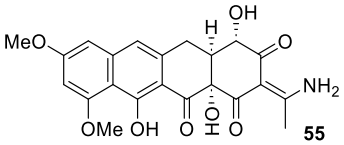
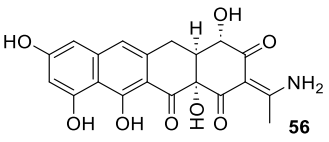
Ultimately, ketol **54** was subjected, in the last stage of the synthesis, to the global deprotection strategy. By implementing Stork's protocol of masking 1,3-diketo-functionalities as isoxazoles (*chapter 2.2.4*),[64] the final decorations at the A-ring of natural product **1** were unveiled *via* the hydrogenolytic cleavage of the heterocycle. Successful ring-scission under mild, neutral conditions thus gave a precursor bearing an enamine functionality at the *C*2-position (compound **55** in **tab. 7**). This undesired functionality remained, therefore, to be converted *via* acid hydrolysis to the corresponding methyl ketone in an additional step, along with the removal of the silyl ether at *C*4. And while the removal of the protective group was successfully achieved through the implemented protocol, the enamine moiety was found to remain intact, with the unsuccessful outcome of the reaction initiating a lengthy quest towards establishing proper hydrolysis conditions. Despite the numerous strategies that were attempted in order to accomplish this task (summarized in **tab. 5**; *chapter 4.1.3*), a successful outcome was never observed. The natural product-derived dimedone enamine **56** was nevertheless obtained upon cleaving the methyl ethers at the *C*8- and *C*10-positions, with 14 steps (and a combined yield of **2,22%**) being required for its preparation from enone **24**.
By comparing the recorded chemical shifts of the synthesized compound **56** with those reported for demethylpremithramycinone (**1**),[18] a high similarity between the compounds could be established, the only discrepancies lying in the comparison of the south-east regions of the molecules. Nevertheless, the accuracy of the assignment of the signals corresponding to the south-east region of the molecule was later confirmed by comparing the data with those provided by Chu et al. for the synthetically prepared enamine dimedone 2'-amino-*N*-carbobenzoxychelocardin **57** (structure shown in **fig. 4.1.10**).[119] The chemical shifts of the two reference compounds **1** and **57**, along with those recorded for the synthesized demethylpremithramycinone-derived enamine **56**, were summarized in chapter 4.1.3, in **tab. 4.1** (^{1}H-shifts) and **4.2** (^{13}C-shifts), respectively.

In order to overcome the impediment of unsuccessfully generating the methyl ketone functionality at *C*2, a slightly modified approach (**path B'**; *chapter 4.1.4*), relying on the use of isoxazoline-bearing C8a-deoxy eastern fragment **64** (**fig. 5.1.2**), was attempted for the preparation of demethylpremithramycinone (**1**). In this instance, the hydrolysis of an unconjugated *C*2-positioned enamine, resulting from the hydrogenolytic cleavage of the isoxazoline architecture, was hypothesized to proceed smoother, thus allowing for the installation of the required end-functionality. By following this path, an additional oxidation of the *C*3-position of the natural product would have been required. Thus, an advanced isoxazoline-bearing precursor **67** (structure in analogy to ketol **53**) was prepared by following the approach shown in **scheme 5.1.1** and subjected to various hydrogenation conditions (**tab. 6**; *chapter 4.1.4*). Since after several cleavage trials the required transformation failed to set in, the route was ultimately abandoned. The failed conversion of the enamine towards the methyl ketone moiety or, in the case of using isoxazoline-bearing architectures, the repeatedly unsuccessful cleavage of the heterocycle represents the limiting factor of the routes, with the preparation of the natural product targets **1** – **4** not being possible by the envisioned means. Ultimately, except for the preparation of an advanced *C*12a-deoxy tetracycline precursor from the premithramycinone (**2**) synthesis (*chapter 4.1.5*), no further attempts at synthesizing targets **2** – **4** were conducted.

Despite the unfinished preparation of the originally envisioned targets, the path elaborated for their synthesis (**fig.5.1.1**) managed to prove its potential on account of three fulfilled premises:
(I) by providing convenient access to structurally diverse eastern fragments *via* a divergent approach;
(II) through a rapid and facile construction of the naphthacene core bearing most of the required final decorations *via* a [4+2]-cycloaddition key step (**scheme. 5.1.1**); and
III) by the ability to generate both (*R*)- and (*S*)- configured tertiary alcohols at the *C*12a position starting from deoxy-precursors *via* the unprecedented α-ketol rearrangement.

Lastly, since one of the aims of this work was represented by the biological evaluation of the prepared compounds and/ or derivatives thereof, the inhibitory properties of three *C*4-deamino-hydroxyox tetracyclines against several pathogens of the ESKAPE panel (*chapter 2.1*), which included both Gram-negative (***A***, ***B***, ***C***, ***E***, ***G, I***) as well as Gram-positive bacteria (***D***, ***F***, ***H***), were investigated. While ketols **55** and **56** originated from the final deprotection stages of the attempted total synthesis of demethylpremithramycinone (**1**), *C*12a-deoxy compound **152** was prepared in accordance with the procedure described in chapter 6.2.3.4 from the precursor of ketol **56**. The results of the conducted MIC-analyses, kindly provided by Dr. Jennifer Herrmann and Alexandra Amann from the Helmholtz Institute for Pharmacological Research Saarland (HIPS), are summarized in **tab. 7**.

Tab. 7: MIC determination-assay for three fully synthetic tetracycline-derived compounds.

strain	 **152**	 **55**	 **56**
A	>64 µg/ ml	>64 µg/ ml	>64 µg/ ml
B	>64 µg/ ml	>64 µg/ ml	>64 µg/ ml
C	>64 µg/ ml	>64 µg/ ml	>64 µg/ ml
D	>64 µg/ ml	**64 µg/ ml**	>64 µg/ ml
E	>64 µg/ ml	>64 µg/ ml	>64 µg/ ml
F	>64 µg/ ml	>64 µg/ ml	>64 µg/ ml
G	>64 µg/ ml	>64 µg/ ml	>64 µg/ ml
H	>64 µg/ ml	>64 µg/ ml	>64 µg/ ml
I	>64 µg/ ml	>64 µg/ ml	>64 µg/ ml

A: *A. baumannii* [DSM-30008] **D**: *B. subtilis* [DSM-10] **G**: *E. coli* WT [BW25113]
B: *E. coli* WT [BW25113]+ PMBN **E**: *P. aeruginosa* PA14 [DSM-19882] **H**: *E. faecium* [DSM-20477]
C: *K. pneumoniae* [DSM-30104] **F**: *S. aureus* [Newman] **I**: *E.coli* acrB [JW0451-2]

By lacking the characteristic amino-group at the C4-position (part of the minimally required pharmacophore of the class),[4] the compounds included in **tab. 7** failed to show any bioactivity towards the test panel, with ketol **55** showing only mild antibiotic properties towards the highly sensitive strain of *B. subtilis* [DSM-10] (***D***). However, since the investigated compounds do not fully share the structural features of the antibacterial tetracyclines, they are to be included in the category of non-antibacterial tetracycline compounds, which, by definition, are substantially or completely lacking any antimicrobial activity. Nevertheless, despite being ineffective in treating pathologies of bacterial origin, numerous members of the chemically modified tetracycline class (CMTs), including *C*4-oxygenated tetracyclines, were found to bear other valuable bioactivities, such as antiproliferative and apoptotic properties against various cancer cell lines.[27,169-172] Further studies that may contribute to the fight against multidrug-resistant and apoptosis-resistant cancers are therefore highly recommendable.

5.2 Carbamidochelocardin

Lastly, as the only natural product derivative of the originally proposed target panel bearing a nitrogen atom at *C*4, the discussion of the progress made towards the preparation of carbamidochelocardin (**5**; in **fig. 5.1.1**) will be treated independently. Nevertheless, despite its structural particularities, the synthesis of tetracycline **5** was also intended to proceed *via* the originally proposed path shown in **fig. 5.1.2**. Therefore, the naphthacene core was to be constructed through a Diels–Alder reaction with furan between a phthalide-based western fragment **106** (structure shown in **scheme 4.3.1**) and eastern fragment **105** (**fig. 5.2.1**). Since the generation of phthalide **106** proceeded smoothly by following literature-known approaches (*chapter 4.3*), its further discussion will be omitted, with the current chapter focusing solely on the attempted syntheses of eastern fragment **105**.
With the successful elaboration of the divergent path shown in **fig. 5.1.2**, the opportunity of addressing fragment **105** arose, with enantiomerically pure diol **96**, originally elaborated for the synthesis of chromocyclin (**4**), being repurposed for achieving this task. Thus, precursor **96** was converted in four steps into the *C*4-carbamate-bearing precursor **114** (**fig. 5.2.1**). By successfully derivatizing both *C*1- and *C*4-positions in a highly regioselective manner (*chapter 4.3.1*), the desired (*R*)-configured amino-group was introduced *via* a stereoconservative Tsuji–Trost reaction, the four-step sequence affording precursor **114** with a **24%** yield. Since carbamidochelocardin (**5**), in contrast to targets **1** – **4**, bears an amide side chain at the *C*2-position, the further construction of the heterocycle moiety was adapted accordingly, its generation *via* a 1,3-dipolar cycloaddition requiring the use of 1,1-dibromoformaldoxime. By altering the original path, the modified approach failed to show its feasibility, with the unsuccessful installation of the benzyloxy-isoxazole moiety at the A-ring not allowing for further advances towards target **105**. Ultimately, the explored strategy was abandoned, and the synthesis of eastern fragment **105** was attempted through a second approach.

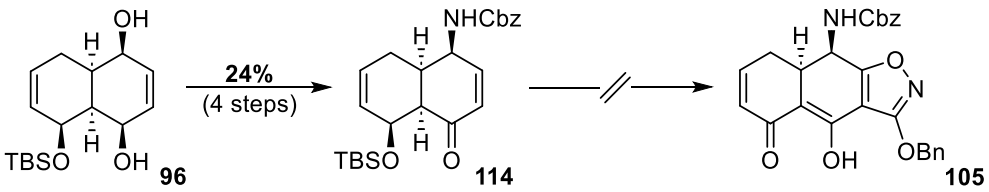


Fig. 5.2.1: Attempted preparation of eastern fragment **105** in the total synthesis of amidochelocardin (**5**). Starting from diol **96**, the (*R*)-configured amino-group at *C*4 was introduced *via* a stereoselective Tsuji–Trost reaction.

In a second attempt at preparing decalin-enone **105**, a route originally elaborated by the Myers laboratories for accessing various tetracycline-derived compounds was considered (**fig. 5.2.2**).[55] In contrast to the previously presented efforts of generating the isoxazole motif *via* a [3+2]-cycloaddition, the adapted approach utilized a diastereoselective Michael–Claisen cascade for the construction of the A/B-ring motif. By following the retrosynthetic path shown in **fig. 5.2.2**, the envisioned diastereoselective cyclization cascade required the preparation of two building blocks: enone **134**– a chiral equivalent of cyclohexenone,[159,160] and isoxazole **135**. And while enone **134** was easily prepared in four linear steps, including a Diels–Alder reaction between benzoquinone and a silylated cyclopentadiene derivative (*chapter 4.3.2*), the synthesis of a suitable isoxazole precursor **135** remained unaccomplished. Despite the rapid construction of the heterocycle and the generation of the *C*4-positioned ester moiety, a successful generation of the desired benzylamine at *C*5 has never been achieved, although several efforts have been made in this direction.

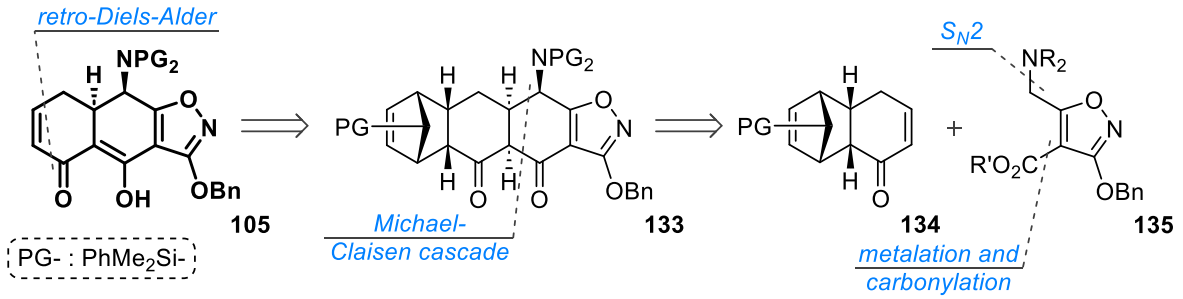


Fig. 5.2.2: Second-generation approach towards isoxazole-bearing decalin-enone **105** in the total synthesis of carbamidochelocardin (**5**). By employing a literature-inspired Michael–Claisen protocol, the construction of the decalin core is aimed in a convergent fashion from enone **134** and isoxazole **135**.[55]

Finally, due to the repeatedly unsuccessful generation of a suitable isoxazole precursor **135**, and thus the inability to provide access to a suitable eastern fragment **105**, the last attempted total synthesis of a tetracycline-derived compound was ultimately halted. Nevertheless, given the high relevance of the topic, alternative strategies might be considered in order to successfully synthesize carbamidochelocardin (**5**). Based on the insights gained by exploring the previously addressed paths, the development of a novel, improved strategy would have to provide primarily an alternative to the failed installation of the benzyloxy-isoxazole moiety or a different masking strategy for the polar functionalities at the A-ring altogether. Furthermore, since the late-stage introduction of the amine functionality to an already elaborated tetracycline architecture by means of substitution was found to be challenging, the functionality would need to be generated prior to the construction of the naphthacene core.

6 Experimental part

The last chapter comprises the experimental procedures for the previously discussed methods that led to a successful preparation of the aimed compounds, providing a detailed overlook of the used methodologies. Furthermore, an extensive characterization of the synthesized compounds is given by the end of each individual chapter. In most instances this include melting points, chromatographic and optical parameters, as well as spectrometric and spectroscopic data. Several recuring, general aspects however are only to be mentioned in the following introductory part and will be further omitted from the method-discussions.

6.1 Generalities

reagents, dry solvents and general reaction conditions

All used reagents and solvents, if not mentioned otherwise, were purchased from common chemical vendors in the highest purity available. The use of technical grade solvents, as well as the purity of technical grade reagents are always indicated in the procedures. Deionized water was used for washing and extraction steps.
Most dry solvents were either purchased as such from common vendors, or were dried as needed by SPS (*solvent purification system*; SPS-800, MBRAUN®). Dry THF, CH_2Cl_2, Et_2O and NEt_3 were freshly distilled under an inert atmosphere (Ar) by using established protcols.[173]
Room temperature is defined as the ambient temperature at which the reactions were performed without external cooling, or heating, and ranges between 18,5 °C and 23,5 °C.

handling of air- and moisture-sensitive compounds

All air- and moisture-sensitive reactions were performed exclusively under an argon-atmosphere in suitable flame-dried glassware by using the Schlenk technique. Schlenk-flasks were used when needed and in accordance with available capacities. Regular round-bottom flasks, equipped with Teflon®- or silicon-septa however were also successfully used in handling sensitive reactions.

thin-layer chromatography

Thin-layer chromatography on silica-coated aluminium plates (25 x 25 cm; MACHEREY-NAGEL®; cut to size as needed) was used as a routine-method for checking the progress of reactions, as well as for the characterization of pure compounds. Detection of the probes was achieved both by UV-irradiation of the plate (254 nm), as well as staining with common reagents such as vanillin-stain or the cerium-molybdate based Seebach's reagent. Vinylogous acid-bearing compounds could be successfully stained by using a 0,1M aqueous ferric chloride-solution. Furthermore, all synthesized tetra- and pentacyclic precursors have been found to show yellow-green fluorescence upon irritation with 254 nm light, this phenomenon coinciding with the emission of the TLC-plate. For a proper recognition of these compounds, a 365 nm UV-lamp was used alongside the previously mentioned staining reagents.

flash column chromatography	Separation of mixtures was almost exclusively achieved *via* flash column chromatography. The crude products were purified on suitable glass-columns with a SiO_2-stationary phase (0,04 – 0,053 mm), the eluents being indicated within each individual procedure.
HPLC	High-performance liquid chromatography (Agilent Tech ProStar solvent delivery systems with one incorporated 4000 psi/ 200 ml pressure module) was employed for purifying advanced polar intermediates. The separation was carried out on a Dr. Maisch GmbH Reprosphere 100 column (10 μm, 250 x 20 mm; UV-detection at 254 nm and 310 nm) with var. H_2O/ MeCN-gradients. The injected volumes (Knauer Smartline valve drive) alongside further parameters are individually indicated within the procedures. The fractions were automatically collected by a Cetac Autosampler ASX-7400 and the chromatograms analyzed with the PrepCon-software (*version 5.06.039*; SCPA GmbH).
enantiomeric excess determination– chiral HPLC	High-performance liquid chromatography (modular Merck HITACHI LaChrom L-7000-series, equipped with an L-7000 interface, L-7150 pump-module, L-7200 autosampler, L7400 UV-detector) was employed for determining enantiomeric excesses. The separation was carried out on a Chiralcel® OB-H column (5 μm; UV-detection at 250 nm). Isocratic elution was performed with 0,5% ^{i}PrOH in hexane at a flow-rate of 0,5 ml/ min. Specific volumes were automatically injected and the obtained chromatograms analyzed with the Merck Hitachi D-7000 HSM-software (*version 4.1*).
solvent removal	Solvent-evaporation under reduced pressure was carried out by using rotary evaporators (HEILDOPH; var. models) equipped with membrane pumps (VACUUBRAND®; var. models), the temperature being constantly kept at 40 °C and the pressure adjusted in accordance with the used solvents.
***melting points* (m.p.)**	The determination of melting points for all isolated solid precursors was carried out by an automatic capillary-melting point apparatus (MPA100 *by* SRS®), when sufficient quantities of material were available. In the instances where recrystallization was considered as a purifying method, the used solvents are indicated alongside the measured melting points.
optical activity **($[\alpha]^T$)**	For the measurement of optical rotations, a P8000-polarimeter (KRÜSS®) with temperature sensor was used. The samples were dissolved in spectroscopy-grade solvents (common vendors), the angles determined three times and the measured values corrected. The used solvent, the measuring-temperature T, as well as the sample-concentrations (mg/ml) are given for each measurement.
mass spectrometry	High-resolution ESI-spectra (Micromass LCT Premier with HPLC-module Arc 2695; WATERS™) were measured for all synthesized compounds. The samples were diluted with spectroscopy-grade solvents prior to injection.

NMR-spectroscopic data

For the accurate structure-assignment of the prepared compounds, NMR-analyses were carried out by using various spectrometers from BRUKER® (Ultrashield 400 MHz (ULS400) or Ascend 400 MHz), the reported spectra being evaluated with the Mnova-software (*version 14.3.1*; MESTRELAB RESEARCH®). Deuterated solvents, as well as the measuring frequencies are reported for each measurement individually. The solvent residual peaks were used for referencing the spectra. The values used for referencing ^{1}H-spectra are: 1,94 ppm (CD_3CN), 3,31 ppm (CD_3OD), 7,16 ppm (C_6D_6) and 7,26 ppm ($CDCl_3$) and those for ^{13}C-spectra: 118,3 ppm (CD_3CN), 49,0 ppm (CD_3OD), 128,1 ppm (C_6D_6) and 77,2 ppm ($CDCl_3$).[174]
The acronyms and abbreviations used to describe the signals are: m (multiplet; when an assignment cannot be carried out unambiguously), *s* (singlet), *br. s* (broad singlet), *d* (doublet), *t* (triplet), *q* (quartet), *p* (pentiplet), *dd* (doublet of doublets), *dt* (doublet of triplets), *dq* (doublet of quartets), *ddd* (doublet of doublet of doublets), *ddt* (doublet of doublet of triplets), *ddq* (doublet of doublet of quartets), *dtd* (doublet of triplet of doublets), *dddd* (doublet of doublet of doublet of doublets), *ddtd* (doublet of doublet of triplet doublets), *td* (triplet of doublets), *tt* (triplet of triplets), *qd* (quartet of doublets), *ABq* (AB-quartet).

atom-labeling in context of NMR-analysis

Lastly, since in some instances, the prepared compounds seemed to bear a high affinity towards solvents such as EtOAc, a complete solvent-removal could not be achieved in some instances. The chemical shifts for this solvents are not listed, they are however marked in the actual spectra (see appendix) and in accordance with prior observations.[174]

The numbering system used in the assignment of both ^{1}H- and ^{13}C-signals is arbitrary and based on the numbering traditionally used for tetracycline architectures. While carbon-atoms are numbered with arabic numerals, geminal hydrogen-atoms are labeled with letters.

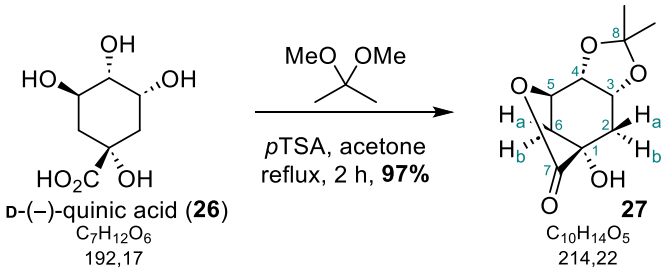
high-pressure set-up

High-pressure Diels−Alder reactions were performed by subjecting reaction solutions in sealed Teflon®-tubes (Ø 1,25 cm) to pressures of up to 15.000 bar. A special set-up (Andreas Hofer Hochdrucktechnik GmbH; model-nr.: HP14), consisting of a cylindrical reaction chamber filled with silicone oil and equipped with an external hydraulic pump (ext.-pressure up to 450 bar; conversion-rate for calculating internal pressures 1 : 33,64 bar) was employed for this task.

6.2 Demethylpremithramycinone

6.2.1 Enones **32, 64** and **35**

6.2.1.1 (3a*R*,4*R*,7*S*,8a*R*)-7-hydroxy-2,2-dimethyltetrahydro-4,7-methano[1,3]dioxolo- [4,5-*c*]-oxepin-6(4*H*)-one **27**



D-(–)-quinic acid (**26**)
$C_7H_{12}O_6$
192,17

27
$C_{10}H_{14}O_5$
214,22

For the synthesis of **27**, 19,5 g (101 mmol, 1,0 equiv.) D-(–)-quinic acid (**26**) alongside 45,0 ml (366 mmol, 3,6 equiv.) 2,2-dimethoxypropane and 1,95 g (10,3 mmol, 10 mol-%) *para*-toluenesulfonic acid monohydrate were dissolved in 675 ml technical grade acetone in a 1-l one-neck round-bottom flask. The formed cloudy mixture was refluxed for two hours after which it was neutralized with 3,0 ml wet NEt_3. The formed pale yellow solution was then concentrated under reduced pressure to yield an off-white crystalline powder (21,1 g, 90,6 mmol, **97%**), which was identified as title compound **27**.

R_f = 0,54 (PE/ EtOAc = 1:1 (v/v));

m.p. = 143 °C [*lit.: 143-144 °C*][65];

$[\alpha]_D^{22,1}$ = –39,00° ($CHCl_3$, *0,77*) [*lit.:* $[\alpha]_D^{19}$ = *–36,00° ($CHCl_3$, 0,80)*][65];

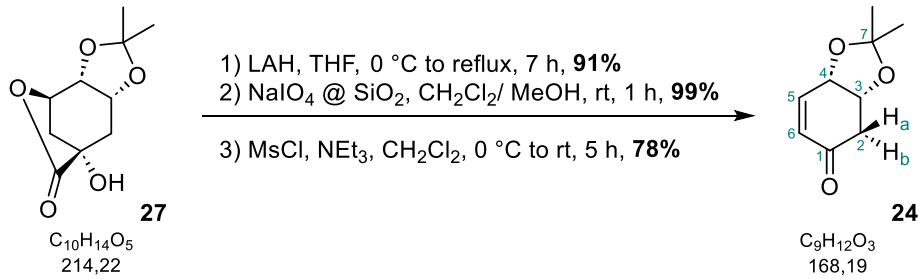
HR-ESI-MS: $[C_{10}H_{14}O_5Na]^+$: m/z = 237,0739, found m/z = 237,0207;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 1,31 (s, **3H**, CH_3), 1,51 (s, **3H**, CH_3), 2,16 (dd, *J* = 14,7, 2,9 Hz, **1H**, H6a), 2,28–2,33 (m, **1H**, H2a), 2,36 (ddd, *J* = 14,6, 7,7, 2,3 Hz, **1H**, H6b), 2,62 (d, *J* = 11,8 Hz, **1H**, H2b), 3,22 (s, **1H**, OH), 4,29 (ddd, *J* = 6,5, 2,6, 1,4 Hz, **1H**, H4), 4,46–4,51 (m, **1H**, H5), 4,71 (dd, *J* = 6,1, 2,6 Hz, **1H**, H3);

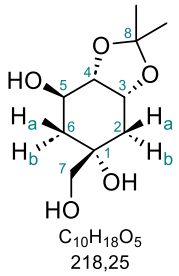
^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 24,4 (**1C**, CH_3), 27,1 (**1C**, CH_3), 34,4 (**1C**, C2), 38,2 (**1C**, C6), 71,6 (**1C**, C1), 71,7 (**1C**, C5), 72,2 (**1C**, C4), 76,0 (**1C**, C3), 109,9 (**1C**, C8), 179,1 (**1C**, C7).

The synthesis was carried out by following the protocol described by Kawashima et al.,[65] with the recorded spectroscopic data being in accordance with those reported by the authors.

6.2.1.2 (3a*R*,7a*S*)-2,2-dimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-5(4*H*)-one **24**



LAH-reduction (synthesis of (3a*S*,4*R*,6*R*,7a*R*)-6-(hydroxymethyl)-2,2-dimethylhexahydrobenzo[*d*] [1,3] dioxole-4,6-diol): A flame-dried 500-ml three-neck round-bottom flask, equipped with a condenser was charged with 4,71 g (124 mmol, 1,3 equiv.) lithium aluminium hydride, suspended in 263 ml dry THF. Upon cooling of the mixture to 0 °C, a solution consisting of 21,1 g (90,6 mmol, 1,0 equiv.) ester **27**, dissolved in 123 ml dry THF was added *via* cannula. The formed cloudy suspension was refluxed for seven hours, after which it was cooled again to 0 °C. Any unreacted alanate-residues were then neutralized by the careful addition of 4,5 ml of water, followed by 4,5 ml of 15% aqueous NaOH-solution and further 4,5 ml of water, and the mixture allowed to warm to room temperature. The precipitated aluminium salts were bonded with Na_2SO_4, filtered off *via* a sintered glass funnel and the filtrate concentrated *in vacuo* to yield the aimed triol-intermediate (19,5 g, 89,3 mmol, **91%**) as a white crystalline powder.



R_f = 0,54 (EtOAc);

m.p. = 103 °C [*lit.: 117-117,5 °C*][66];

$[\alpha]_D^{22,1}$ = –46,47° ($CHCl_3$, *2,94*) [*lit.:* $[\alpha]_D^{25}$ = *–56,07° (MeOH, 1,44)*][66];

HR-ESI-MS: $[C_{10}H_{18}O_5Na]^+$: m/z = 241,1052, found m/z = 240,9976;

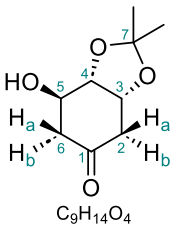
^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 1,35 (s, **3H**, CH_3), 1,48–1,51 (m, **1H**, Hb5), 1,52 (s, **3H**, CH_3), 1,84 (dd, *J* = 15,7, 3,8 Hz, **1H**, Ha2), 1,97 (ddd, *J* = 13,7, 4,4, 2,2 Hz, **1H**, Ha5), 2,21 (dt, *J* = 15,7, 2,5, 2,5 Hz, **1H**, Hb2), 3,41 (ABq, *J* = 3,4 Hz, **2H**, H7), 3,95 (t, *J* = 6,1, 6,1 Hz, **1H**, H4), 4,06 (ddd, *J* = 10,4, 6,3, 4,4 Hz, **1H**, H5), 4,46 (ddd, *J* = 5,6, 3,9, 2,7 Hz, **1H**, H3);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 25,7 (**1C**, CH_3), 28,3 (**1C**, CH_3), 33,2 (**1C**, C2), 38,3 (**1C**, C6), 68,7 (**1C**, C5), 70,2 (**1C**, C7), 72,6 (**1C**, C1), 74,3 (**1C**, C3), 80,2 (**1C**, C4), 109,1 (**1C**, C8).

The synthesis was carried out by following the protocol described by Trost et al.,[66] *with the recorded spectroscopic data being in accordance with those reported by the authors.*

periodate cleavage (synthesis of (3a*R*,7*R*,7a*S*)-7-hydroxy-2,2-dimethyltetrahydrobenzo[*d*][1,3] dioxol-5(4*H*)-one): A 2-l one-neck round-bottom flask was charged with the previously prepared triol (19,5 g, 89,3 mmol, 1,0 equiv.) and a mixture consisting of 595 ml CH_2Cl_2 and 30,0 ml MeOH was added. For the preparation of the SiO_2-supported $NaIO_4$-mixture, 134 g SiO_2 were gradually added to a saturated aqueous solution of 28,6 g (134 mmol, 1,5 equiv.) $NaIO_4$ in 62,0 ml boiling water. The thus formed reagent-matrix was added portion wise (*exothermic reaction*) to the CH_2Cl_2/ MeOH-solution of the triol and the suspension allowed to stir for one hour (progress monitored by TLC).

Upon completion the solids were filtered, washed with warm 5% EtOH in CH_2Cl_2 and the filtrate concentrated under reduced pressure to yield 16,5 g (88,6 mmol, **99%**) of the aimed title compound as a pale yellow oil, which was further used without any purification.



$C_9H_{14}O_4$
186,21

R_f = 0,50 (PE/ EtOAc = 5:3 (v/v));

$[\alpha]_D^{22,0}$ = +127,33° ($CHCl_3$, *10,0*) [*lit.:* $[\alpha]_D^{19}$ = *+135° (CHCl₃, 0,92)*][65];

HR-ESI-MS: $[C_9H_{14}O_4Na]^+$: m/z = 209,0790, found m/z = 209,0789;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 1,37 (s, **3H**, CH_3), 1,44 (s, **3H**, CH_3), 2,46 (ddd, *J* = 17,9, 3,8, 1,9 Hz, **1H**, Hb6), 2,65–2,66 (m, **1H**, Ha6), 2,69–2.70 (m, **1H**, Hb2), 2,81 (dd, *J* = 17,5, 3,7 Hz, **1H**, Ha2), 4,24 (ddt, *J* = 4,5, 2,9, 1,4, 1,4 Hz, **1H**, H5), 4,31 (ddd, *J* = 7,2, 2,6, 1,8 Hz, **1H**, H4), 4,71 (dddd, *J* = 7,2, 3,6, 2,8, 0,8 Hz, **1H**, H3);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 24,0 (**1C**, CH_3), 26,5 (**1C**, CH_3), 40,3 (**1C**, C2), 41,7 (**1C**, C6), 68,3 (**1C**, C5), 72,4 (**1C**, C3), 75,1 (**1C**, C4), 108,9 (**1C**, C7), 208,0 (**1C**, C1).

The synthesis was carried out by following the protocol described by Wang et al.,[67] with the recorded spectroscopic data being in accordance with those reported by the authors.

elimination (synthesis of **24**): For the last step of the sequence, 15,2 g (81,6 mmol, 1,0 equiv.) of the previously prepared β-ketol were charged in a flame-dried 1-l one-neck round-bottom flask and dissolved in 513 ml dry CH_2Cl_2. The solution was then cooled to 0 °C upon which dry NEt_3 (34,2 ml, 245 mmol, 3,0 equiv.) and MsCl (7,6 ml, 98,3 mmol, 1,2 equiv.) were added. The formed reaction mixture was then stirred under an inert atmosphere for five hours at room temperature. Upon completion, 150 ml $NaHCO_3$-sol. (sat., aq.), followed by 300 ml of water were added and the mixture charged in a separatory funnel. The organic phase was separated and the aqueous phase extracted two times with a total of 300 ml CH_2Cl_2. The combined organic phases were then dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the raw material *via* flash column chromatography (SiO_2, PE/ EtOAc = 2:1 (v/v)) finally yielded the aimed enone **24** (10,7 g, 63,3 mmol, **78%**) as a colorless oil

R_f = 0,51 (PE/ EtOAc = 3:2 (v/v));

m.p. = < 4 °C;

$[\alpha]_D^{22,8}$ = +133,33° ($CHCl_3$, *1,00*) [*lit.:* $[\alpha]_D^{19}$ = *+138° (CHCl₃, 0,54)*][65];

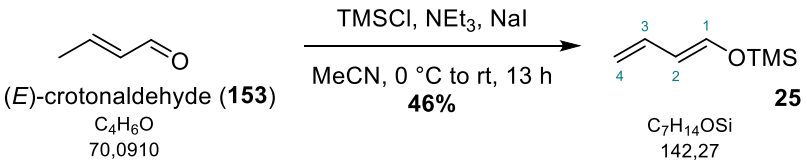
HR-ESI-MS: $[C_9H_{12}O_3Na]^+$: m/z = 191,0684, found m/z = 191,0683;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 1,34 (s, **3H**, CH_3), 1,35 (s, **3H**, CH_3), 2,63–2,69 (dd, *J* = 17,6, 3,8 Hz, **1H**, Ha2), 2,86–2,91 (ddd, *J* = 17,5, 2,6, 1,1 Hz, **1H**, Hb2), 4,64–4,66 (m, **1H**, H4), 4,68–4,70 (m, **1H**, H3), 5,97–6,00 (dt, *J* = 10,3, 1,3, 1,3 Hz, **1H**, H6), 6,59–6,63 (ddd, *J* = 10,4, 2,7, 1,8 Hz, **1H**, H5);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 26,7 (**1C**, CH_3), 27,9 (**1C**, CH_3), 38,9 (**1C**, C2), 71,2 (**1C**, C4), 73,5 (**1C**, C3), 110,1 (**1C**, C7), 129,0 (**1C**, C6), 146,0 (**1C**, C5), 195,5 (**1C**, C1).

The synthesis was carried out by following the protocol described by Kawashima et al.,[65] with the recorded spectroscopic data being in accordance with those reported by the authors.

6.2.1.3.1 (*E*)-(buta-1,3-dien-1-yloxy)trimethylsilane **25**



(*E*)-crotonaldehyde (**153**; 13,0 g, 15,4 ml, 186 mmol, 1,0 equiv.) and dry NaI (44,5 g, 297 mmol, 1,6 equiv.) were dissolved in a flame-dried three-neck round-bottom flask in 185 ml dry acetonitrile. The orange-colored suspension was then cooled to 0 °C and dry NEt_3 (41,4 ml, 297 mmol, 1,6 equiv.) added. Lastly, TMSCl (35,3 ml, 278 mmol, 1,5 equiv.) was added and the milky solution allowed to stir under an inert atmosphere at room temperature for 13 hours. Upon completion the mixture was diluted with 150 ml *n*-pentane. The MeCN-phase was then extracted with *n*-pentane (3x150 ml) after which it was discarded. The combined solutions were then washed with 250 ml $NaHCO_3$-sol. ($^1/_2$-sat., aq.), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude *via* vacuum-distillation ($T_{ex.}$*=72 °C,* $T_{int.}$*=55 °C; P = 40 mbar*) afforded title compound **25** (12,2 g, 86,0 mmol, **46%**) as a colorless oil.

R_f = 0,92 (PE/ EtOAc = 9:1 (v/v));

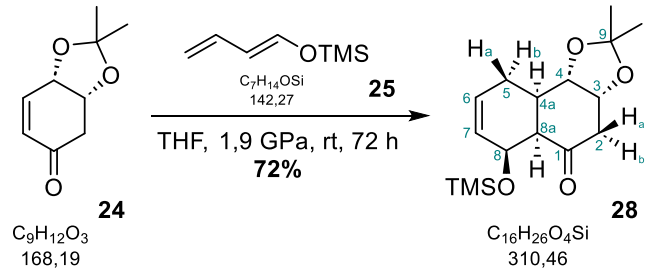
b.p. = 148 °C [*lit.: 133,1 °C*][175];

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,21 (s, **9H**, TMS), 4,82 (d, *J* = 10,5 Hz, **1H**, H4-(*Z*)), 4,99 (d, *J* = 17,0 Hz, **1H**, H4-(*E*)), 5,69–5,75 (m, **1H**, H2), 6,22 (dt, *J* = 17,0, 10,6, 10,6 Hz, **1H**, H3), 6,54 (d, *J* = 12,0 Hz, **1H**, H1);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –0,3 (**3C**, TMS), 112,2 (**1C**, C4), 114,5 (**1C**, C2), 133,4 (**1C**, C3), 144,8 (**1C**, C1).

The synthesis was carried out by following the protocol described by Böse et al.,[68] *with the recorded spectroscopic data being in accordance with those reported by the authors.*

6.2.1.3.2 (3a*R*,5a*R*,6*S*,9a*R*,9b*S*)-2,2-dimethyl-6-((trimethylsilyl)oxy)-3a,5a,6,9,9a,9b-hexahydro-naphtho[1,2-*d*][1,3]dioxol-5(4*H*)-one **28**



The previously prepared enone **24** (5,45 g, 32,4 mmol, 1,0 equiv.) and diene **25** (11,5 g, 81,0 mmol, 2,5 equiv.) were dissolved in 10,1 ml dry THF in a Teflon® sealed-tube. The reaction was then carried out for 72 hours at room temperature under 1,5 GPa. Upon completion the tube was unsealed, the volatiles removed *in vacuo* and the oily residue charged on a flash chromatography column (SiO_2). Gradual elution (PE→PE/ EtOAc = 9:1→5:1 (v/v)) afforded decalin **28** (7,29 g, 23,5 mmol, **72%**) as a colorless oil.

R_f = 0,83 (PE/ EtOAc = 3:1 (v/v));

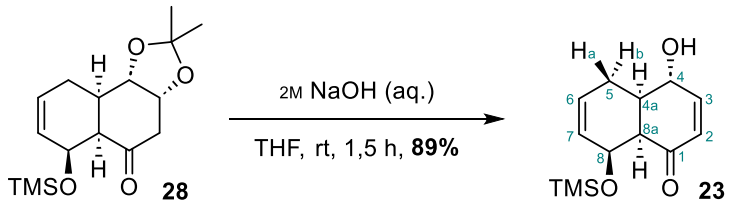
$[\alpha]_D^{22,3}$ = +110,53° ($CHCl_3$, *3,80*);

HR-ESI-MS: $[C_{16}H_{26}O_4SiNa]^+$: m/z = 333,1498, found m/z = 333,0356;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0.07 (s, **9H**, TMS), 1,35 (s, **3H**, CH_3), 1,50 (s, **3H**, CH_3), 2,23–2,31 (m, **1H**, Hb5), 2,37 (dd, *J* = 10,4, 5,0 Hz, **1H**, Ha4), 2,41–2,42 (m, **1H**, Ha5), 2,45 (t, *J* = 4,8, 4,8 Hz, **1H**, Ha8), 2,51 (dd, *J* = 16,3, 9,1 Hz, **1H**, Hb2), 2,78 (dd, *J* = 16,3, 6,4 Hz, **1H**, Ha2), 4,37–4,40 (m, **1H**, H8), 4,41–4,43 (m, **1H**, H3), 4,61 (dd, *J* = 10,1, 7,5 Hz, **1H**, H4), 5,74–5,78 (m, **1H**, H7), 5,80–5,84 (m, **1H**, H8);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –0,3 (**3C**, TMS), 24,2 (**1C**, CH_3), 26,4 (**1C**, C5), 27,4 (**1C**, CH_3), 32,8 (**1C**, C4a), 44,7 (**1C**, C2), 49,4 (**1C**, C8a), 64,8 (**1C**, C3), 72,2 (**1C**, C8), 74,4 (**1C**, C4), 108,4 (**1C**, C9), 127,9 (**1C**, C6), 128,0 (**1C**, C7), 211,5 (**1C**, C1).

6.2.1.4 (4*R*,4a*R*,8*S*,8a*R*)-4-hydroxy-8-((trimethylsilyl)oxy)-4a,5,8,8a-tetrahydronaphthalen-1-(4*H*)-one **23**



For the synthesis of **23**, the previously prepared decalin **28** (7,29 g, 23,5 mmol, 1,0 equiv.) was dissolved in a 100-ml one-neck round-bottom flask under ambient conditions in 47,0 ml THF and treated with 2,4 ml (2,75 mmol, 20 mol-%) aqueous NaOH-solution (2M). The reaction was then stirred for 1,5 hours at room temperature and terminated by the addition of 50 ml of water. After extraction with MTBE (3x100 ml), the organic phase was dried over Na_2SO_4, the volatiles removed under reduced pressure and the residue purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 4:1 (v/v)) to finally afford the title compound (5,29 g, 20,9 mmol, **89%**) as a colorless oil.

R_f = 0,63 (PE/ EtOAc = 1:1 (v/v));

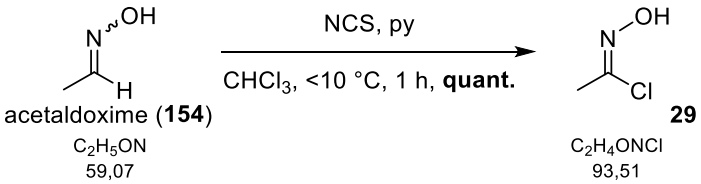
$[\alpha]_D^{22,1}$ = +337,24° ($CHCl_3$, *3,22*);

HR-ESI-MS: $[C_{13}H_{20}O_3SiNa]^+$: m/z = 275,1080, found m/z = 275,0041;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,00(s, **9H**, TMS), 1,79 (d, *J* = 7,1 Hz, **1H**, OH), 2,12–2,19 (m, **1H**, Hb5), 2,37 (dt, *J* = 10,9, 5,8, 5,8 Hz, **1H**, H4a), 2,54–2,60 (m, **1H**, Ha5), 2,68 (t, *J* = 4,9, 4,9 Hz, **1H**, H8a), 4,33 (td, *J* = 4,4, 4,3, 1,6 Hz, **1H**, H8), 4,82 (t, *J* = 8,2, 8,2 Hz, **1H**, H4), 5,78–5,80 (m, **2H**, H6, H7), 5,98 (ddd, *J* = 10,2, 2,2, 0,9 Hz, **1H**, H3), 6,90 (dd, *J* = 10,2, 1,7 Hz, **1H**, H2);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 0,1 (**3C**, TMS), 24,9 (**1C**, C5), 40,0 (**1C**, C4a), 50,0 (**1C**, C8a), 64,4 (**1C**, C8), 67,4 (**1C**, C4), 127,1 (**1C**, C7), 128,6 (**1C**, C6), 130,0 (**1C**, C3), 154,4 (**1C**, C2), 200,9 (**1C**, C1).

6.2.1.5.1 (*Z*)-*N*-hydroxyacetimidoyl chloride **29**



acetaldoxime (**154**)
C_2H_5ON
59,07

C_2H_4ONCl
93,51

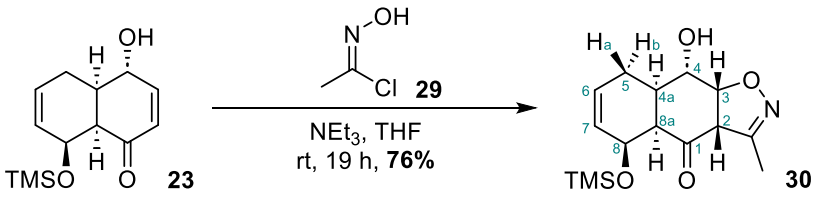
A 100-ml one-neck round-bottom flask was charged with 39,0 ml dry $CHCl_3$ and 3,8 ml (62,0 mmol, 1,0 equiv.) acetaldoxime (**154**) alongside 0,1 ml (1,24 mmol, 20 mol-%) pyridine added. The mixture was cooled to 0 °C and 8,29 g (62,1 mmol, 1,0 equiv.) NCS were added portion wise. The reaction was then stirred for one hour while the temperature was carefully maintained bellow 10 °C. During the reaction, the color may change from an initial dark grey to magenta or blue. Upon completion, the cloudy mixture, mainly consisting of **29** and *N*-hydroxysuccinimide, can be directly transferred *via* cannula to the further described reaction (*procedure 6.2.1.6.2*). The isolation and characterization of the title compound were however initially attempted.
For this, the initial reaction-volume was carefully concentrated under reduced pressure and 50 ml of water were added. Extraction with Et_2O (3x30 ml), followed by drying of the organic phases over Na_2SO_4 and removal of the solvent under vacuum afforded crude product **27**, which shortly decomposed violently, releasing HCl-fumes. Ethereal solutions of the product of various concentrations (>1,5M) have shown however a shelf life of several days when stored at temperatures below 0 °C. While an accurate yield-determination was successfully carried out, a complete characterization remained unsuccessful.

R_f = 0,73 (PE/ EtOAc = 1:1 (v/v));

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,27 (s, **3H**), 8,09 (s, **1H**).

The synthesis was carried out by following the protocol described by Hylse et al.,[78] with the recorded spectroscopic data being in accordance with the one reported by the authors.

6.2.1.5.2 (3a*S*,4a*R*,5*S*,8a*R*,9*S*,9a*R*)-9-hydroxy-3-methyl-5-((trimethylsilyl)oxy)-a,5,8,8a,9,9a-hexahydronaphtho[2,3-*d*]isoxazol-4(3a*H*)-one **30**



$C_{13}H_{20}O_3Si$
252,39

$C_{15}H_{23}O_4NSi$
309,44

For the preparation of the isoxazoline-bearing precursor **30**, a flame-dried 100-ml one-neck round-bottom flask was charged under an inert atmosphere at 0 °C with 22,0 ml dry THF, to which 4,47 g (17,7 mmol, 1,0 equiv.) decalin **23** and 9,2 ml (65,6 mmol, 3,7 equiv.) dry NEt_3 were added. The mixture was then treated with a solution of **29** (3,5 equiv.; freshly prepared in accordance with 6.2.1.5.1 and added *via* cannula) and the reaction allowed to stir at room temperature for 19 hours. Upon completion, the reaction was diluted with 50 ml of water and transferred to a separatory funnel. After extraction with MTBE (3x50 ml) the organic phases were dried over Na_2SO_4, concentrated *in vacuo* and the residue purified *via* flash column chromatography (SiO_2, CH_2Cl_2[17]; *then* PE/ EtOAc = 4:1 (v/v)). Product **30** (4,15 g, 13,4 mmol, **76%**) was isolated as a single diastereo- and regioisomer in form of a white microcrystalline powder.

R_f = 0,40 (PE/ EtOAc = 3:2 (v/v));

m.p. = 124 °C;

$[\alpha]_D^{22,1}$ = +280,70° ($CHCl_3$, *4,75*);

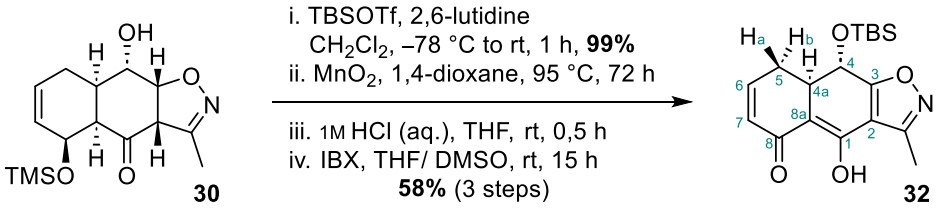
HR-ESI-MS: $[C_{15}H_{23}O_4NSiNa]^+$: m/z = 332,1294, found m/z = 332,1295;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,07 (s, **9H**, TMS), 2,00–2,02 (m, **1H**, OH), 2,05 (td, *J* = 4,2, 4,0, 2,2 Hz, **1H**, Hb5), 2,12 (s, **3H**, CH_3), 2,39 (dt, *J* = 11,0, 5,3, 5,3 Hz, **1H**, H4a), 2,67 (d, *J* = 5,4 Hz, **1H**, H8a), 2,70–2,72 (m, **1H**, Ha5), 3,65–3,68 (m, **1H**, H2), 4,35–4,38 (m, **1H**, H8), 4,75 (dd, *J* = 11,9, 4,3 Hz, **1H**, H4), 4,88 (dd, *J* = 10,2, 4,3 Hz, **1H**, H3), 5,74–5,82 (m, **1H**, H7), 5,85 (ddd, *J* = 10,1, 5,5, 2,1 Hz, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 0,3 (**3C**, TMS), 13,2 (**1C**, CH_3), 23,7 (**1C**, C5), 31,6 (**1C**, C4a), 52,2 (**1C**, C8a), 63,0 (**1C**, C2), 65,3 (**1C**, C8), 65,8 (**1C**, C4), 80,5 (**1C**, C3), 127,0 (**1C**, C7), 128,1 (**1C**, C6), 155,1 (**1C**, C=N), 205,1 (**1C**, C1).

[17] For the elution of the UV-active dimeric 3,4-dimethyl-1,2,5-oxadiazole 2-oxide;[176]
R_f = 0,42 (PE/ EtOAc = 3:2 (v/v));
^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,12 (s, **3H**, CH_3), 2,31 (s, **3H**, CH_3);
^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 7,5 (**1C**, CH_3), 11,1 (**1C**, CH_3), 113,1 (**1C**, C=N), 154,6 (**1C**, $C=N^+$).

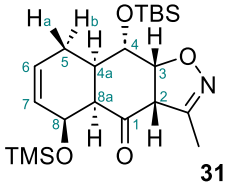
6.2.1.6 (8a*R*,9*S*)-9-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-3-methyl-8a,9-dihydronaphtho-[2,3-*d*]-isoxazole-5(8*H*)-one **32**



$C_{15}H_{23}O_4NSi$
309,44

$C_{18}H_{25}O_4NSi$
347,49

TBS-protection (synthesis of **31**; (3a*S*,4a*R*,5*S*,8a*R*,9*S*,9a*R*)-9-((*tert*-butyldimethylsilyl)oxy)-3-methyl -5-((tri-methyllsilyl)oxy)-4a,5,8,8a,9,9a-hexahydronaphtho[2,3-*d*]isoxazol-4(3a*H*)-one): In a flame-dried 100-ml one-neck round-bottom flask 3,45 g (11,1 mmol, 1,0 equiv.) of **8** were dissolved under an inert atmosphere in 32,0 ml dry CH_2Cl_2. The solution was then cooled to –78 °C and 2,6-lutidine (2,6 ml, 22,3 mmol, 2,0 equiv.), followed by 3, 3 ml (14,5 mmol, 1,3 equiv.) TBSOTf were added and the reaction allowed to stir while maintaining the initial temperature. After one hour the cooling bath was removed, the reaction allowed to warm to room temperature and diluted with 50 ml of water. Extraction with MTBE (3x50 ml), followed by drying over Na_2SO_4 and concentration under reduced pressure gave the desired intermediate (4,68 g, 11,1 mmol, **99%**) as a pale yellow oil, which was used further without any purification.



$C_{21}H_{37}O_4NSi_2$
423,70

R_f = 0,69 (PE/ EtOAc = 4:1 (v/v));

$[\alpha]_D^{22,3}$ = +273,81° ($CHCl_3$, *1,68*);

HR-ESI-MS: $[C_{21}H_{37}O_4NSi_2Na]^+$:
m/z = 446,2159, found m/z = 446,2158;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,08 (s, **9H**, TMS), 0,09 (s, **3H**, CH_3 (TBS)), 0,10 (s, **3H**, CH_3 (TBS)), 0,93 (s, **9H**, CH_3 (TBS)), 1,97–2,03 (m, **1H**, Hb5), 2,14 (s, **3H**, CH_3), 2,51–2,57 (m, **1H**, Ha5), 2,63–2,67 (m, **1H**, Ha4), 2,67–2,70 (m, **1H**, H8a), 3,52 (d, *J* = 9,5 Hz, **1H**, H2), 4,35–4,38 (m, **1H**, H8), 4,72 (dd, *J* = 9,7, 3,7 Hz, **1H**, H3), 5,00 (dd, *J* = 10,9, 3,6 Hz, **1H**, H4), 5,75–5.79 (m, **1H**, H7), 5,80–5,84 (m, **1H**, H6);
^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,5 (**6C**, CH_3 (TBS)), 0,3 (**3C**, TMS), 13,6 (**1C**, CH_3), 18,4 (**1C**, $C_{quat.}$ (TBS)), 23,9 (**1C**, C5), 26,0 (**3C**, CH_3 (TBS)), 30,7 (**1C**, C4a), 52,6 (**1C**, C8a), 62,9 (**1C**, C2), 65,5 (**1C**, C8), 66,6 (**1C**, C4), 81,7 (**1C**, C3), 127,4 (**1C**, C6), 128,3 (**1C**, C7), 154,4 (**1C**, C=N), 205,8 (**1C**, C1).

aromatization (synthesis of (4a*R*,5*S*,8a*R*,9*S*)-9-((*tert*-butyldimethylsilyl)oxy)-3-methyl-5-((trimethylsilyl) oxy)-5,8,8a,9-tetrahydronaphtho[2,3-*d*]isoxazol-4(4a*H*)-one): 2,05 g (4,84 mmol, 1,0 equiv.) **31**, dissolved in 32,0 ml 1,4-dioxane were charged under ambient conditions in a sealed tube and 5,26 g (48,4 mmol, 10,0 equiv.) MnO_2 (80 wt%; technical grade) were added. The tube was then sealed and the reaction allowed to stir at 95 °C for 72 hours. Upon completion (progress checked roughly every 24 hours by ^{1}H-NMR[18]), the black slurry was filtered over a pad of Celite® (MTBE) and concentrated under reduced pressure to give 1,31 g (3,11 mmol) of the aimed crude isoxazole-bearing decalin (**R_f** = 0,77 (PE/ EtOAc = 4:1 (v/v)) as a pale yellow powder.

[18] A low-field shift of the CH_3-group (400 MHz, $CDCl_3$; δ = 2,47 **ppm**) was observed as a result of the aromatization of the system.

TMS-cleavage (synthesis of (4a*R*,5*S*,8a*R*,9*S*)-9-((*tert*-butyldimethylsilyl)oxy)-5-hydroxy-3-methyl-5,8,8a,9-tetrahydronaphtho[2,3-*d*]isoxazol-4(4a*H*)-one): The previously prepared isoxazole-intermediate (1,31 g, 3,11 mmol, 1,0 equiv.), dissolved at room temperature in 124 ml THF was reacted with 24,9 ml (8,0 equiv.) aqueous HCl-solution (1M) for 30 minutes in a 250-ml one-neck round-bottom flask under ambient conditions. The reaction was then neutralized by the addition of 30 ml saturated aqueous $NaHCO_3$-soution followed by the addition of 50 ml MTBE. The aqueous phase was then extracted with MTBE (3x50 ml). The combined ethereal organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to yield 1,08 g (3,09 mmol) of the aimed crude allylic alcohol ($\mathbf{R_f}$ = 0,50 (PE/ EtOAc = 4:1 (v/v)) as a pale yellow oil.

IBX-oxidation (synthesis of **32**): In a flame-dried 100-ml one-neck round-bottom flask, 1,08 g (3,09 mmol, 1,0 equiv.) of the previously prepared crude allylic alcohol were dissolved under an inert atmosphere in 31,0 ml dry THF and 3,0 ml dry DMSO. To the formed solution were then added 2,60 g (9,27 mmol, 3,0 equiv.) IBX and the heterogenous mixture allowed to stir for 15 hours at room temperature. Upon completion, the orange-colored slurry was diluted with a small amount of MTBE and filtered over a pad of Celite®. Removal of the volatiles under reduced pressure yielded a thick, orange-colored oil, which was purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1 (v/v)). Vinylogues acid **32** (0,98 g, 2,82 mmol, **58%** (3 steps)) was finally collected as golden-shimmery, yellow-colored crystalline flakes.

$\mathbf{R_f}$ = 0,84 (PE/ EtOAc = 4:1 (v/v));

m.p. = 131 °C;

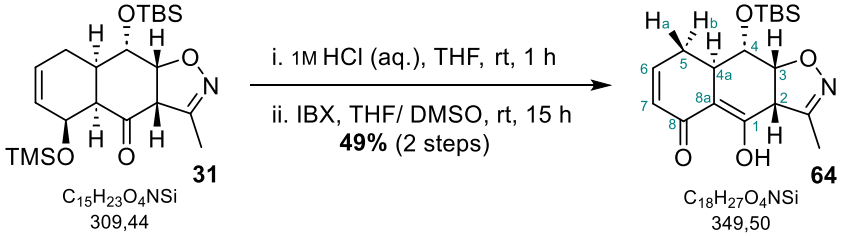
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{19,4}}$ = –12,12° ($CHCl_3$, *1,10*);

HR-ESI-MS: $[C_{18}H_{25}O_4NSiNa]^+$: m/z = 370,1451, found m/z = 370,1445;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,18 (s, **3H**, CH_3 (TBS)), 0,28 (s, **3H**, CH_3 (TBS)), 0,97 (s, **9H**, CH_3 (TBS)), 2,13 (ddt, *J* = 17,8, 15,9, 2,9, 2,9 Hz, **1H**, Ha5), 2,52 (s, **3H**, CH_3), 2,85 (dt, *J* = 17,4, 6,7, 6,7 Hz, **1H**, Hb5), 2,98–3,07 (m, **1H**, H4a), 4,73 (d, *J* = 10,8 Hz, **1H**, H4), 6,15 (dd, *J* = 9,9, 3,1 Hz, **1H**, H7), 6,63 (ddd, *J* = 9,3, 6,2, 2,4 Hz, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,6 (**1C**, CH_3 (TBS)), –4,3 (**1C**, CH_3 (TBS)), 10,8 (**1C**, CH_3), 18,3 (**1C**, $C_{quat.}$ (TBS)), 25,9 (**3C**, CH_3 (TBS)), 29,8 (**1C**, C5), 39,6 (**1C**, C4a), 71,7 (**1C**, C4), 102,8 (**1C**, C8a), 113,2 (**1C**, C2), 125,6 (**1C**, C7), 141,3 (**1C**, C6), 157,7 (**1C**, C=N), 173,5 (**1C**, C3), 177,4 (**1C**, C1), 182,7 (**1C**, C8).

6.2.1.7 (3a*S*,4a*R*,8a*R*,9*S*,9a*R*)-9-((*tert*-butyldimethylsilyl)oxy)-3-methyl-8,8a,9,9a-tetrahydro-naphtho[2,3-*d*]isoxazole-4,5(3a*H*,4a*H*)-dione **64**



TMS-cleavage (synthesis of (3a*S*,4a*R*,5*S*,8a*R*,9*S*,9a*R*)-9-((*tert*-butyldimethylsilyl)oxy)-5-hydroxy-3-methyl-4a,5,8,8a,9,9a-hexahydronaphtho[2,3-*d*]isoxazol-4(3a*H*)-one): The previously prepared TBS-protected intermediate **31** (3,57 g, 8,43 mmol, 1,0 equiv.), dissolved at room temperature in 105 ml THF was reacted with 29,5 ml (3,5 equiv.) aqueous HCl-solution (1M) for one hour in a 250-ml one-neck round-bottom flask under ambient conditions. The reaction was then neutralized by the addition of 40 ml saturated aqueous $NaHCO_3$-soution followed by the addition of 50 ml MTBE. The aqueous phase was then extracted with MTBE (3x50 ml), the resulting ethereal organic phases dried over Na_2SO_4 and concentrated under reduced pressure to yield 2,92 g (8,31 mmol) of the aimed crude allylic alcohol ($\mathbf{R_f}$ = 0,45 (PE/ EtOAc = 4:1 (v/v)) as a pale yellow oil.

IBX-oxidation (synthesis of **64**): In a flame-dried 100-ml one-neck round-bottom flask, 2,92 g (8,31 mmol, 1,0 equiv.) of the previously prepared crude allylic alcohol were dissolved under an inert atmosphere in 37,4 ml dry THF and 3,7 ml dry DMSO. To the formed solution were then added 6,98 g (24,92 mmol, 3,0 equiv.) IBX and the heterogenous mixture allowed to stir for 15 hours at room temperature. Upon completion, the orange-colored slurry was diluted with a small amount of MTBE and filtered over a pad of Celite®. Removal of the volatiles under reduced pressure yielded a thick oil, which was purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 19:1→11,5:1→9:1 (v/v)). Vinylogues acid **64** (1,45 g, 4,14 mmol, **49%** (2 steps)) was finally collected as a thick, yellow oil.

$\mathbf{R_f}$ = 0,79 (PE/ EtOAc = 4:1 (v/v));

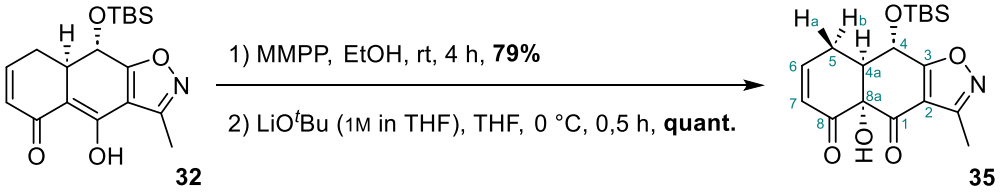
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{27,5}}$ = +146,36° ($CHCl_3$, *7,33*);

HR-ESI-MS: $[C_{18}H_{25}O_4NSiNa]^+$: m/z = 372,1607, found m/z = 372,1596;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,11 (s, **3H**, CH_3 (TBS)), 0,13 (s, **3H**, CH_3 (TBS)), 0,93 (s, **9H**, CH_3 (TBS)), 2,00 (ddt, *J* = 18,4, 13,3, 2,7, 2,7 Hz, **1H**, Hb5), 2,11 (s, **3H**, CH_3), 2,64–2,72 (m, **1H**, Ha5), 3,14–3,22 (m, **1H**, H4a), 3,78–3,81 (m, **1H**, H2), 3,92 (dd, *J* = 9,9, 2,9 Hz, **1H**, H4), 4,73 (dd, *J* = 9,3, 2,9 Hz, **1H**, H3), 6,05–6,08 (m, **1H**, H7), 6,86 (ddd, *J* = 10,0, 6,6, 2,2 Hz, **1H**, H8), 12,12 (weak br. s, **1H**, OH);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,5 (**1C**, CH_3 (TBS)), –4,1 (**1C**, CH_3 (TBS)), 13,1 (**1C**, CH_3), 18,3 (**1C**, $C_{quat.}$ (TBS)), 25,9 (**3C**, CH_3 (TBS)), 28,5 (**1C**, C5), 32,6 (**1C**, C4a), 56,0 (**1C**, C2), 73,5 (**1C**, C4), 81,3 (**1C**, C3), 104,6 (**1C**, C8a), 127,8 (**1C**, C7), 147,5 (**1C**, C6), 155,2 (**1C**, C=N), 173,2 (**1C**, C1), 187,2 (**1C**, C8).

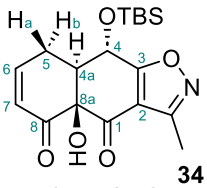
6.2.1.8 (4a*S*,8a*S*,9*S*)-9-((*tert*-butyldimethylsilyl)oxy)-4a-hydroxy-3-methyl-8a,9-dihydronaphtho-[2,3-*d*]isoxazole-4,5(4a*H*,8*H*)-dione **35**



32
$C_{18}H_{25}NO_4Si$
347,49

35
$C_{18}H_{25}O_5NSi$
363,48

α-hydroxylation (synthesis of **34**): A 5-ml one-neck round-bottom flask was charged at room temperature with 125 mg (0,36 mmol, 1,0 equiv.) of **9** and 0,9 ml EtOH. 111 mg (80 wt%, 0,18 mmol, 0,5 equiv.) MMPP·6H_2O were then added and the red-colored solution stirred for four hours. Upon completion the reaction was diluted with 3 ml of water, the organic components extracted with CH_2Cl_2 (3x10 ml) and the combined organic phases dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by flash column chromatography (SiO_2, PE/ EtOAc = 4:1 (v/v)) to yield the aimed ketol **35** (103 mg, 0,28 mmol, **79%**) as an orange-colored solid.



34
$C_{18}H_{25}O_5NSi$
363,48

R$_f$ = 0,44 (PE/ EtOAc = 3:2 (v/v));

m.p. = 142 °C;

$[\alpha]_D^{22,5}$ = –56,67° ($CHCl_3$, *3,00*);

HR-ESI-MS: $[C_{18}H_{25}O_5NSiNa]^+$: m/z = 386,1400, found m/z = 386,1405;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,23 (s, **3H**, CH_3 (TBS)), 0,32 (s, **3H**, CH_3 (TBS)), 0,97 (s, **9H**, CH_3 (TBS)), 2,45 (s, **3H**, CH_3), 2,61–2,72 (m, **2H**, H4a, H5), 2,75–2,80 (m, **1H**, H5), 4,04 (br. s, **1H**, OH), 5,14 (d, *J* = 8,8 Hz, **1H**, H4), 6,14 (dd, *J* = 10,1, 2,3 Hz, **1H**, H7), 7,09 (ddd, *J* = 10,4, 5,9, 1,6 Hz, **1H**, H6);

^{13}C-NMR (101 MHz; C_6D_6): δ [ppm] = –4,7 (**1C**, CH_3 (TBS)), –4,4 (**1C**, CH_3 (TBS)), 10,7 (**1C**, CH_3), 18,3 (**1C**, $C_{quat.}$ (TBS)), 25,1 (**1C**, C5), 25,8 (**3C**, CH_3 (TBS)), 49,3 (**1C**, C4a), 66,0 (**1C**, C4), 75,4 (**1C**, C8a), 112,7 (**1C**, C2), 128,7 (**1C**, C7), 148,7 (**1C**, C6), 158,4 (**1C**, C=N), 179,4 (**1C**, C3), 188,1 (**1C**, C1), 194,1 (**1C**, C8).

α-ketol rearrangement (synthesis of **35**): The previously prepared ketol (100 mg, 0,28 mmol, 1,0 equiv.) was dissolved in 2,8 ml dry THF in a flame-dried 10-ml one-neck round-bottom flask and a LiO^{t}Bu-solution (1M in THF, 647 µl, 0,06 mmol, 20 mol-%) added at 0 °C. After stirring under an inert atmosphere for 30 minutes the mixture was diluted with 5 ml of water, extracted with MTBE (3x10 ml) and the combined organic phases dried over Na_2SO_4. Solvent removal under reduced pressure afforded the rearranged ketol **35** (96,3 mg, 0,28 mmol, **quant.**) as an off-orange powder. Further purification of the product was not required at this stage.

R$_f$ = 0,78 (PE/ EtOAc = 3:2 (v/v));

m.p. = 131 °C;

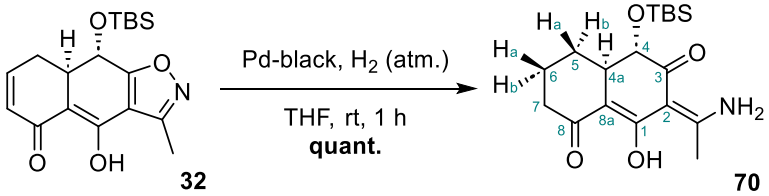
$[\alpha]_D^{26,0}$ = +145,88° ($CHCl_3$, *6,38*);

HR-ESI-MS: $[C_{18}H_{25}O_5NSiNa]^+$: m/z = 386,1400, found m/z = 386,1402;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,16 (s, **3H**, CH_3 (TBS)), 0,26 (s, **3H**, CH_3 (TBS)), 0,95 (s, **9H**, CH_3 (TBS)), 2,52 (s, **3H**, CH_3), 2,66 (dd, *J* = 19,3, 5,5 Hz, **1H**, H5), 2,88–2,93 (m, **1H**, H4a), 2,93–2,95 (m, **1H**, H5), 4,47 (s, **1H**, OH), 4,94 (d, *J* = 8,8 Hz, **1H**, H4), 6,19 (ddd, *J* = 10,3, 2,8, 1,2 Hz, **1H**, H7), 6,97–7,02 (m, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,8 (**1C**, CH_3 (TBS)), –4,3 (**1C**, CH_3 (TBS)), 10,8 (**1C**, CH_3), 18,2 (**1C**, $C_{quat.}$ (TBS)), 24,5 (**1C**, C5), 25,8 (**3C**, CH_3 (TBS)), 51,2 (**1C**, C4a), 64,9 (**1C**, C4), 79,6 (**1C**, C8a), 113,2 (**1C**, C2), 129,0 (**1C**, C7), 148,6 (**1C**, C6), 157,8 (**1C**, C=N), 179,6 (**1C**, C3), 189,6 (**1C**, C1), 192,7 (**1C**, C8).

6.2.1.9 Isoxazole-hydrogenation study ((4a*R*,5*S*,*Z*)-7-(1-aminoethylidene)-5-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-3,4,4a,7-tetrahydronaphthalene-1,6(2*H*,5*H*)-dione **70**)



32 $C_{18}H_{25}O_4NSi$ 347,49 → **70** $C_{12}H_{15}O_4N$ 237,26

50,0 mg (0,14 mmol, 1,0 equiv.) **32** were dissolved under an inert atmosphere in 2,9 ml dry THF in a flame-dried 10-ml three-neck round-bottom flask. To the formed solution, 27,0 mg (0,25 mmol, 1,75 equiv.) Pd-black were added under a stream of argon and the flask evacuated three times (H_2). The reaction was then allowed to stir for one hour under H_2-atmosphere after which the flask was opened and the reaction diluted with 5ml of MTBE. The catalyst was then filtered over Celite® (MTBE) and the filtrate concentrated under reduced pressure to give the enamine **70** (49,8 mg, 0,14 mmol, **quant.**) as a pale yellow powder.

$[\alpha]_D^{21,6}$ = +76,41° ($CHCl_3$, *1,92*);

R_f = 0,67 (PE/ EtOAc = 3:2 (v/v));

HR-ESI-MS: $[C_{18}H_{29}O_4NSiNa]^+$: m/z = 374,1764, found m/z = 374,0918;

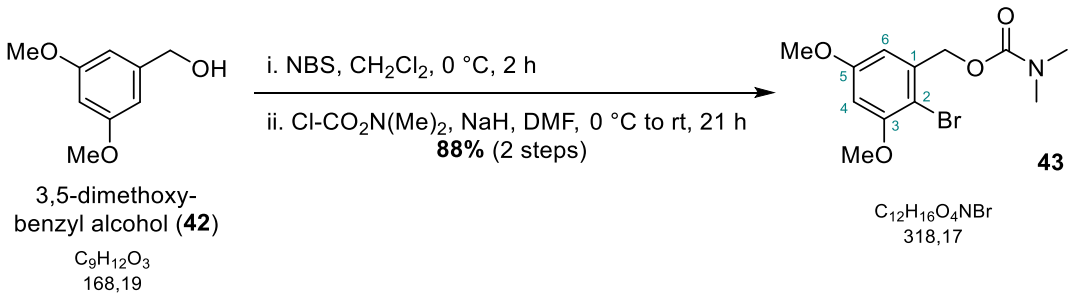
^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,03 (s, **3H**, CH_3 (TBS)), 0,22 (s, **3H**, CH_3 (TBS)), 0,94 (s, **9H**, CH_3 (TBS)), 1,14–1,24 (m, **1H**, Hb5), 1,46–1,58 (m, **1H**, Ha6), 1,89–1,95 (m, **1H**, Hb6), 2,25–2,31 (m, **1H**, Ha5), 2,33–2,39 (m, **2H**, H7), 2,52 (s, **4H**, H4a, CH_3), 2,83 (d, *J* = 12,2 Hz, **1H**, H4);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –5,4 (**1C**, CH_3 (TBS)), –3,7 (**1C**, CH_3 (TBS)), 19,0 (**1C**, $C_{quat.}$ (TBS)), 20,3 (**1C**, C6), 26,2 (**4C**, CH_3, CH_3 (TBS)), 28,1 (**1C**, C5), 30,6 (**1C**, C7), 37,9 (**1C**, C4a), 74,8 (**1C**, C4), 104,2 (**1C**, C8a), 105,0 (**1C**, C2), 171,9 (**1C**, C-NH_2), 177,8 (**1C**, C3), 189,8 (**1C**, C1), 197,5 (**1C**, C8).

Several hydrolysis-attempts towards the generation of a corresponding methyl ketone from **70** were carried out all of the attempts failing however to yield the targeted molecule. An overview of the performed trials is summarized in chapter 4.1.

6.2.2 Phthalides **44** and **45**

6.2.2.1 2-bromo-3,5-dimethoxybenzyl dimethylcarbamate **43**



3,5-dimethoxy-benzyl alcohol (**42**)
$C_9H_{12}O_3$
168,19

$C_{12}H_{16}O_4NBr$
318,17

bromination (synthesis of 2-bromo-3,5-dimethoxybenzyl alcohol): 3,5-dimethoxybenzyl alcohol **42** (12,5 g, 74,3 mmol, 1,0 equiv.) was dissolved under ambient conditions in a 250-ml one-neck round-bottom flask in 203 ml CH_2Cl_2.and cooled to 0 °C. To the formed solution a total of 13,2 g (74,3 mmol, 1,0 equiv.) NBS were added in three portions over a period of 45 minutes. Upon addition the reaction was allowed to stir for a total of two hours ($\mathbf{R_f}$ = 0,27 (PE/ EtOAc = 7:3 (v/v)), after which the volatiles were removed under reduced pressure. The residue was then suspended in 100 ml of water and extracted with EtOAc (3x100 ml). The combined organic phases were then dried over Na_2SO_4 and concentrated *in vacuo* to yield the aimed brominated intermediate (18,0 g, 72,9 mmol) as a white powder.

The synthesis was carried out by following the protocol described by Wright et al.[103].

carbonylation (synthesis of **43**): The previously prepared bromide (18,0 g, 72,9 mmol, 1,0 equiv.) was charged in a flame-dried 250-ml one-neck round-bottom flask and dissolved in 112 ml dry DMF. The solution was then cooled to 0 °C and 3,79 g (94,7 mmol, 1,3 equiv.) NaH (60 wt% in mineral oil) were carefully added (*vigorous gas formation!*). After the addition was completed, the reaction was warmed to room temperature and stirred for 40 minutes, after which it was cooled again to 0 °C. 10,0 ml (109 mmol, 1,5 equiv.) (*N*,*N*)-dimethylcarbamoyl chloride were added and the reaction stirred for 21 hours at room temperature, after which it was carefully diluted with 100 ml of water. The organic components were then extracted with EtOAc (3x100 ml), the combined phases washed once with saturated, aqueous NaCl-solution and a 10%, aqueous LiCl-solution, after which they were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was then crystallized from acetone (*approx.* 150 ml) and 20,8 g (65,5 mmol, **88%** (2 steps)) of the aimed carbamate **43** were collected as a white powder

$\mathbf{R_f}$ = 0,46 (PE/ EtOAc = 1:1 (v/v));

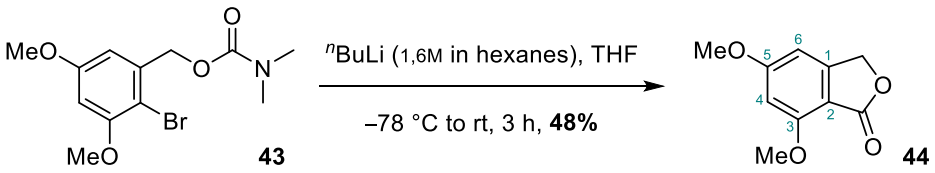
m.p. = 119 °C (acetone);

HR-ESI-MS: $[C_{12}H_{16}O_4NBrNa]^+$: m/z = 340,0160, found m/z = 340,0150;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,96 (s, **6H**, $N(CH_3)_2$), 3,81 (s, **3H**, C5-OCH_3), 3,88 (s, **3H**, C3-OCH_3), 5,18 (s, **2H**, CH_2), 6,45 (d, *J* = 2,8 Hz, **1H**, H4), 6,60 (d, *J* = 2,8 Hz, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 36,1 (**1C**, NCH_3), 36,7 (**1C**, NCH_3), 55,7 (**1C**, OCH_3), 56,5 (**1C**, OCH_3), 66,9 (**1C**, CH_2), 99,1 (**1C**, C4), 103,4 (**1C**, C1), 106,1 (**1C**, C6), 138,3 (**1C**, C2), 156,3 (**1C**, C=O), 156,8 (**1C**, C3), 159,8 (**1C**, C5).

6.2.2.2 5,7-dimethoxyisobenzofuran-1(3*H*)-one **44**



$C_{12}H_{16}O_4NBr$
318,17

$C_{10}H_{10}O_4$
194,19

For the preparation of **44**, 20,8 g (65,5mmol, 1,0 equiv.) **43** were dissolved in 314 ml dry THF in a flame-dried one-neck 500-ml round-bottom flask under an inert atmosphere. The solution was then cooled to –78 °C and treated with a ^{n}BuLi-solution (1,6M in hexanes; 74,7 ml, 119 mmol, 3,8 equiv.). After stirring the reaction at –78 °C for 45 minutes, the cooling bath was removed and the stirring continued for additional 135 minutes at room temperature. Upon completion (TLC), any unreacted Li-base residues were carefully neutralized by the addition of wet MeOH (carefully added until no more gas-formation was observed) and 150 ml of water and the volatiles removed under reduced pressure. The cloudy aqueous solution was extracted with copious amounts of EtOAc (4x200 ml) and the organic phases dried over Na_2SO_4. After concentration *in vacuo*, the obtained solid residue was recrystallized from acetone (200 ml) and thus the desired phthalide **44** was obtained as a snow-white and seven-dwarfy powder (3,20 g, 15,1 mmol, **48%**).

R_f = 0,66 (EtOAc);

m.p. = 152 °C (acetone);

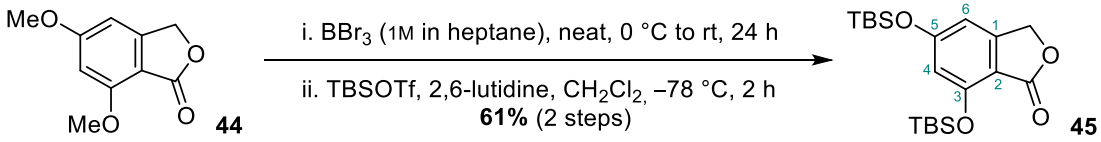
HR-ESI-MS: $[C_{10}H_{10}O_4Na]^+$: m/z = 217,0477, found m/z = 217,0478;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 3,89 (s, **3H**, C5-OCH_3), 3,95 (s, **3H**, C3-OCH_3), 5,17 (s, **2H**, CH_2), 6,42 (d, *J* = 1,8 Hz, **1H**, H4), 6,48 (s, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 56,1 (**2C**, OCH_3), 68,7 (**1C**, CH_2), 97,7 (**1C**, C6), 99,0 (**1C**, C4), 106,8 (**1C**, C1), 151,8 (**1C**, C2), 159,9 (**1C**, C3), 166,9 (**1C**, C5), 169,1 (**1C**, C=O).

The recorded spectroscopic data are in accordance with those reported by Ward et al.[101]

6.2.2.3 5,7-bis((*tert*-butyldimethylsilyl)oxy)isobenzofuran-1(3*H*)-one **45**



$C_{10}H_{10}O_4$
194,19

$C_{20}H_{34}O_4Si_2$
394,66

Methyl-ether cleavage (synthesis of 5,7-dihydroxyisobenzofuran-1(3*H*)-one): A flame-dried 25-ml one-neck round-bottom flask was charged with **44** (0,19 g, 0,98 mmol, 1,0 eq) and treated at 0 °C with a BBr_3-solution (1M in heptane, 9,8 ml, 9,77 mmol, 10,0 equiv.). After the addition was completed, the red solution was allowed to warm to room temperature and stirred under an inert atmosphere for eight hours ($\mathbf{R_f}$ = 0,05 (EtOAc)), after which an additional portion of BBr_3-solution (1M in heptane, 4,9 ml, 4,89 mmol, 5,0 equiv.) was added and stirring continued. After a total stirring-time of 24 hours, the reaction was diluted with 5 ml of a saturated, aqueous $NaHCO_3$-solution, extracted with a copious amount of EtOAc (5x50 ml) and the joined organic phases dried over Na_2SO_4. The volatiles were then removed under reduced pressure to yield the crude diphenol (0,16 g, 0,96 mmol) as a thick, brown oil.

TBS-protection (synthesis of **45**): Lastly, the previously prepared crude diphenol (0,16 g, 0,96 mmol, 1,0 equiv.) was charged into a flame-dried 10-ml one-neck round-bottom flask and 2,8 ml dry CH_2Cl_2 were added. The suspension was then cooled to –78 °C and treated with 0,3 ml (2,89 mmol, 3,0 equiv.) 2,6-lutidine, followed by 0,5 ml (2,02 mmol, 2,1 equiv.) TBSOTf and the reaction stirred under an inert atmosphere for two hours, while maintaining the initial temperature. Upon completion, the reaction was diluted with 15 ml of water and the organic components extracted with PE (3x20 ml). The combined organic phases were then dried over Na_2SO_4, concentrated under reduced pressure and the residue purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 19:1 (v/v)) to yield the aimed precursor **45** (0,22 g, 0,60 mmol, **61%** (2 steps)) as a colorless oil.

$\mathbf{R_f}$ = 0,74 (PE/ EtOAc = 9:1 (v/v));

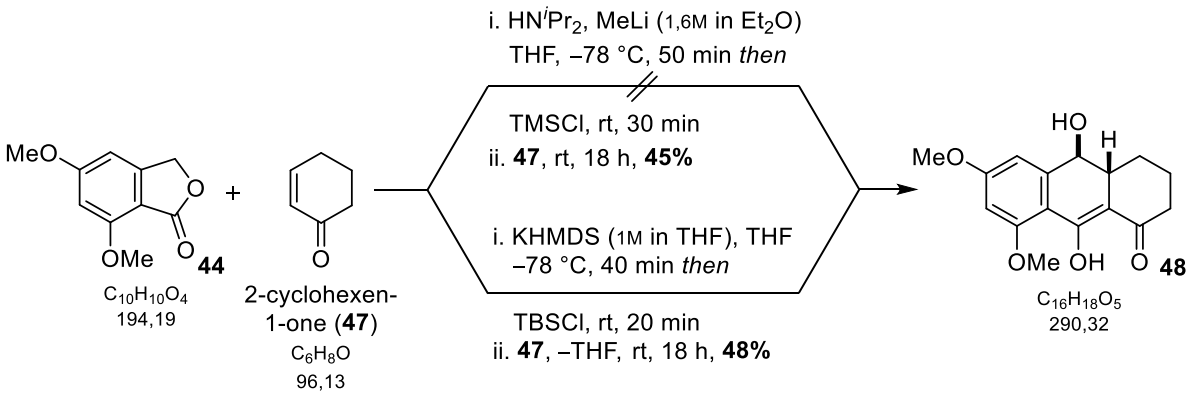
HR-ESI-MS: $[C_{20}H_{34}O_4Si_2Na]^+$: m/z = 417,1893, found m/z = 417,1890;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,23 (s, **6H**, CH_3 (C5-TBS), 0,25 (s, **6H**, CH_3 (C3-TBS), 0,97 (s, **9H**, CH_3 (C5-TBS), 1,03 (s, **9H**, CH_3 (C3-TBS), 5,09 (s, **2H**, CH_2), 6,29 (d, *J* = 1,8 Hz, **1H**, H4), 6,45 (dt, *J* = 1,9, 1,0, 1,0 Hz, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,4 (**1C**, CH_3 (C5-TBS), –4,3 (**1C**, CH_3 (C3-TBS), 18,3 (**1C**, $C_{quat.}$ (TBS)), 18,5 (**1C**, $C_{quat.}$ (TBS)), 25,6 (**3C**, CH_3 (C5-TBS), 25,7 (**3C**, CH_3 (C3-TBS), 68,2 (**1C**, CH_2), 106,5 (**1C**, C6), 109,8 (**1C**, C1), 112,2 (**1C**, C4), 150,6 (**1C**, C2), 156,3 (**1C**, C3), 162,6 (**1C**, C5), 168,6 (**1C**, C=O).

6.2.3 Demethylpremithramycinone **1** from enone **32** and *bio-assay* derivatives

6.2.3.1 Diels–Alder with furan reaction-study (synthesis of (4a*R*,10*S*)-9,10-dihydroxy-6,8-dimethoxy-3,4,4a,10-tetrahydroanthracen-1(2*H*)-one **48**)



route I: For the initial strategy, 50,0 mg (0,26 mmol, 1,0 equiv.) **44** were dissolved in 0,3 ml dry THF in a flame-dried 5-ml one-neck round-bottom flask and the formed suspension cooled to –78 °C. The suspension was then subsequently treated with 0,15 ml (0,13 mmol, 0,5 equiv.) *di*-isopropylamine and 0,4 ml (0,64 mmol, 2,5 equiv.) MeLi-solution (1,6M in Et_2O). The red solution was then stirred for 50 minutes under an inert atmosphere after which 60,0 µl (0,46 mmol, 1,8 eq) TMSCl were added and the solution allowed to warm to room temperature over a period of 30 minutes. 2-cyclohexen-1-one (**47**; 20,0 µl, 0,21 mmol, 0,9 equiv.) was then added to the reaction, the solvent-amount reduced under vacuum to 10% of its original volume[19] and the stirring continued for 18 hours. The reaction was then terminated by the addition of two drops of aqueous HCl-solution (1M) and diluted with 5 ml EtOAc. Further dilution of the reaction by the addition of water was followed by an extraction with EtOAc (4x20 ml) and drying of the combined organic phases over Na_2SO_4, followed by *in vacuo* removal of the volatiles. Purification of the recovered residue *via* flash column chromatography (SiO_2, PE/ EtOAc = 2:3 (v/v)) afforded a white solid (33,5 mg, 0,12 mmol, **45%**), which was later found to be the 1,4-addition product. Since the further protocol managed to yield the desired outcome, a full characterization of the product was omitted.

m.p. = 103 °C;

R_f = 0,84 (EtOAc);

HR-ESI-MS: $[C_{16}H_{18}O_5Na]^+$: m/z = 313,1052, found m/z = 313,1053;

route II: For the second strategy, 150 mg (0,77 mmol, 1,0 equiv.) **44** were dissolved in 1,5 ml dry THF in a flame-dried 10-ml one-neck round-bottom flask and the formed suspension cooled to –78 °C. The suspension was then treated with 1,3 ml (1,31 mmol, 1,7 equiv.) KHMDS-solution (1M in THF) and the red-colored solution stirred for 40 minutes under an inert atmosphere. A 1M TBSCl-solution in THF (0,85 ml, 1,08 mmol, 1,4 equiv.) was then added and the reaction warmed to room temperature over a period of 20 minutes after which 75,0 µl 2-cyclohexen-1-one (**47**; 0,77 mmol, 0,9 equiv.) were added and the solvent-amount reduced under vacuum to 10% of its original volume.
The concentrated slurry was then stirred for additional 18 hours upon which the reaction was acidified by the addition of a few drops of HCl-solution (1M, aq.). The reaction mixture was then diluted with

[19] By not maintaining a high concentration of the reaction, the formation of undefined side products was observed. Therefore, the concentration step turned out to be highly required for a successful outcome.

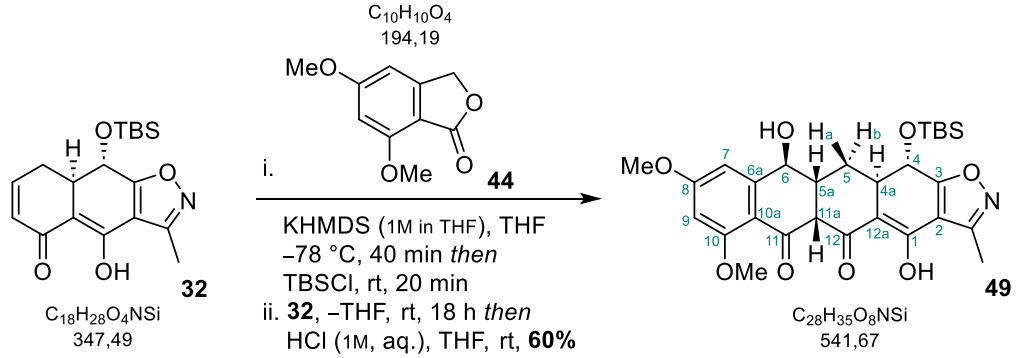
water and extracted with EtOAc (4x40 ml). The combined phases were then dried over Na_2SO_4, the volatiles removed under reduced pressure and the crude product purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 2:3 (v/v)) to give the aimed tricyclic product **48** (97,1 mg, 0,33 mmol, **48%**) as a thick colorless oil. Since the sole purpose of this transformation was the exploration of optimal conditions for the Diels–Alder reaction with furan, only a brief characterization of the product was carried out.

R_f = 0,90 (EtOAc);

HR-ESI-MS: $[C_{16}H_{18}O_5Na]^+$: m/z = 313,1052, found m/z = 313,1053;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 1,65 (dt, *J* = 13,1, 4,1, 4,1 Hz, **1H**), 1,73–1,77 (m, **1H**), 1,92 (qd, *J* = 12,9, 12,9, 12,8, 3,6 Hz, **1H**), 2,02 (d, *J* = 12,9 Hz, **1H**), 2,15 (dq, *J* = 9,9, 3,0, 2,9, 2,9 Hz, **1H**), 2,23–2,28 (m, **1H**),), 2,29–2,35 (m, **2H**), 3,85 (s, **3H**), 3,90 (s, **3H**), 5,32 (d, *J* = 2,5 Hz, **1H**), 6,35 (dd, *J* = 1,8, 0,9 Hz, **1H**), 6,39 (d, *J* = 1,8 Hz, **1H**).

6.2.3.2 (11*S*,11a*R*,12a*R*,13*S*)-13-((*tert*-butyldimethylsilyl)oxy)-4,6,11-trihydroxy-7,9-dimethoxy-3-methyl-11a,12,12a,13-tetrahydrotetraceno[2,3-*d*]isoxazol-5(11*H*)-one **49**



0,46 g (2,37 mmol, 1,5 equiv.) **44** were dissolved in 4,7 ml dry THF in a flame-dried 10-ml one-neck round-bottom flask and the formed suspension cooled to –78 °C. The suspension was then treated with 3,4 ml (3,36 mmol, 2,1 equiv.) KHMDS-solution (1M in THF) and the red-colored solution stirred for 40 minutes under an inert atmosphere. TBSCl (0,55 g, 3,64 mmol, 2,3 equiv.) was then added and the reaction warmed to room temperature over a period of 20 minutes after which 0,55 g (1,58 mmol, 1,0 equiv.) of **32** were added and the solvent-amount reduced under vacuum to 10% of its original volume[20]. The concentrated, dark-green-colored slurry was then stirred for additional 18 hours. Upon completion, the reaction was diluted with 10 ml of water and 10 ml MTBE and the organic components extracted with MTBE (3x20 ml). The combined organic phases were dried over Na_2SO_4, the volatiles removed under reduced pressure and the residue quickly (!) purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 3:2 (v/v) with 1,5 vol-% NEt_3). The fractions containing the impure cycloaddition prodict (**R_f** = 0,89 (PE/ EtOAc = 7:3 (v/v)) were then collected and concentrated under reduced pressure. The oily residue was redissolved in 5 ml THF and the solution acidified by the addition of five drops of HCl-solution (1M, aq.). The mixture was then transferred to a separatory funnel, diluted with water and extracted with EtOAc (4x80 ml). The combined phases were then dried over Na_2SO_4, the volatiles removed under reduced pressure and the crude product purified *via*

[20] In some instances, the formation of a 1,4-addition product could be observed due to insufficient concentration of the reaction. A full characterization of the compound (HPLC: elution under the mentioned conditions at 25-30 min) is given at the end of this subchapter.

preparatory RP-HPLC (injection volume: 1,0 ml (MeCN), elution with H_2O/ MeCN-gradient, flow-rate; 15,00 ml/ min). The fractions eluting at 44-45 min (elution with MeCN) were collected and concentrated to give the aimed tetracycline precursor **49** (0,52 g, 0,95 mmol, **60%**) as a bright yellow solid.

R_f = 0,33 (PE/ EtOAc = 2:3 (v/v))[21];

m.p. = 133 °C;

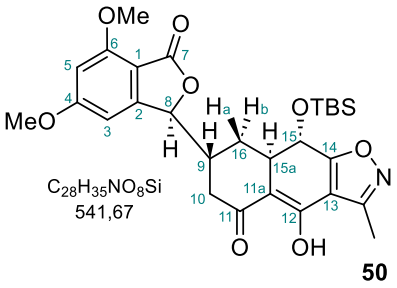
$[\alpha]_D^{22,1}$ = +175,58° ($CHCl_3$, *7,92*);

HR-ESI-MS: $[C_{28}H_{35}O_8NSiNa]^+$: m/z = 564,2030, found m/z = 564,2034;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,15 (s, **3H**, CH_3 (TBS)), 0,21 (s, **3H**, CH_3 (TBS)), 0,92 (s, **9H**, CH_3 (TBS)), 2,08–2,11 (m, **2H**, H5), 2,36 (br. s, **1H**, OH), 2,48 (s, **3H**, CH_3), 2,93–2,95 (m, **2H**, H4a, H5a), 3,80 (d, *J* = 5,2 Hz, **1H**, H11a), 3,84 (s, **3H**, C10-OCH_3), 3,89 (s, **3H**, C8-OCH_3), 4,38 (s, **1H**, H6), 4,96 (d, *J* = 7,1 Hz, **1H**, H4), 6,42 (d, *J* = 2,0 Hz, **1H**, H9), 6,51 (s, **1H**, H7);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,8 (**1C**, CH_3 (TBS)), –4,5 (**1C**, CH_3 (TBS)), 10,7 (**1C**, CH_3), 18,2 (**1C**, $C_{quat.}$ (TBS)), 24,7 (**1C**, C5), 25,7 (**3C**, CH_3 (TBS)), 34,8 (**1C**, C5a), 43,0 (**1C**, C4a), 54,3 (**1C**, C11a), 55,7 (**1C**, C8-OCH_3), 56,1 (**1C**, C10-OCH_3), 64,8 (**1C**, C4), 72,1 (**1C**, C6), 99,3 (**1C**, C9), 102,2 (**1C**, C12a), 105,7 (**1C**, C7), 111,9 (**1C**, C10a), 113,9 (**1C**, C2), 146,7 (**1C**, C6a), 157,8 (**1C**, C=N), 162,6 (**1C**, C10), 164,8 (**1C**, C8), 178,1 (**1C**, C1), 179,1 (**1C**, C3), 185,5 (**1C**, C12), 187,7 (**1C**, C11).

*Analysis of the 1,4-addition product **50**:*



50

HR-ESI-MS: $[C_{28}H_{35}O_8NSiNa]^+$: m/z = 564,2030,
found m/z = 564,2031;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,17 (s, **3H**, CH_3 (TBS)), 0,26 (s, **3H**, CH_3 (TBS)), 0,96 (s, **9H**, CH_3 (TBS)), 1,92 (ddd, *J* = 13,7, 7,6, 3,5 Hz, **1H**, Ha16), 2,15-2,17 (m, **2H**, H10), 2,28 (dt, *J* = 13,2, 6,4, 6,4 Hz, **1H**, Hb16), 2,36-2,38 (m, **1H**, H9), 2,44 (s, **3H**, CH_3), 3,11–3,17 (m, **1H**, H15a), 3,85 (s, **3H**, C4-OCH_3), 3,91 (s, **3H**, C6-OCH_3), 4,70 (d, *J* = 11,1 Hz, **1H**, H8), 5,22 (d, *J* = 4,1 Hz, **1H**, H15), 6,36 (d, *J* = 1,8 Hz, **1H**, H5), 6,47 (s, **1H**, H3);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,7 (**1C**, CH_3 (TBS)), –4,4 (**1C**, CH_3 (TBS)), 10,6 (**1C**, CH_3), 18,3 (**1C**, $C_{quat.}$ (TBS)), 25,8 (**3C**, CH_3 (TBS)), 28,3 (**1C**, C16), 29,1 (**1C**, C10), 35,2 (**1C**, C9), 40,6 (**1C**, C15a), 56,1 (**1C**, OCH_3), 56,1 (**1C**, OCH_3), 70,4 (**1C**, C8), 81,4 (**1C**, C15), 98,5 (**1C**, C5), 98,9 (**1C**, C3), 105,1 (**1C**, C11a), 106,8 (**1C**, C2), 113,4 (**1C**, C13), 152,7 (**1C**, C=N), 157,8 (**1C**, C14), 159,9 (**1C**, C6), 167,0 (**1C**, C4), 167,9 (**1C**, C1), 175,5 (**1C**, C12), 179,2 (**1C**, C7), 185,8 (**1C**, C11).

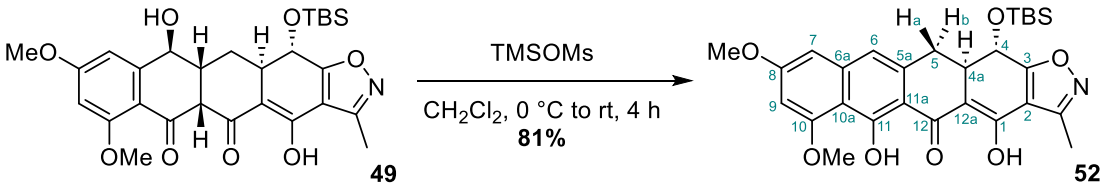
R_f = 0,37 (PE/ EtOAc = 2:3 (v/v));

m.p. = 118 °C;

$[\alpha]_D^{22,9}$ = –51,85° ($CHCl_3$, *2,25*);

[21] The presence of the vinylogous-acid motif in the molecule leads to undefined TLC-spots, as well as inconsistent polarities.

6.2.3.3 (12a*R*,13*S*)-13-((*tert*-butyldimethylsilyl)oxy)-4,6-dihydroxy-7,9-dimethoxy-3-methyl-12a,13-dihydrotetraceno[2,3-*d*]isoxazol-5(12*H*)-one **52**



$C_{28}H_{35}O_8NSi$
541,67

$C_{28}H_{33}O_7NSi$
523,66

Precursor **49** (0,52 g, 0,95 mmol, 1,0 equiv.) was dissolved in 3,8 ml dry CH_2Cl_2 in a flame-dried 10-ml one-neck round-bottom flask and the formed solution cooled to 0 °C. TMSOMs (0,7 ml, 4,23 mmol, 4,5 equiv.) was then added and the red-colored solution stirred for 4 hours at room temperature under an inert atmosphere. Upon completion, the mixture was treated with 3 ml saturated, aqueous $NaHCO_3$-solution and diluted with water and EtOAc. Extraction with EtOAc (6x150 ml), followed by drying of the combined phases over Na_2SO_4 and removal of the volatiles under reduced pressure afforded the crude pentacyclic product. Purification *via* flash column chromatography (SiO_2, PE/ EtOAc = 4:1→3:2 (v/v)) gave the aimed precursor **52** (0,40 g, 0,77 mmol, **81%**) as a bright-yellow solid.

R_f = 0,78 (PE/ EtOAc = 3:2 (v/v));

m.p. = decomp. >120 °C;

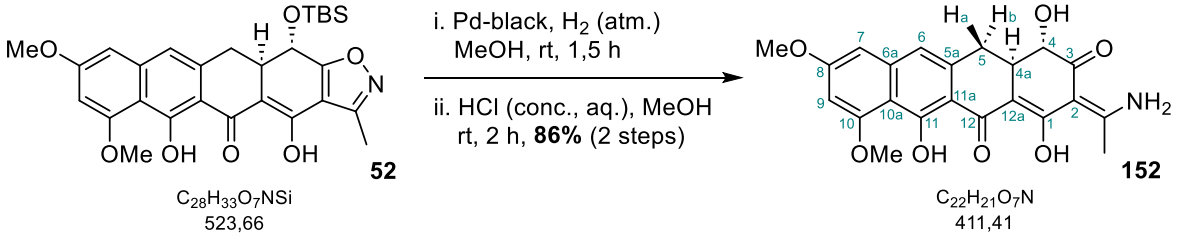
$[\alpha]_D^{21,7}$ = +294,44° ($CHCl_3$, *3,00*);

HR-ESI-MS: $[C_{28}H_{33}NO_7SiNa]^+$: m/z = 546,1924, found m/z = 546,1921;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,24 (s, **3H**, CH_3 (TBS)), 0,31 (s, **3H**, CH_3 (TBS)), 1,03 (s, **9H**, CH_3 (TBS)), 2,50 (s, **3H**, CH_3), 2,73 (t, *J* = 13,3, 13,3 Hz, **1H**, Ha5), 3,19 (td, *J* = 12,7, 12,6, 4,9 Hz, **1H**, H4a), 3,27 (dd, *J* = 14,3, 4,9 Hz, **1H**, Hb5), 3,89 (s, **3H**, C8-OCH_3), 3,90 (s, **3H**, C10-OCH_3), 4,88 (d, *J* = 12,0 Hz, **1H**, H4), 6,44 (d, *J* = 2,2 Hz, **1H**, H9), 6,60 (d, *J* = 2,3 Hz, **1H**, H7), 6,91 (s, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,5 (**1C**, CH_3 (TBS)), –4,2 (**1C**, CH_3 (TBS)), 10,9 (**1C**, CH_3), 18,4 (**1C**, $C_{quat.}$ (TBS)), 25,9 (**3C**, CH_3 (TBS)), 33,9 (**1C**, C5), 41,4 (**1C**, C4a), 55,6 (**1C**, C8-OCH_3), 56,3 (**1C**, C10-OCH_3), 71,8 (**1C**, C4), 98,2 (**1C**, C9), 99,1 (**1C**, C7), 102,7 (**1C**, C12a), 109,3 (**1C**, C11a), 110,7 (**1C**, C2), 111,0 (**1C**, C10a), 116,5 (**1C**, C6), 136,3 (**1C**, C5a), 141,5 (**1C**, C6a), 157,0 (**1C**, C=N), 161,0 (**1C**, C10), 161,9 (**1C**, C8), 164,2 (**1C**, C11), 168,5 (**1C**, C3), 175,7 (**1C**, C1), 190,1 (**1C**, C12).

6.2.3.4 (1*S*,12a*R*,*Z*)-3-(1-aminoethylidene)-1,4,6-trihydroxy-7,9-dimethoxy-12,12a-dihydrotetracene-2,5(1*H*,3*H*)-dione **152**



$C_{28}H_{33}O_7NSi$
523,66

$C_{22}H_{21}O_7N$
411,41

hydrogenation (synthesis of (1*S*,12a*R*)-1-((*tert*-butyldimethylsilyl)oxy)-2,4,6-trihydroxy-3-(1-iminoethyl)-7,9-dimethoxy-12,12a-dihydrotetracen-5(1*H*)-one):, 35,0 mg (0,07 mmol, 1,0 equiv.) **52** were dissolved under an inert atmosphere in 1,3 ml dry MeOH in a flame-dried 5-ml three-neck round-bottom flask. To the formed solution, 8,20 mg (0,08 mmol, 1,15 equiv.) Pd-black were added under argon-stream and the flask evacuated three times and backfilled with H_2. The reaction was then allowed to stir for 90 minutes under a H_2-atmosphere ($\mathbf{R_f}$ = 0,63 (PE/ EtOAc = 3:2 (v/v))), after which the flask was opened and 5 ml EtOAc added. Filtration over Celite® (EtOAc), followed by the removal of the volatiles under reduced pressure gave the aimed title compound[22] (34,4 mg, 0,07 mmol) as a bright-yellow powder, which was used without any further purification.

enamine-hydrolysis and TBS-cleavage (synthesis of **152**): The previously prepared crude enamine (34,4 mg, 0,07 mmol, 1,0 equiv.), dissolved at room temperature in 3,0 ml MeOH in a 10-ml one-neck round-bottom flask was treated with 16,0 µl (8,0 equiv.) concentrated, aqueous HCl-solution and the reaction stirred for two hours under ambient conditions. The pH of the reaction was then adjusted to 6 by the careful addition of a small amount of a saturated, aqueous $NaHCO_3$-solution after which 5 ml of EtOAc were added. The diluted aqueous phase (addition of further 10 ml of H_2O) was then extracted with EtOAc (3x20 ml). The combined organic phases were then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified *via* preparatory RP-HPLC (injection volume: 1,0 ml (MeCN), elution with H_2O/ MeCN-gradient, flow-rate; 15,00 ml/ min). The fractions eluting at 31-32 min (elution with 20% H_2O, 80% MeCN) were collected and concentrated to give 23,7 mg (0,07 mmol, **86%** (2 steps)) of tetracycline **152**, as a bright-yellow powder.

$\mathbf{R_f}$ = 0,51 (PE/ EtOAc = 1:4 (v/v));

m.p. = decomp. >148 °C;

$[\alpha]_D^{22,7}$ = +224,44° ($CHCl_3$, *1,25*);

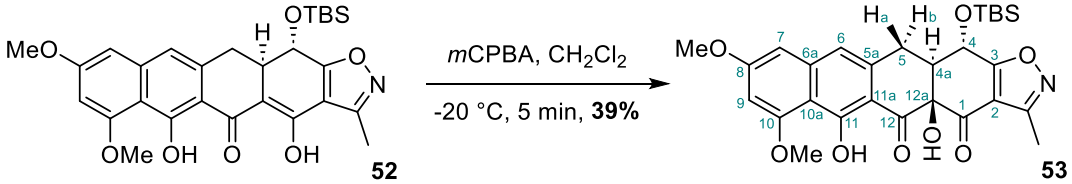
HR-ESI-MS: $[C_{22}H_{21}NO_7Na]^+$: m/z = 434,1216, found m/z = 434,1218;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,62 (s, **3H**, CH_3), 2,72–2,75 (m, *J* = 13,3, 13,3 Hz, **1H**, Ha5), 2,75–2,77 (m, **1H**, H4a), 3,34–3,37 (m, **1H**, Hb5), 3,91 (s, **3H**, C8-OCH_3), 3,95–3,97 (m, **1H**, H4), 3,99(s, **3H**, C10-OCH_3), 4,18 (d, *J* = 1,8 Hz, **1H**, C4-OH), 6,43 (d, *J* = 2,4 Hz, **1H**, H9), 6,59 (d, *J* = 2,3 Hz, **1H**, H7), 6,90 (s, **1H**, H6), 11,49 (s, **1H**, C11-OH), 13,93 (s, **1H**, C3-OH);

^{13}C-NMR (151 MHz; $CDCl_3$): δ [ppm] = 25,9 (**1C**, CH_3), 35,8 (**1C**, C5), 44,0 (**1C**, C4a), 55,6 (**1C**, C8-OCH_3), 56,3 (**1C**, C10-OCH_3), 75,9 (**1C**, C4), 98,1 (**1C**, C9), 99,0 (**1C**, C7), 99,8 (**1C**, C2), 109,6 (**1C**, C10a), 114,0 (**1C**, C11a), 116,2 (**1C**, C6), 129,5 (**1C**, C12a), 136,5 (**1C**, C5a), 141,1 (**1C**, C6a), 160,7 (**1C**, C10), 161,2 (**1C**, C8),), 162,5 (**1C**, C11), 170,7 (**1C**, C=N), 177,2 (**1C**, C1), 186,9 (**1C**, C3), 195,9 (**1C**, C12).

[22] **HR-ESI-MS**: $[C_{28}H_{35}O_7NSiNa]^+$: m/z = 374,2081, found m/z = 548,2065.

6.2.3.5 (4a*R*,12a*S*,13*S*)-13-((*tert*-butyldimethylsilyl)oxy)-4a,6-dihydroxy-7,9-dimethoxy-3-methyl-12a,13-dihydrotetraceno[2,3-*d*]isoxazole-4,5(4a*H*,12*H*)-dione **53**



$C_{28}H_{33}O_7NSi$
523,66

$C_{28}H_{35}O_9NSi$
557,67

73,5 mg (0,14 mmol, 1,0 equiv.) **52** were dissolved in 2,8 ml dry CH_2Cl_2 in a flame-dried 10-ml one-neck round-bottom flask and the formed suspension cooled to -20 °C. *m*CPBA (77 wt%, tech. grade; 34,6 mg, 0,15 mmol, 1,1 equiv.) was then added at once and the red-colored solution stirred for five minutes (**!**) under an inert atmosphere. The reaction was then diluted with 2 ml of water and the pH adjusted to 5 by the addition of saturated, aqueous $NaHCO_3$-solution. The aqueous phase was then extracted with MTBE (3x15 ml)[23], the combined organic phases dried over Na_2SO_4, the volatiles removed under reduced pressure and the crude product purified *via* preparatory RP-HPLC (injection volume: 1,0 ml (MeCN), elution with H_2O/ MeCN-gradient, flow-rate; 15,00 ml/ min). The fractions eluting at 50-52 min (elution with 20% H_2O, 80% MeCN) were collected and concentrated to give the aimed ketol **53** (29,5 mg, 54,7 µmol, **39%**) as a yellow-colored solid.

R_f = 0,56 (PE/ EtOAc = 3:2 (v/v));

m.p. = 198 °C;

$[\alpha]_D^{29,5}$ = +269,11° ($CHCl_3$, *4,10*);

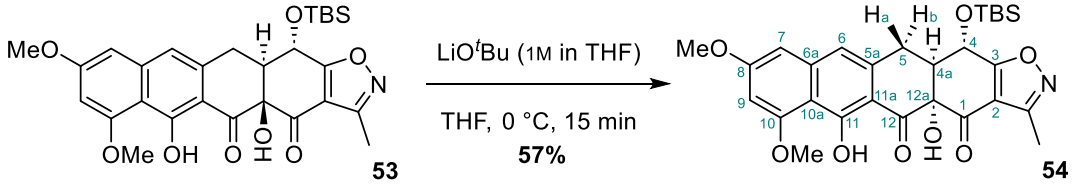
HR-ESI-MS: $[C_{28}H_{33}NO_8SiNa]^+$: m/z = 562,1873, found m/z = 562,1883;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,32 (s, **3H**, CH_3 (TBS)), 0,35 (s, **3H**, CH_3 (TBS)), 1,02 (s, **9H**, CH_3 (TBS)), 2,45 (s, **3H**, CH_3), 2,74 (td, *J* = 9,1, 9,1, 7,1 Hz, **1H**, H4a), 3,18–3,20 (m, **2H**, Ha5, Hb5), 3,90 (s, **3H**, C8-OCH_3), 3,93(s, **3H**, C10-OCH_3), 4,17 (br. s, **1H**, C12a-OH), 5,21 (d, *J* = 9,0 Hz, **1H**, H4), 6,41 (d, *J* = 2,2 Hz, **1H**, H9), 6,57 (d, *J* = 2,2 Hz, **1H**, H7), 6,87 (s, **1H**, H6), 13,80 (s, **1H**, C11-OH);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,6 (**1C**, CH_3 (TBS)), –4,3 (**1C**, CH_3 (TBS)), 10,7 (**1C**, CH_3), 18,4 (**1C**, $C_{quat.}$ (TBS)), 25,9 (**3C**, CH_3 (TBS)), 27,0 (**1C**, C5), 49,8 (**1C**, C4a), 55,6 (**1C**, C8-OCH_3), 56,3 (**1C**, C10-OCH_3), 66,2 (**1C**, C4), 76,3 (**1C**, C12a), 98,3 (**1C**, C9), 99,4 (**1C**, C7), 110,1 (**1C**, C10a), 110,4 (**1C**, C11a), 112,6 (**1C**, C2), 116,3 (**1C**, C6), 136,8 (**1C**, C5a), 142,3 (**1C**, C6a), 158,5 (**1C**, C=N), 161,3 (**1C**, C3), 162,8 (**1C**, C10), 166,5 (**1C**, C8), 179,0 (**1C**, C11), 187,9 (**1C**, C1), 196,4 (**1C**, C12).

[23] The extraction with MTBE was typically carried out until the otherwise orange-colored organic phase turned colorless. A red coloration of the aqueous phase is to be expected.

6.2.3.6 (4a*S*,12a*S*,13*S*)-13-((*tert*-butyldimethylsilyl)oxy)-4a,6-dihydroxy-7,9-dimethoxy-3-methyl-12a,13-dihydrotetraceno[2,3-*d*]isoxazole-4,5(4a*H*,12*H*)-dione **54**



$C_{28}H_{33}O_8NSi$
539,66

$C_{28}H_{33}O_8NSi$
539,66

Finally, **53** (29,5 mg, 54,7 µmol, 1,0 equiv.) was dissolved in 0,7 ml dry THF in a flame-dried 5-ml one-neck round-bottom flask at 0 °C and the solution treated with 73,8 µl (73,8 µmol, 1,4 equiv.) LiO^{t}Bu-solution (1M in THF). The formed brown solution was then stirred at 0 °C for 15 minutes after which 4 ml of water were added. The pH was adjusted to 5 by the addition of 1M aqueous HCl-solution and the aqueous phase extracted with MTBE (3x10 ml)[24]. The combined organic phases were dried over Na_2SO_4, the volatiles removed under reduced pressure and the crude product purified *via* preparatory RP-HPLC (injection volume: 1,0 ml (MeCN), elution with H_2O/ MeCN-gradient, flow-rate; 15,00 ml/ min). The fractions eluting at 45-57 min (elution with 20% H_2O, 80% MeCN) were collected and concentrated to give the rearranged ketol **54** (16,8 mg, 31,1 µmol, **57%**) as a yellow solid.[25]

R_f = 0,78 (PE/ EtOAc = 3:2 (v/v));

m.p. = 147 °C;

$[\alpha]_D^{27,3}$ = +106,67° ($CHCl_3$, *1,00*);

HR-ESI-MS: $[C_{28}H_{33}NO_8SiNa]^+$: m/z = 562,1873, found m/z = 562,1872;

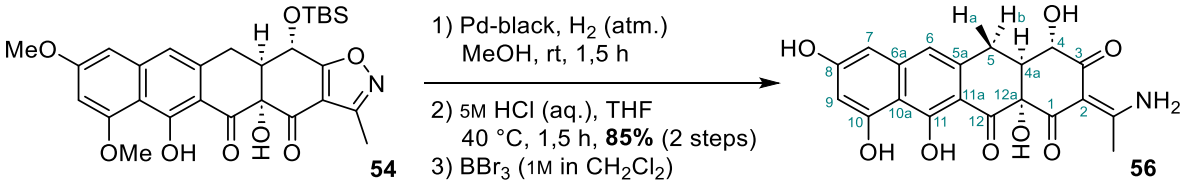
^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,06 (s, **3H**, CH_3 (TBS)), 0,16 (s, **3H**, CH_3 (TBS)), 0,95 (s, **9H**, CH_3 (TBS)), 2,55 (s, **3H**, CH_3), 2,92 (ddd, *J* = 9,1, 4,3, 2,7 Hz, **1H**, H4a), 3,16 (dd, *J* = 17,1, 2,7 Hz, **1H**, Ha5), 3,62 (ddd, *J* = 16,8, 4,4, 1,7 Hz, **1H**, Hb5), 3,93 (s, **3H**, C8-OCH_3), 3,96(s, **3H**, C10-OCH_3), 4,72 (br. s, **1H**, C12a-OH), 4,84 (d, *J* = 9,1 Hz, **1H**, H4), 6,45 (d, *J* = 2,2 Hz, **1H**, H9), 6,58 (d, *J* = 2,3 Hz, **1H**, H7), 6,89 (s, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,7 (**1C**, CH_3 (TBS)), –4,7 (**1C**, CH_3 (TBS)), 10,8 (**1C**, CH_3), 18,2 (**1C**, $C_{quat.}$ (TBS)), 25,8 (**3C**, CH_3 (TBS)), 26,3 (**1C**, C5), 50,9 (**1C**, C4a), 55,7 (**1C**, C8-OCH_3), 56,3 (**1C**, C10-OCH_3), 65,0 (**1C**, C4), 79,8 (**1C**, C12a), 98,5 (**1C**, C9), 99,5 (**1C**, C7), 108,9 (**1C**, C10a), 110,4 (**1C**, C11a), 113,4 (**1C**, C2), 118,1 (**1C**, C6), 135,1 (**1C**, C5a), 142,7 (**1C**, C6a), 157,8 (**1C**, C=N), 161,7 (**1C**, C3), 163,2 (**1C**, C10), 167,9 (**1C**, C8), 179,9 (**1C**, C11), 189,3 (**1C**, C1), 194,9 (**1C**, C12).

[24] The extraction with MTBE was typically carried out until the otherwise yellow-colored organic phase turned colorless. A brown coloration of the aqueous phase is to be expected.

[25] The sequences described in chapters 6.2.3.5 and 6.2.3.6 were repeated several times with various amounts of starting material until a total amount of approx. 80 mg of **54** were prepared. The yields remained highly reproducible throughout the repetitions.

6.2.3.7 (4*S*,4a*S*,12a*S*,*E*)-2-(1-aminoethylidene)-4,8,10,11,12a-pentahydroxy-4a,12a-dihydro-tetracene-1,3,12(2*H*,4*H*,5*H*)-trione **56**

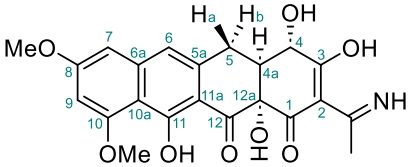


$C_{28}H_{33}O_8NSi$
539,66

$C_{20}H_{17}O_8N$
399,36

hydrogenation and hydrolysis (synthesis of (4*S*,4a*S*,12a*S*)-3,4,11,12a-tetrahydroxy-2-(1-iminoethyl)-8,10-dimethoxy-4a,12a-dihydrotetracene-1,12(4*H*,5*H*)-dione **55**): 71,7 mg (133 µmol, 1,0 equiv.) **54** were dissolved under an inert atmosphere in 2,6 ml dry MeOH in a flame-dried 5-ml three-neck round-bottom flask. To the formed solution, 16,2 mg (152 mmol, 1,15 equiv.) Pd-black were added under argon-stream and the flask evacuated three times and backfilled with H_2. The reaction was then allowed to stir for 90 minutes under a H_2-atmosphere ($\mathbf{R_f}$ = 0,77 (EtOAc)), after which the flask was opened and 3 ml of EtOAc added. Filtration over Celite® (EtOAc), followed by the removal of the volatiles gave the aimed tetracyclic product (70,0 mg, 129 µmol) as a bright-yellow powder.

The crude product (70,0 mg, 192 µmol, 1,0 equiv.) was then dissolved at room temperature in 30,0 ml THF in a 50-ml one-neck round-bottom flask and 0,8 ml (30,0 equiv.) aqueous HCl-solution (5M) added. The reaction was stirred for 90 minutes at 40 °C after which the pH was adjusted to 6 by the careful addition of saturated, aqueous $NaHCO_3$-soution. Further dilution of the reaction with water and EtOAc, followed by the extraction of the aqueous phase with EtOAc (3x50 ml), drying of the combined organic phases over Na_2SO_4 and concentration under reduced pressure afforded the crude product, which was purified *via* preparatory RP-HPLC (injection volume: 1,0 ml (MeCN), elution with H_2O/ MeCN-gradient, flow-rate; 15,00 ml/ min). The fractions eluting at 23-25 min (elution with 35% H_2O, 65% MeCN) were collected and concentrated finally gave 48,0 mg (112 µmol, **85%** (2 steps)) of title compound **55**, as a bright-yellow powder.



$C_{22}H_{21}O_8N$
427,41

55

$\mathbf{R_f}$ = 0,59 (EtOAc);

m.p. = >150 °C (decomp.);

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{22,2}}$ = +191,18° (MeOH, *0,91*);

HR-ESI-MS: $[C_{22}H_{21}NO_8Na]^+$: m/z = 450,1165, found m/z = 450,1161;

^{1}H-NMR (400 MHz; CD_3CN): δ [ppm] = 2,50–2,53 (m, **1H**, H4a), 2,53 (s, **3H**, CH_3), 3,19 (dd, *J* = 17,1, 2,0 Hz, **1H**, Ha5), 3,46 (ddd, *J* = 16,5, 4,4, 1,8 Hz, **1H**, Hb5), 3,89 (s, **3H**, C8-OCH_3), 3,90(s, **3H**, C10-OCH_3), 4,04 (d, *J* = 10,7 Hz, **1H**, H4), 5,27 (br. s, **1H**, C4-OH), 6,48 (d, *J* = 2,3 Hz, **1H**, H9), 6,3 (d, *J* = 2,3 Hz, **1H**, H7), 7,00 (d, *J* = 1,6 Hz, **1H**, H6), 7,96 (br. s, **1H**, NH), 11,49 (br. s, **1H**, C11-OH), 14,19 (s, **1H**, C3-OH);

^{13}C-NMR (101 MHz; CD_3CN): δ [ppm] = 24,7 (**1C**, CH_3), 26,9 (**1C**, C5), 45,5 (**1C**, C4a), 56,3 (**1C**, C8-OCH_3), 56,7 (**1C**, C10-OCH_3), 71,2 (**1C**, C4), 77,9 (**1C**, C12a), 98,9 (**1C**, C9), 100,4 (**1C**, C7), 104,8 (**1C**, C2), 109,7 (**1C**, C11a), 110,8 (**1C**, C11a), 118,3 (**1C**, C6), 136,8 (**1C**, C5a), 143,6 (**1C**, C6a), 162,2 (**1C**, C10), 163,8 (**1C**, C8),), 167,9 (**1C**, C11), 177,5 (**1C**, C=N), 198,6 (**1C**, C1), 203,1 (**1C**, C12).

Me-ether-cleavage (synthesis of **56**): The previously prepared enamine **55** (45,0 mg, 105 µmol, 1,0 equiv.) was charged into a flame-dried 5-ml one-neck round-bottom flask to which 1,3 ml (0,13 mmol, 12,0 equiv.) BBr_3-solution (1M in CH_2Cl_2) were added at room temperature and the deep-red-colored solution stirred under an inert atmosphere for 18 hours. Upon completion, the reaction was diluted with 1 ml of water and 2 ml EtOAc after which the pH was adjusted to 6 by the careful addition of saturated aqueous $NaHCO_3$-soution. Extraction with EtOAc (4x 20 ml), followed by drying of the organic phases over Na_2SO_4 and concentration under reduced pressure gave the crude tetracycline product. After purification *via* preparatory RP-HPLC (injection volume: 1,0 ml (MeCN), elution with H_2O/ MeCN-gradient, flow-rate; 15,00 ml/ min), the fractions eluting at 10-12 min (elution with 10% H_2O, 90% MeCN) were collected and concentrated to give **56** (19,5 mg, 48,8 µmol, **46%**) as a pale yellow powder.

R_f = 0,49 (EtOAc);

m.p. = decomp. >320 °C;

$[\alpha]_D^{24,8}$ = +300,0° ($CHCl_3$, *0,66*);

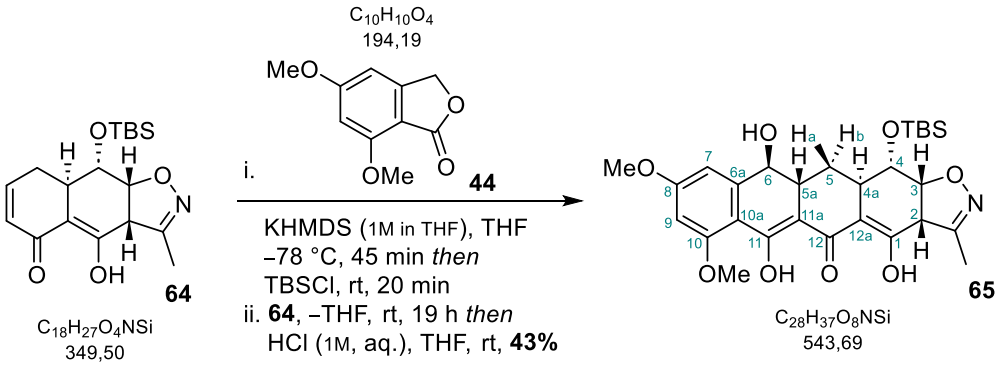
HR-ESI-MS: $[C_{20}H_{17}NO_8Na]^+$: m/z = 422,0852, found m/z = 422,0845;

^{1}H-NMR (400 MHz; CD_3OD): δ [ppm] = 2,49–2,54 (m, **1H**, H4a), 2,57 (s, **3H**, CH_3), 3,23 (m, **1H**, Ha5), 3,47 (dd, *J* = 16,7, 4,4 Hz, **1H**, Hb5), 3,98 (d, *J* = 11,7 Hz, **1H**, H4), 6,32 (d, *J* = 2,1 Hz, **1H**, H9), 6,51 (d, *J* = 2,0 Hz, **1H**, H7), 6,88 (s, **1H**, H6);

^{13}C-NMR (151 MHz; CD_3OD): δ [ppm] = 24,3 (**1C**, CH_3), 27,0 (**1C**, C5), 46,2 (**1C**, C4a), 71,8 (**1C**, C4), 78,2 (**1C**, C12a), 102,5 (**1C**, C9), 103,3 (**1C**, C7), 105,5 (**1C**, C2), 108,1 (**1C**, C10a), 108,3 (**1C**, C11a), 118,6 (**1C**, C6), 135,9 (**1C**, C5a), 143,3 (**1C**, C6a), 161,2 (**1C**, C10), 163,6 (**1C**, C8), 167,5 (**1C**, C11), 177,8 (**1C**, C=N), 193,7 (**1C**, C3), 197,1 (**1C**, C1), 198,5 (**1C**, C12).

6.2.4 Demethylpremithramycinone **1** from enone **64**

6.2.4.1 (3a*S*,5a*R*,11*S*,11a*R*,12a*R*,13*S*,13a*R*)-13-((*tert*-butyldimethylsilyl)oxy)-4,11-dihydroxy-7,9-dimethoxy-3-methyl-11,11a,12,12a,13,13a-hexahydrotetraceno[2,3-*d*]isoxazole-5,6(3a*H*,5a*H*)-dione **65**



0,55 g (2,85 mmol, 1,5 equiv.) **44** were dissolved in 10,0 ml dry THF in a flame-dried 25-ml one-neck round-bottom flask and the formed suspension cooled to –78 °C. The suspension was treated with 3,0 ml (3,05 mmol, 1,6 equiv.) KHMDS-solution (1M in THF) and the red solution stirred for 45 minutes under an inert atmosphere. TBSCl (0,47 g, 3,14 mmol, 1,65 equiv.) was then added and the reaction warmed to room temperature over a period of 20 minutes after which 0,67 g (1,90 mmol, 1,0 equiv.) **64**, dissolved in a small portion of dry THF were added and the reaction reduced under vacuum to 10% of its original volume[26]. The concentrated dark-green slurry was then stirred for additional 19 hours. Upon completion ($\mathbf{R_f}$ = 0,81 (PE/ EtOAc = 3:2 (v/v)), the reaction was diluted with 5 ml of THF and acidified by the addition of a few drops of aqueous HCl-solution (1M). The reaction was then diluted by the addition of water and the organic components extracted with EtOAc (3x40 ml). The combined organic phases were then dried over Na_2SO_4, the volatiles removed under reduced pressure and the crude product purified *via* preparatory RP-HPLC (injection volume: 1,0 ml (MeCN), elution with H_2O/ MeCN-gradient, flow-rate; 15,00 ml/ min). The fractions eluting at 33-35 min (elution with 20% H_2O, 80% MeCN) were collected and concentrated to give the aimed tetracycline precursor **65** (0,44 g, 0,81 mmol, **43%**) as a yellow solid.

$\mathbf{R_f}$ = 0,32 (PE/ EtOAc = 3:2 (v/v));

m.p. = 122 °C;

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{23,3}}$ = +96,32° ($CHCl_3$, *3,25*);

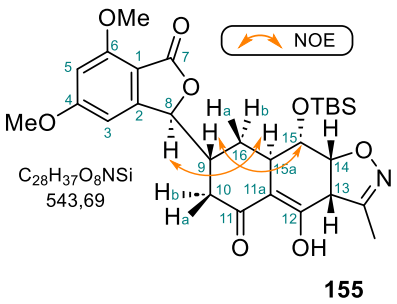
HR-ESI-MS: $[C_{28}H_{37}O_8NSiNa]^+$: m/z = 566,2186, found m/z = 566,2195;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,08 (s, **3H**, CH_3 (TBS)), 0,09 (s, **3H**, CH_3 (TBS)), 0,91 (s, **9H**, CH_3 (TBS)), 1,66 (ddd, *J* = 13,8, 9,6, 7,5 Hz, **1H**, Ha5), 2,07 (s, **3H**, CH_3), 2,29 (dd, *J* = 11,8, 7,0 Hz, **1H**, Hb5), 2,78 (dt, *J* = 7,3, 3,8, 3,8 Hz, **1H**, H4a, H5a), 2,98 (td, *J* = 9,8, 9,7, 5,1 Hz, **1H**, H4a), 3,65 (dd, *J* = 10,1, 3,0 Hz, **1H**, H4), 3,72 (s, **3H**, C10-OCH_3), 3,75 (m, **1H**, H2), 3,77 (s, **3H**, C8-OCH_3), 4,29 (br. s, **1H**, H6), 4,68 (dd, *J* = 9,6, 3,0 Hz, **1H**, H3), 6,27 (d, *J* = 2,3 Hz, **1H**, H9), 6,46 (d, *J* = 2,3 Hz, **1H**, H7), 13,86 (s, **1H**, C11-OH);

[26] In some instances, the formation of a 1,4-addition product could be observed due to insufficient concentration of the reaction. A full characterization of the compound (HPLC: elution under the mentioned conditions at 36-38 min) is given at the end of this subchapter.

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,6 (**1C**, CH_3 (TBS)), –4,3 (**1C**, CH_3 (TBS)), 12,8 (**1C**, CH_3), 18,2 (**1C**, $C_{quat.}$ (TBS)), 25,8 (**3C**, CH_3 (TBS)), 26,8 (**1C**, C5), 31,8 (**1C**, C4a), 35,0 (**1C**, C5a), 55,1 (**1C**, OCH_3), 55,6 (**1C**, C2), 56,0 (**1C**, OCH_3), 73,4 (**1C**, C6), 73,6 (**1C**, C4), 80,6 (**1C**, C3), 99,0 (**1C**, C9), 100,6 (**1C**, C11a), 105,8 (**1C**, C7), 105,9 (**1C**, C12a), 109,9 (**1C**, C10a), 146,0 (**1C**, C6a), 154,8 (**1C**, C=N), 161,4 (**1C**, C10), 163,4 (**1C**, C11), 164,0 (**1C**, C8), 172,2 (**1C**, C1), 189,3 (**1C**, C12).

*Analysis of the 1,4-addition product **155**:*



155

R$_f$ = 0,45 (PE/ EtOAc = 3:2 (v/v));

m.p. = 112 °C;

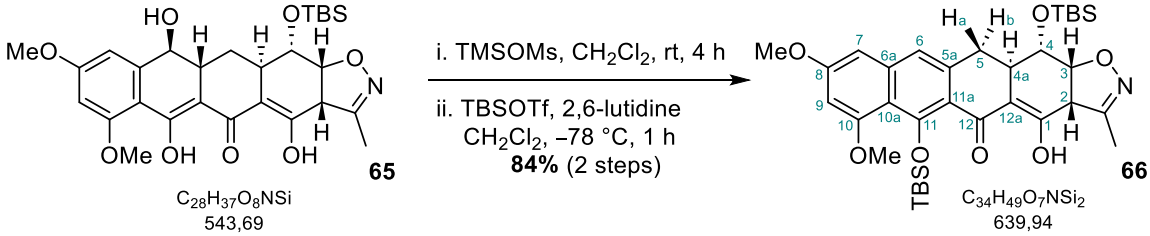
$[\alpha]_D^{22,9}$ = 120,37° ($CHCl_3$, *9,00*);

HR-ESI-MS: $[C_{28}H_{37}O_8NSiNa]^+$: m/z = 566,2186, found m/z = 566,2164;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,08 (s, **3H**, CH_3 (TBS)), 0,11 (s, **3H**, CH_3 (TBS)), 0,91 (s, **9H**, CH_3 (TBS)), 1,57 (ddd, *J* = 13,9, 10,2, 3,5 Hz, **1H**, Hb16), 1,98 (s, **3H**, CH_3), 2,19-2,23 (m, **1H**, H9), 2,32–2,35 (m, **1H**, Ha10), 2,36-2,40 (m, **1H**, Hb16), 2,51 (d, *J* = 19,2 Hz, **1H**, Hb10), 2,99 (td, *J* = 10,2, 10,1, 5,2 Hz, **1H**, H15a), 3,70 (dd, *J* = 10,4, 3,0 Hz, **1H**, H15), 3,84 (s, **3H**, C4-OCH_3), 3,86–3,89 (m, **1H**, H13), 3,90 (s, **3H**, C6-OCH_3), 4,79 (dd, *J* = 10,4, 3,1 Hz, **1H**, H14), 5,16 (d, *J* = 6,9 Hz, **1H**, H8), 6,40 (d, *J* = 1,8 Hz, **1H**, H5), 6,50 (d, *J* = 1,8 Hz, **1H**, H3);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,6 (**1C**, CH_3 (TBS)), –4,4 (**1C**, CH_3 (TBS)), 12,1 (**1C**, CH_3), 18,2 (**1C**, $C_{quat.}$ (TBS)), 25,8 (**3C**, CH_3 (TBS)), 27,5 (**1C**, C16), 30,5 (**1C**, C15a), 33,0 (**1C**, C10), 36,2 (**1C**, C9), 56,0 (**1C**, OCH_3), 56,0 (**1C**, OCH_3), 59,6 (**1C**, C13), 73,7 (**1C**, C15), 80,6 (**1C**, C8), 80,7 (**1C**, C14), 98,6 (**1C**, C5), 99,5 (**1C**, C3), 106,7 (**1C**, C2), 107,0 (**1C**, C11a), 152,6 (**1C**, C1), 153,1 (**1C**, C=N), 159,9 (**1C**, C6), 166,8 (**1C**, C4), 167,6 (**1C**, C7), 185,6 (**1C**, C12), 186,6 (**1C**, C11).

6.2.4.2 (3a*S*,12a*R*,13*S*,13a*R*)-6,13-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-7,9-dimethoxy-3-methyl-12,12a,13,13a-tetrahydrotetraceno[2,3-*d*]isoxazol-5(3a*H*)-one **66**



$C_{28}H_{37}O_8NSi$
543,69

$C_{34}H_{49}O_7NSi_2$
639,94

Tetracycline precursor **65** (0,21 g, 0,39 mmol, 1,0 equiv.) was dissolved at room temperature in 3,2 ml dry CH_2Cl_2 in a flame-dried 10-ml one-neck round-bottom flask and the formed solution treated with TMSOMs (0,4 ml, 2,43 mmol, 3,0 equiv.). The so formed red-colored solution was then stirred for four hours at room temperature under an inert atmosphere. Upon completion, the mixture was neutralized by the addition of a small portion of saturated, aqueous $NaHCO_3$-solution and diluted with water and EtOAc. Extraction with EtOAc (6x150 ml), followed by drying of the combined phases over Na_2SO_4 and removal of the volatiles under reduced pressure afforded a crude, highly polar (**R_f** = 0,15 (PE/ EtOAc = 3:2 (v/v))), aromatized pentacyclic product (136 mg) as an off-red solid, which was further converted without any prior purification.[27]

The previously prepared pentacyclic intermediate (136 mg, 0,33 mmol, 1,0 equiv.) was dissolved in 0,8 ml dry CH_2Cl_2 in a flame-dried 5-ml one-neck round-bottom flask and the solution cooled to –78 °C. 2,6-lutidine (0,2 ml, 1,66 mmol, 5,0 equiv.) was then added, followed by 0,2 ml (0,08 mmol, 2,5 equiv.) TBSOTf and the reaction was allowed to stir for two hours under an inert atmosphere at –78 °C. Upon completion, the cooling bath was removed, the reaction allowed to warm to room temperature and finally diluted with 3 ml of water and 2 ml MTBE. The aqueous phase was the extracted with MTBE (3x10 ml), the organic phases dried over Na_2SO_4 and concentrated under reduced pressure to afford a yellow oil. Purification *via* flash column chromatography (SiO_2, 2 vol-% MeOH in CH_2Cl_2) finally gave the aimed tetracycline precursor **66** (0,21 g, 0,33 mmol, **84%** (2 steps)) as a thick, off-yellow oil.

R_f = 0,63 (PE/ EtOAc = 9:1 (v/v));

$[\alpha]_D^{26,9}$ = +257,71° ($CHCl_3$, *6,70*);

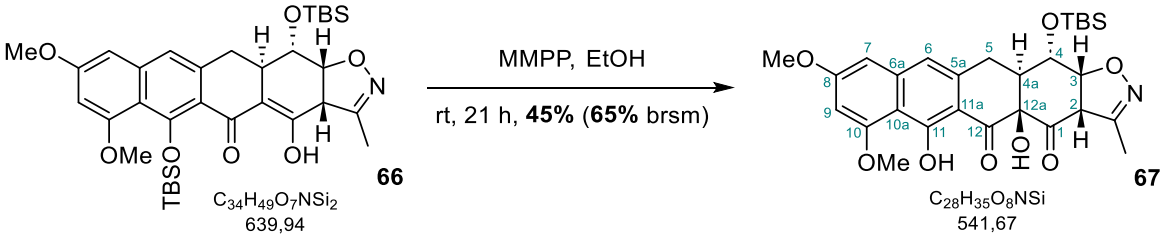
HR-ESI-MS: $[C_{34}H_{49}NO_7Si_2Na]^+$: m/z = 662,1954, found m/z = 662,1965;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,11 (s, **3H**, CH_3 (C4-OTBS)), 0,18 (s, **3H**, CH_3 (C4-OTBS)), 0,18 (s, **3H**, CH_3 (C11-OTBS)), 0,20 (s, **3H**, CH_3 (C11-OTBS)), 0,99 (s, **9H**, CH_3 (C11-OTBS)), 1,07 (s, **9H**, CH_3 (C4-OTBS)), 2,06 (s, **3H**, CH_3), 2,47 (t, *J* = 15,1, 15,1 Hz, **1H**, Ha5), 3,08–3,11 (m, **1H**, H4a), 3,14–3,15 (m, **1H**, Hb5), 3,85 (s, **3H**, C8-OCH_3), 3,87 (d, *J* = 5,1 Hz, **1H**, H2), 3,89 (s, **3H**, C10-OCH_3), 3,92 (dd, *J* = 9,4, 2,9 Hz, **1H**, H4), 4,85 (dd, *J* = 9,9, 2,9 Hz, **1H**, H3), 6,38 (d, *J* = 2,2 Hz, **1H**, H9), 6,58 (d, *J* = 2,3 Hz, **1H**, H7), 7,07 (d, *J* = 1,4 Hz, **1H**, H6);

[27] Analysis by means of **HR-ESI-MS** ($[C_{22}H_{21}NO_7Na]^+$: m/z = 662,1954, found m/z = 434,1214) determined that the obtained product was lacking the silyl-protection group, possibly due to an acidification of the reaction mixture through HOMs.

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –5,2 (**1C**, CH_3 (C4-OTBS)), –4,6 (**1C**, CH_3 (C4-OTBS)), –4,4 (**1C**, CH_3 (C11-OTBS)), –4,0 (**1C**, CH_3 (C11-OTBS)), 12,5 (**1C**, CH_3), 18,4 (**2C**, $C_{quat.}$ (TBS)), 26,0 (**3C**, CH_3 (C4-OTBS)), 26,2 (**3C**, CH_3 (C11-OTBS)), 33,7 (**1C**, C5), 34,2 (**1C**, C4a), 55,2 (**1C**, C10-OCH_3), 55,5 (**1C**, C8-OCH_3), 58,2 (**1C**, C2), 73,8 (**1C**, C4), 82,1 (**1C**, C3), 98,2 (**2C**, C7, C9), 107,5 (**1C**, C12a), 116,0 (**1C**, C10a), 117,7 (**1C**, C11a), 119,2 (**1C**, C6), 138,0 (**1C**, C5a), 140,4 (**1C**, C6a), 154,7 (**1C**, C=N), 155,7 (**1C**, C11), 159,8 (**1C**, C10), 160,7 (**1C**, C8), 179,1 (**1C**, C1), 184,2 (**1C**, C12).

6.2.4.3 (3a*S*,4a*S*,12a*S*,13*S*,13a*R*)-13-((*tert*-butyldimethylsilyl)oxy)-4a,6-dihydroxy-7,9-dimethoxy -3-methyl-12,12a,13,13a-tetrahydrotetraceno[2,3-*d*]isoxazole-4,5(3a*H*,4a*H*)-dione **67**



The previously prepared pentacyclic precursor **66** (49,6 mg, 77,5 µmol, 1,0 equiv.) was dissolved in 0,8 ml dry EtOH at room temperature in a flame-dried 5-ml one-neck round-bottom flask. 26,4 mg (80 wt%, 42,6 µmol, 0,55 equiv.) MMPP·$6H_2O$ were then added and the formed red-colored solution stirred for 21 hours under an inert atmosphere. Upon completion, the reaction was diluted with 4 ml of water, the organic components extracted with EtOAc (4x10 ml) and the combined organic phases dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified *via* preparatory RP-HPLC (injection volume: 1,0 ml (MeCN), elution with H_2O/ MeCN-gradient, flow-rate; 15,00 ml/ min). The fractions eluting at 47-48 min (elution with 20% H_2O, 80% MeCN) were collected and concentrated to give the aimed ketol **67** (19,1 mg, 35,3 µmol, **45**% (**65%** brsm)), while the fractions eluting at 45-46 min gave 15,0 mg (28,5 µmol) starting material **66**, both as highly viscous, yellow-colored oils.

R_f = 0,23 (PE/ EtOAc = 3:2 (v/v));

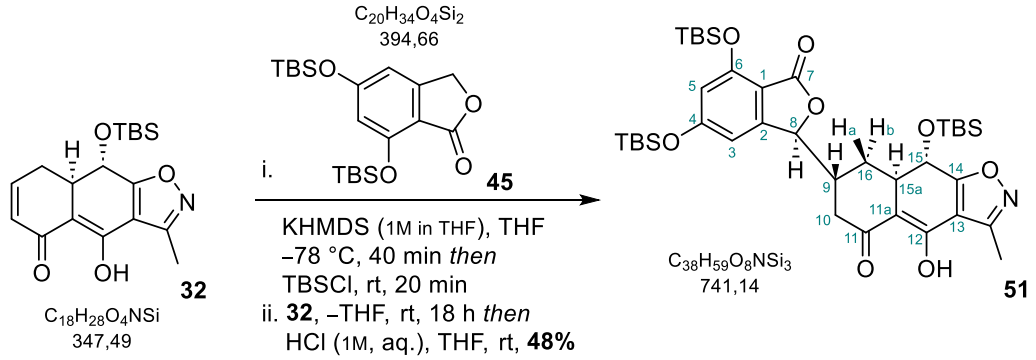
$[\alpha]_D^{21,9}$ = +342,33° ($CHCl_3$, *10,0*);

HR-ESI-MS: $[C_{28}H_{35}NO_8SiNa]^+$: m/z = 564,2108, found m/z = 564,2048;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,19 (s, **3H**, CH_3 (TBS)), 0,20 (s, **3H**, CH_3 (TBS)), 0,99 (s, **9H**, CH_3 (C4-OTBS)), 2,02 (d, *J* = 1,1 Hz, **3H**, CH_3), 2,95–3,04 (m, **1H**, H5), 3,04–3,16 (m, **2H**, H4a, H5), 3,57 (br. s, **1H**, C12a-OH), 3,91 (s, **3H**, C8-OCH_3), 3,97 (s, **3H**, C10-OCH_3), 4,20–4,26 (m, **2H**, H2, H4), 4,91 (dd, *J* = 10,5, 3,4 Hz, **1H**, H3), 6,43 (d, *J* = 2,2 Hz, **1H**, H7), 6,57 (d, *J* = 2,2 Hz, **1H**, H9), 6,93 (s, **1H**, H6), 13,69 (s, **1H**, C11-OH);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,3 (**1C**, CH_3 (TBS)), –4,0 (**1C**, CH_3 (TBS)), 13,2 (**1C**, CH_3), 18,4 (**1C**, $C_{quat.}$ (TBS)), 26,0 (**3C**, CH_3 (TBS)), 33,4 (**1C**, C5), 37,3 (**1C**, C4a), 55,4 (**1C**, C2), 55,6 (**1C**, C8-OCH_3), 56,4 (**1C**, C10-OCH_3), 73,7 (**1C**, C4), 77,4 (**1C**, C12a), 81,4 (**1C**, C3), 98,3 (**1C**, C7), 99,4 (**1C**, C7, C9), 106,1 (**1C**, C10a), 109,5 (**1C**, C11a), 116,6 (**1C**, C6), 137,0 (**1C**, C5a), 142,2 (**1C**, C6a), 155,3 (**1C**, C=N), 161,2 (**1C**, C11), 162,3 (**1C**, C10), 165,1 (**1C**, C8), 168,1 (**1C**, C1), 192,3 (**1C**, C12).

6.2.5 Demethylpremithramycinone **1** from lactone **45** and enone **32** (formation of the 1,4-addition product: (7*R*,8a*R*,9*S*)-7-((*S*)-4,6-bis((*tert*-butyldimethylsilyl)oxy)-3-oxo-1,3-dihydroisobenzofuran-1-yl)-9-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-3-methyl-7,8,8a,9-tetrahydronaphtho[2,3-*d*]isoxazol-5(6*H*)-one **51**)



0,15 g (0,37 mmol, 2,0 equiv.) **45** were dissolved in 0,7 ml dry THF in a flame-dried 5-ml one-neck round-bottom flask and the formed solution cooled to –78 °C. KHMDS-solution (1M in THF, 0,5 ml, 0,45 mmol, 2,4 equiv.) was then added and the formed red-colored solution stirred for 40 minutes under an inert atmosphere. TBSCl (0,07 g, 0,47 mmol, 2,5 equiv.) was then added and the reaction warmed to room temperature over a period of 20 minutes after which 0,06 g (0,19 mmol, 1,0 equiv.) **32** were added and the solvent-amount reduced under vacuum to 10% of its original volume. The concentrated, dark-yellow slurry was then stirred for additional 18 hours. Upon completion, the reaction was acidified with a few drops of THF, diluted with 10 ml of water and the organic components extracted with MTBE (3x15 ml). The combined organic phases were dried over Na_2SO_4, the volatiles removed under reduced pressure and the residue purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1 (v/v)) to exclusively give the undesired 1,4-addition product **51** (61,2 mg, 82,5 µmol, **48%**) as tick, off-yellow oil.

R_f = 0,73 (PE/ EtOAc = 9:1 (v/v));

HR-ESI-MS: $[C_{38}H_{59}O_8NSi_3Na]^+$: m/z = 764,3446, found m/z = 764,3451;

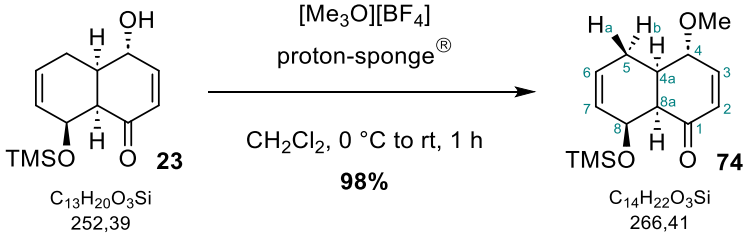
^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,20 (s, **3H**, CH_3 (TBS)), 0,24 (s, **6H**, CH_3 (TBS)), 0,25 (s, **3H**, CH_3 (TBS)), 0,26 (s, **3H**, CH_3 (TBS)), 0,28 (s, **3H**, CH_3 (TBS)), 0,98 (s, **9H**, CH_3 (TBS)), 0,99 (s, **9H**, CH_3 (TBS)), 1,03 (s, **9H**, CH_3 (TBS)), 1,96 (ddd, *J* = 14,0, 7,3, 3,7 Hz, **1H**, Hb16), 2,16–2,23 (m, **2H**, H10), 2,23–2,28 (m, **1H**, Ha16), 2,35–2,40 (m, **1H**, H9), 2,48 (s, **3H**, CH_3), 3,21 (dt, *J* = 12,5, 6,6, 6,6 Hz, **1H**, H15a), 4,73 (d, *J* = 11,2 Hz, **1H**, H15), 5,21 (d, *J* = 4,0 Hz, **1H**, H8), 6,32 (d, *J* = 1,8 Hz, **1H**, H5), 6,43 (dd, *J* = 1,8, 0,9 Hz, **1H**, H3);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,7 (**1C**, CH_3 (TBS)), –4,5 (**1C**, CH_3 (TBS)), –4,4 (**1C**, CH_3 (TBS)), –4,3 (**1C**, CH_3 (TBS)), –4,2 (**1C**, CH_3 (TBS)), –4,1 (**1C**, CH_3 (TBS)), 10,7 (**1C**, CH_3), 18,4 (**2C**, $C_{quat.}$ (TBS)), 18,5 (**1C**, $C_{quat.}$ (TBS)), 25,7 (**6C**, CH_3 (TBS)), 25,9 (**3C**, CH_3 (TBS)), 28,2 (**1C**, C16), 29,1 (**1C**, C10), 35,4 (**1C**, C9), 40,8 (**1C**, C15a), 70,6 (**1C**, C15), 81,1 (**1C**, C8), 105,2 (**1C**, C11a), 106,9 (**1C**, C3), 110,3 (**1C**, C2), 112,5 (**1C**, C5), 113,5 (**1C**, C13), 151,8 (**1C**, C=N), 156,5 (**1C**, C14), 157,8 (**1C**, C6), 162,9 (**1C**, C4), 167,3 (**1C**, C1), 175,6 (**1C**, C12), 179,3 (**1C**, C7), 185,9 (**1C**, C11).

6.3 Premithramycinone

6.3.1 Enones **73** and **79**

6.3.1.1 (4*R*,4a*R*,8*S*,8a*R*)-4-methoxy-8-((trimethylsilyl)oxy)-4a,5,8,8a-tetrahydronaphthalen-1(4*H*)-one **74**



For the synthesis of enone **74**, the previously prepared allylic alcohol **23** (3,11 g, 12,3 mmol, 1,0 equiv.)[28] was dissolved in a flame-dried 250-ml three-neck round-bottom flask in 123,0 ml dry CH_2Cl_2 and the solution cooled to 0 °C. Proton-sponge® (13,2 g, 61,6 mmol, 5,0 equiv.) was then added followed by Meerwein's salt (6,38 g, 18,2 mmol, 3,5 eq; freshly washed (*three times*) with dry CH_2Cl_2) and the so formed heterogenous mixture allowed to warm to room temperature. Stirring under an inert atmosphere was continued for one hour after which the mixture was diluted with aqueous $KHSO_4$ (80 ml, 2M). Extraction with MTBE (3x100 ml), followed by drying of the organic phases over Na_2SO_4 and removal of the volatiles under reduced pressure afforded the crude product as a thick oil. Purification *via* flash column chromatography (SiO_2, PE/ EtOAc = 4:1 (v/v)) gave title compound **74** (3,20 g, 12,0 mmol, **98%**) as a thick, colorless oil.

R_f = 0,85 (PE/ EtOAc = 1:1 (v/v));

$[\alpha]_D^{23,5}$ = +29,17° ($CHCl_3$, *4,00*);

HR-ESI-MS: $[C_{14}H_{22}O_3SiNa]^+$: m/z = 289,1236, found m/z = 289,1234;

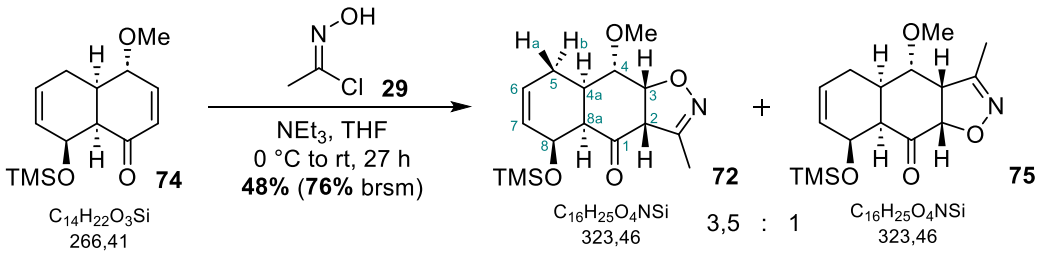
^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,01(s, **9H**, TMS), 2,11 (dd, *J* = 18,0, 6,8 Hz, **1H**, Hb5), 2,45 (dt, *J* = 11,1, 6,0, 6,0 Hz, **1H**, H4a), 2,52 (dd, *J* = 19,1, 2,9 Hz, **1H**, Ha5), 2,67 (t, *J* = 5,0, 5,0 Hz, **1H**, H8a), 3,46 (s, **3H**, OCH_3), 4,32–4,34 (m, **1H**, H8), 4,37 (t, *J* = 1,9, 1,9 Hz, **1H**, H4), 5,79–5,80 (m, **2H**, H6, H7), 6,01 (ddd, *J* = 10,3, 2,0, 0,9 Hz, **1H**, H2), 7,00 (dd, *J* = 10,3, 1,6 Hz, **1H**, H3);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 0,1 (**3C**, TMS), 24,8 (**1C**, C5), 37,2 (**1C**, C4a), 50,0 (**1C**, C8a), 57,0 (**1C**, OCH_3), 64,4 (**1C**, C8), 76,1 (**1C**, C4), 127,5 (**1C**, C7), 128,5 (**1C**, C6), 130,4 (**1C**, C2), 151,0 (**1C**, C3), 200,9 (**1C**, C1).

The synthesis was carried out by following a protocol described by Nakamura et al.[145]

[28] In order to ensure a high conversion, the starting material was divided into two portions, which were then reacted independently. The purifying step was carried out with the combined batches.

6.3.1.2 (3a*S*,4a*R*,5*S*,8a*R*,9*S*,9a*R*)-9-methoxy-3-methyl-5-((trimethylsilyl)oxy)-4a,5,8,8a,9,9a-hexahydronaphtho[2,3-*d*]isoxazol-4(3a*H*)-one **72**



Initially, a direct approach towards **72** starting from the isoxazoline-bearing decalin **30** was attempted. By subjecting **30** (in analogy to the TBS-protection described in chapter 6.2.1.6) to conditions similar to those described in chapter 6.3.1.1, pure methylated product **72** could be isolated, however only with a very poor yield (**5%**). Therefore, the following route had to be implemented. The spectra of **72** obtained *via* direct methylation match those further reported in this chapter.

The previously prepared decalin **74** (1,61 g, 6,03 mmol, 1,0 equiv.) was charged into a flame-dried 100-ml one-neck round-bottom flask and 30,0 ml dry THF added. Dry NEt_3 (3,1 ml, 21,7 mmol, 3,6 equiv.) was then added and the solution cooled to 0 °C. The required amount of oxime **29** (1,97 g, 21,1 mmol, 3,5 equiv.) was freshly prepared in accordance with 6.2.1.5.1 and added as an ethereal solution to the cooled mixture *via* cannula. The reaction was then warmed up to room temperature and stirred under an inert atmosphere for 27 hours. Upon completion, the reaction was diluted with 50 ml of water and transferred to a separatory funnel. After extraction with MTBE (3x80 ml) the collected organic phases were dried over Na_2SO_4, concentrated *in vacuo* and the residue purified *via* flash column chromatography (SiO_2, CH_2Cl_2[29]; *then* PE/ EtOAc = 9:1→4:1 (v/v)) to yield **74** (0,60 g, 2,24 mmol), title compound **72** (white microcrystalline powder; 0,47 g, 1,45 mmol) and a mixed fraction (0,46 g, 1,45 mmol) consisting of both **72**, as well as the regioisomer **75** in a 2:1 ratio (determination *via* ^{1}H-NMR). After a complete characterization of the separated product-fractions was performed, these were combined and the final yield for **72** determined (0,93 g, 2,89 mmol, **48%** (**76%** brsm), ~78% purity). The mixture was further reacted without any other separation-attempt.

R_f = 0,53 (PE/ EtOAc = 3:2 (v/v));

m.p. = 122 °C;

$[\alpha]_D^{28,1}$ = +284,12° ($CHCl_3$, *6,85*);

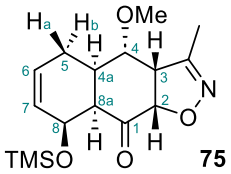
HR-ESI-MS: $[C_{16}H_{25}O_4NSiNa]^+$: m/z = 346,1451, found m/z = 346,1448;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,10 (s, **9H**, TMS), 1,96–2,02 (m, **1H**, Hb5), 2,17 (d, *J* = 0,8 Hz, **3H**, CH_3), 2,62–2,65 (m, **1H**, Ha5), 2,65–2,70 (m, **2H**, H4a, H8a), 3,50 (s, **3H**, OCH_3), 3,54 (d, *J* = 9,6 Hz, **1H**, H2), 4,36 (m, **1H**, H8), 4,42 (dd, *J* = 11,3, 3,7 Hz, **1H**, H4), 4,97 (dd, *J* = 9,6, 3,7 Hz, **1H**, H3), 5,75–5,80 (m, **1H**, H7), 5,83–5,88 (m, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 0,3 (**3C**, TMS), 13,7 (**1C**, CH_3), 23,5 (**1C**, C5), 29,5 (**1C**, C4a), 52,6 (**1C**, C8a), 57,8 (**1C**, OCH_3), 62,8 (**1C**, C2), 65,2 (**1C**, C8), 74,2 (**1C**, C4), 77,7 (**1C**, C3), 127,1 (**1C**, C7), 128,2 (**1C**, C6), 155,0 (**1C**, C=N), 205,7 (**1C**, C1).

[29] For the elution of the UV-active dimeric 3,4-dimethyl-1,2,5-oxadiazole 2-oxide (*chapter 6.2.1.5.2*).

Partial analysis of regioisomer **75** ((3a*S*,4*S*,4a*R*,8*S*,8a*R*,9a*S*)-4-methoxy-3-methyl-8-((trimethylsilyl)oxy)-3a,4a, 5,8,8a,9a-hexahydronaphtho[2,3-*d*]isoxazol-9(4*H*)-one):



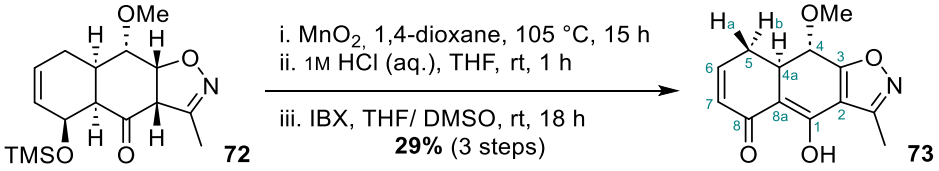
$C_{16}H_{25}O_4NSi$
323,46

R_f = 0,51 (PE/ EtOAc = 3:2 (v/v));

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,10 (s, **9H**, TMS), 1,96–2,03 (m, **1H**, Hb5), 2,07 (d, *J* = 0,8 Hz, **3H**, CH_3), 2,12–2,715 (m, **1H**, H4a), 2,55–2,59 (m, **1H**, Ha5), 2,78 (t, *J* = 5,4, 5,4 Hz, **1H**, H8a), 3,45 (s, **3H**, OCH_3), 3,95–3,99 (m, **1H**, H3), 4,31 (t, *J* = 4,2, 4,2 Hz, **1H**, H8), 4,39 (d, *J* = 5,8 Hz, **1H**, H4), 4,68 (d, *J* = 10,3 Hz, **1H**, H2), 5,75–5,79 (m, **1H**, H7), 5,82–5,87 (m, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 0,3 (**3C**, TMS), 14,0 (**1C**, CH_3), 23,8 (**1C**, C5), 33,9 (**1C**, C4a), 51,4 (**1C**, C3), 52,2 (**1C**, C8a), 58,3 (**1C**, OCH_3), 64,0 (**1C**, C8), 74,2 (**1C**, C4), 82,9 (**1C**, C2), 127,6 (**1C**, C7), 127,6 (**1C**, C6), 157,7 (**1C**, C=N), 207,7 (**1C**, C1).

6.3.1.3.1 (8a*R*,9*S*)-4-hydroxy-9-methoxy-3-methyl-8a,9-dihydronaphtho[2,3-*d*]isoxazol-5(8*H*)-one **73**



$C_{16}H_{25}O_4NSi$
323,46
(as a mixture)

$C_{13}H_{13}O_4N$
247,25

aromatization (synthesis of (4a*R*,5*S*,8a*R*,9*S*)-9-methoxy-3-methyl-5-((trimethylsilyl)oxy)-5,8,8a,9-tetrahydronaphtho[2,3-*d*]isoxazol-4(4a*H*)-one): 0,62 g (1,92 mmol, 1,0 equiv.) **72**, dissolved in 7,7 ml 1,4-dioxane were charged under ambient conditions in a sealed tube and 3,70 g (38,3 mmol, 20,0 equiv.) MnO_2 (80 wt%; technical grade) added. The tube was then sealed and the reaction allowed to stir at 105 °C for 15 hours. Upon completion, the black slurry was diluted with MTBE, filtered over a pad of Celite® and concentrated under reduced pressure to give 0,21 g (0,64 mmol) of the aimed crude isoxazole-bearing decalin (**R_f** = 0,87 (PE/ EtOAc = 3:2 (v/v)) as a pale yellow oil.

TMS-cleavage (synthesis of (4a*R*,5*S*,8a*R*,9*S*)-5-hydroxy-9-methoxy-3-methyl-5,8,8a,9-tetrahydronaphtho[2,3-*d*]isoxazol-4(4a*H*)-one): The previously prepared isoxazole-intermediate (0,21 g, 0,64 mmol, 1,0 equiv.), dissolved at room temperature in 25,5 ml THF was reacted with 5,1 ml (8,0 equiv.) aqueous HCl-solution (1M) for one hour in a 50-ml one-neck round-bottom flask under ambient conditions. The reaction was then neutralized by the addition of 12 ml saturated aqueous $NaHCO_3$-soution followed by the addition of 30 ml of MTBE. The aqueous phase was then extracted with MTBE (3x30 ml), the resulting ethereal organic phases dried over Na_2SO_4 and concentrated under reduced pressure to yield 0,16 g (0,64 mmol) of the aimed crude allylic alcohol (**R_f** = 0,19 (PE/ EtOAc = 1:1 (v/v)) as a pale yellow oil.

IBX-oxidation (synthesis of **73**): In a flame-dried 25-ml one-neck round-bottom flask, 0,16 g (0,64 mmol, 1,0 equiv.) of the previously prepared crude allylic alcohol were dissolved under an inert atmosphere in 6,4 ml dry THF and 0,7 ml dry DMSO. To the formed solution were then added 0,54 g (1,93 mmol, 3,0 equiv.) IBX and the heterogenous mixture allowed to stir for 18 hours at room temperature. Upon completion, the orange-colored slurry was diluted with a small amount of MTBE and filtered over a pad of Celite®. Removal of the volatiles under reduced pressure yielded a thick, orange-colored oil, which was purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1 (v/v)). Vinylogues acid **73** (0,11 g, 0,43 mmol, **29%** (3 steps))[30] was finally collected as golden-shimmery, orange-colored, crystalline flakes.

R_f = 0,73 (PE/ EtOAc = 1:1 (v/v));

m.p. = decomp. >89 °C;

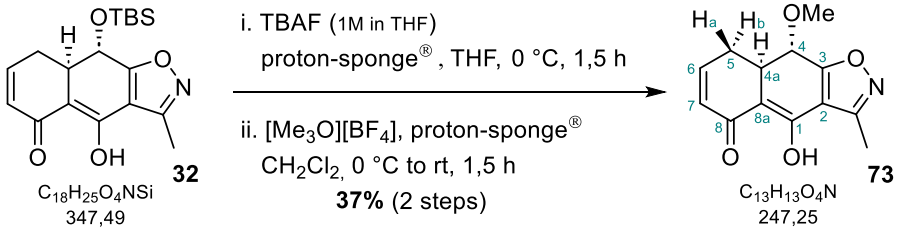
$[\alpha]_D^{29,1}$ = -59,00° ($CHCl_3$, *1,00*);

HR-ESI-MS: $[C_{13}H_{13}O_4NNa]^+$: m/z = 270,0742, found m/z = 270,0754;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,12–2,21 (m, **1H**, Ha5), 2,47 (s, **3H**, CH_3), 2,87 (dt, *J* = 17,6, 6,8, 6,8 Hz, **1H**, Hb5), 3,00 (dddd, *J* = 15,8, 11,1, 7,1, 0,8 Hz,**1H**, H4a), 3,75 (s, **3H**, OCH_3), 4,32 (d, *J* = 11,1 Hz, **1H**, H4), 6,09 (ddd, *J* = 9,9, 3,2, 0,6 Hz, **1H**, H7), 6,60 (dddd, *J* = 9,7, 6,3, 2,4, 0,8 Hz, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 10,6 (**1C**, CH_3), 29,6 (**1C**, C5), 37,2 (**1C**, C4a), 60,2 (**1C**, OCH_3), 79,3 (**1C**, C4), 102,5 (**1C**, C8a), 113,8 (**1C**, C2), 125,4 (**1C**, C7), 141,6 (**1C**, C6), 157,3 (**1C**, C=N), 173,4 (**1C**, C3), 176,9 (**1C**, C1), 182,2 (**1C**, C8).

6.3.1.3.2 (8a*R*,9*S*)-4-hydroxy-9-methoxy-3-methyl-8a,9-dihydronaphtho[2,3-*d*]isoxazol-5(8*H*)-one **73** from decalin precursor **32**



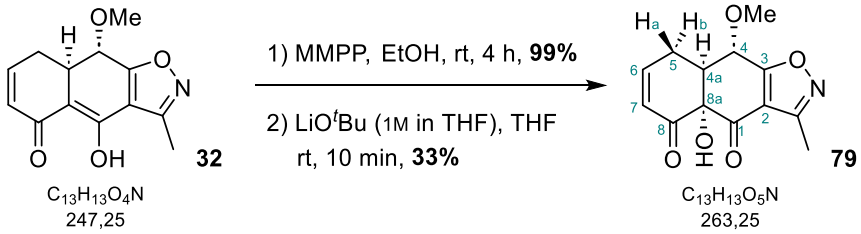
TBS-cleavage (synthesis of (8a*R*,9*S*)-4,9-dihydroxy-3-methyl-8a,9-dihydronaphtho[2,3-*d*]isoxazol-5(8*H*)-one): At first, the previously prepared enone **32** (0,31 g, 0,89 mmol, 1,0 equiv.) was dissolved in a flame-dried 10-ml one-neck round-bottom flask in 2,2 ml dry CH_2Cl_2 and the solution cooled to 0 °C. Proton-sponge® (0,46 g, 2,13 mmol, 2,4 equiv.)[31] was then added, followed by the drop-wise addition of 1,1 ml (1,07 mmol, 1,2 eq) TBAF-solution (1M in THF). The so formed blue-colored solution was then stirred at 0 °C for 1,5 hours after which it was diluted with aqueous $KHSO_4$ (3 ml, 1M). Extraction with MTBE (3x20 ml), followed by drying of the organic phases over Na_2SO_4 and removal of the volatiles under reduced pressure afforded the crude product (0,20 g, 0,86 mmol) as a pale yellow oil (**R_f** = 0,28 (PE/ EtOAc = 3:2 (v/v)).

[30] Yield based on pure educt **27**.

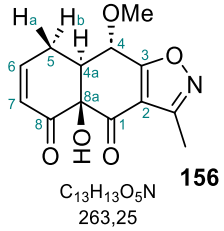
[31] The addition of 1,8-bis((*N*)-dimethylamino)naphthalene has proven to be mandatory for a successful outcome of the reaction; otherwise, an elimination-*retro*–Diels–Alder path leads to the complete decomposition of the starting material. The fragmentation product was found to be 3-methylbenzo[*d*]isoxazol-4-ol (**R_f** = 0,86 (PE/ EtOAc = 3:2 (v/v)).

methylation (synthesis of **73**) The previously prepared allylic alcohol (0,20 g, 0,86 mmol, 1,0 equiv.) was dissolved in a flame-dried 10-ml three-neck round-bottom flask in 2,1 ml dry CH_2Cl_2 and the solution cooled to 0 °C. Proton-sponge® (1,29 g, 6,00 mmol, 7,0 equiv.) was then added followed by Meerwein's salt (0,63 g, 4,29 mmol, 5,0 eq; washed (three times) with dry CH_2Cl_2) and the so formed heterogenous mixture allowed to warm to room temperature. Stirring under an inert atmosphere was continued for 1,5 hours after which the mixture was diluted with aqueous $KHSO_4$ (7 ml, 1M). Extraction with MTBE (3x15 ml), followed by drying of the organic phases over Na_2SO_4 and removal of the volatiles under reduced pressure afforded the crude product, which after purification *via* flash column chromatography (SiO_2, PE/ EtOAc = 3:1 (v/v)) gave pure **73** (67,9 mg, 0,28 mmol, **31%**; **37%** brsm (2 steps)) as orange-colored, crystalline flakes. The measured spectra matched those reported previously (*chapter 6.3.1.3.1*).

6.3.1.4.1 (4a*S*,8a*S*,9*S*)-4a-hydroxy-9-methoxy-3-methyl-8a,9-dihydronaphtho[2,3-*d*]isoxazole-4,5(4a*H*,8*H*)-dione **79**



α-hydroxylation (synthesis of (4a*S*,8a*S*,9*S*)-4a-hydroxy-9-methoxy-3-methyl-8a,9-dihydronaphtho[2,3-*d*] isoxazole-4,5(4a*H*,8*H*)-dione **156**): A 5-ml one-neck round-bottom flask was charged at room temperature with 254 mg (103 µmol, 1,0 equiv.) **32** and 0,3 ml dry EtOH. 318 mg (80 wt%, 51,4 µmol, 0,5 equiv.) MMPP·$6H_2O$ were then added and the red-colored solution stirred for four hours. Upon completion the reaction was diluted with 3 ml of water, the organic components extracted with MTBE (3x10 ml) and the combined organic phases dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by flash column chromatography (SiO_2, PE/ EtOAc = 2:1 (v/v)) to yield the aimed ketol **156** (267 mg, 101 µmol, **99%**) as an orange-red-colored solid.



R_f = 0,35 (PE/ EtOAc = 3:2 (v/v));

m.p. = 138 °C;

$[\alpha]_D^{25,2}$ = –78,00° ($CHCl_3$, *5,00*);

HR-ESI-MS: $[C_{13}H_{13}O_5NNa]^+$: m/z = 286,0691, found m/z = 286,0679;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,46 (s, **3H**, CH_3), 2,65–2,70 (m, **1H**, H4a), 2,70–2,76 (m, **1H**, H5), 2,81–2,89 (m, **1H**, H5), 3,81 (s, **3H**, OCH_3), 4,06 (br. s, **1H**, C8a-OH), 4,74 (d, *J* = 9,2 Hz, **1H**, H4), 6,14 (dd, *J* = 10,0, 1,8 Hz, **1H**, H7), 7,06–7,11 (m, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 10,6 (**1C**, CH_3), 24,6 (**1C**, C5), 47,2 (**1C**, C4a), 60,6 (**1C**, OCH_3), 73,8 (**1C**, C4), 75,1 (**1C**, C8a), 113,3 (**1C**, C2), 128,8 (**1C**, C7), 148,9 (**1C**, C6), 158,2 (**1C**, C=N), 176,8 (**1C**, C3), 188,1 (**1C**, C1), 193,9 (**1C**, C8).

α-ketol rearrangement (synthesis of **79**): The previously prepared ketol **156** (45,6 mg, 173 µmol, 1,0 equiv.) was dissolved at room temperature in 1,7 ml dry THF in a flame-dried 10-ml one-neck round-bottom flask and a LiO^{t}Bu-solution (1M in THF, 41,0 µl, 34,6 µmol, 20 mol-%) added. After stirring under an inert atmosphere for ten minutes the mixture was diluted with 5 ml of water, extracted with MTBE (3x10 ml) and the combined organic phases dried over Na_2SO_4. Solvent removal, followed by flash column chromatography (SiO_2, PE/ EtOAc = 2:1 (v/v)) afforded the rearranged ketol **79** (15,2 mg, 57,7 µmol, **33%**) as an off-orange-colored powder.

R_f = 0,64 (PE/ EtOAc = 1:1 (v/v));

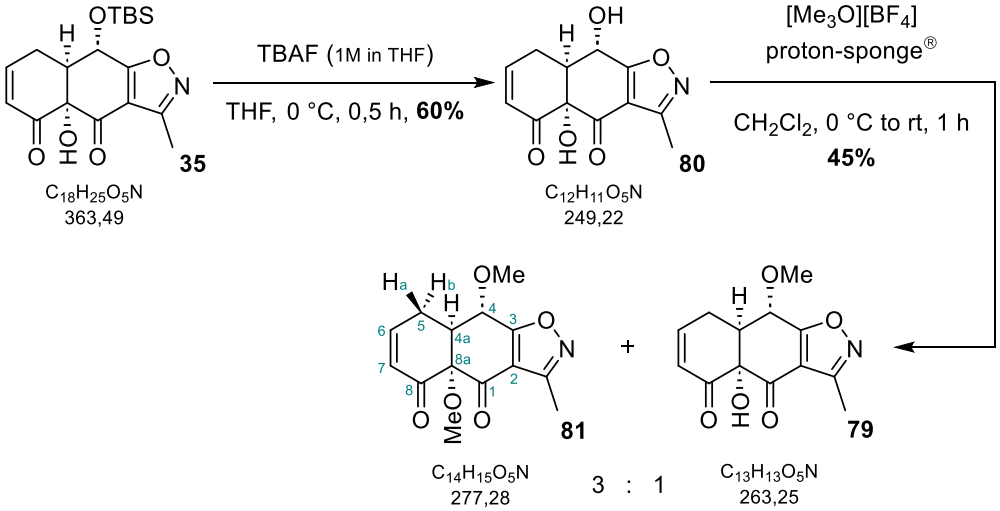
m.p. = 126 °C;

HR-ESI-MS: $[C_{13}H_{13}O_5NNa]^+$: m/z = 286,0691, found m/z = 286,0684;

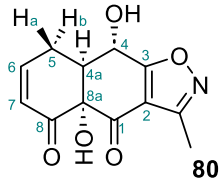
^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,52 (s, **3H**, CH_3), 2,59–2,64 (m, **1H**, Hb5), 2,88–2,91 (m, **1H**, Ha5), 2,95–2,98 (m, **1H**, H4a), 3,73 (s, **3H**, OCH_3), 4,49 (d, *J* = 7,5 Hz, **1H**, H4), 4,54 (br. s, **1H**, C8a-OH), 6,19 (d, *J* = 10,3 Hz, **1H**, H7), 6,99–7,04 (m, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 10,7 (**1C**, CH_3), 25,6 (**1C**, C5), 47,8 (**1C**, C4a), 60,3 (**1C**, OCH_3), 73,0 (**1C**, C4), 79,3 (**1C**, C8a), 114,0 (**1C**, C2), 128,3 (**1C**, C7), 149,1 (**1C**, C6), 157,6 (**1C**, C=N), 178,4 (**1C**, C3), 189,1 (**1C**, C1), 192,9 (**1C**, C8).

6.3.1.4.2 (4a*S*,8a*S*,9*S*)-4a-hydroxy-9-methoxy-3-methyl-8a,9-dihydronaphtho[2,3-*d*]isoxazole-4,5(4a*H*,8*H*)-dione **79** from a **35**-derived precursor **80**



TBS-cleavage (synthesis of (4a*S*,8a*S*,9*S*)-4a,9-dihydroxy-3-methyl-8a,9-dihydronaphtho[2,3-*d*]isoxazole-4,5(4a*H*,8*H*)-dione **80**): At first, the previously prepared ketol **35** (*chapter 6.2.1.8*; 95,3 mg, 262 µmol, 1,0 equiv.) was dissolved in a flame-dried 5-ml one-neck round-bottom flask in 1,3 ml dry THF and the solution cooled to 0 °C. TBAF-reagent (1M in THF; 0,3 ml, 262 µmol, 1,0 equiv.) was then added and the blue-colored solution stirred at 0 °C for 30 minutes after which it was diluted with saturated, aqueous $NaHCO_3$ (3 ml). Extraction with MTBE (3x10 ml), followed by drying of the combined organic phases over Na_2SO_4 and removal of the volatiles under reduced pressure afforded the crude product. Purification *via* flash column chromatography (SiO_2, PE/ EtOAc = 1:1 (v/v)) finally gave the desired product **80** (35,5 mg, 142 µmol, **60%**) as a pale yellow solid.



80

$C_{12}H_{11}O_5N$
249,22

m.p. = 134 °C (EtOAc);

$[\alpha]_D^{25,4}$ = –243,64° ($CHCl_3$, *8,25*);

HR-ESI-MS: $[C_{12}H_{11}NO_5Na]^+$: m/z = 272,0535, found m/z = 272,0550;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,30–2,34 (m, **1H**, Ha5), 2,51 (s, **3H**, CH_3), 2,80 (dt, *J* = 19,9, 4,9, 4,8 Hz, **1H**, Hb5), 3,05–3,09 (m, **1H**, H4a), 3,64 (br. s, **1H**, C4-OH), 4,80 (d, *J* = 10,1 Hz, **1H**, H4), 4,89 (br. s, **1H**, C8a-OH), 6,27 (ddd, *J* = 10,2, 2,8, 1,4 Hz, **1H**, H7), 6,98 (ddd, *J* = 10,1, 5,1, 2,9 Hz, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 10,8 (**1C**, CH_3), 29,8 (**1C**, C5), 48,0 (**1C**, C4a), 64,7 (**1C**, C4), 79,8 (**1C**, C8a), 113,2 (**1C**, C2), 127,5 (**1C**, C7), 149,3 (**1C**, C6), 157,9 (**1C**, C=N), 177,8 (**1C**, C3).

R_f = 0,57 (EtOAc);

methylation (synthesis of **79**): The previously prepared diol **80** (35,5 mg, 142 µmol, 1,0 equiv.) was dissolved in a flame-dried 5-ml three-neck round-bottom flask in 1,4 ml dry CH_2Cl_2 and the solution cooled to 0 °C. Proton-sponge® (214 mg, 997 µmol, 7,0 equiv.) was then added followed by Meerwein's salt (105 mg, 712 µmol, 5,0 eq; washed (*three times*) with dry CH_2Cl_2) and the so formed heterogenous mixture allowed to warm to room temperature. Stirring under an inert atmosphere was continued for one hour after which the mixture was diluted with aqueous $KHSO_4$ (4 ml, 1M). Extraction with MTBE (3x10 ml), followed by drying of the organic phases over Na_2SO_4 and removal of the volatiles under reduced pressure afforded the crude product, which after purification *via* flash column chromatography (SiO_2, PE/ EtOAc = 2:1 (v/v)) gave both pure title compound **79** (4,0 mg, 15,2 µmol, **11%**) as a yellow solid, as well as *di*-methylated product **81** (13,4 mg, 48,3 µmol, **34%**) as a thick yellow oil. The measured spectra of **79** matched those reported previously (see above).

The synthesis was carried out by following a protocol described by Nakamura et al.[145]

Partial analysis of the di-methylation product **81***:*

R_f = 0,50 (PE/ EtOAc = 3:2 (v/v));

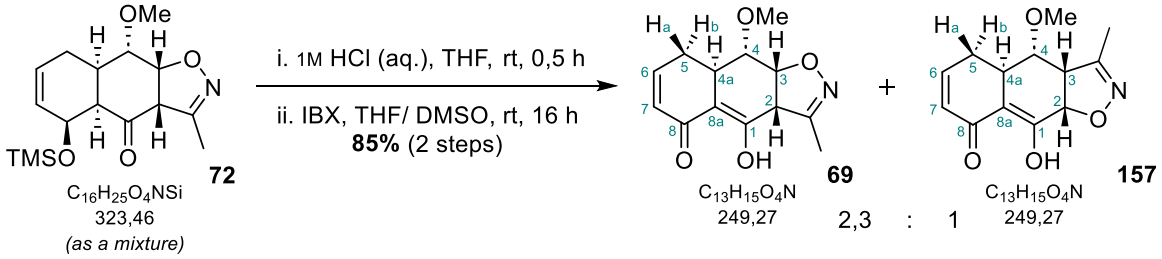
HR-ESI-MS: $[C_{14}H_{15}O_5NNa]^+$: m/z = 300,0848, found m/z = 300,0833;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,51 (s, **3H**, CH_3), 2,63–2,69 (m, **1H**, Ha5), 2,85–2,92 (m, **1H**, Hb5), 3,07 (m, **1H**, H4a), 3,59 (s, **3H**, C8a-OCH_3), 3,74 (s, **3H**, C4a-OCH_3), 4,47 (d, *J* = 9,3 Hz, **1H**, H4), 6,15 (ddd, *J* = 10,3, 2,9, 1,4 Hz, **1H**, H7), 7,00–7,02 (m, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 10,7 (**1C**, CH_3), 25,4 (**1C**, C5), 47,1 (**1C**, C4a), 55,8 (**1C**, OCH_3), 60,3 (**1C**, OCH_3), 72,7 (**1C**, C4), 84,8 (**1C**, C8a), 115,4 (**1C**, C2), 128,6 (**1C**, C7), 149,4 (**1C**, C6), 157,7 (**1C**, C=N), 177,4 (**1C**, C3), 189,1 (**1C**, C1), 193,3 (**1C**, C8).

6.3.2 Enone **69**

6.3.2.1 (3a*S*,8a*R*,9*S*,9a*R*)-4-hydroxy-9-methoxy-3-methyl-8,8a,9,9a-tetrahydronaphtho[2,3-*d*] isoxazol-5(3a*H*)-one **69**



TMS-cleavage (synthesis of (3a*S*,4a*R*,5*S*,8a*R*,9*S*,9a*R*)-5-hydroxy-9-methoxy-3-methyl-4a,5,8,8a,9,9a-hexahydronaphtho[2,3-*d*]isoxazol-4(3a*H*)-one): The previously prepared intermediate **72** (*chapter 6.3.1.2*; 0,69 g, 2,13 mmol, 1,0 equiv.), dissolved at room temperature in 20,0 ml THF was reacted with 0,9 ml (12,0 equiv.) aqueous HCl-solution (1M) for 30 minutes in a 50-ml one-neck round-bottom flask under ambient conditions. The reaction was then neutralized by the addition of 2 ml saturated aqueous $NaHCO_3$-soution followed by the addition of 10 ml MTBE. The aqueous phase was then extracted with MTBE (3x20 ml). The resulting ethereal organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to yield 0,50 g (1,99 mmol) of the aimed crude allylic alcohol ($\mathbf{R_f}$ = 0,16 (PE/ EtOAc = 3:2 (v/v)) as a pale yellow oil.

IBX-oxidation (synthesis of **69**): 0,50 g (1,99 mmol, 1,0 equiv.) of the previously prepared crude allylic alcohol were dissolved under an inert atmosphere in a flame-dried 25-ml one-neck round-bottom flask in 9,0 ml dry THF and 1,0 ml dry DMSO. To the formed solution were then added 1,67 g (5,97 mmol, 3,0 equiv.) IBX and the heterogenous mixture allowed to stir for 16 hours at room temperature. Upon completion, the orange-colored slurry was diluted with MTBE and filtered over a pad of Celite® (MTBE). Removal of the volatiles under reduced pressure yielded a thick, yellow oil, which was purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 4:1 (v/v)). Vinylogues acid **69** was isolated as an orange-colored solid alongside its regioisomer **157** as an inseparable mixture (0,45 g, 1,81 mmol, **85%**) with a ratio of 2,3 : 1. Since the separation of the products seemed to be impossible by means of flash column chromatography, a joint characterization is provided:

$\mathbf{R_f}$ = 0,29 (PE/ EtOAc = 3:2 (v/v));

HR-ESI-MS: $[C_{13}H_{15}O_4NNa]^+$: m/z = 272,0899, found m/z = 272,0896;

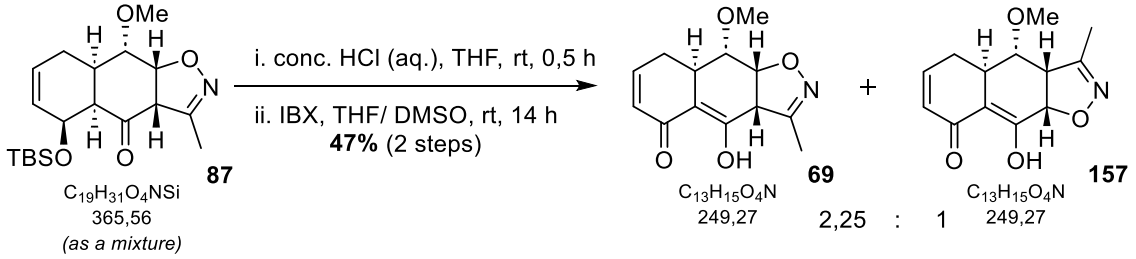
^{1}H-NMR (400 MHz; C_6D_6): δ [ppm] = 1,45–1,55 (m, **1H**, Ha5), 1,91 (d, *J* = 0,7 Hz, **3H**, CH_3), 2,29–2,40 (m, **1H**, Hb5), 2,71 (dd, *J* = 10,2, 2,8 Hz, **1H**, H4a), 3,09 (s, **3H**, OCH_3), 3,10–3,16 (m, **1H**, H4), 3,13 (d, *J* = 10,0 Hz, **1H**, H2), 4,42 (dd, *J* = 9,2, 2,8 Hz, **1H**, H3), 5,81 (ddd, *J* = 10,0, 3,1, 0,8 Hz, **1H**, H6), 5,99–6,04 (m, **1H**, H7);

^{13}C-NMR (101 MHz; C_6D_6): δ [ppm] = 12,8 (s, **1C**, CH_3), 28,0 (**1C**, C5), 31,2 (**1C**, C4a), 55,9 (**1C**, OCH_3), 56,2 (**1C**, C2), 76,5 (**1C**, C3), 80,8 (**1C**, C4), 104,5 (**1C**, C8a), 127,5 (**1C**, C6), 146,9 (**1C**, C7), 154,4 (**1C**, C=N), 174,1 (**1C**, C1), 187,0 (**1C**, C8).

Analysis of **157** (*overlapping signals are marked with "*"*):

^{1}H-NMR (400 MHz; C_6D_6): δ [ppm] = 1,31 (dddd, *J* = 17,8, 12,3, 3,0, 2,2 Hz, **1H**, Ha5), 1,77 (d, *J* = 1,3 Hz, **3H**, CH_3), 2,11 (dtd, *J* = 18,1, 6,4, 6,4, 0,8 Hz, **1H**, Hb5), 2,29–2,40 (m, **1H**, H4a), 2,56 (dd, *J* = 10,2, 4,9 Hz, **1H**, H4), 2,78 (s, **3H**, OCH_3), 3,01–3,05 (m, **1H**, H2), 4,74 (dd, *J* = 10,6, 1,4 Hz, **1H**, H3), 5,85 (ddd, *J* = 10,1, 3,0, 0,8 Hz, **1H**, H6), 5,99–6,04* (m, **1H**, H7);
^{13}C-NMR (101 MHz; C_6D_6): δ [ppm] = 13,7 (s, **1C**, CH_3), 28,0* (**1C**, C5), 34,6 (**1C**, C4a), 49,0 (**1C**, C3), 56,8 (**1C**, OCH_3), 78,1 (**1C**, C2), 80,2 (**1C**, C4), 104,9 (**1C**, C8a), 129,2 (**1C**, C6), 146,4 (**1C**, C7), 155,0 (**1C**, C=N), 169,1 (**1C**, C1), 190,2 (**1C**, C8).

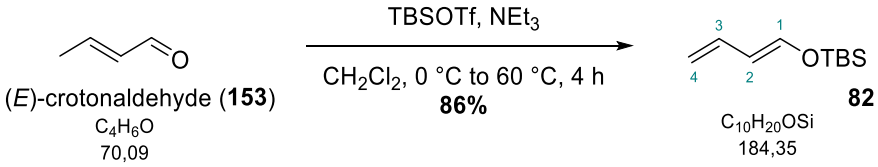
*Alternative preparation of **69** from **87**:*



TBS-cleavage (synthesis of (3a*S*,4a*R*,5*S*,8a*R*,9*S*,9a*R*)-5-hydroxy-9-methoxy-3-methyl-4a,5,8,8a,9,9a-hexahydronaphtho[2,3-*d*]isoxazol-4(3a*H*)-one): The previously prepared intermediate **87** (*chapter 6.3.2.3*; 0,50 g, 1,37 mmol, 1,0 equiv.), dissolved at room temperature in 7,0 ml THF was reacted with 1,36 ml (12,0 equiv.) aqueous HCl-solution (conc.) for 30 minutes in a 25-ml one-neck round-bottom flask under ambient conditions. The reaction was then neutralized by the addition of 7 ml saturated aqueous $NaHCO_3$-soution followed by the addition of 10 ml MTBE. The aqueous phase was then extracted with MTBE (3x20 ml). The resulting ethereal organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to yield 0,17 g (0,68 mmol) of the aimed crude allylic alcohol ($\mathbf{R_f}$ = 0,16 (PE/ EtOAc = 3:2 (v/v)) as a pale yellow oil.

IBX-oxidation (synthesis of **69**): 0,17 g (0,68 mmol, 1,0 equiv.) of the previously prepared crude allylic alcohol were dissolved under an inert atmosphere in a flame-dried 10-ml one-neck round-bottom flask in 3,1 ml dry THF and 0,3 ml dry DMSO. To the formed solution were then added 0,57 g (2,04 mmol, 3,0 equiv.) IBX and the heterogenous mixture allowed to stir for 14 hours at room temperature. Upon completion, the orange-colored slurry was diluted with MTBE and filtered over a pad of Celite® (MTBE). Removal of the volatiles under reduced pressure yielded a thick, yellow oil, which was purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 4:1 (v/v)). Vinylogues acid **69** was isolated as an orange-colored solid alongside its regioisomer **157** as an inseparable mixture (0,16 g, 0,64 mmol, **47%**) with a ratio of 2,25 : 1. The recorded spectra of the mixture were found to be in agreement with the previously reported ones.

6.3.2.2.1 (*E*)-(buta-1,3-dien-1-yloxy)(*tert*-butyl)dimethylsilane **82**



(*E*)-crotonaldehyde (**153**; 11,8 ml, 143 mmol, 1,0 equiv.) was dissolved in a flame-dried three-neck round-bottom flask in 59,0 ml dry CH_2Cl_2. The solution was then cooled to 0 °C and dry NEt_3 (27,8 ml, 200 mmol, 1,4 equiv.) was added. Lastly, TBSOTf (29,5 ml, 128 mmol, 0,9 equiv.) was added and the formed solution allowed to stir under an inert atmosphere at 60 °C for four hours. Upon completion, the cooled reaction-mixture was diluted with 20 ml of an aqueous, saturated $NaHCO_3$-solution and 50 ml of water. The aqueous phase was then extracted with CH_2Cl_2 (2x60 ml), the combined organic phases dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude *via* vacuum-distillation ($T_{ex.}$ *=95 °C,* $T_{int.}$ *=83 °C; P = 35 mbar*) afforded title compound **82**(20,3 g, 110 mmol, **86%**) as a colorless oil.

R_f = 0,69 (PE);

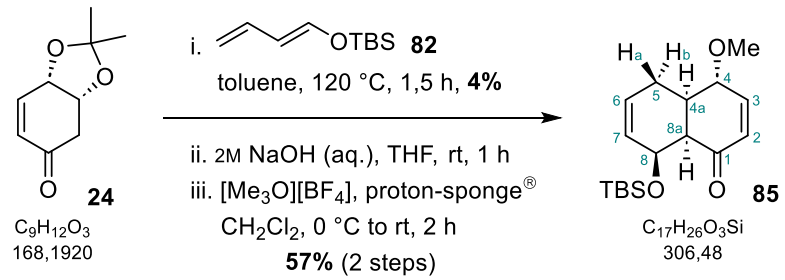
b.p. = 185 °C; [*lit.: 226 °C*][147];

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,16 (s, **6H**, CH_3 (TBS)), 0,92 (s, **9H**, CH_3 (TBS)), 4,81 (dd, *J* = 10,4, 1,8 Hz, **1H**, H4-(*Z*)), 4,98 (dd, *J* = 16,9, 2,1 Hz, **1H**, H4-(*E*)), 5,70–5,76 (m, **1H**, H2), 6,22 (dt, *J* = 17,0, 10,6, 10,6 Hz, **1H**, H3), 6,57 (d, *J* = 11,8 Hz, **1H**, H1);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –5,1 (**2C**, CH_3 (TBS)), 25,7 (**3C**, CH_3 (TBS)), 112,0 (**1C**, C4), 114,3 (**1C**, C2), 133,5 (**1C**, C3), 145,5(**1C**, C1).

The synthesis was carried out by following the protocol described by Imagaw et al.,[147] *with the recorded spectroscopic data being in accordance with those reported by the authors.*

6.3.2.2.2 (4*R*,4a*R*,8*S*,8a*R*)-8-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-4a,5,8,8a-tetrahydro-naphthalen-1(4*H*)-one **85**



Diels–Alder reaction (synthesis of (3a*R*,5a*R*,6*S*,9a*R*,9b*S*)-6-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethyl-3a,5a,6,9,9a,9b-hexahydronaphtho[1,2-*d*][1,3]dioxol-5(4*H*)-one)[32]: The previously prepared enone **24** (*chapter 6.2.1.2*; 2,50 g, 14,9 mmol, 1,0 equiv.) and diene **82** (6,30 g, 34,2 mmol, 2,3 equiv.) were

[32] Several trials were performed in parallel. The isolated products were quickly converted further in one batch without any additional analysis being performed.

dissolved in 5,3 ml dry toluene in a sealed-tube and the reaction carried out for 90 minutes at 120 °C, time in which mainly the unspecific decomposition of enone **24** was observed.
Upon full consumption of **24**, the tube was opened, the volatiles removed *in vacuo* and the oily residue purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1 (v/v); $\mathbf{R_f}$ = 0,54 (PE/ EtOAc = 4:1 (v/v))) to give the aimed decalin (0,2 g, 0,60 mmol, **4%**) as a colorless oil.

elimination (synthesis of (4*R*,4a*R*,8*S*,8a*R*)-8-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4a,5,8,8a-tetra-hydronaphthalen-1(4*H*)-one): The previously prepared decalin (1,45 g, 4,11 mmol, 1,0 equiv.) was dissolved under ambient conditions in a 25-ml one-neck round-bottom flask in 7,4 ml THF and treated with 0,6 ml (1,11 mmol, 20 mol-%) NaOH-solution (aq., 2M). The reaction was then stirred for one hour at room temperature and terminated by the addition of 10 ml of water. After extraction with MTBE (3x25 ml), the organic phases were dried over Na_2SO_4, the volatiles removed under reduced pressure and the yellow-colored oily residue (1,20 g, 4,06 mmol) converted further without any additional purification.

methylation (synthesis of **85**): The previously prepared allylic alcohol (1,20 g, 4,06 mmol, 1,0 equiv.) was dissolved in a flame-dried 25-ml three-neck round-bottom flask in 16,2 ml dry CH_2Cl_2 and the solution cooled to 0 °C. Proton-sponge® (6,09 g, 28,4 mmol, 7,0 equiv.) was then added followed by Meerwein's salt (3,00 g, 20,3 mmol, 5,0 eq; washed (*three times*) with dry CH_2Cl_2) and the so formed heterogenous mixture allowed to warm to room temperature. Stirring under an inert atmosphere was continued for two hours after which the mixture was diluted with aqueous $KHSO_4$ (8 ml, 1M). Extraction with MTBE (3x20 ml), drying of the combined organic phases over Na_2SO_4 and removal of the volatiles under reduced pressure afforded the crude product, which after purification *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1 (v/v)) gave pure title compound **85** (0,72 g, 2,33 mmol, **57%** (2 steps)) as a thick yellow oil.

The synthesis was carried out by following a protocol described by Nakamura et al.[145]

$\mathbf{R_f}$ = 0,69 (PE/ EtOAc = 4:1 (v/v));

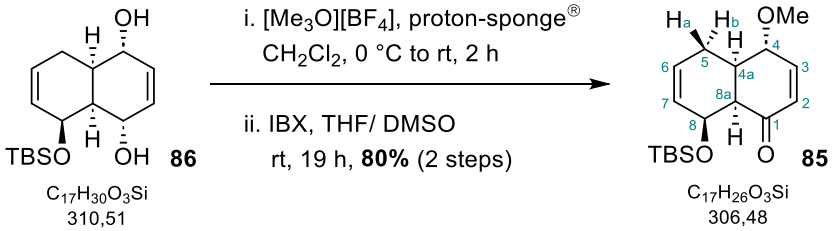
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{22,0}}$ = 221,74° ($CHCl_3$, *5,11*);

HR-ESI-MS: $[C_{17}H_{28}O_3Na]^+$: m/z = 331,1705, found m/z = 331,1709;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = –0,07 (s, **3H**, CH_3 (TBS)), –0,02 (s, **3H**, CH_3 (TBS)), 0,79 (s, **9H**, CH_3 (TBS)), 2,07–2,15 (m, **1H**, Hb5), 2,46 (dt, *J* = 11,1, 6,0, 6,0 Hz, **1H**, H4a), 2,54–2,56 (m, **1H**, Ha5), 2,68 (t, *J* = 5,0, 5,0 Hz, **1H**, H8a), 3,44 (s, **1H**, OCH_3), 4,34–4,36 (m, **1H**, H8), 4,39 (dt, *J* = 10,5, 1,8, 1,8 Hz, **1H**, H4), 5,79–5,80 (m, **1H**, H6,), 5,80–5,81 (m, **1H**, H7), 6,03 (ddd, *J* = 10,3, 2,0, 0,8 Hz, **1H**, H2), 7,01 (dd, *J* = 10,3, 1,6 Hz, **1H**, H3);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –5,2 (**1C**, CH_3 (TBS)), –4,3 (**1C**, CH_3 (TBS)), 17,9 (**1C**, $C_{quat.}$ (TBS)), 24,7 (**1C**, C5), 25,8 (**3C**, CH_3 (TBS)), 37,2 (**1C**, C4a), 49,8 (**1C**, C8a), 57,0 (**1C**, OCH_3), 64,7 (**1C**, C8), 76,3 (**1C**, C4), 127,5 (**1C**, C7), 128,4 (**1C**, C6), 130,7 (**1C**, C2), 151,2 (**1C**, C3), 200,7 (**1C**, C1).

6.3.2.2.3 (4*R*,4a*R*,8*S*,8a*R*)-8-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-4a,5,8,8a-tetrahydro-naphthalen-1(4*H*)-one **85** from enantiomerically pure decalin **86**



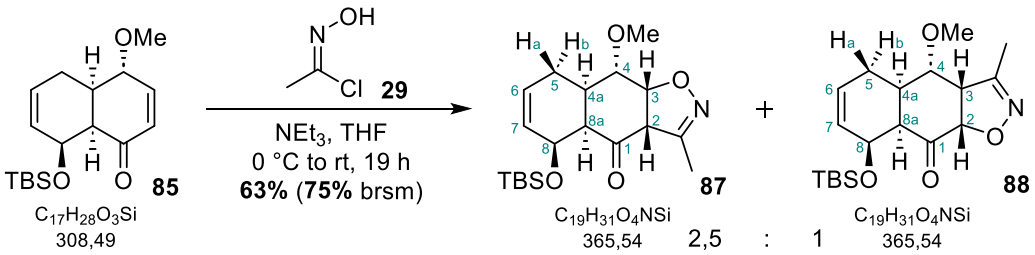
As an alternative, the synthesis of **85** could be carried out from diol **86** (*chapter 4.2*, as well as *chapter 6.4.1.2*) by following a two-step strategy:

methylation (synthesis of (1*S*,4*R*,4a*R*,8*S*,8a*S*)-8-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-1,4,4a,5,8,8a-hexahydronaphthalen-1-ol): Diol **86** (1,00 g, 3,37 mmol, 1,0 equiv.) was dissolved in a flame-dried 25-ml three-neck round-bottom flask in 17,0 ml dry CH_2Cl_2 and the solution cooled to 0 °C. Proton-sponge® (2,89 g, 13,5 mmol, 4,0 equiv.) was then added followed by Meerwein's salt (1,75 g, 11,8 mmol, 3,5 eq; washed (*three times*) with dry CH_2Cl_2) and the so formed heterogenous mixture allowed to warm to room temperature. Stirring under an inert atmosphere was continued for one hour ($\mathbf{R_f}$ = 0,88 (PE/ EtOAc = 1:1 (v/v))) after which the mixture was diluted with 7 ml aqueous $KHSO_4$ (1M) and water. Extraction with MTBE (3x30 ml), followed by drying of the organic phases over Na_2SO_4 and removal of the volatiles under reduced pressure afforded the crude product (0,90 g, 2,90 mmol) as a thick yellow oil, which was converted further without any additional purification steps.

The synthesis was carried out by following a protocol described by Nakamura et al.[145]

IBX-oxidation (synthesis of **85**): 0,90 g (2,90 mmol, 1,0 equiv.) of the previously prepared crude allylic alcohol were dissolved under an inert atmosphere in a flame-dried 25-ml one-neck round-bottom flask in 13,0 ml dry THF and 1,4 ml dry DMSO. To the formed solution were then added 2,43 g (8,70 mmol, 3,0 equiv.) IBX and the heterogenous mixture allowed to stir for 19 hours at room temperature. Upon completion, the orange-colored slurry was diluted with a small amount of MTBE and filtered over a pad of Celite®. Removal of the volatiles under reduced pressure yielded a thick, yellow oil, which was purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 4:1 (v/v)). Enone **85** (0,83 g, 2,69 mmol, **80%** (2 steps)) was finally collected as a thick yellow oil. The measured spectra were in accordance with those reported previously (see above).

6.3.2.3 (3a*S*,4a*R*,5*S*,8a*R*,9*S*,9a*R*)-5-((*tert*-butyldimethylsilyl)oxy)-9-methoxy-3-methyl-4a,5,8,8a,9,9a-hexahydronaphtho[2,3-*d*]isoxazol-4(3a*H*)-one **87**



Decalin **85** (0,72 g, 2,33 mmol, 1,0 equiv.) was charged into a flame-dried 25-ml one-neck round-bottom flask and 4,7 ml dry THF were added. Dry NEt_3 (2,6 ml, 18,7 mmol, 8,0 equiv.) was then added and the solution cooled to 0 °C. The required amount of oxime **29** (1,30 g, 14,0 mmol, 6,0 equiv.) was freshly prepared in accordance with *6.2.1.5.1* and the entire reaction-mixture added to the cooled solution *via* cannula. The reaction was then warmed up to room temperature and stirred under an inert atmosphere for 19 hours. Upon completion, the reaction was diluted with 10 ml of water and extracted with MTBE (3x30 ml). The organic phases were dried over Na_2SO_4, concentrated *in vacuo* and the residue purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 3:2 (v/v)) to yield **85** (0,11 g, 0,35 mmol) and a practically inseparable mixture consisting of **87** and the regioisomer **88** (0,54 g, 1,48 mmol, **63%** (**75%** brsm)) in a 2,5:1 ratio (determination *via* ^{1}H-NMR). Since the separation of the two regioisomers seemed to be impossible by means of flash column chromatography, a joint characterization of the products is provided:

R_f = 0,28 (PE/ EtOAc = 4:1 (v/v));

HR-ESI-MS: $[C_{19}H_{31}O_4NSiNa]^+$: m/z = 388,1920, found m/z = 388,1917;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,01 (s, **3H**, CH_3 (TBS)), 0,09 (s, **3H**, CH_3 (TBS)), 0,86 (s, **9H**, CH_3 (TBS)), 1,97–2,05 (m, **1H**, Hb5), 2,13 (d, *J* = 0,9 Hz, **3H**, CH_3), 2,62–2,65 (m, **1H**, Ha5), 2,66–2,67 (m, **1H**, H4a), 2,68–2,70 (m, **1H**, H8a) 3,48 (s, **3H**, OCH_3), 3,64 (d, *J* = 10,0 Hz, **1H**, H2), 4,38–4,41 (m, **1H**, H8), 4,49 (dd, *J* = 11,5, 3,6 Hz, **1H**, H4), 4,98 (dd, *J* = 10,3, 3,6 Hz, **1H**, H3), 5,74–5,80 (m, **1H**, H7), 5,82–5,88 (m, **1H**, H6);

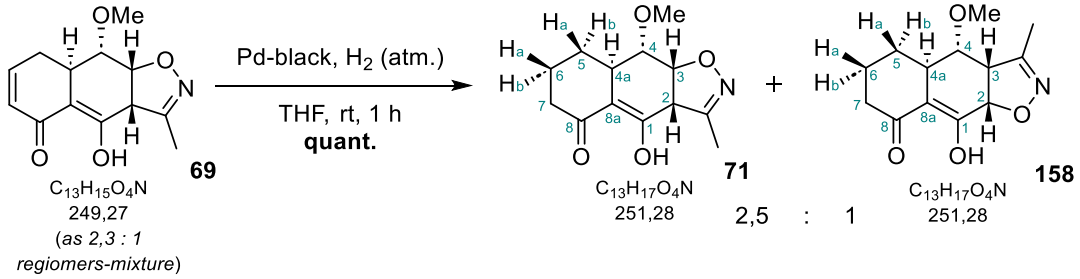
^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –5,0 (**1C**, CH_3 (TBS)), –4,4 (**1C**, CH_3 (TBS)), 17,9 (**1C**, $C_{quat.}$ (TBS)), 13,3 (s, **1C**, CH_3), 23,4 (**1C**, C5), 25,8 (**3C**, CH_3 (TBS)), 29,2 (**1C**, C4a), 52,2 (**1C**, C8a), 57,9 (**1C**, OCH_3), 63,0 (**1C**, C2), 65,6 (**1C**, C8), 74,4 (**1C**, C4), 77,5 (**1C**, C3), 127,1 (**1C**, C7), 128,2 (**1C**, C6), 154,3 (**1C**, C=N), 205,2 (**1C**, C1).

Analysis of **88** (*overlapping signals are marked with "*"*):

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,02 (s, **3H**, CH_3 (TBS)), 0,09* (s, **3H**, CH_3 (TBS)), 0,87 (s, **9H**, CH_3 (TBS)), 1,97–2,05* (m, **1H**, Hb5), 2,08 (d, *J* = 1,2 Hz, **3H**, CH_3), 2,15–2,22 (m, **1H**, H4a), 2,54–2,61 (m, **1H**, Ha5), 2,79 (t, *J* = 5,2, 5,2 Hz, **1H**, H8a) 3,44 (s, **3H**, OCH_3), 3,93 (ddd, *J* = 10,5, 5,8, 1,3 Hz, **1H**, H3), 4,35–4,36 (m, **1H**, H8), 4,43–4,47 (m, **1H**, H4), 4,68 (dd, *J* = 10,4, 0,8 Hz, **1H**, H2), 5,74–5,80* (m, **1H**, H7), 5,82–5,88* (m, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,8 (**1C**, CH_3 (TBS)), –4,5 (**1C**, CH_3 (TBS)), 18,0 (**1C**, $C_{quat.}$ (TBS)), 14,0 (s, **1C**, CH_3), 23,7 (**1C**, C5), 25,9 (**3C**, CH_3 (TBS)), 33,3 (**1C**, C4a), 51,4 (**1C**, C3), 51,8 (**1C**, C8a), 58,5 (**1C**, OCH_3), 64,6 (**1C**, C8), 74,6 (**1C**, C4), 82,9 (**1C**, C2), 127,6 (**1C**, C7), 127,7 (**1C**, C6), 157,6 (**1C**, C=N), 207,0 (**1C**, C1).

6.3.2.4 Isoxazolin-hydrogenation study ((3a*S*,8a*R*,9S,9a*R*)-4-hydroxy-9-methoxy-3-methyl-6,7,8,8a,9,9a-hexahydronaphtho[2,3-*d*]isoxazol-5(3a*H*)-one **71**)



42,4 mg (0,17 mmol, 1,0 equiv.) **69** (regioisomers-mixture; see *6.3.2.1*) were dissolved under an inert atmosphere in 3,4 ml dry THF in a flame-dried 10-ml three-neck round-bottom flask. To the formed solution, 31,7 mg (0,30 mmol, 1,75 equiv.) Pd-black were added under an argon-stream and the flask evacuated three times (H_2). The reaction was then allowed to stir for one hour under H_2-atmosphere after which the flask was opened and diluted with MTBE (5 ml). The solids were then filtered over Celite® (MTBE) and the filtrate concentrated under reduced pressure to give the still isoxazoline-bearing regioisomers **71** and **158** (2,5 : 1 ratio; 42,8 mg, 0,17 mmol, **quant.**) as a pale yellow powder. Since the separation of the two regioisomers seemed to be impossible by means of flash column chromatography, a joint characterization of the products is provided:

R_f = 0,36 (PE/ EtOAc = 3:2 (v/v));

HR-ESI-MS: $[C_{13}H_{17}O_4NNa]^+$: m/z = 274,1055, found m/z = 274,1054;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 1,05–1,15 (m, **1H**, Ha5), 1,56–1,69 (m, **1H**, Hb6), 1,91–1,98 (m, **1H**, Ha6), 2,02 (d, *J* = 0,9 Hz, **3H**, CH_3), 2,25–2,32 (m, **1H**, Hb5), 2,36–2,47 (m, **2H**, H7), 2,78 (td, *J* = 11,0, 11,0, 4,7 Hz, **1H**, H4a), 3,19 (dd, *J* = 10,7, 2,9 Hz, **1H**, H4), 3,48 (s, **3H**, OCH_3), 3,88 (d, *J* = 10,3 Hz, **1H**, H2), 5,08 (dd, *J* = 10,3, 3,0 Hz, **1H**, H3);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 12,3 (s, **1C**, CH_3), 20,6 (**1C**, C6), 26,2 (**1C**, C5), 32,2 (**1C**, C7), 33,2 (**1C**, C4a), 57,6 (**1C**, OCH_3), 59,1 (**1C**, C2), 77,5 (**1C**, C3), 81,5 (**1C**, C4), 107,6 (**1C**, C8a), 153,7 (**1C**, C=N), 185,3 (**1C**, C1), 189,7 (**1C**, C8).

Analysis of **158** (*overlapping signals are marked with "*"*):

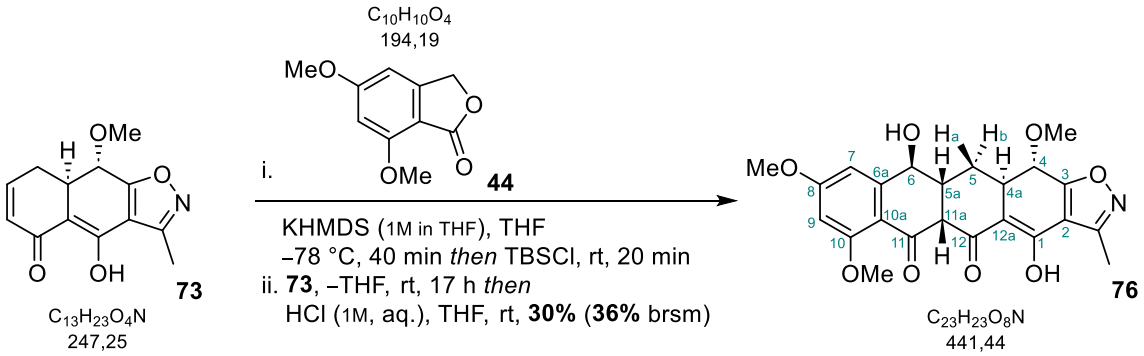
R_f = 0,36 (PE/ EtOAc = 3:2 (v/v));

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 1,05–1,15* (m, **1H**, Ha5), 1,56–1,69* (m, **1H**, Hb6), 1,91–1,98* (m, **1H**, Ha6), 2,07 (d, *J* = 1,2 Hz, **3H**, CH_3), 2,25–2,32* (m, **1H**, Hb5), 2,36–2,47* (m, **2H**, H7), 2,47–2,853 (m, **1H**, H4a), 3,29 (dd, *J* = 10,7, 5,3 Hz, **1H**, H4), 3,47 (s, **3H**, OCH_3), 3,92–3,97 (m, **1H**, H3), 4,90 (d, *J* = 1,2 Hz, **1H**, H2);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 14,0 (s, **1C**, CH_3), 20,6* (**1C**, C6), 26,5 (**1C**, C5), 34,0 (**1C**, C7), 36,9 (**1C**, C4a), 50,6 (**1C**, C3), 58,1 (**1C**, OCH_3), 79,8 (**1C**, C2), 81,3 (**1C**, C4), 107,6* (**1C**, C8a), 156,5 (**1C**, C=N), 179,3 (**1C**, C1), 195,3 (**1C**, C8).

6.3.3 Premithramycinone **2**

6.3.3.1 (5a*R*,11*S*,11a*R*,12a*R*,13*S*)-4,11-dihydroxy-7,9,13-trimethoxy-3-methyl-11a,12,12a,13-tetrahydrotetraceno[2,3-*d*]isoxazole-5,6(5a*H*,11*H*)-dione **76**



80,0 mg (412 µmol, 1,5 equiv.) **44** were dissolved in 0,8 ml dry THF in a flame-dried 10-ml one-neck round-bottom flask and the formed suspension cooled to –78 °C. The suspension was then treated with 0,6 ml (584 µmol, 2,1 equiv.) KHMDS-solution (1M in THF) and the so formed red-colored solution stirred for 40 minutes under an inert atmosphere. TBSCl (95,2 mg, 632 µmol, 2,3 equiv.) was then added and the reaction warmed to room temperature over a period of 20 minutes after which 93,0 mg (275 µmol, 1,0 equiv.) **73** added and the solvent-amount reduced under vacuum to 10% of its original volume. The concentrated, dark-yellow-colored slurry was then stirred for additional 20 hours. Upon completion, the reaction was diluted with water (8 ml) and MTBE (10 ml) and the organic components extracted with MTBE (3x20 ml). The combined organic phases were dried over Na_2SO_4, the volatiles removed under reduced pressure and the residue quickly (!) purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 4:1 (v/v) with 1,5 vol-% NEt_3). The fractions containing the impure cycloaddition product (**R_f** = 0,73 (PE/ EtOAc = 3:2 (v/v)) were then collected and concentrated under reduced pressure. The product was redissolved in 20 ml THF and the solution acidified by the addition of a few drops of HCl-solution (1M, aq.). After two minutes the mixture was diluted with water and extracted with EtOAc (4x40 ml). The combined organic phases were then dried over Na_2SO_4, the volatiles removed under reduced pressure and the crude product purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 3:2→2:3 (v/v)) to give the aimed tetracycline precursor **76** (36,8 mg, 83,4 µmol, **30%** (**36%** brsm)) as a yellow powder.

R_f = 0,10 (PE/ EtOAc = 2:3 (v/v));

m.p. = 139 °C;

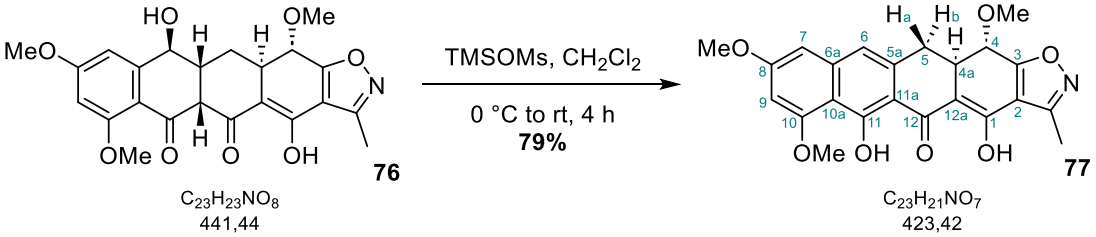
$[\alpha]_D^{22,2}$ = +157,05° ($CHCl_3$, *3,71*);

HR-ESI-MS: $[C_{23}H_{23}O_8NNa]^+$: m/z = 464,1321, found m/z = 464,1326;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,10 (dd, *J* = 7,7, 5,4 Hz, **2H**, H5), 2,50 (s, **3H**, CH_3), 2,94–2,98 (m, **1H**, H4a), 3,00–3,06 (m, **1H**, H5a), 3,67 (s, **3H**, C4-OCH_3), 3,77 (d, *J* = 5,3 Hz, **1H**, H11a), 3,85 (s, **3H**, C10-OCH_3), 3,88 (s, **3H**, C8-OCH_3), 4,42 (d, *J* = 2,6 Hz, **1H**, H4), 4,57 (d, *J* = 7,2 Hz, **1H**, H6), 6,42 (d, *J* = 2,4 Hz, **1H**, H9), 6,51 (d, *J* = 2,3 Hz, **1H**, H7);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 10,8 (**1C**, CH_3), 25,0 (**1C**, C5), 35,2 (**1C**, C4a), 40,4 (**1C**, C5a), 54,4 (**1C**, C11a), 55,8 (**1C**, C8-OCH_3), 56,3 (**1C**, C10-OCH_3), 59,8 (**1C**, C4-OCH_3), 72,4 (**1C**, C4), 72,8 (**1C**, C6), 99,5 (**1C**, C9), 102,3 (**1C**, C12a), 105,7 (**1C**, C7), 112,1 (**1C**, C10a), 113,8 (**1C**, C2), 146,8 (**1C**, C6a), 157,8 (**1C**, C=N), 162,7 (**1C**, C10), 165,0 (**1C**, C8), 177,9 (**1C**, C1), 178,7 (**1C**, C3), 185,9 (**1C**, C12), 187,9 (**1C**, C11).

6.3.3.2 (12a*R*,13*S*)-4,6-dihydroxy-7,9,13-trimethoxy-3-methyl-12a,13-dihydrotetraceno[2,3-*d*]-isoxazol-5(12*H*)-one **77**



76 $C_{23}H_{23}NO_8$ 441,44

77 $C_{23}H_{21}NO_7$ 423,42

An initial trial towards precursor **77** was carried out by following the protocol described in chapter 6.2.3.3. In a flame-dried 1-ml one-neck round-bottom flask, **76** (4,20 mg, 9,50 µmol, 1,0 equiv.) was dissolved under an inert atmosphere in 50 µl dry CH_2Cl_2 and the formed solution cooled to 0 °C. TMSOMs (4,4 µl, 28,5 µmol, 3,0 equiv.) was then added and the red-colored solution stirred for four hours at room temperature. Upon completion, the mixture was treated with 0,5 ml saturated, aqueous $NaHCO_3$-solution, diluted with water (10 ml) and EtOAc (15 ml). Extraction with EtOAc (3x20 ml), followed by drying of the combined organic phases over Na_2SO_4 and removal of the volatiles under reduced pressure afforded the crude pentacyclic product **77** (3,20 mg, 7,60 mmol, **79%**) as a bright yellow-colored solid. Since the handling of the compound has proven to be quite tedious, the highly insoluble product was washed several times with a mixture of PE/ EtOAc (4:1 (v/v)) prior to characterization in order to remove most trace impurities.

R_f = 0,30 (PE/ EtOAc = 3:2 (v/v));

m.p. = decomp. >180 °C;

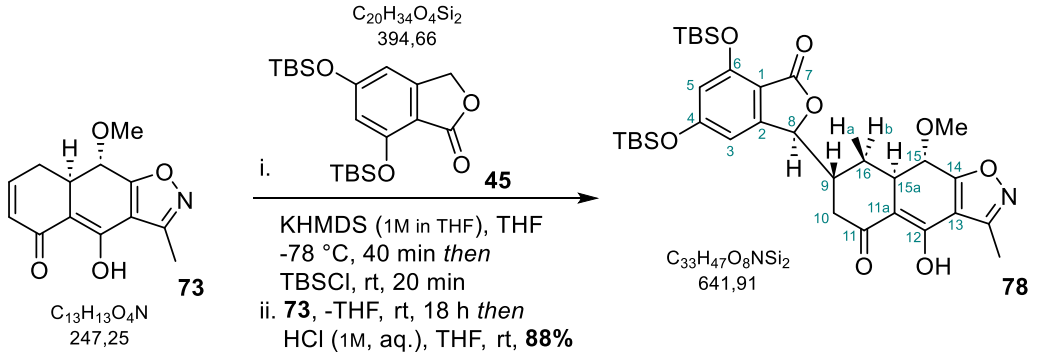
$[\alpha]_D^{20,9}$ = +239,58° ($CHCl_3$, *8,00*);

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,53 (s, **3H**, CH_3), 2,82 (t, *J* = 13,9, 13,9 Hz, **1H**, Ha5), 3,23 (td, *J* = 12,8, 12,8, 4,7 Hz, **1H**, H4a), 3,34 (dd, *J* = 14,3, 4,7 Hz, **1H**, Hb5), 3,85 (s, **3H**, C4-OCH_3), 3,92 (s, **3H**, C8-OCH_3), 3,99 (s, **3H**, C10-OCH_3), 4,53 (d, *J* = 12,2 Hz, **1H**, H4), 6,45 (d, *J* = 2,2 Hz, **1H**, H9), 6,58 (d, *J* = 2,3 Hz, **1H**, H7), 6,90 (s, **1H**, H6), 9,09 (s, **1H**, C11-OH);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 10,8 (**1C**, CH_3), 29,8 (**1C**, C5), 33,8 (**1C**, C4a), 55,6 (**1C**, C8-OCH_3), 56,3 (**1C**, C10-OCH_3), 60,3 (**1C**, C4-OCH_3), 71,8 (**1C**, C4), 98,2 (**1C**, C9), 99,2 (**1C**, C7), 102,7 (**1C**, C12a), 109,4 (**1C**, C11a), 110,8 (**1C**, C2), 116,5 (**1C**, C6), 136,3 (**1C**, C5a), 141,4 (**1C**, C6a), 156,8 (**1C**, C=N), 160,9 (**1C**, C10), 161,9 (**1C**, C8), 163,1 (**1C**, C11), 174,9 (**1C**, C1), 190,4 (**1C**, C12).

Due to poor solubility and limited amount of compound available, the *C*10a- (expected at approx. 111 ppm)- and *C*3 (expected at approx. 168 ppm)-signals are not visible in the spectrum. Nevertheless, the obtained analytical data were considered sufficient for the irrefutable assignment of the isolated material to the targeted tetracycline precursor **77**.

6.3.4 Premithramycinone **2** from lactone **45** and enone **73** (formation of the 1,4-addition product: (7*R*,8a*R*,9*S*)-7-((*S*)-4,6-bis((*tert*-butyldimethylsilyl)oxy)-3-oxo-1,3-dihydroisobenzofuran-1-yl)-4-hydroxy-9-methoxy-3-methyl-7,8,8a,9-tetrahydronaphtho[2,3-*d*]isoxazol-5(6*H*)-one **78**)



0,25 g (0,63 mmol, 2,0 equiv.) **45** were dissolved in 1,3 ml dry THF in a flame-dried 10-ml one-neck round-bottom flask and the formed solution cooled to –78 °C. KHMDS-solution (1M in THF, 0,8 ml, 0,45 mmol, 2,4 equiv.) was then added and the formed red-colored solution stirred for 40 minutes under an inert atmosphere. TBSCl (0,12 g, 0,78 mmol, 2,5 equiv.) was then added and the reaction warmed to room temperature over a period of 20 minutes after which 80,0 mg (0,31 mmol, 1,0 equiv.) **73** were added and the solvent-amount reduced under vacuum to 10% of its original volume. The concentrated, dark yellow slurry was then stirred for additional 18 hours. Upon completion, the reaction was acidified with a few drops of HCl (aq., 1M), diluted with 10 ml of water and the organic components extracted with MTBE (3x20 ml). The combined organic phases were dried over Na_2SO_4, the volatiles removed under reduced pressure and the residue purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1 (v/v)) to exclusively give the undesired 1,4-addition product **78** (0,18 g, 0,28 mmol, **88%**) as a thick, off-yellow oil.

R_f = 0,54 (PE/ EtOAc = 9:1 (v/v));

HR-ESI-MS: $[C_{33}H_{47}O_8NSi_2Na]^+$: m/z = 664,2738, found m/z = 664,2742;

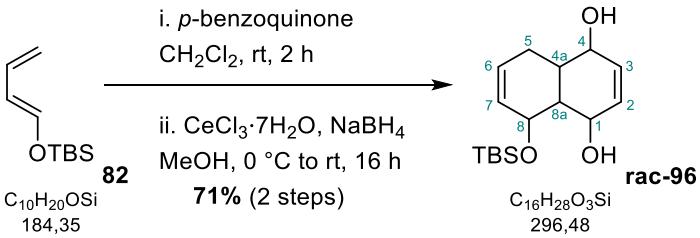
^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,24 (s, **6H**, CH_3 (TBS)), 0,25 (s, **3H**, CH_3 (C4-TBS)), 0,26 (s, **3H**, CH_3 (C6-TBS)), 0,98 (s, **9H**, CH_3 (C4-TBS)), 1,03 (s, **9H**, CH_3 (C6-TBS)), 1,93 (ddd, *J* = 13,8, 8,4, 3,4 Hz, **1H**, Hb16), 2,26–2,31 (m, **1H**, H9), 2,33–2,35 (m, **2H**, H10), 2,44 (dd, *J* = 13,7, 6,0 Hz, **1H**, Ha16), 2,49 (s, **3H**, CH_3), 3,22 (dt, *J* = 11,4, 6,8, 6,8 Hz, **1H**, H15a), 3,80 (s, **3H**, CH_3), 4,34 (d, *J* = 11,2 Hz, **1H**, H15), 5,19 (d, *J* = 5,3 Hz, **1H**, H8), 6,31 (d, *J* = 1,8 Hz, **1H**, H5), 6,50 (s, **1H**, H3);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,4 (**2C**, CH_3 (TBS)), –4,3 (**2C**, CH_3 (TBS)), 10,6 (**1C**, CH_3), 18,3 (**2C**, $C_{quat.}$ (TBS)), 18,5 (**1C**, $C_{quat.}$ (TBS)), 25,6 (**3C**, CH_3 (TBS)), 25,7 (**3C**, CH_3 (TBS)), 28,2 (**1C**, C16), 30,1 (**1C**, C10), 36,0 (**1C**, C9), 38,0 (**1C**, C15a), 60,2 (**1C**, OCH_3), 78,3 (**1C**, C15), 80,4 (**1C**, C8), 104,8 (**1C**, C11a), 107,3 (**1C**, C3), 110,3 (**1C**, C2), 112,7 (**1C**, C5), 114,3 (**1C**, C13), 151,8 (**1C**, C=N), 156,5 (**1C**, C14), 157,6 (**1C**, C6), 162,7 (**1C**, C4), 167,4 (**1C**, C1), 176,2 (**1C**, C12), 178,6 (**1C**, C7), 185,6 (**1C**, C11).

6.4 Chromocyclins

6.4.1 Attempted synthesis of enone **94**

6.4.1.1 5-((*tert*-butyldimethylsilyl)oxy)-1,4,4a,5,8,8a-hexahydronaphthalene-1,4-diol **rac-96**



4,40 g (41,1 mmol, 1,0 equiv.) *para*-benzoquinone were dissolved in a flame-fried 250-ml one-neck round-bottom flask in 50,0 ml dry CH_2Cl_2 and the formed solution treated at room temperature with diene **82** (10,6 g, 57,5 mmol, 1,4 equiv.). The reaction mixture was then stirred for two hours after which it was cooled to 0 °C and diluted with 50,0 ml dry MeOH. 30,6 g (82,2 mmol, 2,0 equiv.) $CeCl_3{\cdot}7H_2O$ were then added to the mixture at once followed by the portion-wise addition of a total of 3,12 g (82,2 mmol, 2,0 eq) $NaBH_4$ (*exothermic reaction*). The so formed mixture was then allowed to warm to room temperature and stirred for a total of 16 hours. Upon completion, 50 ml of water were added and the formed white precipitate dissolved by the gradual addition of aqueous HCl-solution (5 ml, 2M). The organic components were then extracted with EtOAc (3x50 ml), the combined phases dried over Na_2SO_4, concentrated under reduced pressure and the residue purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1→3:2 (v/v)) to give decalin **rac-96** (8,62 g, 29,1 mmol, **71%** (2 steps)) as an off-yellow oil.

$\mathbf{r_f}$ = 0,47 (PE/ EtOAc = 3:2 (v/v));

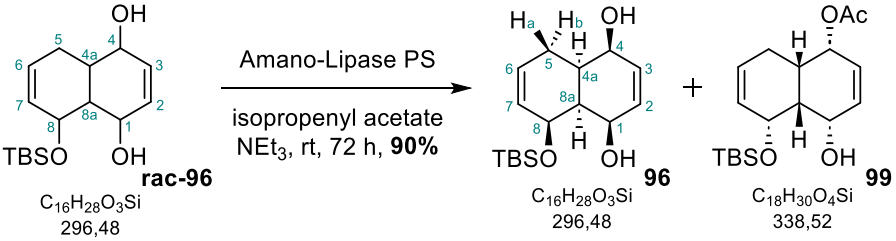
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{26,0}}$ = ±0,00° ($CHCl_3$, *14,90*);

HR-ESI-MS: $[C_{16}H_{28}O_3SiNa]^+$: m/z = 319,1705, found m/z = 319,1695;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,13 (s, **3H**, CH_3 (TBS)), 0,14 (s, **3H**, CH_3 (TBS)), 0,91 (s, **9H**, CH_3 (TBS)), 2,19–2,22 (br. m, **4H**, H4a, H5, H8a), 2,52 (br. s, **2H**, OH), 4,11–4,14 (m, **1H**) and 4,41 (m, **1H**): H1, H4, 4,59 (m, **1H**, H8), 5,65 (dt, *J* = 10,0, 2,6, 2,6 Hz, **1H**, H7), 5,74–5,78 (m, **1H**) and 5,83 (ddd, *J* = 10,2, 3,3, 1,6 Hz, **1H**, H2, H3), 5,89–5,92 (m, **1H**, H6);

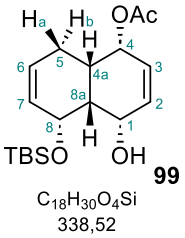
^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,8 (**1C**, CH_3 (TBS)), –4,1 (**1C**, CH_3 (TBS)), 18,2 (**1C**, $C_{quat.}$ (TBS)), 20,7 (**1C**, C5), 25,9 (**3C**, CH_3 (TBS)), 34,5 (**1C**, C4a), 40,2 (**1C**, C8a), 65,8 (**1C**, C1), 67,5 (**1C**, C4), 68,9 (**1C**, C8), 128,8 (**1C**, C7), 130,1 (**1C**, C2), 130,6 (**1C**, C6), 131,0 (**1C**, C3).

6.4.1.2 (1*S*,4*R*,4a*S*,5*S*,8a*R*)-5-((*tert*-butyldimethylsilyl)oxy)-1,4,4a,5,8,8a-hexahydronaphthalene-1,4-diol **96**



The previously prepared diol **rac-96** (8,62 g, 29,1 mmol, 1,0 equiv.), dissolved in a 100-ml one-neck round-bottom flask in 30,0 ml NEt_3, was treated at room temperature with 9,6 ml (88,2 mmol, 3,0 equiv.) isopropenyl acetate. Amano-Lipase PS (immobilized on diatomite; 8,62 g) was then added to the solution and the formed heterogeneous black-colored mixture stirred at room temperature, the progress of the reaction being monitored by NMR roughly every 24 hours. Upon completion (72 hours), the mixture was filtered over a sintered glass funnel[33] (MTBE) and the filtrate concentrated *in vacuo* to yield the crude product-mixture. Purification *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1→4:1 (v/v)) gave decalin-diol **96** (3,84 g, 13,0 mmol, **45%** (**95% ee**); $[\alpha]_D^{26,0}$ = +40,94° ($CHCl_3$, *5,70*)) and acetate **99** (4,40 g, 13,0 mmol, **45%** (**96% ee**)), both as off-yellow oils. The measured spectra of **96**, as well as other analytical parameters matched those previously reported (*chapter 6.4.1.1*) and will not be further discussed.

Analysis of the enantiomerically pure acetate **99**:



R_f = 0,69 (PE/ EtOAc = 4:1 (v/v));

$[\alpha]_D^{26,0}$ = +66,67° ($CHCl_3$, *6,00*);

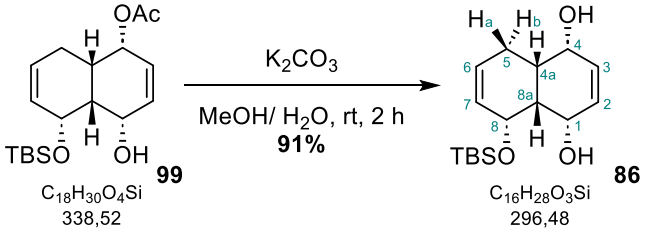
HR-ESI-MS: $[C_{16}H_{28}O_3SiNa]^+$: m/z = 361,1811, found m/z = 361,1796;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,11 (s, **3H**, CH_3 (TBS)), 0,13 (s, **3H**, CH_3 (TBS)), 0,92 (s, **9H**, CH_3 (TBS)), 1,83–1,87 (m, **1H**, Hb5), 2,10 (s, **3H**, CH_3), 2,14–2,20 (m, **1H**, H8a), 2,20–2,28 (m, **1H**, Ha5), 2,39–2,43 (m, **1H**, H4a), 2,94 (s, **1H**, OH), 4,39 (m, **1H**, H1), 4,61–4,64 (m, **1H**, H8), 5,32–5,34 (m, **1H**, H4), 5,57–5,61 (m, **1H**, H7), 5,63 (dq, *J* = 10,3, 1,5, 1,5, 1,5 Hz, **1H**, H2), and 5,81–5,85 (m, **1H**, H5), 5,95 (ddd, *J* = 10,3, 4,3, 2,4 Hz, **1H**, H3);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,8 (**1C**, CH_3 (TBS)), –4,6 (**1C**, CH_3 (TBS)), 18,2 (**1C**, $C_{quat.}$ (TBS)), 21,9 (**1C**, CH_3), 22,4 (**1C**, C5), 25,9 (**3C**, CH_3 (TBS)), 32,7 (**1C**, C4a), 40,1 (**1C**, C8a), 63,6 (**1C**, C1), 69,4 (**1C**, C8), 72,7 (**1C**, C4), 127,8 (**1C**, C2), 129,3 (**1C**, C3), 129,5 (**1C**, C6), 130,4 (**1C**, C7), 170,8 (**1C**, C=O).

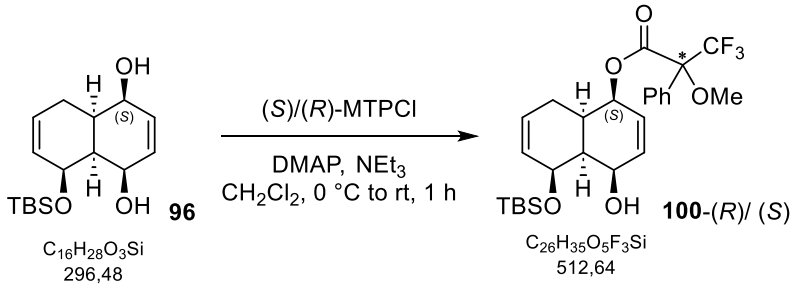
[33] Further washing of the immobilized enzyme with copious amounts of MTBE, followed by drying under high vacuum, enables its recycling for up to two more cycles.

6.4.1.3.1 (1*R*,4*S*,4a*R*,5*R*,8a*S*)-5-((*tert*-butyldimethylsilyl)oxy)-1,4,4a,5,8,8a-hexahydronaphthalene-1,4-diol **86**



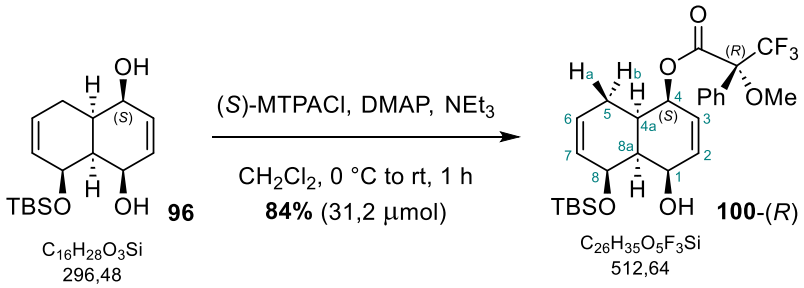
For the Mosher-ester analysis the previously prepared acetate **99** had to be hydrolyzed to diol **86**. For this 1,05 g (3,10 mmol, 1,0 equiv.) **99**, dissolved in a 10-ml one-neck round-bottom flask in 6,0 ml MeOH/ H_2O-mixture (9:1 (v/v)) were reacted with 0,83 g (6,20 mmol, 2,0 equiv.) K_2CO_3 at room temperature for two hours. Upon completion, the mixture was diluted with 5 ml of water, extracted with EtOAc (3x10 ml), the organic phases dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* flash column chromatography (SiO_2, PE/ EtOAc = 3:2 (v/v)) gave decalin-diol **86** (0,84 g, 2,82 mmol, **91%**; $[\alpha]_D^{22,5}$ = –39,28° ($CHCl_3$, *3,80*)) as an off-yellow oil. The measured spectra of **64**, as well as other analytic parameters matched those previously reported (*chapter 6.4.1.1*) and will not be further discussed.

6.4.1.3.2 Mosher-ester analysis of **96** and **86**



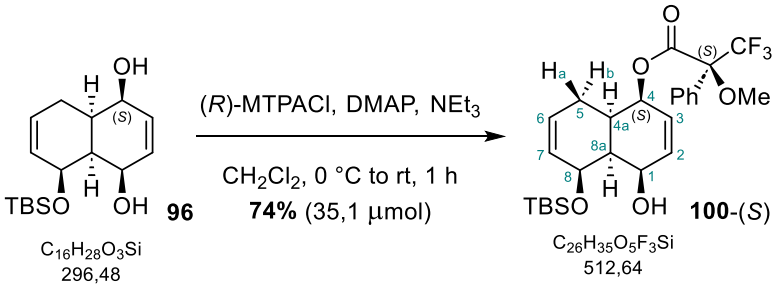
For the determination of the absolute configuration of diols **96** and **86** *via* Mosher's protocol[151], both (*S*)- and (*R*)-configured MTPA-esters of each enantiomer were synthesized. However, since the (*R*)-configured ester of diol **86** is mirroring the (*S*)-configured ester of diol **96** (and the (*S*)-configured, (*R*)), the discussion will be limited to the analysis of the desired enantiomer **96**.

general approach: In both instances each of the two enantiomers **96** and **86** (1,0 equiv.), dissolved at 0 °C in a suitable flame-dried one-neck round-bottom flask in dry CH_2Cl_2 (0,05M-solutions) were treated independently with dry NEt_3 (10,0 equiv.), DMAP (6,0 equiv.) and one of the two α-methoxy-α-(trifluoromethyl)phenylacetyl chlorides (Mosher's acid chlorides; 6,0 equiv.). The formed solutions were then allowed to warm to room temperature and stirred for one hour. NaOH-solution (aq., 2M; 10 ml/ ml solvent) was added upon completion, followed by a suitable amount of MTBE. The organic phase was subsequently washed in a separatory funnel with NaOH- (aq., 2M; 3x), sat., aqueous $NaHCO_3$- (3x) and $CuSO_4$-solutions (aq., 1M; 1x). Finally, the organic phase was washed once with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the desired Mosher-esters as colorless oils, which were characterized by means of NMR without being subjected to any further purifications. The results of the NMR-shift assignments of both (*R*)- and (*S*)-configured esters **96** are given below:



R_f = 0,74 (PE/ EtOAc = 4:1 (v/v));

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,12 (s, **3H**, CH_3 (TBS)), 0,13 (s, **3H**, CH_3 (TBS)), 0,93 (s, **9H**, CH_3 (TBS)), 1,66 (dt, *J* = 17,7, 5,1, 5,1 Hz, **1H**, Hb5), 2,17–2,21 (m, **2H**, Ha5, H8a), 2,39–2,42 (m, **1H**, H4a), 3,58 (d, *J* = 1,3 Hz, **3H**, OCH_3), 4,41 (br. s, **1H**, H1), 4,64 (ddd, *J* = 7,6, 3,8, 2,0 Hz, **1H**, H8), 5,56–5,59 (m, **1H**, H7), 5,59–5,61 (m, **1H**, H4), 5,68–5,72 (m, **1H**, H3), 5,73–5,76 (m, **1H**, H6), 6,00 (ddd, *J* = 10,4, 4,3, 2,3 Hz, **1H**, H2), 7,39–7,42 (m, **3H**, Ph), 7,54–7,56 (m, **2H**, Ph).

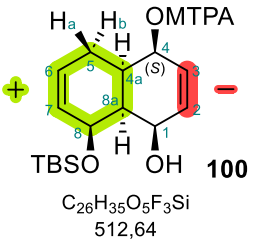


R_f = 0,52 (PE/ EtOAc = 4:1 (v/v));

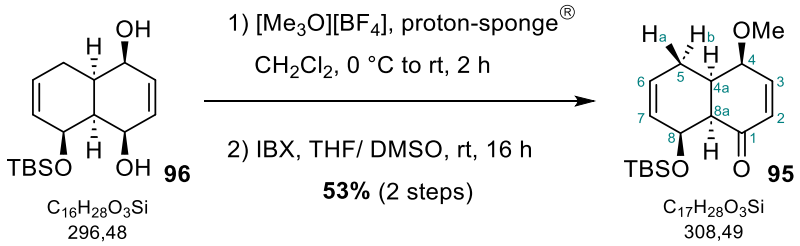
^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,12 (s, **3H**, CH_3 (TBS)), 0,14 (s, **3H**, CH_3 (TBS)), 0,93 (s, **9H**, CH_3 (TBS)), 1,82–1,86 (m, **1H**, Hb5), 2,20 (m, **1H**, H8a), 2,27 (m, **1H**, Ha5), 2,45–2,56 (m, **1H**, H4a), 3,53 (d, *J* = 1,1 Hz, **3H**, OCH_3), 4,41 (m, **1H**, H1), 4,65 (m, **1H**, H8), 5,59–5,62 (m, **3H**, H3, H4, H7), 5,81 (dd, *J* = 10,2, 5,2 Hz, **1H**, H6), 5,95–5,99 (m, **1H**, H2), 7,40–7,42 (m, **3H**, Ph), 7,52–7,52 (m, **2H**, Ph).

By applying Mosher's method,[151] the absolute configuration of the desired diol **96** could be successfully confirmed:

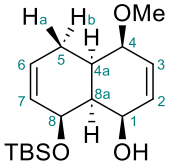
	δ (*R*-ester) [ppm]	**δ (*S*-ester)** [ppm]	**Δ_δ (δ_S–δ_R)** [ppm]
H1	4,41	4,41	±0,00
H2	6,00	5,90	–0,10
H3	5,70	5,61	–0,09
H4	5,60	5,61	+0,01
H4a	2,40	2,45	+0,05
Ha5	2,18	2,27	+0,09
Hb5	1,65	1,84	+0,19
H6	5,53	5,81	+0,28
H7	5,58	5,61	+0,03
H8	4,64	4,65	+0,01
H8a	2,18	2,20	+0,02



6.4.1.4 (4*S*,4a*R*,8*S*,8a*R*)-8-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-4a,5,8,8a-tetra-hydronaphthalen-1(4*H*)-one **95**



methylation (synthesis of (1*R*,4*S*,4a*R*,8*S*,8a*S*)-8-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-1,4,4a,5,8,8a-hexahydronaphthalen-1-ol **160**): For the first step of the synthesis of enone **95**, the previously prepared diol **96** (3,18 g, 10,7 mmol, 1,0 equiv.) was dissolved in a flame-dried 100-ml three-neck round-bottom flask in 54,0 ml dry CH_2Cl_2 and the solution cooled to 0 °C. Proton-sponge® (9,20 g, 42,2 mmol, 4,0 equiv.) was then added followed by Meerwein's salt (5,55 g, 37,5 mmol, 3,5 eq; freshly washed (*three times*) with dry CH_2Cl_2) and the so formed heterogenous mixture allowed to warm to room temperature. Stirring under an inert atmosphere was continued for two hours after which the mixture was diluted with aqueous HCl-solution (20 ml, 1M). Extraction with MTBE (3x100 ml), followed by drying of the combined organic phases over Na_2SO_4 and removal of the volatiles under reduced pressure afforded crude **160** (3,00 g, 9,66 mmol) as a pale yellow oil, which was further used without any additional purification steps.



R_f = 0,60 (PE/ EtOAc = 3:2 (v/v));

HR-ESI-MS: $[C_{17}H_{30}O_3SiNa]^+$: m/z = 333,1862, found m/z = 333,1862;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,12 (s, **3H**, CH_3 (TBS)), 0,14 (s, **3H**, CH_3 (TBS)), 0,93 (s, **9H**, CH_3 (TBS)), 1,89–1,95 (m, **1H**, Ha5), 2,05–2,06 (m, **1H**, H8a), 2,14–2,21 (m, **1H**, Hb5), 2,35–2,38 (m, **1H**, H4a), 2,95 (d, *J* = 2,4 Hz, **1H**, OH), 3,40 (s, **3H**, OCH_3), 3,80 (m, **1H**, H4), 4,38 (m, **1H**, H1), 4,65–4,67 (m, **1H**, H8), 5,58–5,61 (m, **1H**, H7), 5,74 (dd, *J* = 10,3, 1,5 Hz, **1H**, H3), 5,84–5,88 (m, **2H**, H2, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –4,8 (**1C**, CH_3 (TBS)), –4,6 (**1C**, CH_3 (TBS)), 18,2 (**1C**, $C_{quat.}$ (TBS)), 21,8 (**1C**, C5), 26,0 (**3C**, CH_3 (TBS)), 32,5 (**1C**, C4a), 40,4 (**1C**, C8a), 56,5 (**1C**, OCH_3), 64,2 (**1C**, C1), 69,9 (**1C**, C8), 79,1 (**1C**, C4), 127,9 (**1C**, C2), 129,6 (**1C**, C3), 130,1 (**1C**, C6), 130,3 (**1C**, C7).

IBX-oxidation (synthesis of **95**): 3,00 g (9,66 mmol, 1,0 equiv.) of the previously prepared crude methyl-ether **160** were dissolved in a flame-dried 100-ml one-neck round-bottom flask in 43,5 ml dry THF and 4,8 ml dry DMSO. To the formed solution were then added 8,12 g (29,0 mmol, 3,0 equiv.) IBX and the heterogenous mixture allowed to stir for 16 hours at room temperature. Upon completion, the orange-colored slurry was diluted with a small amount of MTBE and filtered over a pad of Celite®. Removal of the volatiles under reduced pressure yielded a thick oil, which was purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 4:1 (v/v)). Enone **95** (1,76 g, 5,71 mmol, **53%** (2 steps)) was finally collected as a thick, pale yellow oil.

R_f = 0,72 (PE/ EtOAc = 3:2 (v/v));

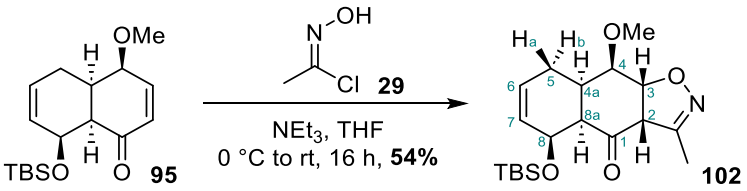
$[\alpha]_D^{28,0}$ = –22,14° ($CHCl_3$, *9,33*);

HR-ESI-MS: $[C_{17}H_{28}O_3SiNa]^+$: m/z = 331,1705, found m/z = 331,1704;

^{1}H-NMR (400 MHz; C_6D_6): δ [ppm] = 0,15 (s, **3H**, CH_3 (TBS)), 0,17 (s, **3H**, CH_3 (TBS)), 1,08 (s, **9H**, CH_3 (TBS)), 1,83–1,91 (m, **1H**, Ha5), 2,02 (ddt, *J* = 19,3, 9,8, 3,0, 3,0 Hz, **1H**, Hb5), 2,40–2,44 (m, **1H**, H4a), 2,56 (t, *J* = 4,3, 4,3 Hz, **1H**, H8a), 2,93 (s, **3H**, OCH_3), 3,60–3,61 (m, **1H**, H4), 4,42 (dt, *J* = 5,7, 2,4, 2,4 Hz, **1H**, H8), 5,35 (dt, *J* = 10,8, 3,5, 3,5 Hz, **1H**, H7), 5,73 (dd, *J* = 10,4, 2,5 Hz, **1H**, H2), 5,86 (dt, *J* = 10,3, 2,0, 2,0 Hz, **1H**, H6), 6,10 (dt, *J* = 10,4, 2,1, 2,1 Hz, **1H**, H3);

^{13}C-NMR (101 MHz; C_6D_6): δ [ppm] = –4,3 (**1C**, CH_3 (TBS)), –4,2 (**1C**, CH_3 (TBS)), 18,5 (**1C**, $C_{quat.}$ (TBS)), 22,5 (**1C**, C5), 26,1 (**3C**, CH_3 (TBS)), 38,8 (**1C**, C4a), 51,1 (**1C**, C8a), 56,1 (**1C**, OCH_3), 70,1 (**1C**, C8), 78,6 (**1C**, C4), 124,7 (**1C**, C7), 130,0 (**1C**, C2), 132,8 (**1C**, C6), 143,9 (**1C**, C3), 194,9 (**1C**, C1).

6.4.1.5 (3a*S*,4a*R*,5*S*,8a*R*,9*R*,9a*R*)-5-((*tert*-butyldimethylsilyl)oxy)-9-methoxy-3-methyl-4a,5,8,8a,9,9a-hexahydronaphtho[2,3-*d*]isoxazol-4(3a*H*)-one **102**



$C_{17}H_{28}O_3Si$
308,49

$C_{19}H_{31}O_4NSi$
365,54

The previously prepared decalin **95** (0,93 g, 3,00 mmol, 1,0 equiv.) was charged into a flame-dried 25-ml one-neck round-bottom flask and 3,0 ml dry THF were added. Dry NEt_3 (3,8 ml, 27,0 mmol, 9,0 equiv.) was then added and the solution cooled to 0 °C. The required amount of oxime **7** (1,96 g, 21,0 mmol, 7,0 equiv.) was freshly prepared in accordance with 6.2.1.5.1 and the whole reaction mixture added to the cooled solution *via* cannula. The reaction was then warmed to room temperature and stirred under an inert atmosphere for 16 hours. Upon completion, the reaction was diluted with 15 ml of water and the organic components extracted with MTBE (3x25 ml). The combined organic phases were dried over Na_2SO_4, concentrated *in vacuo* and the residue purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1 (v/v)) to yield diastereomerically pure **102** (0,59 g, 1,61 mmol, **54%**) as a thick, pale yellow oil.

R_f = 0,50 (PE/ EtOAc = 3:2 (v/v));

$[\alpha]_D^{28,0}$ = +35,00° ($CHCl_3$, *4,67*);

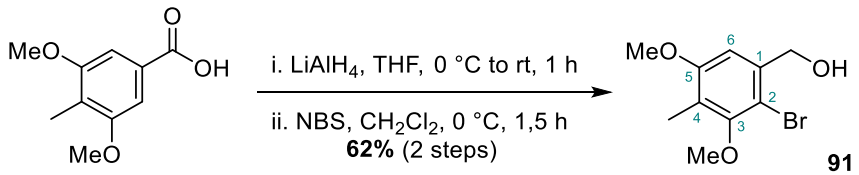
HR-ESI-MS: $[C_{19}H_{31}O_4NSiNa]^+$: m/z = 388,1920, found m/z = 388,1927;

^{1}H-NMR (400 MHz; C_6D_6): δ [ppm] = 0,04 (s, **3H**, CH_3 (TBS)), 0,08 (s, **3H**, CH_3 (TBS)), 0,98 (s, **9H**, CH_3 (TBS)), 1,44–1,49 (m, **1H**, Ha5), 1,74 (d, *J* = 1,4 Hz, **3H**, CH_3), 1,92–1,98 (m, **1H**, Hb5), 2,12 (dq, *J* = 10,6, 5,1, 5,1, 5,1 Hz, **1H**, H4a), 2,32 (t, *J* = 5,1, 5,1 Hz, **1H**, H8a), 3,23 (s, **3H**, OCH_3), 3,27–3,30 (m, **1H**, H4), 3,40 (d, *J* = 11,9 Hz, **1H**, H2), 4,17–4,20 (m, **1H**, H8), 4,61 (dd, *J* = 11,1, 6,6 Hz, **1H**, H3), 5,35 (ddt, *J* = 10,1, 5,0, 2,6, 2,6 Hz, **1H**, H6), 5,7 (ddt, *J* = 10,0, 3,7, 2,2, 2,2 Hz, **1H**, H6);

^{13}C-NMR (101 MHz; C_6D_6): δ [ppm] = –4,6 (**1C**, CH_3 (TBS)), –4,2 (**1C**, CH_3 (TBS)), 11,6 (**1C**, CH_3), 18,2 (**1C**, $C_{quat.}$ (TBS)), 23,0 (**1C**, C5), 25,9 (**3C**, CH_3 (TBS)), 36,2 (**1C**, C4a), 51,1 (**1C**, C8a), 57,6 (**1C**, OCH_3), 63,5 (**1C**, C2), 68,2 (**1C**, C8), 82,1 (**1C**, C4), 85,7 (**1C**, C3), 125,1 (**1C**, C6), 132,2 (**1C**, C7), 152,6 (**1C**, C=N), 199,0 (**1C**, C1).

6.4.2 Phthalide **89**

6.4.2.1 2-bromo-3,5-dimethoxy-4-methylbenzyl alcohol **91**

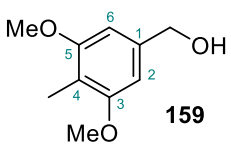


3,5-dimethoxy-4-methyl-benzoic acid (**90**)

$C_{10}H_{12}O_4$
196,20

$C_{10}H_{13}O_3Br$
261,12

LAH-reduction (synthesis of 3,5-dimethoxy-4-methylbenzyl alcohol **159**): A flame-dried 500-ml three-neck round-bottom flask was equipped with a 250-ml drop funnel to which a solution of 3,5-dimethoxy-4-methylbenzoic acid (**90**; 12,5 g, 63,7 mmol, 1,0 equiv.), dissolved in 106 ml dry THF was added. The round bottom-flask was then charged with 3,87 g (102 mmol, 1,6 equiv.) LAH in 127 ml dry THF and cooled to 0 °C. The acid-solution was then carefully added to the LAH-suspension after which the grey, cloudy solution was warmed to room temperature. After one hour of stirring, the alanate-excess was carefully neutralized at 0 °C by the consecutive addition of 4,0 ml of water, 4,0 ml of an aqueous NaOH-solution (15 wt%) and further 4,0 ml of water. Finally, the precipitated aluminum-salts were bound with Na_2SO_4 and filtered through a sintered glass funnel. The clear, colorless filtrate was then concentrated under reduced pressure to yield the desired raw benzyl alcohol **159** (7,78 g, 42,7 mmol) as a snow-white powder.[34]



$C_{10}H_{14}O_3$
182,22

m.p. = 58 °C [*lit.: 68-69 °C*][149];

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,10 (s, **3H**, CH_3), 3,76 (s, **6H**, OCH_3), 4,08 (s, **3H**, OH), 4,55 (s, **2H**, CH_2), 6,49 (s, **2H**, H2, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 7,8 (**1C**, CH_3), 55,2 (**2C**, OCH_3), 64,7 (**1C**, CH_2), 101,8 (**2C**, C2, C6), 112,8 (**1C**, C1), 139,5 (**1C**, C4), 158,0 (**2C**, C3, C5).

R_f = 0,54 (EtOAc);

The recorded spectroscopic data are in accordance with those reported by Sargent[149].

bromination (synthesis of **91**): The previously prepared alcohol **159** (7,78 g, 42,7 mmol, 1,0 equiv.) was dissolved under ambient conditions in a 250-ml one-neck round-bottom flask in 117 ml CH_2Cl_2.and cooled to 0 °C. To the formed solution a total of 7,61 g (42,7 mmol, 1,0 equiv.) NBS were added in three portions over a period of 45 minutes. Upon addition the reaction was allowed to stir for a total of 90 minutes while maintaining the initial temperature, after which 100 ml of water were added. The biphasic solution was then extracted with CH_2Cl_2 (3x100 ml), the combined organic phases dried over Na_2SO_4 and concentrated *in vacuo* to yield the crude brominated intermediate. Recrystallization from EtOH/ H_2O (40 ml; 1:1 (v/v)) gave pure product **91** (10,3 g, 39,3 mmol, **62%** (2 steps)) as an off-white powder.

R_f = 0,73 (PE/ EtOAc = 3:2 (v/v));

[34] By using DIBAl-H as a reducing agent, a slightly increased yield could be observed,[148] but the LAH-method was preferred due to cost-saving reasons.

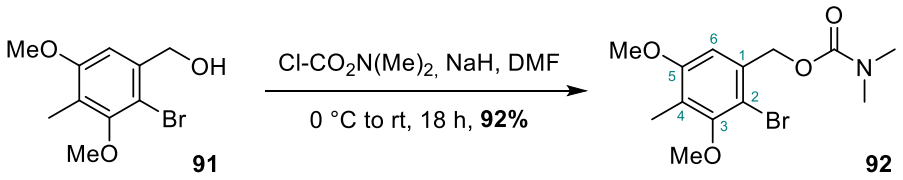
m.p. = 70 °C (EtOH/ H_2O);

HR-ESI-MS: $[C_{10}H_{13}O_3BrNa]^+$: m/z = 282,9946, found m/z = 282,9954;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,18 (s, **3H**, CH_3), 3,77 (s, **3H**, C3-OCH_3), 3,83 (s, **3H**, C5-OCH_3), 4,71 (s, **2H**, CH_2), 6,82 (s, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] =9,7 (**1C**, CH_3), 55,9 (**1C**, *C5*-OCH_3), 60,5 (**1C**, *C3*-OCH_3), 65,5 (**1C**, CH_2), 106,7 (**1C**, C6), 108,3 (**1C**, C1), 120,8 (**1C**, C4), 138,4 (**1C**, C2), 155,7 (**1C**, C3), 158,1 (**1C**, C5).

6.4.2.2 2-bromo-3,5-dimethoxy-4-methylbenzyl dimethylcarbamate **92**



$C_{10}H_{13}O_3Br$
261,12

$C_{12}H_{16}O_4NBr$
318,17

The previously prepared bromide **91** (7,37 g, 28,2 mmol, 1,0 equiv.) was charged in a flame-dried 100-ml one-neck round-bottom flask and dissolved in 43,4 ml dry DMF. The solution was then cooled to 0 °C and 1,69 g (42,4 mmol, 1,5 equiv.) NaH (60 wt% in mineral oil) were carefully added (*vigorous gas formation!*). After the addition was completed, the reaction was warmed to 60 °C and stirred for 30 minutes, after which it was cooled again to 0 °C. 4,7 ml (50,8 mmol, 1,8 equiv.) (*N*,*N*)-dimethylcarbamoyl chloride were added and the reaction stirred for 18 hours at room temperature after which it was carefully diluted with 50 ml of water. The organic components were then extracted with EtOAc (4x100 ml), the combined organic phases washed once with saturated, aqueous NaCl-solution and an aqueous LiCl-solution (10 wt%), dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was then recrystallized from MeOH (*approx.* 80 ml) to afford 8,67 g (26,1 mmol, **92%** (2 steps)) of the aimed carbamate **92** as a white powder

R_f = 0,60 (PE/ EtOAc = 3:2 (v/v));

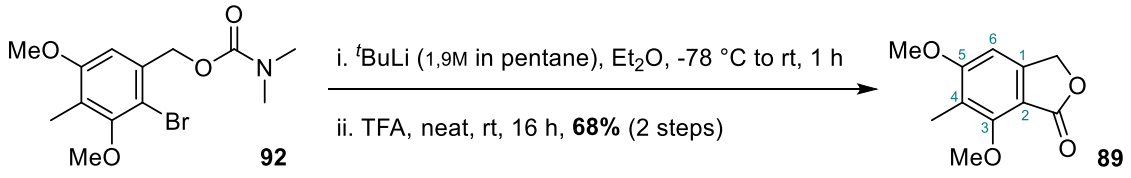
m.p. = 100 °C (MeOH);

HR-ESI-MS: $[C_{13}H_{18}O_4NBrNa]^+$: m/z = 354,0317, found m/z = 354,0312;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,17 (s, **3H**, CH_3), 2,94 (s, **6H**, $N(CH_3)_2$), 3,77 (s, **3H**, C3-OCH_3), 3,81 (s, **3H**, C5-OCH_3), 5,16 (s, **2H**, CH_2), 6,74 (s, **1H**, H6);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] =9,7 (**1C**, CH_3), 36,0 (**1C**, NCH_3), 36,6 (**1C**, NCH_3), 55,8 (**1C**, *C5*-OCH_3), 60,5 (**1C**, *C3*-OCH_3), 67,1 (**1C**, CH_2), 107,8 (**1C**, C6), 109,7 (**1C**, C1), 121,4 (**1C**, C4), 134,6 (**1C**, C2), 155,9 (**1C**, C3), 156,3 (**1C**, C=O), 157,7 (**1C**, C5).

6.4.2.3 5,7-dimethoxy-6-methylisobenzofuran-1(3*H*)-one **89**



$C_{13}H_{18}O_4NBr$
332,19

$C_{11}H_{12}O_4$
208,21

BuLi-mediated intramolecular acylation (synthesis of 6-(hydroxymethyl)-2,4-dimethoxy-(*N*,*N*),3-trimethylbenzamide **93**): The first step in the preparation of **89** consisted of treating 2,00 g (6,02 mmol, 1,0 equiv.) **43**, dissolved in 30,0 ml dry Et_2O in a flame-dried one-neck 100-ml round-bottom flask under an inert atmosphere with a ^{t}BuLi-solution (1,9M in pentane; 12,7 ml, 24,1 mmol, 4,0 equiv.) at –78 °C. After stirring the reaction for 20 minutes, the cooling bath was removed and the stirring continued for an additional hour at room temperature. Upon completion (TLC), any unreacted Li-base residues were carefully neutralized by the addition of wet MeOH (carefully added until no more gas-formation was observed) and 30 ml of water. The cloudy aqueous solution was extracted with EtOAc (4x100 ml) and the organic phases dried over Na_2SO_4. After concentration *in vacuo*, the obtained oily residue (1,37 g, 5,42 mmol), consisting mainly of title compound, was reacted further without any additional purification.

R_f = 0,35 (PE/ EtOAc = 3:2 (v/v));

HR-ESI-MS: $[C_{13}H_{19}O_4NNa]^+$: m/z = 276,1212, found m/z = 276,0673;

intramolecular esterification (synthesis of **89**): Lastly, the previously prepared crude benzyl alcohol **93** (1,37 g, 5,42 mmol, 1,0 equiv.) was charged into a 25-ml one-neck round-bottom flask under ambient conditions and 12,5 ml (163 mmol, 30,0 equiv.) TFA were added. The red solution was then stirred for 16 hours at room temperature, upon which 10 ml of water were added. The solution was then neutralized with 20 ml of a saturated, aqueous $NaHCO_3$-solution and extracted with EtOAc (3x100 ml). The combined organic phases were then dried over Na_2SO_4, concentrated under reduced pressure and the residue purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 7:3 (v/v)) to yield the aimed phthalide **89** (0,58 g, 2,79 mmol, **68%** (2 steps)) as a white solid.

R_f = 0,29 (PE/ EtOAc = 3:2 (v/v));

m.p. = 156 °C [*lit.: 174-176 °C*][149];

HR-ESI-MS: $[C_{11}H_{12}O_4Na]^+$: m/z = 231,0623, found m/z = 231,0634;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,14 (s, **3H**, C4-CH_3), 3,91 (s, **3H**, C5-OCH_3), 4,03 (s, **3H**, C3-OCH_3), 5,18 (s, **2H**, CH_2), 6,63 (s, **1H**, H6);

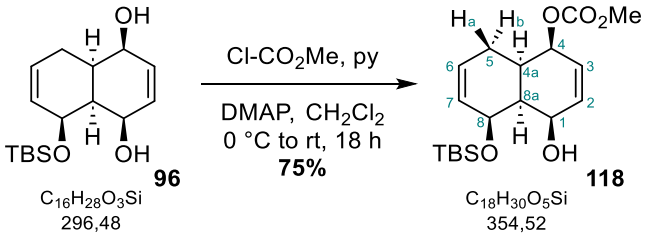
^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 8,7 (**1C**, C4-CH_3), 56,2 (**1C**, C5-OCH_3), 62,3 (**1C**, C3-OCH_3), 68,9 (**1C**, CH_2), 98,6 (**1C**, C6), 109,9 (**1C**, C1), 120,7 (**1C**, C4), 148,3 (**1C**, C2), 157,9 (**1C**, C3), 164,4 (**1C**, C5), 169,1 (**1C**, C=O).

The recorded spectroscopic data are in accordance with those reported by Sargent.[149]

6.5 Carbamidochelocardin

6.5.1 Attempted synthesis of enone **105**

6.5.1.1 (1*S*,4*R*,4a*S*,5*S*,8a*R*)-5-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-1,4,4a,5,8,8a-hexahydro-naphthalen-1-yl methyl carbonate **118**



Diol **96** (0,75 g, 2,53 mmol, 1,0 equiv.) was dissolved in a flame-dried 25-ml one-neck round-bottom flask in 5,0 ml dry CH_2Cl_2 and the solution cooled to 0 °C. DMAP (0,31 g, 0,25 mmol, 0,1 equiv.) was then added, followed by pyridine (1,0 ml, 2,65 mmol, 5,0 eq) and methyl chloroformate (1,0 ml, 2,65 mmol, 5,0 equiv.). The reaction was allowed to warm to room temperature and stirring continued under an inert atmosphere for a total of 18 hours. Upon completion, the solution was diluted with water (8 ml), the organic components extracted with MTBE (3x15 ml) and the combined ethereal phases dried over Na_2SO_4. Removal of the volatiles under reduced pressure afforded the crude mixture, which after purification *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1 (v/v)) afforded **118** (0,67 g, 1,90 mmol, **75%**) as a colorless oil.

R_f = 0,58 (PE/ EtOAc = 4:1 (v/v));

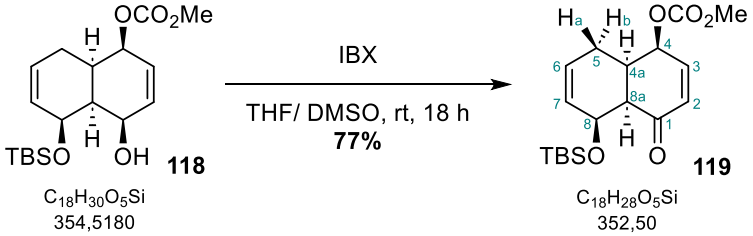
$[\alpha]_D^{23,6}$ = –33,86° ($CHCl_3$, *6,30*);

HR-ESI-MS: $[C_{18}H_{30}O_5SiNa]^+$: m/z = 377,1760, found m/z = 377,1746;

^{1}H-NMR (400 MHz; C_6D_6): δ [ppm] = –0,08 (s, **3H**, CH_3 (TBS)), –0,06 (s, **3H**, CH_3 (TBS)), 0,86 (s, **9H**, CH_3 (TBS)), 1,83 (p, *J* = 4,1, 4,1, 4,0, 4,0 Hz, **1H**, H8a), 2,00–2,07 (m, **1H**, Ha5), 2,41 (dd, *J* = 10,4, 5,5 Hz, **1H**, H4a), 2,61 (ddq, *J* = 16,7, 11,1, 2,8, 2,8, 2,6 Hz, **1H**, Hb5), 2,96 (d, *J* = 2,5 Hz, **1H**, OH), 3,39 (s, **3H**, OCH_3), 4,34 (ddd, *J* = 7,6, 3,7, 2,0 Hz, **1H**, H8), 4,41 (s, **1H**, H1), 5,28 (dq, *J* = 6,4, 2,2, 2,1, 2,1 Hz, **1H**, H4), 5,48–5,52 (m, **1H**, H7), 5,67 (dq, *J* = 10,3, 1,5, 1,5, 1,5 Hz, **1H**, H2), 5,69–5,74 (m, **1H**, H6), 5,98 (ddd, *J* = 10,3, 4,4, 2,4 Hz, **1H**, H2);

^{13}C-NMR (101 MHz; C_6D_6): δ [ppm] = –5,0 (**1C**, CH_3 (TBS)), –4,8 (**1C**, CH_3 (TBS)), 18,1 (**1C**, $C_{quat.}$ (TBS)), 22,6 (**1C**, C5), 25,9 (**3C**, CH_3 (TBS)), 33,5 (**1C**, C4a), 40,4 (**1C**, C8a), 54,3 (**1C**, OCH_3), 63,8 (**1C**, C1), 69,7 (**1C**, C8), 76,5 (**1C**, C4), 127,0 (**1C**, C2), 130,1 (**2C**, C6, C7), 130,4 (**1C**, C3), 155,9 (**1C**, C=O).

6.5.1.2 (1*S*,4a*R*,5*S*,8a*R*)-5-((*tert*-butyldimethylsilyl)oxy)-4-oxo-1,4,4a,5,8,8a-hexahydronaphthalen-1-yl methyl carbonate **119**



In a flame-dried 25-ml one-neck round-bottom flask, the previously prepared carbonate **118** (0,67 g, 1,90 mmol, 1,0 equiv.) was dissolved under an inert atmosphere in 6,0 ml dry THF and 0,6 ml dry DMSO. To the solution were then added 1,10 g (5,70 mmol, 3,0 equiv.) IBX and the heterogenous mixture allowed to stir for 18 hours at room temperature. Upon completion, the orange-colored slurry was diluted with MTBE and filtered over a pad of Celite®. Removal of the volatiles under reduced pressure yielded the crude product, which was purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1 (v/v)) to give enone **119** (0,52 g, 1,46 mmol, **77%**) as a thin yellow oil.

R_f = 0,58 (PE/ EtOAc = 4:1 (v/v));

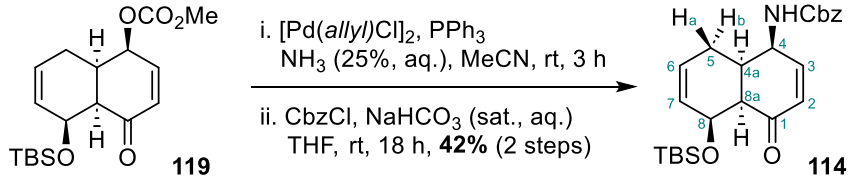
$[\alpha]_D^{23,0}$ = +15,38° ($CHCl_3$, *1,30*);

HR-ESI-MS: $[C_{18}H_{28}O_5SiNa]^+$: m/z = 375,1604, found m/z = 375,1589;

^{1}H-NMR (400 MHz; C_6D_6): δ [ppm] = 0,07 (s, **3H**, CH_3 (TBS)), 0,09 (s, **3H**, CH_3 (TBS)), 1,02 (s, **9H**, CH_3 (TBS)), 1,79 (ddd, *J* = 17,8, 6,2, 3,3 Hz, **1H**, Hb5), 1,93 (ddq, *J* = 18,8, 6,0, 3,2, 3,2, 2,7 Hz, **1H**, Ha5), 2,32 (p, *J* = 6,0, 6,0, 5,9, 5,9 Hz, **1H**, H4a), 2,50 (t, *J* = 4,7, 4,7 Hz, **1H**, H8a), 3,35 (s, **3H**, OCH_3), 4,30 (dt, *J* = 5,0, 2,5, 2,5 Hz, **1H**, H8), 5,23 (p, *J* = 2,5, 2,5, 2,5, 2,5 Hz, **1H**, H4), 5,30–5,35 (m, **1H**, H6), 5,71–5,74 (m, **1H**, H7), 5,74–5,77 (m, **1H**, H2), 6,11 (ddd, *J* = 10,3, 3,1, 1,3 Hz, **1H**, H3);

^{13}C-NMR (101 MHz; C_6D_6): δ [ppm] = –4,6 (**1C**, CH_3 (TBS)), –4,2 (**1C**, CH_3 (TBS)), 18,4 (**1C**, $C_{quat.}$ (TBS)), 23,6 (**1C**, C5), 26,1 (**3C**, CH_3 (TBS)), 36,6 (**1C**, C4a), 49,9 (**1C**, C8a), 54,4 (**1C**, OCH_3), 67,9 (**1C**, C8), 74,1 (**1C**, C4), 125,0 (**1C**, C6), 131,2 (**1C**, C7), 132,2 (**1C**, C2), 140,9 (**1C**, C3), 155,8 (**1C**, C=O), 195,3 (**1C**, C1).

6.5.1.3 benzyl ((1*S*,4a*R*,5*S*,8a*R*)-5-((*tert*-butyldimethylsilyl)oxy)-4-oxo-1,4,4a,5,8,8a-hexahydronaphthalen-1-yl)carbamate **114**



$C_{18}H_{28}O_5Si$
352,50

$C_{24}H_{33}O_4NSi$
427,62

Tsuji–Trost reaction (synthesis of (4*S*,4a*R*,8*S*,8a*R*)-4-amino-8-((*tert*-butyldimethylsilyl)oxy)-4a,5,8,8a-tetrahydronaphthalen-1(4*H*)-one): 20,0 mg (0,06 mmol, 4 mol-%) [Pd(*allyl*)Cl]$_2$ were charged under an inert atmosphere into a flame-dried 50-ml one-neck round-bottom flask. 18 ml dry acetonitrile were then added, followed by PPh_3 (0,04 g, 0,15 mmol, 0,1 equiv.) and the orange-colored solution stirred at room temperature for ten minutes. Enone **119** (0,52 g, 1,46 mmol, 1,0 equiv.), dissolved in 5,3 ml dry acetonitrile, was added to the mixture and after additional 30 minutes of stirring, 3,2 ml (14,6 mmol, 10,0 equiv.) concentrated, aqueous NH_3-solution were carefully added dropwise. Stirring was continued for three hours ($\mathbf{R_f}$ = 0,14 (EtOAc)), after which 10 ml of water were added to the reaction. Extraction with EtOAc (4x20 ml), followed by drying of the organic phases over Na_2SO_4 and concentration under reduced pressure gave title amine (0,25 g, 0,85 mmol) as an orange oil.

Cbz-protection (synthesis of **114**): The previously prepared crude amine (0,25 g, 0,85 mmol, 1,0 equiv.) was charged into a 10-ml one-neck round-bottom flask and 5,0 ml THF added. The solution was then treated with saturated, aqueous $NaHCO_3$-solution (1,2 ml), followed by CbzCl (0,2 ml, 1,02 mmol, 1,2 equiv.) and the reaction stirred at room temperature for 18 hours, after which 3 ml of water were added. After extraction with MTBE (3x15 ml), the combined organic phases were dried over Na_2SO_4, concentrated *in vacuo* and the residue purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 19:1→3:2 (v/v)) to yield **114** (0,26 g, 0,61 mmol, **47%** (2 steps)) as a pale yellow oil.

$\mathbf{R_f}$ = 0,60 (PE/ EtOAc = 3:2 (v/v));

$[\alpha]_D^{25,8}$ = +294,82° ($CHCl_3$, *10*,*30*);

HR-ESI-MS: $[C_{24}H_{33}O_4NSiNa]^+$: m/z = 450,2077, found m/z = 450,2073;

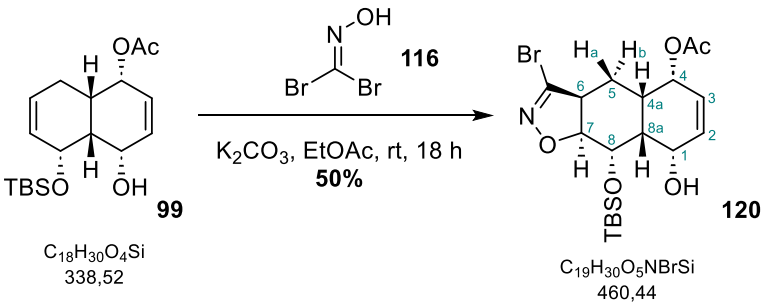
^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = –0,03 (s, **3H**, CH_3 (TBS)), 0,06 (s, **3H**, CH_3 (TBS)), 0,79 (s, **9H**, CH_3 (TBS)), 2,20 (dd, *J* = 19,3, 4,9 Hz, **1H**, Hb5), 2,28–2,35 (m, **1H**, Ha5), 2,67–2,70 (m, **1H**, H4a), 2,73–2,75 (m, **1H**, H8a), 4,44–4,47 (m, **1H**, H8), 4,54 (dt, *J* = 10,9, 5,6, 5,6 Hz, **1H**, H4), 5,09 (ABq, *J* = 12,3, 12,3, 4,1 Hz, **2H**, CH_2-ph), 5,66–5,68 (m, **1H**, H7), 5,80 (dq, *J* = 7,3, 3,0, 3,0, 2,4 Hz, **1H**, H6), 6,09 (d, *J* = 10,1 Hz, **1H**, H2), 6,69 (br. d, *J* = 10,6 Hz, **1H**, NH), 6,83 (dd, *J* = 10,1, 5,6 Hz, **1H**, H3), 7,29–7,38 (m, **5H**, ph);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –5,2 (**1C**, CH_3 (TBS)), –4,6 (**1C**, CH_3 (TBS)), 18,1 (**1C**, $C_{quat.}$ (TBS)), 25,8 (**3C**, CH_3 (TBS)), 26,2 (**1C**, C5), 31,0 (**1C**, C4a), 47,3 (**1C**, C4), 47,9 (**1C**, C8a), 64,5 (**1C**, C8), 66,7 (**1C**, CH_2-ph), 125,8 (**1C**, C7), 127,9 (**2C**, ph), 128,0 (**1C**, ph), 128,4 (**2C**, ph), 130,1 (**1C**, C6), 131,5 (**1C**, C2), 136,9 (**1C**, ph), 147,2 (**1C**, C3), 156,8 (**1C**, C=O), 200,3 (**1C**, C1).

6.5.2 1,3-dipolar cycloaddition-study towards a suitable precursor for enone **105**

6.5.2.1 Derivatives from acetate **99**

6.5.2.1.1 (3a*S*,4a*S*,5*R*,8*S*,8a*R*,9*S*,9a*S*)-3-bromo-9-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-3a,4,4a,5,8,8a,9,9a-octahydronaphtho[2,3-*d*]isoxazol-5-yl acetate **120**



In a flame-dried 10-ml one-neck round-bottom flask, 0,07 g (0,19 mmol, 1,0 equiv.) of acetate **99** were dissolved under an inert atmosphere in 2,0 ml dry EtOAc and the solution cooled to 0 °C. K_2CO_3 (0,16 g, 1,14 mmol, 6,0 equiv.) and 1,1-dibromoformaldoxime (**116**; 0,12 g, 0,57 mmol, 3,0 equiv.) were added and the heterogenous mixture allowed to stir for 18 hours at room temperature. Upon completion, water (5 ml) was added and the organic components extracted with EtOAc (3x 10 ml), dried over Na_2SO_4, concentrated under reduced pressure and purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1 (v/v)). Cycloaddition product **120** (0,45 g, 0,09 mmol, **50%**) was collected as a yellow oil.

R_f = 0,39 (PE/ EtOAc = 4:1 (v/v));

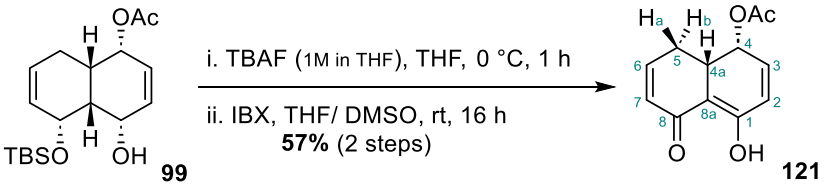
$[\alpha]_D^{22,3}$ = +56,99° ($CHCl_3$, *3,10*);

HR-ESI-MS: $[C_{38}H_{60}O_{10}N_2Br_2Si_2Na]^+$: m/z = 941,2052, found m/z = 941,1738;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,11 (s, **3H**, CH_3 (TBS)), 0,18 (s, **3H**, CH_3 (TBS)), 0,90 (s, **9H**, CH_3 (TBS)), 1,83–1,86 (m, **1H**, Ha5), 2,00–2,02 (m, **1H**, H4a), 2,03–2,05 (m, **1H**, Hb5), 2,09–2,12 (m, **1H**, H8a), 2,38 (s, **1H**, OH), 3,56–3,60 (m, **1H**, H6), 3,81 (t, *J* = 6,7, 6,7 Hz, **1H**, H8), 4,36–4,39 (m, **1H**, H1), 4,80 (dd, *J* = 9,9, 6,6 Hz, **1H**, H7), 5,33 (dt, *J* = 5,6, 2,3, 2,3 Hz, **1H**, H4), 5,61–5,65 (m, **1H**, H3), 5,93 (ddd, *J* = 10,3, 4,3, 2,4 Hz, **1H**, H2);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –5,0 (**1C**, CH_3 (TBS)), –4,4 (**1C**, CH_3 (TBS)), 18,1 (**1C**, $C_{quat.}$ (TBS)), 18,6 (**1C**, C5), 21,1 (**1C**, CH_3), 25,9 (**3C**, CH_3 (TBS)), 31,1 (**1C**, C4a), 41,7 (**1C**, C8a), 49,9 (**1C**, C6), 62,9 (**1C**, C1), 71,6 (**1C**, C4), 75,2 (**1C**, C8), 86,9 (**1C**, C7), 127,7 (**1C**, C3), 129,7 (**1C**, C2), 146,1 (**1C**, C=N), 170,4 (**1C**, C=O).

6.5.2.1.2 (1*R*,8a*S*)-4-hydroxy-5-oxo-1,5,8,8a-tetrahydronaphthalen-1-yl acetate **121**



$C_{18}H_{30}O_4Si$
338,5190

$C_{12}H_{12}O_4$
220,22

TBS-cleavage (synthesis of (1*R*,4*S*,4a*S*,5*R*,8a*S*)-4,5-dihydroxy-1,4,4a,5,8,8a-hexahydronaphthalen-1-yl acetate): Acetate **99** (0,30 g, 0,87 mmol, 1,0 equiv.) was dissolved in a flame-dried 10-ml one-neck round-bottom flask in 2,2 ml dry THF and the solution cooled to 0 °C. 1,1 ml (1,04 mmol, 1,2 eq) TBAF-solution (1M in THF) were then added drop-wise and the so formed blue-colored solution stirred at 0 °C for one hour ($\mathbf{R_f}$ = 0,11 (PE/ EtOAc = 3:2 (v/v)) after which it was diluted with aqueous $KHSO_4$ (2 ml, 1M). Extraction with EtOAc (3x15 ml), followed by drying of the organic phases over Na_2SO_4 and removal of the volatiles under reduced pressure afforded the crude product (0,16 g, 0,52 mmol) as a pale yellow oil.

IBX-oxidation (synthesis of **121**): The previously prepared crude acetate (0,16 g, 0,52 mmol, 1,0 equiv.) was charged into a flame-dried 10-ml one-neck round-bottom flask and dissolved under an inert atmosphere in 2,8 ml dry THF and 0,2 ml dry DMSO. IBX (0,58 g, 2,08 mmol, 4,0 equiv.) was then added and the heterogenous mixture allowed to stir for 16 hours at room temperature. Upon completion, the orange-colored slurry was diluted with MTBE and filtered over a pad of Celite®. Removal of the volatiles under reduced pressure, followed by purification *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1 (v/v)) gave title compound **121** (0,11 g, 0,49 mmol, **57%** (2 steps)) as a yellow oil.

$\mathbf{R_f}$ = 0,22 (PE/ EtOAc = 4:1 (v/v));

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{21,9}}$ = –248,48° ($CHCl_3$, *1,65*);

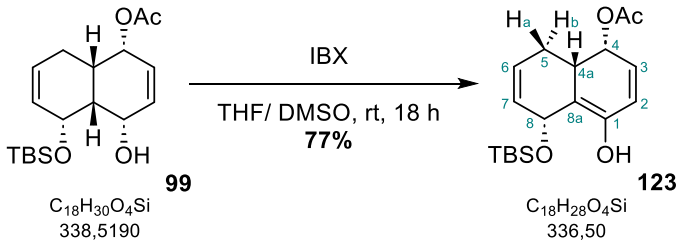
HR-ESI-MS: $[C_{12}H_{12}O_4Na]^+$: m/z = 243,0633, found m/z = 243,0638;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,04 (s, **3H**, CH_3), 2,38 (dddd, *J* = 18,0, 7,1, 6,3, 1,0 Hz, **1H**, Hb5), 2,51 (ddt, *J* = 17,8, 14,0, 2,8, 2,8 Hz, **1H**, Hb5), 3,17–3,24 (m, **1H**, H4a), 5,26–5,29 (m, **1H**, H4), 6,16 (ddd, *J* = 10,1, 3,1, 0,9 Hz, **1H**, H7), 6,32 (d, *J* = 9,9 Hz, **1H**, H2), 6,66 (ddd, *J* = 9,9, 5,8, 0,9 Hz, **1H**, H3), 6,76 (ddd, *J* = 10,0, 6,2, 2,5 Hz, **1H**, H6);[35]

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 20,9 (**1C**, CH_3), 24,7 (**1C**, C5), 33,5 (**1C**, C4a), 65,1 (**1C**, C4), 102,4 (**1C**, C8a), 127,8 (**1C**, C6), 130,2 (**1C**, C7), 135,6 (**1C**, C2), 144,7 (**1C**, C3), 170,7 (**1C**, C=O), 173,7 (**1C**, C1), 184,2 (**1C**, C8).

[35] Even though an initial high purity of the compound was determined by means of TLC-analysis, the measured spectra seem to bear slight traces of impurities, presumably caused by acid-induced decomposition of the sample. It is highly recommended that measurements be carried out in neutral solvents such as C_6D_6.

6.5.2.1.3 (1*R*,4a*S*,5*R*,8a*S*)-5-((*tert*-butyldimethylsilyl)oxy)-4-oxo-1,4,4a,5,8,8a-hexahydro-naphtha-len-1-yl acetate **123**



99 $C_{18}H_{30}O_4Si$ 338,5190

123 $C_{18}H_{28}O_4Si$ 336,50

In a flame-dried 10-ml one-neck round-bottom flask, 0,26 g (0,77 mmol, 1,0 equiv.) of acetate **99** were dissolved under an inert atmosphere in 2,2 ml dry THF and 0,3 ml dry DMSO. To the formed solution were then added 0,42 g (2,30 mmol, 3,0 equiv.) IBX and the heterogenous mixture allowed to stir for 18 hours at room temperature. Upon completion, the orange-colored slurry was diluted with MTBE and filtered over a pad of Celite®. Removal of the volatiles under reduced pressure yielded an orange-colored oil, which was purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1 (v/v)) to give title compound **123** (0,20 g, 0,59 mmol, **77%**) as a yellow oil.

R_f = 0,41 (PE/ EtOAc = 4:1 (v/v));

$[\alpha]_D^{23,5}$ = –50,00° ($CHCl_3$, *2,40*);

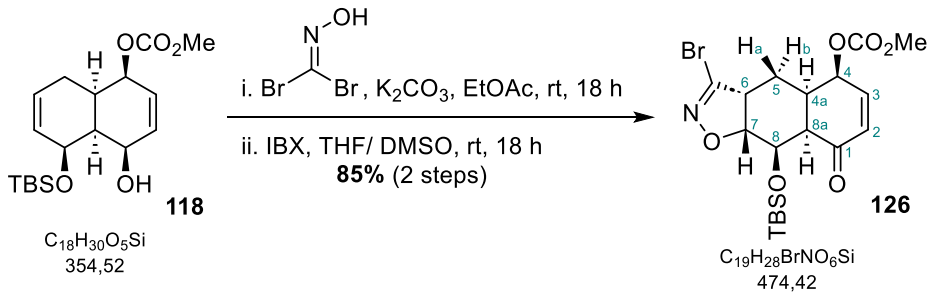
HR-ESI-MS: $[C_{18}H_{28}O_4SiNa]^+$: m/z = 359,1655, found m/z = 359,1641;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,09 (s, **6H**, CH_3 (TBS)), 0,91 (s, **9H**, CH_3 (TBS)), 2,05 (s, **3H**, CH_3), 2,31 (ddd, *J* = 17,9, 8,8, 5,8 Hz, **1H**, Ha5), 2,42–2,53 (m, **1H**, Hb5), 3,13–3,21 (m, **1H**, H4a), 5,34–5,37 (m, **1H**, H4), 6,15–6,25 (m, **2H**, H6, H7), 6,35 (d, *J* = 10,1 Hz, **1H**, H2), 7,06 (dd, *J* = 10,0, 6,0 Hz, **1H**, H3), 7,16–7,19 (m, **1H**, H8); [36]

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –3,4 (**2C**, CH_3 (TBS)), 18,1 (**1C**, $C_{quat.}$ (TBS)), 20,9 (**1C**, CH_3), 25,2 (**1C**, C5), 25,8 (**3C**, CH_3 (TBS)), 35,0 (**1C**, C4a), 65,5 (**1C**, C4), 124,2 (**1C**, C7), 129,5 (**1C**, C8a), 132,2 (**1C**, C8), 133,6 (**1C**, C6), 134,8 (**1C**, C2), 141,5 (**1C**, C3), 170,7 (**1C**, C=O), 185,5 (**1C**, C1).

[36] The measured spectra seem to bear traces of a decomposition product. Even though further investigations have not been conducted, it is highly recommended that measurements be carried out in neutral solvents such as C_6D_6.

6.5.2.2 Derivatives from carbonate **118**; synthesis of (3a*R*,4a*R*,5*S*,8a*R*,9*R*,9a*R*)-3-bromo-9-((*tert*- butyldimethylsilyl)oxy)-8-oxo-3a,4,4a,5,8,8a,9,9a-octahydronaphtho[2,3-*d*]isoxazol-5-yl methyl carbonate **126**



1,3-dipolar cycloaddition (synthesis of (3a*R*,4a*R*,5*S*,8*R*,8a*S*,9*R*,9a*R*)-3-bromo-9-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-3a,4,4a,5,8,8a,9,9a-octahydronaphtho[2,3-*d*]isoxazol-5-yl methyl carbonate): 65,0 mg (183 µmol, 1,0 equiv.) of carbonate **118** were dissolved under an inert atmosphere in a flame-dried 10-ml one-neck round-bottom flask in 2,0 ml dry EtOAc and the solution cooled to 0 °C. K_2CO_3 (152 mg, 1,10 mmol, 6,0 equiv.) and 1,1-dibromoformaldoxime (**116**; 118 mg, 550 µmol, 3,0 equiv.) were added and the heterogenous mixture allowed to stir for 18 hours at room temperature. Upon completion, water was added to the mixture and the organic components extracted with EtOAc (3x 10 ml). The combined organic phases were dried over Na_2SO_4 and the solvent removed under reduced pressure to yield the crude cyclo-addition product (75,0 mg, 158 µmol) as a yellow oil.

IBX-oxidation (synthesis of **126**): 75,0 mg (158 µmol ,1,0 equiv.) of the previously prepared product were dissolved under an inert atmosphere in a flame-dried 5-ml one-neck round-bottom flask into 0,9 ml dry THF and 0,1 ml dry DMSO. To the formed solution were then added 298 mg (315 µmol, 2,0 equiv.) IBX and the heterogenous mixture allowed to stir for 18 hours at room temperature. Upon completion, the orange slurry was diluted with MTBE and filtered over a pad of Celite®. Removal of the volatiles under reduced pressure followed by purification of the crude material *via* flash column chromatography (SiO_2, PE/ EtOAc = 8:2 (v/v)) gave title compound **126** (74,0 mg, 156 µmol, **85%** (2 steps)) as a yellow oil.

R_f = 0,36 (PE/ EtOAc = 4:1 (v/v));

$[\alpha]_D^{22,0}$ = +20,00° ($CHCl_3$, *1,00*);

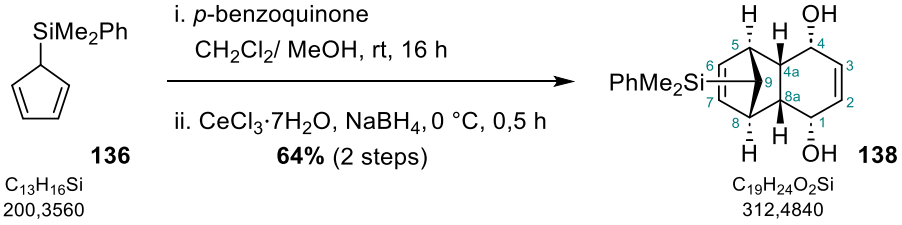
HR-ESI-MS: $[C_{19}H_{28}O_6NBrSiNa]^+$: m/z = 496,0767, found m/z = 496,0750;

^{1}H-NMR (400 MHz; C_6D_6): δ [ppm] = 0,09 (s, **3H**, CH_3 (TBS)), 0,18 (s, **3H**, CH_3 (TBS)), 0,95 (s, **9H**, CH_3 (TBS)), 1,44 (ddd, *J* = 14,8, 13,5, 6,4 Hz, **1H**, Ha5), 1,66–1,72 (m, **1H**, Hb5), 2,11 (ddtd, *J* = 13,8, 5,8, 4,3, 4,3, 2,2 Hz, **1H**, H4a), 2,41–2,43 (m, **1H**, H8a), 2,73 (ddd, *J* = 10,0, 6,3, 1,9 Hz, **1H**, H6), 3,37 (s, **3H**, OCH_3), 3,84 (dd, *J* = 6,5, 4,4 Hz, **1H**, H8), 4,76 (dd, *J* = 9,9, 6,5 Hz, **1H**, H7), 5,10–5,13 (m, **1H**, H4), 5,65 (dd, *J* = 10,4, 2,2 Hz, **1H**, H2), 6,01 (ddd, *J* = 10,3, 2,6, 1,6 Hz, **1H**, H3);

^{13}C-NMR (101 MHz; C_6D_6): δ [ppm] = –5,0 (**1C**, CH_3 (TBS)), –4,4 (**1C**, CH_3 (TBS)), 18,2 (**1C**, $C_{quat.}$ (TBS)), 19,1 (**1C**, C5), 26,0 (**3C**, CH_3 (TBS)), 35,7 (**1C**, C4a), 48,4 (**1C**, C8a), 49,5 (**1C**, C6), 54,7 (**1C**, OCH_3), 70,8 (**1C**, C8), 72,9 (**1C**, C4), 82,6 (**1C**, C7), 131,7 (**1C**, C2), 142,2 (**1C**, C3), 144,3 (**1C**, C=N), 155,3 (**1C**, C=O), 194,7 (**1C**, C1).

6.5.3 Enone **134**

6.5.3.1 (1*R*,4*S*,4a*S*,5*S*,8*R*,8a*R*,9*S*)-9-(dimethyl(phenyl)silyl)-1,4,4a,5,8,8a-hexahydro-1,4-methanonaphthalene-5,8-diol **138**



16,1 g (149 mmol, 1,03 equiv.) *para*-benzoquinone were dissolved in a flame-fried 500-ml one-neck round-bottom flask under an inert atmosphere in 102 ml dry CH_2Cl_2 and 204 ml dry MeOH and the mixture treated at room temperature with a solution of the cyclopentadiene-derived **136**[37] (29,0 g, 145 mmol, 1,00 equiv.) in 17,0 ml dry CH_2Cl_2 and 34,0 ml dry MeOH. The reaction was then stirred for 16 hours at room temperature after which it was cooled to 0 °C and 27,5 g (73,8 mmol, 0,51 equiv.) $CeCl_3{\cdot}7H_2O$ added. A total of 5,64 g (150 mmol, 1,03 eq) $NaBH_4$ were finally carefully added to the mixture portion wise (*exothermic reaction*) and the suspension stirred for additional 30 minutes. The mixture was then concentrated under reduced pressure to half of its original volume and 200 ml EtOAc added. Several washings of the solution were conducted with: 1x 250 ml aqueous citric acid- solution (1M), 2x 130 ml water, 3x 130 ml aqueous K_2CO_3-solution (1M with 10 wt% Na_2SO_3-solution (1M)) and lastly 1x 130 ml brine. The organic phase was then collected, dried over Na_2SO_4 and the solvent removed under reduced pressure to give the crude product. A recrystallization of the crude was successfully performed by first dissolving the solids in 550 ml boiling CH_2Cl_2 and the product precipitated by the addition of 800 ml PE. *Meso*-decalin **138** (27,7 g, 88,0 mmol, **61%** (2 steps)) was isolated as off-white crystals.

R_f = 0,13 (PE/ EtOAc = 3:2 (v/v));

m.p. = 101-104 °C [*lit.: 98-100 °C*][55];

HR-ESI-MS: $[C_{19}H_{24}O_2SiNa]^+$: m/z = 335,1443, found m/z = 335,1429;

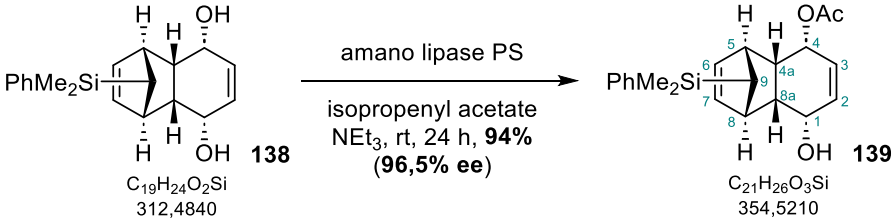
^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,21 (s, **6H**, Si-CH_3), 1,23–1,24 (m, **1H**, H9), 1,69 (br. s, **2H**, OH), 2,77–2,79 (m, **2H**, H4a, H8a), 3,10 (q, *J* = 1,6, 1,6, 1,6 Hz, **2H**, H5, H8), 4,40 (m, **2H**, H1, H4), 5,56 (d, *J* = 1,1 Hz, **2H**, H2, H3), 5,83 (t, *J* = 1,9, 1,9 Hz, **1H**, H6, H7), 7,32–7,33 (m, **3H**, ph), 7,43–7,45 (m, **2H**, ph);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –1,1 (**2C**, Si-CH_3), 45,4 (**2C**, C4a, C8a), 48,0 (**2C**, C5, C8), 52,0 (**1C**, C9), 66,9 (**2C**, C1, C4), 127,8 (**3C**, ph), 128,7 (**1C**, ph), 132,2 (**2C**, C2, C3), 133,7 (**2C**, ph), 135,2 (**2C**, C6, C7).

The synthesis was carried out by following the protocol described by Kummer et al.,[55] with the recorded spectroscopic data being in accordance with those reported by the authors.

[37] Freshly prepared and distilled in accordance with existing literature.[173] A full characterization of the product was omitted due to concerns regarding its stability.

6.5.3.2 (1*S*,4*R*,4a*R*,5*R*,8*S*,8a*S*,9*S*)-9-(dimethyl(phenyl)silyl)-8-hydroxy-1,4,4a,5,8,8a-hexahydro-1,4-methanonaphthalen-5-yl acetate **139**



Meso-diol **138** (14,9 g, 47,4 mmol, 1,0 equiv.), dissolved in a 250-ml one-neck round-bottom flask in 158 ml NEt_3 was treated at room temperature with Amano-Lipase PS (immobilized on diatomite; 14,9 g) and 18,3 ml (166 mmol, 3,5 equiv.) isopropenyl acetate and the heterogeneous black-colored mixture stirred for 24 hours at room temperature. Upon completion (progress monitored by TLC), the mixture was filtered over a sintered glass funnel[38] (MTBE) and the filtrate concentrated under reduced pressure. Purification *via* flash column chromatography (SiO_2, PE/ EtOAc = 4:1 (v/v)) gave the desymmetrized acetate **139** (15,8 g, 44,4 mmol, **94%**; **96,5% ee**) as an off-yellow powder.

R_f = 0,55 (PE/ EtOAc = 3:2 (v/v));

m.p. = 76 °C [*lit.: 68-72 °C*][55];

$[\alpha]_D^{21,2}$ = +48,92° ($CHCl_3$, *2,11*) [*lit.:* $[\alpha]_D^{23}$ = *+46,6° (*$CHCl_3$*, 1,00)*][55];

HR-ESI-MS: $[C_{21}H_{26}O_3SiNa]^+$: m/z = 377,1549, found m/z = 377,1533;

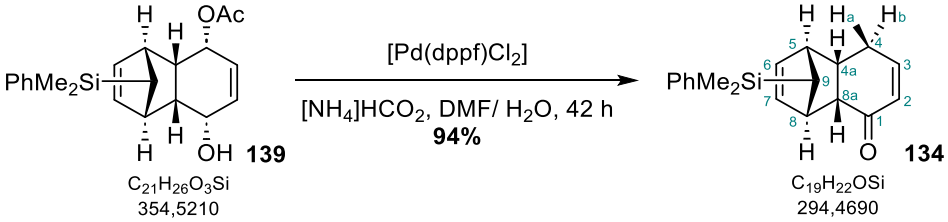
^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,19 (s, **6H**, Si-CH_3), 1,17 (t, *J* = 1,1, 1,1 Hz, **1H**, H9), 1,64 (br. s, **1H**, OH), 2,11 (s, **3H**, CH_3), 2,82–2,88 (m, **1H**, H8a), 2,91 (m, **1H**, H5), 2,99–3,04 (m, **1H**, H4a), 3,14 (m, **1H**, H8), 4,45 (dq, *J* = 8,6, 2,7, 2,7, 2,6 Hz, **1H**, H1), 5,25 (dddd, *J* = 10,3, 3,0, 2,1, 0,8 Hz, **1H**, H2), 5,34–5,38 (m, **1H**, H4), 5,40–5,44 (m, **1H**, H3), 5,69 (dd, *J* = 5,6, 2,8 Hz, **1H**, H6), 5,76 (dd, *J* = 5,6, 2,9 Hz, **1H**, H7), 7,31–7,34 (m, **3H**, ph), 7,41–7,45 (m, **2H**, ph);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –1,1 (**1C**, Si-CH_3), –1,2 (**1C**, Si-CH_3), 21,3 (**1C**, CH_3), 41,0 (**1C**, C4a), 44,2 (**1C**, C8a), 48,0 (**1C**, C8), 48,7 (**1C**, C4), 50,6 (**1C**, C9), 67,0 (**1C**, C1), 70,2 (**1C**, C4), 127,0 (**1C**, C2), 127,8 (**3C**, ph), 128,7 (**1C**, ph), 132,0 (**1C**, C3), 133,7 (**2C**, ph), 135,3 (**1C**, C6), 135,5 (**1C**, C7), 170,9 (**1C**, C=O).

The synthesis was carried out by following the protocol described by Kummer et al.,[55] with the recorded spectroscopic data being in accordance with those reported by the authors.

[38] Further washing of the immobilized enzyme with copious amounts of MTBE, followed by drying under high vacuum, enables its recycling for up to two more cycles.

6.5.3.3 (1*R*,4*S*,4a*S*,8a*R*,9*R*)-9-(dimethyl(phenyl)silyl)-4,4a,8,8a-tetrahydro-1,4-methanonaphthalen-5(1*H*)-one **134**



Warning! *The product was found to be highly thermolabile (decomposition via a retro–Diels–Alder path). Heating of the reaction, the isolated compound and solutions thereof above 20 °C must be strictly avoided.*

Acetate **139** (4,17 g, 11,7 mmol, 1,0 equiv.) was dissolved under ambient conditions in a 50-ml one-neck round-bottom flask in 29,0 ml DMF and 2,2 ml water. Ammonium formate (1,11 g, 17,5 mmol, 1,5 equiv.) was then added and the flask evacuate five times, after which a stream of argon was passed by cannula through the solution for two hours. Finally $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (0,38 g, 0,47 mmol, 3 mol-%) was added to the reaction at once and the solution stirred at room temperature for a total of 42 hours (reaction progress monitored *via* ^{1}H-NMR) after which it was diluted with 20 ml of water and 40 ml MTBE. Activated charcoal-pellets (3,0 g) were added and stirring continued for one hour. The mixture was then filtered over a thin pad of Celite® (MTBE; approx. 250 ml), the filtrate charged into a separatory funnel and washed as follows: 1x 300 ml water, 4x 300 ml brine, 2x 300 ml aqueous, saturated $NaHCO_3$-solution, followed by a last washing with 300 ml of water. The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo* (temperature kept bellow 20 °C) to yield the aimed product **134** (3,28 g, 11,1 mmol, **94%**) as a thick orange oil.
Due to a known acid-lability[55] of the compound, a chromatographic purification step could not be performed. The quality of the isolated product however seems to be satisfactory and therefor it can be used further without any additional purifications.

R_f = 0,83 (4 vol-% MeOH in CH_2Cl_2);

HR-ESI-MS: $[C_{19}H_{22}OSiNa]^+$: m/z = 317,1338, found m/z = 317,1347;

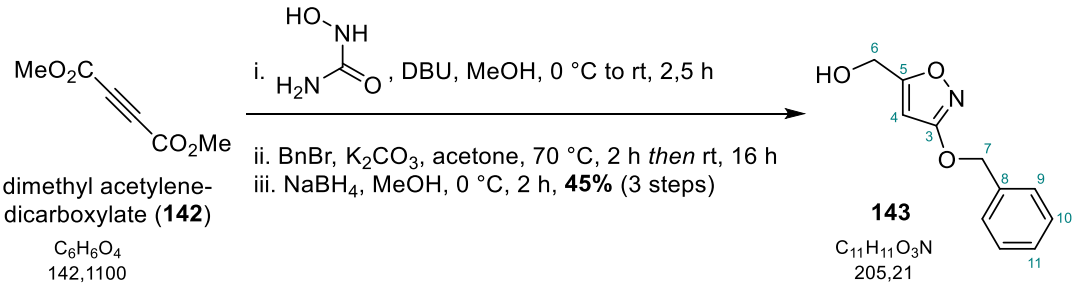
^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,20 (s, **3H**, Si-CH_3), 0,21 (s, **3H**, Si-CH_3), 1,21 (t, *J* = 1,1, 1,1 Hz, **1H**, H9), 1,98 (ddt, *J* = 21,0, 3,9, 2,6, 2,6 Hz, **1H**, Hb4), 2,56 (dddd, *J* = 20,9, 10,4, 3,9, 2,5 Hz, **1H**, Ha4), 2,74 (tt, *J* = 10,1, 10,1, 3,5, 3,5 Hz, **1H**, H4a), 2,92 (ddd, *J* = 9,9, 4,1, 0,8 Hz, **1H**, H8a), 3,07–3,09 (m, **1H**, H5), 3,48–3,51 (m, **1H**, H8), 5,84 (dt, *J* = 10,3, 2,4, 2,4 Hz, **1H**, H2), 5,98 (ddd, *J* = 5,7, 2,9, 1,0 Hz, **1H**, H7), 6,02–6,04 (m, **1H**, H6), 6,63 (dt, *J* = 10,2, 4,1, 4,1 Hz, **1H**, H3), 7,31–7,35 (m, **3H**, ph), 7,42–7,45 (m, **2H**, ph);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –1,4 (**2C**, Si-CH_3), 27,6 (**1C**, C4), 36,4 (**1C**, C4a), 50,7 (**1C**, C9), 51,3 (**1C**, C8a), 51,8 (**1C**, C8), 52,2 (**1C**, C5), 127,8 (**3C**, ph), 128,9 (**1C**, C2), 129,3 (**1C**, ph), 133,7 (**2C**, ph), 134,3 (**1C**, C6), 137,4 (**1C**, C7), 149,5 (**1C**, C3), 200,9 (**1C**, C1).

The synthesis was carried out by following the protocol described by Kummer et al.,[55] with the recorded spectroscopic data being in accordance with those reported by the authors.

6.5.4 Isoxazoles **145** and **141** (attempted)

6.5.4.1 3-benzyloxy-5-(hydroxymethyl)isoxazole **143**



cycloaddition (synthesis of methyl 3-hydroxyisoxazole-5-carboxylate): In a flame-dried 100-ml three-neck round-bottom flask, dimethyl acetylene-dicarboxylate (**142**; 8,1 ml, 65,7 mmol, 1,0 equiv.) was slowly added at 0 °C to solution consisting of hydroxyurea (5,00 g, 65,7 mmol, 1,0 equiv.) and DBU (4,9 ml, 32,9 mmol, 0,5 equiv.) in 66,0 ml dry MeOH. The red-colored solution was then stirred at room temperature for 150 minutes ($\mathbf{R_f}$ = 0,16 (PE/ EtOAc = 1:1 (v/v)) after which 20 ml aqueous HCl-solution (1M) were added. The reaction was further diluted with water and the organic components extracted with EtOAc (3x100 ml). The combined organic phases were then dried over Na_2SO_4, the volatiles removed under reduced pressure and the crude title compound (5,00 g, 34,9 mmol) isolated as a thick, brown oil, which was converted without further purification.

The synthesis was carried out by adapting the protocol described by Frey et al.[164]

benzylation (synthesis of methyl 3-(benzyloxy)isoxazole-5-carboxylate): The previously prepared isoxazole (5,00 g, 34,9 mmol, 1,0 equiv.) was dissolved at room temperature in a flame-dried 250-ml one-neck round-bottom flask in 100 ml dry acetone and K_2CO_3 (9,66 g, 41,9 mmol, 1,2 equiv.), followed by BnBr (5,0 ml, 41,9 mmol, 1,2 equiv.) added to the solution. The suspension was then stirred for two hours at 70 °C and additional 16 hours at room temperature ($\mathbf{R_f}$ = 0,62 (PE/ EtOAc = 3:2 (v/v)) after which the volatiles were removed under reduced pressure and the residue suspended in 50 ml of water. Extraction of the aqueous phase with Et_2O (3x60 ml), followed by the drying of the ethereal phases over Na_2SO_4 and concentration under reduced pressure gave 8,00 g (34, 0 mmol) of the crude title compound as a thick yellow oil which was used in the next transformation without any further purification.

ester-reduction (synthesis of **143**): The previously prepared benzylated isoxazole (8,00 g, 34,0 mmol, 1,0 equiv.) was dissolved at 0 °C in a flame-dried 100-ml one-neck round-bottom flask in 69,0 ml dry MeOH. $NaBH_4$ (1,56 g, 44,2 mmol, 1,2 equiv.) was added carefully to the mixture portion wise (*exothermic reaction*) and the suspension stirred for two hours at 0 °C. The reaction was then terminated by the addition of aqueous HCl-solution (2M, 15 ml) and 50 ml of water and the organic components removed under reduced pressure. The aqueous phase was then extracted with CH_2Cl_2 (5x50 ml), the combined organic phases dried over Na_2SO_4 and the solvent removed under reduced pressure. Purification of the crude mixture *via* flash column chromatography (SiO_2, PE/ EtOAc = 3:1→2:1→1,8:1 (v/v)) gave pure **143** (6,13 g, 29,9 mmol, **45%** (3 steps)) as a colorless oil, which upon standing formed a white, amorphous solid.

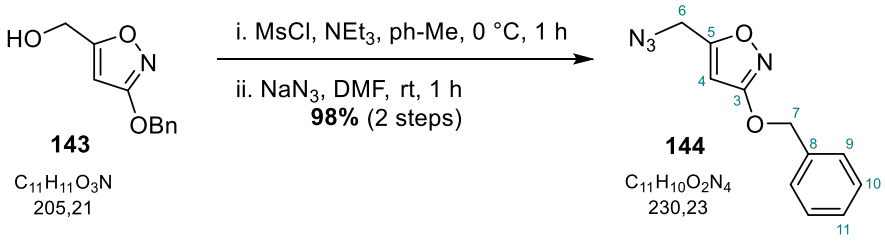
$\mathbf{r_f}$ = 0,30 (PE/ EtOAc = 3:2 (v/v));
HR-ESI-MS: $[C_{11}H_{11}O_3NNa]^+$: m/z = 228,0637, found m/z = 228,0632;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 2,01 (br. s, **1H**, OH), 4,66 (d, *J* = 0,7 Hz, **2H**, H6), 5,26 (s, **2H**, H7), 5,92 (s, **1H**, H4), 7,35–7,42 (m, **3H**, H10, H11), 7,43–7,46 (m, **2H**, H9);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 57,1 (**1C**, C6), 71,8 (**1C**, C7), 93,7 (**1C**, C4), 128,4 (**2C**, C11), 128,7 (**2C**, C10), 128,8 (**2C**, C9), 135,8 (**1C**, C8), 171,8 (**1C**, C3), 172,3 (**1C**, C5).

*The benzylation, as well as the reduction were carried out by following the protocols described by Kummer et al.[55]. The recorded spectroscopic data of **143** are in accordance with those reported by Caroff et al.[177]*

6.5.4.2 5-(azidomethyl)-3-(benzyloxy)isoxazole **144**



mesylation (synthesis of (3-(benzyloxy)isoxazol-5-yl)methyl methanesulfonate): 0,30 g (1,46 mmol, 1,0 equiv.) **143** were dissolved in 5,8 ml dry toluene at 0 °C in a flame-dried 10-ml one-neck round-bottom flask and 0,3 ml (1,90 mmol, 1,3 equiv.) dry NEt_3, followed by 0,15 ml (1,76 mmol, 1,2 equiv.) MsCl added. The formed cloudy solution was stirred for one hour at 0 °C and upon completion (**R_f** = 0,88 (4 vol-% MeOH in CH_2Cl_2)) diluted with 3 ml of water. The biphasic mixture was then extracted with EtOAc (3x10 ml) and the combined organic phases dried over Na_2SO_4. Removal of the volatiles under reduced pressure gave the crude title compound (0,41 g, 1,46 mmol) as a colorless oil, which was converted in the next step without further purification.

The reaction was carried out by following the protocol described by Kummer et al.[55]

azide-formation (synthesis of **144**): The previously prepared mesylate (0,41 g, 1,46 mmol, 1,0 equiv.) was dissolved at room temperature in a flame-dried 5-ml one-neck round-bottom flask in 1,8 ml dry DMF. NaN_3 (0,48 g, 7,31 mmol, 5,0 equiv.) was then added and the formed suspension allowed to stir for one hour. The reaction was then terminated by the addition of 2 ml of water. The aqueous phase was extracted with MTBE (3x5 ml), the ethereal phases dried over Na_2SO_4 and concentrated under reduced pressure to yield 0,33 g (1,43 mmol, **98%** (2 steps)) of azide **144** as a pale yellow oil, which, due to stability concerns, was not further purified.

R_f = 0,70 (PE/ EtOAc = 4:1 (v/v));

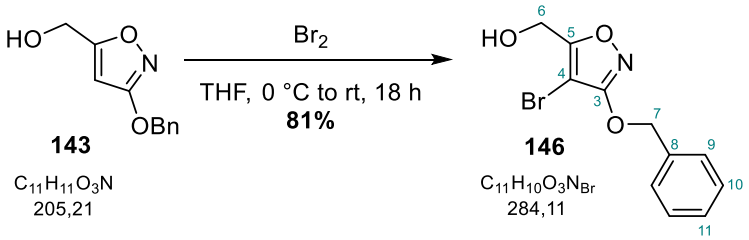
m.p. = < 0 °C;

HR-ESI-MS: $[C_{11}H_{10}O_2N_4Na]^+$: m/z = 253,0701, found m/z = 253,0711;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 4,34 (s, **2H**, H6), 5,28 (s, **2H**, H7), 5,96 (s, **1H**, H4), 7,36–7,46 (m, **5H**, H9, H10, H11);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 45,9 (**1C**, C6), 71,9 (**1C**, C7), 95,1 (**1C**, C4), 128,4 (**1C**, C11), 128,7 (**2C**, C10), 128,8 (**2C**, C9), 135,7 (**1C**, C8), 167,5 (**1C**, C5), 171,7 (**1C**, C3).

6.5.4.3 (3-(benzyloxy)-4-bromoisoxazol-5-yl)methanol **146**



Isoxazole precursor **143** (0,50 g, 2,46 mmol, 1,0 equiv.) was dissolved in a flame-dried 10-ml one-neck round-bottom flask in 4,9 ml dry THF and the cooled (0 °C) solution slowly (!) treated with 0,3 ml (0,94 g, 5,89 mmol, 2,4 equiv.) elemental bromine. Upon addition, the red-colored solution was slowly allowed to warm to room temperature and stirring continued under an inert atmosphere for a total of 18 hours. Finally, any unreacted bromine residues were quenched by the addition of a concentrated aqueous $NaHSO_3$-solution (approx. 4 ml). The biphasic mixture was diluted with 30 ml of MTBE and the aqueous phase separated. The ethereal solution was then washed with water (1x25 ml) and brine (1x25 ml), dried over Na_2SO_4 and concentrated under reduced pressure to give an oily residue. Purification *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1→4:1 (v/v)) afforded pure **146** (0,57g, 1,99 mmol, **81%**) as a pale yellow oil.[39]

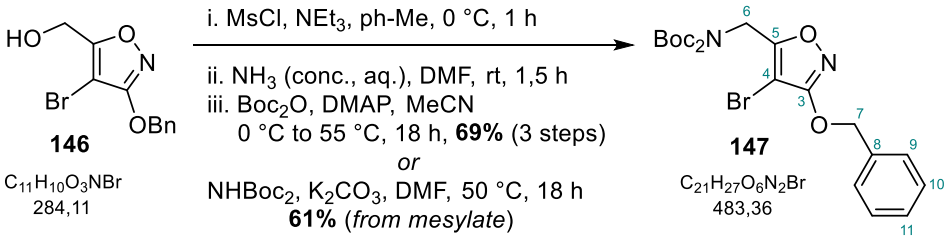
R_f = 0,50 (PE/ EtOAc = 3:2 (v/v));

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 4,68 (s, **2H**, H6), 5,33 (s, **2H**, H7), 7,36–7,42 (m, **3H**, H10, H11), 7,45–7,48 (m, **2H**, H9);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 55,5 (**1C**, C6), 72,3 (**1C**, C7), 128,4 (**3C**, C10, C11), 128,8 (**2C**, C9), 128,8 (**1C**, C4), 135,3 (**1C**, C8), 168,0 (**1C**, C5), 168,7 (**1C**, C3).

The synthesis was carried out by following the protocol described by Myers et al.,[165] with the recorded spectroscopic data being in accordance with those reported by the author.

6.5.4.4 *tert*-butyl ((3-(benzyloxy)-4-bromoisoxazol-5-yl)methyl)(*tert*-butoxycarbonyl) carbamate **147**



mesylation (synthesis of (3-(benzyloxy)-4-bromoisoxazol-5-yl)methyl methanesulfonate): 0,19 g (0,67 mmol, 1,0 equiv.) **146** were dissolved in 1,7 ml dry toluene at 0 °C in a flame-dried 5-ml one-neck round-bottom flask and 0,1 ml (0,87 mmol, 1,3 equiv.) dry NEt_3, followed by 0,1 ml (0,81 mmol, 1,2 equiv.) MsCl added. The cloudy solution was then stirred for one hour at 0 °C and, upon completion (**R_f** = 0,63 (PE/ EtOAc = 1:1 (v/v)) diluted by the addition of 2 ml of water. The biphasic mixture was then transferred to a separatory funnel, the aqueous phase extracted with EtOAc (3x8 ml)

[39] Several batches had to be prepared by following the described path, with the yields being highly reproducible throughout repetition.

and the combined organic phases dried over Na_2SO_4. Removal of the volatiles under reduced pressure gave the crude title compound (0,24 g, 0,66 mmol) as a colorless oil, which was converted in the next step without further purification.

amination (synthesis of (3-(benzyloxy)-4-bromoisoxazol-5-yl)methanamine): The previously prepared mesylate (0,24 g, 0,66 mmol, 1,0 equiv.) was dissolved at room temperature in a 5-ml one-neck round-bottom flask in 0,8 ml DMF. Concentrated, aqueous NH_3-solution (25 wt%, 0,1 ml, 5,30 mmol, 8,0 equiv.) was then added and the resulted solution allowed to stir for 90 minutes (**R_f** = 0,01 (PE/ EtOAc = 3:2 (v/v)). The reaction was then terminated by the addition of 2 ml of water. The aqueous phase was extracted with EtOAc (3x5 ml), the combined organic phases dried over Na_2SO_4 and concentrated under reduced pressure to yield 0,19 g (0,67 mmol) of the highly polar, crude amine-intermediate as a pale yellow oil which was used in the following step without any further purification.

Boc-protection (synthesis of **147**): The previously prepared amine (0,19 g, 0,67 mmol, 1,0 equiv.) was dissolved at 0 °C in a flame-dried 5-ml one-neck round-bottom flask in 0,8 ml dry MeCN. DMAP (0,10 g, 0,81 mmol, 1,2 equiv.) was then added, followed by the careful addition of 0,37 g (1,68 mmol, 2,5 equiv.) Boc_2O and the formed solution stirred for 18 hours at 55 °C. Finally, water (4 ml) was added to the reaction and the aqueous phase extracted with EtOAc (3x8 ml). Drying of the combined organic phases over Na_2SO_4 and concentration under reduced pressure, followed by purification *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1 (v/v)) gave 0,24 g (0,50 mmol, **69%** (3 steps)) of Boc-protected amine **147** as a pale yellow oil.

R_f = 0,67 (PE/ EtOAc = 3:2 (v/v));

HR-ESI-MS: $[C_{21}H_{27}O_6N_2BrNa]^+$: m/z = 505,0950, found m/z = 505,0954;

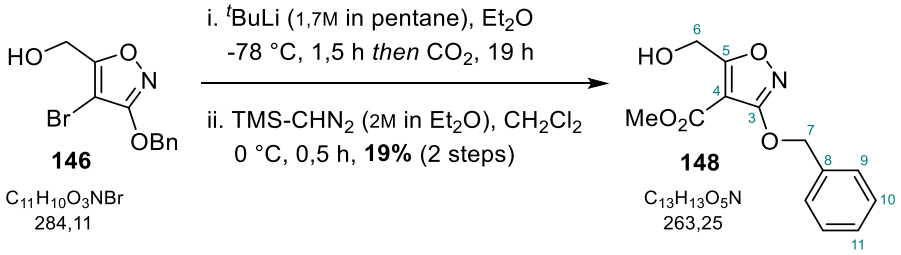
^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 1,49 (s, **18H**, CH_3), 4,85 (s, **2H**, H6), 5,31 (s, **2H**, H7), 7,35–7,41 (m, **3H**, H10, H11), 7,44–7,47 (m, **2H**, H9);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 28,2 (**6C**, CH_3), 41,9 (**1C**, C6), 72,1 (**1C**, C7), 83,6 (**2C**, C_{quat}), 128,3 (**1C**, C11), 128,7 (**2C**, C9), 128,7 (**2C**, C10), 135,4 (**1C**, C8), 151,6 (**1C**, C4), 152,7 (**2C**, C=O), 166,2 (**1C**, C5), 168,7 (**1C**, C3).

direct $NBoc_2$-insertion (synthesis of **83**): The previously prepared mesylate (0,15 g, 0,41 mmol, 1,0 equiv.) was dissolved at room temperature in a flame-dried 5-ml one-neck round-bottom flask in 0,5 ml dry DMF. K_2CO_3 (0,09 g, 0,62 mmol, 1,5 equiv.), followed by $NHBoc_2$ (0,12 g, 0,54 mmol, 1,3 equiv.) were then added to the solution. The suspension was allowed to stir at 50 °C for 18 hours after which water (3 ml) was added to the reaction. The aqueous phase was then extracted with MTBE (3x7 ml), the ethereal phases dried over Na_2SO_4, concentrated under reduced pressure and the residue purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1 (v/v)) to give 0,14 g (0,28 mmol, **66%**) of isoxazole **83** as a pale yellow oil. The recorded analytical data were in accordance with those reported above.

The synthesis was adapted from a protocol described by Oslund et al.[166]

6.5.4.5 methyl 3-(benzyloxy)-5-(hydroxymethyl)isoxazole-4-carboxylate **148**



carboxylation (synthesis of 3-(benzyloxy)-5-(hydroxymethyl)isoxazole-4-carboxylic acid): Isoxazole **146** (2,11 g, 7,43 mmol, 1,0 equiv.) was dissolved under an inert atmosphere at –78 °C in a 100-ml three-neck round-bottom flask in 68,0 ml dry Et_2O and treated with a 1,7M ^{t}BuLi-solution (10,5 ml, 17,8 mmol, 2,4 equiv.) over a period of 40 minutes. After the addition was completed, stirring of the orange solution was continued for additional 50 minutes after which a stream of CO_2 was passed through the reaction for three hours (discoloration of the solution and formation of a fine, white precipitate). Finally, the cooling bath was removed and the reaction stirred under a CO_2-atmosphere for additional 16 hours. Upon completion (**R_f** = 0,17 (PE/ EtOAc = 3:2 (v/v)), an aqueous 2M NaOH-solution (10 ml) was added and the mixture transferred to a separatory funnel. The aqueous phase was washed with MTBE (3x 25 ml), after which it was acidified by the addition of an aqueous1M HCl-solution (approx. 30 ml) and the free acid extracted with EtOAc (4x60 ml). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude acid (0,70 g, 28,09 mmol) as a pale yellow slurry.

esterification (synthesis of **148**): The previously prepared acid (0,70 g, 28,09 mmol) was dissolved at 0 °C in a flame-dried 25-ml one-neck round-bottom flask in 5,6 ml dry CH_2Cl_2 and a TMS-CHN_2-solution (2M in Et_2O; 3,1 ml, 61,8 mmol, 2,2 equiv.) added. The yellow solution was stirred for 30 minutes after which a small portion of MeOH was added and the volatiles removed under reduced pressure. The residue was then purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 9:1→4:1 (v/v)) to give the aimed methyl ester **85** (0,37 g, 1,42 mmol, **19%** (2 steps)) as an off-white solid.

R_f = 0,30 (PE/ EtOAc = 3:2 (v/v));

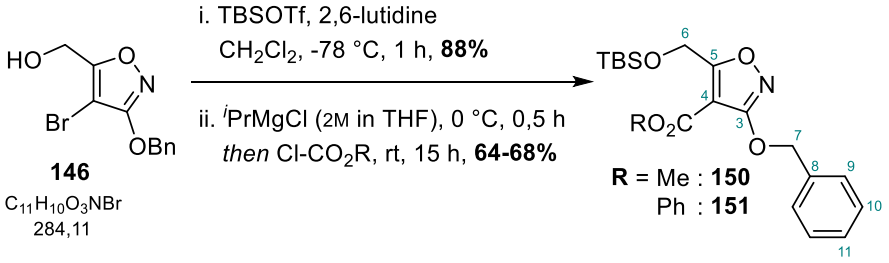
m.p. = 65 °C;

HR-ESI-MS: $[C_{13}H_{13}O_5NNa]^+$: m/z = 286,0691, found m/z = 286,0682;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 3,88 (s, **3H**, CH_3), 4,80 (s, **2H**, H6), 5,35 (s, **2H**, H7), 7,34–7,42 (m, **3H**, H10, H11), 7,45–7,48 (m, **2H**, H9);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 52,5 (**1C**, CH_3), 57,3 (**1C**, C6), 72,1 (**1C**, C7), 101,6 (**1C**, C4), 128,0 (**2C**, C9), 128,6 (**1C**, C11), 128,7 (**2C**, C10), 135,5 (**1C**, C8), 163,1 (**1C**, C=O), 168,7 (**1C**, C3), 179,0 (**1C**, C5).

6.5.4.6 3-(benzyloxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)isoxazole-4-carboxylates **150** and **151**



TBS-protection (synthesis of 3-(benzyloxy)-4-bromo-5-(((*tert*-butyldimethylsilyl)oxy)methyl)isoxazole): Benzyl alcohol **146** (5,84 g, 20,6 mmol, 1,0 equiv.) was dissolved at –78 °C in a flame-dried 50-ml one-neck round-bottom flask in 20,6 ml dry CH_2Cl_2. The solution was then treated subsequently with 2,6-lutidine (3,6 ml, 30,8 mmol, 1,5 equiv.) and TBSOTf (5,0 ml, 21,6 mmol, 1,05 equiv.) and the formed solution allowed to stir for one hour. Upon completion ($\mathbf{R_f}$ = 0,68 (PE/ EtOAc = 4:1 (v/v)), 20 ml of water were added and the organic components extracted with CH_2Cl_2 (3x25 ml). The dried organic phases (Na_2SO_4) were concentrated under reduced pressure and the residue flushed over a flash column (SiO_2, PE/ EtOAc = 49:1 (v/v)) to give 7,21 g (18,1 mmol, **88%**) of the title compound as a colorless oil. Furter characterizations of the product were omitted.

carboxylation (general approach towards esters **150** and **151**)[165] : The previously prepared isoxazole precursor (1,0 equiv.) was dissolved at 0 °C in a flame-dried one-neck round-bottom flask in dry THF (0,2M-solution). The solution was then treated with an ^{i}PrMgCl-solution (2M in THF, 2,0 equiv.) and the reaction stirred for 35 minutes after which chloroformate (neat; 2,5 equiv.) was added and stirring continued for additional 15 hours. Upon completion, the reaction was diluted with water and the aqueous phase extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, concentrated *in vacuo* and the residues purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 49:1 (v/v)) to give the desired esters as colorless oils.

151 ($C_{24}H_{29}O_5NSi$; 0,25 g, 0,56 mmol, **64%**):

$\mathbf{R_f}$ = 0,37 (4 vol-% MeOH in CH_2Cl_2);

HR-ESI-MS: $[C_{19}H_{24}O_2SiNa]^+$: m/z = 335,1443, found m/z = 335,1429;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,13 (s, **6H**, CH_3 (TBS)), 0,93 (s, **9H**, CH_3 (TBS)), 5,08 (s, **2H**, H6), 5,41 (s, **2H**, H7), 7,16–7,18 (m, **2H**, OPh-*o*), 7,28–7,31 (m, **1H**, OPh-*p*), 7,32–7,38 (m, **3H**, H10, H11), 7,39–7,43 (m, **2H**, OPh-*m*), 7,48–7,50 (m, **2H**, H9);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –5,3 (**2C**, CH_3 (TBS)), 18,5 (**1C**, $C_{quat.}$ (TBS)), 25,9 (**3C**, CH_3 (TBS)), 58,0 (**1C**, C6), 72,0 (**1C**, C7), 99,9 (**1C**, C4), 121,7 (**2C**, OPh-*o*), 126,3 (**1C**, OPh-*p*), 127,8 (**2C**, C9), 128,5 (**1C**, C11), 128,7 (**2C**, C10), 129,6 (**2C**, OPh-*m*), 135,6 (**1C**, C8), 150,2 (**1C**, OPh-*i*), 159,4 (**1C**, C=O), 169,1 (**1C**, C5), 178,3 (**1C**, C3).

150 ($C_{19}H_{27}O_5NSi$; 0,26 g, 0,69 mmol, **68%**):

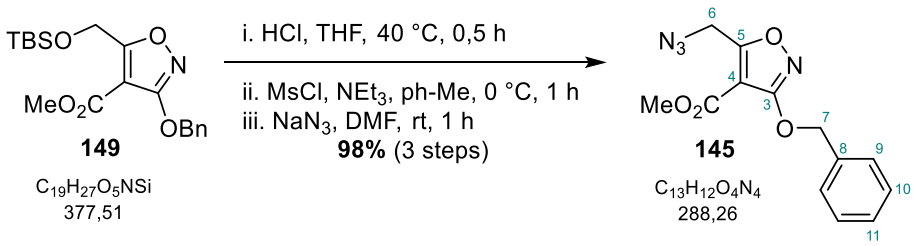
$\mathbf{R_f}$ = 0,32 (4 vol-% MeOH in CH_2Cl_2);

HR-ESI-MS: $[C_{19}H_{27}O_5NSiNa]^+$: m/z = 400,1556, found m/z = 400,1544;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 0,12 (s, **6H**, CH_3 (TBS)), 0,92 (s, **9H**, CH_3 (TBS)), 3,84 (s, **3H**, CH_3), 5,00 (s, **2H**, H6), 5,36 (s, **2H**, H7), 7,34–7,41 (m, **3H**, H10, H11), 7,46–7,49 (m, **2H**, H9);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = –5,3 (**2C**, CH_3 (TBS)), 18,5 (**1C**, $C_{quat.}$ (TBS)), 25,9 (**3C**, CH_3 (TBS)), 52,0 (**1C**, CH_3), 57,8 (**1C**, C6), 71,9 (**1C**, C7), 100,2 (**1C**, C4), 128,0 (**2C**, C9), 128,5 (**1C**, C11), 128,7 (**2C**, C10), 135,7 (**1C**, C8), 161,5 (**1C**, C=O), 169,0 (**1C**, C3), 177,3 (**1C**, C5).

6.5.4.7 methyl 5-(azidomethyl)-3-(benzyloxy)isoxazole-4-carboxylate **145**



TBS-cleavage (synthesis of **148**): 0,26 g (0,69 mmol, 1,0 equiv.) methyl ester **149** were dissolved under ambient conditions in a 10-ml one-neck round-bottom flask in 2,7 ml THF and 1,1 ml (0,03 mmol, 5 mol-%) aqueous, concentrated HCl-solution added. The solution was then stirred for 30 minutes ($\mathbf{r_f}$ = 0,30 (PE/ EtOAc = 3:2 (v/v)) at 40 °C after which it was quenched by the addition of 3 ml of a saturated, aqueous $NaHCO_3$-solution and diluted with 5 ml of water. The mixture was then extracted with EtOAc (3x10 ml) and the combined organic phases dried over Na_2SO_4. Removal of the volatiles under reduced pressure gave the crude **148** (0,18 g, 0,68 mmol) as an off-white solid, which was converted in the next step without further purification.

mesylation (synthesis of methyl 3-(benzyloxy)-5-(((methylsulfonyl)oxy)methyl)isoxazole-4-carboxylate): 0,18 g (0,68 mmol, 1,0 equiv.) **148** were dissolved in 2,7 ml dry toluene at 0 °C in a flame-dried 5-ml one-neck round-bottom flask and 0,1 ml (0,09 g, 0,89 mmol, 1,3 equiv.) dry NEt_3, followed by 0,05 ml (0,82 mmol, 1,2 equiv.) MsCl added. The cloudy solution was then stirred for one hour at 0 °C and, upon completion ($\mathbf{R_f}$ = 0,40 (PE/ EtOAc = 3:2 (v/v)), diluted by the addition of 3 ml of water. The mixture was then extracted with EtOAc (3x8 ml) and the combined organic phases dried over Na_2SO_4. Removal of the volatiles under reduced pressure gave the crude title compound (0,23 g, 0,68 mmol) as a colorless oil, which was converted in the next step without further purification.

azide-formation (synthesis of **145**): The previously prepared mesylate (0,08 g, 0,23 mmol, 1,0 equiv.) was dissolved at room temperature in a flame-dried 1-ml one-neck round-bottom flask in 0,3 ml dry DMF. NaN_3 (0,08 g, 1,17 mmol, 5,0 equiv.) was then added and the formed suspension allowed to stir for one hour. The reaction was then diluted with 1 ml of water and extracted with MTBE (3x5 ml). The combined ethereal phases were dried over Na_2SO_4 and concentrated under reduced pressure to yield 0,07 g (0,23 mmol, **98%** (3 steps)) of azide **145** as a pale yellow slurry, which, due to stability concerns was not further purified.

$\mathbf{R_f}$ = 0,88 (PE/ EtOAc = 3:2 (v/v));

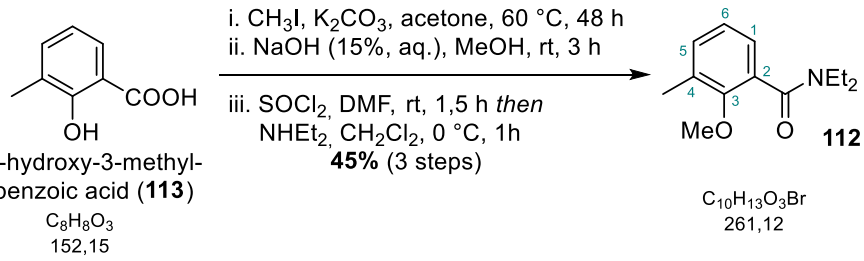
HR-ESI-MS: $[C_{13}H_{12}O_4N_4Na]^+$: m/z = 311,0756, found m/z = 311,0753;

^{1}H-NMR (400 MHz; C_6D_6): δ [ppm] = 3,28 (s, **3H**, CH_3), 3,92 (s, **2H**, H6), 5,15 (s, **2H**, H7), 7,05–7,07 (m, **1H**, H11), 7,09–7,13 (m, **2H**, H10), 7,30–7,32 (m, **2H**, H9);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 45,0 (**1C**, C6), 51,4 (**1C**, CH_3), 72,1 (**1C**, C7), 102,3 (**1C**, C4), 128,4 (**2C**, C9), 128,6 (**1C**, C10), 128,7 (**2C**, C11), 135,9 (**1C**, C8), 160,7 (**1C**, C=O), 169,1 (**1C**, C3), 173,2 (**1C**, C5).

6.5.5 Phthalide **106**

6.5.5.1 (*N*,*N*)-diethyl-2-methoxy-3-methylbenzamide **112**



2-hydroxy-3-methyl-benzoic acid (**113**)
$C_8H_8O_3$
152,15

$C_{10}H_{13}O_3Br$
261,12

methylation (synthesis of methyl 2-methoxy-3-methylbenzoate): A flame-dried 500-ml three-neck round-bottom flask, equipped with a condenser, was charged with 2-hydroxy-3-methylbenzoic acid **113** (20,0 g, 132 mmol, 1,0 equiv.) to which 250 ml dry acetone were added. K_2CO_3 (90,7 g, 657 mmol, 5,0 equiv.) and methyl iodide (73,5 ml, 1,18 mol, 9,0 equiv.) were added to the solution and the obtained mixture stirred at 60 °C for 48 hours. Upon completion, the volatiles were removed under reduced pressure and the residue portioned between 250 ml water and 250 ml EtOAc. Extraction with EtOAc (3x200 ml), followed by drying of the collected organic phases over Na_2SO_4 and concentration under reduced pressure gave the crude title compound (18,9 g, 105 mmol) as a thick yellow oil.

hydrolysis (synthesis of 2-methoxy-3-methylbenzoic acid): The previously prepared methyl ester (18,9 g, 105 mmol, 1,0 equiv.) was dissolved under ambient conditions in a 500-ml one-neck round-bottom flask in 250 ml MeOH, an aqueous NaOH-solution (15%; 130 ml) added and the mixture stirred for three hours at room temperature. The reaction was terminated by the addition of a 2M HCl-solution (20 ml), diluted with 100 ml of water and the organic components extracted with EtOAc (3x150 ml). The combined organic fractions were then dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude acid (16,6 g, 100 mmol) as an amorphous powder.

amidation (synthesis of **112**): The previously prepared benzoic acid derivative (16,6 g, 100 mmol, 1,0 equiv.) was reacted in a 250-ml one-neck round-bottom flask at 0 °C with thionyl chloride (72,5 ml, 1,00 mol, 10,0 equiv.) and DMF (0,3 ml, 3,30 mmol, 3,3 mol-%) for 1,5 hours. Upon completion, any unreacted thionyl chloride was coevaporated with toluene and the residue redissolved in a flame-dried 500-ml one-neck round-bottom flask in 350 ml dry CH_2Cl_2 and cooled to 0 °C. Diethylamine (38,3 ml, 370 mmol, 3,7 equiv.) was then gradually added and the reaction allowed to stir for one hour at 0 °C. Addition of water (150 ml), followed by extraction with EtOAc (4x 200 ml), drying of the organic phases over Na_2SO_4 and removal of the volatiles afforded the crude product-mixture. Purification *via* flash column chromatography (SiO_2, PE/ EtOAc = 4:1 (v/v)) gave pure **112** (15,4 g, 59,3 mmol, **45%** (3 steps)) as a thick colorless oil.

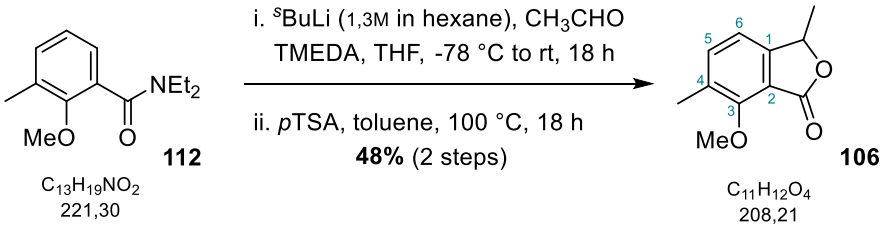
R_f = 0,16 (PE/ EtOAc = 4:1 (v/v));

HR-ESI-MS: $[C_{13}H_{19}O_2NNa]^+$: m/z = 244,1314, found m/z = 244,1310;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 1,02 (t, *J* = 7,1, 7,1 Hz, **3H**, CH_3), 1,26 (t, *J* = 7,1, 7,1 Hz, **3H**, CH_3), 2,29 (s, **3H**, C4-CH_3), 3,13–3,34 (m, **4H**, CH_2), 3,79 (s, **3H**, OCH_3), 7,00–7,07 (m, **2H**, H1, H6), 7,17–7,19 (m, **1H**, H5).

The sequence was carried out in accordance with the protocol described by Egan et al.,[153] with the recorded spectrum being in accordance with that reported by the authors.

6.5.5.2 7-methoxy-3,6-dimethylisobenzofuran-1(3*H*)-one **106**



BuLi-mediated alkylation (synthesis of (*N*,*N*)-diethyl-6-(1-hydroxyethyl)-2-methoxy-3-methyl-benzamide): A ^{s}BuLi-solution (1,3M in hexane; 54,6 ml, 71,0 mmol, 1,2 equiv.), diluted with 148 ml dry THF in a flame-dried one-neck 500-ml round-bottom flask was treated at –78 °C with TMEDA (10,6 ml, 71,0 mmol, 1,2 equiv.) under an inert atmosphere. After stirring for five minutes, amide **112** (15,4 g, 59, 2 mmol, 1,0 equiv.), dissolved in 60,0 ml dry THF was added *via* cannula and stirring continued for one hour. Lastly, 4,3 ml (76,9 mmol, 1,3 equiv.) freshly distilled acetaldehyde[40] were added, the cooling bath removed and stirring continued for additional 18 hours at room temperature. Upon completion, any unreacted Li-base residues were carefully neutralized by the addition of aqueous 1M HCl-solution (20 ml) and 200 ml of water. The cloudy aqueous solution was extracted with EtOAc (4x250 ml) and the organic phases dried over Na_2SO_4. After concentration *in vacuo*, the obtained oily residue (7,85 g, 29,6 mmol), consisting mainly of the title compound, was reacted further without any additional purification.

intramolecular esterification (synthesis of **106**): Lastly, the previously prepared crude benzyl alcohol (7,85 g, 29,6 mmol, 1,0 equiv.) was charged into a 100-ml one-neck round-bottom flask under ambient conditions and 37,0 ml toluene added. 0,28 g (1,48 mmol, 5 mol-%) *p*TSA monohydrate were then added and the formed red solution stirred for 18 hours at 100 °C, upon which 50 ml of water were added. The solution was then neutralized by the addition of a small portion of saturated, aqueous $NaHCO_3$-solution and extracted with EtOAc (4x80 ml). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure and the residue purified *via* flash column chromatography (SiO_2, PE/ EtOAc = 7:3 (v/v)) to yield phthalide **106** (5,91 g, 28,4 mmol, **48%** (2 steps)) as a pale yellow oil.

R_f = 0,46 (PE/ EtOAc = 4:1 (v/v));

HR-ESI-MS: $[C_{11}H_{12}O_3Na]^+$: m/z = 215,0684, found m/z = 215,0676;

^{1}H-NMR (400 MHz; $CDCl_3$): δ [ppm] = 1,59 (d, *J* = 6,7 Hz, **3H**, CH_3), 2,31 (s, **3H**, C4-CH_3), 4,08 (s, **3H**, OCH_3), 5,45 (q, *J* = 6,6, 6,4 Hz, **1H**, CH-ph), 6,99 (d, *J* = 7,6 Hz, **1H**, H6), 7,46 (d, *J* = 7,4 Hz, **1H**, H5);

^{13}C-NMR (101 MHz; $CDCl_3$): δ [ppm] = 15,7 (**1C**, C4-CH_3), 20,8 (**1C**, CH_3), 62,3 (**1C**, OCH_3), 76,7 (**1C**, CH-ph), 116,0 (**1C**, C6), 116,9 (**1C**, C1), 131,7 (**1C**, C4), 137,6 (**1C**, C5), 151,7 (**1C**, C2), 157,5 (**1C**, C3), 168,4 (**1C**, C=O).

The sequence was inspired by the protocol described by Egan et al.[153]

[40] A suitable amount of raw acetaldehyde was treated with one drop of conc. H_2SO_4, and the distillation was carried out under an inert atmosphere at standard pressure.

7 References

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8 Appendix

8.1 Generalities

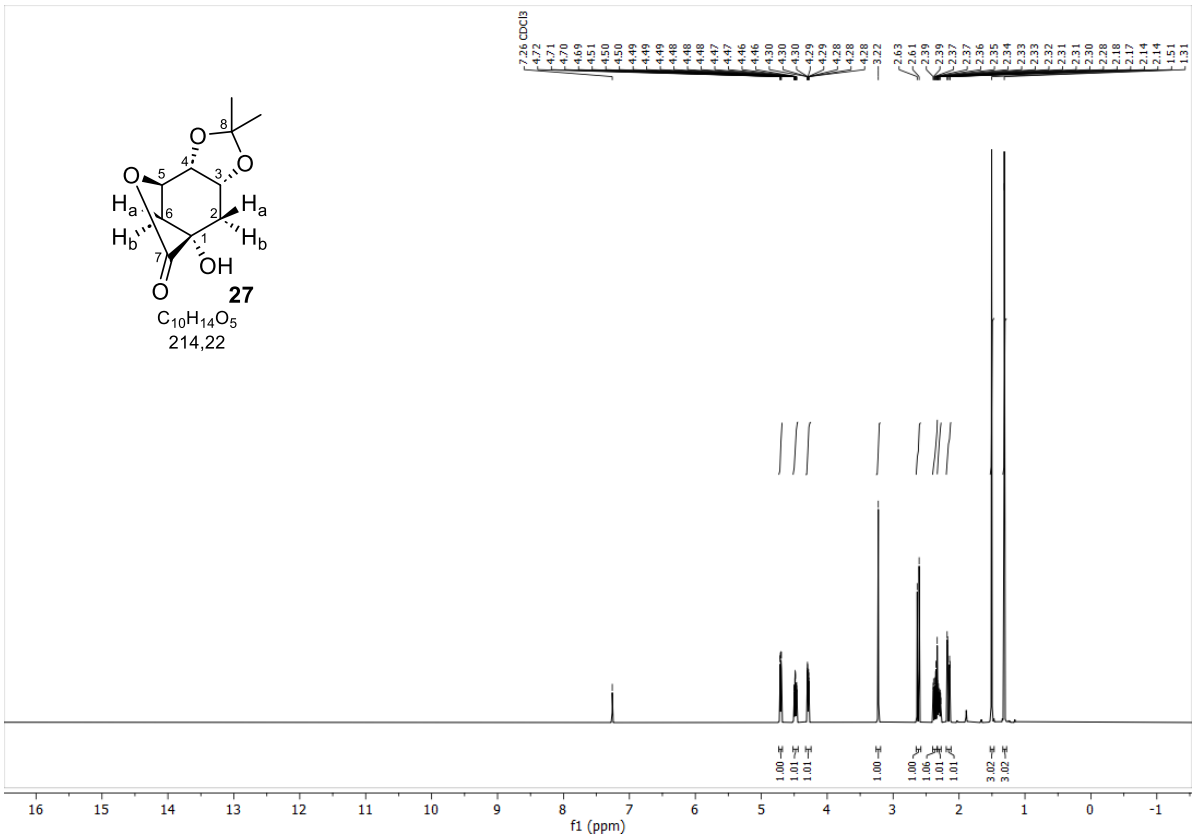
The following chapter comprises the recorded ^{1}H- and ^{13}C-NMR spectra of the previously prepared compounds addressed in chapter 6. Even though crucial for an accurate signal assignment, measured 2D-spectra are reported only for demethylpremitrhamycinone-enamine **56** and were otherwise omitted. The reported data was grouped in accordance with the structure of chapter 6, each subchapter comprising both 1H- and 13C-spectra, and in some instances, NOE- or 2D-spectra, of the title compounds. For complex spectra, a zoom-in cut, showing relevant multiplets by missing blank regions, is provided alongside the full ^{1}H-spectrum of the compound. It is important to stress that no further alterations were carried out in order to modify or enhance the quality of the spectra. Furthermore, for selected compounds, relevant NOE-spectra are shown to support the signal assignments and confirm their absolute configuration.

As it was mentioned in chapter 6.1, all spectra were calibrated by using the solvent residual signal, relevant signals, as well as solvent-traces being clearly indicated. It is important to note that, despite repeated chromatographic steps, the purity of some products has proven to be lacking at times. The measured spectra are nevertheless given in the following chapter, with the trace impurities being, in most instances, successfully removed later in the synthesis, thus allowing a seamless characterization of the more advanced intermediates.

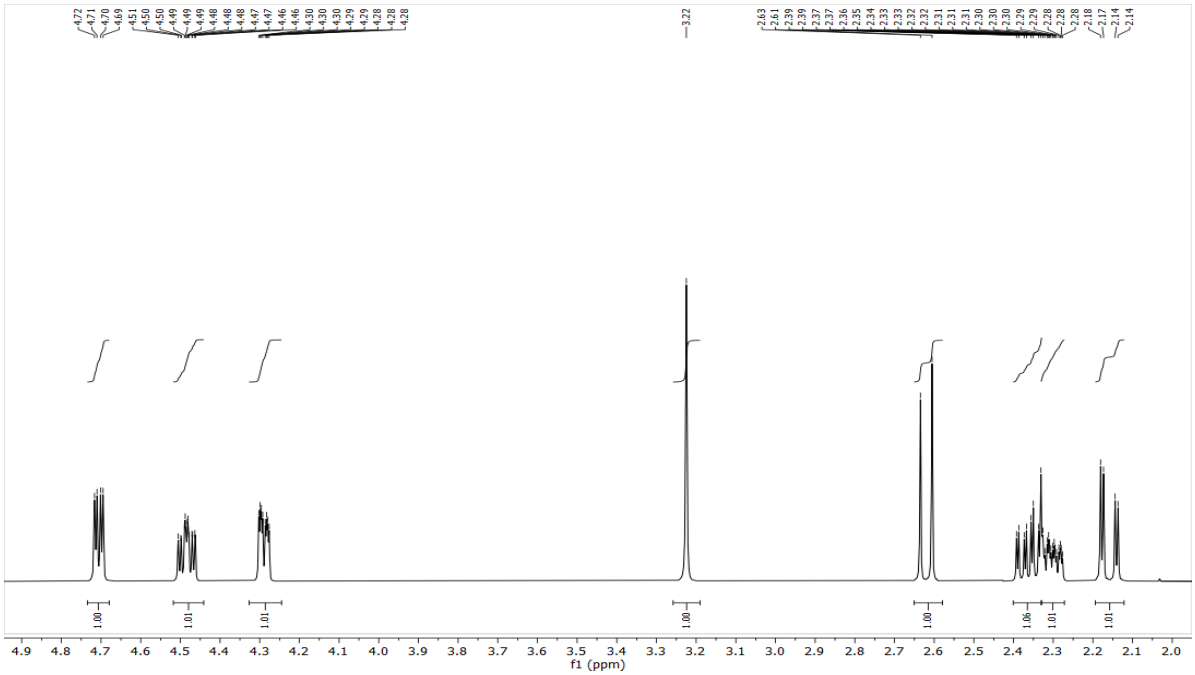
8.2 Demethylpremithramycinone

8.2.1 Enones **32, 64** and **35**

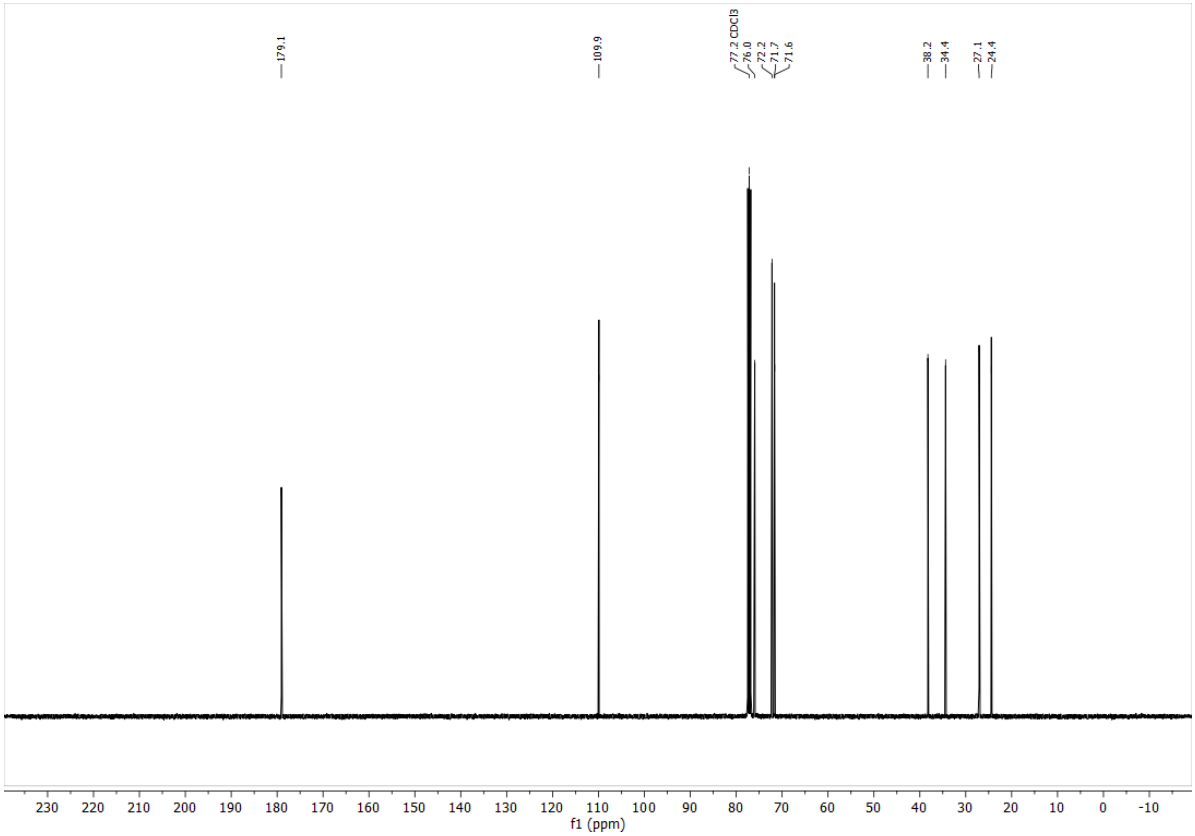
8.2.1.1 (3a*R*,4*R*,7*S*,8a*R*)-7-hydroxy-2,2-dimethyltetrahydro-4,7-methano[1,3]dioxolo- [4,5-*c*]-oxepin-6(4*H*)-one **27**



*^{1}H-spectrum of **27** in $CDCl_3$.*



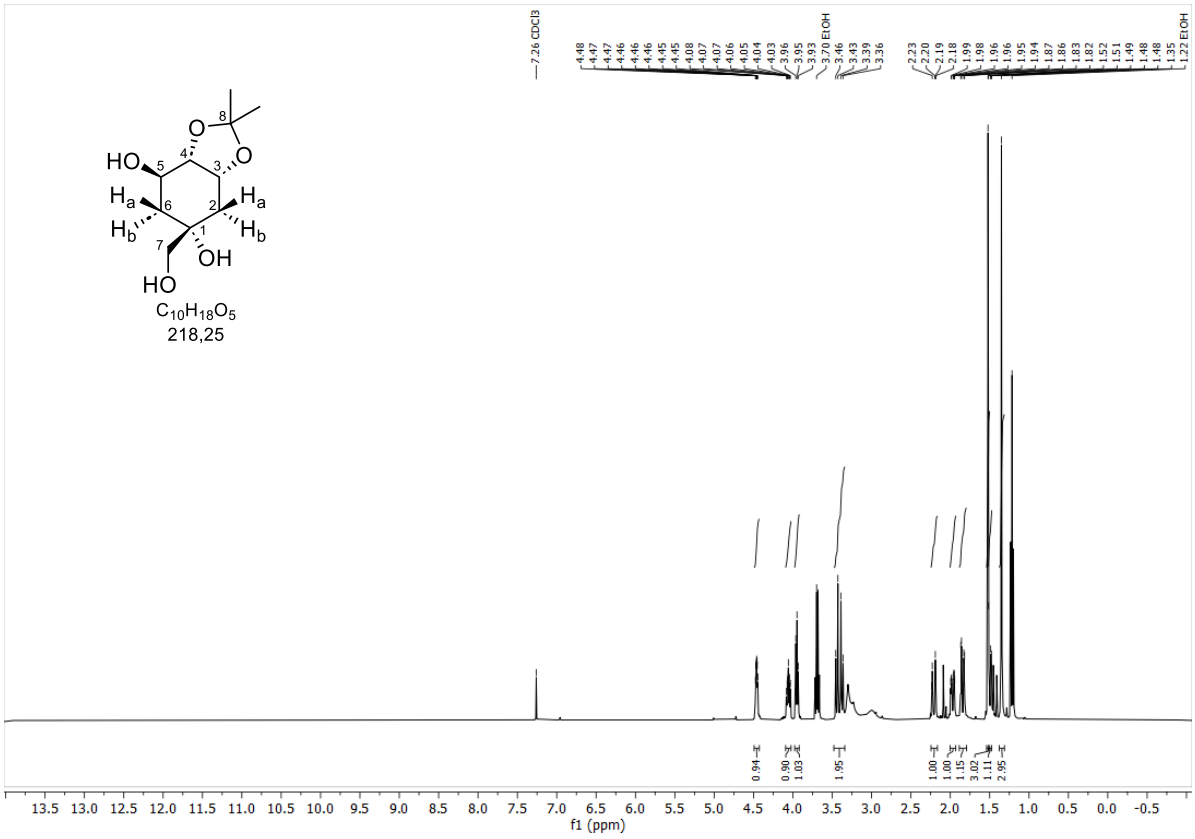
*^{1}H-spectrum of **27** in $CDCl_3$ (region between 2,0-4,9 ppm).*



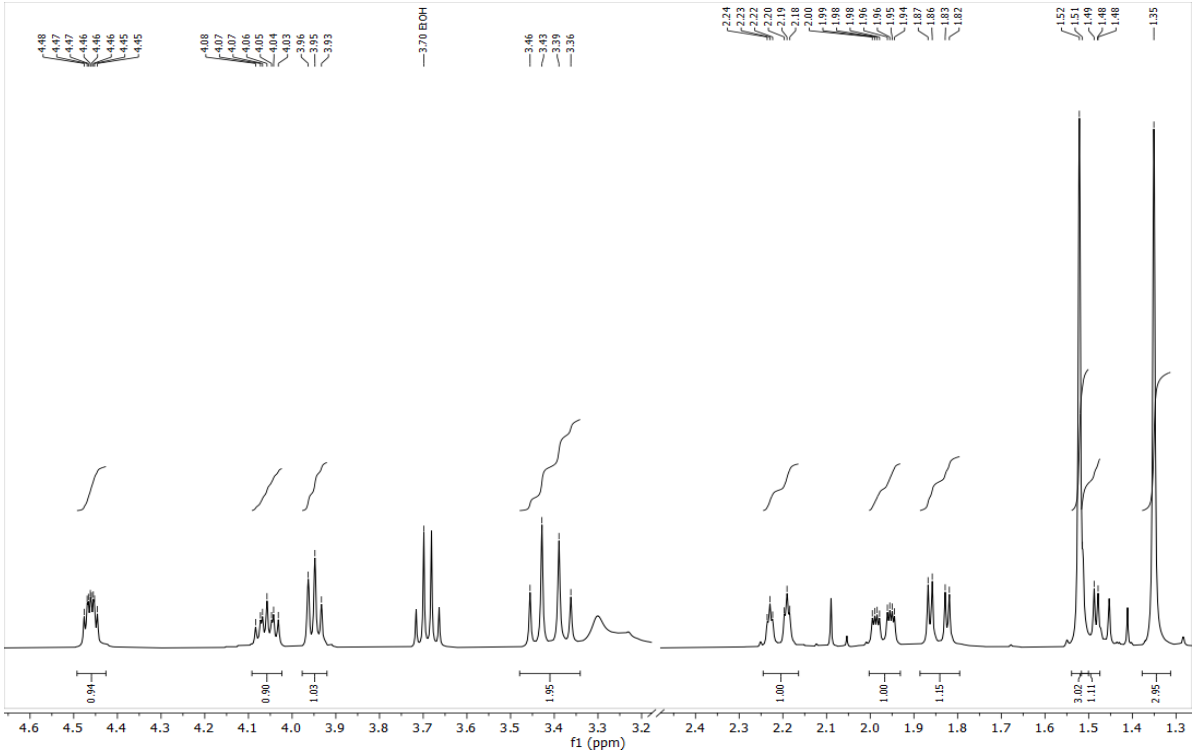
*^{13}C-spectrum of **27** in $CDCl_3$.*

8.2.1.2 (3a*R*,7a*S*)-2,2-dimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-5(4*H*)-one **24**

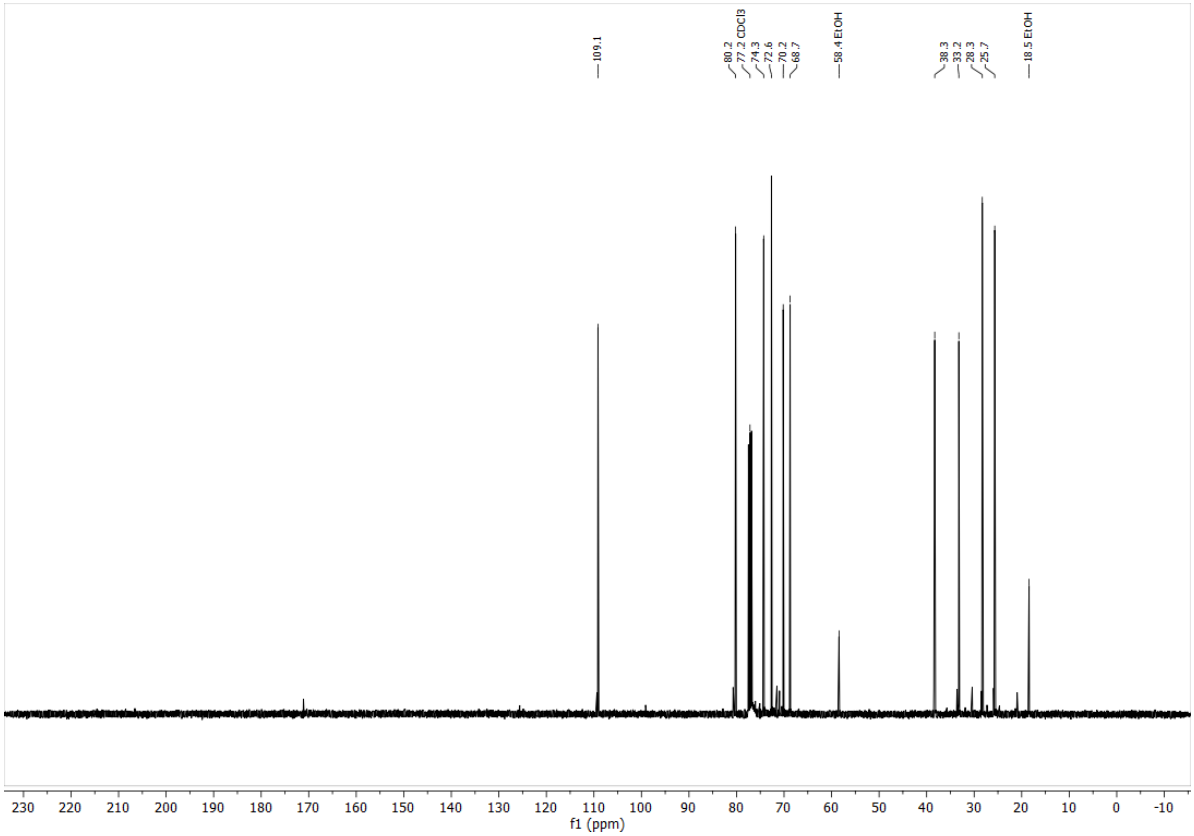
LAH-reduction (synthesis of (3a*S*,4*R*,6*R*,7a*R*)-6-(hydroxymethyl)-2,2-dimethylhexahydrobenzo[*d*] [1,3] dioxole-4,6-diol)



^{1}H-spectrum of (3aS,4R,6R,7aR)-6-(hydroxymethyl)-2,2-dimethylhexahydrobenzo[d] [1,3] dioxole-4,6-diol in $CDCl_3$.

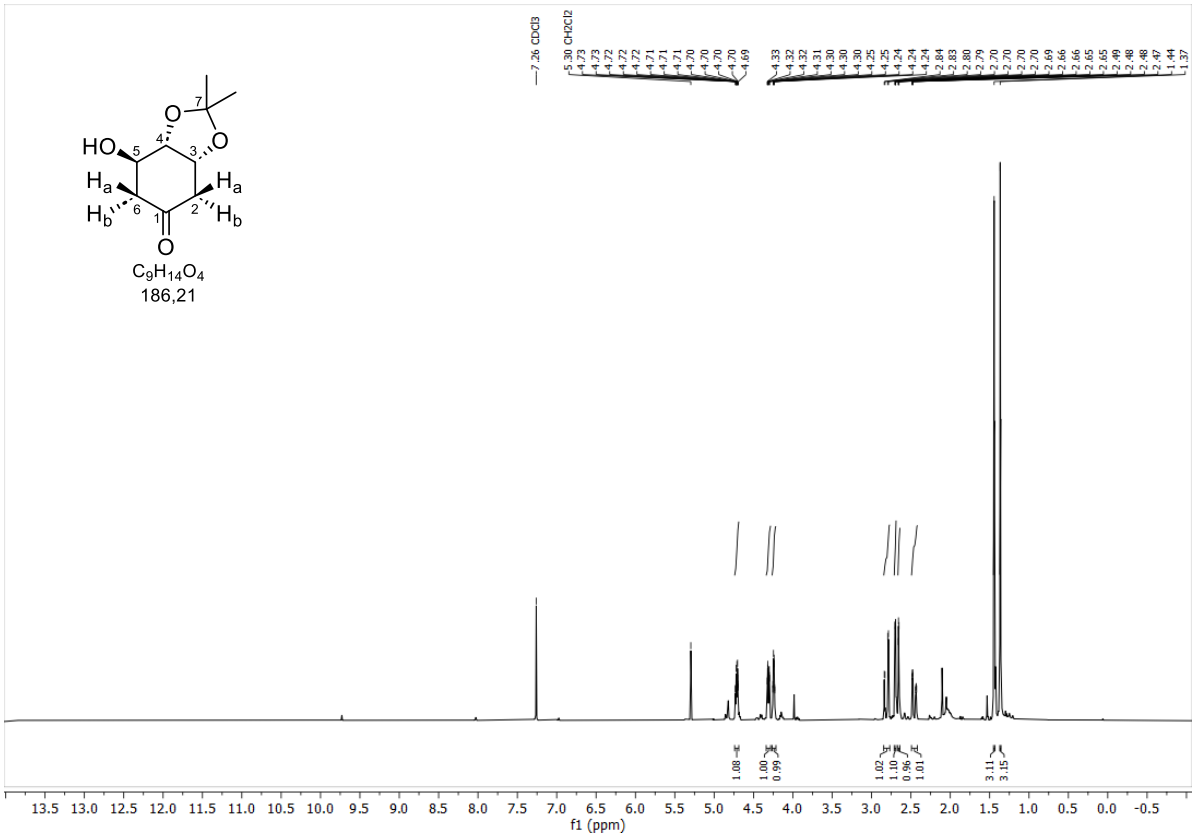


^{1}H-spectrum of (3aS,4R,6R,7aR)-6-(hydroxymethyl)-2,2-dimethylhexahydrobenzo[d] [1,3] dioxole-4,6-diol in $CDCl_3$ (selected regions between 2,3-5,1 ppm).

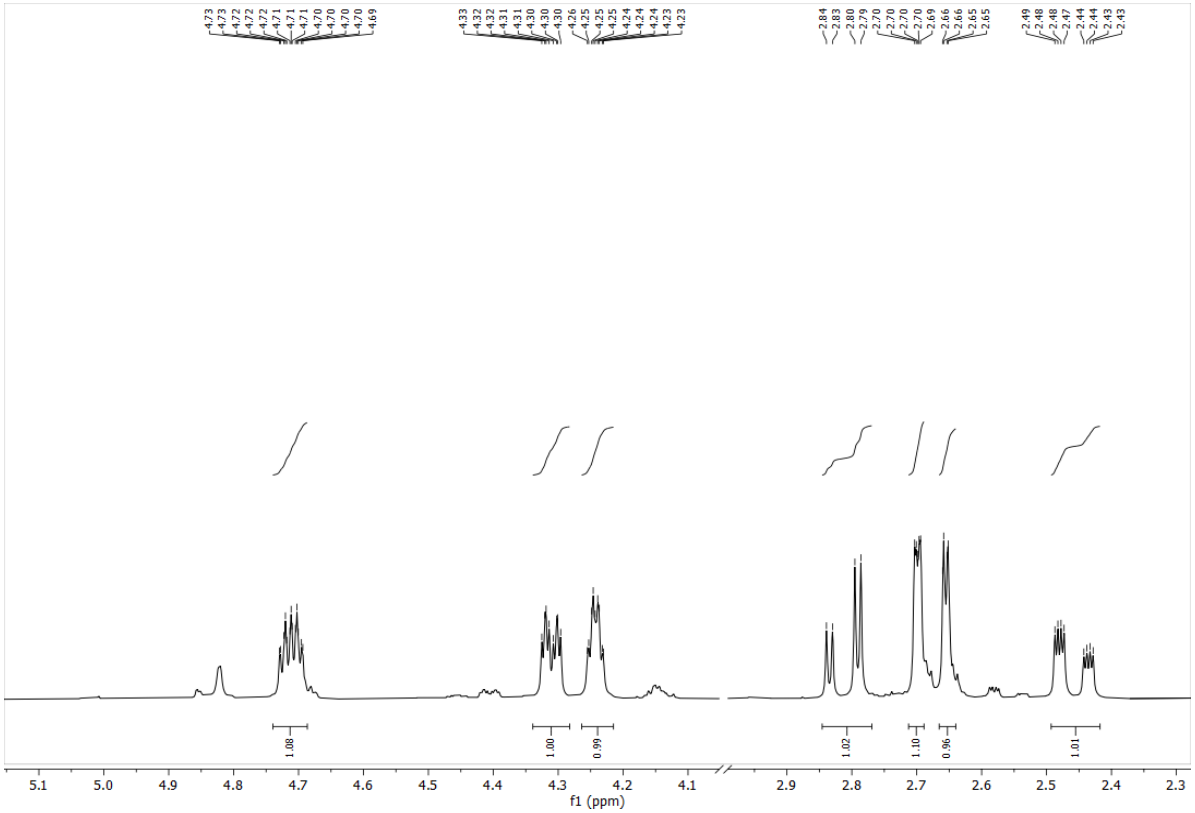


^{13}C-spectrum of (3aS,4R,6R,7aR)-6-(hydroxymethyl)-2,2-dimethylhexahydrobenzo[d] [1,3] dioxole-4,6-diol in $CDCl_3$.

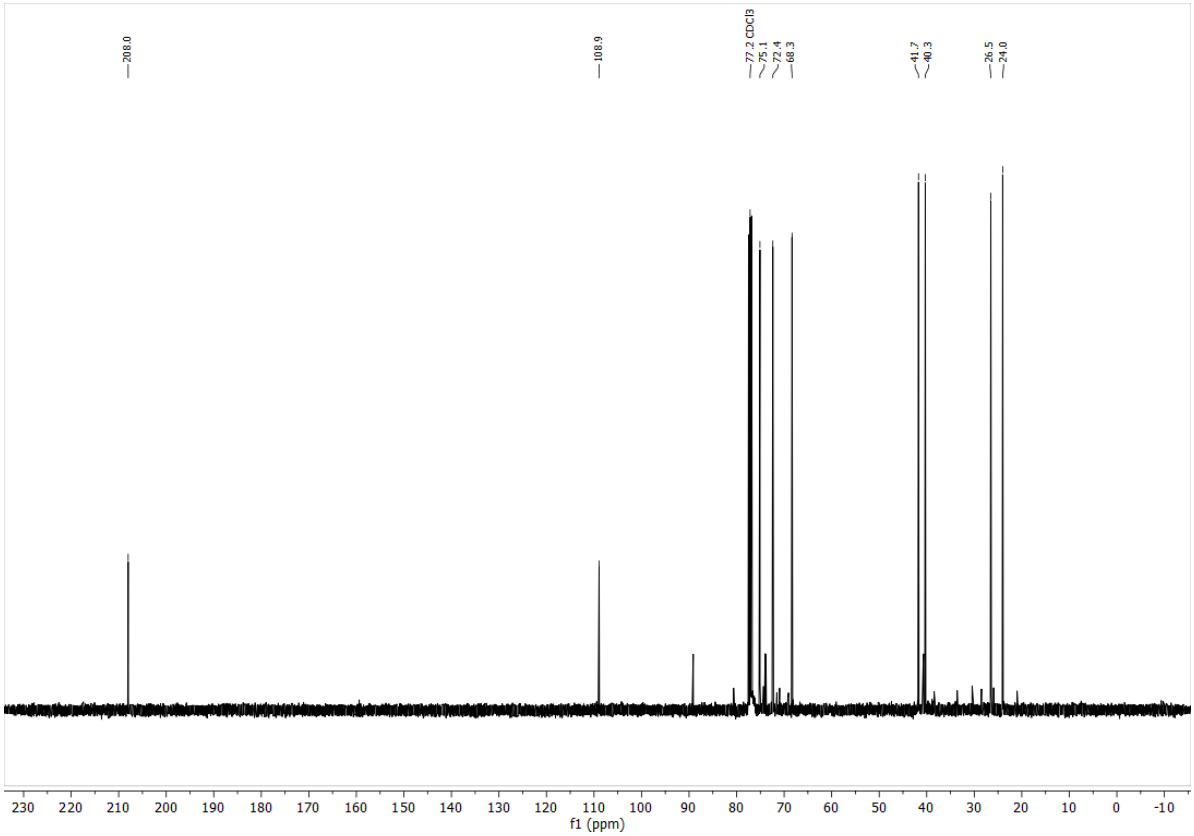
periodate cleavage (synthesis of (3a*R*,7*R*,7a*S*)-7-hydroxy-2,2-dimethyltetrahydrobenzo[*d*][1,3] dioxol-5(4*H*)-one)



^{1}H-spectrum of (3aS,4R,6R,7aR)-6-(hydroxymethyl)-2,2-dimethylhexahydrobenzo[d] [1,3] dioxole-4,6-diol in $CDCl_3$.

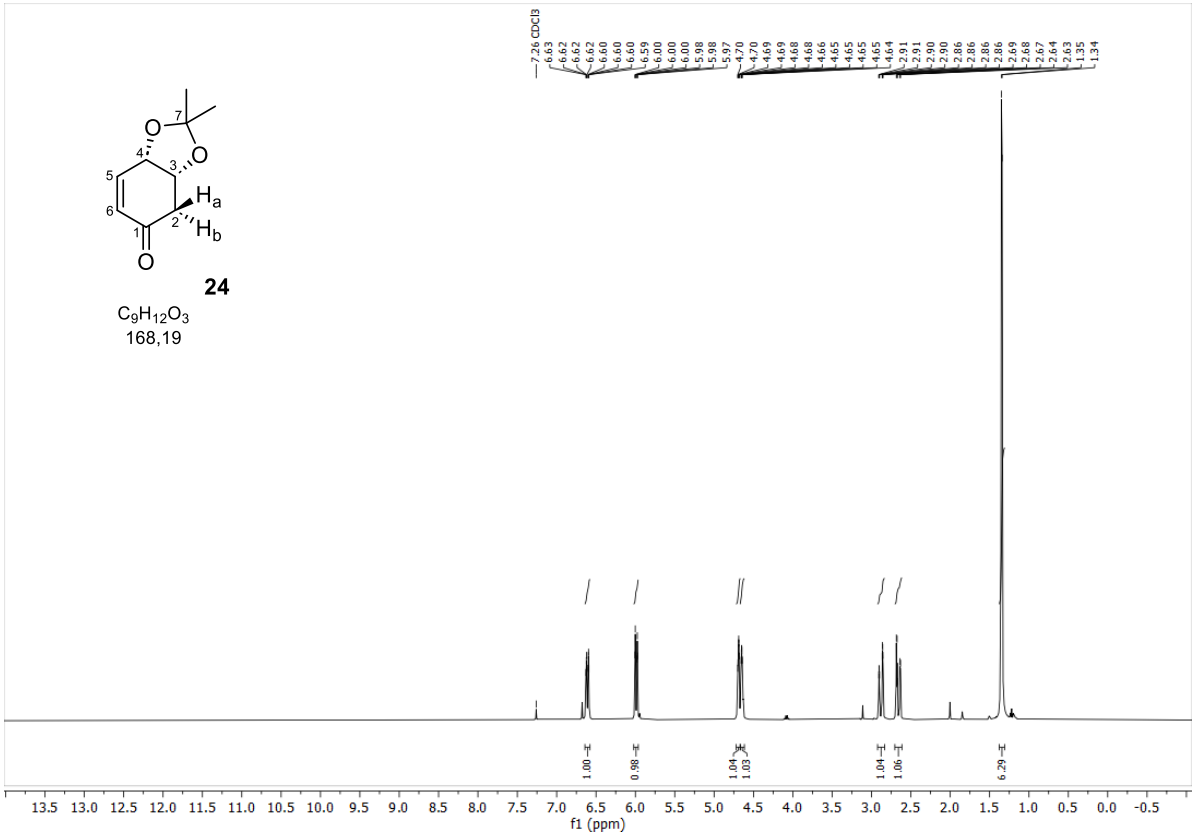


^{1}H-spectrum of (3aS,4R,6R,7aR)-6-(hydroxymethyl)-2,2-dimethylhexahydrobenzo[d] [1,3] dioxole-4,6-diol in $CDCl_3$ (selected regions between 2,3-5,1 ppm).

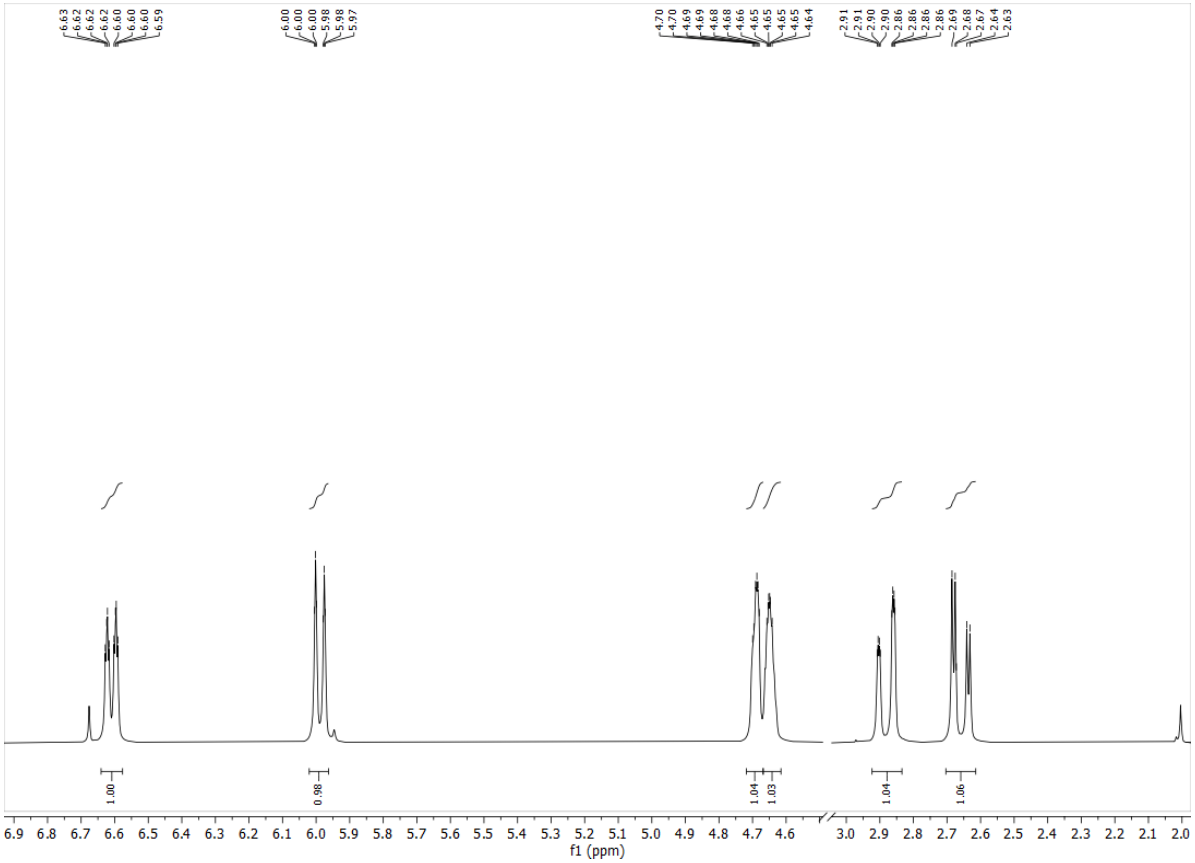


^{13}C-spectrum of (3aS,4R,6R,7aR)-6-(hydroxymethyl)-2,2-dimethylhexahydrobenzo[d] [1,3] dioxole-4,6-diol in $CDCl_3$.

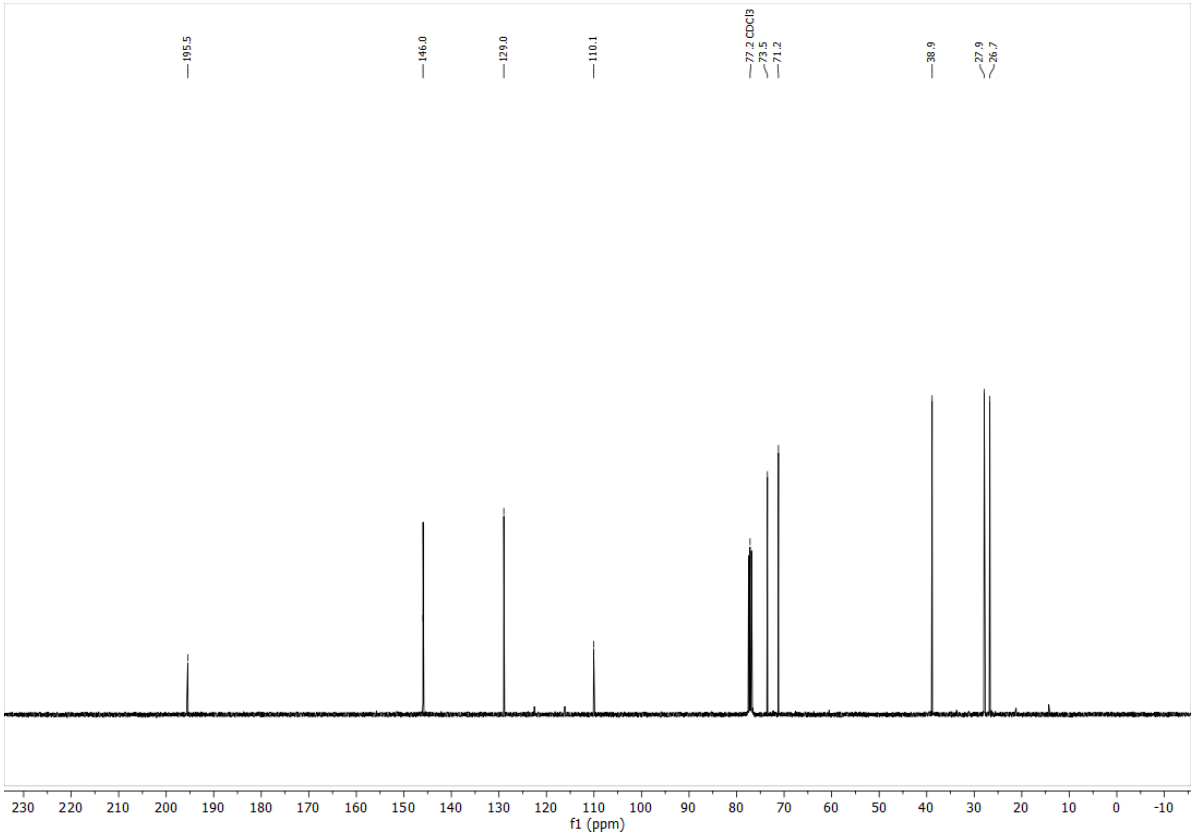
elimination (synthesis of **24**)



*^{1}H-spectrum of **24** in $CDCl_3$.*

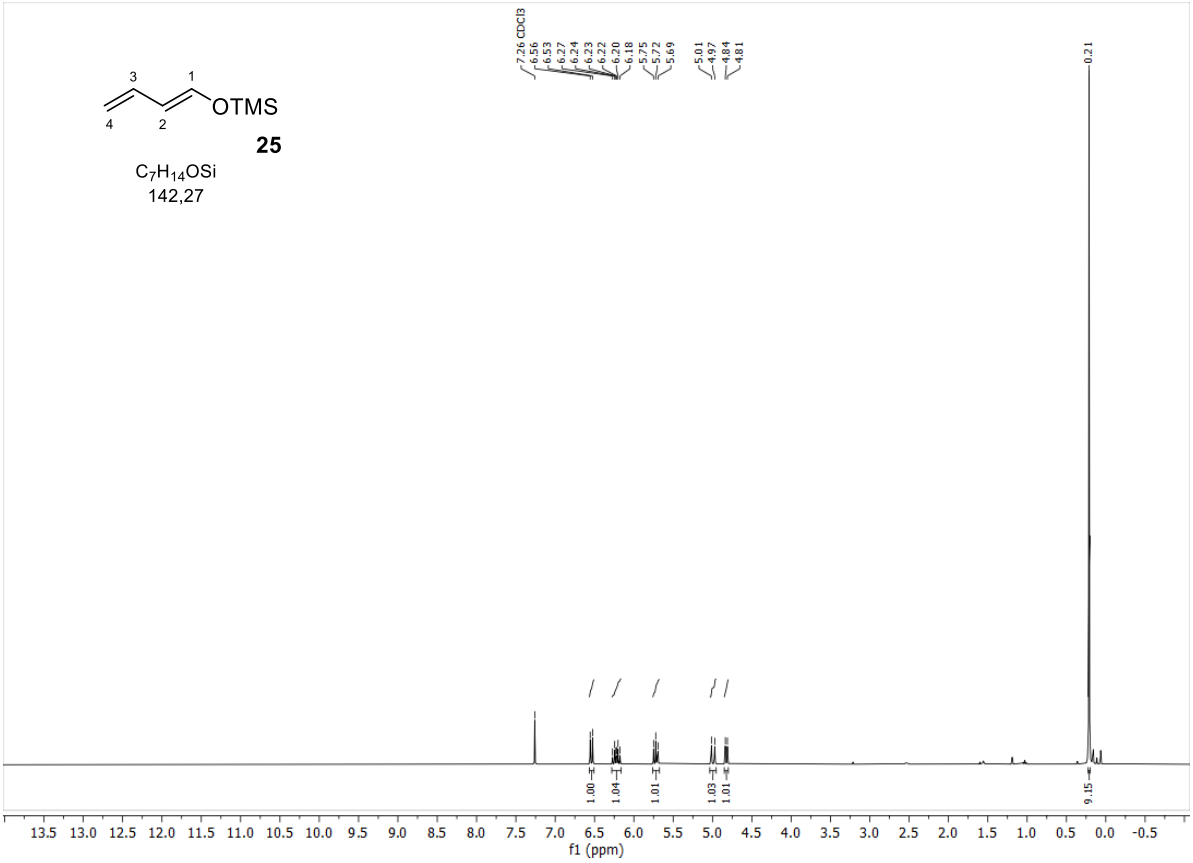


*^{1}H-spectrum of **24** in $CDCl_3$ (selected regions between 2,0-6,9 ppm).*

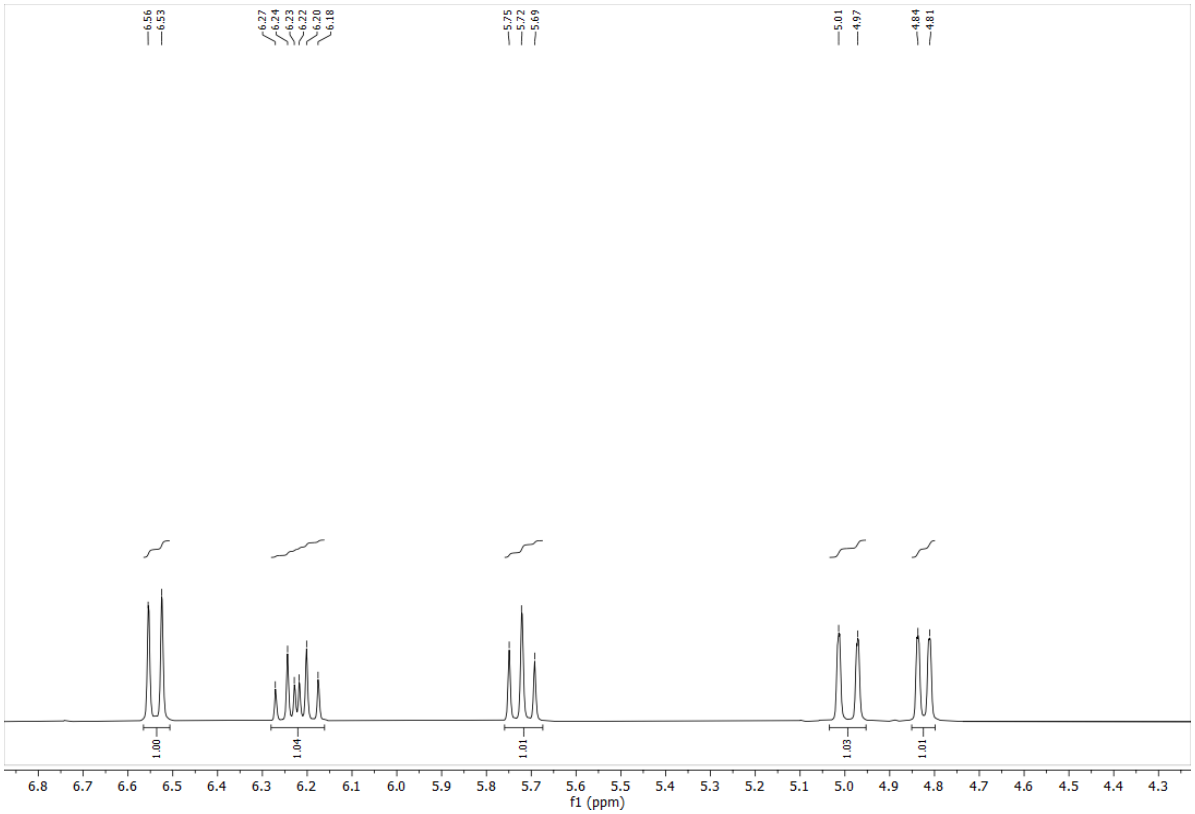


*^{13}C-spectrum of **24** in $CDCl_3$.*

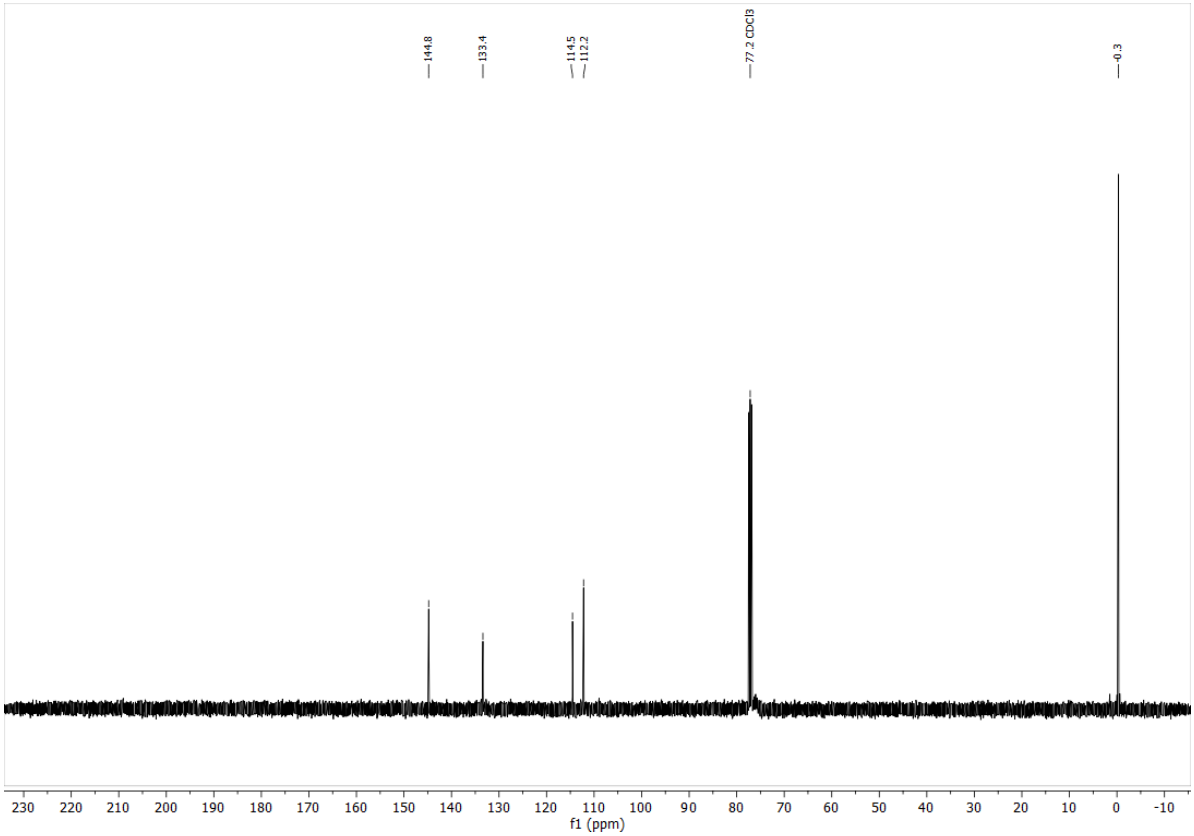
8.2.1.3.1 (*E*)-(buta-1,3-dien-1-yloxy)trimethylsilane **25**



*^{1}H-spectrum of **25** in $CDCl_3$.*

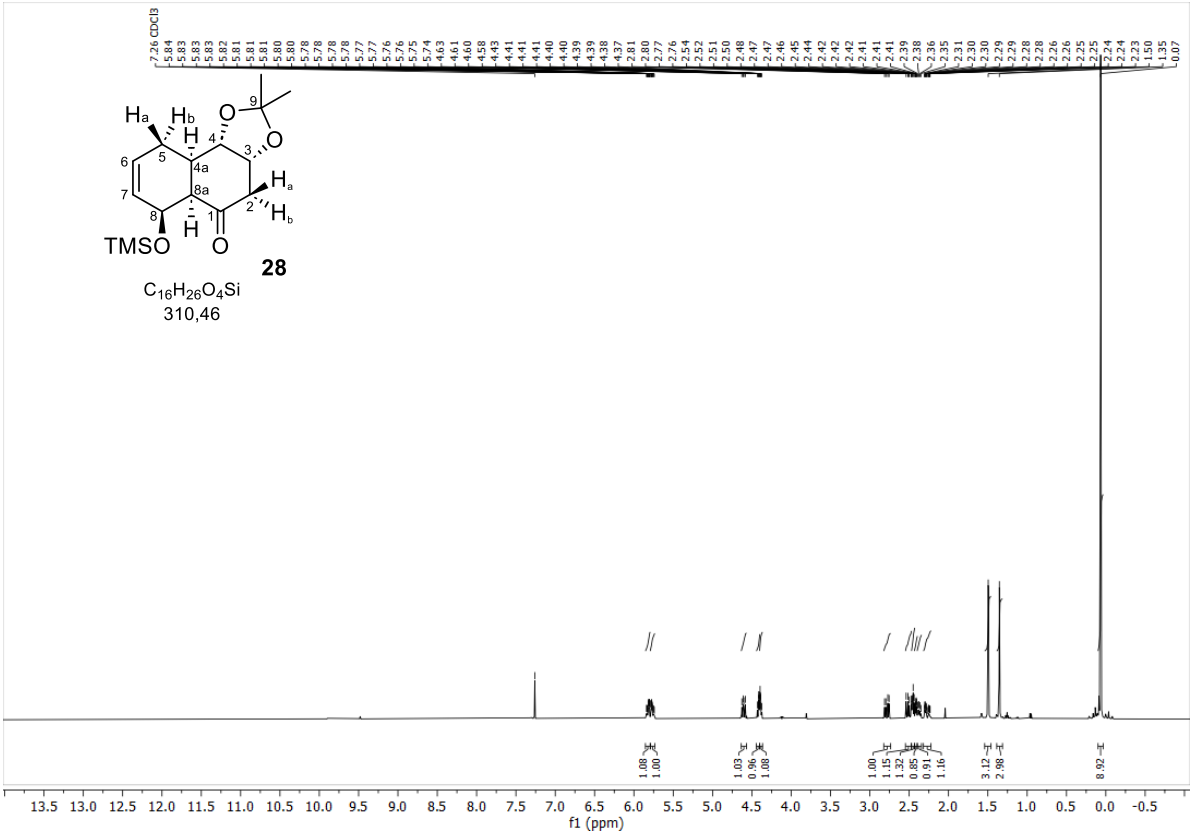


*^{1}H-spectrum of **25** in $CDCl_3$ (region between 4,3-6,8 ppm).*

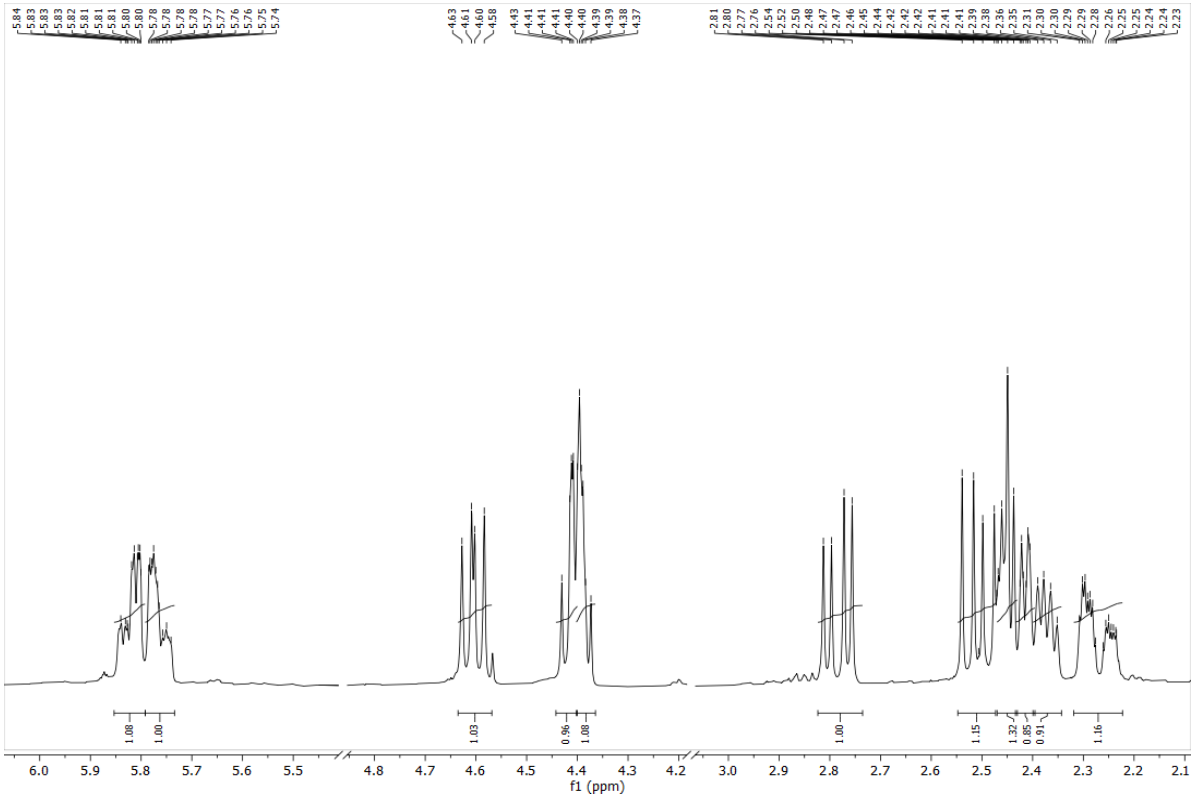


*^{13}C-spectrum of **25** in $CDCl_3$.*

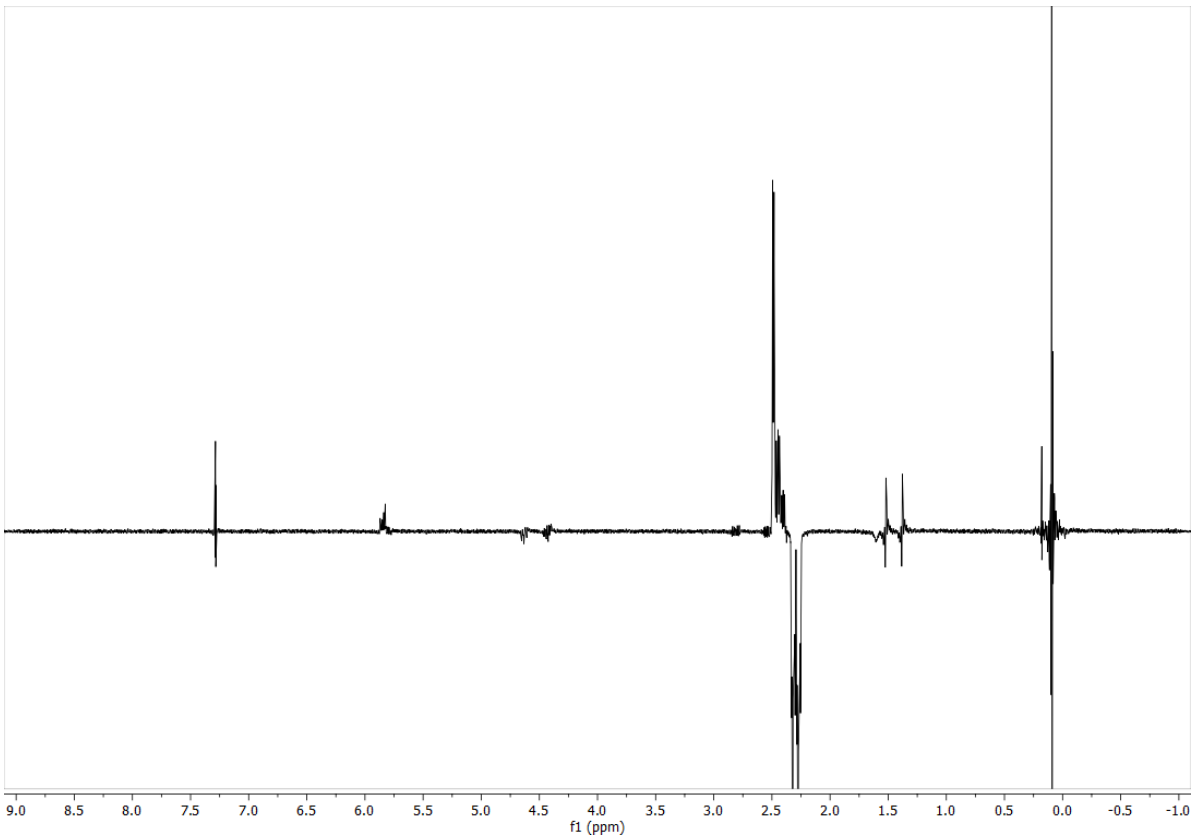
8.2.1.3.2 (3a*R*,5a*R*,6*S*,9a*R*,9b*S*)-2,2-dimethyl-6-((trimethylsilyl)oxy)-3a,5a,6,9,9a,9b-hexahydro-naphtho[1,2-*d*][1,3]dioxol-5(4*H*)-one **28**



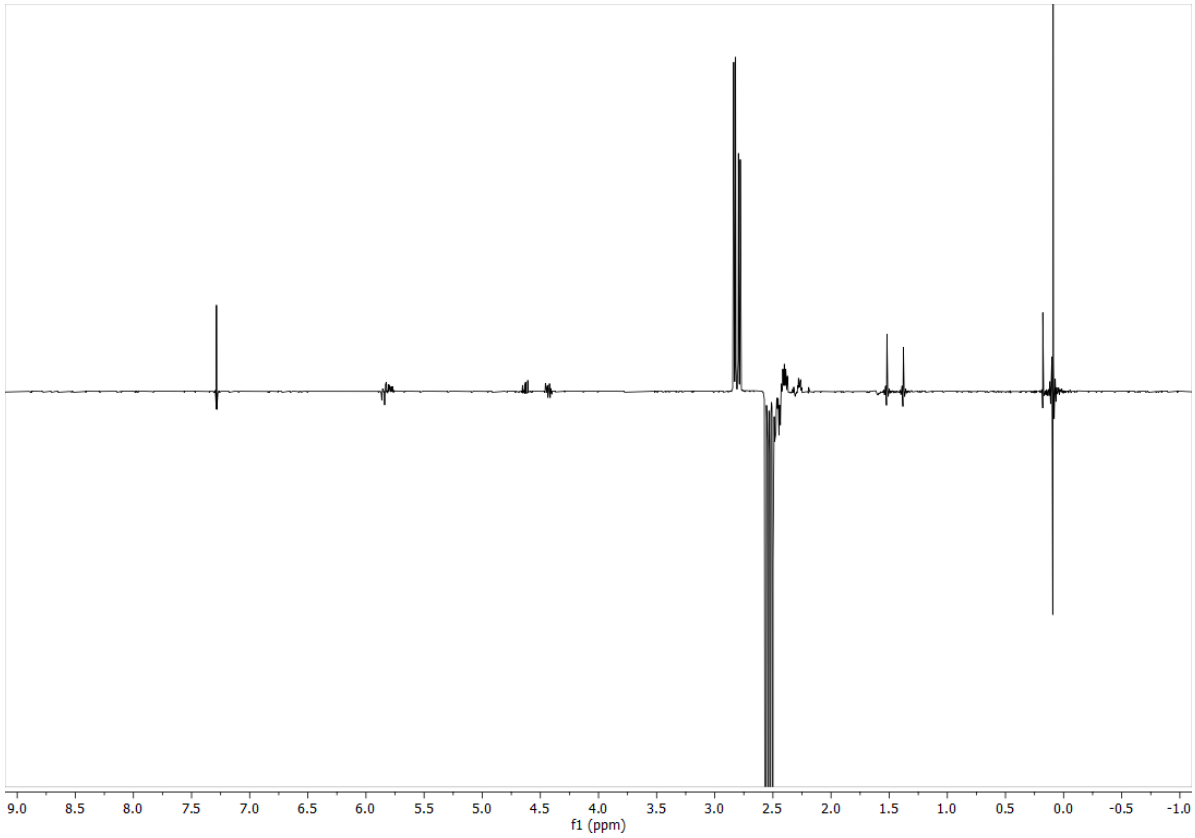
*^{1}H-spectrum of **28** in $CDCl_3$.*



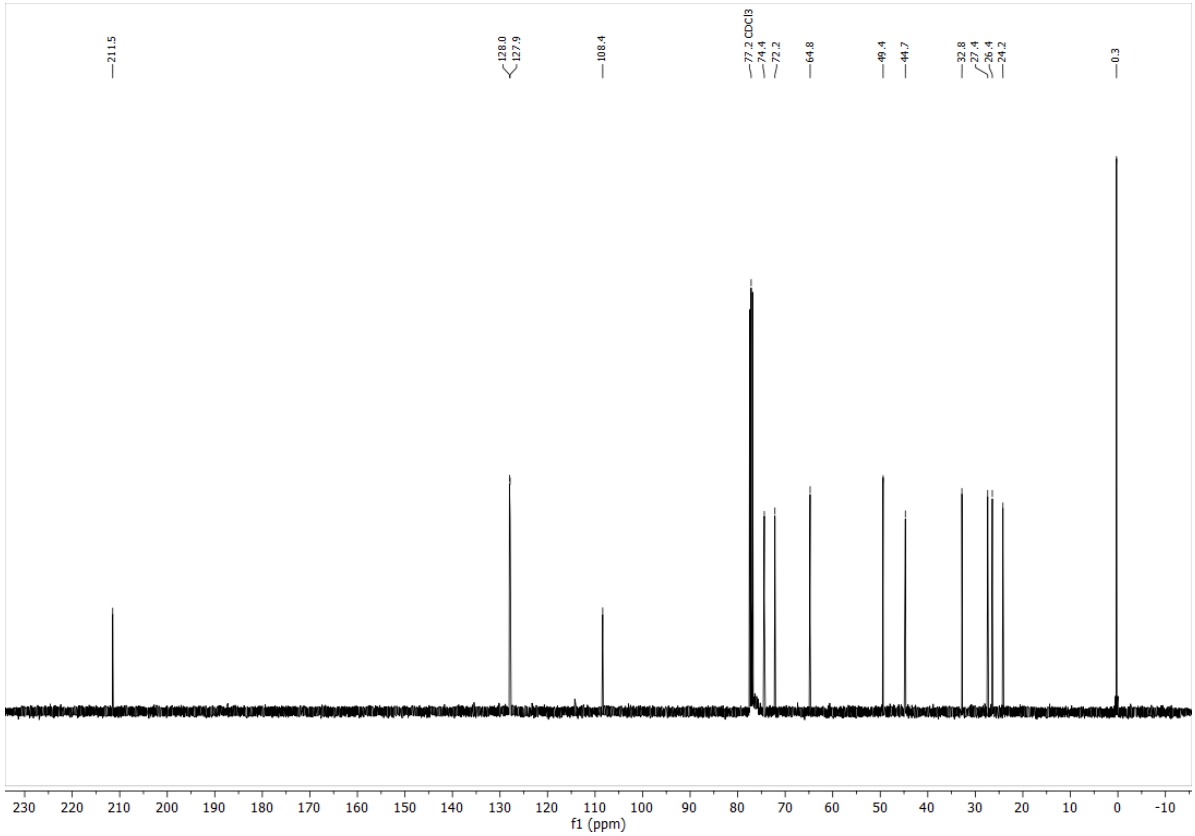
*^{1}H-spectrum of **28** in $CDCl_3$ (selected regions between 2,1-6,0 ppm).*



*NOE-spectrum of **28** in $CDCl_3$ (frequency saturation at 2,28 ppm).*

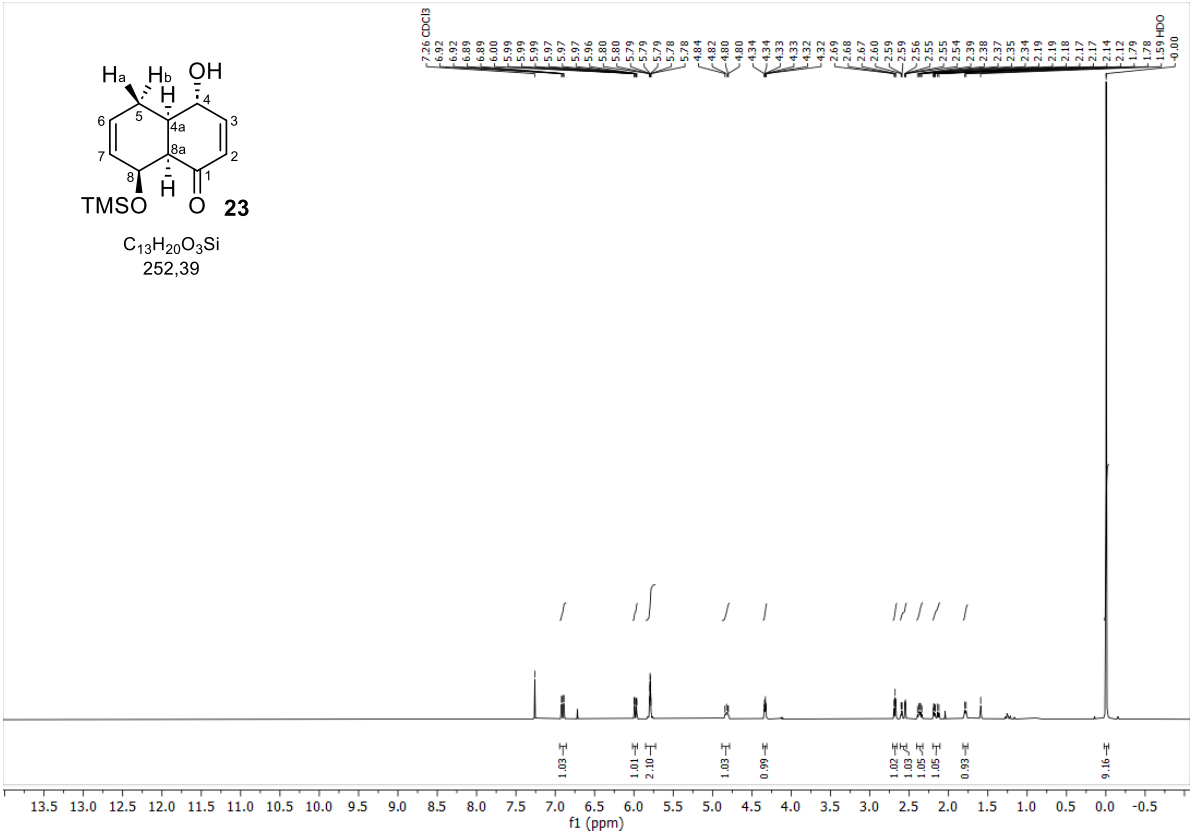


*NOE-spectrum of **28** in $CDCl_3$ (frequency saturation at 2,53 ppm).*

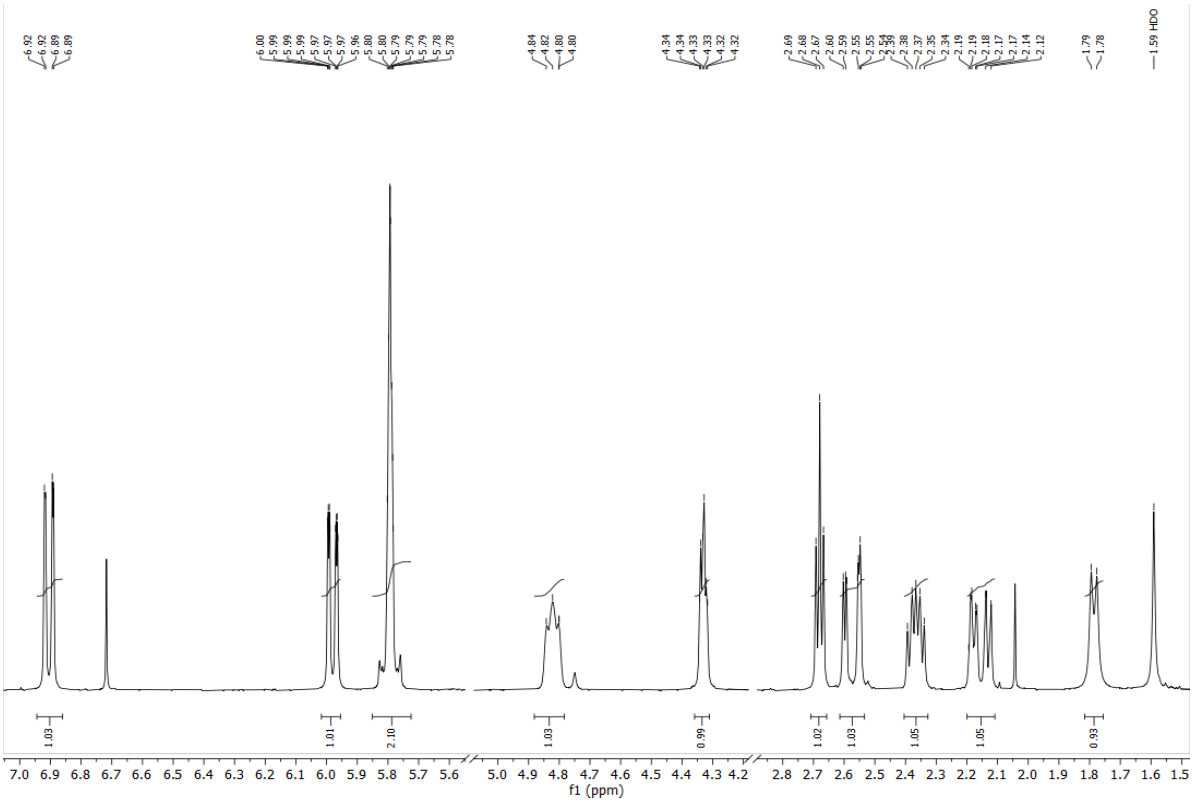


*^{13}C-spectrum of **28** in $CDCl_3$.*

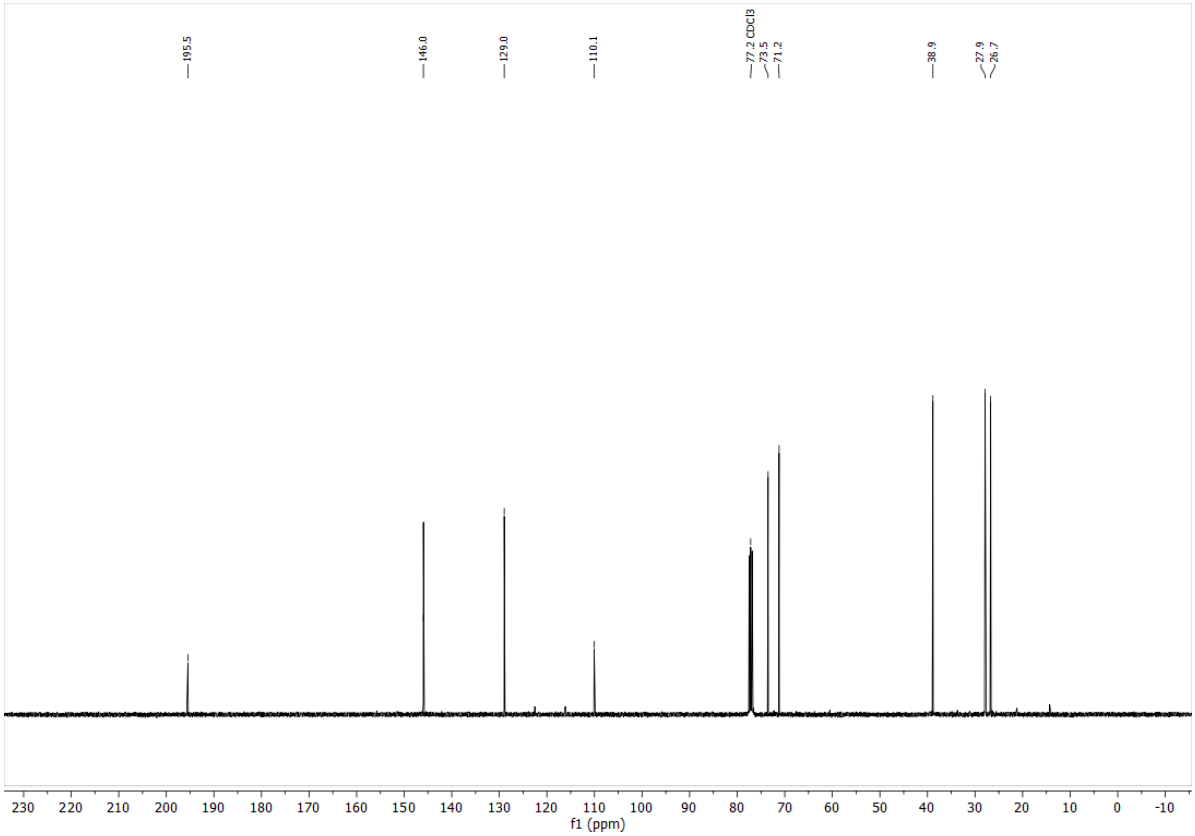
8.2.1.4 (4*R*,4a*R*,8*S*,8a*R*)-4-hydroxy-8-((trimethylsilyl)oxy)-4a,5,8,8a-tetrahydronaphthalen-1-(4*H*)-one **23**



*^{1}H-spectrum of **23** in $CDCl_3$.*

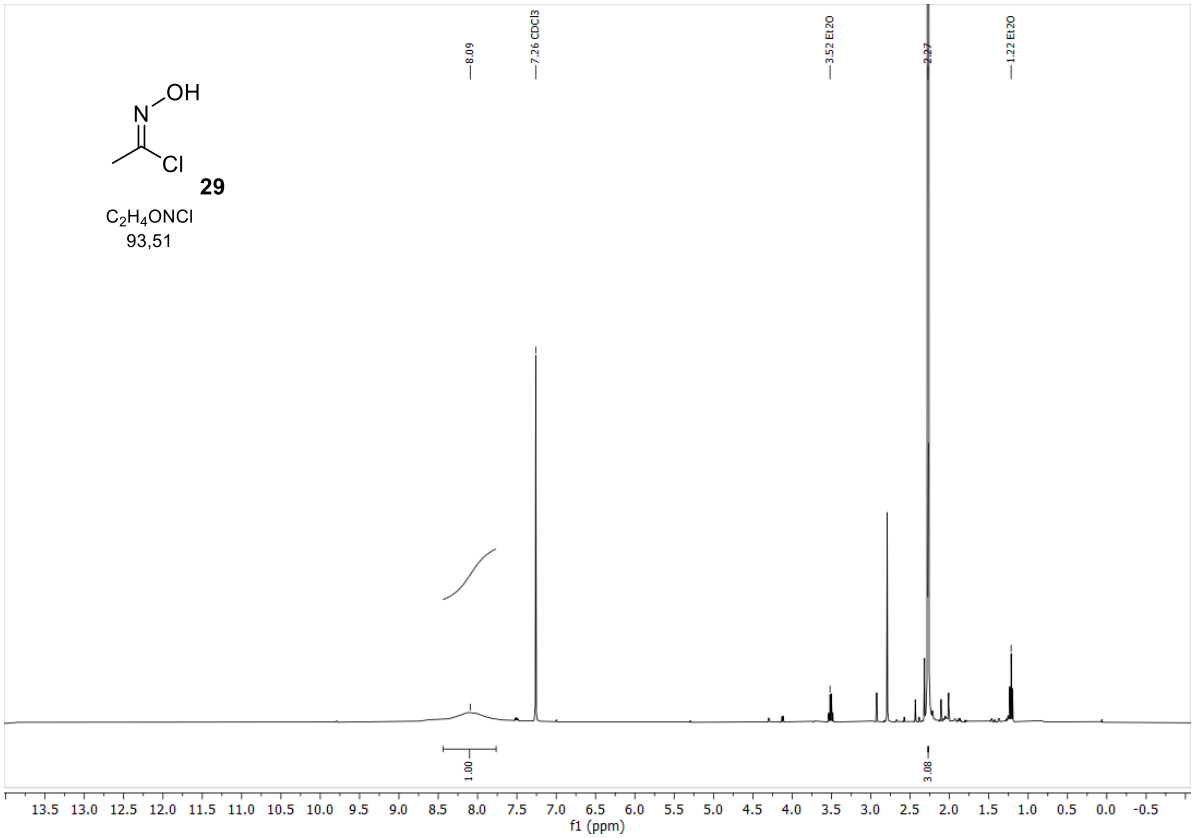


*^{1}H-spectrum of **23** in $CDCl_3$ (selected regions between 1,5-7,0 ppm).*



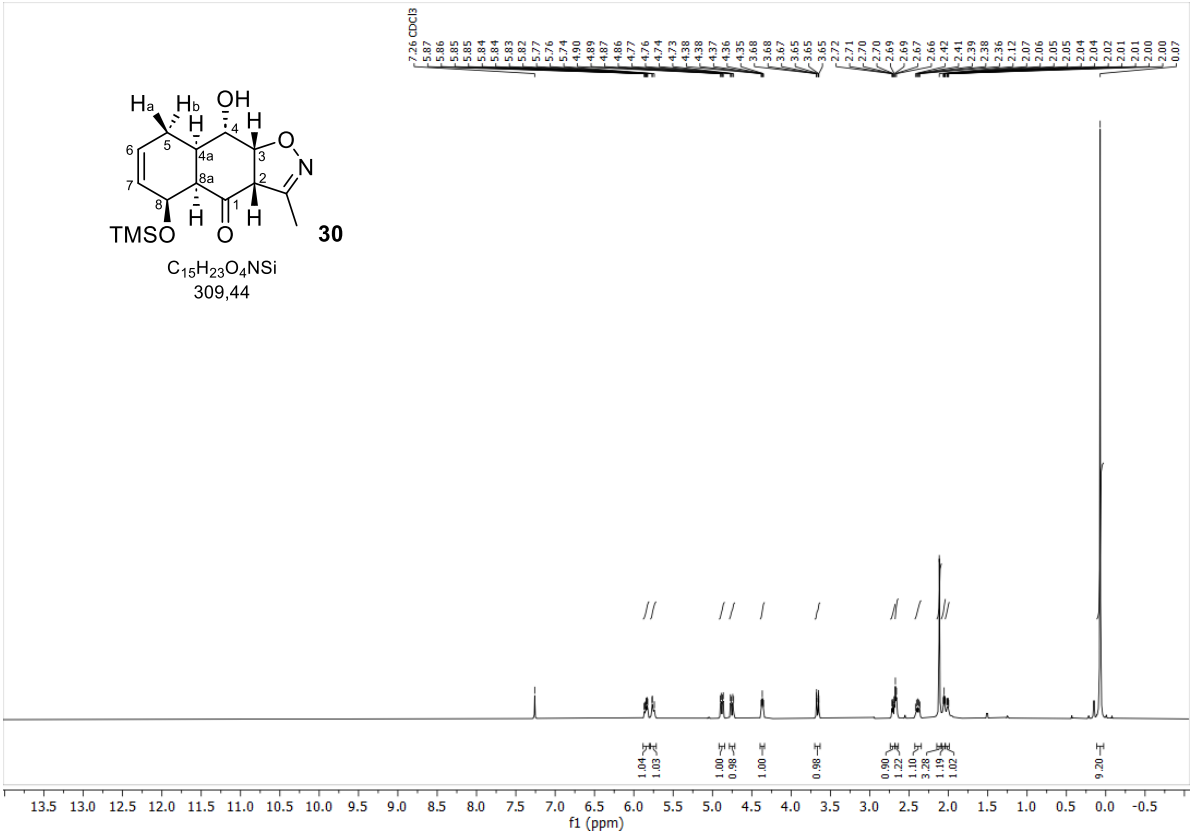
*^{13}C-spectrum of **24** in $CDCl_3$.*

8.2.1.5.1 (*Z*)-*N*-hydroxyacetimidoyl chloride **29**

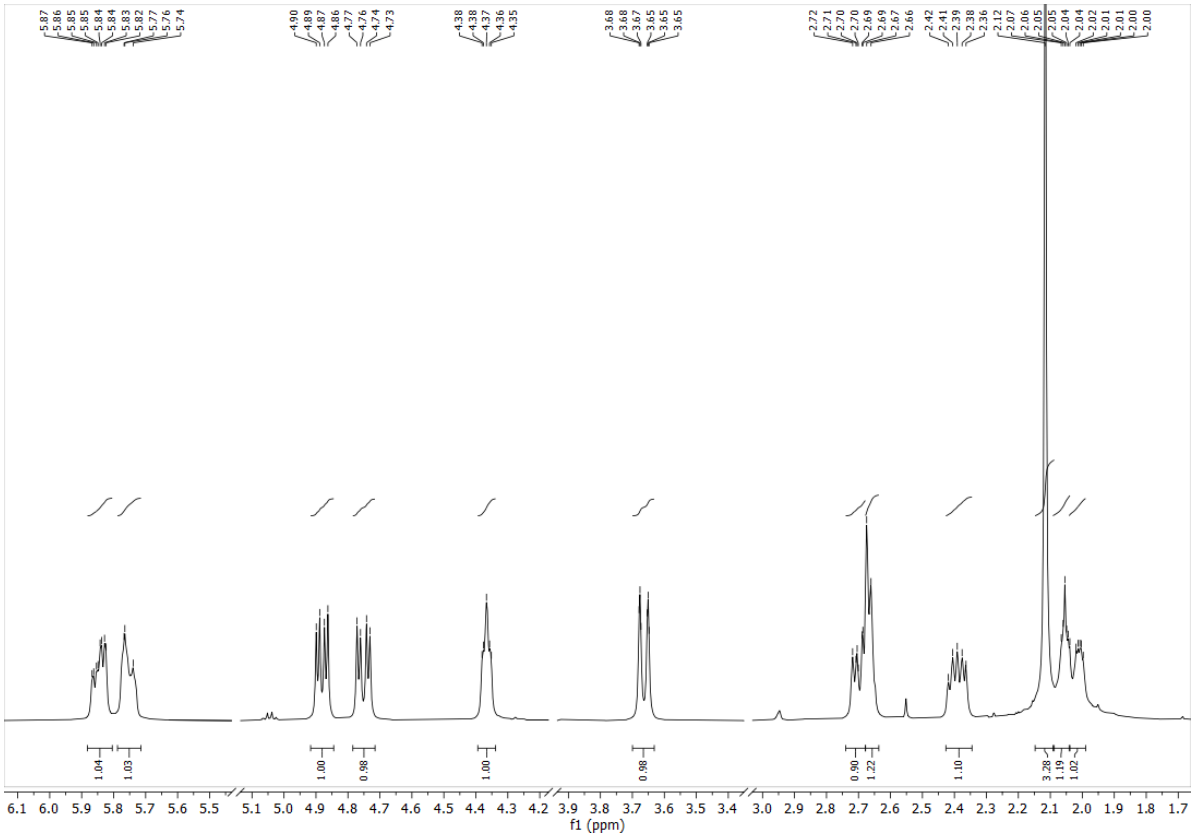


*^{1}H-spectrum of **29** in $CDCl_3$.*

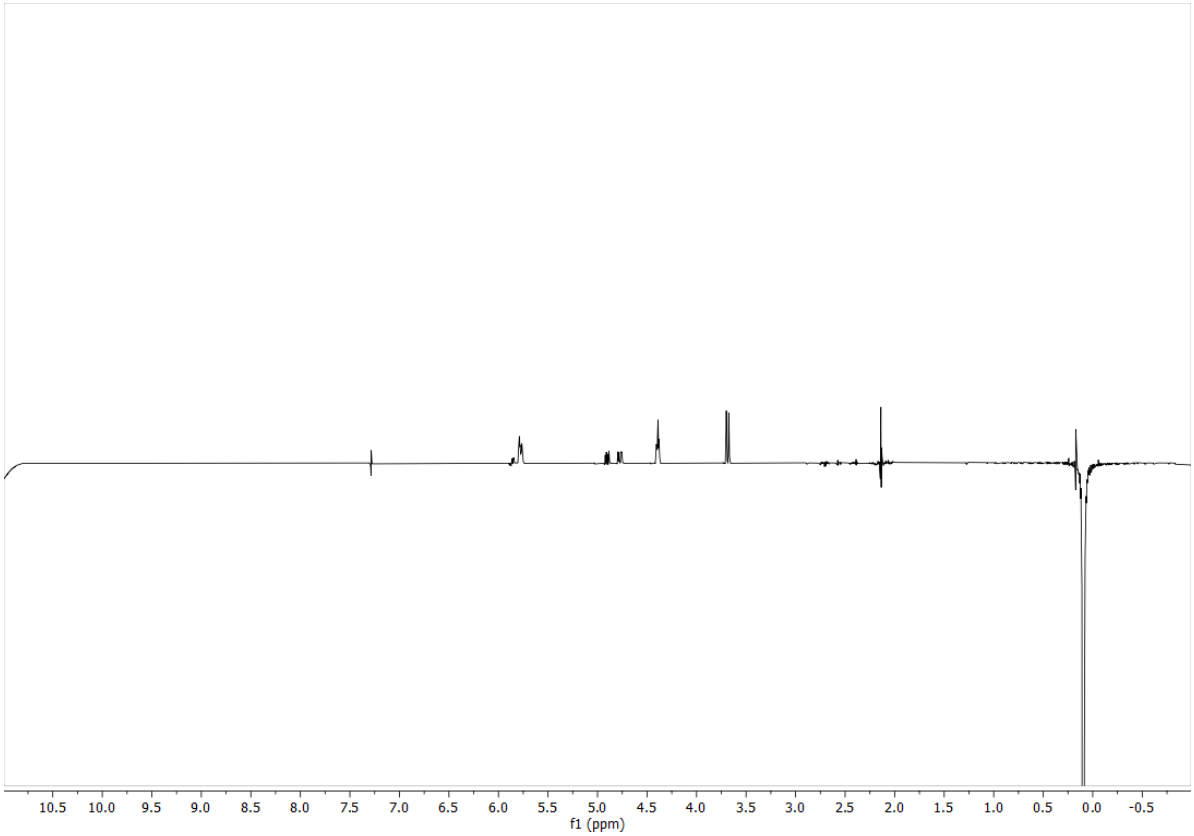
8.2.1.5.2 (3a*S*,4a*R*,5*S*,8a*R*,9*S*,9a*R*)-9-hydroxy-3-methyl-5-((trimethylsilyl)oxy)-a,5,8,8a,9,9a-hexahydronaphtho[2,3-*d*]isoxazol-4(3a*H*)-one **30**



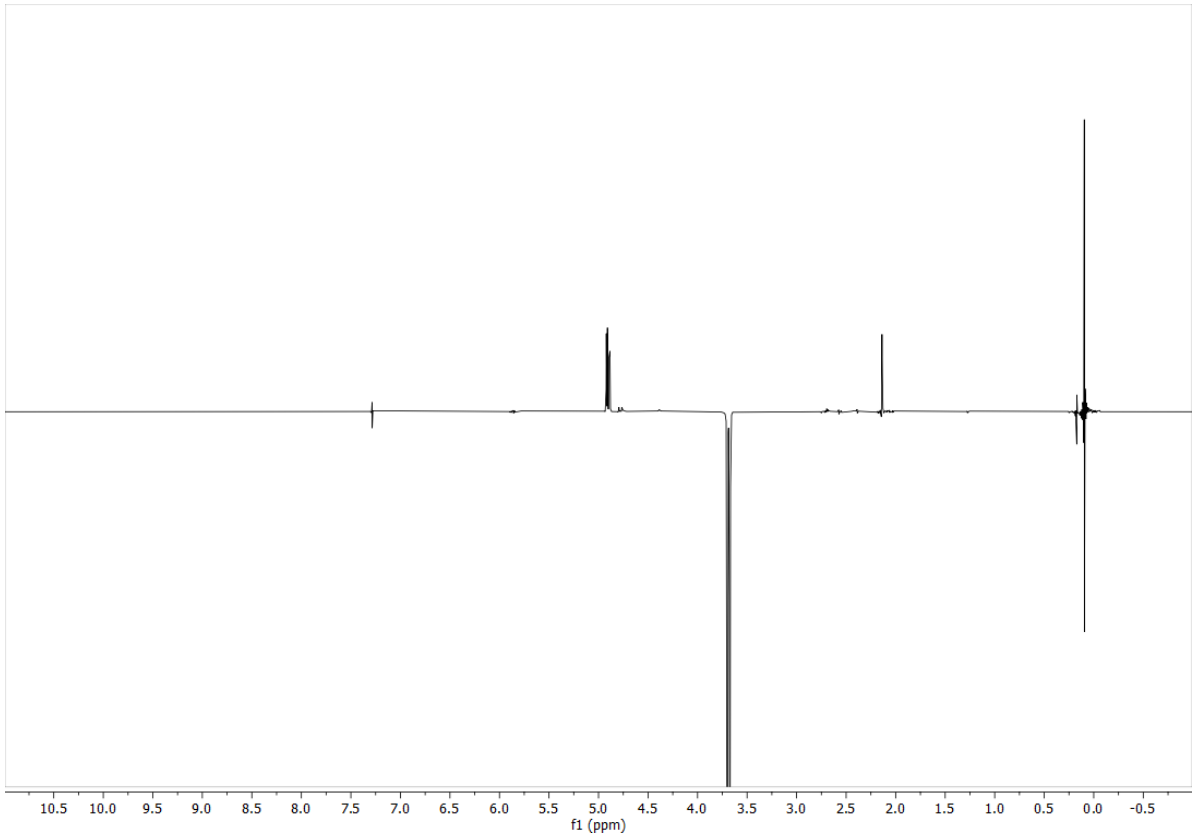
*^{1}H-spectrum of **30** in $CDCl_3$.*



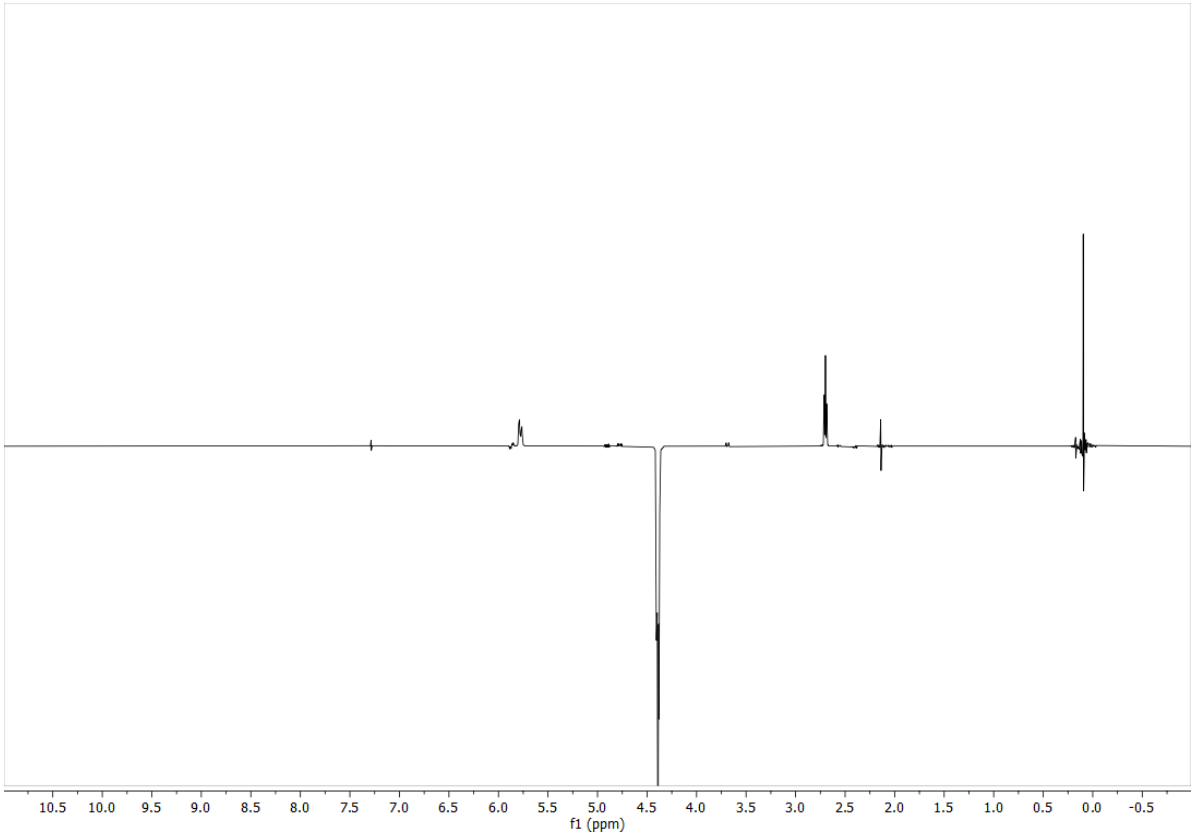
*^{1}H-spectrum of **30** in $CDCl_3$ (selected regions between 1,7-6,1 ppm).*



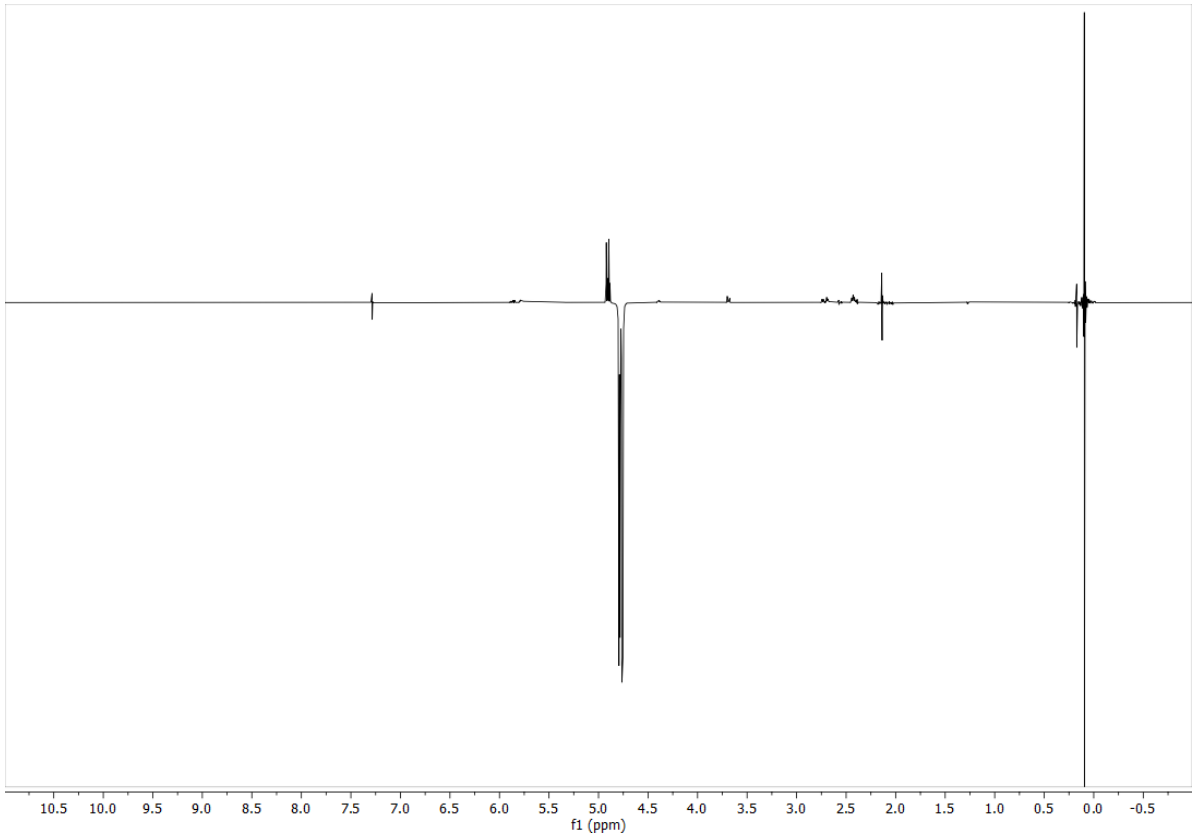
*NOE-spectrum of **30** in $CDCl_3$ (frequency saturation at 0,07 ppm).*



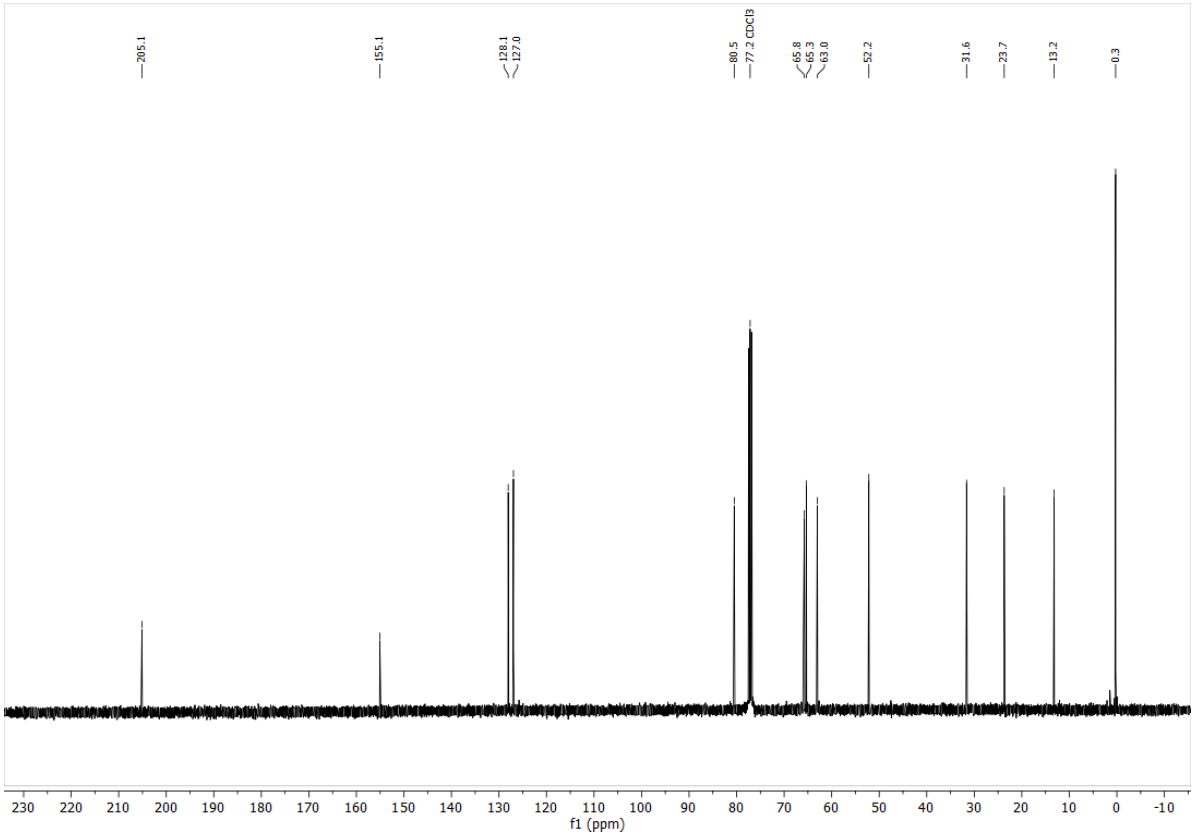
*NOE-spectrum of **30** in $CDCl_3$ (frequency saturation at 3,67 ppm).*



*NOE-spectrum of **30** in $CDCl_3$ (frequency saturation at 4,37 ppm).*

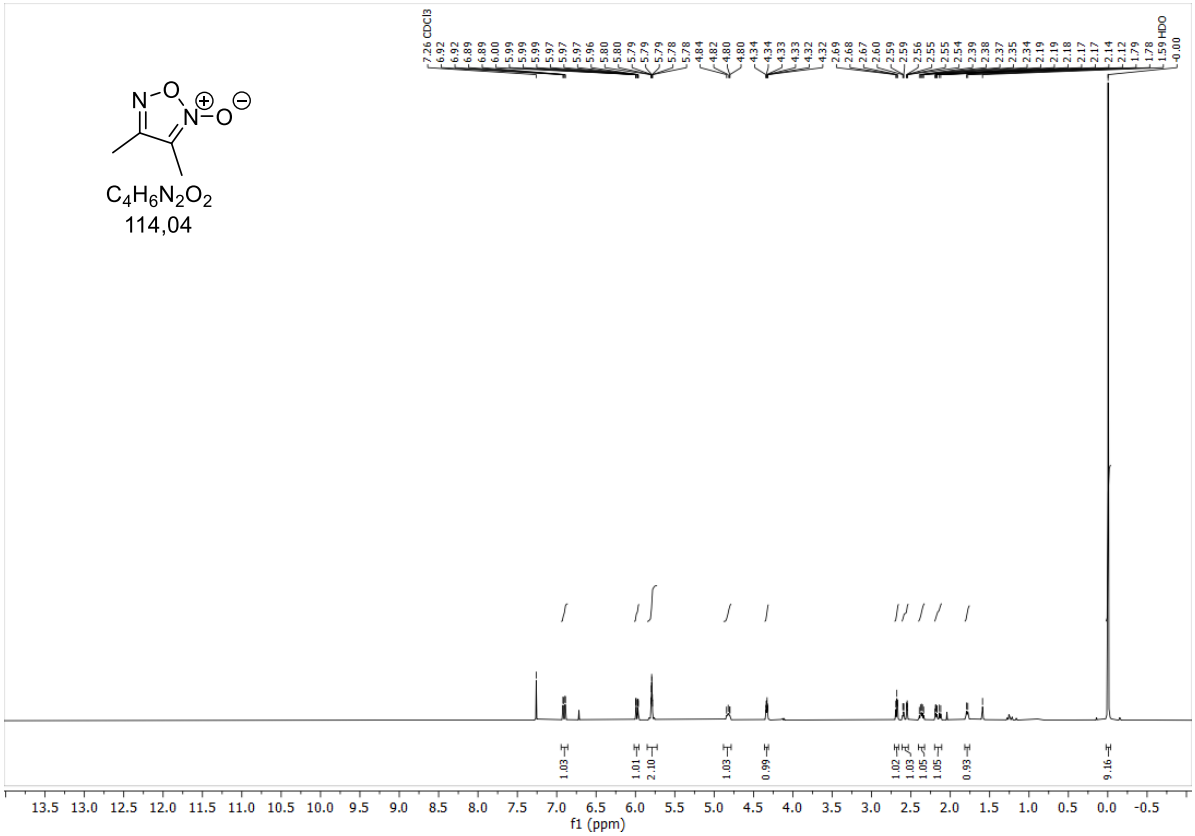


*NOE-spectrum of **30** in $CDCl_3$ (frequency saturation at 4,75 ppm).*

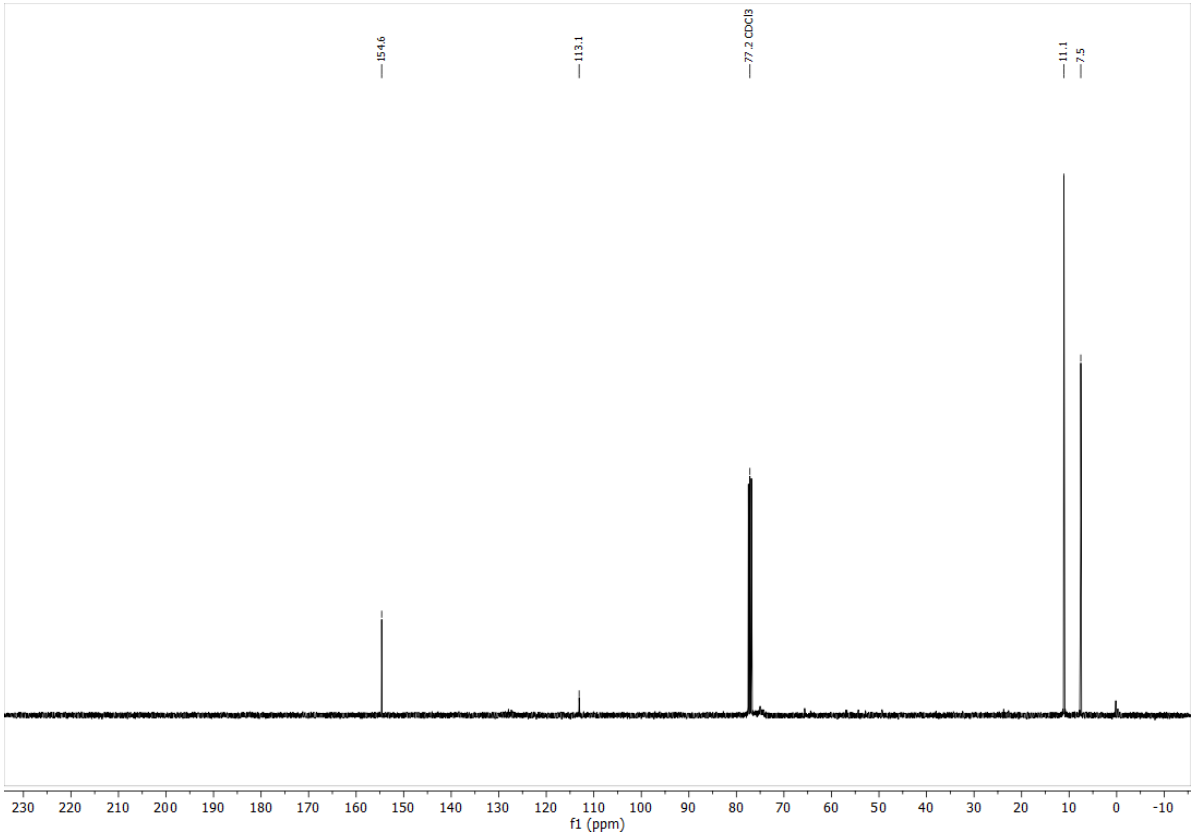


*^{13}C-spectrum of **30** in $CDCl_3$.*

3,4-dimethyl-1,2,5-oxadiiazole 2-oxide:



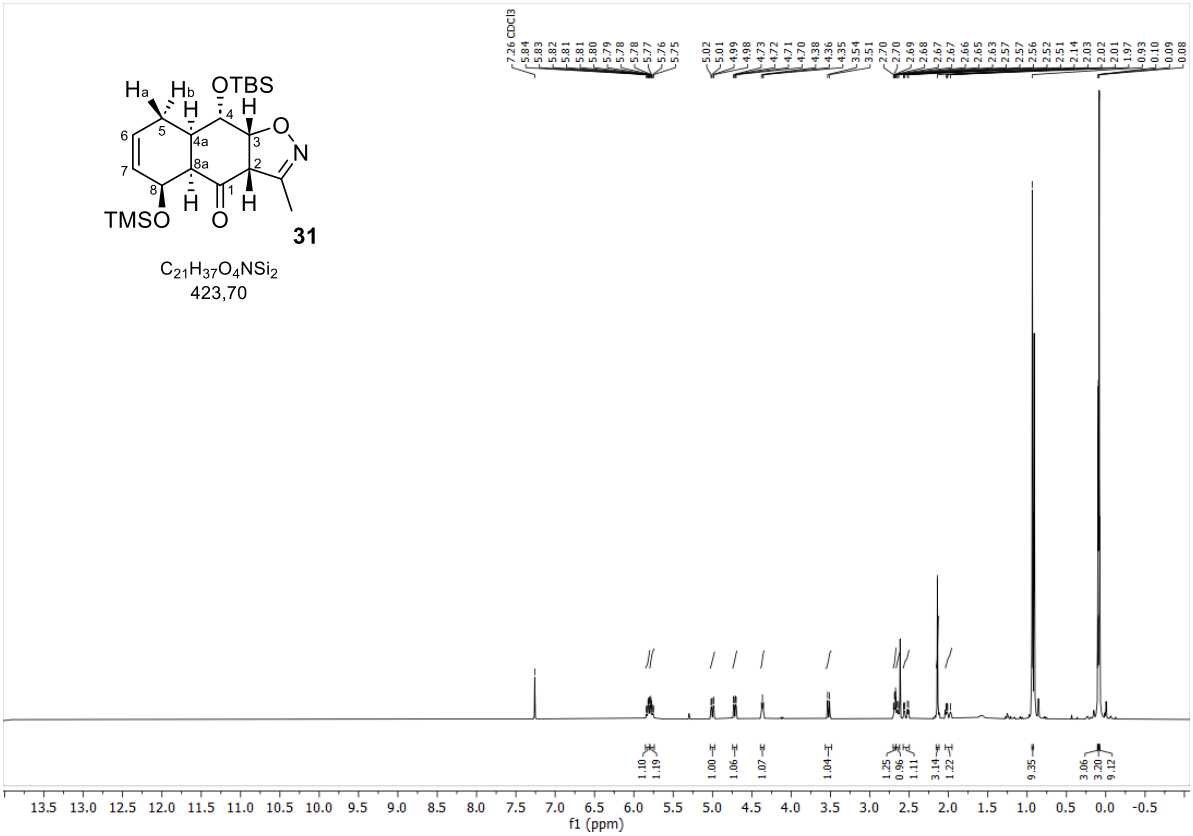
[1]H-spectrum of 3,4-dimethyl-1,2,5-oxadiiazole 2-oxide in $CDCl_3$.



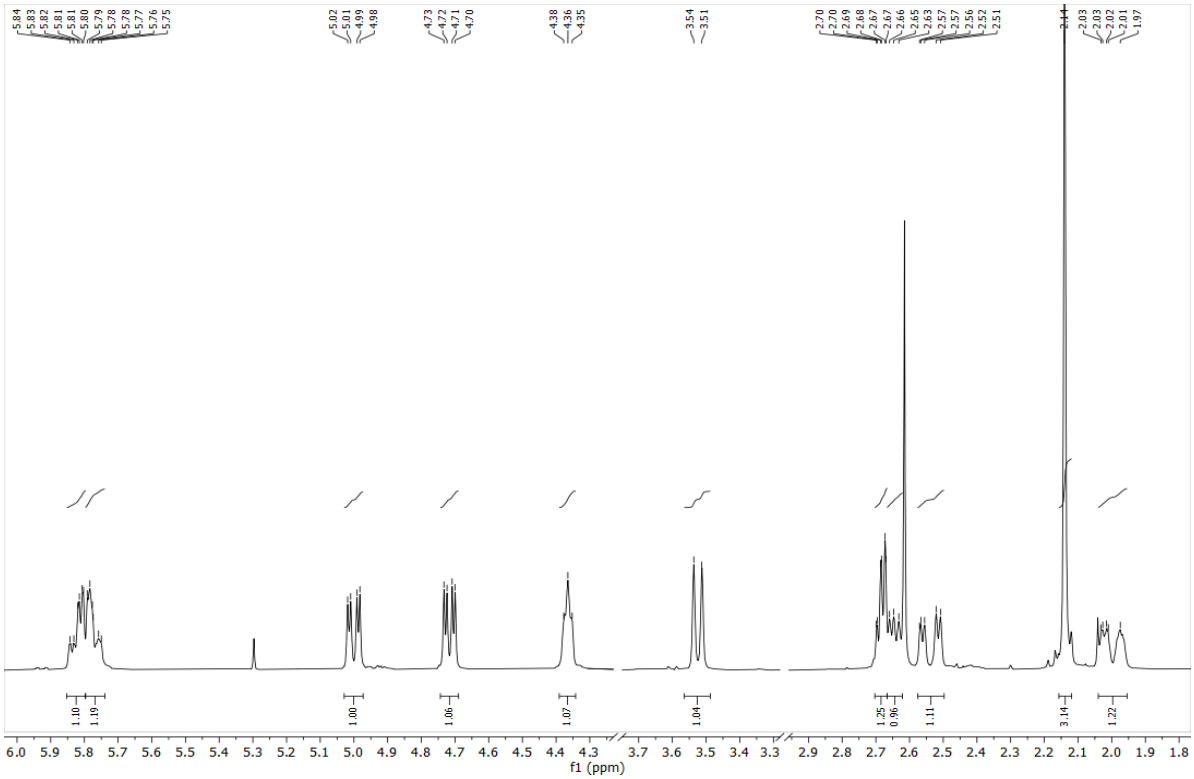
[13]C-spectrum of 3,4-dimethyl-1,2,5-oxadiiazole 2-oxide in $CDCl_3$.

8.2.1.6 (8a*R*,9*S*)-9-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-3-methyl-8a,9-dihydronaphtho-[2,3-*d*]-isoxazole-5(8*H*)-one **32**

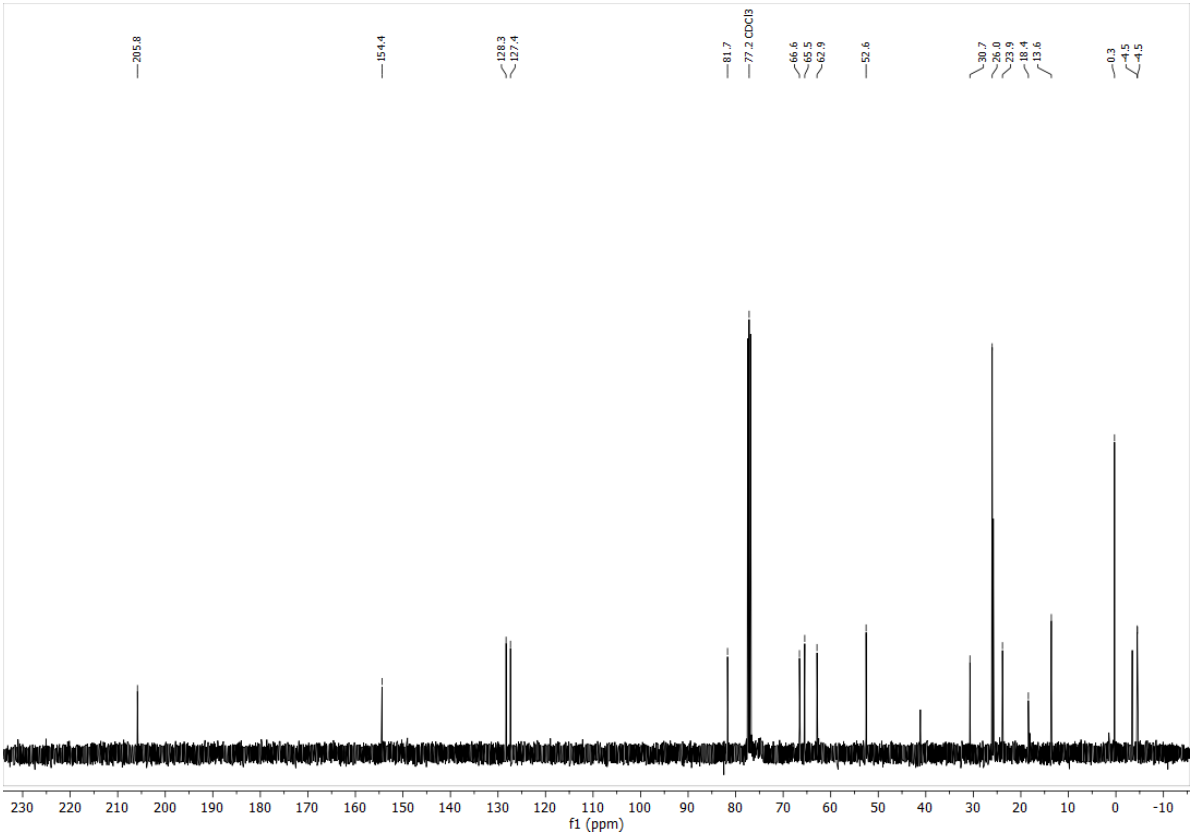
TBS-protection (synthesis of **31**)



*^{1}H-spectrum of **31** in $CDCl_3$.*

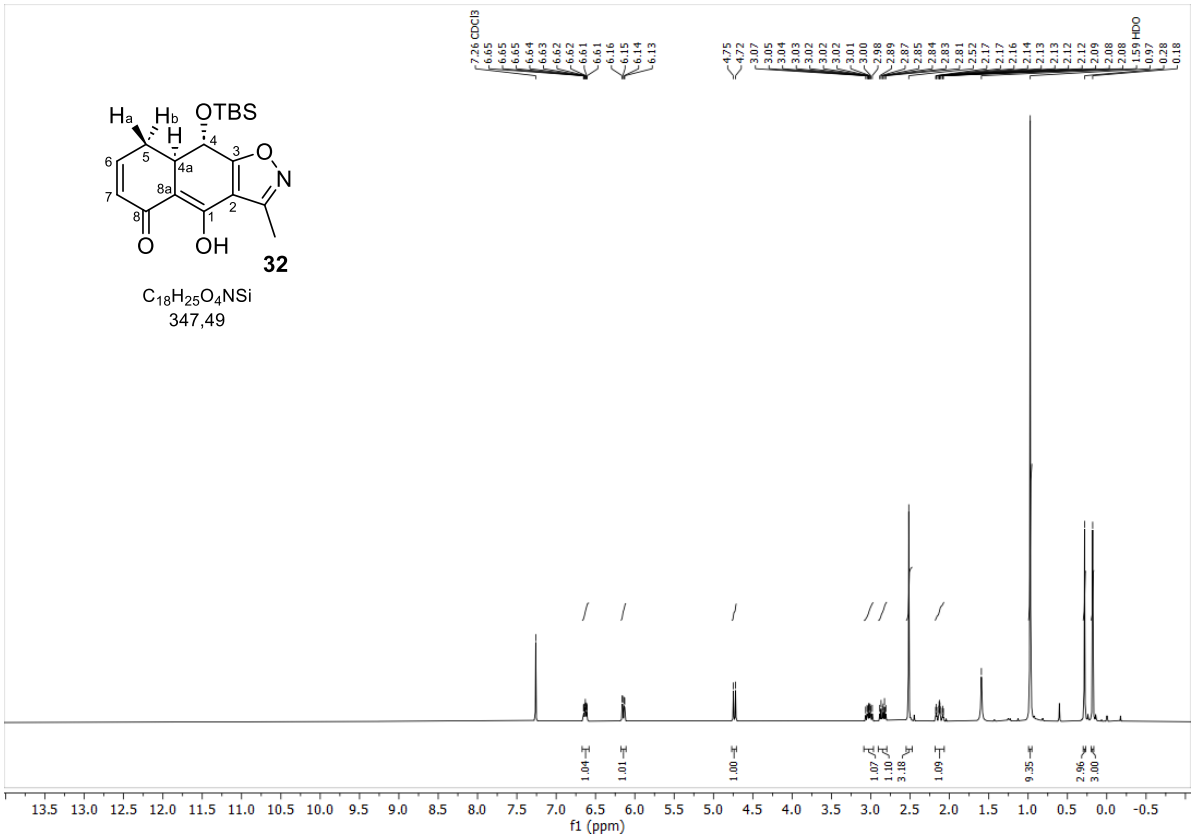


*^{1}H-spectrum of **31** in $CDCl_3$ (selected regions between 1,8-6,0 ppm).*

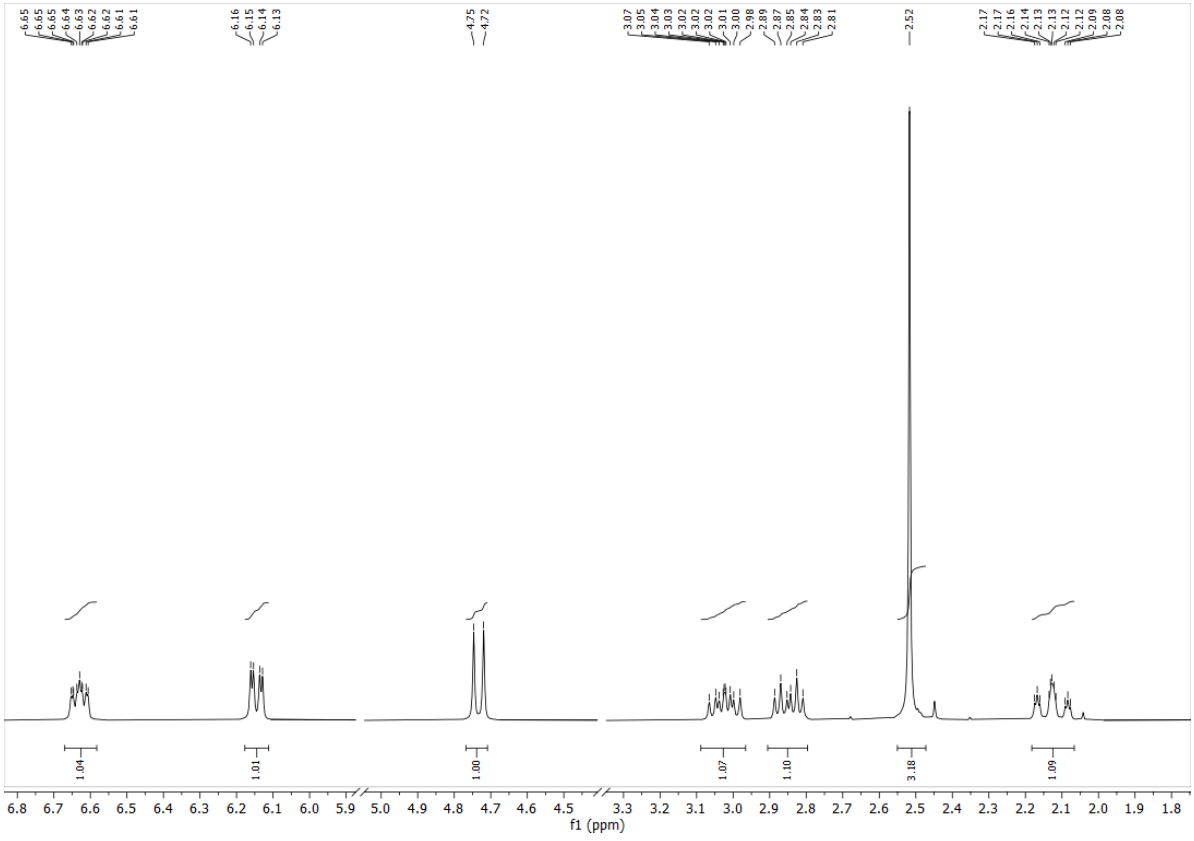


*^{13}C-spectrum of **31** in $CDCl_3$.*

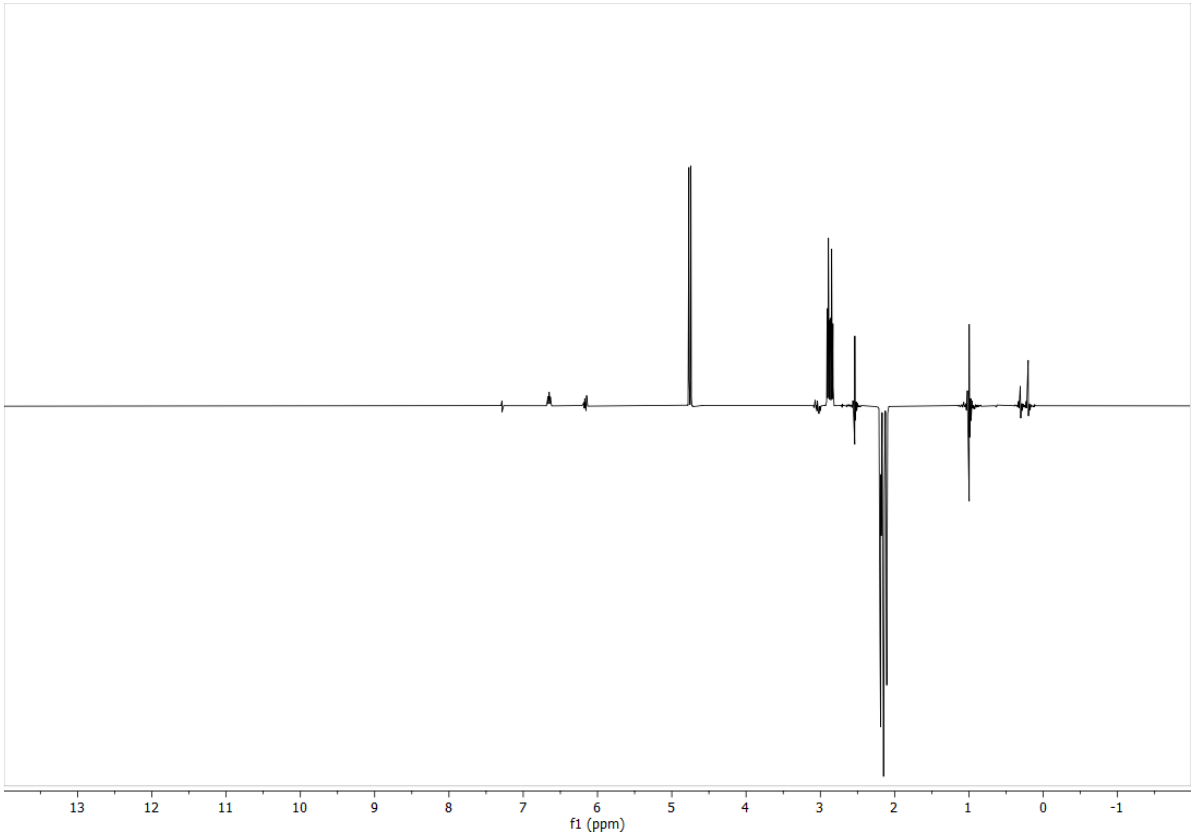
IBX-oxidation (synthesis of **32**)



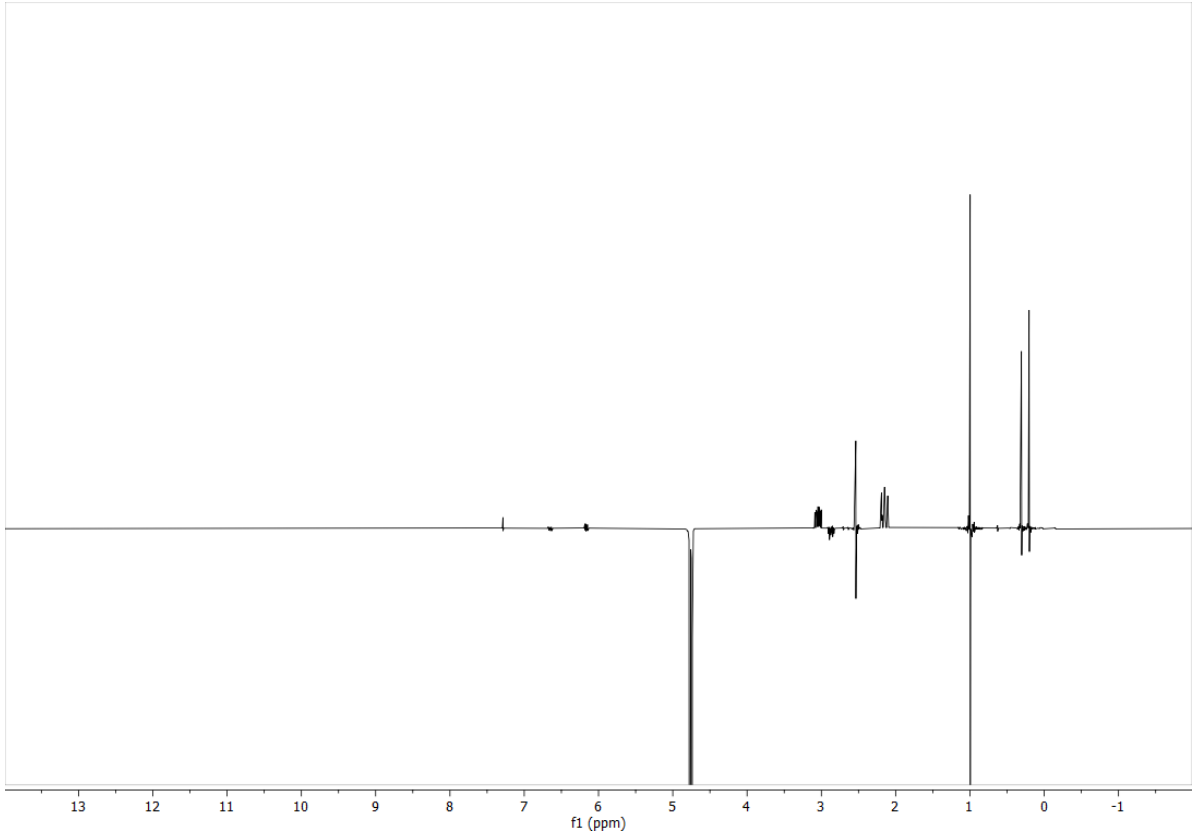
*^{1}H-spectrum of **32** in $CDCl_3$.*



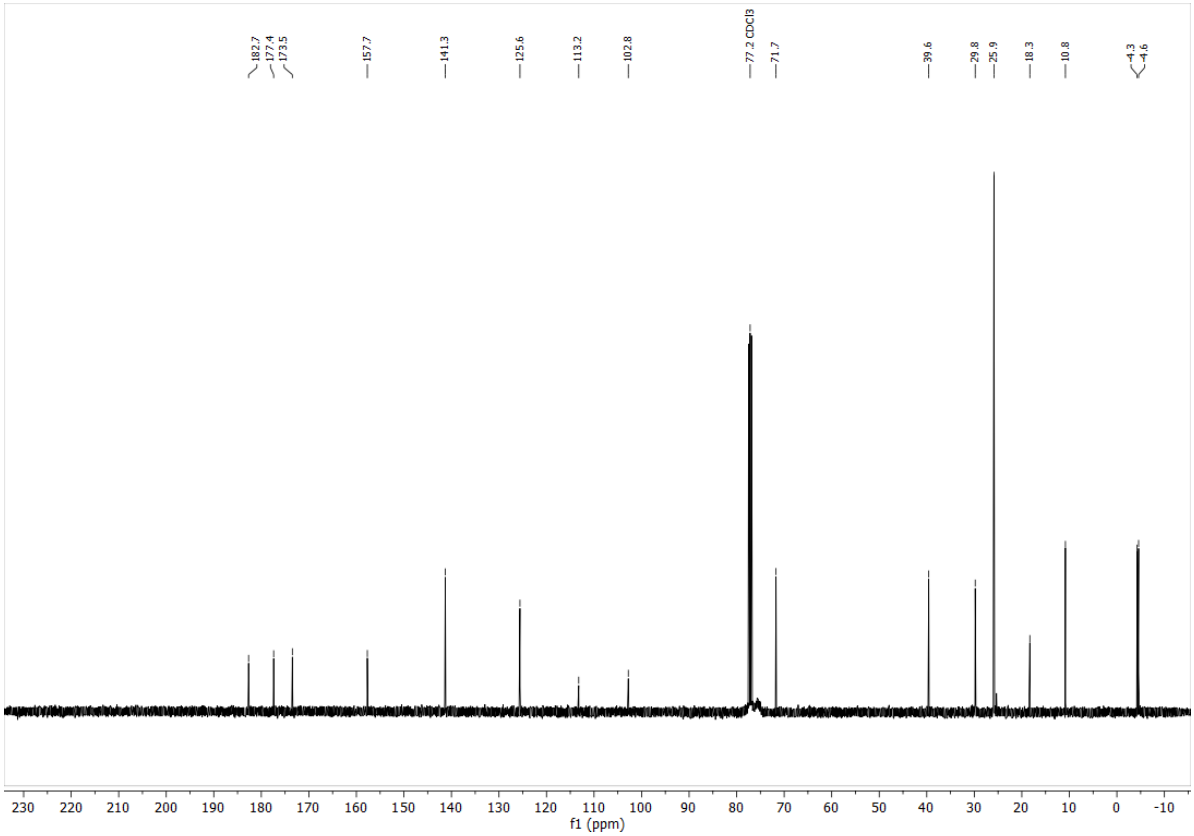
*^{1}H-spectrum of **32** in $CDCl_3$ (selected regions between 1,8-6,8 ppm).*



*NOE-spectrum of **32** in $CDCl_3$ (frequency saturation at 2,15 ppm).*

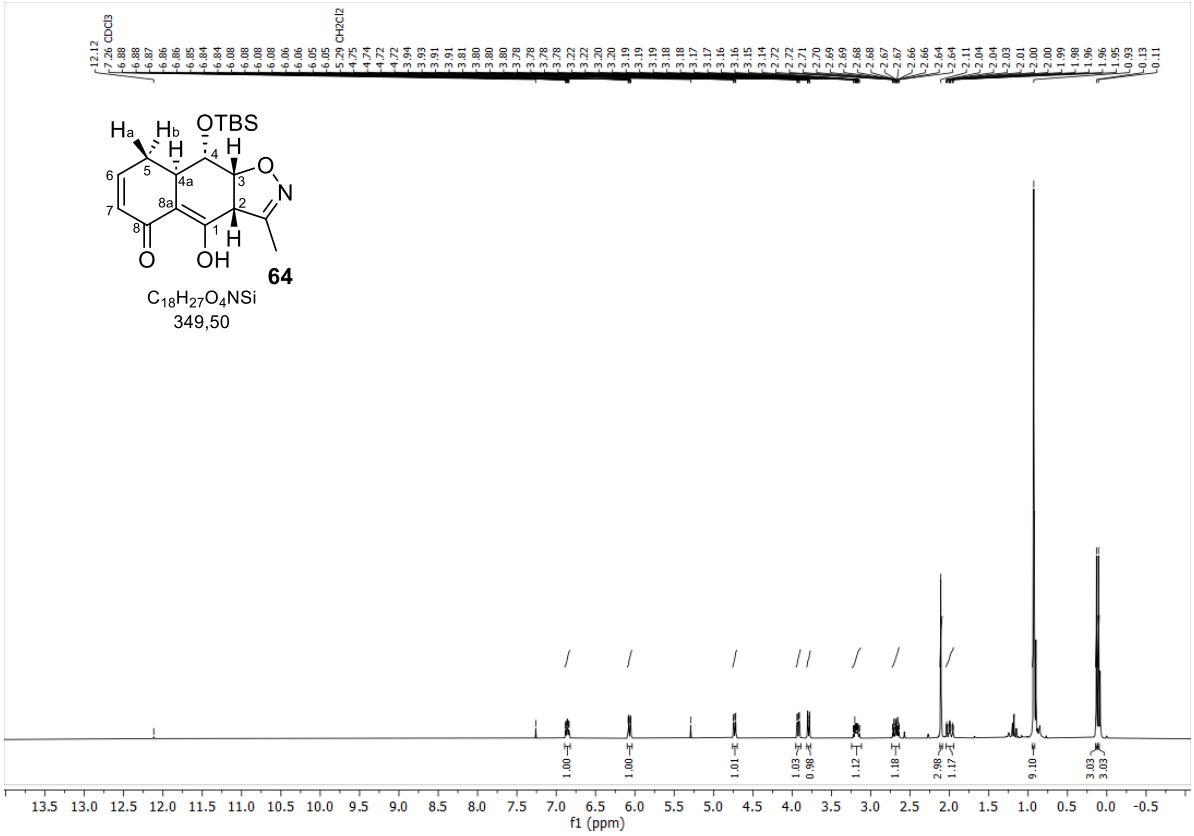


*NOE-spectrum of **32** in $CDCl_3$ (frequency saturation at 4,76 ppm).*

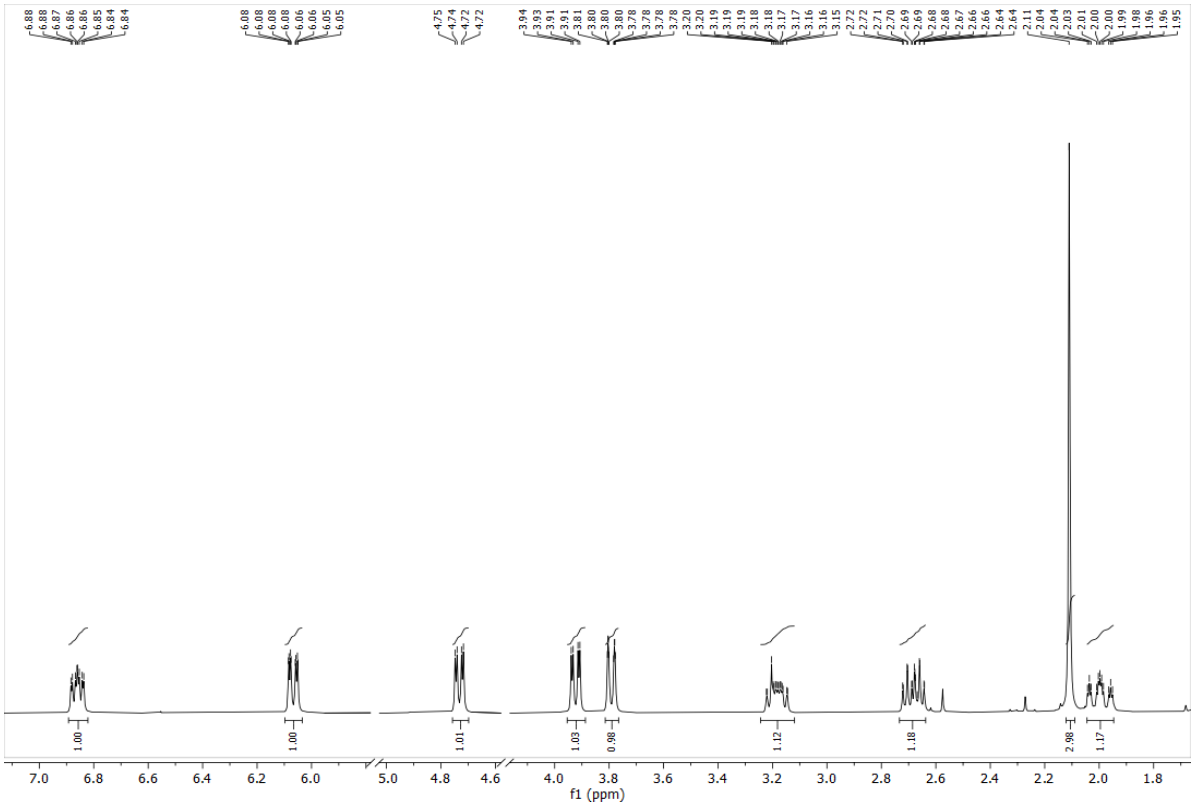


*^{13}C-spectrum of **32** in $CDCl_3$.*

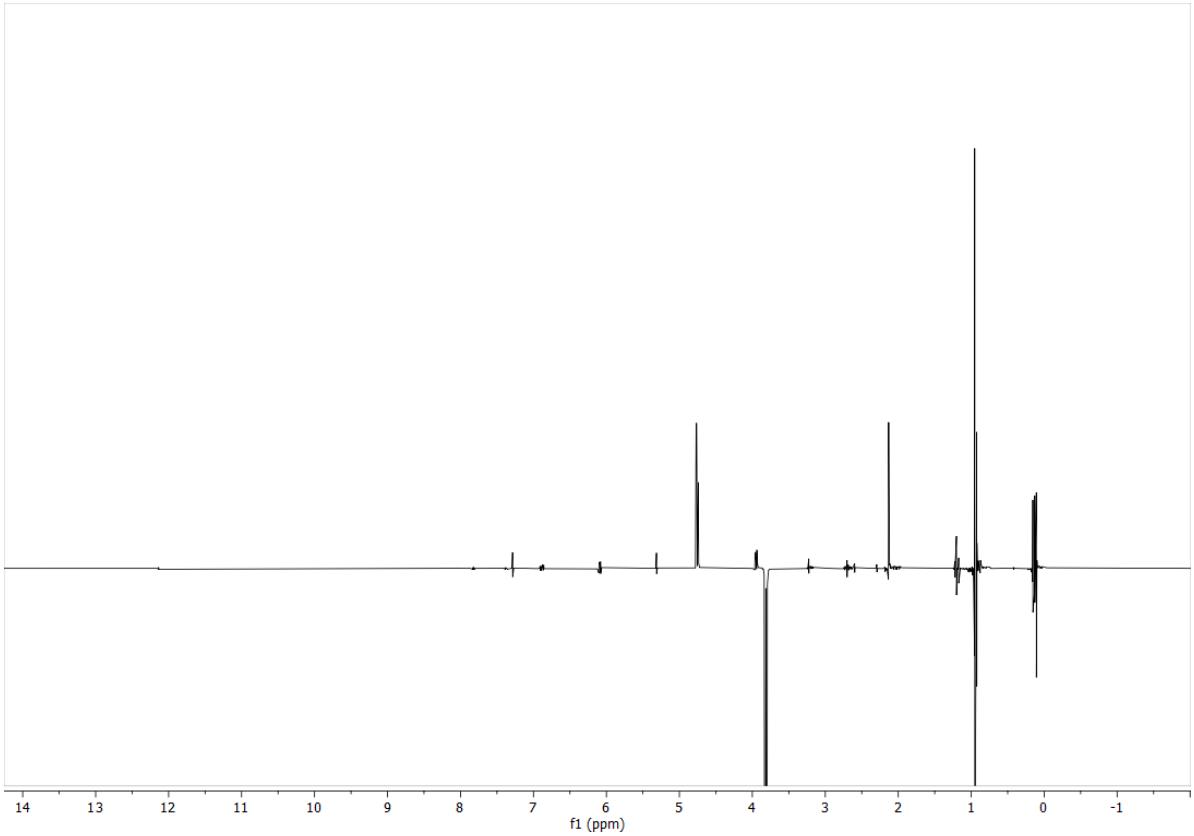
8.2.1.7 (3a*S*,4a*R*,8a*R*,9*S*,9a*R*)-9-((*tert*-butyldimethylsilyl)oxy)-3-methyl-8,8a,9,9a-tetrahydro-naphtho[2,3-*d*]isoxazole-4,5(3a*H*,4a*H*)-dione **64**



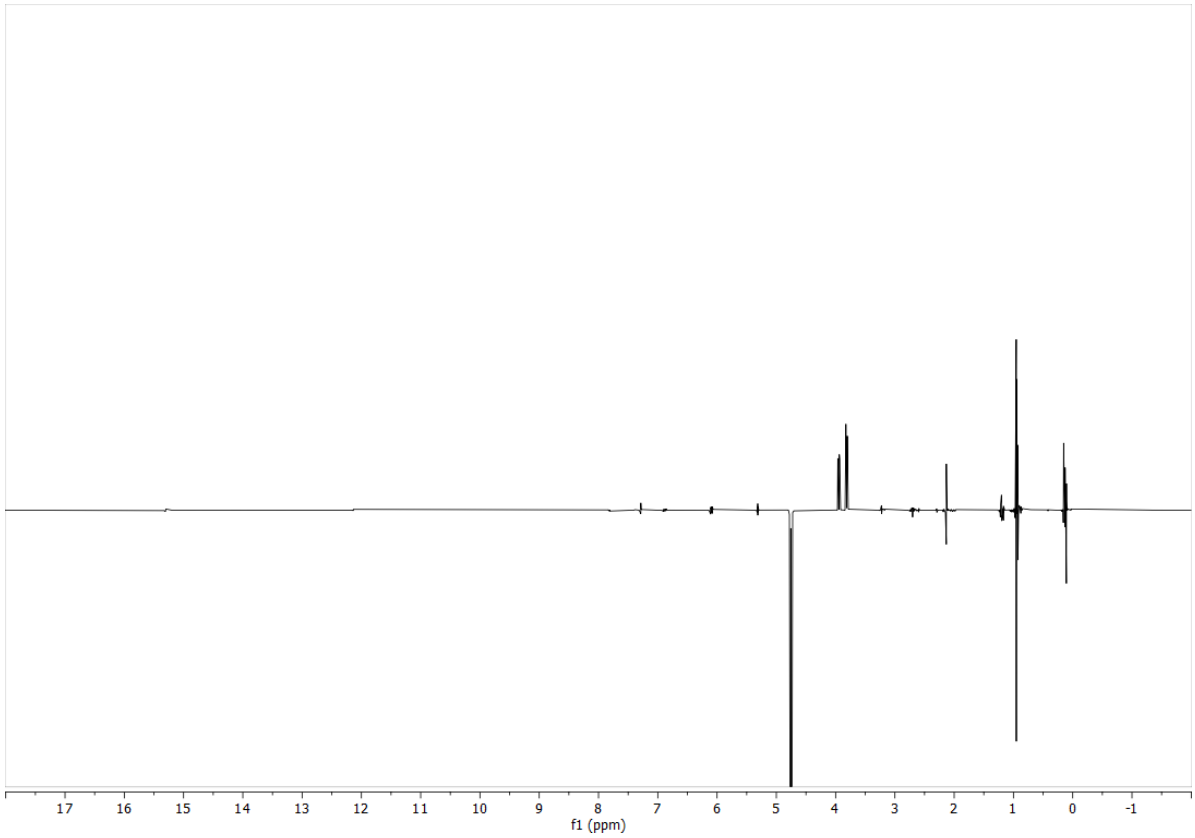
*^{1}H-spectrum of **64** in $CDCl_3$.*



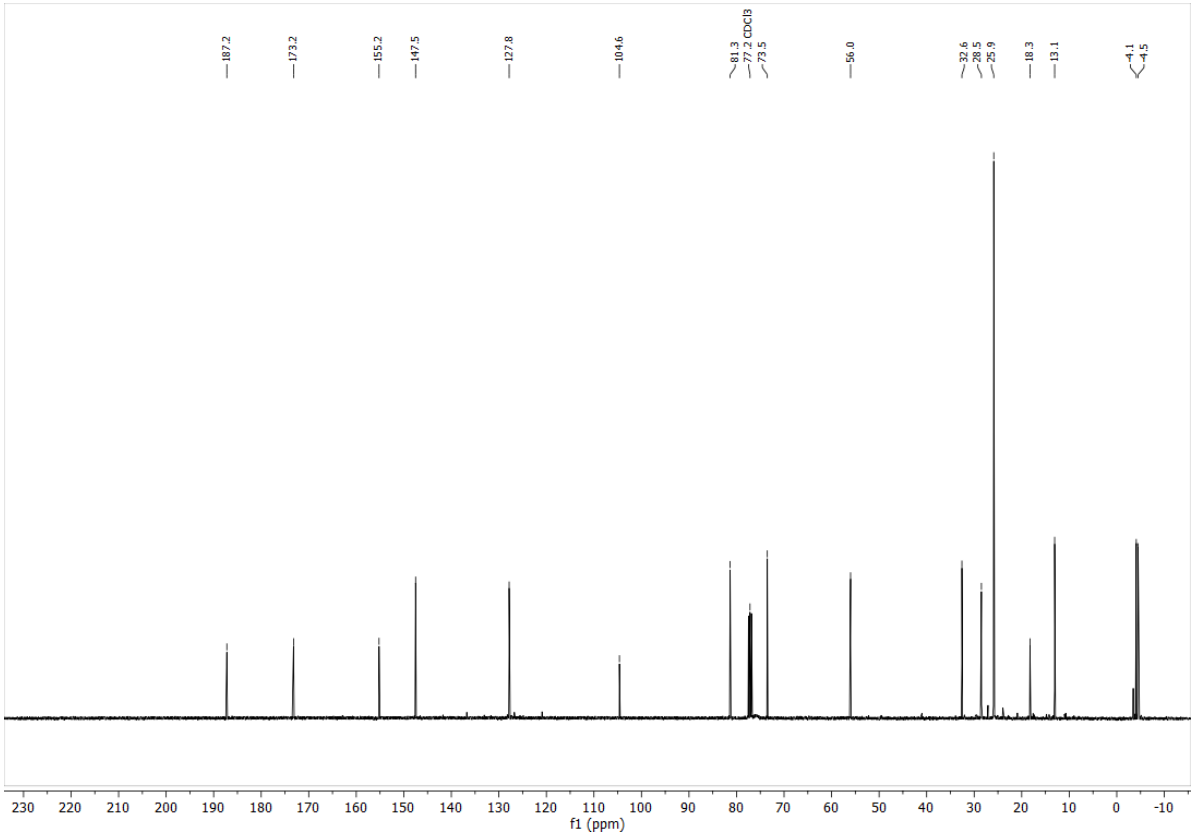
*^{1}H-spectrum of **64** in $CDCl_3$ (selected regions between 1,8-7,0 ppm).*



*NOE-spectrum of **64** in $CDCl_3$ (frequency saturation at 3,81 ppm).*



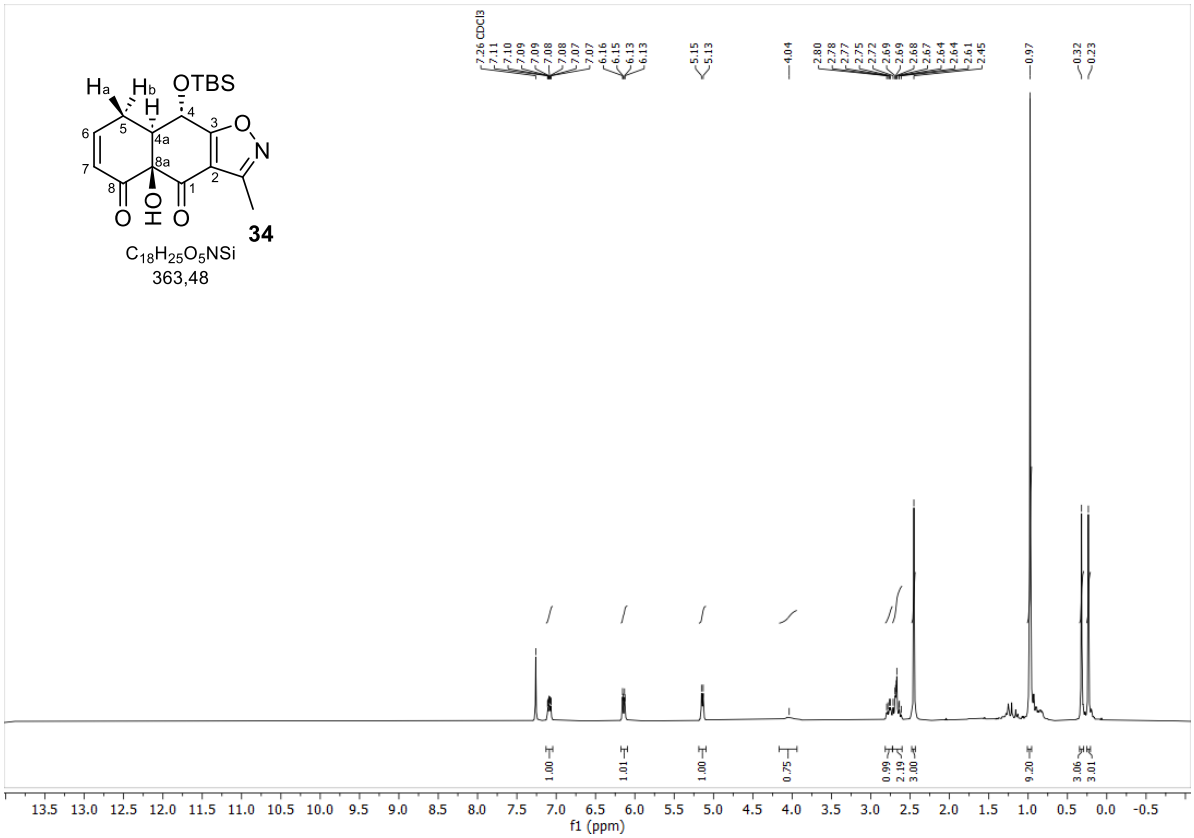
*NOE-spectrum of **64** in $CDCl_3$ (frequency saturation at 4,75 ppm).*



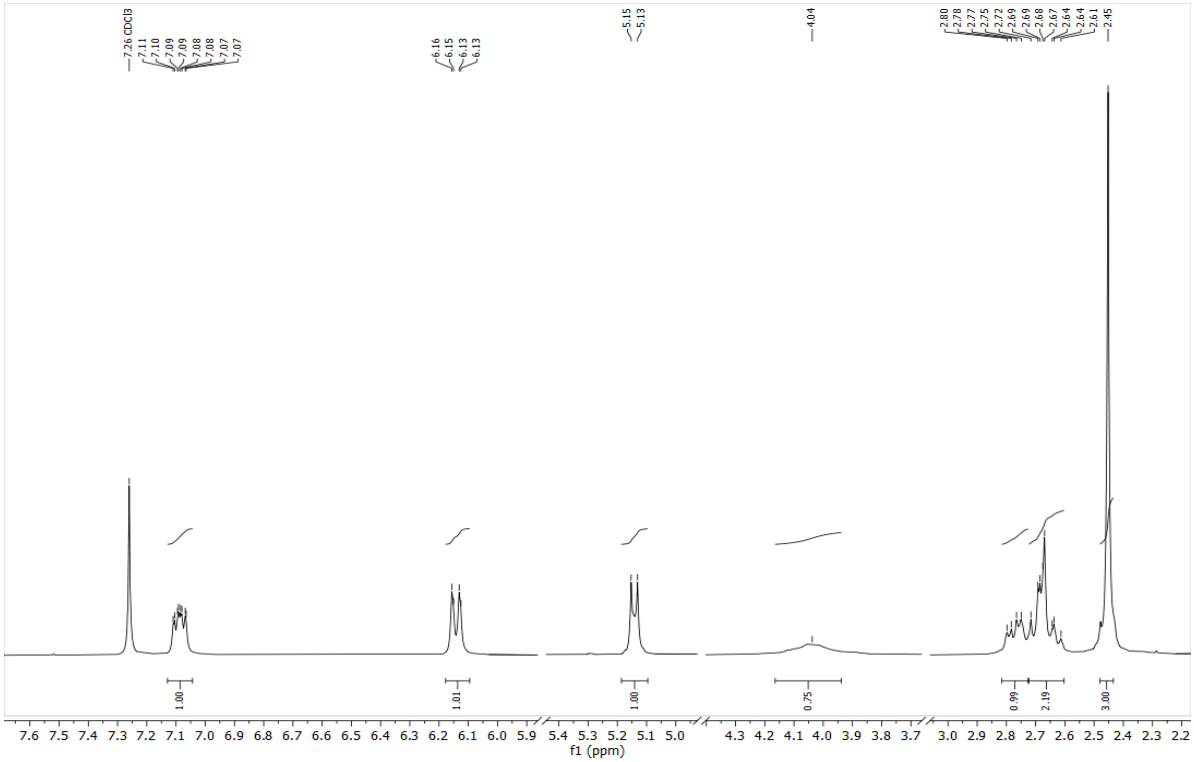
*^{13}C-spectrum of **64** in $CDCl_3$.*

8.2.1.8 (4a*S*,8a*S*,9*S*)-9-((*tert*-butyldimethylsilyl)oxy)-4a-hydroxy-3-methyl-8a,9-dihydronaphtho-[2,3-*d*]isoxazole-4,5(4a*H*,8*H*)-dione **35**

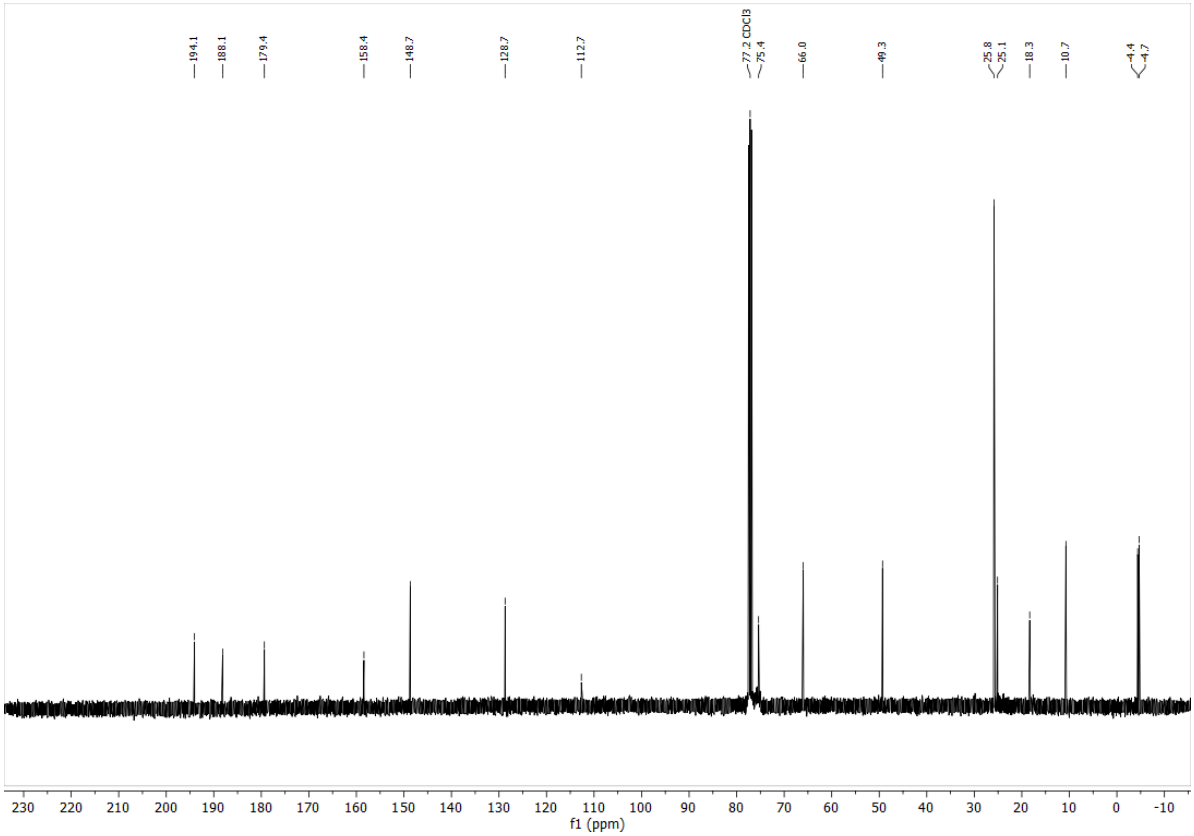
α-hydroxylation (synthesis of **34**)



*^{1}H-spectrum of **34** in $CDCl_3$.*

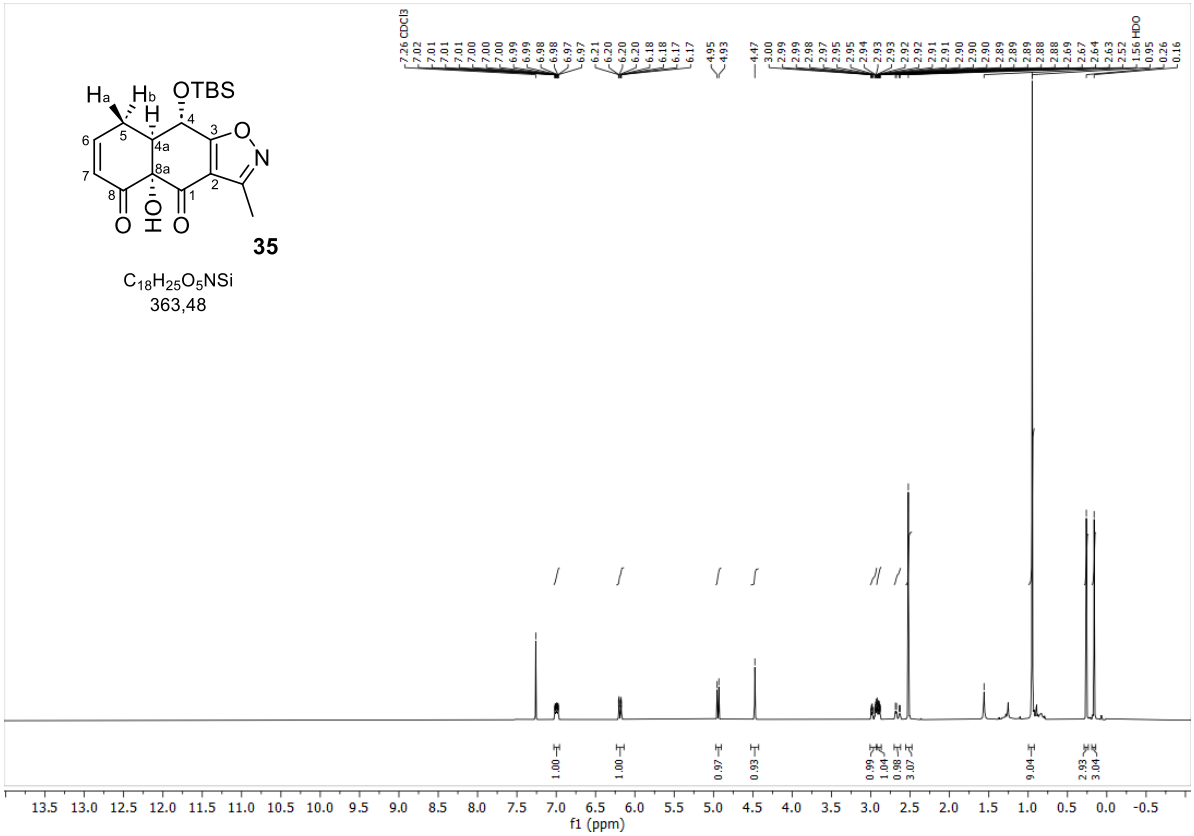


*^{1}H-spectrum of **34** in $CDCl_3$ (selected regions between 2,2-7,6 ppm).*

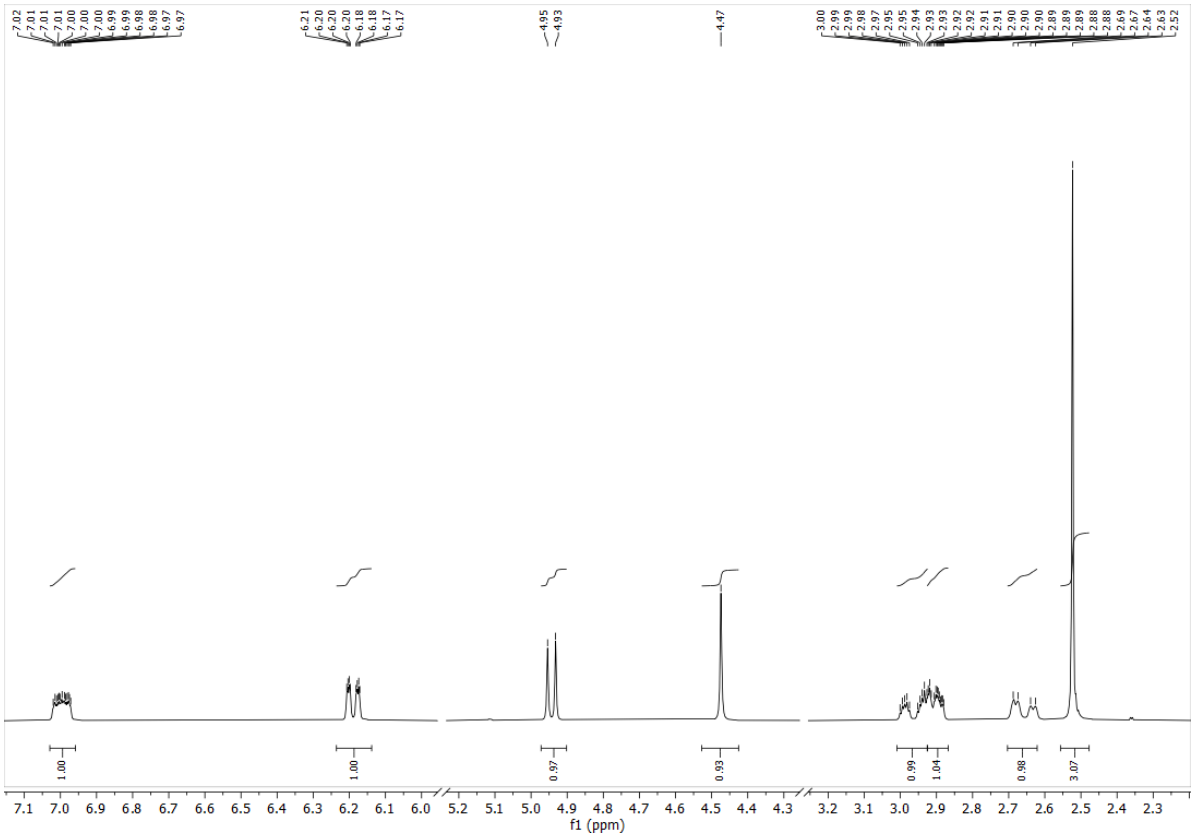


*^{13}C-spectrum of **34** in $CDCl_3$.*

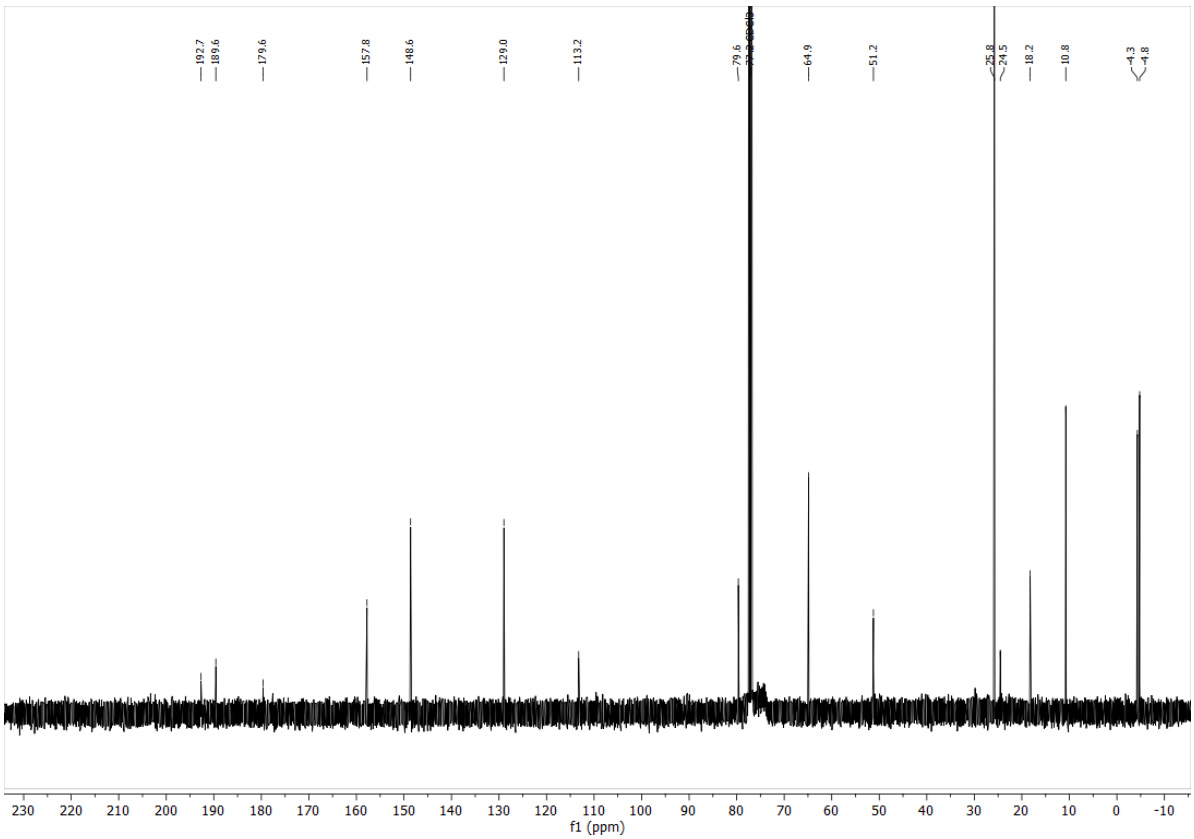
α-ketol rearrangement (synthesis of **35**)



*^{1}H-spectrum of **35** in $CDCl_3$.*

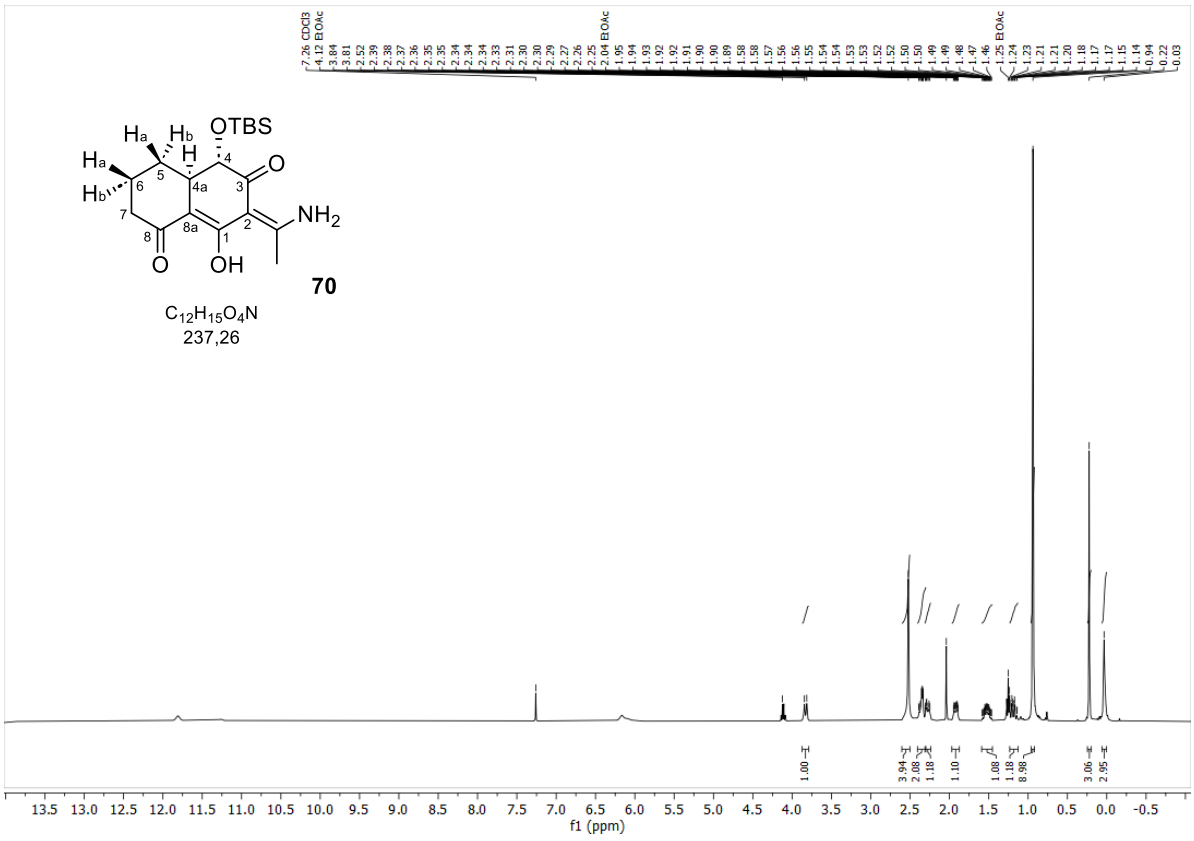


*^{1}H-spectrum of **35** in $CDCl_3$ (selected regions between 2,3-7,1 ppm).*

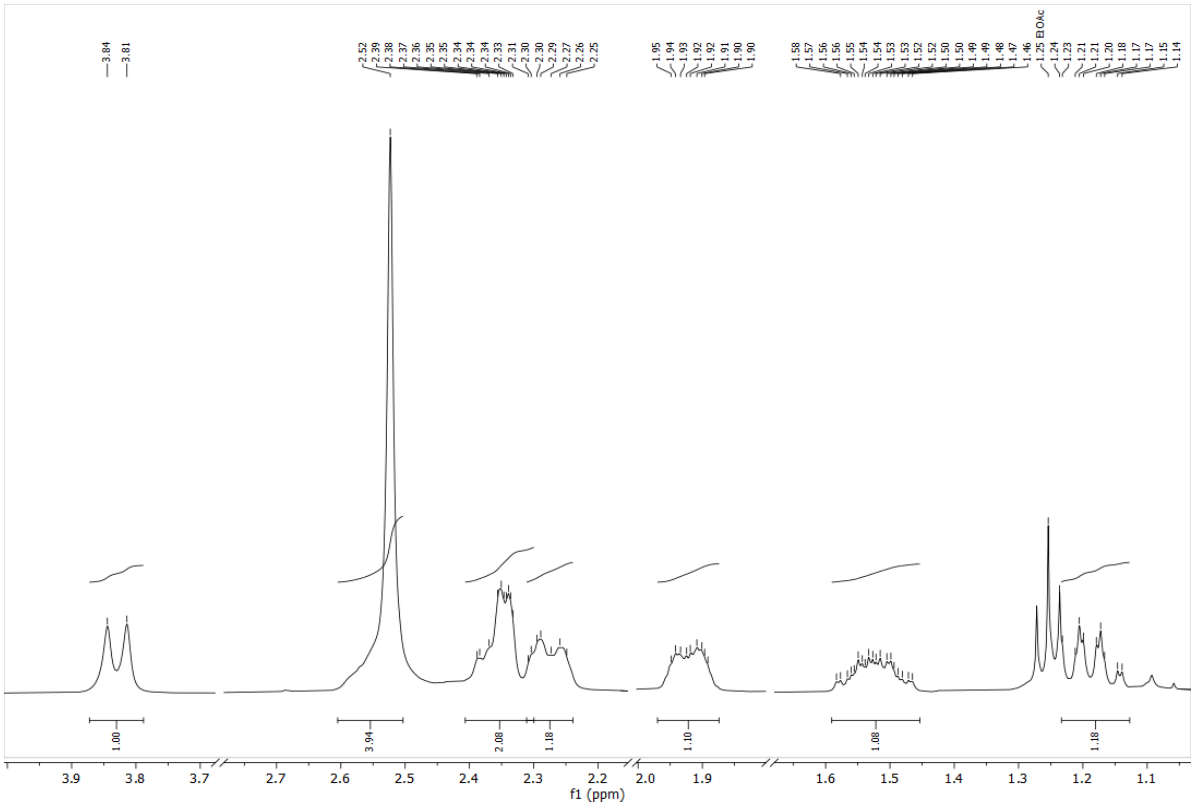


*^{13}C-spectrum of **35** in $CDCl_3$.*

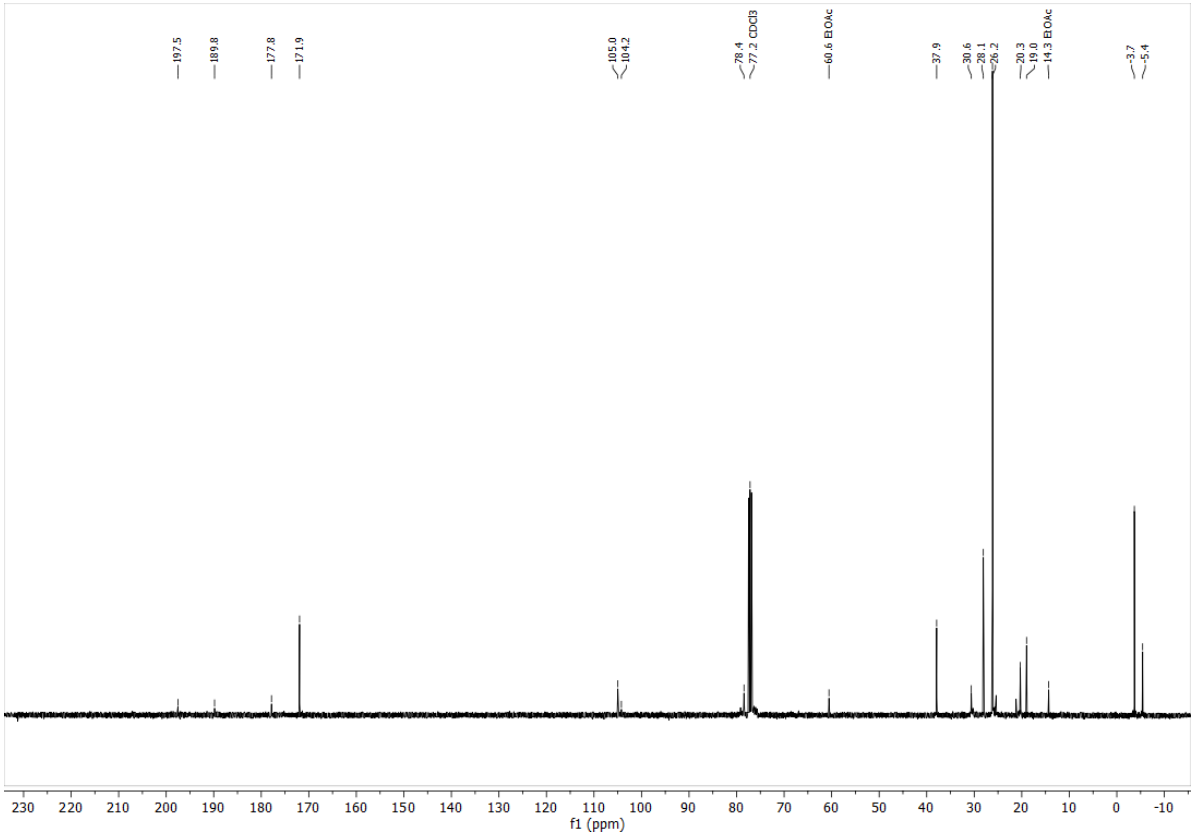
8.2.1.9 Isoxazole-hydrogenation study ((4a*R*,5*S*,*Z*)-7-(1-aminoethylidene)-5-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-3,4,4a,7-tetrahydronaphthalene-1,6(2*H*,5*H*)-dione **70**)



*^{1}H-spectrum of **70** in $CDCl_3$.*



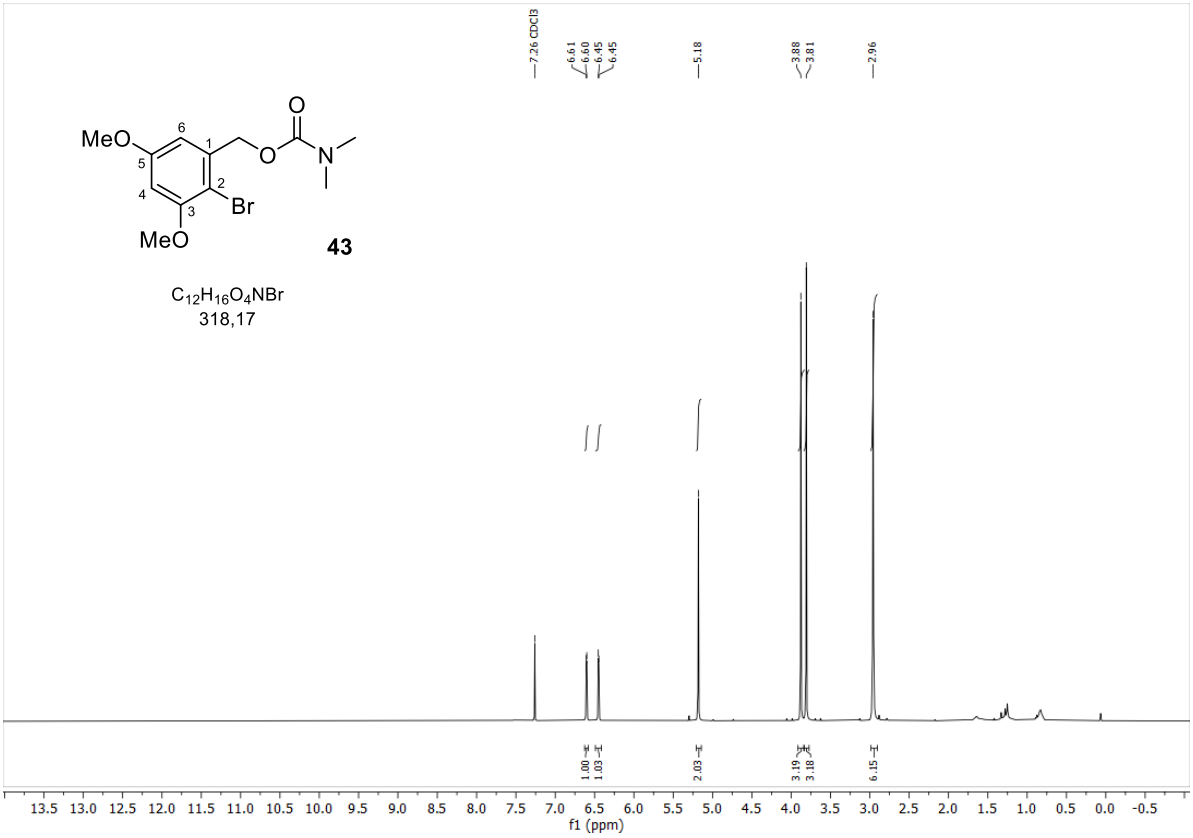
*^{1}H-spectrum of **70** in $CDCl_3$ (selected regions between 2,0-6,9 ppm).*



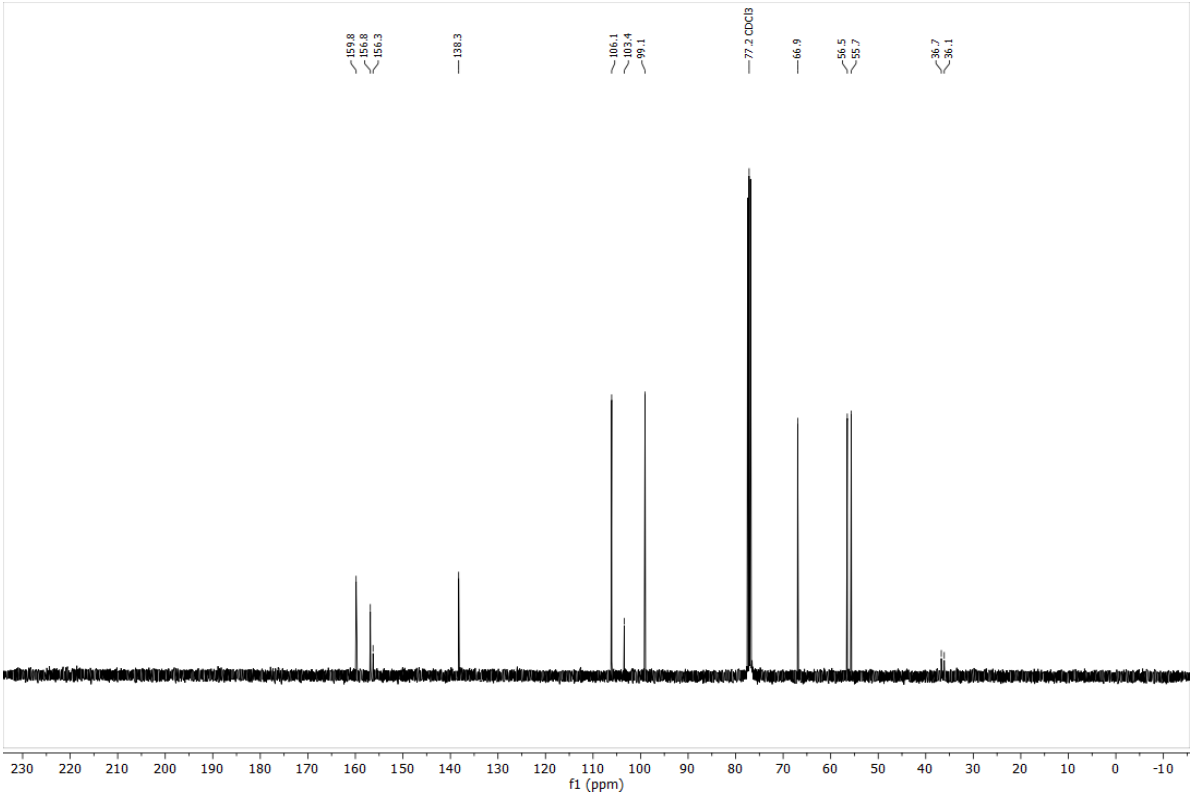
*^{13}C-spectrum of **70** in $CDCl_3$.*

8.2.2 Phthalides **44** and **45**

8.2.2.1 2-bromo-3,5-dimethoxybenzyl dimethylcarbamate **43**

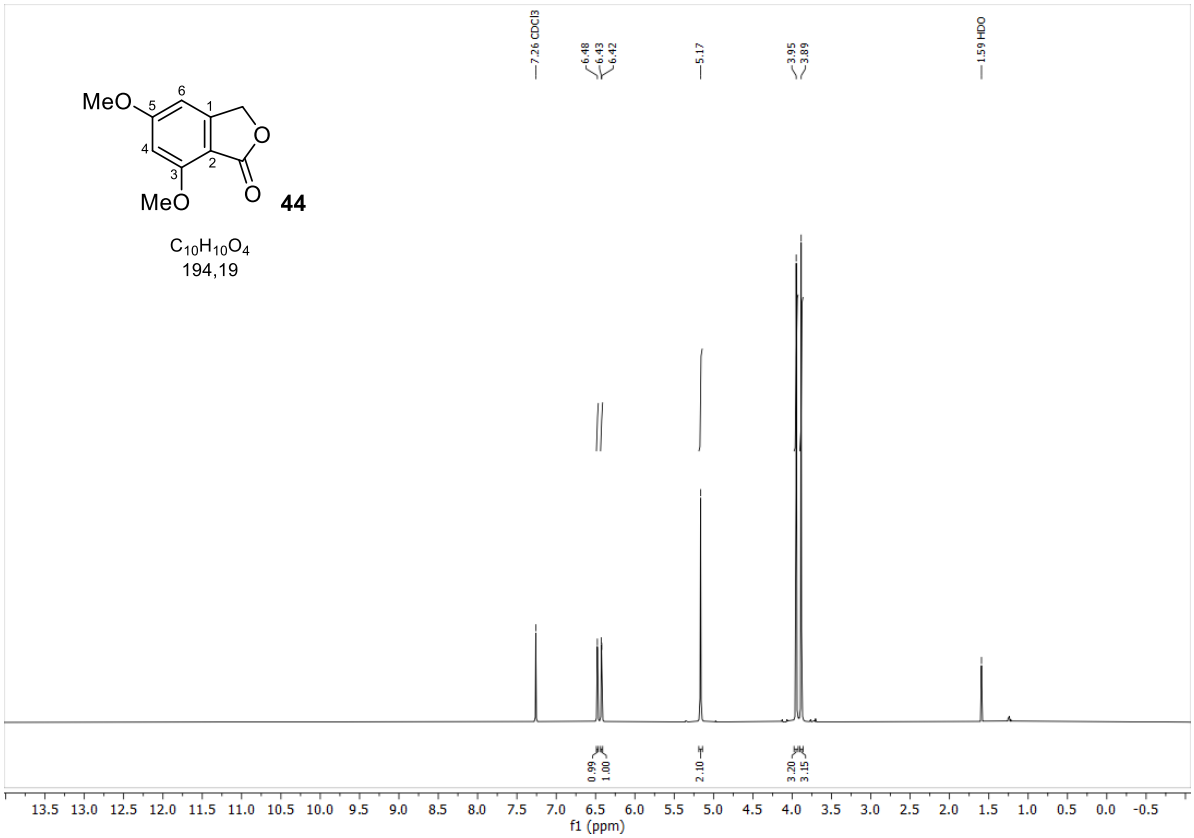


*^{1}H-spectrum of **43** in $CDCl_3$.*

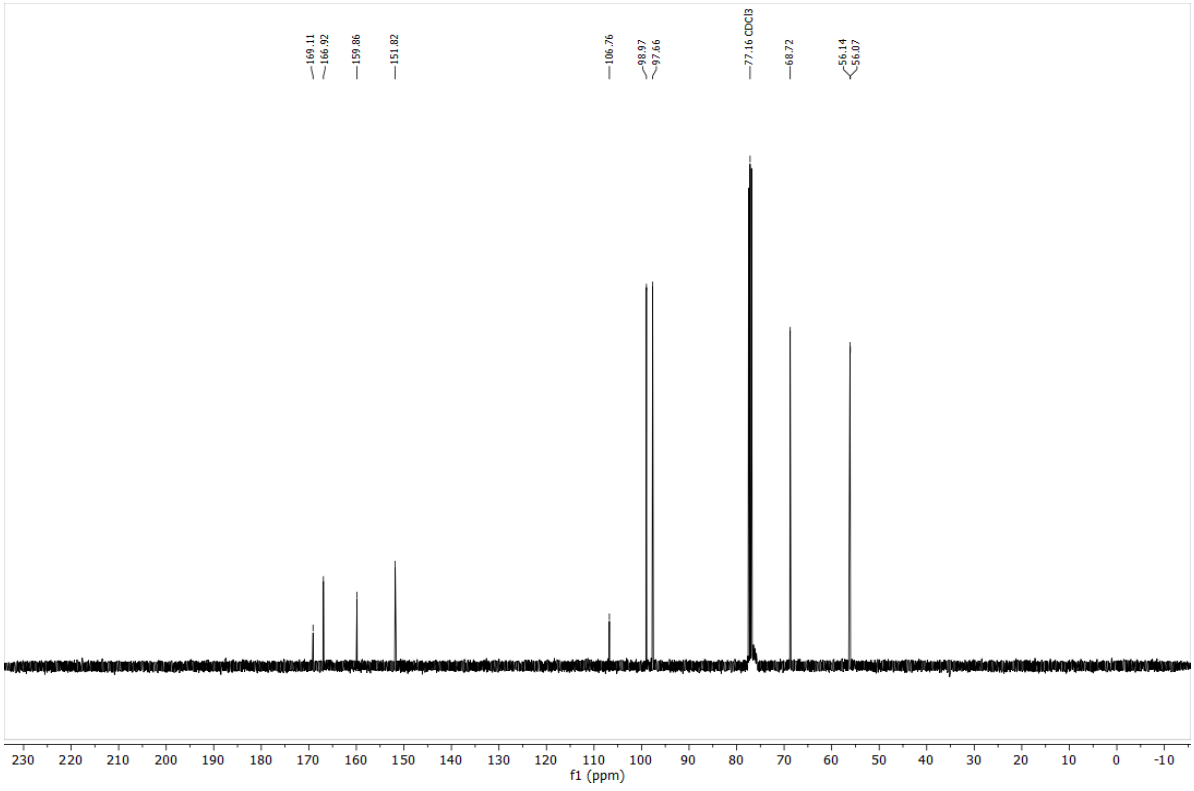


*^{13}C-spectrum of **43** in $CDCl_3$.*

8.2.2.2 5,7-dimethoxyisobenzofuran-1(3*H*)-one **44**

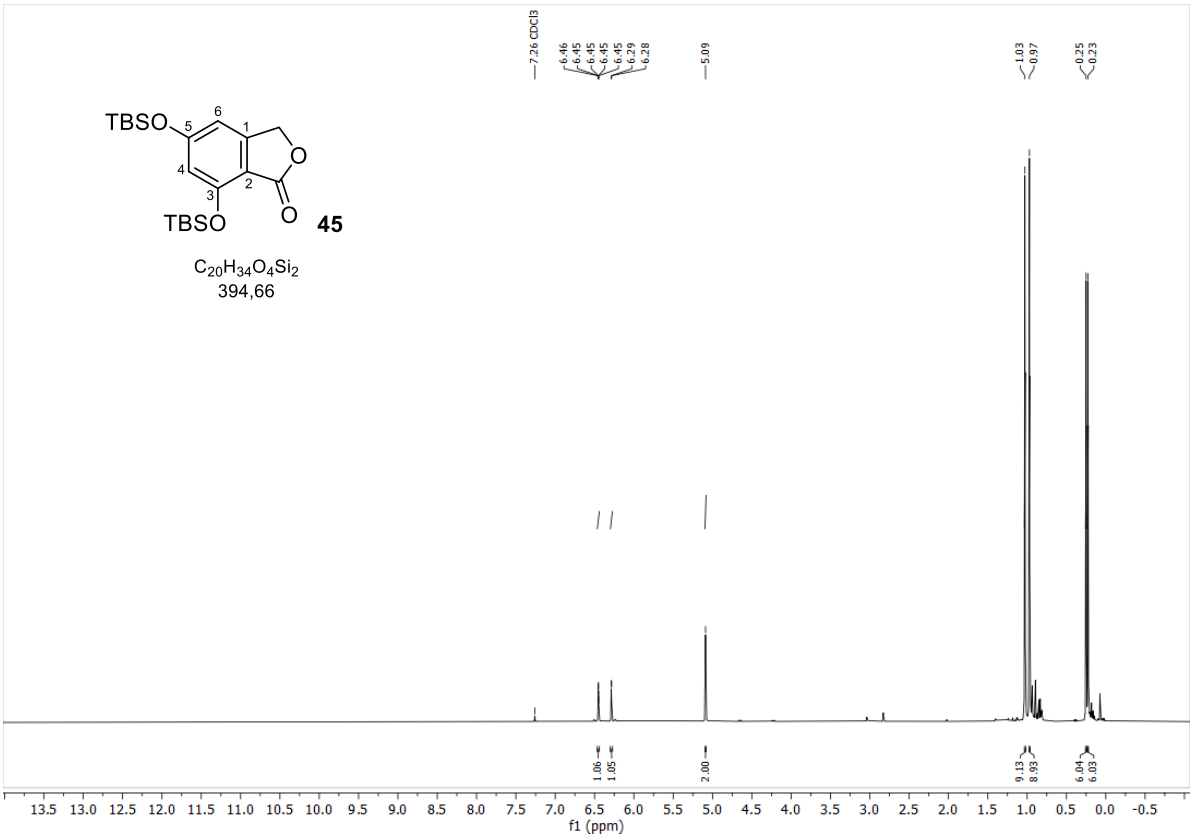


*[1]H-spectrum of **44** in $CDCl_3$.*

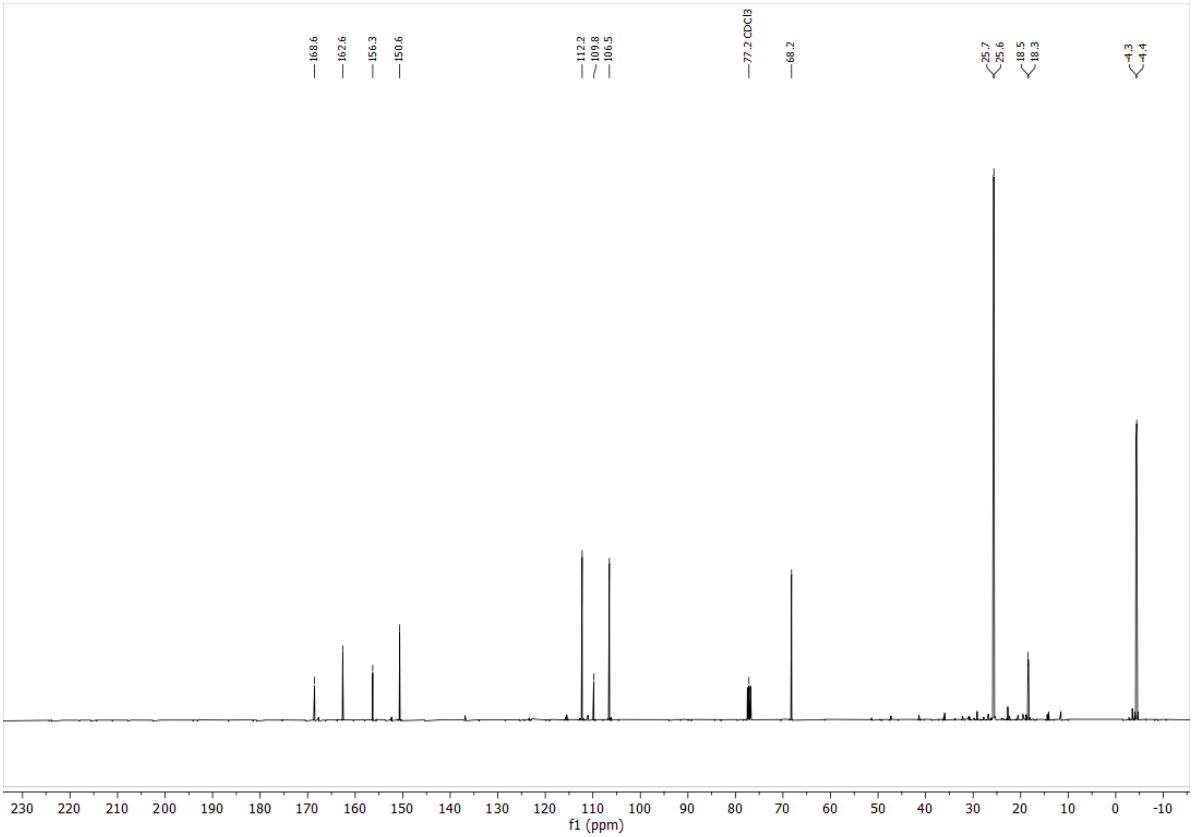


*[13]C-spectrum of **70** in $CDCl_3$.*

8.2.2.3 5,7-bis((*tert*-butyldimethylsilyl)oxy)isobenzofuran-1(3*H*)-one **45**



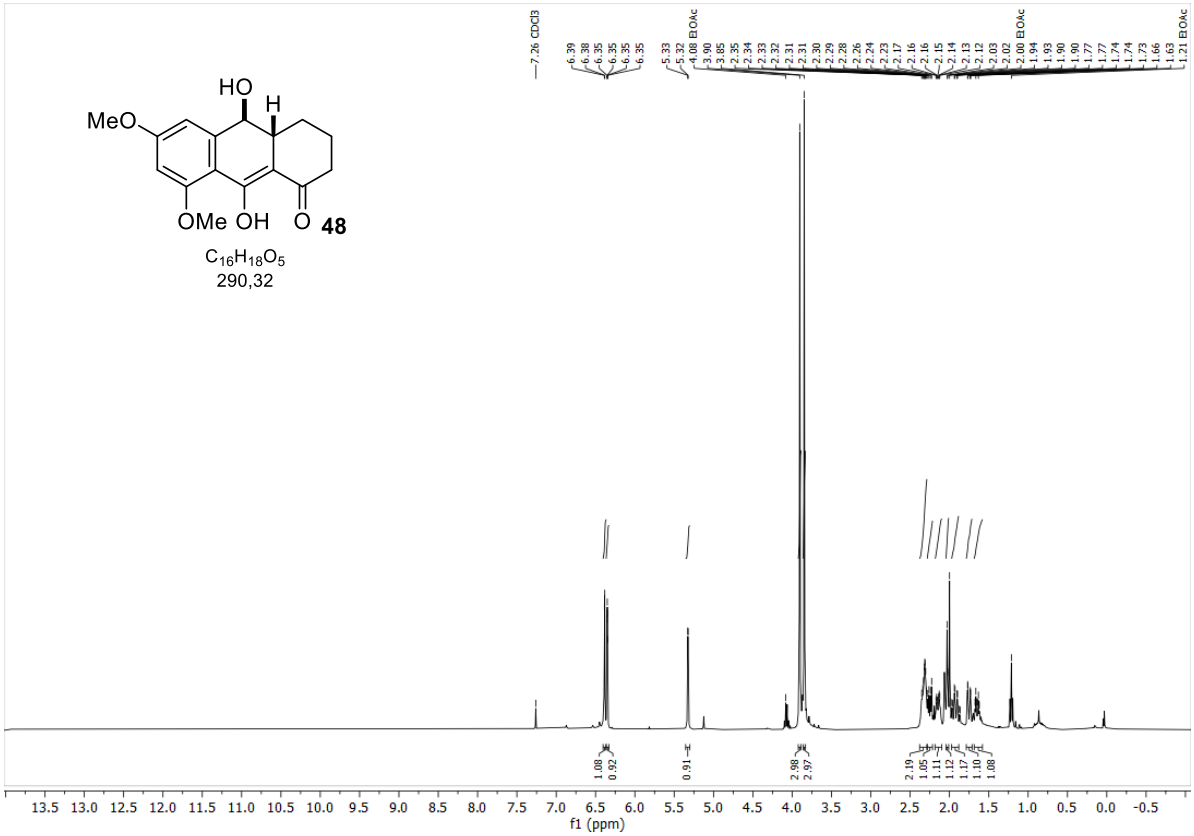
*^{1}H-spectrum of **45** in $CDCl_3$.*



*^{13}C-spectrum of **45** in $CDCl_3$.*

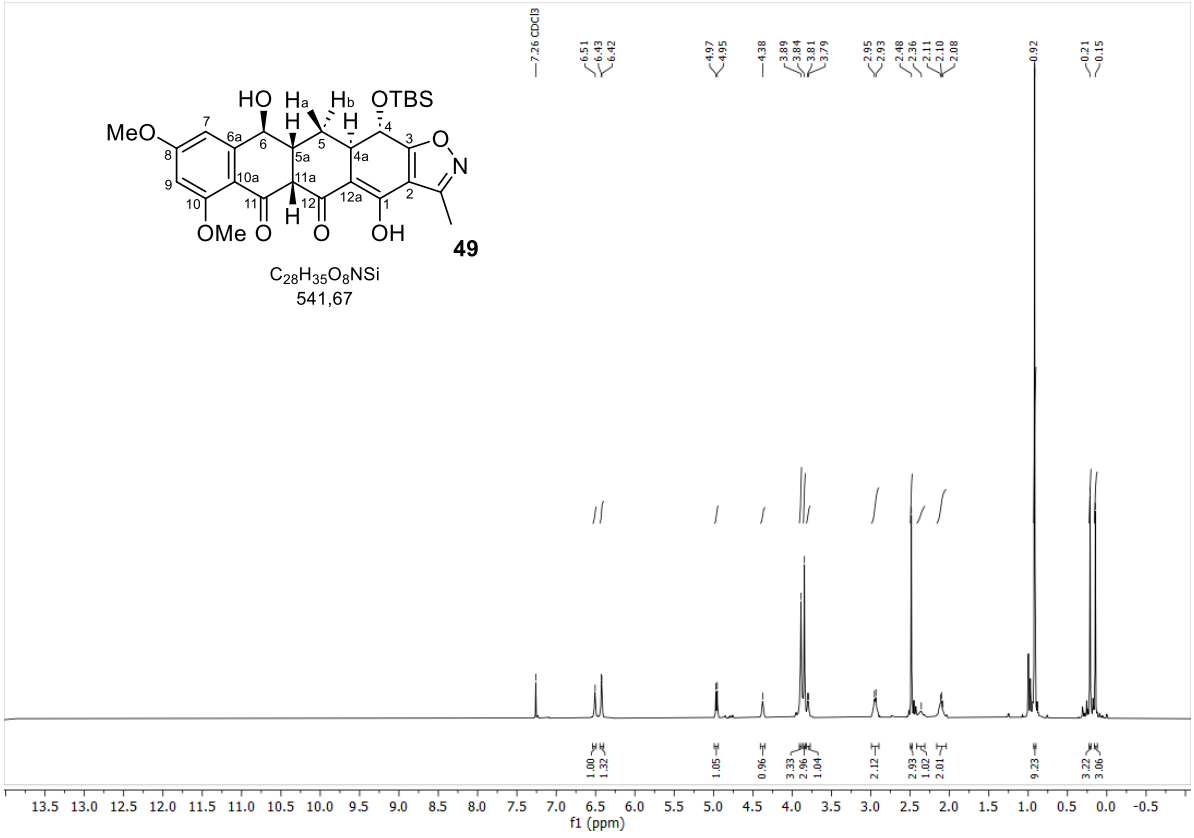
8.2.3 Demethylpremithramycinone **1** from enone **32** and *bio-assay* derivatives

8.2.3.1 Diels–Alder with furan reaction-study (synthesis of (4a*R*,10*S*)-9,10-dihydroxy-6,8-dimethoxy-3,4,4a,10-tetrahydroanthracen-1(2*H*)-one **48**)

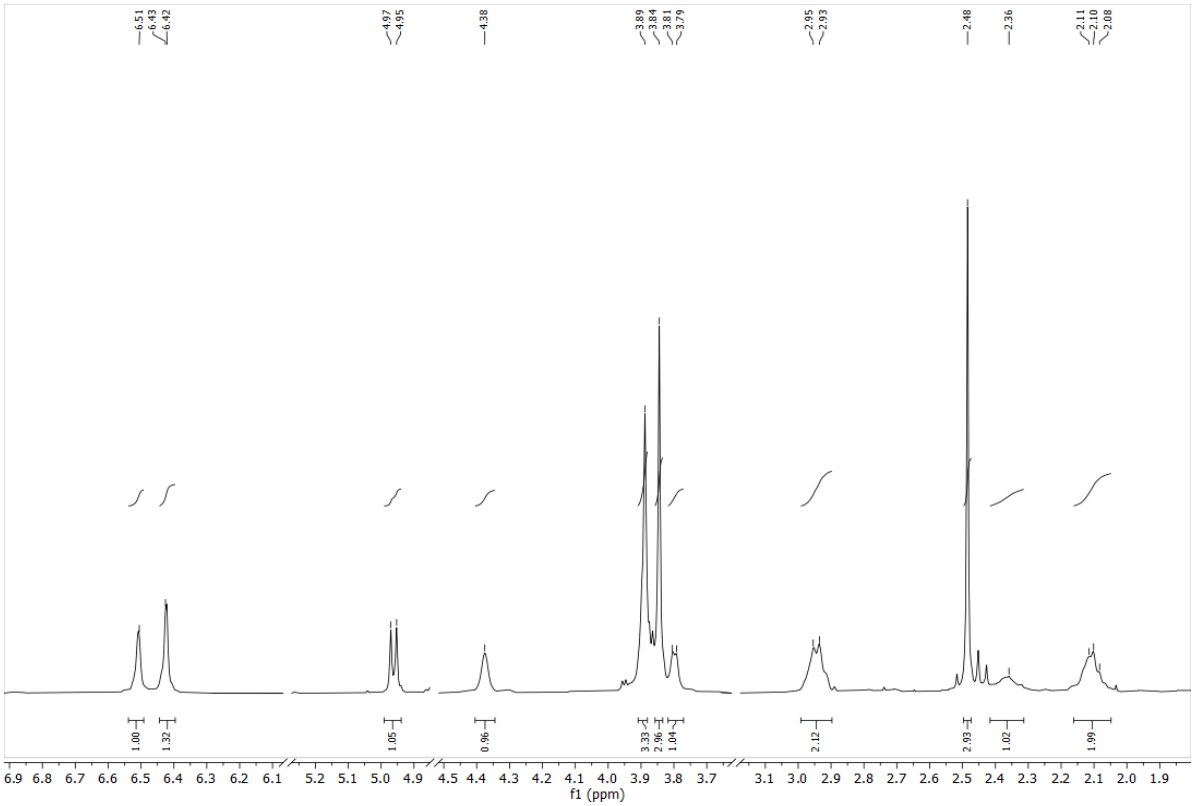


*^{1}H-spectrum of **48** in $CDCl_3$.*

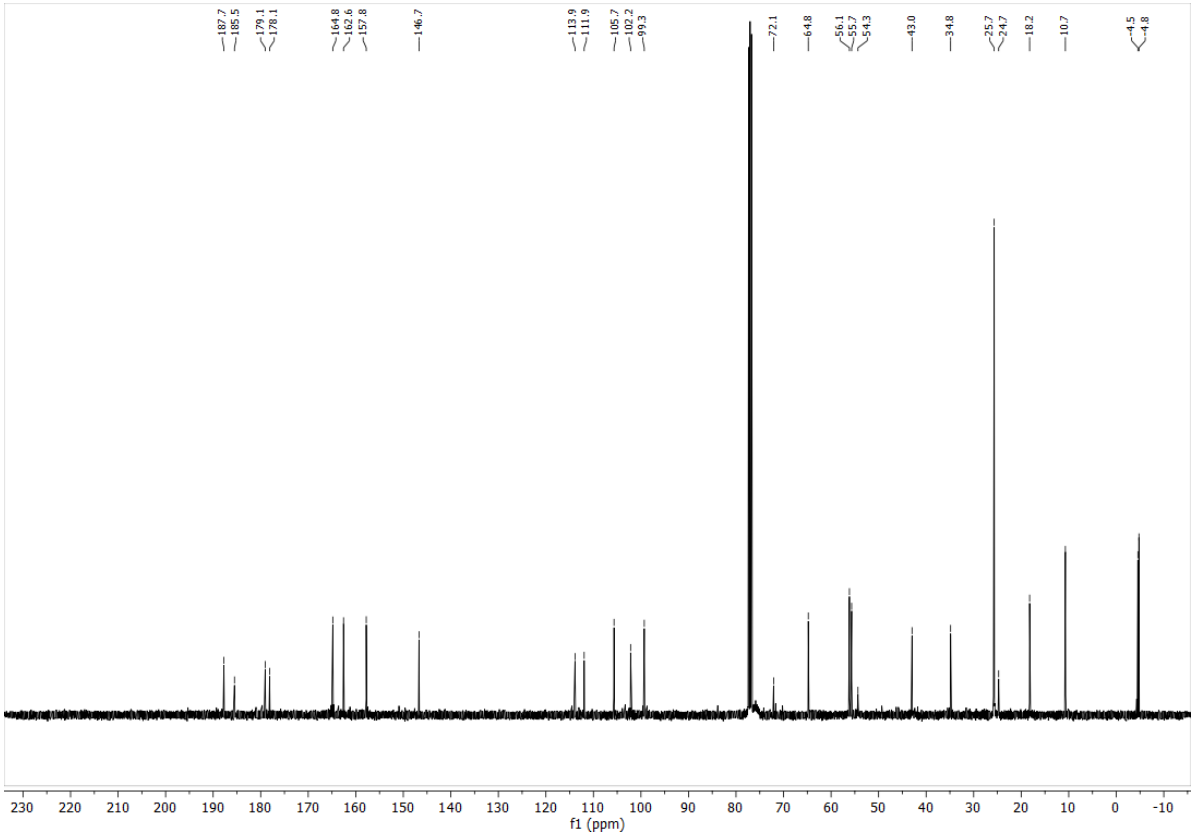
8.2.3.2 (11*S*,11a*R*,12a*R*,13*S*)-13-((*tert*-butyldimethylsilyl)oxy)-4,6,11-trihydroxy-7,9-dimethoxy-3-methyl-11a,12,12a,13-tetrahydrotetraceno[2,3-*d*]isoxazol-5(11*H*)-one **49**



*^{1}H-spectrum of **49** in $CDCl_3$.*



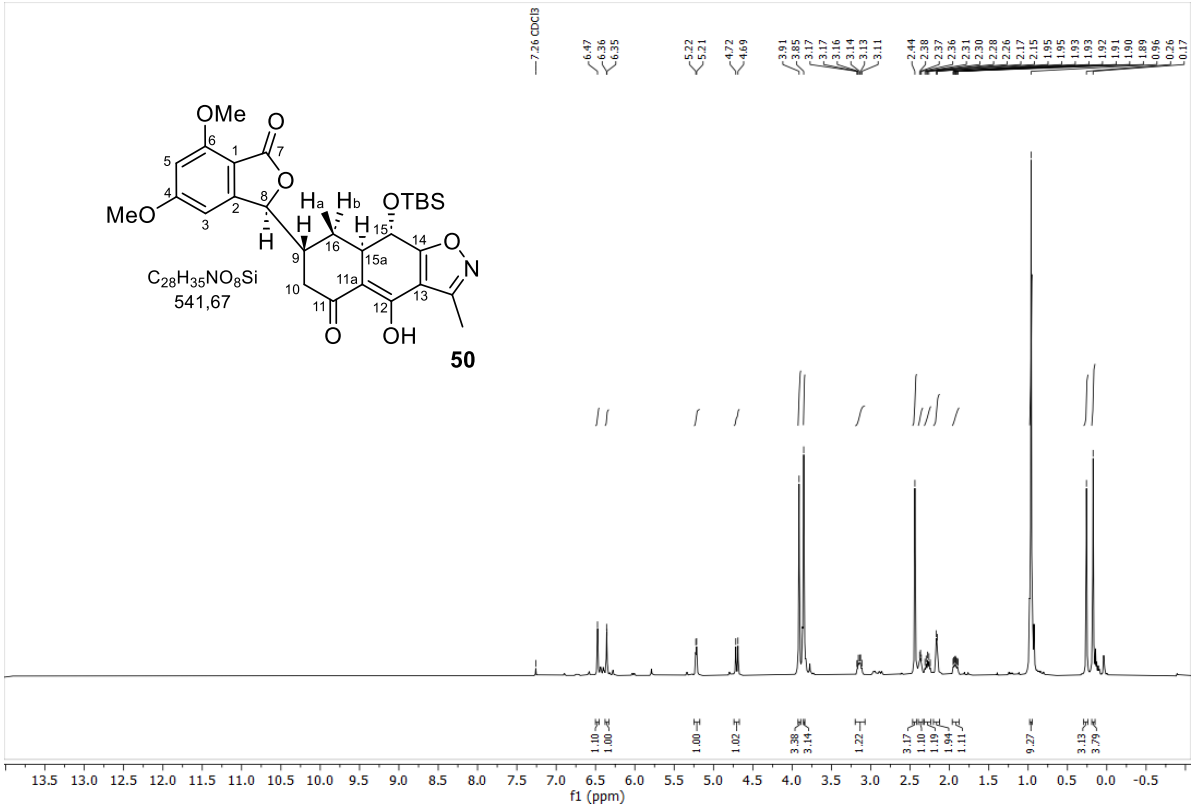
*^{1}H-spectrum of **49** in $CDCl_3$ (selected regions between 1,9-6,9 ppm).*



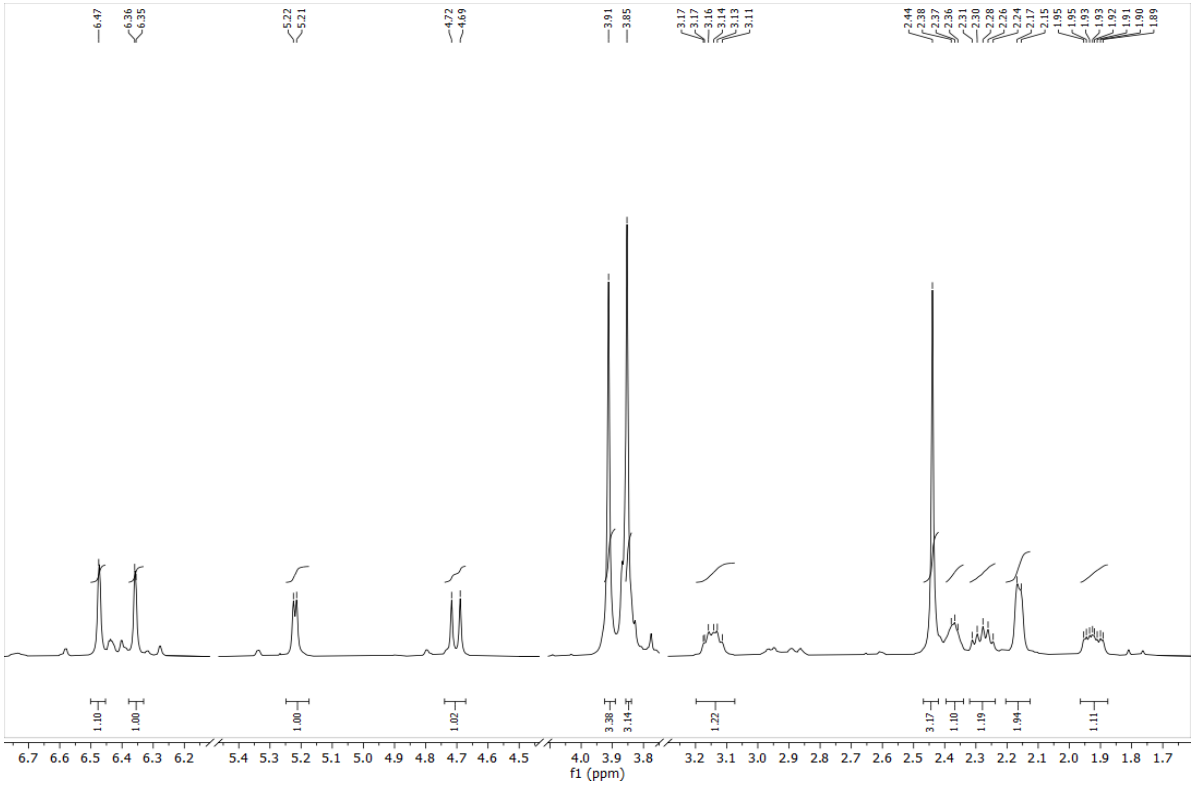
*^{13}C-spectrum of **49** in $CDCl_3$.*

1,4-addition product **50**

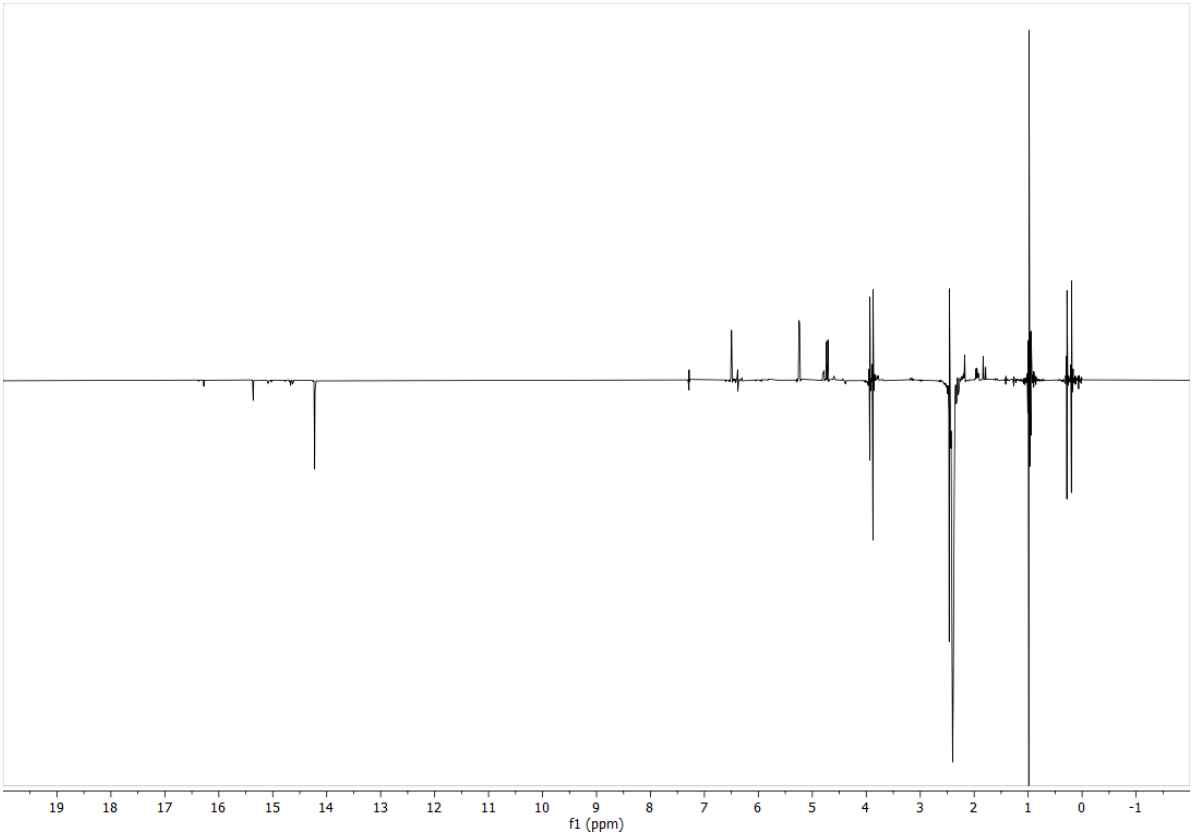
((7*R*,8a*R*,9*S*)-9-((*tert*-butyldimethylsilyl)oxy)-7-((*S*)-4,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-4-hydroxy-3-methyl-7,8,8a,9-tetrahydronaphtho[2,3-d]isoxazol-5(6*H*)-one)



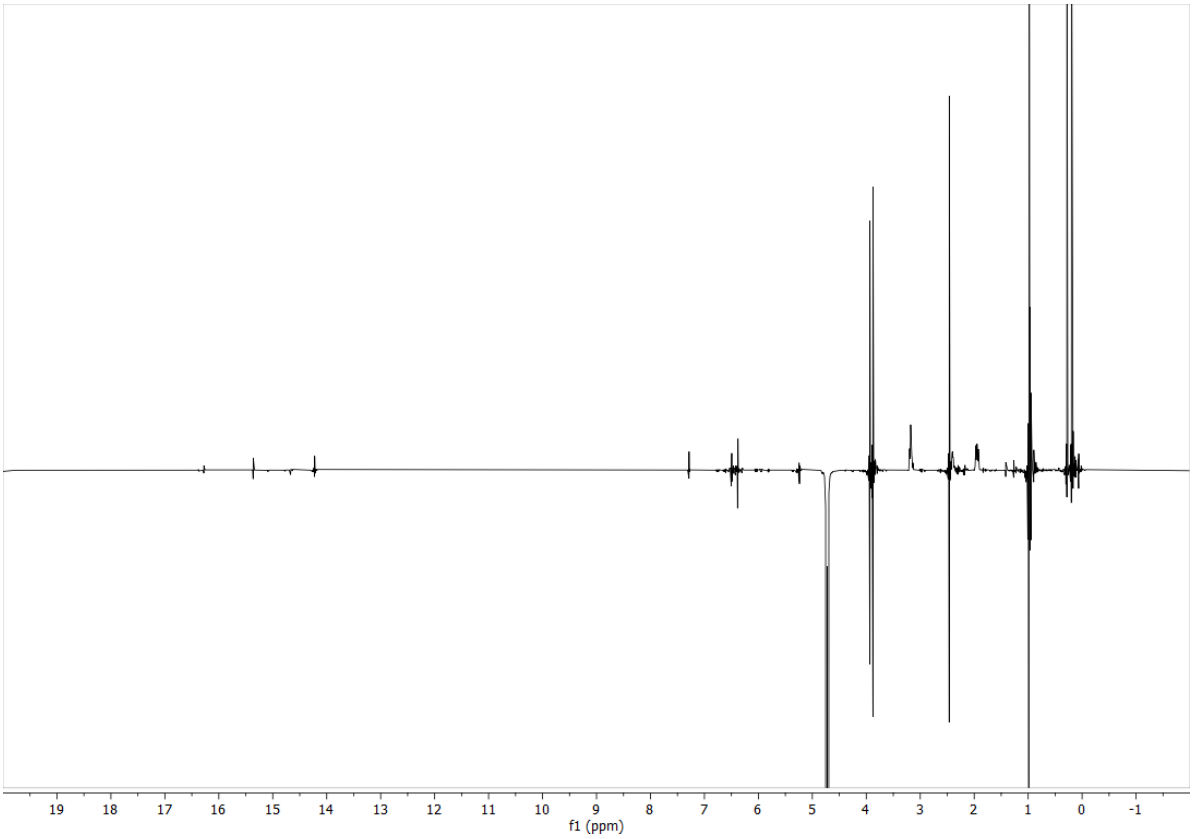
*^{1}H-spectrum of **50** in $CDCl_3$.*



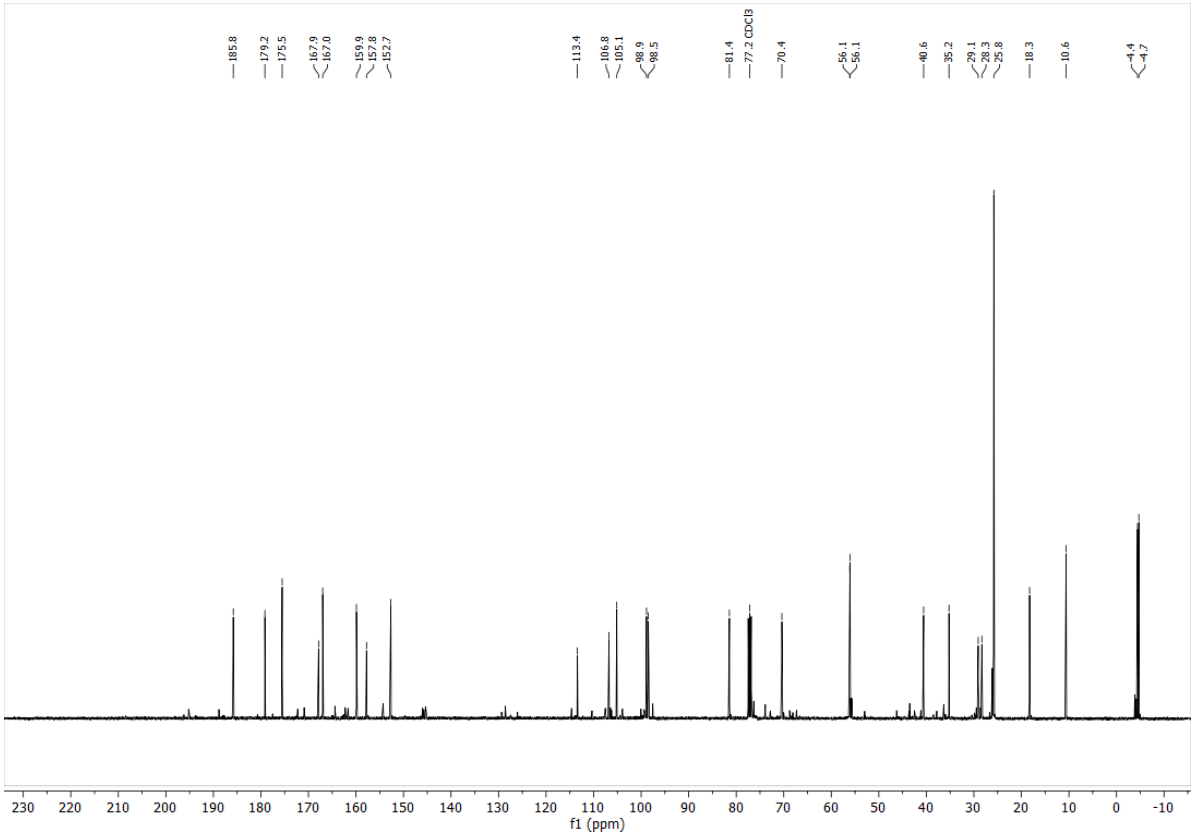
*^{1}H-spectrum of **50** in $CDCl_3$ (selected regions between 1,7-6,7 ppm).*



*NOE-spectrum of **50** in $CDCl_3$ (frequency saturation at 2,37 ppm).*

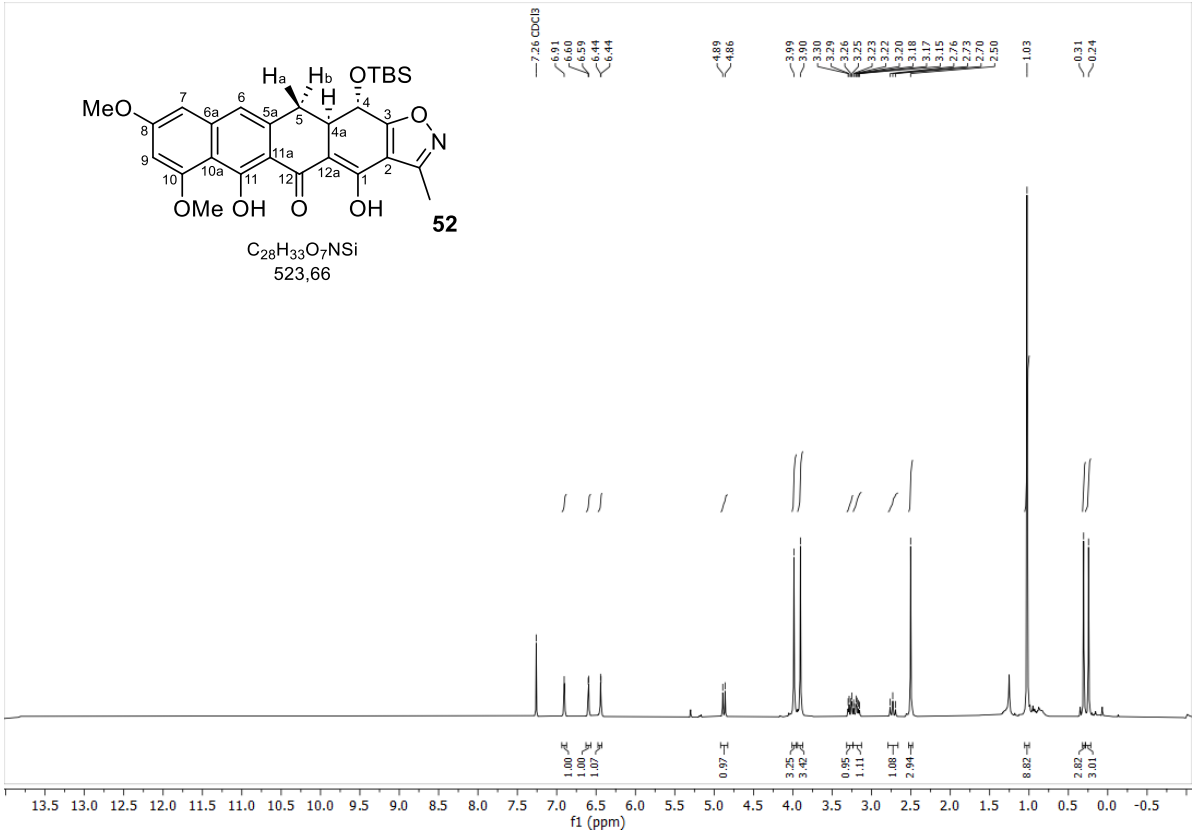


*NOE-spectrum of **50** in $CDCl_3$ (frequency saturation at 4,70 ppm).*

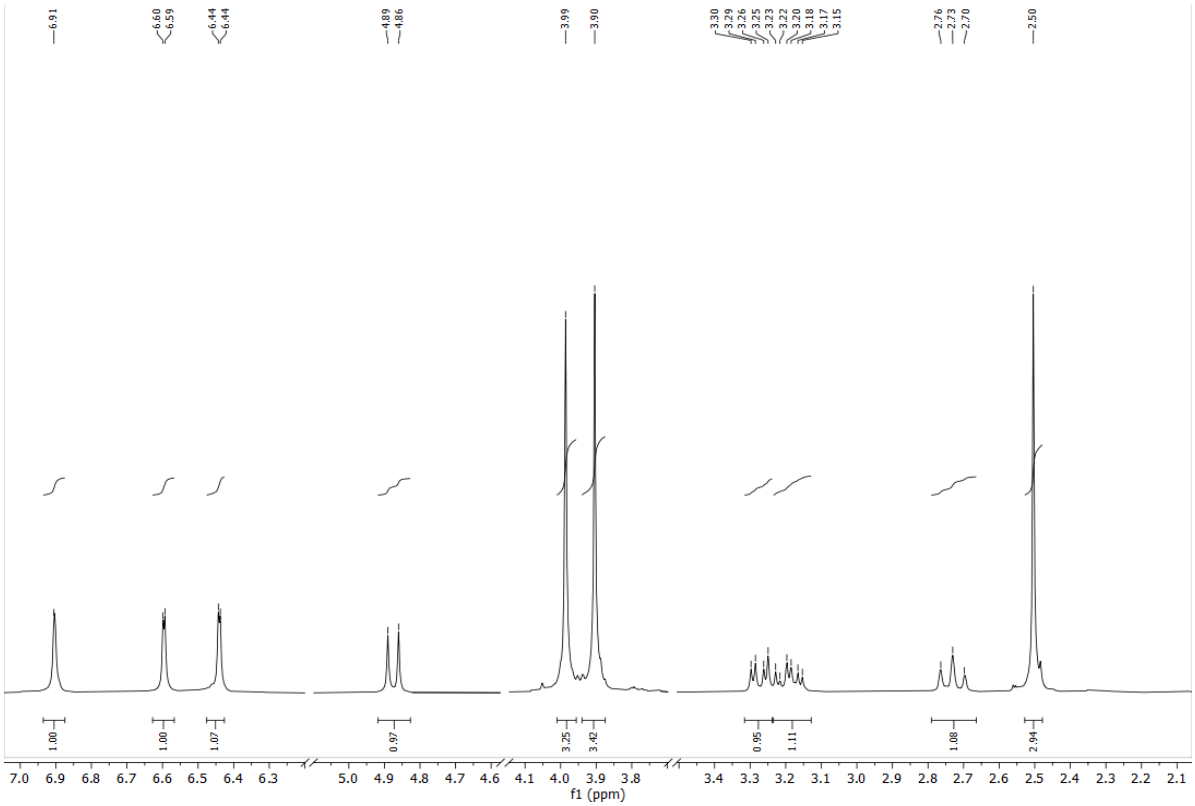


*^{13}C-spectrum of **50** in $CDCl_3$.*

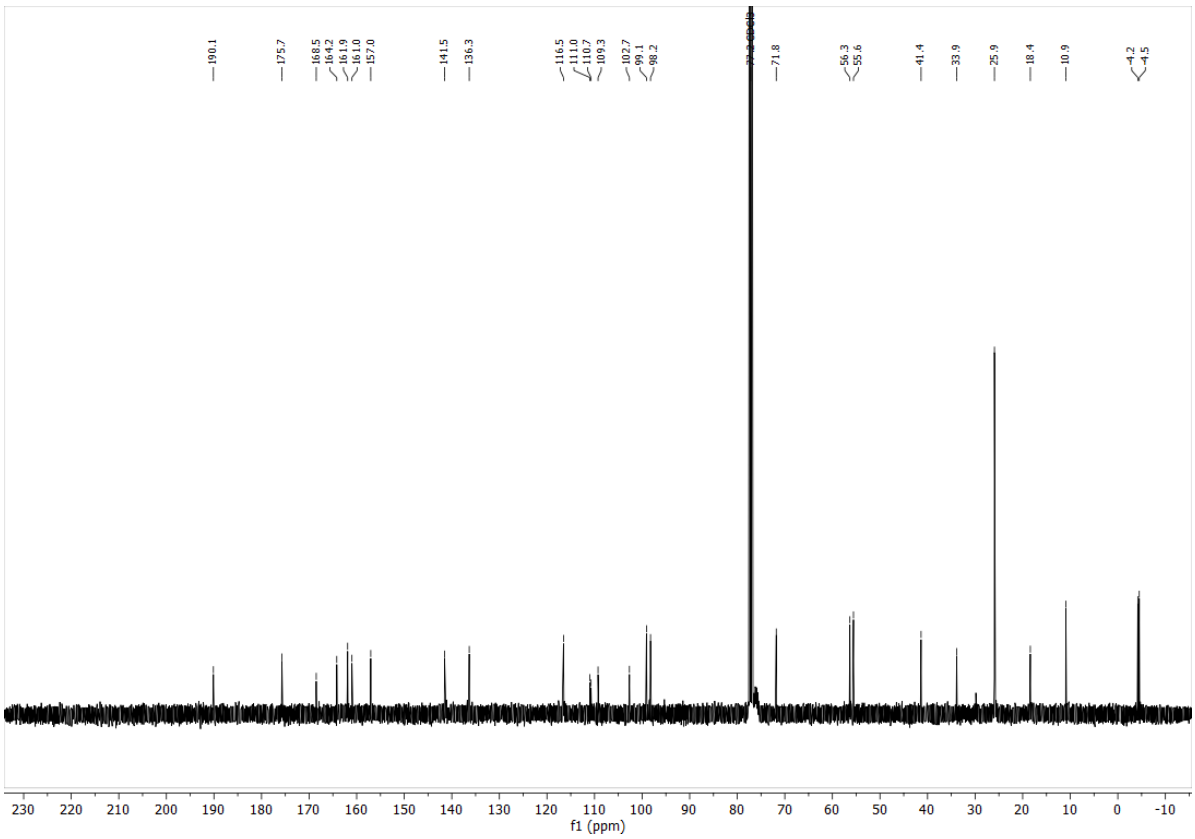
8.2.3.3 (12a*R*,13*S*)-13-((*tert*-butyldimethylsilyl)oxy)-4,6-dihydroxy-7,9-dimethoxy-3-methyl-12a,13-dihydrotetraceno[2,3-*d*]isoxazol-5(12*H*)-one **52**



*^{1}H-spectrum of **52** in $CDCl_3$.*

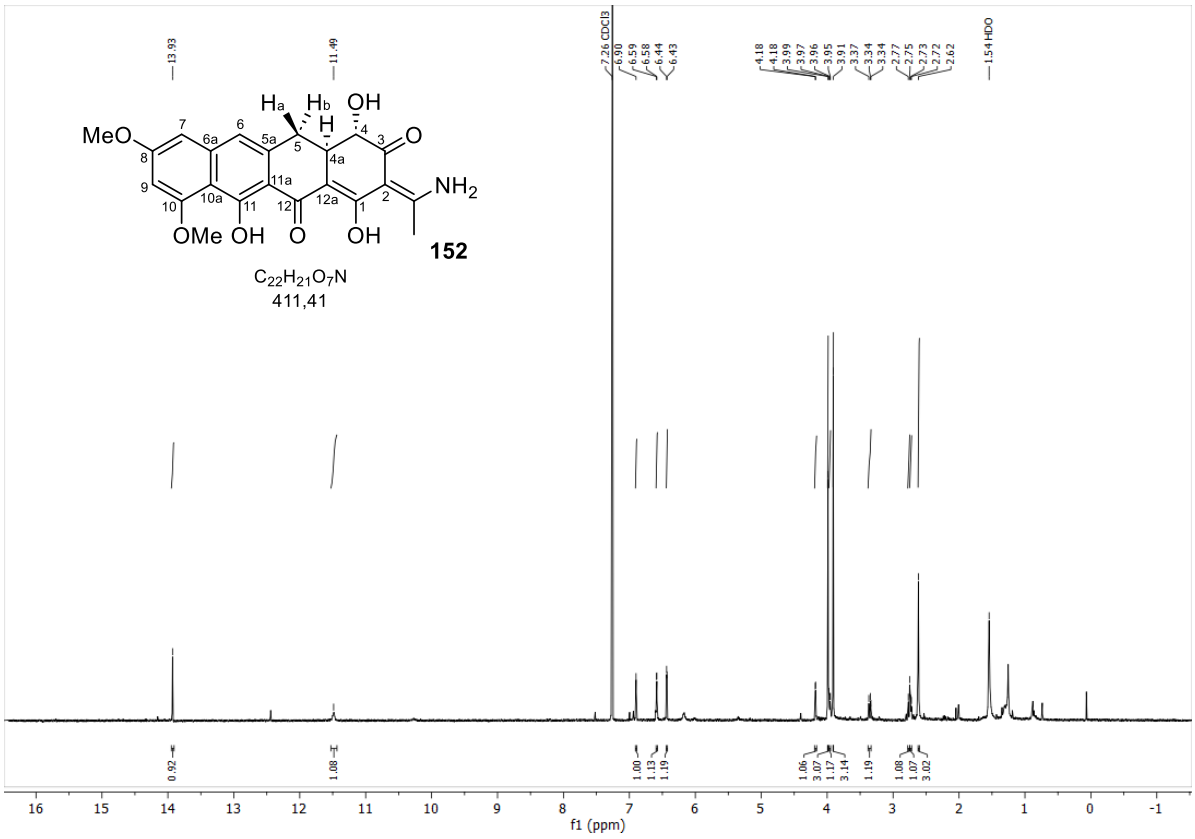


*^{1}H-spectrum of **52** in $CDCl_3$ (selected regions between 2,1-7,0 ppm).*

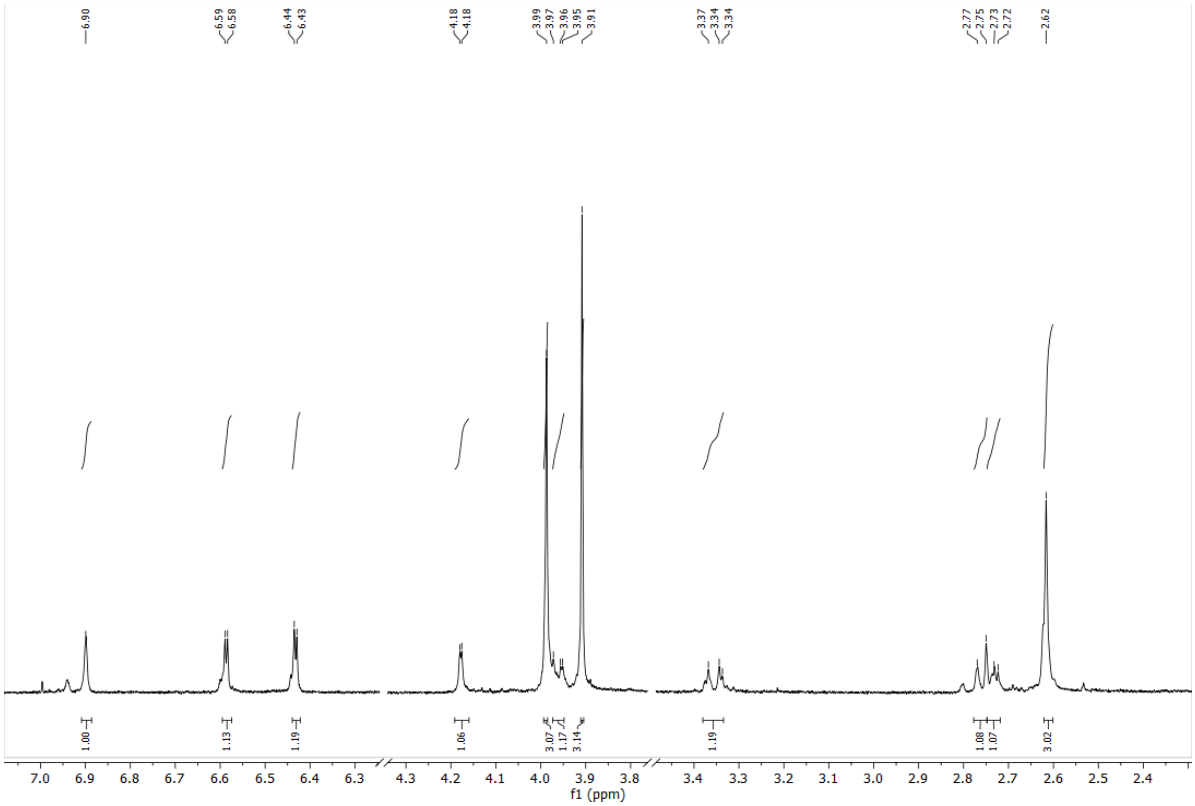


*^{13}C-spectrum of **52** in $CDCl_3$.*

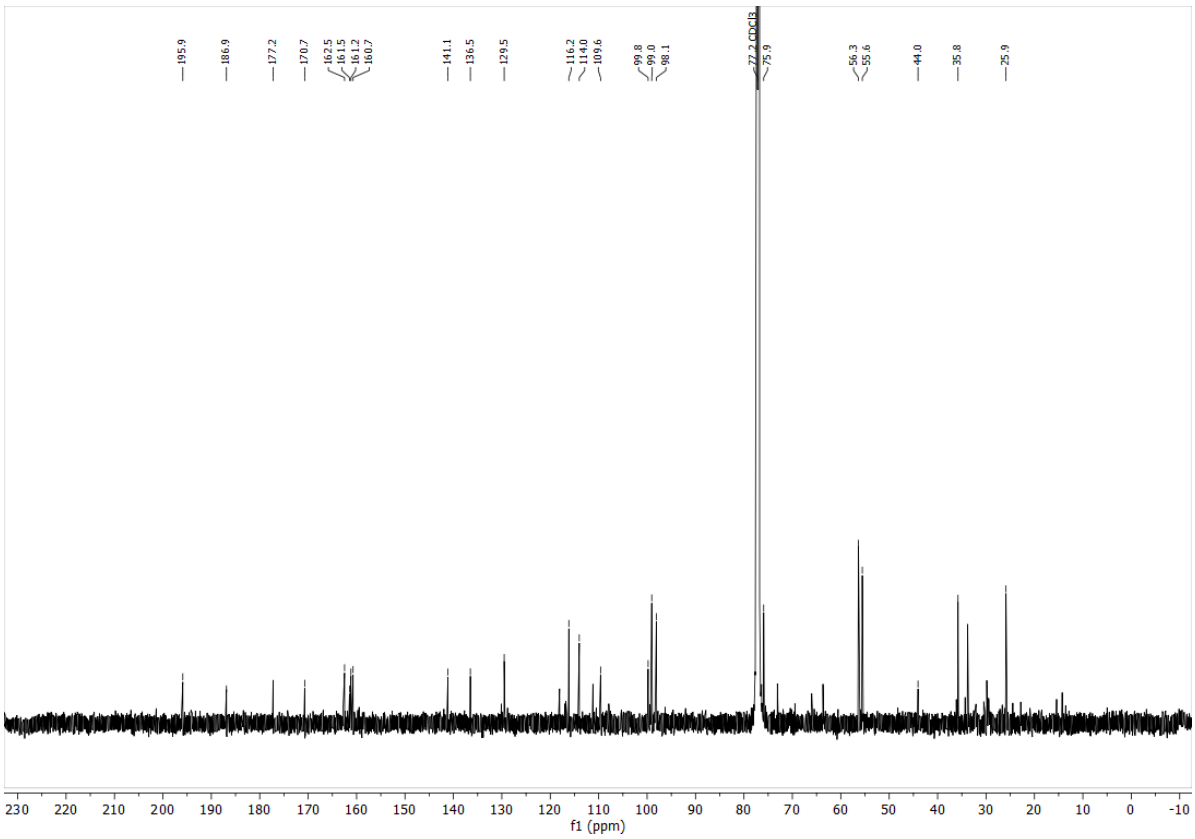
8.2.3.4 (1*S*,12a*R*,*Z*)-3-(1-aminoethylidene)-1,4,6-trihydroxy-7,9-dimethoxy-12,12a-dihydrotetracene-2,5(1*H*,3*H*)-dione **152**



*^{1}H-spectrum of **152** in $CDCl_3$.*

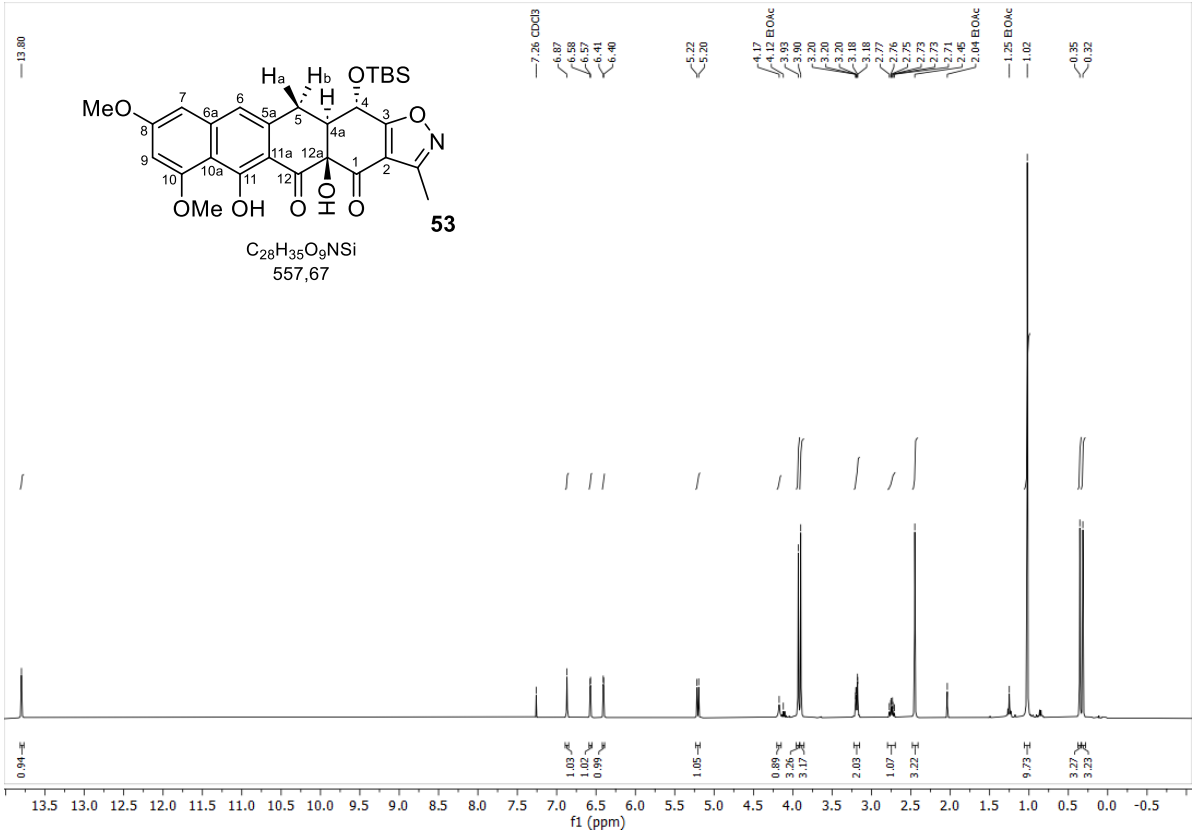


*^{1}H-spectrum of **152** in $CDCl_3$ (selected regions between 2,4-7,0 ppm).*

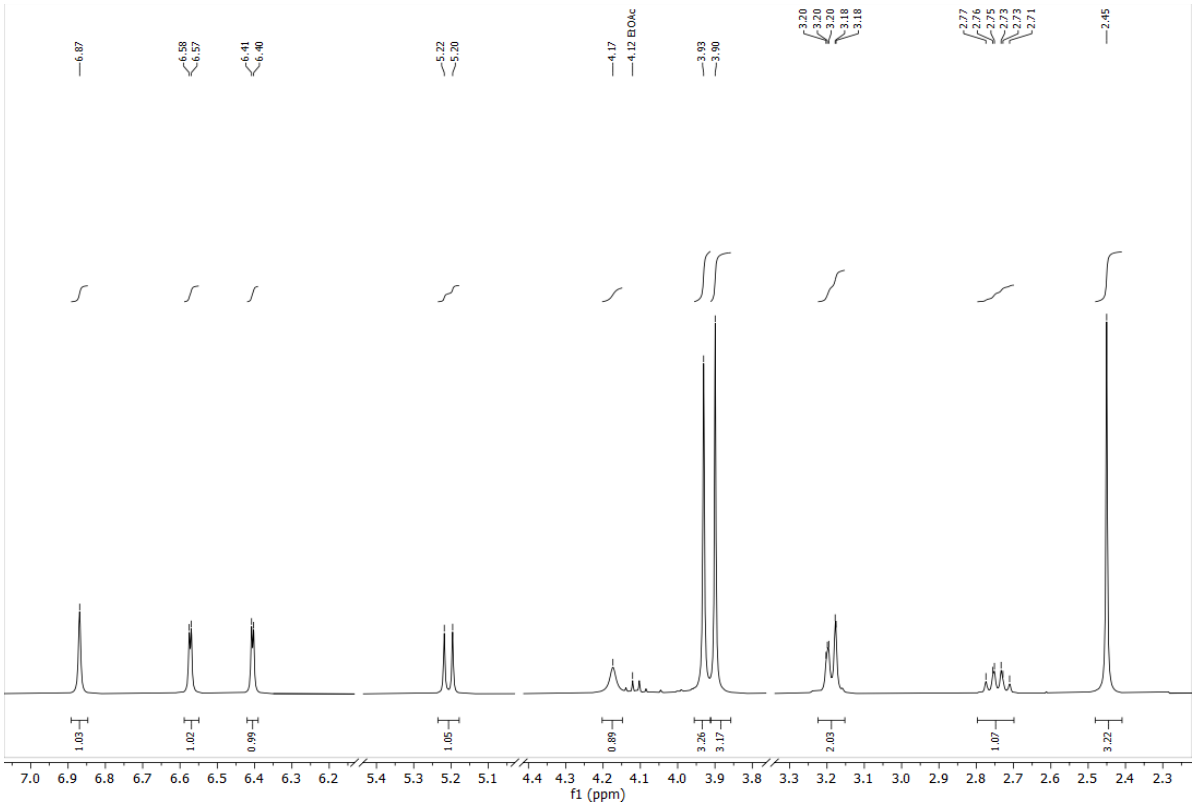


*^{13}C-spectrum of **152** in $CDCl_3$.*

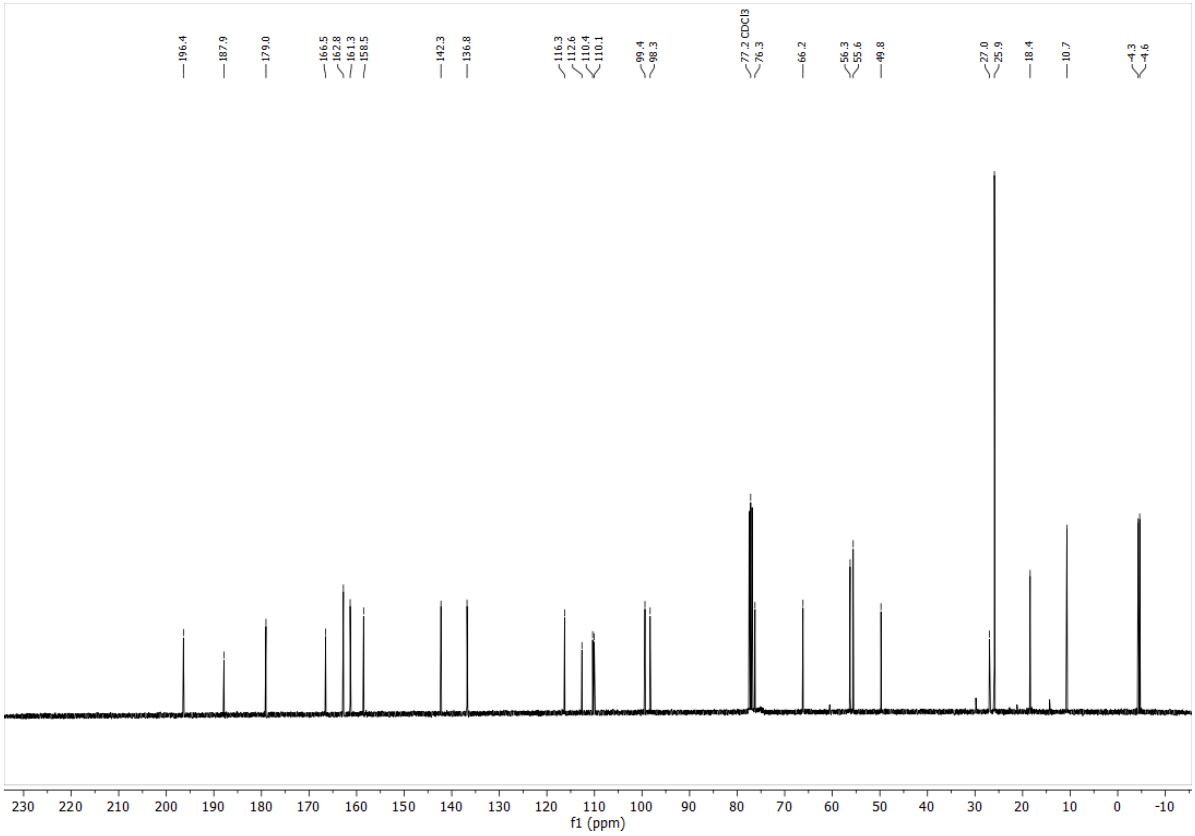
8.2.3.5 (4a*R*,12a*S*,13*S*)-13-((*tert*-butyldimethylsilyl)oxy)-4a,6-dihydroxy-7,9-dimethoxy-3-methyl-12a,13-dihydrotetraceno[2,3-*d*]isoxazole-4,5(4a*H*,12*H*)-dione **53**



*^{1}H-spectrum of **53** in $CDCl_3$.*

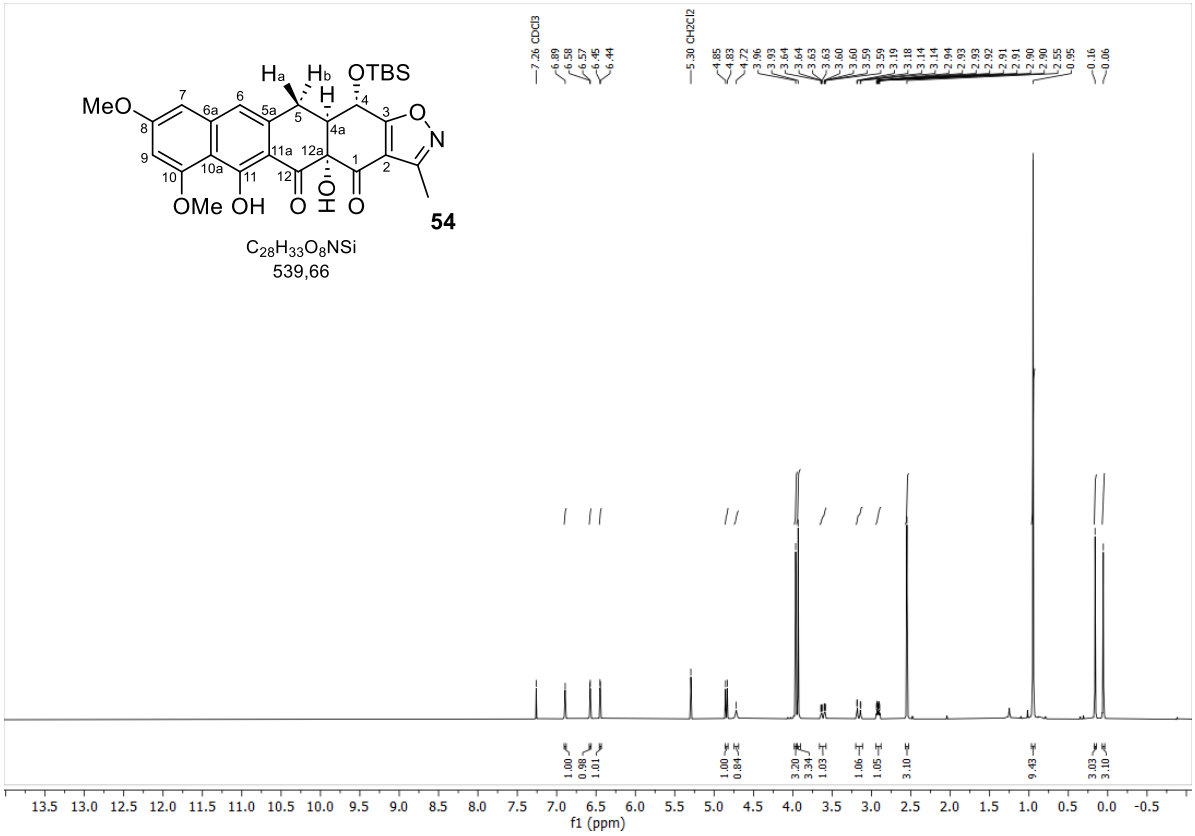


*^{1}H-spectrum of **53** in $CDCl_3$ (selected regions between 2,3-6,9 ppm).*

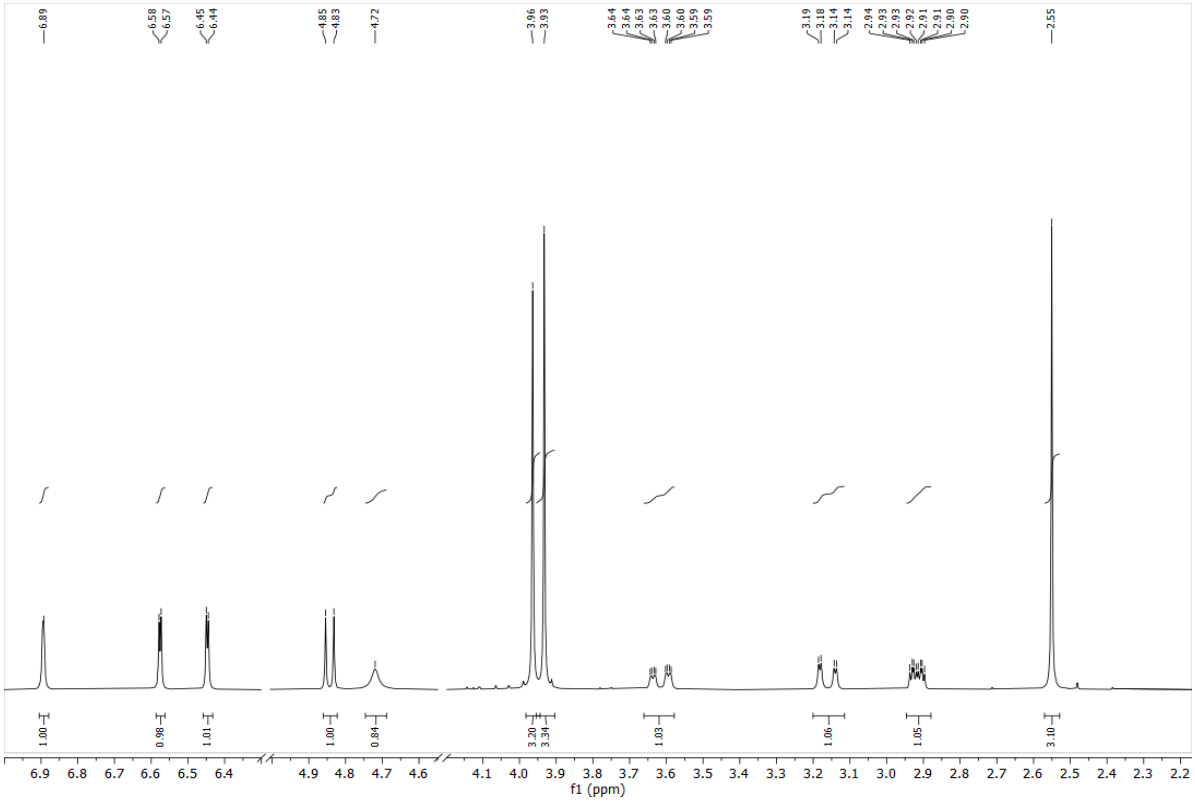


*^{13}C-spectrum of **53** in $CDCl_3$.*

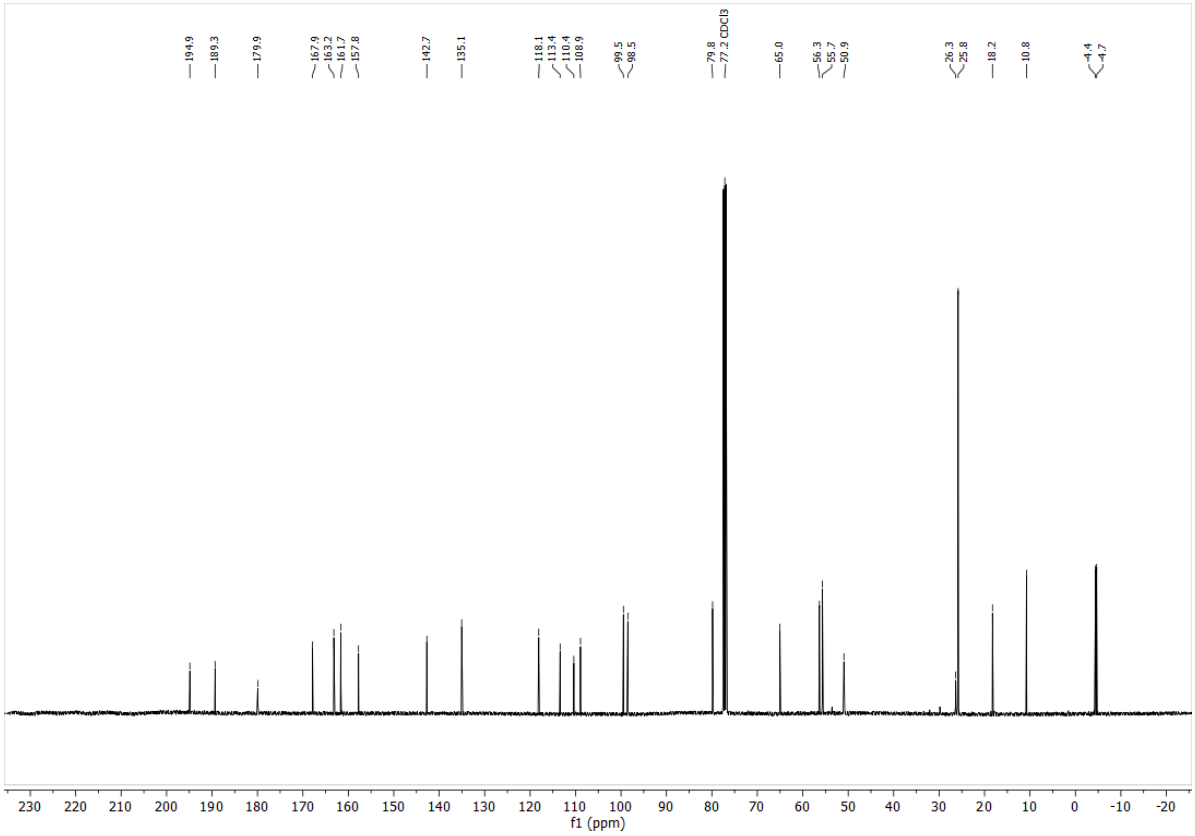
8.2.3.6 (4a*S*,12a*S*,13*S*)-13-((*tert*-butyldimethylsilyl)oxy)-4a,6-dihydroxy-7,9-dimethoxy-3-methyl-12a,13-dihydrotetraceno[2,3-*d*]isoxazole-4,5(4a*H*,12*H*)-dione **54**



*^{1}H-spectrum of **54** in $CDCl_3$.*



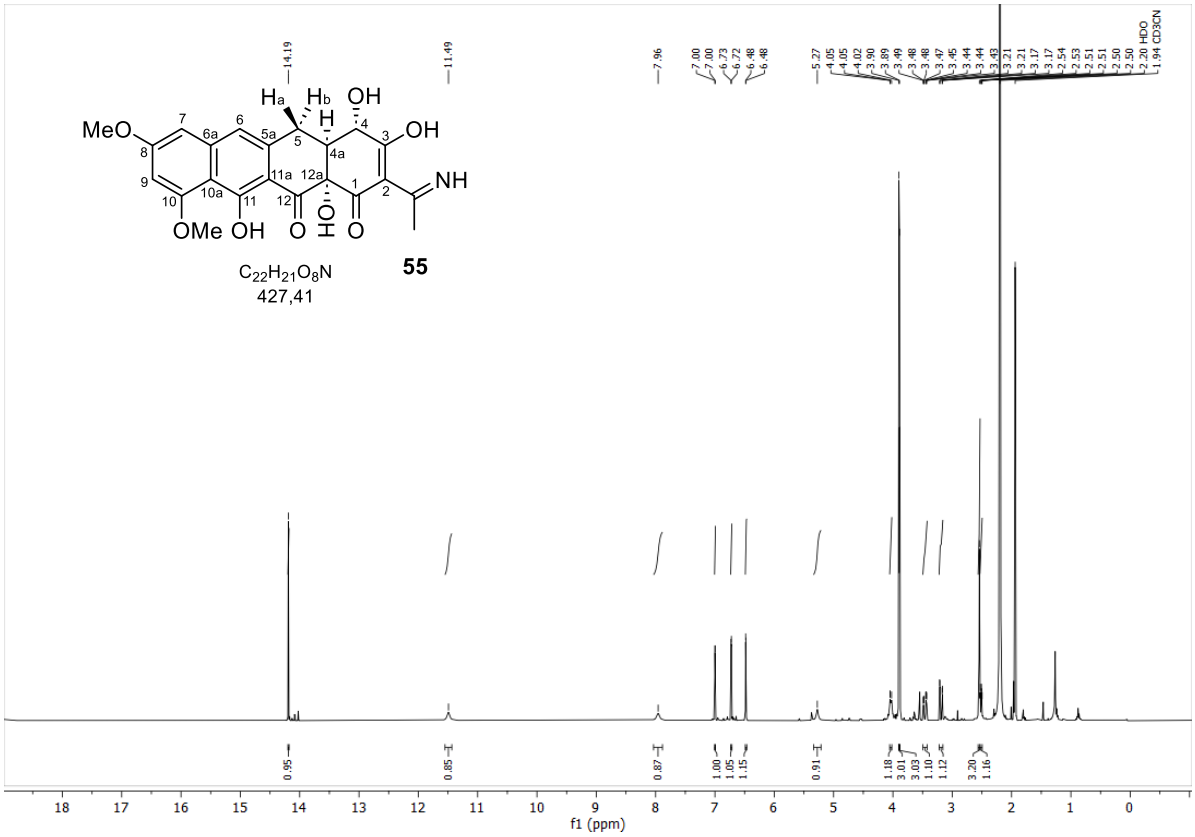
*^{1}H-spectrum of **54** in $CDCl_3$ (selected regions between 2,2-6,9 ppm).*



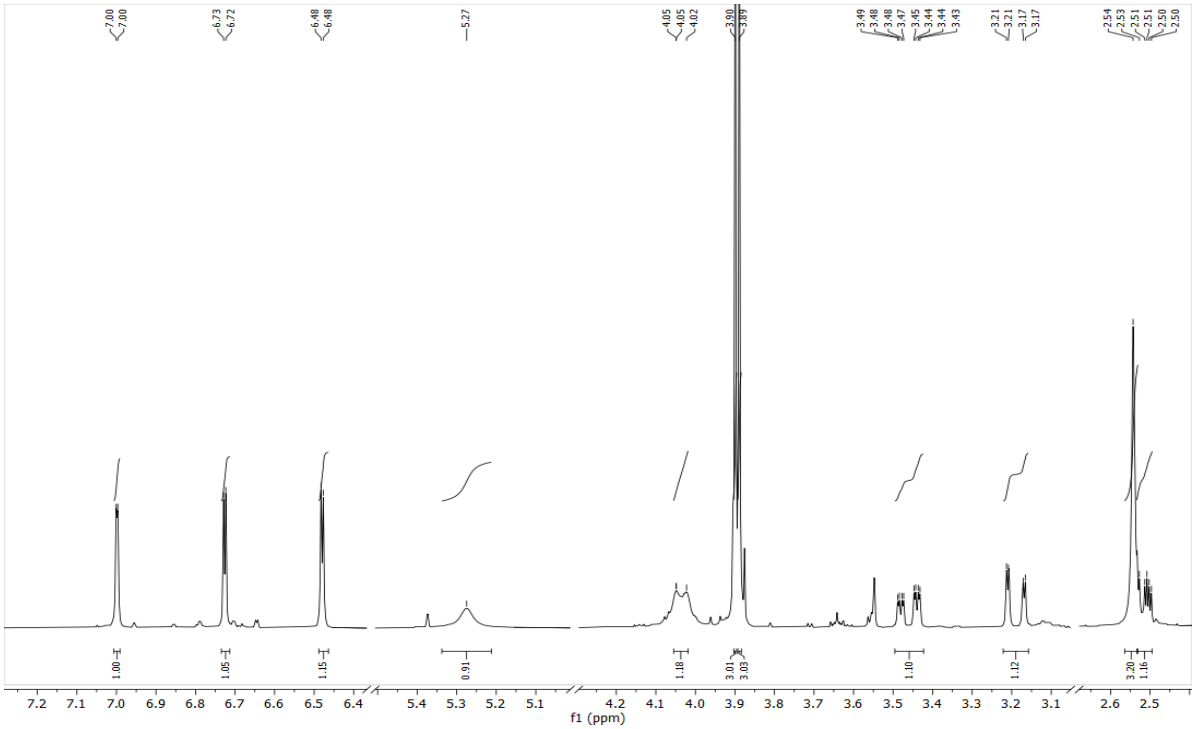
*^{13}C-spectrum of **54** in $CDCl_3$.*

8.2.3.7 (4*S*,4a*S*,12a*S*,*E*)-2-(1-aminoethylidene)-4,8,10,11,12a-pentahydroxy-4a,12a-dihydro-tetracene-1,3,12(2*H*,4*H*,5*H*)-trione **56**

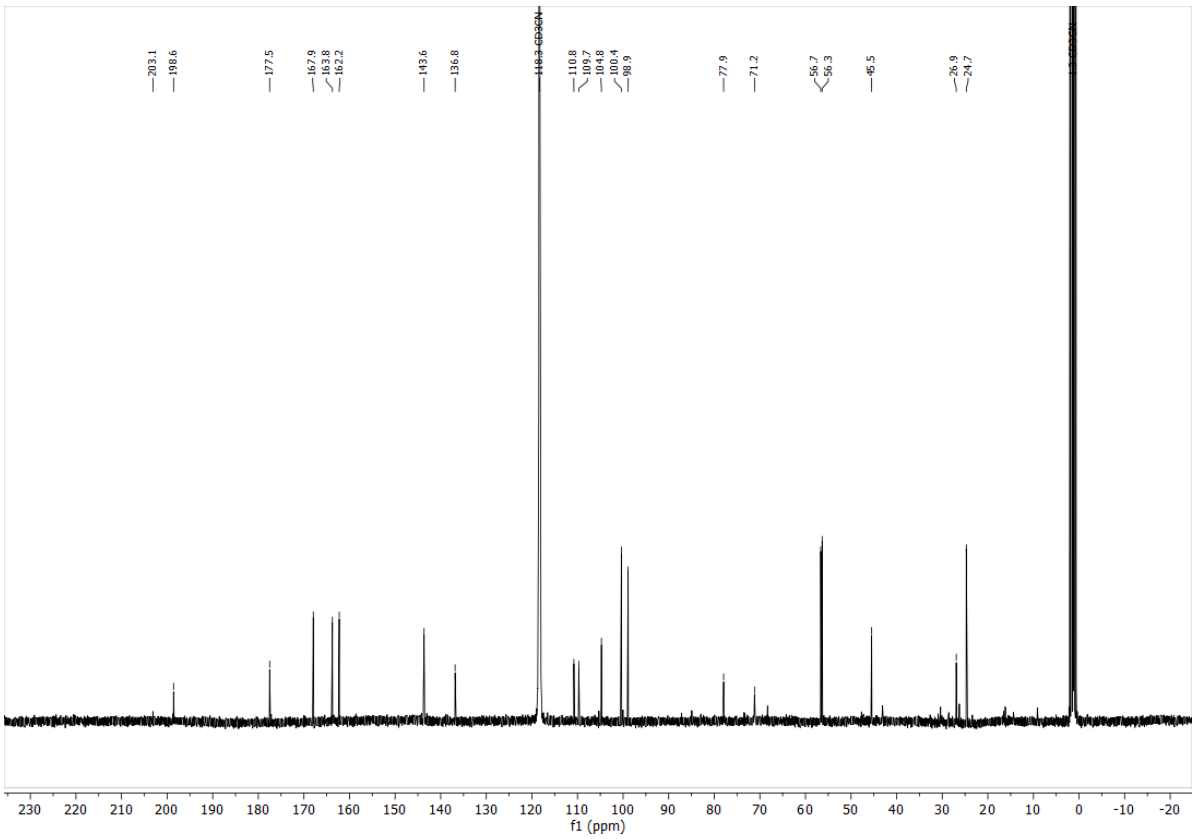
hydrogenation and hydrolysis (synthesis of (4*S*,4a*S*,12a*S*)-3,4,11,12a-tetrahydroxy-2-(1-iminoethyl)-8, 10-dimethoxy-4a,12a-dihydrotetracene-1,12(4*H*,5*H*)-dione **55**)



*^{1}H-spectrum of **55** in CD_3CN.*

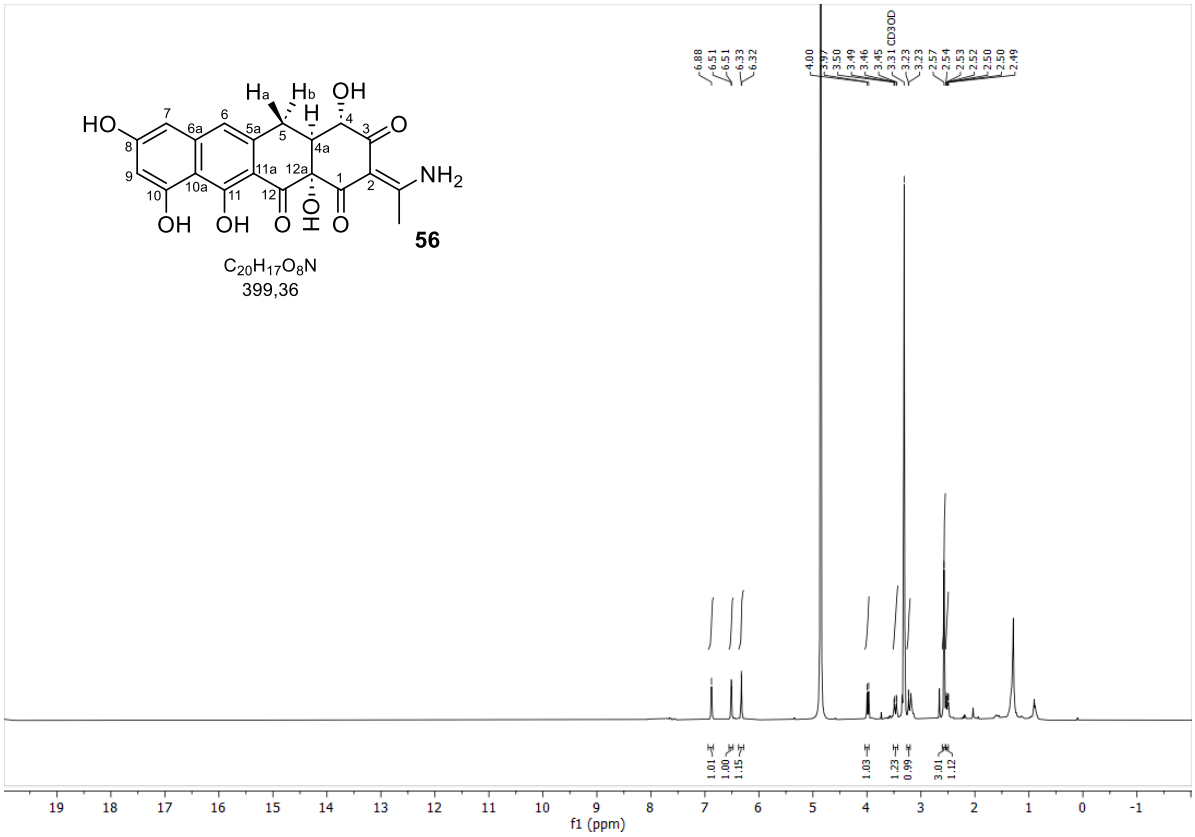


*^{1}H-spectrum of **55** in CD_3CN (selected regions between 2,5-7,2 ppm).*

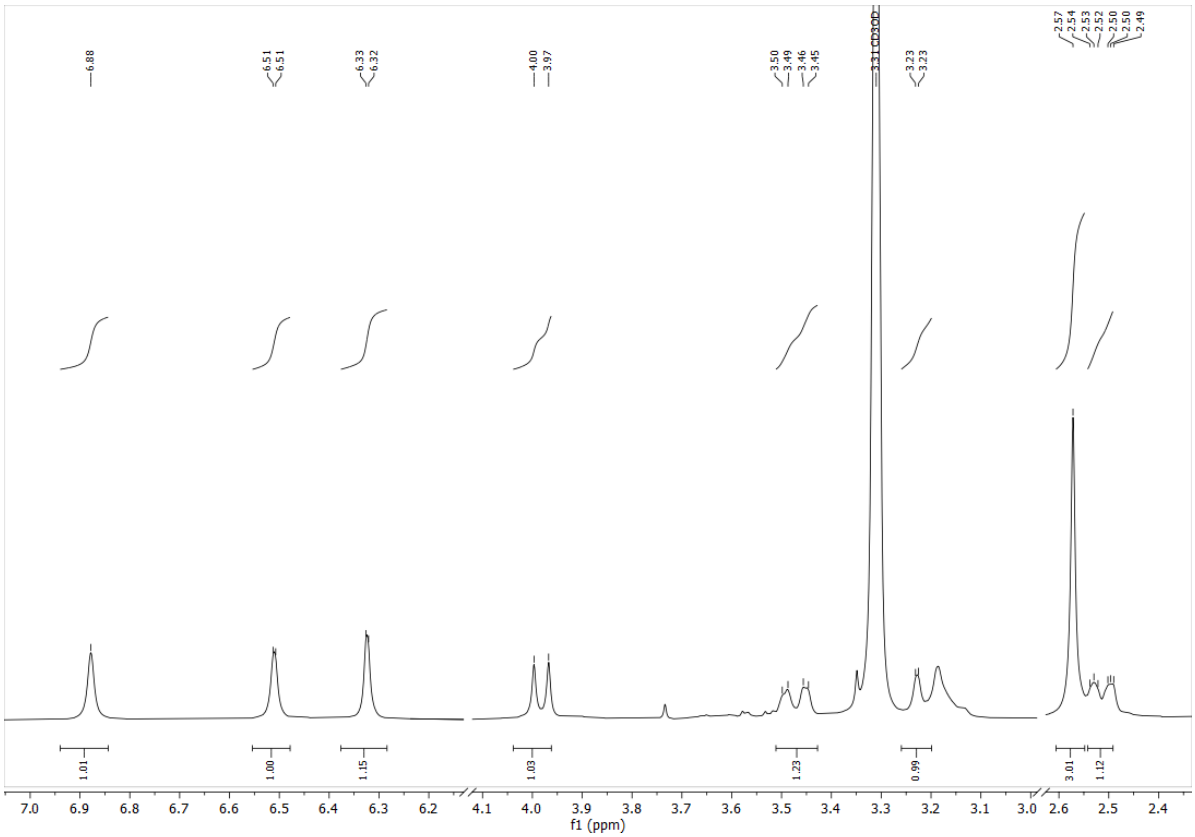


*^{13}C-spectrum of **55** in CD_3CN.*

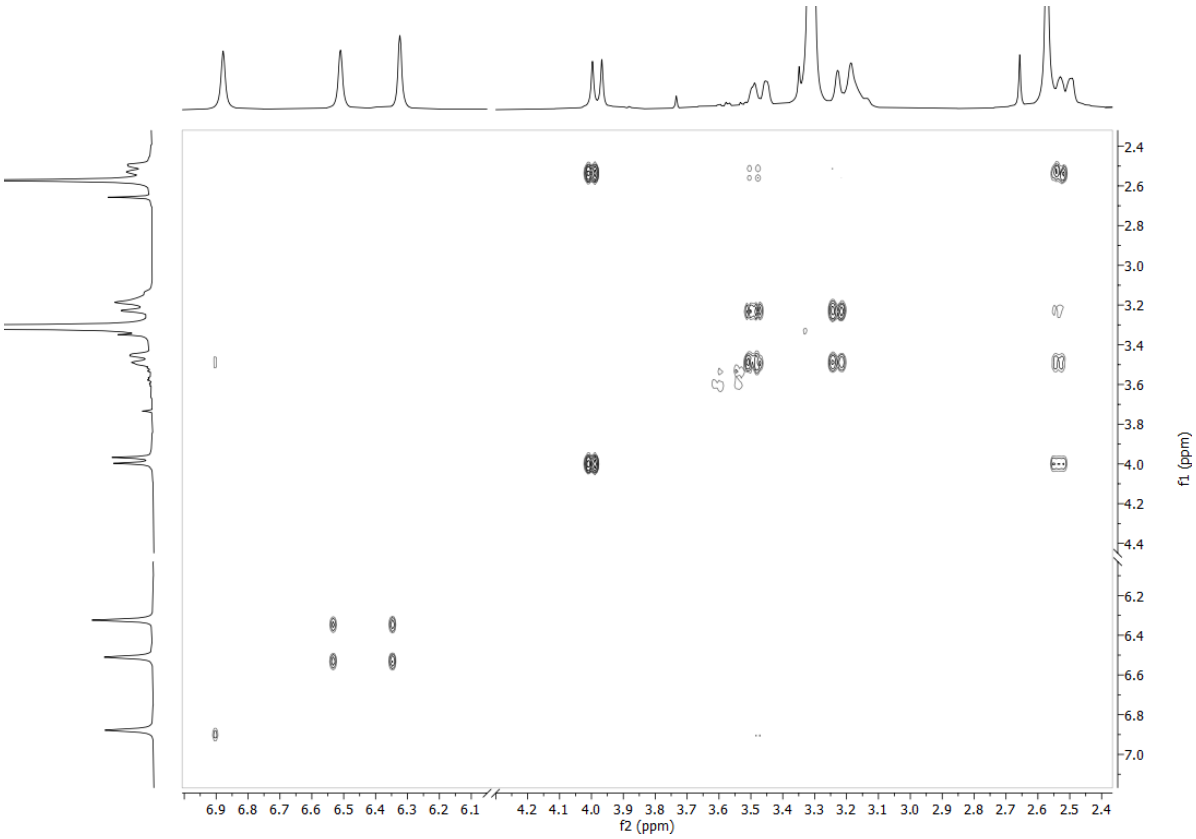
Me-ether-cleavage (synthesis of **56**)



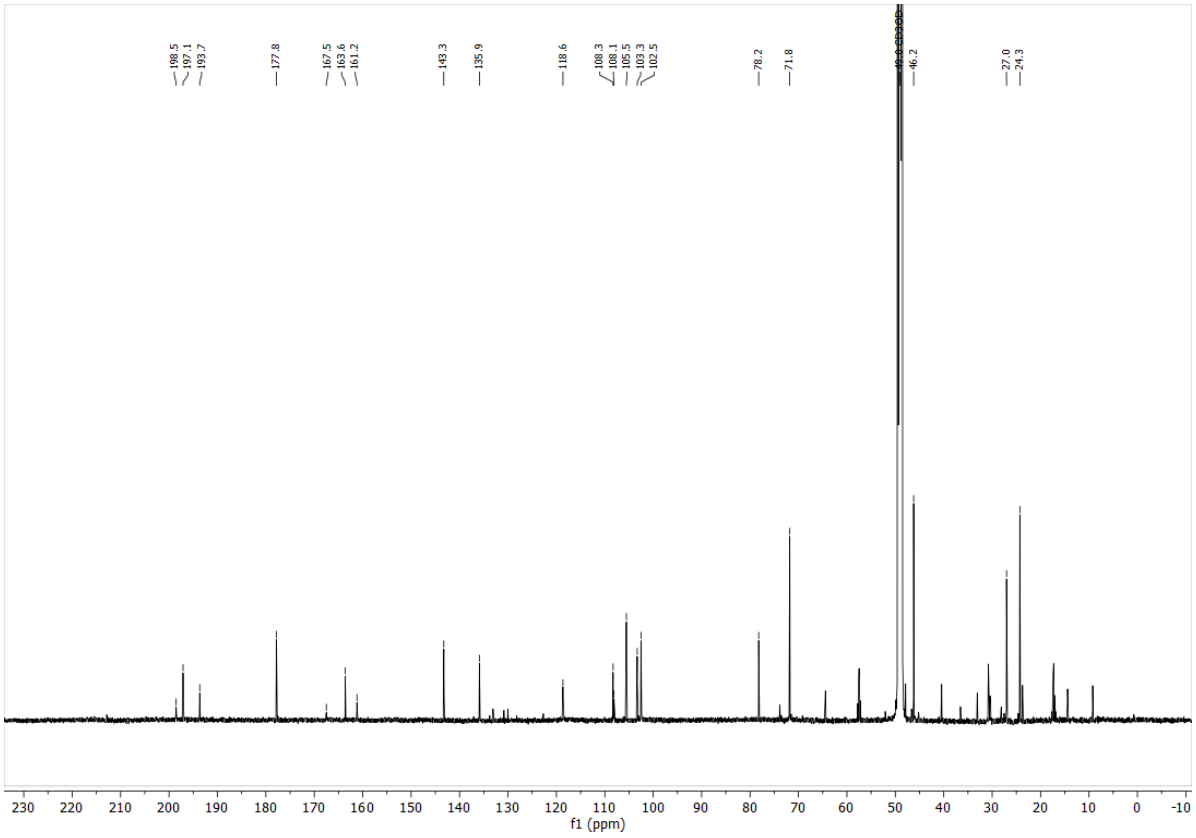
*^{1}H-spectrum of **56** in CD_3OD.*



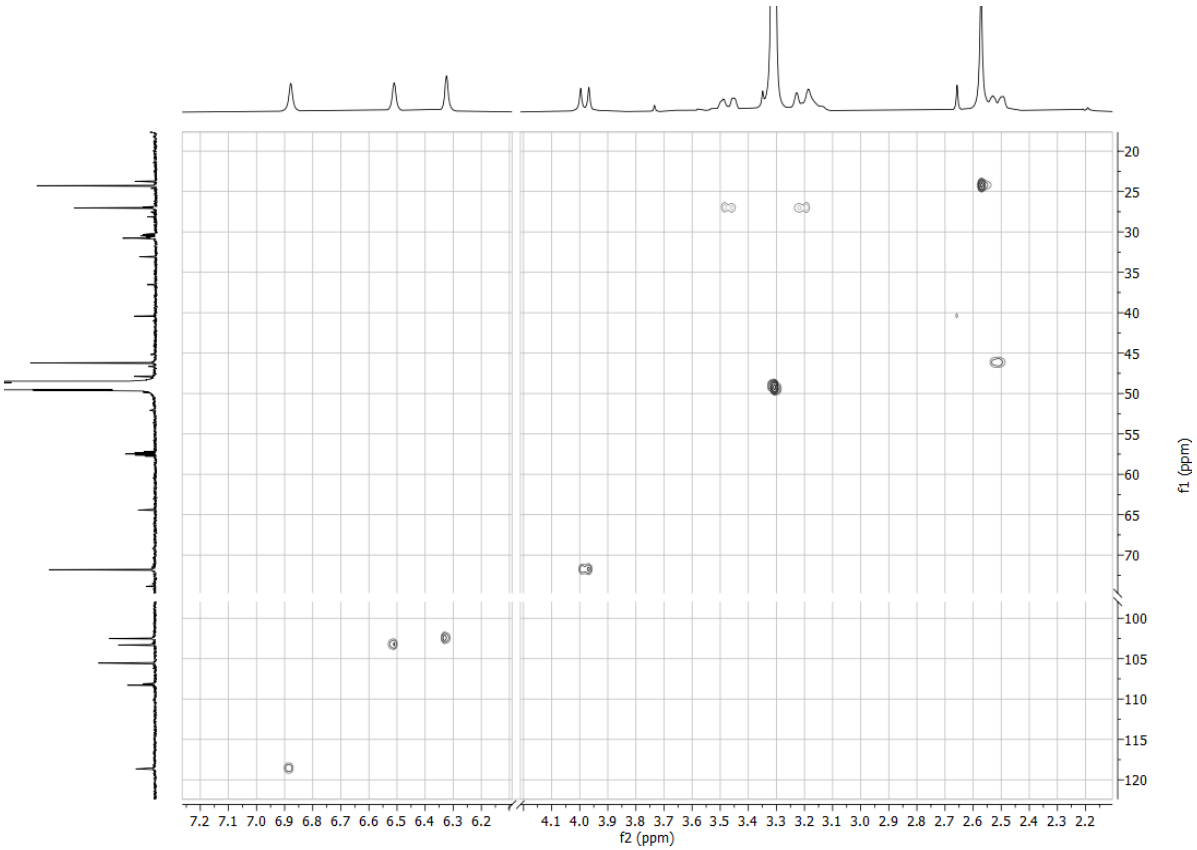
*^{1}H-spectrum of **56** in CD_3OD (selected regions between 2,4-7,0 ppm).*



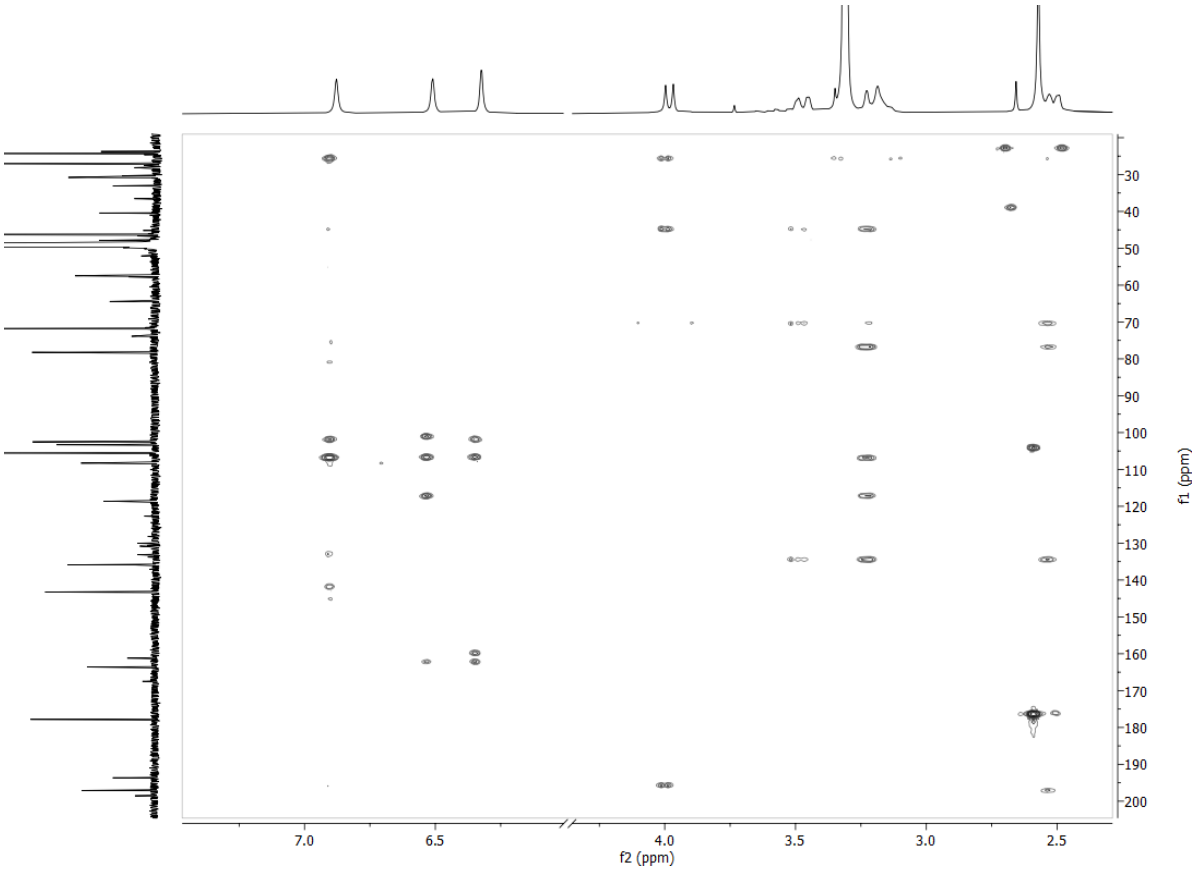
*$^{1}H,^{1}H$-COSY-spectrum of **56** in CD_3OD (selected regions between 2,4-7,0 ppm).*



*^{13}C-spectrum of **56** in CD_3OD.*



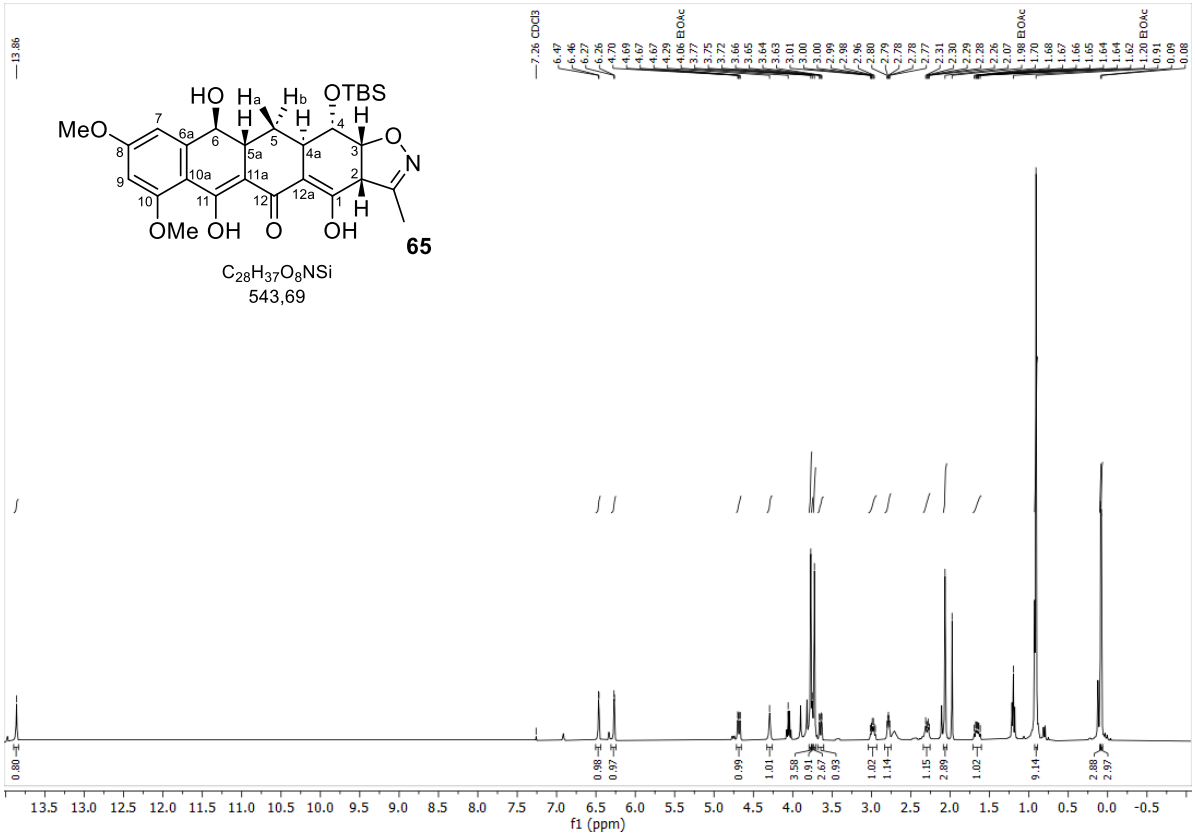
*$^{1}H,^{13}C$-HSQC-spectrum of **56** in CD_3OD (selected regions).*



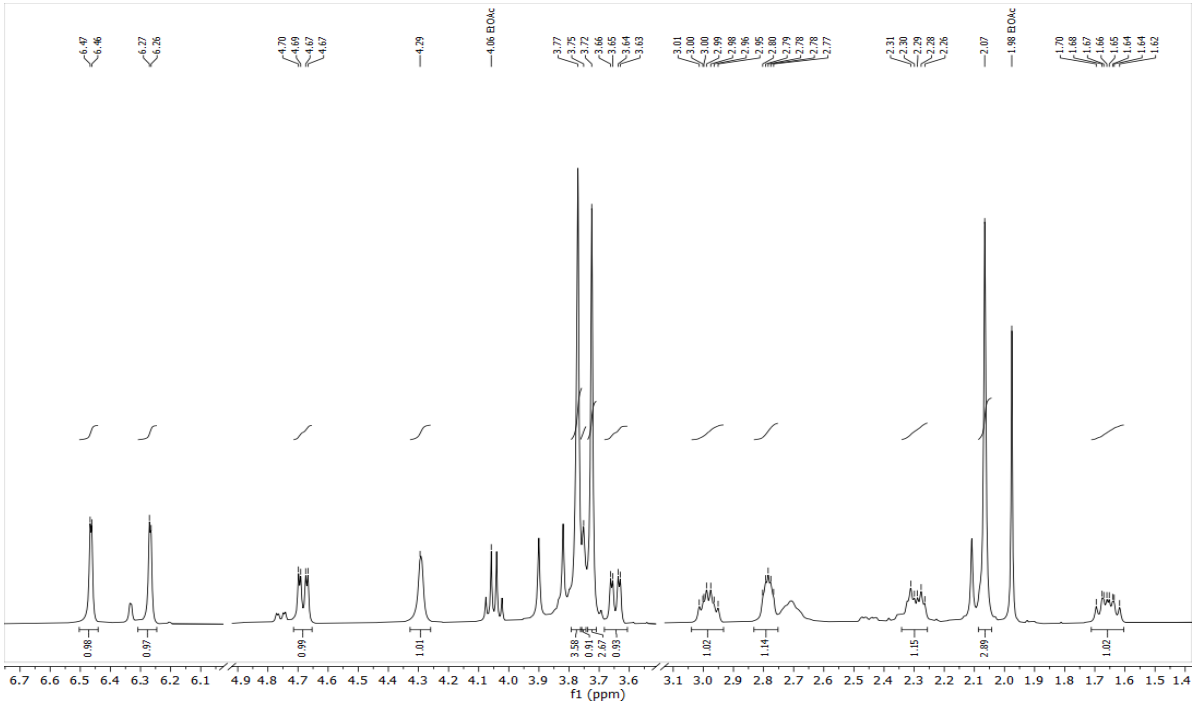
*$^{1}H,^{13}C$-HMBC-spectrum of **56** in CD_3OD (selected regions).*

8.2.4 Demethylpremithramycinone **1** from enone **64**

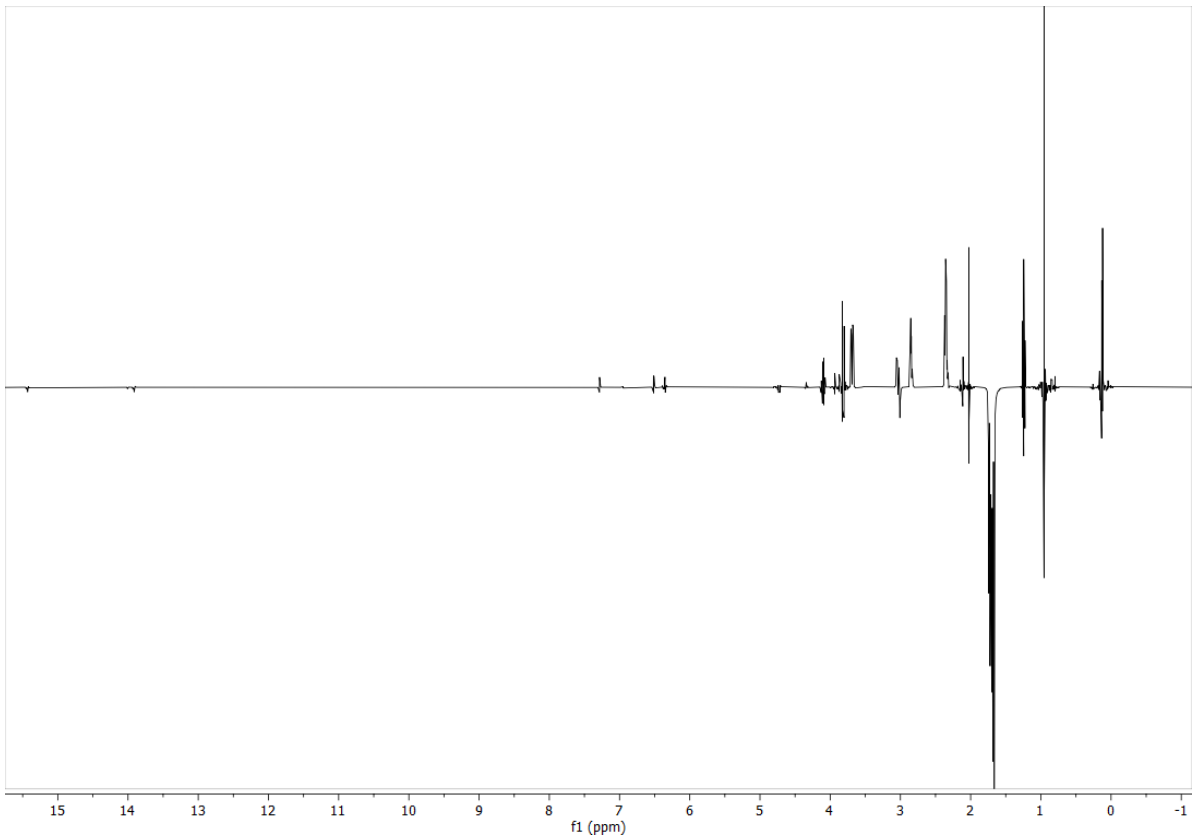
8.2.4.1 (3a*S*,5a*R*,11*S*,11a*R*,12a*R*,13*S*,13a*R*)-13-((*tert*-butyldimethylsilyl)oxy)-4,11-dihydroxy-7,9-dimethoxy-3-methyl-11,11a,12,12a,13,13a-hexahydrotetraceno[2,3-*d*]isoxazole-5,6(3a*H*,5a*H*)-dione **65**



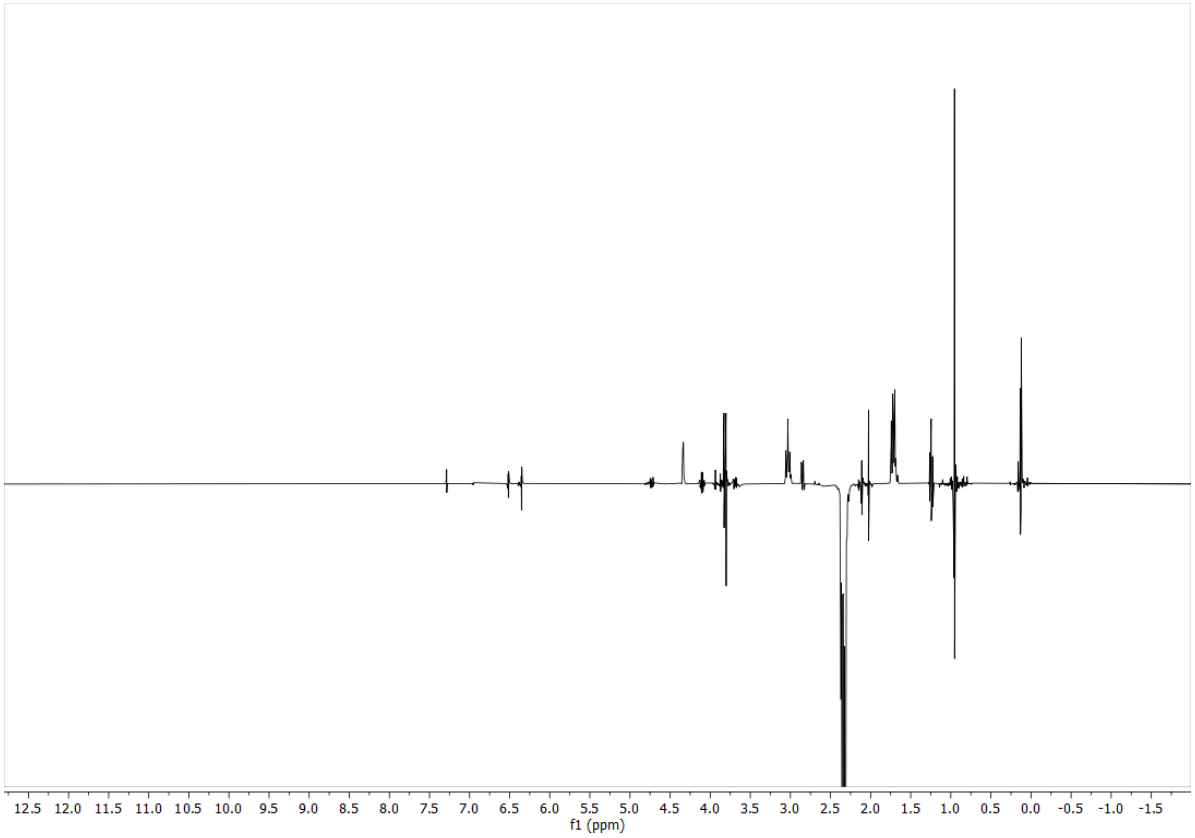
*^{1}H-spectrum of **65** in $CDCl_3$.*



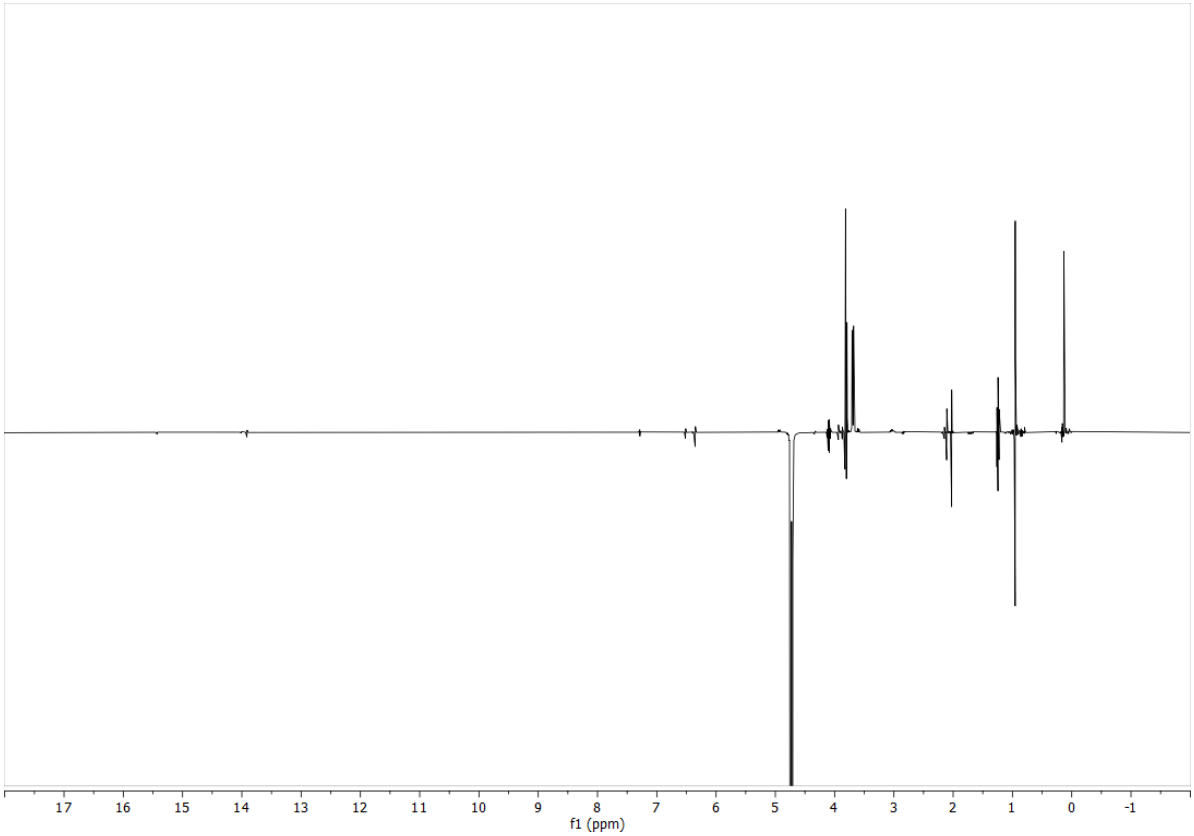
*^{1}H-spectrum of **65** in $CDCl_3$ (selected regions between 1,4-6,7 ppm).*



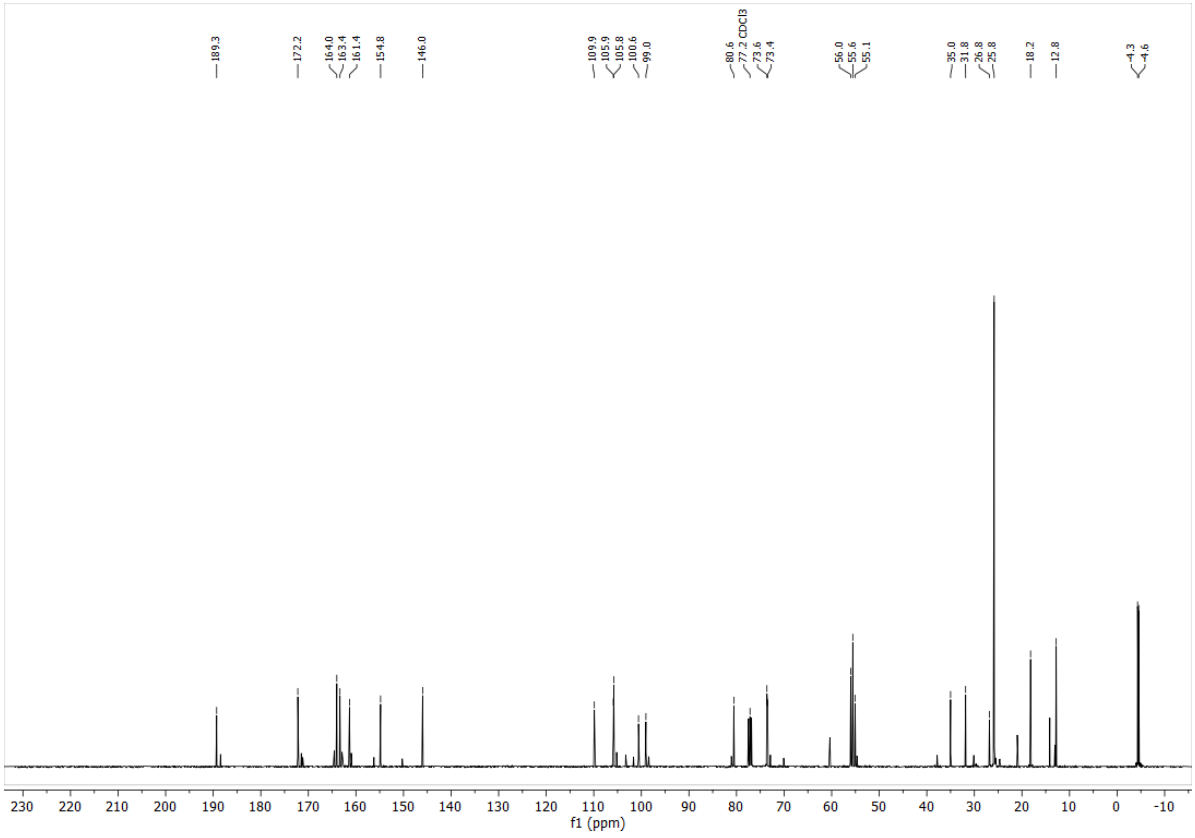
*NOE-spectrum of **65** in $CDCl_3$ (frequency saturation at 1,70 ppm).*



*NOE-spectrum of **65** in $CDCl_3$ (frequency saturation at 2,34 ppm).*

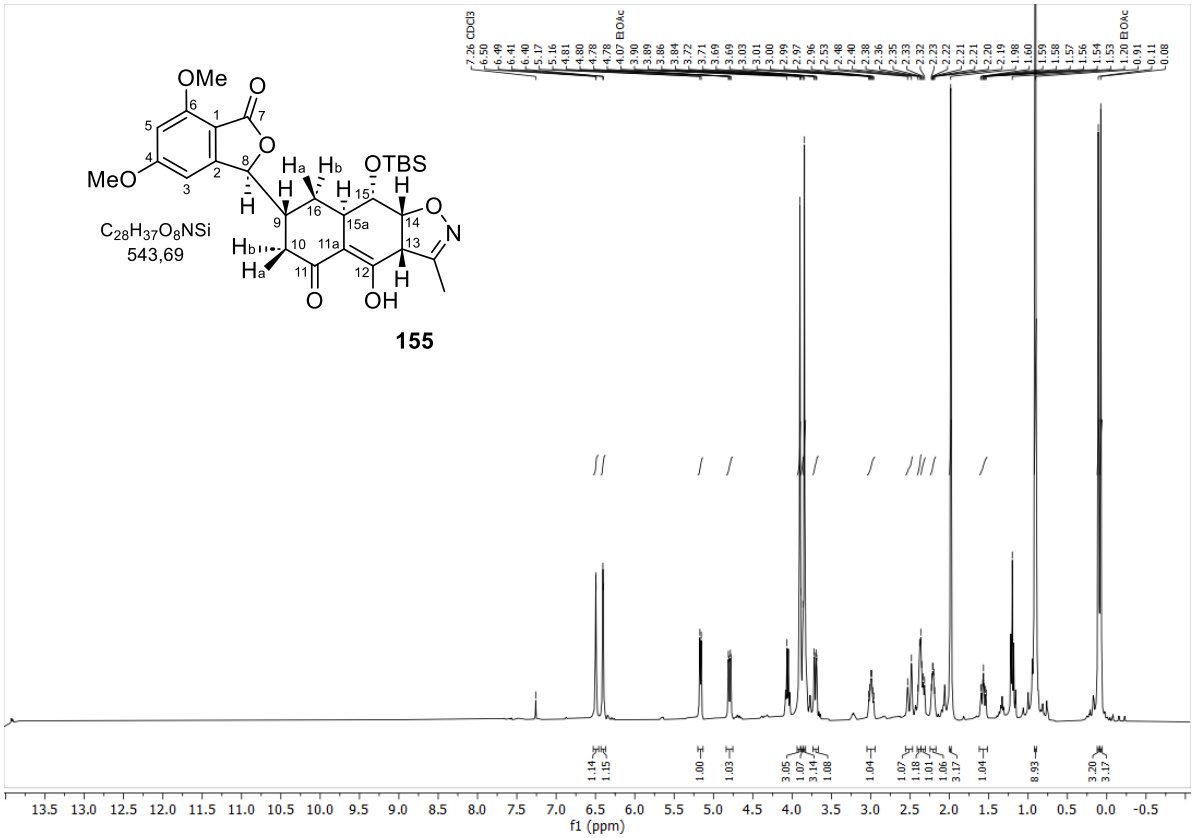


*NOE-spectrum of **65** in $CDCl_3$ (frequency saturation at 4,69 ppm).*

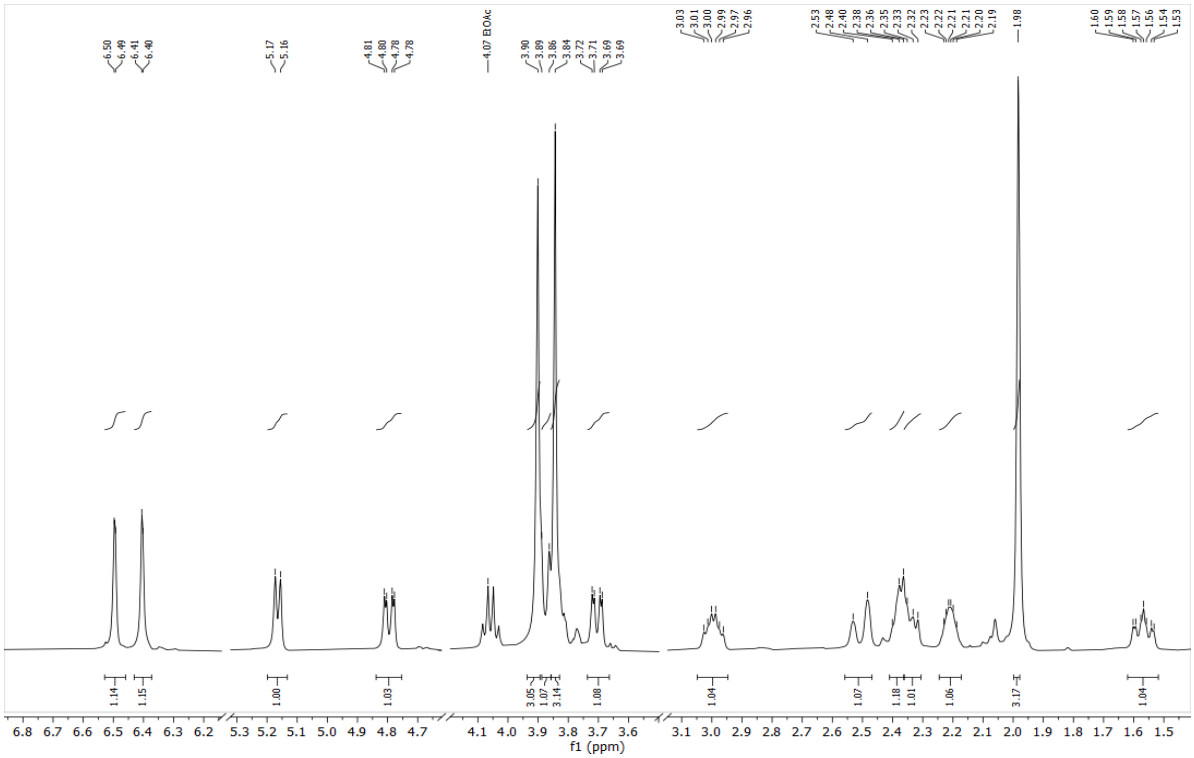


*^{13}C-spectrum of **65** in $CDCl_3$.*

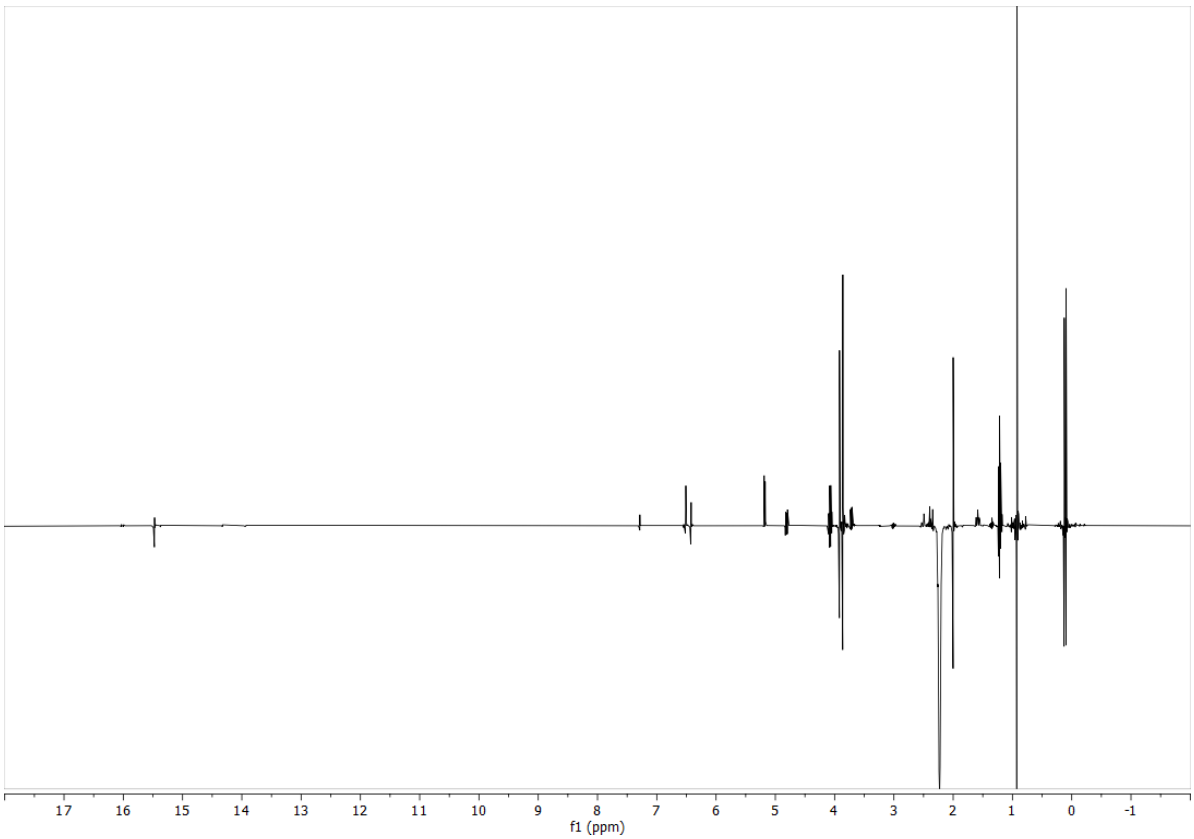
1,4-addition product **155** ((3a*S*,7*R*,8a*R*,9*S*,9a*R*)-9-((*tert*-butyldimethylsilyl)oxy)-7-((*S*)-4,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-4-hydroxy-3-methyl-6,7,8,8a,9,9a-hexahydronaphtho[2,3-d]isoxazol-5(3a*H*)-one)



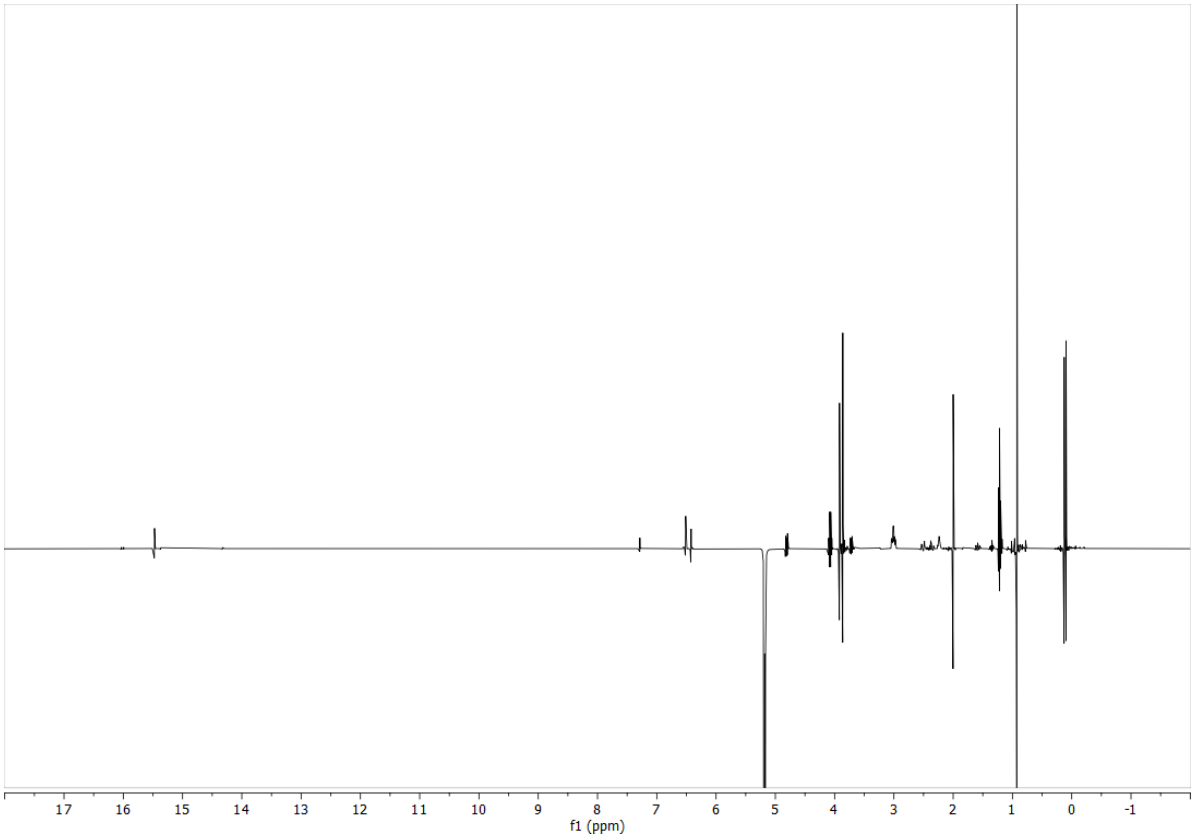
*^{1}H-spectrum of **155** in $CDCl_3$.*



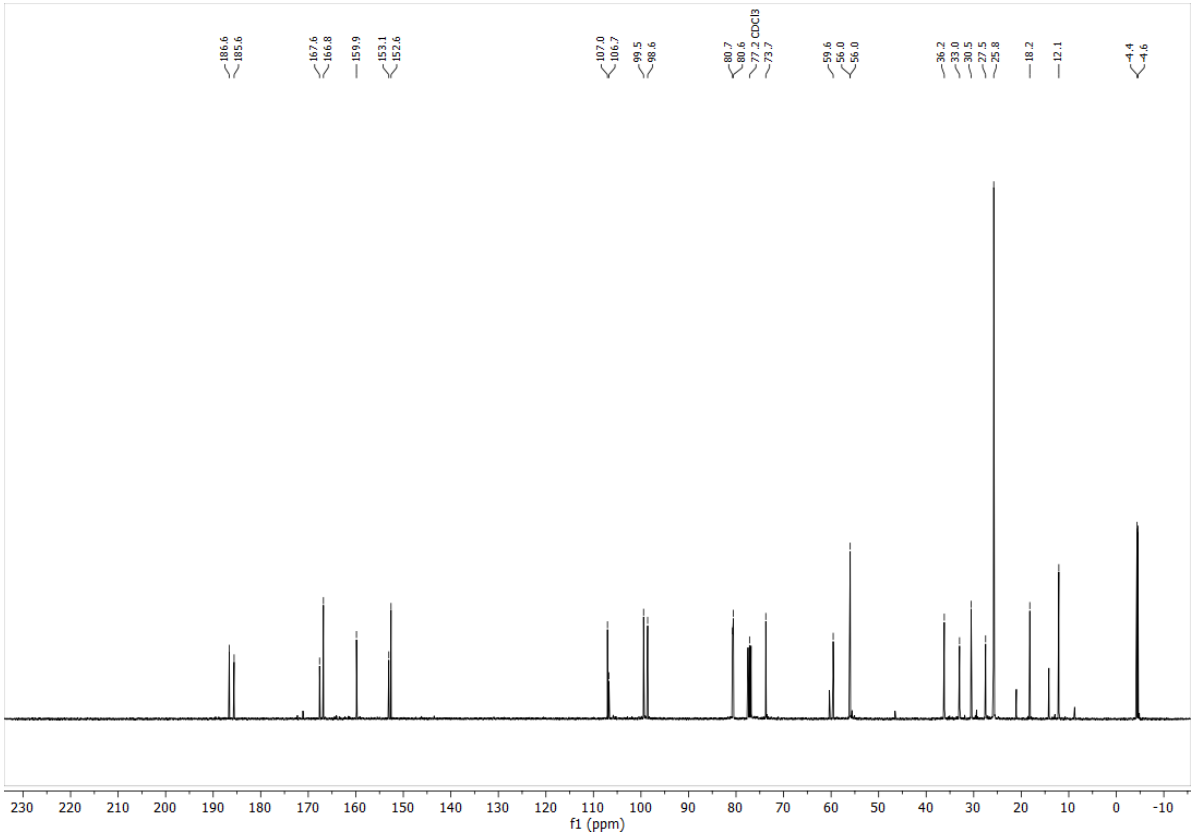
*^{1}H-spectrum of **50** in $CDCl_3$ (selected regions between 1,5-6,8 ppm).*



*NOE-spectrum of **155** in $CDCl_3$ (frequency saturation at 2,23 ppm).*

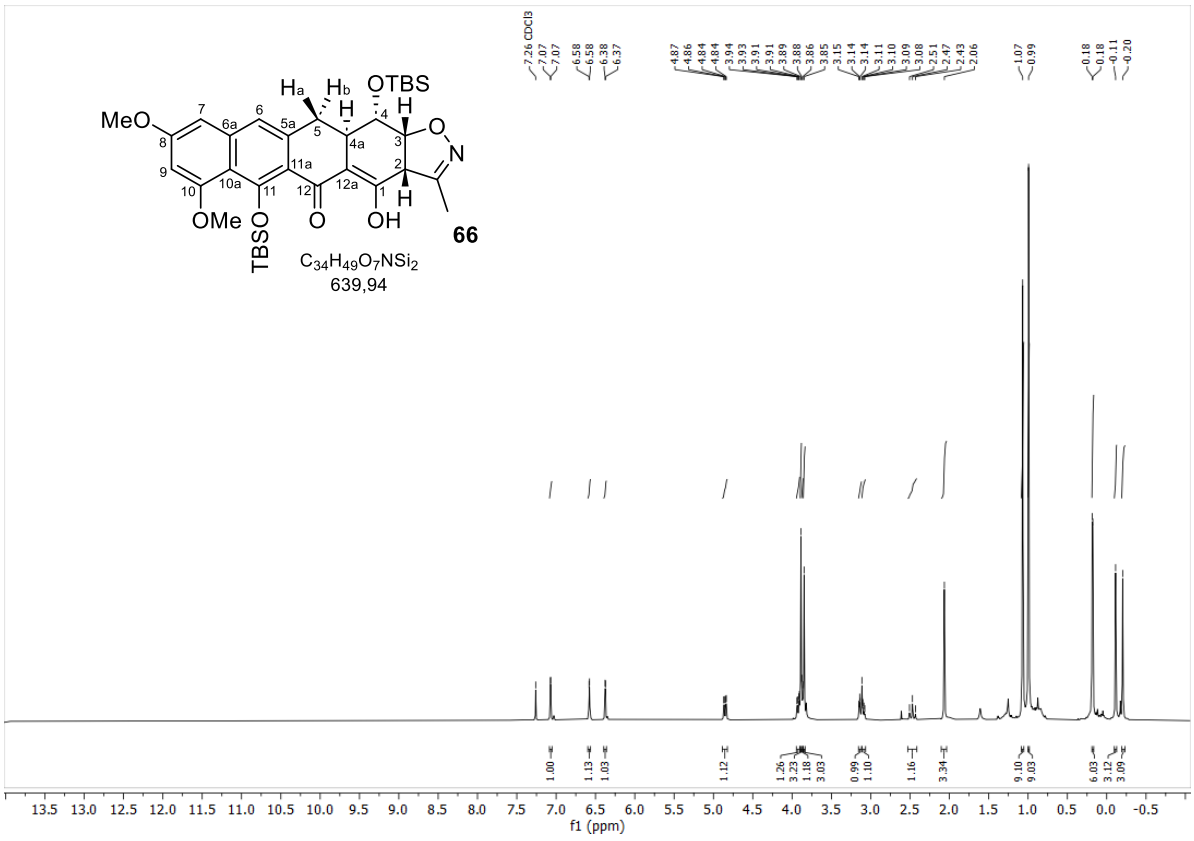


*NOE-spectrum of **155** in $CDCl_3$ (frequency saturation at 5,17 ppm).*

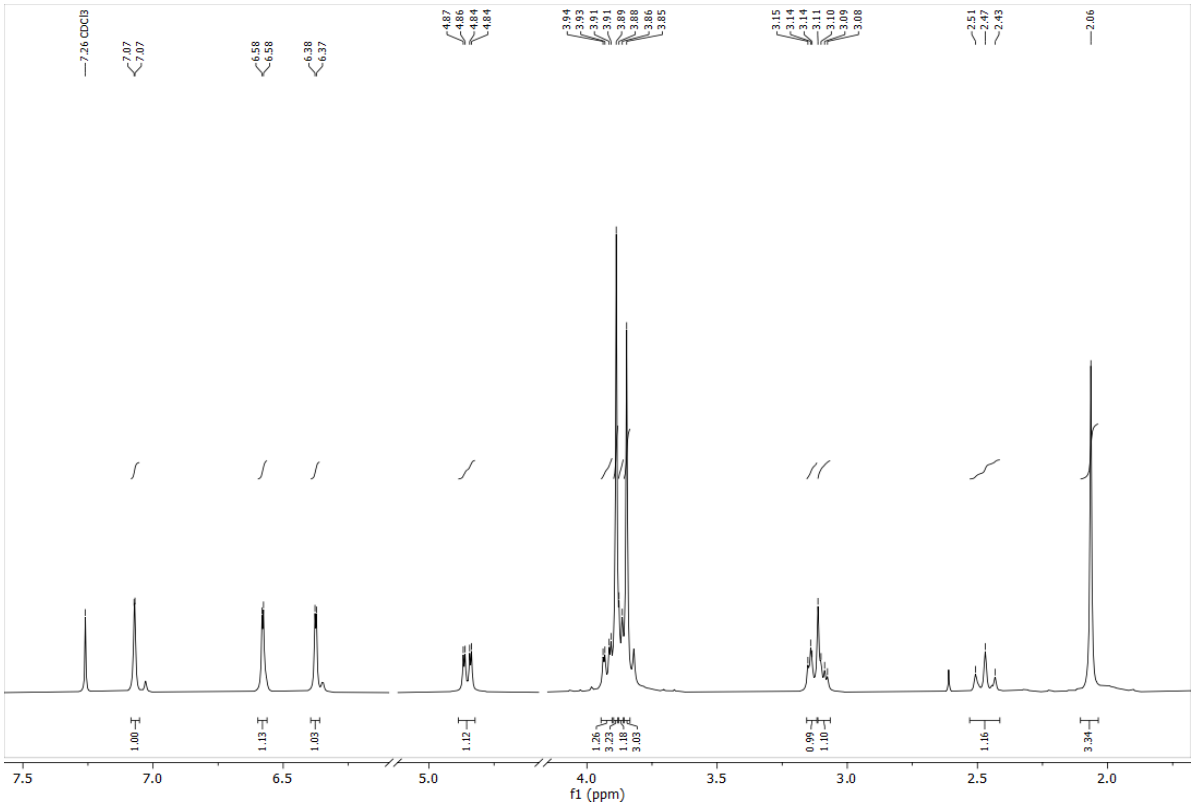


*^{13}C-spectrum of **155** in $CDCl_3$.*

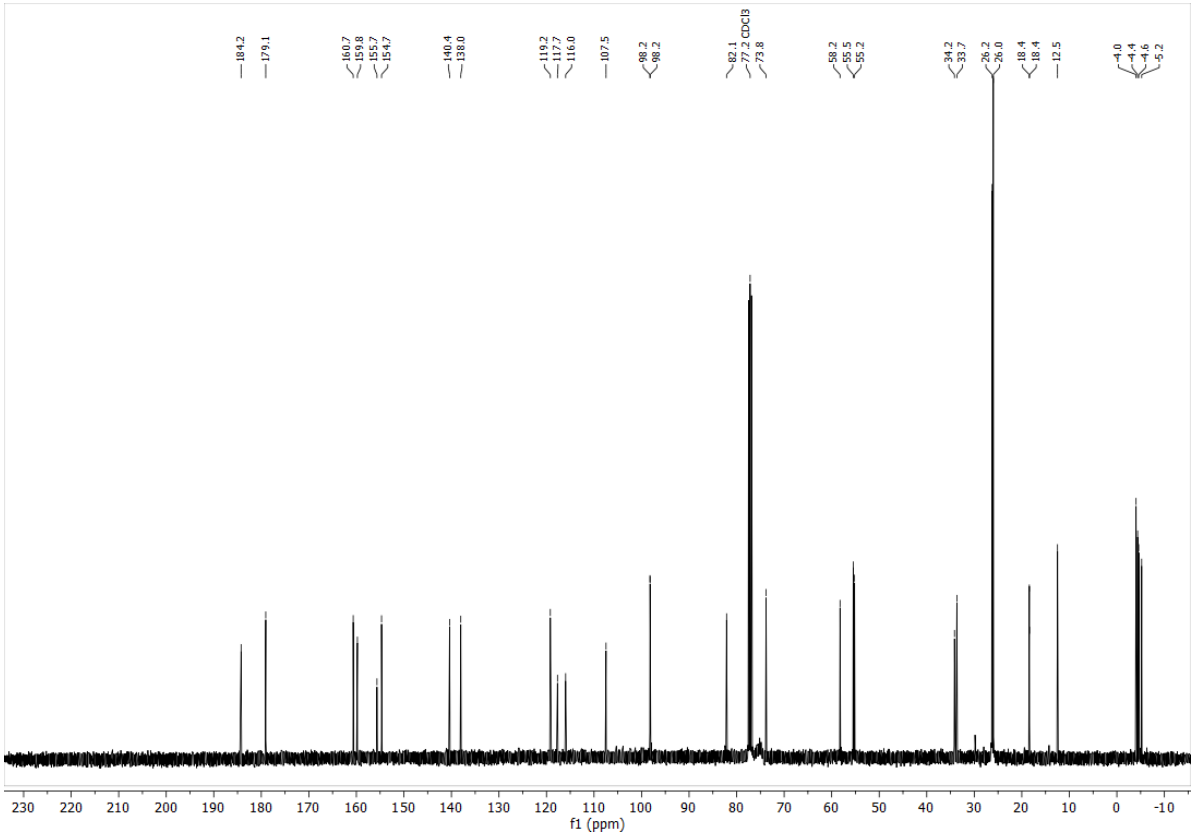
8.2.4.2 (3a*S*,12a*R*,13*S*,13a*R*)-6,13-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-7,9-dimethoxy-3-methyl-12,12a,13,13a-tetrahydrotetraceno[2,3-*d*]isoxazol-5(3a*H*)-one **66**



*^{1}H-spectrum of **66** in $CDCl_3$.*

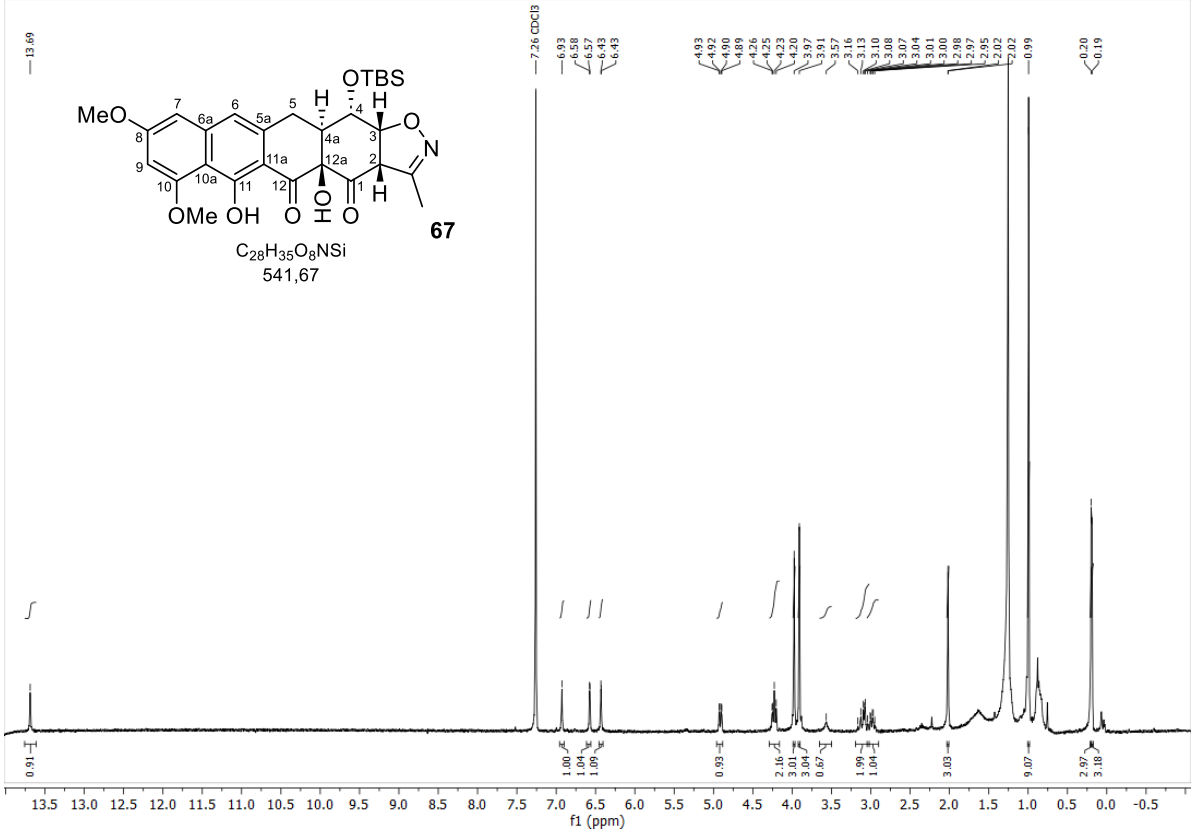


*^{1}H-spectrum of **66** in $CDCl_3$ (selected regions between 2,0-7,5 ppm).*

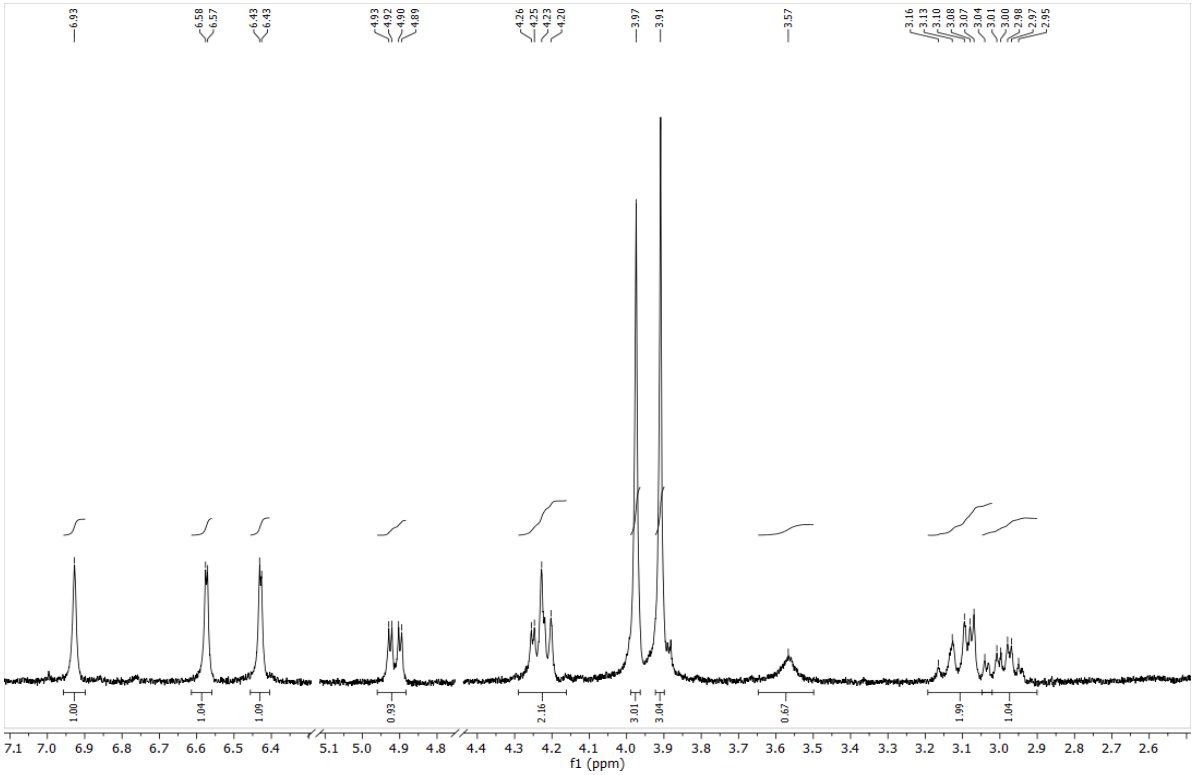


*^{13}C-spectrum of **66** in $CDCl_3$.*

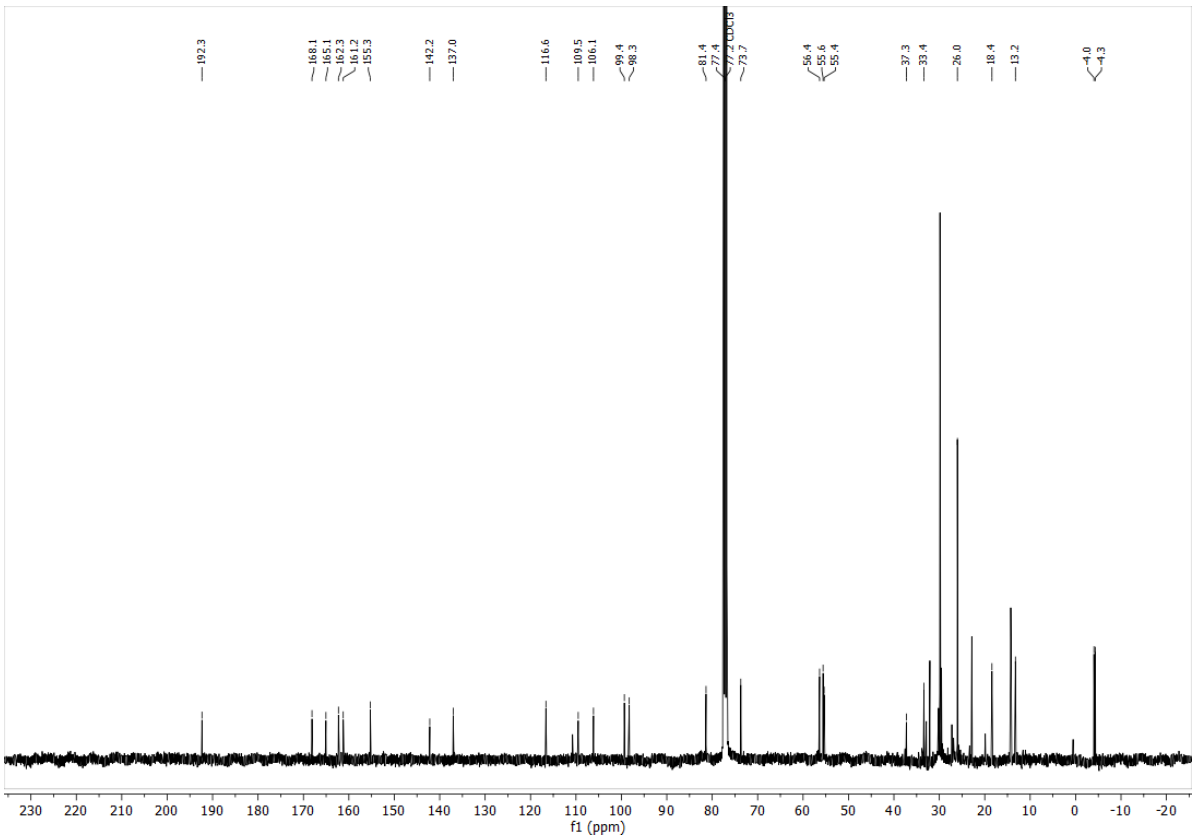
8.2.4.3 (3a*S*,4a*S*,12a*S*,13*S*,13a*R*)-13-((*tert*-butyldimethylsilyl)oxy)-4a,6-dihydroxy-7,9-dimethoxy -3-methyl-12,12a,13,13a-tetrahydrotetraceno[2,3-*d*]isoxazole-4,5(3a*H*,4a*H*)-dione **67**



*^{1}H-spectrum of **67** in $CDCl_3$.*

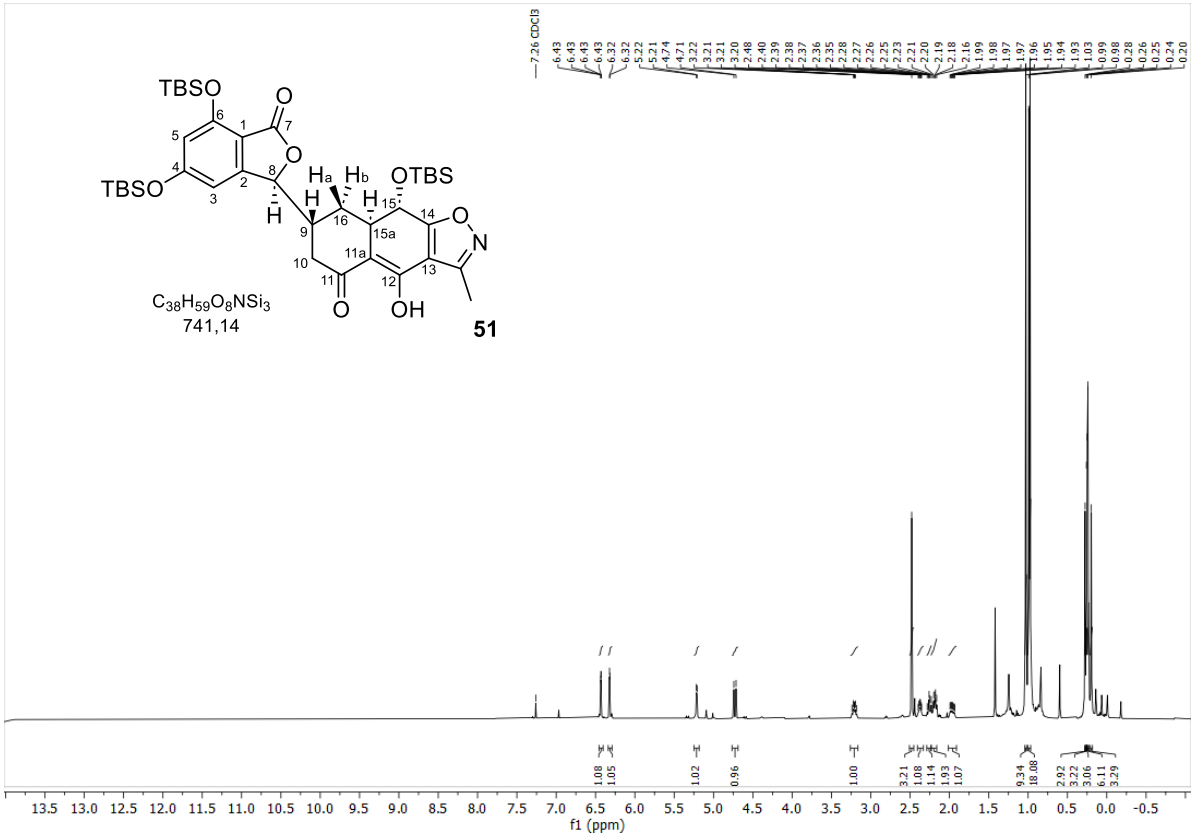


*^{1}H-spectrum of **67** in $CDCl_3$ (selected regions between 2,6-7,1 ppm).*

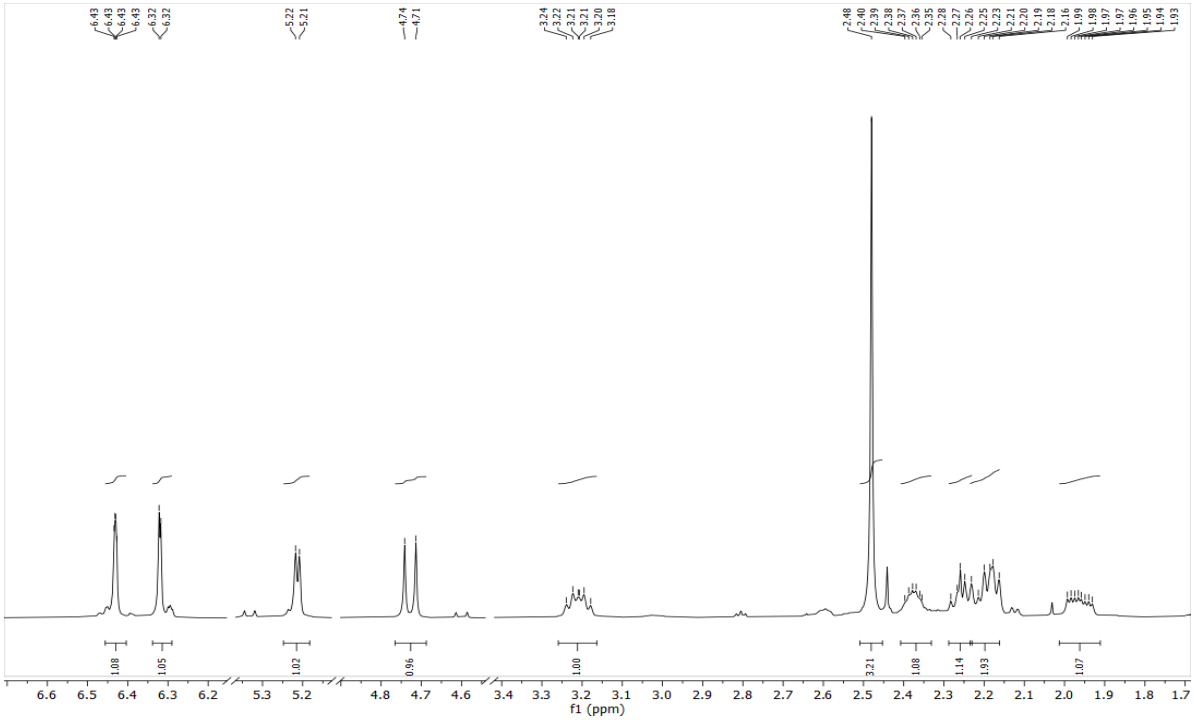


*^{13}C-spectrum of **67** in $CDCl_3$.*

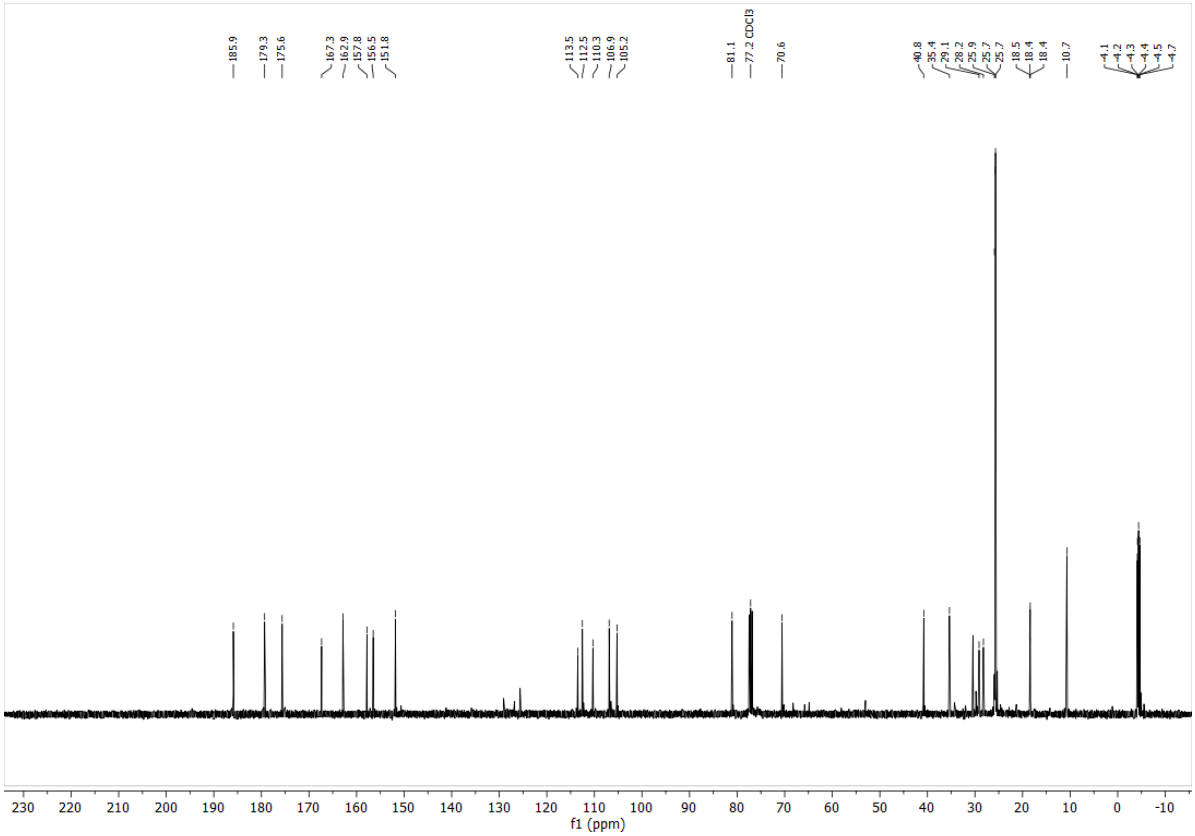
8.2.5 Demethylpremithramycinone **1** from lactone **45** and enone **32** (formation of the 1,4-addition product: (7*R*,8a*R*,9*S*)-7-((*S*)-4,6-bis((*tert*-butyldimethylsilyl)oxy)-3-oxo-1,3-dihydroisobenzofuran-1-yl)-9-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-3-methyl-7,8,8a,9-tetrahydronaphtho[2,3-*d*]isoxazol-5(6*H*)-one **51**)



*^{1}H-spectrum of **51** in $CDCl_3$.*



*^{1}H-spectrum of **51** in $CDCl_3$ (selected regions between 1,7-6,6 ppm).*

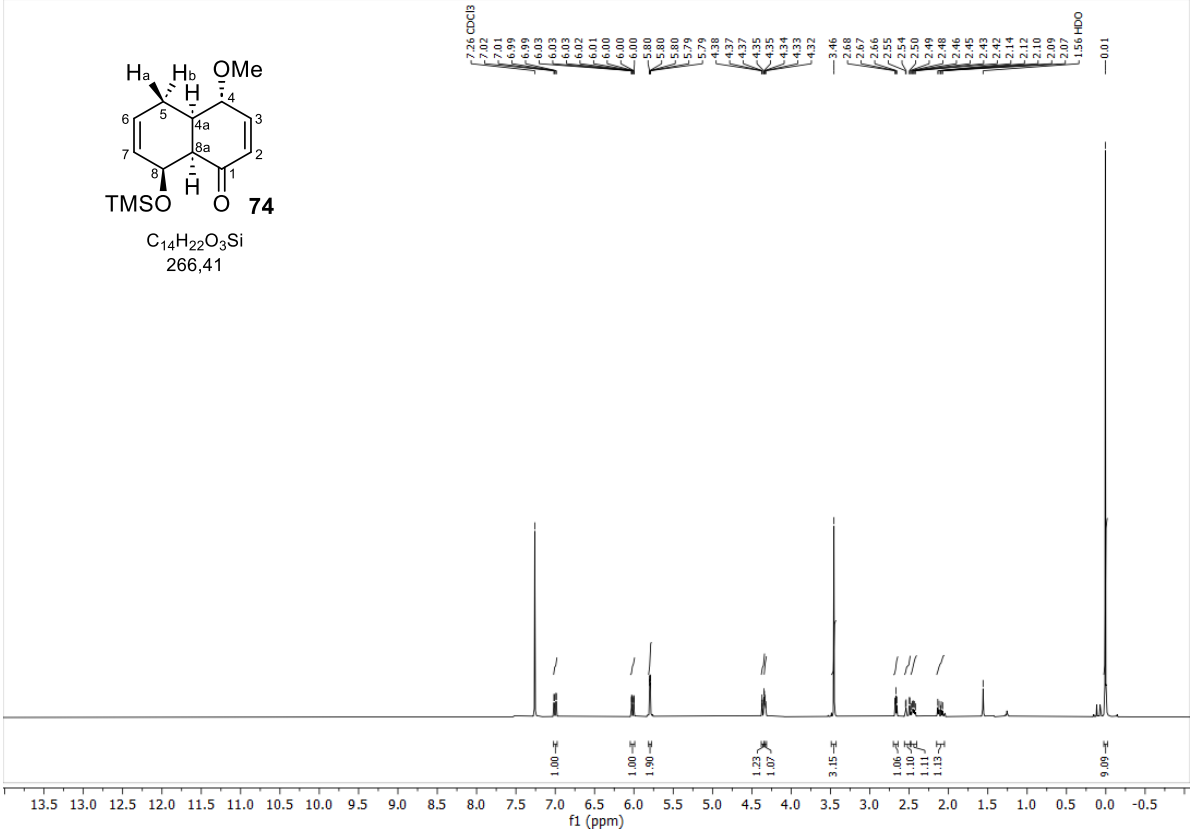


*^{13}C-spectrum of **51** in $CDCl_3$.*

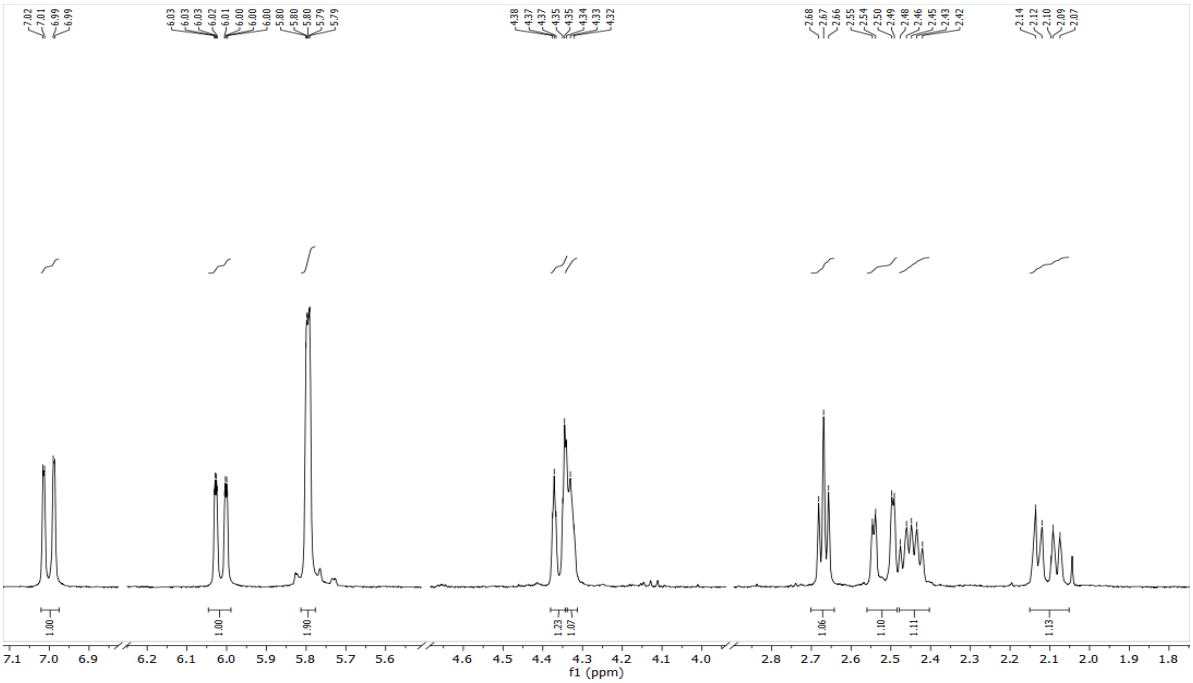
8.3 Premithramycinone

8.3.1 Enones **73** and **79**

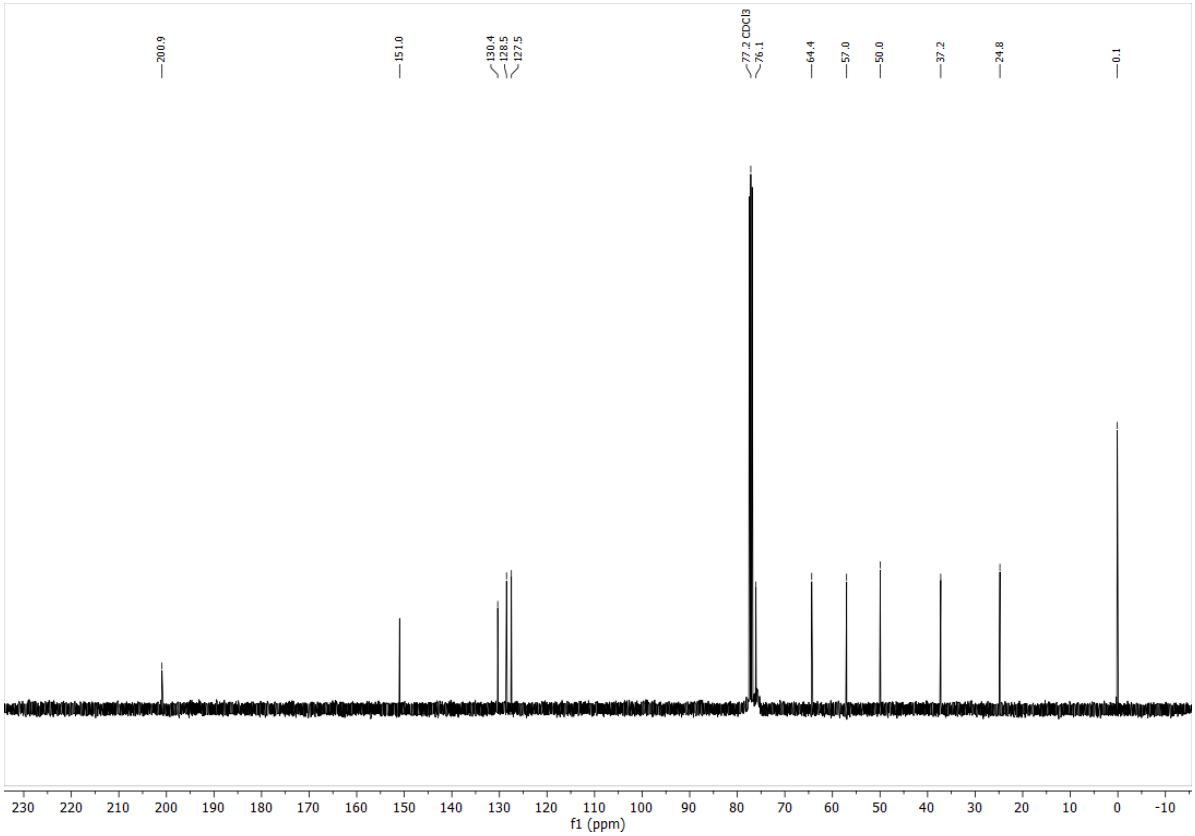
8.3.1.1 (4*R*,4a*R*,8*S*,8a*R*)-4-methoxy-8-((trimethylsilyl)oxy)-4a,5,8,8a-tetrahydronaphthalen-1(4*H*)-one **74**



*^{1}H-spectrum of **74** in $CDCl_3$.*

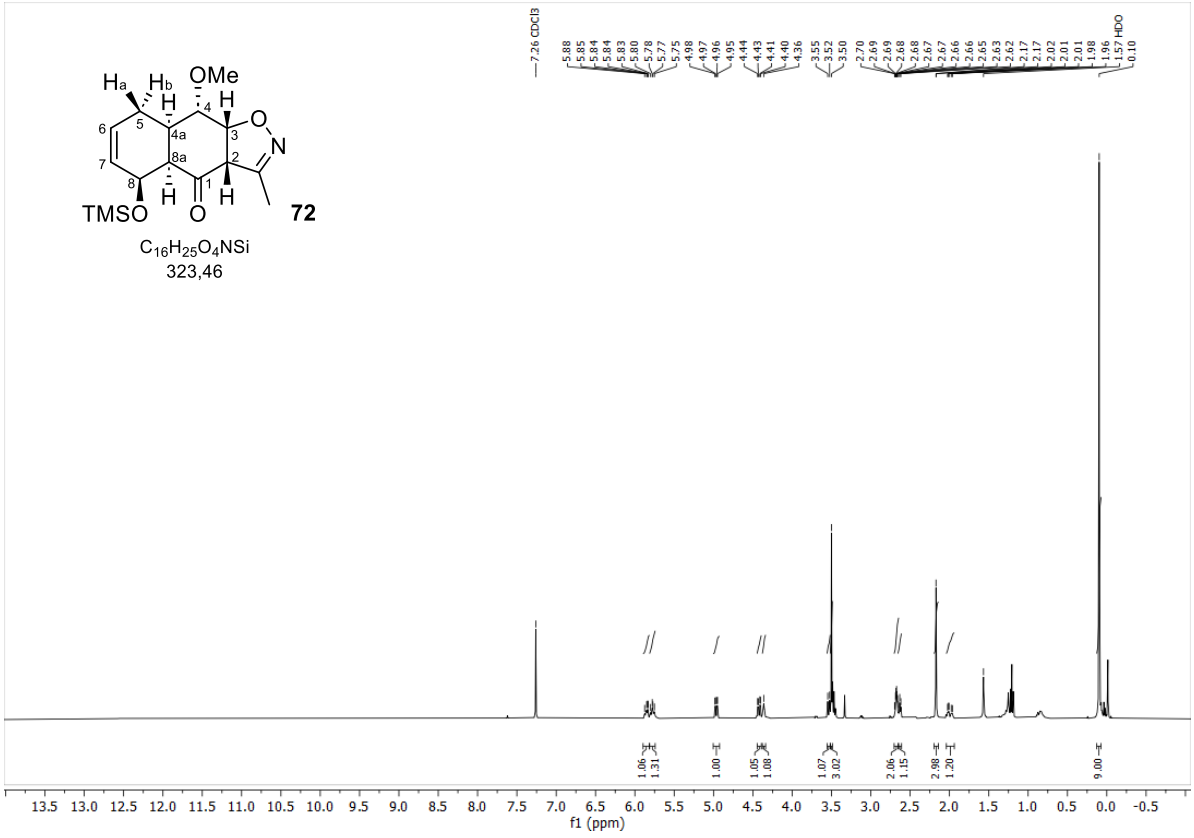


*^{1}H-spectrum of **74** in $CDCl_3$ (selected regions between 1,8-7,1 ppm).*

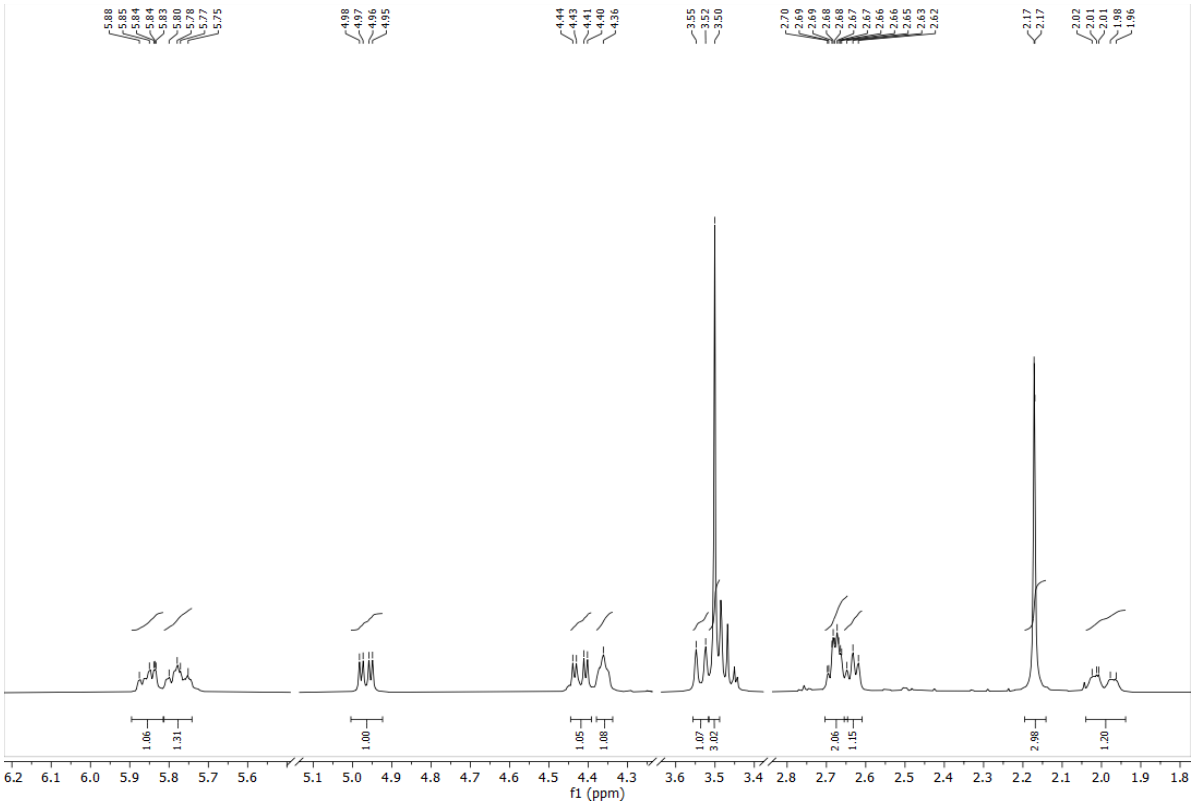


*^{13}C-spectrum of **74** in $CDCl_3$.*

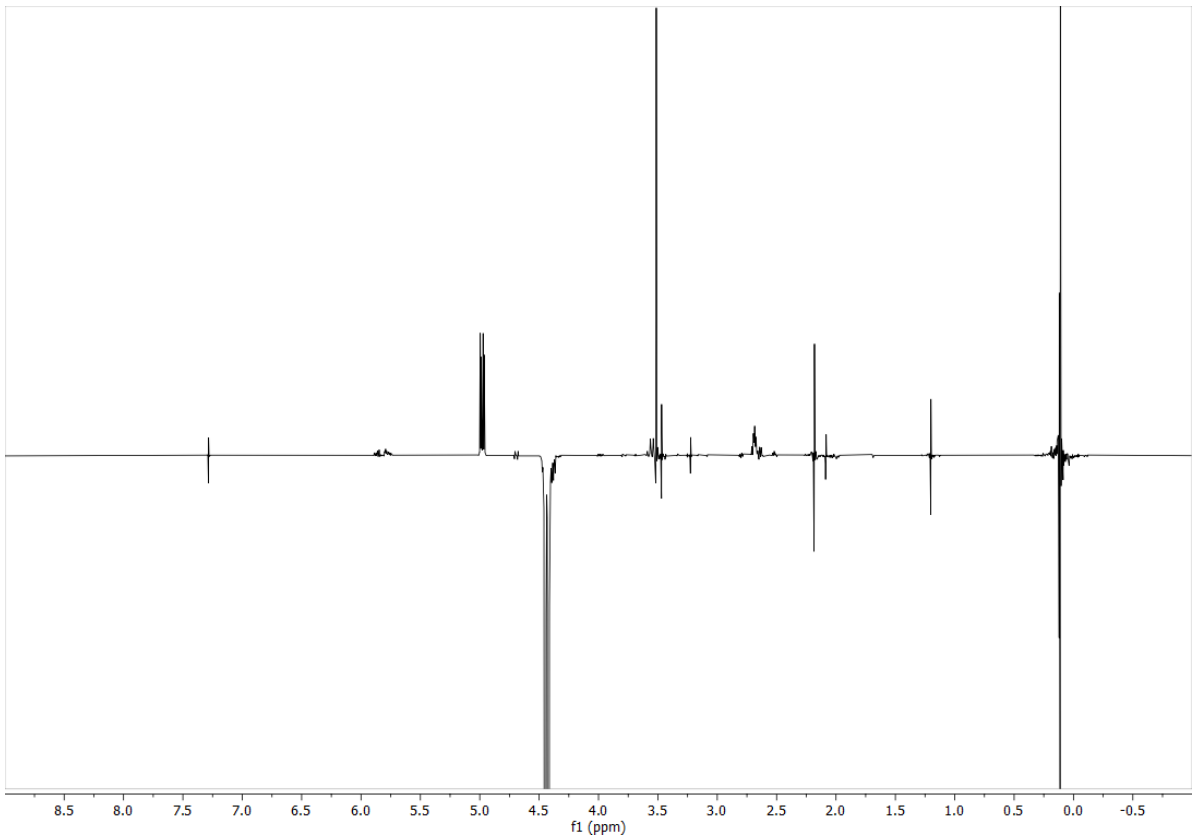
8.3.1.2 (3a*S*,4a*R*,5*S*,8a*R*,9*S*,9a*R*)-9-methoxy-3-methyl-5-((trimethylsilyl)oxy)-4a,5,8,8a,9,9a-hexahydronaphtho[2,3-*d*]isoxazol-4(3a*H*)-one **72**



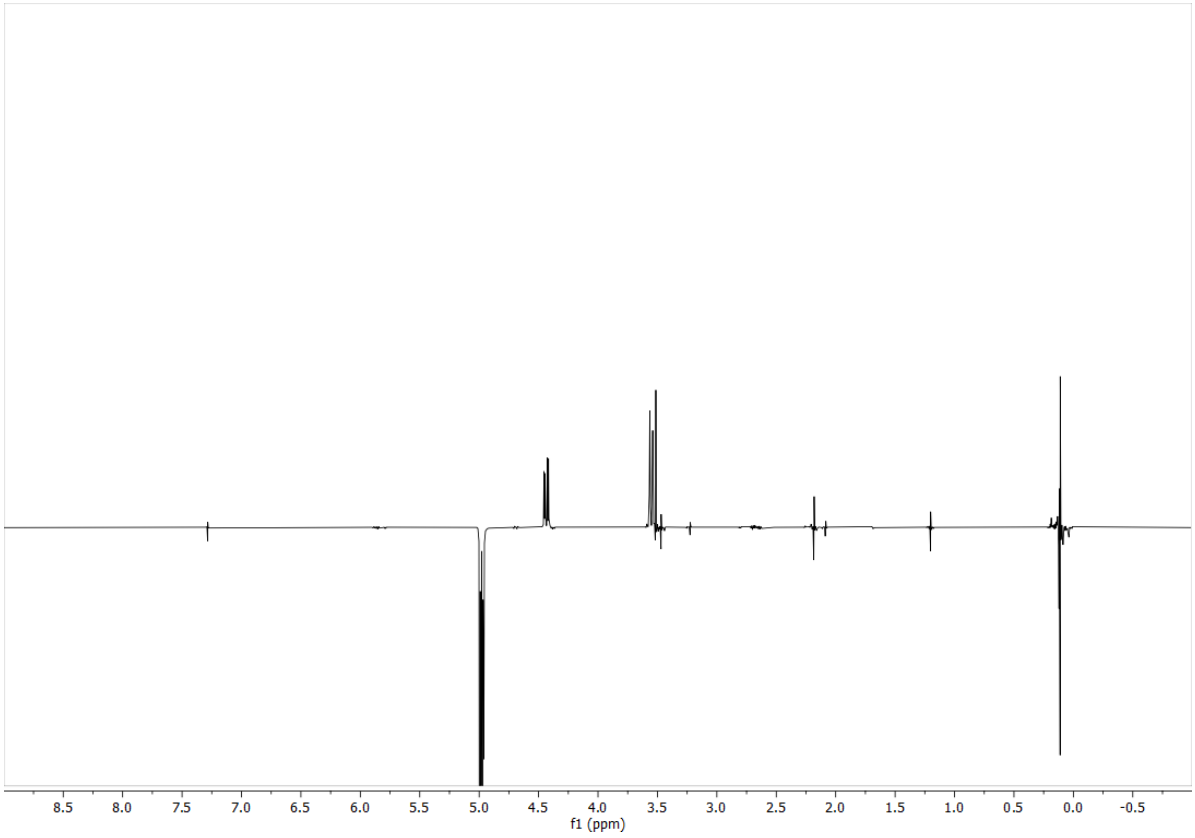
*^{1}H-spectrum of **72** in $CDCl_3$.*



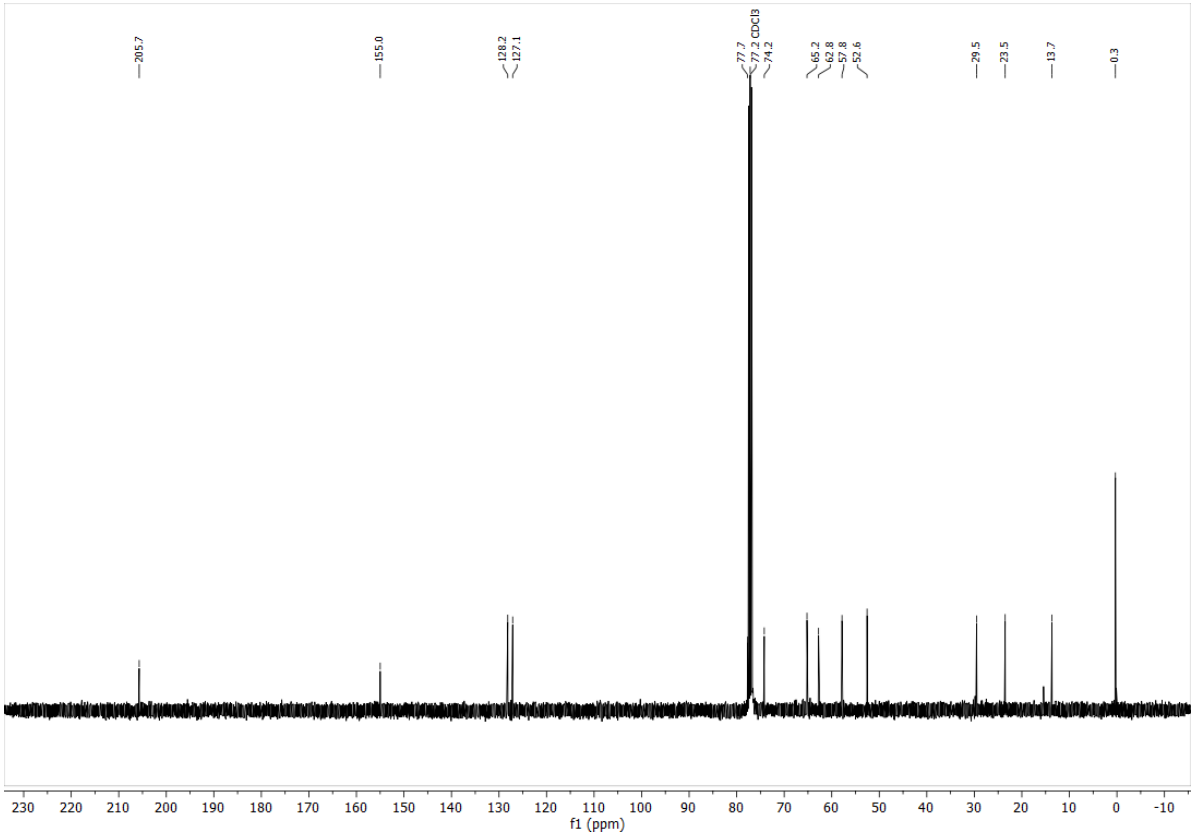
*^{1}H-spectrum of **72** in $CDCl_3$ (selected regions between 1,8-6,2 ppm).*



*NOE-spectrum of **72** in $CDCl_3$ (frequency saturation at 4,43 ppm).*

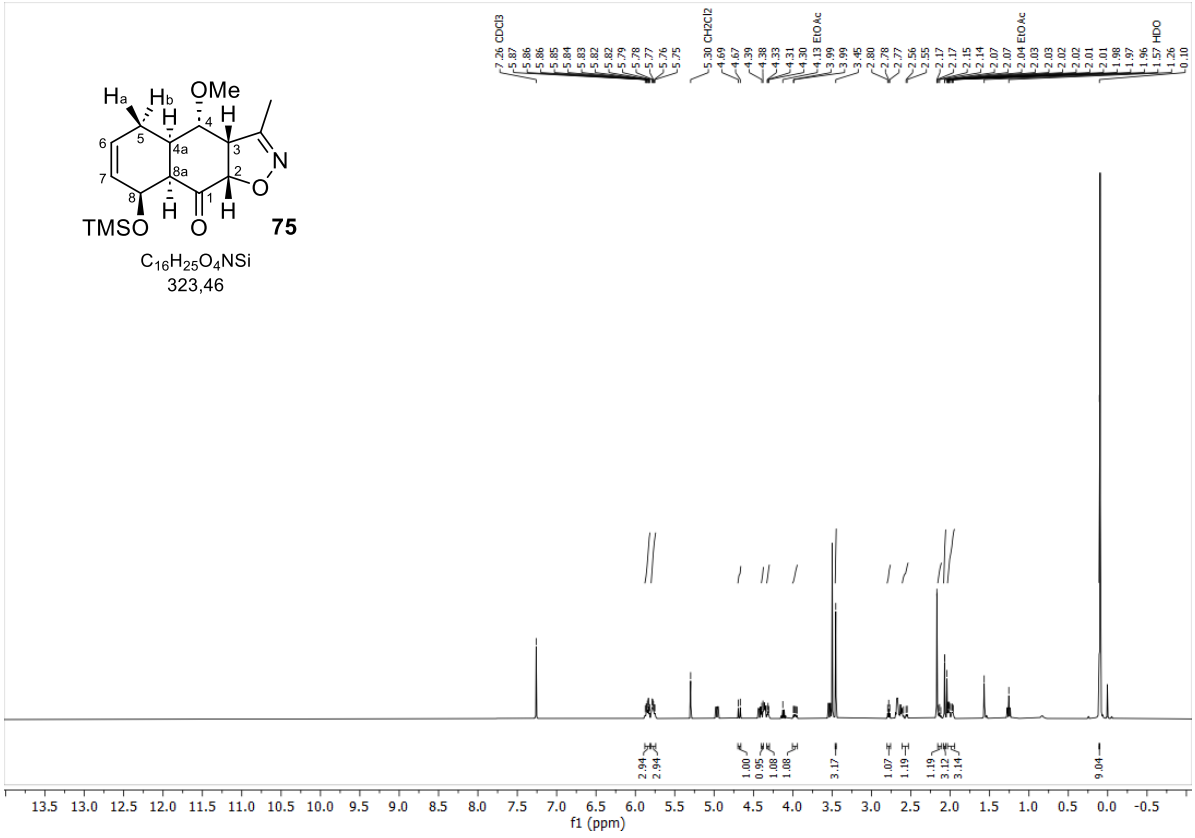


*NOE-spectrum of **72** in $CDCl_3$ (frequency saturation at 4,98 ppm).*

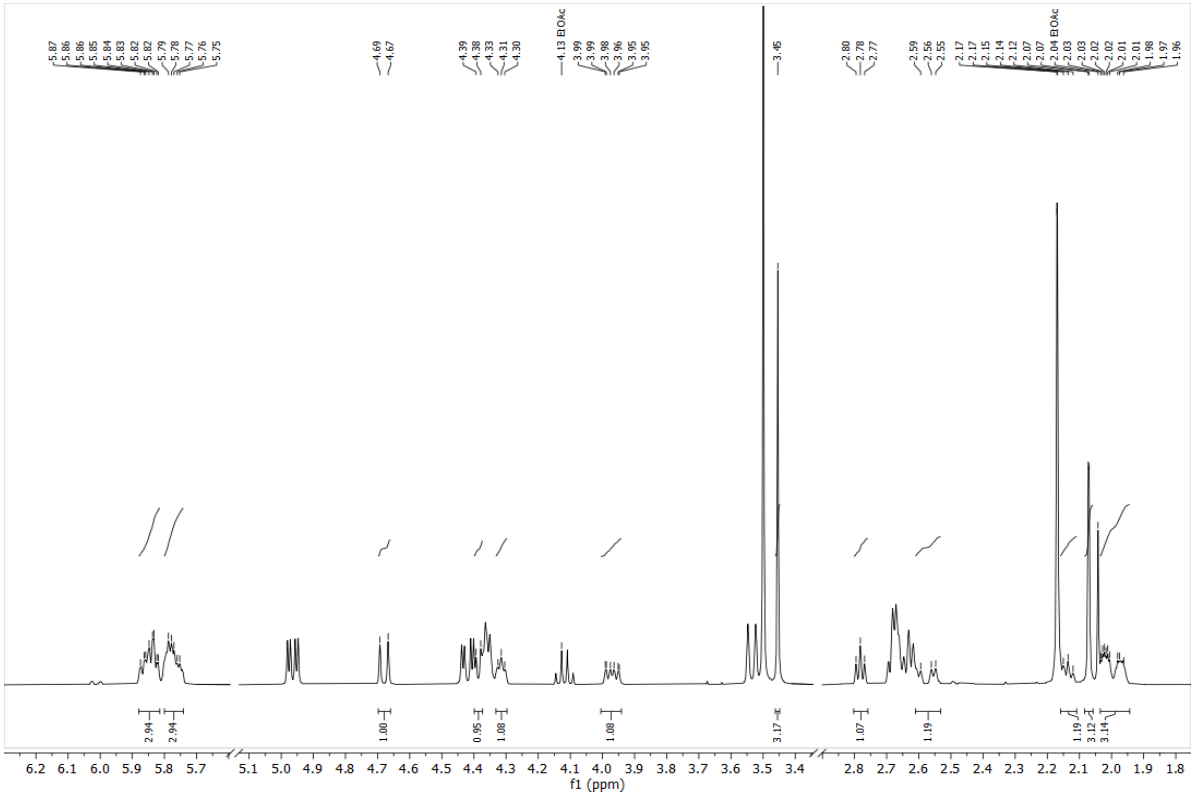


*^{13}C-spectrum of **72** in $CDCl_3$.*

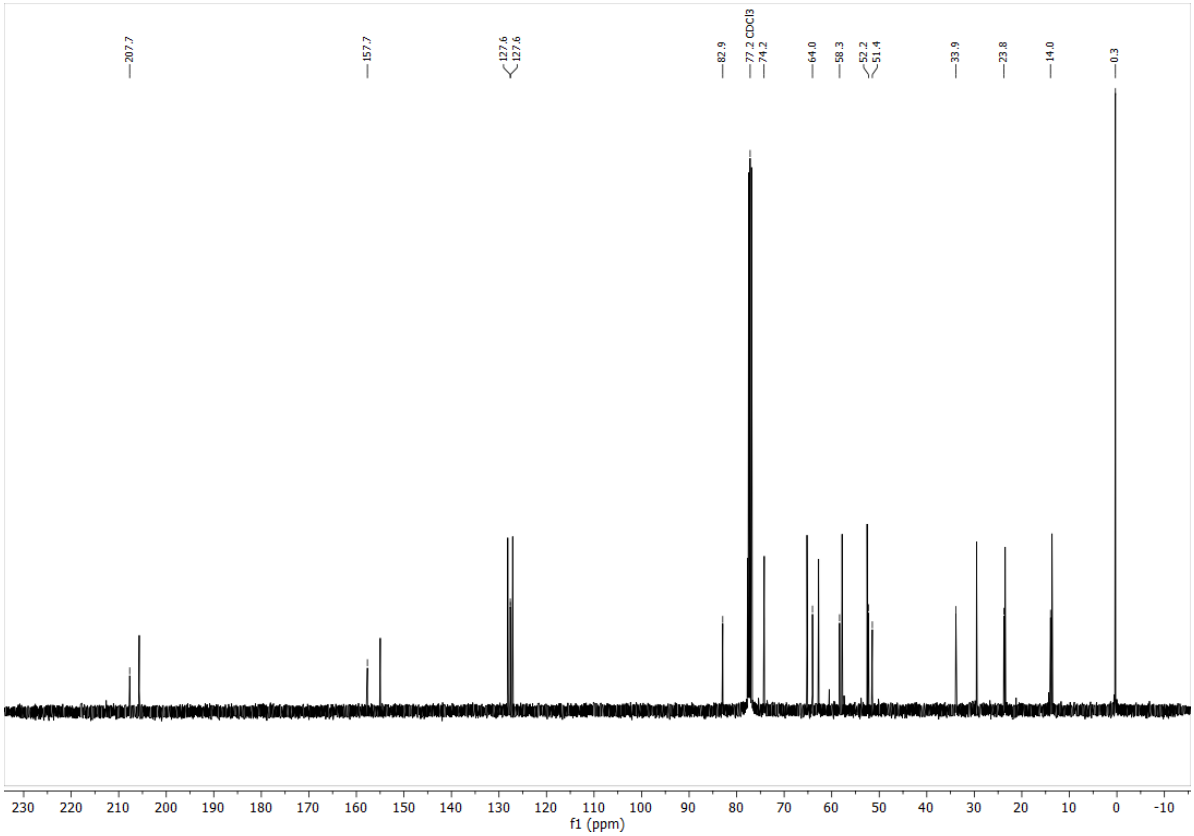
Regioisomer **75** ((3a*S*,4*S*,4a*R*,8*S*,8a*R*,9a*S*)-4-methoxy-3-methyl-8-((trimethylsilyl)oxy)-3a,4a, 5,8,8a,9a-hexahydronaphtho[2,3-*d*]isoxazol-9(4*H*)-one) as a 3,5:1 mixture with **72**



*^{1}H-spectrum of **75** in $CDCl_3$.*

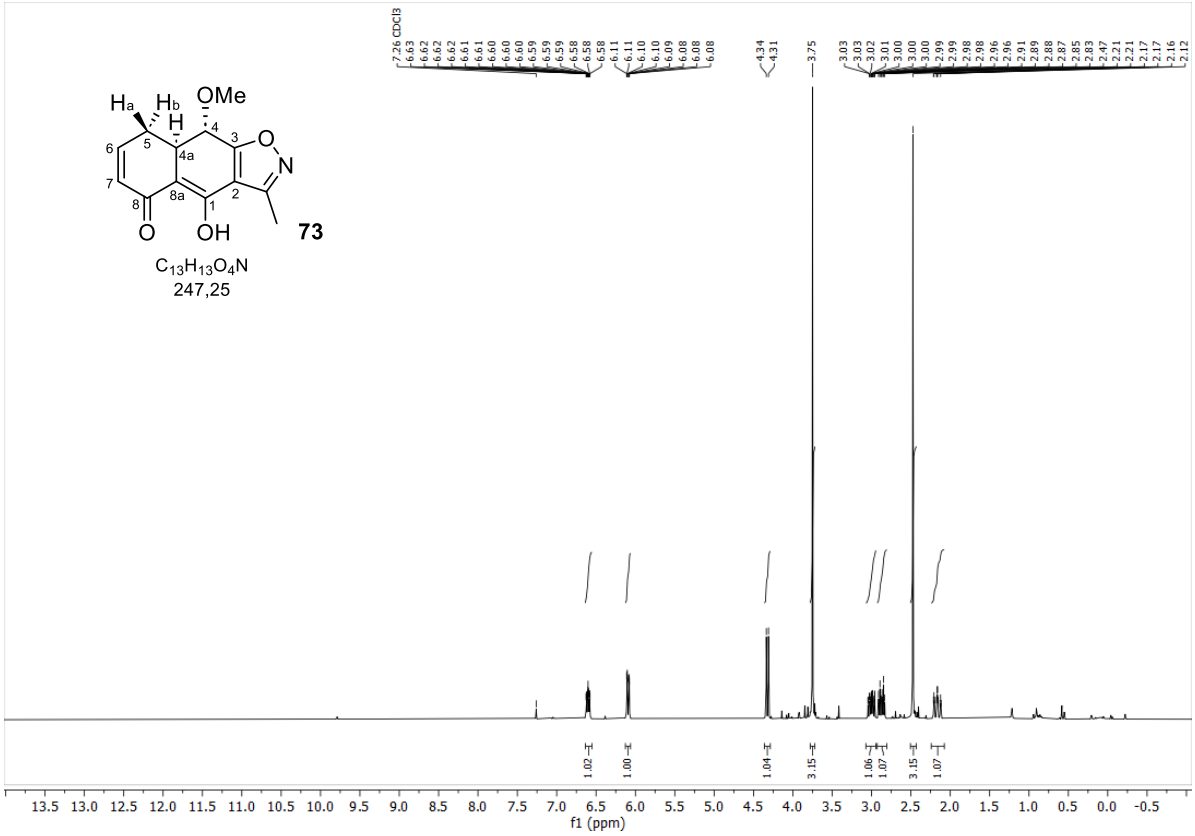


*^{1}H-spectrum of **75** in $CDCl_3$ (selected regions between 1,8-6,2 ppm).*

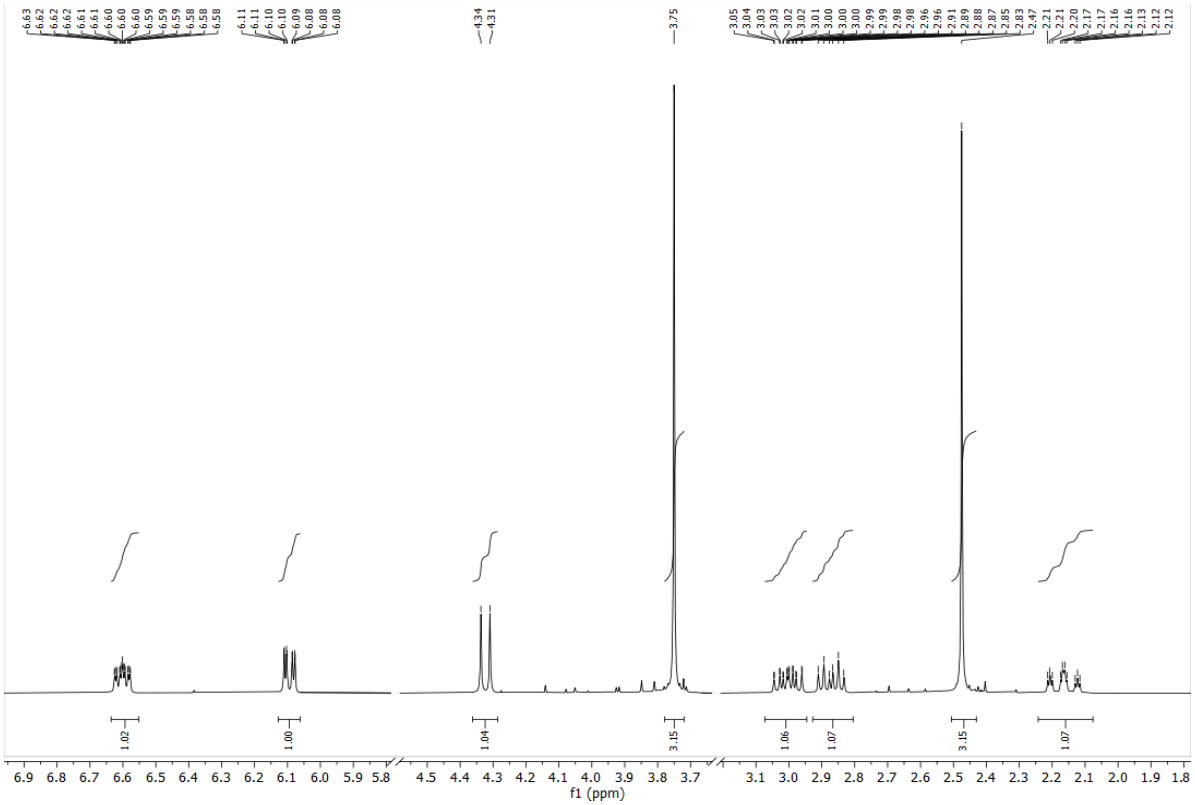


*^{13}C-spectrum of **75** in $CDCl_3$.*

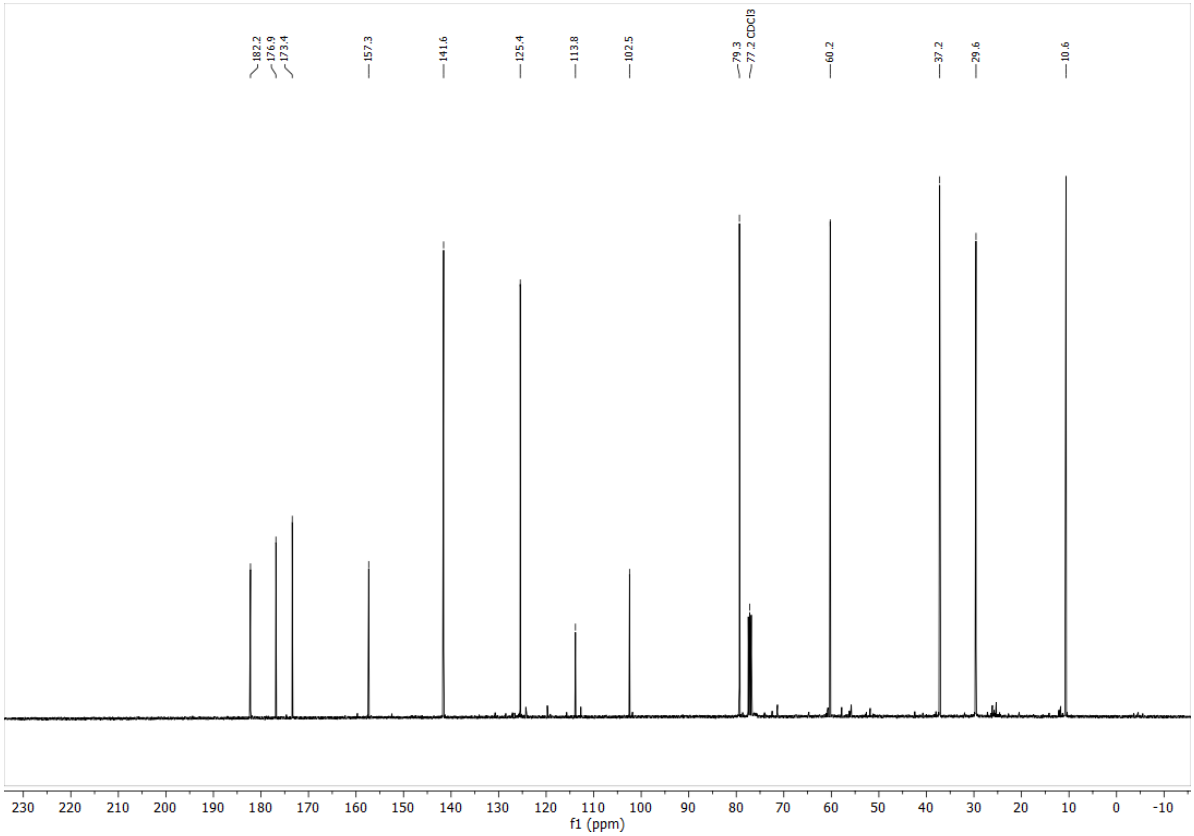
7.3.1.3 (8a*R*,9*S*)-4-hydroxy-9-methoxy-3-methyl-8a,9-dihydronaphtho[2,3-*d*]isoxazol-5(8*H*)-one **73**



*^{1}H-spectrum of **73** in $CDCl_3$.*



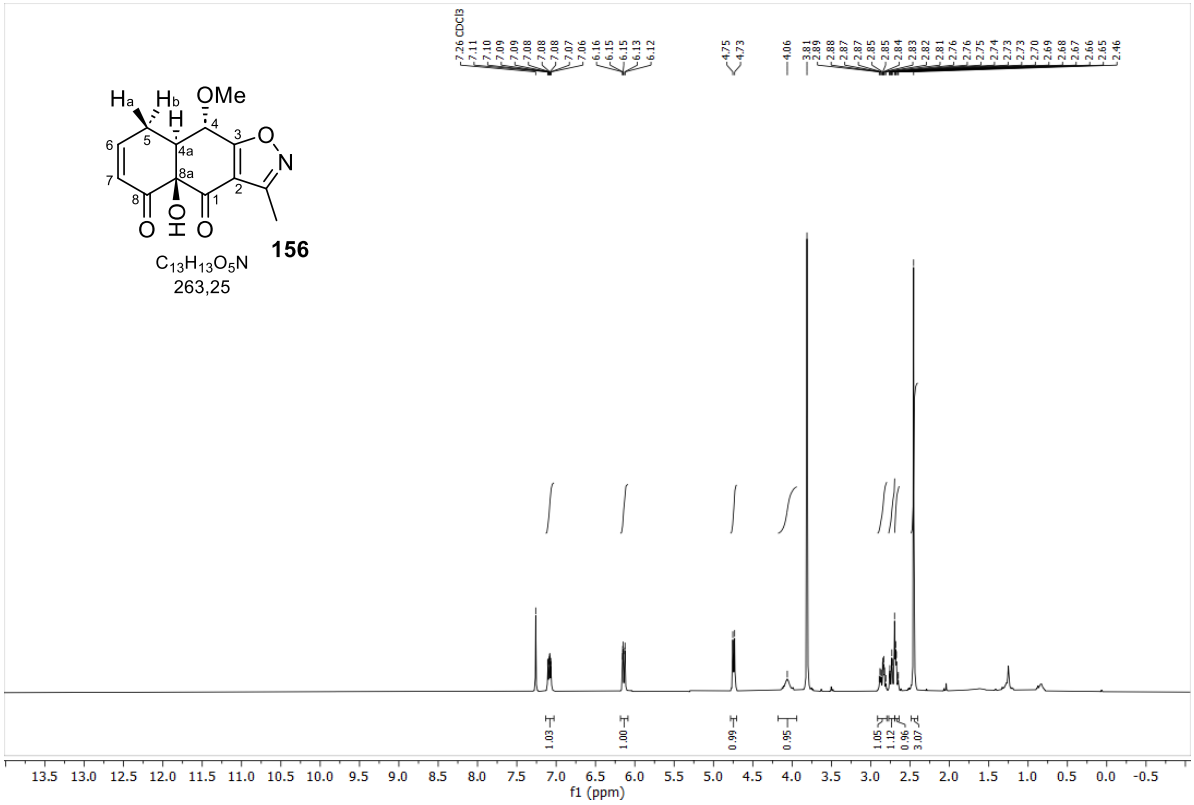
*^{1}H-spectrum of **73** in $CDCl_3$ (selected regions between 1,8-6,9 ppm).*



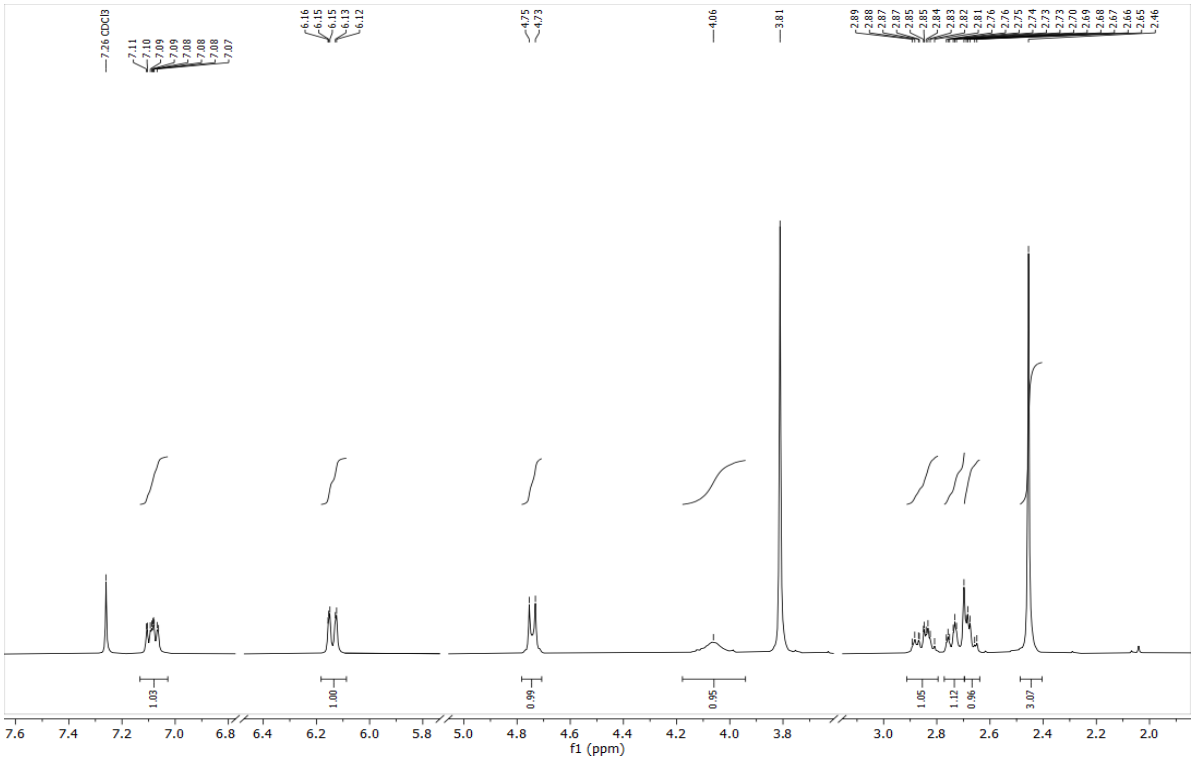
*^{13}C-spectrum of **73** in $CDCl_3$.*

8.3.1.4.1 (4a*S*,8a*S*,9*S*)-4a-hydroxy-9-methoxy-3-methyl-8a,9-dihydronaphtho[2,3-*d*]isoxazole-4,5(4a*H*,8*H*)-dione **79**

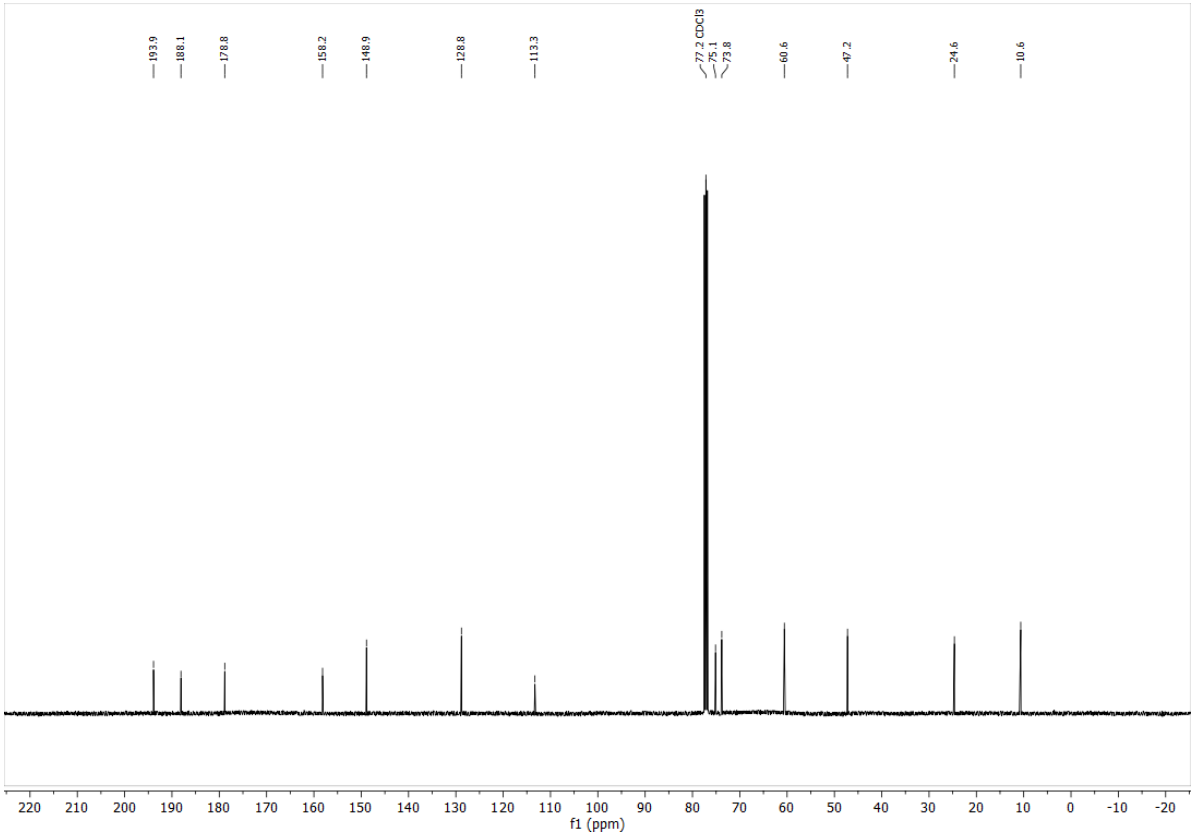
α-hydroxylation (synthesis of (4a*S*,8a*S*,9*S*)-4a-hydroxy-9-methoxy-3-methyl-8a,9-dihydronaphtho[2,3-*d*] isoxazole-4,5(4a*H*,8*H*)-dione **156**)



*^{1}H-spectrum of **156** in $CDCl_3$.*

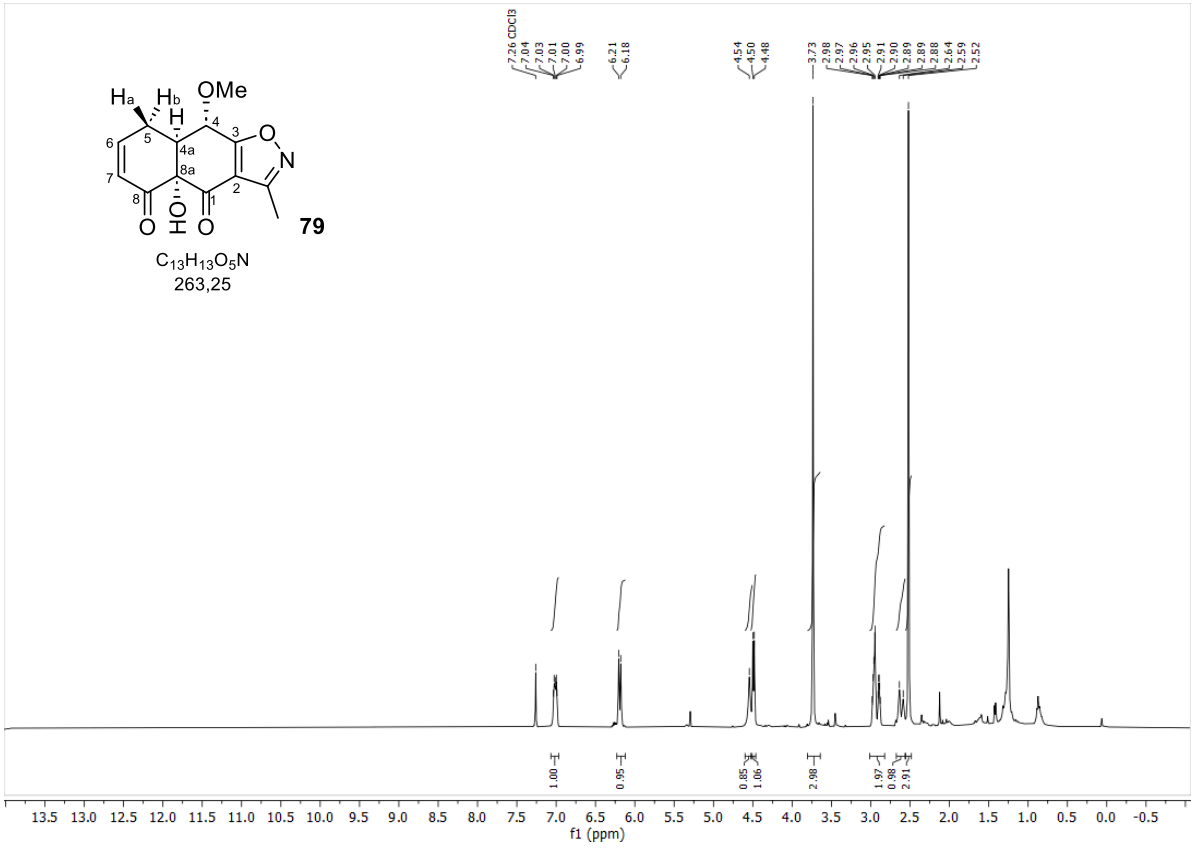


*^{1}H-spectrum of **156** in $CDCl_3$ (selected regions between 2,0-7,6 ppm).*

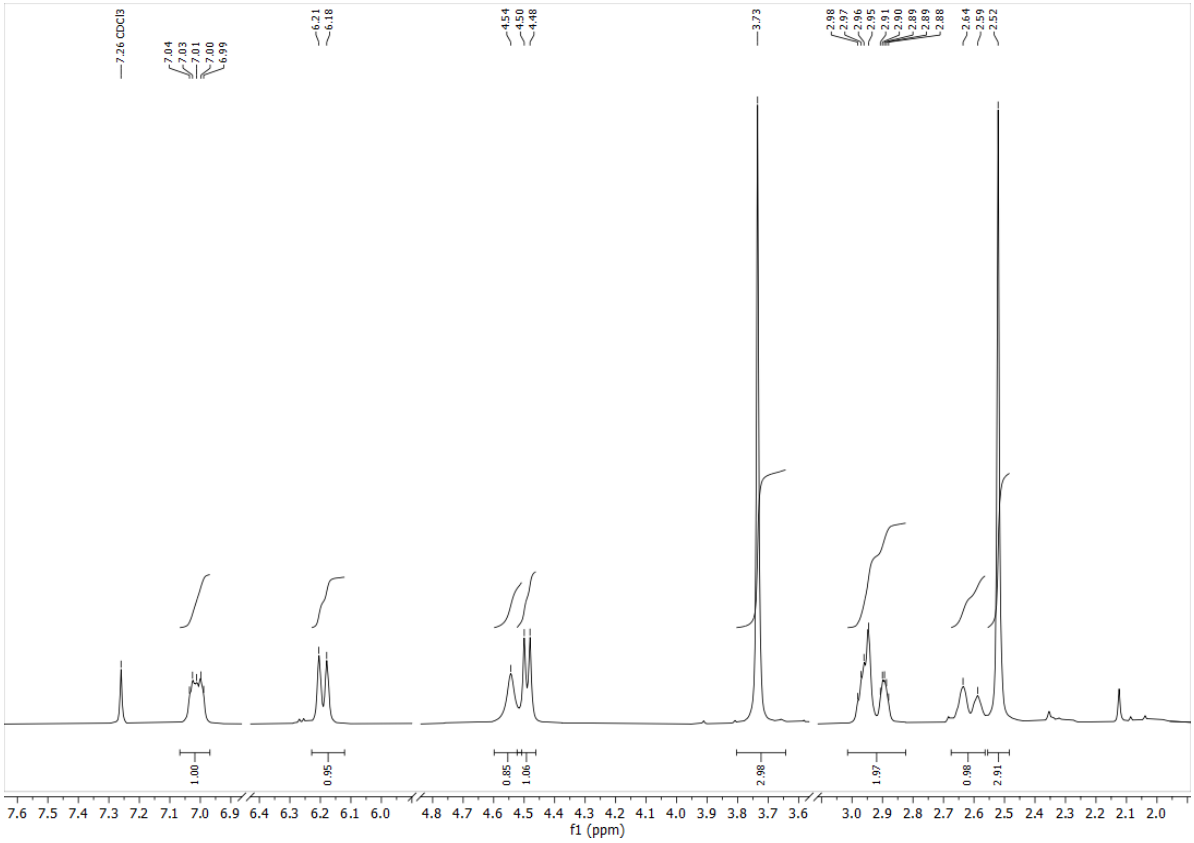


*^{13}C-spectrum of **156** in $CDCl_3$.*

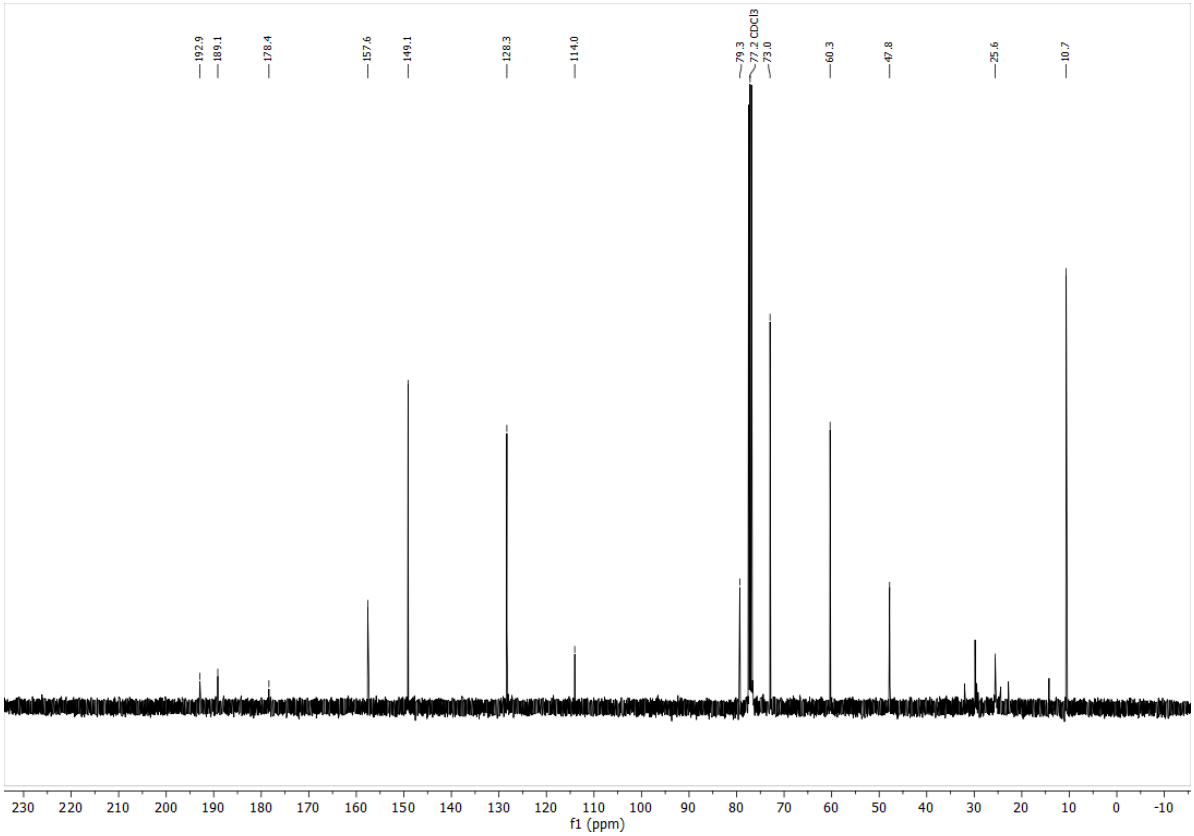
α-ketol rearrangement (synthesis of **79**)



*^{1}H-spectrum of **79** in $CDCl_3$.*



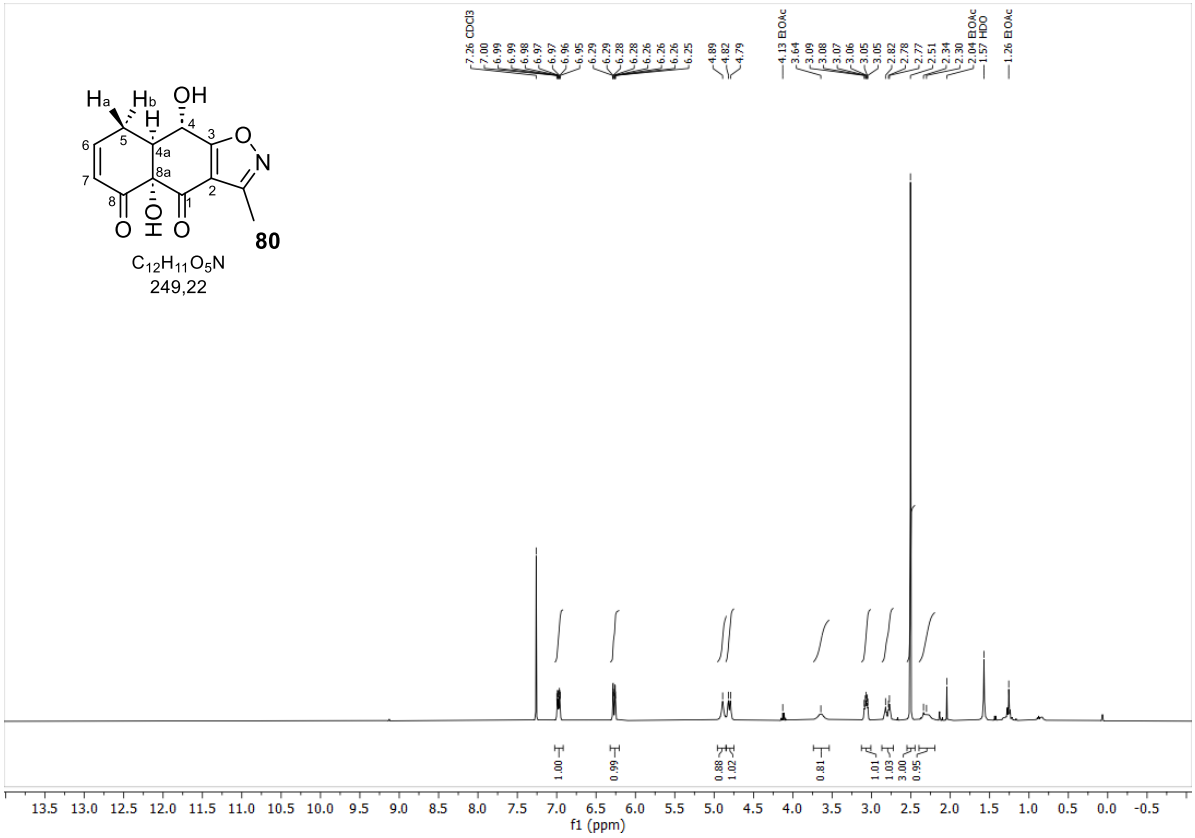
*^{1}H-spectrum of **79** in $CDCl_3$ (selected regions between 2,0-7,6 ppm).*



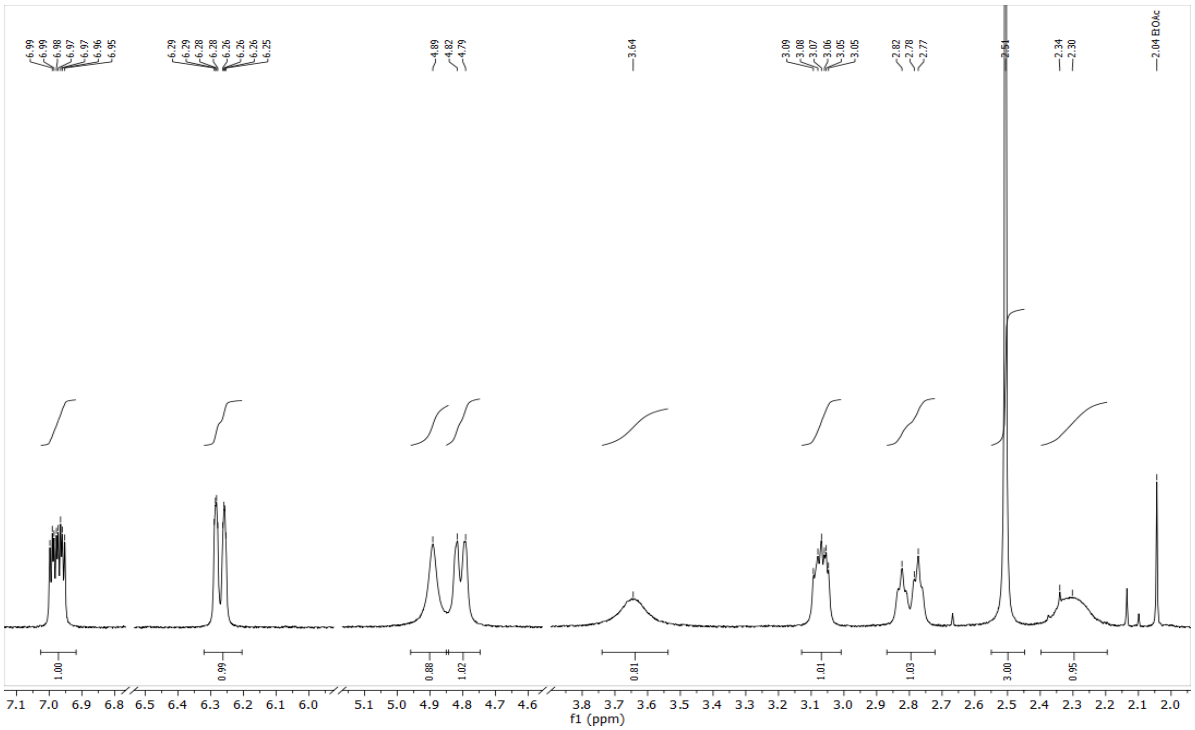
*^{13}C-spectrum of **79** in $CDCl_3$.*

8.3.1.4.2 (4a*S*,8a*S*,9*S*)-4a-hydroxy-9-methoxy-3-methyl-8a,9-dihydronaphtho[2,3-*d*]isoxazole-4,5(4a*H*,8*H*)-dione **79** from a **35**-derived precursor **80**

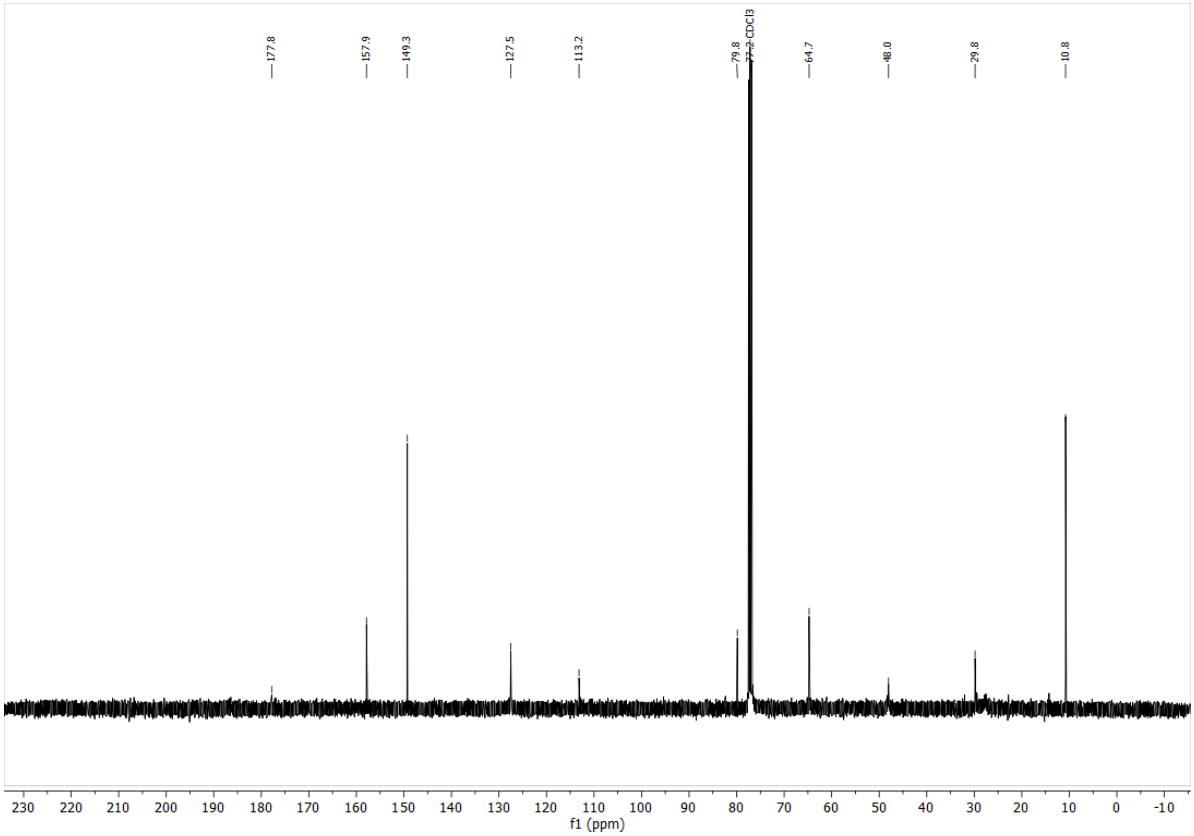
TBS-cleavage (synthesis of (4a*S*,8a*S*,9*S*)-4a,9-dihydroxy-3-methyl-8a,9-dihydronaphtho[2,3-*d*]isoxazole-4,5(4a*H*,8*H*)-dione **80**)



*^{1}H-spectrum of **80** in $CDCl_3$.*

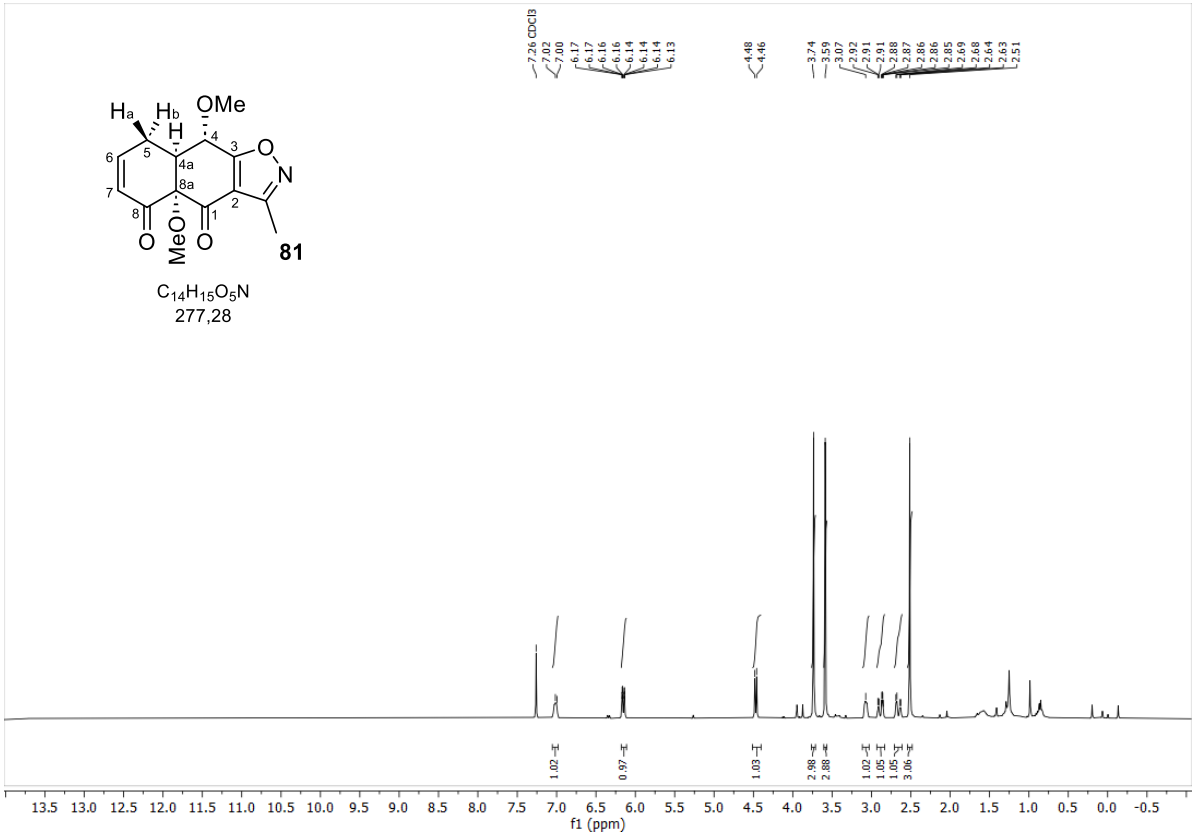


*^{1}H-spectrum of **80** in $CDCl_3$ (selected regions between 2,0-7,1 ppm).*

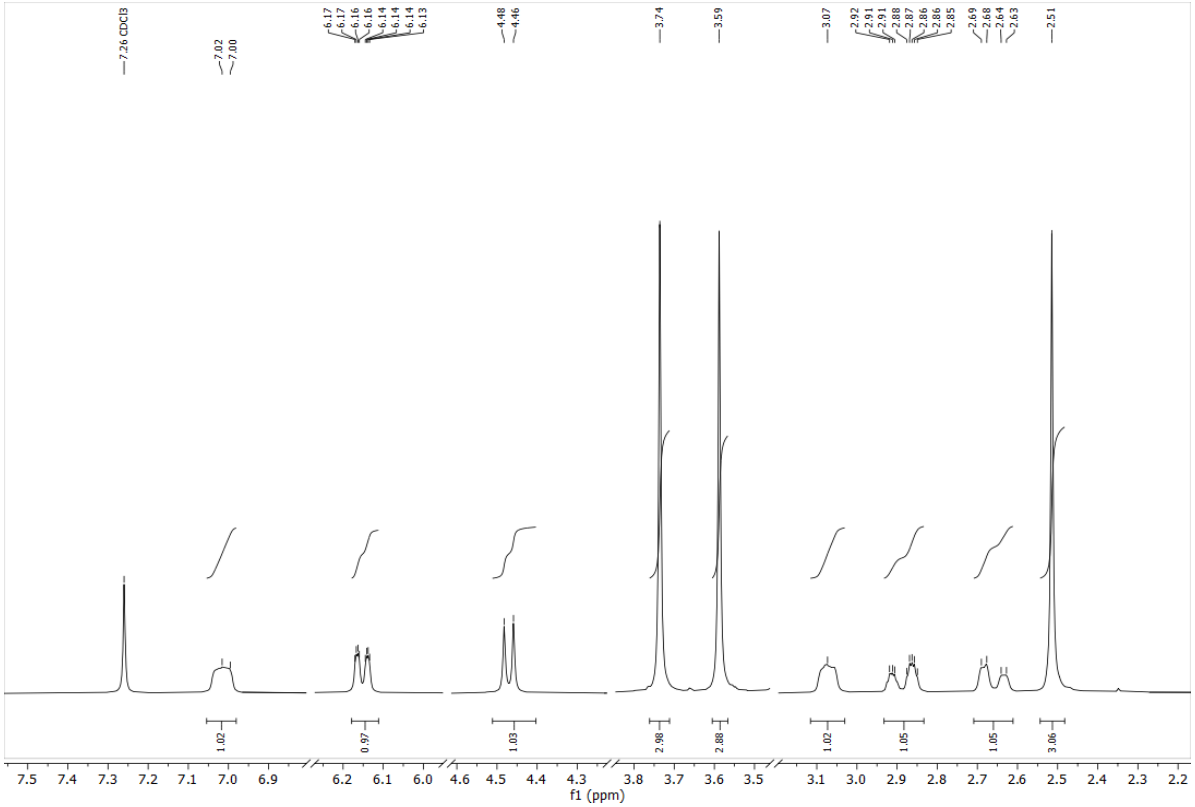


*^{13}C-spectrum of **80** in $CDCl_3$.*

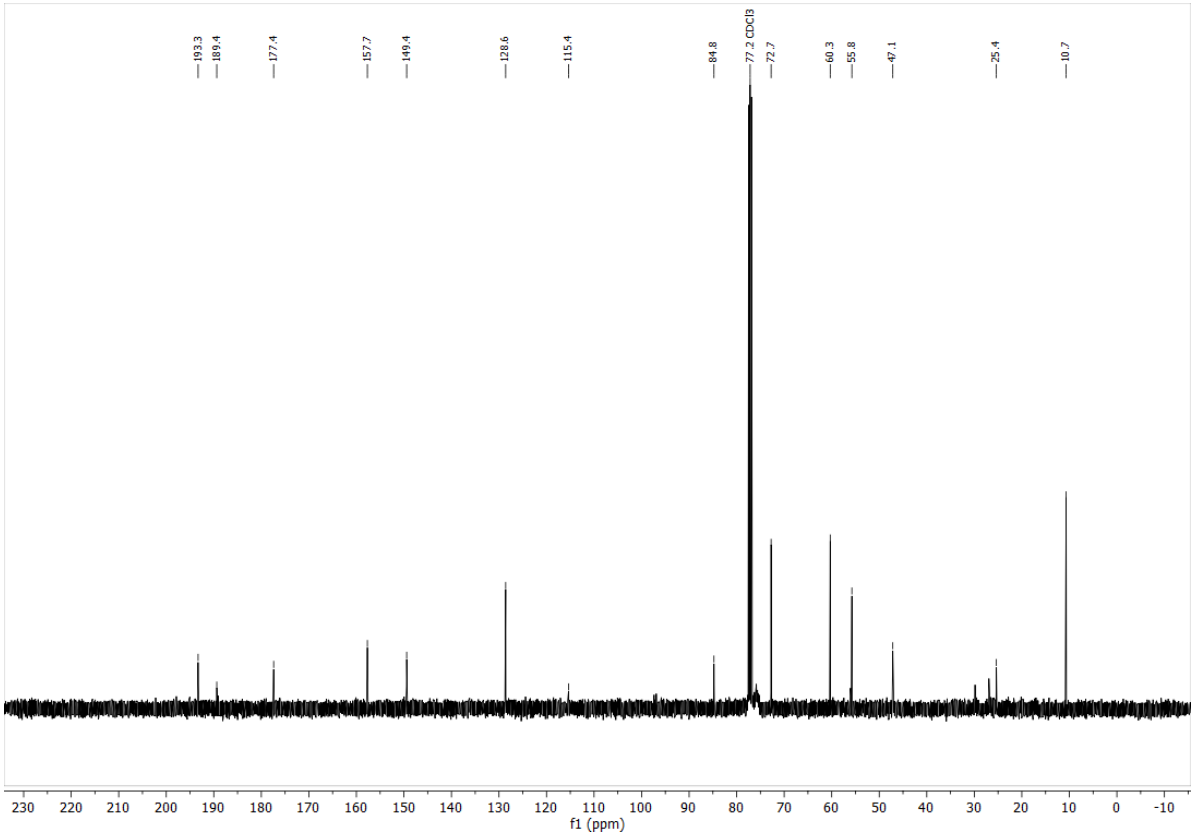
di-methylation product **81** ((4a*S*,8a*S*,9*S*)-4a,9-dimethoxy-3-methyl-8a,9-dihydronaphtho[2,3-d]-isoxazole-4,5(4a*H*,8*H*)-dione)



*^{1}H-spectrum of **81** in $CDCl_3$.*



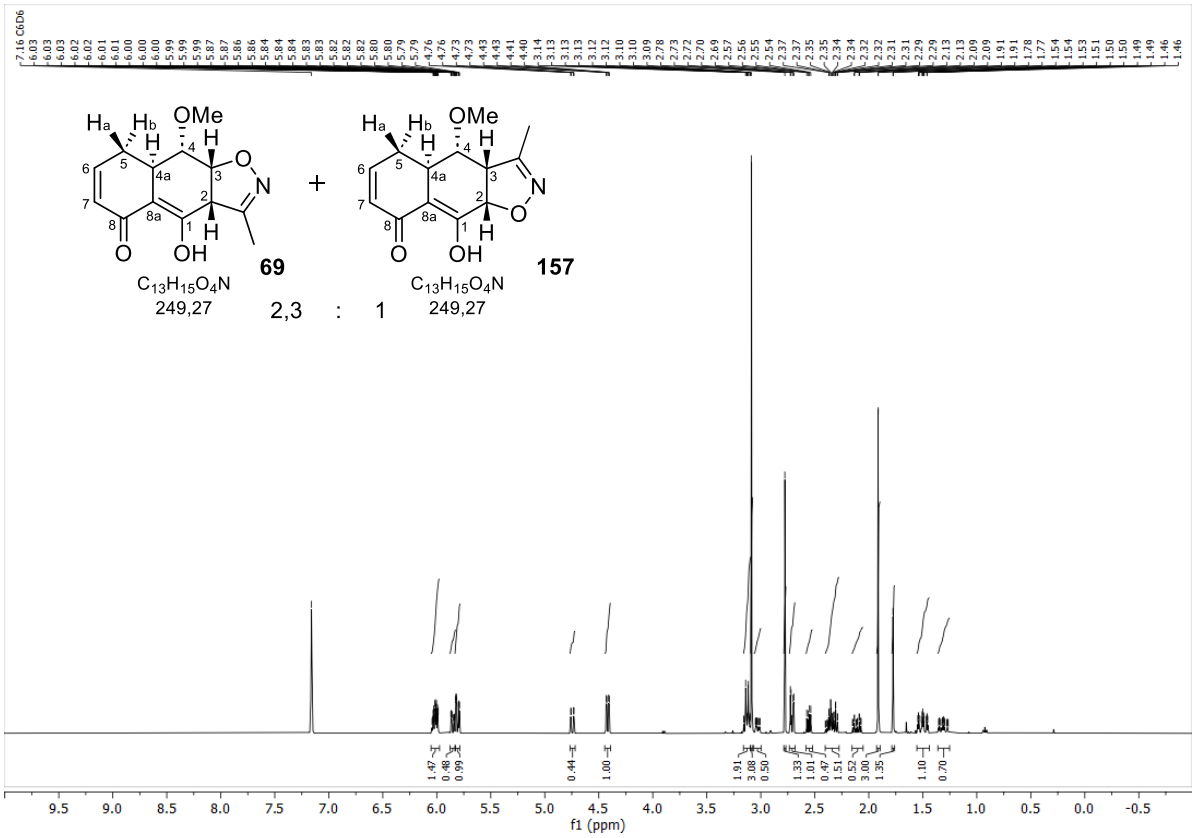
*^{1}H-spectrum of **81** in $CDCl_3$ (selected regions between 2,2-7,5 ppm).*



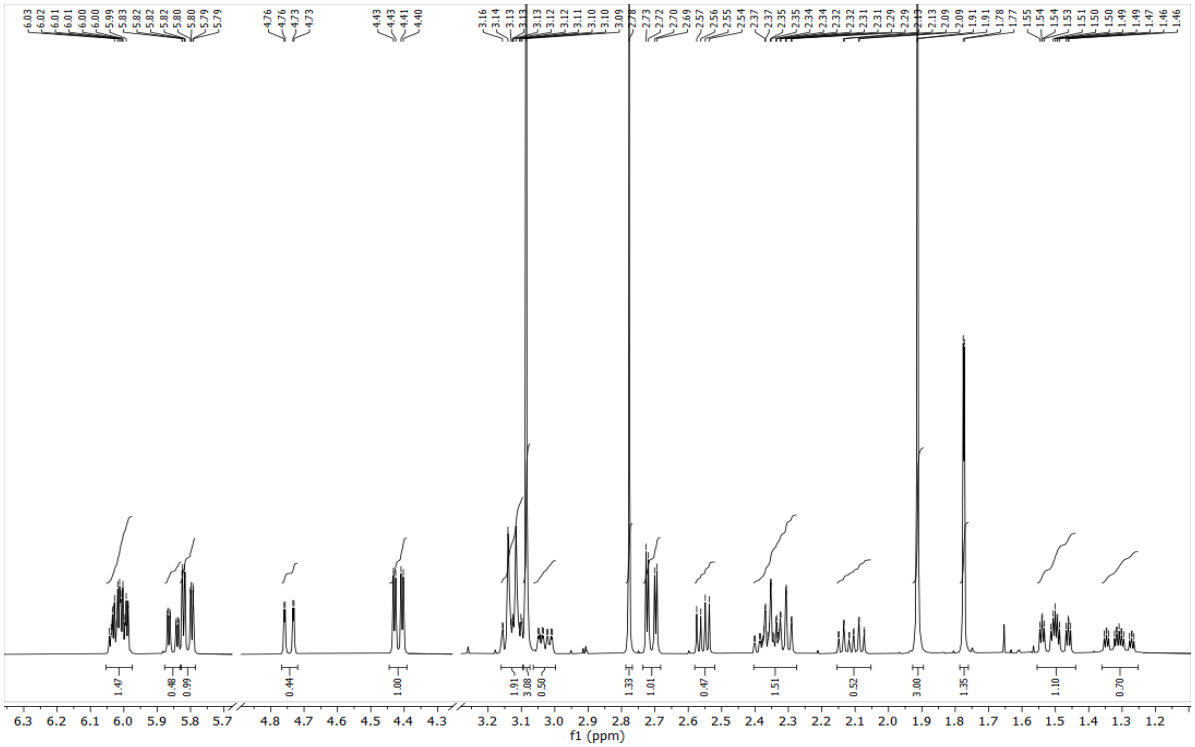
*^{13}C-spectrum of **81** in $CDCl_3$.*

8.3.2 Enone **69**

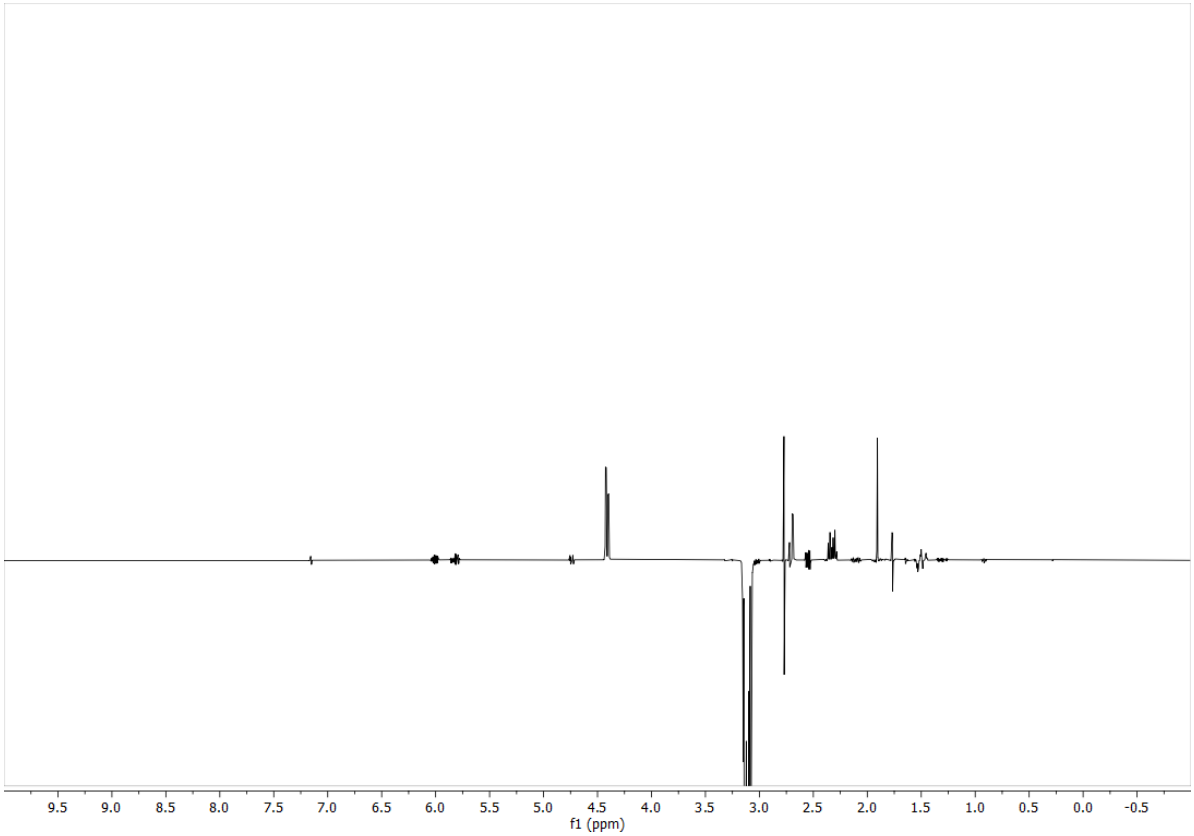
8.3.2.1 (3a*S*,8a*R*,9*S*,9a*R*)-4-hydroxy-9-methoxy-3-methyl-8,8a,9,9a-tetrahydronaphtho[2,3-*d*] isoxazol-5(3a*H*)-one **69**



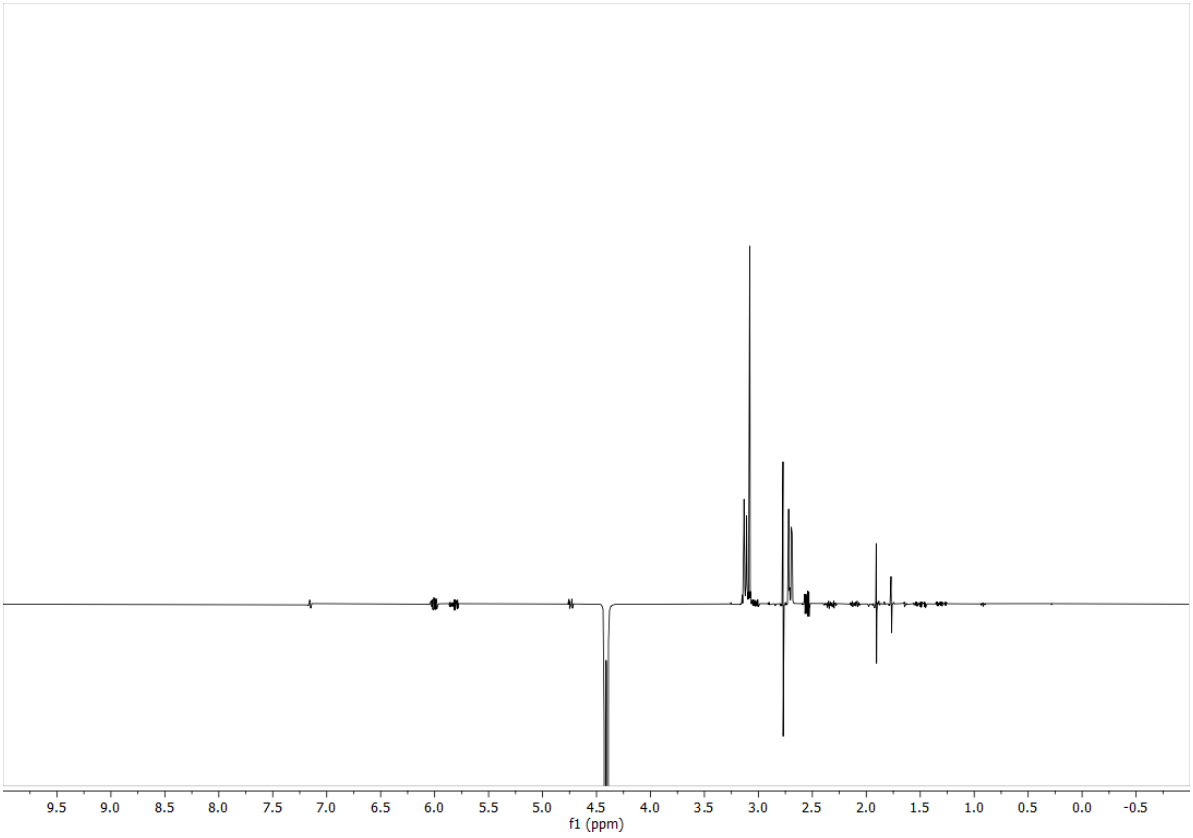
*^{1}H-spectrum of **69** in $CDCl_3$.*



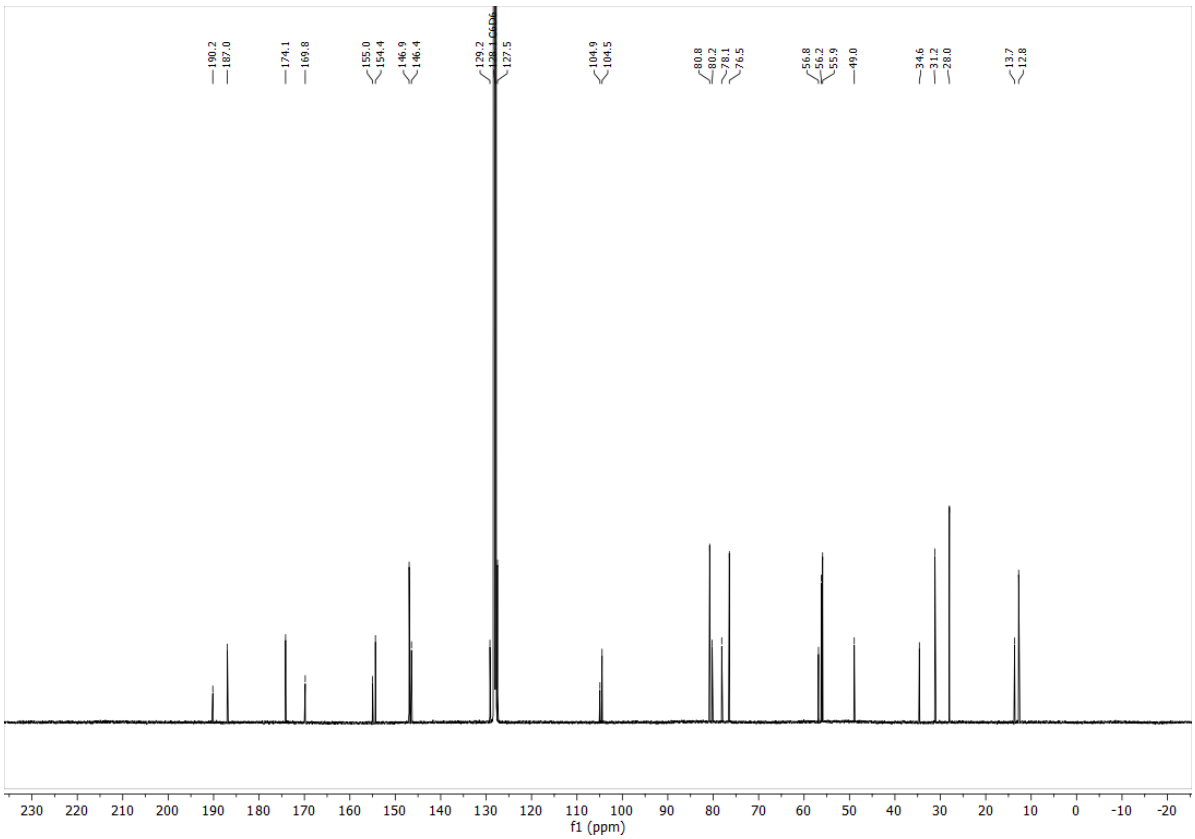
*^{1}H-spectrum of **69** in $CDCl_3$ (selected regions between 1,2-6,3 ppm).*



*NOE-spectrum of **69** in $CDCl_3$ (frequency saturation at 3,12 ppm).*

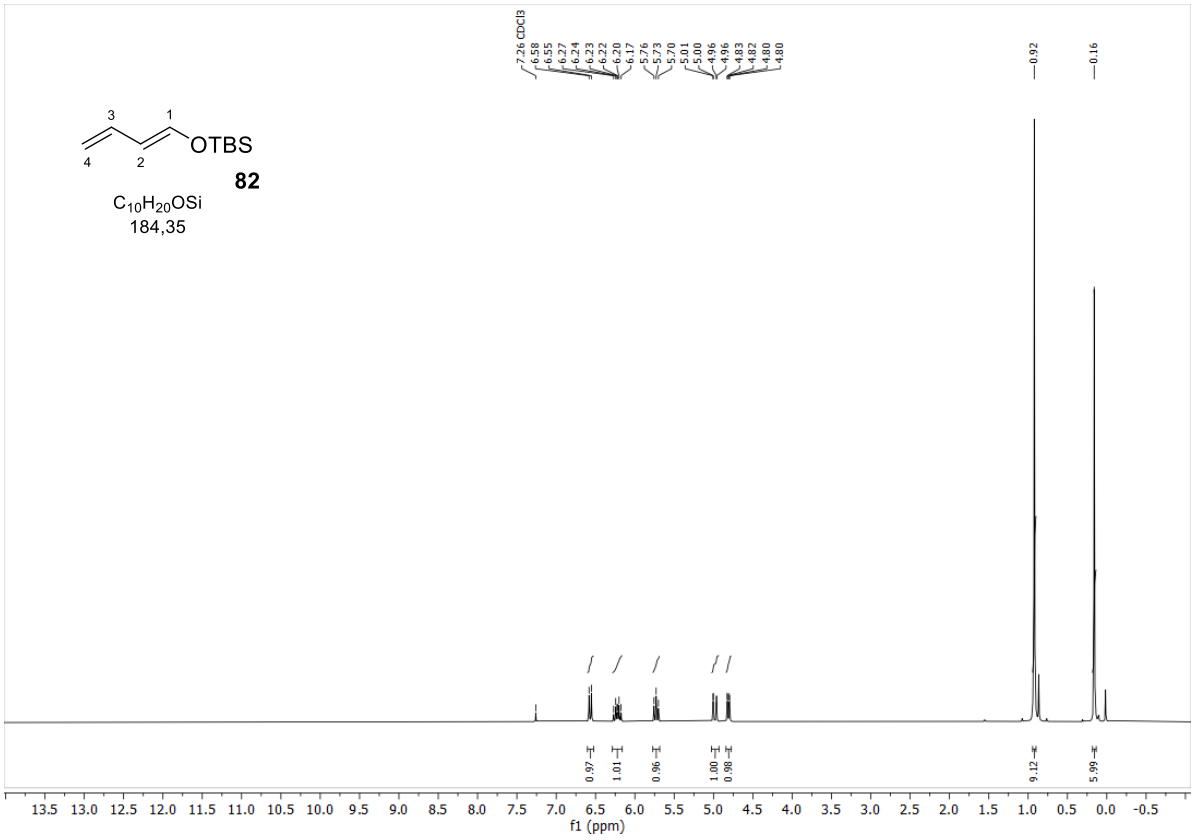


*NOE-spectrum of **69** in $CDCl_3$ (frequency saturation at 4,41 ppm).*

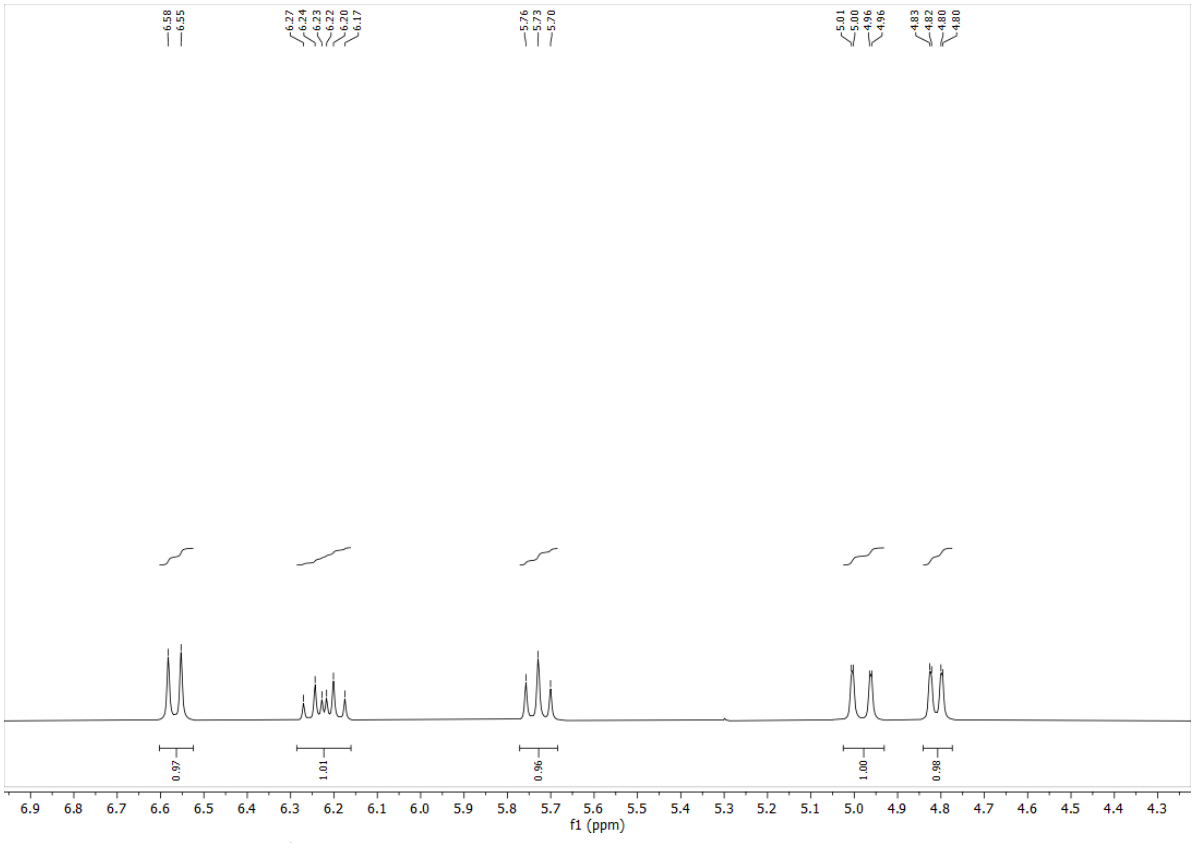


*^{13}C-spectrum of **69** in $CDCl_3$.*

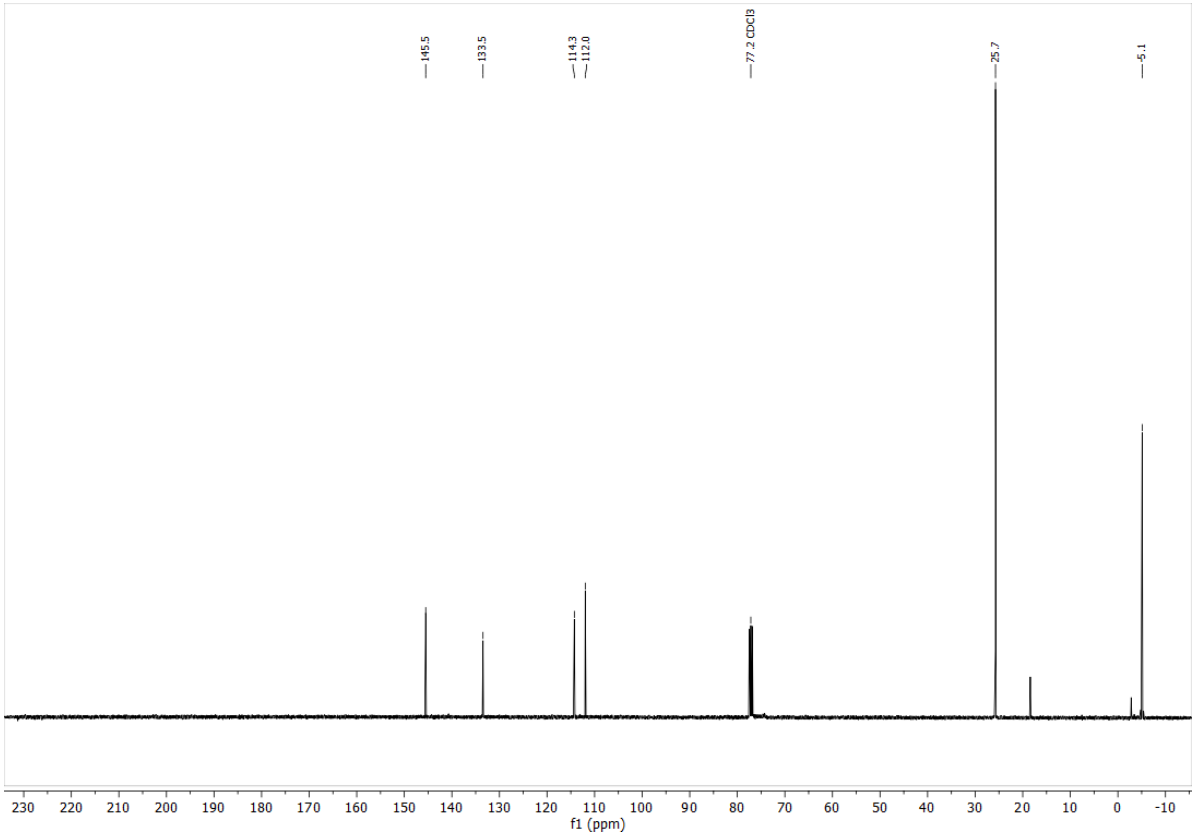
8.3.2.2.1 (*E*)-(buta-1,3-dien-1-yloxy)(*tert*-butyl)dimethylsilane **82**



*^{1}H-spectrum of **82** in $CDCl_3$.*

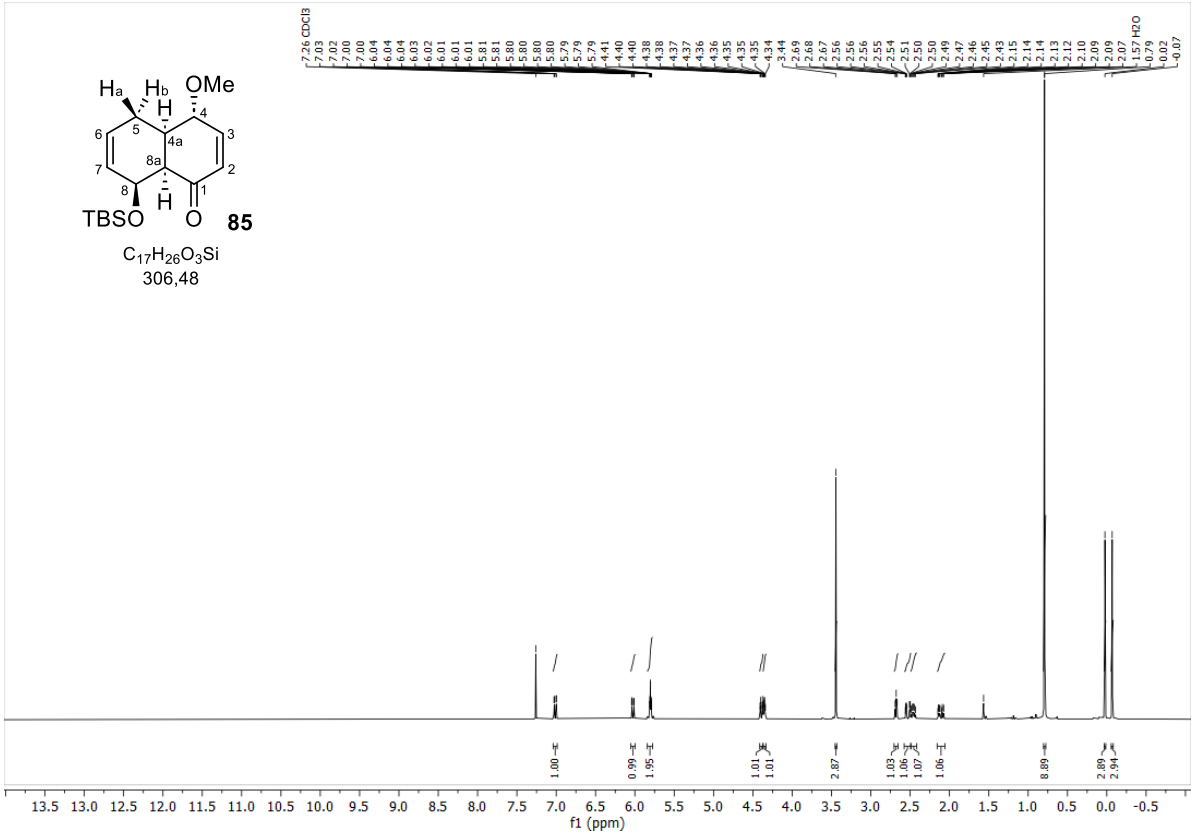


*^{1}H-spectrum of **82** in $CDCl_3$ (region between 4,3-6,9 ppm).*

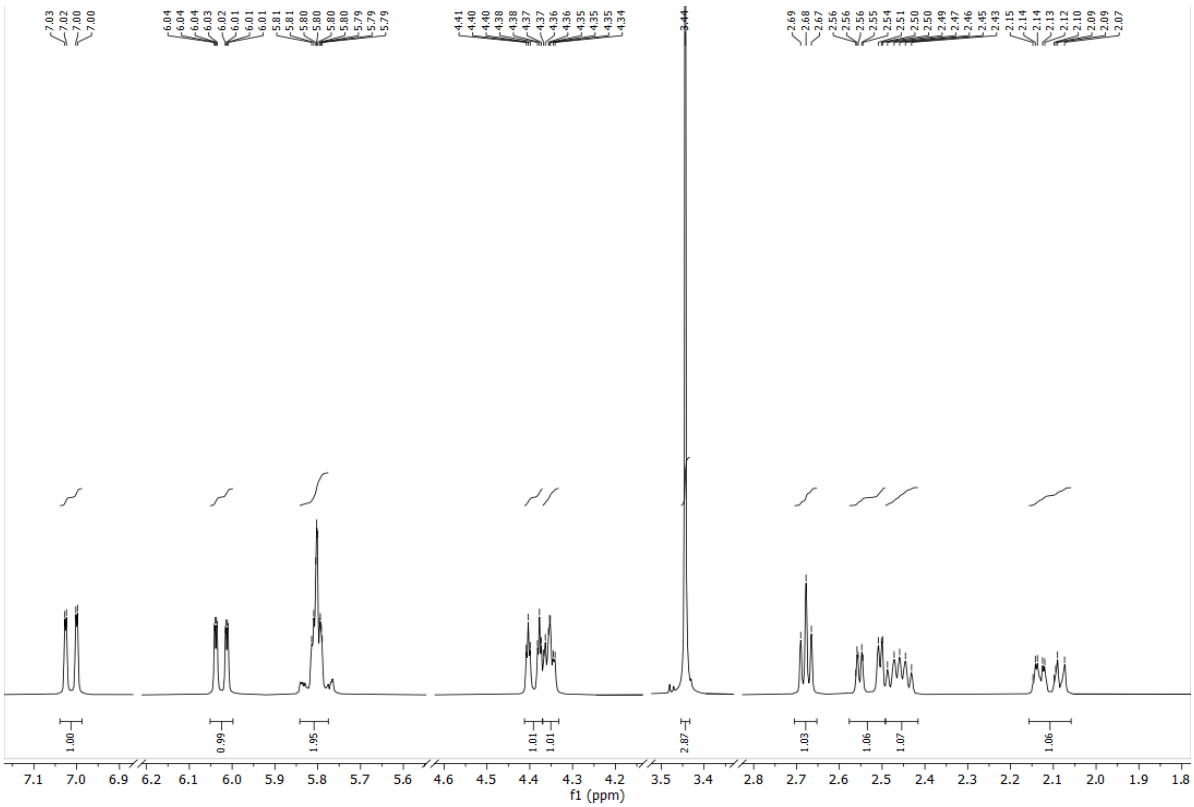


*^{13}C-spectrum of **82** in $CDCl_3$.*

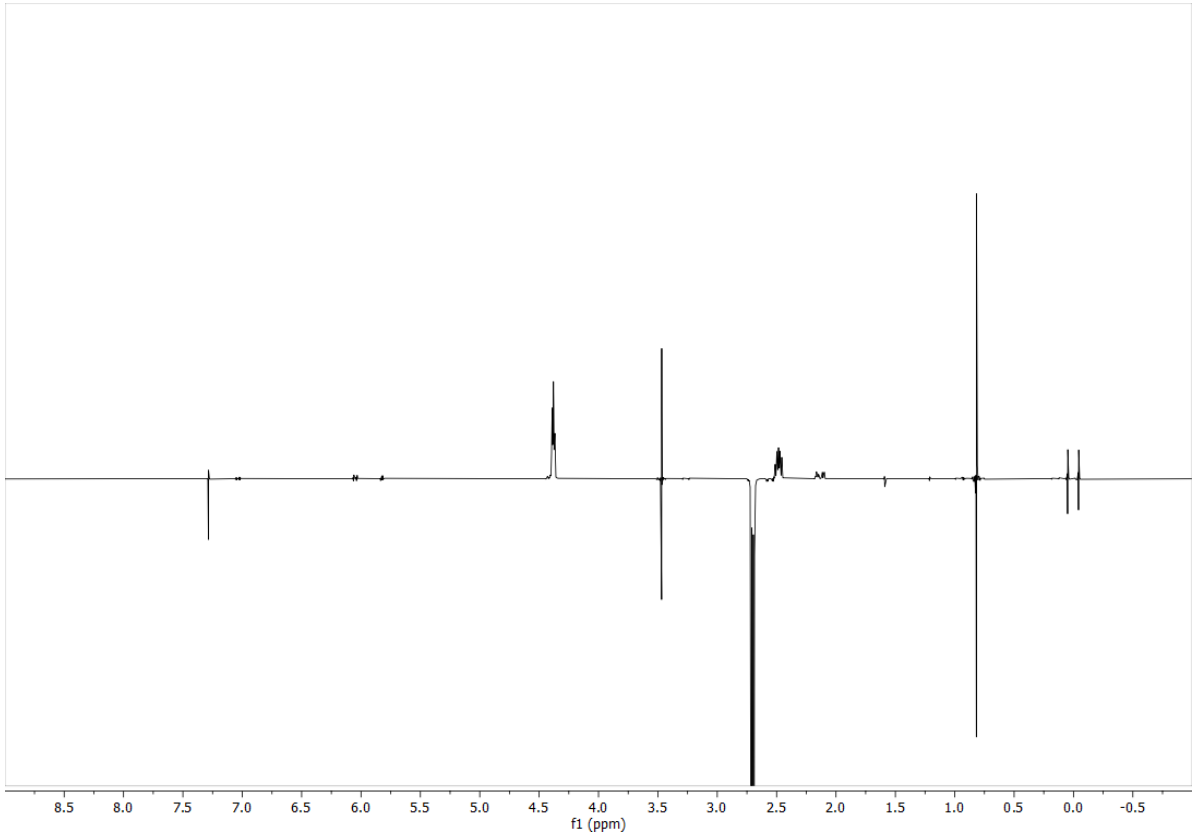
8.3.2.2.2 (4*R*,4a*R*,8*S*,8a*R*)-8-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-4a,5,8,8a-tetrahydro-naphthalen-1(4*H*)-one **85**



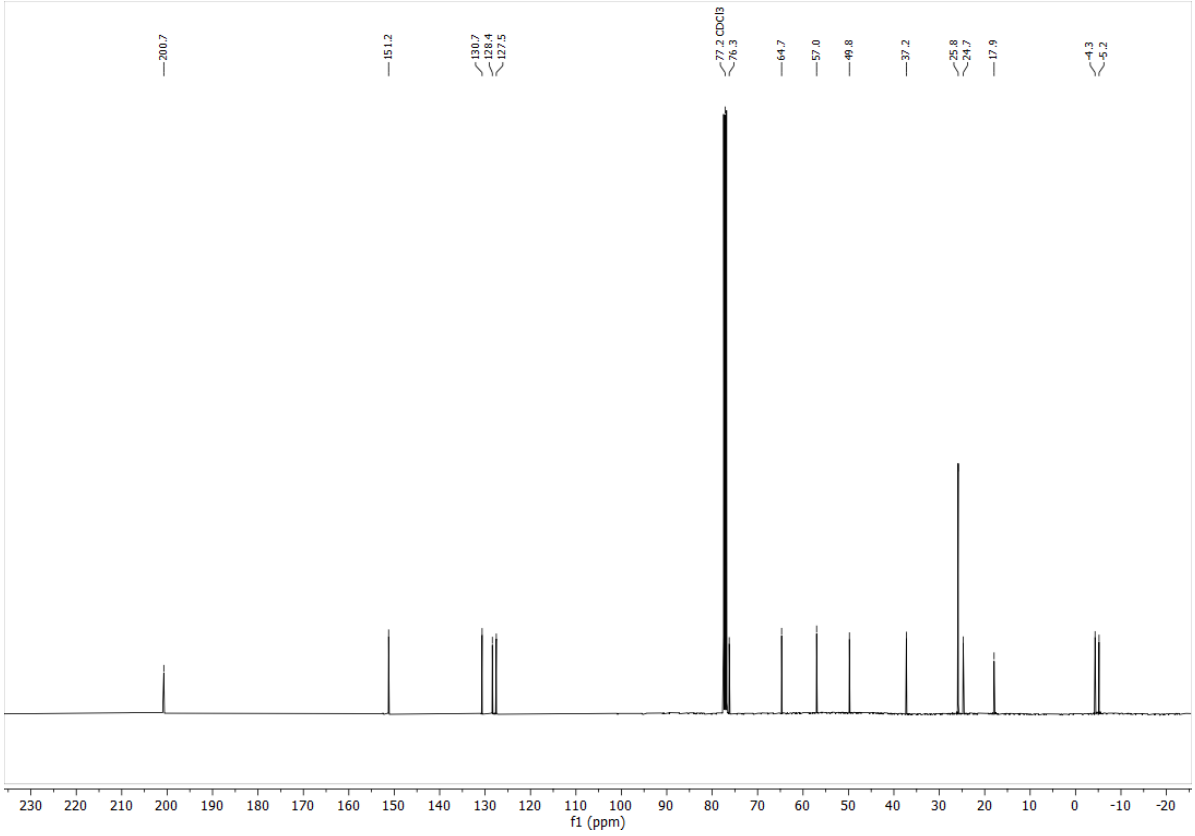
*^{1}H-spectrum of **85** in $CDCl_3$.*



*^{1}H-spectrum of **85** in $CDCl_3$ (selected regions between 1,8-7,1 ppm).*

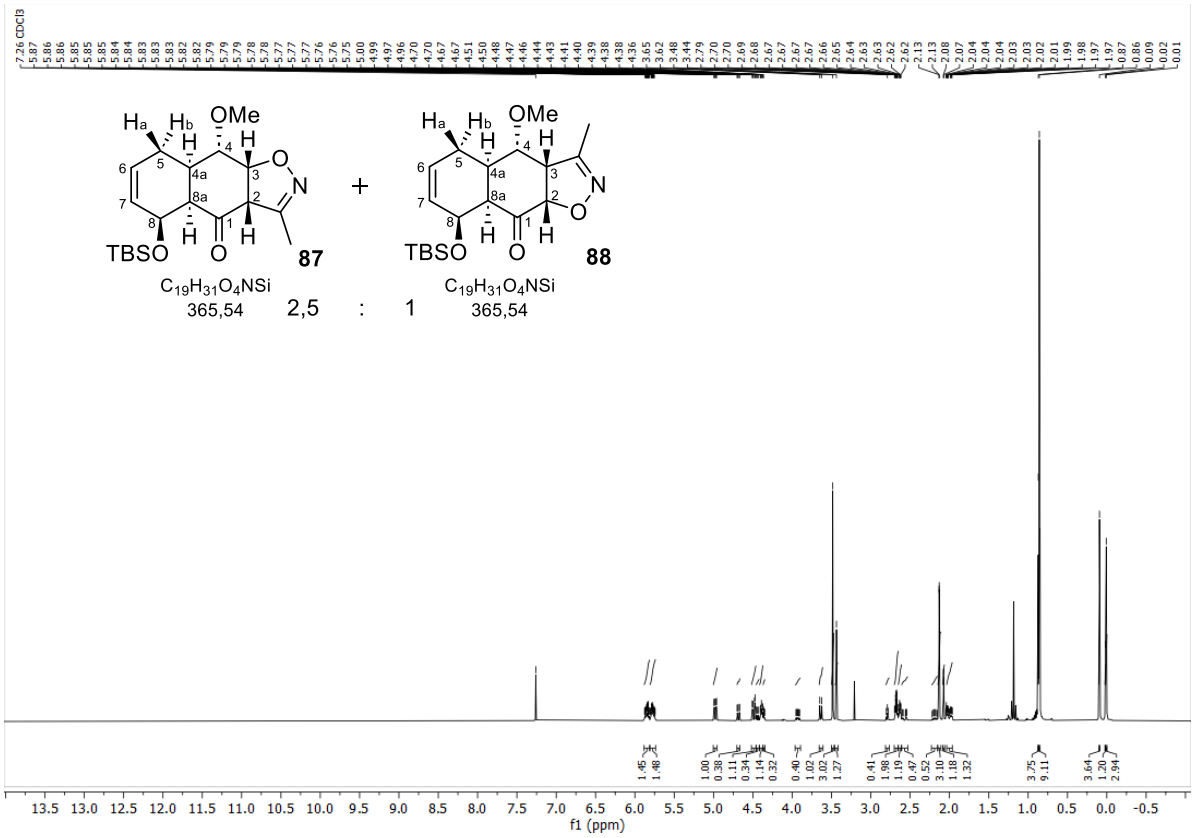


*NOE-spectrum of **85** in $CDCl_3$ (frequency saturation at 2,70 ppm).*

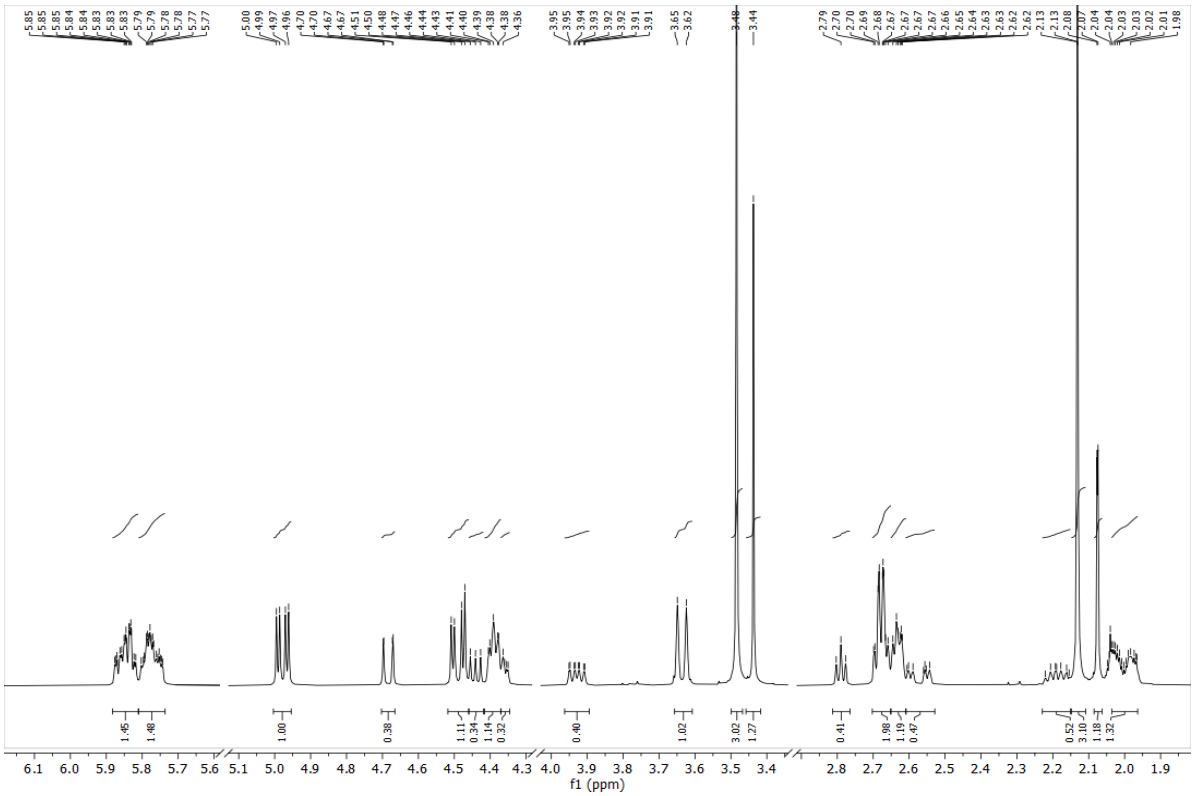


*^{13}C-spectrum of **85** in $CDCl_3$.*

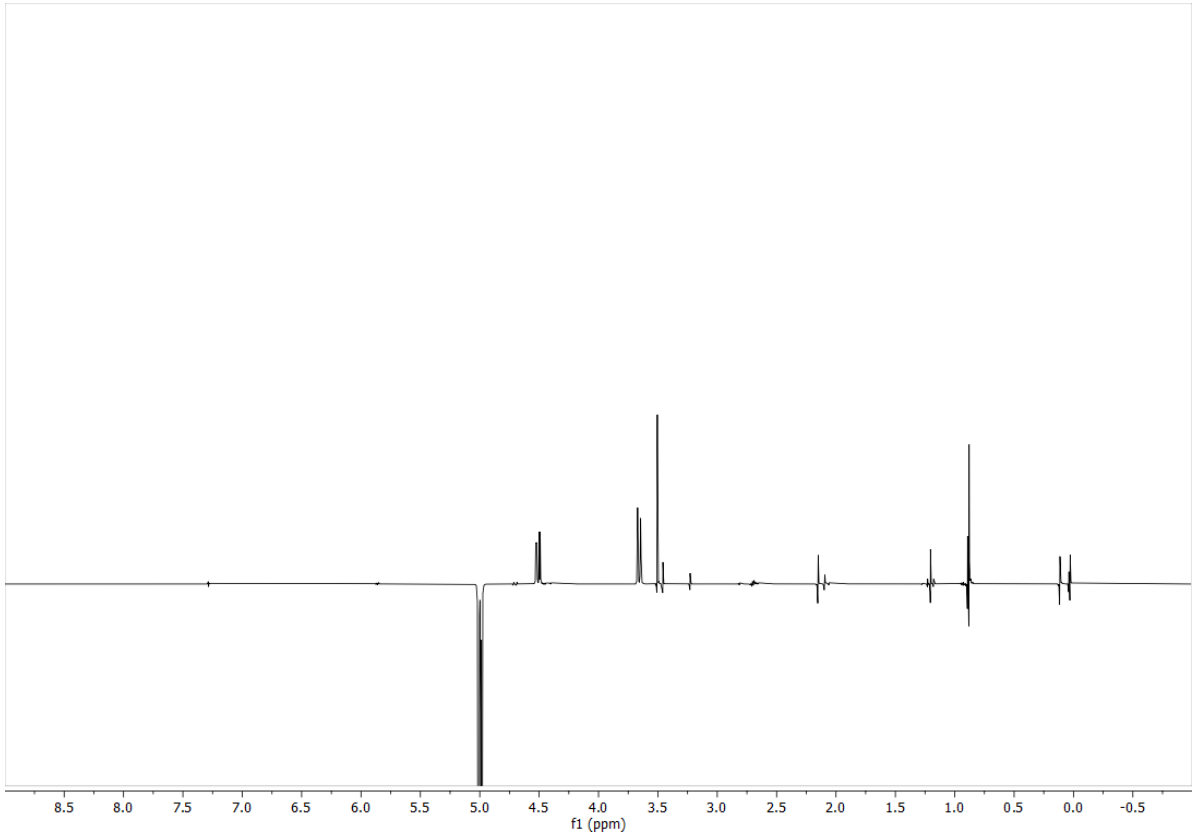
8.3.2.3 (3a*S*,4a*R*,5*S*,8a*R*,9*S*,9a*R*)-5-((*tert*-butyldimethylsilyl)oxy)-9-methoxy-3-methyl-4a,5,8,8a, 9,9a-hexahydronaphtho[2,3-*d*]isoxazol-4(3a*H*)-one **87**



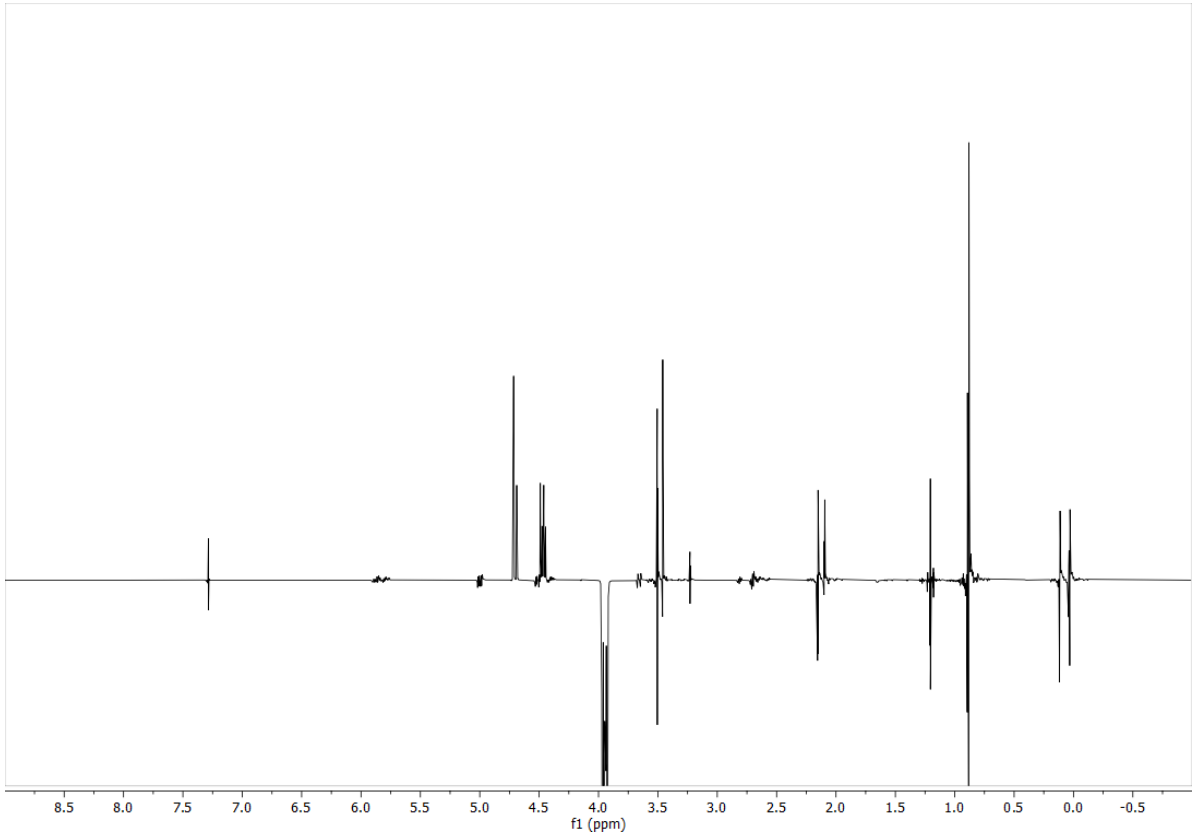
*^{1}H-spectrum of **87** in $CDCl_3$.*



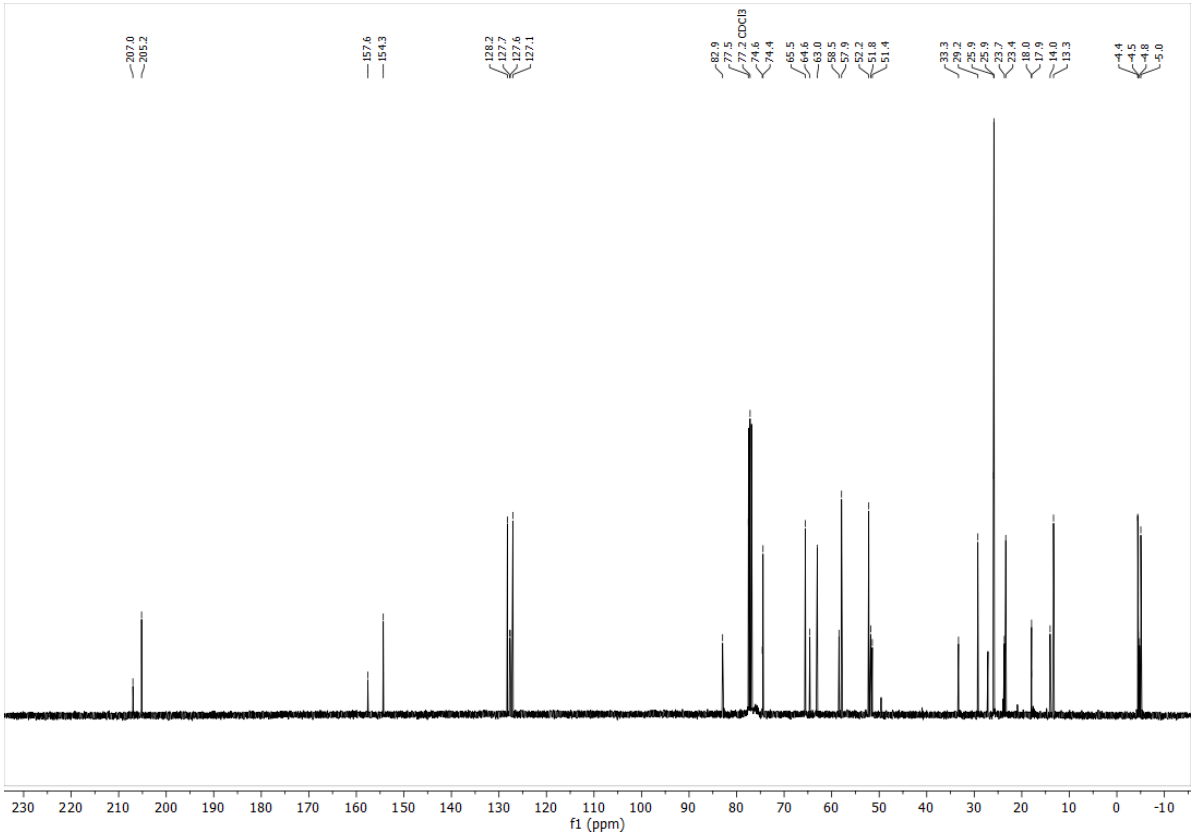
*^{1}H-spectrum of **87** in $CDCl_3$ (selected regions between 1,9-6,1 ppm).*



*NOE-spectrum of **87** in $CDCl_3$ (frequency saturation at 5,00 ppm).*

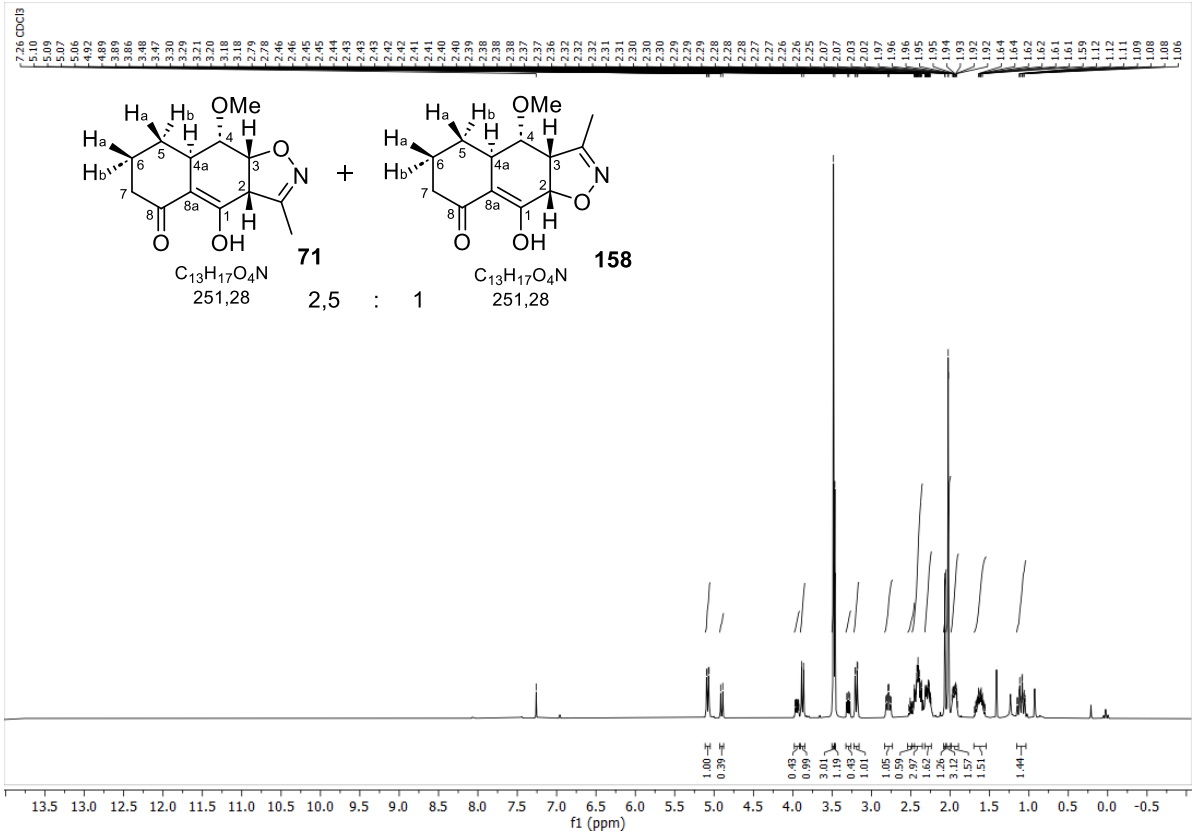


*NOE-spectrum of **88** in $CDCl_3$ (frequency saturation at 3,95 ppm).*

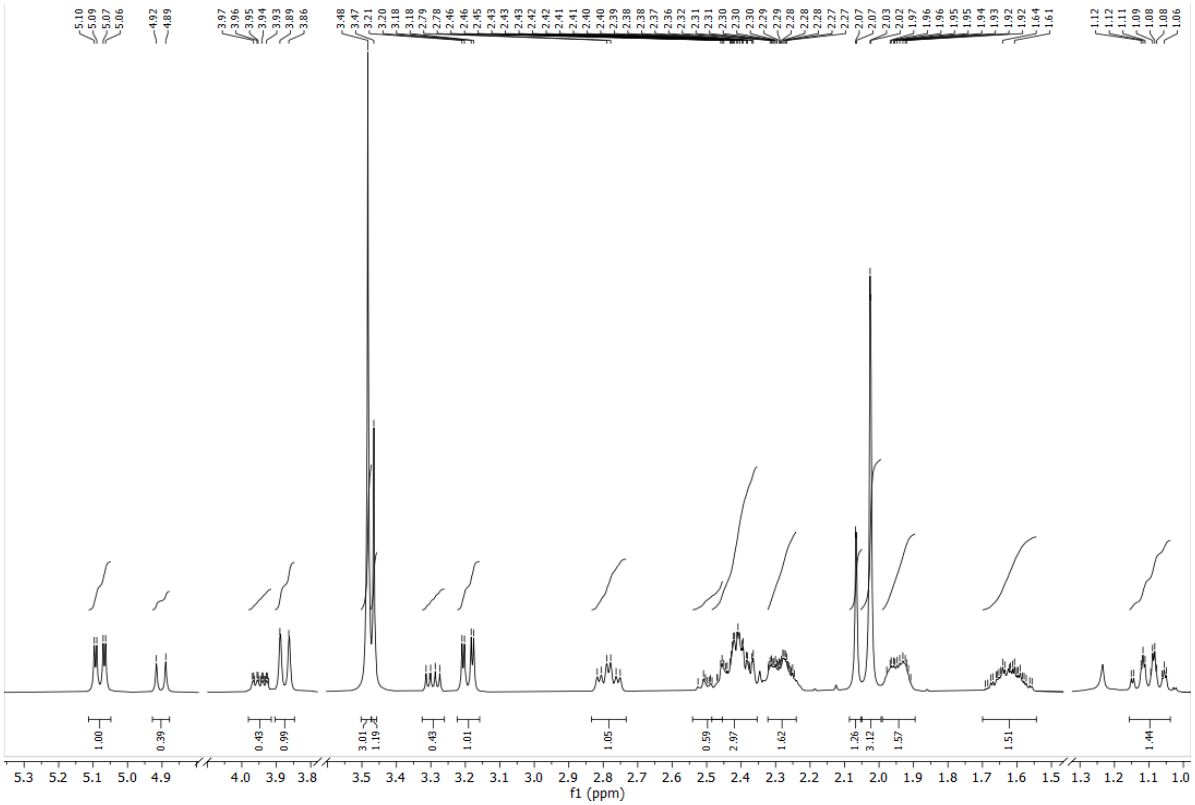


*^{13}C-spectrum of **87** in $CDCl_3$.*

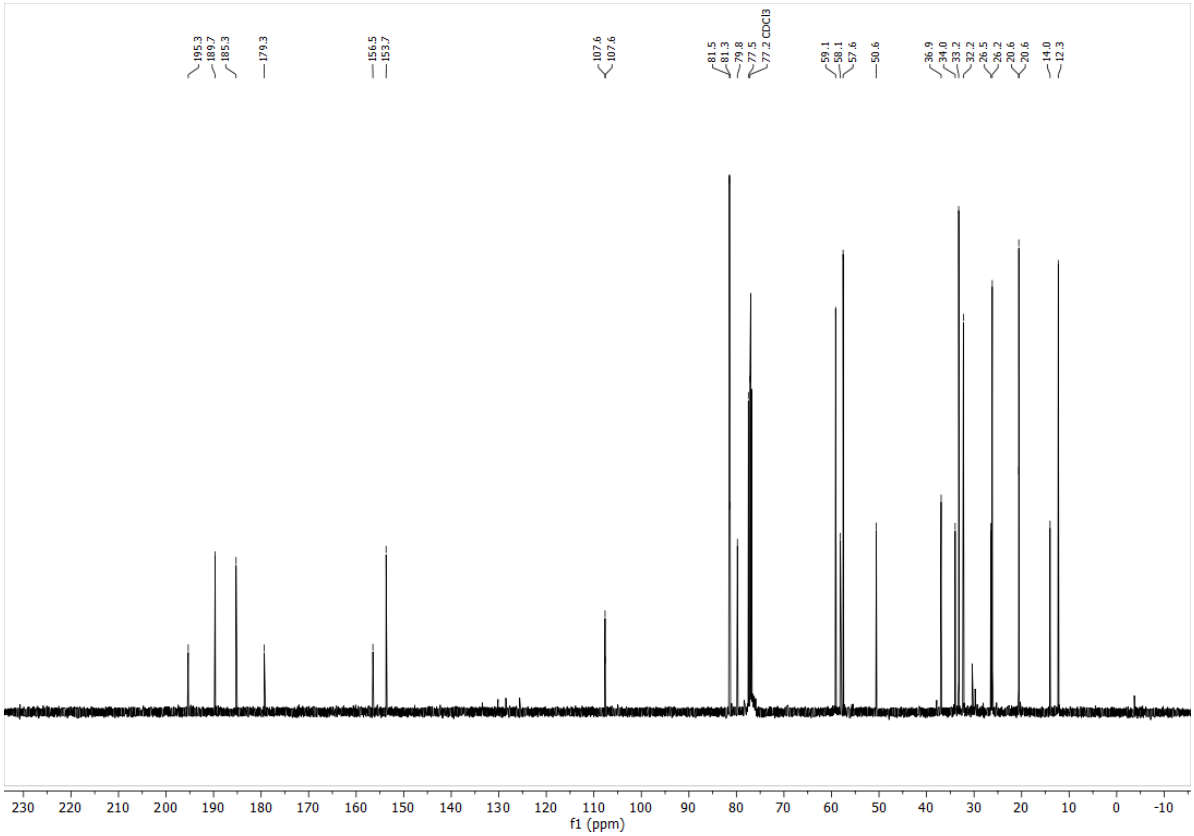
8.3.2.4 Isoxazolin-hydrogenation study ((3a*S*,8a*R*,9S,9a*R*)-4-hydroxy-9-methoxy-3-methyl-6,7,8,8a,9,9a-hexahydronaphtho[2,3-*d*]isoxazol-5(3a*H*)-one **71**)



*^{1}H-spectrum of **71** in $CDCl_3$.*



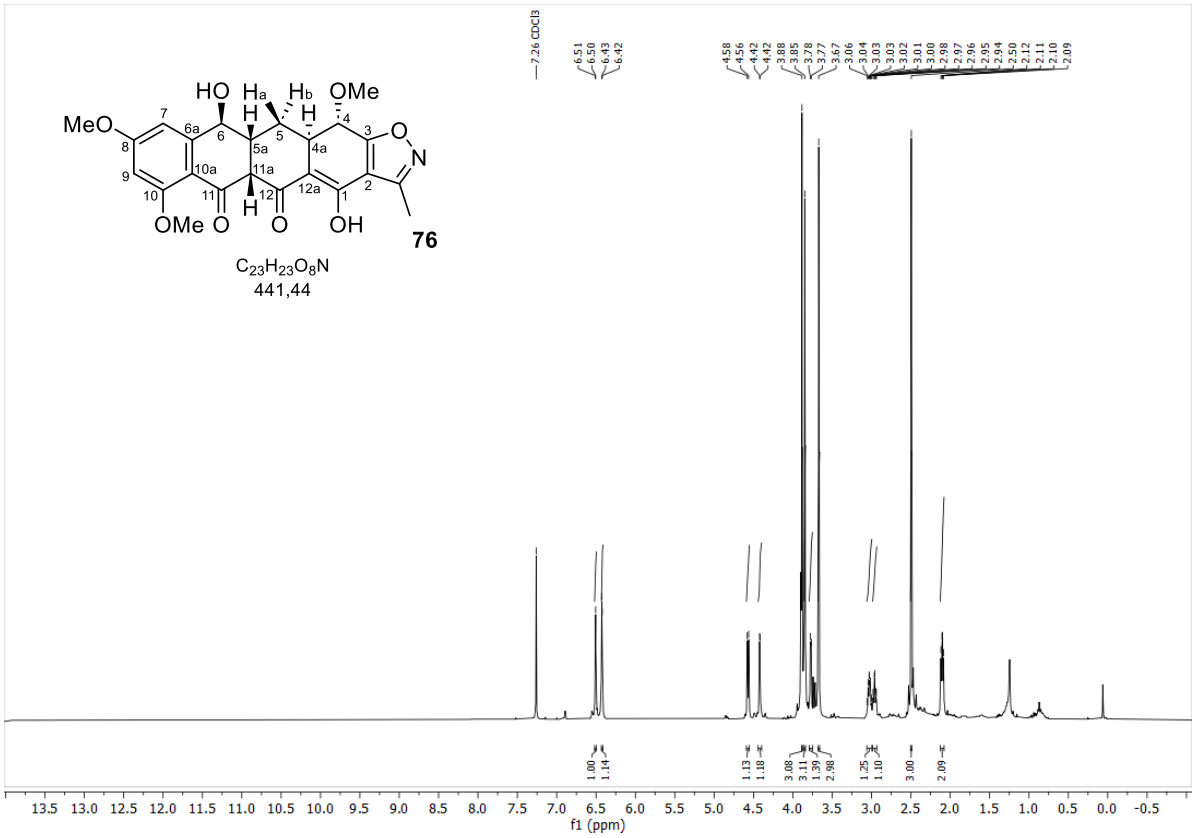
*^{1}H-spectrum of **71** in $CDCl_3$ (selected regions between 1,0-5,3 ppm).*



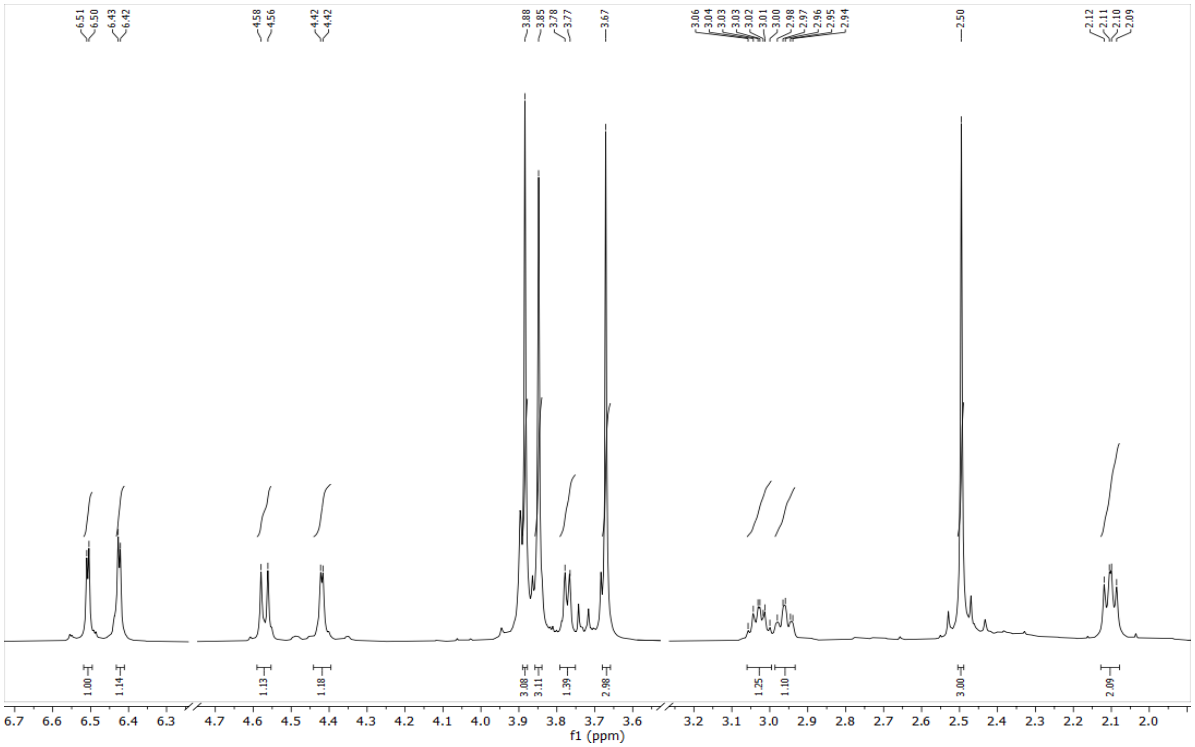
*^{13}C-spectrum of **71** in $CDCl_3$.*

8.3.3 Premithramycinone **2**

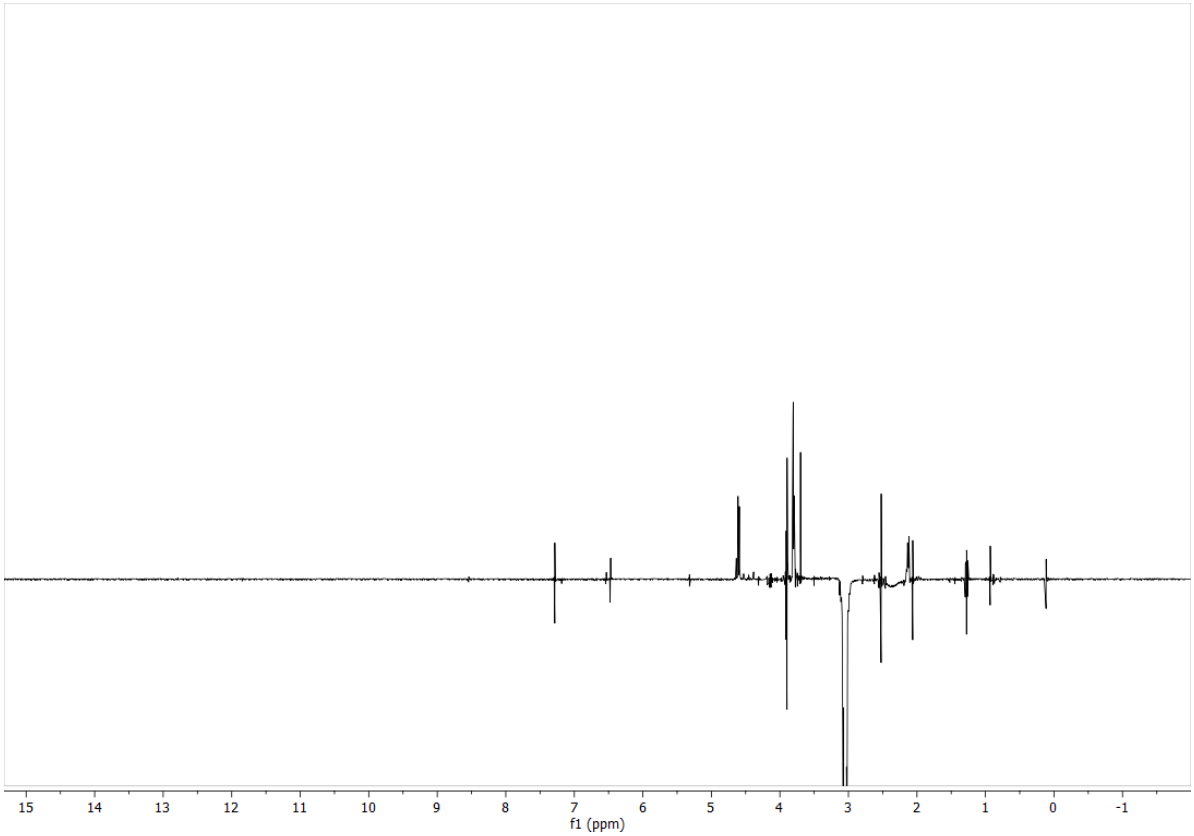
8.3.3.1 (5a*R*,11*S*,11a*R*,12a*R*,13*S*)-4,11-dihydroxy-7,9,13-trimethoxy-3-methyl-11a,12,12a,13-tetrahydrotetraceno[2,3-*d*]isoxazole-5,6(5a*H*,11*H*)-dione **76**



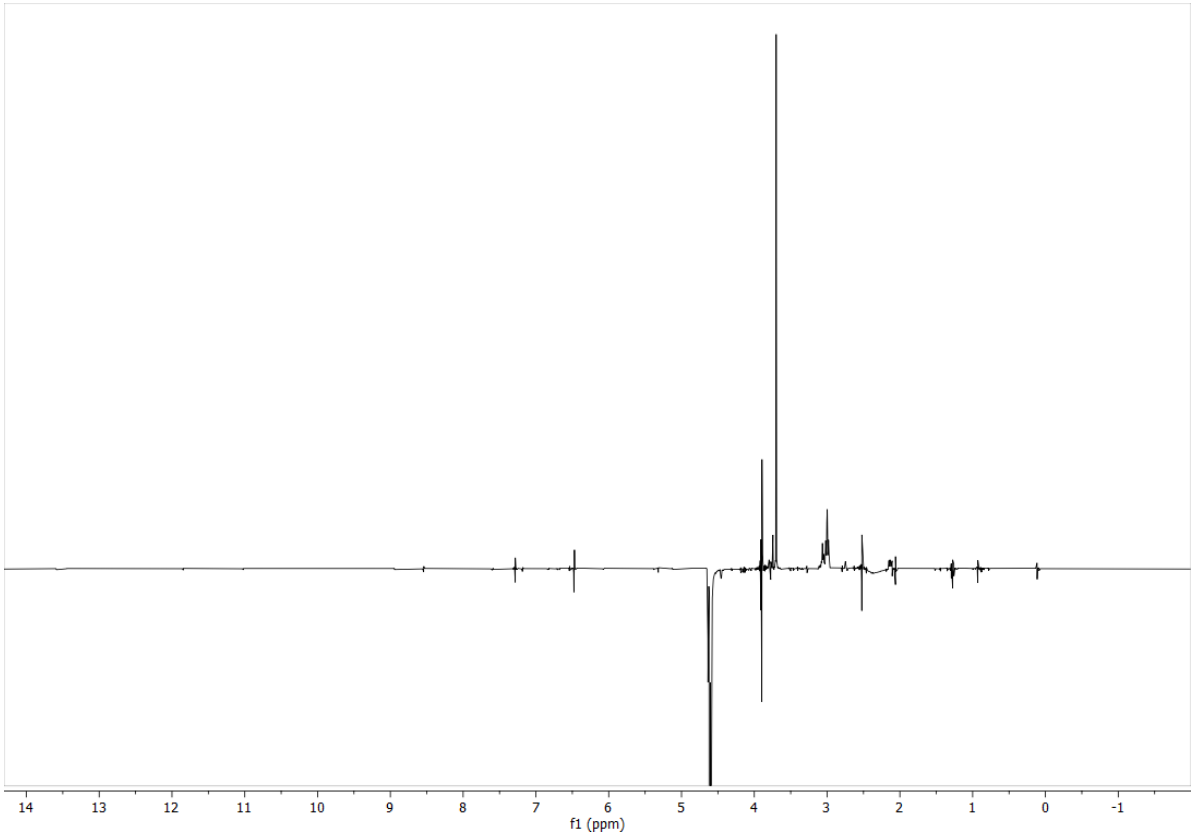
*^{1}H-spectrum of **76** in $CDCl_3$.*



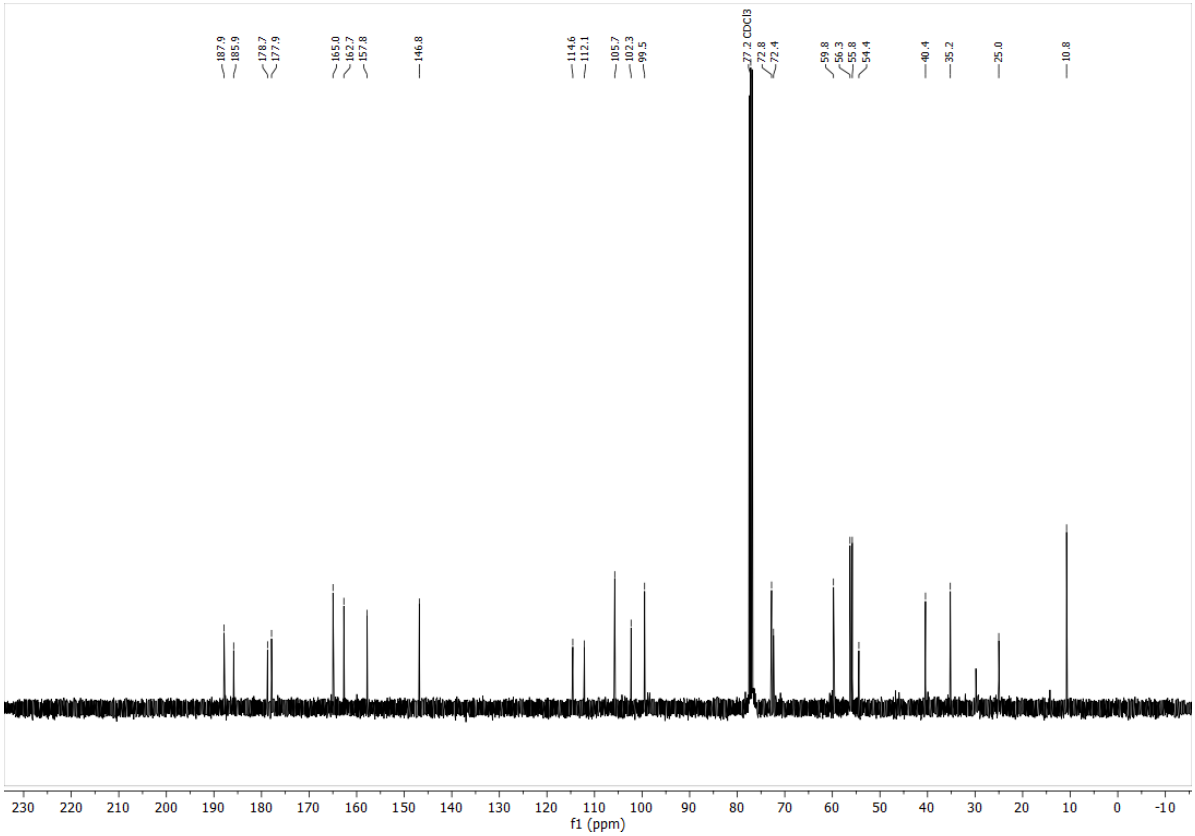
*^{1}H-spectrum of **76** in $CDCl_3$ (selected regions between 2,0-6,7 ppm).*



*NOE-spectrum of **76** in $CDCl_3$ (frequency saturation at 3,05 ppm).*

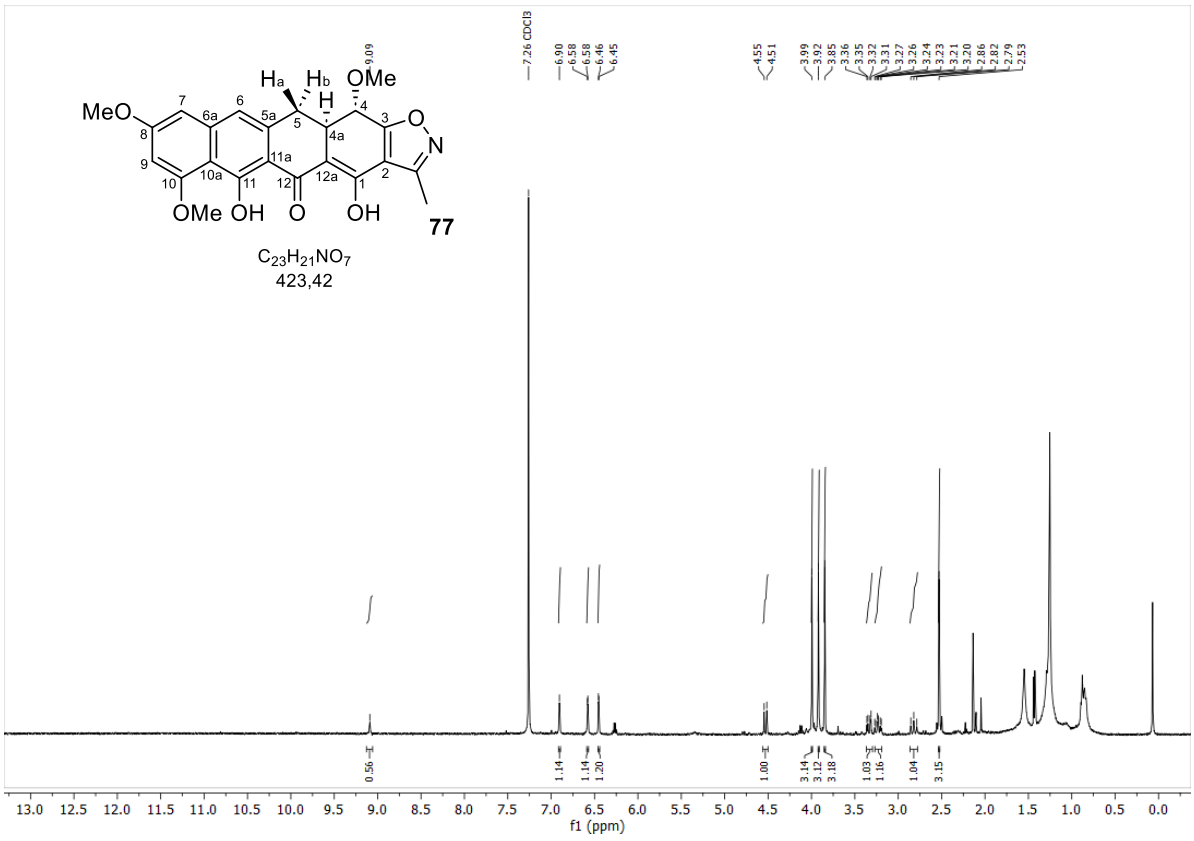


*NOE-spectrum of **76** in $CDCl_3$ (frequency saturation at 4,57 ppm).*

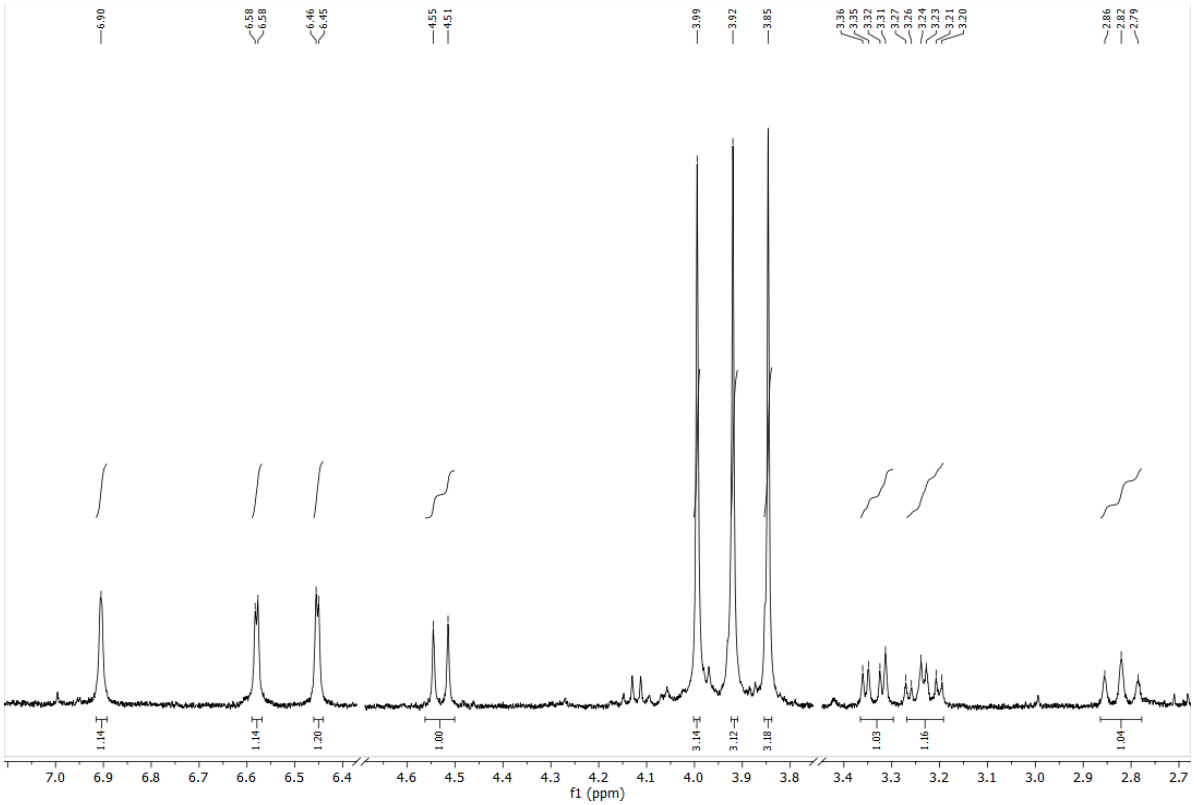


*^{13}C-spectrum of **76** in $CDCl_3$.*

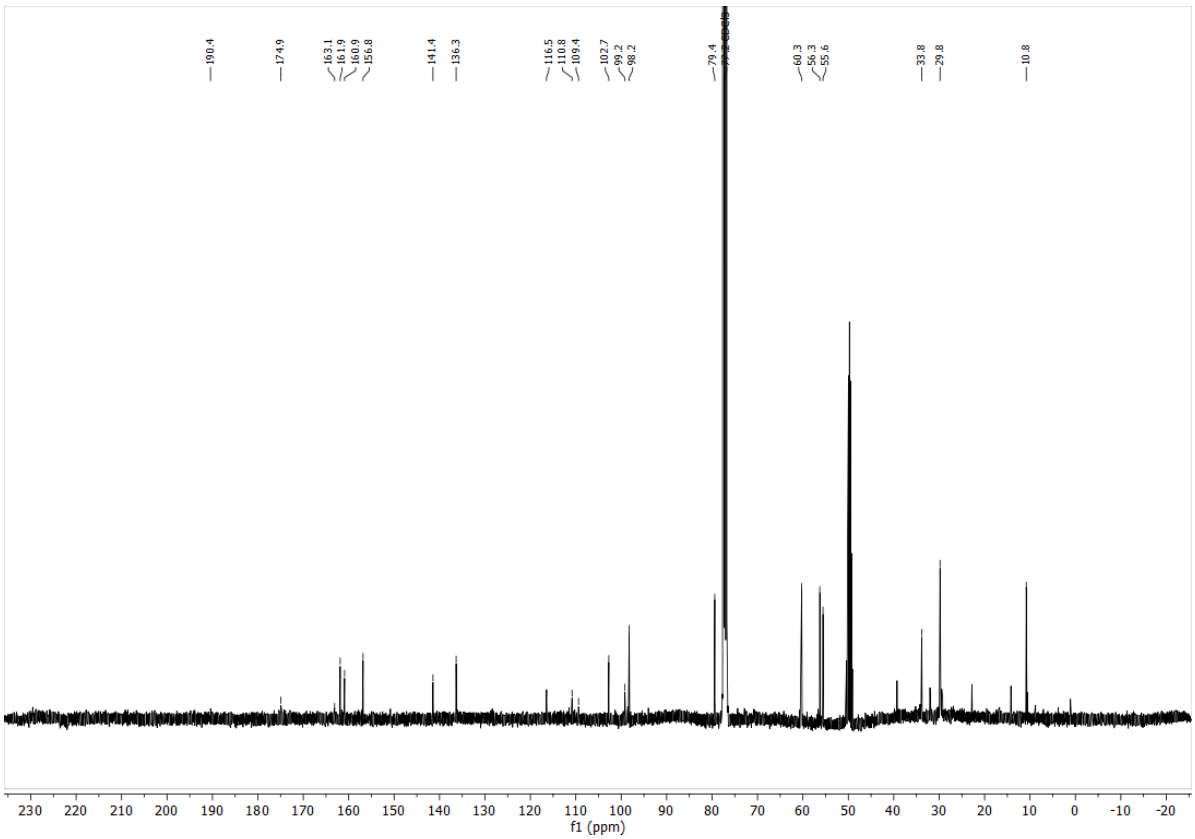
8.3.3.2 (12a*R*,13*S*)-4,6-dihydroxy-7,9,13-trimethoxy-3-methyl-12a,13-dihydrotetraceno[2,3-*d*]-isoxazol-5(12*H*)-one **77**



*^{1}H-spectrum of **77** in $CDCl_3$.*

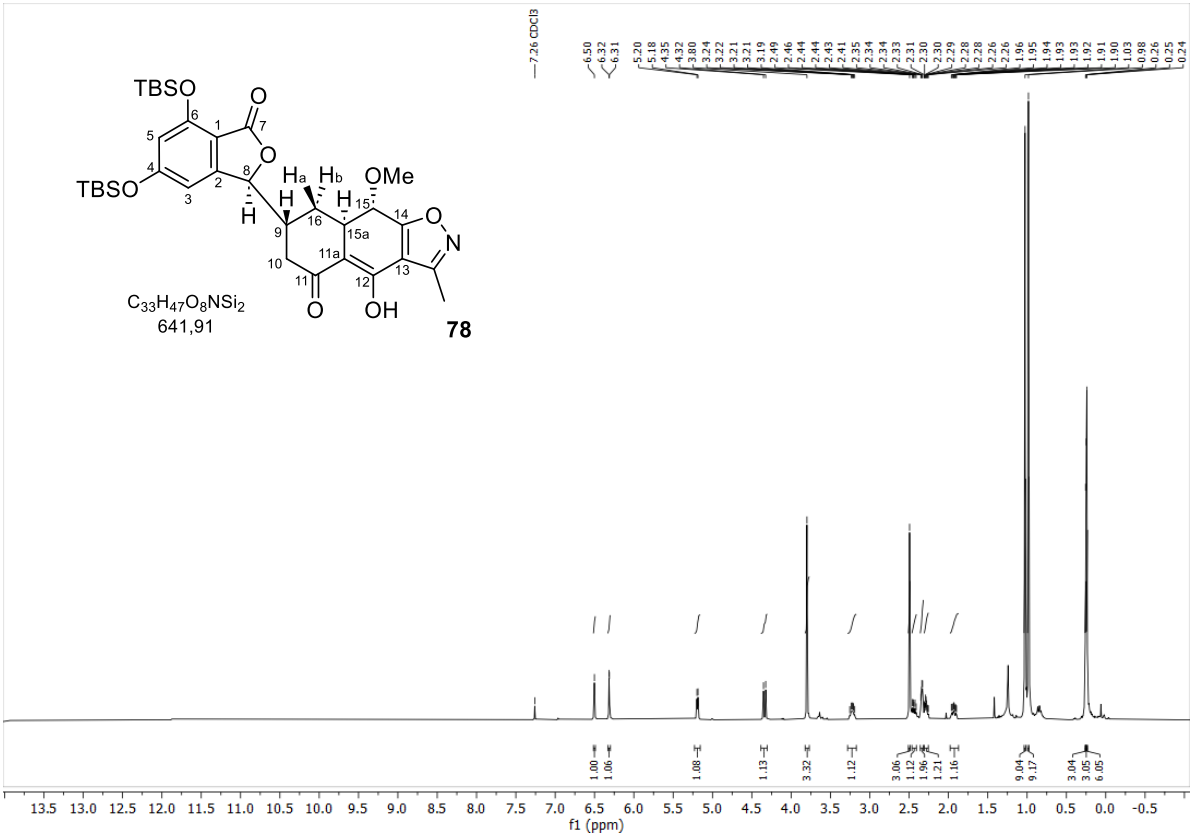


*^{1}H-spectrum of **77** in $CDCl_3$ (selected regions between 2,7-7,0 ppm).*

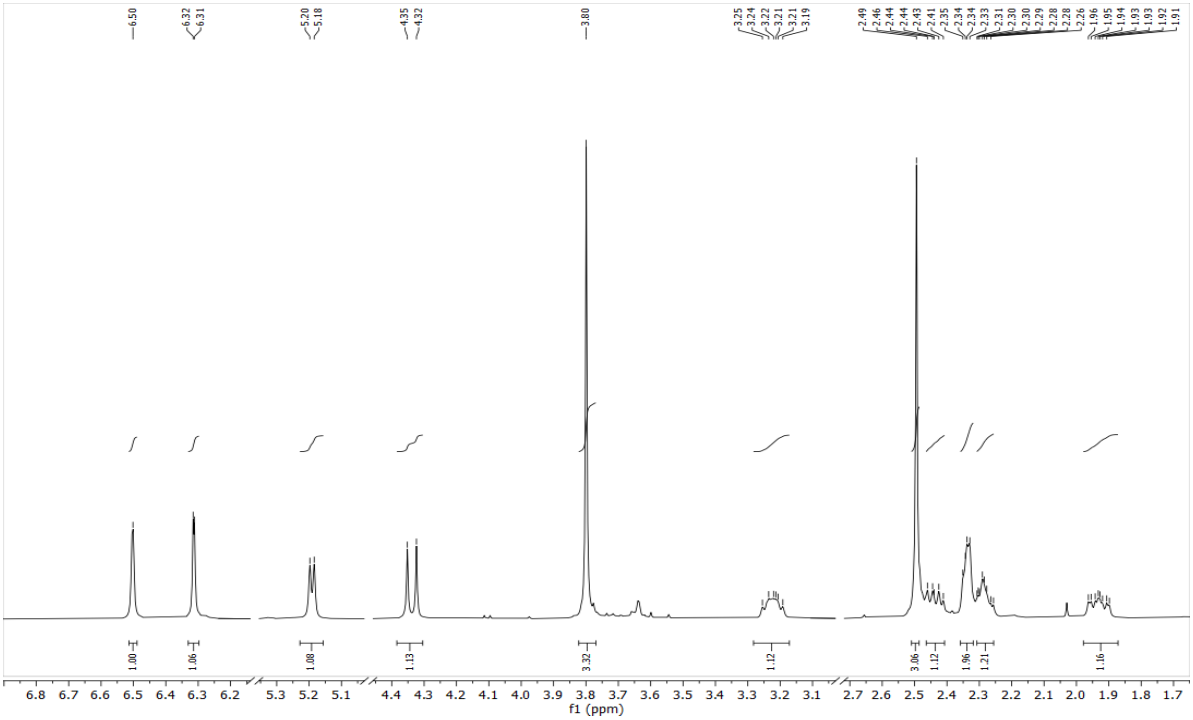


*^{13}C-spectrum of **77** in $CDCl_3$.*

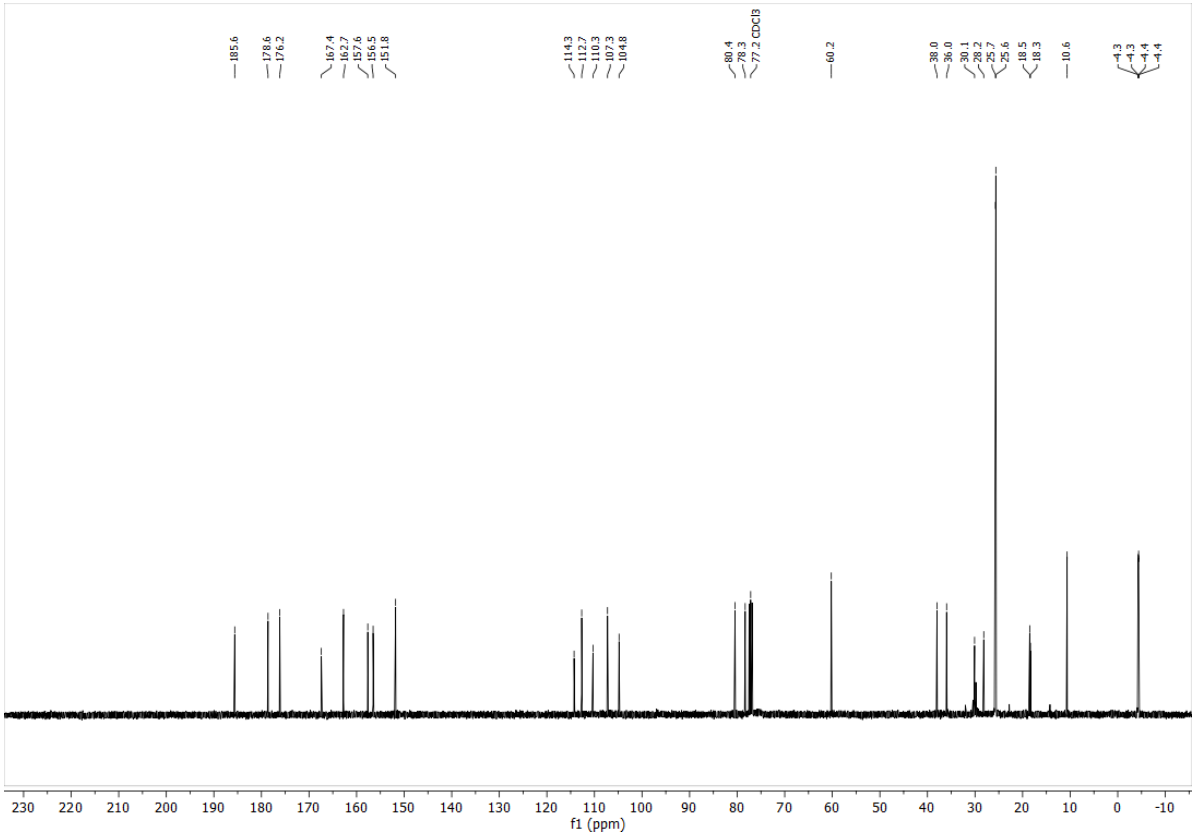
8.3.4 Premithramycinone **2** from lactone **45** and enone **73** (formation of the 1,4-addition product: (7*R*,8a*R*,9*S*)-7-((*S*)-4,6-bis((*tert*-butyldimethylsilyl)oxy)-3-oxo-1,3-dihydroisobenzofuran-1-yl)-4-hydroxy-9-methoxy-3-methyl-7,8,8a,9-tetrahydronaphtho[2,3-*d*]isoxazol-5(6*H*)-one **78**)



*^{1}H-spectrum of **78** in $CDCl_3$.*



*^{1}H-spectrum of **78** in $CDCl_3$ (selected regions between 1,7-6,8 ppm).*

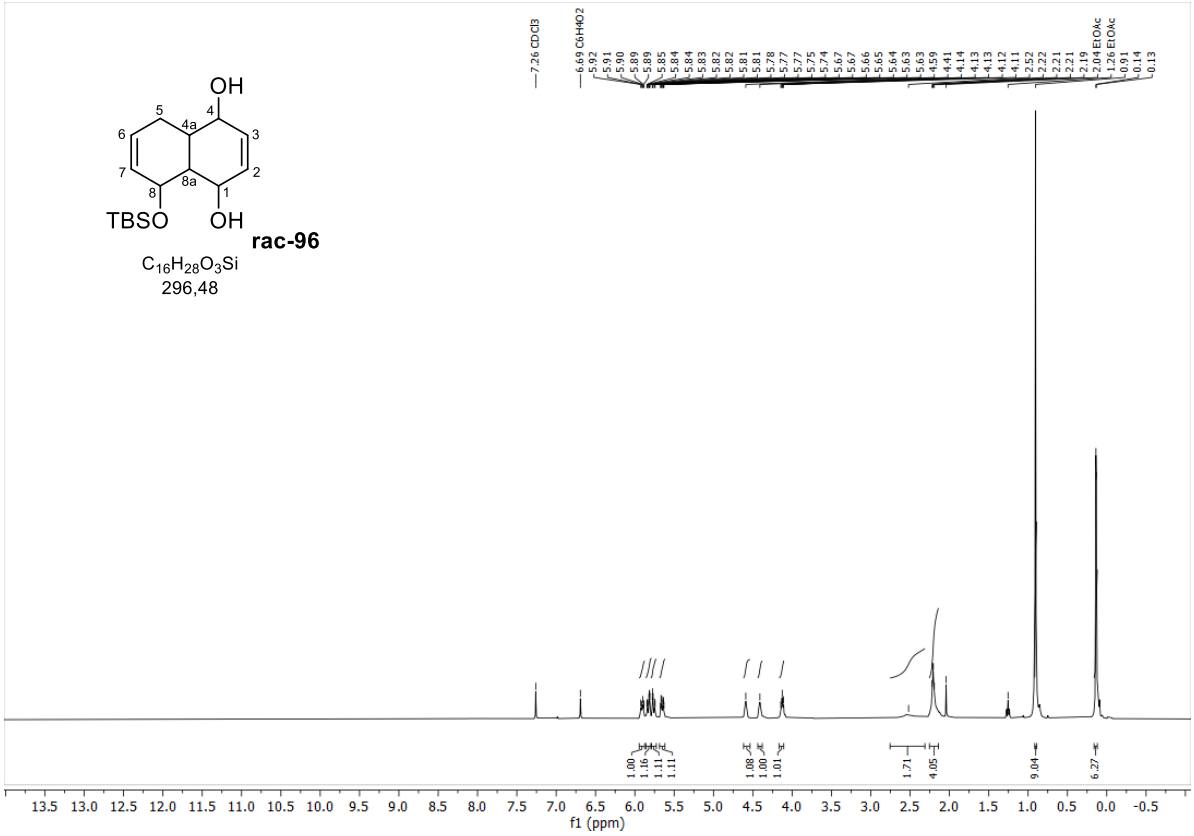


*^{13}C-spectrum of **78** in $CDCl_3$.*

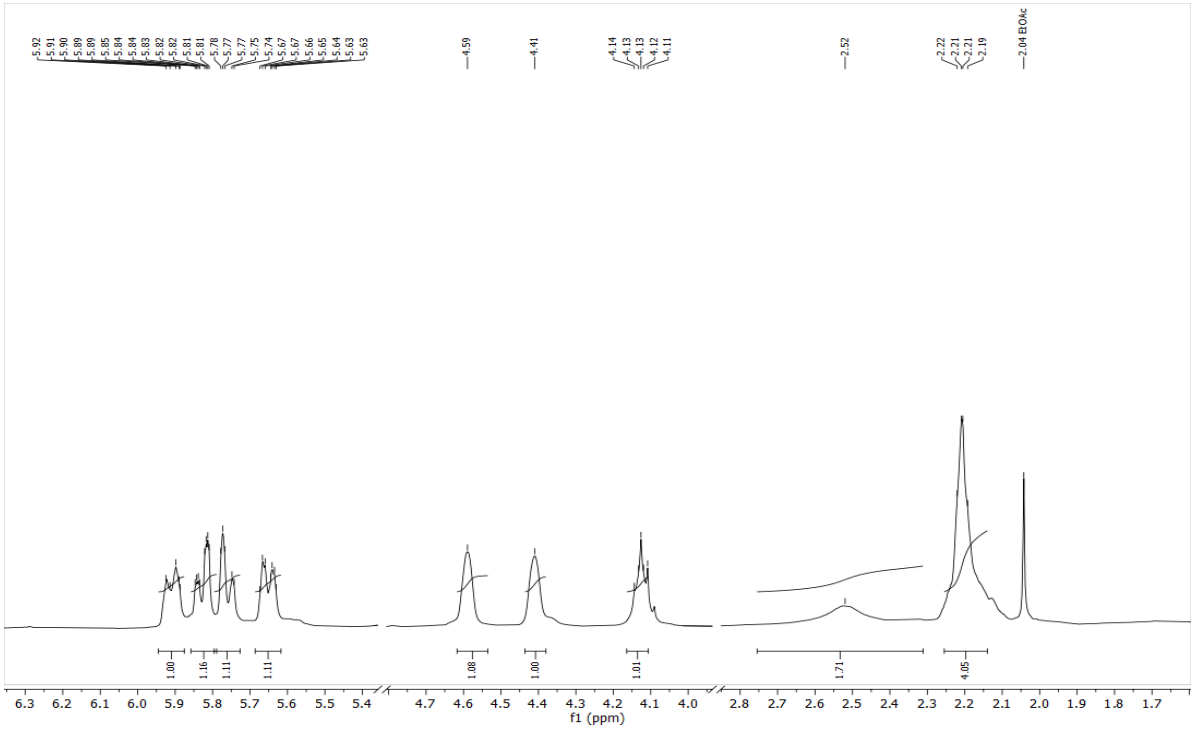
8.4 Chromocyclins

8.4.1 Attempted synthesis of enone **94**

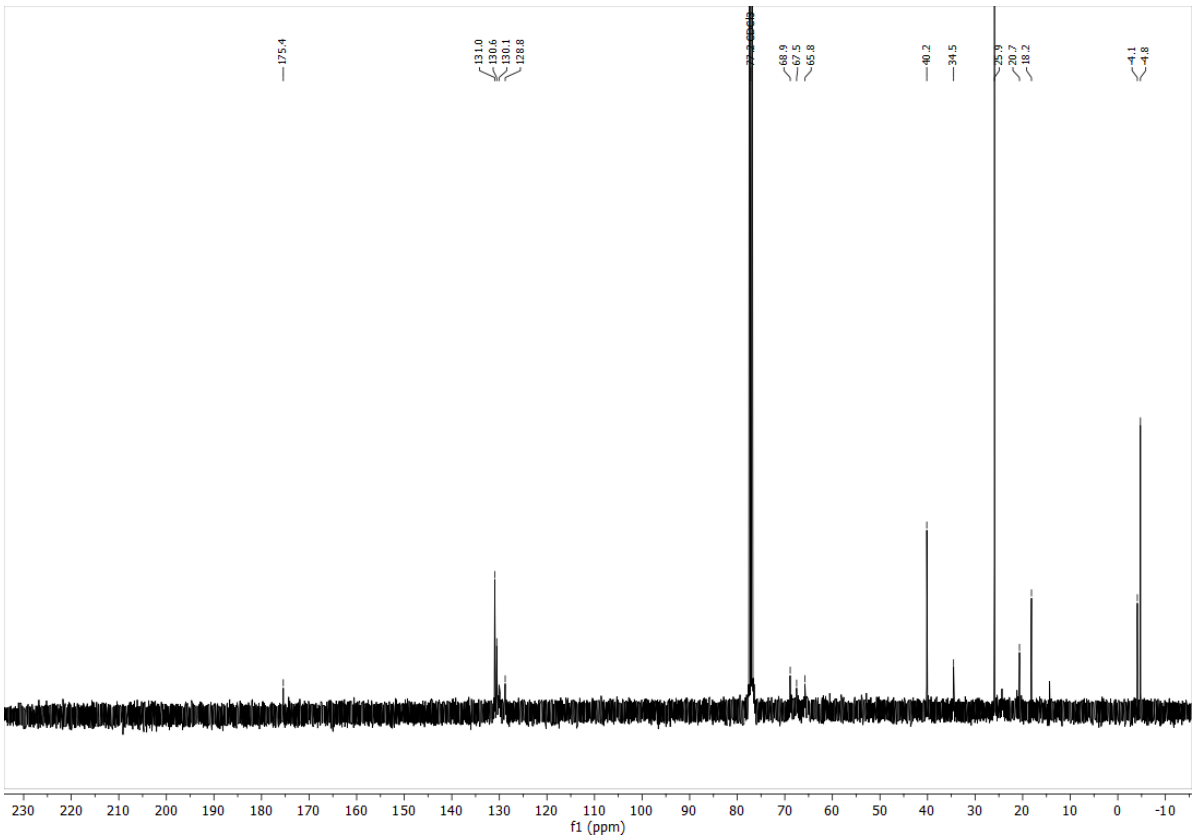
8.4.1.1 5-((*tert*-butyldimethylsilyl)oxy)-1,4,4a,5,8,8a-hexahydronaphthalene-1,4-diol **rac-96**



*[1]H-spectrum of **rac-96** in $CDCl_3$.*

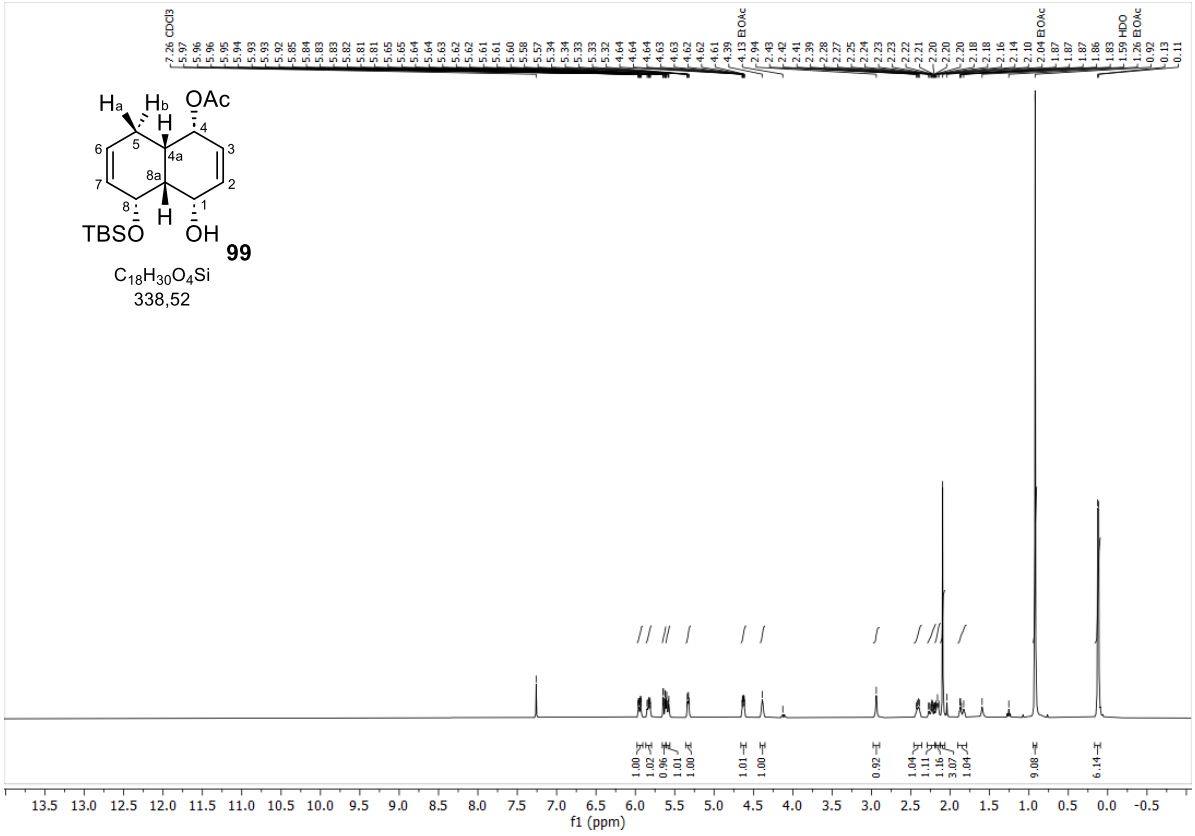


*[1]H-spectrum of **rac-96** in $CDCl_3$ (selected regions between 1,7-6,3 ppm).*

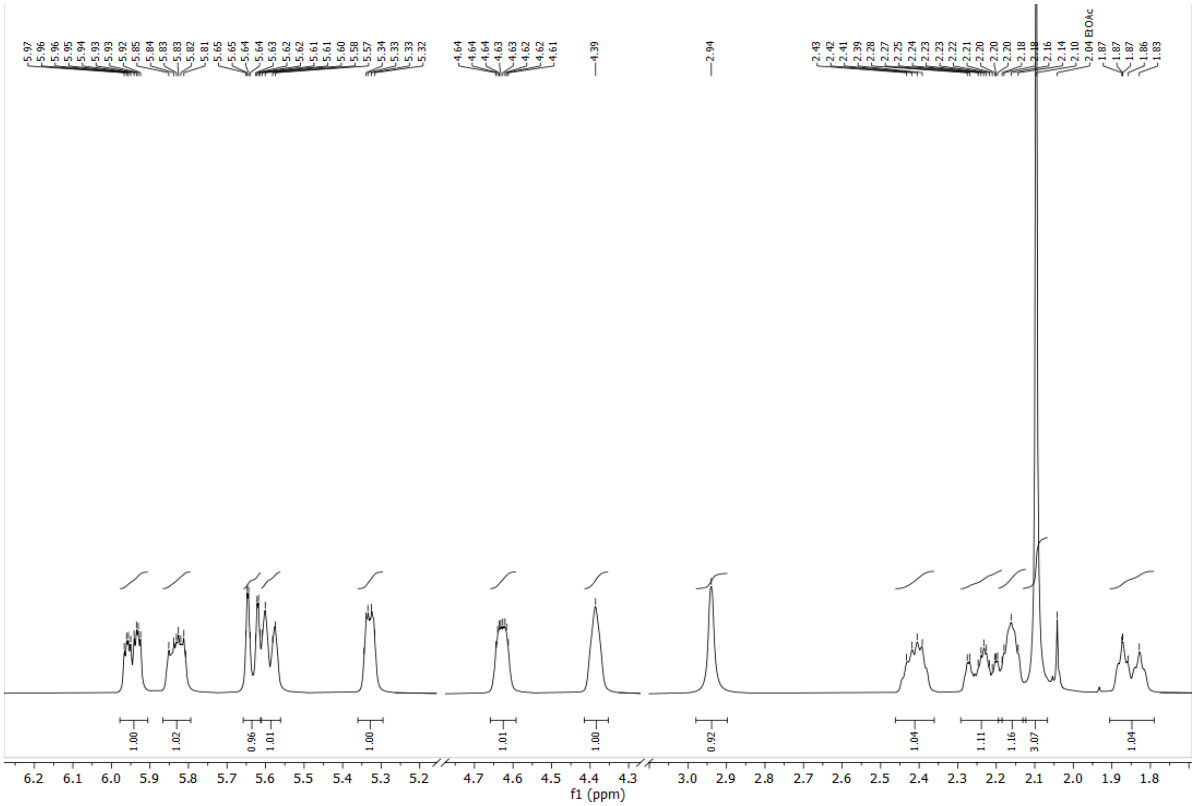


*^{13}C-spectrum of **rac-96** in $CDCl_3$.*

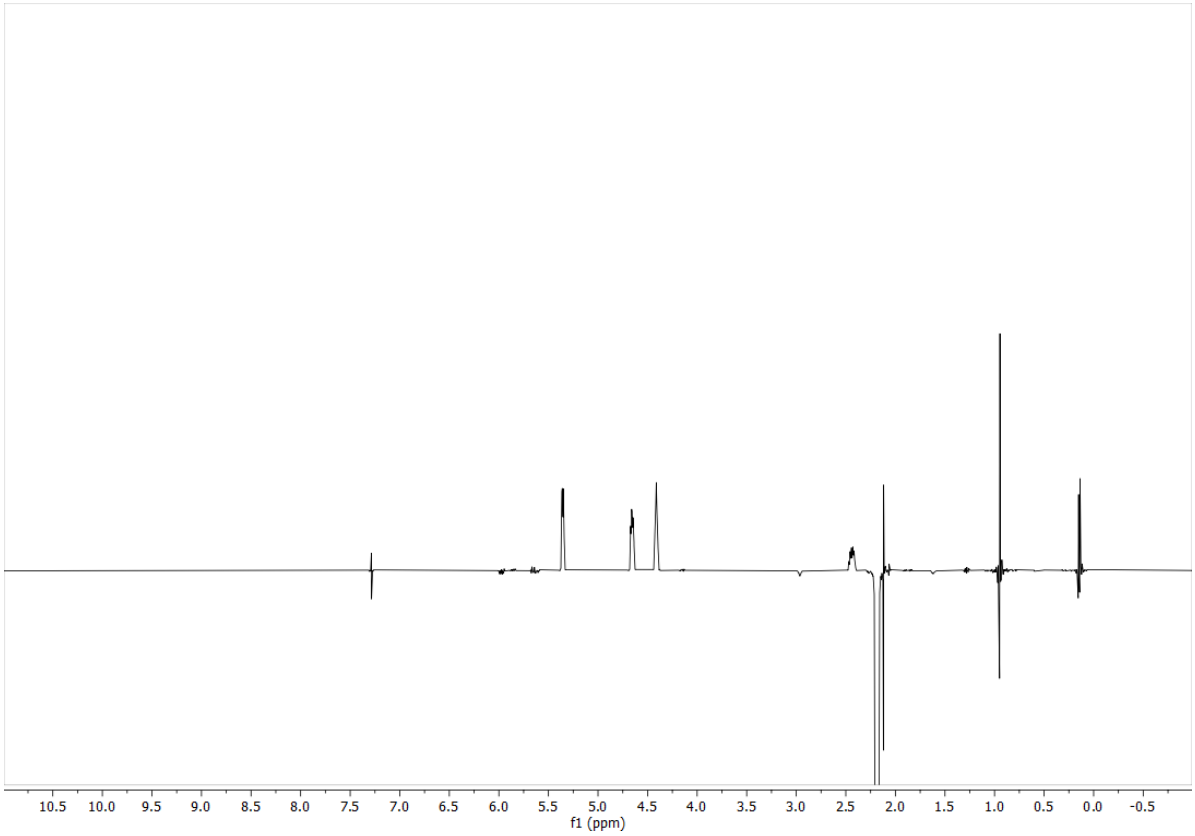
8.4.1.2 (1*R*,4*S*,4a*R*,5*R*,8a*S*)-5-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-1,4,4a,5,8,8a-hexahydro-naphthalen-1-yl acetate **99**



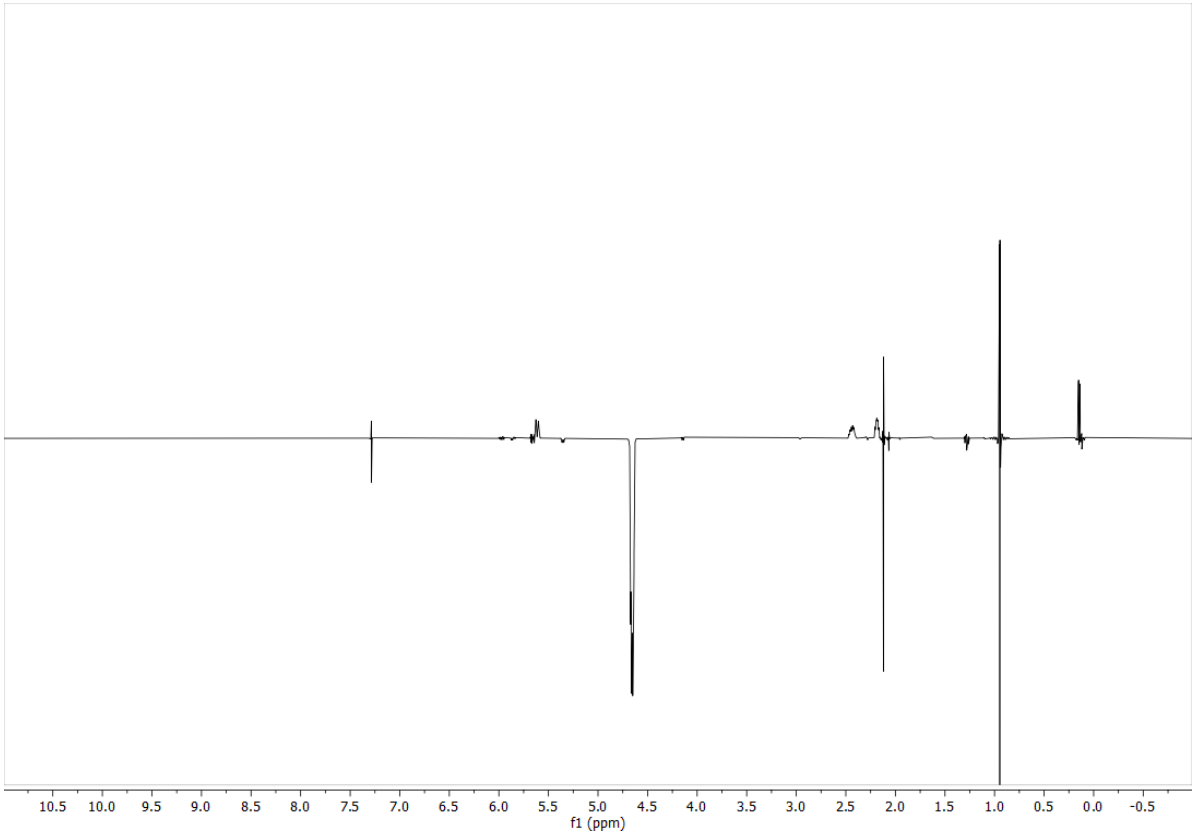
*^{1}H-spectrum of **99** in $CDCl_3$.*



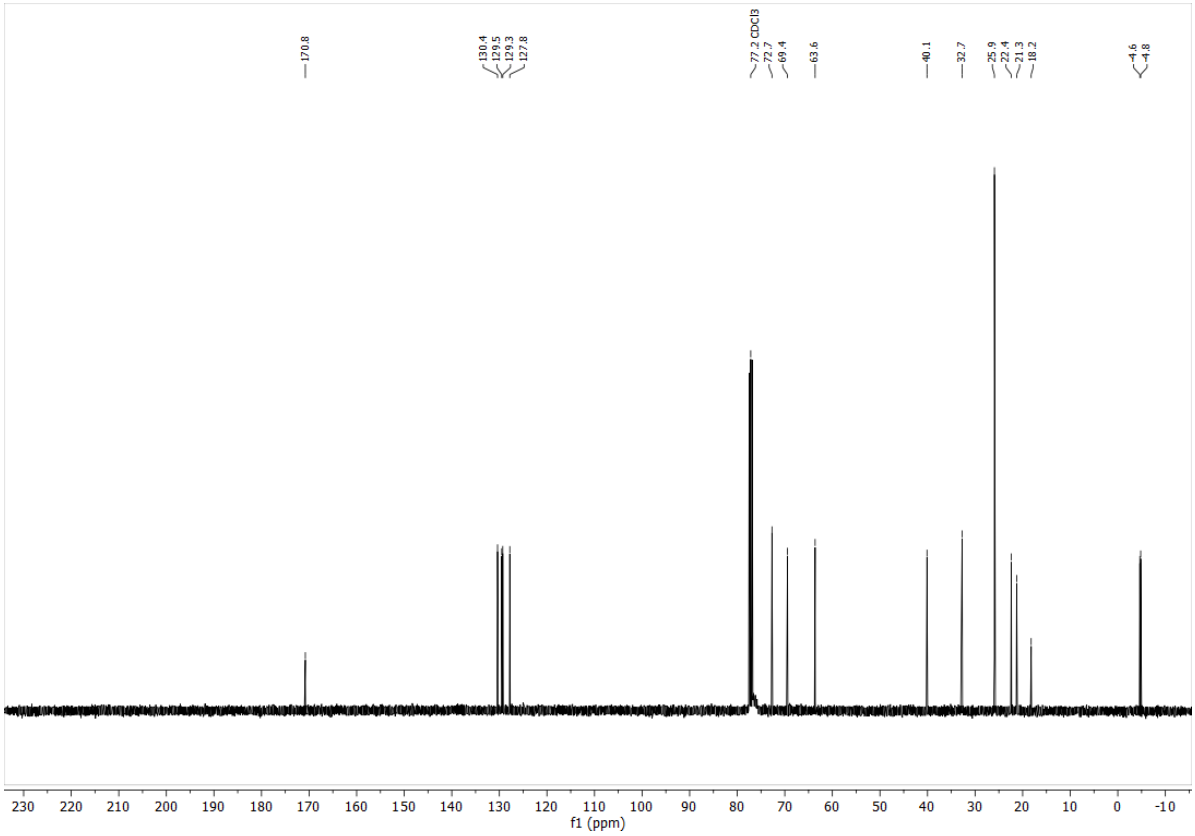
*^{1}H-spectrum of **99** in $CDCl_3$ (selected regions between 1,8-6,2 ppm).*



*NOE-spectrum of **99** in $CDCl_3$ (frequency saturation at 2,19 ppm).*

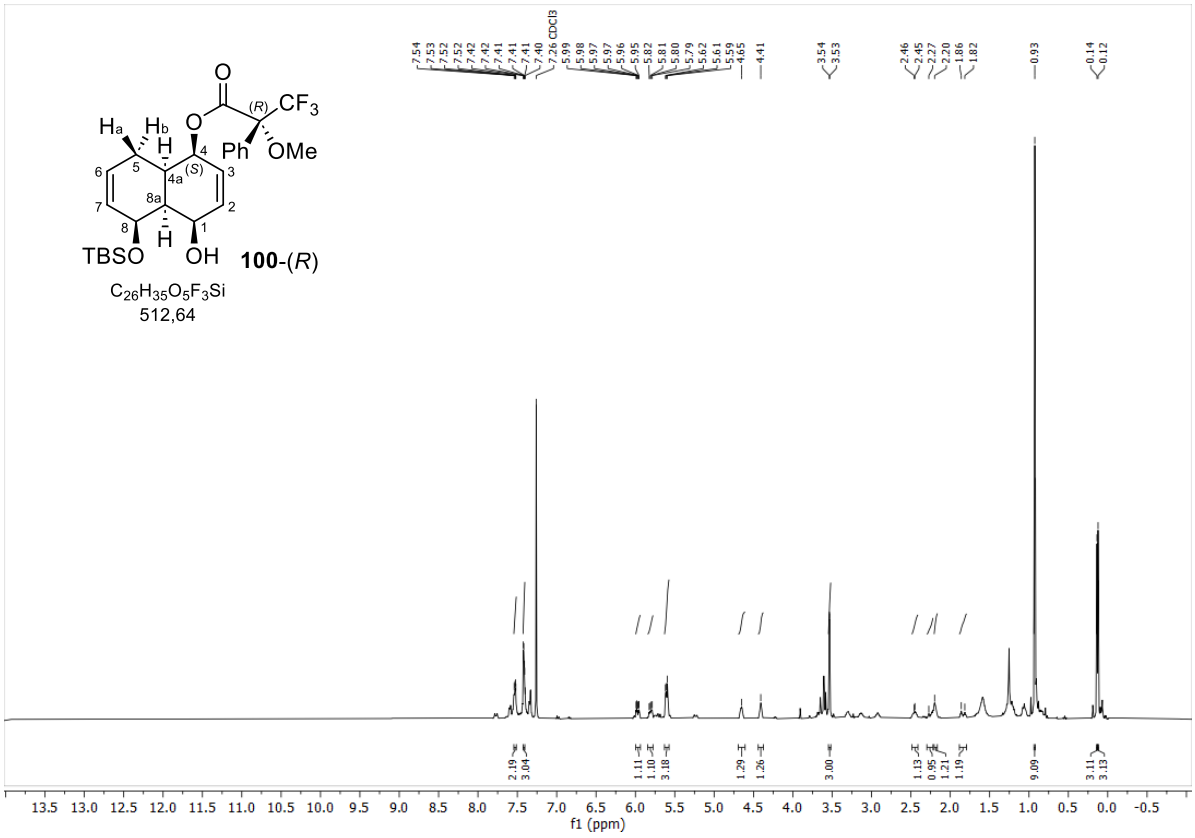


*NOE-spectrum of **99** in $CDCl_3$ (frequency saturation at 4,65 ppm).*

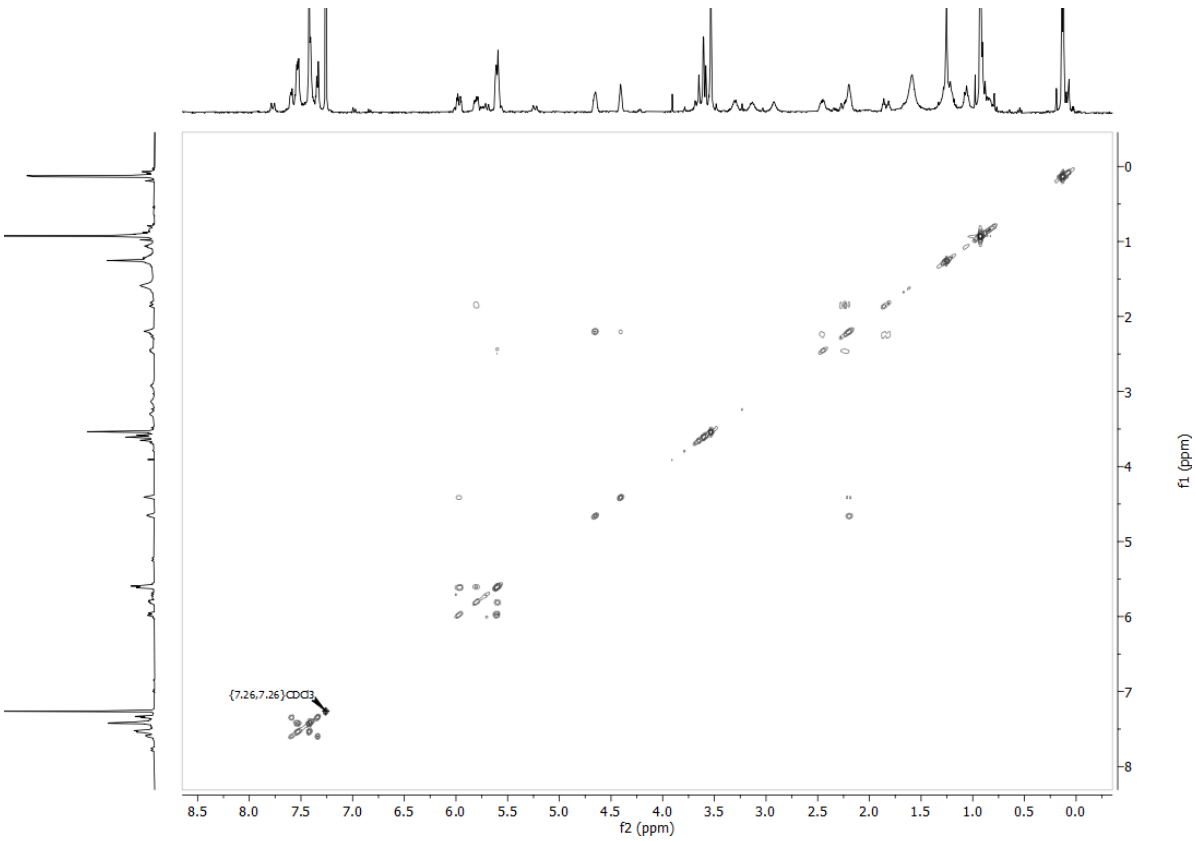


*^{13}C-spectrum of **99** in $CDCl_3$.*

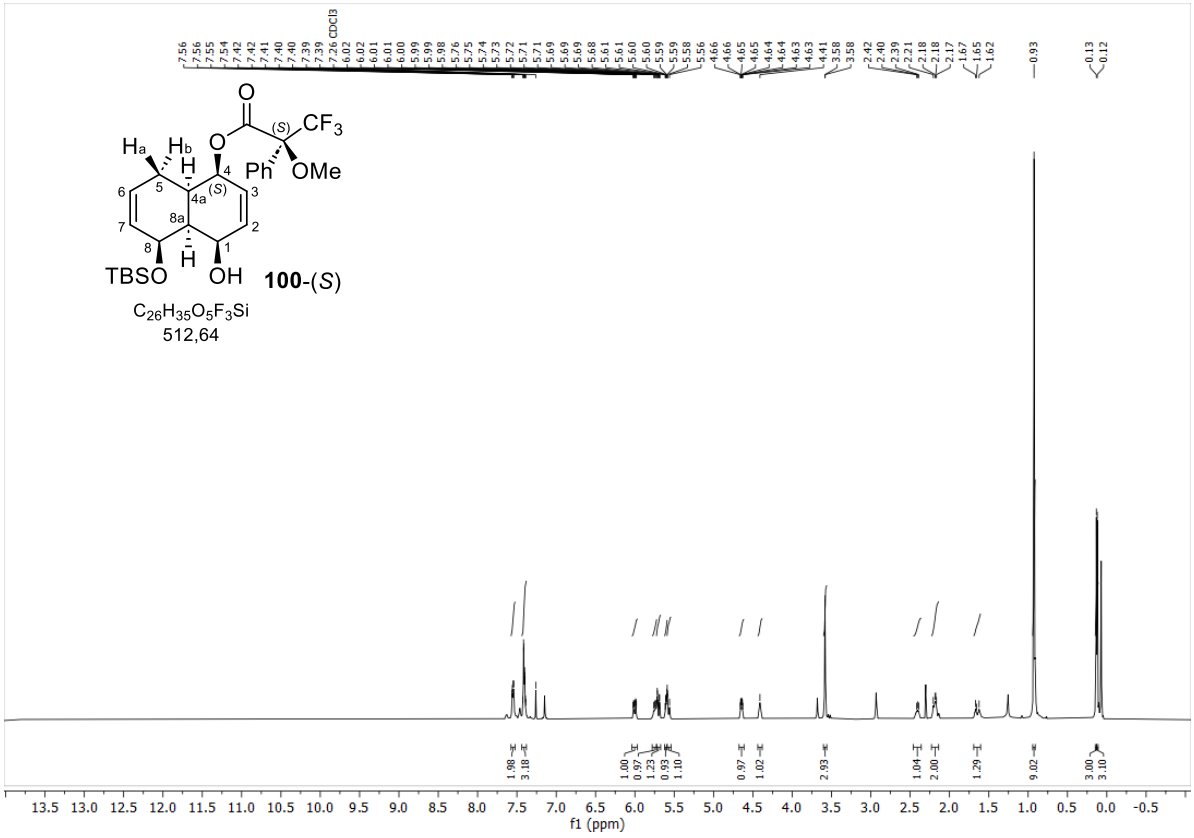
8.4.1.3 Mosher-ester analysis of **96** and **86**



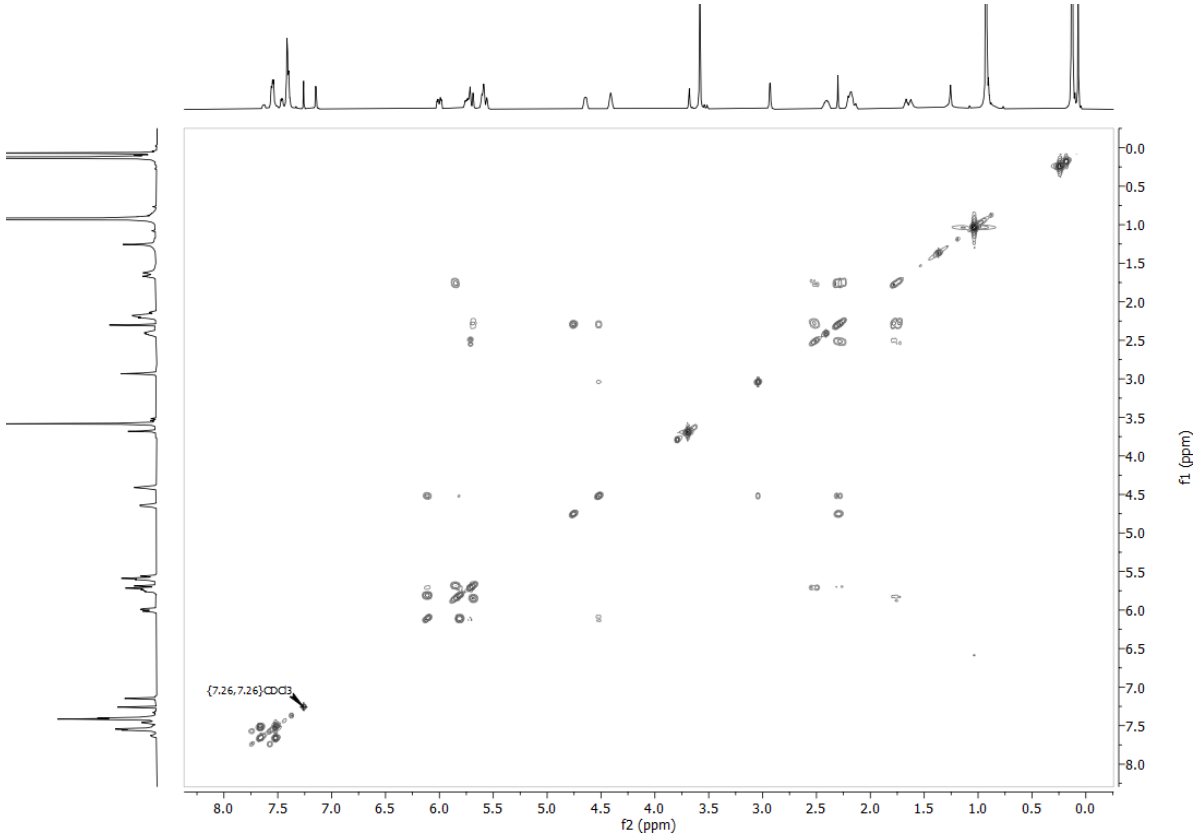
*^{1}H-spectrum of **100-(R)** in $CDCl_3$.*



*^{1}H,^{1}H-COSY-spectrum of **100-(R)** in $CDCl_3$.*



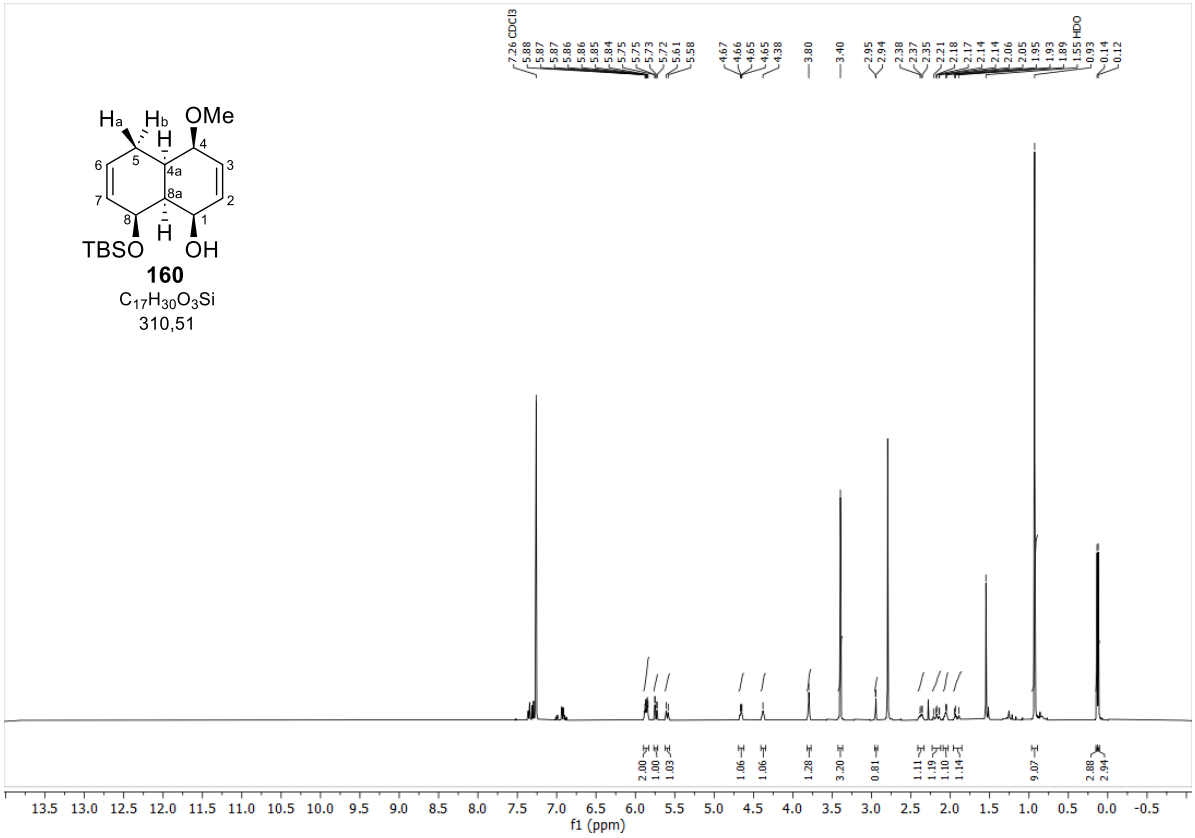
*^{1}H-spectrum of **100-(S)** in $CDCl_3$.*



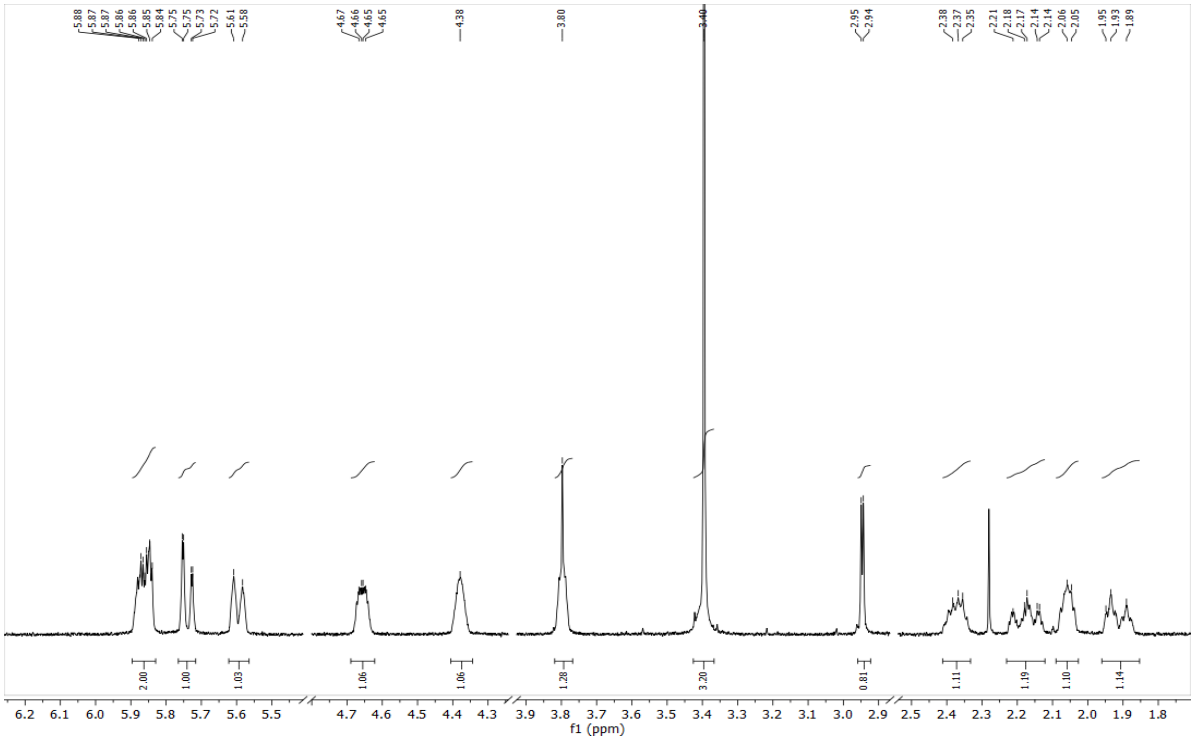
*^{1}H,^{1}H-COSY-spectrum **100-(S)** in $CDCl_3$.*

8.4.1.4 (4*S*,4a*R*,8*S*,8a*R*)-8-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-4a,5,8,8a-tetra-hydronaphthalen-1(4*H*)-one **95**

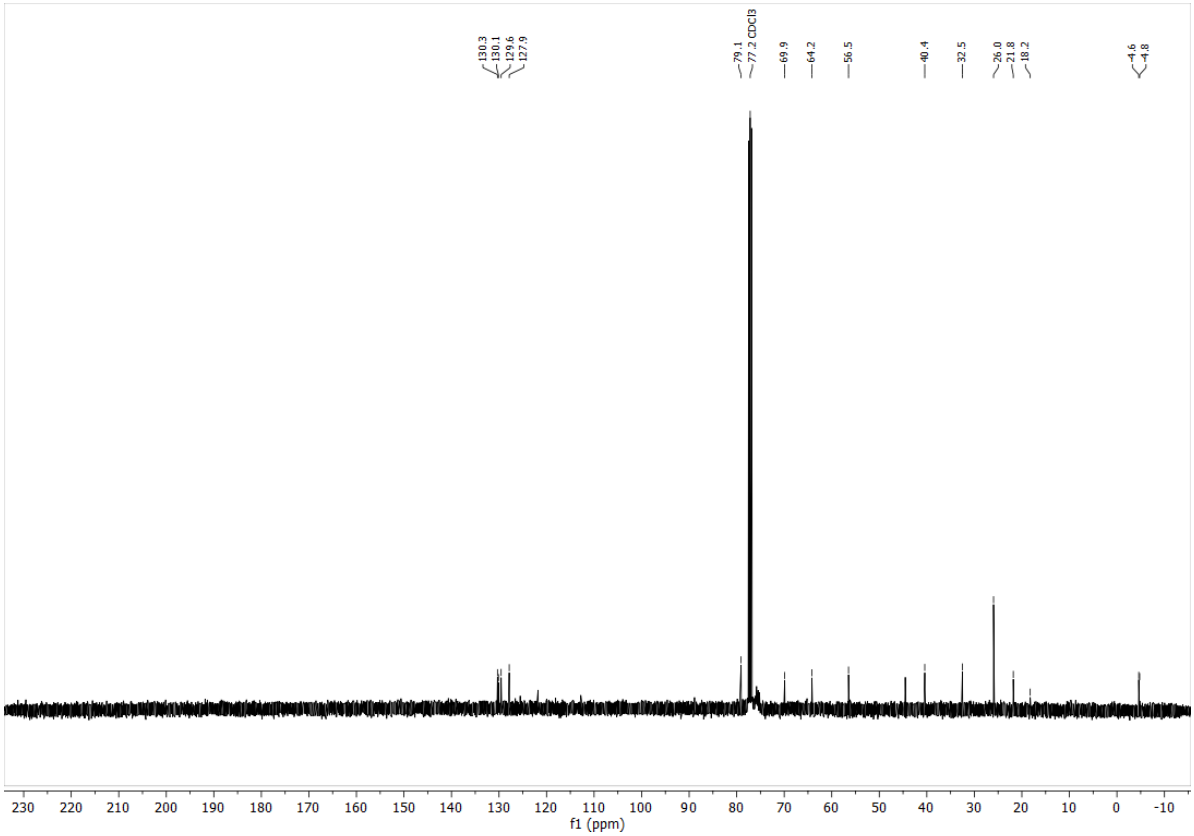
methylation (synthesis of (1*R*,4*S*,4a*R*,8*S*,8a*S*)-8-((*tert*-butyldimethylsilyl)oxy)-4-methoxy-1,4,4a,5,8,8a-hexahydronaphthalen-1-ol **160**)



*^{1}H-spectrum of **160** in $CDCl_3$.*

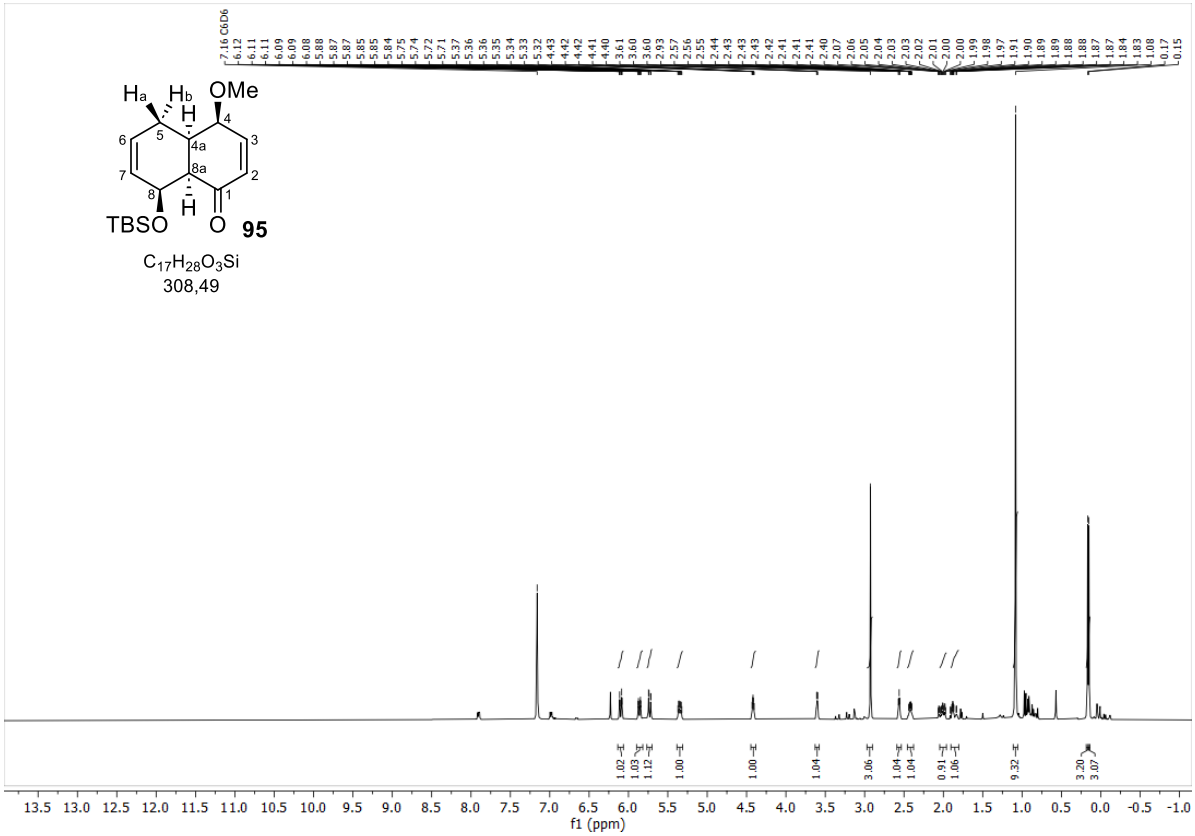


*^{1}H-spectrum of **160** in $CDCl_3$ (selected regions between 1,7-6,1 ppm).*

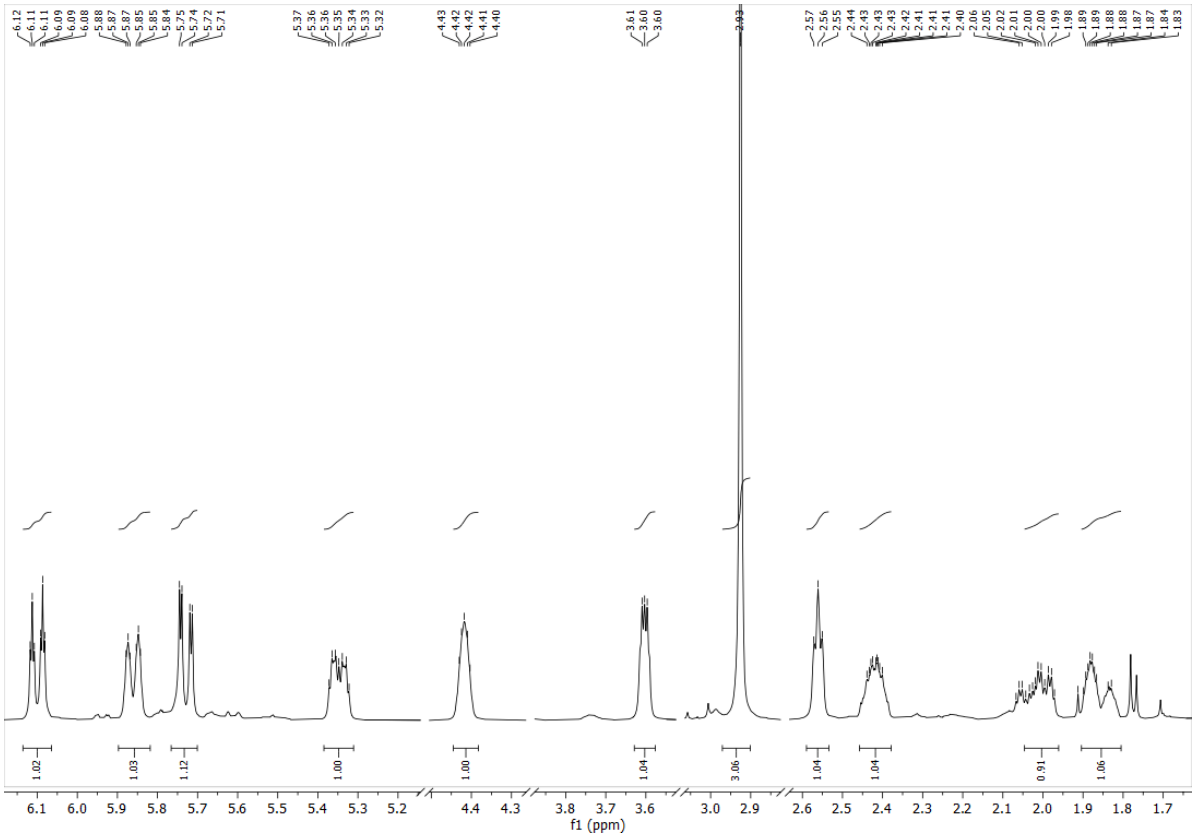


*^{13}C-spectrum of **160** in $CDCl_3$.*

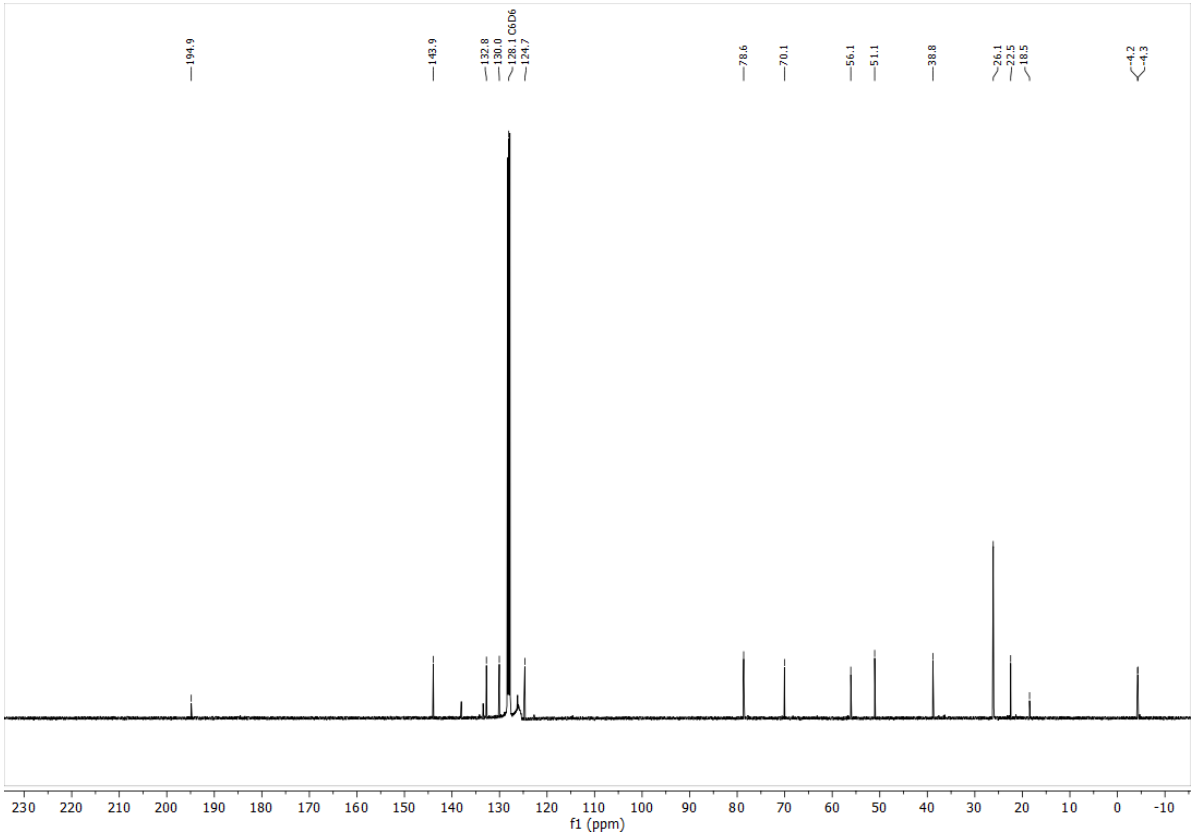
IBX-oxidation (synthesis of **95**)



*^{1}H-spectrum of **95** in C_6D_6.*

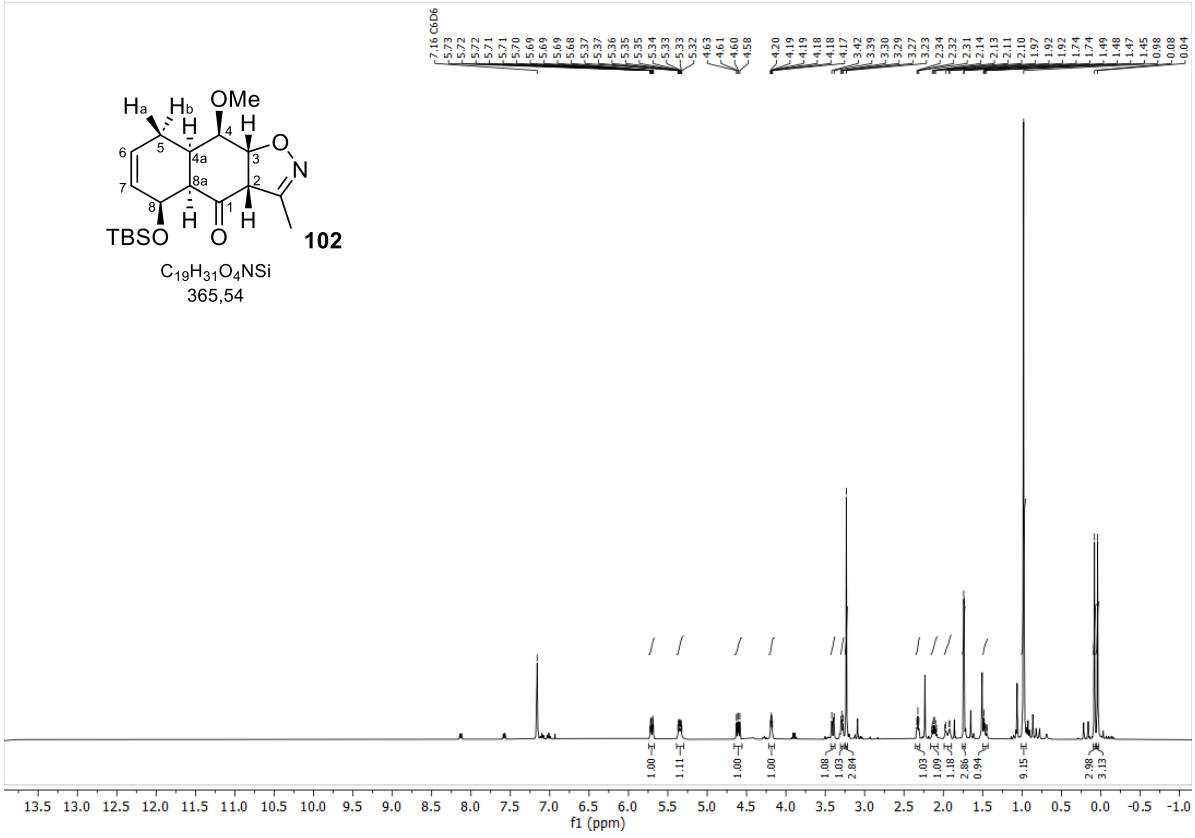


*^{1}H-spectrum of **95** in C_6D_6 (selected regions between 1,7-6,1 ppm).*

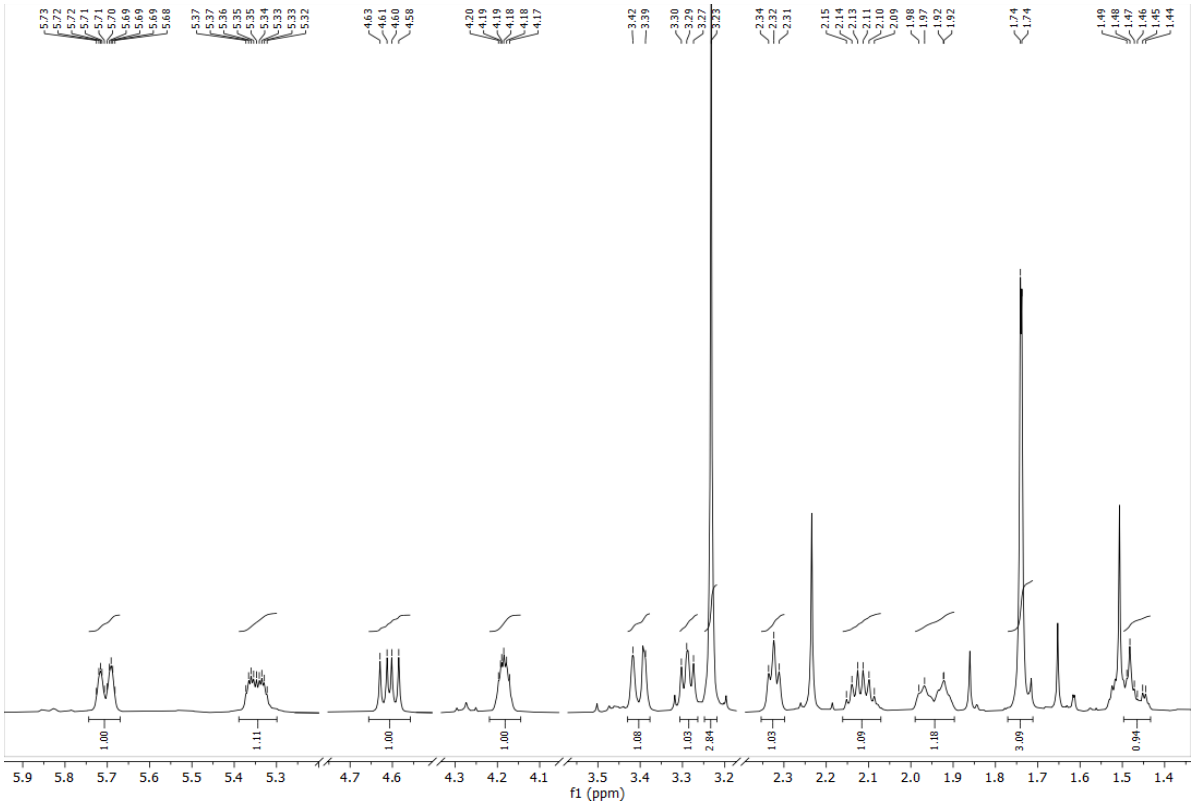


*^{13}C-spectrum of **95** in C_6D_6.*

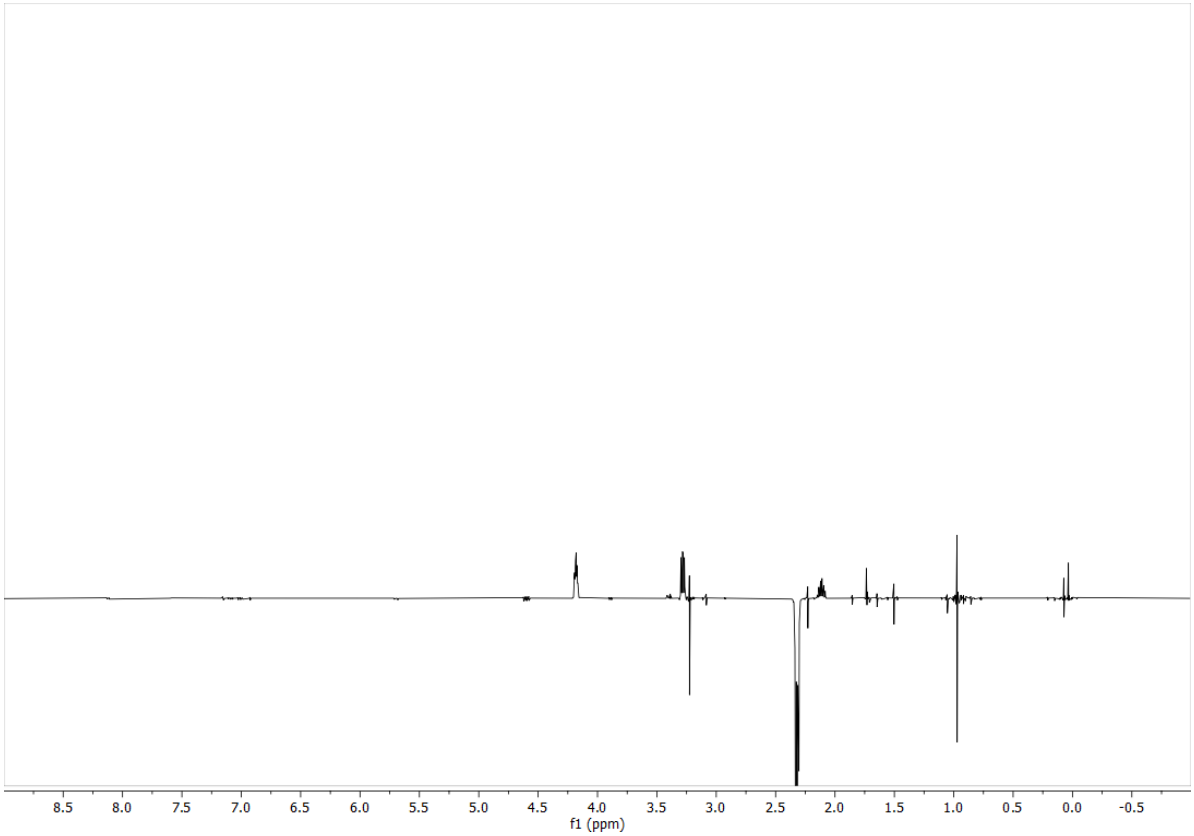
8.4.1.5 (3a*S*,4a*R*,5*S*,8a*R*,9*R*,9a*R*)-5-((*tert*-butyldimethylsilyl)oxy)-9-methoxy-3-methyl-4a,5,8,8a,9,9a-hexahydronaphtho[2,3-*d*]isoxazol-4(3a*H*)-one **102**



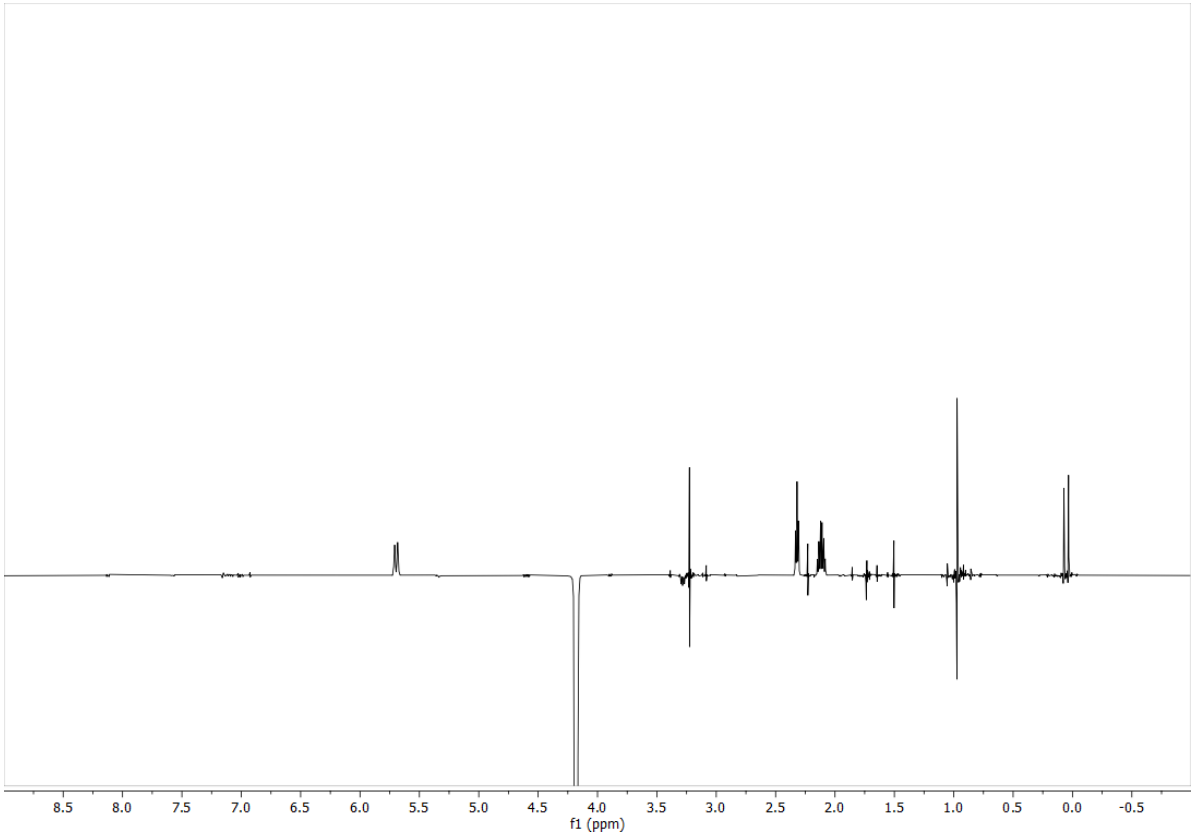
*^{1}H-spectrum of **102** in C_6D_6.*



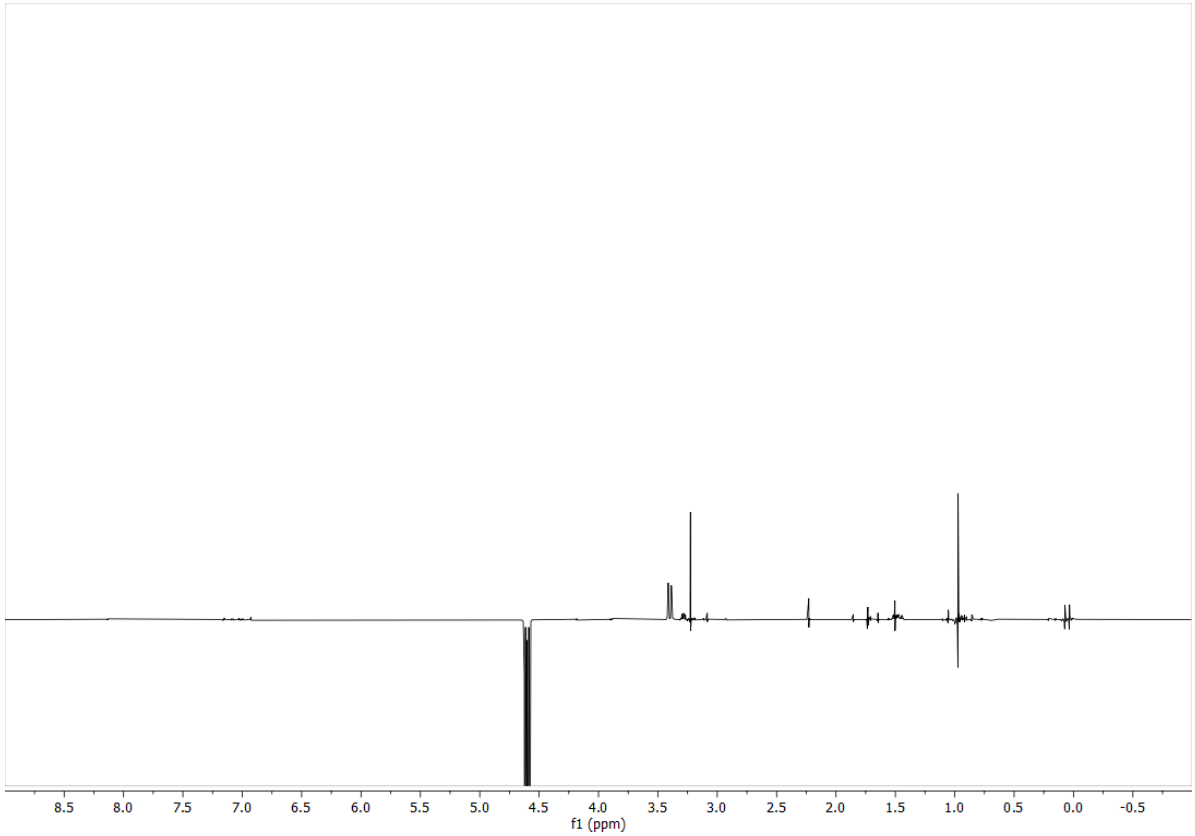
*^{1}H-spectrum of **102** in C_6D_6 (selected regions between 1,4-5,9 ppm).*



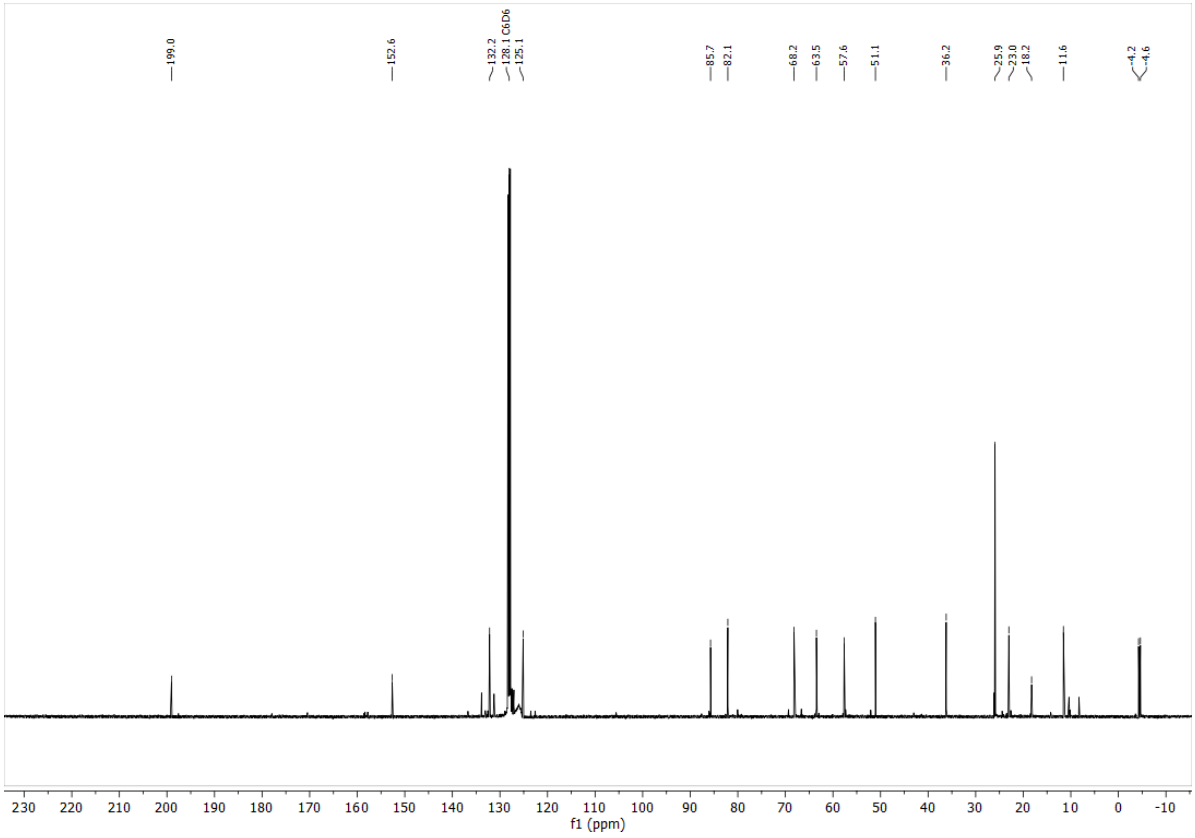
*NOE-spectrum of **102** in C_6D_6 (frequency saturation at 2,32 ppm).*



*NOE-spectrum of **102** in C_6D_6 (frequency saturation at 4,18 ppm).*



*NOE-spectrum of **102** in C_6D_6 (frequency saturation at 4,60 ppm).*

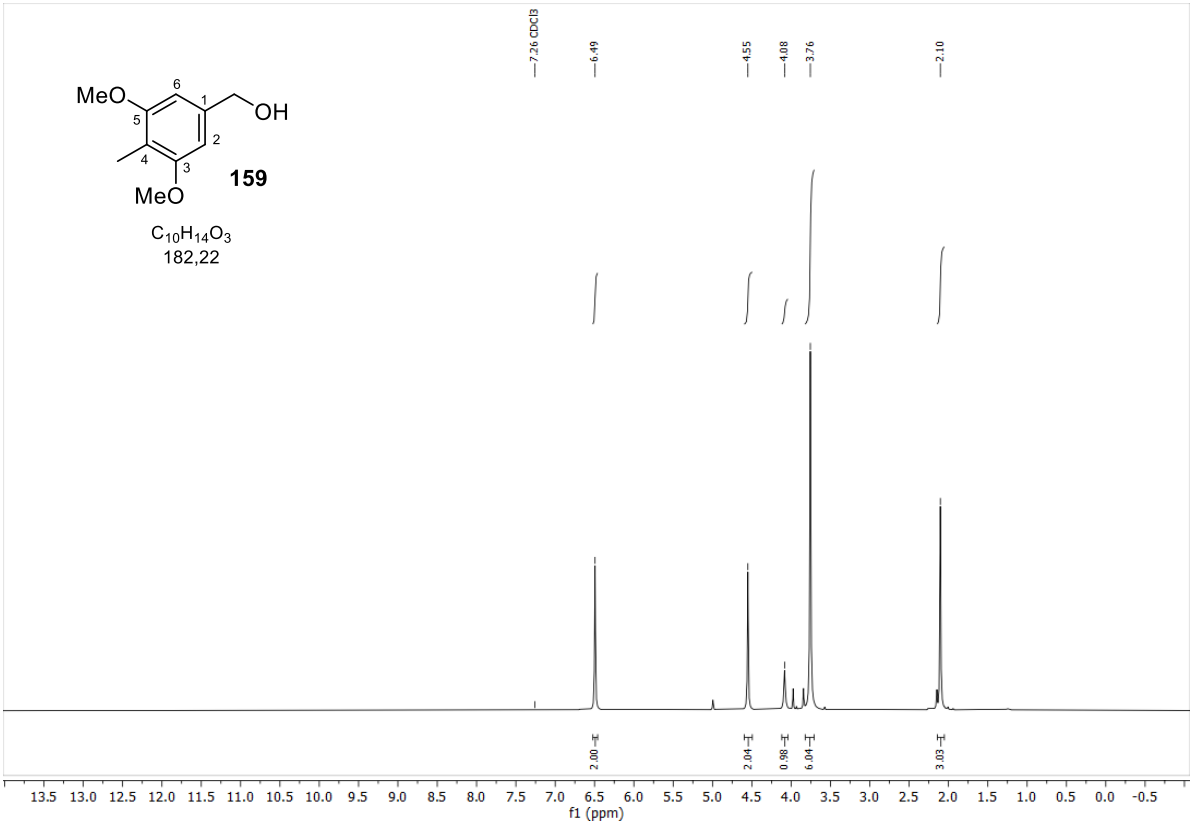


*^{13}C-spectrum of **102** in C_6D_6.*

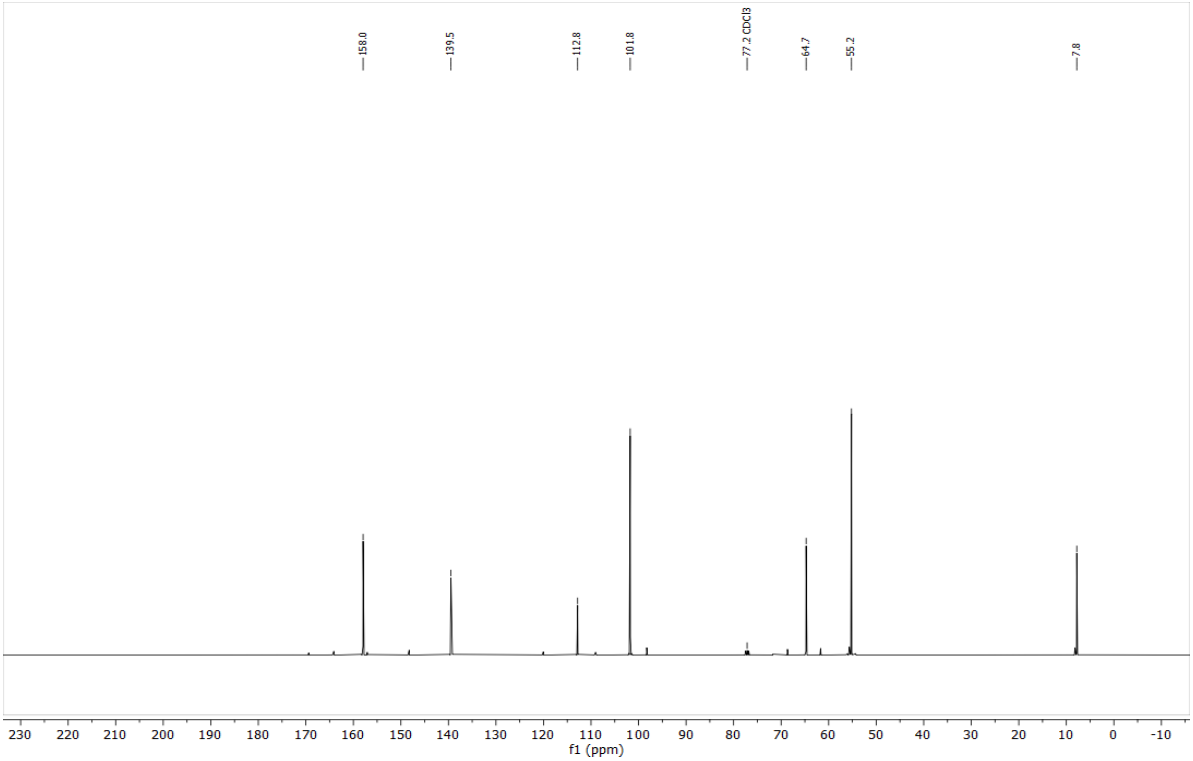
8.4.2 Phthalide **89**

8.4.2.1 2-bromo-3,5-dimethoxy-4-methylbenzyl alcohol **91**

LAH-reduction (synthesis of 3,5-dimethoxy-4-methylbenzyl alcohol **159**)

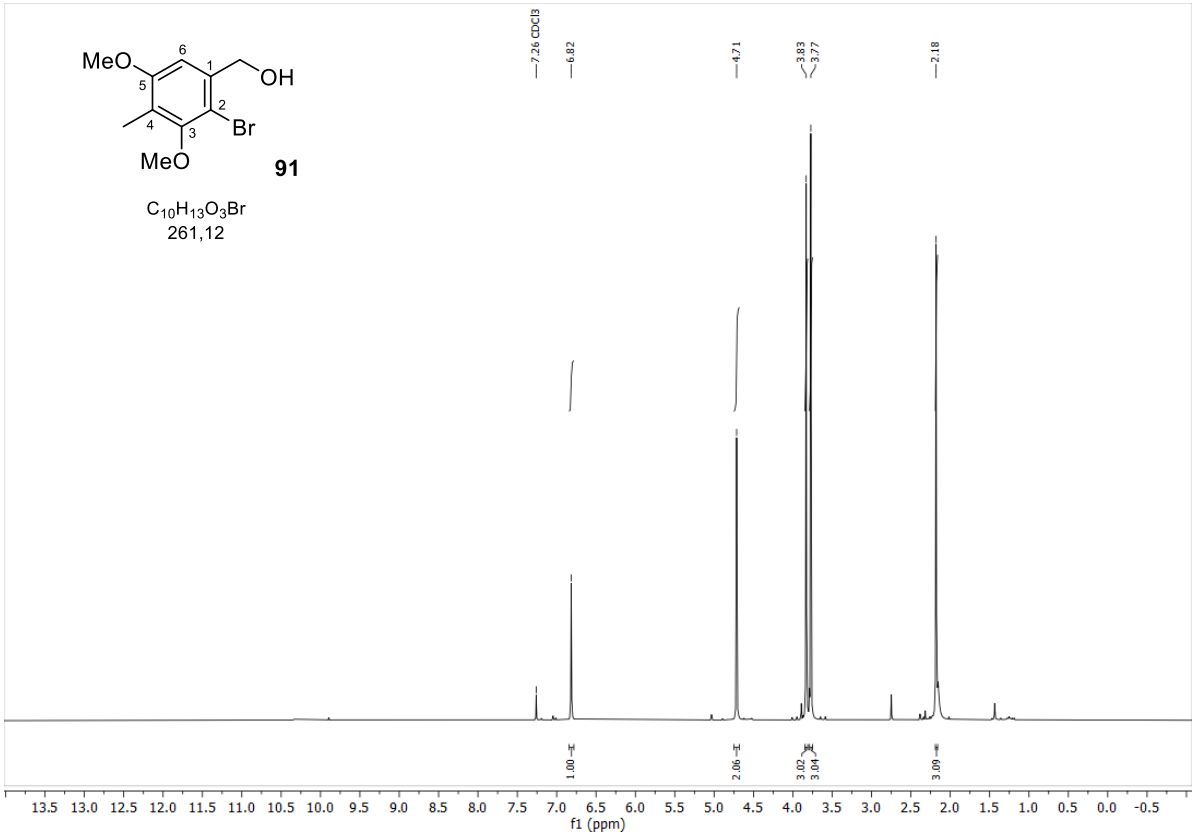


*^{1}H-spectrum of **159** in $CDCl_3$.*

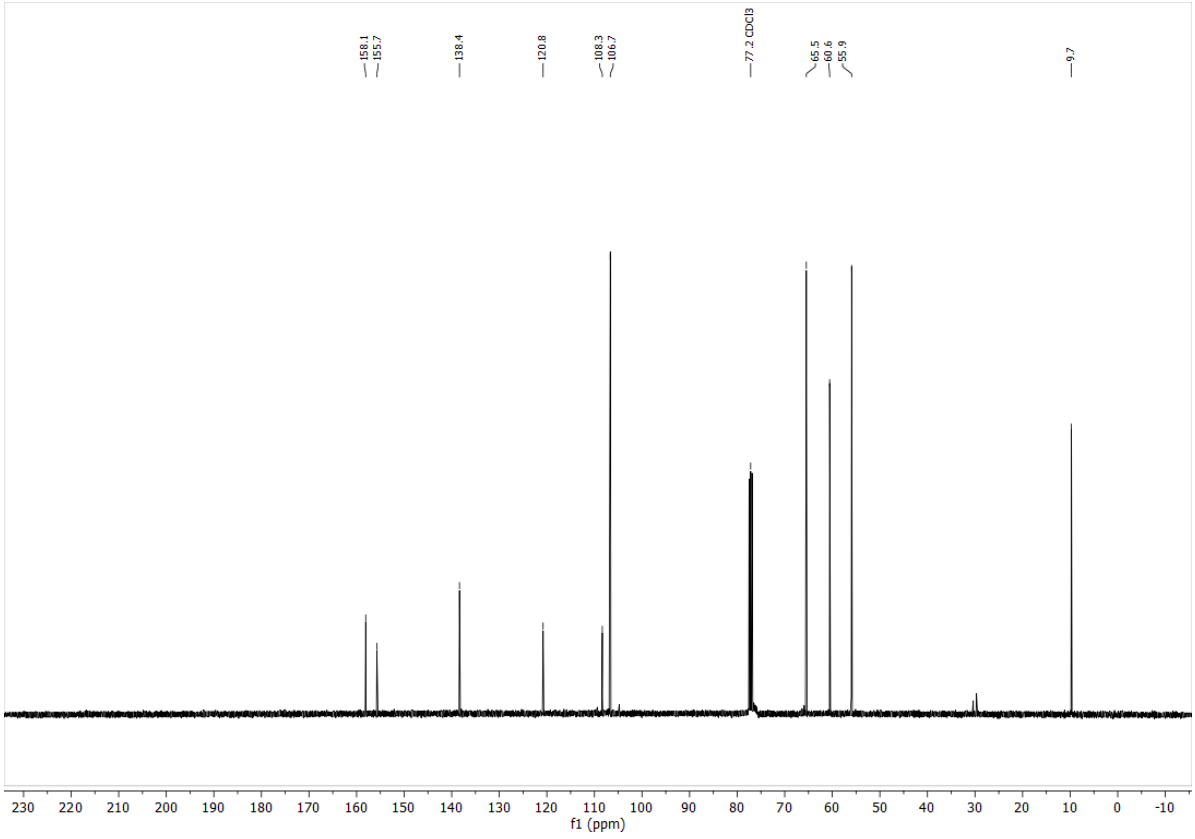


*^{13}C-spectrum of **159** in $CDCl_3$.*

bromination (synthesis of **91**)

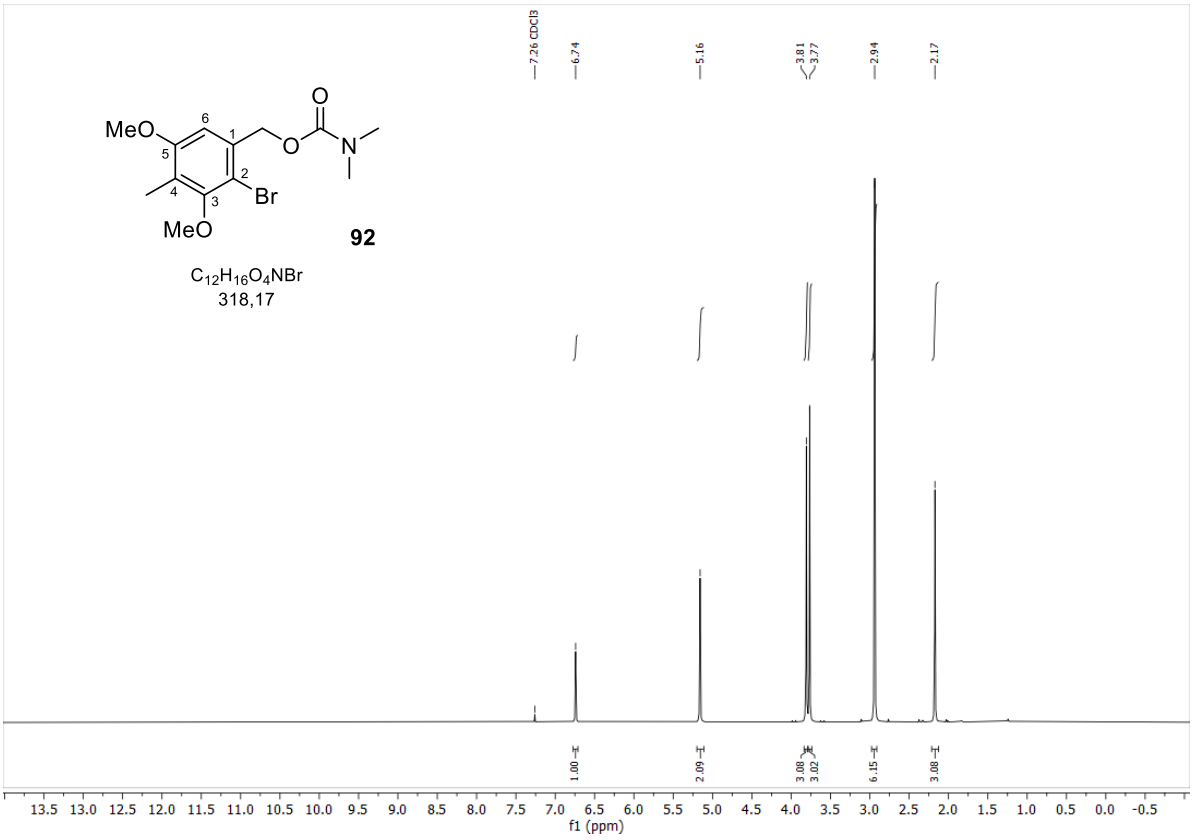


*^{1}H-spectrum of **91** in $CDCl_3$.*

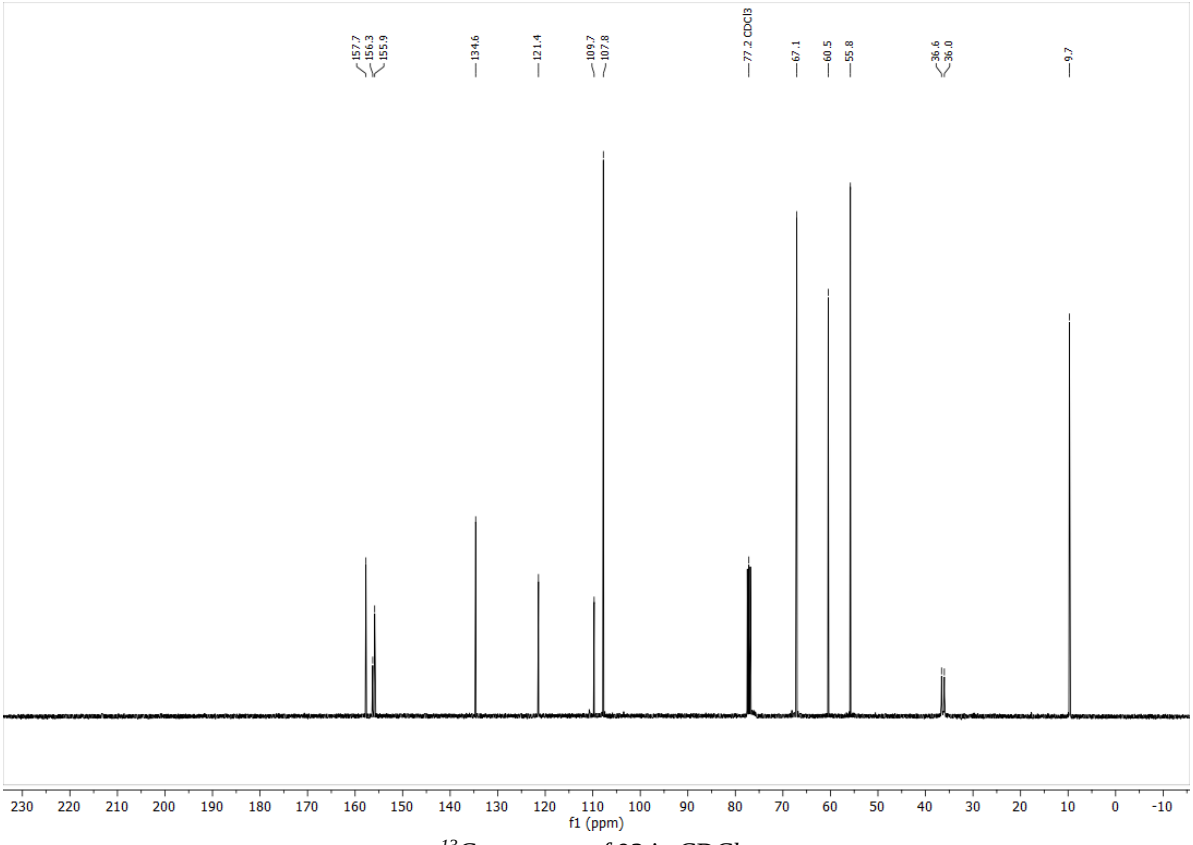


*^{13}C-spectrum of **91** in $CDCl_3$.*

8.4.2.2 2-bromo-3,5-dimethoxy-4-methylbenzyl dimethylcarbamate **92**

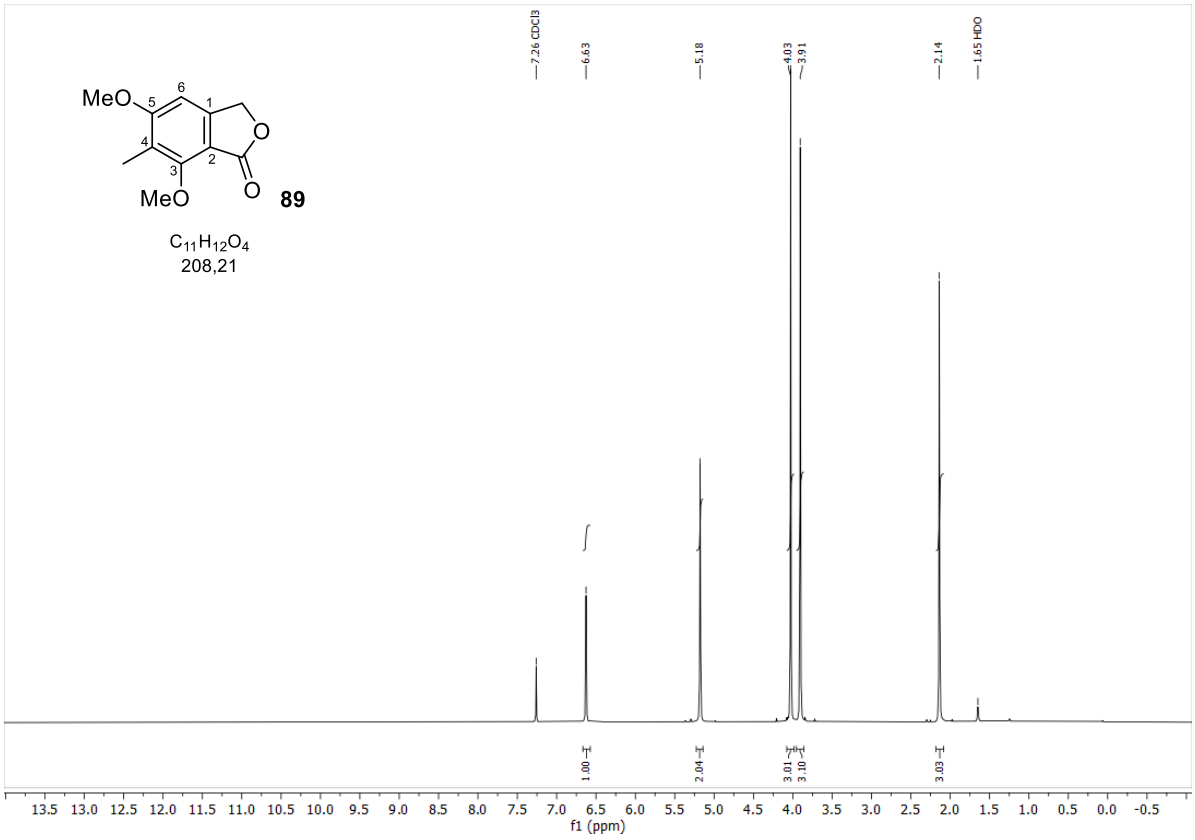


*^{1}H-spectrum of **92** in $CDCl_3$.*

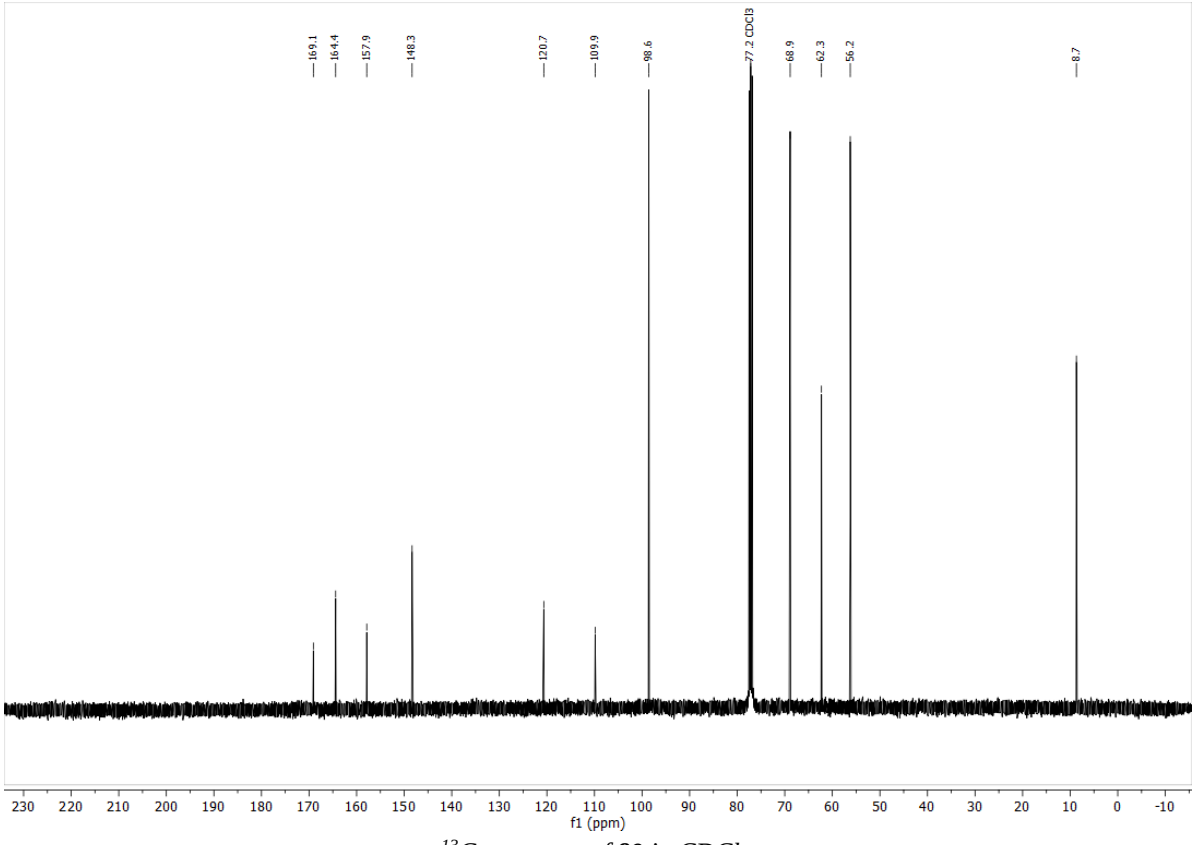


*^{13}C-spectrum of **92** in $CDCl_3$.*

8.4.2.3 5,7-dimethoxy-6-methylisobenzofuran-1(3*H*)-one **89**



*^{1}H-spectrum of **89** in $CDCl_3$.*

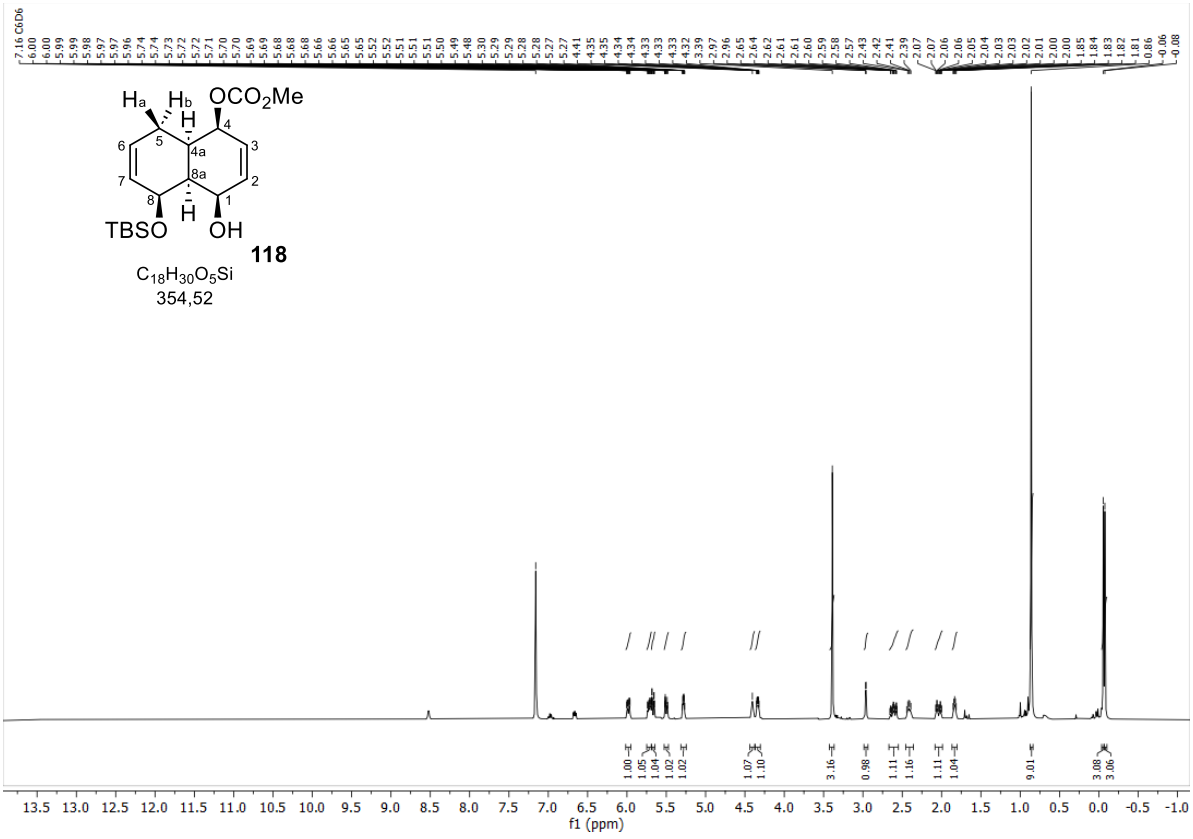


*^{13}C-spectrum of **89** in $CDCl_3$.*

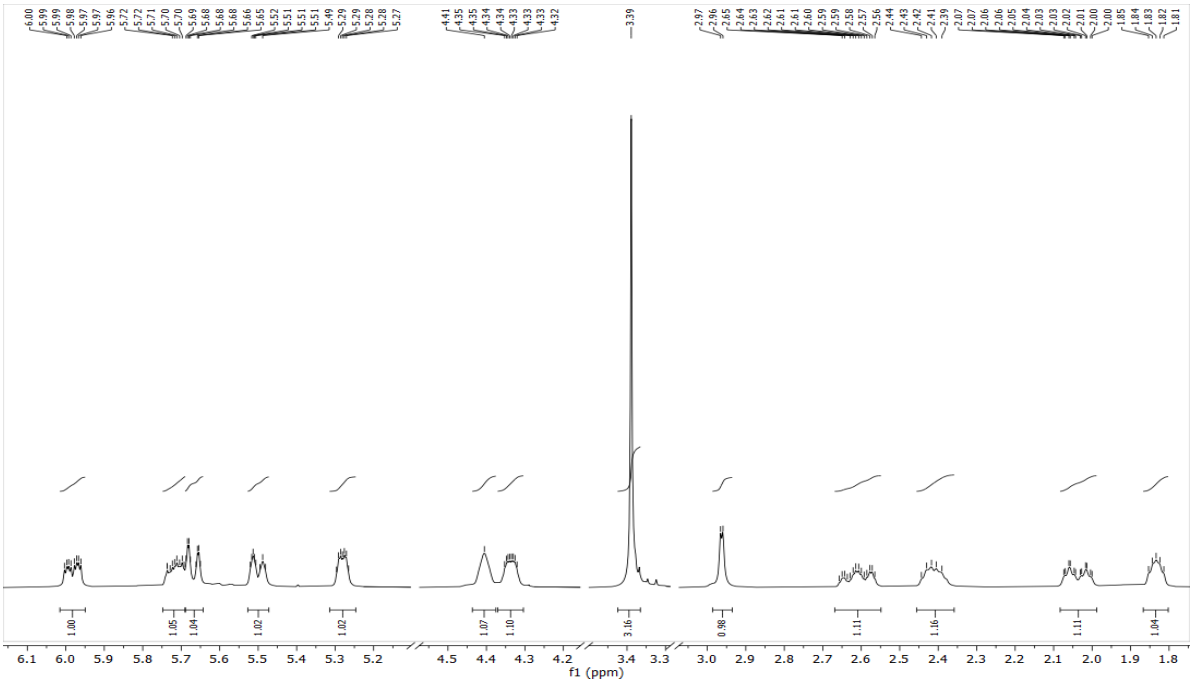
8.5 Carbamidochelocardin

8.5.1 Attempted synthesis of enone **105**

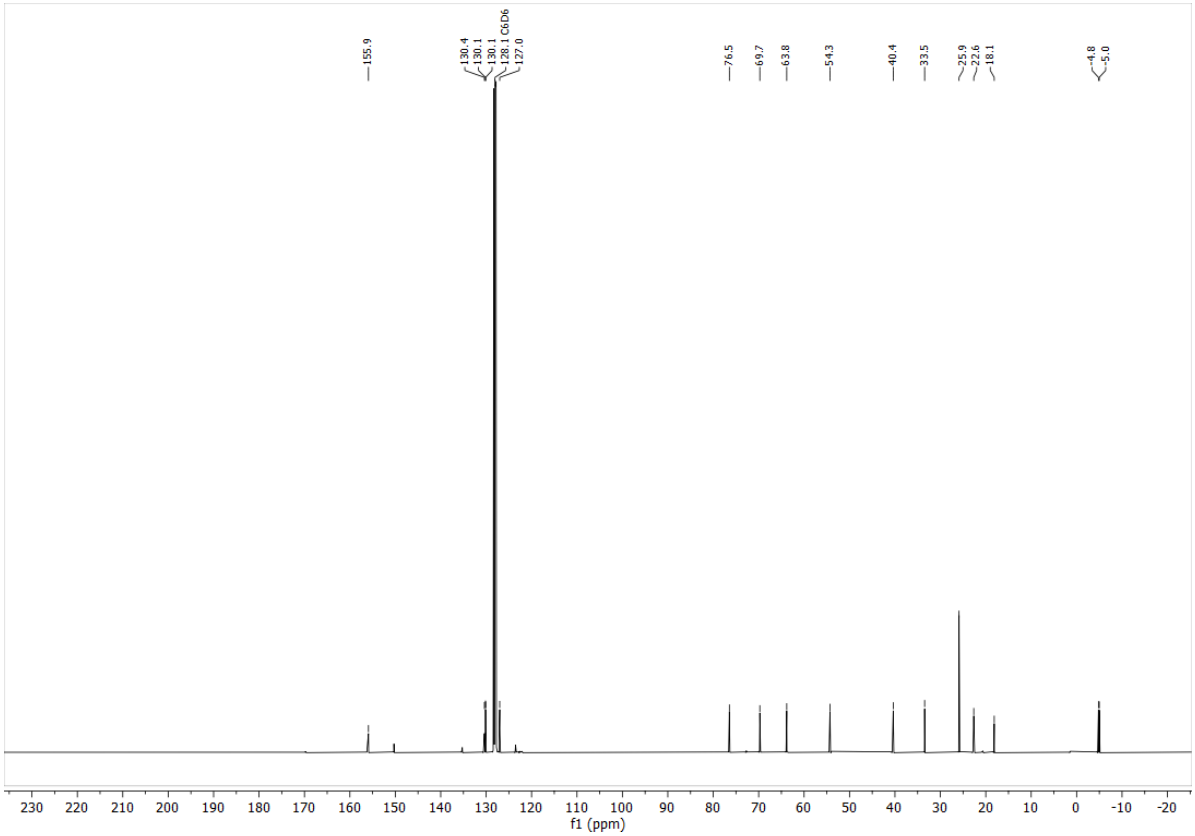
8.5.1.1 (1*S*,4*R*,4a*S*,5*S*,8a*R*)-5-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-1,4,4a,5,8,8a-hexahydro-naphthalen-1-yl methyl carbonate **118**



*^{1}H-spectrum of **118** in C_6D_6.*

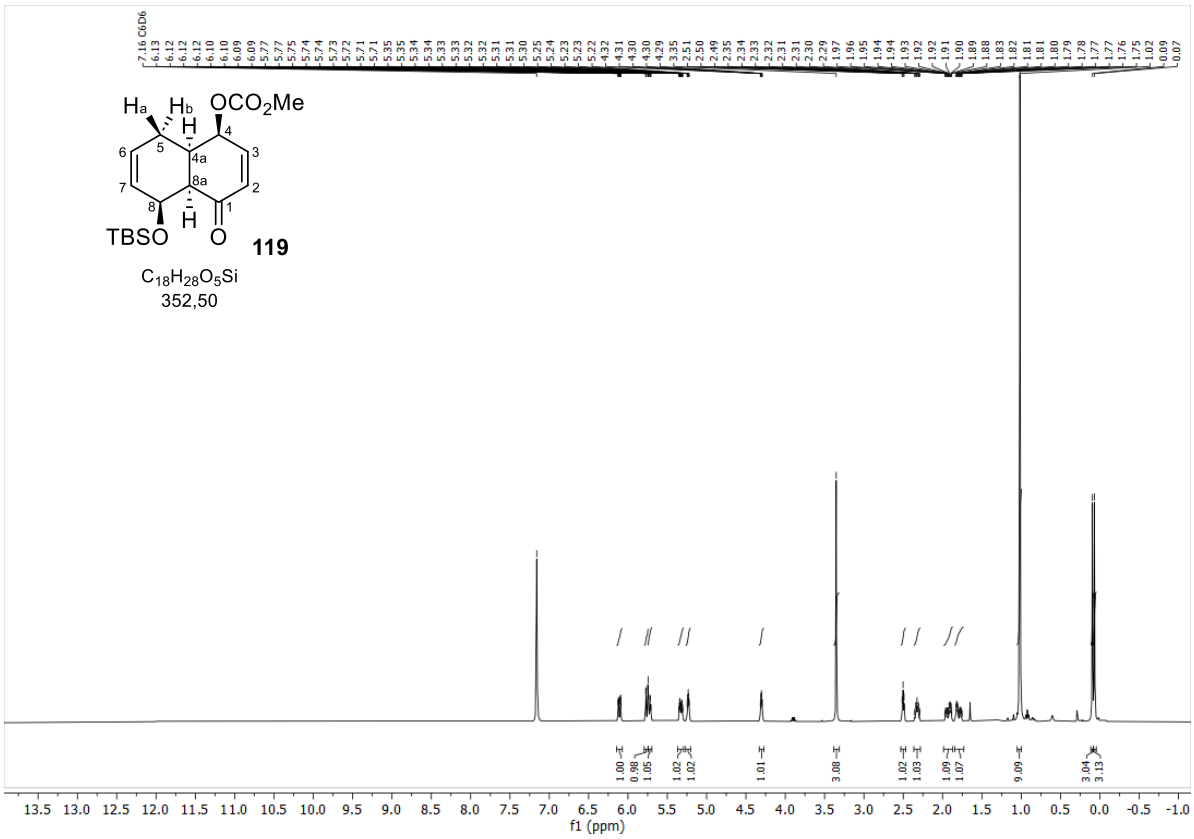


*^{1}H-spectrum of **118** in C_6D_6 (selected regions between 1,8-6,1 ppm).*

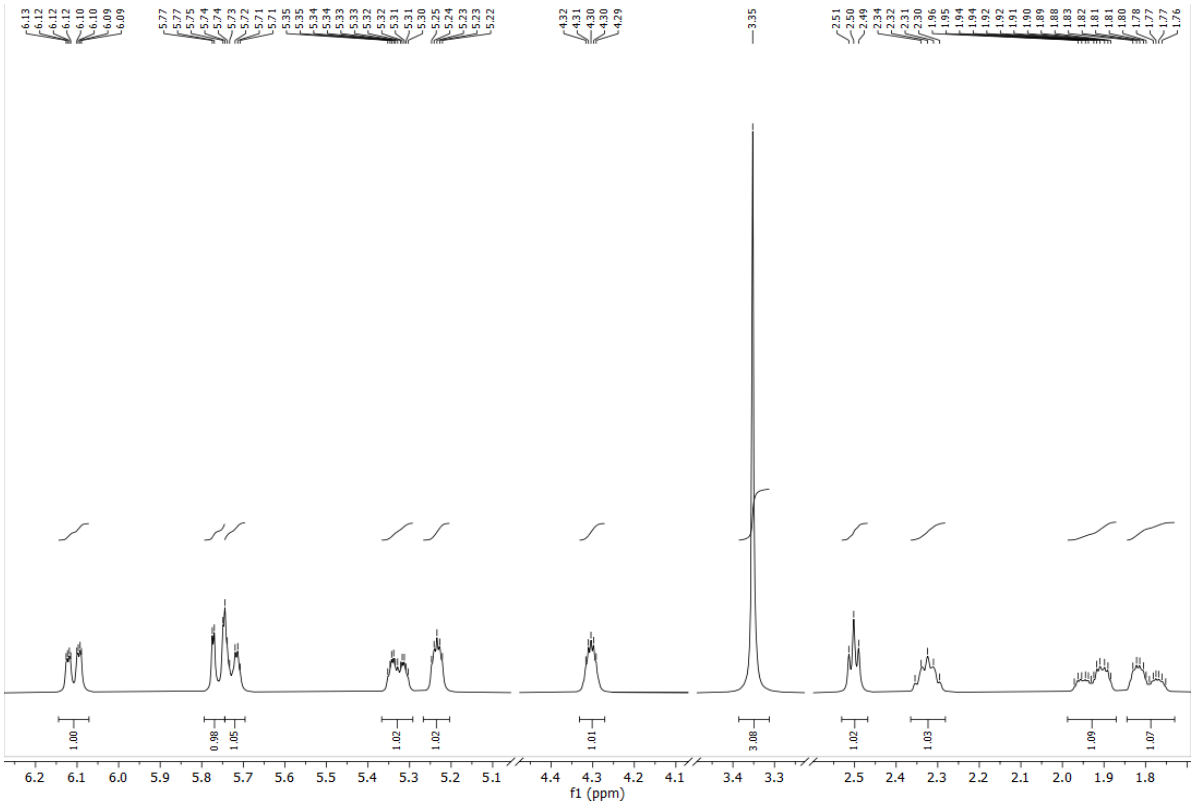


*^{13}C-spectrum of **118** in C_6D_6.*

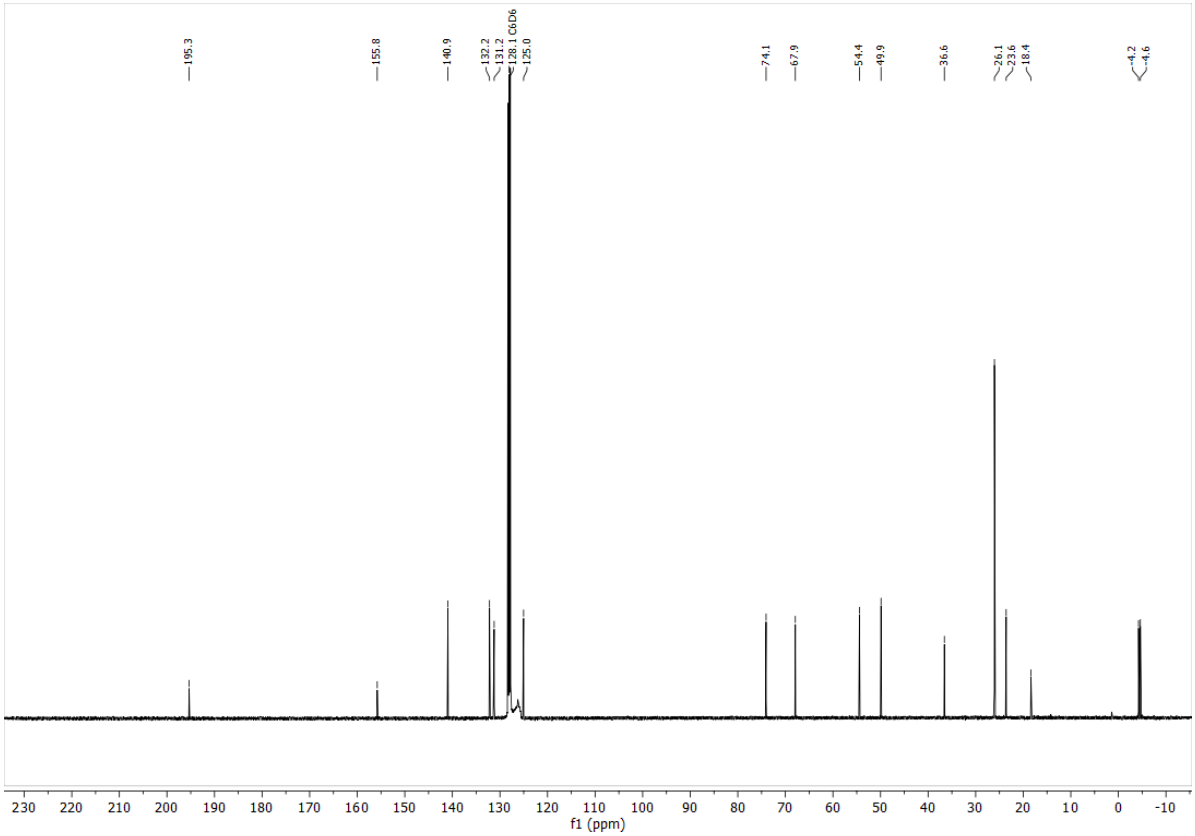
8.5.1.2 (1*S*,4a*R*,5*S*,8a*R*)-5-((*tert*-butyldimethylsilyl)oxy)-4-oxo-1,4,4a,5,8,8a-hexahydronaphthalen-1-yl methyl carbonate **119**



*^{1}H-spectrum of **119** in C_6D_6.*

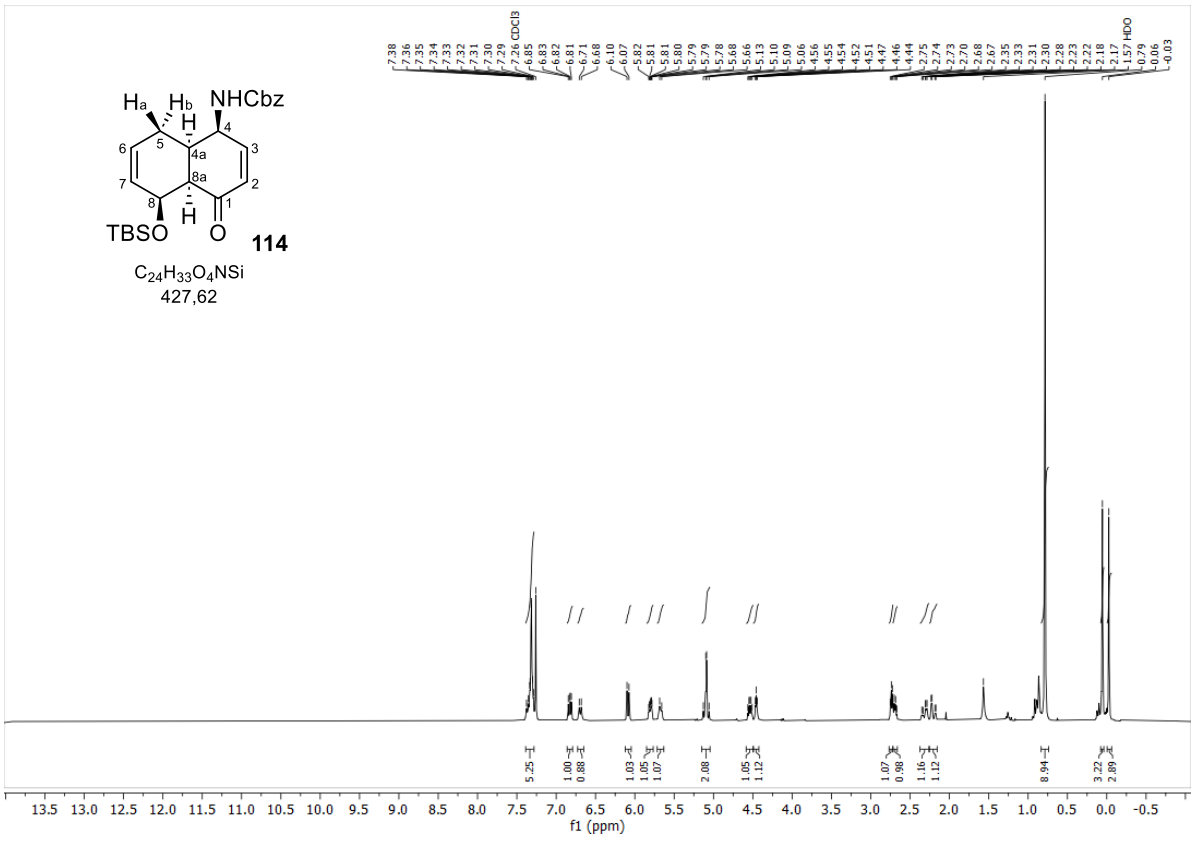


*^{1}H-spectrum of **119** in C_6D_6 (selected regions between 1,8-6,2 ppm).*

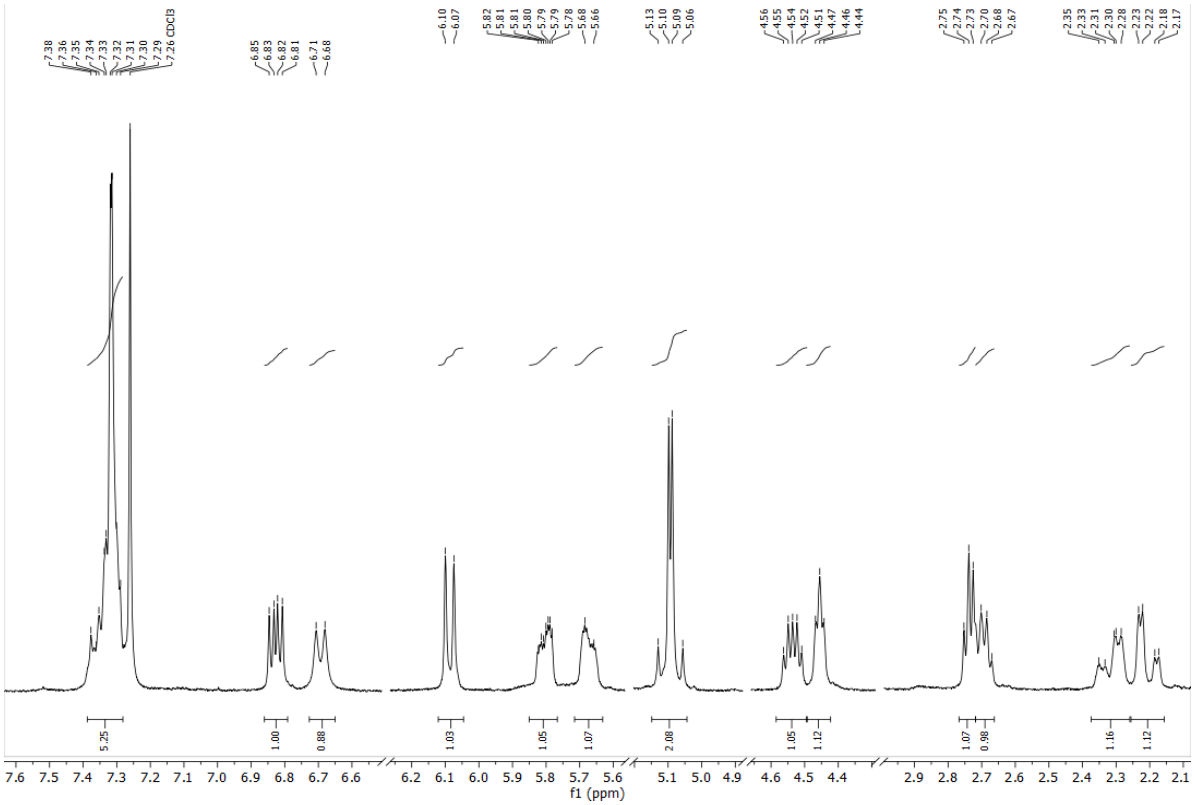


*^{13}C-spectrum of **119** in C_6D_6.*

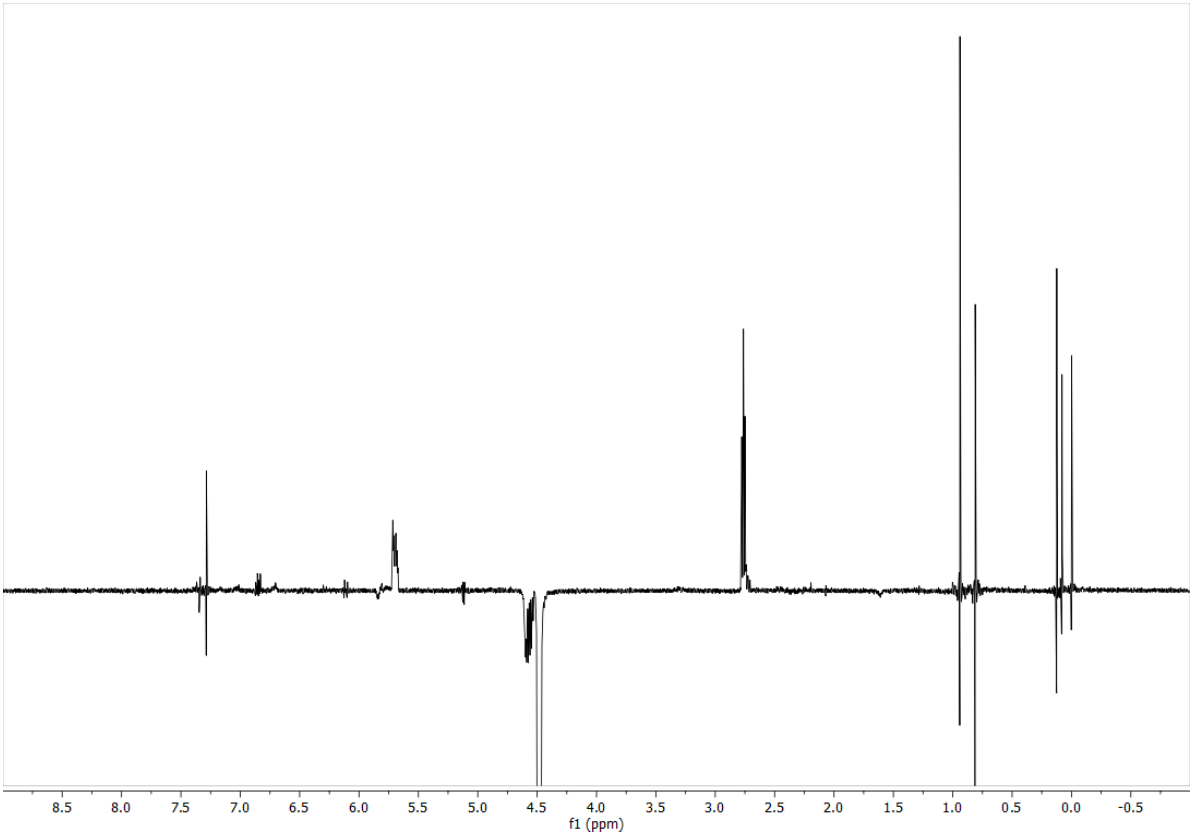
8.5.1.3 benzyl ((1*S*,4a*R*,5*S*,8a*R*)-5-((*tert*-butyldimethylsilyl)oxy)-4-oxo-1,4,4a,5,8,8a-hexahydronaphthalen-1-yl)carbamate **114**



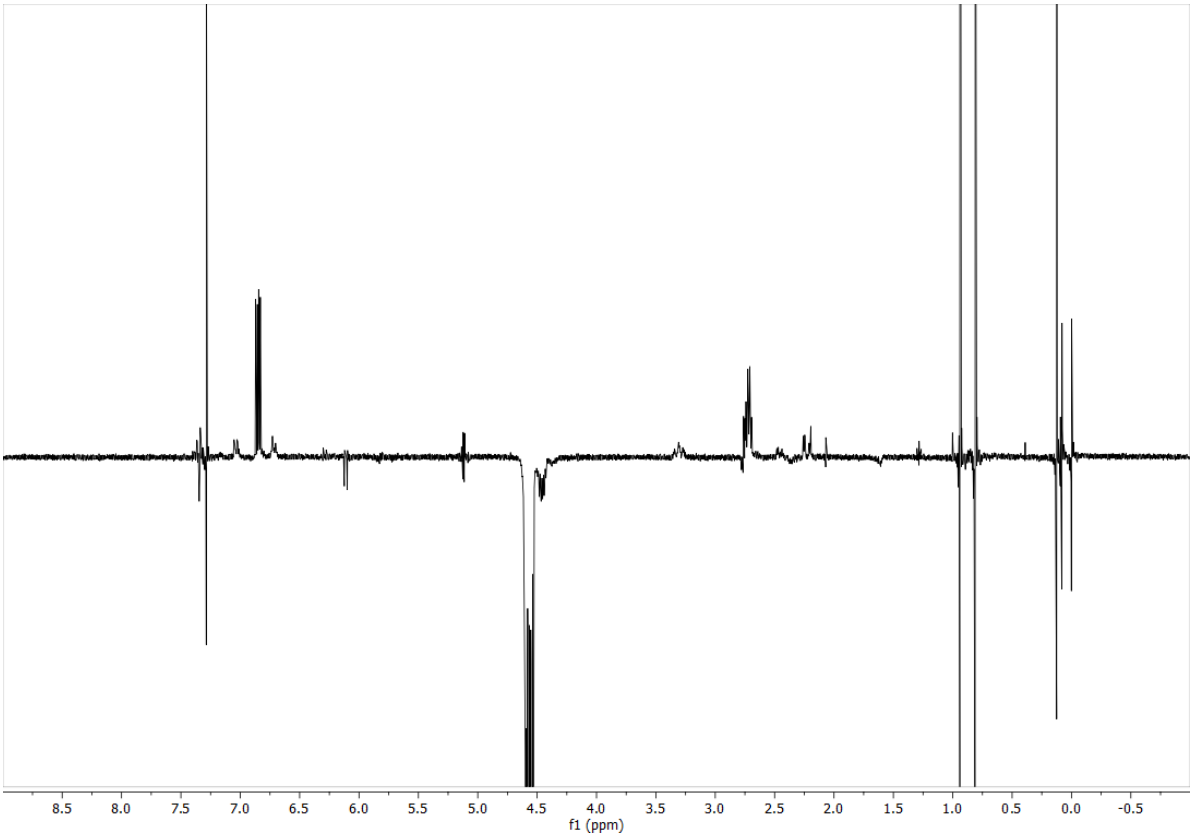
*^{1}H-spectrum of **114** in $CDCl_3$.*



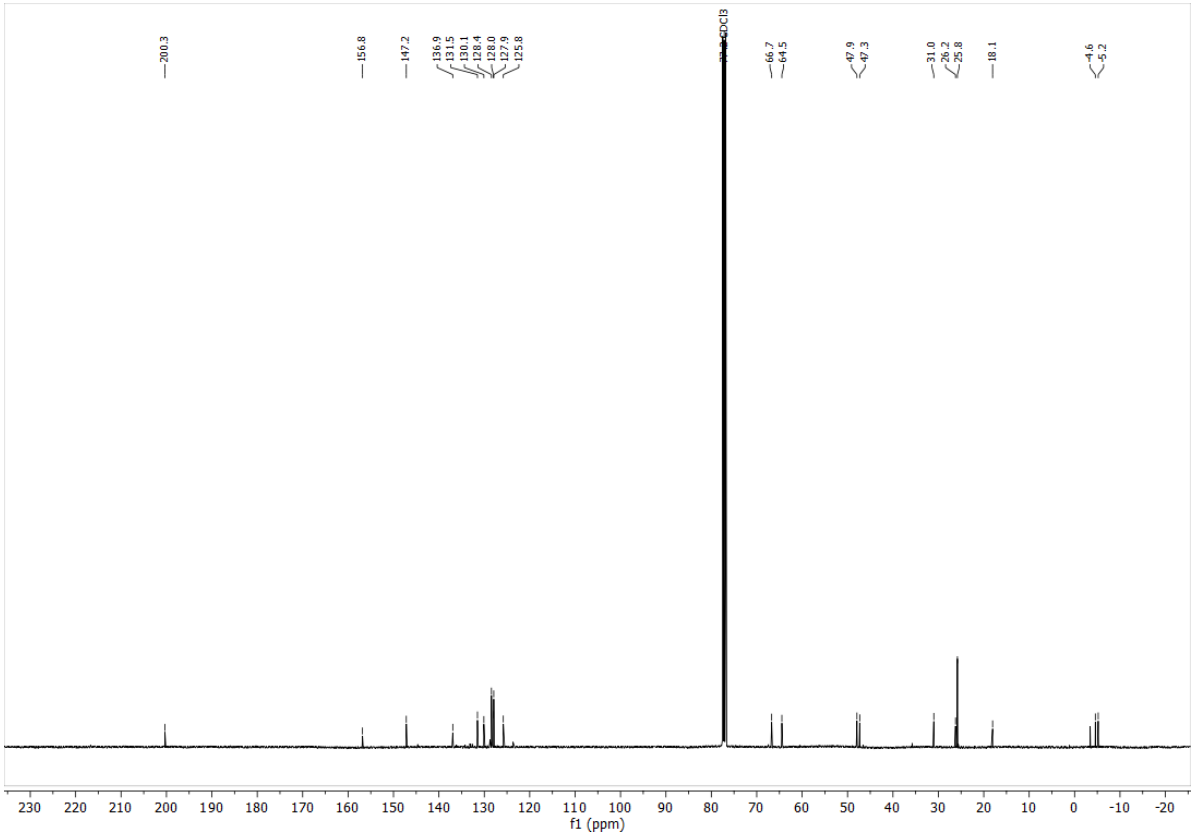
*^{1}H-spectrum of **114** in $CDCl_3$ (selected regions between 2,1-7,6 ppm).*



*NOE-spectrum of **114** in $CDCl_3$ (frequency saturation at 4,48 ppm).*



*NOE-spectrum of **114** in $CDCl_3$ (frequency saturation at 4,56 ppm).*

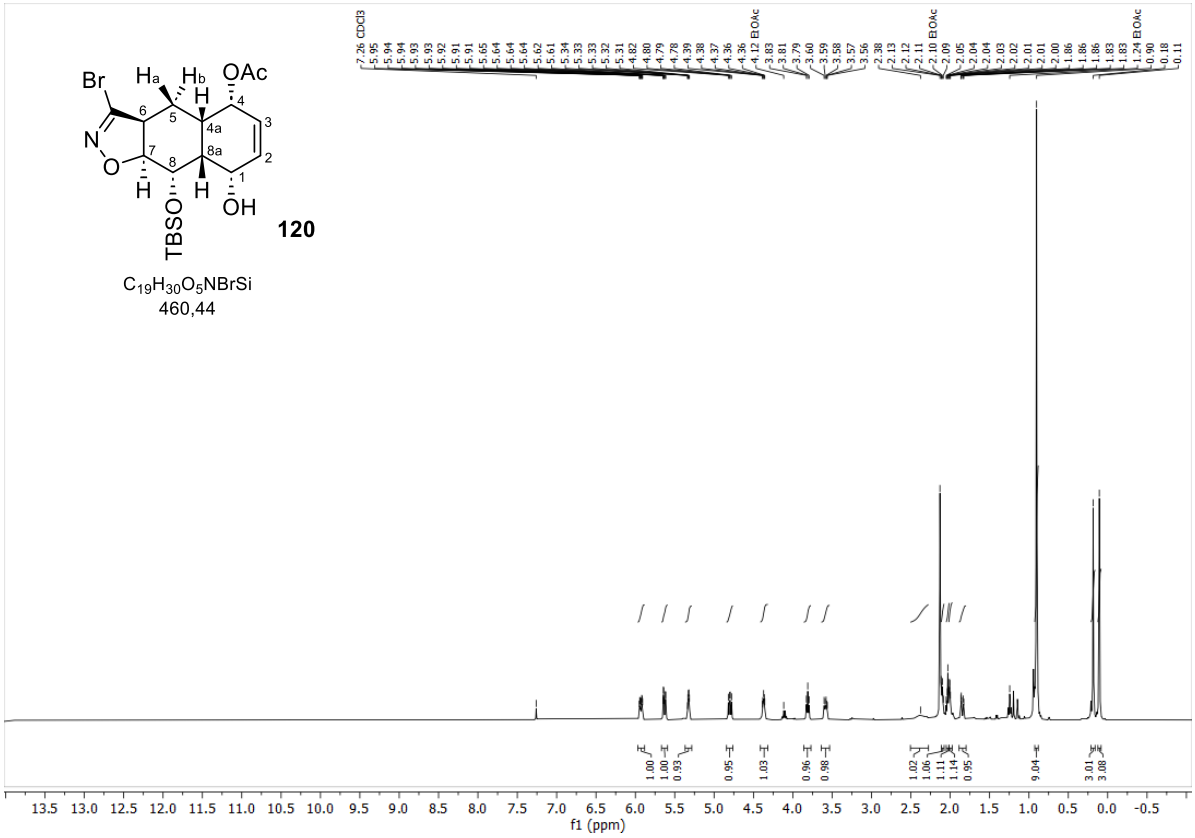


*^{13}C-spectrum of **114** in $CDCl_3$.*

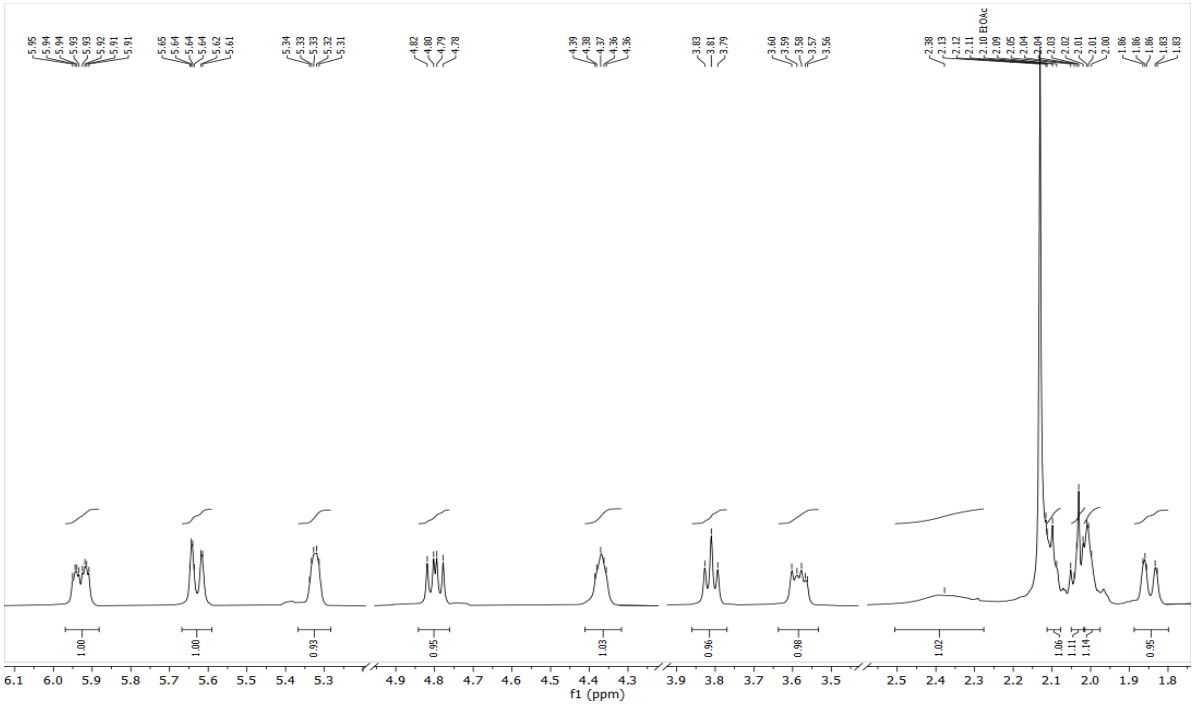
8.5.2 1,3-dipolar cycloaddition-study towards a suitable precursor for enone **105**

8.5.2.1 Derivatives from acetate **99**

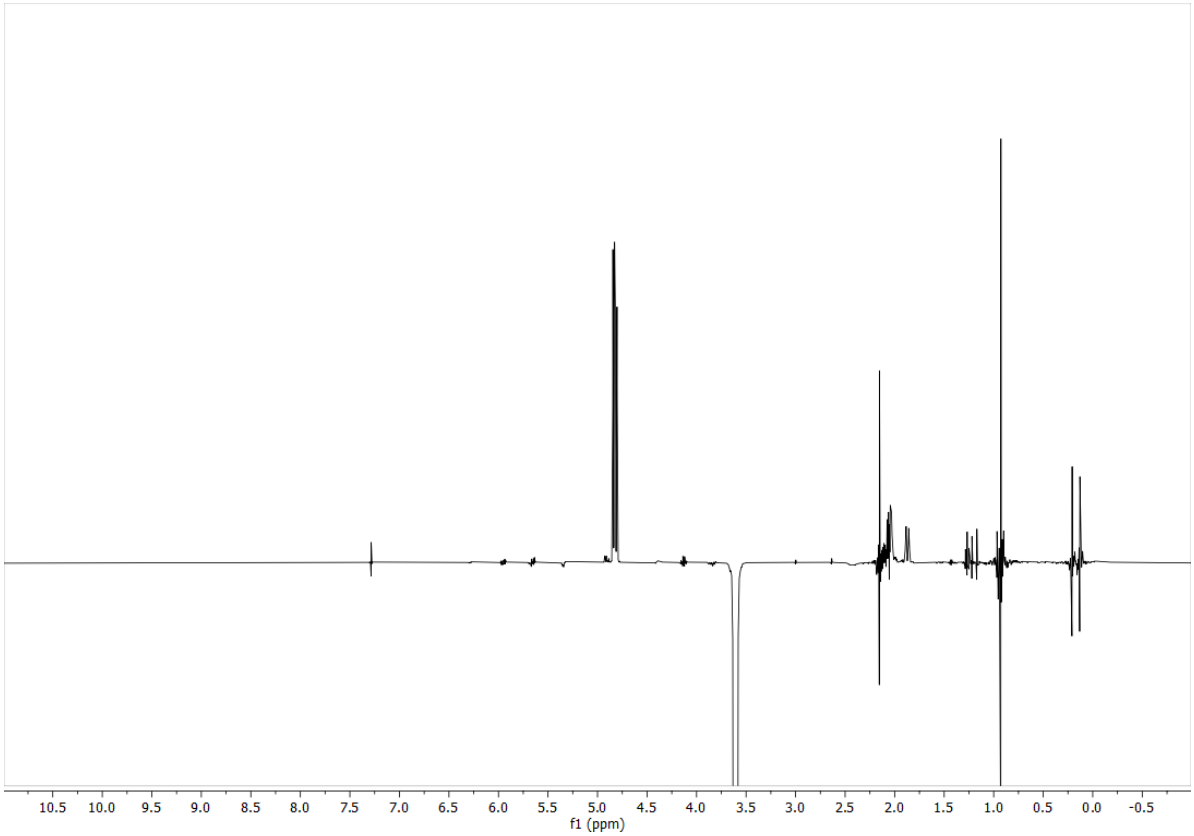
8.5.2.1.1 (3a*S*,4a*S*,5*R*,8*S*,8a*R*,9*S*,9a*S*)-3-bromo-9-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-3a,4,4a,5,8,8a,9,9a-octahydronaphtho[2,3-*d*]isoxazol-5-yl acetate **120**



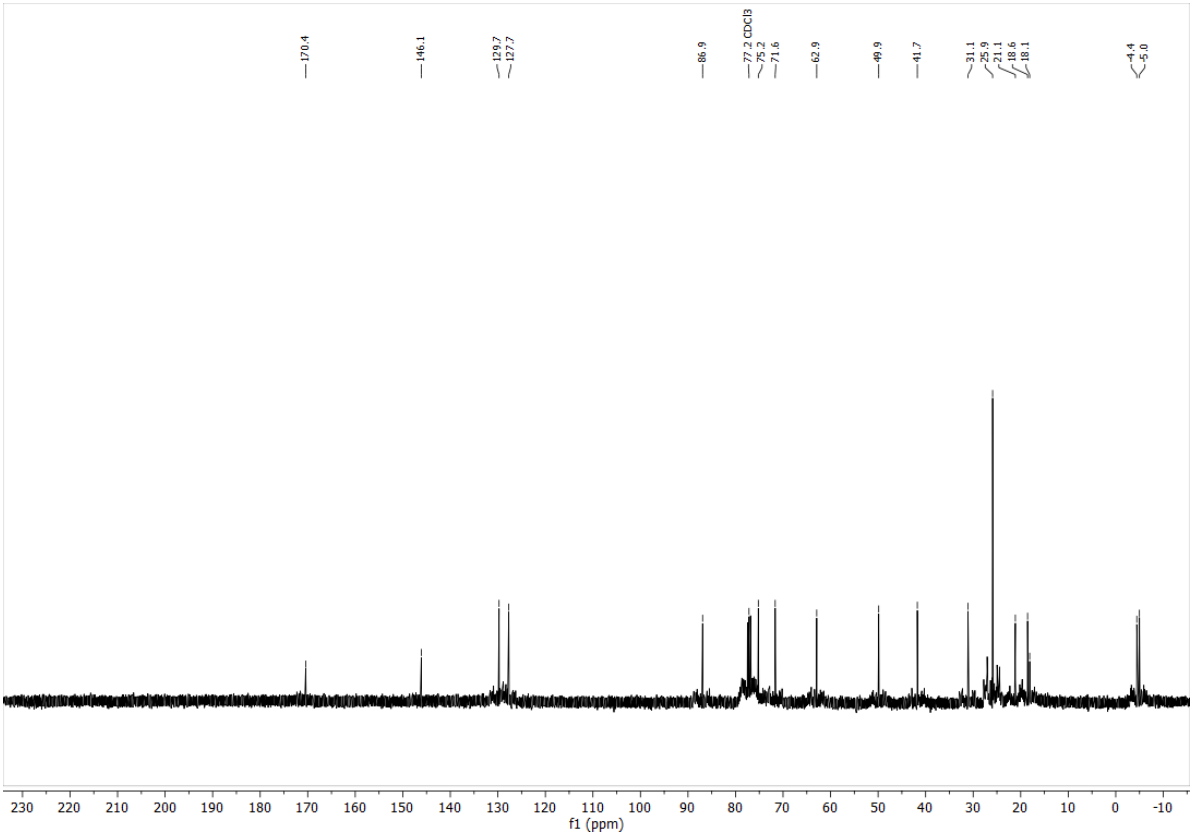
*^{1}H-spectrum of **120** in $CDCl_3$.*



*^{1}H-spectrum of **120** in $CDCl_3$ (selected regions between 1,8-6,1 ppm).*

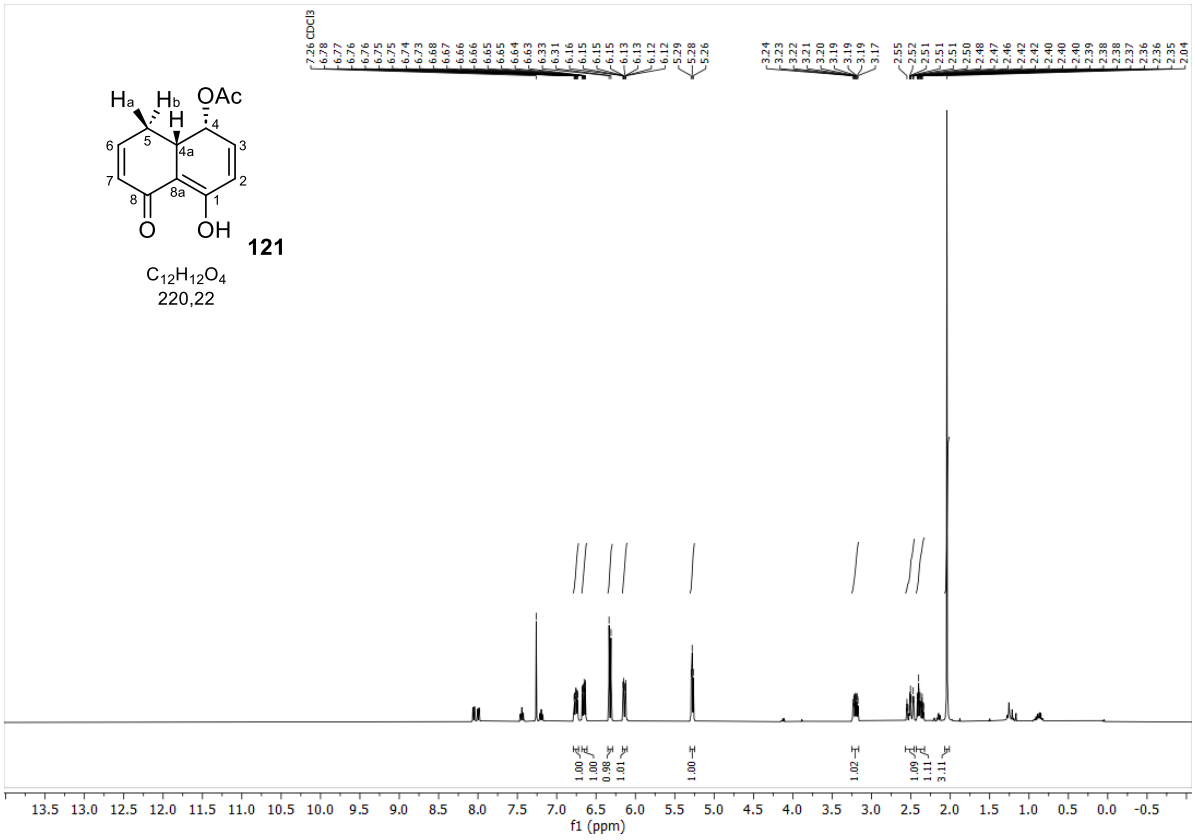


*NOE-spectrum of **120** in $CDCl_3$ (frequency saturation at 3,58 ppm).*

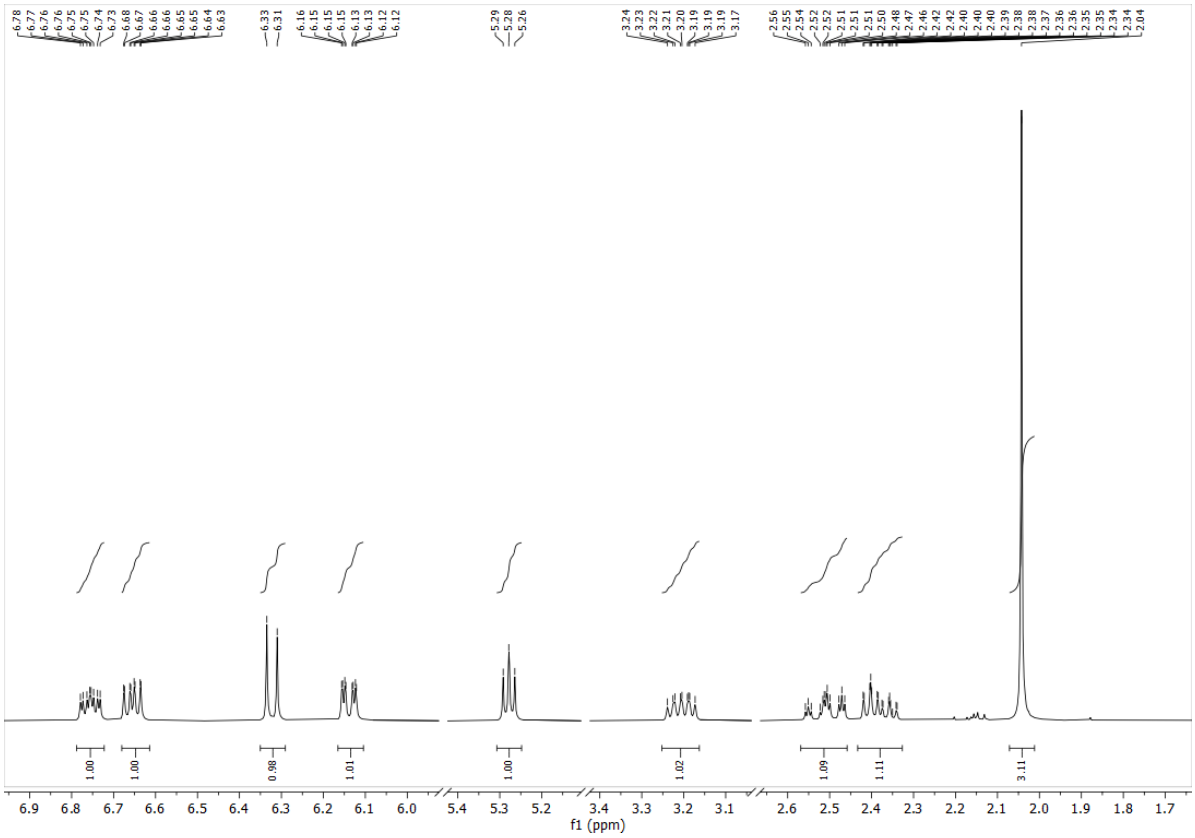


*^{13}C-spectrum of **120** in $CDCl_3$.*

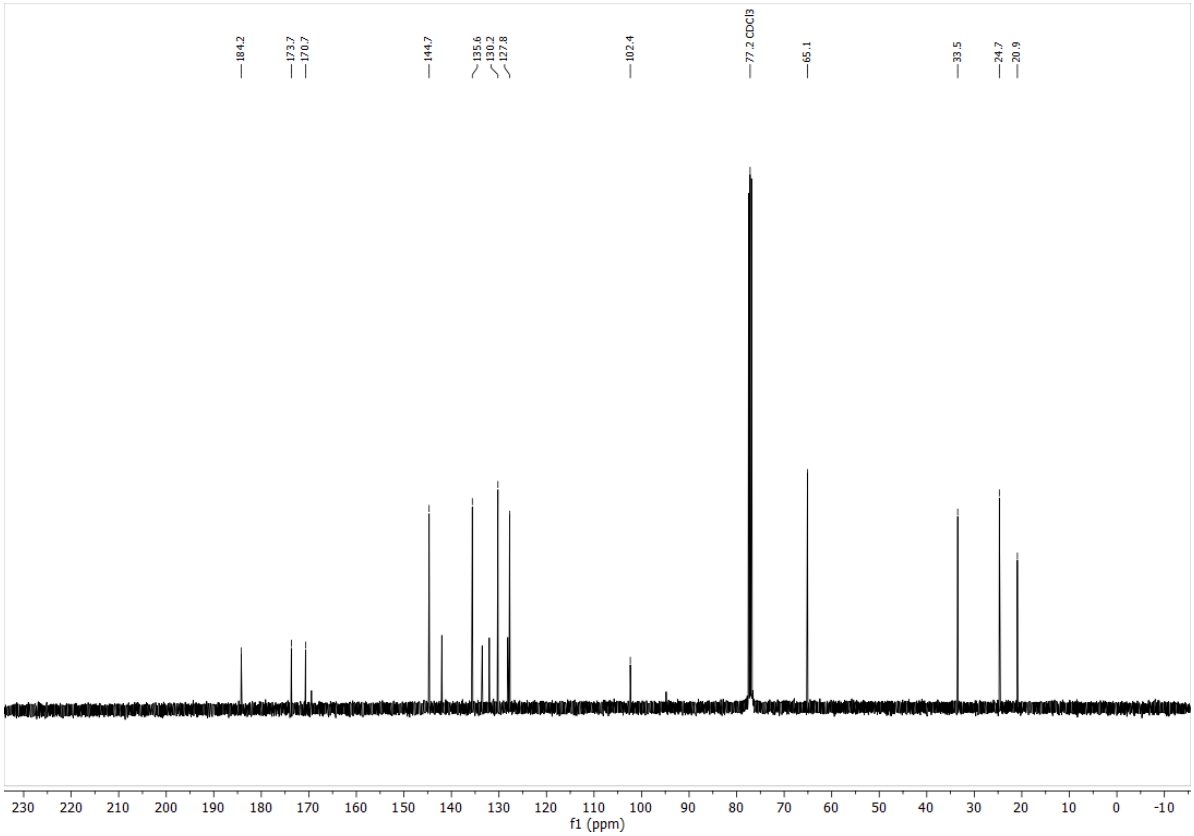
8.5.2.1.2 (1*R*,8a*S*)-4-hydroxy-5-oxo-1,5,8,8a-tetrahydronaphthalen-1-yl acetate **121**



*^{1}H-spectrum of **121** in $CDCl_3$.*

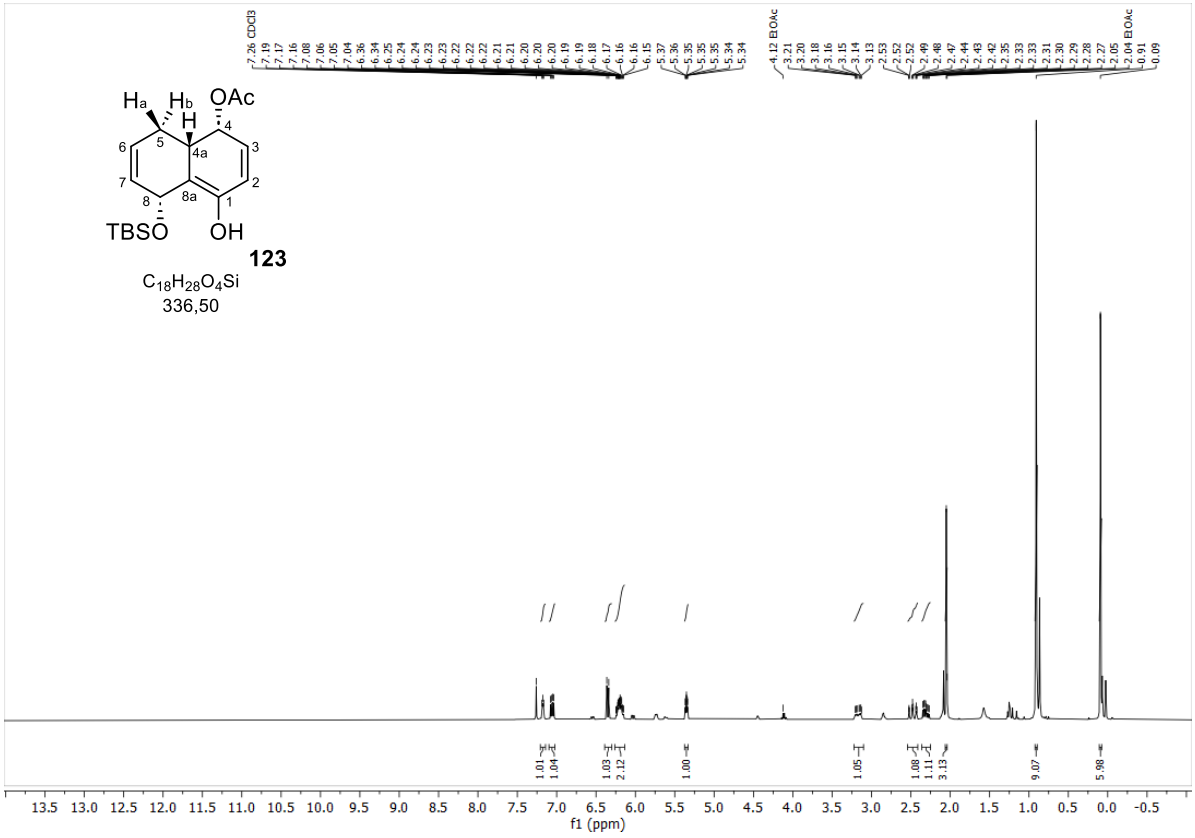


*^{1}H-spectrum of **121** in $CDCl_3$ (selected regions between 1,7-6,9 ppm).*

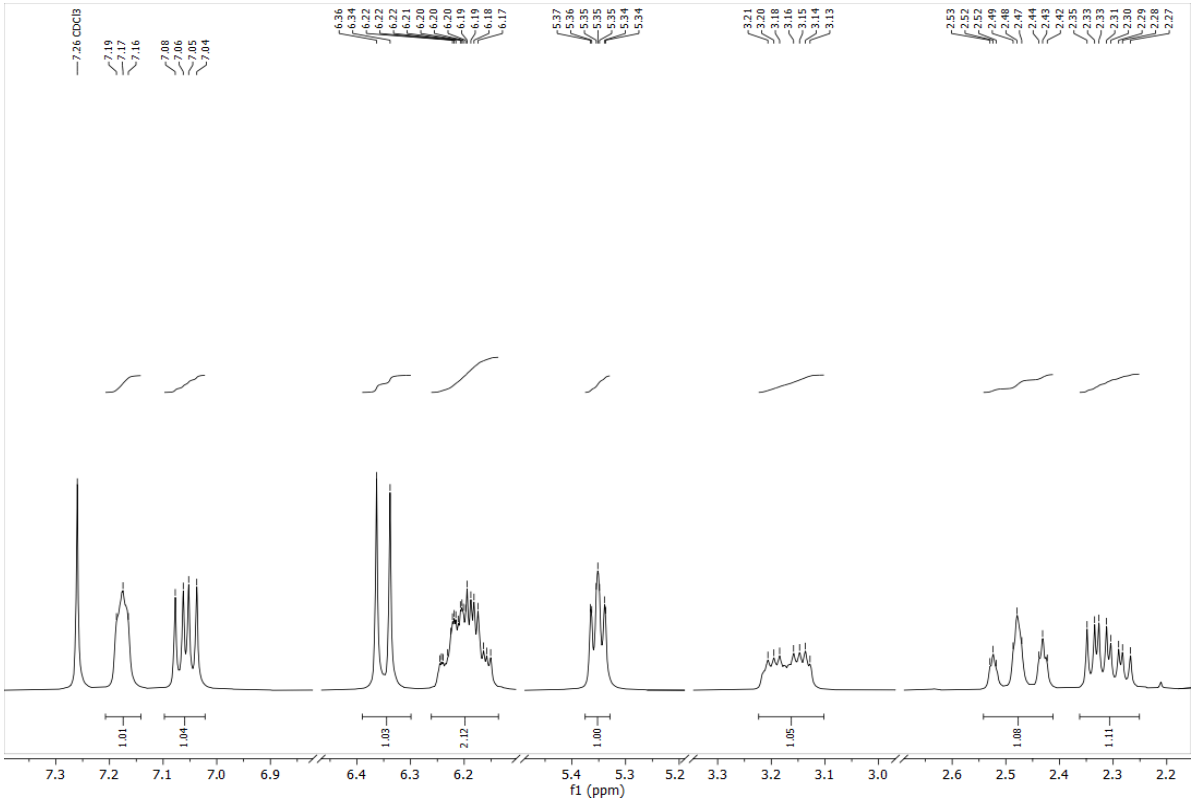


*^{13}C-spectrum of **121** in $CDCl_3$.*

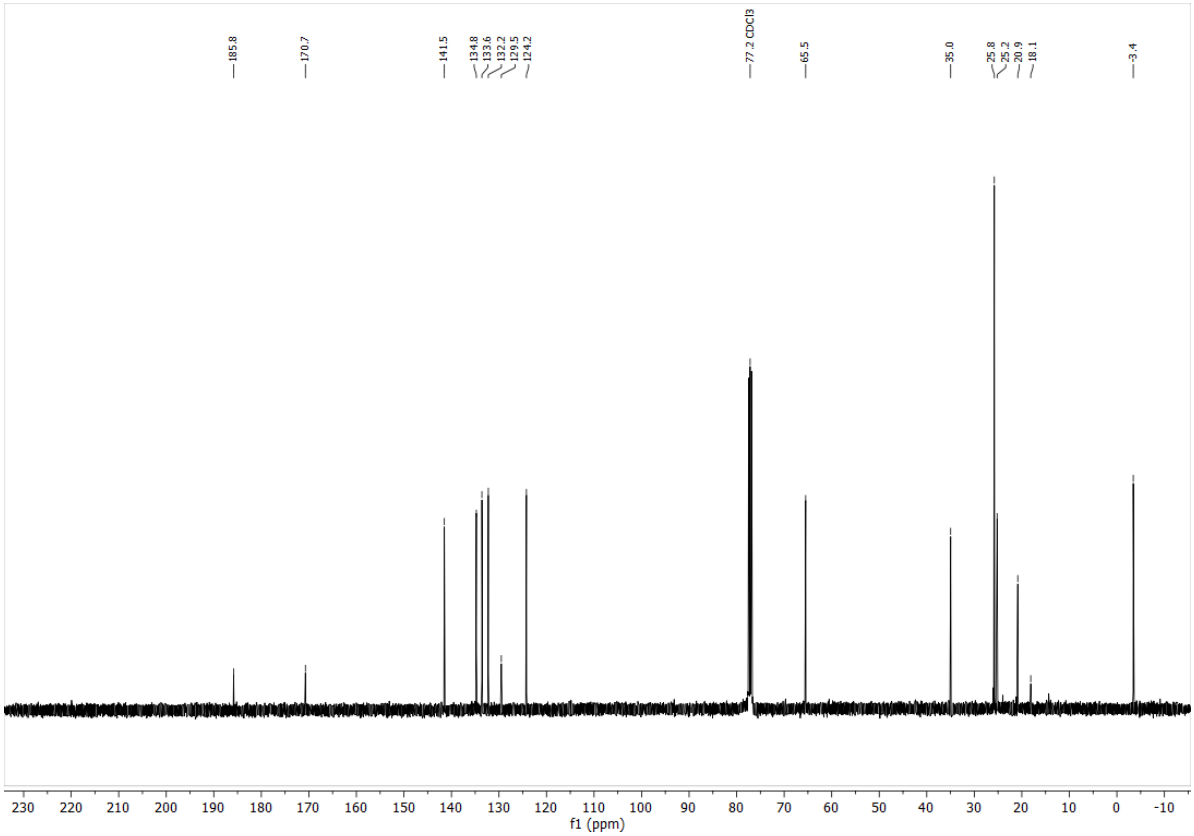
8.5.2.1.3 (1*R*,4a*S*,5*R*,8a*S*)-5-((*tert*-butyldimethylsilyl)oxy)-4-oxo-1,4,4a,5,8,8a-hexahydro-naphtha-len-1-yl acetate **123**



*^{1}H-spectrum of **123** in $CDCl_3$.*

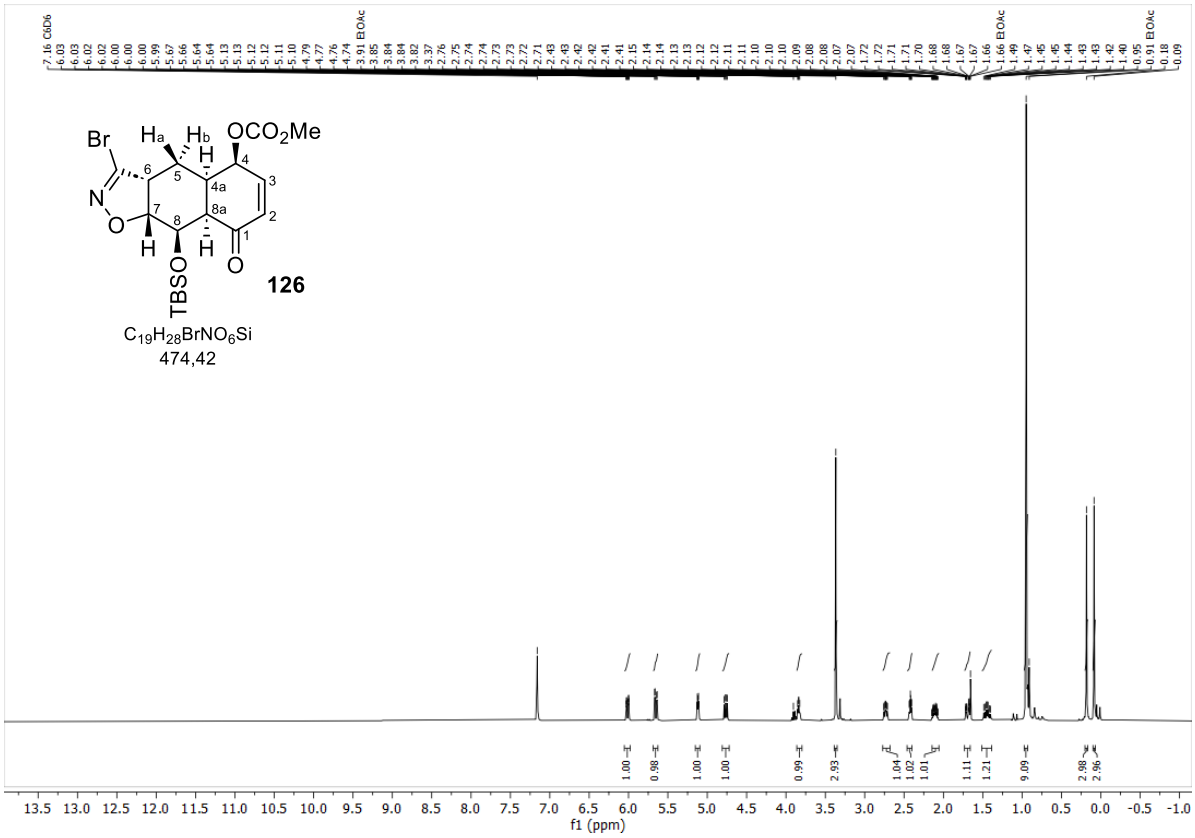


*^{1}H-spectrum of **123** in $CDCl_3$ (selected regions between 2,2-7,3 ppm).*

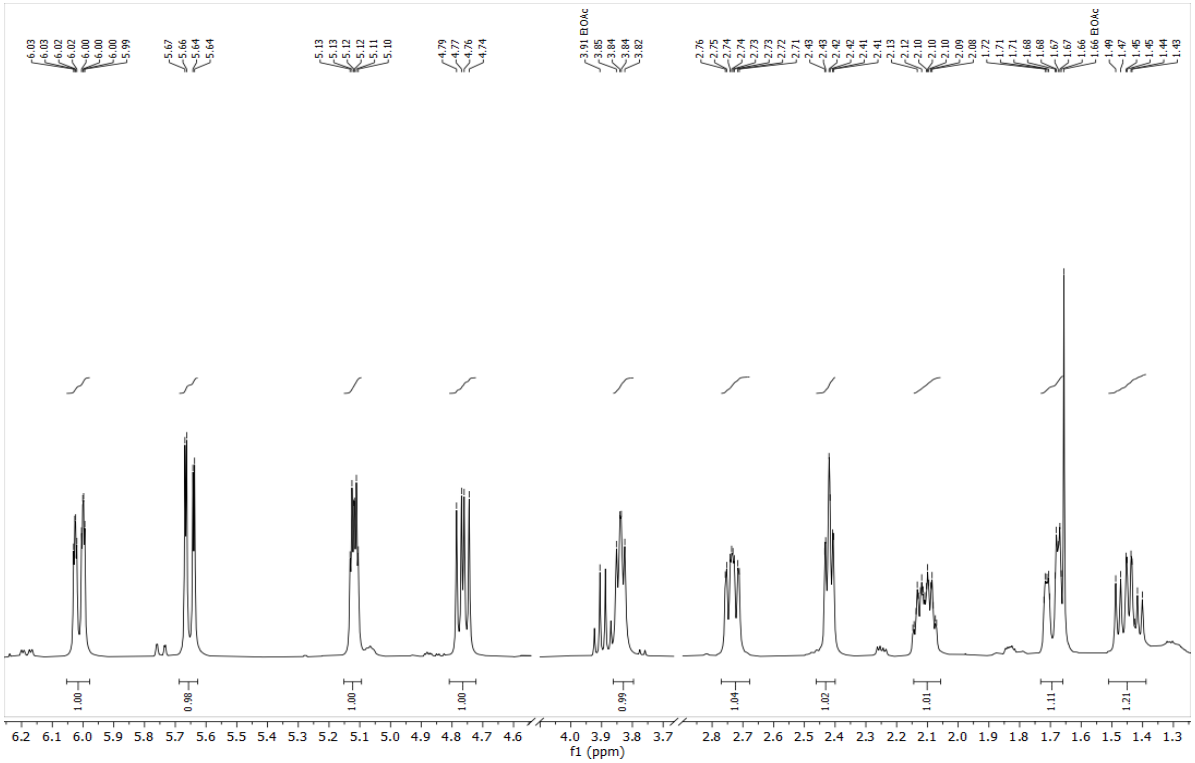


*^{13}C-spectrum of **123** in $CDCl_3$.*

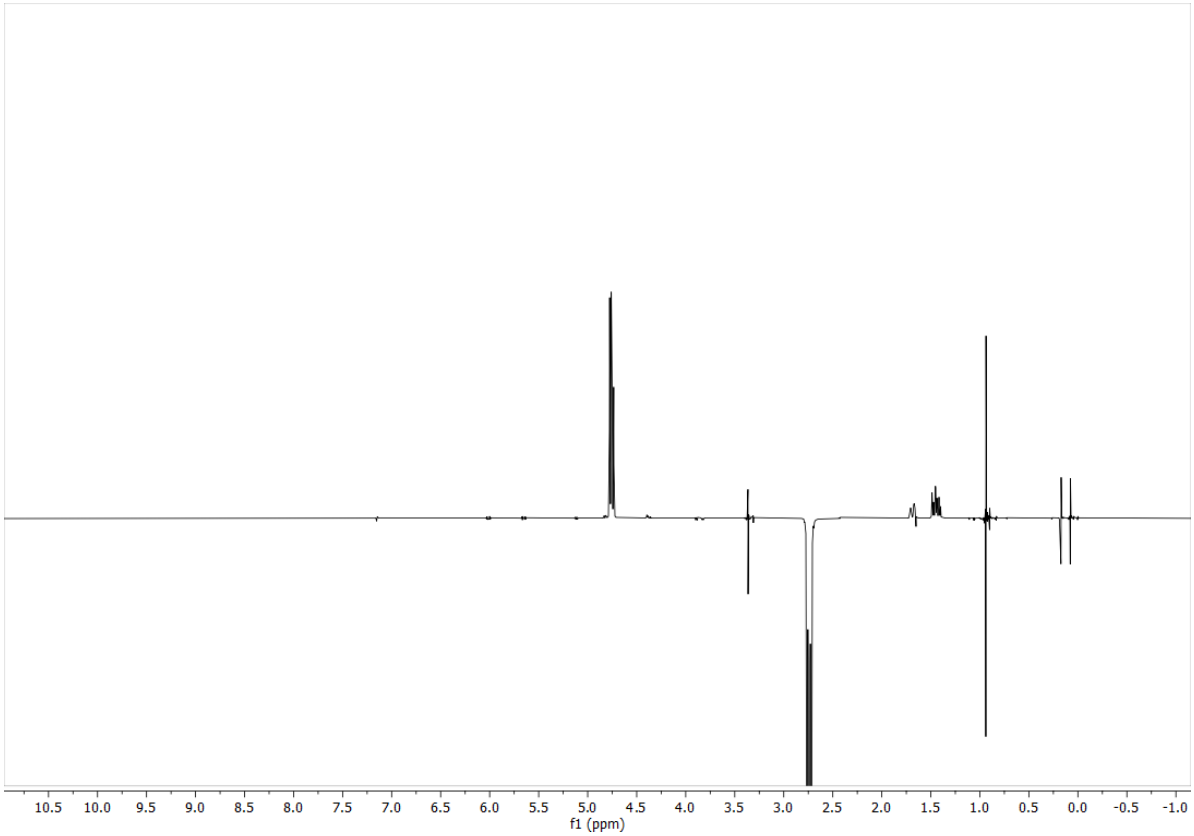
8.5.2.2 Derivatives from carbonate **118**; synthesis of (3a*R*,4a*R*,5*S*,8a*R*,9*R*,9a*R*)-3-bromo-9-((*tert*- butyldimethylsilyl)oxy)-8-oxo-3a,4,4a,5,8,8a,9,9a-octahydronaphtho[2,3-*d*]isoxazol-5-yl methyl carbonate **126**



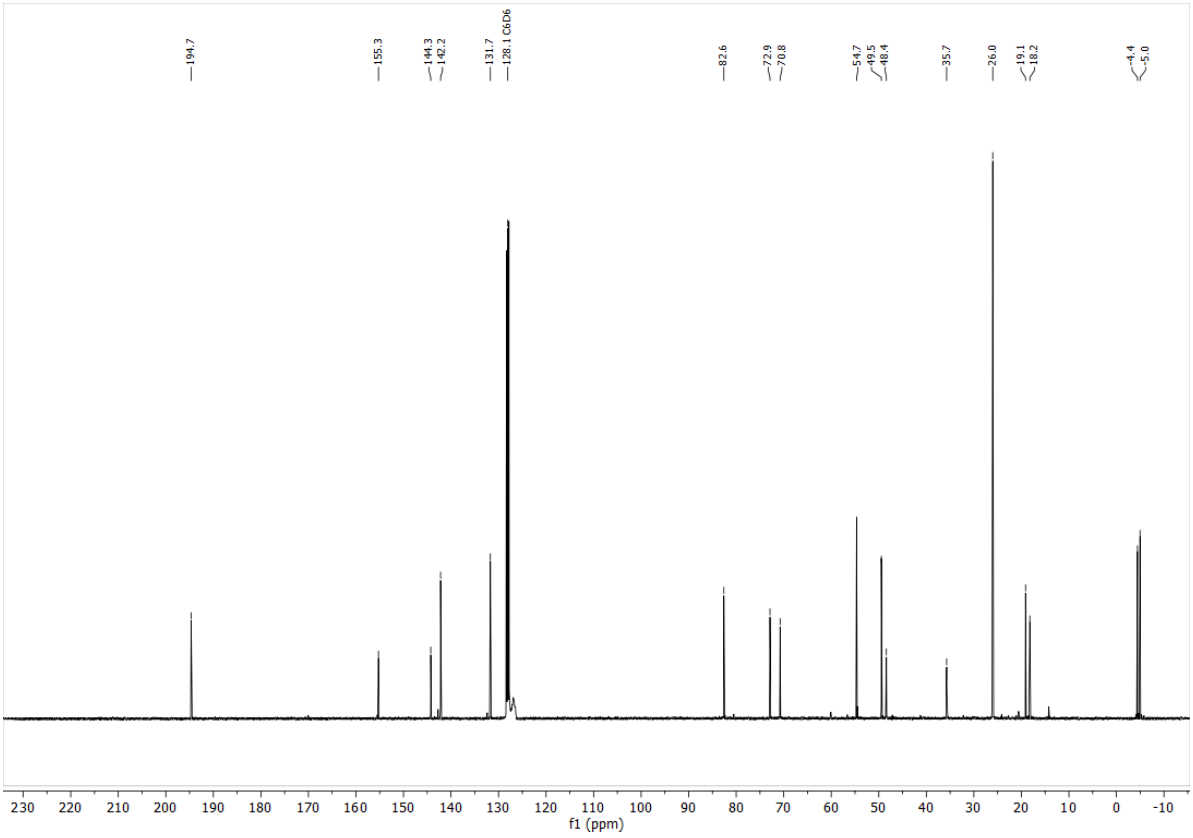
*^{1}H-spectrum of **126** in C_6D_6.*



*^{1}H-spectrum of **126** in C_6D_6 (selected regions between 1,3-6,2 ppm).*



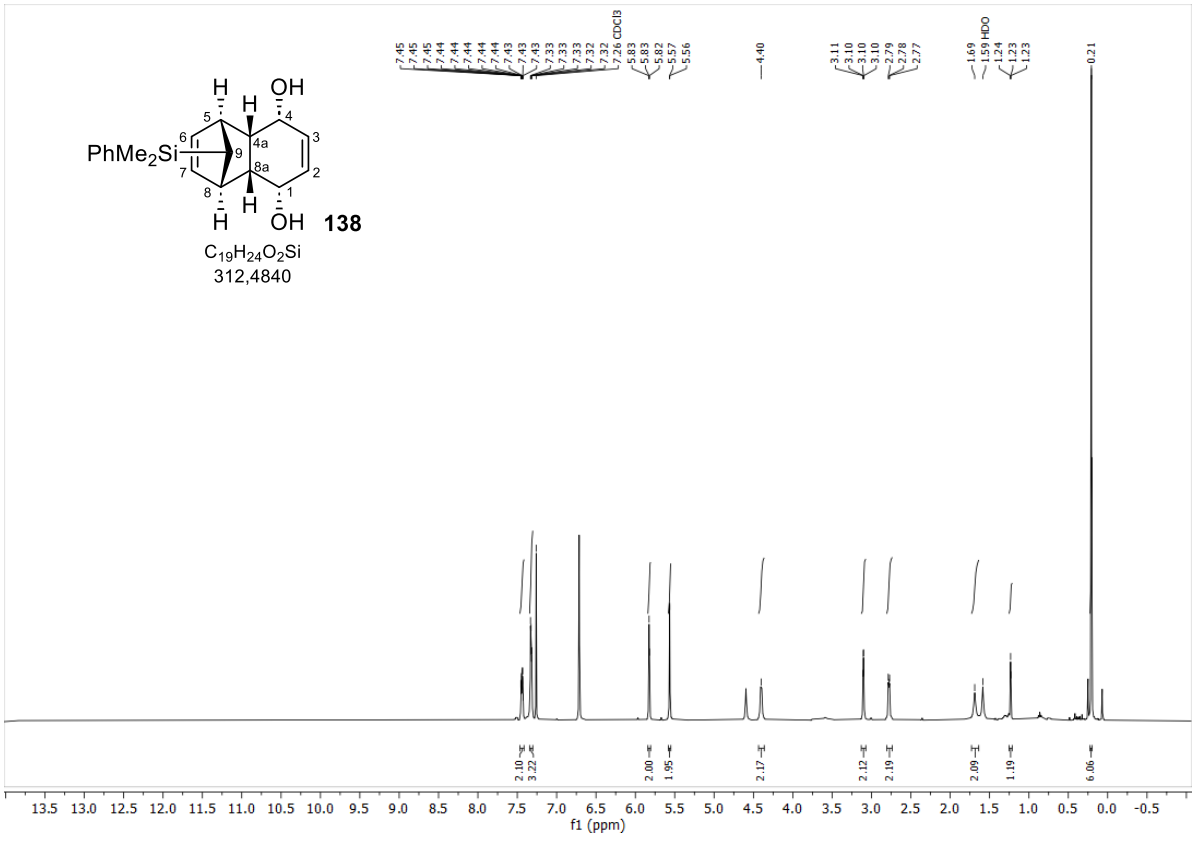
*NOE-spectrum of **126** in C_6D_6 (frequency saturation at 2,74 ppm).*



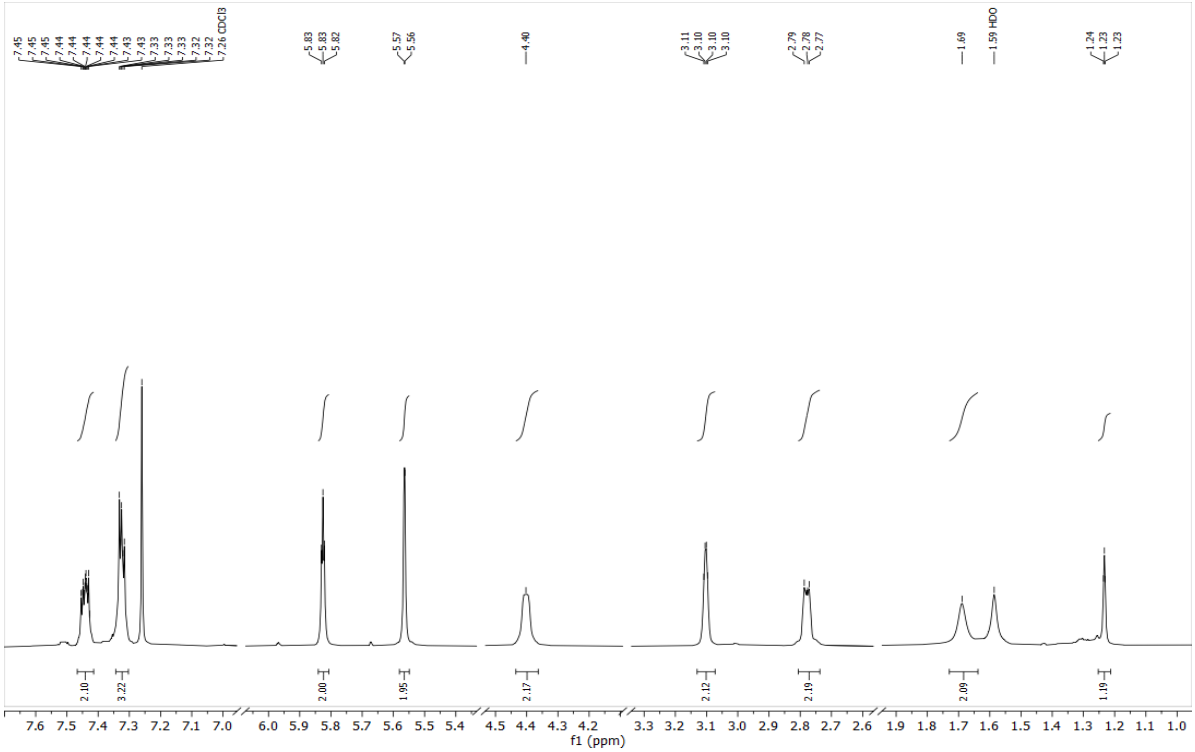
*^{13}C-spectrum of **126** in C_6D_6.*

8.5.3 Enone **134**

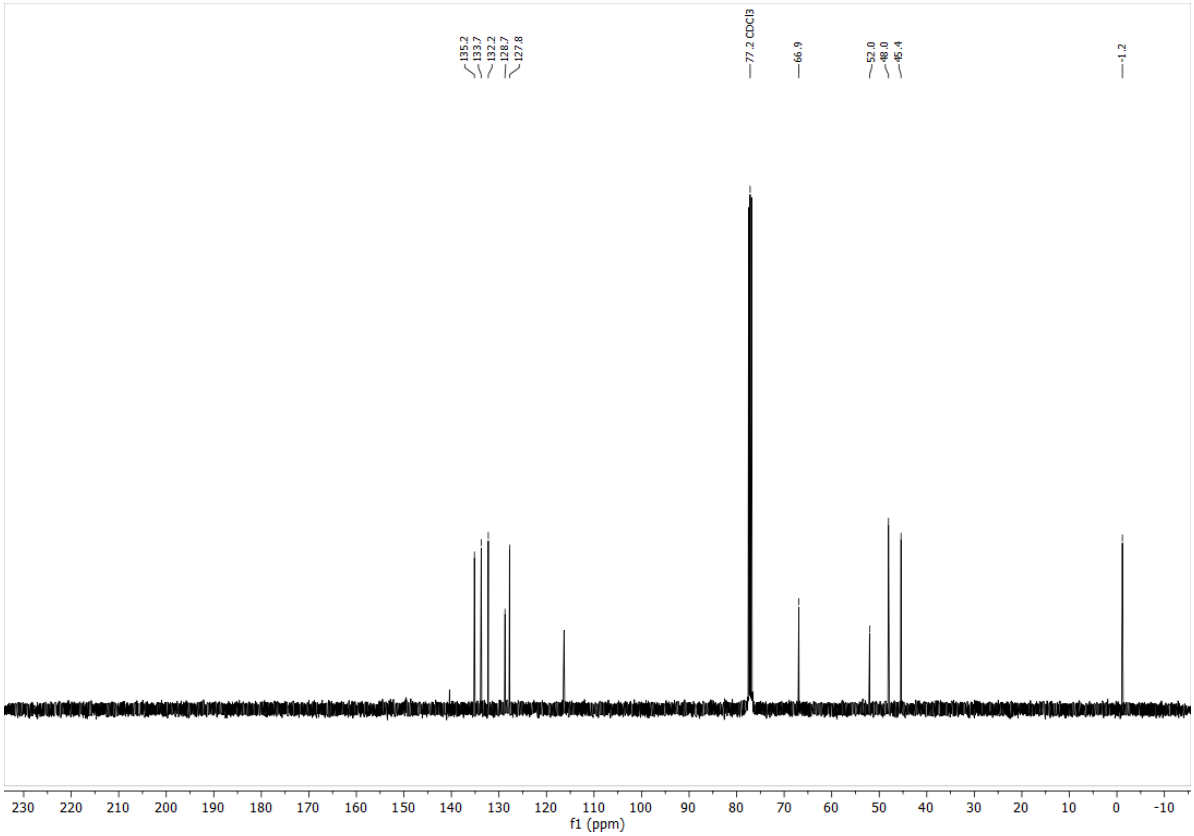
8.5.3.1 (1*R*,4*S*,4a*S*,5*S*,8*R*,8a*R*,9*S*)-9-(dimethyl(phenyl)silyl)-1,4,4a,5,8,8a-hexahydro-1,4-methanonaphthalene-5,8-diol **138**



*^{1}H-spectrum of **138** in $CDCl_3$.*

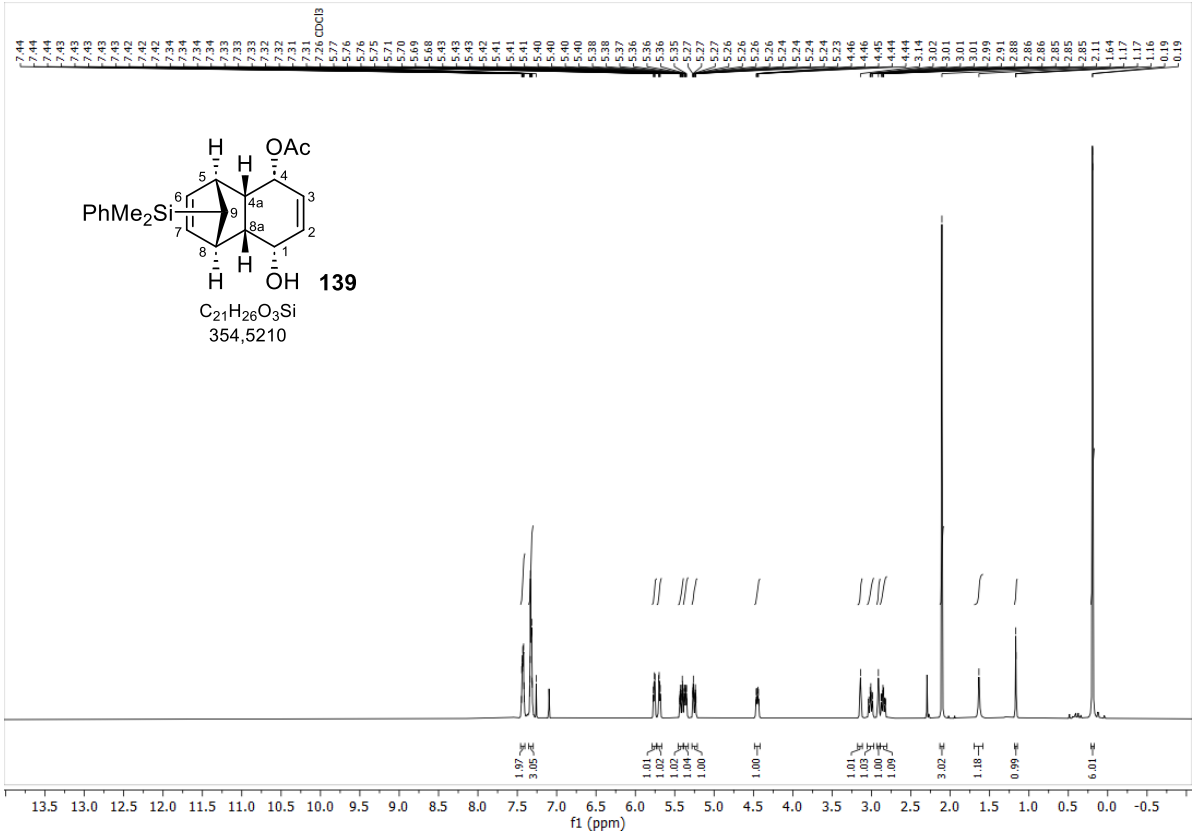


*^{1}H-spectrum of **138** in $CDCl_3$ (selected regions between 1,0-7,6 ppm).*

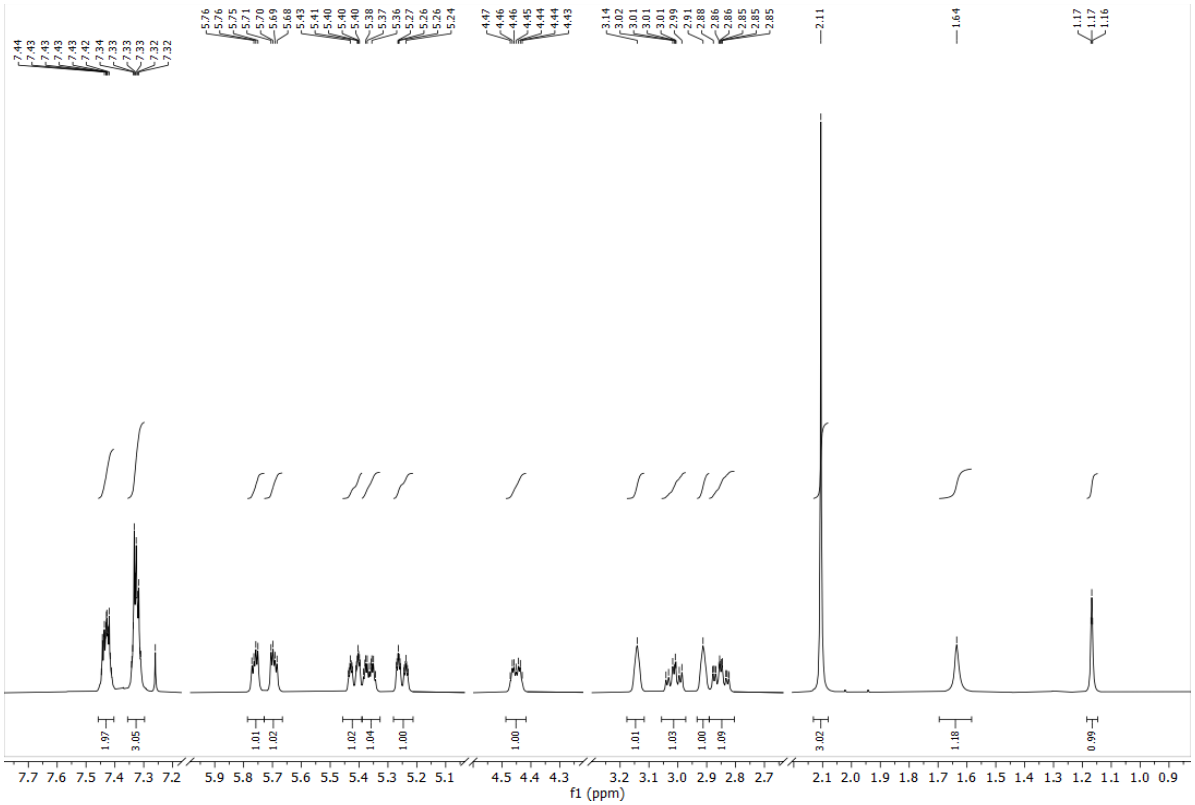


*^{13}C-spectrum of **138** in $CDCl_3$.*

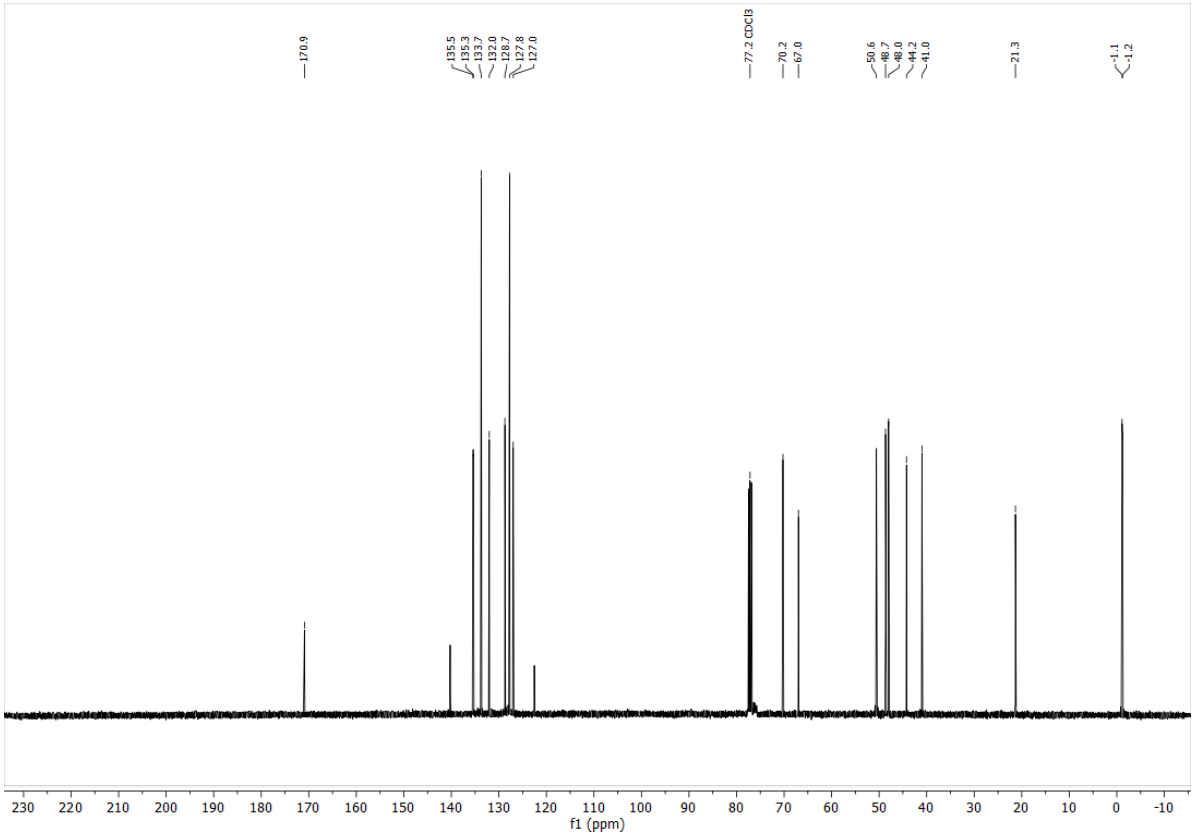
8.5.3.2 (1*S*,4*R*,4a*R*,5*R*,8*S*,8a*S*,9*S*)-9-(dimethyl(phenyl)silyl)-8-hydroxy-1,4,4a,5,8,8a-hexahydro-1,4-methanonaphthalen-5-yl acetate **139**



*^{1}H-spectrum of **139** in $CDCl_3$.*

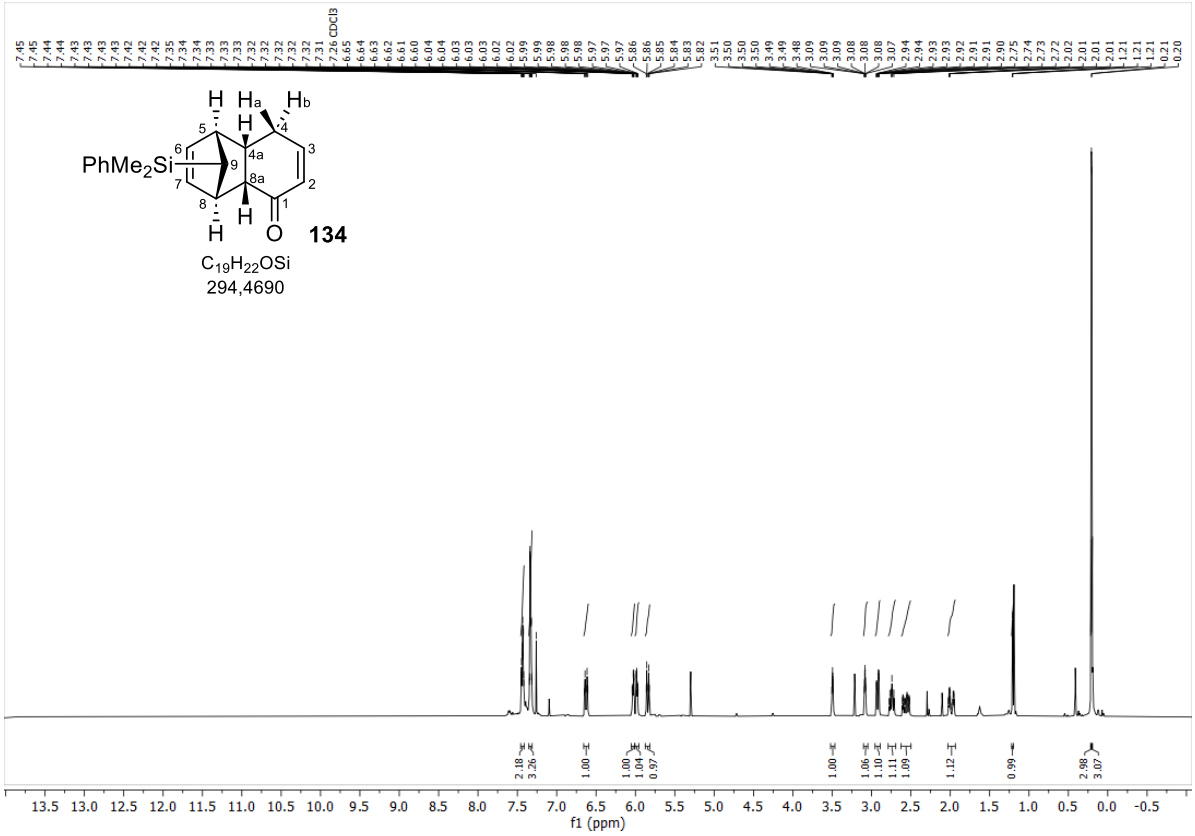


*^{1}H-spectrum of **139** in $CDCl_3$ (selected regions between 0,9-7,7 ppm).*

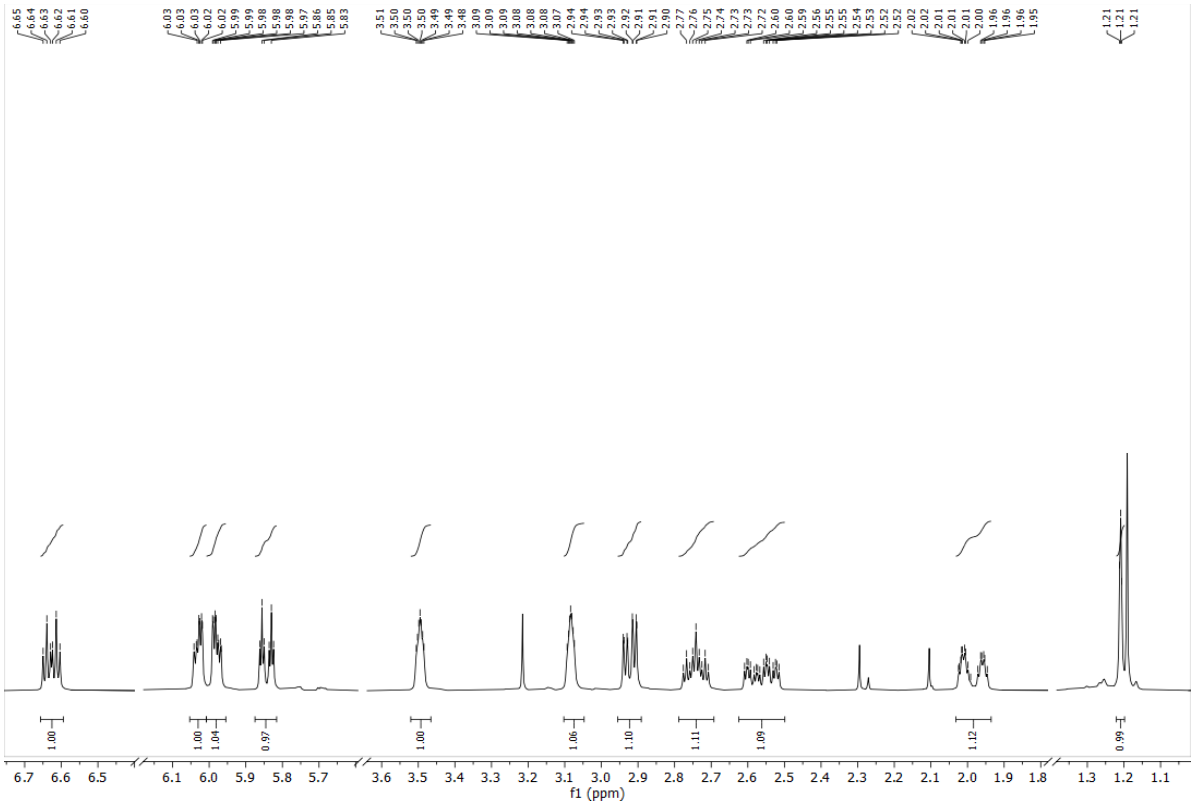


*^{13}C-spectrum of **139** in $CDCl_3$.*

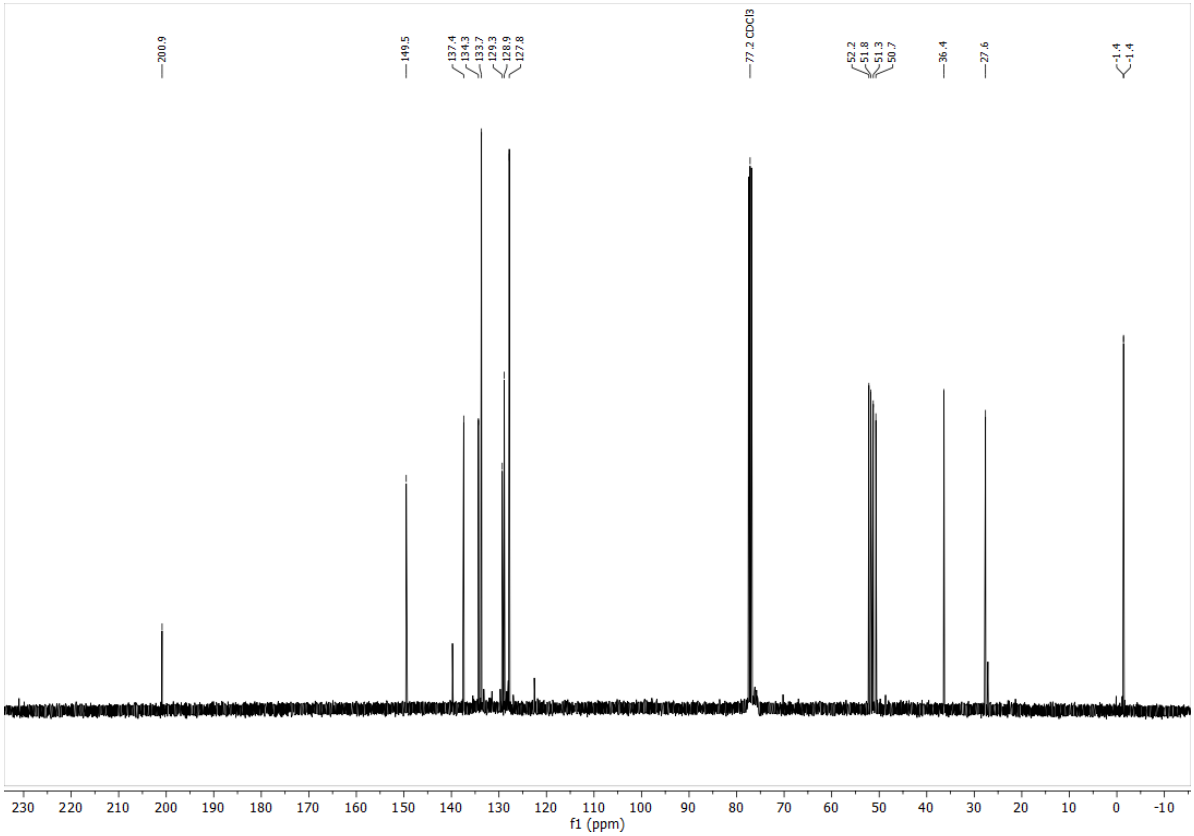
8.5.3.3 (1*R*,4*S*,4a*S*,8a*R*,9*R*)-9-(dimethyl(phenyl)silyl)-4,4a,8,8a-tetrahydro-1,4-methanonaphthalen-5(1*H*)-one **134**



*^{1}H-spectrum of **134** in $CDCl_3$.*



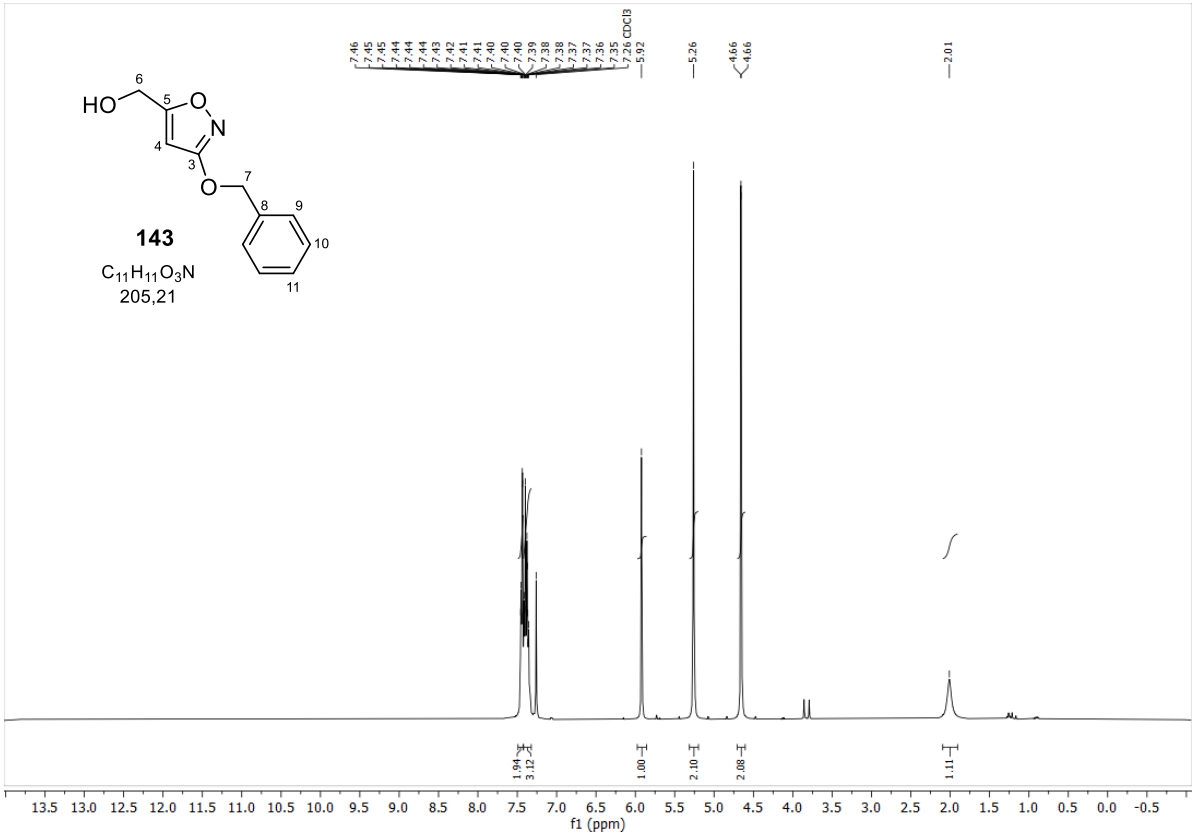
*^{1}H-spectrum of **134** in $CDCl_3$ (selected regions between 1,1-6,7 ppm).*



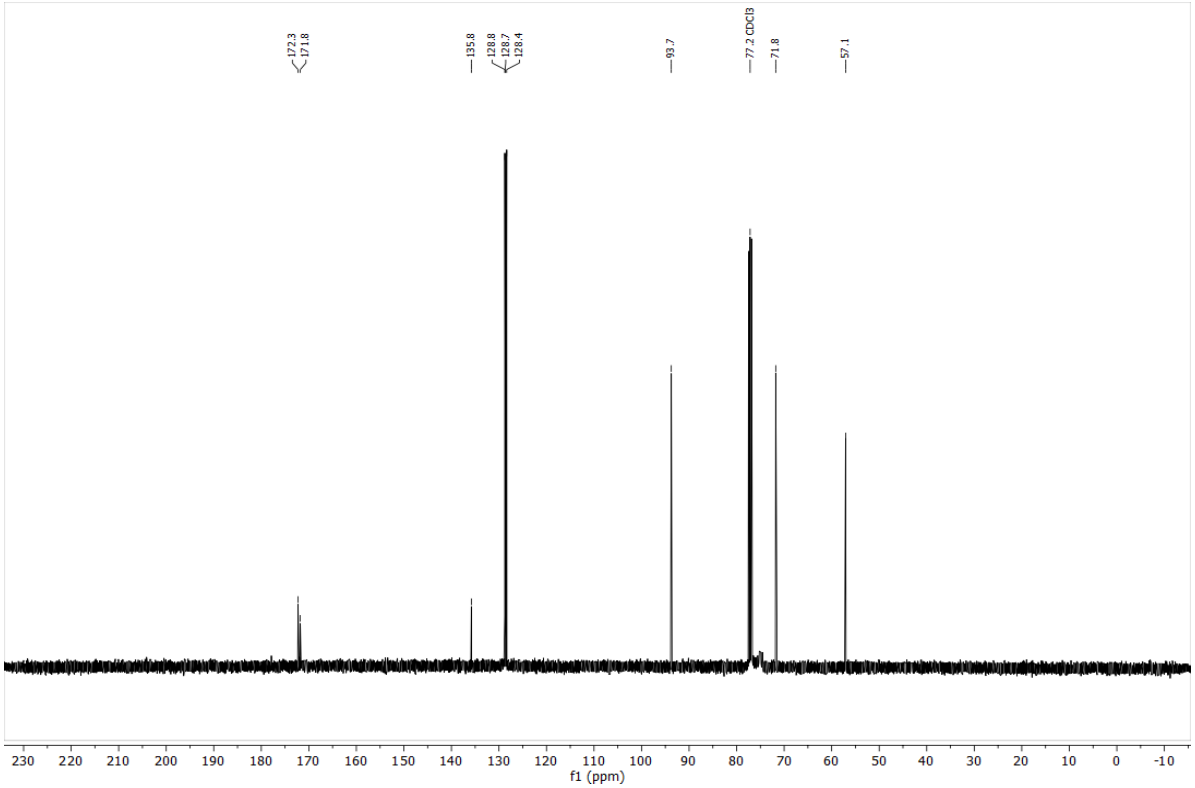
*^{13}C-spectrum of **134** in $CDCl_3$.*

8.5.4 Isoxazoles **145** and **141** (attempted)

8.5.4.1 3-benzyloxy-5-(hydroxymethyl)isoxazole **143**

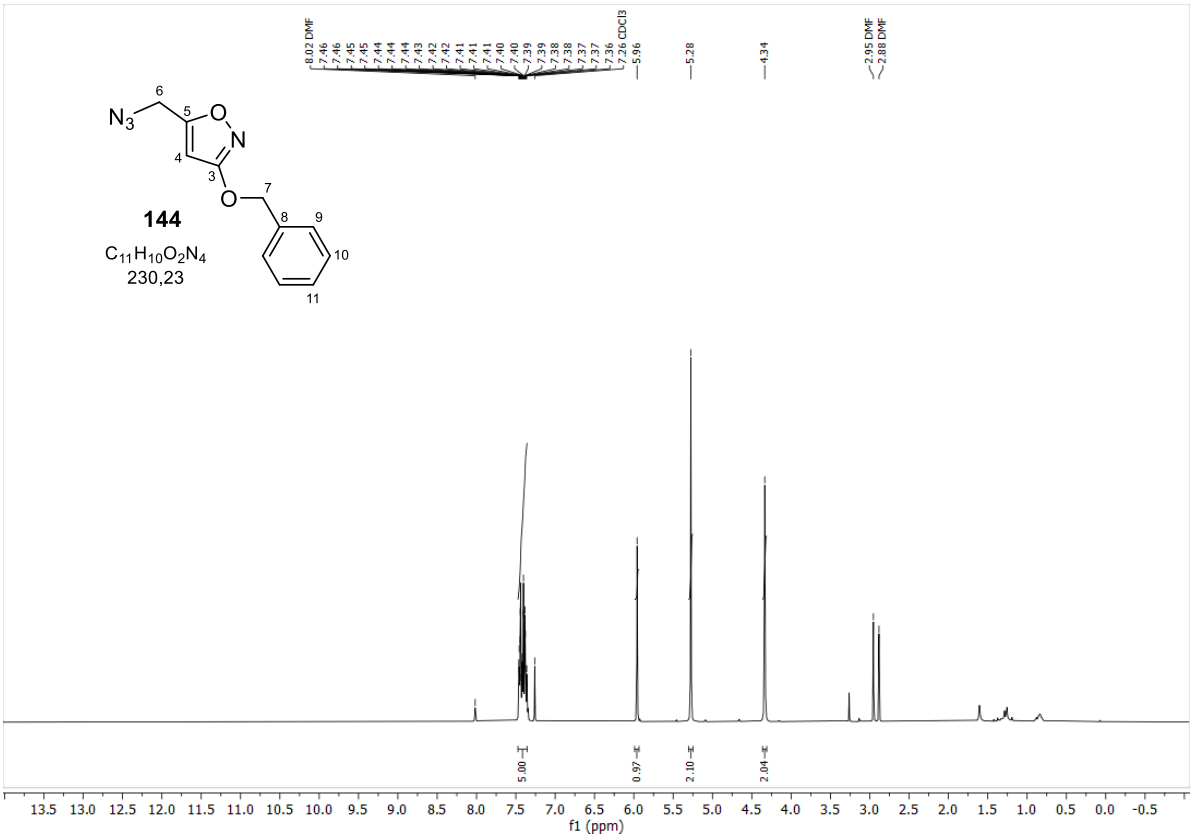


*^{1}H-spectrum of **143** in $CDCl_3$.*

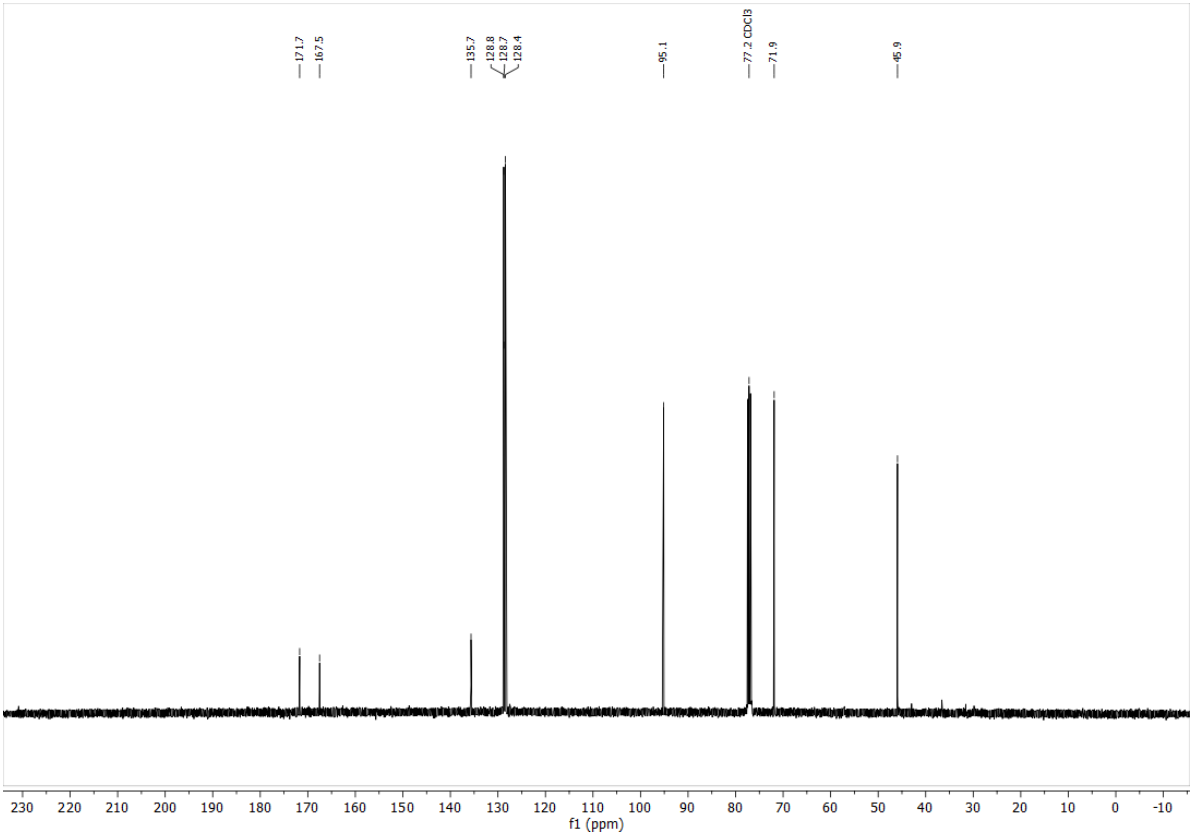


*^{13}C-spectrum of **143** in $CDCl_3$.*

8.5.4.2 5-(azidomethyl)-3-(benzyloxy)isoxazole **144**

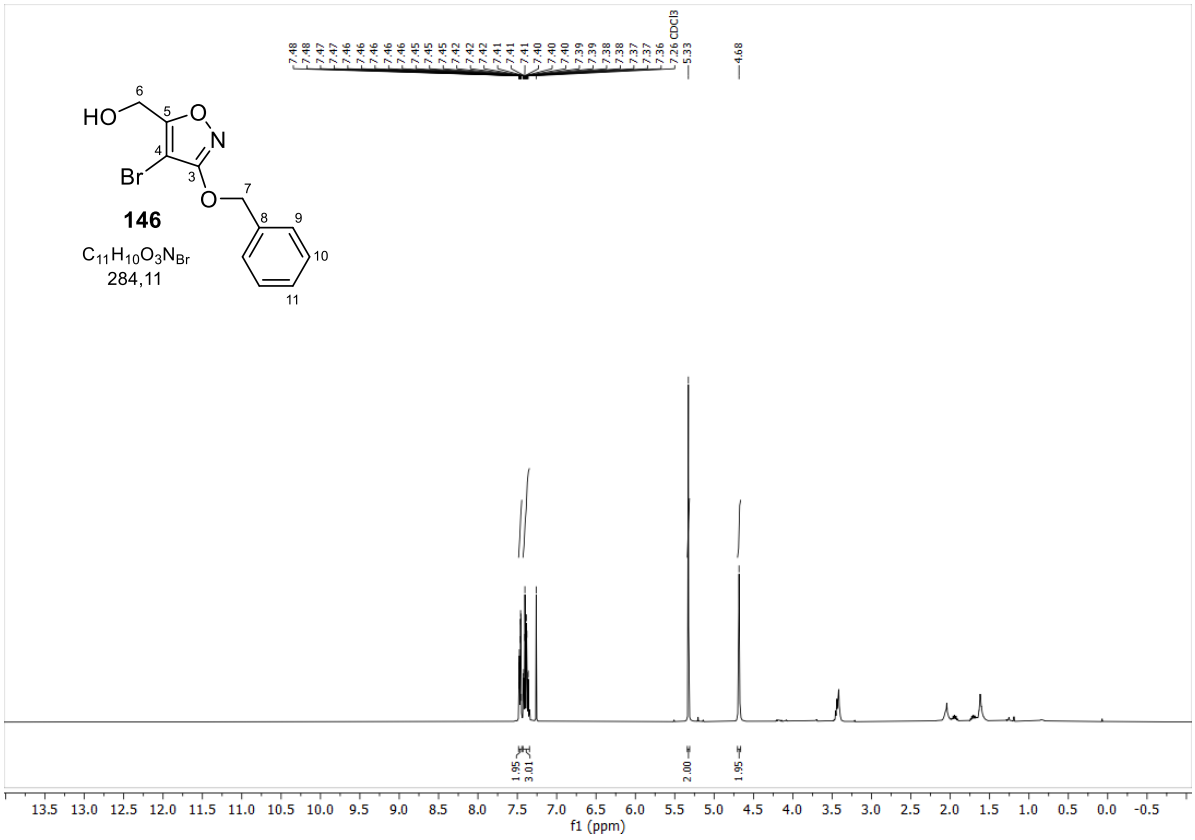


*^{1}H-spectrum of **144** in $CDCl_3$.*

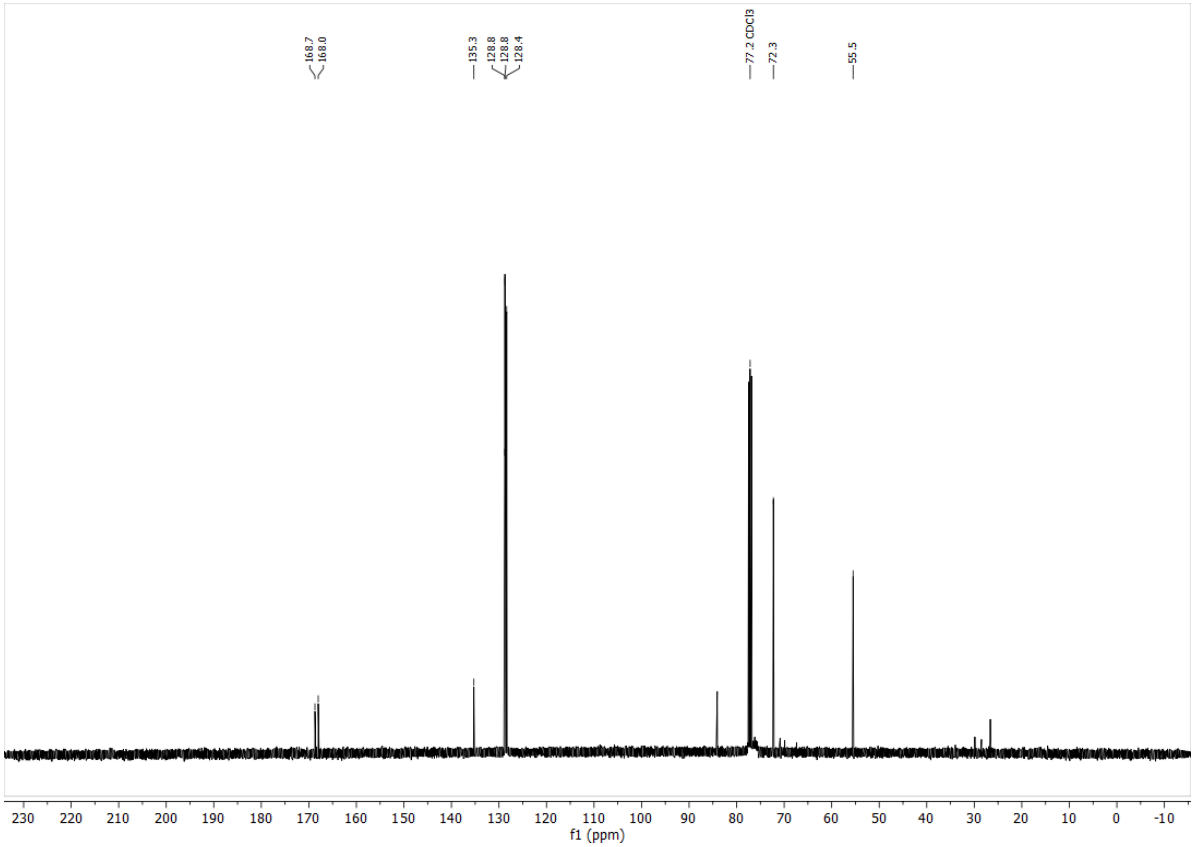


*^{13}C-spectrum of **144** in $CDCl_3$.*

8.5.4.3 (3-(benzyloxy)-4-bromoisoxazol-5-yl)methanol **146**

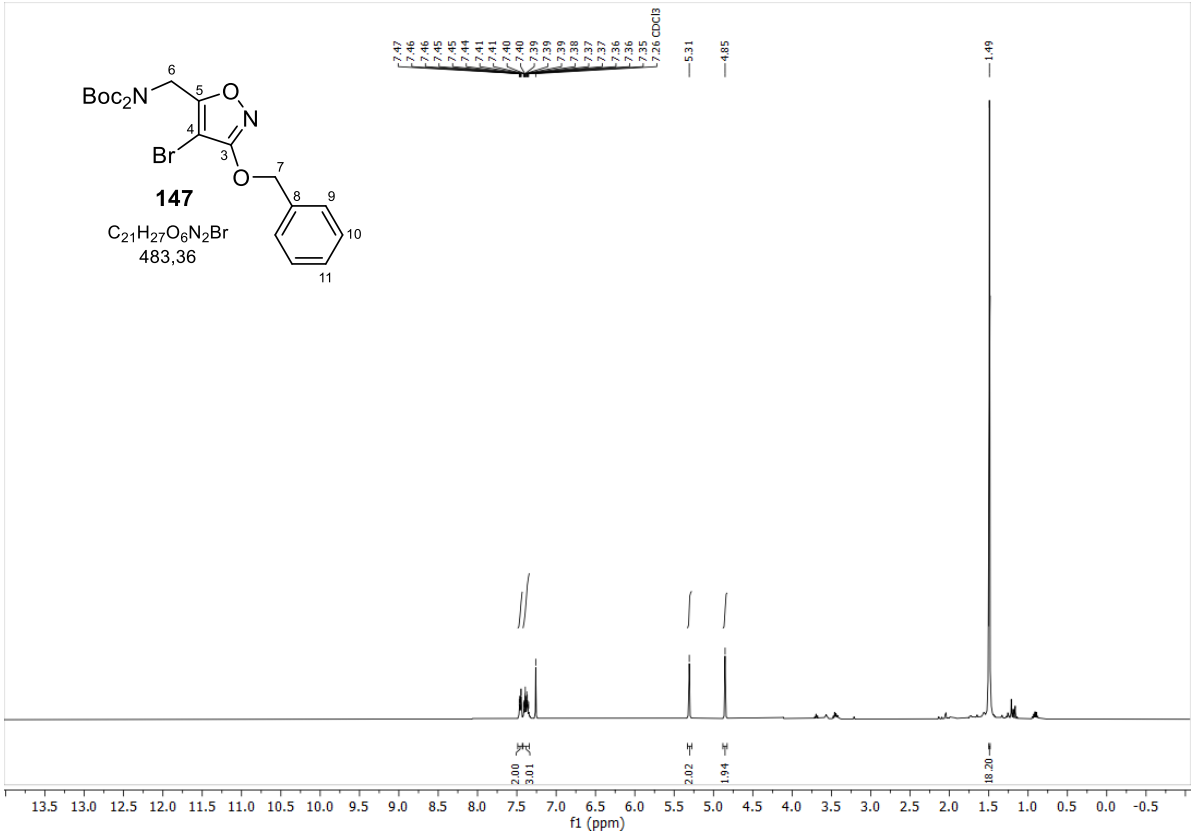


*^{1}H-spectrum of **146** in $CDCl_3$.*

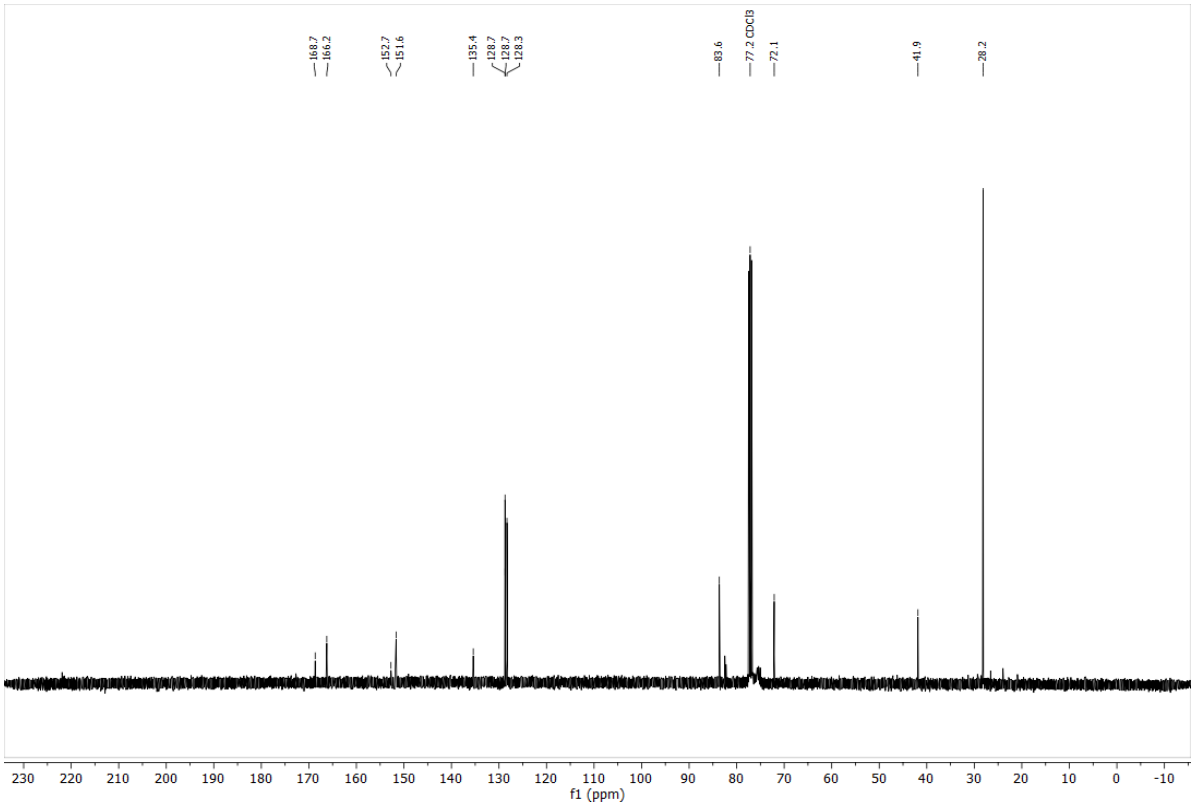


*^{13}C-spectrum of **146** in $CDCl_3$.*

8.5.4.4 *tert*-butyl ((3-(benzyloxy)-4-bromoisoxazol-5-yl)methyl)(*tert*-butoxycarbonyl) carbamate **147**

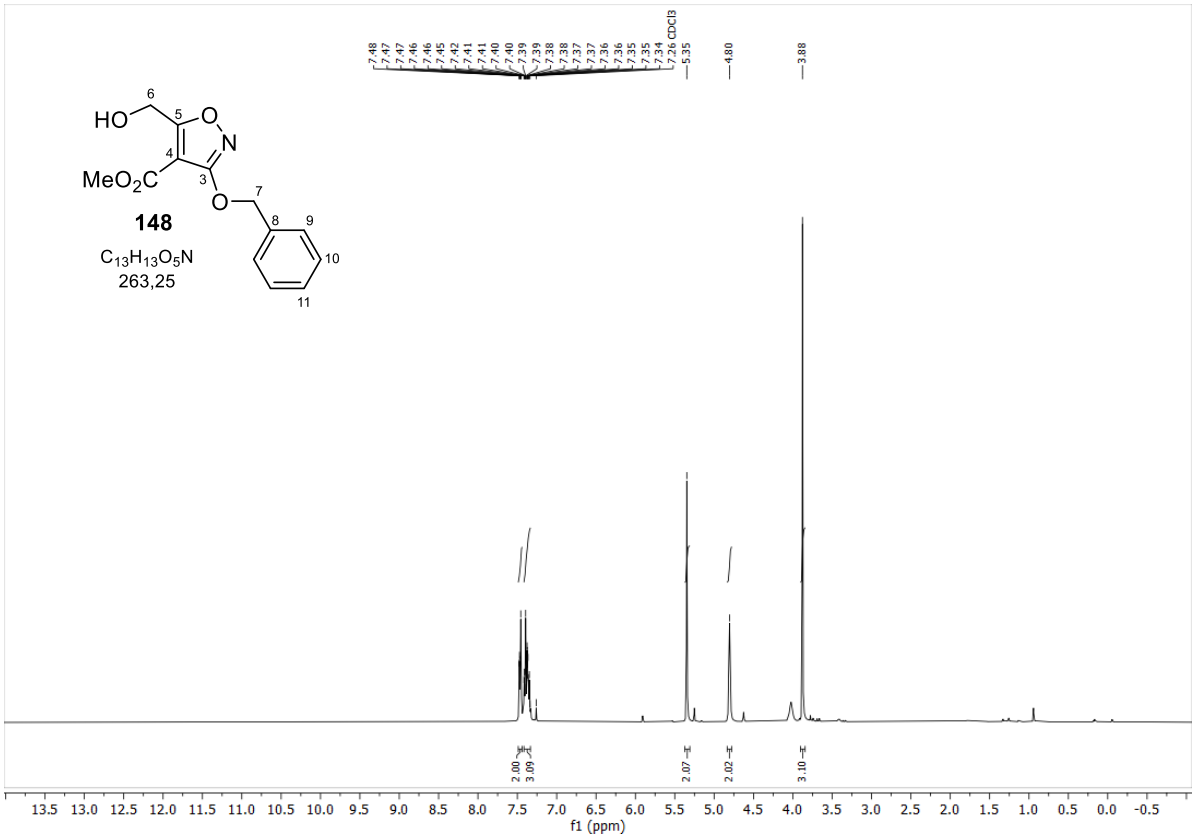


*^{1}H-spectrum of **147** in $CDCl_3$.*

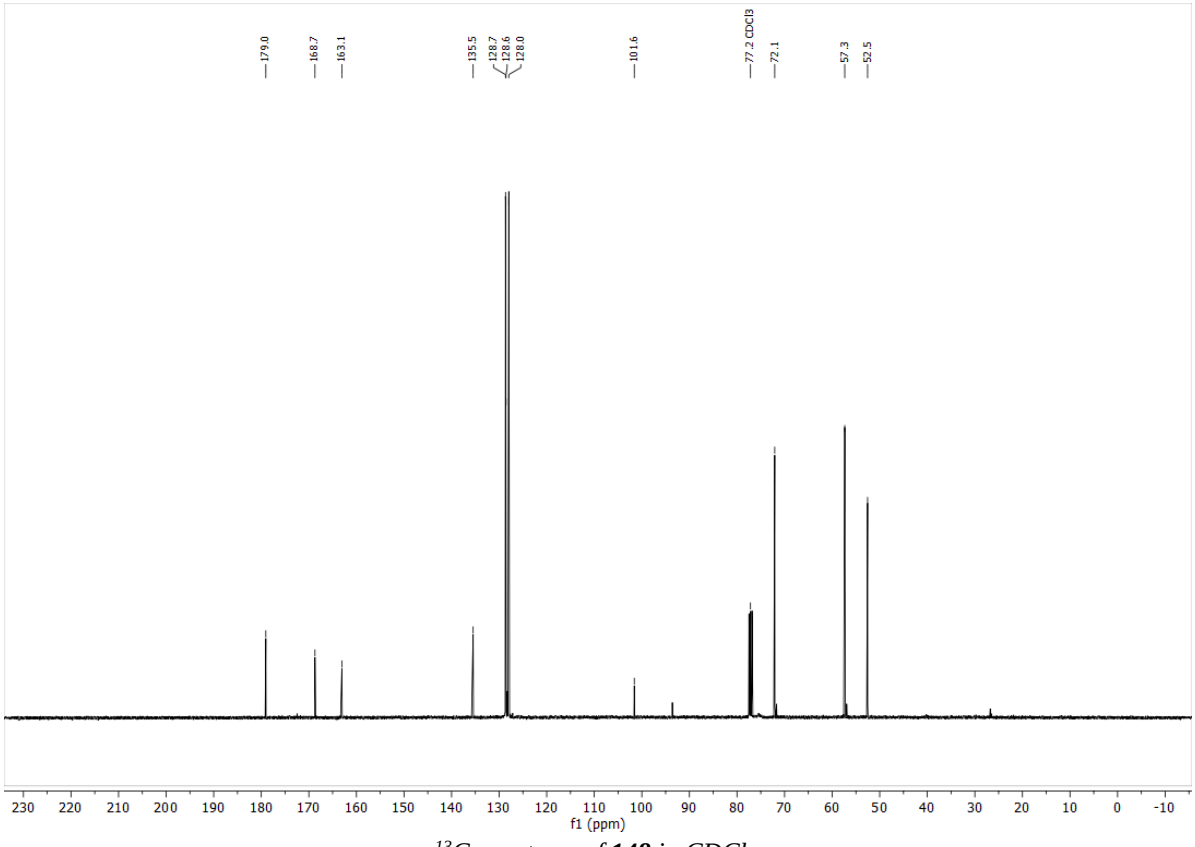


*^{13}C-spectrum of **147** in $CDCl_3$.*

8.5.4.5 methyl 3-(benzyloxy)-5-(hydroxymethyl)isoxazole-4-carboxylate **148**

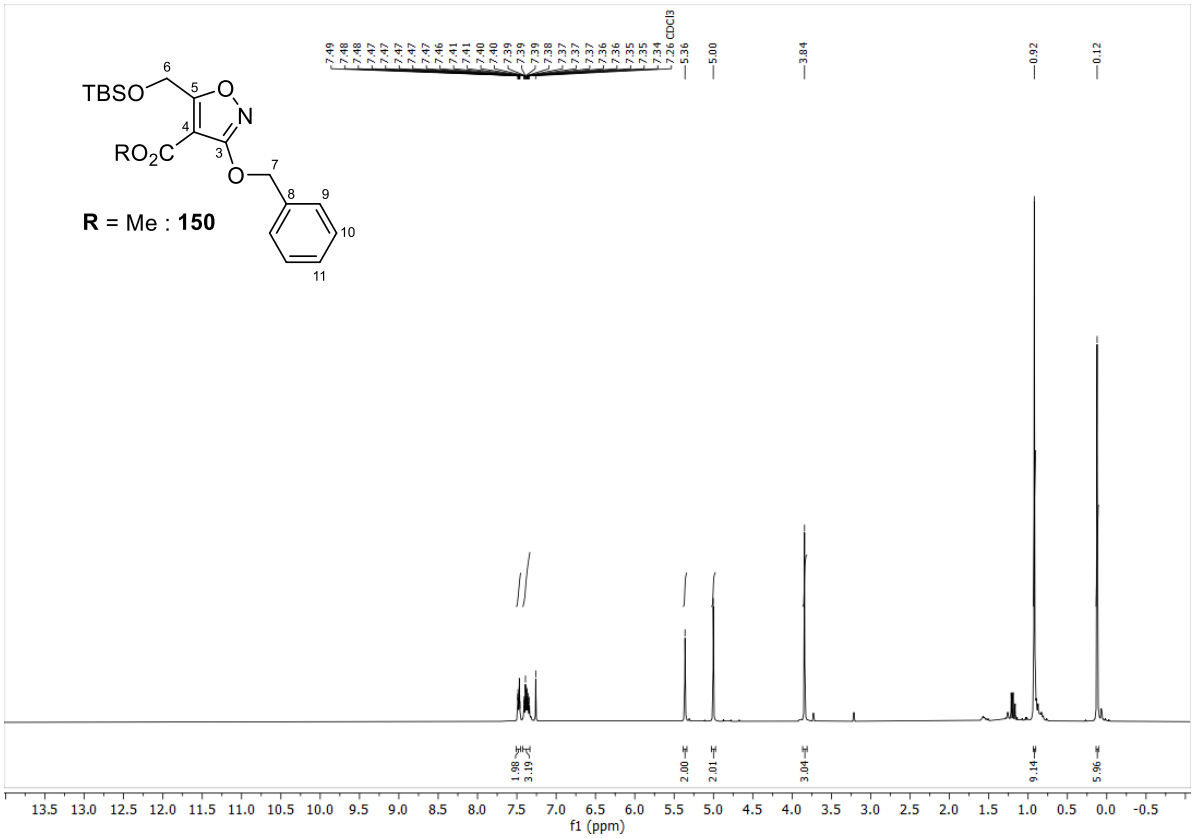


*^{1}H-spectrum of **148** in $CDCl_3$.*

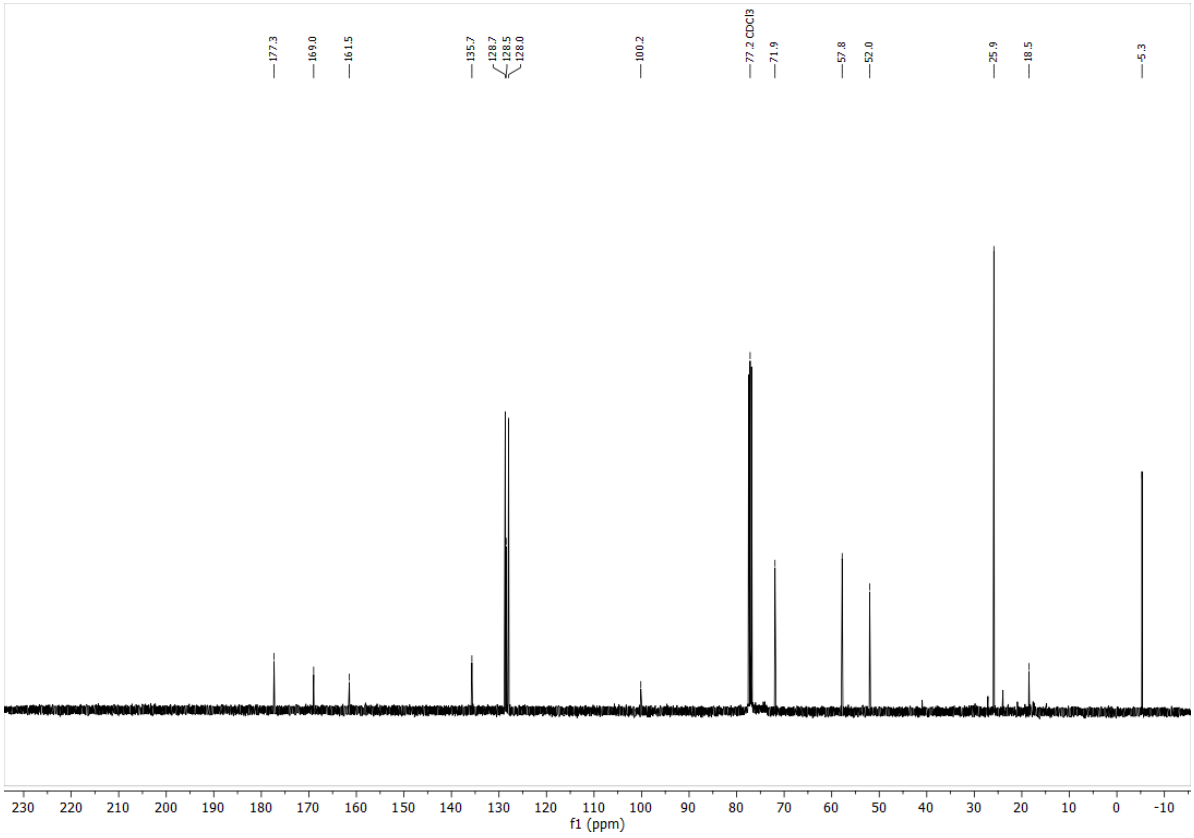


*^{13}C-spectrum of **148** in $CDCl_3$.*

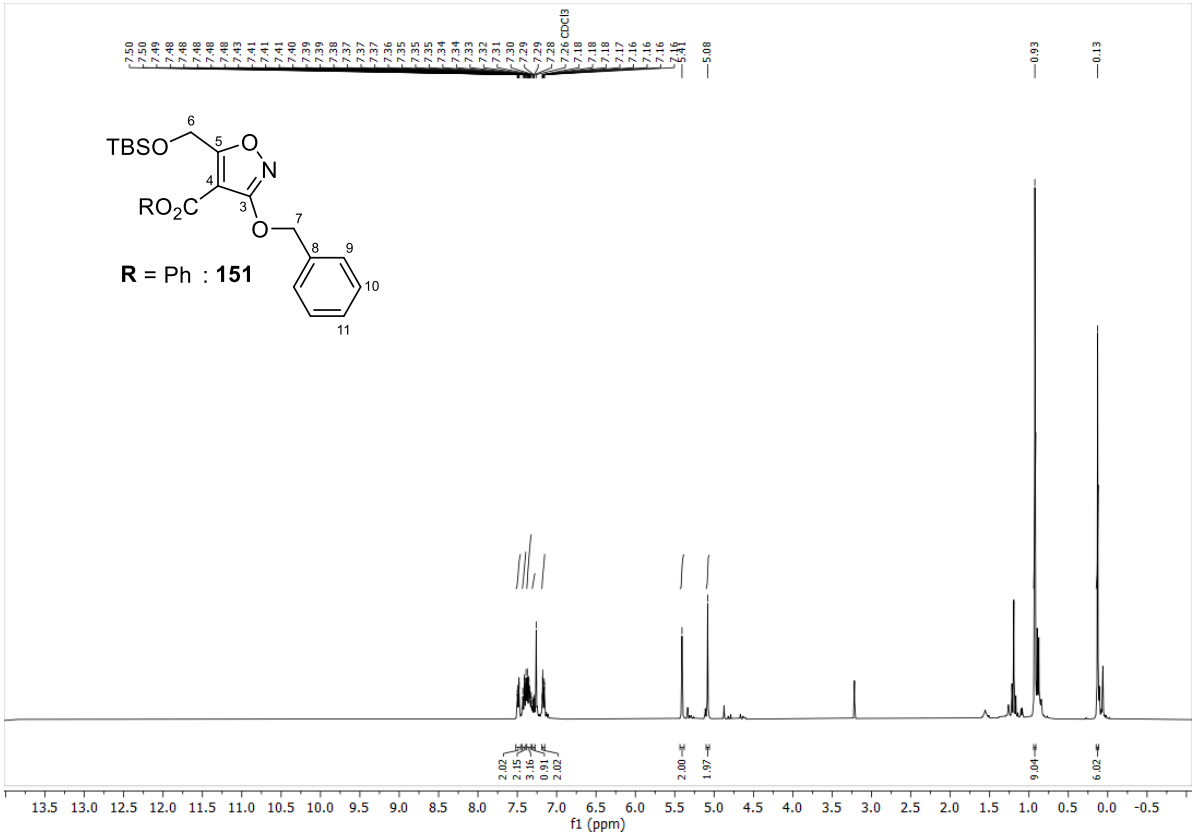
8.5.4.6 3-(benzyloxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)isoxazole-4-carboxylates **150** and **151**



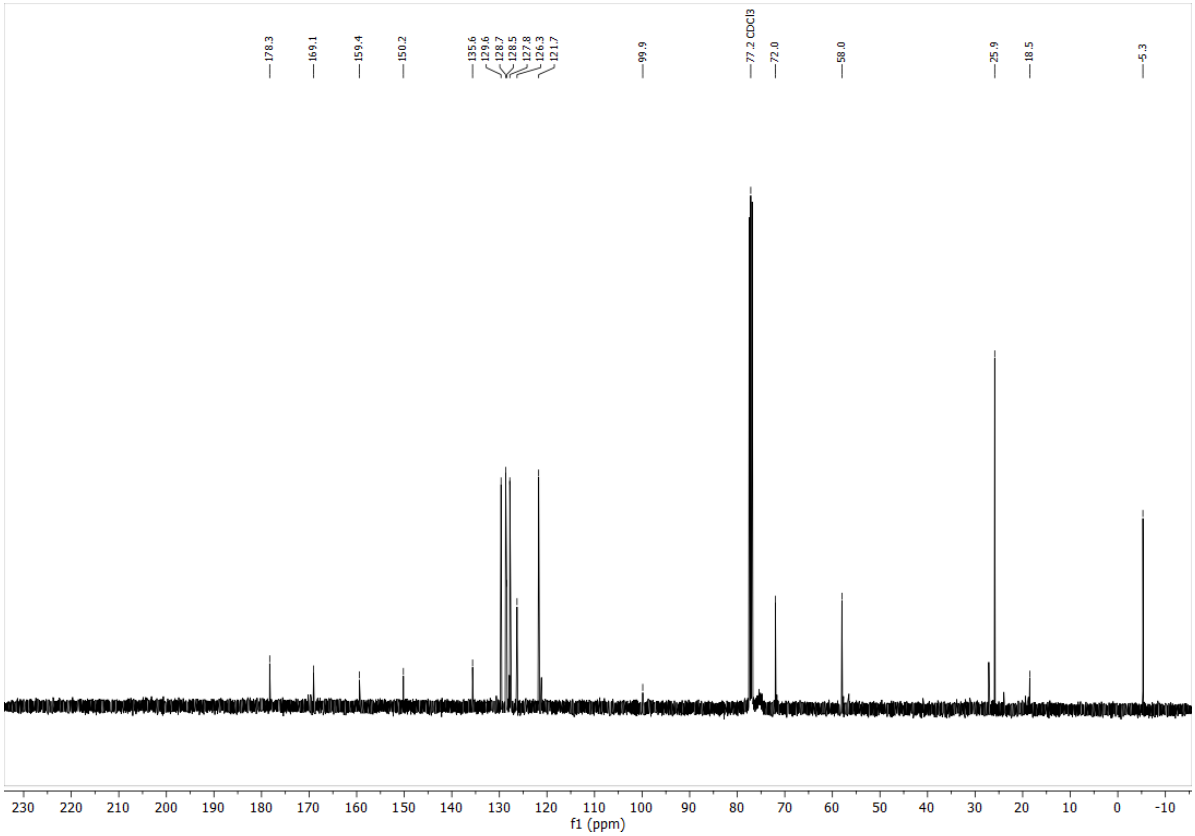
*^{1}H-spectrum of **150** in $CDCl_3$.*



*^{13}C-spectrum of **150** in $CDCl_3$.*

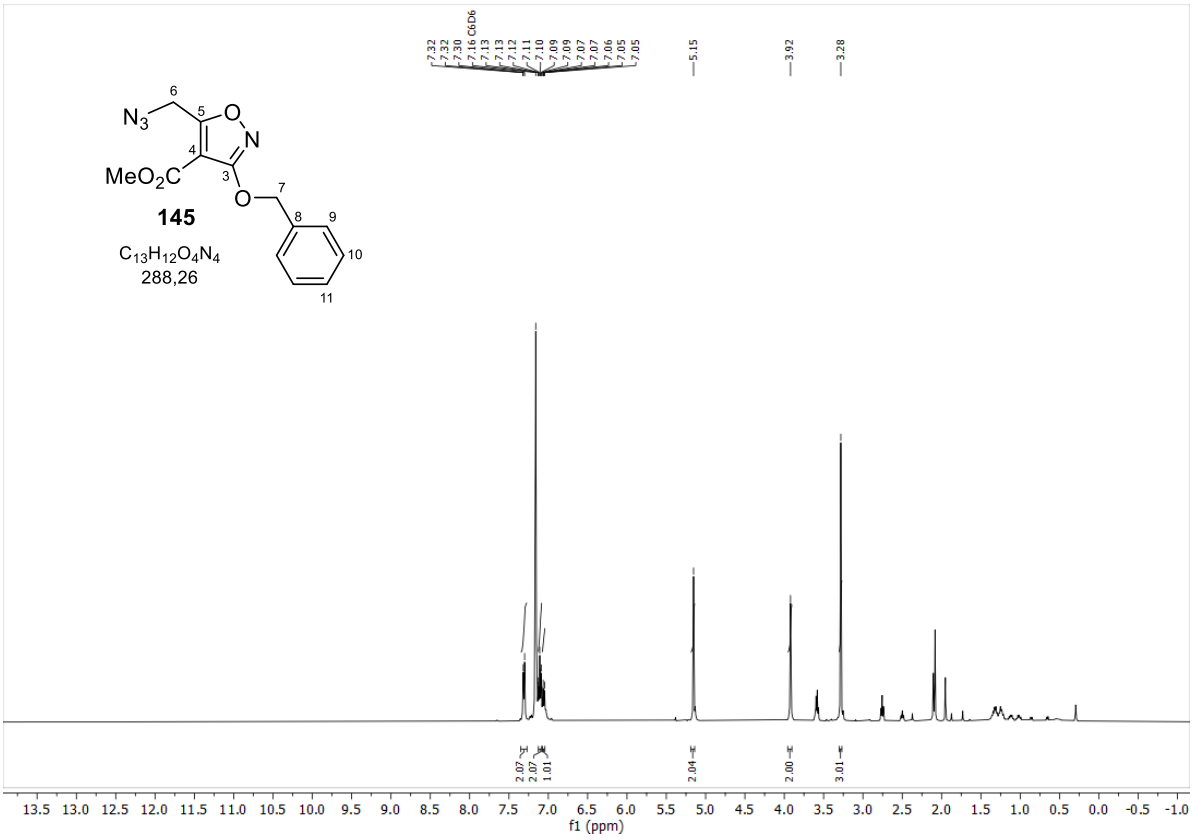


*^{1}H-spectrum of **151** in $CDCl_3$.*

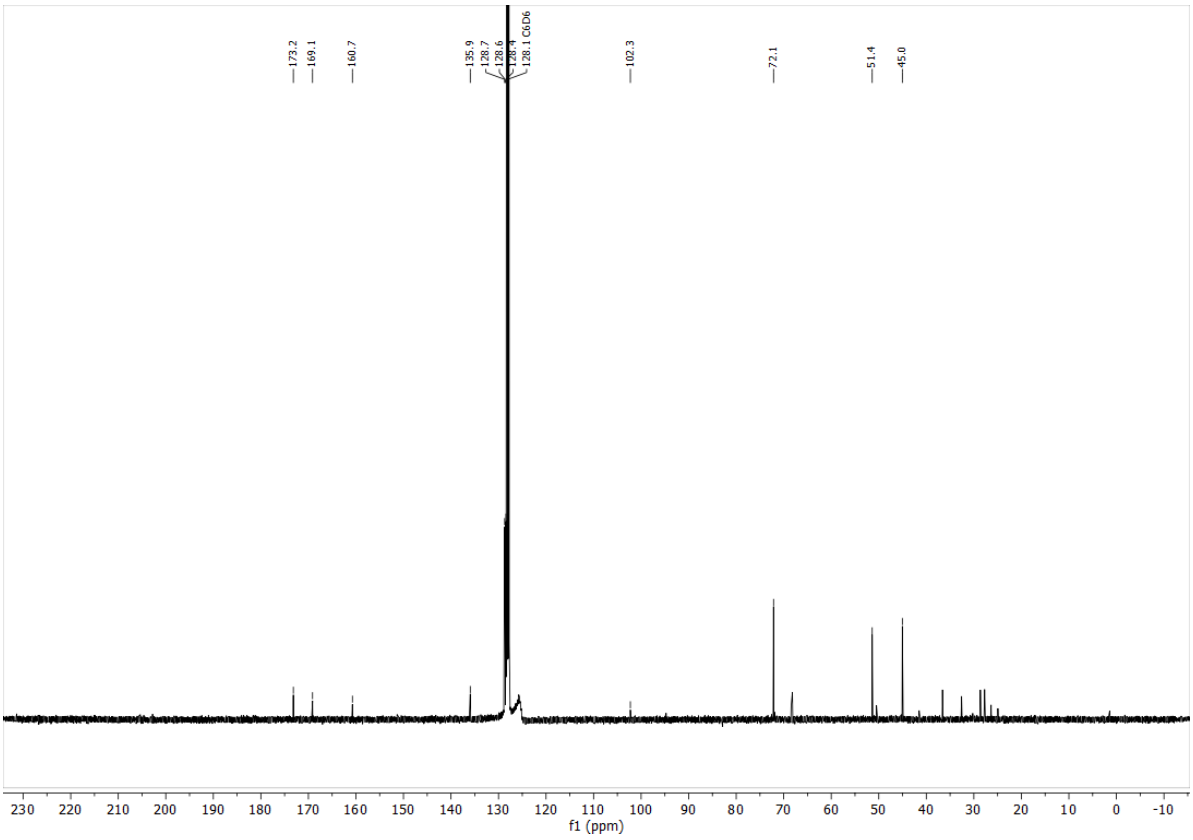


*^{13}C-spectrum of **151** in $CDCl_3$.*

8.5.4.7 methyl 5-(azidomethyl)-3-(benzyloxy)isoxazole-4-carboxylate **145**

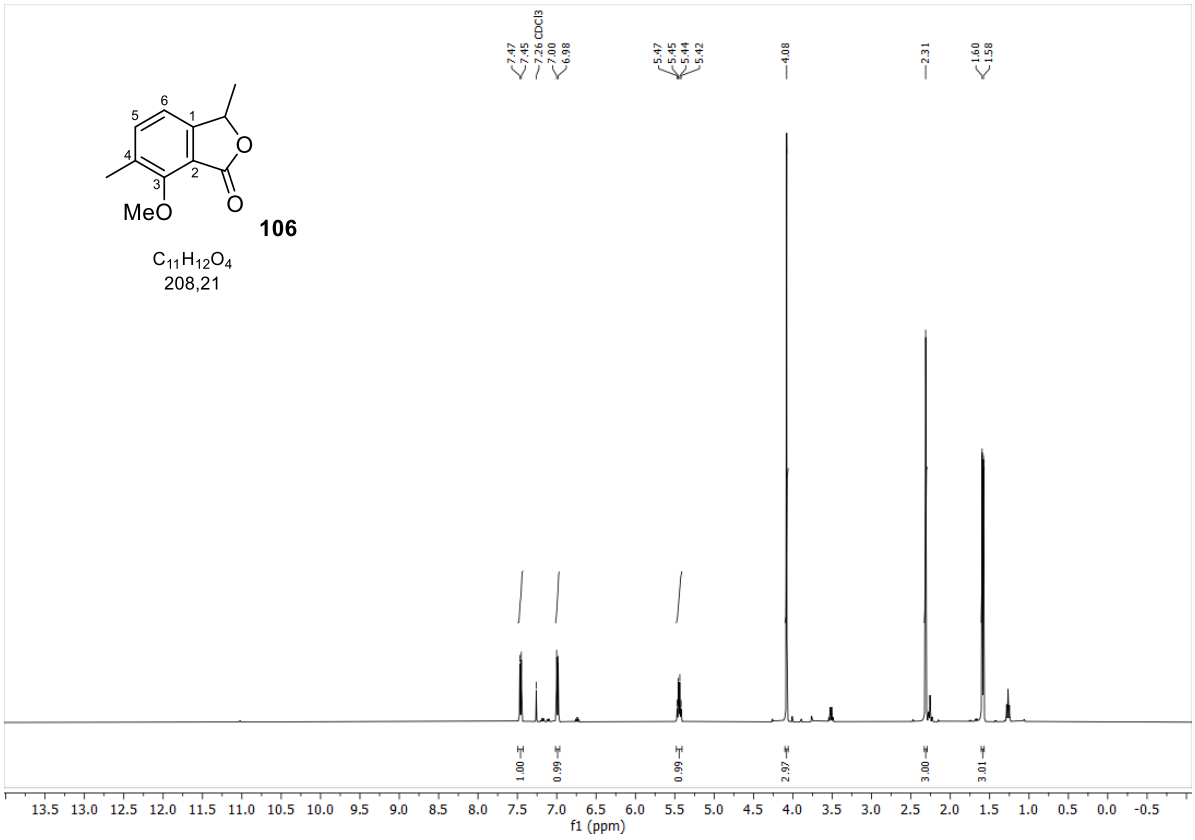


*^{1}H-spectrum of **145** in C_6D_6.*

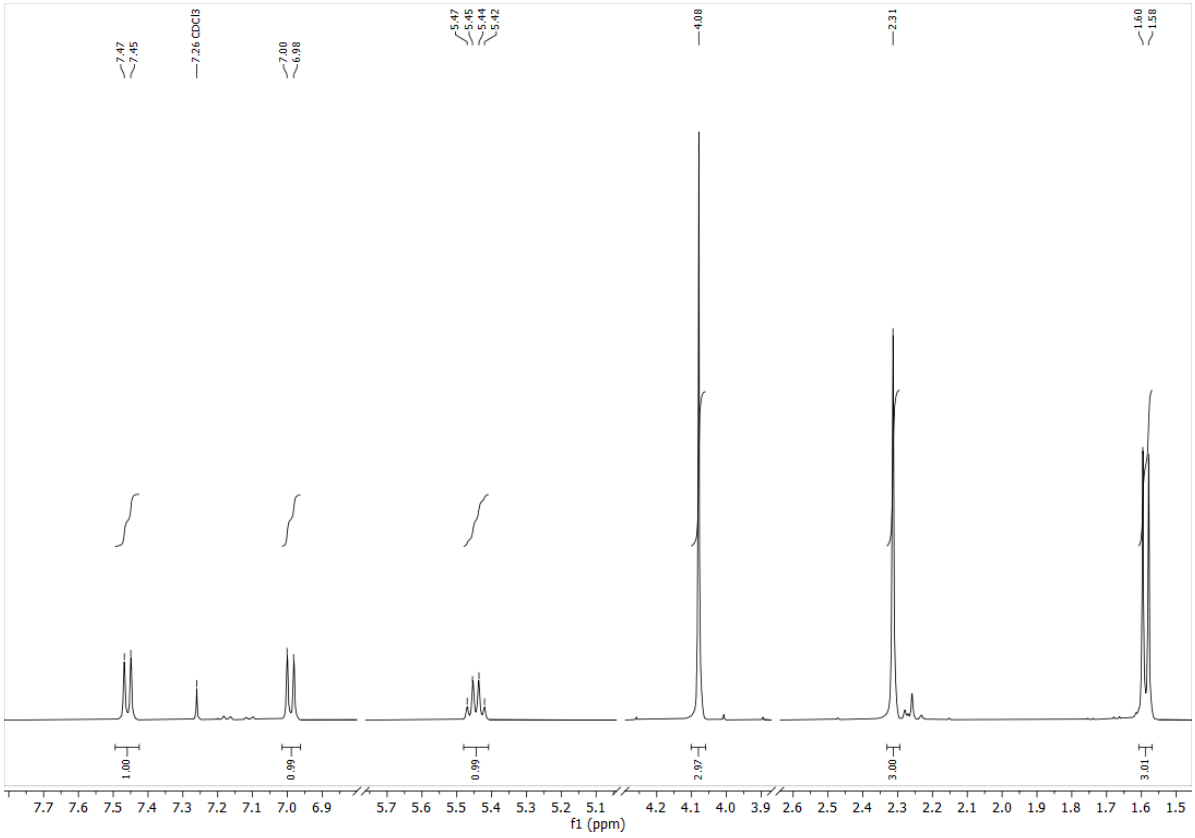


*^{13}C-spectrum of **145** in C_6D_6.*

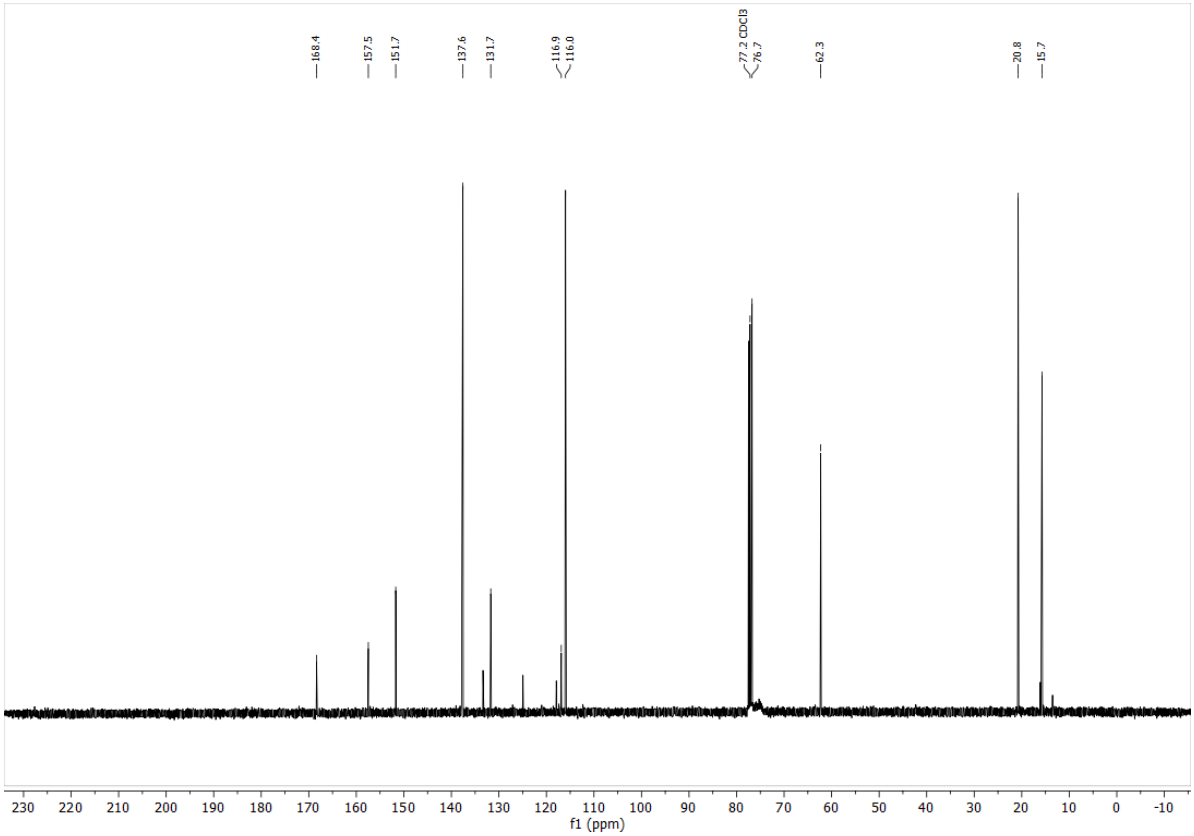
8.5.5 Phthalide **106**



*^{1}H-spectrum of **106** in $CDCl_3$.*



*^{1}H-spectrum of **106** in $CDCl_3$ (selected regions between 1,5-7,7 ppm).*



*^{13}C-spectrum of **106** in $CDCl_3$.*

Curriculum vitae

Education

15.08.2019 – 30.08.2023 — Doctoral studies at *Leibniz Universität Hannover*
supervisor: Prof. Dr. Markus Kalesse
thesis: *Synthese neuer Tetracyclin-Abkömmlinge und weiterer bioaktiver, naturstoff-basierter Derivate*

01.04.2017 – 15.03.2019 — Master of science at *Universität Leipzig*
master thesis: *Synthesis of two novel 6-functionalized 2,4-diaminopteridine-based derivatives as potential neuronal nitric oxide synthase-inhibitors*
(supervised by Prof. Dr. A. Giannis)

01.10.2013 – 22.02.2017 — Bachelor of science at *Universität Leipzig*
bachelor thesis: *Synthese naturstoffähnlicher Phloroglucin-Derivate als potentielle Fungizide für Mikroalgen-Massenkulturen*
(supervised by Prof. Dr. D. Sicker)

15.09.2001 – 30.05.2013 — Formal education at *J. Haltrich Gymnasium Schäßburg*
upper-level specialty: mathematics – informatics
final-exam: *Baccalaureat*

Scientific interests

Natural product chemistry
Organic synthesis
Medicinal chemistry
Coordinative and metalorganic chemistry

Languages

Romanian (native speaker)
German (C1)
English (high proficiency)

Scientific contributions

- Publications

2022: *Latest Applications of Diels-Alder Reaction in the Synthesis of Natural Products (2017-2020)*; with Um-e-Farwa, Aamer Saeed and Markus Kalesse; in: *Synthesis*, **2022**, *54(4)*, 975–998 (DOI: 10.1055/a-1532-4763).

- Conference attendances

2022: 13th Wädenswil Day of Life Science: *Competencies in Drug Discovery*; attended with a poster: *Towards old and new Tetracyclines*; June 9, 2022; Wädenswil (CH)

HZI (Helmholtz Zentrum für Infektionsforschung) annual meeting: *Novel AntiBiotics*; attended with an oral presentation: *Recent advances towards the total synthesis of chelocardin-antibiotics*; March 30, 2022; Braunschweig