Studies Toward the Total Synthesis of the Marine Macrolide Macplocimine A

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presented by

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Dedicated to my parents

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Abstract

Macplocimine A (**I**) (*Figure I*) is an 18-membered macrolide that was isolated from the marine-derived filamentous sulfur bacteria *Thioploca sp.* by Magarvey and co-workers in 2013. A unique structural feature that distinguishes macplocimine A (**I**) from other natural macrolides is the presence of a nucleic acid base directly attached to the macrolactone ring. Neither the absolute nor the relative configuration of macplocimine A (**I**) has been elucidated, except for the *anti*-configuration of the substituents at C(11) and C(12). No biological data have been reported for **I** to date; likewise, no synthetic work on **I** has been documented in the literature.

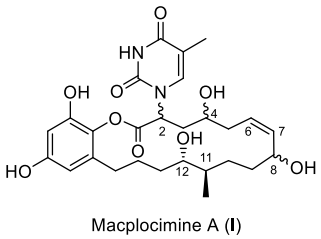
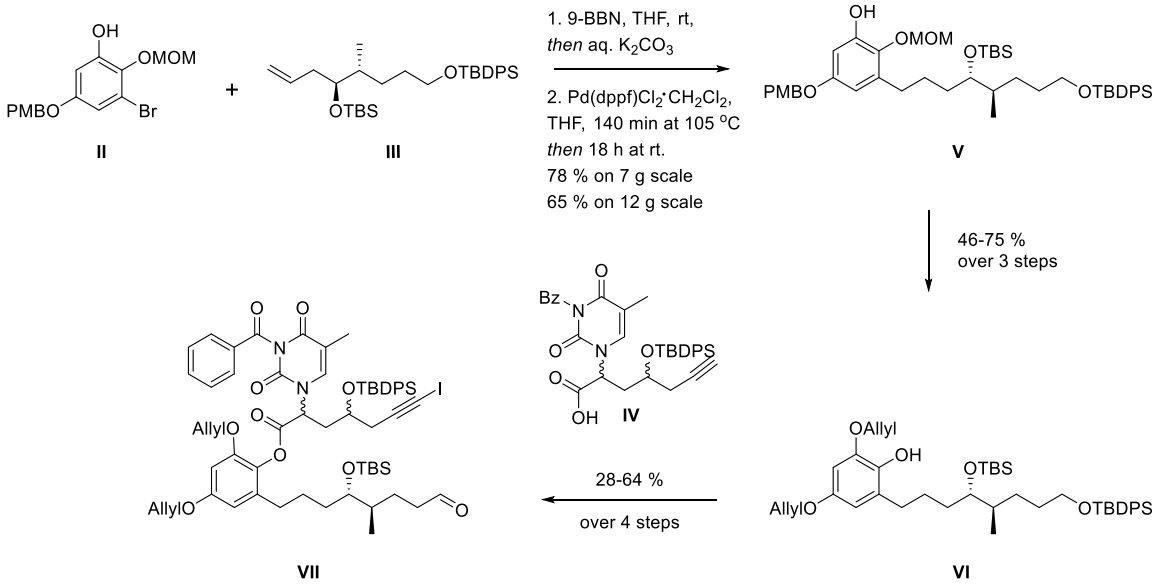


Figure I. Structure of macplocimine A (**I**).

This PhD thesis describes synthetic efforts towards different diastereomers of **I** *via* the assembly of building blocks **II**, **III**, and **IV** by Suzuki coupling of **II** + **III** and esterification with **IV** (*Scheme I*) followed bysubsequent macrocycle formation by intramolecular Nozaki-Hiyama-Kishi (NHK) coupling (*Scheme II*).

Aryl bromide **II** was obtained in five steps and 12-21% overall yield from 5-bromovanillin, while **III** was prepared from 1,4-butanediol in eleven steps and 10-14% overall yield.

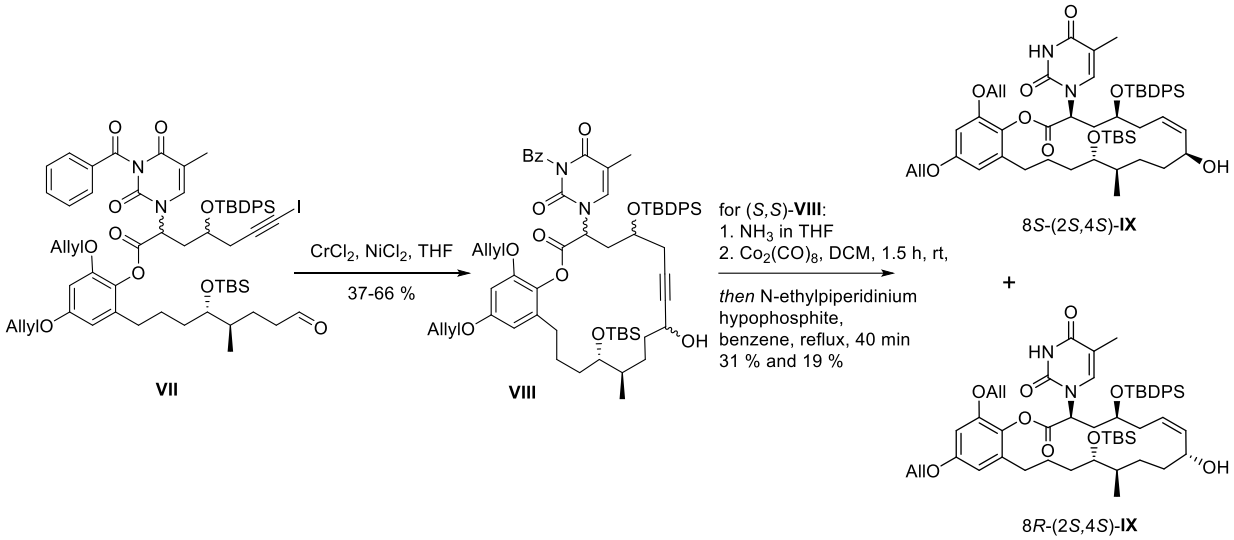


Scheme I. Synthesis of iodoynals **VII**.

Three diastereosisomers of acid **IV** were prepared in eleven steps from D- or L-malic acid in overall yields of 0.75-5.5% and one alcohol precursor (*S,R*)-**69** in eight steps in 0.9 % yield.

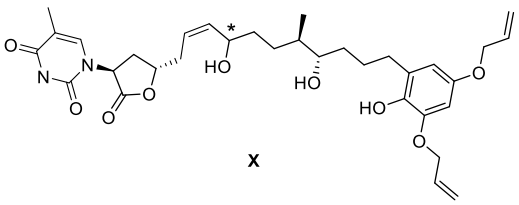
Building blocks **II**, **III**, and **IV** were elaborated into all four possible diastereomeric iodoynals **VII** in overall yields of 8.4-40% (*Scheme I*). Of note, the Suzuki coupling between **II** and **III** under optimized conditions proceeded in excellent yield (65-78%) on a decagram scale.

Three of the diastereomeric iodoynals **VII** were successfully cyclized by NHK to the fully protected macrocycles **VIII** in yields between 37 and 66% (*Scheme II*). Of these macrocycles, the 2*S,*4*S* isomers could be debenzoylated and semi-reduced with $Co_2(CO)_8$/N-ethylpiperidinium hypophosphite to give a separable mixture of diastereomers **IXa** and **IXb** in yields of 31% and 19%, respectively.



Scheme II. Nozaki-Hiyama-Kishi mediated macrocyclization of iodoynals **VII** and reduction of the triple bond.

Unfortunately, treatment of these compounds with HF·Pyr not only resulted in the desired silyl-ether cleavage but also caused macrocycle opening *via* intramolecular transesterification and butyrolactone **X** formation (*Figure II*).



X

Figure II. Structure of the product of the intramolecular transesterification (**X**).

Due to time limitations, no further efforts could be undertaken on the deprotection of macrolactones **IX**.

Zusammenfassung

Macplocimin A (**I**) (*Abbildung I*) ist ein 18-gliedriges Makrolid, das 2013 von Magarvey und Mitarbeitern aus dem filamentösen marinen Schwefelbakterium *Thioploca sp.* isoliert wurde. Ein einzigartiges Strukturmerkmal, das Macplocimin A (**I**) von anderen natürlich vorkommenden Makroliden unterscheidet, ist das Vorhandensein einer Nukleinsäurebase direkt am Makrolactonring. Die absolute und relative Konfiguration von Macplocimin A (**I**) ist bis auf die Antikonfiguration der Substituenten an C(11) und C(12) nicht vollständig geklärt. Bisher wurden keine biologischen Daten für **I** publiziert; ebenso wenig sind in der Literatur synthetische Arbeiten an **I** dokumentiert.

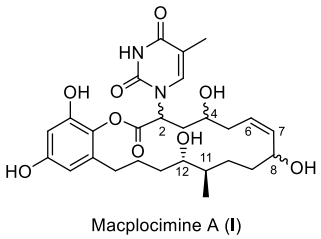
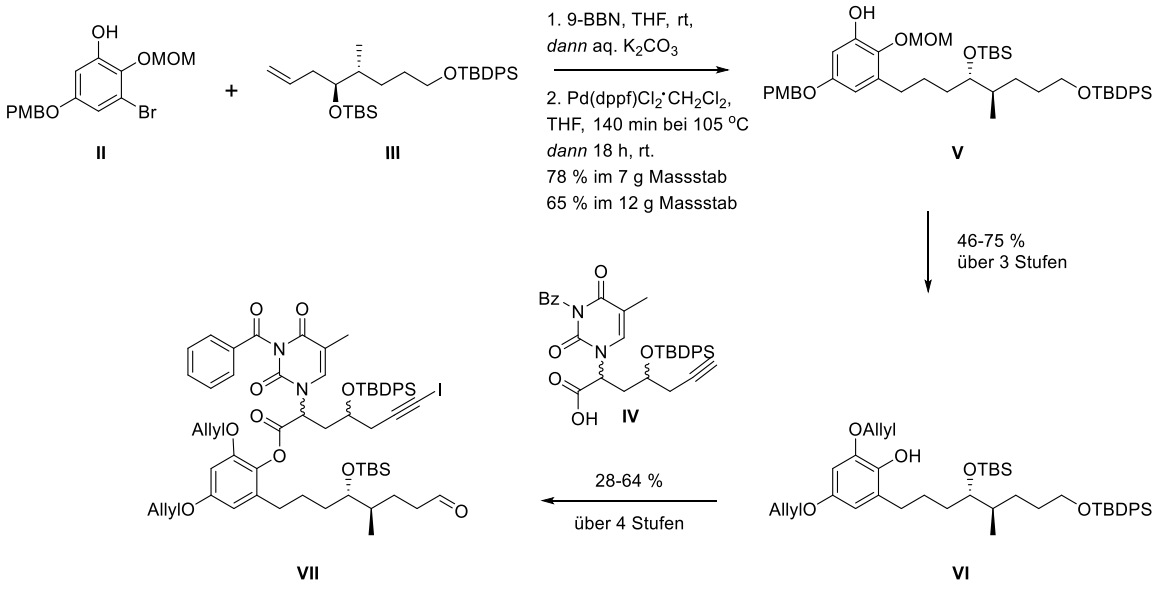


Abbildung I. Struktur von Macplocimin A (**I**).

In dieser Dissertation werden die synthetischen Bemühungen zur Herstellung verschiedener Diastereomere von **I** beschrieben. Dies umfasst den Aufbau der Bausteine **II**, **III** und **IV** mittels Suzuki-Kupplung von **II** + **III** und Veresterung mit **IV** (*Schema I*), sowie die anschliessende Makrozyklisierung durch intramolekulare Nozaki-Hiyama-Kishi-(NHK)-Kupplung (*Schema II*).



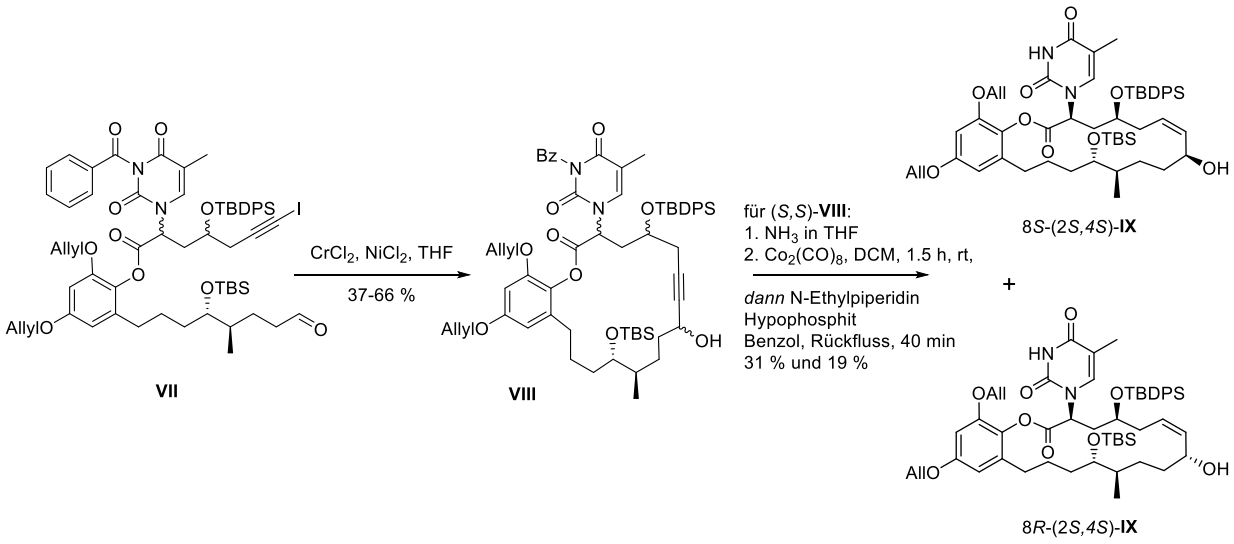
Schema I. Synhthese von Iodoynalen **VII**.

Arylbromid **II** wurde in fünf Schritten mit einer Gesamtausbeute von 12-21% aus 5-Bromvanillin synthetisiert, während **III** in elf Schritten mit einer Gesamtausbeute von 10-14% aus 1,4-Butandiol

hergestellt wurde. Die drei Diastereomere der Säure **IV** wurden jeweies in elf Schritten aus *D*- oder *L*-Äpfelsäure in Gesamtausbeuten von 0,75-5,5% erhalten.

Die Bausteine **II**, **III** und **IV** wurden erfolgreich in alle vier möglichen diastereomeren Iodoynale **VII** umgewandelt, wobei eine Gesamtausbeute von 8,4-40% erzielt wurde (*Schema I*). Bemerkenswert ist, dass die Suzuki-Kupplung zwischen **II** und **III** unter optimierten Bedingungen im Dekagramm-Massstab mit einer ausgezeichneten Ausbeute von 65-78% erfolgte.

Drei der diastereomeren Iodoynale **VII** wurden erfolgreich mitttels NHK zu den vollständig geschützten Makrozyklen **VIII** zyklisiert, wobei Ausbeuten zwischen 37 und 66 % erzielt wurden (*Schema II*). Von diesen Makrozyklen konnten die 2*S,*4*S*-Isomere debenzoyliert und mit $Co_2(CO)_8$/N-Ethylpiperidinium Hypophosphit halbreduziert werden, um ein trennbares Gemisch der Diastereomere **IXa** und **IXb** mit Ausbeuten von 31 % und 19 % zu erhalten.



Schema II. Nozaki-Hiyama-Kishi vermittelte Makrozyklisierung von Iodoynalen **VII** und Reduktion der Dreifachbindung.

Leider führte die Umsetzung dieser Verbindungen mit HF·Pyr nicht nur zur gewünschten Spaltung der Silyl-Ether, sondern auch zur unerwünschten Öffnung des Makrozyklus durch intramolekulare Umesterung und Bildung von Butyrolacton **X** (Abbildung II).

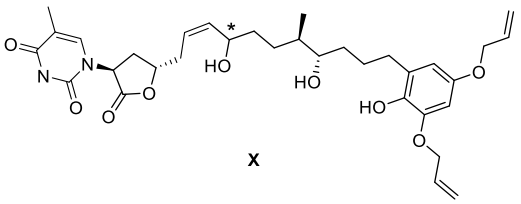


Abbildung II. Struktur des Produkts der intramolekularen Umesterung (**X**).

Aufgrund zeitlicher Einschränkugnen konnten keine weiteren Versuche zur Entschützung der Makrolactone **IX** durchgeführt werden.

Abbreviations and Dimension Units

A

$[\alpha]\frac{D}{T}$	specific rotation at temperature T at the sodium (D) line
AcOH	acetic acid
ACP	acyl carrier protein
ADC	antibody-drug conjugate
amylene	2-methyl-2-butene
app.	apparent
AT	acyltransferase
atm	atmosphere

B

9-BBN	9-borabicyclo[3.3.1]nonane
Bu	Butyl

C

˚C	degree Celsius
ca.	approximately
cat.	catalytic
CoA	acetyl-coenzyme A
COSY	correlated spectroscopy
CSA	camphorsulfonic acid
CYP	cytochrome enzyme

D

d	doublet

DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPT-Q	distortionless enhancement by polarization transfer (NMR)
DH	dehydratase
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylamino-pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio

E

EA	ethyl acetate
ee	enantiomeric excess
equiv.	equivalents
ER	enoyl reductase
EtOH	ethanol

F

FC	flash column chromatography

G

g	gram

H

h	hour
Hal	halogen
Hex	hexane
HFIP	hexafluoroisopropanol
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence spectroscopy
HPLC	high-performance liquid chromatography
HRES	high-resolution (mass spectrometry)
HRESIMS	high-resolution electrospray ionization mass spectrometry
HRMS	high-resolution mass spectrometry
hrPKS	highly-reducing PKS
HSQC	heteronuclear single quantum coherence spectroscopy
HWE	Horner-Wadsworth-Emmons
Hz	hertz

I

IR	infrared

J

J	coupling constant

K

KB	cell line exhibiting epithelial morphology
KR	ketoreductase

KS	ketosynthase

L

LLS	longest linear sequence

M

m	multiplet
M	mole, molar
MAT	malonyl-CoA:ACP transacylase
Me	methyl
MeOH	methanol
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mM	millimole per liter
MMAE	monomethyl auristatin E
mmol	millimole
MNP, MNPs	marine natural product(s)
mol%	mole percent
MOM	methoxymethyl
MS	mass spectrometry or molecular sieves
MT	methyltransferase
MTPA	(*S*)-(-)- and (*R*)-(+)-α-methoxy-α-trifluoromethylphenyl-acetic acid
MW	microwave

N

n.d.	not determined
NCE	new chemical entity
NDA	new drug application
NHK	Nozaki-Hiyama-Kishi
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NO/cGMP	nitric oxide (NO)/cyclic guanosine 3′,5′-monophosphate (cGMP)
NOESY	nuclear Overhauser effect spectroscopy
NP, NPs	natural product(s)
n-PrSH	1-propanethiol
nrPKS	non-reducing PKS
NSCLC	non-small cell lung cancer
Nu	nucleophile

P

p	*para*
$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	[1,1′-Bis-(diphenylphosphino)-ferrocen]-dichloro palladium(II) complex with dichloromethane
Pg	protecting group
Ph	phenyl
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PT	product template (domain)

Py	pyridine

Q

q	quartet
quant.	quantitative (yield)
quint.	quintet

R

RAL	resorcylic acid lactone
RAL_{12}	12-membered resorcylic acid lactone
RAL_{14}	14-membered resorcylic acid lactone
RAL_{16}	16-membered resorcylic acid lactone
RCM	ring-closing olefin metathesis
R_f	retention factor
R^F(in DEAD)	$C_8F_{17}CH_2CH_2C_6H_4$
R^F(in PPh_3)	$C_8F_{17}CH_2CH_2C_6H_4$
rt	room temperature

S

s	singlet
SAR	structure-activity relationship
SAT	ACP transacylase
SM	starting material
SNAC	N-acetylcysteamine thioester
δ	NMR chemical shift in ppm.

T

t	triplet
t	*tert*
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
t-BuOH	*tert*-butyl alcohol
TE	thioesterase
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TNF	tumor necrosis factor
TRAIL	tumor necrosis factor related apoptosis-inducing ligand

U

UV	ultraviolet

1 Introduction

1.1 Natural products: structures, biosynthesis, and physiological relevance

The term "natural product" (NP), in its broadest sense, encompasses all substances that are synthesized by living organisms.

Based on their biological function, natural products can be classified into primary or secondary metabolites.[1][2][3] Primary metabolites are molecules vital to the survival of an organism.[4][5] They include amino acids, carbohydrates, fatty acids, or nucleosides all of which play crucial roles in basic biological processes at the cellular level.[6] In contrast, secondary metabolites do not directly contribute to the growth and development of an organism; but they are often essential for its survival, or even the survival of an entire species, in its natural environment.[7] For example, in bacteria, secondary metabolites are produced as defense tools against competing species; likewise, they can protect plants against bacterial infections, feeding insects, or predatory animals.[8] Secondary metabolites can also serve as facilitators of metal transport, contributors to plant-microbe symbiosis, stimulators of plant growth, pheromones, or influencers of differentiation.[9] Importantly, the wide range of biological activities associated with secondary metabolites has made them a highly prolific source of lead structures for drug discovery[10] (see Chapter 1.2).

To date, the most common sources of bioactive secondary metabolites have been terrestrial bacteria, fungi, and plants; however, as will be discussed below, marine organisms such as sponges, algae, corals, marine bacteria and fungi should provide an equally rich pool of compounds with interesting biological activities.[11][12]

While various classification systems exist for secondary metabolites, they are most commonly categorized based on their biosynthetic origin.[13] The major biosynthetic pathways underlying the production of secondary metabolites in microorganisms, fungi, and plants are (1) the acetate/malonate or polyketide pathway, leading to aromatic or non-aromatic polyketides; (2) the shikimic acid pathway, leading to non-polyketide aromatic compounds; and (3) the acetate/mevalonate or methylerythritol phosphate (MEP) pathway leading to terpenes. A major class of natural products that are not biosynthesized *via* any of these three pathways and that are mostly derived from amino acids are alkaloids. Other important classes of secondary metabolites are glucosinolates and non-ribosomal peptides (*Scheme 1*).[14] Modifications of the structures formed *via* the canonical biosynthetic pathways, for example by rearrangements or oxidations, lead to a multitude of diverse structures that can be associated with a plethora of bioactivities.[15]

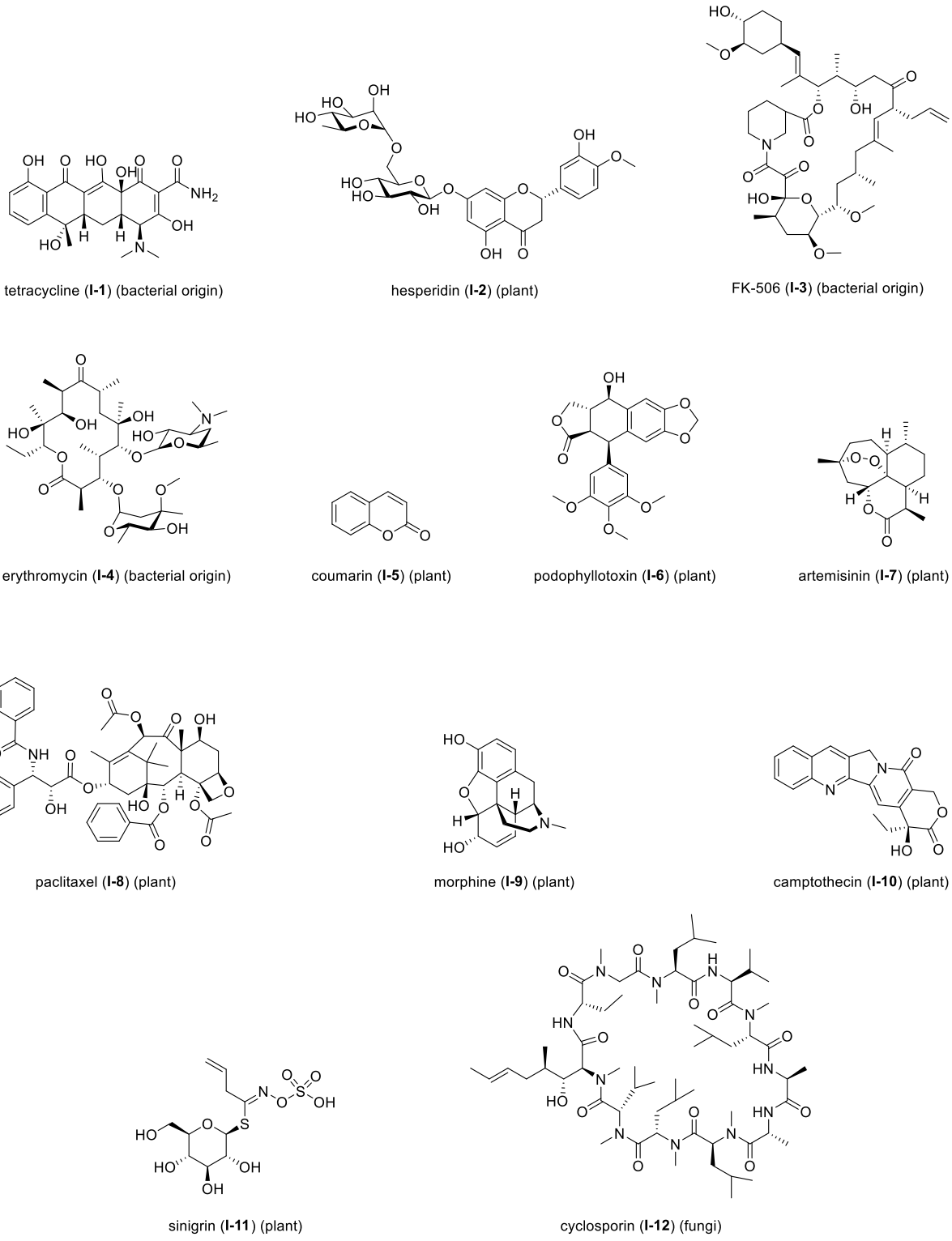


Figure 1. Examples of secondary metabolites from different classes: tetracycline (**I-1**), (aromatic polyketide, PKS type II), hesperidin (**I-2**) (flavanone glucoside, PKS type III), FK-506 (**I-3**) (non-aromatic polyketide, PKS type I), erythromycin (**I-4**) (polyketide), coumarin (**I-5**) (flavonoid), podophyllotoxin (**I-6**) (lignan), artemisinin (**I-7**) (sesquiterpene lactone), paclitaxel (**I-8**) (tetracyclic diterpene), morphine (**I-9**) (alkaloid), camptothecin (**I-10**) (monoterpenoid indole-alkaloid), sinigrin (**I-11**) (glucosinolate), cyclosporin (**I-12**) (non-ribosomal peptide). All of these compounds originate from terrestrial sources.

The major producers of aromatic polyketides are terrestrial plants, but they are also found in bacteria or fungi; the same is true for shikimate-derived secondary metabolites. Interestingly, mammals have no capacity to synthesize aromatic compounds. Most non-aromatic polyketides are produced by terrestrial bacteria or fungi, but also by marine organisms.[16] The majority of terpenes are found in plants, but also in microorganisms or fungi both of terrestrial and marine origin. The vast majority of alkaloids originate from plants, but they have also been found in bacteria, fungi, and animals.[17][18] Bacteria and fungi can also produce non-ribosomal peptides, while glucosinolates occur mostly in plants.[19][20][21] In total, various literature sources estimate the number of known natural products as of 2022 to range between 300 000 and 600 000.[22][23][24][25][26]

1.1.1 Marine natural products

As alluded to above, secondary metabolites produced by marine organisms should represent a diverse and attractive pool of bioactive substances. According to MarinLit, a database published by the Royal Society of Chemistry since 2014 that is dedicated to marine natural products research, approximately 40 000 natural products have been isolated from marine organisms ("marine natural products", MNPs).[27] The first documented work on marine natural products dates back to the 1940s and 1950s,[28] while the systematic exploration of the marine environment as a source of new NPs only began in the 1970s. (For comparison, morphine (**I-9**), the first natural product ever to be obtained in pure form, was isolated in 1805).[29][30] Within a decade this led to the discovery of around 2500 new metabolites.[31] Today, thousands of marine natural products are discovered every year, due to the improvement of the equipment and methods for sampling.[32]. Thus, more than 1400 marine natural products were isolated every year from 2020 to 2022.[33][34][35] While these numbers are impressive, secondary metabolites from marine macro- and microorganisms have been explored much less extensively than those from their terrestrial counterparts, mostly due to past limitations in sample collection and analytical techniques.[36][37] At the same time, the marine environment covers approximately 70% of the Earth's surface and hosts a largely unexplored biodiversity. The world's oceans contain 34 of the 36 known phyla of life,[38] and 8 of these are exclusive to the marine environment.[38][39] Thus, although terrestrial organisms remain a promising source of new bioactive secondary metabolites, it is also clear that the potential for the discovery of new structures from marine sources is underexploited by far.

It is presumed that the first living organisms appeared in the sea 3.5 billion years ago. This long evolutionary period has made marine organisms very adaptable to the extreme conditions of the deep sea, which are characterized by exceptionally high pressures, low levels of oxygen, low temperatures, and darkness.[40] In response to these challenges, marine organisms have evolved specific physiological and biochemical traits to ensure their survival.[41][42] Due to life in a wide range of competitive and hostile ecosystems, they have also developed unique defense strategies and they produce bioactive

compounds whose structures are in some cases unparalleled by those from terrestrial organisms.[43] The marine environment is also rich in halides and this is reflected in the chemical structures of many marine secondary metabolites.[44][45] Due to the high dilution in the sea and a lack of physical means for self-defense, some marine organisms are highly cytotoxic.[46] Tropical regions tend to exhibit a higher chemical diversity of secondary metabolites than polar regions.[47] Finally, 70% of marine natural products have been isolated from aquatic invertebrates.[48][49]

Based on a recent cheminformatics study by Hou and co-workers[50] on the structural and physico-chemical property differences between terrestrial and marine natural products, the latter (1) exhibit lower solubility and often have a higher molecular weight than their terrestrial counterparts; (2) contain larger rings, especially 8- to 10-membered rings; (3) are richer in halogens, especially bromine; and (4) contain more nitrogen atoms in their structures.[50] The two latter features have been suggested to reflect a greater diversity in biosynthetic pathways for MNPs.[50] Examples of natural products unique to marine microbes are the cyclic peptide odobromoamide (**I-13**)[51] or the diterpene indole alkaloid halomide (**I-14**) that was isolated from *Bacillus amyloliquefaciens* GAS 00152 collected at a depth of 11 000 m (*Figure 2*).[52] Subtipyrroline C (**I-15**), an alkaloid isolated from the bacterium *Bacillus subtilis* SY2101, showed weak antiproliferative activity against human glioma U251 and U87MG cells and antimicrobial activity against *E. coli and C. albicans.*[53] Scedapin A (**I-16**) [54] is an alkaloid isolated from the marine fungus *Scedosporium apiospermum* F41−1 (*Figure 2*).

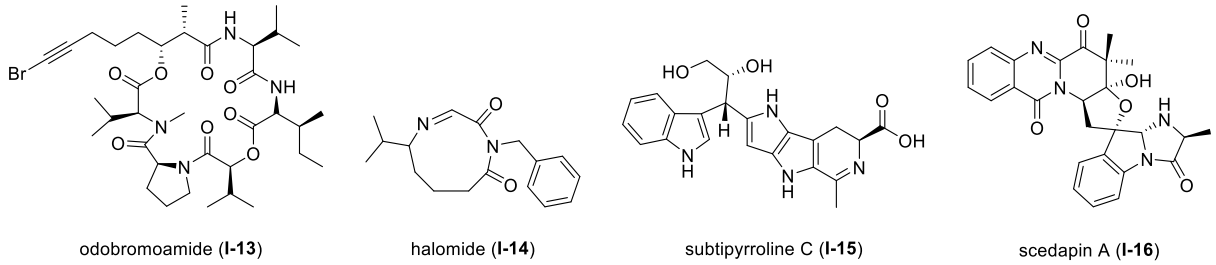


Figure 2. Examples of marine natural products that are unique to the marine environment and do not exist in terrestrial organisms.[55]

Carroll and co-workers conducted a cluster analysis of chemical fingerprints and molecular scaffolds of 55 817 compounds extracted from two databases MarinLit and NPAtlas, which included NPs isolated from (1) terrestrial microorganisms (22 761), (2) marine microorganisms (9 598), and (3) marine invertebrates, marine algae, and seagrass. Compounds from the three latter types of organisms were grouped together as “marine macroorganisms” (23 458 compounds). Fingerprint cluster analysis of NPs derived from terrestrial and marine microorganisms showed that the structures of NPs isolated from marine microbes are 23.3% unique compared to terrestrial microbial natural products and that the remainder (76.7%) share structural features with NPs produced by terrestrial counterparts. The analysis

of all three groups showed that marine microbial natural products have a 14.3% unique scaffold compared to terrestrial microbial natural products and NPs from marine macroorganisms.[55] Interestingly, the study also showed that NPs isolated from marine macroorganisms have a greater overlap with terrestrial microbial NPs than marine microbial NPs.[55] This study concluded that the overall uniqueness of microbial MNPs is low, due to the difficulty and necessity of laboratory cultivation of unique marine microorganisms, thus pointing out the urge for innovation in strain selection of understudied genera and development of marine cultivation techniques. Although this study might not be comprehensive as it is limited to the fingerprints of 55 817 natural products from microbial microorganisms, invertebrates, seaweeds, and seagrasses, it provides a new perspective and calls for more innovation in contrast to other studies that generally agree on the fact that MNPs are unique and prosperous.

Finally, marine natural products are often only available in very small quantities from natural sources. Therefore, total synthesis and synthesis-based molecular preparation are in many cases of central importance for comprehensive biological profiling of marine secondary metabolites and for the study of structure-activity relationships (SARs).[56]

1.2 Natural products in drug discovery and development

The first records of the use of natural sources as medicines, dating back to 2900 BC, originate from Mesopotamia and describe various oils from plants.[57][58] Around 700 plant-based drugs were documented by the Egyptian pharmaceutical record, the Ebers Papyrus in 1500 BC;[59] they include different formulations (gargles, snuffs, poultices, infusions, pills) and embrocations with various substances. Traditional Chinese medicine has been extensively documented, the first record dating back to 1100 BC contains 52 prescriptions by Wushi'er Bingfang. In addition, Shen-nong's Herbal Classics describes 365 drugs and dates back to 100 BC.[60] The documentation of the Indian Ayurvedic system dates back to 1000 BC.[61] The earliest records by Greeks were documented by Theophrastus in 300 BC,[62] and the list can be continued. While plants were more commonly used in traditional medicine, there are examples of the use of fungi, for example, *Piptoporus betulinus* was used as an antiseptic and disinfectant.[63] Examples of other organisms are also reported.[64]

In more modern times, ever since the first isolation of a natural product (i.e. a secondary metabolite) in pure form (morphine (**I-9**), 1805)[29][30] natural products have had a major impact on the discovery of new medicines and the development of the modern pharmaceutical industry.[64]

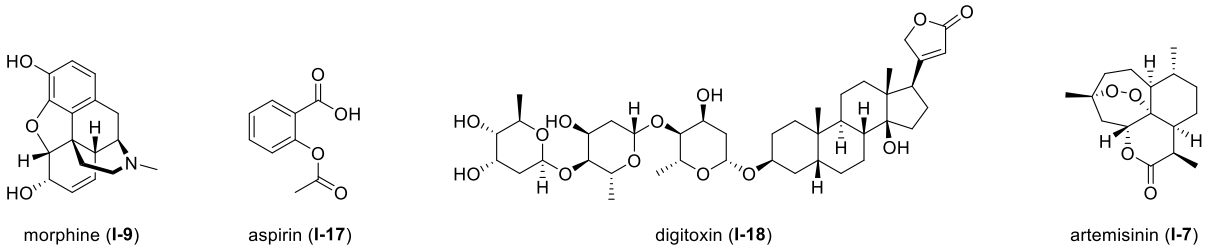


Figure 3. Examples of plant-derived medicines: morphine (I-9) (plant), aspirin (I-17) (plant), digitoxin (I-18) (plant), and artemisinin (I-7) (plant).

To highlight one of the major historical events in NP-based drug research, "penicillin" was discovered by Alexander Fleming in 1928; "penicillin" was the term Fleming used for an extract of the mold *Penicillium rubens* that showed antibacterial activity.[65][66] Subsequent work by Florey and Chain in the 1940s identified penicillin G (I-19) as the active component of this extract.[67] From this, the discovery and development of a multitude of β-lactam antibiotics derived from either the penicillin or the cephalosporin (I-22) core structure followed.

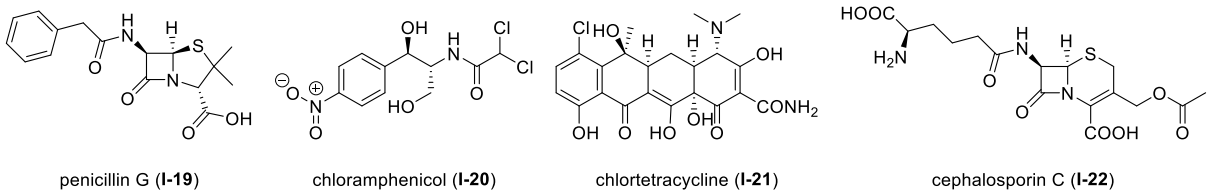


Figure 4. Examples of antibiotics: penicillin G (I-19), chloramphenicol (I-20), chlortetracycline (I-21), and cephalosporin C (I-22).

According to an analysis by Newman and Cragg in 2020, [68] 73% of drugs approved by the FDA between 1981 and 2019 were small molecules, amounting to a total of 1379 new chemical entities (NCEs) (*Figure 5*). Out of these, 427 are unaltered natural products or natural product derivatives, while 489 are inspired by natural products, even if they are synthetic in nature (*Figure 5*). Based on this analysis, Newman and Cragg concluded that 65% of all small molecule drugs approved by the FDA over the last 40 years have their origin in a natural product; in other words, these drugs would not exist without the natural product.

Somewhat different numbers have been derived in other studies. Thus, Patridge and colleagues analyzed all FDA-approved drugs through the end of 2013 and concluded that more than one-third (38%) of all NCEs were derived from natural products.[10]

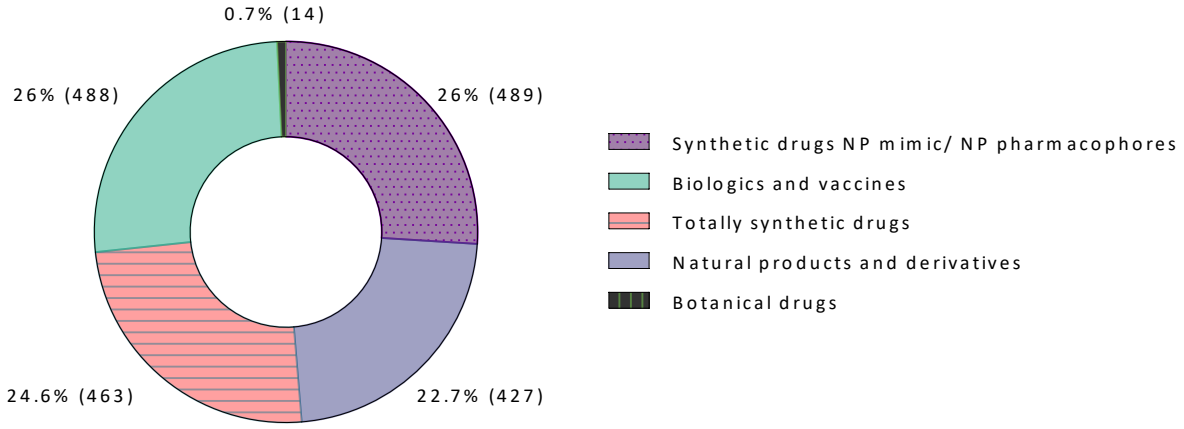


Figure 5. 1881 FDA-approved drugs between 1981 and 2019. Biologics and vaccines are combined in one subgroup for clarity. Subcategories of natural product mimics and natural product pharmacophores are also combined. Adapted from D.J. Newmann and G.M. Cragg, *J. Nat. Prod.* 2020*, 83,* 770–803.[68]

This encompasses unmodified natural compounds, their semi-synthetic derivatives, or synthetic structures inspired by natural products; biologics based on mammalian proteins were excluded from the scope.[10] The same study looked at the number of new natural product-derived drugs approved by the FDA and found that it increased rapidly between 1930 and 1990, although it should be noted that this growth happened at the same rate as an overall increase in FDA approvals. The relative number of approvals based on natural products amounted to more than half of all approvals in the 1930s and 1970s and a third (33%) in the 1950s. The relative and absolute number of NMEs based on natural products has fallen since then and amounted to a quarter (24%) or an average of 7.7 NMEs per year in 2013.[10] The reason for the pharmaceutical industry's move away from NPs towards synthetic compounds has been ascribed to the effort required to develop a successful NP-based drug, including isolation, identification, and total synthesis.[69] On the other hand, Ganesan found that 24 natural products discovered after 1970 led to 49 approved drugs in the period 1981-2006.[70] According to his criteria, there were a total of 58 NCEs derived from NP from 33 natural products as of 2011.[71] This can be considered a success because it means that every year a completely new and unique chemotype derived from a natural product has been converted into a drug, and natural products should not be overlooked.[70]

Independent of the exact numbers, NPs have unquestionably proven to be an important and very productive source of drug candidates and lead structures for drug discovery.[72] This success has been ascribed to a history of co-evolution of NPs with the target sites in biological systems.[73] The strategic integration of a natural product scaffold during the lead optimization process thus allows the creation of successful drug candidates.

1.2.1 Marine natural products in drug discovery

As already discussed in Chapter 1.1, the marine environment represents a largely untapped source of natural products with promising biological activity,[36] some of which belong to chemical classes that are not found in terrestrial environments.[74]

As of March 2024, 12 FDA-approved drugs can be traced back to a marine NP, with an additional two drugs on local markets in Australia and China.[75] While this number is small when compared to HTS-based drug discovery success rates, a total of 14 marketed drugs out of around 40,000 known marine natural products is quite impressive.[76] In addition, 22, 17, and 3 marine-derived drug candidates are in Phase I, II, and III clinical trials, of which 4, 3, and 2 are small molecules, respectively, as the total number also includes antibody-drug conjugates (ADCs).[77]

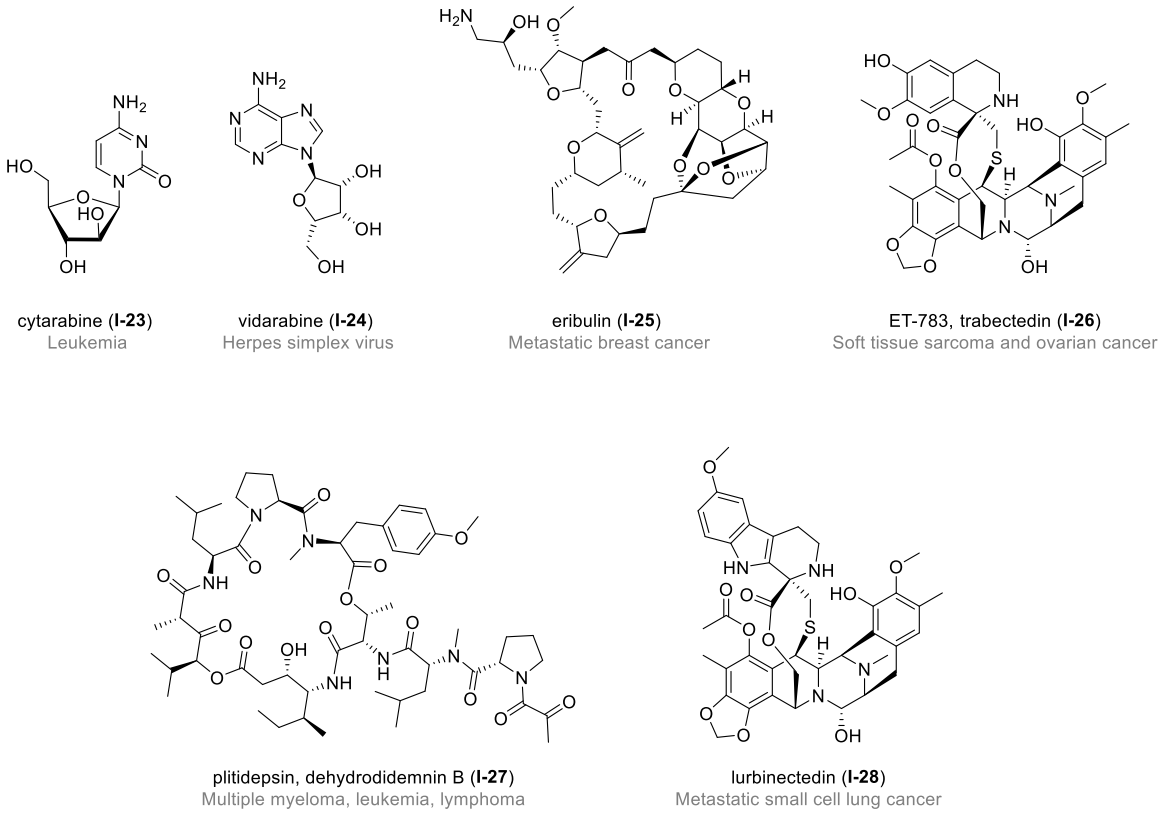


Figure 6. Selected examples of marine NP-derived drugs: cytarabine (**I-23**), vidarabine (**I-24**), eribulin (**I-25**) from the sponge *Halichondria* okadai, ET-783 (**I-26**) from the Caribbean tunicate *Ecteinascidia turbinata*, plitidepsin (**I-27**) from the sea squirt *Aplidium albicans*, and lurbinectedin (**I-28**).

Some examples of marine natural product-derived drugs are depicted in *Figure 6*. The first-ever MNP-inspired FDA-approved drug was cytarabine (ara-C, arabinosylcytosine) (**I-23**) (marketed as Cytozar-U®), which was launched in 1969 as an anti-leukemia drug and is still in use today. This was followed in 1976 by the approval of vidarabine (ara-A, arabinosyladenine) (**I-24**) (marketed as Arasena A®) as an antiviral drug; the latter is no longer used.[75] The NPs that inspired these two nucleoside drugs are

spongothymidine (**I-29**)[78] and spongouridine (**I-30**),[79] which were isolated from the sponge *Tectitethya crypta* in 1951 and 1955, respectively (*Figure 7*).

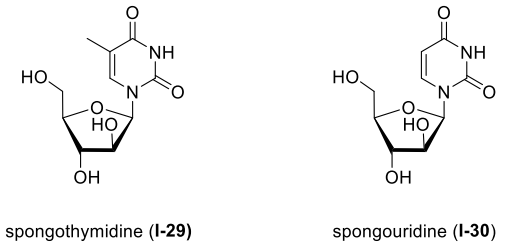


Figure 7. Structures of spongothymidine (**I-29**) and spongouridine (**I-30**), both isolated from *Tectitethya crypta*.

The discovery of these drugs will be discussed in more detail in Chapter 1.3, as they are pioneers not only in drugs that derive from marine sources but also in the area of nucleoside analogs.[31]

It took almost three decades for the next approval of a marine NP-derived drug, namely the snail peptide ziconotide in 2004 (marketed as Prialt®).[80] Ziconotide is an analgesic used for the treatment of severe and chronic pain.[81] The next three drugs (Lovaza®, Vascepa®, and Epanova®) were all polyunsaturated acid derivatives isolated from fish and approved in 2004, 2012, and 2014, respectively, for the treatment of hypertriglyceridemia; Epanova® was discontinued in 2021.[75]

Halichondrin B is a marine macrolide that was isolated from the marine sponge *Halichondria okadai* by Hirata and Uemura in 1986.[82] Eribulin (**I-25**) (*Figure 6*) is a fully synthetic, truncated congener of halichondrin B;[83][84] it is a tubulin polymerization inhibitor that was approved by the FDA in 2010 under the trade name Halaven® for the treatment of metastatic breast cancer.[85] Another structurally complex marine-derived small molecule anticancer drug is the tetrahydroisoquinoline alkaloid ET-783 (**I-26**) (*Figure 6*) (generic name trabectedin). ET-783 was isolated simultaneously by two independent groups from *Ecteinascidia turbinata* in 1990.[86][87] It was approved in Europe in 2007 and in the US in 2015 under the trade name Yondelis®. In Europe, it was approved for the treatment of soft tissue sarcoma[88] and for the treatment of relapsed platinum-sensitive ovarian cancer, whereas in the US for the treatment of liposarcoma or leiomyosarcoma.[85] Although a genuine marine natural product, trabectedin is produced by semi-synthesis from a terrestrial natural product, cyanosafracin B.[89] More recently, an analog of trabectedin, lurbinectedin (**I-28**) (*Figure 6*) was approved under the trade name Zepzelca™ for the treatment of small cell lung cancer;[85] like trabectedin, lurbinectedin is obtained by semi-synthesis from cyanosafracin B, which is produced by fermentation of *Pseudomonas fluorescens*.[90] In 2018, the cyclic depsipeptide plitidepsin (**I-27**) (*Figure 6*) was approved in Australia (as Aplidin®) for the treatment of multiple myeloma, leukemia, and lymphoma. Plitidepsin, also called dehydrodidemnin B, was originally isolated from *Aplidium albicans* in 1991 by Rinehart and Lithgow-Bertelloni;[91] however, the clinical material is produced by chemical synthesis.[92]

Monomethyl auristatin E (MMAE) is a synthetic analog of the marine peptide dolastatin 10, which was first isolated from the sea hare *Dolabella auricularia* by Pettit *et. al.* in 1993.[93] MMAE has gained significant importance as a payload for antibody-drug conjugates. ADCs are composed of an antibody that specifically binds to a cancer-specific antigen, which is connected to a cytotoxic drug cargo through a specifically designed linker.[94] Currently, four ADCs incorporating MMAE as the cytotoxic drug cargo have been approved by the FDA; one additional MMAE-based ADC is approved only in China.

As alluded to above, as of March 2024, three marine-derived drugs are undergoing Phase III clinical trials, two small molecules and one ADC.[95] Tetrodotoxin (**I-31**) is a marine alkaloid with a unique pentacyclic structure (*Figure 8*) that was isolated from a pufferfish.[96] This compound is undergoing phase III clinical trials for chronic/severe pain. Plinabulin (**I-32**) is a synthetic analog of the diketopiperazine phenylahistin (halimide) isolated in 1998 from *Aspergillus sp.* by Jensen and co-workers.[97] **I-32** acts by specific interaction with the colchicine-binding domain of β-tubulin, thereby inhibiting tubulin polymerization;[98] it is being developed for the treatment of non-small cell lung cancer (NSCLC) and brain tumors (*Figure 8*).[95] A new drug application (NDA) for the compound was rejected by the FDA in 2021.

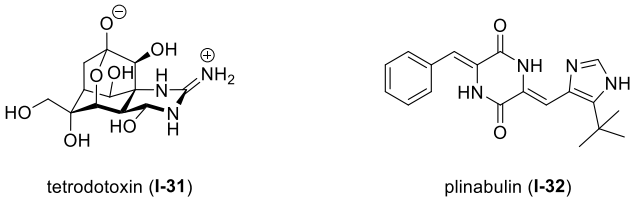
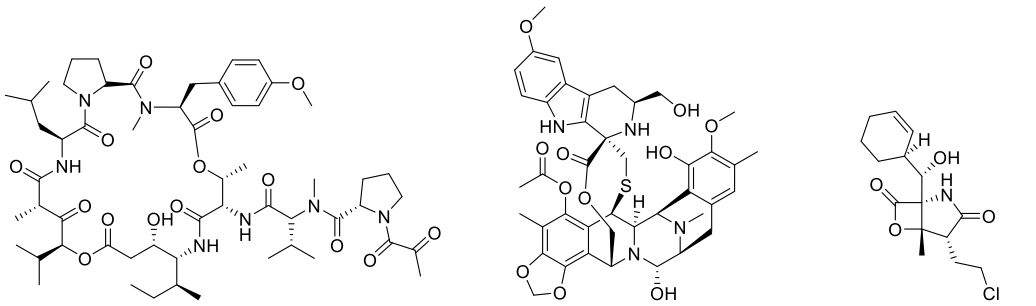


Figure 8. Marine-derived small drug candidates in Phase III clinical trials: tetrodotoxin (**I-31**) and plinabulin (**I-32**).

Phase II clinical trials with marine-derived drug candidates include 14 ADCs, the depsipeptide plitidepsin (**I-27**), the tetrahydroisoquinoline alkaloid analog ecubectedin (**I-33**), and the densely functionalized bicyclic γ-lactam-β-lactone salinosporamide A (**I-34**) (*Figure 9*).[99] Plitidepsin (**I-27**) is the active ingredient of aplidin® (*vide supra*) but it is now also in a Phase II clinical trial against SARS-CoV-2.[100] Ecubectedin (**I-33**), which is an analog of trabectedin and lurbinectedin is being developed for the treatment of solid tumors. Salinosporamide A (**I-34**) is being developed as an anticancer agent.



plitidepsin (**I-27**) ecubectedin (**I-33**) salinosporamide A (**I-34**)

Figure 9. Stage II clinical trials of marine natural products: plitidepsin (**I-27**), ecubectedin (**I-33**). salinosporamide A (**I-34**).

The above analysis of the clinical pipeline of marine-derived drug candidates shows that the majority of them are ADCs (30 out of 42 in total (71%)). However, the distinguishing feature of these ADCs is the targeting antibody, while they are based on only eight different marine-derived payloads. It is also noteworthy that 45 out of 57 marine-derived drugs or drug candidates (79%) are cytotoxic and are being developed for various cancer indications. As discussed in Chapter 1.1, marine organisms may have evolved to produce highly cytotoxic secondary metabolites to ensure effective self-defense under high dilution conditions.[46] Yuan and co-workers have found that 56% of all bioactive marine natural products discovered between 1985 and 2012 exhibit cytotoxic/antiproliferative activity; 13% showed antibacterial properties.[48] Analysis of the website "the Global Marine Pharmaceuticals Pipeline" shows that most marine-derived drugs and drug candidates were isolated from mollusks/cyanobacteria (57.9%), followed by sponges (15.7%), tunicates (10.5%), and fish (8.8%).[77] However, marine flora and fauna are not limited to these types of organisms, there are also marine-sourced fungi and bacteria (e.g. sulfur bacteria). The improvement of sampling techniques (e.g. microbial symbionts, in-situ recovery of expressed and secreted NPs, etc.) together with sampling from new habitats,[32] such as the deep sea, and analytical methods (analytics and informatics) will conceivably enable the discovery of new structurally unique marine natural products from a variety of organisms.

1.2.2 Macrocyclic natural products in drug discovery

While the IUPAC definition of the term "macrocycle" only refers to macromolecular structures,[101] it is commonly understood that macrocycles of lower molecular weight are molecules based on a cyclic framework of 12 or more atoms.[102] This is in line with the IUPAC definition of a "macrolide" as a "macrocyclic lactone with a ring of twelve or more members."

Macrocyclic secondary metabolites are found in organisms from all kingdoms of life, including both terrestrial as well as marine organisms,[103] and they are represented in all major classes of natural products, such as terpenes, peptides, polyketides, or alkaloids.[104] Macrocyclic natural products have

provided the basis for the development of important drugs, either as such or in the form of semi-synthetic derivatives.

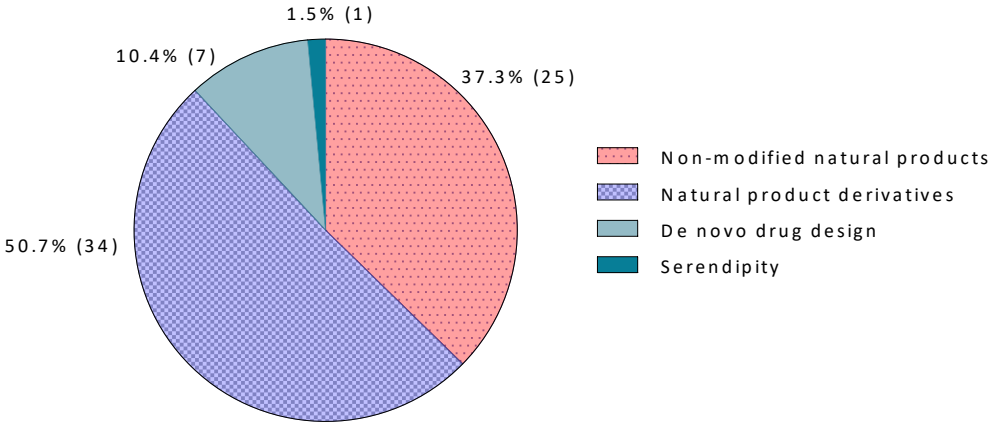


Figure 10. Macrocyclic natural products approved by the FDA as of September 1, 2022. The information was retrieved from the supplementary information of the original publication *J. Med. Chem*. **2023**, *66,* 5377–5396.[105]

As of 2022, 67 macrocyclic drugs have been approved by the FDA,[105][106] of which 25 are unmodified natural products and 34 are natural product derivatives, i.e. 88% of macrocyclic drugs are natural product-derived (*Figure 10*). The majority of these drugs are used to treat cancer or bacterial infections.[105]

Macrocycles can bind to biological targets without major entropic loss and occupy regions of the chemical space that are not covered by smaller molecules. Their conformational flexibility allows them to interact with target proteins across multiple binding sites. They can effectively interact with binding sites that are large, highly polar, lipophilic, flexible, flat, or featureless and thus bind to targets that would be considered "undruggable" by smaller molecules. At the same time, the stereochemical complexity of macrocyclic natural products in particular, combined with a preorganized, rigid structure, allows them to bind to their targets selectively.[107][108] Despite their sometimes considerable size, occupying chemical space outside the conventional rule-of-five drug-like space, macrocycles often exhibit cell-penetrating ability[109] and they can be orally bioavailable.[110]

This PhD thesis is centered on the synthesis of the polyketide-derived marine macrolide macplocimine A. To emphasize the importance of these types of natural products for drug development, *Figure* 12 depicts four examples of (partially) polyketide-derived macrolides that are either drugs themselves or have served as leads for the development of semi-synthetic drugs. In total, 15 of the 67 FDA-approved macrocyclic drugs are derived from six polyketide-derived macrolides alone.[105]

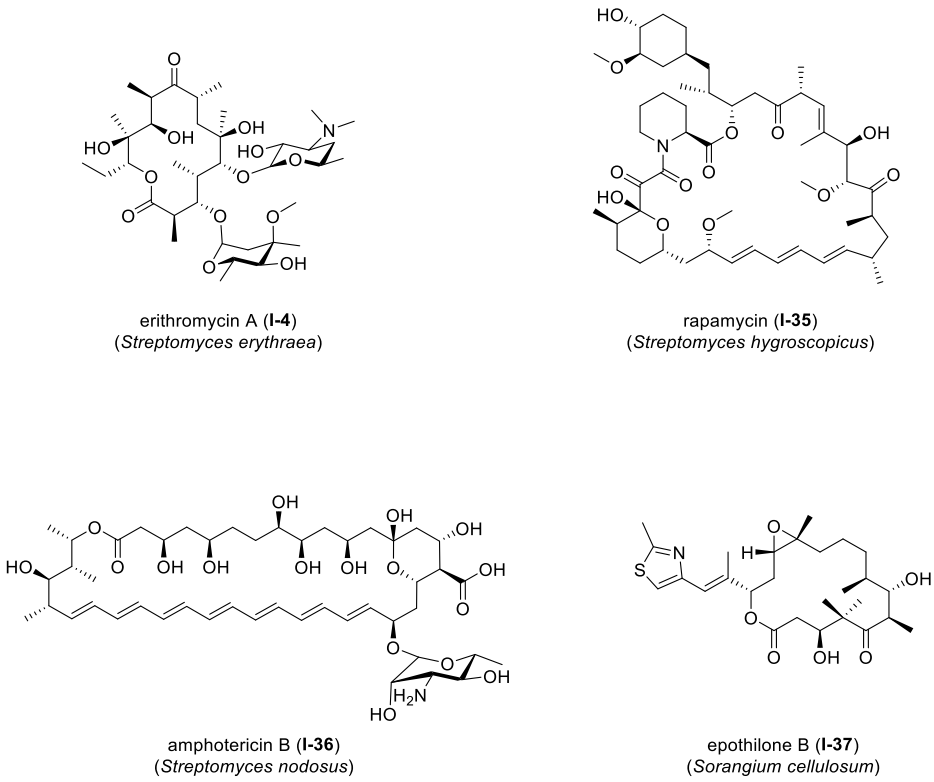


Figure 11. Examples of polyketide-derived macrolide drugs/drug leads along with their producing organism. Erythromycin A (**I-4**), an antibiotic approved in 1952; rapamycin (**I-35**), lymphangioleiomyomatosis; amphotericin B (**I-36**), an antifungal medication approved in the 1990s to treat infections including leishmaniasis; epothilone B (**I-37**), microtubule stabilizing agent.

In addition to those compounds that have led to a marketed drug, a plethora of other bioactive polyketide-derived macrolides have been isolated from both terrestrial and marine organisms.

Of particular interest in the context of this PhD thesis are polyketide-derived marine macrolides. According to an analysis by Zhang and co-workers,[111] 505 new macrolides have been isolated from marine organisms between 1990 and 2020, encompassing a wide range of ring sizes and biological activities. The most frequently observed activity was inhibition of cell growth/cytotoxicity (see also Chapter 1.2.1.).[111] The majority of compounds were isolated from sponges (34%) followed by marine fungi (19%) (*Figure 12*). Marine-sourced bacteria as a source account for 8.5% of all macrocyclic polyketides isolated between 1990 and 2020, including macplocimine A (**I-42**), which is the subject of this PhD thesis.

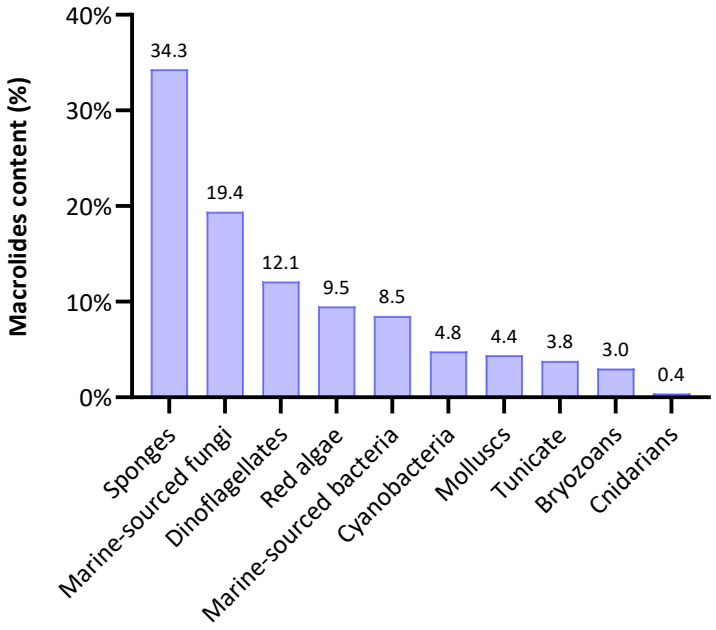
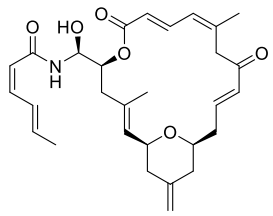
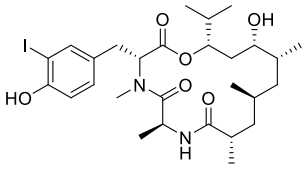


Figure 12. Shares of macrolides from various marine organisms. Adapted from H. Zhang, *et.al. Mar. Drugs* **2021**, *19*, 180, in reference [111].

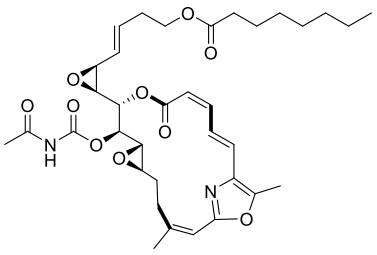
Figure 13 shows four deliberately chosen examples of polyketide-derived macrolides of marine origin that have been the subject of previous synthetic and biological studies in the Altmann group.



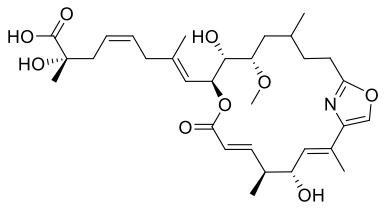
(-)-zampanolide (**I-38**)



doliculide (**I-39**)



salarin C (**I-40**)



leiodolide A (**I-41**)

Figure 13. (-)-Zampanolide (**I-38**), doliculide (**I-39**), salarin C (**I-40**), leiodolide A (**I-41**).

1.3 Macplocimine A

Macplocimine A (**I-42**) (*Figure 14*) is a macrocyclic marine polyketide that was isolated from filamentous sulfur bacteria *Thioplica sp.* in 2013 by Magarvey and co-workers.[112] The structure of macplocimine A features an 18-membered macrolide ring, which is fused to the C(5)-C(6) bond of a resorcinol unit and which carries an N(1)-linked thymine moiety at the carbon α to the ester carbonyl group.

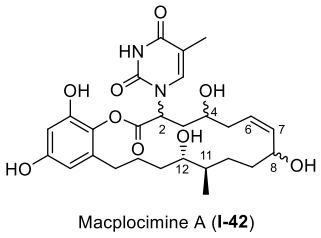


Figure 14. Macplocimine A structure.[1]

The structure of macplocimine A (**I-42**) was elucidated by a combination of HRES mass spectrometry, UV-vis spectroscopy, and different multidimensional NMR experiments. Thus, the molecular formula of macplocimine A (**I-42**) was deduced from an exact molecular mass of 531.2355 $[M-H]^-$ to be $C_{27}H_{36}O_9N_2$. The ^1H, HSQC, and DEPT-Q experiments indicated the presence of a heterocyclic proton at δ_H=7.95 ppm, one N-methine proton at δ_H=5.92 ppm, two olefinic protons at δ_H=5.37 and 5.43 ppm, two aromatic protons at δ_H=6.11 and 6.17 ppm, two methyl groups at δ_H=2.39 and 0.80 ppm, one methine proton at δ_H=1.52 ppm, oxygenated methine groups at δ_H=4.39, 3.80, and 3.46 ppm, and seven methylene groups in the region δ_H=2.73-0.94 ppm.

The connectivity within the backbone structure was established by ^1H, DEPT-Q, ^1H-^1H COSY, HMQC, HMBC, and NOESY NMR experiments (*Figure 15*). The ^{13}C NMR chemical shifts were assigned by analysis of ^1H, ^1H-^1H COSY, HSQC, and HMBC spectroscopic data.

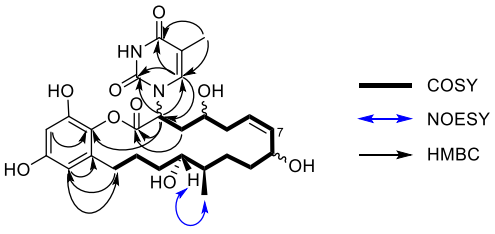


Figure 15. 2D NMR correlations of macplocimine A.

The structure of the thymine moiety and its linkage position to the macrocycle was established by HMBC. Tetra-substitution of the aromatic ring was also determined by HMBC.

[1] Atom numbering is adapted from the original isolation publication.[10]

The *Z* geometry of the double bond was deduced from the vicinal coupling constant between H-6 and H-7.

Importantly, while the planar structure of macplocimine A (**I-42**) could be fully established, its relative and absolute configuration could only be assigned to a very limited extent due to the small amount of material available and the lack of crystals for X-ray analysis. (Only 1.5 mg of material were isolated by extraction). As the only stereochemical feature apart from the *Z* geometry of the C(6)-C(7) double bond, the relative configuration of the methyl group at C(11) and the OH-group at C(12) was assigned as *anti* by NOESY experiments.

The structure of macplocimine A (**I-42**) is unique among macrolides for two major reasons:

(1) Macplocimine A (**I-42**), to the best of my knowledge, is the only macrolide natural product that incorporates a *phenyl ester* moiety. This contrasts with a multitude of natural macrolactones with a *benzoic acid-derived* ester linkage (see Chapter 1.4.).

In contrast to phenyl ester-based macrolactones, non-macrocyclic phenyl esters are widespread in nature. The most abundant class of natural phenyl esters are the coumarins, which are benzopyrone derivatives that are widely distributed across the entire plant kingdom but are also found in bacteria (for example the antibiotic novobiocin (**I-44**)). They protect plants from infection and play a crucial role in plant physiology and biochemistry.[113] Dicoumarol (**I-45**), which is a strong anticoagulant, formed the basis for the development of the anticoagulant drugs warfarin (**I-46**) and phenprocoumon (*Figure 16*).[114]

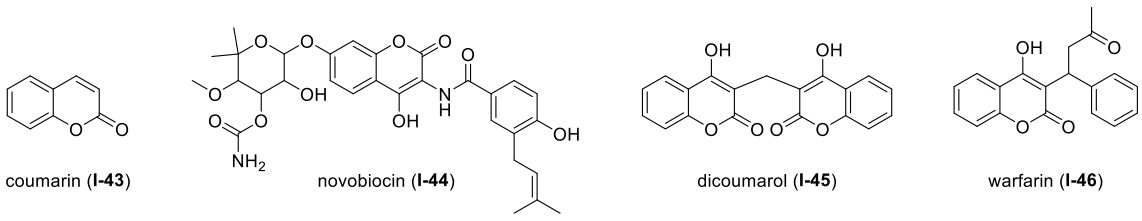


Figure 16. Examples of naturally occurring coumarins as a major class of natural phenyl esters and warfarin (**I-46**) as a synthetic analog of coumarins.

Coumarins, in contrast to macplocimine A (**I-42**), are not polyketides, rather they are produced *via* the shikimate pathway.[115]

(2) Macplocimine A (**I-42**) is the only macrocyclic natural product that carries a nucleobase appended to its backbone structure.

In contrast to nucleobase-bearing macrocycles, secondary metabolites incorporating either furanose- or pyranose-derived N- or C-nucleoside motifs are widespread in nature. These

compounds, which are commonly referred to as nucleoside antibiotics, form a diverse group of secondary metabolites with a wide range of biological activities, including antibacterial, antifungal, antitumor, antiviral, antitrypanosomal, herbicidal, insecticidal, immunostimulatory, and immunosuppressive effects.[116][117] The earliest examples of nucleoside antibiotics are the marine natural products spongothymidine (**I-29**) and spongouridine (**I-30**) (*Figure 17*), which inspired the discovery of the anticancer drugs cytarabine (**I-23**) and vidarabine (**I-24**) that were discussed in Chapter 1.2.1. The discovery of **I-29** and **I-30** in the 1950s by Bergmann and Freeney[78][79] not only stimulated research interest in MNPs but also led to the synthesis of various other arabinose-derived nucleoside analogs [118] such as arabinosylcytosine (**I-23**) and arabinosyladenine (**I-24**), both synthesized in 1959[119] and 1960,[120] respectively. Nikkomycin Z (**I-47**) is a secondary metabolite that was first isolated in 1970 from *Streptomyces tendae* Tü 901 by Dähn *et.al.*[121] and shows fungicidal activity against dimorphic fungi.[122]

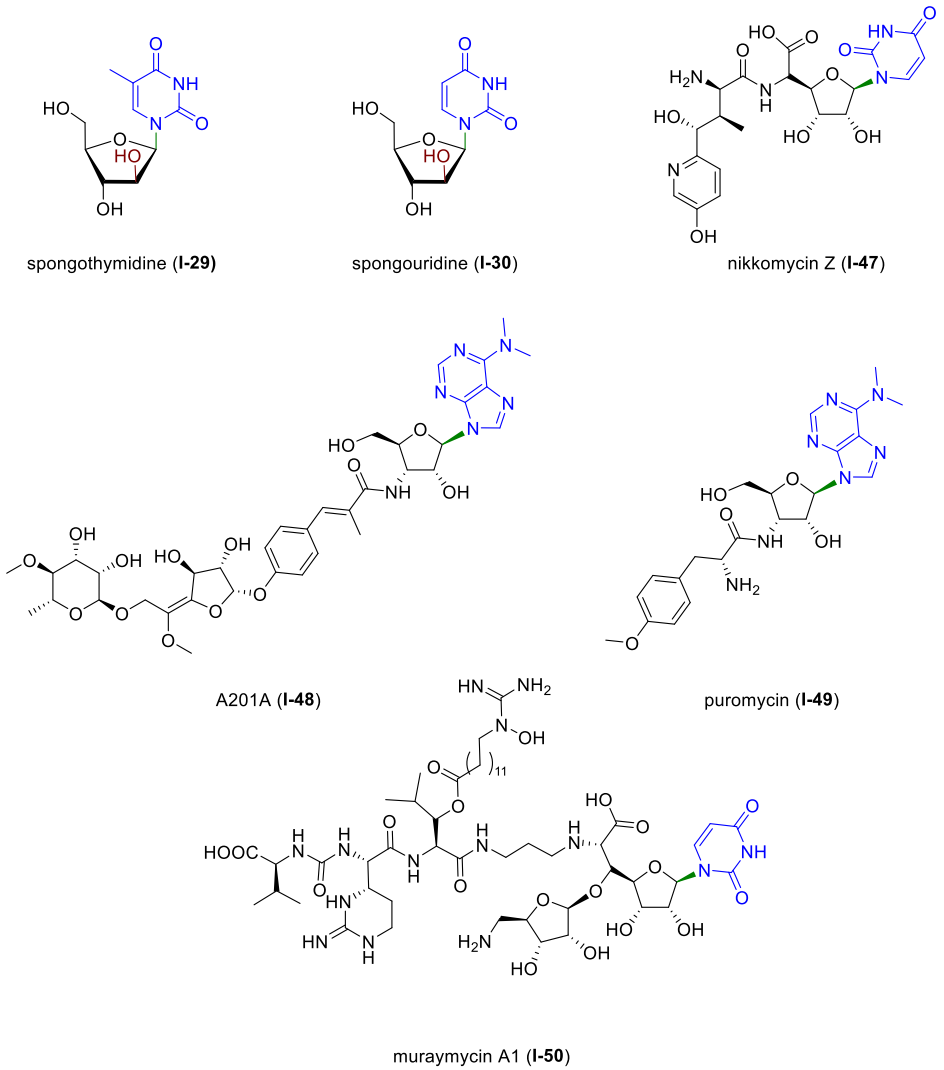


Figure 17. Structures of the natural products spongothymidine (**I-29**) and spongouridine (**I-30**), and other selected examples of nucleoside antibiotics: nikkomycin Z (**I-47**), A201A (**I-48**), puromycin (**I-49**), and muraymycin A1 (**I-50**).

A201A (**I-48**) was first isolated in 1976 from a strain of *Streptomyces capreolus* by Kirst *et.al.*[123] In 2012, it was isolated from *Actinomycetes thermotolerans* collected from deep-sea sediment by Zhu *et.al.*[124] The first total synthesis of **I-48** was achieved by Yu and co-workers in 2014.[125] Puromycin (**I-49**) is an aminonucleoside antibiotic produced by *Streptomyces alboniger.*[126] In 2002, 19 muraymycins, a class of nucleoside-peptide antibiotics, including muramycin A1 (**I-50**), were isolated from a broth of *Streptomyces sp.* by McDonald *et.al.*[127] Muramycin A1 (**I-50**) exhibits activity against gram-positive bacteria (*Staphylococcus* MIC: 2–16 μg/mL, *Enterococcus* MIC: 16–64 μg/mL) and some gram-negative bacteria (*E. coli* MIC: 0.03 μg/mL).[127]

As for macplocimine A (**I-42**), nothing is known about its biological activity and it remains to be determined whether the compound may display activities similar to those of nucleoside antibiotics. Likewise, the biosynthesis of **I-42** has not been investigated. Based on its structure, however, it has been suggested that macplocimine A (**I-42**) is of polyketide origin. Finally, no synthetic efforts related to **I-42** have been reported in the literature.

Of particular note, to the best of my knowledge, no secondary metabolites other than **I-42** have been reported from *Thioploca* and *Beggiatoa,* which are two genera of sulfur-oxidizing bacteria that are abundant in highly specific sulfur-rich marine environments, such as continental shelves, cold seeps, and deep-sea hydrothermal vents.[128] Whether the particular source of macplocimine A can explain its special structural features remains speculative at this point.

Given the structural singularity of macplocimine as a natural product, it is difficult to place the compound into a narrower structural context. The closest structural relationship of macplocimine A (**I-42**) to a specific subclass of macrolide natural products is with a group of resorcylic acid-derived macrolactones that are commonly referred to as "resorcylic acid lactones" (RALs). In light of this structural similarity, the structures, biosynthesis, biological activities, and total syntheses of RALs will be briefly discussed in the following chapter.

1.4 Resorcylic acid lactones (RALs)

1.4.1 Structural properties

Resorcylic acid lactones (RALs) are a family of naturally occurring macrolides of 2,4-dihydroxybenzoic acid (resorcylic acid) (*Figure 18*).[129] They are all fungal metabolites, with the vast majority isolated from terrestrial organisms; however, individual RALs are also produced by marine fungi.[130]

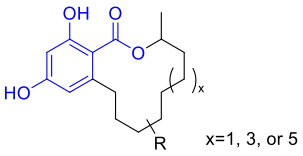


Figure 18. Generalized structure of resorcylic acid lactones (RALs). The resorcylic acid unit is shown in blue.

RALs can be divided into three subclasses based on the size of the macrolactone ring, which can comprise 12, 14, or 16 atoms.[129] The majority of RALs are 14-membered macrolactones, with more than 100 representatives of this subgroup reported as of mid-2021, followed by more than 40 12-membered RALs.[129] RALs with a 16-membered ring are a relatively recent discovery, the first examples of this subgroup were isolated and characterized only in 2020.[131]

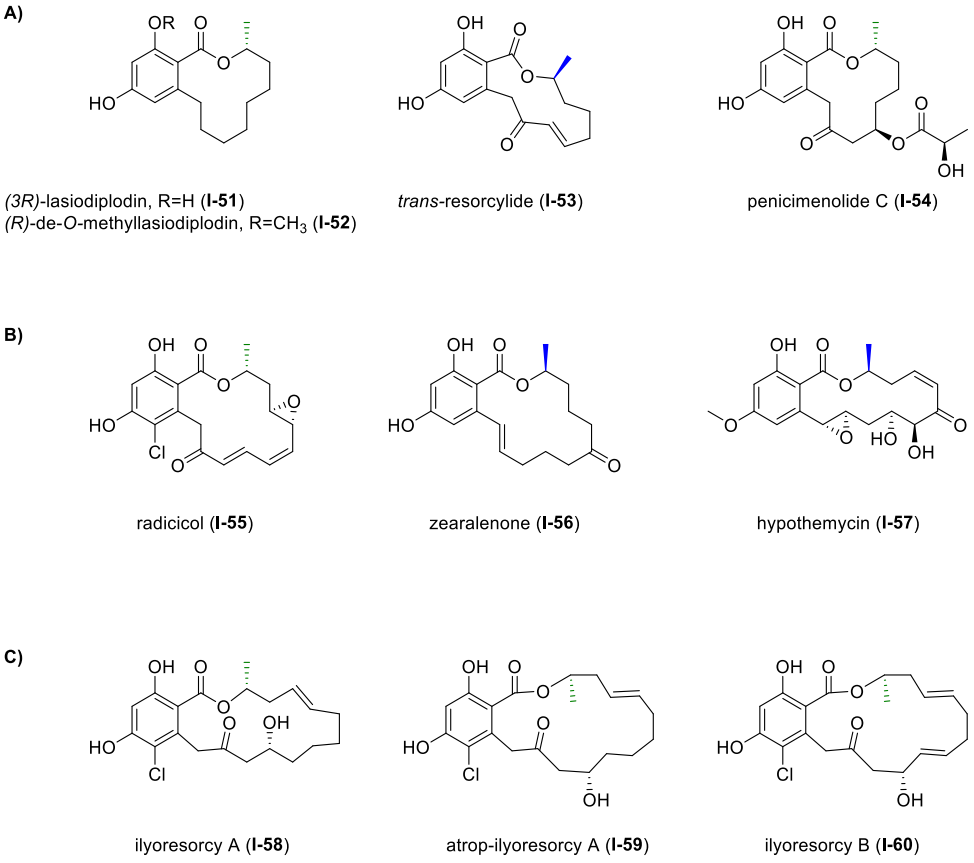


Figure 19. Selected 12-membered (A), 14-membered (B), and 16-membered RALs (C).

Importantly, no RALs with ring sizes >16 have been described so far. Examples of selected RALs with different ring sizes are shown in *Figure 19*. The first RAL to be isolated was radicicol (**I-55**) in 1953 from *Monosporium bonorden*.[132] Other prominent 14-membered RALs are zearalenone (**I-56**) (isolated in 1962)[133] and hypothemycin (**I-57**) (isolated in 1980).[134] Lasiodiplodin (**I-51**) and (*R*)-de-*O*-methyllasiodiplodin (**I-52**) as the first 12-membered RALs were isolated in 1971 from the plant pathogen *Lasiodiplodia theobromae*.[135] Only three 16-membered RALs have been reported so far by Zhou and co-workers in 2020, ilyoresorcy A (**I-58**), atrop-ilyoresorcy A (**I-59**), and ilyoresorcy B (**I-76**) from the soil-derived fungus *Ilyonectria sp.* sb65.[131]

Interestingly, **I-58** and **I-59** have the same planar structures and absolute configurations, confirmed by X-ray crystallography, but the benzene part is spatially arranged differently in the two natural products.[131]

All of the above RALs were originally isolated from terrestrial fungi. However, as alluded to at the beginning of this section, more recently RALs have also been obtained from marine sources. These include compounds that are also produced by terrestrial fungi, such as zearalenone (*Figure 19*, **I-56**), which was previously isolated from corn infected by *Gibberella zeae*[133] and also isolated from a marine strain of the fungus *Penicillium sp.,*[136] and hypothemycin (**I-57**), which was previously isolated from *Hypomyces trichothecoides*[134] and later from the marine-sourced mangrove fungus *Aigialus parvus* BCC 5311 together with other new RALs.[137]

However, a number of marine-derived RALs are currently unique to marine fungi, although this does not exclude the possibility that they are also produced by terrestrial organisms. RALs that have been isolated only from marine fungi include 8'-hydroxyzearalanone[2,3] (*Figure 20*, **I-61**) and 2'-hydroxyzearalanol (*Figure 20*, **I-62**) isolated from a marine strain of *Penicillium sp.*[136] Aigialomycins B, C, and D,[4] (*Figure 20*, **I-63**, **I-64**, **I-65**) were isolated from the marine-sourced mangrove fungus *Aigialus parvus* BCC 5311.[137] 5-Bromozeaenol (**I-66**) and 3,5-dibromozeaenol (**I-67**) were isolated from the marine-derived fungus *Cochliobolus lunatus* in 2014.[138] Cochliomycin A, B, and 5-chlorinated cochliomycin C (*Figure 20*, **I-68**, **I-69**, **I-70**, respectively) were isolated from marine fungi *Cochliobolus lunatus* obtained from the gorgonian *Dichotella gemmacea*.[139]

[2] Atom numbering is adapted from the original isolation publication.[136]

[3] The isolation paper uses the older numbering system.

[4] [3]Atom numbering is adapted from the original isolation publication.[137]

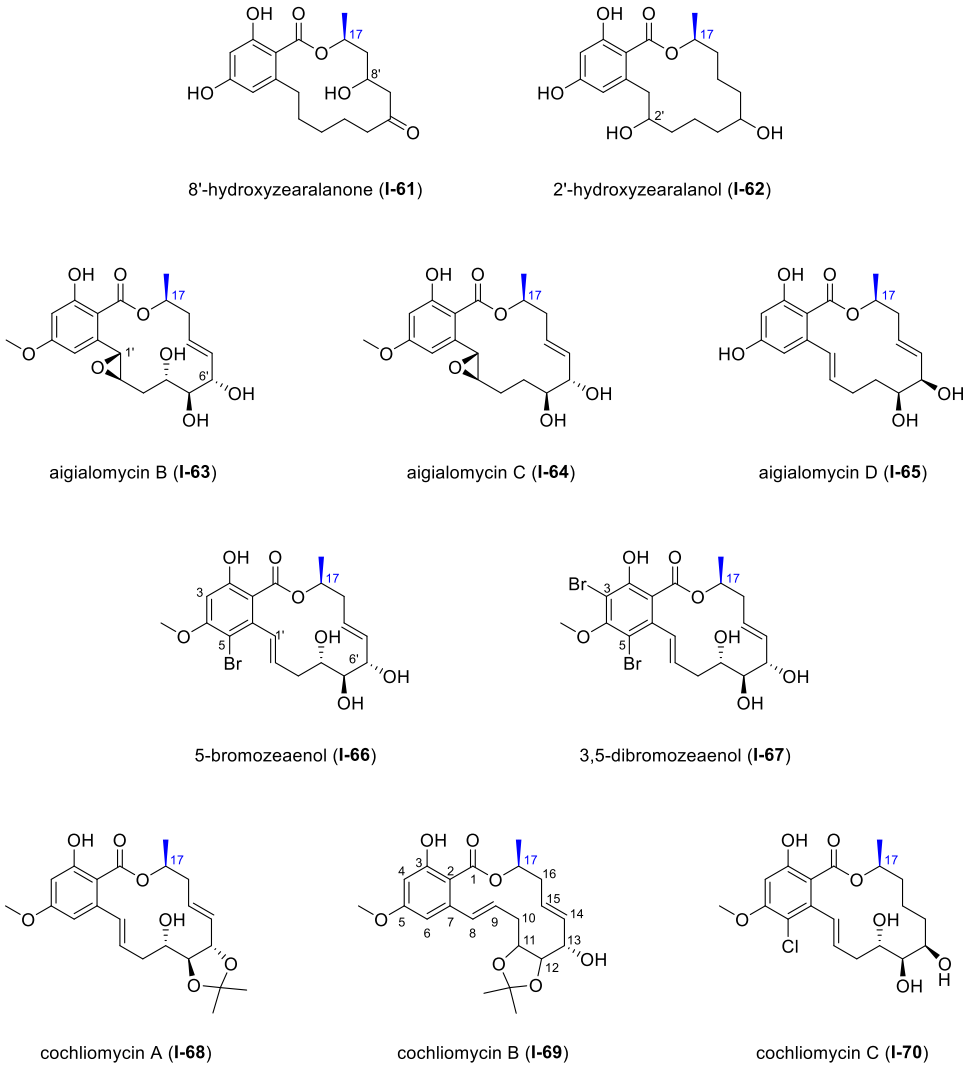


Figure 20. Marine-derived new zearalanone (RAL) analogs.

Although it may not be obvious from the examples shown above, in general, 14-membered RALs with *17S*[5] configuration are more common than RALs with *17R*.[140] Finally, it should be noted that the genera *Monocillium* and *Pochonia* mainly produce RALs with *17S* configuration (for example, zearalenone (**I-56**) or hypothemycin (**I-57**)), whereas *Fusarium, Cochliobolus,* and *Hypomyces sp.* produce *17R* RALs. There are also rare examples of fungi that produce RALs with both configurations at C(17).[141]

[5]Numbering adapted from the original publication.[140] In the old numbering system, it would be position 10', and in the IUPAC system, it would be position 3.[314]

1.4.2 Biosynthesis of RALs

1.4.2.1 General principles of polyketide biosynthesis

Polyketides are classified by their structure and the type of polyketide synthase (PKS) that produces them. The three categories of polyketides are type I, type II, and type III, which are produced by type I PKS, type II PKS, and type III PKS, respectively. Polyketide synthases are a family of enzymes or enzyme complexes with multiple domains that enable the stepwise assembly of various carbon skeletons from simple activated carboxylic acid units.[142] The key step is the C-C bond-forming condensation between an α-carboxyacyl moiety (malonyl CoA, methylmalonyl CoA, etc.) and an acyl moiety (for example of the acetyl-coenzyme A [CoA]) that releases CO_2. The type I PKS possesses a multidomain architecture, whereas the type II PKS consists of discrete monofunctional enzymes.[142] In contrast, the type III PKSs are smaller homodimeric proteins (40 kDa) that produce a polyketide within a single active site.[143] It is also possible to classify PKSs into iterative and non-iterative: iterative type I PKSs are common for fungi, and non-iterative type I PKSs are common for bacteria.[144]

The PKS I contains several modules that consist of domains with defined functions. The assembly starts with a loading module (acyltransferase (AT), acyl carrier protein (ACP)), and the chain elongation takes place with a variety of other modules. For example, the chain growth is achieved *via* decarboxylative Claisen condensation through the ketosynthase (KS). Among the other important domains that would provide the structural diversity of the produced polyketides in the elongation stage are the ketoreductase (KR) domain that reduces the ketone, the dehydratase (DH) domain that generates the α,β-unsaturated moiety through dehydration, the enoyl reductase (ER) that can further reduce it to a fully saturated chain, and the methyltransferase (MT) domain.[145] The fully functionalized and elongated chain is then transferred to a termination/release domain, e.g. a thioesterase (TE) domain.

Selected examples of type I polyketides are presented in *Figure 21*. As can be seen from the figure, epothilone B (**I-35**) and rifamycin S (**I-72**) do not exclusively come from the PKS I, and in fact, many secondary metabolites are of mixed origin, for example, polyketide/non-ribosomal peptide[146] or polyketide/shikimic acid origin.[147]

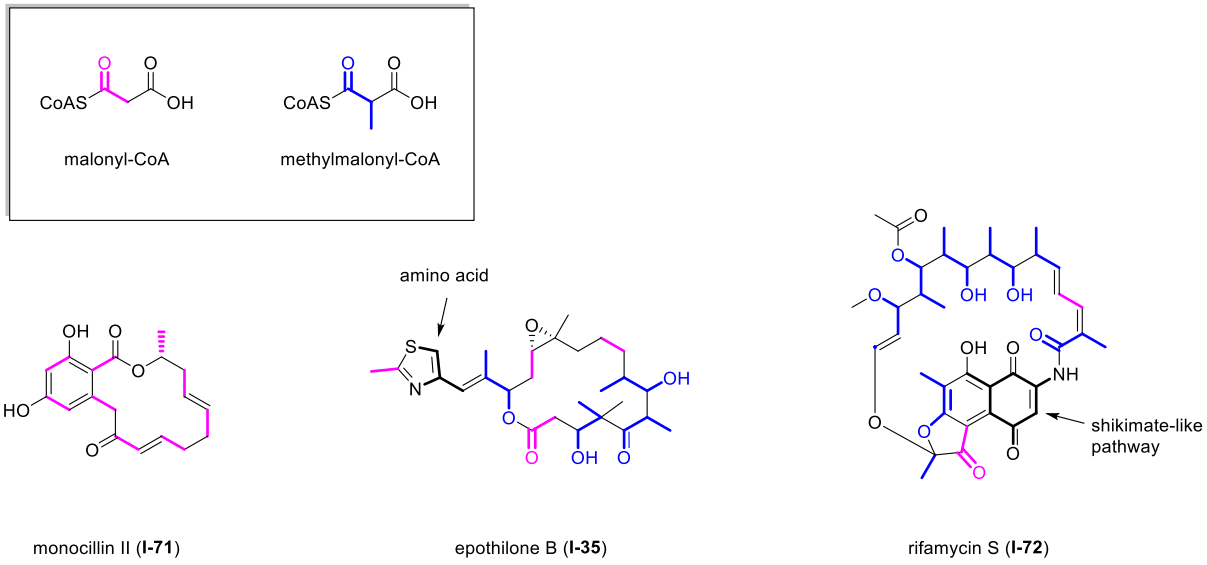


Figure 21. "Retrobiosynthetic" analysis of representative polyketide metabolites that illustrate their assembly from two acyl-CoA precursors – malonyl-CoA (in pink) and methylmalonyl-CoA (in blue). The parts of the molecules depicted in black derive from alternative classes of monomers that are indicated in black. Adapted from *Compr. Nat. Prod. III, Elsevier,* **2020**, *pp. 4–46.*[148] Monocillin II (**I-71**),[149] epothilone B (**I-35**),[150] and rifamycin S (**I-72**)[151].

PKSs II are found in bacteria and fungi. Examples of type II polyketides are given in *Figure 22* and include well-known molecules such as doxocycline (**I-73**), tetracycline (**I-1**), and doxorubicin (**I-74**).[152]

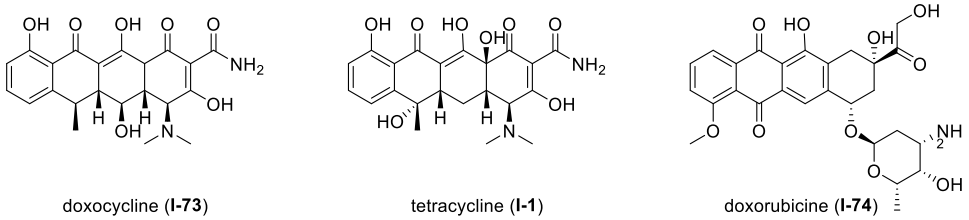


Figure 22. Polyketides assembled by PKSs type II: doxocycline (**I-73**), tetracycline (**I-1**), and doxorubicin (**I-74**).

The type III PKSs are the smallest and simplest of all PKS enzymes[153] and are found in higher plants. Examples of type III polyketides are given in *Figure 23*. A well-known substance, curcumin (**I-75**), is produced by two type III PKSs.[154] Stilbenes, such as combretastatin A4 (**I-76**), also belong to the family of type III polyketides.[155] Strobopinin (**I-77**) is another example of a molecule produced by this type of PKS.[143]

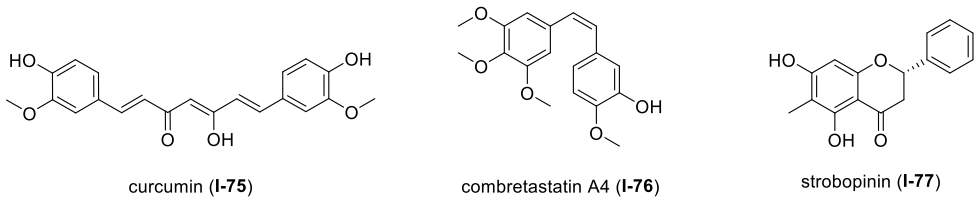


Figure 23. Polyketides assembled by type III PKSs: curcumin (**I-75**), combretastatin A4 (**I-76**), and strobopinin (**I-77**).[143]

1.4.2.2 Biosynthesis of 14-membered RALs

The biosynthesis of the carbon scaffold of 14-membered RALs is schematically illustrated in *Figure 24* for radicicol. The pathway involves two highly cooperative *iterative* type I PKSs: a highly reducing PKS (hrPKS) (Rdc5) and a non-reducing PKS (nrPKS) (Rdc1).

The hrPKS Rdc5 contains the following domains: the acyl carrier protein (ACP), which serves as the tether of the growing chain, the malonyl-CoA:ACP transacylase (MAT), which selects the building block malonyl-CoA, and the ketosynthase (KS), which performs the decarboxylative condensation. It also has the complete ensemble of modification domains (KR, DH, and ER, discussed earlier).

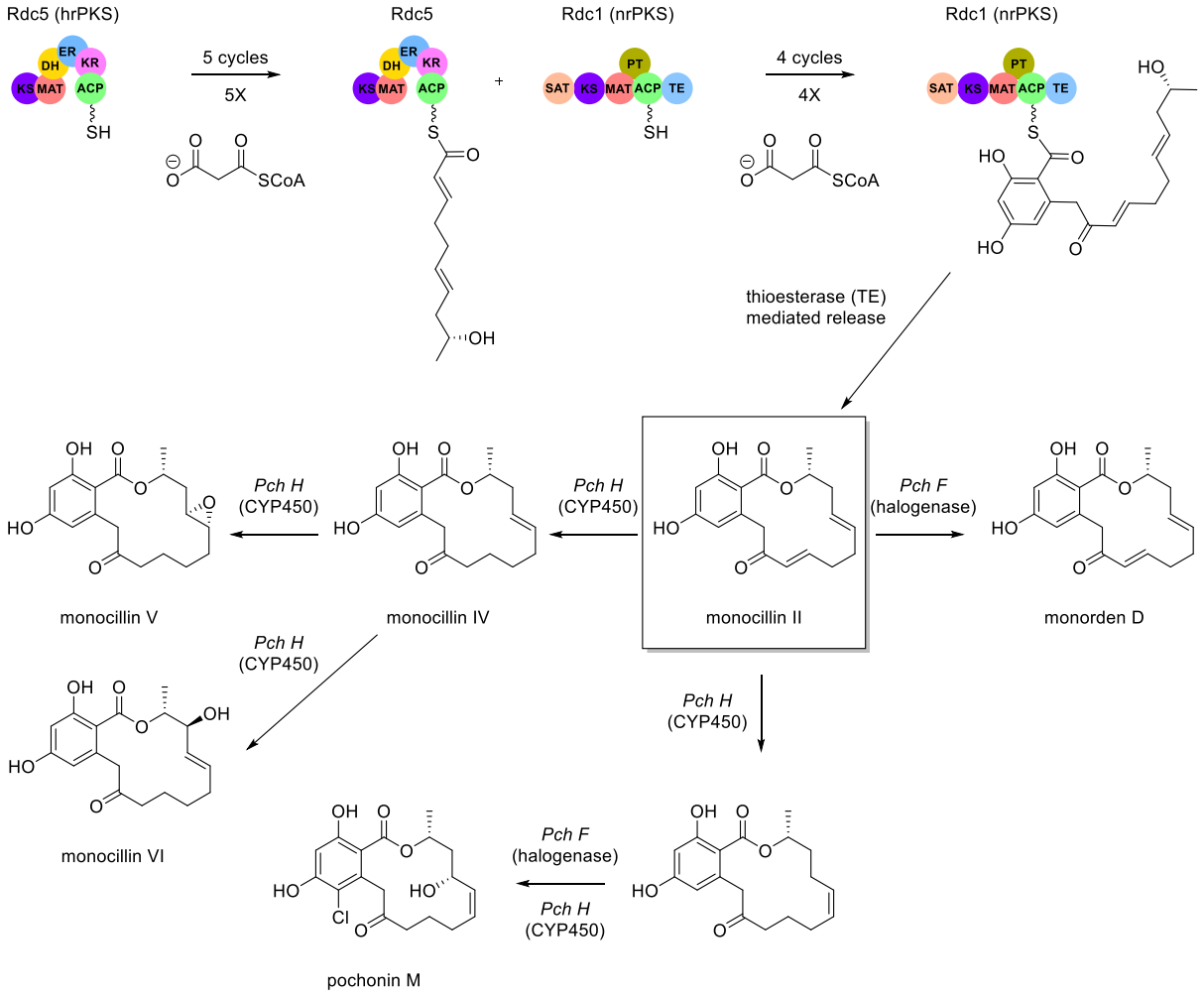


Figure 24. Biosynthesis of the 14-membered RAL radicicol. Two main iterative PKSs (hrPKS and nrPKS).Acyl carrier protein (ACP), malonyl-CoA:ACP transacylase (MAT), ketosynthase (KS), ketoreductase (KR), dehydratase (DH), enoyl reductase (ER), thioesterase (TE), CYP (cytochrome enzyme). Adapted from *Arch. Pharm. Res*. **2020**, *43*, 1093–1113.[140]

The hrPKS Rdc5 generates the alkyl portion of the RAL from five malonate units and processes them to the final oxidation state at each carbon.

The nrPKS Rdc1 consists of an N-terminal starter unit: the ACP transacylase (SAT), which transfers the reduced polyketide from Rdc5 to Rdc1. Insertion of four additional malonate units without subsequent carbonyl reduction generates a nonaketide, which is then cyclized at the product template (PT) domain to form the resorcylate core.[156] The C-terminal thioesterase (TE) domain performs macrolactonization with simultaneous release from the nrPKS.[157]

Most biosyntheses of RALs follow this mechanistic pathway to the point of monocillin II. Monocillin II can then be converted into a variety of different biosynthetic end products by subsequent tailoring reactions with different enzymes (such as oxidations, reductions, or halogenations); this includes, for example, monorden D, pochonin M, monocillin V, or monocillin VI (*Figure 24*).[140]

Radicicol (*Figure 19* B, **I-55**) and zearalenone (*Figure 19* B, **I-56**) have the same structural skeleton but the opposite stereochemical configuration at C(17)[6], which derives from the opposite stereochemical configurations of the secondary alcohol involved in lactone formation.[158]

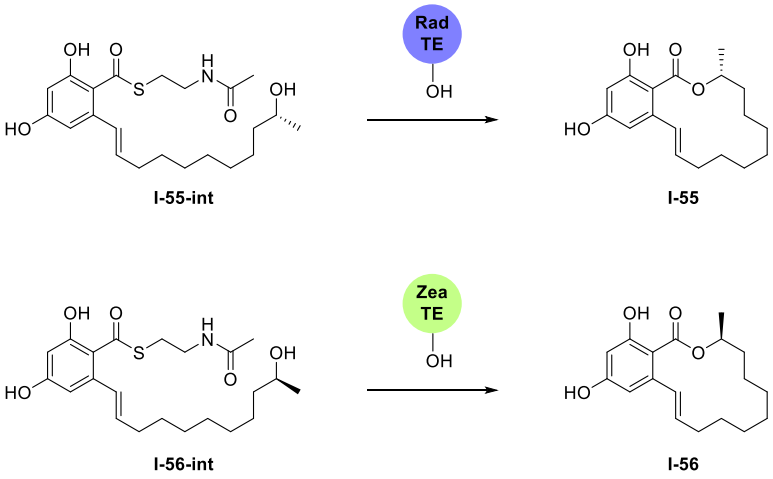


Figure 25. Radicicol (**I-55**) and zearalenone (**I-56**) released by the TE domain. Rad TE: radicicol biosynthesis TE domain; Zea TE: zearalenone biosynthesis TE domain. Adapted from the reference *Org. Lett*. **2014**, *16,* 5858–5861.[158].

Heberlig *et.al.*[158] synthetically prepared enantioenriched substrates that mimic the native linear completed polyketide intermediates **I-55-int** and **I-56-int**. N-acetylcysteamine thioester (SNAC) is used to activate the carboxylate for reaction with the active site serine of the thioesterase (TE) and to mimic the phosphopantheteine arm of the ACP domain that delivers the linear polyketide to the TE *in vivo*. The TEs from the biosynthetic pathways of radicicol and zearalenone were shown to macrocyclize both D- and *L*-configured synthetic substrate analogs, therefore confirming that these enzymes were highly stereotolerant (*Figure 25*).[158]

[6] Numbering adapted from the original publication.[140] In the old numbering system, it would be position 10', and in the IUPAC system, it would be position 3.[314]

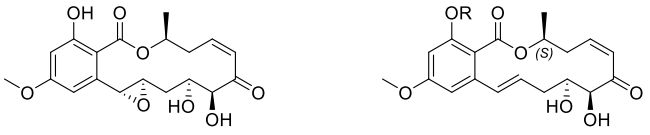
The biosynthesis of 12-membered RALs (RAL_{12}) is similar to that of 14-membered RALs (RAL_{14}). The iterative polyketide synthases hrPKS and nrPKS are involved, however, using one malonyl-CoA unit less. Overall, RAL_{12} consists of eight malonate-derived C_2 units instead of nine for RAL_{14}. Thus, instead of the five malonate-derived C_2 units utilized in the first step (hrPKS) to form the alkyl portion of RAL_{14}, five or four malonate units may form the alkyl portion of the structure for RAL_{12}. The nrPKS uses three or four malonate-derived C_2 units instead of four malonate-derived C_2 units used in the biosynthesis of RAL_{14}, , depending on how many were involved in the decarboxylative condensation in the first step by the hrPKS.[159]

To the best of my knowledge, the biosynthesis of 16-membered resorcylic acid lactones has not been elucidated yet, but it can be speculated that an additional building block is incorporated during chain elongation, mediated by eitherthe hrPKS or the nrPKS.

1.4.3 Biological activity of RALs

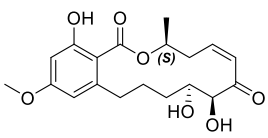
RALs have been reported to exhibit a wide range of biological activities, including antibiotic, cytotoxic, antimalarial, antiproliferative, or estrogenic effects; they have also been shown to inhibit Hsp90, WNT-5A, and a number of protein kinases. These effects have been reviewed[160] and shall not be discussed here in detail.

In the context of possible biological activities of macplocimine A (**I-42**), it is important to note, however, that highly potent protein kinase inhibition has only been observed for those RALs that incorporate an enone moiety as part of their macrolactone ring (hypothemycin (**I-57**), 5Z-7-oxo-zeaenol (**I-78**), L-783,277 (**I-79**), and LL-Z1640-2 (**I-80**) depicted in *Figure 26*). The latter can react with protein kinases that contain a cysteine residue in their ATP binding site leading to covalent enzyme inhibition.

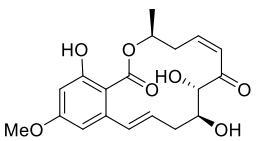


hypothemycin (**I-57**)

5Z-7-oxo-zeaenol (**I-78**)



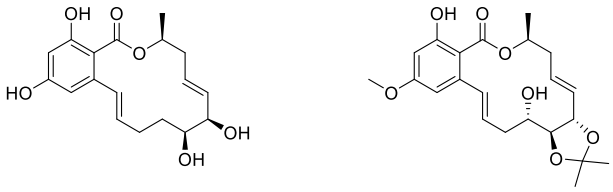
L-783,277 (**I-79**)



LL-Z1640-2 (**I-80**)

Figure 26. 14-membered RALs with potential anticancer activities.

As macplocimine A (**I-42**) does not incorporate an enone moiety, it may not be expected to be a potent kinase inhibitor. Therefore, this subchapter discusses activities other than kinase inhibition. In addition, the focus is on marine-derived RALs and 16-membered RALs, as the latter are closest in terms of ring size, since macplocimine A (**I-42**) is an 18-membered macrolide and an MNP.



aigialomycin D (**I-65**) cochliomycin A (**I-68**)

Figure 27. RALs with promising biological activity that do not incorporate an enone moiety.

Aigialomycin D (**I-65**), a 14-membered RAL of exclusively marine origin that also bears an enol moiety similar to that of macplocimine, was shown to be cytotoxic against cancer cells KB (IC_{50} = 3 µg/mL) and have a moderate antimalarial activity.[137] Aigialomycins were also tested against Vero cells (African green monkey kidney fibroblasts) and aigialomycin D (**I-65**) showed the best result with IC_{50}=1.8 µg/mL, while other compounds were inactive at concentrations of 20 µg/mL. Aigialomycin D (**I-65**, *Figure 27*) also showed moderate kinase inhibition activity, even though it does not have the necessary *cis*-enone moiety.[161] Another family of 14-membered RALs, the cochliomycins, was tested against the larval settlement of the barnacle *Balanus amphitrite,* and cochliomycin A (**I-68**, *Figure 27*) showed potent antifouling activity with an EC_{50} 1.2 µg/mL and an LC_{50}/EC_{50} > 16.7.[139] The mechanism of action has been studied and elucidated to act by activating the NO/cGMP pathway.[162]

The 16-membered RALs ilyoresorcy A, ilyoresorcy B, and atrop-ilyoresorcy A (*Figure 19*, C), which are structurally closest to macplocimine A in terms of ring size, have been shown to have the ability to resist tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) in TRAIL-resistant A549 human lung adenocarcinoma cells.[131] Atrop-ilyoresorcy A (*Figure 19*, **I-59**) also showed inhibition of ConA-induced T-cell proliferation, with an IC_{50} of 4.1 µM and of LPS-induced B-cell proliferation with an IC_{50} of 9.8 µM.[131]

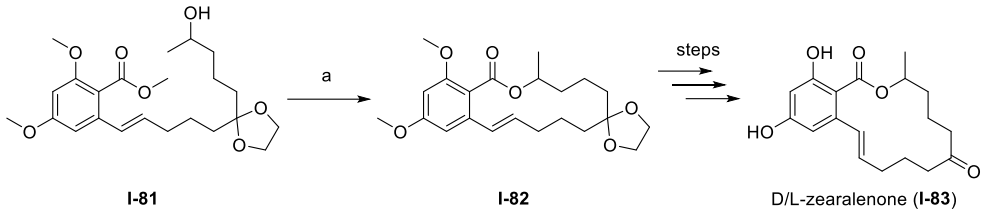
1.4.4 Total synthesis of RALs: acrocyclization approaches

To provide at least some general context for the projected total synthesis of macplocimine A (**I-42**), this chapter will provide a brief review of some of the essential aspects of the work that has been reported on the total synthesis of RALs. Particular emphasis will be put on the methods that have been employed for macrocyclic ring closure.

1.4.4.1 Macrolactonization

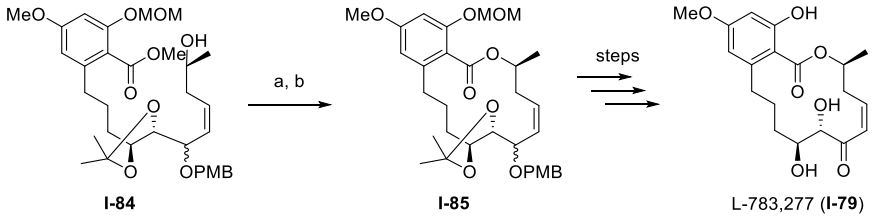
Macrolactonization of a *seco* acid (or *seco* acid ester) is the most frequently employed macrocyclization method in the synthesis of RALs, either by C(=O)–O (carboxylate activation) or by C(=O)O–C (hydroxy group activation) bond formation.[160][163]

Thus, the first total synthesis of D/L-zearalenone (**I-83**) by Vlattas in 1968[164] was based on the sodium *t*-amyloxide-mediated transesterification of the *seco* ester **I-81** to deliver the macrocyclic intermediate **I-82**, albeit in low yield (8%) (*Scheme 1*).



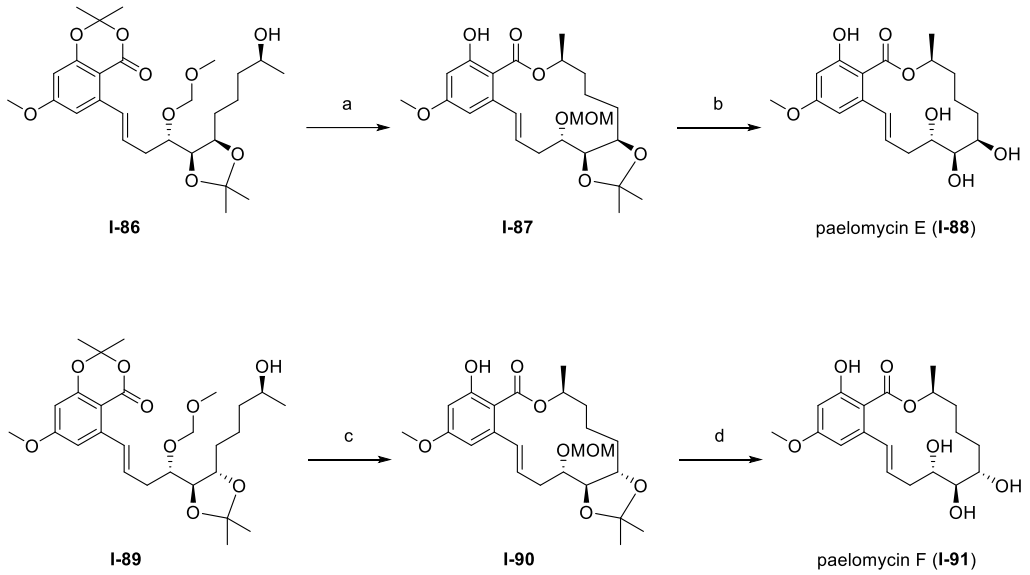
Scheme 1. Total synthesis of D/L-zearalenone by L. Vlattas *et.al.*[164] Reagents and conditions: a) Na *tert*-pentoxide, 8%.

More recently, Sim and co-workers employed a Yamaguchi macrolactonization protocol[165] for the macrocyclization of a *seco* acid starting from ester **I-84** as part of their total synthesis of L-783,277 (**I-79**) (*Scheme 2*).[166] Macrolactone **I-85** was obtained in 23% yield from *seco* ester **I-84** in two steps.



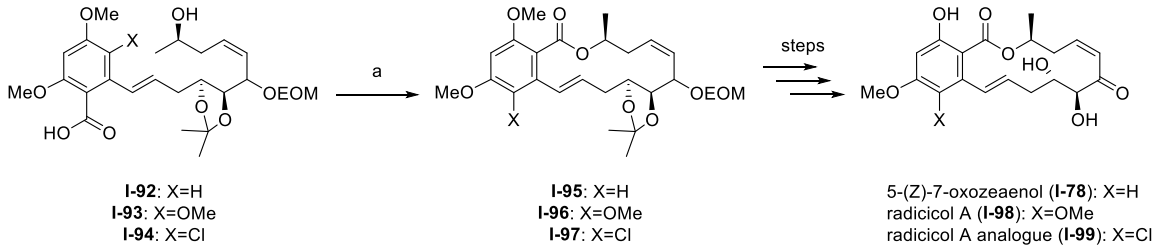
Scheme 2. Total synthesis of L-783,277 by H. G. Choi *et.al.*[166] Reagents and conditions: a) NaOH, EtOH/H_2O, 120 ˚C, 8 h; b) 2,4,6-trichlorobenzoyl chloride, TEA, THF, rt, 3 h, DMAP, toluene, reflux, 24 h, 23% (over 2 steps).

In 2015, Bhunia & Das reported the stereoselective total synthesis of paecilomycins E (**I-88**) and F (**I-91**) *via* base-mediated macrolactonization of dioxolanones **I-86** and **I-89**, respectively, followed by acetonide cleavage (*Scheme 3*).[167] The macrocyclizations proceeded in 79% and 89 % yield, respectively.



Scheme 3. Total synthesis of paecilomycins E and F by Bhunia & Das.[161] Reagents and conditions: a) NaHMDS, THF, –78 °C to rt, 6 h, 79%; b) 2 M HCl, THF, 10 h, 89%; c) NaHMDS, THF, –78 °C to rt, 81%; d) 2 M HCl, THF, 10 h, 86%.

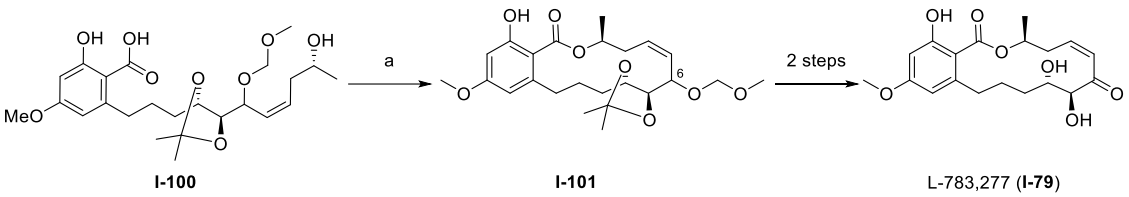
While the macrolactonizations described above were all based on activation of the carboxy group of a *seco* acid, macrolactonizations in RAL syntheses have also been achieved *via* activation of the hydroxy group of a *seco* acid precursor. For example, Winssinger and co-workers have reported the synthesis of 5-(Z)-oxozeaenol (**I-78**), radicicol A (**I-98**), and its 14-Cl analog[7](**I-99**) *via* Mitsunobu[168]-based macrolactonization of *seco* acids **I-92**, **I-93**, and **I-94**, respectively, using polymer-bound reagents in a combination with fluorous tag-isolation (*Scheme 4*).[169]



Scheme 4. Total synthesis of radicicol A, its' 14-Cl analog[1], and 5-(Z)-oxozeaenol by Dakas *et.al*. [169] Reagents and conditions: a) R^FPh_3P (2.0 equiv.), R^FDEAD (2.0 equiv.), toluene (10 mm), 23 ˚C, 2 h, 81%; $R^F=C_8F_{17}CH_2CH_2C_6H_4$ (in PPh_3) and $R^F=C_6F_{13}$ (in DEAD).

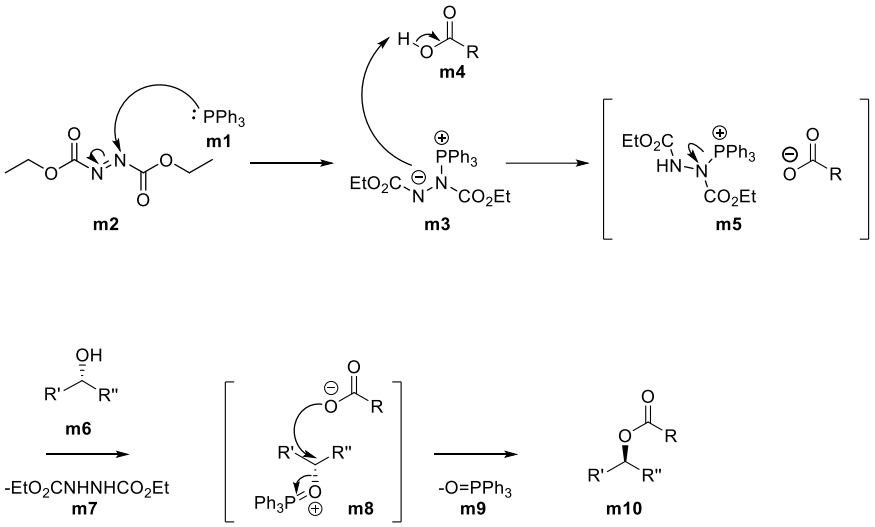
A Mitsunobu-based macrolactonization was also part of Hoffman & Altmann's total synthesis of the potent kinase inhibitor L-783,277 (**I-79**) (*Scheme 5*).[170]

[7] Atom numbering is adapted from the original isolation publication.[315]



Scheme 5. Total synthesis of L-783,277 by Hoffman & Altmann.[170] Reagents and conditions: a) DIAD, Ph_3P, toluene, 25 min, 59% (major isomer at C-6); 74% (minor isomer at C-6).

The mechanism of the Mitsunobu reaction has been discussed extensively.[171][172][173] The reaction is initiated by the nucleophilic attack of triphenylphosphine (**m1**) on diethyl azodicarboxylate (DEAD) (**m2**) in an irreversible addition, forming a zwitterionic adduct (**m3**) that deprotonates the acid (**m4**) to form an ion pair (**m5**) (*Scheme 6*).

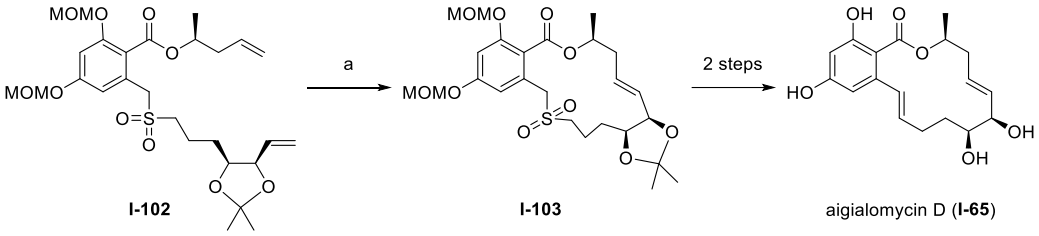


Scheme 6. General mechanism of Mitsunobu reaction.

The alcohol (**m6**) reacts with the protonated DEAD/PPh_3 adduct to form the key oxyphosphonium ion (**m8**) *in situ*,[174] which is attacked by the carboxylate anion to give, upon release of triphenylphophine oxide (**m9**), the desired ester (**m10**) with inversion of the configuration of the secondary alcohol (*Scheme 6*).[175] While Mitsunobu-based macrolactonizations play a prominent role in RAL syntheses, it should be noted that the method cannot be applied to the synthesis of macplocimine A (**I-42**) due to the phenolic nature of the hydroxy component of the ester linkage.

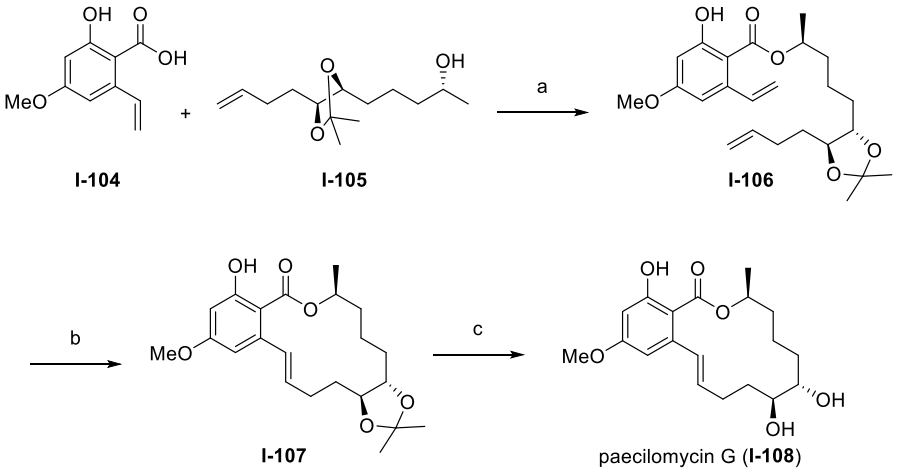
1.4.4.2 Ring-closing olefin metathesis

Ring-closing olefin metathesis (RCM) has been successfully employed for macrocycle formation in a number of total syntheses of RALs, with the total synthesis of aigialomycin D (**I-65**) by Harvey and co-workers being the earliest example (*Scheme 7*).[176]



Scheme 7. Total synthesis of aigialomycin D by Baird *et.al*.[176] Reagents and conditions: a) Grubbs II (10 mol%), DCM, MW, 75 ˚C, 30 min, 86%.

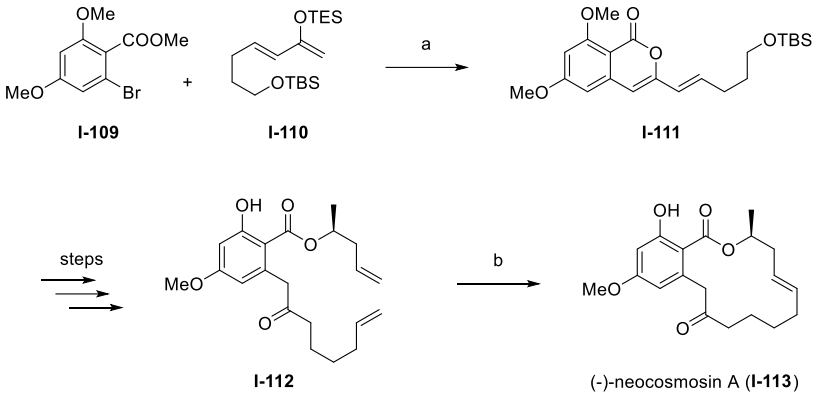
RCM-based ring closure was also central to the first stereoselective total synthesis of paecilomycin G (**I-108**) by Bujaranipalli & Das in 2016 (*Scheme 8*).[177] The diene precursor for RCM (**I-106**) was synthesized *via* a Mitsunobu reaction between **I-104** and **I-105**. RCM of **I-106** with 10 mol% Hoveyda-Grubbs second generation catalyst provided **I-107** in excellent yield. Acetonide removal then furnished paecilomycin G (**I-108**).



Scheme 8. Total synthesis of paecilomycin G by Bujaranipalli & Das.[177] Reagents and conditions: a) PPh_3, DIAD, toluene, 0 ˚C, 30 min, 84%; b) HG II (10 mol%), toluene, 80 ˚C, 4 h, 86%; c) 2N HCl/THF (1:1), 6 h, rt, 93%.

RCM-based total syntheses have also been reported for cochliomycin C (**I-70**) by Mahankali & Srihari in 2015[178] and zeaenol together with cochliomycin A (**I-68**) by Nasam & Pabbaraja in 2022.[179]

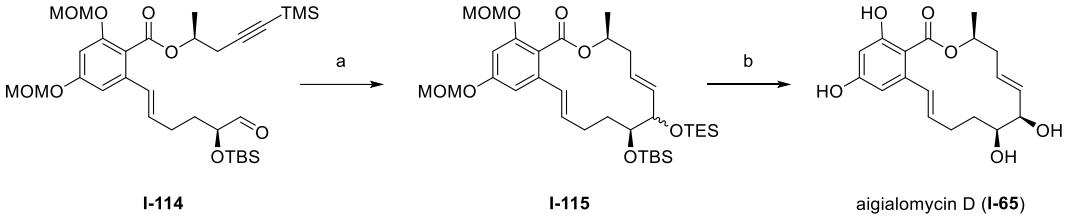
Most recently, Kapur and co-workers have described the RCM-based total synthesis of (-)-neocosmosin A (**I-113**).[180] While the synthesis of (-)-neocosmosin A (**I-113**) *via* RCM-mediated ring closure was previously reported earlier by Ward and co-workers,[181] Kapur's synthesis is noteworthy primarily for the assembly of the RCM precursor **I-112**. The latter was obtained *via* palladium-catalyzed α-arylation of enone **I-110** to give intermediate **I-111**, which could be elaborated into diene **I-112** (*Scheme 9*).



Scheme 9. Total synthesis of (-)-neocosmosin A by Pawar *et.al.*[180] Reagents and conditions: a) $Pd(OAc)_2$, D^tBPF, CsF, Bu_3SnF, toluene, 85 ˚C, 4-5 h, 65%; b) Grubbs II (10 mol%), DCM, reflux, 68%.

1.4.4.3 Ynal macrocyclization

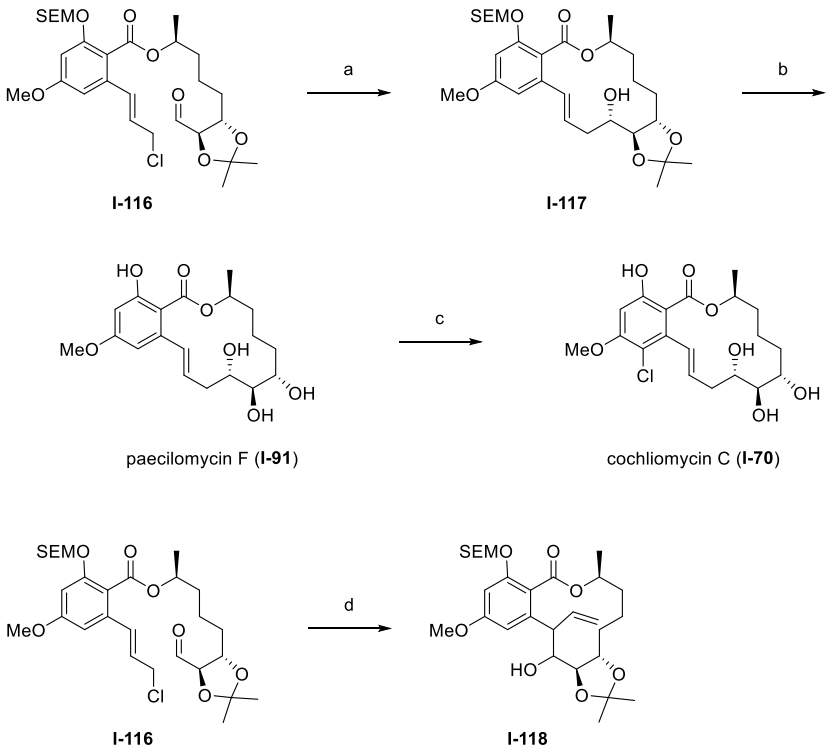
In 2008, Montgomery and co-workers reported a total synthesis of aigialomycin D (**I-65**) based on the nickel-catalyzed cyclization of ynal **I-114** with triethylsilane as a reducing agent (*Scheme 10*).[182] The reaction afforded the macrocyclic *E* alkene **I-115** in 61% yield; the latter was subsequently elaborated into aigialomycin D (**I-65**) in one step followed by a separation of diastereomers.



Scheme 10. Total synthesis of aigialomycin D by Chrovian *et.al.*[182] Reagents and conditions: a) $Pd(Ph_3P)_4$, 90%; b) Et_3SiH, $Ni(COD)_2$, IMes·HCl, *t*-BuOK, 61%, b) aq. HCl, MeOH, then HPLC separation, 46% of aigialomycin D, and 44% of the second diastereomer.

1.4.4.4 Macrocyclization *via* Loh-type α-allylation

Willis and co-workers have reported the total synthesis of the 14-membered RALs paecilomycin F (**I-91**) and cochliomycin C (**I-70**) *via* intramolecular Loh-type α-allylation[183] as the macrocyclization step (*Scheme 11*).[184] Thus, chloro aldehyde **I-116** could be converted into **I-117** in 61% yield when treated with a suspension of indium metal in dichloromethane containing water. Macrolactone **I-117** was then converted into paecilomycin F (**I-91**) and cochliomycin C (**I-70**) in one and two steps, respectively.

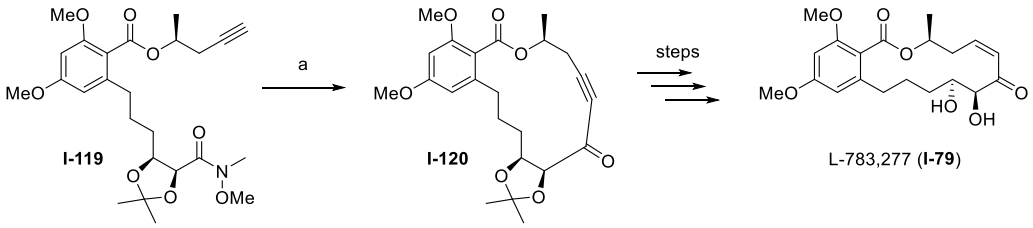


Scheme 11. Total synthesis of paecilomycin F and cochliomycin C by Ma *et.al.*[184] Reagents and conditions: a) In, DCM, H_2O, 22 ˚C, 48 h, 61%; b) HCl, MeOH/H_2O, 22 ˚C, 3 h, 91%; c) SO_2Cl_2, DCM, 0 ˚C, 30 min, 90%; d) $CrCl_2$, $NiCl_2$, DMF, 22 ˚C, 73 h, 33%.

Interestingly, treatment of **I-116** with $CrCl_2$ and $NiCl_2$ in DMF (Nozaki-Hiyama-Kishi (NHK) conditions) instead of the desired **I-117** gave the 12-membered lactone **I-118** as a single diastereomer.

1.4.4.5 Intramolecular Weinreb ketone synthesis

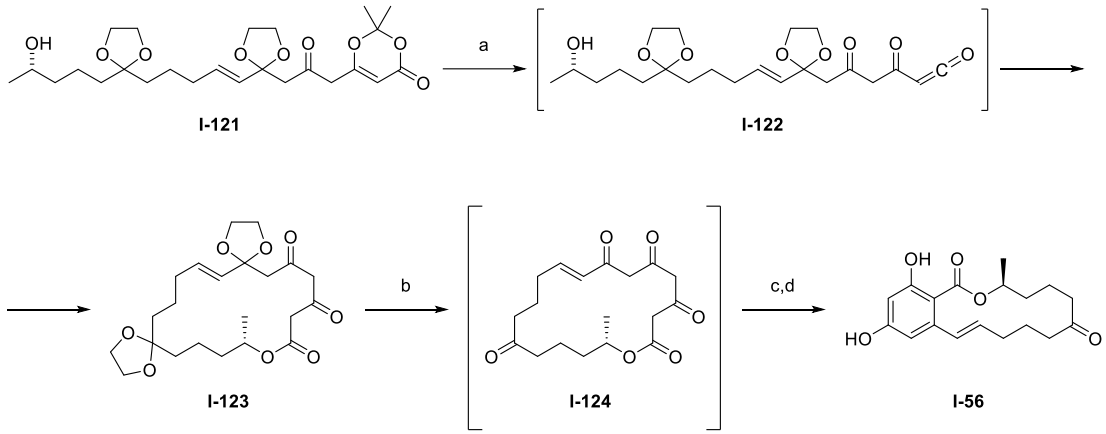
The intramolecular addition of an acetylide anion to a Weinreb amide group[185] in **I-119** was exploited by Banwell and co-workers in the synthesis of L-783,277 (**I-79**) (*Scheme 12*).[186] Weinreb amide **I-119** was treated with a base to afford **I-120** in moderate yield; further modifications of **I-120** furnished the desired RAL L-783,277 (**I-79**).



Scheme 12. Total synthesis of L-783,277 by Banwell *et.al*.[186] Reagents and conditions: a) LHMDS, THF, -35 ˚C to rt, 45%.

1.4.4.6 Aromatic ring construction after macrocycle formation

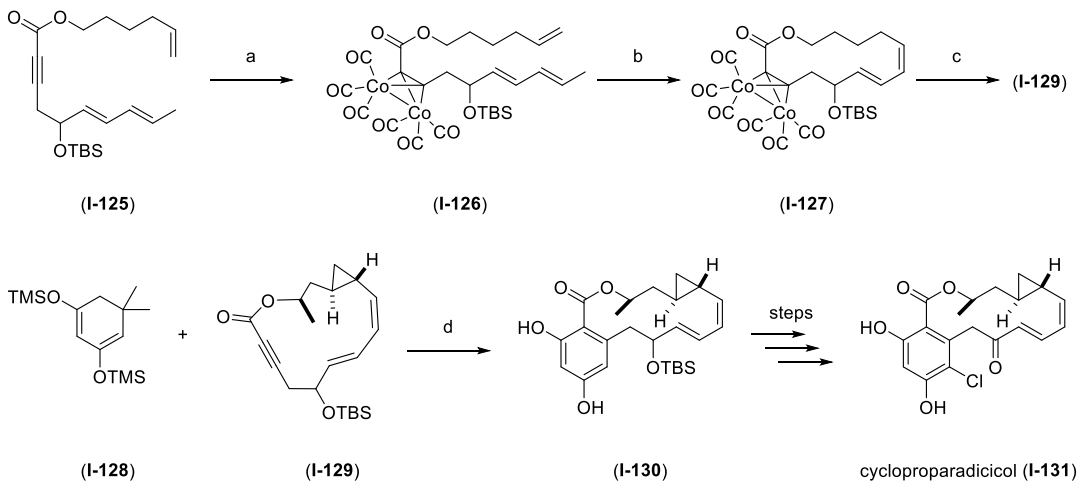
A transannular aromatization to construct the β-resorcylate part of the RAL was used for the synthesis of (S)-(-)-zearalenone by Miyatake-Ondozabal & Barrett (*Scheme 13*).[189] The macrocyclization of the hydroxy-keto-dioxinone **I-121** was achieved *via* retro-Diels-Alder fragmentation, the resulting ketene **I-122** was trapped by the secondary alcohol furnishing the triketo-lactone **I-123**, which was then directly submitted to ketal hydrolysis. The transannular aromatization resulted in the desired (S)-(-)-zearalenone **I-56** in 46% yield over four steps from **I-121**.



Scheme 13. Total synthesis of (S)-(-)-zearalenone by Miyatake-Ondozabal & Barrett.[189] Reagents and conditions: a) toluene, 110 ˚C; b) *p*-TSA, H_2O, acetone, 23 ˚C; c) Cs_2CO_3, MeOH; d) AcOH, then 1 M aq. HCl, 46% over four steps.

Danishefsky and co-workers employed the Diels-Alder reaction for the construction of the aromatic moiety in RALs.[190] The cyclic ynolide precursor (**I-129**) was obtained *via* RCM of **I-126**; RCM was also attempted with **I-125**, but no reaction and no cyclic product were observed. To prevent the acetylene moiety from interfering with the RCM,[191] alkyne **I-125** was protected as cobalt complex **I-126**. The

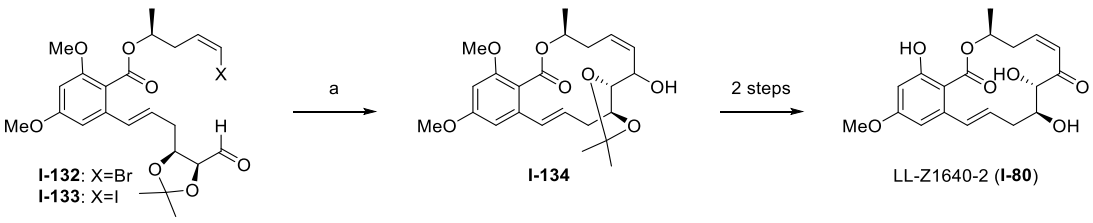
benzo-system of the cycloproparadicicol (**I-131**) was constructed *via* a Diels-Alder reaction between cyclic diene (**I-128**) and ynolide (**I-129**) to furnish **I-130** in an excellent 78% yield (*Scheme 14*). Further elaboration provided the desired cycloproparadicicol (**I-131**). The total synthesis of aigialomycin D (**I-65**) was also reported in the same paper.



Scheme 14. Total synthesis cycloproparadicicol (**I-131**) by Danishefsky and co-workers.[190] Reagents and conditions: a) $Co_2(CO)_8$, toluene, 86%; b) Grubbs II (20 mol%), DCM, rt, 57%; c) CAN, acetone, -10 ˚C, 92%; d) 160 ˚C neat, then silica gel, 78%.

1.4.4.7 Macrocyclization *via* Nozaki-Hiyama-Kishi reaction

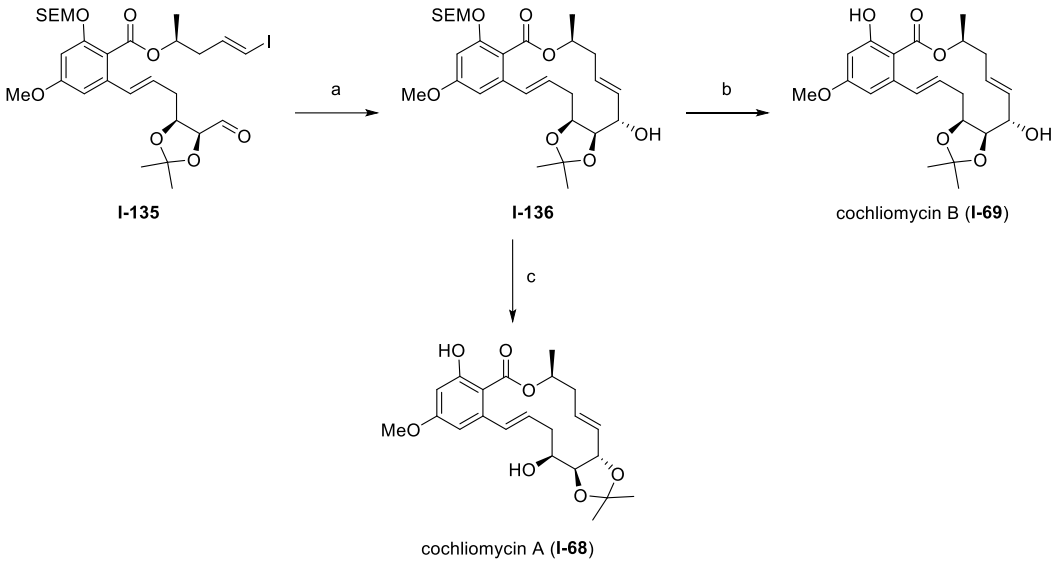
The use of the Nozaki-Hiyama-Kishi (NHK) reaction for macrocyclic ring closure in the total synthesis of RALs was first reported by LeClair *et. al.* in 2010 as part of their total synthesis of LL-Z1640-2 (**I-80**) (*Scheme 15*).[192] In their synthesis, treatment of **I-132** or **I-133** with chromium (II) chloride and a catalytic amount of nickel (II) chloride gave macrolactone **I-134** in 35% and 61% yield, respectively. Bromide **I-132** needed additional heating for the reaction to proceed, whereas the reaction of the iodide proceeded at room temperature. Oxidation and deprotection then gave LL-Z-1640-2.



Scheme 15. Total synthesis of LL-Z1640-2 by LeClair *et.al.*[192] Reagents and conditions: a) $CrCl_2$, $NiCl_2$ (cat.), DMF, X=Br: 50 ˚C, 48 h, 35%, X=I: rt, 24 h, 61%.

An NHK cyclization was also employed by Wardand co-workers in their synthesis of the marine RALs cochliomycin A (**I-68**) and B (**I-69**) (*Scheme 16*).[193] The NHK reaction with iodoaldehyde **I-135** proceeded

smoothly, delivering the 14-membered macrocycle **I-136** in excellent yield (77%). The macrocyclization product was then readily converted into cochliomycin B (**I-68**) and cochliomycin A (**I-69**).



Scheme 16. Total synthesis of cochliomycins A and B by Bolte *et.al.*[193] Reagents and conditions: a) $CrCl_2$, $NiCl_2$, DMF, 22 °C, 30 h, 77%; b) TBAF, THF, 66 °C, 12 h, 73%; c) HCl, MeOH, ca. 22 °C, 1 h, 91%.

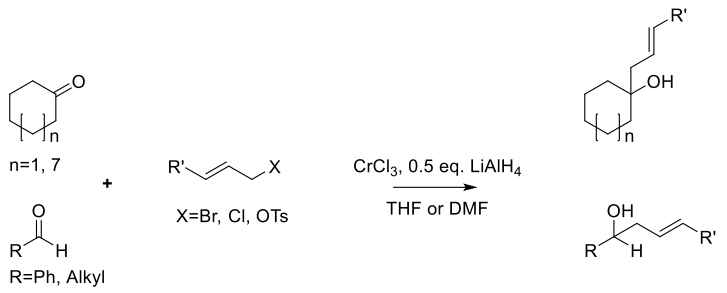
1.4.4.8 Conclusions

In principle, all of the methods for macrocyclization discussed in this chapter could also be applied to the total synthesis of macplocimine A (**I-42**), with the exception of the Mitsunobu reaction (*vide supra*). It should also be kept in mind that all RCM-based cyclizations discussed here preferentially gave the *E* double bond, whereas macplocimine A (**I-42**) incorporates a *Z* double bond; however, metathesis catalysts for *Z*-selective RCM have become available over the last decade[187] and the geometry of the double bond formed may also depend on the size of the ring. More generally, there are many ways to implement each of these methods and a plethora of other macrocyclization methods exists. These have been reviewed in detail[104][188] and a comprehensive discussion of each of these methods is beyond the scope of this introduction.

For reasons that will be discussed in more detail later, the method that was eventually pursued to construct the macplocimine A macrocycle was the Nozaki-Hiyama-Kishi coupling. To put this work in context, examples of macrolactonizations based on intramolecular NHK reactions shall be discussed in the following chapter.

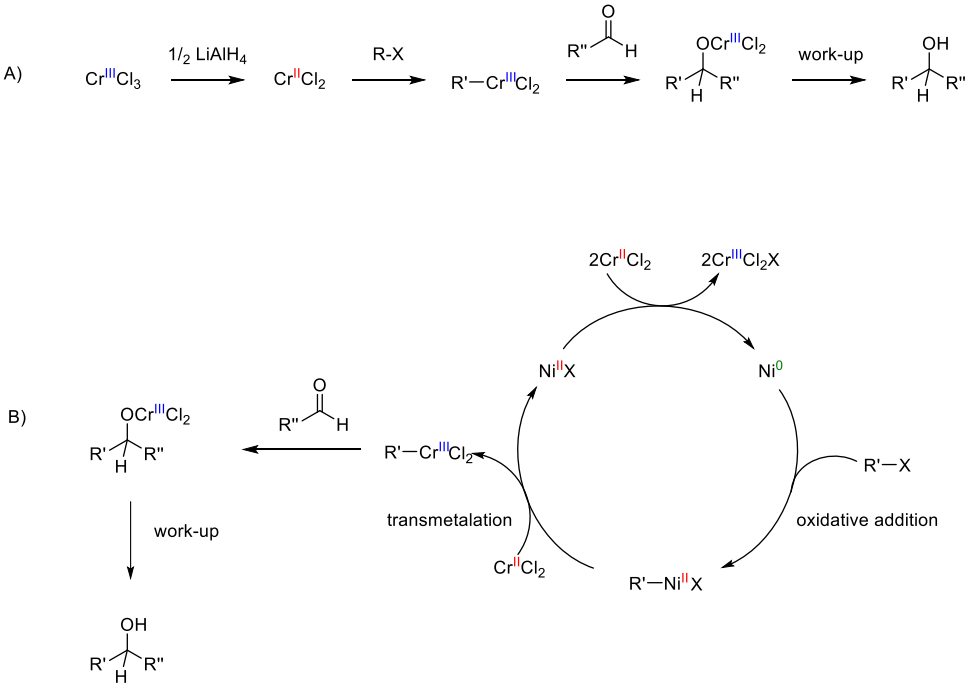
1.5 Total synthesis of macrocyclic natural products other than RALs *via* intramolecular Nozaki-Hiyama-Kishi reaction

The Nozaki-Hiyama-Kishi (NHK) reaction (sometimes also referred to as Nozaki-Hiyama-Takai-Kishi (NHTK) reaction)[194] was first reported by Hiyama and co-workers in 1977 as a Grignard-type reaction between allylic halides and carbonyl compounds mediated by a chromium (II) salt (*Scheme 17*).[195]



Scheme 17. General scheme of the first Grignard-type carbonyl addition of allyl halides mediated by chromium salt. A chemospecific synthesis of homoallyl alcohols.[195]

The scope of the reaction was subsequently shown by Takai, Hiyama, and co-workers to also encompass aryl halides, vinyl halides, and vinyl triflates;[196] its applicability to alkynyl halides was demonstrated by Takai, Oshima, and co-workers. In 1986, Takai and co-workers[197] and Kishi and co-workers[198] independently recognized that the reaction was accelerated by catalytic amounts of nickel. The mechanisms for the uncatalyzed and the Ni-catalyzed NHK reaction are depicted in *Scheme 18*.



Scheme 18. Mechanisms of the NHK reaction. Non-catalytic reaction mechanism (A); catalytic reaction mechanism (B).[198][199]

In the first publication, chromium (II) chloride was prepared *in situ* by reducing chromium (III) chloride with a half-equivalent lithium aluminum hydride in an aprotic solvent (e.g. THF). The chromium (II) species then reduces an organic halide to form an organochromium intermediate, followed by a Grignard-type addition of the latter to the carbonyl compound (*Scheme 18*, A).[199]

In the reaction, which is accelerated with catalytic amounts of nickel, the NHK reaction begins with the reduction of Ni (II) to Ni (0), followed by the oxidative addition of an alkenyl iodide to Ni (0). Transmetallation with Cr (II) produces an organochromium intermediate, which then reacts with the carbonyl group. Ni (II) is regenerated by the excess chromium and should be used in low amounts to avoid the formation of side products (*Scheme 18*, B).[198]

Finally, it should be noted that aldehydes are significantly more reactive in NHK couplings than ketones, which enables the selective allylation/alkenylation/arylation/alkynylation of aldehydes in the presence of other carbonyl groups.

The NHK reaction has been widely used for the construction of medium-sized rings, including cyclizations of highly functionalized substrates[194][200][201][202] It has also been successfully used in a number of total syntheses where an NHK coupling has been used as a macrocyclization step, which will be discussed below. In comparison with ring-closing olefin metathesis, cyclizations under NHK conditions do not produce polymerized products and they allow for the control of double bond geometry in the cyclization product if couplings are conducted with stereopure vinyl halides.[203] Of note, an intramolecular NHK reaction is also part of the industrial process for the production of the anticancer drug eribulin (see *Figure 6*, Chapter 1.2.1.)[204][205][206] Two examples of macrocyclizations by intramolecular NHK reaction have already been discussed in Chapter 1.4.4.7 for the 14-membered RALs **I-68**, **I-69**, and **I-135**. This chapter discusses additional examples of NHK-based macrocyclizations, with an emphasis on the formation of 2-en-ols or propargylic alcohols (*Figure 28*); these types of reactions could also be used to construct the 18-membered macrocycle in macplocimine A (**I-42**), either directly or after reduction of the triple bond of a propargylic alcohol product to produce the required 2-en-ol moiety at C(8). However, macrocyclizations involving the formation of 2-methyl-2-en-ols,[207] 3-methyl-2-en-ols,[208] *gem*-disubstituted-2-en-ols,[209] and *exo*-homoallylic alcohols[210] have also been described (*Figure 28*).

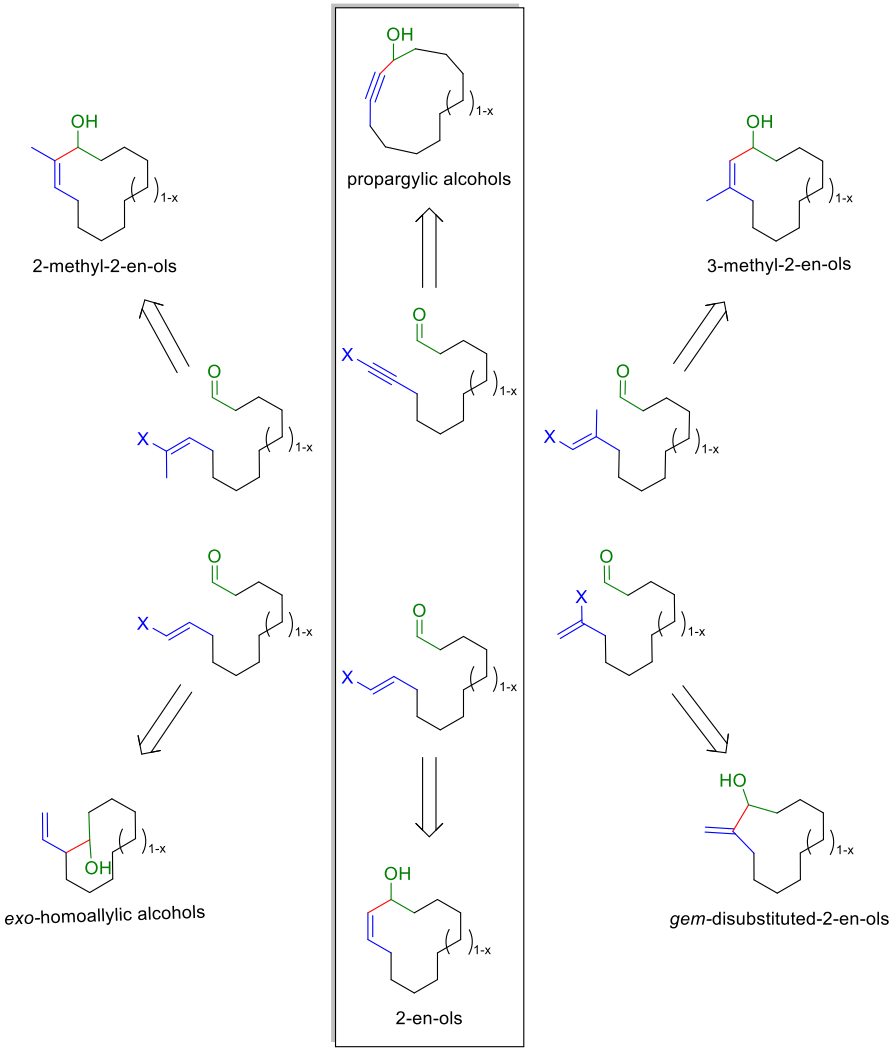
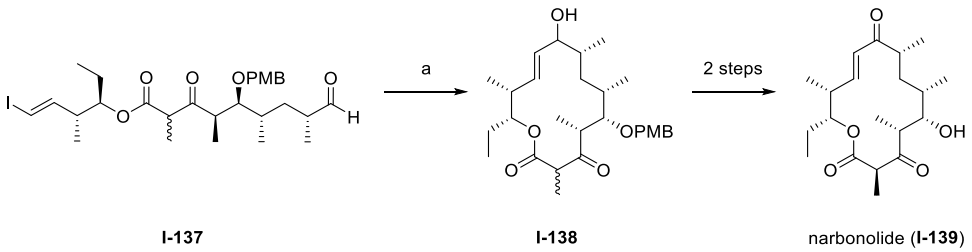


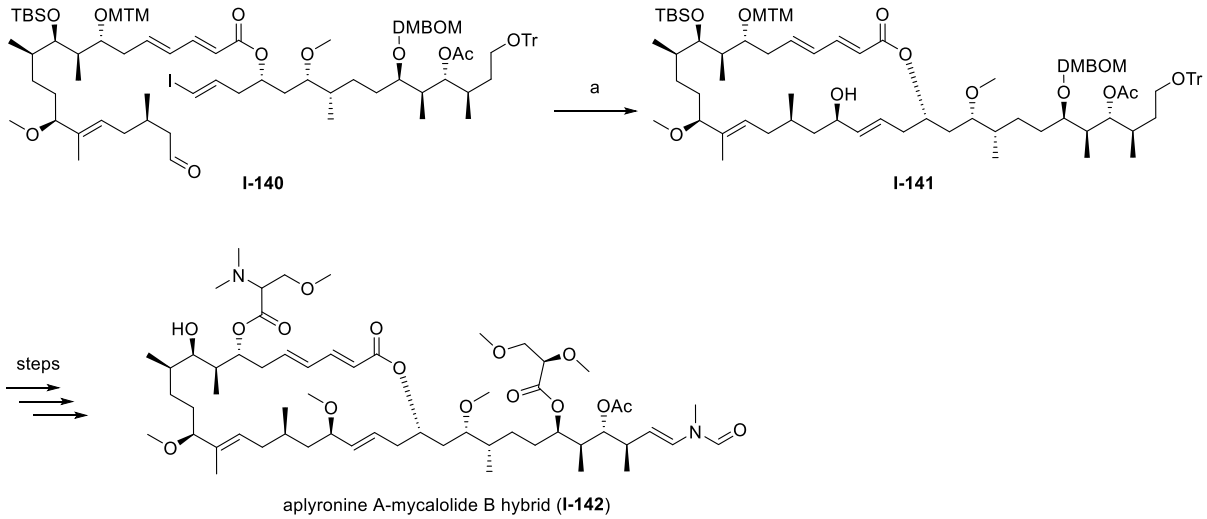
Figure 28. Possible intramolecular NHK macrocyclization reactants and their outcomes. Adapted from *Chem. Rev.* **2017**, *117*, 8420–8446.[194]

The total synthesis of narbonolide (**I-139**) was achieved by Fecik and co-workers via NHK macrocyclization as the key step.[211] Thus, intramolecular NHK reaction of aldehyde **I-137** afforded 14-membered macrolide **I-138** in excellent yield (89%) (*Scheme 19*).



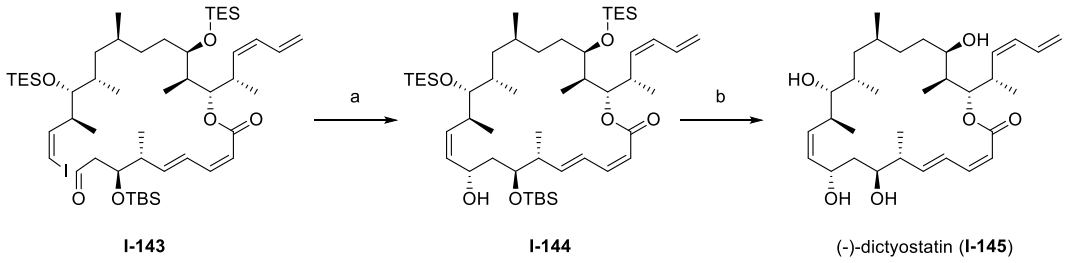
Scheme 19. Total synthesis of narbonolide by Felix and co-workers. [211] Reagents and conditions: a) $CrCl_2$, $NiCl_2$, 89%.

The synthesis of an aplyronine A-mycalolide B hybrid (**I-142**) has been reported by Kogoshi and co-workers *via* the NHK-based macrocyclization of **I-140** to establish the 24-membered ring. Macrolide **I-141** was obtained in 46% yield as a 1:1 mixture of diastereoisomers (*Scheme 20*).[212]



Scheme 20. Reagents and conditions: a) $CrCl_2$, $NiCl_2$, DMSO, 46%, *dr*=1:1.

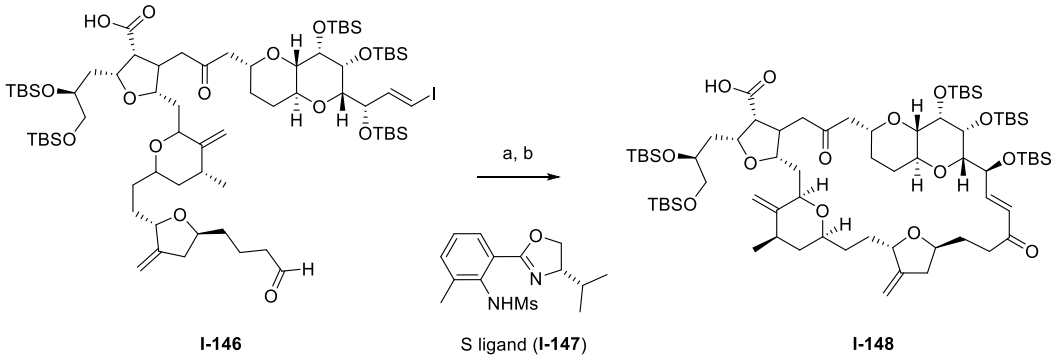
The synthesis of (-)-dictyostatin (**I-145**) *via* NHK-mediated macrocyclization of **I-143** to form the 22-membered ring has been reported by Curran and co-workers (*Scheme 21*).[213] The cyclization step was executed in a stereoselective manner with 4,4'-di-tert-butyl-2,2'-dipyridyl as a ligand, yielding the desired **I-144** as the major product (78:22 to its epimer at C(19)[8]). The following global desilylation afforded (-)-dictyostatin (**I-145**) in good yield.



Scheme 21. Streamlined syntheses of (-)-dictyostatin by Zhu *et. al.* [213] Reagents and conditions: a) $CrCl_2$, $NiCl_2$(dppf), 4,4'-di-tert-butyl-2,2'-dipyridyl as a ligand, 55%, mixture of two isomers 78:22 ((**I-144**:C(19)-epimer) were separable; b) HF·py, 77%.

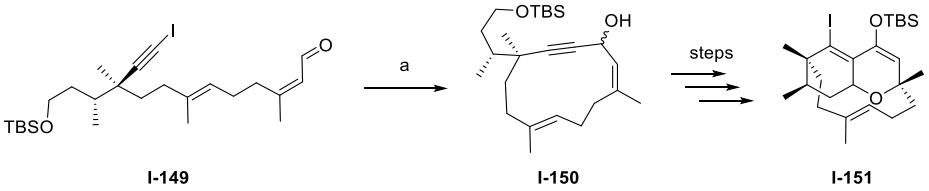
In the commercial synthesis of eribulin, the 26-membered core (**I-148**) was established using the NHK reaction of **I-146**, stereoselectivity is not necessary in this case due to the following oxidation, yet the reaction rates were higher in the presence of ligand **I-147** (*Scheme 22*).[214] After the subsequent oxidation with Dess-Martin periodinane, this intermediate was obtained on an impressive scale of over 500 g in 60-80% yield over two steps.[214]

[8] Atom numbering is adapted from the original isolation publication. [213]



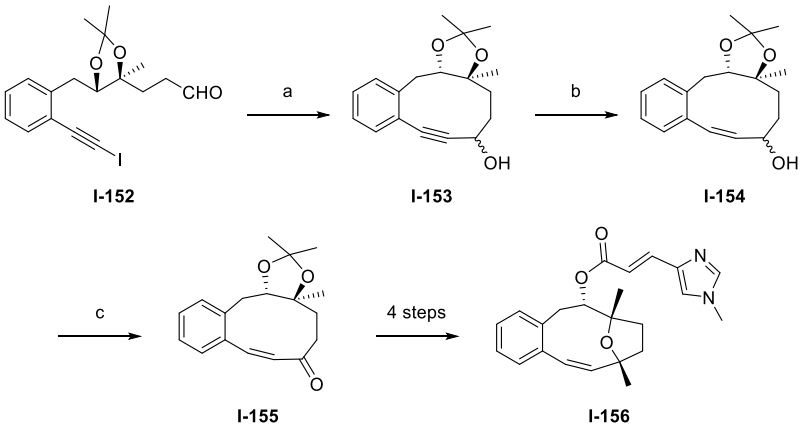
Scheme 22. Commercial manufacture of Halaven® by Austad *et.al.* [214] Reagents and conditions: a) $CrCl_2$, $NiCl_2$, Et_3N, **I-147**, MeCN, THF, 25 ˚C, 4-5 days, high dilution; b) DMP, DCM, cat. H_2O, 60-80% over two steps.

While all of the above examples involve NHK-based macrocyclizations *via* the reaction of vinyl halide and aldehyde end groups, macrocycle formation has also been achieved with alkynyl halide end groups. For example, the intramolecular NHK reaction of **I-149** was used for the construction of the 12-membered core of phomactin A (**I-150**) by *Ciesielski* et.al. (*Scheme 23*).[215]



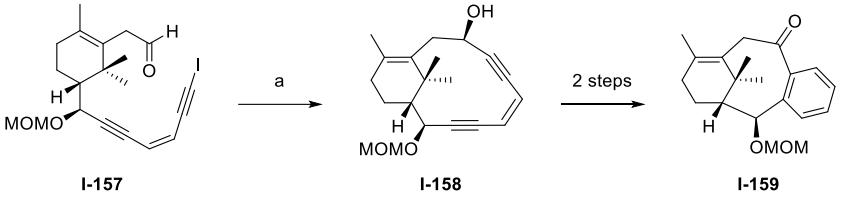
Scheme 23. Synthesis of the ABD core of phomactin A by Ciesielski *et.al*. [215] Reagents and conditions: a) $CrCl_2$, $NiCl_2$, THF, rt, 3 h, 63%.

In the synthesis of the 15-seco-eleutheside analog **I-156**, an intramolecular NHK reaction of the alkynyl halide **I-152** provided the propargylic alcohol **I-153**. Subsequent reduction afforded the allylic alcohol **I-154**, which was oxidized to the α,β-unsaturated ketone **I-155**, which could be further elaborated to the 15-seco-eleutheside analog **I-156** (*Scheme 24*).[216][217]



Scheme 24. Synthesis of a 15-seco-eleutheside analog by Sandoval *et.al.*[216] Reagents and conditions: a) $CrCl_2$, $NiCl_2$, THF, 85%; b) $Pd/BaSO_4$, quinoline, 90%; c) DMP, 98%.

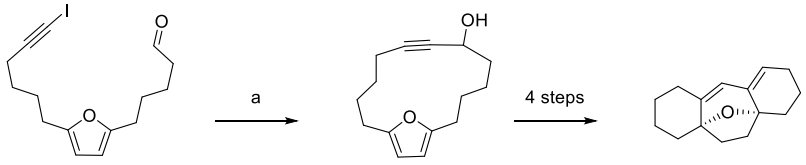
A new synthetic route to aromatic taxanes was investigated *via* cycloaromatization of bicyclo[9.3.1]pentadecadienediyne (**I-158**), which formed as a single diastereomer when **I-157** was submitted to $CrCl_2$–$NiCl_2$-mediated coupling without any chiral ligand.[218] The phenomenon was explained by an exclusive *Si* face attack due to the conformational preorganization of the molecule.[218] The propargylic alcohol was further submitted to cycloaromatization conditions, followed by oxidation to deliver the desired aromatic ketone **I-159** (*Scheme 25*).



I-157 **I-158** **I-159**

Scheme 25. Synthesis of taxamycins by Lu *et. al.*[218] Reagents and conditions: a) $CrCl_2$, $NiCl_2$, (cat.), THF, 21°C, 4 h, 60%.

Another example of the utility of NHK reactions involving alkynyl halides is found in a method for constructing the tricyclic core structures of natural products such as cortistatin A[219] *via* a transannular [4+3] cycloaddition reaction of macrocyclic propargyl esters (**I-161**).[220] For that alkynyl halide **I-160** was converted into the 14-membered cyclic propargylic alcohol **I-161**, which was further elaborated into an ester and then into the carbon core structure of cortistatin A (**I-162**) in four steps including a gold-catalyzed tandem 3,3-rearrangement/transannular [4+3] cycloaddition reaction (*Scheme 26*).



I-160 **I-161** **I-162**

Scheme 26. Gold-catalyzed transannular [4+3] cycloaddition reactions by Gung *et.al.*[220] Reagents and conditions: a) $CrCl_2$, $NiCl_2$, THF, 78-79%.

Although intramolecular NHK reactions with alkynyl halides are not frequently used to construct macrocycles, the construction of propargyl alcohols allows for a number of further modifications.

The above examples illustrate that the NHK reaction is a powerful tool for the construction of macrocycles with the concomitant formation of an allylic or a propargylic alcohol motif; the latter can be transformed into the former by the reduction of the triple bond. As will be discussed in Chapter 3.4.2, an NHK-based macrocyclization approach was also pursued in this PhD thesis for the total synthesis of macplocimine A (**I-42**).

2 Aims and scope

As discussed in Chapter 1.3, macplocimine A (**1**) (*Figure 29*) is a unique marine natural product that has been isolated from the marine-derived filamentous sulfur bacteria *Thioploca sp.* as a highly unusual source.[112] The relative and absolute configuration of **1** is unknown, with the exception of the *anti*-stereochemistry of the C(11)-methyl and the C(12)-hydroxy group (highlighted in red in *Figure 29*) and no synthetic work or biological activity studies on the compound have been documented in the literature.

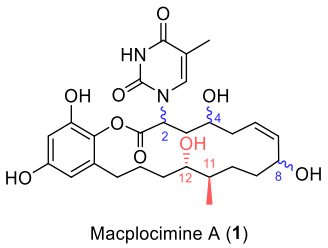


Figure 29. Structure of macplocimine A (**1**). Atom numbering is adapted from the original publication by Li *et.al.*[112]

At a high level of structural analysis macplocimine A (**1**) could be perceived as a hybrid structure between a resorcylic-type macrolide and a nucleoside antibiotic. Given the broad range of biological activities associated with either of these types of secondary metabolites, it could then be speculated that **1** could also be expected to exhibit interesting biological effects. Given the lack of availability of natural macplocimine A (**1**), this question could only be addressed by means of synthesis. At the same time, its unique structural features made **1** an interesting and demanding target for total synthesis in itself.

With this in mind, this PhD project had two interconnected objectives:

(1) As the primary goal of the project, a synthetic route towards macplocimine A (**1**) was to be developed, irrespective of the specific configuration of the individual stereocenters, except for a C(11)-*R**/C(12)-*S** configuration (*vide supra*); i.e. at least one of the 8 possible macplocimine diastereomers with a C(11)/C(12) *R*/S** configuration was to be prepared.

(2) As an extended objective, the synthesis of all 8 possible macplocimine diastereomers with a C(11)-*R**/C(12)-*S** configuration should be targeted in order to determine the relative configuration of the natural product by comparison with the published spectroscopic data.

In general, the availability of the above isomer set would also allow the assignment of the absolute configuration of the natural product, as it includes either the natural product itself or its enantiomer. However, the sign of the specific rotation of macplocimine A (**1**) was not reported by the isolation group. As a consequence, based on the currently available data, it will remain impossible to determine the

biological activity of natural macplocimine A (**1**). Even if one of the two enantiomers of the natural diastereoisomer were found to be biologically active, it could not be assumed *a priori* that this was the natural product. Only if neither isomer was active could one conclude with certainty that macplocimine A (**1**) was devoid of the particular activity tested for. However, these questions were outside of the scope of this PhD project.

All of the macplocimine isomers prepared were to be tested in various biological assays, either by collaborators or by commercial providers.

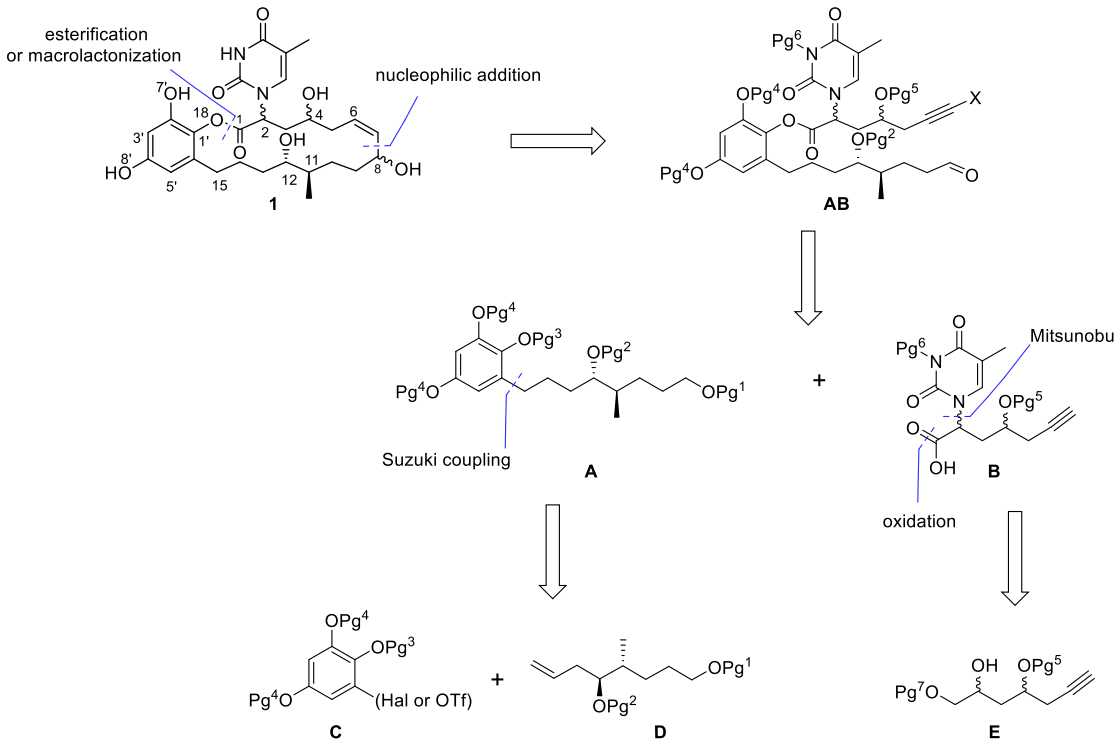
Finally, it should be noted that this project was initiated by a former PhD student in the group, Dr. Melanie Zechner.[9] The previous work will be referred to and acknowledged in Chapter 3, wherever appropriate.

[9] Melanie Zechner, ETH Dissertation NO 26342

3 Results and Discussion

3.1 Global Synthetic Planning

As should be obvious from the previous chapters, the construction of the macplocimine A (**1**) macrocycle could have been approached in multiple different ways. However, given the specific synthetic objectives that were outlined for the project in Chapter 2, it was clear that any ring-opening disconnection within the C(9)-O(18) segment would not be sensible, as this sub-structure would be invariable for the entire set of macplocimine diastereoisomers that would possibly be targeted. As a consequence, this segment should be prepared separately in an appropriately functionalized and protected format and used as a common advanced intermediate for the assembly of all individual macrocyclization precursors; in practice, this building block also included C(8) (*Scheme 27*, protected building block **A**). On the other hand, the C(2), C(4), and C(8) stereocenters in the C(1)-C(8) segment would have to be varied. Based on these considerations, two strategies were considered, whereby a maximum of 4 diastereomeric C(1)-C(7) building blocks would be prepared (*Scheme 27*, protected building blocks **B**), while the C(8) stereocenter would be established either in the process of building block assembly or in the macrocyclization step.



Scheme 27. Global retrosynthesis of **1**. Pg = protecting group or H. Hal = halogen; OTf = OSO_2CF_3. X = H or I.

The strategy that had been proposed by Zechner in her PhD thesis for the synthesis of **1** foresaw the construction of the C(8) stereocenter by the stereoselective acetylide addition of building block **B** to the aldehyde derived from **A** by selective deprotection of the primary hydroxy group and oxidation; ring

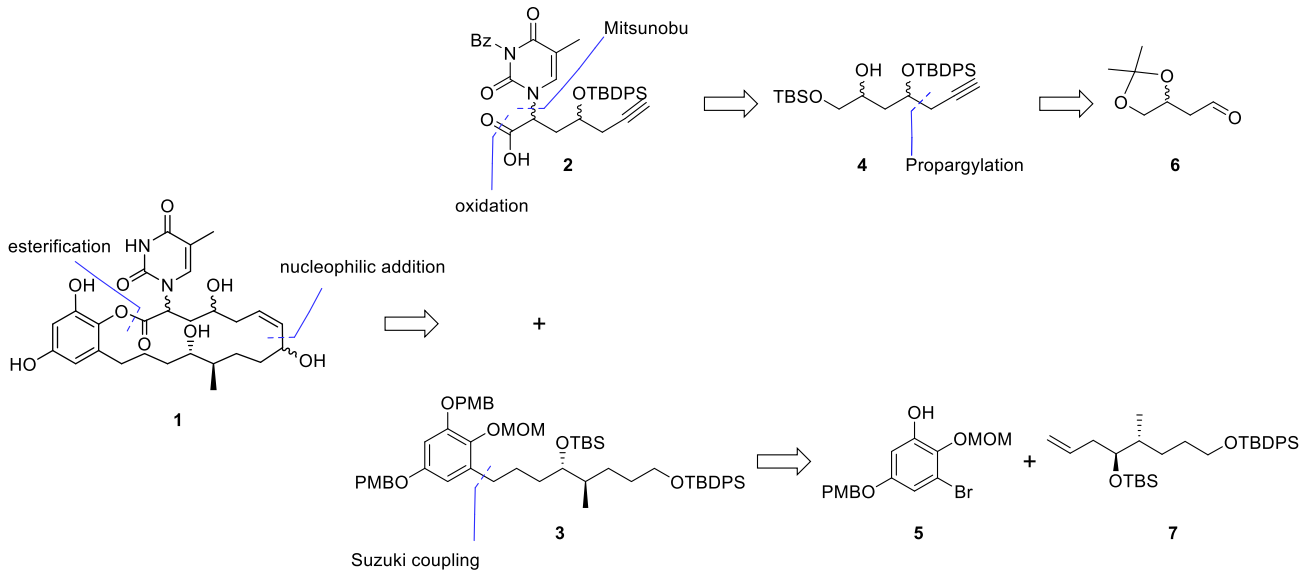
closure was to be achieved by macrolactonization. This strategy would produce a different cyclization precursor for each macplocimine diastereoisomer.

In this PhD project, a slightly different approach was pursued that would involve first ester formation between acid building blocks **B** and partially deprotected building block **A**, while macrocyclization would be based on intramolecular alkynylation or Nozaki-Hiyama-Kishi coupling with an alkynyl iodide end group at C(7); partial reduction would give the *Z* double bond. While the cyclization was expected to be non-selective, it was assumed that the cyclic diastereoisomers would be separable, thus allowing the synthesis of two diastereoisomers from a single precursor. Obviously, the same result could be achieved by performing the *inter*molecular addition of **B** to the **A**-derived aldehyde in a non-stereoselective fashion. However, the resulting mixture of diastereomers would have to be carried through additional steps (protection of the newly formed allylic OH-group, ester saponification) which would make analytical characterization more tedious.

Building block **A** was to be prepared from olefinic building block **D** and an appropriately protected phenol **C** *via* Suzuki or Heck coupling. Building block **B** was envisioned to be accessed from partially protected triol **E** (*vide infra*) by Mitsunobu reaction with an N(3)-protected thymine derivative; alkyne **E**, in turn, would be obtained by propargylation of an aldehyde precursor.

One of the major challenges in the projected synthesis of **1** according to the strategy outlined above was the choice of appropriate, selectively cleavable protecting groups. Thus, Pg^3 in **A** would have to be selectively cleavable in the presence of all other protecting groups, in order to allow clean esterification with acids **B**. For the subsequent transformation of the ester product into aldehyde **AB**, the selective removal of protecting group Pg^1 appeared highly desirable, to exclude difficulties with unprotected secondary OH-groups in the oxidation step (although methods for the selective oxidation of primary hydroxy groups in the presence of secondary ones do exist).[221] The protecting group on the thymine moiety was the least critical and would only serve to ensure clean alkylation at N(1).

A possible protecting group strategy that was considered to enable the synthesis of **1** according to the basic route outlined in *Scheme 27* is depicted in *Scheme 28*.



Scheme 28. Global retrosynthesis of **1** with protecting groups specified.

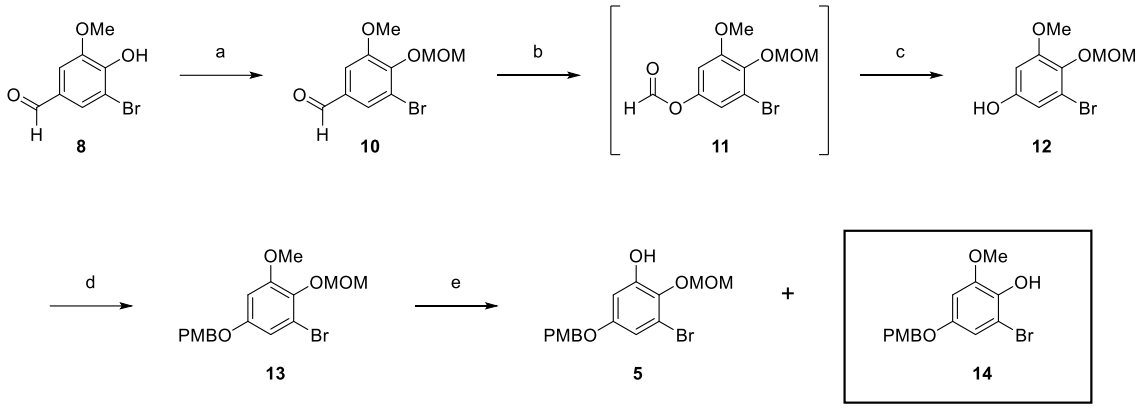
While the selective cleavage of the MOM-ether in **3** was still expected to be challenging and require optimization, literature precedent exists for the (at least partially selective) cleavage of MOM-ethers in the presence of PMB-ethers.[222] Likewise aromatic MOM-ether cleavage in the presence of aliphatic silyl-ethers has been described.[222] As will be discussed in the following chapter, the choice of a TBDPS-group as Pg^1, rather than a TBS- or TES-group (*Scheme 27*), was dictated by the synthetic route towards olefin **7**.[223] At the same time, primary TBDPS-ethers can be cleaved selectively over secondary TBS-ethers.[224] The choice of a TBDPS protecting group on the acid fragment **2** was determined by the difficulty of the scale-up of the acetonide group removal in the presence of a secondary TBS-ether. From a retrosynthetic point of view, a TBS-ether would have been more logical, especially since the route with a TBS-group was established on a small scale by Zechner.[1] Finally, aryl bromide **5** was chosen as an intermediate *en route* to **3**, as its synthesis had already been elaborated by Zechner.[10]

[10] Melanie Zechner, ETH Dissertation NO 26342.

3.2 Synthesis of building block A

3.2.1 Synthesis of aryl bromide 5

As indicated above, the synthesis of aryl bromide **5** was described by Zechner as part of her PhD thesis. The synthesis proceeded through known MOM-ether **12**,[225] which was obtained from commercially available 5-bromovanillin (**8**) *via* reaction with MOMCl and DIPEA in DCM to give MOM-ether **10**, followed by *m*-CPBA-induced Bayer-Villiger rearrangement[226] and cleavage of the resulting formyl ester **11** with aq. KOH/MeOH in 51-66% overall yield (*Scheme 29*).

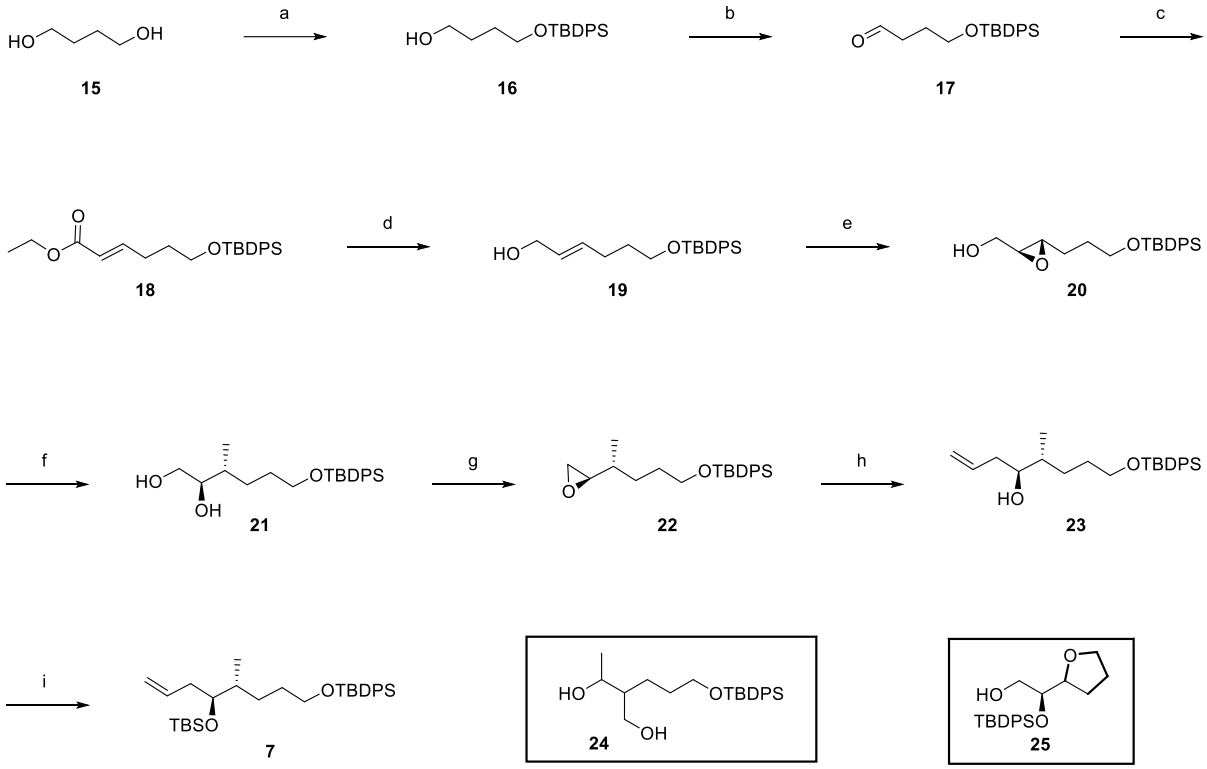


Scheme 29. Reagents and conditions: a) MOMCl, DIPEA, DCM, rt, 94%; b) *m*-CPBA, DCM, 0 ˚C; c) 1.78 M aq. KOH/MeOH, rt , 54-70% over two steps; d) PMBCl, K_2CO_3, DMF, rt, 64%; e) EtSH, NaH, DMF, 110 ˚C, 60-65%.

The reaction of **12** with PMBCl and K_2CO_3[227] in DMF then gave PMB-ether **13**. Treatment of **13** with *in situ*-generated sodium thioethoxide (NaH/EtSH)[228] in DMF for 1.5 h at 110 ˚C gave the free phenol **5** in 60-65% yield. As a by-product, phenol **14**, resulting from cleavage of the MOM-ether group under the reaction conditions, was isolated in 12-21% yield (*Scheme 29*). The 5-step route from bromovanillin (**8**) to **5** was reproducible and scalable up to decagram quantities of aryl bromide **5** with overall yields ranging from 21% to 27%.

3.2.2 Synthesis of olefin 7

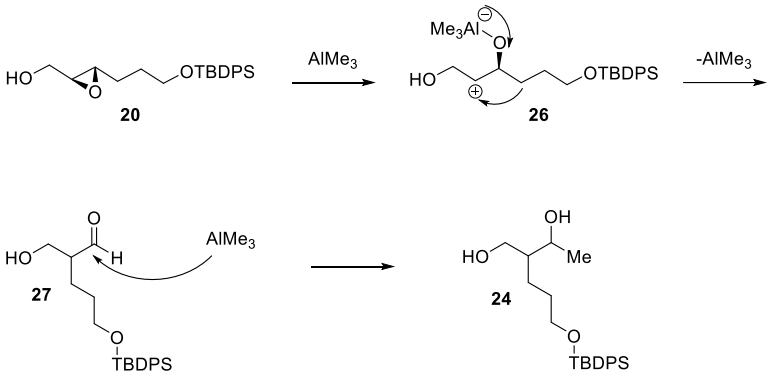
The synthesis of olefin **7** started from 1,4-butanediol (**9**) and proceeded through known epoxide **22** as a key intermediate;[229] the further elaboration of **22** into **7** was based on the work described by Zechner in her PhD thesis, although optimization was required for this part of the route. Thus, an excess of 1,4-butanediol was reacted with TBDPSCl and NEt_3 in DCM to furnish mono-TBDPS-ether **16** in quantitative yield (*Scheme 30*). Oxidation of **16** with Dess-Martin periodinane (DMP)[230] then gave aldehyde **17** in 90% yield, which was submitted to Horner-Wadsworth-Emmons (HWE) olefination with ethyl diethylphosphonoacetate;[231][232][233] subsequent reduction of the resulting enoate with diisobutylaluminum hydride (DIBAL-H)[234] delivered allylic alcohol **19**[235] in 45% overall yield from **17**.



Scheme 30. Reagents and conditions: a) TBDPSCl, NEt_3, DCM, rt, quant.; b) DMP, $NaHCO_3$, DCM, rt, 90%; c) ethyl diethyl phosphonoacetate, NaH, THF, -20 ˚C to 0 ˚C, 77%; d) DIBAL-H, DCM, -78 ˚C, 58%; e) (+)-DET, TBHP, Ti(IV)-isopropoxide, DCM, -20 ˚C, 75-89%; >99% ee; f) Me_3Al, *n*-hexane, -35 ˚C, 54-60% of **21**; 15% of **25**; g) NaH, tosyl imidazole, THF, rt, 72%; h) vinylmagnesium bromide, CuI, THF, -78 ˚C, then -20 ˚C, 94%; i) TBSCl, imidazole, DMF, rt, 87%.

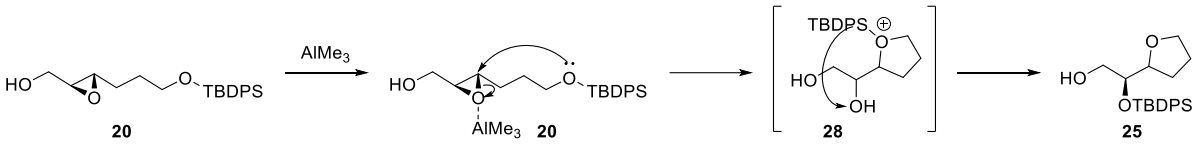
Allylic alcohol **19** was then converted into epoxy alcohol **20**[229] in excellent yield (75-89%) and excellent *ee* (>99%) using Sharpless-epoxidation conditions.[236][237] The subsequent epoxide opening step then required some optimization. Rajesh and co-workers[223] as well as Zechner in her PhD thesis had reported the treatment of **20** with $AlMe_3$ in *n*-hexane at 0 ˚C to furnish **21** in 52% yield, with no mention of potential side products. However, in my hands, these conditions gave an inseparable 2:1 mixture of the desired diol **21** and its constitutional isomer **24** in a total yield of 52%. In contrast, when a solution of **20** was slowly added to a solution of $AlMe_3$ in *n*-hexane below -35 ˚C with internal control of the temperature, the formation of **24** could be largely (10:1 of **21**:**24**) or even completely suppressed, which could be determined by NMR analysis of the crude product mixture after extractive workup. The conditions were scalable and on a 5 g scale of **20** gave **21** in 56% yield exclusively, and on a 25 g scale of **20** gave **21** in 56% yield, with 14:1 ratio of **21**:**24** (*Scheme 30*).

Although **21** and **24** were inseparable , the structure of the **24** was elucidated after conversion into its primary tosylate, which remained unreacted in the epoxidation step that delivered **22** (see experimental). Diol **24** is likely formed *via* Meinwald-type rearrangement.[238] As illustrated in *Scheme 31*, the $AlMe_3$-mediated opening of epoxide **26** could lead to a cation that would undergo a 1,2-alkyl shift. Subsequent methyl addition (from $AlMe_3$) to **27** would then furnish **24**.



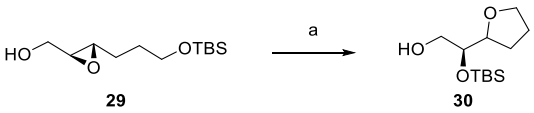
Scheme 31. Proposed mechanism for the formation of diol **24** from **20** and $AlMe_3$.

The reaction of **20** with $AlMe_3$ also produced the separable tetrahydrofuran **25** as a by-product in ca. 15% yield. A plausible mechanism for the formation of **25** is depicted in *Scheme 32*. According to this mechanism, the intramolecular attack of the lone pair of the silyl-protected oxygen on the epoxide moiety gives oxonium intermediate **28**. This is followed by silyl group migration[239][240] to furnish **25**.



Scheme 32. Proposed mechanism for side product formation.

Importantly, as discovered by Zechner in her PhD thesis, the reaction of TBS-ether **29** with $AlMe_3$ was found to furnish tetrahydrofuran **30** as the only isolable product, even when the reaction was carried out at -78 ˚C (*Scheme 33*).

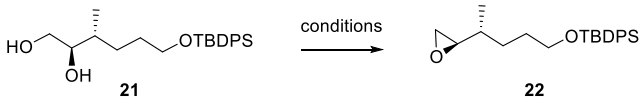


Scheme 33. Reagents and conditions: Me_3Al, *n*-hexane, 0 °C or -20 °C or -78 °C, 15 min, 80%.

This finding then necessitated the use of the TBDPS group as Pg^1 in building block **D** (*Scheme 30*).

With the desired **21** in hand, the latter was then converted into epoxide **22** (*Scheme 30, Table 1*). The reaction required some minor optimization, as the conditions reported by Rajesh and co-workers (*Table 1*, entry 1)[223] gave **22** in only moderate yield (55%; 61% reported in ref.[223]). Significantly improved yields of close to 80% were obtained with NaH/tosyl imidazole[241] (*Table 1*, entries 2 and 3,) even on scales up to 15 g of **21**.

Table 1. Optimization of the reaction conditions for the scale-up of the terminal epoxide **22**.



21 **22**

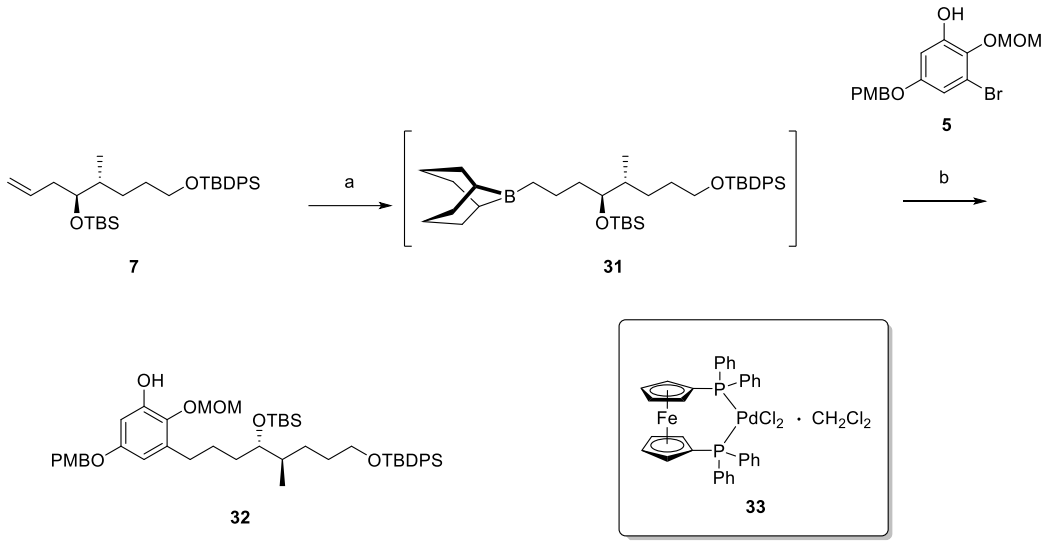
Entry	Scale (**21**)	Conditions	Time	Yield (**22**)
1	2.9 g[a]	*p*-TsCl, DMAP, Et_3N, DCM, then K_2CO_3, MeOH	2-48 h	1.6 g, 55%
2	2.8 g	NaH, tosyl imidazole, THF (c=0.3 M)	4 h	2.0 g, 77%
3	14.5 g	NaH, tosyl imidazole, THF (c=0.3 M)	6 h	10.0 g, 72%

[a] The same yield was observed on a milligram scale (2.0 mmol).

Copper(I)-mediated nucleophilic epoxide opening with vinylmagnesium bromide at -78 ˚C to -20 ˚C following the protocol reported in Zechner's PhD thesis and by Akkapali and co-workers[223] then gave homoallylic alcohol **23** in excellent yield (94%) (*Scheme 30*); scale-up of the reaction up to 18 g of **22** was unproblematic. Finally, the reaction of **23** with TBSCl furnished the desired building block **7** in 84% yield. Overall, **7** was obtained from 1,4-butanediol in nine steps in yields ranging from 8.9% to 13% on scales up to 30 g of **7**.

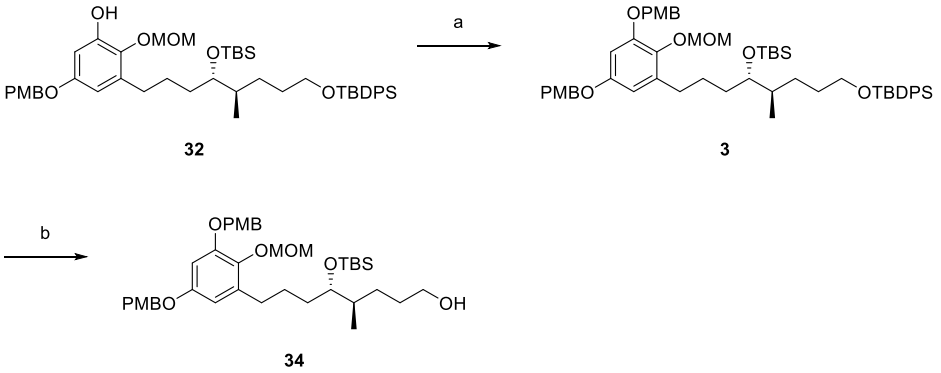
3.2.3 Suzuki-Miyaura coupling between olefin 7 and aryl bromide 5

The Suzuki-Miyaura cross-coupling[242] between the *in situ*-generated borane **31** and aryl bromide **5** had already been optimized by Zechner on a small scale (*Scheme 34*). Thus, a yield of 78% of **32** is reported by Zechner under the conditions specified in *Scheme 34*. These results were readily reproduced and **32** was obtained in yields of 48-72% on a 50 – 500 mg scale.



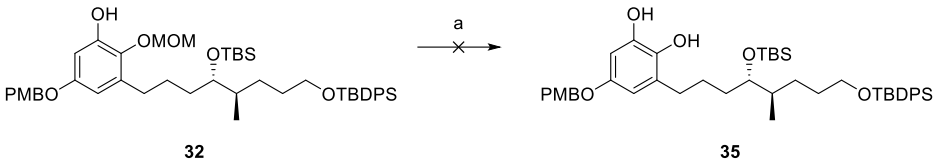
Scheme 34. Reagents and conditions: a) 9-BBN (1.67 equiv.), 5 h at 0 ˚C to rt, then K_2CO_3 (2.0 equiv.) solution in H_2O b) 0.2 mol% $Pd(dppf)_2Cl_2{\cdot}CH_2Cl_2$, K_2CO_3, H_2O/THF, 105 °C in MW, 45 min 78% (M. Zechner).

According to the protecting group strategy delineated in *Scheme 28*, the next step would be to convert **32** into bis-PMB-ether **3**. Treatment of **32** with PMBCl and K_2CO_3 in DMF delivered the desired product **3** in 84% yield (*Scheme 35*). Later in the synthesis, the TBDPS protecting group on the primary alcohol would have to be removed in the presence of the aromatic PMB-ether, therefore conditions for the removal of the primary TBDPS group were tested (*Scheme 35*) using a buffer of TBAF and acetic acid in THF, however, only 24% of the desired product could be obtained. The low yield could be explained by a partial PMB removal from **3**, since also PMBOH and mono-PMB protected substrate were isolated as the products of the reaction.



Scheme 35. Reagents and conditions: a) PMBCl, K_2CO_3, DMF, rt, 30 min, 84%; b) TBAF/AcOH (1:1), THF, rt, 24%.

According to the protecting group strategy in *Scheme 28*, it would also have to be possible to selectively remove MOM from **3** in the presence of PMB-ethers. In order to assess the viability of this approach, the selective cleavage of the MOM-ether in **32** was investigated. However, the investigated conditions employing zinc bromide and propanethiol,[222] unfortunately, did not give any isolable products (*Scheme 36*).



32 35

Scheme 36. Reagents and conditions: a) $ZnBr_2$, *n*-PrSH, DCM, then satd. $NaHCO_3$, 0 ˚C.

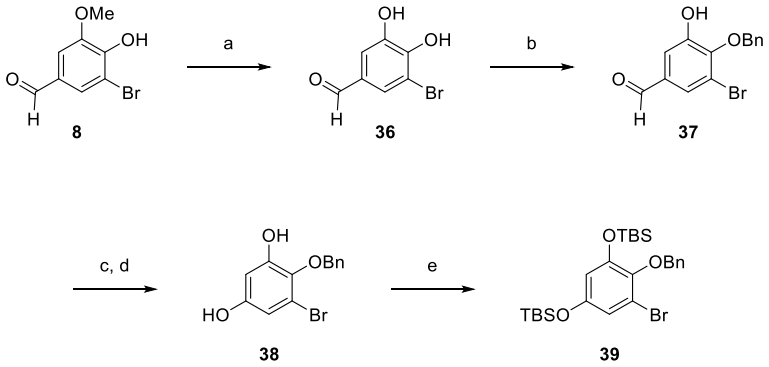
Other procedures for MOM-cleavage were deemed not to be compatible with the PMB-ether, due to their acidity.

3.2.4 Synthesis of alternative aromatic building blocks C

The initial results of the above screening of methods for selective MOM- and TBDPS-cleavage in the presence of a PMB-ether appeared highly discouraging. In light of this finding, the focus was shifted towards other protecting group combinations in building block **C**. Specifically, the following Pg^3/Pg^4 combinations were evaluated: Pg^3 = Bn, Pg^4 = TBS (aryl bromide **39**, Chapter 3.2.4.1.) and Pg^3 = MOM, Pg^4 = allyl (aryl bromide **50**, Chapter 3.2.4.2.).

3.2.4.1 Synthesis of aryl bromide 39

The design of aryl bromide **39** (*Scheme 37*) was based on the idea that the benzyl-protecting group could be selectively removed by hydrogenation in the presence of all silyl protecting groups; in addition, protection of the other phenolic hydroxy groups as TBS-ethers would have allowed global deprotection of the product after macrocycle construction in a single step. The synthesis of **39** is summarized in *Scheme 37*. The methyl ether moiety in **8** was cleaved with aluminum trichloride[243][244] to give **36** in 93% yield.

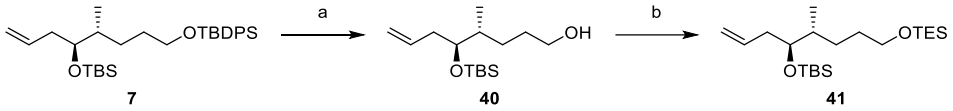


8 36 37 38 39

Scheme 37. Regents and conditions: a) $AlCl_3$, Py, DCM, 45 ˚C, 93%; b) BnBr, Li_2CO_3, DMF, 45 ˚C, 6%; c) *m*-CPBA, DCM, 0 ˚C; d) KOH, MeOH, rt, 67%; e) TBSCl, imidazole, DMF, rt, 88%.

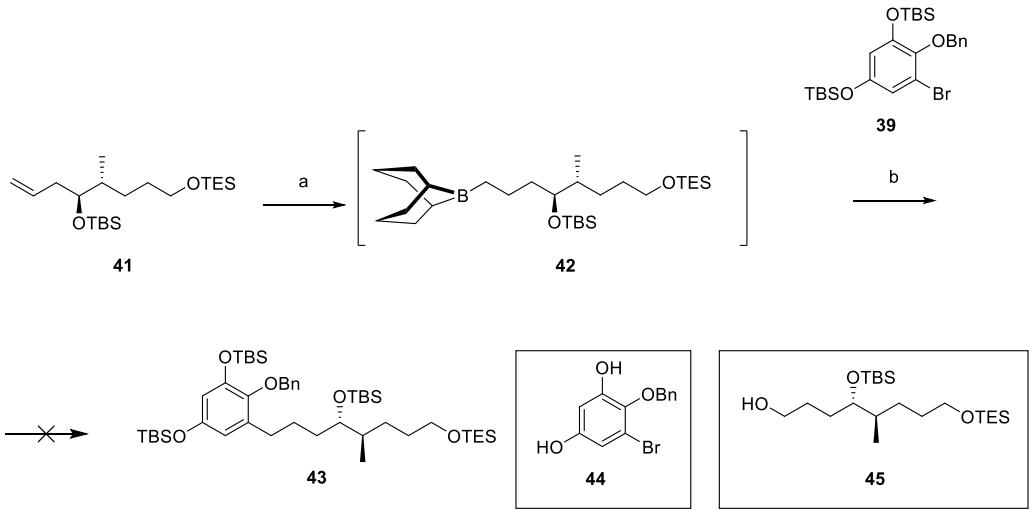
This was followed by selective benzylation of the more acidic hydroxy group with BnBr in the presence of Li_2CO_3[245] in DMF to furnish **37**, albeit in very low yield (6%); most of the starting material was recovered. Baeyer-Villiger reaction with **37** followed by cleavage of the ensuing formyl ester furnished

38; double protection of the free phenolic hydroxy groups as TBS-ethers by reaction with TBSCl and imidazole [246] delivered aryl bromide **39** in 88% yield. In order to ensure the viability of the TBS/Bn aromatic protecting group strategy, the TBDPS group in **7** was replaced with a more labile TES group. Primary TES-ether **41** was obtained from **7** by selective cleavage of the primary TBDPS group with TBAF buffered with acetic acid[224] followed by reaction with TESCl and Et_3N in 60% overall yield (*Scheme 38*).[247]



Scheme 38. Reagents and conditions: a) TBAF with AcOH (1:1), DMF, rt, 81%; b) TESCl, Et_3N, DCM, rt, 74%.

Unfortunately, for reasons that are unclear at this point, none of the desired product **43** could be isolated after reaction between **39** with *in situ*-generated borane **42** under the optimized conditions for the reaction of olefin **7** with aryl bromide **5** (*Scheme 39*). The only isolable products obtained from the reaction were **44** (14%) and **45** (37%), the rest could not be identified.



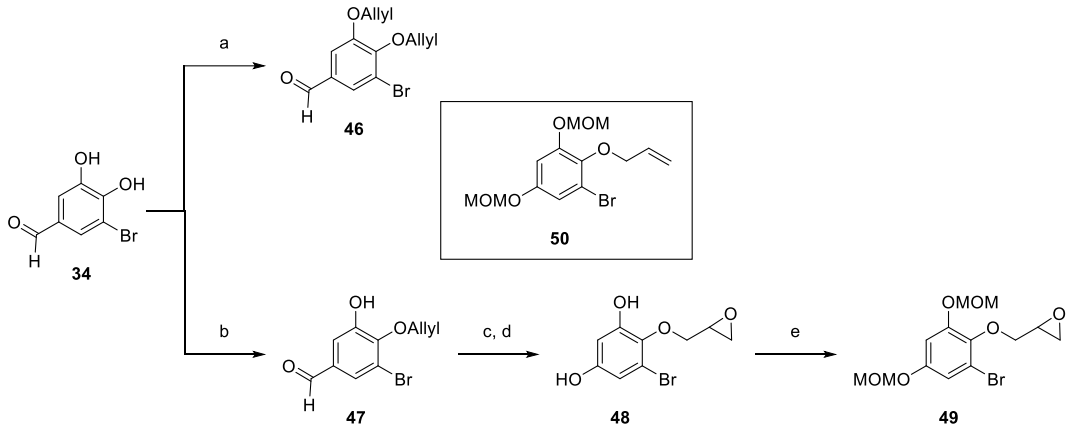
Scheme 39. Reagents and conditions: a) **41** (1.0 equiv.), 9-BBN (1.67 equiv.), 5 h at 0 ˚C to rt, then K_2CO_3 (2.0 equiv.) solution in H_2O b) Pd(dppf)Cl_2·CH_2Cl_2 (0.2 equiv.), **39** (1.0 equiv.) in THF, overall THF: H_2O ratio = 5:1, **44** (<14%), **45** (37%).

3.2.4.2 Synthesis of aryl bromide 50

In an attempt to exploit the relative stability of the MOM protecting group, an aromatic protecting group strategy was conceived in which Pg^3 in building block **A** would be allyl, while Pg^4 would be MOM; allyl- and MOM-ether protecting groups are fully orthogonal and the conditions for allyl-ether cleavage are also compatible with the presence of silyl-ether protecting groups. However, the implementation of this strategy in the first step required the synthesis of the corresponding precursor building block **C**, i.e. **50** (*Scheme 40*), and it was unclear if the route that had led to aryl bromide **37** would also be suitable for

the synthesis of **50**. While Baeyer-Villiger rearrangements in the presence of terminal double bonds have been reported,[248][249][250][251] there was still concern about possible epoxidation of the allyl moiety.

As depicted in *Scheme 40*, aldehyde **34** was converted into mono-allyl-ether **47** by reaction with allyl bromide in the presence of 1.1 equiv. Li_2CO_3 in DMF[252] in 92% yield. Interestingly, the use of 1.1 equiv. K_2CO_3 instead of Li_2CO_3 gave bis-allyl-ether **46** in 78% yield. Thus, the weaker base lithium carbonate allowed selective deprotonation of the more acidic hydroxy group, leading only to the desired mono-allylated product **47**.[252] Reaction of **47** with 2.0 equiv. of *m*-CPBA followed by treatment of the crude product with aq. KOH/MeOH gave a mixture of two products (including **48**), which was directly submitted to reaction with MOMCl. Unfortunately, only epoxide **49** could be isolated from this reaction in 50% yield.



Scheme 40. Reagents and conditions: a) AllylBr, K_2CO_3, DMF, rt, 18 h, 78%; b) AllylBr, Li_2CO_3, DMF, rt to 55 ˚C, 18 h, 92%; c) *m*-CPBA, DCM, 0 ˚C; d) 1.78 M aq. KOH/MeOH, rt, 44% mixture of two substrates; e) MOMCl, NaH 60% in mineral oil, DCM, rt, 22% over three steps from **47**.

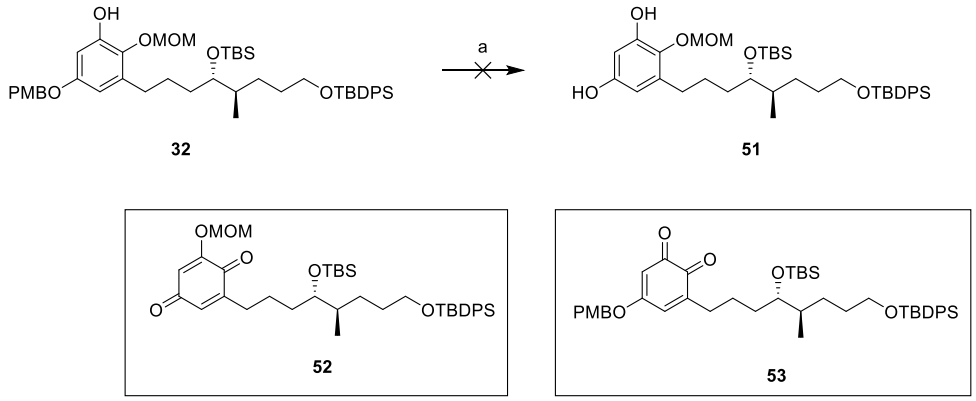
The most logical step at this point would be to investigate the Baeyer-Villiger rearrangement using 1.0 equivalent of *m*-CPBA. However, the approach was completely abandoned due to possible difficulties in optimizing the Suzuki coupling with an aryl substrate containing a terminal double bond of an allyl-protecting group.

3.2.5 Synthesis of building block A with Pg^3 = MOM and Pg^4 = allyl and selective MOM-ether cleavage

At this point, rather than trying to optimize the Suzuki cross-coupling conditions for a new aromatic building block, it was decided to retain the MOM group present in **32** as the protecting group Pg^3 in building block **A** (see *Scheme 27*) and instead protect the other two hydroxy groups as allyl-ethers. The orthogonality of Pg^3 and Pg^4 would thus be maintained, but the order of removal of the MOM-and allyl-ether groups would be inverted. However, before elaborating a synthesis for another aromatic building block **C** and establishing conditions for the Suzuki coupling with a new substrate, it was first investigated

if the corresponding building block **A** with Pg^3 = MOM and Pg^4 = allyl could be accessed from **32** *via* PMB removal and bis-allylation. While this approach, obviously, entailed a higher step count than the direct approach *via* a protected aryl bromide precursor, it offered the advantage of an established Suzuki coupling step. In addition, it would also exclude the risk of the terminal double bonds of the allyl protecting groups interfering with the Suzuki coupling by engaging in a Heck reaction with the Pd complex formed upon oxidative addition to the aryl bromide.[253]

PMB cleavage from **32** was first attempted with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) under a number of conditions.[254] Unfortunately, the desired phenol **51** was not formed under any of the conditions investigated. The reaction was plagued by oxidation to *ortho*- and *para*-quinones, **53** and **52**, respectively, which were the sole isolable products (*Scheme 41*).



Scheme 41. Reagents and conditions: a) DDQ, phosphate buffer, H_2O, DCM, -78 ˚C to rt.

The results of the cleavage experiments with DDQ are summarized in *Table 2*.

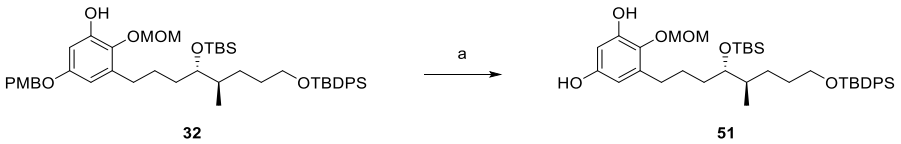
Table 2. Attempts to remove the *p*-methoxybenzyl protecting group from **32** with DDQ

Entry[a]	Conditions[b]	Time	Yield[c] / observations
1	DDQ (1.2 equiv.), rt.[d]	20 h	**52**, 44%
2	DDQ (1.0 equiv.), pH=7 buffer, rt.	110 min	**52**, 47% and **53**, 30%
3	DDQ (1.0 equiv.), pH=7 buffer, -5 to 0 ˚C	55 min	NMR monitoring to understand the effect of temperature, **52** : **53** = 1:0.8
4	DDQ (1.0 equiv.), pH=7 buffer, -78 ˚C	5 min	**32** : **52** : **53** = 1 to 2.5 to 3.3 by NMR; **52**, 41%
5	DDQ (1.0 equiv.), pH=7 buffer, rt.	15 min	**52**, 40% and **53**, 17%

[a] for all entries the scale of the reactions was in the range of 5 µmol0.1 mmol; [b] DCM was used as a solvent unless otherwise stated; [c] isolated yield unless otherwise stated; [d] DCM/H_2O = 10:1; phosphate buffer (Na_2HPO_4, KH_2PO_4, NaCl, KCl).

NMR monitoring during the course of the reaction showed that the formation of **52** and **53** occurs immediately without the desired product **51** being formed, even when the starting material has not yet been completely consumed.

When it became clear that the oxidative cleavage of the PMB-ether in **32** was not successful, I focused on the possible removal of the protecting group by catalytic hydrogenation over Pd/C (*Scheme 42, Table 3*).



32 **51**

Scheme 42. Hydrogenolysis of the PMB-ether in **32**. Reagents and conditions: See Table 5.

A first reaction was carried out at ambient pressure in MeOH (*Table 3,* entry 1), but the reaction did not proceed. When the pressure was increased to 3.5 atm, **51** was obtained in 20% yield and 33% of the starting material was re-isolated. While the yield was low, it was encouraging that **51** could be isolated at all. Part of the reason for the low yield might have been a partial loss of the silyl groups as silyl residues were isolated.[255] On a larger scale, however, decomposition was observed in methanol (*Table 3,* entry 2). Gratifyingly, when the solvent was changed to EtOH, **51** was obtained in 78% yield on a 50 mg scale and in 72% yield using 650 mg of **32**. The reaction was reproducible and highly scalable, even if

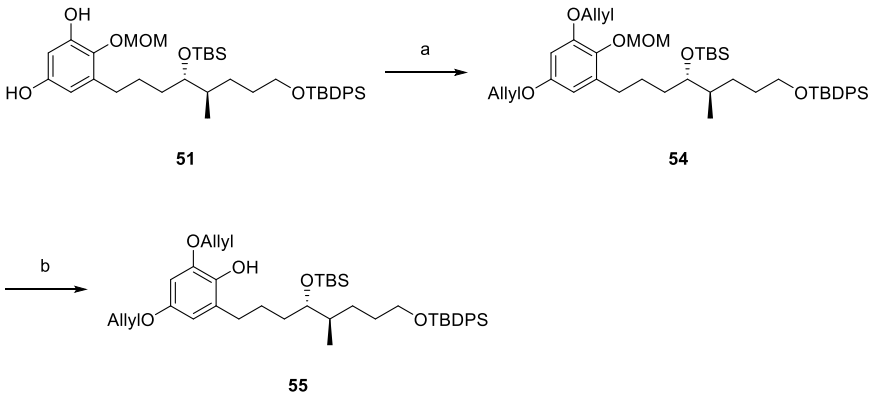
the rate was significantly lower on a larger scale; when carried out on a 22 g scale of **32**, **51** was obtained in 76% yield.

Table 3. Selected examples for the hydrogenolytic cleavage of the PMB-ether in **32**.

Entry	Scale	Conditions	Solvent	Time	Yield (**51**)[a]
1	15 mg	10% w/t Pd/C (20% w/w), H_2 (1 - 3.5 atm)	MeOH (c=0.1)	2 d	20% [b]
2	100 mg	10% w/t Pd/C (20% w/w), H_2 (5 atm)	MeOH (c=0.03)	18 h	Decomp.
3	50 mg	10% w/t Pd/C (20% w/w), H_2 (3.5 atm)	EtOH (c=0.03)	6 h	33 mg, 79%
4	659 mg	20% w/t Pd/C (16% w/w), H_2 (3.5 atm)	EtOH (c=0.035)	2 d	462 mg, 74%

[a] Isolated yield; [b] Additionally, 33% of the starting material was reisolated. w/t = weight.

The conversion of **51** into bis-allyl-ether **54** with allyl bromide in the presence of K_2CO_3 in DMF proceeded uneventfully; **54** was obtained in yields between 77% and 95% (*Scheme 43*). Under optimized conditions with 10 equivalents of AllylBr and K_2CO_3 in DMF at 50°C, the reaction delivered **54** in 83% yield on a 13 g scale of **51**.



Scheme 43. Reagents and conditions: a) AllylBr, K_2CO_3, rt, to 45-50 ˚C, DMF, 77-95%; b) $TiCl_4$, Et_3N, amylene, DCM, -78 ˚C, 30 min, 80-100%.

Different conditions reported in the literature for the selective cleavage of MOM-ethers in the presence of silyl protecting groups were then investigated (*Table 4*). Montmorillonite clay[256] gave no reaction (*Table 4,* entry 1); the same result was obtained with magnesium (II) bromide diethyl ether complex (*Table 4,* entry 2).[257] Treatment of **54** with zinc bromide and 1-propanethiol[222] proved to be non-selective, resulting in both MOM removal and loss of both silyl protecting groups.

Table 4. Conditions investigated for selective MOM-removal from **54**.

Entry	Conditions[a]	Solvent	Time	Yield (**55**)[b] / observations
1	Montmorillonite clay, rt. to 50 ˚C	Benzene	24 h	SM
2	$MgBr_2 \cdot Et_2O$, 0 ˚C to rt.	THF	6 h	SM
3	$ZnBr_2$, *n*-PrSH, rt.	DCM	65 min	29% (loss of TBS and MOM) 49% (loss of TBDPS, TBS, MOM)
4	$TiCl_4$, Et_3N, -78°C	DCM	30 min	95%

[a] Reactions scales were between 3.8 µmol and 18.4 µmol; [b] isolated yield of **55**.

Finally, treatment of **54** with titanium tetrachloride in DCM at -78 ˚C for 30 min gave the desired free phenol **55** in excellent yields between 80% and 100% (*Scheme 43, Table 4,* entry 4). The reaction was scalable and on a 12 g scale of **54** delivered **55** in 87% yield. It should be noted here that a significant number of solvent mixtures had to be screened in order to find an eluent that allowed separation of **54** and **55** by TLC and enabled monitoring of the reaction progress. Ultimately, toluene/EtOAc 50:1 was identified as the eluent of choice.

3.2.5.1 Optimization of the scale-up of the Suzuki coupling between olefin 7 and aryl bromide 5

Based on the results discussed above, the scalability of the Suzuki coupling between **5** and **7** was assessed. Importantly, Zechner had obtained high yields for this reaction only with microwave irradiation, while heating in an oil bath gave **32** in yields <50%. However, these conditions did not lend themselves to efficient scale-up, as the microwave reactor available in the laboratory could only be operated with vials holding a maximum volume of 20 mL. Therefore, the conditions for the Suzuki-Miyaura coupling were revisited here and the results are summarized in *Table 5.*

As alluded to above, similar yields of **32** to the ones reported by Zechner were obtained when using the conditions reported in her PhD thesis (*Table 5*, entry 1).

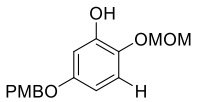
Table 5. Scale-up optimization of the B-alkyl Suzuki- Miyaura coupling between olefin **7** and aryl bromide **5**.

Entry[a]	Scale (**7**)	Conditions[b]	Yield of **32**[c]
1	50-500 mg	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (**33**) (0.2 equiv.), **5** (1.0 equiv.) in THF, overall THF/H_2O = 5:1, 90 min, 105 ˚C, MW	48-72%
2	235 mg	MW vial, oil bath heating, THF/H_2O =5:1, 100 min at 105 ˚C, then 14 h at rt.	67%
3	2.1 g	autoclave, oil bath heating, THF/H_2O =5:1, 140 min at 105 ˚C, then 18 h at rt.	82%
4	6.9 g	autoclave, oil bath heating, THF/H_2O =5:1, 140 min at 105 ˚C, then 18 h at rt.	78%
5	235 mg	oil bath heating, CPME[d]/H_2O =5:1, 140 min at 105 ˚C, then 18 h at rt.	33%
6	12 g	autoclave, oil bath heating, THF/H_2O =5:1, 6 h at 105 ˚C, then 6 h to rt.	65%[e]

[a] Olefin **7** was reacted 9-BBN (1.67 equiv.) in THF for 3-5 h at rt, and 1.1 M aq. K_2CO_3 (2.0 equiv.) were then added. Within 10 min after the addition of K_2CO_3, aryl bromide **5** (1.0 equiv.) and catalyst **33** (0.1 equiv) were added to the solution at rt, and then heated to 105 ˚C. [b] conditions for the Suzuki coupling; [c] isolated yields; [d] the boiling point of CPME, bp(CPME)=106 ˚C; [e] in this entry mixed fractions of the product with **56** and **7** were additionally isolated.

Surprisingly in light of Zechner's work, however, using the same setup and conditions, i. e. still carrying out the reaction in a MW vial, but heating it in an oil bath instead of a MW reactor, gave a similar result (*Table 5,* entry 2). Based on this finding, the reaction was scaled up to 2, 6, and 12 grams of **7** (*Table 5*, entries 3, 4, and 6, respectively); for safety reasons, the reactions were performed in an autoclave. Replacing THF with cyclopentyl methyl ether (CPME), which has a higher boiling point, led to a substantial decrease in yield (*Table 5,* entry 5).

In the optimized B-alkyl Suzuki-Miyaura coupling between olefin **7** and aryl bromide **5** (*Table 5,* entries 1-6), around 20-25% of **7** remained unreacted. It is also interesting to note that NMR experiments indicated full conversion of olefin **7** in the hydroboration step, in spite of the fact that 20-25% of **7** could be re-isolated from the reaction mixture. Apparently, the re-isolated **7** arises from β-hydride elimination that competes with reductive elimination in the cross-coupling reaction.[258] In addition, protodehalogenated aryl fragment **56** was formed as a by-product in 16% yield (*Scheme 44*).

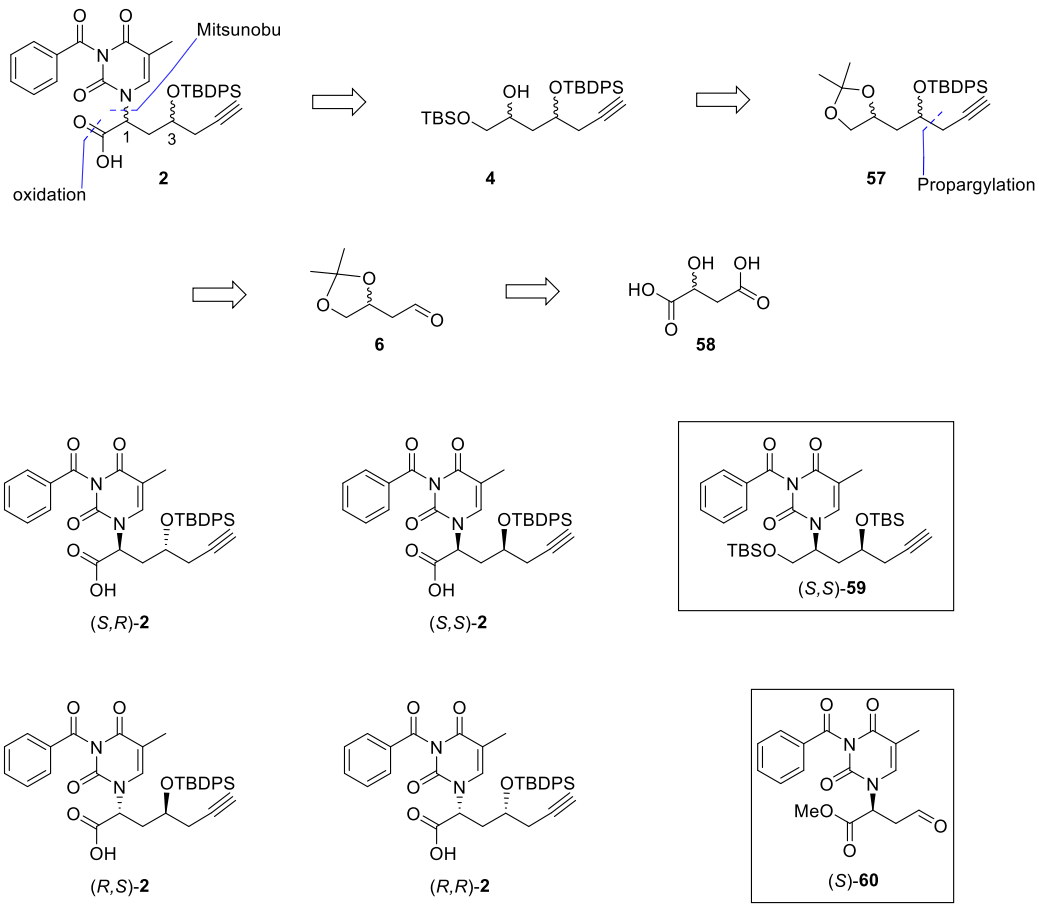


56

Scheme 44. The structure of **56**.

3.3 Synthesis of acids B

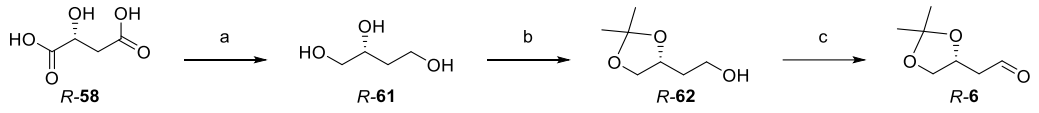
As outlined in Chapter 3.1, the synthesis of building blocks **2** was envisioned to proceed *via* partially protected triols **4**, which were to be converted into acids **2** *via* Mitsunobu reaction with N(3)-benzoyl thymine followed by deprotection and oxidation. Alcohols **4** would be obtained from acetonides **57**, which in turn would be derived from aldehydes **6** by propargylation and TBDPS protection; the latter can be prepared from D- or L-malic acid (**58**) (*Scheme 45*). The proof-of-concept for this strategy was already established by Zechner, whose PhD thesis describes the synthesis of (*S,S*)-**59** (as precursor for **B** (*Scheme 27*)), including the selective cleavage of the acetonide moiety in the TBS-protected analog of (R,S)-**57**. However, the yield for this latter step was only 37% on a 180 mg scale and it was unclear if the reaction would be scalable. In addition, Zechner also described the synthesis of ester aldehyde (*S*)-**60** directly from malic acid (i. e. without the need for reduction/oxidation), but the indium-mediated propargylation of **6** with propargyl bromide under Barbier-like conditions with (1*S,*2*R*)-(+)-2-amino-1,2-diphenylethanol as a chiral ligand[259][260] was found to be only moderately selective; more importantly, the isomers were not separable, which led to the design of the strategy depicted in *Scheme 45*.



Scheme 45. Retrosynthesis of building blocks **2**.

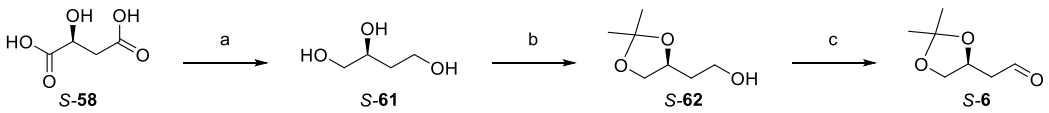
3.3.1 Synthesis of the aldehydes 6

The synthesis of homopropargylic alcohols **4** started from *D*- or *L*-malic acid (**58**) and proceeded through known aldehydes **6** as key intermediates.[261][262] The synthesis of aldehyde *R*-**6** is summarized in *Scheme 46*. Reduction of *D*-malic acid (*R*-**58**) with $B(OCH_3)_3$, $(CH_3)_2S{\cdot}BH_3$ gave triol *R*-**61** in 76% yield, which was then converted into acetonide *R*-**62** by treatment with 2,2-dimethoxypropane and a catalytic amount of *p*-TsOH in DCM[263] (60% yield). Finally, Parikh-Doering oxidation[264] furnished aldehyde *R*-**6** in 27% overall yield from *D*-malic acid (R-58).[264]



Scheme 46. Reagents and conditions: a) $B(OCH_3)_3$, $(CH_3)_2S{\cdot}BH_3$, THF, 17 h, rt, then stirring in MeOH, 76%; b) *p*-TsOH (cat.), 2,2-dimethoxypropane, DCM, 1 h, rt, 60%; c) DIPEA, DMSO, SO_3·pyridine, DCM, 0.5 h, rt, 60%.

Aldehyde *S*-**6** was prepared in the same way from *L*-malic acid (*S*-**58**) (*Scheme 47*).



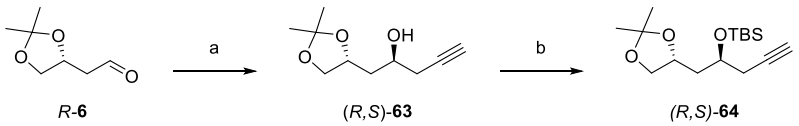
*Scheme 47.*Reagents and conditions: a) $B(OCH_3)_3$, $(CH_3)_2S{\cdot}BH_3$, THF, 17 h, , rt; b) 2,2-dimethoxypropane, *p*-TsOH (cat.), DCM, 1 h, , rt, 55% over two steps; c) Et_3N, DMSO, $SO_3{\cdot}$pyridine, DCM, 0.5 h, , rt, 56%.

These syntheses were carried out on a multi- or decagram scale.

3.3.2 Synthesis of homopropargylic alcohols 63

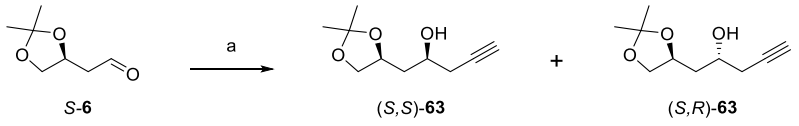
3.3.2.1 Indium-mediated asymmetric propargylation of aldehydes *S*- and *R*-6

Initial work towards the synthesis of homopropargylic alcohol (*R,S*)-**63** was based on the indium-mediated asymmetric Barbier-type propargylation[259][260] of *R*-**6** with (1*S,*2*R*)-(+)-2-amino-1,2-diphenyl ethanol as a chiral ligand, as described in Zechner's PhD thesis (*Scheme 48*). The propargylation product was directly reacted with TBSCl, to furnish TBS-ether (*R,S*)-**64** as a 6:1 mixture of diastereoisomers in 50% yield. No effort was made to separate the diastereomers at this point because the reaction was selective and it was clear which diastereomer is major.



Scheme 48. Asymmetric propargylation of aldehyde *R*-**6** and following alcohol protection. Reagents and conditions: a) (1*S,*2*R*)-(+)-2-amino-1,2-diphenylethanol, indium powder, pyridine, 80% propargyl bromide solution in toluene, rt, 30 mins, then at -78 ˚C for the addition of the aldehyde *R*-**6**; b) TBSCl, imidazole, DMF, rt, 52% over two steps, *dr*=6:1.

When aldehyde *S*-**6** was reacted with propargyl bromide under the same conditions, the reaction was completely non-selective and produced a 1:1 mixture of diastereomeric homopropargylic alcohols (*S,S*)-**63** and (*S,R*)-**63** in 69% yield (*Scheme 49*).



Scheme 49. Asymmetric propargylation of aldehyde *S*-**6**. Reagents and conditions: a) (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol, indium powder, pyridine, 80% propargyl bromide solution in toluene, rt, 30 mins, then at -78 ˚C for the addition of the aldehyde *S*-**6**, 69%, *dr*=1:1.

Diastereomers (*S,S*)-**63** and (*S,R*)-**63** were separated by FC employing gradient elution with DCM/EtOAc from 100:0 to 10:1 (*Figure 30*). This was the first attempt to separate the diastereomers in the propargylation reaction. Previously, the separation had not been initiated due to the presence of a major diastereomer.

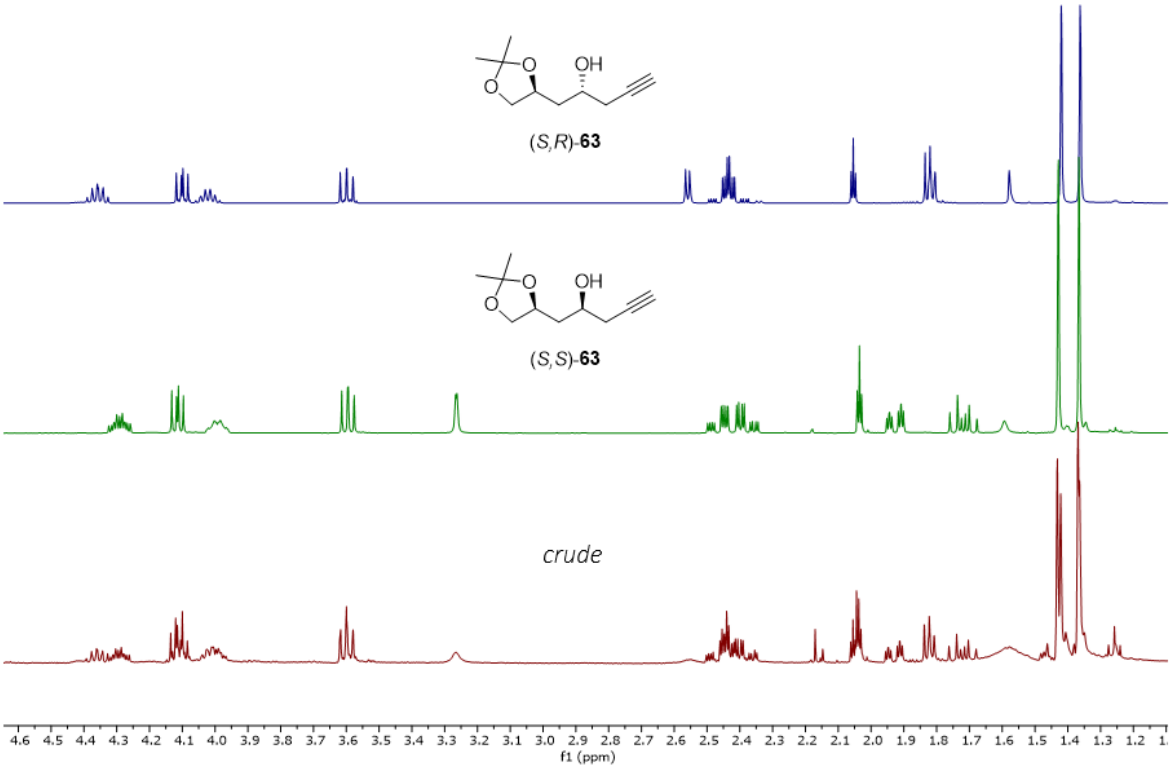
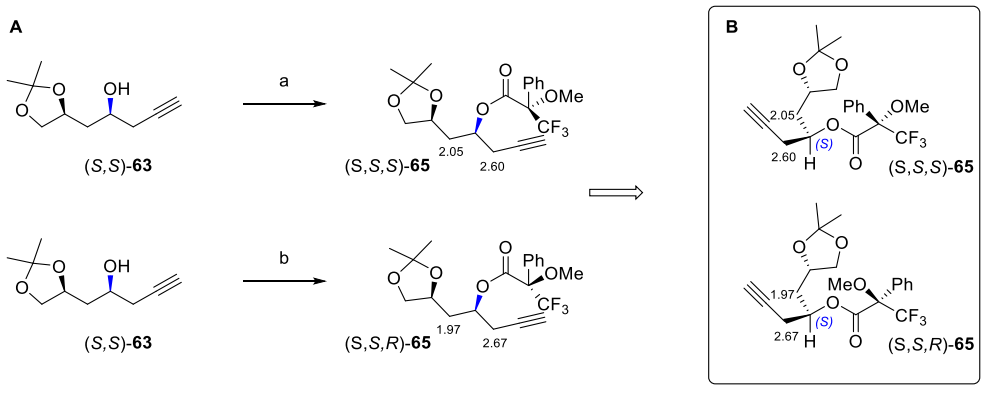


Figure 30. Comparison of the NMR spectra of (*S,R*)-**63** and (*S,S*)-**63**, and the crude propargylation product obtained after aqueous work-up before chromatography.

The configuration of the newly formed stereocenter in (*S,S*)-**63** was determined by Mosher ester analysis (*Scheme 50*).[265] Thus, (*S,S*)-**63** was converted into the Mosher esters (*S,S,S*)-**65** and (*S,S,R*)-**65** under Yamaguchi esterification conditions with (*S*)-(-)- and (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA), 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP in toluene in quantitative and 95% yield, respectively (*Scheme 50*).[165]



Scheme 50. Mosher ester analysis of the homopropargylic alcohol (*S,S*)-**63**. A) Reagents and conditions: a) (S)-(-)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA), 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, rt, 3 h, quant; b) (R)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, rt, 3 h, 95%. B) The molecule is drawn according to the MTPA plane using $\Delta\delta=\delta_S-\delta_R$.

Based on the analysis of the ($\Delta\delta=\delta_S-\delta_R$) values in the ^{1}H-NMR spectra of (*S,S,S*)-**65** and (*S,S,R*)-**65**, the alcoholic stereocenter in (*S,S*)-**63** must be *S*-configured; by inference, it must be *R*-configured in the second diastereomer (*S,R*)-**63**.

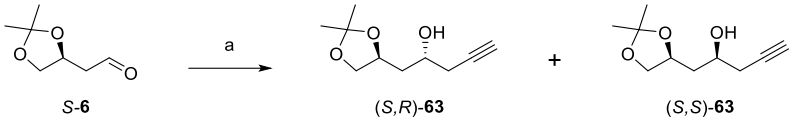
Importantly, the complete lack of stereoselectivity in the propargylation of *S*-**6** with (*1S,2R*)-(+)-2-amino-1,2-diphenylethanol as the chiral ligand meant that the propargylation of *R*-**6** in the presence of *(1R,2S)*-(-)-2-amino-1,2-diphenylethanol would also be equally non-selective. As a consequence, both (*R,R*)-**63** and (*S,S*)-**63** would be accessible by this method only as ca. 1:1 mixtures with their diastereoisomers (*R,S*)-**63** and (*S,R*)-**63**, respectively, thus necessitating chromatographic separation even when applying what has generally been shown to be a stereoselective propargylation method. In light of these findings, and as (*S,S*)-**63** and (*S,R*)-**63** had been found to be separable by FC, I considered it more reasonable to dispense with the use of chiral reagents for the propargylation of **6** and employ a less sophisticated approach and simply rely on isomer separation to access two diastereomers *via* a single reaction.

3.3.2.2 Zn-mediated Barbier-type propargylation of aldehydes *S*- and *R*-6

The Zn-mediated Barbier-type propargylation of a compound related to *R*-**6** (2-((*4R,5R*)-2,2,5-trimethyl-1,3-dioxolan-4-yl)acetaldehyde) was previously reported by Thomas and co-workers[266] to furnish a 4:1 mixture of (*R,R,S*) and (*R,R,R*) diastereomers. Later, the same procedure was employed by Krische and co-workers[267] for *R*-**6** to afford a 3.5:1 mixture of (*R,S*)-**63** and (*R,R*)-**63**, respectively. When applying Krische's conditions to the propargylation of *S*-**6** on a 300 mg scale, the reaction proceeded with a *dr* of 2:1, furnishing (*S,R*)-**63** and (*S,S*)-**63** in 29% and 10% yield, respectively, after FC (*Table 6*, entry 1).

Treatment of *S*-**6** with a propargyl Grignard reagent in the presence of zinc bromide[268] gave no reaction (*Table 6*, entry 2). Employing indium metal in the absence of a chiral ligand gave (*S,R*)-**63** and (*S,S*)-**63** in 50% and 44% yield, respectively, after FC; the *dr* of the crude product after extractive work-up was 1:1 (*Table 6*, entry 3). At the same time, scaling up the Zn-mediated reaction to 5 g of *S*-**6** gave (*S,R*)-**63** and (*S,S*)-**63** in 65% and 19% isolated yield, respectively (*Table 6*, entry 4). Given this success, no effort was made to scale up the indium-mediated reaction. A possible explanation for the increased yield of the Zn-mediated propargylation on a larger scale (*Table 6*, entry 4 vs. entry 1), could be that traces of HCl from TMSCl were more critical on a smaller scale than on a larger scale.

Table 6. Conditions screening for the propargylation of *S*-**6**.

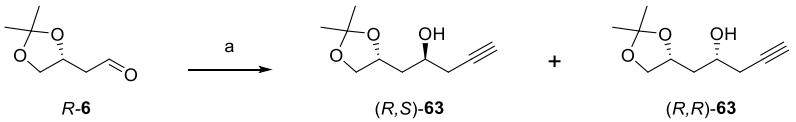


S-**6** (*S*,*R*)-**63** (*S*,*S*)-**63**

entry	Conditions[a]	Scale	Yield[b] /remarks
1	Zn dust, 1,2-dibromoethane, 80% propargyl bromide solution in toluene, TMSCl, THF, -10°C to -78°C to -50 ˚C	300 mg	(*S,R*)-**63** (29%) (*S,S*)-**63** (10%), *dr*=2:1[c]
2	Mg, $ZnBr_2$, 80% propargyl bromide solution in toluene, Et_2O, THF, 0 ˚C	50 mg	No reaction
3	In powder, pyridine, 80% propargyl bromide solution in toluene, -78 ˚C, THF, 3 h	50 mg	(*S,R*)-**63** (50%) (*S,S*)-**63** (44%), *dr*=1:1[c]
4	Zn dust, 1,2-dibromoethane, 80% propargyl bromide solution in toluene, TMSCl, THF, -10 ˚C to -78 ˚C to -50 ˚C	5 g	(*S,R*)-**63** (65%) (*S,S*)-**63** (19%), *dr*=2:1[c]

[a] equivalents of the reagents can be found in the experimental section; [b] isolated yields; [c] *dr* of the crude product after extractive work-up.

Zn-mediated propargylation with aldehyde *R*-**6** on a 10-gram scale afforded the diastereomers (*R,S*)-**63** and (*R,R*)-**63** in 42% and 21% isolated yield, respectively (*Scheme 51*).



R-**6** (*R*,*S*)-**63** (*R*,*R*)-**63**

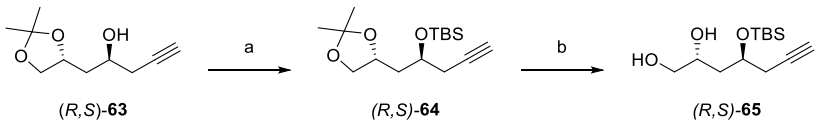
Scheme 51. Zn-mediated propargylation of *R*-**6**. Reagents and conditions: a) zinc dust, 1,2-dibromoethane, 80% propargyl bromide solution in toluene, TMSCl, THF, -10°C to -78 ˚C to -50 ˚C, (*R,S*)-**63** (42%), (*R,R*)-**63** (21%), *dr* = 3:1 (determined by NMR of the crude product after extractive work-up).

Thus, the Zn-mediated non-selective propargylation of aldehydes *S*-**6** and *R*-**6** provided efficient access to all four homopropargylic alcohol isomers (*S,R*)-**63**, (*S,S*)-**63**, (*R,S*)-**63**, and (*R,R*)-**63** in a reproducible and scalable manner.

3.3.3 Synthesis of acids 2

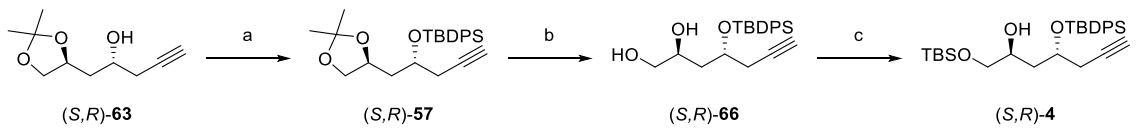
3.3.3.1 Protection of homopropargyl alcohols 63 and acetonide cleavage

As outlined in *Scheme 52*, the elaboration of homopropargylic alcohols **63** into acids **2** should involve, as a first step, protection of the newly formed hydroxy group as a silyl-ether followed by selective cleavage of the acetonide moiety. As alluded to, this transformation is described in Zechner's PhD thesis with a yield of 37%, employing $CuCl_2$ as the cleavage catalyst. In my hands, however, the procedure with $CuCl_2$ worked only once on a 50 mg scale (*Scheme 52*). On a larger scale the starting material (*R,S*)-**64** was reisolated.



Scheme 52. Reagents and conditions: a) TBSCl, imidazole, DMF, rt, 62%; b) $CuCl_2 \cdot 2H_2O$, CH_3CN, -5 °C, 2 h, <47% impure.

Therefore, other conditions[269][270] were examined for this acetonide removal scale-up, such as the use of cerium chloride,[271] however, the starting material was reisolated. With acidic conditions such as PTSA [272] and acetic acid,[273] the desired diol **65** was not observed and the TBS protecting group was additionally removed,[274][275] (based on TLC analysis of the reaction mixture and ^{1}H NMR spectroscopic analysis of the crude product obtained after aqueous work-up). Based on these findings, the original protecting group strategy was modified such as to convert the homopropargylic alcohols **63** into the corresponding TBDPS-ethers, even if this would require more forcing conditions in one of the final deprotection steps than originally envisaged. As depicted in *Scheme 53* for (*S,R*)-**63**, the latter was readily converted into its TBDPS-ether (*S,R*)-**63** by reaction with TBDPSCl in DCM in the presence of imidazole and catalytic DMAP in quantitative yield.



Scheme 53. Reagents and conditions: a) TBDPSCl, imidazole, DMAP (cat.), DCM, rt, 15 h, quant.; b) TFA, DCM, 0 °C to rt, 3 h, 83%; c) TBSCl, imidazole, 0 °C, 20 min, 89%.

Gratifyingly, treatment of (*S,R*)-**57** with TFA in DCM led to selective acetonide cleavage to furnish the free diol (*S,R*)-**66** in 83% yield; this reaction was carried out on a 9-gram scale. Selective protection of the primary hydroxy group in (*S,R*)-**66** as a TBS-ether (TBSCl, imidazole)[246] then gave (*S,R*)-**4** in 89% yield.

Partially protected triols (*S,S*)-**4**, (*R,R*)-**4** , and (*R,S*)-**4** (*Figure 31*) were obtained from homopropargylic alcohols **63** in analogy to the synthesis of (*S,R*)-**4** (*Scheme 53*) in overall yields of 30%, 32%, and 39%, respectively.

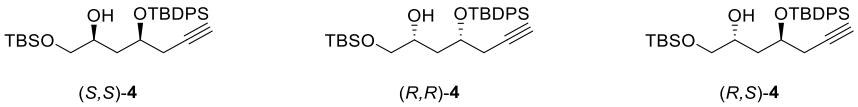
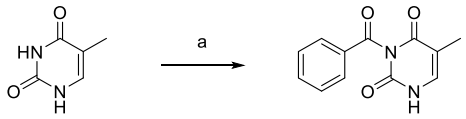


Figure 31. Partially protected triols **4**.

3.3.3.2 Elaboration of alcohols 4 into acids 2

3.3.3.2.1 Synthesis of N(3)-benzoyl thymine (68)

The synthesis of N(3)-benzoyl thymine (**68**) from thymine (**67**) was carried out according to the literature[276] with pyridine and benzoyl chloride in acetonitrile, followed by treatment of the resulting di-benzoate with K_2CO_3 in dioxane/H_2O to furnish **68** in 75% yield (*Scheme 54*). The structure of the product was confirmed by 2D NMR (COSY, HSQC, and HMBC).

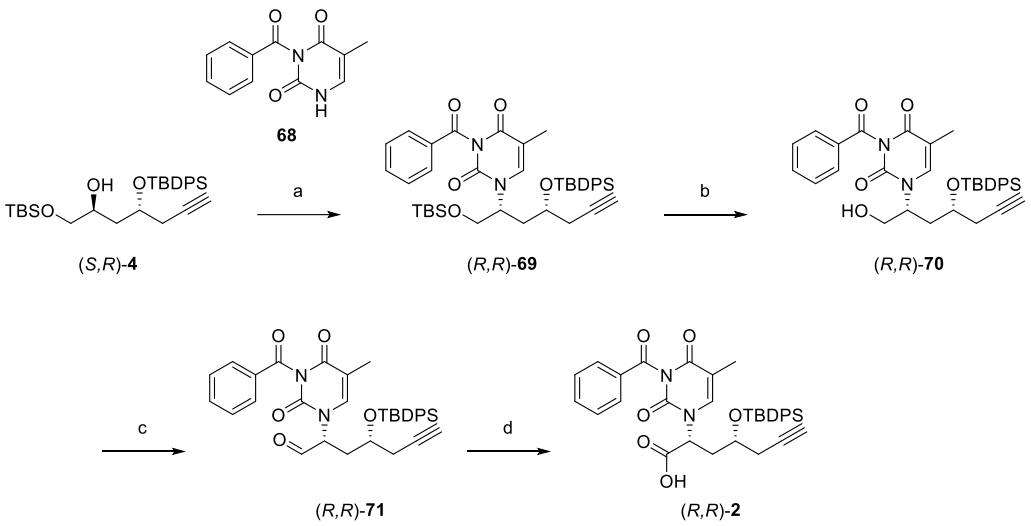


Scheme 54. Reagents and conditions: a) Py, benzoyl chloride, CH_3CN, rt, 3 d, then K_2CO_3 in dioxane/H_2O (1:1), rt, 18 h, 75%.

3.3.3.2.2 Thymine attachment and oxidation to acids 2

In the following, the elaboration of alcohol (*S,R*)-**4** into acid (*R,R*)-**2** will be discussed. The synthesis of acids (*R,S*)-**2** and (*S,S*)-**2** followed the same route.

The reaction of (*S,R*)-**4** with N(3)-benzoyl thymine (**68**) under Mitsunobu conditions[168] gave the desired thymine derivative (*R,R*)-**69** in 60% yield, with inversion of the configuration at the original OH-bearing stereocenter (*Scheme 55*).



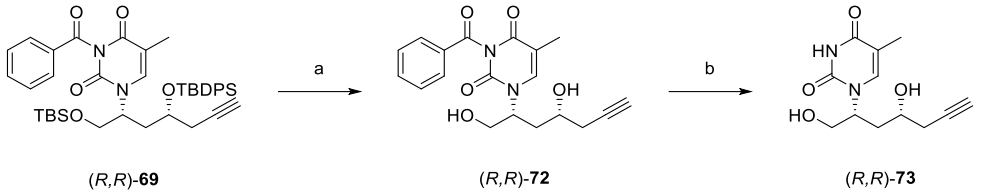
Scheme 55. Reagents and conditions: a) PPh_3, DEAD (dropwise), dioxane, rt, 18 h, 60%. b) (±)-CSA, DCM/MeOH (1:1), 3 h, 86%; c) DMP, $NaHCO_3$, DCM, rt, 3-4 h; d) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, *t*-BuOH, H_2O, 0 ˚C to rt, 3 h, 73% over two steps, *dr*=10:1.

The selective cleavage of the primary TBS-ether in (*R,R*)-**69** was first investigated with PPTS in MeOH, which gave (*R,R*)-**70** in 40% yield after a reaction time of 20 h; no reaction was observed upon treatment of (*R,R*)-**69** with PTSA/Bu_4NHSO_4 in MeOH[277] at 0 °C or 1 h or with $InCl_3$ in CH_3CN/H_2O. [278] Finally, it was found that the use of (±)-CSA[269][279] in DCM/MeOH 1:1 at room temperature for 3 h furnished the desired free alcohol (*R,R*)-**70** in 86% yield on a 100 mg scale (*Scheme 55*). The reaction was scalable and provided (*R,R*)-**70** in 96% yield on a 1.8 g scale. Attempts to directly oxidize (*R,R*)-**70** to the carboxylic acid (*R,R*)-**2** were unsuccessful. No reaction occurred with BIAB and catalytic TEMPO in H_2O/DCM 1:1 at rt for 3 h. The reaction with PDC in DMF at rt was very slow; while acid (*R,R*)-**2** was detectable by TLC after two days, the starting material (*R,R*)-**70** was not fully consumed and several other products were observed.

Based on these findings, a two-step approach was implemented for the conversion of (*R,R*)-**70** into (*R,R*)-**2**. DMP oxidation[230] of alcohol (*R,R*)-**70** to aldehyde (*R,R*)-**71** was a spot-to-spot reaction (TLC monitoring). The aldehyde proved to be unstable on silica and was therefore directly submitted to Pinnick oxidation[280] to furnish acid (*R,R*)-**2** in 73% overall yield (*Scheme 55*); the reaction was scalable and on a 0.5 g scale of alcohol (*R,R*)-**70** gave acid (*R,R*)-**2** in 73% yield. Acid (*R,R*)-**2** was obtained as an inseparable 10:1 mixture of diastereoisomers due to epimerization at the α-center at the aldehyde stage (based on ^{1}H-NMR spectroscopic analysis of aldehyde (*R,R*)-**71**). In summary, acid (*R,R*)-**2** was obtained from L-malic acid (*S*-**58**) in 11 steps and 5.5% overall yield.

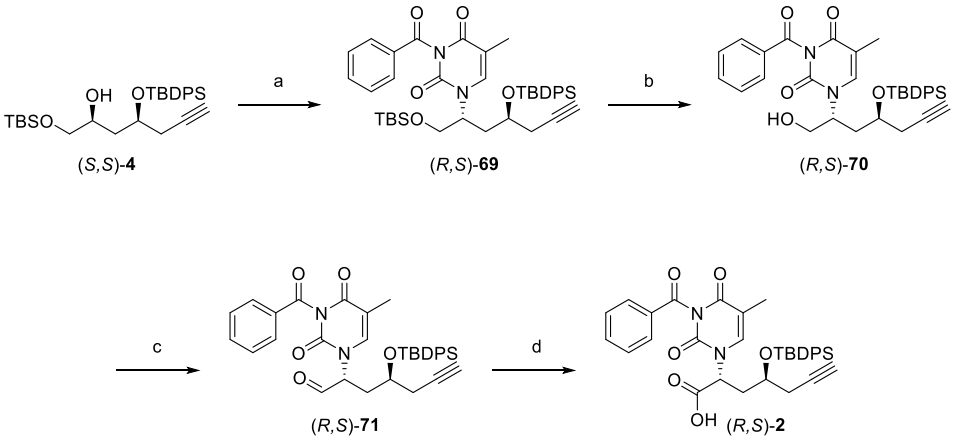
Unfortunately, neither acid (*R,R*)-**2** nor any of the advanced intermediates could be crystallized. Assuming that this might be related to the presence of the silyl protecting groups, (*R,R*)-**69** was converted into the free diol (*R,R*)-**72** (*Scheme 56*) by sequential treatment with excess TBAF and

NH_3/MeOH to remove the benzoyl group. However, unfortunately, (*R,R*)-**72** could not be crystallized either.

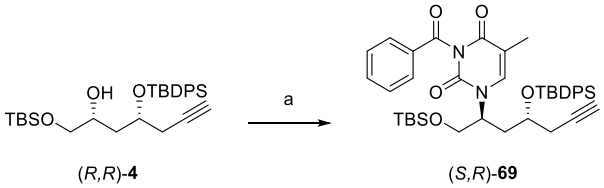


Scheme 56. Protecting group removal from (*R,R*)-**69**. Reagents and conditions: a) TBAF, THF, 0 ˚C to rt, 71%; b) 7N NH_3 in MeOH solution, rt, 62%.

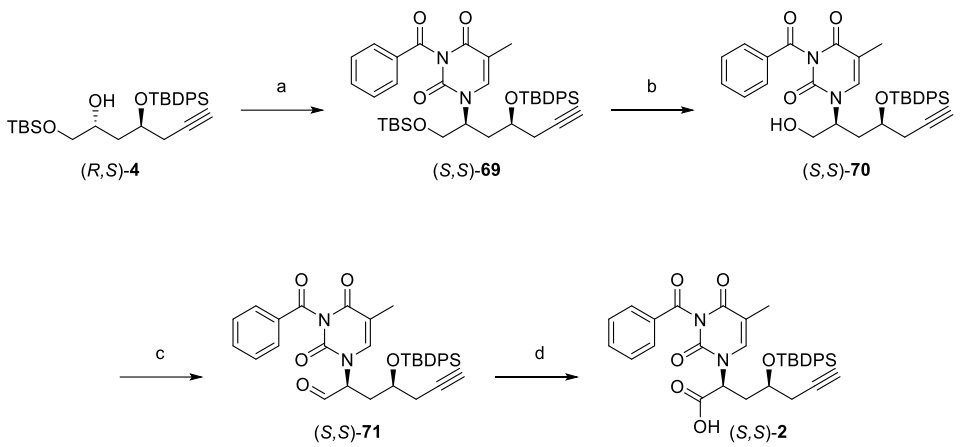
As indicated above, the synthesis of acids **2** from homopropargylic alcohols **63** followed the same route as the synthesis of (*R,R*)-**2** from (*S,R*)-**4**. These syntheses are summarized in *Schemes 57-59*.



Scheme 57. Reagents and conditions: a) **68**, PPh_3, DEAD (dropwise), dioxane, rt, 18 h, 60%; b) (±)-CSA, DCM/MeOH (1:1), 3 h, 87%; c) DMP, $NaHCO_3$, DCM, rt, 3-4 h; d) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, *t*-BuOH, H_2O, 0 ˚C to rt, 3 h, 81% over two steps, *dr*=20:1.



Scheme 58. Reagents and conditions: a) **68**, PPh_3, DEAD (dropwise), dioxane, rt, 18 h, 49%.



Scheme 59. Reagents and conditions: a) **68**, PPh_3, DEAD (dropwise), dioxane, rt, 18 h, 71%; b) (±)-CSA, DCM/MeOH (1:1), 3 h, 80%; c) DMP, $NaHCO_3$, DCM, rt, 3-4 h; d) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, *t*-BuOH, H_2O, 0 ˚C to rt, 3 h, 60% over two steps, *dr*=10:1.

No significant differences in the yields of individual steps were observed between different diastereoisomers. The only difference in the overall synthetic sequence yields is coming from the propargylation step where the homopropargylic alcohols **63** were obtained with *dr* ratios of 2:1 and 3:1. Total yields from *L*- or *D*-malic acids were as follows: 5.5% for (*R,R*)-**2**, 0.75% for (*R,S*)-**2**, 1.5 % for (*S,S*)-**2** over 11 steps, and 0.9% over 8 steps for (*S,R*)-**69**.

Interestingly, the O-alkylation product (*S,S*)-**74** was isolated as a minor side product from the Mitsunobu reaction of (*R,S*)-**4** and N(3)-benzoyl thymine (*Figure 32*).

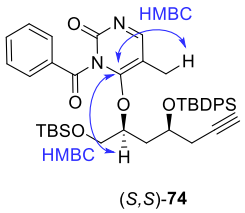
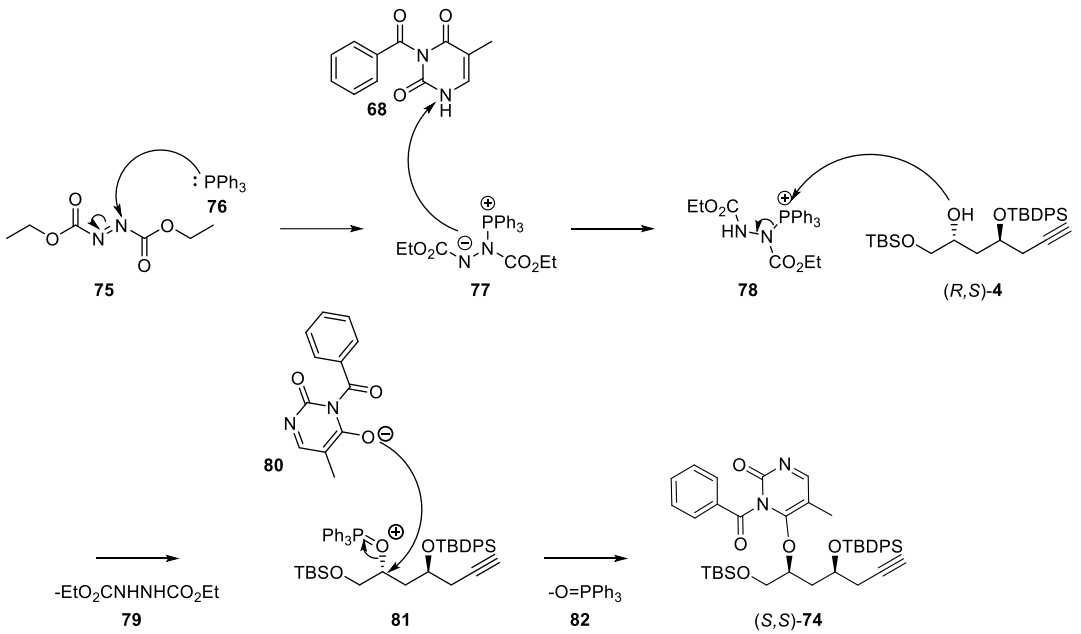


Figure 32. Structure of the side product (*S,S*)-**74** and its HMBC correlations that reveal the structure of the molecule.

The analogous side products were also observed in the Mitsunobu reactions with the other alcohols **4**, but they had not been isolated and characterized.

The alkylation of **4** under Mitsunobu conditions is well established in the literature[281][282] and the mechanism of the reaction is outlined in *Scheme 60*.

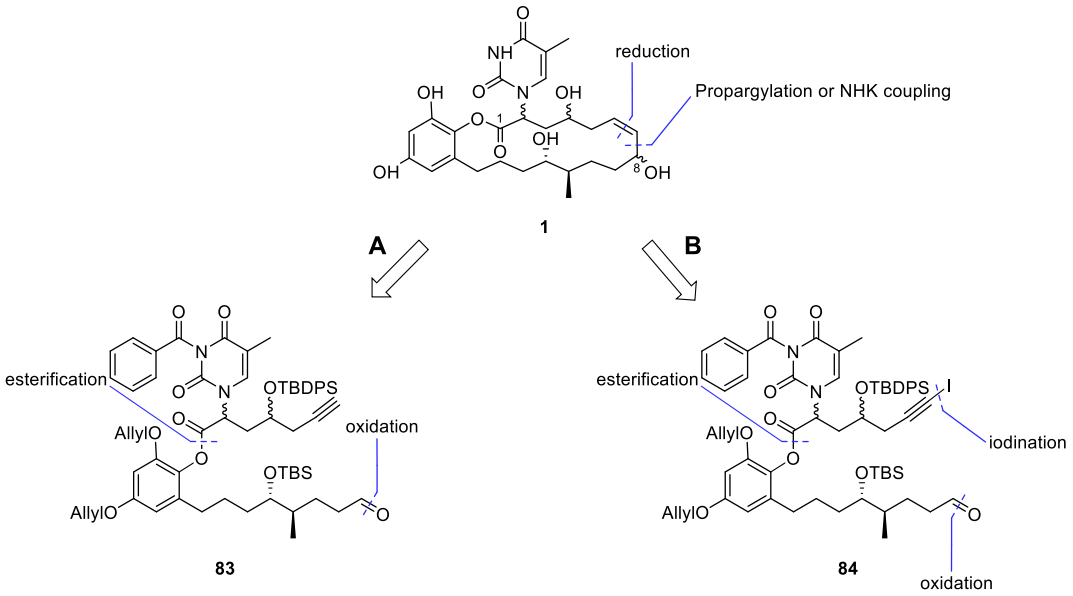


Scheme 60. A proposed mechanism of the side product (*S,S*)-**74** formation.

As was already discussed in Chapter 1.4.1.3.1., the nucleophilic attack of triphenylphosphine (**76**) upon DEAD (**75**) irreversibly forms a zwitterionic adduct (**77**) . Subsequently, **77** abstracts a proton from N(3)-benzoyl thymine (**68**). The alcohol (*R,S*)-**4** reacts with the protonated DEAD/PPh_3 adduct and forms the key oxyphosphonium ion **81**, which is then attacked by **80** to give (*S,S*)-**74** with inversion of the configuration of the secondary alcohol upon release of triphenylphophine oxide (**82**) (*Scheme 60*).[175]

3.4 Building block assembly and macrocycle construction

As discussed in Chapter 3.1, the elaboration of building blocks **A** and **B** into macplocimine A (**1**) was to be based on the intramolecular construction of the C(7)-C(8) bond either through direct alkynylation (pathway A in *Scheme 61*) or through NHK coupling (pathway B in *Scheme 61*). This would be followed by a partial reduction of the triple bond and protecting group removal. The order in which these latter steps would be performed best could not be defined *a priori* but would have to be determined experimentally. These concepts are re-iterated in *Scheme 61*.



Scheme 61. Macrocyclization via alkynylation (**A**) or Nozaki-Hiyama-Kishi reaction (**B**).

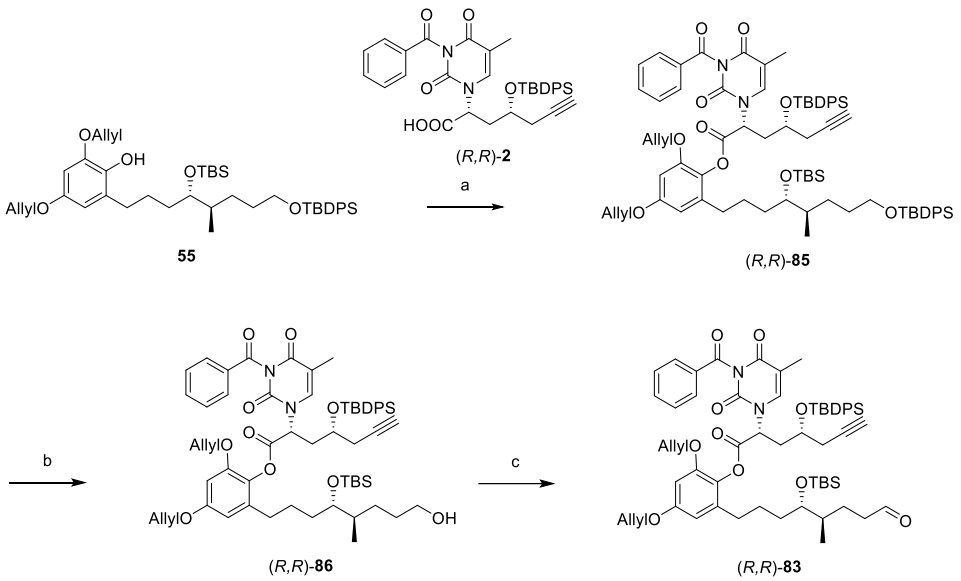
In the following, the experiments conducted towards the implementation of the two different macrocyclization approaches will be discussed. Importantly, the stereochemical prefixes (*R*/*S*, *R*/*S*) refer to the configuration at C(2) and (C4) (macplocimine numbering) for all intermediates following the esterification step between building block **A** and building blocks **C**.[11]

3.4.1 Macrocylization *via* propargylation

3.4.1.1 Synthesis of aldehyde (*R,R*)-83

As the first step in the elaboration of aldehyde (*R,R*)-**83**, phenol **55** and acid (*R,R*)-**2** were condensed into ester (*R,R*)-**85** under Steglich esterification conditions[283] with dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in DCM (*Scheme 62*). Under optimized conditions (2.2 equiv. DCC, 0.2 equiv. DMAP, rigorously dried starting materials), ester (*R,R*)-**85** was obtained in 82% yield on an 850 mg scale.

[11] For example, the designation (*S,S*)-**2** refers to the 2*S*,4*S*-isomer of chemical structure **2**.



Scheme 62. Reagents and conditions: a) DCC, DMAP, DCM, rt, 24 h, 82%; b) NH_4F, HFIP, rt, 42-48 h, 55-79%; c) DMP, $NaHCO_3$, DCM, rt, 3 h, 69-75%.

Not unexpectedly, the selective TBDPS removal from (*R,R*)-**85** proved to be challenging. Treatment of (*R,R*)-**85** with TBAF buffered with acetic acid, surprisingly, only gave products of ester bond cleavage, i.e. **87** and **88** (*Figure 33*) (*Table 7,* entry 1).

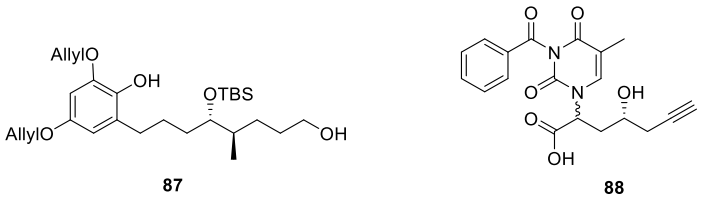


Figure 33. Products of ester bond cleavage of (*R,R*)-**85**.

Table 7. Conditions tested for the selective cleavage of the TBDPS-ether in (*R,R*)-**85**.

Entry[a]	Conditions[b]	Time	Yield
1	TBAF, AcOH (2.4 equiv. each)	18 h	16% (**88**)[c] and 35% (**87**)
2	TBAF (1 M solution in THF)	3 h	55% (**88**)[c] and quant. (**87**)[d]
3	TBAF, AcOH (1 equiv. each) stock solution in THF	16 h	48% (**88**)[c] and 61% (**87**)
4	TBAF (1.2 equiv.), PPTS (1.2 equiv)[e]	27 h	reisolated (*R,R*)-**85**

[a] scales of the reaction between 5.2-11.8 µmol; [b] in THF (c=0.1 M); [d] impure; [e] THF (c=0.3 M).

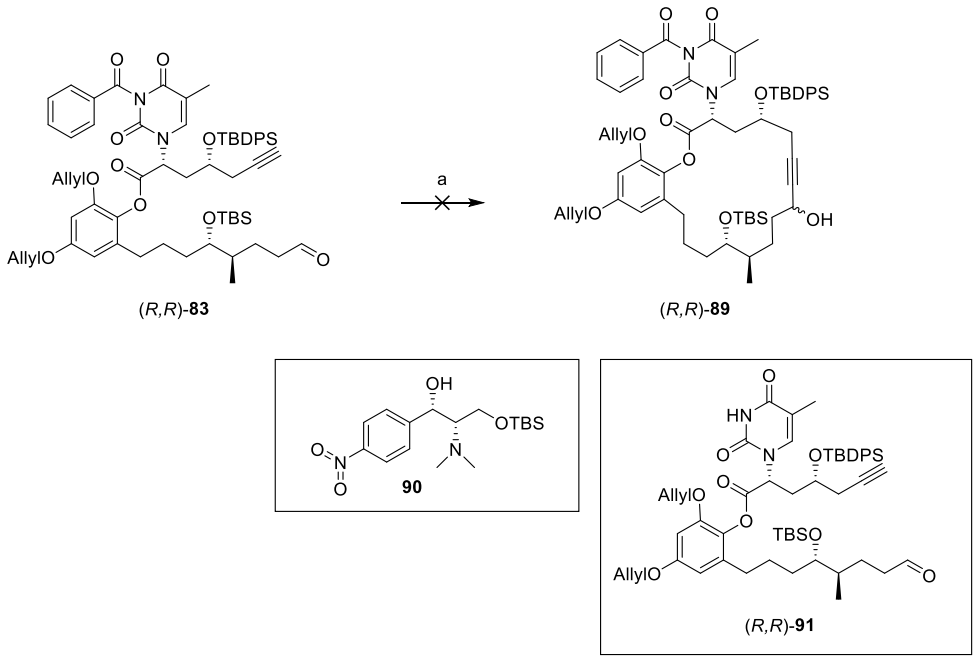
Based on ^{1}H NMR spectroscopic analysis, acid **88** was obtained as a 1:0.66 mixture of diastereoisomers, which I tentatively assign to epimerization of the stereocenter α to the thymine moiety. TBAF alone gave no improvement, rather the yields of **88** and **87** got even higher (*Table 7,* entry 2). A stock solution of a 1/1 mixture of TBAF and AcOH in THF was used with control of the pH of the reaction and less equivalents of both reagents, but again the reaction yielded only products of ester bond cleavage (*Table 7*, entry 3). It was suspected that the ester bond cleavage might be caused by the water present in commercial TBAF solutions.[284][285][286] An attempt to buffer TBAF with PPTS (*Table 7,* entry 4) only led to the recovery of the starting material.

In light of these failures, a thorough literature search was conducted on non-standard methods for the cleavage of silyl-ethers. This search revealed that ammonium fluoride in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) had been successfully employed for the selective cleavage of a primary TIPS-ether in the presence of a secondary TBS-ether;[287] in contrast, the use of methanol or 2,2,2-trifluoroethanol had not been successful.[287] Even more interestingly, ammonium fluoride in HFIP has also been reported to enable the selective cleavage of a primary TBDPS-ether in the presence of a secondary TBS-ether in 69% yield.[288] Gratifyingly, when *(R,R)*-**85** was treated with 15 equiv. of NH_4F in HFIP for 48 h at room temperature, the desired free primary alcohol *(R,R)*-**86** was obtained in quantitative yield (*Scheme 62*).

With the selective cleavage of the primary TBDPS-ether accomplished, the subsequent oxidation of (*R,R*)-**86** with Dess-Martin periodinane proceeded smoothly to furnish aldehyde (*R,R*)-**83** reproducibly in yields around 70% on different scales up to 100 mg.

3.4.1.2 Attempted intramolecular propargylation of aldehyde (*R,R*)-83

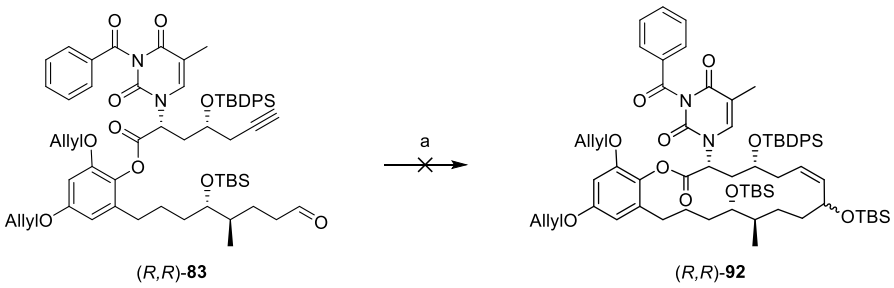
Different methods were investigated to affect macrocyclization of aldehyde (*R,R*)-**83** to macrolactone (*R,R*)-**89** *via* intramolecular propargylation (*Scheme 61*). The use of LiHDMS in combination with cerium (III) chloride,[289] which is known to suppress enolization in Grignard-type processes,[290] did not give any of the desired macrolactone (*R,R*)-**89**. The reaction did not proceed to completion (half of the starting material was re-isolated) and no defined product could be isolated.



Scheme 63. Reagents and conditions: a) LiHMDS, $CeCl_3$, -78 ˚C to rt, 18 h; or $Zn(OTf)_2$, **90**, Et_3N, toluene, 25 h, rt.

Likewise, no macrocyclization was observed under modified[291] Carreira alkynylation[292] conditions with zinc (II) triflate, Et_3N, and ligand **90** (*Scheme 63*); the only isolable product from the reaction was the debenzoylated aldehyde (*R,R*)-**91** (*Scheme 63*), which was obtained in 27% yield. The chiral ligand **90** was developed by Xiong and Jiang specifically for the alkynylation of (α-unbranched) aldehydes;[291] **90** was synthesized in two steps from commercially available (*1S,2S*)-2-amino-1-(4-nitrophenyl)propane-1,3-diol according to the literature[293] *via* Eschweiler-Clarke methylation followed by TBS-ether formation in 17% overall yield.

Finally, the use of SmI_2 was also investigated, which in principle could have led directly to the desired macrocyclic *Z* alkene (*R,R*)-**92** (*Scheme 64*). SmI_2 has been successfully employed for the construction of medium-sized cycloalkenes from terminal ynones or ynals,[294] but no macrocyclization product (*R,R*)-**92** was observed. While the aldehyde signal in the ^{1}H-NMR spectrum had disappeared in the crude product mixture obtained after the aqueous work-up, the signal of the terminal ≡CH proton was still present.



Scheme 64. Reagents and conditions: a) Sm, 1,2-diiodoethane, HMPA, *t*-BuOH, THF, rt, 24 h.

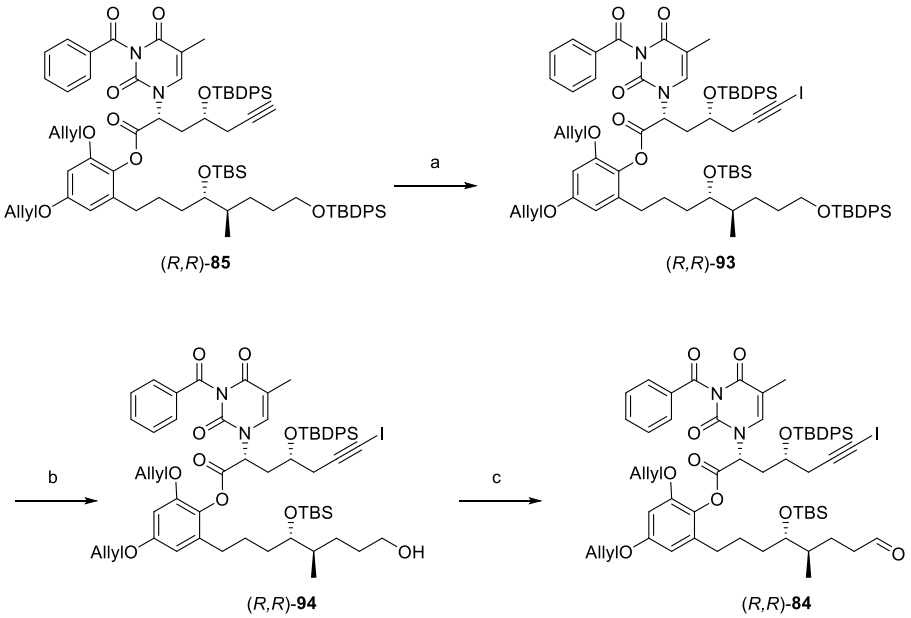
The nickel-catalyzed ynal macrocyclization, which was successfully employed by Montgomery and co-workers in their total synthesis of aigialomycin D (see Chapter 1.4.1.3.3).[182] was not considered, as the method selectively produces *E* alkenes.

In light of these results, attempts to achieve macrocyclization by direct propargylation were abandoned and the focus was put on the NHK approach.

3.4.2 Macrocyclization via Nozaki-Hiyama-Kishi reaction and downstream macrocycle processing

3.4.2.1 Synthesis of Iodoynals 84

In order to enable the NHK-based construction of the macplocimine macrocycle, the synthesis of iodo-ynals **84** (see *Scheme 61*) was required. As exemplified in *Scheme 65* for the respective (*R,R*)-**84** isomer, the first step involved the iodination of the alkyne (*R,R*)-**85** with N-iodosuccinimide and silver nitrate in DMF.[295][296][297] The conditions for this transformation had been previously optimized with alkyne (*R,R*)-**69** (see *Scheme 55* for structure) and were directly transferable to (*R,R*)-**85**.[12] The desired iodoalkyne (*R,R*)-**93** was obtained in yields between 63% and 88%.

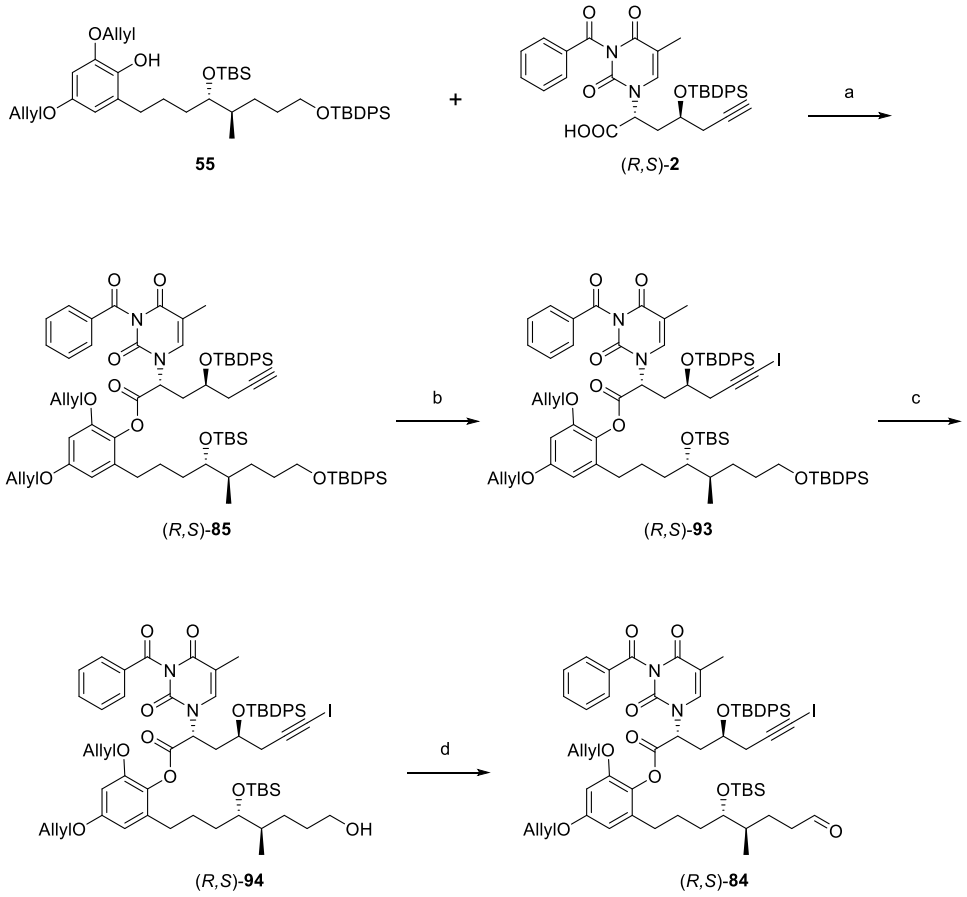


Scheme 65. Reagents and conditions: a) NIS, $AgNO_3$, DMF, rt, 3-7 h, 63-88%; b) NH_4F, HFIP, rt, 23 h, 78-94%; c) DMP, $NaHCO_3$, DCM, rt, 5 h, 85-94%.

The primary silyl-ether was then cleaved with ammonium fluoride in HFIP to furnish the free alcohol (*R,R*)-**93** in excellent yields (78-94%). Subsequent DMP oxidation of (*R,R*)-**93** proceeded smoothly, providing the desired iodo-ynal (*R,R*)-**84** in high yields (85-94%) on a close to gram-scale.

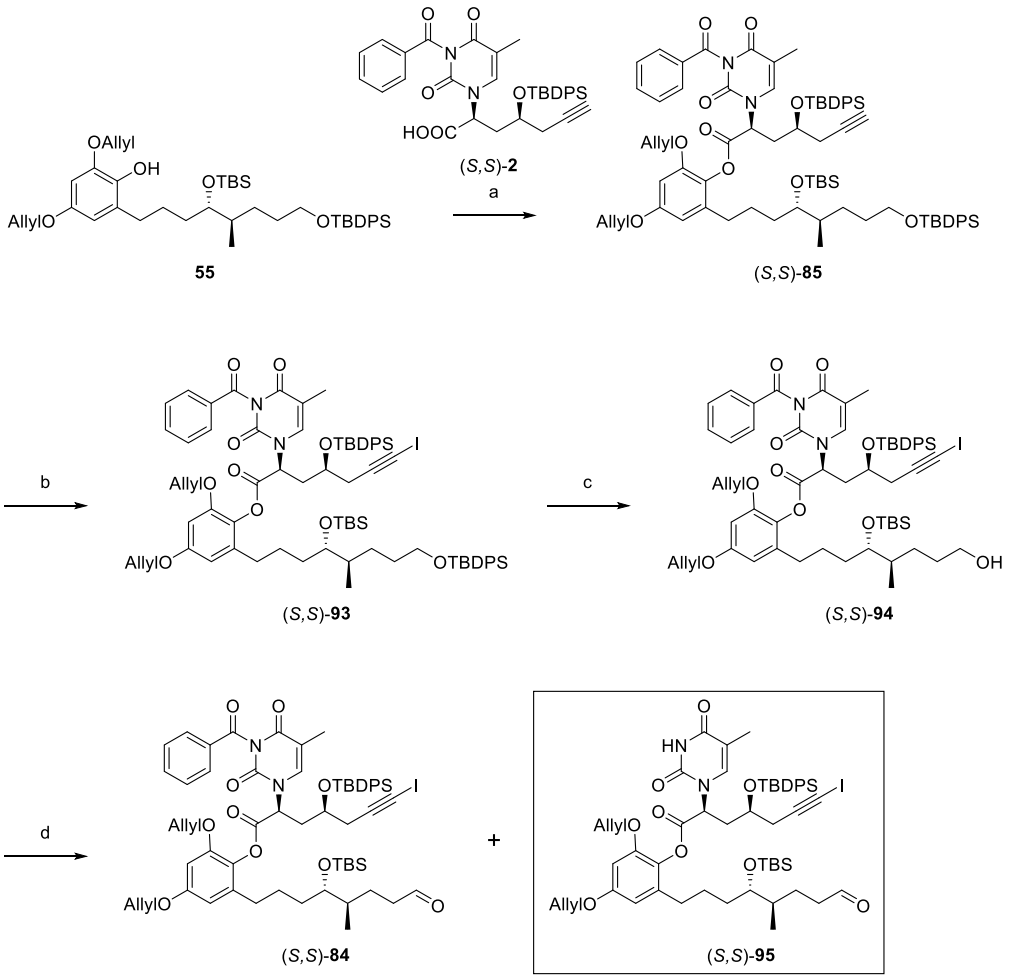
[12] For details on the optimization of the iodination reaction with (*R,R*)-**85**, see the Experimental Section.

Iodo-ynals (*R,S*)-**84** and (*S,S*)-**84** were obtained from phenol **55** and the respective acids (*R,S*)-**2** and (*S,S*)-**2** in analogy to the synthesis of (*R,R*)-**84**. The corresponding syntheses are summarized in *Scheme 66* and *67*, respectively.



Scheme 66. Reagents and conditions: a) DCC, DMAP, DCM, 0 ˚C- rt, 50 h, 53-58%; b) NIS, $AgNO_3$, DMF, rt, 7 h, 82-93%; c) NH_4F, HFIP, rt, 48 h, 92%; d) DMP, $NaHCO_3$, DCM, rt, 2 h, 71%.

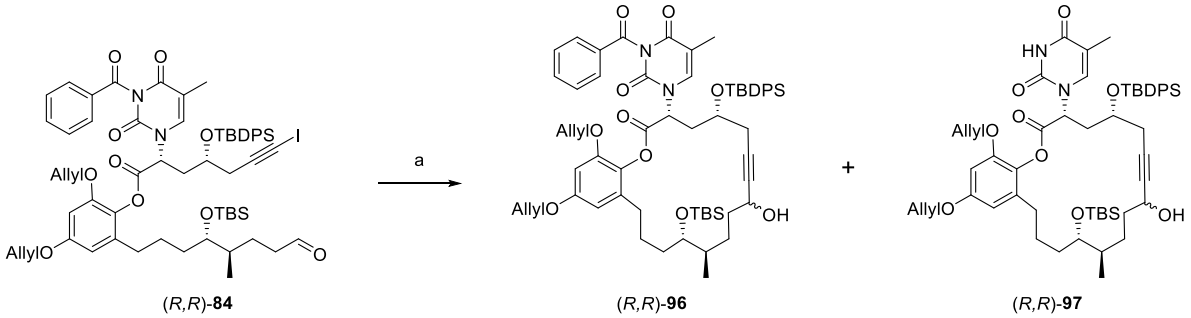
In the synthesis of (*S,S*)-**84**, the debenzoylated aldehyde (*S,S*)-**95** was isolated in 24% yield together with (*S,S*)-**84** (59% yield) after the DMP oxidation in one experiment (*Scheme 67*). The compound was not detectable by TLC in the reaction mixture before aqueous work-up and, thus, must have been formed during the extended basic work-up of the DMP reaction.



Scheme 67. Reagents and conditions: a) DCC, DMAP, DCM, 0 ˚C- rt, 24 h, 54%; b) NIS, $AgNO_3$, DMF, rt, 6 h, 93%; c) NH_4F, HFIP, rt, 48-72 h, 72-80%; d) DMP, $NaHCO_3$, DCM, rt, 5 h, 89%.

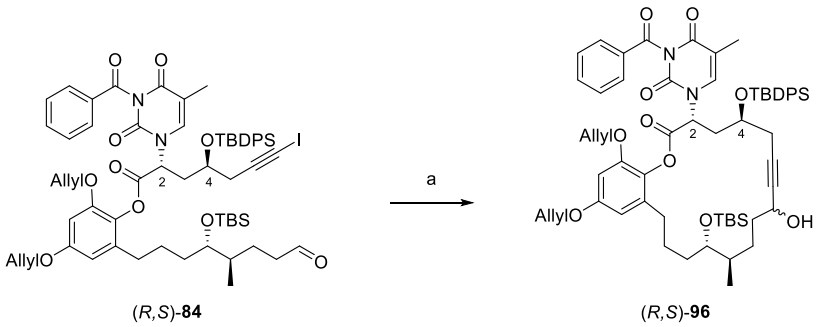
3.4.2.2 Macrocyclization

The Nozaki-Hiyama-Kishi mediated macrocyclization was first investigated with iodo-ynal (*R,R*)-**84.** Treatment of (*R,R*)-**84** with 10.0 equiv. of $CrCl_2$ and 0.2 equiv. of $NiCl_2$ in THF at a concentration of 0.007 M at room temperature for 18 h, gratifyingly, delivered macrocycle (*R,R*)-**96** as a 1/1 mixture of diastereomers at C(8) in 56-64% yield; in addition, the debenzoylated macrocycle (*R,R*)-**97** was isolated in 17% yield.



Scheme 68. Reagents and conditions: a) $CrCl_2$, $NiCl_2$, THF (0.007 M), rt, 18 h, 56-64%, *dr*=1:1; (*R,R*)-**97**, 17%.

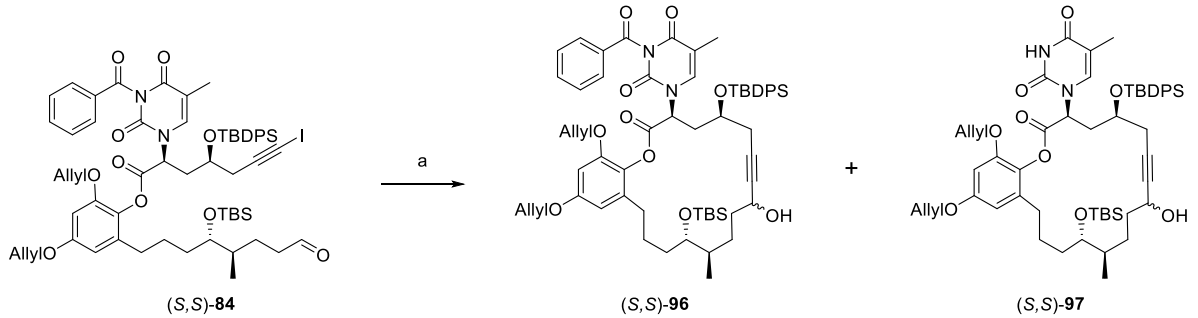
The reaction proved to be robust and gave (*R,R*)-**96** in 60% yield also on a 900 mg scale together with 17% of (*R,R*)-**97**. However, isomer separation of (*R,R*)-**96** or (*R,R*)-**97** was not possible at this stage. When the above conditions were applied to iodo-ynal (*R,S*)-**84**, the reaction was slower but accidentally was worked up after 18 h (as for (*R,R*)-**84**), although significant amounts of starting material remained unreacted. The crude product obtained after the aqueous work-up was thus re-submitted to the NHK conditions to furnish macrolactone (*R,S*)-**96** in 34% yield (*Scheme 69*); no debenzoylated product was isolated due to the lower scale of the reaction and a lower reaction efficiency overall. The lower yield of (*R,S*)-**96** compared to (*R,R*)-**96** may be partly explained by the intermittent work-up, which may have led to loss of material. At the same time, the difference is substantial and seems to indicate that a 2*R,*4*R* configuration in **84** promotes macrocyclization more efficiently than a 2*S,*4*R* configuration.



(*R,S*)-**84** (*R,S*)-**96**

Scheme 69. Reagents and conditions: a) $CrCl_2$, $NiCl_2$, THF (0.007 M), rt, 18 h, then a second cycle of $CrCl_2$, $NiCl_2$, THF (0.007 M), rt, 18 h, 34%, *dr*=1:1.

Interestingly, the NHK-mediated macrocyclization of (*S,S*)-**84** (*Scheme 70*) gave the corresponding macrocycle (*S,S*)-**96** in a similar yield as (*R,R*)-**96** (66%), together with 4% debenzoylated product. This may suggest that macrocylization is favored by a 1,3-*syn* configuration of the C(2)-thymine moiety and the C(4)-hydroxy group in the precursor iodo-ynal **84**, although this conclusion remains speculative at this point.

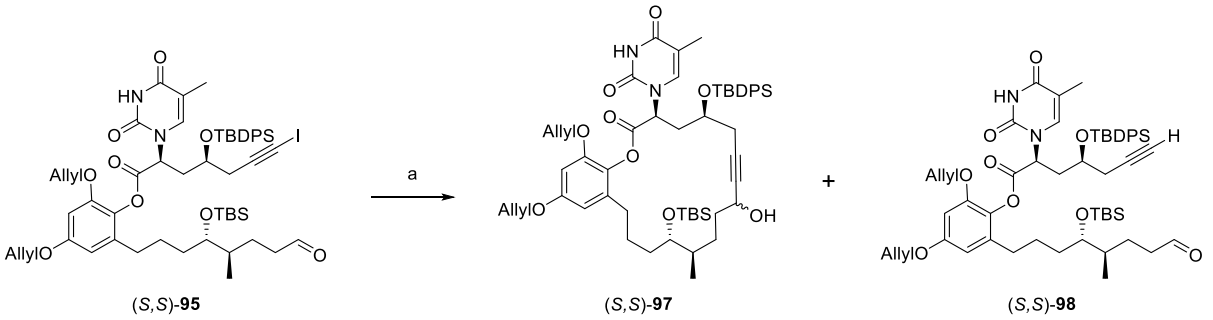


(*S,S*)-**84** (*S,S*)-**96** (*S,S*)-**97**

Scheme 70. Reagents and conditions: a) $CrCl_2$, $NiCl_2$, THF (0.007 M), rt, 18 h, 66%, *dr*=1:1; (*S,S*)-**97**, 4%.

In light of the fact that the macrocyclization was accompanied by partial debenzoylation, at least in some cases, and that the protection of the thymine moiety was not considered critical in the final steps

of the total synthesis, NHK macrocyclization was also investigated with N(3)-unprotected *(S,S)*-**95** (*Scheme 71*). The latter was obtained as a side product in the DMP oxidation of (*S,S*)-**94** together with (*S,S*)-**84** (*Scheme 67*).



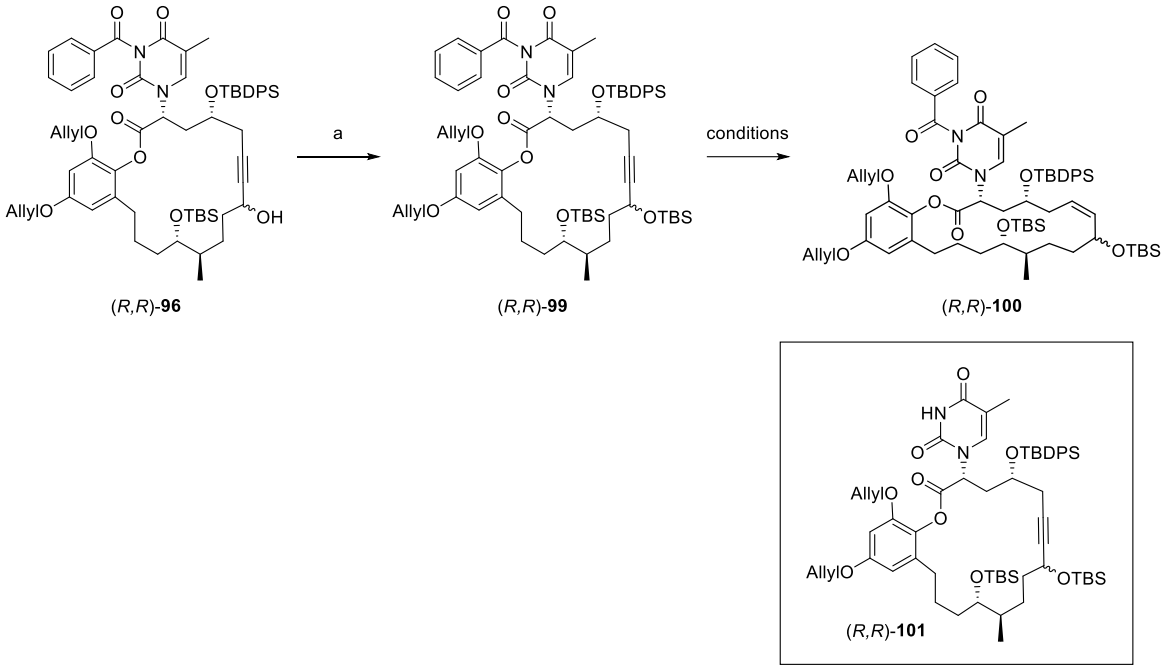
(*S,S*)-**95** (*S,S*)-**97** (*S,S*)-**98**

Scheme 71. Reagents and conditions: b) $CrCl_2$, $NiCl_2$, THF (0.007 M), rt, 18 h, 67% of (*S,S*)-**97**; 19% of the deiodinated side product (*S,S*)-**98**.

The NHK reaction produced the macrolactone (*S,S*)-**97** in 67% yield together with 19% of the deiodinated ynal (*S,S*)-**98**. In contrast to the macrocyclization of the benzoyl-protected precursors, this side product cannot be further processed towards **1**, at least not directly, and thus no experiments were conducted on the macrocyclization of other isomers of *(S,S)*-**95**.

3.4.2.3 Triple bond reduction

A seemingly obvious and operationally simple approach to convert the triple bond in macrocyclic alkynes **96** into a *Z* double bond was hydrogenation over Lindlar catalyst ($Pd/CaCO_3/Pb(OAc)_2$).[298][299]



Scheme 72. Reagents and conditions: a) TBSCl, imidazole, DMF, 98%; condition optimization for the second step is presented in *Table 8*.

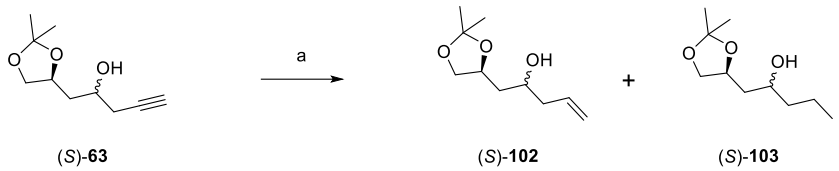
To assess this possibility, macrolactone (*R,R*)-**96** was first converted into silyl ether (*R,R*)-**99** and the feasibility of semi-reduction by hydrogenation was assessed with Lindlar catalyst in EtOH at 3 bar hydrogen pressure for 18 h (*Scheme 72*). No triple bond reduction was observed under these conditions and 42% of the starting material (*R,R*)-**99** was re-isolated. The ^{1}H NMR spectroscopic analysis of a second isolated fraction indicated reduction of the double bonds in the allyl protecting groups, based on the presence of propyl signals, however, this second fraction also contained 20 % of the SM due to the close retention factors (R_f) of the two compounds. Based on the NMR of the crude material, the overall ratio of the SM to the allyl reduction product was 1.3 to 1. Similar results were obtained with a P2-Ni catalyst (obtained from $Ni(OAc)_2{\cdot}4H_2O$ and $NaBH_4$)[300] in EtOH at 3 bar for 18 h (*Table 8*, entry 2).

Table 8. Conditions screened for the semi-reduction of cyclic alkyne (*R,R*)-**99** into the *cis*-alkene (*R,R*)-**100**.

Entry[a]	Reagent	Solvent[b]	H_2 pressure	Time	Observation
1	$Pd/CaCO_3$, 5 wt.% loading, poisoned with $Pb(OAc)_2$[c]	EtOH	atm. to 3 bar	18 h	Partial reduction of allyl group (43%)[d]; (*R,R*)-**99** re-isolated (42%)
2	$Ni(OAc)_2$, $NaBH_4$, $C_2H_4N_2H_4$	EtOH	atm. to 3 bar	18 h	Partial reduction of allyl group 30%[d]; (*R,R*)-**99** re-isolated (70%)
3	Zn/Cu/Ag, TMSCl	MeOH:H_2O= 1:1	atm. to 3 bar		(*R,R*)-**101**, 72%
4	(i) $Co_2(CO)_8$ (ii) N-ethylpiperidinium hypophosphite	(i) DCM (ii) benzene		(i) 90 min at rt (ii) 30 min at 80 ˚C	(*R,R*)-**100**, 39%

[a] scales of reactions were between 0.01 mmol-0.031 mmol; [b] c=0.0137 M; [c] commercially available; [d] based on the NMR of the crude material that was obtained by filtering the catalyst off through a plug of celite or silica, and rinsing with a solvent.

In order to verify whether the Lindlar catalyst used from Acros Organics® ($Pd/CaCO_3$, 5% Pd, poisoned with 3.5% $Pb(OAc)_2$) was in fact active, an experiment was carried out with (*S*)-**63** (*Scheme 73*). This experiment indicated that the catalyst batch used was indeed functional. However, NMR monitoring of the reaction also revealed that overreduction to (*S*)-**103** occurred within minutes after the start of the reaction.



(*S*)-**63** (*S*)-**102** (*S*)-**103**

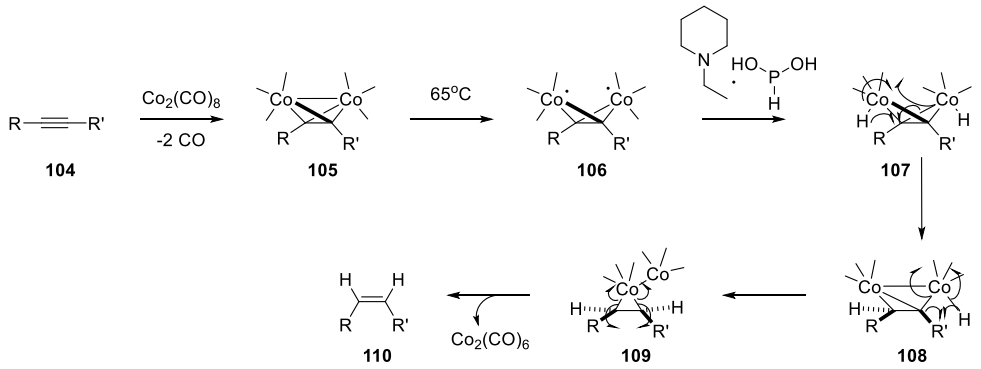
Scheme 73. Reagents and conditions: a) Lindlar catalyst, quinolone, EtOAc, H_2 (atm.), rt, 12 h, (*S*)-**103** (quant. without FC); (*S*)-**63** is a 1:1 mixture of (*S,R*)-**63** and (*S,S*)-**63**.

After 1 min a sample of the reaction was collected, filtered through a plug of celite, and concentrated under reduced pressure. The NMR indicated that the ratio of (*S*)-**102** to (*S*)-**103** was 1:0.3, while the starting material (*S*)-**63** was not yet fully consumed. Over time, the ratio of (*S*)-**102** to (*S*)-**103** increased continuously. These findings were in line with the observed (partial) reduction of allyl ether groups in *(R,R)*-**99**.

As an alternative to Lindlar reduction, partial triple bond reduction was attempted with Zn/Ag/Cu[301][302]. However, these conditions only resulted in debenzoylation and gave macrocycle alkyne (*R,R*)-**101** in 72% yield (*Table 8*, entry 3).

Isobe reduction[303] has previousily been used for complex conjugated systems such as selective *cis*-olefin formation from an alkyne in the presence of five other *Z* and *E* double bonds in the molecule.[304] Reduction of the macrocyclic alkyne with dicobaltoctacarbonyl and N-ethylpiperidinium hypophosphite has also been used by Altmann and co-workers in their total synthesis of rhizoxin F.[305] While in the former publication, Ph_3SnH was found to be a better reductive decomplexation reagent, in the latter, N-ethylpiperidinium hypophosphite was chosen as the ultimate reducing agent. Gratifyingly, the reaction of (*R,R*)-**100** with dicobaltoctacarbonyl and the formation of a biscobalthexacarbonyl-alkyne complex, followed by reductive decomplexation with N-ethylpiperidinium hypophosphite finally furnished the desired *Z* alkene (*R,R*)-**100** in 39% yield on a 30 mg scale (*Table 8*, entry 4).[303]

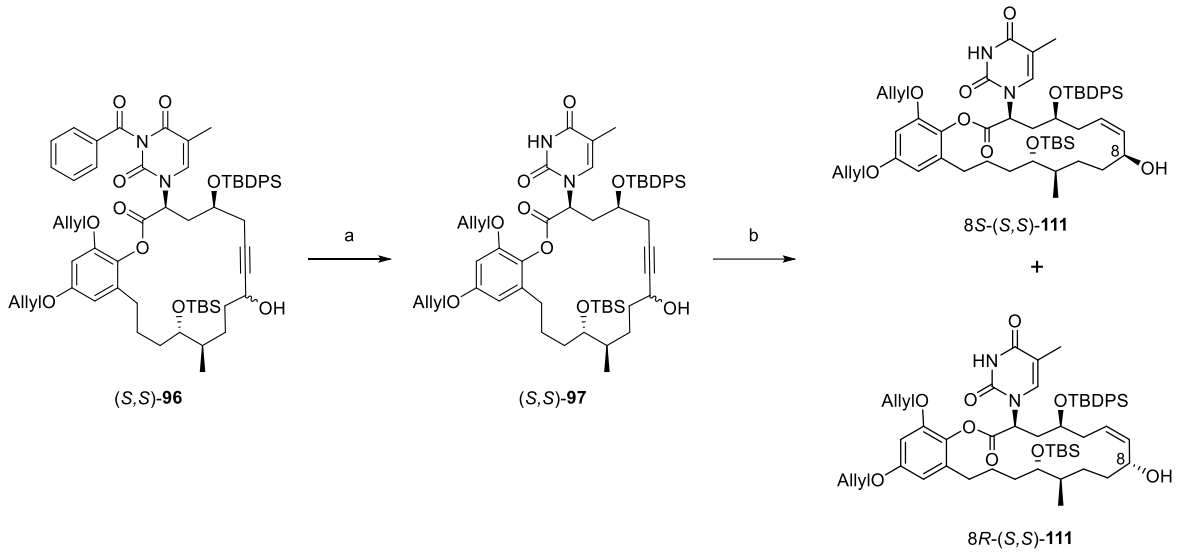
The mechanism of the reductive decomplexation of dicobalthexacarbonyl-alkyne complex **105** (*Scheme 74*) by N-ethylpiperidininium hypophosphite has been proposed by Isobe[303] to involve heat-induced homolytic Co-Co bond cleavage to give the biradical **106**. Hydrogen abstraction from hypophosphite produces **107** (and a P-centered radical), which is then followed by a rearrangement to **108** and **109**. Finally, reductive elimination gives *Z* olefin **110** and dicobalthexacarbonyl.



Scheme 74. Proposed mechanism for the formation of *Z* olefins from dicobaltoctacarbonyl-alkyne complexes mediated by N-ethylpiperidinium hypophosphite.[303]

The above conditions were then also applied to the reduction of macrocyclic alkyne (*S,S*)-**97**. The latter was obtained from NHK product (*S,S*)-**96** by treatment with 0.5M NH_3 in dioxane in 77% yield; the

conditions for debenzoylation had been optimized with (*R,R*)-**86**. Importantly, the use of a freshly prepared or newly opened commercial ammonia solution was crucial for the success of the reaction; the use of older commercial solutions gave no conversion of **96**. The use of NH_3 in MeOH led to cleavage of the phenyl ester bond (see the experimental part for details). Gratefully, the $Co_2(CO)_8$/N-ethylpiperidinium hypophosphite-mediated reduction of (*S,S*)-**97** proceeded with similar efficiency as for (*R,R*)-**99**. However, as an important improvement, the resulting diastereomers at C(8) were now separable by FC and could be isolated as single isomers in 31% and 19% yield.



Scheme 75. Reagents and conditions: a) $Co_2(CO)_8$, DCM, 1.5 h, rt, then N-ethylpiperidinium hypophosphite, benzene, reflux, 40 min, 31% and 19% for separated diastereomers 8*S*-(*S,S*)-**111** and 8*R*-(*S,S*)-**111**. Yields cannot be assigned to specific stereoisomers (see text).

The reaction was carried out multiple times and a lower yield was observed when the treatment time with N-ethylpiperidinium hypophosphite exceeded 40 min. After this point, the formation of degradation products became continuously more prominent (according to TLC analysis), together with a reduction in the mass of the crude material obtained after filtration of the reaction mixture through celite and evaporation, before FC.

The configuration of the C(8)-stereocenter in the two isomers was not determined due to the preciousness of the material and in order to advance the synthesis; however, this would be readily feasible by means of Mosher ester analysis.[265]

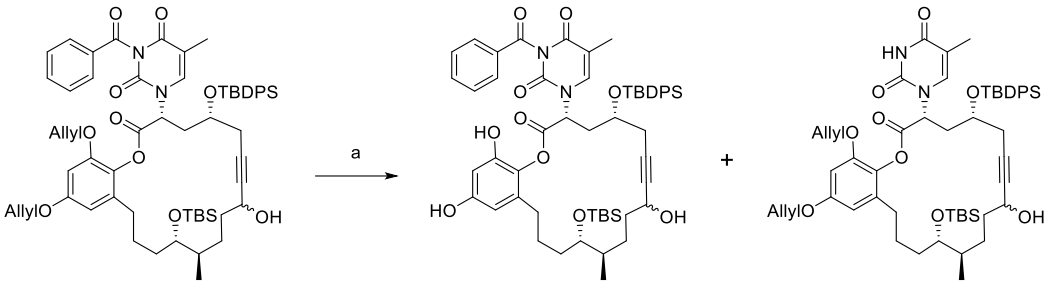
3.4.2.4 Protecting group removal

3.4.2.4.1 Deallylation of (*R,R*)-96

While the experiments to reduce the triple bond in macrocyclic alkynes (*R,R*)-**99** and (*S,S*)-**97** were ongoing, the removal of the allyl protecting groups from the phenolic OH-groups *prior* to the reduction step was also investigated. These studies were intended to provide alternative substrates for triple bond reduction in case the experiments with (*S,S*)-**97** were unsuccessful. After it was discovered that the reduction could be achieved with $Co_2(CO)_8$/N-ethylpiperidinium hypophosphite, the removal of the allyl protecting groups at the stage of the macrocyclic alkyne was deemed not to be on the critical path towards **1** and the further processing of the deallylated product was not considered a priority. However, given the problems that surfaced later with the deallylation of (*S,S*)-**111** (*vide infra*), the results of the deprotection experiment with (*R,R*)-**96** are relevant and, therefore, shall be discussed here.

A plethora of methods have been described for allyl ether cleavage,[306] most of which are ultimately based on the Pd-mediated transfer of the allyl-group to a nucleophile. A variety of nucleophiles can be used as allyl scavengers, for example, morpholine or phenylsilane.[307]

Table 9. Conditions investigated for the removal of the allyl protecting groups from (*R,R*)-**96**.



(*R,R*)-**96** (*R,R*)-**112** (*R,R*)-**97**

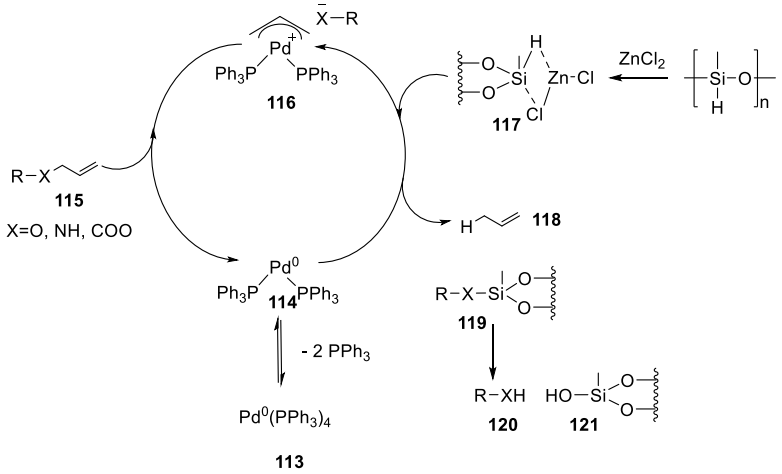
Entry	Scale	Conditions	Solvent[a]	Yield[b]
1	10 mg	$Pd(PPh_3)_4$, morpholine	THF	(*R,R*)-**97**, 98%
2	10.2 mg	$Pd(PPh_3)_4$, $ZnCl_2$, PMHS, 16 h at rt, then 3 h at 45 ˚C	THF	(*R,R*)-**112**, 66%
3	100-119 mg[c]	$Pd(PPh_3)_4$, $ZnCl_2$, PMHS, 5 h at 45 ˚C	THF	(*R,R*)-**112**, 82-90%

[a] c=0.125 M; [b] isolated yields; [c] could be reproduced multiple times; PMHS = polymethylhydrosiloxane.

As shown in *Table 9*, treatment of alkyne (*R,R*)-**96** with tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) and morpholine only led to loss of the benzoyl protecting group on thymine to give (*R,R*)-**97**

in 98% yield. In contrast, employing $Pd(PPh_3)_4$ in combination with $ZnCl_2$ and polymethylhydrosiloxane (PMHS) as a nucleophilic allyl scavenger, the desired product (*R,R*)-**112** was obtained multiple times in yields of up to 92% (*Table 9*, entries 2 and 3,).

The mechanism of allyl-ether (or -ester) cleavage by polymethylhydrosiloxane–$ZnCl_2$/$Pd(PPh_3)_4$, as proposed by Chandrasekhar and co-workers,[308] is depicted in *Scheme 76*. Thus, $Pd(PPh_3)_4$ **113** dissociates to form palladium complex **114**, which reacts with allyl ether **115** forming π-allyl palladium complex **116**.[309][310] Zinc (II) chloride activates Si-H bonds in PMHS[311] in a pentavalent silicate **117** associated with the zinc Lewis acid center.

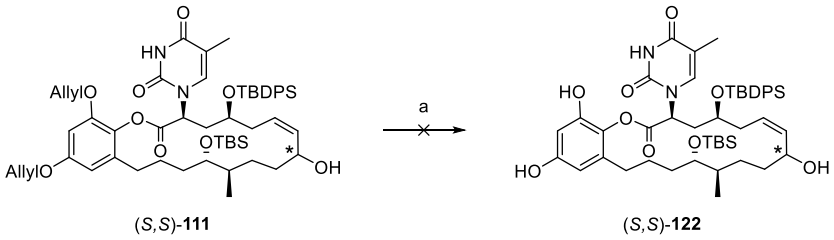


Scheme 76. Proposed reaction mechanism of allyl-ether cleavage by polymethylhydrosiloxane–$ZnCl_2$/$Pd(PPh_3)_4$.[308]

Intermediate **117** acts as a nucleophile, donating hydride to attack the π-allyl palladium complex **116**, resulting in the formation of propene **118** and intermediate **119**, which then releases the desired deallylated product **120** and by-product **121**.

3.4.2.4.2 Attempted deallylation of (*S,S*)-111

After the successul installation of the *Z* double bond, only two protecting group removal steps remained for the conversion of (*S,S*)-**111** into (*S,S*)-macplocimine, namely the cleavage of the allyl- and silyl-ethers. First, the allyl protecting group removal was examined. The conditions optimized for (*R,R*)-**96** were employed for (*S,S*)-**111** (*Scheme 77*).

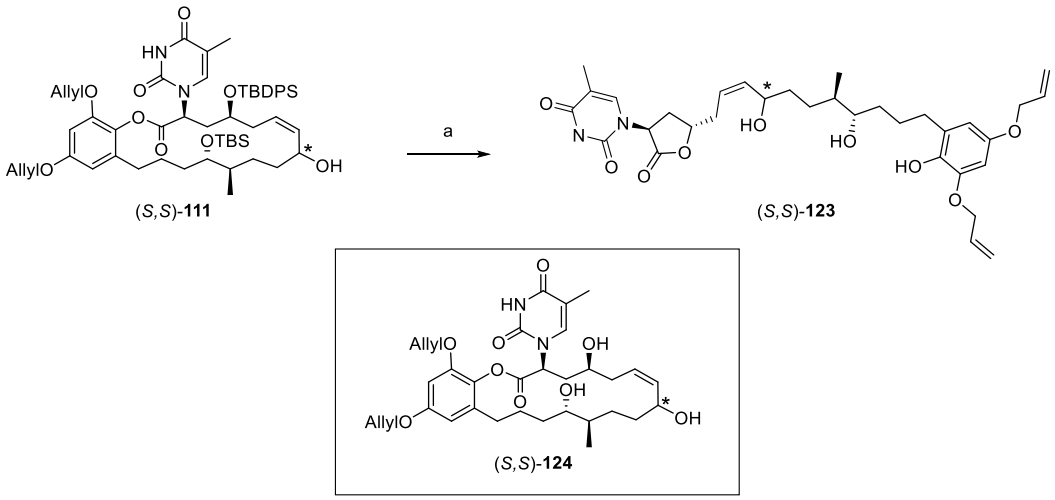


Scheme 77. Reagents and conditions: a) $Pd(PPh_3)_4$, $ZnCl_2$, PMHS, THF, 45 °C, 1.5 h.

However, unfortunately, the desired free bis-phenol (*S,S*)-**122** was not obtained, no isolable and characterizable product was detected. The reaction was carried out two times on a 2 mg and 4 mg scale of (*S,S*)-**111**, and it is conceivable that larger scales would have allowed to isolate the (*S,S*)-**122** at least in low yields. At the same time, it may also be that the allylic alcohol moiety present in (*S,S*)-**111** may interfere with clean Pd-catalyzed aryl allyl-ether cleavage even though there is a literature precedent using similar conditions with $Pd(PPh_3)_4$ and a different nucleophile as the allyl scavenger for the allyl-ether removal from phenol in the presence of an allylic alcohol.[312][313]

3.4.2.4.3 Attempted desilylation of 8*S*-(*S,S*)-111 and 8*R*-(*S,S*)-111

While the reasons for the failure to deallylate (*S,S*)-**111** were unclear, it was still considered sensible to invert the order of the final deprotection steps and investigate cleavage of the two silyl ethers at C(4) and C(12) prior to deallylation. When the major isomer obtained from the reduction of (*S,S*)-**97** was treated with an excess of pyridine-buffered HF·Py in THF, a product was obtained in 92% yield that exhibited the expected mass and whose ^{1}H and ^{13}C NMR spectra in $CDCl_3$ seemed to confirm the expected structure of (*S,S*)-**124** (*Scheme 78*). Based on this initial analysis, the experiment was repeated two times on 35 mg and 9 mg scales; in addition, the same conditions were applied to achieve the desilylation of the minor diastereomer of (*S,S*)-**111** (*vide infra*). Only later, careful analysis of NMR spectra in DMSO-d_6 revealed that the desired and expected product (*S,S*)-**124** had not been obtained; rather, the desilylation had led to the formation of butyrolactone (*S,S*)-**123**. The latter is the product of an intramolecular transesterification that occurs after cleavage of the C(4)-TBDPS ether and that is favored by the formation of a 5-membered ring and also by the increased reactivity of the phenyl ester group (relative to an alkyl ester).



Scheme 78. Desilylation of the major diastereomer of (*S,S*)-**111** from the reduction of (*S,S*)-**97** with $Co_2(CO)_8$/N-ethylpiperidnium hypophosphite. Reagents and conditions: a) HF·Py, Py, THF, 0 °C to rt, 92% on a 6 mg scale, 64% on a 35 mg scale, and 47% on an 8.8 mg scale.

In the ^{1}H-NMR spectrum of (*S,S*)-**123** in DMSO-d_6, the phenolic OH proton can be clearly identified (*Figure 34*).

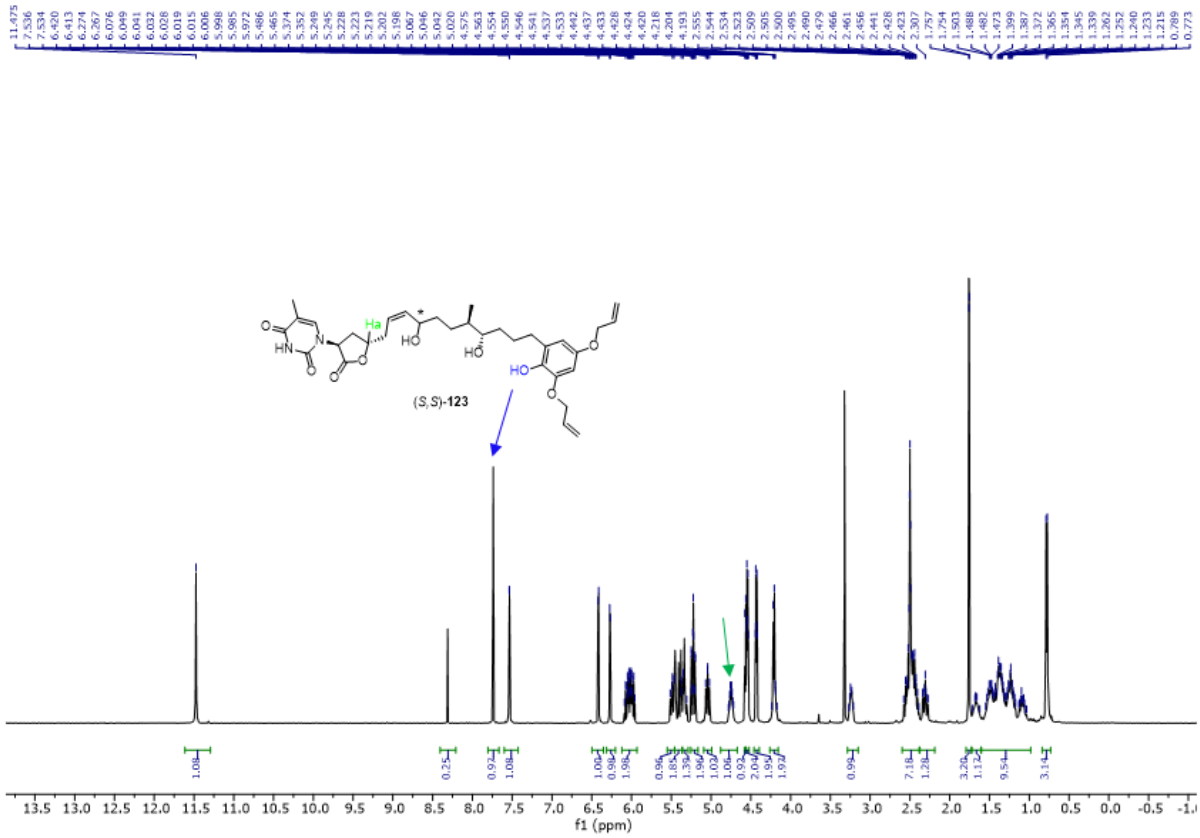
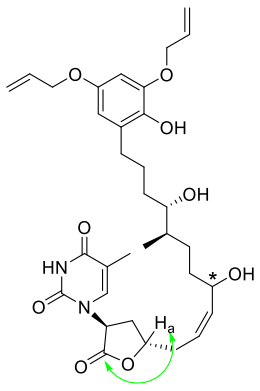


Figure 34. ^{1}H NMR spectrum of (*S,S*)-**123** in DMSO-d_6. The phenolic proton is at 7.74 ppm, indicated with a blue arrow, and the Ha proton is at 4.75 ppm, indicated with a green arrow.

As expected, this proton correlates with carbons of the aromatic ring (cross-peaks in the blue box in *Figure 36*) in a heteronuclear multiple bond correlation (HMBC) experiment.



(*S,S*)-**123**

Figure 35. HMBC-correlation (in green) that supports the presence of a 5-membered lactone ring in (*S,S*)-**123**.

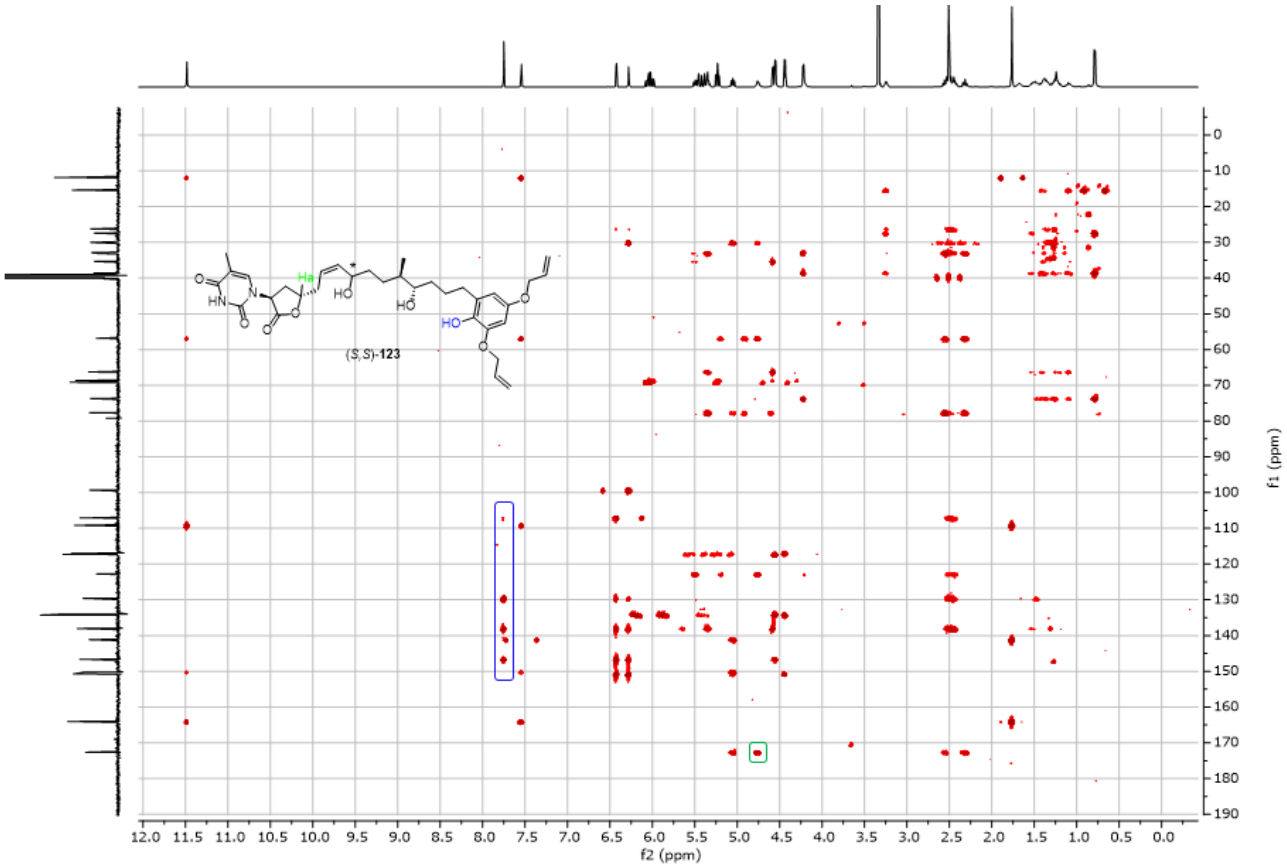
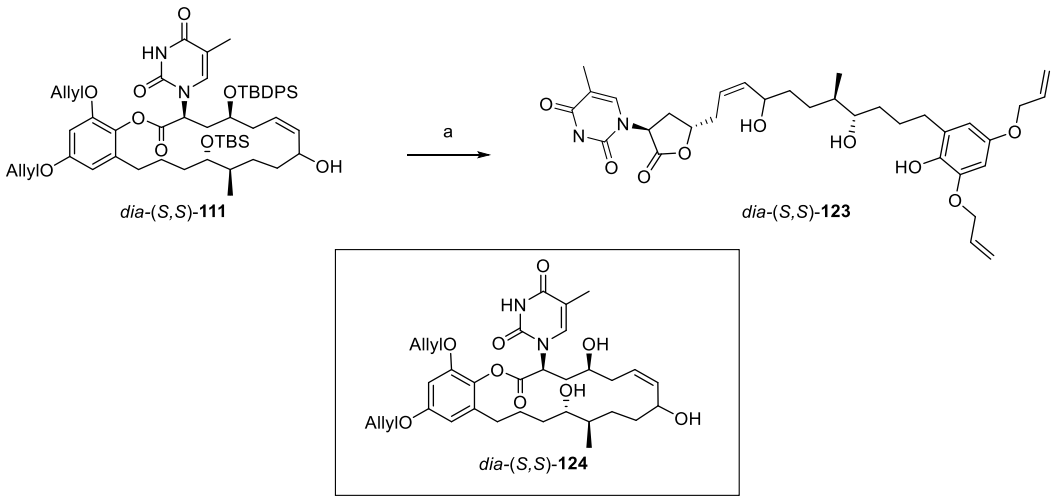


Figure 36. HMBC spectrum of (*S,S*)-**123** in DMSO-d_6. Cross-peaks between the phenolic H and the aromatic ring carbons are boxed in blue; the cross-peak between the proton Ha in the lactone ring and the carbonyl, that would not be observed without the presence of the lactone.

The HMBC experiment also showed a correlation between the carbonyl carbon C(1) and H_a (cross peak in the green box in *Figure 36* and schematic representation in *Figure 35*).

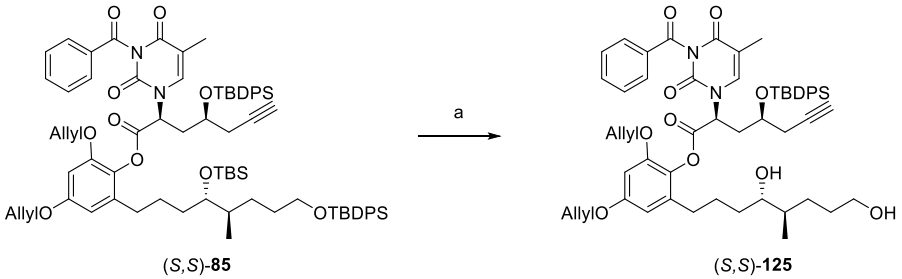
Finally, the chemical shift of Ha (4.75 ppm) clearly indicates that this proton is located α to an acylated oxygen rather than to a free OH group; in the latter case, this proton would be expected to show a chemical shift of 3-4 ppm.

As would have been predicted had the above transesterification been recognized before performing the experiment, treatment of the minor diastereomer (*S,S*)-**111** from the reduction of (*S,S*)-**97** with pyridine-buffered HF·Py in THF gave the C(8)-diastereomer of (*S,S*)-**123** (*dia*-(*S,S*)-**123**) in 68% and 44% yield on scales of 6 and 20 mg, respectively (*Scheme 79*).



Scheme 79. Desilylation of the minor diastereomer *dia*-(*S,S*)-**111**. Reagents and conditions: a) HF·Py, Py, THF, 0 ˚C to rt, 68% on a 6 mg scale and 44% on a 20 mg scale of the transesterified substrate *dia*-(*S,S*)-**123**.

Due to time constraints no further work on the deprotection of (*S,S*)-**111** could be carried out. However, an experiment conducted with intermediate (*S,S*)-**85** and only 10 equiv. of HF·Py reagent (*vs*. 500 equiv. with (*S,S*)-**111**) (*Scheme 80*).

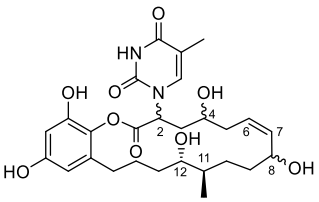


Scheme 80. Steps toward the optimization of the silyl-protecting group removal. Reagents and conditions: a) HF·Py (10 equiv.), Py, THF, 0 ˚C to rt, 4 h, 79%.

Under these conditions, no cleavage of the secondary TBDPS-ether occurred after 4 h and free diol (*S,S*)-**125** was isolated in 80% yield. Further optimization will be necessary to understand if it is possible to remove the TBDPS-protecting group in (*S,S*)-**111** without transesterification.

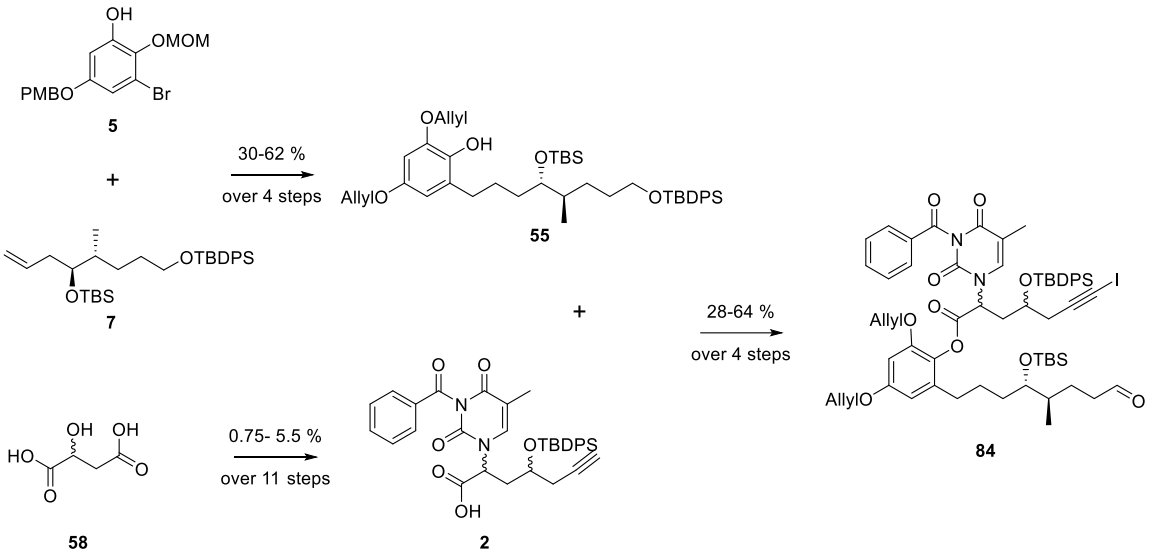
4 Conclusion and outlook

In the present thesis, studies toward the total synthesis of the macrocyclic marine natural product macplocimine A (**1**) were carried out.



Macplocimine A (**1**)

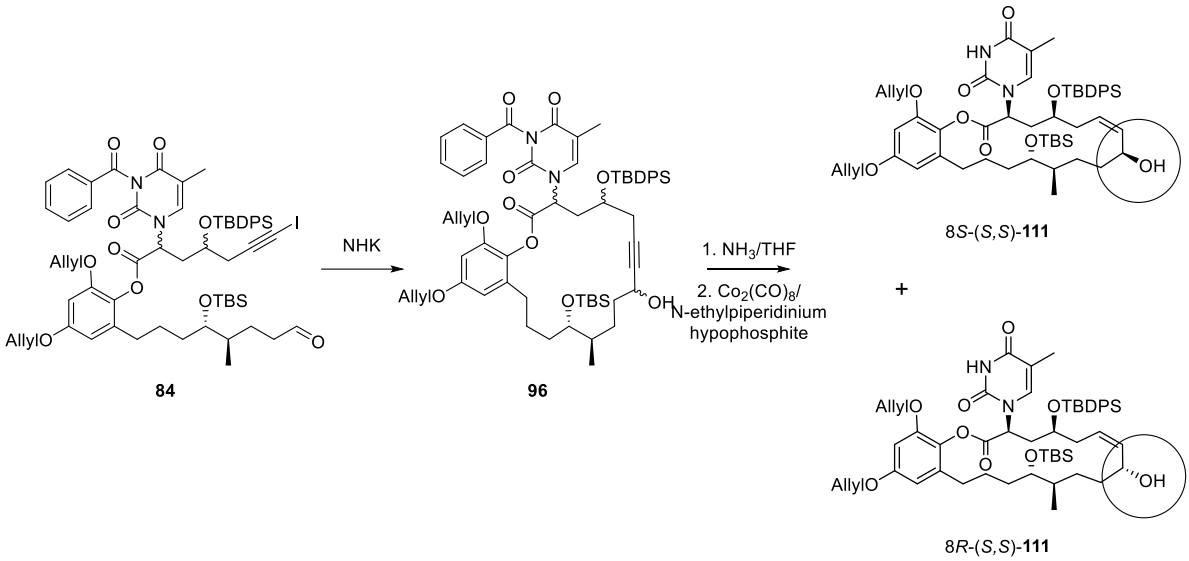
The synthesis of protected derivatives of two different diastereomeric versions of the natural product (out of 8 possible) was achieved based on the development of robust and scalable routes for the synthesis of building blocks **2** and **55** (*Scheme 81*). Specifically, the common building block **55** was synthesized on a decagram scale in 15 steps for the LLS from 1,4-butanediol in 3-8.8% overall yield. Three acid building blocks **2** ((*R,R*)-**2**, (*R,S*)-**2**, and (*S,S*)-**2**) and one alcohol precursor ((*S,R*)-**69**) were synthesized in 11 and 8 steps, respectively, from L- and D- malic acid. The acid building blocks were elaborated into three different diastereomers of iodoalkyne **84** ((*R,R*)-**84**, (*R,S*)-**84**, and (*S,S*)-**84**) in good yields on a multigram scale (*Scheme 81*).



Scheme 81. High-level summary of the synthesis of iodoynals **84**.

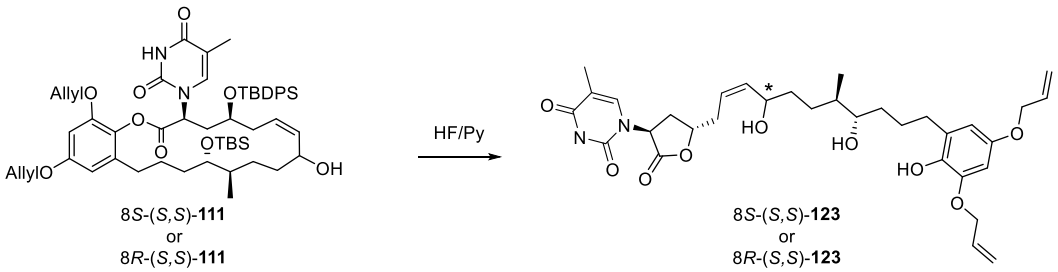
One of the key steps in the syntheses was the formation of the macrocycle *via* intramolecular Nozaki-Hiyama-Kishi reaction of iodoynals **84**. In all three cases investigated ((*R,R*)-**84**, (*R,S*)-**84**, and (*S,S*)-**84**), the reaction provided the corresponding 18-membered macrolactone **96**, irrespective of the configuration of the iodoalkyne **84**, in yields of 37-66%; as was in fact desired, the transformation was non-stereoselective and in each case two diastereomers were obtained at C(8) in a ca. 1:1 ratio (*Scheme*

82). Macrolactone (*S,S*)-**96** could be elaborated into the separable, protected macplocimine A diastereomers 8*S*-(*S,S*)-**111** and 8*R*-(*S,S*)-**111**.



Scheme 82. Nozaki-Hiyama-Kishi mediated macrocyclization of iodoynals **84** and reduction of the triple bond.

In principle, only two steps remained at this point to convert 8*S*-(*S,S*)-**111** and 8*R*-(*S,S*)-**111** into the corresponding macplocimine A isomers, namely the cleavage of the allyl- and silyl-ether protecting groups, respectively. Surprisingly, when trying to execute either of these transformations on **111**, the desired deprotected products were not obtained. Deallylation failed under conditions that had been successfully employed to deallylate macrocyclic alkyne (*R,R*)-**96** to produce (*R,R*)-**112**. It would have to be determined whether the allylic alcohol moiety present in **111** might interfere with clean Pd-catalyzed aryl-allyl-ether cleavage. As for the removal of the silyl-ether protecting groups from **111**, the reaction was accompanied by the opening of the macrocycle *via* intramolecular transesterification and formation of butyrolactone **123** (*Scheme 83*).



Scheme 83. Intramolecular transesterification of **111** to form butyrolactone **123**.

In spite of these difficulties, I still believe that the macrocyclic alkynes **96**, for which an efficient and reproducible route has been established in this thesis, should be viable intermediates for the synthesis of macplocimine A (**1**). The problem with the deallylation of **111** should be negotiable by performing the reduction of the triple bond *after* deallylation, i.e. at the stage of **96** or **97**. At the same time, only one

method has been investigated so far for both desilylation and deallylation; it should be possible to refine the conditions for this reaction so that intramolecular transesterification would be suppressed. Unfortunately, due to time constraints, it was not possible to assess these questions as part of this PhD thesis.

5 Experimental part

5.1 General methods

All reactions were carried out under an argon atmosphere in heatgun-dried glassware (650 ˚C) with dry solvents under anhydrous conditions with standard syringe/septa techniques unless otherwise stated. Yields refer to chromatographically and spectroscopically (1H-NMR) isolated homogenous materials unless otherwise stated.

Solvents: Dichloromethane, tetrahydrofuran, and diethyl ether used for reactions were distilled under argon before use (CH_2Cl_2 with CaH_2, THF, and Et_2O with Na/benzophenone). Other anhydrous solvents were purchased from Acros Organics® (extra dry over molecular sieves, AcroSeal™, H_2O <0.005 %) and used as received. Deuterated solvents were purchased from Eurisotop® (chloroform) or Cambridge Isotope Laboratories, Inc. (all other solvents). Solvents for workups, extractions, column chromatography (FC), and thin-layer chromatography (TLC) were purchased on a commercial grade. Hexane, ethyl acetate, and diethyl ether were distilled prior to use. Reactions were magnetically stirred. Reactions were monitored by TLC carried out on Merck Silica gel 60 F254 aluminum plates 20x20 using UV light (λ = 254 and 366 nm) as a visualizing agent and staining with $KMnO_4/K_2CO_3$ or $Ce_2(SO_4)_3$/phosphomolybdic acid/H_2SO_4 (CPS) solutions and brief heating with a heat gun as developing agents. Chromatographic purification of products (FC) was performed using Fluka silica gel 60 for preparative column chromatography (particle size 40-63 µm).

Reagents were purchased from Sigma Aldrich, abcr GmbH, Acros Organics, Tokyo Chemical Industry Co., Ltd., or Fluorochem Ltd. at the highest commercial quality and used without further purification unless otherwise stated. Standard solutions: Dess-Martin work-up solution: $NaHCO_3$ (80 g) and $Na_2S_2O_3 \bullet 5H_2O$ (14 g) dissolved in 1.0 L deionized water. Phosphate buffer pH 7.2: Phosphate buffer APHA, pH 7.2, Sigma Aldrich_17202 (34 g) dissolved in 1.0 L deionized water.

NMR spectra were recorded at ETH Zürich on a Bruker 400 MHz UltraShield™ spectrometer at room temperature 298 K. Chemical Shifts (δ) are reported in ppm and are referenced to chloroform-*d* (δ 7.26 ppm for ^{1}H NMR, δ 77.16 ppm for ^{13}C NMR) or DMSO-d_6 (δ 2.50 ppm for ^{1}H NMR, δ 39.52 for ^{13}C NMR) as an internal reference and an external reference for ^{19}F NMR (CCl_3F: δF = 0 ppm). The following abbreviations were used to define multiplicities: app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, ddddd = doublet of doublet of doublet of doublet of doublets, dq = doublet of quartets, ddq = doublet of doublet of quartets, dqd = doublet of quartet of doublets, dt = doublet of triplets, qdd = quartet of doublets of doublets, td = triplet of doublets, tdd = triplet of doublets of doublets, tt = triplet of triplets.

Infrared (IR) spectra were recorded on a Jasco FT/IR-6200 instrument. Resonance frequencies are given as wavenumbers in cm^{-1}.

High-resolution mass spectra (HRMS) were recorded by the ETH Zürich MS service team on one of the following devices: waters' AutoSpec Ultima (EI), Thermo Scientific Q Exactive GC Orbitrap (EI), Bruker's maXis (ESI), or Bruker's solariX (MALDI) AutoSpec Ultima spectrometer (EI).

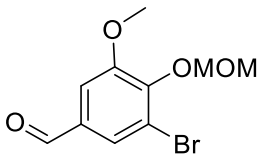
Optical rotations were recorded on an Anton-Paar MCP 300 at the sodium D line with a 10 mm path length cell, at 293 K, wavelength 589 nm and are reported as follows: $[\alpha]_{DT}$: (concentration (g/100 mL) and solvent).

The compounds are referred to by ascending numbers **X**, which follow the sequential references in the main text. In the case of diastereomers of the acid fragment, all synthesic steps follow each other consequently. For example, for *(R,R)*-**X**, the experimental section will start from the reduction of *L*-malic acid to give the triol *S*-**61** and continues until the acid *(R,R)*-**2**, same applies to other diastereomers of the acid. The **SI-X** names correspond to the intermediate compounds, which do not have a number in the main part of the thesis.

5.2 Preparation of common building blocks

5.2.1 Aromatic building block 5

*3-bromo-5-methoxy-4-(methoxymethoxy)benzaldehyde (**10**)*



A solution of 5-bromovanillin (25.0 g, mmol, 1.0 equiv.) in DCM (225 ml, c=0.48 M) was prepared and cooled down to 0 °C. Then, DIPEA (30.2 ml, 1.6 equiv.) and MOMCl (10.684 ml, mmol, 1.3 equiv.) were added at 0 ˚C, slowly warmed to room temperature, and stirred at rt for 30 min. After completion of the reaction by TLC, it was quenched with aq. sat. NH_4Cl and extracted with DCM (3 x). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The Crude material M=37.58 g was purified by FC=10 cm (hexane/EtOAc 3/1) obtaining **10** (31.24 g, quant) in fractions 3-8 as a colourless oil.

Yield: 31 g (100 %);

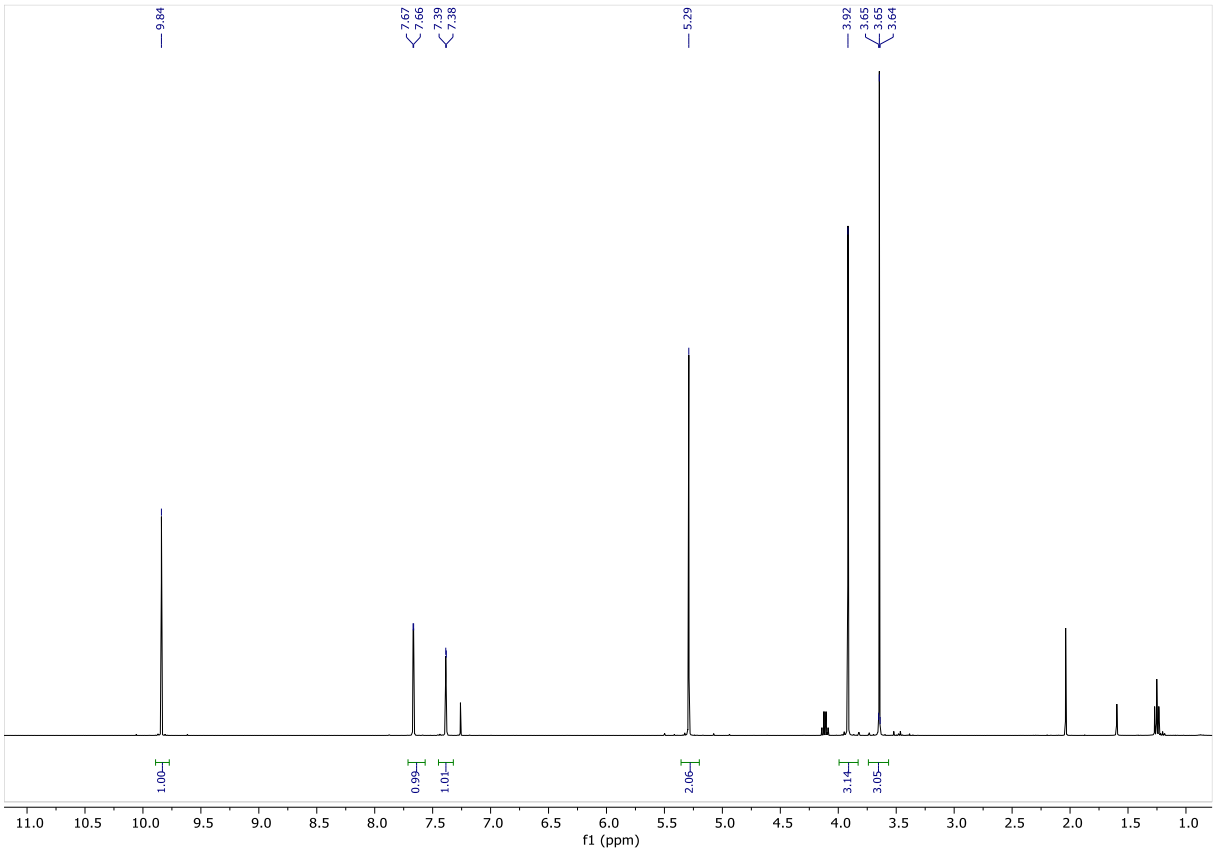
R_f = 0.267 (4:1 EA: hex - run 2 times), CPS staining;

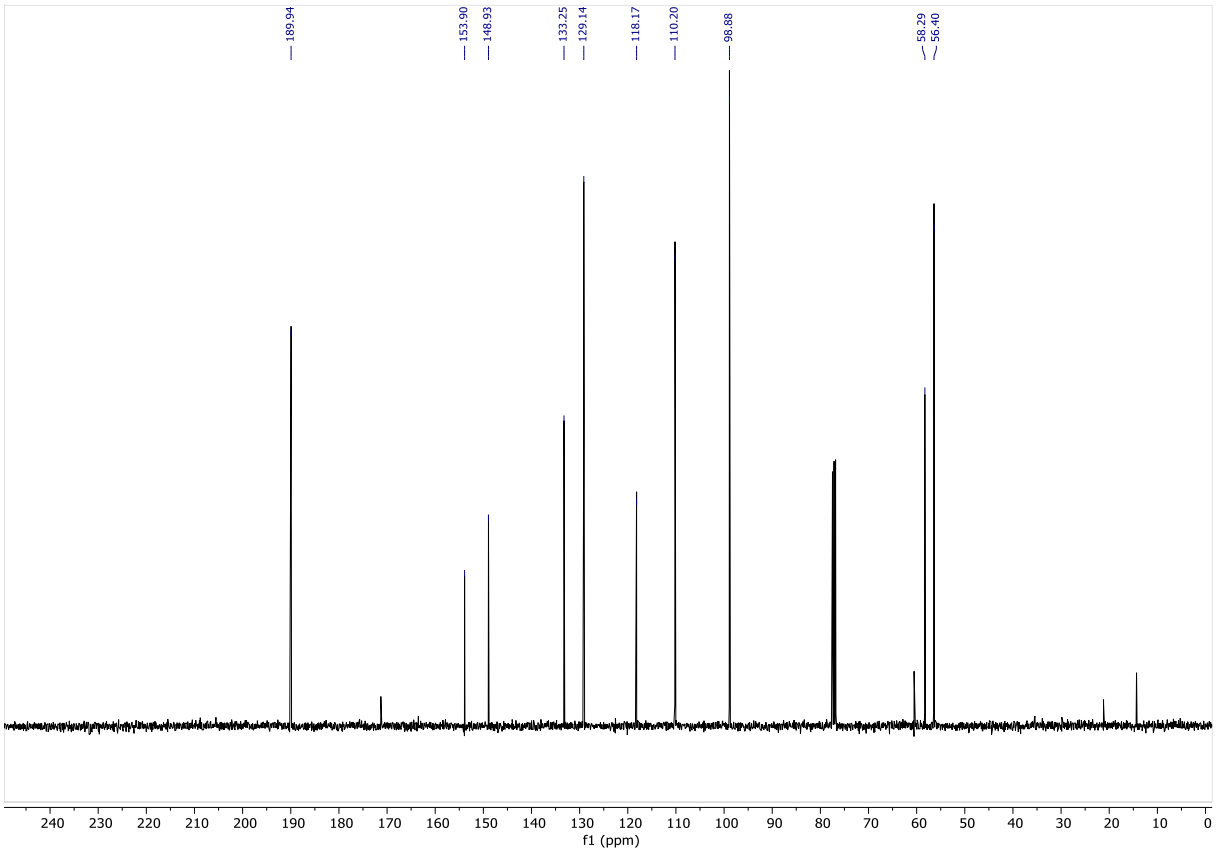
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.84 (s, 1H), 7.67 (d, J = 1.8 Hz, 1H), 7.38 (d, J = 1.8 Hz, 1H), 5.29 (s, 2H), 3.92 (s, 3H), 3.65 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.9, 153.9, 148.9, 133.3, 129.1, 118.2, 110.2, 98.9, 58.3, 56.4;

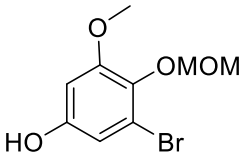
IR (film): ν = 2939, 2326, 2116, 1928, 1693, 1588, 1567, 1482, 1463, 1416, 1386, 1308, 1274, 1234, 1208, 1158, 1134, 1080, 1042, 927, 855, 839, 814, 743, 699, 661, 598, 570, 553;

HRMS (ESI-TOF) m/z calcd. for $C_{10}H_{12}BrO_4$ $[M+H]^+$ 274.9913, found 274.9913.


9.84
7.67
7.66
7.39
7.38
5.29
3.92
3.65
3.65
3.64
1.00
0.99
1.01
2.06
3.14
3.05
f1 (ppm)


189.94
153.90
148.93
133.25
129.14
118.17
110.20
98.88
58.29
56.40
f1 (ppm)

*3-bromo-5-methoxy-4-(methoxymethoxy)phenol (**12**)*[1]



1st step: A solution of **10** (31 g, mmol, 1.0 equiv.) in DCM (227 ml, c=0.5) was prepared. Then, *m*-CPBA (77%, 49 g, 21.8 mmol, 2.0 equiv.) was added at rt and the reaction was stirred at rt for 15 h. Since it was quite tricky to follow by TLC, due to similar R_f values of the SM and the product (however, it should be noted that SM and the product have different colors after CPS-staining), the reaction was controlled by MS. After 16 h added 20 ml of DCM, because seemed like the reaction is not very homogeneous. After 18 h one could still see peaks of the SM in positive mode (277 and 279 doubling signal due to different isotopes of bromine) together with a clear peak of the product in the negative mode. After 23 h, SM was not detected by MS. The reaction was diluted with DCM and washed with aq. sat. $NaHSO_3$. The organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure.

2nd step: The crude formate **11** was dissolved in methanol (120 ml, c=0.95M)-(synthesis grade, but not extra dry, since the reaction is anyways with water solution of KOH) and treated with 10% aq. potassium hydroxide (17 ml). the reaction solution became pink. The resulting reaction mixture was stirred for 15 h at rt. When my MS and TLC there was no SM anymore, the reaction was quenched by diluting with water, neutralizing with 10% aqueous hydrochloric acid (the same amount as KOH added), and extraction with ethyl acetate (2 x). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by FC (hexane/EtOAc 4/1) obtaining **12** (20.27 g, 68 % over two steps) as yellow oil.

Yield: 20.27 g (68 %);

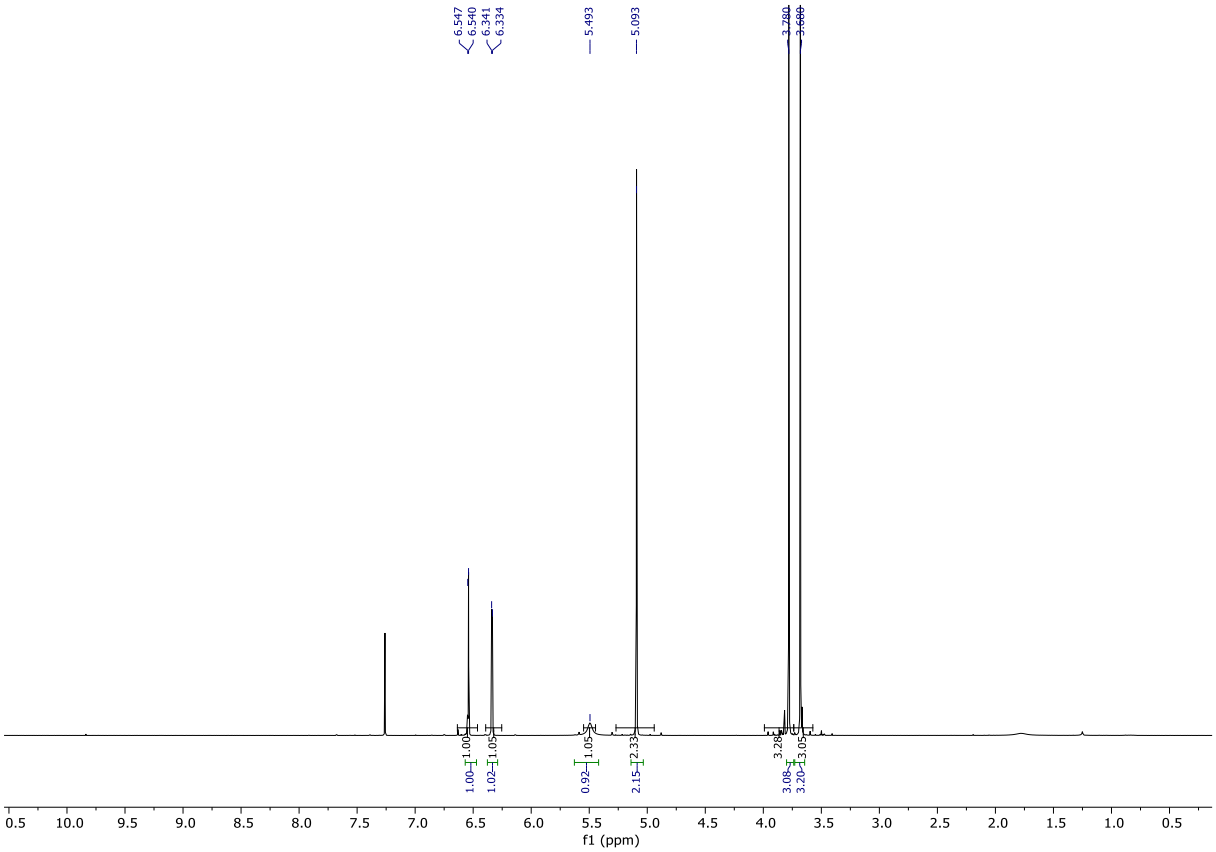
R_f = 0.63 (1:1 ea: hex), CPS staining;

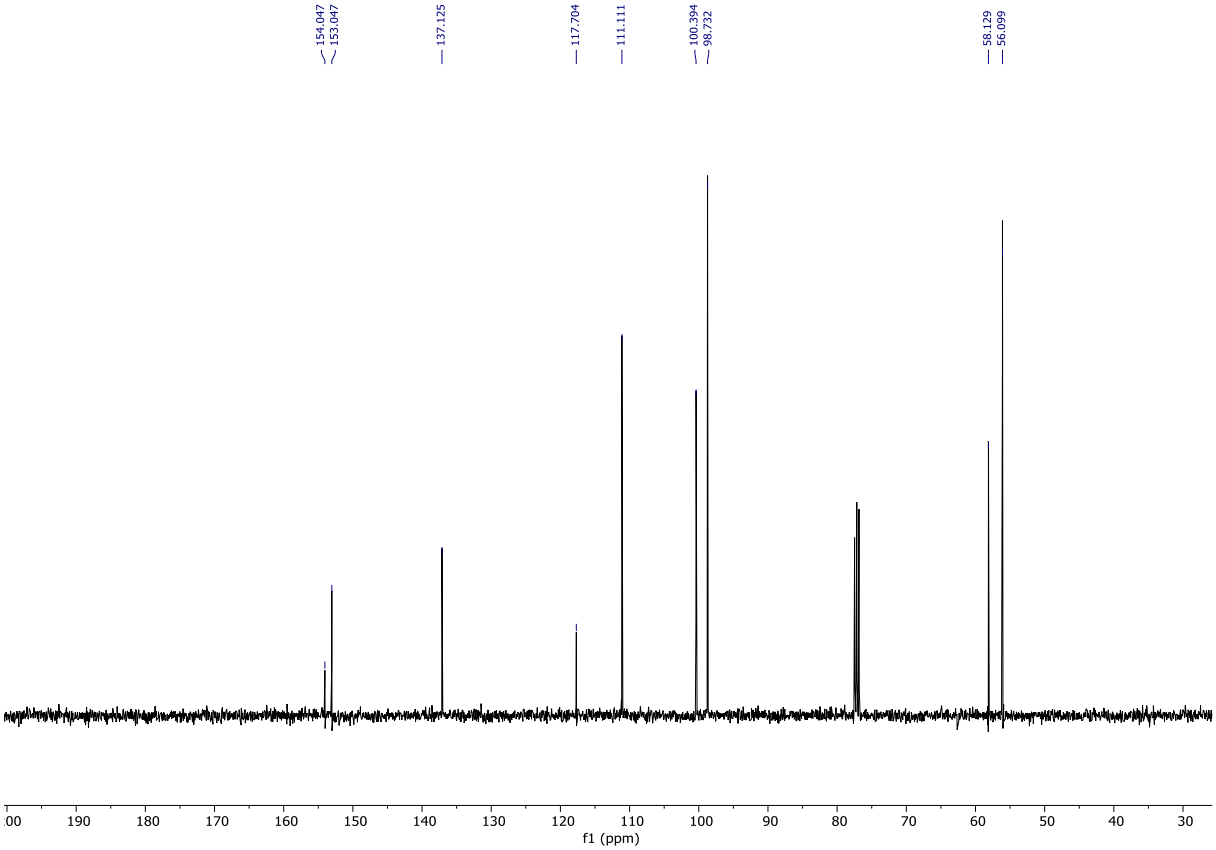
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.54 (d, *J* = 2.8 Hz, 1H), 6.34 (d, *J* = 2.8 Hz, 1H), 5.49 (s, 1H), 5.09 (s, 2H), 3.78 (s, 3H), 3.68 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.1, 153.1, 137.1, 117.7, 111.1, 100.4, 98.7, 58.1, 56.1;

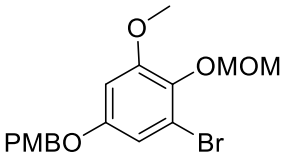
IR (film): ν = 3360, 2941, 2839, 1604, 1583, 1490, 1468, 1431, 1403, 1338, 1295, 1225, 1195, 1154, 1076, 1041, 975, 825, 766, 626, 579, 553, 540;

HRMS (ESI-TOF) m/z calcd. for $C_9H_{11}BrNaO_4$ $[M+Na]^+$ 284.9733, found 284.9731.


6.547
6.540
6.341
6.334
5.493
5.093
3.780
3.688
1.00
1.05
1.02
0.92
1.05
2.15
2.33
3.28
3.08
3.20
3.05
f1 (ppm)


154.047
153.047
137.125
117.704
111.111
100.394
98.732
58.129
56.099
f1 (ppm)

*1-bromo-3-methoxy-5-((4-methoxybenzyl)oxy)-2-(methoxymethoxy)benzene (**13**)*



A solution of **12** (9.5 g, 36.11 mmol, 1.0 equiv.) in DMF (181 ml, c=0.2 M) was prepared. K_2CO_3 (7.5 g, 54.164 mmol, 1.5 equiv.) was added to the solution and stirred at rt for 30 min. Then, PMBCl (5.4 ml, 39.72 mmol, 1.1 equiv.) was added at rt and the reaction was stirred at this temperature for 15 h. Once the reaction was done by TLC, it was quenched with water and extracted with DCM (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material (M=13.94 g) was purified by FC (hexane/EtOAc 5/1) obtaining **13** (10.51 g, 76%) as a colorless oil.

Yield: 10.51 g (76 %);

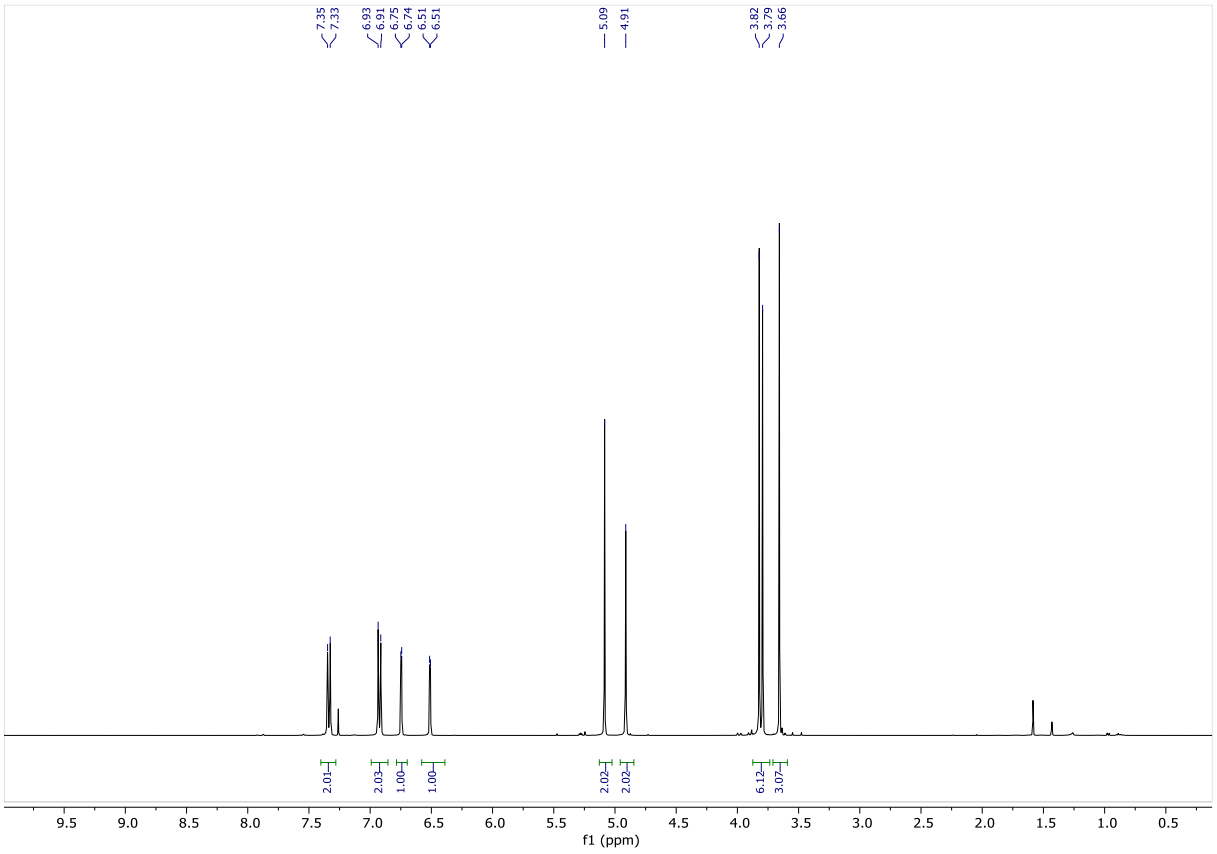
R_f = 0.235 (3:1 ea: hex), CPS staining;

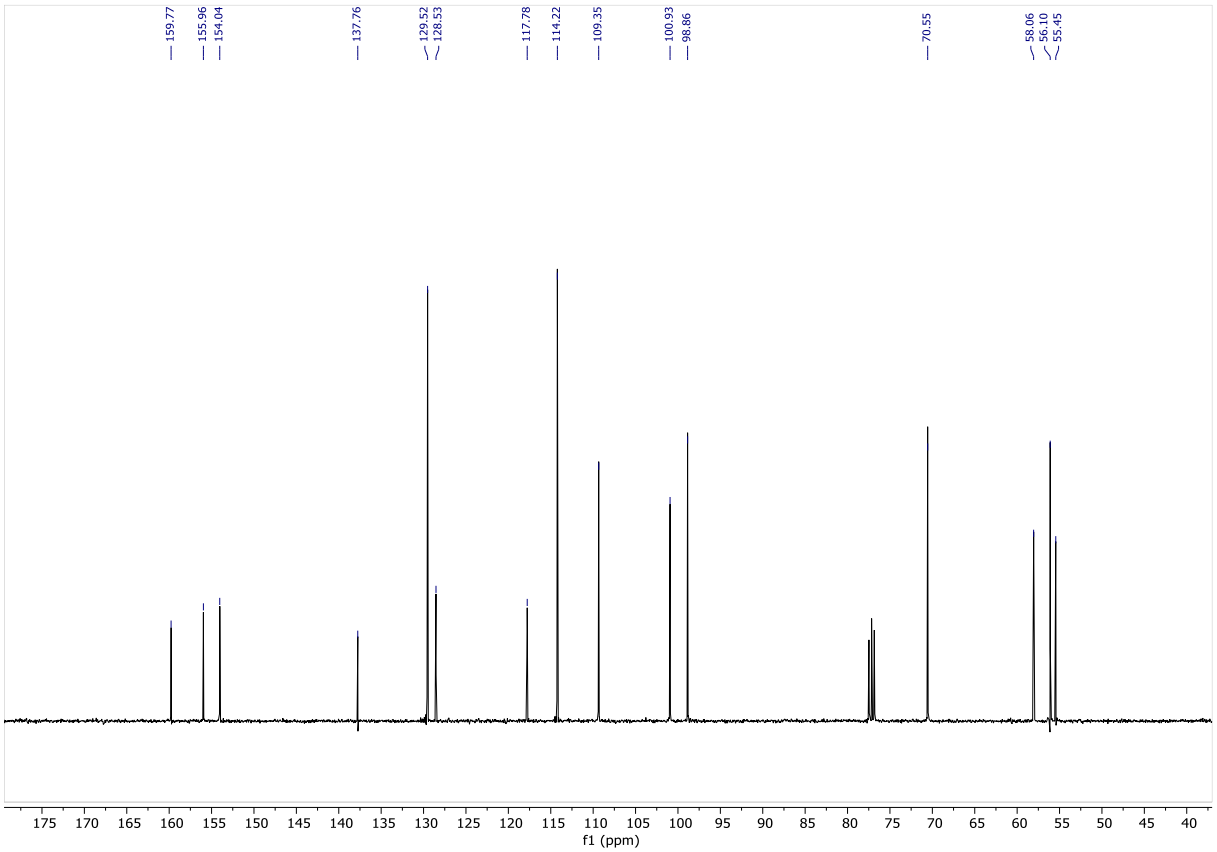
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 6.75 (d, J = 2.8 Hz, 1H), 6.51 (d, J = 2.8 Hz, 1H), 5.09 (s, 2H), 4.91 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.66 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.8, 156.0, 154.0, 137.8, 129.5 (2C), 128.5, 117.8, 114.2 (2C), 109.4, 100.9, 98.9, 70.6, 58.1, 56.1, 55.5;

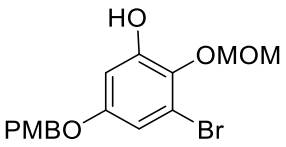
IR (film): ν = 2999, 2937, 2837, 1600, 1570, 1515, 1488, 1464, 1415, 1379, 1320, 1304, 1250, 1194, 1175, 1156, 1079, 1043, 956, 859, 825, 757, 444;

HRMS (ESI-TOF) m/z (ESI) $C_{17}H_{19}BrNaO_5$ $[M+Na]^+$ 405.0308, found 405.0304.


7.35
7.33
6.93
6.91
6.75
6.74
6.51
6.51
5.09
4.91
3.82
3.79
3.66
2.01
2.03
1.00
1.00
2.02
2.02
6.12
3.07
f1 (ppm)


159.77
155.96
154.04
137.76
129.52
128.53
117.78
114.22
109.35
100.93
98.86
70.55
58.06
56.10
55.45
f1 (ppm)

*3-bromo-5-((4-methoxybenzyl)oxy)-2-(methoxymethoxy)phenol (**5**)*



In a heatgun-dried 100 ml flask, a solution of sodium hydride (670 mg, 27.92 mmol, 1.74 equiv.) in DMF (55.87 ml, c=0.288 M) was prepared at room temperature Then, ethanethiol (2.38 ml, 32.18 mmol, 2.0 equiv.) was added

upon cooling with an ice bath and the solution was stirred for 10 minutes. Then, the SM **13** (6.17 g, 16.09 mmol, 1 equiv.) in DMF (10 ml for washing out of 56 ml) was added, and the solution turned yellow. Then, the reaction was stirred at 110 ˚C with a reflux condenser for 1.5 h. Over time yellow solution became dark red-brown. When the reaction was finished by TLC, the reaction mixture was quenched with 1 M HCl and extracted with EtOAc (3 x). The combined organic layers were evaporated on a stinky rotary evaporator, using a high vacuum after. The crude material (Mcrude=5.8 g) was purified by FC=10 cm (hexane/EtOAc 10/1) obtaining **5** (3.86 g, 65 %) as a slightly pinkish oil, which became peachy solid with a pearl shine upon storage in the fridge.

Yield: 3.86 g (65 %);

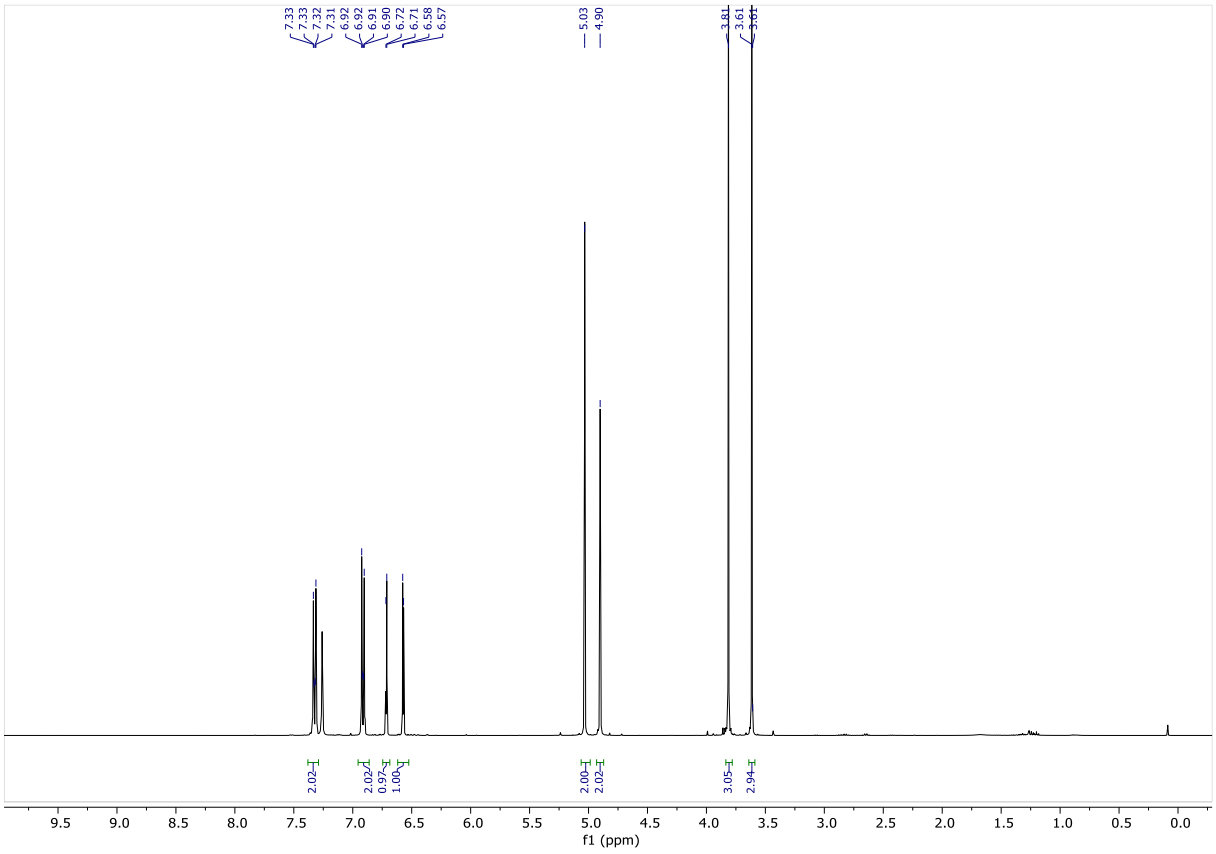
R_f = 0.322 (3:1 ea: hex), CPS staining;

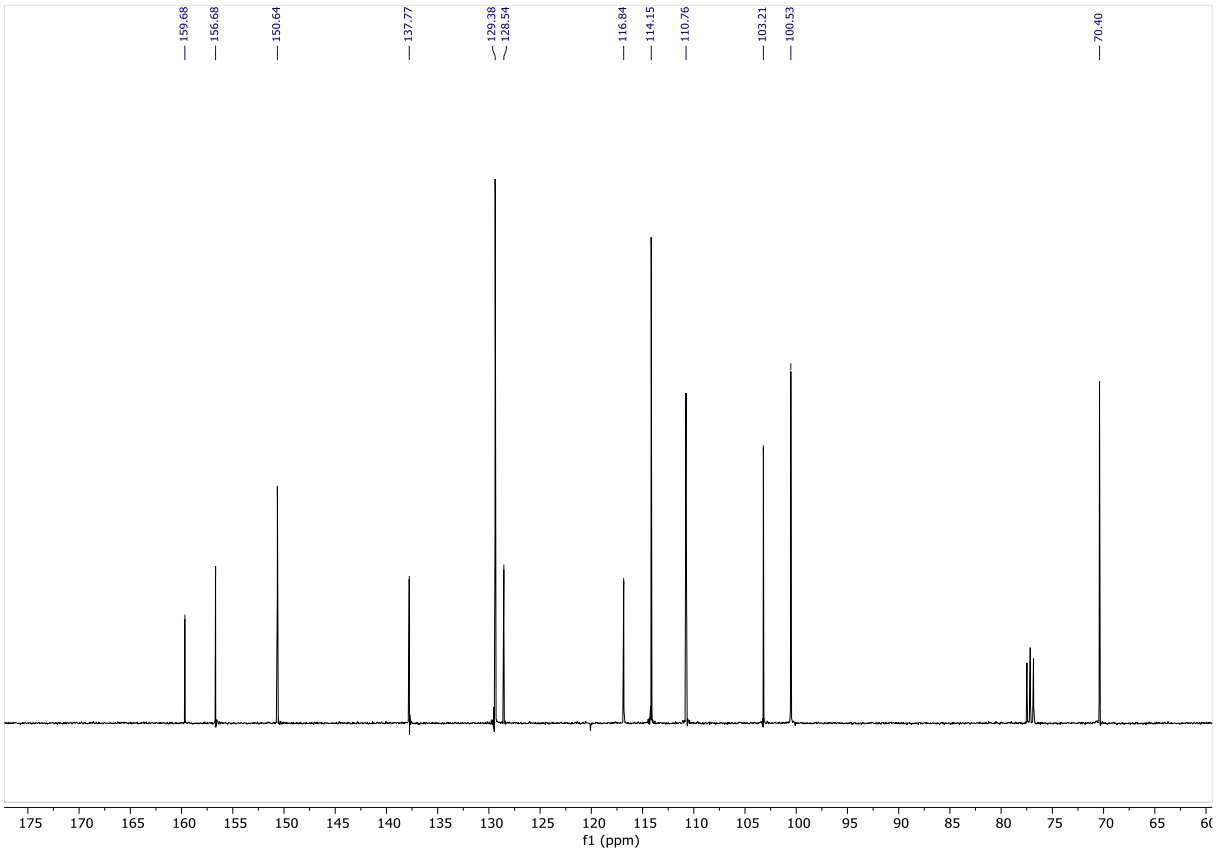
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.29 (m, 2H), 7.04 – 6.79 (m, 2H), 6.72 (d, J = 3.0 Hz, 1H), 6.57 (d, J = 2.8 Hz, 1H), 5.03 (s, 2H), 4.90 (s, 2H), 3.81 (s, 3H), 3.61 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.7, 156.7, 150.6, 137.8, 129.4 (2C), 128.5, 116.8, 114.2 (2C), 110.8, 103.2, 100.5, 70.4;

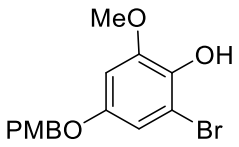
IR (film): ν = 3379, 2936, 2836, 1611, 1575, 1514, 1486, 1464, 1422, 1403, 1380, 1325, 1303, 1247, 1200, 1172, 1127, 1058, 1022, 974, 864, 828, 776, 753, 623, 600, 519;

HRMS (ESI-TOF) m/z (ESI) $C_{16}H_{17}BrNaO_5$ $[M+Na]^+$ 391.0152, found 391.0150.


7.33
7.33
7.32
7.31
6.92
6.92
6.91
6.90
6.72
6.71
6.58
6.57
5.03
4.90
3.81
3.61
3.61
2.02
2.02
0.97
1.00
2.00
2.02
3.05
2.94
f1 (ppm)


159.68
156.68
150.64
137.77
129.38
128.54
116.84
114.15
110.76
103.21
100.53
70.40
f1 (ppm)

*2-bromo-6-methoxy-4-((4-methoxybenzyl)oxy)phenol (**14**)*



Yield: 1.13 g (21 %);

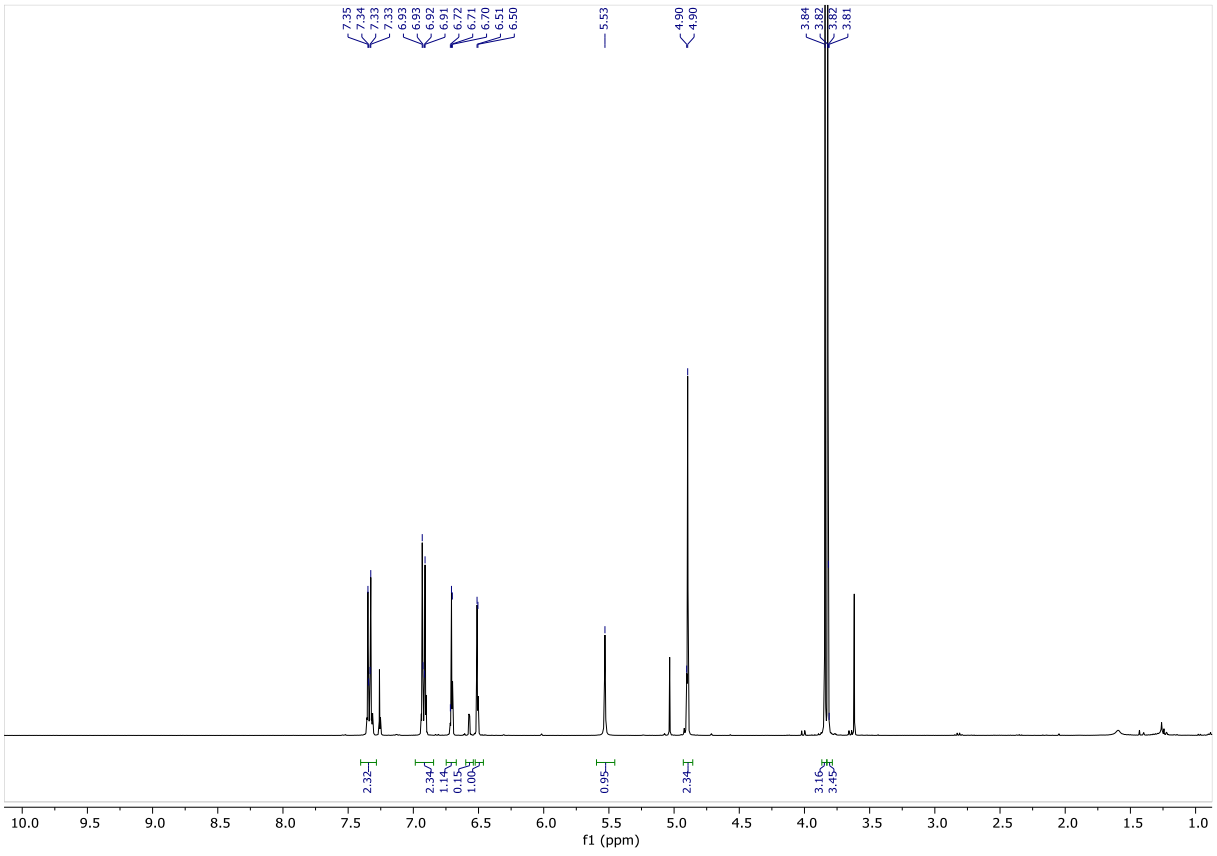
R_f = 0.326 (3:1 ea: hex), CPS staining;

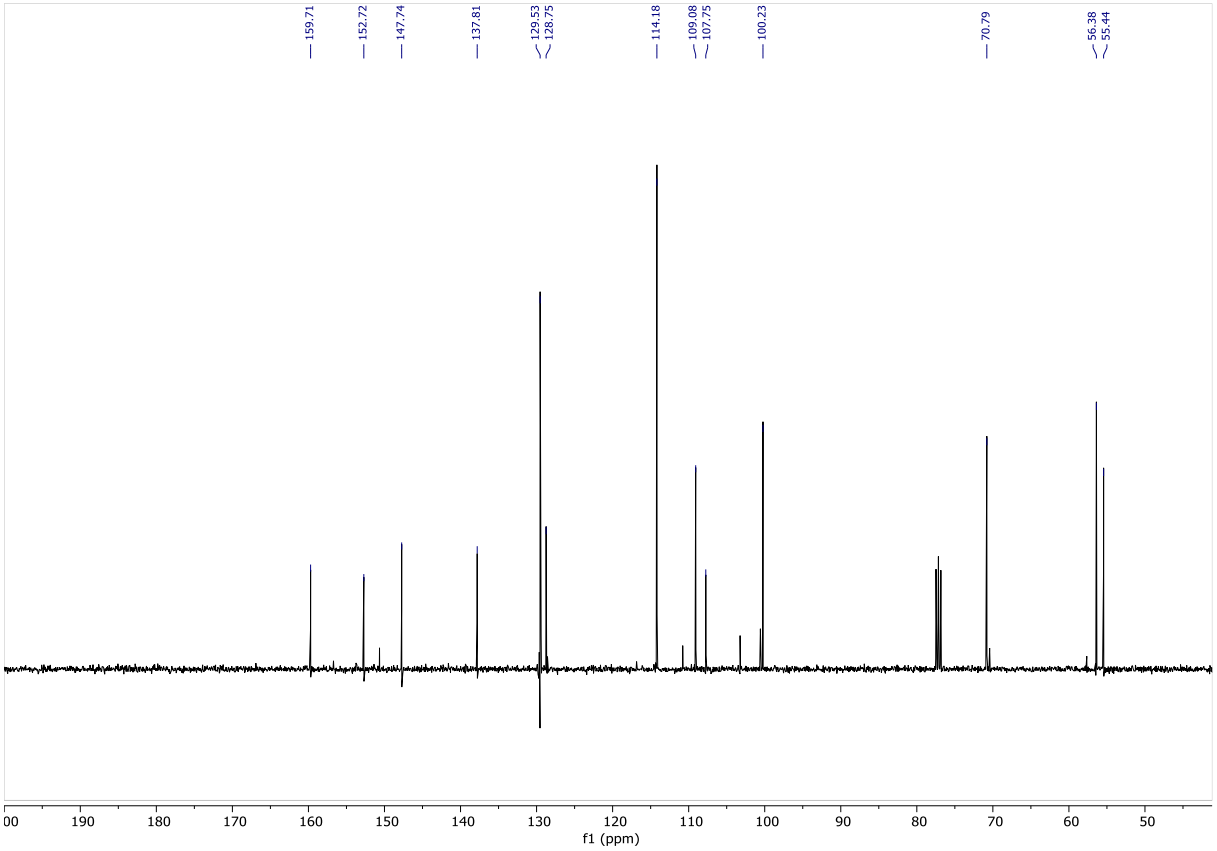
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.30 (m, 2H), 7.03 – 6.84 (m, 2H), 6.70 (d, J = 2.7 Hz, 1H), 6.51 (d, J = 2.7 Hz, 1H), 5.53 (s, 1H from OH), 4.90 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.7, 152.7, 147.7, 137.8, 129.5, 128.8, 114.2, 109.2, 107.8, 100.2, 70.8, 56.4, 55.4;

IR (film): ν = 3499, 2936, 2836, 1611, 1586, 1514, 1496, 1464, 1452, 1421, 1372, 1303, 1280, 1245, 1231, 1195, 1173, 1135, 1022, 953, 859, 828, 795, 773, 758, 647, 615, 538, 521;

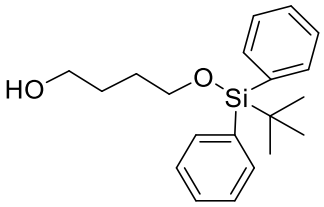
HRMS (ESI-TOF) m/z (ESI) $C_{15}H_{15}BrNaO4$ $[M+Na]^+$ 361.0046, found 361.0048.


7.35
7.34
7.33
7.33
6.93
6.92
6.91
6.72
6.71
6.70
6.51
6.50
5.53
4.90
4.90
3.84
3.82
3.82
3.81
2.32
2.34
1.14
0.15
1.00
0.95
2.34
3.16
3.45
f1 (ppm)


159.71
152.72
147.74
137.81
129.53
128.75
114.18
109.08
107.75
100.23
70.79
56.38
55.44
f1 (ppm)

5.2.2 Olefin 7

*4-((tret-butyldiphenylsilyl)oxy)butane-1-ol (**16**)*[2]



In a flame-dried round bottom flask charged with a stirring bar 1,4-butanediol (30.0ml, 337.55 mmol, 3.0 equiv.) was dissolved in DCM (230 ml). Then, to this solution, NEt_3 (23.5 ml, 168.8 mmol, 1.5 equiv.) was added. To the resulting colorless solution TBDPSCl (29.3 ml, 112.5 mmol, 1.0 equiv.) was added dropwise over 20 min. The resulting solution was stirred overnight. After completion of the reaction, verified by TLC the reaction mixture was diluted with DCM (300 ml). Quenched with water (150 ml), and aq sat $NaHCO_3$ (150 ml) and extracted with DCM (3 x 150 ml). The organic layers were washed with brine, combined, and dried over $MgSO_4$. After filtration over wool to get rid of $MgSO_4$, the solvent was concentrated under reduced pressure to obtain the crude material. The crude material was purified by FC (d= 10 cm) eluent Hex: EA=8:1 product **16** came out in fractions 31-90.

Yield: 28.6 g (77 %);

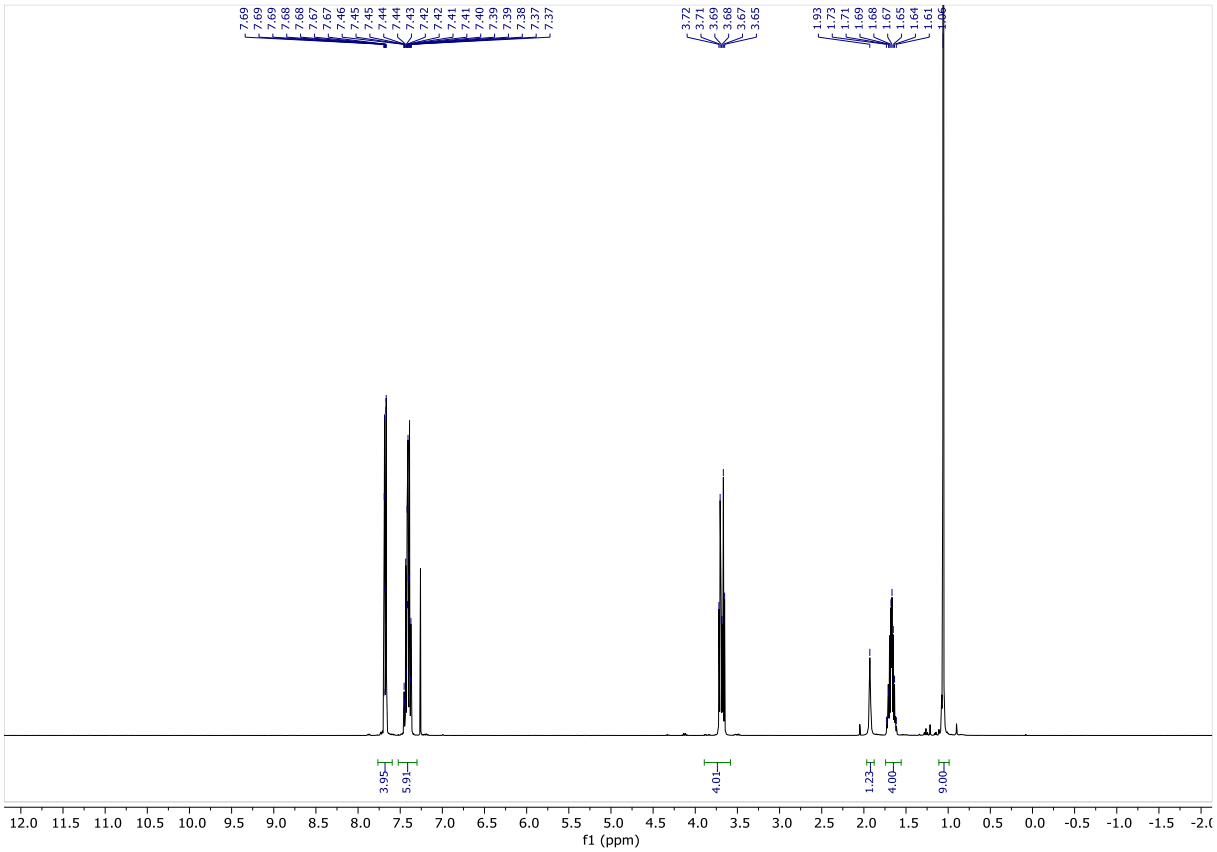
R_f = 0.613 (Hexane / EtOAc = 3:2);

1H NMR (400 MHz, Chloroform-d) δ 7.71 – 7.65 (m, 4H), 7.47 – 7.35 (m, 6H), 3.69 (dt, J = 15.5, 5.9 Hz, 4H), 1.93 (s, 1H), 1.67 (dq, J = 12.0, 6.0 Hz, 4H), 1.06 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-d) δ 136.0, 134.1, 130.1, 128.1, 64.5, 63.3, 30.3, 29.7, 27.3, 19.6.

IR (film): ν = 3341, 3071, 3050, 2931, 2895, 2857, 1589, 1472, 1445, 1427, 1389, 1362, 1262, 1188, 1109, 1062, 1029, 1008, 998, 941, 822, 793, 740, 701, 687, 613, 503.

HRMS (ESI-TOF) m/z calcd. for $C_{20}H_{28}NaO_2Si$ $[M+Na]^+$ 351.1751, found 351.1752


7.69
7.69
7.69
7.68
7.68
7.67
7.67
7.46
7.45
7.45
7.44
7.44
7.43
7.42
7.42
7.41
7.41
7.40
7.39
7.39
7.38
7.37
7.37
3.72
3.71
3.69
3.68
3.67
3.65
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1.73
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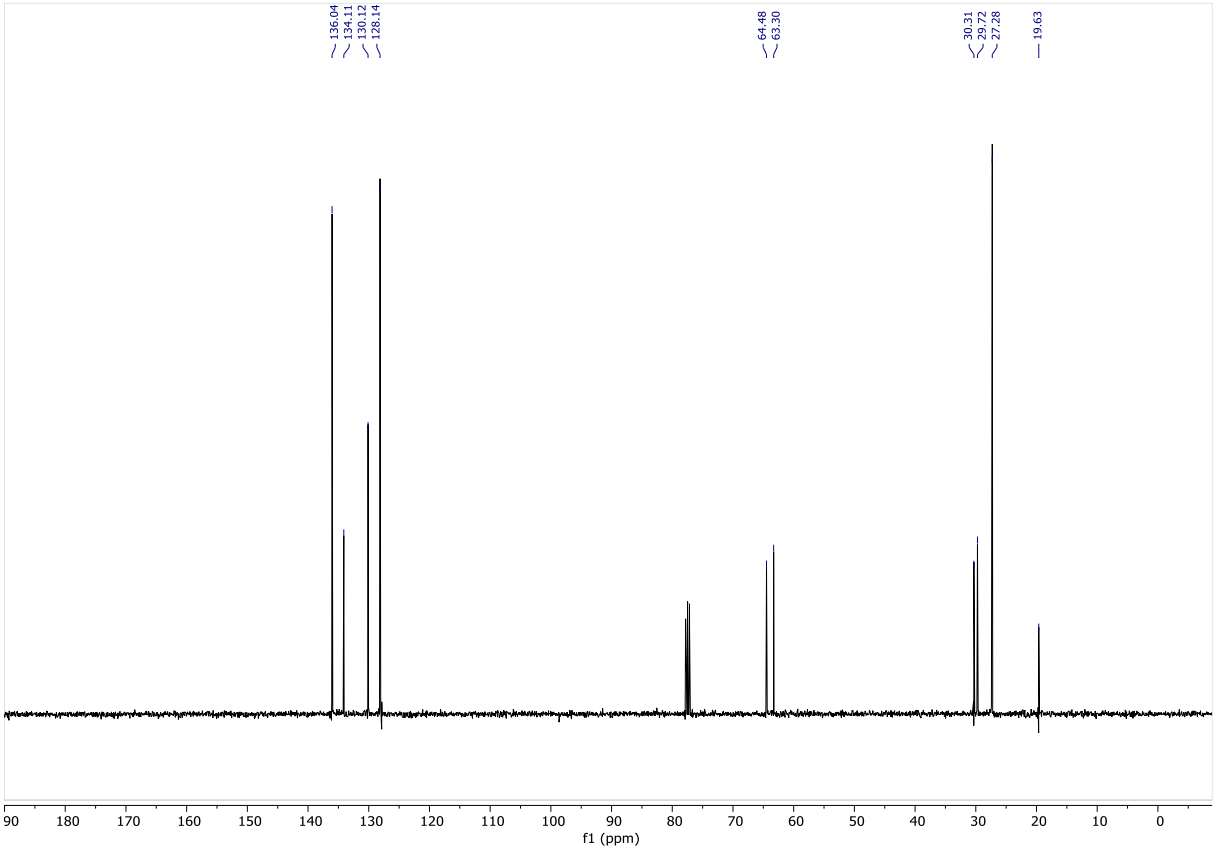
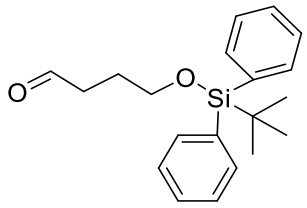
4.01
1.23
4.00
9.00
f1 (ppm)


136.04
134.11
130.12
128.14
64.48
63.30
30.31
29.72
27.28
19.63
f1 (ppm)

*4-((tert-butyldiphenylsilyl)oxy)butanal (**17**)*[2]



In a flame-dried 1 liter flask with a stirring bar, a solution of oxalyl chloride (20.9 ml, 246.6 mmol, 3.0 equiv.) in dry DCM (620 ml) was prepared and cooled to -78 ˚C. Once the desired temperature was reached, DMSO (35.0 ml, 493.1 mmol, 6.0 equiv.) was added to DROPWISE with a syringe pump (gas evolution) over 30 min, it is very important to add it dropwise to form the correct reacting species. After stirring at -78 ˚C for 30 min to let the reagents fully react, a solution of the alcohol **16** (27.0 g, 82.2 mmol, 1.0equiv.) in DCM (50 ml) was added also dropwise. Then, the reaction was stirred at -78 ˚C for another 30 min. After this time, triethylamine (91.7 ml, 657.5 mmol, 8.0 equiv.) was added and the reaction was stirred at -78 ˚C until there was no more SM left by TLC and then the reaction mixture was allowed to warm to 0 ˚C and then to room temperature The reaction was quenched with 300 ml of brine and extracted with DCM (3 x 200 ml). The combined organic layers were collected and dried over $MgSO_4$ and the solvent was removed under reduced pressure. Here, it is very important to do the column directly after the reaction, so plan the work correctly, because otherwise the aldehyde decomposes in the fridge overnight and loses the TBDPS protecting group. The crude of **17** was purified by FC (10 cm).

Yield: 8.8 g (59 %)+12 g of SM recovered back;

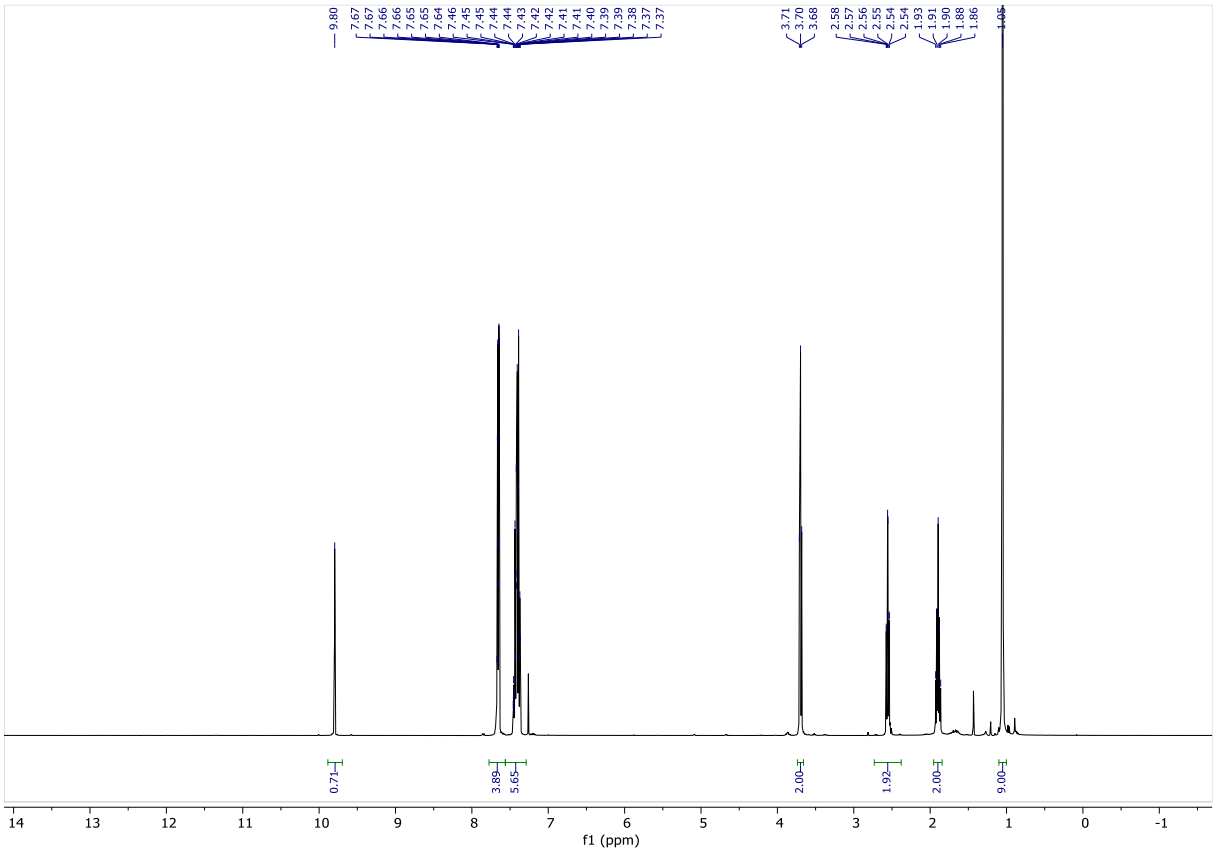
R_f = 0.63 (hexane / EtOAc = 4:1);

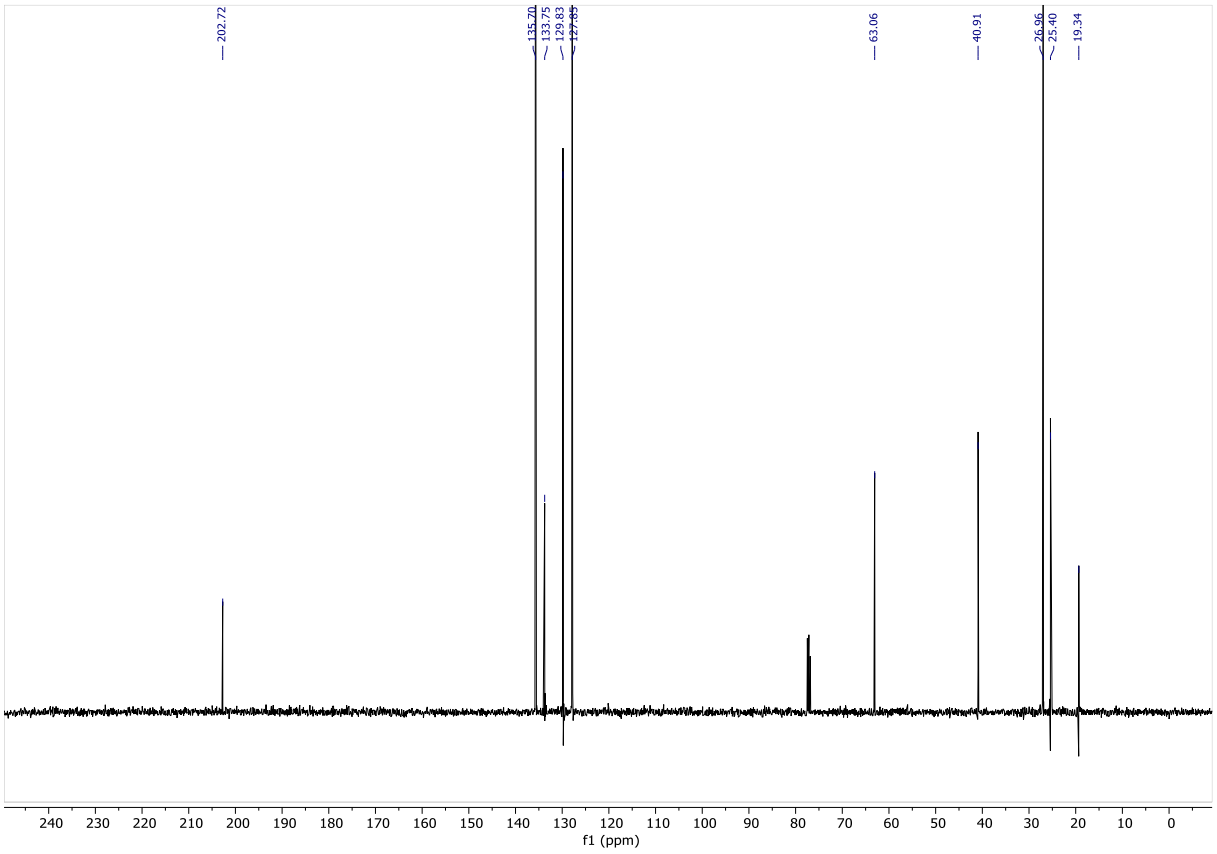
^{1}H NMR (400 MHz, Chloroform-d) δ 9.80 (s, 1H), 7.65 (dt, J = 6.5, 1.6 Hz, 4H), 7.48 – 7.34 (m, 6H), 3.70 (t, J = 6.0 Hz, 2H), 2.56 (td, J = 7.2, 1.7 Hz, 2H), 2.07 – 1.74 (m, 2H), 1.05 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-d) δ 202.7, 135.7, 133.8, 129.8, 127.9, 63.1, 40.9, 27.0, 25.4, 19.3.

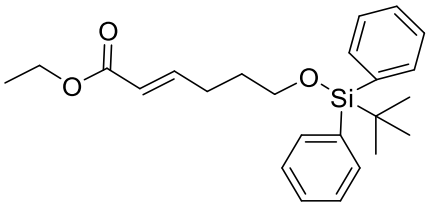
IR (film): ν = 3071, 2952, 2929, 2894, 2857, 1472, 1462, 1445, 1428, 1389, 1361, 1254, 1197, 1104, 1089, 1030, 1007, 983, 938, 835, 774, 738, 700, 687, 663, 613, 504.

HRMS (ESI-TOF) m/z calcd. for $C_{20}H_{26}NaO_2Si$ $[M+Na]^+$ 349.1594, found 349.1601


9.80
7.67
7.67
7.66
7.66
7.65
7.65
7.64
7.46
7.45
7.45
7.44
7.44
7.43
7.42
7.42
7.41
7.41
7.40
7.39
7.39
7.38
7.37
7.37
3.71
3.70
3.68
2.58
2.57
2.56
2.55
2.54
2.54
1.93
1.91
1.90
1.88
1.86
1.05
0.71
3.89
5.65
2.00
1.92
2.00
9.00
f1 (ppm)


202.72
135.20
133.75
129.83
127.85
63.06
40.91
26.96
25.40
19.34
f1 (ppm)

*ethyl (E)-6-((tert-butyldiphenylsilyl)oxy)hex-2-enoate (**18**)*[3]



Solution of NaH (60% in mineral oil, 2.6 g, 40.43 mmol, 1.5 equiv.) in THF (35.0 ml, c=0.78 M) was prepared in a flame-dried glassware under Ar atmosphere and cooled to -20 ˚C. When the temperature was reached, triethyl phosphonacetate (8.021 ml, 40.43 mmol, 1.5 equiv.) was added dropwise to this solution (the solution was bubbling, H_2 formation). Then, the reaction mixture was stirred at this temperature for 45 min. After letting it stir to deprotonate triethyl phosphonacetate, the aldehyde **17** (8.8 g, 26.95 mmol, 1.0 equiv.) was added and the reaction was stirred at -20 ˚C for a further 20 min and then after completion of the reaction, verified by TLC allowed to warm to room temperature Then, the reaction mixture was diluted with diethyl ether at room temperature And the mixture was washed with aq. sat. NH_4Cl, aq. sat. $NaHCO_3$ and brine.

Combined organic layers were dried over $MgSO_4$ and solvent was removed under reduced pressure. The crude material M=14.32 g was purified by column chromatography (Hex/EtOAc 20/1) affording **18** in fractions 12-40 as slightly yellow oil. M after the first column is 10.55 g,

Yield: 10.28 g, (96 %)

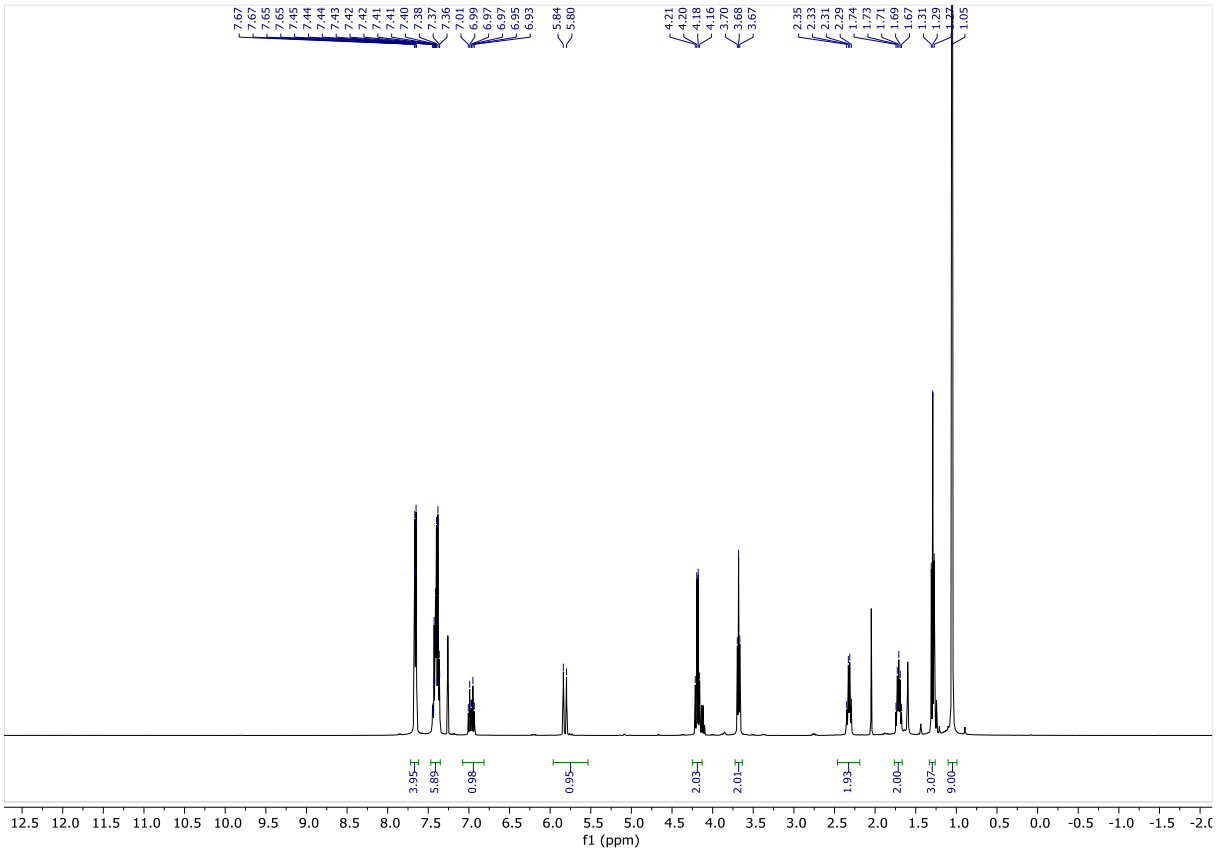
R_f = 0.828 (hexane / EtOAc = 1:1)

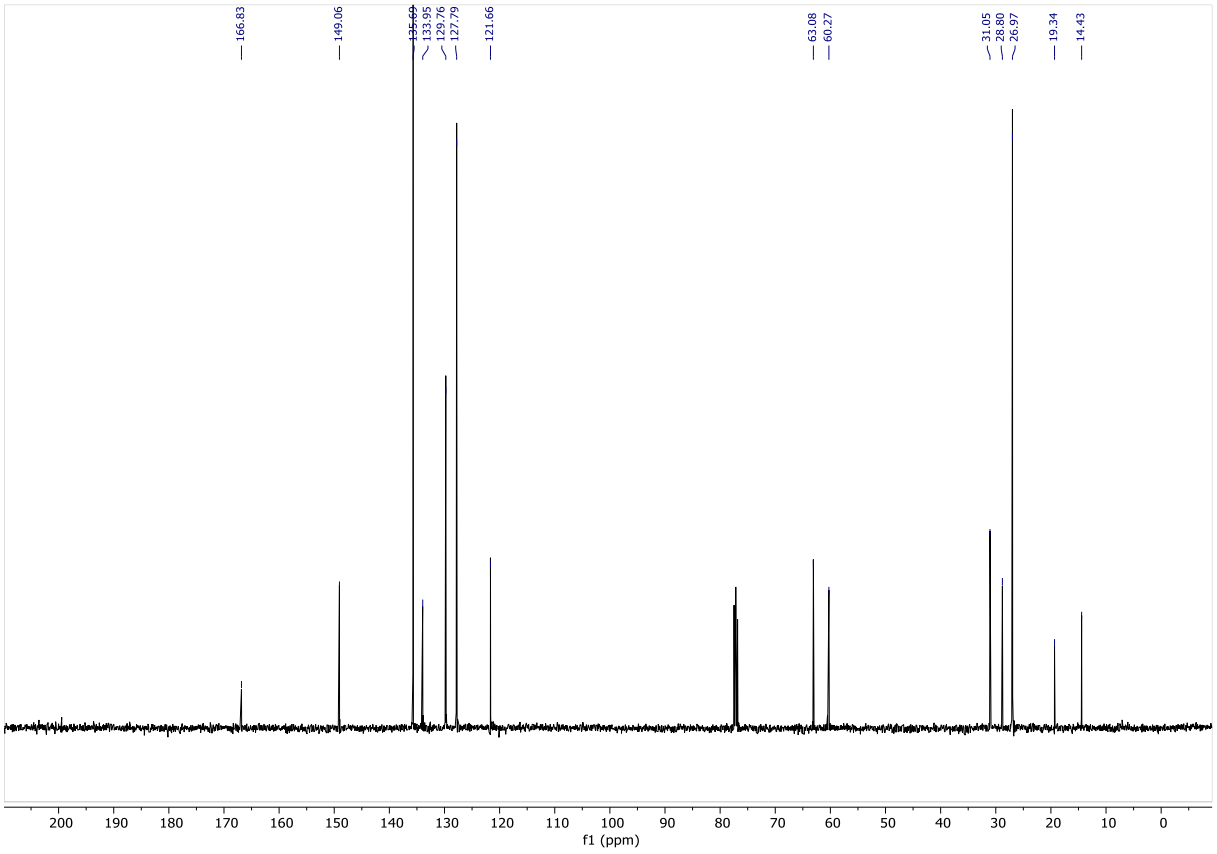
^{1}H NMR (400 MHz, Chloroform-d) δ 7.66 (dd, J = 7.8, 1.5 Hz, 4H), 7.50 – 7.29 (m, 6H), 6.97 (dt, J = 15.6, 6.9 Hz, 1H), 5.82 (d, J = 15.7 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.68 (t, J = 6.1 Hz, 2H), 2.32 (q, J = 8.2 Hz, 2H), 1.71 (dt, J = 13.4, 6.3 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.05 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-d) δ 166.8, 149.1, 135.7, 134.0, 129.8, 127.8, 121.7, 63.1, 60.3, 31.1, 28.8, 27.0, 19.3, 14.4.

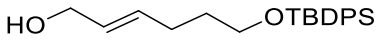
IR (film): ν = 3071, 2931, 2896, 2858, 1719, 1655, 1472, 1445, 1428, 1389, 1366, 1319, 1306, 1267, 1236, 1203, 1163, 1106, 1042, 1007, 998, 981, 939, 855, 823, 801, 740, 701, 687, 613, 505.

HRMS (ESI-TOF) m/z calcd. for $C_{24}H_{32}NaO_3Si$ $[M+Na]^+$ 419.2013, found 419.2015


7.67
7.67
7.65
7.65
7.45
7.44
7.44
7.43
7.42
7.42
7.41
7.41
7.40
7.38
7.37
7.36
7.01
6.99
6.97
6.97
6.95
6.93
5.84
5.80
4.21
4.20
4.18
4.16
3.70
3.68
3.67
2.35
2.33
2.31
2.29
1.74
1.73
1.71
1.69
1.67
1.31
1.29
1.25
1.05
3.95
5.89
0.98
0.95
2.03
2.01
1.93
2.00
3.07
9.00
f1 (ppm)


166.83
149.06
135.69
133.95
129.76
127.79
121.66
63.08
60.27
31.05
28.80
26.97
19.34
14.43
f1 (ppm)

*(E)-6-((tert-butyldiphenylsilyl)oxy)hex-2-en-1-ol (**19**)*[3][4]



In flame-dried glassware charged with a stirring bar, under an argon atmosphere, a solution of **18** (10 g, 25.214 mmol, 1.0 equiv.) was prepared in dry DCM (52 mL) at room temperature Then, a solution of DIBAL-H was slowly added (1M in hexane, 55.5 ml, 55.47 mmol, 2.2 equiv.) at -78 ˚C. The reaction mixture was stirred for 1 h. Then, diethyl ether (150 ml) and sat. Rochelle's salt (250 ml) was added at room temperature, while vigorous stirring was maintained for 1 h. The aq. The layer was extracted with diethyl ether (3 x 75 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by FC (hexane/EtAc 10/1→3/1) yielded 8.3 g (93 %) of **19** in fractions 46-120 as colorless oil.

Yield: 8.3 g (93 %);

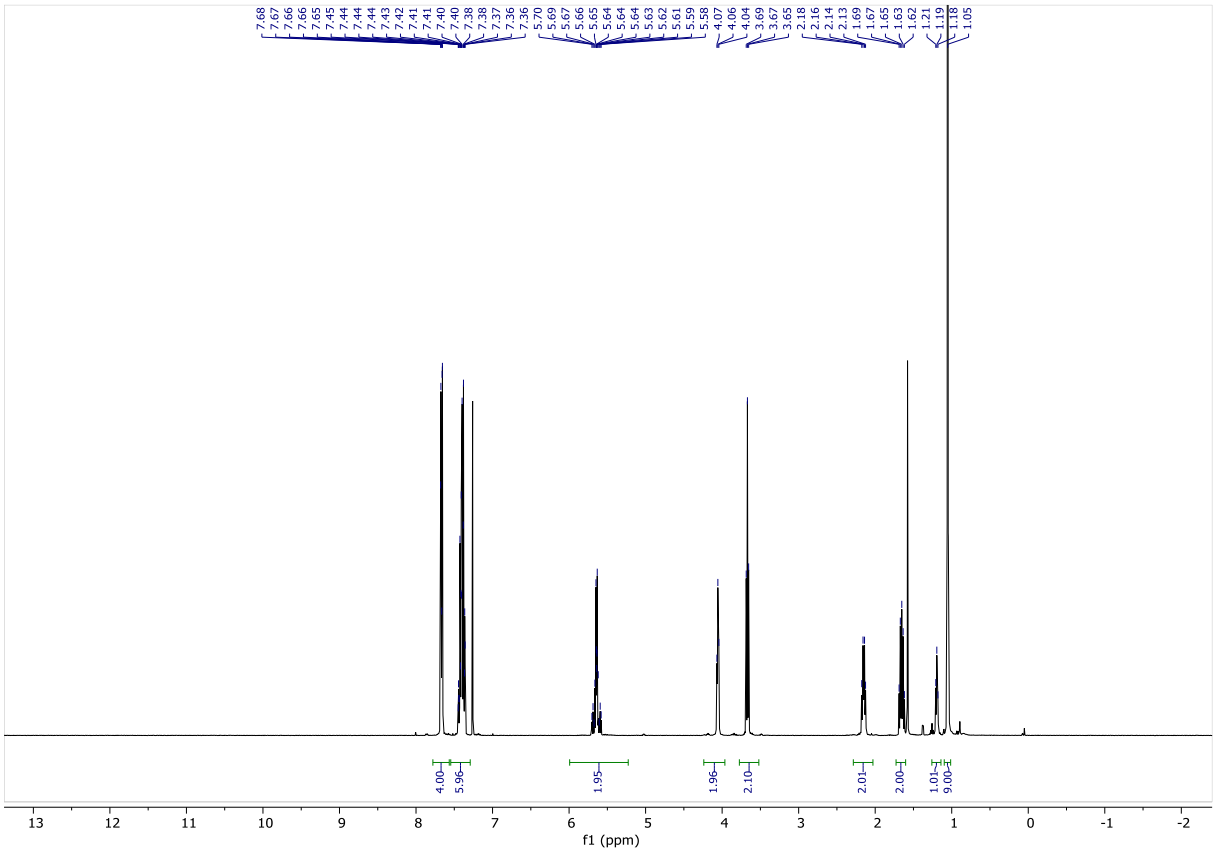
R_f = 0.515 (hexane / EtOAc = 1:1)

^{1}H NMR (400 MHz, Chloroform-d) δ 7.71 – 7.60 (m, 4H), 7.46 – 7.32 (m, 6H), 5.75 – 5.52 (m, 2H), 4.06 (t, J = 5.1 Hz, 2H), 3.67 (t, J = 6.3 Hz, 2H), 2.25 – 2.01 (m, 2H), 1.65 (dt, J = 13.5, 6.4 Hz, 2H), 1.19 (t, J = 5.6 Hz, 1H), 1.05 (s, 9H);

^{13}C NMR (101 MHz, Chloroform-d) δ 135.7, 134.2, 133.0, 129.7, 129.4, 127.8, 63.9, 63.3, 32.1, 28.6, 27.0, 19.4.

IR (film): ν = 3381, 3070, 3048, 2930, 2857, 1731, 1589, 1472, 1463, 1427, 1389, 1362, 1258, 1220, 1188, 1158, 1107, 1029, 1008, 999, 969, 939, 853, 822, 740, 700, 687, 613, 503.

HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{30}NaO_2Si$ $[M+Na]^+$ 377.1907, found 377.1908


7.68
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7.44
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7.40
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5.64
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5.63
5.62
5.61
5.59
5.58
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4.06
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3.67
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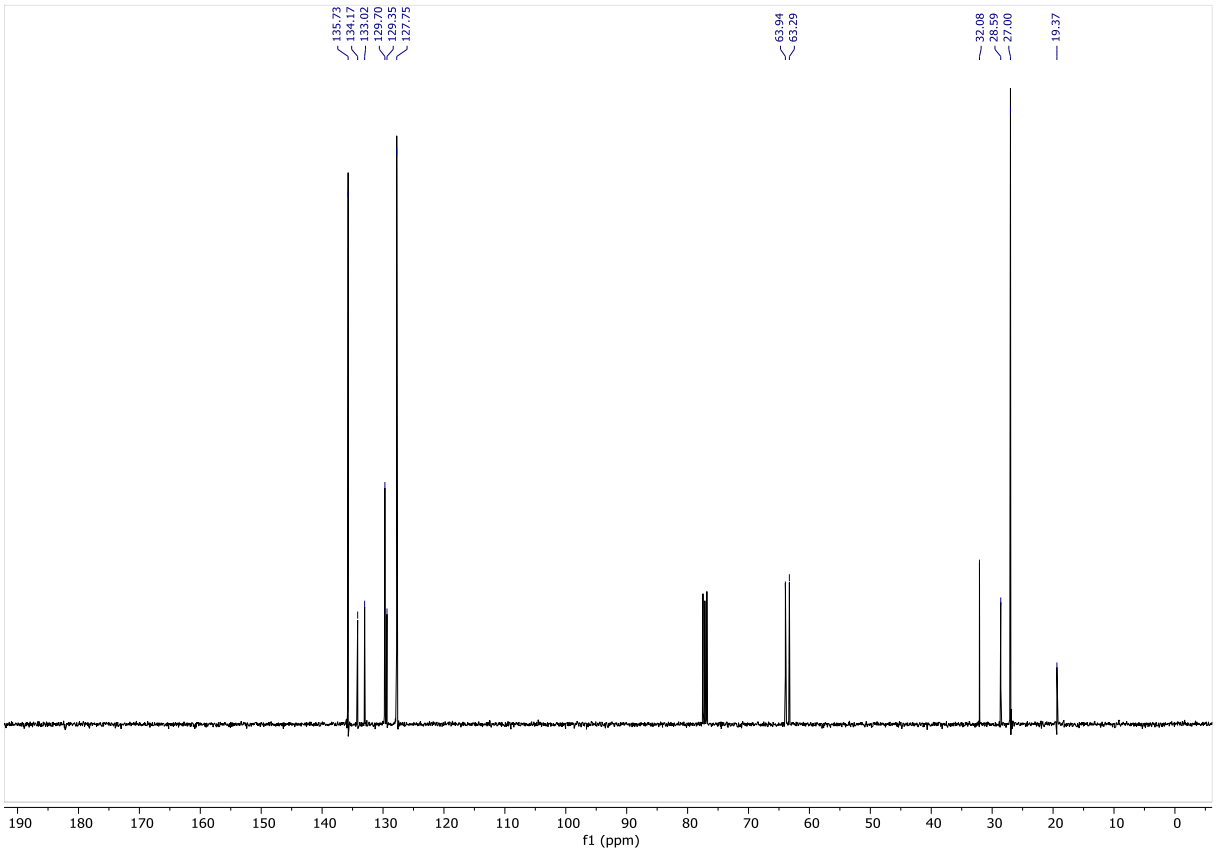
9.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)


135.73
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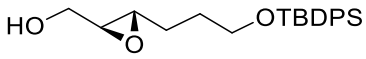
63.29
32.08
28.59
27.00
19.37
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

*(2S,3S)-3-(3-((tert-butyldiphenylsilyl)oxy)propyl)oxiran-2-yl)methanol (**20**)*[2]



Flame-dried glassware, argon atmosphere. Powder molecular sieves were preheated for 1 h (4 A mol sieves, powder 60 mg/mmol=23.4086*60 mg=1404 mg) using a Schlenk line vacuum and a heat gun (250 ˚C). In a 500 ml flask (M of the rxn flask = 190.15 g) with the preheated molecular sieves was added dry DCM (185-190 mL, from distillation), and the suspension was cooled to -20 ˚C. Once the desired temperature was achieved reagents were added in the following order:- (+)-DET (0.77 ml, 4.513 mmol, 0.2 equiv.), Ti-(IV)-isopropoxide (1.37 ml, 4.513 mmol, 0.2 equiv.) and TBHP (5.5 M in decane, 8.2ml, 45.13 mmol, 2.0 equiv.) at -20 ˚C. The reaction mixture was stirred for 30 min to form the desired confirmation of the catalyst. Then, the solution of **19** (8 g, 22.56 mmol, 1.0 equiv.) in DCM (10 ml) was added and the reaction was stirred at -20 ˚C overnight. After completion of the reaction, verified by TLC overnight, the reaction was quenched with a mixture of 30 % aq. Sol. NaOH in aq. sat. NaCl (120 ml) and the mixture was warmed to 0 ˚C, stirred for 30 min, and filtered through a pad of celite. Wash the celite carefully, and check it with TLC. The aq. layer was extracted with DCM (3x100 ml). The combined organic layers were dried over $MgSO_4$ and concentrated Mcrude=13.67 g of crude. Purification by FC 5.5 cm, 1.6 liters (hexane/EtAc 2/1) yielded 6.3g (76 %) of **20** as colorless oil in fractions 21-40.

Yield: 6.300 g (76 %) of pure + mixed fractions

R_f = 0.2647 (hexane / EtOAc = 2:3);

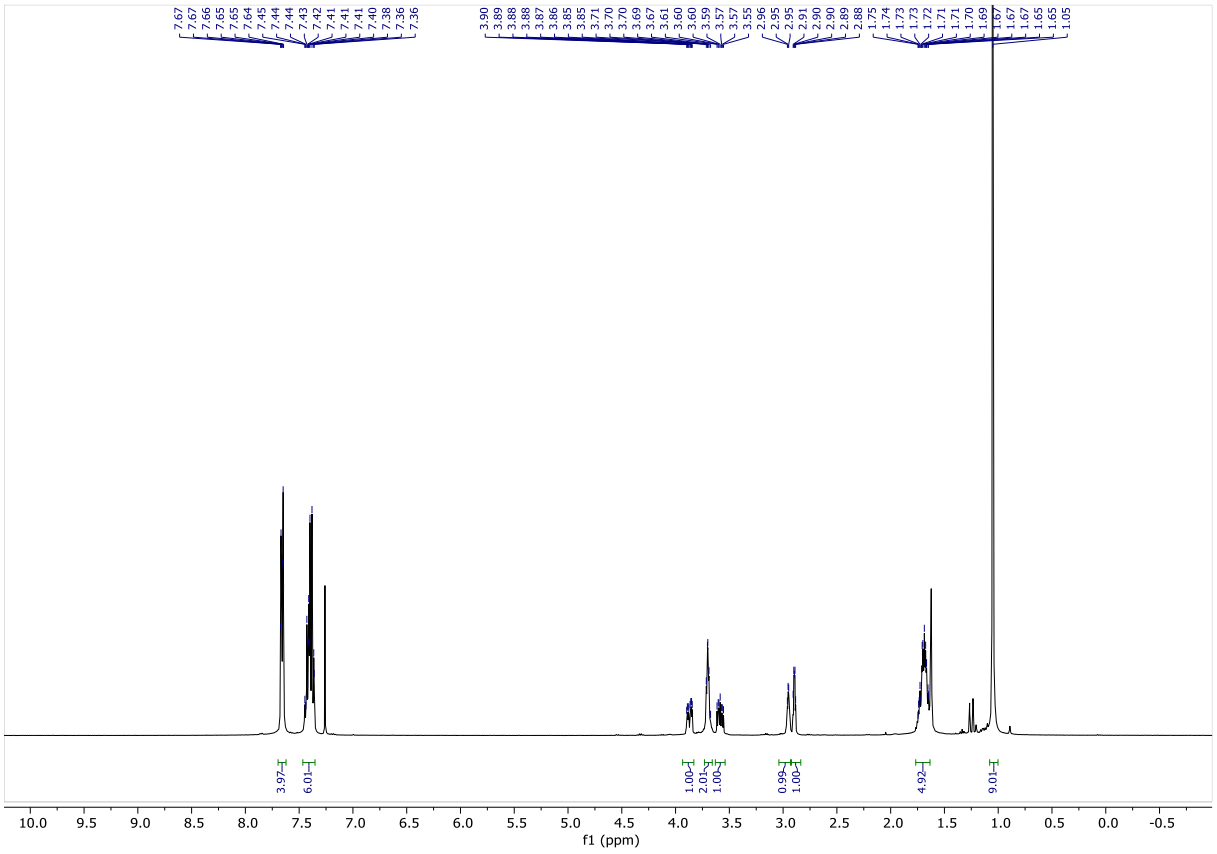
$[\alpha]_{20}^{D}$: -10 (c = 7.5 mg / 1 mL, $CHCl_3$, 20°C)

^{1}H NMR (400 MHz, Chloroform-d) δ 7.66 (dt, J = 8.0, 1.6 Hz, 4H), 7.47 – 7.33 (m, 6H), 3.87 (ddd, J = 12.5, 5.4, 2.6 Hz, 1H), 3.74 – 3.64 (m, 2H), 3.58 (ddd, J = 12.3, 7.2, 4.3 Hz, 1H), 3.01 – 2.92 (m, 1H), 2.90 (dt, J = 4.7, 2.5 Hz, 1H), 1.84 – 1.64 (m, 5H), 1.05 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-d) δ 135.7, 134.0, 129.8, 127.8, 63.4, 61.8, 58.5, 55.8, 29.0, 28.2, 27.0, 19.4.

IR (film): ν = 3418, 3071, 3050, 2930, 2857, 1744, 1472, 1428, 1389, 1362, 1259, 1194, 1107, 1029, 1008, 999, 970, 939, 890, 854, 822, 800, 740, 701, 687, 613, 504.

HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{30}NaO_3Si$ $[M+Na]^+$ 393.1856, found 393.1854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3.71
3.70
3.70
3.69
3.67
3.61
3.60
3.60
3.59
3.57
3.57
3.55
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2.91
2.90
2.90
2.89
2.88
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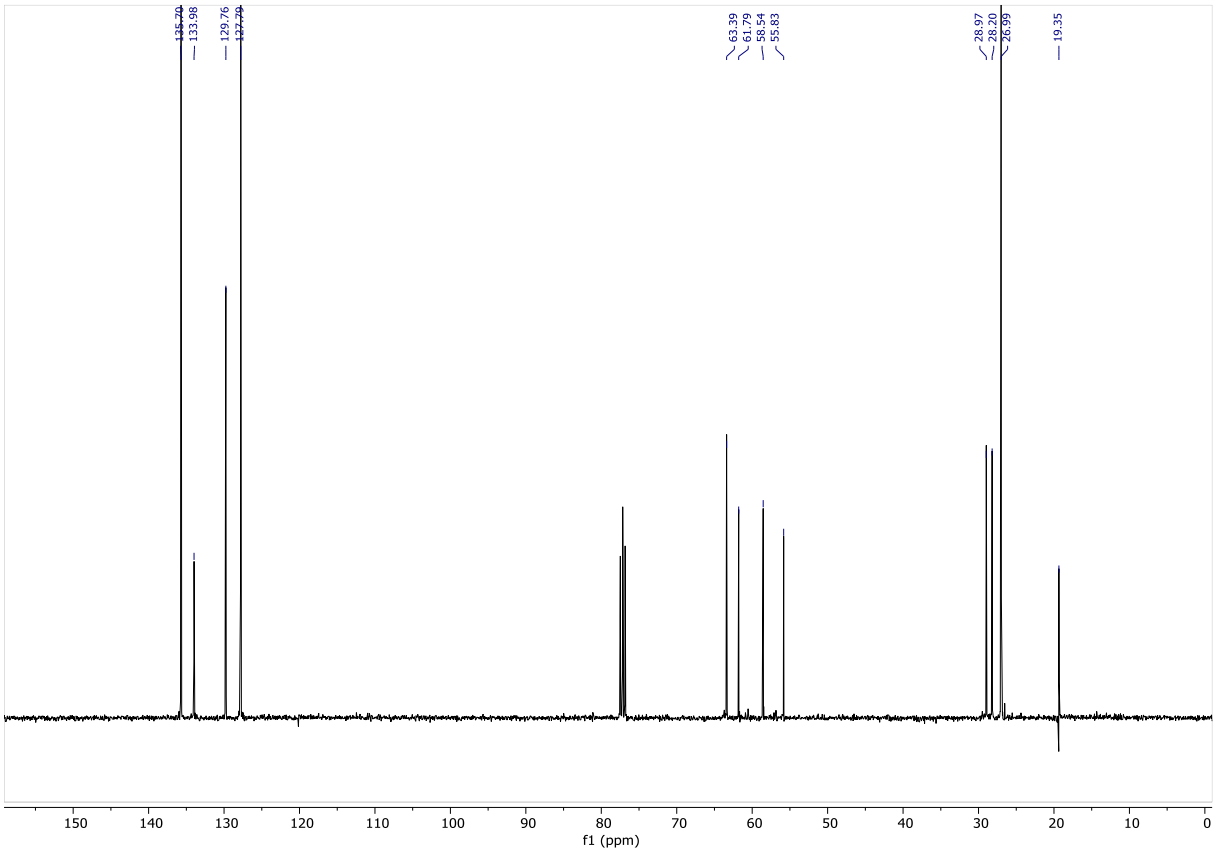
1.73
1.73
1.72
1.71
1.71
1.70
1.69
1.67
1.67
1.67
1.65
1.65
1.05
3.97
6.01
1.00
2.01
1.00
0.99
1.00
4.92
9.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


135.20
133.98
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127.79
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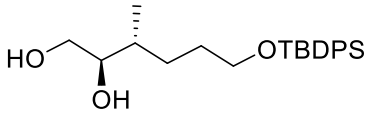
61.79
58.54
55.83
28.97
28.20
26.99
19.35
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

*(2R,3R)-6-((tert-butyldiphenylsilyl)oxy)-3-methylhexane-1,2-diol (**21**)*[5]



In a flame-dried 50 ml flask charged with a stirring bar under an argon atmosphere **20** (2.0 g, 5.397 mmol, 1.0 equiv.) was dissolved in hexane (20.0 mL) and the solution was cooled to -45 ˚C to -40 ˚C. Then, a solution of Me_3Al (2.0 M in toluene, 10 ml, 16.19 mmol, 3.0 equiv.) was added dropwise at - 40 ^{o}C. And the reaction was stirred at -40 ˚C, for 1.5 h. then warmed to -37 ˚C under TLC control. In 1 h reaction was completed, and when checked by TLC, no SM. The reaction was quenched with NH_4Cl (20 ml) by very slow dropwise addition! Be careful, gas evaluation! and then warmed to 0 ˚C using an ice bath. Later reaction mixture was filtered over a pad of celite and washed with DCM. Here, it is very important to be careful, because on a big scale, the product tends to stay on celite, so better to wash the celite with EtOAc several times and always check by TLC. Then, the aq. layer was extracted with DCM (3 x 50 ml), dried over $MgSO_4$, and concentrated under low pressure. The crude material was purified by FC (5.5 cm) (Column: 0.5 l of 10:1, 1.6 l of 5:1, 0.5 l of 4:1, 0.8 l of 3:1) yielded **21** (1.4 g, 68 %) in fractions 169-200 as a colorless oil, side product **25** (15 %) in fractions 67-97.

Yield: 1.4 g, (68 %)

R_f = 0.33 (hexane / EtOAc = 1:1)

$[\alpha]_{20}^{D}$: -4.35 (c = 4.6 mg / 1 mL, $CHCl_3$, 20°C)-of the mixture

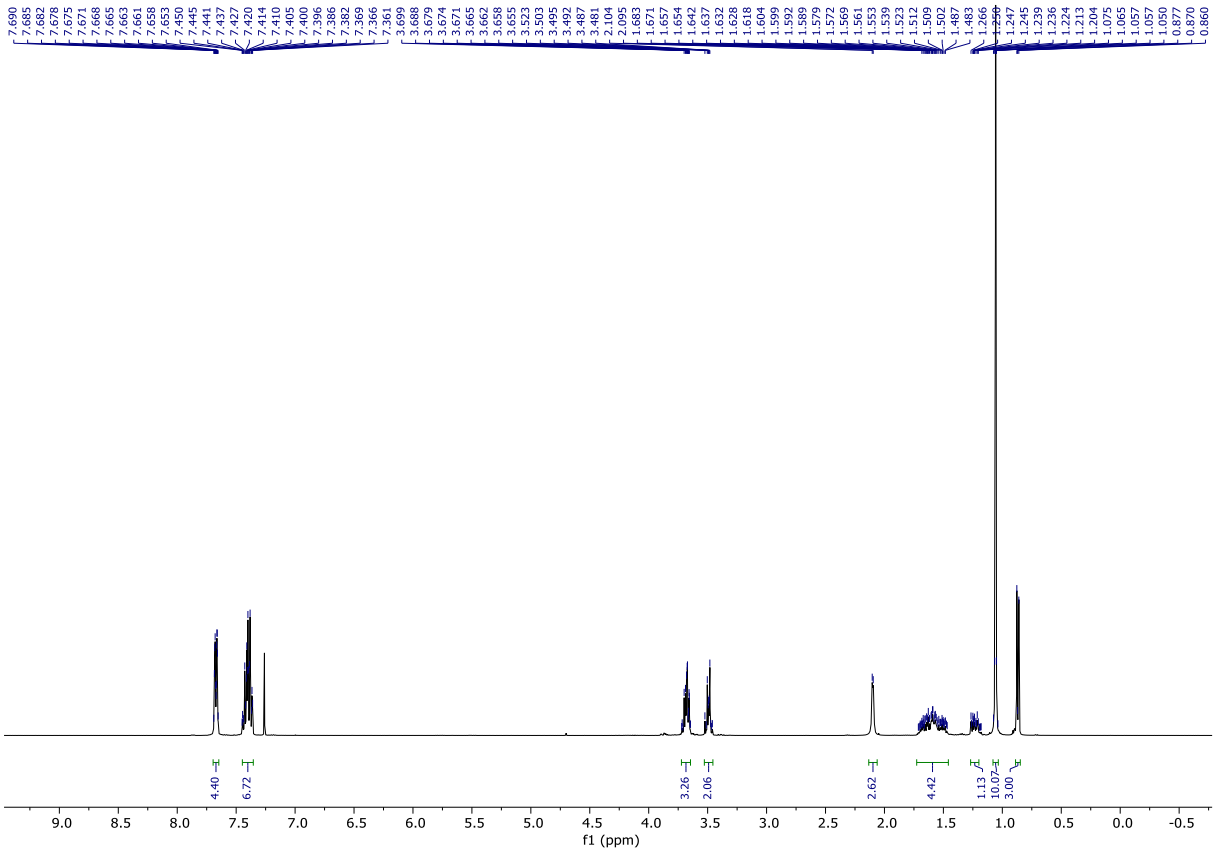
^{1}H NMR (400 MHz, Chloroform-d) δ 7.59 (dq, J = 6.3, 1.3 Hz, 4H), 7.48 – 7.24 (m, 6H), 3.79 – 3.50 (m, 3H), 3.53 – 3.31 (m, 2H), 1.88 (s, 3H), 1.74 – 1.30 (m, 4H), 0.98 (s, 9H), 0.79 (d, J = 6.8 Hz, 3H).

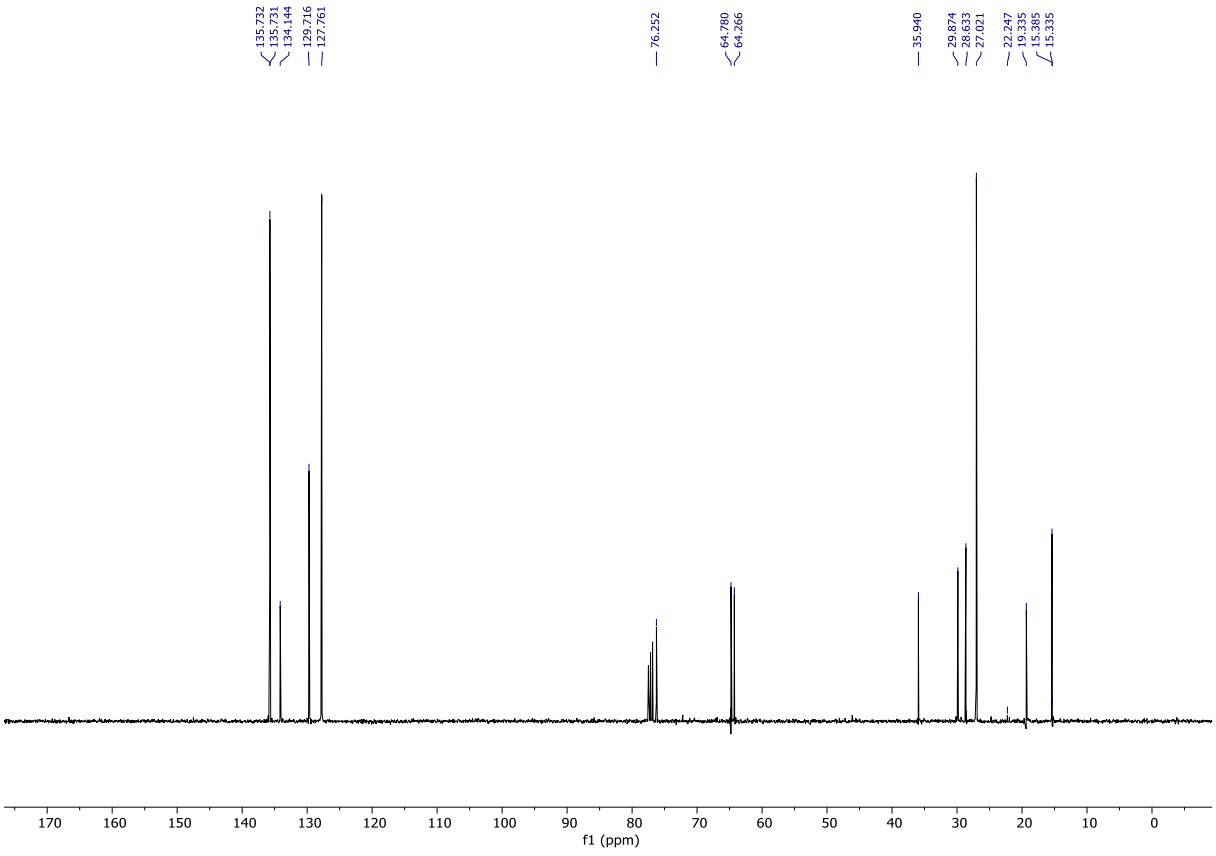
-EA inside the spectra, will be retaken in the future because when tried to do a dry NMR sample kept for future analytics, started decomposing

^{13}C NMR (101 MHz, Chloroform-d) δ 135.7, 134.1, 129.7, 127.8, 76.2, 64.8, 64.3, 35.9, 29.9, 28.6, 27.0, 19.3, 15.4.

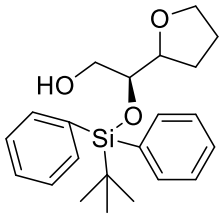
IR (film): ν = 3374, 2930, 2858, 1472, 1462, 1427, 1389, 1361, 1110, 1092, 1008, 938, 822, 795, 774, 740, 701, 688, 613, 504.

HRMS (ESI-TOF) m/z calcd. for $C_{23}H_{34}NaO_3Si$ $[M+Na]^+$ 409.2169, found 409.2168.


7.690
7.685
7.682
7.678
7.675
7.671
7.668
7.665
7.663
7.661
7.658
7.653
7.450
7.445
7.441
7.437
7.427
7.420
7.414
7.410
7.405
7.400
7.396
7.386
7.382
7.369
7.366
7.361
3.699
3.688
3.679
3.674
3.671
3.665
3.662
3.658
3.655
3.523
3.503
3.495
3.492
3.487
3.481
2.104
2.095
1.683
1.671
1.657
1.654
1.642
1.637
1.632
1.628
1.618
1.604
1.599
1.592
1.589
1.579
1.572
1.569
1.561
1.553
1.539
1.523
1.512
1.509
1.502
1.487
1.483
1.266
1.255
1.247
1.245
1.239
1.236
1.224
1.213
1.204
1.075
1.065
1.057
1.057
1.050
0.877
0.870
0.860
4.40
6.72
3.26
2.06
2.62
4.42
1.13
10.07
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


135.732
135.731
134.144
129.716
127.761
76.252
64.780
64.266
35.940
29.874
28.633
27.021
22.247
19.335
15.385
15.335
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

*(2S)-2-((tert-butyldiphenylsilyl)oxy)-2-(tetrahydrofuran-2-yl)ethan-1-ol (**25**)*



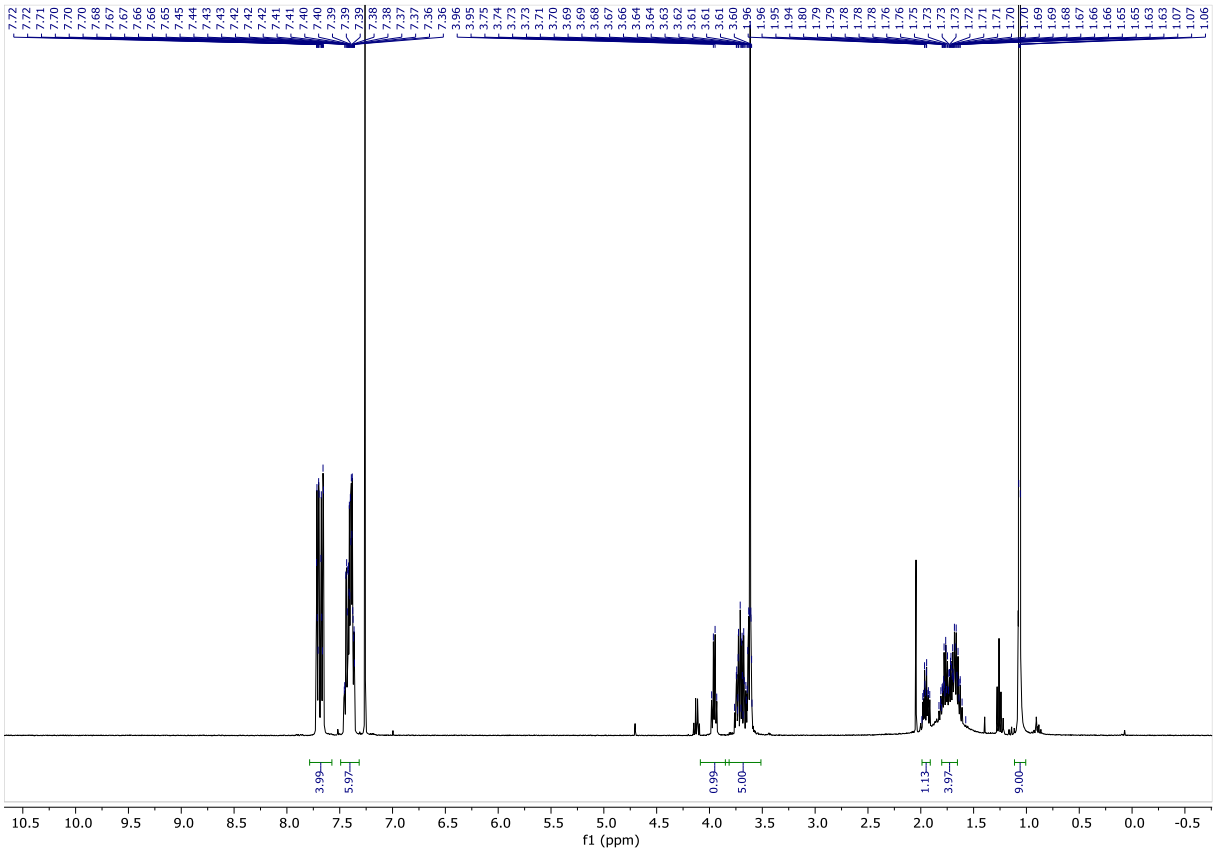
Yield: ca. 15 % in every reaction

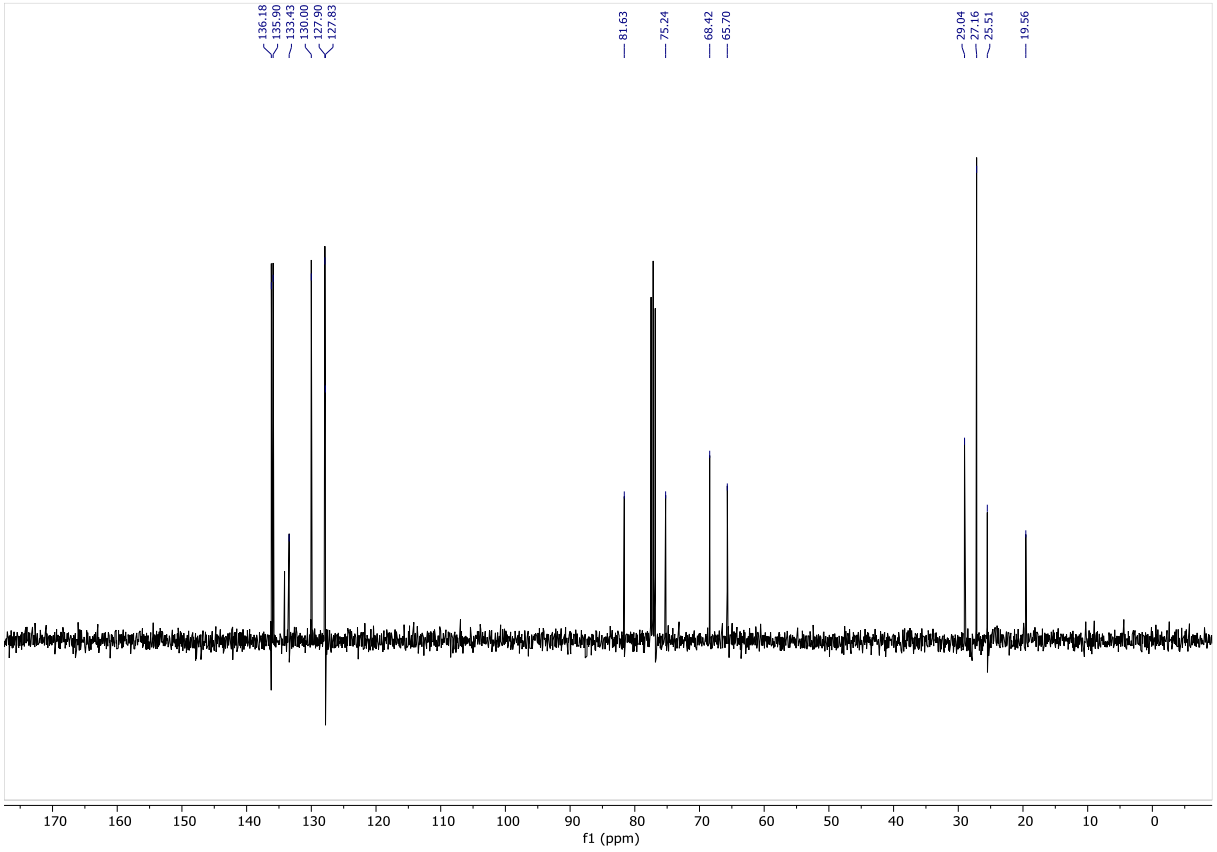
R_f = 0.4324 in 1:1 hex:EA

^{1}H NMR (400 MHz, Chloroform-d) δ 7.69 (ddt, J = 16.6, 6.6, 1.5 Hz, 4H), 7.49 – 7.34 (m, 6H), 3.96 (q, J = 6.4 Hz, 1H), 3.77 – 3.52 (m, 5H), 1.99 – 1.89 (m, 1H), 1.84 – 1.56 (m, 4H), 1.07 (s, 9H).

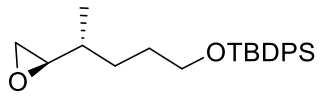
^{13}C NMR (101 MHz, Chloroform-d) δ 136.2, 135.9, 133.4, 130.0, 127.9, 127.8, 81.6, 75.2, 68.4, 65.7, 29.0, 27.2, 25.5, 19.6.

HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{30}NaO_3Si$ $[M+Na]^+$ 393.1856, found 393.1859


7.72 7.72 7.71 7.70 7.70 7.70 7.68 7.67 7.67 7.66 7.66 7.65 7.45 7.44 7.43 7.43 7.42 7.42 7.42 7.41 7.41 7.40 7.40 7.39 7.39 7.38 7.38 7.38 7.37 7.36 7.36 3.96 3.95 3.75 3.74 3.73 3.73 3.71 3.70 3.69 3.69 3.68 3.67 3.66 3.64 3.64 3.63 3.62 3.61 3.61 3.61 3.60 1.96 1.96 1.95 1.94 1.80 1.79 1.79 1.78 1.78 1.78 1.76 1.76 1.75 1.73 1.73 1.73 1.72 1.71 1.71 1.70 1.70 1.69 1.69 1.68 1.67 1.66 1.66 1.65 1.65 1.63 1.63 1.07 1.07 1.06
3.99
5.97
0.99
5.00
1.13
3.97
9.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


136.18
135.90
133.43
130.00
127.90
127.83
81.63
75.24
68.42
65.70
29.04
27.16
25.51
19.56
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

*tert-butyl(((R)-4-((R)-oxiran-2-yl)pentyl)oxy)diphenylsilane (**22**)*[5]



In a flame-dried 100 ml flask (1.1 g, 2.87 mmol, 1.0 equiv.) **21** in DCM (29 mL, c=0.1 M) were dissolved and cooled to 0 ˚C. Then, the reagents were added in the following order: Et3N (0.291 ml, 2.87 mmol, 1.0 equiv.), DMAP (35.1 mg, 0.287 mmol, 0.1 equiv.), and p-TsCl (548 mg, 2.87 mmol, 1.0 equiv.) at 0 ˚C. The reaction was stirred for 2 h. at 0 ˚C. After 3 h, comparison by TLC with the crude of **22** showed that there is still a lot of SM, so have decided to add 0.1 equiv. of each reagent again at 0 ˚C and stir it longer. After TLC, the reaction was filtered over a pad of celite, washed with DCM, and concentrated under reduced pressure. Obtained 2.290 g of crude after the second step and put it into the next step directly. The residue was dissolved in 90 ml of dry MeOH and (1.86 g, 6.35 mmol, 1.86 equiv.) of K_2CO_3 was added and the reaction was stirred for 3 h at room temperature The reaction was quenched with water (100 ml), and extracted with DCM (3 x 100 ml), then also washed with brine. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material M=4.2 g was purified by FC (3.5 cm) (hexane/EtAc 10/1-850 ml) and yielded **22** (600 mg, 57 %) in fractions 12-25 as a colorless oil.

Yield: 600 mg, (57 %)

R_f = 0.67 (hexane / EtOAc = 2:1);

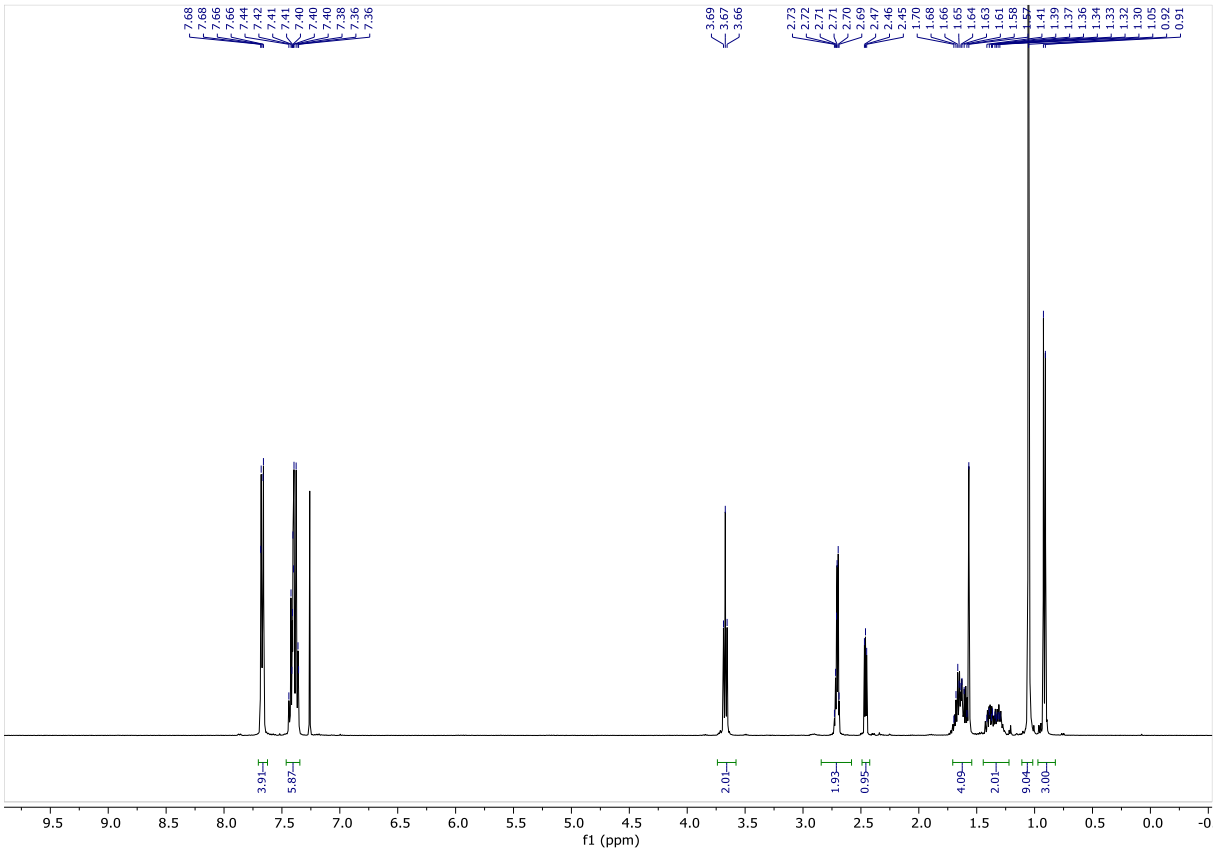
$[\alpha]\frac{D}{20}$: = +4.28 (c = 7 mg / 1 mL, $CHCl_3$, 20 ˚C)

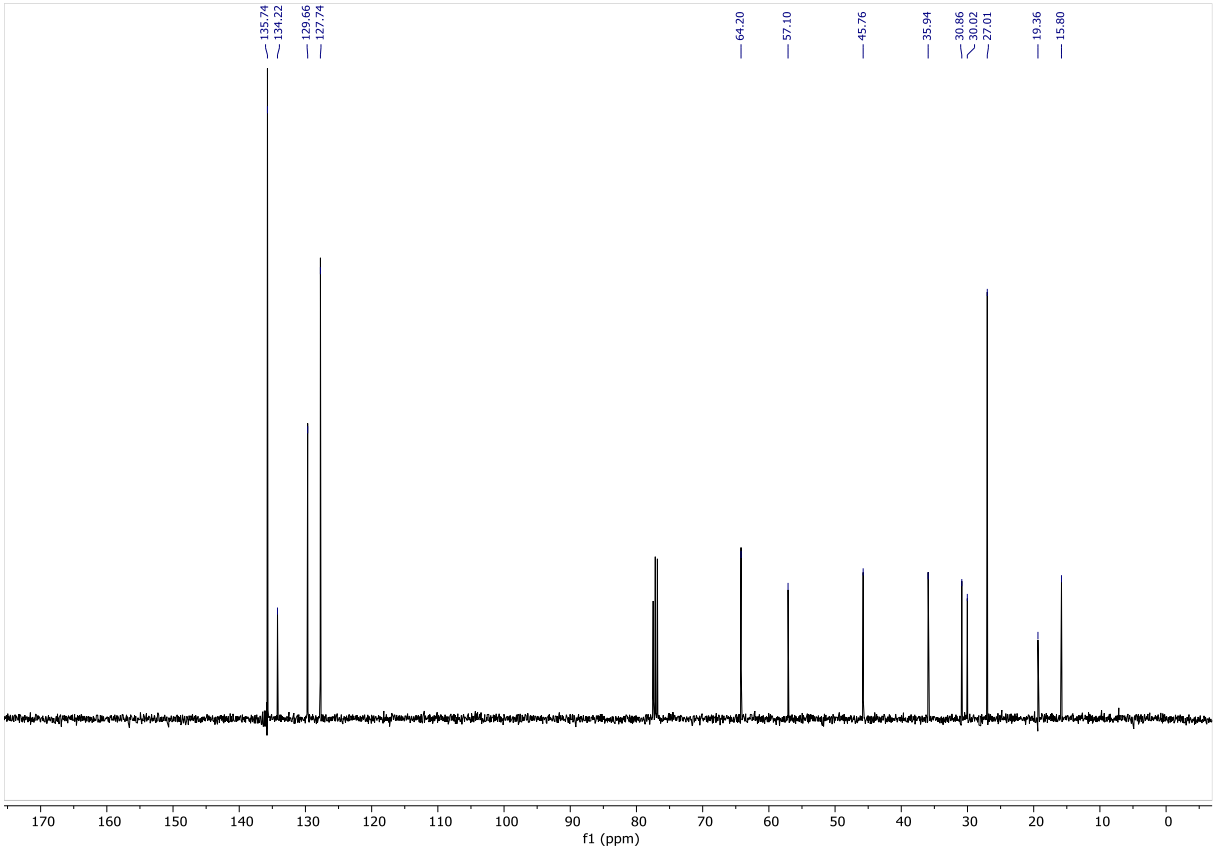
^{1}H NMR (400 MHz, Chloroform-d) δ 7.67 (dd, J = 7.8, 1.6 Hz, 4H), 7.48 – 7.29 (m, 6H), 3.67 (t, J = 6.2 Hz, 2H), 2.71 (dd, J = 5.5, 3.5 Hz, 2H), 2.58 – 2.33 (m, 1H), 1.74 – 1.49 (m, 3H), 1.46 – 1.23 (m, 2H), 1.05 (s, 9H), 0.92 (d, J = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-d) δ 135.74, 134.22, 129.66, 127.74, 64.20, 57.10, 45.76, 35.94, 30.86, 30.02, 27.01, 19.36, 15.80.

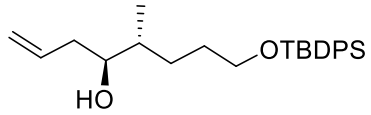
IR (film): ν = 3070, 3050, 2957, 2931, 2857, 1472, 1461, 1428, 1389, 1362, 1111, 1092, 1040, 1007, 936, 823, 774, 741, 726, 702, 688, 614, 542.

HRMS (ESI-TOF) m/z calcd. for $C_{23}H_{32}NaO_2Si$ $[M+Na]^+$ 391.2064, found 391.2064


7.68
7.68
7.66
7.66
7.44
7.42
7.41
7.41
7.40
7.40
7.40
7.38
7.36
7.36
3.69
3.67
3.66
2.73
2.72
2.71
2.71
2.70
2.69
2.47
2.46
2.45
1.70
1.68
1.66
1.65
1.64
1.63
1.61
1.58
1.57
1.41
1.39
1.37
1.36
1.34
1.33
1.32
1.30
1.05
0.92
0.91
3.91
5.87
2.01
1.93
0.95
4.09
2.01
9.04
3.00
f1 (ppm)


135.74
134.22
129.66
127.74
64.20
57.10
45.76
35.94
30.86
30.02
27.01
19.36
15.80
f1 (ppm)

*(4S,5R)-8-((tert-butyldiphenylsilyl)oxy)-5-methyloct-1-en-4-ol (**23**)*[5]



In a flame-dried 25 ml flask (196 mg, 0.972 mmol, 0.2 equiv.) CuI was dissolved in THF (1.500 mL) and cooled to -78 ˚C. Then, vinylmagnesium bromide was added (1.0 M solution, 6.4 ml, 6.32 mmol, 1.1 equiv.) at -78 ˚C. Terminal epoxide **22** (1.8 g, 4.86 mmol, 1.0 equiv.) was separately dissolved in THF (2.5 ml) and then slowly added at -78 ˚C to the reaction mixture. The solution was stirred overnight at -20 ˚C. Then, at 0 ˚C for 45 min. The next day. Brown solution. The reaction was quenched with NH_4Cl (5 ml) and extracted with Diethyl ether (3 x 10 ml). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material M=1.83 g was purified by 5.5 cm FC (hexane/EtAc 40/1) and yielded **23** (820 mg, 43 %) as colorless oil in fractions 92-137.

Yield: 820 mg (43 %)+600 mg reisolated SM, if count to reacted SM (64%)

R_f = 0.55 (hexane / EtOAc = 2:1);

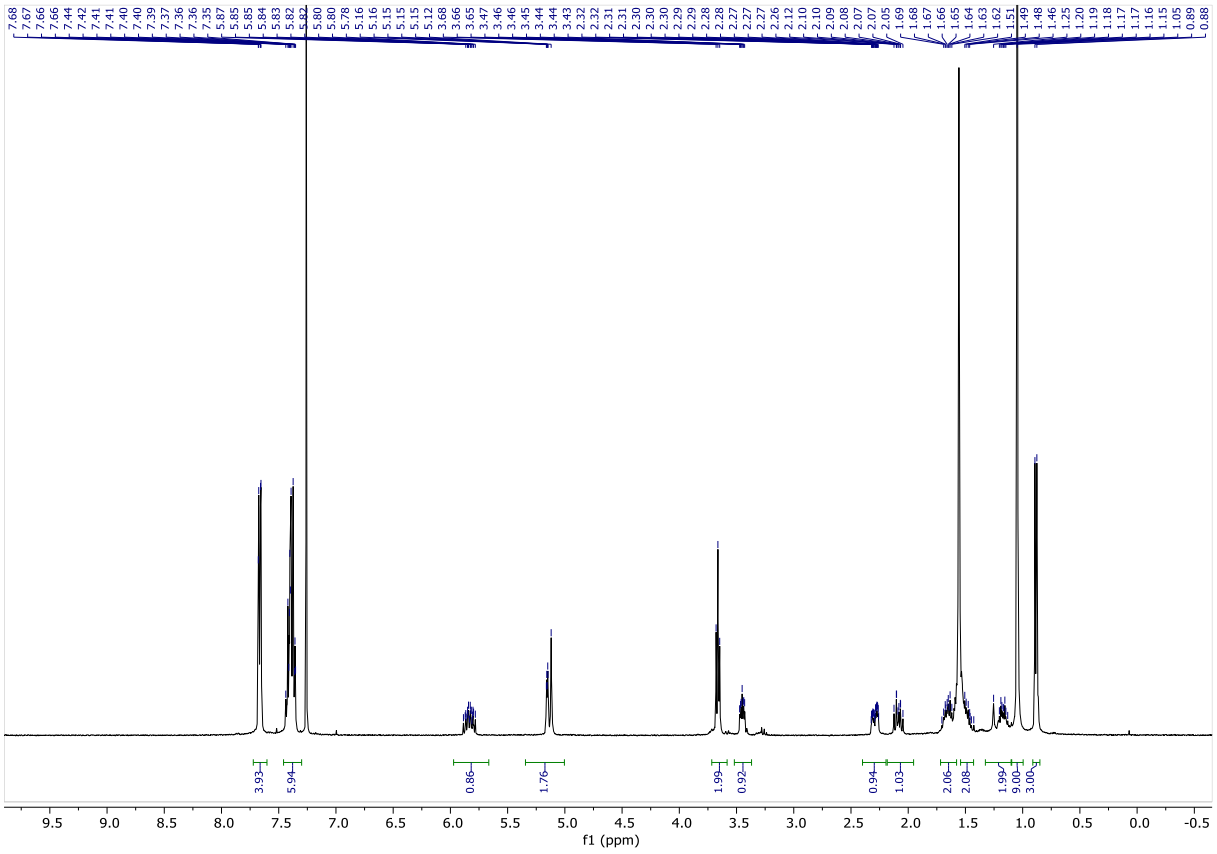
$[\alpha]_{20}^{D}$: -+7.14 (c = 7 mg / 1 mL, $CHCl_3$, 20°C)

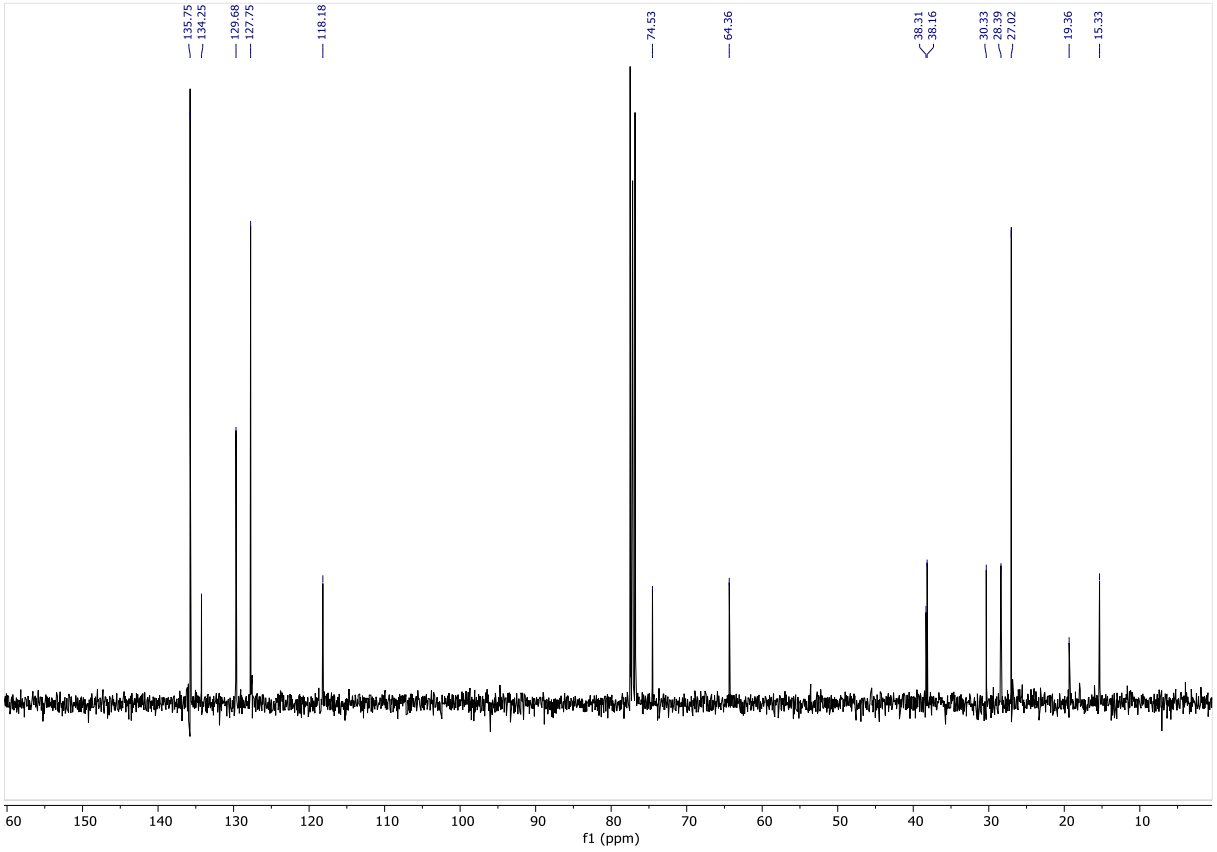
^{1}H NMR (400 MHz, Chloroform-d) δ 7.67 (dd, J = 7.7, 1.5 Hz, 4H), 7.45 – 7.33 (m, 6H), 5.93 – 5.71 (m, 1H), 5.23 – 4.97 (m, 2H), 3.66 (t, J = 6.3 Hz, 2H), 3.45 (ddd, J = 8.7, 5.2, 3.2 Hz, 1H), 2.29 (dddt, J = 14.0, 6.0, 3.0, 1.3 Hz, 1H), 2.14 – 2.03 (m, 1H), 1.72 – 1.39 (m, 4H), 1.31 – 1.10 (m, 2H), 1.05 (s, 9H), 0.88 (d, J = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-d) δ 135.8, 134.3, 129.7, 127.8, 118.2, 74.5, 64.4, 38.3, 38.2, 30.3, 28.4, 27.0, 19.4, 15.3.

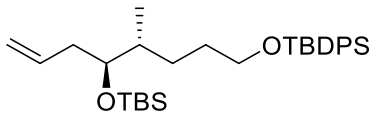
IR (film): ν = 3442, 3071, 3052, 2998, 2956, 2931, 2895, 2858, 1640, 1589, 1472, 1462, 1428, 1389, 1362, 1261, 1217, 1189, 1110, 1093, 1029, 1007, 998, 937, 915, 823, 798, 758, 741, 701, 687, 613, 504.

HRMS (ESI-TOF) m/z calcd. for $C_{25}H_{36}NaO_2Si$ $[M+Na]^+$ 419.2377, found 419.2374


f1 (ppm)


135.75
134.25
129.68
127.75
118.18
74.53
64.36
38.31
38.16
30.33
28.39
27.02
19.36
15.33
f1 (ppm)

*(5S,6R)-5-allyl-2,2,3,3,6,12,12-heptamethyl-11,11-diphenyl-4,10-dioxa-3,11-disilatridecane (**7**)*



In a flame-dried glassware with a stirring bar under an Ar atmosphere, a solution of **23** (800 mg, 2.02 mmol, 1.0 equiv.) in DMF (20 ml) was prepared at the room temperature Then, imidazole (412 mg, 6.051 mmol, 3.0 equiv.) and TBSCl (426 mg, 2.824 mmol, 1.4 equiv.) were added at room temperature and the reaction was stirred at room temperature overnight. The next day, the reaction was quenched with brine (20 ml) and extracted with EtOAc (3 x 50 ml). The combined organic layers were washed with water (20 ml), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by FC=4.5 cm(hexane/EtOAc 20/1) obtaining **7** (940 mg, 91 %) in fractions 6-17 as a colorless oil.

Yield: 940 mg, (91 %)

R_f = 0.68 (hexane / EtOAc = 4:1);

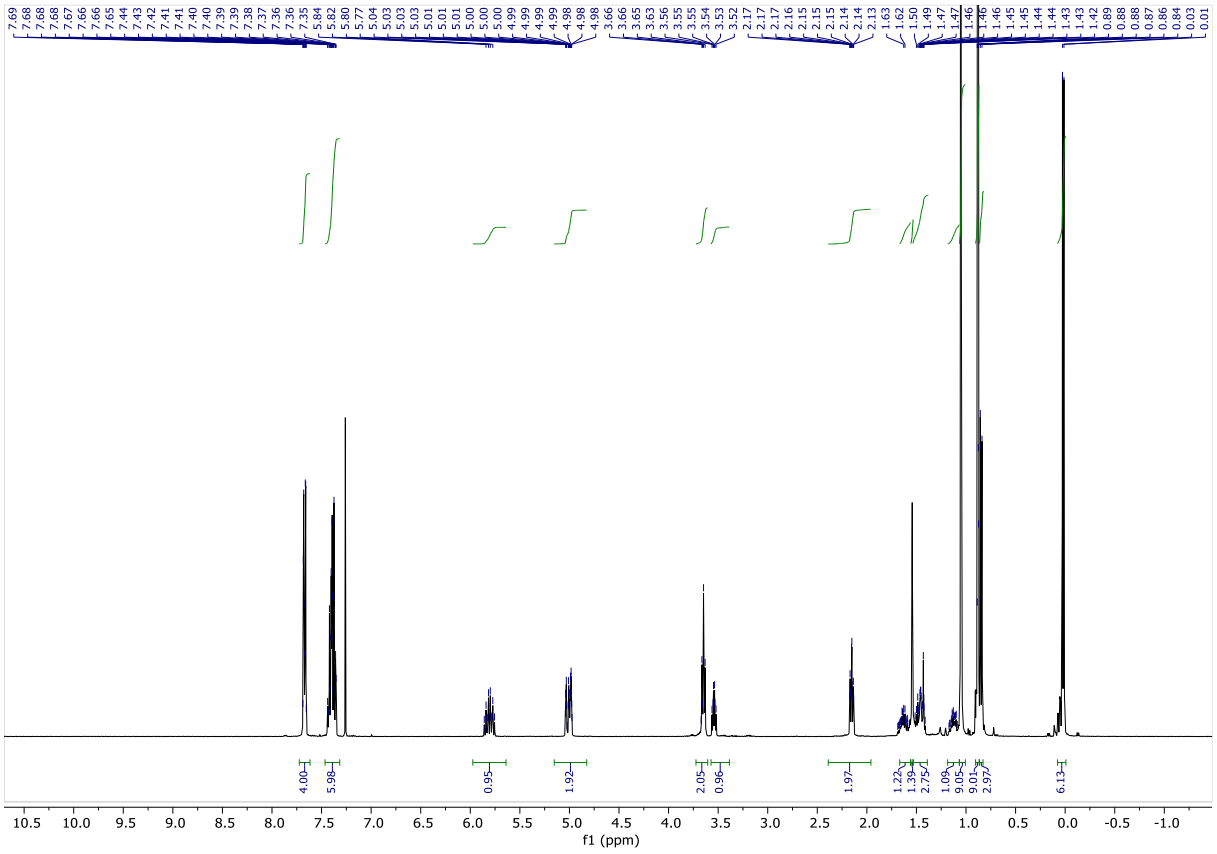
$[\alpha]_{20}^{D}$: + 5.0 (c = 10 mg / 1 mL, $CHCl_3$, 20°C)

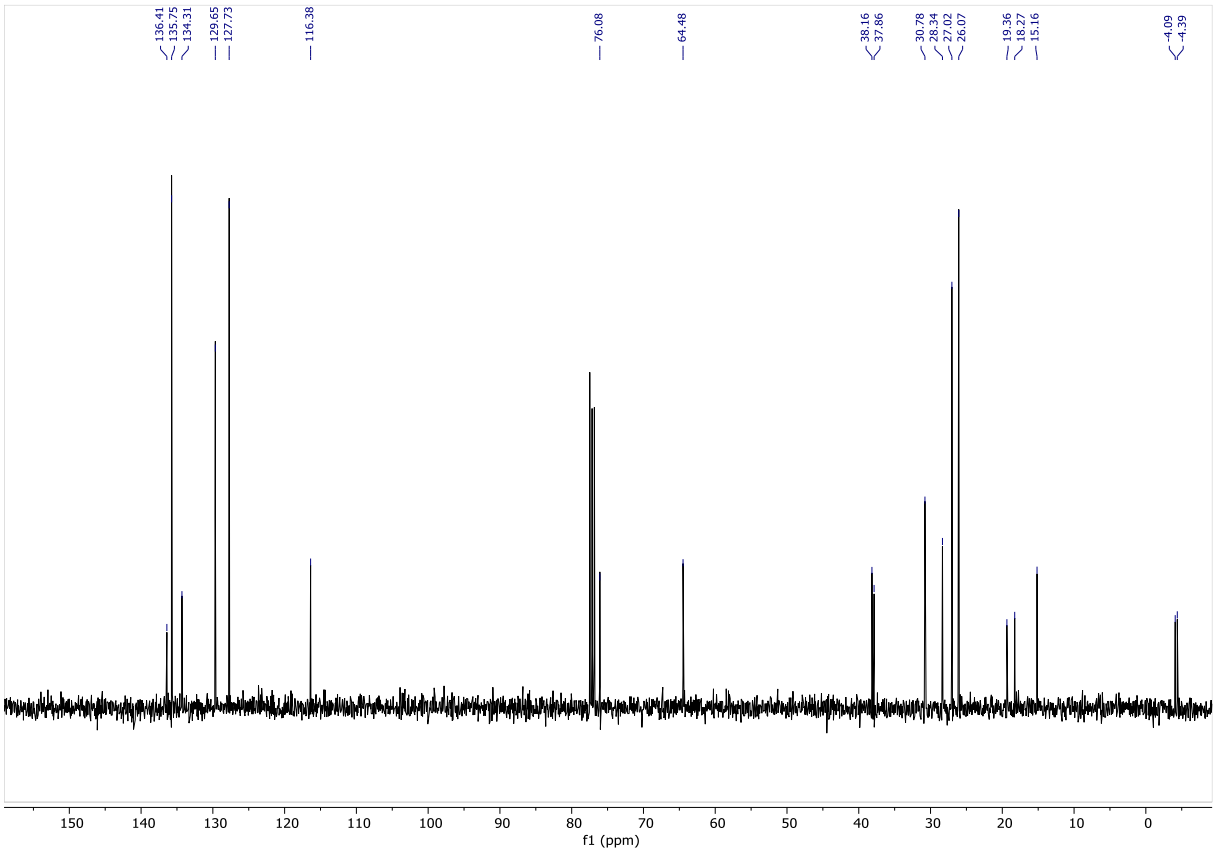
^{1}H NMR (400 MHz, Chloroform-d) δ 7.73 – 7.60 (m, 4H), 7.47 – 7.31 (m, 6H), 5.81 (ddt, J = 17.3, 10.2, 7.1 Hz, 1H), 5.10 – 4.78 (m, 2H), 3.65 (t, J = 6.4 Hz, 2H), 3.54 (td, J = 5.9, 4.3 Hz, 1H), 2.15 (ddt, J = 7.2, 5.9, 1.3 Hz, 2H), 1.71 – 1.58 (m, 1H), 1.54 (s, 1H), 1.52 – 1.35 (m, 3H), 1.13 (dddd, J = 11.6, 7.1, 4.7, 2.4 Hz, 1H), 1.05 (s, 9H), 0.88 (s, 9H), 0.85 (d, J = 6.8 Hz, 3H), 0.02 (d, J = 6.0 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-d) δ 136.4, 135.8, 134.3, 129.7, 127.7, 116.4, 76.1, 64.5, 38.2, 37.9, 30.8, 28.3, 27.0, 26.1, 19.4, 18.4, 15.2, -4.1, -4.4.

IR (film): ν = 3072, 2956, 2930, 2895, 2857, 2014, 1472, 1462, 1428, 1389, 1362, 1254, 1111, 1092, 1006, 939, 911, 836, 806, 774, 740, 701, 687, 614, 560.

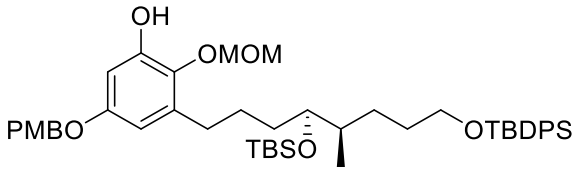
HRMS (ESI-TOF) m/z calcd. for $C_{31}H_{50}NaO_2Si_2$ $[M+Na]^+$ 533.3242, found 533.3239


f1 (ppm)


f1 (ppm)

5.2.3 Suzuki between 5 and 7

*3-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-((tert-butyldiphenylsilyl)oxy)-5-methyl octyl)-5-((4-methoxybenzyl)oxy)-2-(methoxymethoxy)phenol (**32**)*



All solvents were degassed for 30 min with argon, 8:09-8:40. In a heatgun heated 10 ml flask, dried under high vacuum overnight, a solution of **7** (0.586 g, 1.147 mmol, 0.985 equiv.) in THF (2.00 ml) was prepared. Then, 9-BBN (0.500 M in THF, 3.890 ml, 1.945 mmol, 1.67 equiv.) was added and the mixture was stirred for 5 hours at room temperature Then, K_2CO_3 (322 mg, 2.329 mmol, 2.00 equiv.) and water (2.00 ml) were added to the mixture and stirred for 30 min (solution A). In a separate dry flask, **5** (430 mg, 1.165 mmol, 1.00 equiv.) and $Pd(dppf)_2Cl_2$*DCM (190 mg, 0.233 mmol, 0.20 equiv.) were dissolved THF (1.50 ml) and stirred for 5 min to give an orange suspension (solution B). Solution A was then added at room temperature to solution B (3.00 ml THF for washing). The reaction mixture was put into the microwave and stirred at 105 °C for 90 min. The reaction was quenched with water and extracted with DCM (3 x). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material (m=870 ml) was purified by FC 3 cm (hexane/EtOAc 50/1 to 20/1) affording **32** as a slightly yellow oil in fractions 114-157 (5% impurity)-500 mg +mixed fractions 158-173 (+20 % impurity)-230 mg if subtracting impurity 659 mg of **32**. Unreacted linear starting material came out in fractions 22-28: 151.7 mg. Slightly starts to decompose over time, and should be kept in the freezer. Additionally, ca. 16 % of 5-((4-methoxybenzyl)oxy)-2-(methoxymethoxy)phenol (**56**) was isolated.

Yield: 659 mg (71 %);

R_f = 0.707 (3:1 ea: hex), CPS staining;

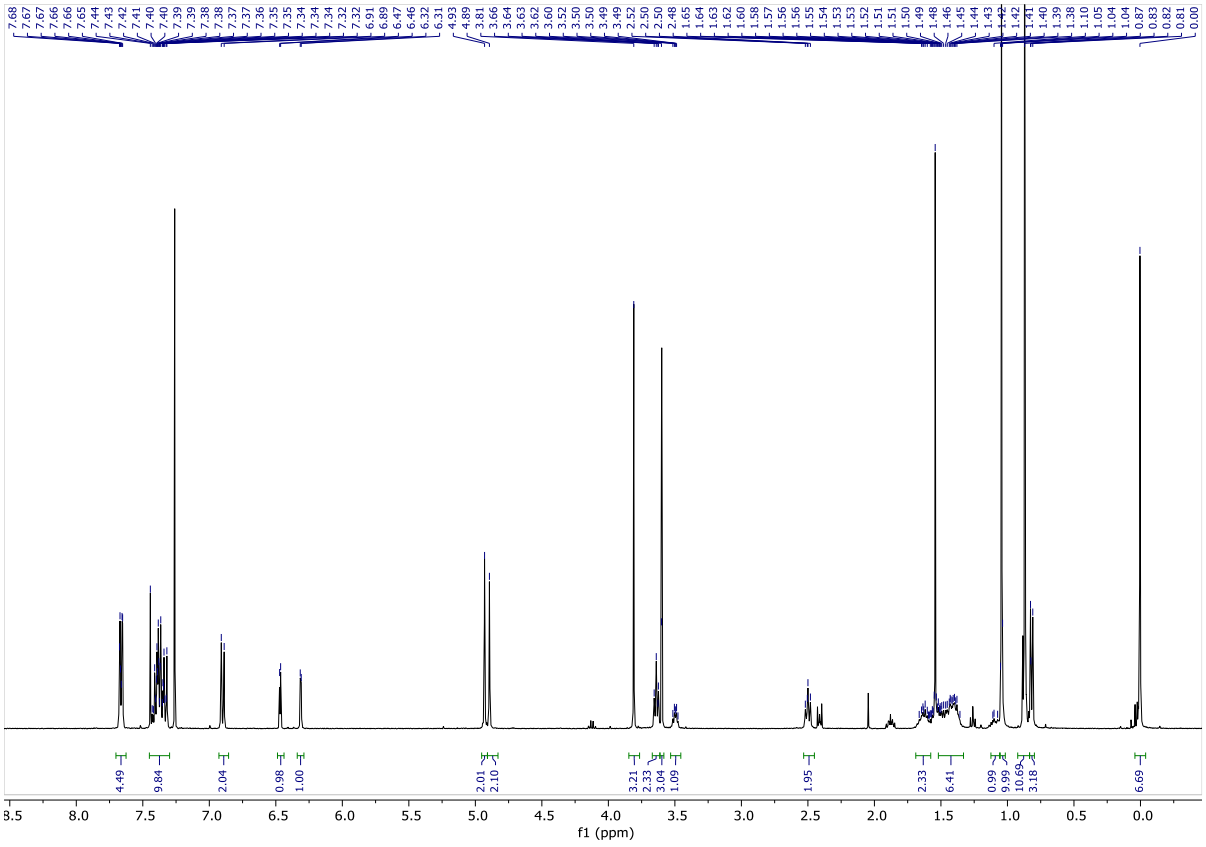
$[\alpha]_{20}^{D}$: + 2.0 (c = 10 mg / 1 mL, $CHCl_3$, 20°C)

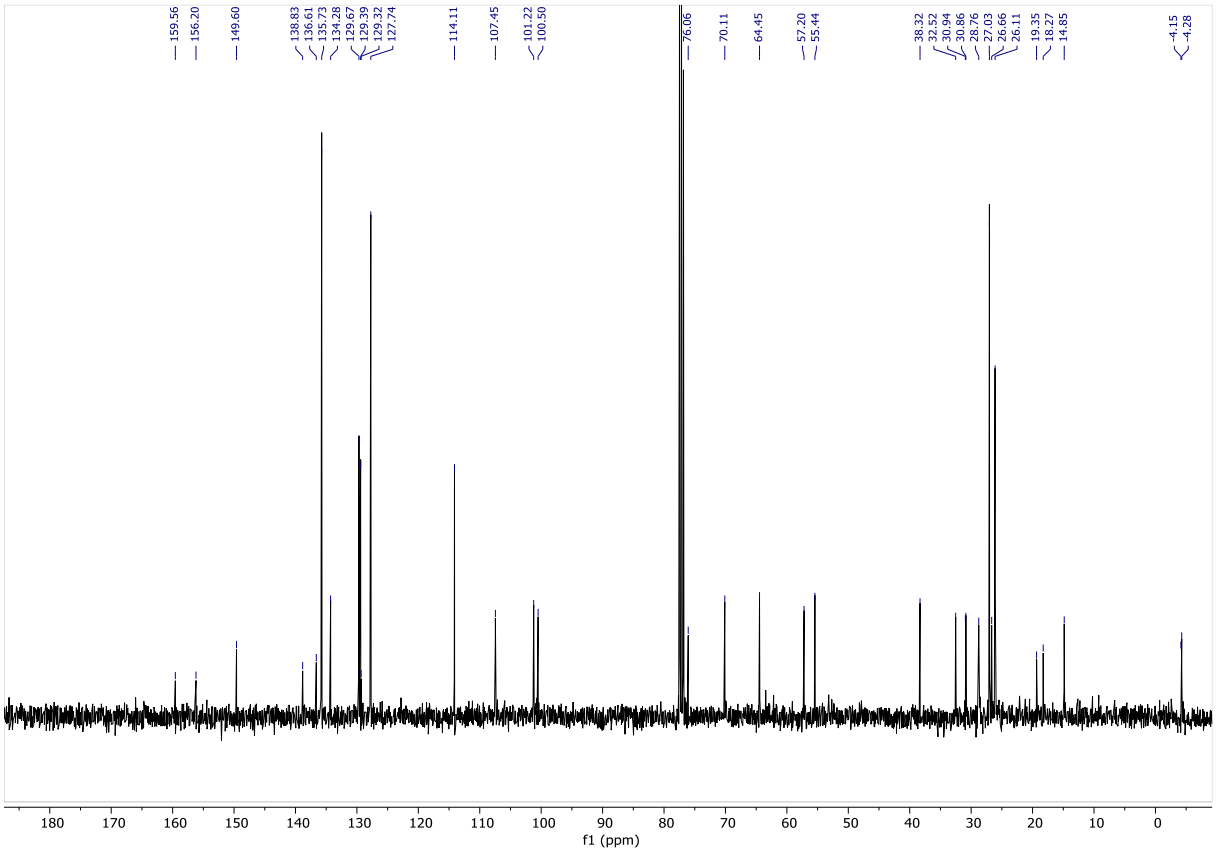
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 – 7.61 (m, 4H), 7.49 – 7.29 (m, 9H), 6.90 (d, J = 8.6 Hz, 2H), 6.47 (d, J = 3.0 Hz, 1H), 6.31 (d, J = 3.0 Hz, 1H), 4.93 (s, 2H), 4.89 (s, 2H), 3.81 (s, 3H), 3.64 (t, J = 6.4 Hz, 2H), 3.60 (s, 3H), 3.50 (dt, J = 6.5, 4.4 Hz, 1H), 2.50 (dd, J = 8.6, 6.7 Hz, 2H), 1.70 – 1.31 (m, 8H), 1.12-1.06 (m, 1H), 1.04 (s, 9H), 0.87 (s, 9H), 0.82 (d, J = 6.8 Hz, 3H), 0.00 (s, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.6, 156.2, 149.6, 138.8, 136.6, 135.7 (4C), 134.3 (2C), 129.7 (2C), 129.4 (2C), 129.3, 127.7 (4C), 114.1 (2C), 107.5, 101.2, 100.5, 76.1, 70.1, 64.5, 57.2, 55.4, 38.3, 32.5, 30.9, 30.9, 28.8, 27.0 (3C), 26.7, 26.1 (3C), 19.4, 18.3, 14.9, -4.3, -4.2;

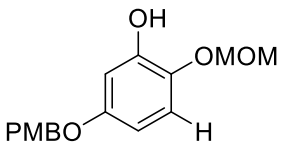
IR (film): ν = 2953, 2930, 2894, 2857, 1615, 1591, 1515, 1496, 1471, 1462, 1428, 1387, 1361, 1340, 1303, 1250, 1173, 1146, 1111, 1087, 1066, 1036, 1006, 939, 835, 824, 774, 741, 703, 687, 669, 614, 504, 491, 482.

HRMS (ESI-TOF) m/z (ESI) $C_{47}H_{72}NO_7Si_2$ $[M+NH_4]^+$ 818.4842, found 818.4841.




159.56
156.20
149.60
138.83
136.61
135.73
134.28
129.67
129.39
129.32
127.74
114.11
107.45
101.22
100.50
76.06
70.11
64.45
57.20
55.44
38.32
32.52
30.94
30.86
28.76
27.03
26.66
26.11
19.35
18.27
14.85
-4.15
-4.28
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

*5-((4-methoxybenzyl)oxy)-2-(methoxymethoxy)phenol (**56**)*

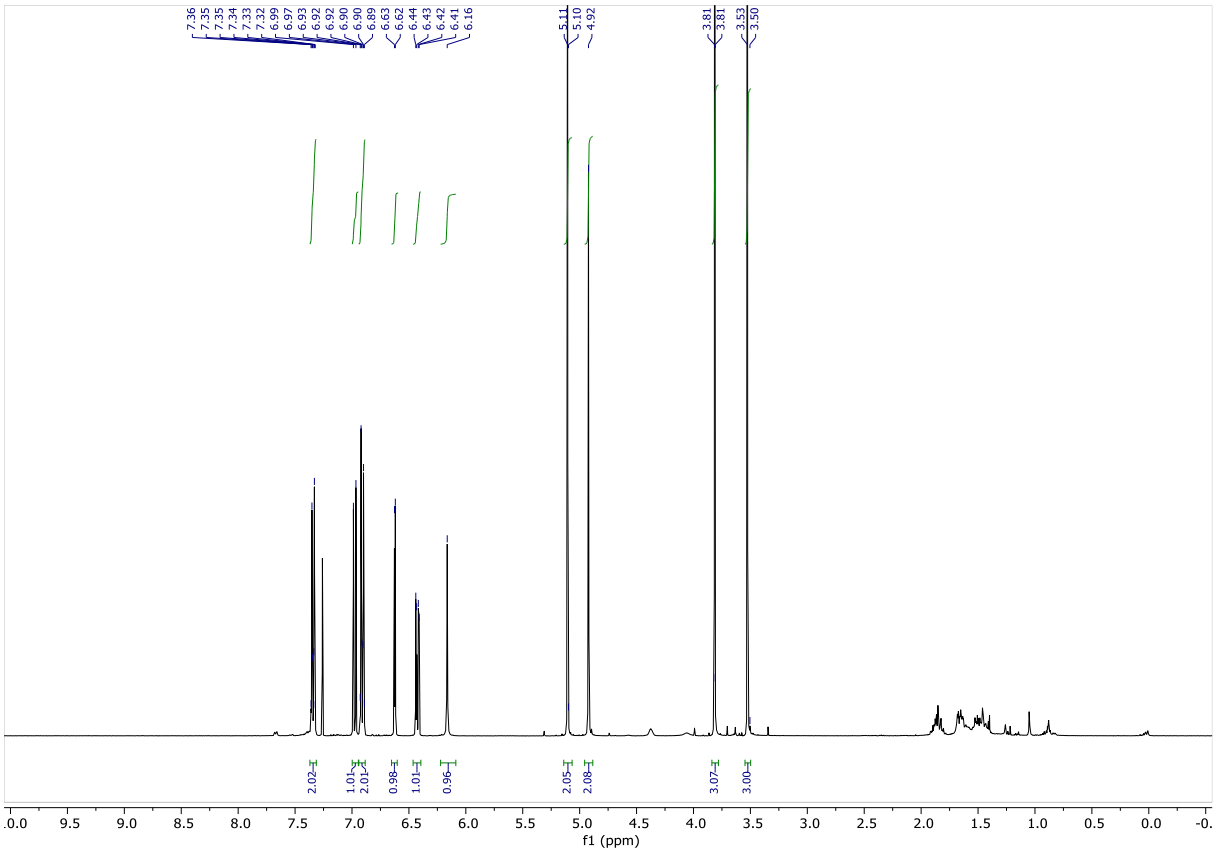


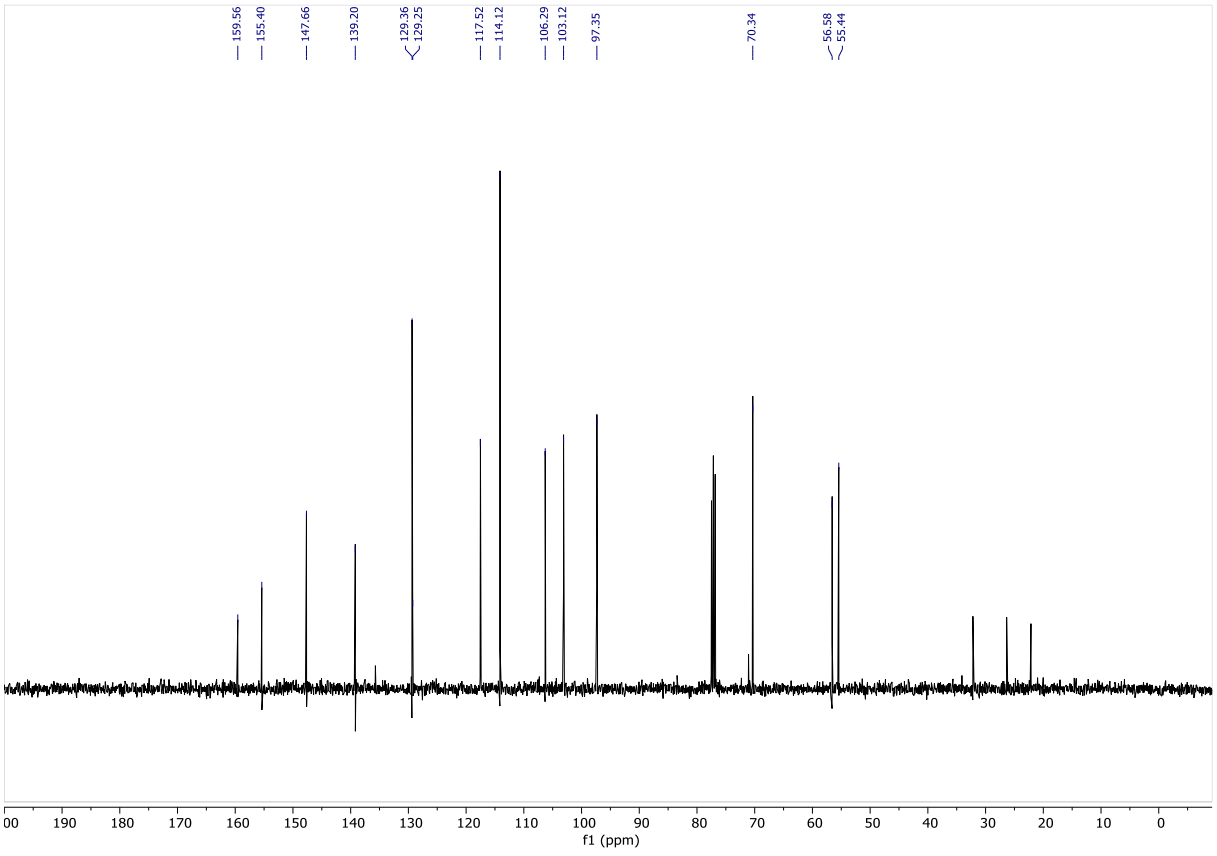
^{1}H NMR (400 MHz, Chloroform-d) δ 7.40 – 7.30 (m, 2H), 6.98 (d, J = 8.9 Hz, 1H), 6.94 – 6.85 (m, 2H), 6.62 (d, J = 2.9 Hz, 1H), 6.42 (dd, J = 8.8, 3.0 Hz, 1H), 6.16 (s, 1H), 5.11 (s, 1H), 4.92 (s, 2H), 3.81 (s, 3H), 3.53 (s, 2H).

^{13}C NMR (101 MHz, Chloroform-d) δ 159.56, 155.40, 147.66, 139.20, 129.36, 129.25, 117.52, 114.12, 106.29, 103.12, 97.35, 70.34, 56.58, 55.44.

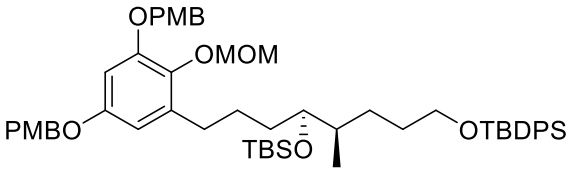
IR (film): v = 3383, 2932, 1612, 1598, 1506, 1463, 1442, 1379, 1302, 1243, 1149, 1110, 1077, 922, 895, 822, 759, 729, 706.

HRMS (ESI): m/z calcd for C16H18NaO5 M+Na 313.1046, found 313.1043.




159.56
155.40
147.66
139.20
129.36
129.25
117.52
114.12
106.29
103.12
97.35
70.34
56.58
55.44
f1 (ppm)

*(5S,6R)-5-(3-(3,5-bis((4-methoxybenzyl)oxy)-2-(methoxymethoxy)phenyl)propyl)-2,2,3,3,6,12,12-heptamethyl-11,11-diphenyl-4,10-dioxa-3,11-disilatridecane (**3**)*



To a solution of **32** (10 mg, 1.0 equiv.) in DMF (0.2 ml) was added K_2CO_3 (4.1 mg, 1.50 equiv.). The reaction mixture was stirred at room temperature for 30 min. Then, PMBCl (3 mkl, 1.1 equiv.) was added at room temperature and the reaction was stirred at this temperature for 15 h. The reaction was quenched with water and extracted with DCM (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude material was purified by FC (hexane/EtOAc 5/1) obtaining **3** (5 mg, 84 %) as colorless oil.

Yield: 9 mg (84 %);

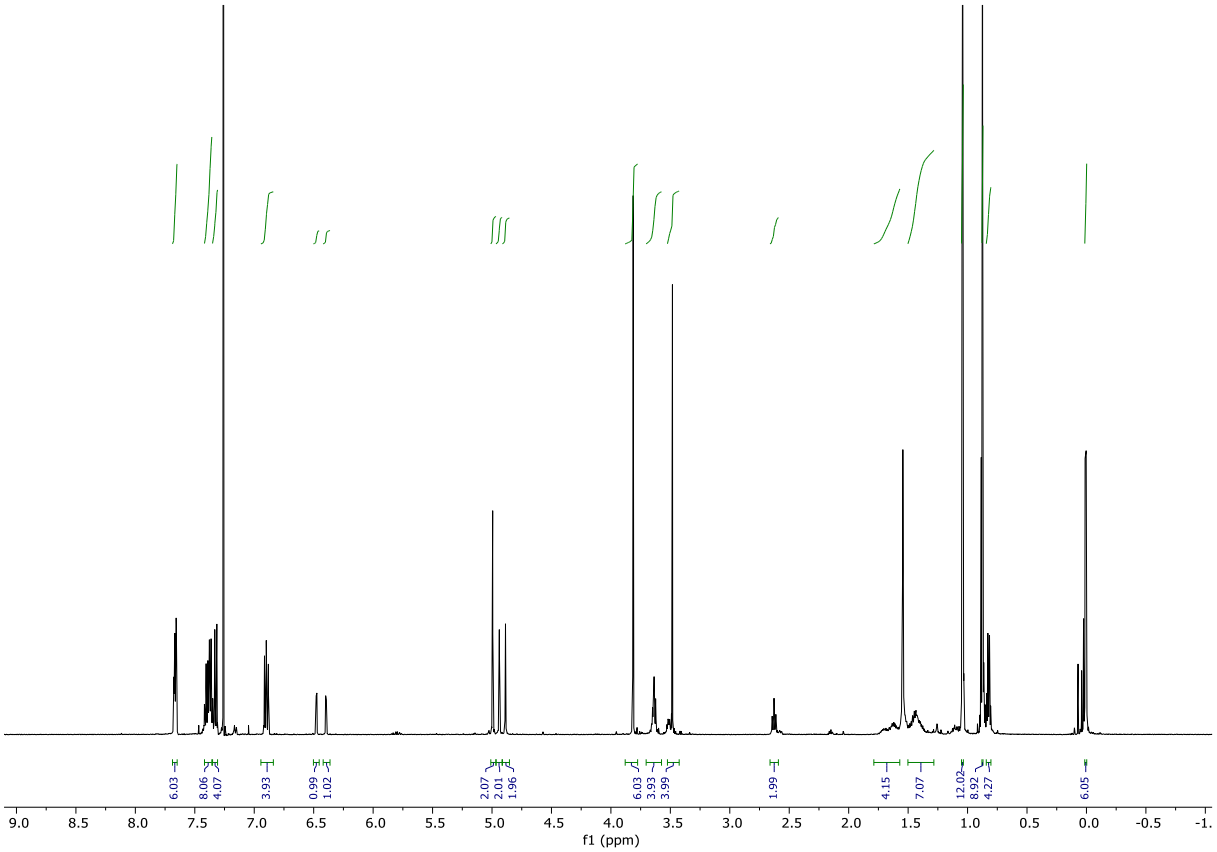
R_f =0.7679 (EtOAc), CPS staining;

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.68 – 7.65 (m, 6H), 7.42 – 7.36 (m, 8H), 7.33 – 7.31 (d, 4H), 6.91 – 6.88 (m, 4H), 6.48-6.39 (m, 2H), 4.99 – 4.89 (m, 6H), 3.81 (m, 6H), 3.66-3.62 (m, 4H), 3.48 (s, 4H), 2.64 – 2.61 (m, 2H), 1.04 (m, 12H), 0.87 (s, 9H), 0.84-0.81 (m, 4H), 0.01 (d, J = 3.6 Hz, 6H).

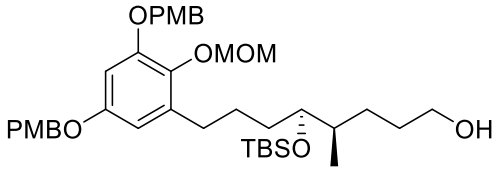
^{13}C NMR (101 MHz, Chloroform-*d*): δ 159.4, 159.3, 155.2, 151.8, 144.3, 142.6, 141.4, 139.6, 138.5, 137.1, 136.2, 135.5, 134.1, 129.4, 129.2, 129.1, 129.0, 128.8, 128.2, 128.1, 127.5, 125.5, 116.1, 113.9, 106.3, 100.0, 98.9, 75.9, 70.4, 70.0, 64.2, 63.2, 57.2, 55.2, 55.2, 38.1, 38.0, 32.9, 30.6, 30.5, 29.0, 28.7, 28.4, 28.3, 27.4, 26.8, 26.8, 26.5, 25.9, 19.1, 18.1, 14.7, 0.9, -4.6.

IR (film): $\tilde{\nu}$ 2953.45, 2930.31, 2857.02, 1613.16, 1514.81, 1487.81, 1462.74, 1428.03, 1376.93, 1249.65, 1173.47, 1154.19, 1110.8, 1090.55, 1036.55, 1006.66, 977.733, 835.026, 774.279, 741.496, 702.926, 614.217, 505.258, 487.902.

HRMS (ESI): m/z calcd for $C_{55}H_{76}NaO_8S_{i2}$ $[M+Na]^+$ 943.4971, found 943.4945


6.03
8.06
4.07
3.93
0.99
1.02
2.07
2.01
1.96
6.03
3.93
3.99
1.99
4.15
7.07
12.02
8.92
4.27
6.05
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
f1 (ppm)

*(4R,5S)-8-(3,5-bis((4-methoxybenzyl)oxy)-2-(methoxymethoxy)phenyl)-5-((tert-butyldimethylsilyl)oxy)-4-methyloctan-1-ol (**34**)*



To a solution of **3** (5 mg, 1.0 equiv.) in DMF (0.2 ml) was added TBAF (2.7 mkl, 0.50 equiv.) and AcOH (1.9 mkl, 0.5 equiv.). The reaction mixture was stirred at room temperature for 23 h. The reaction was quenched with water and extracted with DCM (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude material **34** was purified by FC (EtOAc:Hex 7:3) obtaining fractions 23-26 with TBDPS deprotected product **34**.

Yield: 24 %;

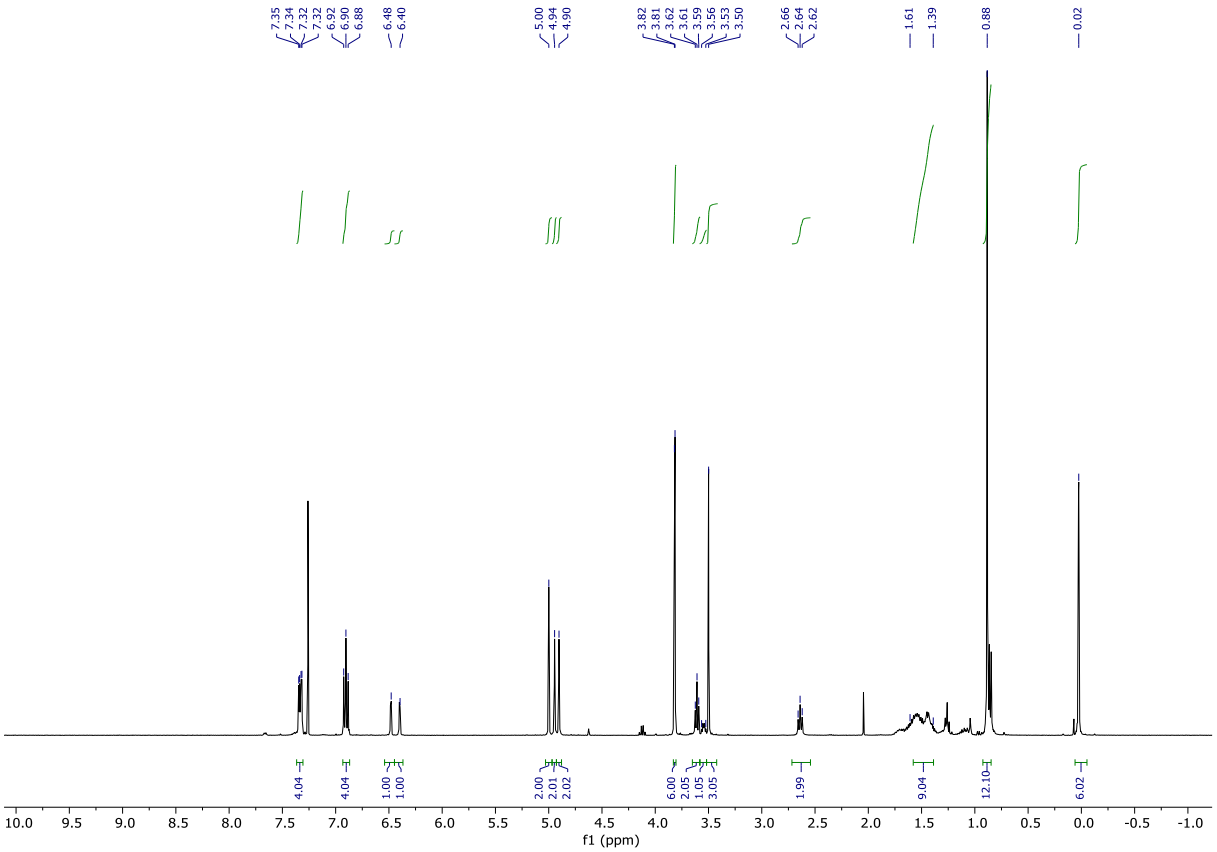
R_f = 0.7286 (EtOAc 1), CPS staining;

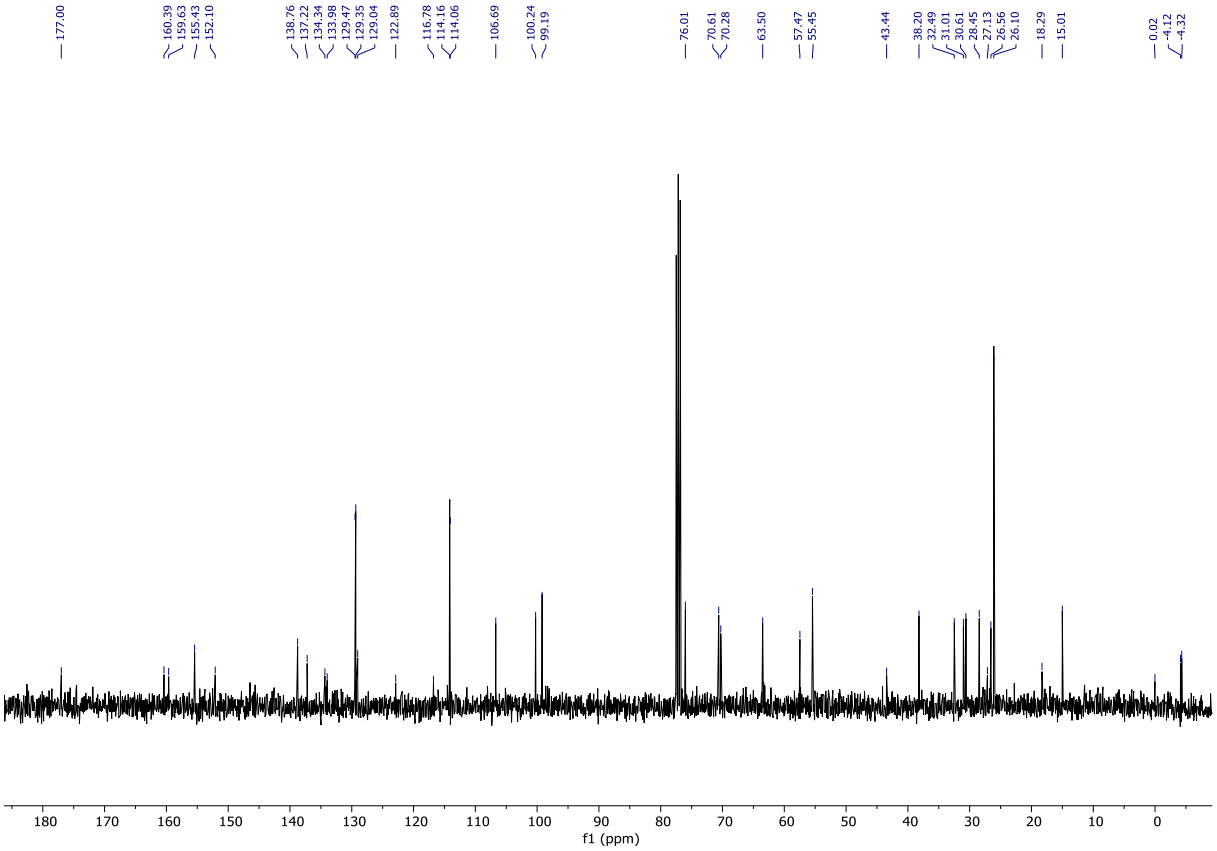
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.35 – 7.32 (dd, J=7.33, 3.36 Hz, 4H), 6.92 – 6.88 (t, J=6.9 Hz, 4H), 6.49 (d, J=2.82 Hz, 1H), 6.40 (d, J=2.82 Hz, 1H), 5.00 (s, 2H), 4.94 (s, 2H), 4.90 (s, 2H), 3.82 (d, J=2.30 Hz, 6H), 3.62 – 3.59 (t, J=6.46 Hz, 2H), 3.56-3.53 (m, 1H), 3.50 (s, 3H), 2.66 – 2.62 (t, J=7.45 Hz, 2H), 1.61-1.39 (m, 9H), 0.88 (s, 12H), 0.02 (s, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*): δ 177.0, 160.4, 159.6, 155.4, 152.1, 138.8, 137.2, 134.3, 134.0, 129.5, 129.4, 129.0, 122.9, 116.8, 114.2, 11.2, 114.1, 106.7, 100.2, 99.2, 76.0, 70.6, 70.3, 63.5, 57.5, 55.5, 43.4, 38.2, 32.5, 31.0, 30.6, 28.5, 27.1, 26.6, 26.1, 18.3, 15.0, -0.0, -4.1, -4.3.

IR (film): $\tilde{\nu}$ 2901.38, 2359.48, 1613.16, 1599.66, 1514.81, 1488.78, 1463.71, 1440.56, 1375.96, 1302.68, 1249.65, 1174.44, 1155.15, 1066.44, 1056.8, 1036.55, 978.697, 857.204, 834.062, 774.279, 523.579, 515.865.

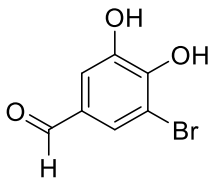
HRMS (ESI): m/z calcd for $C_{39}H_{58}NaO_8Si$ $[M+Na]^+$ 705.3793, found 705.3781.


7.35
7.34
7.32
7.32
6.92
6.90
6.88
6.48
6.40
5.00
4.94
4.90
3.82
3.81
3.62
3.61
3.59
3.56
3.53
3.50
2.66
2.64
2.62
1.61
1.39
0.88
0.02
4.04
4.04
1.00
1.00
2.00
2.01
2.02
6.00
2.05
1.05
3.05
1.99
9.04
12.10
6.02
f1 (ppm)


177.00
160.39
159.63
155.43
152.10
138.76
137.22
134.34
133.98
129.47
129.35
129.04
122.89
116.78
114.16
114.06
106.69
100.24
99.19
76.01
70.61
70.28
63.50
57.47
55.45
43.44
38.20
32.49
31.01
30.61
28.45
27.13
26.56
26.10
18.29
15.01
0.02
-4.12
-4.32
f1 (ppm)

5.2.4 Alternative aromatic building blocks C

*3-bromo-4,5-dihydroxy benzaldehyde (**36**)*



To a 100 mL round bottom flask equipped with a magnetic stir bar was added 5-bromovanillin (5 g, 21.64 mmol, 1.0 equiv.) and aluminum trichloride (3.18 g, 23.8 mmol). The flask was charged with 38 mL of anhydrous DCM and degassed under Argon atmosphere 16:15 . Pyridine (7.67 mL, 95.22 mmol) was added via syringe over 10 minutes and the reaction then was heated in an oil bath overnight at 45° C. The rxn mixture was poured into 100 mL 3N HCl (250 ml=65.1 ml concentrated HCl+185 ml of water) and diluted with 100 mL EtOAc containing 5% methanol. The aqueous layer was extracted 2 x 30 mL EtOAc and the combined organics were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. **36** was obtained in 93 % yield after FC.

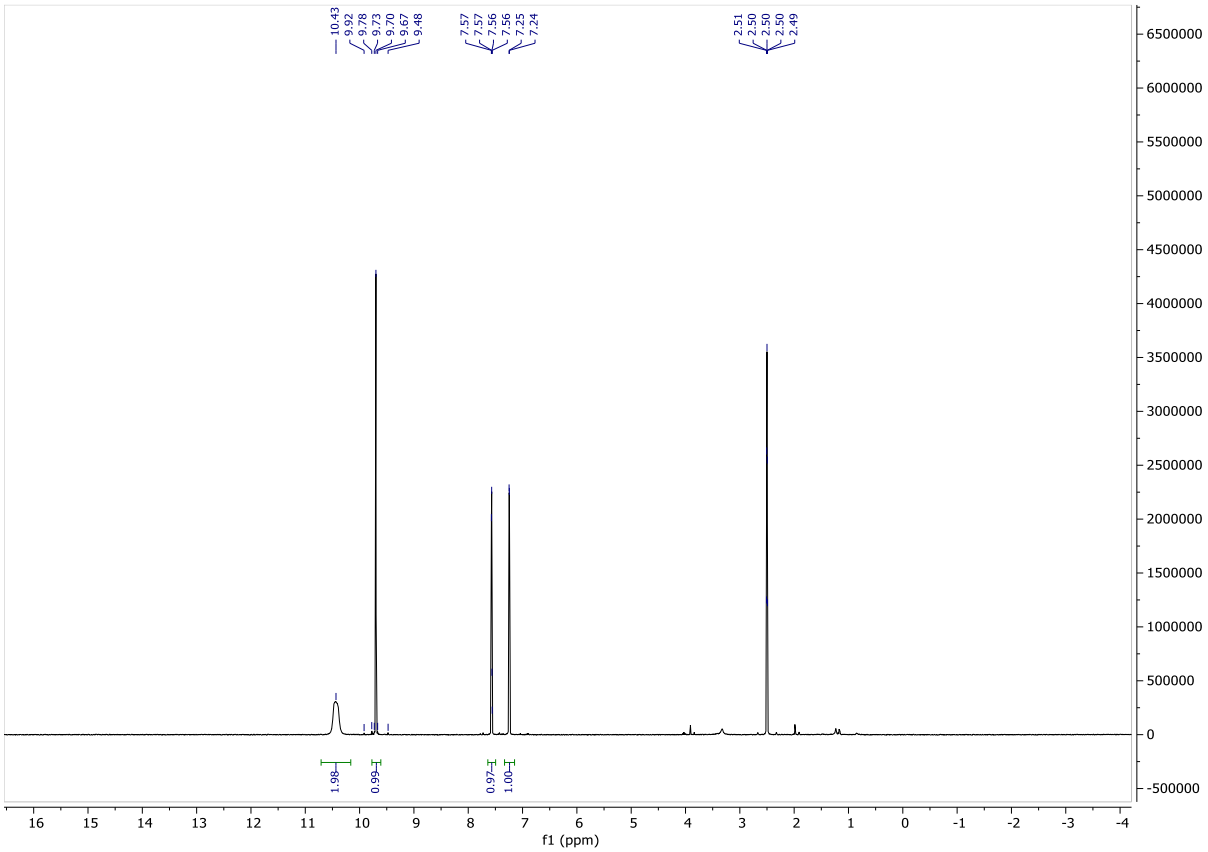
Yield: 4.37 g (93 %);

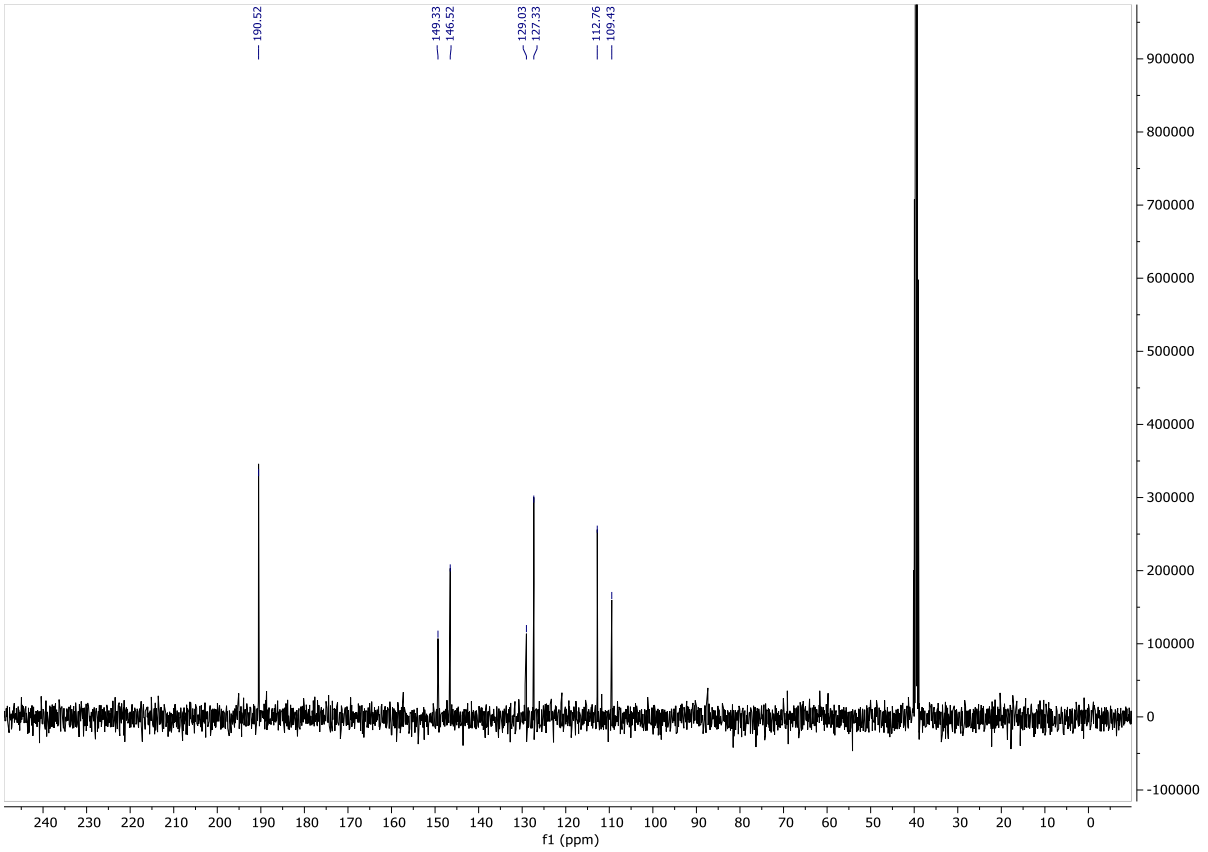
R_f =0.34 (hexane / EtOAc = 1:1), CPS staining;

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (broad s, 2H), 9.70 (s, 1H), 7.57 (d, J = 1.9 Hz, 1H), 7.25 (d, J = 2.0 Hz, 1H);

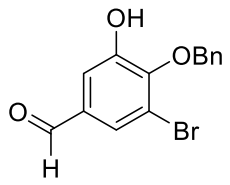
^{13}C NMR (101 MHz, DMSO-d_6) δ 190.5, 149.3, 146.5, 129.0, 127.3, 112.8, 109.4;

HRMS (ESI-TOF) m/z (ESI) $C_7H_4BrO_3$ [M-H] 214.9349, found 214.9354;


10.43
9.92
9.78
9.73
9.70
9.67
9.48
7.57
7.57
7.56
7.56
7.25
7.24
2.51
2.50
2.50
2.50
2.49
1.98
0.99
0.97
1.00
f1 (ppm)


190.52
149.33
146.52
129.03
127.33
112.76
109.43
f1 (ppm)

*4-(benzyloxy)-3-bromo-5-hydroxybenzaldehyde (**37**)*[6]



In a flame-dried 100 ml flask was prepared solution of 3-bromo-4,5- dihydroxybenzaldehyde **36** (2.0 g, 9.16 mmol, 1.0 equiv.) in dry DMF (40 mL, c=0.230 M). Then, Li_2CO_3 (1.76 g, 23.82 mmol, 2.6 equiv.) was added to the solution 14:31 . This solution was vigorously stirred and heated to 45 °C for 1 h followed by dropwise addition of benzyl bromide (2.83 mL, 23.82 mmol, 2.6 equiv.) over 5 minutes. After 45 min, the reaction was quenched with HCl (aq, 1.0 N) resulting in precipitation of the crude product. The precipitate was filtered, and washed with water and the solvent was removed under reduced pressure. Then, m crude=2.5 g was purified by flash chromatography (SiO_2, DCM/hexane, 9:1) to yield **37** in fractions 52-71 as a pale yellow solid.

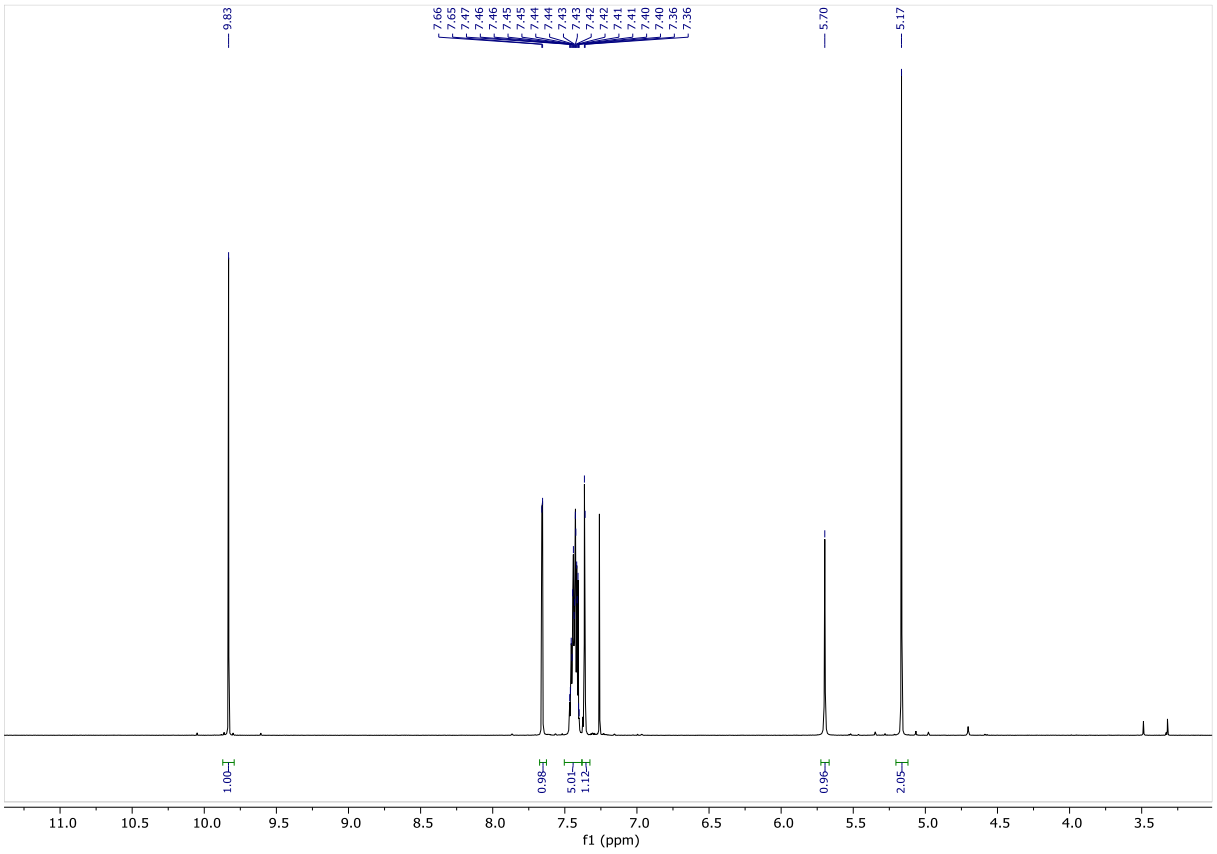
Yield: 172 mg (6 %), recovered SM back;

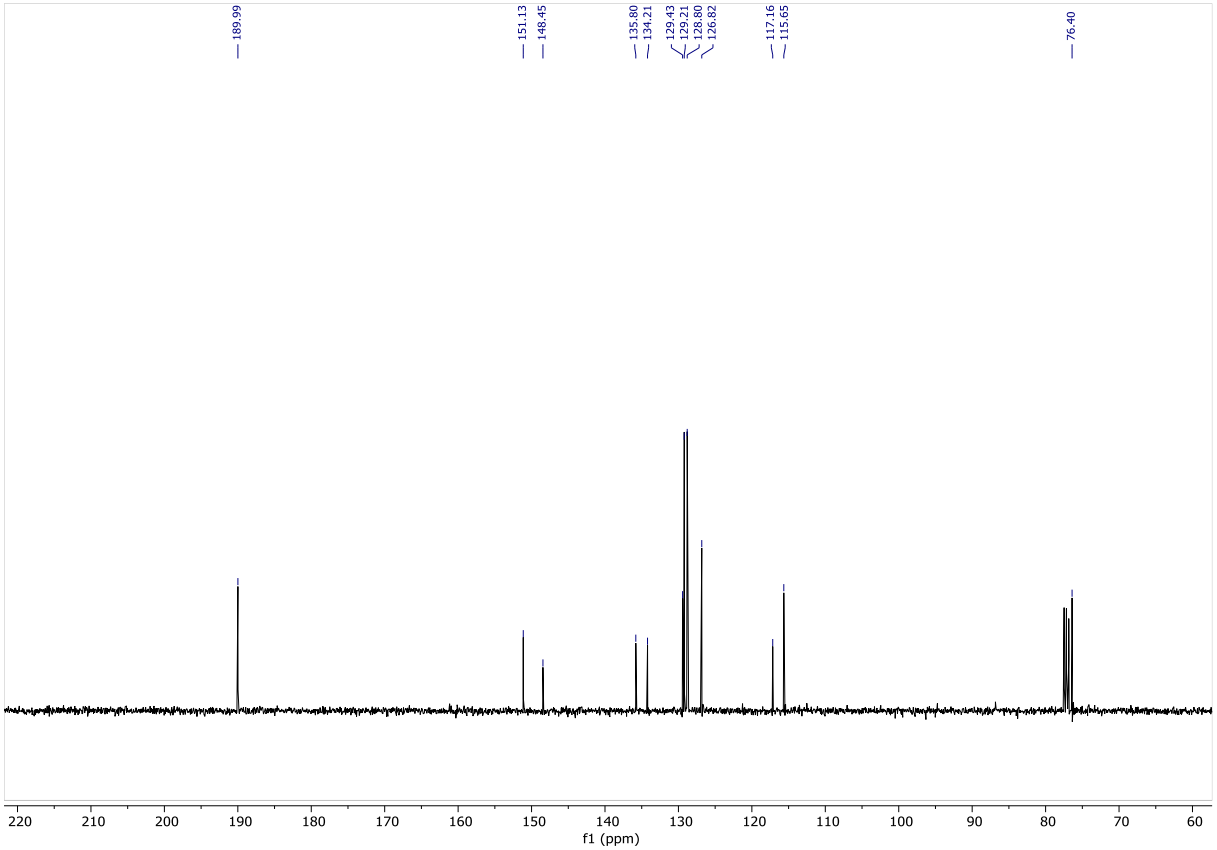
R_f = 0.66 (hexane / EtOAc = 1:1), CPS staining;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.83 (s, 1H), 7.66 (d, J = 1.9 Hz, 1H), 7.52 – 7.39 (m, 5H), 7.36 (d, J = 1.8 Hz, 1H), 5.70 (s, 1H), 5.17 (s, 2H);

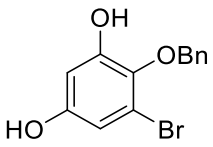
^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.0, 151.1, 148.5, 135.8, 134.2, 129.4 (2C), 129.2, 128.8 (2C), 126.8, 117.2, 115.7, 76.4;

HRMS (ESI-TOF) m/z (ESI) $C_{14}H_{10}BrO_3$ [M-H] 304.9819, found 304.9819;


9.83
7.66
7.65
7.47
7.46
7.46
7.45
7.45
7.44
7.44
7.43
7.43
7.42
7.42
7.41
7.41
7.40
7.40
7.36
7.36
5.70
5.17
1.00
0.98
5.01
1.12
0.96
2.05
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
f1 (ppm)


189.99
151.13
148.45
135.80
134.21
129.43
129.21
128.80
126.82
117.16
115.65
76.40
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
f1 (ppm)

*4-(benzyloxy)-5-bromobenzene-1,3-diol (**38**)*



In a flame-dried 25 ml flask with a stirring bar solution of **37** (172 mg, 0.56 mmol, 1.0 equiv.) in DCM (5.6 ml) was prepared under Argon atmosphere. When the starting material was dissolved, *m*-CPBA (77 %, 251 mg, 1.12 mmol, 2.0 equiv.) was added at room temperature and the reaction was stirred overnight for 18 h. After 18 h, the reaction was diluted with DCM and washed with sat. aq. $NaHCO_3$. Combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was directly used for the next step.

2nd rxn: A solution of crude was dissolved in methanol (0.8 ml) was treated with 10 % aqueous potassium hydroxide (0.2 ml), and turned pink. The resulting reaction mixture was stirred for 2 h at room temperature Then, it was diluted with water, neutralized with 2.0 M aqueous hydrochloric acid, and extracted with ethyl acetate (2 x). In the separation funnel yellow and pinkish layers. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by 2 cm column chromatography (hexane/EtOAc 20/1→6:1) obtaining **38** in fractions 52-71 (110.1 mg, 67 %) as a colorless oil.

Yield: 110 mg (67 %);

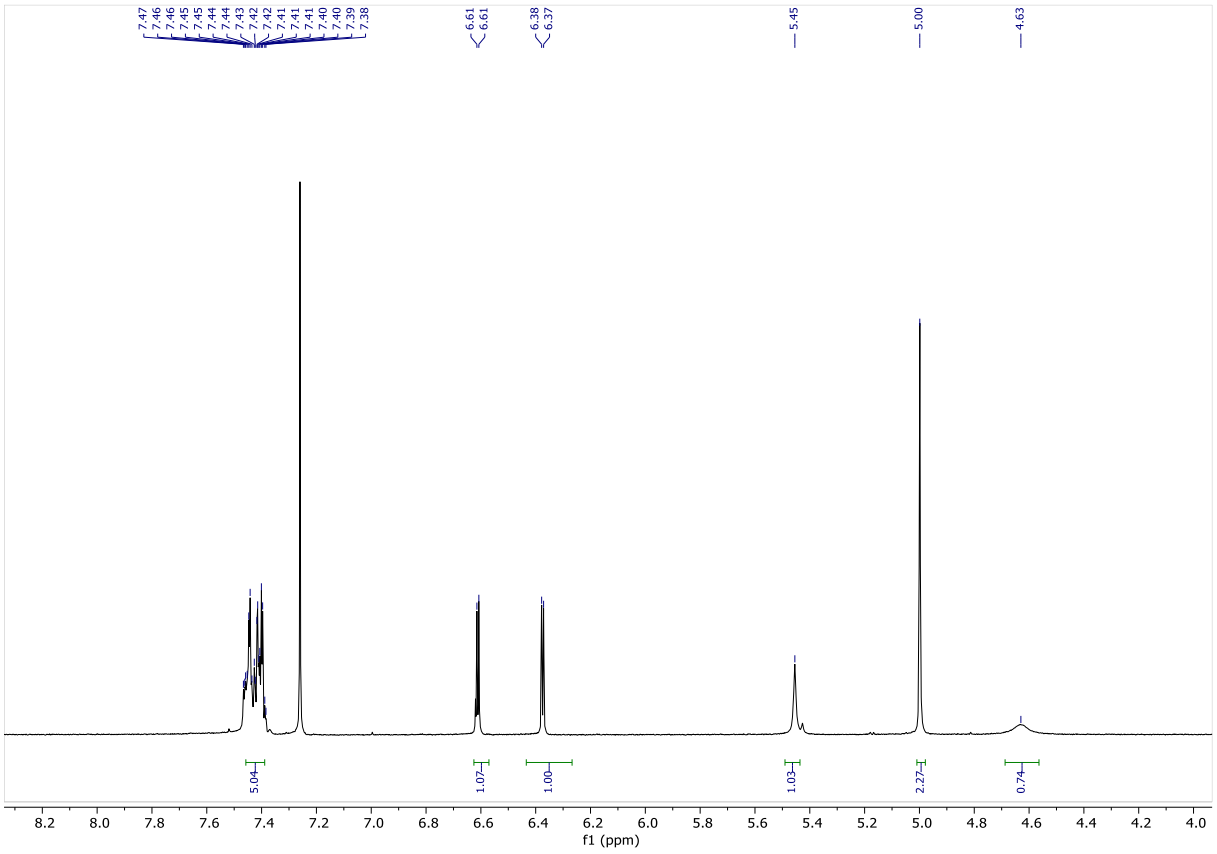
R_f = 0.322 (hexane / EtOAc = 5:1), CPS staining;

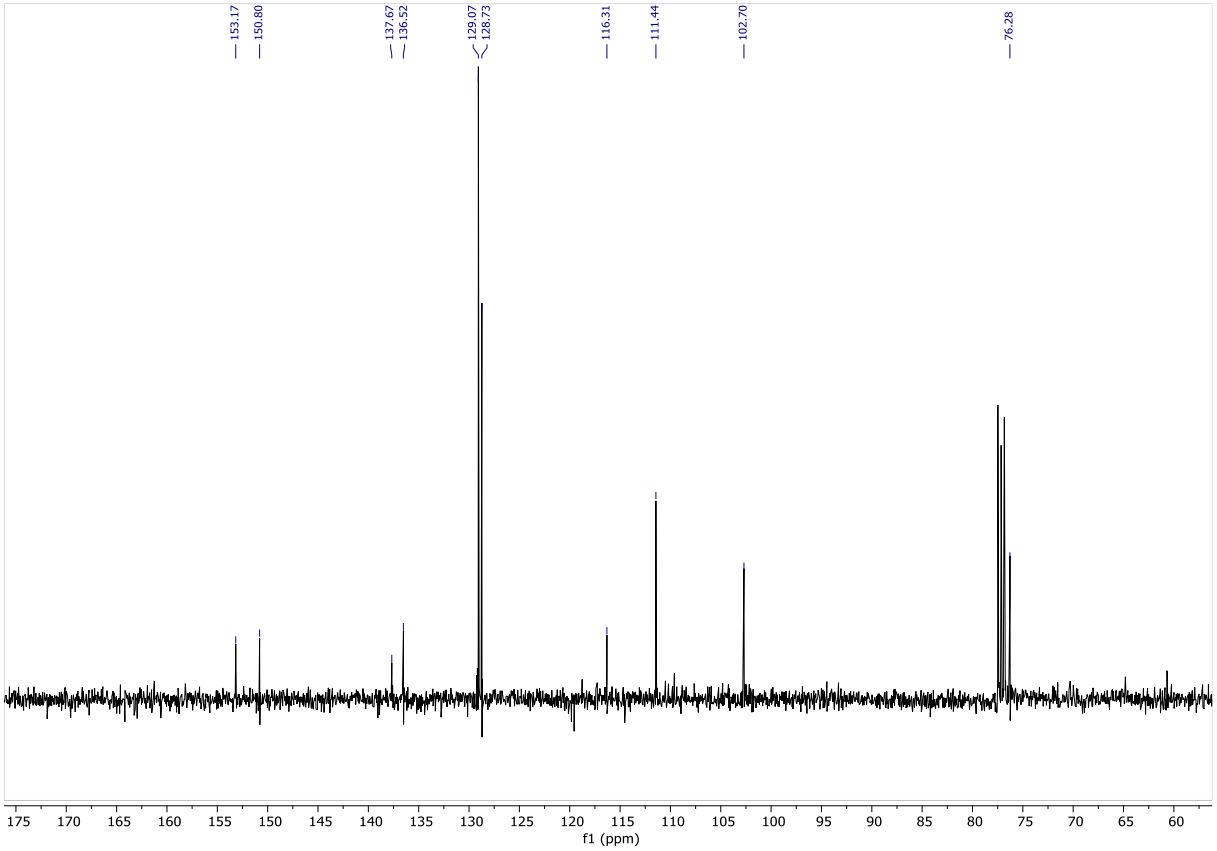
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 – 7.32 (m, 5H), 6.61 (d, J = 2.9 Hz, 1H), 6.37 (d, J = 2.8 Hz, 1H), 5.45 (s, 1H), 5.00 (s, 2H), 4.63 (s, 1H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 153.2, 150.8, 137.7, 136.5, 129.1 (3C), 128.7 (2C), 116.3, 111.4, 102.7, 76.3;

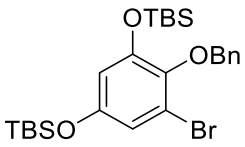
IR (film): ν = 3493, 3028, 2924, 2853, 1603, 1494, 1445, 1372, 1298, 1177, 1155, 1099, 1075, 1030, 998, 959, 911, 876, 836, 792, 728, 698;

HRMS (ESI-TOF) m/z (ESI) $C_{13}H_{11}BrNaO_3$ $[M+Na]^+$ 316.9784, found 316.9789.


7.47
7.46
7.46
7.45
7.45
7.44
7.44
7.43
7.42
7.42
7.41
7.41
7.40
7.40
7.39
7.38
6.61
6.61
6.38
6.37
5.45
5.00
4.63
5.04
1.07
1.00
1.03
2.27
0.74
f1 (ppm)


153.17
150.80
137.67
136.52
129.07
128.73
116.31
111.44
102.70
76.28
f1 (ppm)

*((4-(benzyloxy)-5-bromo-1,3-phenylene)bis(oxy))bis(tert-butyldimethylsilane) (**39**)*



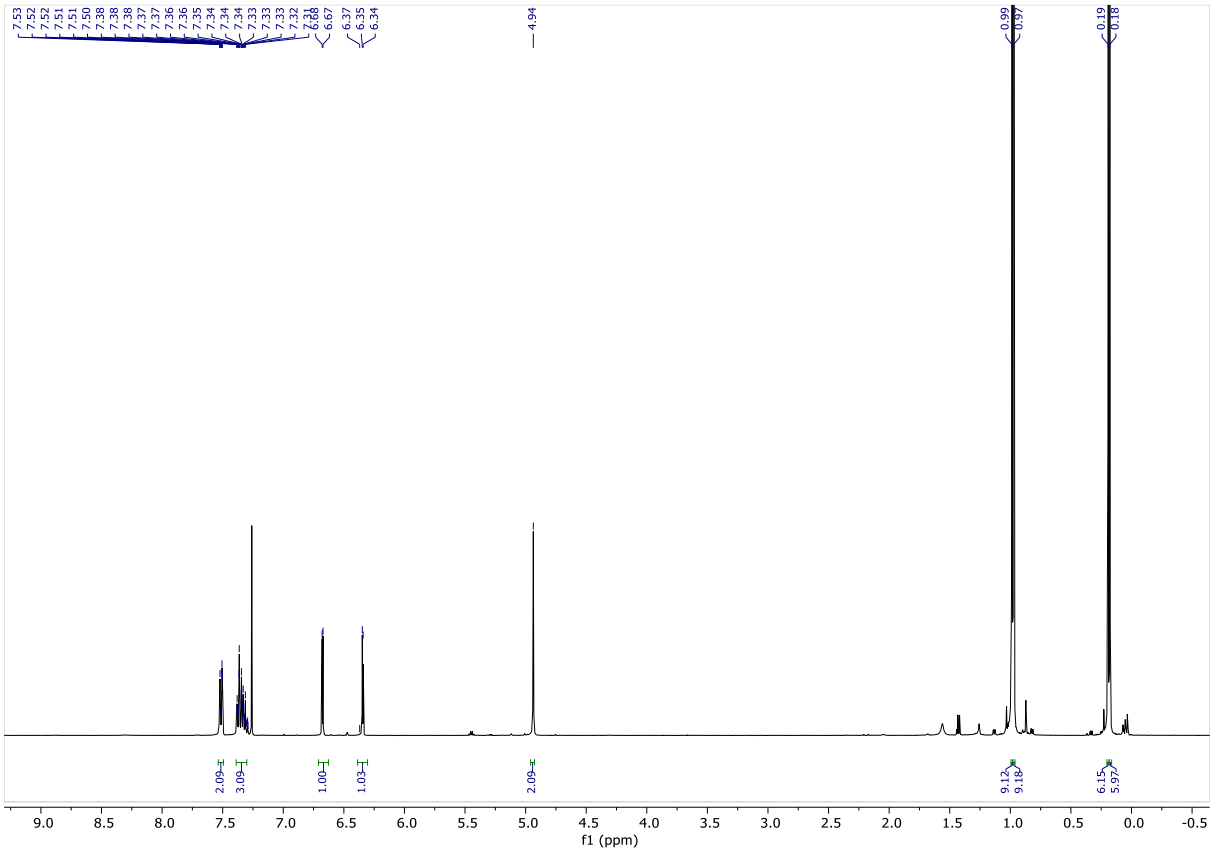
To a solution of **38** (0.1 g, 0.34 mmol, 1.0 equiv.) in DMF (3.4 ml) were added imidazole (69.2 mg, 1.02 mmol, 3.0 equiv.) and TBSCl (112.4 mg, 0.75 mmol, 2.2equiv.) at room temperature and the reaction was stirred at room temperature overnight. The reaction was quenched with brine and extracted with EtOAc (3 x). The combined organic layers were washed with water (3 x), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by FC= 2 cm (hexane/EtOAc 20/1) obtaining **39** (0.156 g, 88 %) as a colorless oil.

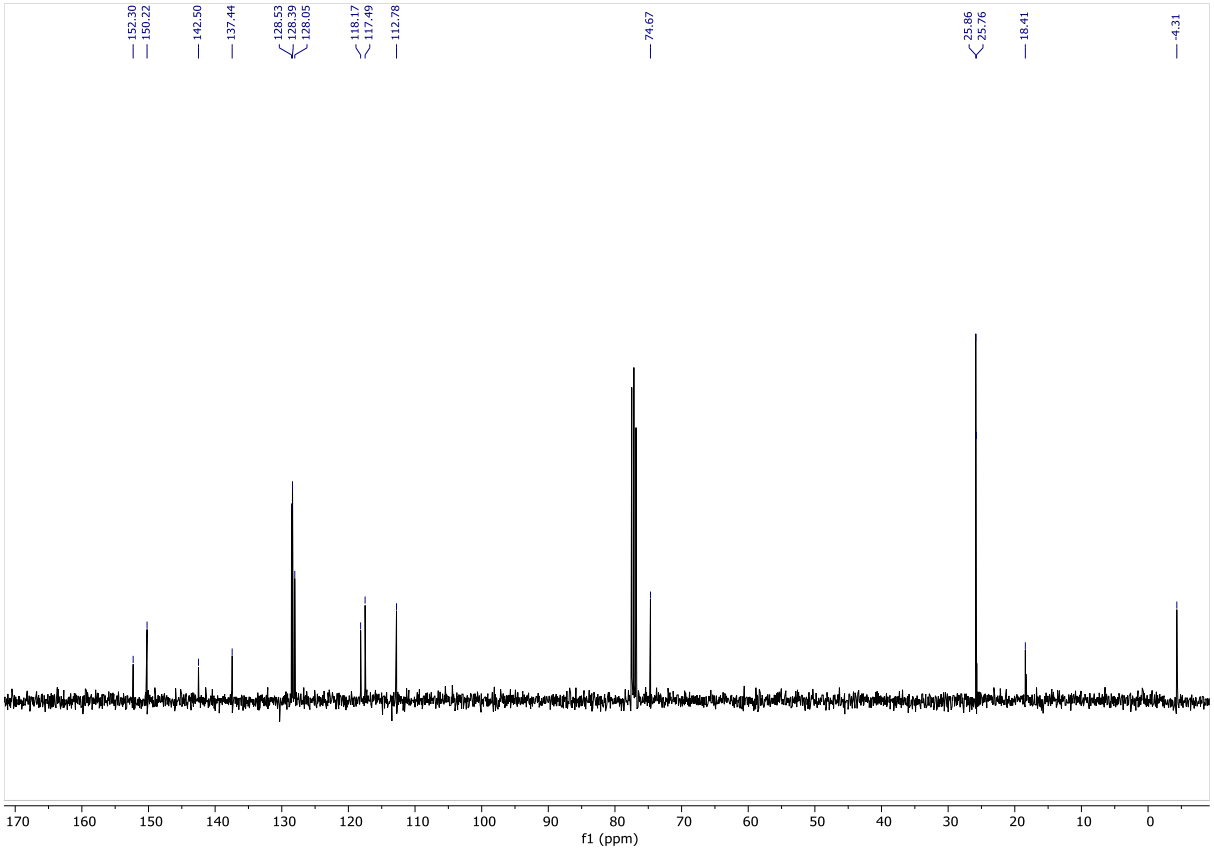
Yield: 156 mg (88 %);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.46 (m, 2H), 7.43 – 7.28 (m, 3H), 6.68 (d, J = 2.8 Hz, 1H), 6.34 (d, J = 2.8 Hz, 1H), 4.94 (s, 2H), 0.99 (s, 9H), 0.97 (s, 9H), 0.19 (s, 6H), 0.18 (s, 6H);

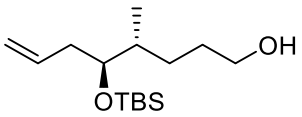
^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.3, 150.2, 142.5, 137.4, 128.5 (2C), 128.4 (2C), 128.1, 118.2, 117.5, 112.8, 74.7, 25.8 (3C), 25.8 (3C), 18.4 (2C), -4.3 (4C);

IR (film): v = 2954, 2929, 2899, 2858, 2357, 1593, 1557, 1497, 1470, 1419, 1390, 1374, 1327, 1255, 1216, 1192, 1142, 1077, 1023, 1006, 981, 915, 859, 830, 781, 739, 713, 695, 671;
HRMS (ESI-TOF) m/z (ESI) $C_{25}H_{40}BrO_3Si_2$ $[M+H]^+$ 523.1694, found 523.1693.


7.53
7.52
7.52
7.51
7.51
7.50
7.38
7.38
7.38
7.37
7.37
7.36
7.36
7.35
7.34
7.34
7.34
7.33
7.33
7.33
7.32
6.68
6.67
6.37
6.35
6.34
4.94
0.99
0.97
0.19
0.18
2.09
3.09
1.00
1.03
2.09
9.12
9.18
6.15
5.97
f1 (ppm)


152.30
150.22
142.50
137.44
128.53
128.39
128.05
118.17
117.49
112.78
74.67
25.86
25.76
18.41
-4.31
f1 (ppm)

*(4R,5S)-5-((tert-butyldimethylsilyl)oxy)-4-methyloct-7-en-1-ol (**40**)*



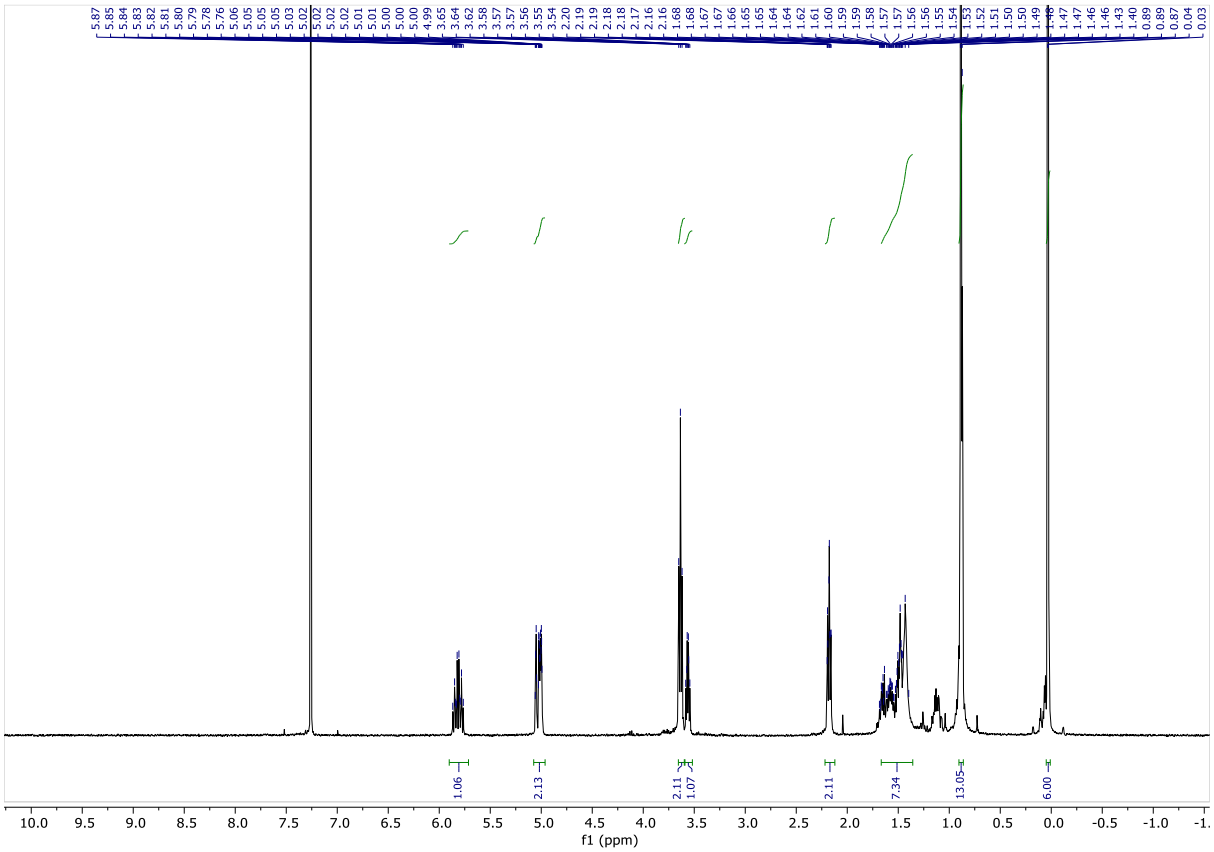
A solution of compound **7** (300 mg, 0.59 mmol, 1.0 equiv.) in DMF (165 mL) was prepared under argon atm. Acetic acid (40.3 mkl, 0.705 mmol, 1.2 equiv.) and TBAF (1 M in THF, 0.71 ml, 0.705 mmol, 1.2 equiv.) were added at 0 °C to this solution. The mixture was stirred overnight. The reaction was quenched with water and the aq. layer was extracted with tert-butyl methyl ether, the combined organic phases were dried over $MgSO_4$, filtered, and evaporated. The crude material was purified by flash chromatography (hexane/EtOAc, 80:20) to afford the product **40** as a colorless oil (130 mg, 81%).

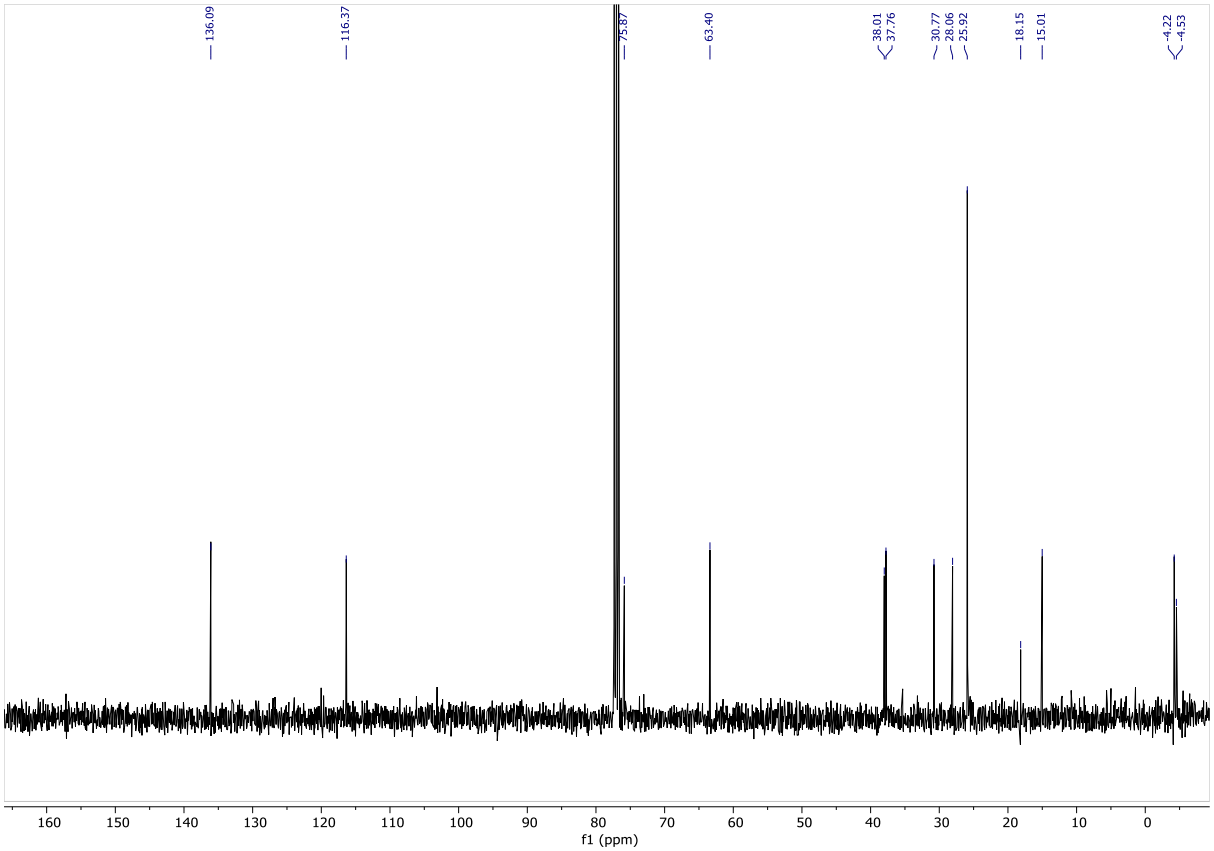
Yield: 130 mg (81 %);

^{1}H NMR (400 MHz, Chloroform-d) δ 5.82 (ddt, J = 17.1, 10.1, 7.0 Hz, 1H), 5.17 – 4.82 (m, 2H), 3.64 (t, J = 6.6 Hz, 2H), 3.56 (td, J = 5.8, 4.4 Hz, 1H), 2.18 (ddd, J = 6.6, 5.3, 1.2 Hz, 2H), 1.74 – 1.33 (m, 6H), 0.89 (s, 11H), 0.87 (s, 2H), 0.03 (d, J = 2.7 Hz, 6H).

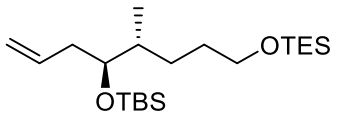
^{13}C NMR (101 MHz, Chloroform-d) δ 136.1, 116.4, 75.9, 63.4, 38.0, 37.8, 30.8, 28.1, 25.9, 18.2, 15.0, -4.2, -4.5.

IR (film): v = 3338,2931, 2876, 2359, 1743, 1725, 1641, 1462, 1434, 1379, 1255, 1097, 1053, 990, 910, 836, 811, 775, 707, 659, 618, 595, 572, 537, 525, 507.


1.06
2.13
2.11
1.07
2.11
7.34
13.05
6.00
f1 (ppm)


136.09
116.37
75.87
63.40
38.01
37.76
30.77
28.06
25.92
18.15
15.01
-4.22
-4.53
f1 (ppm)

*(5S,6R)-5-allyl-11,11-diethyl-2,2,3,3,6-pentamethyl-4,10-dioxa-3,11-disilatridecane (**41**)*



To a solution of **40** (130 mg, 0.4771 mmol, 1 equiv.) in dry pyridine (8.5 mL, c=0.06 M), Et_3N (0.1 ml, 1.5 equiv.) and triethylsilyl chloride (0.12 mL, 1.5 equiv.) were added. After overnight at room temperature, the reaction was diluted with DCM to a volume of 20 mL and extracted with sat. aq. $NaHC0_3$ (1 X 40 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo, residual pyridine was removed by high vacuum rotary evaporator. The crude product was purified by FC, 4:1 hexane-EtOAc as eluent to afford 137 mg (74 %) of **41**.

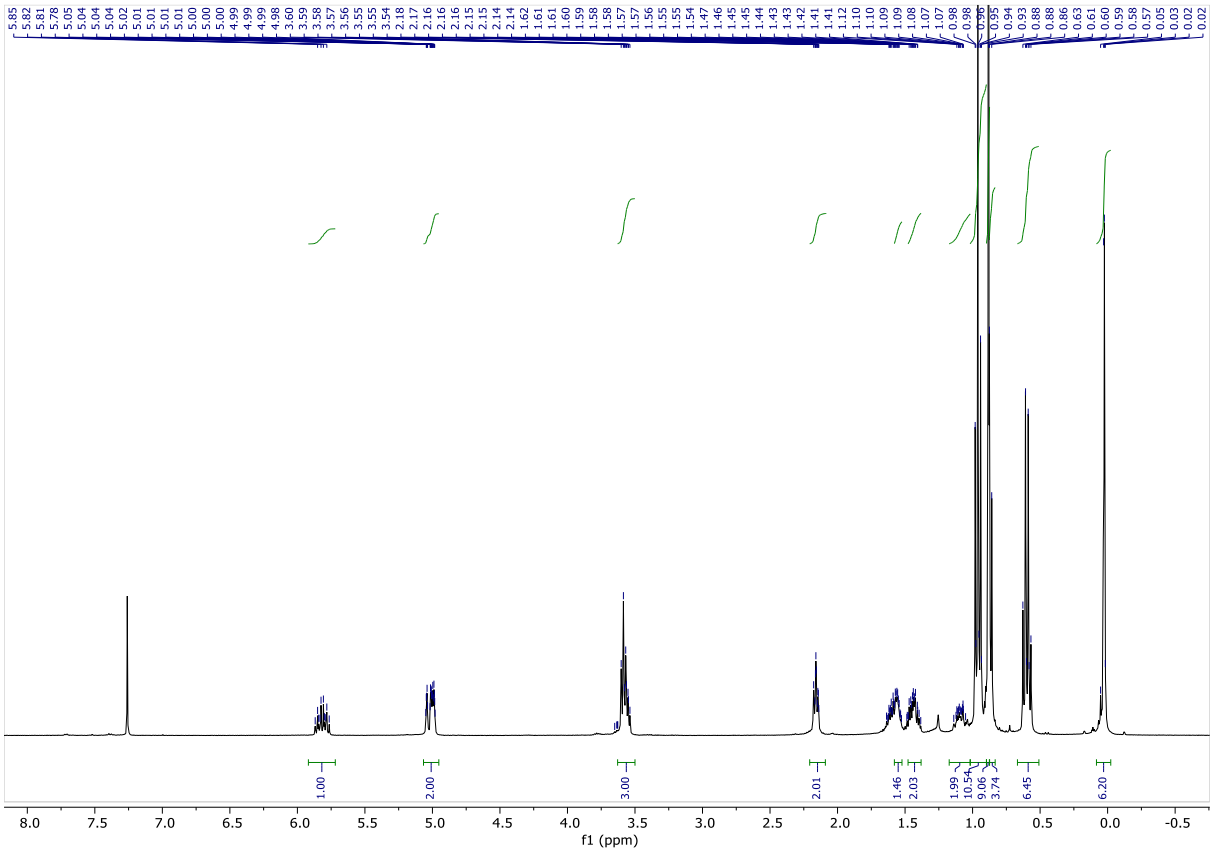
Yield: 137 mg (74 %);

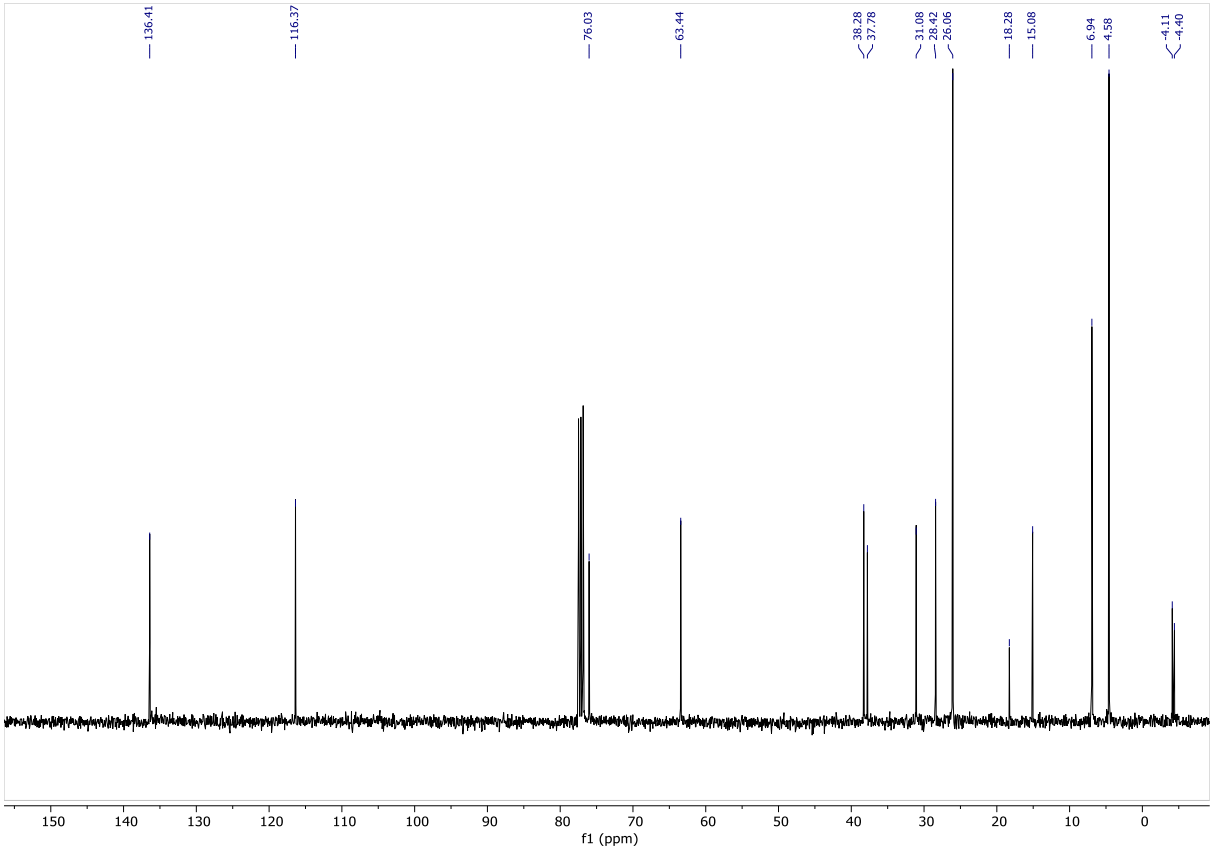
^{1}H NMR (400 MHz, Chloroform-d) δ 5.82 (ddt, J = 17.3, 10.3, 7.1 Hz, 1H), 5.08 – 4.88 (m, 2H), 3.68 – 3.48 (m, 3H), 2.27 – 2.03 (m, 2H), 1.69 – 1.51 (m, 2H), 1.44 (tdd, J = 10.9, 7.8, 4.8 Hz, 2H), 1.16 – 1.05 (m, 1H), 0.96 (t, J = 7.9 Hz, 10H), 0.88 (s, 8H), 0.88 (s, 3H), 0.86 (s, 1H), 0.60 (q, J = 8.0 Hz, 6H), 0.03 (d, J = 2.3 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-d) δ 136.4, 116.4, 76.0, 63.4, 38.3, 37.8, 31.1, 28.4, 26.1, 18.3, 15.1, 6.9, 4.6, -4.1, -4.4.

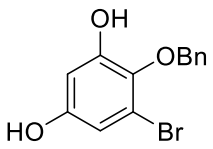
IR (film): ν = 3073, 3052, 2955, 2930, 2888, 2857, 1472, 1463, 1428, 1389, 1362, 1253, 1110, 1092, 1006, 938, 911, 836, 808, 774, 740, 700, 612, 507.

HRMS (ESI-TOF) m/z (ESI) $C_{21}H_{46}NaO_2Si_2$ $[M+Na]^+$ 409.2929, found 409.2933.


f1 (ppm)


136.41
116.37
76.03
63.44
38.28
37.78
31.08
28.42
26.06
18.28
15.08
6.94
4.58
-4.11
-4.40
f1 (ppm)

*4-(benzyloxy)-5-bromobenzene-1,3-diol (**44**)*



All solvents were degassed for 30 min with argon. In a heatgun heated 10 ml flask, dried under high vacuum overnight, a solution of **41** (13.5 mg, 0.026 mmol, 1.1 equiv.) in THF (0.1 ml) was prepared. Then, 9-BBN (0.5 M in THF, 0.121 ml, 1.7 equiv.) was added and the mixture was stirred for 5 hours at room temperature Then, K_2CO_3 (6.6 mg, 0.048 mmol, 2.0 equiv.) and water (0.07 ml) were added to the mixture and stirred for 30 min (solution A). In a separate dry flask, **39** (8.9 mg, 0.024 mmol, 1.0 equiv.) and $Pd(dppf)_2Cl_2$*DCM (0.4 mg, 0.20 equiv.) were dissolved THF (0.3 ml) and stirred for 5 min to give an orange suspension (solution B). Solution A was then added at room temperature to solution B. The reaction mixture was put into the microwave and stirred at 105 °C for 90 min. The reaction was quenched with water and extracted with DCM (3 x). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by FC cm (hexane/EtOAc 50/1 to 20/1), none of the desired product was isolated, and two undesired products could be isolated and characterized. **44** – slightly impure, some impurity in the aliphatic region observed by 1H NMR, therefore <14 %, and **45** isolated in 37 % yield.

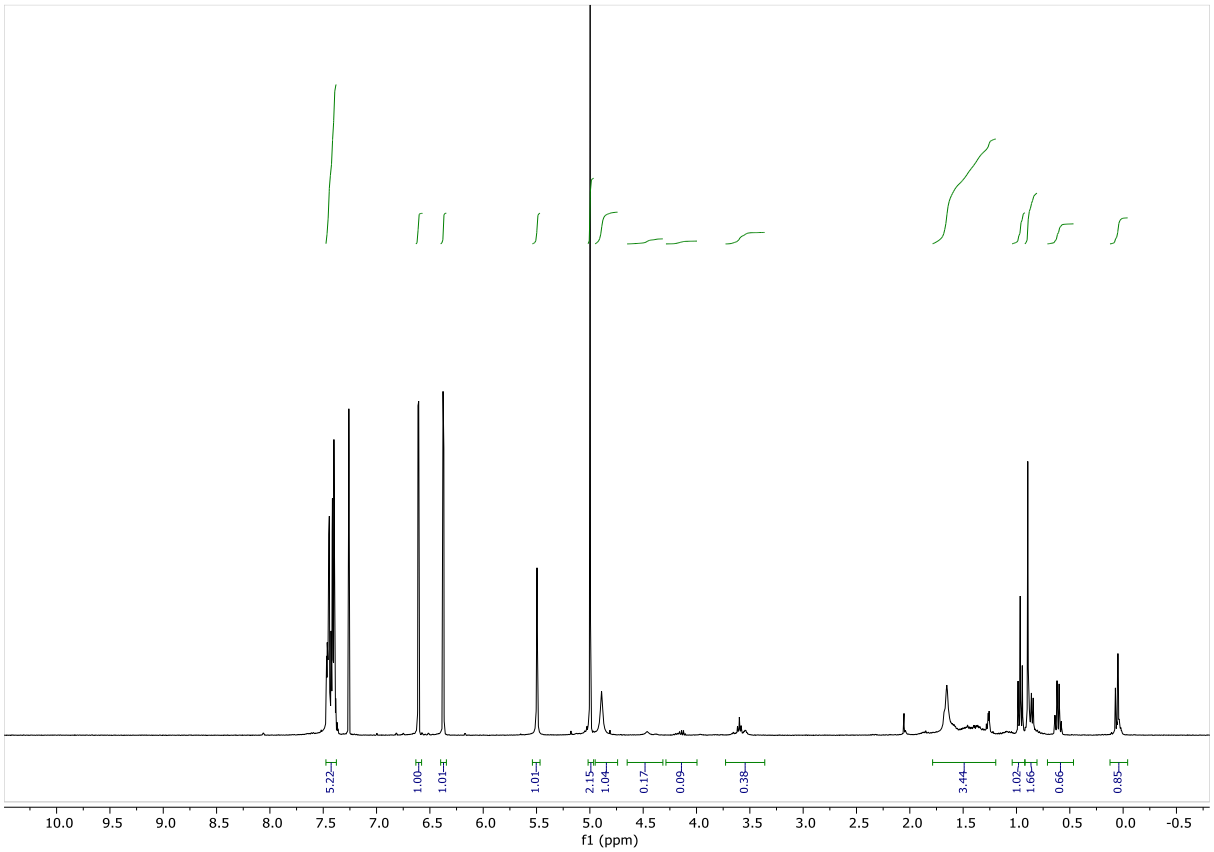
Yield: <14 %;

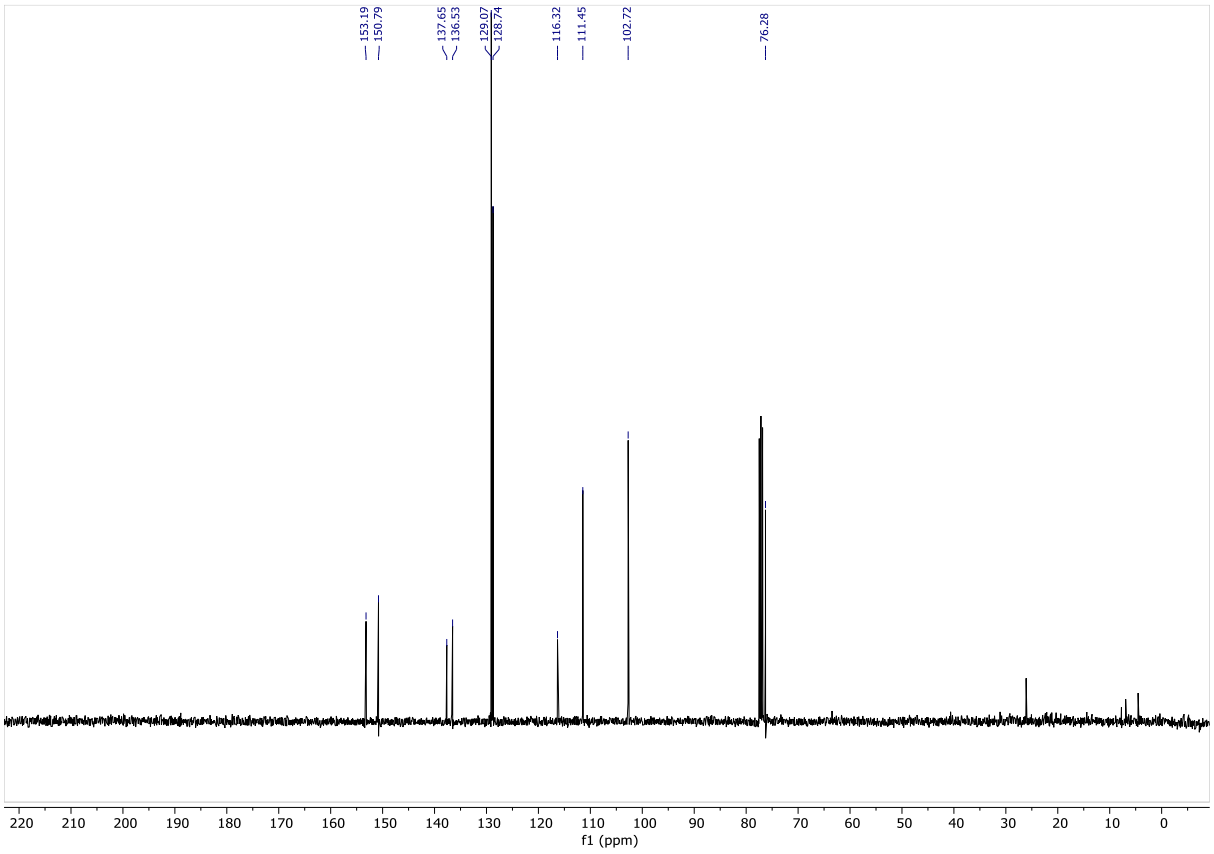
^{1}H NMR (400 MHz, Chloroform-d) δ 7.58 – 7.34 (m, 5H), 6.61 (d, J = 2.8 Hz, 1H), 6.37 (d, J = 2.9 Hz, 1H), 5.50 (s, 1H), 5.00 (s, 2H), 4.89 (s, 1H).

^{13}C NMR (101 MHz, Chloroform-d) δ 153.19, 150.79, 137.65, 136.53, 129.07, 128.74, 116.32, 111.45, 102.72, 76.28.

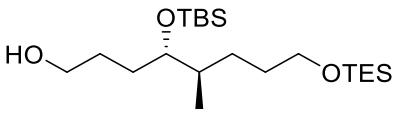
IR (film): ν = 3369, 2936, 1617, 1591, 1489, 1454, 1379, 1310, 1240, 1201, 1158, 999, 915, 842, 788, 749, 697, 619, 605.

HRMS (ESI-TOF) m/z (ESI) C13H11BrNaO3 $[M+Na]^+$ 316.9784, found 316.9789.


5.22
1.00
1.01
1.01
2.15
1.04
0.17
0.09
0.38
3.44
1.02
1.66
0.66
0.85
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


153.19
150.79
137.65
136.53
129.07
128.74
116.32
111.45
102.72
76.28
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

*(4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-methyl-8-((triethylsilyl)oxy)octan-1-ol (**45**)*

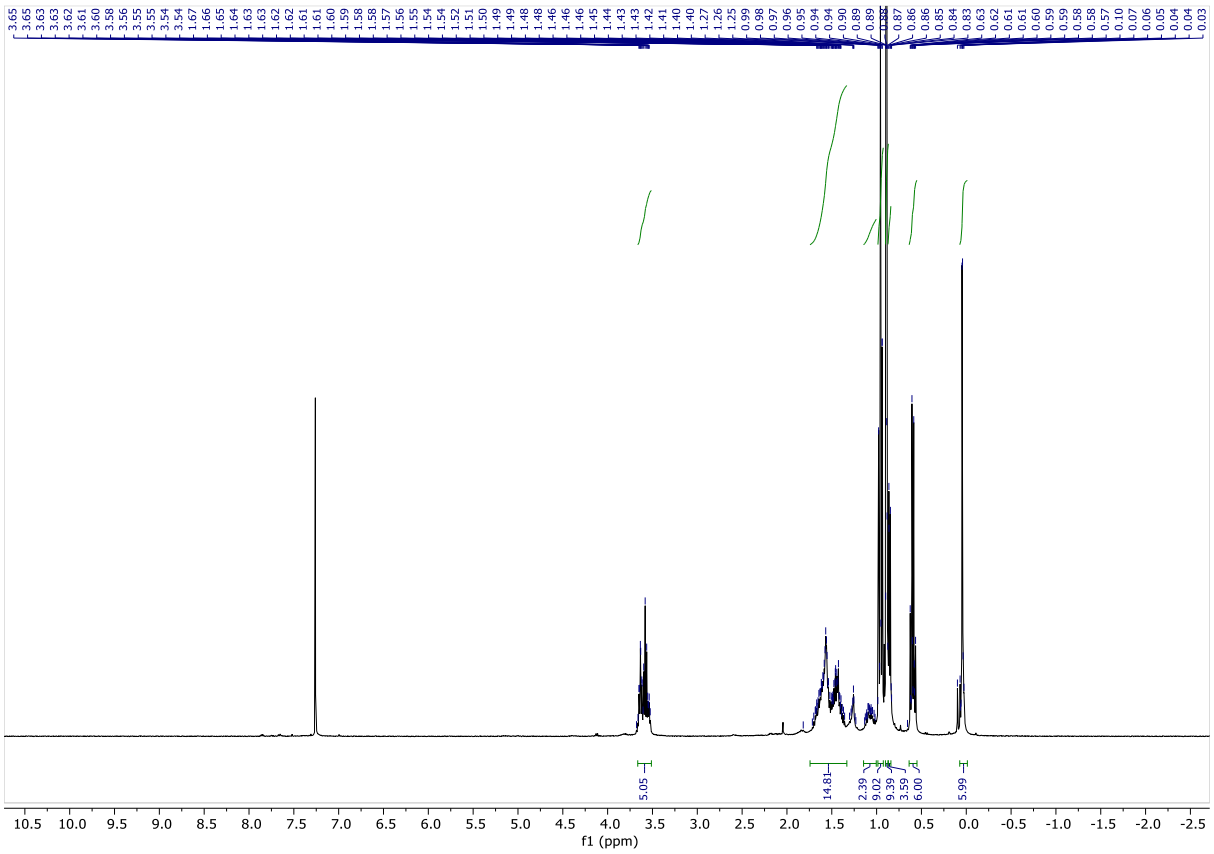


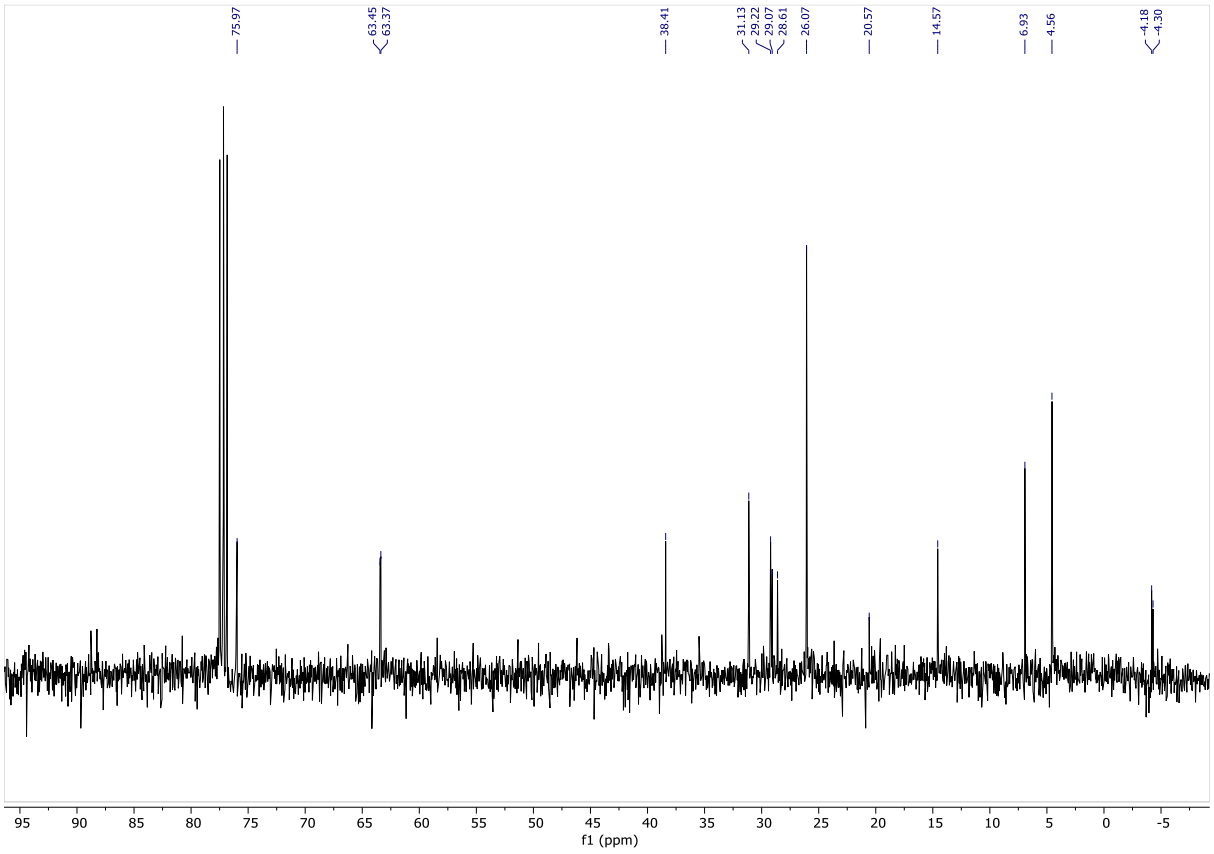
Yield: 37 %;

^{1}H NMR (400 MHz, Chloroform-d) δ 3.81 – 3.43 (m, 1H), 1.83 – 1.19 (m, 1H), 1.14 – 1.01 (m, 0H), 0.96 (t, J = 7.9 Hz, 2H), 0.89 (s, 1H), 0.87 – 0.80 (m, 1H), 0.60 (q, J = 7.9 Hz, 1H), 0.14 – -0.16 (m, 1H).

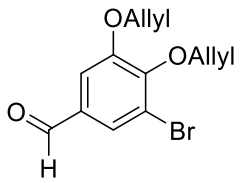
^{13}C NMR (101 MHz, Chloroform-d) δ 75.97, 63.41 (d, J = 7.9 Hz), 38.41, 31.13, 29.22, 29.07, 28.61, 26.07, 14.57, 6.93, 4.56, -4.18.

HRMS (ESI-TOF) m/z (ESI) C21H48NaO3Si2 $[M+Na]^{+}$ 427.3034, found 427.3029.




75.97
63.45
63.37
38.41
31.13
29.22
29.07
28.61
26.07
20.57
14.57
6.93
4.56
4.18
4.30
95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5
f1 (ppm)

*3,4-bis(allyloxy)-5-bromobenzaldehyde (**46**)*



A solution of 3,4-dihydroxy-5-brvanillin **36** (0.5 g, 2.3 mmol, 1.0 equiv.) in DMF (23 mL) was prepared. Then, potassium carbonate (350 mg, 1.1 equiv.) and allyl bromide (0.2 mL, 1.0 equiv.) were added to this solution at room temperature overnight. The reaction was quenched with water, the aq. layer was extracted with EtOAc, the combined organic phases were dried over $MgSO_4$, filtered and evaporated. FC of the crude material afforded 460 mg (78 %) of **46**.

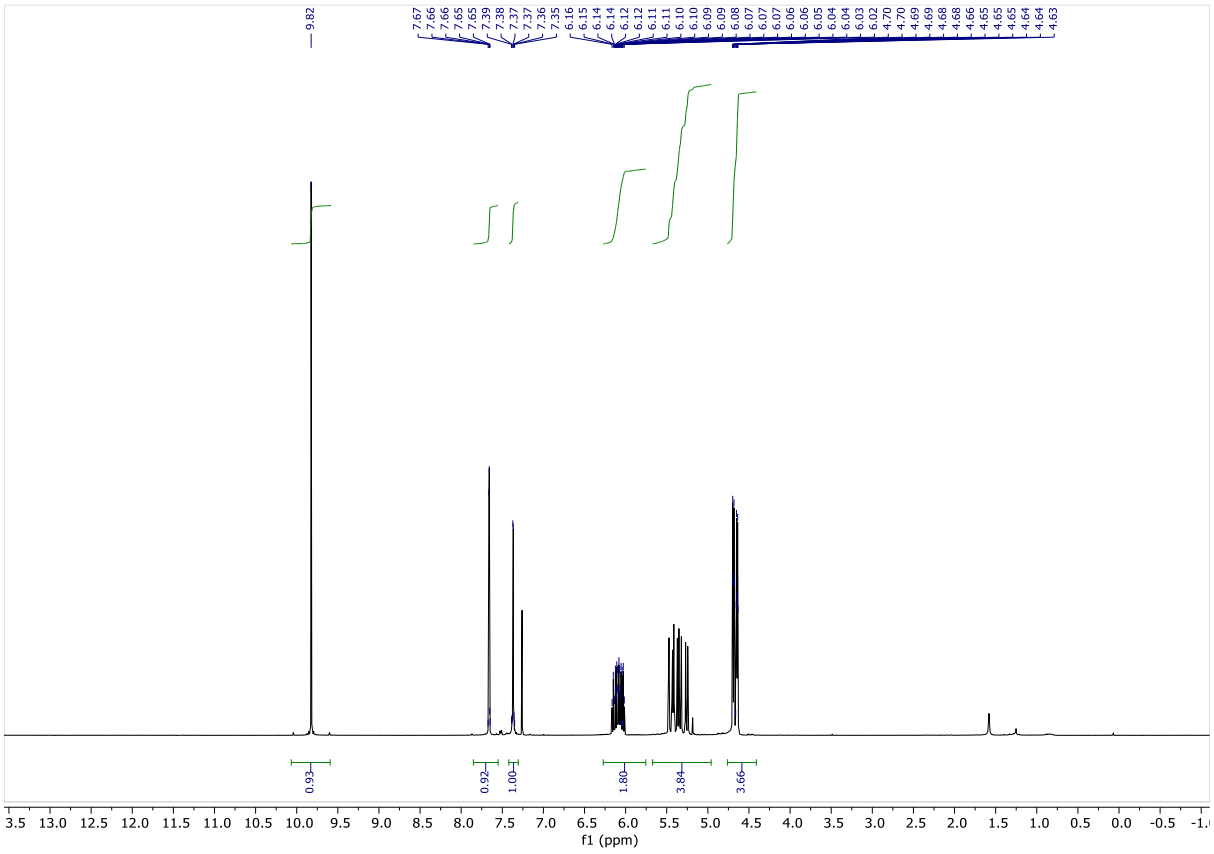
Yield: 460 mg (78 %);

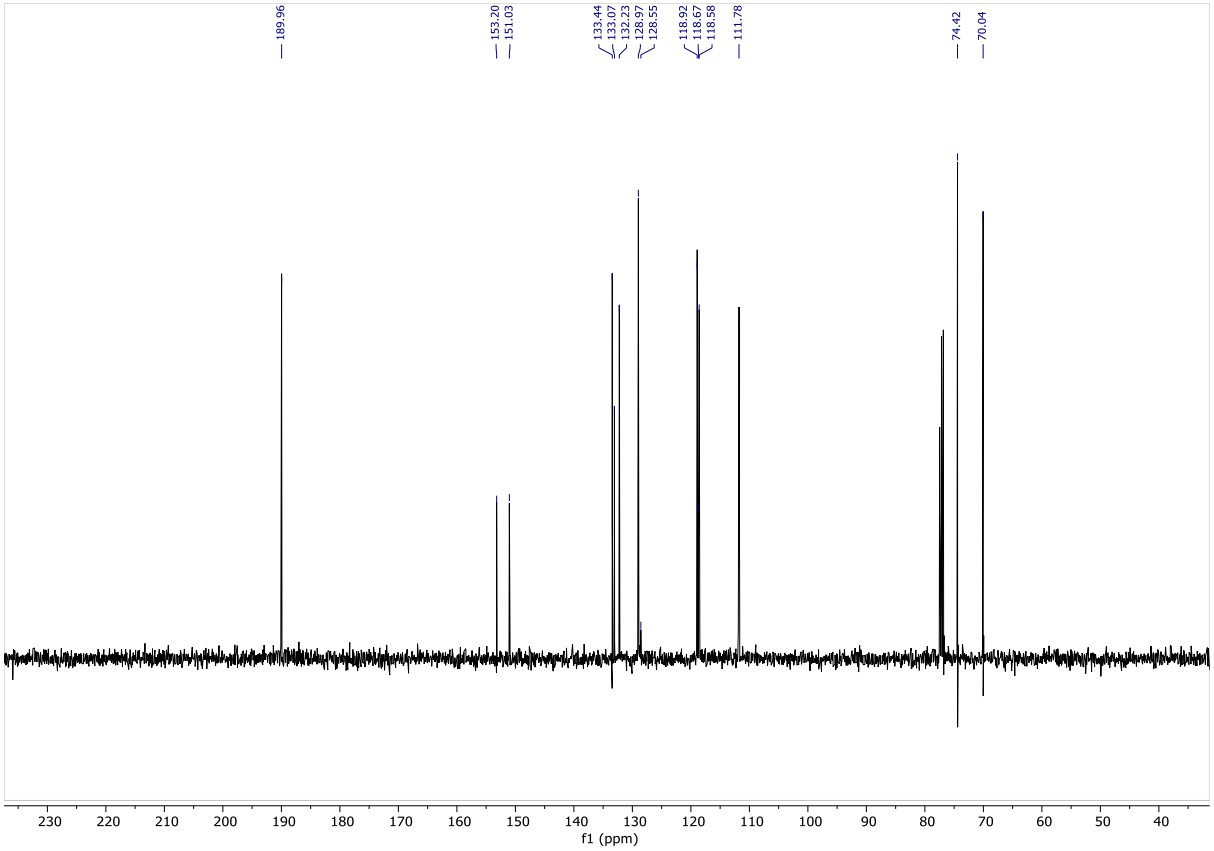
^{1}H NMR (400 MHz, Chloroform-d) δ 9.82 (s, 1H), 7.66 (d, J = 1.9 Hz, 1H), 7.37 (d, J = 1.8 Hz, 1H), 6.52 – 5.86 (m, 2H), 4.69 (dt, J = 5.9, 1.3 Hz, 2H), 4.64 (dt, J = 5.3, 1.5 Hz, 2H).

^{13}C NMR (101 MHz, Chloroform-d) δ 189.96, 153.20, 151.03, 133.44, 133.07, 132.23, 128.97, 118.92, 118.67, 118.58, 111.78, 74.42, 70.04.

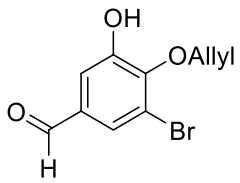
IR (film): v = 1694, 1587, 1566, 1477, 1420, 1387, 1307, 1276, 1216, 1134, 1031, 932, 854, 809, 748.

HRMS (ESI-TOF) m/z (ESI) C13H13BrNaO3 $[M+Na]^+$ 318.9940, found 318.9946.


9.82
7.67
7.66
7.66
7.65
7.65
7.38
7.37
7.37
7.36
7.35
6.16
6.15
6.14
6.14
6.12
6.12
6.11
6.11
6.10
6.10
6.09
6.09
6.08
6.07
6.07
6.06
6.06
6.05
6.04
6.04
6.03
6.02
4.70
4.70
4.69
4.69
4.68
4.68
4.66
4.65
4.65
4.65
4.64
4.64
4.63
0.93
0.92
1.00
1.80
3.84
3.66
f1 (ppm)


189.96
153.20
151.03
133.44
133.07
132.23
128.97
128.55
118.92
118.67
118.58
111.78
74.42
70.04
f1 (ppm)

*4-(allyloxy)-3-bromo-5-hydroxybenzaldehyde (**47**)*



A solution of 3,4-dihydroxy-5-brvanillin **36** (1.06 g, 4.866 mmol, 1.0 equiv.) in DMF (48.7 mL) was prepared. Then, lithium carbonate (395.5 mg, 5.353 mmol, 1.1 equiv.) and allyl bromide (0.42 mL, 4.866 mmol, 1.0 equiv.) were added to this solution at room temperature The reaction was stirred at 55 °C overnight and poured into a 0.5 M HCl solution (50 mL) at 0°C. The product was extracted with ethyl acetate (3 x). Organic layers were combined, washed with dilute HCl solution (3 x), and brine (1 x), and dried over $MgSO_4$. After filtration, the organic solvent was removed under reduced pressure, and the brown oily crude was purified by silica gel column chromatography (hexane/EtOAc, 10/1). The allyl monoprotected product **47** was obtained as a white powder 1.145 g (92 %).

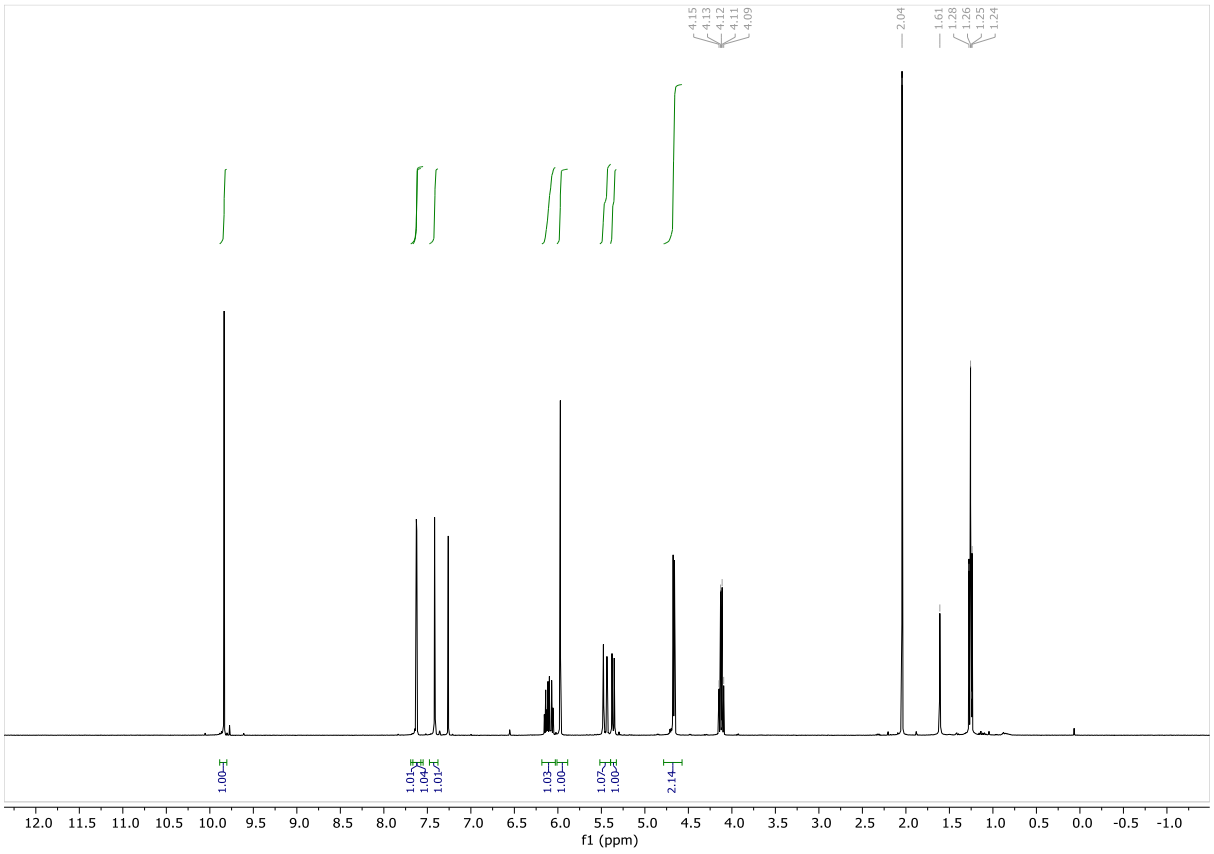
Yield: 1.145 g (92 %);

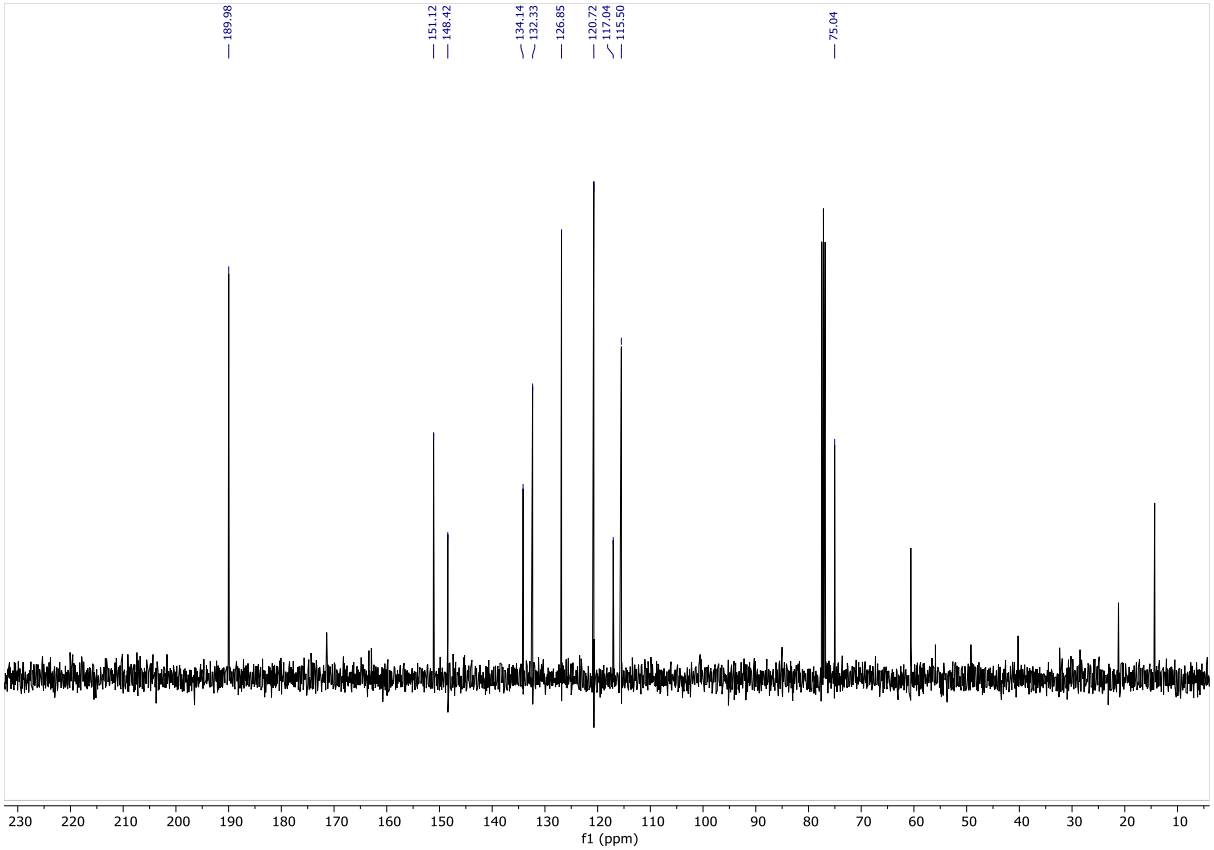
R_f = 0.628 (hexane / EtOAc = 1:1), CPS staining;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.83 (s, 1H), 7.62 (d, J = 1.9 Hz, 1H), 7.41 (d, J = 1.9 Hz, 1H), 6.11 (ddt, J = 16.5, 10.2, 6.2 Hz, 1H), 5.97 (s, 1H), 5.46 (m, 1H), 5.36 (m, 1H), 4.67 (dt, J = 6.3, 1.2 Hz, 2H); EtOAc is present

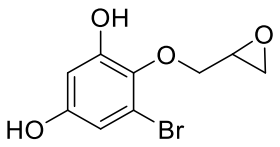
^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.0, 151.1, 148.4, 134.1, 132.3, 126.9, 120.7, 117.0, 115.5, 75.0; EtOAc is present

IR (film): v = 3082, 2953, 2923, 2871, 1681, 1647, 1602, 1561, 1475, 1450, 1421, 1389, 1365, 1326, 1302, 1232, 1218, 1166, 1109, 1031, 992, 958, 932, 860, 814, 801, 742, 689, 622, 580, 537, 499;


4.15
4.13
4.12
4.11
4.09
2.04
1.61
1.28
1.26
1.25
1.24
1.00
1.01
1.04
1.01
1.03
1.00
1.07
1.00
2.14
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


189.98
151.12
148.42
134.14
132.33
126.85
120.72
117.04
115.50
75.04
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

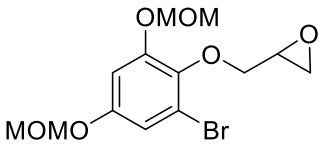
*5-bromo-4-(oxiran-2-ylmethoxy)benzene-1,3-diol (**48**)*



In a flame-dried 25 ml flask with a stirring bar solution of **47** (0.4 g, 1.56 mmol, 1.0 equiv.) in DCM (15.6 ml) was prepared under Argon atmosphere. When the starting material was fully dissolved, *m*-CPBA (77%, 0.7 g, 3.1 mmol, 2.0 equiv.) was added at room temperature and the reaction was stirred overnight for 18 h. After 18 h, the reaction was diluted with DCM and washed with sat. aq. $NaHCO_3$. Combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure and was directly used for the next step.

2nd rxn: A solution of crude material dissolved in methanol (2.52 ml, c=0.617 M) was treated with 10% aqueous potassium hydroxide (0.35 ml, 6.224 mmol, 4.0 equiv.), which turned dark purple. The resulting reaction mixture was stirred for 2 h at room temperature Then, it was diluted with water, neutralized with 2M aqueous hydrochloric acid, and extracted with ethyl acetate (2 x). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. In separation funnel yellow and pinkish layers. The crude product was purified by 2 cm column chromatography (hexane/EtOAc 20/1→6:1). The starting aldehyde **47** and the product **48** were not separable by column, thus, they were used for the next reaction as a mixture.

*2-((2-bromo-4,6-bis(methoxymethoxy)phenoxy)methyl)oxirane (**49**)*



In two separate flasks, a suspension of 60% NaH (34 mg, 1.408 mmol, 2.3 equiv.) in DMF (3.12 mL) and a solution of **48** (0.15 g, 0.61 mmol, 1.0 equiv.) in DMF (3 mL) were prepared. Then, NaH suspension was added to the solution of **48** at 0 °C. The mixture was stirred at 0 °C under an Argon atmosphere for 15 min. Then, chloromethyl methyl ether (102.3 mkl, 1.35 mmol, 2.2 equiv.) was added, and stirring was continued at room temperature overnight. The reaction mixture was poured into ice-cold water (5 mL) and extracted with EtOAc (2 x). The organic layers were collected, washed with water (2 x) and brine (1 x), dried over $MgSO_4$, and the solvent was removed under reduced pressure. **49** was obtained in 50 % over three steps.

Yield: 92 mg (50 %) or 54 % over three steps;

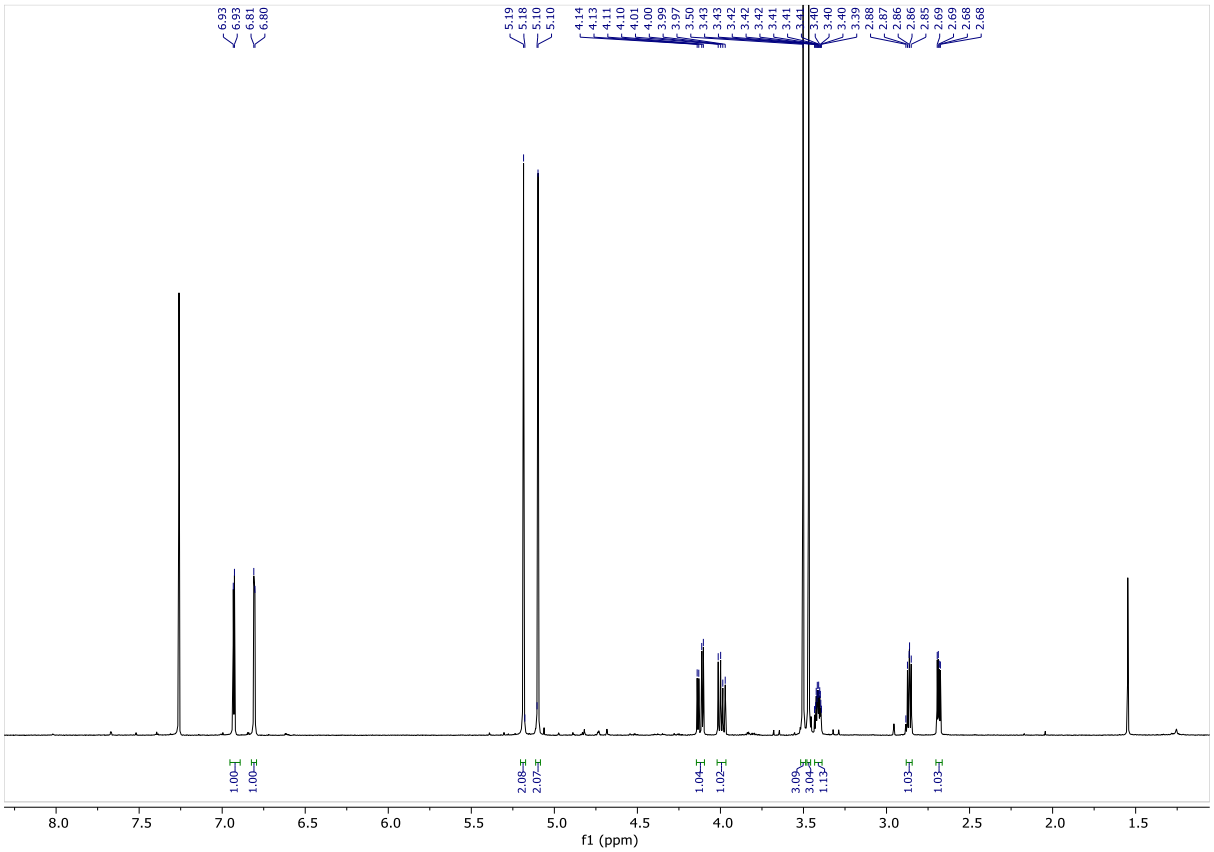
R_f = 0.47 (EtOAc), CPS staining;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.93 (d, J = 2.8 Hz, 1H), 6.81 (d, J = 2.8 Hz, 1H), 5.19 (s, 2H), 5.10 (s, 2H), 4.12-3.99 (ddd, J = 11.0, 5.9, 3.9 Hz, 2H), 3.50 (s, 3H), 3.47 (s, 3H), 3.44 – 3.36 (m, 1H), 2.86-2.69 (ddd, J = 5.0, 4.1, 2.6 Hz, 2H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.3, 151.5, 117.9, 113.5, 105.7, 95.7, 95.1, 74.5, 56.6, 56.3, 50.5, 45.0;

IR (film): ν = 2927, 2898, 2850, 2825, 1722, 1610, 1577, 1485, 1455, 1438, 1404, 1390, 1351, 1297, 1249, 1217, 1190, 1149, 1123, 1109, 1077, 1035, 1014, 924, 872, 840;

HRMS (ESI-TOF) m/z (ESI) $C_{13}H_{17}BrNaO_6$ $[M+Na]^+$ 371.0101, found 371.0102;


6.93
6.93
6.81
6.80
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5.18
5.10
5.10
4.14
4.13
4.11
4.10
4.01
4.00
3.99
3.97
3.50
3.43
3.43
3.42
3.42
3.42
3.41
3.41
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3.40
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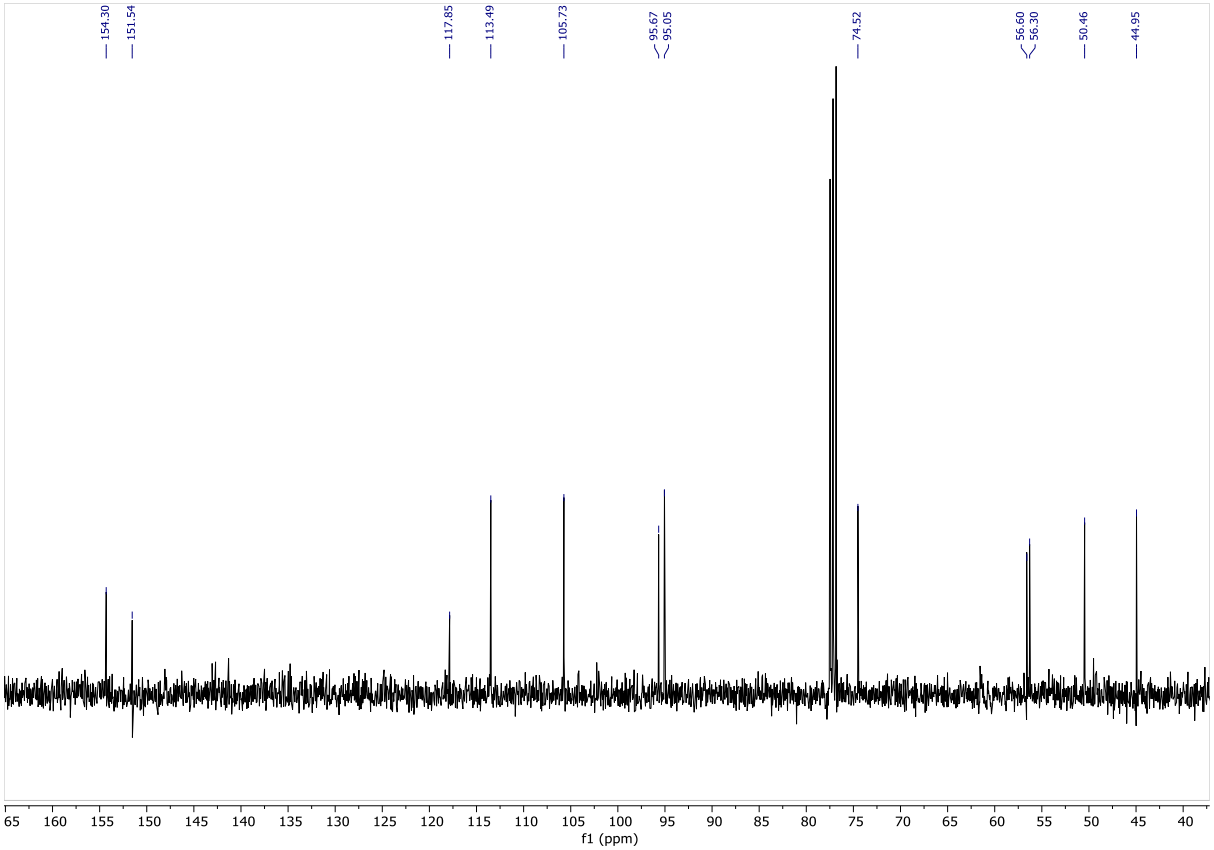
3.40
3.39
2.88
2.87
2.86
2.86
2.85
2.69
2.69
2.68
2.68
1.00
1.00
2.08
2.07
1.04
1.02
3.09
3.04
1.13
1.03
1.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)


154.30
151.54
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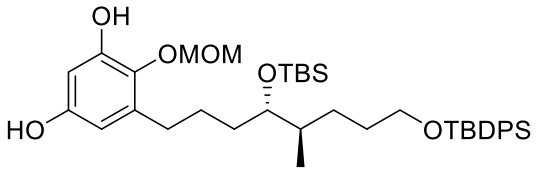
113.49
105.73
95.67
95.05
74.52
56.60
56.30
50.46
44.95
65
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
f1 (ppm)

5.2.5 Synthesis of building block A with Pg^3 = MOM and Pg^4 = allyl

*5-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-((tert-butyldiphenylsilyl)oxy)-5-methyloctyl)-4-(methoxymethoxy)benzene-1,3-diol (**51**)*



To a solution of **32** (659 mg, 0.823 mmol, 1.0 equiv.) in EtOH-extra dry (23.5 mL, c=0.035 M) was added 10 wt % Pd/C (103 mg, 15.63 wt % of Pd/C). After three to five vacuum/argon to remove air from the reaction flask, the reaction mixture was hydrogenated (also 3-5 vacuum/H_2) cycles at 3.5 bar in the autoclave directly. The reaction was constantly checked by TLC and NMR (to see the ratio between SM and prod), overall the reaction took 69 h before SM was completely consumed (even though on a 100 mg scale it was always done after 8 h). After 69 hours, and completion by TLC, the reaction was filtered over a pad of celite, washed with EA, and concentrated under reduced pressure. The crude material (m=710 mg) was purified by 3 cm FC chromatography, with eluent 10:1 hex: ea and then 5:1 hex: ea. The desired product **51** came out in fractions 24-55 as 461.5 mg colorless oil.

Yield: 462 mg (82 %);

R_f = 0.237 (1:5 ea: hex), CPS staining;

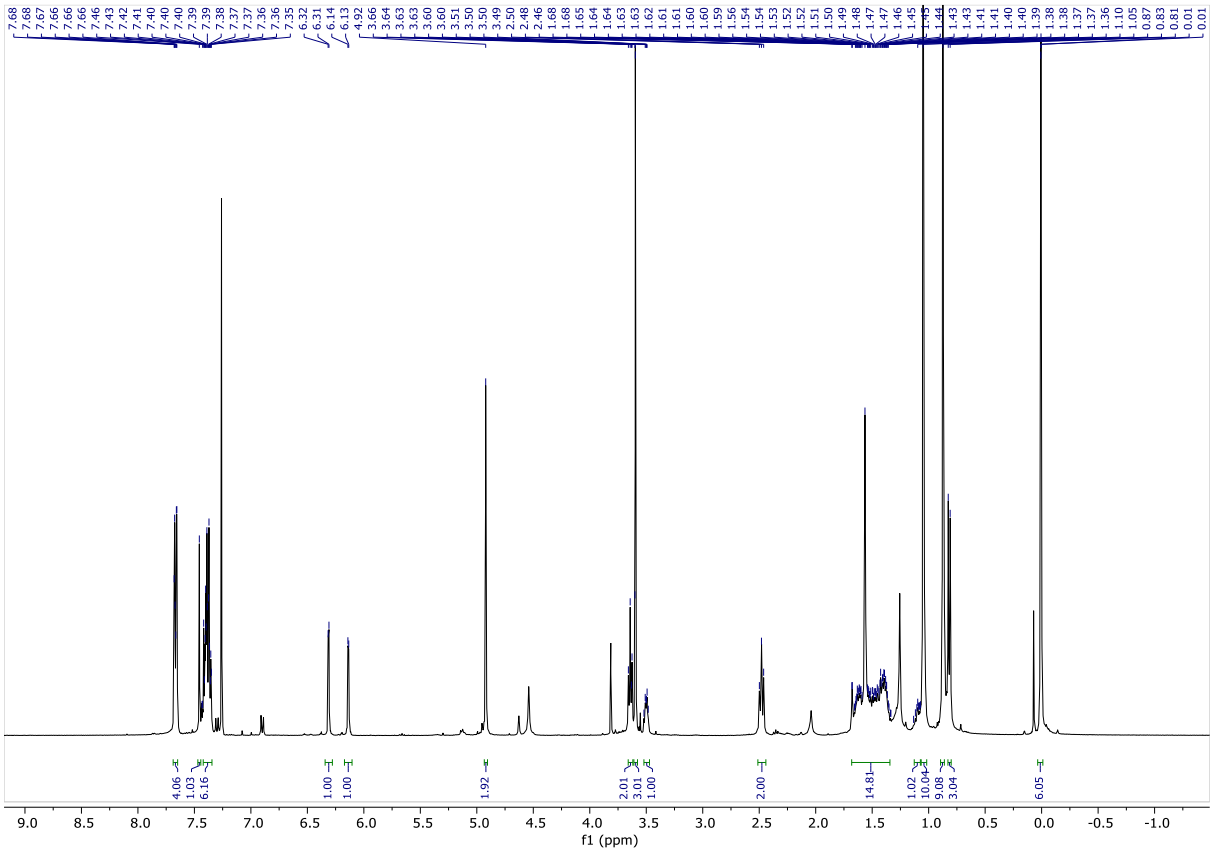
α_D^{20}: -3.95, c=3.8 mg / 0.5 ml (c=0.76, $CHCl_3$, 20°C, l=589 nm);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 – 7.59 (m, 4H), 7.46 (s, 1H), 7.43 – 7.33 (m, 6H), 6.31 (d, J = 3.0 Hz, 1H), 6.14 (d, J = 3.0 Hz, 1H), 4.92 (s, 2H), 3.64 (t, J = 6.4 Hz, 2H), 3.60 (s, 3H), 3.50 (dt, J = 6.3, 4.2 Hz, 1H), 2.48 (t, J = 7.5 Hz, 2H), 1.70 – 1.33 (m, 9H), 1.14-1.07 (m, 1H), 1.05 (s, 9H), 0.87 (s, 9H), 0.82 (d, J = 6.8 Hz, 3H), 0.01 (d, J = 1.1 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.8, 149.8, 138.8, 136.9, 135.7 (4C), 134.3 (2C), 129.7 (2C), 127.7 (4C), 107.4, 102.0, 100.5, 76.0, 64.5, 57.2, 38.3, 32.4, 30.8, 30.7, 28.8, 27.0 (3C), 26.5, 26.1 (3C), 19.4, 18.3, 14.8, -4.2, -4.3;

IR (film): ν = 3362, 2932, 2857, 2372, 2346, 2325, 2154, 2032, 1996, 1982, 1974, 1602, 1463, 1428, 1255, 1143, 1111, 1086, 1004, 836, 805, 774, 742, 703, 607, 518;

HRMS (ESI-TOF) m/z (ESI) $C_{39}H_{60}NaO_6Si_2$ $[M+Na]^+$ 703.3821, found 703.3815.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7.41
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7.40
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7.39
7.38
7.37
7.36
7.35
6.32
6.31
6.14
6.13
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1.40
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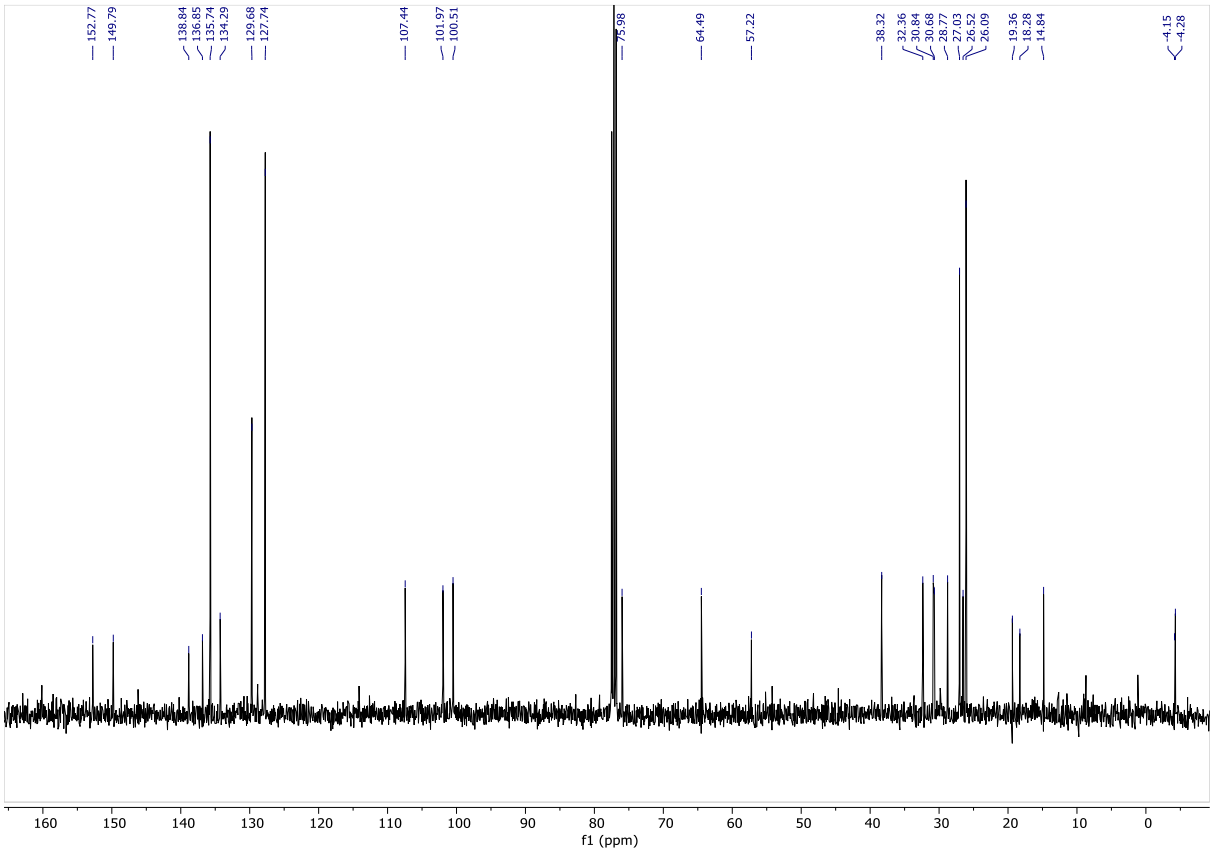
1.39
1.38
1.38
1.37
1.37
1.36
1.10
1.05
0.87
0.83
0.81
0.01
0.01
4.06
1.03
6.16
1.00
1.00
1.92
2.01
3.01
1.00
2.00
14.81
1.02
10.04
9.08
3.04
6.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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134.29
129.68
127.74
107.44
101.97
100.51
75.98
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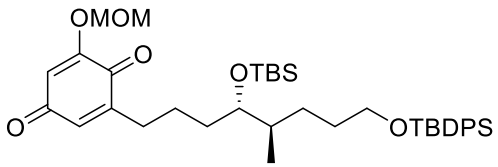
57.22
38.32
32.36
30.84
30.68
28.77
27.03
26.52
26.09
19.36
18.28
14.84
-4.15
-4.28
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

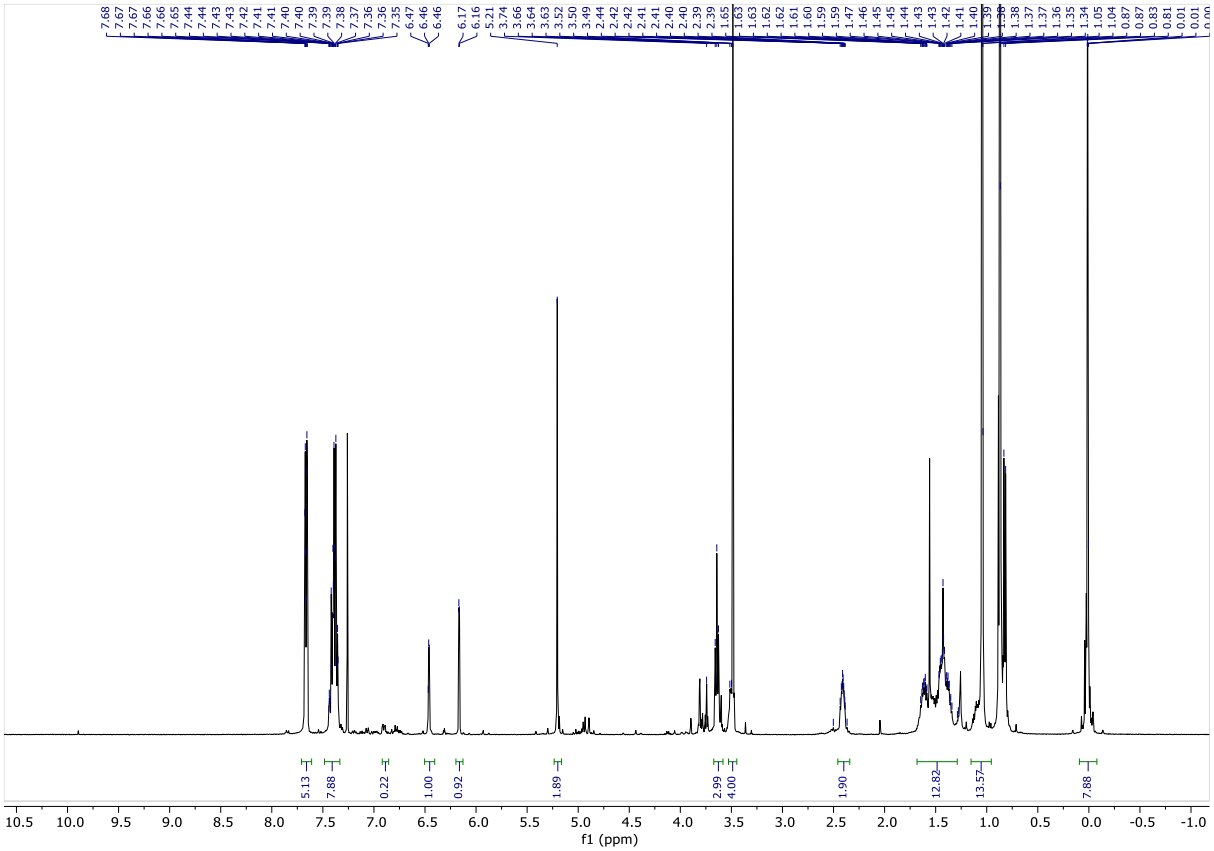
*2-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-((tert-butyldiphenylsilyl)oxy)-5-methyloctyl)-6-(methoxymethoxy)cyclohexa-2,5-diene-1,4-dione (**52**)*

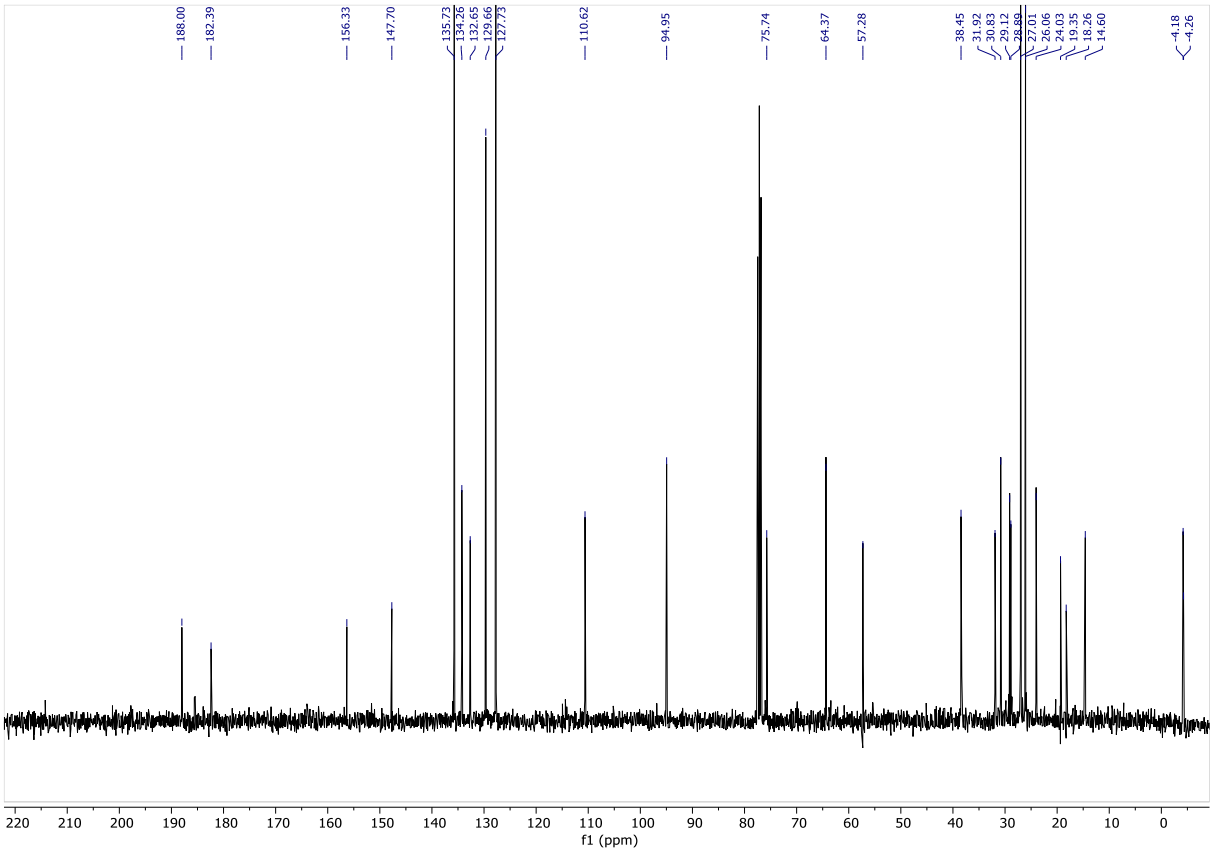


^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 – 7.60 (m, 4H), 7.55 – 7.32 (m, 6H), 6.46 (d, J = 2.3 Hz, 1H), 6.17 (d, J = 2.4 Hz, 1H), 5.21 (s, 2H), 3.64 (t, J = 6.4 Hz, 2H), 3.53 – 3.49 (m, 1H), 3.49 (s, 3H), 2.54 – 2.20 (m, 2H), 1.69 – 1.56 (m, 3H), 1.47 – 1.28 (m, 5H), 1.11 (m, 1H), 1.05 (s, 9H), 0.87 (s, 9H), 0.82 (d, J = 6.8 Hz, 3H), 0.01 (d, J = 1.7 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.0, 182.4, 156.3, 147.7, 135.7 (4C), 134.3 (2C), 132.7, 129.7 (2C), 127.7 (4C), 110.6, 95.0, 75.7, 64.4, 57.3, 38.5, 31.9, 30.8, 29.1, 28.9, 27.0 (3C), 26.1 (3C), 24.0, 19.4, 18.3, 14.6, -4.2, -4.3;

HRMS (ESI-TOF) m/z (ESI) $C_{39}H_{62}NO_6Si_2$ $[M+NH_4]^+$ 696.4110, found 696.4111.




188.00
182.39
156.33
147.70
135.73
134.26
132.65
129.66
127.73
110.62
94.95
75.74
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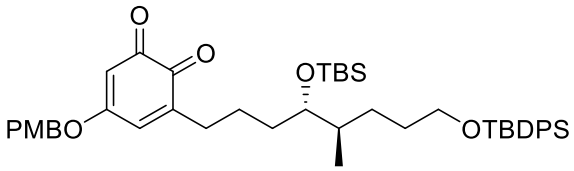
57.28
38.45
31.92
30.83
29.12
28.88
27.01
26.06
24.03
19.35
18.26
14.60
-4.18
-4.26
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

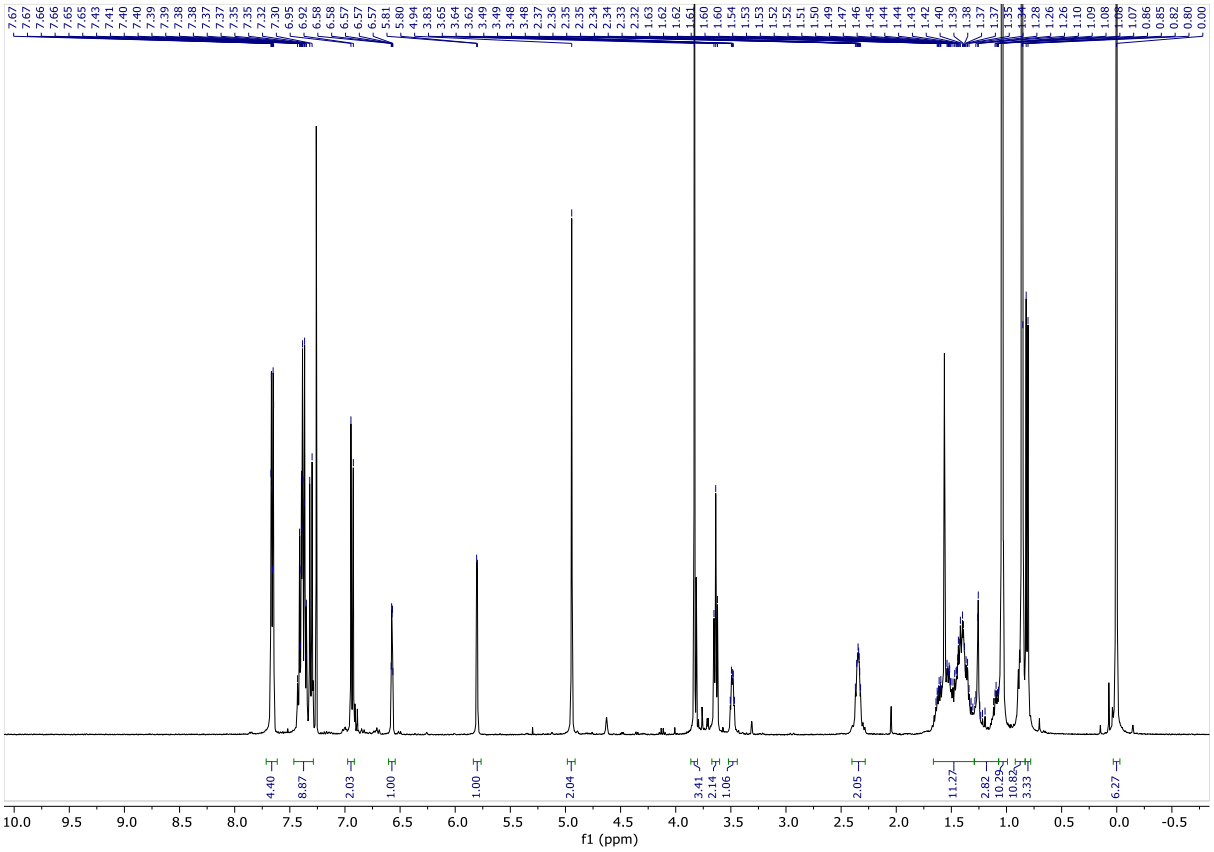
*3-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-((tert-butyldiphenylsilyl)oxy)-5-methyloctyl)-5-((4-methoxybenzyl)oxy)cyclohexa-3,5-diene-1,2-dione (**53**)*

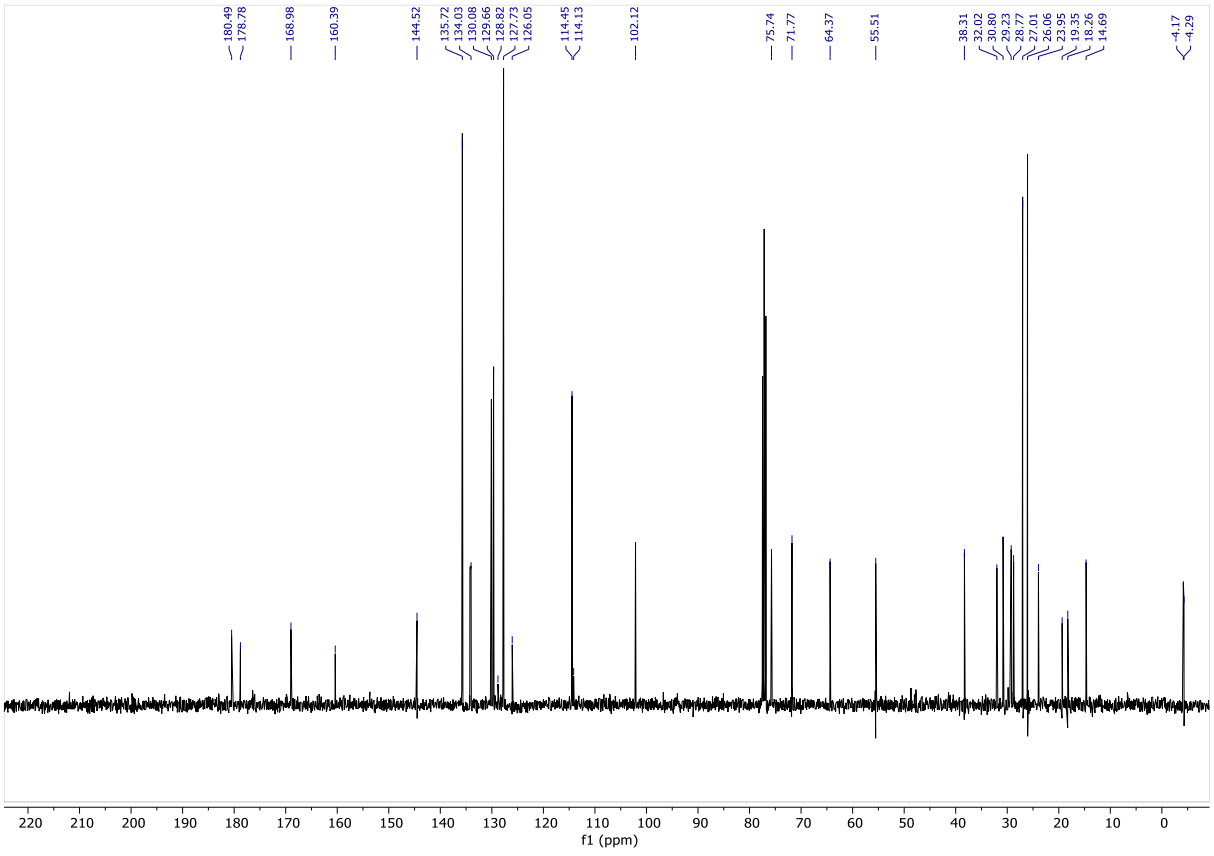


^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 – 7.58 (m, 4H), 7.52 – 7.35 (m, 6H), 7.31 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.81 – 6.38 (m, 1H), 5.80 (d, J = 2.9 Hz, 1H), 4.94 (s, 2H), 3.83 (s, 3H), 3.64 (t, J = 6.4 Hz, 2H), 3.49 (dt, J = 6.4, 4.1 Hz, 1H), 2.44 – 2.25 (m, 2H), 1.70 – 1.59 (m, 2H), 1.54 – 1.19 (m, 6H), 1.14 – 1.07 (m, 1H), 1.04 (s, 9H), 0.86 (s, 9H), 0.81 (d, J = 6.8 Hz, 3H), 0.00 (s, 6H);

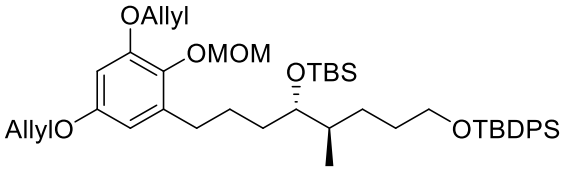
^{13}C NMR (101 MHz, Chloroform-*d*) δ 180.5, 178.8, 169.0, 160.4, 144.5, 135.7 (4C), 134.3, 134.0 (2C), 130.1 (2C), 129.7 (2C), 127.7 (4C), 126.1, 114.5 (2C), 102.1, 75.7, 71.8, 64.4, 55.5, 38.3, 32.0, 30.8, 29.2, 28.8, 27.0 (3C), 26.1 (3C), 24.0, 19.4, 18.3, 14.7, -4.2, -4.3;

HRMS (ESI-TOF) m/z (ESI) $C_{45}H_{62}NaO_6Si_2$ $[M+Na]^+$ 777.3977, found 777.3983.




180.49
178.78
168.98
160.39
144.52
135.72
134.03
130.08
129.66
128.82
127.73
126.05
114.45
114.13
102.12
75.74
71.77
64.37
55.51
38.31
32.02
30.80
29.23
28.77
27.01
26.06
23.95
19.35
18.26
14.69
-4.17
-4.29
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

*(5S,6R)-5-(3-(3,5-bis(allyloxy)-2-(methoxymethoxy)phenyl)propyl)-2,2,3,3,6,12,12-heptamethyl-11,11-diphenyl-4,10-dioxa-3,11-disilatridecane (**54**)*



In a 25 ml flask, a solution of **51** (405.5 mg, 0.595 mmol, 1.0 equiv.) was dissolved in DMF (5.95 ml, c=0.1). K_2CO_3 (823 mg, 5.95 mmol, 10 equiv.) was added at room temperature – the color of the solution changed from yellow to light pink. Then, Allyl bromide (0.514 ml, 5.95 mmol, 10 equiv.) was added at the same temperature. The reaction was monitored by TLC and was completed after 18 hours of stirring at room temperature. The reaction solution was quenched with water and extracted with DCM (10 ml) three times. The crude material was purified with 3 cm FC with eluent 5:1 hex: EtOAc and the product **54** came out in fractions 4-13. No monoallylation was detected with 10 equivalents of reagents.

Yield: 411 mg (91 %);

R_f = 0.565 (5:1 hexane: EtOAc), CPS staining;

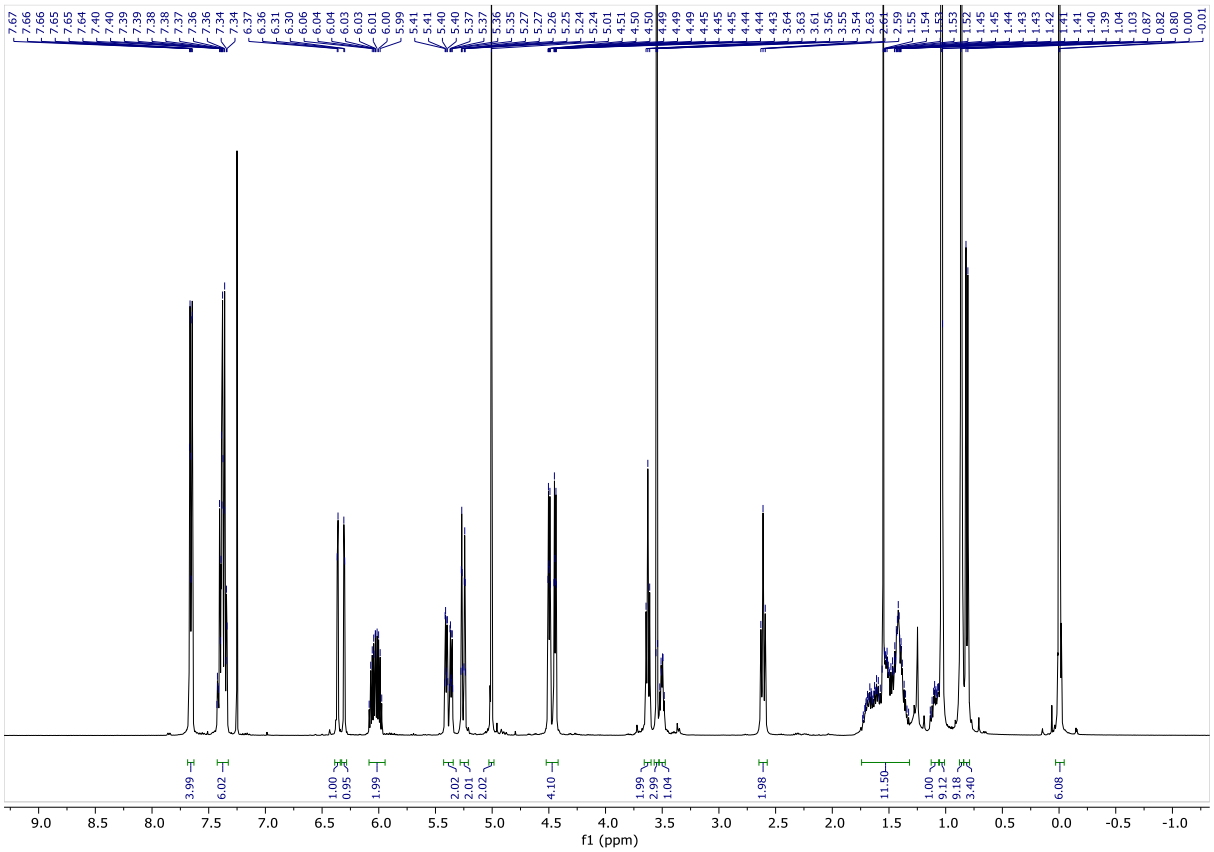
α_D^{20}: -2.86, c=4.2 mg / 0.6 ml (c=0.7, $CHCl_3$, 20°C, l=589 nm);

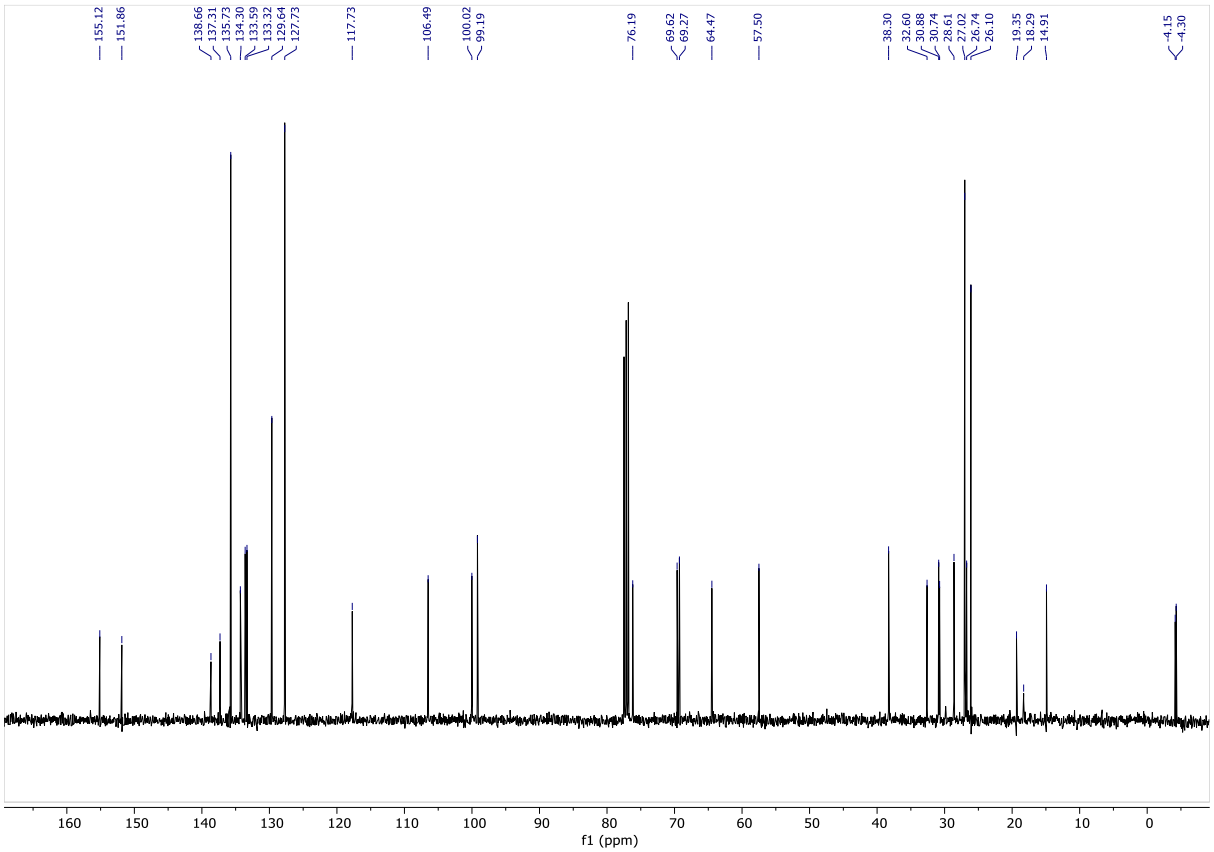
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 (m, 4H), 7.49 – 7.29 (m, 6H), 6.36 (d, J = 2.8 Hz, 1H), 6.30 (d, J = 2.9 Hz, 1H), 6.11 – 5.95 (m, 2H), 5.38 (m, 2H), 5.26 (m, 2H), 5.01 (s, 2H), 4.47 (ddt, J = 21.2, 5.4, 1.5 Hz, 4H), 3.63 (t, J = 6.5 Hz, 2H), 3.55 (s, 3H), 3.50 (m, 1H), 2.61 (t, J = 7.8 Hz, 1H), 1.77 – 1.32 (m, 9H), 1.14 – 1.06 (m, 1H), 1.04 (s, 9H), 0.87 (s, 9H), 0.81 (d, J = 6.7 Hz, 3H), -0.00 (d, J = 2.6 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.1, 151.9, 138.7, 137.3, 135.7 (4C), 134.3 (2C), 133.6, 133.3, 129.6 (2C), 127.7 (4C), 117.7 (2C), 106.5, 100.0, 99.2, 76.2, 69.6, 69.3, 64.5, 57.5, 38.3, 32.6, 30.9, 30.7, 28.6, 27.0 (3C), 26.7, 26.1 (3C), 19.4, 18.3, 14.9, -4.2, -4.3;

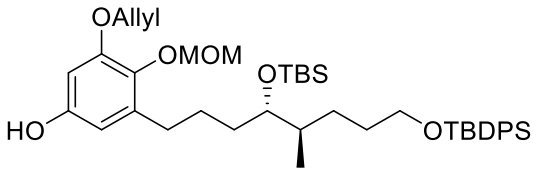
IR (film): ν = 3072, 2954, 2930, 2857, 2365, 2208, 2160, 2149, 2015, 2006, 1600, 1489, 1472, 1462, 1427, 1361, 1255, 1190, 1159, 1111, 1089, 981, 928, 835, 807, 773, 741, 703, 687, 670, 613, 505;

HRMS (ESI-TOF) m/z (ESI) $C_{45}H_{68}NaO_6Si_2$ $[M+Na]^+$ 783.4447, found 783.4441.


f1 (ppm)


f1 (ppm)

*3-(allyloxy)-5-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-((tert-butyldiphenylsilyl)oxy)-5-methyloctyl)-4-(methoxymethoxy)phenol (**SI-54**)*



Monoallylation product was detected once with 6 equivalents of AllylBr and K_2CO_3 instead of 10. Biallylation is a slightly yellow oil, monoallylation-yellow oil.

Yield: 11 mg (3 %);

R_f = 0.355 (5:1 hexane: EtOAc), CPS staining;

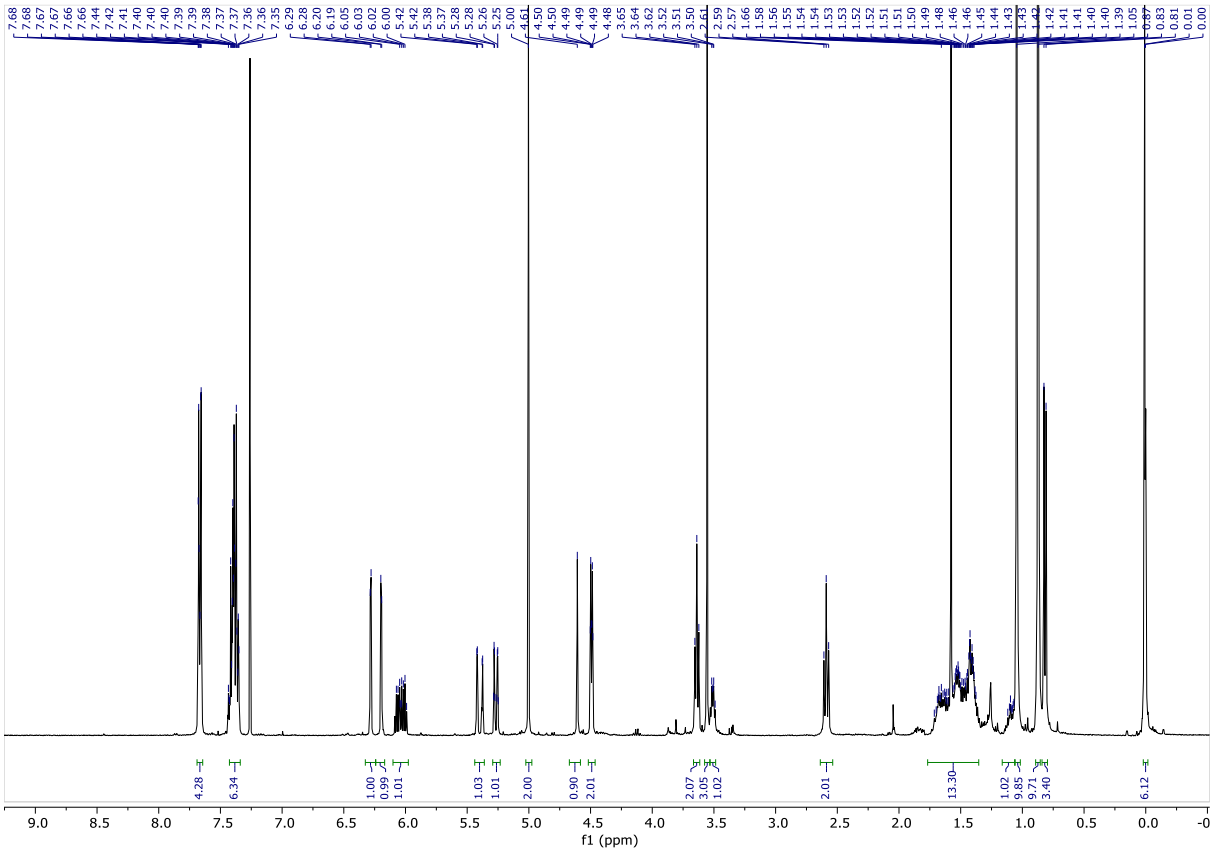
α_D^{20}: -34.28, c=4.2 mg / 0.6 ml (c=0.7, $CHCl_3$, 20°C, l=589 nm);

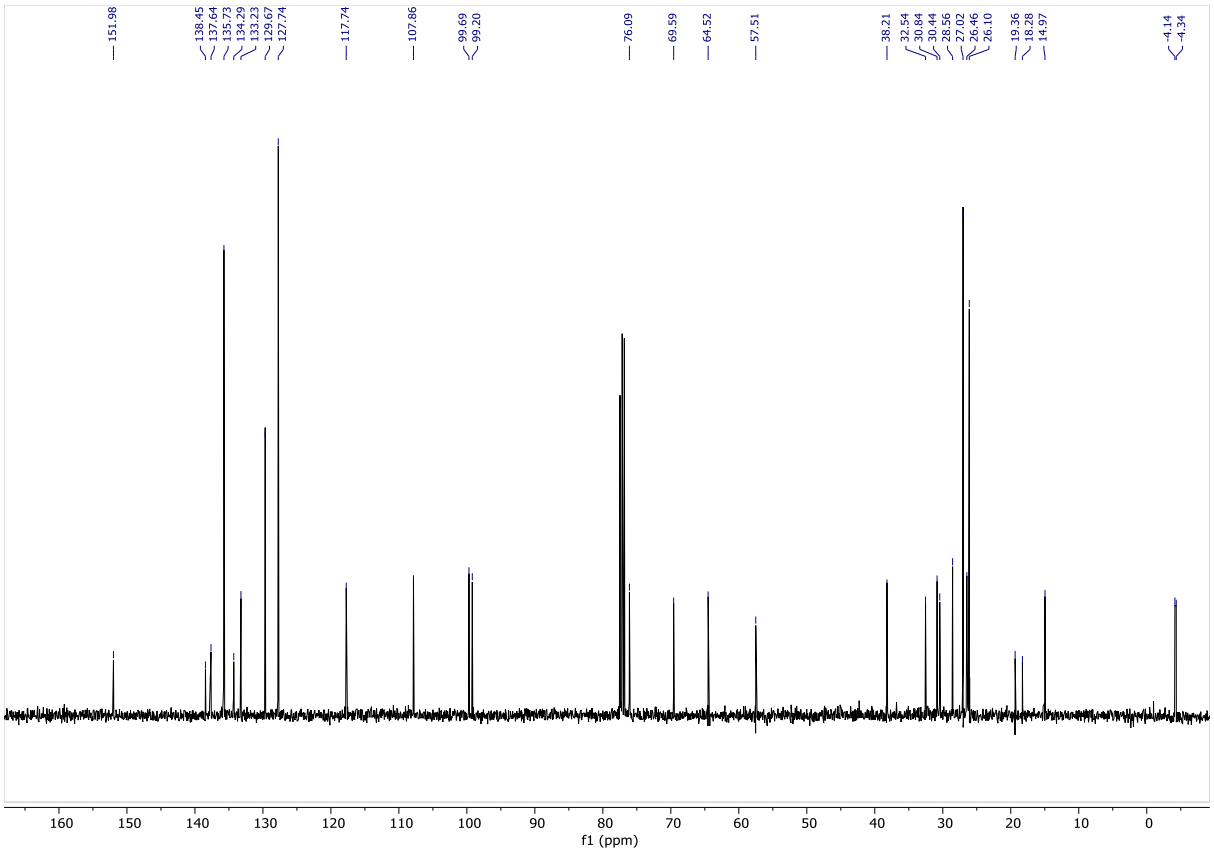
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 – 7.54 (m, 4H), 7.50 – 7.32 (m, 6H), 6.28 (d, J = 2.8 Hz, 1H), 6.20 (d, J = 2.8 Hz, 1H), 6.09 – 5.89 (m, 1H), 5.42-5.37 (dd, J = 17.3, 1.7 Hz, 1H), 5.27 (m, 1H), 5.00 (s, 2H), 4.61 (s, 1H from OH), 4.49 (m, 2H), 3.64 (t, J = 6.4 Hz, 2H), 3.56 (s, 3H), 3.54 – 3.48 (m, 1H), 2.59 (t, J = 7.7 Hz, 2H), 1.72 – 1.37 (m, 8H), 1.15 – 1.07 (m, 1H), 1.05 (s, 9H), 0.87 (s, 9H), 0.82 (d, J = 6.8 Hz, 3H), 0.01 (d, J = 2.8 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.0 (2C), 138.5, 137.6, 135.7 (4C), 134.3 (2C), 133.2, 129.7 (2C), 127.7 (4C), 117.7, 107.9, 99.7, 99.2, 76.1, 69.6, 64.5, 57.5, 38.2, 32.5, 30.8, 30.4, 28.6, 27.0 (3C), 26.5, 26.1 (3C), 19.4, 18.3, 15.0, -4.1, -4.3;

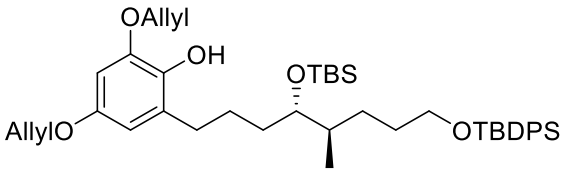
IR (film): ν = 3385, 2930, 2857, 2360, 2336, 2012, 1991, 1603, 1462, 1428, 1361, 1254, 1190, 1158, 1110, 1087, 983, 936, 836, 773, 741, 702, 614, 558, 544;

HRMS (ESI-TOF) m/z (ESI) $C_{42}H_{64}NaO_6Si_2$ $[M+Na]^+$ 743.4134, found 743.4137.


f1 (ppm)


f1 (ppm)

*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-((tert-butyldiphenylsilyl)oxy)-5-methyloctyl)phenol (**55**)*



In a 25 ml flask, a solution of MOM ether **54** (250 mg, 0.328 mmol, 1.0 equiv.) in DCM (12.394 mL, c=0.0265) was prepared at room temperature Then, amylene (1.24 mL, 11.66 mmol, 35.5 equiv.) was added and the solution was cooled to -78 ˚C. Then, Et_3N (0.411 mL, 2.956 mmol, 9.0 equiv.) -not freshly distilled and $TiCl_4$ (1.0 M yellow solution in DCM, 0.739 mL, 0.739 mmol, 2.25 equiv.) were added at −78 °C. The reaction solution is dark brown. In 30 minutes completion of the reaction was detected by TLC, and it was worked up with saturated aqueous $NaHCO_3$ solution at -78 °C, directly changed to 0 °C, and then allowed to warm to the room temperature while stirring. The resulting mixture was diluted with DCM (10 ml) and the organic phase was separated, then the water phase was extracted two more times with EtOAc (15 ml) and the combined organic layer was dried over anhydrous $MgSO_4$, and concentrated. The crude material (m=247 mg) was purified with 1 cm column chromatography with toluene as an eluent, switching to 50:1 Toluene: EtOAc, and then 20:1. The desired product **55** is a colorless oil (237.3 mg).

Yield: 237 mg (100 %);

R_f = 0.71 (50:1=Toluene:EtOAc), CPS staining;

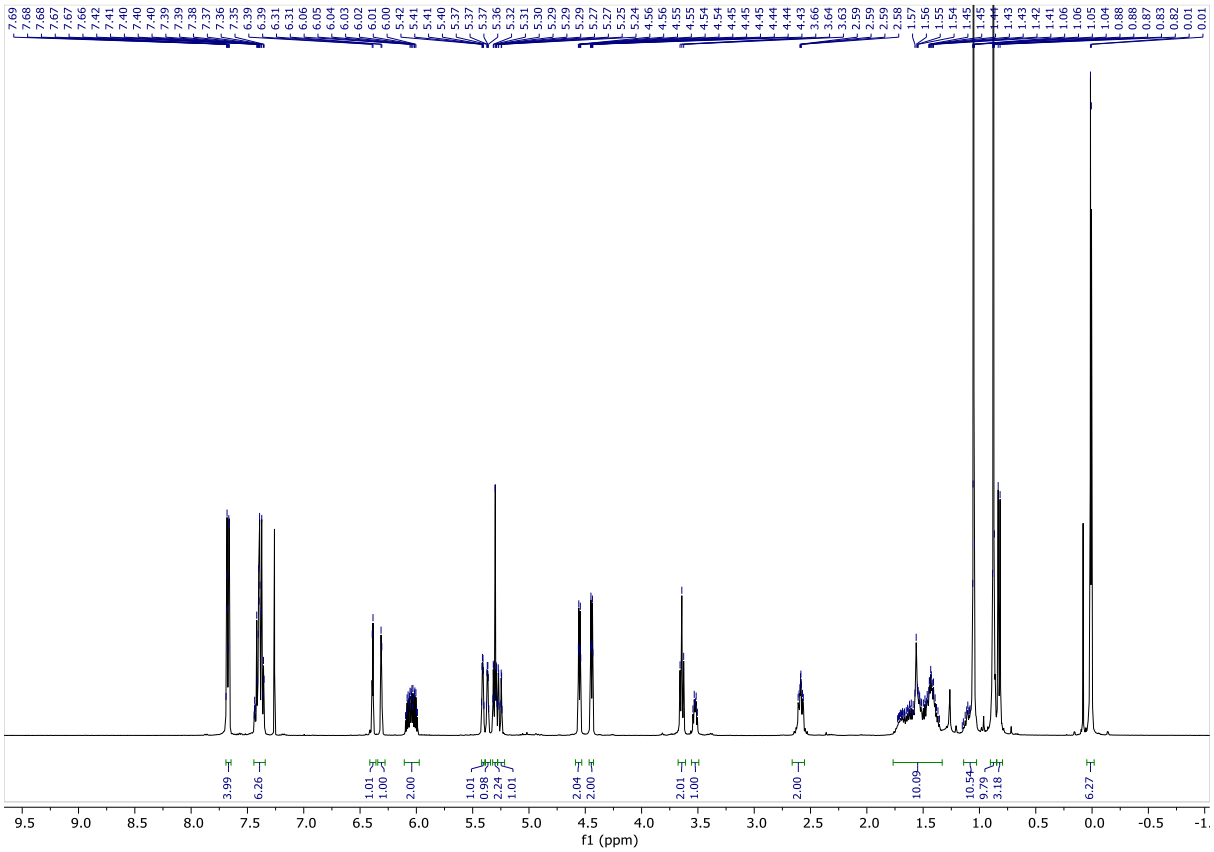
α_D^{20}: -1.00, (c=1.00, $CHCl_3$, 20°C, l=589 nm);

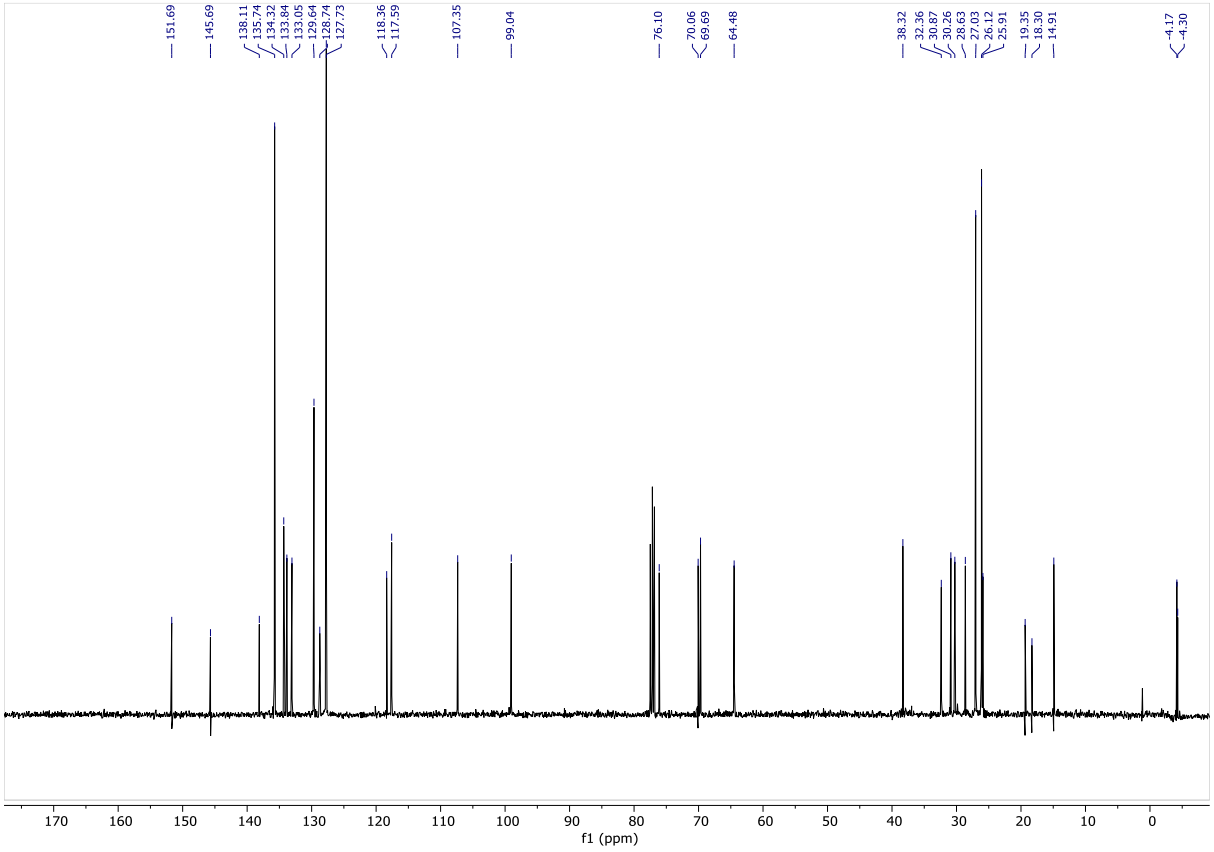
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 – 7.50 (m, 4H), 7.50 – 7.35 (m, 6H), 6.39 (d, J = 2.8 Hz, 1H), 6.31 (d, J = 2.7 Hz, 1H), 6.12 – 5.95 (m, 2H), 5.41 (m, 1H), 5.37 (m, 1H), 5.32 (m, 1H and 1OH), 5.26 (m, 1H), 4.55 (dt, J = 5.4, 1.5 Hz, 2H), 4.44 (dt, J = 5.3, 1.5 Hz, 2H), 3.64 (t, J = 6.4 Hz, 2H), 3.55 – 3.48 (m, 1H), 2.65 – 2.52 (m, 2H), 1.80 – 1.33 (m, 8H), 1.17 – 1.07 (m, 1H), 1.05 (s, 9H), 0.88 (s, 9H), 0.83 (d, J = 6.8 Hz, 3H), 0.01 (d, J = 3.2 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 151.7, 145.7, 138.1, 135.7 (4C), 134.3 (2C), 133.8, 133.1, 129.6 (2C), 128.7, 127.7 (4C), 118.4, 117.6, 107.4, 99.0, 76.1, 70.1, 69.7, 64.5, 38.3, 32.4, 30.9, 30.3, 28.6, 27.0 (3C), 26.1 (3C), 25.9, 19.4, 18.3, 14.9, -4.2, -4.3;

IR (film): ν = 3553, 3072, 2954, 2930, 2857, 2358, 2000, 1609, 1496, 1472, 1462, 1427, 1387, 1362, 1254, 1222, 1148, 1111, 1089, 1007, 927, 835, 773, 741, 702, 613, 547, 535, 505;

HRMS (ESI-TOF) m/z (ESI) $C_{43}H_{64}NaO_5Si_2$ $[M+Na]^+$ 739.4184, found 739.4181.

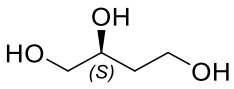

f1 (ppm)


f1 (ppm)

5.2.6 Synthesis of acids 2

Synthesis of (*R,R*)-2[7]

*(S)-butane-1,2,4-triol (S-**61**)*

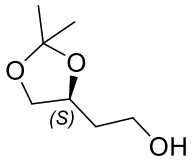


In a 50 ml flask solution of *L*-malic acid (1.4 g, 1.0 equiv.) in THF (17 ml, c=0.62 M) was prepared. Then, trimethyl borate (4.9 ml, 4.2 equiv.) was added over 15 minutes *via* syringe, and the solution was stirred at room temperature for 1 h. After stirring for 1 h at room temperature, borane dimethyl sulfide (2 M in THF, 12.53 ml, 2.4 equiv.) was added slowly via a syringe while being cooled with an ice bath. The reaction was stirred at room temperature for 17 h overnight. After the completion of the reaction by TLC, the solvent was removed under reduced pressure. The residue was dissolved in MeOH (10 ml) and evaporated 2 times. The crude material of *S*-**61** was submitted to the next step directly.

Yield: 1.1 g (99 %);

R_f = 0.457 (DCM:MeOH = 4:1), $KMnO_4$ staining;

*(S)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethan-1-ol (S-**62**)*



In a 2 l flask, a solution of 1,2,4-butanetriol *S*-**61** (1.1 g, 1.0 equiv.) in dry DCM (21 ml) was cooled to 0 °C. Then, 2,2-dimethoxypropane (2.6 ml, 2.0 equiv.) and a catalytic amount of p-TsOH (0.2 g, 0.10 equiv.), were stirred for 1.5 hours at room temperature After completion of the reaction, it was quenched with sat. $NaHCO_3$ and the water layer were extracted with DCM (3 x 10 ml). The organic layer was washed with brine and dried over anhydrous $MgSO_4$. Removal of the solvent gave a crude product S-**62**, which was purified via column chromatography using Ea: Hex gradient as an eluent.

Yield: g (55 % over 2 steps);

R_f = 0.108 (hexane/EA 2/1), CPS staining;

$[\alpha]_{20}^{D}$: = +5.0 (c = 1.0; $CHCl_3$, 20°C) - freshly synthesized substrate;

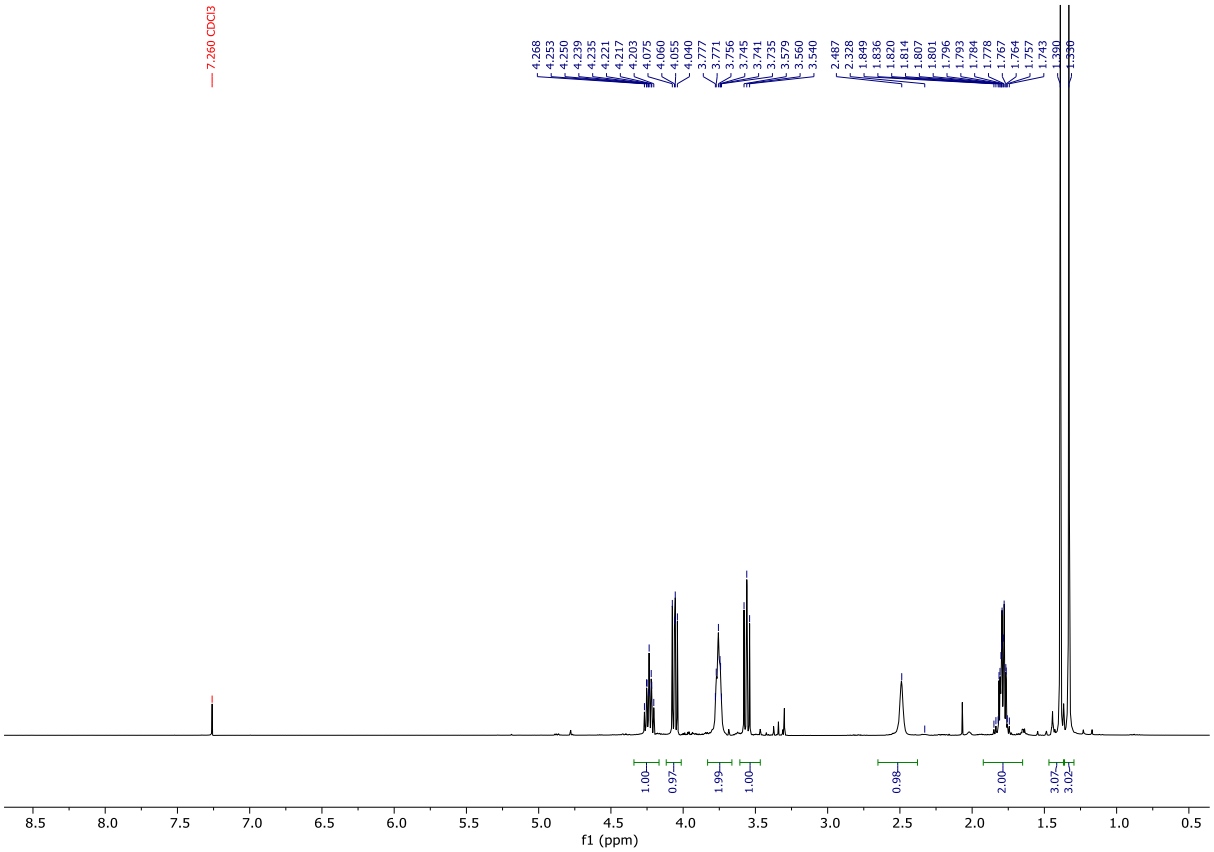
$[\alpha]_{20}^{D}$: = +3.0 (c = 1.0; $CHCl_3$, 20°C) – commercially available material;

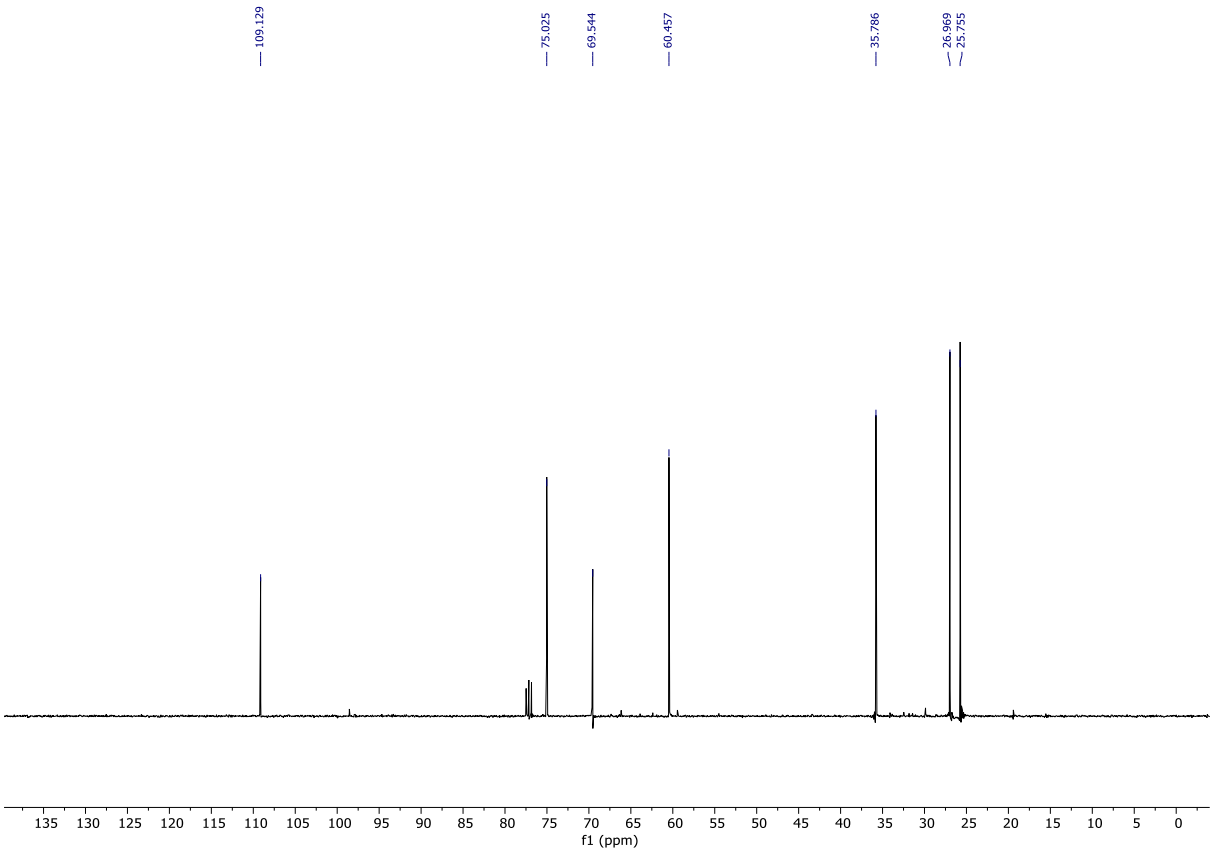
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.24 (ddd, J = 12.8, 7.2, 5.7 Hz, 1H), 4.06 (dd, J = 8.1, 5.9 Hz, 1H), 3.75 (m, 2H), 3.58 – 3.53 (m, 1H), 2.49 (s, 1H), 1.92 – 1.63 (m, 2H), 1.39 (s, 3H), 1.33 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 109.1, 75.0, 69.5, 60.5, 35.8, 27.0, 25.8.

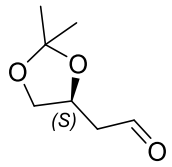
IR (film): ν = 3410, 2985, 2938, 2878, 1371, 1246, 1216, 1157, 1055, 990, 854, 514, 409;

HRMS (ESI-TOF) *m/z* calcd. for $C_7H_{14}NaO_3$ $[M+Na]^+$ 169.0835, found 169.0834.


7.260 CDCl3
4.268
4.253
4.250
4.239
4.235
4.221
4.217
4.203
4.075
4.060
4.055
4.040
3.777
3.771
3.756
3.745
3.741
3.735
3.579
3.560
3.540
2.487
2.328
1.849
1.836
1.820
1.814
1.807
1.801
1.796
1.793
1.784
1.778
1.767
1.764
1.757
1.743
1.390
1.330
1.00
0.97
1.99
1.00
0.98
2.00
3.07
3.02
f1 (ppm)


109.129
75.025
69.544
60.457
35.786
26.969
25.755
f1 (ppm)

*(S)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (S-**6**)* [7]



In a dried round bottom, a 500 ml flask charged with a stirring bar (10 g, 68.404 mmol 1.0 equiv.) of S-**62** from the bottle was dissolved in DCM (250 ml) under Argon at room temperature After complete dissolution of the starting material NEt_3 (30.5 ml, 218.9 mmol, 3.2 equiv.) was added and the mixture stirred for 5-10 min. Then (48.6 mL) DMSO was added to the reaction mixture and stirred for another 10 min. The last step was the addition of SO_3*pyridine complex (34.8 g, 218.9 mmol, 3.2 equiv.) and further stirring for another at 30 min room temperature with TLC control. When the reaction was completed (verified by TLC), 200 ml of saturated aqueous $NaHCO_3$ was added and then the reaction mixture was extracted with DCM (3 x 150 mL). After extraction, the combined organic phases were washed with brine (150 ml), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude material was purified by FC (diethyl ether: hexane = 1:2), obtaining S-**6** (5.5 g, 56 %) as a colorless oil.

Yield: 5.5 g (56 %);

R_f = 0.27 (hexane/Et_2O 1/1), $KMnO_4$ staining;

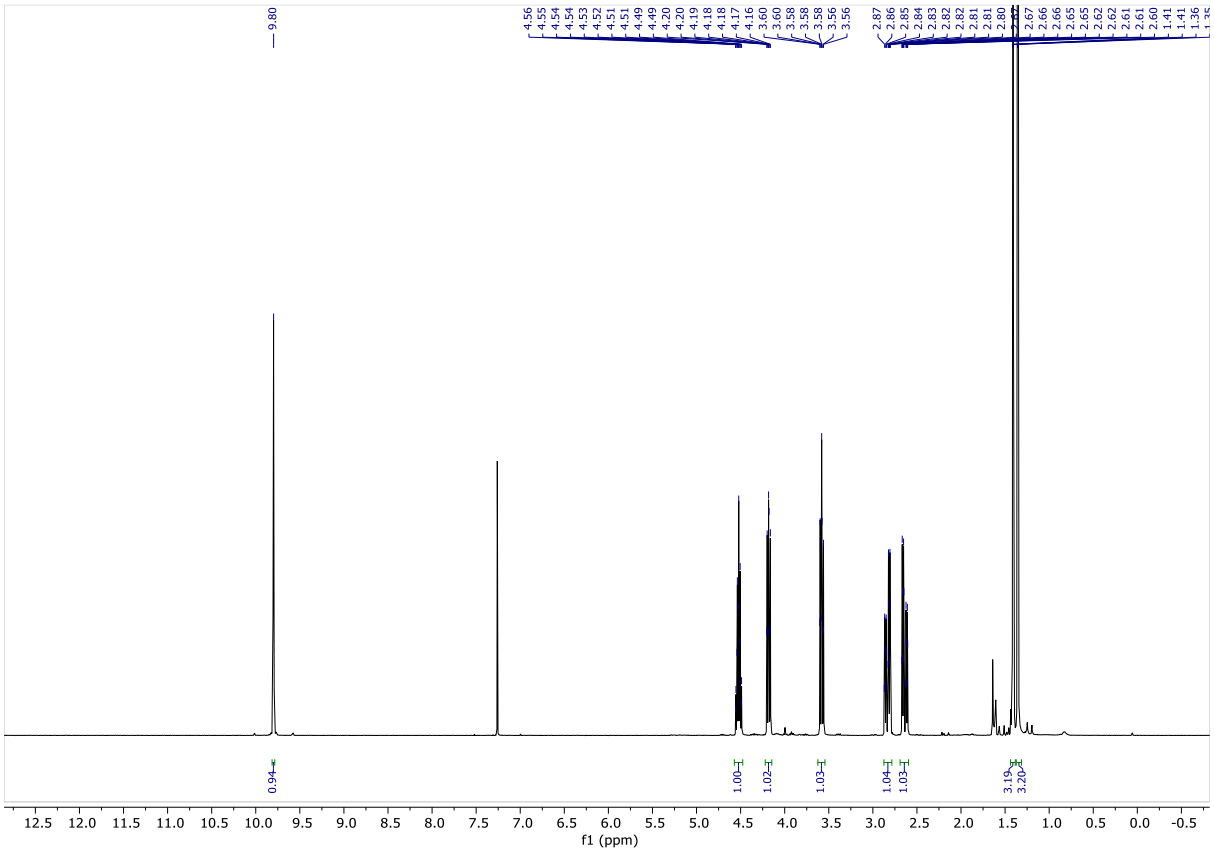
$[\alpha]_{20}^{D}$: = +16.0 (c = 1.0; $CHCl_3$, 20°C);

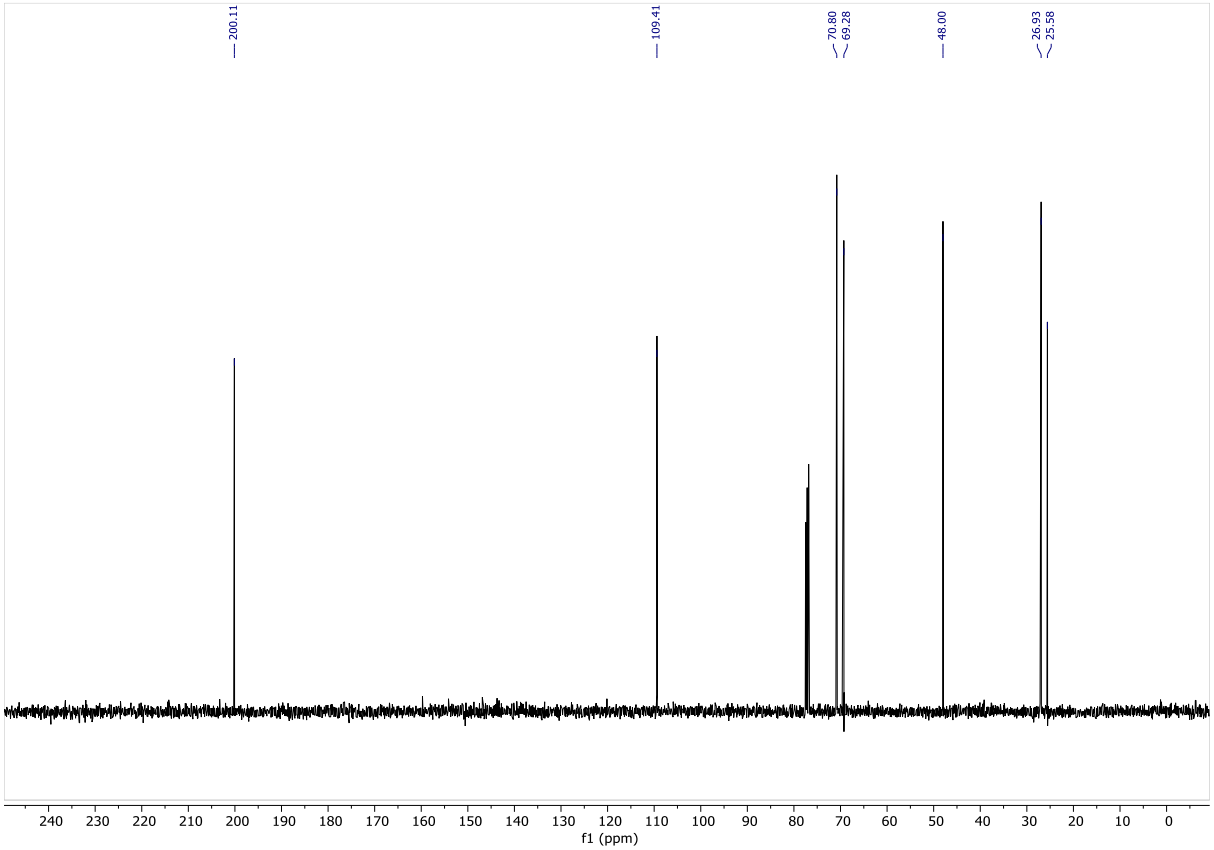
^{1}H NMR (400 MHz, Chloroform-d) δ 9.80 (s, 1H), 4.52 (pd, J = 6.4, 1.6 Hz, 1H), 4.18 (ddd, J = 8.1, 6.1, 1.7 Hz, 1H), 3.58 (ddd, J = 8.3, 6.6, 1.6 Hz, 1H), 2.84 (ddt, J = 17.2, 6.6, 1.9 Hz, 1H), 2.64 (ddt, J = 17.3, 6.1, 1.5 Hz, 1H), 1.41 (s, 3H), 1.36 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-d) δ 200.1, 109.4, 70.8, 69.3, 48.0, 26.9, 25.6;

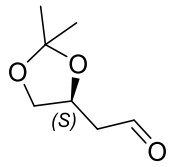
IR (film): ν = 3434, 2986, 2936, 2877, 2359, 1725, 1455, 1438, 1379, 1371, 1242, 1213, 1159, 1119, 1062, 970, 850, 533, 522, 511;

HRMS (ESI-TOF) *m/z* calcd. for $C_7H_{13}O_3$ $[M+H]^+$ 145.0859, found 145.0859.


9.80
4.56
4.55
4.54
4.54
4.53
4.52
4.51
4.51
4.49
4.49
4.20
4.20
4.19
4.18
4.18
4.17
4.16
3.60
3.58
3.58
3.56
3.56
2.87
2.86
2.85
2.84
2.83
2.82
2.82
2.81
2.81
2.80
2.67
2.66
2.66
2.65
2.62
2.62
2.61
2.61
2.60
1.41
1.41
0.94
1.00
1.02
1.03
1.04
1.03
3.19
3.20
f1 (ppm)


200.11
109.41
70.80
69.28
48.00
26.93
25.58
f1 (ppm)

*(S)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (S-**6**)* [7] *PCC oxidation* [8]



Molecular sieves (3°A, 10.6 g) were heated using a heat gun for 1 hour under a high vacuum. 9:25-10:25. Then, the suspension of freshly activated molecular sieves (3°A, 10.6 g) in dry DCM (50 mL) was prepared. PCC (10.6 g, 49 mmol, 3.6 equiv.) was added slowly to this solution at room temperature S-**62** (2 g, 13.6 mmol, 1 equiv.) was dissolved in 5 mL DCM in a separate flask, added to the mixture of PCC with molecular sieves, and stirred for 2 h at room temperature The mixture was then diluted using Et_2O, filtered through silica gel, and concentrated under reduced pressure, to give 1.8 g of the crude material, which was then purified by silica gel column chromatography (diethyl ether: hexane = 1:2) to yield 500 mg of S-**6** (25%).

Yield: 0.5 g (25 %);

R_f = 0.27 (hexane/Et_2O 1/1), $KMnO_4$ staining;

$[\alpha]_{20}^{D}$: = +16.0 (c = 1.0; $CHCl_3$, 20°C);

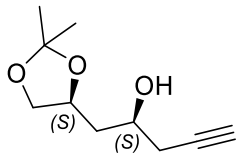
^{1}H NMR (400 MHz, Chloroform-d) δ 9.80 (s, 1H), 4.52 (pd, J = 6.4, 1.6 Hz, 1H), 4.18 (ddd, J = 8.1, 6.1, 1.7 Hz, 1H), 3.58 (ddd, J = 8.3, 6.6, 1.6 Hz, 1H), 2.84 (ddt, J = 17.2, 6.6, 1.9 Hz, 1H), 2.64 (ddt, J = 17.3, 6.1, 1.5 Hz, 1H), 1.41 (s, 3H), 1.36 (, 3H);

^{13}C NMR (101 MHz, Chloroform-d) δ 200.1, 109.4, 70.8, 69.3, 48.0, 26.9, 25.6;

IR (film): ν = 3434, 2986, 2936, 2877, 2359, 1725, 1455, 1438, 1379, 1371, 1242, 1213, 1159, 1119, 1062, 970, 850, 533, 522, 511;

HRMS (ESI-TOF) *m/z* calcd. for $C_7H_{13}O_3$ $[M+H]^+$ 145.0859, found 145.0859.

*(S)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-yn-2-ol ((S,S)-**63**)*



Preactivated with HCL Zinc dust (6.0 g, 86.69 mmol, 2.5 equiv.) was suspended in 62 mL of THF containing 1,2- dibromoethane (0.78 mL, 8.669 mmol, 0.25 equiv.). The suspension was heated to 65 °C for 10 min before cooling to 25 °C. After 46 min, chlorotrimethylsiliane (1.175 mL, 8.669 mmol, 0.25 equiv.) was added dropwise *via a* syringe. became sediment from a nice powder. The suspension was stirred vigorously for an additional 30 min and then cooled to -10 °C. Propargyl bromide (80 % in toluene, 9.672 mL, 86.691 mmol, 2.5 equiv.) was added slowly *via* syringe over 20 min. The suspension was stirred for 2.5 h below -12 °C. Then it was added over 45 min through a cannula to a solution of aldehyde S-**6** (5.2 g, 34.677 mmol, 1.0 equiv.) in toluene (230 mL) at -78 °C. The resulting reaction was slowly warmed to -40- (-45) °C and stirred at this temperature for 22 h. It was then warmed to 0 °C and quenched with saturated aqueous NH4Cl solution (100 mL). The mixture was extracted with EtOAc three times and the combined organic fractions were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by slow gradient flash column chromatography (0% → 30% EtOAc/ DCM) to afford homopropargylic alcohol (S,S)-**63** (1.33 g) as a colorless oil and its major diastereomer (S,R)-**63** (4.05 g) as a pale yellow oil, and a mixture of two diastereomers (0.9 g). The combined yield of the product: 5.38 g (84%), *dr* = 3.5:1 (based on crude reaction mixture). The residue was purified by slow gradient flash column chromatography (0% → 30% EtOAc/DCM).

Yield: 5.380 g in total (84%);

R_f = 0.209 (hexane / EtOAc = 2:1), CPS staining;

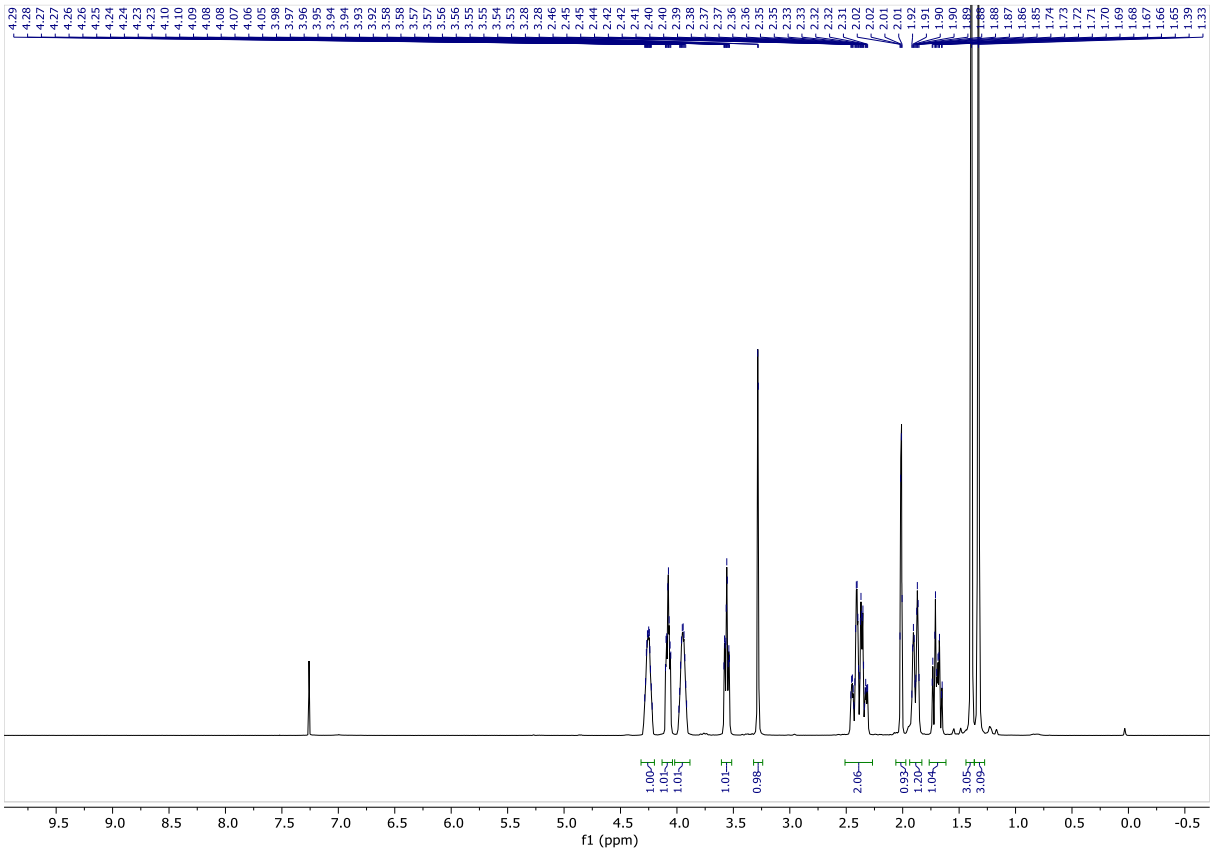
α_D^{20}: 20.99 (c = 1 mg / 0.7 mL, $CHCl_3$, 20°C)

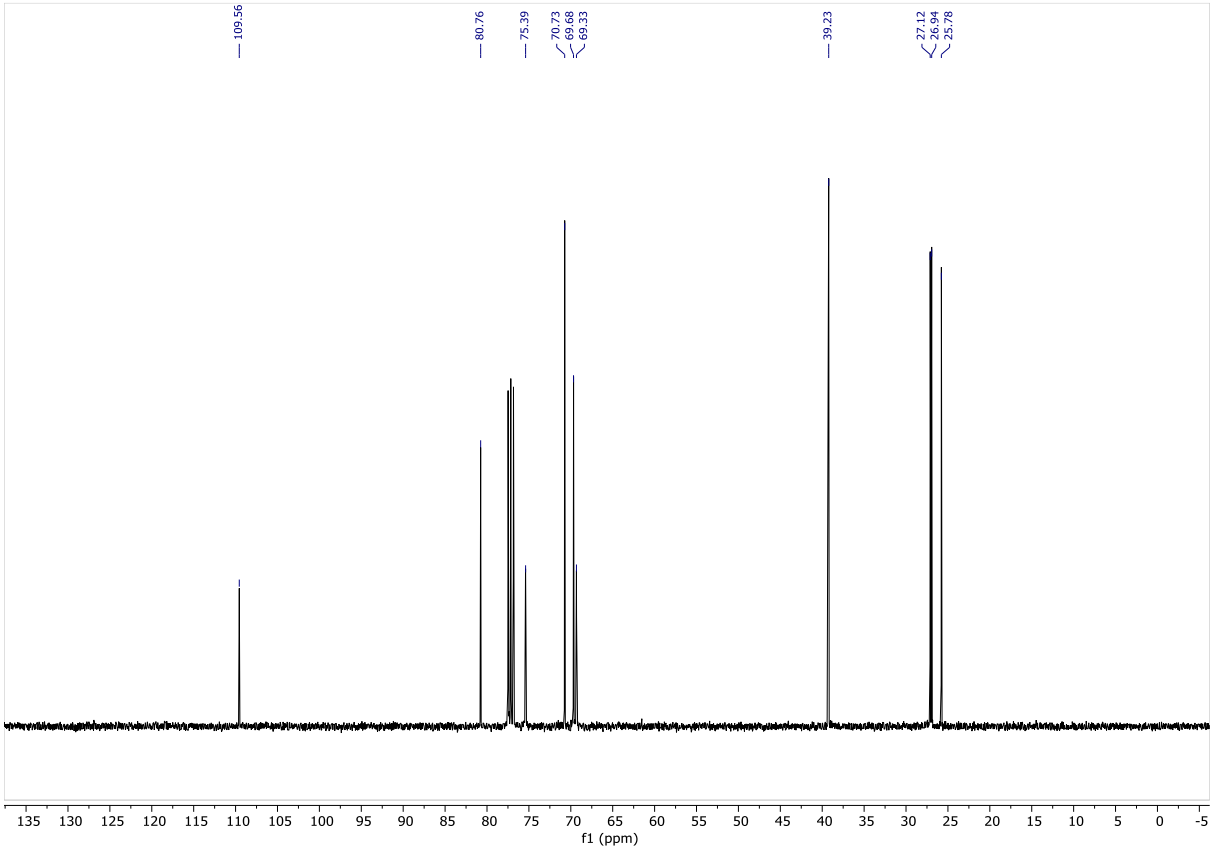
^{1}H NMR (400 MHz, Chloroform-d) δ 4.25 (m, 1H), 4.08 (m, 1H), 3.95 (m, 1H), 3.56 (m, 1H), 3.28 (s, 1H), 2.58 – 2.18 (m, 2H), 2.01 (m, 1H), 1.89 (m, 1H), 1.78 – 1.57 (m, 1H), 1.39 (s, 3H), 1.33 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-d) δ 109.6, 80.8, 75.4, 70.7, 69.7, 69.3, 39.2, 27.1, 26.9, 25.8;

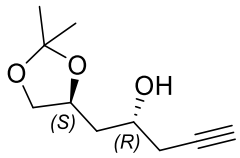
IR (film): ν = 3289, 3041, 2992, 2983, 2938, 2149, 1426, 1399, 1371, 1260, 1213, 1156, 1119, 1093, 1070, 1061, 1031, 979, 914, 842, 790, 742, 639;

HRMS (ESI-TOF) m/z calcd. for $C_{10}H_{16}NaO_3$ $[M+Na]^+$ 207.0992, found 207.0992.


4.29 4.28 4.27 4.27 4.26 4.26 4.25 4.24 4.24 4.23 4.10 4.09 4.08 4.08 4.07 4.06 4.05 3.98 3.97 3.96 3.95 3.94 3.94 3.93 3.92 3.58 3.57 3.57 3.56 3.56 3.55 3.55 3.54 3.53 3.28 3.28 2.46 2.45 2.45 2.44 2.42 2.42 2.41 2.40 2.40 2.39 2.38 2.37 2.37 2.36 2.36 2.35 2.35 2.33 2.33 2.32 2.32 2.31 2.02 2.02 2.01 2.01 1.92 1.91 1.90 1.90 1.89 1.88 1.87 1.86 1.85 1.74 1.73 1.72 1.71 1.70 1.69 1.68 1.67 1.66 1.65 1.39 1.33
1.00 1.01 1.01 1.01 0.98 2.06 0.93 1.20 1.04 3.05 3.09
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


109.56
80.76
75.39
70.73
69.68
69.33
39.23
27.12
26.94
25.78
135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5
f1 (ppm)

*(R)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-yn-2-ol ((S,R)-**63**)*



Preactivated with HCL Zinc dust (6.0 g, 86.69 mmol, 2.5 equiv.) was suspended in 62 mL of THF containing 1,2- dibromoethane (0.78 mL, 8.669 mmol, 0.25 equiv.). The suspension was heated to 65 °C for 10 min before cooling to 25 °C. After 46 min, chlorotrimethylsiliane (1.175 mL, 8.669 mmol, 0.25 equiv.) was added dropwise *via a* syringe. became sediment from a nice powder. The suspension was stirred vigorously for an additional 30 min and then cooled to -10 °C. Propargyl bromide (80 % in toluene, 9.672 mL, 86.691 mmol, 2.5 equiv.) was added slowly *via* syringe over 20 min. The suspension was stirred for 2.5 h below -12 °C. Then it was added over 45 min through a cannula to a solution of aldehyde S-**6** (5.2 g, 34.677 mmol, 1.0 equiv.) in toluene (230 mL) at -78 °C. The resulting reaction was slowly warmed to -40- (-45) °C and stirred at this temperature for 22 h. It was then warmed to 0 °C and quenched with saturated aqueous NH4Cl solution (100 mL). The mixture was extracted with EtOAc three times and the combined organic fractions were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by slow gradient flash column chromatography (0% → 30% EtOAc/DCM) to afford homopropargylic alcohol (S,S)-**63** (1.33 g) as a colorless oil and its major diastereomer (S,R)-**63** (4.05 g) as a pale yellow oil, and a mixture of two diastereomers (0.9 g). The combined yield of the product: 5.38 g (84%), *dr* = 3.5:1 (based on crude reaction mixture). The residue was purified by slow gradient flash column chromatography (0% → 30% EtOAc/DCM).

Yield: 5.380 g in total (84%);

R_f = 0.1298 (hexane / EtOAc = 2:1), CPS staining;

α_D^{20}: -5.62 (c = 1.6 mg / 0.9 mL, $CHCl_3$, 20°C)

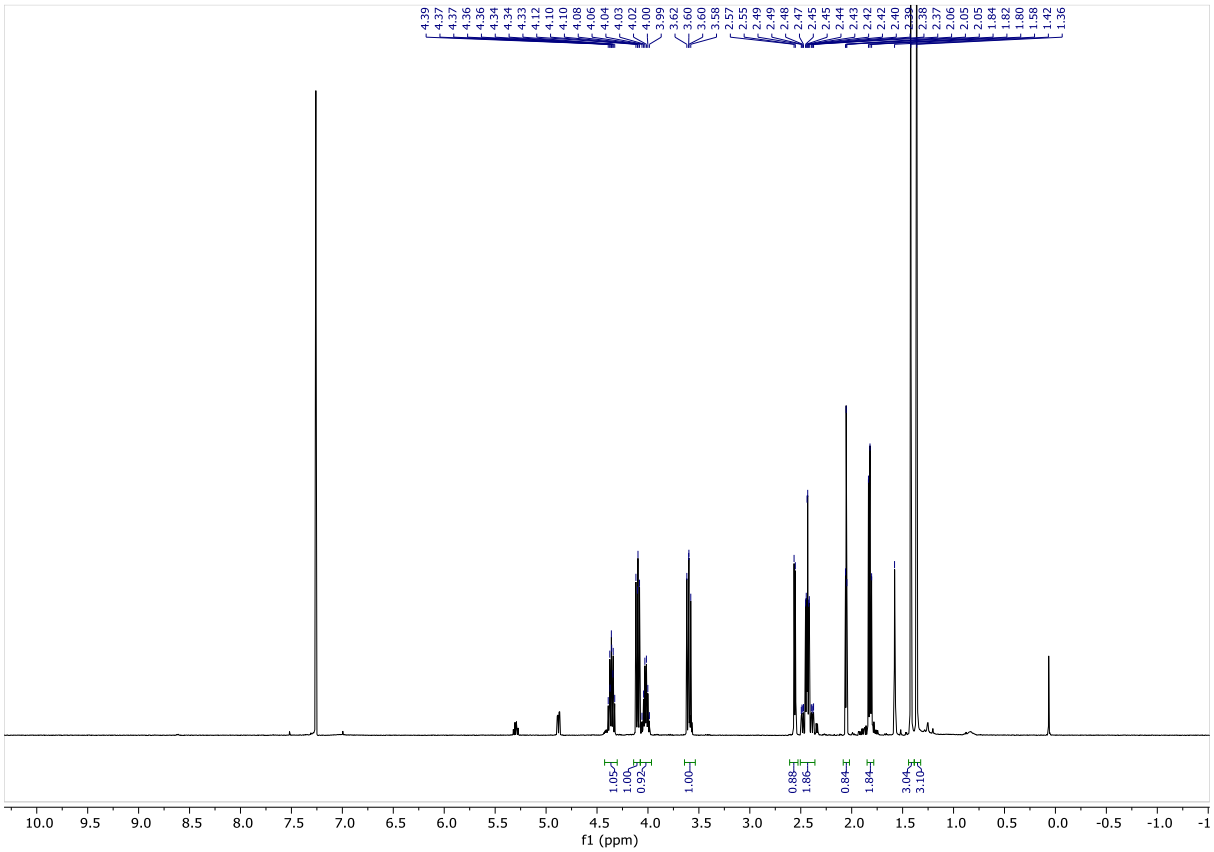
^{1}H NMR (400 MHz, Chloroform-d) δ 4.36 (dq, J = 7.2, 6.0 Hz, 1H), 4.10 (dd, J = 8.1, 6.1 Hz, 1H), 4.02 (h, J = 6.3 Hz, 1H), 3.60 (dd, J = 8.1, 7.4 Hz, 1H), 2.56 (d, J = 5.0 Hz, 1H), 2.53 – 2.33 (m, 2H), 2.05 (t, J = 2.7 Hz, 1H), 1.82 (t, J = 5.8 Hz, 2H), 1.58 (t, J = 5.8 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H).

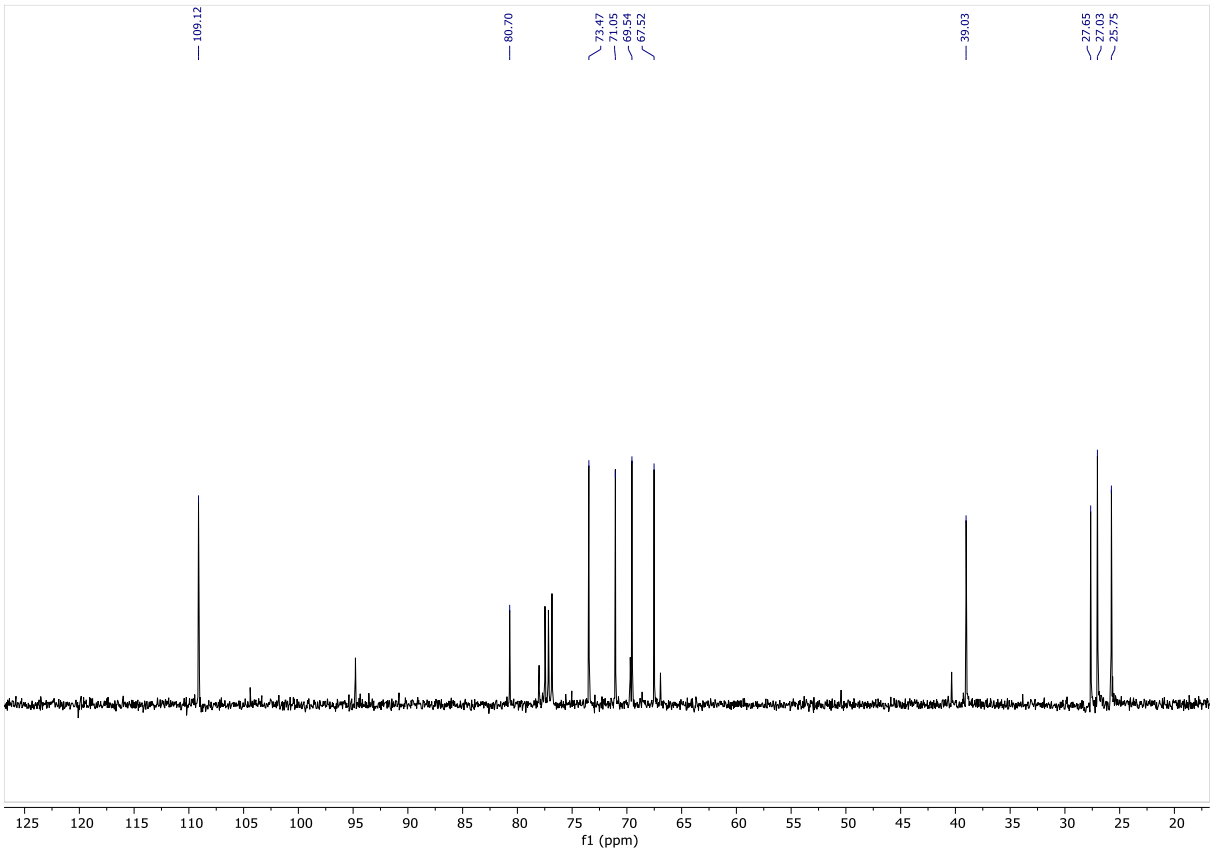
^{13}C NMR (101 MHz, Chloroform-d) δ 109.1, 80.7, 73.5, 71.1, 69.5, 67.5, 39.0, 27.7, 27.0, 25.8;

IR (film): v = 2360, 2342, 2169, 2009, 1372, 1216, 1157, 1067, 913, 828, 745, 670, 661

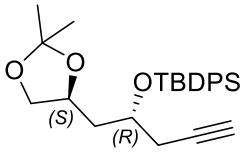
HRMS (ESI-TOF) *m/z* calcd. for $C_{10}H_{16}NaO_3$ $[M+Na]^+$ 207.0992, found 207.0992

J. Am. Chem. Soc. 2016, 138, 40, 13415-13423, S56-S61


4.39
4.37
4.37
4.36
4.36
4.34
4.34
4.33
4.12
4.10
4.10
4.08
4.06
4.04
4.03
4.02
4.00
3.99
3.62
3.60
3.60
3.58
2.57
2.55
2.49
2.49
2.48
2.47
2.45
2.45
2.44
2.43
2.42
2.42
2.40
2.38
2.38
2.37
2.06
2.05
2.05
1.84
1.82
1.80
1.58
1.42
1.36
1.05
1.00
0.92
1.00
0.88
1.86
0.84
1.84
3.04
3.10
f1 (ppm)


109.12
80.70
73.47
71.05
69.54
67.52
39.03
27.65
27.03
25.75
f1 (ppm)

*tert-butyl(((R)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-yn-2-yl)oxy)diphenylsilane ((S,R)-**57**)*



In a flame dried under Argon atmosphere 500 ml flask charged with a stirring bar a solution of homopropargylic alcohol (S,R)-**63** (4.05 g, 21.98 mmol, 1.0 equiv.) in dry DCM (220 mL, 0.1 M) was prepared at room temperature Then, the reagents were added in the following order: imidazole (4.9 g, 65.95 mmol, 3.0 equiv.), DMAP (268.6 mg, 2.198 mmol, 0.1 equiv.) and tert-butyldiphenylchlorosilane (8.439 mL, 32.97 mmol, 1.5 equiv.). The reaction was stirred at room temperature overnight and after verification of the completion of the reaction by TLC, the solution was quenched by the addition of H_2O (50 ml). Then, the mixture was extracted with DCM three times (100 ml), and the combined organic fractions were dried over $MgSO_4$, and concentrated under reduced pressure. The crude material (S,R)-**57** (9.29 g, quant) was used for the next reaction directly since the product is fully characterized.

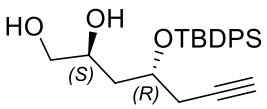
Yield: 9.29 g (quant);

R_f = 0.19 (hexane/EtOAc 10:1);

HRMS (ESI-TOF) *m/z* calcd. for $C_{26}H_{34}NaO_3Si$ $[M+Na]^+$ 445.2169, found 445.2169.

J. Am. Chem. Soc. 2016, 138, 40, 13415-13423, S62.

*(2S,4R)-4-((tert-butyldiphenylsilyl)oxy)hept-6-yne-1,2-diol ((S,R)-**66**)*



In a flame-dried round bottom 1-liter flask charged with a stirring bar, a solution of acetonide (S,R)-**57** (9.29 g, 21.98 mmol, 1.0 equiv.) in dichloromethane (450 mL) was prepared under Argon atmosphere at room temperature Then, the solution was cooled to 0 °C using an ice bath, and after the solution was cool trifluoroacetic acid (16.8 mL, 219.8 mmol, 10 equiv.) was added at 0 °C. The reaction mixture was stirred for 3 h. After verification of the reaction completion by TLC, no SM this time, the workup was normal with $NaHCO_3$ and extraction with EtOAc, drying over $MgSO_4$, and evaporation of the solvent under reduced pressure. The crude residue was purified by flash column chromatography (3:1 → 1:2 hexanes/EtOAc) to yield diol (S,R)-**66** (7 g, 83 %) in fractions 35-100 as a colorless oil + mixed fractions (0.87 g, 94 %) over two steps.

Yield: 7.0 g (83 %);

R_f = 0.1 (hexane/EtOAc 2:1), CPS staining;

α_D^{20}: -12.82 (c = 7.8 mg / 1 mL, $CHCl_3$, 20°C, 589 nm)

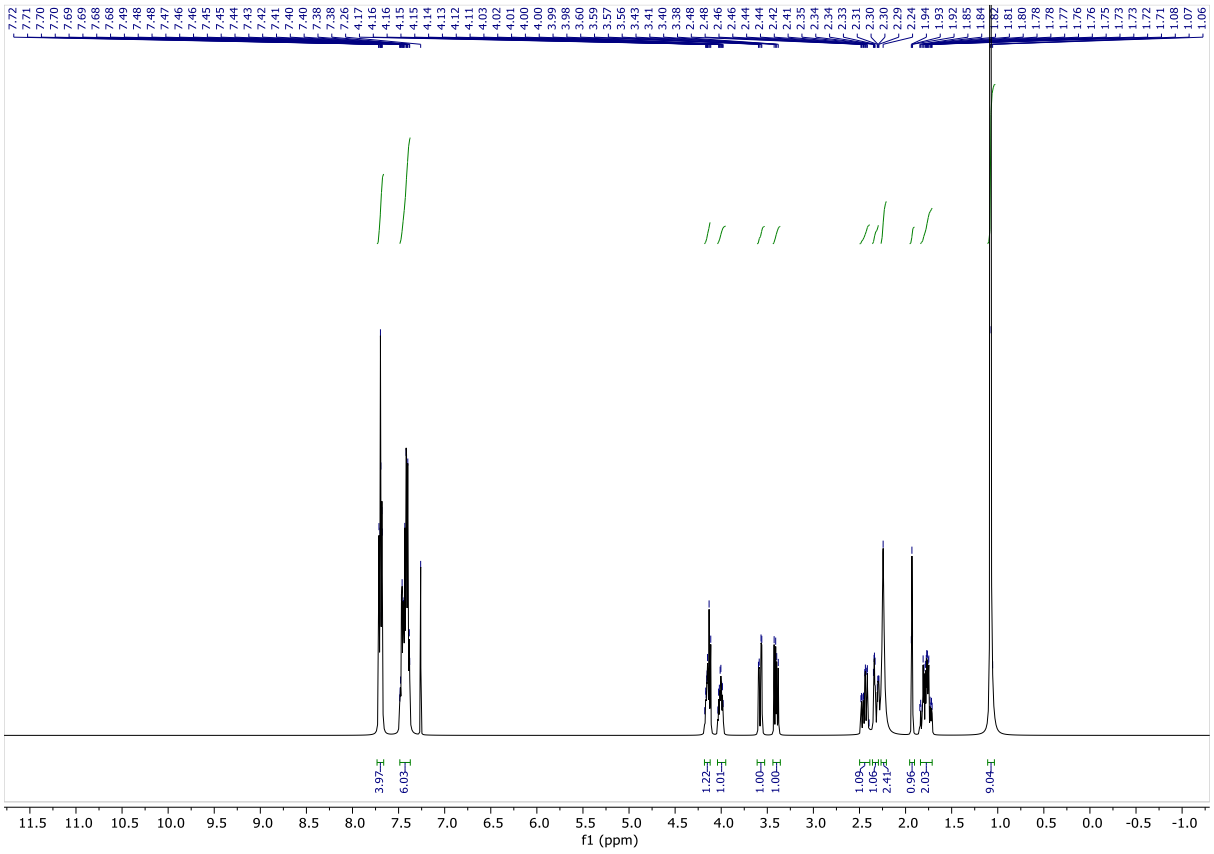
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 (m, 4H), 7.53 – 7.25 (m, 6H), 4.22 – 4.08 (m, 1H), 4.01 (ddt, J = 9.9, 6.6, 3.1 Hz, 1H), 3.58 (dd, J = 11.2, 3.3 Hz, 1H), 3.40 (dd, J = 11.2, 6.7 Hz, 1H), 2.45 (ddd, J = 16.7, 8.5, 2.7 Hz, 1H), 2.32 (m, 1H), 2.24 (s, 2H), 1.93 (t, J = 2.7 Hz, 1H), 1.87 – 1.67 (m, 2H), 1.08 (s, 9H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 136.0 (2C), 136.0 (2C), 133.5, 133.0, 130.3, 130.2, 128.1 (2C), 127.9 (2C), 80.5, 70.9, 69.9, 68.7, 67.1, 37.9, 27.1 (3C), 26.5, 19.4;

IR (film): ν = 3419, 3408, 3372, 3309, 3071, 3048, 2930, 2857, 1472, 1427, 1111, 1031, 1008, 998, 822, 771, 738, 703, 688, 634, 613, 511, 502;

HRMS (ESI-TOF) *m/z* calcd. for $C_{23}H_{30}NaO_3Si$ $[M+Na]^+$ 405.1856, found 405.1853.

J. Am. Chem. Soc. **2016**, 138, 40, 13415-13423


3.97
6.03
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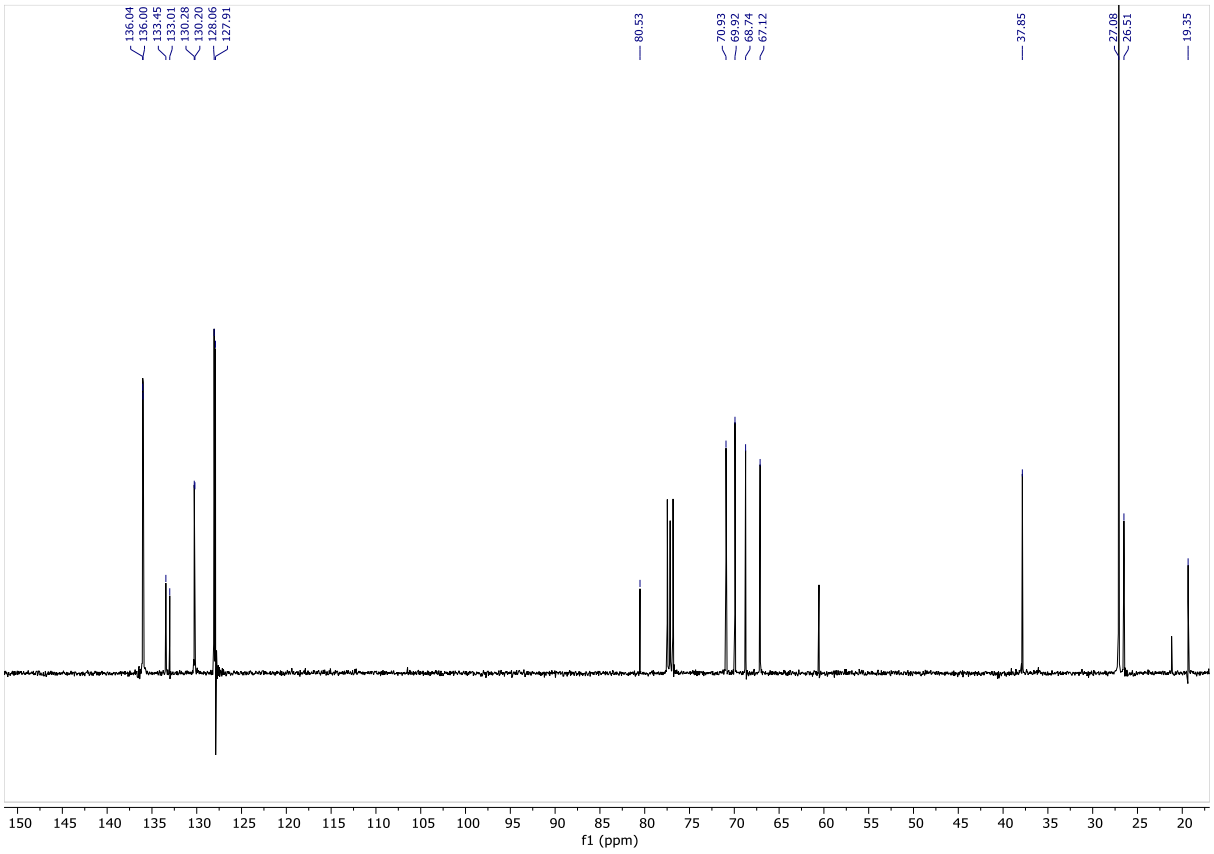
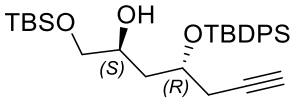
1.01
1.00
1.00
1.09
1.06
2.41
0.96
2.03
9.04
f1 (ppm)


136.04
136.00
133.45
133.01
130.28
130.20
128.06
127.91
80.53
70.93
69.92
68.74
67.12
37.85
27.08
26.51
19.35
f1 (ppm)

*(6S,8R)-2,2,3,3,11,11-hexamethyl-10,10-diphenyl-8-(prop-2-yn-1-yl)-4,9-dioxa-3,10-disiladodecan-6-ol ((S,R)-**4**)*



In a flame-dried round bottom flask charged with a stirring bar, a solution of (S,R)-**66** (6.0 g, 15.68 mmol, 1.0 equiv.) in DCM (157 ml) was prepared under Argon atmosphere and cooled to 0 °C. Then, imidazole (1.6 g, 23.53 mmol, 1.5 equiv.) and TBSCl (2.56 mg, 23.53 mmol, 1.5 equiv.) were added at 0 °C. Then, the reaction was stirred at room temperature for 20 min. After completion of the reaction, verified by TLC, the reaction mixture was quenched with aq. sat. NH_4Cl (100 ml) and extracted with EtOAc (3 x 70 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material (8.07 g) was purified by column chromatography (hexane/EtOAc 100/1) because it is very difficult to separate the product from TBSOH (had to do 3 columns) affording the secondary alcohol (S,R)-**4** (6.92 g, 89 %) as colorless oil in fractions 35-49.

Yield: 6.92 g (89 %);

R_f = 0.85 (hexane/EtOAc 1/1), CPS and $KMnO_4$ staining;

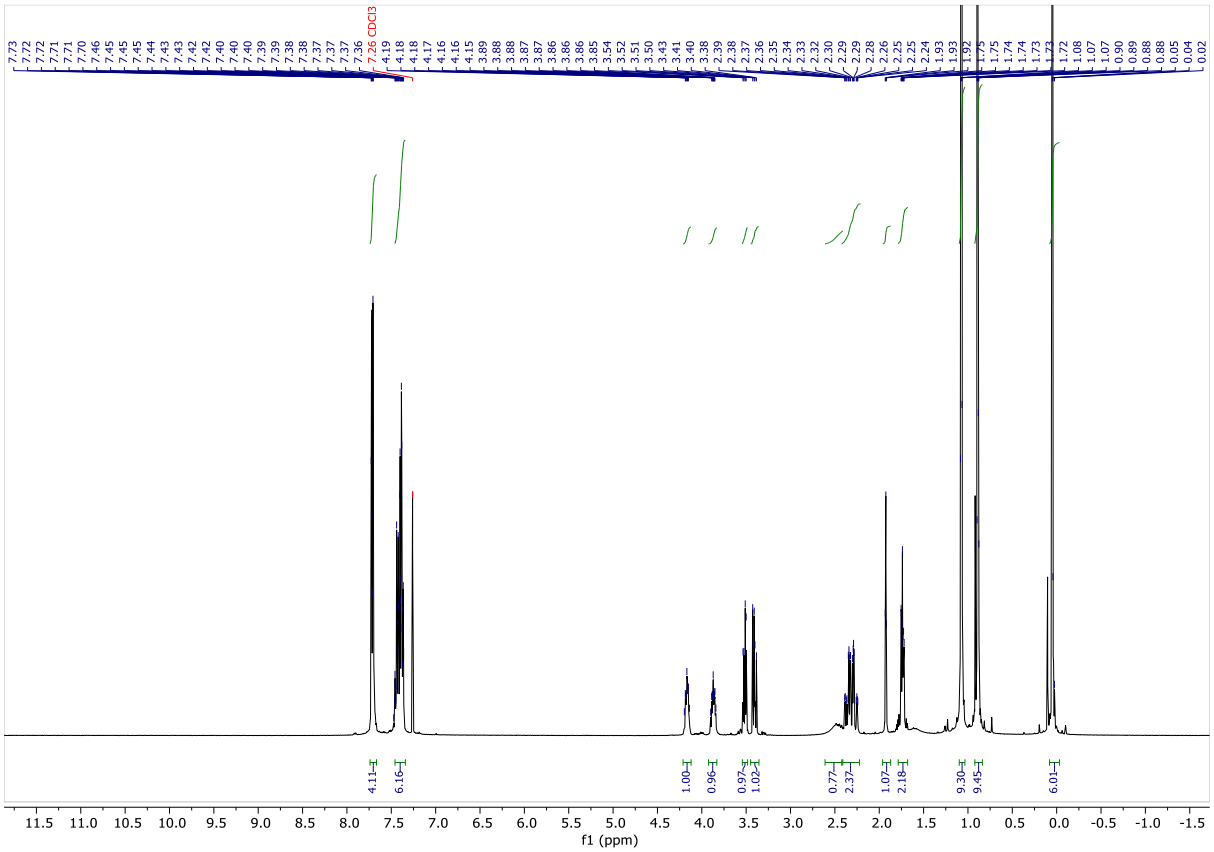
α_D^{20}: -20.37, (c=5.4 mg / 1 ml, $CHCl_3$, 20°C, l=589 nm);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 – 7.69 (m, 4H), 7.50 – 7.41 (m, 6H), 4.17 (m, 1H), 3.87 (m, 1H), 3.52 (dd, J = 9.9, 4.2 Hz, 1H), 3.41 (dd, J = 9.9, 6.8 Hz, 1H), 2.48 (br, 1H), 2.36 (ddd, J = 16.7, 7.4, 2.7 Hz, 1H), 2.27 (ddd, J = 16.6, 4.3, 2.7 Hz, 1H), 1.93 (t, J = 2.7 Hz, 1H), 1.79 – 1.63 (m, 2H), 1.07 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 136.07 (4C), 134.1, 133.6, 129.9, 129.9, 127.8 (2C), 127.7 (2C), 81.0, 70.6, 69.5, 68.7, 67.6, 39.2, 27.3, 27.1 (3C), 26.0 (3C), 19.5, 18.4, -5.2 (2C);

IR (film): v = 3311, 2954, 2928, 2900, 2857, 1472, 1463, 1428, 1408, 1391, 1379, 1362, 1254, 1222, 1106, 1086, 1006, 938, 836, 823, 777, 739, 703, 688, 632, 623, 612, 506;

HRMS (ESI-TOF) *m/z* calcd. for $C_{29}H_{44}NaO_3Si_2$ $[M+Na]^+$ 519.2721, found 519.2717;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4.11
6.16
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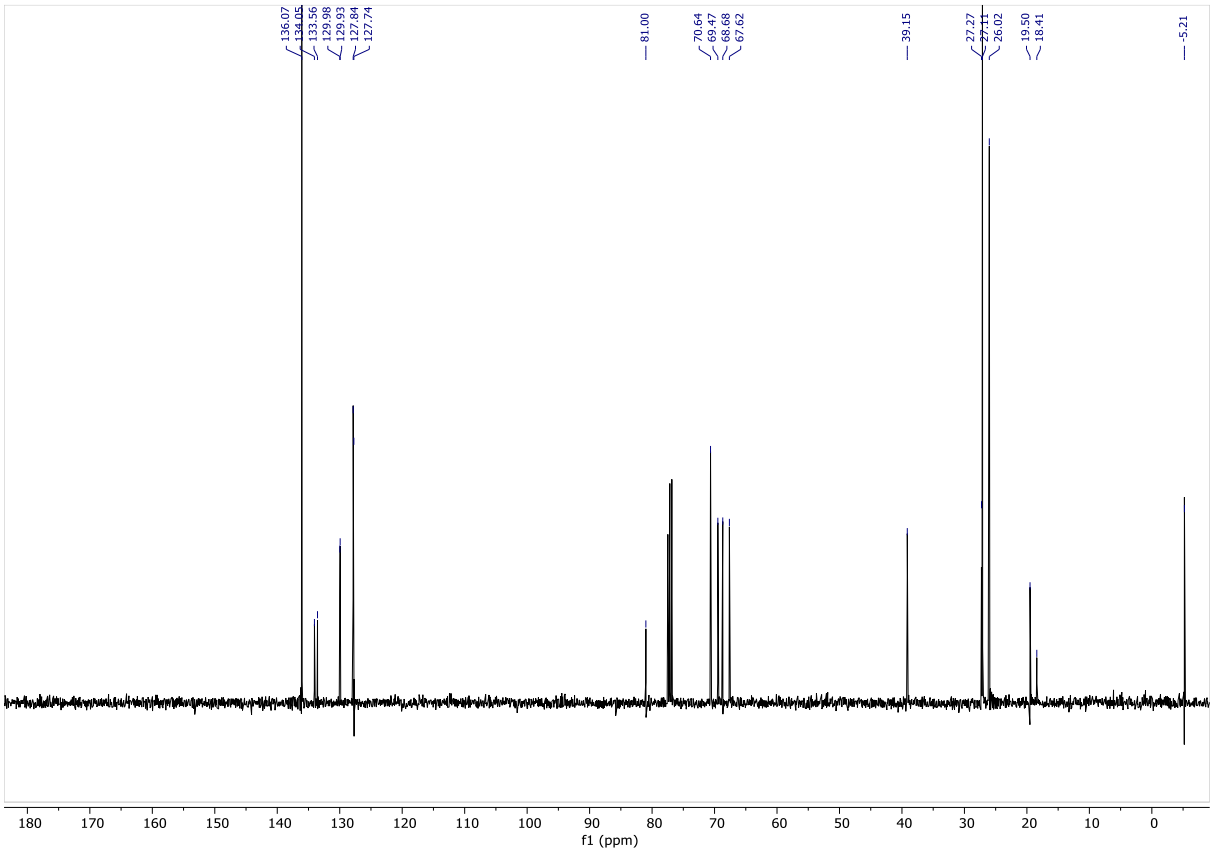
0.97
1.02
0.77
2.37
1.07
2.18
9.30
9.45
6.01
f1 (ppm)


136.07
134.05
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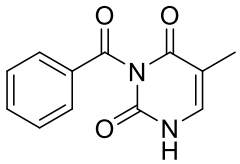
129.93
127.84
127.74
81.00
70.64
69.47
68.68
67.62
39.15
27.27
27.11
26.02
19.50
18.41
-5.21
f1 (ppm)

*3-benzoyl-5-methylpyrimidine-2,4(1H,3H)-dione (**68**)*



In a flame-dried glassware, under an argon atmosphere thymine (10 g, 79.29 mmol, 1.0 equiv.) was dissolved in CH3CN (79.000 ml, 1 M) at room temperature Pyridine (25.55 ml, 317.16 mmol, 4.0 equiv.) was added to the solution at room temperature Then, Benzoyl chloride (36.85 ml, 317.16 mmol, 4.0 equiv) was added slowly at room temperature and the reaction was stirred for 3 days. The suspension was evaporated to dryness on a stinky rotary evaporator. Then, the residue was dissolved in dioxane/water 1/1 (240 ml) and potassium carbonate (16.44 g, 118.93 mmol, 1.5 equiv.) was added at room temperature and the suspension was stirred at this temperature for 18 h. The solvent was removed under reduced pressure until dryness and kept in the freezer overnight. The next day the residue was suspended in aq. sat. $NaHCO_3$ (400 ml) for 1 h, the precipitate was filtered off and washed with cold water several times. The crude product was 18.380 g. Even though the NMR of the filtrate was already clean, it was recrystallized from methanol.

Yield: 13.6 g (75 %);

R_f = 0.12 (hexane / EtOAc = 1:1), CPS staining;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.93 (d, J = 5.6 Hz, 1H), 7.94 (dd, J = 8.4, 1.3 Hz, 2H), 7.68 (m, 1H), 7.52 (app. t, J = 7.8 Hz, 2H), 7.01 (m, 1H), 1.90 (d, J = 1.2 Hz, 3H);

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.37 (s, 1H), 8.01 – 7.88 (m, 2H), 7.77 (t, J = 7.4 Hz, 1H), 7.60 (t, J = 7.8 Hz, 2H), 7.53 (s, 1H), 1.82 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.9, 163.4, 151.8, 136.3, 135.4, 131.6, 130.7, 129.4, 111.2, 12.4;

- solubility in $CDCl_3$ is poor.

^{1}H NMR (400 MHz, Methanol-*d4*) δ 8.14 – 7.88 (m, 2H), 7.84 – 7.63 (m, 1H), 7.63 – 7.45 (m, 2H), 7.38 (q, J = 1.2 Hz, 1H), 1.90 (d, J = 1.2 Hz, 3H);

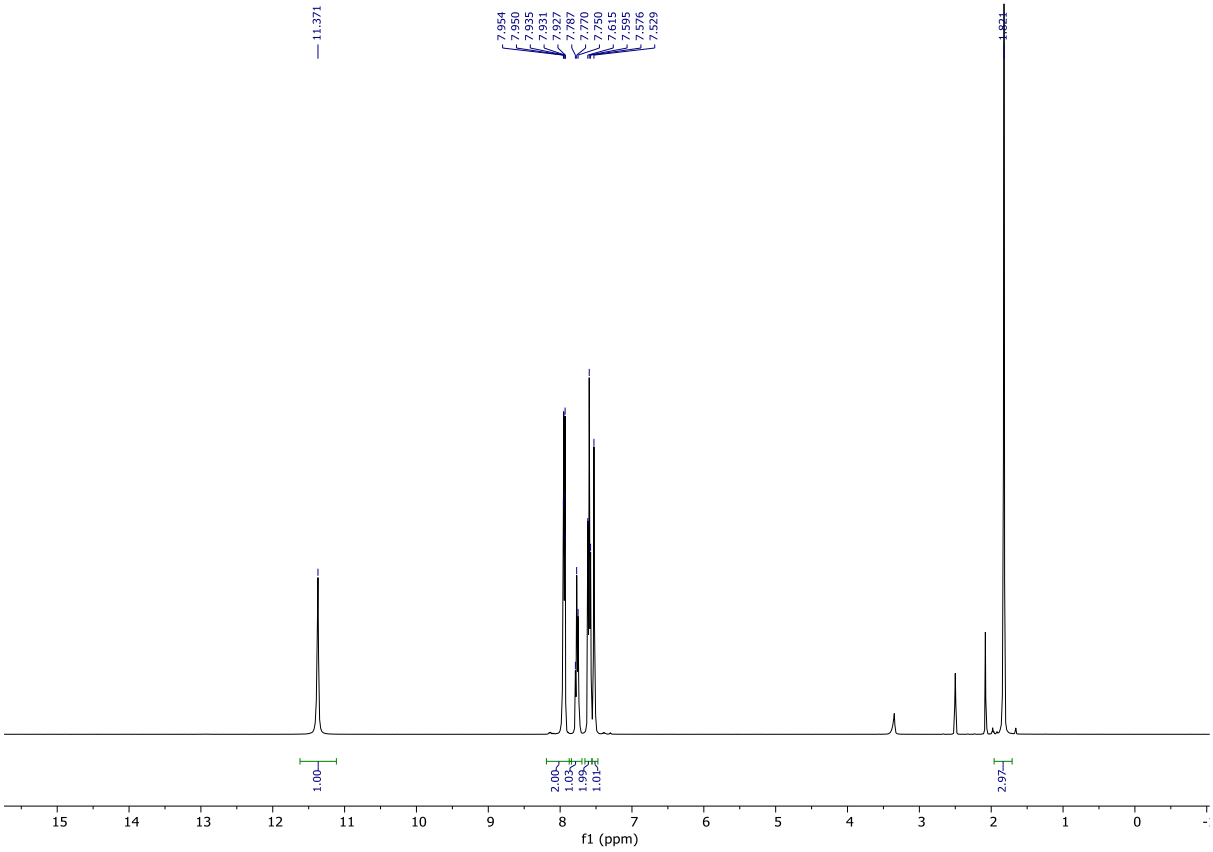
^{13}C NMR (101 MHz, Methanol-*d4*) δ 198.8, 194.0, 167.7, 164.4, 161.3, 159.6, 158.5, 138.7, 40.3;

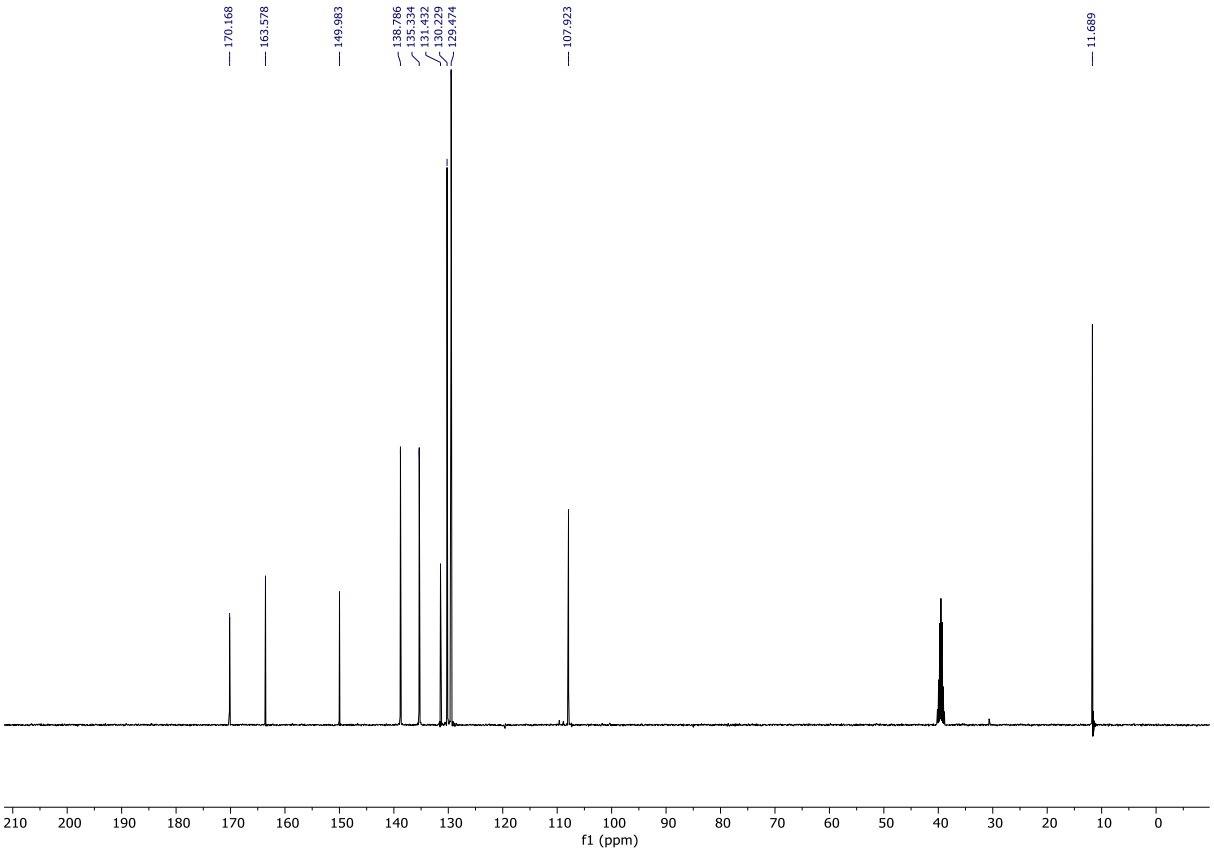
^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.37 (s, 1H), 8.01 – 7.88 (m, 2H), 7.77 (t, J = 7.4 Hz, 1H), 7.60 (t, J = 7.8 Hz, 2H), 7.53 (s, 1H), 1.82 (s, 3H);

^{13}C NMR (101 MHz, DMSO-*d6*) δ 170.2, 163.6, 150.0, 138.8, 135.3, 131.4, 130.2, 129.5, 107.9, 11.7;

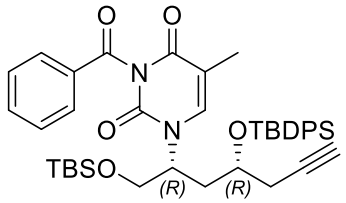
IR (film): ν = 3252, 3174, 2928, 1746, 1709, 1637, 1598, 1476, 1450, 1416, 1386, 1253, 1223, 1179, 967, 841, 783, 764, 702, 685, 619, 604, 582, 549.

HRMS (ESI-TOF) *m/z* calcd. for $C_{12}H_{10}N_2NaO_3$ $[M+Na]^+$ 253.0584, found 253.0582




170.168
163.578
149.983
138.786
135.334
131.432
130.229
129.474
107.923
11.689
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

*3-benzoyl-1-((6R,8R)-2,2,3,3,11,11-hexamethyl-10,10-diphenyl-8-(prop-2-yn-1-yl)-4,9-dioxa-3,10-disiladodecan-6-yl)-5-methylpyrimidine-2,4(1H,3H)-dione ((R,R)-**69**)*



In flame-dried glassware, under an argon atmosphere, a solution of (S,R)-**4** (5.3 g, 14.22 mmol, 1.0 equiv.) in dioxane (100 ml) was prepared at room temperature Then, the reagents were added in the following order: thymine moiety **68** (3.87 g, 16.78 mmol, 1.18 equiv.), PPh_3 (4.1 g, 15.643 mmol, 1.1 equiv.), and DEAD (very slowly, dropwise, 2.68 ml, 17.07 mmol, 1.2 equiv.), and the reaction was stirred for at room temperature for 18 h. After completion of the reaction, verified by TLC, the reaction was concentrated under reduced pressure. The crude material M=18.9 g was purified by FC (hexane/EtOAc 10/1) affording the compound (R,R)-**69** in 4.5 g (60 %) yield as a colorless oil.

Yield: 4.5 g (60 %);

R_f = 0.27 (hexane/EtOAc 4/1), CPS staining;

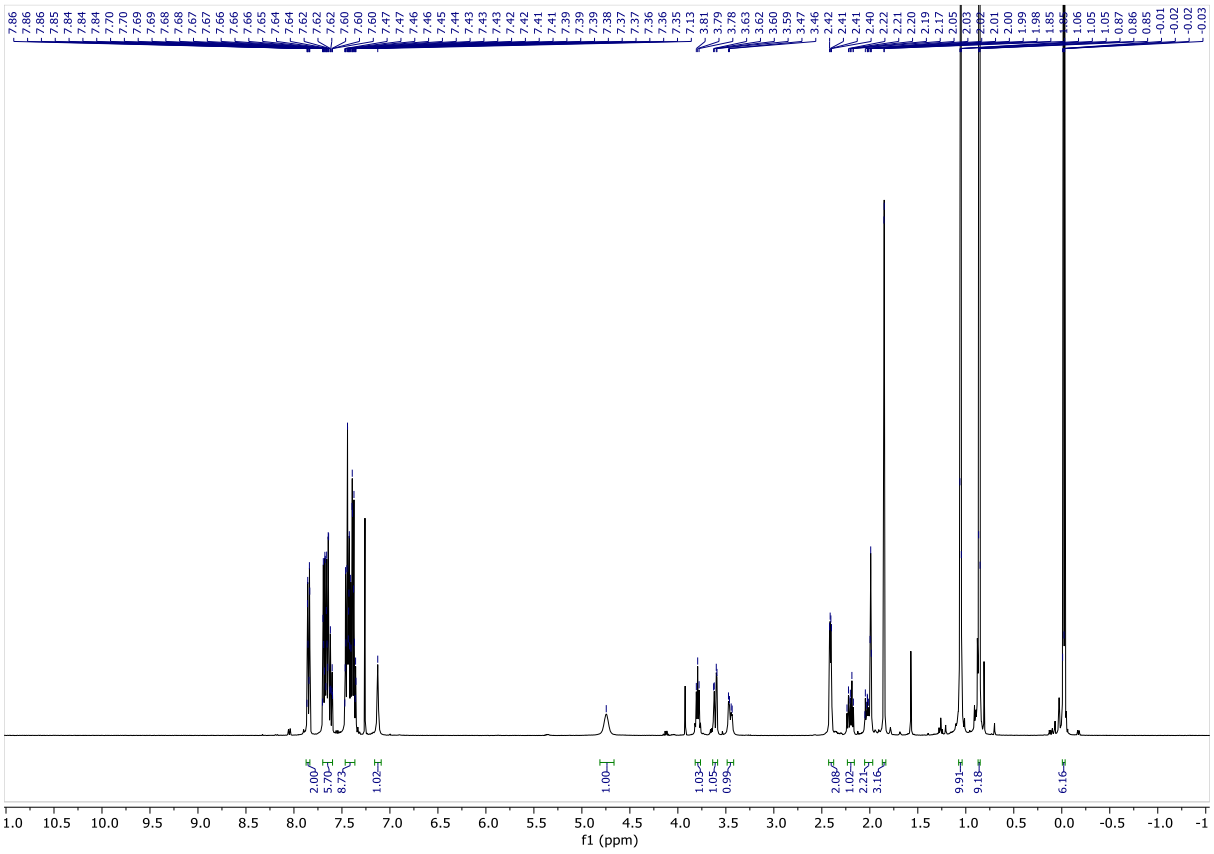
α_D^{20}: +9.33, (c=7.5 mg / 1 ml, $CHCl_3$, 20°C, l=589 nm);

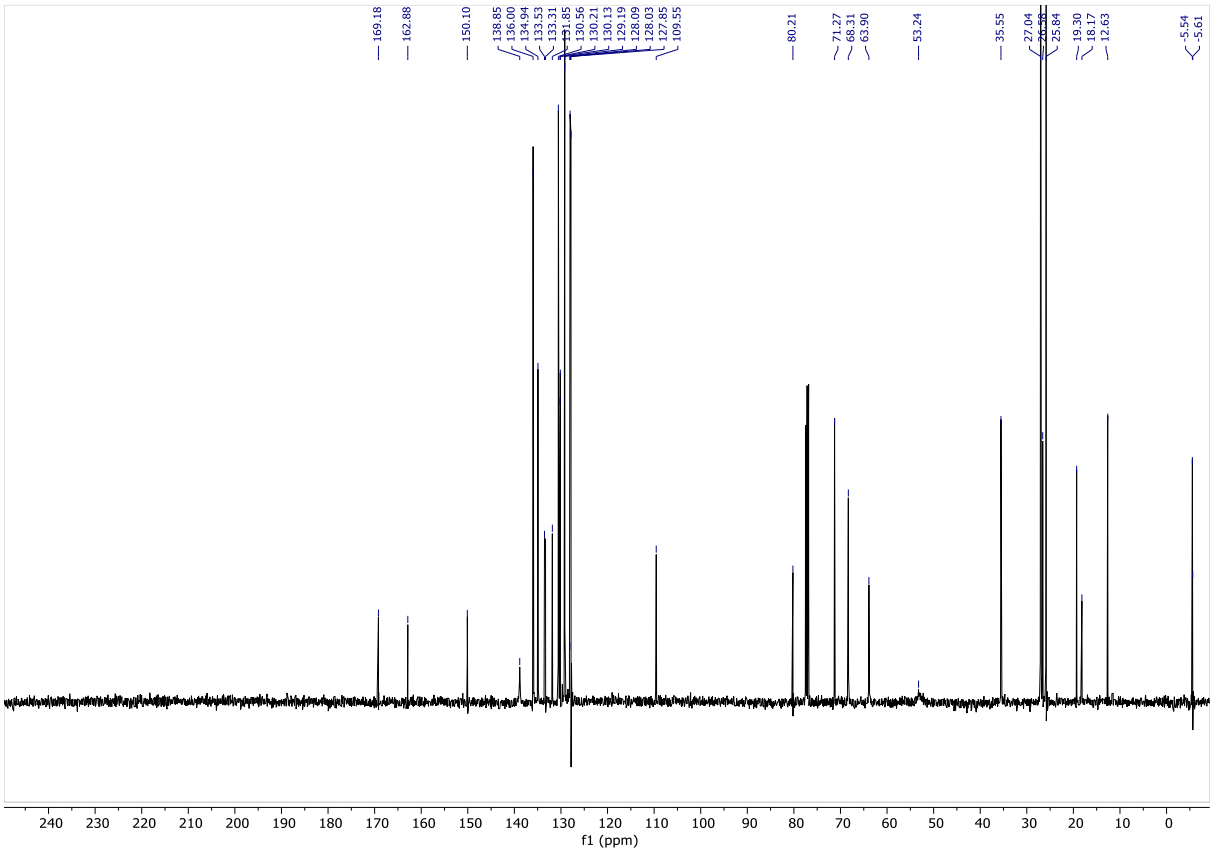
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 – 7.79 (m, 2H), 7.74 – 7.57 (m, 5H), 7.50 – 7.33 (m, 8H), 7.13 (s, 1H), 4.75 (s, 1H), 3.79 (p, J = 5.7 Hz, 1H), 3.61 (dd, J = 11.1, 2.9 Hz, 1H), 3.45 (dd, J = 11.2, 4.1 Hz, 1H), 2.41 (dd, J = 5.5, 2.6 Hz, 2H), 2.20 (ddd, J = 14.2, 6.3, 1 Hz, 1H), 2.05 – 1.94 (m, 2H), 1.85 (d, J = 1.1 Hz, 3H), 1.05 (s, 9H), 0.86 (s, 9H), -0.02 (d, J = 5.6 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.2, 162.9, 150.1, 138.9, 136.0 (4C), 134.9, 133.5, 133.3, 131.9, 130.6 (2C), 130.2, 130.1, 129.2 (2C), 128.0 (2C), 127.9 (2C), 109.6, 80.2, 71.3, 68.3, 63.9, 53.2, 35.6, 27.0 (3C), 26.6, 25.8 (3C), 19.3, 18.2, 12.6, -5.5, -5.6;

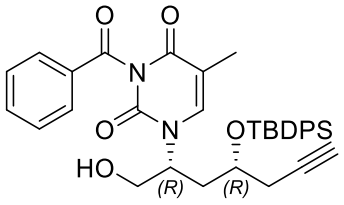
IR (film): ν = 2953, 2929, 2894, 2857, 1750, 1699, 1657, 1600, 1471, 1462, 1430, 1364, 1289, 1256, 1111, 982, 835, 775, 741, 704, 687, 665, 613;

HRMS (ESI-TOF) *m/z* calcd. for $C_{41}H_{53}N_2O_5Si_2$ $[M+H]^+$ 709.3488, found 709.3483


f1 (ppm)


f1 (ppm)

*3-benzoyl-1-((2R,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-hydroxyhept-6-yn-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione ((R,R)-**70**)*



In a flame-dried 10 ml flask solution of (R,R)-**69** (0.62 g, 0.87 mmol, 1.0 equiv.) in DCM: MeOH 1:1 (17.5 ml, 0.05 M) was prepared under Argon atmosphere at room temperature Then, the solution was cooled in an ice bath and CSA (85.3 mg, 0.37 mmol, 0.42 equiv.) was added at 0 °C. After 25 min, the mixture was allowed to warm to room temperature and stirred for 18 h. When the completion of the reaction by TLC was achieved, sat. aq. $NaHCO_3$ (10 ml) was added and the layers were separated. The aqueous layer was extracted with DCM (3 x 10 ml). The combined organic layers were washed with brine (10 ml), dried over $MgSO_4$, and concentrated under reduced pressure. The crude material 82 mg was purified by 2 cm column chromatography (hexane/EtOAc 2/1) to yield (R,R)-**70** (500 mg, 96 %) as a colorless oil.

Yield: 500 mg (96%);

R_f = 0.276 (hexane / EtOAc = 1:1), CPS staining;

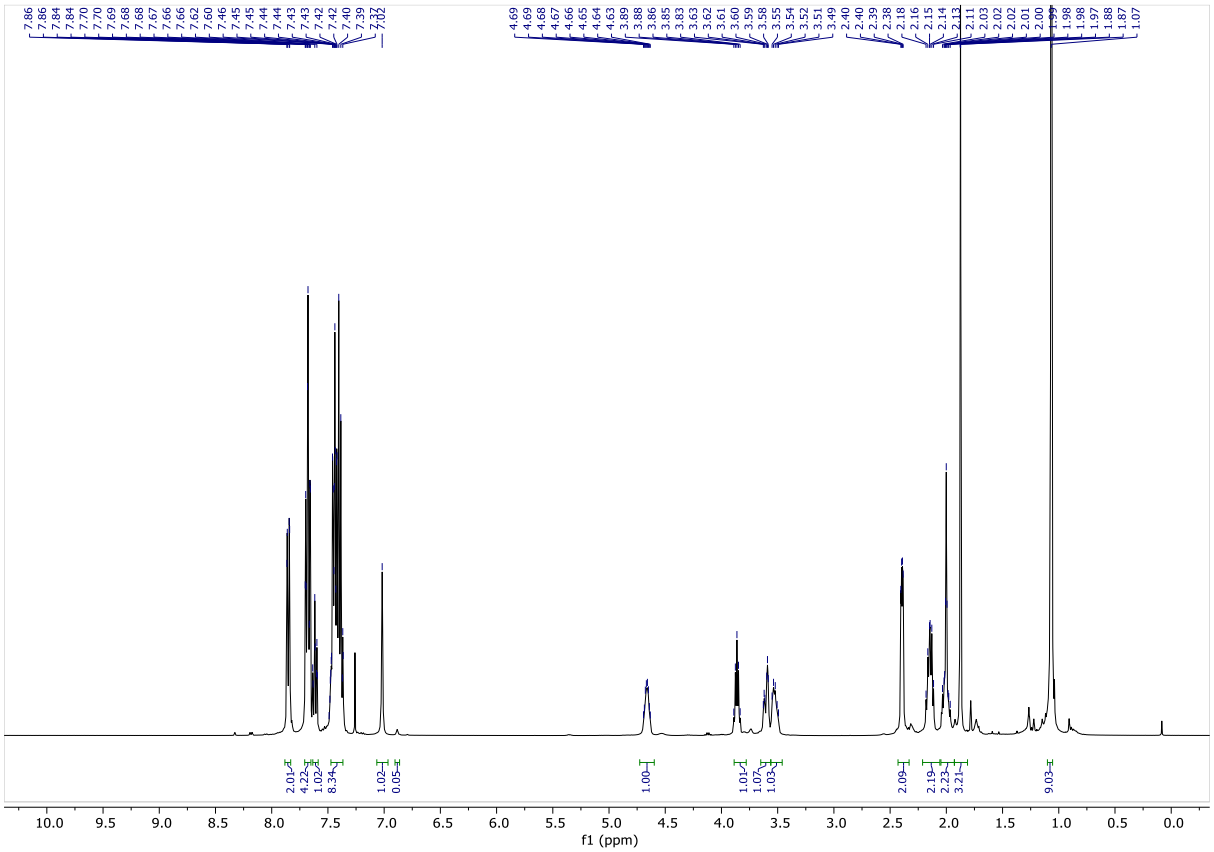
α_D^{20}: -8.82, (c=6.8 mg / 0.5 ml (1.36 g / 100 cm^3), $CHCl_3$, 20°C, l=589 nm);

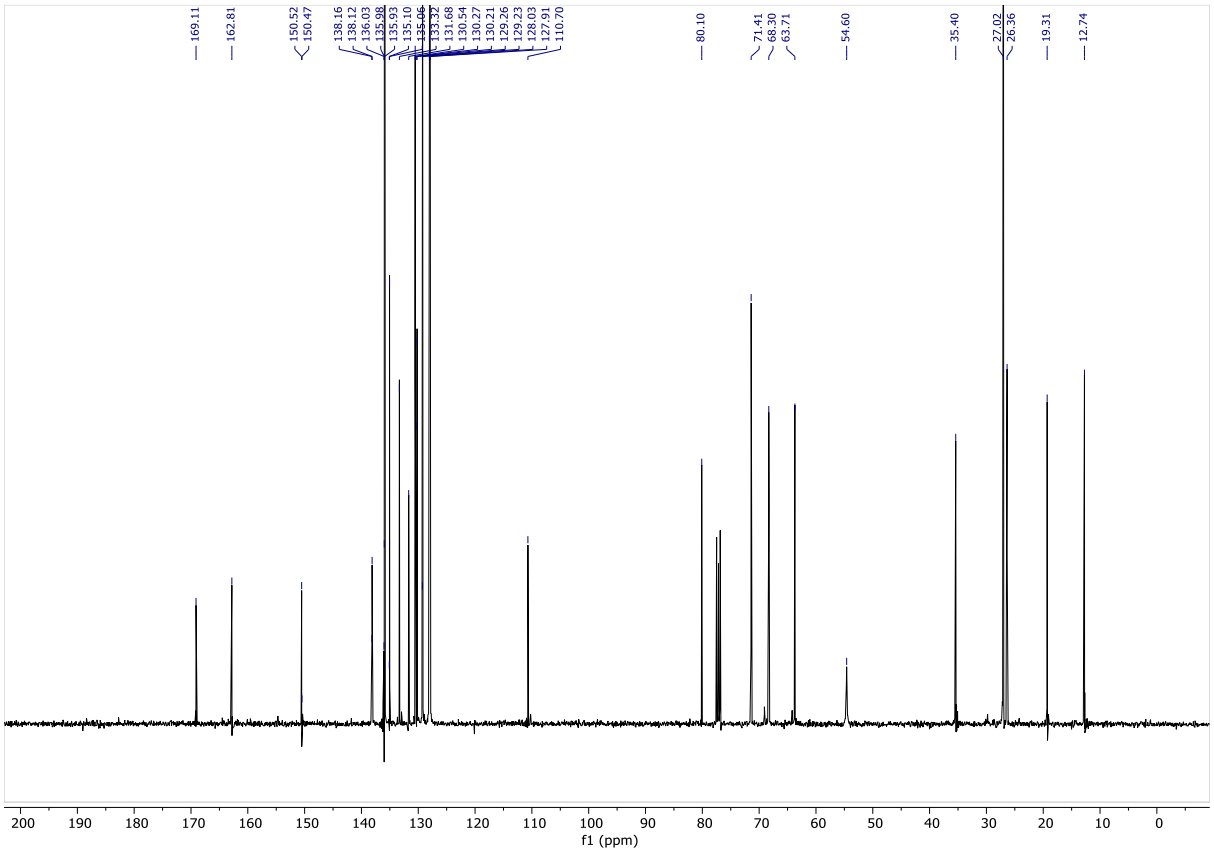
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 – 7.80 (m, 2H), 7.68 (m, 4H), 7.65 – 7.56 (m, 1H), 7.51 – 7.31 (m, 8H), 7.02 (s, 1H), 4.66 (m, 1H), 3.86 (p, J = 5.7 Hz, 1H), 3.67 – 3.41 (m, 2H), 2.39 (dd, J = 5.6, 2.7 Hz, 2H), 2.16 (ddd, J = 20.5, 9.7, 3.3 Hz, 2H), 2.04 – 1.94 (m, 2H), 1.87 (s, 3H), 1.07 (s, 9H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.1, 162.8, 150.5, 138.1, 135.9 (4C), 135.0, 133.3 (2C), 131.7, 130.5 (2C), 130.3, 130.2, 129.2 (2C), 128.0 (2C), 127.9 (2C), 110.7, 80.1, 71.4, 68.3, 63.7, 54.6, 35.4, 27.0 (3C), 26.3, 19.3, 12.7;

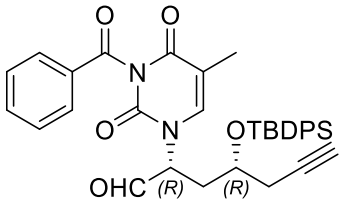
IR (film): ν = 2930, 2857, 2362, 2188, 2044, 1977, 1964, 1748, 1697, 1650, 1600, 1429, 1389, 1365, 1258, 1177, 1111, 1029, 980, 912, 822, 765, 741, 721, 706, 688, 613;

HRMS (ESI-TOF) m/z (ESI) $C_{35}H_{38}N_2NaO_5Si$ $[M+Na]^+$ 617.2442, found 617.


f1 (ppm)


f1 (ppm)

*(3R,5R)-3-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-5-((tert-butyldiphenylsilyl)oxy)oct-7-ynal ((R,R)-**71**)*



In a flame-dried 50 ml flask, a solution of (R,R)-**70** (500 mg, 0.84 mmol, 1.0 equiv.) in dry DCM (22.72 ml, c=0.037 M) was prepared under Argon atmosphere at room temperature. Then, DMP (534.8 mg, 1.26 mmol, 1.50 equiv.) and $NaHCO_3$ (264.8 mg, 3.15 mmol, 3.75 equiv. to neutralize AcOH in DMP and AcOH which is produced in the reaction) were added at room temperature. The reaction was stirred at room temperature for 3-4 h while being monitored by TLC. (If not done then repeat DMP and $NaHCO_3$). When the reaction was finished by TLC, it was diluted with DCM (10 ml) and quenched with 15 ml of DMP quenching solution ($Na_2S_2O_3$ and $NaHCO_3$). The aqueous layer was extracted with DCM (20 ml x 3). The combined organic layers were washed with brine, dried over magnesium sulfate, and filtered; the solvent was removed under reduced pressure. The crude material was used for the next step as a crude. The aldehyde (R,R)-**71** is decomposing on silica, therefore it is used as a crude for the next step.

Yield: 500 mg (quant. crude, used for the next step), *dr*=10:1;

$[\alpha]_{20}^{D}$: = -8.0 (c = 0.5 ; $CHCl_3$, 20°C);

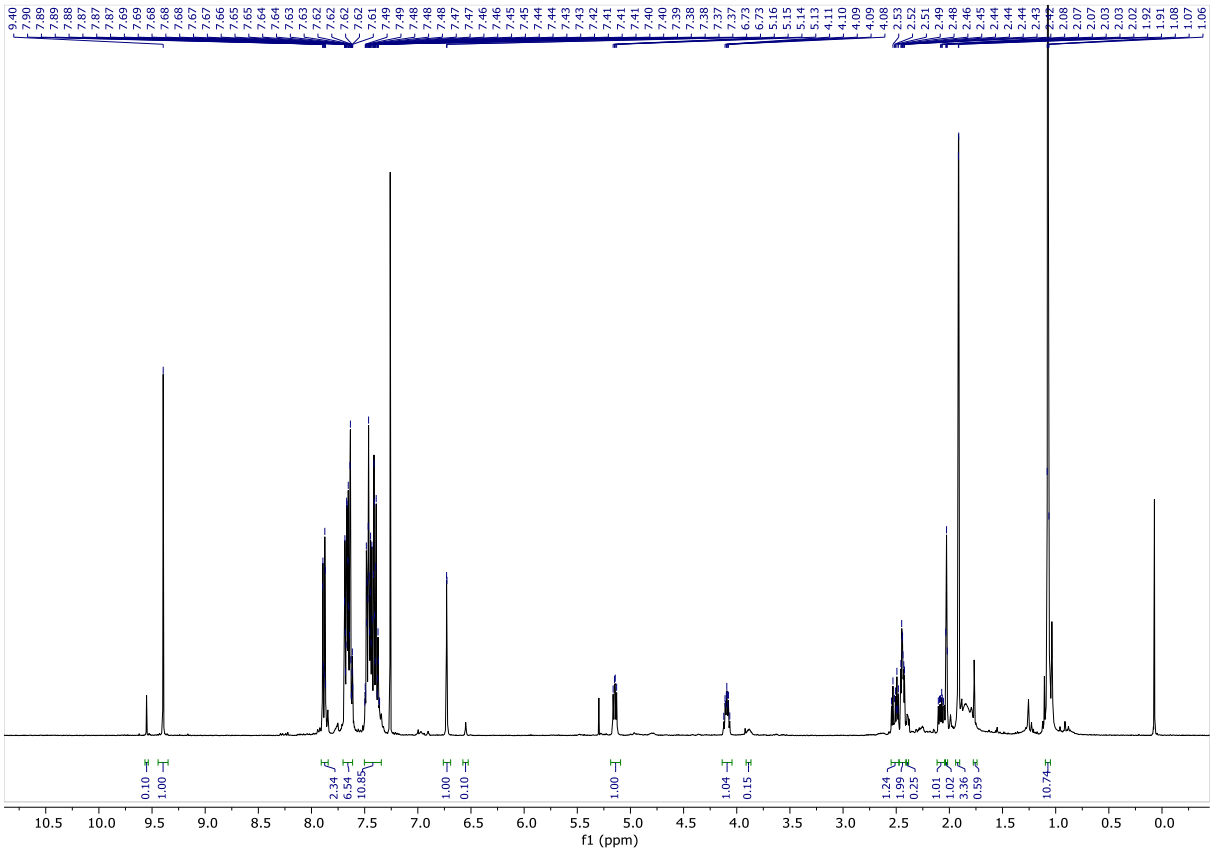
R_f = 0.5 (hexane / EtOAc = 1:1), CPS staining; better to control via MS.

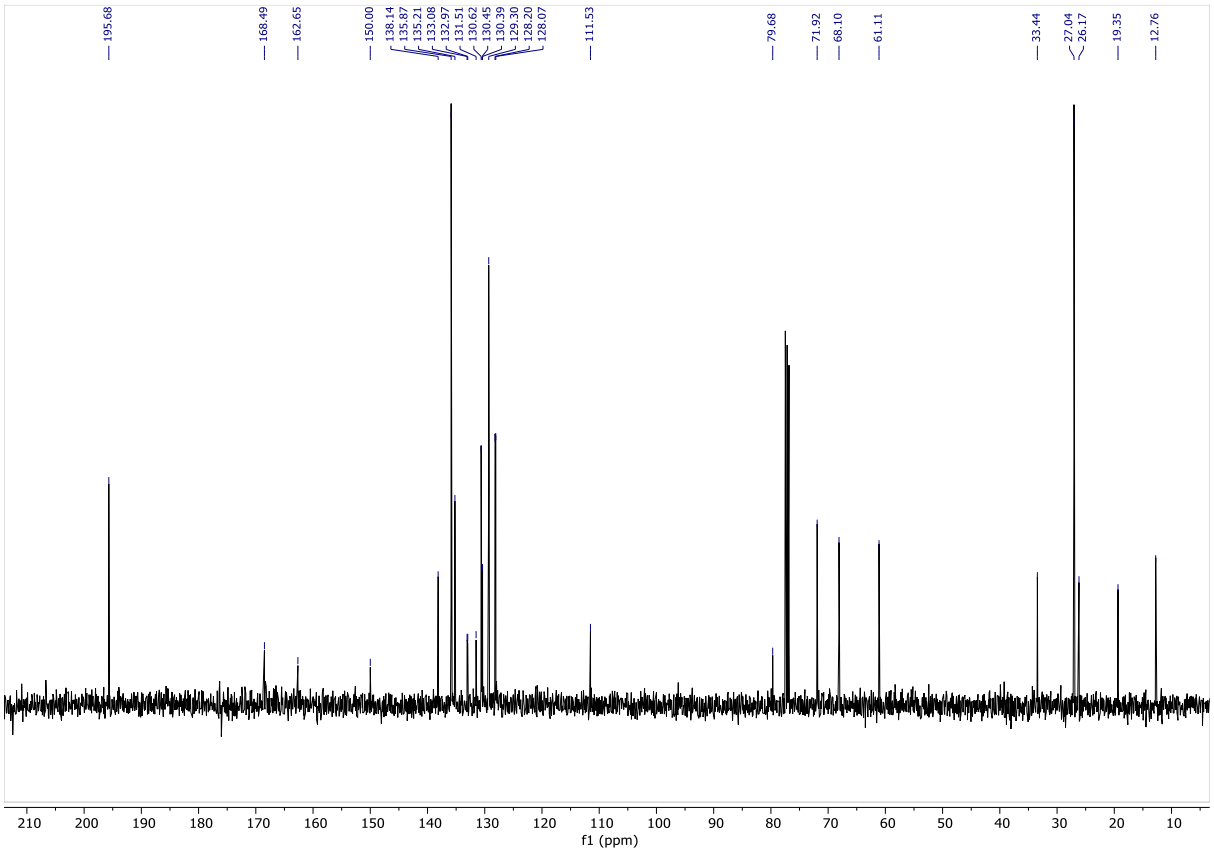
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.40 (s, 1H), 7.98 – 7.84 (m, 2H), 7.73 – 7.58 (m, 5H), 7.50 – 7.32 (m, 8H), 6.73 (d, J = 1.3 Hz, 1H), 5.15 (dd, J = 8.1, 5.1 Hz, 1H), 4.09 (dt, J = 7.2, 4.9 Hz, 1H), 2.60 – 2.47 (m, 1H), 2.44 (m, 2H), 2.13 – 2.05 (m, 1H), 2.03 (t, J = 2.7 Hz, 1H), 1.91 (d, J = 1.2 Hz, 3H), 1.07 (s, 9H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.7, 168.5, 162.7, 150.0, 138.1, 135.9 (4C), 135.2, 133.1, 133.0, 131.5, 130.6 (2C), 130.5, 130.4, 129.3 (2C), 128.2 (2C), 128.1 (2C), 111.5, 79.7, 71.9, 68.1, 61.1, 33.4, 27.0 (3C), 26.2, 19.6, 12.8;

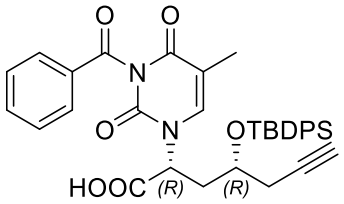
IR (film): ν = 3290, 3072, 2931, 2858, 2359, 2328, 2165, 2050, 2021, 1749, 1699, 1657, 1600, 1461, 1429, 1389, 1363, 1256, 1229, 1179, 1111, 1000, 978, 937, 822, 793, 762, 742, 704, 687, 665, 646, 611, 579, 561, 552, 540, 507;

HRMS (ESI-TOF) m/z (ESI) $C_{35}H_{37}N_2O_5Si$ $[M+H]^+$ 593.2466, found 593.2464.


f1 (ppm)


f1 (ppm)

*(3R,5R)-3-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-5-((tert-butyldiphenylsilyl)oxy)oct-7-ynal ((R,R)-**2**)*



In a flame-dried 50 ml flask solution of crude (R,R)-**71** (500 mg, 0.84 mmol, 1.0 equiv.) was solubilized in a mixture (1:1) of t-BuOH (9.92 ml, c=0.085 M) and 2-methyl-butene (9.92 ml, c=0.085 M) at 0 °C (solution A). Meanwhile, in a separate flask, a solution of $NaClO_2$ (80%, 244.0 mg, 2.70 mmol, 3.2 equiv.) and NaH_2PO_4 dihydrate (526 mg, 3.374 mmol, 4.0 equiv.) in water (6.75 ml, c=0.5 M) was prepared (solution B). Then, solution B was added to solution A dropwise at 0°C. The reaction was stirred for 3 h while slowly allowing it to go from 0 ˚C to room temperature. Once the reaction was completed by TLC, the reaction was diluted with DCM (10.0 ml) and brine (10.0 ml), extracted three times with DCM (15.0 ml), dried over $MgSO_4$, and concentrated under reduced pressure. The crude material (m=630 mg) was columned by a 1 cm column with an eluent (hex:ea=5:1), slowly going to pure ethyl acetate, then ethyl acetate with 1% AcOH. (R,R)-**2** is a shiny and fluffy material.

Yield: 373.4 mg (73 %), *dr*=10:1;

R_f = baseline, fire-like (hexane / EtOAc = 1:1), CPS staining;

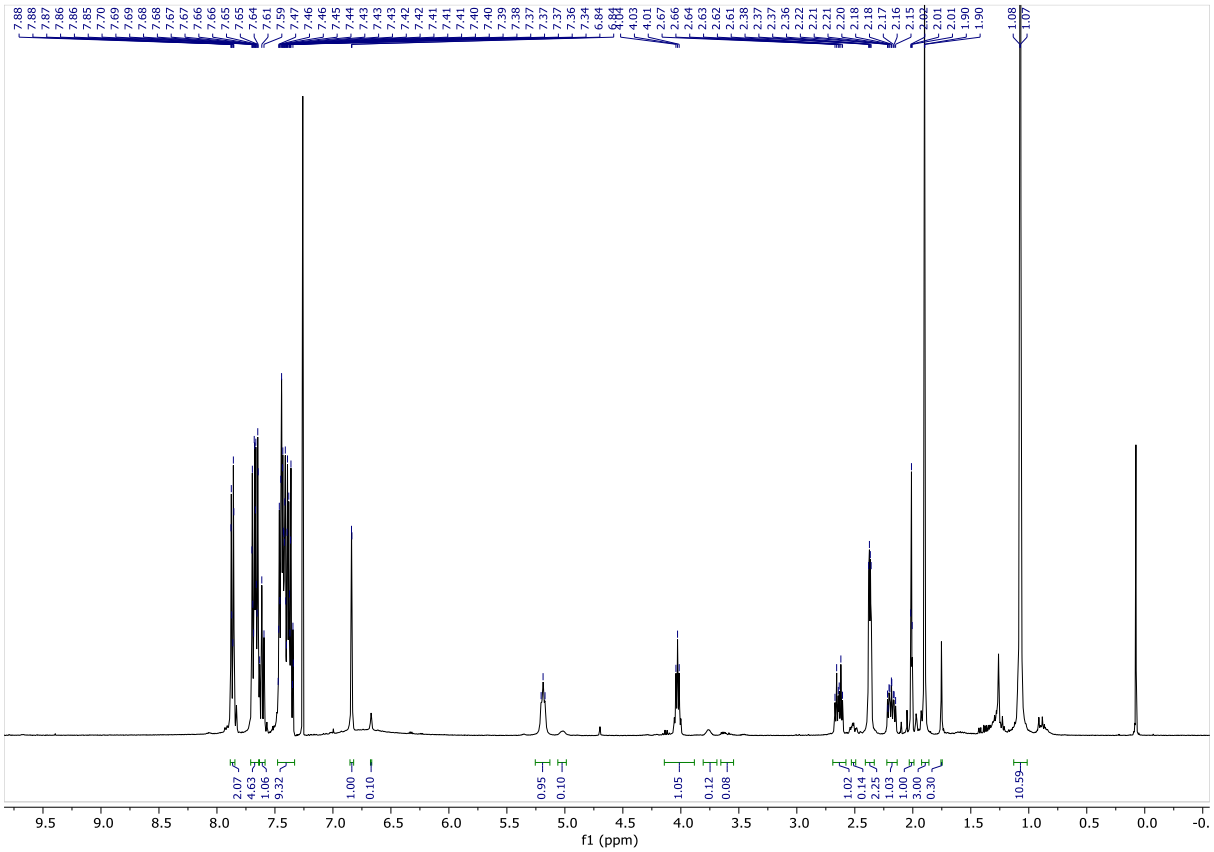
$[\alpha]_{20}^{D}$: = +7.0 (c = 0.5 ; $CHCl_3$, 20°C);

1H NMR (400 MHz, Chloroform-d) δ 7.94 – 7.76 (m, 2H), 7.74 – 7.55 (m, 5H), 7.50 – 7.32 (m, 8H), 6.84 (d, J = 1.3 Hz, 1H), 5.19 (t, J = 6.7 Hz, 1H), 4.03 (t, J = 5.7 Hz, 1H), 2.64 (dt, J = 14.6, 5.7 Hz, 1H), 2.37 (dd, J = 5.9, 2.7 Hz, 2H), 2.18 (ddd, J = 14.5, 7.9, 5.2 Hz, 1H), 2.01 (t, J = 2.6 Hz, 1H), 1.90 (d, J = 1.1 Hz, 3H), 1.07 (s, 9H);

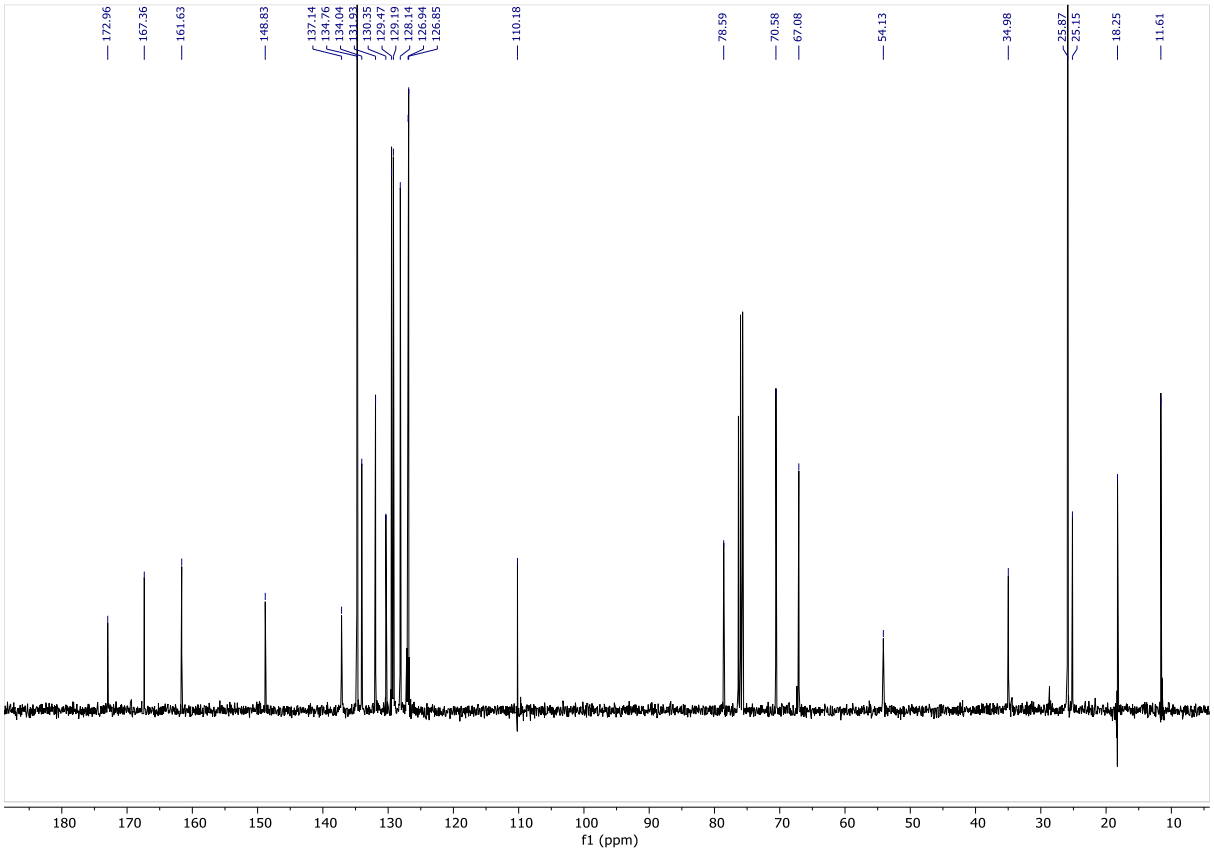
^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.0, 167.4, 161.6, 148.8, 137.1, 134.8 (4C), 134.0, 131.9 (2C), 130.4, 129.5 (2C), 129.2 (2C), 128.1 (2C), 126.9 (2C), 126.9 (2C), 110.2, 78.6, 70.6, 67.1, 54.1, 35.0, 25.9 (3C), 25.2, 18.3, 11.6;

IR (film): ν = 3452, 3306, 3015, 2955, 2930, 2893, 2858, 1748, 1697, 1646, 1600, 1461, 1428, 1388, 1365, 1309, 1255, 1235, 1179, 1105, 1089, 1028, 1000, 979, 937, 899, 843, 822, 809, 790, 753, 703, 687, 665, 638, 623, 611, 576;

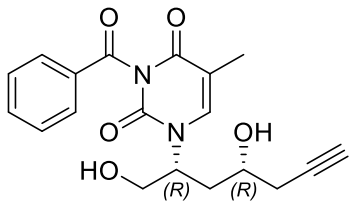
HRMS (ESI-TOF) m/z (ESI) $C_{35}H_{37}N_2O_6Si$ $[M+H]^+$ 609.2415, found 609.2431.



Silicone grease is present in the spectra+minor diastereomer signals are shown



*3-benzoyl-1-((2R,4R)-1,4-dihydroxyhept-6-yn-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione ((R,R)-**72**)*



In a flame-dried 10 ml flask a solution of (R,R)-**69** (60 mg, 0.07 mmol, 1.0 equiv.) in THF (2.3 mL) was prepared at 0 °C. TBAF (0.38 mL, 0.38 mmol, 1 M in THF, 4.5 equiv.) was added at 7:53 and the reaction mixture was allowed to warm to the room temperature at 8:03 and stirred for 2 h at room temperature. TLC after 1.5 hours showed that the reaction was done. The reaction was quenched with a saturated solution of NH_4Cl (5 mL) and diluted with EA (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate three times. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material (m=207.9 mg) was purified by silica gel FC 1.5 cm (hex: ea =5:1) to afford (R,R)-**72** as white oil, badly soluble in fractions 28-41.

Yield: 21.5 mg (71 %);

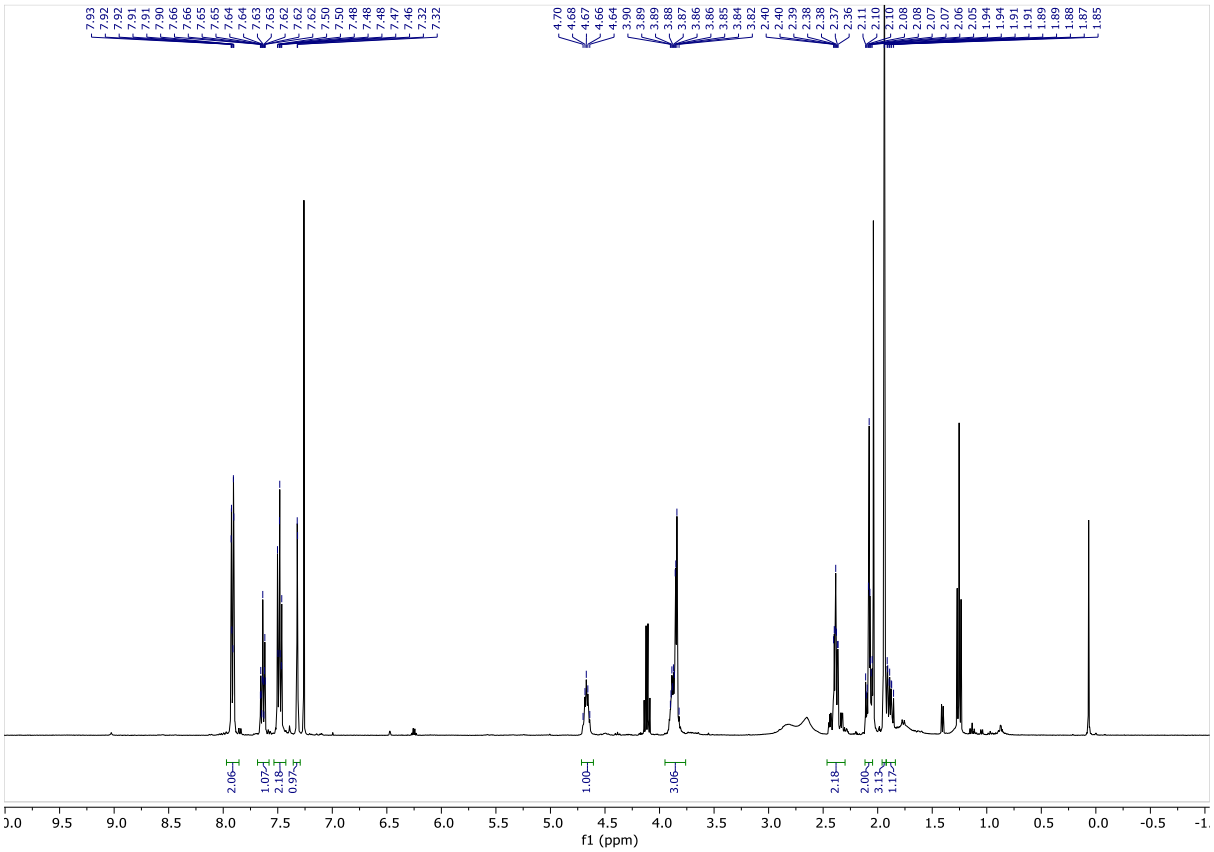
R_f = 0.398 (EtOAc), CPS staining;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 – 7.79 (m, 2H), 7.77 – 7.57 (m, 1H), 7.56 – 7.39 (m, 2H), 7.32 (d, J = 1.2 Hz, 1H), 4.67 (app. p, J=7.1 Hz, 1H), 3.90 – 3.78 (m, 3H), 2.38 (m, 2H), 2.11-2.05 (m, 2H), 1.94 (d, J = 1.1 Hz, 3H), 1.91-1.84 (m, 1H);

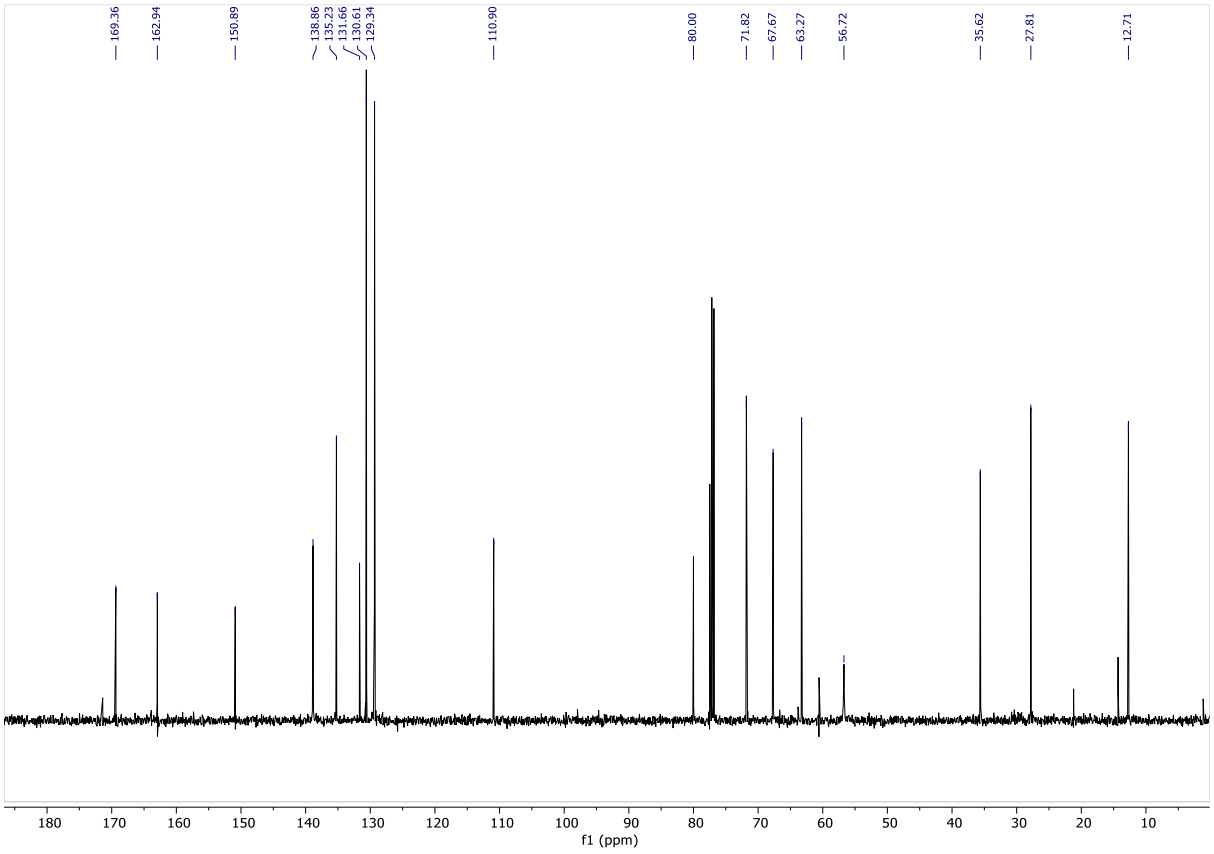
^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.4, 162.9, 150.9, 138.9, 135.2, 131.7, 130.6 (2C), 129.3 (2C), 110.9, 80.0, 71.8, 67.7, 63.3, 56.7, 35.6, 27.8, 12.7;

IR (film): ν = 3458, 3303, 3014, 2928, 1743, 1691, 1634, 1599, 1443, 1388, 1368, 1257, 1237, 1179, 1148, 1048, 1020, 1002, 980, 900, 809, 791, 750, 714, 685, 665, 637, 554;

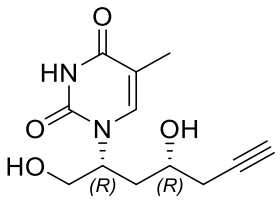
HRMS (ESI-TOF) m/z (ESI) $C_{19}H_{19}N_2O_5$ $[M-H]^-$ 355.1299, found 355.1290; $C_{19}H_{20}N_2NaO_5$ $[M+Na]^+$ 379.1264, found 379.1258;



EtOAc is present



*1-((2R,4R)-1,4-dihydroxyhept-6-yn-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione ((R,R)-**73**)*



Benzoylated thymine fragment (R,R)-**72** was dissolved in a methanolic ammonia solution (7 N, 100 equiv.) at room temperature overnight. After 26 h the reaction showed completion by TLC (no SM spot), and the solvent was removed under reduced pressure. The crude residue (m=6.9 mg) was purified, using pipet flash column chromatography with elution gradient of EtOAc/Hex (1:3) to methanol to yield the desired compound as amorphous solid (R,R)-**73** in fractions 10-11 (3.7 mg).

Yield: 3.7 mg (62 %);

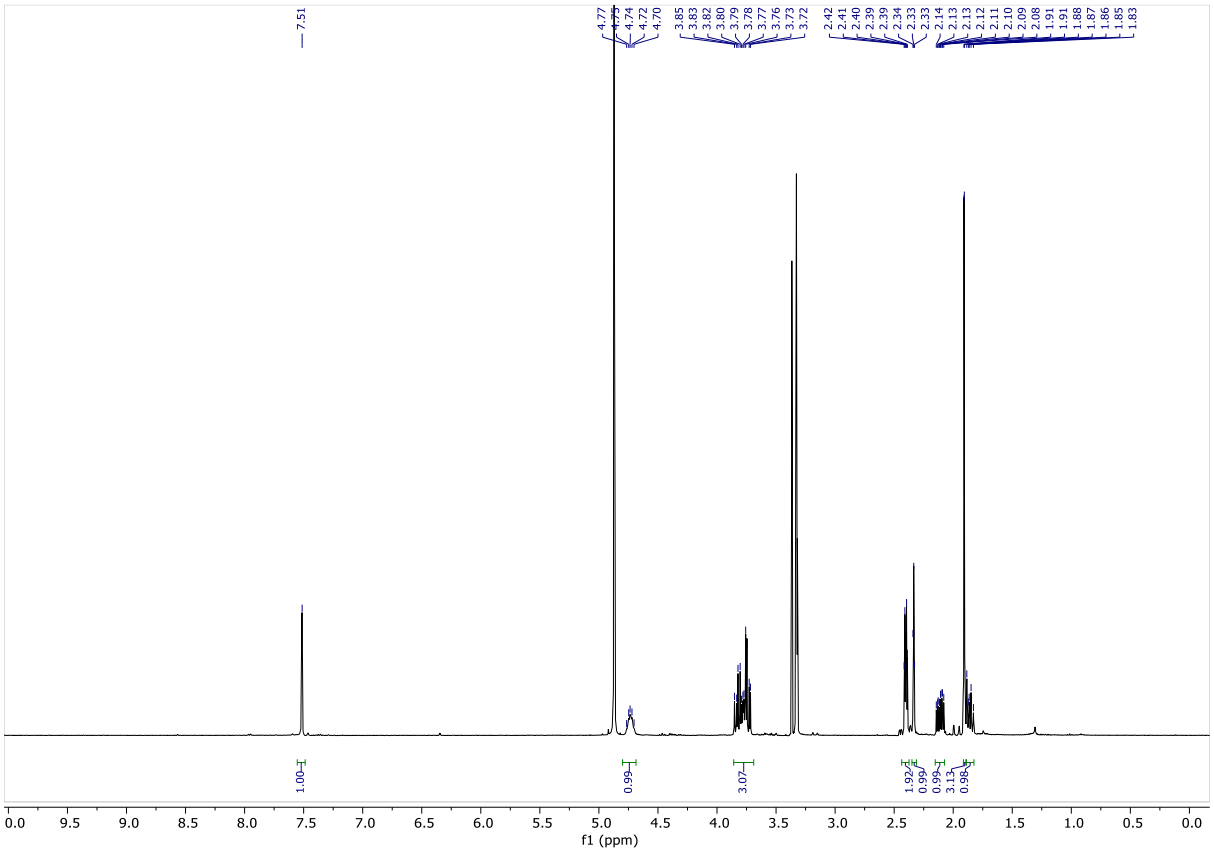
R_f = 0.095 (EtOAc), CPS staining;

^{1}H NMR (400 MHz, Methanol-*d4*) δ 7.51 (s, 1H), 4.73 (p, J = 7.0 Hz, 1H), 3.90 – 3.64 (m, 3H), 2.40 (dt, J = 5.8, 2.6 Hz, 2H), 2.33 (t, J = 2.7 Hz, 1H), 2.11 (ddd, J = 14.3, 6.4, 4.5 Hz, 1H), 1.91 (d, J = 1.1 Hz, 3H), 1.89 – 1.82 (m, 1H);

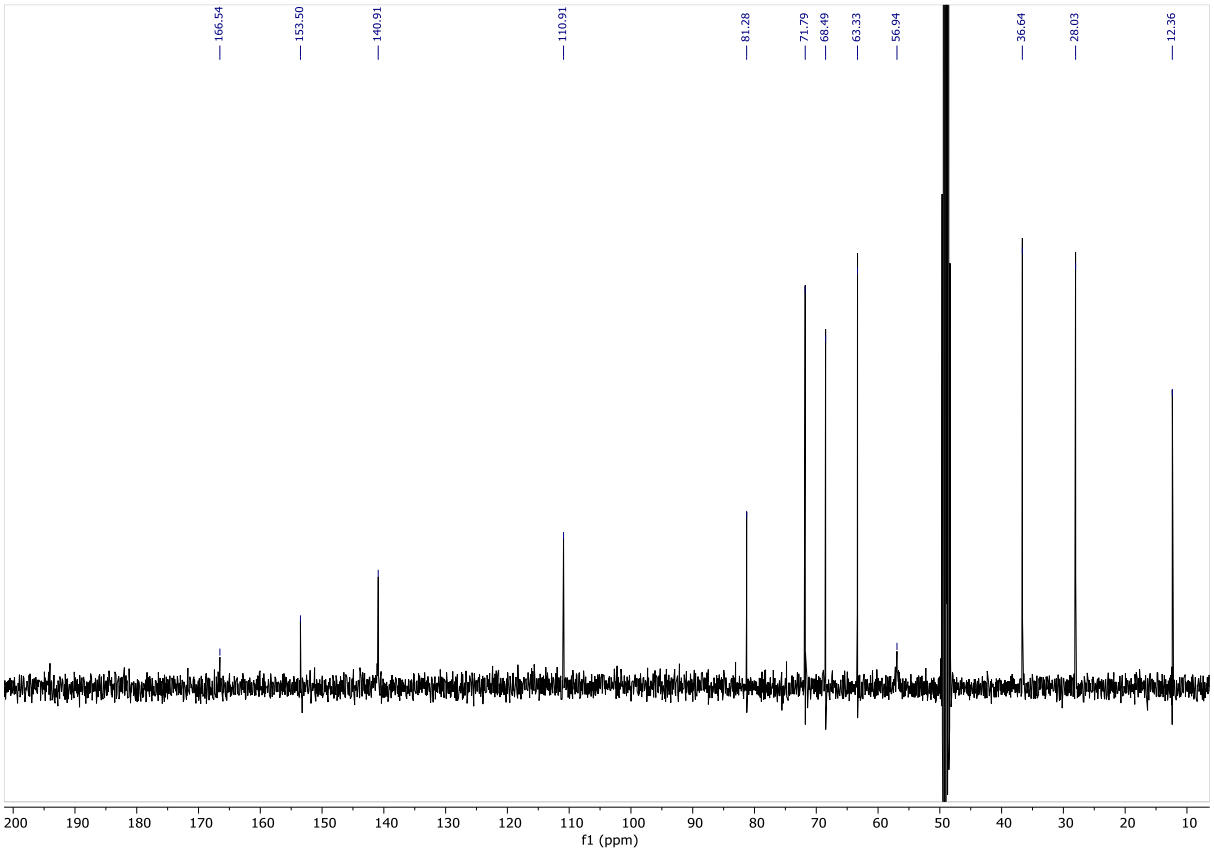
^{13}C NMR (101 MHz, Methanol-d4) δ 166.5, 153.5, 140.9, 110.9, 81.3, 71.8, 68.5, 63.3, 56.9, 36.6, 28.0, 12.4;

IR (film): ν = 3288, 2922, 2193, 2136, 2088, 2024, 1679, 1470, 1420, 1262, 1215, 751, 685, 666, 617, 591, 554, 521, 511;

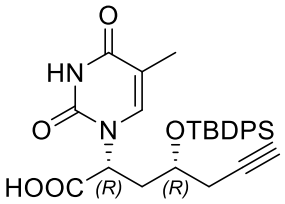
HRMS (ESI-TOF) m/z (ESI) $C_{12}H_{16}N_2NaO_4$ $[M+Na]^+$ 275.1002, found 275.0998.



1NH and 2OH are not seen



*(2R,4R)-4-((tert-butyldiphenylsilyl)oxy)-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)hept-6-ynoic acid (**SI-(R,R)-2**)*



In a flame-dried 10 ml flask solution of the acid (R,R)-**2** was dissolved in methanolic ammonia solution (7 N, 100 equiv) at room temperature and stirred overnight. After 15 h at room temperature when the reaction was complete by TLC and MS, the solvent was removed under reduced pressure, and the crude residue was purified, using flash chromatography with elution gradient of AcOEt/MeOH to yield the desired SI-(R,R)-**2** as an amorphous solid.

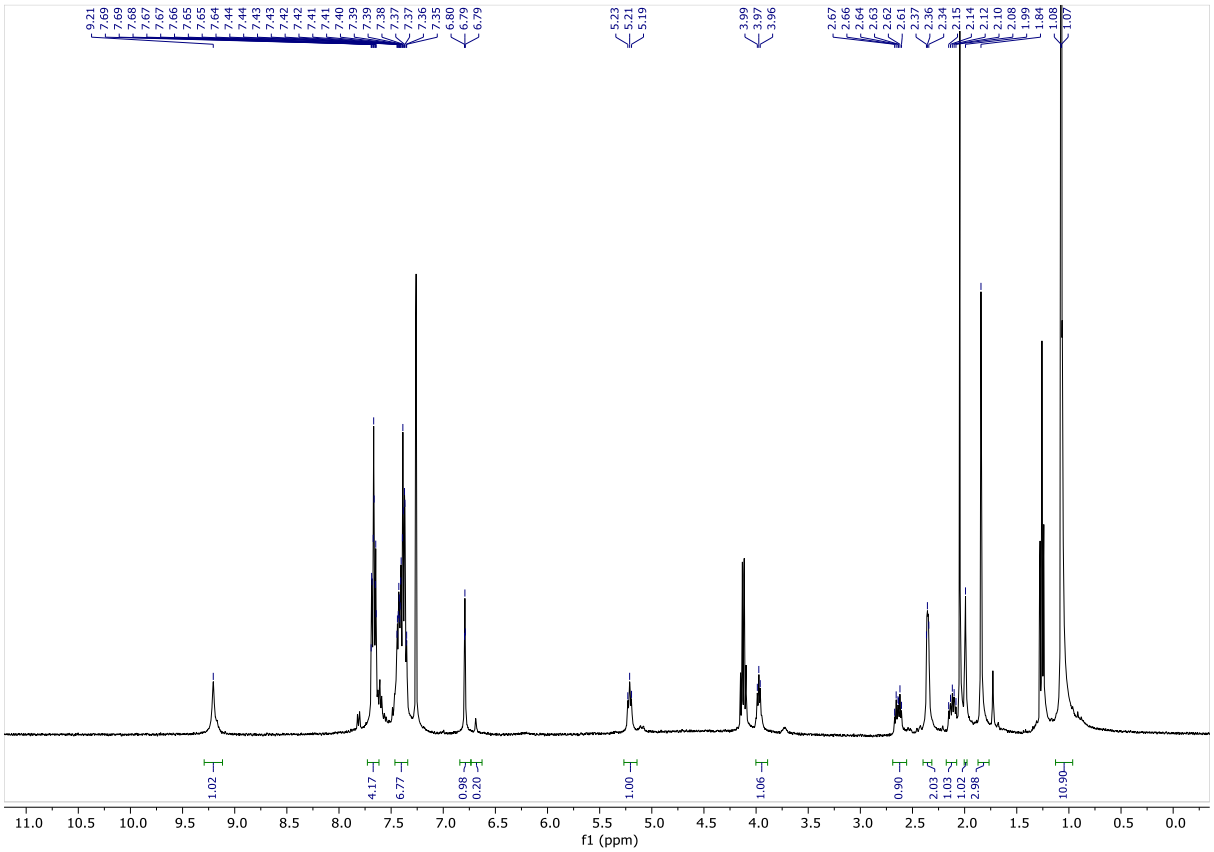
Yield: 42 mg (25 %);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.21 (s, 1H), 8.04 – 7.52 (m, 4H), 7.52 – 7.28 (m, 6H), 6.79 (d, J = 1.5 Hz, 1H), 5.21 (t, J = 7.2 Hz, 1H), 4.00 – 3.94 (m, 1H), 2.64 (m, 1H), 2.35 (m, 2H), 2.12 (m, 1H), 1.99 (s, 1H), 1.84 (s, 3H), 1.07 (s, 9H); one proton from COOH is missing

^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.1, 164.3, 150.9, 138.8, 135.9 (4C), 133.3 (2C), 130.2 (2C), 128.0 (2C), 127.9 (2C), 111.1, 79.0, 71.6, 68.2, 55.0, 36.3, 27.0 (3C), 26.4, 19.4, 12.6;

IR (film): ν = 3292, 3184, 3071, 3047, 2957, 2932, 2894, 2858, 1694, 1590, 1472, 1428, 1387, 1372, 1265, 1225, 1111, 1090, 999, 967, 910, 822, 764, 737, 704, 648, 623, 612, 589, 578, 506;

HRMS (ESI-TOF) m/z (ESI) $C_{28}H_{32}N_2NaO_5Si$ $[M+Na]^+$ 527.1973, found 527.1975.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7.64
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7.36
7.35
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6.79
6.79
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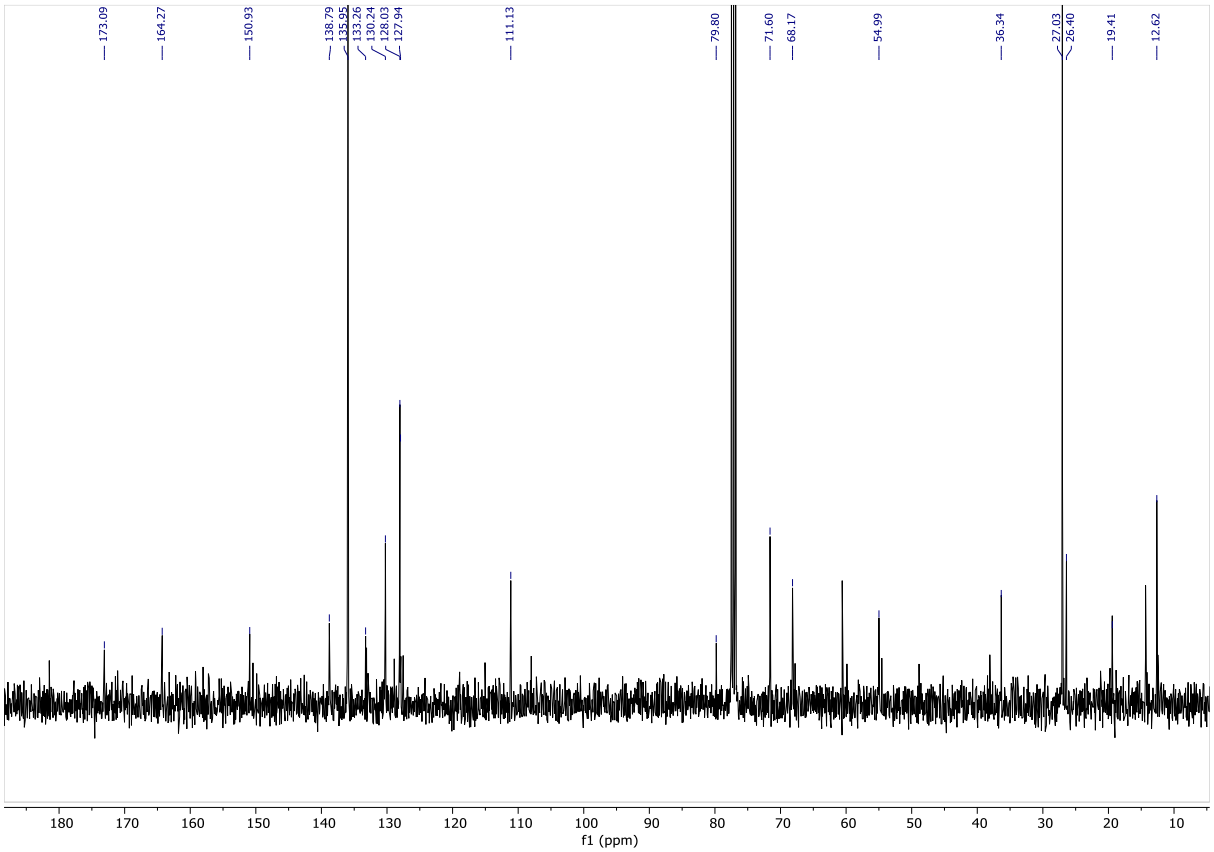
5.19
3.99
3.97
3.96
2.67
2.66
2.64
2.63
2.62
2.61
2.37
2.36
2.34
2.15
2.14
2.12
2.10
2.08
1.99
1.84
1.08
1.07
1.02
4.17
6.77
0.98
0.20
1.00
1.06
0.90
2.03
1.03
1.02
2.98
10.90
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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138.79
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133.26
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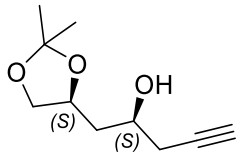
128.03
127.94
111.13
79.80
71.60
68.17
54.99
36.34
27.03
26.40
19.41
12.62
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

Synthesis of (*R,S*)-2

*(S)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-yn-2-ol ((S,S)-**63**)*



Preactivated with HCL Zinc dust (6.0 g, 86.69 mmol, 2.5 equiv.) was suspended in 62 mL of THF containing 1,2- dibromoethane (0.78 mL, 8.669 mmol, 0.25 equiv.). The suspension was heated to 65 °C for 10 min before cooling to 25 °C. After 46 min, chlorotrimethylsiliane (1.175 mL, 8.669 mmol, 0.25 equiv.) was added dropwise *via a* syringe. became sediment from a nice powder. The suspension was stirred vigorously for an additional 30 min and then cooled to -10 °C. Propargyl bromide (80 % in toluene, 9.672 mL, 86.691 mmol, 2.5 equiv.) was added slowly *via* syringe over 20 min. The suspension was stirred for 2.5 h below -12 °C. Then it was added over 45 min through a cannula to a solution of aldehyde S-**6** (5.2 g, 34.677 mmol, 1.0 equiv.) in toluene (230 mL) at -78 °C. The resulting reaction was slowly warmed to -40- (-45) °C and stirred at this temperature for 22 h. It was then warmed to 0 °C and quenched with saturated aqueous NH4Cl solution (100 mL). The mixture was extracted with EtOAc three times and the combined organic fractions were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by slow gradient flash column chromatography (0% → 30% EtOAc/ DCM) to afford homopropargylic alcohol (S,S)-**63** (1.33 g) as a colorless oil and its major diastereomer (S,R)-**63** (4.05 g) as a pale yellow oil, and a mixture of two diastereomers (0.9 g). The combined yield of the product: 5.38 g (84%), *dr* = 3.5:1 (based on crude reaction mixture). The residue was purified by slow gradient flash column chromatography (0% → 30% EtOAc/DCM).

Yield: 5.38 g in total (84%);

R_f = 0.209 (hexane / EtOAc = 2:1), CPS staining;

α_D^{20}: +20.99 (c = 1 mg / 0.7 mL, $CHCl_3$, 20°C)

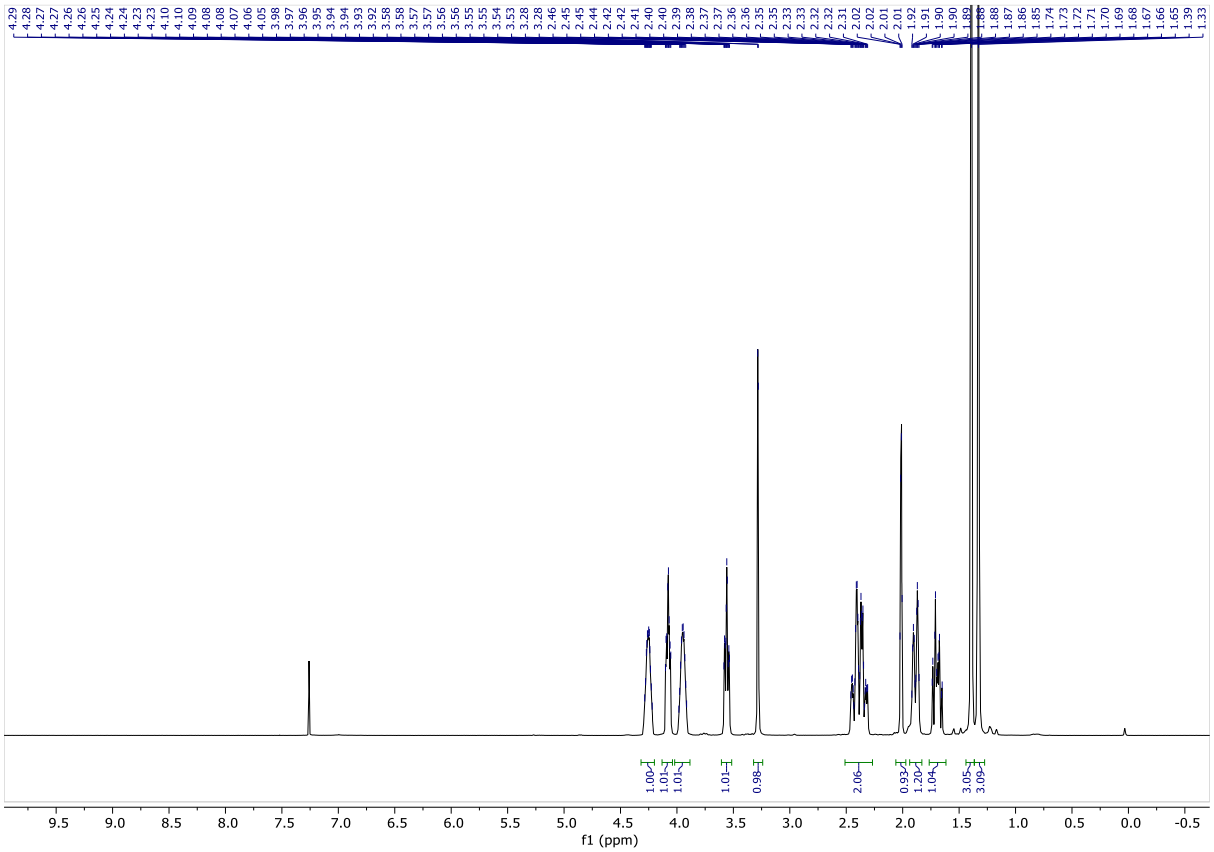
^{1}H NMR (400 MHz, Chloroform-d) δ 4.25 (m, 1H), 4.08 (m, 1H), 3.95 (m, 1H), 3.56 (m, 1H), 3.28 (s, 1H), 2.58 – 2.18 (m, 2H), 2.01 (m, 1H), 1.89 (m, 1H), 1.78 – 1.57 (m, 1H), 1.39 (s, 3H), 1.33 (s, 3H);

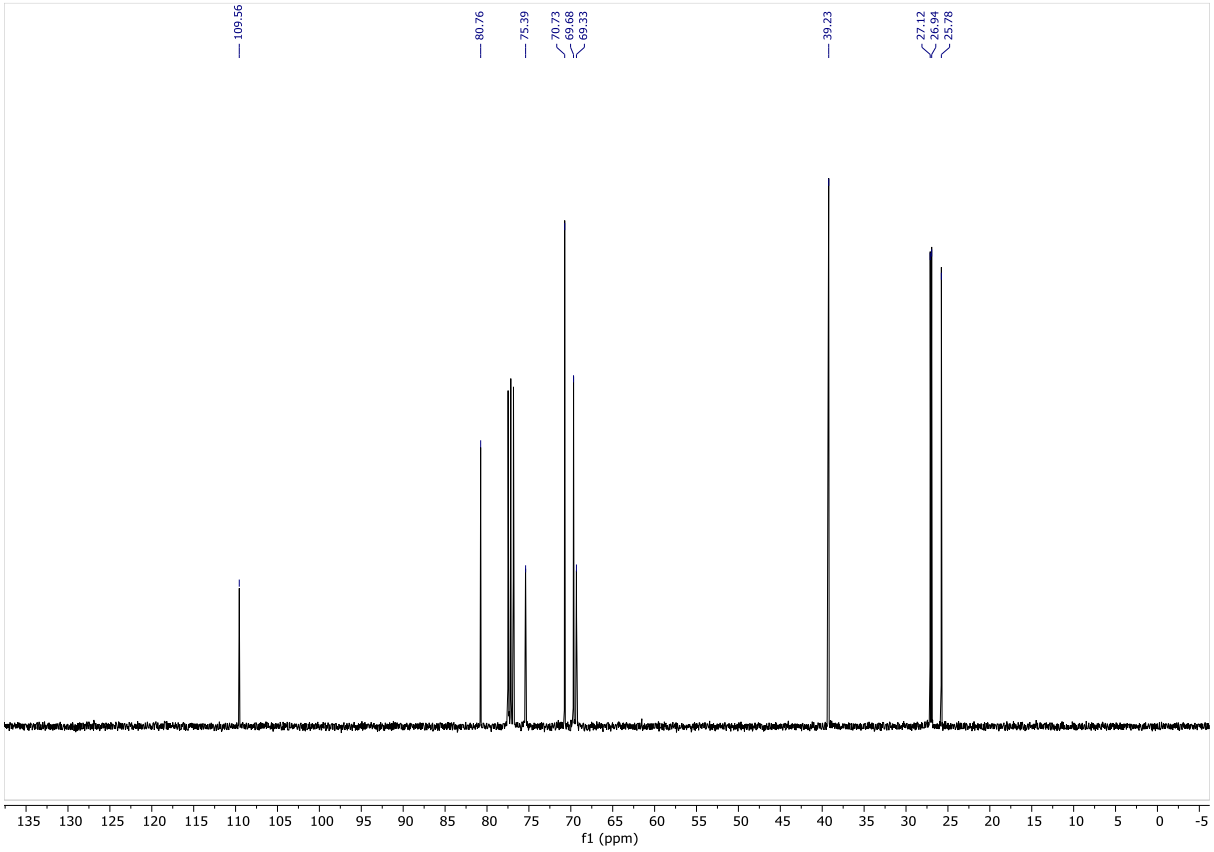
^{13}C NMR (101 MHz, Chloroform-d) δ 109.6, 80.8, 75.4, 70.7, 69.7, 69.3, 39.2, 27.1, 26.9, 25.8;

IR (film): ν = 3289, 3041, 2992, 2983, 2938, 2149, 1426, 1399, 1371, 1260, 1213, 1156, 1119, 1093, 1070, 1061, 1031, 979, 914, 842, 790, 742, 639;

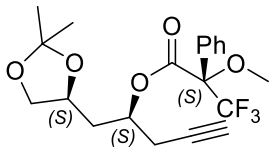
HRMS (ESI-TOF) m/z calcd. for $C_{10}H_{16}NaO_3$ $[M+Na]^+$ 207.0992, found 207.0992.

J. Am. Chem. Soc. 2016, 138, 40, 13415-13423, S56-S61


4.29 4.28 4.27 4.27 4.26 4.26 4.25 4.24 4.24 4.23 4.10 4.09 4.08 4.08 4.07 4.06 4.05 3.98 3.97 3.96 3.95 3.94 3.94 3.93 3.92 3.58 3.57 3.57 3.56 3.56 3.55 3.55 3.54 3.53 3.28 3.28 2.46 2.45 2.45 2.44 2.42 2.42 2.41 2.40 2.40 2.39 2.38 2.37 2.37 2.36 2.36 2.35 2.35 2.33 2.33 2.32 2.32 2.31 2.02 2.02 2.01 2.01 1.92 1.91 1.90 1.90 1.89 1.88 1.87 1.86 1.85 1.74 1.73 1.72 1.71 1.70 1.69 1.68 1.67 1.66 1.65 1.39 1.33
1.00 1.01 1.01 1.01 0.98 2.06 0.93 1.20 1.04 3.05 3.09
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


109.56
80.76
75.39
70.73
69.68
69.33
39.23
27.12
26.94
25.78
135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5
f1 (ppm)

*Mosher ester analysis of (S)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-yn-2-ol. (S)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-yn-2-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ((S,S,S)-**65**)*



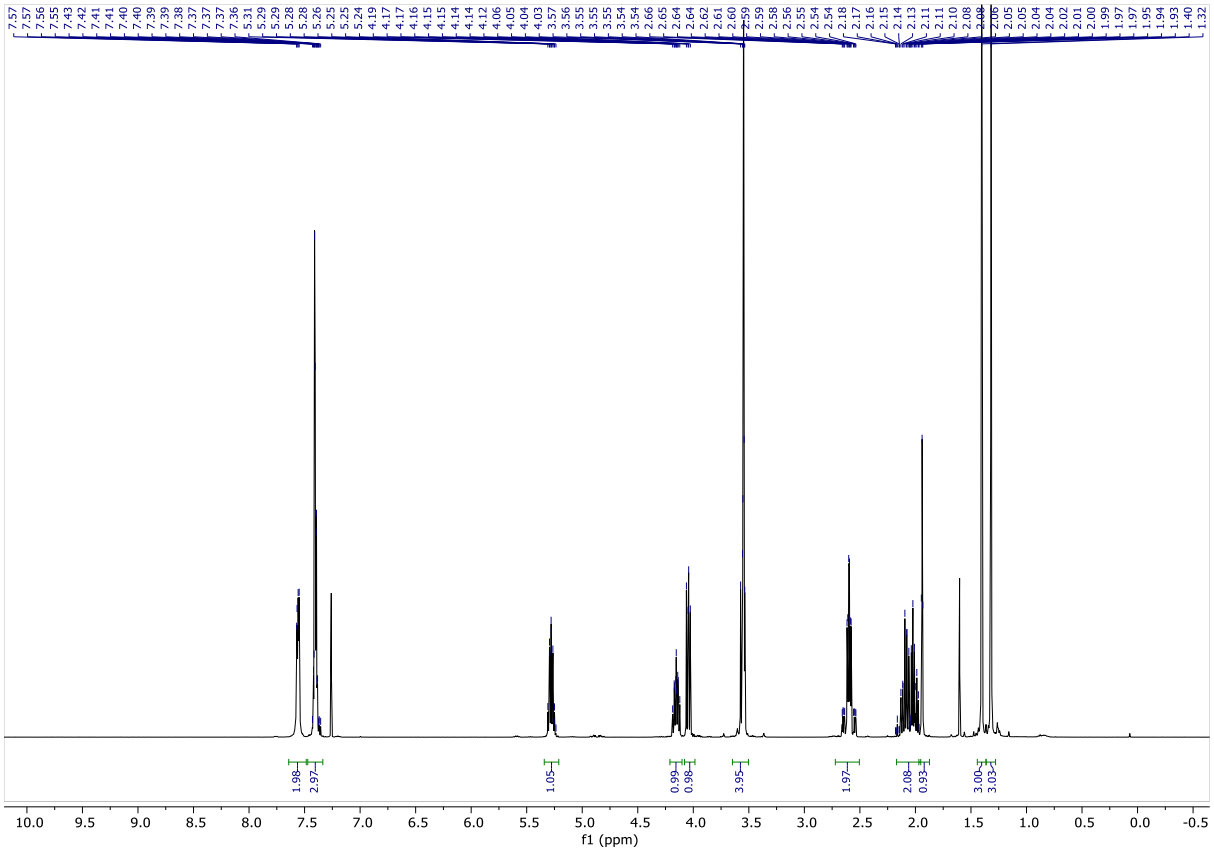
(S)- MTPA (30 mg, 0.14 mmol, 2.1 equiv.) were weighted in the glove box. *(S)*-MTPA was solubilized in toluene (0.68 mL). Then, TEA (0.021 mL, 0.15 mmol, 2.3 equiv.) and trichlorobenzoyl chloride (0.021 mL, 0.14 mmol, 2.1 mmol) were added to the flask at room temperature. The reaction appeared as a colorless solution. Immediately, (S,S)-**63** (10 mg, 0.065 mmol, 1.0 equiv.), previously solubilized in toluene in a vial (0.1 mL), was added to the flask, immediately, DMAP (18.3 mg, 0.15 mmol, 2.3 equiv.) was added and the reaction appeared as a milky suspension. The reaction was stirred at room temperature for 3h then, was quenched by adding pH 7 phosphate buffer and H_2O. The aqueous layer was extracted with EtOAc (3 x 2 ml). The combined organic layers were washed with brine (1 ml), dried over $MgSO_4$, and concentrated under reduced pressure, affording *S*-MTPA crude product. The crude material was purified by FC column using a gradient elution (first starting with hexane and, then, 1:30 to 1:20 EtOAc/Hex) to afford (S,S,S)-**65** 26 mg, 100% yield.

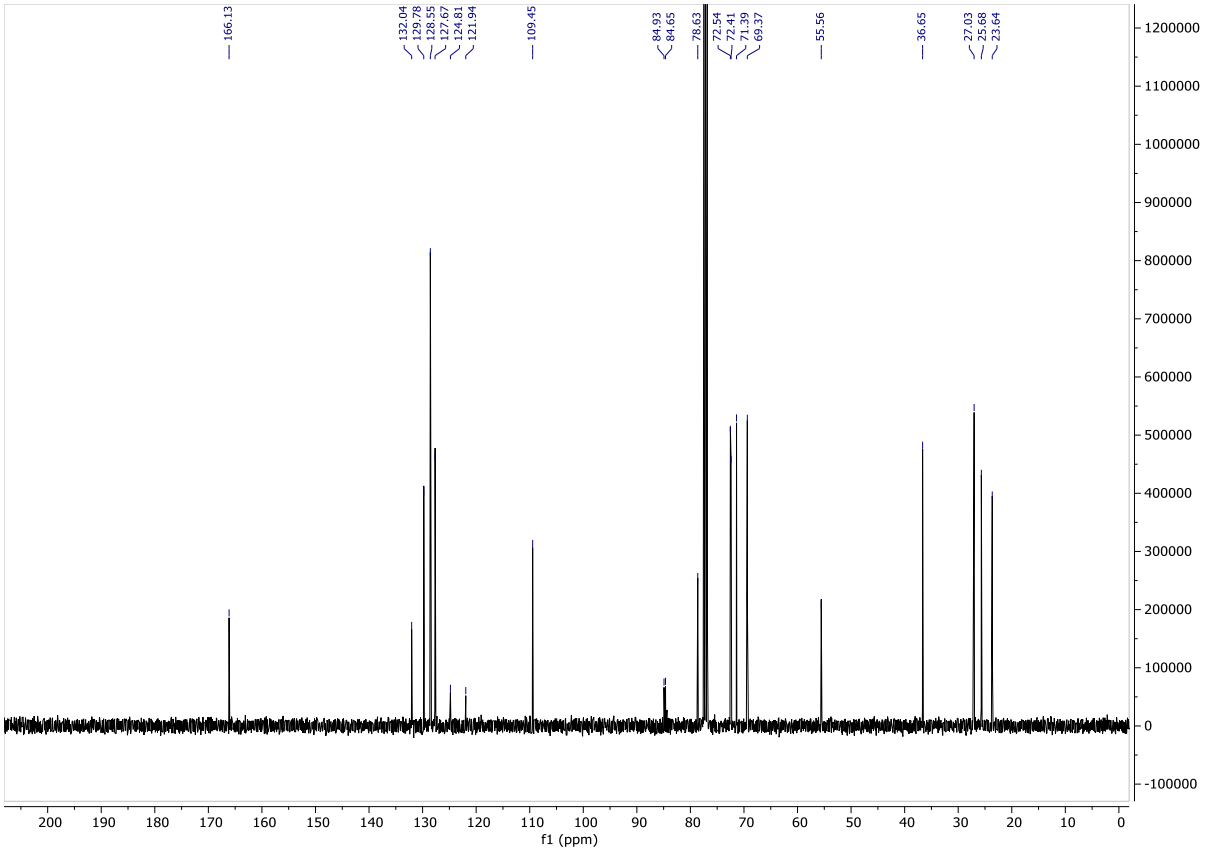
Yield: 26 mg (100 %)

^{1}H NMR (400 MHz, Chloroform-d) δ 7.56 (dd, J = 6.5, 2.6 Hz, 4H), 7.40 (tt, J = 5.1, 2.9 Hz, 4H), 5.60 – 4.89 (m, 1H), 4.15 (tt, J = 7.4, 5.7 Hz, 1H), 4.04 (dd, J = 8.1, 6.0 Hz, 1H), 3.60 – 3.49 (m, 4H), 2.68 – 2.52 (m, 2H), 2.18 – 1.96 (m, 2H), 1.94 (t, J = 2.7 Hz, 1H), 1.40 (s, 3H), 1.32 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-d) δ 166.1, 132.0, 129.8, 128.6, 127.7, 124.8, 121.9, 109.5, 84.93, 84.7, 78.6, 72.5, 72.4, 71.4, 69.4, 55.7, 36.7, 27.0, 25.7, 23.6.

Nat. Prot., **2007**, 2, 10, 2453-2458.


f1 (ppm)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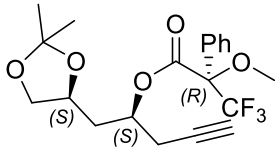
72.41
71.39
69.37
55.56
36.65
27.03
25.68
23.64
f1 (ppm)

*Mosher ester analysis of (S)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-yn-2-ol. (S)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-yn-2-yl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ((S,S,R)-**65**)*

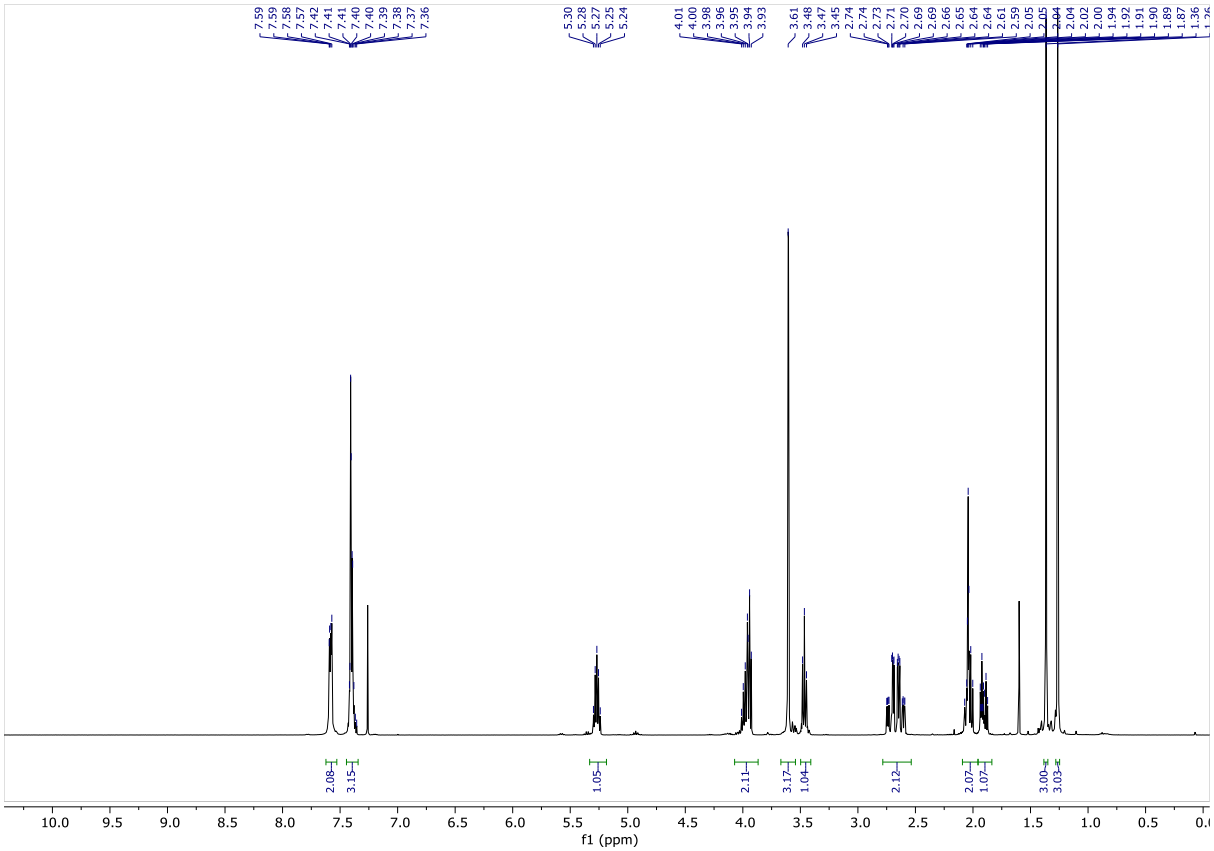


(R)-MTPA (30 mg, 0.14 mmol, 2.1 equiv.) were weighted in the glove box. *(R)*-MTPA was solubilized in toluene (0.68 mL). Then, TEA (0.021 mL, 0.15 mmol, 2.3 equiv.) and trichlorobenzoyl chloride (0.021 mL, 0.14 mmol, 2.1 equiv.) were added to the flask at room temperature. The reaction appeared as a colorless solution. Immediately, (S,S)-**63** (10 mg, 0.065 mmol, 1.0 equiv.), previously solubilized in toluene in a vial (0.10 mL), was added to the flask, immediately, DMAP (18.3 mg, 0.15 mmol, 2.3 equiv.) was added and the reaction appeared as a milky suspension. The reaction was stirred at room temperature for 3h Then, was quenched by adding pH 7 phosphate buffer and H_2O. The aqueous layer was extracted with EtOAc (3 x 2 ml). The combined organic layers were washed with brine (1 ml), dried over $MgSO_4$, and concentrated under reduced pressure, affording *R*-MTPA crude product. The crude material was purified by FC column using a gradient elution (first starting with hexane and, then, 1:30 to 1:20 EtOAc/Hex) to afford (S,S,R)-**65** 22.7 mg, 95% yield.

Yield: 22.7 mg (95 %)

^{1}H NMR (400 MHz, Chloroform-d) δ 7.58 (dd, J = 6.6, 2.4 Hz, 2H), 7.43 – 7.34 (m, 3H), 5.27 (p, J = 6.0 Hz, 1H), 4.08 – 3.81 (m, 2H), 3.61 (s, 2H), 3.46 (t, J = 6.8 Hz, 1H), 2.76 – 2.57 (m, 2H), 2.08 – 1.99 (m, 2H), 1.96 – 1.84 (m, 1H), 1.36 (s, 3H), 1.26 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-d) δ 166.1, 132.3, 129.8, 128.5, 127.4, 124.8, 122.0, 109.3, 84.8, 84.5, 79.1, 72.3, 72.1, 71.5, 69.2, 55.8, 36.4, 27.0, 25.6, 23.8.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1.91
1.90
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1.07
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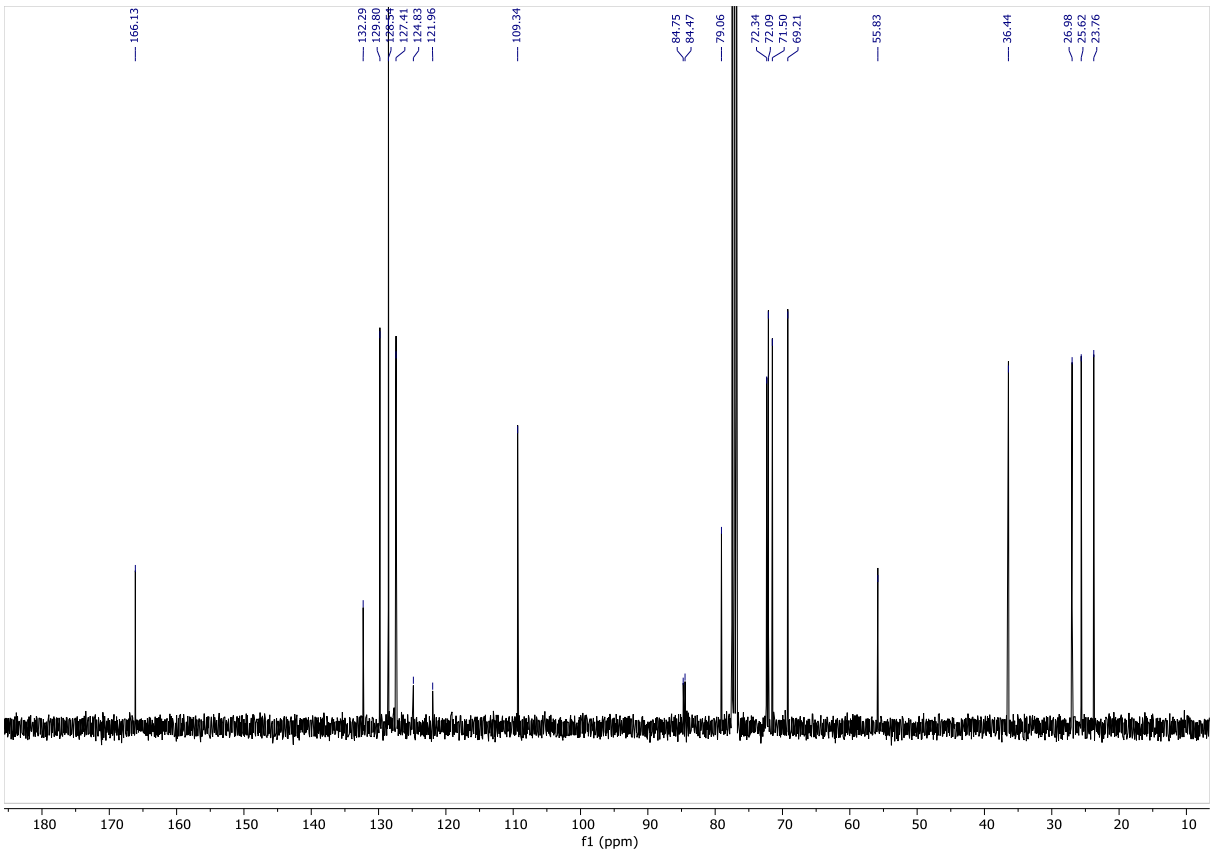
3.03
f1 (ppm)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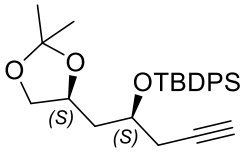
84.47
79.06
72.34
72.09
71.50
69.21
55.83
36.44
26.98
25.62
23.76
f1 (ppm)

*tert-butyl(((S)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-yn-2-yl)oxy)diphenylsilane ((S,S)-**57**)*



In a flame dried under Argon atmosphere 100 ml flask charged with a stirring bar a solution of homopropargylic alcohol (S,S)-**63** (803 mg, 4.36 mmol, 1.0 equiv.) in DCM (50 mL, 0.1 M) was prepared at room temperature. Then, the reagents were added in the following order: imidazole (890 mg, 13.1 mmol, 3.0 equiv.), DMAP (53.2 mg, 0.44 mmol, 0.1 equiv.) and tert-butyldiphenylchlorosilane (1.68 mL, 6.54 mmol, 1.5 equiv.). The reaction was stirred at room temperature overnight and after verification of the completion of the reaction by TLC, the solution was quenched by the addition of H_2O (50 ml). Then, the mixture was extracted with DCM for three times (30 ml), and the combined organic fractions were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (100:1 → 70:1 hexanes/EtOAc) to provide TBDPS-ether (S,S)-**57** 1.56 g (84.7 %)) as a colorless oil.

Yield: 1.560 g (85 %)

R_f = 0.67 (hexane/EtOAc 1:1).

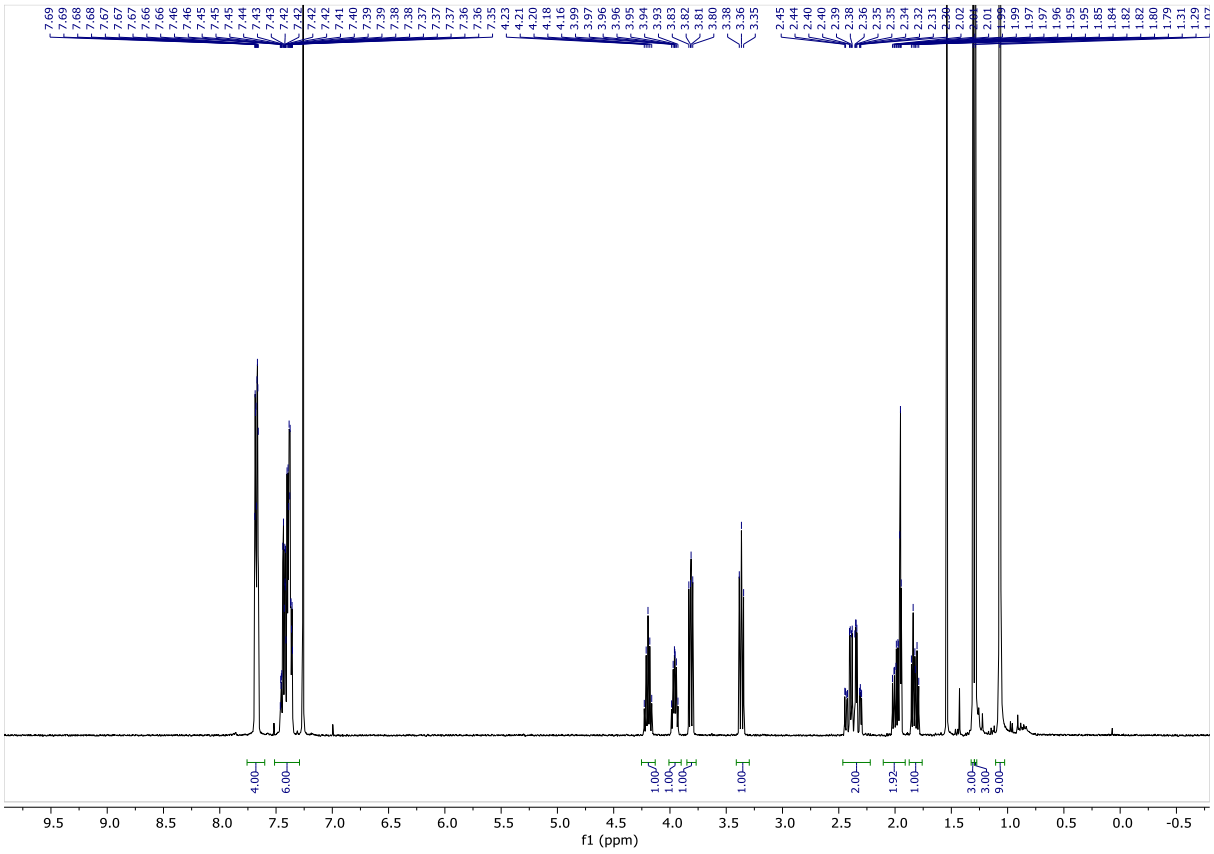
$[\alpha]_{20}^{D}$: 26.31 (c = 0.114 g / 100 mL, $CHCl_3$, 20°C, 589 nm);

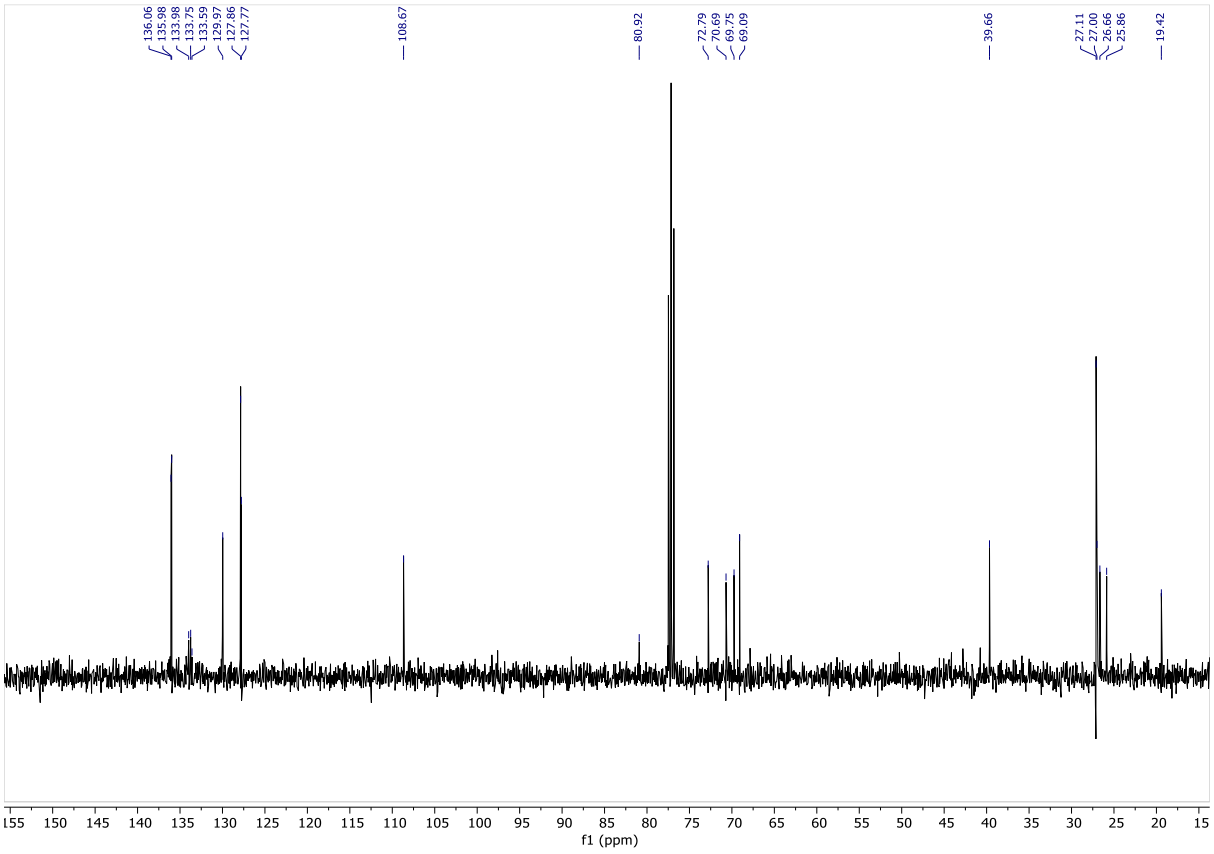
^{1}H NMR (400 MHz, Chloroform-d) δ 7.70 – 7.63 (m, 4H), 7.48 – 7.34 (m, 6H), 4.20 (p, J = 6.8 Hz, 1H), 4.00 – 3.92 (m, 1H), 3.81 (dd, J = 8.0, 5.9 Hz, 1H), 3.36 (t, J = 7.3 Hz, 1H), 2.37 (ddd, J = 16.7, 7.0, 2.6 Hz, 2H), 2.05 – 1.95 (m, 1H), 1.95 (t, J = 2.6 Hz, 1H), 1.82 (dt, J = 13.8, 6.1 Hz, 1H), 1.31 (s, 3H), 1.29 (s, 3H), 1.07 (s, 9H);

^{13}C NMR (101 MHz, Chloroform-d) δ 136.1, 136.0, 134.0, 133.8, 133.6, 130.0, 127.9, 127.8, 108.7, 80.9, 72.8, 70.7, 69.8, 69.1, 39.7, 27.1, 27.0, 26.7, 25.9, 19.4;

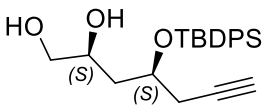
IR (film): ν = 3299, 2932, 2905, 2858, 1771, 1473, 1428, 1370, 1246, 1157, 1110, 998, 938, 845, 822, 741, 702, 612, 506;

HRMS (ESI-TOF) *m/z* calcd. for $C_{26}H_{34}NaO_3Si$ $[M+Na]^+$ 445.2169, found 445.2169.


f1 (ppm)


f1 (ppm)

*(2S,4S)-4-((tert-butyldiphenylsilyl)oxy)hept-6-yne-1,2-diol ((S,S)-**66**)*



In a flame-dried round bottom flask charged with a stirring bar, a solution of acetonide (S,S)-**57** (300 mg, 0.71 mmol, 1.0 equiv.) in dichloromethane (10.0 mL) was prepared under Argon atmosphere at room temperature. Then, the solution was cooled to 0 °C using an ice bath, and after the solution was cooled trifluoroacetic acid (0.55 mL, 7.10 mmol, 10.0 equiv.) was added at 0 °C. The reaction mixture was stirred for 1 h. After verification of the reaction completion by TLC, no SM, the mixture was concentrated under reduced pressure to evaporate TFA with the solvent. (Actually, here is a good idea would be to do a normal workup, maybe then the yield will be better). The crude residue was purified by flash column chromatography (2:1 → 1:2 hexanes/EtOAc) to yield diol (S,S)-**66** (137 mg, 50.4 %) as a colorless oil.

Yield: 137.000 mg (50 %);

R_f = 0.2424 (hexane/EtOAc 1:1);

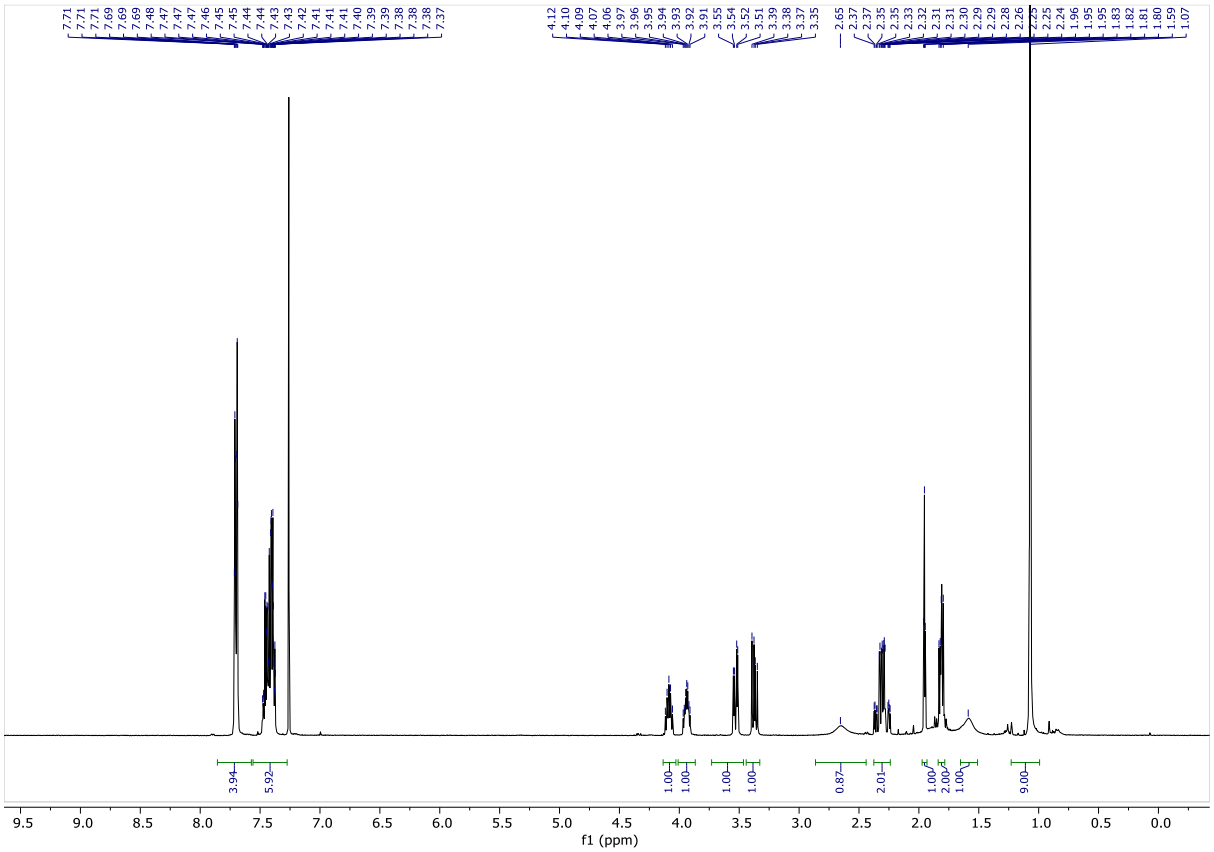
$[\alpha]_{20}^{D}$: 42.67 (c = 0.164 g / 100 mL, $CHCl_3$, 20°C, 589 nm)

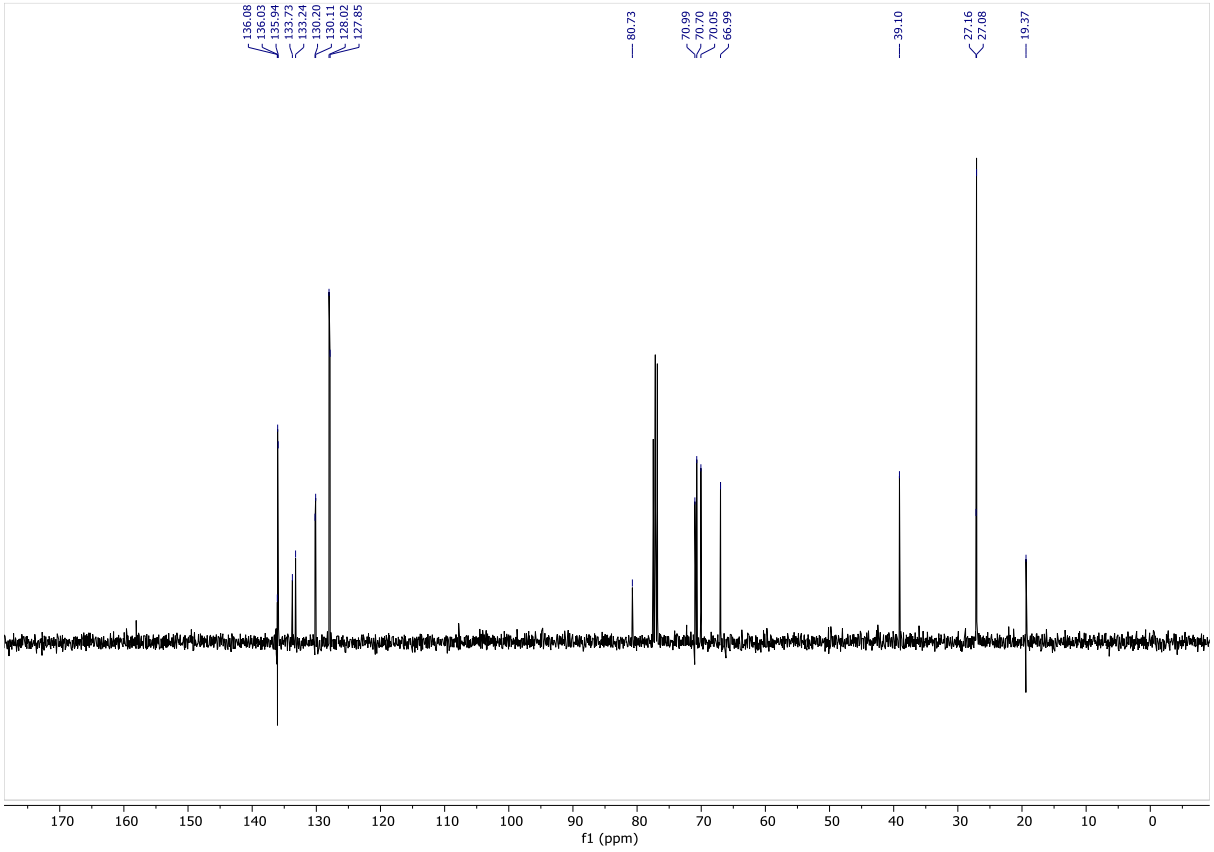
^{1}H NMR (400 MHz, Chloroform-d) δ 7.70 (dt, J = 8.1, 1.6 Hz, 4H), 7.56 – 7.32 (m, 6H), 4.09 (dt, J = 11.9, 6.0 Hz, 1H), 3.94 (tt, J = 7.4, 3.5 Hz, 1H), 3.53 (dd, J = 11.1, 3.4 Hz, 1H), 3.37 (dd, J = 11.1, 6.8 Hz, 1H), 2.65 (s, 1H), 2.40 – 2.18 (m, 2H), 1.95 (t, J = 2.7 Hz, 1H), 1.87 – 1.71 (m, 2H), 1.59 (s, 1H), 1.07 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-d) δ 136.1, 136.0, 135.9, 133.7, 133.2, 130.2, 130.1, 128.0, 127.9, 80.7, 71.0, 70.7, 70.1, 67.0, 39.1, 27.2, 27.1, 19.4.

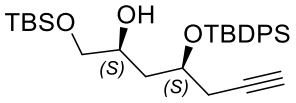
IR (film): ν = 3309, 2957, 2933, 2859, 2360, 1787, 1760, 1473, 1428, 1390, 1370, 1226, 1169, 1111, 1065, 1009, 998, 937, 861, 822, 740, 703, 690, 611, 533, 509, 501;

HRMS (ESI-TOF) *m/z* calcd. for $C_{23}H_{30}NaO_3Si$ $[M+Na]^+$ 405.1856, found 405.1855


7.71 7.71 7.71 7.69 7.69 7.48 7.47 7.47 7.46 7.45 7.45 7.44 7.44 7.43 7.42 7.41 7.41 7.40 7.39 7.38 7.38 7.37
4.12 4.10 4.09 4.07 4.06 3.97 3.96 3.95 3.94 3.93 3.92 3.91 3.55 3.54 3.52 3.51 3.39 3.38 3.37 3.35
2.65 2.37 2.37 2.35 2.35 2.33 2.32 2.31 2.31 2.30 2.29 2.29 2.28 2.26 2.25 2.24 1.96 1.95 1.95 1.83 1.82 1.81 1.80 1.59 1.07
3.94 5.92 1.00 1.00 1.00 1.00 0.87 2.01 1.00 2.00 1.00 9.00
f1 (ppm)


136.08 136.03 135.94 133.73 133.24 130.20 130.11 128.02 127.85
80.73
70.99 70.70 70.05 66.99
39.10
27.16 27.08
19.37
f1 (ppm)

*(6S,8S)-2,2,3,3,11,11-hexamethyl-10,10-diphenyl-8-(prop-2-yn-1-yl)-4,9-dioxa-3,10-disiladodecan-6-ol ((S,S)-**4**)*



In a flame-dried round bottom flask charged with a stirring bar, a solution of (S,S)-**66** (235 mg, 0.61 mmol, 1.0 equiv.) in DCM (10.0 ml) was prepared under Argon atmosphere and cooled to 0 °C. Then, imidazole (62.7 mg, 0.92 mmol, 1.5 equiv.) and TBSCl (100.1 mg, 0.92 mmol, 1.5 equiv.) were added at 0 °C. Then, the reaction was stirred at room temperature for 20 min. After completion of the reaction, verified by TLC, the reaction mixture was quenched with aq. sat. NH_4Cl (10 ml) and extracted with EtOAc (3 x 10 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (hexane/EtOAc 100/1) because it is very difficult to separate the product from TBSOH (had to do 3 columns) affording the secondary alcohol (S,S)-**4** (214 mg, 70 %) as colorless oil in fractions 145-195.

Yield: 214 mg (70 %);

R_f = 0.4545 (hexane/EtOAc 4/1);

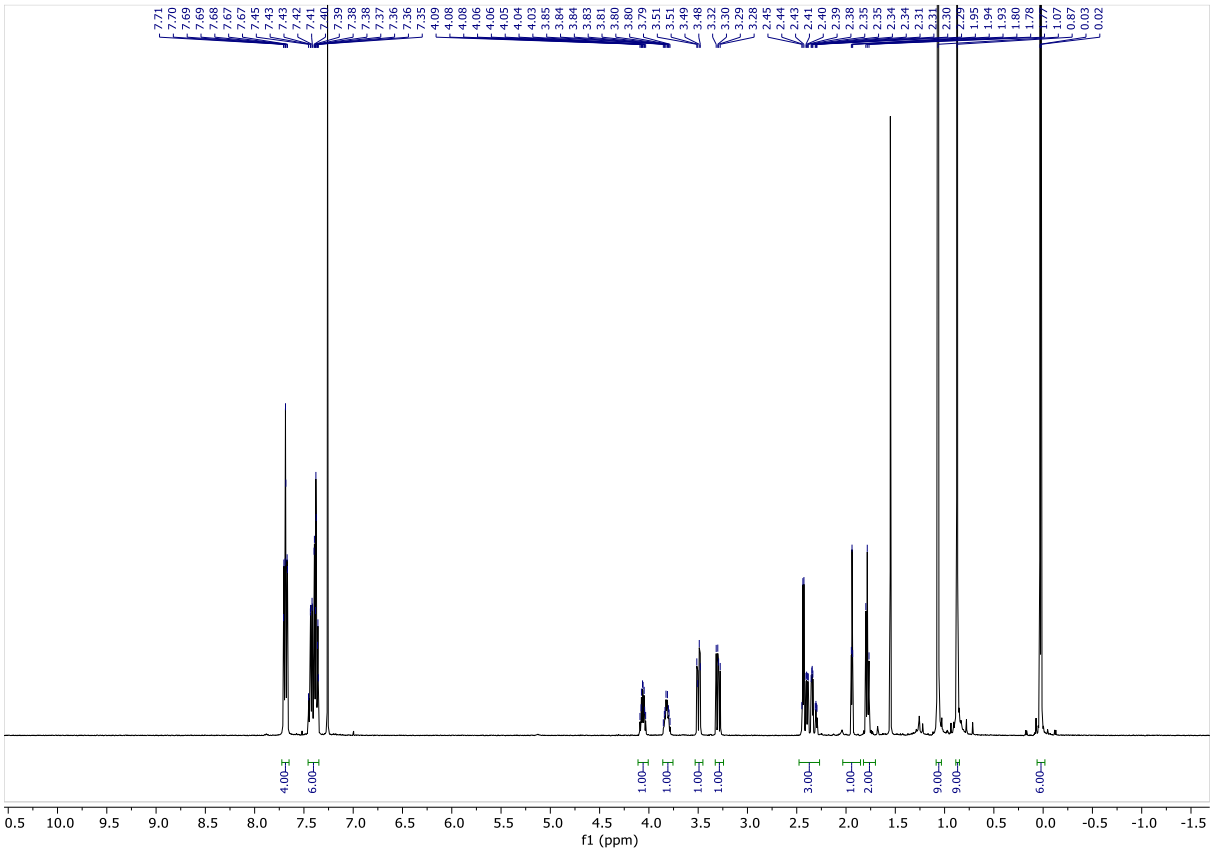
$[\alpha]_{20}^{D}$: 23.94, (c=0.0834 g / 100 ml, $CHCl_3$, 20°C);

^{1}H NMR (400 MHz, Chloroform-d) δ 7.69 (ddd, J = 8.1, 6.7, 1.5 Hz, 4H), 7.46 – 7.34 (m, 6H), 4.06 (qd, J = 6.0, 4.4 Hz, 1H), 3.88 – 3.77 (m, 1H), 3.50 (dd, J = 10.3, 3.9 Hz, 1H), 3.30 (dd, J = 9.9, 6.5 Hz, 1H), 2.48 – 2.26 (m, 3H), 1.94 (t, J = 2.6 Hz, 1H), 1.78 (t, J = 6.4 Hz, 2H), 1.07 (s, 9H), 0.87 (s, 9H), 0.03 (d, J = 4.3 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-d) δ 136.1, 136.0, 134.1, 133.8, 130.0, 129.9, 127.9, 127.7, 81.2, 70.5, 69.6, 69.0, 67.1, 38.9, 27.1, 26.7, 26.0, 19.4, 18.4, -5.2.

IR (film): ν = 3311, 3072, 3050, 2954, 2929, 2898, 2858, 1472, 1463, 1428, 1408, 1390, 1362, 1254, 1229, 1106, 1080, 1007, 939, 910, 837, 823, 778, 739, 703, 689, 622, 612, 504;

HRMS (ESI-TOF) *m/z* calcd. for $C_{29}H_{44}NaO_3Si_2$ $[M+Na]^+$ 519.2721, found 519.2721;


7.71
7.70
7.69
7.69
7.68
7.67
7.67
7.45
7.43
7.42
7.41
7.40
7.39
7.38
7.38
7.37
7.36
7.36
7.35
4.09
4.08
4.08
4.06
4.06
4.05
4.04
4.03
3.85
3.84
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3.80
3.80
3.79
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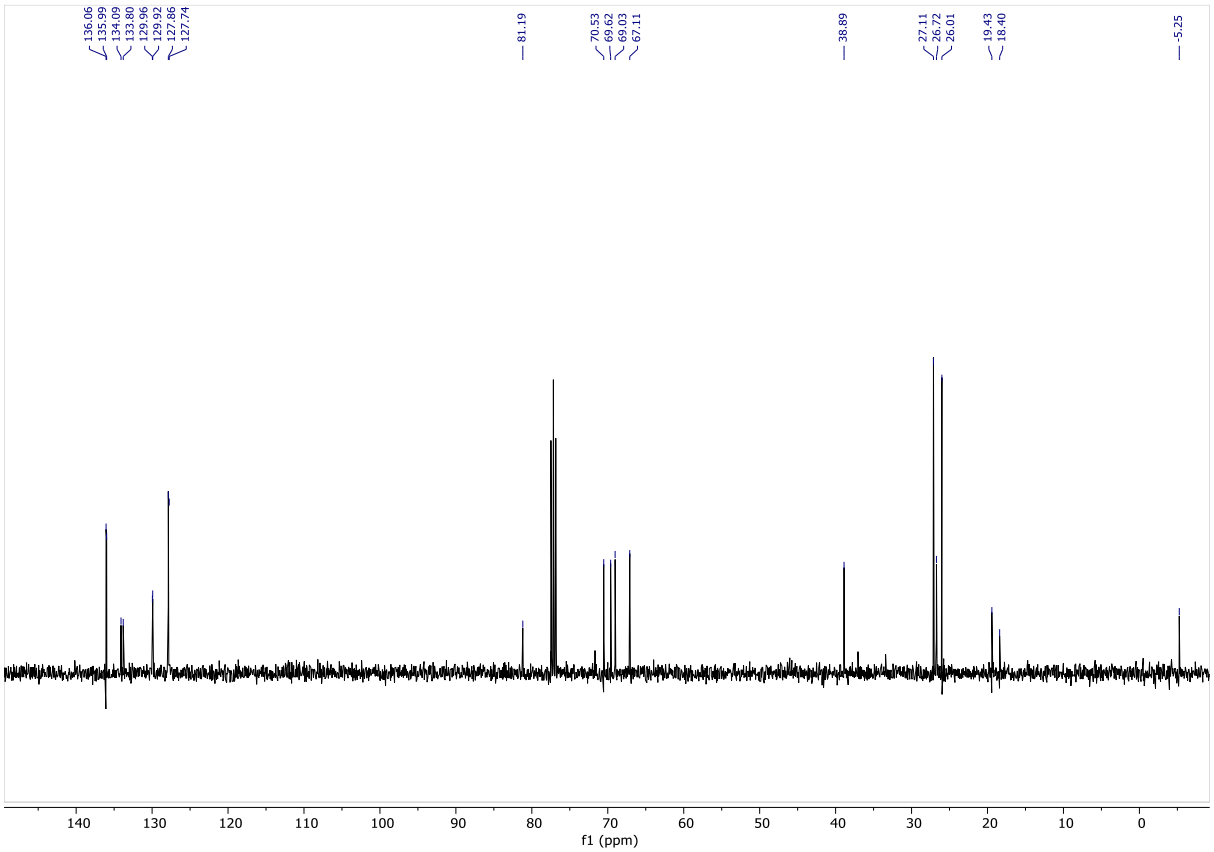
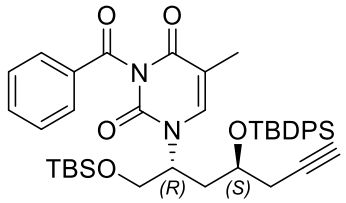
3.51
3.49
3.48
3.32
3.30
3.29
3.28
2.45
2.44
2.43
2.41
2.40
2.38
2.35
2.34
2.34
2.31
2.31
2.30
2.25
1.95
1.94
1.93
1.80
1.78
1.77
1.07
0.87
0.03
0.02
4.00
6.00
1.00
1.00
1.00
1.00
3.00
1.00
2.00
9.00
9.00
6.00
f1 (ppm)


136.06
135.99
134.09
133.80
129.96
129.92
127.86
127.74
81.19
70.53
69.62
69.03
67.11
38.89
27.11
26.72
26.01
19.43
18.40
-5.25
f1 (ppm)

*3-benzoyl-1-((6R,8S)-2,2,3,3,11,11-hexamethyl-10,10-diphenyl-8-(prop-2-yn-1-yl)-4,9-dioxa-3,10-disiladodecan-6-yl)-5-methylpyrimidine-2,4(1H,3H)-dione ((R,S)-**69**)*



In flame-dried glassware, under an argon atmosphere, a solution of (S,S)-**4** (200 mg, 0.54 mmol, 1.0 equiv.) in dioxane (3.0 ml) was prepared at room temperature. Then, the reagents were added in the following order: thymine moiety **68** (145.8 mg, 0.63 mmol, 1.18 equiv.), PPh_3 (0.14 ml, 0.59 mmol, 1.1 equiv.), and DEAD (very slowly, dropwise, 0.101 ml, 0.64 mmol, 1.2 equiv.), and the reaction was stirred for 30 min at room temperature. After completion of the reaction, verified by TLC, the reaction was concentrated under reduced pressure. The crude material was purified by FC (hexane/EtOAc 10/1) affording the compound (R,S)-**69** in 170.4 mg (60 %) yield as a colorless oil.

Yield: 170.4 mg (60 %);

R_f = 0.234375 (hexane/EtOAc 4/1);

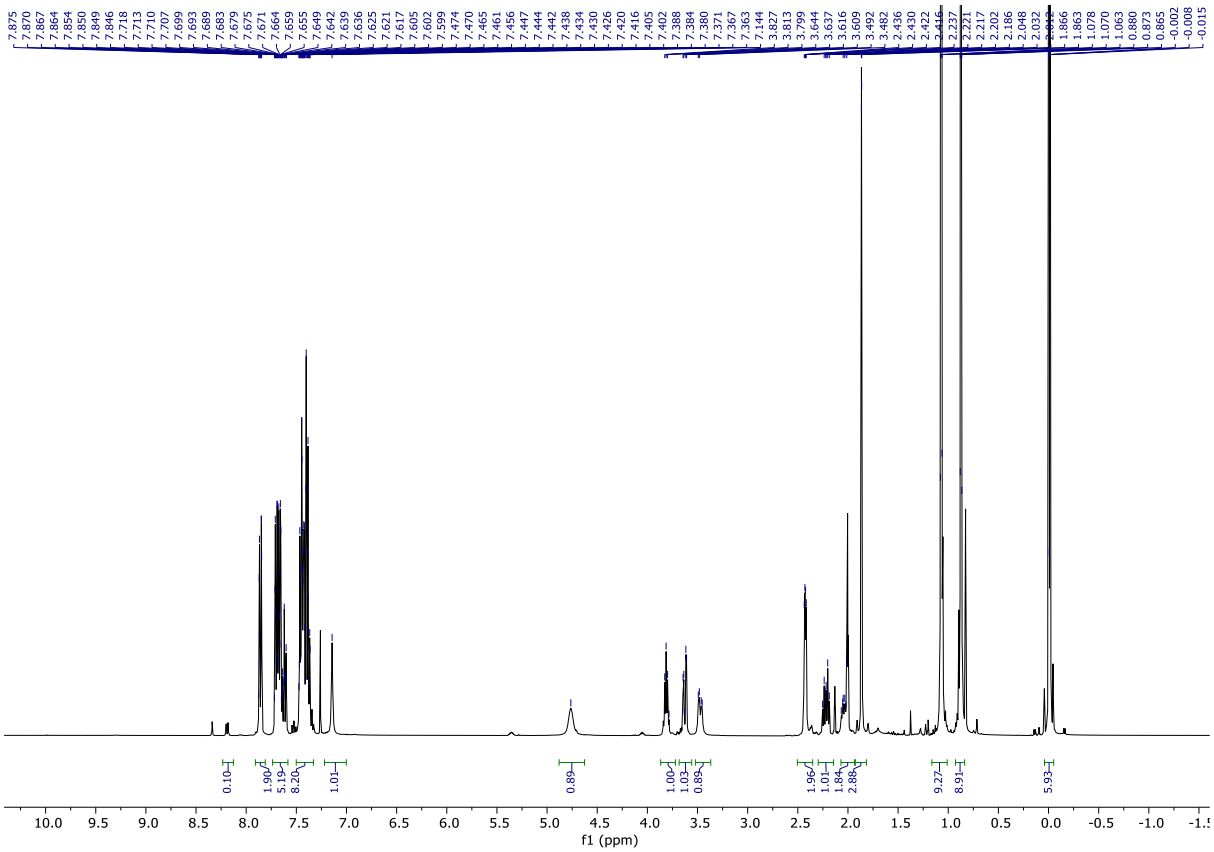
$[\alpha]_{20}^{D}$: +6.0, (c=1.0, $CHCl_3$, 20°C);

^{1}H NMR (400 MHz, Chloroform-d) δ 7.91 – 7.80 (m, 2H), 7.76 – 7.56 (m, 6H), 7.49 – 7.33 (m, 8H), 7.14 (s, 1H), 4.76 (s, 1H), 3.81 (q, J = 5.7 Hz, 1H), 3.63 (dd, J = 11.1, 2.9 Hz, 1H), 3.47 (dd, J = 11.4, 4.1 Hz, 1H), 2.43 (dd, J = 5.5, 2.7 Hz, 2H), 2.22 (dt, J = 14.2, 6.3 Hz, 1H), 2.04 (dt, J = 11.6, 5.5 Hz, 1H), 2.01 (s, 1H), 1.86 (d, J = 1.1 Hz, 3H), 1.07 (s, 9H), 0.87 (s, 9H), -0.01 (d, J = 5.3 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-d) δ 169.1, 162.8, 150.1, 138.8, 136.0, 135.0, 133.5, 133.3, 131.8, 130.5, 130.2, 130.1, 129.2, 128.0, 127.8, 109.5, 80.2, 71.3, 68.3, 63.9, 53.1, 35.5, 27.0, 26.6, 25.8, 19.3, 18.1, 12.6, -5.6, -5.7;

IR (film): 3311, 2954, 2930, 2895, 2857, 1750, 1699, 1657, 1600, 1471, 1462, 1429, 1389, 1364, 1308, 1256, 1178, 1111, 980, 912, 836, 779, 741, 704, 687, 665, 637, 613, 505;

HRMS (ESI-TOF) *m/z* calcd. for $C_{41}H_{53}N_2O_5Si_2$ $[M+H]^+$ 709.3488, found 709.3477


7.875
7.870
7.867
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7.850
7.849
7.846
7.718
7.713
7.710
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7.693
7.689
7.683
7.679
7.675
7.671
7.664
7.659
7.655
7.649
7.642
7.639
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7.625
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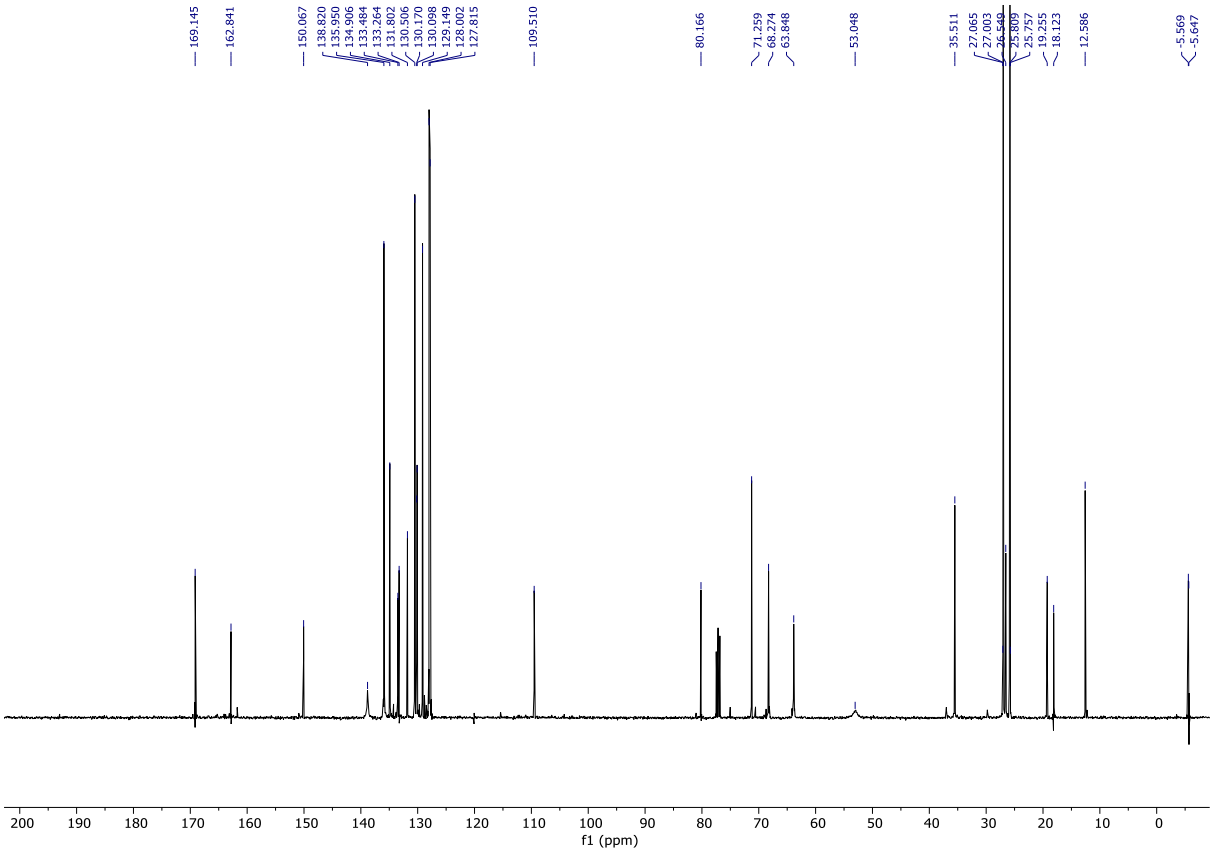
2.221
2.217
2.202
2.186
2.048
2.032
1.866
1.863
1.078
1.070
1.063
0.880
0.873
0.865
-0.002
-0.008
-0.015
0.10
1.90
5.19
8.20
1.01
0.89
1.00
1.03
0.89
1.96
1.01
1.84
2.88
9.27
8.91
5.93
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


169.145
162.841
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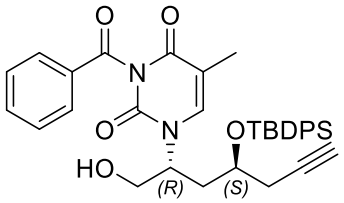
138.820
135.950
134.906
133.484
133.264
131.802
130.506
130.170
130.098
129.149
128.002
127.815
109.510
80.166
71.259
68.274
63.848
53.048
35.511
27.065
27.003
26.549
25.809
25.757
19.255
18.123
12.586
-5.569
-5.647
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

*3-benzoyl-1-((2R,4S)-4-((tert-butyldiphenylsilyl)oxy)-1-hydroxyhept-6-yn-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione ((R,S)-**70**)*



In a flame-dried 10 ml flask solution of (20 mg, 0.028 mmol, 1.0 equiv.) (R,S)-**69** in (1.0 ml) MeOH was prepared under Argon atmosphere at room temperature. Then, PPTS (7.9 mg, 0.031 mmol, 1.1 equiv.) was added at room temperature and the solution was stirred overnight. TLC of the reaction mixture overnight showed that there still was SM, so I added 2.0 mg of PPTS and let it stir for 1h. After 0.2 equiv. addition and second overnight. When the completion of the reaction by TLC was achieved, MeOH was evaporated. Then, the residue was dissolved in EtOAc and washed with sat. aq. $NaHCO_3$, water, and brine are concentrated to dryness. The crude material was purified by FC (hexane/EtOAc 5/1) affording the compound (R,S)-**70** (6.6 mg, 40%) as a colorless oil.

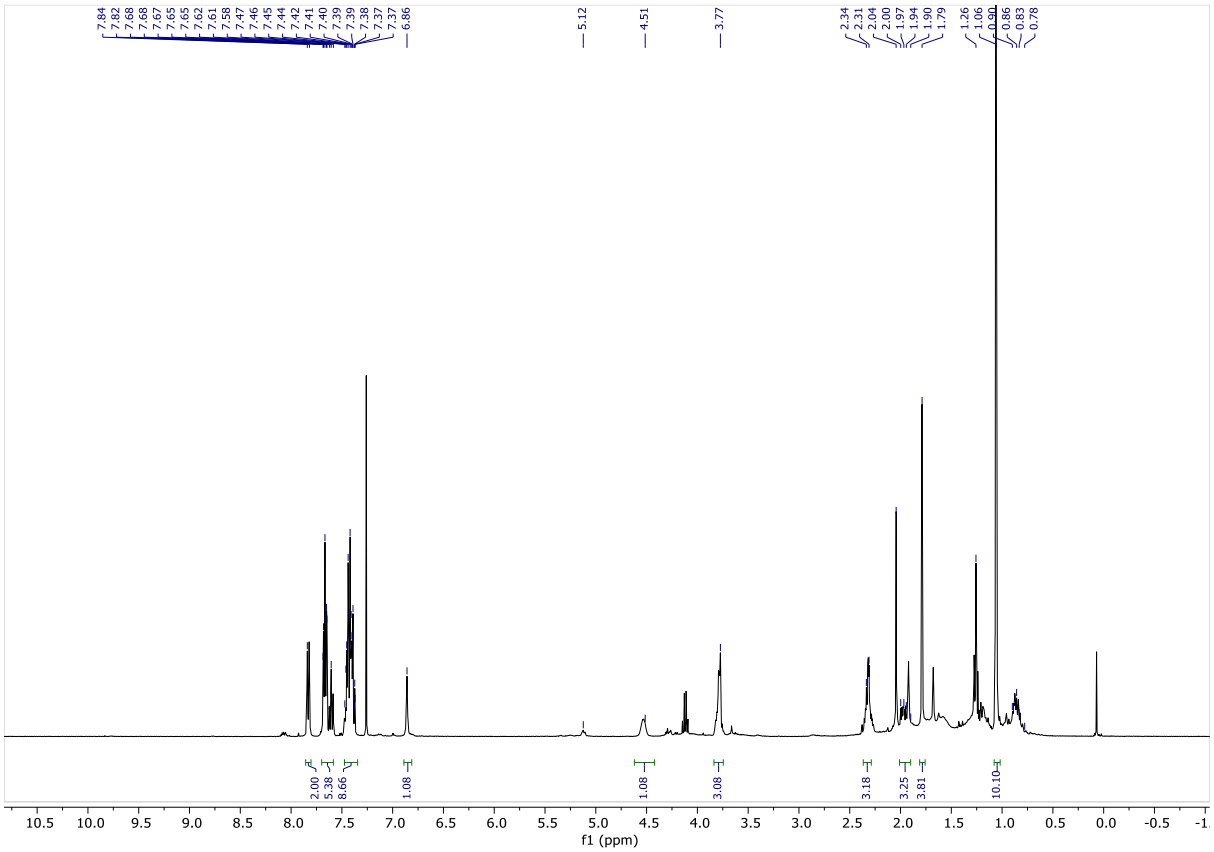
Yield: 6.600 mg (40%)

R_f = 0.1875 (hexane / EtOAc = 1:1)

^{1}H NMR (400 MHz, Chloroform-d) δ 7.83 (d, J = 8.4 Hz, 2H), 7.72 – 7.63 (m, 3H), 7.63 – 7.56 (m, 2H), 7.50 – 7.30 (m, 8H), 6.86 (s, 1H), 4.51 (s, 1H), 3.77 (m, 3H), 2.32 (m, 3H), 2.04 (s, 1H), 2.01 – 1.89 (m, 2H), 1.79 (s, 3H), 1.06 (s, 9H)-on a more comfortable scale purerer NMR will be obtained, because impure.

^{13}C NMR (101 MHz, Chloroform-d) δ 169.1, 162.8, 150.5, 139.5, 136.0, 135.9, 135.0, 130.6, 130.3, 130.2, 129.2, 128.2, 127.9, 110.4, 80.1, 71.5, 69.1, 64.3, 60.6, 35.1, 27.3, 27.1, 19.3, 12.6.

HRMS (ESI-TOF) m/z (ESI) $C_{35}H_{38}N_2NaO_5Si$ $[M+Na]^+$ 617.2442, found 617.2439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7.82
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7.68
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7.61
7.58
7.47
7.46
7.45
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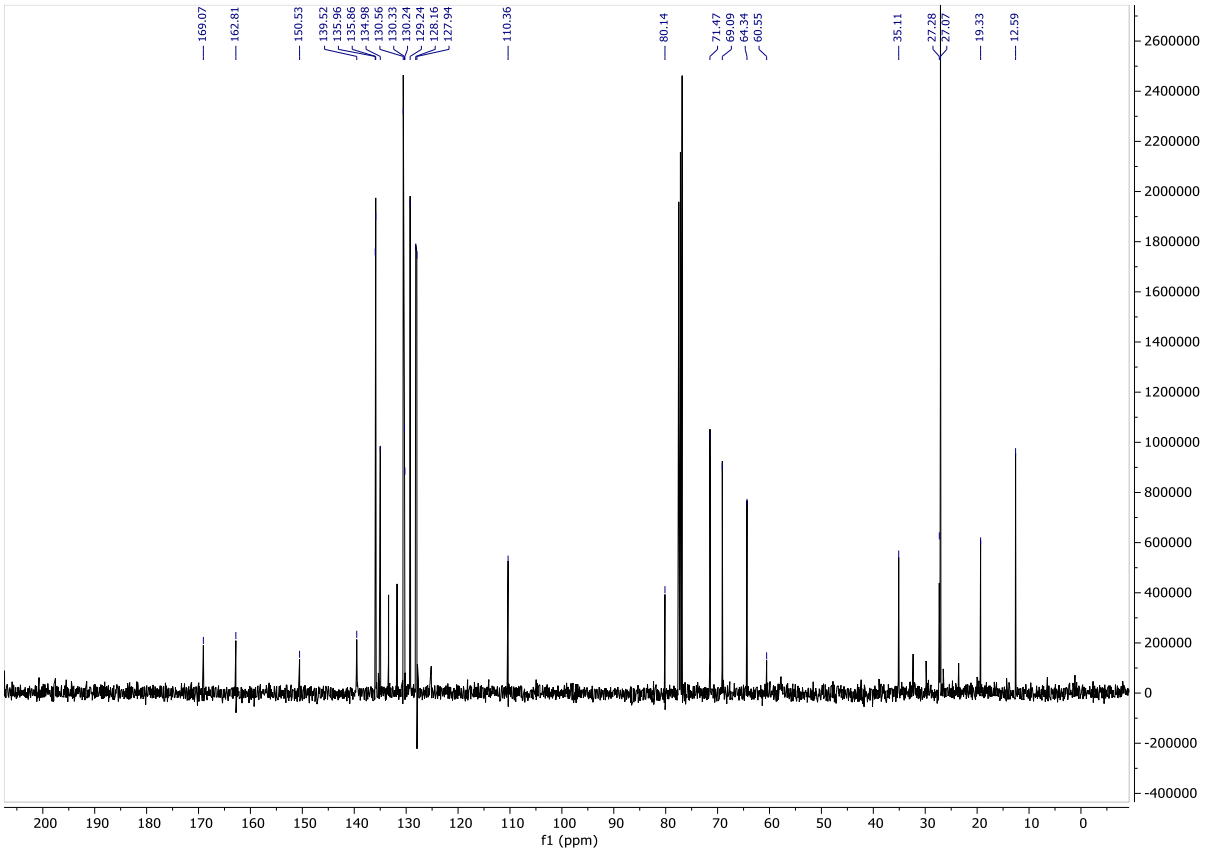
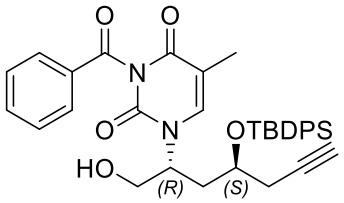
7.42
7.41
7.40
7.39
7.39
7.38
7.37
7.37
6.86
5.12
4.51
3.77
2.34
2.31
2.04
2.00
1.97
1.94
1.90
1.79
1.26
1.06
0.90
0.86
0.83
0.78
2.00
5.38
8.66
1.08
1.08
3.08
3.18
3.25
3.81
10.10
f1 (ppm)


169.07
162.81
150.53
139.52
135.96
135.86
134.98
130.56
130.33
130.24
129.24
128.16
127.94
110.36
80.14
71.47
69.09
64.34
60.55
35.11
27.28
27.07
19.33
12.59
f1 (ppm)

*3-benzoyl-1-((2R,4S)-4-((tert-butyldiphenylsilyl)oxy)-1-hydroxyhept-6-yn-2-yl)-5-methyl pyrimidine-2,4(1H,3H)-dione ((R,S)-**70**)*



In a flame-dried 10 ml flask solution of (R,S)-**69**(1.0 g, 1.41 mmol, 1.00 equiv.) in DCM: MeOH 1:1 (28.2 ml, 0.05 M) was prepared under Argon atmosphere at room temperature. Then, the solution was cooled in an ice bath and CSA (137.6 mg, 0.59 mmol, 0.42 equiv.) was added at room temperature. After 25 min, the mixture was allowed to warm to room temperature and stirred for 18 h. When the completion of the reaction by TLC was achieved, sat. aq. $NaHCO_3$ (10 ml) was added and the layers were separated. The aqueous layer was extracted with DCM (3 x 10 ml). The combined organic layers were washed with brine (10 ml), dried over $MgSO_4$, and concentrated under reduced pressure. The crude material 82 mg was purified by 2 cm column chromatography (Hex: EtOAc 2/1) to yield (R,S)-**70** (730 mg, 87 %) as a colorless oil.

Yield: 730 mg (87 %);

R_f = 0.2973 (2:1 Hexane: EtOAc), CPS staining;

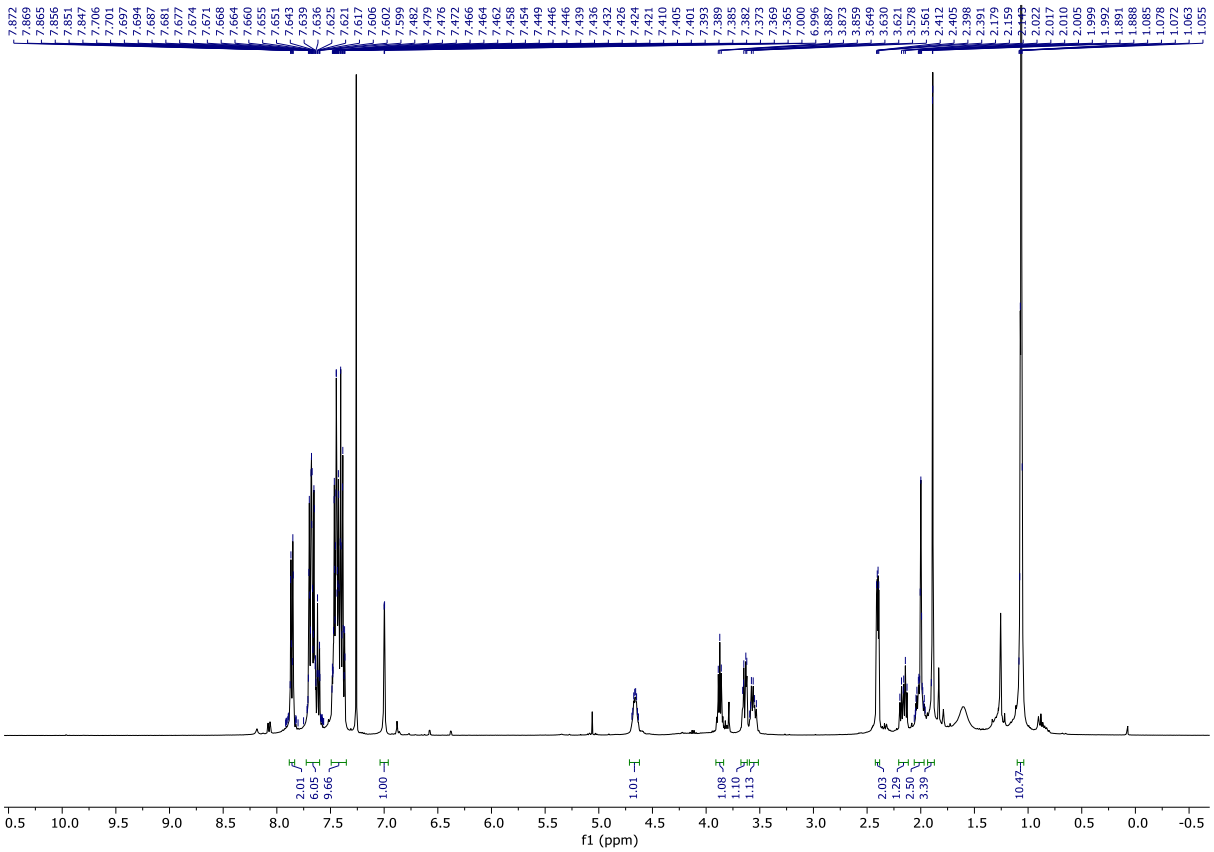
$[\alpha]_{20}^{D}$: = -9.0 (c = 1.0; $CHCl_3$, 20°C);

^{1}H NMR (400 MHz, Chloroform-d) δ 7.93 – 7.79 (m, 2H), 7.76 – 7.55 (m, 6H), 7.52 – 7.33 (m, 9H), 7.00 (d, J = 1.5 Hz, 1H), 4.66 (qd, J = 6.9, 3.4 Hz, 1H), 3.87 (t, J = 5.6 Hz, 1H), 3.68 – 3.61 (m, 1H), 3.55 (dd, J = 11.8, 6.8 Hz, 1H), 2.40 (dd, J = 5.7, 2.7 Hz, 2H), 2.16 (dt, J = 14.3, 6.1 Hz, 1H), 2.07 – 1.96 (m, 2H), 1.89 (d, J = 1.1 Hz, 3H), 1.06 (s, 9H);

^{13}C NMR (101 MHz, Chloroform-d) δ 169.1, 162.8, 150.6, 138.1, 136.0, 135.1, 133.3, 131.8, 130.6, 130.3, 130.3, 129.3, 128.1, 128.0, 110.8, 80.1, 71.4, 68.4, 63.9, 54.8, 35.4, 27.1, 26.5, 19.4, 12.8;

IR (film): ν = 3476, 3303, 3072, 2931, 2858, 1748, 1697, 1650, 1600, 1461, 1438, 1429, 1389, 1366, 1259, 1179, 1111, 1028, 980, 938, 900, 843, 822, 809, 790, 764, 741, 704, 687, 667, 641, 621, 613;

HRMS (ESI-TOF) m/z (ESI) $C_{35}H_{38}N_2NaO_5Si$ $[M+Na]^+$ 617.2442, found 617.2434.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7.865
7.856
7.851
7.847
7.706
7.701
7.697
7.694
7.687
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7.677
7.674
7.671
7.668
7.664
7.660
7.655
7.651
7.643
7.639
7.636
7.625
7.621
7.617
7.606
7.602
7.599
7.482
7.479
7.476
7.472
7.466
7.464
7.462
7.458
7.454
7.449
7.446
7.446
7.439
7.436
7.432
7.426
7.424
7.421
7.410
7.405
7.401
7.393
7.389
7.385
7.382
7.373
7.369
7.365
7.000
6.996
3.887
3.873
3.859
3.649
3.630
3.621
3.578
3.561
2.412
2.405
2.398
2.391
2.179
2.159
2.143
2.022
2.017
2.010
2.005
1.999
1.992
1.891
1.888
1.085
1.078
1.072
1.063
1.055
2.01
6.05
9.66
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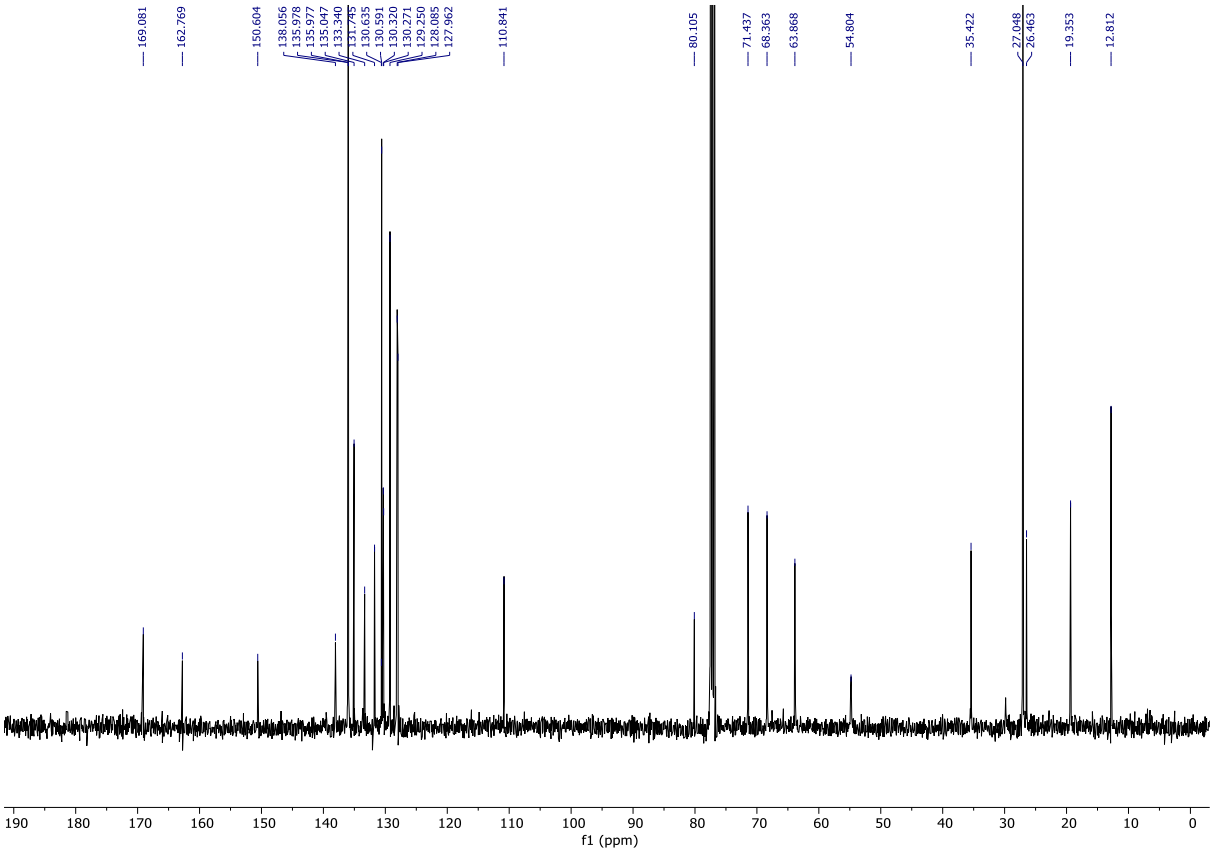
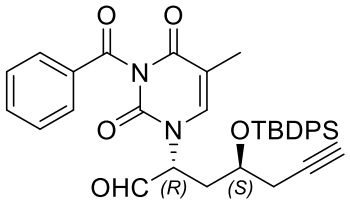
1.08
1.10
1.13
2.03
1.29
2.50
3.39
10.47
f1 (ppm)


169.081
162.769
150.604
138.056
135.978
135.977
135.047
133.340
131.745
130.635
130.591
130.320
130.271
129.250
128.085
127.962
110.841
80.105
71.437
68.363
63.868
54.804
35.422
27.048
26.463
19.353
12.812
f1 (ppm)

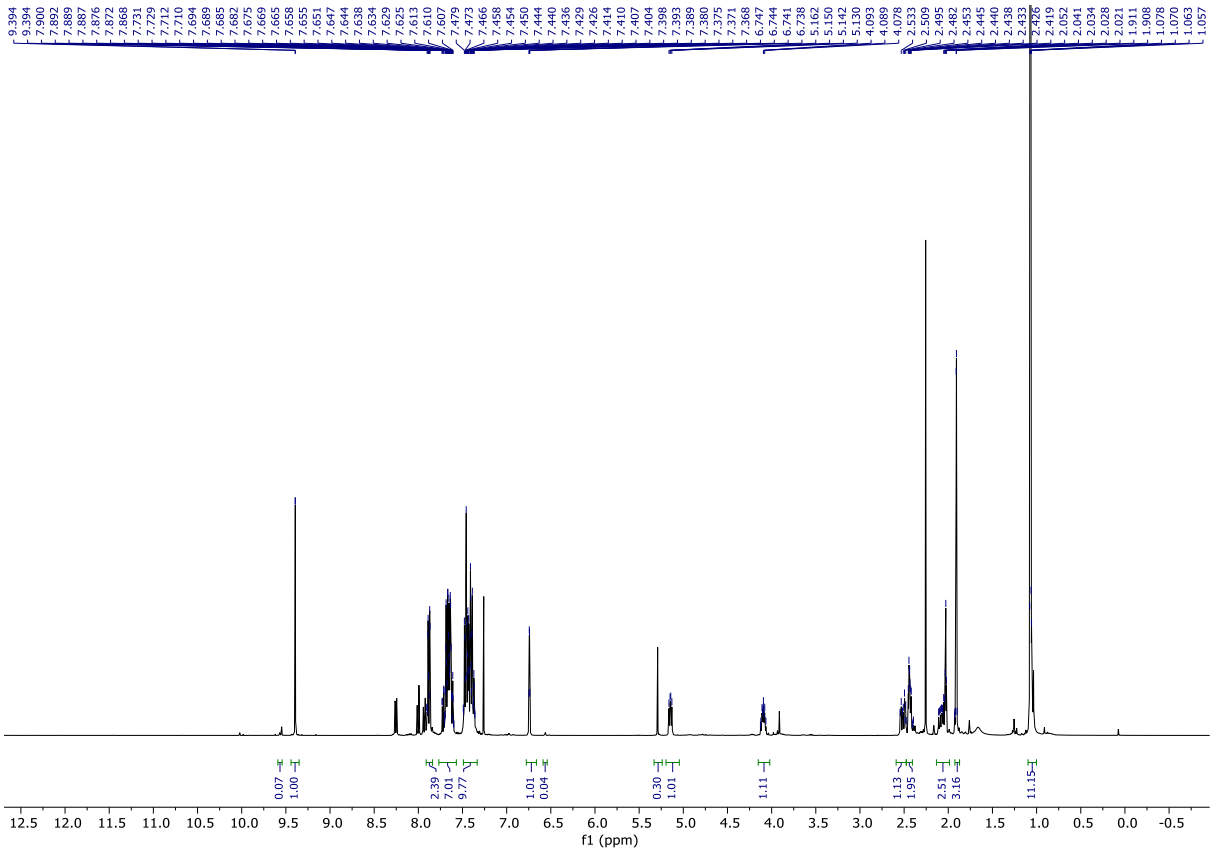
*(2R,4S)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)hept-6-ynal ((R,S)-**71**)*



In a flame-dried 100 ml flask, a solution of (R,S)-**70** (0.73 g, 1.23 mmol, 1.00 equiv.) in dry DCM (33.171 ml, c=0.037 M) was prepared under Argon atmosphere at room temperature. Then, DMP (780.8 mg, 1.84 mmol, 1.50 equiv.) and $NaHCO_3$ (386.6 mg, 4.60 mmol, 3.75 equiv.) were added at room temperature. Control by TLC. The reaction was controlled by NMR as well. The reaction was stirred at room temperature for 3-4 h while being monitored by TLC. When the reaction was finished by TLC, it was diluted with DCM (20 ml) and quenched with 30 ml of DMP quenching solution ($Na_2S_2O_3$ and $NaHCO_3$). The aqueous layer was extracted with DCM (30 ml x 3). The combined organic layers were washed with brine, dried over magnesium sulfate, and filtered; the solvent was removed under reduced pressure. The crude material was used for the next step as a crude. The aldehyde (R,S)-**71** is decomposing on silica, therefore it is used as a crude for the next step.

Yield: 730 mg (quant, used as crude for the next step), *dr*=20:1;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 – 7.84 (m, 2H), 7.75 – 7.56 (m, 6H), 7.52 – 7.34 (m, 9H), 6.74 (q, J = 1.2 Hz, 1H), 5.15 (dd, J = 8.1, 5.0 Hz, 1H), 4.10 (ddt, J = 9.6, 7.3, 3.5 Hz, 1H), 2.51 (dt, J = 14.6, 5.4 Hz, 2H), 2.46 – 2.39 (m, 1H), 2.15 – 2.05 (m, 1H), 2.03 (t, J = 2.6 Hz, 1H), 1.91 (d, J = 1.2 Hz, 3H), 1.07 (s, 9H);


9.394
9.394
7.900
7.892
7.889
7.887
7.876
7.872
7.868
7.731
7.729
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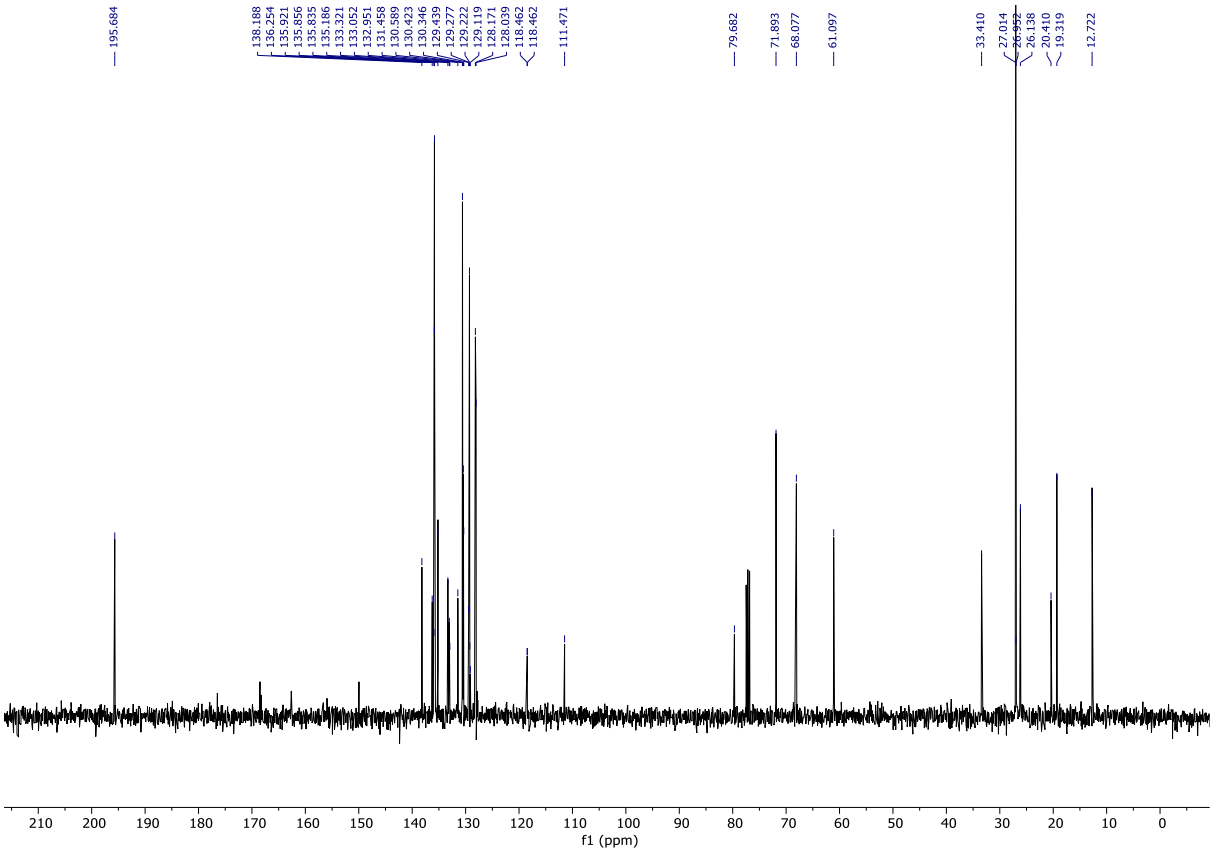
7.694
7.688
7.685
7.682
7.675
7.669
7.665
7.658
7.655
7.651
7.647
7.644
7.638
7.634
7.629
7.625
7.613
7.610
7.607
7.479
7.473
7.466
7.458
7.454
7.450
7.444
7.440
7.436
7.429
7.426
7.414
7.410
7.407
7.404
7.398
7.393
7.389
7.380
7.375
7.371
7.368
6.747
6.744
6.741
6.738
5.162
5.150
5.142
5.130
4.093
4.089
4.078
2.533
2.509
2.495
2.482
2.453
2.445
2.440
2.438
2.433
2.426
2.419
2.052
2.041
2.034
2.028
2.021
1.911
1.908
1.078
1.070
1.063
1.057
0.07
1.00
2.39
7.01
9.77
1.01
0.04
0.30
1.01
1.11
1.13
1.95
2.51
3.16
11.15
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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133.321
133.052
132.951
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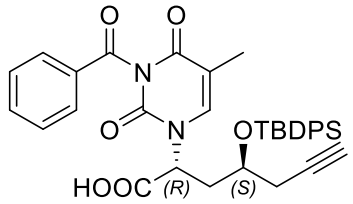
130.589
130.423
130.346
129.439
129.277
129.222
129.119
128.171
128.039
118.462
118.462
111.471
79.682
71.893
68.077
61.097
33.410
27.014
26.952
26.138
20.410
19.319
12.722
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

*(2R,4S)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)hept-6-ynoic acid ((R,S)-**2**)*



In a flame-dried 50 ml flask solution of crude (R,S)-**71** (0.78 g, 1.32 mmol, 1.0 equiv.) was solubilized in a mixture (1:1) of t-BuOH (15.48 ml, c=0.085 M) and 2-methyl-butene (15.48 ml, c=0.085 M) at 0 °C (solution A). Meanwhile, in a separate flask, a solution of $NaClO_2$ (80%, 0.381 g, 4.211 mmol, 3.2 equiv.) and NaH_2PO_4 dihydrate (0.82 g, 5.26 mmol, 4.0 equiv.) in water (10.53 ml, c=0.500 M) was prepared (solution B). Then, solution B was added to solution A dropwise at 0°C. The reaction was stirred for 3 h while slowly allowing it to go from 0 ˚C to room temperature. Once the reaction was completed by TLC, the reaction was diluted with DCM (10.0 ml) and brine (10.0 ml), extracted three times with DCM (15.0 ml), dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was columned by a 1 cm column with an eluent (hex:ea=5:1), slowly going to pure ethyl acetate, then ethyl acetate with 1% AcOH. (R,S)-**2** is a shiny and fluffy material.

Yield: 650 mg (81 %) over 2 steps;

R_f = 0.26 (EtOAc), CPS staining;

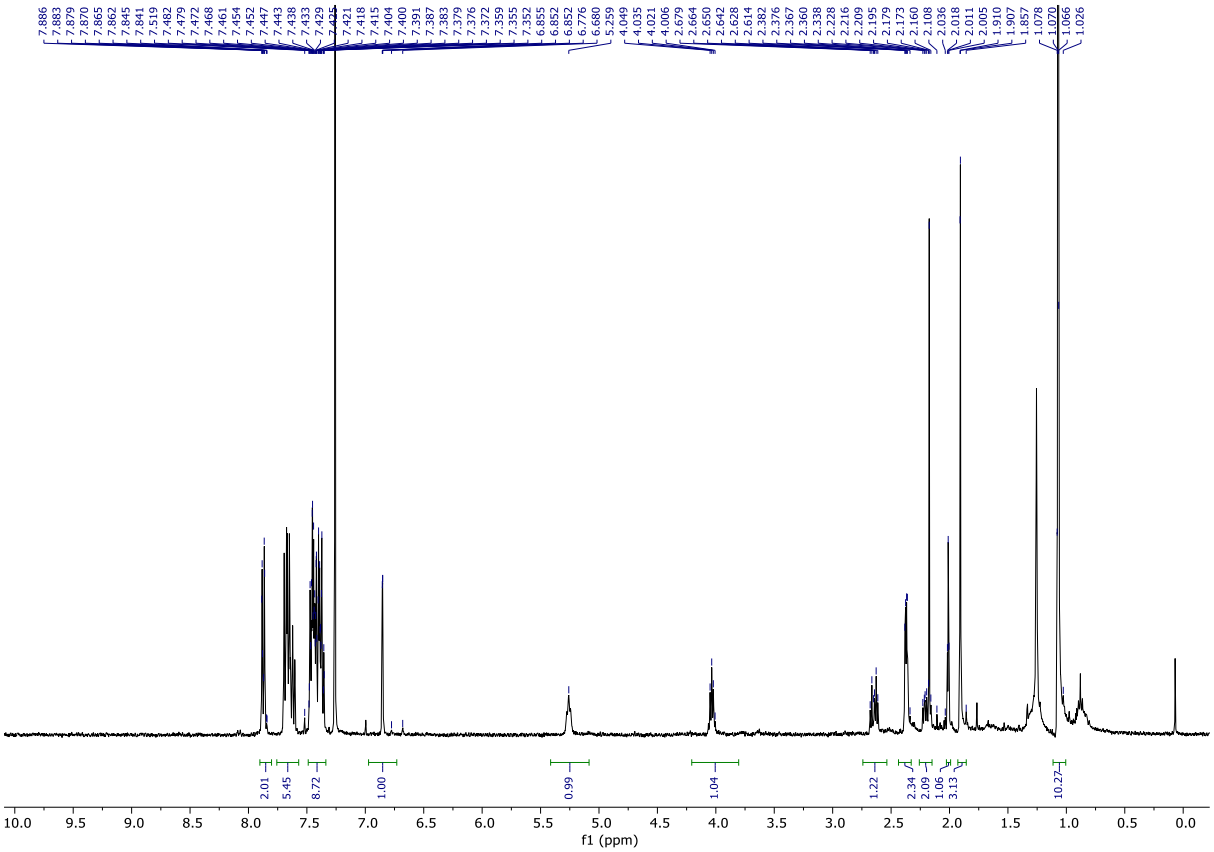
$[\alpha]_{20}^{D}$: = +2.0 (c = 1.0; $CHCl_3$, 20°C);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 – 7.79 (m, 2H), 7.72 – 7.56 (m, 5H), 7.51 – 7.31 (m, 9H), 6.85 (d, J = 1.3 Hz, 1H), 5.26 (s, 1H), 4.04 (p, J = 5.8 Hz, 1H), 2.65 (dt, J = 14.6, 5.8 Hz, 1H), 2.37 (dd, J = 6.0, 2.7 Hz, 2H), 2.17 (s, 1H), 2.01 (t, J = 2.6 Hz, 1H), 1.91 (d, J = 1.2 Hz, 3H), 1.07 (s, 9H);

^{13}C NMR (126 MHz, Chloroform-*d*) δ 168.5, 162.7, 150.0, 138.0, 135.9, 135.2, 133.1, 133.1, 131.6, 130.6, 130.4, 129.3, 128.1, 128.0, 111.4, 79.7, 71.7, 68.3, 54.8, 36.2, 32.1, 31.1, 29.9, 27.0, 26.2, 19.4, 12.8;

IR (film): ν = 3071, 2931, 2858, 1750, 1698, 1651, 1600, 1472, 1428, 1363, 1254, 1227, 1179, 1110, 1089, 999, 974, 939, 909, 822, 790, 764, 732, 702, 686, 647, 622, 611;

HRMS (ESI-TOF) m/z (ESI) $C_{35}H_{36}N_2NaO_6Si$ [M+Na]+ 631.2235, found 631.2227.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7.865
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7.845
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7.519
7.482
7.479
7.472
7.468
7.461
7.454
7.452
7.447
7.443
7.438
7.433
7.429
7.425
7.421
7.418
7.415
7.404
7.400
7.391
7.387
7.383
7.379
7.376
7.372
7.359
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7.352
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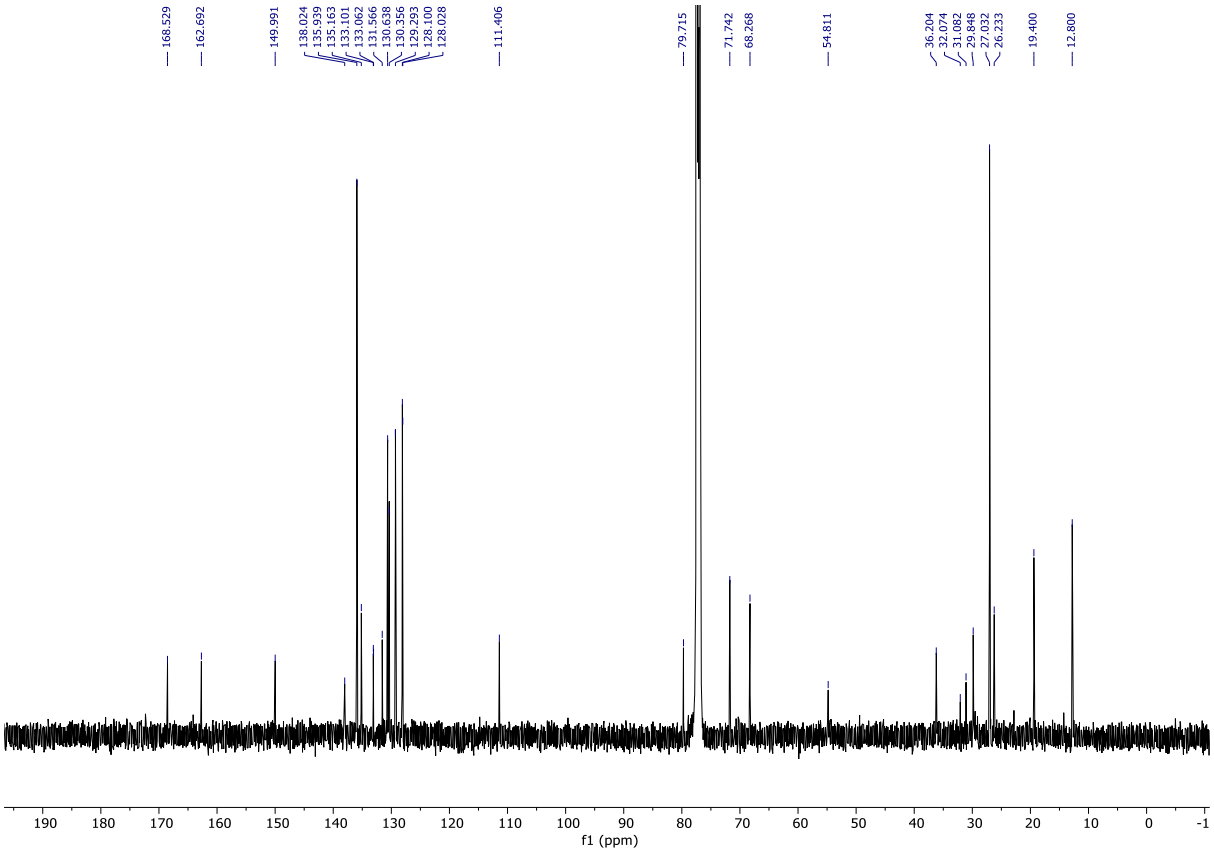
2.650
2.642
2.628
2.614
2.382
2.376
2.367
2.360
2.338
2.228
2.216
2.209
2.195
2.179
2.173
2.160
2.108
2.036
2.018
2.011
2.005
1.910
1.907
1.857
1.078
1.070
1.066
1.026
2.01
5.45
8.72
1.00
0.99
1.04
1.22
2.34
2.09
1.06
3.13
10.27
f1 (ppm)


168.529
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133.101
133.062
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130.638
130.356
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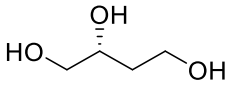
128.028
111.406
79.715
71.742
68.268
54.811
36.204
32.074
31.082
29.848
27.032
26.233
19.400
12.800
f1 (ppm)

Synthesis of (*S,S*)-2

*(R)-Butane-1,2,4-triol (R-**61**)* [9]



In 2 liter flask a solution of (R)-malic acid (60 g, 1.0 equiv.) in THF (700 ml, c=0.62 M) was prepared. Then, trimethyl borate (210 ml, 4.2 equiv.) was added **over 15 minutes** *via* an addition funnel (+24 ml of THF for rinsing the addition funnel), and the solution was stirred at room temperature for 1 h. The first step is endothermic, the temperature dropped from 19.9 °C to 18.3 °C. After stirring for 1 h at room temperature, borane dimethyl sulfide (2 M in THF, 540 ml, 2.4 equiv.) was added slowly via syringe 60 ml (x10) while being cooled with an ice bath. The reaction was stirred at room temperature for 17 h overnight. Then, the solvent was removed under reduced pressure. The residue was dissolved in MeOH (100 ml) and evaporated 2 times. M(Crude material)=89.32 g. The crude material R-**61** was columned with the biggest 10 cm column, however, since it was so much material, of course, the column was not enough and I had still some impurities in the cleanest fractions and also I had a lot of mixed fractions. Column with the eluent system 5:1 DCM: MeOH and increasing to 3:1 DCM: MeOH. 3 different batches were collected: flask 1 (13.50 g), flask 2 (16.31 g) and flask 3 (7.15 g). For future setups, flask 2+3 was collected together and flask 1 with more impurities was kept separately.

Yield: 36 g (76 %);

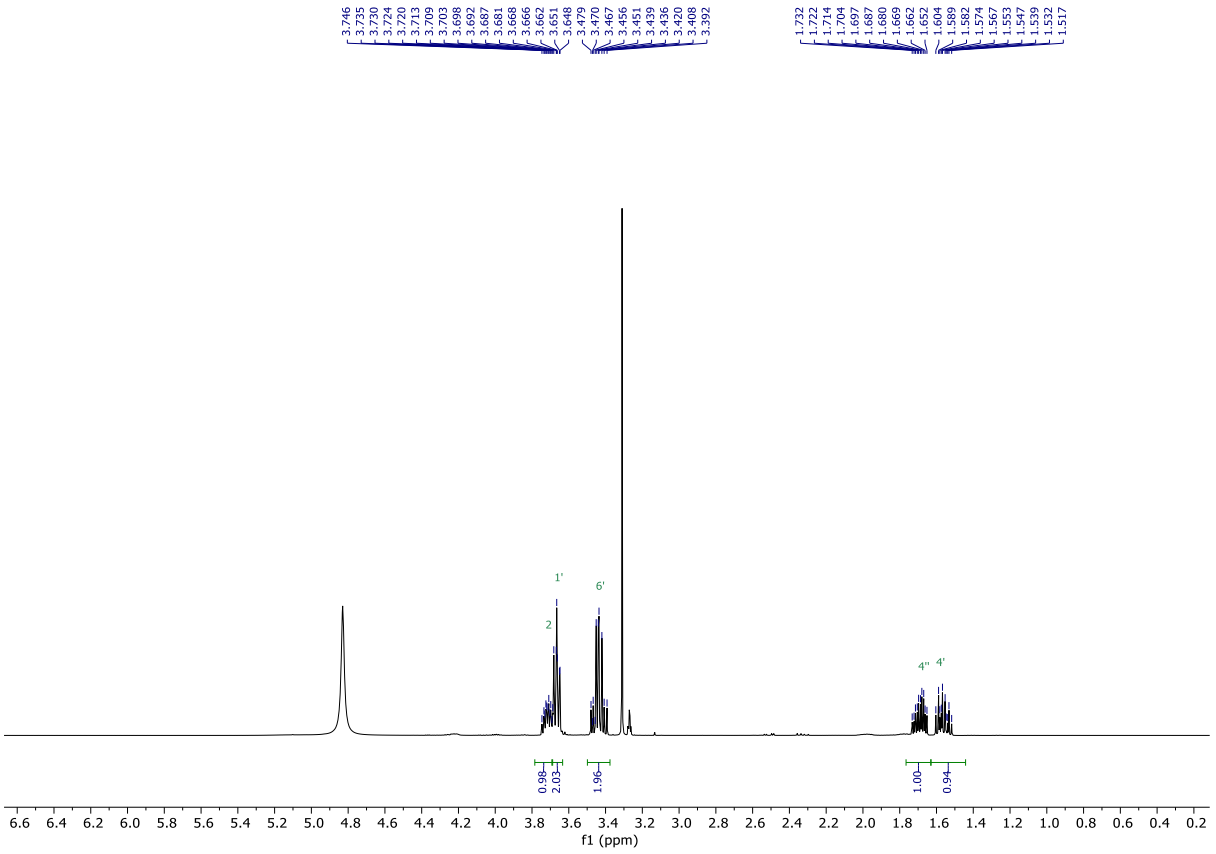
R_f = 0.4568 (DCM:MeOH = 4:1), $KMnO_4$ staining;

^{1}H NMR (400 MHz, Methanol-d_4) δ 3.77 – 3.67 (m, 1H), 3.71 – 3.63 (m, 2H), 3.51 – 3.37 (m, 2H), 1.69 (dtd, *J* = 14.1, 7.1, 4.1 Hz, 1H), 1.56 (ddt, *J* = 14.3, 8.6, 5.9 Hz, 1H);

^{13}C NMR (101 MHz, Methanol-d_4) δ 70.8, 67.5, 60.0, 37.1.

IR (film): v = 3359, 2940, 2888, 2502, 1731, 1440, 1283, 1223, 1179, 1110, 1085, 1053, 903, 870, 789, 780, 766, 759, 661, 626, 583, 546, 504.

HRMS (ESI-TOF) m/z calcd. for $C_4H_{10}NaO_3$ $[M+Na]^+$ 129.0522, found 129.0523.


3.746
3.735
3.730
3.724
3.720
3.713
3.709
3.703
3.698
3.692
3.687
3.681
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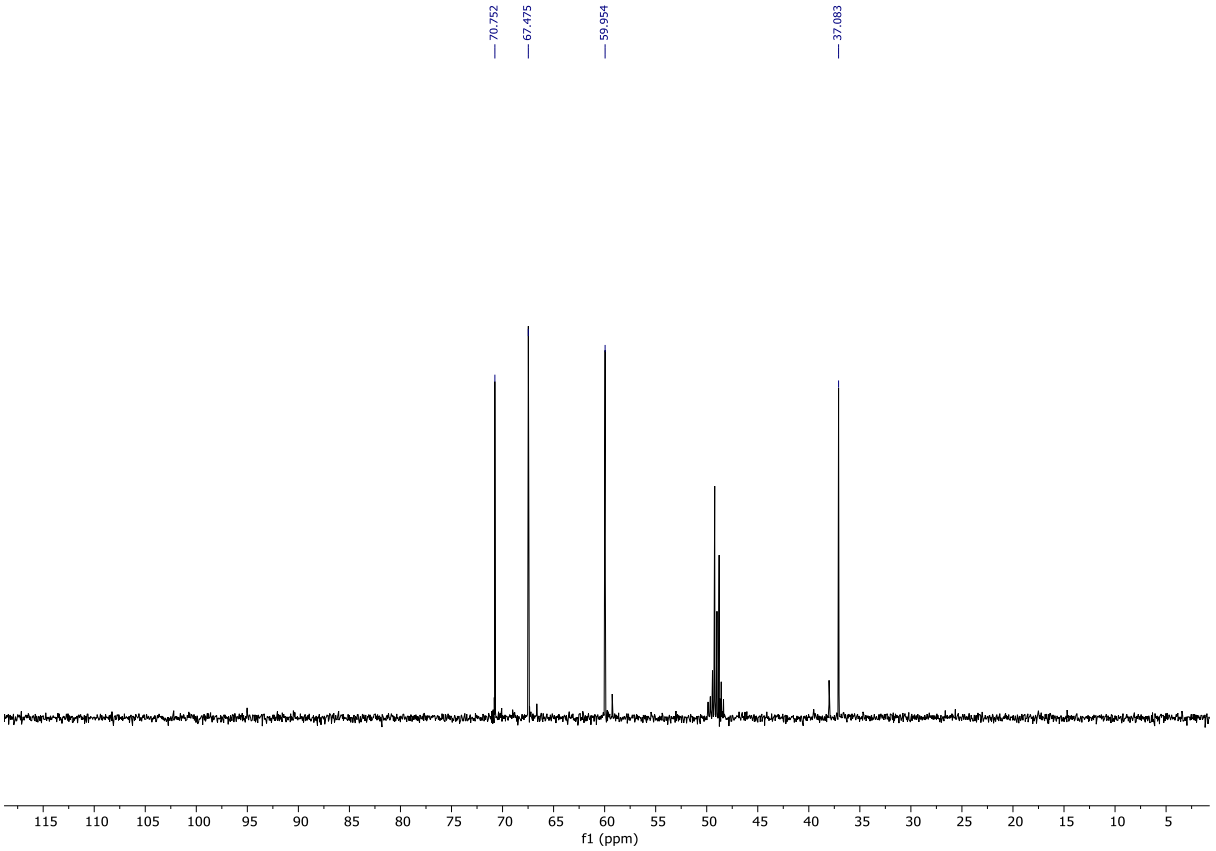
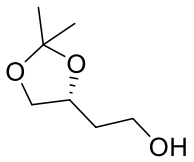
3.666
3.662
3.651
3.648
3.479
3.470
3.467
3.456
3.451
3.439
3.436
3.420
3.408
3.392
1.732
1.722
1.714
1.704
1.697
1.687
1.680
1.669
1.662
1.652
1.604
1.589
1.582
1.574
1.567
1.553
1.547
1.539
1.532
1.517
1'
6'
2
4''
4'
0.98
2.03
1.96
1.00
0.94
f1 (ppm)


70.752
67.475
59.954
37.083
f1 (ppm)

*(R)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethan-1-ol (R-**62**)*



Procedure 1: To a solution of R-**61** (1.1 g, 10.4 mmol, 1.0 equiv.) in acetone (60 ml) was added p-TsOH*H_2O (79 mg, 0.46 mmol, 4 mol%) and the reaction was stirred at room temperature for 15 h. Then, triethylamine NEt_3 (50.76 ml) was added. The solvent was removed under reduced pressure. The crude material was purified by FC (hexane/EtOAc 1/1) affording the acetal R-**62** (519 mg, 34.26 %) as a colorless oil.

Procedure 2: To stirred solution 1,2,4-butanetriol R-**61** (7.90 g, 1.0 equiv.) in dry DCM (143 ml) cooled to 0 °C, were added 2,2-dimethoxypropane (15.53 ml, 2.0 equiv.) and a catalytic amount of *p*-TsOH (1.93 g, 0.1 equiv.), then stirred for 1 h at room temperature. After completion of the reaction, it was quenched with sat. $NaHCO_3$ and the water layer extracted with DCM (2 x 100 ml). The organic layer was washed with brine and dried over anhydrous $MgSO_4$. Removal of the solvent gave a crude product R-**62** 11.32 g (70%), which was used in the next step without further purification.

Yield: 16.7 g (60 %);

R_f = 0.525 (EA), $KMnO_4$ or CPS staining;

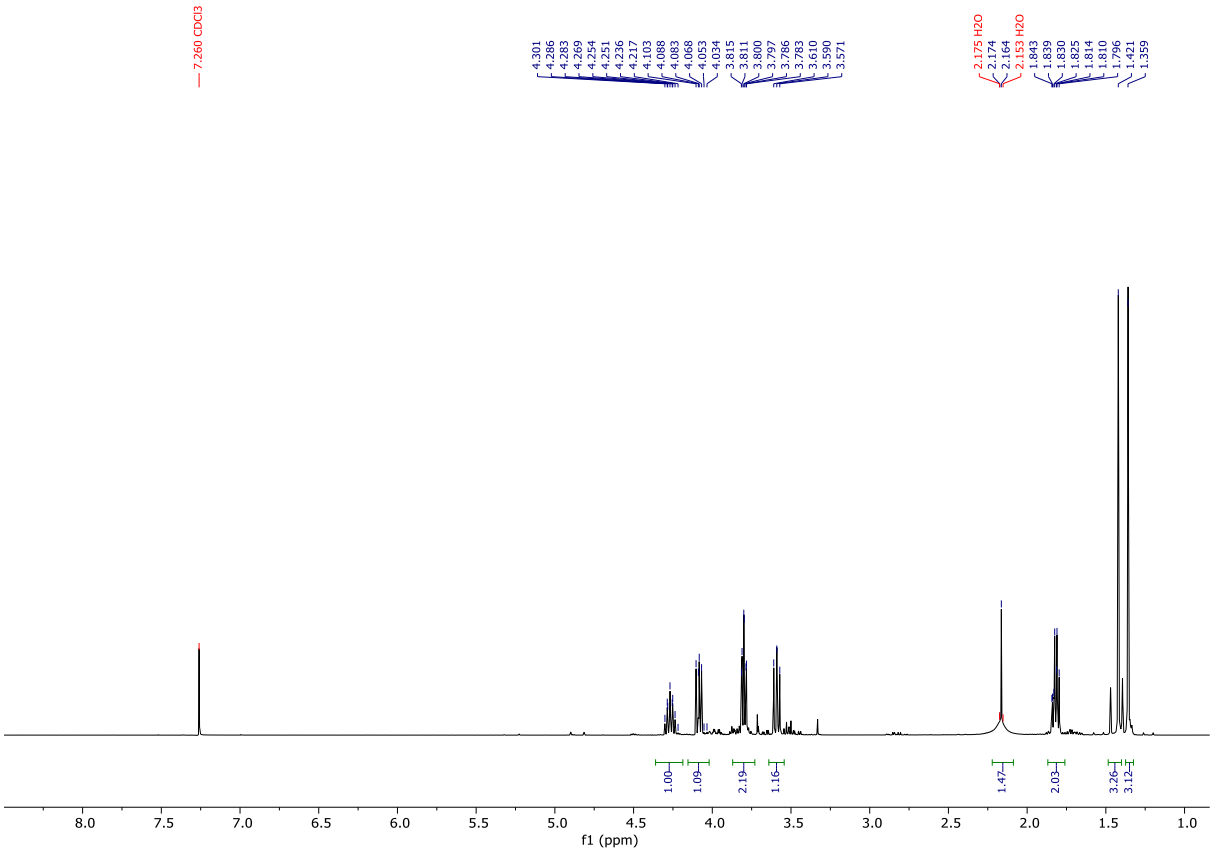
$[\alpha]\frac{D}{20}$: = -1.0 (c = 1.0; $CHCl_3$, 20°C);

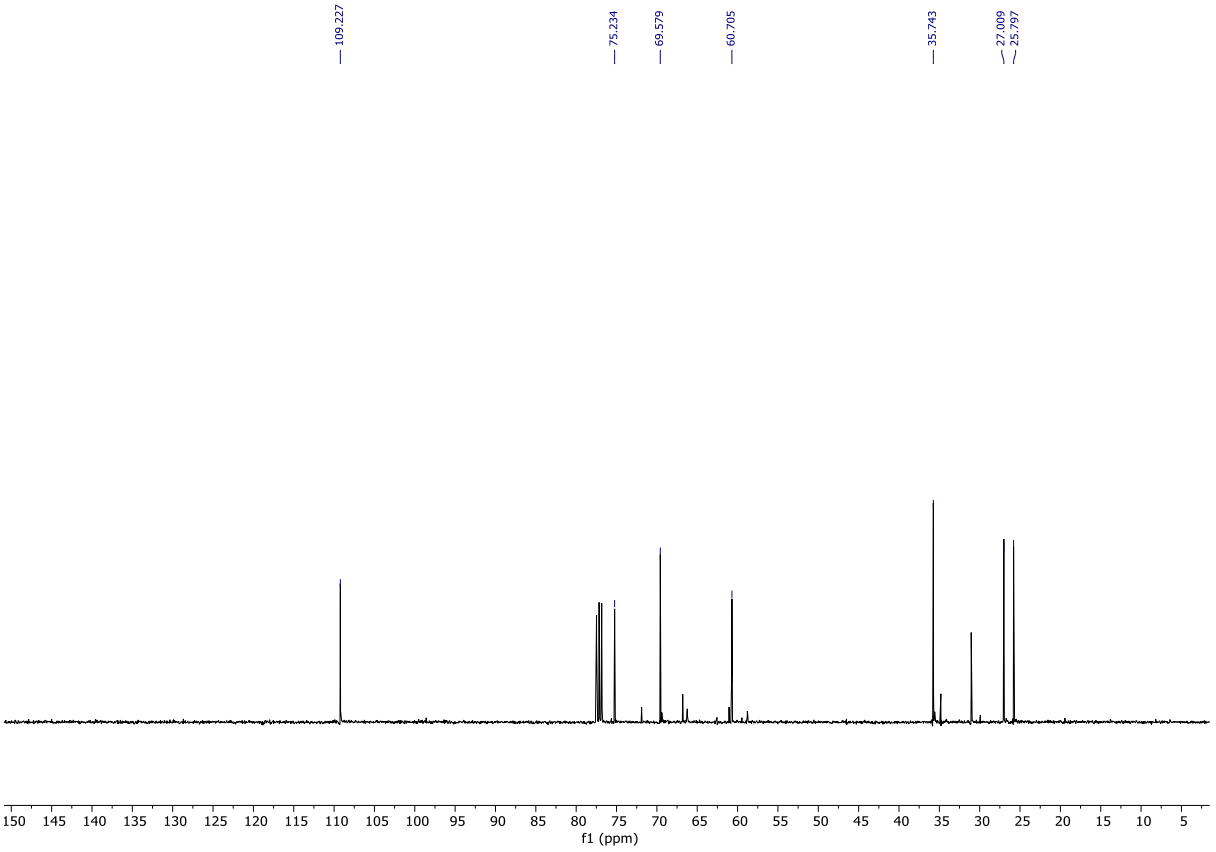
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.27 (ddd, J = 12.9, 7.2, 6.0 Hz, 1H), 4.09 (dd, J = 8.1, 6.0 Hz, 1H), 3.80 (td, J = 5.8, 1.4 Hz, 2H), 3.65 – 3.50 (m, 1H), 2.16 (br.s, 1H), 1.90 – 1.70 (m, 2H), 1.42 (s, 3H), 1.36 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-d) δ 109.2, 75.2, 69.6, 60.7, 35.7, 27.0, 25.8;

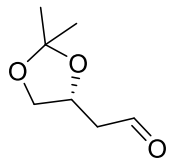
IR (film): v = 3419, 2986, 2937, 2878, 1743, 1455, 1439, 1371, 1245, 1215, 1157, 1055, 989, 918, 854, 822, 792, 732, 647, 514.

HRMS (ESI-TOF) m/z calcd. for $C_7H_{14}NaO_3$ $[M+Na]^+$ 169.0835, found 169.0836.


7.260 CDCl3
4.301
4.286
4.283
4.269
4.254
4.251
4.236
4.217
4.103
4.088
4.083
4.068
4.053
4.034
3.815
3.811
3.800
3.797
3.786
3.783
3.610
3.590
3.571
2.175 H2O
2.174
2.164
2.153 H2O
1.843
1.839
1.830
1.825
1.814
1.810
1.796
1.421
1.359
1.00
1.09
2.19
1.16
1.47
2.03
3.26
3.12
f1 (ppm)


109.227
75.234
69.579
60.705
35.743
27.009
25.797
f1 (ppm)

*(R)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)acetaldehyde (R-**6**)*



To a solution of R-**62** (1.0 g, 6.84 mmol, 1.00 equiv.) in DCM (40 ml) was added DIPEA (5.26 ml, 29.55 mmol, 4.32 equiv.) and stirred for 5 mins. After 5 mins, DMSO (4.86 ml) was added and the mixture was stirred for another 10 mins. Then SO_3*pyridine (2.72 g, 17.10 mmol, 2.50 equiv.) and the reaction was stirred at room temperature for 30 min. Saturated aqueous $NaHCO_3$ was added and extracted with DCM (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by FC (diethyl ether: hexane = 1:1), fractions 8-15 obtaining R-**6** (560 g, 57%) as a colorless oil.

Yield: 16.7 g, 60 %;

R_f = 0.7288 (EA), CPS staining;

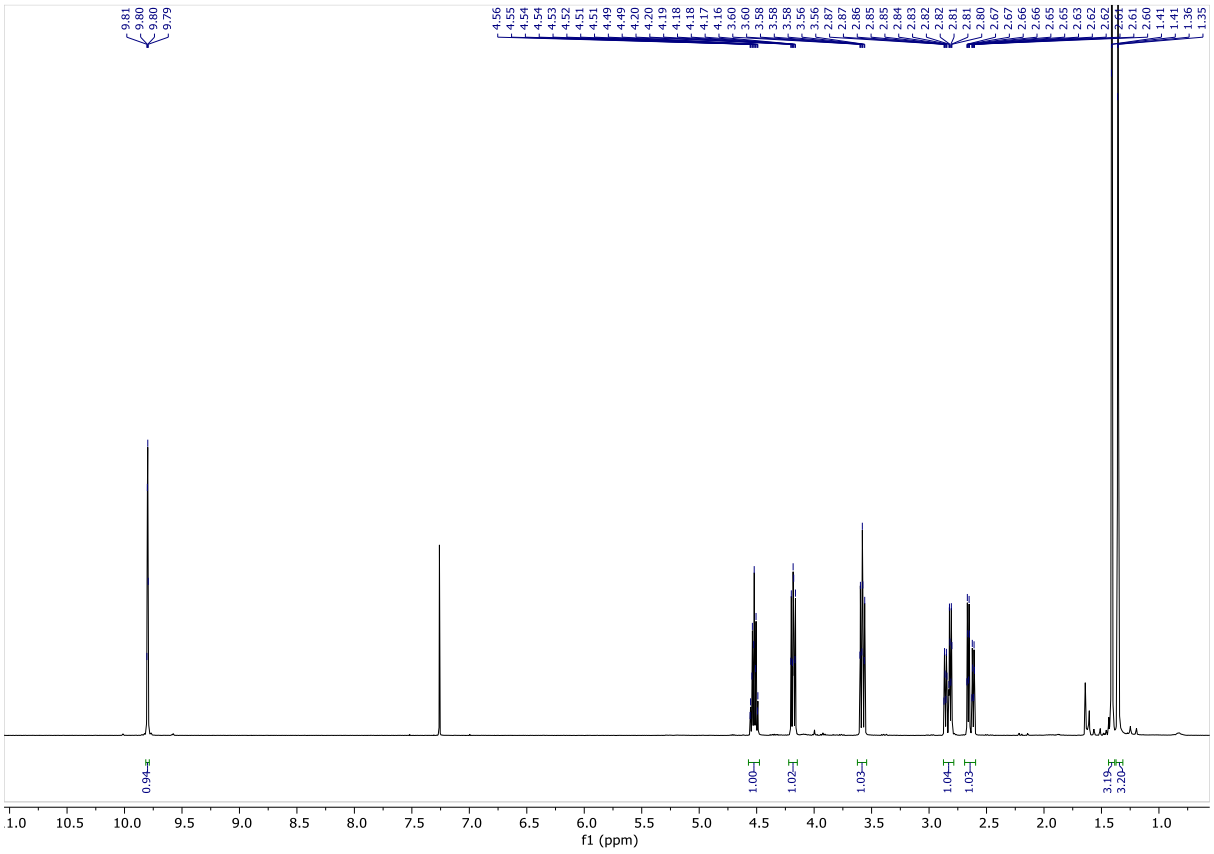
$[\alpha]_{20}^{D}$: = -9.0 (c = 1.0; $CHCl_3$, 20°C);

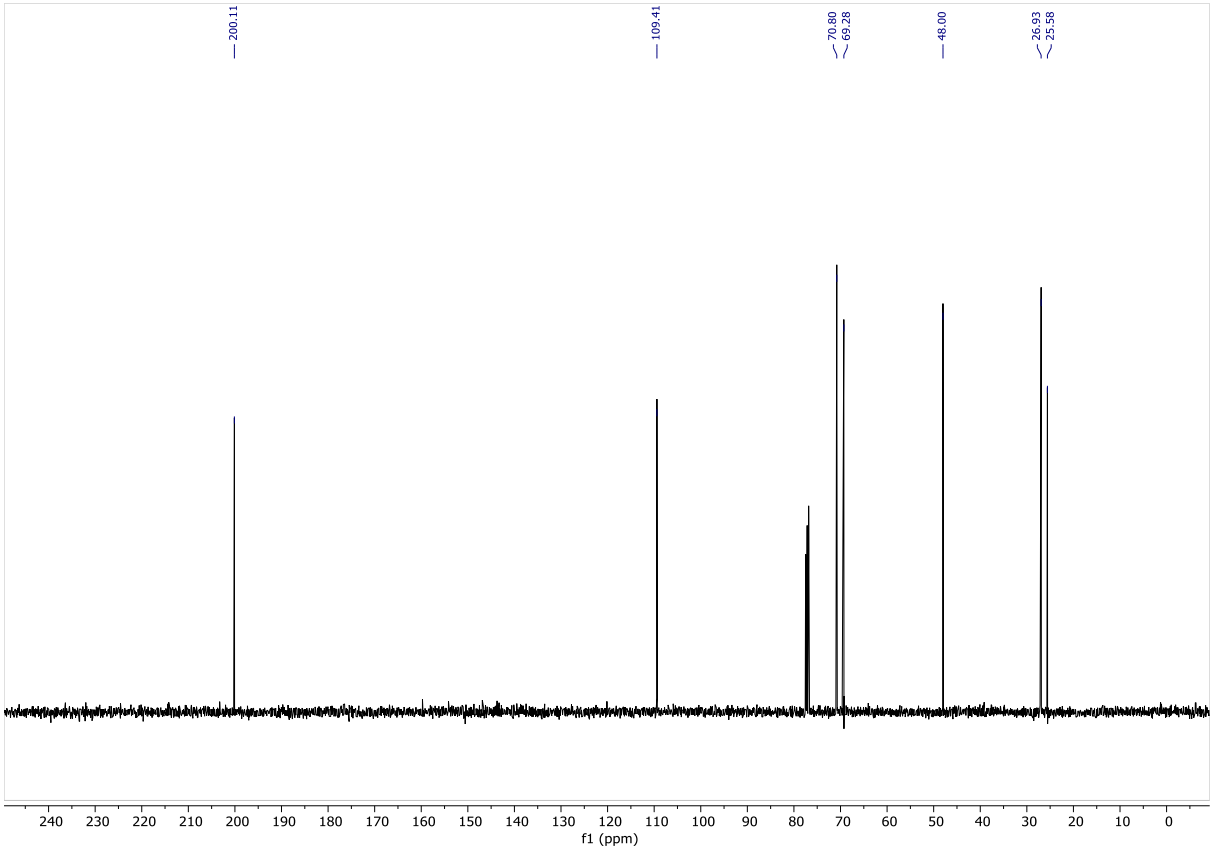
^{1}H NMR (400 MHz, Chloroform-*d*): δ 9.81 (s, 1H), 4.53 (p, *J* = 6.3 Hz, 1H), 4.19 (dd, *J* = 8.3, 6.0 Hz, 1H), 3.59 (dd, *J* = 8.3, 6.7 Hz, 1H), 2.87-2.81 (ddd, *J* = 17.2, 6.6, 1.8 Hz, 1H), 2.67-2.61 (ddd, *J* = 17.2, 6.1, 1.3 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*): δ 200.1, 109.4, 70.8, 69.2, 47.9, 26.9, 25.5.

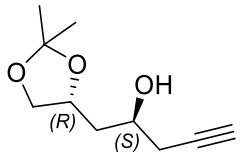
IR (film): ν = 3454, 2929, 2882, 1735, 1433, 1385, 1114, 1011, 972, 916, 812, 773, 764, 732, 512.

HRMS (ESI-TOF) m/z calcd. for $C_7H_{12}NaO_3$ $[M+Na]^+$ 167.0679, found 167.0680.


9.81
9.80
9.80
9.79
4.56
4.55
4.54
4.54
4.53
4.52
4.51
4.51
4.49
4.49
4.20
4.19
4.18
4.18
4.17
4.16
3.60
3.58
3.58
3.56
3.56
2.87
2.87
2.86
2.85
2.85
2.84
2.83
2.82
2.82
2.81
2.81
2.80
2.67
2.67
2.66
2.66
2.65
2.65
2.63
2.62
2.62
2.61
2.60
1.41
1.41
1.36
1.35
0.94
1.00
1.02
1.03
1.04
1.03
3.19
3.20
f1 (ppm)


200.11
109.41
70.80
69.28
48.00
26.93
25.58
f1 (ppm)

*(S)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-yn-2-ol ((R,S)-**63**)*[10]



Zinc dust (11.34 g, 173.4 mmol, 2.50 equiv.), preactivated with HCL was suspended in 123.0 mL of THF containing 1,2- dibromoethane (1.49 mL, 17.3 mmol, 0.25 equiv.). The suspension was heated to 65 °C for 10 min before cooling to 25 °C. After 45 min, chlorotrimethylsiliane (2.20 mL, 17.34 mmol, 0.25 equiv.) was added dropwise *via a* syringe. It became a sediment from a nice powder. The suspension was stirred vigorously for an additional 30 min and then cooled to -10 °C. Propargyl bromide (80 % in toluene, 13.14 mL, 173.4 mmol, 2.50 equiv.) was added slowly *via* syringe over 20 min. The suspension was stirred for 2.5 h below -12 °C. Then R-**62** was added over 45 min through a cannula to a solution of aldehyde (10.0 g, 69.4 mmol, 1.00 equiv.) in toluene (462.35 mL, c=0.15 M) at -78 °C. The resulting reaction was slowly warmed to -40- (-45) °C and stirred at this temperature overnight from 18:00 to 16:00 the next day. TLC in the evening of setup day It was then warmed to 0 °C and quenched with saturated aqueous NH4Cl solution (100.0 mL). The mixture was extracted with EtOAc three times and the combined organic fractions were dried over $MgSO_4$, and concentrated under reduced pressure. The residue (dr=1:3 = RR: RS) was purified by slow gradient flash column chromatography (0% → 30% EtOAc/ DCM) to afford homopropargylic alcohol (R,R)-**63** (1.13 g, 21 %) as a colorless oil and its major diastereomer (R,S)-**63** (5.37 g, 42 %) as a pale yellow oil, and a mixture of two diastereomers (ca. 5 g). The combined yield of the product: 6.5 g (63 %), *dr* = 3:1 (based on crude reaction mixture). The residue was purified by slow gradient flash column chromatography (0% → 30% EtOAc/ DCM, the best separation is at 0.5-0.6 % EtOAc in DCM).

Yield: dr=1:3 (RR: RS)

Yield: 5.37 g, 42 %;

R_f = 0.1282 (EA:DCM=1:9), CPS staining;

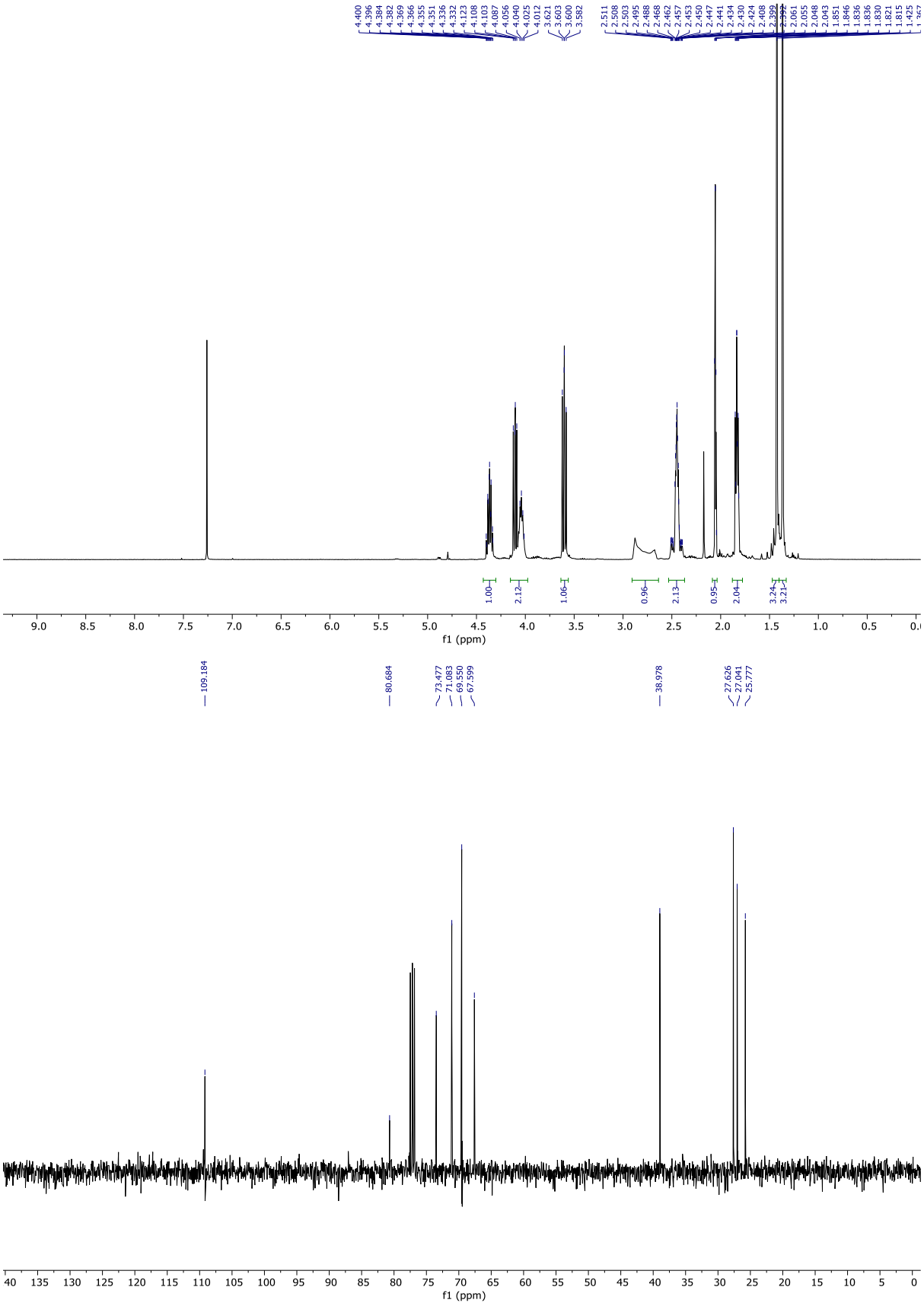
$[\alpha]_{20}^{D}$: = +5.0 (c = 1.0; $CHCl_3$, 20°C);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.46 – 4.29 (m, 1H), 4.11 (dd, J = 8.2, 6.1 Hz, 1H), 4.03 (q, J = 5.8, 5.4 Hz, 1H), 3.60 (dd, J = 8.3, 7.4 Hz, 1H), 2.57 – 2.34 (m, 2H), 2.05 (t, J = 2.7 Hz, 1H), 1.83 (tt, J = 5.9, 2.3 Hz, 2H), 1.42 (s, 3H), 1.37 (s, 3H);

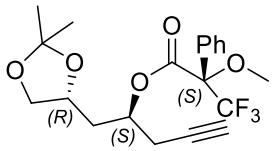
^{13}C NMR (101 MHz, Chloroform-*d*) δ 109.2, 80.7, 73.5, 71.1, 69.6, 67.6, 39.0, 27.6, 27.0, 25.8;

IR (film): ν = 3437, 3290, 2987, 2936, 2879, 1739, 1456, 1432, 1381, 1372, 1216, 1159, 1125, 1064, 988, 864, 839, 791, 645, 516.

HRMS (ESI-TOF) m/z calcd. for $C_{10}H_{16}NaO_3$ $[M+Na]^+$ 207.0992, found 207.0991.



*SI-(R,S,S)-**63** (Mosher-S)*

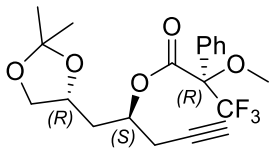


R_f = 0.575 (EA:Hex=1:2), CPS staining;

IR (film): ν = 3306, 2987, 2950, 1748, 1453, 1382, 1372, 1272, 1246, 1170, 1121, 1081, 1062, 1020, 994, 908, 871, 842, 824, 796, 788 , 780, 770, 765, 720, 698, 682, 649, 538, 512;

HRMS (ESI-TOF) m/z calcd. for $C_{20}H_{23}F_3NaO_5$ $[M+Na]^+$ 423.1390, found 423.1384.

*SI-(R,S,R)-**63** (Mosher R)*

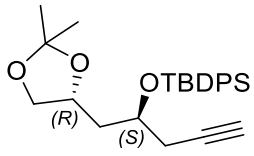


R_f = 0.6757 (EA:Hex=1:2), CPS staining;

IR (film): ν = 3295, 2986, 2951, 1748, 1497, 1453, 1381, 1371, 1254, 1169, 1123, 1107, 1081, 1063, 1020, 993, 915, 872, 845, 821, 778, 767, 717, 698, 645, 537, 517;

HRMS (ESI-TOF) m/z calcd. for $C_{20}H_{24}F_3O_5i$ $[M+H]^+$ 401.1570, found 401.1569.

*tert-butyl(((S)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-yn-2-yl)oxy)diphenylsilane ((R,S)-**57**)*[10]



In a flame dried under Argon atmosphere 500 ml flask (213.3 g) charged with a stirring bar a solution of homopropargylic alcohol (R,S)-**63** (4.50 g, 24.43 mmol, 1.0 equiv.) in dry DCM (244.25 mL, c=0.10 M) was prepared at room temperature. Then, the reagents were added in the following order: imidazole (4.99 g, 73.27 mmol, 3.0 equiv.), DMAP (298 mg, 2.44 mmol, 0.1 equiv.) and tert-butyldiphenylchlorosilane (9.38 mL, 36.64 mmol, 1.5 equiv.). The reaction was stirred at room temperature overnight and after verification of the completion of the reaction by TLC, the solution was quenched by the addition of H_2O (70 ml). Then, the mixture was extracted with DCM three times (100 ml), and the combined organic fractions were dried over $MgSO_4$, and concentrated under reduced pressure. The crude material (m=12.8 g: prod+TBDPSOH) was purified by FC (100:0 → 70:1 hexanes/EtOAc), affording (R,S)-**57** (8.6 g, 83 %).

Yield: 8.6 g, 83 %;

R_f = 0.625 (EA:Hex=1:3), CPS staining;

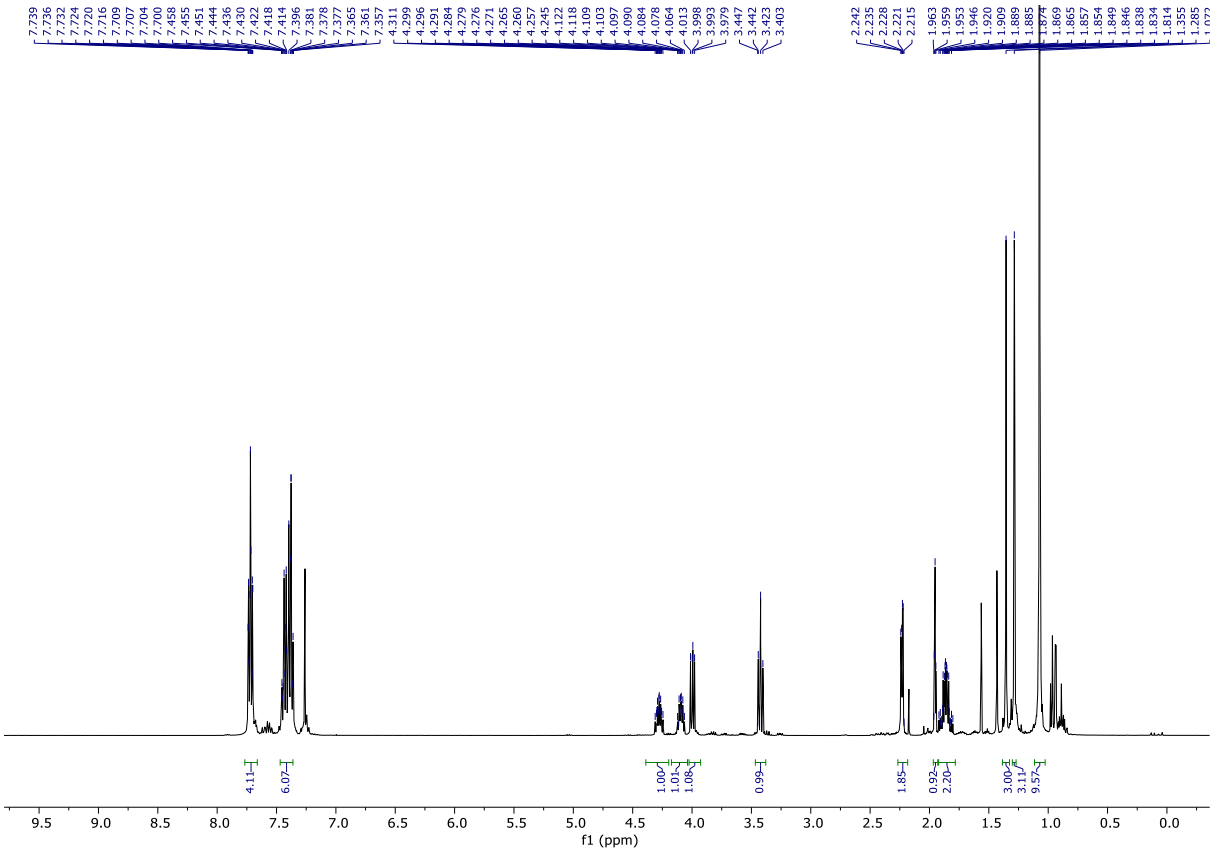
$[\alpha]_{20}^{D}$: = +15.0 (c = 1.0; $CHCl_3$, 20°C);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.72 (ddd, J = 8.0, 6.4, 1.5 Hz, 4H), 7.54 – 7.28 (m, 6H), 4.28 (tdd, J = 7.9, 5.9, 4.6 Hz, 1H), 4.09 (dq, J = 7.6, 5.3 Hz, 1H), 4.00 (dd, J = 7.8, 5.9 Hz, 1H), 3.42 (t, J = 7.8 Hz, 1H), 2.23 (dd, J = 5.5, 2.7 Hz, 2H), 1.95 (t, J = 2.6 Hz, 1H), 1.93 – 1.76 (m, 2H), 1.35 (s, 3H), 1.29 (s, 3H), 1.07 (s, 9H);

^{13}C NMR (101 MHz, Chloroform-d) δ 136.1 (4C), 134.9, 134.2, 133.7, 129.9 (2C), 127.8 (2C), 127.7 (2C), 108.8, 80.9, 72.8, 70.8, 69.9, 69.1, 40.5, 27.7, 27.1 (3C), 25.9, 19.6;

IR (film): ν = 3309, 3071, 2984, 2932, 2858, 1473, 1428, 1379, 1370, 1245, 1218, 1157, 1110, 1077, 1050, 999, 939, 893, 822, 740, 703, 641, 611, 504.

HRMS (ESI-TOF) m/z calcd. for $C_{26}H_{34}NaO_3Si$ $[M+Na]^+$ 445.2169, found 445.2163.


7.739
7.736
7.732
7.724
7.720
7.716
7.709
7.707
7.704
7.700
7.458
7.455
7.451
7.444
7.436
7.430
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3.423
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2.242
2.235
2.228
2.221
2.215
1.963
1.959
1.953
1.946
1.920
1.909
1.889
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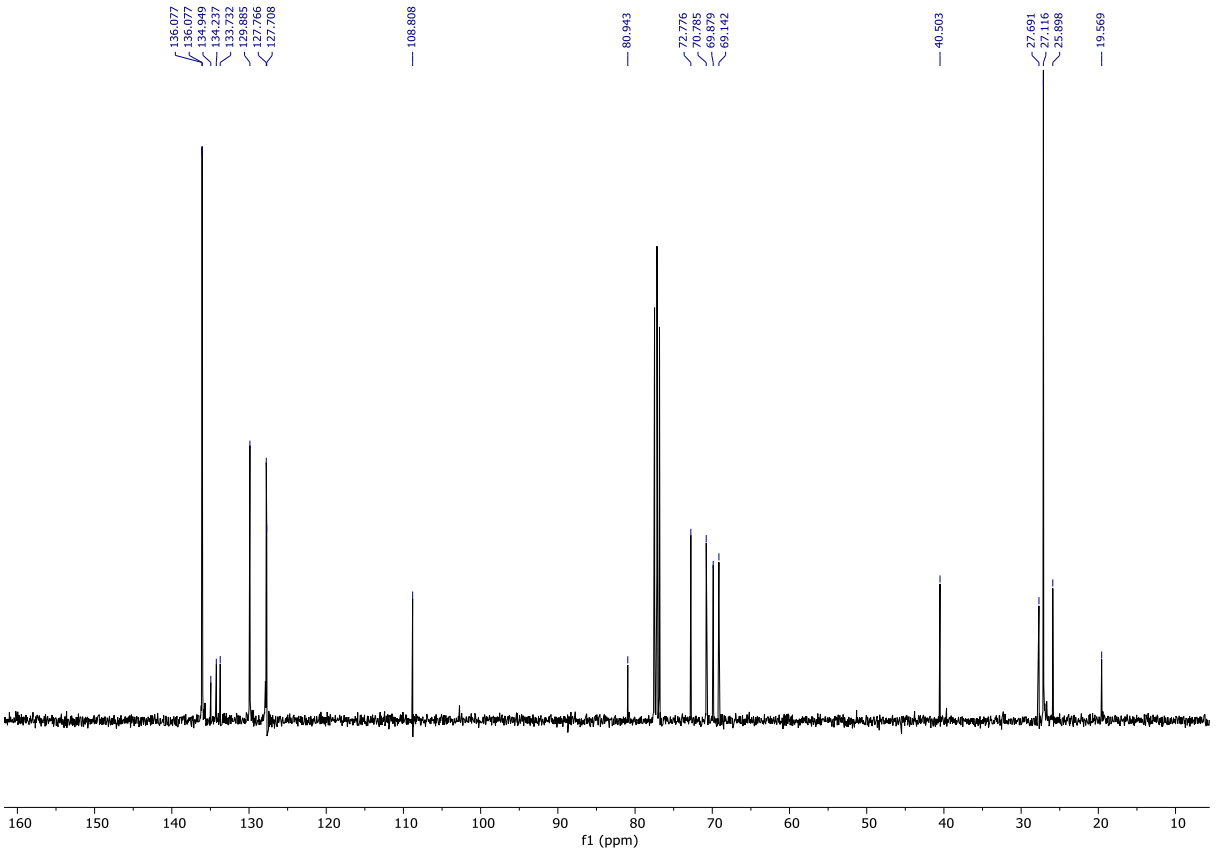
1.849
1.846
1.838
1.834
1.814
1.355
1.285
4.11
6.07
1.00
1.01
1.08
0.99
1.85
0.92
2.20
3.00
3.11
9.57
f1 (ppm)


136.077
136.077
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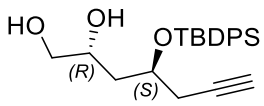
134.237
133.732
129.885
127.766
127.708
108.808
80.943
72.776
70.785
69.879
69.142
40.503
27.691
27.116
25.898
19.569
f1 (ppm)

*(2R,4S)-4-((tert-butyldiphenylsilyl)oxy)hept-6-yne-1,2-diol ((R,S)-**66**)*



In a flame-dried round bottom 1-liter flask charged with a stirring bar, a solution of acetonide (R,S)-**57** (8.6 g, 20.35 mmol, 1.0 equiv.) in dichloromethane (424 mL, c=0.048 M) was prepared under Argon atmosphere at room temperature. Then, the solution was cooled to 0 °C using an ice bath, and after the solution had reached 0 °C, trifluoroacetic acid (23.2 mL, 203.48 mmol, 10.0 equiv.) was added at 0 °C. The reaction mixture was stirred for 3 h. After verification of the reaction completion by TLC, no SM this time, the workup was normal with $NaHCO_3$ and extraction with EtOAc, drying over $MgSO_4$, and evaporation of the solvent under reduced pressure. The crude residue was purified by flash column chromatography (3:1 → 1:2 hexanes/EtOAc) to yield diol (R,S)-**66** (5.8 g, 75 %) in fractions 25-50 as a colorless oil.

Yield: 5.8 g, 75 %;

R_f = 0.333 (EA:Hex=1:1), CPS staining;

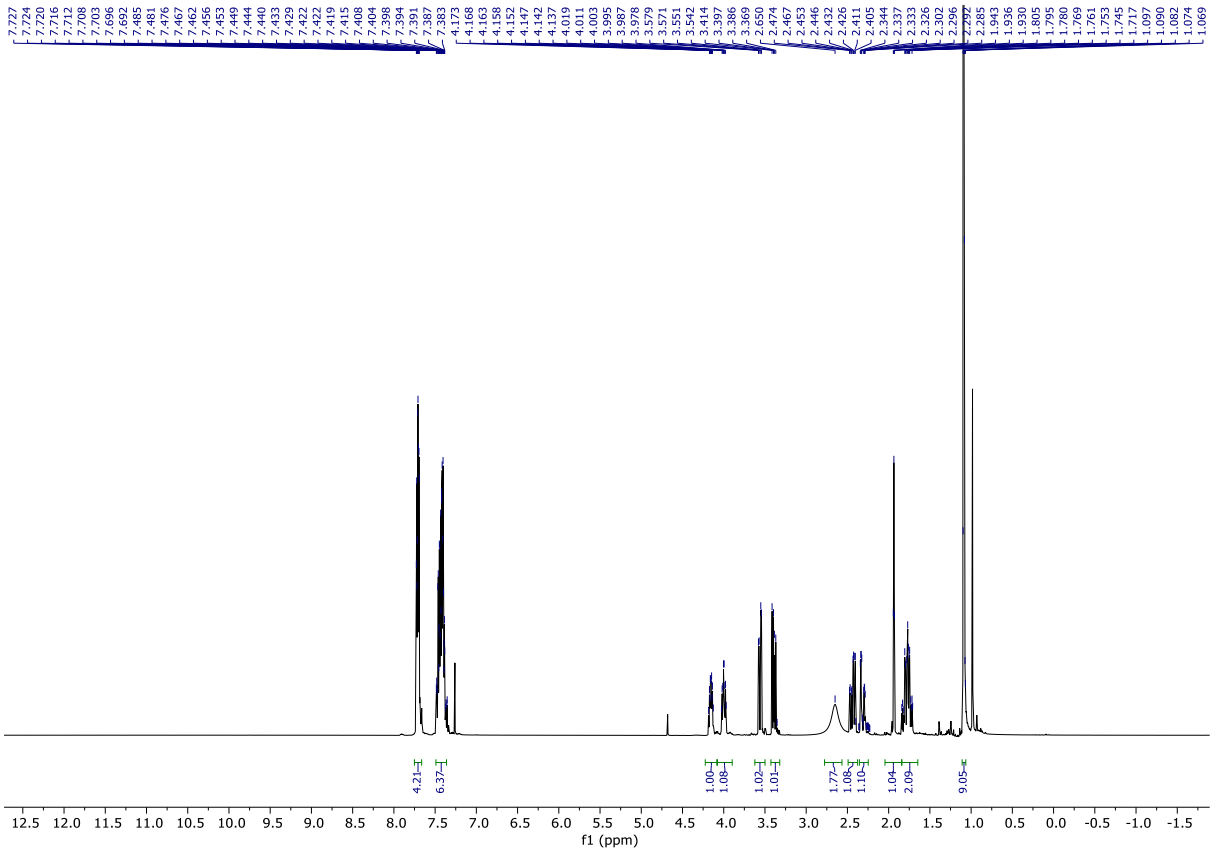
$[\alpha]\frac{D}{20}$: = +18.0 (c = 1.0; $CHCl_3$, 20°C);

^{1}H NMR (400 MHz, Chloroform-d) δ 7.71 (ddd, J = 8.1, 4.6, 1.5 Hz, 4H), 7.53 – 7.33 (m, 8H), 4.15 (ddt, J = 8.2, 6.1, 4.1 Hz, 1H), 4.00 (ddt, J = 9.9, 6.5, 3.1 Hz, 1H), 3.56 (dd, J = 11.3, 3.3 Hz, 1H), 3.39 (dd, J = 11.2, 6.8 Hz, 1H), 2.65 (s, 2H), 2.44 (ddd, J = 16.7, 8.3, 2.7 Hz, 1H), 2.31 (ddd, J = 16.6, 4.3, 2.7 Hz, 1H), 1.94 (t, J = 2.7 Hz, 1H), 1.86 – 1.62 (m, 2H), 1.09 (s, 9H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 136.0, 135.9, 133.0, 132.7, 130.5, 130.4, 128.1, 128.0, 80.0, 71.3, 71.2, 69.6, 66.2, 60.9, 37.3, 27.0, 26.2, 21.2, 19.3, 14.3;

IR (film): ν = 3424, 3311, 2954, 2930, 2857, 2366, 1472, 1428, 1390, 1362, 1255, 1110, 1007, 938, 837, 822, 779, 740, 703, 622, 612, 516, 508.

HRMS (ESI-TOF) m/z calcd. for $C_{23}H_{30}NaO_3Si$ $[M+Na]^+$ 405.1856, found 405.1851.


7.727
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7.716
7.712
7.708
7.703
7.696
7.692
7.485
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7.476
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7.462
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7.429
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3.369
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2.453
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1.082
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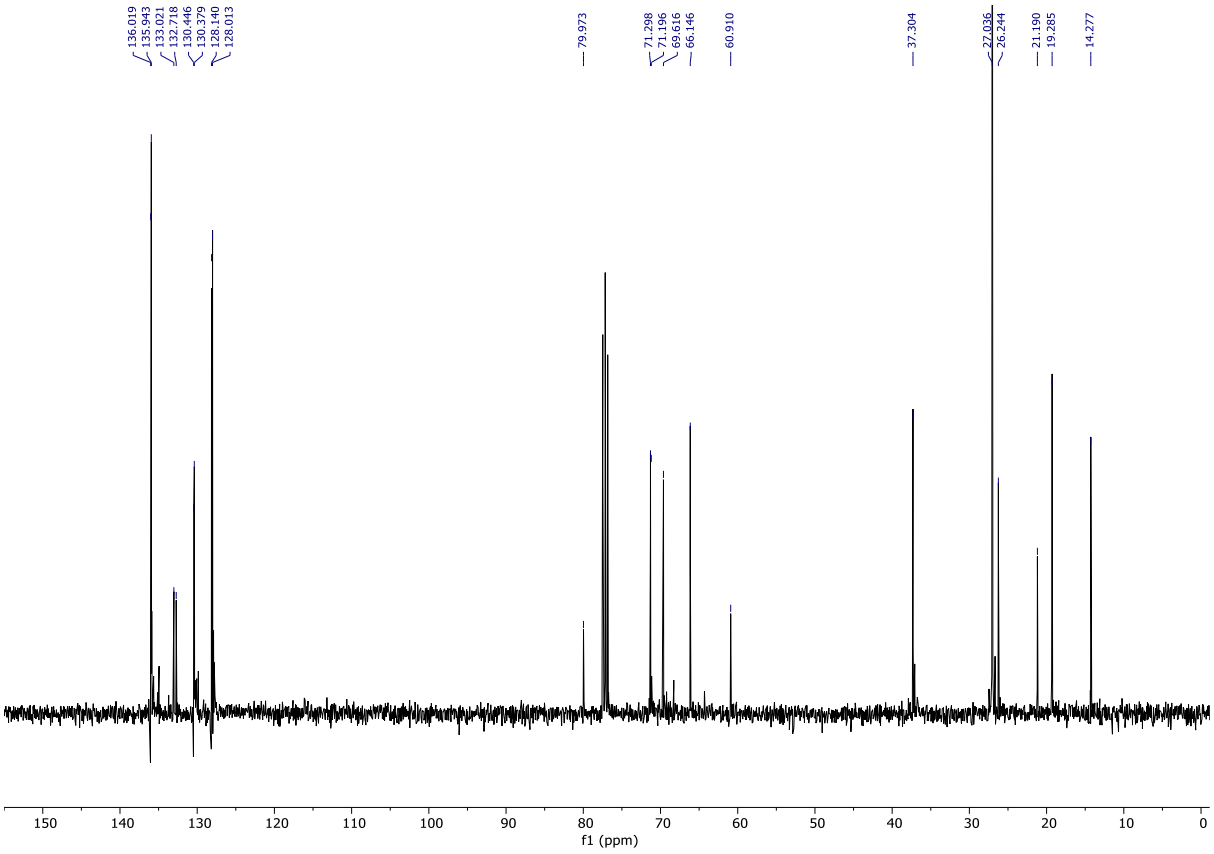
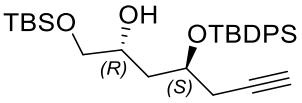
6.37
1.00
1.08
1.02
1.01
1.77
1.08
1.10
1.04
2.09
9.05
f1 (ppm)


136.019
135.943
133.021
132.718
130.446
130.379
128.140
128.013
79.973
71.298
71.196
69.616
66.146
60.910
37.304
27.036
26.244
21.190
19.285
14.277
f1 (ppm)

*(6R,8S)-2,2,3,3,11,11-hexamethyl-10,10-diphenyl-8-(prop-2-yn-1-yl)-4,9-dioxa-3,10-disiladodecan-6-ol ((R,S)-**4**)*



In a flame-dried round bottom flask charged with a stirring bar, a solution of (R,S)-**66** (3.90 g, 10.19 mmol, 1.00 equiv.) in DCM (102 ml, c=0.1 M) was prepared under Argon atmosphere and cooled to 0 °C. Then, imidazole (0.73 g, 10.70 mmol, 1.05 equiv.) and TBSCl (1.11 g, 10.19 mmol, 1.00 equiv.) were added at 0 °C. Then, the reaction was stirred at room temperature for 130 min. The reaction was not proceeding after a certain point, SM remained there, which was verified by TLC. However, the reaction mixture was quenched with aq. sat. NH_4Cl (70 ml) and extracted with EtOAc (3 x 50 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (hexane/EtOAc 100/1) because it is very difficult to separate the product from TBSOH (had to do 3 columns) affording the secondary alcohol (R,S)-**4** (3.2 g, 63 % (92 % brsm) + SM back (1.23 g, 32 %)) as colorless oil in fractions 7-21.

Yield: 3.2 g, 63 % (92 % brsm);

R_f = 0.7875 (EA:Hex=1:2), CPS staining;

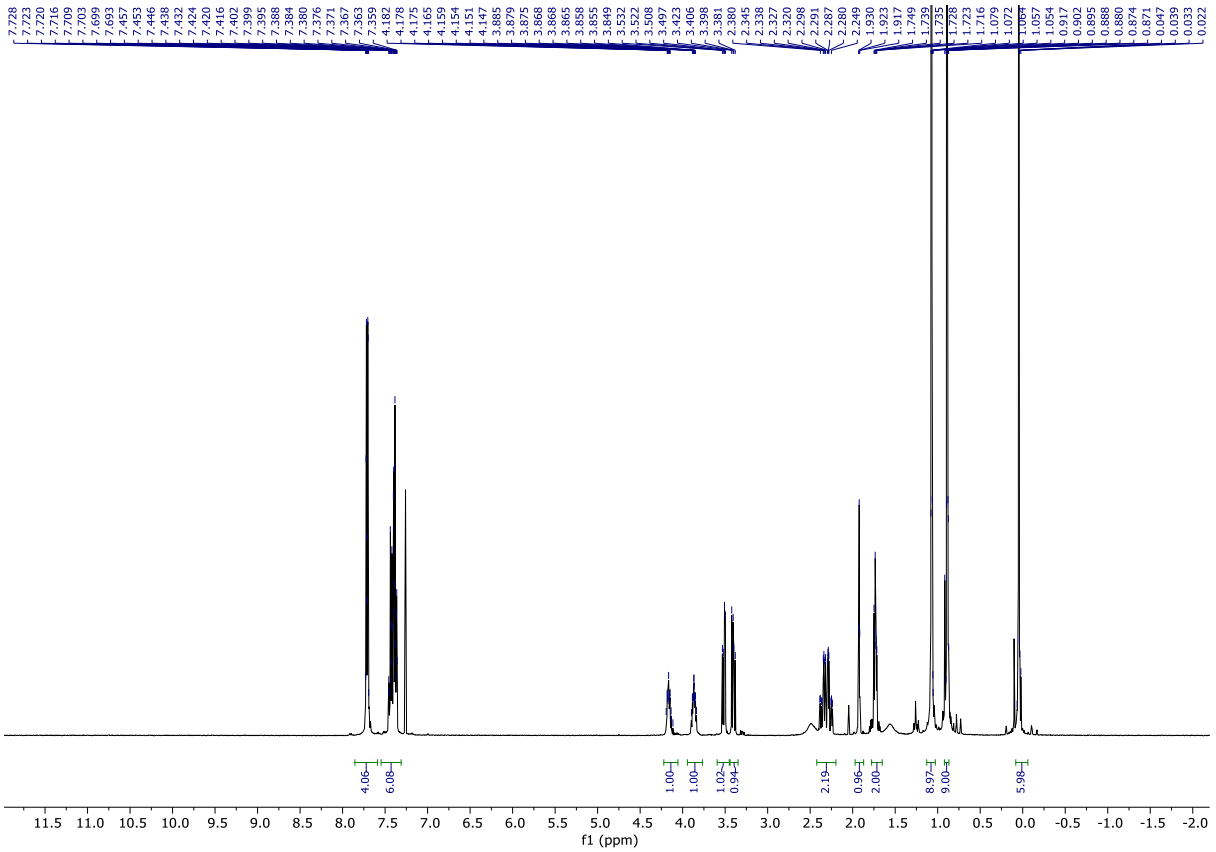
$[\alpha]_{20}^{D}$: = +17.0 (c = 1.0; $CHCl_3$, 20°C);

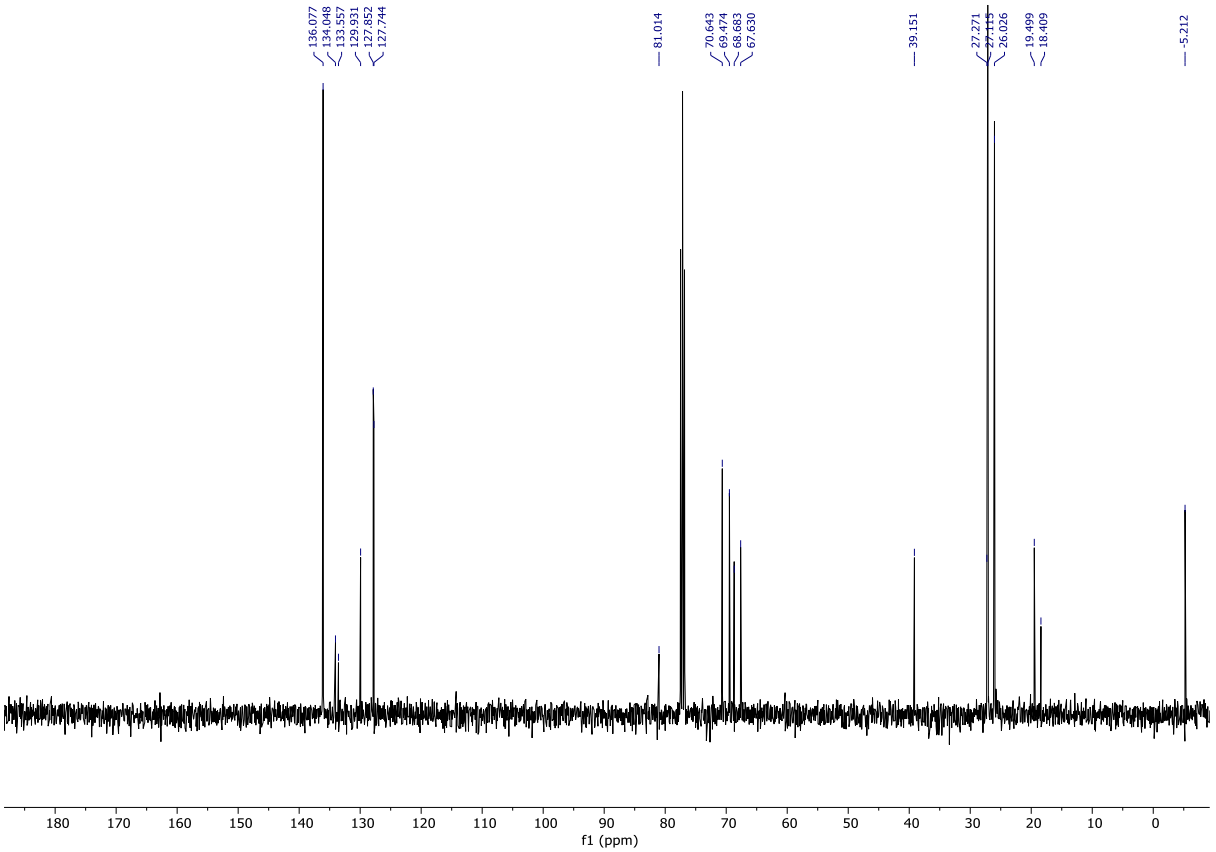
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94 – 7.55 (m, 4H), 7.53 – 7.30 (m, 6H), 4.36 – 4.06 (m, 1H), 3.96 – 3.75 (m, 1H), 3.51 (dd, J = 9.9, 4.3 Hz, 1H), 3.40 (dd, J = 9.9, 6.8 Hz, 1H), 2.45 – 2.19 (m, 2H), 1.92 (t, J = 2.6 Hz, 1H), 1.73 (td, J = 5.1, 4.5, 3.2 Hz, 2H), 1.07 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 136.1, 134.1, 133.6, 129.9, 127.9, 127.7, 81.0, 70.6, 69.5, 68.7, 67.6, 39.2, 27.3, 27.1, 26.0, 19.5, 18.4, -5.2;

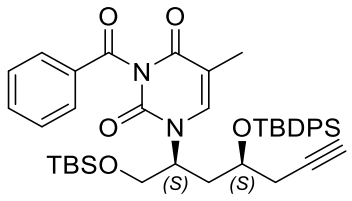
IR (film): ν = 3424, 3311, 2954, 2930, 2857, 2366, 1472, 1428, 1390, 1362, 1255, 1110, 1007, 938, 837, 822, 779, 740, 703, 622, 612, 516, 508;

HRMS (ESI-TOF) m/z calcd. for $C_{29}H_{44}NaO_3Si_2$ $[M+Na]^+$ 519.2721, found 519.2722.


7.728
7.723
7.720
7.716
7.709
7.703
7.699
7.693
7.457
7.453
7.446
7.438
7.432
7.424
7.420
7.416
7.402
7.399
7.395
7.388
7.384
7.380
7.376
7.371
7.367
7.363
7.359
4.182
4.178
4.175
4.165
4.159
4.154
4.151
4.147
3.885
3.879
3.875
3.868
3.868
3.865
3.858
3.855
3.849
3.532
3.522
3.508
3.497
3.423
3.406
3.398
3.381
2.380
2.345
2.338
2.327
2.320
2.298
2.291
2.287
2.280
2.249
1.930
1.923
1.917
1.749
1.739
1.735
1.728
1.723
1.716
1.079
1.072
1.064
1.057
1.054
0.917
0.902
0.895
0.888
0.880
0.874
0.871
0.047
0.039
0.033
0.022
4.06
6.08
1.00
1.00
1.02
0.94
2.19
0.96
2.00
8.97
9.00
5.98
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0
f1 (ppm)


136.077
134.048
133.557
129.931
127.852
127.744
81.014
70.643
69.474
68.683
67.630
39.151
27.271
27.115
26.026
19.499
18.409
-5.212
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

*3-benzoyl-1-((6S,8S)-2,2,3,3,11,11-hexamethyl-10,10-diphenyl-8-(prop-2-yn-1-yl)-4,9-dioxa-3,10-disiladodecan-6-yl)-5-methylpyrimidine-2,4(1H,3H)-dione ((S,S)-**69**)*



In flame-dried glassware, under an argon atmosphere, a solution of alcohol (R,S)-**4** (400 mg, 14.22 mmol, 1.00 equiv.) in dioxane (100.0 ml) was prepared at room temperature. Then, the reagents were added in the following order: the thymine moiety **68** (291.6 mg, 1.27 mmol, 1.18 equiv.), PPh_3 (309.7 mg, 1.18 mmol, 1.10 equiv.), and DEAD (very slowly, dropwise, 0.202 ml, 1.29 mmol, 1.20 equiv.), and the reaction was stirred for at room temperature for 18 h. After completion of the reaction, verified by TLC, the reaction was concentrated under reduced pressure. The crude material was purified by FC (hexane/EtOAc 10/1) affording the compound alcohol (S,S)-**69** in 540 mg (71 %) yield as a colorless oil.

Yield: 540 mg, 71 % (2.2 g scale: 2.33 g, 56 %);

R_f = 0.363 (EA:Hexane = 1:2), CPS staining;

α_D^{20}: -10.47 (c = 1.05, $CHCl_3$, 20°C);

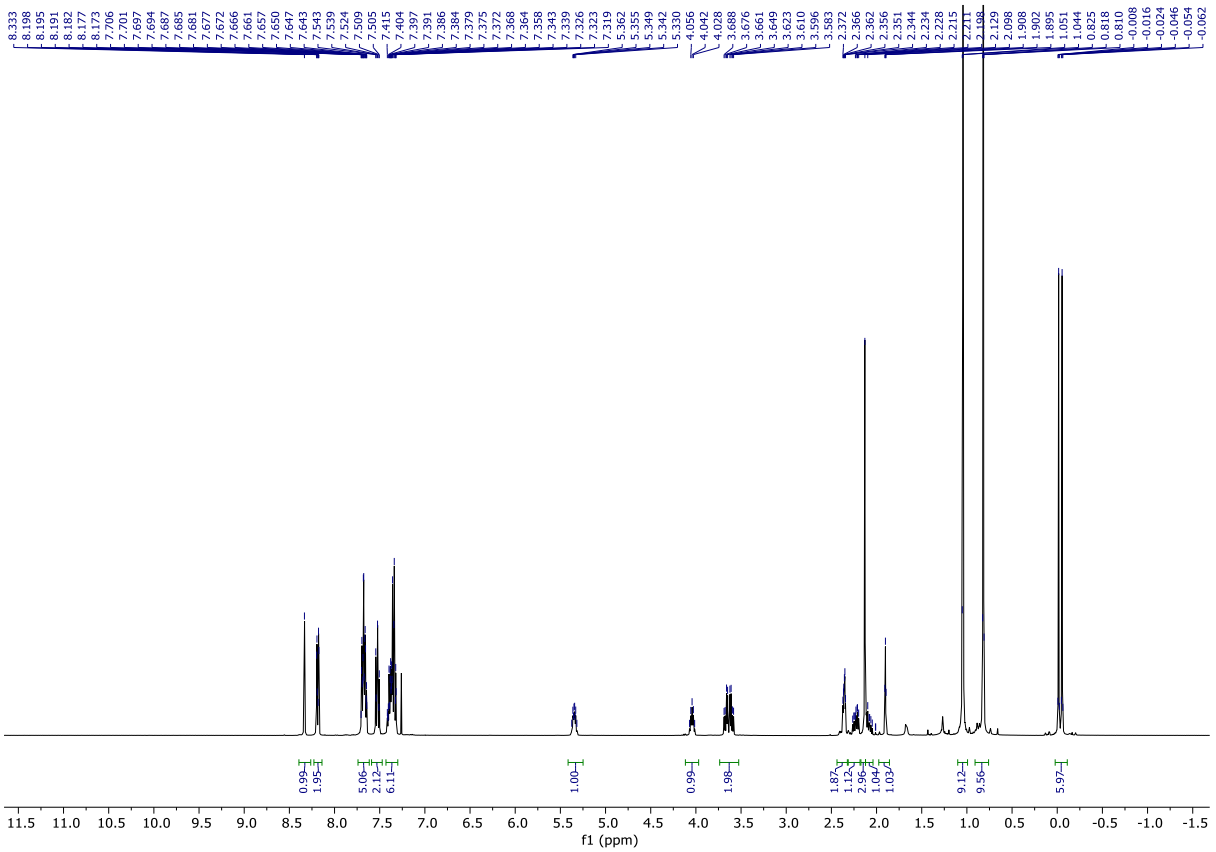
$[\alpha]\frac{D}{20}$: = -7.0 (c = 1.0; $CHCl_3$, 20°C);

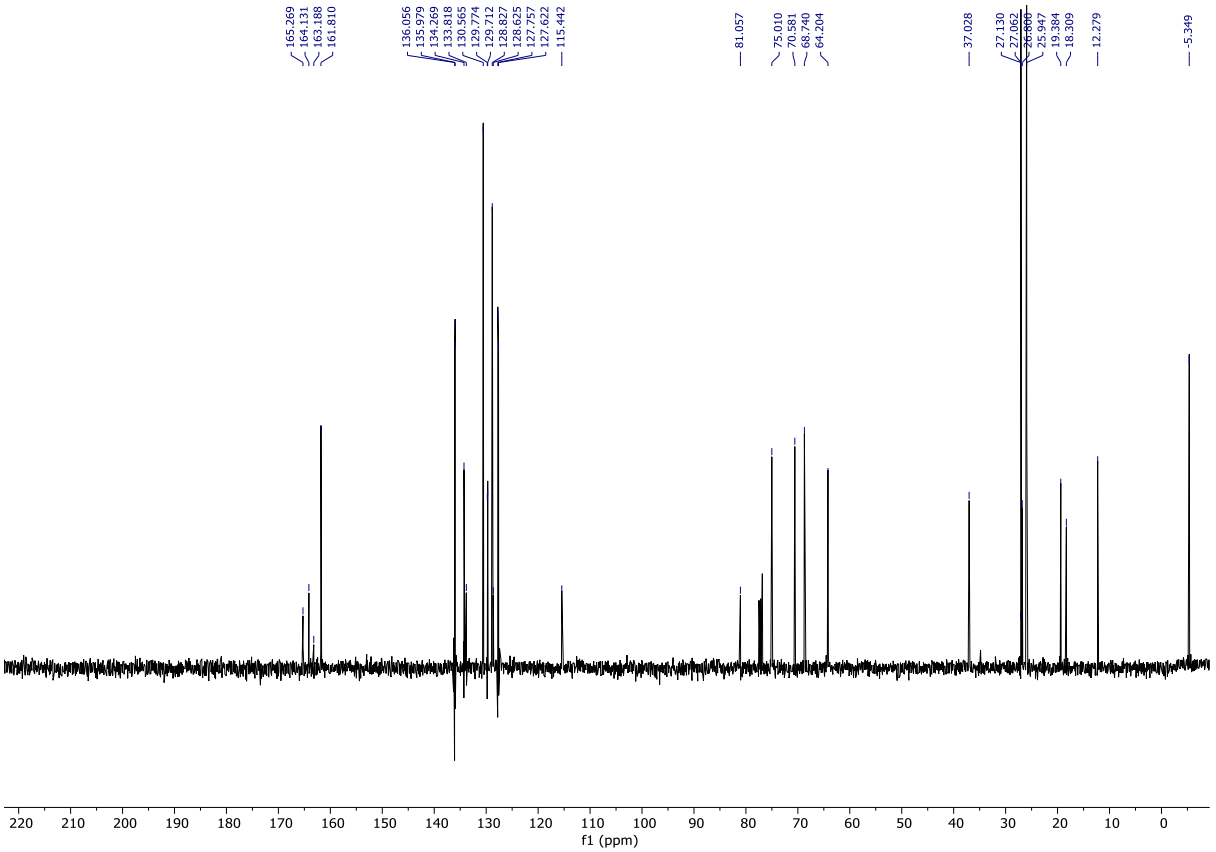
^{1}H NMR (400 MHz, Chloroform-d) δ 8.33 (s, 1H), 8.25 – 8.08 (m, 2H), 7.82 – 7.59 (m, 5H), 7.58 – 7.46 (m, 2H), 7.45 – 7.28 (m, 6H), 5.35 (dq, J = 7.8, 5.0 Hz, 1H), 4.04 (p, J = 5.5 Hz, 1H), 3.80 – 3.48 (m, 2H), 2.41 – 2.32 (m, 2H), 2.23 (ddd, J = 14.2, 6.8, 5.2 Hz, 1H), 2.13 (s, 3H), 2.11 – 1.99 (m, 1H), 1.90 (t, J = 2.6 Hz, 1H), 1.04 (s, 9H), 0.82 (s, 9H), -0.02 (s, 3H), -0.05 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-d) δ 165.3, 164.1, 161.8, 136.0 (d, J = 7.7 Hz), 134.3, 133.8, 130.6, 129.7 (d, J = 6.2 Hz), 128.8, 128.6, 127.8, 127.6, 115.4, 81.1, 75.0, 70.6, 68.7, 64.2, 37.0, 27.13, 27.1, 26.8, 26.0, 19.4, 18.3, 12.3, -5.4;

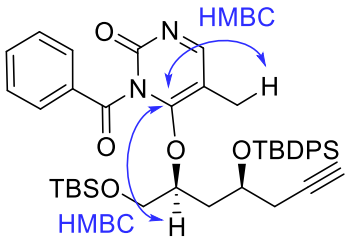
IR (film): ν = 3310, 3071, 2954, 2929, 2895, 2857, 1749, 1698, 1655, 1600, 1557, 1471, 1462, 1429, 1389, 1364, 1308, 1289, 1255, 1178, 1156, 1106, 1048, 1002, 981, 938, 909, 834, 779, 739, 704, 687, 667, 641, 613, 553, 505.

HRMS (ESI-TOF) m/z calcd. for $C_{41}H_{53}N_2O_5Si_2$ $[M+H]^+$ 709.3488, found 709.3478.


f1 (ppm)


f1 (ppm)

*1-benzoyl-6-((2,2,3,3,11,11-hexamethyl-10,10-diphenyl-8-(prop-2-yn-1-yl)-4,9-dioxane-3,10-disiladodecan-6-yl)oxy)-5-methyl pyrimidine-2(1H)-one ((S,S-**74**))*



Yield: 5-10 % in each reaction;

R_f = 0.4597 (EA:Hexane = 1:2), CPS staining;

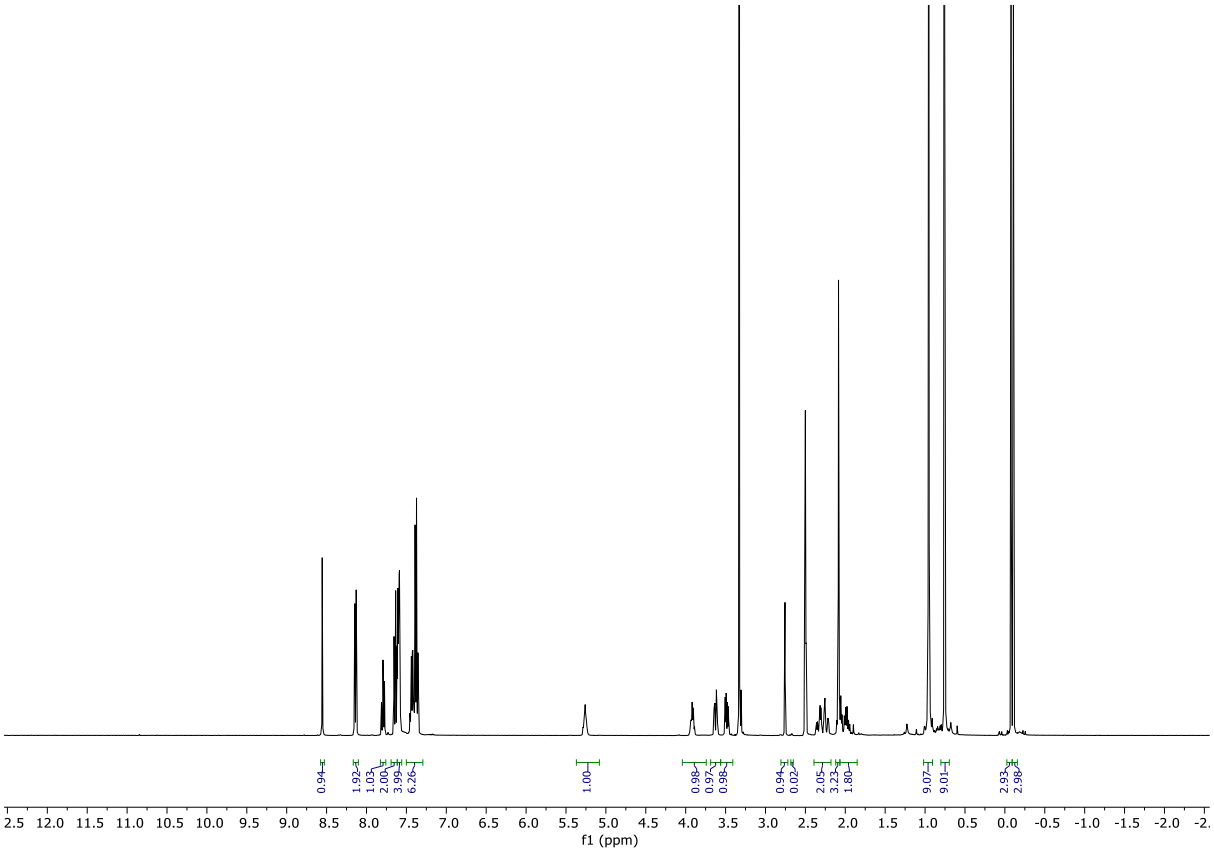
$[\alpha]_{20}^{D}$: = -2.0 (c = 1.0; $CHCl_3$, 20°C);

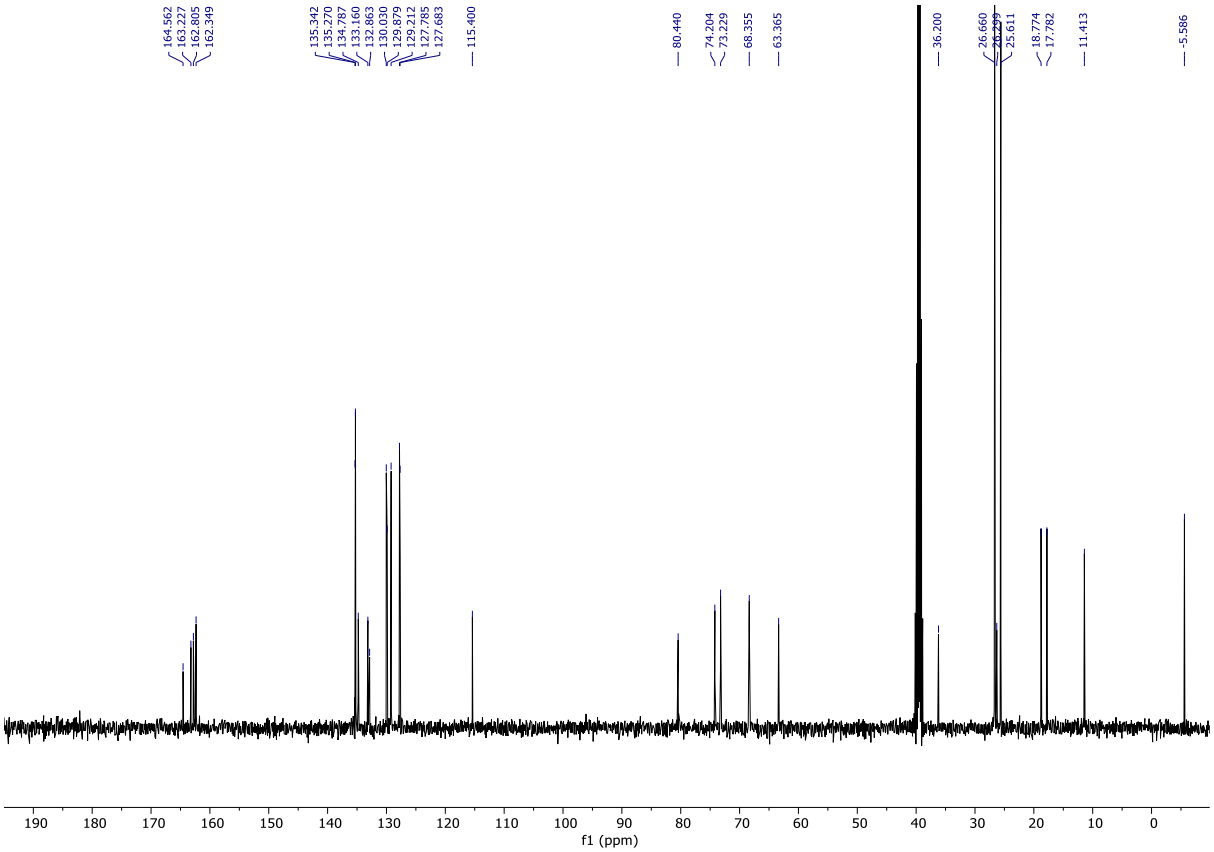
^{1}H NMR (400 MHz, DMSO-d6) δ 8.55 (d, J = 0.8 Hz, 1H), 8.23 – 8.06 (m, 2H), 7.84 – 7.74 (m, 2H), 7.70 – 7.54 (m, 4H), 7.52 – 7.28 (m, 6H), 5.26 (p, J = 5.0 Hz, 1H), 4.04 – 3.79 (m, 1H), 3.62 (dd, J = 11.2, 3.8 Hz, 1H), 3.48 (dd, J = 11.2, 4.9 Hz, 1H), 2.76 (t, J = 2.5 Hz, 1H), 2.41 – 2.16 (m, 2H), 2.08 (s, 3H), 2.06 – 1.86 (m, 2H), 0.95 (s, 9H), 0.76 (s, 9H), -0.08 (s, 3H), -0.11 (s, 3H);

^{13}C NMR (101 MHz, DMSO-d6) δ 164.6, 163.2, 162.8, 162.4, 135.3, 135.3, 134.8, 133.2, 132.9, 130.0, 129.9, 129.2, 127.8, 127.7, 115.4, 80.4, 74.2, 73.2, 68.4, 63.4, 36.2, 26.7, 26.3, 25.6, 18.8, 17.8, 11.4, -5.6;

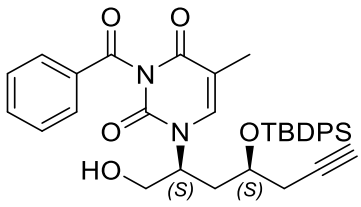
IR (film): ν = 3309, 3071, 2954, 2929, 2894, 2857, 1747, 1612, 1554, 1471, 1462, 1432, 1389, 1362, 1320, 1242, 1216, 1156, 1109, 1077, 1056, 1025, 1002, 973, 938, 836, 779, 740, 703, 637, 611, 505;

HRMS (ESI-TOF) m/z calcd. for $C_{41}H_{53}N_2O_5Si_2$ $[M+H]^+$ 709.3488, found 709.3496.


0.94
1.92
1.03
2.00
3.99
6.26
1.00
0.98
0.97
0.98
0.94
0.02
2.05
3.23
1.80
9.07
9.01
2.93
2.98
f1 (ppm)


164.562
163.227
162.805
162.349
135.342
135.270
134.787
133.160
132.863
130.030
129.879
129.212
127.785
127.683
115.400
80.440
74.204
73.229
68.355
63.365
36.200
26.660
26.239
25.611
18.774
17.782
11.413
-5.586
f1 (ppm)

*3-benzoyl-1-((2S,4S)-4-((tert-butyldiphenylsilyl)oxy)-1-hydroxyhept-6-yn-2-yl)-5-methyl pyrimidine-2,4(1H,3H)-dione ((S,S-**70**))*



In a flame-dried 100 ml flask solution of (S,S)-**69** (1.00 g, 1.41 mmol, 1.00 equiv.) in DCM: MeOH 1:1 (28.2 ml, 0.05 M) was prepared under Argon atmosphere at room temperature. Then, the solution was cooled in an ice bath and CSA (138.0 mg, 0.59 mmol, 0.42 equiv.) was added at room temperature. After 7 hours 0.42 equiv of CSA (138.0 mg, 0.59 mmol, 0.42 equiv.) more. After 21 hours quenched with sat. aq. $NaHCO_3$ (10 ml) was added and the layers were separated. The aqueous layer was extracted with EA (3 x 20-30 ml). The combined organic layers were washed with brine (10 ml), dried over $MgSO_4$, and concentrated under reduced pressure. The crude material (840 mg) was purified by 2 cm flash column chromatography (hexane/EtOAc 2/1) to yield (S,S)-**70** (660 mg, 80 %) as a colorless oil.

Yield: 660 mg (80 %), *dr*=20:1;

R_f = 0.37 (1:1 Hexane: EtOAc), CPS staining;

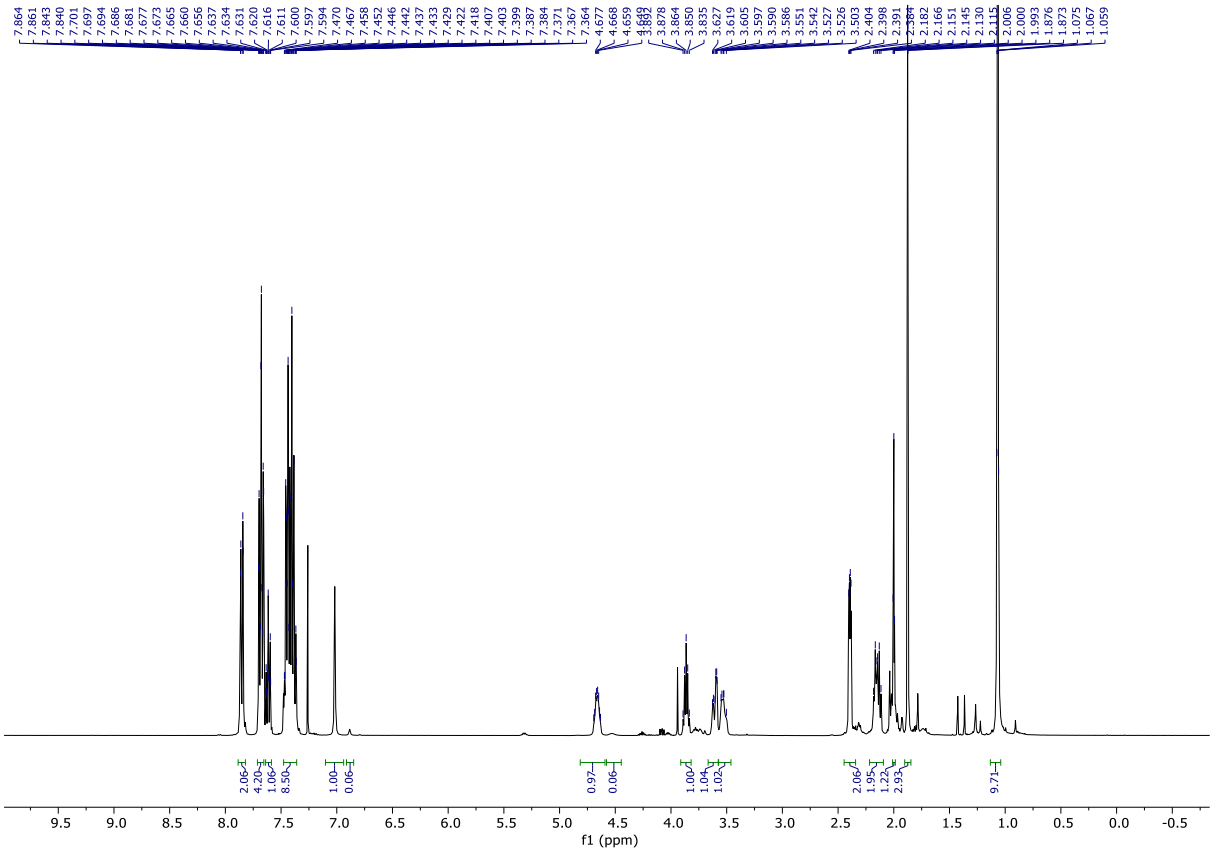
$[\alpha]_{20}^{D}$: = +2.00 (c = 0.5 ; $CHCl_3$, 20°C);

^{1}H NMR (400 MHz, Chloroform-d) δ 7.86 (d, J = 1.2 Hz, 1H), 7.98 – 7.79 (m, 1H), 7.68 (ddt, J = 8.1, 6.6, 1.5 Hz, 4H), 7.66 – 7.57 (m, 1H), 7.49 – 7.33 (m, 8H), 4.66 (dh, J = 6.7, 3.4 Hz, 1H), 3.86 (p, J = 5.7 Hz, 1H), 3.65 – 3.56 (m, 1H), 3.57 – 3.46 (m, 1H), 2.39 (dd, J = 5.6, 2.6 Hz, 2H), 2.15 (dt, J = 14.5, 6.2 Hz, 2H), 2.00 (t, J = 2.6 Hz, 1H), 1.87 (d, J = 1.2 Hz, 3H), 1.07 (s, 9H);

^{13}C NMR (101 MHz, Chloroform-d) δ 169.0, 162.8, 150.4, 138.2, 135.8, 135.0, 133.3, 131.5, 130.4, 130.2, 130.1, 129.2, 127.9, 127.8, 110.5, 80.1, 77.4, 71.3, 68.2, 63.4, 54.2, 35.3, 26.9, 26.2, 19.2, 12.6;

IR (film): ν = 3480, 3303, 2931, 2891, 2858, 1748, 1696, 1649, 1600, 1471, 1461, 1428, 1389, 1365, 1282, 1256, 1179, 1110, 1089, 1029, 1000, 980, 936, 908, 822, 809, 790, 765, 735, 704, 687, 665, 647, 612, 503;

HRMS (ESI-TOF) m/z (ESI) $C_{35}H_{38}N_2NaO_5Si$ $[M+Na]^+$ 617.2442, found 617.2435.


7.864
7.861
7.843
7.840
7.701
7.697
7.694
7.686
7.681
7.677
7.673
7.665
7.660
7.656
7.637
7.634
7.631
7.620
7.616
7.611
7.600
7.597
7.594
7.470
7.467
7.458
7.452
7.446
7.442
7.437
7.433
7.429
7.422
7.418
7.407
7.403
7.399
7.387
7.384
7.371
7.367
7.364
4.677
4.668
4.659
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2.151
2.145
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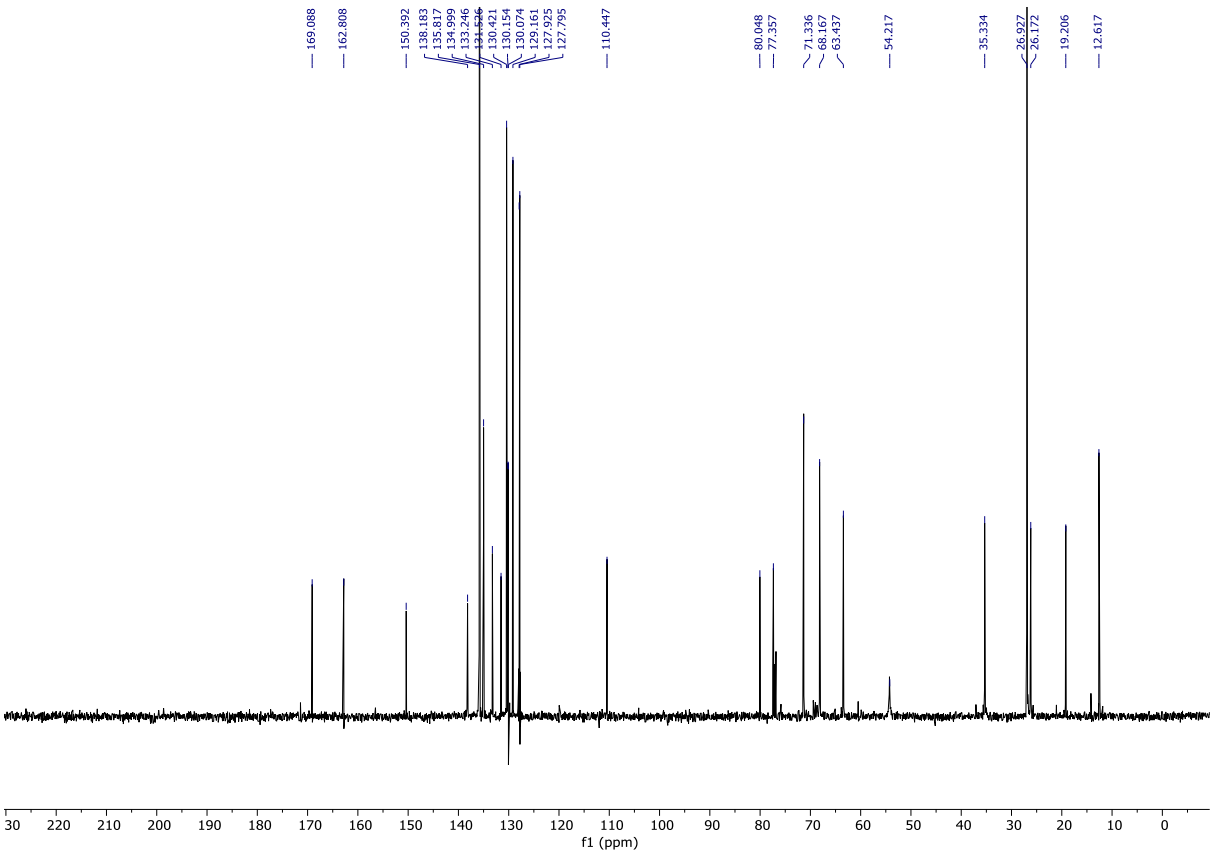
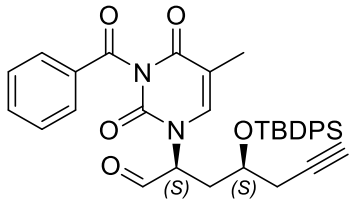
1.993
1.876
1.873
1.075
1.067
1.059
2.06
4.20
1.06
8.50
1.00
0.06
0.97
0.06
1.00
1.04
1.02
2.06
1.95
1.22
2.93
9.71
f1 (ppm)


169.088
162.808
150.392
138.183
135.817
134.999
133.246
131.526
130.421
130.154
130.074
129.161
127.925
127.795
110.447
80.048
77.357
71.336
68.167
63.437
54.217
35.334
26.927
26.172
19.206
12.617
f1 (ppm)

*(2S,4S)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)hept-6-ynal ((S,S-**71**))*



In a flame-dried 100 ml flask, a solution of (S,S)-**70** (0.63 g, 1.51 mmol, 1.00 equiv.) in dry DCM (28.7 ml, c=0.037 M) was prepared under Argon atmosphere at room temperature. Then, DMP (0.67 g, 1.59 mmol, 1.50 equiv.) and $NaHCO_3$ (0.33 g, 3.97 mmol, 3.75 equiv. to neutralize AcOH in DMP and AcOH which is produced in the reaction) were added at room temperature. The reaction was stirred at room temperature for 4 h while being monitored by TLC, MS, and NMR. When the reaction was finished it was diluted with DCM (10 ml) and quenched with 15 ml of DMP quenching solution ($Na_2S_2O_3$ and $NaHCO_3$). The aqueous layer was extracted with DCM (20 ml x 3). The combined organic layers were washed with brine, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure. The crude material (630 mg) was used for the next step as a crude. The aldehyde (S,S)-**71** is decomposing on silica, therefore it is used as a crude for the next step.

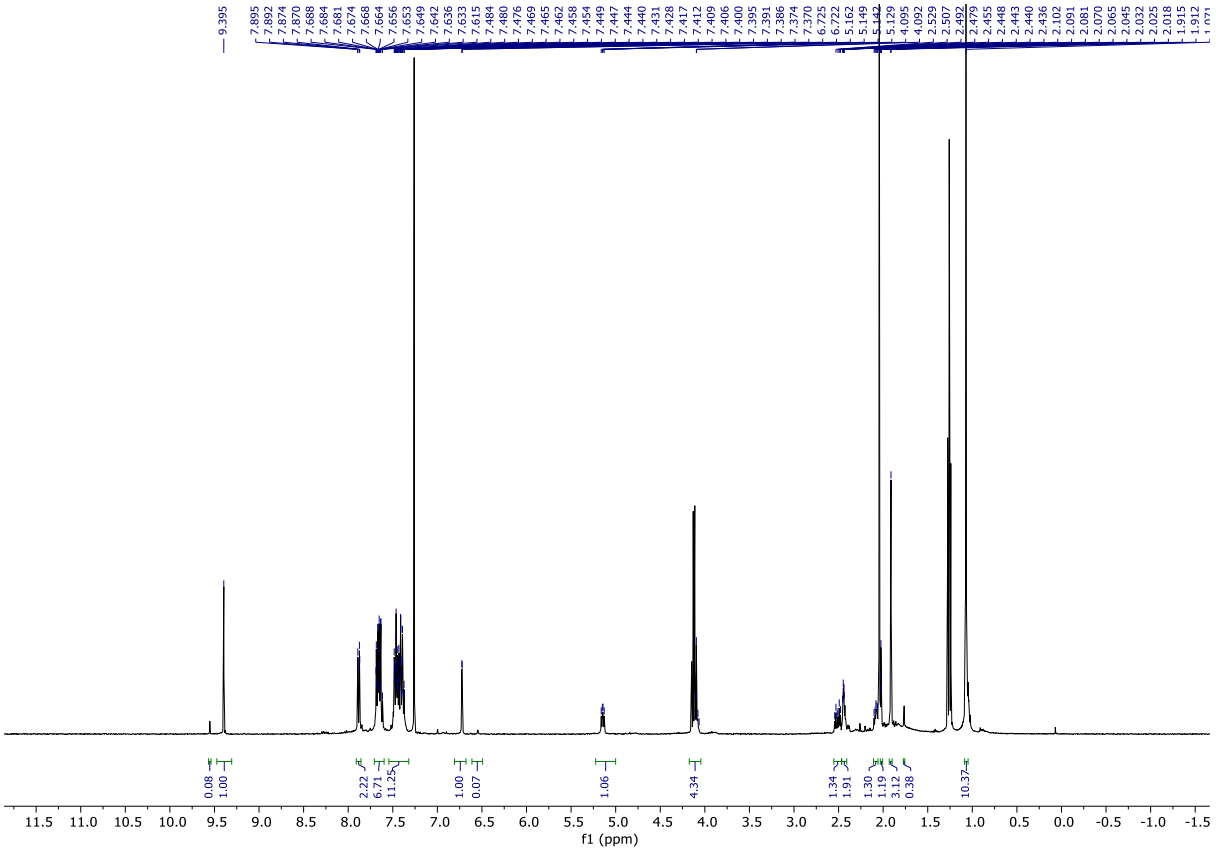
Yield: 630 mg (quant, used as crude for the next step), *dr*=14:1;

R_f = 0.54 (1:1 Hexane: EtOAc), CPS staining;

^{1}H NMR (400 MHz, Chloroform-d) δ 9.40 (s, 1H), 7.88 (dd, J = 8.4, 1.3 Hz, 2H), 7.73 – 7.53 (m, 5H), 7.50 – 7.27 (m, 10H), 6.72 (d, J = 1.3 Hz, 1H), 5.15 (dd, J = 8.2, 5.1 Hz, 1H), 4.10 – 4.05 (m, 1H), 2.51 (dt, J = 14.7, 5.5 Hz, 1H), 2.47 – 2.41 (m, 2H), 2.12 – 2.06 (m, 1H), 2.03 (t, J = 2.7 Hz, 1H), 1.91 (d, J = 1.2 Hz, 3H), 1.07 (s, 9H);

IR (film): ν = 3301, 3071, 2931, 2893, 2858, 1747, 1698, 1656, 1599, 1488, 1472, 1461, 1428, 1385, 1362, 1255, 1229, 1178, 1110, 1025, 1000, 978, 936, 909, 822, 763, 731, 703, 687, 664, 648, 623, 613, 503;

HRMS (ESI-TOF) m/z (ESI) $C_{35}H_{37}N_2NaO_5Si$ $[M+H]^+$ 593.2466, found 593.2457.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7.653
7.649
7.642
7.636
7.633
7.615
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7.480
7.476
7.469
7.465
7.462
7.458
7.454
7.449
7.447
7.444
7.440
7.431
7.428
7.417
7.412
7.409
7.406
7.400
7.395
7.391
7.386
7.374
7.370
6.725
6.722
5.162
5.149
5.142
5.129
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4.092
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2.492
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2.443
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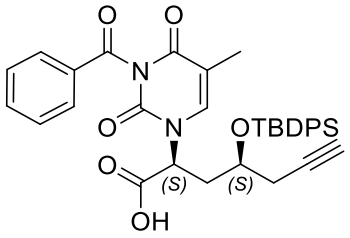
2.436
2.102
2.091
2.081
2.070
2.065
2.045
2.032
2.025
2.018
1.915
1.912
0.08
1.00
2.22
6.71
11.25
1.00
0.07
1.06
4.34
1.34
1.91
1.30
1.19
3.12
0.38
10.37
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

*(2S,4S)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)hept-6-ynoic acid ((S,S-**2**))*



In a flame-dried 50 ml flask solution of crude (S,S)-**71** (0.60 g, 1.01 mmol, 1.0 equiv.) was solubilized in a mixture (1:1) of t-BuOH (11.9 ml, c=0.085 M) and 2-methyl-butene (11.9 ml, c=0.085 M) at 0 °C (solution A). Meanwhile, in a separate flask, a solution of $NaClO_2$ (80%, 0.293(*100/80=0.366 mg), 3.24 mmol, 3.2 equiv.) and NaH_2PO_4 dihydrate (0.63 g, 4.05 mmol, 4.0 equiv.) in water (8.10 ml, c=0.500 M) was prepared (solution B). Then, solution B was added to solution A dropwise at 0°C. The reaction was stirred for 3 h while slowly allowing it to go from 0 ˚C to room temperature. Once the reaction was completed by TLC, the reaction was diluted with DCM (10.0 ml) and brine (10.0 ml), extracted three times with DCM (15.0 ml), washed with HCl aq., dried over $MgSO_4$, and concentrated under reduced pressure. The crude material (m=1.01 g) was columned by a 5 cm column with an eluent (hex:ea=5:1), slowly going to pure ethyl acetate, then ethyl acetate with 1% AcOH. (S,S)-**2** is a shiny and fluffy material.

Yield: 370 mg (60 %), dr=10:1;

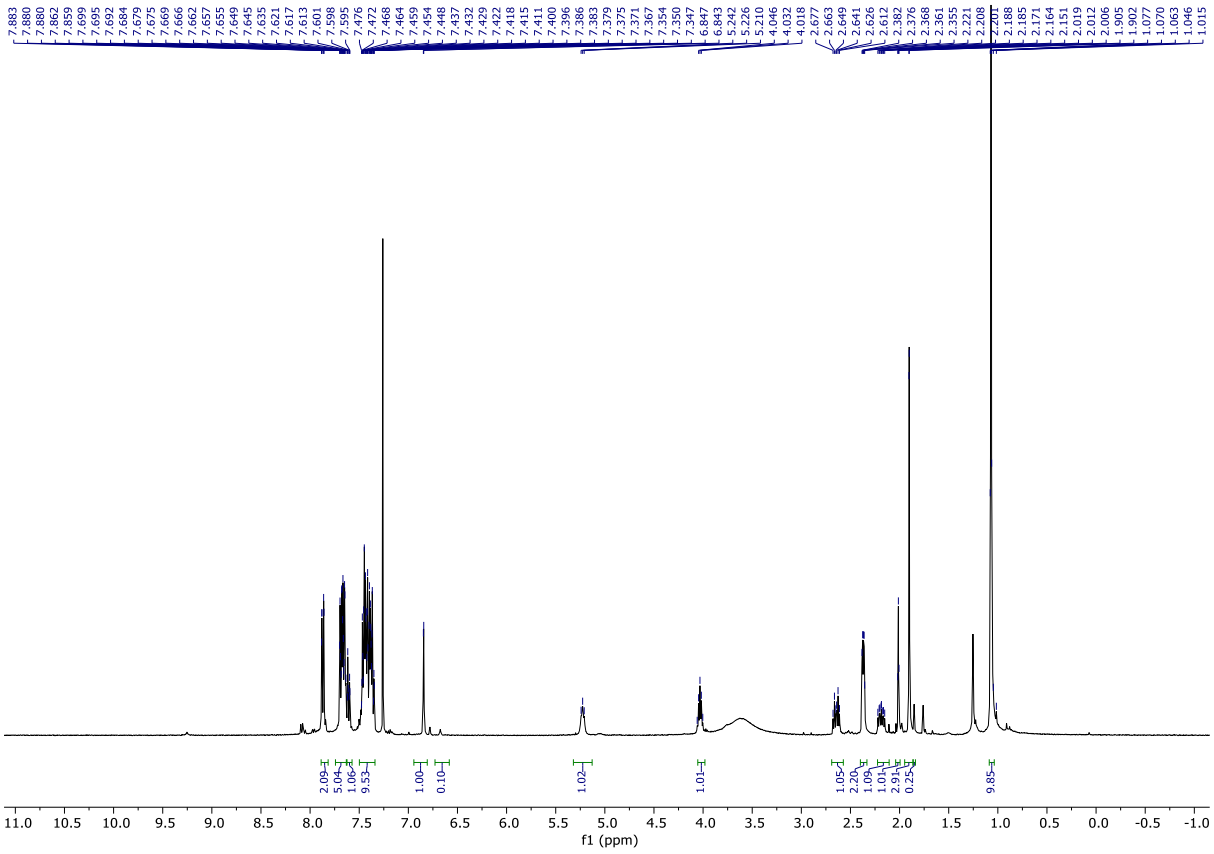
R_f = 0.0219 (EtOAc+1 % AcOH), CPS staining;

$[\alpha]_{20}^{D}$: = -4.00 (c = 0.5; $CHCl_3$, 20°C);

^{1}H NMR (400 MHz, Chloroform-d) δ 7.91 – 7.84 (m, 2H), 7.67 (ddt, J = 11.9, 6.6, 1.5 Hz, 4H), 7.66 – 7.57 (m, 1H), 7.50 – 7.30 (m, 8H), 6.85 (d, J = 1.4 Hz, 1H), 5.23 (t, J = 6.3 Hz, 1H), 4.03 (p, J = 5.8 Hz, 1H), 2.64 (dt, J = 14.6, 5.8 Hz, 1H), 2.37 (dd, J = 6.0, 2.7 Hz, 2H), 2.19 (ddd, J = 14.7, 8.0, 5.2 Hz, 1H), 2.01 (t, J = 2.5 Hz, 1H), 1.90 (d, J = 1.2 Hz, 3H), 1.07 (s, 9H);

IR (film): v = 3301, 2931, 2857, 1750, 1702, 1659, 1600, 1462, 1429, 1363, 1256, 1228, 1178, 1111, 1000, 977, 938, 910, 848, 822, 763, 737, 704, 686, 637, 611, 549, 507;

HRMS (ESI-TOF) m/z (ESI) $C_{35}H_{36}N_2NaO_6Si$ [M+Na]+ 631.2235 1, found 631.2231.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7.645
7.635
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7.617
7.613
7.601
7.598
7.595
7.476
7.472
7.468
7.464
7.459
7.454
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7.418
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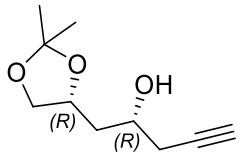
2.171
2.164
2.151
2.019
2.012
2.006
1.905
1.902
1.077
1.070
1.063
1.046
1.015
2.09
5.04
1.06
9.53
1.00
0.10
1.02
1.01
1.05
2.20
1.09
1.01
2.91
0.25
9.85
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

Synthesis toward the acid of (*S,R*)-2

*(R)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-yn-2-ol ((R,R)-**63**)*



Zinc dust (11.34 g, 173.4 mmol, 2.50 equiv.), preactivated with HCL was suspended in 123.0 mL of THF containing 1,2- dibromoethane (1.49 mL, 17.3 mmol, 0.25 equiv.). The suspension was heated to 65 °C for 10 min before cooling to 25 °C. After 45 min, chlorotrimethylsiliane (2.20 mL, 17.34 mmol, 0.25 equiv.) was added dropwise *via a* syringe. It became a sediment from a nice powder. The suspension was stirred vigorously for an additional 30 min and then cooled to -10 °C. Propargyl bromide (80 % in toluene, 13.14 mL, 173.4 mmol, 2.50 equiv.) was added slowly *via* syringe over 20 min. The suspension was stirred for 2.5 h below -12 °C. Then R-**62** was added over 45 min through a cannula to a solution of aldehyde (10.0 g, 69.4 mmol, 1.00 equiv.) in toluene (462.35 mL, c=0.15 M) at -78 °C. The resulting reaction was slowly warmed to -40- (-45) °C and stirred at this temperature overnight from 18:00 to 16:00 the next day. TLC in the evening of setup day It was then warmed to 0 °C and quenched with saturated aqueous NH4Cl solution (100 mL). The mixture was extracted with EtOAc three times and the combined organic fractions were dried over $MgSO_4$, and concentrated under reduced pressure. The residue (dr=1:3 = RR: RS) was purified by slow gradient flash column chromatography (0% → 30% EtOAc/ DCM) to afford homopropargylic alcohol (R,R)-**63** (1.13 g, 21 %) as a colorless oil and its major diastereomer (R,S)-**63** (5.37 g, 42 %) as a pale yellow oil, and a mixture of two diastereomers (ca. 5 g). The combined yield of the product: 6.5 g (63 %), *dr* = 3:1 (based on crude reaction mixture). The residue was purified by slow gradient flash column chromatography (0% → 30% EtOAc/ DCM, the best separation is at 0.5-0.6 % EtOAc in DCM).

Yield: dr=1:3 (RR: RS);

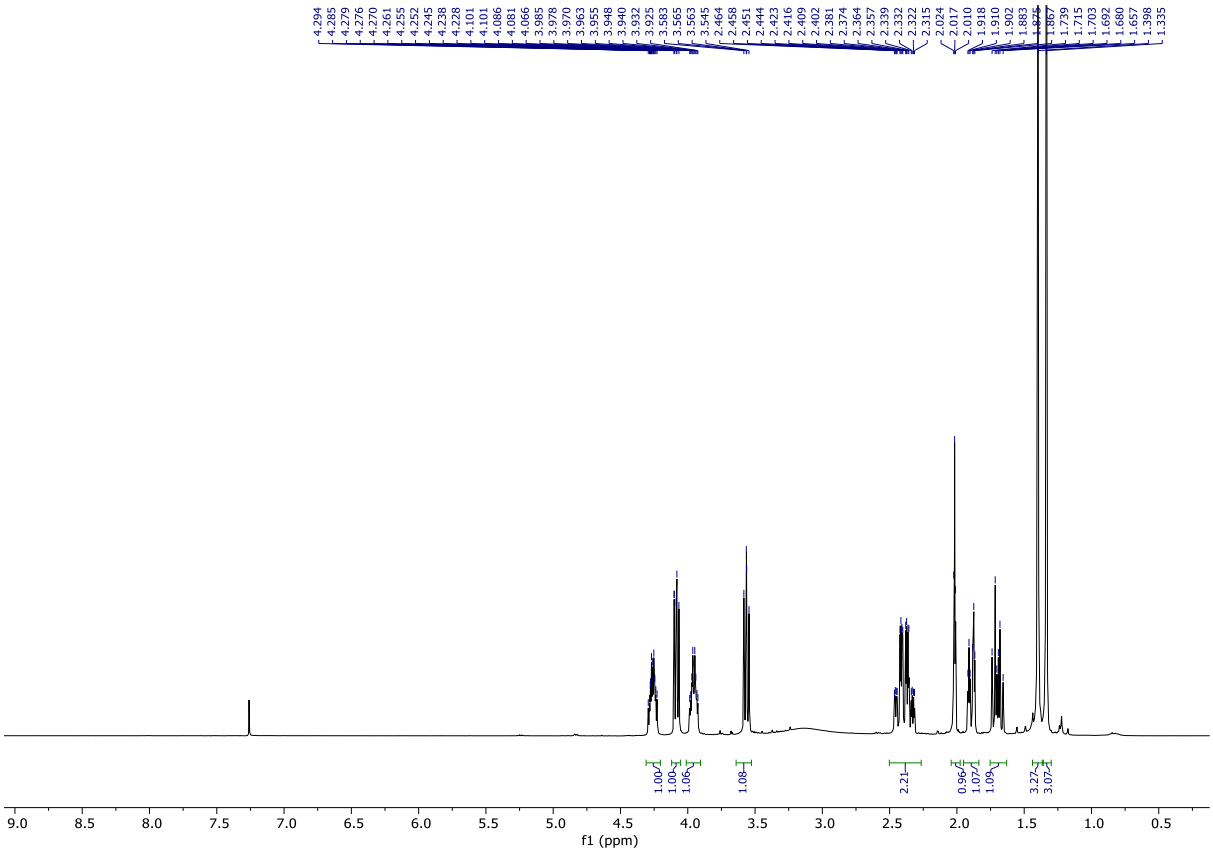
Yield: 1.13 g, 21 %;

R_f = 0.1923 (EA:DCM=1:9), CPS staining;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.26 (dtd, J = 9.5, 6.3, 3.6 Hz, 1H), 4.08 (dd, J = 8.1, 6.0 Hz, 1H), 3.96 (dtd, J = 9.2, 6.2, 2.8 Hz, 1H), 3.56 (dd, J = 8.1, 7.1 Hz, 1H), 2.39 (qdd, J = 16.7, 6.1, 2.7 Hz, 2H), 2.02 (t, J = 2.7 Hz, 1H), 1.89 (dt, J = 14.0, 3.2 Hz, 1H), 1.70 (dt, J = 14.1, 9.3 Hz, 1H), 1.40 (s, 3H), 1.34 (s, 3H);

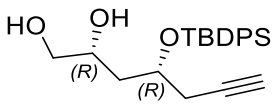
IR (film): ν = 3437, 3289, 2987, 2936, 2879, 1739, 1456, 1432, 1381, 1372, 1216, 1159, 1125, 1064, 988, 864, 839, 791, 645, 517, 502;

HRMS (ESI-TOF) m/z calcd. for $C_{10}H_{16}NaO_3$ $[M+Na]^+$ 207.0992, found 207.0988.



Col4, spot 1, 150 mg

*(2R,4R)-4-((tert-butyldiphenylsilyl)oxy)hept-6-yne-1,2-diol ((R,R)-**66**)*



1st step: In a 250 ml flask a solution of homopropargylic alcohol of (R,R)-**63** (1.43 g, 7.76 mmol., 1.0 equiv.) in DCM (77.62 mL, 0.10 M) was prepared. Then imidazole (1.59 g, 3.0 equiv.) was added, followed by DMAP (94.8 mg, 0.1 equiv.) and tert-butyldiphenylchlorosilane - TBDPSCl (2.98 mL, 1.5 equiv.). The reaction was stirred at room temperature for 14 hours and was quenched by the addition of H_2O (100 ml). The mixture was extracted with DCM for three times and the combined organic fractions were dried over $MgSO_4$, and concentrated under reduced pressure. Crude material (3.5 g, 107 %) was used for the next step without further purification.

2nd step: In a round bottom 500 ml flask a solution of acetonide (R,R)-**57** (3.5 g, 1.0 equiv.) in dichloromethane (172.5 mL, c=0.048 M) trifluoroacetic acid: water = 10:1 mixture (6.34 ml, 10.0 equiv.) at room temperature was added. The reaction mixture was stirred for 3-5 hours until completion. Then concentrated under reduced pressure. The crude residue was purified by flash column 5.5 cm chromatography (3:1 → 1:2 hexanes/EtOAc) to yield diol (R,R)-**66** (1.59 g, 50 % over two steps) as a colorless oil.

Yield: 50 % over 2 steps

R_f = 0.424 (1:1 Hexane:EtOAc)

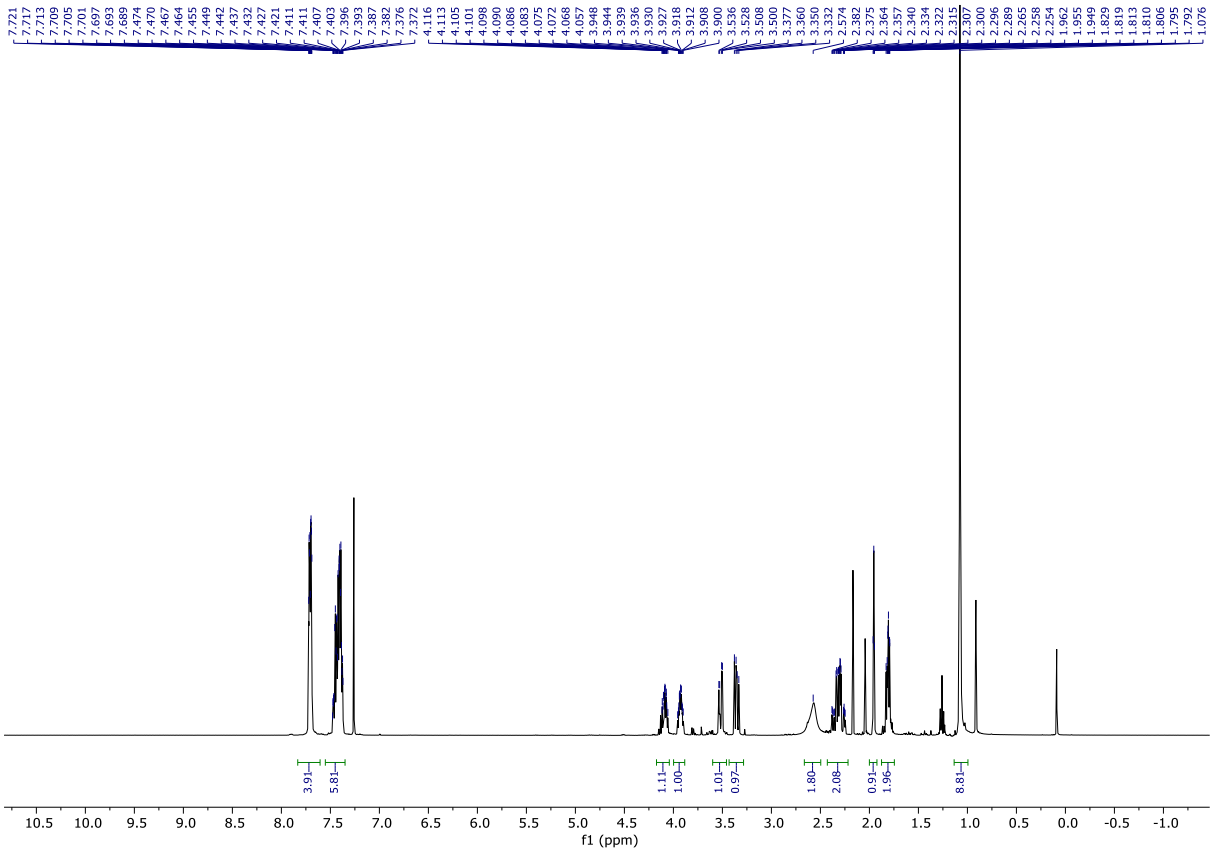
$[\alpha]\frac{D}{20}$: = -31.99 (c = 1.0; $CHCl_3$, 20°C);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (ddd, J = 7.9, 3.2, 1.5 Hz, 4H), 7.41 (dddd, J = 14.2, 9.9, 5.7, 2.1 Hz, 6H), 4.17 – 4.03 (m, 1H), 3.97 – 3.87 (m, 1H), 3.52 (dd, J = 11.2, 3.3 Hz, 1H), 3.35 (dd, J = 11.2, 6.9 Hz, 1H), 2.57 (br.s, 2H), 2.40 – 2.22 (m, 2H), 1.96 (t, J = 2.6 Hz, 1H), 1.86 – 1.77 (m, 2H), 1.08 (s, 9H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 136.0, 135.9, 133.7, 133.3, 130.1, 130.1, 128.0, 127.8, 80.8, 71.0, 70.5, 70.0, 66.9, 39.0, 27.1, 19.3;

IR (film): ν = 3399, 3303, 2931, 2858, 1738, 1712, 1472, 1427, 1391, 1362, 1240, 1222, 1105, 1046, 999, 937, 822, 739, 702, 689, 636, 623, 611, 508;

HRMS (ESI-TOF) m/z calcd. for $C_{23}H_{30}NaO_3Si$ $[M+Na]^+$ 405.1856, found 405.1855.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1.806
1.795
1.792
1.076
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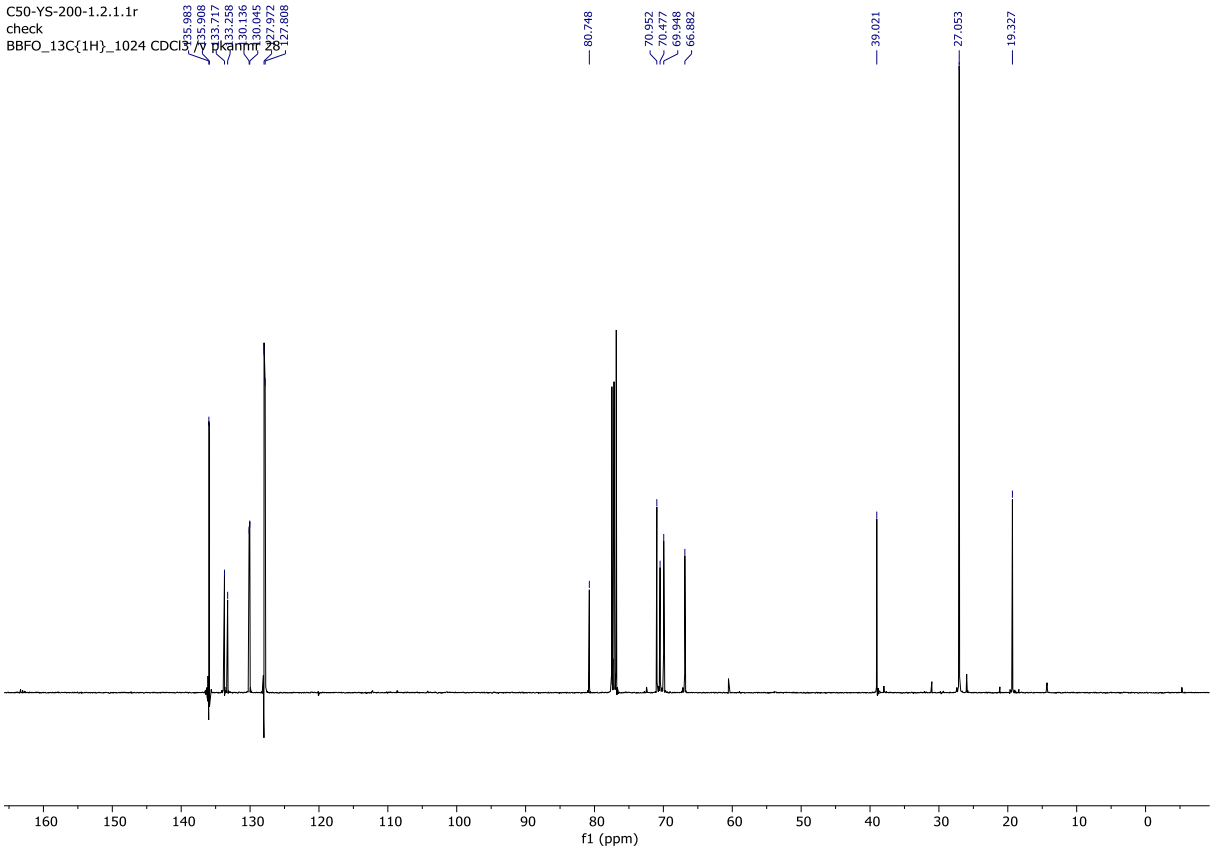
1.01
0.97
1.80
2.08
0.91
1.96
8.81
f1 (ppm)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BBFO_13C{1H}_1024 CDCl3 77 ppmm 28
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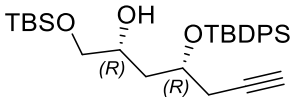
135.908
133.717
133.258
130.136
130.045
127.972
127.808
80.748
70.952
70.477
69.948
66.882
39.021
27.053
19.327
f1 (ppm)

*(6R,8R)-2,2,3,3,11,11-hexamethyl-10,10-diphenyl-8-(prop-2-yn-1-yl)-4,9-dioxa-3,10-disiladodecan-6-ol ((R,R)-**4**)*



To a solution of (R,R)-**66** (0.30 g, 0.78 mmol., 1.00 equiv.) in DCM (7.84 ml, c=0.10 M) were added imidazole (58.7 mg, 0.86 mmol., 1.10 equiv.) and TBSCl (90 mg, 0.82 mmol., 1.05 equiv.) at 0 °C. The reaction was stirred at room temperature for 120 min. The reaction was quenched with aq. sat. NH_4Cl and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (hexane/EtOAc 100/1 to 10:1 to 2:1) affording (R,R)-**4** (250 mg, 64 %) as a colorless oil, and recovered starting material (80 mg, 27 %).

Yield: 250 mg, 64 %, 88 % brsm;

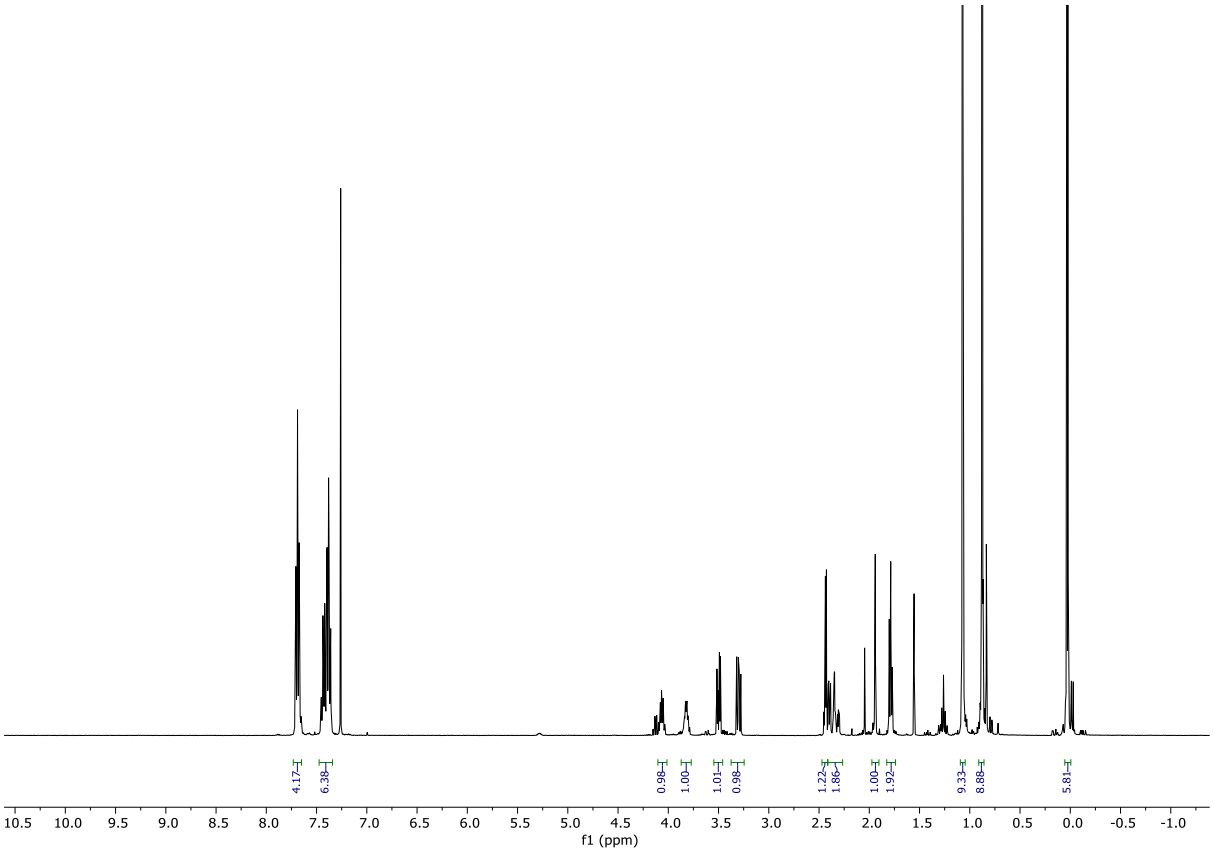
R_f = 0.85 (hexane/EtOAc 1/1), CPS staining;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 (m, 4H), 7.50 – 7.34 (m, 6H), 4.06 (qd, J = 6.0, 4.3 Hz, 1H), 3.87 – 3.76 (m, 1H), 3.50 (dd, J = 10.0, 3.9 Hz, 1H), 3.30 (dd, J = 10.0, 6.5 Hz, 1H), 2.46 – 2.42 (m, 1H), 2.42 – 2.27 (m, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.83 – 1.74 (m, 2H), 1.07 (s, 9H), 0.88 (s, 9H), 0.03 (d, J = 4.3 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 136.1, 136.0, 134.1, 133.8, 130.0, 129.9, 127.9, 127.7, 81.2, 70.5, 69.6, 69.0, 67.1, 38.9, 27.1, 26.7, 26.0, 19.4, 18.4, -5.2;

IR (film): ν = 3311, 3072, 2953, 2930, 2895, 2857, 1472, 1463, 1428, 1390, 1362, 1254, 1223, 1170, 1105, 1007, 984, 938, 836, 823, 778, 739,702, 689, 623, 612, 504;

HRMS (ESI-TOF) m/z calcd. for $C_{29}H_{44}NaO_3Si_2$ $[M+Na]^+$ 519.2721, found 519.2711.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0.98
1.22
1.86
1.00
1.92
9.33
8.88
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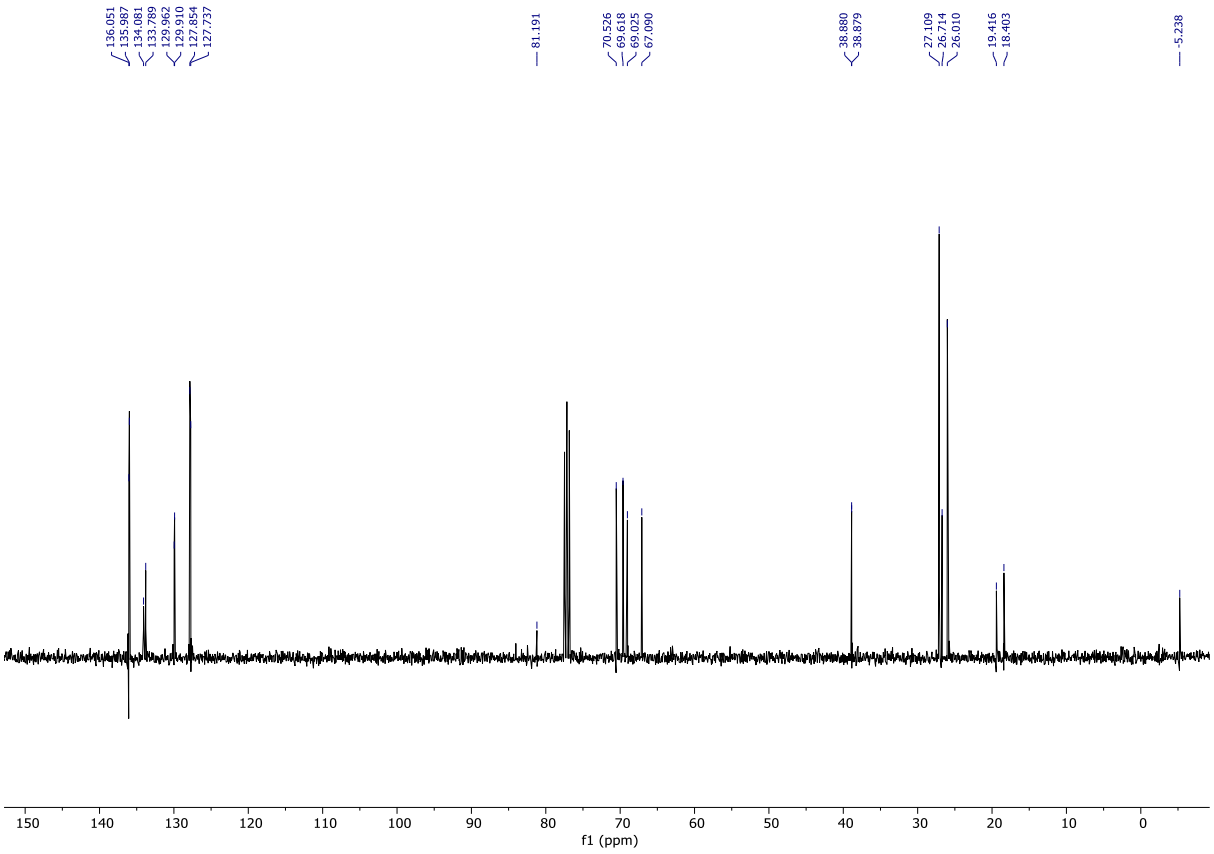
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


136.051
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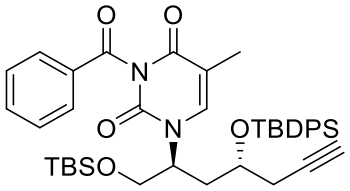
129.962
129.910
127.854
127.737
81.191
70.526
69.618
69.025
67.090
38.880
38.879
27.109
26.714
26.010
19.416
18.403
-5.238
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

*3-benzoyl-1-((6S,8R)-2,2,3,3,11,11-hexamethyl-10,10-diphenyl-8-(prop-2-yn-1-yl)-4,9-dioxa-3,10-disiladodecan-6-yl)-5-methylpyrimidine-2,4(1H,3H)-dione ((S,R)-**69**)*



In a flame-dried glassware, under argon atmosphere a solution of (R,R)-**4** (225 mg, 0.60 mmol, 1.00 equiv.) in dioxane (3.02 ml) was prepared at room temperature. Then, the reagents were added in a following order: thymine moiety **68** (164 mg, 0.71 mmol, 1.18 equiv.), PPh_3 (174.2 mg, 0.72 mmol, 1.10 equiv.), and DEAD (very slowly, dropwise, 0.114 ml, 0.72 mmol, 1.20 equiv.), and the reaction was stirred for at room temperature for 18 h. After completion of the reaction, verified by TLC, the reaction was concentrated under reduced pressure. The crude material was purified by FC (hexane/EtOAc 12/1) affording the compound (S,R)-**69** in 210 mg (49 %) yield as a colourless oil.

Yield: 210 mg, 49 %;

R_f = 0.371 (hexane/EtOAc 5/1), UV-visible, CPS staining;

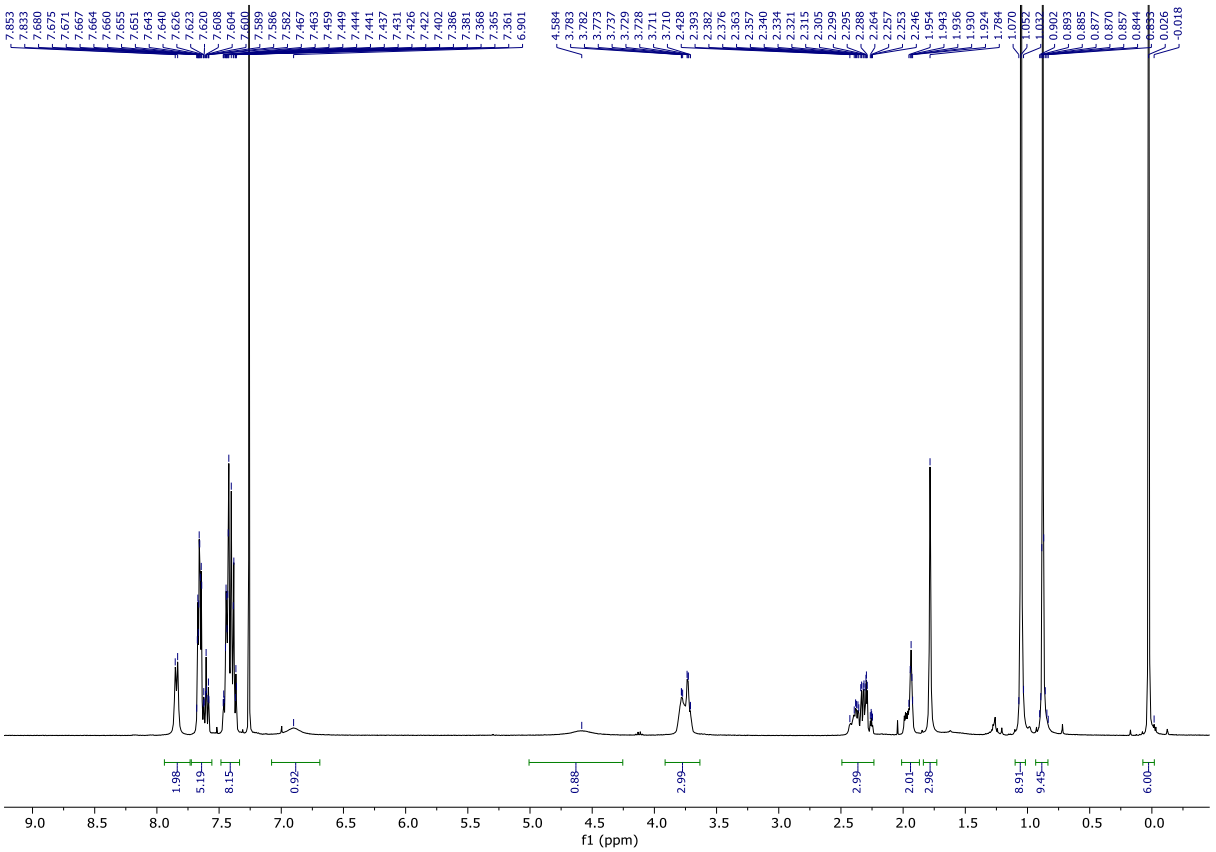
$[\alpha]_{20}^{D}$: = +12.00 (c = 1.0 ; $CHCl_3$, 20°C);

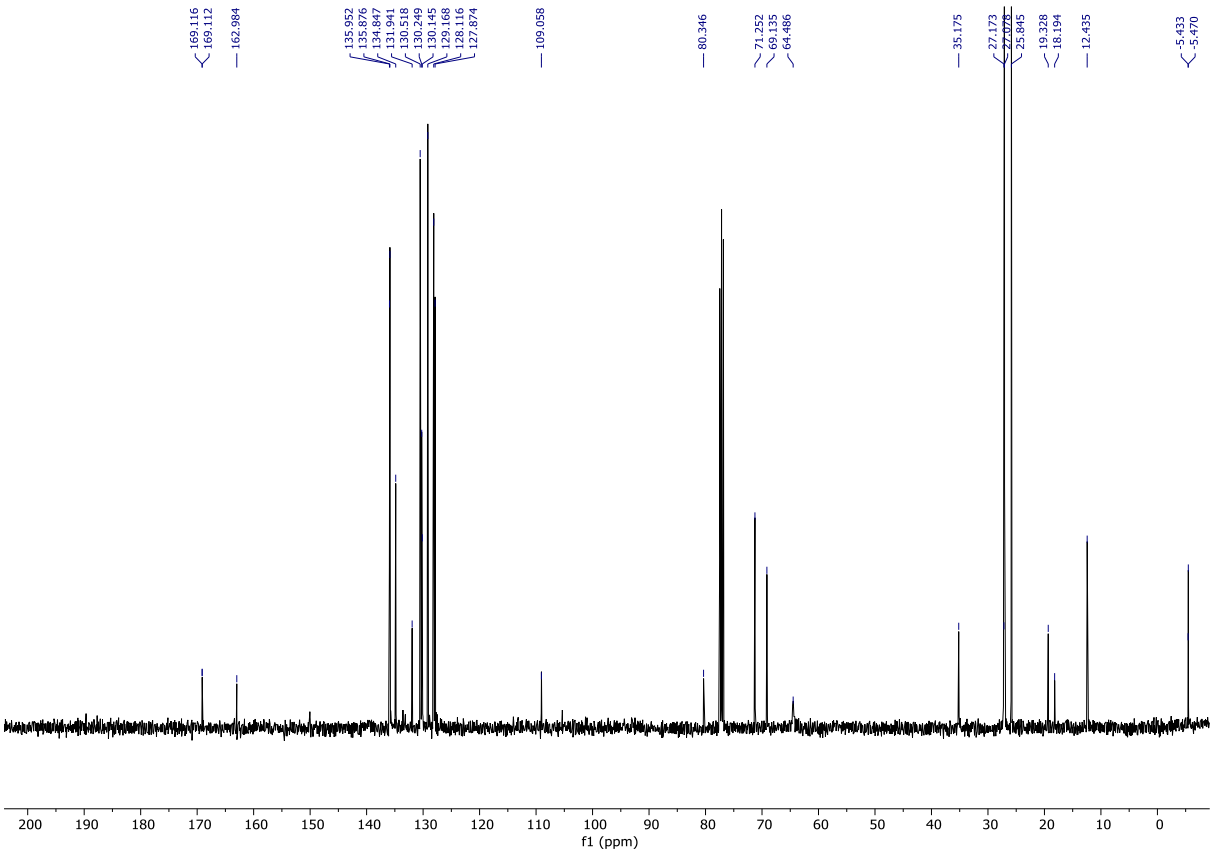
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 (d, J = 7.7 Hz, 2H), 7.69 – 7.53 (m, 5H), 7.49 – 7.29 (m, 8H), 6.87 (s, 1H), 4.56 (s, 1H), 3.86 – 3.74 (m, 1H), 3.74 – 3.63 (m, 2H), 2.29 (dddd, J = 19.5, 16.7, 9.4, 5.6 Hz, 3H), 1.91 (q, J = 3.4, 2.5 Hz, 1H), 1.76 (s, 3H), 1.03 (s, 9H), 0.85 (s, 10H), 0.00 (s, 6H);

^{13}C NMR (101 MHz, Chloroform-d) δ 172.2 – 166.7 (m), 163.0, 136.0, 135.9, 134.9, 131.9, 130.5, 130.25, 130.1, 129.2, 128.1, 127.9, 109.1, 80.4, 71.3, 69.1, 64.5, 35.2, 27.1, 25.9, 19.3, 18.2, 12.4, -5.5 (d, J = 3.7 Hz);

IR (film): ν = 3309, 3072, 2955, 2931, 2858, 1750, 1699, 1654, 1601, 1555, 1472, 1463, 1429, 1408, 1389, 1363, 1311, 1254, 1178, 1157, 1104, 1077, 1061, 1027, 1002, 979, 938, 908, 834, 778, 729, 702, 685, 666, 647, 622, 611;

HRMS (ESI-TOF) m/z calcd. for $C_{41}H_{53}N_2O_5Si_2$ $[M+H]^+$ 709.3488, found 709.3475.


7.853
7.833
7.680
7.675
7.671
7.667
7.664
7.660
7.655
7.651
7.643
7.640
7.626
7.623
7.620
7.608
7.604
7.600
7.589
7.586
7.582
7.467
7.463
7.459
7.449
7.444
7.441
7.437
7.431
7.426
7.422
7.402
7.386
7.381
7.368
7.365
7.361
6.901
4.584
3.783
3.782
3.773
3.737
3.729
3.728
3.711
3.710
2.428
2.393
2.382
2.376
2.363
2.357
2.340
2.334
2.321
2.315
2.305
2.299
2.295
2.288
2.264
2.257
2.253
2.246
1.954
1.943
1.936
1.930
1.924
1.784
1.070
1.052
1.032
0.902
0.893
0.885
0.877
0.870
0.857
0.844
0.833
0.026
-0.018
1.98
5.19
8.15
0.92
0.88
2.99
2.99
2.01
2.98
8.91
9.45
6.00
f1 (ppm)

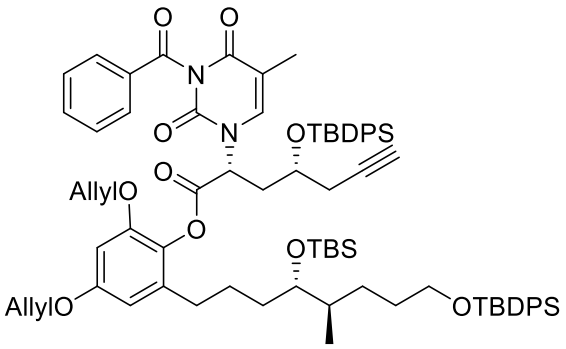

169.116
169.112
162.984
135.952
135.876
134.847
131.941
130.518
130.249
130.145
129.168
128.116
127.874
109.058
80.346
71.252
69.135
64.486
35.175
27.173
27.078
25.845
19.328
18.194
12.435
-5.433
-5.470
f1 (ppm)

5.3 Building block assembly

5.3.1 Macrocyclization via alkynylation approach

5.3.1.1 Synthesis of ynal (*R,R*)-83

*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-((tert-butyldiphenylsilyl)oxy)-5-methyl octyl)phenyl (2R,4R)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)hept-6-ynoate ((R,R)-**85**)*



Important: both starting materials were dried by co-evaporation with toluene on a high vacuum rotary evaporator for several hours+keeping under a high vacuum before starting the reaction. A solution of (R,R)-**2** (850 mg, 1.4 mmol, 1.0 equiv.) in dry DCM (11.64 mL, c=0.12 M) was prepared. Then, the phenol **55** (0.9 g, 1.256 mmol, 0.9 equiv.) was added, followed by DMAP (34.1 mg, 0.28 mmol, 0.2 equiv.). The resulting solution was cooled to 0 °C and stirred for 15 min. And then the DCC (634 mg, 3.1 mmol, 2.20 equiv.) was added. The DCC was not dried this time. The reaction was stirred for 2 hours at 0 °C and then slowly allowed to warm up to room temperature and left overnight. When the reaction was done after 1 day, the rxn mixture was diluted with hexane and filtered off through celite, and concentrated. The crude material (M=2.345 g) was purified via column chromatography (d=5.5 cm) with toluene as an eluent, switching to 50:1 tol: EtOAc, better to keep the ratio of 50:1 until all the desired product is out for better separation. (R,R)-**85** was isolated with the best so far yield (1.5 g, 82 %).

Yield: 1.5 g (82 %), still can see *dr*=10:1;

R_f = 0.102 (50:1 Toluene: EtOAc), CPS staining;

$[\alpha]_{20}^{D}$: = -6.0 (c = 0.5 ; $CHCl_3$, 20°C);

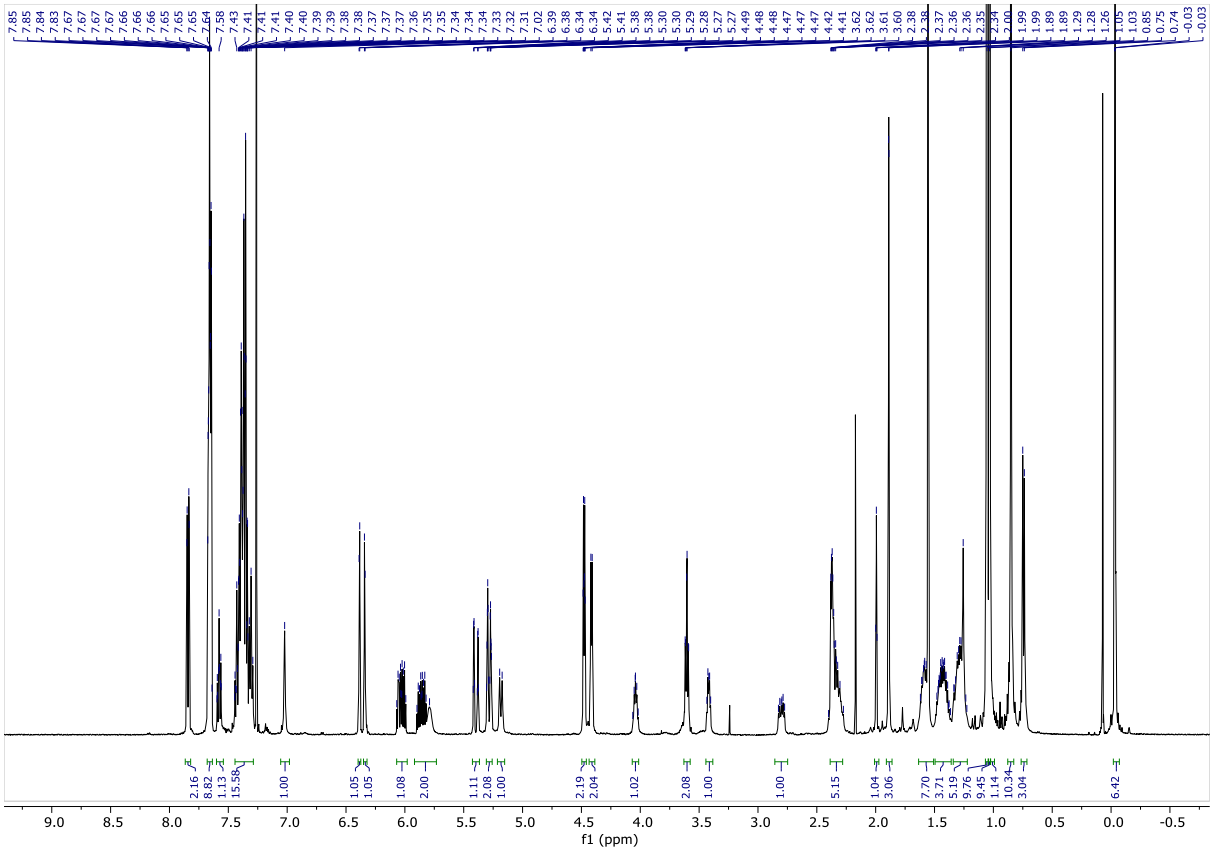
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.84 (dd, J = 8.3, 1.1 Hz, 2H), 7.71 – 7.61 (m, 8H), 7.62 – 7.54 (m, 1H), 7.46 – 7.28 (m, 14H), 7.02 (s, 1H), 6.39 (d, J = 2.7 Hz, 1H), 6.34 (d, J = 2.7 Hz, 1H), 6.03 (ddt, J = 17.3, 10.6, 5.3 Hz, 1H), 5.86 (ddt, J = 17.4, 10.7, 5.4 Hz, 1H), 5.79 (s, 1H), 5.42-5.37 (m, 1H), 5.31 – 5.25 (m, 2H), 5.18 (d, J = 10.5 Hz, 1H), 4.48 (dt, J = 5.3, 1.6 Hz, 2H), 4.41 (d, J = 5.4 Hz, 1H), 4.07 – 4.02 (m, 1H), 3.60 (td, J = 6.6, 1.5 Hz, 2H), 3.42 (dt, *J* = 7.7, 4.3 Hz, 1H), 3.42 – 3.38 (m, 1H), 2.86 – 2.74 (m, 1H), 2.44

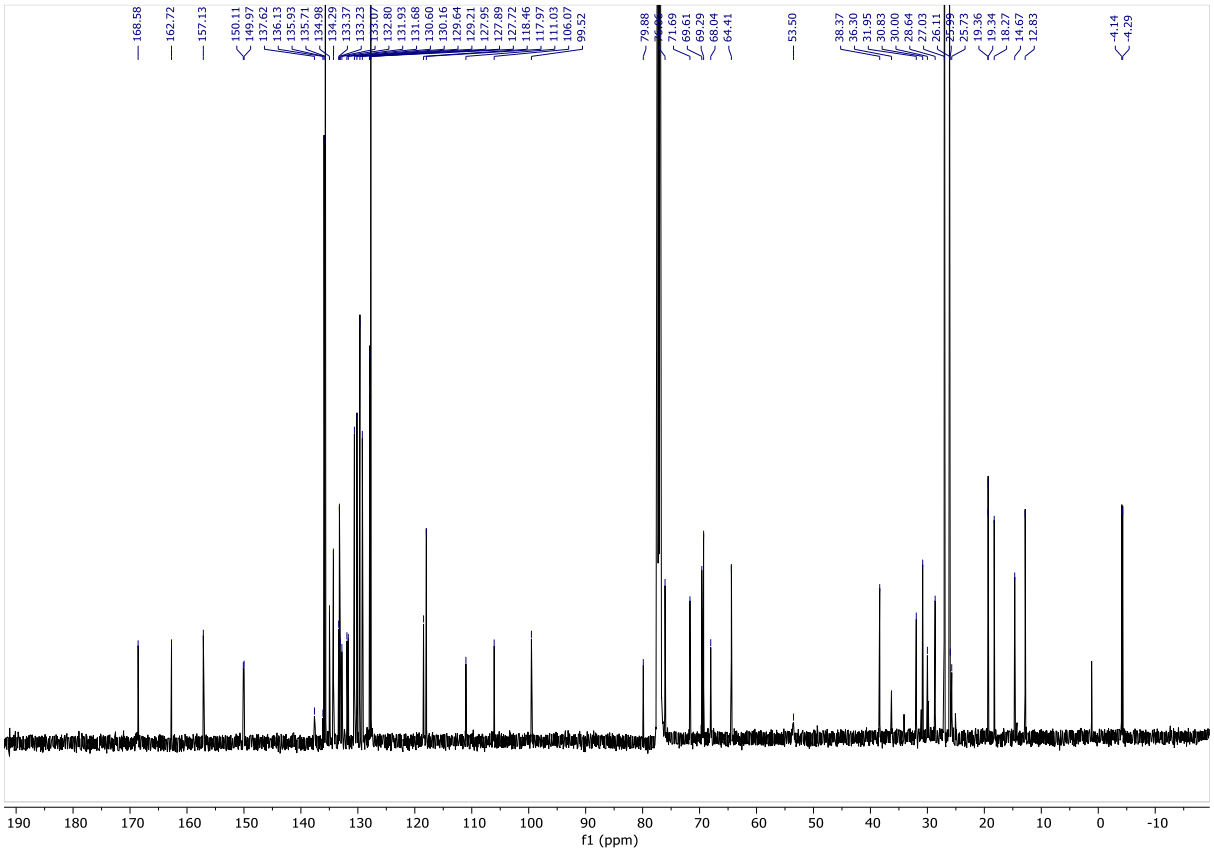
– 2.21 (m, 5H), 1.99 (t, J = 2.7 Hz, 1H), 1.89 (d, J = 1.1 Hz, 3H), 1.64 – 1.56 (m, 2H), 1.51 – 1.36 (m, 3H), 1.36 – 1.20 (m, 3H), 1.05 (s, 9H), 1.03 (s, 9H), 1.02 (m, 1H) 0.85 (s, 9H), 0.74 (d, J = 6.8 Hz, 3H), -0.03 (d, J = 1.8 Hz, 6H);

^{13}C NMR (126 MHz, Chloroform-*d*) δ 168.6, 162.7, 157.1, 150.1, 150.0, 137.6, 136.1, 135.9 (4C), 135.7 (4C), 135.0, 134.3 (2C), 133.4, 133.2, 133.1, 132.8, 131.9, 131.7, 130.6 (2C), 130.2 (2C), 129.6 (2C), 129.2 (2C), 128.0 (2C), 127.9 (2C), 127.7 (4C), 118.5, 118.0, 111.0, 106.1, 99.5, 79.9, 76.1, 71.7, 69.6, 69.3, 68.0, 64.4, 53.5, 38.4, 36.3, 32.0, 30.8, 30.0, 28.6, 27.0 (6C), 26.1 (3C), 25.99, 25.7, 19.4, 19.3, 18.3, 14.7, 12.8, -4.1, -4.3; carbon of ester is not found

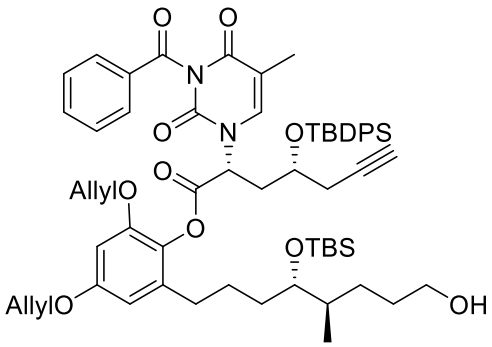
IR (film): ν = 2930, 2857, 2361, 2010, 1994, 1754, 1704, 1666, 1599, 1488, 1462, 1428, 1363, 1256, 1229, 1185, 1111, 1091, 1000, 982, 937, 835, 823, 772, 742, 703, 687, 612, 550, 536, 507;

HRMS (ESI-TOF) m/z (ESI) $C_{78}H_{102}N_3O_{10}Si_3$ $[M+NH_4]^+$ 1324.6868, found 1324.6860.




168.58
162.72
157.13
150.11
149.97
137.62
136.13
135.93
135.71
134.98
134.29
133.37
133.23
133.07
132.80
131.93
131.68
130.60
130.16
129.64
129.21
127.95
127.89
127.72
118.46
117.97
111.03
106.07
99.52
79.88
71.69
69.61
69.29
68.04
64.41
53.50
38.37
36.30
31.95
30.83
30.00
28.64
27.03
26.11
25.99
25.73
19.36
19.34
18.27
14.67
12.83
-4.14
-4.29
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-hydroxy-5-methyloctyl)phenyl (2R,4R)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)hept-6-ynoate ((R,R)-**86**)*



Ammonium fluoride (27.0 mg, 15.0 equiv.) was added to a solution of (R,R)-**85** (63.6 mg, 1.00 equiv.) in 1,1,1,3,3,3-hexafluro-2-propanol (0.486 ml, c=0.1 M) and the resulting solution stirred at ambient temperature with continuous control via TLC. After 14 h already quite a lot of product, but even after 23 h, SM is still there. After 2 days in total, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (2-3 ml) and the aqueous phase was extracted with DCM (5 mL) four times. The combined organic extracts were dried over $MgSO_4$ and concentrated. The crude material (m=56 mg) was purified by pipet flash chromatography, starting with 20:1 tol: ea to 5:1 ea, then flush with ea. The desired product (R,R)-**86** came out in fractions 7-14 (35 mg, 68 %). By NMR of the product fractions *dr* 10:1 is still there – can be seen by a methyl group on the thymine moiety (1.8 ppm doubling signals in 2D NMR-HMBC).

Yield: 19 mg (79 %); 35 mg (68 %) still *dr*=10:1, checked by thymine methyl signal around 1.8 ppm;

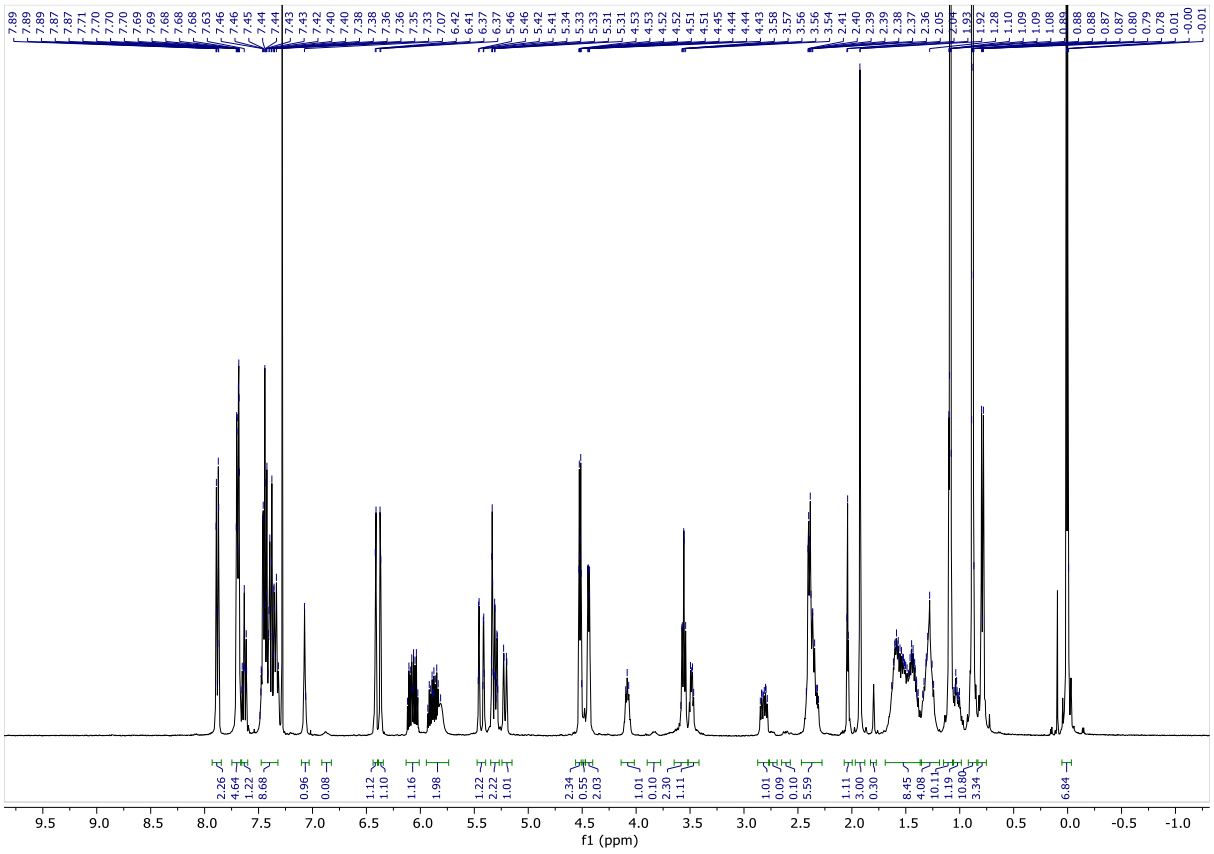
R_f = 0.46 (5:1=Toluene:EtOAc), CPS staining;

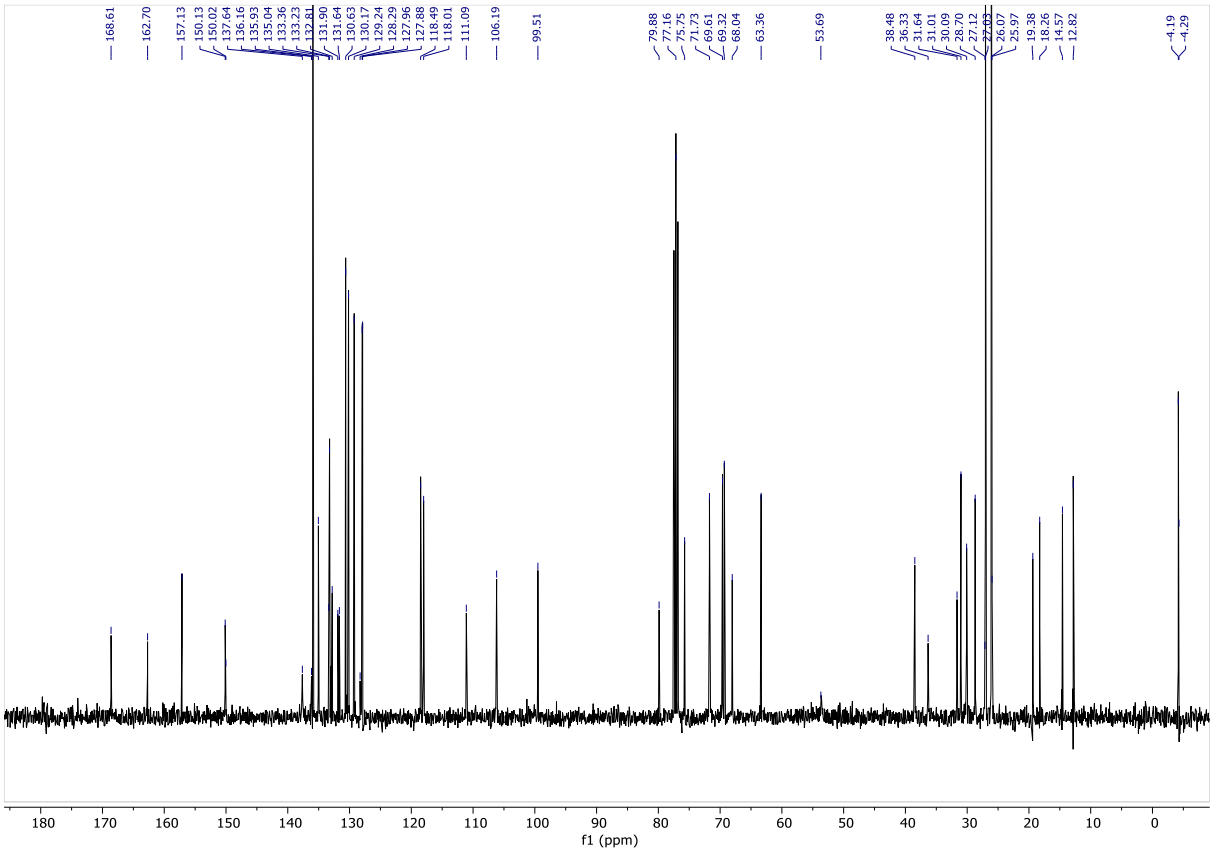
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.80 (m, 2H), 7.74 – 7.59 (m, 4H), 7.66 – 7.60 (m, 1H), 7.49 – 7.30 (m, 8H), 7.07 (d, J = 4.6 Hz, 1H), 6.41 (d, J = 2.7 Hz, 1H), 6.37 (d, J = 2.7 Hz, 1H), 6.07 (ddt, J = 17.2, 10.6, 5.3 Hz, 1H), 5.87 (ddt, J = 19.5, 14.3, 7.1 Hz, 1H), 5.81 (bs, 1H), 5.44 (m, 1H), 5.37 – 5.26 (m, 2H), 5.21 (d, J = 10.3, 1H), 4.52 (dt, J = 5.3, 1.6 Hz, 2H), 4.44 (d, J=4.8 Hz, 2H), 4.14 – 3.96 (m, 2H), 3.66 – 3.52 (m, 1H), 3.49 (dt, J = 7.5, 4.3 Hz, 1H), 2.82 (ddd, J = 14.6, 6.6, 4.6 Hz, 1H), 2.49 – 2.19 (m, 5H), 2.04 (t, J = 2.6 Hz, 1H), 1.92 (d, J = 1.0 Hz, 3H), 1.71 – 1.35 (m, 5H), 1.29 (m, 3H), 1.09 (s, 9H), 1.05-1.00 (m, 1H), 0.88 (s, 9H), 0.79 (d, J = 6.8 Hz, 3H), 0.01 (d, J = 4.1 Hz, 6H); no alcohol proton

^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.6, 162.7, 157.1, 150.1, 150.0, 137.6, 136.2, 135.9 (4C), 135.0, 133.4, 133.2, 132.8, 131.9, 131.6 (2C), 130.6 (2C), 130.2 (2C), 129.2 (2C), 128.0 (2C), 127.9 (2C), 118.5, 118.0, 111.1, 106.2, 99.5, 79.9, 75.8, 71.7, 69.6, 69.3,j 68.0, 63.4, 53.7, 38.5, 36.3, 31.6, 31.0, 30.1, 28.7, 27.1, 27.0 (3C), 26.1 (3C), 26.0, 19.4, 18.3, 14.6, 12.8, -4.2, -4.3; carbon of the ester is missing

IR (film): ν = 2930, 2857, 2355, 2343, 2013, 1994, 1983, 1973, 1754, 1704, 1665, 1599, 1488, 1462, 1429, 1365, 1256, 1229, 1185, 1106, 1090, 1062, 985, 830, 821, 812, 803, 795, 775, 745, 704, 683, 617, 607, 596, 554, 543;

HRMS (ESI-TOF) m/z (ESI) $C_{62}H_{80}N_2NaO_{10}Si_2$ $[M+Na]^+$ 1091.5244, found 1091.5236.




168.61
162.70
157.13
150.13
150.02
137.64
136.16
135.93
135.04
133.36
133.23
132.81
131.90
131.64
130.63
130.17
129.24
128.29
127.96
127.88
118.49
118.01
111.09
106.19
99.51
79.88
77.16
75.75
71.73
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69.32
68.04
63.36
53.69
38.48
36.33
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31.01
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28.70
27.12
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26.07
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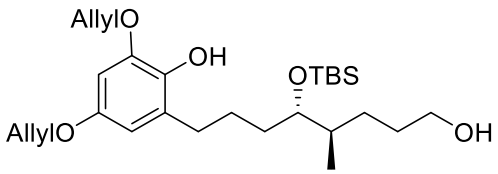
19.38
18.26
14.57
12.82
-4.19
-4.29
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-hydroxy-5-methyloctyl)phenol (**87**)*



A solution of (R,R)-**85** (12 mg, 1 equiv.) in anhydrous THF (0.08 ml, c=0.12) was prepared and cooled to 0 ˚C. Then, acetic acid and TBAF stock solution (9.7 mkL, 1 M in THF, 1 equiv.) were added. The reaction mixture was stirred overnight gradually allowing it to warm to r.t. When the TLC indicated the complete consumption of the starting material, the solvent was evaporated to provide the crude product, which was purified by FC, to afford two ester bonf cleavage products in 61 % and 48 % yield of **87** and **88** respectively.

Yield: 2.7 mg (61 %);

R_f = 0.37 (1:10 ea: hex), CPS staining;

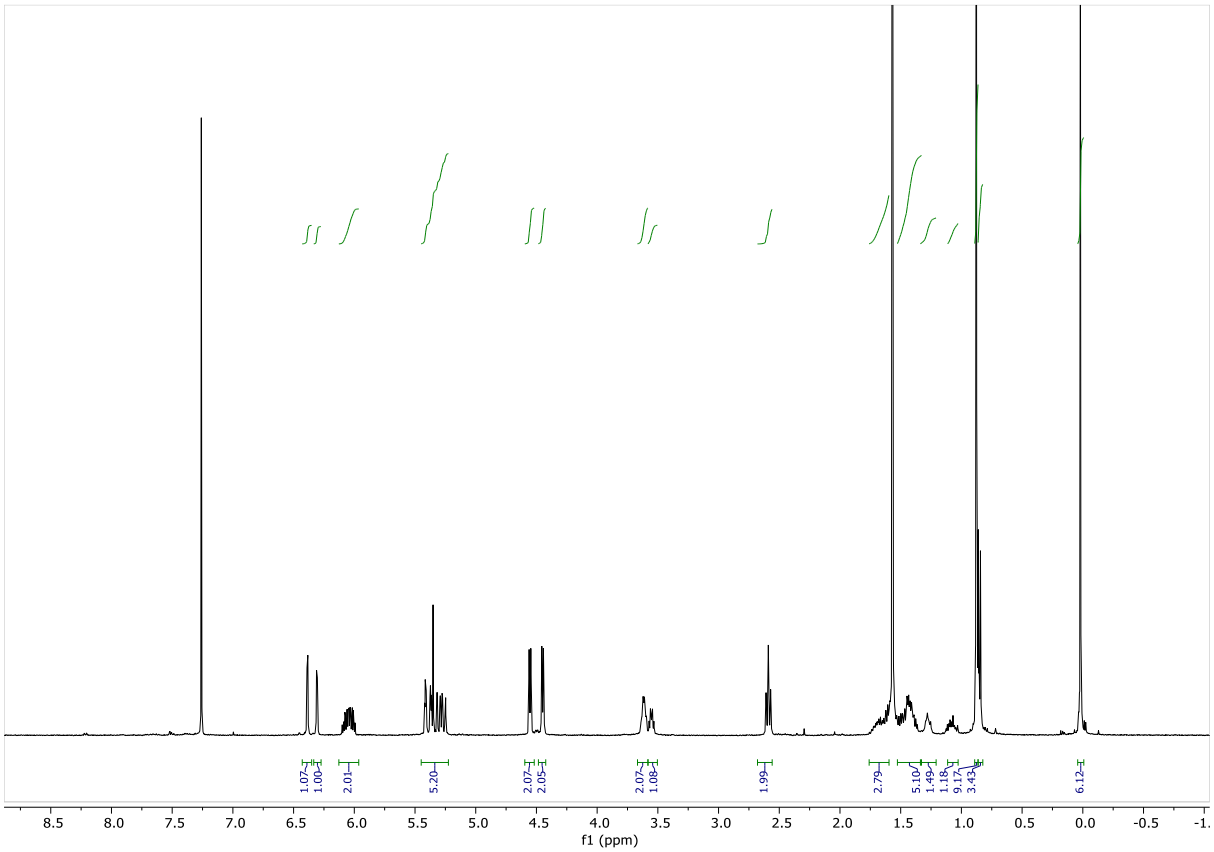
α_D^{20}: -2.86, c=3.5 mg / 0.5 ml (c=0.7, $CHCl_3$, 20°C, l=589 nm);

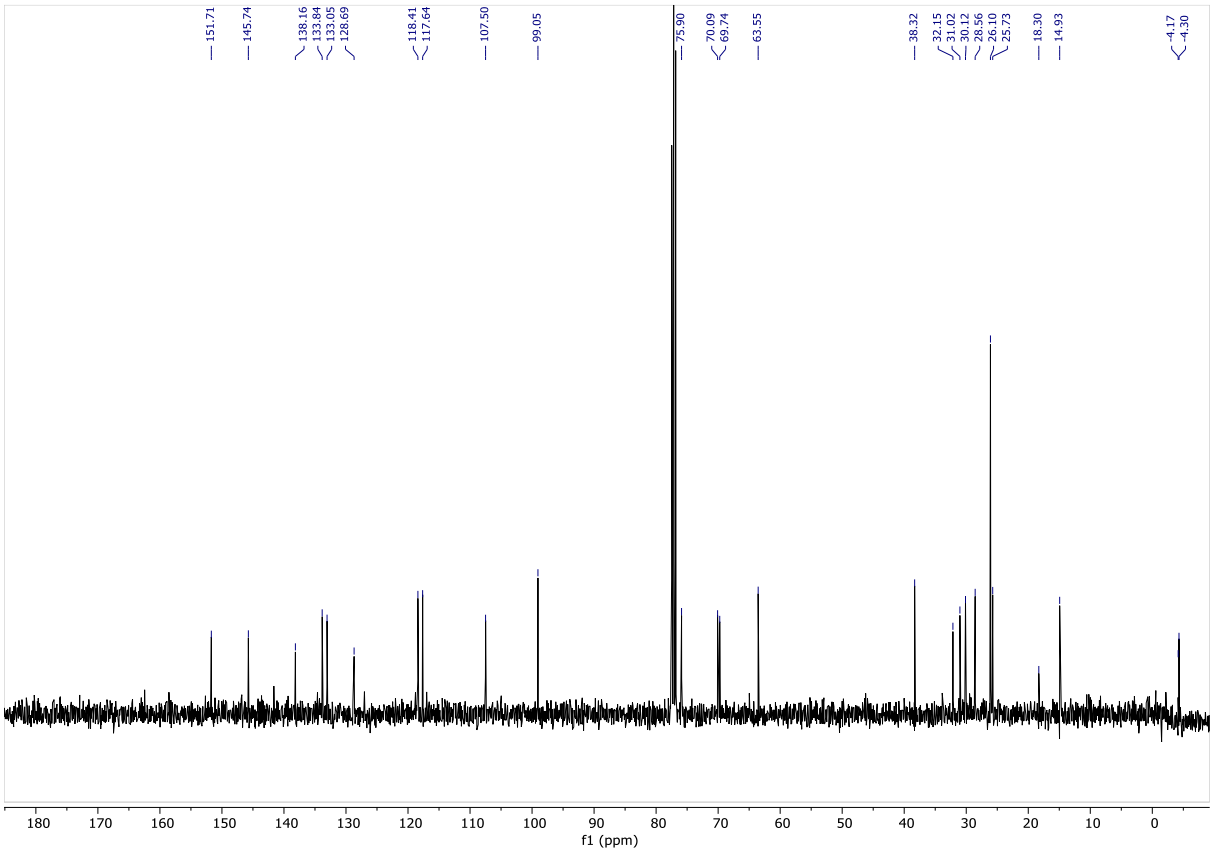
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.39 (d, J = 2.8 Hz, 1H), 6.31 (d, J = 2.8 Hz, 1H), 6.12 – 5.94 (m, 2H), 5.50 – 5.17 (m, 4H+1 from OH), 4.55 (dt, J = 5.5, 1.5 Hz, 2H), 4.45 (dt, J = 5.4, 1.5 Hz, 2H), 3.62 (m, 2H), 3.55 (dt, J = 6.8, 4.6 Hz, 1H), 2.59 (t, J = 7.6 Hz, 2H), 1.75 – 1.59 (m, 3H), 1.55 – 1.26 (m, 6H), 1.13 – 0.99 (m, 1H), 0.88 (s, 9H), 0.85 (d, J = 6.8 Hz, 3H), 0.02 (s, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 151.7, 145.7, 138.2, 133.8, 133.1, 128.7, 118.4, 117.6, 107.5, 99.1, 75.9, 70.1, 69.7, 63.6, 38.3, 32.2, 31.0, 30.1, 28.6, 26.1 (3C), 25.7, 18.3, 14.9, -4.2, -4.3;

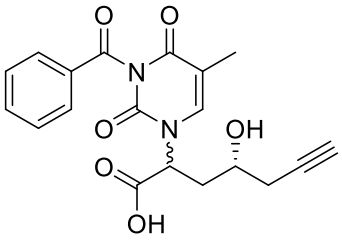
IR (film): ν = 3545, 2929, 2857, 2359, 2154, 1606, 1496, 1461, 1424, 1379, 1254, 1222, 1148, 1058, 927, 835, 773, 703, 671, 560, 533;

HRMS (ESI-TOF) m/z (ESI) $C_{27}H_{46}NaO_5Si$ $[M+Na]^+$ 501.3007, found 501.3005.


1.07
1.00
2.01
5.20
2.07
2.05
2.07
1.08
1.99
2.79
5.10
1.49
1.18
9.17
3.43
6.12
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


151.71
145.74
138.16
133.84
133.05
128.69
118.41
117.64
107.50
99.05
75.90
70.09
69.74
63.55
38.32
32.15
31.02
30.12
28.56
26.10
25.73
18.30
14.93
-4.17
-4.30
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

*(4R)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-hydroxyhept-6-ynoic acid (**88**)*

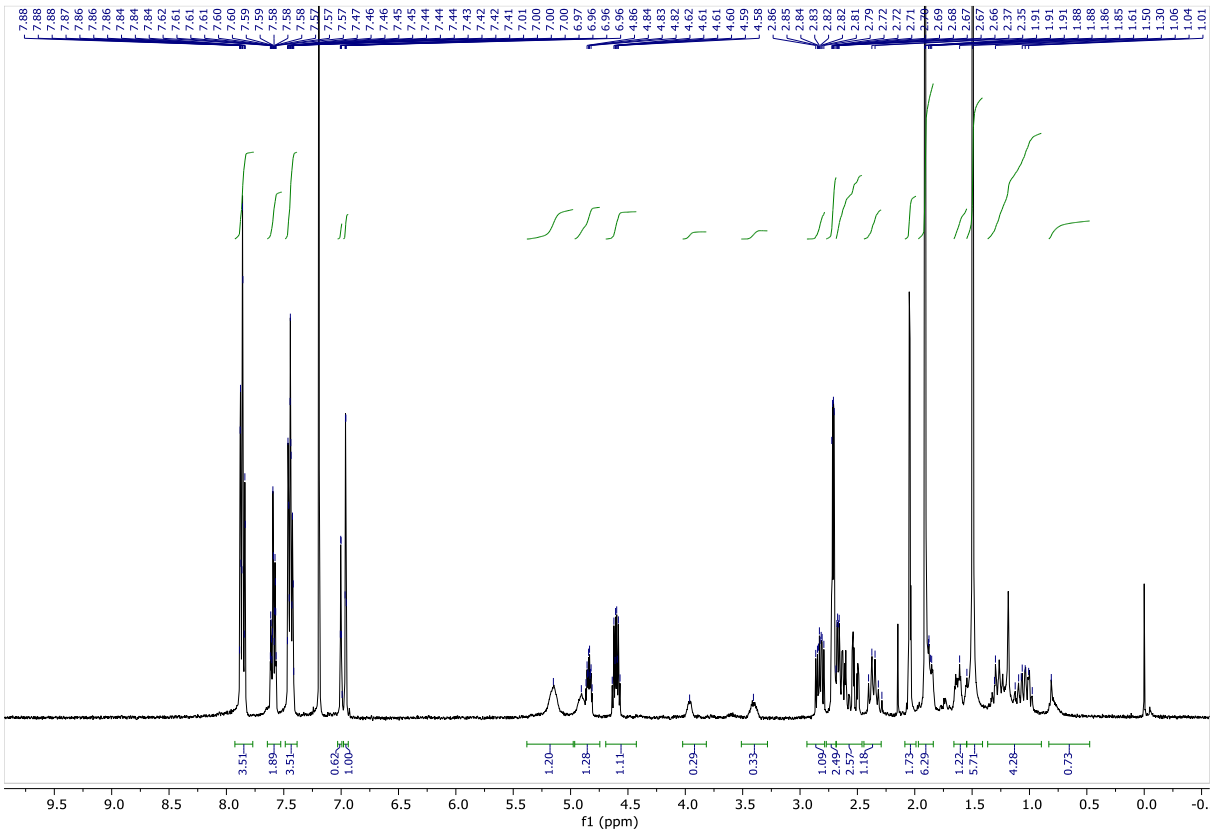


Yield: 2.7 mg (48%);

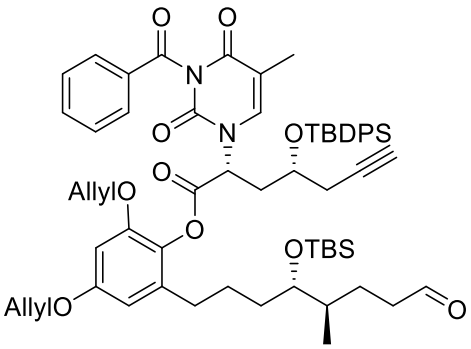
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 (td, J = 8.2, 1.3 Hz, 3H), 7.71 – 7.49 (m, 1H), 7.44 (ddd, J = 8.6, 7.4, 2.6 Hz, 3H), 7.00 (q, J = 1.2 Hz, 1H), 6.96 (q, J = 1.3 Hz, 1H), 5.15 (s, 1H), 5.02 – 4.72 (m, 1H), 4.60 (dq, J = 9.7, 5.8 Hz, 1H), 3.96 (s, 0H), 3.41 (s, 0H), 2.83 (ddd, J = 12.9, 9.4, 6.1 Hz, 1H), 2.69 (ddd, J = 17.4, 5.6, 2.7 Hz, 2H), 2.35 (dt, J = 23.9, 11.9 Hz, 1H), 1.91 (d, J = 1.1 Hz, 4H), 1.50 (s, 4H), 1.13 – 0.76 (m, 1H).

IR (film): v = 2971, 1670, 1066, 621, 611, 606.

HRMS (ESI-TOF) m/z (ESI) $C_{19}H_{16}N_2NaO_5$ $[M+Na]^+$ 375.0951, found 375.0949.



*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-hydroxy-5-methyloctyl)phenyl (2R,4R)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)hept-6-ynoate ((R,R)-**83**)*



In a 5 ml flame-dried flask a solution of the alcohol (R,R)-**86** (8.8 mg, 0.0082 mmol, 1.00 equiv.) in dry DCM (0.222 ml, c=0.037) was prepared. DMP (4.5 mg, 0.0107 mmol, 1.30 equiv.) and $NaHCO_3$ (2.8 mg, 0.0504 mmol, 4.00 equiv.) were added at room temperature The reaction was stirred at room temperature for 1 h and was checked by MS: Saiyyna 191, 192 –aldehyde is detected and TLC. After 3 h at room temperature after seeing the reaction NMR, the reaction mixture was quenched with $NaHCO_3$+$Na_2S_2O_3$ solution (2 ml) and stirred for 30 min. The aqueous layer was extracted with EtOAc (1-2 ml) four times. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude material was purified by pipet FC with 10:1 tol: EtOAc and then washed with pure EtOAc, yielding the desired product (R,R)-**83** as a colorless oil.

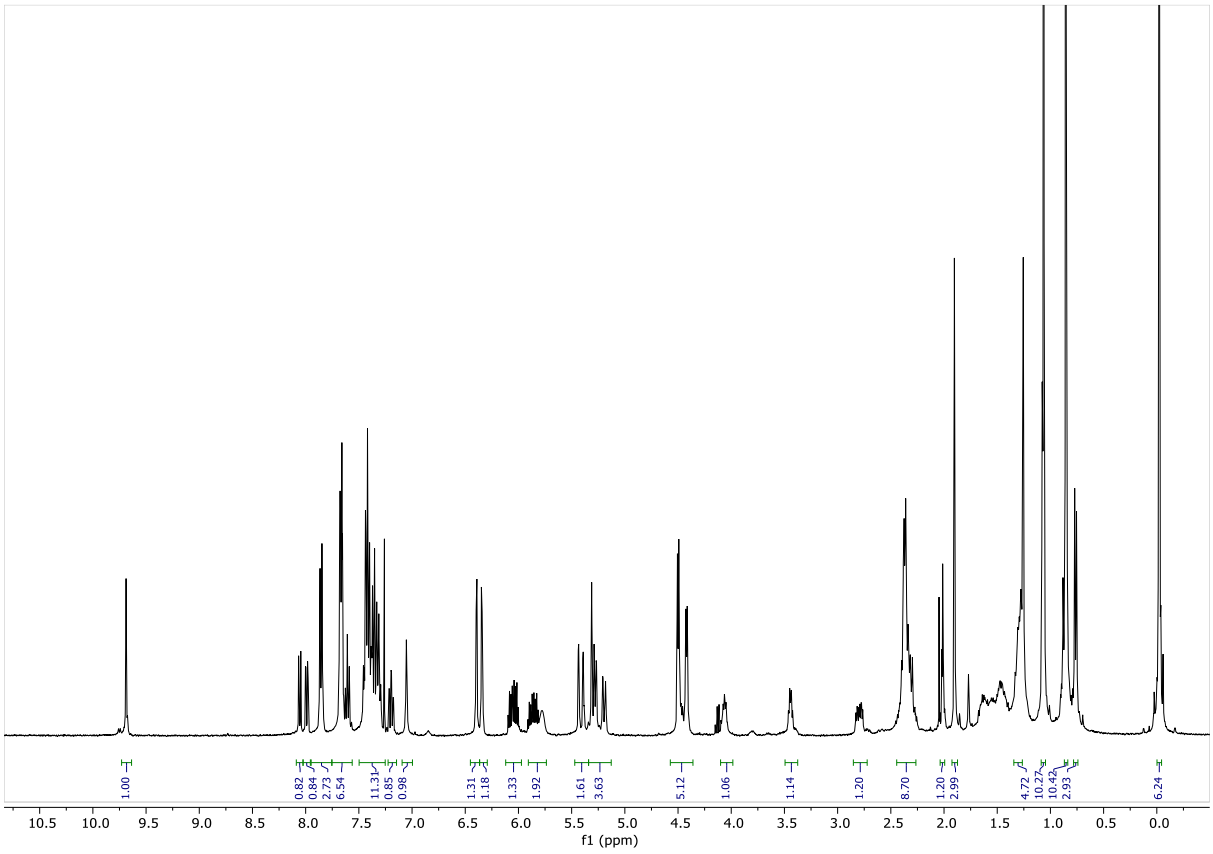
Yield: 6.6 mg (75 %);

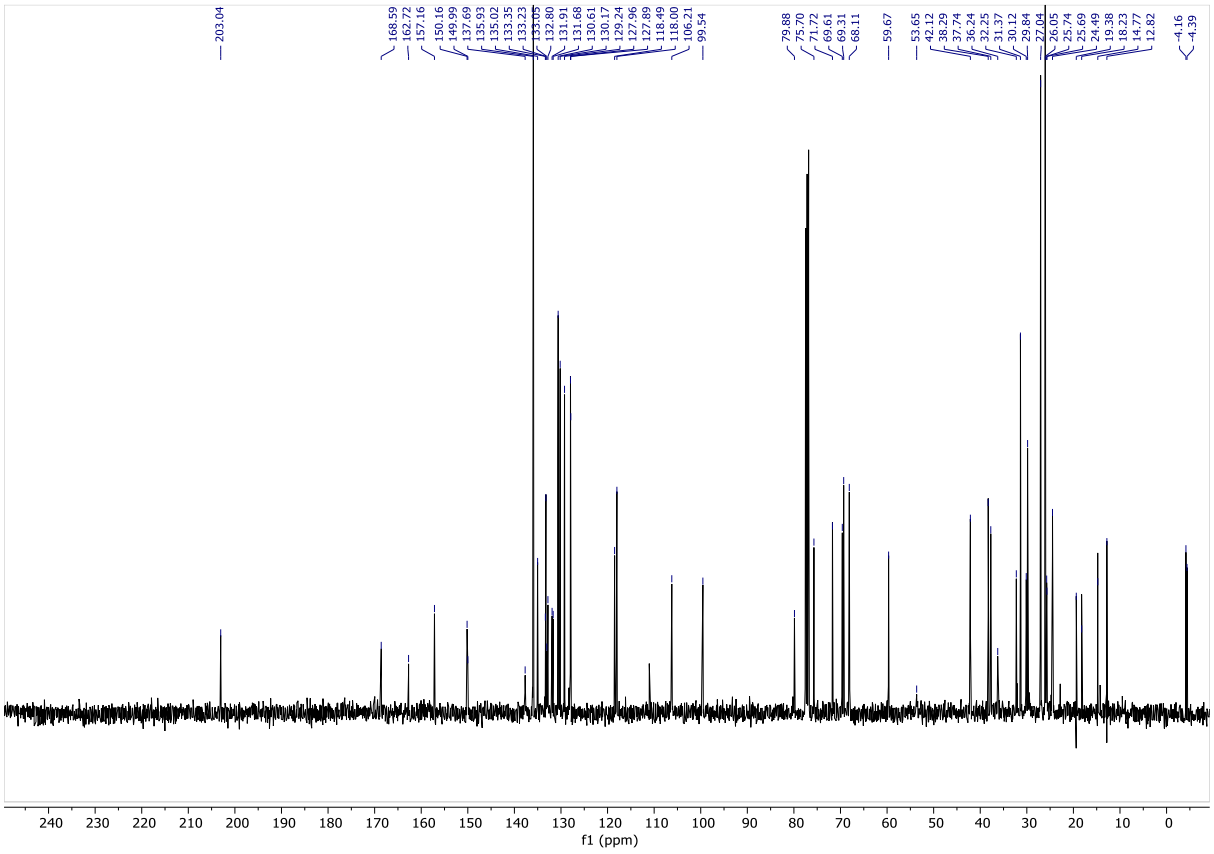
R_f = 0.6058 (5:1=Toluene:EtOAc), CPS staining;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.69 (t, J = 1.8 Hz, 1H), 8.00 – 7.74 (m, 2H), 7.74 – 7.63 (m, 4H), 7.63 – 7.51 (m, 1H), 7.48 – 7.29 (m, 8H), 7.05 (s, 1H), 6.39 (d, J = 2.7 Hz, 1H), 6.34 (d, J = 2.7 Hz, 1H), 6.05 (ddt, J=17.3, 10.6, 5.3 Hz, 1H), 5.86 (ddt, J = 17.5, 10.7, 5.4 Hz, 1H), 5.78 (br.s, 1H), 5.41 (dt, J = 17.3, 1.6 Hz, 1H), 5.35 – 5.23 (m, 2H), 5.23 – 5.14 (m, 1H), 4.50 (dt, J = 5.4, 1.5 Hz, 2H), 4.42 (d, J = 5.3 Hz, 2H), 4.10 – 4.02 (m, 1H), 3.44 (dt, J = 6.7, 4.6 Hz, 1H), 2.80 (ddd, J = 14.7, 6.6, 4.6 Hz, 1H), 2.43 – 2.20 (m, 7H), 2.01 (t, J = 2.6 Hz, 1H), 1.90 (d, J = 1.1 Hz, 3H), 1.70 – 1.43 (m, 4H), 1.34 – 1.28 (m, 3H), 1.06 (s, 9H), 0.85 (s, 9H), 0.76 (d, J = 6.8 Hz, 3H), -0.02 (d, J = 2.3 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 203.0, 168.6, 162.7, 157.2, 150.2, 150.0, 137.7, 135.9 (4C), 135.0, 133.4, 133.2, 132.8, 131.9, 131.7, 130.6 (2C), 130.2 (2C), 129.2 (2C), 128.0, 127.9 (4C), 118.5, 118.0, 111.1, 106.2, 99.5, 79.9, 75.7, 71.7, 69.6, 69.3, 68.1, 59.7, 53.7, 42.1, 38.3, 37.7, 36.2, 32.3, 31.4, 30.1, 29.8, 27.0 (3C), 26.1 (3C), 24.5, 19.4, 18.2, 14.8, 12.8, -4.2, -4.4;

IR (film): ν = 2953, 2924, 2852, 2360, 1753, 1722, 1703, 1665, 1599, 1487, 1462, 1429, 1388, 1365, 1258, 1229, 1185, 1104, 1089, 982, 937, 835, 822, 806, 773, 761, 742, 704, 687, 672, 631, 611, 504; HRMS (ESI-TOF) m/z (ESI) $C_{62}H_{82}N_3NaO_{10}Si_2$ $[M+NH_4]^+$ 1084.5533, found 1084.5530.

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157.16
150.16
149.99
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135.93
135.02
133.35
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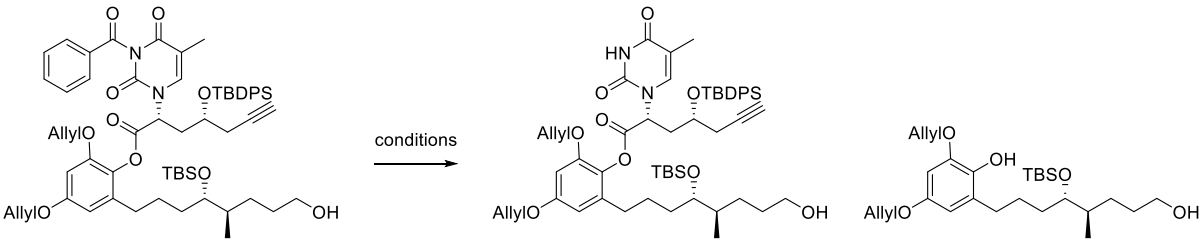
133.05
132.80
131.91
131.68
130.61
130.17
129.24
127.96
127.89
118.49
118.00
106.21
99.54
79.88
75.70
71.72
69.61
69.31
68.11
59.67
53.65
42.12
38.29
37.74
36.24
32.25
31.37
30.12
29.84
27.04
26.05
25.74
25.69
24.49
19.38
18.23
14.77
12.82
-4.16
-4.39
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Optimization of benzoyl-protecting group removal conditions

At this stage, also benzoyl protecting group removal strategies were screened to ensure that they would work at the end of the synthesis. Based on the results obtained on *(R,R)*-**73**, where conditions of ammonia in methanol[11] were used, the same conditions were also applied to the more advanced substrate *(R,R)*-**86** (*Table 10*, entry 1). Unfortunately, only the ester bond cleavage product **SI**-*(R,R)*-**86-2** was isolated when these conditions were used. Then, the solvent was changed to an aprotic, less nucleophilic solvent, 0.5 M solution of ammonia in 1,4-dioxane that had previously been used.[12][13] However, at first, the reaction did not proceed (*Table 10*, entry 2). The reason for the lack of success of this experiment could derive from the quality of the commercial bottle of ammonia in dioxane used, especially if it had been opened a long time ago and stored at room temperature since the solubility of ammonia in dioxane is not very high. On the contrary, when the ammonia-dioxane solution was freshly prepared, the reaction proceeded smoothly and with a good yield, producing the desired product **SI**-*(R,R)*-**86-1**, without affecting the ester bond (*Table 10*, entry 3).

Table 10. Search for conditions for the benzoyl-protecting group removal.



Entry	Scale	Conditions	Time	Yield[a]/Remarks
1	5 mg	7 N solution of NH_3 in methanol, c=0.1 M	23 h	**87**, 66 %
2	5 mg	0.5 M solution of NH_3 in dioxane, c=0.1 M	7 days	No reaction
3	10 mg	NH_3 in dioxane (freshly prepared), c=0.0015 M	42 h	**SI**-*(R,R)*-**86-1**, 67 %

[a] isolated yield.

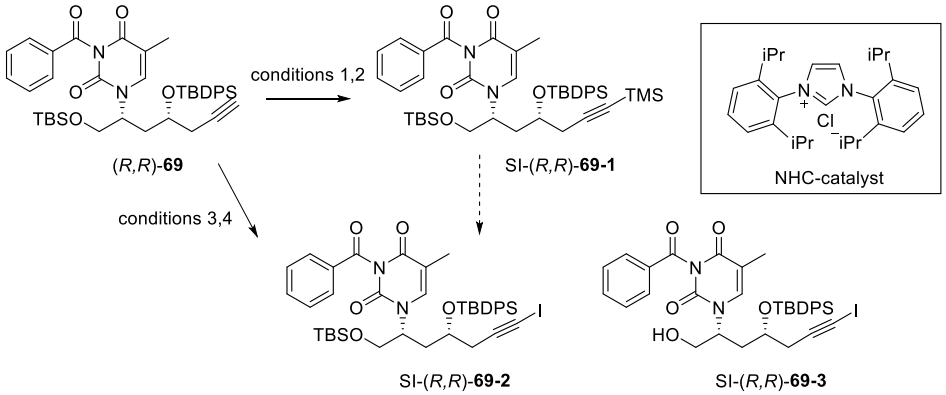
The ester bond in the molecule appears to be labile, as the undesired cleavage of the ester bond is observed for the second time.

5.3.2 Macrocyclization via NHK

5.3.2.1 Iodoynal (*R,R*)-84

The conditions for iodination of the terminal alkyne were screened and optimized on the thymine-bearing substrate *(R,R)*-**69** (*Table SI-2*). The first conditions included a two-step approach, where the terminal alkyne was trimethylsilylated using a Ruppert reagent catalyzed by an NHC-catalyst 1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride (**SI**-*(R,R)*-**69-1**) (*Table SI-2*, entry 1),[14] followed by a dysilylative iodination of **SI**-*(R,R)*-**69-1** to form **SI**-*(R,R)*-**69-2.** However, the process of silylating the terminal alkyne did not work, the starting material was reisolated. The next procedure employed for the trimethylsililation of the alkyne *(R,R)*-**69** is described in entry 2, *Table SI-2*.

Table SI-2. Search for Iodination conditions



Entry	Scale	Conditions	Time	Yield[a]/Remarks
1	123 mg	NHC-catalyst, CF_3SiMe_3, NaH, Ligand	2 d	SM
2	50 mg	n-BuLi (1.2 equiv.), TMSCl, THF	3 h	**SI**-*(R,R)*-**69-1**, 18 %; *(R,R)*-**69**, 10 %; Unidentified 2 side products
3	96 mg	n-BuLi (1.2 equiv.), I_2, THF	18 h	**SI**-*(R,R)*-**69-2**, 10 %; *(R,R)*-**69**, 71 %
4	63 mg	NIS (3 equiv.), $AgNO_3$, DMF, 0°C to r.t	28 h	**SI**-*(R,R)*-**69-3**, 60 %
5	180 mg	NIS (1.45 equiv.), $AgNO_3$, DMF, 0°C to r.t	12h	**SI**-*(R,R)*-**69-2**, 70 %

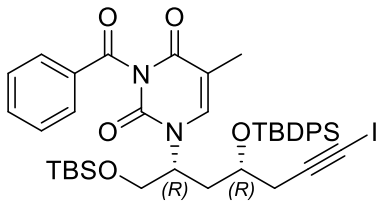
[a] isolated yield.

In this attempt, 18 % of the silylated substrate **SI**-*(R,R)*-**69-1** was isolated together with 10 % of *(R,R)*-**69**, and the rest of the crude could not be identified. Then the decision to go directly for the primary alkyne iodination was made and the conditions described in entry 3, *Table SI-2* were applied to substrate *(R,R)*-**69**. Only 10 % of the desired product was isolated and the reaction did not proceed further. The last conditions with N-iodosuccinimide (NIS) and silver (I) nitrate have proven to be the best for this substrate (*Table SI-2*, entry 4).[15][16] The silver nitrate coordinates with the alkyne and activates it for the NIS to attack.[17] The drawback of the reaction was that the TBS removal occurred in the presence of NIS, which is not unique to this reagent, NIS was described to remove silyl protecting groups, where it happened unintentionally.[18] Additionally, a methodology with catalytic amount of NIS in methanol is used for a chemoselective removal of aliphatic TBS-ethers was reported.[19] When the NIS was used without a large excess, the reaction delivered the desired product **SI**-*(R,R)*-**69-2** in good yield (*Table SI-2*, entry 5).

The confirmation of the iodoalkyne formation can be done with the mass of the substrate and the disappearing alkyne signal in the proton NMR, however, it was additionally confirmed by an unusual and characteristic shift of the primary alkyne atom next to the iodine at -3.32 ppm in the carbon NMR, instead of the usual shifts at about 60-100 ppm.

This phenomenon can be explained by the "heavy-atom effect" that results from the spin-orbit interaction of iodine, which reduces the chemical shift of the carbon bonded to it, and from the interaction of the polarizable single electron pair of iodine with the cylindrical π-system of the carbon-carbon triple bond, which results in significant shielding of the carbon nucleus.[20]

*Iodination of the Thymine fragment. 3-benzoyl-1-((6R,8R)-8-(3-iodoprop-2-yn-1-yl)-2,2,3,3,11,11-hexamethyl-10,10-diphenyl-4,9-dioxane-3,10-disiladodecan-6-yl)-5-methyl pyrimidine-2,4(1H,3H)-dione (**SI**-(R,R)-**69-2**)*



A solution of *(R,R)*-**69** (180 mg, 0.254 mmol, 1.0 equiv.) in dry DMF (1.27 ml, c=0.2 M) was prepared at room temperature under an argon atmosphere. The flask was covered with aluminium foil to avoid light in the reaction and cooled with an ice bath to 0 ˚C. And then the N-iodosuccinimide (83 mg, 0.37 mmol, 1.45 equiv.) and silver nitrate (17.2 mg, 0.1 mmol, 0.4 equiv.) were added at room temperature and stirred for 12 h. When the reaction was complete by TLC, it was poured into a saturated $Na_2S_2O_3$ for quenching. Washed with $NaHCO_3$ (**important for removing succinimide** formed in the reaction, otherwise extremely difficult to separate by column). Extraction with EA was followed by evaporation of the solvent giving crude of M=340 mg. The crude product was purified by silica-gel column chromatography (EA: Hex=5:1) yielding **SI**-*(R,R)*-**69-2** (148 mg, 70 %) in fractions 6-11.

Yield: 148 mg (70 %);

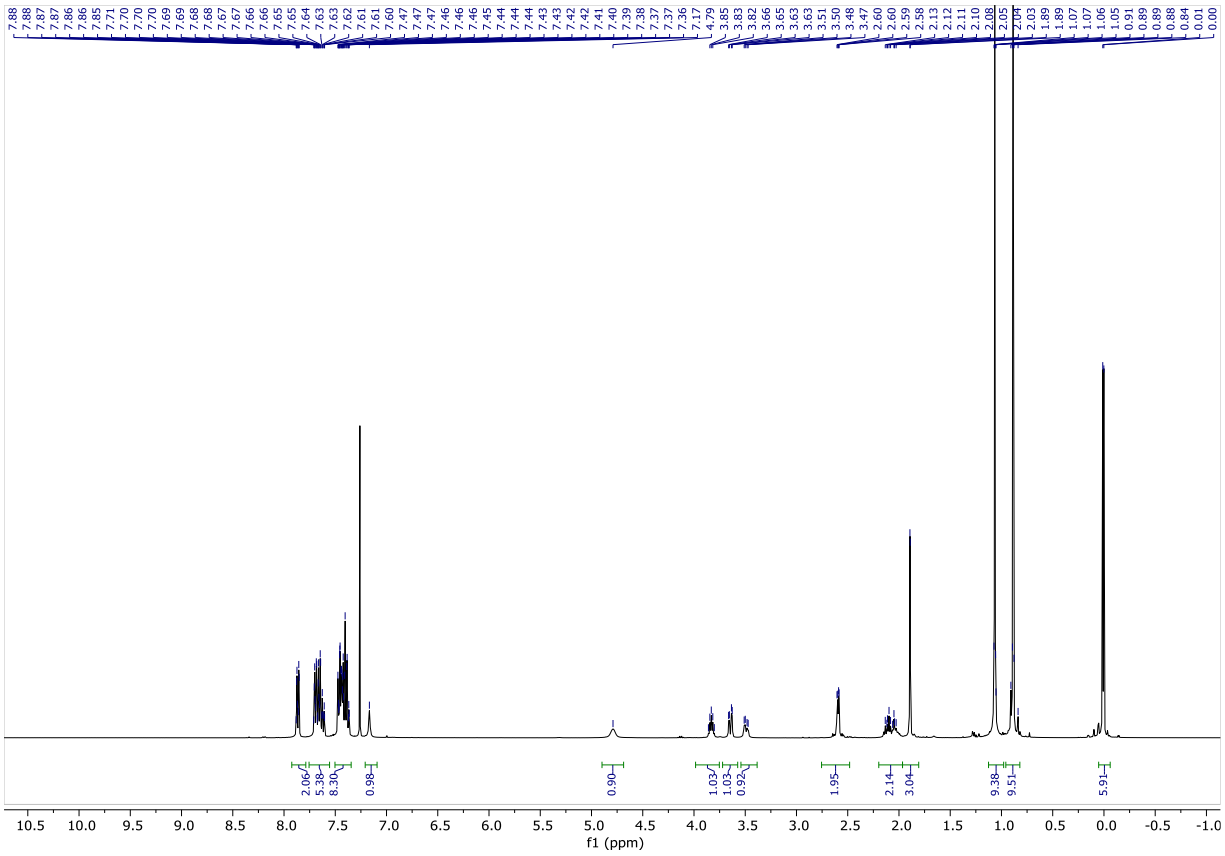
R_f = 0.613 (2:1 Toluene: EtOAc), CPS staining;

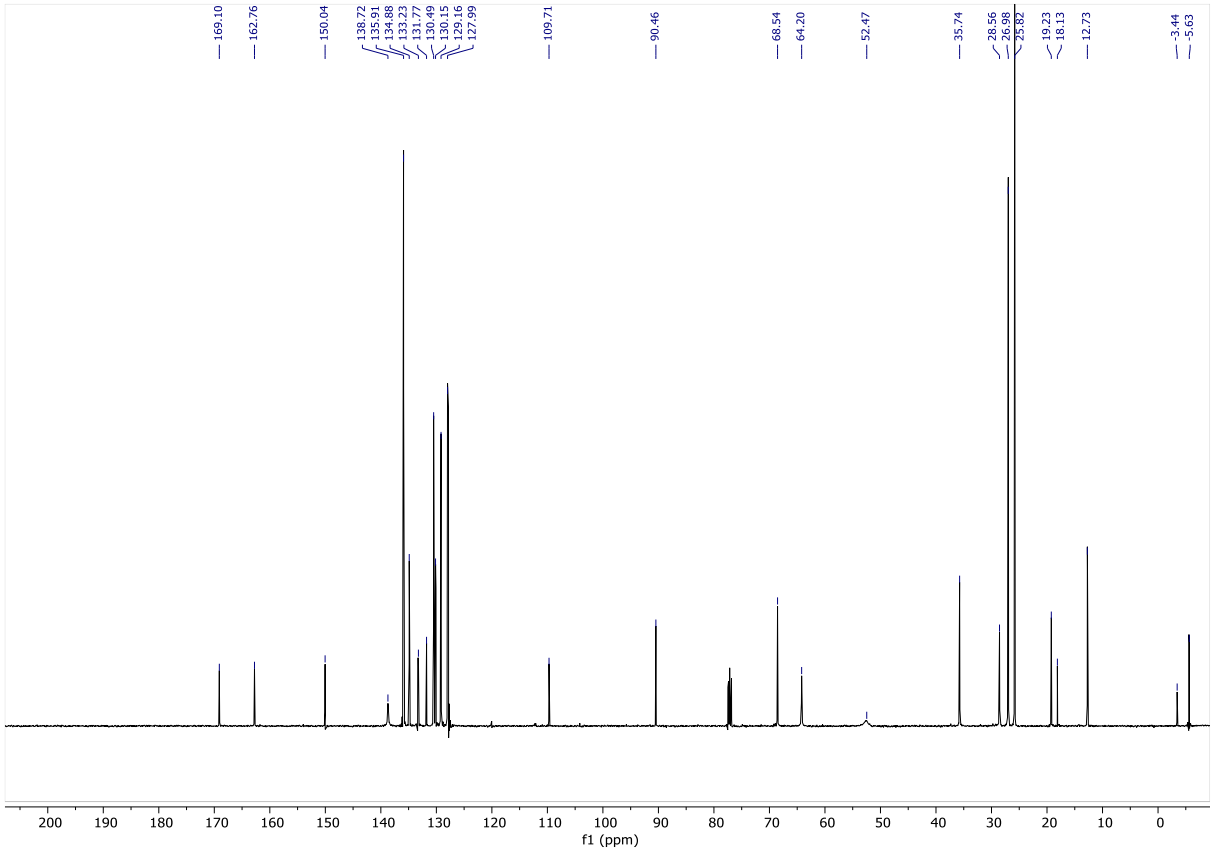
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 – 7.78 (m, 2H), 7.73 – 7.57 (m, 5H), 7.52 – 7.35 (m, 8H), 7.17 (s, 1H), 4.79 (s, 1H), 3.83 (p, J = 5.7 Hz, 1H), 3.64 (dd, J = 11.1, 3.0 Hz, 1H), 3.49 (dd, J = 11.2, 4.3 Hz, 1H), 2.59 (dd, J = 5.7, 2.5 Hz, 2H), 2.20 – 1.98 (m, 2H), 1.89 (d, J = 1.2 Hz, 3H), 1.07 (s, 9H), 0.89 (s, 9H), 0.01 (d, J = 4.2 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.1, 162.8, 150.0, 138.7, 135.9 (4C), 134.9, 133.4, 133.2, 131.8, 130.5 (2C), 130.2, 130.1, 129.2 (2C), 128.0 (2C), 127.8 (2C), 109.7, 90.5, 68.5, 64.2, 52.5, 35.7, 28.6 (3C), 27.0, 26.0 (3C), 19.2, 18.1, 12.7, -3.4, -5.6, -5.6;

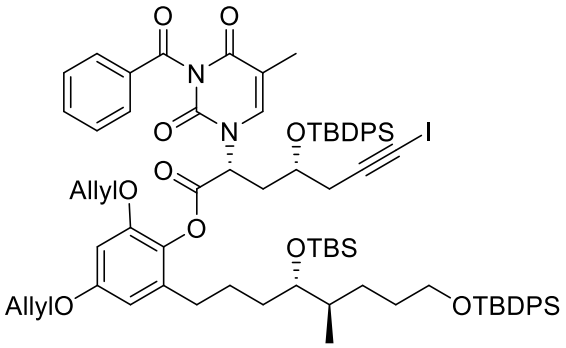
IR (film): *v* = 2954, 2930, 2894, 2857, 1749, 1697, 1651, 1600, 1471, 1462, 1429, 1388, 1363, 1307, 1288, 1255, 1178, 1105, 1046, 1002, 982, 937, 907, 833, 779, 763, 729, 702, 685, 665, 648, 612;

HRMS (ESI-TOF) m/z (ESI) $C_{41}H_{52}IN_2O_5Si_2$ $[M+H]^+$ 835.2454, found 835.2461.


f1 (ppm)


f1 (ppm)

*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-((tert-butyldiphenylsilyl)oxy)-5-methyloctyl)phenyl(2R,4R)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)-7-iodohept-6-ynoate ((R,R)-**93**)*



A solution of (R,R)-**85** (1.51 g, 1.15 mmol., 1.0 equiv.) in dry DMF (14.43 ml, c=0.08 M) was prepared at room temperature under argon atmosphere. Then, the N-iodosuccinimide (377 mg, 1.67 mmol, 1.45 equiv.) and silver nitrate (39.2 mg, 0.231 mmol, 0.2 equiv.) were added at room temperature When the reaction was complete by TLC, after 7 hours, it was poured into a saturated $Na_2S_2O_3$ for quenching (color turned bright yellow and precipitated, then disappeared-AgI?). Washed with $NaHCO_3$, to remove succinimide. Extraction with EA was followed by evaporation of the solvent giving crude of M=2.15 g. The crude material (R,R)-**93** was purified by pipet silica-gel column chromatography (pure toluene, then EA: Tol=1:50, 1:20), to afford 1.45 of the desired product.

Yield: 1.45 g (88 %);

R_f = 0.222 (50:1 Toluene: EtOAc), CPS staining;

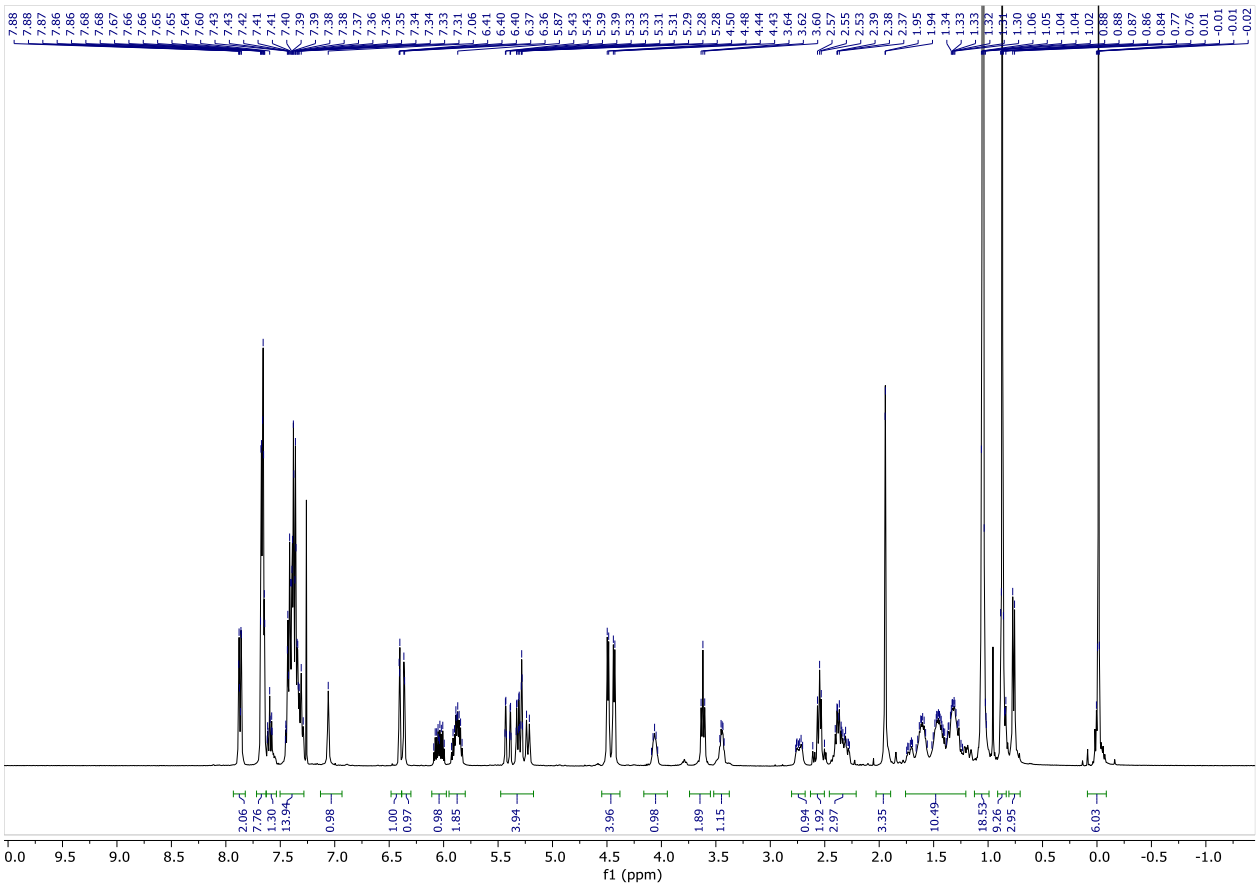
$[\alpha]_{20}^{D}$: = -24.0 (c = 0.5; 5 mg / 1 mL, $CHCl_3$, 20°C);

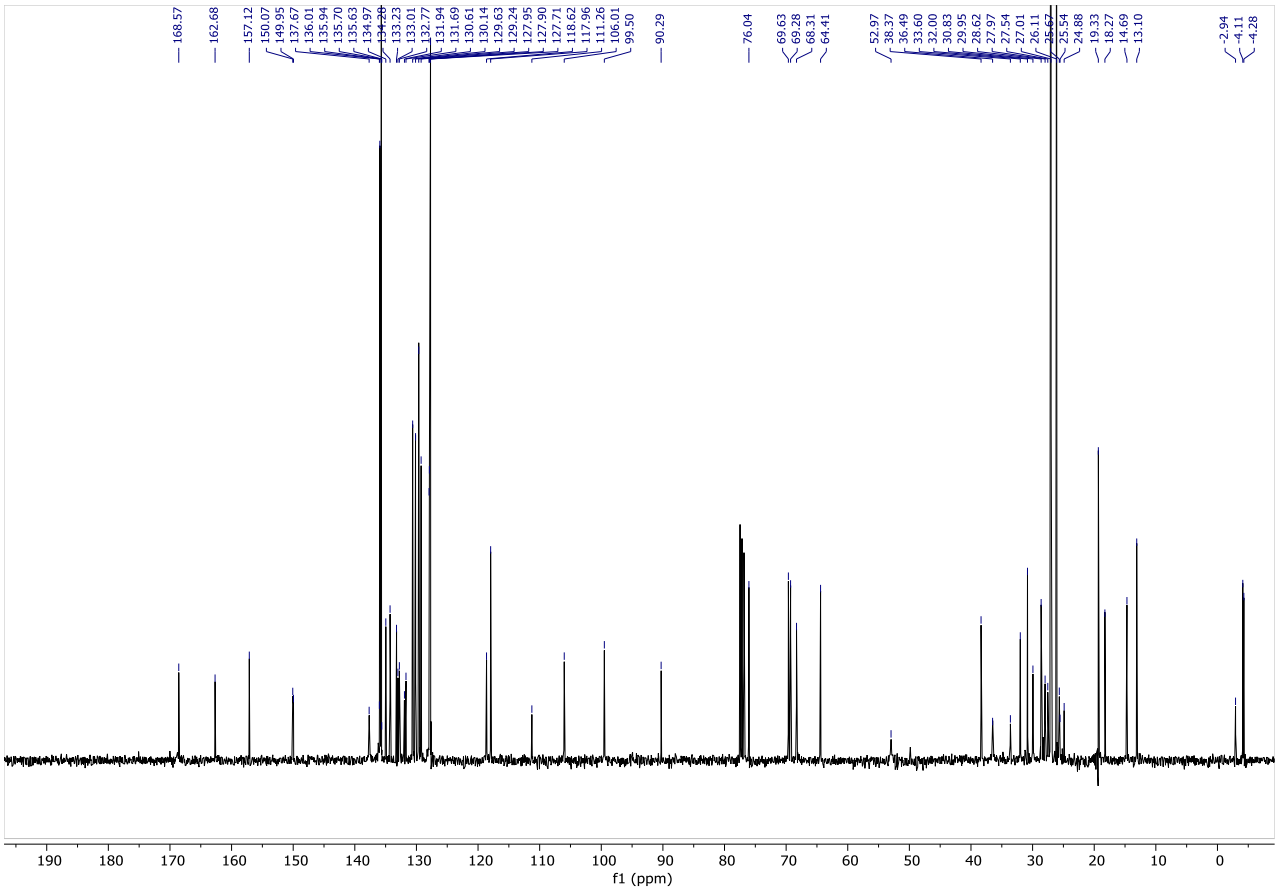
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 – 7.80 (m, 2H), 7.66 (m, 8H), 7.60 (td, J = 7.4, 1.4 Hz, 1H), 7.49 – 7.28 (m, 14H), 7.06 (s, 1H), 6.41 (d, J = 2.7 Hz, 1H), 6.36 (d, J = 2.7 Hz, 1H), 6.04 (ddt, J = 17.5, 10.6, 5.3 Hz, 1H), 5.94 – 5.79 (m, 2H), 5.41 (dq, J = 17.2, 1.6 Hz, 1H), 5.35 – 5.26 (m, 2H), 5.23 (d, J = 10.4 Hz, 1jH), 4.49 (d, J = 5.3 Hz, 2H), 4.44 (d, J = 5.5 Hz, 2H), 4.06 (p, J = 5.7 Hz, 1H), 3.62 (t, J = 6.7 Hz, 2H), 3.44 (dt, J = 7.3, 4.4 Hz, 1H), 2.74 (m, 1H), 2.61 – 2.50 (m, 2H), 2.34 (m, 3H), 1.95 (s, 3H), 1.76 – 1.22 (m, 10H), 1.05 (d, J = 3.4 Hz, 18H), 0.87 (s, 9H), 0.77 (d, J = 6.7 Hz, 3H), -0.01 (s, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.6, 162.7, 157.1, 150.0, 137.7, 135.9, 135.7, 135.0, 134.3, 133.2, 133.0, 132.8, 131.9, 131.7, 130.6, 130.1, 129.6, 129.2, 127.9, 127.7, 118.6, 118.0, 111.3, 106.0, 99.5, 90.3, 76.0, 69.6, 69.3, 68.3, 64.4, 53.0, 38.4, 36.5, 33.6, 32.0, 30.8, 30.0, 28.6, 28.0, 27.5, 27.0, 26.1, 25.7, 25.5, 24.9, 19.3, 18.3, 14.7, 13.1, -2.9, -4.1, -4.3.

IR (film): ν = 2954, 2929, 2856, 1754, 1704, 1665, 1598, 1488, 1471, 1461, 1428, 1362, 1255, 1227, 1185, 1110, 1088, 1000, 981, 936, 835, 823, 772, 759, 741, 702, 687, 672, 613, 505;

HRMS (ESI-TOF) m/z (ESI) $C_{78}H_{101}IN_3O_{10}Si_3$ $[M+NH_4]^+$ 1450.5834, found 1450.5832.

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150
140
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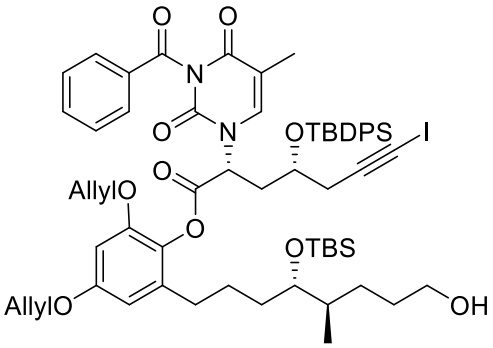
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-hydroxy-5-methyloctyl)phenyl (2R,4R)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)-7-iodohept-6-ynoate ((R,R)-**94**)*



A solution of (R,R)-**93** (1.45 g, 1.01 mmol., 1.0 equiv.) in dry HFIP (10.1 ml, c=0.2 M) was prepared at room temperature under an argon atmosphere. Then, ammonium fluoride (750 mg, 20.23 mmol, 20 equiv.) was added at room temperature After 23 h at room temperature the reaction was completed by TLC. The reaction mixture was quenched with sat. aq. $NaHCO_3$, the organic layer was separated and the water phase was extracted with EA. Combined organic layers were dried over Mg2SO4 and evaporated on a rotary evaporator. The crude material (M=1.88 g) was purified by pipet silica-gel column chromatography (pure toluene, then EA: Tol=1:50, 1:20) and afforded pure (R,R)-**94** in 92 % yield.

Yield: 0.99 g (92 %);

R_f = 0.357 (5:1 Toluene: EtOAc), CPS staining;

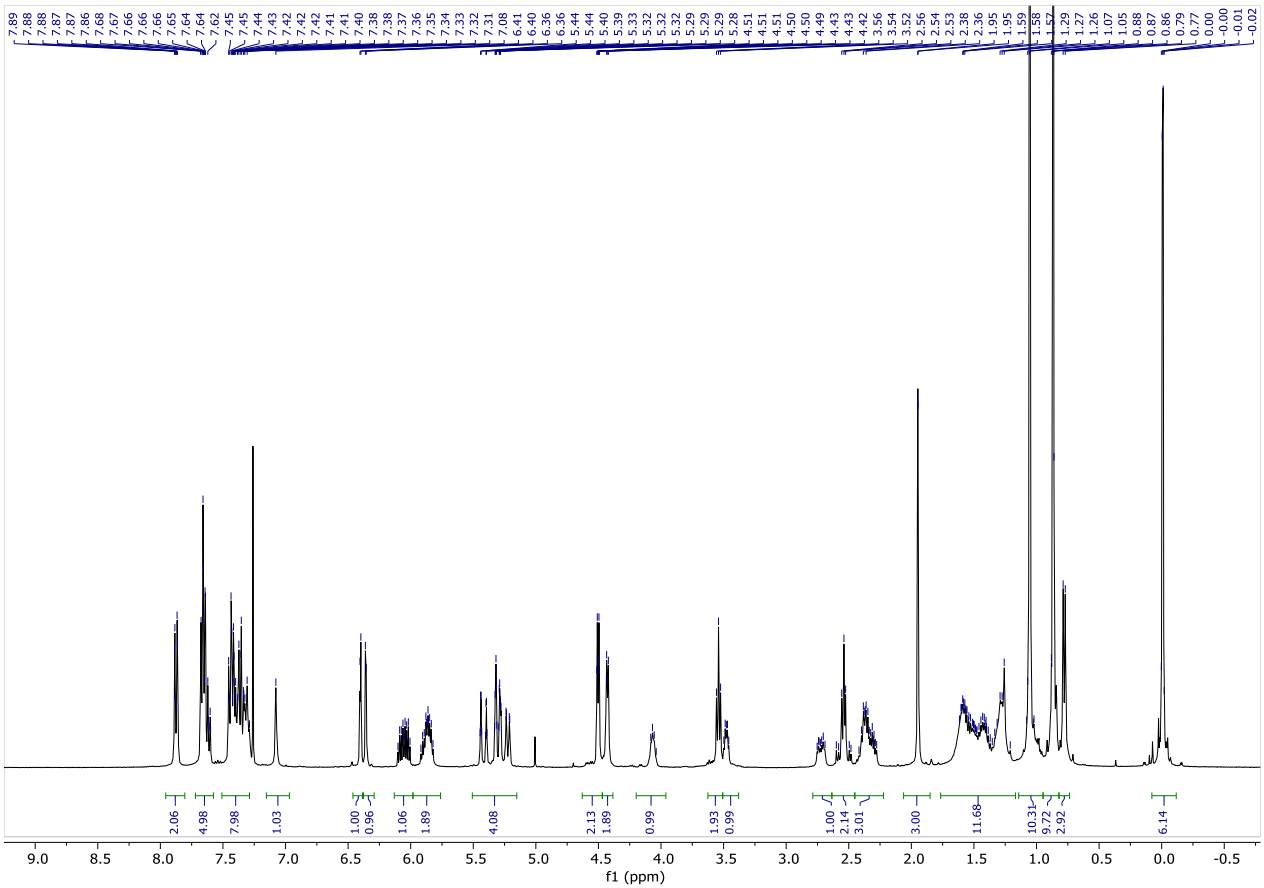
$[\alpha]\frac{D}{20}$: = -21.15 (c = 0.52 ; 5.2 mg / 1 mL, $CHCl_3$, 20°C);

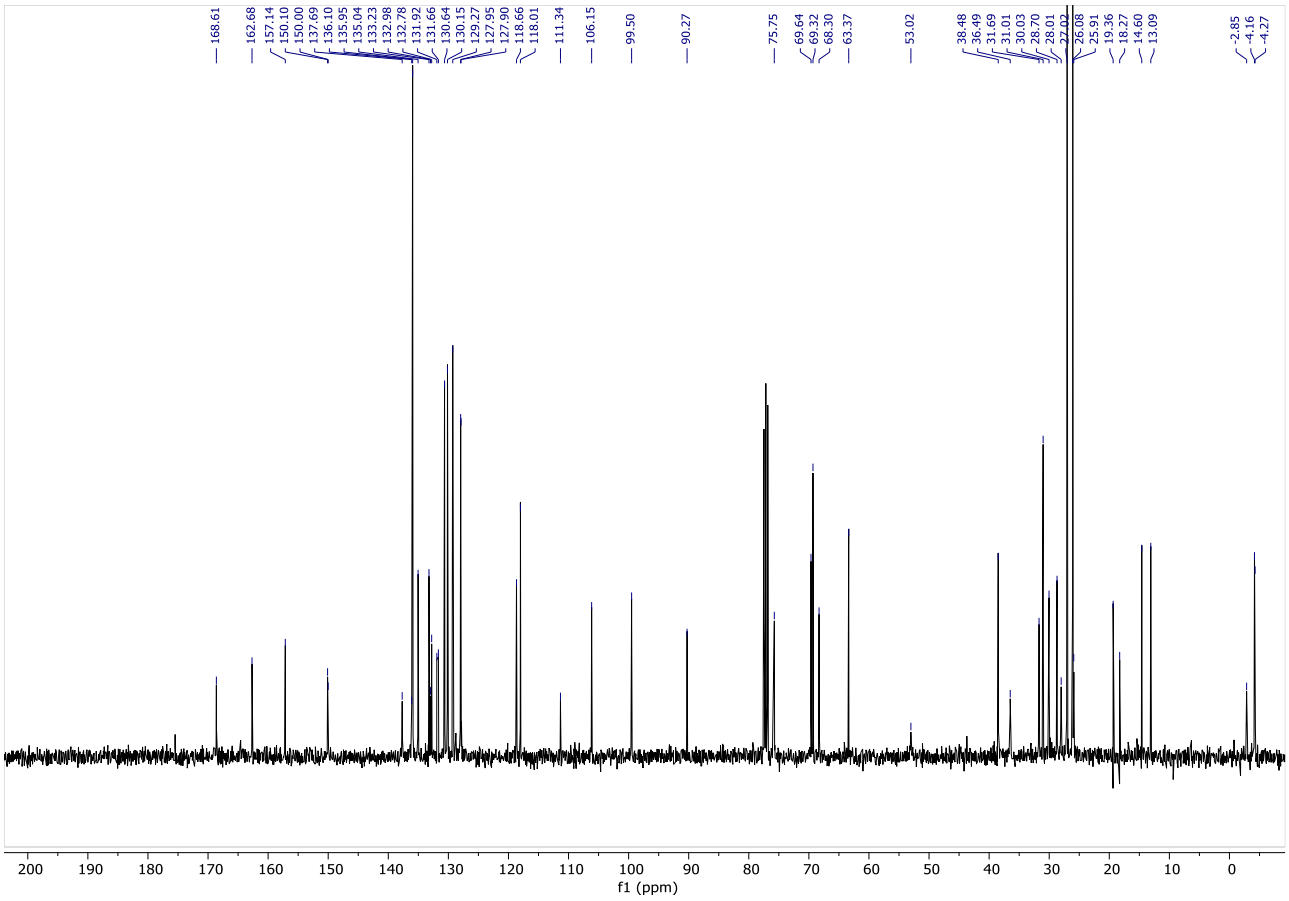
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 – 7.77 (m, 2H), 7.73 – 7.51 (m, 5H), 7.51 – 7.28 (m, 8H), 7.08 (s, 1H), 6.40 (d, J = 2.8 Hz, 1H), 6.36 (d, J = 2.8 Hz, 1H), 6.05 (ddt, J = 17.4, 10.6, 5.3 Hz, 1H), 5.93 – 5.78 (m, 2H), 5.42 (dq, J = 17.2, 1.6 Hz, 1H), 5.38 – 5.26 (m, 2H), 5.25 – 5.17 (m, 1H), 4.50 (dt, J = 5.3, 1.5 Hz, 2H), 4.43 (d, J = 5.4 Hz, 2H), 4.08-4.05 (m, 1H), 3.54 (t, J = 6.6 Hz, 2H), 3.48 (dt, J = 7.7, 4.2 Hz, 1H), 2.77 – 2.64 (m, 1H), 2.61 – 2.45 (m, 2H), 2.41-2-27 (m, 3H), 1.95 (d, J = 1.1 Hz, 3H), 1.70 – 1.18 (m, 11H), 1.05 (s, 9H), 0.87 (s, 9H), 0.78 (d, J = 6.9 Hz, 3H), -0.01 (d, J = 2.9 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.6, 162.7, 157.1, 150.1, 150.0, 137.7, 136.1, 136.0 (4C), 135.0, 133.2, 133.0, 132.8, 131.9, 131.7, 130.6 (2C), 130.2 (2C), 129.3 (2C), 128.0 (2C), 127.9 (2C), 118.7, 118.0, 111.3, 106.2, 99.5, 90.3, 75.8, 69.6, 69.3, 68.3, 63.4, 53.0, 38.5, 36.5, 31.7, 31.0, 30.0, 28.7, 28.0, 27.0 (3C), 26.1 (3C), 25.9, 19.4, 18.3, 14.6, 13.1, -2.9, -4.2, -4.3.

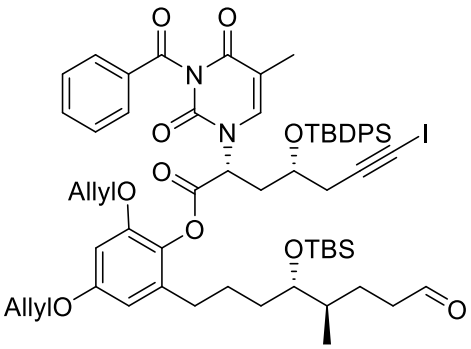
IR (film): v = 2930, 2857, 1753, 1703, 1662, 1599, 1488, 1461, 1428, 1363, 1256, 1228, 1185, 1112, 1089, 1057, 982, 835, 773, 744, 705;

HRMS (ESI-TOF) m/z (ESI) $C_{62}H_{80}IN_2O_{10}Si_2$ $[M+H]^+$ 1195.4391, found 1195.4381.




168.61
162.68
157.14
150.10
150.00
137.69
136.10
135.95
135.04
133.23
132.98
132.78
131.92
131.66
130.64
130.15
129.27
127.95
127.90
118.66
118.01
111.34
106.15
99.50
90.27
75.75
69.64
69.32
68.30
63.37
53.02
38.48
36.49
31.69
31.01
30.03
28.70
28.01
27.02
26.08
25.91
19.36
18.27
14.60
13.09
-2.85
-4.16
-4.27
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-methyl-8-oxooctyl)phenyl (2R,4R)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)-7-iodohept-6-ynoate ((R,R)-**84**)*



In a flame-dried flask, a solution of the alcohol (R,R)-**93** (999 mg, 0.84 mmol, 1.0 equiv.) in dry DCM (22.6 ml, c=0.037 M) was prepared. DMP (400 mg, 0.94 mmol, 1.13 equiv.) and $NaHCO_3$ (351 mg, 4.18 mmol, 5.0 equiv.) were added at room temperature After 5 h at room temperature after seeing the reaction completion by TLC, the reaction mixture was quenched with $NaHCO_3$+$Na_2S_2O_3$ solution (20 ml) and stirred for 60 min. The aqueous layer was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude material (m=1 g) was purified by FC (2 cm) with an eluent mixture of Toluene: EtOAc (20:1 to 5:1) yielding the desired product (R,R)-**84** (910 mg, 91 %) as a colorless oil.

Yield: 0.91 g (91 %);

R_f = 0.574 (5:1 Toluene: EtOAc), CPS staining;

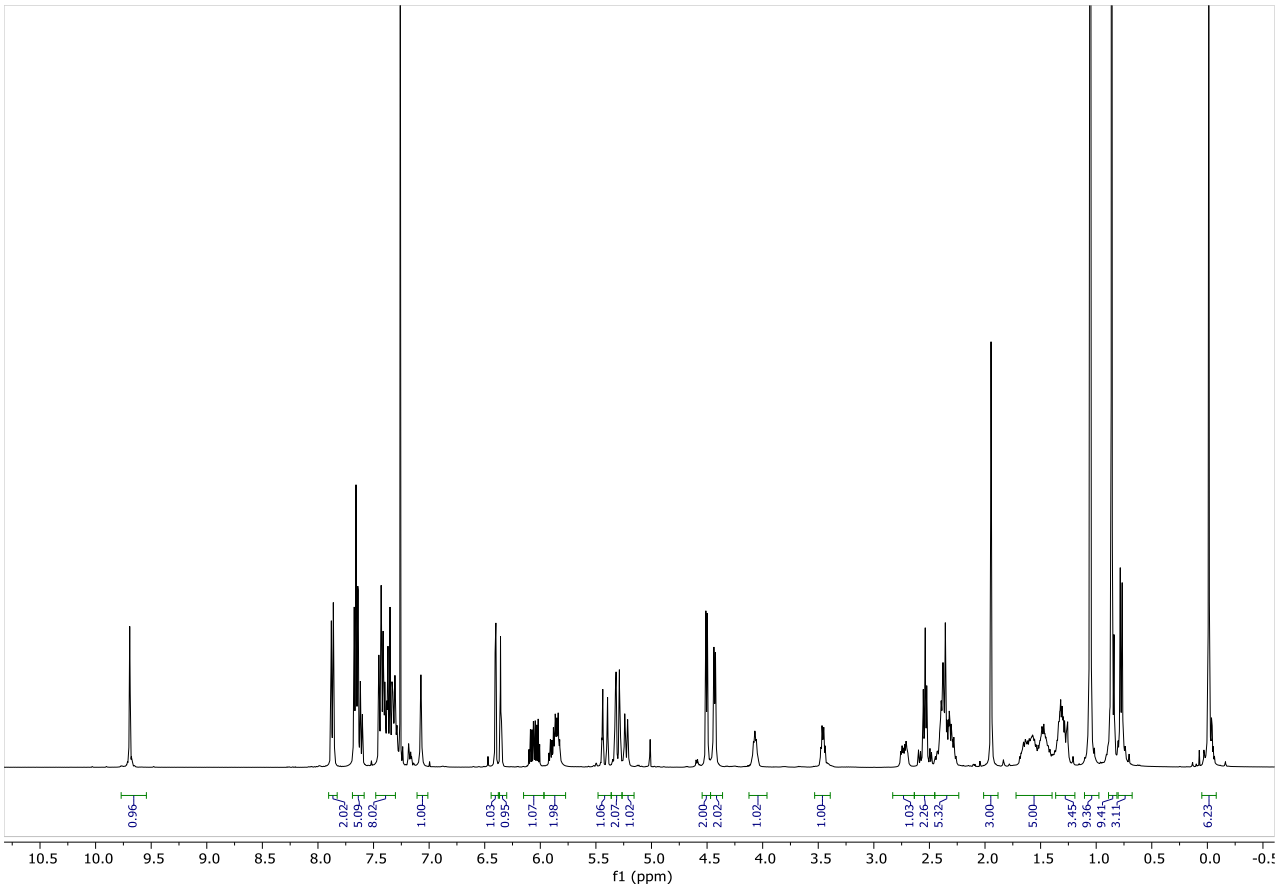
$[\alpha]_{20}^{D}$: = -19.23 (c = 0.52 ; 2.6 mg / 0.5 mL, $CHCl_3$, 20°C);

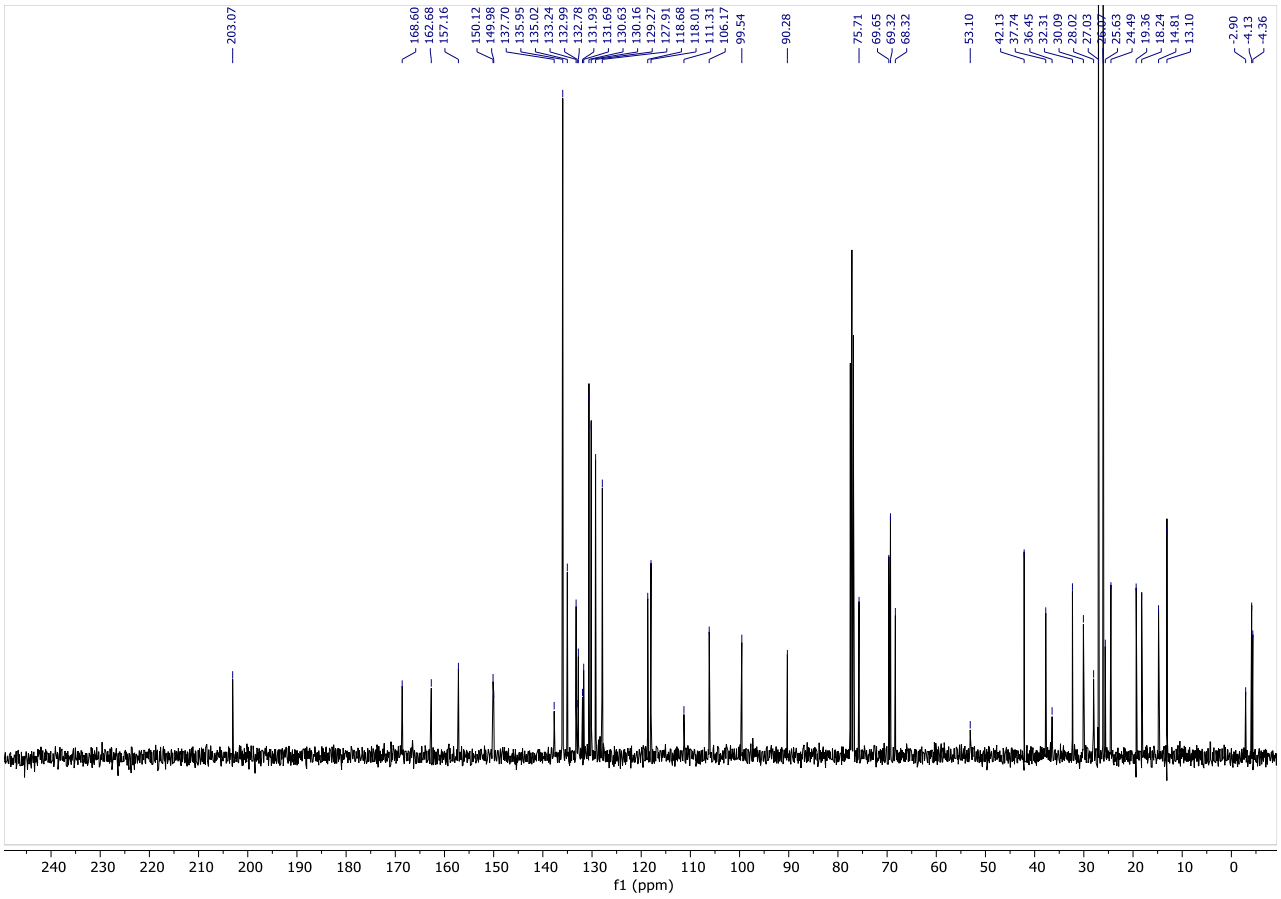
^{1}H NMR (400 MHz, Chloroform-d) δ 9.69 (t, J = 1.9 Hz, 1H), 8.02 – 7.76 (m, 2H), 7.75 – 7.55 (m, 5H), 7.47 – 7.27 (m, 8H), 7.07 (d, J = 1.4 Hz, 1H), 6.40 (d, J = 2.7 Hz, 1H), 6.35 (d, J = 2.7 Hz, 1H), 6.05 (ddt, J = 17.3, 10.6, 5.3 Hz, 1H), 5.93 – 5.77 (m, 2H), 5.42 (dq, J = 17.3, 1.6 Hz, 1H), 5.35 – 5.17 (m, 3H), 4.50 (dt, J = 5.3, 1.5 Hz, 2H), 4.43 (dt, J = 5.7, 1.5 Hz, 2H), 4.19 – 3.95 (m, 1H), 3.46 (dt, J = 6.6, 4.6 Hz, 1H), 2.73 (ddd, J = 14.7, 6.2, 4.1 Hz, 1H), 2.54 (t, J = 6.2 Hz, 2H), 2.44 – 2.22 (m, 5H), 1.95 (d, J = 1.1 Hz, 3H), 1.73 – 1.19 (m, 8H), 1.05 (s, 9H), 0.86 (s, 9H), 0.78 (d, J = 6.8 Hz, 3H), -0.01 (d, J = 0.8 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 203.1, 168.6, 162.7, 157.2, 150.1, 150.0, 137.7, 136.0 (4C), 135.0, 133.2, 132.8, 131.9, 131.7, 130.6 (2C), 130.2 (2C), 129.3 (2C), 128.0 (2C), 127.9 (2C), 118.7, 118.0, 111.3, 106.2, 99.5, 90.3, 75.7, 69.7, 69.3, 68.3, 53.1, 42.1, 37.7, 36.5, 32.3, 30.1, 28.0, 27.0 (3C), 26.1 (3C), 25.6, 24.5, 19.4, 18.2, 14.8, 13.1, -2.9, -4.1, -4.4;

IR (film): *v* = 2954, 2930, 2885, 2857 (CHO), 1752, 1721 (C=O), 1703, 1662, 1598, 1488, 1471, 1461, 1428, 1363, 1255, 1228, 1184, 1111, 1088, 1000, 982, 936, 910, 835, 773, 761, 735, 704, 686, 673, 613, 545, 506;

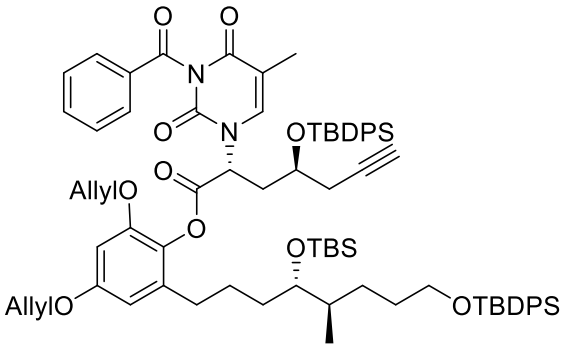
HRMS (ESI-TOF) m/z (ESI) $C_{62}H_{81}IN_3O_{10}Si_2$ $[M+NH_4]^+$ 1210.4500, found 1210.4495.




203.07
168.60
162.68
157.16
150.12
149.98
137.70
135.95
135.02
133.24
132.99
132.78
131.93
131.69
130.63
130.16
129.27
127.91
118.68
118.01
111.31
106.17
99.54
90.28
75.71
69.65
69.32
68.32
53.10
42.13
37.74
36.45
32.31
30.09
28.02
27.03
26.02
25.63
24.49
19.36
18.24
14.81
13.10
-2.90
-4.13
-4.36
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

5.3.2.2 Iodoynal (*R,S*)-84

*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-((tert-butyldiphenylsilyl)oxy)-5-methyloctyl)phenyl (2R,4S)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)hept-6-ynoate ((R,S)-**85**)*



A solution of predried acid (R,S)-**2** (580 mg, 0.953 mmol, 1.0 equiv.) in dry DCM (7.94 mL, c=0.12 M) was prepared. And then, the phenol **55** (752 mg, 1.048 mmol, 1.00 equiv.) was added. and DMAP (23.3 mg, 0.191 mmol, 0.2 equiv.). The resulting solution was cooled to 0 °C and stirred for 15 min. And then the DCC (432.5 mg, 2.1 mmol, 1.2 equiv.) was added at 0 °C. The DCC was also dried. The reaction was stirred at 0 °C and then slowly allowed to warm up to room temperature and left overnight for 50 hours. When checked by TLC the reaction was done after 50 h, the rxn mixture was diluted with hexane and filtered off through celite, and concentrated. The crude material was purified via 1cm column chromatography with toluene as an eluent, switching to 50:1 tol: EtOAc to afford the desired product (R,S)-**85** (0.66 g, 53 %) in good yield.

Yield: 0.66 g (53 %);

R_f = 0.255 (5:1 Hexane: EtOAc), CPS staining;

$[\alpha]_{20}^{D}$: = +2.0 (c = 1.0; $CHCl_3$, 20°C);

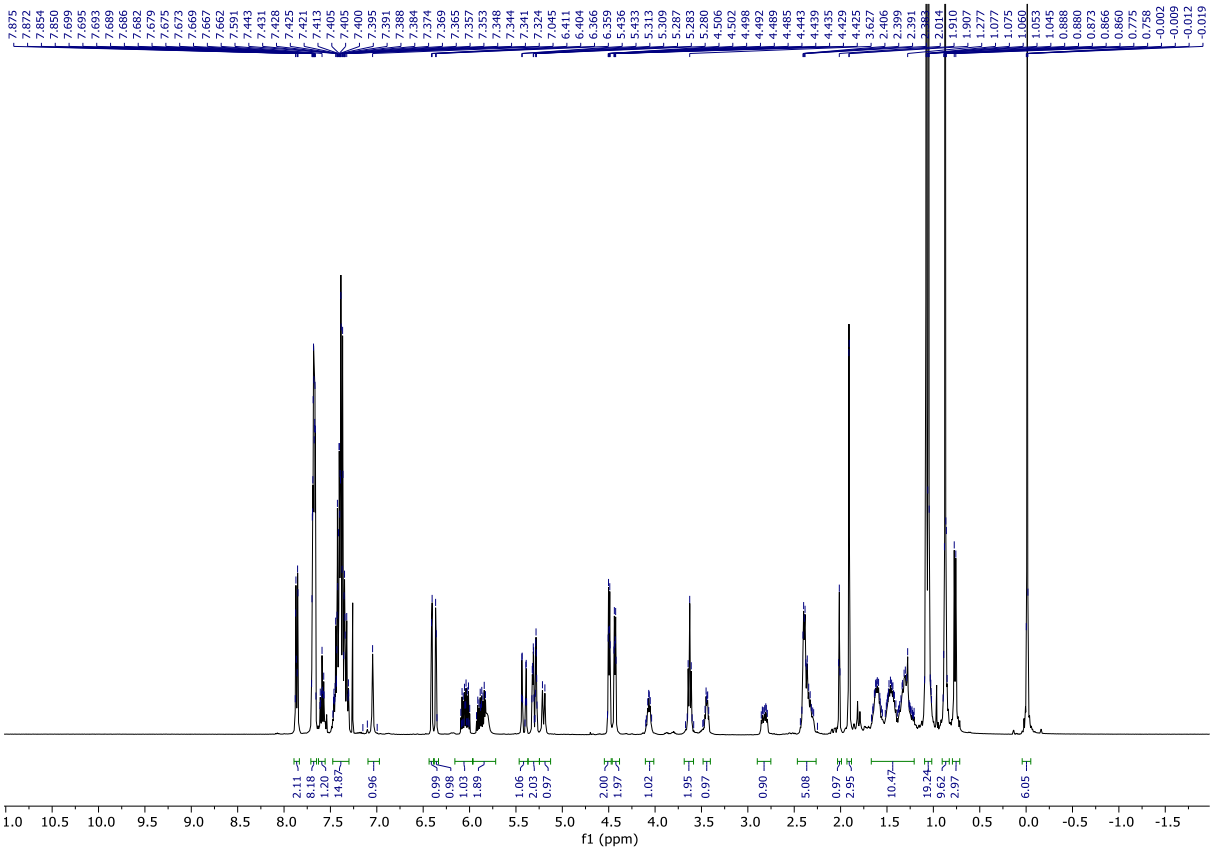
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 – 7.82 (m, 2H), 7.68 (ddt, J = 6.6, 4.2, 1.4 Hz, 8H), 7.63 – 7.56 (m, 1H), 7.50 – 7.28 (m, 17H), 7.05 (s, 1H), 6.41 (d, J = 2.8 Hz, 1H), 6.36 (d, J = 2.7 Hz, 1H), 6.05 (ddt, J = 17.3, 10.5, 5.3 Hz, 1H), 5.88 (ddt, J = 17.3, 10.6, 5.4 Hz, 1H), 5.41 (dq, J = 17.2, 1.6 Hz, 1H), 5.34 – 5.26 (m, 2H), 5.20 (d, J = 10.4 Hz, 1H), 4.50 (dt, J = 5.3, 1.5 Hz, 2H), 4.43 (dt, J = 5.5, 1.5 Hz, 2H), 4.06 (dt, J = 10.2, 5.1 Hz, 1H), 3.63 (t, J = 6.7 Hz, 2H), 3.44 (dt, J = 7.0, 4.4 Hz, 1H), 2.82 (ddd, J = 14.5, 6.7, 4.5 Hz, 1H), 2.48 – 2.23 (m, 5H), 2.05 – 1.97 (m, 1H), 1.91 (d, J = 1.2 Hz, 3H), 1.68 – 1.19 (m, 9H), 1.08 (s, 7H), 1.05 (s, 9H), 0.87 (s, 9H), 0.77 (d, J = 6.8 Hz, 3H), -0.01 (d, J = 1.2 Hz, 6H);

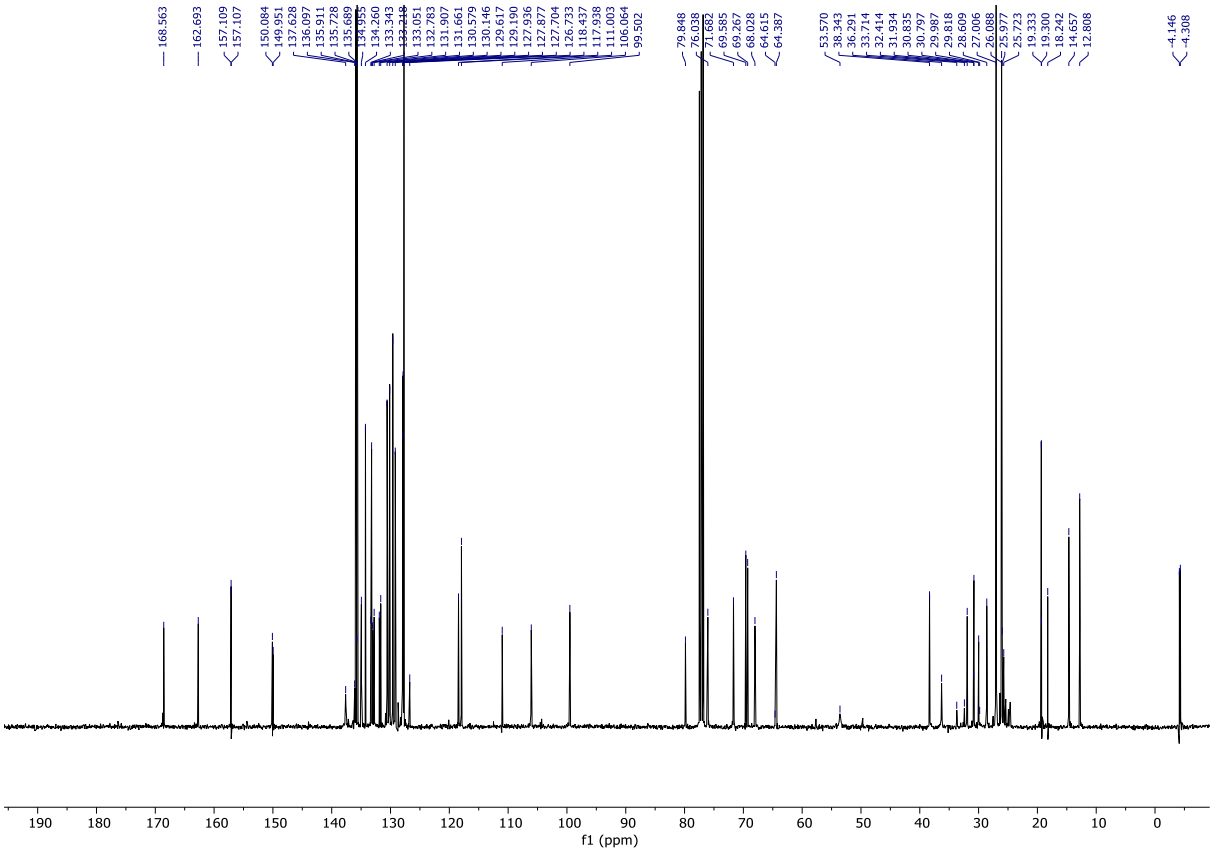
^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.6, 162.7, 157.1, 150.1, 150.0, 137.6, 136.1, 135.9, 135.7, 135.0, 134.3, 133.3, 133.2, 133.1, 132.8, 131.9, 131.7, 130.6, 130.2, 129.6, 129.2, 127.9, 127.9, 127.7, 126.7,

118.4, 117.9, 111.0, 106.1, 99.5, 79.9, 76.0, 71.7, 69.6, 69.3, 68.0, 64.4, 53.6, 38.3, 36.3, 33.7, 32.4, 31.9, 30.8, 30.0, 28.6, 27.0, 26.1, 26.0, 25.7, 19.3, 18.2, 14.7, 12.8, -4.2, -4.3;

IR (film): ν = 3309, 3072, 2931, 2894, 2857, 1754, 1703, 1664, 1599, 1488, 1472, 1462, 1428, 1362, 1256, 1229, 1184, 1110, 1087, 999, 981, 936, 908, 834, 823, 773, 730, 701, 685, 672, 648, 622, 612;

HRMS (ESI-TOF) m/z (ESI) $C_{78}H_{98}N_2NaO_{10}Si_3$ $[M+Na]^+$ 1329.6421, found 1329.6438.




168.563
162.693
157.109
157.107
150.084
149.951
137.628
136.097
135.911
135.728
135.689
134.995
134.260
133.343
132.751
132.703
131.907
131.667
130.578
130.146
129.617
129.190
127.936
127.877
127.704
126.733
118.437
117.938
111.003
106.064
99.502
79.848
76.038
71.682
69.585
69.267
68.028
64.615
64.387
53.570
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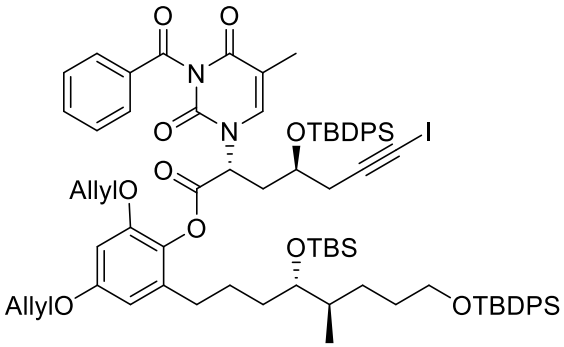
36.291
33.714
32.414
31.934
30.955
29.987
29.818
28.609
27.006
26.088
25.977
25.723
19.333
19.300
18.242
14.657
12.808
-4.146
-4.308
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-((tert-butyldiphenylsilyl)oxy)-5-methyloctyl)phenyl (2R,4S)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)-7-iodohept-6-ynoate ((R,S)-**93**)*



A solution of (R,S)-**85** (660 mg, 0.51 mmol, 1.0 equiv.) in dry DMF (6.31 ml, c=0.08 M) was prepared at room temperature under argon atmosphere. And then the N-iodosuccinimide (164.6 mg, 0.732 mmol, 1.45 equiv.) and silver nitrate (17.1 mg, 0.101 mmol, 0.2 equiv.) were added at room temperature When the reaction was complete by TLC, at 16:20, it was poured into a saturated $Na_2S_2O_3$ for quenching (color turned bright yellow and precipitated, then disappeared-AgI?). Washed with $NaHCO_3$, to get rid of succinimide. Extraction with EA was followed by evaporation of the solvent gave the crude product, which was purified by silica-gel column chromatography (pure toluene, then ea: tol=1:50, 1:20) affording the product (R,S)-**93** (590, 82 %) as a white foamy substrate.

Yield: 590 mg (82 %);

R_f = 0.3934 (50:1 = Toluene: EtOAc), CPS staining;

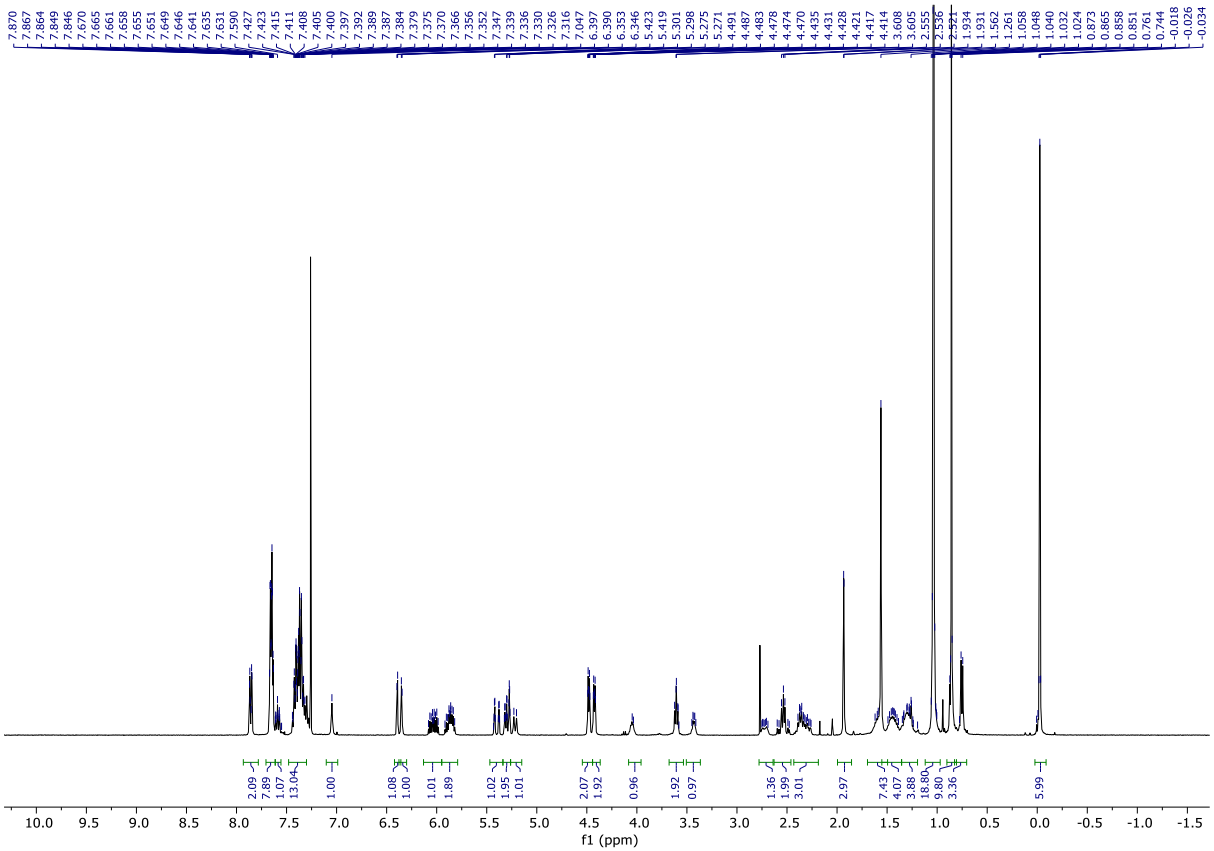
$[\alpha]\frac{D}{20}$: = -15.00 (c = 1.0; $CHCl_3$, 20°C);

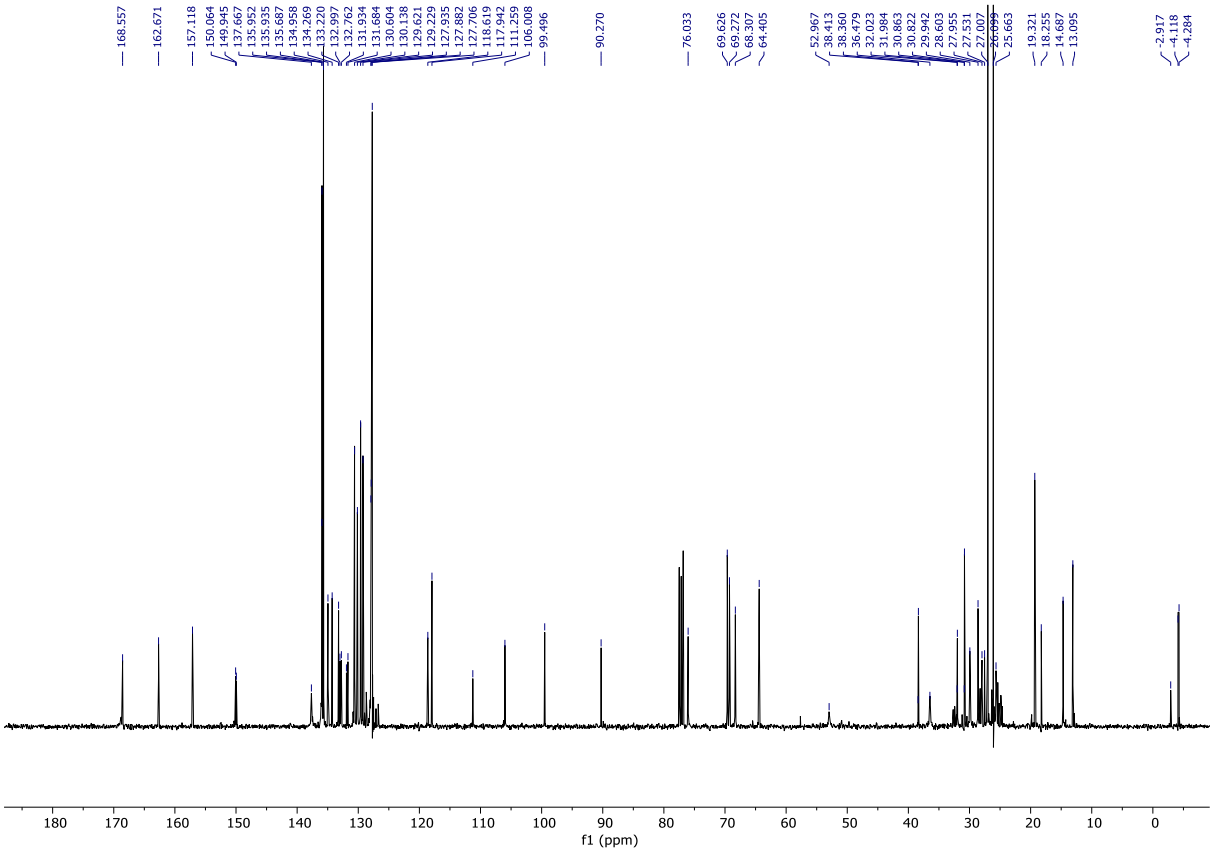
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 – 7.76 (m, 2H), 7.74 – 7.61 (m, 8H), 7.59 (td, J = 7.3, 1.3 Hz, 1H), 7.46 – 7.30 (m, 12H), 7.05 (s, 1H), 6.39 (d, J = 2.7 Hz, 1H), 6.35 (d, J = 2.7 Hz, 1H), 6.03 (ddt, J = 17.3, 10.6, 5.3 Hz, 1H), 5.94 – 5.75 (m, 2H), 5.40 (dq, J = 17.2, 1.6 Hz, 1H), 5.35 – 5.26 (m, 2H), 5.22 (d, J = 10.4 Hz, 1H), 4.48 (dt, J = 5.3, 1.6 Hz, 2H), 4.42 (dt, J = 5.5, 1.4 Hz, 2H), 4.05 (s, 1H), 3.70 – 3.51 (m, 2H), 3.43 (dt, J = 7.4, 4.3 Hz, 1H), 2.77 – 2.66 (m, 2H), 2.61 – 2.43 (m, 2H), 2.41 – 2.20 (m, 3H), 1.93 (d, J = 1.1 Hz, 3H), 1.68 – 1.19 (m, 14H), 1.04 (s, 10H), 1.03 (s, 9H), 0.86 (s, 9H), 0.75 (d, J = 6.7 Hz, 3H), -0.03 (s, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.6, 162.7, 157.1, 150.1, 149.9, 137.7, 135.9, 135.7, 135.0, 134.3, 133.2, 133.0, 132.8, 131.9, 131.7, 130.6, 130.1, 129.6, 129.2, 128.0, 127.9, 127.9, 127.7, 118.6, 117.9, 111.3, 106.0, 99.5, 90.3, 76.0, 69.6, 69.3, 68.3, 64.4, 53.0, 38.4, 36.5, 32.0, 30.8, 29.9, 28.6, 28.0, 27.5, 27.0, 26.1, 25.7, 19.3, 18.3, 14.7, 13.1, -2.9, -4.1, -4.3;

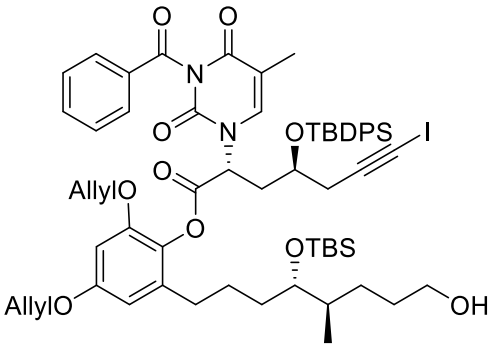
IR (film): v = 3410, 1752, 1702, 1661, 1049, 1024, 1001, 823, 762, 704, 627, 532, 502;

HRMS (ESI-TOF) m/z (ESI) $C_{78}H_{97}IN_2NaO_{10}Si_3$ $[M+Na]^+$ 1455.5388, found 1455.5394.





*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-hydroxy-5-methyloctyl)phenyl (2R,4S)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)-7-iodohept-6-ynoate ((R,S)-**94**)*



Ammonium fluoride (366.2 mg, 31.5 equiv.) was added to a solution of (R,S)-**93** (450 mg, 0.314 mmol, 1.0 equiv.) in 1,1,1,3,3,3-hexafluro-2-propanol (3.1385 mL, c=0.1 M) and the resulting solution stirred at an ambient temperature (13:40) with continuous control via TLC. After 2 days in total, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (2-3 ml) and the aqueous phase was extracted with DCM (5 mL) four times. The combined organic extracts were dried over $MgSO_4$ and concentrated. The crude material was purified by pipet flash chromatography, starting with 10:1 hex: ea to 2:1 hex: ea, then flush with ea. The desired product (R,S)-**94** came out in fractions 39-46 (345 mg, 92 %).

Yield: 0.345 g (92 %);

R_f = 0.145 (3:1 Hexane: EtOAc), CPS staining;

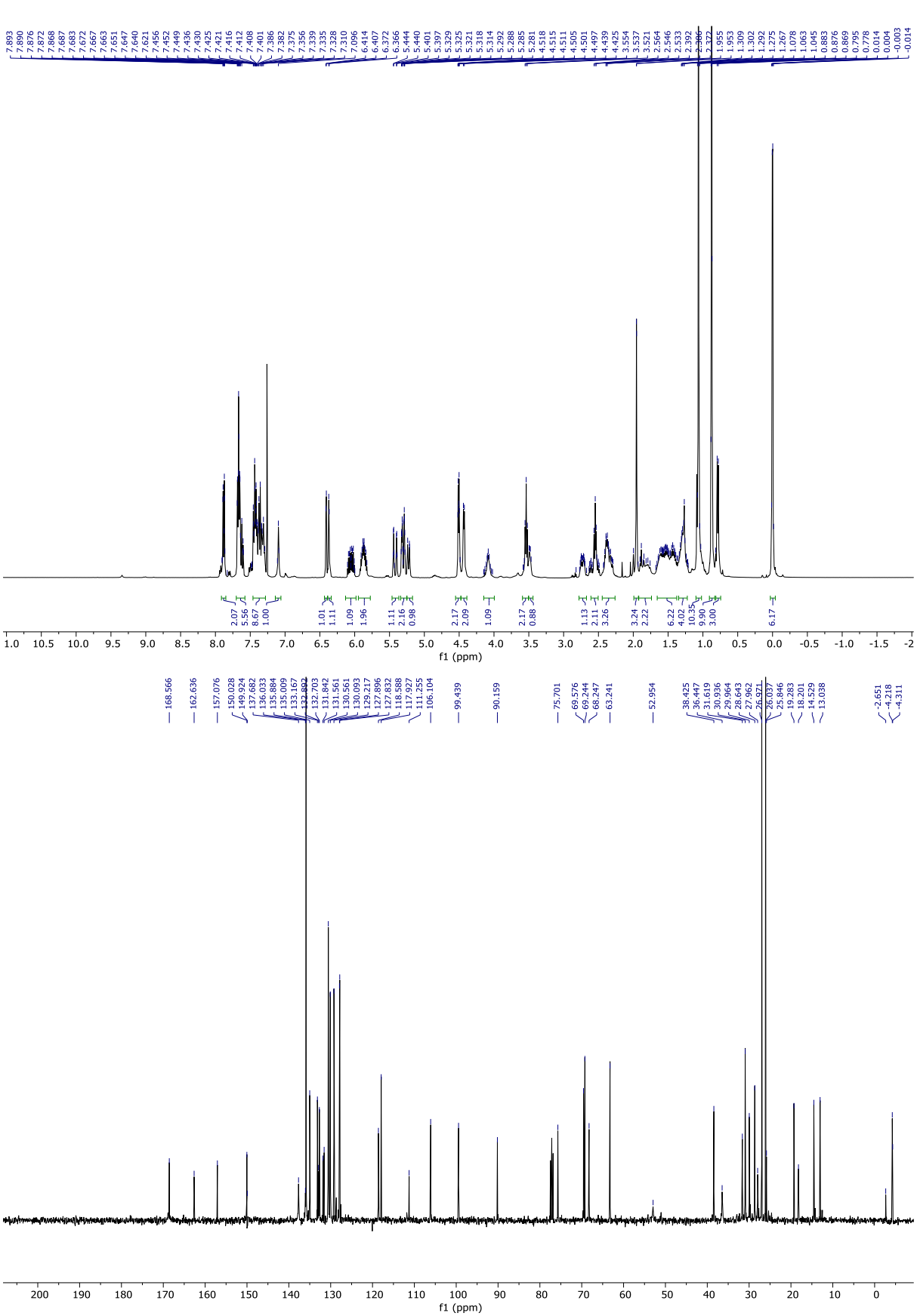
$[\alpha]\frac{D}{20}$: = -22.00 (c = 0.5 ; $CHCl_3$, 20°C);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.08 (tq, J = 13.1, 7.2 Hz, 1H), 3.54 (t, J = 6.6 Hz, 2H), 3.48 (q, J = 4.0 Hz, 1H), 2.83 – 2.66 (m, 1H), 2.64 – 2.47 (m, 2H), 2.45 – 2.25 (m, 3H), 1.99 – 1.93 (m, 3H), 1.91 – 1.20 (m, 6H), 1.06 (s, 9H), 0.87 (d, J = 2.6 Hz, 10H), 0.79 (d, J = 6.9 Hz, 3H), 0.00 (d, J = 3.0 Hz, 6H), 7.90 – 7.86 (m, 2H), 7.73 – 7.57 (m, 6H), 7.49 – 7.27 (m, 8H), 7.09 (d, J = 3.2 Hz, 1H), 6.41 (d, J = 2.7 Hz, 1H), 6.37 (d, J = 2.6 Hz, 1H), 6.05 (ddt, J = 17.4, 10.6, 5.3 Hz, 1H), 5.94 – 5.81 (m, 2H), 5.42 (dq, J = 17.3, 1.6 Hz, 1H), 5.36 – 5.26 (m, 2H), 5.26 – 5.20 (m, 1H), 4.51 (dt, J = 5.4, 1.5 Hz, 2H), 4.43 (d, J = 5.5 Hz, 2H);

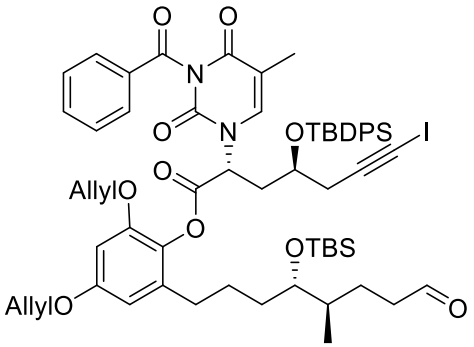
^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.6, 162.6, 157.1, 150.0, 149.9, 137.7, 136.0, 135.9, 135.0, 133.2, 132.9, 132.7, 131.8, 131.6, 130.6, 130.1, 129.2, 127.9, 127.8, 118.6, 117.9, 111.3, 106.1, 99.4, 90.2, 75.7, 69.6, 69.2, 68.3, 63.2, 53.0, 38.4, 36.5, 31.6, 30.9, 30.0, 28.6, 28.0, 27.0, 26.0, 25.9, 19.3, 18.2, 14.5, 13.0, -2.7, -4.2, -4.3;

IR (film): ν = 3588, 2931, 2855, 1753, 1701, 1664, 1598, 1429, 1363, 1257, 1185, 1113, 980, 834, 704, 662, 618;

HRMS (ESI-TOF) m/z (ESI) $C_{62}H_{79}IN_2NaO_{10}Si_2$ $[M+Na]^+$ 1217.4210, found 1217.4187.



*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-methyl-8-oxooctyl)phenyl (2R,4S)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)-7-iodohept-6-ynoate ((R,S)-**84**)*



In a flame-dried 50 ml flask, a solution of (R,S)-**94** (0.29 g, 0.243 mmol, 1.0 equiv.) in dry DCM (6.56 ml, c=0.037 M) was prepared under Argon atmosphere at room temperature Then, DMP (154.3 g, 1.5 equiv.) and $NaHCO_3$ (76.4 mg, 3.75 equiv.) were added at room temperature The reaction was stirred at room temperature for 2 h while being monitored by TLC. When the reaction was finished by TLC, it was diluted with DCM (10 ml) and quenched with 15 ml of DMP quenching solution ($Na_2S_2O_3$ and $NaHCO_3$) for 3-5 mins (not more). The aqueous layer was extracted with DCM (20 ml x 3). The combined organic layers were washed with brine, dried over magnesium sulfate, and filtered; the solvent was removed under reduced pressure. The crude material was purified by 2 cm FC (3:1 hex: ea to pure ea), obtaining the desired product (R,S)-**84** (204.5 mg, 71 %) in fractions 8-30.

Yield: 204.5 mg (71 %);

R_f = 0.6837 (2:1 Hexane: EtOAc), CPS staining;

$[\alpha]_{20}^{D}$: = -24.99 (c = 1.0; $CHCl_3$, 20°C);

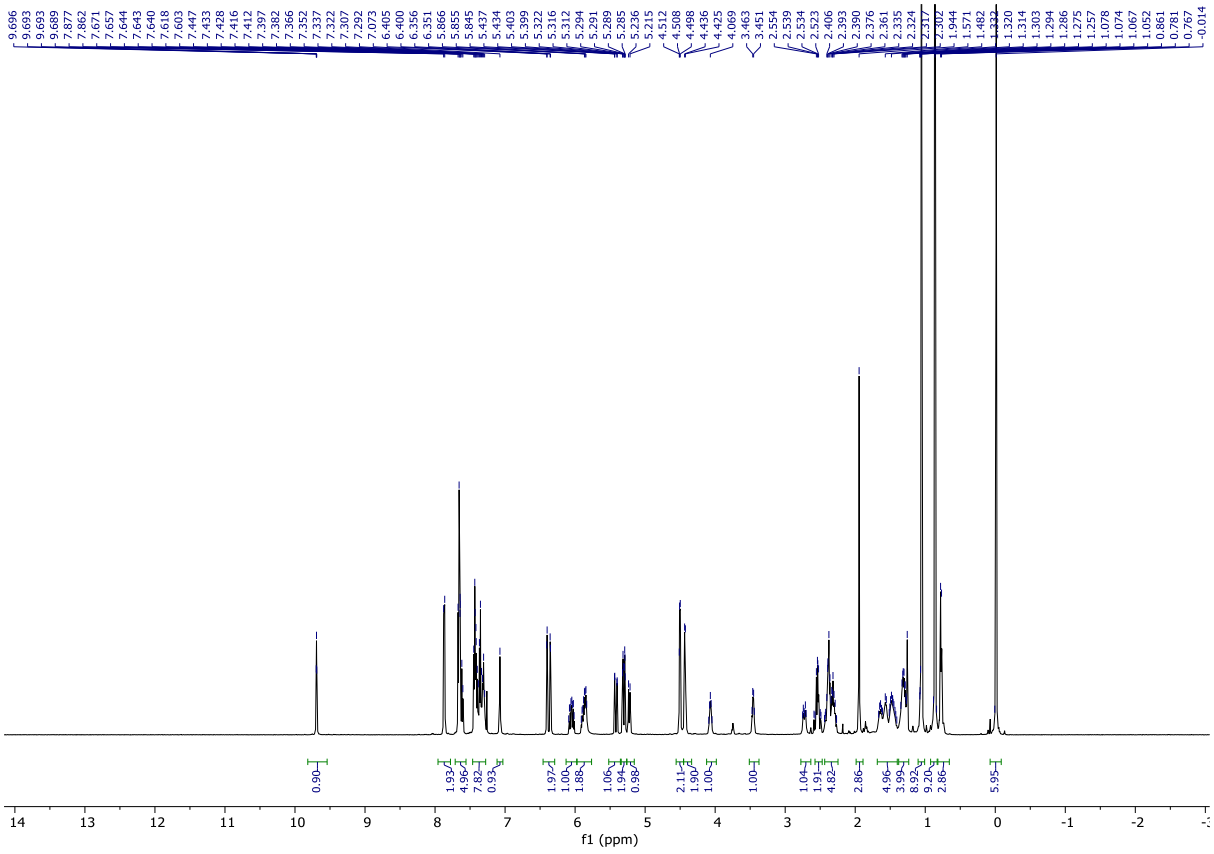
^{1}H NMR (500 MHz, Chloroform-d) δ 9.69 (d, J = 1.7 Hz, 1H), 7.87 (d, J = 7.7 Hz, 2H), 7.64 (dt, J = 18.6, 7.5 Hz, 6H), 7.47 – 7.28 (m, 9H), 7.07 (s, 1H), 6.40 (d, J = 2.7 Hz, 1H), 6.35 (d, J = 2.7 Hz, 1H), 6.05 (ddt, J = 16.2, 10.5, 5.3 Hz, 1H), 5.87 (ddt, J = 16.1, 10.5, 5.4 Hz, 2H), 5.42 (dd, J = 17.2, 1.8 Hz, 1H), 5.36 – 5.27 (m, 2H), 5.23 (d, J = 10.5 Hz, 1H), 4.50 (d, J = 5.1 Hz, 2H), 4.43 (d, J = 5.5 Hz, 2H), 4.07 (p, J = 5.9 Hz, 1H), 3.46 (q, J = 4.8 Hz, 1H), 2.73 (dt, J = 14.9, 5.3 Hz, 1H), 2.61 – 2.46 (m, 2H), 2.36 (dtt, J = 29.4, 15.4, 8.1 Hz, 6H), 1.94 (s, 3H), 1.73 – 1.38 (m, 4H), 1.39 – 1.21 (m, 3H), 1.05 (s, 11H), 0.86 (s, 10H), 0.77 (d, J = 6.8 Hz, 3H), -0.01 (s, 7H);

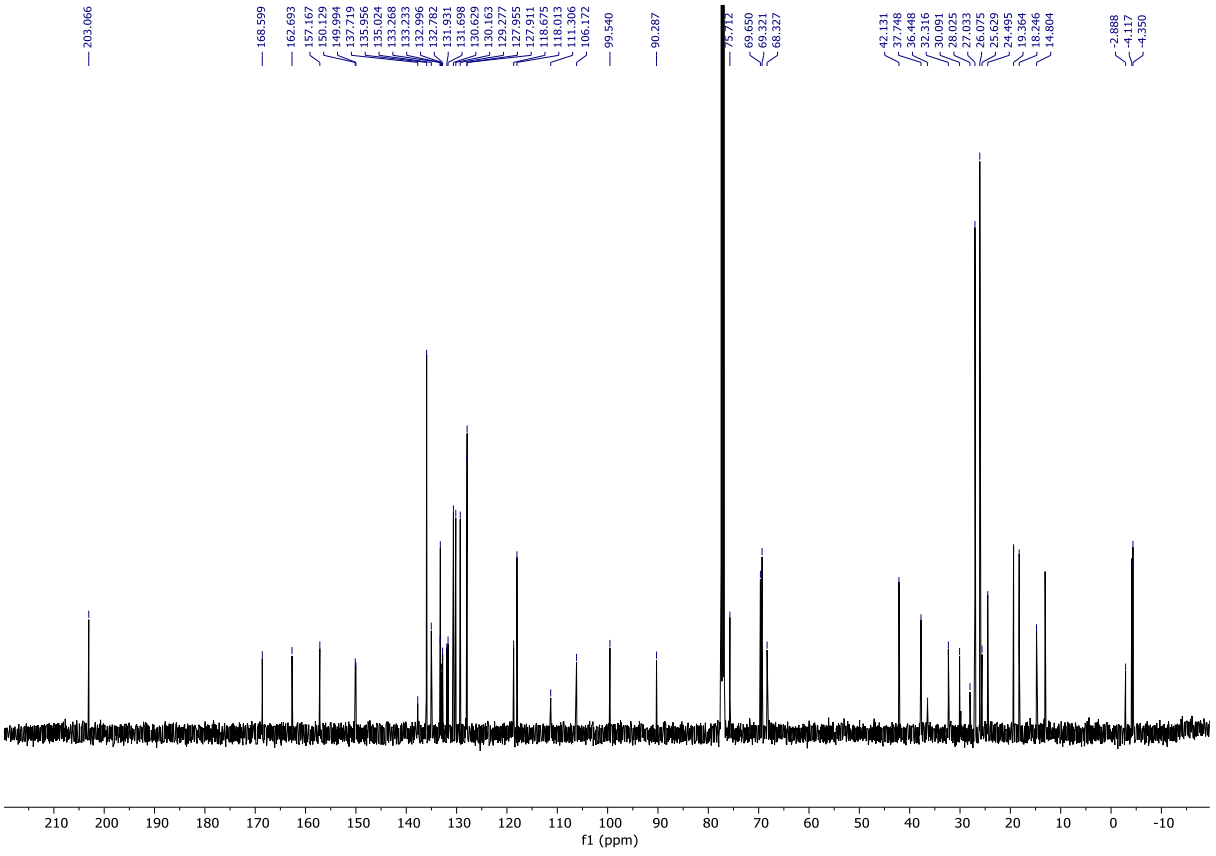
^{13}C NMR (126 MHz, Chloroform-d) δ 203.1, 168.6, 162.7, 157.2, 150.1, 150.0, 137.7, 136.0, 135.0, 133.3, 133.2, 133.0, 132.8, 131.9, 131.7, 130.6, 130.2, 129.3, 128.0, 127.9, 118.7, 118.0, 111.3, 106.2, 99.5,

90.3, 75.7, 69.7, 69.3, 68.3, 42.1, 37.8, 36.5, 32.3, 30.1, 28.0, 27.0, 26.1, 25.6, 24.5, 19.4, 18.3, 14.8, -2.9, -4.1, -4.4;

IR (film): ν = 3072, 2954, 2930, 2857, 1753, 1702, 1664, 1598, 1488, 1472, 1461, 1428, 1363, 1256, 1228, 1184, 1111, 1089, 1000, 982, 936, 885, 835, 774, 742, 704, 686, 673, 612;

HRMS (ESI-TOF) m/z (ESI) $C_{62}H_{77}IN_2NaO_{10}Si_2$ $[M+Na]^+$ 1215.4054, found 1215.4055.

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157.167
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149.994
137.719
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133.233
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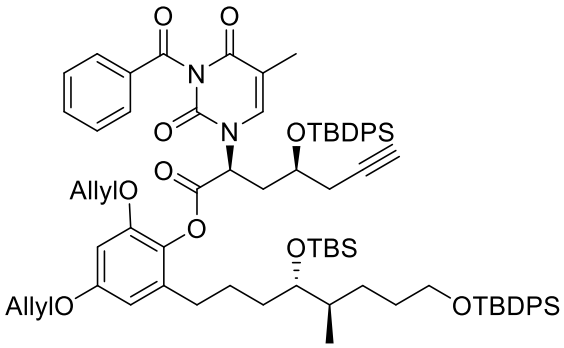
131.931
131.698
130.629
130.163
129.277
127.955
127.911
118.675
118.013
111.306
106.172
99.540
90.287
75.712
69.650
69.321
68.327
42.131
37.748
36.448
32.316
30.091
28.025
27.033
26.075
25.629
24.495
19.364
18.246
14.804
-2.888
-4.117
-4.350
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

5.3.2.3 Iodoynal (*S,S*)-84

*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-((tert-butyldiphenylsilyl)oxy)-5-methyloctyl)phenyl (2S,4S)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)hept-6-ynoate ((S,S)-**85**)*



Important: both starting materials were dried by co-evaporation with toluene on a high vacuum rotary evaporator for several hours+keeping under a high vacuum before starting the reaction. A solution of (S,S)-**2** (370 mg, 0.61 mmol, 1.0 equiv.) in dry DCM (5.065 mL, c=0.12 M) was prepared. Then, the phenol **55** (479.5 mg, 0.67 mmol, 1.10 equiv.) was added, followed by DMAP (14.9 mg, 0.12 mmol, 0.2 equiv.). The resulting solution was cooled to 0 °C and stirred for 15 min. And then the DCC (275.9 mg, 1.34 mmol, 2.2 equiv.) was added. The DCC was not dried this time. The reaction was stirred for 2 hours at 0 °C and then slowly allowed to warm up to room temperature and left overnight. When the reaction was done after 1 day, the rxn mixture was diluted with hexane and filtered off through celite, and concentrated. The crude material (M=918 mg) was purified via column chromatography (d=5.5 cm) with toluene as an eluent, switching to 50:1 tol: EtOAc , better to keep the ratio of 50:1 until all the desired product is out for better separation. (S,S)-**85** was isolated (430 g, 54 %).

2nd way to obtain this material from SI-(S,S)-85 Bz PG installation:

The residue was co-evaporated with dry pyridine (3 X 2 mL) and dried under a high vacuum for 1 h. **SI**-(S,S)-**85** (610 mg, 0.51 mmol, 1.0 equiv.) was dissolved in anhydrous pyridine (2.534 mL, c=0.2 M) and the solution was cooled to 0 ˚C. Benzoyl chloride (442 mkL, 3.8 mmol., 7.5 equiv.) was added dropwise at 0 ˚C. The reaction mixture was allowed to room temperature and stirred for 3 days until completion indicated by TLC. The reaction was worked up by dissolving in DCM (6.33 mL, c=0.08M) and the organic layer was washed with water (10 mL), followed by a saturated aqueous solution of $NaHCO_3$ (6.33 mL) and dried over $MgSO_4$. The crude material (M=1.3g) was purified by column chromatography on silica gel (1:10 to 1:8 EtOAc/hexane) to afford (S,S)-**85** (650 mg, 98 %).

Yield: 430 mg (54 %), still can see *dr*=10:1;

R_f = 0.267 (20:1 Toluene:EtOAc), R_f = 0.284 (5:1 Hexane:EtOAc), CPS staining;

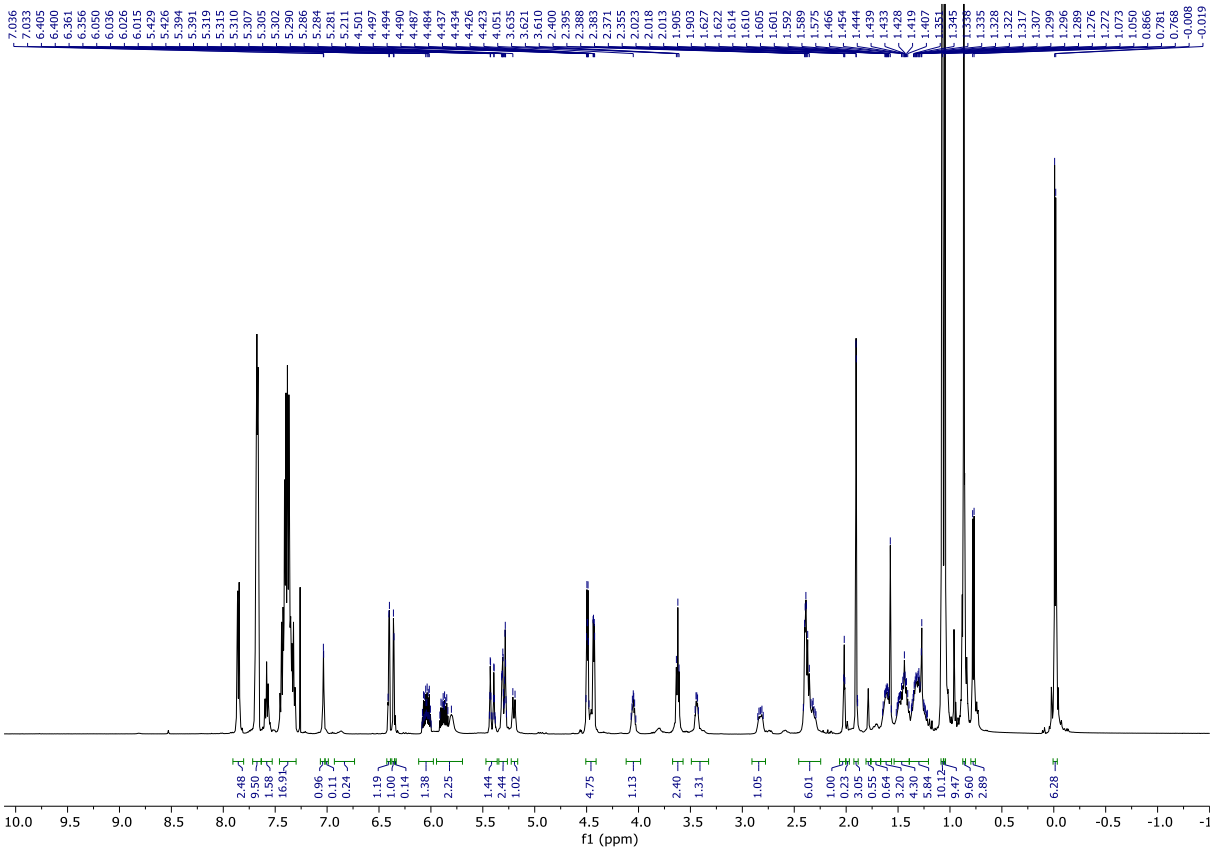
$[\alpha]_{20}^{D}$: = -4.00 (c = 0.5 ; $CHCl_3$, 20°C);

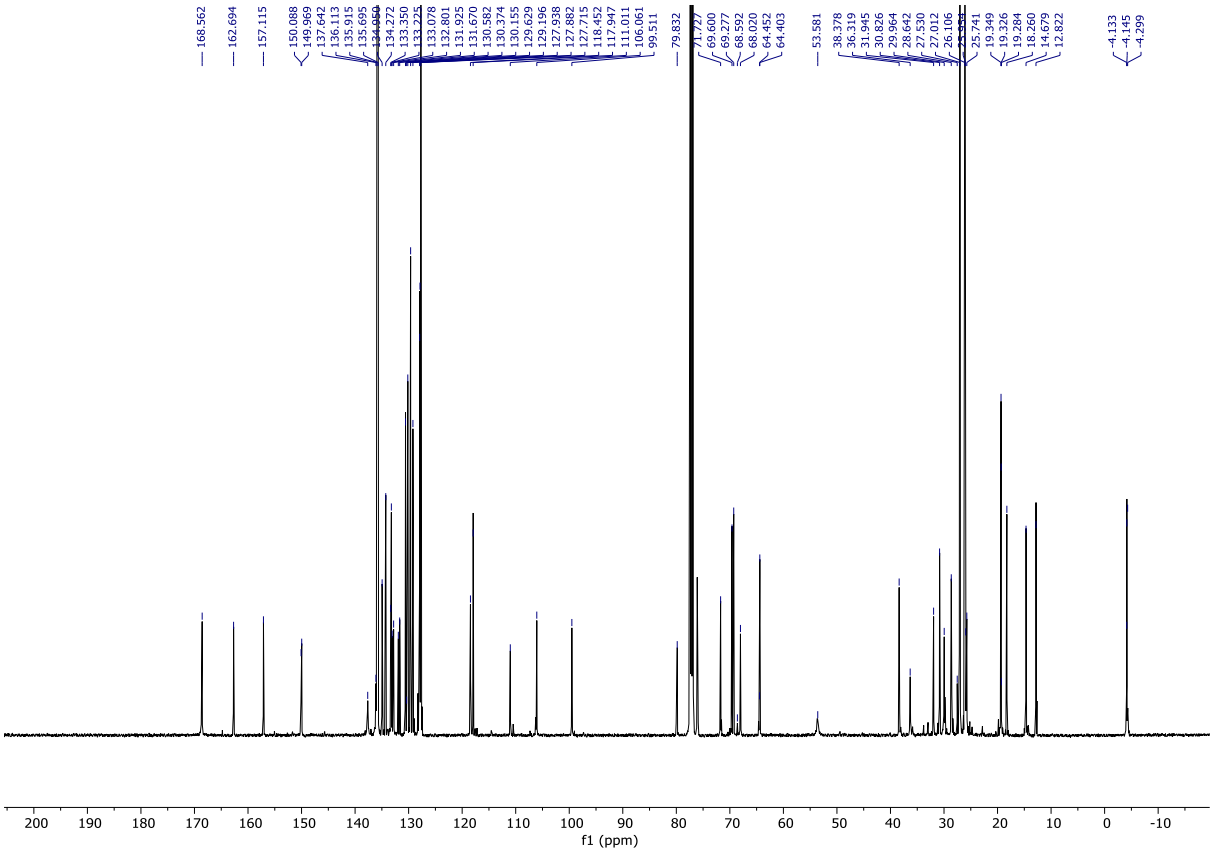
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.85 (dt, J = 7.3, 1.3 Hz, 2H), 7.67 (dtd, J = 8.0, 2.7, 1.3 Hz, 9H), 7.64 – 7.52 (m, 1H), 7.48 – 7.30 (m, 14H), 7.04 (s, 1H), 6.40 (d, J = 2.7 Hz, 1H), 6.36 (d, J = 2.7 Hz, 1H), 6.04 (ddtd, J = 19.1, 10.7, 5.3, 3.1 Hz, 1H), 5.88 (ddt, J = 17.4, 10.7, 5.4 Hz, 1H), 5.80 (s, 1H), 5.41 (dq, J = 17.2, 1.7 Hz, 1H), 5.30 (ddq, J = 12.4, 3.3, 1.9 Hz, 2H), 5.20 (d, J = 10.5 Hz, 1H), 4.49 (dq, J = 3.1, 2.1, 1.5 Hz, 2H), 4.43 (dd, J = 5.6, 1.7 Hz, 2H), 4.05 (tt, J = 10.1, 4.9 Hz, 1H), 3.62 (t, J = 6.3 Hz, 2H), 3.44 (dt, J = 7.7, 4.2 Hz, 1H), 2.88 – 2.73 (m, 1H), 2.46 – 2.24 (m, 4H), 2.02 (t, J = 2.6 Hz, 1H), 1.90 (d, J = 1.2 Hz, 3H), 1.67 – 1.55 (m, 2H), 1.46 (dddd, J = 19.2, 16.9, 9.6, 5.6 Hz, 2H), 1.38 – 1.22 (m, 3H), 1.07 (s, 7H), 1.05 (s, 10H), 0.87 (s, 9H), 0.77 (d, J = 6.8 Hz, 3H), -0.01 (d, J = 5.4 Hz, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 168.6, 162.7, 157.1, 150.1, 150.0, 137.6, 136.1, 135.9, 135.7, 135.0, 134.3, 133.4, 133.2, 133.1, 132.8, 131.9, 131.7, 130.6, 130.4, 130.2, 129.6, 129.2, 127.9, 127.9, 127.7, 118.5, 118.0, 111.0, 106.1, 99.5, 79.8, 71.7, 69.6, 69.3, 68.0, 64.4, 53.6, 38.4, 36.3, 31.9, 30.8, 30.0, 28.6, 27.5, 27.0, 26.1, 26.0, 25.7, 19.4, 19.3, 18.3, 14.7, 12.8, -4.2, -4.3;

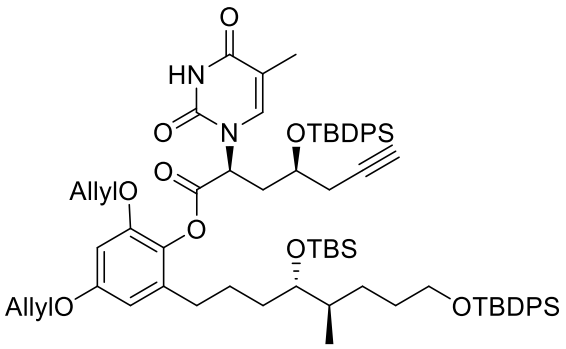
IR (film): ν = 2929, 2856, 2117, 1754, 1705, 1667, 1600, 1488, 1472, 1462, 1450, 1427, 1361, 1294, 1254, 1187, 1158, 1108, 1088, 1044, 1005, 983, 936, 835, 823, 790, 773, 739, 702, 687, 640, 613, 505;

HRMS (ESI-TOF) m/z (ESI) $C_{78}H_{98}N_2NaO_{10}Si_3$ $[M+Na]^+$ 1329.6421, found 1329.6446.


f1 (ppm)


f1 (ppm)

*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-((tert-butyldiphenylsilyl)oxy)-5-methyl octyl)phenyl (2S,4S)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)hept-6-ynoate (**SI**-(S,S)-**85**)*



A solution of predried acid (S,S)-**85** (1.6 g, mmol, 2.63 mmol., 1.0 equiv.) in freshly distilled DCM (22 mL, c=0.12 M) was prepared. And then, the phenol **55** (2.26 g, 3.15 mmol., 1.2 equiv.) and DMAP (64.2 mg, 0.53 mmol., 0.2 equiv.) were added. The resulting solution was cooled to 0 °C and stirred for 30 min. And then the DCC (1.19 g, 5.78 mmol., 2.2 equiv.) was added at 0 °C. The reaction was stirred at 0 °C and then slowly allowed to warm up to room temperature and left overnight for 50 hours. When checked by TLC the reaction was done after 50 h, the reaction mixture was diluted with hexane and filtered off through celite, and concentrated. The crude material was purified by column chromatography with toluene as an eluent, switching to 50:1 toluene: EtOAc. The desired product (S,S)-**85** was isolated in lower yield (1.4 g, 41 %), the substrate without benzoyl PG **SI**-(S,S)-**85** (0.54 g, 17 %), in addition, ca. 12 % of mixed fractions were isolated.

Yield: 0.54 g (17 %), still can see *dr*=10:1;

R_f = 0.217 (5:1 Hexane: EtOAc), CPS staining;

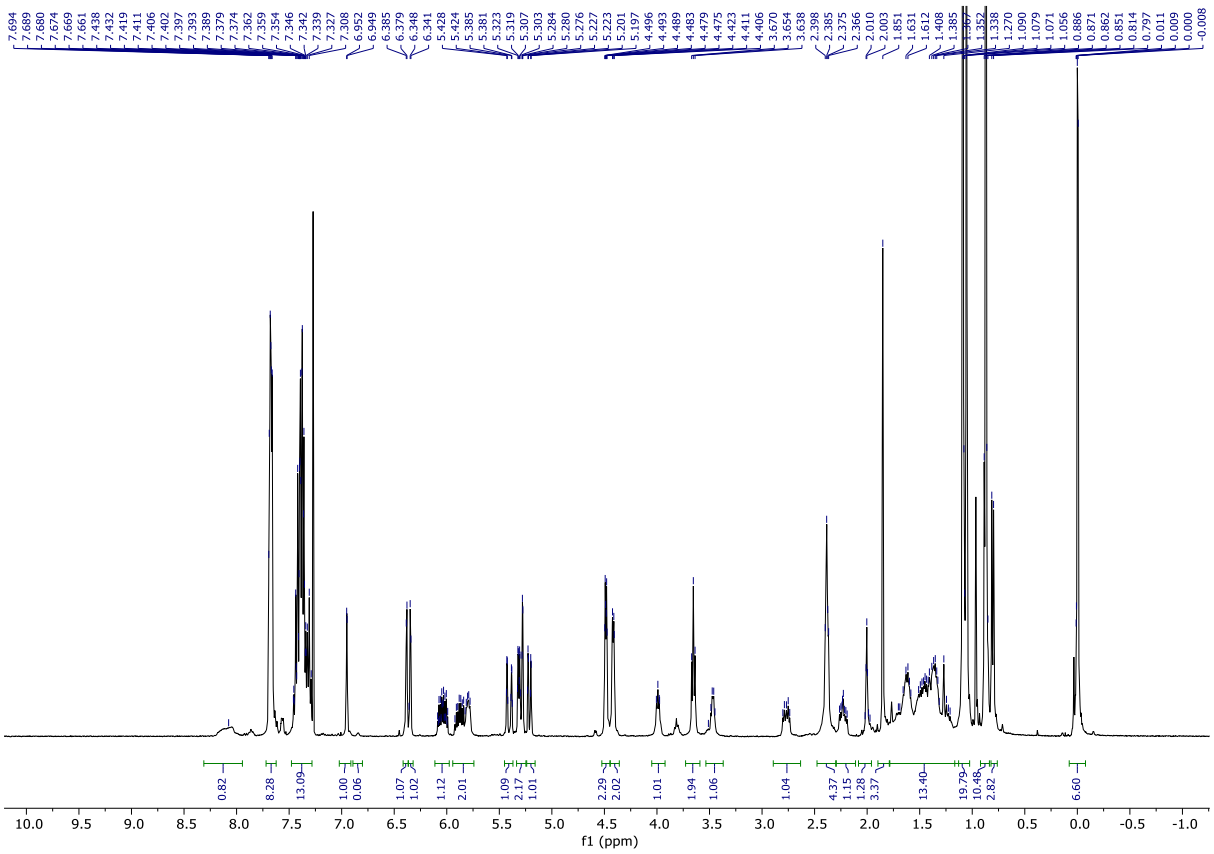
$[\alpha]_{20}^{D}$: = -10.00 (c = 0.5 ; $CHCl_3$, 20°C);

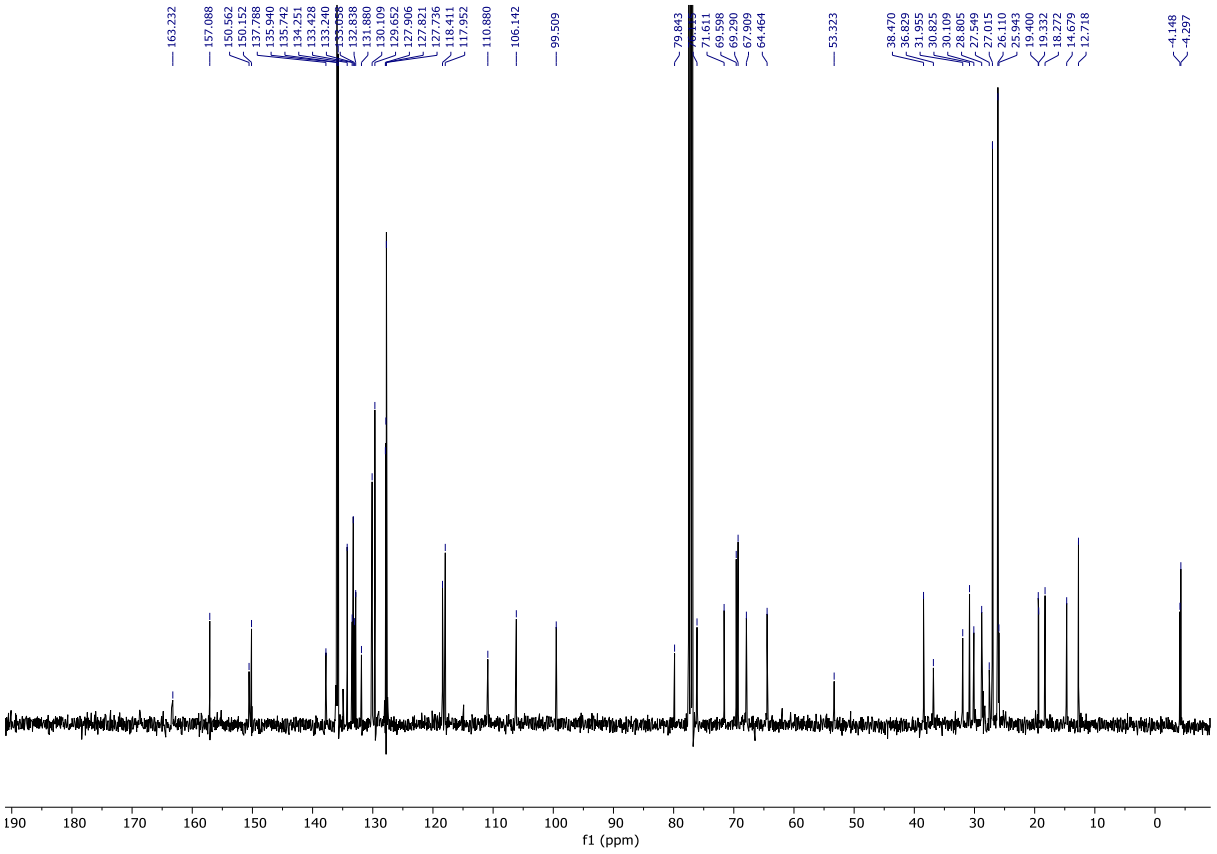
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 (s, 1H), 7.68 (td, J = 5.4, 2.5 Hz, 8H), 7.49 – 7.28 (m, 13H), 7.05 – 6.71 (m, 1H), 6.38 (d, J = 2.7 Hz, 1H), 6.34 (d, J = 2.8 Hz, 1H), 6.19 – 5.93 (m, 1H), 5.87 (ddt, J = 16.4, 10.7, 5.5 Hz, 1H), 5.80 (dd, J = 9.3, 5.0 Hz, 1H), 5.40 (dq, J = 17.2, 1.6 Hz, 1H), 5.35 – 5.29 (m, 1H), 5.28 (d, J = 1.6 Hz, 1H), 5.21 (dt, J = 10.4, 1.5 Hz, 1H), 4.49 (dt, J = 5.6, 1.5 Hz, 2H), 4.44 – 4.35 (m, 2H), 4.09 – 3.93 (m, 1H), 3.65 (t, J = 6.5 Hz, 2H), 3.47 (q, J = 4.8 Hz, 1H), 2.77 (dt, J = 12.6, 5.9 Hz, 1H), 2.38 (q, J = 4.4, 3.5 Hz, 4H), 2.23 (ddt, J = 14.3, 9.6, 4.9 Hz, 1H), 2.00 (t, J = 2.8 Hz, 1H), 1.85 (s, 3H), 1.72 – 1.17 (m, 7H), 1.09 (s, 10H), 1.06 (s, 9H), 0.87 (s, 11H), 0.81 (d, J = 6.8 Hz, 3H), -0.00 (d, J = 3.3 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.2, 157.1, 150.6, 150.2, 137.8, 135.9, 135.7, 134.3, 133.4, 133.2, 133.1, 132.8, 131.9, 130.1, 129.7, 127.9, 127.8, 127.7, 118.4, 118.0, 110.9, 106.1, 99.5, 79.8, 76.1, 71.6, 69.6, 69.3, 67.9, 64.5, 53.3, 38.5, 36.8, 32.0, 30.8, 30.1, 28.8, 27.6, 27.0, 26.1, 25.9, 19.4, 19.3, 18.3, 14.7, 12.7, -4.1, -4.3;

IR (film): ν = 2931, 2858, 1767, 1691, 1598, 1464, 1428, 1375, 1259, 1188, 1112, 823, 775, 742, 703, 669, 640, 625, 617, 603;

HRMS (ESI-TOF) m/z (ESI) $C_{71}H_{94}N_2NaO_9Si_3$ $[M+Na]^+$ 1225.6159, found 1225.6169.

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69.598
69.290
67.909
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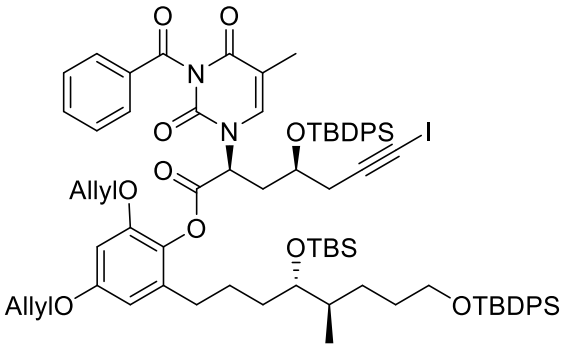
53.323
38.470
36.829
31.955
30.825
30.109
28.805
27.549
27.015
26.110
25.943
19.400
19.332
18.272
14.679
12.718
-4.148
-4.297
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-((tert-butyldiphenylsilyl)oxy)-5-methyloctyl)phenyl (2S,4S)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)-7-iodohept-6-ynoate ((S,S)-**93**)*



A solution of (S,S)-**85** (418 mg, 1 equiv.) in dry DMF (4 ml, c=0.09 M) was prepared at room temperature under argon atmosphere. And then the N-iodosuccinimide (105 mg, 1.5 equiv.) and silver nitrate (11 mg, 0.2 equiv.) were added at room temperature After 6 hours the reaction was complete by TLC, it was poured into a saturated $Na_2S_2O_3$ for quenching (color turned bright yellow and precipitated, then disappeared-AgI?). Washed with $NaHCO_3$, to get rid of succinimide. Extraction with EA was followed by evaporation of the solvent gave crude of M=421.4 mg. The crude product (S,S)-**93** was purified by pipet silica-gel column chromatography (pure toluene, then ea: tol=1:50, 1:20).

Yield: 425 mg (93 %);

R_f = 0.303 (4:1 Hexane: EtOAc), CPS staining;

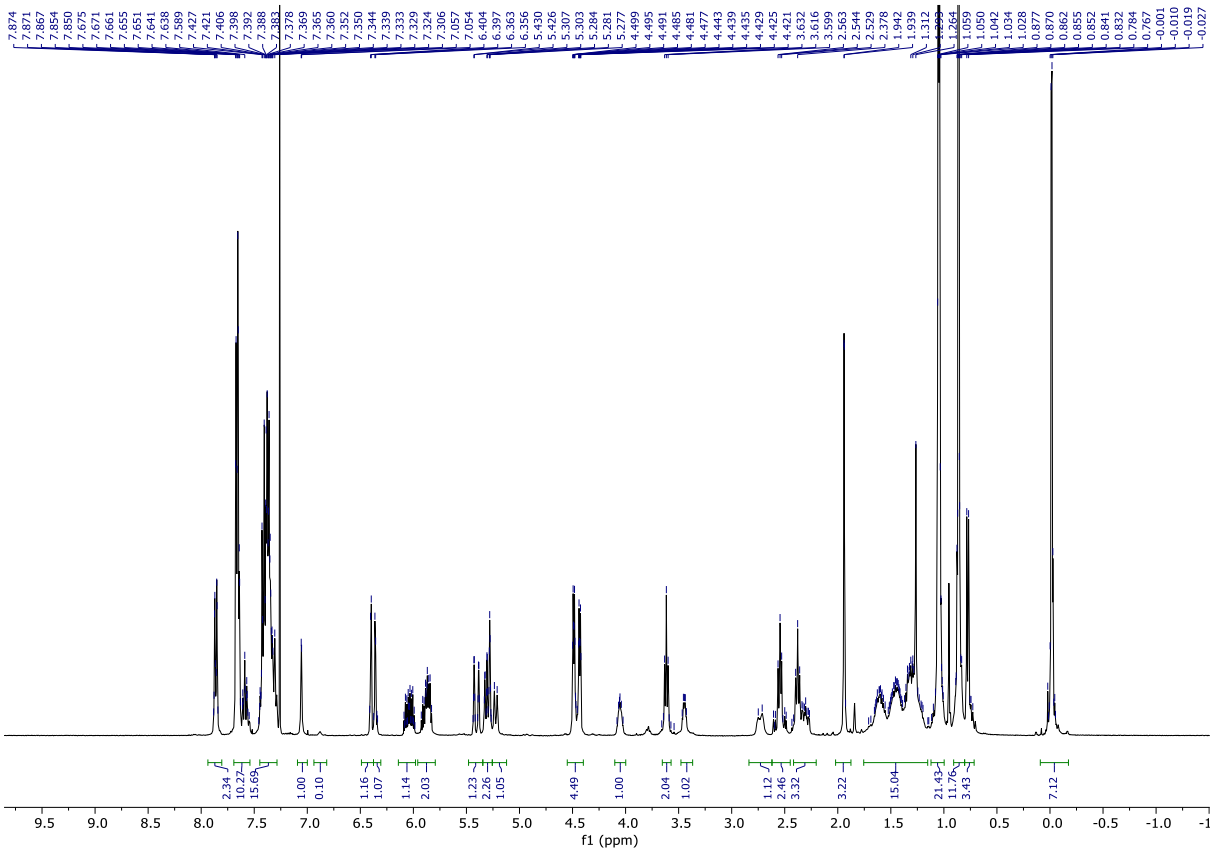
$[\alpha]_{20}^{D}$: = +14.00 (c = 0.5 ; $CHCl_3$, 20°C);

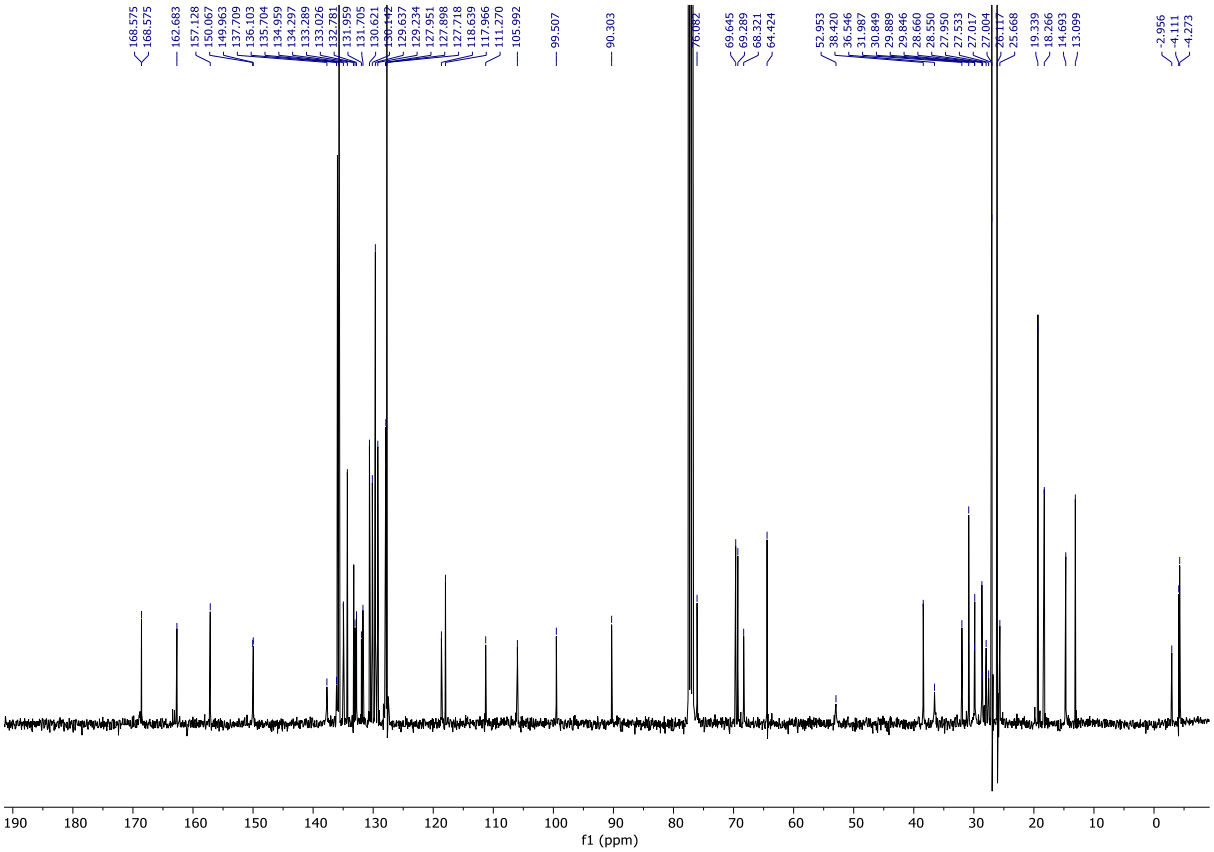
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 – 7.83 (m, 2H), 7.71 – 7.63 (m, 2H), 7.62 – 7.58 (m, 5H), 7.48 – 7.29 (m, 9H), 7.07 (d, J = 1.5 Hz, 1H), 6.41 (d, J = 2.8 Hz, 1H), 6.36 (d, J = 2.7 Hz, 1H), 6.13 – 5.97 (m, 1H), 5.88 (ddd, J = 17.0, 10.5, 5.2 Hz, 2H), 5.42 (dq, J = 17.3, 1.6 Hz, 2H), 5.35 – 5.27 (m, 2H), 5.26 – 5.16 (m, 1H), 4.50 (dt, J = 5.4, 1.6 Hz, 2H), 4.44 (dt, J = 5.6, 1.5 Hz, 2H), 4.07 (dt, J = 10.9, 6.1 Hz, 1H), 3.54 (t, J = 6.5 Hz, 2H), 3.47 (dt, J = 7.1, 4.3 Hz, 1H), 2.86 – 2.66 (m, 1H), 2.62 – 2.47 (m, 2H), 2.47 – 2.21 (m, 3H), 1.95 (d, J = 1.2 Hz, 3H), 1.72 – 1.46 (m, 1H), 1.46 – 1.21 (m, 12H), 1.06 (s, 9H), 0.87 (s, 9H), 0.81 (d, J = 6.8 Hz, 3H), -0.00 (d, J = 6.1 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-d) δ 169.30 – 167.91 (m), 162.68, 157.13, 150.07, 149.96, 137.71, 136.10, 135.70, 134.96, 134.30, 133.29, 133.03, 132.78, 131.96, 131.71, 130.62, 130.14, 129.64, 129.23, 127.95, 127.90, 127.72, 118.64, 117.97, 111.27, 105.99, 99.51, 90.30, 76.08, 69.65, 69.29, 68.32, 64.42, 52.95, 38.42, 36.55, 31.99, 30.85, 29.89, 29.85, 28.61 (d, J = 11.1 Hz), 27.95, 27.53, 27.02, 26.12, 25.67, 19.34, 18.27, 14.69, 13.10, -2.96, -4.11, -4.27.

IR (film): *v* = 2925, 2854, 1754, 1704, 1666, 1599, 1488, 1462, 1428, 1363, 1255, 1228, 1185, 1111, 1090, 999, 980, 937, 835, 824, 808, 799, 792, 783, 775, 768, 761, 743, 703, 688, 614, 503;

HRMS (ESI-TOF) m/z (ESI) $C_{78}H_{97}IN_2NaO_{10}Si_3$ [M+Na]+ 1455.5388, found 1455.5406.




168.575
168.575
162.683
157.128
150.067
149.963
137.709
136.103
135.704
134.959
134.297
133.289
133.026
132.611
131.959
131.705
130.621
130.442
129.637
129.234
127.951
127.898
127.718
118.639
117.966
111.270
105.992
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90.303
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29.846
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28.550
27.950
27.533
27.017
27.004
26.117
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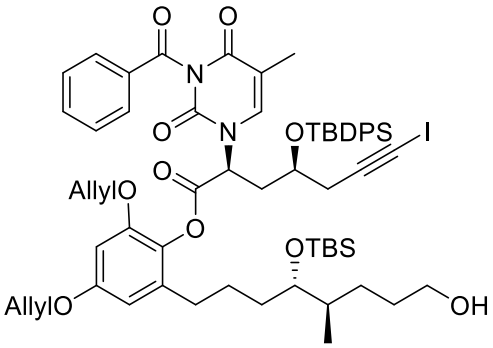
19.339
18.266
14.693
13.099
-2.956
-4.111
-4.273
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-8-hydroxy-5-methyloctyl)phenyl (2R,4R)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)-7-iodohept-6-ynoate ((S,S)-**94**)*



In a 25 ml heatgun dried pointed flask, ammonium fluoride (347 mg, 32 equiv.) was added to a solution of (S,S)-**93** (420 mg, 1 equiv.) in 1,1,1,3,3,3-hexafluro-2-propanol (2.93 mL, c=0.1 M) and the resulting solution stirred at an ambient (room) temperature with continuous control *via* TLC. After 3h could see some product, but more of SM. After 2-3 days the conversion is normally the best. Workup with $NaHCO_3$, extraction with DCM, then EtOAc. M crude = 342 mg crude. The crude material is better columned with tol:ea=50:1 to 20:1 to 5:1, however hex: ea is also good starting with 30:1 and a gradient to 5:1, 2:1. The product (S,S)-**94** is obtained in fractions 30-45 (0.25 g, 80 %).

Yield: 0.25 g (80 %), on a 1 g scale the yield is 540 mg (72 %);

R_f = 0.267 (20:1 Toluene: EtOAc), CPS staining;

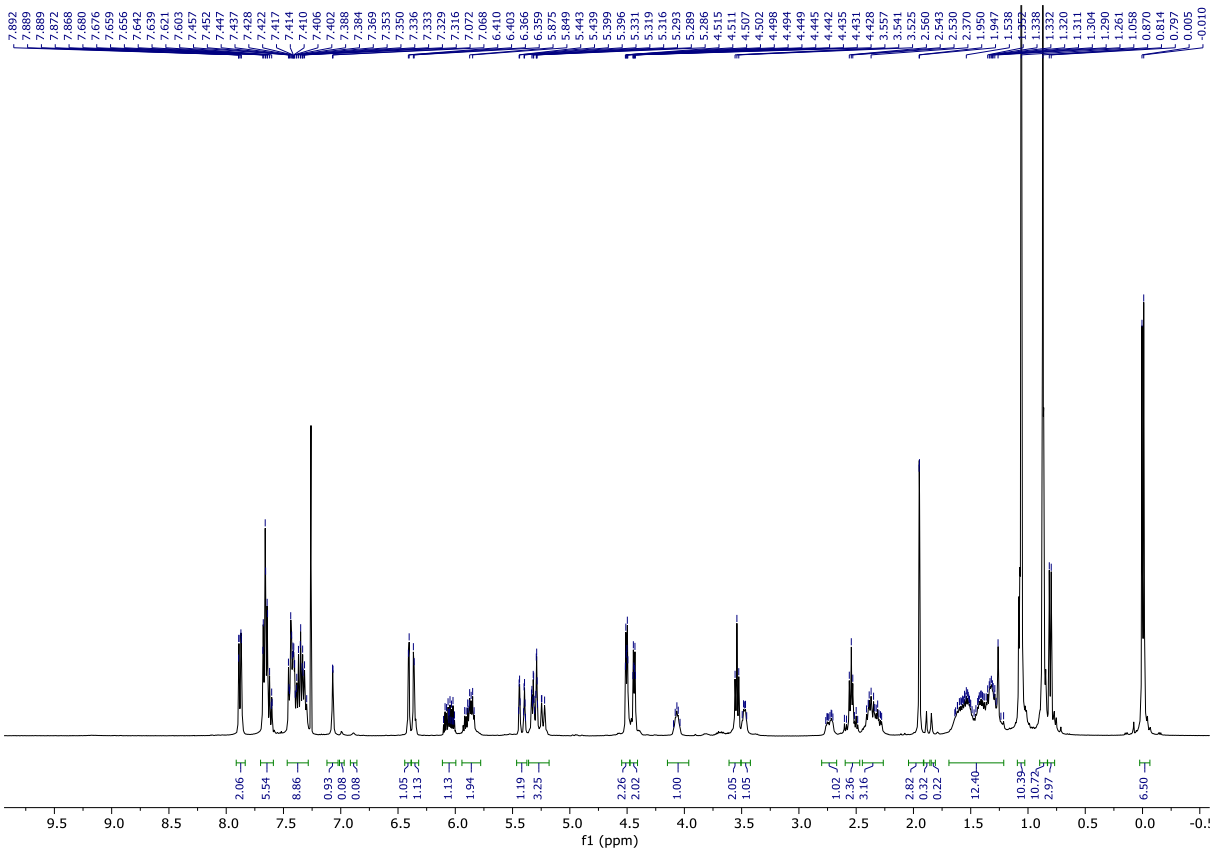
$[\alpha]\frac{D}{20}$: = +18.00 (c = 0.5 ; $CHCl_3$, 20°C);

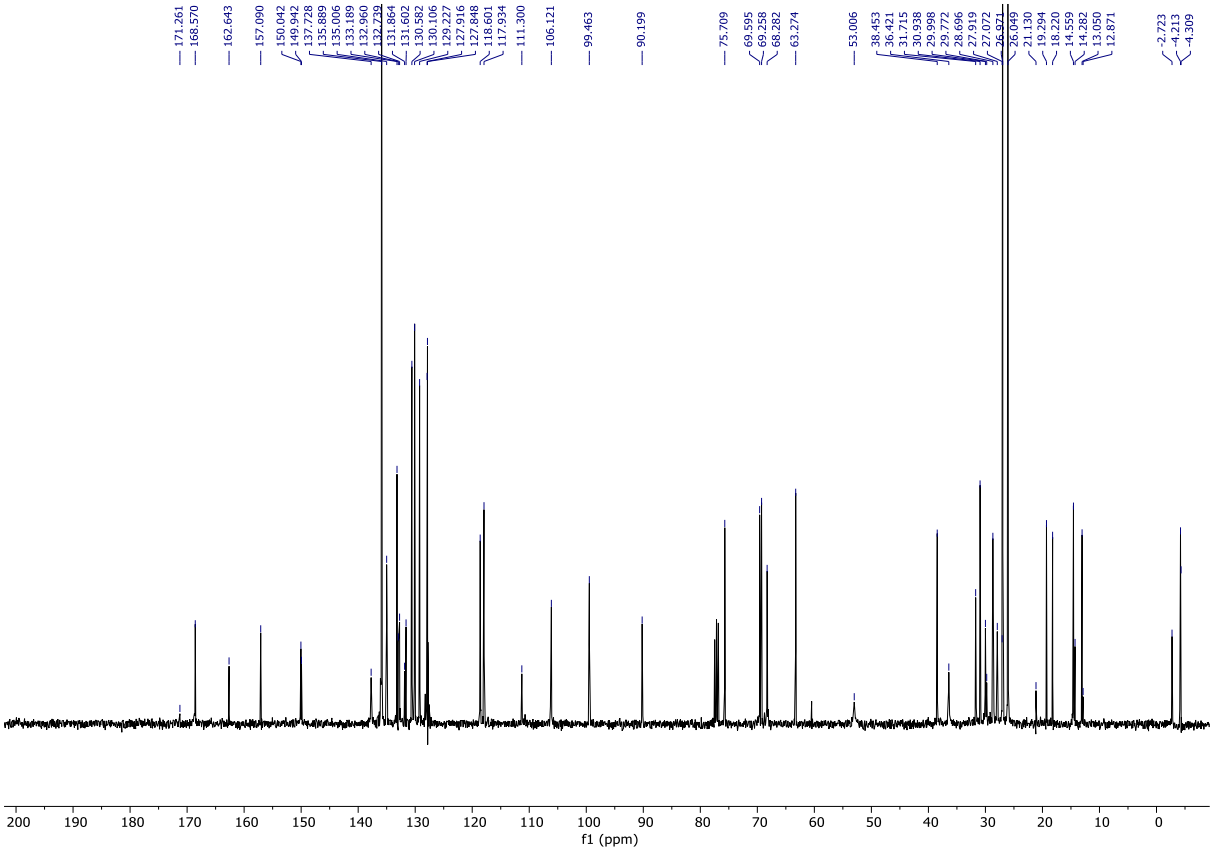
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 – 7.83 (m, 1H), 7.71 – 7.63 (m, 2H), 7.62 – 7.58 (m, 0H), 7.48 – 7.29 (m, 4H), 7.07 (d, J = 1.5 Hz, 0H), 6.41 (d, J = 2.8 Hz, 0H), 6.36 (d, J = 2.7 Hz, 0H), 6.13 – 5.97 (m, 1H), 5.88 (ddd, J = 17.0, 10.5, 5.2 Hz, 1H), 5.42 (dq, J = 17.3, 1.6 Hz, 1H), 5.35 – 5.27 (m, 1H), 5.26 – 5.16 (m, 1H), 4.50 (dt, J = 5.4, 1.6 Hz, 1H), 4.44 (dt, J = 5.6, 1.5 Hz, 1H), 4.07 (dt, J = 10.9, 6.1 Hz, 0H), 3.54 (t, J = 6.5 Hz, 1H), 3.47 (dt, J = 7.1, 4.3 Hz, 1H), 2.86 – 2.66 (m, 1H), 2.62 – 2.47 (m, 1H), 2.47 – 2.21 (m, 1H), 1.95 (d, J = 1.2 Hz, 1H), 1.72 – 1.46 (m, 1H), 1.46 – 1.21 (m, 2H), 1.06 (s, 4H), 0.87 (s, 4H), 0.81 (d, J = 6.8 Hz, 1H), -0.00 (d, J = 6.1 Hz, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.3, 168.6, 162.6, 157.1, 150.0, 149.9, 137.7, 135.9, 135.0, 133.2, 133.0, 132.7, 131.9, 131.6, 130.6, 130.1, 129.2, 127.9, 127.9, 118.6, 117.9, 111.3, 106.1, 99.5, 90.2, 75.7, 69.6, 69.3, 68.3, 63.3, 53.0, 38.5, 36.4, 31.7, 30.9, 30.0, 29.8, 28.7, 27.9, 27.1, 27.0, 26.1, 21.1, 19.3, 18.2, 14.6, 14.3, 13.1, 12.9, -2.7, -4.2, -4.3;

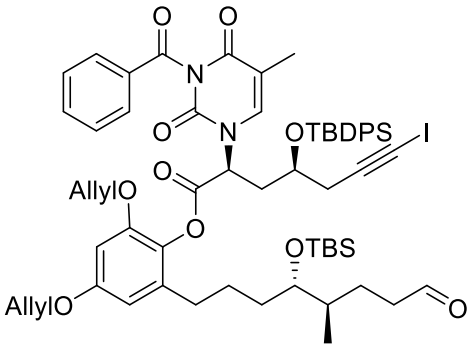
IR (film): ν = 2925, 2854, 1754, 1703, 1663, 1599, 1488, 1461, 1429, 1363, 1256, 1185, 1111, 1089, 833, 774, 744, 702, 518, 506;

HRMS (ESI-TOF) m/z (ESI) $C_{62}H_{79}IN_2NaO_{10}Si_2$ $[M+Na]^+$ 1217.4210, found 1217.4217.





*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-methyl-8-oxooctyl)phenyl (2S,4S)-2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-((tert-butyldiphenylsilyl)oxy)-7-iodohept-6-ynoate ((S,S)-**84**)*



In a flame-dried 25 ml flask, a solution (S,S)-**94** (225 mg, 0.188 mmol, 1.0 equiv.) in dry DCM (5.1 ml, c=0.037 M) was prepared under Argon atmosphere at room temperature Then, DMP (0.120 g, 1.5 equiv.) and $NaHCO_3$ (60 mg, 3.75 equiv.) to neutralize AcOH in DMP and AcOH which is produced in the reaction) were added at room temperature The reaction was controlled by TLC and MS. After 5 h at room temperature the reaction was diluted with DCM (10 ml) and quenched with 15 ml of DMP quenching solution ($Na_2S_2O_3$ and $NaHCO_3$). Note: the quenching shouldn't be too long, max 5-10 mins, otherwise the Benzoyl PG gets removed under basic conditions. The aqueous layer was extracted with DCM (20 ml x 3) and EtOAc (20 ml) once. The combined organic layers were dried over magnesium sulfate, and filtered; the solvent was removed under reduced pressure. The crude material was purified using FCC (Hex: EA=20:1 to 2:1) to afford (S,S)-**84** in an excellent yield of 89 %.

Yield: 0.2 g (89 %); on 0.5 scale after extended time of the workup obtained: (S,S)-**84** (280 mg, 54 %) and (S,S)-**95**– side prod w/o Bz PG (110 mg, 24 %)

R_f = 0.615 (5:1 Toluene: EtOAc), CPS staining;

$[\alpha]_{20}^{D}$: = +16.00 (c = 1.0 ; $CHCl_3$, 20°C);

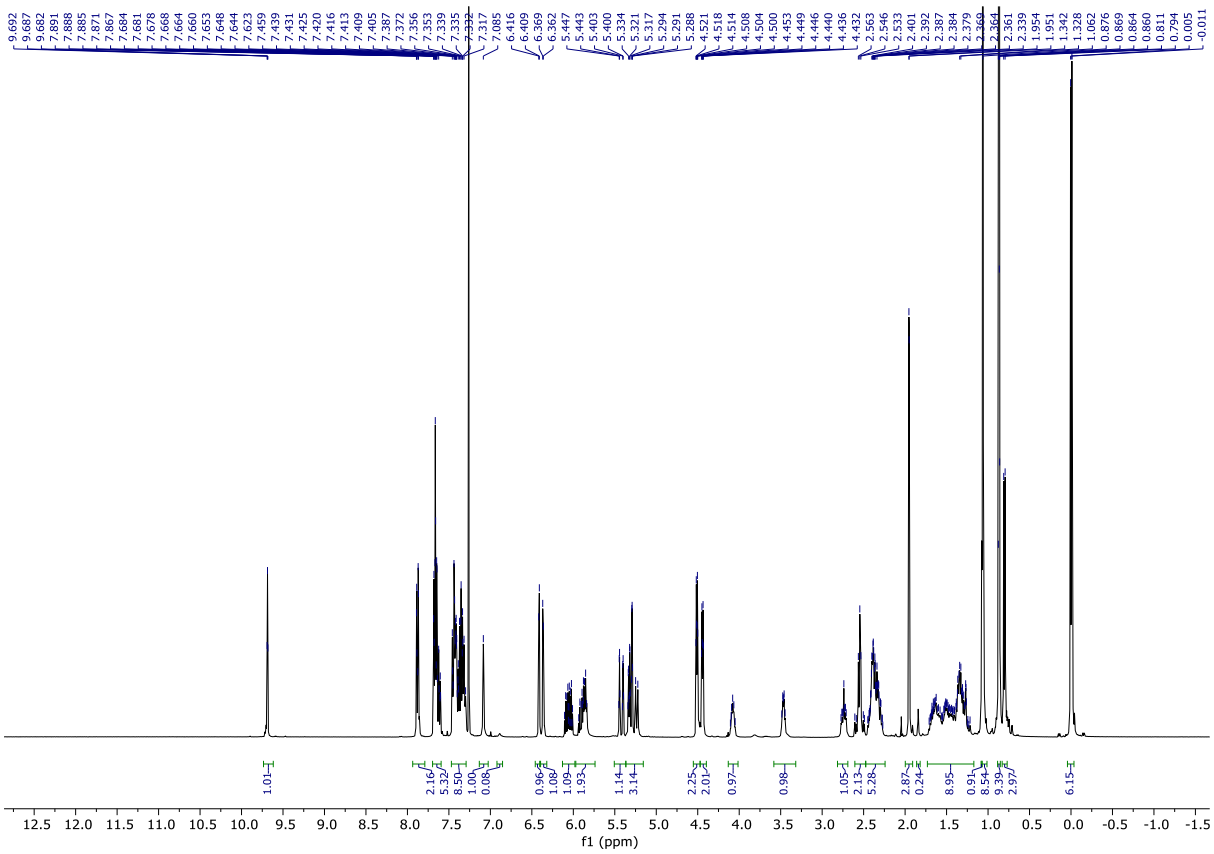
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.69 (t, J = 1.9 Hz, 1H), 7.88 (dt, J = 7.5, 1.3 Hz, 2H), 7.71 – 7.57 (m, 6H), 7.53 – 7.29 (m, 10H), 7.08 (s, 1H), 6.41 (d, J = 2.7 Hz, 1H), 6.37 (d, J = 2.7 Hz, 1H), 6.06 (ddt, J = 17.3, 10.6, 5.3 Hz, 1H), 5.89 (ddt, J = 16.6, 10.1, 5.1 Hz, 2H), 5.42 (dq, J = 17.2, 1.6 Hz, 1H), 5.33 (dq, J = 6.5, 1.5 Hz, 1H), 5.29 (q, J = 1.4 Hz, 1H), 5.24 (d, J = 10.7 Hz, 1H), 4.51 (dt, J = 5.4, 1.5 Hz, 2H), 4.44 (dt, J = 5.4, 1.5 Hz, 2H), 4.08 (p, J = 5.9 Hz, 1H), 3.47 (dt, J = 6.6, 4.6 Hz, 1H), 2.79 – 2.67 (m, 1H), 2.63 – 2.47 (m,

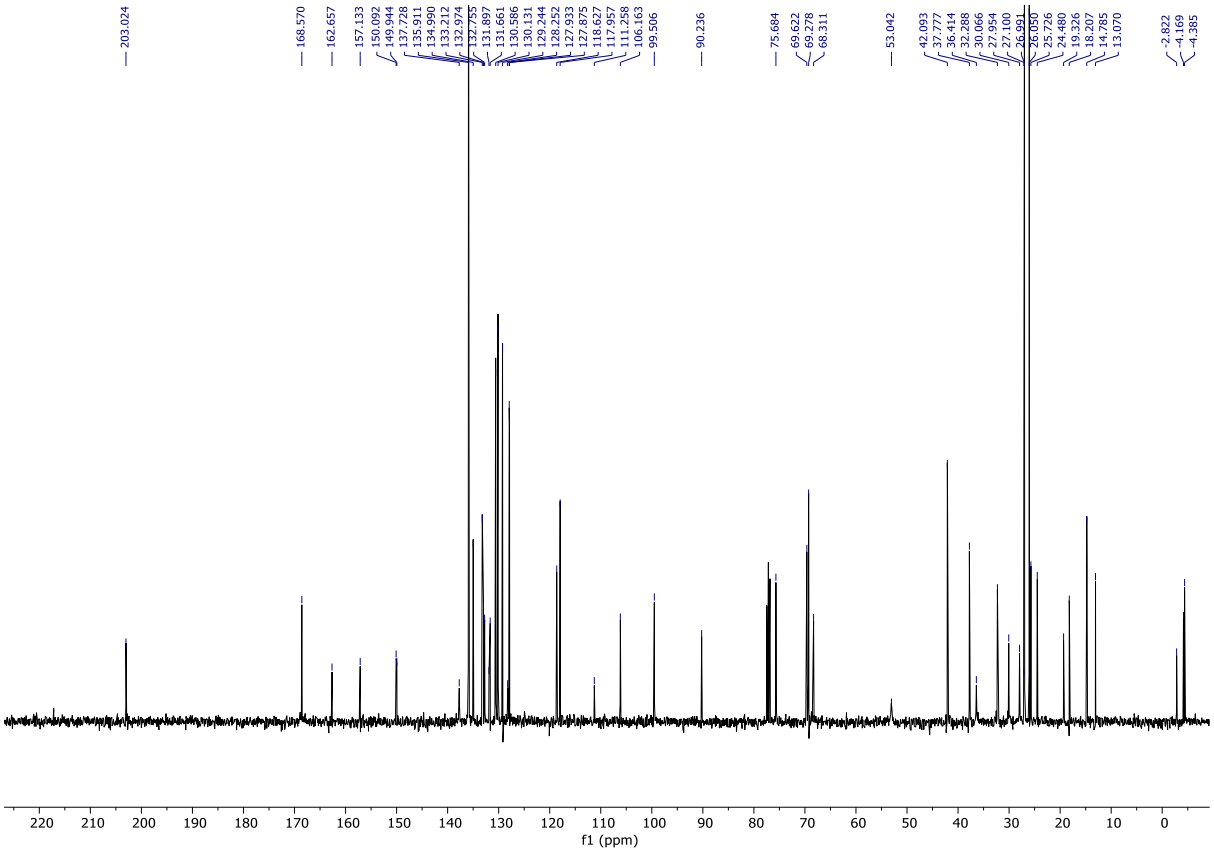
2H), 2.45 – 2.24 (m, 4H), 1.95 (d, J = 1.1 Hz, 3H), 1.74 – 1.21 (m, 5H), 1.06 (s, 9H), 0.87 (s, 9H), 0.80 (d, J = 6.8 Hz, 3H), -0.00 (d, J = 6.3 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 203.0, 168.6, 162.7, 157.1, 150.1, 149.9, 137.7, 135.9, 135.0, 133.2, 133.0, 132.8, 131.9, 131.7, 130.6, 130.1, 129.2, 128.3, 127.9, 127.9, 118.6, 118.0, 111.3, 106.2, 99.5, 90.2, 75.7, 69.6, 69.3, 68.3, 53.0, 42.1, 37.8, 36.4, 32.3, 30.1, 28.0, 27.1, 27.0, 26.1, 25.7, 24.5, 19.3, 18.2, 14.8, 13.1, -2.8, -4.2, -4.4;

IR (film): v = 2955, 2922, 2851, 1707, 1664, 1606, 1463, 1377, 1260, 1186, 1081, 1019, 969, 807, 799, 785, 777, 770, 764, 755, 741, 731, 718, 706, 691, 607, 595;

HRMS (ESI-TOF) m/z (ESI) $C_{62}H_{77}IN_2NaO_{10}Si_2$ $[M+Na]^+$ 1215.4054, found 1215.4069.

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135.911
134.990
133.212
132.974
132.795
131.897
131.661
130.586
130.131
129.244
128.252
127.933
127.875
118.627
117.957
111.258
106.163
99.506
90.236
75.684
69.622
69.278
68.311
53.042
42.093
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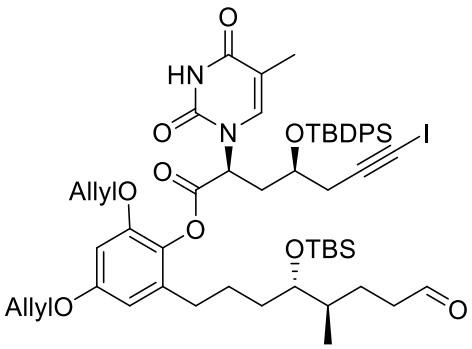
24.480
19.326
18.207
14.785
13.070
-2.822
-4.169
-4.385
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

*2,4-bis(allyloxy)-6-((4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-methyl-8-oxooctyl)phenyl (2S,4S)-4-((tert-butyldiphenylsilyl)oxy)-7-iodo-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)hept-6-ynoate ((S,S)-**95**)*



Yield: 24 %

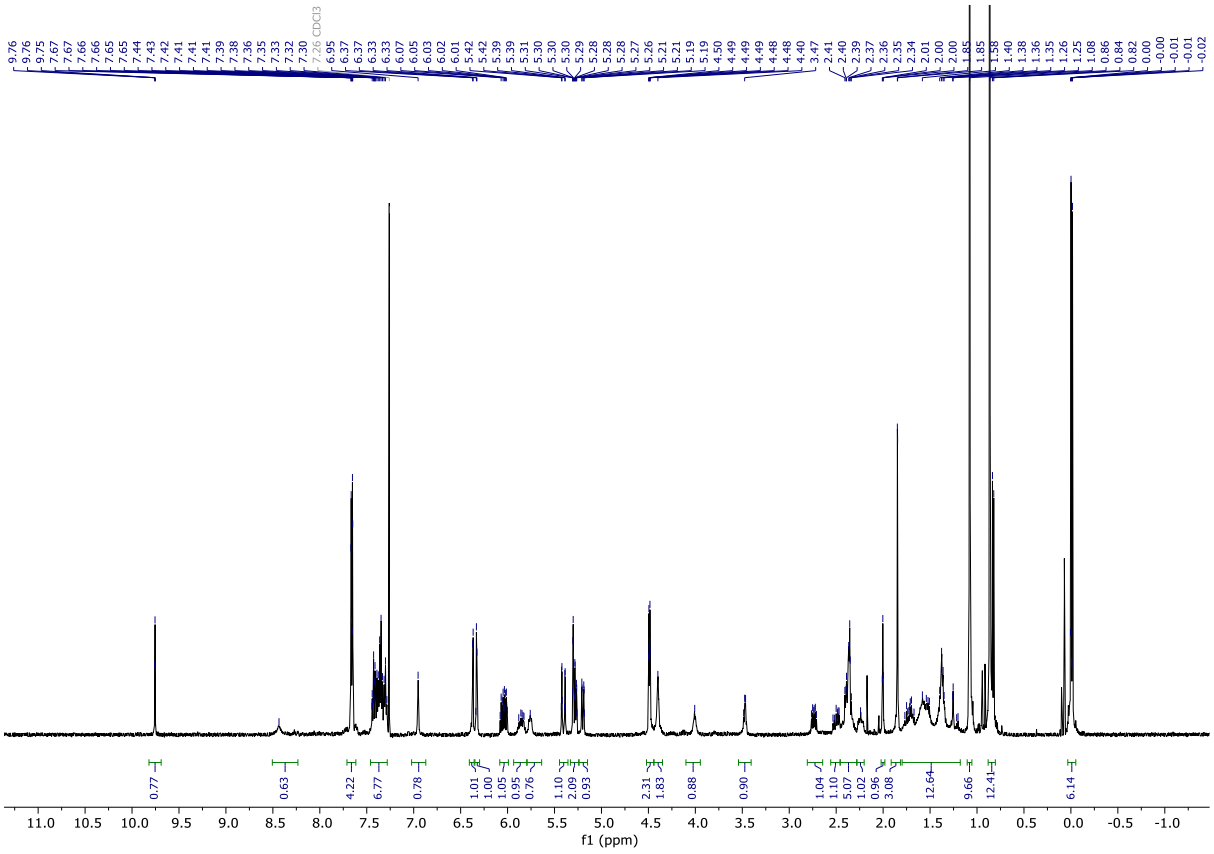
$[\alpha]_{20}^{D}$: = +6.91 (c = 4.05; $CHCl_3$, 20°C);

^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.76 (t, J = 1.7 Hz, 1H), 8.43 (s, 0H), 7.73 – 7.58 (m, 3H), 7.48 – 7.27 (m, 5H), 6.95 (s, 1H), 6.37 (d, J = 2.7 Hz, 1H), 6.33 (d, J = 2.7 Hz, 1H), 6.04 (ddt, J = 17.2, 10.6, 5.3 Hz, 1H), 5.91 – 5.80 (m, 1H), 5.76 (s, 1H), 5.41 (dq, J = 17.2, 1.6 Hz, 1H), 5.34 – 5.24 (m, 1H), 5.20 (dd, J = 10.4, 1.4 Hz, 1H), 4.49 (dt, J = 5.4, 1.5 Hz, 1H), 4.40 (s, 1H), 4.01 (s, 1H), 3.56 – 3.40 (m, 1H), 2.74 (dt, J = 14.3, 6.0 Hz, 1H), 2.57 – 2.43 (m, 1H), 2.43 – 2.30 (m, 3H), 2.24 (s, 1H), 2.00 (t, J = 2.6 Hz, 1H), 1.85 (d, J = 1.2 Hz, 2H), 1.80 – 1.19 (m, 8H), 1.08 (s, 7H), 0.86 (s, 6H), 0.83 (d, J = 6.8 Hz, 2H), -0.01 (d, J = 7.7 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 203.3, 163.5, 157.1, 150.7, 150.2, 137.8, 136.0, 133.3, 133.2, 133.0, 132.8, 131.8, 130.1, 127.9, 127.8, 118.6, 118.0, 111.0, 106.2, 99.5, 90.2, 75.8, 69.6, 69.3, 68.2, 53.2, 42.3, 37.9, 36.8, 32.2, 31.1, 30.2, 28.4, 27.0, 26.1, 24.5, 19.4, 18.2, 14.6, 12.9, -3.0, -4.2, -4.4;

IR (film): ν = 3175, 3072, 3019, 2954, 2930, 2890, 2857, 2721, 1765, 1687, 1596, 1488, 1472, 1463, 1427, 1373, 1336, 1256, 1217, 1185, 1152, 1111, 1087, 1044, 1006, 935, 885, 835, 823, 755, 703, 667, 622, 613;

HRMS (ESI-TOF) m/z (ESI) $C_{55}H_{73}IN_2NaO_9Si_2$ $[M+Na]^+$ 1111.3792, found 1111.3776.


9.76
9.76
9.75
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7.66
7.66
7.65
7.65
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7.43
7.42
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7.41
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7.39
7.38
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1.40
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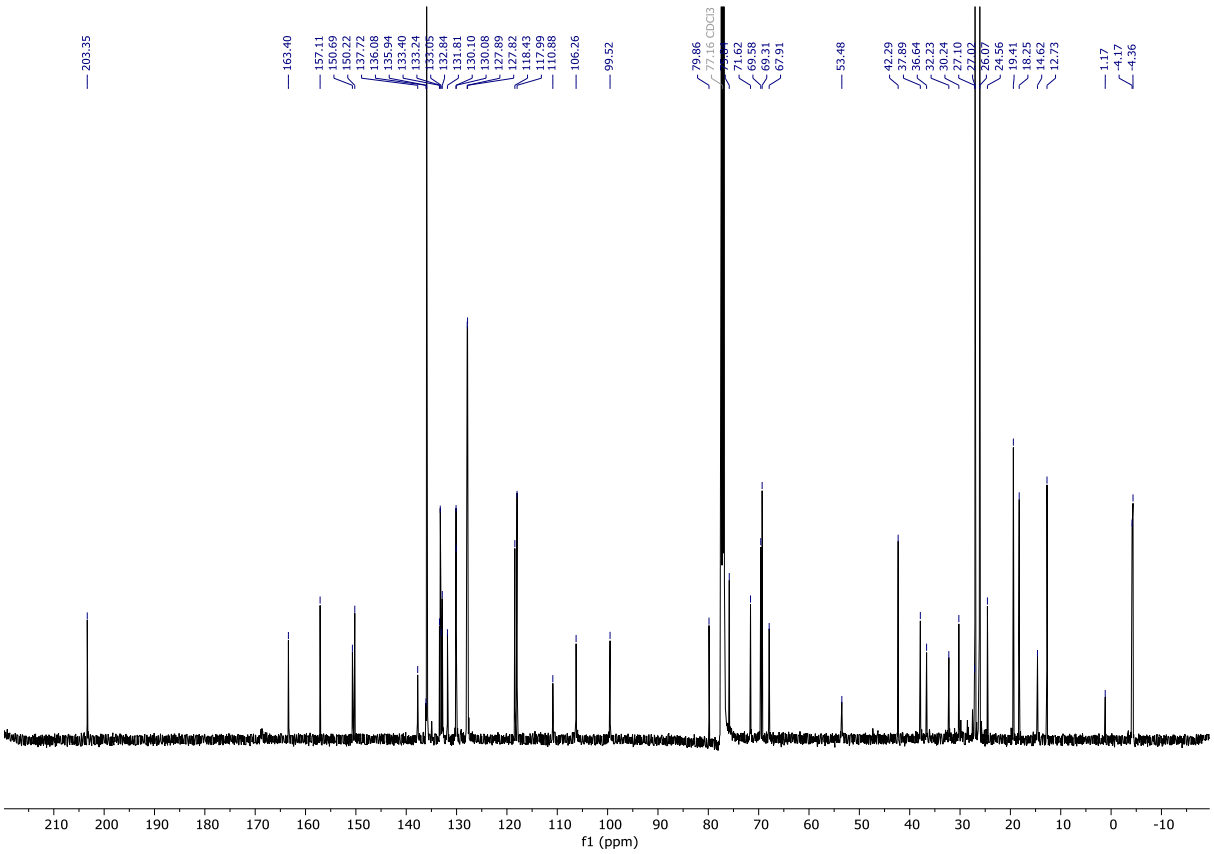
1.36
1.35
1.26
1.25
1.08
0.86
0.84
0.82
0.00
-0.00
-0.01
-0.01
-0.02
0.77
0.63
4.22
6.77
0.78
1.01
1.00
1.05
0.95
0.76
1.10
2.09
0.93
2.31
1.83
0.88
0.90
1.04
1.10
5.07
1.02
0.96
3.08
12.64
9.66
12.41
6.14
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


203.35
163.40
157.11
150.69
150.22
137.72
136.08
135.94
133.40
133.24
133.05
132.84
131.81
130.10
130.08
127.89
127.82
118.43
117.99
110.88
106.26
99.52
79.86
77.16 CDCl3
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71.62
69.58
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30.24
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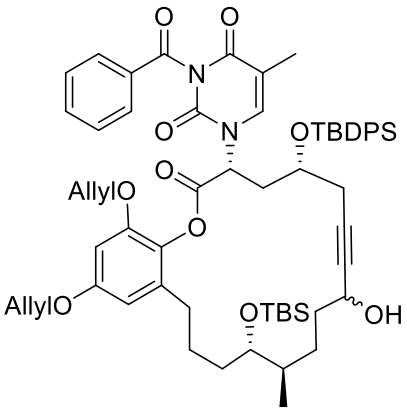
24.56
19.41
18.25
14.62
12.73
1.17
-4.17
-4.36
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

5.3.3 Macrocyclization

5.3.3.1 *R,R*-18-membered macrocycle

*(R,R)-**96***



THF was thoroughly degassed (with the Freeze-Pump-Thaw technique). $CrCl_2$ (927 mg, 7.54 mmol, 10.0 equiv.) was dried for at least 2 h at 200 °C under vacuum (200 °C, 1.5-2 mbar). The reaction was performed in a Schleck tube 50 ml (dried with a heat gun at 650°C and high vacuum). Separately 2 solutions were prepared: (R,R)-**84** (900 mg, 0.754 mmol, 1.0 equiv.) was dissolved in THF (18.85 ml, c=0.04 M), 2 - vigorously stirring solution of predried $CrCl_2$ (927 mg, 7.54 mmol, 10.0 equiv.) and $NiCl_2$ (20 mg, 0.15 mmol, 0.2 equiv.) in THF (82.42 ml, c=0.092 M). The first solution with substrates was slowly added dropwise, over 5 minutes to a vigorously stirring solution of catalysts. The reaction was left overnight. After 17 h reaction looks complete, worked up by quenching with 50 mL of saturated NH_4Cl solution, extracted with EtOAc (3x), washed with $Na_2S_2O_3$ (50 mL), H_2O (20 mL), brine (20 mL) dried over $MgSO_4$, and concentrated. The crude material (Mcrude=950 mg) was purified by FC (5 cm) with an eluent mixture Hexane: EtOAc (6:1 to 5:1 to 2:1 to EA pure) to give pure (R,R)-**96** (483 mg, 0.452 mmol, 60 %) in fractions 120-200 as a colorless oil.

Yield: 483 mg (60 %); + 17 % of (R,R)-**97**

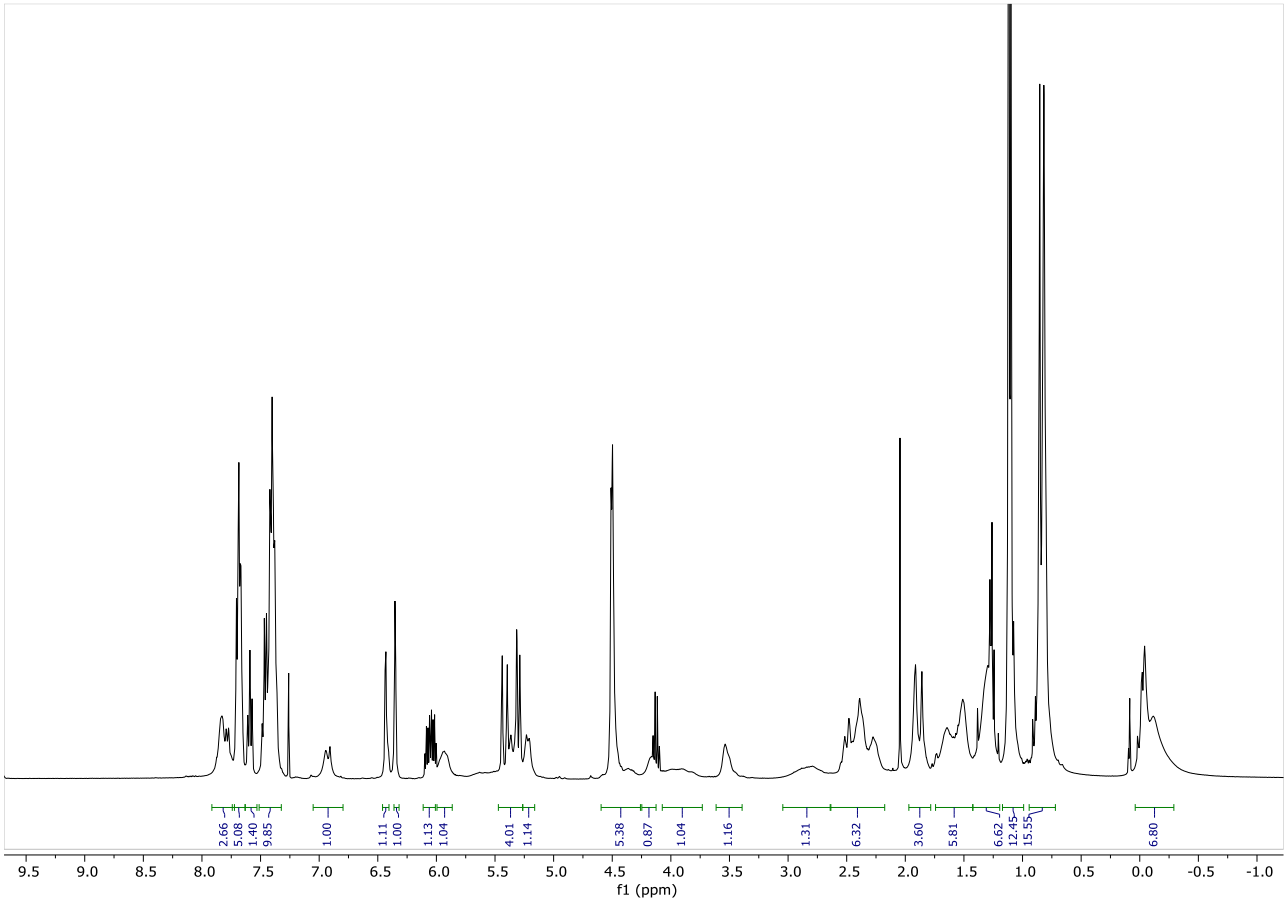
R_f = 0.54, 1 spots (5:1 Toluene:EtOAc), CPS staining;

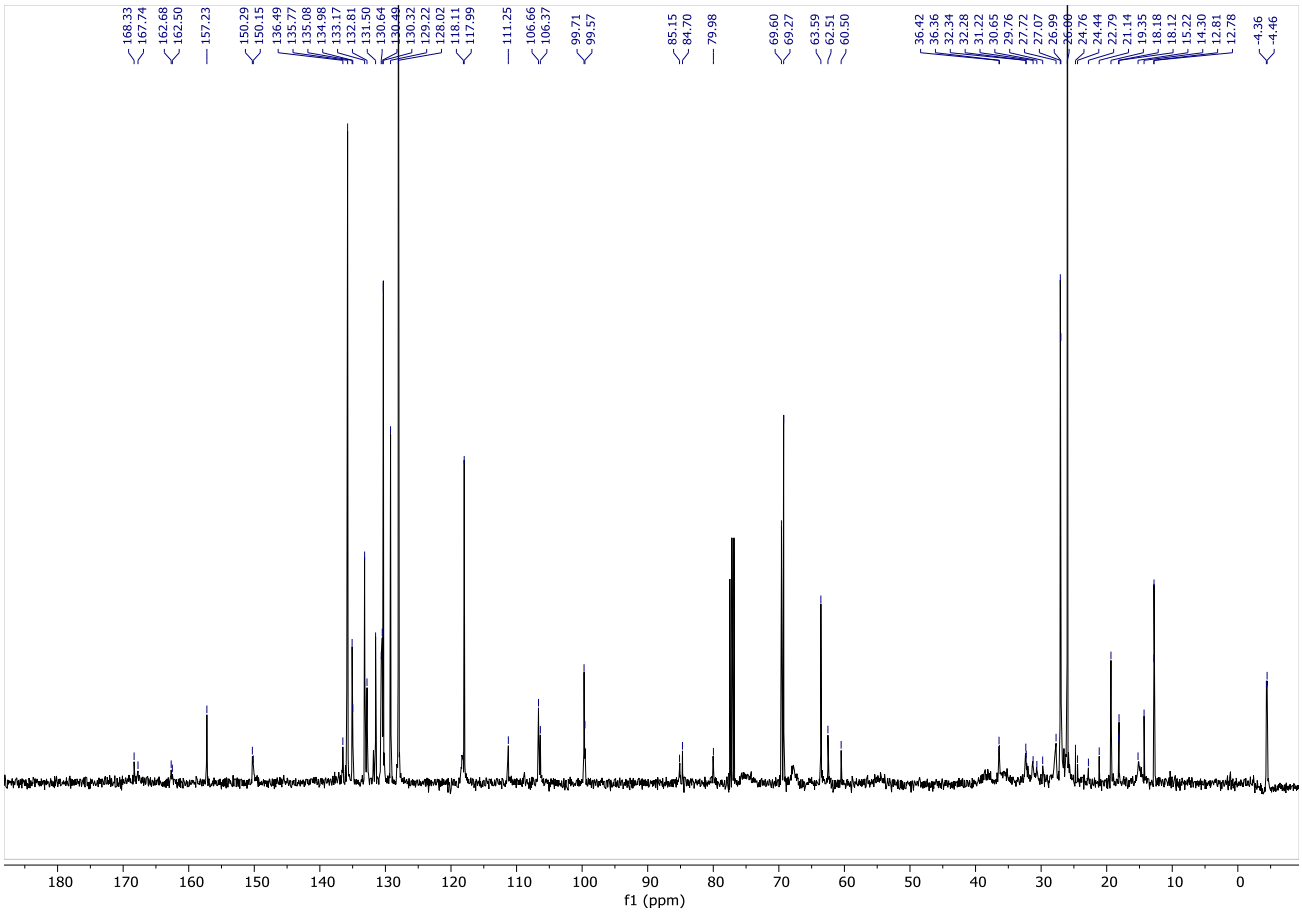
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88-7.75 (m, 2H), 7.73 – 7.63 (m, 5H), 7.59 (t, J = 7.4 Hz, 1H), 7.49-7.36 (m, 9H), 6.93 (d, J = 14.3 Hz, 1H), 6.49 – 6.25 (m, 1H), 6.35 (d, J = 2.8 Hz, 1H), 6.17 – 5.98 (m, 1H), 5.99 – 5.84 (m, 1H), 5.42 (dd, J = 17.2, 1.8 Hz, 1H), 5.30 (d, J = 10.7 Hz, 2H), 5.22 (d, J = 10.4 Hz, 1H), 4.50 (d, J = 5.4 Hz, 4H), 4.36 (br.s, 1H), 4.29 – 4.12 (m, 1H), 4.04 – 3.82 (m, 1H), 3.53 (s, 1H), 2.82 (s, 1H), 2.60 – 2.11 (m, 2H), 1.99 – 1.78 (m, 1H), 1.76 – 1.43 (m, 5H), 1.41 – 1.19 (m, 6H), 1.11 (d, J = 7.9 Hz, 12H), 0.94 – 0.71 (m, 15H), 0.05 – -0.31 (m, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.33, 162.6, 157.2, 150.3, 136.5, 135.8, 135.1, 135.0, 133.2, 132.8, 131.5, 130.6, 130.5, 130.3, 129.2, 128.0, 118.0, 111.3, 106.7, 106.4, 99.7, 99.6, 85.2, 84.7, 80.0, 67.7, 63.6, 62.5, 60.5, 35.6, 32.3, 31.2, 30.7, 29.8, 27.7, 27.1, 27.0 (3C), 26.0 (3C), 24.8, 24.4, 22.8, 21.1, 19.4, 18.2, 18.1, 15.2, 14.3, 12.8, 12.8, -4.4, -4.5; -doubling peaks, due to diastereomeric mixture

IR (film): v = 3312 (OH), 2927, 2854, 1708, 1640, 1556, 1517, 1450, 1253, 1227, 1187, 1150, 1090, 833, 771, 703, 688, 666, 640, 610, 560;

HRMS (ESI-TOF) m/z (ESI) $C_{62}H_{82}N_3O_{10}Si_2$ $[M+NH_4]^+$ 1084.5533, found 1084.5526.




168.33
167.74
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162.50
157.23
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150.15
136.49
135.77
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4.46
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160
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20
10
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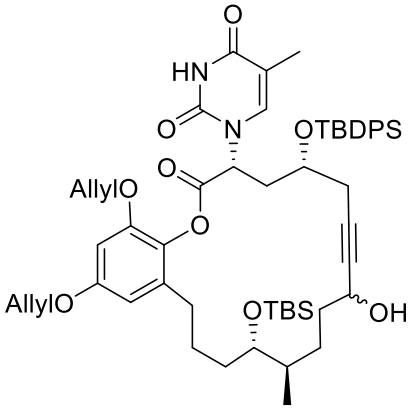
f1 (ppm)

*(R,R)-**97***



Yield: 100 mg (14 %);

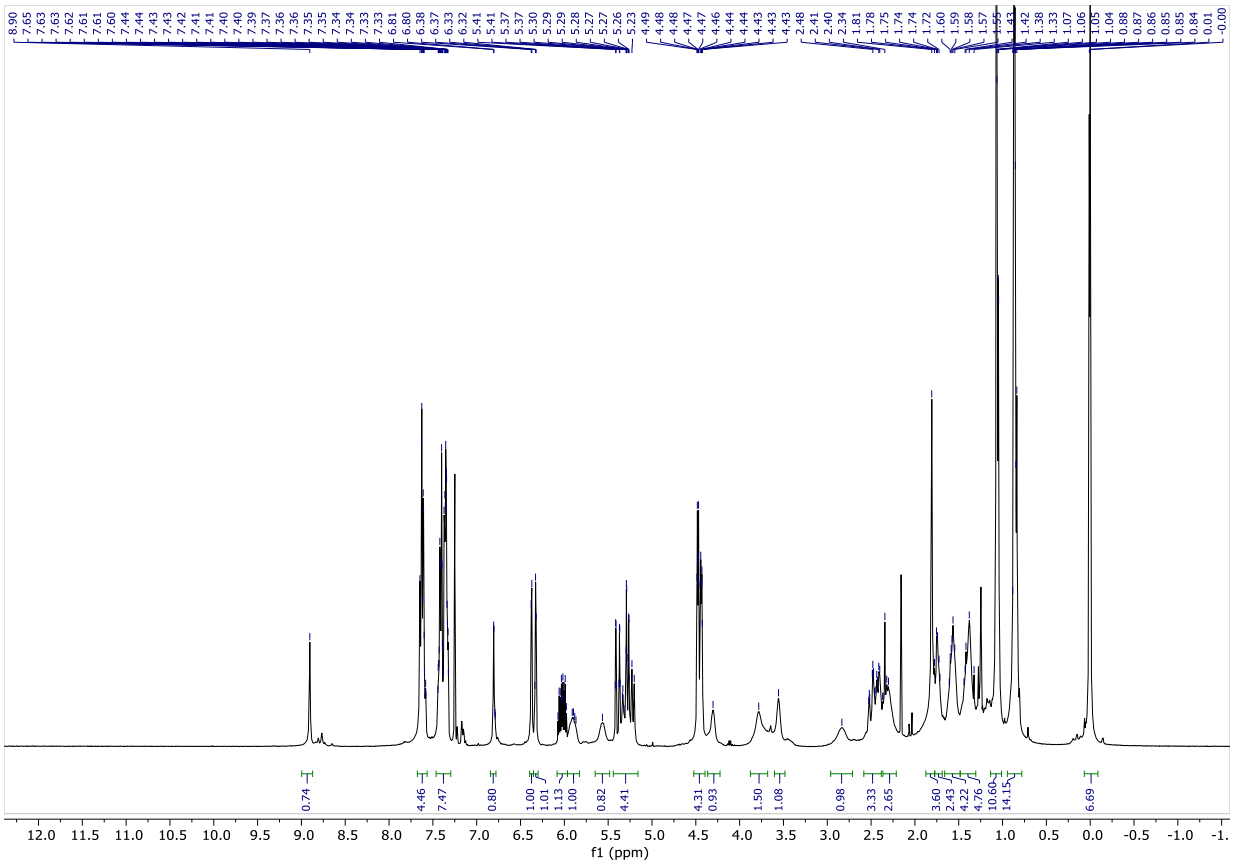
R_f = 0.092 (5:1 Toluene: EtOAc), CPS staining;

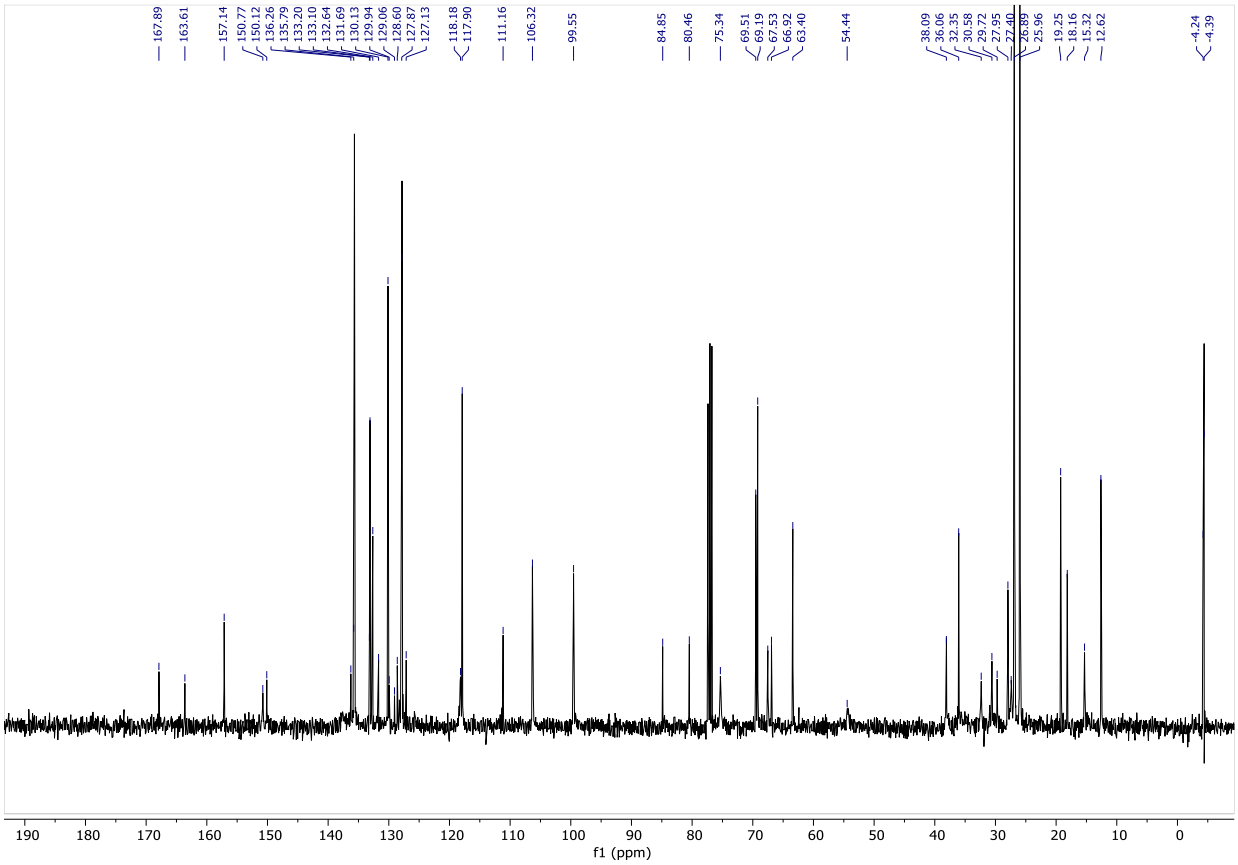
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.90 (s, 1H, NH), 7.82 – 7.49 (m, 4H), 7.47 – 7.29 (m, 6H), 6.80 (br.s, 1H), 6.37 (d, J = 2.7 Hz, 1H), 6.32 (d, J = 2.8 Hz, 1H), 6.02 (ddt, J = 17.3, 10.6, 5.4 Hz, 1H), 5.93-5.87 (m, 1H), 5.57 (br.s, 1H), 5.43 – 5.12 (m, 4H), 4.60 – 4.34 (m, 4H), 4.30 (br.s, 1H), 3.78 (br.s, 1H), 3.56 (br.s, 1H), 2.83 (br.s, 1H), 2.61 – 2.21 (m, 6H), 1.81 (s, 3H), 1.77 – 1.68 (m, 2H), 1.66 – 1.50 (m, 4H), 1.48 – 1.31 (m, 5H), 1.07 (s, 9H), 1.05 (d, J = 1.3 Hz, 2H), 0.89 – 0.82 (m, 9H), 0.00 (d, J = 3.7 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.9, 163.6, 157.1, 150.8, 150.1, 136.3, 135.8 (4C), 133.2, 133.1, 132.6, 131.7, 130.1 (2C), 129.9, 129.1, 128.6, 127.9 (2C), 127.8 (2C), 127.1, 118.2, 117.9, 111.2, 106.3, 99.6, 84.9, 80.5, 75.3, 69.5, 69.2, 67.5, 66.9, 63.4, 54.4, 38.1, 36.1, 32.4, 30.6, 29.7, 28.0, 27.4, 26.9 (2C), 26.0 (2C), 19.25, 18.16, 15.32, 12.62, -4.24, -4.39;

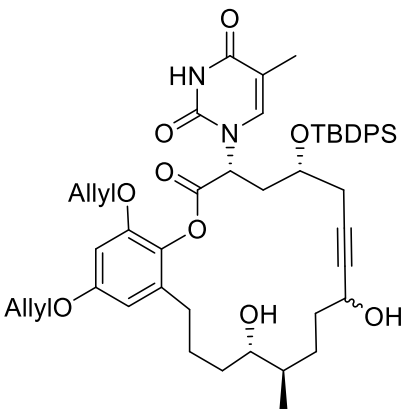
IR (film): ν = 3071, 2954, 2929, 2856, 2169, 1753, 1703, 1666, 1598, 1488, 1462, 1428, 1363, 1257, 1185, 1105, 1088, 1002, 982, 936, 835, 823, 774, 742, 704, 687, 612;

HRMS (ESI-TOF) m/z (ESI) $C_{55}H_{74}N_2NaO_9Si_2$ $[M+Na]^+$ 985.4825, found 985.4815.


f1 (ppm)


f1 (ppm)

SI-(R,R)-97



The substrate occurred upon extended storage

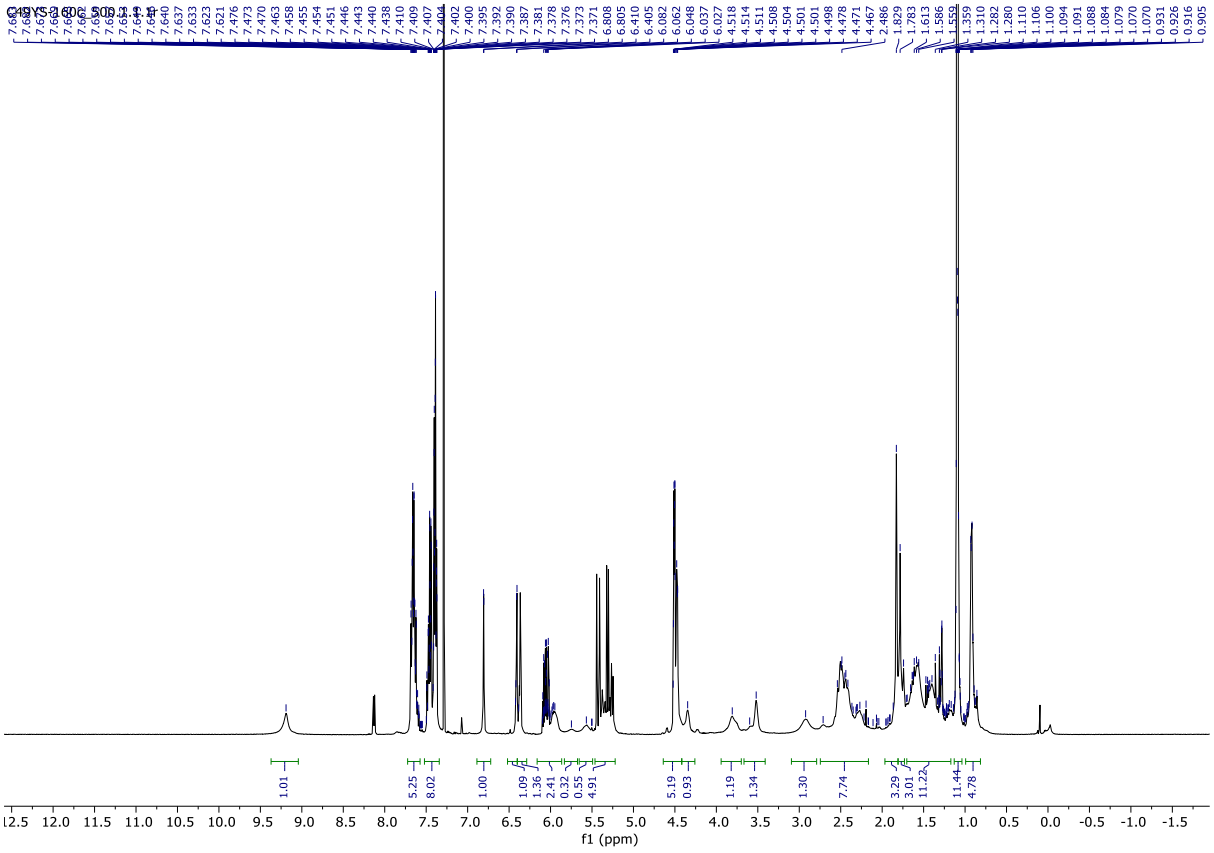
R_f = 0.288 (20:1 DCM: MeOH), CPS staining;

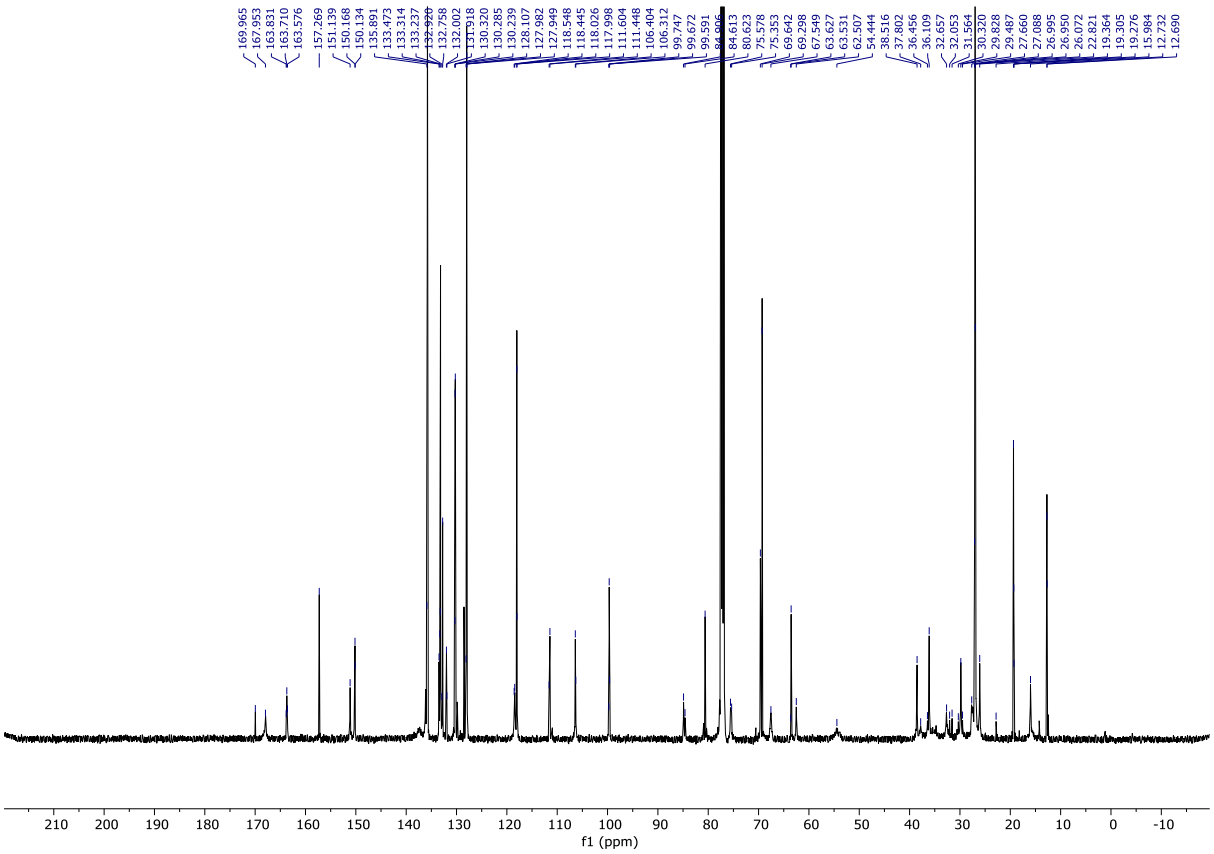
^{1}H NMR (500 MHz, Chloroform-d) δ 9.19 (s, 1H), 7.79 – 7.54 (m, 6H), 7.54 – 7.34 (m, 7H), 6.89 – 6.73 (m, 1H), 6.41 (d, J = 2.7 Hz, 1H), 6.39 (s, 0H), 6.11 – 6.00 (m, 1H), 6.00 – 5.90 (m, 1H), 5.75 (s, 0H), 5.54 (d, J = 32.1 Hz, 1H), 4.60 – 4.40 (m, 7H), 4.35 (s, 1H), 3.81 (s, 1H), 3.52 (s, 1H), 3.10 – 2.02 (m, 9H), 1.96 – 1.19 (m, 12H), 1.18 – 0.99 (m, 11H), 0.99 – 0.65 (m, 4H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.9, 163.6, 157.1, 150.8, 150.1, 136.3, 135.8 (4C), 133.2, 133.1, 132.6, 131.7, 130.1 (2C), 129.9, 129.1, 128.6, 127.9 (2C), 127.8 (2C), 127.1, 118.2, 117.9, 111.2, 106.3, 99.6, 84.9, 80.5, 75.3, 69.5, 69.2, 67.5, 66.9, 63.4, 54.4, 38.1, 36.1, 32.4, 30.6, 29.7, 28.0, 27.4, 26.9 (2C), 26.0 (2C), 19.25, 18.16, 15.32, 12.62, -4.24, -4.39;

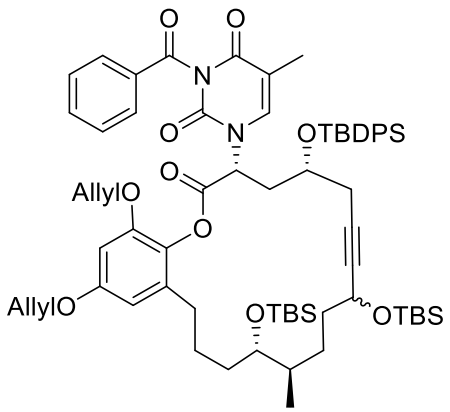
IR (film): ν = 3418, 3190, 3071, 2931, 2860, 1765, 1687, 1598, 1488, 1463, 1428, 1373, 1336, 1267, 1185, 1152, 1112, 1086, 998, 965, 912, 823, 777, 734, 704, 648, 612;

HRMS (ESI-TOF) m/z (ESI) $C_{49}H_{60}N_2NaO_9Si$ $[M+Na]^+$ 871.3960, found 871.3953.


f1 (ppm)


f1 (ppm)

*(R,R)-**99***



(*R*,*R*)-**99**

To a solution (R,R)-**96** (75 mg, 1.0 equiv.) in DMF (0.7 ml) were added imidazole (14.3 mg, 3.0 equiv.) and TBSCl (14.8 mg, 1.4 equiv.) at room temperature and the reaction was stirred at room temperature overnight. After 16 h the reaction is not complete yet, SM is present by TLC and MS, added more reagents: imidazole (14.3 mg, 3.0 equiv.) and TBSCl (14.8 mg, 1.4 equiv.) at room temperature After two additional hours the reaction was done by TLC. The reaction mixture was quenched with water, washed with brine, and extracted with EtOAc (3 x). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by FC 1.5 cm with 5:1 hex: ea, and the product (R,R)-**99** (86 mg, 98 %) came out in fractions 1-10 as a colorless foamy substrate.

Yield: 86 mg (98 %);

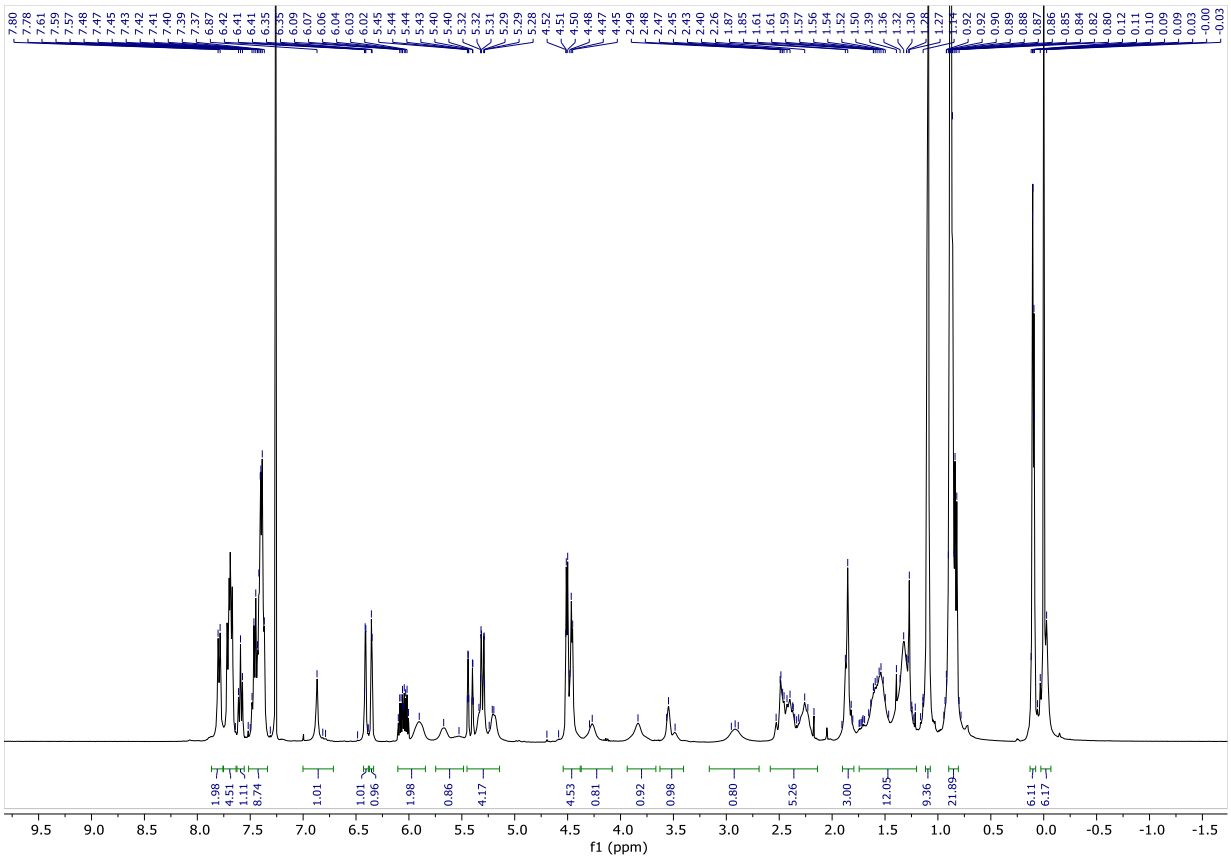
R_f = 0.748 (5:1 Toluene: EtOAc), CPS staining;

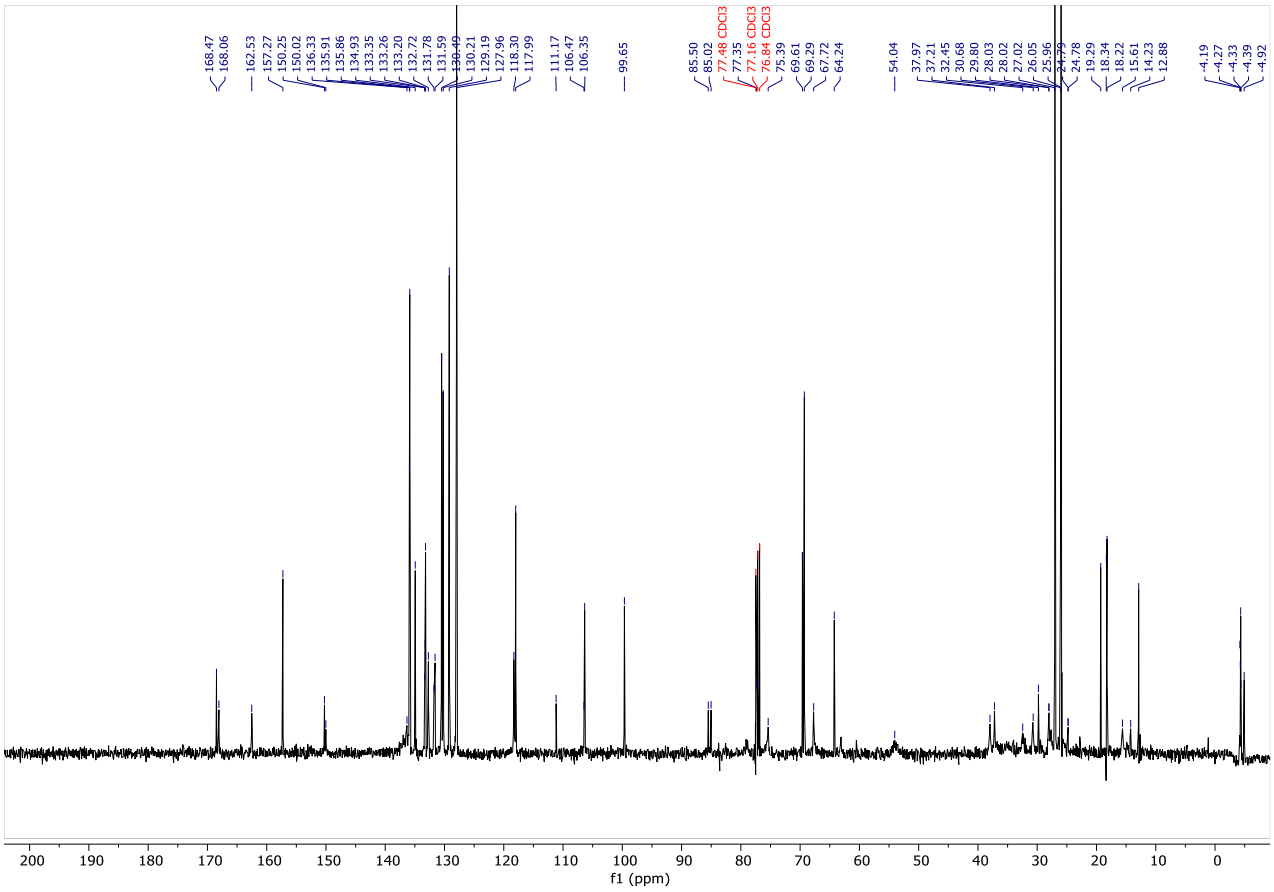
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 (d, J = 7.9 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.51 – 7.29 (m, 8H), 6.87 (s, 1H), 6.41 (d, J = 2.5 Hz, 1H), 6.35 (d, J = 2.7 Hz, 1H), 6.05 (ddt, J = 17.5, 10.6, 5.3 Hz, 1H), 5.90 (s, 1H), 5.67 (s, 0H), 5.42 (dq, J = 17.2, 1.7 Hz, 1H), 5.37 – 5.24 (m, 1H), 5.20 (s, 1H), 4.48 (dd, J = 18.8, 5.3 Hz, 4H), 4.27 (s, 1H), 3.83 (s, 1H), 3.52 (d, J = 24.8 Hz, 1H), 2.92 (s, 1H), 2.63 – 2.09 (m, 4H), 1.86 (d, J = 9.0 Hz, 3H), 1.74 – 1.41 (m, 4H), 1.43 – 1.13 (m, 15H), 1.00 – 0.68 (m, 22H), 0.22 – 0.05 (m, 6H), -0.01 (d, J = 10.9 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.5, 168.1, 162.5, 157.3, 150.3, 150.0, 136.3, 135.9, 134.9, 133.4, 133.3, 133.2, 132.7, 131.8, 131.6, 130.5, 130.2, 129.2, 128.0, 118.3, 118.0, 111.2, 106.5, 106.4, 99.7, 85.5, 85.0, 76.0, 74.6, 54.04, 39.5, 36.7, 37.21, 32.5, 31.1, 30.2, 29.8, 28.7, 27.7, 19.3, 18.3, 18.2, 16.4, 14.6, 14.2, 12.9, -4.2, -4.3, -4.4, -4.9.

IR (film): v = 2954, 2930, 2893, 2857, 1756, 1706, 1668, 1599, 1489, 1462, 1429, 1362, 1256, 1186, 1111, 1086, 836, 774, 741, 704, 686, 670, 611, 508;

HRMS (ESI-TOF) m/z (ESI) $C_{68}H_{92}KN_2O_{10}Si_3$ $[M+K]^+$ 1219.5691, found 1219.5697.

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106.35
99.65
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85.02
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77.35
77.16 CDCl3
76.84 CDCl3
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180
170
160
150
140
130
120
110
100
90
80
70
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30
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10
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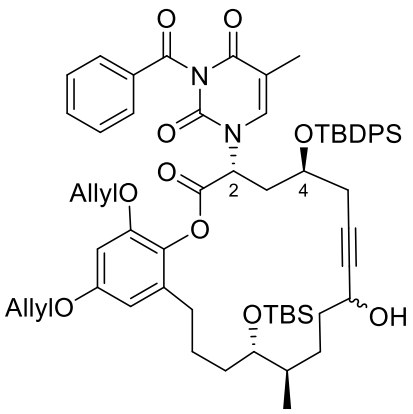
f1 (ppm)

5.3.3.2 *R,S*-18-membered macrocycle

*(R,S)-**96***



$CrCl_2$ (250 mg) was dried for 2 h at 200 °C under vacuum (200 °C, <1.1 mbar). The reaction was performed in a 250 ml flask (dried with a heat gun at 650°C and then high vacuum). Separately two solutions were prepared: (R,S)-**84** (190 mg, 0.159 mmol, 1 equiv.) was diluted in 5 mL of THF (4 ml, c=0.04 M +1 ml for washing). Sol2 - vigorously stirring solution of $CrCl_2$ (196 mg, 1.59 mmol.,10 equiv.) and $NiCl_2$ (1.7 mg, 0.013 mmol, 0.4 equiv.) in THF (17.4 ml, c=0.0915 M). The first solution with substrates was slowly added dropwise, over 5 minutes to a vigorously stirring solution of catalysts. The reaction was stirred for 10 hours and quenched with water (20 ml) addition. However the reaction was not complete, therefore the same cycle was repeated. The crude material was purified and the fractions containing the product+SM mixture were submitted to the reaction conditions again. The second cycle of the reaction was run for 20 hours until the starting material was fully consumed as indicated by TLC. The reaction was worked up by quenching with water, extracted with EtOAc, and dried over $MgSO_4$. The organic phase was then filtered off and evaporated under reduced pressure. The crude material was purified by flash column chromatography. The desired product (R,S)-**96** was isolated in 34 % yield.

Yield: 50 mg (34 %), *dr*=1:1;

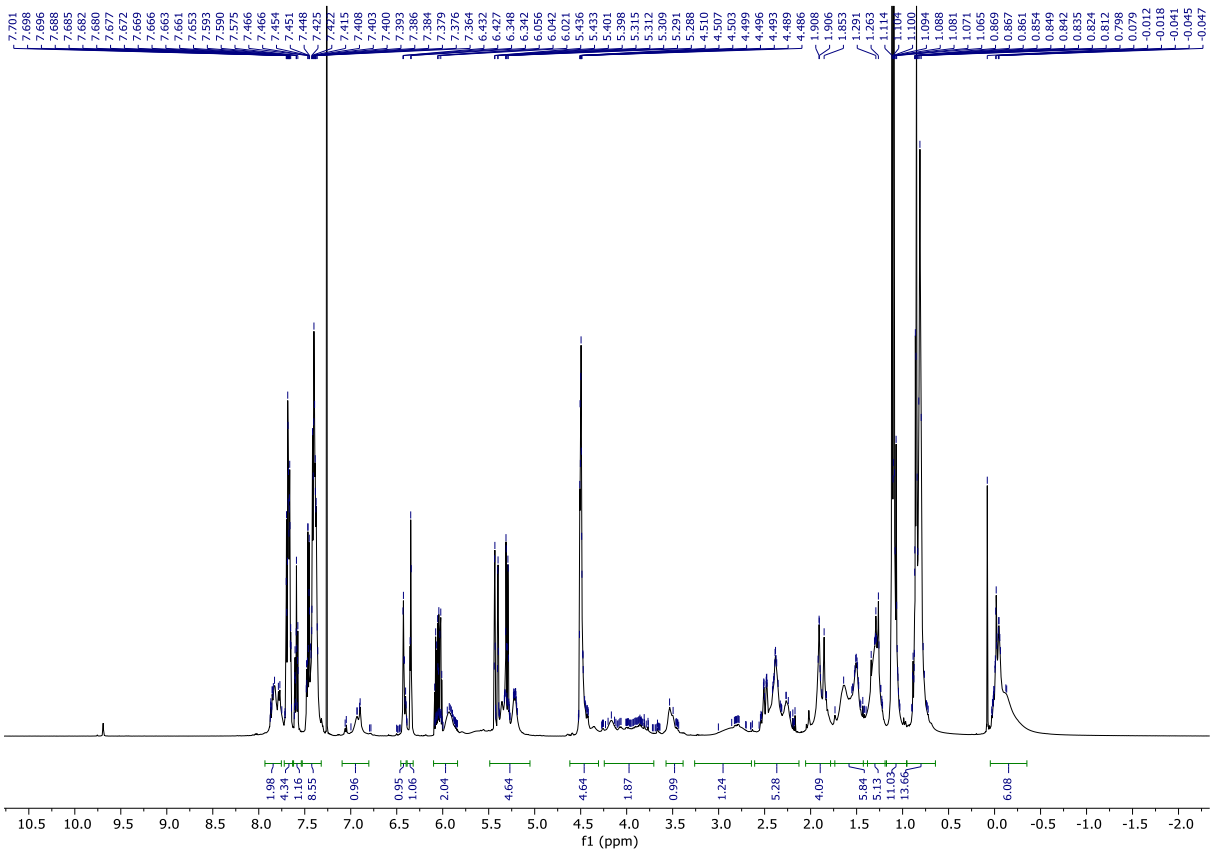
R_f = 0.56 (2:1 Hexane: EtOAc), CPS staining;

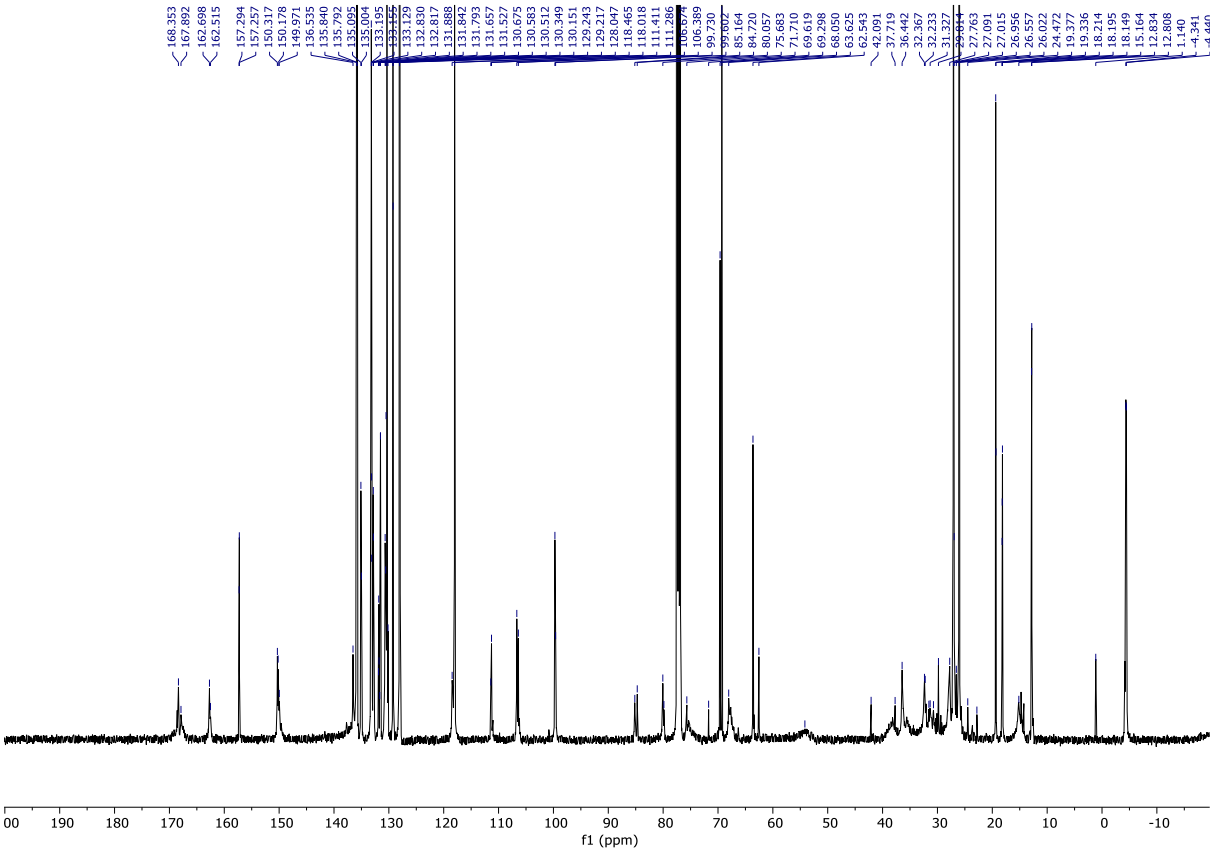
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.92 – 7.74 (m, 3H), 7.67 (dtt, J = 9.6, 5.5, 1.5 Hz, 4H), 7.59 (tt, J = 7.4, 1.3 Hz, 1H), 7.50 – 7.33 (m, 10H), 7.11 – 6.76 (m, 1H), 6.51 – 6.38 (m, 1H), 6.35 (t, J = 3.0 Hz, 1H), 6.11 – 6.01 (m, 1H), 6.01 – 5.81 (m, 1H), 5.42 (dq, J = 17.2, 1.6 Hz, 1H), 5.33 – 5.14 (m, 3H), 4.50 (ddt, J = 4.8, 3.3, 1.5 Hz, 4H), 4.28 – 3.63 (m, 0H), 3.61 – 3.32 (m, 1H), 3.06 – 2.62 (m, 0H), 2.58 – 2.17 (m, 5H), 1.97 – 1.77 (m, 3H), 1.77 – 1.19 (m, 9H), 1.09 (dd, J = 12.4, 9.3 Hz, 10H), 0.91 – 0.67 (m, 13H), 0.19 – -0.36 (m, 8H);

^{13}C NMR (126 MHz, Chloroform-*d*) δ 168.4, 167.9, 162.7, 162.5, 157.3, 157.3, 150.3, 150.2, 150.0, 136.5, 135.8, 135.8, 135.1, 135.0, 133.2, 132.8, 132.8, 131.8, 131.5, 130.7, 130.6, 130.5, 130.4, 130.2, 129.2, 129.2, 128.1, 118.5, 118.0, 111.4, 111.3, 106.7, 106.4, 99.7, 99.6, 85.2, 84.7, 80.1, 79.9, 75.7, 71.7, 69.6, 69.3, 68.1, 63.6, 62.5, 54.2, 42.1, 37.7, 36.4, 32.4, 32.2, 31.6, 31.3, 30.7, 29.8, 27.8, 27.1, 26.6, 26.0, 24.5, 22.8, 19.4, 19.3, 18.2, 18.2, 18.2, 15.2, 12.8, 12.8, 1.1, -4.3, -4.4;

IR (film): ν = 2957, 2926, 2856, 1754, 1706, 1668, 1595, 1485, 1462, 1429, 1363, 1260, 1185, 1086, 837, 703, 668, 626;

HRMS (ESI-TOF) m/z (ESI) $C_{62}H_{78}N_2NaO_{10}Si_2$ $[M+Na]^+$ 1089.5087, found 1089.5075.

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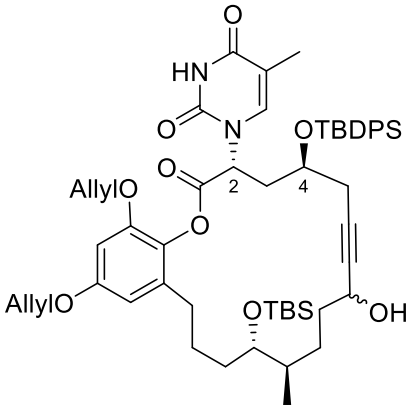
19.377
19.336
18.214
18.195
18.149
15.164
12.834
12.808
1.140
-4.341
-4.440
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

*(R,S)-**97***



Benzoylated (R,S)-**96** (8 mg, 0.0075 mmol, 1 equiv.) was dried thoroughly under a high vacuum in a 10 ml flask. A 0.5 M solution of ammonia in THF (5.00 ml, c=0.0015 M) was added to (R,S)-**96**. After 2 days the reaction was complete and the solvent was evaporated. The crude material was purified by FC with an eluent system from 50:1 DCM: MeOH to 10:1 DCM: MeOH. The pure product (R,S)-**97** was isolated as a colorless oil with a good yield of 57 %.

Yield: 4.1 mg (57 %), *dr*=1:1;

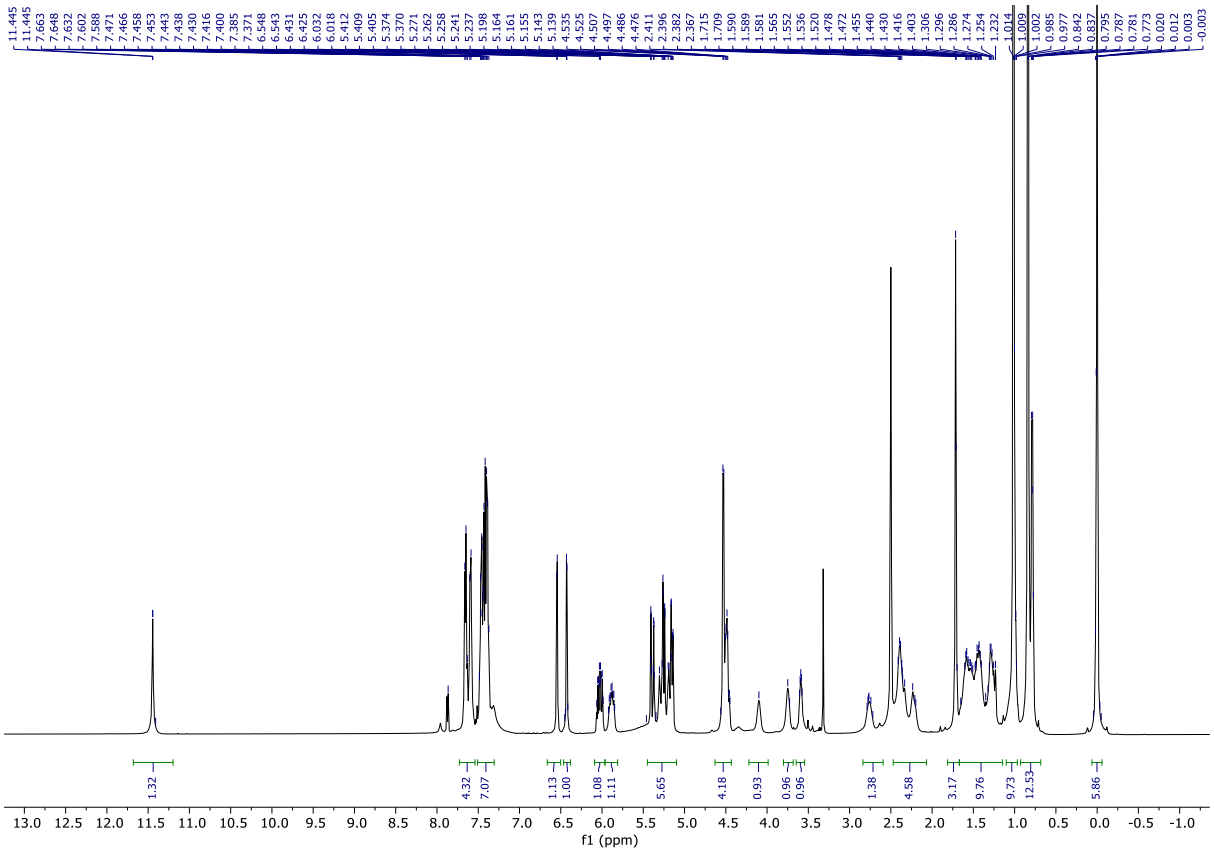
R_f = 0.25 (25:1 DCM: MeOH), CPS staining;

^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.45 (s, 1H), 7.96 – 7.56 (m, 4H), 7.43 (ddt, J = 29.8, 14.8, 7.0 Hz, 6H), 6.55 (d, J = 2.7 Hz, 1H), 6.43 (d, J = 2.7 Hz, 1H), 6.03 (ddt, J = 17.4, 10.6, 5.3 Hz, 1H), 5.88 (ddt, J = 15.7, 9.9, 4.9 Hz, 1H), 5.49 – 5.06 (m, 5H), 4.58 – 4.36 (m, 4H), 4.10 (s, 1H), 3.75 (s, 1H), 3.59 (dt, J = 8.0, 3.8 Hz, 1H), 2.88 – 2.61 (m, 1H), 2.44 – 2.11 (m, 4H), 1.71 (d, J = 3.1 Hz, 3H), 1.64 – 1.20 (m, 9H), 1.01 (d, J = 2.6 Hz, 9H), 0.84 (d, J = 2.6 Hz, 9H), 0.78 (dd, J = 6.8, 4.3 Hz, 3H), 0.00 (t, J = 3.7 Hz, 6H);

^{13}C NMR (126 MHz, DMSO-*d6*) δ 167.85, 163.57, 157.86 – 154.60 (m), 150.73, 149.85, 135.29, 135.25, 135.19, 134.26, 133.62, 133.08, 133.02, 132.56, 131.37, 131.18, 129.99 (d, J = 4.9 Hz), 128.18, 127.84 (d, J = 4.4 Hz), 127.44, 117.07, 109.61, 106.32 (d, J = 11.2 Hz), 99.54, 85.86, 78.39, 74.96, 67.53, 61.65, 36.50, 28.99, 27.66, 26.67, 25.78, 25.03, 18.78 (d, J = 2.7 Hz), 17.79, 14.75, 14.34, 12.17, -4.41, -4.48;

IR (film): ν = 2931, 2858, 1766, 1693, 1597, 1488, 1463, 1428, 1373, 1259, 1186, 1111, 1089, 835, 774, 740, 704, 643, 612;

HRMS (ESI-TOF) m/z (ESI) $C_{55}H_{74}N_2NaO_9Si_2$ $[M+Na]^+$ 985.4825, found 985.4823.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7.663
7.648
7.632
7.602
7.588
7.471
7.466
7.458
7.453
7.443
7.438
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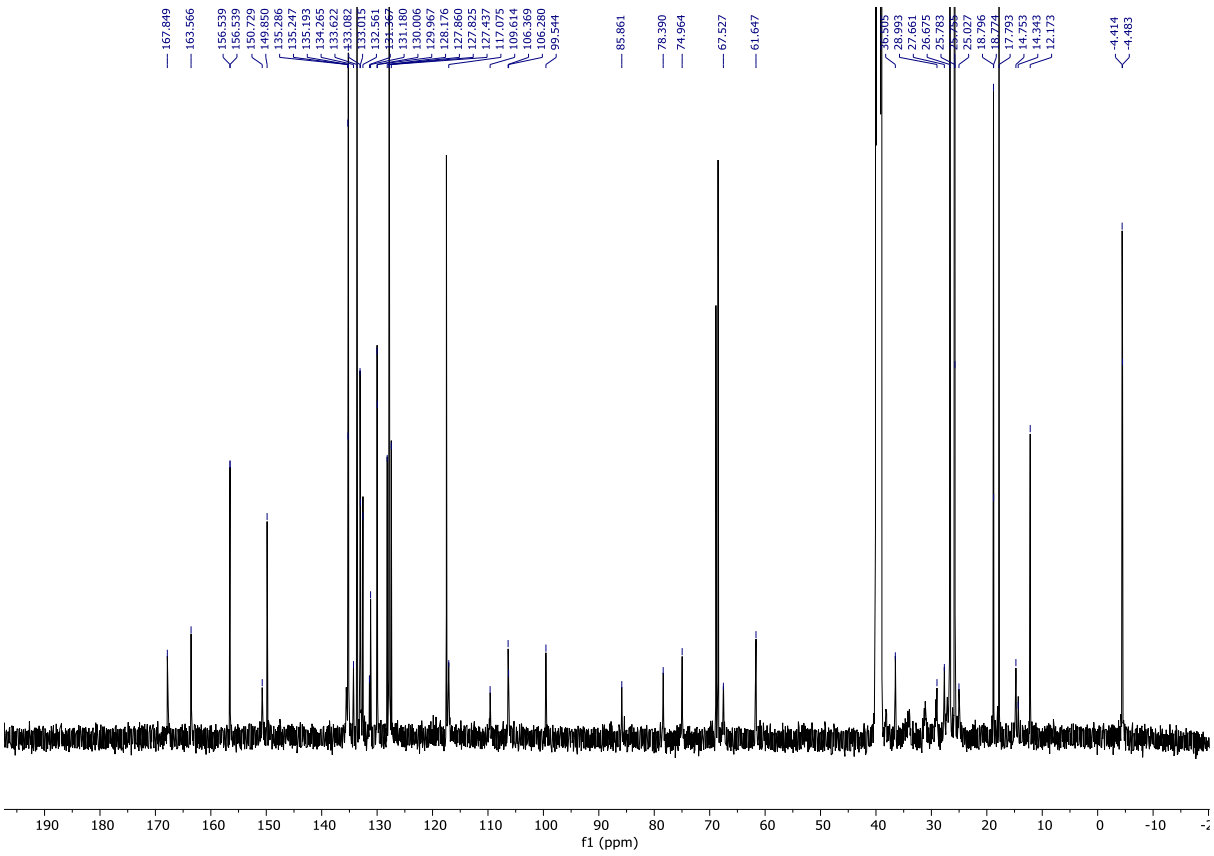
7.416
7.400
7.385
7.371
6.548
6.543
6.431
6.425
6.032
6.018
5.412
5.409
5.405
5.374
5.370
5.271
5.262
5.258
5.241
5.237
5.198
5.164
5.161
5.155
5.143
5.139
4.535
4.525
4.507
4.497
4.486
4.476
2.411
2.396
2.382
2.367
1.715
1.709
1.590
1.589
1.581
1.565
1.552
1.536
1.520
1.478
1.472
1.455
1.440
1.430
1.416
1.403
1.306
1.296
1.286
1.274
1.254
1.232
1.014
1.009
1.002
0.985
0.977
0.842
0.837
0.795
0.787
0.781
0.773
0.020
0.012
0.003
-0.003
1.32
4.32
7.07
1.13
1.00
1.08
1.11
5.65
4.18
0.93
0.96
0.96
1.38
4.58
3.17
9.76
9.73
12.53
5.86
f1 (ppm)


167.849
163.566
156.539
156.539
150.729
149.850
135.286
135.247
135.193
134.265
133.622
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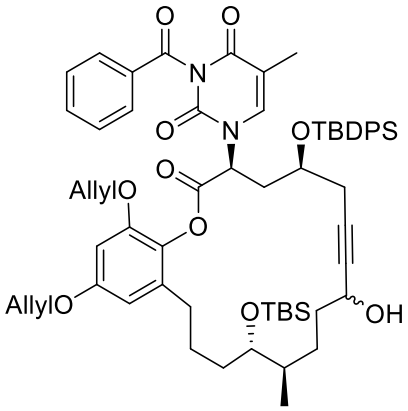
133.015
132.561
131.388
131.180
130.006
129.967
128.176
127.860
127.825
127.437
117.075
109.614
106.369
106.280
99.544
85.861
78.390
74.964
67.527
61.647
36.505
28.993
27.661
26.675
25.783
25.027
18.796
18.274
17.793
14.753
14.343
12.173
-4.414
-4.483
f1 (ppm)

5.3.3.3 *S,S*-18-membered macrocycle

*(S,S)-**96***



THF was thoroughly degassed (with Freeze-Pump-Thaw technique, three times – ca. 1.5 hours) in a heatgun-dried glassware. $CrCl_2$ (400 mg) was dried for at least 2.5 h at 200 °C under vacuum (200 °C, <1.1 mbar). The reaction was performed in a Schleck tube 100 ml (thoroughly dried with a heat gun at 650°C and then high vacuum). Separately two solutions were prepared: (S,S)-**84** (275 mg, 1 equiv.) was diluted in 4 mL of THF (+3+1 ml for washing), sol2 - vigorously stirring solution of $CrCl_2$ (283 mg, 10 equiv.) and $NiCl_2$ (60 mg, 0.2 equiv.) in 25.2 mL of THF. The solution with substrates was slowly added dropwise, over 5 minutes, to a vigorously stirring solution of catalysts. The reaction solution was left overnight, and after 22 h reaction looked complete, spot-to-spot conversion. The reaction was worked up after 22 h by quenching with 20 mL of saturated NH_4Cl solution, extracted with EA (3 x 30 mL), washed with $Na_2S_2O_3$ (15 mL), H_2O (15 mL), brine (15 mL) dried over $MgSO_4$, and concentrated. Mcrude=360 mg was purified by FCC to obtain (S,S)-96 in 66 % yield.

Yield: 0.164 g (66 %), *dr*=1:1;

R_f = 0.564 (2:1 Hexane: EtOAc), CPS staining;

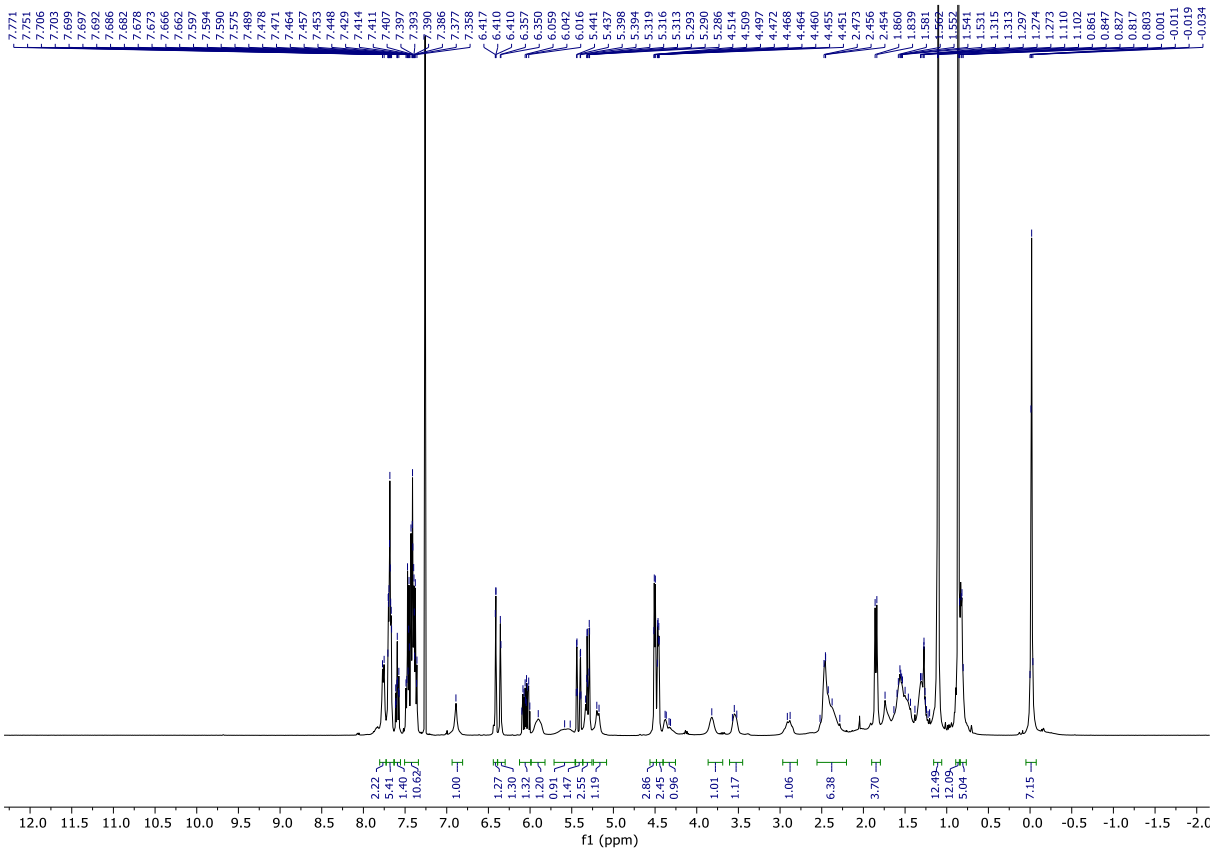
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, J = 7.8 Hz, 2H), 7.69 (ddt, J = 8.1, 4.3, 1.5 Hz, 4H), 7.63 – 7.55 (m, 1H), 7.50 – 7.33 (m, 9H), 6.89 (s, 1H), 6.47 – 6.37 (m, 2H), 6.35 (d, J = 2.8 Hz, 1H), 6.05 (ddt, J = 17.3, 10.5, 5.3 Hz, 1H), 5.90 (s, 1H), 5.70 – 5.48 (m, 1H), 5.42 (dq, J = 17.2, 1.6 Hz, 1H), 5.37 – 5.26 (m, 2H), 5.19 (d, J = 10.6 Hz, 1H), 4.50 (d, J = 5.2 Hz, 3H), 4.46 (dt, J = 5.4, 1.6 Hz, 2H), 4.41 – 4.24 (m, 1H), 3.82 (s, 1H), 3.53 (d, J = 12.1 Hz, 1H), 2.90 (d, J = 13.3 Hz, 1H), 2.58 – 2.22 (m, 6H), 1.85 (d, J = 8.4 Hz, 3H), 1.77 – 1.20 (m, 9H), 1.11 (s, 4H), 1.10 (s, 8H), 0.86 (s, 8H), 0.84 – 0.77 (m, 2H), -0.01 (d, J = 3.3 Hz, 6H);

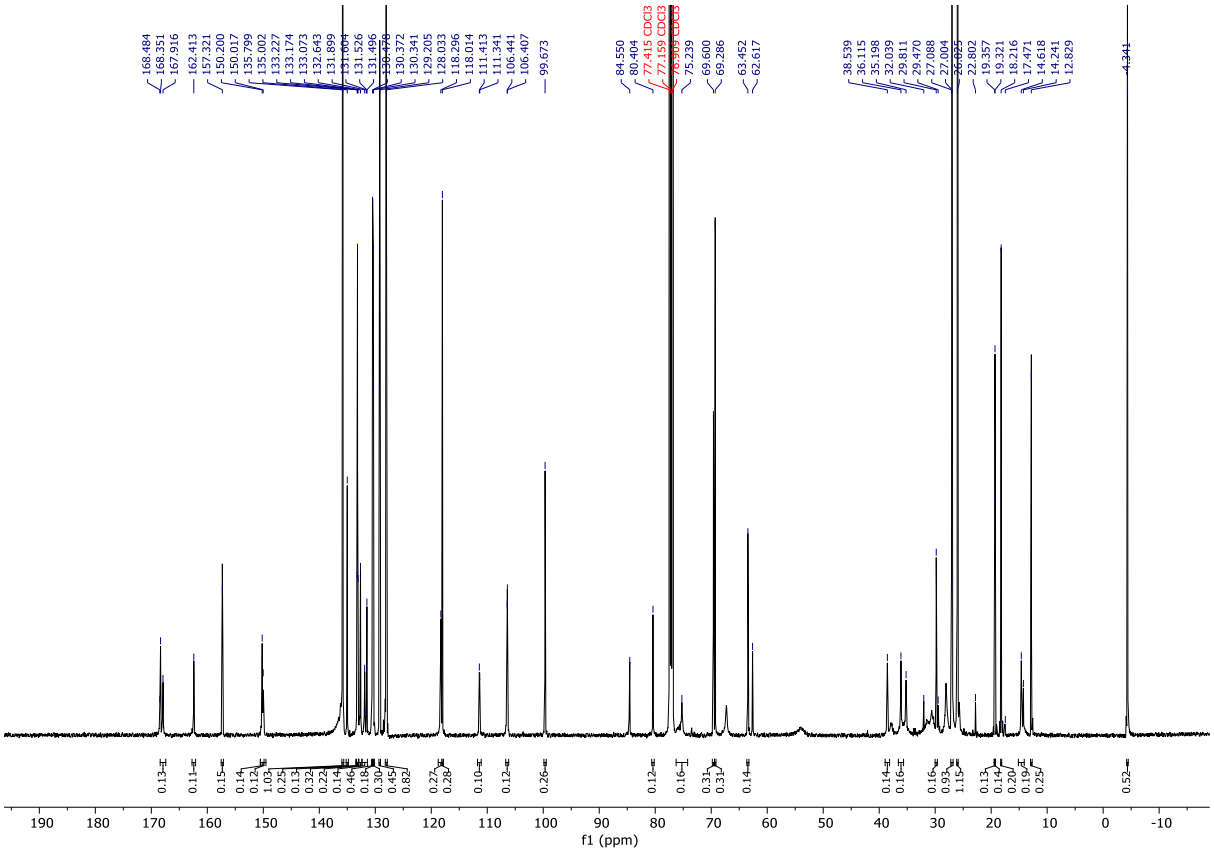
^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.42 – 168.1 (m), 167.9, 162.4, 157.3, 150.2, 135.8, 135.01 (d, J = 4.0 Hz), 133.17 (d, J = 4.2 Hz), 132.6, 131.5, 130.5, 130.3, 129.2, 128.0, 118.3, 118.0, 111.4, 106.4,

99.7, 84.5, 80.4, 75.2, 69.6, 69.3, 63.4, 62.6, 38.5, 36.1, 35.2, 28.0, 27.0, 26.0, 19.3, 18.2, 14.6, 12.8, -4.4.

IR (film): ν = 2955, 2922, 2851, 1707, 1664, 1606, 1463, 1377, 1260, 1186, 1081, 1019, 969, 807, 799, 785, 777, 770, 764, 755, 741, 731, 718, 706, 691, 607, 595;

HRMS (ESI-TOF) m/z (ESI) $C_{62}H_{78}N_2NaO_{10}Si_2$ $[M+Na]^+$ 1089.5087, found 1089.5084.




168.484
168.351
167.916
162.413
157.321
150.200
150.017
135.799
135.002
133.227
133.174
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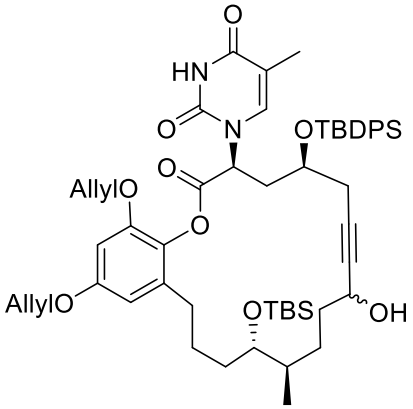
131.899
131.526
131.496
130.372
130.341
129.205
128.033
118.296
118.014
111.413
111.341
106.441
106.407
99.673
84.550
80.404
77.415 CDCl3
77.159 CDCl3
76.909 CDCl3
75.239
69.600
69.286
63.452
62.617
38.539
36.115
35.198
32.039
29.811
29.470
27.088
27.004
26.825
22.802
19.357
19.321
18.216
17.471
14.618
14.241
12.829
4.341
0.13
0.11
0.15
0.14
0.12
1.03
0.25
0.13
0.32
0.22
0.14
0.46
0.18
0.30
0.45
0.82
0.27
0.28
0.10
0.12
0.26
0.12
0.16
0.31
0.31
0.14
0.14
0.16
0.16
0.93
1.15
0.13
0.14
0.20
0.19
0.25
0.52
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

*(S,S)-**97***



(S,S)-**97** from (S,S)-**95** procedure**:** THF was thoroughly degassed (with argon flow 14:02 - 15:15) the glassware (15:40-15:55). $CrCl_2$ (213 mg) was dried for at least for 2 h at 200 °C under haus vacuum (8:10-14:00). Reaction was performed in a Schleck tube 50 ml (dried with a heat gun at 650°C and then high vacuum, 12:35-15:00). Separately 2 solutions were prepared: (S,S)-**95** (100 mg, 1 equiv.) was diluted in 2.25 mL of THF (3 ml for washing). Sol2 - vigorously stirring solution of $CrCl_2$ (113 mg,) and $NiCl_2$ (1 mg, 0.4 equiv.) in 10 mL of THF. The first solution with substrates was slowly added dropwise, over 10 minutes (15:40-15:50), to a vigorously stirring solution of catalysts. Left overnight after 22 h reaction looks complete, worked up after 17h quenched with 10 mL of saturated NH4Cl solution, extracted with EA (3 x 20 mL), washed with NaS2O3 (5 mL), H2O (5 mL), brine (5 mL) dried over $MgSO_4$, and concentrated. Mcrude=360 mg, Fr 19-25, deiodinated substrate (S,S)-**98** (19 %) Fr 31-44 was the desired product (S,S)-**97**, 58.8 mg.

(S,S)-**97** from (S,S)-**96** procedure: Benzoylated (S,S)-**96** (330 mg, 0.3091 mmol, 1 equiv.) was dried thoroughly under a high vacuum in a 50 ml flask. A solution of ammonia in THF (0.5 M) was added (155 ml, c=0.002 M) to (S,S)-**96**. The reaction was monitored by TLC. The reaction seems to be proceeding, but there is still a lot of SM. After 3 days the reaction was stopped by evaporation of the solvent. The crude material (M=450 mg) was purified, using column chromatography (2-3 cm col), eluent (20:1 hex: ea). The product (S,S)-**97** was obtained in fractions 17-23 (228 mg, 77 %) + some starting material was recovered in fractions 14-16 (44 mg, 13 %).

Yield: 228 mg (77 %), *dr*=1.33:1;

R_f = 0.295 (2:1 Hexane: EtOAc), CPS staining;

$[\alpha]_{20}^{D}$: = not applicable;

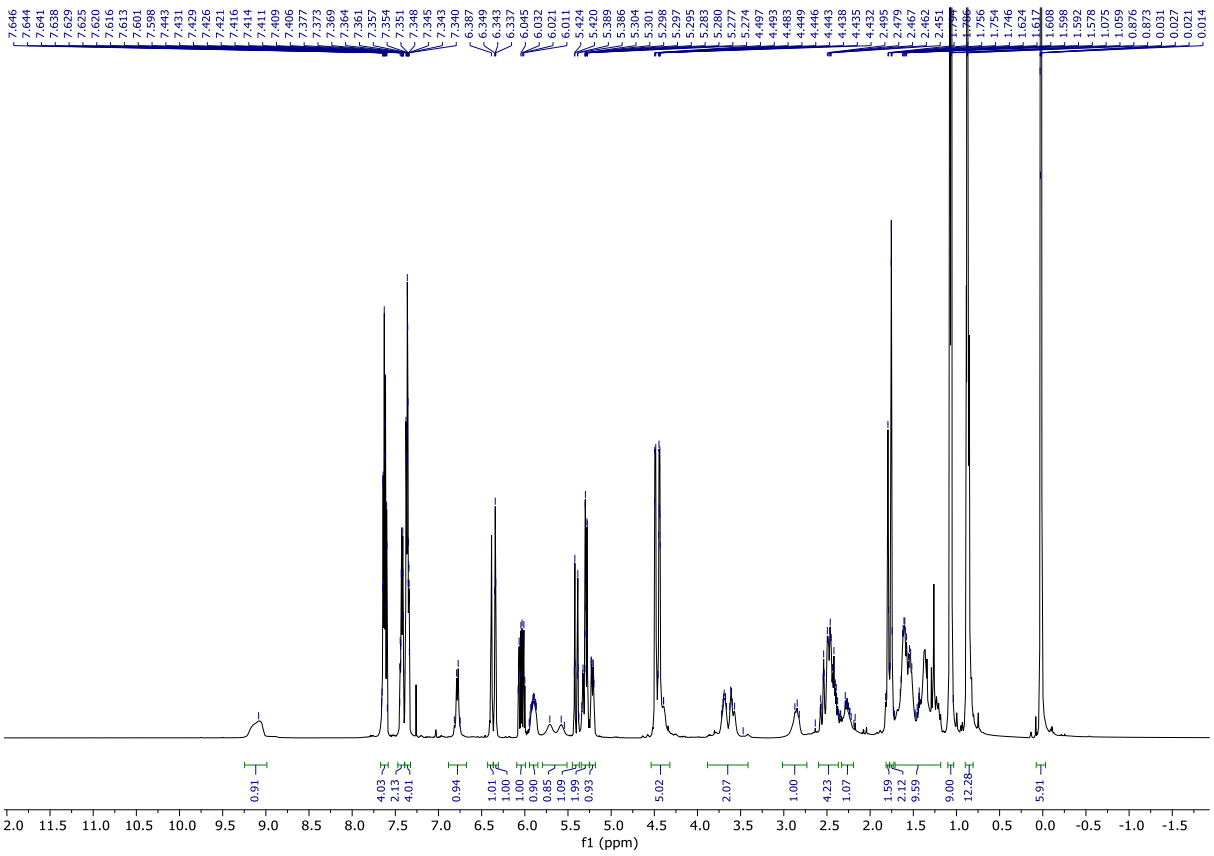
^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.08 (s, 1H), 7.80 – 7.54 (m, 5H), 7.49 – 7.39 (m, 2H), 7.39 – 7.30 (m, 4H), 6.78 (d, J = 9.4 Hz, 1H), 6.39 (s, 1H), 6.34 (t, J = 3.2 Hz, 1H), 6.04 (ddt, J = 17.4, 10.6, 5.3 Hz, 1H),

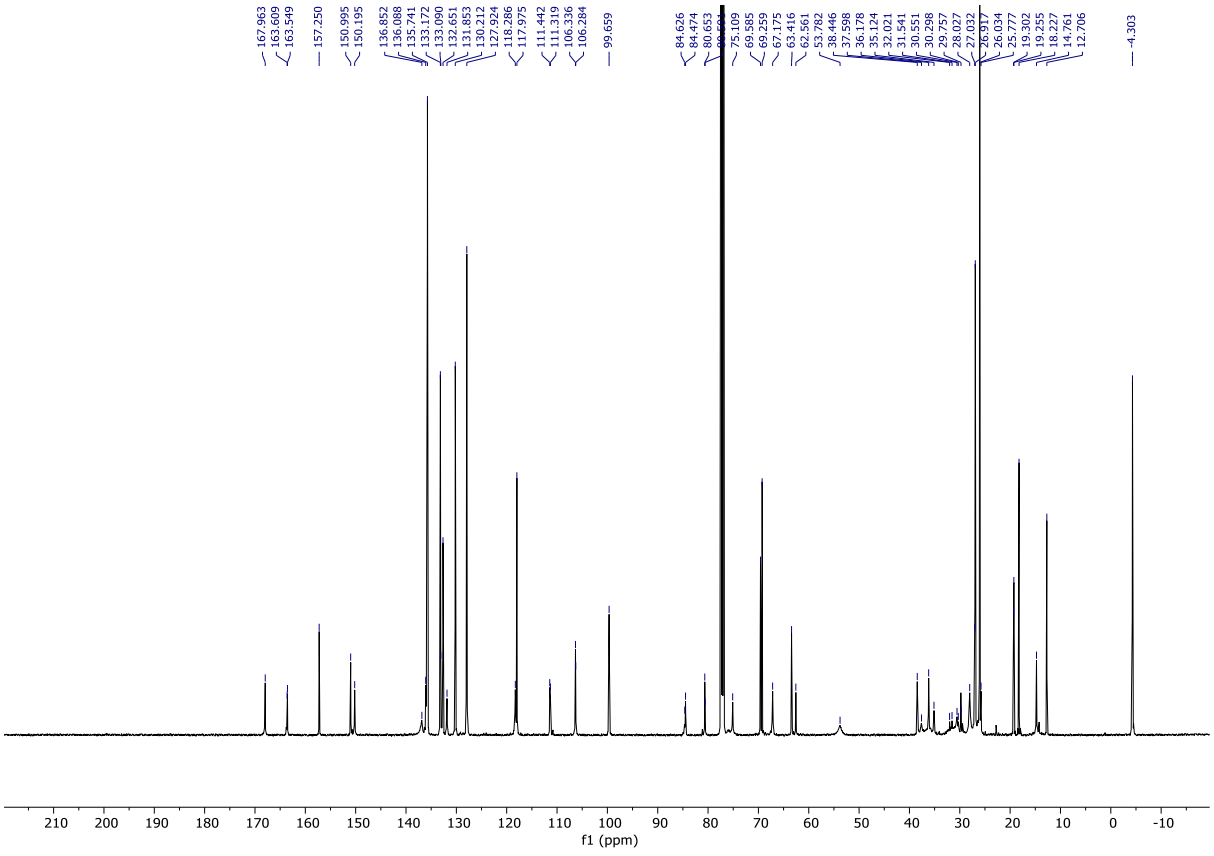
5.91 (dtd, J = 19.5, 10.9, 5.4 Hz, 1H), 5.71 (s, 0H), 5.58 (s, 0H), 5.42 (q, J = 1.7 Hz, 1H), 5.39 (q, J = 1.7 Hz, 1H), 5.35 – 5.31 (m, 1H), 5.30 (q, J = 1.4 Hz, 1H), 5.28 (q, J = 1.4 Hz, 1H), 5.25 – 5.18 (m, 1H), 4.54 – 4.46 (m, 2H), 4.44 (dt, J = 5.4, 1.6 Hz, 2H), 4.39 (s, 1H), 3.75 – 3.65 (m, 1H), 3.63 – 3.46 (m, 1H), 2.83 (d, J = 12.1 Hz, 0H), 2.69 – 2.34 (m, 3H), 2.31 – 2.17 (m, 1H), 1.79 (s, 1H), 1.75 (d, J = 1.1 Hz, 2H), 1.68 – 1.43 (m, 3H), 1.07 (s, 3H), 1.06 (s, 6H), 0.87 (d, J = 1.3 Hz, 8H), 0.02 (dd, J = 5.7, 2.8 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.0, 168.0, 163.7, 163.6, 157.2, 157.2, 151.0, 150.2, 136.9, 136.1, 135.7, 133.2, 133.1, 132.6, 131.8, 130.2, 127.9, 118.3, 118.0, 111.4, 111.3, 106.3, 106.3, 99.7, 84.6, 84.5, 80.6, 80.6, 75.1, 69.6, 69.3, 67.2, 63.4, 62.5, 53.8, 38.4, 36.2, 35.1, 31.5, 30.6, 29.8, 28.1, 28.0, 27.0, 26.9, 26.0, 25.8, 19.3, 19.2, 18.2, 14.7, 12.7, -4.3;

IR (film): ν = 2955, 2929, 2856, 1767, 1693, 1597, 1488, 1463, 1428, 1374, 1259, 1187, 1110, 1088, 936, 834, 775, 741, 703, 667, 646, 629, 597, 560;

HRMS (ESI-TOF) m/z (ESI) $C_{55}H_{74}N_2NaO_9Si_2$ $[M+Na]^+$ 985.4825, found 985.4825.

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25.777
19.302
19.255
18.227
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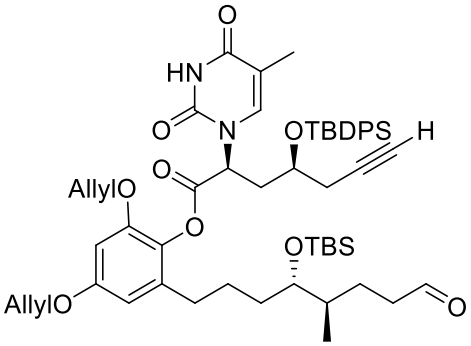
-4.303
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

*(S,S)-**98***



Yield: 19 %;

R_f = 0.5 (2:1 Hexane: EtOAc), CPS staining;

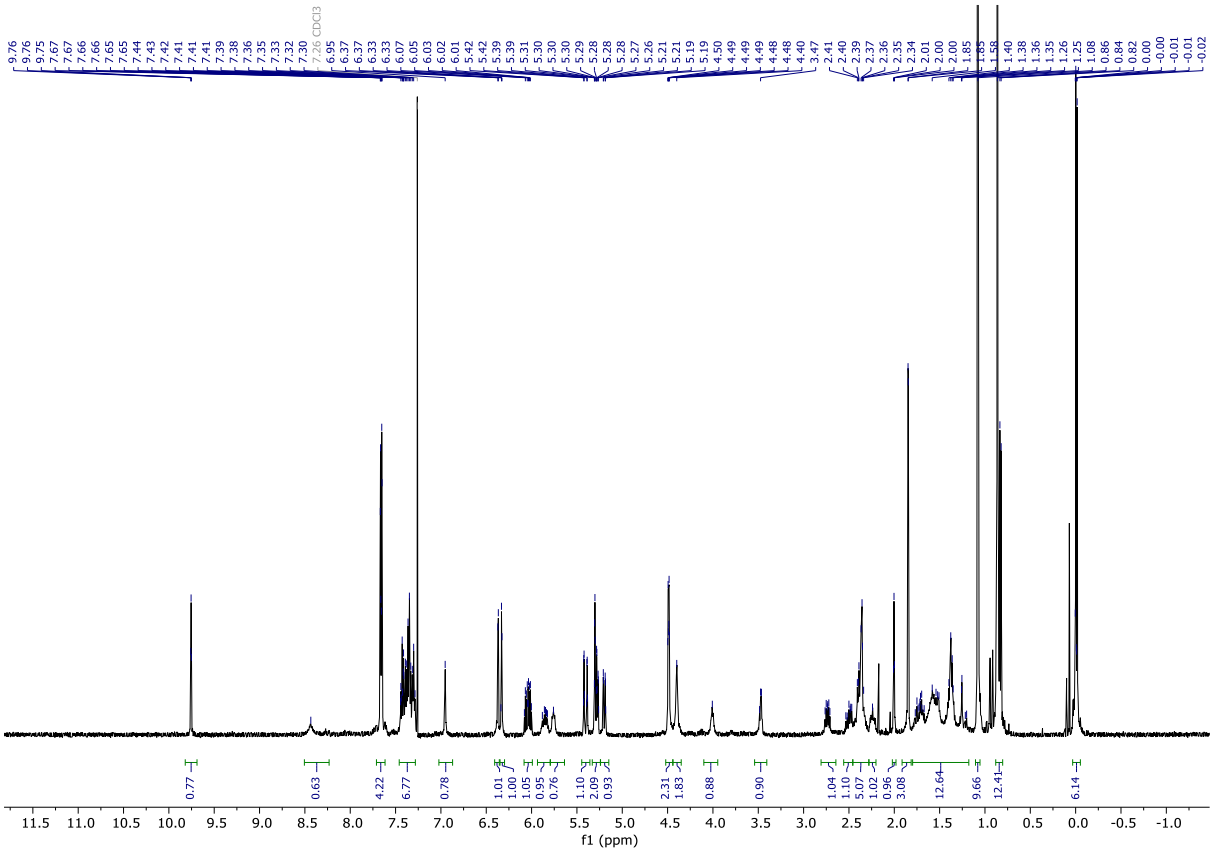
$[\alpha]_{20}^{D}$: = -17.00 (c = 1.0; $CHCl_3$, 20 °C);

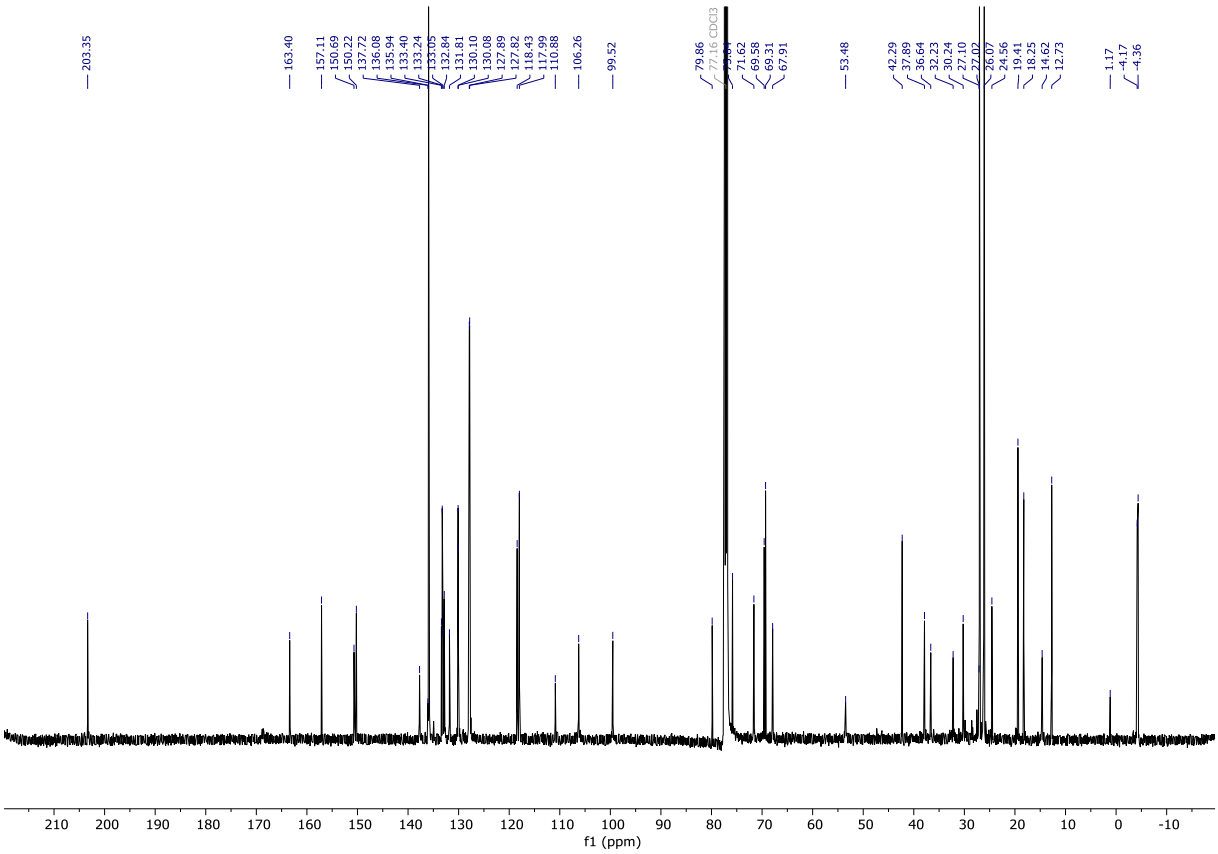
^{1}H NMR (500 MHz, Chloroform-*d*) *δ* 9.76 (t, J = 1.7 Hz, 1H), 8.43 (s, 0H), 7.73 – 7.58 (m, 3H), 7.48 – 7.27 (m, 5H), 6.95 (s, 1H), 6.37 (d, J = 2.7 Hz, 1H), 6.33 (d, J = 2.7 Hz, 1H), 6.04 (ddt, J = 17.2, 10.6, 5.3 Hz, 1H), 5.91 – 5.80 (m, 1H), 5.76 (s, 1H), 5.41 (dq, J = 17.2, 1.6 Hz, 1H), 5.34 – 5.24 (m, 1H), 5.20 (dd, J = 10.4, 1.4 Hz, 1H), 4.49 (dt, J = 5.4, 1.5 Hz, 1H), 4.40 (s, 1H), 4.01 (s, 1H), 3.56 – 3.40 (m, 1H), 2.74 (dt, J = 14.3, 6.0 Hz, 1H), 2.57 – 2.43 (m, 1H), 2.43 – 2.30 (m, 3H), 2.24 (s, 1H), 2.00 (t, J = 2.6 Hz, 1H), 1.85 (d, J = 1.2 Hz, 2H), 1.80 – 1.19 (m, 8H), 1.08 (s, 7H), 0.86 (s, 6H), 0.83 (d, J = 6.8 Hz, 2H), -0.01 (d, J = 7.7 Hz, 4H);

^{13}C NMR (126 MHz, Chloroform-*d*) δ 203.4, 163.4, 157.1, 150.7, 150.2, 137.7, 136.1, 135.9, 133.4, 133.2, 133.1, 132.8, 131.8, 130.1, 130.1, 127.9, 127.8, 118.4, 118.0, 110.9, 106.3, 99.5, 79.9, 75.8, 71.6, 69.6, 69.3, 67.9, 53.5, 42.3, 37.9, 36.6, 32.2, 30.2, 27.0, 26.1, 24.6, 19.4, 18.3, 14.6, 12.7, 1.2, -4.2, -4.4;

IR (film): ν = 3309, 3179, 3072, 3051, 2955, 2930, 2892, 2858, 1765, 1689, 1597, 1488, 1472, 1463, 1427, 1373, 1336, 1257, 1186, 1153, 1111, 1105, 1088, 1053, 1006, 999, 970, 912, 888, 836, 824, 775, 735, 703, 690, 665, 647, 623, 612;

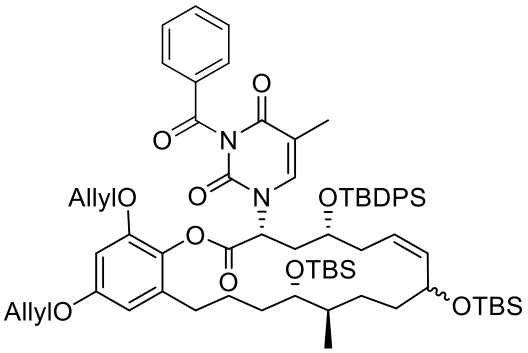
HRMS (ESI-TOF) m/z (ESI) $C_{55}H_{74}N_2NaO_9Si_2$ $[M+Na]^+$ 985.4825, found 985.4801.


f1 (ppm)


f1 (ppm)

5.3.4 Triple bond reduction

*(R,R)-**100***



(*R*,*R*)-**100**

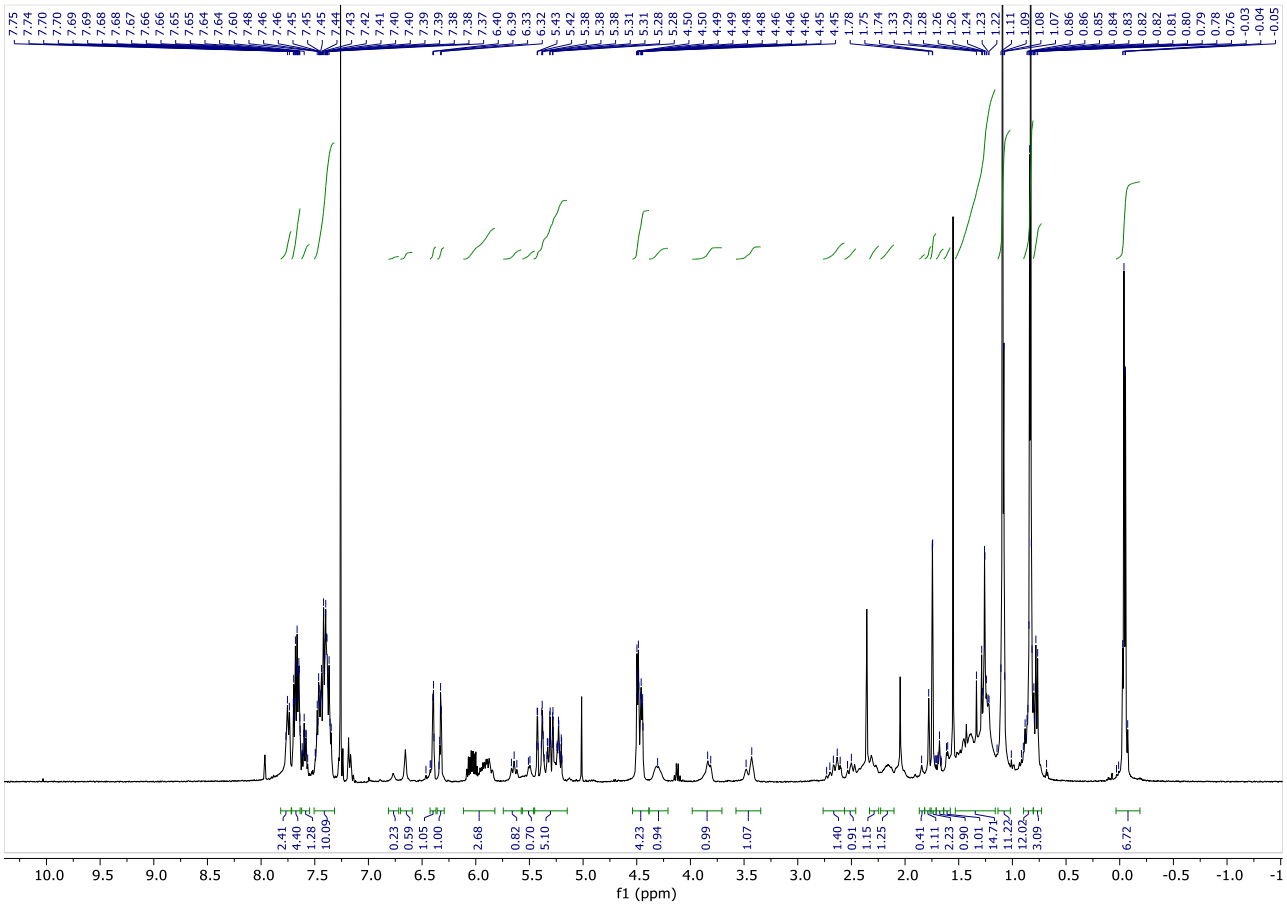
(R,R)-**99** (30 mg, 0.025 mmol, 1.0 equiv.) and Co2(CO)8 (26.4 mg, 2.5 equiv.) were dissolved in DCM (1.15 ml, c=0.027 M). A dark brownish mixture formed and was stirred for 100 min. when the control by TLC, indicated that the reaction was reaction is done (no SM by TLC), the solvent was removed under reduced pressure. Then, the brown residue dissolved in benzene (3.3 ml) and N-ethylpiperidine hypophosphite (50 mg, 10.0 equiv.) was added and the mixture refluxed under argon for 30 min. (oil bath temp.: 80 °C). A dark precipitate was formed. The aq. phase was extracted with ether and the combined org. layers were dried over $MgSO_4$. The crude product was purified by pipet FC (Hex:EtOAc = 10:1-3:1) and the product (R,R)-**100** (13 mg, 39 %) was isolated.

Yield: 13 mg, 39 %;

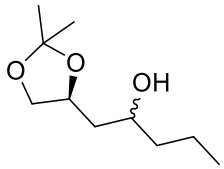
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 – 7.62 (m, 6H), 7.62 – 7.55 (m, 1H), 7.55 – 7.34 (m, 8H), 6.49 – 6.37 (m, 1H), 6.33 (t, J = 3.0 Hz, 1H), 5.64 (t, J = 10.1 Hz, 1H), 5.50 (d, J = 5.6 Hz, 1H), 5.43 – 5.16 (m, 4H), 4.47 (ddt, J = 15.5, 5.4, 1.5 Hz, 4H), 4.31 (s, 1H), 3.82 (d, J = 11.5 Hz, 1H), 3.45 (d, J = 21.2 Hz, 1H), 2.88 – 2.49 (m, 1H), 1.86 – 1.57 (m, 3H), 1.36 – 1.20 (m, 4H), 1.09 (d, J = 5.2 Hz, 9H), 0.93 – 0.66 (m, 14H), -0.04 (t, J = 5.2 Hz, 6H).

IR (film): v = 3492, 3070, 2953, 2929, 2857, 1754, 1704, 1665, 1599, 1489, 1462, 1429, 1363, 1255, 1230, 1186, 1111, 1092, 1065, 1004, 980, 940, 890, 835, 773, 741, 704, 687, 613, 572, 558, 536, 527, 505.

HRMS (ESI-TOF) m/z (ESI) $C_{62}H_{80}N_2NaO_{10}Si_2$ $[M+Na]^+$ 1091.5244, found 1091.5243.


f1 (ppm)

*(S)-**103***



A stock solution of 0.05 ml=50 mkl of quinolone in 10 ml hexane was prepared. Solution of the S-**63** (26.4 mg, 0.143 mmol, 1.0 equiv.) was prepared in EtOAc (10.42 ml, 0.0137 M). 0.05 ml of quinolone solution was added to the solution of SM. Lindlar catalyst (14.7 mg) was added to the solution. Then the reaction was stirred under 1 atm of H_2, bubbling through and then balloon. A sample of the reaction was taken out after 1, 2, 3, and 10 mins, filtered through celite and checked by NMR. NMR after 1 min, already indicated 1:0.3=prod:overreduced, while the starting material was not fully consumed yet. After 2 min – 3:1 prod:overreduced, no SM. Further in time the overreduced prod amount is growing. After 12 hours, completely reduced substrate S-**103** was isolated by filtration of the reaction mixture over celite, and concentration under the reduced pressure.

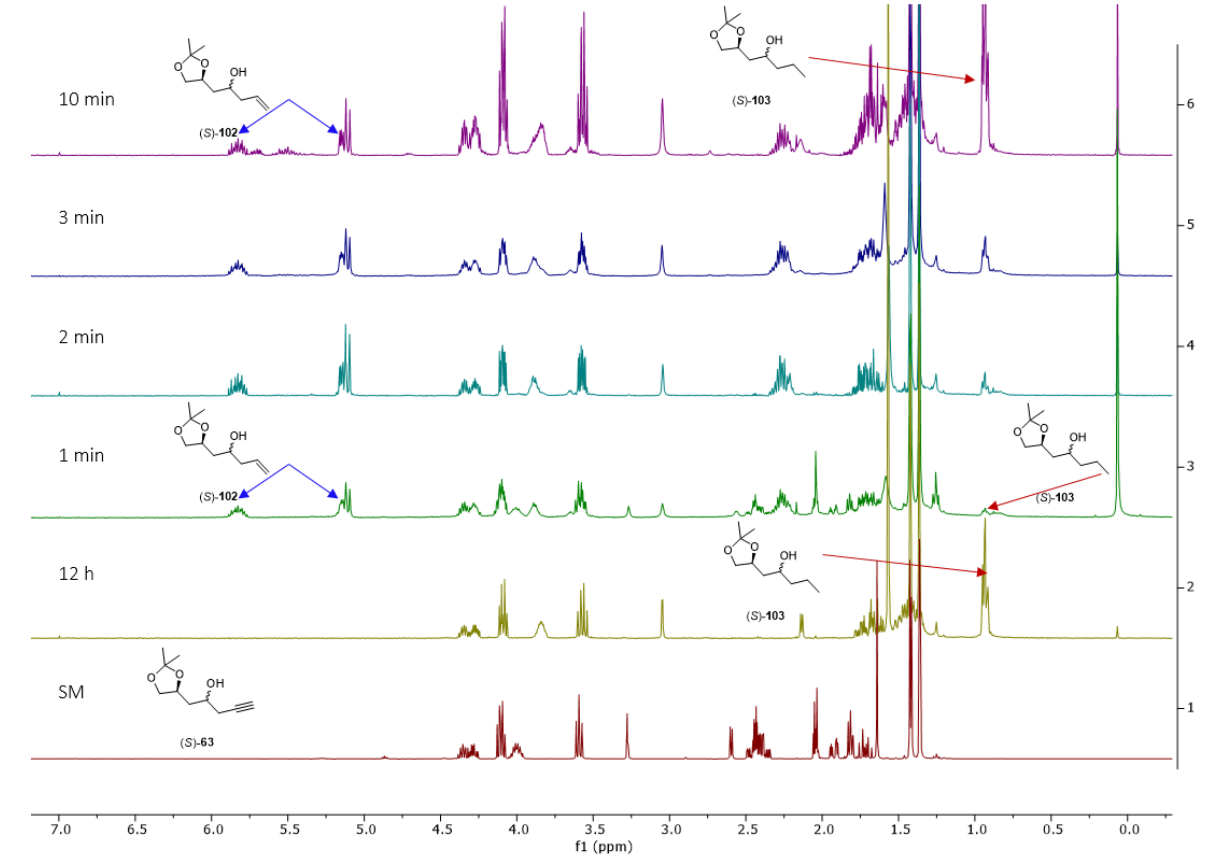
Yield: 24 mg, quant. crude; mix of two diasteromers, as the SM is also a mixture of diastereomers.

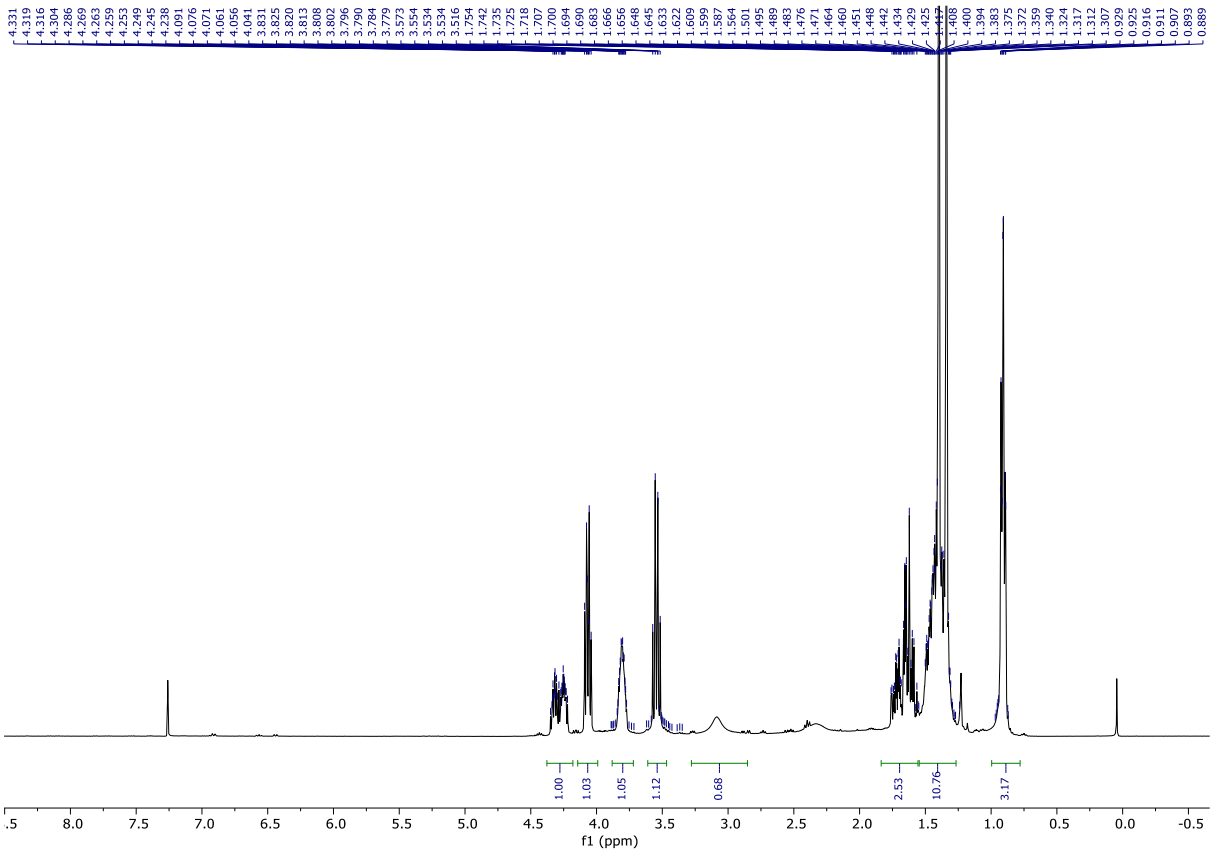
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.40 – 4.18 (m, 1H), 4.07 (dt, J = 8.0, 5.9 Hz, 1H), 3.80 (dddt, J = 9.7, 7.4, 4.7, 2.6 Hz, 1H), 3.64 – 3.33 (m, 1H), 1.85 – 1.55 (m, 3H), 1.50 – 1.23 (m, 10H), 0.91 (td, J = 7.1, 1.6 Hz, 3H).

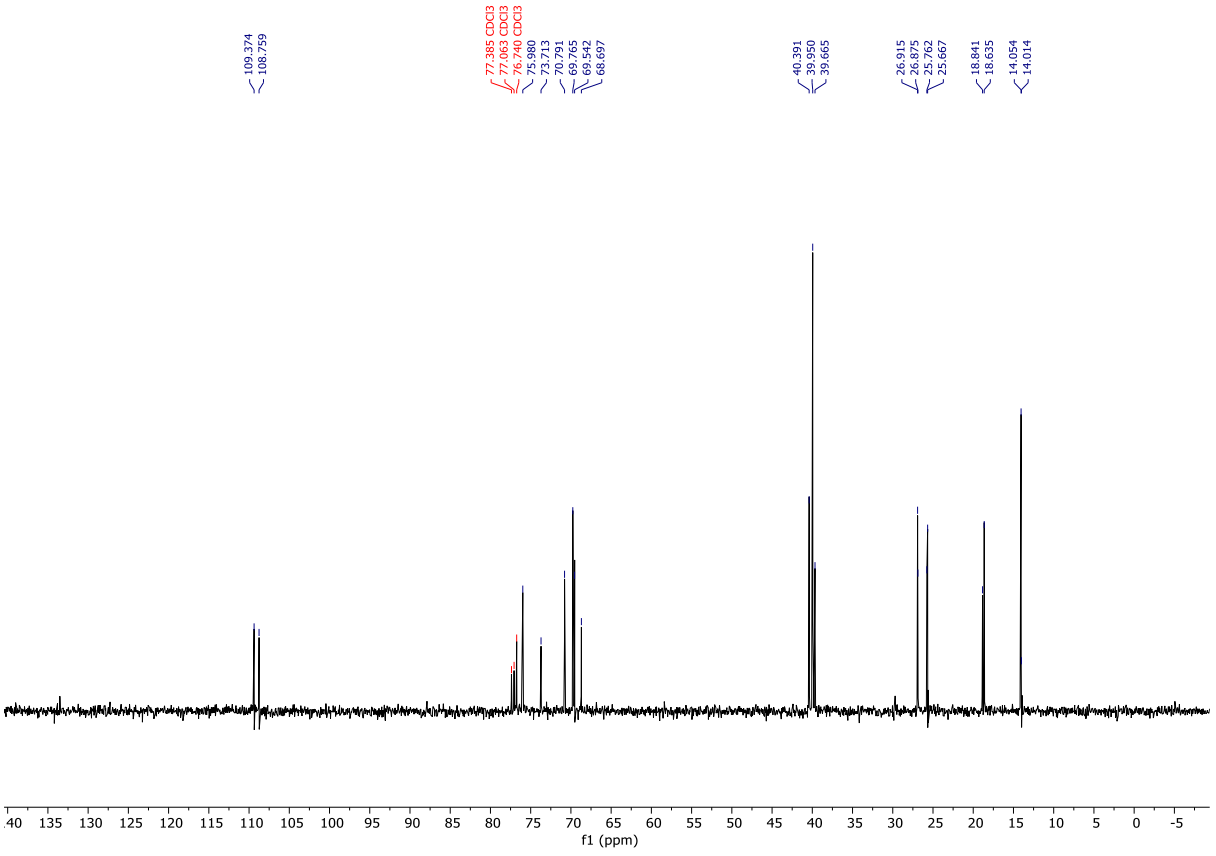
^{13}C NMR (101 MHz, Chloroform-*d*) δ 109.4, 108.8, 76.0, 73.7, 70.8, 69.8, 69.5, 68.7, 40.4, 40.0, 39.7, 26.9, 26.9, 25.8, 25.7, 18.8, 18.6, 14.1.

IR (film): ν = 2935, 1371, 1216, 1057, 750, 667.

HRMS (ESI-TOF) m/z (ESI) $C_{10}H_{20}NaO_3$ $[M+Na]^+$ 211.1305, found 211.1302.

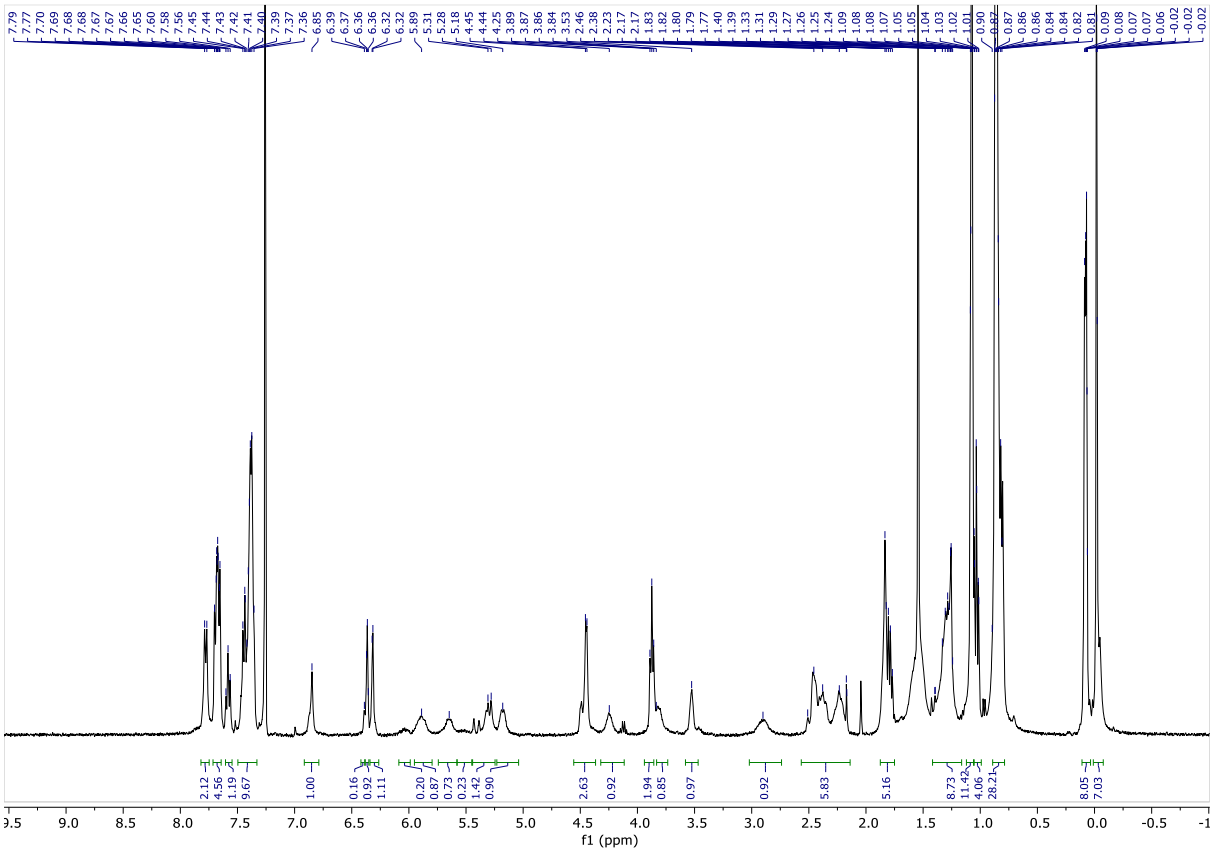

10 min
3 min
2 min
1 min
12 h
SM
(S)-102
(S)-103
(S)-63
f1 (ppm)

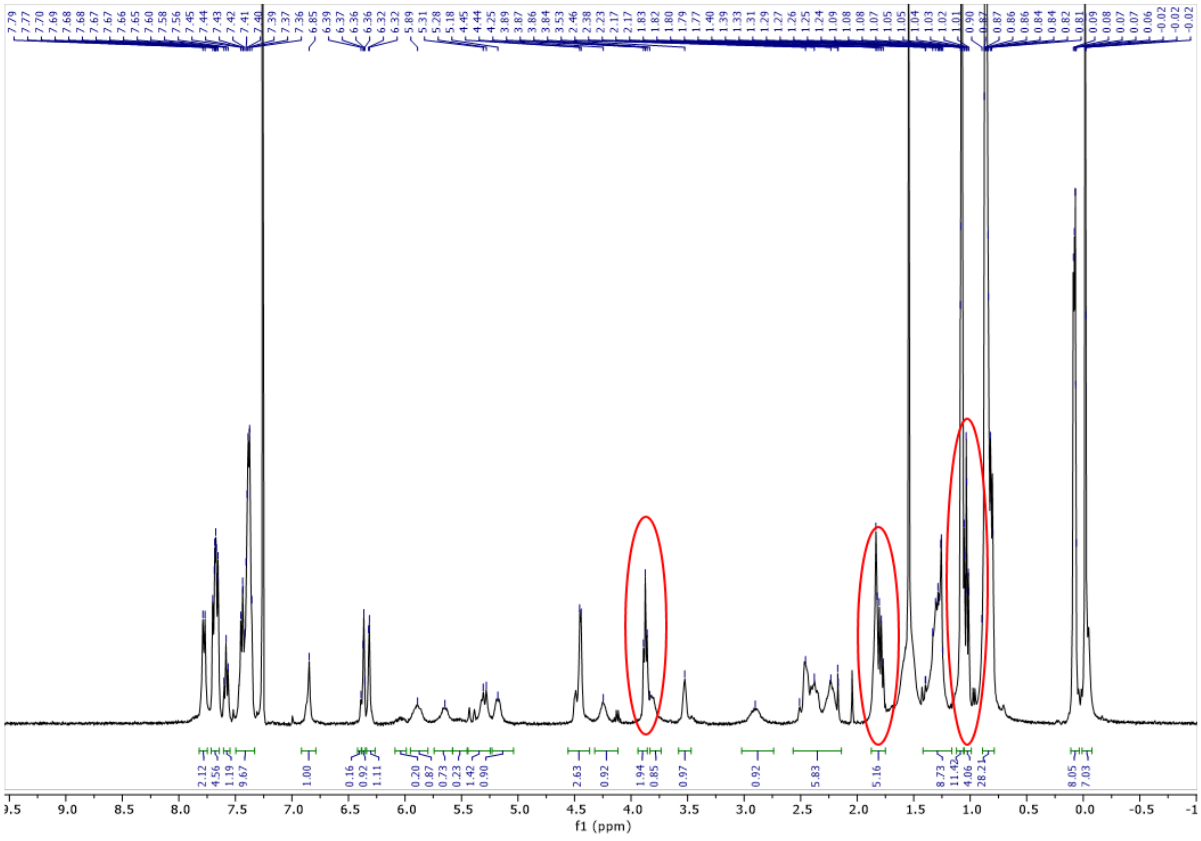

1.00
1.03
1.05
1.12
0.68
2.53
10.76
3.17
f1 (ppm)

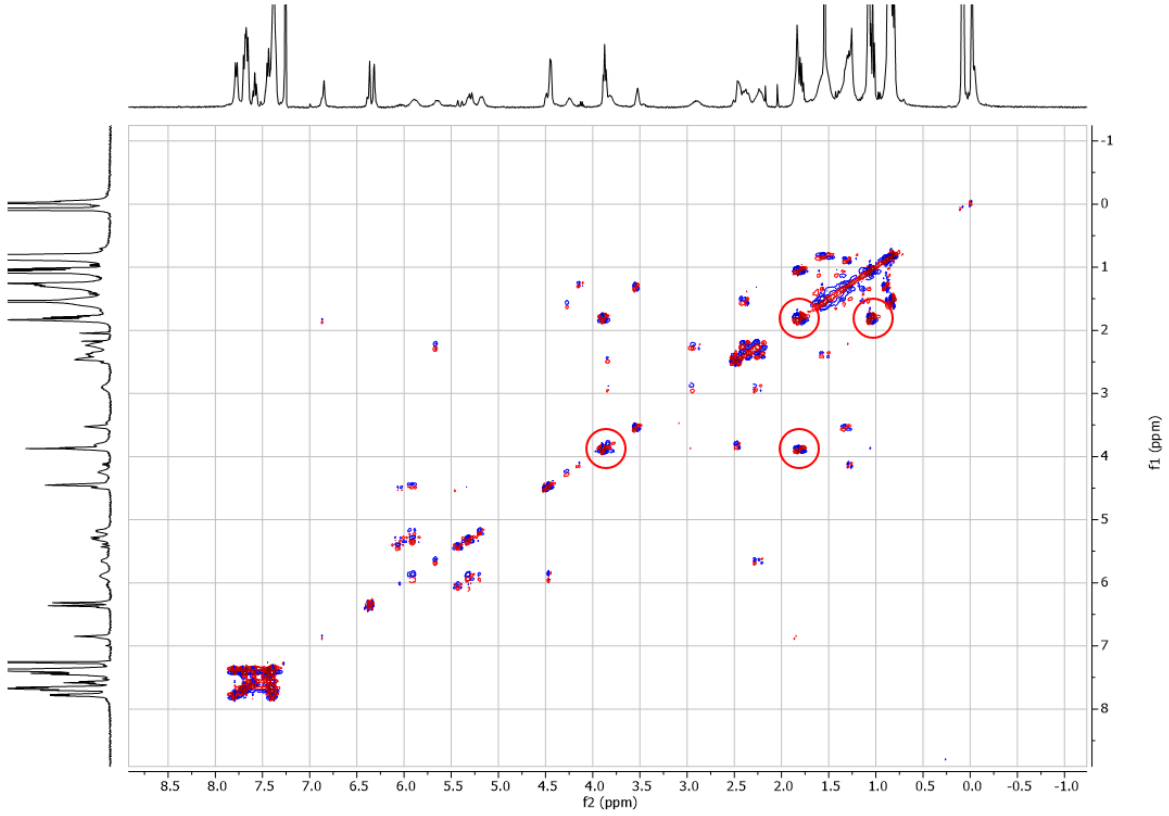

109.374
108.759
77.385 CDCl3
77.063 CDCl3
76.740 CDCl3
75.980
73.713
70.791
69.765
69.542
68.697
40.391
39.950
39.665
26.915
26.875
25.762
25.667
18.841
18.635
14.054
14.014
f1 (ppm)

*SI-(R,R)-**100** (reduction of Allyls)*

The NMRs that hint on the reduction of the double bond in allyl protecting groups.

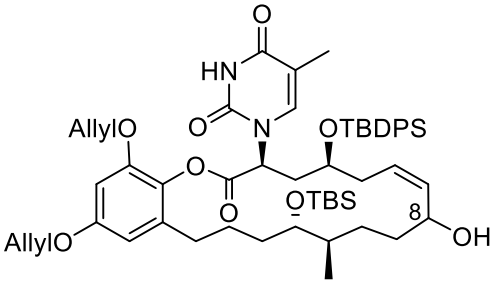






Note that these fraction contain ca. 20 % of the starting material.

*(S,S)-**111**-major*



In a 25 ml flask, a solution of (S,S)-**97** (50 mg, 0.052 mmol, 1.00 equiv.) was added to $Co_2(CO)_8$ (35.5 mg, 0.104 mmol, 2.00 equiv.) in a glovebox and DCM (2.076 mL, c=0.025 M) was added at rt. And stirred for 90 minutes. After stirring for 1 h 30 mins, the reaction was controlled by TLC, and it indicated that the SM was gone, the solvent was evaporated and the residue was dried under reduced pressure. To the dark brown foam was added N-ethyl piperidine hypophosphite (93 mg, 0.519 mmol, 10 equiv.) in a glovebox followed by benzene (2.359 mL, c=0.022 M), and the mixture was refluxed (80.4 degrees Celsius) for 35 min (NOT MORE! Starts to decompose and the yield drops). (S,S)-**111-**major was obtained in 31 % yield and (S,S)-**111-**minor in 19 %.

Yield: 15.5 mg (31 %);

R_f = 0.444 (2:1 Hexane: EtOAc), CPS staining;

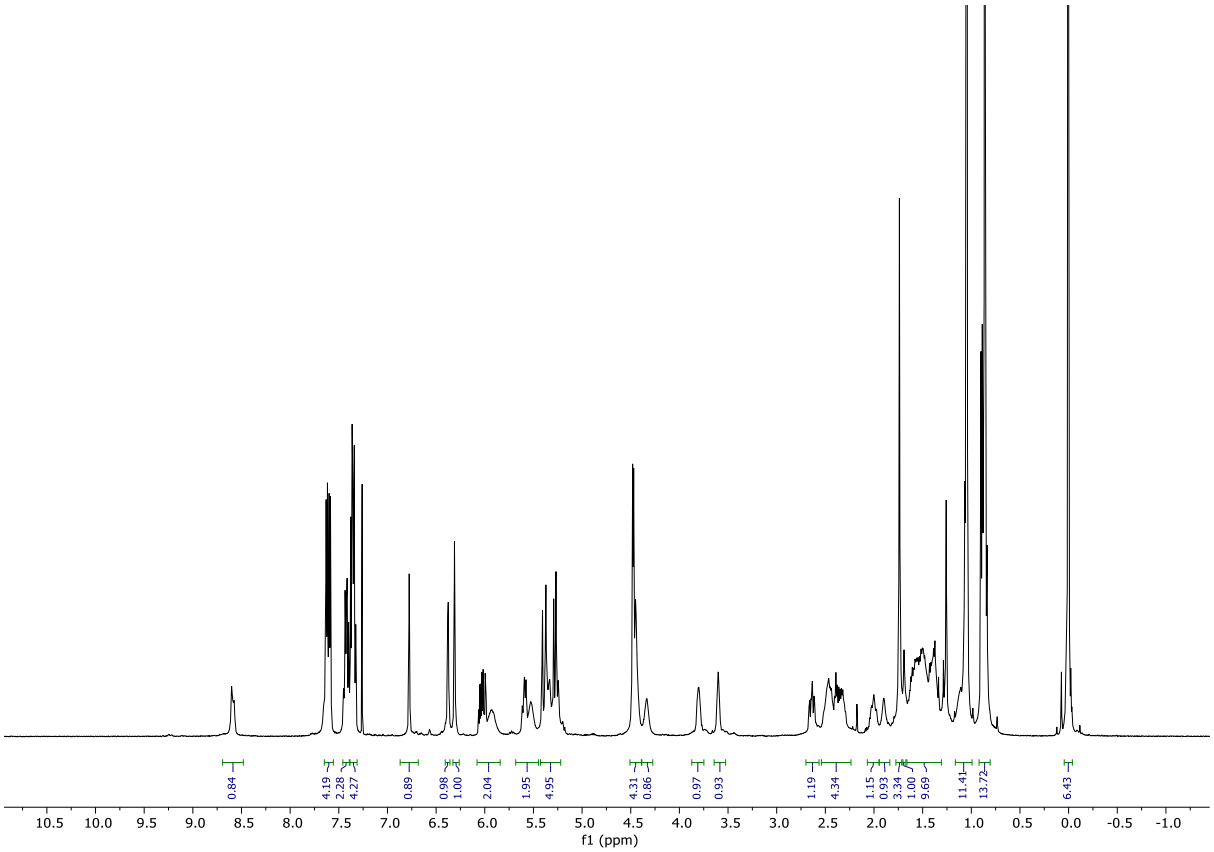
$[\alpha]_{20}^{D}$: = -39.99 (c = 0.125; $CHCl_3$, 20 °C);

^{1}H NMR (500 MHz, Chloroform-d) δ 8.59 (d, J = 11.7 Hz, 1H), 7.61 (ddt, J = 15.4, 6.8, 1.4 Hz, 6H), 7.47 – 7.39 (m, 2H), 7.39 – 7.31 (m, 5H), 6.82 – 6.71 (m, 1H), 6.38 (d, J = 2.7 Hz, 1H), 6.31 (d, J = 2.7 Hz, 1H), 6.02 (ddt, J = 17.3, 10.6, 5.3 Hz, 1H), 5.93 (s, 2H), 5.65 – 5.47 (m, 3H), 5.45 – 5.31 (m, 5H), 5.32 – 5.19 (m, 2H), 4.51 – 4.39 (m, 6H), 4.34 (s, 1H), 3.80 (s, 1H), 3.61 (d, J = 7.3 Hz, 1H), 2.64 (ddd, J = 14.3, 10.5, 3.1 Hz, 1H), 2.55 – 2.24 (m, 7H), 2.09 – 1.85 (m, 2H), 1.74 (s, 4H), 1.64 – 1.31 (m, 4H), 1.05 (s, 14H), 0.87 (d, J = 13.4 Hz, 18H), 0.00 (s, 10H);

^{13}C NMR (126 MHz, Chloroform-d) δ 168.5, 163.5, 157.2, 150.9, 150.0, 137.5, 136.5, 136.3, 135.8, 135.8, 133.6, 133.2, 133.2, 132.6, 131.7, 130.2, 130.1, 127.9, 124.9, 118.9, 118.0, 111.2, 107.1, 99.6, 75.6, 69.7, 69.4, 69.3, 67.5, 54.5, 37.4, 35.9, 34.5, 33.8, 33.0, 31.1, 29.8, 27.0, 26.0, 25.7, 19.4, 18.3, 16.3, 12.6, -4.1, -4.4;

IR (film): ν = 2955, 2925, 2854, 1768, 1689, 1598, 1488, 1463, 1428, 1377, 1257, 1187, 1111, 1073, 938, 836, 776, 741, 704, 689, 633, 620;

HRMS (ESI-TOF) m/z (ESI) $C_{55}H_{76}N_2NaO_9Si_2$ $[M+Na]^+$ 987.4982, found 987.4983.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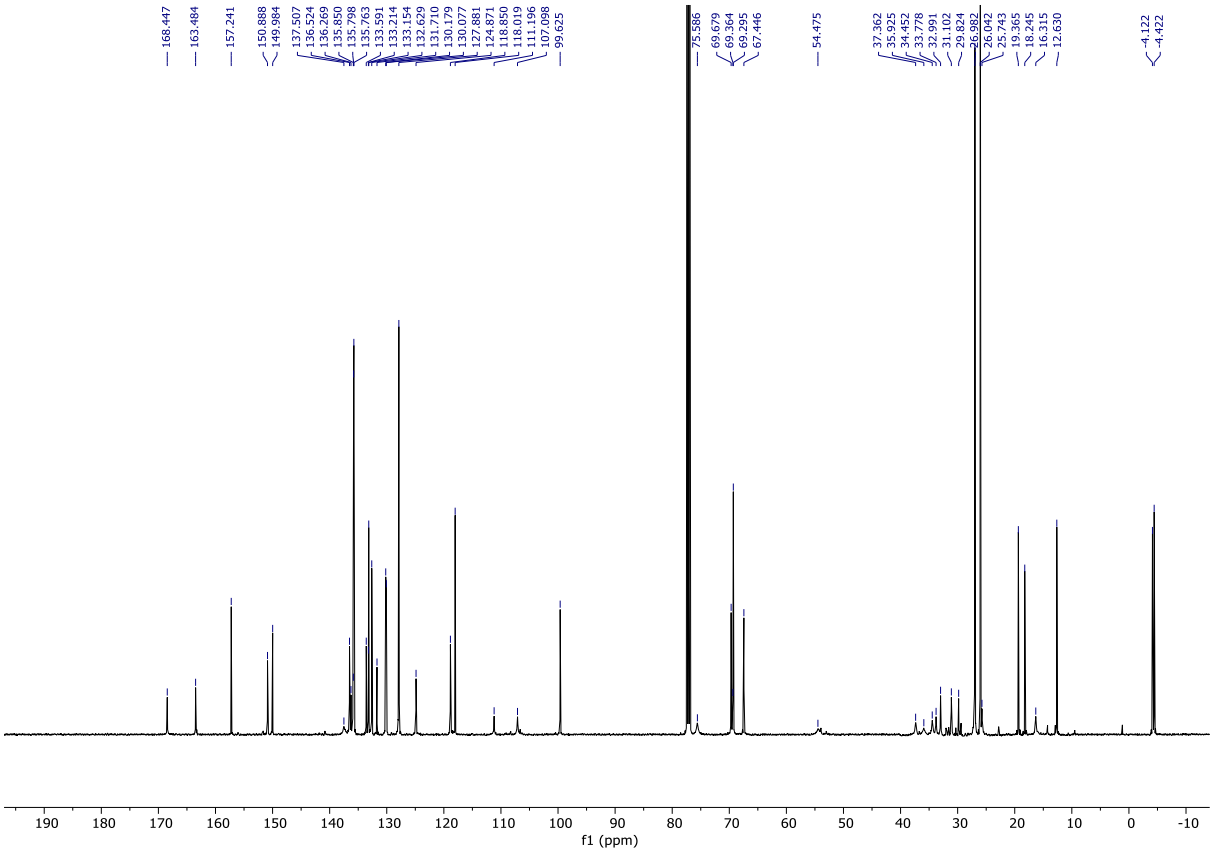
4.19
2.28
4.27
0.89
0.98
1.00
2.04
1.95
4.95
4.31
0.86
0.97
0.93
1.19
4.34
1.15
0.93
3.34
1.00
9.69
11.41
13.72
6.43
f1 (ppm)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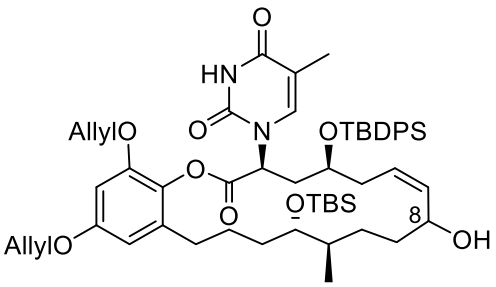
157.241
150.888
149.984
137.507
136.524
136.269
135.850
135.798
135.763
133.591
133.214
133.154
132.629
131.710
130.179
130.077
127.881
124.871
118.850
118.019
111.196
107.098
99.625
75.586
69.679
69.364
69.295
67.446
54.475
37.362
35.925
34.452
33.778
32.991
31.102
29.824
26.982
26.042
25.743
19.365
18.245
16.315
12.630
-4.122
-4.422
f1 (ppm)

*(S,S)-**111**-minor*



Yield: 10 mg (20 %)+10 % impurity;

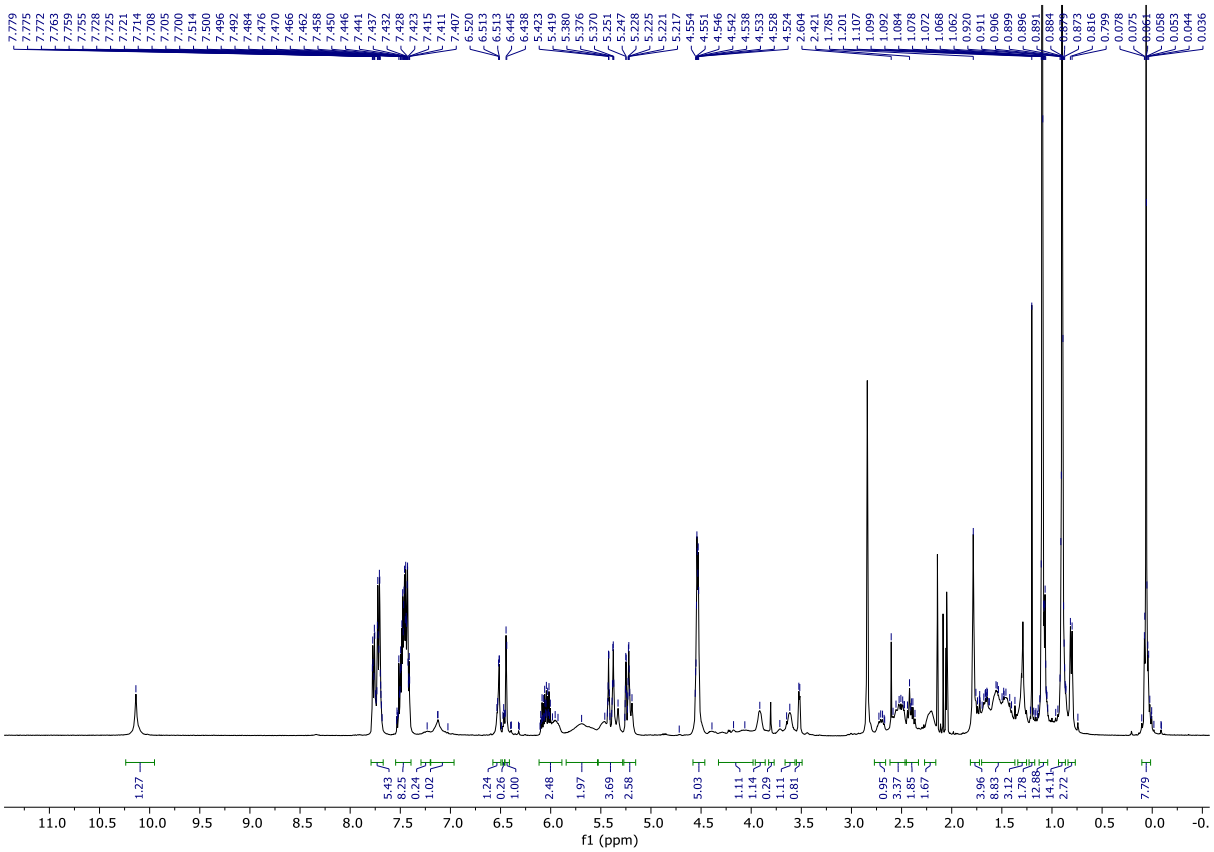
R_f = 0.1667 (30:1 DCM:MeOH), R_f = 0.217 (2:1 Hexane:EtOAc), CPS staining;

^{1}H NMR (400 MHz, Acetone-*d6*) δ 10.14 (s, 1H), 7.96 – 7.60 (m, 4H), 7.57 – 7.28 (m, 6H), 7.18 (d, J = 42.9 Hz, 1H), 6.66 – 6.49 (m, 1H), 6.49 – 6.28 (m, 1H), 6.22 – 5.80 (m, 1H), 5.69 (s, 2H), 5.60 – 5.30 (m, 2H), 5.28 – 5.07 (m, 2H), 4.73 – 4.36 (m, 4H), 3.99 (d, J = 59.7 Hz, 1H), 3.75 – 3.51 (m, 2H), 2.78 – 2.60 (m, 0H), 2.65 – 2.31 (m, 2H), 1.85 – 1.36 (m, 4H), 1.20 (s, 1H), 1.10 (d, J = 3.1 Hz, 9H), 0.90 (d, J = 1.6 Hz, 10H), 0.81 (d, J = 6.7 Hz, 3H), 0.16 – -0.35 (m, 6H).

^{13}C NMR (101 MHz, Acetone-*d6*) δ 164.1, 158.1, 151.9, 151.2, 137.9, 136.9, 136.7, 136.6, 134.6, 134.3, 134.1, 132.9, 130.9, 130.8, 128.8, 128.6, 124.4, 118.0, 117.5, 111.4, 107.2, 100.1, 76.6, 70.0, 69.6, 67.4, 54.7, 39.6, 36.6, 36.5, 35.6, 32.0, 31.9, 31.0, 27.4, 26.3, 19.8, 18.7, 14.3, 12.8, -4.1, -4.2.

IR (film): ν = 3397, 3176, 3071, 2954, 2930, 2857, 1766, 1688, 1597, 1488, 1463, 1428, 1375, 1257, 1186, 1151, 1111, 1088, 1044, 1007, 937, 835, 824, 774, 742, 704, 689, 665, 612;

HRMS (ESI-TOF) m/z (ESI) $C_{55}H_{76}N_2NaO_9Si_2$ $[M+Na]^+$ 987.4982, found 987.4983.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7.763
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7.755
7.728
7.725
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7.714
7.708
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7.496
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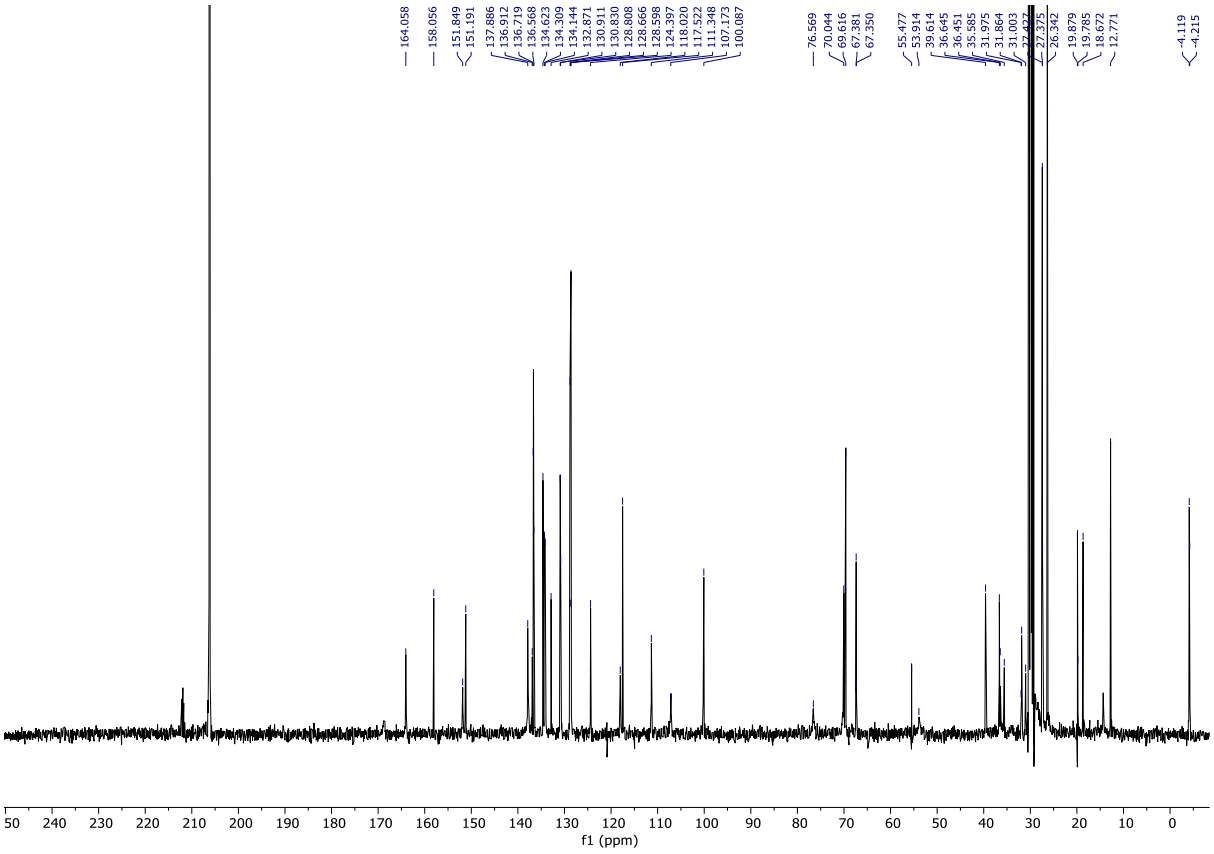
2.604
2.421
1.785
1.201
1.107
1.099
1.092
1.084
1.078
1.072
1.068
1.062
0.920
0.911
0.906
0.899
0.896
0.891
0.884
0.879
0.873
0.816
0.799
0.078
0.075
0.058
0.053
0.044
0.036
1.27
5.43
8.25
0.24
1.02
1.24
0.26
1.00
2.48
1.97
3.69
2.58
5.03
1.11
1.14
0.29
1.11
0.81
0.95
3.37
1.85
1.67
3.96
8.83
3.12
1.78
12.88
14.11
2.72
7.79
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.
f1 (ppm)


164.058
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136.719
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134.623
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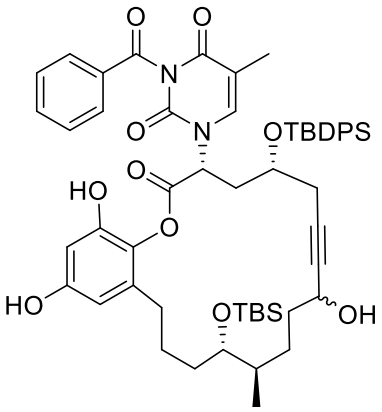
130.911
130.830
128.808
128.666
128.598
124.397
116.020
117.522
111.348
107.173
100.087
76.569
70.044
69.616
67.381
67.350
55.477
53.914
39.614
36.645
36.451
35.585
31.975
31.864
31.003
27.422
27.375
26.342
19.879
19.785
18.672
12.771
-4.119
-4.215
50
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

5.3.5 Protecting group removal

*(R,R)-**112***



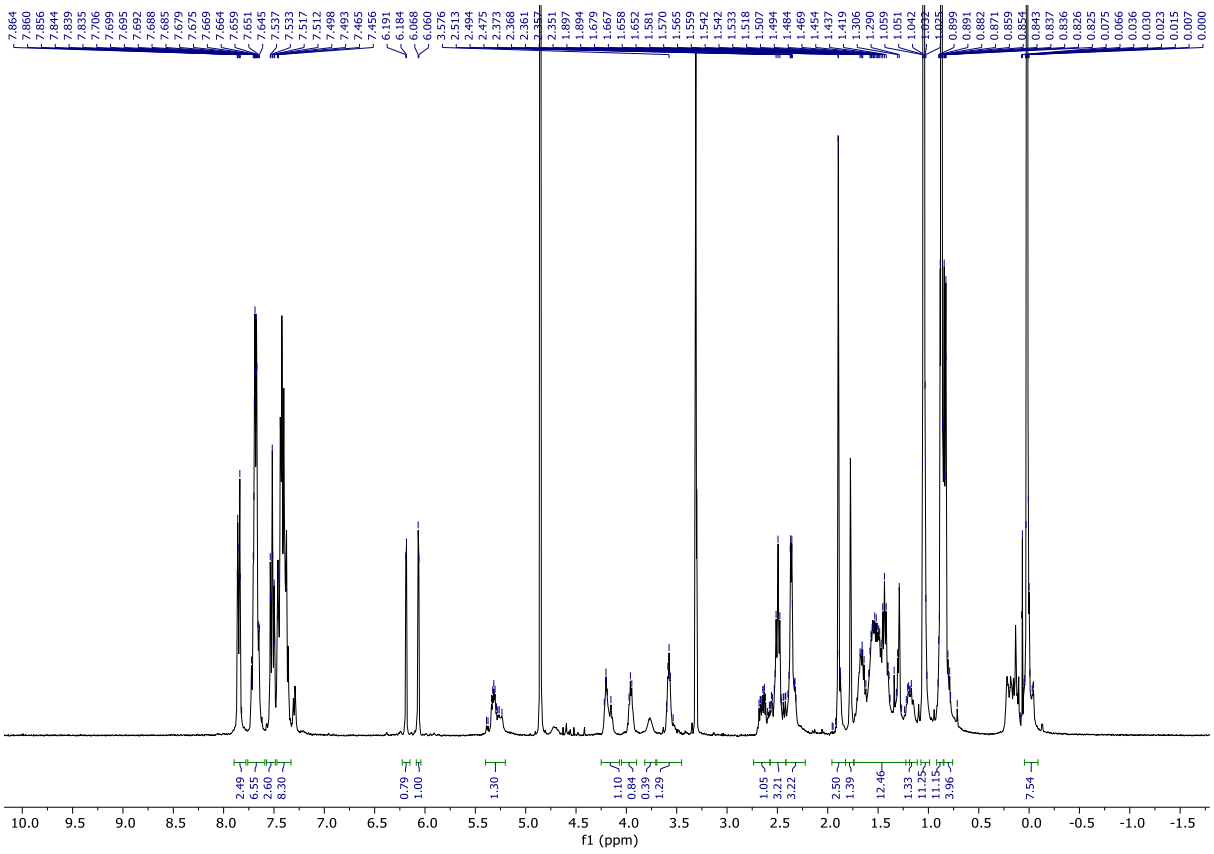
A stirred solution of (R,R)-**99** (119 mg, 0.11 mmol, 1.0 equiv.) in THF (0.9 mL, c=0.125 M) was prepared at room temperature. And then the reagents were added in a following order: polymethylhydrosiloxane (0.13 ml, 4.0 equiv.), tetrakis(triphenylphosphine)palladium (25.7 mg, 20 mol %) and ZnCl2 (60.7 mg, 4.0 equiv.). Then the reaction mixture was heated to 45 ˚C. After completion of the reaction, the mixture was diluted with water +5 mL), extracted with diethyl ether (2x10 mL) and dried ($MgSO_4$), followed by concentration. Crude material M=120.3 mg was purified by FC. The desired product was obtained in 91 mg (82 %) yield.

Yield: 91 mg (82 %);

^{1}H NMR (400 MHz, Methanol-*d4*) δ 7.85 (dt, J = 8.5, 1.6 Hz, 2H), 7.77 – 7.61 (m, 6H), 7.52 (td, J = 7.8, 1.8 Hz, 2H), 7.46 (m, 8H), 6.19 (d, J = 2.8 Hz, 1H), 6.06 (d, J = 3.0 Hz, 1H), 5.45 – 5.11 (m, 2H), 4.27 – 4.07 (m, 3H), 3.96 (t, J = 5.5 Hz, 1H), 3.58 (q, J = 5.2 Hz, 1H), 2.72 – 2.59 (m, 1H), 2.59 – 2.43 (m, 3H), 2.43 – 2.24 (m, 3H), 1.90 (d, J = 1.2 Hz, 3H), 1.68 – 1.17 (m, 15H), 1.05 (d, J = 3.6 Hz, 15H), 0.87 (s, 13H), 0.85 – 0.67 (m, 7H), 0.09 – -0.07 (m, 6H).

IR (film): v = 2953, 2930, 2857, 1766, 1690, 1598, 1488, 1463, 1427, 1373, 1257, 1186, 1111, 1090, 1038, 835, 774, 739, 704, 665, 613, 570, 557, 547, 513, 500;

HRMS (ESI-TOF) m/z (ESI) $C_{55}H_{74}N_2NaO_9Si_2$ $[M+Na]^+$ 985.4825, found 985.4824.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7.844
7.839
7.835
7.706
7.699
7.695
7.692
7.688
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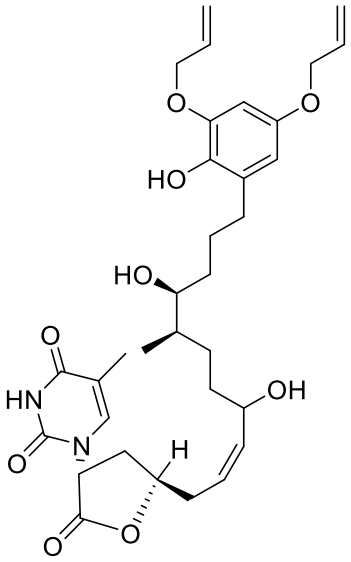
7.679
7.675
7.669
7.664
7.659
7.651
7.645
7.537
7.533
7.517
7.512
7.498
7.493
7.465
7.456
6.191
6.184
6.068
6.060
3.576
2.513
2.494
2.475
2.373
2.368
2.361
2.352
2.351
1.897
1.894
1.679
1.667
1.658
1.652
1.581
1.570
1.565
1.559
1.542
1.533
1.518
1.507
1.494
1.484
1.469
1.454
1.437
1.419
1.306
1.290
1.059
1.051
1.042
1.032
1.025
0.899
0.891
0.882
0.871
0.859
0.854
0.843
0.837
0.836
0.826
0.825
0.075
0.066
0.036
0.030
0.023
0.015
0.007
0.000
2.49
6.55
2.60
8.30
0.79
1.00
1.30
1.10
0.84
0.39
1.29
1.05
3.21
3.22
2.50
1.39
12.46
1.33
11.25
11.15
3.96
7.54
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
f1 (ppm)

*(*R,R*)-**123***



In a plastic vial charged with a stirring bar, a solution of (R,R)-**101** (30.9 mg, 0.026 mmol) in THF (1.716 mL, c=0.01524 M) was prepared. The solution was cooled to 0 °C. Then, pyridine (1.716 mL) and HF·pyridine (1.716 mL) were slowly added via a plastic syringe at 0 °C. 15:10 the reaction started. Stirring was continued at this temperature for 15 min and then switched to go to the ambient temperature (room temperature). At 7:50 the next day the reaction was checked by TLC, inconclusive. Took an aliquot of 0.13 ml and quenched with $KHCO_3$ and extracted with EtOAc x 4, evaporated to make an NMR and MS (the product mass is found, but the mass of other intermediates is not detected). By NMR ((R,R)-**123**) no SM, 0.3 prod to 1.00 of TBDPS on intermediate. 25 % of the product and 75 % of TBDPS. Also, TLC in pure EA showed that there are 2 spots (less polar with a bigger spot and a smaller spot below, which makes sense). After seeing that the reaction after 17 h deprotected TBDPS only 25 %, decided to add more of HF*Py without additional Py buffering (it will be an additional 156 equiv of HF and 73 equiv of py; overall HF=620 equiv. and py=1000 equiv.). After 1.5 days 23.02.2022, the reaction was quenched at 15:50 by slow addition of the reaction mixture to sat. $KHCO_3$ solution (40 ml) in a plastic Erlenmeyer (even though not necessary). Bu crude NMR 10% of minor product and mainly major product, after the column one can see what is what. The crude residue (m = 21 mg.) was purified by 1 cm flash chromatography (hex: ea 5:1 to 4:1 to 2:1 to 1:1 to pure ea since the product is quite polar) to give the desired compound (R,R)-**123** in fractions 28-41 as a white amorphous solid (11 mg, 59 %).

Yield: 11 mg (59 %), dr=10:1;

R_f = 0.548 (EtOAc), CPS staining;

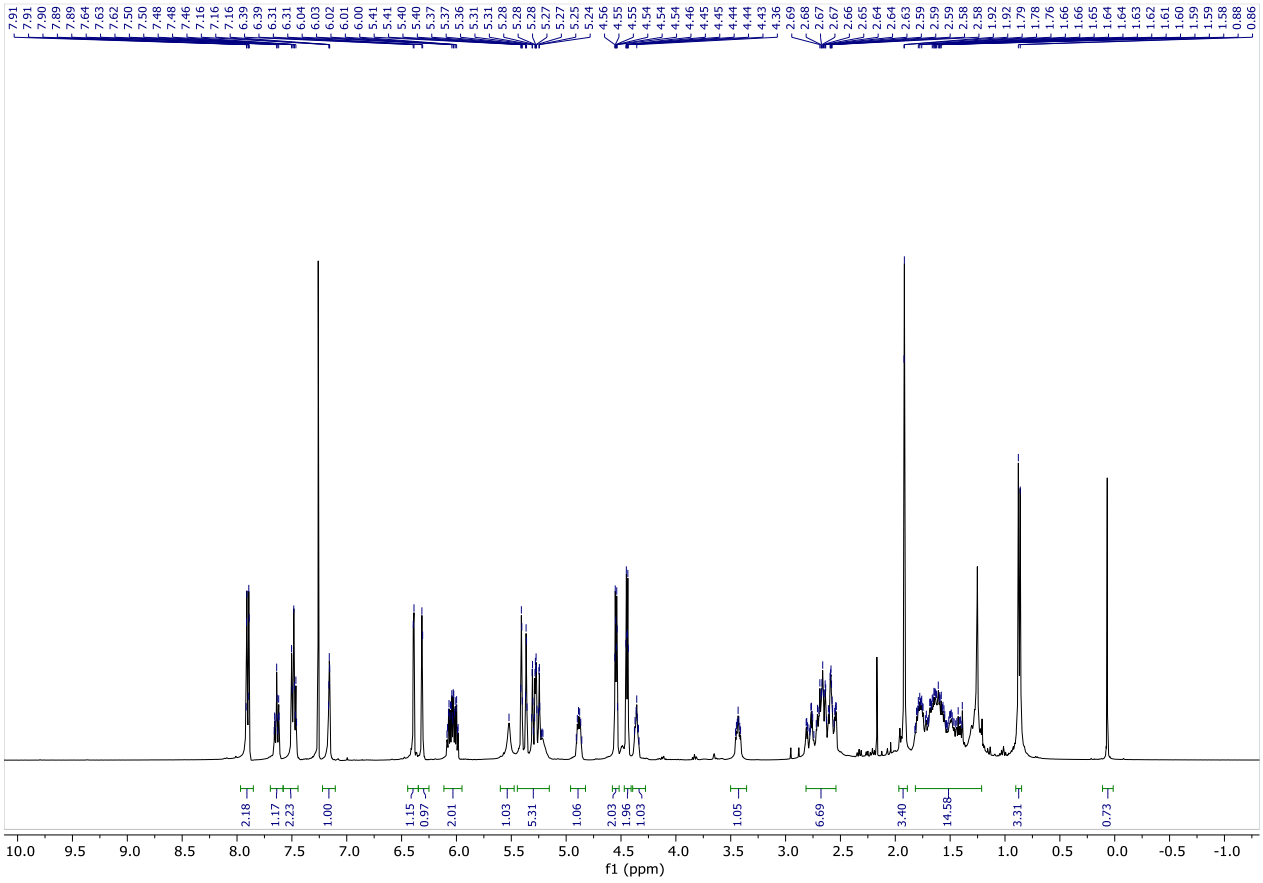
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 (dt, J = 8.5, 1.5 Hz, 2H), 7.64 (td, J = 7.3, 1.5 Hz, 1H), 7.48 (td, J = 7.8, 2.3 Hz, 2H), 7.16 (dd, J = 2.8, 1.5 Hz, 1H), 6.39 (d, J = 2.8 Hz, 1H), 6.31 (d, J = 2.7 Hz, 1H), 6.04 (ddtd, J = 17.8, 10.6, 5.4, 2.0 Hz, 2H), 5.52 (s, 1H), 5.47 – 5.08 (m, 5H), 4.88 (dq, J = 7.8, 3.8 Hz, 1H), 4.55

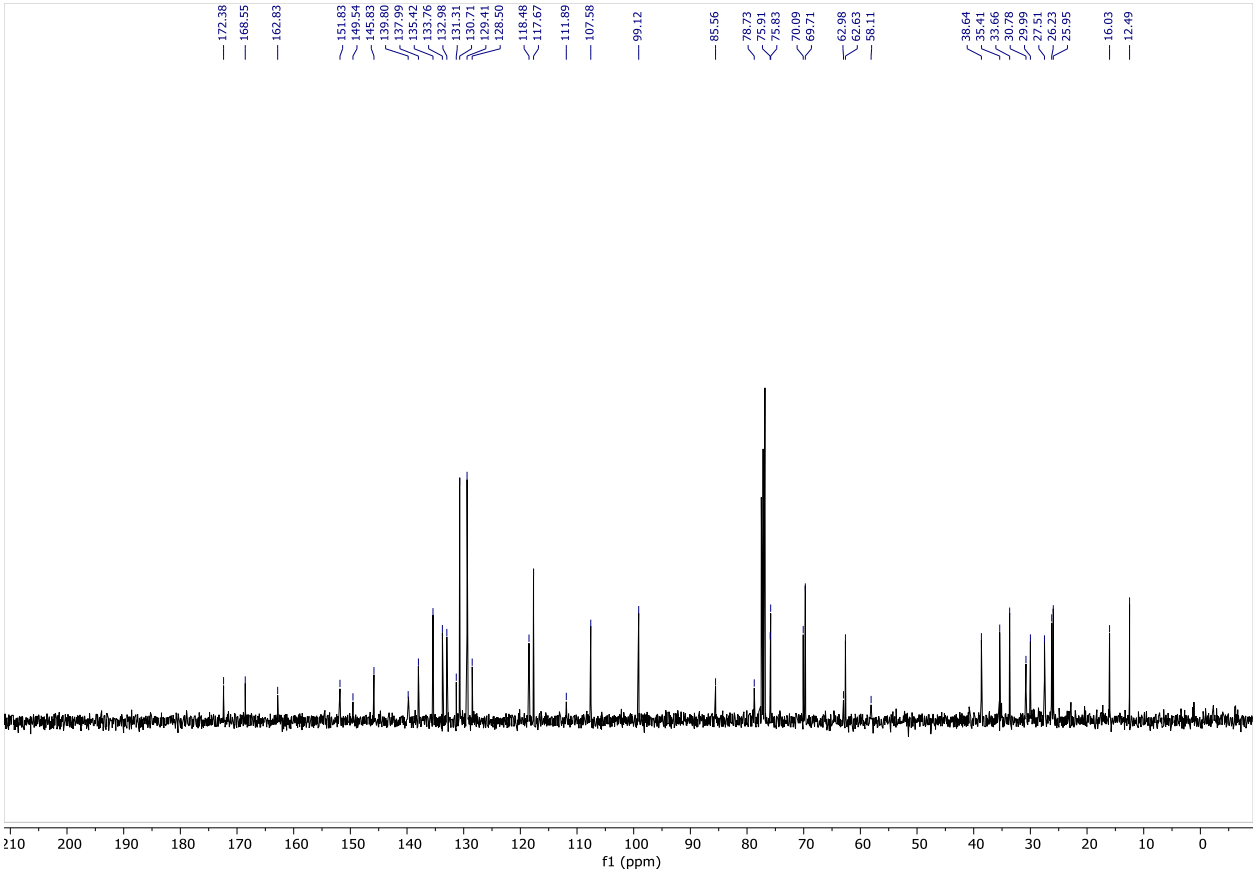
(dt, J = 5.3, 1.5 Hz, 2H), 4.44 (dt, J = 5.3, 1.6 Hz, 1H), 4.36 (ddt, J = 6.3, 4.1, 2.1 Hz, 1H), 3.43 (ddd, J = 9.0, 6.2, 3.1 Hz, 1H), 2.82 – 2.42 (m, 6H), 1.92 (d, J = 1.3 Hz, 3H), 1.83 – 1.35 (m, 14H), 0.87 (d, J = 6.8 Hz, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.4, 168.6, 162.8, 151.8, 149.5, 145.8, 139.8, 138.0, 135.4, 133.8, 133.0, 131.3, 130.7, 129.4, 128.5, 118.5, 117.7, 111.9, 107.6, 99.1, 85.6, 78.7, 75.9, 75.8, 70.1, 69.7, 63.0, 62.6, 58.1, 38.6, 35.4, 33.7, 30.8, 30.0, 27.5, 26.2, 26.0, 16.0, 12.5;

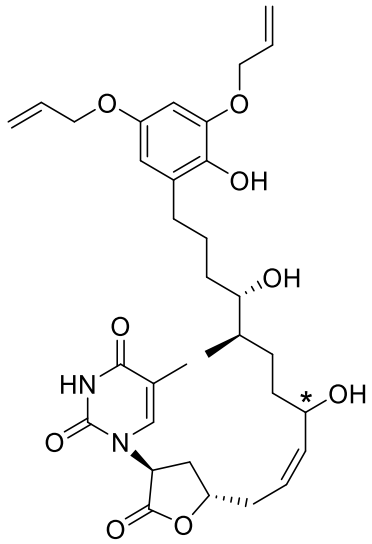
IR (film): ν = 3671, 3447, 2972, 2901, 2165, 2157, 2146, 1964, 1940, 1778, 1749, 1699, 1659, 1495, 1441, 1394, 1255, 1221, 1066, 1055, 893, 772, 685, 671, 634, 583, 560, 529, 517;

HRMS (ESI-TOF) m/z (ESI) $C_{40}H_{47}N_2O_{10}$ $[M+H]^+$ 715.3225, found 715.3218.




172.38
168.55
162.83
151.83
149.54
145.83
139.80
137.99
135.42
133.76
132.98
131.31
130.71
129.41
128.50
118.48
117.67
111.89
107.58
99.12
85.56
78.73
75.91
75.83
70.09
69.71
62.98
62.63
58.11
38.64
35.41
33.66
30.78
29.99
27.51
26.23
25.95
16.03
12.49
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

*(S,S)-**123***



In a plastic vial charged with a stirring bar, a solution of (S,S)-**111**-major (35 mg, 0.036 mmol, 1 equiv.) in THF (0.731 mL, c=0.05 M) was prepared. The solution was cooled to 0 °C. Then, pyridine (2.544 mL, 31.578 mmol, 876 equiv.) and HF·pyridine (70:30, 2.295 mL, 19.43 mmol:7.714 mmol, 539 equiv.:214 equiv.) were slowly added via plastic syringe at 0 °C. The reaction started. Stirring was continued at this temperature and then gradually was allowed to go to the ambient temperature (room temperature). After almost 2 days (42 hours), the reaction was diluted with 5 ml of EA, and quenched by slow addition of the reaction mixture to sat. $KHCO_3$ solution (40 ml) in a plastic Erlenmeyer. After checking the pH with a pH paper=8, the solution was extracted with EA (20 ml x 3), dried over $MgSO_4$, and the solvent was evaporated. The crude material (m = 54 mg) was purified by 2 FC. First, 1 cm FC with hex:ea= 2:1 with a gradient to pure ea. The product was obtained in fractions 77-101 (21 mg, 95 %), they were not pure, so the second purification took place with a different solvent system. The second FC – a pipet column with 30:1=DCM: MeOH to 15:1 to 2:1. The product (S,S)-**123** was obtained in fractions 11-23 (14.1 mg, 64 %) as a colorless oil, with time became yellow.

Yield: 14.1 mg (64 %);

R_f = 0.225 (15:1 DCM: MeOH), CPS staining;

$[\alpha]_{20}^{D}$: = -10.00 (c = 0.4 ; $CHCl_3$, 20°C) ((S,S)-**123**);

$[\alpha]_{20}^{D}$: = -7.50 (c = 0.4 ; $CHCl_3$, 20°C) ((S,S)-**123**);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.33 (s, 1H), 7.01 – 6.92 (m, 1H), 6.39 (d, J = 2.8 Hz, 1H), 6.31 (d, J = 2.8 Hz, 1H), 6.03 (ddt, J = 20.6, 10.2, 5.0 Hz, 2H), 5.66 (t, J = 9.9 Hz, 1H), 5.52 – 5.39 (m, 1H), 5.43 – 5.34 (m, 2H), 5.33 – 5.21 (m, 2H), 4.99 – 4.81 (m, 2H), 4.55 (d, J = 5.3 Hz, 2H), 4.44 (d, J = 5.4 Hz, 2H), 4.37 (q, J = 7.1 Hz, 1H), 3.46 (t, J = 7.3 Hz, 1H), 2.67 (ddd, J = 14.8, 9.2, 6.0 Hz, 1H), 2.58 (tt, J = 6.5, 3.4 Hz, 7H),

2.50 (dd, J = 9.5, 6.5 Hz, 2H), 1.88 (s, 3H), 1.82 – 1.32 (m, 8H), 1.28 – 1.18 (m, 1H), 0.88 (d, J = 6.5 Hz, 3H);

^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.3, 163.8, 151.8, 150.6, 145.9, 139.2, 138.0, 137.8, 133.8, 133.0, 128.7, 123.9, 118.4, 117.7, 112.1, 107.7, 99.2, 78.0, 75.7, 70.1, 69.7, 67.9, 57.1, 38.7, 35.0, 33.6, 33.4, 31.4, 30.1, 27.7, 26.3, 16.0, 12.5;

In DMSO

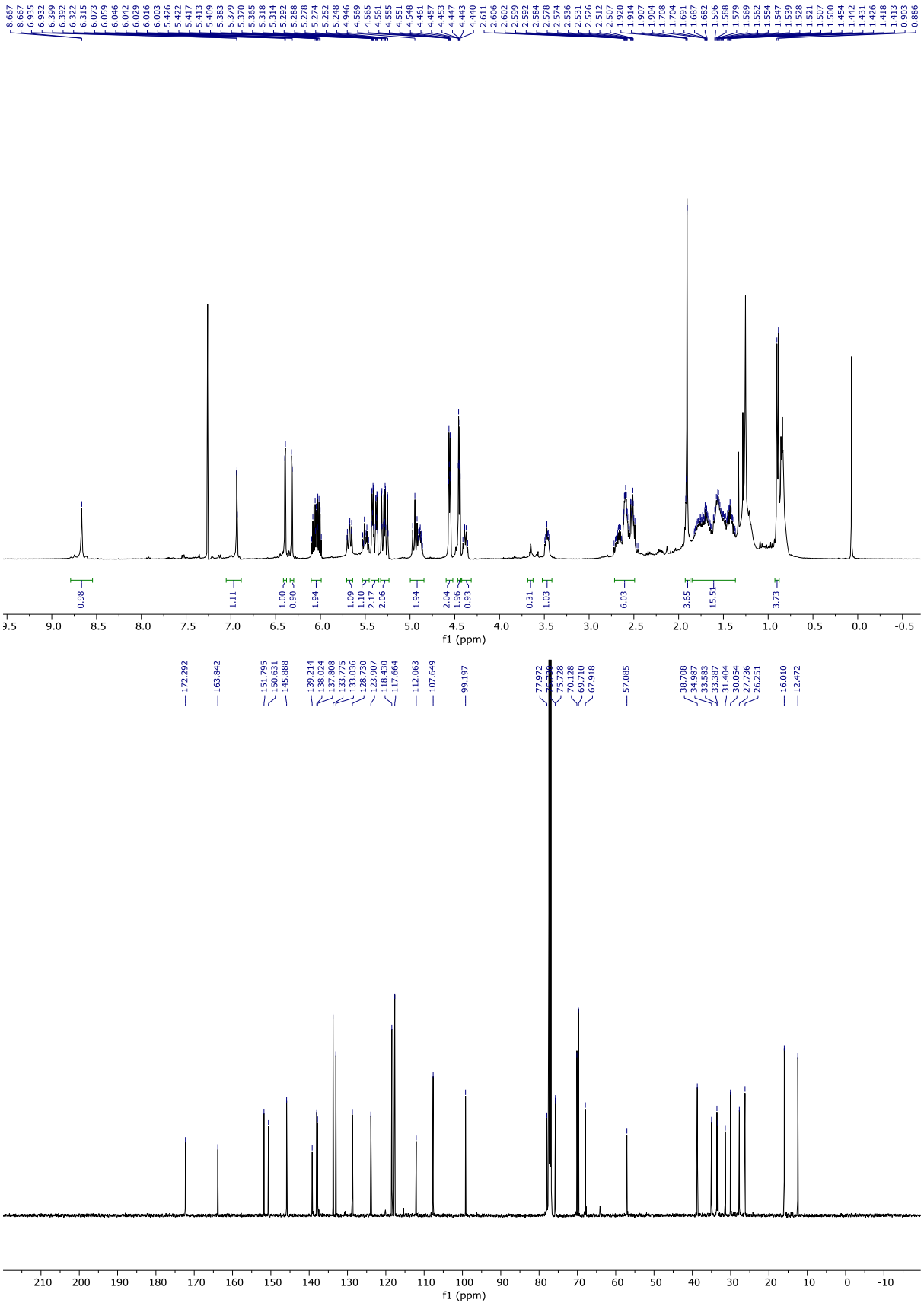
^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.48 (s, 1H), 7.63 – 7.36 (m, 2H), 6.42 (d, J = 2.8 Hz, 1H), 6.27 (d, J = 2.8 Hz, 1H), 6.02 (dddt, J = 17.3, 13.7, 10.5, 5.2 Hz, 2H), 5.56 – 5.28 (m, 2H), 5.22 (tt, J = 8.6, 1.7 Hz, 2H), 5.04 (dd, J = 10.4, 8.6 Hz, 1H), 4.75 (qd, J = 7.8, 6.4, 4.8 Hz, 1H), 4.61 – 4.51 (m, 3H), 4.43 (dt, J = 5.2, 1.7 Hz, 2H), 4.20 (t, J = 6.2 Hz, 2H), 3.24 (q, J = 7.4, 5.6 Hz, 1H), 2.61 – 2.38 (m, 6H), 2.31 (ddd, J = 13.2, 10.3, 3.4 Hz, 1H), 1.76 (d, J = 1.3 Hz, 3H), 1.72 – 1.60 (m, 0H), 1.56 – 1.00 (m, 5H), 0.78 (d, J = 6.6 Hz, 3H);

^{13}C NMR (101 MHz, DMSO-*d6*) δ 173.1, 164.5, 151.2, 150.7, 147.1, 141.6, 138.5, 138.5, 134.7, 134.5, 130.1, 123.3, 117.7, 117.5, 109.6, 107.6, 99.8, 79.7, 78.2, 74.2, 69.7, 69.1, 66.7, 57.3, 35.8, 33.5, 33.3, 30.6, 30.5, 27.9, 26.7, 15.9, 12.4;

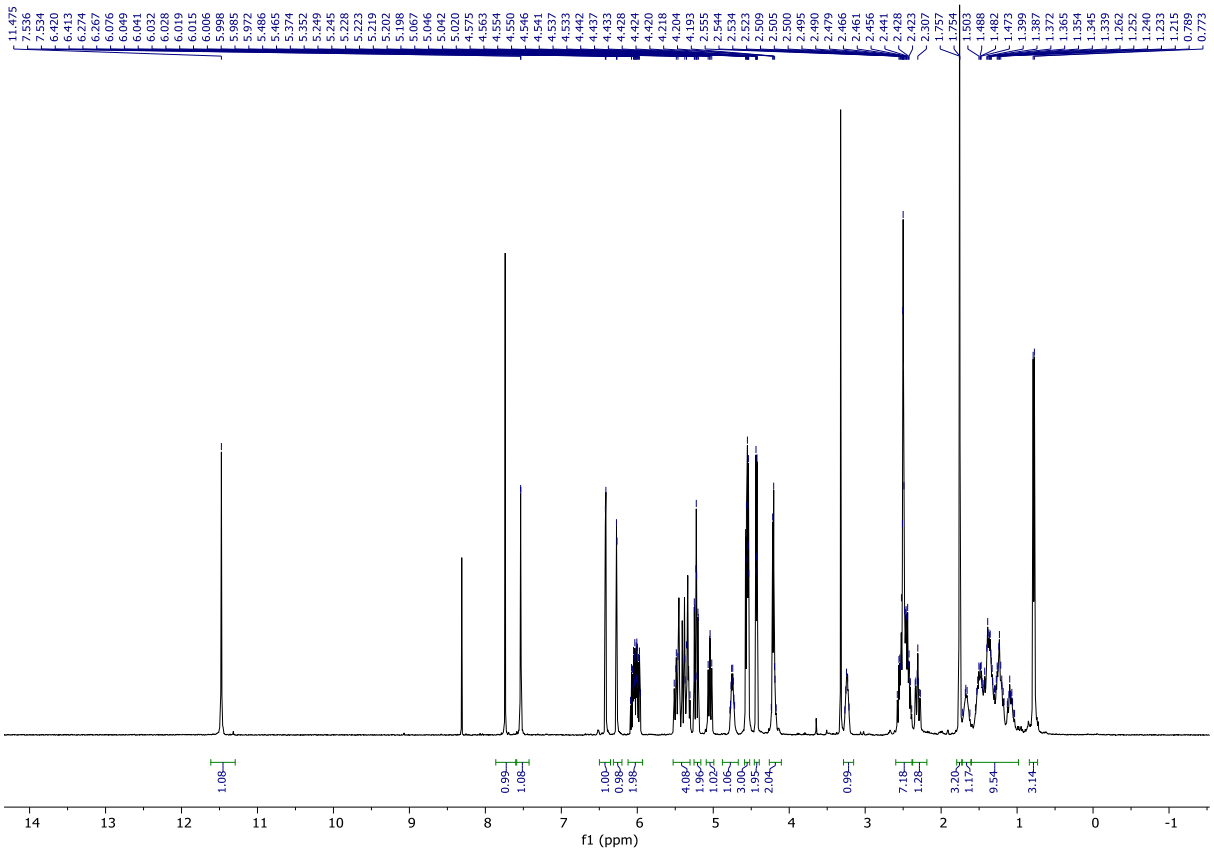
IR (film): ν = 3433, 2930, 2857, 2043, 1781, 1700, 1495, 1464, 1353, 1260, 1198, 1162, 1117, 997, 820, 702, 661, 645, 618, 610;

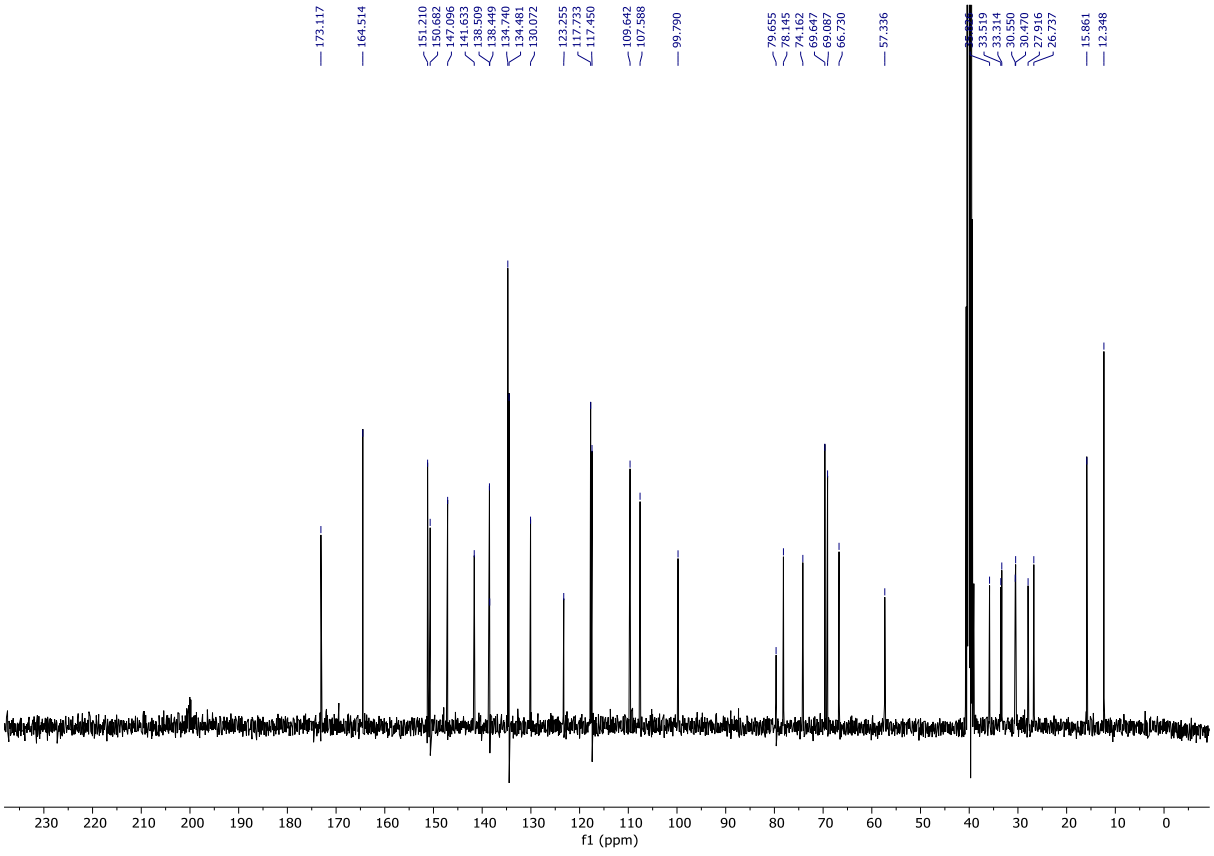
HRMS (ESI-TOF) m/z (ESI) $C_{33}H_{44}N_2NaO_9$ $[M+Na]^+$ 635.2939, found 635.2935.

NMR in Chloroform-*d*

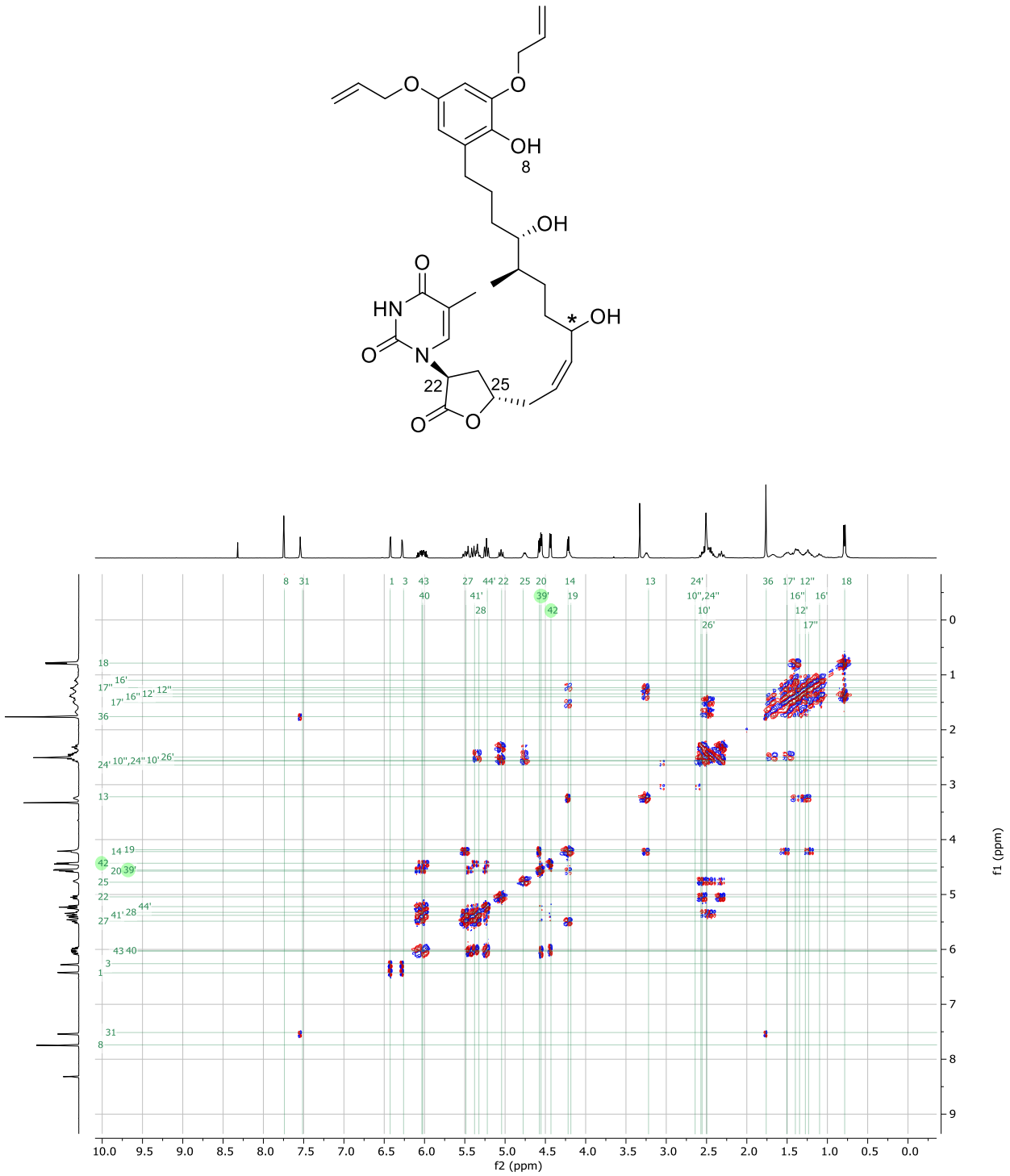


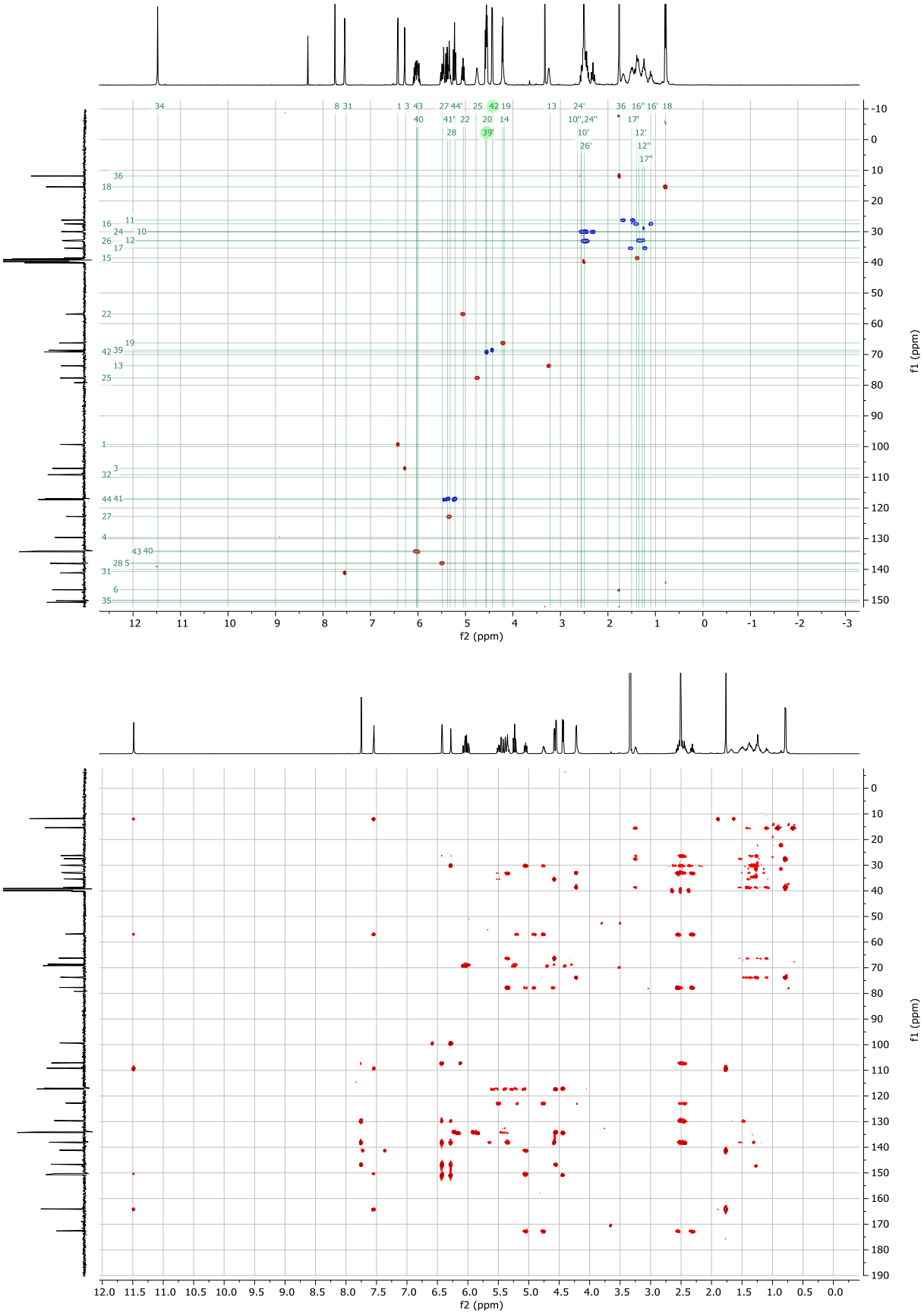
NMR in DMSO-*d6*



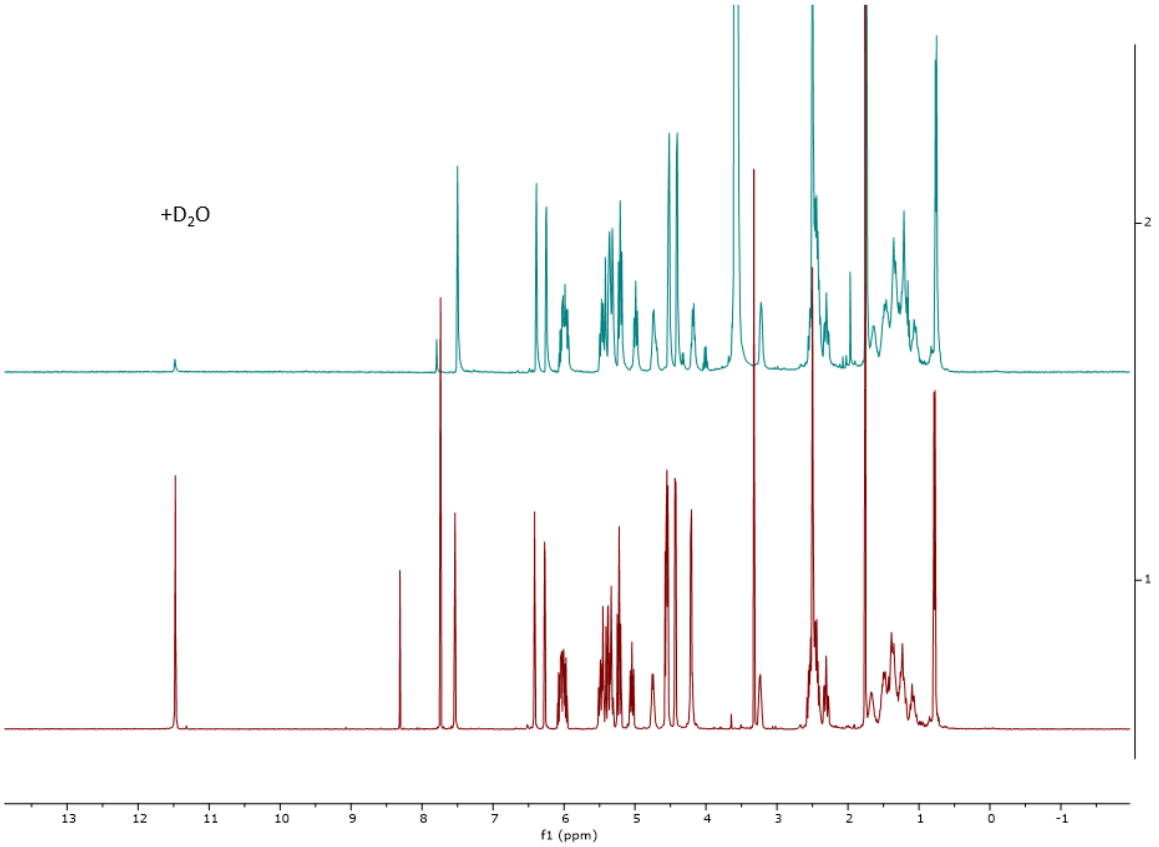


2D NMR of the transesterification product (*S,S*)-**123**

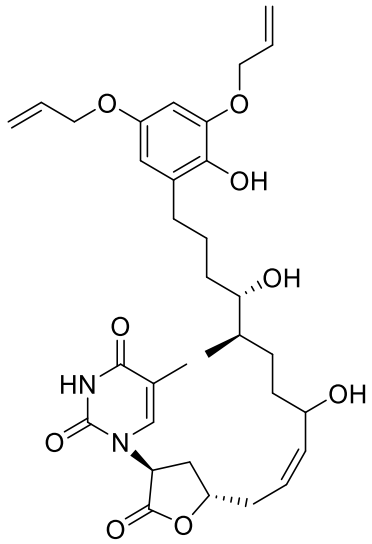




Additionally, an experiment with D_2O was conducted to confirm that phenolic proton disappears:


+D2O
2
1
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

*dia-(S,S)-**123***



In a plastic vial charged with a stirring bar, a solution of (S,S)-**111-**minor(6 mg, 0.006 mmol, 1 equiv.) in THF (0.124 mL, c=0.05 M) was prepared. The solution was cooled to 0 °C. Then, pyridine (0.439 mL, 5.44 mmol, 876 equiv.) and HF·pyridine (70:30, 0.396 mL, 3.35 mmol:1.33 mmol, 539 equiv.:214 equiv.) were slowly added via plastic syringe at 0 °C. The reaction started. Stirring was continued at this temperature and then gradually was allowed to go to the ambient temperature (room temperature). After almost 2 days (42 hours), the reaction was diluted with 2 ml of EA, and quenched by slow addition of the reaction mixture to sat. $KHCO_3$ solution (20 ml) in a plastic Erlenmeyer. After checking the pH with a pH paper=8, the solution was extracted with EA (10 ml x 3), dried over $MgSO_4$, and the solvent was evaporated. The crude material was purified by 2 FC. Pipet FC with hex:ea= 2:1 with a gradient to pure ea. The second FC – a pipet column with 30:1=DCM: MeOH to 15:1 to 2:1. The product dia-(S,S)-**123** was obtained in fractions 24-29 (2.6 mg, 68 %) as a colorless oil, and with time became yellow.

Yield: 2.6 mg (68 %);

R_f = 0.225 (15:1 DCM: MeOH), CPS staining;

$[\alpha]\frac{D}{20}$: = -22.50 (c = 0.4 ; $CHCl_3$, 20°C);

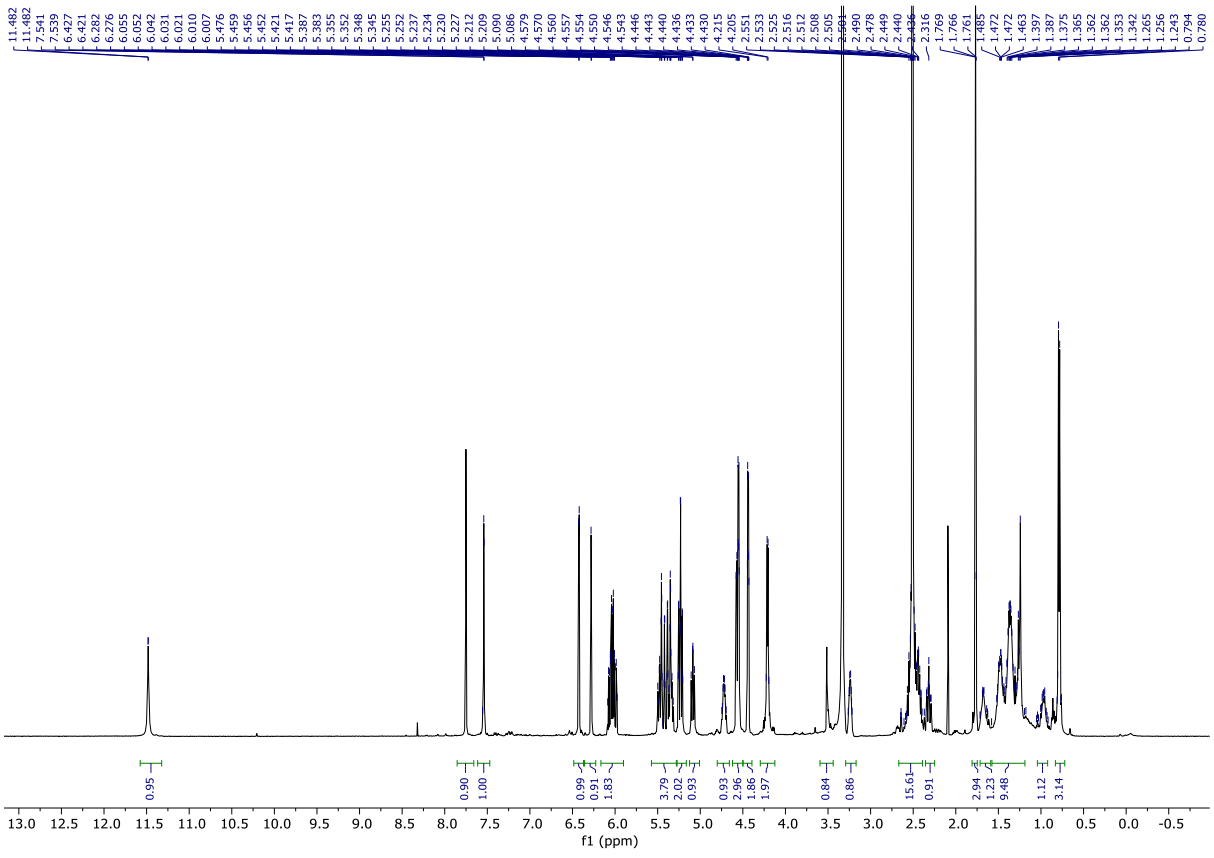
^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.55 – 11.31 (m, 21H), 7.54 (d, J = 1.4 Hz, 1H), 6.42 (d, J = 2.8 Hz, 1H), 6.28 (d, J = 2.8 Hz, 1H), 6.03 (tdt, J = 17.3, 10.5, 5.2 Hz, 2H), 5.53 – 5.31 (m, 4H), 5.23 (tq, J = 10.7, 1.6 Hz, 2H), 5.09 (dd, J = 10.3, 8.7 Hz, 1H), 4.72 (td, J = 9.9, 6.7 Hz, 1H), 4.59 – 4.51 (m, 3H), 4.44 (dt, J = 5.3, 1.5 Hz, 2H), 4.21 (t, J = 5.0 Hz, 2H), 3.27 – 3.19 (m, 1H), 2.65 – 2.38 (m, 14H), 2.32 (ddd, J = 13.2, 10.4, 3.4 Hz, 1H), 1.77 (d, J = 1.2 Hz, 3H), 1.72 – 1.62 (m, 1H), 1.58 – 1.16 (m, 7H), 1.05 – 0.91 (m, 1H), 0.79 (d, J = 6.8 Hz, 3H);

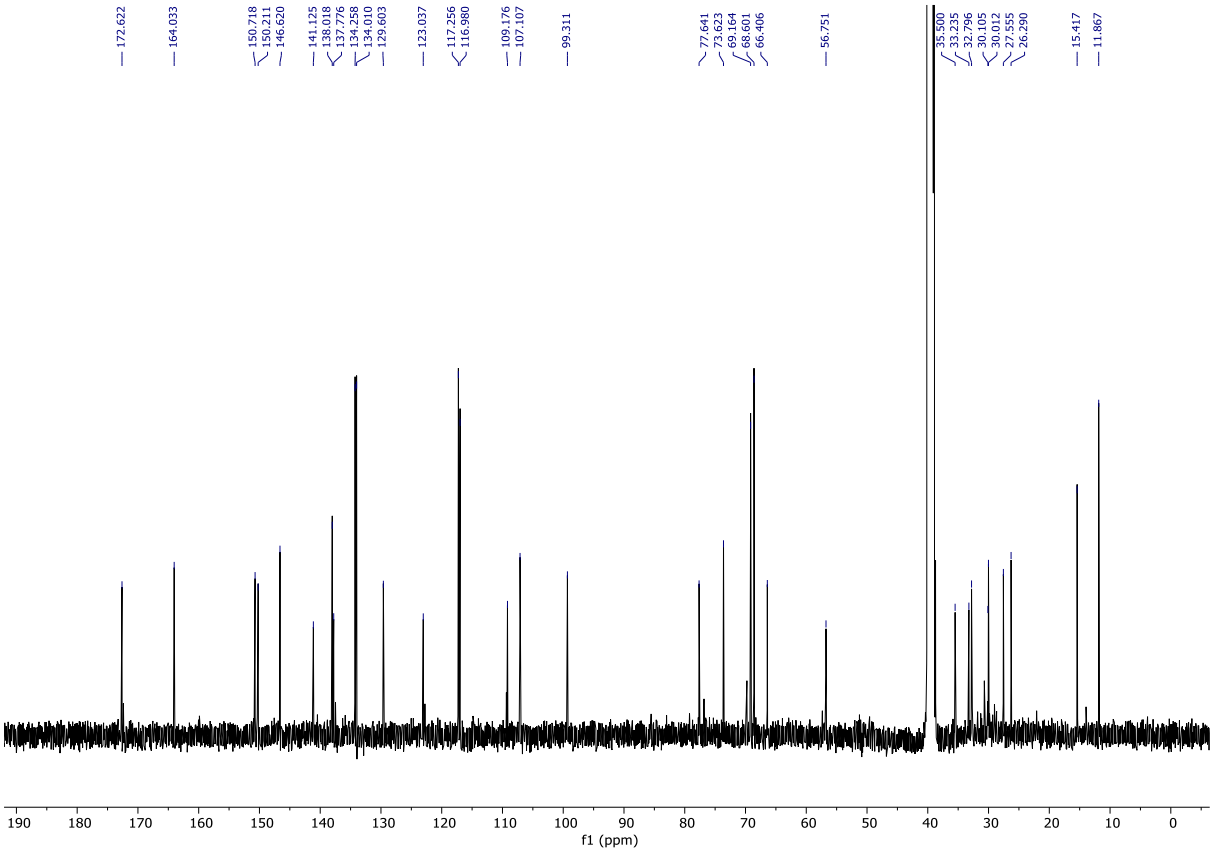
^{13}C NMR (126 MHz, DMSO-*d6*) δ 172.6, 164.0, 150.7, 150.2, 146.6, 141.1, 138.0, 137.8, 134.3, 134.0, 129.6, 123.0, 117.3, 117.0, 109.2, 107.1, 99.3, 77.6, 73.6, 69.2, 68.6, 66.4, 56.8, 35.5, 33.2, 32.8, 30.1, 30.0, 27.6, 26.3, 15.4, 11.9;

IR (film): ν = 3394, 2925, 2855, 1780, 1702, 1603, 1495, 1463, 1377, 1354, 1260, 1208, 1159, 1027, 799, 758, 668, 642, 622, 609;

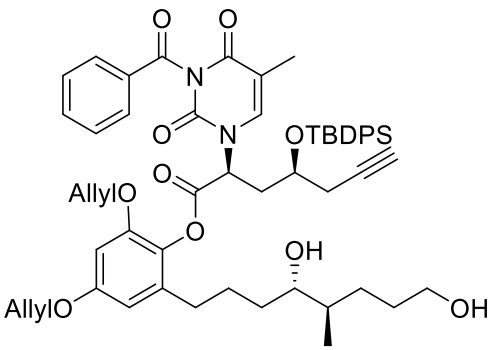
HRMS (ESI-TOF) m/z (ESI) $C_{33}H_{44}N_2NaO_9$ $[M+Na]^+$ 635.2939, found 635.2935.

NMR in DMSO-*d6*




172.622
164.033
150.718
150.211
146.620
141.125
138.018
137.776
134.258
134.010
129.603
123.037
117.256
116.980
109.176
107.107
99.311
77.641
73.623
69.164
68.601
66.406
56.751
35.500
33.235
32.796
30.105
30.012
27.555
26.290
15.417
11.867
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

*(S,S)-**125***



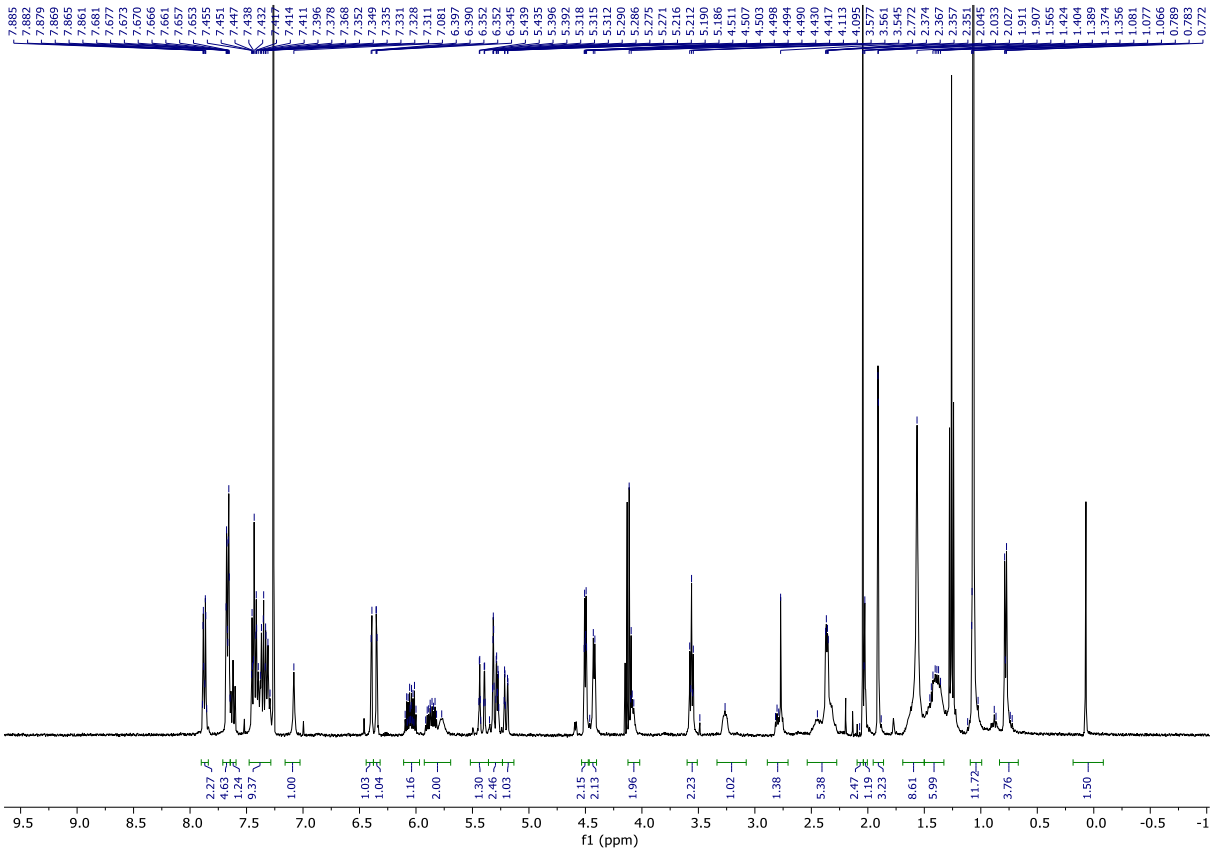
To a stirred solution of (S,S)-**85** (10 mg, mmol) in THF (0.21 mL) in a vial was added HF·pyridine (10 mkl, 10 equiv) at 0 °C. The reaction mixture was stirred for for hours allowing to go to room temperature. Then, the reaction was diluted with DCM and quenched with sat. aq. $KHCO_3$. The layers were separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (Hex/EtOAc = 2:1) to afford 5 mg (79 %) of (S,S)-**125** in fractions 10-20.

Yield: 5 mg (79 %);

R_f = 0.116 (1:1 Hex: EtOAc), CPS staining;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.72 (m, 2H), 7.67 (dq, J = 6.8, 1.6 Hz, 4H), 7.51 – 7.27 (m, 8H), 7.08 (s, 1H), 6.39 (d, J = 2.7 Hz, 1H), 6.39 – 6.23 (m, 2H), 6.13 – 5.98 (m, 1H), 5.95 – 5.69 (m, 2H), 5.42 (dq, J = 17.2, 1.6 Hz, 1H), 5.33 – 5.24 (m, 2H), 5.22 – 5.16 (m, 1H), 4.50 (dt, J = 5.4, 1.5 Hz, 2H), 4.42 (d, J = 5.5 Hz, 2H), 4.12 – 4.06 (m, 2H), 3.56 (t, J = 6.4 Hz, 2H), 3.26 (s, 1H), 2.79 (d, J = 12.7 Hz, 1H), 2.36 (dd, J = 6.7, 2.7 Hz, 3H), 2.05 (s, 3H), 1.91 (d, J = 1.4 Hz, 3H), 1.56 (s, 6H), 1.40 (td, J = 13.2, 6.3 Hz, 3H), 1.07 (s, 11H), 0.88 – 0.71 (m, 3H).

HRMS (ESI-TOF) m/z (ESI) $C_{56}H_{66}N_2NaO_{10}Si$ $[M+Na]^+$ 977.4379, found 977.4376.


7.885
7.882
7.879
7.869
7.865
7.861
7.681
7.677
7.673
7.670
7.666
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7.657
7.653
7.455
7.451
7.447
7.438
7.432
7.417
7.414
7.411
7.396
7.378
7.368
7.352
7.349
7.335
7.331
7.328
7.311
7.081
6.397
6.390
6.352
6.345
5.439
5.435
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5.392
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5.315
5.312
5.290
5.286
5.275
5.271
5.216
5.212
5.190
5.186
4.511
4.507
4.503
4.498
4.494
4.490
4.430
4.417
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