TECHNISCHE UNIVERSITÄT WIEN
Vienna University of Technology

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Master Thesis

STUDIES TOWARDS THE TOTAL SYNTHESIS OF ELSAMICIN A, B AND CHARTREUSIN

conducted at

Ludwig-Maximilians-University Munich

Department of Chemistry

Under the supervision of

Dr. Thomas Magauer

Ao.Univ.Prof. Dipl.-Ing. Dr.techn. Peter Gärtner

submitted at the

Technical University of Vienna

Institute of Applied Synthetic Chemistry

by

Sofia Torres Venegas, B.Sc.

Reisnerstraße 17/6, A-1030 Vienna

Vienna, 09.01.2017

Statutory Declaration

I declare that I have authored this thesis independently, that I have not used other than the declared sources/resources, and that I have explicitly marked all material which has been quoted either literally or by content from the used sources.

Vienna, _____

Eidesstattliche Erklärung

Ich erkläre an Eides statt, dass ich die vorliegende Arbeit selbstständig verfasst, andere als die angegebenen Quellen/Hilfsmittel nicht benutzt, und die den benutzten Quellen wörtlich und inhaltlich entnommene Stellen als solche kenntlich gemacht habe.

Wien, _____

Table of Contents

List of Figures

List of Tables

List of Schemes

Acknowledgements

First of all, I would like to thank Dr. Thomas Magauer for giving me the opportunity to work in his research group and assigning me this interesting topic. I am especially thankful for the motivating conversations, the valuable support and his guidance throughout this project.

Furthermore, I want to thank Teresa Unzner and Andreas Baumann for their insight and all the ideas they provided. Without them this project couldn't have progressed this smoothly.

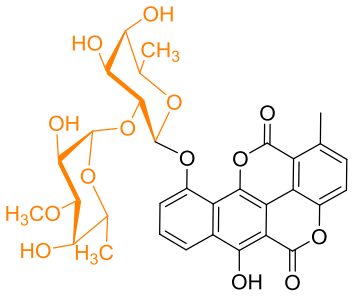
I also want to thank the whole group of Prof. Dr. Trauner and the current and past members of Dr. Magauer's group: Adriana Grossmann, Simon Schnell, Lara Weisheit, Tatjana Huber, Klaus Speck and Cedric Hugelshofer for always having an open ear and never holding back on helpful suggestions even after long hours.

Special thanks to my lab mates of the IR Lab, Johannes Feierfeil, Raphael Wildermuth, Franz-Lucas Haut and Alexander Rode for their (especially culinary) care during this time.

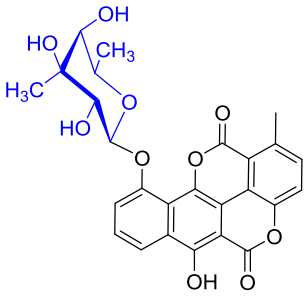
Finally, I want to thank my mother for her love and support during my studies.

Abstract

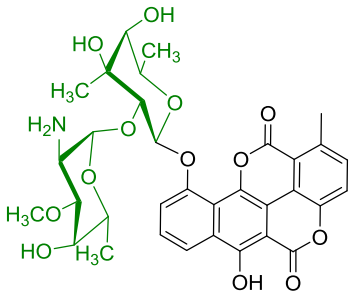
Chartreusin (**1**), elsamicin A (**2**) and B (**3**) are prominent examples of glycosidic polyketide antibiotics. They share a common aglyonce connected as *O*-fucoside at the C11-hydroxyl group. Their antiproliferative activities against various tumor cell lines makes them interesting targets for natural product synthesis.



chartreusin (**1**)

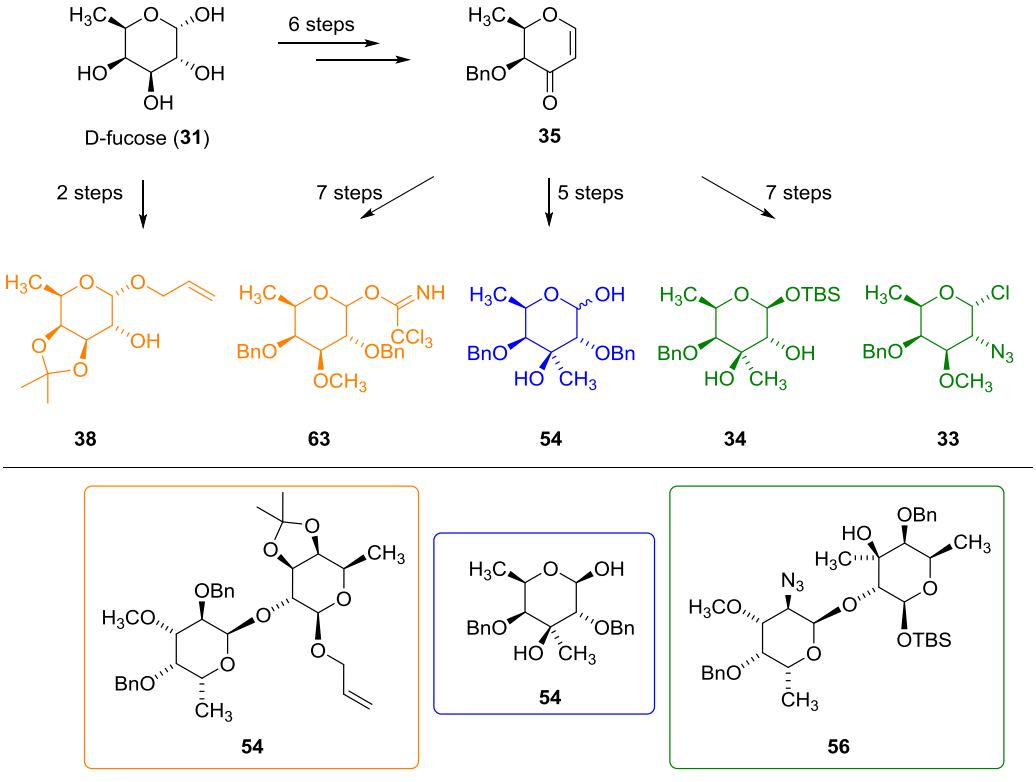


elsamicin B (**2**)



elsamicin A (**3**)

This master thesis describes the studies towards the synthesis of the carbohydrate units and formation of the gylcosidic bond between the sugar moieties and the polyketide aglycone. The synthesis of 4 of 5 building blocks proceeds through a common intermediate enone **35**, which was prepared in 6 linear steps from commercially avaiblable fucose (**31**). Glycosyl acceptor **38** and trichloroacetimidate **63** furnished disaccharide **54** under standard Schmidt-gylcosylation condtions. Treatment of azido fucoside **33** and diol **34** under optimized Koenigs–Knorr condtions furnished disaccharide **56**. Starting from D-fucose (**31**), the synthesis of all protected saccharide units was accomplished in a highly convergent manner.



List of Abbreviations

°C	degree Celsius
2D	two-dimensional
δ	chemical shift in ppm downfield from standard
AllocCl	allyl chloroformate
calcd	calculated
Bn	benzyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DNA	desoxyribonucleic acid
DMAP	4-(dimethylamino)-pyridin
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
EI	electron impact ionization
equiv	equivalents
ESI	electrospray ionization
FTIR	Fourier transform infrared spectroscopy
Et_2O	diethyl ether
g	gram
h	hour(s)
HRMS	high resolution mass spectrometry
HQ	hydroquinidine
Hz	Hertz
IR	infrared spectroscopy
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide

LA	Lewis acid
LDA	lithium diisopropylamide
LG	leaving group
LHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
M	molar
MDCA	methyl dichloroacetate
min	minutes
mL	milliliter
mmol	milimole
MOM	methoxymethyl
MS	mass spectroscopy
NDP	nucleoside diphosphate
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NMI	*N*-methylimidazole
PG	protecting group
PivCl	pivaloyl chloride
ppm	parts per million
R_f	ratio of fronts (TLC)
s	seconds
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
t-BuLi	*tert*-butyllithium
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	tosyl

1. Introduction

1.1. Natural Products of the Benzonaphthopyranone Class

Natural products of the benzonaphthopyranone class, such as chartreusin, gilvocarcins chrymutasin, hayumicins are a distinct group of glycosidic polyketide antibiotics.

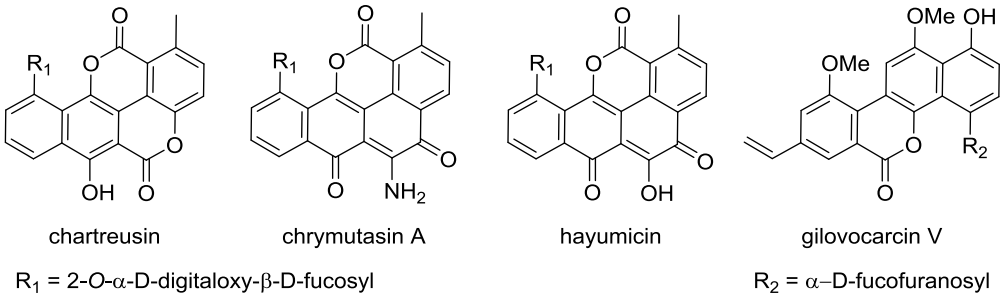


Figure 1: Structures of benzonaphthopyranone antibiotics.[1]

They are produced by several *Streptomyces* strains and are the best-known lactone-bridged biaryls due to their interesting antitumor activities.[1] The members of this class represent potent leads for future anticancer therapeutics and antibiotics. Therefore, several respresentatives of this group have been the subject of synthetic reseach activity.[1][2][3]

1.2. Isolation and Biological Activitiy

Chartreusin

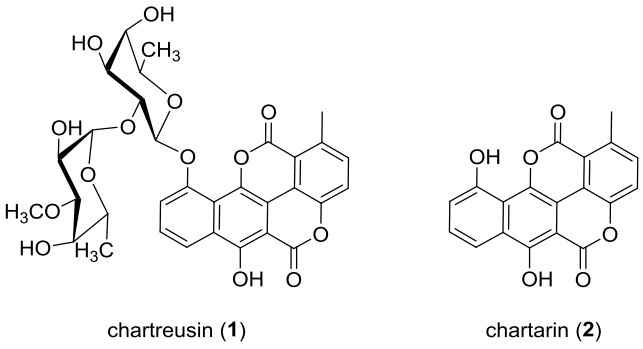


Figure 2: Structure of chartreusin (1) and chartarin (2).

Chartreusin (**1**), an aromatic polyketide glycoside, was first isolated in 1953 out of *Streptomyces chartreusis*. It consists of D-fucose, D-digitalose (3-*O*-methyl-D-fucose) and a bislactone aglycone, named chartarin (**2**).[4] While chartreusin already then showed interessting activitiy against certain Gram-positive organisms and mycobacteria,[4] further

studies releaved its significant antitumor activity against murine tumors P388 and L1210 leukemia and B16 melanoma.[5]

Pharmacological studies showed chartreusin (**1**) exerts its antibiotic activity through binding to DNA, followed by radical-mediated single-strand breaks, and inhibition of topoisomerase II.[6] Unfortunately, the development of chartreusin (**1**) as a drug has been hampered by its unfavorable pharmacokinetics due to rapid biliary excretion and slow gastrointestinal absorption.[7] There is considerable interest to adress these pharmacokinetic shortcomings by accessing natural and synthetic chartreusin analogs with improved properties in vivo to access the remarkably high antitumor activitiy in vitro[8].

Elsamicin A and B

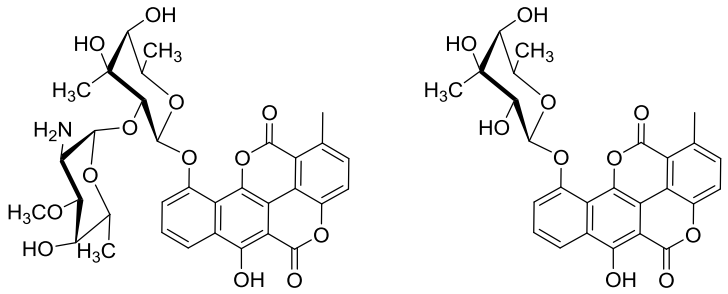


Figure 3: Structure of elsamicin A and B.

Elsamicin A (**3**) and B (**4**) are natural derivatives of (**1**), containing the common aglycone chartarin but different sugar moieties. Elsamicin A (**3**) and B (**4**), produced by an actinomycete strain J5907-21, were first isolated in 1987.[9] They showed the same antibacterial activity as (**1**), though elsamicin A (**3**) expressing a 4-8 times higher activity than elsamicin B (**4**) and chartreusin (**1**).[10] The higher activity derives from the increased water solubility due to the amino sugar moiety. Chartreusin (**1**) and elsamicin A (**3**) recognize almost the same G+C-rich DNA sequences[11], and analogs modifying the disaccharide portion of (**1**) resulted in retention of the antileukemic effects in vivo.[12] Concluding, chartarin (**2**) is a key element for bioactivity.[13]

Both elsamicin A (**3**) and a semisynthetic derivative of chartreusin (**1**), pro-drug IST-622, have reached phase II clinical trails.[8] [14]

1.3. Proposed Biosynthesis of Chartreusin

The proposed biosynthetisis of chartreusin (**1**) (Scheme **4**) was based on ^{13}C-isotope labeling studies, the analysis of the chartreusin gene cluster and the isolation of metabolite resomycin

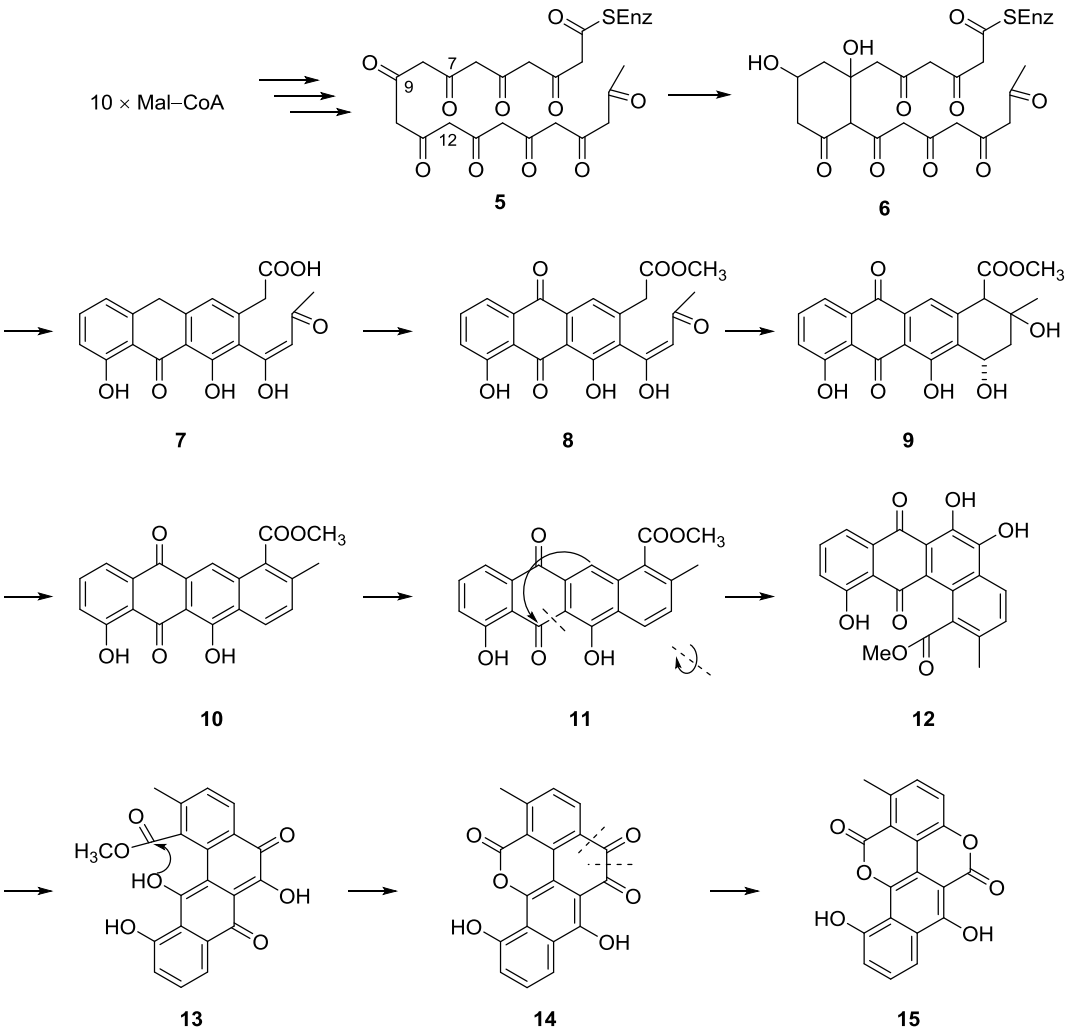
C (**10**) from a rationally designed mutant. The studies revealed that chartarin (**2**) is derived from a anthracyclic precursor through oxidative rearrangement.[7]

Strong evidence suggests that the formation of chartarin (**2**) is derived from a decaketide **5** progenitor, producing anthracylic polyketide **10**. The decaketide **5** would then undergo a reduction after 7/12 cyclization followed by aromatization of the three rings. Oxidation of the nogalic acid intermediate and methylation of the carboxy group would lead to **8**. Upon methylation, an aldol-type cyclization would lead to the formation of the fourth ring.

Studies are still ongoing to gain a deeper insight into the next reaction cascade furnishing framework **12**. Two possible pathways are envisioned to yield **12**.

The pathway depicted in Scheme **1** shows first an aromatization of **9** furnishing compound **10** which is identical to resomycin C, a recently identified metabolie of another chartreusin (**1**) producter.[15] The incorporation pattern suggests a ring cleavage adjacent to the anthaquinone carbony in a Bayer-Villiger-type oxygenation and would lead to a new C-C bond formation between the carbonyl and the unsubstituted carbon of the third ring. Hydroxyl group could be introduced either by hydroxylation of the angucyclic intermediate or during ring cleavage.

The first lactone ring would be formed by an attack of quinone oxygen on the methyl ester carbonyl. The proposed intermediate **14** might then be subject to another rearrangement reaction which would result in the loss of carbon dioxide and subsequent lactone formation, forming the chartarin aglycone (**2**).

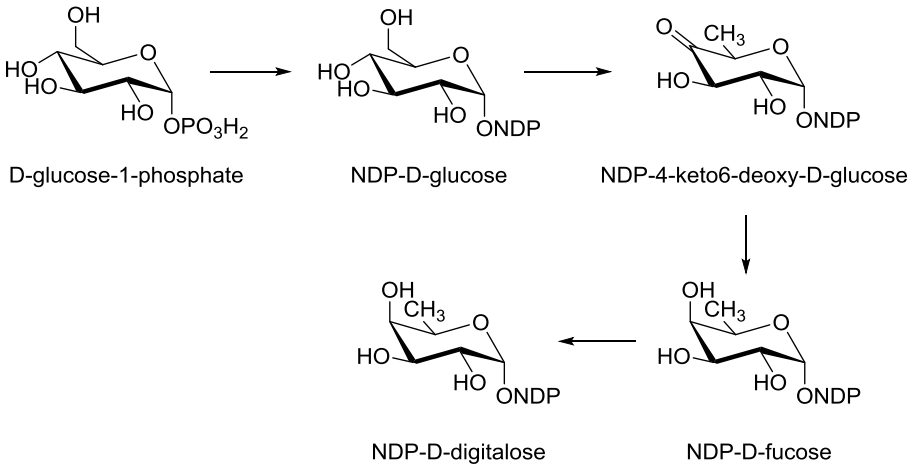


Scheme 1: Proposed biosynthesis of chartarin (2).

Several genes involved in the biosynthesis and attachment of the D-fucose and D-digitalose units to the chartarin agylcone have been detected in the *cha* gene cluster. This studies lead to a proposed pathway for the biosynthesis of the sugar moieties depicted in Scheme **2**.

The biosynthesis of the sugar moieties would start from D-glucose-1-phosphate followed by activation to the corresponding NDP-hexose. Subsequent conversion to NDP-4-keto-6-deoxy-D-glucose followed by reduction would furnish NDP-D-fucose.

NDP-D-digitalose would be accessible by C3 methylation and activation to the corresponding NDP-hexose. The two deoxysugars, D-fucose and D-digitalose would then be introduced by a corresponding glycosyltransferase, first attaching D-fuocse to the aromatic polyketide followed by a C2 glycosylation with NDP-D-digitaolse.



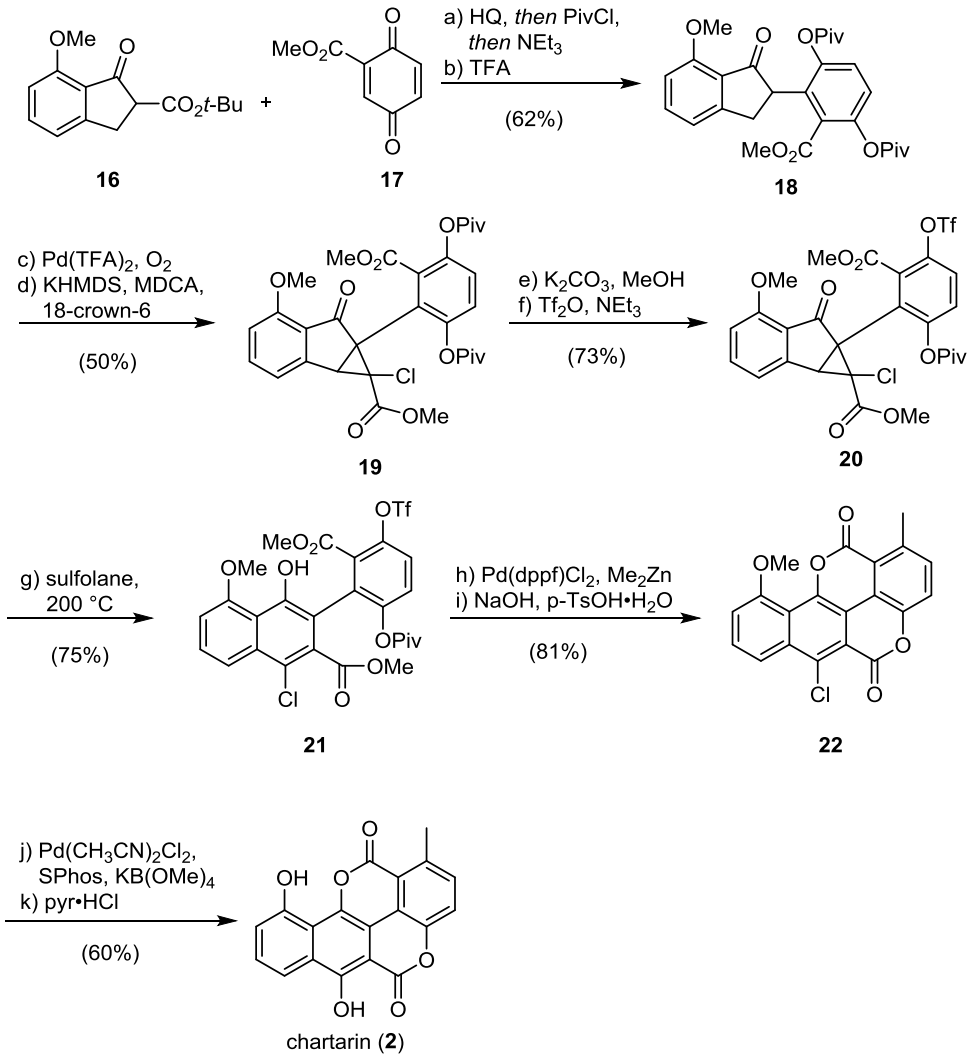
Scheme 2: Proposed biosynthesis pathway of sugar moieties in chartreusin.[16]

1.4. Literature Synthesis

Synthesis of Chartarin

The total synthesis of chartarin (**5**) was achieved by our group using a practical ring opening/1,2-migration transformation as key step.[17]

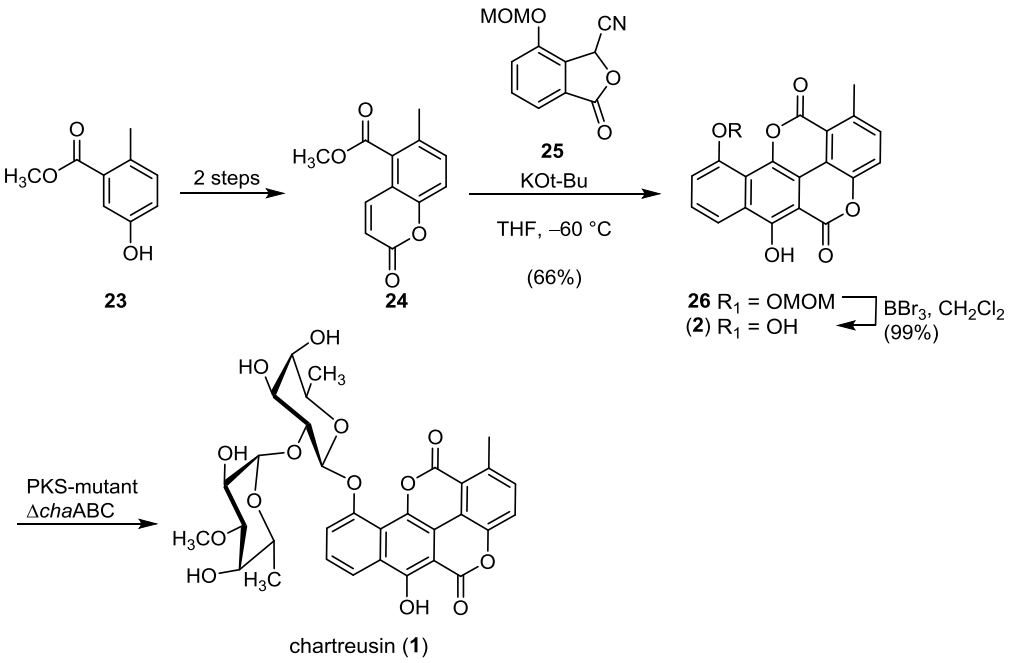
The synthesis starts with the conjugate addition of **17** to **16**, trapping the formed hydroquinone as its bis-pivalate ester. Subsequent decarboxylation gave 2-arylated indanone **18**. Oxidation to the enone, followed by cyclopropanation and subsequent replacement of one pivalte ester provided triflate **20**. The key-step features a thermally induced ring opening of the cyclopropane with simultaneous 1,2-chloride shift furnishing **21**. Installation of the methyl group was accomplished upon exposure of **21** to an excess of dimethyl zinc in the presence of $Pd(dppf)Cl_2$. Lactone formation was promoted upon hydrolysis of remaining pivalate ester and acid catalyzed ring closure. Substitution of the chloride was accomplished by Suzuki reaction of **21**, incorporating the desired methoxy group. Global deprotection was achieved by treatment with pyridine hydrochloride at elevated temperature, furnishing (**2**).[17]



Scheme 3: Synthesis of chartarin – cyclopropane ring opening.[17]

Semisynthetic Assembly of Chartreusin

In 2013, the synthesis of chartreusin (**1**) and analogs was accomplished by Hertweck and co-workers. Their chemo-biosynthetic approach included synthetic preparation of the chartarin (**2**) core, complemented by the use of a *cha* PKS mutant which completed this pathway yielding chartreusin (**1**) and derivatives. Previously synthesized building blocks coumarin **24** and phthlalide **25** were subjected to Hauser annulation conditions which had proven to be a viable method to construct pentaxyclic ring system of the aglycone.[18][1] Hauser annulation gave protected chartarin **26** which was deprotected and subsequently added to cultures Δ*chaABC* mutant yielding chartreusin (**1**).[19]



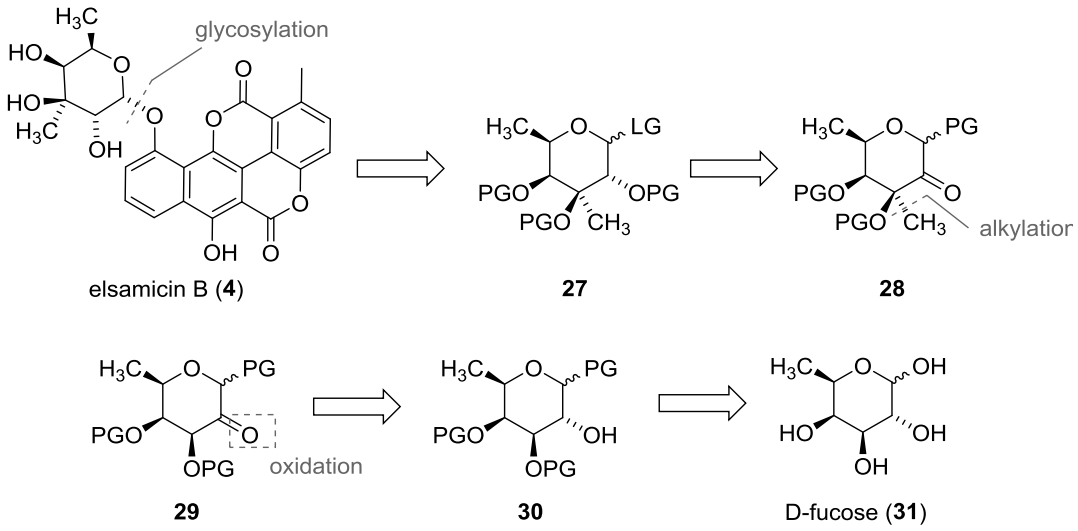
Scheme 4: Chemo-biosynthetic route of chartreusin (1).[19]

1.5. Retrosynthetic Analysis

For the development of a retrosynthetic strategy for elsamicin A (**3**), B (**4**) and chartreusin (**1**), it was assumed that the reactivity of the two hydroxyl groups would be significantly different. Through H-bond interactions with neighbouring lactone, C6-hydroxyl group was envisioned to be less reactive than C11-hydroxyl group thereby ensuring C11-hyrdoxyl group to be the preferred reaction side.

Elsamicin B

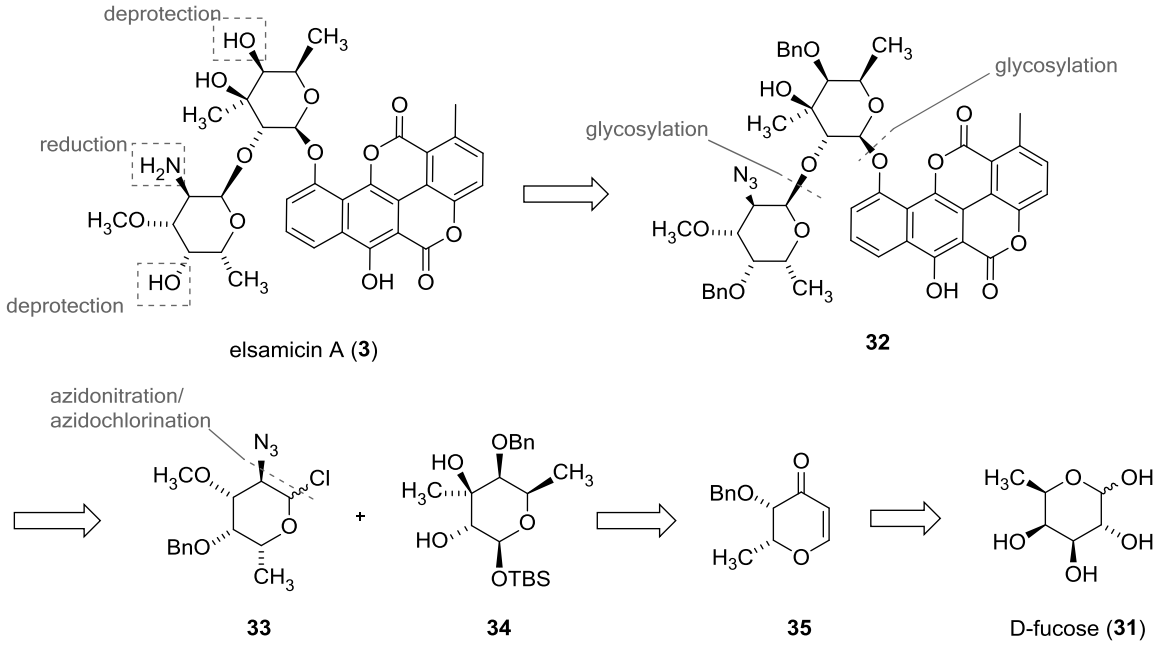
Retrosynthetically, the glycosidic bond was envisioned to be formed through suitable glycosylation conditions for chartarin (**2**) with glycosyl donor **27**, which could be generated through stereoselective reduction of ketone **28**. C3-methyl group of **28** was to be introduced by alkylation of previously formed ketone **29**. Finally, **29** could be traced back to a C1, C3, C4 protected D-fucose derivative.



Scheme 5: Retrosynthetic analysis for elsamicin B (4).

Elsamicin A

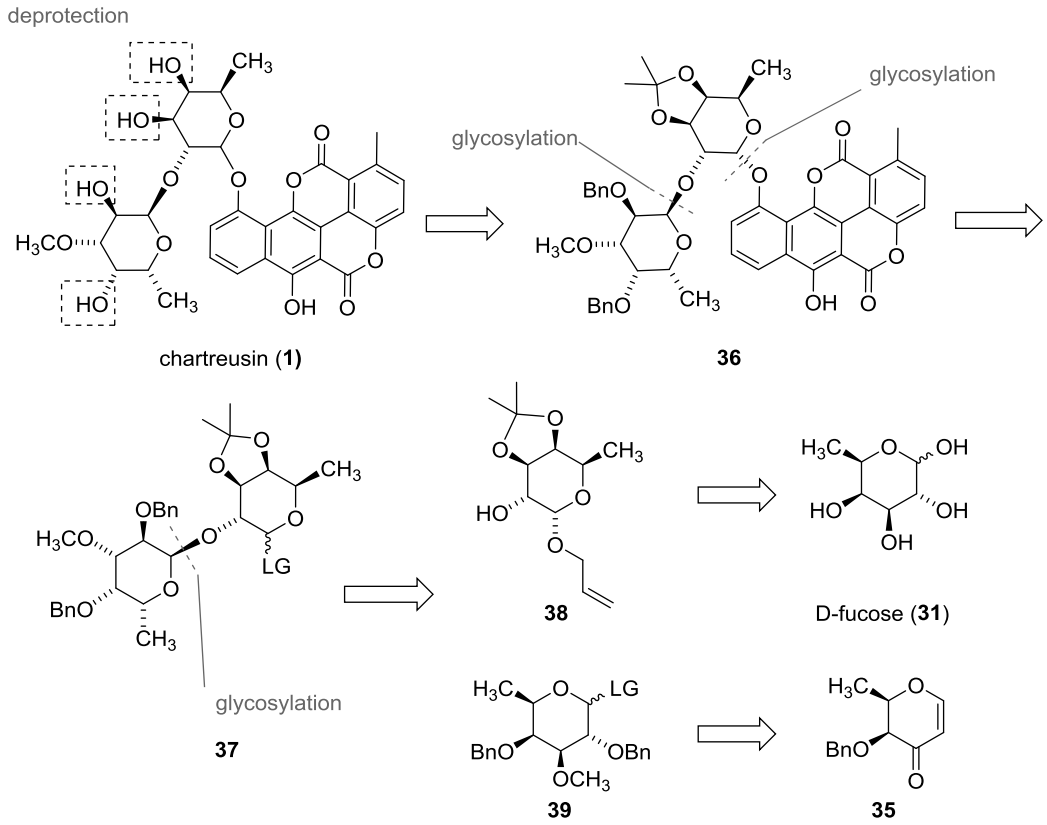
For elsamicin A (**3**), the introduction of the amino functionality was envisioned late stage via reduction of the corresponding azide and simultaneous global deprotection of the disaccharide in **32**. The protected disaccharide should be generated through C2-glycosylation of building blocks **33** and **34**. The azide functionality in **33** was supposed to be introduced via azidochlorination/azidonitraion. Both building blocks could be traced back to enone **35** which could be synthesized from D-fucose (**31**).



Scheme 6: Retrosynthetic analysis for elsamicin B (4).

Chartreusin

The synthesis of chartreusin (**1**) was intended to proceed via glycosylation of disaccharide **37** and chartarin. Compound **37** should be formed by C2-glycosylation of building blocks **38** and **39**. The glycosyl acceptor **38** would be synthesized according to elsamicin B route and **39** could be traced back to enone **35** which again derived from D-fucose (**31**).

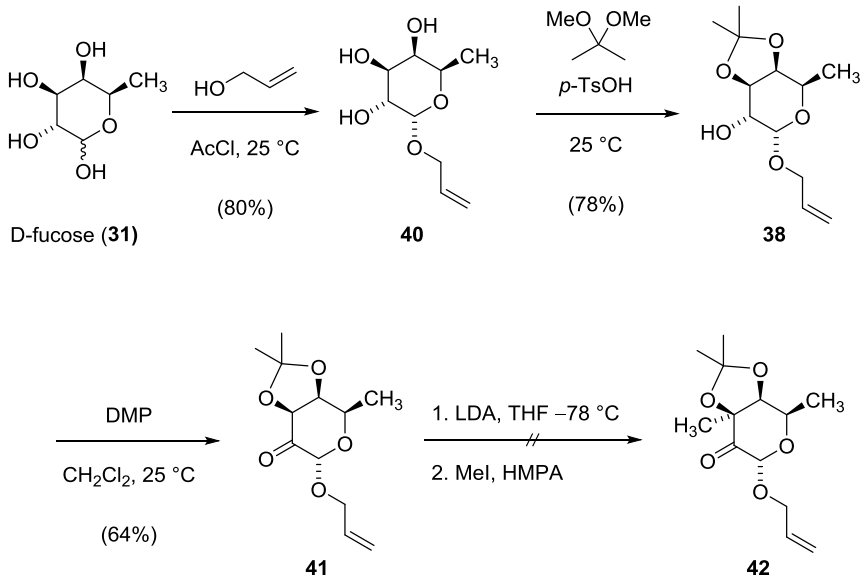


Scheme 7: Retrosynthetic analysis for chartreusin (1)

2. Results and Discussions

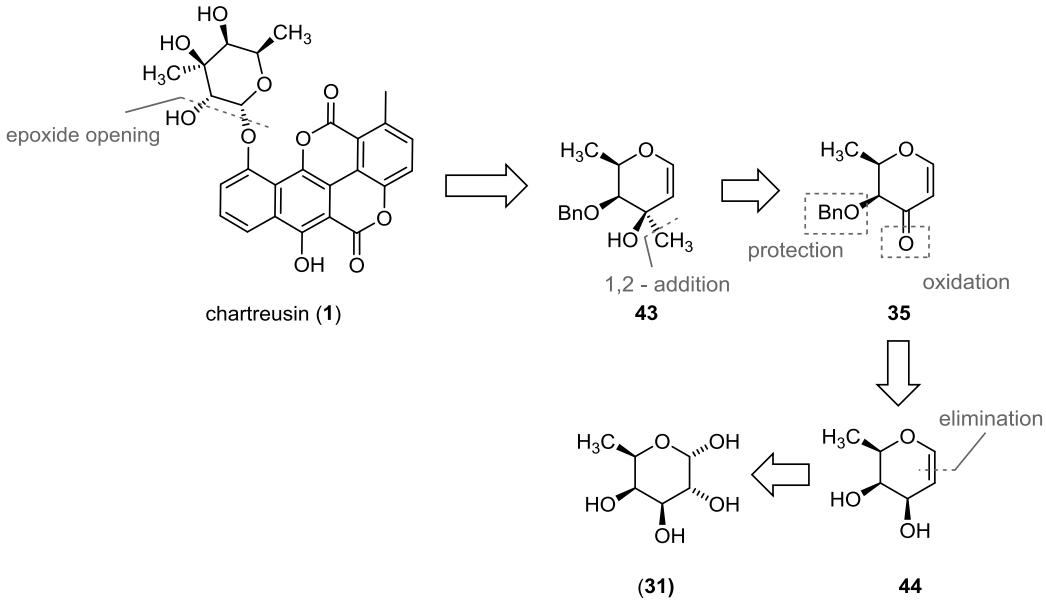
2.1. Synthetic Studies Towards the Carbohydrate Moiety of Elsamicin B

Following the retrosynthetic analysis, the C3-methyl group was attempted to be introduced through a protecting group pattern which left the C2 hydroxyl group free to be oxidized.
The anomeric hydroxy group was protected with allyl alcohol in acetyl chloride yielding selectivly the α-anomer. Acetal protection of C3- and C4-hydroxy groups with subsequent oxidation of **38** with Dess-Martin Periodine (DMP) furnished ketone **41** in good yields. Unfortunately, the deprotonation of ketone **41** with lithium diisopropylamide (LDA) or sodium hydride (NaH) followed by an addition of methyl iodide (MeI) lead only to decomposition of the starting material.



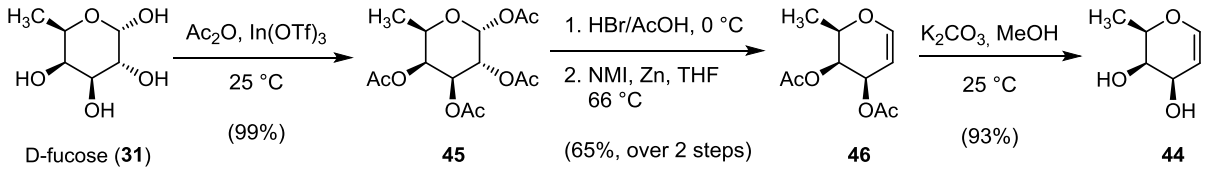
Scheme 8: Enolate approach.

Therefore, a different approach was envisioned, where the glycosidic bond should be formed by the opening of an in situ formed α-epoxide of **43** (Scheme **9**). The C3-methyl group would be introduced by 1,2-addition to the enone **35**. Compound **35** could be traced back to an oxidation of the C3-hydroxyl group and protection of fucal **44**, which could be synthesized in 3 steps from D-fucose (**31**).



Scheme 9: Retrosynthetic analysis elsamicin B – 2. generation.

The first steps towards enone **35** started by peracetylation[20] of D-fucose (**31**) with acetic anhydride and indium(III) triflate, followed by bromination at the anomeric position and elimination with zinc in *N*-methylimidazole (NMI)[21] to furnish di-*O*-acetyl-D-fucal **46** in good yield (65% over 2 steps). Deprotection with potassium carbonate (K_2CO_3) gave fucal **44.**[22]

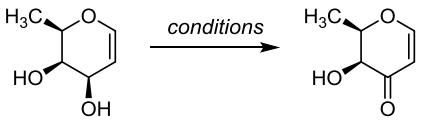


Scheme 10: Fucal synthesis.

For the oxidation, several conditions were screened to oxidize selectively at C3-position to yield enone **47.** The results are summarized in Table **1**.

Due to the acid and temperature sensitivity of enone **47** only mild conditions for allylic oxidations were screened. Since the best conditions, using nitrobenzene as hydrogen acceptor lead only to 15% of the desired product **47** and the product appeared to be volatile, a different approach was pursued.

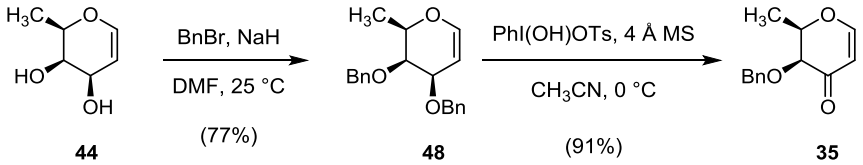
Table 1: C3 – oxidation conditions.



44 **47**

entry	oxidation agent	equiv.	time [h]	T [°C]	yield
1[23]	MnO_2	25	12	25 °C	no reaction
2	MnO_2	35	36	25 °C	5%
3[24]	PDC	1	4	25 °C	decomposition
4[25]	Ag_2CO_3 – Celite	3.6	8	80 °C	traces
5[26]	$NO_2C_6H_5$, Pd/C	0.33, 0.1	48	50 °C	15%

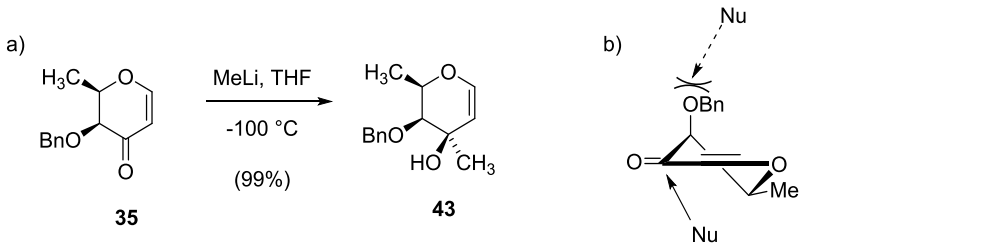
Here, first benzyl protection of both alcohols, followed by an organoiodine – promoted oxidation[27] gave enone **35** in good yields. The use of koser reagent (PhI(OH)OTs) allows the direct conversion of fully protected fucals into 2,3-dihydryo-4*H*-pyran-4-ones.



44 **48** **35**

Scheme 11: Oxidative deprotection to common intermediate 35.

Having synthesized enone **35** – the common intermediate for the building blocks of the carbohydrate units of elsamicin A, B and chartreusin – the synthesis continued by introducing a C3-methyl group through a 1,2-addition with methyllithium (MeLi)[23] to give tertiary alcohol **43** in 86% as a single diastereomer. The selectivity was rationalized through steric considerations depicted in Scheme **12**: the axial benzyl group preventing attack from the *Re* face in this half-chair conformation.[23] The stereochemistry was confirmed by 2D NMR analysis once the chair conformation was re-established.

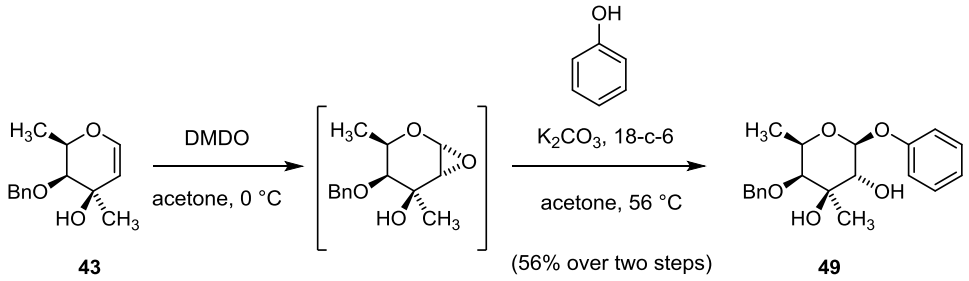


35 **43**

Scheme 12: a) Nucleophilic addition to enone 35. . b) Preffered side for nucleophilic attack.

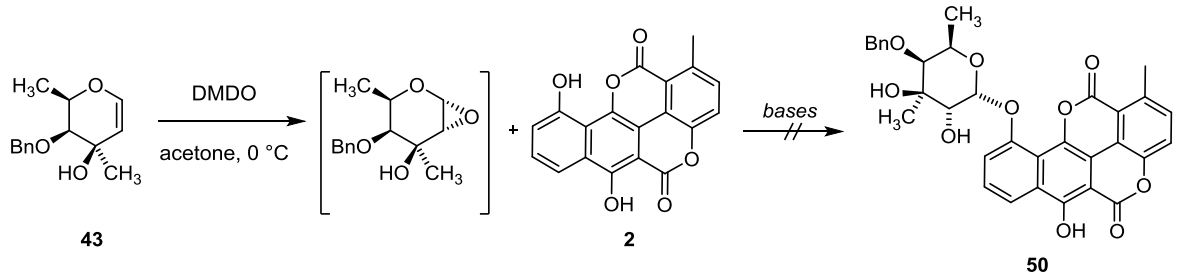
Therefore, the next objective was to install the last two stereocenters at C2 and C1. Epoxidation accompanied by subsequent stereo- and regioselective opening has proven a useful method to functionalize the double bond in glucals. [28][29][29][30][31]

Thus, epoxidation with dimethyldioxirane (DMDO) followed by epoxide opening by phenolate, prepared from previous refluxing of phenol, K_2CO_3 and 18-crown-6 in acetone,[28] furnished phenyl β-glycoside **49** (56% yield over 2 steps).



Scheme 13: Epoxide opening by phenolate.

Since the stereochemistry was now confirmed, the same conditions were applied to form the glycosylic bond of elsamicin B (**4**). Unfortunately, these conditions did not lead to the formation of the natural product, but resulted in an opening of the two lactones.



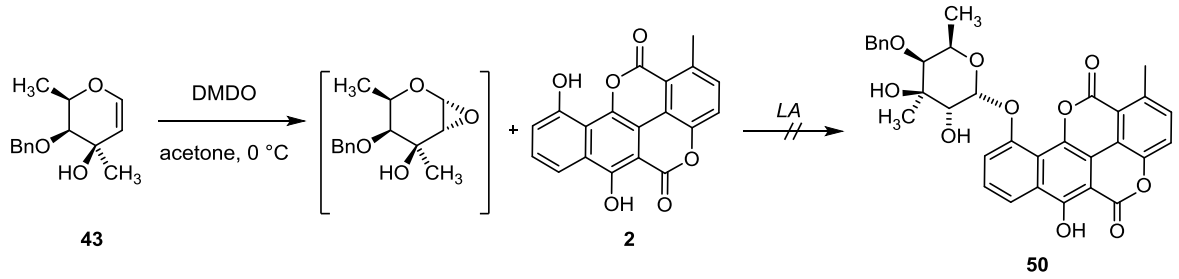
Scheme 14: Epoxide opening by chartarin

Different bases, (LHMDS, KHMDS, NaH, KH) and work-ups were screened however, they only resulted in decomposition of chartarin (**2**).

Thus, epoxide opening was attempted through several Lewis acids under various reaction conditions depicted in Table **2**.

Reaction with different equivalents of zinc chloride ($ZnCl_2$), zinc bromide ($ZnBr_2$), aluminium chloride ($AlCl_3$) and BF_3•OEt_2 as Lewis acids resulted in no reaction and the aglycone could be fully recovered.

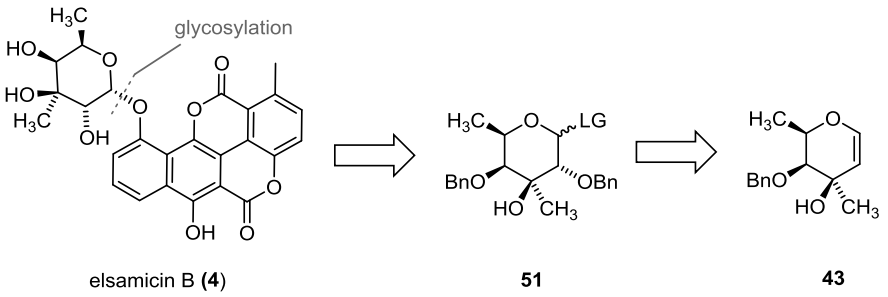
Table 2: Epoxide opening approach by various Lewis acids.



entry	Lewis acid	equiv.	reaction time [h]	T [°C]	yield (%)
1[30]	$ZnCl_2$	0.1	12	25 °C	no reaction
2	$ZnBr_2$	0.5	36	25 °C	no reaction
3	BF_3•OEt_2	0.01	12	-78 °C to 25 °C	no reaction
4	BF_3•OEt_2	0.1	24	-78 °C to 25 °C	no reaction
5	BF_3•OEt_2	1	24	-78 °C to 25 °C	no reaction
5	$AlCl_3$	0.1	12	-78 °C to 25 °C	no reaction

Thus, the epoxide approach was discarded.

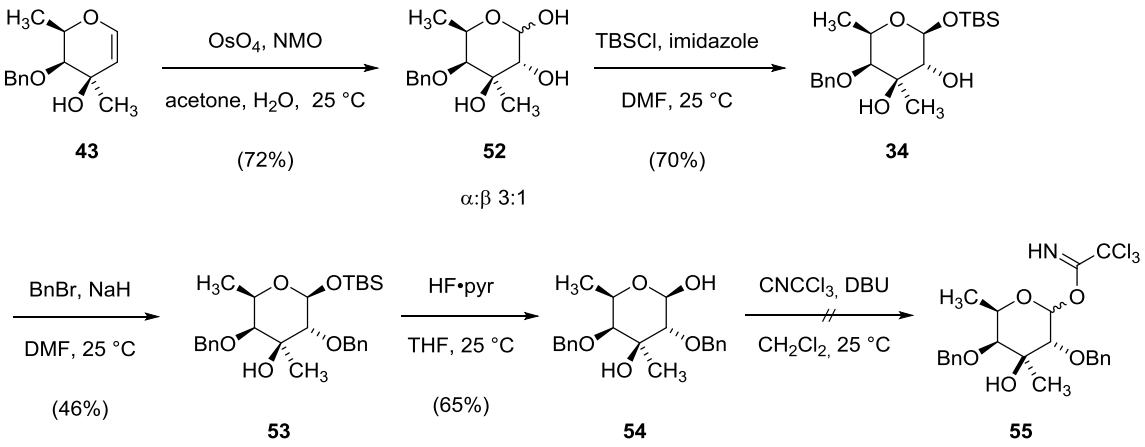
Glycosidic bond formation was then attempted via standard glycosylation procedures, of glycosyl donor **51** with chartarin. (Scheme **15**)



Scheme 15: Gylcosylation towards elsamicin B.

The tertiary alcohol **43** was dihydroxylated with osmium tetroxide (OsO_4) and *N*-methylmorpholine-*N*-oxide [32] furnishing triol **52** in 72% yield as a 3:1 mixture of α/β anomers (Scheme **16**). Selective allylcarbonylation of the C2-hydroxy group in triol **52** was attempted by the reaction with dibutyltin oxide (*n*-Bu_2SnO), followed by quenching with allyl chloroformate (AllocCl),[32] which mostly lead to decomposition with just traces of the desired compound. Therefore, standard protecting group transformations were applied to selectively protect the C2-hydroxyl group. The introduction of a *tert*-butyldimethylsilyl (TBS) protecting group on the anomeric position furnished selectively the β–anomer,[33] followed by C2 protection by the benzyl group. The anomeric TBS group could subsequently only be removed with HF•pyr[34]. Milder conditions including TBAF[33] and TBAF/acetic acid[35] did not

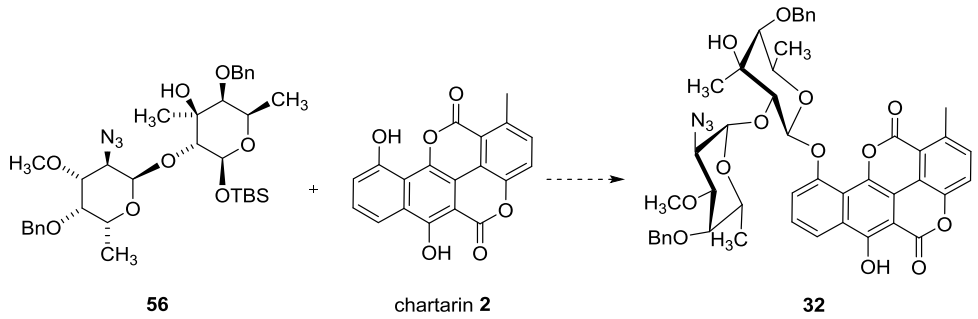
show any conversion to **54**. Unfortunately, the attempt for the formation of trichloroacetimidate **55** lead partially to reaction with the C3-hydroxyl group. Due to time issues, protection of tertiary alcohol and finalization of elsamicin B could not be accomplished.



Scheme 16: Synthesis of towards glycosyl donor 55.

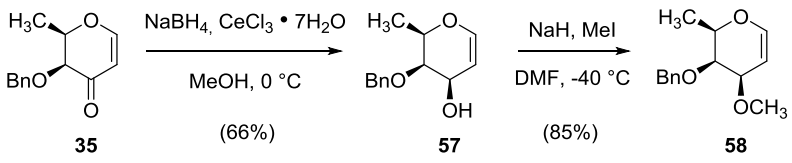
2.2. Synthetic Studies Towards the Carbohydrate Moiety of Elsamicin A

Since the attempts to form the glycosidic bond for elsamicin B (**4**) were not successful, the protected disaccharide (**56**) was synthesized separately to be glycosylated as last step with chartarin (**2**).



Scheme 17: Attempted synthesis of protected elsamicin A 32.

Starting from the common intermediate enone **35**, Luche reduction[36] gave **57** as a single diastereomer, which was directly methylated with NaH and MeI to give protected fucal **58** (Scheme **18**).



Scheme 18: Synthesis of the precursor for the azidochlorination.

Through recrystallization, suitable crystals were obtained for X-ray diffraction, which confirmed the stereochemistry at the C3-position, its molecular structure being depicted in Figure **4.**

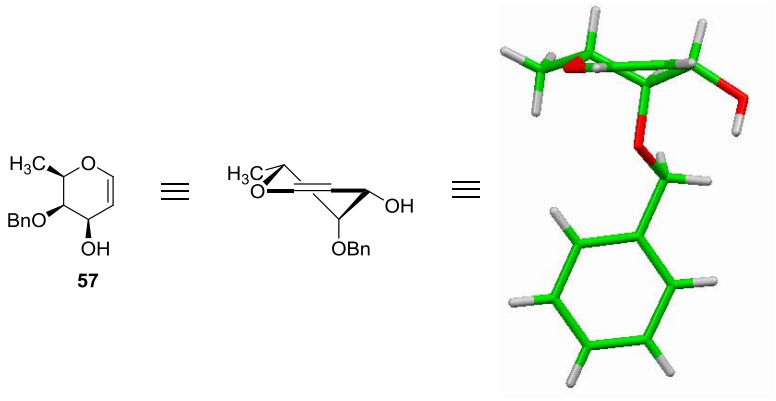
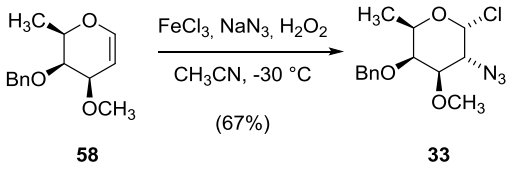


Figure 4: Molecular structure of 57.

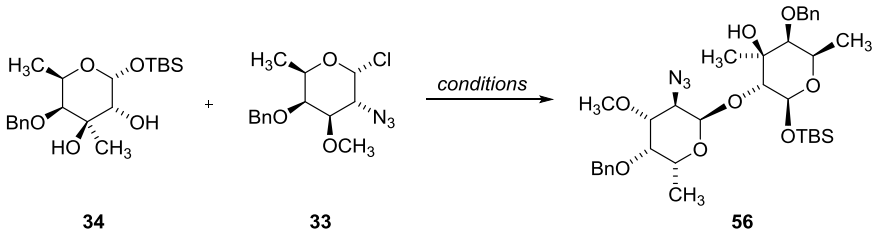
To introduce the azido functionality, a one pot azidochlorination[37] through an in situ-generated azide radical and chloride ion yielded **33** in 67% yield, which set the stage for the subsequent Koenigs-Knorr glycosylation[38]. Previous approach azidonitration, followed by hydrolysis and transformation to a appropriate leaving group was discarded due to low yields in the first step.[39]



Scheme 19: Azidochlorination.

Glycosylation of fucosyl chloride **33** with diol **34** was attempted using different desiccants and silver and cadmium promotor systems. Disaccharide **56** was finally prepared under Koenig – Knorr conditions, using $Ag_2CO_3/AgClO_4$ with 4 Å molecular sieves furnishing **56** in 22% yield with a 8:1 α/β ratio, recovering 80% of the glycosyl acceptor **34**.

Table 3: Koenigs – Knorr glycosylation

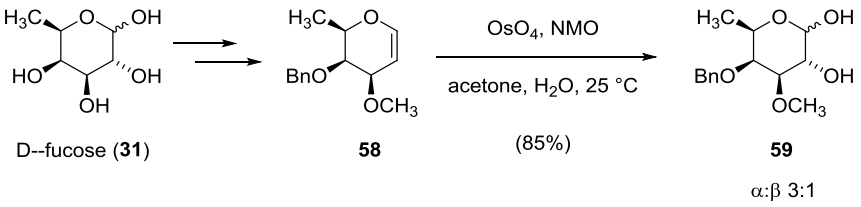


entry	promotor	equiv	desiccants	reaction time [h]	T [°C]	yield (%)
1[40]	$CdCO_3$	1.5	4 Å MS	12	110 °C	traces
2	$CdCO_3$	3	4 Å MS	36	110 °C	traces
3	$Ag_2CO_3/AgClO_4$	2/1	4 Å MS	16	25 °C	5
4[37]	$Ag_2CO_3/AgClO_4$	3/1	4 Å MS	16	25 °C	22
5	$Ag_2CO_3/AgClO_4$	3/1	Na_2SO_4	16	25 °C	10
6	$Ag_2CO_3/AgClO_4$	6/2	4 Å MS	48	25 °C	20
7[41]	Ag_2O	3	4 Å MS	24	25 °C	5
8	Ag_2O	5	4 Å MS	24	25 °C	5

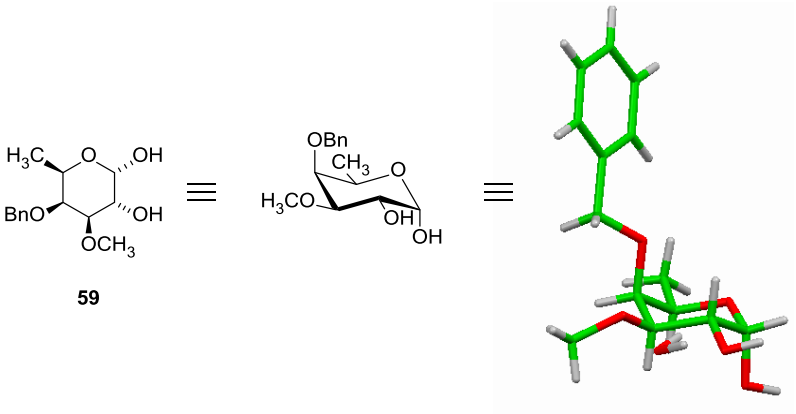
The low yields are suspected to arise from the relatively low nucleophilicity of a C2-hydroxyl group in the glycosyl acceptor and possible steric hinderance of both neighbouring groups. Thus, a different protecting group for the anomeric position could be introduced and more promotor systems for sterically hindered carbohydrates screened.

2.3. Synthetic Studies Towards the Carbohydrate Moiety of Chartreusin

For the synthesis of chartreusin (**1**), previously prepared fucal **58** was dihydroxylated and the stereochemical outcome determined by X-ray diffraction of suitable crystals of diol **59**.



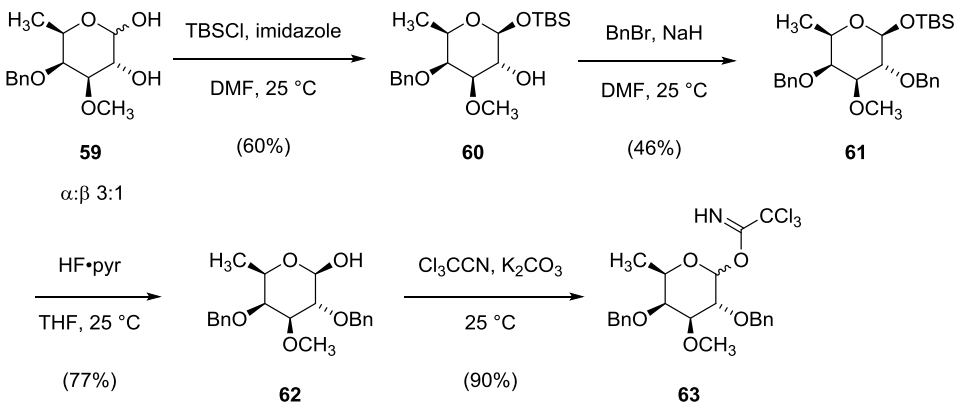
Scheme 20: Diastereoselective dihydroxylation of 58.



59

Figure 5: Molecular structure of diol 59.

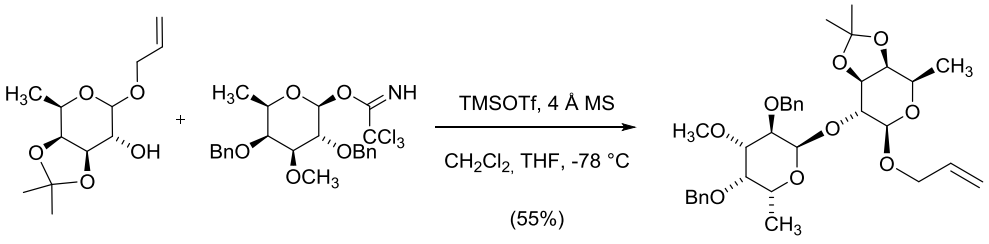
Protecting group transformations similar to the third approach for elsamicin B (**4**), were applied. Temporary TBS protection of the anomeric center, followed by benzyl protection of the C2-hyroxy group and subsequent cleavage of the silyl group, gave **62**, which was subsequently converted to acetimidate **63**.



59 α:β 3:1 **60** **61** **62** **63**

Scheme 21: Synthesis of glycosyl donor 63.

Schmidt glycosylation was performed using TMSOTf[42] as Lewis acid at –78 °C yielding **64** with a 6:1 α/β ratio, which concluded the synthesis of the protected chartreusin carbohydrate unit.



38 **63** **64**

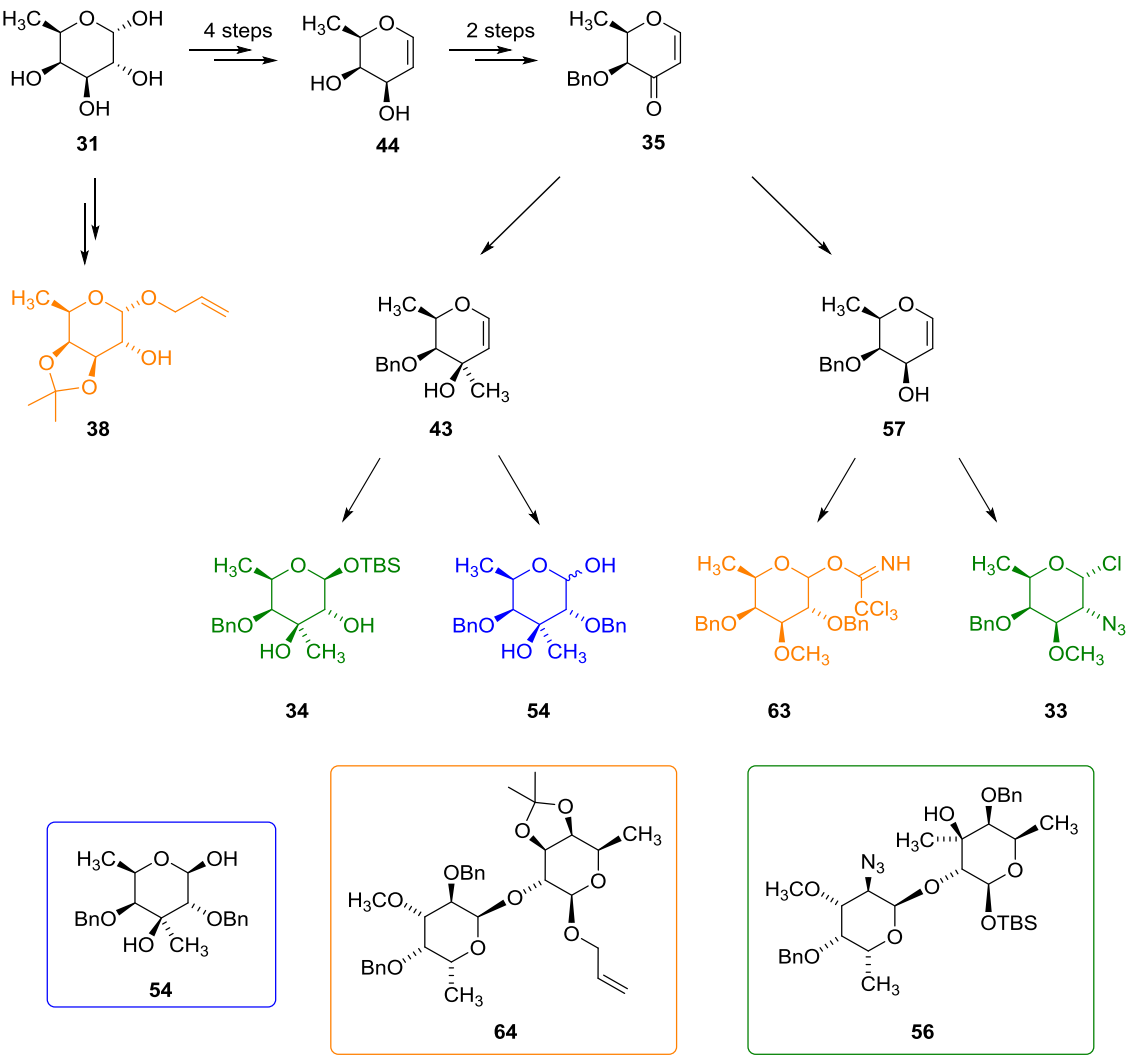
Scheme 22: Protected carbohydrate unit of chartreusin.

3. Conclusion and Perspective

In summary, the synthesis of the carbohydrate precursors towards elsamicin A (**3**), B (**4**) and chartreusin (**1**) was accomplished. Starting from D-fucose, the synthesis of 4 of 5 building blocks proceeds through a common intermediate **35**, which was prepared in 6 linear steps.

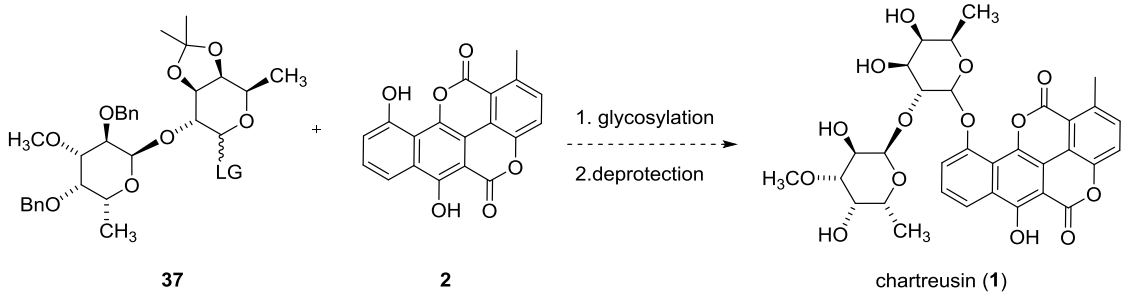
From enone **35**, elsamicin B carbohydrate unit was accessible through a diastereoselective C3-methylation followed by dihydroxylation. An applied protecting group pattern left the anomeric hydroxyl group free, ready to be converted to an appropriate leaving group for the final glycosylation.

Elsamicin A carbohydrate unit was synthesized by Koenigs-Knorr glycosylation of C3-methyl branched fucose derivate **54** with fucosyl chloride **62** using a $Ag_2CO_3/AgClO_4$ promotor system[37]. Chartreusin carbohydrate unit was prepared by classic Schmidt-glycosylation[42] of glycosyl donor **68** with acceptor **38** yielding disaccharide **69** in 6:1 α/β ratio.



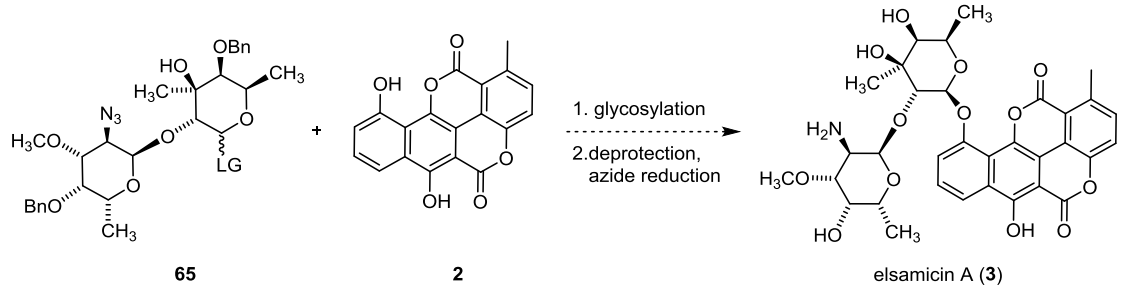
Scheme 23: Summary for the carbohydrate building blocks.

In order to finalize the synthesis of elsamicin A (**3**) and chartreusin (**1**), selective deprotection[34] of the anomeric hydroxyl group followed transformation to trichloracetimidate[32][43] and Schmidt glycosylation[42] would yield the protected natural products. Acetal cleavage by Lewis acids followed by reductive cleavage of the benzyl protecting group would achieve the synthesis of chartreusin. Reduction of the azide and benzyl cleavage for elsamicin A (**3**) should be accomplished in one step by reductive cleavage.



37 **2** chartreusin (**1**)

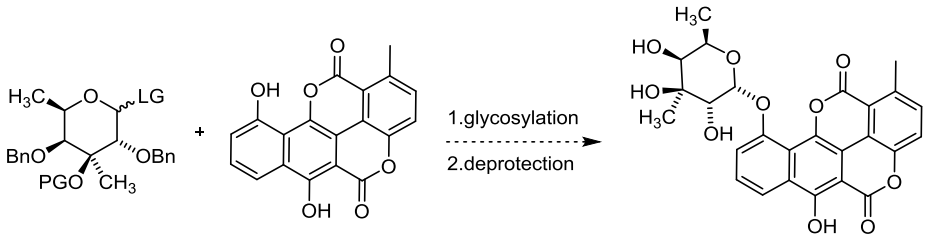
Scheme 24: Final steps towards chartreusin.



65 **2** elsamicin A (**3**)

Scheme 25: Final steps towards elsamicin A.

Towards elsamicin B (**4**), protection of the tertiary alcohol[44] needs to be accomplished to avoid side reactions during glycosylation. The final step would be a global deprotection by H_2 Pd/C.



66 **2** elsamicin B (**4**)

Scheme 26: Final steps towards elsamicin B.

4. Experimental Part

4.1. General Experimental Details

All reactions were performed in oven-dried or flame-dried glassware fitted with rubber septa under a positive pressure of nitrogen, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula through rubber septa. Solids were added under inert gas counter flow or were dissolved in appropriate solvents. Low temperature-reactions were carried out in a Dewar vessel filled with a cooling agent: acetone/dry ice (–78 °C), H_2O/ice (0 °C). Reaction temperatures above 25 °C were conducted in a heated oil bath. The reactions were carried out with magnetic stirring and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC), using aluminium plates precoated with silica gel (0.25 mm, 60 Å pore size, Merck) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV, 254 nm) and/or stained by submersion in aqueous ceric ammonium molybdate solution (CAM), potassium permanganate solution ($KMnO_4$) or *p*-anisaldehyde (ANIS) and were developed by heating with a heat gun (150–600 °C). Flash column chromatography was performed as described by Still et al.[45] using silica gel (60 Å, 40–63 µm, Merck KGaA) and with a pressure of 1.3–1.5 bar. The yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure material.

4.2. Materials

Dichloromethane (CH_2Cl_2), triethylamine (NEt_3) and *N*,*N*-diisopropylamine (DIPA) were distilled from CaH_2 prior to use. Toluene (PhMe), acetonitrile (MeCN), dimethyl formamide (DMF) and methanol (MeOH), acetone and tetrahydrofuran (THF) were purchased from *Acros Organics* as ‚extra dry reagents and used as received. All other reagents were purchased from chemical suppliers (*Sigma-Aldrich*, *Acros Organics*, *Alfa Aesar*, *Strem Chemicals*, *ABCR*) and were used without further purification. Solvents for extraction and flash column chromatography were purchased in technical grade and distilled under reduced pressure prior to use. 4 Å molecular sieves were washed (methanol, acetone, dichloromethane) and then dried at 100 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 140 °C (760 mmHg); the molecular sieves were flame dried under vacuum (0.1 mmHg) for 4–5 min immediately prior to use.

The concentration of freshly prepared dimethyldioxirane solutions[46] was determined by iodometric titration as follows: A 0.02 M aqueous stock solution of sodium thiosulfate pentahydrate (124 mg $Na_2S_2O_3 \cdot 5H_2O$ in 25 mL H_2O) was prepared in a 25 mL graduated cylinder. A 100 mL flask was charged with water (30 mL), sodium iodide (2.00 g) and glacial

acetic acid (1 mL), whereupon the dimethyldioxirane solution (2 mL) was added. The resulting brown mixture was rapidly titrated with the sodium thiosulfate stock solution until disappearance of the yellow iodine color occurred. The concentration of the dimethyldioxirane solution was calculated according to the following equation:

$$c(DMDO) = \frac{M(titrant)x\ V(titrant)}{V(DMDO)x\ 2}$$

and was generally in the range of 0.04 M to 0.08 M.

4.3. NMR Spectroscopy

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian VNMRS 300, VNMRS 400, INOVA 400, VNMRS 600 and Bruker Avance III HD 400 spectrometers. Proton chemical shifts are expressed in parts per million (δ scale) and are calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$: δ 7.26, CH_2Cl_2: δ 5.32, DMSO: δ 2.50). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = quintett, m = multiplet or combinations thereof. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian VNMRS 300, VNMRS 400, INOVA 400, VNMRS 600 and Bruker Avance III HD 400 spectrometers. Carbon chemical shifts are expressed in parts per million (δ scale) and are referenced to the carbon resonances of the solvent ($CHCl_3$: δ 77.16, CH_2Cl_2: δ 53.84, DMSO: δ 39.52). Additionally, to ^{1}H and ^{13}C NMR measurements, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond coherence (HMBC) were used to assist signal assignment. For further elucidation of 3D structures of the products, nuclear Overhauser enhancement spectroscopy (NOESY) was conducted. All raw FID files were processed and the spectra analyzed using the program *MestReNOVA 9.*0 *from Mestrelab Research S. L.*

4.4. Mass Spectometry

All mass spectra were measured by the analytic section of the Department of Chemistry, *Ludwig-Maximilians-Universität München*. High resolution mass spectra (HRMS) were recorded on a Thermo Finnigan MAT 95 spectrometer for electron impact ionization (EI) and on a Thermo Finnigan LTQ FT spectrometer for electrospray ionization (ESI). The mass of the detected ion given in dependency on the ionic charge in form of m/z. The method used is reported at the relevant section of the experimental section.

4.5. IR Spectroscopy

Infrared (IR) spectra were recorded on a *PerkinElmer* Spectrum BX II FT-IR system. If required, substances were dissolved in dichloromethane prior to direct application on the ATR unit. Data are presented as follows: frequency of absorption (cm^{-1}), and intensity of absorption (*br* = broad, *vs* = very strong, *s* = strong, *m* = medium, *w* = weak).

4.6. Optical Rotation

Optical rotation Optical rotation values were recorded on a *PerkinElmer 241 or Anton Paar MCP 200* polarimeter. The specific rotation is calculated as follows:

$$[\alpha]_{\lambda}^{\varphi} = \frac{[\alpha] \cdot 100}{c \cdot d}$$

Thereby, the wavelength λ is reported in nm and the measuring temperature φ in °C. α represents the recorded optical rotation, *c* the concentration of the analyte in 10 mg/mL and *d* the length of the cuvette in dm. Thus, the specific rotation is given in 10^{-1}·deg·cm^2·g^{-1}. Usage of the sodium D line (λ = 589 nm) is indicated by D instead of the wavelength in nm. The respective concentration as well as the solvent is reported at the relevant section of the experimental section.

4.7. Melting Point

Melting points (m.p.) were determined on a B-450 melting point apparatus from *BÜCHI Labortechnik AG*. The values are uncorrected.

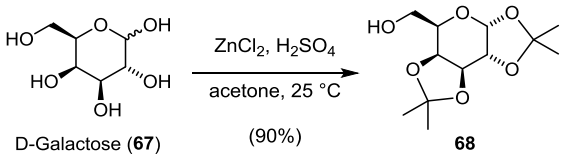
4.8. X-ray

X-Ray structural analyses were performed on a BrukerD8Venture instrument using Mo-K_α radiation.

4.9. Reaction Procedures

4.9.1. Synthesis of D-Fucose (31)

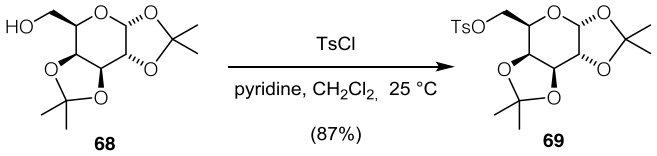
1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose 68



To a solution of $ZnCl_2$ (22.7g, 0.170 mol,1.50 equiv) in acetone (0.23 L) was added H_2SO_4 (770 µL, 14.5 mmol, 0.130 equiv) and D-galactose (**67**) (20.0 g, 0.110 mmol, 1 equiv) at 25 °C. After 16 hours, saturated aqueous sodium bicarbonate solution (0.20 L) was added dropwise over 30 min. The resulted suspension was filtered through a pad of celite and the pad washed with acetone (0.15 L). The filtrate was concentrated to half its volume and extracted with ether (3 × 250 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to afford a colorless oil. The crude product was purified by flash column chromatography (25% ethyl acetate in hexanes) to afford **68** (26 g, 90%) as a colorless oil.

The obtained analytical data was in full accordance with the values reported in the literature.[45]

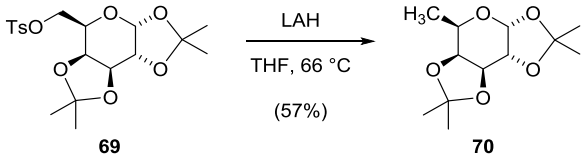
1,2:3,4-Di-O-isopropylidene-6-O-(4-toluenesulfonyl)-α-D-galactopyranose 69



Diacetonide **68** (26.0 g, 99.9 mmol, 1 equiv) was dissolved in a mixture of dichloromethane and pyridine (v/v = 1:3, 400 mL) at 0 °C. Tosylchloride (21.0 g, 0.110 mmol, 1.10 equiv) was added and the reaction mixture allowed to warm to 25 °C. After 4.5 h, water (50 mL) was added and the mixture stirred for another 30 minutes. Additional water (50 mL) was added and the layers separated. The aqueous layer was extracted with diethyl ether (2 × 200 mL). The combined organic layers were washed with aqueous hydrochloric acid (0.5 M, 2 × 150 mL), water (150 mL) and saturated aqueous sodium chloride solution (150 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford a clear oil. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to yield **69** (36 g, 87%) as a colorless oil.

The obtained analytical data was in full accordance with the values reported in the literature.[45]

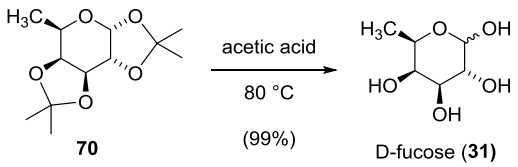
1,2:3,4-Di-O-isopropylidene-α-D-fucopyranose 70



A solution of tosyl fucoside **69** (35.0 g, 84.4 mmol, 1 equiv) was dissolved in tetrahydrofuran (120 mL) and the mixture was cooled to 0 °C. A suspension of lithium aluminiumhydride (0.75 M in tetrahydrofuran, 350 mL, 264 mmol, 3.15 equiv) was added dropwise and the resulting mixture was heated at reflux. After 3 h, the mixture was cooled to 0 °C and the excess lithium aluminiumhydride quenched with aqueous sodium hydroxide solution (15%, 9.9 mL) and water (30 mL). The suspension was diluted with diethyl ether (350 mL), filtered through a pad of celite and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% to 15% ethyl acetate in hexanes) to afford the **70** (11.7 mg, 57%) as a colorless oil.

The obtained analytical data was in full accordance with the values reported in the literature.[45]

D-fucose (31)

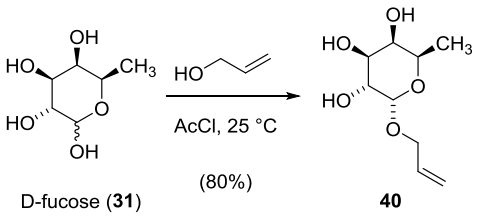


A solution of diacetonide **70** (10.0 g, 40.9 mmol, 1 equiv) was dissolved in aqueous acetic acid (80%, 180 mL) and the mixture was heated at 80 °C. After 6 h, the mixture was concentrated and dried by azeotropic distillation (toluene) to afford **31** (4.4 g, 99%) as a colorless oil. The crude product used in the next step without purification.

The obtained analytical data was in full accordance with the values from commercially available D-fucose.

4.9.2. Synthesis of carbohydrate precursors

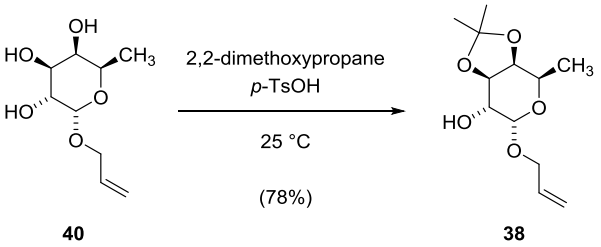
1-*O*-Allyl-α-D-fucopyranose (40)



Acetyl chloride (383 µl, 4.87 mmol, 2.00 equiv) was added to allyl alcohol (2.1 mL) at 0 °C. After 1 h, D-fucose (400 mg, 2.44 mmol, 1 equiv) was added in two equal portions. After 12 h, the suspension was diluted with saturated sodium bicarbonate solution (2 mL) and concentrated. The residue was purified by flash column chromatography on silica gel (10% methanol in dichloromethane) to afford **40** (396 mg, 80%) as a white solid.

The obtained analytical data was in full accordance with the values reported in the literature. [3]

1-Allyl-3,4-*O*-isopropylidene-α-D-fucopyranoside 38



Allyl fucoside **40** (30.0 mg, 0.147 mmol, 1 equiv) was dissolved in 2,2-dimethoxypropane (0.900 mL, 0,734 mmol, 5.00 equiv) and *p*-toluenesulfonic acid monohydrate (1.00 mg, 20.0 µmol, 0.110 equiv) added at 25 °C. After 2 h, the reaction mixture was diluted with dichloromethane (5 mL) and saturated sodium bicarbonate solution (3 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to afford a yellow oil and the crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes), to yield **38** (28 mg, 78%) as a white solid.

TLC: (28% ethyl acetate in hexanes): R_f = 0.31 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91 (dddd, *J* = 17.0, 10.4, 6.1, 5.3 Hz, 1H), 5.29 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.21 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.87 (d, *J* = 3.9 Hz, 1H), 4.28–4.19 (m, 2H), 4.14 (qd, *J* = 6.7, 2.3 Hz, 1H), 4.05 (dq, *J* = 6.7, 2.2 Hz, 2H), 3.79 (td, *J* = 6.8, 3.9 Hz, 1H), 2.29 (d, J = 7.0 Hz, 1H), 1.51 (s, 3H), 1.35 (s, 3H), 1.31 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.9, 117.8, 109.3, 96.8, 76.3, 75.8, 69.6, 68.6, 64.1, 27.9, 26.1, 16.4.

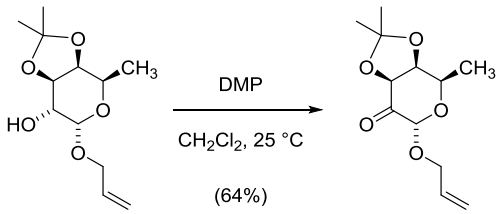
m.p.: 47 – 48 °C

$[\alpha]_D^{20}$= +20.1° (c=0.52, $CHCl_3$)

HR-MS (ESI): calcd for $C_{12}H_{20}O_5$ $[M + H]^+$ 245.1383; found: 245.1389.

IR (Diamond-ATR, neat): υ_{max}^{u} = 3420 (br), 2990 (s), 2950 (s), 1452 (m), 1388 (vs), 1309 (m), 1285 (vs), 1221 (vs), 1989 (s), 1152 (s), 1097 (vs), 1005 (vs), 912 (m), 902 (s), 772 (m), 696 (w) cm^{-1}.

1-Allyl-3,4-*O*-isopropylidene-α-D-fucopyranoside-2-ulose 41



Acetonide **38** (20.0 mg, 0.0820 mmol, 1 equiv) was dissolved in dichloromethane (1 mL) at 25 °C. Dess–Martin periodinane (104 mg, 0.246 mmol, 3.00 equiv) was added and the resulting suspension stirred for 3 h. The reaction mixture was diluted with saturated sodium bicarbonate solution (3 mL) and dichloromethane (3 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to afford a yellow oil and the crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes), to yield **41** (11 mg, 56%) as a colorless oil.

TLC: (28% ethyl acetate in hexanes): R_f = 0.35 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00–5.79 (m, 1H), 5.37–5.28 (m, 1H), 5.25 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.81 (s, 1H), 4.65 (d, *J* = 5.5 Hz, 1H), 4.48 (qd, *J* = 6.7, 2.0 Hz, 1H), 4.36 (dd, *J* = 5.6, 2.0 Hz, 1H), 4.29–4.20 (m, 1H), 4.13–4.04 (m, 1H), 1.45 (s, 3H), 1.40 (d, *J* = 6.7 Hz, 3H), 1.38 (s, 3H).

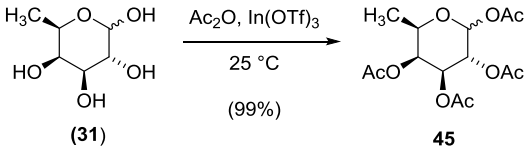
^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.5, 133.0, 118.7, 110.7, 98.8, 80.3, 75.6, 69.0, 64.0, 27.4, 26.3, 16.3.

$[\alpha]_D^{20}$= +36.8° (c=0.78, $CHCl_3$)

HR-MS (ESI): calcd for $C_{12}H_{18}O_5$ $[M + H]^+$ 243.1227; found: 243.129.

IR (Diamond-ATR, neat): υ_{max}^{u} = 2990 (s), 2950 (s), 1750 (s), 1700 (vs), 1683 (vs), 1388 (vs), 1311 (s), 1285 (vs), 1221 (vs), 1989 (s), 1152 (s), 1097 (vs), 1011 (s), 902 (s), 772 (m), 697 (w) cm^{-1}.

1,2,3,4-Tetra-*O*-acetyl-α-D-fucopyranose 45

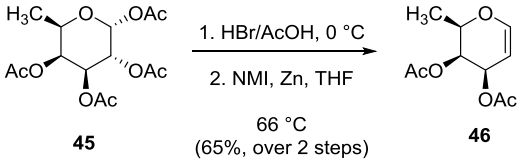


(**31**) **45**

D-fucose (**31**) (3.50 g, 21.3 mmol, 1 equiv) was dissolved in acetic anhydride (22 mL) and $In(OTf)_3$ (4.00 mg, 6.00 µmol, 0.00300 equiv) was added at 25 °C. The yellow mixture was stirred for 30 minutes, before the solution was diluted with dichlormethane (50 mL) and neutralized with saturated aqueous sodium bicarbonate solution (110 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to afford a yellow oil and the crude product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes), to yield **45** as (7.00 g, α/β ratio 3:1, 99%) as a colorless oil.

The obtained analytical data was in full accordance with the values reported in the literature.[4]

3,4-Di-*O*-acetyl-D-fucal 46



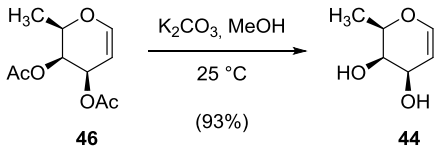
45 **46**

Acetylated D-fucopyranoside **45** (5.40 g, 16.4 mmol, 1 equiv) was dissolved in dichloromethane (15 mL). The solution was cooled to 0 °C and HBr (30% in acetic acid, 13.4 mL, 73.9 mmol, 4.50 equiv) was added dropwise over a period of 30 minutes and the reaction mixture was then allowed to warm to 25 °C. After 4 h, the mixture was cooled to 0 °C and diluted with water (20 mL) and dichloromethane (15 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (30 mL), followed by saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to afford a yellow syrup (assumed: 5.80 g, 16.4 mmol), which was used in the next step without purification.

Zinc dust (12.7 g, 98.4 mmol, 6.00 equiv) and 1-methylimidazole (1.36 g, 16.6 mmol, 1.01 equiv) were suspended in tetrahydrofuran (48 mL) at 25 °C and stirred for 15 minutes.
A solution of fucosyl bromide (assumed: 5.78 g, 16.4 mmol, 1 equiv) in tetrahydrofuran (17 mL) was added and the suspension was heated to reflux. After refluxing for 1 h, the mixture was cooled to 25 °C and filtered through a pad of celite. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to yield **46** (2.30 g, 65%) as a clear oil.

The obtained analytical data was in full accordance with the values reported in the literature.[5]

D-Fucal 44



46 **44**

Acetylated D-fucal **46** (1.50 g, 7.00 mmol, 1 equiv) was dissolved in methanol (49 mL) and potassium carbonate (580 g, 4.20 mmol, 0.60 equiv) added. The mixture was stirred at 25 °C for 3 h. The methanol was removed under reduced pressure and the residue was purified by

flash chromatography on silica gel (75% ethyl acetate in hexanes) to yield **44** (851 mg, 93%) as a white solid.

TLC: (80% ethyl acetate in hexanes): R_f = 0.37 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (d, *J* = 6.2, 1.7 Hz, 1H), 4.69 (dt, *J* = 6.2, 2.0 Hz, 1H), 4.46–4.31 (m, 1H), 4.04 (qd, *J* = 6.6, 0.9 Hz, 1H), 3.71 (ddd, *J* = 8.5, 4.7, 1.9 Hz, 1H), 2.33 (d, *J* = 9.4 Hz, 1H), 2.00 (d, *J* = 8.4 Hz, 1H), 1.38 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9, 103.4, 73.5, 68.5, 65.1, 17.0.

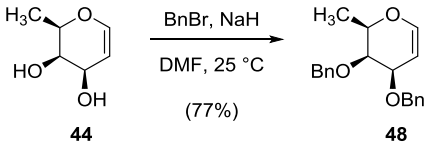
m.p.: 49 – 50 °C

$[\alpha]_D^{20}$= +10.5 (c=0.98, CH_2Cl_2)

HR-MS (ESI): calcd for ($C_6H_{10}O_3Na$) $[M + Na]^+$: 153.0522; found: 153.0524.

IR (Diamond-ATR, neat): υ_{max}^{μ} = 3030 (br), 2995 (w), 2930 (w), 1745 (br), 1650 (m), 1375 (m), 1200 (br), 1090 (s), 1080 (m) cm^{-1}.

1,2-Di-*O*-benzyl-D-fucal 48



44 **48**

A solution of fucal **44** (450 mg, 3.46 mmol, 1 equiv) in *N*,*N*-dimethylformamide (18 mL) was cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 415 mg, 10.4 mmol, 3.00 equiv) was added. After 30 minutes, benzyl bromide (1.45 mL, 12.1 mmol, 3.50 equiv) was added and the suspension stirred for 14 h at 25 °C. The suspension was cooled to 0 °C and diluted with water (10 mL) and diethyl ether (15 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford a clear oil. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to yield **48** (830 mg, 77%) as a colorless oil.

TLC: (10% ethyl acetate in hexanes): R_f = 0.26 (UV, CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.26 (m, 10H), 6.37 (dd, *J* = 6.3, 1.8 Hz, 1H), 4.97 (d, *J* = 12.0 Hz, 1H), 4.83 (ddd, *J* = 6.3, 2.4, 1.6 Hz, 1H), 4.76–4.66 (m, 2H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.25 (ddt, *J* = 4.1, 2.7, 1.4 Hz, 1H), 4.05 (qt, *J* = 6.6, 1.5 Hz, 1H), 3.70 (dt, *J* = 3.8, 1.7 Hz, 1H), 1.27 (d, *J* = 6.6 Hz, 3H).

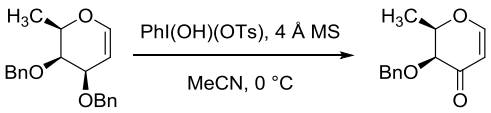
^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.7, 138.7, 138.6, 128.5, 128.5, 128.4, 127.8, 127.7, 127.6, 99.6, 73.8, 73.2, 73.0, 72.3, 70.9, 16.7.

$[\alpha]_D^{20}$= +40.2 (c=1.00, CH_2Cl_2)

HR-MS (ESI): calcd for $C_{20}H_{26}O_3N$ $[M + NH_4]^+$ 328.1907; found: 328.1914.

IR (Diamond-ATR, neat): υ_{max}^{u} = 3030 (w), 2870 (w), 1644 (m), 1496 (w), 1453 (m), 1382 (w), 1346 (m), 1233 (s), 1171 (m), 1100 (vs), 1064 (vs), 1027 (s), 735 (s), 697 (vs) cm^{-1}.

(–)-(2S,3R)-3-(Benzyloxy)-2-methyl-2,3-dihydro-4*H*-pyran-4-one 35



48 (91%) **35**

A suspension of 3,4-di-*O*-benzylfucal **48** (725 mg, 2.34 mmol, 1 equiv) and grinded 4 Å molecular sieves (440 mg) in acetonitrile (47 mL) was stirred at 0 °C for 15 minutes. [Hydroxy(tosyloxy)iodo]benzene (1.10 g, 2.80 mmol, 1.20 equiv) was added in one portion and the suspension was allowed to warm to 25 °C. After 75 minutes, the mixture was filtered through celite and rinsed with diethyl ether (15 mL). The filtrate was concentrated and the residue was immediately subjected to flash column chromatography on silica gel (10% ethyl acetate in hexanes) to furnish **35** (465 mg, 91%).

TLC: (15% ethyl acetate in toluene): R_f = 0.51 (UV, CAM, ANIS).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 5H), 5.42 (dd, *J* = 6.0, 1.5 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.44 (qdd, *J* = 6.7, 2.6, 0.8 Hz, 1H), 3.51 (dd, *J* = 2.6, 1.5 Hz, 1H), 1.46 (d, *J* = 6.8 Hz, 3H).

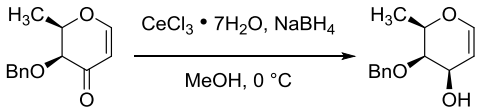
^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.6, 163.1, 137.2, 128.4, 128.3, 128.0, 104.6, 78.2, 76.6, 72.0, 15.0.

$[\alpha]_D^{20}$= +4.3° (c=1.04, CH_2Cl_2)

HR-MS (ESI): calcd for $C_{13}H_{15}O_3$ $[M + H]^+$: 219.1016; found: 219.1021.

IR (Diamond-ATR, neat): υ_{max}^{μ} = 3064 (w), 3032 (w), 2987 (w), 2938 (w), 2878 (w), 1676 (vs), 1595 (vs), 1454 (m), 1411 (m), 1281 (s), 1230 (s), 1154 (m), 1116 (m), 1085 (m), 1054 (vs), 1027 (m), 918 (m), 813 (m), 741 (m), 698 (m) cm^{-1}.

4-*O*-Benzyl-D-fucal 57



35 (77%) **57**

A solution of pyranone **35** (247 mg, 1.13 mmol, 1 equiv) in methanol (7 mL) was cooled to 0 °C and cerium(III) chloride heptahydrate (422 mg, 1.13 mmol, 1 equiv) was added. Sodium borohydride (42.8 mg, 1.13 mmol, 1 equiv) was added in two equal portions within 15 minutes. After 1 h, the mixture was quenched with water (2 mL) and the suspension filtered through celite. The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 8 mL.). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford a colorless oil. The crude was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes) to afford **57** (191 mg, 77%) as a white solid.

TLC: (27% ethyl acetate in hexanes): R_f = 0.21 (CAM, ANIS).

^{1}H NMR (400 MHz, $CDCl_3$): 7.46–7.27 (m, 5H), 6.35 (d, *J* = 6.2, 1.6 Hz, 1H), 4.83–4.75 (m, 2H), 4.70 (ddd, *J* = 6.2, 2.5, 1.4 Hz, 1H), 4.45–4.31 (m, 1H), 4.07 (qt, *J* = 6.7, 1.3 Hz, 1H), 3.65 (dt, *J* = 5.1, 1.6 Hz, 1H), 2.19 (dd, *J* = 9.8, 1.3 Hz, 1H), 1.32 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 128.5, 128.2, 127.9, 127.6, 99.3, 74.8, 74.0, 73.6, 72.9, 56.6, 16.6.

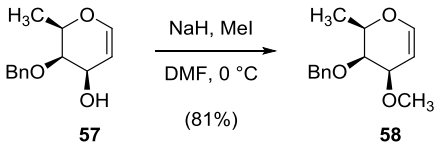
m.p.: 51 – 53 °C

$[\alpha]_D^{20}$= – 42.1 (c=1.00, CH_2Cl_2)

HR-MS (ESI): calcd for $C_{13}H_{20}O_3N$ $[M + NH_4]^+$: 238.1437; found: 238.1438.

IR (Diamond-ATR, neat): υ^{u}_{max} = 3321 (br), 2993 (w), 2917 (w), 1643 (s), 1497 (w), 1453 (m), 1357 (s), 1232 (vs), 1168 (s), 1094 (vs), 1083 (vs), 1069 (vs), 1059 (vs), 1041 (s), 960 (m), 848 (m), 793 (m), 741 (vs), 697 (s) cm^{-1}.

4-*O*-Benzyl-3-*O*-methyl-D-fucal 58



57 **58**

A solution of monoprotected fucal **57** (181 mg, 0.822 mmol, 1 equiv) was dissolved in *N*,*N*-dimethylformamide (8 mL) and sodium hydride (60% dispersion in mineral oil, 49.0 mg, 1.23 mmol, 1.50 equiv) added at 0 °C. After 30 minutes, iodomethane (117mg, 0.822, 1 equiv) was added dropwise and the suspension was allowed to warm to 25 °C and stirred for 3 h. Upon completion the reaction mixture was diluted with water (5 mL) and diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford a yellow oil. The crude was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **58** (161 mg, 81%) as a colorless oil.

TLC: (20% ethyl acetate in hexanes): R_f = 0.34 (CAM).

^{1}H NMR (400 MHz, C_6D_6): δ = 7.43–7.25 (m, 2H), 7.15–7.05 (m, 3H), 6.26 (d, *J* = 6.3, 1.7 Hz, 1H), 4.87 (d, *J* = 11.7 Hz, 1H), 4.72 (ddd, *J* = 6.3, 2.6, 1.5 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 3.84 (qt, *J* = 6.5, 1.6 Hz, 1H), 3.72 (td, *J* = 2.7, 1.4 Hz, 1H), 3.34 (dt, *J* = 3.9, 1.8 Hz, 1H), 3.14 (s, 3H), 1.32 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, C_6D_6): δ = 144.6, 128.5, 128.2, 127.9, 127.6, 99.3, 74.8, 74.0, 73.6, 72.9, 56.6, 16.6.

$[\alpha]_D^{20}$= – 36.6° (c=1.00, CH_2Cl_2)

HR-MS (ESI): calcd for $C_{14}H_{18}O_3$ $[M + H]^+$: 234.1256; found: 234.1259.

IR (Diamond-ATR, neat): υ^{μ}_{max} = 2981 (w), 2934 (m), 2884 (m), 2822 (w), 1645 (s), 1496 (w), 1454 (m), 1398 (m), 1381 (w), 1348 (m), 1234 (s), 1193 (m), 1171 (m), 1106 (vs), 1070 (vs), 1026 (s), 987 (m), 798 (m), 735 (s), 698 (s) cm^{-1}.

4-*O*-Benzyl-3-*O*-methyl-1-*O*-(tert-butyldimethylsilyl)-D-fucopyranose 60

58 (51% over two steps) **60**

Osmium tetroxide (4% solution in water, 40.0 µl, 0.0500 equiv) was added to a solution of fucal **58** (30.0 mg, 0.128 mmol, 1 equiv) and *N*-methylmorpholine *N*-oxide (23.0 mg, 0.192 mmol, 1.50 equiv) in acetone (3 mL). After 14 h, the reaction mixture was diluted with saturated aqueous sodium bicarbonate solution. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford a slightly yellow oil. The crude was used for the next step without further purification.

A solution of assumed triol **59** (20.0 mg, 0.075 mmol, 1 equiv) in dichloromethane (0.5 mL) was cooled to 0 °C. Imidazole (11.0 mg, 0.162 mmol, 2.18 equiv) and *tert*-butyldimethylsilyl chloride (12.4 mg, 82.0 µmol, 1.10 equiv) were added subsequently and the reaction mixture allowed to warm to 25 °C. After 3 h, water (3 mL) and ethyl acetate (5 mL) was added and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **60** (17.0 mg, 51%) as a colorless oil.

TLC: (20% ethyl acetate in hexanes): R_f = 0.31 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.24 (m, 5H), 4.89 (d, *J* = 11.7 Hz, 1H), 4.68 (d, *J* = 11.8 Hz, 1H), 4.44 (d, *J* = 7.3 Hz, 1H), 3.77 (ddd, *J* = 9.4, 7.4, 1.6 Hz, 1H), 3.62 (d, *J* = 2.9 Hz, 1H), 3.48 (s, 3H), 3.54–3.41 (m, 1H), 3.16 (dd, *J* = 9.9, 2.9 Hz, 1H), 2.22 (d, *J* = 1.8 Hz, 1H), 1.21 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 9H), 0.13 (d, *J* = 3.4 Hz, 6H).

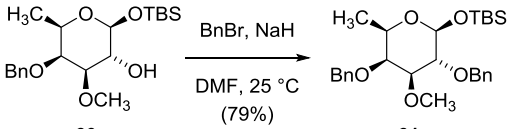
^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7, 128.5, 128.3, 127.7, 98.3, 84.7, 74.7, 74.6, 72.8, 70.9, 58.3, 26.0, 18.3, 17.2, -3.9, -4.8.

$[\alpha]_D^{20}$ = +9.5° (c=0.99, CH_2Cl_2)

HR-MS (ESI): calcd for $C_{19}H_{36}O_5N$ $[M + NH_4]^+$: 386.2357; found: 386.2359.

IR (Diamond-ATR, neat): υ_{max}^{u} =3469 (br), 2930 (m), 2885 (m), 2856 (m), 1496 (w), 1472 (w), 1378 (w), 1360 (m), 1251 (m), 1178 (w), 1140 (m), 1119 (s), 1075 (vs), 1028 (m), 986 (w), 837 (vs), 781 (s), 731 (m), 697 (m) cm^{-1}.

2,4-*O*-Dibenzyl-3-*O*-methyl-1-*O*-(tert-butyldimethylsilyl)-D-fucopyranose 61



60 **61**

A solution of secondary alcohol **60** (14.0 mg, 0.0360 mmol, 1 equiv) was dissolved in *N*,*N*-dimethylformamide (0.4 mL) was cooled to 0°C. Sodium hydride (60% dispersion in mineral oil, 3.00 mg, 0.0550 mmol, 1.50 equiv) was added. After 30 minutes, Benzyl bromide (10.0 µl, 0.0730 mmol, 2.00 equiv) was added and the reaction mixture allowed to warm to 25 °C. After 4 h, the suspension was diluted with ethyl acetate (2 mL) and water (3 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **61** (14 mg, 79%) as a colorless oil.

TLC: (10% ethyl acetate in hexanes): R_f = 0.32 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.27 (m, 10H), 4.91 (d, *J* = 5.8 Hz, 1H), 4.88 (d, *J* = 5.8 Hz, 1H), 4.69 (d, *J* = 11.9 Hz, 1H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.24 (d, *J* = 7.4 Hz, 1H), 3.86 (dd, *J* = 9.4, 7.5 Hz, 1H), 3.61 (d, *J* = 2.7 Hz, 1H), 3.45 (q, *J* = 6.4 Hz, 1H), 3.40 (s, 3H), 3.04 (dd, *J* = 9.5, 2.8 Hz, 1H), 1.23 (d, *J* = 6.4 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.04 (s, 3H).

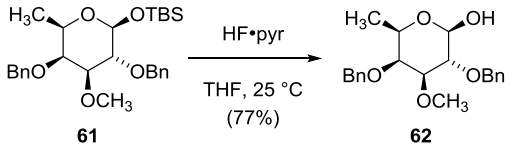
^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9, 137.8, 128.7, 128.4, 128.2, 128.2, 127.7, 127.5, 102.6, 86.3, 74.4, 74.4, 71.9, 70.6, 70.4, 58.1, 26.0, 18.5, 17.2, -4.3, -4.4.

$[\alpha]_D^{20}$ = – 16.5° (c=1.04, CH_2Cl_2)

HR-MS (ESI): calcd for $C_{27}H_{44}O_5NSi$ $[M + NH_4]^+$: 490.2983; found: 490.2994.

IR (Diamond-ATR, neat): υ_{max}^{u} = 3030 (w), 2928 (m), 2884 (m), 2855 (m), 1497 (w), 1472 (w), 1454 (m), 1388 (w), 1358 (m), 1306 (w), 1250 (m), 1200 (w), 1142 (m), 1120 (m), 1105 (m), 1089 (m), 1071 (vs), 1046 (m), 1006 (m), 873 (m), 836 (s), 778 (s), 735 (m), 697 (m) cm^{-1}.

2,4-*O*-Dibenzyl-3-*O*-methyl-D-fucopyranose 62



61 **62**

A solution of protected alcohol **61** (12.0 mg, 0.0250 mmol, 1 equiv) in tetrahydrofuran (0.5 mL) was cooled to –10 °C. HF•pyr (70% in pyridine, 0.070 mL, 2.54 mmol, 100 equiv) was added and the reaction mixture allowed to warm to 25 °C. After 18 h, the reaction mixture was diluted with dichloromethane and saturated sodium bicarbonate solution (9 mL). Solid sodium bicarbonate was added until no further gas evolution was observed. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (60% ethyl acetate in hexanes) to afford **62** (7 mg, 77%) as a colorless oil.

TLC: (75% ethyl acetate in hexanes): R_f = 0.36 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.27 (m, 5H), 4.92 (dd, *J* = 15.8, 11.8 Hz, 1H), 4.68 (d, *J* = 11.8 Hz, 1H), 4.61 (d, *J* = 11.9 Hz, 0H), 4.30 (d, *J* = 7.6 Hz, 0H), 4.00–3.88 (m, 1H), 3.65 (d, *J* = 2.8 Hz, 0H), 3.51 (q, *J* = 6.7 Hz, 1H), 3.48 (s, 0H), 3.18 (dd, *J* = 9.8, 2.9 Hz, 1H), 1.27 (d, *J* = 6.5 Hz, 2H).

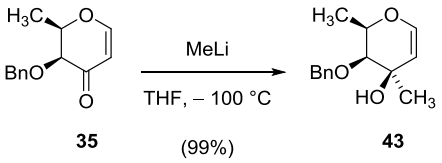
^{13}C NMR (100 MHz, $CDCl_3$): δ = 128.4, 128.2, 128.1, 127.8, 127.7, 101.7, 84.7, 74.6, 74.2, 70.8, 70.5, 58.1, 17.0.

$[\alpha]_D^{20}$ = – 21.5 (c=0.87, CH_2Cl_2)

HR-MS (ESI): calcd for $C_{27}H_{44}O_5NSi$ $[M + NH_4]^+$: 490,2983; found: 490.2994.

IR (Diamond-ATR, neat): υ^{u}_{max} = 3460 (br), 3030 (w), 2928 (m), 2865 (m), 1555 (m), 1463 (m), 1080 (m), 1065 (vs), 1040 (m), 996 (m), 865 (m), 830 (s), 770(s), 737 (m), 697 (m) cm^{-1}.

4-*O*-Benzyl-3-*C*-methyl-D-fucal 43



35 (99%) **43**

Pyranone **35** (200 mg, 0.916 mmol, 1 equiv) was dissolved in tetrahydrofuran (10 mL) and the solution cooled to –100 °C. Methyllithium (1.5 M in diethyl ether, 0.860 mL, 1.37 mmol, 1.50 equiv) was added dropwise. After 30 minutes, saturated aqueous ammonium chloride solution was added at –100 °C and the reaction mixture was allowed to warm to 25 °C. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford a slighty yellow oil. The crude was purified by flash column chromatography on silica gel (15% ethyl acetate in toluene) to afford **43** (213 mg, 99%) as a colorless oil.

TLC: (15% ethyl acetate in toluene): R_f = 0.41 (CAM, ANIS).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.29 (m, 5H), 6.28 (d, *J* = 6.2 Hz, 1H), 4.85–4.75 (m, 2H), 4.67 (dd, *J* = 6.2, 1.8 Hz, 1H), 4.14–4.04 (m, 1H), 3.28 (s, 1H), 2.59 (d, *J* = 1.1 Hz, 1H), 1.37 (s, 3H), 1.32 (d, *J* = 6.6 Hz, 3H).

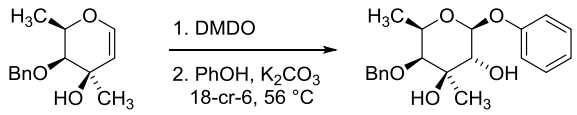
^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 137.7, 128.7, 128.4, 128.4, 128.2, 107.5, 81.6, 76.3, 72.2, 67.7, 29.1, 29.0, 17.4.

$[\alpha]_D^{20}$= +7.9° (c=0.98, CH_2Cl_2)

HR-MS (ESI): calcd for $C_{14}H_{18}O_3$ $[M + H]^+$: 234.1256; not found.

IR (Diamond-ATR, neat): υ^{u}_{max} = 3309 (br), 2899 (w), 1641 (s), 1503 (w), 1450 (m), 1357 (s), 1222 (vs), 1175 (s), 1094 (vs), 1080 (vs), 1050 (vs), 1045 (vs), 1040 (s), 793 (m), 731 (vs), 697 (s) cm^{-1}.

Phenyl-4-*O*-benzyl-3-*C*-methyl-β-D-fucopyranose 59



43 (56%) **49**

Phenol (22.0 mg, 0.235 mmol, 5.00 equiv), potassium carbonate (65.0 mg, 0.469 mmol, 10.0 equiv) and 18-crown-6 (0.1 mg, 5.00 µmol, 0.100 equiv) were suspended in acetone (1.5 mL) and heated at reflux for 3 h. In a separate flask tertiary alcohol **43** (11.0 mg, 0.0500 mmol, 1 equiv) was dissolved in acetone (0.2 mL) at 0 °C. Freshly prepared dimethyldioxirane solution (0.057 M in acetone, 0.990 mL, 0.0560 mmol, 1.20 equiv) was added dropwise to the solution and stirred for 30 minutes. The epoxide was concentrated by passing a stream of nitrogen over the reaction mixture at 0 °C and was subsequently dried under vacuum for 1 h. The epoxide was then redissolved in acetone (0.6 mL) and added a solution of phenoxide at 56 °C. After refluxing the mixture for additional 5 h, the mixture was allowed tocool to 25 °C and diluted with diethyl ether (5 mL) and filtered through celite. The filtrate was concentrated and the residue was taken up in ethyl acetate (10 mL) washed with aqueous sodium hydroxide solution (1 M, 10 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford a colorless oil. The crude was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford **49** (9 mg, 56%) as a clear oil.

TLC: (25% ethyl acetate in hexanes): R_f = 0.36 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.32 (m, 5H), 7.30 – 7.27 (m, 2H), 7.10–7.00 (m, 3H), 4.89 (d, *J* = 8.0 Hz, 1H), 4.85 (d, *J* = 11.3 Hz, 1H), 4.71 (d, *J* = 11.3 Hz, 1H), 4.01–3.96 (m, 1H), 3.89 (d, *J* = 8.0 Hz, 1H), 3.30 (d, *J* = 1.1 Hz, 1H), 2.66 (s, 1H), 2.27 (s, 1H), 1.39 (d, *J* = 6.5 Hz, 3H), 1.34 (s, 3H).

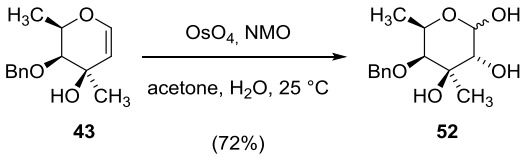
^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.6, 128.8, 128.3, 128.1, 122.8, 117.1, 100.4, 85.4, 74.5, 74.3, 70.2, 29.9, 18.6, 17.6, 1.2.

$[\alpha]_D^{20}$= – 44.1° (c=1.02, CH_2Cl_2)

HR-MS (ESI): calcd for $C_{20}H_{28}O_3N$ $[M + NH_4]^+$: 362.1962; found: 362.1961.

IR (Diamond-ATR, neat): υ_{max}^{u} = 3348 (br), 2904 (s), 2883 (s), 1500 (m), 1455 (m), 1439 (m), 1370 (s), 1321 (m), 1189 (m), 1054 (vs), 1006 (vs), 994 (s), 943 (vs), 891 (m), 754 (vs) cm^{-1}.

4-*O*-Benzyl-3-*C*-methyl-D-fucopyranose 52



43 (72%) **52**

Osmium tetroxide (4% solution in water, 0.260 ml, 0.0500 equiv) was added to a solution of tertiary alcohol **43** (200 mg, 0.854 mmol, 1 equiv) and *N*-methylmorpholine *N*-oxide (150 mg, 1.28 mmol, 1.50 equiv) in acetone (4 mL) at 25 °C. After stirring for 14 h, the reaction mixture was diluted with saturated aqueous sodium bicarbonate solution. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford a slightly yellow oil. The crude was purified by flash column chromatography on silica gel (75% ethyl acetate in hexanes) to afford **52** (165 mg, 72%) as colorless oil.

TLC: (80% ethyl acetate in hexanes): R_f = 0.16 (CAM, $KMnO_4$).

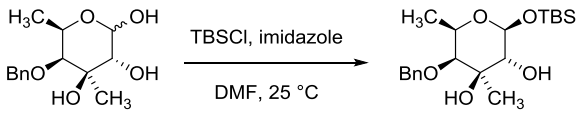
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.27 (m, 12H), 5.30 (d, J = 3.8 Hz, 1H), 4.81 (dd, J = 11.3, 7.1 Hz, 2H), 4.67 (dd, J = 11.3, 2.3 Hz, 2H), 4.60 (d, J = 7.9 Hz, 2H), 4.39–4.24 (m, 1H), 3.90 (qd, J = 6.4, 1.2 Hz, 1H), 3.80 (d, J = 4.1 Hz, 1H), 3.54 (d, J = 7.9 Hz, 1H), 3.34 (d, J = 1.4 Hz, 1H), 3.25 (d, J = 1.2 Hz, 1H), 1.40 (s, 3H), 1.35 (d, J = 6.5 Hz, 3H), 1.30 (d, J = 6.6 Hz, 3H), 1.27 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 128.8, 128.3, 128.2, 128.2, 95.9, 92.5, 85.5, 85.3, 74.3, 73.1, 72.6, 70.2, 65.9, 20.3, 18.5, 17.5, 17.3.

HR-MS (ESI): calcd for $C_{14}H_{24}O_5N$ $[M + NH_4]^+$: 286.1649; found: 286.1649.

IR (Diamond-ATR, neat): υ_{max}^{u} = 3047 (br), 3031 (w), 2980 (m), 2871 (m), 1722 (m), 1602 (s), 1584 (m), 1496 (s), 1463 (m), 1366 (s), 1285 (m), 1251 (s), 1071 (s), 1027 (s), 908 (m), 739 (s), 710(m) cm^{-1}.

4-*O*-Benzyl-3-*C*-methyl-1-*O*-(tert-butyldimethylsilyl)-D-fucopyranose 34



52 **34**

A solution of triol **52** (35.0 mg, 0.130 mmol, 1 equiv) in dichloromethane (0.5 mL) was cooled to 0 °C. Imidazole (18.0 mg, 0.264 mmol, 2.03 equiv) and *tert*-butyldimethylsilyl (22.0 mg, 0.146 mmol, 1.12 equiv) were added subsequently and the reaction mixture was allowed to warm to 25 °C. After 3 h, water (3 mL) and ethyl acetate (5 mL) were added and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **34** (35 mg, 70%) as a colorless oil.

TLC: (25% ethyl acetate in hexanes): R_f = 0.27 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.12 (m, 5H), 4.69 (d, *J* = 11.4 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.38 (d, *J* = 7.7 Hz, 1H), 3.68 (qd, *J* = 6.4, 1.2 Hz, 1H), 3.39 (dd, *J* = 7.7, 1.1 Hz, 1H), 3.08 (d, *J* = 1.2 Hz, 1H), 2.51 (s, 1H), 1.96 (s, 1H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.15 (s, 3H), 0.80 (s, 9H), 0.02 (d, *J* = 4.3 Hz, 6H).

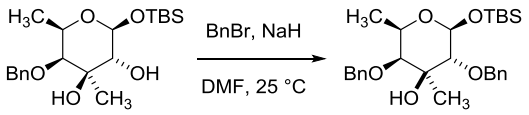
^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 128.7, 128.1, 128.1, 96.8, 85.8, 76.8, 76.7, 74.1, 69.8, 26.0, 18.5, 18.3, 17.5, -3.9, -4.8.

$[\alpha]_D^{20}$ = +14.4° (c=1.00, CH_2Cl_2)

HR-MS (ESI): calcd for $C_{20}H_{38}O_5N$ $[M + NH_4]^+$: 400.2514; found: 400.2518.

IR (Diamond-ATR, neat): υ_{max}^{u} = 3451 (br), 2928 (m), 2883 (m), 2856 (m), 1496 (w), 1471 (w), 1462 (w), 1360 (w), 1250 (m), 1194 (m), 1142 (m), 1075 (vs), 1027 (m), 974 (w), 907 (w), 855 (s), 837 (s), 781 (m), 734 (w), 696 (w), 669 (w) cm^{-1}.

2,4-*O*-Dibenzyl-3-*C*-methyl-1-*O*-(tert-butyldimethylsilyl)-D-fucopyranose 53



34 **53**

A solution of diol **34** (28.0 mg, 0.0730 mmol, 1 equiv) in *N*,*N*–dimethylformamide (0.7 mL) was cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 4.00 mg, 0.0880 mmol, 1.20 equiv) was added. After 30 minutes, benzyl bromide (20.0 µl, 0.146 mmol, 2.00 equiv) was added and the reaction mixture was allowed to warm to 25 °C. After 4 h, the suspension was diluted with ethyl acetate (4 mL) and water (3 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **53** (16 mg, 46%) as a colorless oil as an anomeric mixture.

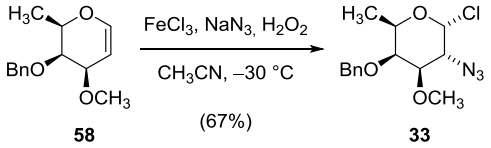
^{1}H NMR (400 MHz, $CDCl_3$): major anomer β: δ = 7.42–7.23 (m, 10H), 4.90 (d, *J* = 11.9 Hz, 1H), 4.83 (d, *J* = 11.5 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.27 (d, *J* = 7.7 Hz, 1H), 3.77 (qd, *J* = 6.4, 1.2 Hz, 1H), 3.60 (d, *J* = 7.7 Hz, 1H), 3.23 (d, *J* = 1.2 Hz, 1H), 2.37 (d, *J* = 1.0 Hz, 1H), 2.14 (s, 1H), 1.31 (d, *J* = 6.4 Hz, 3H), 1.19 (d, *J* = 0.8 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), -0.03 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 128.7, 128.3, 128.2, 128.2, 128.2, 127.6, 101.5, 86.0, 76.0, 75.0, 70.8, 69.4, 26.5, 26.06, 26.0, 19.4, 18.5, 17.5, -4.12, -4.62.

HR-MS (ESI): calcd for $C_{27}H_{44}O_5NSi$ $[M + NH_4]^+$: 490.2983; found: 490.2984.

IR (Diamond-ATR, neat): υ_{max}^{μ} = 2930 (m), 2887 (m), 2856 (m), 1495 (w), 1472 (w), 1378 (w), 1360 (m), 1251 (m), 1178 (w), 1140 (m), 1119 (s), 1075 (vs), 1028 (m), 986 (w), 907 (w), 837 (vs), 781 (s), 732 (m), 698 (m) cm^{-1}.

2-Azido-4-*O*-benzyl-2-deoxy-3-*O*-methyl-2-desoxy-D-fucopyranosyl chloride 33



A solution of fucal **58** (20.0 mg, 0.0850 mmol, 1 equiv) in acetonitrile (0.8 mL) was cooled to –40 °C. $FeCl_3 \cdot H_2O$ (20.0 mg, 0.0770 mmol, 0.900 equiv), sodium azide (6.00 mg, 0.0940 mmol, 1.10 equiv) and hydrogen peroxide (30% solution in water, 10.0 µL, 0.0940, 1.10 equiv) were added in sequence. After 4 h, the reaction mixture was diluted with ethyl acetate (4 mL) and the suspension was allowed to warm to 25 °C. The suspension was washed with water (3 × 4 mL) and saturated aqueous sodium bicarbonate (5 mL) and saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford **33** a slightly yellow oil (18 mg, 67%) which was used in the next step without purification.

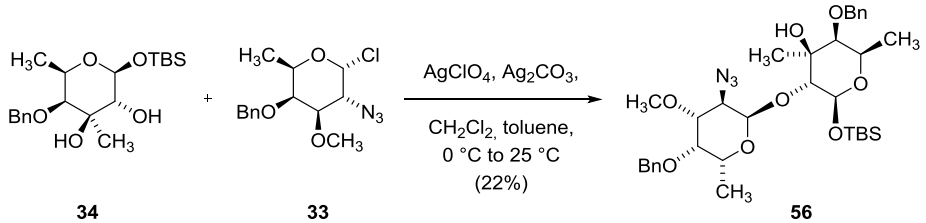
TLC: (20% ethyl acetate in hexanes): R_f = 0.43 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.28 (m, 5H), 6.12 (d, *J* = 3.8 Hz, 1H), 4.95 (d, *J* = 11.3 Hz, 1H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.21–4.15 (m, 1H), 4.12 (dd, *J* = 10.3, 3.8 Hz, 1H), 3.80 (dd, *J* = 2.8, 1.2 Hz, 1H), 3.77–3.71 (m, 2H), 3.55 (s, 3H), 1.25 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 128.5, 128.4, 128.1, 95.1, 80.0, 75.2, 74.5, 70.4, 60.4, 57.7, 16.6.

IR (Diamond-ATR, neat): υ_{max}^{u} = 2987 (w), 2936 (w), 2111 (vs), 1725 (w), 1497 (w), 1454 (m), 1381 (w), 1310 (w), 1253 (m), 1156 (m), 1118 (vs), 1103 (s), 1066 (s) 1027 (m), 969 (m), 935 (w), 818 (w), 740 (m), 698 (m) cm^{-1}.

2-Azido-4-*O*-benzyl-2-deoxy-3-*O*-methyl-2-desoxy-D-fucopyranosyl-(1→2)-4-*O*-Benzyl-3-*C*-methyl-1-*O*-(tert-butyldimethylsilyl)-D-fucopyranoside 56



Glycosyl acceptor **34** (15.0 mg, 0.0390 mmol, 1.75 equiv), grinded 4 Å molecular sieves (180 mg) and silver carbonate (19.0 mg, 0.0700 mmol, 3.08 equiv) were dissolved in a mixture of

dichlormethane and toluene (v/v = 2:3, 0.55 mL) and stirred for 30 minutes in the dark. Silverperchlorate (5.00 mg, 0.0240 mmol, 1.07 equiv) dissolved in toluene (0.15 mL) was added to the reaction mixture. After 40 minutes, a solution of fucosyl chloride **33** (7 mg, 0.024 mmol, 1 equiv) in a mixture of dichloromethane and toluene (v/v = 1:1, 0.5 mL) was added and the reaction mixture allowed to warm to 25 °C. After 16 h, the mixture was diluted with dichloromethane (5 mL) and filtered through celite. The filtrate was washed with water (4 mL) and saturated aqueous sodium bicarbonate solution (4 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford a slightly yellow oil (16 mg). The crude was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford **56** (3 mg, 22%) as colorless oil.

TLC: (20% ethyl acetate in hexanes): R_f = 0.26 (CAM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.29 (m, 10H), 5.41 (d, *J* = 3.7 Hz, 1H), 4.88 (dd, *J* = 11.6, 9.4 Hz, 3H), 4.68 (d, *J* = 7.7 Hz, 1H), 4.63 (s, 1H), 4.59 (d, *J* = 5.8 Hz, 1H), 4.56 (s, 1H), 4.36 (q, *J* = 6.4 Hz, 1H), 3.82–3.66 (m, 3H), 3.58 – 3.52 (m, 2H), 3.50 (s, 3H), 3.16 (s, 1H), 2.55 (s, 1H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.22 (s, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 128.5, 128.4, 128.1, 98.3, 97.2, 86.8, 80.1, 79.1, 77.1, 76.9, 75.5, 75.2, 69.7, 66.9, 59.6, 57.7, 19.3, 17.5, 16.9.

HR-MS (ESI): calcd for $C_{34}H_{55}O_8N_4Si$ $[M + NH_4]^+$: 675.3783; found: 675.3805.

IR (Diamond-ATR, neat): υ^{u}_{max} = 2985 (w), 2936 (w), 2876 (m), 2856 (m), 2111 (vs), 1725 (w), 1497 (w), 1470 (w), 1453 (s), 1377 (w), 1310 (w), 1253 (m), 1190 (w), 1156 (m), 1118 (vs), 1103 (s), 1070 (vs), 1066 (s) 1027 (m), 969 (m), 934 (w), 818 (w), 740 (m), 698 (m) cm^{-1}.

5. References

[1] D. Mal, A. Patra, H. Roy, *Tetrahedron Lett.* **2004**, *45*, 7895–7898.

[2] T. Hosoya, E. Takashiro, T. Matsumoto, S. Keisuke, *J. Am. Chem. Soc.* **1994**, *116*, 1004–1015.

[3] C. a. James, V. Snieckus, *Tetrahedron Lett.* **1997**, *38*, 8149–8152.

[4] B. E. Leach, K. M. Calhoun, L. E. Johnson, C. M. Teeters, W. G. Jackson, *J. Am. Chem. Soc.* **1953**, *75*, 4011–4012.

[5] J. Douros, G. L. Neil, S. L. Crampton, M. I. Robinson, *Cancer Res.* **1977**, *37*, 1666–1672.

[6] A. Lorico, B. H. Long, *Eur. J. Cancer* **1993**, *29A*, 1985–1991.

[7] Z. Xu, K. Jakobi, K. Welzel, C. Hertweck, *Chem. Biol.* **2005**, *12*, 579–588.

[8] J. Verweij, J. Wanders, A. L. Nielsen, N. Pavlidis, Calabresi, W. T. Huinink, U. Bruntsch, M. Piccart, H. Franklin, S. B. Kaye, *Ann. Oncol.* **1994**, *5*, 375–376.

[9] O. F. Antibiotics, *J. Antibiot. (Tokyo).* **1982**, *2*, 888–901.

[10] M. Konishi, K. Sugawara, F. Kofu, Y. Nishiyama, K. Tomita, T. Miyaki, H. Kawaguchi, *J. Antibiot. (Tokyo).* **1986**, *39*, 784–791.

[11] X. Salas, J. Portugal, *FEBS Lett.* **1991**, *292*, 223–228.

[12] F. Barceló, J. Portugal, *FEBS Lett.* **2004**, *576*, 68–72.

[13] M. Takai, Y. Uehara, J. . Beisler, *J. Med. Chem.* **1980**, *23*, 549–553.

[14] G. Asai, N. Yamamoto, M. Toi, E. Shin, K. Nishiyama, T. Sekine, Y. Nomura, S. Takashima, M. Kimura, T. Tominaga, *Cancer Chemother. Pharmacol.* **2002**, *49*, 468–472.

[15] R. P. Maskey, I. Grün-Wollny, H. Laatsch, *J. Antibiot. (Tokyo).* **2003**, *56*, 795–800.

[16] Z. Xu, K. Jakobi, K. Welzel, C. Hertweck, B. E. Leach, K. M. Calhoun, L. E. Johnson, C. M. Teeters, W. G. Jackson, E. Simonitsch, et al., *Chem. Biol.* **2005**, *12*, 579–588.

[17] T. A. Unzner, A. S. Grossmann, T. Magauer, *Angew. Chemie - Int. Ed.* **2016**, *55*, 9763–9767.

[18] N. Ueberschaar, H. M. Dahse, T. Bretschneider, C. Hertweck, *Angew. Chemie - Int. Ed.* **2013**, *52*, 6185–6189.

[19] U. Nico, X. Zhongli, K. Scherlach, M. Mets[a]-Ketel[a], T. Bretschneider, H.-M. Dahse, G. Helmar, C. Hertweck, *J. Am. Chem. Soc.* **2013**, *135*, 17408–17416.

[20] S. K. Giri, M. Verma, K. P. R. Kartha, *J. Carbohydr. Chem.* **2008**, *27*, 464–478.

[21] H. Grugel, F. Albrecht, M. M. K. Boysena, *Adv. Synth. Catal.* **2014**, *356*, 3289–3294.

[22] D. B. Berkowitz, S. J. Danishefsky, G. K. Schulte, *J Am Chem Soc* **1992**, *114*, 4518–4529.

[23] A. J. Pihko, K. C. Nicolaou, A. M. P. Koskinen, *Tetrahedron* **2001**, *12*, 937–942.

[24] S. C. Timmons, D. L. Jakeman, *Carbohydr. Res.* **2007**, *342*, 2695–2704.

[25] I. Pelyvás, F. Sztaricskai, R. Bognár, *Carbohydr. Res.* **1979**, *76*, 257–260.

[26] T. Tanaka, H. Kawabata, M. Hayashi, *Tetrahedron Lett.* **2005**, *46*, 4989–4991.

[27] A. Kirschning, *J. Org. Chem.* **1995**, *60*, 1228–1232.

[28] J. Gervay, S. Danishefsky, *J. Org. Chem.* **1991**, *56*, 5448–5451.

[29] C. Ernst, M. Piacenza, S. Grimme, W. Klaffke, *Carbohydr. Res.* **2003**, *338*, 231–236.

[30] R. L. Halcomb, S. J. Danishefsky, *J. Am. Chem. Soc.* **1989**, *111*, 6661–6666.

[31] C. Ernst, W. Klaffke, *Tetrahedron Lett.* **2001**, *42*, 2973–2975.

[32] K. C. Nicolaou, H. J. Mitchell, N. F. Jain, T. Bando, R. Hughes, N. Winssinger, S. Natarajan, a E. Koumbis, *Chem. Eur. J.* **1999**, *5*, 2648–2667.

[33] H. X. Bing, R. R. Schmidt, *Justus Liebigs Ann. Chem.* **1992**, 817–823.

[34] J. L. De Paz, C. Noti, P. H. Seeberger, *J. Am. Chem. Soc.* **2006**, *128*, 2766–2767.

[35] W. Ke, D. M. Whitfield, J. R. Brisson, G. Enright, H. C. Jarrell, W. G. Wu, *Carbohydr. Res.* **2005**, *340*, 355–372.

[36] T. Fujiwara, M. Hayashi, *J. Org. Chem.* **2008**, *73*, 9161–9163.

[37] C. Plattner, M. Höfener, N. Sewald, *Org. Lett.* **2011**, *13*, 545–547.

[38] H. Paulsen, K. Adermann, *Justus Liebigs Ann. Chem.* **1989**, 751–769.

[39] R. U. Lemieux, R. M. Ratcliffe, *Can. J. Chem.* **1979**, *57*, 1244–1251.

[40] R. B. Conrow, S. Bernstein, *J. Org. Chem.* **1971**, *36*, 836–870.

[41] K. Radkowski, J. Grabowski, C. Wirtz, R. Mynott, A. Fürstner, *J. Org. Chem.* **2000**, *65*, 8758–8762.

[42] Z. Wang, *Comprehensive Organic Name Reactions and Reagents*, JohnWiley & Sons, Inc, Hoboken, NJ, USA, **2010**.

[43] H. Ito, T. Kamachi, E. Yashima, *Chem. Commun.* **2012**, *48*, 5650.

[44] F. Marcelo, F. V. M. Silva, M. Goulart, J. Justino, P. Sinaÿ, Y. Blériot, A. P. Rauter, *Bioorg. Med. Chem.* **2009**, *17*, 5106–5116.

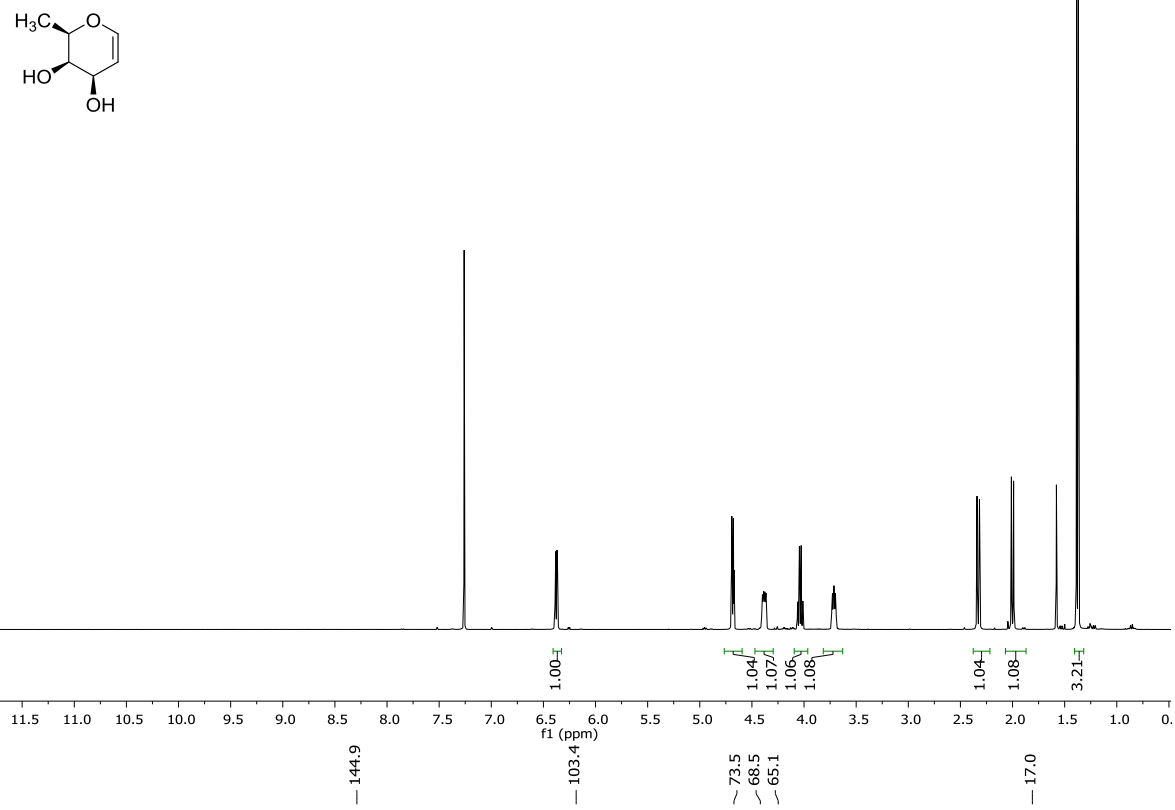
[45] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

[46] D. F. Taber, P. W. Dematteo, R. A. Hassan, *Org. Synth.* **2013**, *90*, 350.

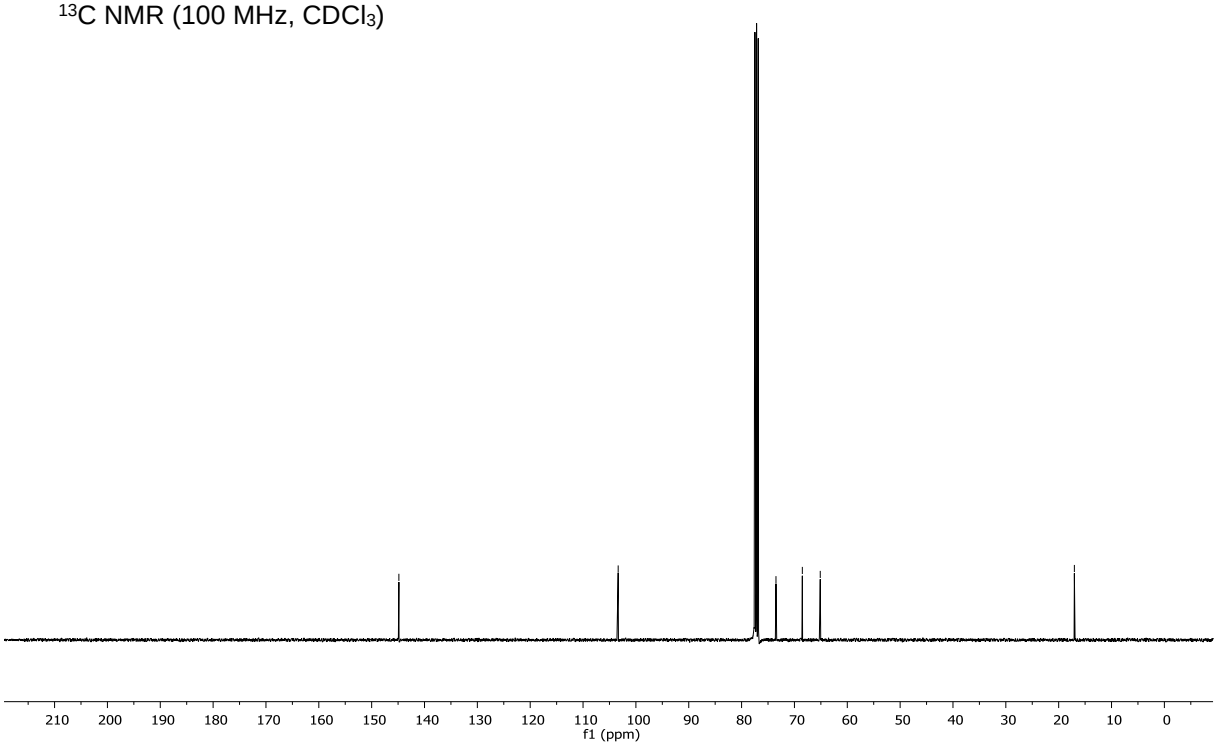
6. Appendix

6.1. NMR Spectra

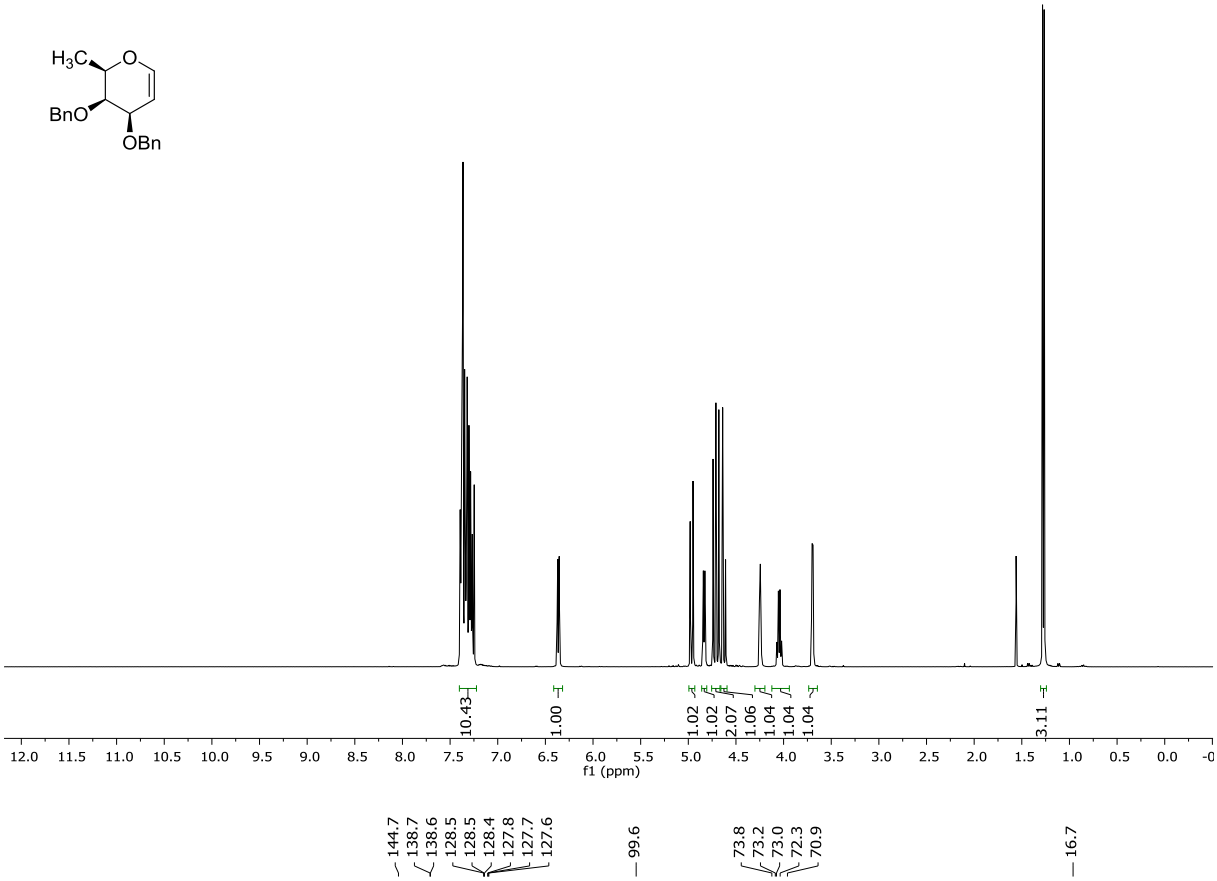
^{1}H NMR (400 MHz, $CDCl_3$)



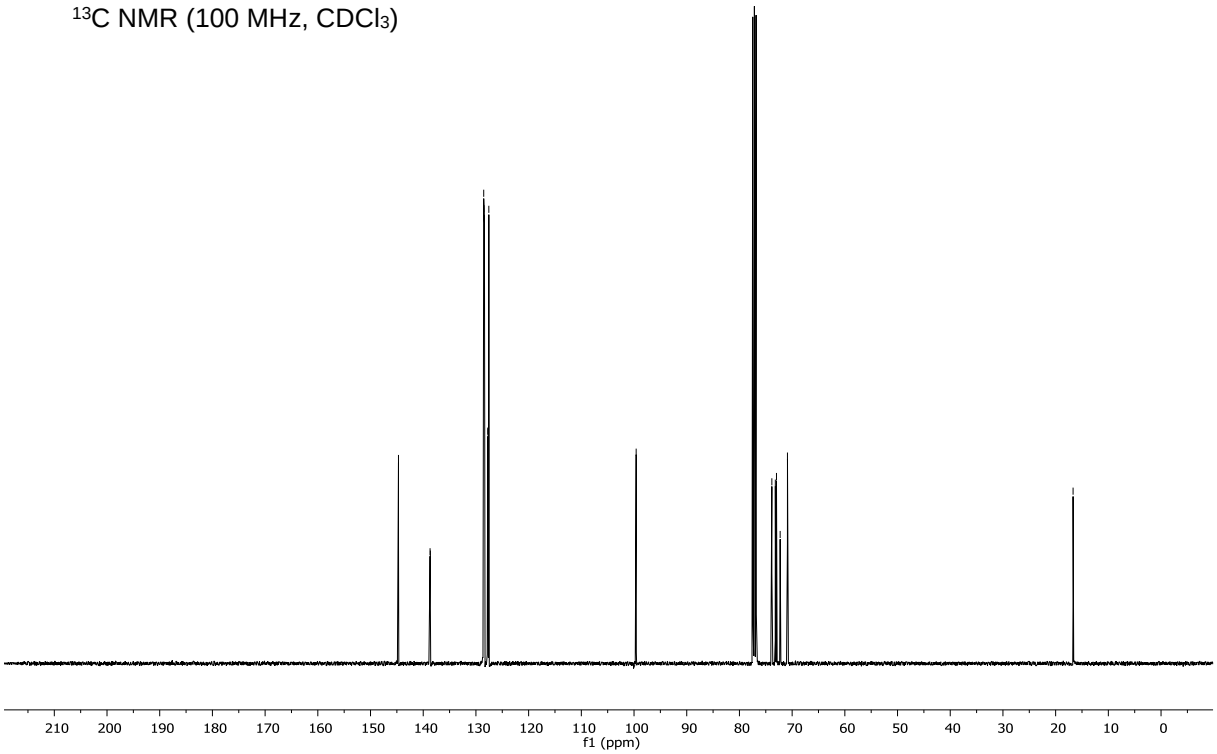
^{13}C NMR (100 MHz, $CDCl_3$)



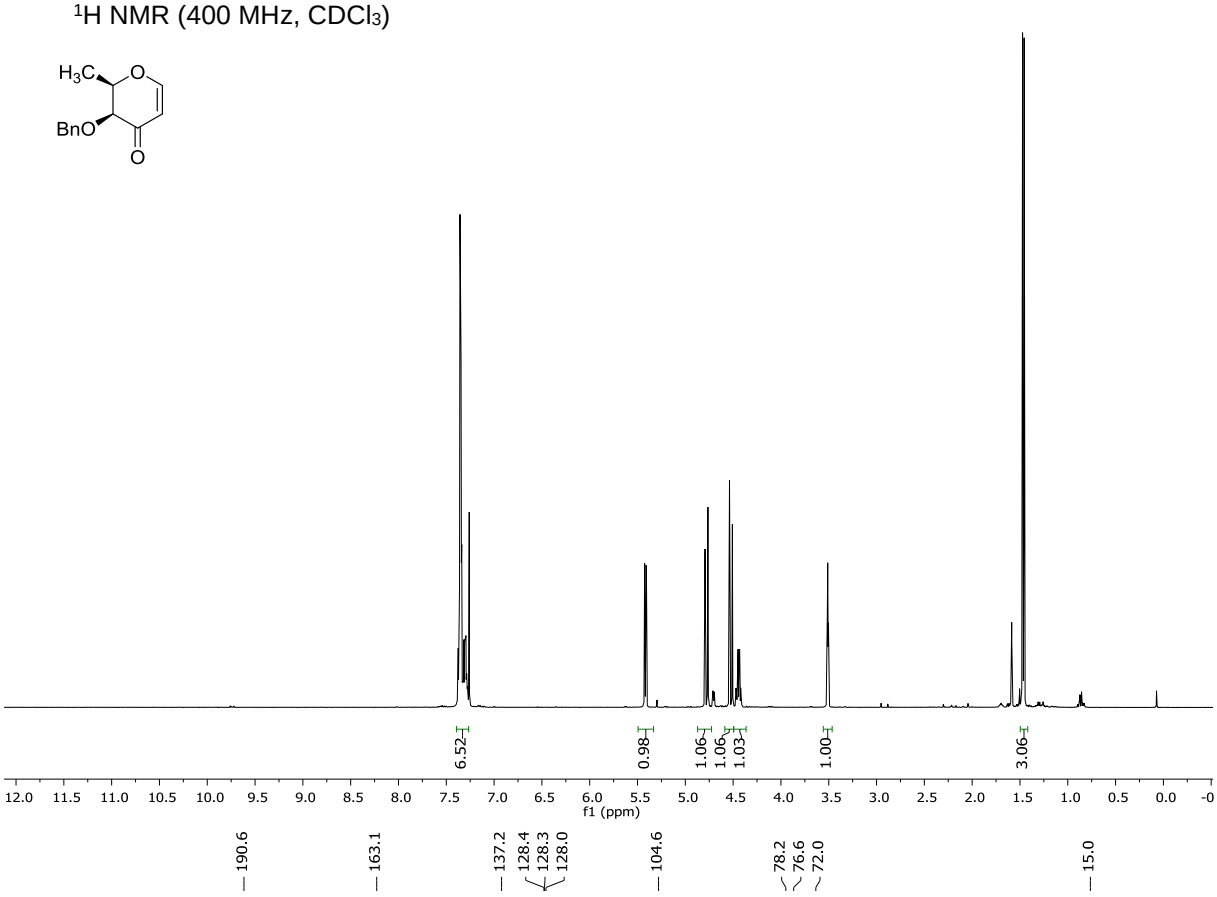
^{1}H NMR (400 MHz, $CDCl_3$)



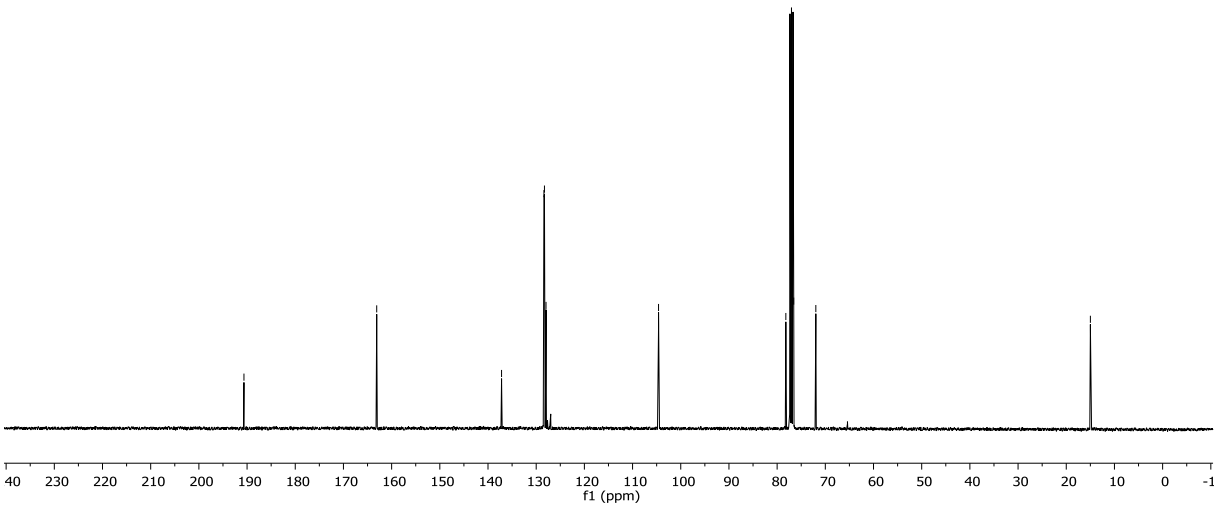
^{13}C NMR (100 MHz, $CDCl_3$)



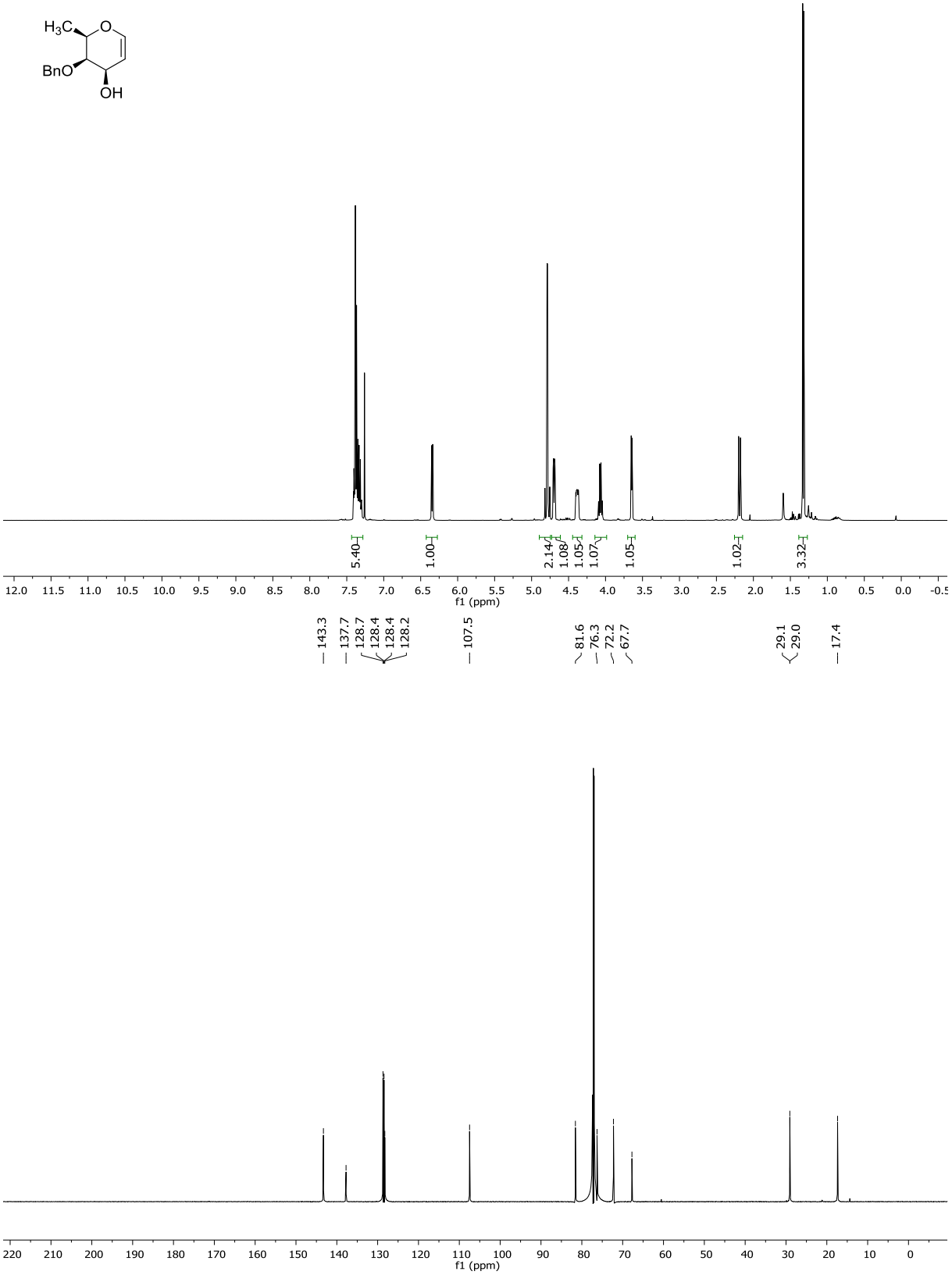
^{1}H NMR (400 MHz, $CDCl_3$)



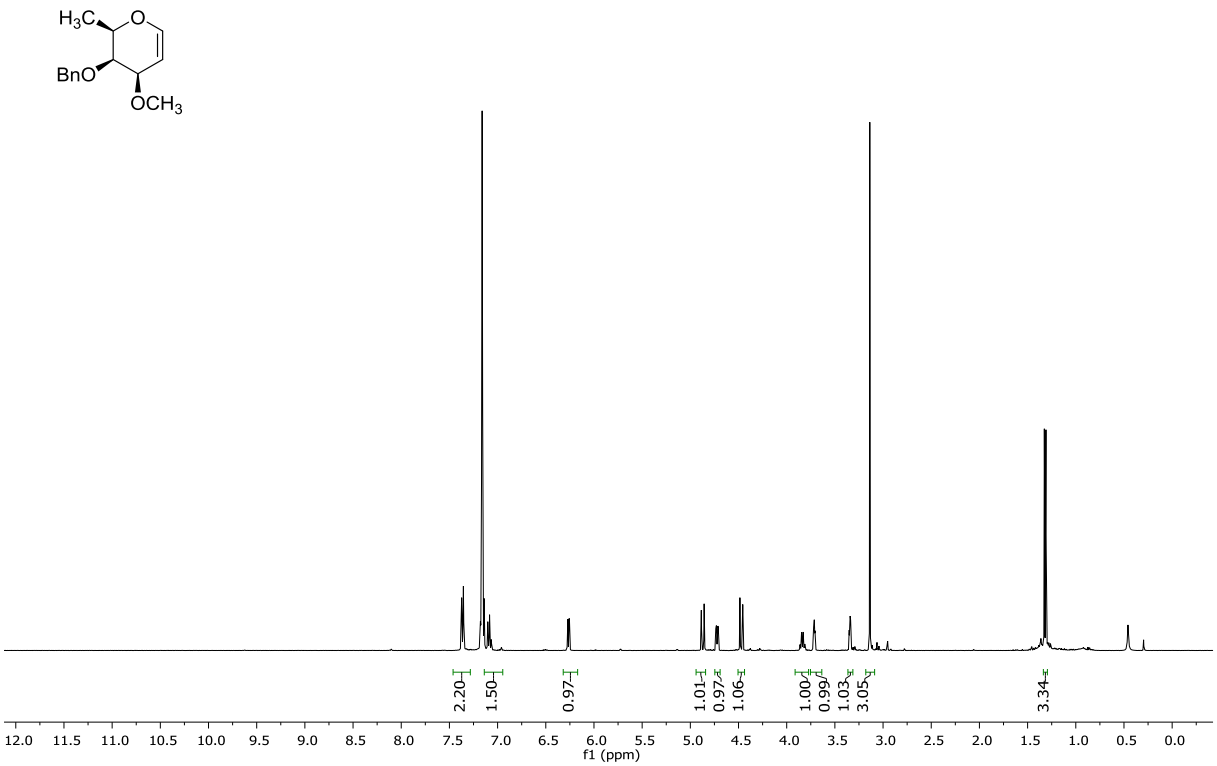
^{13}C NMR (100 MHz, $CDCl_3$)



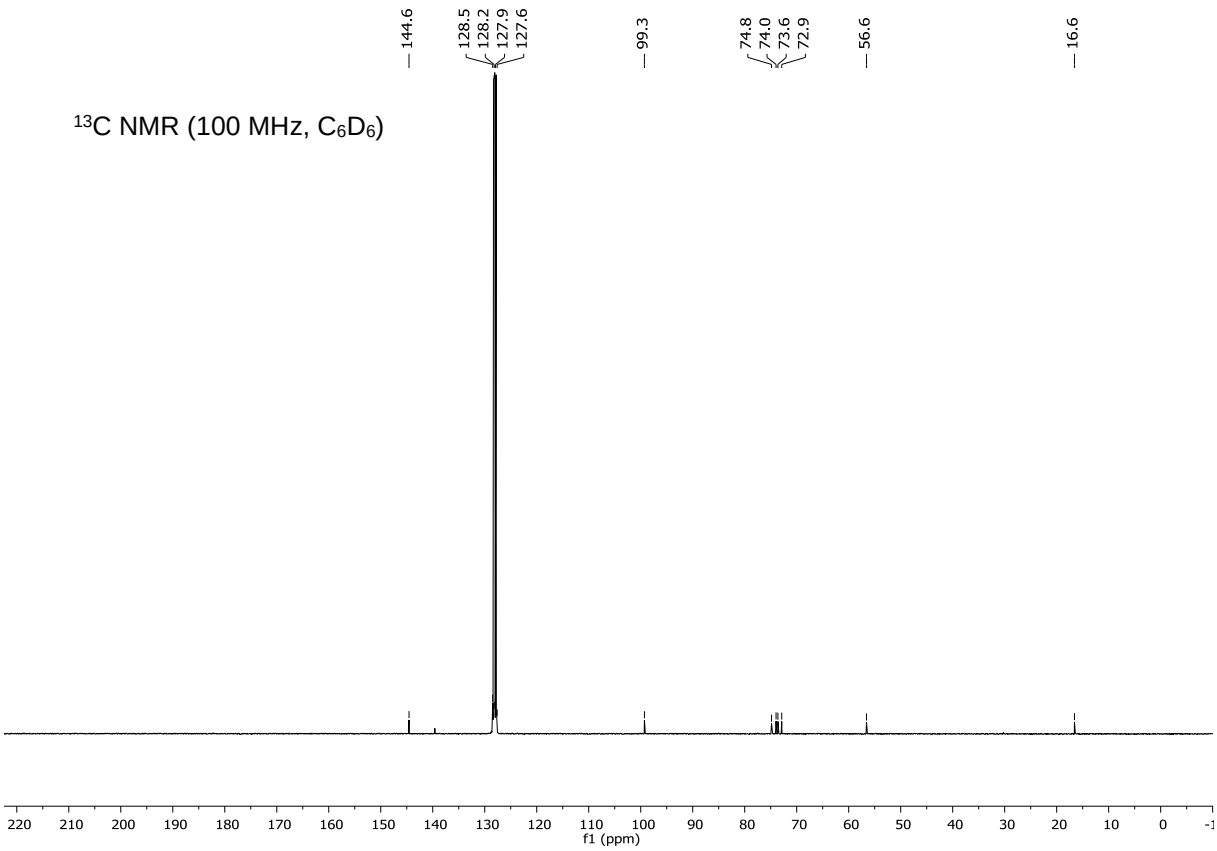
^{1}H NMR (400 MHz, $CDCl_3$)



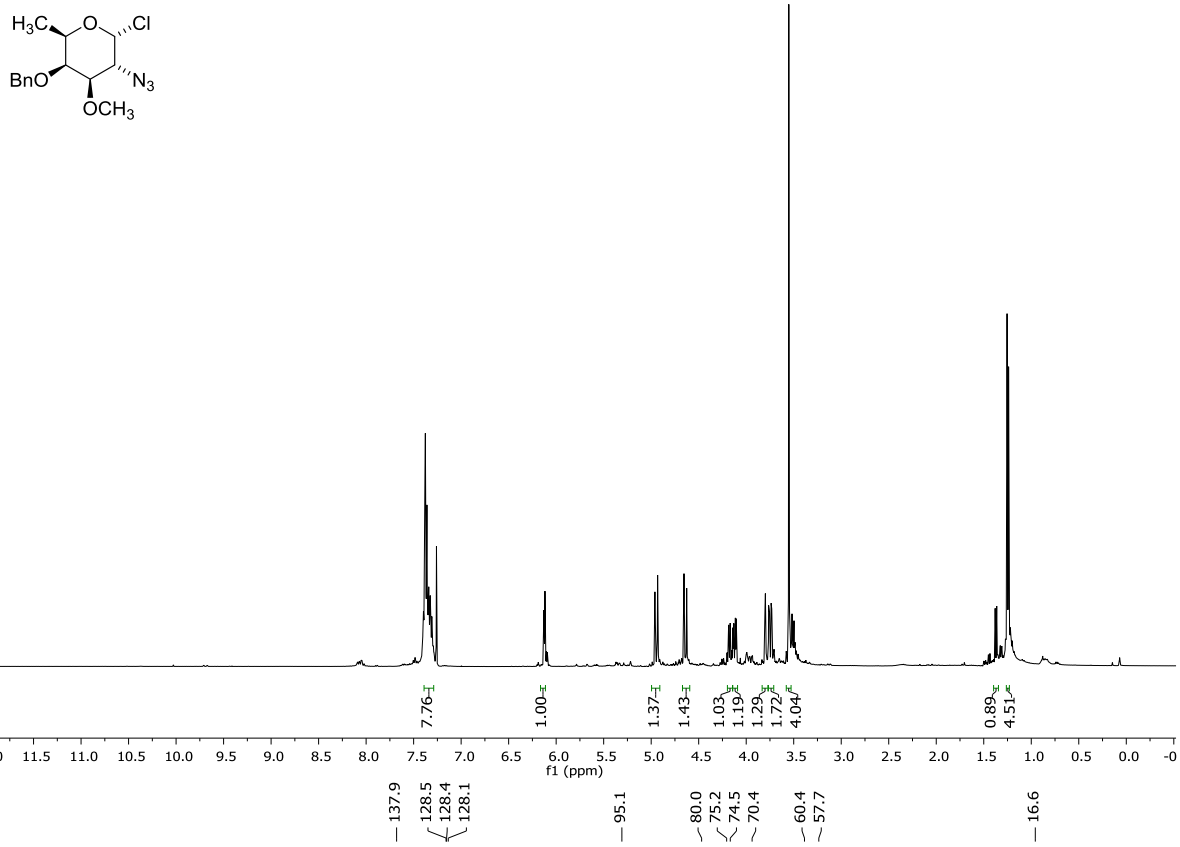
^{1}H NMR (400 MHz, C_6D_6)



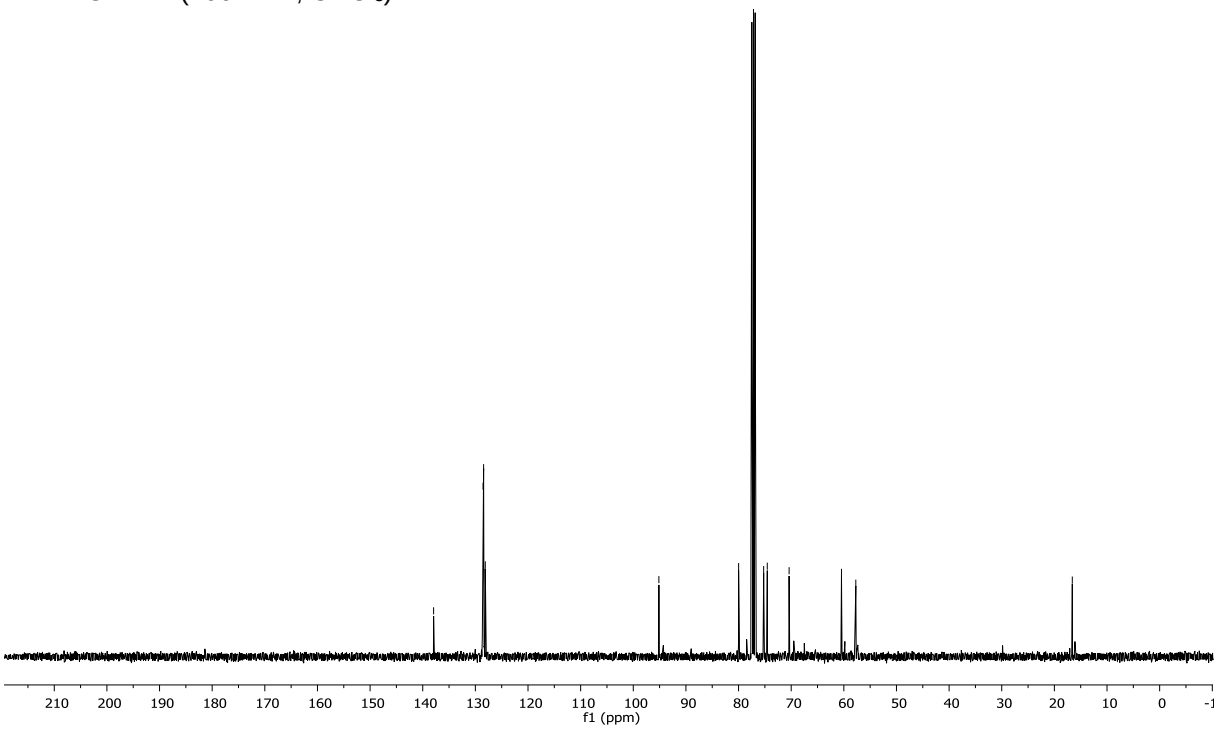
^{13}C NMR (100 MHz, C_6D_6)



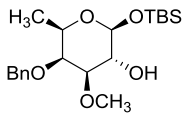
^{1}H NMR (400 MHz, $CDCl_3$)

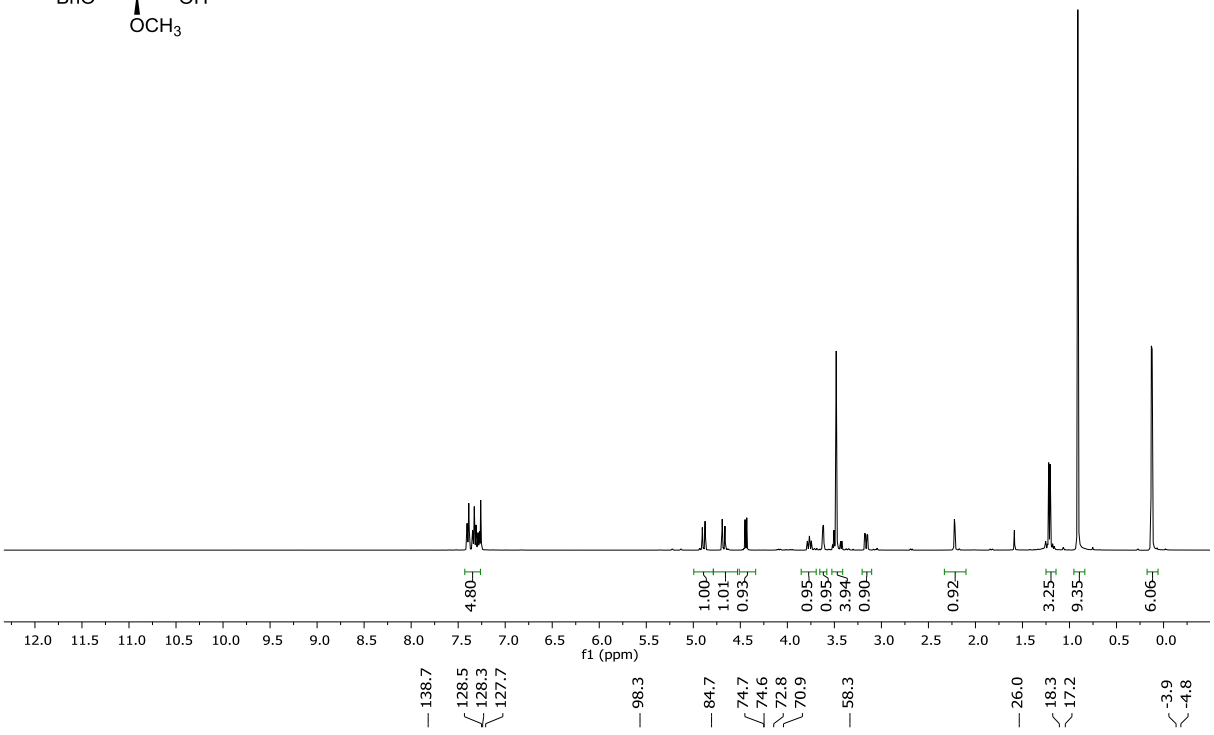


^{13}C NMR (100 MHz, $CDCl_3$)

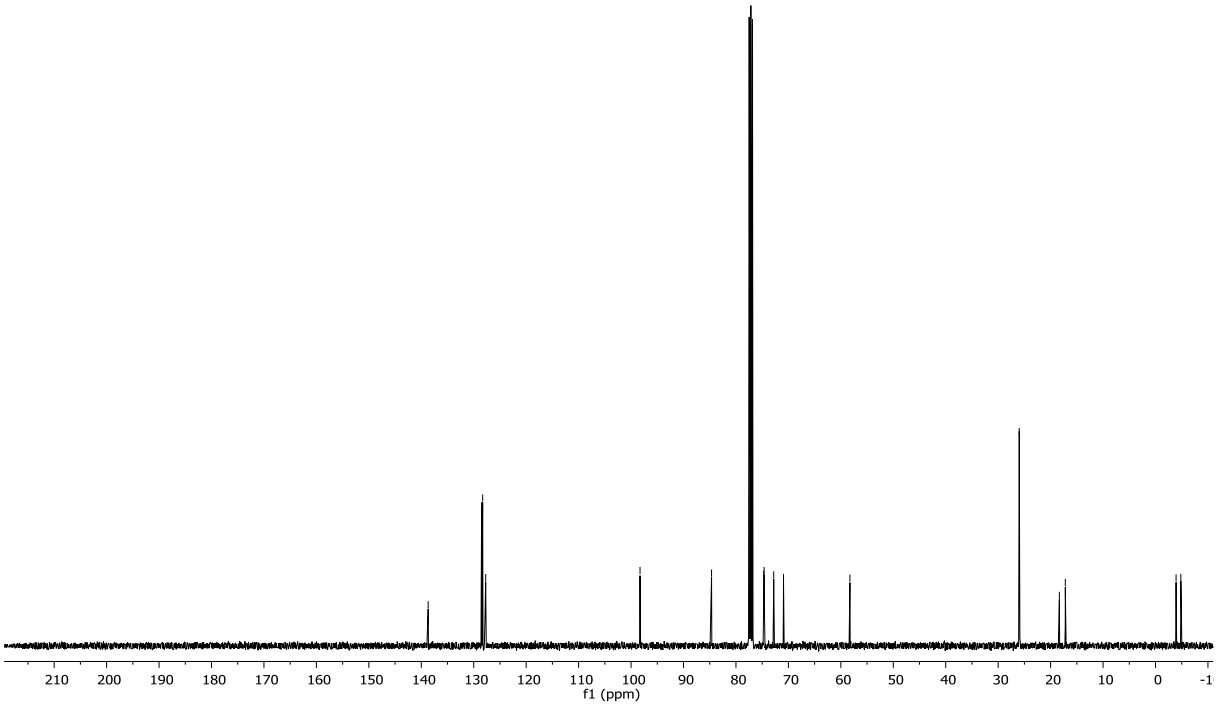


^{1}H NMR (400 MHz, $CDCl_3$)

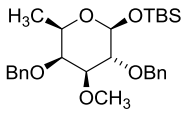




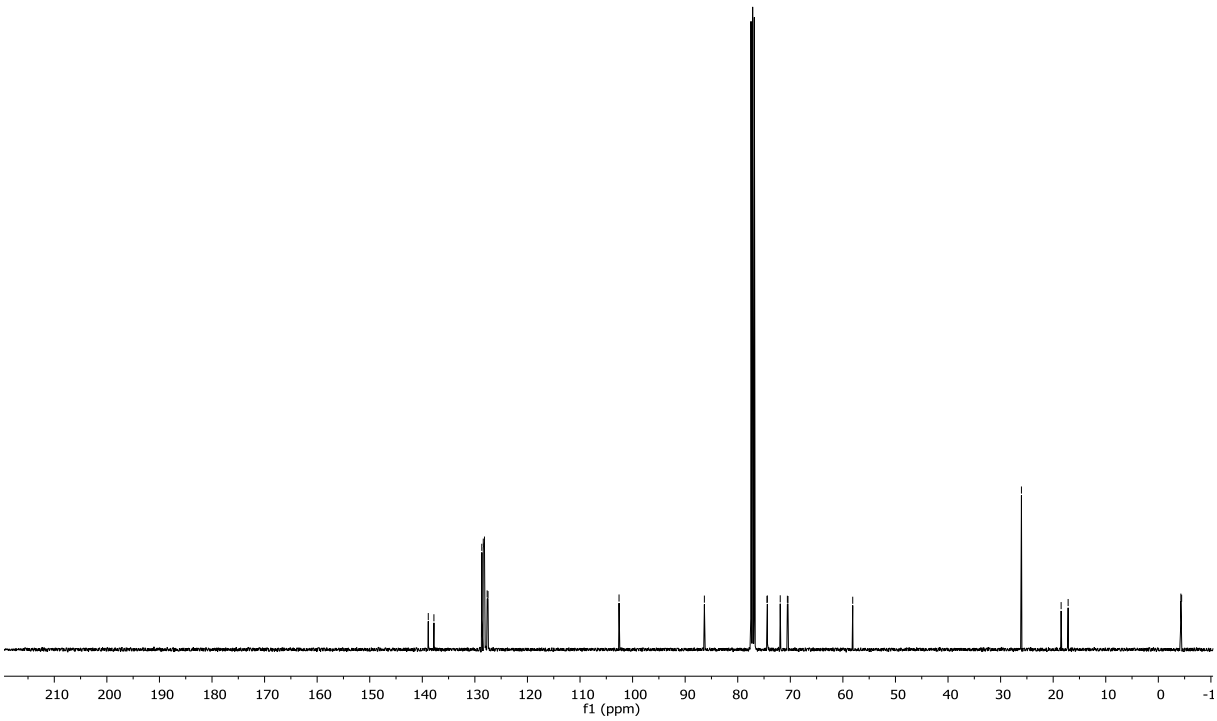
^{13}C NMR (100 MHz, $CDCl_3$)



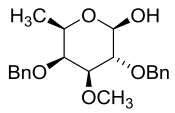
^{1}H NMR (400 MHz, $CDCl_3$)

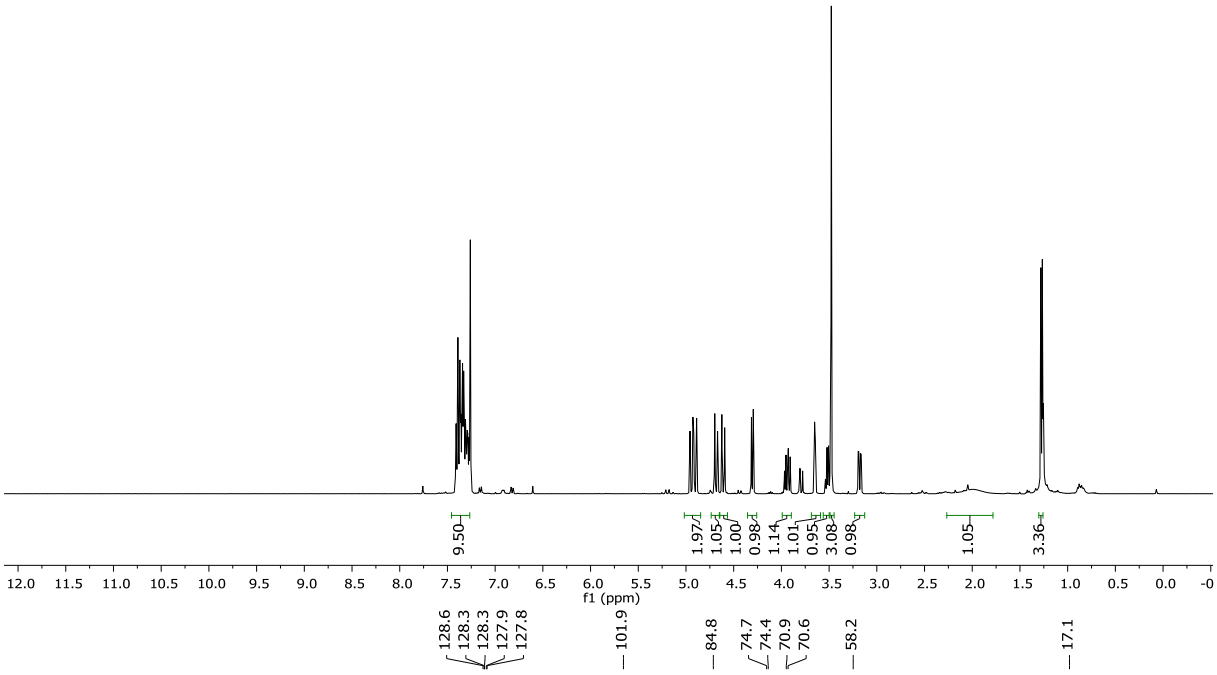


^{13}C NMR (100 MHz, $CDCl_3$)

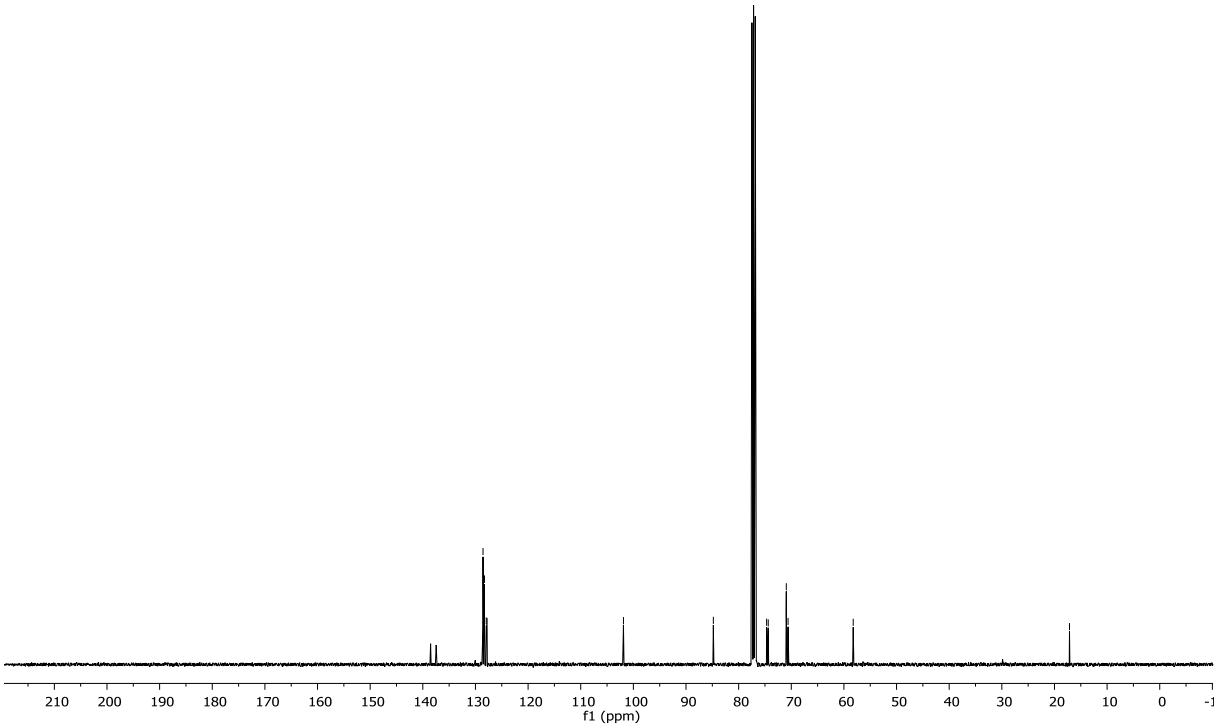


^{1}H NMR (400 MHz, $CDCl_3$)

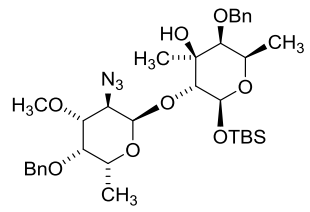


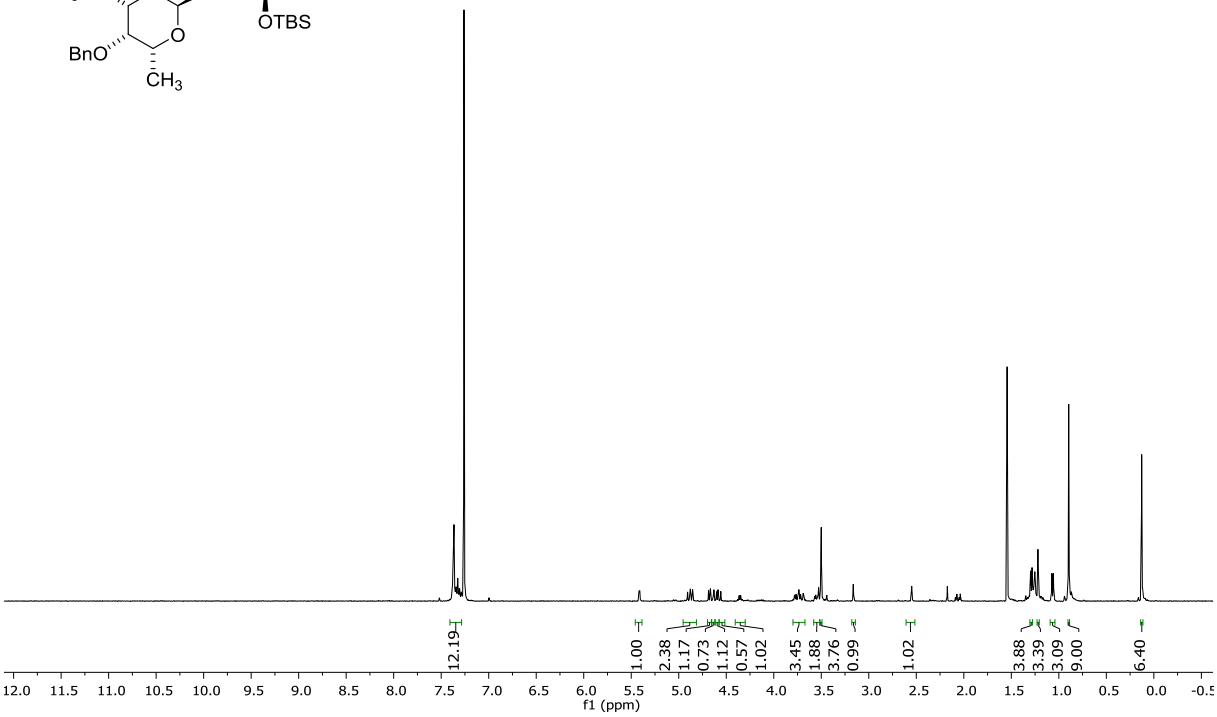


^{13}C NMR (100 MHz, $CDCl_3$)

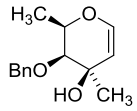


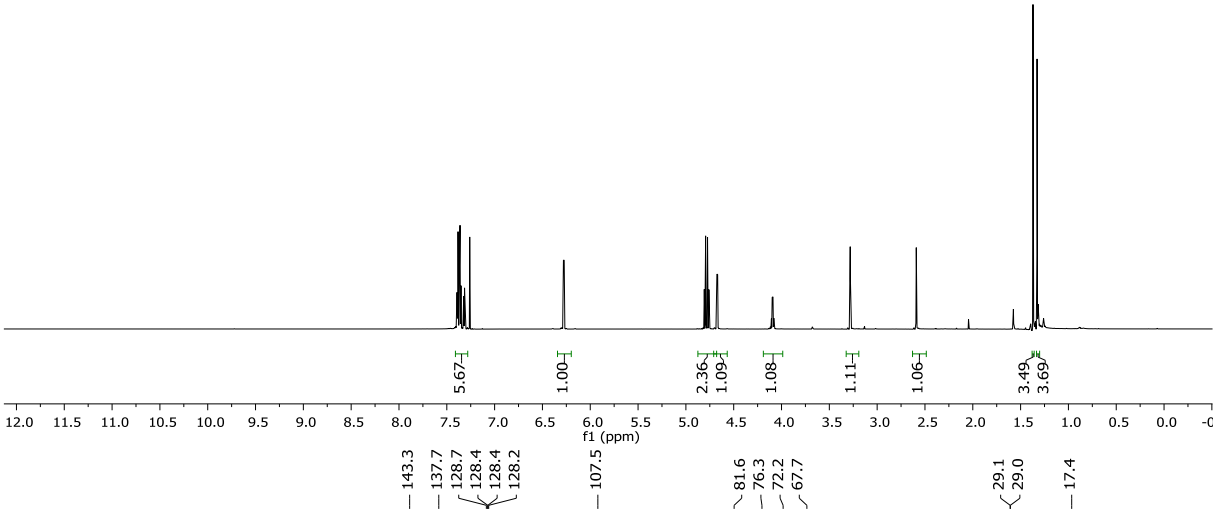
^{1}H NMR (400 MHz, $CDCl_3$)



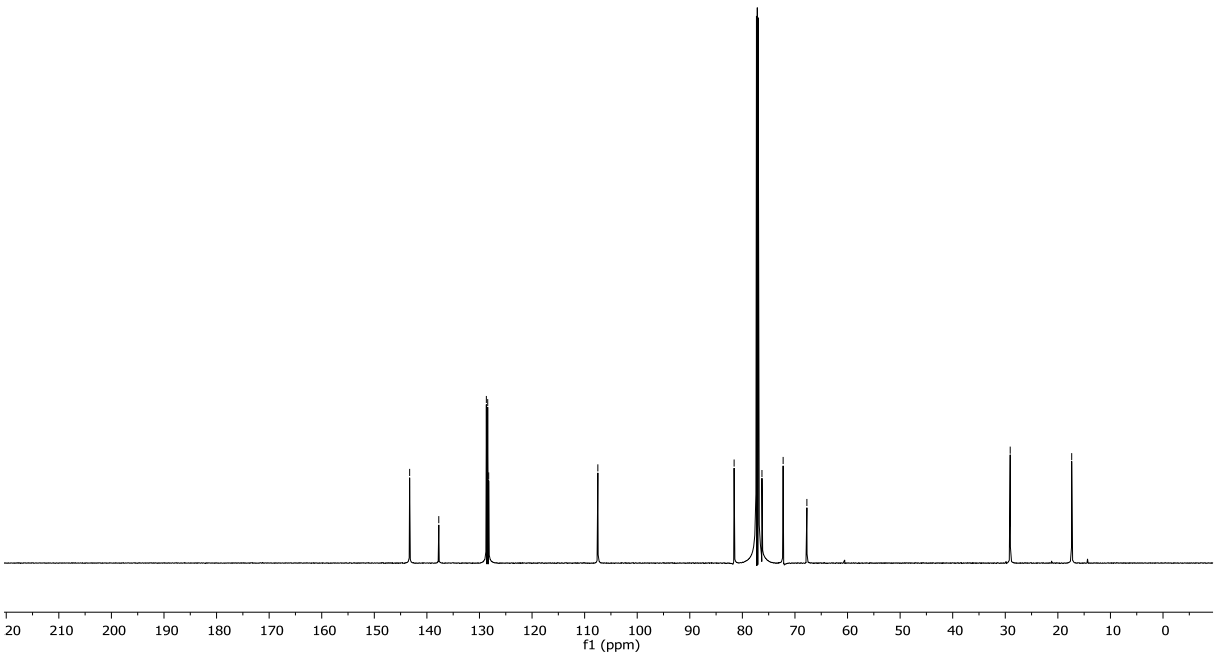


^{1}H NMR (400 MHz, $CDCl_3$)

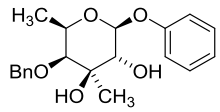


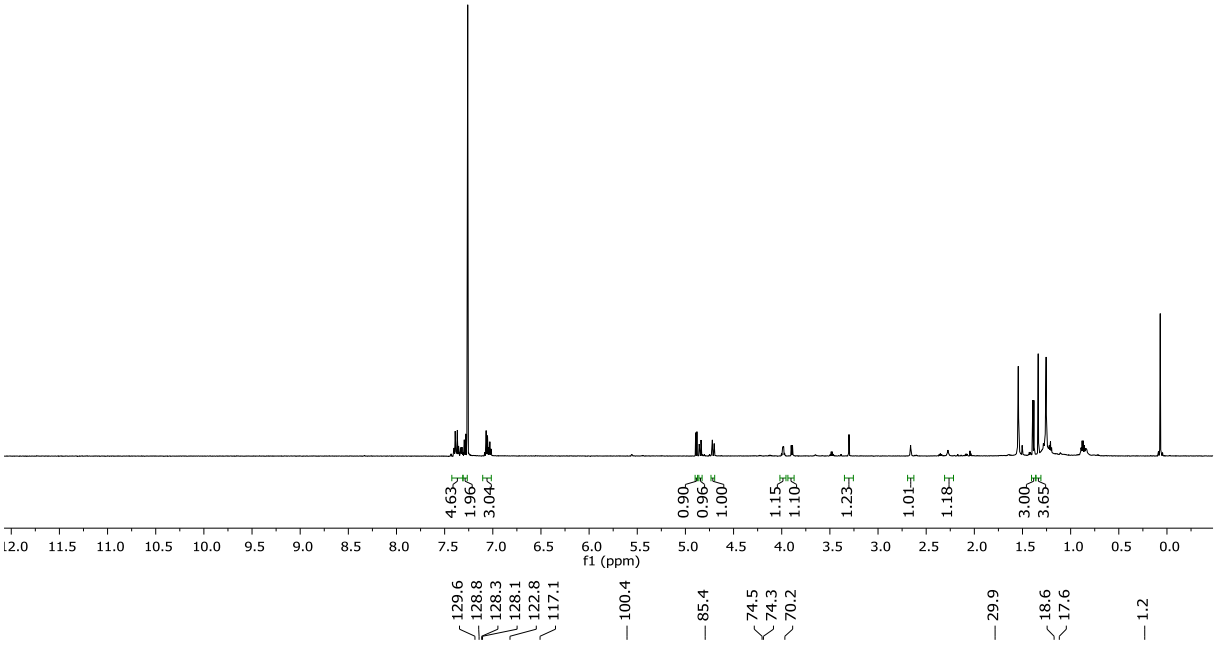


^{13}C NMR (100 MHz, $CDCl_3$)

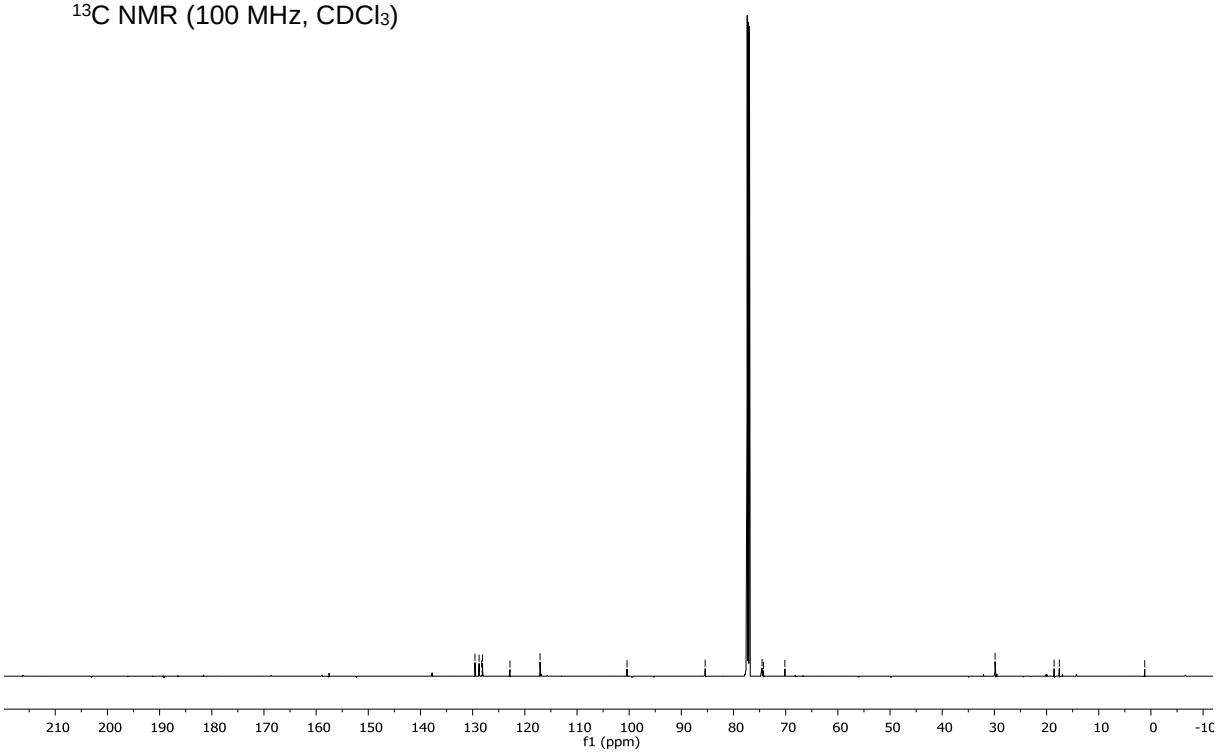


^{1}H NMR (400 MHz,

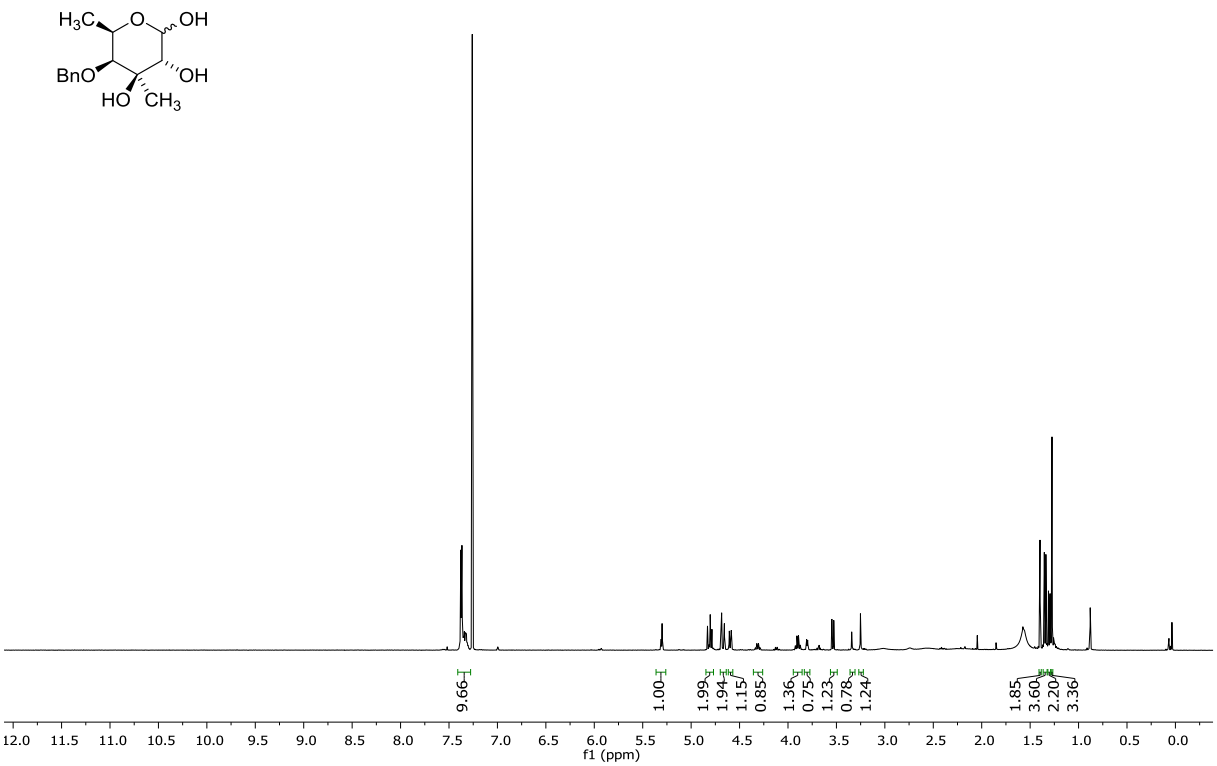




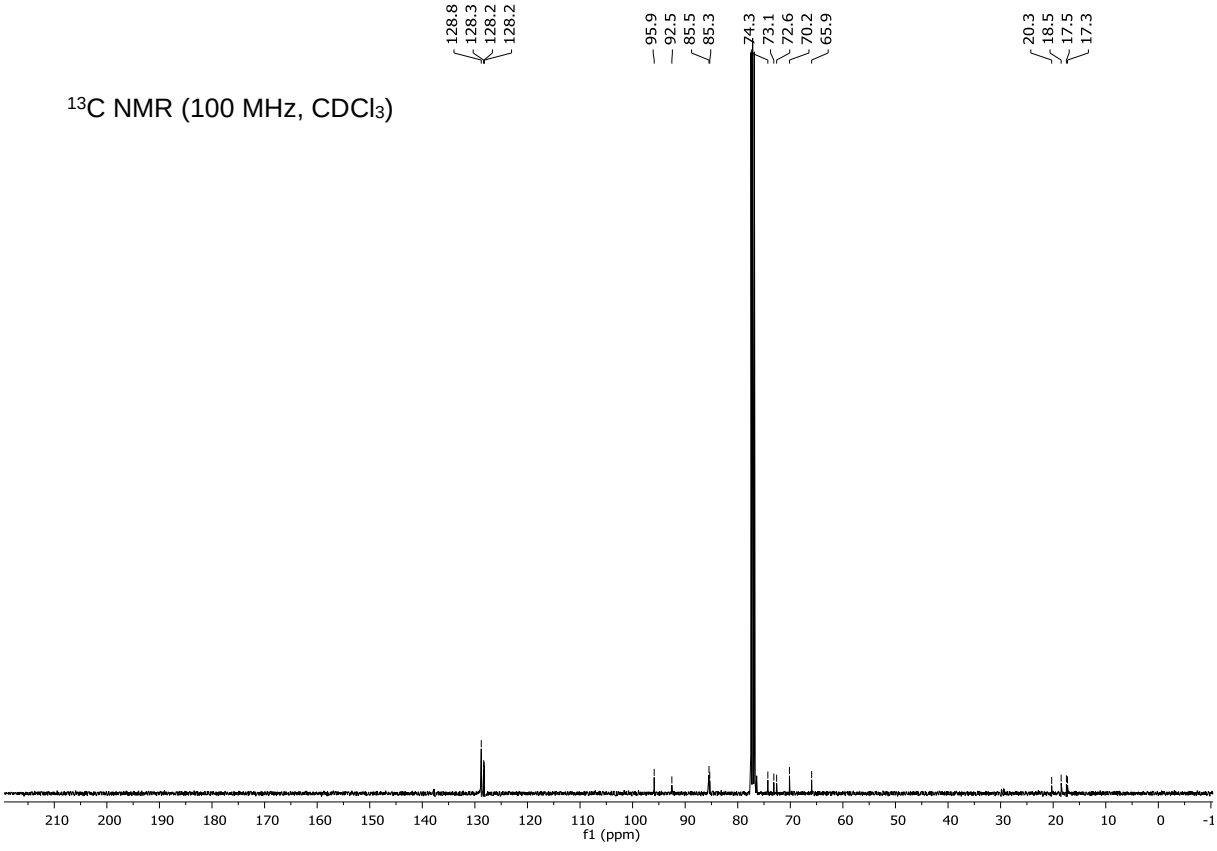
^{13}C NMR (100 MHz, $CDCl_3$)



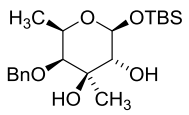
^{1}H NMR (400 MHz, $CDCl_3$)



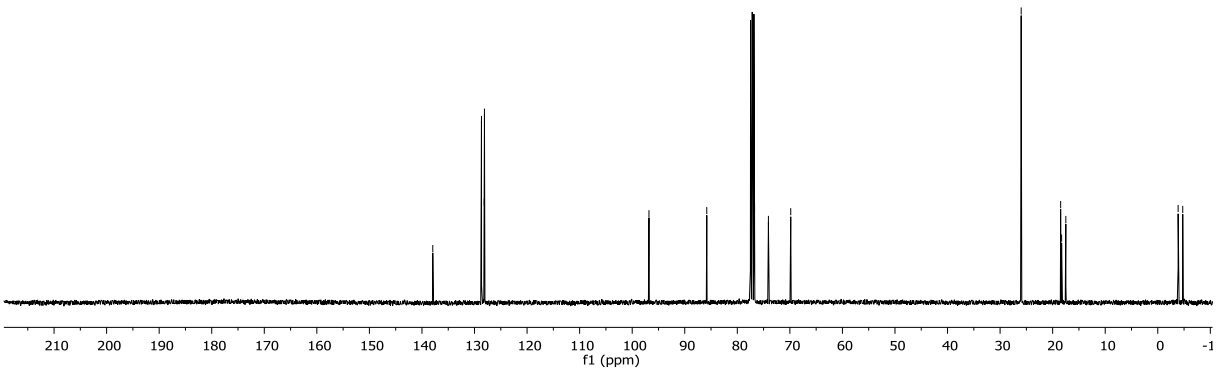
^{13}C NMR (100 MHz, $CDCl_3$)



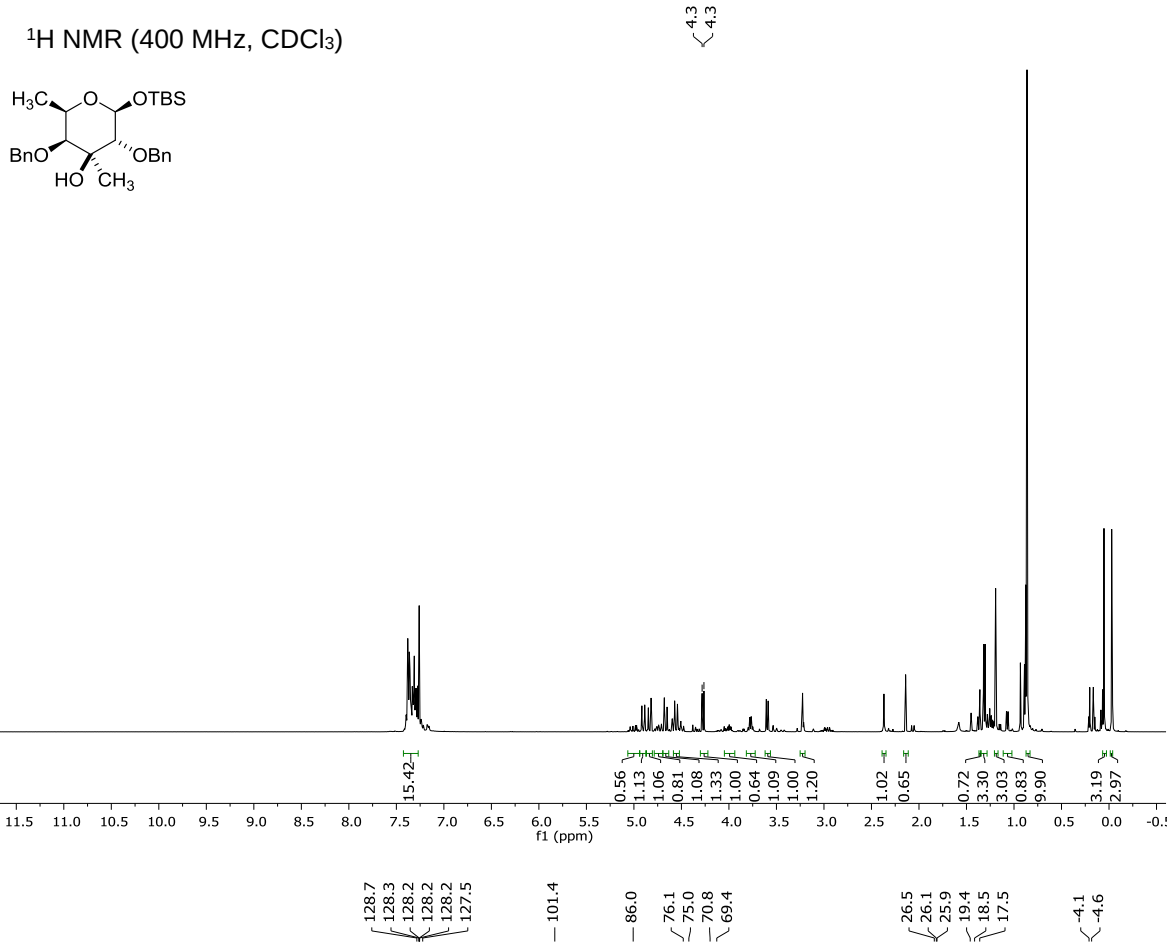
^{1}H NMR (400 MHz, $CDCl_3$)



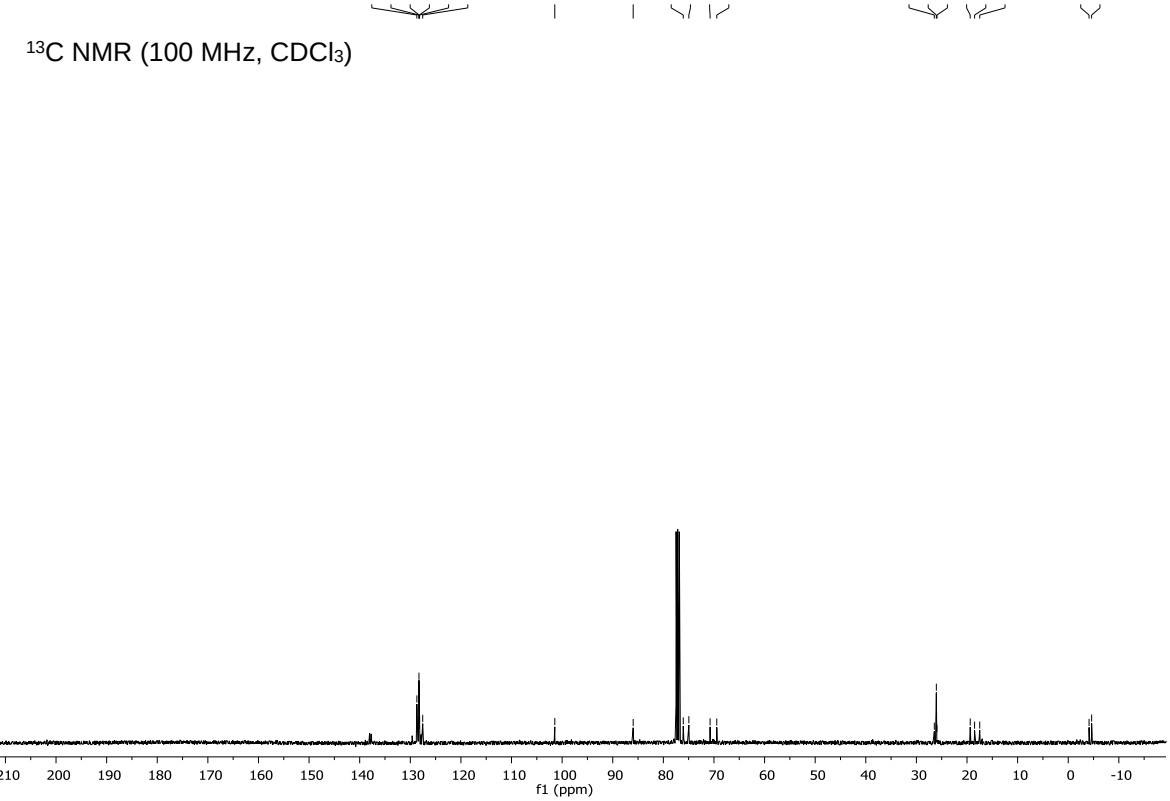
^{13}C NMR (100 MHz, $CDCl_3$)



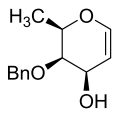
^{1}H NMR (400 MHz, $CDCl_3$)



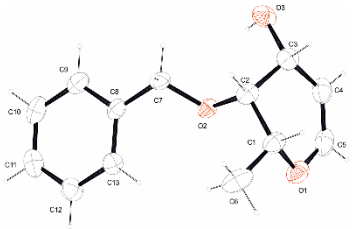
^{13}C NMR (100 MHz, $CDCl_3$)



6.2. Crystallographic Data

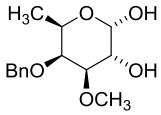


57

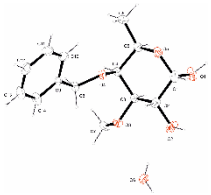


net formula	$C_{13}H_{16}O_3$
M_r/g mol^{-1}	220.26
crystal size/mm	0.100 × 0.040 × 0.010
T/K	153.(2)
radiation	MoK_α
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	4.8750(4)
b/Å	10.0610(8)
c/Å	23.8003(19)
α/°	90
β/°	90
γ/°	90
V/Å^3	1167.34(16)
Z	4
calc. density/g cm^{-3}	1.253
μ/mm^{-1}	0.088
absorption correction	Multi-Scan
transmission factor range	0.8983–0.9705
refls. measured	12761
R_{int}	0.0812
mean σ(I)/I	0.0692
θ range	3.270–26.370
observed refls.	1709
x, y (weighting scheme)	0.0342, 1.0736

hydrogen refinement	C-H: constr, O-H: refxyz
Flack parameter	–0.5(10)
refls in refinement	2376
parameters	149
restraints	1
$R(F_{obs})$	0.0641
$R_w(F^2)$	0.1380
S	1.090
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.203
min electron density/e Å^{-3}	–0.222



59



net formula	$C_{14}H_{22}O_6$
M_r/g mol^{-1}	286.31
crystal size/mm	0.100 × 0.010 × 0.010
T/K	100.(2)
radiation	MoK_α
diffractometer	'Bruker D8 Venture TXS'
crystal system	monoclinic
space group	'P 1 21 1'
a/Å	7.695(3)
b/Å	4.965(2)
c/Å	19.323(8)
α/°	90
β/°	99.237(10)
γ/°	90
V/Å^3	728.7(5)
Z	2
calc. density/g cm^{-3}	1.305
μ/mm^{-1}	0.101
absorption correction	Multi-Scan
transmission factor range	0.8908–0.9705
refls. measured	12863
R_{int}	0.0451
mean σ(*I*)/*I*	0.0537
θ range	3.149–28.699
observed refls.	3044
x, y (weighting scheme)	0.0555, 0.4104
hydrogen refinement	H(C) constr, H(O) refxyz
Flack parameter	–0.6(5)

refls in refinement	3764
parameters	195
restraints	8
$R(F_{obs})$	0.0563
$R_w(F^2)$	0.1347
S	1.056
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.590
min electron density/e Å^{-3}	–0.257