Complex cyclohexanes and tetrahydropyrans via oxocarbenium ion cyclizations

by

Fatoumata Camara

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The city University of New York

2007

UMI Number: 3284380

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This manuscript has been read and accepted for the
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dissertation requirement for the degree of Doctor of Philosophy.

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ABSTRACT

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By

Fatoumata Camara

Mentor: Professor David R. Mootoo

The synthesis and medicinal chemistry of highly oxygenated cyclohexanes and tetrahydropyrans have attracted considerable attention. Two examples of such compounds are fumagillin and C-glycoside of 2-amino-2-deoxy-galactose. Fumagillin, a natural product is known to inhibit angiogenesis and endothelial cell proliferation. Structure activity studies suggest that the C-4 side chain interacts with lipophilic amino acids on the proposed cellular target, the protein methionine aminopepetidase 2 (MetAP-2). As a result, there is interest in fumagillin analogues with different side chains. Galactosamine is an important subunit of many glycoconjugates that are involved in a number of biological processes. C-linked galactosamines are of interest as biochemical tools.

The work reported in this thesis involves the application of oxocarbenium ion cyclizations to the synthesis of side chain analogues of fumagillin and β-C-glycoside of galactosamine. The initial plan, for the modified side chain analogue of fumagillin, involved the oxocarbenium cyclization on a precursor containing the pre-installed side chain. This plan was promising in a model study on a tetrahydropyran framework, but encountered problems in the synthesis of the cyclization precursor and the key cyclization step when applied to the real cyclohexane system. The eventual solution was to perform the oxocarbenium ion cyclization on a less complex substrate, followed by elaboration of the side chain via the Kocienski modification of the Julia reaction.

The key step in the synthesis of β-C-glycoside of galactosamine was the formation of a C1-substituted glycal via an oxocarbenium ion-enol ether cyclization. The enol ether-thioacetal substrate for the cyclization step was obtained by DCC coupling of a thio-isopropilidene acetal (TIA) and an acid precursor, followed by Tebbe olefination of the ester. Attempts to convert the glycal intermediate using synthetic methodologies for the direct transformation of glycals to 2-aminosugars were not successful. The successful solution entailed conversion of the C1-substituted glycal to a 2-deoxy-2-oxime methyl ether followed by a stereoselective reduction, using $Bu_3SnH/BF_3.OEt_2$. An attempt to apply this approach to the C-glycoside analogue of GalNAc1ManNAc was unsuccessful.

ACKNOWLEDGMENTS

The road to obtaining a Ph.D degree is not always a smooth one. However, along the way you encounter many remarkable people who help to make the experience a pleasurable. I would like to express sincere gratitude to everyone who directly or indirectly helped me transcend these significant milestones and kept me on the path to success.

First and foremost I must thank God who gave me the strength and the courage I needed to obtain my Ph.D degree.

I would also like to express sincere gratitude to my mentor Dr David R. Mootoo for his invaluable advice and encouragement. In addition of teaching me organic and carbohydrate chemistry, Professor Mootoo taught me the required discipline for success.

Mention must also be made of my committee members: Dr Richard. W. Franck, Dr Mahesh K. Lakshman, and Dr William W. Berkowitz, for their comments and suggestions.

I am truly grateful to Dr Klaus Grohmann for all the help and the attention he provided during my stay at Hunter College.

I would like to express my appreciation to Dr Clifford E. Soll and Dr Michael Blumenstein for their help with mass and NMR experiment, respectively.

Thanks to the Chemistry Department at Hunter and more notably the Graduate Center for giving me the opportunity to acquire this Ph.D degree. I am very grateful to Mrs. Diane Adebowale for her invaluable encouragement and advice.

Thanks to the members of The Mootoo group. Dr Govinderaj Kumaran, Dr Darrin R. Dabideen, Dr Lei Zhu, Dr Richard Denton, Clayton Mattis, Steawart Bachan, Feng Wang, Xiaohua Li, and Jialiang Li.

Special thanks goes to Dr Line Augustin, Sunej Hans, and Dr Tony Kurissery, for their extreme help and friendship that pulled me through the rough time. Their kindness drove me towards my Ph.D degree.

I would like to thank my parents: Elhaj Aboubacar Camara and Hadja Mahawa Camara for their unconditional love, and moral support throughout all these years. They have giving me the most valuable gift that a child could ever get: my education. I am extremely grateful. Thanks to my brothers and sisters: Bintou, Mohamed, Madiou and Nafissatou. Thanks also go to Bintou's family for their moral support: her husband Mamady and their children: Aly Bader, Malik and Myriam.

Last but by no means least; I would like to thank my husband and my lovely daughters Hawa (Nanette) and Kadija (Diana). My daughters are true source of inspiration that keeps me going. They have giving me tremendous amount of joy and I thank God for having them.

.

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LIST OF SYMBOLS and ABBREVIATIONS

Ac	Acetyl
Ac_2O	acetic anhydride
$BF_3.Et_2O$	boron trifluoride etherate
Bn	benzyl
Brine	saturated aqueous sodium chloride solution
brs	broad singlet
Bu	butyl
^0C	degree Celsius
calcd	calculated
^{13}C NMR	carbon-13 nuclear magnetic resonance spectrometry
CSA	camphorsulfonic acid
δ	chemical shift in ppm
d	doublet
DIB	iodobenzene diacetate
DCC	dicyclohexylcarboiimide
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
ee	enantiomeric excess
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol

eq	equivalent
FCC	flash column chromatography
g	gram
h	hour
^{1}H NMR	proton nuclear magnetic resonance spectrometry
Hz	hertz
IDCP	iodonium dicollidine perchlorate
J	coupling constant
m	multiplet
M	molar
Me	methyl
MeOH	methanol
MeOTf	methyl triflate
mg	milligram
min	minute
mL	milliliter
mmol	millimole
MS	molecular sieves
NOE	Nuclear Overhauser effect
Ph	phenyl
ppm	parts per million
PPTS	*para*-pyridinium toluenesulfonate
q	quartet

rt	room temperature
s	singlet
t	triplet
TBDPS	*tert*-butyl diphenyl silyl
TIA	1-thio-1,2-isopropylidene acetal
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	toluenesulfonyl
Vs	versus

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PART 1:

Synthesis of fumagillin analogues via oxcarbenium ion cyclization.

CHAPTER I

Biological activity and previous syntheses

1.1 Background

Fumagillin **1.1T**[1], was isolated in 1951 by Elbe and Hanson from the microbial organism *Aspegillus fumigatus*. Chemical degradation[2] and X-ray crystallography[3] contributed to the elucidation of fumagillin's chemical structure. Fumagillin contains six contiguous stereogenic centers on a highly functionalized cyclohexane frame work which includes a vicinal cis diol and also epoxides (**Figure 1.1**).

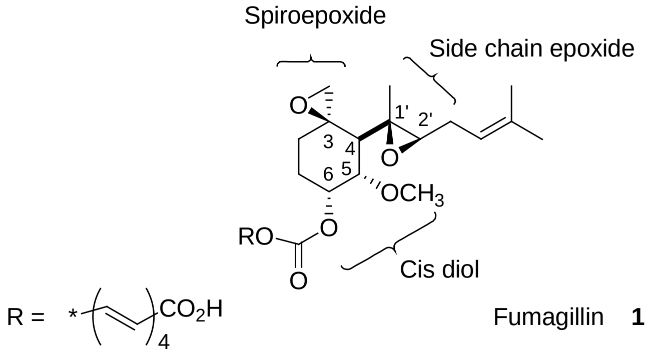
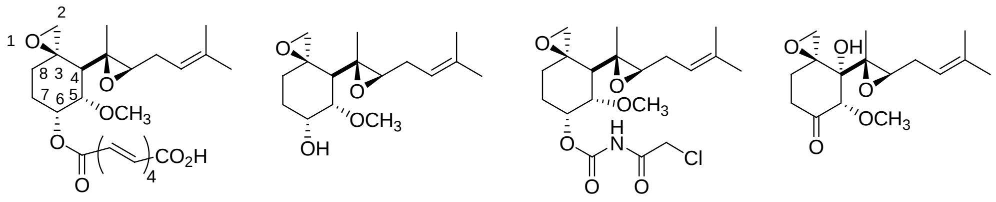


Figure 1.1. Fumagillin **1.1**.

Originally, fumagilin was described as an antimicrobial agent.[4] However, in 1990, Igber et al[5] reported that fumagillin showed potent antiangiogenic activity and inhibited endothelial cell proliferation *in vitro* and tumor–induced angiogenesis *in vivo*.[6,7] Angiogenesis, the process by which the tumor vascularizes is essential for tumor growth and metastasis.[8,9] During angiogenesis, endothelial cells proliferate and migrate to the neighboring tissue. The development of antiangiogenic agents as antitumor agents[10] has been widely pursued. Unfortunately fumagillin causes severe weight loss and is rapidly hydrolyzed to fumagillol **1.3** under basic conditions, which limits its therapeutic use (**Figure 1.2**).

Considerable effort has been made to develop more efficacious fumagillin analogues. Because of the easy accessibility of structures with different ester residues and modified C4 appendages, through transformations on the natural product, structure activity studies have been largely confinied to such analogues. (**Figure 1.2**).



Fumagillin **1.1** Fumagillol **1.3** TNP-470 **1.2** Ovalicin **1.4**

Inhibitors of endothelial cell poliferation

Figure 1.2 Fumagillin and its related analogues

The most prominent derivative is TNP-470 **1.2**, which contains an unnatural ester subunit[11]. TNP-470 is currently being evaluated in phase III clinical trial for the treatment of a variety of cancers.[12] However, though more potent than fumagillin, TNP-470 has a low half life neurotoxic side effects such as fatigue, and vertigo, and possibly disrupts normal angiogenesis processes (e.g. female reproductive system, wound healing). Several other analogues have been examined. The structure acitivity trend is discussed in the following section.

1.2 Binding of fumagillin to methionine aminopeptidase 2

It has been suggested that the common molecular target for fumagillin is methinine aminopeptidase 2 (MetAP-2) (**Figure 1.3**). [13].

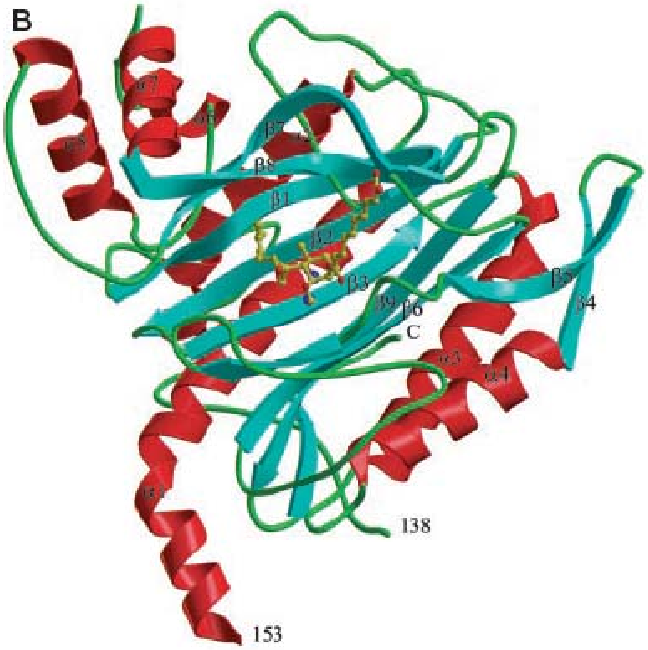


Figure 1.3.[13] Overall structure of the complex between human MetAP-2 and fumagillin.

There are two MetAP family members, MetAP-1 and MetAP-2. Together, they are reponsable for the cleavage of the initial methionine from the N termini of nascent proteins.[14] It has been shown that the ability of various fumagillin analogues to inhibit endothelial cell growth correlates with their MetAP-2 enzymatic inhibitory activity *in vitro*.[15] However, the mechanism by which MetAp-2 interacts leading to inhibition of angiogenesis is not clear.[16]

Additionally, it was proposed that fumagillin covalently binds to MetAp-2. This hypothesis was later supported by an X-ray structure of fumagillin-MetAP-2[17] adduct in which the spiro-epoxide on fumagillin was opened by Hist-231 of the protein MetAP-2 (**Figure 1.4**).

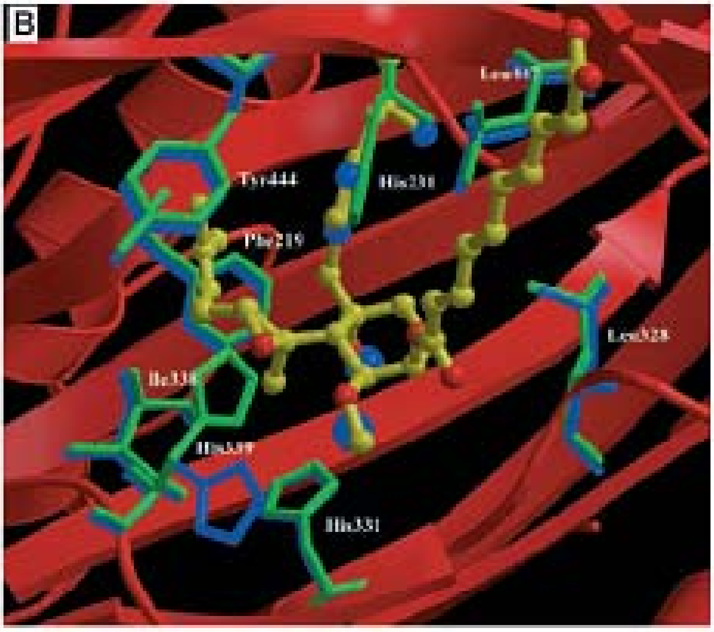


Figure 1.4.[13] Fumagillin in the active site of HsMetAP-2.

This X-ray structure also indicated that, the oxygen liberated from the epoxide ring opening is coordinated with cobalt (3.28 A), and occupies the approximate position of the cobalt-associated water molecule in the un-complexed structure of the position (**Figure 1.4**). A water molecule that is equidistant from both cobalts forms a hydrogen bond with this fumagillin oxygen (**Figure 1.5**).[13] The latter observations allows a rational design for the modification of cyclohexane ring of fumagillin molecule. Indeed, the spiroepoxide could be converted into an alternative functional group which would allow for the retention of the bonding distance between the C2 carbon in fumagillin and the N of His231 in MetAp-2 (**Figure 1.4**).

The side chain epoxide of fumagillin occupies the pocket near the active site. The side chain appears to be involved in the recognition process in two ways. In addition to establishing hydrophobic interactions with several lipophilic aminoacids (His 331, Tyr444, Ile338, His339, and Phe219) it interacts with the protein via the side chain epoxide which functions as an H-bond acceptor for a defined water molecule within the enzyme's recongnition site. (**Figure 1.5**).[13]

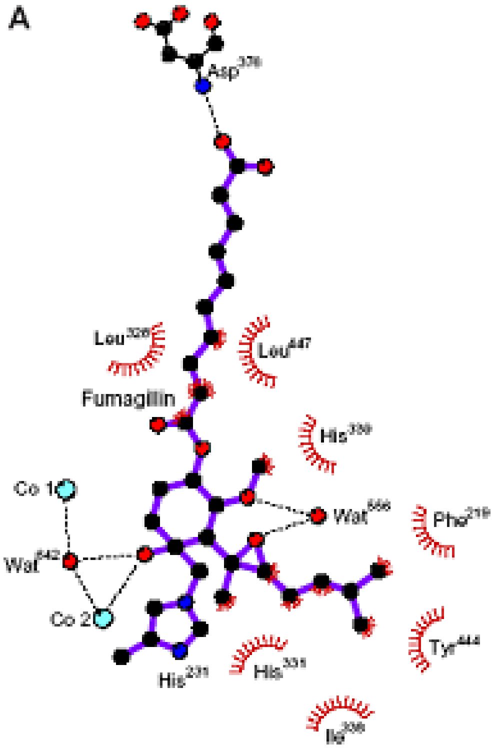


Figure 1.5.[13] LIGPLOT of fumagillin in the binding pocket.

The latter latter hypothesis provides important information for targeted modified side chain analogues of fumagillin.

The long unsaturated side chain protrudes from the binding pocket and makes two hydrophobic contacts with Leu328 and Leu447. The terminal carboxyl group of the side chain makes a hydrogen bond with Asp376 (**Figure 1.5**). [18] This last observation shows the importance of the acyl group and allows a rational design of fumagillin analogues containing mosified ester group.

1.3 Fumagillin analogues

The X-ray structure provided a model for the design of simpler analogues of fumagillin.

1.3.1 C6 side chain modifications

Kyoung Tai No *et al*[19] performed a structure-based drug design of fumagillin analogues from homology modeling. Using the MetAP-2-fumagillin x-ray structure, a series of fumagillin derivatives with different aromatic ester groups at C6. were designed. It was assumed that the aromatic ring would engage in a hydrophobic interaction with the Leu 447 of MetAP-2 (**Figure 1.6**). The antiproliferative activities of these fumagillin analogues were evaluated against calf pulmonary artery (SPAE, ATTIC HRL 209) endothelial cells, lymphoma EL-4 cells and murine leukemia P388D. Among the designed compounds, the cinnamic acid ester **1.5-1.7** and benzyl carbamates **1.8-1.11** showed more potent activity than TNP-470.

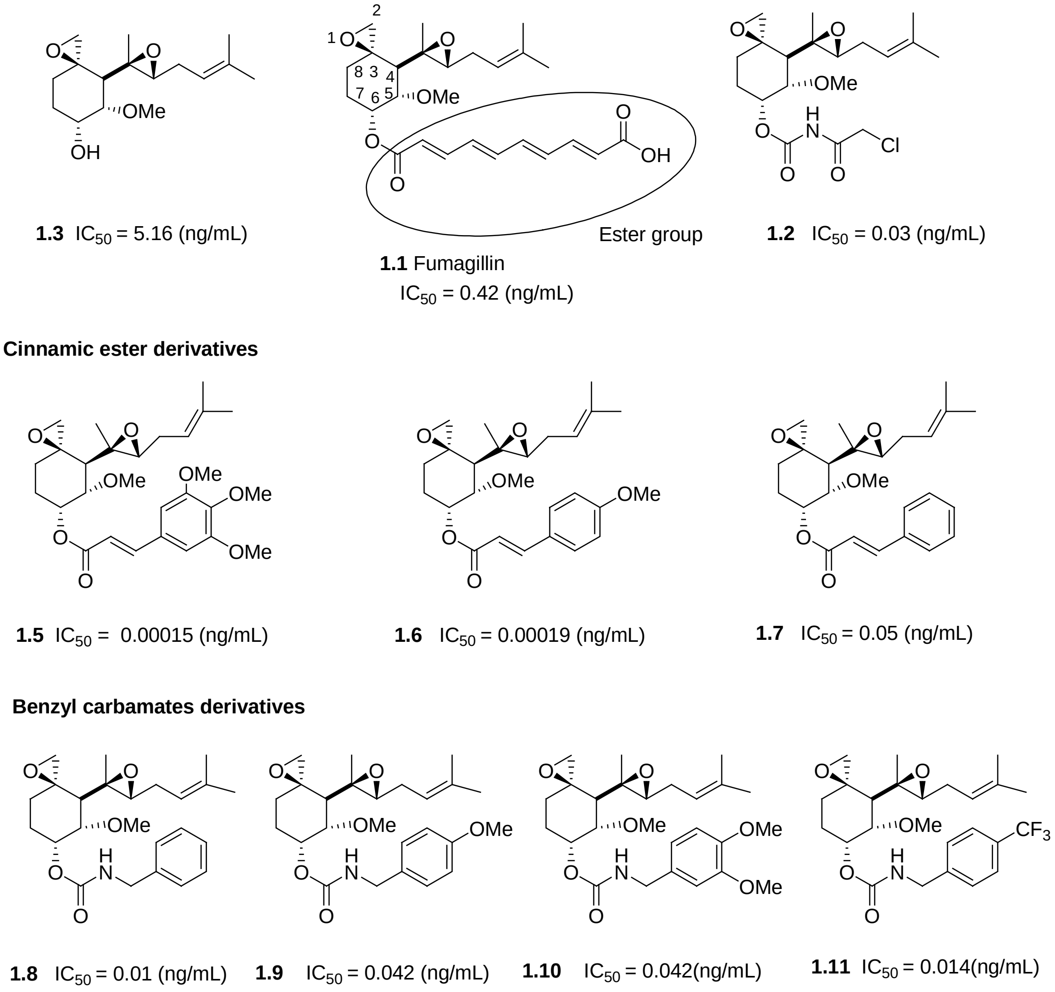
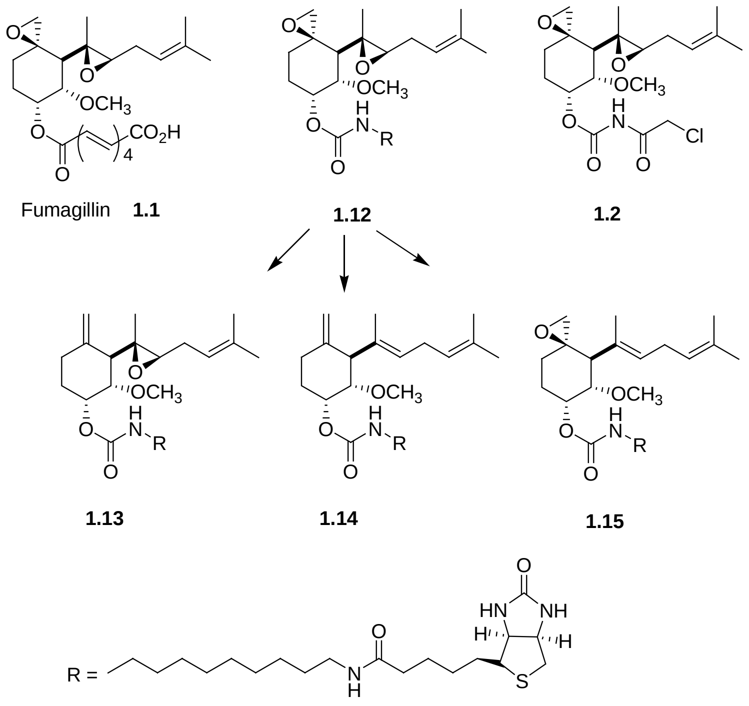


Figure 1.6. Modified C6 analogues: In vitro cell proliferation activity of fumagillin derivatives against lymphoma EL-4 cell.

1.3.2 C4 side chain modification

In another study conducted by Liu *et al*, it was demonstrated that removal of side chain epoxide in biotin-esters and biotin-carbamates of fumagillol (**Scheme 1.1.**) did not result in significant loss of activity in a MetAP-2 binding assay (**Table 1.1**. **1.12** IC$_{50}$ = 1.04x10^{-8}M; **1.15** IC$_{50}$ = 3.40x10^{-9}M).



Scheme 1.1.Chemical structure of biotin-funagillin conjugate

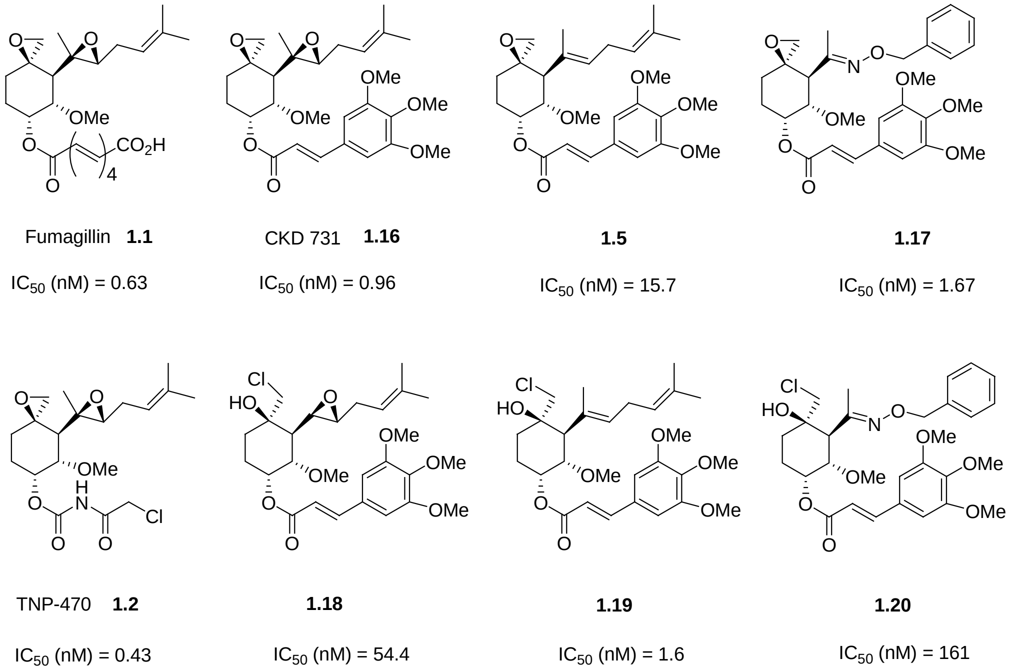
Table1.1. IC_{50} values for deoxyfumagillin analogues

In MetAP-2 and in endothelial cell proliferation

	IC_{50}, M	
	MetAP-2 activity	BAEC proliferation
1.12	$1.04\text{x}10^{-8}$	$1.77\text{x}10^{-10}$
1.13	4.00x10-3	$1.59\text{x}10^{-9}$
1.14	$> 1.0\text{x}10^{-4}$	$8.25\text{x}10^{-3}$
1.15	$3.40\text{x}10^{-9}$	$5.35\text{x}10^{-9}$

However, the removal of the ring epoxide caused a significant decrease of potency (10/1000 to the original level), suggesting that the ring epoxide plays a crucial role in the binding of fumagillin to MetAp-2

Fardis and co-workers investigated the effect of modifications at C4 and C6.[20] On the basis that the exocyclic epoxide was not essential,[12,21] a series of fumagillin analogues were synthesized and evaluated (**Figure 1.7**).



Fumagillin **1.1**
IC_{50} (nM) = 0.63

CKD 731 **1.16**
IC_{50} (nM) = 0.96

1.5
IC_{50} (nM) = 15.7

1.17
IC_{50} (nM) = 1.67

TNP-470 **1.2**
IC_{50} (nM) = 0.43

1.18
IC_{50} (nM) = 54.4

1.19
IC_{50} (nM) = 1.6

1.20
IC_{50} (nM) = 161

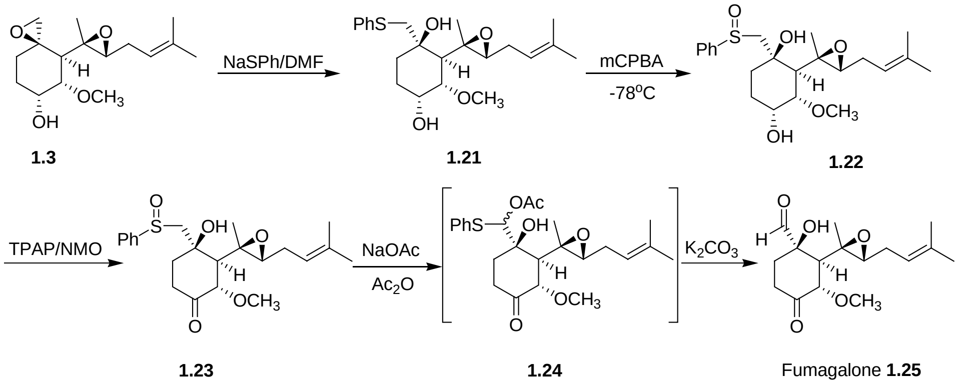
Figure 1.7. Activity of a series of fumagillin derivatives in enzymatic assay (MetAP-2).

Analogues containing the cinnamoyl moiety at C6 were initially prepared, since the CKD-731 **1.16** was reported to be one of the most potent inhibitors of MetAP-2. A series of analogues in which the spiroepoxide was replaced with a chlorohydrin residue were also evaluated, because the replacement of the spiroepoxide in fumagillin with chlorohydrin was shown to be as effective as the parent compound.[22] In addition, fumagillin analogues in which the exocyclic epoxide is replaced with oxime functionality were also synthesized. The MetAP-2 assays indicated that C4 alteration from the exocyclic epoxide to the E-oxime was tolerated, although activity of these compounds was slightly decreased (fumagillin IC_{50} = 0.63 vs **1.17** IC_{50} = 1.67 nM). Compounds **1.5** and **1.16-1.20** were synthesized from fumagillol, the hydrolyzed product of fumagillin.

1.3.3 Modification of cyclohexane ring

In addition to changes at C4 and C6 of the cyclohexane ring, a series of modified cyclohexane analogues in which the spiroepoxide is modified were also synthesized and evaluated. As mentioned above, Fardis and co-workers demonstrated that the chlorohydrin analogue of the fumagillin spiroepoxide is as effective as the parent compound.

Following the latter result, Liu and co-workers[23] reported the synthesis of fumagalone in which the spiroepoxide is replaced by an aldehyde (**Scheme 1.2**).



Scheme 1.2. Synthesis of fumagalone

According to Liu's study, the irreversible binding of TNP-470 to MetAP-2 could be responsible in part for its dose-limiting side effects. Thus, a reversible inhibitor, such as fumagalone represent a good candidate for developing new angiogenesis inhibitors that are less toxic than TNP-470. Liu reasoned that conversion of the spiroepoxide into an aldehyde would allow for the retention of the bonding distance between the C2 carbon in fumagillin and the nitrogen of His231 in MetAp-2. The biological evaluation conducted on fumagalone showed that fumagalone is active as an inhibitor of MetAP-2 *in vitro* and endothelial cell proliferation *in vivo* (**Table 1.2**). However, the latter study showed a decrease in potency of fumagalone as compared to fumagillin.

Table 1.2. biological activity of fumagillin and fumagalone

	IC_{50} (μM)	
	BAEC Proliferation	MetAP-2
Fumagillin	0.001	0.2
Fumagalone	0.0052	8.0

Eustache *et al* developed an enantioselective approach to analogues of fumagalone and evaluated their biological activity against MetAP-2 (**Figure 1.8**). [24] Except for aldehyde **1.26**, which showed weak biological activity, none of the other analogues significantly, inhibited MetAP-2.

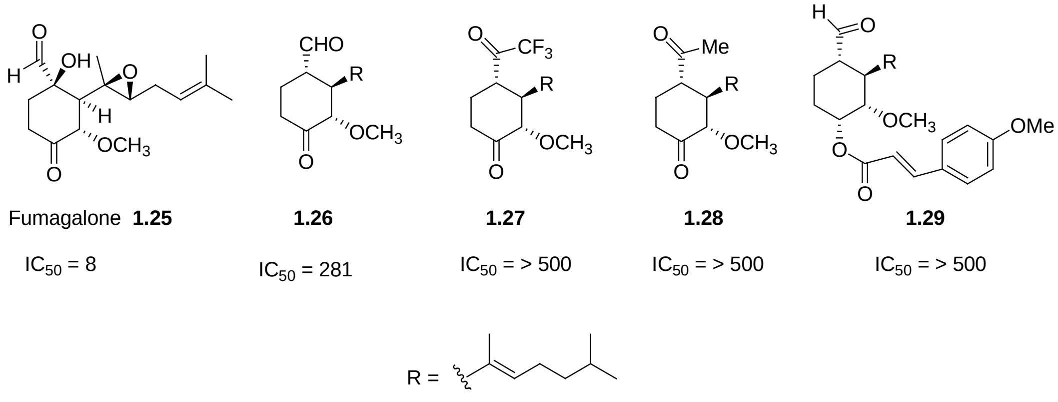


Figure 1.8. MetAP-2 inhibition by compound **1.26**, **1.27**, **1.28**, and **1.29**.

In a different study, Eustache reported a strategy that allows both modification of the side chain and cyclohexane ring (**Figure 1.9**).[25]

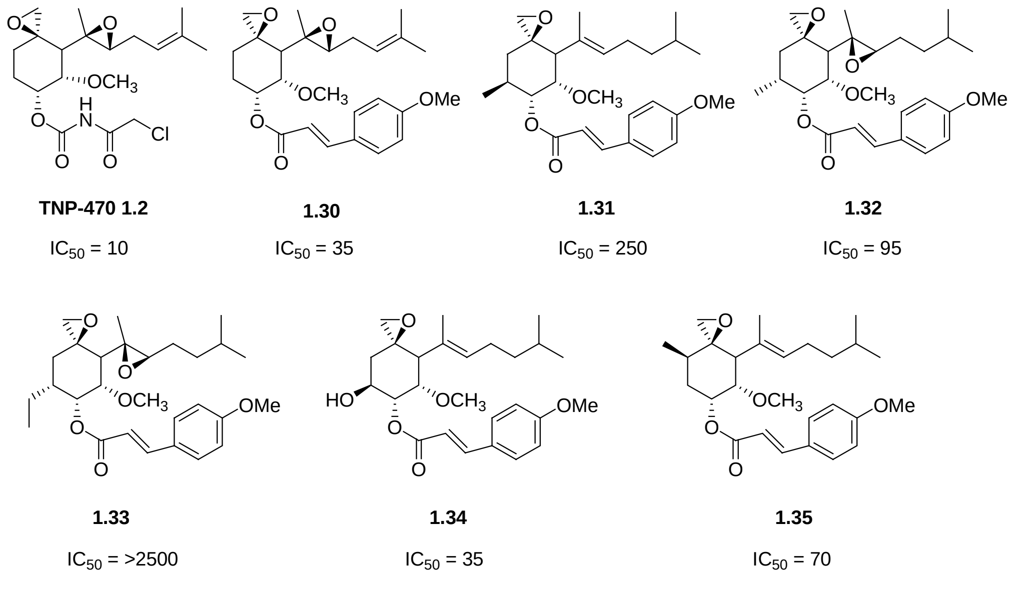
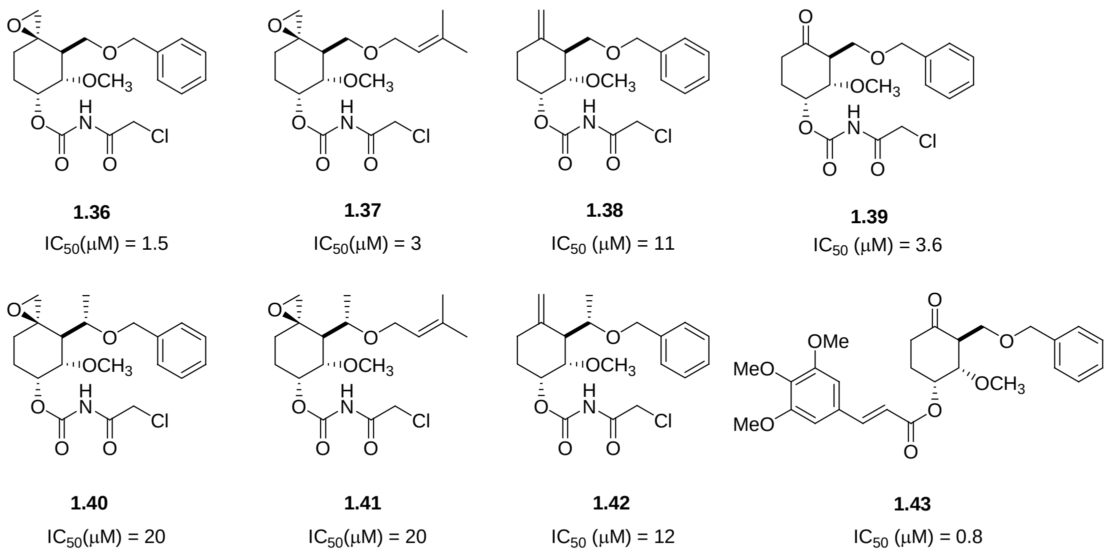


Figure 1.9. MetAP-2 Inhibition by TNP-470 and Ring-modified analogues. IC$_{50}$ (nM).

The biological activity of the latter analogues against MetAP-2 was measured. Preliminary results obtained with the C7-C8 modified compounds suggested that modification in this part of the fumagillin skeleton is limited to the introduction of small substituents.

More recently, Mazitschek and Giannis examined the activity of fumagillin and ovalicin analogues (analogues lacking one or both reactive epoxides) in an endothelial cell proliferation assay. [26] (**Figure 1.10**). Although these analogues, showed encouraging biological activity, their IC_{50} values remained much higher than the parent compound (TNP-470 **1.2** $IC_{50} = 2.5\ 10^{-11}$M) (**Figure 1.10**).



1.36 IC_{50}(μM) = 1.5

1.37 IC_{50}(μM) = 3

1.38 IC_{50} (μM) = 11

1.39 IC_{50} (μM) = 3.6

1.40 IC_{50}(μM) = 20

1.41 IC_{50}(μM) = 20

1.42 IC_{50} (μM) = 12

1.43 IC_{50} (μM) = 0.8

Figure 1.10. Side chain modified analogues: Giannis's synthesis

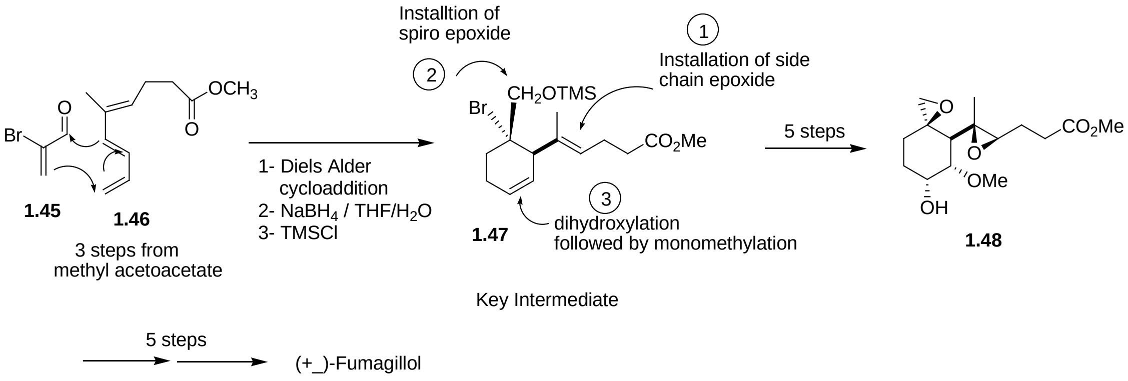
According to the IC_{50} values in (**Figure 1.10**), the presence of spiroepoxide has no major impact on the activity in comparison to the ketones or methylene derivatives. To explain this result, Giannis and co-workers suggested that these new analogues might be binding with a modified geometry to the target, resulting in inactive orientation of the epoxide.

Among these tested fumagillin analogues, compound **1.43**, which lacks both reactive epoxides and posses the cinnamyl ester at C6, was found to be the most potent inhibitor of endothelial cells proliferation. Thus, this derivative represents a new lead structure for the development of potent anti-angiogenic drugs.

1.4 Synthetic approach to fumagillin analogues

Corey and Snider conducted the first total synthesis of fumagillin, in racemic form, in 1972[27]. Following this elegant synthesis, this area of research remained calm for about 25 years. In the past seven years, five enantioselective and two racemic syntheses of (-)-fumagillin/(-)-fumagillol[28,29,30,31,32,33,34,35] have been published.

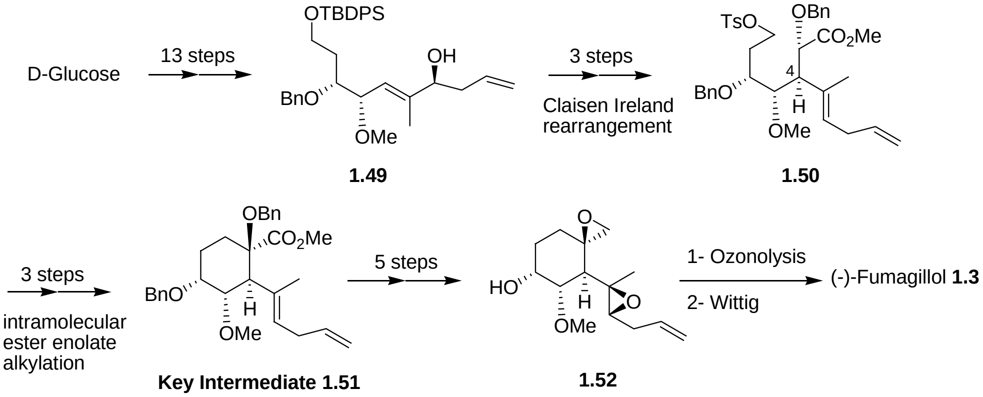
The Corey's synthesis [27] started with the Diels Alder reaction of 2-bromoacrolein **1.45** and triene **1.46**, followed by elaboration of the Diels Alder adduct to the key intermediate **1.47** (**Scheme 1.3**). Stereoselective epoxidation of the more reactive double



Scheme 1.3. Corey's synthesis

bond was followed by installation of the spiro epoxide with inversion of configuration at the brominated carbon. Dihydroxylation of the endocyclic double bond followed by selective methylation of the resulting diol afforded compound **1.48**. Installation of the tetra-enyl ester side chain completed the synthesis of racemic fumagillin in 16 steps from the methyl acetoacetate.

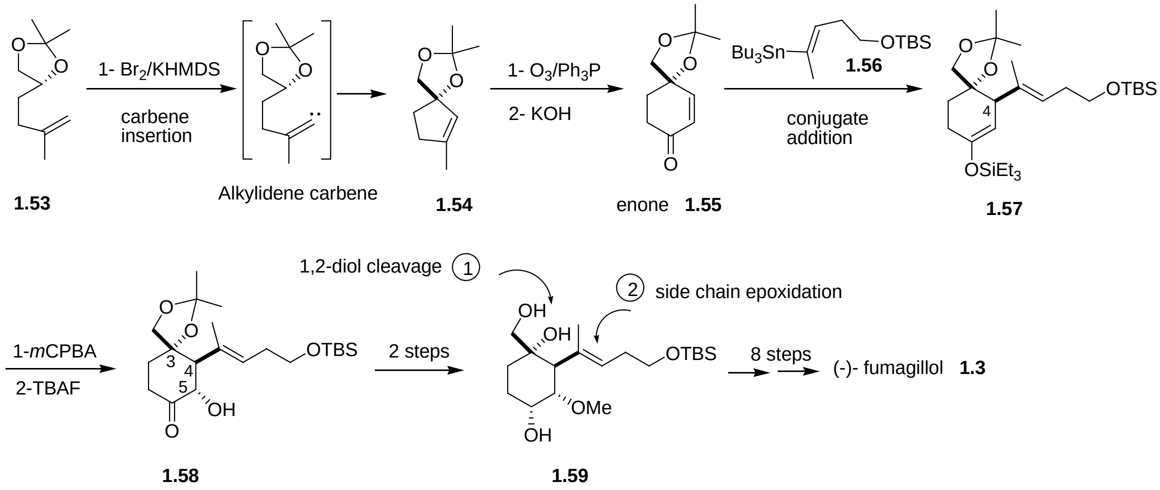
The first enantioselective synthesis of (-)- fumagillol was completed by Kim *et al.* [32] The key steps were Claisen Irland rearrangement on glycolate-diene **1.49** and an intra-molecular ester enolate alkylation on tosylate-ester **1.50** (**Scheme 1.4**). Several points are



Scheme 1.4. Kim’s synthesis

noteworthy. High stereocontrol was obtained at the evantual C-4 position in the rearrangement leading to **1.50** .The two epoxides were installed in succession: The spiro epoxide was installed by internal Williamson ether formation; and the side chain epoxide was next introduced by oxidation of the more reactive alkene with *m*-CPBA. Ozonolysis of the mono-substituted double bond in **1.52** followed by Wittig olefination completed the synthesis of (-)-fumagillol in 26 steps from D-glucose.

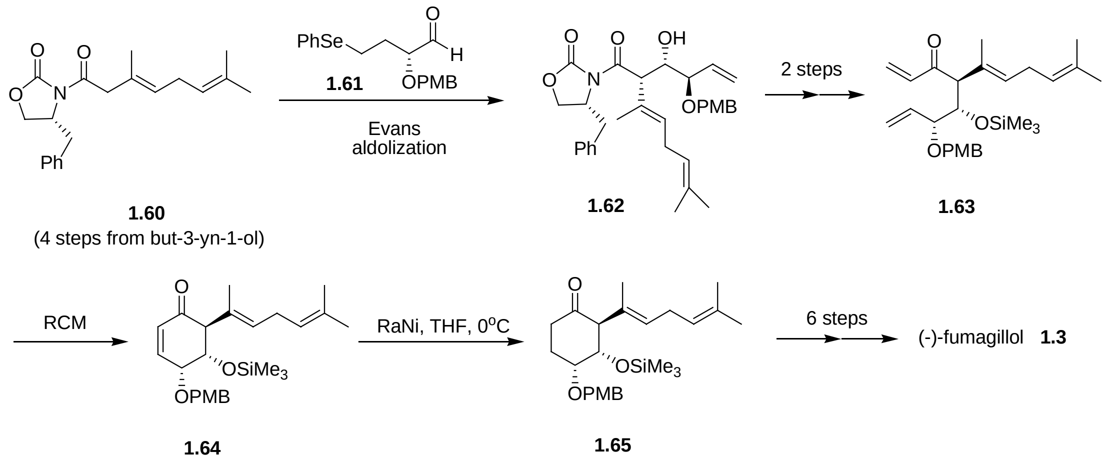
The second stereoselective synthesis of fumagillin was completed by Taber *et al.* [31] Taber's approach was characterized by conjugate addition to the enantiomerically pure enone **1.55**, followed by oxygenation of the derived enolate (**Scheme 1.5**). The key step



Scheme 1.5. Taber's synthesis

in the synthesis of enone **1.55** was the conversion of alkene **1.53** into the C-H insertion product **1.54** via the intermediate alkylidene carbene. The side chain was installed stereoselectively by conjugated addition of cuprate derived from the silylether **1.56** to enone **1.55**. Selective desilylation of **1.57** with TBAF/THF buffered with solid NH_4Cl afforded hydroxy ketone **1.58**. The configuration at the newly formed stereocenter (C5) was apparently controlled by the stereochemistry at C4. Methylation of the secondary hydroxyl group followed by stereoselective reduction of the ketone provided the desired intermediate **1.59** as a single isomer. Introduction of the spiro epoxide with the correct configuration at C3 was accomplished by oxidative cleavage of the viccinal diol moiety in **1.59**, followed by the selective sulfoxonium ylide attack on the resulting ketone. Side chain epoxidation was followed by desilylation of the primary alcohol and oxidation to the corresponding aldehyde. Wittig olefination completed the asymmetric total synthesis of fumagillol in 15 steps from enone **1.55**.

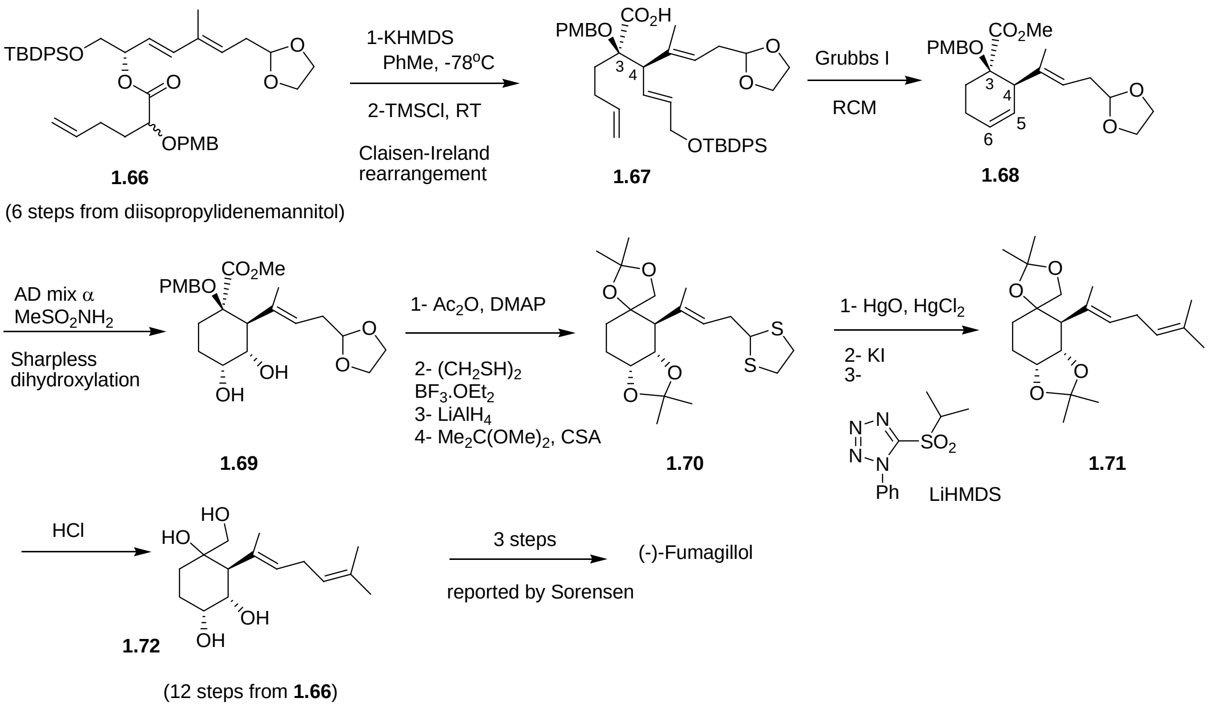
Three common strategic points characterize the syntheses described above: construction of a functionalized cyclohexane ring, sequential installation of the functional groups (the ring diol, the spiro epoxide, and the side chain epoxide), and elaboration of the side chain. Eustache's group[28] described a third enantioselective synthesis of (-)-fumagillin by a totally different strategy (**Scheme 1.6**).



Scheme 1.6. Eustache's synthesis

This new approach is based on two key-steps: an Evans aldol condensation (of **1.60**, a substrate containing a pre-installed side chain, and aldehyde **1.61**) to secure the relative relationship of the three stereogenic centers (C4, C5, C6, fumagillin ring numbering), and a ring closing metathesis on **1.63** to generate the cyclohexene **1.64**. Reduction of the α-β-unsaturated ketone in **1.64** with Raney nickel afforded the substituted cyclohexanone **1.65**. As in Taber's synthesis, the spiro-epoxide was introduced via selective sulfoxonium ylide attack on **1.65**. Selective epoxidation, followed by extension of side chain completed the synthesis of fumagillol in 10 steps from **1.60** (**Scheme 1.6**).

More recently, Langlois[30,33] presented a formal synthesis of (-)-fumagillol, involving a Claisen-Ireland rearrangement (on ester **1.66**), and a ring closing metathesis (on **1.67**) (**Scheme 1.7**). Eustache's synthesis is based on unusual disconnection between

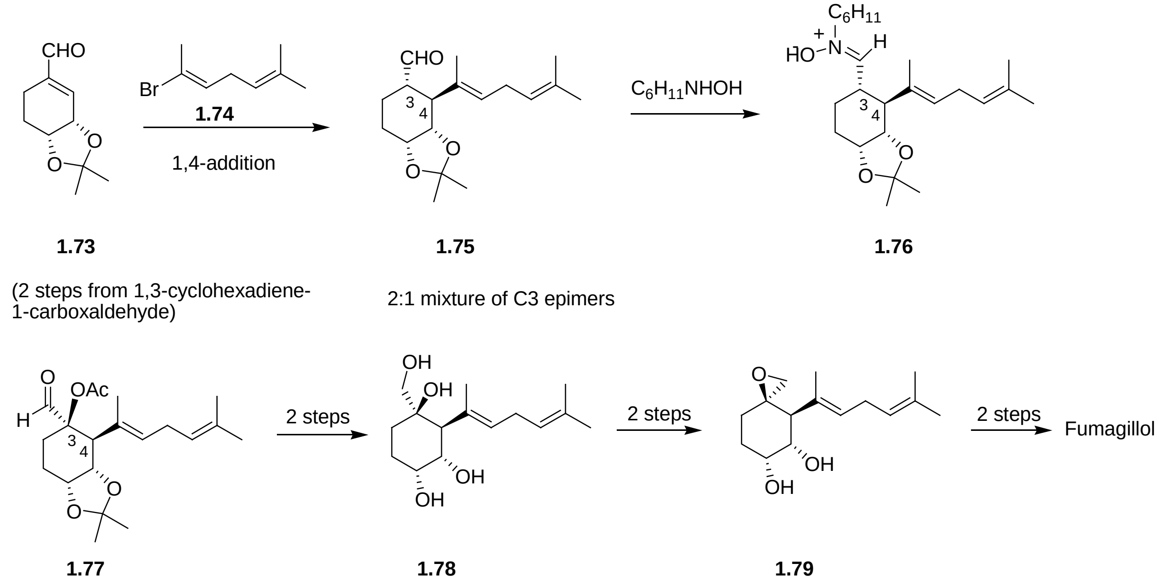


Scheme 1.7. Langlois's synthesis.

C5 and C6. The relative stereochemistry of C3 and C4 in **1.67** is controlled in the rearrangement step. The challenge in this approach was selective dihydroxylation of the endocyclic double bond in presence of the theoretically more reactive tri-substituted side chain double bond in **1.68**. Careful, application of Sharpless dihydroxylation protocol afforded the desired diol **1.69** in 50% yield. At this stage, all the stereogenic centers have been fixed. Diol **1.69** was converted to the bis(acetonide) dithioacetal **1.70** in 4 straitforward steps. Cleavage of the dithioacetal with a mixture of $HgO/HgCl_2$ in acetone/water, followed by treatment with an aqueous solution of KI, and a subsequent Julia-Kocienski olefination reaction[36] afforded the diene **1.71**. Final hydrolysis of the acetonides in **1.71** provided the tetrol **1.72** in 12 steps from ester **1.66.** Sorensen has converted Tetrol **1.72** into fumagillol in three steps.

In addition to the enantioselective syntheses of fumagillin/fumagillol presented above, two more racemic syntheses of fumagillin/fumagillol, based on a very similar approach, were published. This common approach is characterized by a nucleophilic addition of a pre-constructed side chain to a cyclohexane residue containing an electrophilic site.

The essence of Sorensen's synthesis is a vicinal difunctionalization of the electron-deficient alkene of enal **1.73**. [35] Thus, treatment of enal **1.73** with organocuprate reagent derived from vinyl bromide **1.74** afforded a 2:1 mixture of C3 epimers in favor of aldehyde **1.75 (Scheme 1.8)**. The cyclic protecting group in enal **1.73** dictated the stereochemical course of the crucial carbn-carbon bond formation. The next task was to introduce the needed C3 oxygen via an enolate or silyl enol ether of aldehyde **1.75**.

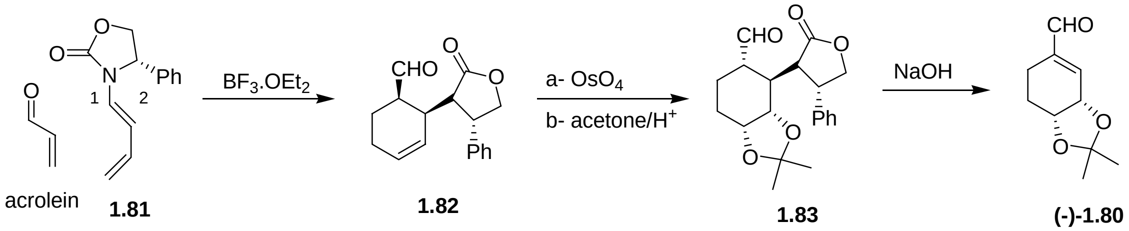


Scheme 1.8. Sorensen synthesis

However, according to Sorensen, significant difficulties were encountered. An alternative solution was to convert aldehyde **1.75** into N-cyclohexylnitrone **1.76** followed by treatment with acetyl chloride and triethyl amine, and subsequent hydrolysis with mild aqueous acid to afford aldehyde **1.77**. Aldehyde **1.77** was converted to tetrol **1.78** in 2 straightforward steps. Selective conversion of the primary alcohol in **1.78** into the corresponding methanesulfonate ester followed by treatment with methanolic sodium hydroxide solution afforded the spiroepoxide **1.79**. Selective epoxidation of the interior side chain double via Sharpless's vanadium-based epoxidation and subsequent treatment with tert-butoxide and iodomethane resulted in the selective formation of (±)-fumagillol.

With a synthesis of (±)-fumagillol accomplished, Sorensen subsequently developed an enantioselective version of this synthesis starting from opticallyl pure enal

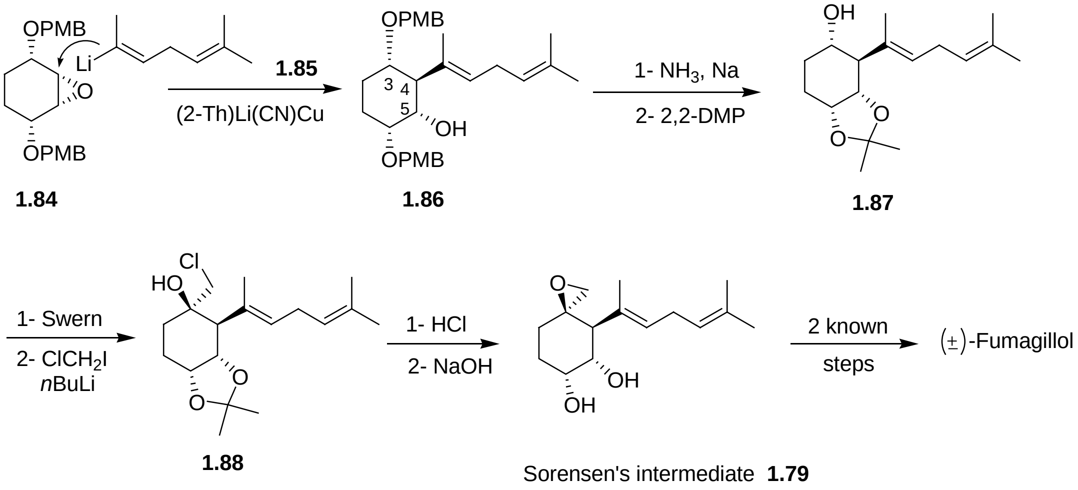
1.80. [29] The synthesis of **1.80** utilized a chiral auxiliary-controlled Diels Alder reaction on Stevenson's chiral diene **1.81** [37](**Scheme 1.9**). Treatment of chiral diene **1.81** with



Scheme 1.9.

acrolein and $BF_3.OEt_2$ produced endo cycloadduct **1.82** as the sole product. Dihydroxylation under Upjhn conditions exclusively occurred on the less-hindered face of the ring, and acid-catalyzed ketalization provided isopropylidene **1.83** with an equatorial aldehyde after epimerization. Enantiomerically pure **1.80** was then obtained by β-elimination of the oxazolidinone auxiliary.

Simpkins developed a very similar approach to Sorensen's. Simpkins's stategy was based on the ring opening of the *meso*-epoxide **1.84** (obtained from cyclohexadiene in three steps) with the cuprate derived from alkenyllithium **1.85** (**Scheme 1.10**).[34]



Scheme 1.10. Simpkins's synthesis

As in Sorensen's strategy, introduction of the pre-assembled side chain allows the control of the relative configurations at C4, C5 and C6. Removal of PMB protecting groups in **1.86** under Birch conditions followed by ketalization of vicinal diol provided the hydroxyacetonide **1.87**. Installation of the spiro epoxide was effected by conversion of **1.87** to the chlorohydrin **1.88** in two straightforward steps. Exposure of **1.88** to base provided epoxy-diol **1.79** identical to an intermediate in the Sorensen synthesis.

Summary

Since the discovery that fumagillin is a potent inhibitor of angiogenesis, many semi synthetic and synthetic fumagillin analogues, resulting from modification of the acyl group, have been synthesized. TNP-470 (an acyl modified side chain) was found to be the most active against MetAP-2. TNP-470 is currently in phase III clinical trial for the treatment of a variety of cancers.[38] However, angiogenic activity of TNP-470 has been associated with significant side effects. Hence, the search for new analogs is an active area of research.

On the basis of inspection of the MetAP-2-fumagillin complex, Clardy et al. determined several sites of the fumagillin molecule important for the binding to MetAP-2:

1. The spiroepoxide moiety plays a crucial role by creating a covalent bond with His231.
2. The long unsaturated side chain makes two hydrophobic contacts with Leu328 and Leu447. The terminal carboxyl group of the side chain makes hydrogen bonds with Asp376.
3. The side chain is involved in the recognition process in two ways. In addition to establishing hydrophobic interactions with several lipophilic amino acids, it interacts with the protein via the side chain epoxide which functions as an H-bond acceptor for a defined water molecule within the enzyme's recognition site.

This binding model has been used for targeted modification of the fumagillin structure. Accordingly, a wide range of structures using a variety of strategies have been developed:

1. C6 side chain modification: the cinnamic acid ester and benzyl carbamates derivatives showed more potent activity than TNP-470.
2. C4 side chain modification: The MetAP-2 assays showed that C4 side chain epoxide is dispensable. Indeed, C4 alteration from exocyclic epoxide to E-oxime was tolerated, although activivty of these compounds was decreased.
3. Cyclohexane ring modification: It has been shown that the chlorohydrin analogue of the fumagillin spiroepoxide is as effective as the parent compound. However,

conversion of the spiroepoxide in fumagillin into an aldehyde (fumagalone) shows a decrease in potency.

The aim in this part I of this thesis research was the development of synthetic strategies towards different C4 side chain analogs. Such syntheses are relevant to structure activity relationship investigations aimed at understanding how side chain modification affects the overall pharmacology of this group of antiangiogenic agents. While it is clear that modification of the C4 side chain attenuates activity to different degrees, the mechanisms of action of these analogs are not clear. These changes may impact the contact interaction with the proposed target MetAP-2.

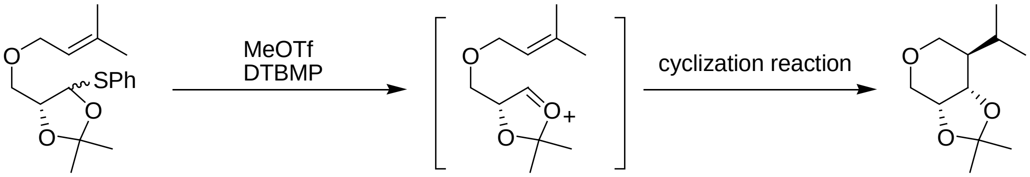
A synthetic strategy that allows for a wide variety of C4 side chain analogs would be valuable for understanding the effect of C4 side chain modification on the overall pharmacology.of this class od antiangiogenic agents.

CHAPTER II:

Synthesis of fumagillin analogues via cyclization of precursor containing pre-installed side chain

2.1 Retrosynthesis

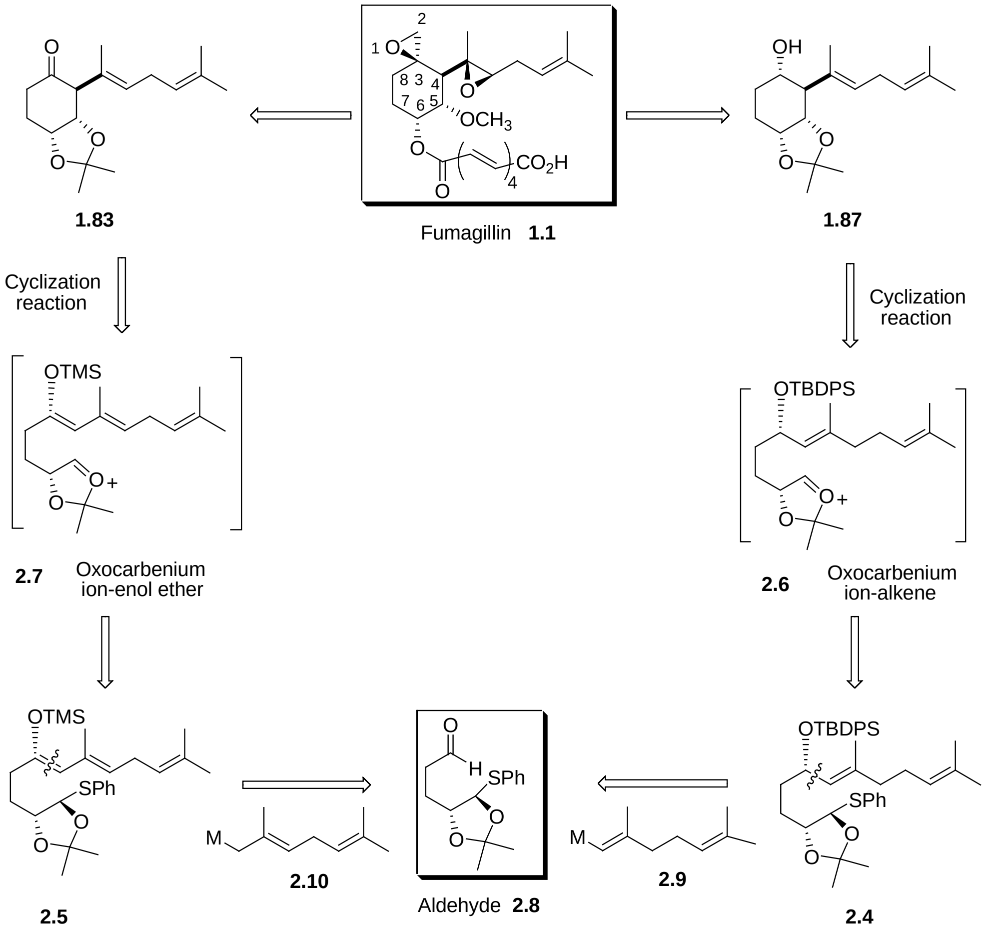
Our approach to fumagillin analogues is based on previous studies from our laboratory, on the cyclization of complex oxocarbenium ions.[39] Treatment of the 1-phenylthio-1,2-O-isopropylidene acetal-alkene **2.1** with methyl triflate led to a single diastereomer **2.2**, in which the isopropenyl appendage was *anti* to the *syn* isopropylidene residue. This reaction presumably proceeds through cyclization of the oxocarbenium ion-alkene intermediate **2.3** (**Scheme 2.1**).



2.1 Oxocarbenium ion **2.3** **2.2**

Scheme 2.1. C-branched cyclitols via oxocarbenium ion cyclization.

Application of this concept to **1.87** and **1.83** (Simpkins' intermediates to fumagillol) could proceed through cyclization precursors such as **2.4** and **2.5**, respectively (**Scheme 2.2**). Simpkins' synthesis showed that **1.87** and **1.83** could be converted into fumagillin **1.1** in five and six steps, respectively. Thus, **2.4** and **2.5** could provide oxocarbenium ion-alkene **2.6** and oxocarbenium ion-enol ether **2.2**, which would lead to **1.87** and **1.83** respectively. The synthesis of cyclization precursors **2.4** and **2.5** could be achieved from the common starting aldehyde **2.8** by alkylation with **2.9** and **2.10**, respectively.



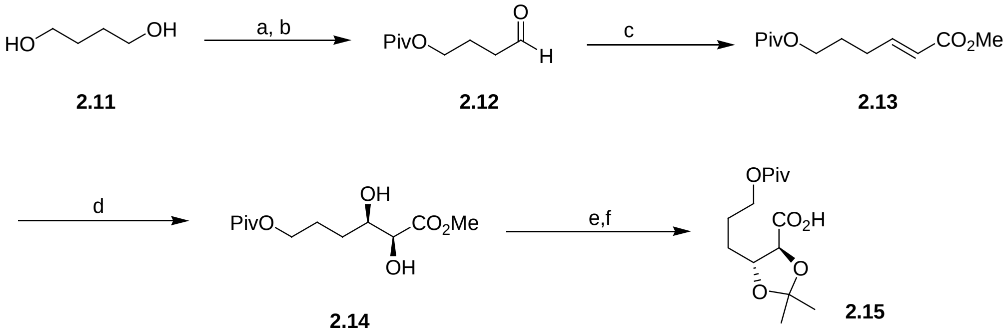
Scheme 2.2. Retrosynthesis

The synthesis of aldehyde **2.8** is first presented, followed by the attempted synthesis of **1.83** and **1.87**.

2.2 Results and discussion

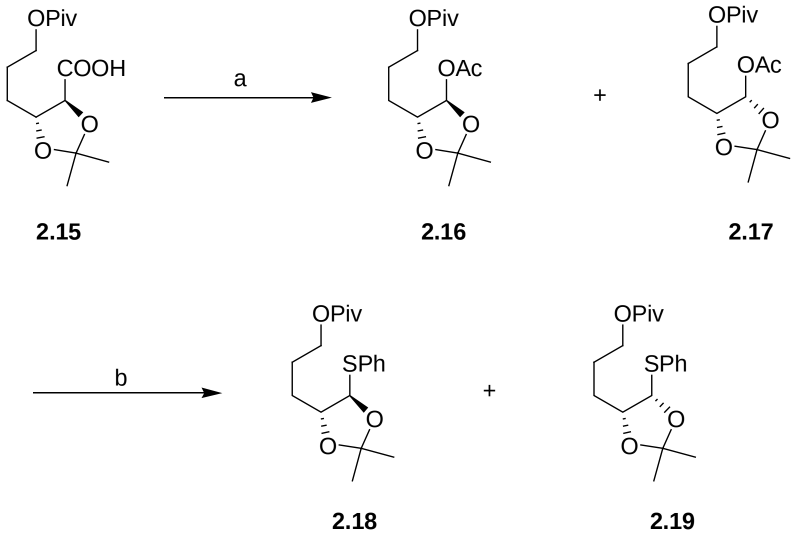
2.2.1 Synthesis of aldehyde 2.8

Aldehyde **2.8** was prepared from commercially available 1,4-butane diol **2.11** (**Scheme 2.3**). Selective protection of the diol **2.11** as the mono-pivalate ester,[40] followed by PCC oxidation of the resulting alcohol afforded aldehyde **2.12**. The protected aldehyde **2.12** was subjected to Wittig olefination to afford methyl (*E*)-1-pivaloylxy-2-hexenoate **2.13**, which was then treated under Sharpless asymmetric dihydroxylation conditions with AD-mix-β to afford the diol **2.14**. Mosher ester of **2.14** indicated an ee of greater than 95%. The absolute stereochemistry of **2.14** was based on the results for the dihydroxylation of closely related *E*-disubstituted alkenes.[41] Protection of the diol **2.14**, followed by selective hydrolysis of the methyl ester, furnished **2.15**, in 69% over six steps from **2.11**.



Scheme 2.3. (a) PivCl, DMAP, Pyr, CH_2Cl_2, 60%; (b) PCC, CH_2Cl_2, 95%; (c) PhP=$CHCO_2Me$, CH_3CN, 93%; (d) AD-mixβ, tBuOH-H_2O, $MeSONH_2$, 90%; (e) $(MeO)_2CMe_2$, CSA, CH_2Cl_2, 97%; (f) THF-aq KOH, 92%.

The synthesis of the 1-phenylthio-1,2-*O*-isopropylidene acetal followed a variation of the Suarez radical fragmentation of 1,2-O-isopropylidene sugars.[42] Thus, exposure of **2.15** to iodosobenzene diacetateand iodine under anhydrous conditions provided an unseparated mixture of 1-acetoxy-1,2-*O*-isopropylidine acetals **2.16** and **2.17** (**Scheme 2.4**). Boron trifluoride catalyzed acetal exchange on this mixture with thiophenol at low temperature led to a 9/1 mixture of *anti*/*syn* acetal isomers **2.18** and **2.19**, in 80% yield from **2.15**. The relative stereochemistry of **2.18** and **2.19** was tentatively assigned by examination of the proton NMR trends for anti/syn pairs of 1,2-diol acetonides (**Table 2.1**). The isomer for which the two methyl groups appeared as a 6H singlet (s 1.46 ppm) was assigned as *trans* (i.e., **2.18**), and the other which showed resolved 3H singlets (d, 1.38 and 1.63 ppm), was assigned as *syn* (i.e, **2.19**).[43]

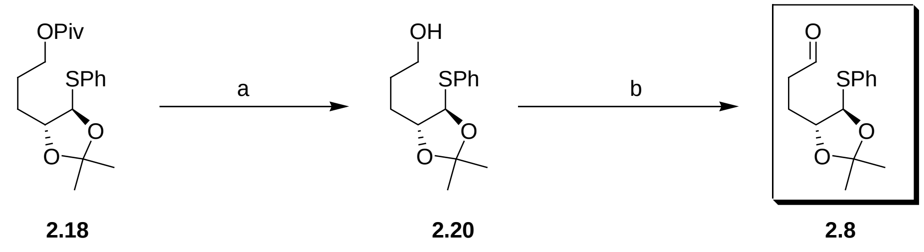


Scheme 2.4. (a) PhI(OAc)$_2$, I$_2$, CH$_2$Cl$_2$; (b) PhSH, BF$_3$.OEt$_2$, CH$_2$Cl$_2$, 80% for two steps

Table 2.1. ^{1}H and ^{13}C NMR of acetonide methyl groups

	^{1}HNMR, ppm	^{13}C NMR, ppm
1,2 acetonide **2.18**	1.46	28.2
1,2 acetonide **2.19**	1.38 and 1.63	29.5 and 27.8

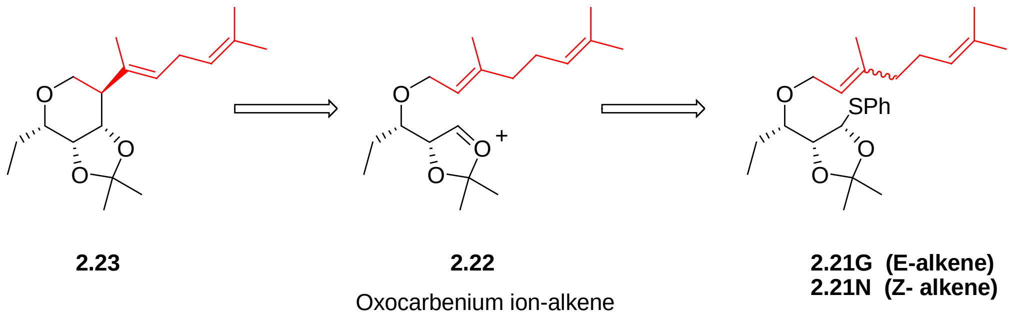
The subsequent reactions were carried out on the major *anti* isomer, **2.18**. DIBALH reduction of **2.18** and oxidation of the resulting alcohol **2.20** gave aldehyde **2.8** (**Scheme 2.5**).



Scheme 2.5. (a) DIABALH, CH_2Cl_2, -78 °C, 94%; (b) Swern, CH_2Cl_2, -78 °C, 94%.

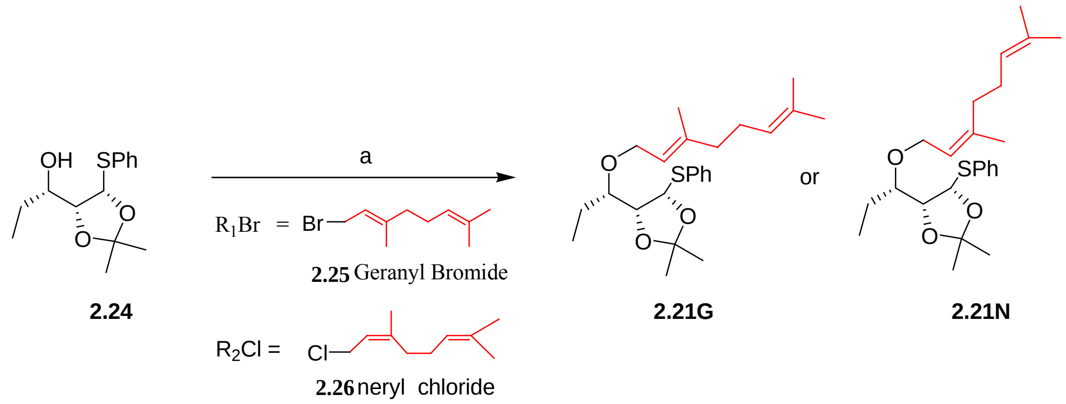
2.2.2 Model study for 1.87

With the aldehyde **2.8** in hand, our next task was the synthesis of cyclization precursor **2.6** followed by the key cyclizations reaction (**Scheme 2.2**). However, we decided to evaluate the cyclization process on the easily accessed dienes **2.21G** and **2.21N** (**Scheme 2.6**). There are two key questions with this approach. First, could the cyclization reaction of the oxocarbenium ion **2.22** deliver a product in which the side chain appendage and the *cis*-fused isopropylidene exist in an *anti* relationship? Second, would the tri-substituted alkene (in the cyclization product) have the *E* configuration (as required in fumagillin synthesis)?



Scheme 2.6.

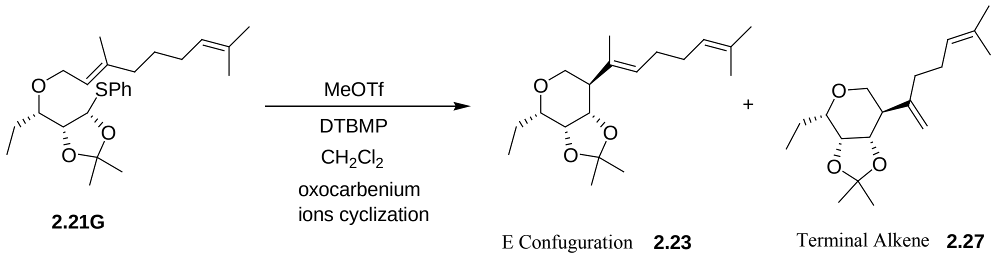
Compound **2.21G** and **2.21N** were obtained by alkylation of known alcohol **2.24**[44] (obtained in five steps from xylofuranose) with geranyl bromide **2.25** and neryl chloride **2.26**, respectively, in an average 62% yield (**Scheme 2.7**). With **2.21N** and **2.21G** in



Scheme 2.7. (a) **2.25** or **2.26**, NaH, Bu$_4$NI, 50 °C, DMF, 62%.

hand, we next investigated the oxocarbenium ion cyclization reaction. Thus, treatment of **2.21G** with MeOTf in presence of a 2,6-*di-tert-butyl*-methylpyridine afforded a separable

2:1 mixture of two regio-isomers **2.23** (desired product) and **2.27** in 67% yield (**Scheme 2.8**). The stereochemistry in **2.23** and **2.27** was assigned by analysis of coupling constant



2.21G

E Confuguration **2.23**

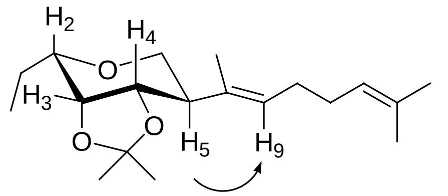
Terminal Alkene **2.27**

Scheme 2.8.

values for vicinal protons on the THP ring (**Table 2.2**). Indeed, the side chain appendage and the *cis*-fused isopropylidene were found to be in the trans relationship. Thus, the cyclization of **2.21G** delivered **2.23** with the desired stereochemistry of the THP ring and the side chain alkene. Additionally, the NOE spectrum analysis reveals that the configuration of the tri-substituted alkene is consistent with an E configuration (**Figure 2.1**).

Table 2.2 Coupling constant values for **2.23**

reagent	yield	Ratio (**2.23**:**2.27**)	J values (Hz)
MeOTf /DTBMP	67%	2:1	$J_{9,3}$ = 10.0 Hz $J_{3,4}$ = 5.0 Hz $J_{4,6}$ = 2.0 Hz



2.23

Figure 2.1 Configuration of 2.23

In an attempt to improve the regioselectivity of the cyclization reaction (**Scheme 2.8**), we decided to use IDCP (iodonium dicollidine perchlorate) to promote the cyclization instead of DTBMP. We presumed that collidine which is more basic and less hindered than 2,6-di-*tert*-butyl-methylpyridine might favor the formation of the desired product **2.23** over the terminal alkene **2.27**. Hence, treatment of **2.21G** with IDCP, in dichloromethane at rt provided a 3:1 ratio of **2.23** and **2.27** in a slightly lower yield (60%, as compared to 67% reported earlier). Thus, the use of IDCP improved slightly the regioselectivity of the cyclizations reaction towards **2.23**, but the yield was lower compared to the reaction with MeOTf. Based on these observations, the MOTf/DTBMP was used as the promoter in subsequent cyclizations.

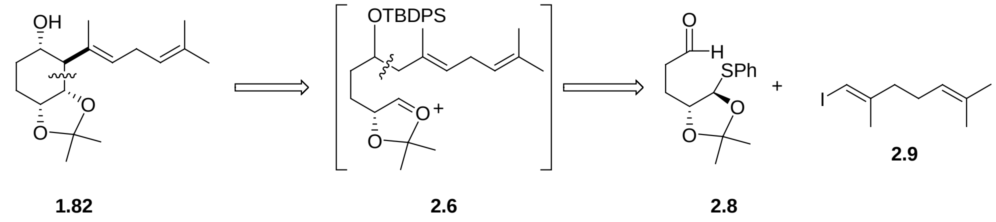
The cyclization of **2.21N** (the tri-substituted alkene with the Z configuration) was next examined. Treatment of **2.21N** with methyl triflate and DTBMP provided a 5:1 ratio of **2.23** and **2.27** in 65% yield. The latter result showed an improvement in regioselectivity toward the desired product **2.23** compared to the reaction of **2.21G**. However the yield of the reaction remained unchanged. Thus, apparently the *Z*-

configuration of the tri-substituted double bond in the cyclization precursor, favors the desired product.

With these encouraging results in hand, the application of this approach to the synthesis to our target molecule **1.87** was next attempted..

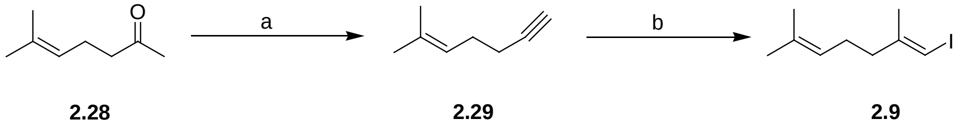
Attempted synthesis of 1.87

This plan entailed coupling of aldehyde **2.8** and the vivnyllithium reagent derived from iodide **2.9** to give **2.6**, followed by the key cyclization reaction. The synthesis of aldehyde **2.8** has been presented earlier (**Scheme 2.9**).



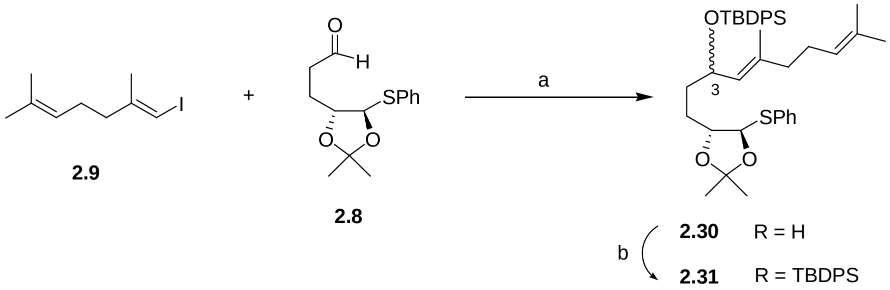
Scheme 2.9.

The synthesis of **2.9** started with the commercially available ketone **2.28**, which was converted to the alkyne **2.29** by a sequential treatment with LiTMP, ClP=O(OEt)$_2$ and LiTMP[45] (**Scheme 2.10**). Carboalumination of **2.29** with Me$_3$Al and Cp$_2$ZrCl followed by a quenching of the resulting aluminium species with I$_2$ afforded the (*E*)-vinyl iodide **2.9** in 51% yield.[46] Next, the iodide **2.9** was treated with *n*BuLi at –78 ^{o}C to generate the



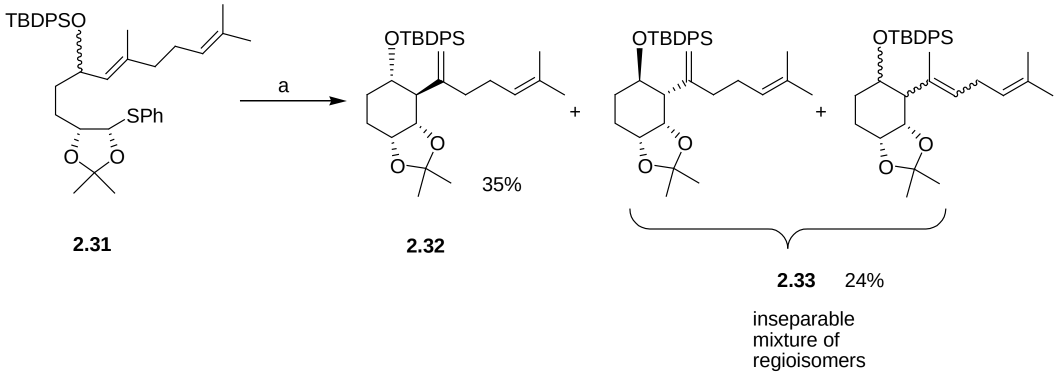
Scheme 2.10. (a) 1-LiTMP (1eq), -78 °C, 2- $ClP{=}O(OEt)_2$, rt, 3- LiTMP(2.5eq), -78 °C; (b) Cp_2ZrCl_2, $AlMe_3$, CH_2ClCH_2Cl, then I_2, 50%.

corresponding alkyl lithium reagent. To the resulting mixture was then added a solution of aldehyde **2.8** in anhydrous ether to give the alcohol **2.30** as a 1:1 mixture of diastereoisomers (in 91% yield). Treatment of **2.30** with TBDPSCl in presence of imidazole provided the silyl ether **2.31** in quantitative yield.



Scheme 2.11. (a) *n*BuLi, -78 °C, Et_2O, 91%; (b) TBDPSCl, imid, 50 °C, DMF, quant.

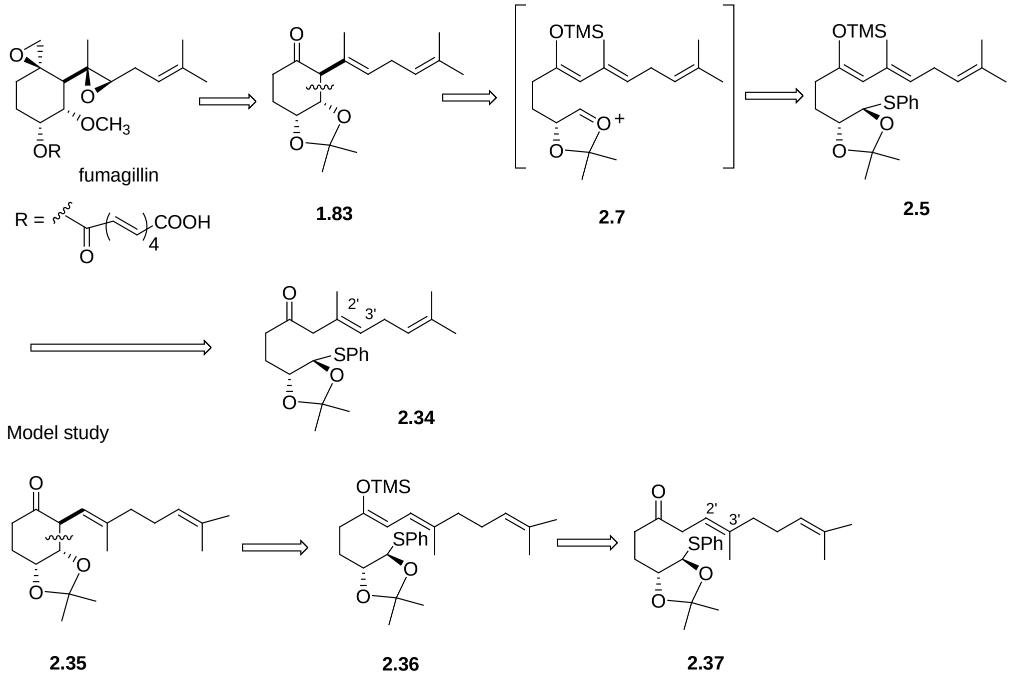
With the intermediate **2.31** in hand, the key cyclization reaction was next examined. To our disappointment, exposure of **2.31** with MeOTf and DTBMP provided a 3:2 mixture of **2.32**:**2.33** (**scheme 2.12**). Partial Chromatographic separation provided **2.32** in 35% yield, based on the starting silyl ether **2.31**. Chromatographic separation of regioisomers **2.33** was not possible. Hence, the stereochemical assignment of different isomers in **2.33** was impossible. The disappointing result led to the evaluation of our second route, i.e synthesis of **1.83** (**Scheme 2.13**).



Scheme 2.12. (a) MeOTf, DTBMP, CH_2Cl_2, rt.

2.2.3 Model study for 1.83

We envisaged that the ketone **1.83** could be obtained from TMS-enol ether **2.5** via cyclization of an enol ether-oxocarbenium ion **2.7**. The enol ether **2.7** should be obtainable from ketone **2.34** (**Scheme 2.13**). The model **2.37** was first used to test the key cyclization reaction. **2.37** and **2.34** are structurally very similar. The side chain in **2.37** is one carbon longer than in **2.34**. Compound **2.37** posses the C3' substituted methyl group, whereas in **2.34** the methyl group is positioned on C2'.



Scheme 2.13.

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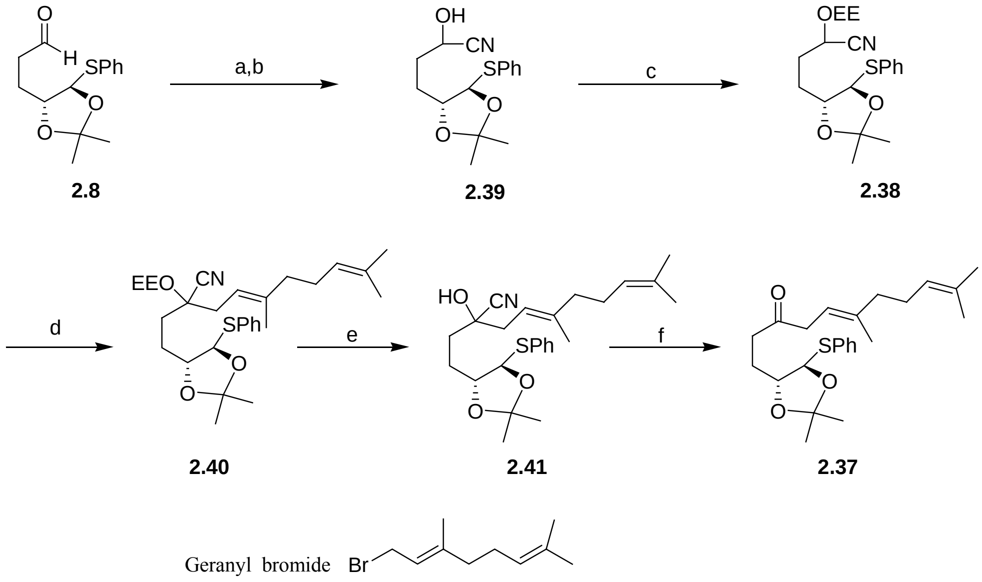
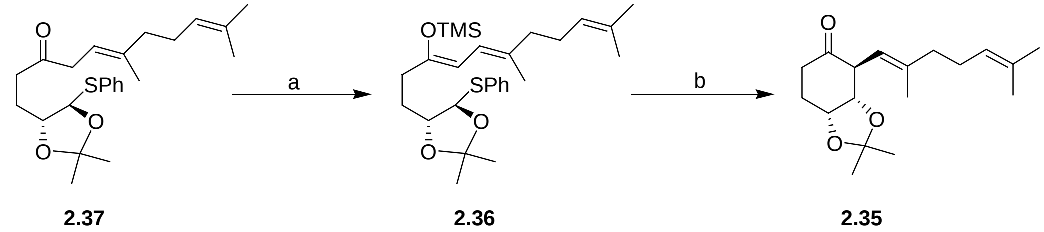
Compound **2.37** was prepared via the coupling of the protected cyanohydrin **2.38** and geranyl bromide following the Stork methodology (**Scheme 2.14**). The synthesis of protected cyanohydrin **2.38** started with the reaction of aldehyde **2.8** with trimethylsilylcyanide in presence of catalytic amount of KCN/18-Crown-6. The crude silylated cyanohydrin so obtained was next treated with TBAF to provide the cyanohydrin **2.39** in 81% yield.[47] Subsequent protection of **2.39** with ethyl vinyl ether afforded **2.38** in quantitative yield. Compound **2.38** was next treated with geranyl bromide in presence of NaHMDS to give the alkylated product **2.40** in 61%.



Scheme 2.14. (a) TMSCN, KCN, 18-Crown-6, THF; (b) H_2O, TBAF, THF, 81% for two steps; (c) Ethyl vinyl ether, PPTs, quant. (d) geranyl bromide, NaHMDS, -78 ^{o}C, THF, 61%; (e) PPTs, 0 ^{o}C, MeOH; (f) 0.5N NaOH, quant.

Regeneration of the corresponding ketone **2.37** was achieved by hydrolysis of 2.**40** to cyanohydrin **2.41**, and subsequent treatment of **2.41** with 0.5N aqueous NaOH.[39] The silylenolether **2.36** was formed by treatment of ketone **2.37** with LDA, followed by quenching with TMSCl (**Scheme 2.15**). Because of the instability of **2.36**, the crude material was used without purification in the cyclization reaction. Treatment of **2.36** with methyl triflate (7 moles equivalents) in presence of DTBMP (9 moles equivalents) provided the cyclization product **2.35** in a relatively low yield (~30% from **2.37**). In order to optimize this transformation, we decided to decrease the amount of the base used in the cyclization step. Accordingly, **2.36** was treated with 3 moles equivalent of base (2,6-di-*tert*-butyl-4-methylpyridine) and 4 moles equivalent of methyl triflate to afford the desired cyclization product **2.35** in a slightly improved yield (50%).



Scheme 2.15. (a) LDA, TMSCl, -78 ^{o}C, THF. (b) DTBMP, MeOTf, CH_2Cl_2, 50%.

The relative stereochemistry of **2.35** was confirmed by analysis of J values for vicinal protons on the cyclohexane ring. Values of $J_{4,5}$ (3.66 Hz) and $J_{5,6}$ (7.32 Hz) suggested a $^{4}C_1$ chair conformation with an equatorial-equatorial arrangement between H_4 and H_5 and equatorial-axial relationship between H_5 and H_6 (**Figure 2.2**).

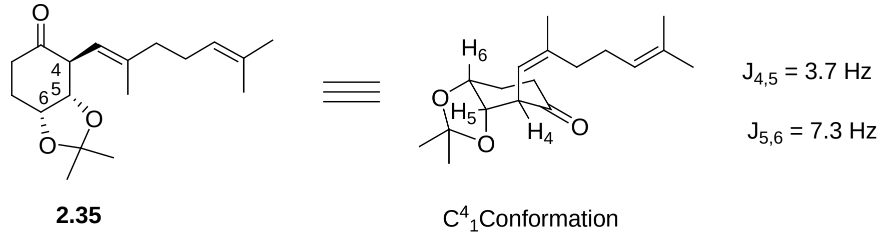
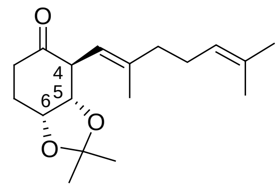


Figure 2.2 Conformational analysis of 2.35

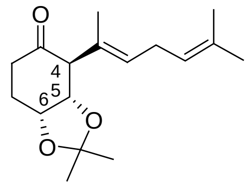
To confirm this result, we compared the $J_{4,5}$ and $J_{5,6}$ values for compound **2.35** to that for **1.83**, an intermediate previously prepared by Simpkins. The $J_{4,5}$ and $J_{5,6}$ values for **2.35** were consistent to that for **1.83** (**Figure 2.3**).



2.35

$J_{4,5}$ = 3.66 Hz

$J_{5,6}$ = 7.32 Hz



1.87

$J_{4,5}$ = 4.0 Hz

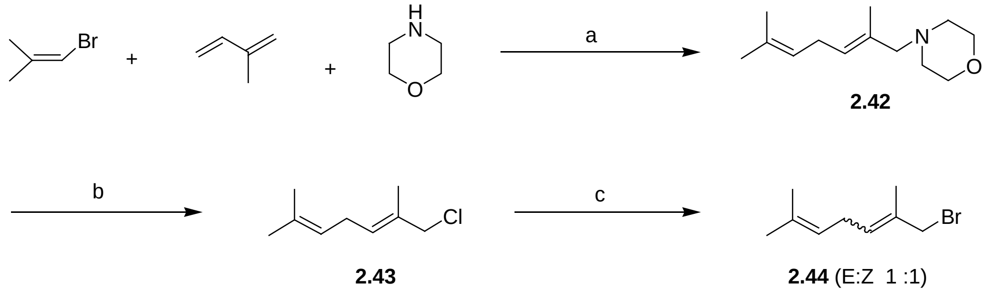
$J_{5,6}$ = 7.0 Hz

Figure 2.3. Coupling constant values of 2.35 and 1.87

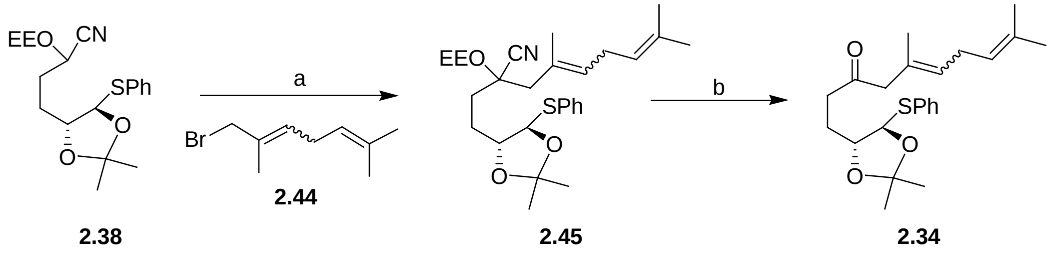
Having demonstrated the feasibility of the transformation of **2.37** to **2.35**, we next turned our attention to application of this strategy to the real system, i.e **2.5** to **1.83** (**Scheme 2.13**).

Attempted synthesis of fumagillin 1.83

First the side chain synthon **2.44** was prepared via a known method (**Scheme 2.16**). Thus, the reaction of 1-bromo-2-methyl propene, isoprene, morpholine, palladium acetate and trio-*o*-tolylphosphine at 100 °C for 4 days provided the pure diene **2.42** in 30%.[48] Treatment of **2.42** with methyl chloroformate gave the allylic chloride **2.43**, which next was converted to the more reactive allyl bromide **2.44** via a halide exchange reaction. However, the halide exchange reaction caused an olefin izomerization giving an E:Z mixture **2.44**. The mixture **2.44** was used in the next step. Hence, cyanohydrin **2.38** was treated with **2.44** in presence of NaHMDS to afford the alkylated cyanohydrin **2.45** in 54% yield (**Scheme 2.17**). The ketone **2.3** was then generated as previously described.

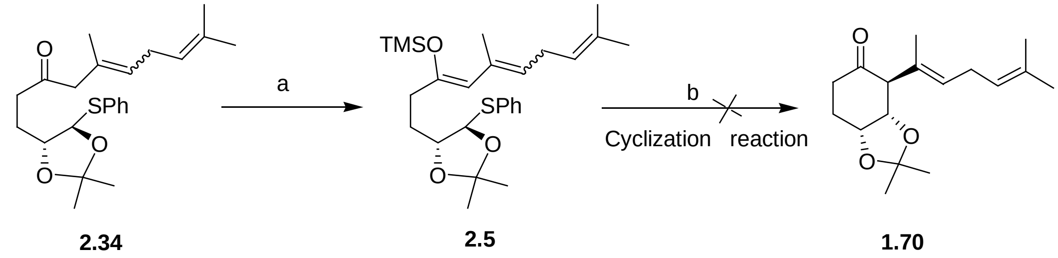


Scheme 2.16. (a) 1% Pd(OAc)$_2$, 2% P(otol)$_3$, 100 ^{o}C for 4 days, 30%; (b) ClCO$_2$CH$_3$, quant; NaBr, Acetone.



Scheme 2.17. (a) **43**, NaHMDS, THF, -78 ^{o}C, 54%; (b) pTsOH then 0.5N NaOH, quant.

Ketone **2.34** was next treated with LDA followed by TMSCl to afford the TMS-enol ether **2.5**, which was then subjected to the cyclization reaction without purification (**Scheme 2.18**). Once again the stability of the TMS-enol-ether **2.5** was very problematic. Extensive decomposition was noticed before the exposure of **2.5** to the cyclization conditions. All attempts to control the stability of **2.5** by decreasing the time of the work up and keeping it in a basic environment led to no change in the stability. Because of the problems encountered in this synthesis and the stability of **2.5**, this route was abandoned.



Scheme 2.18. (a) LDA, TMSCl, -78 °C, THF; (b) DTBMP, MeOTf, CH_2Cl_2.

Summary

We have attempted two strategies for the synthesis of advanced intermediates of fumagillin (**1.83** and **1.87**): These approaches involved oxocarbenium ion-alkene and oxocarbenium ion-enol ether cyclizations, respectively. For each of the stragey, a model study was initially conducted. The oxocarbenium ion-alkene cyclization methodology on a model system provided a 5:1 mixture of the desired cyclization product **2.23** (containing a tri-substituted double bond on the side chain) and the undesired exocyclic product **2.27**. Application of the latter strategy to the synthesis of **1.87** (real system) provided mainly the undesired exocyclic product **2.32**. The oxocarbenium ion cyclization of the model enol-ether **2.36** provided the desired cyclization product **2.35**. However, application of latter methodology to the synthesis of fumagillin intermediate **1.83** did not provide any desired product, presumably due the unstability of the cyclization precursor TMS-enolether **2.5**.

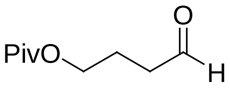
As a result, a new route to **1.87** using a more convergent strategy was devised. This is the subject of the following chapter.

2.3 Experimental Section

General Experimental

TLC was performed on aluminum sheets precoated with silica gel 60 (HF-254, E. Merck) to a thickness of 0.25 mm. Flash column chromatography (FCC) was performed using Kieselgel 60 (230-400 mesh, E. Merck) and employed a solvent polarity gradient, correlated with TLC mobility. Unless otherwise stated, ^{1}H NMR spectra were recorded at 300 MHz on a GE/Bruker QE300 MHz spectrometer with a TECMAG upgrade, in $CDCl_3$ solutions, with $CHCl_3$ as internal standard. ^{13}C NMR spectra were recorded at 75 MHz and at 125 MHz on Brucker Avance 500 MHz spectrometer, equipped with a 3mm 13C-1H (DUL) cryoprobe, in $CDCl_3$ solutions, with $CHCl_3$ as internal standard. High resolution mass spectroscopy was carried out at the Mass Spectrometry Facility at the University of Illinois at Urbana-Champaign.

1,4-Butanediol monopivalate 2.11.

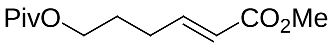


2.12

To a mixture of butan-1,4-diol **2.11** (20 g, 0.22 mmol), DMAP (5.40 g, 0.04 mmol) and pyridine (36 mL, 0.44 mmol) in dry dichloromethane was added dropwise a solution of pivaloyl chloride (27.6 mL, 0.22 mmol) in dry dichloromethane (120 mL). The reaction mixture was stirred at rt for 4h, then poured into water. The aqueous phase was extracted with ether, and the combined organic extract was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC of the residue gave the monoportected alcohol (20 g, 52%), as a colorless oil: R_f = 0.58 (60% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 9H), 1.75-1.61 (m, 4H), 3.68 (t, 2H, J = 6.2 Hz), 4.09 (t, 2H, J = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 27.9, 29.9, 39.5, 63.0, 64.8,179.1; MS(ESI):192.2 [M + NH_4^+].

To a mixture of PCC (46.6 g, 215 mmol), florisil (51 g), sodium acetate (17.6 g, 215 mmol), freshly activated, powdered 4A molecular sieves (51 g) and Celite (51 g) in dry dichloromethane (800 mL), was added dropwise a solution of alcohol from the previous step (17.0 g, 97.7 mmol) in dry dichloromethane (600 mL). The mixture was stirred at rt for 1h, then diluted with ether (1200 mL) and filtered through a column of florisil. The filtrated was evaporated *in vacuo* and the residue purified by FCC to afford aldehyde **2.12** (16.0 g, 95 %) as a light yellow oil: R_f = 0.81 (60% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 9H), 1.99 (t, 2H, J = 7.0 Hz), 2.54 (t, 2H, J = 7.1 Hz), 4.09 (m, 2H), 9.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.9, 28.1, 29.4, 51.9, 64.0**,** 178.5, 201.2; MS(ESI): 206.2 [M+NH_4^+].

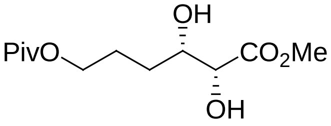
Methyl (E)-6-pivaloxy-2-hexenoate 2.13



2.13

A portion of the aldehyde **2.12** from the previous step (9.20 g, 53.5 mmol) and $Ph_3P{=}CO_2Me$ (25.0 g, 74.9 mmol) in dry acetonitrile (120 mL) was stirred at 65 ^{0}C for 1h. The reaction mixture was then filtered and concentrated under reduced pressure. FCC of the residue provided **2.13** (11.3 g, 93%); R_f = 0.76 (20% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.78-1.85 (m, 2H), 2.25-2.33 (m, 2H), 3.73 (s, 3H), 4.07 (m, 2H), 5.82-5.88 (m, 1H), 6.91-7.02 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$). 27.9, 28.0, 29.4, 39.5, 52.0, 64.0, 122.4, 148.3, 167.2, 178.8; HRMS (EI) calcd for $C_{12}H_{21}O_4$ (M+H) 229.1440, found 229.1445.

Diol 2.14.

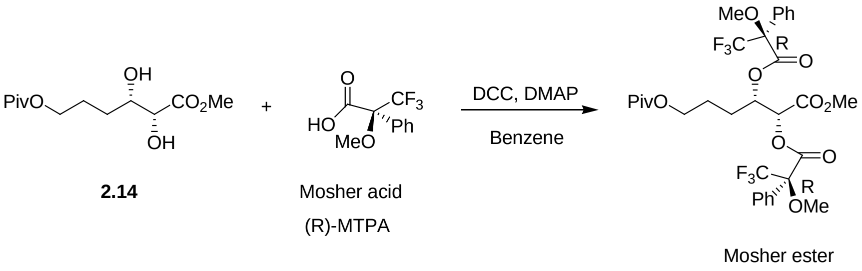


2.14

A 500 mL round-bottomed flask, equipped with a magnetic stirrer, was charged with *tert*-butyl alcohol (200 mL), water (200 mL) and AD-mix-β (65.5 g) Stirring at rt produced two clear phases; the lower aqueous phase was bright yellow. Methanesulfonamide (4.46 g, 46.94 mmol) was added at this point. The mixture was cooled to 0 °C, whereupon some of the dissolved salts precipitated. Methyl (E)-6-pivaloxy-hex-2-enoate **2.13**(10.8 g, 47.4 mmol) was added, and the heterogeneous slurry was stirred vigorously at 0 °C for 6h. Solid sodium metabisulfite (7.1 g) was then added, the mixture warmed to rt, stirred for an additional 1 h, and then extracted with ethyl acetate. The combined organic extract was washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by FCC to give the diol **2.14** (11.2 g, 90%) as a colorless oil: R_f = 0.36 (40% ethyl acetate:petroleum ether); $[\alpha]_D$ +11 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.60–1.95 (m, 4H), 2.02–2.11 (br s, 1H), 3.09 (br s, 1H), 3.85 (s, 3H), 3.94 (m, 1H), 4.12 (t, 3H, J = 6.9 Hz); ^{13}C NMR (75

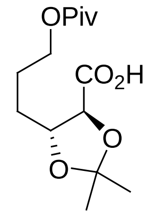
MHz, $CDCl_3$) δ 25.8, 27.9, 30.8, 39.5, 53.3, 64.7, 72.7, 74.0, 174.2, 179.1; HRMS(EI) calcd for $C_{12}H_{23}O_6$ (M+H) 263.1495, found 263.1497.

Bis-(R)-MTPA ester of AD-mix product



DMAP (15 mg, 0.02 mmol) and DCC (154 mg, 0.74 mmol) was added to a solution of the diol **2.14** (65 mg, 0.25mmol) and (R)-MTPA (174, 0.74 mmol) in dry benzene (3 mL) at 0 °C under an atmosphere of argon. The mixture was stirred at rt for 3h, then diluted with ether and filtered. The solvent was evaporated under reduced pressure and the residue was purified by FCC to afford the *bis*-Mosher ester derivative as a colorless oil (150 mg, 87%); R_f = 0.44 (20% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 9H), 1.42-1.52 (m, 2H), 1.60-1.88 (m, 2H), 3.38 (s, 3H), 3.47 (s, 3H), 3.73 (s, 3H), 3.95 (t, 2H, J = 6.23 Hz), 5.33 (d, 1H, J = 2.20 Hz), 5.57-5.65 (m, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 25.1, 27.8, 28.4, 39.3, 53.0, 56.0, 56.2, 63.6, 74.5, 74.7, 130-133.0 (several signals).

Acid 2.15



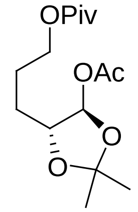
2.15

A solution of 2,2-dimethoxypropane (24.6 mL, 200 mmol), camphorsulfonic acid (2.77 g, 12.0 mmol) and diol **2.14** (10.5 g, 40 mmol) in dry dichloromethane (100 mL) was stirred at rt for 2h, then poured into saturated aqueous $NaHCO_3$. The mixture was extracted with ether and the combined organic layer washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC of the residue provided the methyl ester derivative (11.7 g, 97%): $R_f = 0.84$ (40% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 9H), 1.43 (s, 3H), 1.46 (s, 3H), 1.71-1.88 (m, 4H), 3.77 (s, 3H), 4.08-4.13 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 26.5, 27.9, 30.7, 39.5, 52.8, 64.5, 79.4, 79.8, 111.6, 171.6, 178.8; MS(ESI): 320.2 [M + NH_4^+].

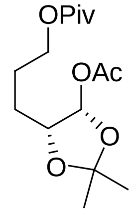
Aqueous 1N KOH (15 mL) was added at rt to a solution of the material from the previous step (10.8 g, 35.8 mmol) in 1/1 THF/H_2O (100 mL). The solution was maintained below pH 11. When TLC indicated complete disappearence of the starting material, the reaction mixture was adjusted to pH 4 by addition of 1N HCl. The solvent was then removed *in vacuo* and the residue triturated with ethyl acetate and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue purified by FCC to afford carboxylic acid **2.15** (10.0 g, 98%) as a colorless oil; $R_f = 0.14$ (40% ethyl acetate:petroleum ether); $[\alpha]_D$ +7.4 (c 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.19

(s, 9H), 1.41 (s, 3H), 1.44 (s, 3H), 1.71-2.00 (m, 4H), 4.07-4.11 (m, 4H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 26.6, 27.9, 30.8, 39.5, 64.6, 79.5, 79.9, 111.1, 128.9, 178.9. HRMS(EI) calc for $C_{14}H_{25}O_6$ (M+H) 289.1651, found 289.1550.

(1R, 2R) and (1S, 2R) - 1-*O*-Acetyl-1,2-*O*-isopropylidene-5-pivaloxy-pentane-hemiacetal (2.16) and **(2.17).**



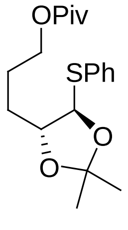
2.16



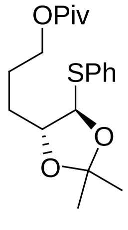
2.17

To a solution of the carboxylic acid **2.15** (10.3 g, 35.8 mmol) in dry dichloromethane (150 mL) were added diacetoxyiodobenzene (13.8 g, 42.9 mmol) and iodine (9.0 g, 35.8 mmol), The reaction mixture was stirred under argon for 4 h then poured into saturated aqueous Na_2SO_3. The mixture was extracted with ether and the organic phase dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC of the residue provided an inseparable mixture of **2.16** and **2.17** as a light yellow oil (9.5 g, 88%); $R_f = 0.60$ (20% ethyl acetate:peroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ. 1.19 (s, 9H), 1.38, 1.48, 1.50 (all s, 6H), 1.67-1.78 (m, 4H), 2.09 (s, 3H), 4.07-4.11 (m, 2H), 4.18-4.22 (m, 1H), 5.96, 6.20 (both d, 1H, J = 3.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 21.8, 25.4, 25.9, 26.1, 26.5, 27.4, 27.9, 28.5, 28.9. MS(ESI): [M + NH_4^+].

(1S, 2R) and (1R, 2R) - 1-*S*-phenylthio-1,2-*O*-isopropylidene-5-pivaloxy-pentane-*S*-phenyl-monothiohemiacetal (2.20) and (2.21).



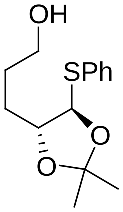
2.18



2.19

$BF_3.OEt_2$ (3.69 mL, 29.1 mmol) was slowly added to a solution of mixture **2.16**/**2.17** (8.8 g, 29.1 mmol) and thiophenol (5.98 mL, 58.3 mmol) in anhydrous CH_2Cl_2 (100 mL), at –78 °C, under an atmosphere of argon. The temperature was warmed to –40 °C and stirring continued at this temperature for 1h, or until the TLC indicated complete disappearance of the starting material. The reaction mixture was quenched by addition of triethylamine (5 mL), poured into saturated aqueous $NaHCO_3$ (150 mL) and extracted with ether. The organic extract was washed with brine (150 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. FCC of the residue gave **2.18** (8.45 g, 82%) and **2.19** (0.95 g, 9 %)**.** For **2.18**: $R_f = 0.54$ (10% ethyl acetate:petroleum ether); $[\alpha]_D$ +113 (c 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 9H), 1.46 (s, 6H), 1.62-1.85 (m, 4H), 4.01-4.08 (m, 1H), 4.10 (t, 2H, J = 5.9 Hz), 5.06 (d, 1H, J = 7.3 Hz), 7.26-7.52 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ. 25.9, 26.7, 28.0, 28.3, 30.1, 39.5, 64.5, 81.0, 89.2, 111.5, 128.0, 129.5, 132.4, 134.9, 178.9; HRMS(ESI) calcd for $C_{19}H_{29}O_4S$ (M+H) 353.1787, found 353.1788. For **2.19**: $R_f = 0.43$ (10% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 9H), 1.38 (s, 3H), 1.63 (s, 3H), 1.75-1.95 (m, 4H), 4.05-4.2 (m, 2H), 4.3 (m, 1H), 5.58 (d, 1H, J = 4.8 Hz), 7.24-7.53 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4, 27.0, 28.0, 28.1, 28.8, 39.5, 64.6, 79.7, 89.4, 110.9, 127.7, 129.5, 132.4, 135.6, 178.9.

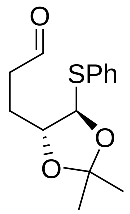
Alcohol 2.20



2.20

A 1M solution of DIBALH in heptane (45.9 mL, 45.9 mmol) was added dropwise over 10 min, to a solution of **2.18** (7.70 g, 21.9 mmol) in dry dichloromethane (80 mL), at –78 °C, under an atmosphere of nitrogen. The reaction was allowed to warm to rt, stirred at this temperature for 1h, then poured into saturated aqueous NH_4Cl and extracted with ether. The organic phase was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by FCC to afford **2.20** (5.53 g, 94%) as a colorless oil: R_f = 0.24 (20% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 6H), 1.65-1.95 (m, 4H), 3.68 (t, 2H, J = 5.9 Hz), 4.00 (m, 1H), 5.07 (d, 1H, J = 7.3 Hz), 7.26-7.52 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 28.3, 29.8, 30.2, 63.2, 81.3, 89.2, 111.4, 128.0, 129.5, 132.4, 135.0; HRMS(ESI) calcd for $C_{14}H_{21}O_3S$ (M+H) 269.1211, found 269.1210.

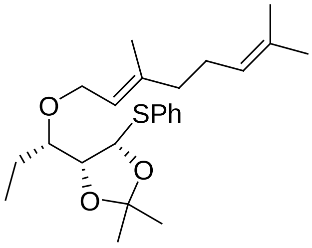
Aldehyde 2.8



2.8

A 250 mL round-bottom flask, equipped with a magnetic stirring bar, was charged with oxalyl chloride (4.20 mL, 48.8 mmol) and CH_2Cl_2 (60 mL). The set-up was purged with argon and cooled to –78 °C. DMSO (6.80 mL, 97.0 mmol) was added dropwise to the mixture and stirring continued for 20 min. Then a solution of alcohol **2.20** from the previous step (5.20 g, 19.5 mmol) in CH_2Cl_2 was added dropwise. The reaction was stirred for 25 min at –78 °C, at which time Et_3N (20.8 mL) was added. After warming to rt, the mixture was stirred for an additional 10 min, diluted with ether, washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated *in vacuo*. FCC of the residue afforded aldehyde **2.8** (4.90 g, 94%) as a yellow oil; R_f = 0.60 (20% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 6H), 1.94 (m, 1H), 2.15 (m, 1H), 2.64 (t, 2H, J = 7.0 Hz), 4.02 (m, 1H), 5.06 (d, 1H, J = 7.3 Hz), 7.26-7.52 (m, 5H), 9.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 26.7, 28.2, 40.6, 80.4, 89.0, 111.6, 128.1, 129.55, 132.5, 134.6, 201.3. HRMS(ESI) calcd for $C_{14}H_{19}O_3S$ (M+H) 267.1055, found 267.1067.

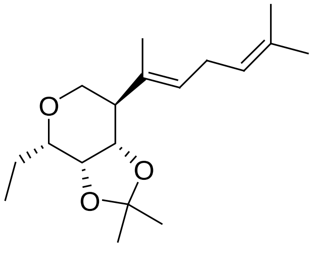
Thio-isopropylidene ether 2.21N



2.21N

To a solution of alcohol **2.24** (200 mg, 0.75 mmol), dissolved in dry DMF (5.0 mL), was added at 0 ^{0}C Bu_4NI (27.5 mg, 0.04 mmol) and sodium hydride (104.5 mg, 2.61mmol, 60% in mineral oil). The mixture was stirred at this temperature for 30 min. At this point, geranyl bromide (0.45mL, 2.24 mmol) was introduced and the reaction mixture was stirred at rt for 2 h. The mixture was then diluted with water and extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC to give **2.21N** as a colorless oil (188 mg, 94%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, 3H, J = 7.3 Hz), 1.48 (s, 3H), 1.50 (s, 3H), 1.59 (s, 3H), 1.62-1.69 (m, 2H), 1.63 (s, 3H), 1.68 (s, 3H), 1.95-2.12 (m, 4H), 3.37 (q, 1H, J = 7.3 Hz), 4.10-4.14 (m, 3H), 5.07 (t, 1H, J = 6.6 Hz), 5.31-5.36 (m, 1H), 5.34 (d, 1H, J = 6.9 Hz), 7.26-7.52 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.5, 16.7, 17.9, 24.1, 25.9, 26.0, 26.6, 27.5, 39.8, 67.3, 78.9, 82.5, 85.7, 111.4, 121.2, 124.2, 127.4, 129.1, 131.6, 134.9, 140.3.

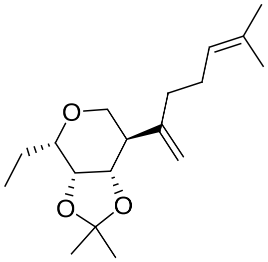
General procedure for oxocarbenium ion cyclizations: **Synthesis of THP 2.23 and 2.27**



2.23

A portion of the mixture of **2.21N** (126 mg, 0.31 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (576.49 mg, 2.81 mmol), and freshly activated powdered 4A molecular sieves (700 mg) in anhydrous dichloromethane (8.0 mL), was stirred for 15 mIn, at rt, under an argon atmosphere, then cooled to 0 °C. Methyl triflate (0.25 mL, 2.18 mmol) was then introduced, and the mixture warmed to rt and stirred for an additional 18 h, at which time, Et_3N (0.50 mL) was added. The mixture was diluted with ether (20mL), washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. FCC of the residue afforded **2.23** (50 mg, 65% based on recovered starting material), **2.27** (10 mg, 13 %) and, recovered staring material **2.21N** (48 mg). For **2.23**. R_f = 0.53 (4% ethyl acetate:petroluem ether). ^{1}H NMR (300MHz, $CDCl_3$) δ 1.00 (t, J = 7.3 Hz, 3H), 1.34 (s, 3H), 1.56 (s, 3H), 1.61 (s, 3H), 1.65 (s, 3H), 1.68 (s, 3H), 1.71-2.36 (m, 2H), 2.36-2.43 (m, 1H), 2.72 (t, 1H, J = 7.0 Hz), 3.14 (t, J = 11.7 Hz, 1H), 3.42-3.47 (m, 1H), 3.78 (dd, 1H, J = 4.8 Hz, J = 11.7 Hz), 3.99 (dd, 1H, J = 2.2 Hz, J = 5.1 Hz), 4.11 (dd, 1H, J = 5.1Hz, J = 9.9Hz), 5.07 (t, 1H, J = 7.0 Hz,), 5.20 (t, 1H J = 7.3 Hz), 7.26-7.52 (m, 5H). ^{13}C NMR (75MHz, $CDCl_3$), δ 11.0, 16.3, 18.5, 25.7, 26.4, 27.2, 27.8, 29.4, 49.4, 69.7, 74.4, 76.9, 78.9, 109.4, 123.6, 126.9, 132.9. (M+H) 295.0992.

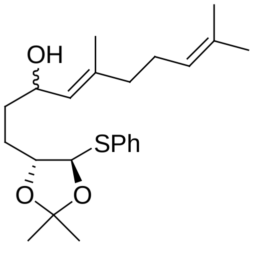
Compound 2.27



2.27

For **2.27.** R_f = 0.59 (4% ethyl acetate:petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (t, 3H, J = 7.7 Hz), 1.34 (s, 3H), 1.55 (s, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 1.70-1.85 (m, 2H), 2.40-2.50 (m, 1H), 3.08 (t, 1H, J = 11.3 Hz), 3.44-3.50(m, 1H), 3.82 (dd, 1H, J= 4.4 Hz, J= 11.7 Hz), 4.01 (dd, 1H, J = 2.2 Hz, J= 5.1 Hz), 4.11(dd, 1H, J= 5.1 Hz, J= 9.9 Hz), 4.81 (s, 1H), 4.94 (s, 1H), 5.07-5.11 (m, 1H), 7.26-7.52 (m, 5H).

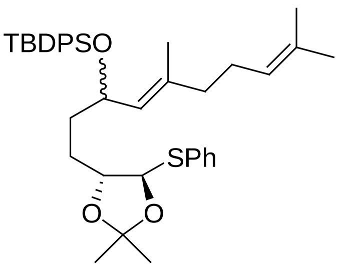
Alcohol 2.30



2.30

To a solution of iodide **2.9** (350 mg, 1.40 mmol), in dry ether (3.0 mL) at –78 °C, was added nBuLi (0.56mL, 1.40 mmol, 2.5 M in hexane). The reaction mixture was stirred at this temperature for 1h, at which time a solution of aldehyde **2.8** (124 mg, 0.47 mmol) in dry ether (2 mL) was added dropwise. The resulting reaction mixture was stirred at –78 °C until TLC indicated the complete consumption of the starting material. The reaction was then warmed to rt for 30 min at which point, saturated aqueous NH_4Cl was introduced. The organic phase was extracted with ether. The combined extracts was washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. FCC of the residue gave alcohol **2.30** (165 mg, quantitative yield) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 6H), 1.59 (s, 3H), 1.67 (s, 6H), 1.95-2.10 (m, 8H), 3.99-4.05 (m, 1H), 4.35-4.44 (m, 1H), 5.05-5.10 (m, 1H), 5.06 (d, 1H, J = 7.3 Hz), 7.26-7.52 (m, 5H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 18.5, 26.4, 26.6, 27.2, 28.3, 29.5, 34.5, 40.3, 69.0, 69.1, 81.3, 87.4, 89.1, 89.3, 111.4, 124.5, 128.17, 128.2, 129.5, 132.2, 132.22, 132.3, 135.0, 135.05, 139.4.

Silyl ether 2.31

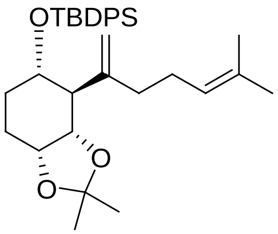


2.31

A sample of the alcohol mixture **2.30** from the previous step (75 mg, 0.19 mmol), TBDPSCl (0.06 mL, 0.0.4 mmol), imidazole (28 mg, 0.41 mmol), in anhydrous DMF

(3.0 mL) was stirred at 50 °C for 4h. The reaction mixture was then diluted with water and extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC to give a mixture of silyl ether **2.31** (104 g, 100%) as a yellow oil; $R_f = 0.80$ (10% ethyl acetate:petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.13 (s, 3H), 1.43 (s, 6H), 1.56 (s, 3H), 1.65 (s, 3H), 1.82-1.95 (m, 8H), 3.90-3.97 (m, 1H), 4.30-4.42 (m, 1H), 4.97-5.07 (m, 2H), 5.16-5.19 (m, 1H), 7.20-7.40 (m, 9H), 7.41-7.50 (m, 2H), 7.60-7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1, 17.15, 18.3, 20.0, 26.3, 26.7, 27.1, 27.8, 28.3, 28.9, 29.2, 35.1, 35.18, 40.1, 70.9, 70.95, 77.8, 81.6, 81.7, 89.3, 89.4, 111.2, 124.8, 127.8, 127.82, 128.0, 128.6, 129.4, 129.8, 129.9, 131.9, 132.2, 135.3, 136.5, 136.5.

Diene 2.32

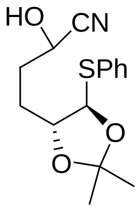


2.32

Treatment of **2.31** (100 mg, 0.16 mmol) under the standard cyclization conditions provided **2.32** (30 mg, 35%) as a colorless oil; $R_f = 0.55$ (10% ethyl acetate:petroluem ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.30 (s, 3H, CH_3), 1.56 (s, 3H), 1.60 (s, 3H), 1.70 (s, 3H), 1.90-2.08 (m, 2H), 2.15-2.24 (m, 2H), 2.38 (t, 1H, J = 9.9 Hz), 3.38-

3.45 (m, 1H), 3.84-3.9 (m, 1H), 4.00-4.08 (brs, 1H), 4.90 (s, 1H), 5.00 (s, 1H), 5.06-5.12 (m, 1H), 7.30-7.70 (m, 10H).

General procedure for the formation of aldehyde cyanohydrins: synthesis of 2.39



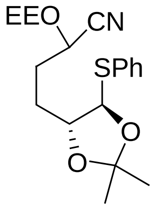
2.39

To a cooled (0 °C) solution of aldehyde **2.8** (100.0 mg, 0.37 mmol), KCN (5.0mg, 0.07 mmol) and 18-crown-6 (20.0 mg, 0.07 mmol) in dry THF (3 mL) was added dropwise trimetylsilylcyanide (0.1 mL, 0.75 mmol). The reaction mixture was stirred at this temperature until TLC indicated disappearance of starting material, at which time water (0.3 mL) was added. The organic phase was extracted with ether. The combined organic extract was dried (Na_2SO_4). Removal of solvent under reduced pressure followed by FCC of the residue afforded a mixture of TMS-protected cyanohydrins. ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.191 (s, 9H), 1.43, 1.52 (s, 6H), 1.77-1.79, 1.89-1.96 (m, 4H), 3.98 (dd, 1H, J = 3.7 Hz, J = 6.6Hz), 4.48 (q, 1H, J = 4.4 Hz), 5.04 (dt, 1H, J = 5.1 Hz, J = 7.3 Hz), 7.22-7.55 (m, 5H, Ph).

The mixture from previous step was treated with PPTs (10 mg) in a mixture of methanol/THF (4/0.45 mL). The reaction mixture was stirred at rt for 20 min. The reaction was quenched by addition of few drops of water and the solvent was removed under reduced pressure. The residue was purified by FCC to give the free cyanohydrin

2.39 (90 mg, 81%) a 1:1 mixture of isomers; $R_f = 0.58$ (20% ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$). δ 1.48, 1.49, 1.50, 1.53 (s, 6H), 2.00-2.16 (m, 4H), 3.18 (br s, 1H), 3.86 (d, 1H, J = 6.83 Hz), 3.98-4.02 (m, 1H), 4.04-4.08 (m, 1H), 4.60-4.65 (m, 2H), 4.61, 5.09 (d, 1H, J = 7.43 Hz), 5.11 (d, 1H, J = 7.45 Hz), 7.30-7.38 (m, 3H), 7.50-7.55 (m, 2H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 26.0, 26.2, 27.59, 27.6, 27.9, 28.2, 32.0, 32.4, 61.2, 61.3, 79.7, 80.2, 88.3, 88.7, 111.4, 111.7, 119.5, 119.7, 127.9, 128.0, 129.3, 129.3, 132.1, 132.2, 132.8

Ethyl vinyl ether protected cyanohydrin 2.38



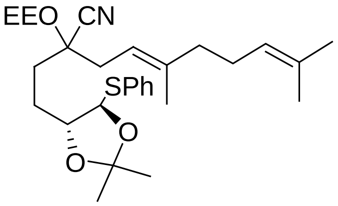
2.38

A mixture of cyanohydrin **2.39** (60 mg, 0.20 mmol), ethylvinylether (0.19 mL, 2.04 mmol) and PPTS (10 mg, 0.04 mmol) in dry dichloromethane (2 mL) was stirred at rt under nitrogen atmosphere for 2h. The reaction mixture was then diluted with saturated aqueous $NaHCO_3$ and extracted with ether. The organic phase was concentrated in *vaccuo*. FCC of the residue on neutral alumina provided the protected cyanohydrin **2.38** as yellow oil (75 mg, 100%). For major peaks: ^{1}H NMR (500 MHz, $CDCl_3$). δ 1.24 (dt, 3H, J = 2.8 Hz, J = 7.0 Hz), 1.38 (d, 3H, 5.3 HZ), 1.83-1.88 (m, 1H), 1.99-2.09 (m, 1H), 3.50-3.56 (m, 1H), 3.65-3.73 (m, 1H), 4.02-4.05 (m, 1H), 4.56-4.62 (m, 1H), 4.94 (q, 1H, J = 5.3 Hz), 5.012-5.06 (t, 1H, J = 7.0 Hz), 7.29-7.36 (m, 3H), 7.53-7.54 (m, 2H).

^{13}CNMR (125MHz, $CDCl_3$) δ 15.38, 15.39, 19.74, 19.76, 26.0, 26.1, 27.7, 28.1, 30.2, 30.25, 61.4, 62.6, 80.0, 88.5, 88.52, 99.14, 99.17, 111.2, 111.3, 118.6, 118.7, 127.7, 127.72, 129.2, 131.8, 131.9, 134.2, 134.23.

General procedure for alkylation of protected cyanohydrins: Synthesis of 2.40

To a solution of sodium bis (trimethylsilyl)amide (54.4 mL, 1M in THF) in dry THF (2.5 mL) under an atmosphere of nitrogen at -78 °C, was added dropwise a solution of **2.38** (320 mg, 0.88 mmol) in dry THF (1 mL). The mixture was stirred for 15 min at –78 ^{0}C, at which time geranyl bromide (1.4 mL, 7.01 mmol) was added dropwise. Stirring continued at –78 °C until TLC revealed disappearance of starting material. The reaction was quenched by addition of water. The solvent was removed in *vacuo*. To the resulting mixture was added ether and the organic phase was separated, washed with brine, and dried (Na_2SO_4). The sovent was concentrated in *vacuo*. FCC of the residue provided **2.40** as yellow oil (300 mg, 70%); R_f = 0.59 (10% ethyl acetate:petroluem ether).

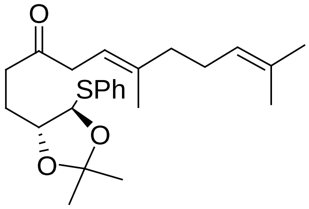


2.40

For major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (m, 3H), 1.37 (dd, 3H, J = 0.8 Hz, J = 6.9 Hz), 1.48 (s, 6H), 1.62 (s, 3H), 1.69 (s, 6H), 2.04-2.12 (m, 6H), 2.47-2.63 (m, 2H), 3.54-3.60 (m, 1H), 3.64-3.72 (m, 1H), 3.98-4.04 (m, 1H), 5.08-5.13 (m, 3H), 5.19 (t, 1H, J = 7.2 Hz), 7.29-7.36 (m, 3H), 7.52-7.54 (m, 2H). ^{13}CNMR (125 MHz, $CDCl_3$)

δ 15.3, 15.31, 15.4, 16.9, 17.9, 21.5, 25.9, 26.1, 26.6, 27.8, 40.0, 61.1, 76.1, 80.3, 88.6, 98.0, 111.2, 116.0, 120.1, 123.5, 124.0, 127.6, 129.23, 131.8, 134.5, 141.0.

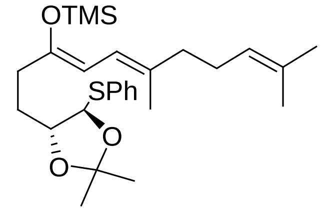
Ketone 2.37



2.37

To a solution of **2.40** (55 mg, 0.11 mmol) in dry methanol (1 mL) was added at 0 ^{o}C pTsOH (8.5 mg, 0.02 mmol). The stirring was continued at this temperature until TLC indicated complete disappearance of the starting material. The reaction mixture was then quenched by addition of saturated aqueous $NaHCO_3$ and extracted with ether. The organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated in *vacuo*. The residue was dissolved in ether (1 mL) and to that solution was added (0.9 mL) of NaOH (0.5M). The resulting mixture was shaking for 10min. The organic phase was extracted and dried (Na_2SO_4). FCC of the residue gave the pure ketone **2.37** (42 mg, 96%) as a colorless oil. R_f = 0.93 (10% ethyl acetate:petroluem ether); ^{1}H NMR (300 MHz, $CDCl_3$). δ 1.45 (s, 6H), 1.61 (s, 3H), 1.64 (s, 3H), 1.69 (s, 3H), 1.83-1.92 (m, 2H), 2.02-2.19 (m, 4H), 2.59-2.67 (m, 2H), 3.15 (d, 2H J = 7.0 Hz), 3.97-4.03 (m, 1H), 5.07 (d, 1H, J = 7.3 Hz), 5.09 (br s, 1H), 5.33 (t, 1H, J = 7.0 Hz), 7.22-7.55 (m, 5H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 16.8, 18.0, 26.0, 26.2, 26.8, 26.9, 27.8, 38.3, 39.9, 43.0, 80.0, 88.7, 111.0115.9, 124.1, 124.15, 127.6, 129.1, 131.8, 131.9, 134.3, 139.6, 208.2.

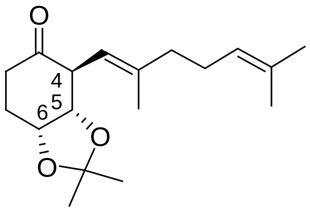
TMS-enol ether 2.36



2.36

To a solution LDA (0.02 mL, 0.15 mmol) in anhydrous THF (2 mL) at –78 °C was added a solution of ketone **2.37** (40 mg, 0.1 mmol) in THF (0.5 mL). The resulting mixture was stirred at –78 ^{0}C for 30 min then warmed to 0 ^{0}C and stirred for another 30 min. At that time the mixture was re-cooled to –78 °C, and TMSCl (0.02 mL, 0.15 mmol) was introduced. The mixture was warmed to 0 ^{0}C and stirred for 5 min. At that time the ice bath was removed and the reaction mixture was stirred at rt for another 30 min. The reaction mixture was then quenched by addition of triethylamine (0.04 mL). The resulting mixture was diluted with water and the organic phase was extracted with ether. The organic extract was washed with brine, dried (Na_2SO_4) and evaporated in *vacuo*. The residue [R_f = 0.8 (4% ethyl aceate:petroluem ether) on basic alumina plate] was used in the next step without purification

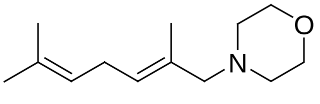
Ketone 2.35



2.35

A mixture of **2.36** (45 mg, 0.09 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (58.5 mg, 0.27 mmol), and freshly activated powdered 4A molecular sieves (400 mg) in anhydrous CH_2Cl_2 (4 mL), was stirred for 15 min, at rt, under an argon atmosphere, then cooled to 0 °C. Methyl triflate (0.075 mL, 0.66 mmol) was then introduced, and the mixture warmed to rt and stirred for additional 18 h at which time, Et_3N (0.08 mL) was added. The mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and evaporated under pressure. FCC of the residue provided the cyclization product (~10 mg, 50%). R_f = 0.21 (4% ethyl acetate:petroluem ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.42 (s, 3H), 1.56 (s, 3H), 1.65 (s, 3H), 1.68 (s, 3H), 2.00-2.10 (m, 4H), 3.47 (dd, 1H, J = 3.7Hz, J = 8.8 Hz), 4.33 (dd, 1H, J = 3.7 Hz, J = 7.3 Hz), 4.50 (m, 1H), 4.93 (d, 1H, J = 8.4 Hz), 5.00-5.05 (m, 1H). ^{13}CNMR (75 MHz, $CDCl_3$) δ 17.6, 18.4, 24.9, 25.6, 26.4, 27.1, 27.2, 33.6, 40.6, 48.7, 53.1, 72.1, 78.9, 83.6, 108.7, 116.8, 124.4, 132.3, 143.2, 209.4.

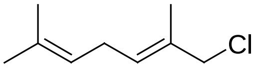
Compound 2.42



2.42

In a 100 mL Pyrex bottle was placed (5 mL, 50 mmol) of 1-bromo-2-methyl-1-propene, (6.26 mL, 62.50 mmol) of isoprene, (13 mL, 150 mmol) of morpholine, (0.11 g, 05 mmol) of palladium acetate, and (0.3 g, 1.0 mmol) of tri-*o*-tolylphosphine. The bottle was flushed with nitrogen and capped with a self-sealing rubber cap. The homogeneous solution was then heated at 100 °C for 4 days. The cooled, solid reaction mixture was then stirred with excess aqueous sodium hydroxide and ether. The ether layer was separated, dried (Na_2SO_4), filtered and distilled under reduced pressure (1 mmHg) to give the diene **2.42** as light yellow liquid (3.0 g, 30% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (s, 3H), 1.66 (s, 3H), 1.69 (s, 3H), 2.33 (t, 4H, J = 4.4 Hz), 2.71 (t, J = 6.6 Hz, 2H), 2.81 (s, 2H), 3.69 (t, 4H, J = 4.8 Hz), 5.08 (t, 1H, J = 7.3 Hz), 5.27 (t, 1H, J = 7.32 Hz).

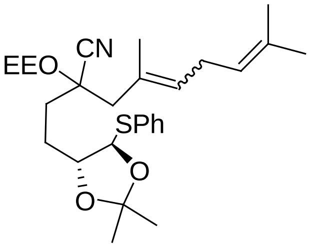
Allyl chloride 2.43



2.43

A solution of compound **2.42** (2.5 g, 12.01 mmol) and methyl choloroformate (1.4 mL, 18.02 mmol) was stirred at room temperature for 18 h. The entire solution was then put on a silica gel column, and the chloride was eluted with cyclohexane. Evaporation of cyclohexane under reduced pressure at rt gave the allyl chloride **2.43** (2.0g, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (s, 3H), 1.70 (s, 3H), 1.76 (s, 3H), 2.73 (t, 2H, J = 7.3 Hz), 4.02 (s, 2H), 5.08 (m, 1H), 5.50 (t, 1H, J = 7.0 Hz).

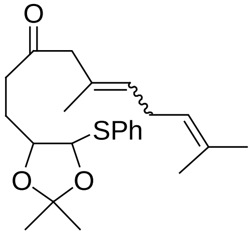
Protected cyanohydrin 2.45



2.45

Treatment of **2.38** (140 mg, 0.38 mmol) with **2.44** (364 mg, 2.30 mmol) and NaHMDS (2.70 mL, 2.68 mmol) under the alkylation procedure provided **2.45** (65 mg, 54%) as a colorless oil; recovered starting material **2.38** (50 mg). ^{1}H NMR (300 MHz, $CDCl_3$). δ 1.20-1.31 (m, 3H), 1.36 (t, 3H, J = 5.5 Hz), 1.47 (s, 6H), 1.58 (s, 3H), 1.64 (s, 3H), 1.70 (s, 3H), 1.86-2.10 (m, 4H,), 2.66-2.80 (m, 2H), 3.54-3.70 (m, 2H), 3.98-4.05 (m, 1H), 5.05-5.12 (m, 3H), 5.33-5.40 (m, 1H), 7.22-7.55 (m, 5H). ^{13}CNMR (75MHz, $CDCl_3$) δ 15.5, 18.0, 18.12, 21.3, 25.9, 26.2, 27.6, 27.7, 27.9, 28.028.2, 30.7, 35.4, 60.9, 61.0, 79.9, 80.4, 88.5, 88.6, 98.4, 111.1, 122.4, 127.5, 128.4, 129.1, 131.1, 131.9.

Ketone 2.34



2.34

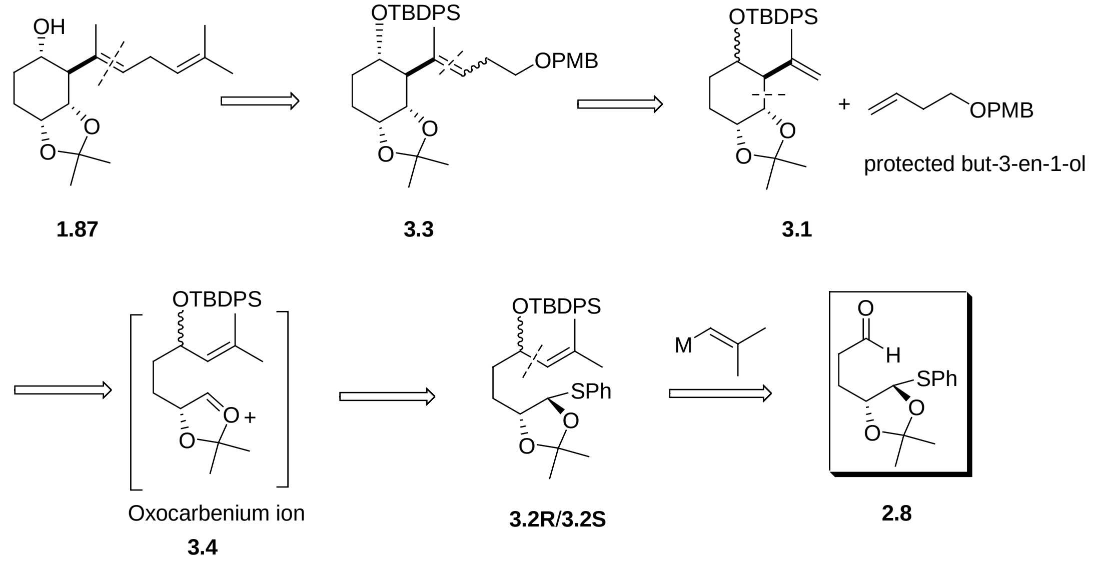
Treatment of **2.47** (55 mg, 0.11 mmol) with catalytic amount of PPTS in methanol (0.8 mL) followed by treatment with aqueous NaOH (0.9 mL, 0.5N) afforded ketone **2.34** (42 mg, 97%) as a colorless oil; R_f = .045 (4% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 6H), 1.52 (s, 3H), 1.60 (s, 3H), 1.66 (s, 3H), 2.52-2.72 (m, 2H), 3.04, 3.13 (s, 2H), 3.92-3.98 (m, 1H), 4.98-5.09 (m, 1H), 5.02 (d, J = 7.3 Hz, 1H), 5.19-5.24 (m, 1H), 5.30-5.38 (m, 1H), 7.22-7.55 (m, 5H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 26.0, 26.3, 27.0, 27.9, 30.7, 46.9, 52.0, 54.3, 83.2, 88.7, 104.2, 111.0, 123.0, 127.6, 128.9, 129.2, 132.0.

CHAPTER III:

Synthesis of a fumagillin precursor with a truncated C4 side chain

3.1 Introduction

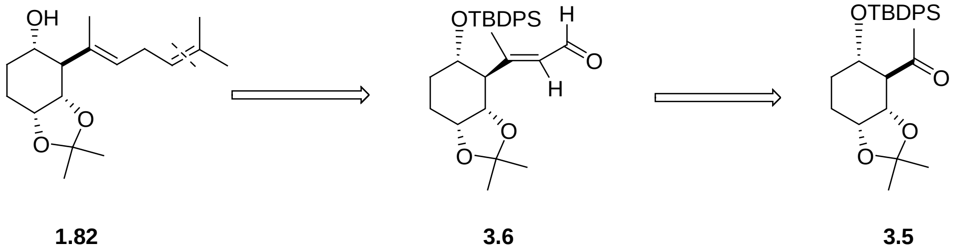
An alternative synthesis of target molecule **1.87** involves the synthesis of the C4 truncated intermediate **3.1** via our key oxocarbenium ion-alkene cyclization reaction, followed by elaboration of **3.1** to **1.87** (**Scheme 3.1**). We envisaged that **3.1** could be obtained from cyclization precursors such as **3.2R**/**3.2S**, which may be derived from aldehyde **2.8**. However, it is not clear how the configuration at the allylic alcohol position would affect the stereochemical outcome of the oxocarbenium cyclization. Hence, the cyclization of both **3.2R** and **3.2S** were examined.



Scheme 3.1.

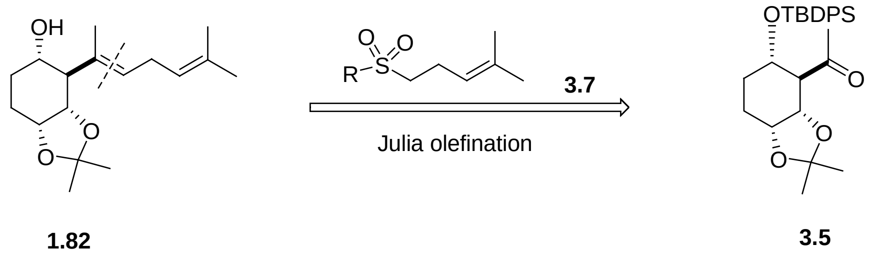
Our initial plans for the extension of the side chain in **3.1**, consisted of an olefin metathesis approach between **3.1** and a protected but-3-en-1-ol to afford **3.3**. As in Kim's synthesis,[32] the isobutenyl moiety would be introduced by deprotection of the PMB group in **3.3** followed by oxidation and a subsequent Wittig olefination reaction.

However, an alternative approach for the extension of the side chain was also investigated. Indeed, elaboration of the side chain in **3.1** could be achieved from the methyl ketone **3.5** derived from ozonolysis of **3.1**. We envisaged that ketone **3.5** could be converted to **1.87** via series of functional transformations previously reported in the literature (**Scheme 3.2**).[30]



Scheme 3.2.

Additionally, we envisaged that **1.87** could be derived from ketone **3.5** and the sulfone **3.7**, under a modified Julia olefination condition (**Scheme 3.3**).

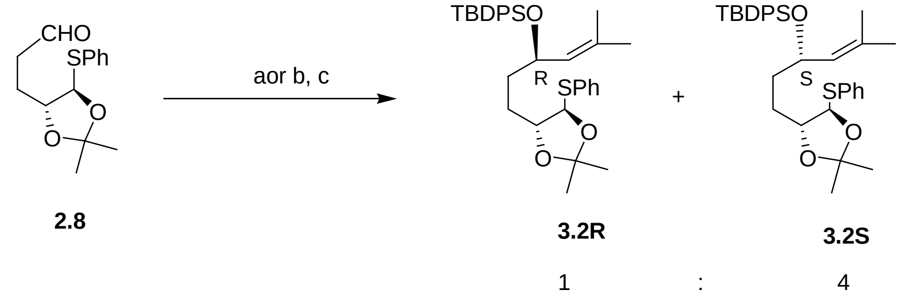


Scheme 3.3.

3.2 Results and discussion

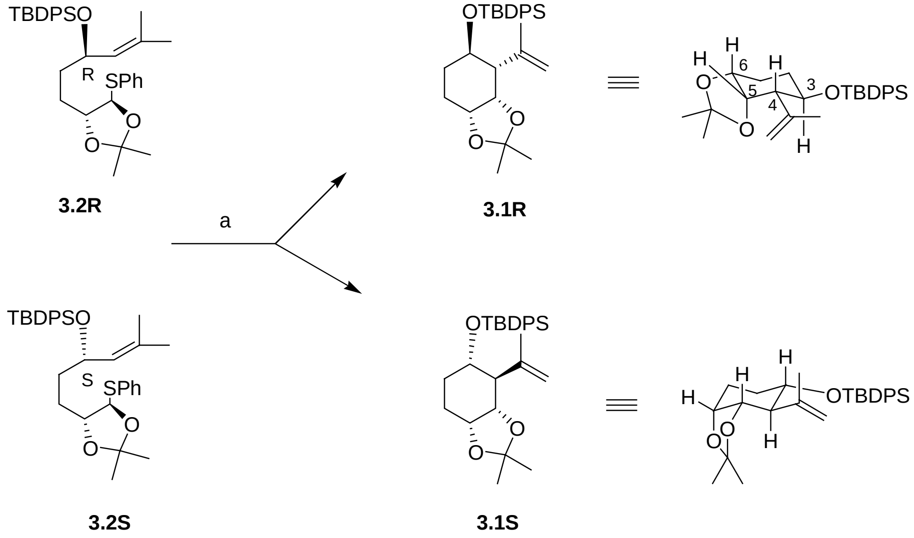
3.2.1 Synthesis of cyclohexane adduct 3.1

Aldehyde **2.8** was treated with 2-propenyllithium to provide a 1/1 inseparable mixture of allylic alcohols, which was converted to their silyl ether derivative **3.2R** and **3.2S**, in 61% yield from aldehyde **2.8** (**Scheme 3.4).** Attempted separation of mixture **3.2R/3.2S** was not successful. The configuration of the newly formed carbinol carbon was assigned in later derivatives. As the results of the subsequent cyclization studies unfolded, it became necessary to develop a stereoselective synthesis of **3.2S**. Accordingly, aldehyde **2.8** was added to a mixture of 2-propenyllithium, zinc bromide, and lithium (1S,1R)-N-methylephedrate, following the Oppolzer[49] procedure for the addition of chiral alkenyl zinc reagents to aldehydes. Silylation of the reaction product gave an approximate 1/4 ratio of **3.2R/3.2S** in 83% overall yield from **2.8**.



Scheme 3.4. (a) 2-methyl-1-propene, *t*-BuLi, ether, -78 °C; (b) 2-methyl-1-propene, *t*-BuLi, ether, -78 ^{0}C, $ZnCl_2$, lithium (1S,2R)-*N*-methylephedrate, 0 °C, 83%; (c) TBDPSCl, imidazole, 50 °C, DMF, quant.

The cyclization of **3.2R/3.2S** was next investigated. Treatment of the 1/1 mixture of **3.2R/3.2S** with methyl triflate and 4-methyl-2,6-di-*tert*-butylpyridine in anhydrous dichloromethane led to a 1/1 ratio of two cyclization products **3.1R** and **3.1S** (chromatographically separable), in a combined yield of 89% (**Scheme 3.5**). Under similar conditions, the 1/4 mixture of **3.2R/3.2S** afforded **3.1R** and **3.1S** in respective yields of 20% and 74% (**Scheme 3.5**).



Scheme 3.5. (a) MeOTf, DTBMP, CH_2Cl_2, **3.2R** (45%) and **3.2S** (44%) from **3.2R/3.8S** (1/1); **3.1R** (20%) and **3.1S** (74%) from **3.2R/3.2S** (1/4).

Stereochemical analysis

The absence of any other diastereomeric cycloadducts suggests that the cyclization process was essentially; completely stereoselective; That is **3.2R** and **3.2S** produced **3.1R** and **3.1S**, respectively. Once again the setereochemistry of **3.1R** and **3.1S** was assigned by analysis of J values for vicinal protons on the cyclohexane ring. The stereochemistry of **3.2R** and **3.2S** was assigned by analysis of coupling constant values (J, Hz) for vicinal protons on the cyclohexane ring (**Table 3.1**).

Table 3.1 Coupling constant values of 3.2R and 3.2S

	$J_{3,4}$ (Hz)	$J_{4,5}$ (Hz)	$J_{5,6}$ (Hz)
Compound **3.2R**	9.9	3.5	5.3
Compound **3.2S**	10.0	10.0	4.8

For the compound **3.2R** the J values in the **Table 3.1** are in the agreement with a trans diaxial arrangement between H_3 and H_4, and axial-equatorial relationships between H_4 and H_5, and H_5 and H_6. For compound **3.2S**, the corresponding J values (**Table 3.1**) are consistent with a mutually trans-diaxial type arrangemnt for H_3, H_4 and H_5, and a cis axial-equatorial relationship between H_5 and H_6 (**scheme 3.5**).

In the absence of additional data, the stereochemical results appear to be controlled by conformational effects in the cyclization of the intermediate oxocarbenium ions **3.4R/S**. For both **3.2R** and **3.2S**, transition states leading to a *cis* fused isopropylidene are expected to be favored over ones leading to the more strained *trans* fused system. Therefore four chairlike[50] transition states **R1-R4** and **S1-S4** may be considered for **3.2R** or **3.2S**, respectively, corresponding to 'flip-chair' conformations and an α- or β-orientation of the C4 substituent (**Figure 3.1**). For **3.2S**, **S1** in which the eventual C3, C4, and C5 substituents on the cyclohexane ring are mutually trans and all pseudo-equatorial appears to be a reasonable pathway to **3.2S**. For **3.2R**, the inverted chairlike conformation **R1** in which the C3, C4 and C5 substituents adopt pseudo-equatorial, pseudo-equatorial, pseudo-axial orientations, respectively, are in agreement with the observed result. Thus, the configurations at C3 and C6 in the precursor apparently dictate the stereochemistry at the newly formed centers at C4 (trans to C3) and C5 (cis to C6), respectively.

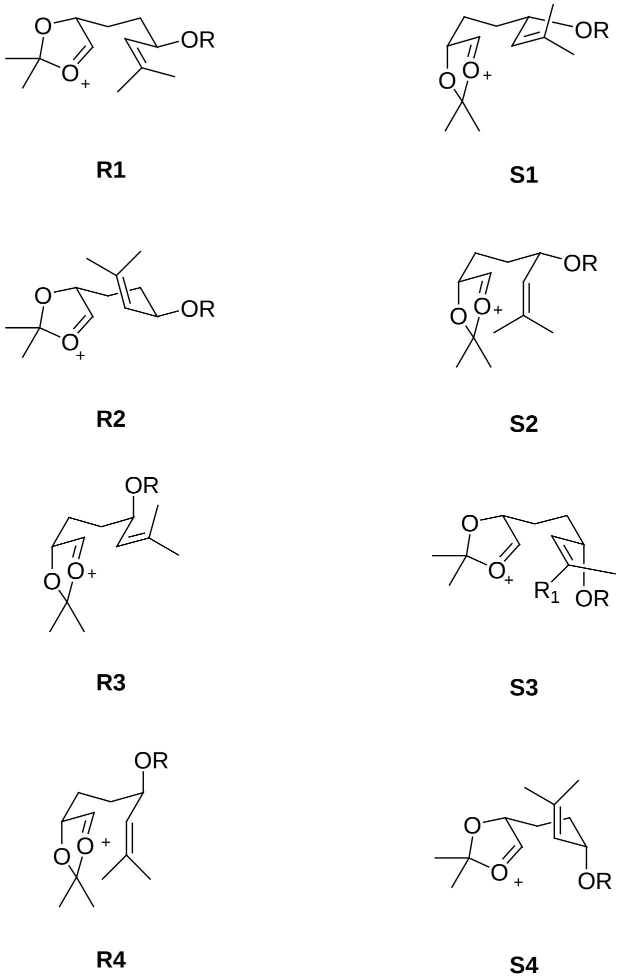
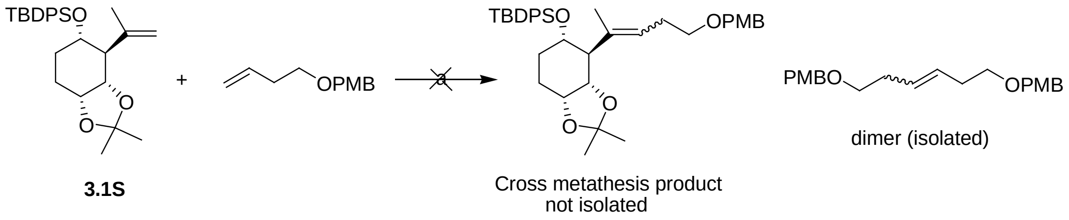


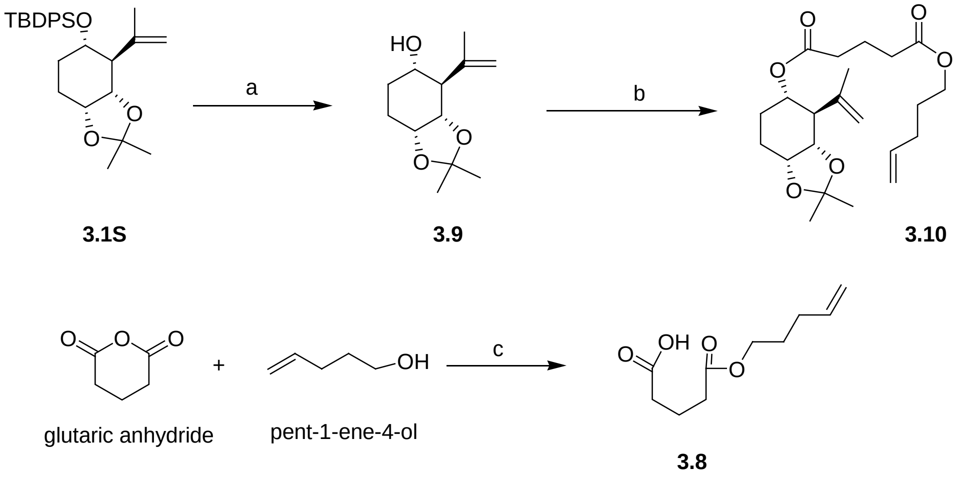
Figure 3.1 Stereochemical analysis

3.2.2 Attempted extension of the side chain: Metathesis approach

The extension of the side chain from the cyclization product **3.1S** was next investigated. A cross metathesis (CM) on **3.1S** was initially explored. However, treatment of **3.1S** with butene-1-ol in presence of Grubbs catalyst in anhydrous dichloromethane did not provide any CM product (**Scheme 3.6**). A ring closing metathesis (RCM) strategy on **3.1S** was next explored. Removal of the silyl-protecting group in **3.1S** afforded the corresponding alcohol **3.9** in quantitative yield (**Scheme 3.7)**. The DCC mediated esterification reaction between alcohol **3.9** and acid **3.8**, derived from coupling of butene-1-ol and glutaric, furnished the mixed diester **3.10** in 80% yield.

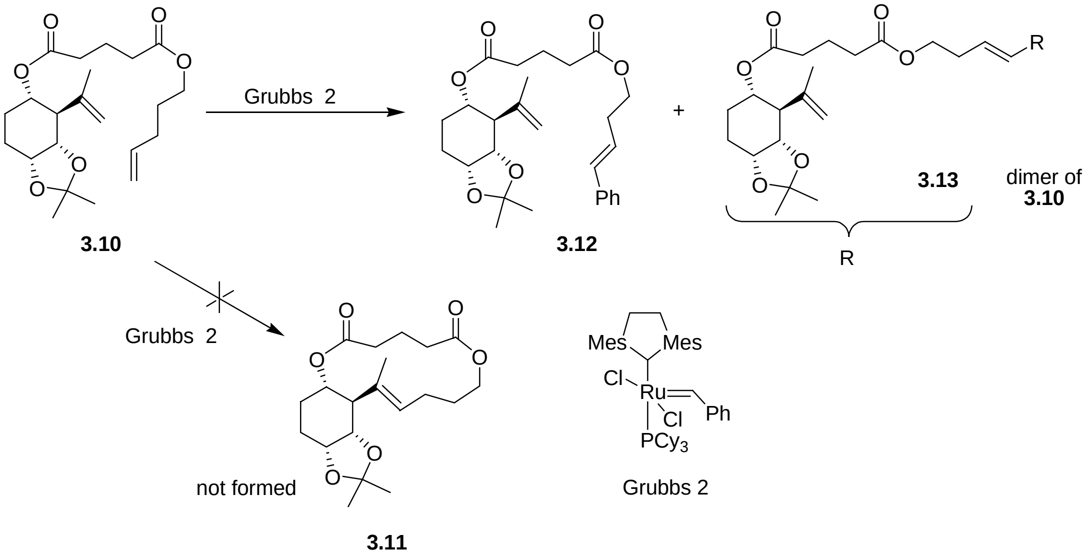


Scheme 3.6. (a) Grubbs II 10% mole, CH_2Cl_2, reflux.



Scheme 3.7. (a) TBAF, THF, rt, quant; (b) **3.9**, DCC, DMAP, C_6H_6, 80% (c) Pyr, CH_2Cl_2, 90%.

Unfortunately, the RCM on the diester **3.10** in anhydrous CH_2Cl_2, did not provide the desired product **3.11** (**Scheme 3.8**). Instead, a 3:1 separable mixture of **3.12** and **3.13** was obtained. With this result, we presumed that the 1,1-disubstituted alkene in **3.10** was not reactive under the standard metathesis condition.

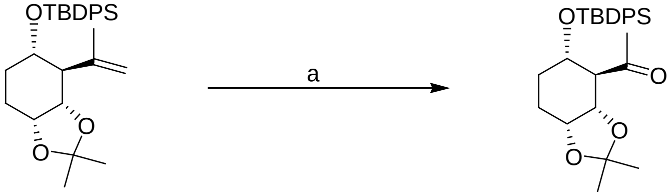


Scheme 3.8. Grubbs 10% mol, CH_2Cl_2, reflux.

3.2.3 Extension of the side chain: from the methyl ketone

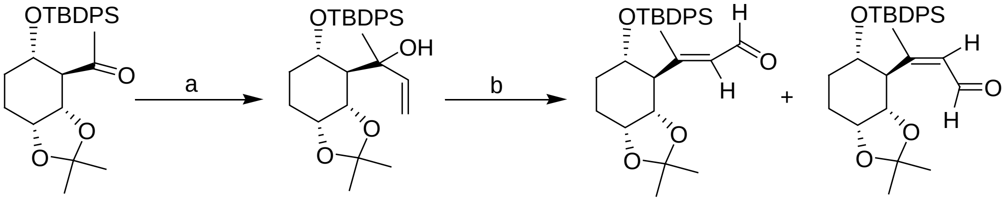
An alternative approach involving conversion of methyl ketone **3.5** to the required C4 side chain intermediate was next pursued. Ozonolysis of **3.1S** provided methyl ketone **3.5** (**Scheme 3.9**). With the methyl ketone **3.5S** in hand, we attempted the synthesis of **1.87** via a five-step sequence that was previously reported on a similar substrate. Thus, nucleophilic attack of vinyl magnesium bromide on the methyl ketone **3.5** afforded the tertiary alcohol **3.14** in 69% (**Scheme 3.10**). Treatment of **3.14** to an oxidative rearrangement with PCC, furnished the α,β,-unsaturated aldehyde **3.6** in a 3:1 mixture of

(E/Z). The configuration of the tri-substituted double bond in **3.6E** and **3.6Z** was assigned by NOE experiment.



3.1S **3.5**

Scheme 3.9. (a) O_3, CH_2Cl_2/MeOH, -78 °C, 85%.



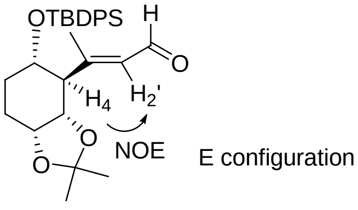
3.5 **3.14** **3.6E** **3.6Z**

3 : 1

Scheme 3.10. (a) CH_2=CHMgBr, THF, 0 °C, 69%; (b) PCC, CH_2Cl_2, rt, 75%.

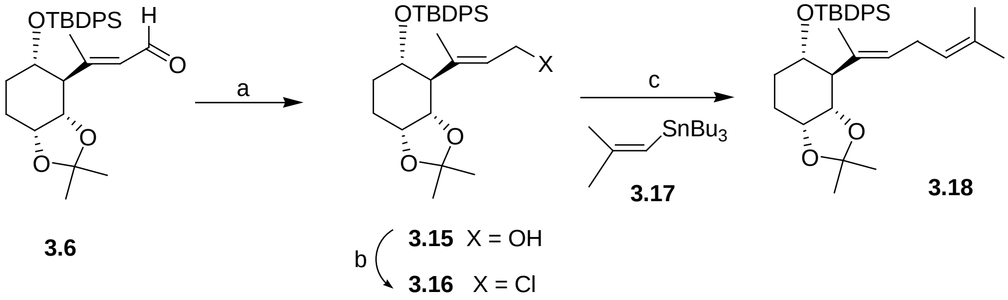
Indeed, analysis of NOE spectrum of **3.6E** indicated a correlation between H_4 and $H_{2'}$ confirming the E configuration of the tri-substituted double bond (**Figure 3.2**). With the introduction of the required E configuration of the alkene in **3.6E**, we pursued the elongation of the side chain. Reduction of **3.6E** with $NaBH_4$ furnished the allylic alcohol **3.15**, which was converted to the allylic-chloride **3.16** in 88% yield over two steps (**Scheme 3.11**). Stille coupling of **3.16** with isobutenyltributyltin **3.17** in the presence of

$Pd(PPh_3)_4$ provided **3.18** in a relatively low yield (30%). Considering the low yield of the Stille coupling reaction and the difficulty in the purification step and the fact that compound **3.18** was obtained in a lengthy sequence, we decided to explore a more convergent route for the installation of the side chain from the methyl ketone **3.5**.



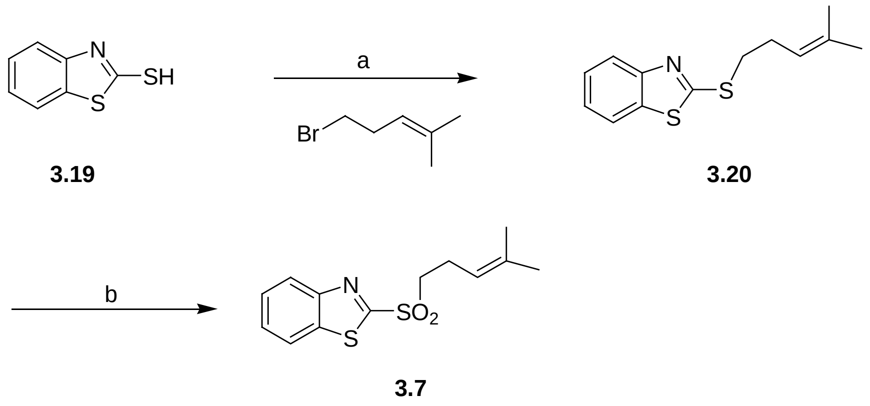
3.6

Figure 3.2 Configuration of aldehyde 3.6

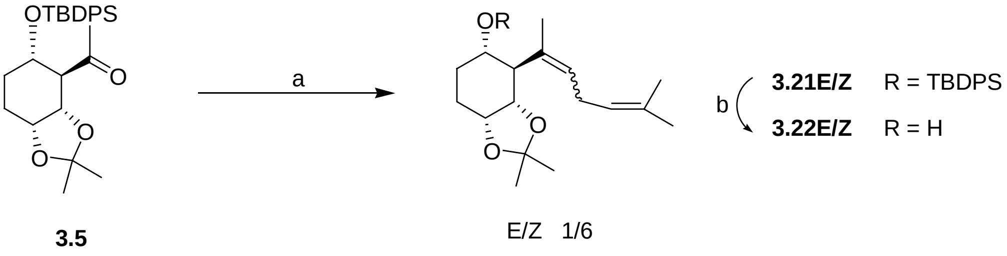


Scheme 3.11. (a) DiBALH, CH_2Cl_2, -78 °C, 88%; (b) MsCl. LiCl, Collidine, DMF, quant yield; (c) **3.19**, $Pd(PPh_3)_4$, $CHCl_3$, 30%.

An olefination strategy was therefore explored. However, treatment of **3.5** with unstabilized or the stabilized Wittig reagent, or conventional Julia reagents resulted in no reaction. Fortunately, the Kocienski modification[51] of the Julia reaction using benzothiazole sulfone **3.7** (obtained in two steps from commercially available benzothiazole **3.19** and 5-bromo-2-methyl-2-propene) was more successful. However, the undesired isomer **3.21Z** was obtained as the major product (Z:E, 6:1) (**Scheme 3.12**, **Scheme 3.13**). All attempts to improve the E/Z selectivity in **3.22E/Z** by varying the base, solvent and the reaction temperature led to no significant change.

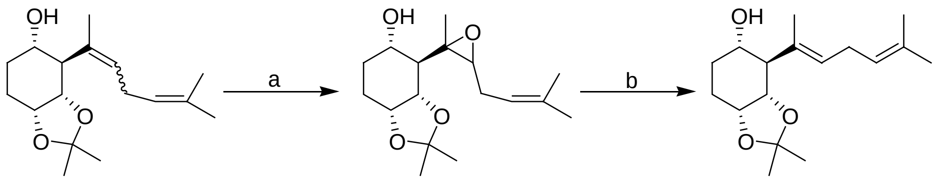


Scheme 3.12. (a) NaH, DMF, quant; (b) H_2O_2, NH_4Mo, EtOH; 0 °C, 83%.



Scheme 3.13. (a) **3.7**, LiHMDS, THF, -78 °C, 87%; (b) *n*-Bu_4NF, THF, quant.

The isomerization of **3.22E/Z** was therefore investigated. The direct thiol-mediated procedures under photochemical or thermal conditions were unsuccessful, leading to intractable product mixtures. An eventual solution was found in the Vedejs' two-steps isomerization protocol[52]. Thus, $VO(acac)_2$ promoted, regiospecific epoxidation of the homoallylic alcohols **3.22E/Z** led to a mixture of epoxides **3.23**, which was chromatographically separated (**Scheme 3.14**). Reaction of the major product with Ph_2Pli, followed by treatment of the product with methyl iodide, led to **3.24E** as a single isomer, in 67% overall yield from the original mixture of homoallylic alcohols **3.22E/Z** (E/Z 1/6). None of the Z isomer that would have resulted from stereospecific inversion of the minor E isomer in the starting mixture of **3.22E/Z** was observed. This result is presumably due to chromatographic removal of the epoxide derivative from **3.24E** prior to the reaction with Ph_2PH.



3.22E/Z

3.23

3.24E

Scheme 3.14. (a) $VO(acac)_2$, TBHP, CH_2Cl_2, 86%; (b) Ph_2Pli, THF, then MeI, 67%.

The ^1H and ^{13}C NMR data for **3.24E** were essentially identical to compound **1.87**, intermediate previously prepared.

Table 3.2. ^{13}C data of **1.87** and **3.24E**

	1.87 (ppm)	**3.24E** (ppm)
C2	108.6	108.8
C3	76.7	77.0
C4	58.9	59.1
C5	68.0	68.3
C6	27.9	28.2
C7	23.8	24.1
C7a	73.0	73.2
C8	131.2	131.5
C9	130.9	130.8
C10	27.3	27.6
C11	122.7	122.8
C12	132.1	132.2
C13	25.7	25.9
C14	17.8	18.1
C15	13.1	13.5
C16	26.4	26.7
C17	28.6	28.8

Table 3.3. ^{1}H data for **1.87** and **3.24E**

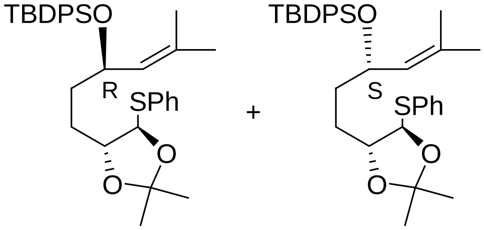
CDCl$_3$	17H (3H)	16H (3H)	6H (1H)(1H)	14H (3H)	15H (6H)	7H (1H)(1H)	OH	4-H (1H)	10-H (2H)	5-H (1H)	3a-H (1H)	7a-H (1H)	11-H (1H)	9-H (1H)
Simpkins **1.87** (400MHz)	1.36	1.54	1.56-1.61 1.84-1.89	1.64	1.70	1.72-1.77 2.18-2.24	1.78	2.13	2.75-2.86	3.38-3.44	4.02	4.20-4.23	5.10-5.14	5.36-5.40
3.24E (500MHz)	1.33	1.51	1.55-1.59 1.81-1.87	1.61	1.67	1.69-1.76 2.16-2.23	1.78	2.10	2.68-2.87	3.37	4.00	4.16-4.21	5.08	5.36

Summary

The highly substituted cyclohexane **3.1S** was prepared via an oxocarbenium ion-alkene cyclization. Our initial plan for the conversion of 3.1S to the known fumagillin relay compound **1.87** consisted of the side chain extension in **3.1S** via a metathesis reaction. However, neither the CM nor RCM approaches were successful. Alkene **3.1S** was therefore transformed to the methyl ketone **3.5**, and elaboration of **3.5** was pursued. Compound **3.5** was first subjected to the four-step side chain extension protocol previously reported in the literature. However, a low yield of the transformation made the approach impractical. As a result, a more direct side chain extension strategy was investigated. The Kocienski modification of the Julia reaction using benzothiazole sulfone **3.7** and **3.5** led to a mixture of **3.21E/Z** (E/Z: ca. 1/6), with the undesired Z isomer as the predominant product. The isomerization of **3.21E/Z** was therefore investigated. Direct, thiol-mediated procedures under photochemical or thermal conditions were unsuccessful. An eventual solution was found in the Vedej's two-step isomerization protocol on **3.21E/Z** leading to the desired **1.87**. The ^{1}H NMR and ^{13}C NMR data for **1.87** were essentially identical to the intermediate previously prepared by Simpkins.

3.3 Experimental

Alcohol 3.2R/3.2S



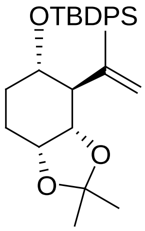
3.2R **3.2S**

tert-Butyllithium (1.7 M in hexane, 15.5 mL, 26.3 mmol) was added dropwise to a solution of 2-methyl-1-bromopropene (1.60 mL, 15.8 mmol) in dry ether, at -78 ^{o}C, under an argon atmosphere,. The mixture was warmed to -35 ^{o}C and stirred at this temperature for 2h. A solution of $ZnBr_2$ (0.6 M in ether, 15.8 mmol) was then added, and the mixture warmed to 0 ^{o}C and maintained at this temperature for an additional 1h. A solution of lithium (1S, 2R)-N-methylephedrate, [prepared by addition of n-BuLi (1.6 M in hexanes, 6.50 mL, 15.8 mmol) to (-)-N-methylephedrine (2.80 g, 15.8 mmol) in toluene (60 mL) at 0 ^{o}C], was next slowly introduced. The resulting, clear, colorless solution was stirred for 1h at 0 ^{o}C at which time a solution of aldehyde **2.8** (700 mg, 2.60 mmol) in dry ether (10 mL) was added dropwise. After an additional 1h at 0 ^{o}C the reaction was quenched by addition of saturated aqueous NH_4Cl, the organic phase separated, and the aqueous layer extracted with ether. The organic phase was washed with a second portion of aqueous NH_4Cl, dried (Na_2SO_4) and concentrated under reduced pressure. FCC of the residue gave a mixture of allylic alcohols **3.2R/3.2S** (700 mg, 83%) as an inseparable mixture. The ratio of epimeric alcohols was estimated at 4:1 based on the relative ratio of the signals for isomeric carbinol (81.5 vs. 81.6 ppm) and isomeric acetal (89.3 vs. 89.2 ppm) carbons, respectively (see below) For mixture: R_f = 0.27 (20% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, C_6D_6) δ 1.40 (s, 3H), 1.44 (s, 6H), 1.48 (1.48, 3H), 1.70-2.0 (m, 4H), 4.15-4.22 (m, 1H), 4.23-4.32 (m, 1H), 5.16 (d, 1H, J = 8.4 Hz), 5.23 (d, 1H, J = 6.9 Hz), 5.24 (d, 1H, J = 6.9 Hz); ^{13}C NMR (75 MHz, C_6D_6) 19.0, 26.4, 26.7, 28.3, 29.5, 34.5, 69.0, 81.5 (major) 81.6(minor), 89.3 (major), 89.2(minor), 111.3, 129.5, 135.0.

A sample of the alcohol mixture from the previous step (1.70 g, 5.27 mmol), TBDPS (1.78 mL, 6.86 mmol), imidazole (719 mg, 10.6 mmol), in anhydrous DMF (15 mL) was stirred at 50 °C for 4h. The reaction mixture was then diluted with water and extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC to give an inseparable mixture of **3.2S** and **3.2R** (3.00 g, 100%) as a yellow oil: R_f = 0.80 (10% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.12 (s, 3H), 1.43 (s, 6H), 1.53 (s, 3H), 1.57-1.73 (m, 4H), 3.93 (br s, 1H), 4.36 (br s, 1H), 4.99 (t, 1H, J = 7.3 Hz), 5.13 (d, 1H, J = 8.1 Hz), 7.25-7.70 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ18.7, 20.0, 26.1, 26.7, 27.8, 28.3, 29.0, 29.2, 35.1, 71.0, 81.6, 89.4, 111.2, 127.8, 128.0, 128.9, 129.4, 129.9, 132.3, 135.4, 136.5; HRMS(ESI) calcd for $C_{34}H_{43}O_3Si$ (M+H) 559.2702, found 559.2700.

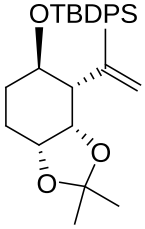
Cyclitols (3.1S) and **(3.1R)**.

A portion of the mixture of **3.2R/3.2S** from the previous step (720 mg, 1.28 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (2.37 g, 11.6 mmol), and freshly activated powdered 4A molecular sieves (2.0 g) in anhydrous dichloromethane (15 mL), was stirred for 15 min, at rt, under an argon atmosphere, then cooled to 0 °C. Methyl triflate (1.00 mL, 8.99 mmol) was then introduced, and the mixture warmed to rt and stirred for an additional 18 h, at which time, Et_3N (1.6 mL) was added. The mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. FCC afforded **10 S** (433 mg, 74%) and **10 R** (113 mg, 20%).



3.1S

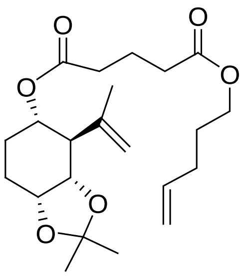
$R_f = 0.60$ (10% ethyl acetate:petroleum ether); $[\alpha]_D$ +14.0 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 9H), 1.24-1.65 (m, 4H), 1.31 (s, 3H), 1.57 (s, 3H), 1.67 (s, 3H), 2.40 (t, 1H, J = 9.9 Hz), 3.39 (m, 1H), 3.82 (dd, 1H, J = 4.8 Hz, J = 9.5 Hz), 4.05 (br s, 1H), 4.88 (s, 1H), 4.99 (s, 1H), 7.35-7.80 (m, 10H);^{13}CNMR (75 MHz, $CDCl_3$) δ 19.6, 19.7, 24.1, 26.5, 27.2, 28.7, 30.0, 57.2, 71.9, 72.9, 77.9, 108.6, 114.5, 127.4, 129.5, 136.0, 143.8; HRMS(FAB) calcd for $C_{28}H_{37}O_3Si$ (M-H) 449.2512, found 449.2511.



3.2R

R_f = 0.68 (10% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ1.01 (s, 9H), 1.23 (s, 3H), 1.33 (s, 3H), 1.77 (s, 3H), 2.43 (dd 1H, J = 6.6 Hz, J = 9.9 Hz), 4.01-4.09 (m, 2H), 4.16 (dd, 1H, J = 3.7 Hz, J = 5.1 Hz), 4.87 (s, 1H), 4.91 (s, 1H), 7.35-7.80 (m, 10H); ^{13}CNMR (75 MHz, $CDCl_3$) δ19.7, 22.0, 25.7, 26.9, 27.3, 28.1, 30.7, 53.6, 69.5, 74.5, 78.7, 108.1, 113.9, 127.5, 127.6, 129.5, 129.7, 136.0, 136.1, 145.2. HRMS(ESI) calcd for $C_{28}H_{39}O_3Si$ (M+H) 451.2668, found 451.2690.

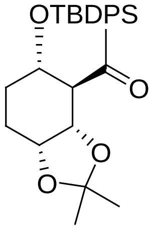
Diester 3.10



3.10

A stirred solution of alcohol **3.9** (90 mg, 0.42 mmol), acid (170.0 mg, 0.85 mmol), DMAP (26.0 mg, 0.08 mmol) in anhydrous benzene (5.0 mL) at 0 °C was treated with DCC (175.2 mg, 0.85 mmol). After stirring for 1 h at rt, diethyl ether was added and the mixture was filtered through Celite. Concentration of the filtrate followed by FFC of the residue provided the diester **3.10** (130 mg, 78%) as alight yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.58 (s, 3H), 1.75 (s, 3H), 1.80-1.87(m, 2H), 1.94 (qt, 2H, J = 7.4 Hz), 2.12-2.17 (m, H), 2.22-2.26 (m, 1H), 2.36 (q, 4H, J = 7.5 Hz), 2.45 (dd, 1H, J = 9.4 Hz, J = 11.4 Hz), 4.03 (dd, 1H, J = 4.8 Hz, J = 9.5 Hz), 4.11 (t, 2H, J = 6.6 Hz), 4.24-4.27 (m, 1H), 4.75 (dt, 1H, J = 3.7 Hz, J = 11.0 Hz), 4.86 (s, 1H), 4.97 (t, 1H, J = 1.5 Hz), 5.01-5.09 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 19.8, 20.5, 23.9, 26.2, 26.5, 28.0, 28.7, 30.2, 33.5, 33.7, 54.0, 64.1, 71.1, 72.8, 109.0, 115.3, 115.5, 137.6, 142.3, 172.4, 173.2. HRMS (FAB) calcd for $C_{22}H_{34}O_6$ (M+1) 395.2482 found 395.2490.

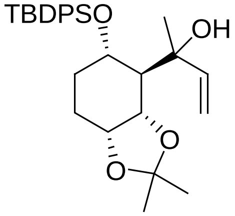
Methyl ketone 3.5



3.5

Alkene **3.1S** (350 mg, 0.77 mmol) was dissolved in a 5:1 mixture of CH_2Cl_2 / MeOH (19 mL). The solution was cooled to –78 °C and treated with a stream of O_3 in O_2 until TLC indicated the complete disappearance of the starting material. The reaction was then purged with N_2 and triphenylphosphine (700 mg) was added. The mixture was warmed to rt, stirred for 1h at this temperature, and concentrated under reduced pressure. FCC of the residue afforded **3.5** (300 mg, 85%) as a colorless oil: R_f = 0.32 (10% ethyl aceate:petroleum ether). $[\alpha]_D$ = - 39.0 (c 0.35, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.99 (s, 9H), 1.31 (s, 3H), 1.62 (s, 3H), 2.36 (s, 3H), 3.02 (t, 1H, J = 9.2 Hz), 3.74 (dt, ,1H, J = 3.3 Hz, J = 10.6 Hz, J = 14.3 Hz), 3.99-4.08 (m, 2H), 7.30-7.80 (m, 10H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 20.0, 24.4, 26.9, 27.6, 29.2, 29.7, 34.8, 62.5, 72.9, 73.1, 109.5, 128.2, 128.9, 130.1, 130.4, 133.7, 135.3, 136.4, 136.5 , 211.8. HRMS (ESI) calcd for $C_{27}H_{37}O_4Si$ [M+H] 453.2461, found 453.2480.

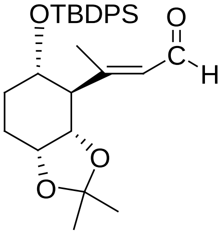
Tertiary alcohol 3.14



3.14

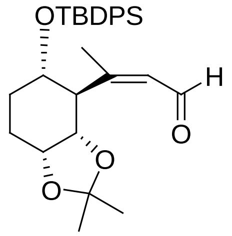
A solution of vinyl magnesium bromide (1.66 mL, 1.66 mmol) in dry THF (5mL) was cooled to 0 °C. To the solution was added dropwise a solution of ketone **3.5** (150 mg, 0.33 mmol) in dry THF. The mixture was then stirred at 0 °C for 1h or until a TLC indicates the disappearance of the starting material. The reaction was then quenched by addition of saturated solution of NH_4Cl. The organic phase was extracted with ether. The organic solvents were evaporated under reduced pressure to give a residue that was purified by FCC. The pure alcohol **3.14** was obtained as a colorless oil (110 mg, 69%): R_f = 0.3 (10% ethyl acetate:petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 9H, tBu), 1.29 (s, 3H), 1.39 (s, 3H), 2.11 (t, 1H, J = 9.1 Hz), 3.64 (dt, 1H, J = 2.9 Hz, J = 10.6 Hz, J = 13. Hz), 3.79 (dd, 1H, J = 5.1 Hz, J = 8.4 Hz), 3.98 (br s, 1H), 5.20 (d, 1H, J = 11.0 Hz), 5.47 (d, 1H, J = 18.7 Hz), 6.09 (dd, 1H, J = 10.6 Hz, J = 17.2 Hz), 7.30-7.80 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 24.9, 27.1, 27.7, 28.6, 29.1, 30.0, 56.6, 73.5, 75.6, 76.4, 76.9,108.7, 114.5, 128.1, 128.4, 128.9, 130.3, 130.6, 136.2, 136.4, 143.1. HRMS(ESI) calcd for $C_{29}H_{41}O_4Si$ (M+H) 481.2774 found 481.2774.

α,β-unsaturated aldehyde 3.6E



3.6E

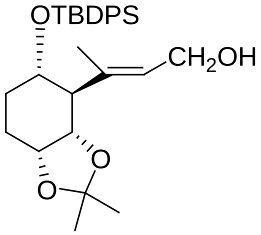
To a solution of PCC (67.37 mg, 0.31 mmol), florisil (150 mg), sodium acetate (25 mg, 0.31 mmol), molecular sieves (150 mg) and celite (150 mg) in dry dichloromethane (3 mL) was added dropwise a solution of tertiary alcohol **3.14** (50 mg, 0.10 mmol) in dry dichloromethane (2 mL). The resultant mixture was stirred at rt until the TLC indicated the disappearance of the starting material. The reaction mixture was then diluted with ether and filtered. FCC of the residue provided the pure aldehyde **3.6** as a light yellow oil (30 mg, 75%). R_f = 0.60 (10% ethyl acetate:petroluem ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.30 (s, 3H), 2.10 (s, 3H), 2.51 (s, 1H), 3.42-3.50 (m, 1H), 3.85 (dd, 1H, J = 4.8 Hz, J = 9.5 Hz,), 4.07 (br s, 1H), 5.95 (d, 1H, J = 8.1 Hz), 7.30-7.80 (m, 10H), 10.00 (d, 1H, J = 8.1 Hz). ^{13}C NMR (75MHz, $CDCl_3$), δ 17.2, 20.0, 24.4, 26.9, 29.3, 30.4, 60.6, 72.4, 73.1, 109.6, 128.1, 128.3, 130.3, 130.5, 131.0, 133.8, 134.9, 136.4, 136.5, 162.9, 191.0. HRMS(ESI) calcd for $C_{29}H_{39}O_4Si$ (M+H) 479.2618, found 479.2643.



3.6Z

R_f = 0.70 (10% ethyl acetate:petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 9H), 1.30 (s, 3H), 1.55 (s, 3H), 2.05 (s, 3H), 2.00-2.10 (m, 1H), 3.45-3.52 (m, 1H), 3.90-3.915 (m, 1H), 4.12-4.15 (m, 1H), 6.12 (d, 1H, J = 9.16 Hz,), 10.11 (d, 1H, J = 8.05 Hz).

Allyl alcohol 3.15

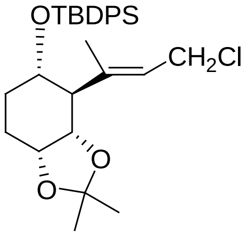


3.15

To a solution of **3.6E** (125 mg, 0.26 mmol) in toluene (2.6 mL) under nitrogen at –78 °C was slowly added DIBALH (0.30 mL, 0.31 mmol, 1M in hexane). The reaction mixture was stirred at this temperature for 20 min. The resulting reaction mixture was quenched by addition of water and extracted with ethyl acetate. The organic extract was successively washed with saturated aqueous solution of NH_4Cl (10 mL), saturated aqueous solution of $NaHCO_3$, brine, dried, (Na_2SO_4), filtered, and concentrated in vacuo. FCC of the residue afforded the primary alcohol **3.15** (110 mg, 88%) as colorless oil. ^{1}H

NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.21-1.31 (m, H), 1.22 (s, 3H), 1.44-1.51 (m, 1H), 1.48 (s, 3H), 1.49 (s, 3H), 1.54-1.64 (m, 1H), 1.89-1.92 (m, 1H), 2.25 (t, 1H, J = 10.0 Hz), 3.37 (dt, 1H, J = 3.0 Hz, J = 10.0 Hz), 3.73 (dd, 1H, J = 5.0 Hz, J = 9.5 Hz), 3.96 (brs, H), 4.09 (d, 2H, J = 6.0 Hz), 5.41 (t, 1H, J = 6.0 Hz), 7.30-7.80 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 15.1, 19.6, 24.1, 26.7, 27.2, 28.9, 30.1, 58.7 , 60.0, 108.7, 127.6, 127.7, 128.2, 128.5, 129.7, 129.8, 136.1, 137.3.

Allyl chloride 316

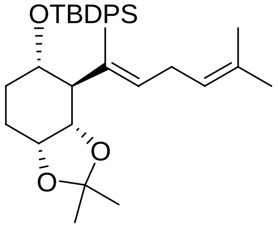


3.16

A solution of **3.15** (35 mg, 0.07 mmol), collidine (0.06 mL, 0.44 mmol), lithium chloride (18.5 mg, 0.44 mmol), and methanesulfonyl chloride (0.04 mL, 0.48 mmol) in dry DMF (1.5 mL) under an atmosphere of argon was stirred at room temperature for 3hrs. The reaction was quenched by addition of water (1 mL). The organic phase was extracted with ethyl acetate. The combined extract was successively washed with saturated aqueous solution of NH_4Cl, saturated aqueous solution of $NaHCO_3$, brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. FCC of the residue afforded the primary chloride **3.16** (40 mg, 100%) as light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.24-1.39 (m, 1H), 1.31 (s, 3H), 1.52-1.60 (m, 1H), 1.57 (s, 3H), 1.62-1.70 (m, 1H), 1.64 (s, 3H), 1.97-2.00 (m, 1H), 2.37 (t, 1H, J = 10.0 Hz), 3.43 (t, 1H, J = 10.0 Hz), 3.79 (dd, 1H, J =

5.0 Hz, J = 9.5 Hz), 4.05 (brs, 1H), 4.10-4.20 (m, 2H), 5.55 (t, 1H, J = 7.5 Hz), 7.30-7.80 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 14.7, 19.6, 24.1, 26.7, 27.3, 28.9, 30.1, 41.1, 58.7, 71.7, 72.9, 108.8, 124.7, 127.6, 127.7, 129.7, 129.8, 135.0, 136.1, 140.1. HRMS(ESI) calcd for $C_{29}H_{40}O_3Si^{35}Cl$ (M+H) 499.2435, found 499.2457.

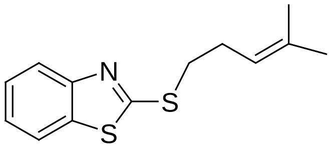
Diene 3.18



3.18

A mixture of **3.16** (12 mg, 0.02 mmol), tetrakis(triphenylphosphine) palladium(0) (10 mg, 20% mol), and tributylisobutenyltin (83 mg, 0.24 mmol) in anhydrous $CHCl_3$ (1.0 mL) under an atmosphere of argon was stirred at 40 ^{0}C for 18 h. The reaction mixture was concentrated under *vaccuo* and the residue purified by FCC to give **3.18** (4 mg, 28%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (s, 9H), 1.23-1.35 (m, 1H), 1.32 (s, 3H), 1.52-1.58 (m, 1H), 1.56 (s, 3H), 1.57 (s, 3H), 1.65 (s, 3H), 1.71 (s, 3H), 1.93-1.97 (m, 1H), 2.30 (t, 1H, J = 10.0 Hz), 2.75-2.82 (m, 2H), 3.40 (dt, 1H, J = 3.5 Hz, J = 11.0 Hz), 3.81 (dd, 1H, J = 4.5 Hz, J = 12.0 Hz), 4.04 (br s, H), 5.16 (t, 1H, J = 7.5 Hz), 5.25 (t, 1H, J = 7.0 Hz), 7.30-7.80 (m, 10H).

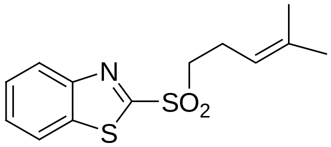
Benzothiazole sulfide 3.20[53]



3.20

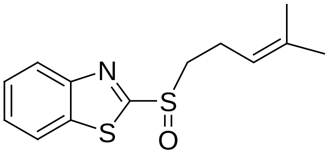
A mixture of mercaptobenzothiazole **3.19** (500 mg, 2.98 mmol), NaH (299 mg of 60% dispersion in mineral oil, 7.47 mmol), and Bu_4NI (110 mg, 0.29 mmol) in dry DMF (5 mL) under argon was stirred at rt for 30 min. 5-bromo-2-methyl-2-pentene (0.80 mL, 5.98 mmol) was then added to the reaction mixture, and stirring continued for 1.5 h. The reaction was quenched with water and the mixture extracted with ether. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated in *vacuo*. The residue was purified by FCC to give the derived thioether **3.20** as a colorless oil (720 mg, 97%). $R_f = 0.9$ (20% ethyl acetate:petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.63 (s, 3H), 1.69 (s, 3H), 2.49 (q, 2H, J = 7.3 Hz), 3.31 (t, 2H, J = 7.3 Hz), 5.19 (t, 1H, J = 7.3 Hz), 7.20-7.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 26.0, 28.4, 34.1, 121.1, 121.7, 121.8, 124.3, 126.1, 134.7, 135.4, 153.6, 167.3.

Sulfone 3.7



3.7

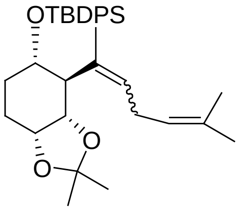
Ammonium molybdate (1.90 g) and hydrogen peroxide (7.72 mL) were combined at 0 °C and stirred for 15 min. This bright yellow solution was added dropwise at 0 °C, over 90 min, to a solution of the sulfide **3.20** (200 mg, 0.80 mmol) in EtOH (7.40 mL). The progress of the reaction was carefully monitored by TLC. Upon disappearence of the starting material, the mixture was diluted with water and extracted with ether. The organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified by FCC to provide sulfone **3.7** (187 mg, 83%) as white solid, and the sulfoxide derivative (17 mg, 7%) as a colorless oil; R_f's 0.63 and 0.53 (20% ethyl acetate:petroleum ether), respectively. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 (s, 6H), 2.55 (q, 2H, J = 8.0 Hz), 3.50 (t, 2H, J = 7.7 Hz), 4.99 (t, 1H, J = 8.8 Hz), 7.50-8.20 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 21.7, 25.8, 54.8, 119.1, 122.5, 125.6, 127.7, 128.1, 136.9, 152.9, 202.6. MS(ESI): [M + NH_4^+].



sulfoxide

For sulfoxide.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.65 (s, 3H), 2.30-2.49 (m, 1H), 2.57 (m, 1H), 3.10-3.30 (m, 2H), 5.10 (t, 1H, J = 7.5 Hz), 7.40-7.59 (m, 2H), 7.90-8.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1, 20.9, 25.9, 57.0, 120.0, 122.4, 124.1, 126.2, 127.0, 135.6, 136.2, 154.1, 178.1.

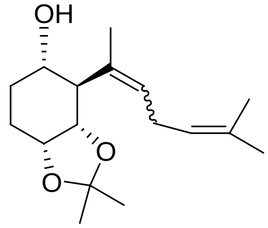
Diene 3.21E/Z



3.21E/Z (E/Z 1/6)

LiHMDS (1.0 M in THF, 0.5 mL, 0.49mmol) was added dropwise to a solution of sulfone **3.7** (140 mg, 0.49 mmol), and methyl ketone **3.5** (50 mg, 0.11 mmol) in THF (5 mL), at –78 ^{o}C. The resulting light yellow solution was stirred for 1.5 h, then allowed to warm to rt, and stirred for 10 min at this temperature. The reaction was then quenched by the addition of saturated aqueous NH_4Cl, and the mixture extracted with ether. The organic extract was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. FCC of the residue afforded an inseparable 1:8 mixture of **3.21E/Z** (50 mg, 87%) as a colorless oil: R_f = 0.60 (10% ethyl acetate:petroleum ether). The E/Z ratio was determined by integration of the signals at δ 5.16 and 5.43 ppm, respectively. For **3.21Z**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (1.00) (s, 9H), 1.31 (s, 3H), 1.49-1.74 (m, 4H), 1.56 (s, 3H), 1.60 (s, 3H), 1.66 (s, 3H), 1.70 (s, 3H), 1.96-2.02 (m, 1H), 2.82-2.90 (m, 2H), 2.96-3.02 (m, 1H), 3.38 (dt, 1H, J = 3.50, J = 10.5 Hz), 3.88 (dd, 1H, J = 5.5, 9.50 Hz), 4.08 (brs, 1H), 5.23 (t, 1H, J = 7.0Hz), 5.43 (t, 1H, J = 7.0 Hz), 7.28-7.70 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 19.6, 24.4, 25.9, 26.5, 27.2, 27.5, 28.7, 30.3, 50.9, 71.2, 72.8, 108.6, 124.1, 127.5, 127.6, 129.6, 129.7, 129.8, 131.2, 132.3, 134.1, 135.3, 136.1; For **3.21E** (selected signals): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.31 (t, 1H, J = 10.5 Hz), 2.76-2.81 (m, 1H), 3.82 (dd, 1H, J = 5.0 Hz, J = 9.5 Hz), 4.02-4.06 (m, 1H), 5.16 (t, 1H, J = 6.5 Hz), 5.23 (t, 1H, J = 7.0 Hz); HRMS of mixture (ESI) calcd for $C_{33}H_{47}O_3Si$ [M+H] 519.3294, found 519.3317.

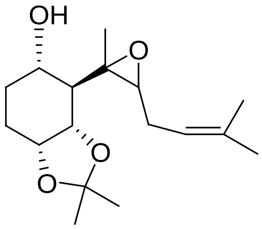
Homoallyl alcohol 3.22E/Z



3.22E/Z E/Z 1/6

A mixture of **3.21E/Z** (45 mg, 0.08 mmol) in THF (0.5 mL) and Bu_4NF (1.0 M in THF, 0.2 mL) was stirred at rt fo 18 h, then concentrated *in vacuo*. The residue was purified by FCC to give an inseparable mixture **3.22E/Z** as a colorless oil (15 mg, 62%): $R_f = 0.25$ (20% ethyl acetate:petroleum ether). For **3.22Z**: ^{1}H NMR (300 MHz, $CDCl_3$) δ1.26 (s, 1H), 1.36 (s, 3H), 1.56 (1.55) (s, 3H), 1.64 (1.61) (s, 3H), 1.69 (s, 3H), 1.74-1.79 (m, 2H), 1.86-1.92 (m, 1H), 2.23-2.27 (m, 1H), 2.71 (2.15) (t, 1H, J = 10 Hz), 2.73-2.92 (m, 2H), 3.42 (t, 1H, J = 9.0 Hz), 4.09 (4.03) (dd, 1H, J = 5.5, J = 9.5 Hz), 4.26-4.28 (4.21-4.24) (br s, 1H), 5.11 (t, 1H, J = 7.5 Hz), 5.62 (5.40) (t, 1H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 19.2, 24.3, 25.9, 26.5, 27.3, 28.5, 28.8, 51.0, 68.4, 73.1, 79.1, 108.8, 123.1, 130.7, 132.2, 132.4. For **3.22E**, see below. MS(ESI) of mixture: [M + NH_4^+].

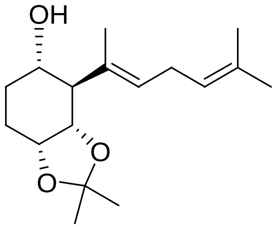
Epoxide 3.24



3.23

tert-Butyl hydroperoxide in decane (52.2 mL, 0.30 mmol) was added to a solution of **3.22E/Z** (50 mg, 0.17 mmol) and vanadyl acetylacetonate (5mg, 0.02 mmol), in dry CH_2Cl_2 (17 mL), at –10 °C under argon. The mixture was stirred at this temperature for 1h, then quenched dimethyl sulfide (0.12 mL), and stirred at 0 °C for an additional 30 min. The volatiles were then *in vacuo* and the residue purified by FCC to yield the derived epoxide as a single isomer (52mg, 94%) as a colorless oil. R_f = 0.35 (20% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.38 (s, 3H), 1.47 (s, 3H), 1.55-1.80 (m, 4H), 1.62 (s, 3H), 1.71 (s, 3H), 2.09-2.17 (m, 2H), 2.47-2.52 (m, 1H), 2.74 (dd, 1H, J = 4.0, J = 8.1 Hz), 3.49 (s, 1H), 3.77-3.81 (m, 1H), 3.98 (dd, 1H, J = 5.6, J = 9.37 Hz), 4.22-4.24 (m, 1H), 5.24-5.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 23.5, 25.7, 25.9, 27.9, 28.0, 28.2, 48.8, 62.6, 64.1, 69.1, 72.9, 75.3, 108.9, 119.4, 134.4; MS(ESI): 297.2 [M+H].

Homoallyl alcohol 3.24E



3.24E

A 0.5M stock solution of Ph_2PLi was prepared by the addition of a hexane solution of n-butyllithium (1.0 mL, 1.6 M) to a solution of Ph_2PH (0.3 mL, 1.68 mmol) in dry THF (2 mL) at rt under an argon atmosphere, followed by stirring for an additional 1h. An aliquot of the red solution of Ph_2PLi (1.95 mL, 1.00 mmol), was added to a solution the epoxide **3.24** derivative from the previous step, and (25 mg, 0.08 mmol), in dry THF (0.8 mL), at rt under an atmosphere of argon, and stirring continued for an additional 2h. At that time freshly distilled MeI (0.06 mL, 1.0 mmol) was added. The reaction mixture was stirred at rt for an additional 1h, then cooled to –78 ^{o}C. *n*-Butyllithium (1.0 mL, 1.6M) was next added until the red-yellow color persisted, at which time the mixture was diluted with ether and filtered through Celite. The filtrate was concentrated in *vacuo* and the residue purified by FCC to afford **3.25E** as a light yellow oil (18 mg, 76% from **3.22E/Z**). R_f = 0.47 (20% ethyl acetate:petroleum ether). $[\alpha]_D$ -107.2 (c 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ1.33 (s, 3H), 1.51 (s, 3H), 1.55-1.59 (m, 1H), 1.61 (s, 3H), 1.67 (s, 6H), 1.69-1.76 (m,1H), 1.81-1.87 (m, 1H), 2.10 (t, 1H, J=10Hz), 2.16-2.2.23 (m, 1H), 2.68-2.87 (m, 2H), 3.37 (dt,1H, J = 3.7, J = 10.2, J = 13.9 Hz), 4.00 (dd, 1H, J = 4.8 Hz, J = 9.5 Hz), 4.16-4.21 (m, 1H), 5.08 (t, 1H, J = 13.0 Hz), 5.36 (t, 1H, J = 6.6 Hz), ^{13}C NMR (125

MHz, $CDCl_3$) δ. 13.5, 18.1, 24.1, 25.9, 26.7, 27.6, 28.2, 28.8, 59.1, 68.3, 73.2, 77.0, 108.8, 122.8, 130.8, 131.5, 132.2; MS(ESI): 281.2 [M+H].

PART 2:

Synthesis of β-C-glycosides of galactosamine

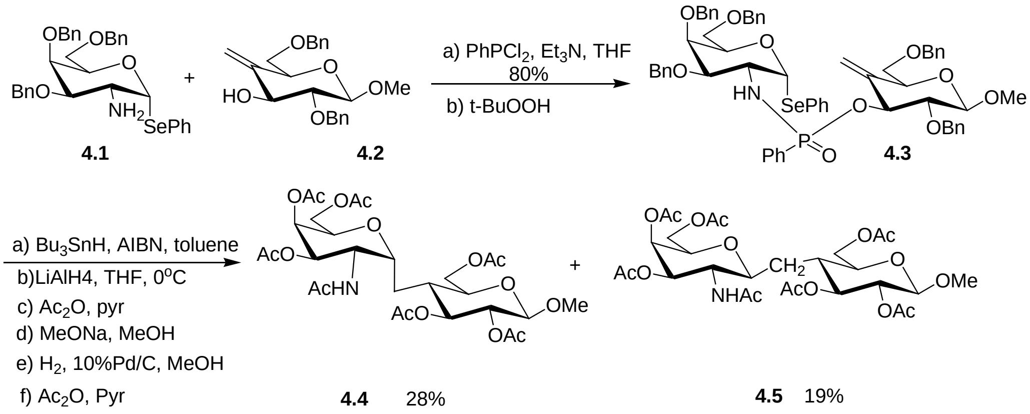
Chapter IV

Methodology development for β-C-glycosides of galactosamine

4.1 Background

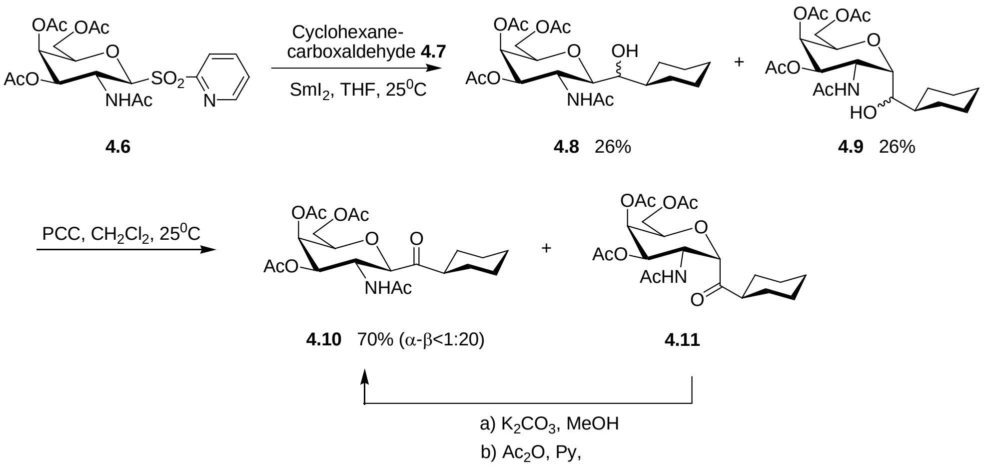
Mimics of carbohydrate involved in disease have attracted attention as mechanistic tools.[54] Probe structures based on disaccharide scaffolds are attractive because they allow for libraries of closely related analogues, and the complexity of individual structures is relevant to issues of recognition specificity.[55,56] C-glycosides (analogues in which the glycosidic oxygen is replaced by a methylene group), are an especially important subset of glycoside mimetics. [57] Their hydrolytic stability combined with their conformational differences to O-glycosides make them unique structure activity probes.

2-Amino-2-deoxy amino sugars are important subunits of many glycoconjugates such as glycoproteins,[58] chitin,[59] and heparin.[60] They are involved in number of biological processes and are attractive targets for the design of C-linked mimetics. Application of known C-glycosidation strategies[61,62] to derivatives of 2-amino sugars are complicated by the presence of the 2-amino substituent. Indeed, only a relatively small number of methods for the synthesis of the β-C-galactosamine disaccharide have been reported. Sinay[63] disclosed an intramolecular delivery strategy in which the 2-amino-β-C-disaccharide **4.5** was obtained in a relatively low yield (19% from compound **4.3**) (**Scheme 4.1**).



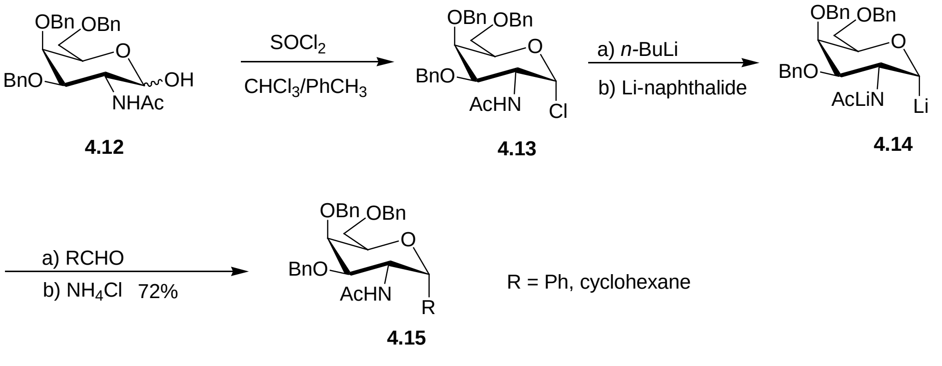
Scheme 4.1

Jean-Marie Beau and co-workers reported a strategy involving a samarium-di-iodide mediated Barbier coupling of sulfone **4.6** with aldehydes (**Scheme 4.2**).[64] In one example treatment of sulfone **4.6** with samarium diiodide in presence of cyclohexanecarboxaldehyde **4.7** at room temperature provided alcohols **4.8** and **4.9**, which were subjected to PCC oxidation. The two-anomeric ketones **4.10** and **4.11** were obtained in a 1:1 mixture. Treament of ketone **4.11** with potassium carbonate in methanol, followed by acetylation afforded, the isomeric β-ketone **4.10** (70%). The pure ketone **4.10** was obtained from sulfone **4.6** in a 42% overall yield.



Scheme 4.2

Kessler and co-workers devised a synthesis of α-C-galactosamines from the glycosyl dianion **4.14** (**Scheme 4.3**).[65] The configurationally stable α-glycosyl dianion **4.14** was prepared by reductive lithiation of the chloride **4.13**. The reaction of **4.14** with different aldehydes provided the α-C-galactosamine derivative **4.15**.

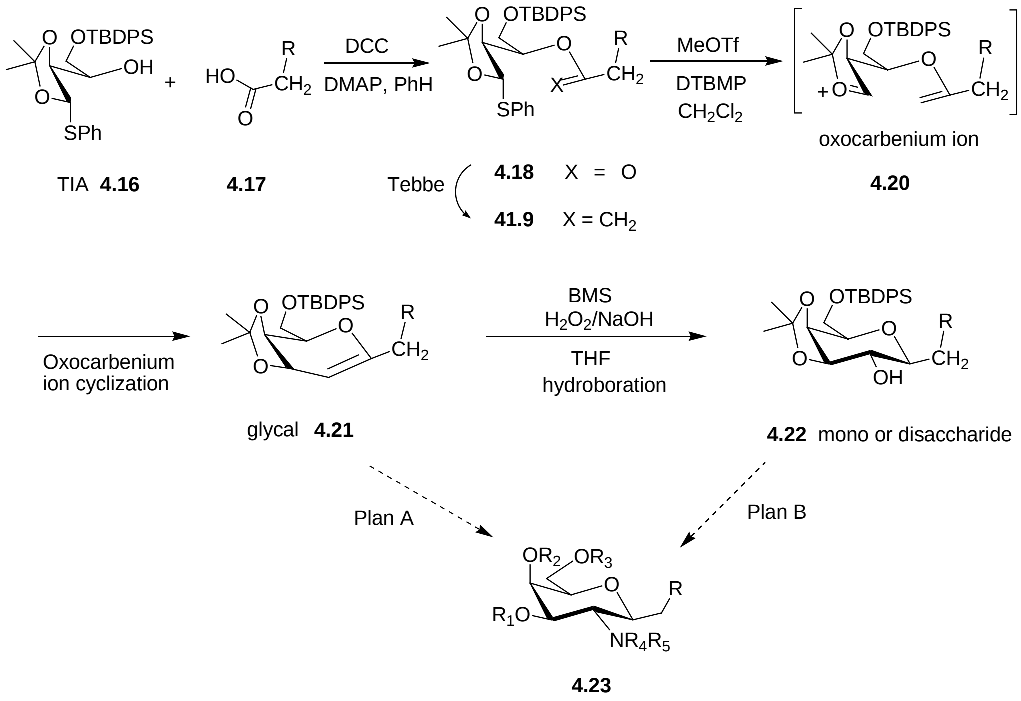


Scheme 4.3.

We envisaged a stereoselective synthesis of 2-amino-β-C-glycoside that is based on extension of the oxocarbenium ion cyclizations described in part I.

4.2 Synthetic plan

Our plan centers on a C-glycoside methodology discovered in our laboratory. [66] The DCC-mediated coupling between the thio-isopropylidene acetal (TIA) **4.16** and acid **4.17** provides the ester **4.18** (**Scheme 4.4**). Olefination of ester **4.18** to an enol ether **4.19** followed by activation of the thioacetal in **4.19** gives the C1-substituted glycal **4.21** which may be transformed to the 2-amino-β-C-glycoside **4.23**. Alternatively **4.23** may be obtained by first conversion of **4.21** to the β-C-glycoside **4.22**, and the latter transformed to **4.23** in a separate step.



Scheme 4.4.

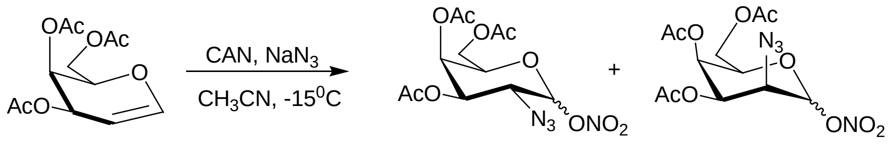
In the following section, methods for the direct and stepwise conversion of glycals to 2-amino-glycosides will be reviewed.

4.3 Synthetic strategies for 2-amino sugars from glycals

The biological importance of 2-amino sugars has inspired the development of synthetic methods for the preparation of 2-aminoglycosides.[67] Special interest has been devoted to the conversion of glycals 2-aminosugars. [68]

Direct insertion of nitrogen into the glycal

The pioneering work of Lemieux and Ratcliffe reported that conversion of triacetyl-D-galactal **4.24** to azido-nitrates **4.25** and **4.26** occurred in a very good yield with excellent stereoselectivity (**Scheme 4.5**).[16d] These 2-azido-glycosyl nitrates **4.25** were converted to the corresponding anomeric halides and used as glycosyl donors in the synthesis of 2-amino-α-D-pyranosides.[69]

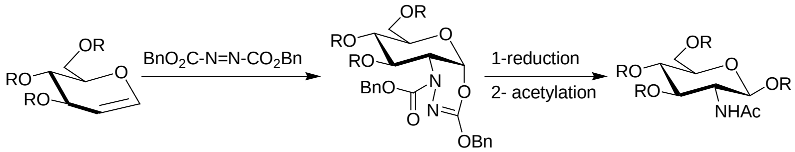


4.24 **4.25** **4.26**

Scheme 4.5.

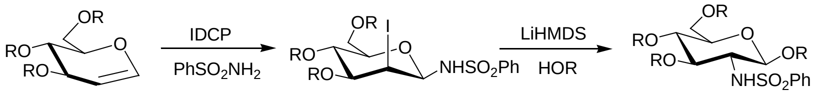
In the late 1980's to early 1990's Fitzsimmons/Leblanc[16d] and Danishefsky/Griffith[16b] coupled amination with glycosylation into concise synthesis of 2-amino-glycosides (**Scheme 4.6**).

Fitzsimmons and Leblanc cycloaddition



glucal **4.27** **4.28** **4.29**

Danishefsky and Griffith sulfonamidoglycosylation

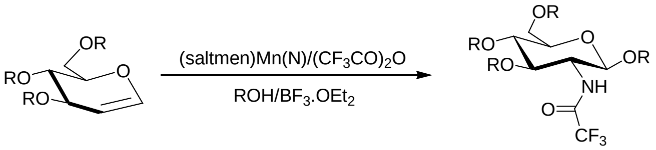


glucal **4.30** **4.31** **4.32**

Scheme 4.6.

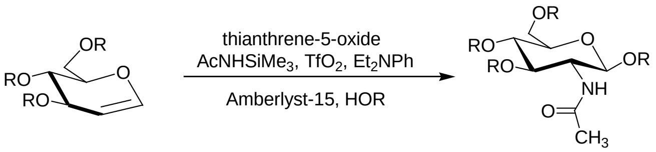
A recent approach by Du Bois and Carreira[16a] allowed the aziridination of glycals with (Saltmen) Mn(N) and trifluoroacetic acid anhydride (**Scheme 4.7**). An alternative

Du Bois and Carreira Method



glucal **4.33** **4.34**

Gin Acetamidoglycosylation



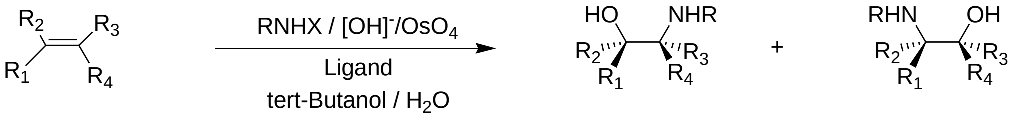
glucal **4.35** **4.36**

Scheme 4.7

approach for the direct synthesis of 2-N-acetamido-β-pyranosides from glycal derivative was developed by Gin and co-workers[16f].

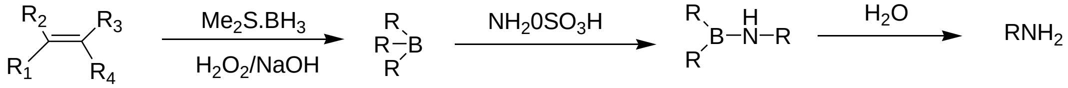
In addition to the above approaches, other methodologies for stereoselective hydro- or hydroxy-amination of double bonds could provide a direct route for transformation of glycals to sugars. Brown[70] and co-workers have developed methods for hydroamination of olefins, that involve oxidation of boranes intermediates with various nitrogen sources (e.g. Chloramine,[71] hydroxamine-O-sulfinic acid (HAS)) [20,72] (**Scheme 4.8**). Sharpless[73] has developed stereoselective procedure for hydroxy amination of alkenes.

Sharpless Osmium-catalyzed Asymmetric Aminohydroxylation



alkene **4.37** **4.38** **4.39**

Brown aminoboration

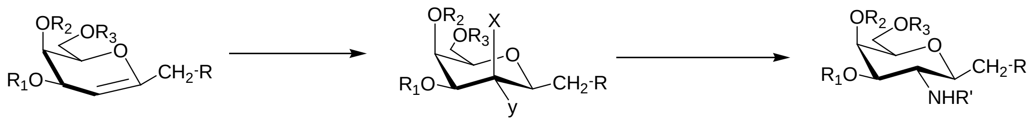


alkene **4.40** **4.41** **4.42** **4.43**

Scheme. 4.8.

Stepwise insertion of nitrogen into the glycal

An alternative synthesis of 2-deoxyamino-C-glycosides involves conversion of the glycal derivative to the corresponding 2-hydroxy-C-glycoside, followed by conversion of the 2-OH to an imine or oxime and a subsequent reduction (**Scheme 4.9**).



4.44

4.45 X = H, Y= OH

4.46 X,Y = NHR

4.23 2-deoxyamino C- glycoside

Scheme 4.9.

4.4 Results and discussion

4.4.1 Attempted conversion of glycal into the 2-aminosugar

The glycal substrates **4.21** were prepared by our oxocarbenim ion cyclizations strategy. Accordingly, TIA **4.16** and acids **4.47**, **4.48** and **4.49** were subjected to our C-glycoside protocol (**Figure 4.1**). TIA **4.16** was obtained by a route that was previously developed in our group. [74] Acid **4.48**[75] was prepared by standard procedures on known precursors. The synthesis of acid **4.49**[76] started with 6-aminohexanoic acid **4.50** (**Scheme 4.10**). Treatment of **4.50** with toluene sulfonyl chloride in a 10% solution of sodium hydroxide afforded the sulfonamide derivative **4.51** in 73%. Benzylation of the tosyl amide **4.51** provided the acid **4.49** in 58%.

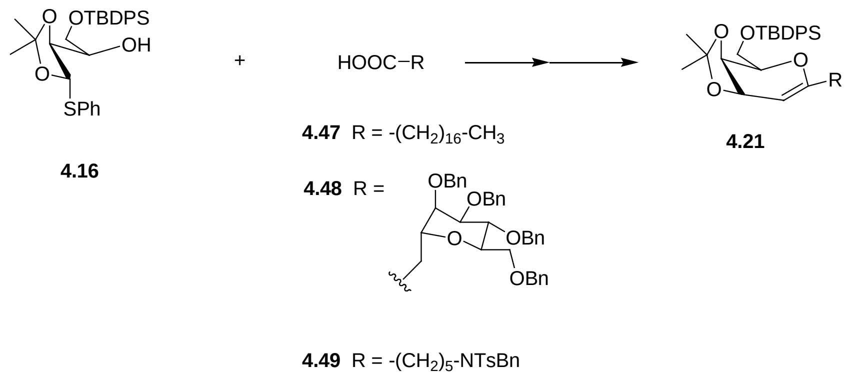
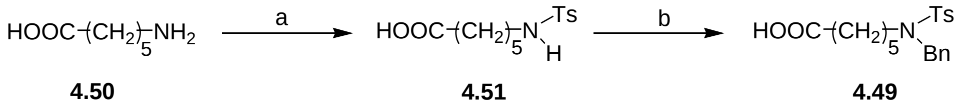
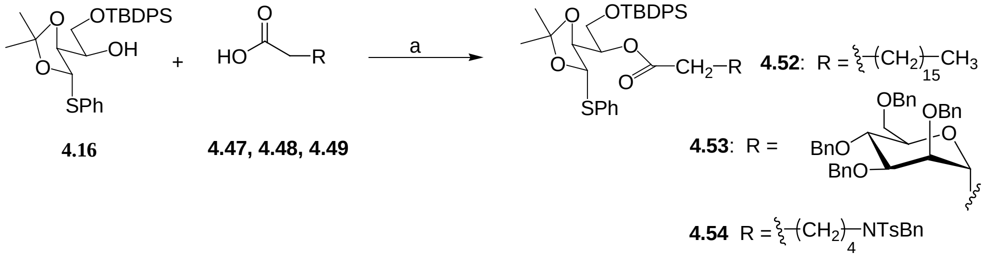


Figure 4.1

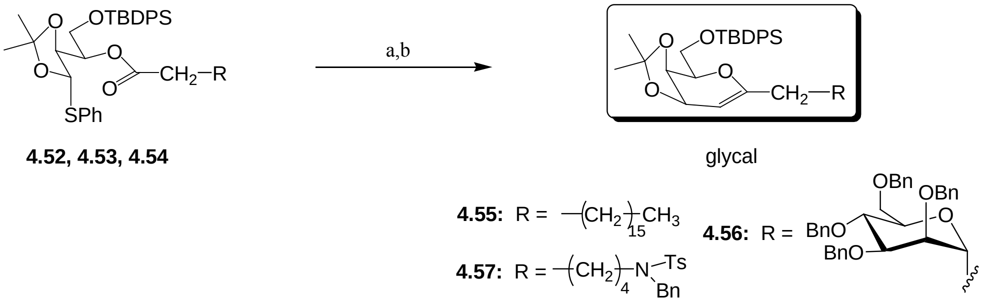


Scheme 4.10. (a) TsCl, 10% NaOH, 73%. (b) BnBr, 50% NaOH, benzene, 58%.

Coupling of TIA **4.16** with a suitable acid such as stearic acid **4.47, 4.48**, and **4.49** provided ester **4.52**, **5.53** and **5.54** respectively in 80% average yield (**Scheme 4.11**). Tebbe olefination of **4.52**,**4.53**, and **4.54** followed by methyl triflate mediated oxocarbenium ions cyclization afforded the glycals **4.55**, **4.56** and **4.57** respectively (**Scheme 4.12**). With the above glycals in hand, we pursued our investigation towards the synthesis of galactose-β-C-glycosides.

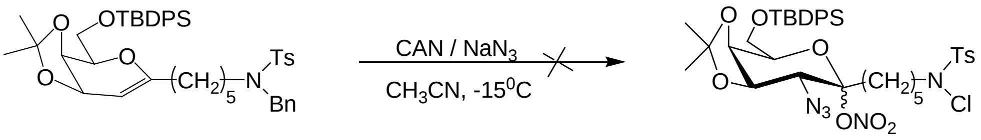


Scheme 4.11. (a) DCC / DMAP, benzene, 81%.



Scheme 4.12. (a) Tebbe, toluene, 80%. (b) MeOTf / DTBMP, CH_2Cl_2, 70%.

Glycal **4.57** was subjected to established azidonitration condition. However, no desired 2-azido-glycoside derivative was isolated. The reaction condition produced several unidentified compounds (**Scheme 4.13**).

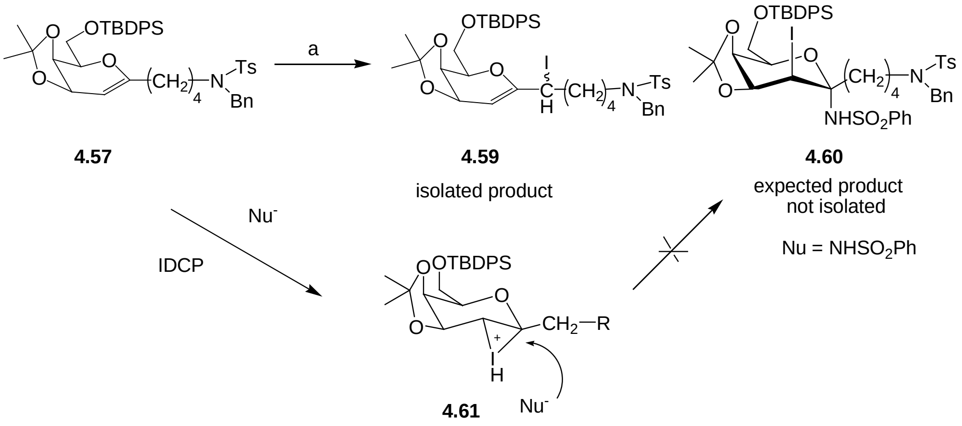


4.57

4.58 expected product not isolated

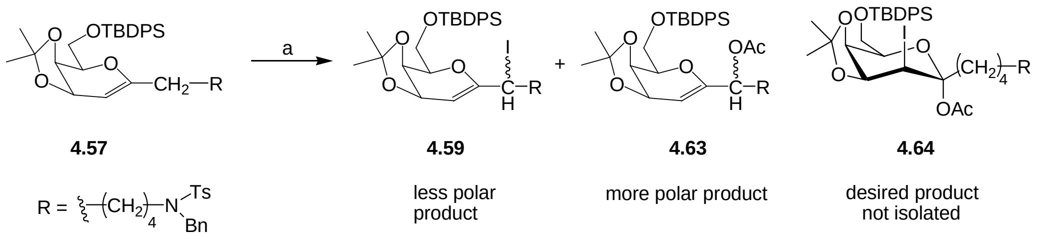
Scheme 4.13.

Following the latter result, we decided to investigate Danishefsky's sulfonamidoglycosylation strategy. Thus, glycal **4.57** was treated with IDCP (di-*syn*-collidine perchlorate) and benzenesulfonamide in anhydrous methylene chloride at 0 °C. Unfortunately, the expected trans-diaxial iodosulfonamide **4.60** was not isolated. Instead compound **4.59** was obtained as the sole product (**Scheme 4.14**). The structure of **4.59** was assigned by analysis of ^{1}HNMR and ^{13}CNMR spectra. At this point, we speculated that the benzenesulfonamide might not be nucleophilic enough to attack the iodonium intermediate **4.61** which is presumed to be formed in the reaction.



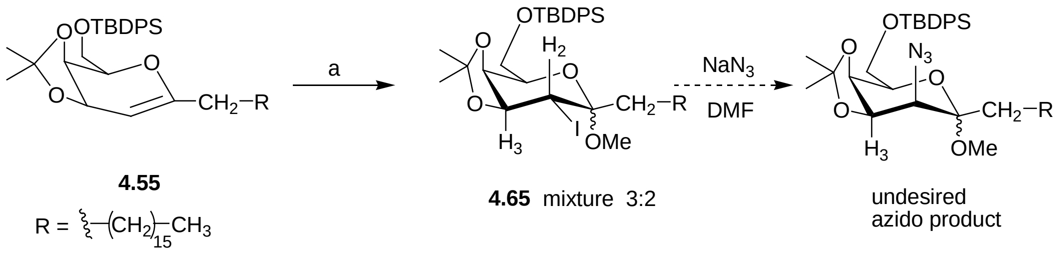
Scheme 4.14. (a) H_2NSO_2Ph / IDCP, CH_2Cl_2, 4A sieves, 0 ^{o}C.

Thus, we decided to replace the benzenesulfonamide with a better nucleophile (i.e. acetate). Our plan was to isolate the 1-acetoxy-2-iodo **4.64** (Nu = OAc), and displace the 2-iodo substituent by azide in order to introduce the nitrogen at C-2 position (**Scheme 4.15**). Treatment of **4.57** with IDCP and acetic acid provided two chromatographically separable products **4.59** and **4.63** (2:1 mixture in 50% yield). The less polar major product was identical to **4.59** (product obtained in the reaction with benzene sulfonamide). The more polar minor product was characterized to be **4.63** (the acetate derivative of **4.59**). Once again, the expected 1-acetoxy-2-iodo product **4.64** was not formed under the reaction conditions.



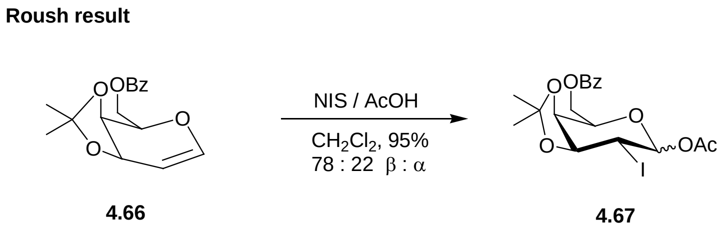
Scheme4.15. (a) AcOH / IDCP, 4A sieves, CH_2Cl_2, 50%

We next examined the IDCP promoted reaction of glycal **4.55** in methanol. Hence, the iodo methyl glycoside **4.65** was obtained as a 3:2 mixture of anomers (**Scheme 4.16**). The structure of **4.65** was assigned after proton NMR and ^{1}H COSY analysis. The values of vicinal coupling constants were in agreement with the structure of **4.65** in **scheme 4.16** (H_2: d, $J_{2,3}$ = 9.52 Hz; H_3: dd, $J_{2,3}$ = 9.34 Hz, $J_{3,4}$ = 4.8 Hz). These coupling constant values indicate the diaxial arrangement of H_2 and H_3. Thus, the iodide was introduced at C-2 in the equatorial position. The SN2 displacement (by aizde) of the 2-iodo substitutent in **4.65** would provide the undesired azido product. Hence, **4.65** is not a useful intermediate for our 2-amino-sugar synthesis.



Scheme 4.16. (a) IDCP / MeOH, molecular sieves, rt, 80%.

The latter result was not very surprising. Indeed, Roush and co-workers[77] obtained a similar result, when they treated a 3,4-acetonide-protected glycal **4.66** with NIS and AcOH (**Scheme 4.17**).



Scheme 4.17.

In view of the problems encountered in the azidonitration and iodination reactions on the glycals substrates, we next investigated the Carreira protocol for the conversion of glycals to 2-amino-glycosides. This method involves direct transition metal-promoted amination of glycals. The reaction employs an easily prepared manganese nitrido complex, which upon activation with trifluoroacetic anhydride, serves as a reactive nitrogen transfer agent (**Figure 4.2**).

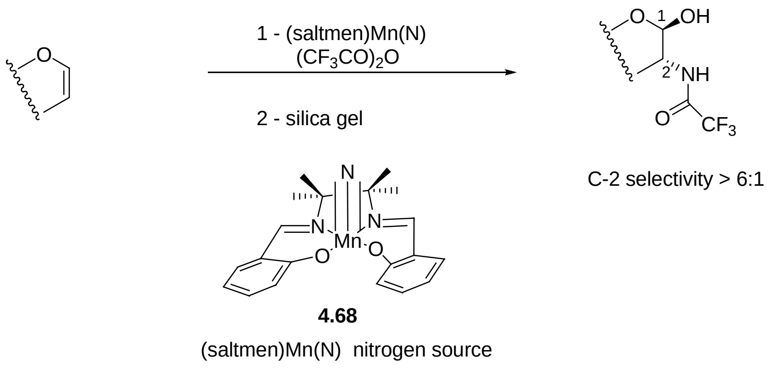
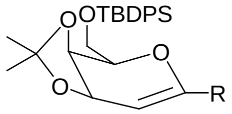
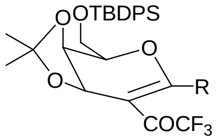
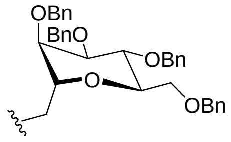
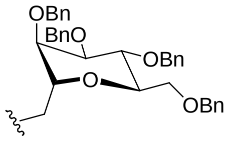


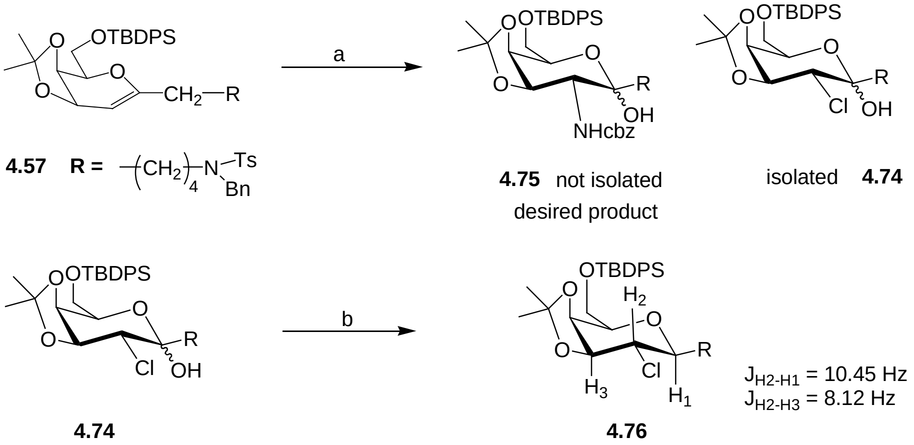
Figure 4.2. Carreira's methodology

Treatment of glycals **4.55**, **4.56** and **4.57** with a solution of (saltmen)Mn(N) reagent **4.68** in methylene chloride in presence of trifluoroacetic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine afforded a 1:1 mixture of **4.69**:**4.70**, **4.71** and **4.72**:**4.73** respectively (**Table 4.1**). ^{1}HNMR and ^{13}CNMR analysis suggested that the less polar materials as the 2-C-trifluoroacetyl-2-deoxy-glycals (**4.69**, **4.71** and **4.72**, **Table 4.1**). As an example, the NMR spectra of **4.71** indicated the absence of the H-2 proton on the galactose ring, whereas the ^{13}CNMR showed the presence of the trifluoroacetyl group [C=O: δ =181.2 ppm (q, J = 34.25 Hz); C-F: δ = 116.83 ppm (q, J = 290.62 Hz)]. The more polar compounds **4.70** and **4.73** were not identified.

Table 4.1. Application of Carreira's approach to our glycals

Starting material	Product
	
4.55 R = $(CH_2)_{16}CH_3$ **4.57** R = $(CH_2)_5$NTsBn **4.56** R = 	Less polar materials: **4.69** R = $(CH_2)_{16}CH_3$ **4.71** R =  **4.72** R = $(CH_2)_5$NTsBn More polar materials: **4.70** and **4.73** were not fully characterized

Next, we attempted Sharpless catalytic asymmetric aminohydroxylations approach. Hence, treatment of glycal **4.57** with OsO_4, dihydroqunidine-p-chlorobenzoate [$(DHQD)_2$-CLB] and dihydroquinidine-pyridine [(DHQD)2-PYR] (used as ligands), and chloramines-T (used as nitrogen source) afforded the hemiacetal **4.74** (**Scheme 4.18**). For structure identification purpose, **4.74** was treated with Et_3SiH / $BF_3.OEt_2$ in anhydrous CH_2Cl_2 to afford the 2-deoxy-2-chloro-glycoside **4.77** in 57% yield.

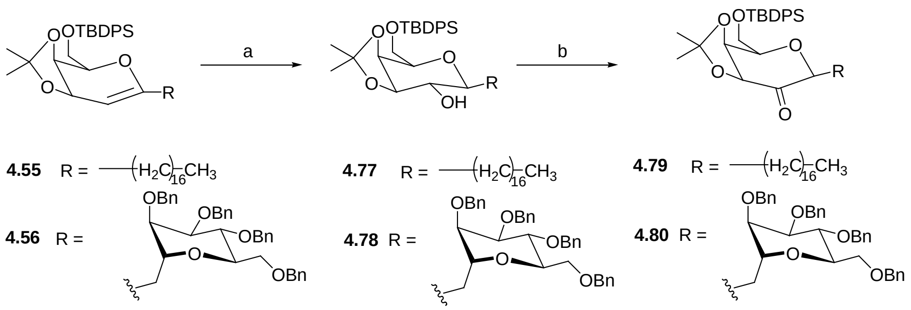


Scheme 4.18. (a) OsO_4/chloramines-T, ligands, tert-butanol/H_2O(1:1), quant. (b) $Et_3SiH/BF_3.OEt_2$, CH_2Cl_2, 57%.

In light of these unsuccessful attempts to convert the glycal substrates directly to 2-amino-C-glycosides, we next turned our attention to the elaboration of the 2-hydroxy-β-C-galactosides, which had been previously obtained from hydroboration of these glycals.

4.4.2 Synthesis of 2-amino-β-C-galactosides from 2-amino-hydroxy-β-C-galactosides

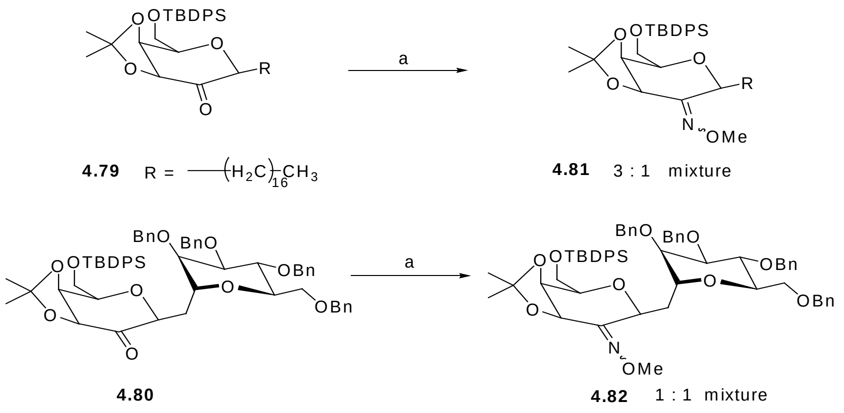
Glycal **4.55** and **4.56** were treated with $BH_3.Me_2S$ complex and H_2O_2/NaOH to give the hydroboration products **4.77**[78]and **4.78**[79], respectively in 65% yield (**Scheme 4.19**). Treatment of alcohols **4.77** and **4.78** with PCC afforded ketone **4.79** and **4.80** respectively.



Scheme 4.19. (a) $BH_3.Me_2S$, H_2O_2/NaOH, THF, 65%.

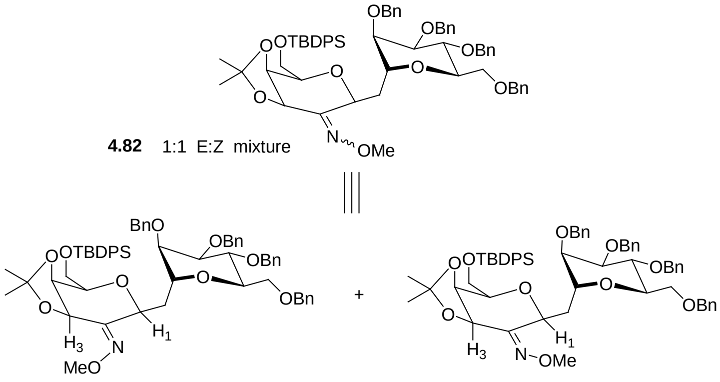
(b) PCC/NaOAc, molecular sieves, CH_2Cl_2, 94%.

Reaction of ketone **4.79** and **4.80** with MeONHOH.HCl[80] in presence of sodium acetate in a 1:1 mixture of THF and H_2O afforded oximes **4.81** and **4.82**, respectively (**Scheme 4.20**). Oximes **4.81** and **4.82** were obtained as (3/1 and 1/1 respectively).



Scheme 4.20. (a) MeONHOH.HCl / NaOAc, THF / H_2O, 98%.

Along with literature data on conformational study of oxime *O*-methyl ether derivatives,[81] we conducted a conformational analysis of our oxime **4.82** (**Figure 4.3** and **Table 4.2**). Our data in **Table 4.3** was in agreement with the reported data in the literature. Indeed, We observed a deshielding effect of the oxime oxygen on the neighboring proton (δ H_3 = 5.60 ppm in **4.82-E** vs δ H_3 = 4.80 ppm in **4.82-Z**). However, the carbon *syn* to the OMe group was found to be shielded (δ C_3 = 66.6 ppm in **4.82-E** vs δ C_3 = 74.8 ppm in **4.82-Z**).



4.82 1:1 E:Z mixture

4.82-E E isomer
more rective isomer

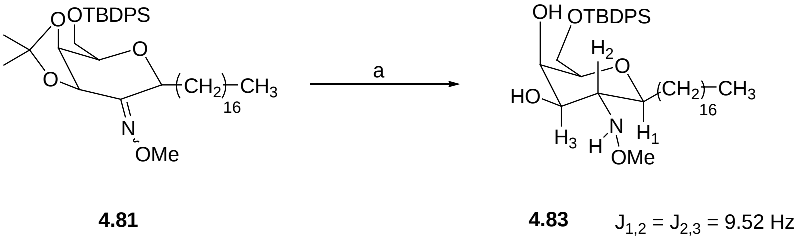
4.82-Z Z isomer
less reactive isomer

Figure 4.3. Conformational analysis of oxime

Table 4.2. ^{1}H and ^{13}C data for oxime **4.82E** and **4.82Z**

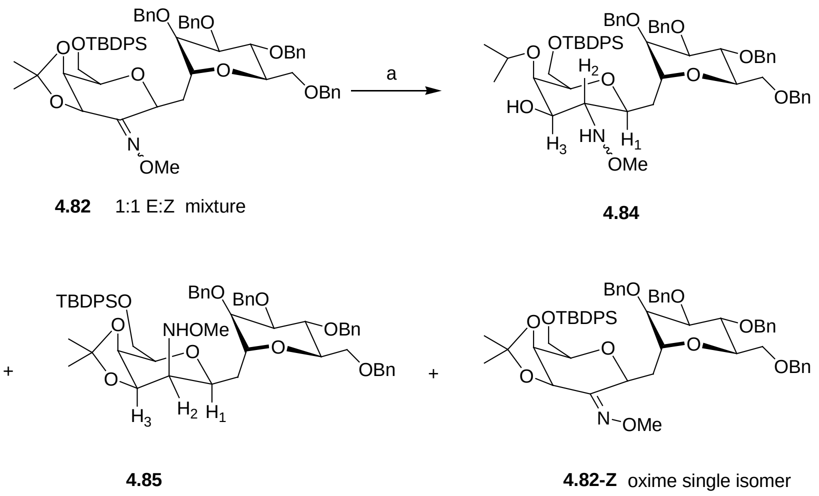
		4.82-E (ppm)		**4.82-Z** (ppm)
^{1}H NMR (C_6D_6, 500 MHz)	H_1	δ = 4.72	H_1	δ = 5.04
	H_3	δ = 5.60	H_3	δ = 4.80
^{13}C NMR (C_6D_6, 125 MHz)	C1	δ = 70-72	C1	δ = 73.2
	C3	δ = 66.6	C3	δ = 74.8

Next, the key stereoselective reduction of oximes **4.81** and **4.82** was investigated. Treatment of **4.81** and **4.82** with $LiAlH_4$ in anhydrous THF afforded several unidentified products. None of the isolated compounds corresponded to the expected product. However, the reaction of **4.81** with Bu_3SnH[82] (4 mole eq) and $BF_3.OEt_2$ (2 mole eq) in anhydrous CH_2Cl_2 at rt provided compound **4.83** in 61% yield (**Scheme 4.21**). The stereochemical assignment of **4.83** was effected through analysis of the ^1H NMR and COSY data. The structure of **4.83** supported J values of $J_{1,2} = J_{2,3} = 9.5$ Hz (H_2, triplet).



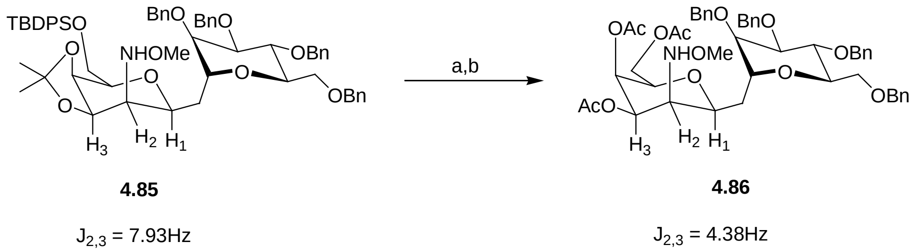
Scheme 4.21. (a) $Bu_3SnH/BF_3.OEt_2$, CH_2Cl_2, 61%.

Application of the hydrostannation condition to oxime **4.82** afforded a mixture of chromatographically separable **4.84** and **4.85** along with unreacted starting material **4.82-Z** (**Scheme 4.22**). The stereochemistry of **4.84** was assigned by analysis of J values for vicinal protons on the galactose ring. The observed J values of 9.9 Hz was in agreement with a trans-diaxial arrangement between H1/H2 and H2/H3 respectively. It should be noted that the reaction proceeded with acetonide cleavage, presumably due to the presence of $BF_3.OEt_2$ in the reaction. For **4.85**, the observed J value of 7.9 Hz ($J_{2,3}$) was not consistent with the chair conformation depicted in **scheme 4.22**. Therefore, for structure confirmation, **4.85** was converted to the triacetate **4.86 (Scheme 4.23)**.



Scheme 4.22. Bu_3SnH / $BF_3.OEt_2$, CH_2Cl_2, 50% (for **4.84**).

The observed the observed J value of 4.38 Hz ($J_{2,3}$) for **4.86** was in agreement with the C-2 axial amino substitutent. Therefore, we concluded that the galactose ring in **4.85** exists in a distorted chair conformation (**Scheme 4.23**).

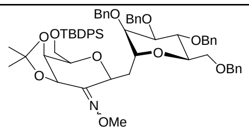
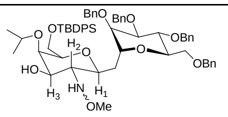
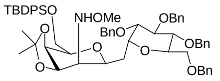
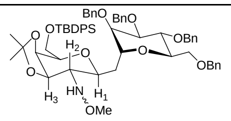
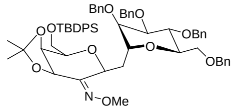
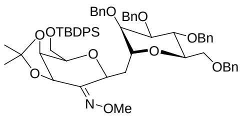
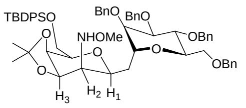
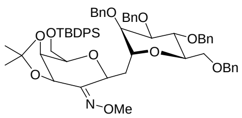
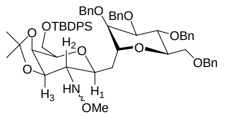
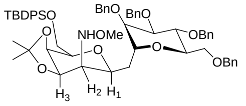


Scheme 4.23. (a) HCl, MeOH. (b) Ac_2O, DMAP, pyridine, EtOAc, 60% (from **4.85**).

Surprisingly, analysis of ^{1}H NMR and ^{13}C NMR of the recovered starting material revealed the presence of a single isomer of the oxime (**4.82**). This observation suggested that one isomer was more reactive than the other.

At this point, we decided to optimize the hydrostanation reaction. To avoid the formation of the undesired isopropyl group (**4.84**), we attempted the hydrostannation reaction at 0 °C instead of rt. Fortunately, treatment of oxime **4.82** with Bu_3SnH / $BF_3.OEt_2$ at 0 °C afforded the desired 2-amino-2-deoxy-β-C-disaccharide **4.87** in 66% (**Table 4.2**).

Table 4.3. Hydrostanation of oxime

Oxime Starting material	Room temperature $Bu_3SnH(4eq)/BF_3.OEt_2(2eq)$ Product	0 °C $Bu_3SnH(4eq)/BF_3.OEt_2(2eq)$ Product
 **4.82** 1:1 E:Z mixture	 **4.84** 50% yield  **4.85** 24% yield **4.82-Z** 12% yield	 **4.87** 61% yield  **4.82-Z** 28% yield
 **4.82-Z** single isomer	 **4.85** 30% yield  **4.82-Z** 45% yield **4.87** 20% yield	 **4.87** 20% yield  **4.85** 35% yield **4.82-Z** 40% yield

Once again, the ^{1}H NMR and ^{13}C NMR analysis determined that the recovered starting material was a single isomer. Treatment of oxime **4.82-Z** under the optimized hydrostannation condition (0 ^{o}C) provided a 3:2 mixture of **4.85**:**4.87** in 50% combined yield (**Table 4.2**).

The latter observations on the hydrostanation reaction suggested that at 0 ^{0}C **4.82-Z** is slowly converted to the more reactive **4.82-E**. Additionally, BF_3 coordinates to **4.82-E** to form a six membered ring. Thus, the hydride attack occurred on the top face of the oxime to give **4.87** (**Figure 4.2**).

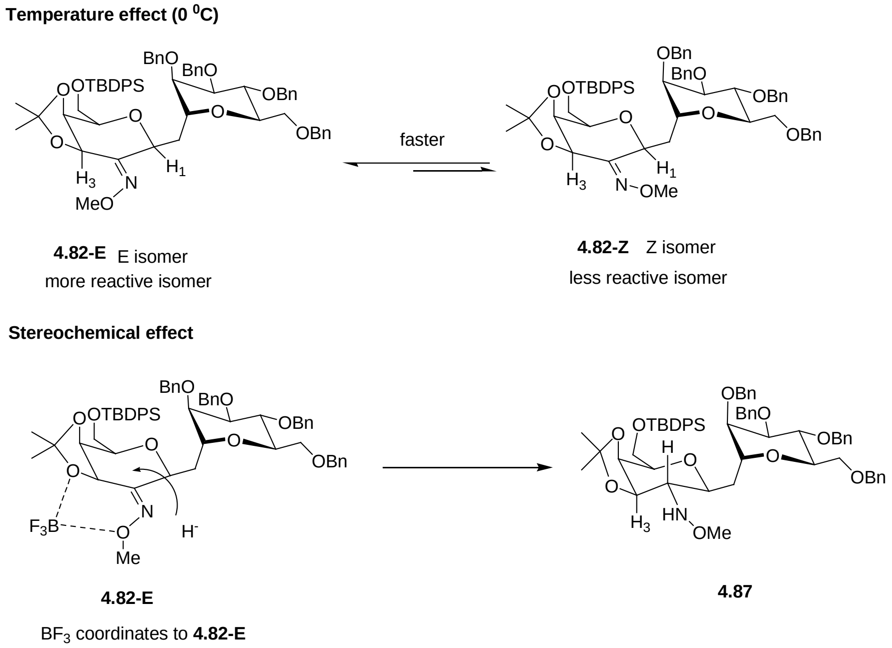
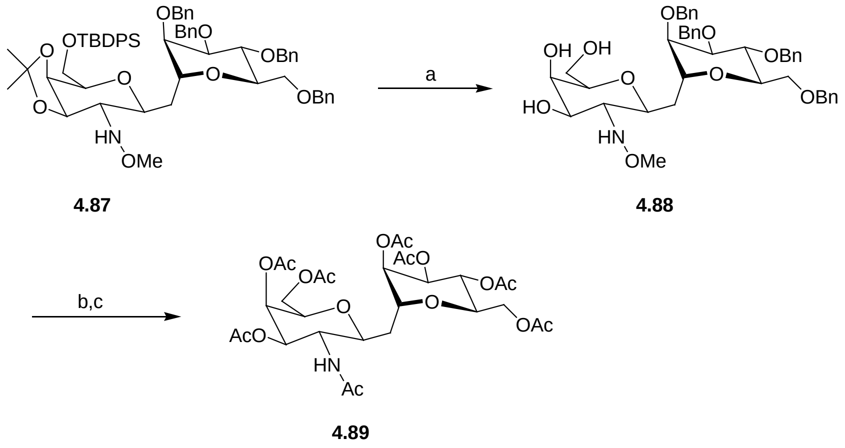


Figure 4.2. Temperature and stereo chemical effects of oxime **4.82-E**.

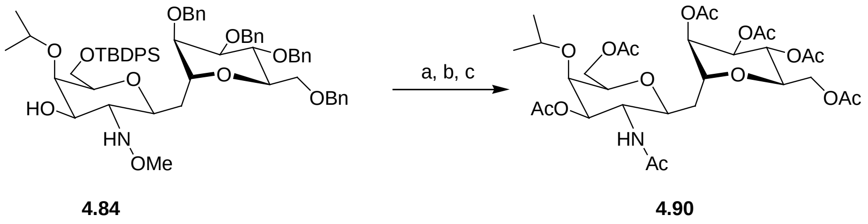
Next, was attempted the conversion of **4.87** to the 2-NAc-2-deoxy-β-C-disaccharide. Treatment of **4.87** with HCl in methanol provided the triol **4.88** in a quantitative yield. Compound **4.88** was subjected to the Na/NH_3 reaction followed by acetylation of the crude mixture to afford the octaacetate product **4.89** in 50% yield (**Scheme 4.24**).



4.87 4.88 4.89

Scheme 4.24. (a) HCl, MeOH, quant. (b) Na/NH$_3$, THF. (c) Ac$_2$O, EtOAc, DMAP, Pyr, 50%.

Similarly, intermediate **4.84** was converted to the corresponding NAc-2-deoxy-β-C-glycoside **4.90**.



4.84 4.90

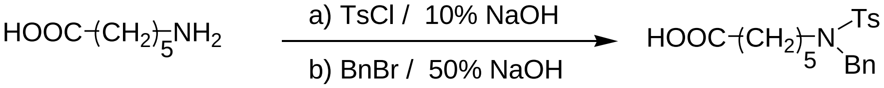
Scheme 4.24. (a) Bu$_4$NI, THF quant. (b) Na/NH$_3$, THF. (c) Ac$_2$O, EtOAc, Pyridine, 50%

Summary

Our initial plan for the synthesis of galactosamine-β-C-disaccharide consisted of direct insertion of nitrogen into the C1 substituted glycal such as **4.55** and **4.56**, based on known methodologies on sugar glycals. However, this approache was unsuccessful. The eventual solution was conversion of the C1-substituted glycal into the 2-deoxy-2-oxime methylether, followed by a stereoselective reduction, using Bu_3SnH / $BF_3.OEt_2$. The next goal was to apply this approach to the synthesis of the C-glycoside analogue of disaccharide GalNAcβ→ ManNAc.

4.5 Experimental section

Acid 4.49



4.50

4.49

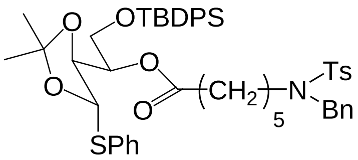
Toluene sulfonyl chloride (4.4 g, 23.18 mmol) was added dropwise to a mixture of 6-aminohexanoic acid **4.50** (2.0 g, 15.25 mmol) and 10% aqueous NaOH (25.4 mL), with constant stirring. The reaction mixture was stirred for an additional 3h, then acidified with 5% HCl and extracted with CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), filtered and concentrated in *vaccuo*. FCC of the residue provided **4.51** (3.2 g, 73%) as white solid. $R_f = 0.18$ (60% ethyl acetate:petroleum ether). ^1H NMR (500 MHz, $CDCl_3$) δ 1.32-1.38 (m, 2H), 1.48-1.54 (m, 2H), 1.57-1.63 (m, 2H), 2.34 (t, 2H, J = 7.31

Hz), 2.45 (s, 3H), 2.97 (q, 2H, J = 6.8 Hz), 4.69 (t, 1H, J = 6.1 Hz), 7.33 (d, 2H, J = 8.0 Hz), 7.76 (d, 2H, J = 8.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 24.2, 26.0, 29.4, 33.8, 43.1, 127.3, 129.9, 137.1, 143.6, 179.0.

Benzyl bromide (1.1 mL, 10.52 mmol) in benzene (10 mL) was added dropwise over 15 min, with efficient stirring to a refluxing mixture of the sulfonamide **4.51** (2.5 g, 8.77 mmol), 50% NaOH (10 mL), tetrabutylammonium hydrogen sulfate (300 mg, 0.88 mmol), and benzene (20 mL). Stirring continued fro 2 h at reflux temperature. The mixture was then cooled to rt and diluted with water (40 mL). The aqueous phase was extracted with water. The combined aqueous phase was acidified with 1% HCl. The organic phase was then extracted with ethyl acetate, dried (Na_2SO_4), filtered and concentrated under *vaccuo*. FCC of the residue provided the acid **4.49** (2.3 g, 70%) as a white solid. R_f = 0.18 (30% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03-1.17 (m, 2H), 1.31-1.36 (m, 2H), 1.41-1.47 (m, 2H), 2.21 (t, 2H, J = 7.4 Hz), 2.46 (s, 3H), 3.10 (t, 2H, J = 7.5 Hz), 4.32 (s, 2H), 7.28-7.35 (m, 7H), 7.75 (d, 2H, J = 8.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 24.2, 26.1, 27.9, 33.8, 48.2, 52.4, 127.4, 128.0, 128.5, 128.7, 129.9, 136.7, 137.1, 143.4, 179.9.

General esterification procedure

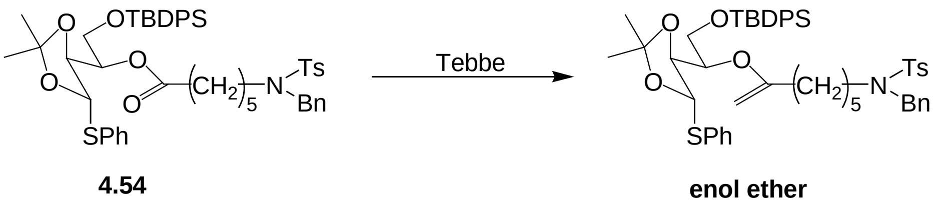
DCC (609.20 mg, 2.95 mmol) was added at 0 °C to a mixture of TIA alcohol **4.16** (1.00 g, 1.97 mmol), acid **4.49** (886.00 mg, 2.36 mmol) and DMAP (72.00 mg, 0.19 mmol) in anhydrous benzene (30 mL). The reaction mixture was warmed to rt and stirred for 3h, or until TLC indicated complete disappearance of the starting material. The mixture was then diluted with ether and filtered. The filtrate was successively washed with 0.1 N aqueous HCl and brine, dried (Na_2SO_4), filtered, and evaporated under *vaccuo*. FCC of the residue gave ester **4.54** (1.40 g, 81% from alcohol) as color less oil.



4.54

R_f = 0.21 (10% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.08-1.13 (m, 2H), 1.27-1.39 (m, 4H), 1.41 (s, 3H), 1.50 (s, 3H), 2.14-2.19 (m, 2H), 2.45 (s, 3H), 3.06 (t, 2H, J = 7.5 Hz), 3.79-3.85 (m, 2H), 4.31 (s, 2H), 4.34 (dd, 1 H, J = 3.9 Hz, J = 6.4 Hz), 5.21-5.24 (m, 1H), 5.25 (d, 1H, J = 6.53 Hz), 7.25-7.76(m, 19H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 21.7, 24.5, 26.3, 26.5, 26.9, 27.4, 28.0, 34.2, 48.2, 52.3, 62.6, 71.9, 79.4, 85.5, 111.9, 127.4, 127.89, 127.92, 127.96, 127.98, 128.5, 128.7, 129.2, 129.9, 129.98, 130.01, 132.5, 133.2, 133.3, 133.9, 135.78, 135.85, 136.8, 137.3, 143.4, 172.9.

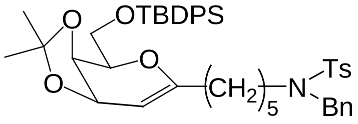
Tebbe reaction (General procedure)



To a mixture of ester **4.54** (2.80 g, 3.18 mmol), and pyridine (0.30 mL) in anhydrous 3:1 Toluene : THF (60 mL), was added, under an argon atmosphere and at –78 °C, the Tebbe reagent (16.0 mL, 0.5M in THF). The reaction mixture was warmed to rt and stirred at this temperature for 1h, or until the TLC indicated complete disappearance of the starting material. The reaction mixture was then slowly poured into a solution of 1N aqueous NaOH at 0 °C, and the resulting suspension extracted with ether. The combined organic phase washed with brine, dried over (Na_2SO_4), filtered and concentrated under *vacuo*. FCC of the residue on basic alumina provided the enol ether (2.20 g, 79%) as a light yellow oil. R_f (on alumina plate) = 0.35 (10% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (s, 9H), 1.19-1.24 (m, 6H), 1.39 (s, 3H), 1.45 (s, 3H), 1.78-1.89 (m, 2H), 2.41 (s, 3H), 3.00 (t, 2H, J = 7.6 Hz), 3.71 (dd, 2H, J = 2.3 Hz, J = 7.9 Hz), 3.81 (d, 2H, J = 6.31 Hz), 4.18 (dt, 1H, J = 2.5 Hz, J = 6.3 Hz), 4.27 (s, 2H), 4.39 (dd, 1H, J = 2.5 Hz, J = 7.1 Hz), 5.31 (d, 1H, J = 7.1 Hz), 7.21-7.29 (10H), 7.34-7.49 (m, 6H), 7.65-7.71 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 21.7, 26.2, 26.5, 26.7, 27.0, 27.1, 27.4, 27.9,35.0, 48.2, 52.1, 61.6, 73.8, 77.0, 77.2, 77.4, 77.5, 79.8, 82.1, 84.7, 111.5, 127.4, 127.7, 127.9, 127.92, 127.96, 128.5, 128.7, 129.1, 129.9, 129.93, 130.0, 132.3, 133.4, 133.6, 134.1, 135.9, 136.9, 137.5, 143.3, 162.0.

General procedure for cyclization reactions

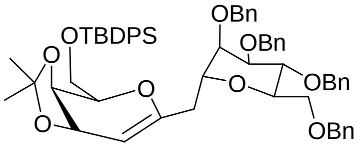
Glycal 4.57



4.57

A mixture of enol ether from the previous step (1.20 g, 1.36 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (5.60 g, 27.30 mmol), and freshly activated, powdered 4A molecular sieves (5.0 g) in anhydrous CH_2Cl_2 (60 mL), was stirred for 15 min, at rt, under atmosphere of argon, then cooled to 0 °C. Methyl triflate (2.50 mL) was then introduced, and the mixture warmed to rt, and stirred for an additional 18h, at which time, triethyl amine (5.00 mL) was added. The mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and evaporated under *vacuo*. FCC of the residue provided the glycal **4.57** (900 mg, 86% yield) as light yellow oil.

R_f (on alumina plate) = 0.30 (10% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.22-1.31(m, 6H), 1.32 (s, 3H), 1.35 (s, 3H), 1.75-1.87 (m,2H), 2.40 (s, 3H), 3.03 (t, 2H, J = 7.9 Hz), 3.89-3.95 (m, 3H), 4.26 (s, 2H), 4.37 (d, 1H, J = 5.8 Hz), 4.47 (d, 1H, J = 2.0 Hz), 7.22-7.28 (m, 7H), 7.34-7.42 (m, 6H), 7.66-7.70 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.5, 21.7 26.2, 26.4, 27.0, 27.9, 28.4, 33.8, 48.2, 52.1, 63.3, 70.0, 71.8, 75.8, 97.9, 110.1, 127.4, 127.88, 127.91, 127.95, 128.5, 128.8, 129.2, 129.8, 129.90, 129.91, 133.70, 133.78, 135.84, 135.87, 136.8, 137.5, 143.3, 156.2.



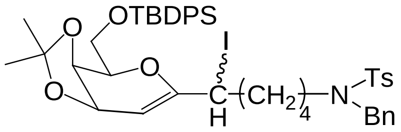
4.56

Tebbe olefination on **4.53** followed by the oxocarbenium ion cyclization delivered the title compound **4.56** as a light yellow oil in 75% yield. R_f = 0.29 (15% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, C_6D_6) δ 1.29 (s, 9H), 1.49 (s, 3H), 1.65 (s, 3H), 2.39 (t, 2H, J = 7.6 Hz), 2.46 (t, 1H, J = 3.7 Hz), 3.93 (dd, 1H, J = 2.9 Hz, J = 7.5 Hz), 3.99 (t, 1H, J = 3.54 Hz), 4.02-4.06 (m, 2H), 4.22-4.34 (m, 3H), 4.42 (d, 1H, J = 6.2 Hz), 4.55-4.69 (m, 9H), 4.77 (d, 1H, J = 1.9 Hz), 4.87 (d, 1H, J = 11.6 Hz), 7.19-7.47 (m, 30H), 7.89-7.93 (m, 4H). ^{13}C NMR (125 MHz, C_6D_6) δ 19.3, 26.8, 27.1, 28.5, 35.2, 63.5, 69.8, 70.6, 71.2, 71.6, 71.7, 72.0, 73.4, 73.8, 74.2, 75.4, 75.8, 76.4, 78.1, 100.4, 110.1, 127.2, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 127.9, 128.0, 128.1, 128.2, 128.2, 128.3, 129.8, 129.9, 133.57, 133.60, 135.7, 135.8, 138.98, 139.0, 139.3, 139.3, 152.4.

Danishefsky's sulfonamidoglycosylation (General procedure)

To a suspension of glycal **4.57** (50 mg, 0.06mmol), benzene sulfonamide (11 mg, 0.07 mmol), and powdered 4-A molecular sieves (approximately equal to the weight of the glycal) in CH_2Cl_2 (0.6 mL) was added solid IDCP (40.3 mg, 0.08 mmol). Once TLC indicated that the reaction was complete (10 to 20 min), the mixture was filtered and diluted with ether. The combined organics layers were washed with saturated $Na_2S_2O_3$, saturated NaCl, dried (Na_2SO_4), and concentrated under *vacuo*. FCC of the residue provided the iodide derivative **4.59** (40 mg, 70 %).

Iodo-glycal 4.59

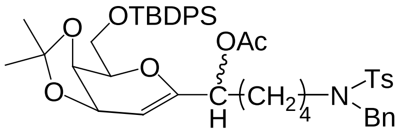


4.59

R_f = 0.55 (20% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (s), 1.10 (s), 1.37 (br s), 1.38 (br s), 1.44 (s), 1.61 (s), 2.45 (s), 2.46 (s), 3.02-3.12 (m), 3.97 (m), 4.21 (m), 4.42 (d, J = 10.1 Hz, minor), 4.39 (d, J = 6.1 Hz, major), 4.61 (dd, J = 3.2 Hz, J = 6.2 Hz, major), 4.67 (dd, J = 3.1 Hz, J = 6.2 Hz, minor), 4.86 (dd, J = 1.0 Hz, J = 3.0 Hz, minor), 4.90 (dd, J = 1.0 Hz, J = 3.2 Hz, major), 7.25-7.76 (m). ^{13}C NMR

(125MHz, $CDCl_3$) δ 19.8, 22.1, 27.0, 27.07, 27.09, 27.2, 27.3, 27.4, 27.6, 28.8, 29.0, 29.7, 31.2, 37.2, 48.37, 48.43, 52.7, 63.4 (major), 63.7 (minor), 70.0 (major), 70.1 (minor), 76.8, 98.79 (minor), 98.87 (major), 110.7 (major), 110.9 (minor), 127.7, 128.26, 128.31, 128.35, 128.38, 128.4, 128.8, 129.2, 130.3, 133.8 (minor), 133.9 (major), 136.2, 137.0, 137.39 (minor), 137.43 (major), 143.8 (major), 143.85 (minor), 155.5 (minor), 155.7 (major).

Compound 4.63

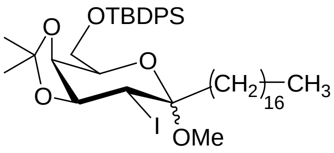


4.63

To a suspension of glycal **4.57** (60 mg, 0.07mmol), acetic acid (40 mg, 0.68 mmol), and powdered 4-A molecular sieves (approximately equal to the weight of the glycal) in CH_2Cl_2 (1.0 mL) was added solid IDCP (48.3 mg, 0.10 mmol). Once TLC indicated that the reaction was complete (10 to 20 min), the mixture was filtered and diluted with ether. The combined organics layers were successively washed with saturated $Na_2S_2O_3$, saturated NaCl, dired (Na_2SO_4), and concentrated under *vacuo*. FCC of the residue provided separately, the iodide derivative **4.59** and the acetate derivative **4.63** (20 mg, 50% of combined yield). **For 4.63**: $R_f = 0.32$ (20% ethyl acetate:petroleum ether). ^1H NMR (500MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.37 (t, 6H, J = 5.2 Hz), 1.32-1.55 (m, 6H), 2.00 (s, major), 2.05 (s, minor), 2.45 (s, 3H), 3.06 (t, 2H, J = 7.4 Hz), 3.91-4.04 (m, 3H), 4.30 (s, 2H), 4.43 (d, 1H, J = 6.1 Hz), 4.71 (dt, 1H, J = 3.1 Hz, J = 6.1 Hz), 4.78 (dd, 1H, J =

13.5 Hz, J = 2.4 Hz), 4.93 (t, J = 6.6 Hz, major), 4.97 (t, J = 6.9 Hz, minor), 7.25-7.76 (m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 21.2, 21.3, 21.7, 22.5, 22.6, 26.9, 27.1, 27.9, 27.92, 28.3, 28.35, 31.1, 31.5, 48.1, 52.1, 63.1, 69.3, 69.4, 71.6, 71.7, 72.7, 73.1, 76.0, 76.1, 99.2, 99.5, 110.3, 127.3, 127.88, 127.91, 128.4, 128.7, 129.90, 129.95, 133.5, 133.52, 135.8, 136.6, 136.65, 137.143.4, 152.6, 153.1, 170.2.

2-Iodo-2-deoxy-β-C-galactoside 4.65



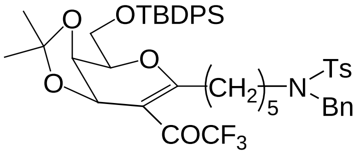
4.65

To a solution of glycal **4.55** (40 mg, 0.06 mmol) and powdered molecular sieves (100 mg) in anhydrous methanol (1 mL) at 0 °C was added in one portion IDCP (83 mg, 0.18 mmol). The resulting mixture was stirred at the same temperature for 10-15 min. The reaction was then quenched by addition of saturated solution of sodium thiosulfate. The organic phase was extracted with ether, washed with brine, and dried (Na_2SO_4). The solvent was removed under *vacuo* and the residue was purified by FCC to give **4.65** as a 3:2 mixture of isomers; R_f = 0.8 (10% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ. 0.9 (t, 3H), 1.09 (s, 9H), 1.21-1.36 (m, 26H), 1.38 (s, minor), 1.39 (s, major), 1.51 (s, minor), 1.42-1.63 (m, 2H), 1.54 (s, major), 1.80-1.92 (m, 1H), 2.10-2.19 (m, minor), 2.45 (t, J = 8.0 Hz, minor), 3.25 (s, minor), 3.31 (s, major), 3.88-4.00 (m), 4.03 (dt, J = 2.3 Hz, J = 6.3 Hz, minor), 4.09-4.11 (m, 1H), 4.18 (d, J = 9.5 Hz, 1H), 4.52 (dd, J = 4.8 Hz, J = 9.5 Hz, major), 4.62 (dd, J = 4.8 Hz, J = 9.3 Hz, minor), 7.27-7.76 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 19.4, 21.3, 22.9, 23.5, 24.1, 26.2, 26.3, 27.0, 27.1, 28.8, 28.85, 29.4, 29.6, 29.62, 29.65, 29.93, 30.6, 31.8, 32.1, 34.8, 35.7, 35.7, 43.5, 48.1, 48.4, 63.3, 63.4, 69.6, 72.2, 73.2, 73.5, 79.9, 81.1, 100.9, 101.5, 109.0, 109.2, 127.85, 128.88, 129.88, 129.9, 133.66, 133.68, 133.79, 133.80, 135.85, 135.9. HRMS(ESI) calcd for $C_{43}H_{69}O_5I_1Si_1$ (M+Na) 843.38512, found 843.38504.

Saltmen Mn(N) reaction (general procedure)

A 25 mL flask was flushed with nitrogen and charged with glycal **4.57** (50 mg, 0.05 mmol), 2,6-di-tert-butyl-4-methylpyridine (18.0 mg, 0.08 mmol), and of CH_2Cl_2 (0.2 mL). Freshly distilled TFAA (28.0 μL, 0.20 mmol) was then added. A solution of (saltmen)Mn(N) (24.0 mg, 0.05 mmol) in CH_2Cl_2 (2.0 mL) was drawn into a syringe and transferred dropwise with the aid of syringe pump to the reaction mixture (overnight addition period). Following the addition of (saltmen)Mn(N), silica gel (100 mg) and celite (100 mg) were added to the resultant dark brown solution along with 5.0 mL of hexane. The dark brown slurry was stirred vigorously for 30 min before being filtered through a short column of silica gel using diethyl ether as eluent. Concentration of the filtrate in *vacuo* afforded a light yellow residue, which was purified by FCC to give two colorless oils (**4.72**: less polar material and **4.73**: more polar material).

2-Trifluoracetyl-2-deoxy-glycal 4.72



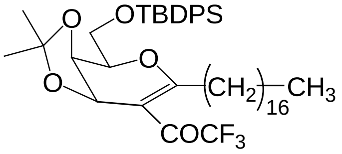
4.72

less polar

For less polar material: R_f = 0.70 (20% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.10-1.19 (m, 2H), 1.29 (s, 3H), 1.32-1.41 (m, 4H), 1.37 (s,3H), 2.25-2.32 (m, 1H), 2.41-2.49 (m, 1H), 2.45 (s, 3H), 3.07 (t, 2H, J = 7.6 Hz), 3.97 (m, 2H), 4.11 (dt, 1H, J = 1.1 Hz, J = 6.9 Hz), 4.31 (s, 2H), 4.54 (dd, 1H, J = 1.3 Hz, J = 7.1 Hz), 7.50-7.33 (m, 7H), 7.40-7.48 (m, 6H), 7.70-7.75 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.7, 19.8, 22.1, 26.98, 27.0, 27.2, 27.3, 28.2, 28.22, 30.7, 34.4, 48.5, 52.5, 63.0, 69.3, 71.7, 76.7, 108.3, 111.3, 117.2 (q, J = 290.87 Hz), 116.8, 127.1, 128.27, 128.34, 128.36, 128.5, 128.8, 129.0, 130.3, 130.47, 130.49, 133.50, 133.55, 136.1, 136.12, 137.1, 137.6, 143.7, 175.4, 181.1 (q, J = 34.12 Hz). HRMS(ESI) calcd for $C_{46}H_{54}N_1O_7S_1Si_1F_3$ (M+NH_4) 867.36806, found 867.36861.

For the more polar material: **4.73**: R_f = 0.43 (20% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.15-1.20 (m, 2H), 1.26-1.35 (m, 2H), 1.33 (s, 3H), 1.48-52 (m, 2H), 1.54 (s, 3H), 2.45-2.47 (m, 4H), 2.50-2.62 (M, 2h), 3.05-3.11 (m, 4H), 3.80 (t, 1H, J = 6.2 Hz), 3.87-3.93 (m, 2H), 4.31 (s, 2H), 4.53 (dd, 1H, J = 1.3 Hz, J = 8.2 Hz), 4.66 (dd, 1H, J = 2.5 Hz, J = 8.2 Hz), 6.13 (br s, 1H), 7.30-7.46 (m, 13H), 7.67-7.75 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8, 22.1, 22.9, 24.8, 26.1, 26.3, 27.3, 28.4, 29.9, 44.0, 46.3, 48.7, 53.0, 62.8, 71.6, 72.6, 73.4, 94.7 (q, J = 32.4 Hz), 111.3, 123.24 (q, J = 294.12 Hz), 127.7, 128.18, 128.26, 128.35, 128.9, 129.1, 130.28, 130.30, 130.32, 133.8, 136, 0, 136, 2, 136.2, 139.0, 207.0.

2-Trifluoracetyl-2-deoxy-glycal 4.70

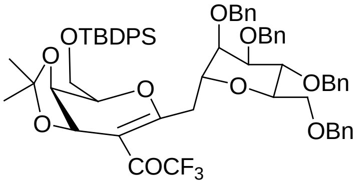


4.69

less polar

For the less polar material **4.69**: R_f = 0.6 (10% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, J = 6.8 Hz), 1.10 (s, 9H), 1.06-1.40 (m, 28H), 1.34 (s, 3H), 1.38 (s, 3H), 1.55-1.62 (m, 2H), 2.40-2.50 (m, 1H), 2.58-2.63 (m, 1H), 3.99-4.08 (m, 2H), 4.13 (dt, 1H, J = 1.3 Hz, J = 6.5 Hz), 4.54 (dd, 1H, J = 1.4 Hz, J = 6.55 Hz), 5.25 (d, 1H, J = 6.0 Hz), 7.28-7.75 (m, 10 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 19.8, 22.7, 26.7, 27.0, 27.6, 29.3, 29.35, 29.4, 29.6, 29.65, 29.7, 31.9, 34.0, 62.7, 68.83, 68.85, 68.87, 70.6, 71.4, 76.3, 107.8, 110.8, 127.7, 127.75, 129.7, 133.1, 135.6, 175.4. For the more polar material **4.70**: R_f = 0.5 (10% ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 8.0 Hz), 1.08 (s, 9H), 1.25-1.33 (m, 28H), 1.34 (s, 3H), 1.55(s, 3H), 2.61-2.75 (m, 2H), 3.12 (d, 1H, J = 2.6 Hz), 3.81 (t, 1H, J = 7.0 Hz), 3.87-3.96 (m, 2H), 4.53 (dd, 1H, J = 1.4 Hz, J = 8.3 Hz), 4.68 (dd, 1H, J = 2.6 Hz, J = 8.2 Hz), 6.23 (s, 1H), 7.35-7.75 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.5, 22.9, 23.3, 24.5, 25.9, 27.0, 29.1, 29.6, 29.7, 29.88, 29.89, 29.91, 29.93, 32.2, 44.0, 47.0, 62.6, 71,4, 72.3, 73.1, 111.0, 127.8, 127.9, 127.98, 129.95. 129.97, 133.56, 133.58, 135.8, 135.84, 135.9, 207.2. (M+Na) 781.4466.

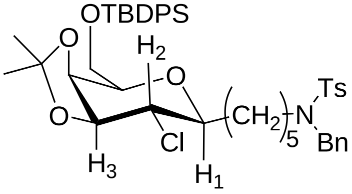
2-Trifluoracetyl-2-deoxy-glycal 4.71



4.71

Subjection of glycal **4.56** to the Saltmen Mn (N) reaction provided the title compound **4.71** in 60% yield. $R_f = 0.55$ (15% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.34 (s, 3H), 1.40 (s, 3H), 2.73 (dd, 1H, J = 8.83 Hz, 13.39 Hz), 3.08 (dd, 1H, J = 5.4 Hz, J = 13.4 Hz), 3.64-3.67 (m, 3H), 3.76-3.81 (m, 2H), 3.92-4.02 (m, 3H), 4.08-4.11 (m, 1H), 4.39-4.44 (m, 2H), 4.49-4.64 (m, 7H), 4.77 (d, 1H, J = 11.0 Hz), 5.19 (d, 1H, J = 5.8 Hz), 7.17-7.20 (m, 2H), 7.36-7.44 (m, 16H), 7.67-7.71 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 26.6, 27.0, 27.8, 34.4, 62.0, 68.6, 69.3, 71.1, 71.7, 72.0, 73.5, 74.0, 74.5, 74.8, 75.6, 76.1, 78.2, 109.5, 111.0, 116.8 (q, J = 290.62 Hz), 127.6, 127.8, 127.82, 127.9, 128.0, 128.1, 128.2, 128.3, 128.48, 128.50, 128.53, 128.55, 130.12, 130.15, 133.0, 133.2, 135.7, 135.8, 138.3, 138.4, 138.5, 138.55, 172.8, 181.2 (q, J = 34.25 Hz).

2-Chloro-2-deoxy-β-C-glycoside 4.76

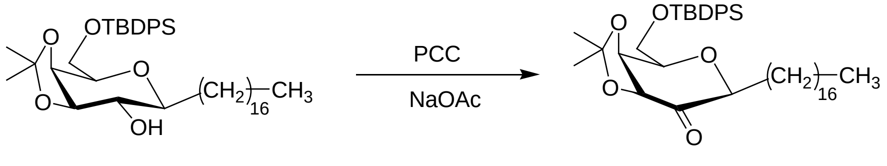


4.76

A 15 mL flask was charged with benzyl carbamate (12 mg, 0.08 mmol) and *tert*-BuOH (0.3 mL). To this stirred solution was added a freshly prepared aqueous solution of NaOH (1.5 mL), followed by tert-butyl hypochlorite (9 mg). After 5 min a solution of $(DHQD)_2PHAL$ (4 mg, 0.004 mmol) in *tert*-BuOH (0.2 mL)was added. The glycal **4.57** (35 mg, 0.04 mmol, dissolved in 1 mL of ether) was introduced at this point, followed by OsO_4 (60 μL, 10 mol %). The resulting mixture was stirred at 25 ^{o}C until TLC indicated total consumption of the starting material. The reaction was then quenched by the addition of a saturated aq sodium sulfite solution (1 mL) and stirred for 15 min. The two phases were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water, brine, dried (Na_2SO_4), and concentrated *vacuo*. FCC of the residue provided a hemi-acetal (37 mg, 99%) as a colorless oil.

To a sample of the hemi-acetal from the previous step (20 mg, 0.02 mmol) in dry dichloromethane (0.6 mL) were added at –20 ^{o}C, $BF_3.OEt_2$ (7 μL, 0.05 mmol) and Et_3SiH (14 μL, 0.09 mmol). The reaction mixture was stirred at this temperature until TLC revealved complete disappearance of the starting material. The reaction was then quenched by addition of saturated aq $NaHCO_3$ solution. The organic phase was extracted with ether. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and evaporated in *vacuo*. FCC of the residue afforded the chloride derivative **4.76** (10 mg, 57%) as a colorless oil. R_f = 0.43 (20% ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.09-1.14 (m, 1H), 1.27-1.38 (m, 6H), 1.59 (s, 3H), 1.73 (m, 1H), 2.45 (s, 3H), 3.07 (t, 2H, J = 7.6 Hz), 3.14 (dt, 1H, J = 2.2 Hz, J = 10.4 Hz), 3.51 (dd, 1H, J = 8.1 Hz, J = 10.4 Hz), 3.81-3.90 (m, 2H), 4.17 (dd, 1H, J = 5.2 Hz, J = 8.1 Hz), 4.29-4.30 (m, 2H), 7.26-7.33 (m, 7H), 7.38-7.47 (m, 6H), 7.70-7.74 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 21.7, 24.6, 26.3, 26.6, 26.9, 27.9, 28.6, 29.9, 31.9, 48.2, 52.0, 62.8, 63.1, 74.0, 76.6, 78.8, 80.5, 110.2, 127.3, 127.8, 127.9, 128.4, 128.7, 129.9, 129.94, 133.4, 133.5, 135.8, 135.83, 136.7, 137.2, 143.3. HRMS(ESI) calcd for $C_{44}H_{56}N_1O_6S_1Cl_1Si_1$ (M+NH4) 807.36244, found 807.36250.

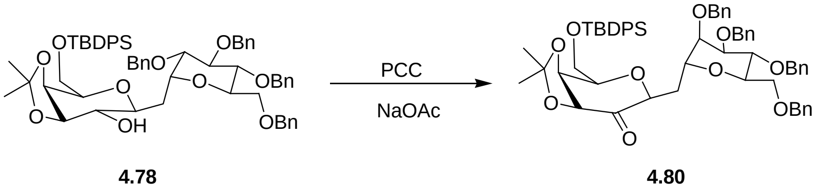
PCC oxidation (General procedure)



4.77 **4.79**

To a solution of PCC (188.50 mg, 0.87 mmol), florisil (720 mg), sodium acetate (71.70 mg, 0.87 mmol), freshly activated, powdered 4A molecular sieves (720 mg) and Celite (720 mg) in dry dichloromethane (5 mL), was added dropwise a solution of alcohol **4.77** (240 mg, 0.35 mmol) in dry dichloromethane (5 mL). The reaction mixture was stirred at rt until TLC indicated total consumption of the starting material. The mixture was then diluted with ether and filtered through a column of florisil. The filtrate was evaporated in *vacuo* and the residue purified by FCC to afford the ketone derivative **5.79** (185 mg, 77%) as a colorless oil. R_f = 0.49 (10% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, J = 7.50 Hz), 1.09 (s, 9H), 1.28 (br s, 30H), 1.39 (s, 3H), 1.44 (s, 3H), 1.65-1.85 (m, 2H), 3.82 (dd, 1H, J = 4.31 Hz, J = 8.12 Hz), 3.88 (dt, 1H, J = 1.56 Hz, J = 5.88 Hz), 3.95 (d, 2H, J = 6.55 Hz), 4.37 (d, 1H, J = 6.27 Hz), 4.68 (dd, 1H, J = 1.57 Hz, J = 6.21 Hz), 7.27-7.76 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$, $CDCl_3$) δ 14.3, 19.4, 22.9, 25.5, 26.1, 26.3, 27.0, 27.04, 29.58, 29.7, 29.8, 29.9, 29.92, 30.4, 32.1, 33.2, 62.4, 62.9, 74.5, 75.4, 75.9, 110.0, 127.8, 129.7, 134.0, 135.9, 135.95, 201.2.

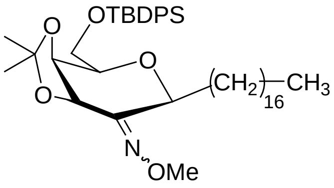
Ketone 4.80



PCC oxidation of **4.78** (150 mg, 0.15 mmol) afforded **4.80** (110 mg, 73%) as a colorless oil; R_f = 0.43 (30% ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.41 (s, 3H), 1.43 (s, 3H), 1.87-1.94 (m, 1H), 2.02-2.11 (m, 1H), 3.62 (t, 1H, J = 3.52 Hz), 3.68-3.75 (m, 3H), 3.77-3.80 (m, 1H), 3.84-3.91 (m, 3H), 3.95-4.00 (m, 2H), 4.21-4.25 (m, 1H), 4.30 (d, 1H, J = 5.7 Hz), 4.48-4.58 (m, 6H), 4.63 (m, 2H), 4.75-4.77 (m, 1H), 7.21-7.22 (m, 2H), 7.28-7.33 (m, 10H), 7.36-7.45 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.5, 19.4, 26.2, 27.0, 27.3, 29.9, 48.8, 69.4, 69.8, 71.5, 72.2, 73.5, 73.7, 74.7, 75.2, 76.1, 76.9, 77.6, 77.8, 110.9, 127.6, 127.7, 127.9, 127.9, 127.9, 128.0, 128.1, 128.2, 128.5, 128.53, 128.56, 204.2. . HRMS(ESI) calcd for $C_{60}H_{68}O_{10}Si_1$ (M+NH_4) 994.49200, found 994.49153.

Formation of oxime *O*-methyl ether (General procedure)

Oxime 4.81

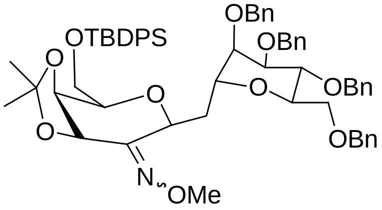


4.81

To a solution of ketone **4.79** (90 mg, 0.13 mmol) in a 1:1 mixture THF/MeOH (2.80 mL), was added a solution of *O*-methyl hydroxylamine hydrochloride (110.0 mg, 1.31 mmol) and AcONa (194 mg, 1.44 mmol) in water (1.20 mL), adjusted to pH = 4.5 with few drops of glycial acetic acid. The reaction mixture was stirred at rt for 4h or until TLC indicated the completion of the reaction. The reaction mixture was then diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and water, dried (Na_2SO_4) and filtered. The solvent was removed under *vacuo* to give a 3:1 mixture of oxime *O*-methyl ether **4.81** (90 mg, 96%) as a colorless oil. R_f = 0.77 (10% ethyl acetate: petroleum ether). R_f = 0.8 (10% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, J = 6.8 Hz), 1.07 (s, 9H, major), 1.08 (s, 9H, minor), 1.30 (s, 28H), 1.38 (s, 3H, major), 1.39 (s, 3H, minor), 1.44 (s, 3H, minor), 1.46 (major), 1.51-1.56 (brs, 2H), 1.75-1.86 (m, 2H), 3.38 (dt, 1H, J = 1.6 Hz, J = 6.6 Hz, minor), 3.47 (dt, 1H, J = 1.5 Hz, J = 6.4 Hz, major), 3.81-3.95 (m), 3.91 (s, 3H, minor), 3.92 (s, 3H, major), 4.23 (dd, 1H, J = 4.2 Hz, J = 7.9 Hz), 4.37 (d, 1H, J = 6.2 Hz), 4.42 (dd, 1H, J = 1.50 Hz, J = 7.93 Hz, major), 4.49

(dd, 1H, J = 1.7 Hz, J = 7.8 Hz, minor), 4.64 (dd, 1H, J = 3.5 Hz, J = 8.1 Hz, minor), 4.67 (dd, 1H, J = 1.6 Hz, J = 6.2 Hz), 5.51 (d, 1H, J = 7.9 Hz, major), 7.27-7.76 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 22.9, 25.2, 25.5, 26.1, 26.3, 26.36, 27.01, 27.03, 29.6, 29.64, 29.7, 29.75, 29.8, 29.88, 29.89, 29.9, 32.2, 32.4, 36.9, 62.4, 62.45, 62.96, 63.06, 65.8, 73.9, 74.5, 75.4, 75.9, 76.5, 78.0, 111.0, 111.2, 127.8, 127.81, 129.7, 129.77, 129.8, 133.86, 133.88, 133.9, 134.0, 135.9, 135.96, 154.8, 156.2. HRMS(ESI) calcd for $C_{43}H_{69}N_1O_5Si_1$ (M+NH$_4$) 725.5283.

Oxime 4.82



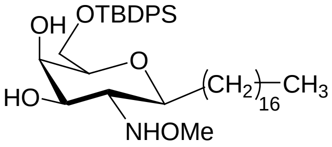
4.82

4.82 was obtained from oximation of ketone **4.80**. The title compound was isolated as a color less oil in 97%. R_f = 0.7 (20% ethyl acetate:petroleum ether). ^{1}H NMR (500MHz, C_6D_6, ppm) δ 1.18 (s, 9H), 1.40 (s, 3H), 1.42 (s, 3H), 2.34-2.40 (m, 1H), 2.45-2.51 (m, 1H), 3.29 (dt, 1H, J = 1.8 Hz, J = 6.4 Hz), 3.40 (dt, 1H, J = 1.7 Hz, J = 6.5 Hz), 3.64 (s, 3H), 3.70 (s, 3H), 3.80-3.83 (m, 2H), 3.87-3.92 (m, 6H), 3.94-3.98 (m, 2H), 3.99-4.04 (m, 4H), 4.07-4.10 (m, 1H), 4.19-4.26 (m, 3H), 4.30 (t, 1H, J = 7.8 Hz), 4.43-4.64 (m, 14H), 4.68-4.72 (m, 4H), 4.81 (d, 2H, J = 8.0 Hz), 4.92 (dt, 1H, J = 2.9 Hz, J = 8.5 Hz), 5.60 (d, 1H, 7.81 Hz), 7.18-7.30 (m, 12H), 7.32-7.38 (m, 8H), 7.44-7.51 (m, 6H), 7.92-7.97 (m, 4H) . ^{13}C NMR (125 MHz, C_6D_6) δ 14.6, 19.8, 19.86, 20.9, 25.4, 25.5, 26.7, 26.74, 35.1, 37.5, 60.4, 62.4, 62.6, 63.3, 63.5, 66.6, 70.1, 70.4, 70.44, 71.5, 72.2, 72.5, 72.6, 73.2, 73.9, 73.98,74.1, 74.6, 74.8, 74.9, 75.0, 75.4, 76.1, 76.11, 76.14, 76.5, 76.9, 77.6, 77.62, 78.8, 79.9, 111.3, 111.4, 127.7, 127.8, 127.83, 127.84, 127.87, 127.99, 128.0, 128.1, 128.8, 128.82, 128.9, 128.92, 128.94, 130.36, 130.37, 130.4, 134.2, 134.22, 134.27, 134.3, 136.4, 136.5, 139.7, 139.8, 139.83, 139.85, 139.9, 140.0, 140.02, 154.7, 155.9. HRMS(ESI) calcd for $C_{61}H_{71}N_1O_{10}Si_1$ (M+NH_4) 1023.5177.

Hydrostannation of oxime methyl ether

To a mixture of oxime *O*-methyl ether **4.81** (30 mg, 0.04 mmol), and Bu_3SnH (60.0 μL) in CH_2Cl_2 (1.0 mL), was added at 0 °C, $BF_3.OEt_2$ (15 μL). The mixture was then warmed to rt and stirred for 12h. After TLC indicated the completion of the reaction, the resulting reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phase was dried (Na_2SO_4) and concentrated in *vacuo*. FCC of the residue afforded intermediate **4.83** (16.0 mg, 56% over the two steps) as a colorless oil.

Galactosamine-β-C-glycoside 4.83



4.83

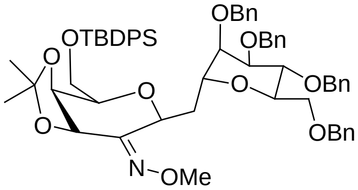
R_f = 0.21 (30% ethyl acetate:petroleum ether). ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H J = 6.00 Hz), 1.07 (s, 9H), 1.27 (br s, 27H), 1.51-1.58 (m, 4H), 1.87-1.90 (m, 1H), 2.75 (t, J = 9.45 Hz, 1H), 2.81 (d, 1H, J = 3.3 Hz), 2.84-2.92 (br s, 1H), 3.41-3.44 (m, 1H), 3.46

(t, 1H, J = 5.3 Hz), 3.57 (s, 3H), 3.82 (d, 1H, J = 7.8 Hz), 3.88-3.95 (m, 2H), 4.16 (br s, 1H), 7.27-7.76 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 19.4, 22.9, 25.6, 29.6, 29.90, 29.94, 29.98, 32.2, 32.4, 62.7, 62.9, 64.3, 69.5, 70.06, 70.08, 71.4, 70.8, 127.96,128.0, 130.0, 133.3, 133.5, 135.8, 135.9. HRMS(ESI) calcd for $C_{40}H_{67}N_1O_5Si_1$ (M+H) 670.48613, found 670.48646.

Hydrostannation of oxime methyl ether (disaccharide)

To a mixture of oxime *O*-methyl ether **4.82** (240 mg, 0.23 mmol), and Bu_3SnH (0.45 mL, 1.78 mmol) in CH_2Cl_2 (5 mL), was added at 0 ^{o}C, $BF_3.OEt_2$ (0.14 mL, 1.19 mmol). The mixture was stirred at the rt for overnight. At which time TLC revealed about 70% consumption of the starting material. The reaction mixture was then diluted with saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated in *vaccuo*. FCC of the residue afforded a separable mixture of **4.82-Z** (30 mg, 12%), **4.84** (120 mg, 50%), and **4.85** (60 mg, 24%) as colorless oil.

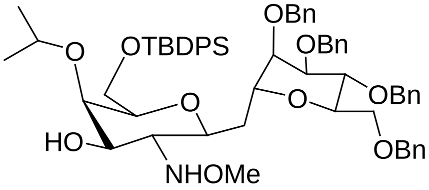
Oxime 4.82-Z



4.82-Z

Recovered starting material from the above reaction. R_f = 0.7 (20% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, C_6D_6) δ 1.26 (s, 3H), 1.29 (s, 9H), 1.52 (s, 3H), 2.46-2.51 (m, 1H), 2.57-2.62 (m, 1H), 3.40 (dt, 1H, J = 1.8 Hz, J = 6.4 Hz), 3.75 (s, 3H), 3.91-3.94 (m, 1H), 3.98-4.01 (m, 1H), 4.03-4.09 (m, 3H), 4.12 (t, 2H, J = 6.1 Hz), 4.37 (dd, 1H, J = 1.8 Hz, J = 7.8 Hz), 4.42 (t, 1H, J = 7.8 Hz), 4.57-4.59 (m, 1H), 4.65-4.76 (m, 6H), 4.82-4.85 (m, 1H), 4.92-4.94 (m, 2H), 5.04 (dd, 1H, J = 2.9 Hz, J = 8.5 Hz), 7.18-7.30 (m, 12H), 7.32-7.38 (m, 8H), 7.44-7.51 (m, 6H), 7.92-7.97 (m, 4H). ^{13}C NMR (125 MHz, C_6D_6, ppm) δ 19.8, 25.5, 26.7, 27.4, 30.5, 35.1, 62.6, 63.3, 70.4, 71.5, 72.2, 72.5, 73.2, 74.0, 74.6, 74.8, 75.0, 76.1, 76.14, 76.5, 77.6, 79.9, 111.4, 127.8, 127.8, 127.85, 128.0, 128.1, 128.3, 128.5, 128.7, 128.78, 128.79, 128.8, 128.9, 130.4, 134.2, 134.2, 136.4, 136.5, 139.8, 155.9.

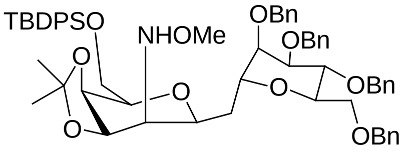
Compound 4.84



4.84

R$_f$ = 0.2 (20% ethyl acetate:petroleum ether). ^{1}HNMR (500 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.11 (d, 3H, J = 6.2 Hz), 1.21 (d, 3H, J = 6.0 Hz), 1.92-1.97 (m, 2H), 2.54 (d, 1H, J = 7.4 Hz), 2.73 (t, 1H, J = 9.9 Hz), 3.38-3.45 (m, 2H), 3.42 (s, 3H), 3.66 (t, 1H, J = 2.9 Hz), 3.68-3.81 (m, 7H), 3.91-3.98 (m, 2H), 4.00 (d, 1H, J = 3.2 Hz), 4.33-4.39 (m, 1H), 4.49-4.63 (m, 7H), 4.82 (d, 1H, J = 11.0 Hz), 6.21 (br s, 1H), 7.19-7.46 (m, 26H), 7.64-7.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 17.7, 19.4, 22.9, 23.0, 27.1, 28.0, 31.5, 62.0, 62.5, 62.6, 69.6, 69.8, 70.7, 71.5, 71.9, 73.1, 73.3, 73.5, 73.6, 74.7, 74.8, 75.4, 75.8, 78.4, 78.8, 127.6, 127.7, 127.8, 127.9, 127.97, 127.99, 128.1, 128.2, 128.4, 128.44, 128.51, 128.52, 130.0, 133.4, 133.45, 135.69, 135.71, 138.6, 138.65.

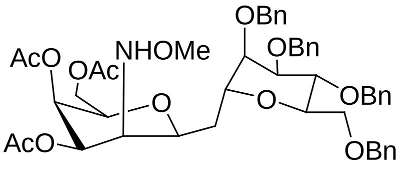
Compound 4.85



4.85

R_f = 0.65 (20% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.35 (s, 3H), 1.60 (s, 3H), 1.90-2.02 (m, 2H), 3.26 (dt, 1H, J = 2.2 Hz, J = 7.9 Hz), 3.40 (dt, 1H, J = 2.2 Hz, J = 8.4 Hz), 3.43 (s, 3H), 3.43-3.49 (m, 2H), 3.54 (t, 1H, J = 3.1 Hz), 3.66-3.71 (m, 1H), 3.74-3.79 (m, 4H), 3.87-3.92 (m, 2H), 4.13-4.14 (m, 1H), 4.16-4.20 (m, 2H), 4.29-4.34 (m, 1H), 4.51-4.61 (m, 5H), 4.67-4.70 (m, 1H), 4.82-4.84 (m, 1H), 5.95 (d, 1H, J = 7.9 Hz), 7.23-7.44 (m, 26H), 7.68-7.73 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 25.6, 25.9, 27.0, 27.1, 31.1, 57.4, 61.6, 62.8, 69.7, 70.3, 71.47, 71.49, 72.3, 73.1, 73.5, 73.7, 74.5, 75.5, 75.9, 76.4, 78.6, 109.3, 127.6, 127.7, 127.76, 127.8, 127.86, 127.9, 128.0, 128.07, 128.09, 128.46, 128.50, 128.56, 129.8, 129.8, 133.6, 133.8, 135.7, 135.76, 135.9, 138.5, 138.6, 138.64, 138.7. HRMS(ESI) calcd for $C_{61}H_{73}N_1O_{10}Si_1$ (M+NH_4) 1008.5076, found 1008.5073.

Compound 4.86



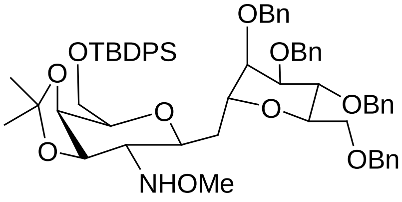
4.86

R_f = 0.1 (100% ethyl acetate). ^{1}H NMR (500 MHz, C_6D_6) δ 1.76 (s, 3H), 1.77 (s, 3H), 1.92 (s, 3H), 2.43 (t, 2H, J = 7.4 Hz), 3.48-3.50 (m, 1H), 3.49 (s, 3H), 3.78-3.81 (m, 1H), 3.83 (dd, 1H, J = 2.9 Hz, J = 5.0 Hz), 3.92-4.03 (m, 5H), 4.15 (t, 1H, J = 6.4 Hz), 4.22 (m, 3H), 4.58-4.76 (m, 8H), 5.04 (t, 1H, J = 3.6 Hz), 5.42 (d, 1H, J = 2.9 Hz), 6.59 (d, 1H, J = 8.6 Hz). ^{13}C NMR (125 MHz, C_6D_6) δ 20.5, 20.6, 21.0, 30.5, 33.0, 58.9, 61.9, 62.5, 67.9, 69.6, 70.2, 71.2, 72.3, 73.0, 73.9, 73.95, 74.6, 75.8, 76.3, 76.8, 78.0, 78.3, 127.8, 128.8, 128.88, 128.92, 128.95, 128.96, 128.99, 139.5, 139.60, 139.62, 139.64, 169.9, 169.98, 170.1.

Hydrostannation of oxime methyl ether (optimized condition)

To a mixture of oxime *O*-methyl ether **4.82** (33 mg, 0.03 mmol), and freshly distilled Bu_3SnH (35 μL, 0.13 mmol) in CH_2Cl_2 (0.3 mL), was added at 0 °C, $BF_3.OEt_2$ (8.2 μL). The mixture was stirred at the same temperature for 2h. At which time TLC revealed 50% consumption of the starting material. The reaction mixture was then diluted with saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phase was dried (Na_2SO_4) and concentrated in *vacuo*. FCC of the residue afforded a separable mixture of **4.82-Z** (7 mg, 27%) as a colorless oil and **4.87** (16 mg, 61%) as a colorless oil.

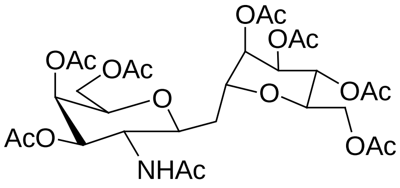
Galactosamine-β-C-dissacharide 4.87



4.87

R_f = 0.43 (20% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.40 (s, 3H), 1.50 (s, 3H), 1.82-1.90 (m, 2H), 2.72 (t, 1H, J = 8.9 Hz), 3.35-3.38 (m, 1H), 3.45 (s, 3H), 3.63 (t, 1H, J = 3.0 Hz), 3.70-3.84 (m, 7H), 3.91-3.96 (m, 2H), 4.32-4.35 (m, 1H), 4.38-4.39 (m, 1H), 4.49-4.64 (m, 8H), 4.77 (d, 1H, J = 11.21 Hz), 6.00 (br s, 1H), 7.20-7.44 (m, 26H), 7.69-7.75 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.5, 26.6, 27.0, 27.1, 28.7, 29.8, 31.9, 62.6, 62.88, 62.96, 64.1, 69.7, 70.6, 71.6, 72.3, 73.2, 73.23, 73.5, 73.8, 74.2, 74.5, 75.4, 76.0, 76.4, 78.5, 109.4, 127.6, 127.67, 127.8, 127.9, 127.93, 127.97, 128.0, 128.1, 128.2, 128.44, 128.47, 128.55, 128.56, 129.8, 129.9, 133.6, 133.8, 135.8, 135.9, 138.71, 138.77. HRMS(ESI) calcd for $C_{61}H_{73}N_1O_{10}Si_1$ (M+NH_4) 1008.5076, found 1008.5076

NAc-β-C-disaccharide 4.89



4.89

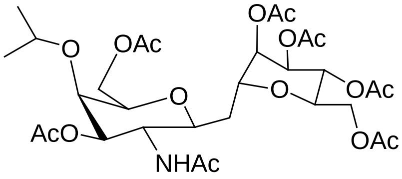
To a solution of **4.87** (70 mg, 0.07 mmol) in methanol (1 mL) was added dropwise a diluted solution of HCl in methanol. Once the reaction mixture reached pH 2, addition of HCl was stopped and the resulting mixture was stirred at room temperature for 3h. The reaction mixture is then neutralized (to pH 6-7) by dropwise addition of concentrated sodium methoxide. The resulting solution was concentrated under *vaccuo* and the residue was used in the next step without any purification.

To a mixture of liquid NH_3 (3 mL) and THF (0.6 mL) at –78 °C was added small pieces of sodium metal until the blue color persisted. To the resulting dark blue solution, was added a solution of the product (from the previous steps) in THF (1 mL). Additional pieces of sodium was added to the reaction mixture to maintain the blue color of the solution. The resulting mixture was then stirred for 1 h at –78 °C. At this point, solid NH_4Cl was added and the mixture was slowly warmed to rt. The solvent was removed under *vacuo* and the residue was used in the next step without further purification.

A mixture of the crude material from the previous step (15 mg, 0.02 mmol), DMAP (3 mg, 0.02 mmol) and acetic anhydride (0.5 mL), in ethyl acetate was stirred at rt for 1 h. The solvent was then concentrated under *vacuo*. FCC of the residue gave the acetylated product **4.89** (10 mg, 57% from **4.87**) as a colorless oil.

$R_f = 0.15$ (100% ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.03 (s, 3H), 2.04 (s, 3H), 2.05 (s, 3H), 2.06 (s, 3H), 2.10 (s, 3H), 2.149 (s, 3H), 2.15 (s, 3H), 2.18 (s, 3H), 2.08-2.15 (m, 2H), 3.39-3.43 (m, 1H), 3.84 (dt, 1H, J = 0.8 Hz, J = 7.2 Hz), 3.95 (m, 1H), 4.00-4.03 (m, 2H), 4.04-4.13 (m, 2H), 4.15-4.18 (m, 1H), 4.27 (q, 1H, J = 10.1 Hz), 4.55 (dd, 1H, J = 6.3 Hz, J = 12.2 Hz), 4.99 (dd, 1H, J = 3.3 Hz, J = 10.9 Hz), 5.19-5.21 (m, 2H), 5.38 (d, 1H, J = 2.5 Hz), 5.75 (d, 1H, J = 9.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.90, 20.91, 20.94, 20.96, 21.0, 21.11, 21.14, 23.5, 32.8, 50.3, 60.6, 61.9, 62.2, 67.0, 67.2, 68.8, 69.5, 71.8, 71.85, 71.9, 74.5, 76.6, 169.8, 170.1, 170.4, 170.5, 170.7, 170.9, 171.1, 171.2. . HRMS(ESI) calcd for $C_{29}H_{41}N_1O_{17}$ (M+Na) 698.22667, found 698.22715.

Compound 4.90



4.90

4.90 was obtained from hydrostannation of oxime **4.82** followed by deprotection and acetylation sequence. The title compound was isolated as a color less oil in 50% yield. R_f = 0.2 (100% ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ1.14 (d, 3H, J = 6.11Hz), 1.26 (d, 3H, J = 6.14Hz), 2.03 (s, 3H), 2.04 (s, 3H), 2.08 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 2.14 (s, 3H), 2.15 (s, 3H), 4.35 (q, 1H, J = 10.1 Hz), 4.45 (dd, 1H, J = 6.0 Hz, J = 12.2 Hz), 4.89 (dd, 1H, J = 2.8 Hz, J = 10.8 Hz), 5.16-5.25 (m, 3H), 5.65 (d, 1H, J = 9.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 20.96, 20.99, 21.0, 21.12, 21.13, 22.3, 23.1, 23.5, 32.0, 51.0, 62.5, 63.1, 66.9, 69.1, 69.7, 71.4, 72.7, 74.3, 75.0, 76.1, 129.0, 169.8, 170.2, 170.5, 17.7, 170.8, 171.0, 171.5. HRMS(ESI) calcd for $C_{30}H_{45}N_1O_{16}$ (M+NH_4) 693.3076, found 693.3076.

CHAPTER V

Attempted synthesis of C-glycoside analogue of GalNAcβ→ManNAc

5.1 Background

Interaction between sialylated or sulfated oligosaccharides and the NKR-P1A protein on the surface of rat natural killer cells is believed to activate NK cells for the destruction of malignantly transformed or virally infected cells, and production of various cytokines (**Figure 5.1**).[83] Mimetics of these carbohydrate ligands have potential as immunostimulators. Consequently, in view of development of new therapeutic agents, there is interest in stable, low molecular weight compounds with potent binding to NKR-P1A (**Figure 5.1**).

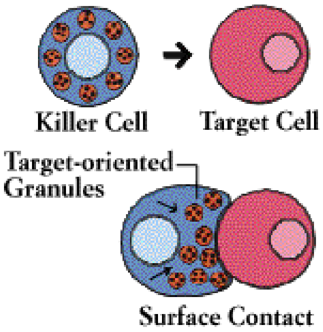
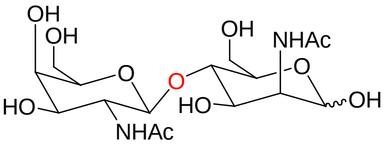
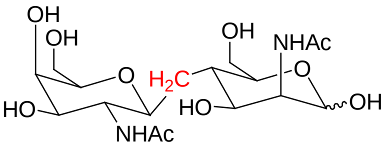


Figure 5.1. Natural killer cell destroys infected cell.[84]



GalNAcβ-ManNAc

5.1 O-disaccharide



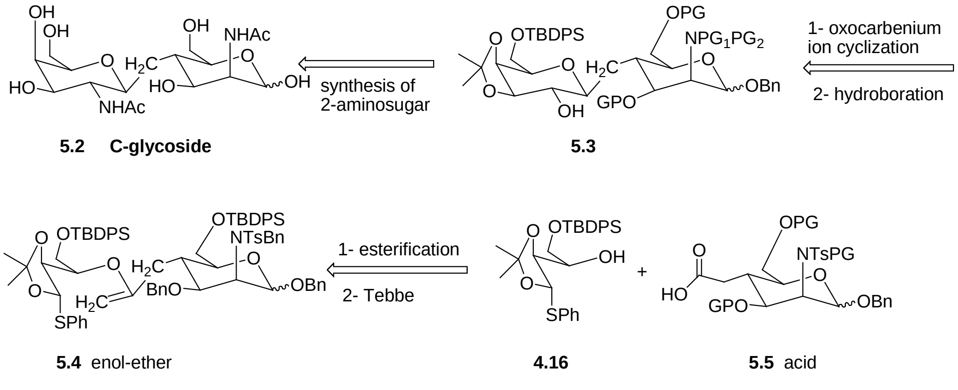
5.2 C-disaccharide

Figure 5.2. GalNAc-β-ManNAc and its C-glycoside analogue

Along these lines, the disaccharide GalNAcβ1→ManNAc **5.1** is a highly active small molecule ligand (IC_{50} ca 10^{-10} M). We were interested in the C-disaccharide **5.2** for two reasons. First the glycosylation stability of the C-glycoside makes it attractive as a potential drug. Second the constitutional and conformational difference to the O-glycoside are interesting from a structure activity standpoint.

5.2 Retrosynthesis

We envisaged that the earlier developed protocol for conversion of 2-hydroxy-C-glycosides to the 2-aminoderivatives could be applied to alcohol **5.3**. The latter would arise from enol ether **5.4** via an oxocarbenium ion cyclization followed by hydroboration of the resulting glycal. Esterification of TIA **4.16** and the acid **5.5** followed by the Tebbe olefination reaction of the resulting ester should deliver the desired enol ether **5.4** **(Scheme 5.1)**.



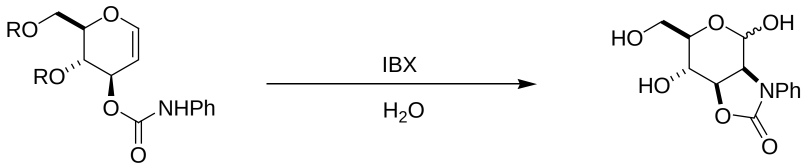
Scheme 5.1.

The overall plan can be divided in three major stages: (i) an efficient synthesis of acid **5.5**; (ii) synthesis of 2-hydroxy-C-glycoside **5.3** and (iii) conversion of the 2-hydroxy-C-glycoside to the amine derivative. It is noteworthy that contrary to the previous C-glycoside synthesis conducted in our laboratory, the synthesis of C-glycoside **5.2** is characterized by an oxocarbenion ion cyclization on a substrate containing a nitrogen substituent. We have demonstrated in the previous chapter that the oxocarbenium ion cyclization is compatible with the presence of a sulfonamide in the cyclization precursor (see **Scheme 4.13**, glycal **4.57**). Thus, the nitrogen in acid **5.5** will be protected as a sulfonamide.

5.3 Synthesis of acid 5.5.

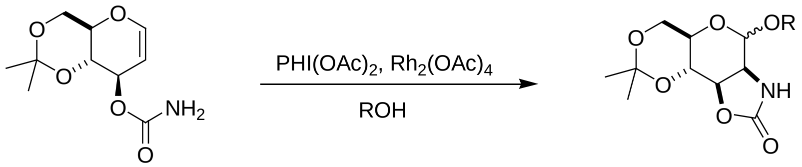
The synthesis of acid **5.5** entails an intramolecular delivery of nitrogen at the C2 position of a glycal followed by installation of a C-branch at the C4 position. [85] Intramolecular glycol functionalization offers unique opportunities for the synthesis of mannosamine derivatives. Nicolaou has applied radical approach to the cyclization of glucal N-aryl urethanes **(Scheme 5.2)**.[86] More recently, Rojas developed a similar strategy based on rhodium mediated delivery of nitrogen from glucal 3-carbamates **5.8**, in the presence of alcohol acceptor to afford 2-N-acetamido-mannotopyranosides **5.9** (**Scheme 5.2**).

Nicolaou IBX-mediated method



5.6 **5.7**

Rojas glucal amidation methodology

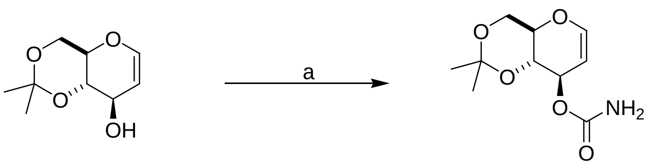


5.8 **5.9**

IBX = *o*-iodoxybenzoic acid; 1-hydroxy-1,2benziodoxol-3(1H)-one 1-oxide)

Scheme 5.2.

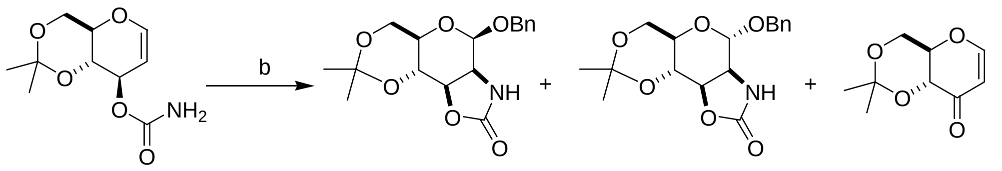
Rojas's strategy was applied to the synthesis of the required acid **5.5**. The synthesis started with glucal 3-carbamate **5.10**,[87] which is readily available through the method of Kocovsky[88] via the known allylic alcohol **5.11**.[89] (**Scheme 5.3).**



5.11 **5.10**

Scheme 5.3. (a) Trichloroacetyl isocyanate, CH_2Cl_2, 0 °C, 30 min, Then K_2CO_3, MeOH, 3h, 93%.

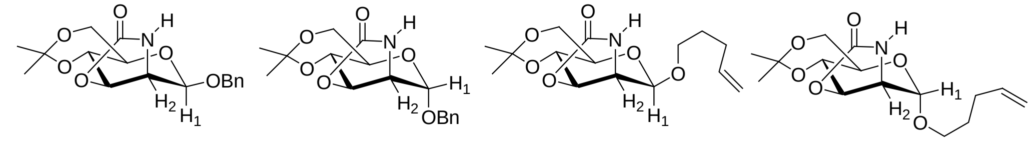
Treatment of **5.10** with iodosobenzene (PhIO) in presence of dirhodium (II) tetraacetate and benzyl alcohol provided the benzyl 2-amidomannoside **5.12-α** and **5.12-β** as a chromatographically separable 1:1 mixture of anomers, along with the by-product **5.13** (**Scheme 5.4**).



5.10 **5.12-β** **5.12α** **5.13** by product

Scheme 5.4. (a) PhIO, $Rh_2(OAc)_4$, CH_2Cl_2, 40^0C, 35%.

The stereochemistry of **5.12-α** and **5.12-β** was assigned by examination of the 1H NMRs and by comparison of the data reported by Rojas. The less polar anomer showed a singlet at 4.94 ppm that was assigned to H1. The more polar H1 appeared as a doublet (J = 2.8 Hz) at 4.78 ppm (**Figure 5.3**). In agreement with Rojas's finding, we assigned the less polar isomer as benzyl-α-2-amidomannoside **5.12-α** and the more polar anomer as benzyl-β-2-amidomannoside **5.12-β**. The subsequent reactions were carried out on the α-anomer **5.12-α**.



5.12-β more polar anomer H_1: d (δ = 4.78 ppm, J = 2.78 Hz)

5.12-α less polar anomer H_1: s (δ = 4.94 ppm)

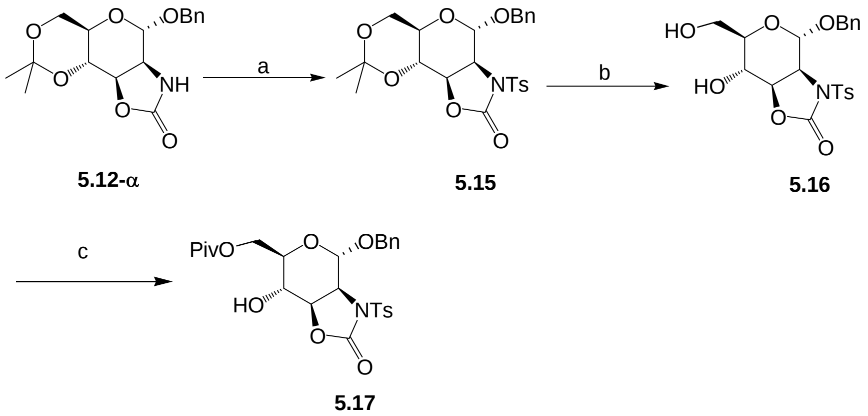
5.14-β more polar anomer H_1 d (δ = 4.70 ppm, J = 2.70Hz)

5.14-α less polar anomer H_1: s (δ = 4.84 ppm)

Rojas's intermediate

Figure 5.3. Stereochemical analysis of mannosamine derivatives

With the mannosamine **5.12-α** in hand, we next investigated the insertion of acid side chain at C4 position. Treatment of **5.12-α** with TsCl and triethylamine in anhydrous CH_2Cl_2 provided the tosylamide derivative **5.15** in quantitative yield (**Scheme 5.5**).

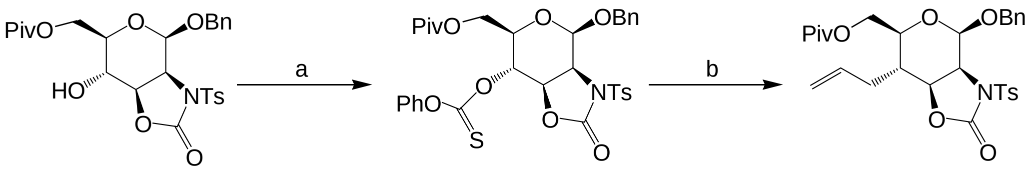


Scheme 5.5. (a) TsCl / Et_3N / DMAP, CH_2Cl_2, quant.

(b) HCl, MeOH, quant. (c) PivCl/Pyr, CH_2Cl_2, 80%.

Cleavage of the acetonide protecting group provided the corresponding diol **5.16** in quantitative yield. Selective protection of the primary alcohol as its pivalate ester afforded compound **5.17** in 80%.

At this pointa method for the stereoselective introduction of the acid side chain at C4 of the pyranose ring was needed. The Keck allylation[90] strategy seemed well-suited for this task, since this would correspond to the favored facial attack on the C4 radical. The radical precursor[91] **5.18** was obtained by treatment of alcohol **5.17** with PhOCSOCl. (**Scheme 5.6**). Compound **5.18** was subjected to the thermally promoted allylation conditions[92] to afford the C4 equatorial product **5.19** as a single isomer in 80% yield.

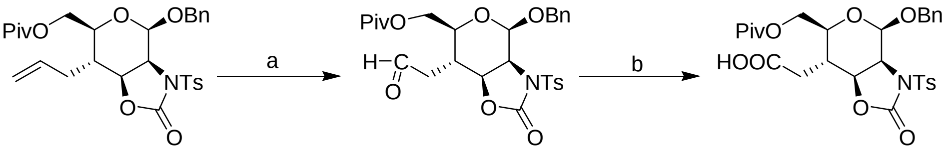


5.17 **5.18** **5.19**

Scheme 5.6. (a) PhOCSOCl / DMAP / Pyridine, Toluene, 80%.

(b) allyltributyltin / AIBN, toluene, 80%.

Oxidative cleavage of the double bond in **5.19** provided the aldehyde **5.20** in 94% yield (**Scheme 5.7**). Pinnick oxidation of **5.20** delivered the needed C4 equatorial acid **5.5** in a quantitative yield.



5.19 **5.20** **5.5**

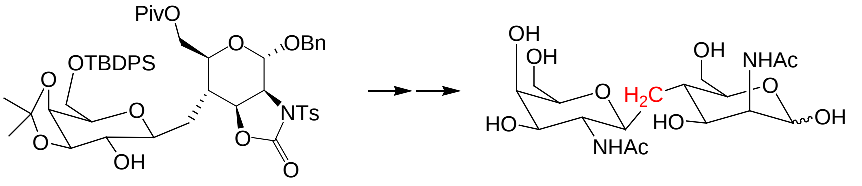
Scheme 5.7. (a) O_3 / Ph_3P, CH_2Cl_2 / MeOH 4:1, 94%.

(b) $NaClO_2$ / H_2O_2, NaH_2PO_4:H_2O, quant.

We have successfully accomplished the synthesis of acid **5.5** in 9 steps from the allyl alcohol **5.11** in 40 % overall yield. Our next task consisted of the synthesis of glycal **5.3**.

5.4 Attempted synthesis of 2-hydroxy-C-glycoside 5.3.

With our acid **5.5** in hand, we next attempted the synthesis of 2-hydroxy-C-glycoside **5.3** (**Figure 5.4**)

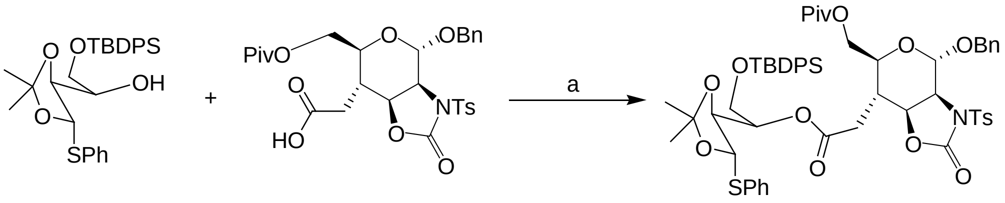


5.3

5.2 **galactosamine-β-C-mannoside**

Figure 5.4.

The synthesis of **5.3** started as usual. The DCC mediated coupling of acid **5.5** and TIA **4.8** afforded the desired ester derivative **5.21** in 67% yield (**Scheme 5.8**).



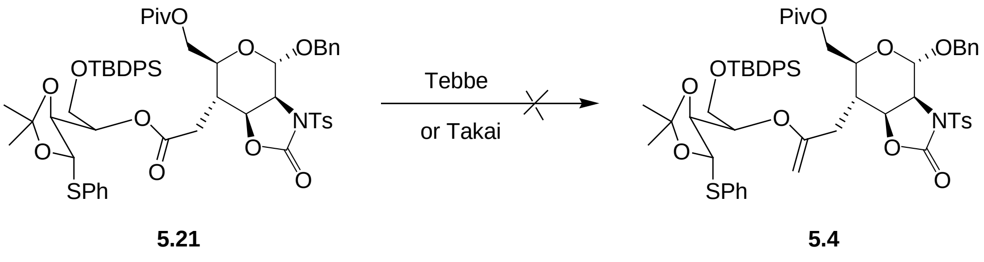
4.16 TIA

5.5

5.21

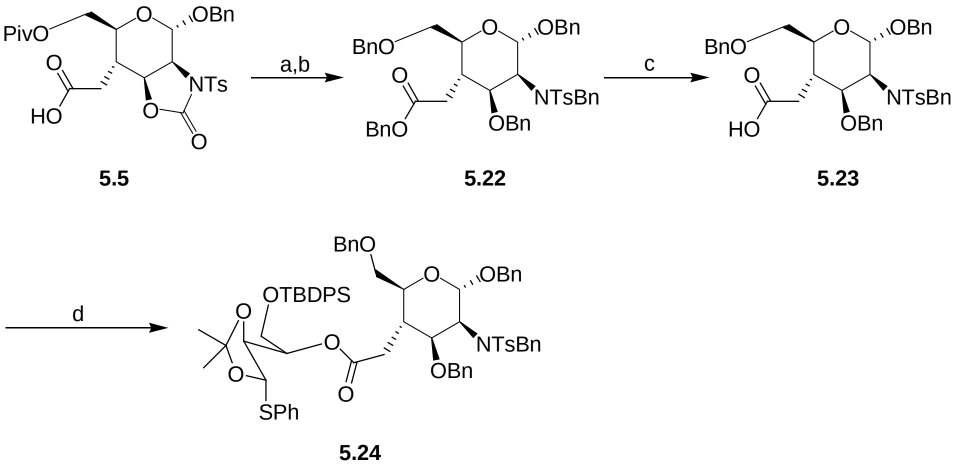
Scheme 5.8. (a) DCC, DMAP, benzene, 67%.

The conversion of ester **5.21** to the corresponding enol ether **5.4** was next attempted. However, neither Tebbe nor Takai olefination protocol was successful (**Scheme 5.9**).



Scheme 5.9.

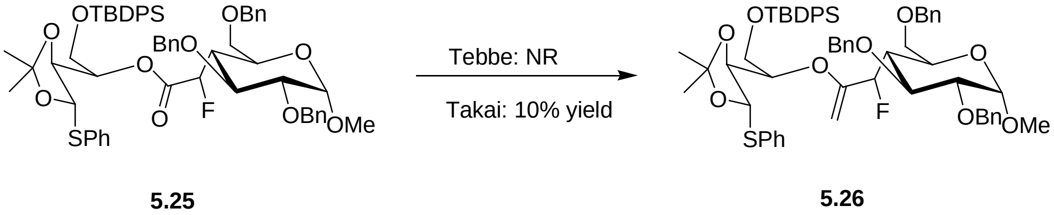
We presumed that the cyclic carbamate in the ester **5.21** was incompatible with the olefination condition. As a result, the bicyclic acid **5.5** was converted to the sulfonamide acid **5.23** in three straightforward steps (**Scheme 5.10**). Conversion of acid **5.23** to the corresponding ester **5.24** was effected as usual.



Scheme 5.10. (a) K_2CO_3, MeOH / H_2O.[93] (b) BnBr, NaH, Bu_4NI, DMF, 80%. (c) NaOH, MeOH/H_2O, 65%.

Methylenation of ester **5.24** was next attempted. Once again, to our disappointment, neither Tebbe nor Takai olefination strategy provided the expected enol ether **5.4**.

The difficulties we encountered in the methylenation of ester derivative such as **5.21** and **5.24** is presumably due to the steric hindrance at C4 of the mannose ring, or to the 1,3 diaxial interaction between the axial nitrogen at C2 and the H4. Indeed, other experiment from the laboratory suggested that methylenation of related C4 linked esters can be problematic (e.g **5.25** →**5.26**, scheme **5.11**)



Scheme 5.11.

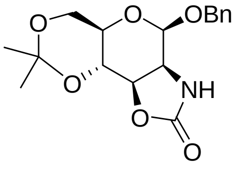
In view of the difficulty in methylenation of C4 linked ester derivatives, it was not possible to continue the plan.

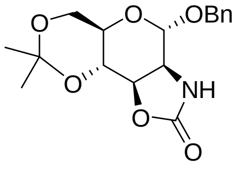
Summary

We planed to synthesized the disaccharide **5.2** via our galactosamine-β-C-glycoside strategy presented ealier. We have developed the synthesis of complex acid **5.5** via the manosamine synthesis reported earlier by Rojas. Thus, acid **5.5** was converted to the ester **5.21** via a DCC coupling with TIA alcohol **4.16**. Conversion of ester to the corresponding enolether was next investigated. Unfortunately, neither Tebbe nor Takai olefination protocol were successful. We presumed that the reactivity of ester **5.21** was affected by the presence of the cyclic cabamate. Hence, the bicyclic acid was converted to the monocyclic acid **5.23**, which was then converted to the ester **5.24** as usual. Once again, neither Tebbe nor Takai olefination ptotocol on ester **5.24** provided the expected enolether. As a result the key oxocarbenium ion cyclization could not be tested.

5.5 Experimental section

1-*O*-benzyl-2-amino-2-N,3-*O*-carbonyl-2-deoxy-4,6-isopropylidene-manopyranoside (5.12-β and 5.12-α).


5.12-β

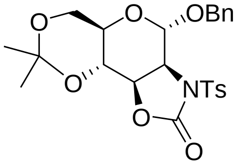

5.12-α

In a re-sealable reaction vessel were combined $Rh_2(OAc)_4$ (10.0 mg, 0.02 mmol), activated 4A^o molecular sieves (150 mg), carbamate **5.10** (50.0 mg, 0.22 mmol), and iodozobenzene (96.0 mg, 0.43 mmol). A solution of benzyl alcohol (0.12 mL, 1.09 mmol) in CH_2Cl_2 (3 mL) was added and the reaction vessel was sealed to prevent the lost of solvent. The reaction mixture was stirred thoroughly at rt during 4 hr. The reaction mixture was then filtered through celite, rinsing with CH_2Cl_2. The filtrate was concentrated in *vacuo* and the residue purified by FCC to afford **5.12-α** (14 mg, 19%), and **5.12-β** (12 mg, 16%), both as colorless oil.

For **5.12-α**: $R_f = 0.3$ (40% ethyl acetate:petroleum ether);^1H (500 MHz, $CDCl_3$) δ 1.45 (s, 3H), 1.55 (s, 3H), 3.70-3.75 (m, 1H), 3.81 (t, 1H, J = 10.3 Hz), 3.87-3.91 (m, 1H), 3.95

(dd, 1H, J = 8.0 Hz, J = 10.1 Hz), 4.16 (d, 1H, J = 7.9 Hz), 4.61 (ABq, 2H, Δ = 0.2ppm, J = 11.7 Hz), 4.66 (t, 1H, J = 7.8 Hz), 4.94 (s, 1H), 5.33 (br s, 1H), 7.34-7.42 (m, 5H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 19.2, 29.2, 56.5, 61.0, 62.2, 69.8, 71.9, 75.7, 96.3, 100.4, 128.5, 128.6, 128.9, 136.5, 158.6. For **5.12-β**: R_f = 0.2 (40% ethyl acetate:petroleum ether); ^{1}H (500 MHz, $CDCl_3$) δ 1.44 (s, 3H), 1.51 (s, 3H), 3.28-3.34 (m, 1H), 3.77 (t, 1H, J = 10.4 Hz), 3.95-3.99 (m, 1H), 4.12 (dd, 1H, J = 2.8 Hz, J = 8.0 Hz), 4.20 (dd, 1H, J = 7.4 Hz, J = 10.5 Hz), 4.58 (t, 1H, J = 7.6 Hz), 4.78 (ABq, 2H, Δδ = 0.27 ppm, J = 11.9 Hz), 4.78 (d, 1H, J = 2.8 Hz), 5.48 (br s, 1H), 7.34-7.41 (m, 5H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 19.1, 29.1, 54.7, 62.5, 65.5, 70.9, 71.7, 76.6, 96.3, 100.3, 128.3, 128.5, 128.9, 136.7, 158.6.

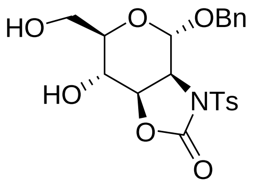
1-*O*-benzyl-2-amino-2-N-tosyl-2-N,3-*O*-carbonyl-2-deoxy-4,6-isopropylidene-α-D-manopyranoside 5.15.



5.15

To a mixture of amidoglycolated product **5.12-α** (1.80 g, 5.40 mmol), DMAP (329.20 mg, 2.69 mmol), and Et_3N (2.24 mL, 16.17 mmol) in CH_2Cl_2 (20 mLwas added TsCl (2.0 g, 10.77 mmol). The reaction mixture was stirred at rt until TLC indicated disappearance of starting material. The reaction mixture was then quenched by addition of MeOH (5 mL), washed with saturated $NaHCO_3$ (100 mL), and extracted with ether. The organic extracts were concentrated under reduced pressure and the residue was purified on silica gel column to give **5.15** as a white solid (1.50 g, 100%). R_f = 0.8 (40% ethyl acetate:petroleum ether). ^{1}H (500 MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.51 (s, 3H), 2.50 (s, 3H), 3.74-3.82 (m, 2H), 3.87-3.89 (m, 1H), 4.32 (d, 1H, J = 8.0 Hz), 4.57 (t, 1H, J = 7.9 Hz), 4.69 (ABq, 2H, Δδ = 0.13 ppm, J = 11.7 Hz), 5.88 (s, 1H), 7.38-7.47 (m, 7H), 7.85 (d, 2H, J = 8.4 Hz). ^{13}C (125 MHz, $CDCl_3$) δ 19.6, 22.3, 29.5, 60.8, 61.0, 62.4, 70.9, 72.3, 73.8, 96.9, 100.9, 128.8, 128.9, 129.2, 129.4, 130.5, 133.4, 137.1, 146.8, 153.0.

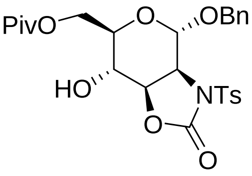
1-*O*-benzyl-2-amino-2-N-tosyl-2-N,3-*O*-carbonyl-2-deoxy-4,6-diol-α-D-manopyranoside 5.16.



5.16

To a mixture of compound **5.15** (2.3 g, 4.70 mmol) in dry methanol (60 mL) was added dropwise a solution of HCl in ether (2.0M in ether). The addition of HCl was stopped when the pH of the reaction mixture reached 2. The reaction mixture was then let to stir at rt until complete disappearance of starting material, at which time the pH of the reaction mixture was adjusted to 6 by addition of NaOMe. The resulting solution was then evaporated under *vacuo*. The residue was purified by FCC to give the diol **5.16** (2.1g, 99 %) as a light yellow semi-solid. R_f = 0.23 (50% ethyl acetate:petroleum ether); ^{1}H (500 MHz, $CDCl_3$) δ 1.62 (br s, 1H), 1.98 (t, 1H, J = 6.4 Hz), 2.48 (s, 3H), 3.13 (d, 1H, J = 6.6 Hz), 3.75-3.85 (m, 2H), 3.86-3.92 (m, 1H), 4.38 (d, 1H, J = 8.0 Hz), 4.63-4.66 (m, 1H), 4.74 (ABq, 2H, Δδ = 0.16 ppm, J = 11.6 Hz), 5.70 (s, 1H), 7.37 (d, 2H, J = 8.1 Hz), 7.39-7.47 (m, 5H), 7.84 (d, 2H, J = 8.4 Hz). ^{13}C (125 MHz, $CDCl_3$) δ 22.3, 59.5, 63.1, 67.3, 71.1, 71.3, 75.6, 96.0, 128.9, 129.1, 129.2, 129.3, 130.5, 134.0, 136.4, 146.8, 152.5.

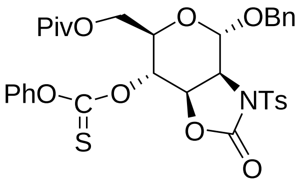
1-*O*-benzyl-2-amino-2-N-tosyl-2-N,3-*O*-carbonyl-2-deoxy-4-hydroxy-6-O-triacetylcarbonyl-α-D-manopyranoside 5.17.



5.17

To a mixture of diol **5.16** (1.0 g, 2.23 mmol), DMAP (60 mg, 0.44 mmol), and pyridine (0.40 mL, 4.46 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise PivCl (0.30 mL, 2.45 mmol). The reaction mixture was stirred at rt for 2 hr. The reaction was then quenched by addition of methanol (0.30 mL). The residue was purified by FCC to give the pivaloyl ester **5.17** (1.1g, 93%) as a light yellow solid. R_f = 0.83 (50% ethyl acetate:petroleum ether). ^{1}H (500 MHz, $CDCl_3$) δ 1.23 (s, 9H), 1.62 (br s, 1H), 2.48 (s, 3H), 3.37 (d, 1H, J = 6.1 Hz), 3.57-3.97(m, 1H), 3.94-3.97 (m, 1H), 4.19 (dd, 1H, J = 3.6 Hz, J = 12.0 Hz), 4.38 (d, 1H, J = 7.92 Hz), 4.46 (dd, 1H, J = 4.8 Hz, J = 12.0 Hz), 4.64 (dt, 1H , J = 6.7 Hz, J = 7.9 Hz), 4.74 (ABq, 2H, Δδ = 0.16 ppm, J = 11.6 Hz), 5.74 (s, 1H),), 7.37 (d, 2H, J = 8.1 Hz), 7.39-7.47 (m, 5H). ^{13}C (125 MHz, $CDCl_3$) δ 22.3, 27.7, 39.5, 59.7, 63.5, 67.4, 69.3, 70.9, 76.1, 96.0, 128.8, 129.1, 129.2, 129.3, 130.5, 134.1, 136.6, 146.7, 152.6, 179.8.

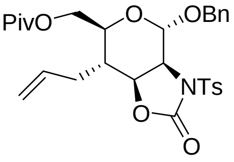
Compound 5.18



5.18

Phenyl chlorothionoformate (0.10 mL, 0.56 mmol) was added dropwise to a suspension of the alcohol **5.17** (100 mg, 0.19 mmol) and DMAP (12 mg, 0.09 mmol), in dry toluene (3 mL) at rt. Pyridine (0.05 mL, 0.56 mmol) was then added and the resulting suspension was stirred for 1h30 mn at rt. The reaction mixture was then washed with HCl (1M), saturated $NaHCO_3$ and the organic extracts were dried (Na_2SO_4) and concentrated under *vacuo*. FCC of the residue gave the product **5.18** as a white solid (100 mg, 80%). R_f = 0.63 (30% ethyl acetate:petroleum ether). ^{1}H (500 MHz, $CDCl_3$) δ 1.24 (s, 9H), 2.48 (s, 3H), 4.25-4.29 (m, 2H), 4.34-4.38 (m, 1H), 4.50 (d, 1H, J = 8.0 Hz), 4.77 (ABq, 2H, Δδ = 0.19 ppm, J = 6.9 Hz), 4.92 (dd, 1H, J = 5.8 Hz, J = 7.9 Hz), 5.67 (t, 1H, J = 6.7 Hz), 5.70 (s, 1H), 7.10-7.12 (m, 2H), 7.29-7.46 (m, 10H), 7.83 (m, 2H). ^{13}C (125 MHz, $CDCl_3$) δ 22.3, 27.7, 27.74, 39.4, 59.3, 63.3, 66.8, 70.7, 73.6, 76.1, 95.9, 121.3, 122.2, 127.5, 128.7, 129.0, 129.19, 129.23, 129.3, 130.2, 130.6, 134.2, 136.6, 146.8, 151.8, 153.9, 178.6, 194.3.

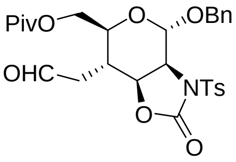
Compound 5.19



5.19

A mixture of starting material **5.18** (50 mg, 0.07 mmol), allyl tributyltin (0.06 mL, 0.18 mmol), and AIBN (3mg, 0.01mmol) in dry toluene (1 mL) was heated to reflux for 3hrs or until TLC indicated the disappearance of starting material. The reaction mixture was then evaporated and the crude mixture was purified by column chromatography over silica gel to afford the allyl derivative **5.19** (46 mg, 99%) as a light yellow oil. $R_f = 0.52$ (20% ethyl acetate:petroleum ether). ^{1}H (500 MHz, $CDCl_3$) δ 1.23 (s, 9H), 1.94-1.98 (m, 1H), 2.27-2.37 (m, 2H), 2.47 (s, 3H), 3.89 (sept, 1H, J = 3.1 Hz), 4.12-4.17 (m, 1H), 4.26 (d, 2H, J = 7.2 Hz), 4.30 (dd, 1H, J = 3.1 Hz, J = 11.9 Hz), 4.68 (ABq, 2H, Δδ = 11.75 Hz), 4.64 (t, 1H, J = 7.4 Hz), 5.10-5.16 (m, 2H), 5.64 (s, 1H), 5.68-5.76 (m, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.39-7.46 (m, 5H), 7.83 (d, 2H, J = 8.3 Hz). ^{13}C (125 MHz, $CDCl_3$) δ 14.8, 22.3, 33.7, 37.6, 39.4, 58.1, 65.0, 76.2, 70.3, 73.9, 95.8, 119.8, 128.7, 128.9, 129.1, 129.2, 130.4, 133.7, 134.5, 137.0, 146.4, 152.7, 178.8.

Aldehyde 5.20

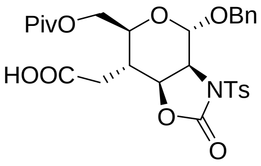


5.20

Compound **5.19** (400 mg, 0.72 mmol) was dissolved in a 4/1 mixture of CH_2Cl_2:MeOH (20.0 mL). The solution was cooled to –78 °C and treated with ozone until TLC indicated the complete disappearance of the starting material. The reaction mixture was then purged with nitrogen, and triphenyl phosphine (400 mg, 1.52 mmol) was added. The mixture was warmed to room temperature, stirred for 1h at this temperature, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford aldehyde **5.20** (380 mg, 94 %) as a white solid.

R_f = 0.22 (30% ethyl acetate:petroleum ether). ^1H (500 MHz, $CDCl_3$) δ 1.22 (s, 9H), 2.30-2.36 (m, 1H), 2.77 (ABq, 2H, Δδ = 0.19 ppm, J = 6.2 Hz, J = 18.8 Hz), 4.04-4.07 (m, 1H), 4.11-4.15 (m, 1H), 4.19-4.23 (m, 1H), 4.28 (d, 1H, J=7.5Hz), 4.68 (t, 1H, J = 7.5Hz), 4.70 (ABq, 2H, Δ δ= 0.19 ppm, J=11.7 Hz), 5.68 (s, 1H), 7.34 (m, 7H), 7.82 d, 2H, J = 8.3 Hz). ^{13}C ($CDCl_3$, 125MHz) 21.9, 27.3, 27.3, 33.4, 39.0, 42.9, 57.7, 64.6, 66.9, 70.1, 74.0, 95.5, 128.3, 128.5, 128.7, 128.8, 130.1, 134.0, 136.5, 146.1, 152.0, 178.3, 199.4.

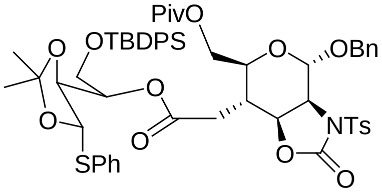
Acid 5.5



5.5

To a solution of aldehyde **5.20** in a 5:1 mixture of $CH_3CN:H_2O$ (20 mL), at 0 °C was added NaH_2PO_4 3:H_2O (866 mg, 6.27 mmol), and a solution of $NaClO_2$ (68mg, 0.75 mmol) in H_2O (9.50 mL), and H_2O_2 (0.1 mL). The mixture was stirred at 0 °C until TLC indicated the disappearance of the starting material. Na_2SO_3 was then added to the reaction. The reaction mixture was diluted with water and the organic phase was extracted with ether. The combined extracts were dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography to give the acid **5.5** in quantitative yield as a white solid. ^1H (500 MHz, $CDCl_3$,) δ 1.21 (s, 9H), 2.30-2.34 (m, 1H), 2.46 (s, 3H), 2.65 (ABq, 2H, Δ d= 0.17 ppm, J = 5.2 Hz, J = 17.2 Hz), 4.07 (br s, 1H), 4.19-4.29 (m, 2H), 4.70 (ABq, 2H, Δδ = 0.20 ppm, J=12.0 Hz), 4.81 (t, 1H, J = 5.7 Hz), 5.67 (s, 1H),), 7.37 (d, 2H, J = 8.1 Hz), 7.39-7.47 (m, 5H). ^{13}C (125 MHz, $CDCl_3$) δ 21.9, 27.2, 27.3, 32.8, 35.1, 39.1, 57.7, 64.6, 66.7, 70.1, 73.6, 95.5, 128.3, 128.5, 128.7, 128.9, 130.1, 134.0, 136.5, 146.1, 152.1, 175.0, 178.0.

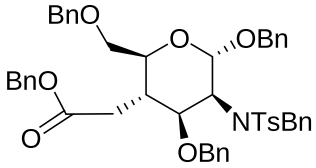
Ester 5.21



5.21

Esterification of TIA **4.8** and acid **5.5** provided ester **5.21** in 97%. R_f = 0.27 (20% ethyl acetate:petroleum ether).^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.19 (s, 9H), 1.38 (s, 3H), 1.46 (s, 3H), 2.25-2.75 (m, 1H), 2.46 (s, 3H), (ABq, 2H, Δδ = 0.18 ppm, J = 5.4 Hz), 3.79-3.86 (m, 2H), 4.07-4.10 (m, 1H), 4.13-4.17 (m, 1H), 4.20-4.23 (m, 2H), 4.25-4.28 (m, 1H), 4.65 (ABq, 2H, Δδ = 0.20 ppm, J = 11.9 Hz), 4.72-4.74 (m, 1H), 5.20-5.22 (m, 2H), 5.57 (s, 1H), 7.27-7.40 (m, 12H), 7.42-7.47 (m, 6H), 7.65-7.67 (m, 4H), 7.78-7.80 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 21.9, 26.4, 26.9, 27.36, 27.38, 33.1, 34.6, 39.0, 57.6, 62.6, 64.6, 66.8, 70.0, 73.4, 73.5, 79.2, 85.6, 95.5, 112.1, 127.9, 127.98, 128.0, 128.4, 128.5, 128.55, 128.7, 128.8, 129.2, 130.06, 130.09, 130.1, 132.3, 132.9, 133.1, 133.9, 134.3, 135.7, 135.9, 136.5, 146.0, 152.0, 170.2, 178.2. HRMS(ESI) calcd for $C_{57}H_{67}N_1O_{13}S_2Si_1$ (M+NH$_4$) 1083.41613, found 1083.41612.

Benzyl ester 5.39

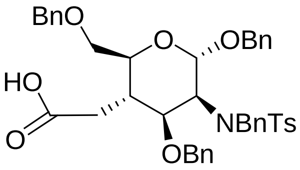


5.22

A solution of carbamate **5.5** (30 mg, 0.05 mmol) and potassium carbonate (15 mg, 0.11 mmol) in methanol/water (6:1 0.7 mL) was heated to 60 °C for 1.5 h. Acetic acid (few drops) was added and the reaction was concentrated in *vacuo*. The resulting residue was dried (azetroped with benzene) and used in the next step without any water work up.

A solution of the crude material from the previous step (20 mg, 0.04 mmol), sodium hydride (40 mg, 1.01 mmol), tetrabutyl ammonium iodide (5 mg, 0.01mmol) in dry DMF (0.5 mL), was stirred at 0 °C for 30 min. To the resulting mixture was added benzyl bromide (0.1 mL, 0.84 mmol). The reaction mixture was stirred at rt overnight. At that time, the reaction mixture was quenched by addition of water. The organic phase was extracted with ether. The combined organic extracts were dried (Na_2SO_4) and concentrated in *vacuo*. FCC of the residue provided the benzylated compound **5.24** in 61% yield from acid **5.5**. R_f = 0.54 (20% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.16-2.20 (m, 1H), 2.33-2.39 (m, 4H), 2.41-2.44 (m, 1H), 3.41-3.42 (m, 2H), 3.77 (dt, 1H, J = 4.3, J = 8.2 Hz), 3.87 (dd, 1H, J = 4.6, J = 8.04 Hz), 4.12-4.16 (m, 1H), 4.35-4.41 (m, 2H), 4.48-4.51 (m, 2H), 4.54-4.63 (m, 3H), 4.69-4.77 (m, 3H), 4.89-4.92 (m, 3H), 7.07-7.13 (m, 4H), 7.19-7.41 (m, 23H), 7.61-7.62 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 33.7, 36.2, 49.5, 56.2, 66.5, 69.1, 70.6, 70.9, 71.1, 73.4, 98.4, 126.8, 127.5, 127.6, 127.7, 127.8, 127.84, 127.96, 128.1, 128.12, 128.22, 128.3, 128.4, 128.5, 128.54, 128.6, 128.7, 129.7, 136.0, 137.7, 138.1, 138.3, 138.4, 143.4, 171.7. HRMS(ESI) calcd for $C_{50}H_{51}N_1O_8S_1$ (M+NH_4) 843.36736, found 843.36753.

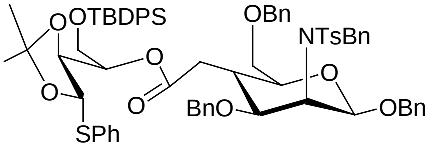
Acid 5.40



5.23

To a solution of **5.22** (20 mg, 0.02 mmol) in MeOH:THF:H_2O (1:1:1, 0.6 mL) was added (1N) NaOH (few drops). The reaction mixture was stirred at room temperature for 3h. The resulting mixture was acidified with 1N HCl (to pH 4) and the solvent removed under *vaccuo*. The residue was then passed through a short silical gel column to afford acid **5.23** in a quantitative yield. $R_f = 0.23$ (40% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.07-2.14 (m, 1H), 2.26-2.37 (m, 5H), 3.45-3.46 (m, 2H), 3.73-3.75 (m, 1H), 3.83-3.85 (m, 1H), 4.12-4.14 (m, 1H), 4.42-4.44 (m, 1H), 4.47-4.49 (m, 1H), 4.52-4.55 (m, 3H), 4.70-4.76 (m, 3H), 4.85-4.88 (m, 1H), 7.09-7.15 (m, 4H), 7.22-7.38 (m, 18H), 7.62-7.64 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 30.1, 34.0, 35.9, 49.6, 56.1, 69.6, 70.8, 71.3, 71.69, 74.0, 96.9, 99.0, 127.7, 128.2, 128.5, 128.7, 128.8, 128.9, 129.3, 129.4, 129.43, 130.6, 138.3, 138.4, 138.7, 138.9, 144.4, 173.9. HRMS(ESI) calcd for $C_{43}H_{45}N_1O_8S_1$ (M+NH$_4$) 753.32041, found 753.32056

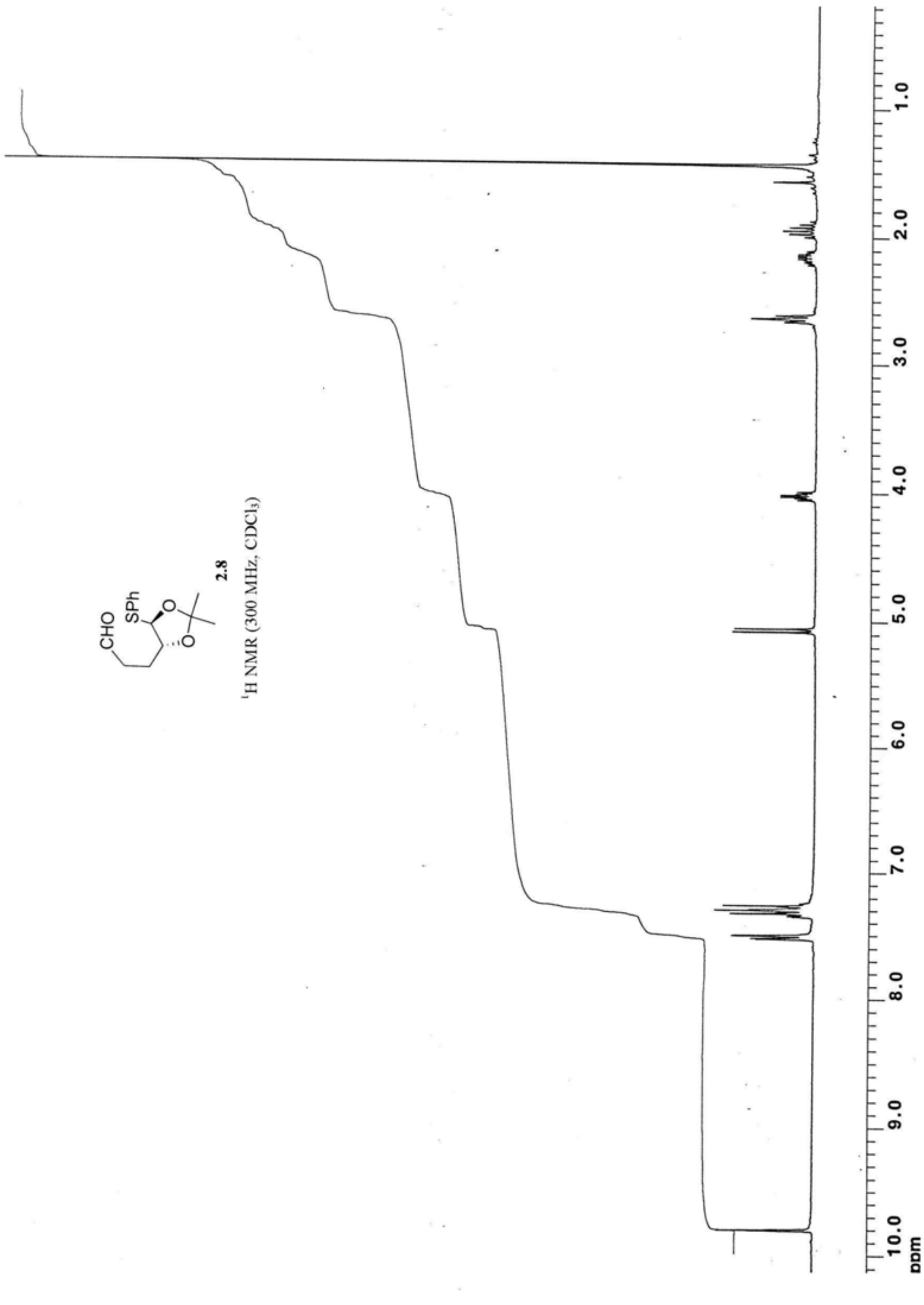
Ester 5.24



5.24

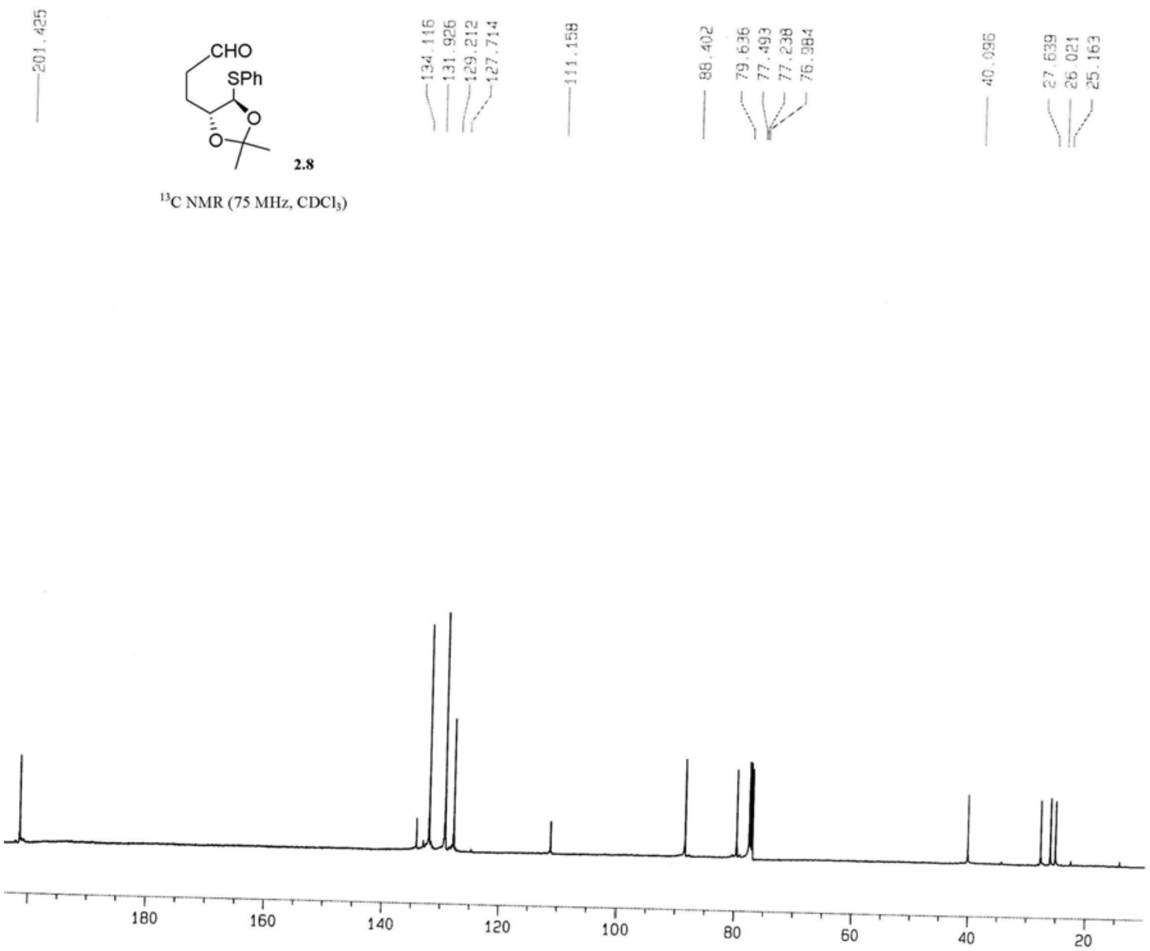
DCC coupling of TIA **8** and acid **5.23** provided ester **5.24** (15 mg, 65%). Recovered starting material (5 mg). For **5.25**: R_f = 0.61 (20% ethyl acetate:petroleum ether). ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.03 (s, 9H), 1.37 (s, 3H), 1.45 (s, 3H), 2.75 (ABq, Δδ = 0.32 ppm, J = 5.78 Hz, 1H), 2.76 (ABq, 1H, Δδ = 0.24 ppm, J = 5.8 Hz), 2.30-2.35 (m, 4H), 3.40 (d, 2H, J = 3.8 Hz), 3.71-3.79 (m, 2H), 3.87-3.94 (m, 2H), 4.10 (d, 1H, J = 11.8 Hz), 4.30-4.34 (m, 3H), 4.43-4.71 (m, 6H), 4.76 (ABq, 2H, Δδ = 0.25 ppm, J = 17.4 Hz), 5.16 (q, 1H, J = 5.6 Hz), 5.24 (d, 1H, J = 6.6 Hz), 7.03-7.16 (m, 8H), 7.22-7.48 (m, 25H), 7.57-7.67 (m, 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 19.3, 21.7, 25.1, 25.8, 26.3, 26.9, 27.3, 32.5, 34.2, 35.6, 49.5, 56.1, 62.3, 68.8, 70.4, 70.8, 70.9, 72.4, 73.4, 79.0, 85.3, 98.1, 111.9, 127.4, 127.5, 127.8, 127.8, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 129.2, 129.7, 130.0, 132.5, 133.06, 133.11, 133.8, 135.8, 135.8, 137.5, 137.6, 138.1, 138.2, 138.3, 143.3, 171.2. HRMS(ESI) calcd for $C_{72}H_{79}N_1O_{11}S_2Si_1$ (M+Na) 1248.47560, found 1248.47686.

Appendix



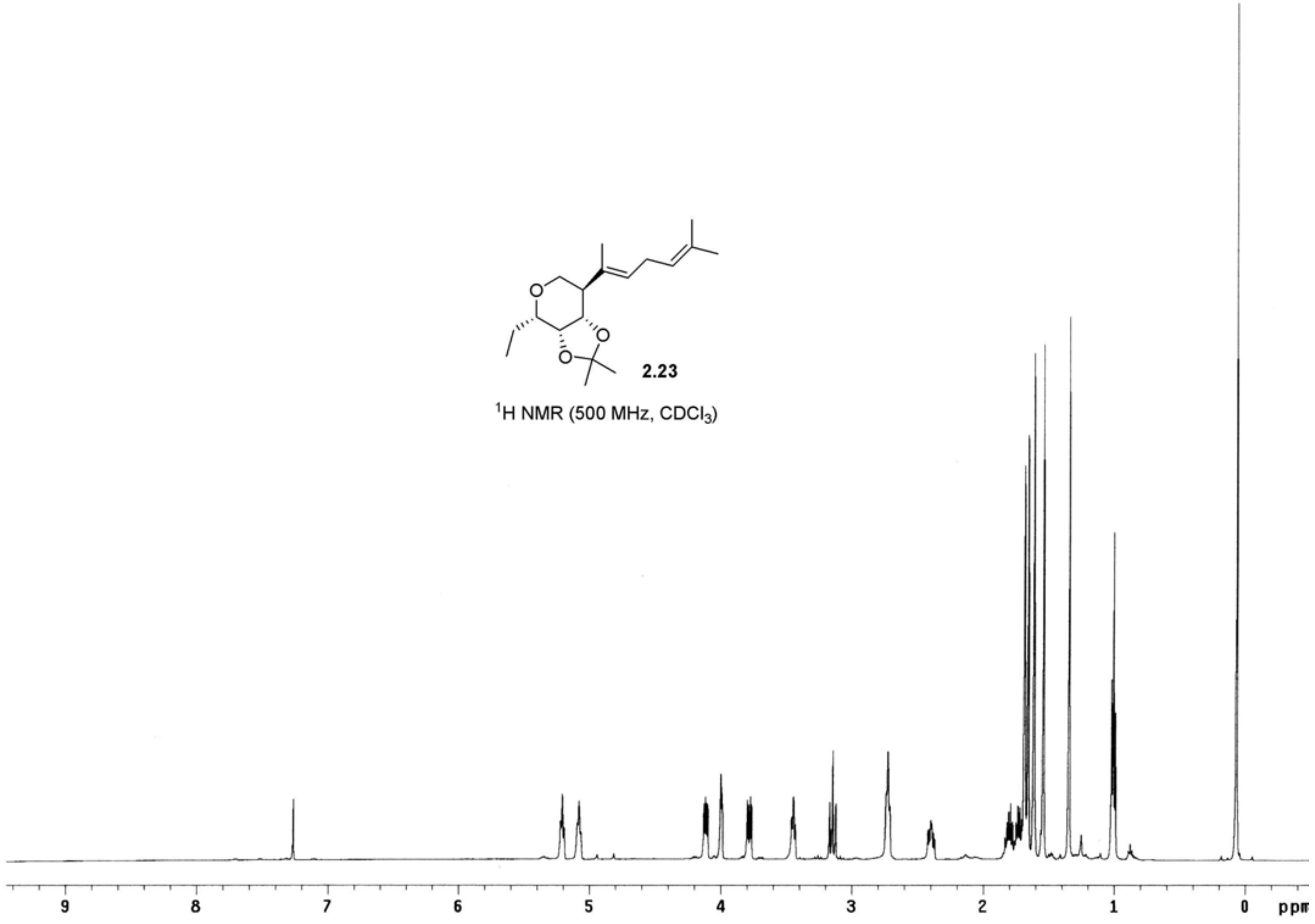
2.8

^{1}H NMR (300 MHz, CDCl$_3$)



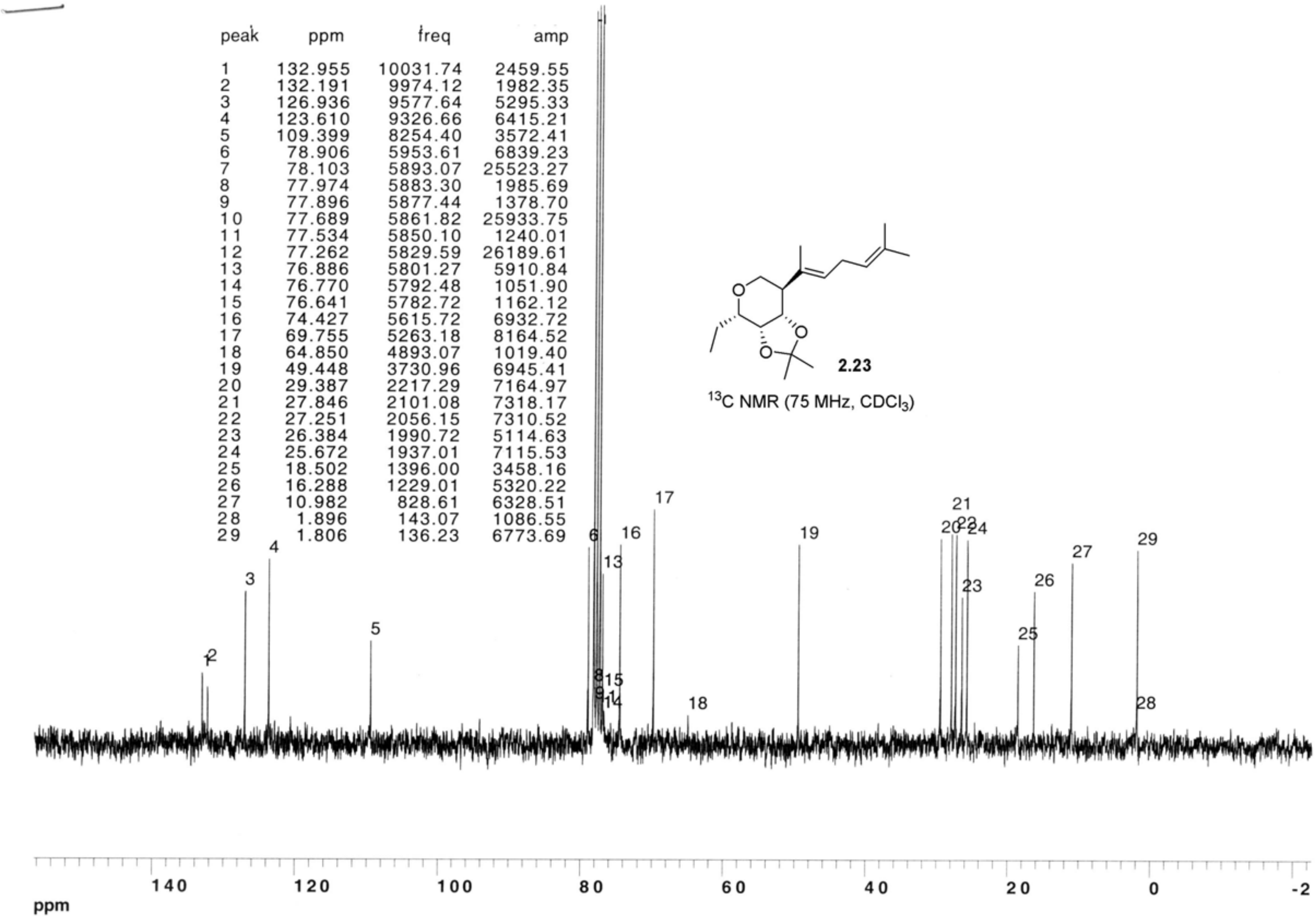
2.8

^{13}C NMR (75 MHz, CDCl$_3$)



2.23

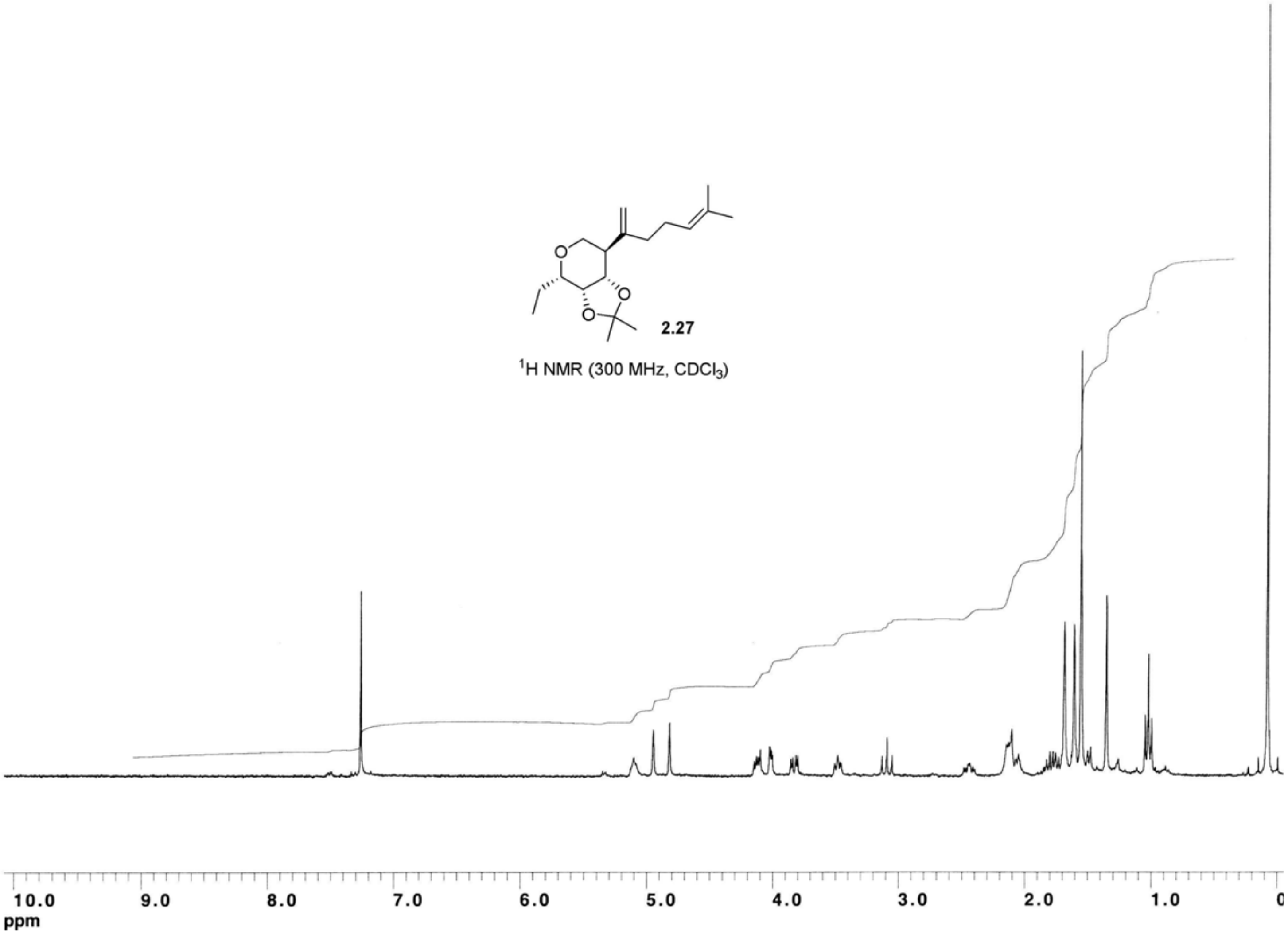
^{1}H NMR (500 MHz, CDCl$_3$)



2.23

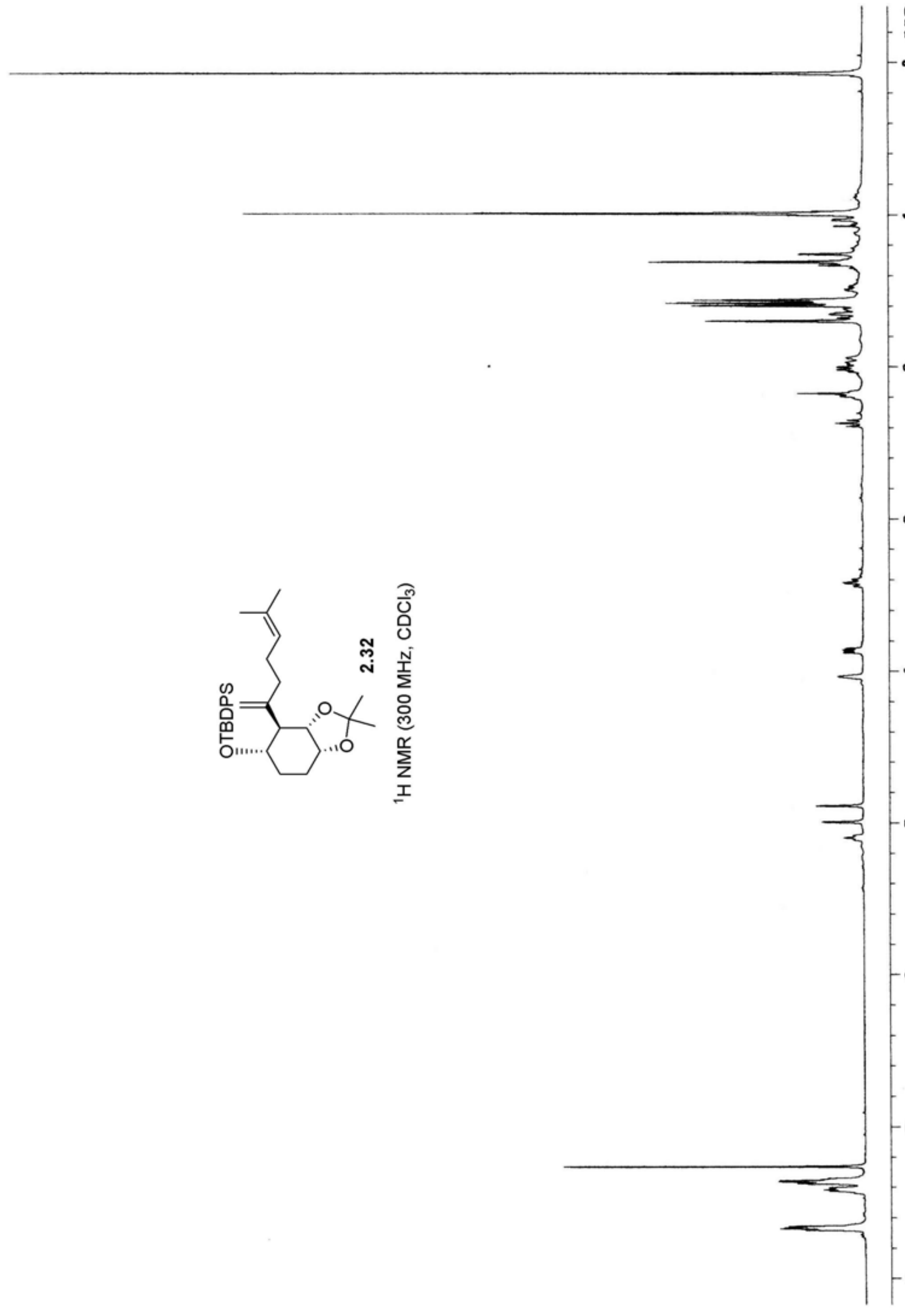
^{13}C NMR (75 MHz, CDCl$_3$)

peak	ppm	freq	amp
1	132.955	10031.74	2459.55
2	132.191	9974.12	1982.35
3	126.936	9577.64	5295.33
4	123.610	9326.66	6415.21
5	109.399	8254.40	3572.41
6	78.906	5953.61	6839.23
7	78.103	5893.07	25523.27
8	77.974	5883.30	1985.69
9	77.896	5877.44	1378.70
10	77.689	5861.82	25933.75
11	77.534	5850.10	1240.01
12	77.262	5829.59	26189.61
13	76.886	5801.27	5910.84
14	76.770	5792.48	1051.90
15	76.641	5782.72	1162.12
16	74.427	5615.72	6932.72
17	69.755	5263.18	8164.52
18	64.850	4893.07	1019.40
19	49.448	3730.96	6945.41
20	29.387	2217.29	7164.97
21	27.846	2101.08	7318.17
22	27.251	2056.15	7310.52
23	26.384	1990.72	5114.63
24	25.672	1937.01	7115.53
25	18.502	1396.00	3458.16
26	16.288	1229.01	5320.22
27	10.982	828.61	6328.51
28	1.896	143.07	1086.55
29	1.806	136.23	6773.69



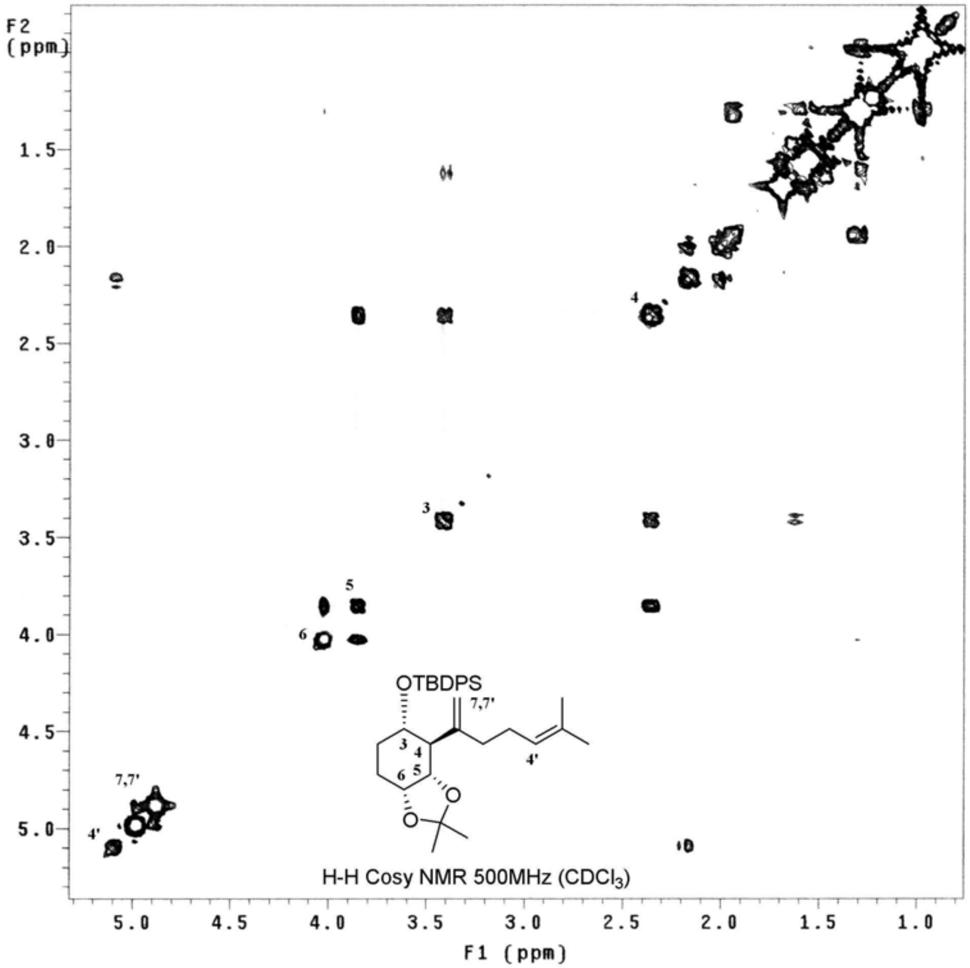
2.27

^{1}H NMR (300 MHz, $CDCl_3$)

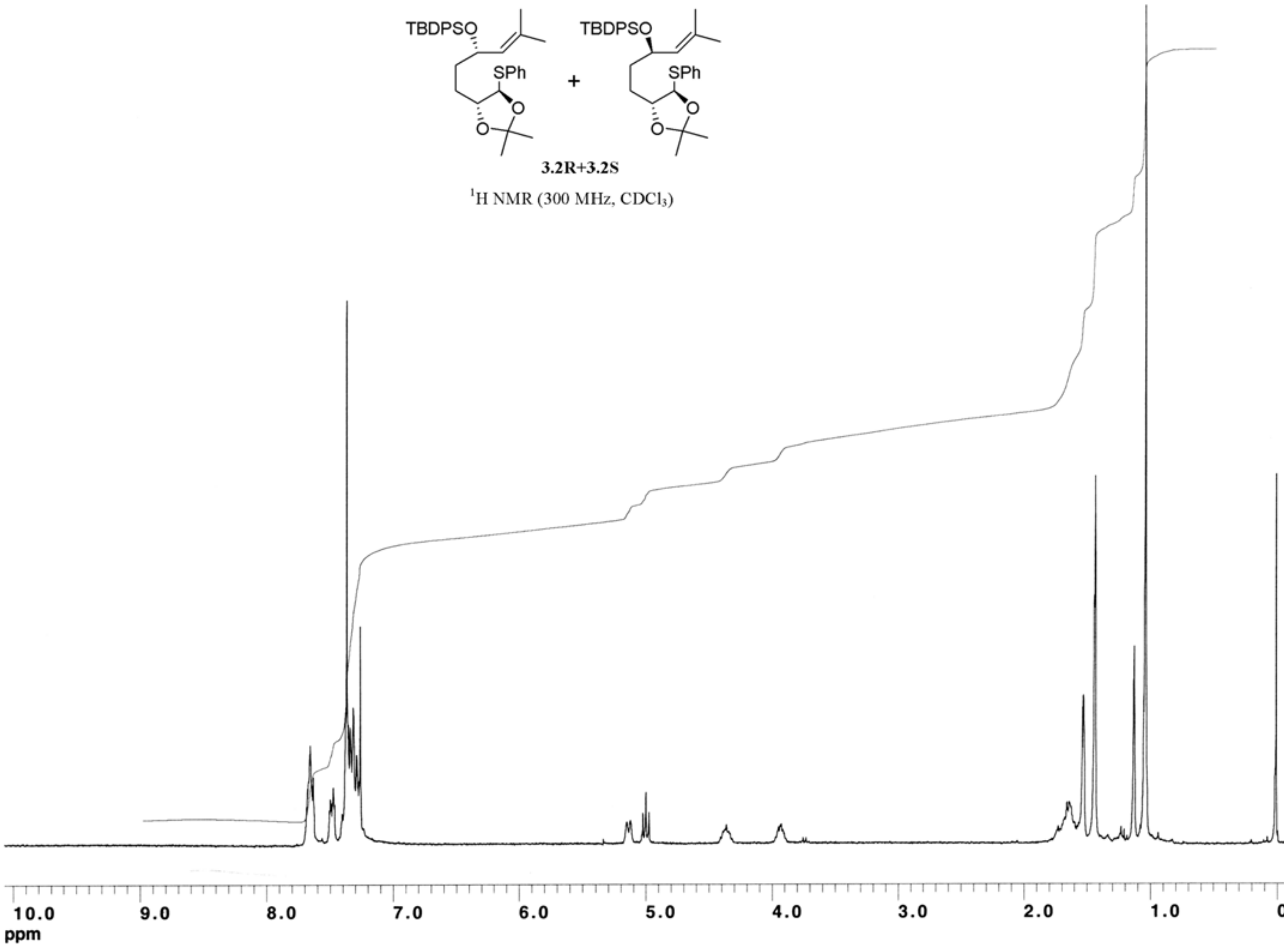


2.32

^{1}H NMR (300 MHz, $CDCl_3$)

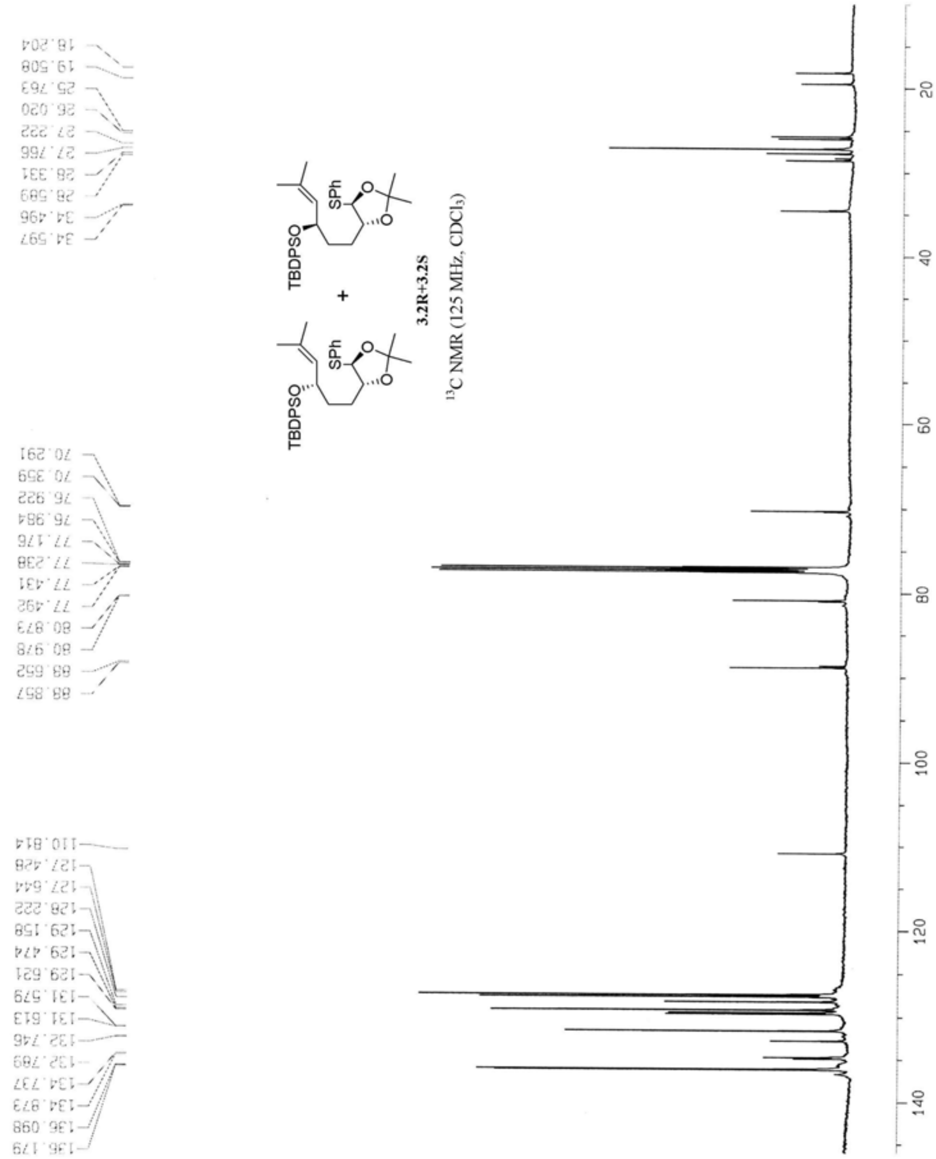


H-H Cosy NMR 500MHz ($CDCl_3$)



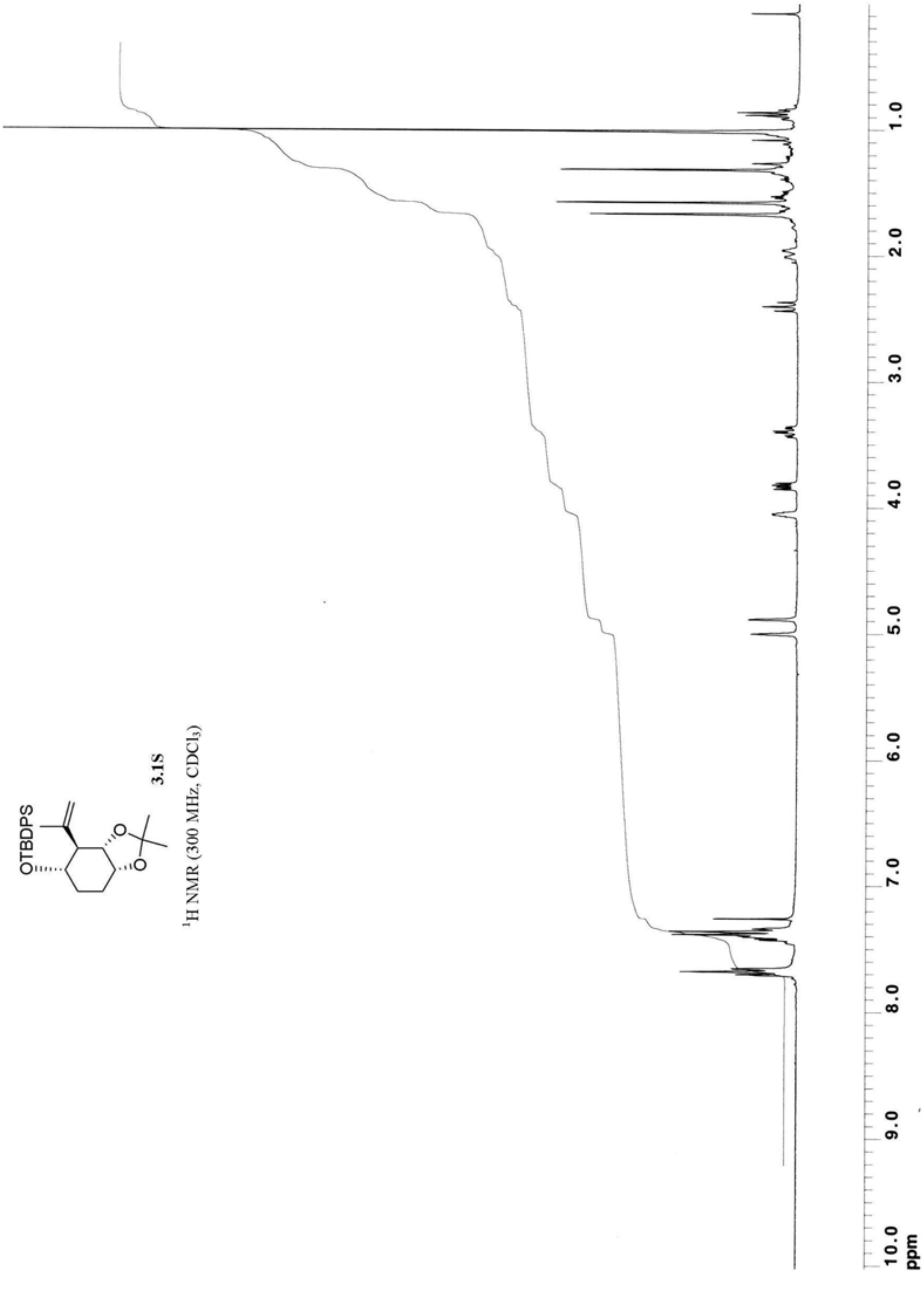
3.2R+3.2S

^{1}H NMR (300 MHz, CDCl$_3$)



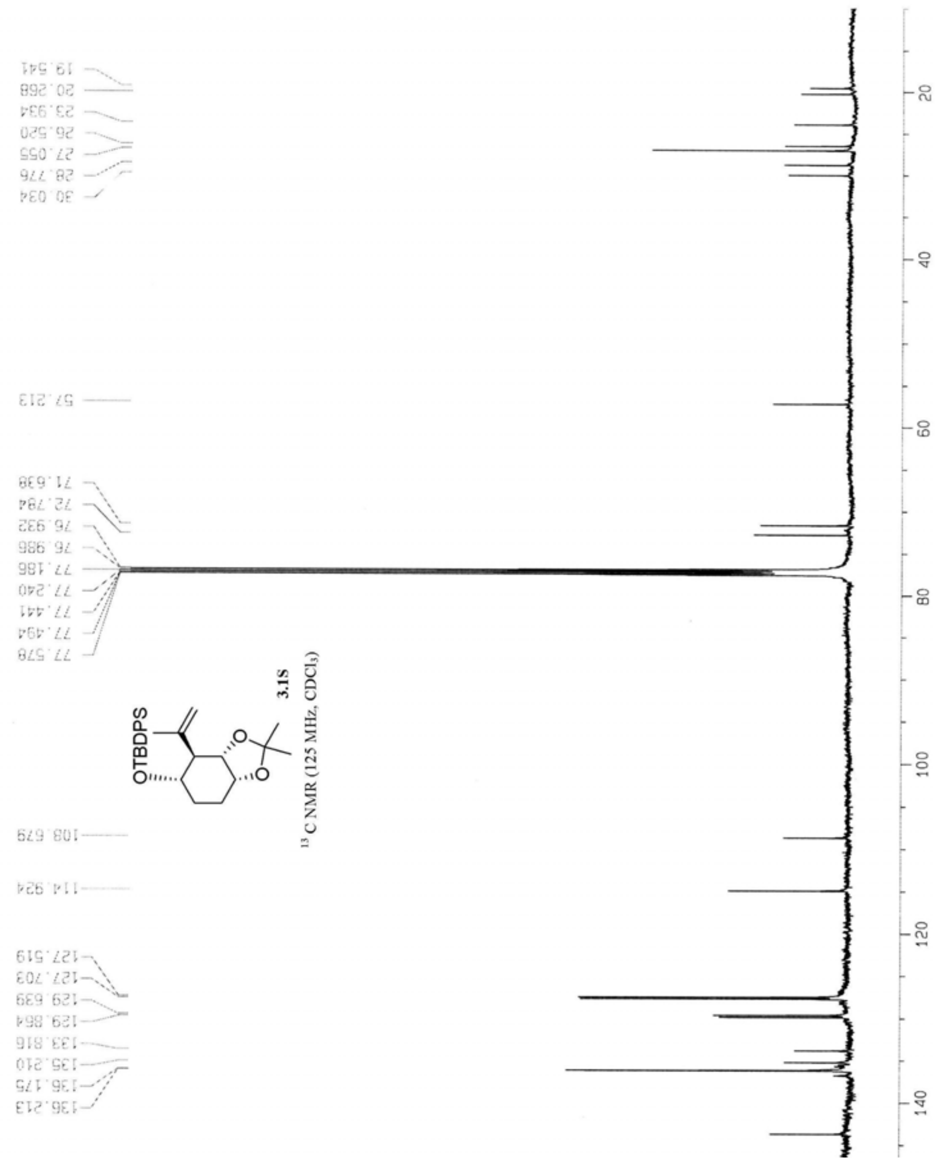
3.2R+3.2S

^{13}C NMR (125 MHz, CDCl$_3$)



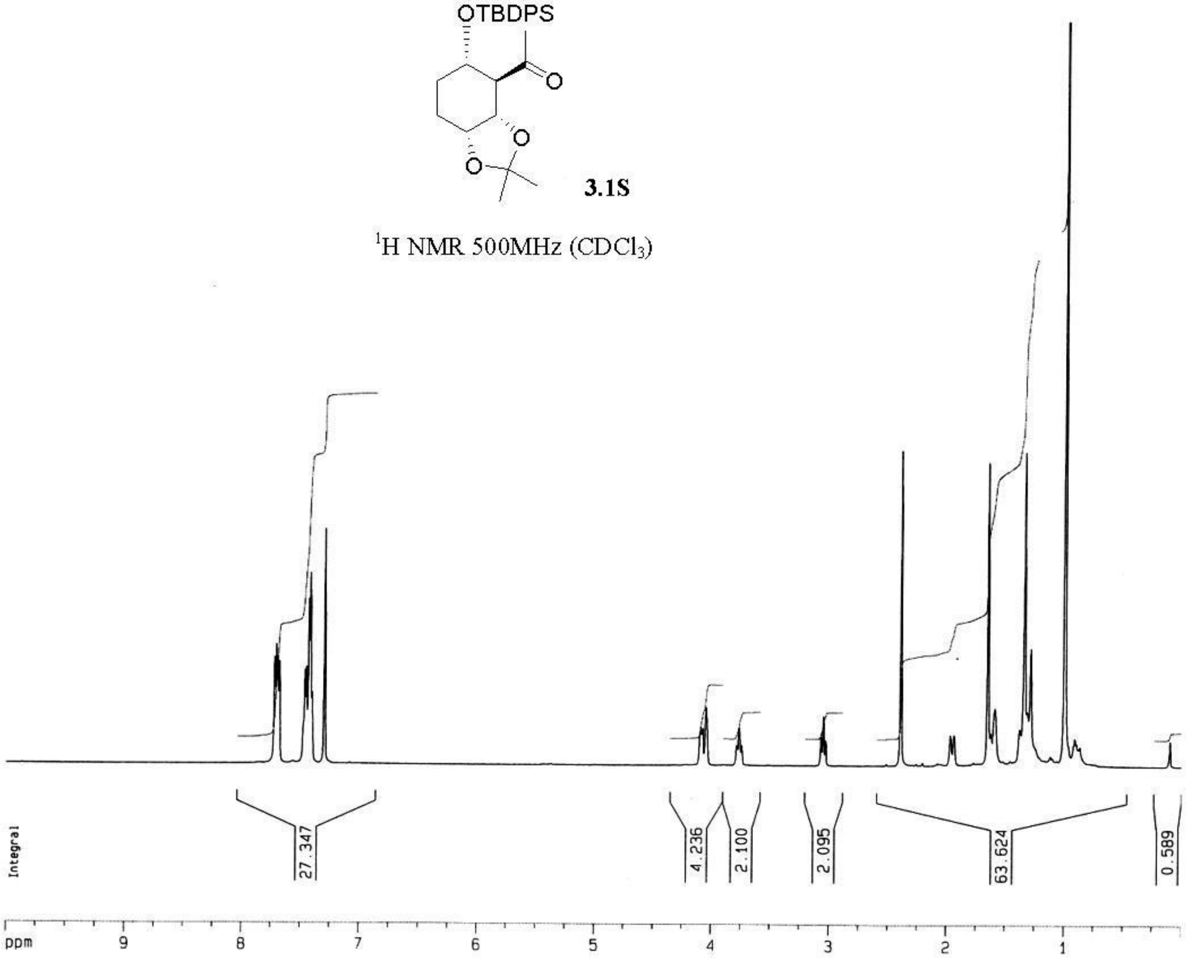
3.1S

^{1}H NMR (300 MHz, CDCl$_3$)



3.1S

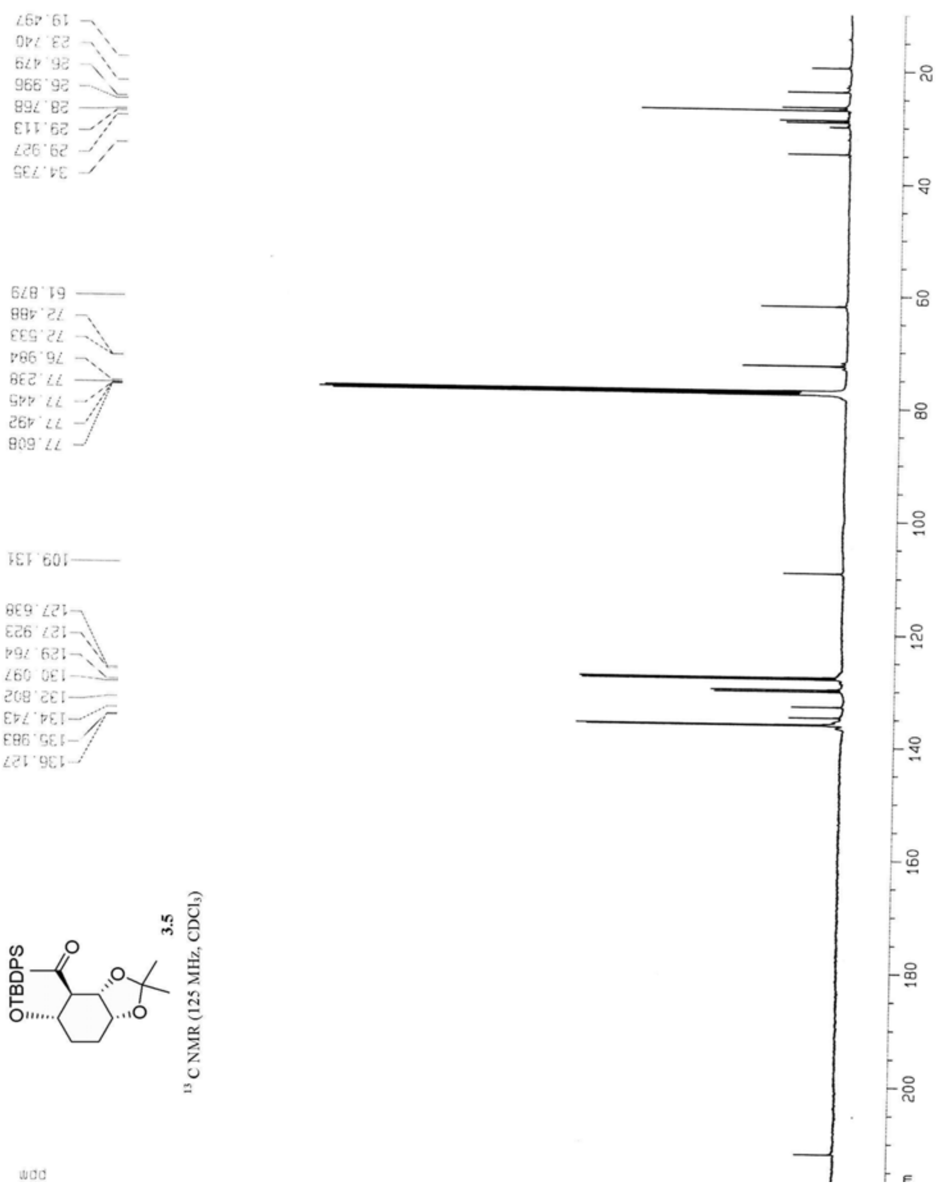
^{13}C NMR (125 MHz, CDCl$_3$)



3.1S

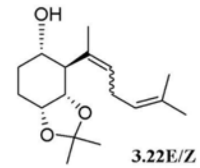
^{1}H NMR 500MHz (CDCl$_3$)

```
Current Data Parameters
NAME            04040501
EXPNO                 12
PROCNO                 1

F2 - Acquisition Parameter
Date_           20050404
Time               15.56
INSTRUM            spect
PROBHD   3 mm CPDUL 13C
PULPROG             zg30
TD                 32768
SOLVENT             C6D6
NS                     8
DS                     2
SWH             6666.667 Hz
FIDRES          0.203451 Hz
AQ             2.4577250 se
RG                   181
DW                75.000 us
DE                  6.00 us
TE                 303.0 K
D1            1.00000000 se
MCREST        0.00000000 se
MCWRK         0.01500000 se

======== CHANNEL f1 ======
NUC1                  1H
P1                 10.00 us
PL1                12.20 dB
SFO1         500.1330885 MH

F2 - Processing parameters
SI                 32768
SF           500.1300000 MH
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 22.00 cm
CY                 15.85 cm
F1P               10.000 pp
F1               5001.30 Hz
F2P                0.000 pp
F2                  0.00 Hz
PPMCM            0.45455 pp
HZCM           227.33182 Hz
```



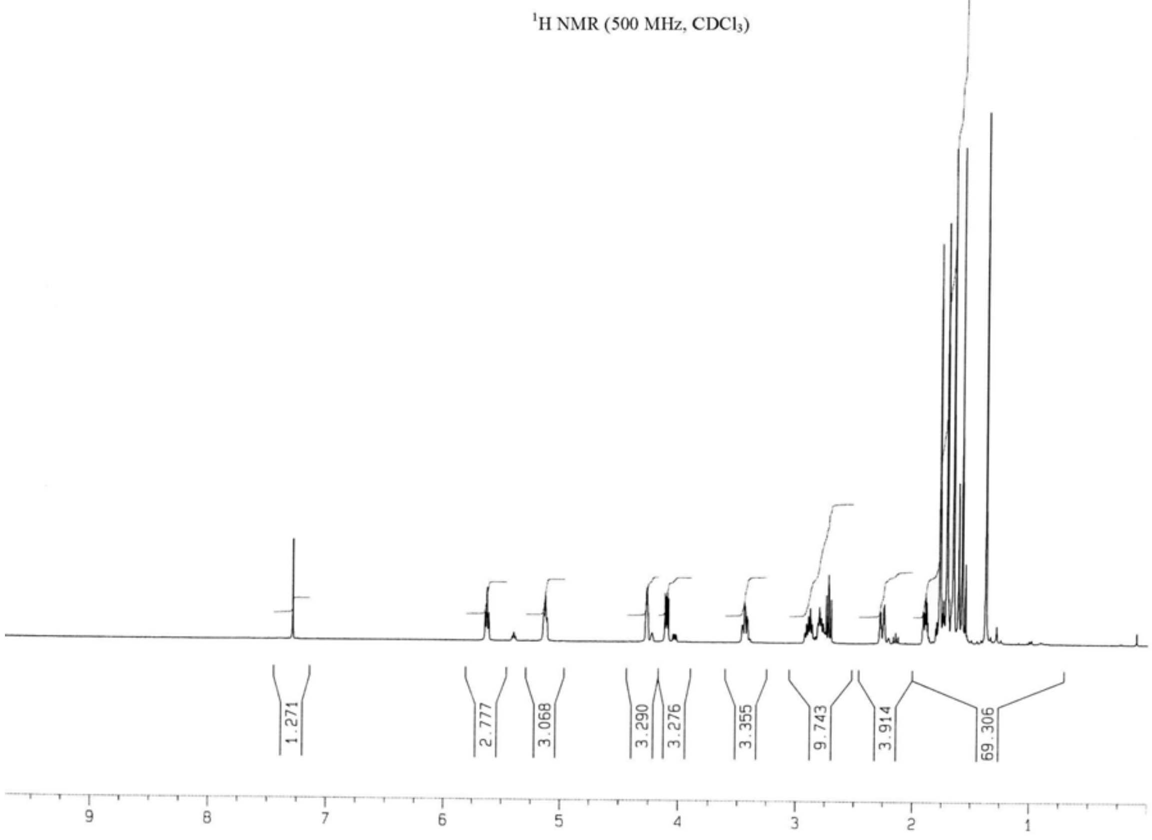
3.5

^{13}C NMR (125 MHz, CDCl$_3$)

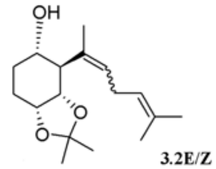


3.22E/Z

^{1}H NMR (500 MHz, CDCl$_3$)

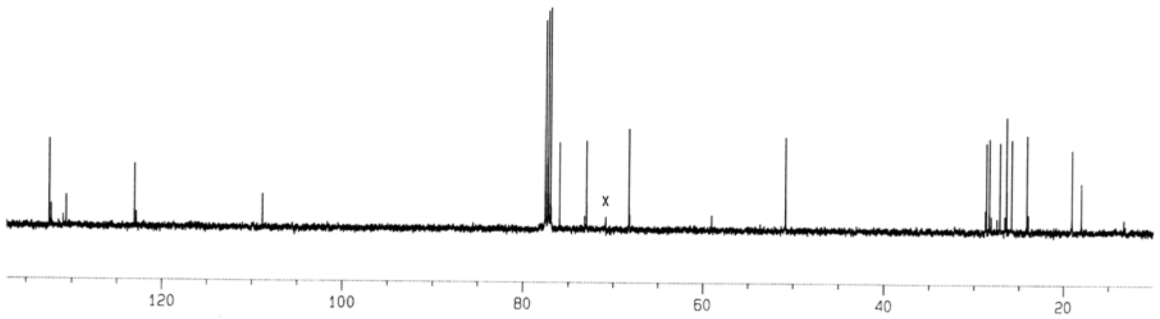


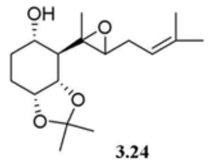
```
Current Data Parameters
NAME            07140401
EXPNO                  6
PROCNO                 1

F2 - Acquisition Parameters
Date_           20040714
Time               15.31
INSTRUM            spect
PROBHD   5 mm DUL 13C-1
PULPROG             zg30
TD                 32768
SOLVENT             C6D6
NS                     8
DS                     2
SWH             6666.667 Hz
FIDRES          0.203451 Hz
AQ             2.4577250 sec
RG                   181
DW                75.000 usec
DE                  6.00 usec
TE                 303.0 K
D1            1.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                  8.45 usec
PL1                -3.00 dB
SFO1         500.1330885 MHz

F2 - Processing parameters
SI                 32768
SF           500.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 22.00 cm
CY                 10.04 cm
F1P               10.000 ppm
F1               5001.30 Hz
F2P                0.000 ppm
F2                  0.00 Hz
PPMCM            0.45455 ppm/cm
HZCM           227.33182 Hz/cm
```



3.2E/Z

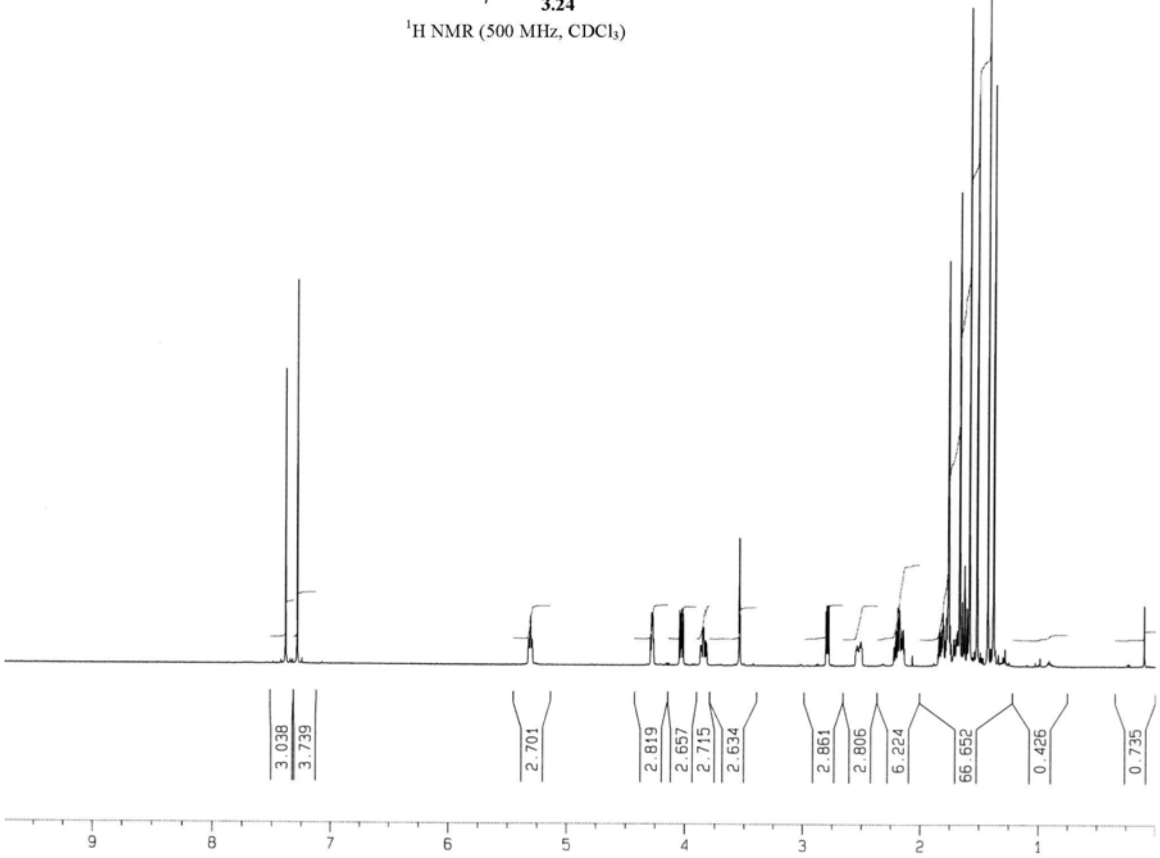
^{13}C NMR (125 MHz, CDCl$_3$)



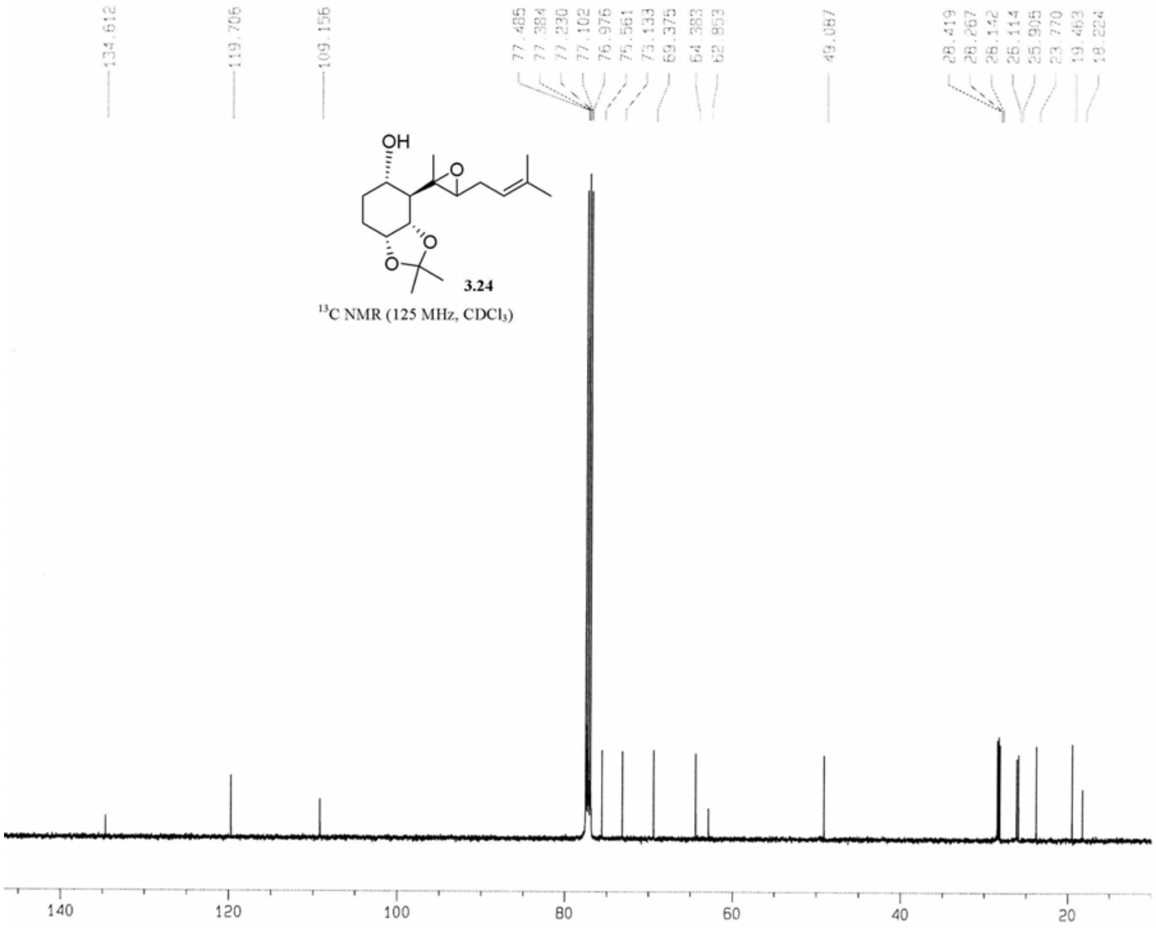


3.24

^{1}H NMR (500 MHz, $CDCl_3$)

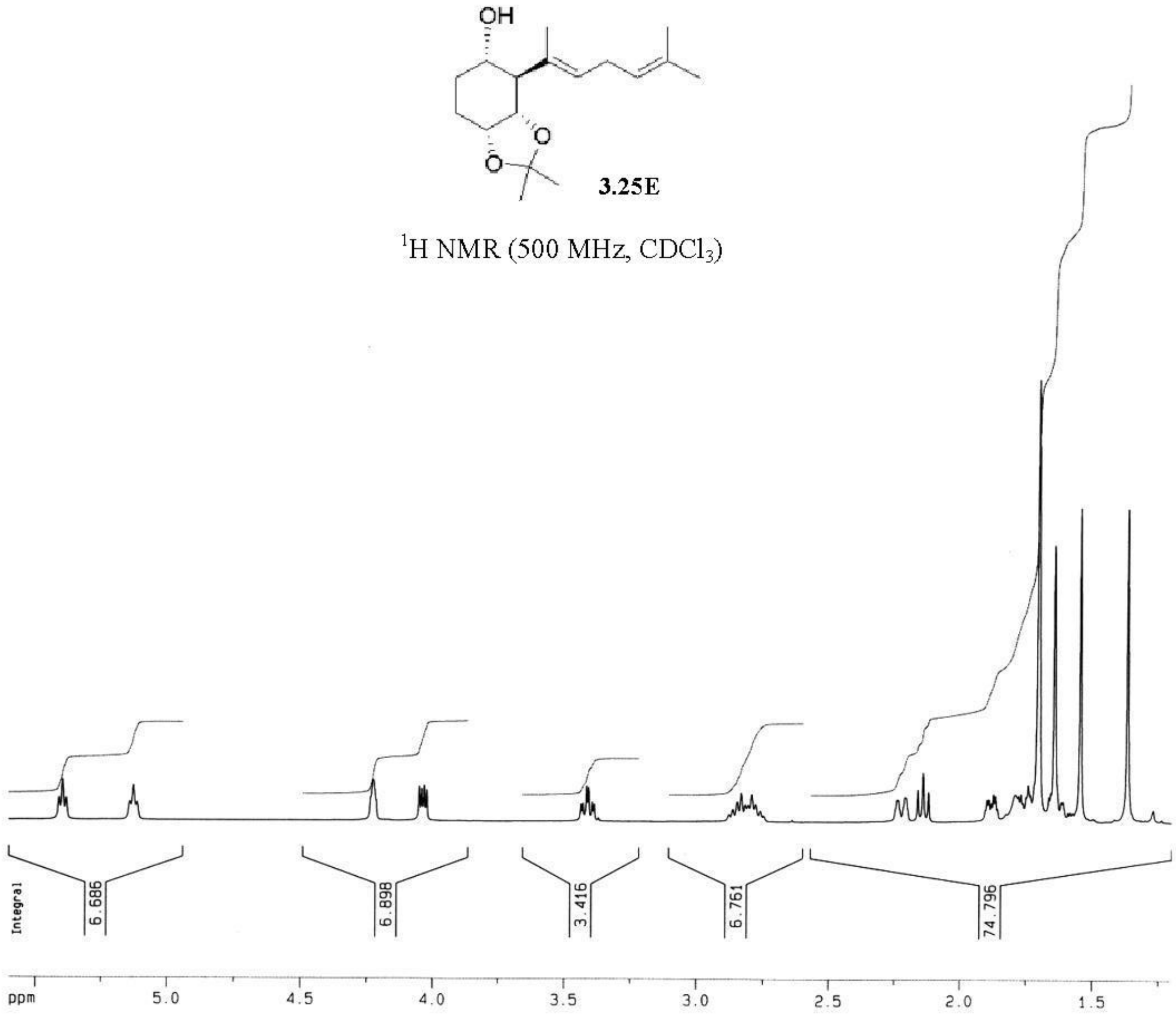


```
Current Data Parameters
NAME              08260401
EXPNO                   10
PROCNO                   1

F2 - Acquisition Parameters
Date_             20040826
Time                 18.04
INSTRUM              spect
PROBHD   5 mm DUL 13C-1
PULPROG               zg30
TD                   32768
SOLVENT               C6D6
NS                       8
DS                       2
SWH               6666.667 Hz
FIDRES            0.203451 Hz
AQ               2.4577250 sec
RG                     256
DW                  75.000 usec
DE                    6.00 usec
TE                   303.0 K
D1            1.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.30 usec
PL1                  -3.00 dB
SFO1           500.1330885 MHz

F2 - Processing parameters
SI                   32768
SF             500.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00

1D NMR plot parameters
CX                   22.00 cm
CY                   13.97 cm
F1P                 10.000 ppm
F1                 5001.30 Hz
F2P                  0.000 ppm
F2                    0.00 Hz
PPMCM              0.45455 ppm/cm
HZCM             227.33182 Hz/cm
```



3.24

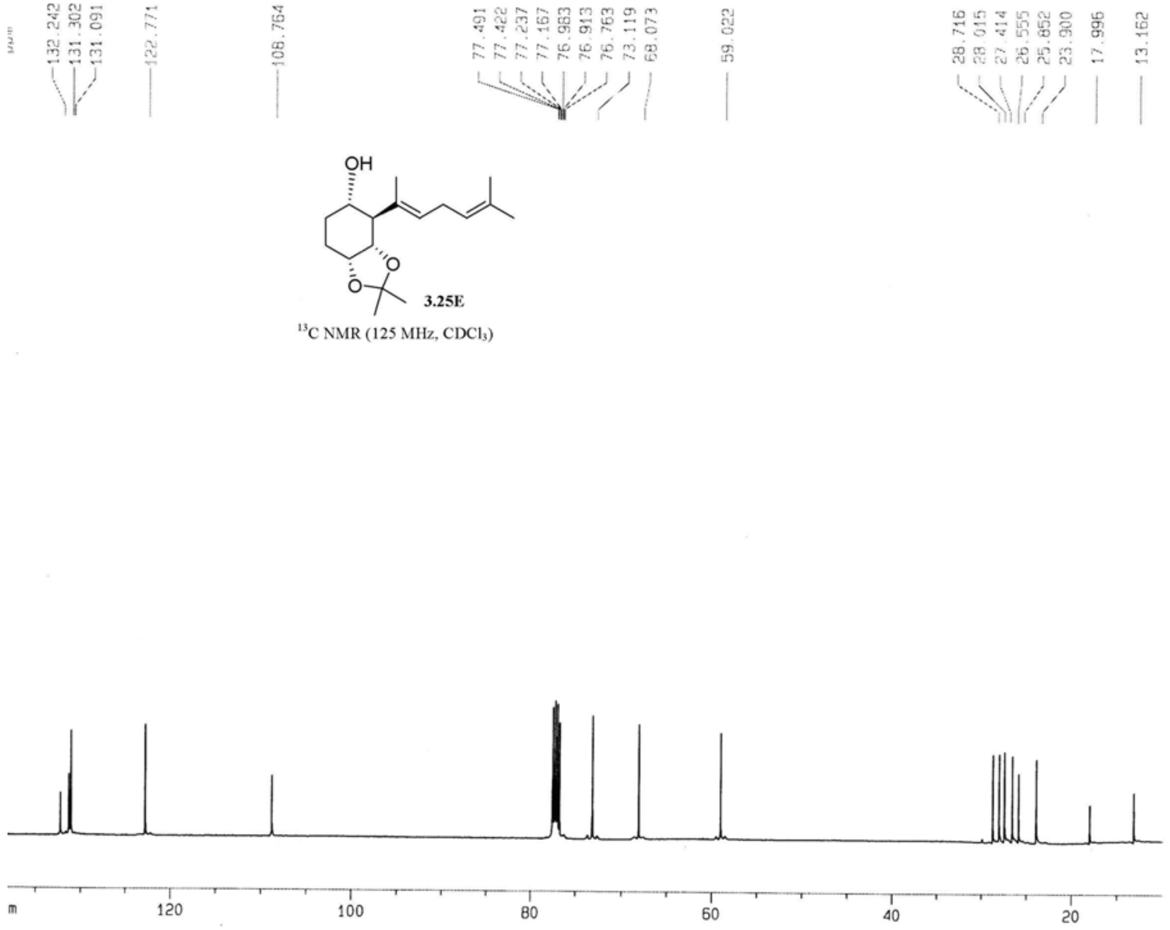
^{13}C NMR (125 MHz, CDCl$_3$)



3.25E

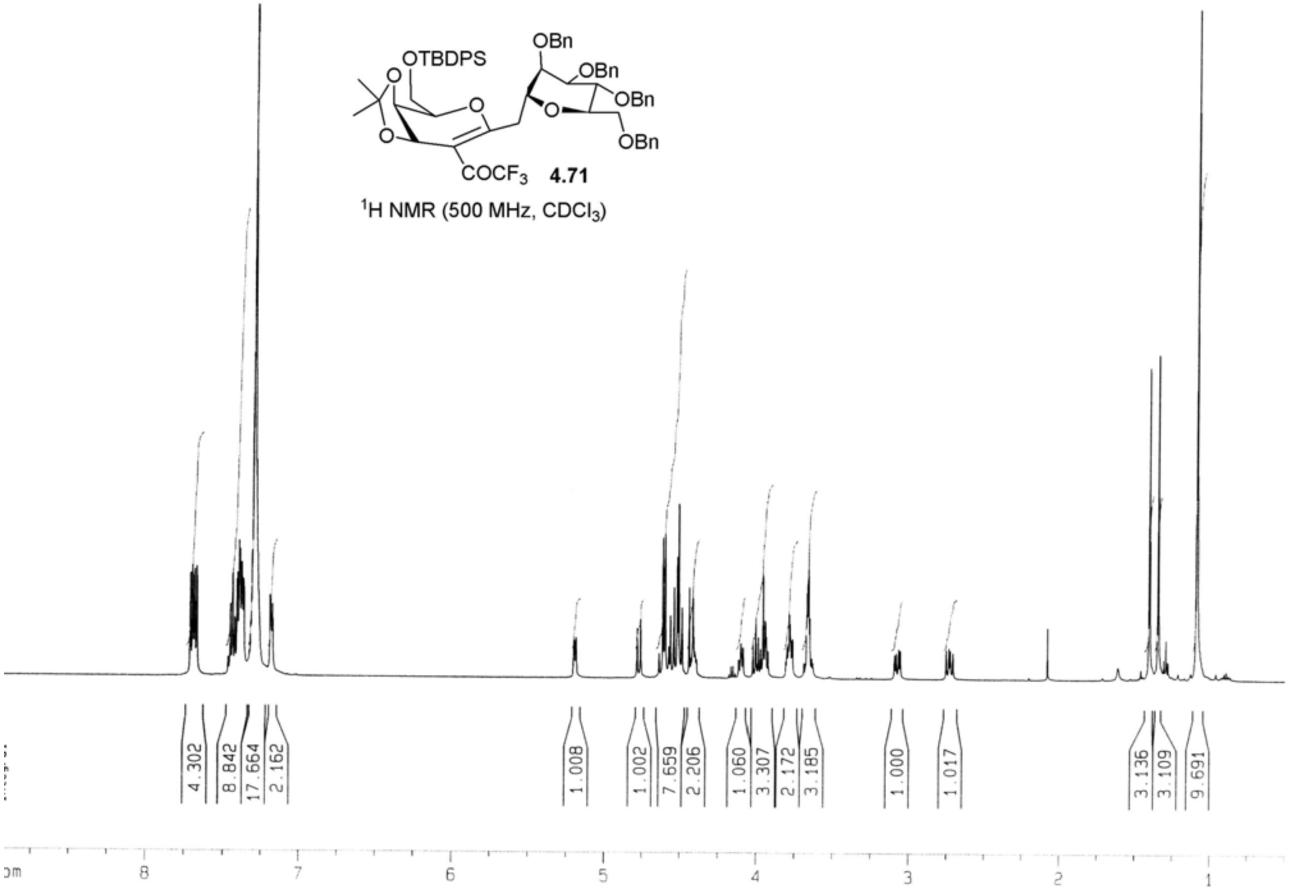
^{1}H NMR (500 MHz, $CDCl_3$)

```
Current Data Parameters
NAME          04140501
EXPNO               10
PROCNO               1

F2 - Acquisition Parameter
Date_         20050414
Time             14.28
INSTRUM          spect
PROBHD   3 mm CPDUL 13C
PULPROG           zg30
TD               32768
SOLVENT           C6D6
NS                   8
DS                   2
SWH           6666.667 Hz
FIDRES        0.203451 Hz
AQ           2.4577250 se
RG                  18
DW              75.000 us
DE                6.00 us
TE               303.0 K
D1          1.00000000 se
MCREST      0.00000000 se
MCWRK       0.01500000 se

======== CHANNEL f1 ======
NUC1                1H
P1               10.00 us
PL1              12.20 dB
SFO1       500.1330885 MH

F2 - Processing parameters
SI               32768
SF         500.1300000 MH
WDW                 EM
SSB                  0
LB                0.30 Hz
GB                   0
PC                1.00

1D NMR plot parameters
CX               22.00 cm
CY                8.39 cm
F1P              5.600 ppi
F1             2800.73 Hz
F2P              1.200 ppi
F2              600.16 Hz
PPMCM          0.20000 ppi
HZCM         100.02600 Hz,
```



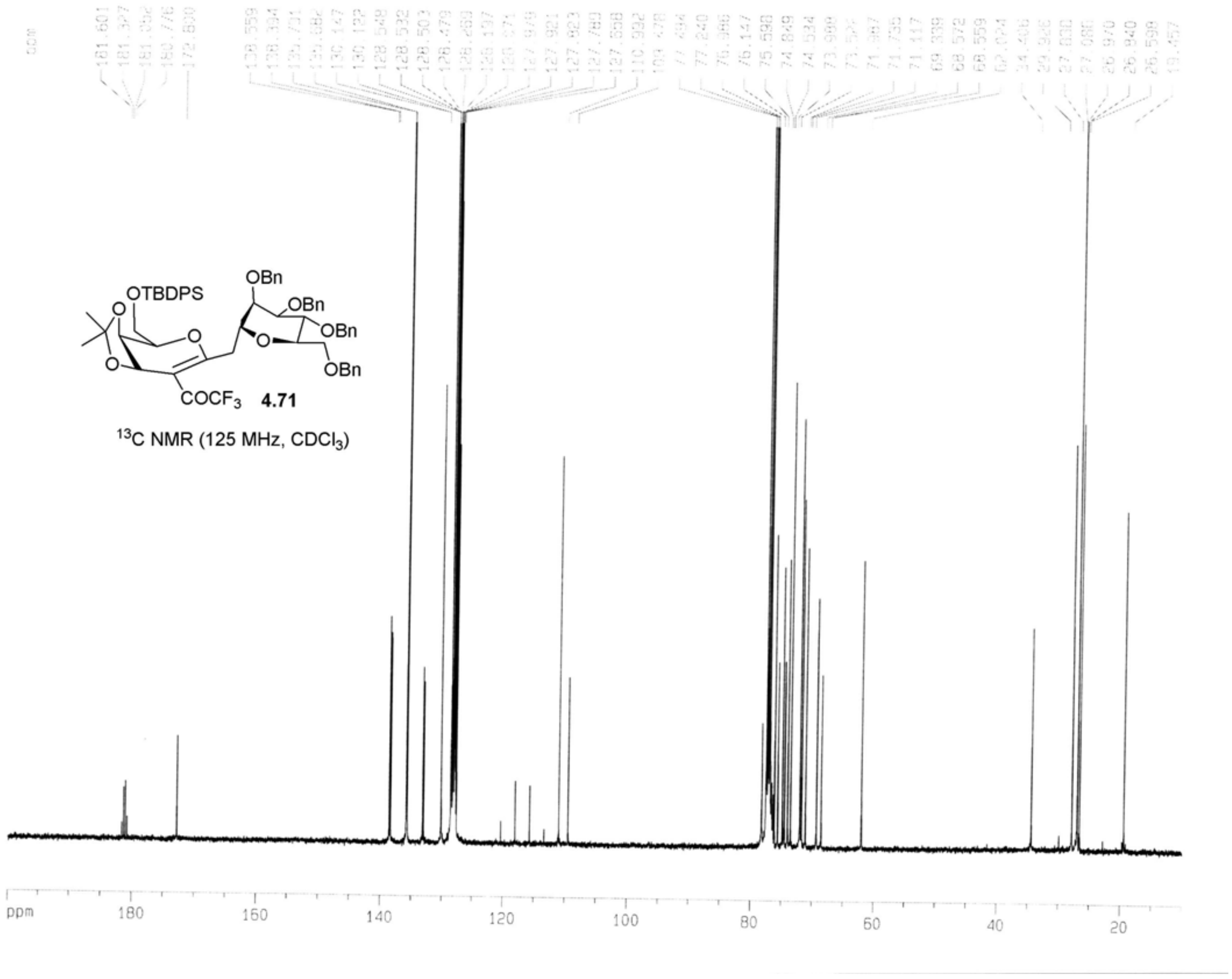
3.25E

^{13}C NMR (125 MHz, CDCl$_3$)


4.71

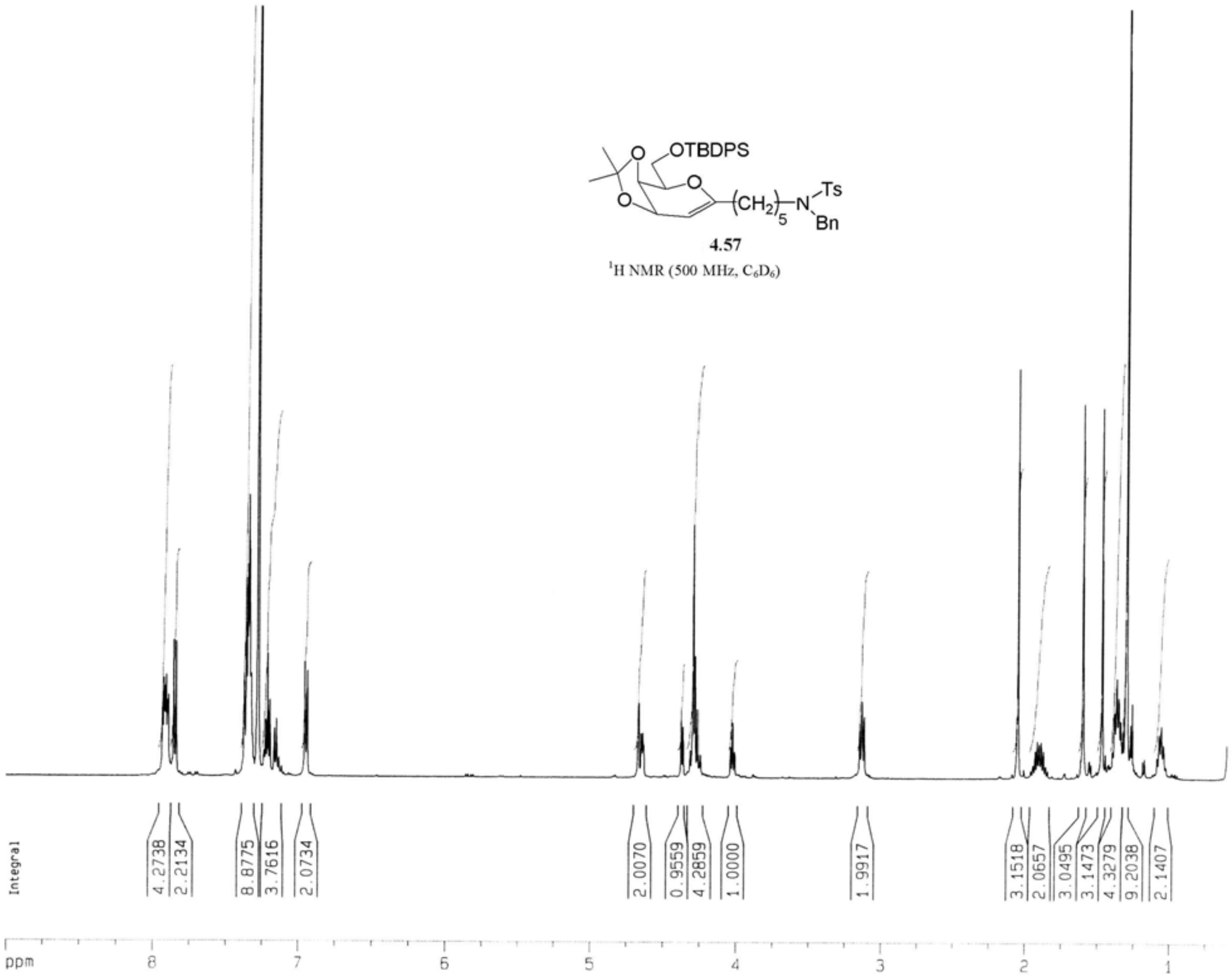
^{1}H NMR (500 MHz, CDCl$_3$)

```
Current Data Parameters
NAME             03030601
EXPNO                   7
PROCNO                  1

F2 - Acquisition Parameter
Date_            20060303
Time                13.04
INSTRUM             spect
PROBHD   5 mm DUL 13C-1
PULPROG              zg30
TD                  32768
SOLVENT              C6D6
NS                      8
DS                      2
SWH              8012.820 Hz
FIDRES           0.244532 Hz
AQ              2.0448356 se
RG                  143.7
DW                 62.400 us
DE                   6.00 us
TE                  294.7 K
D1             1.00000000 se
MCREST         0.00000000 se
MCWRK          0.01500000 se

======== CHANNEL f1 ======
NUC1                   1H
P1                   9.30 us
PL1                 -3.00 dB
SF01          500.1330885 MH

F2 - Processing parameters
SI                  32768
SF            500.1300000 MH
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                  22.00 cm
CY                  22.04 cm
F1P                 9.000 ppr
F1                4501.17 Hz
F2P                 0.500 ppr
F2                 250.06 Hz
PPMCM             0.38636 ppr
HZCM            193.23204 Hz,
```



4.71

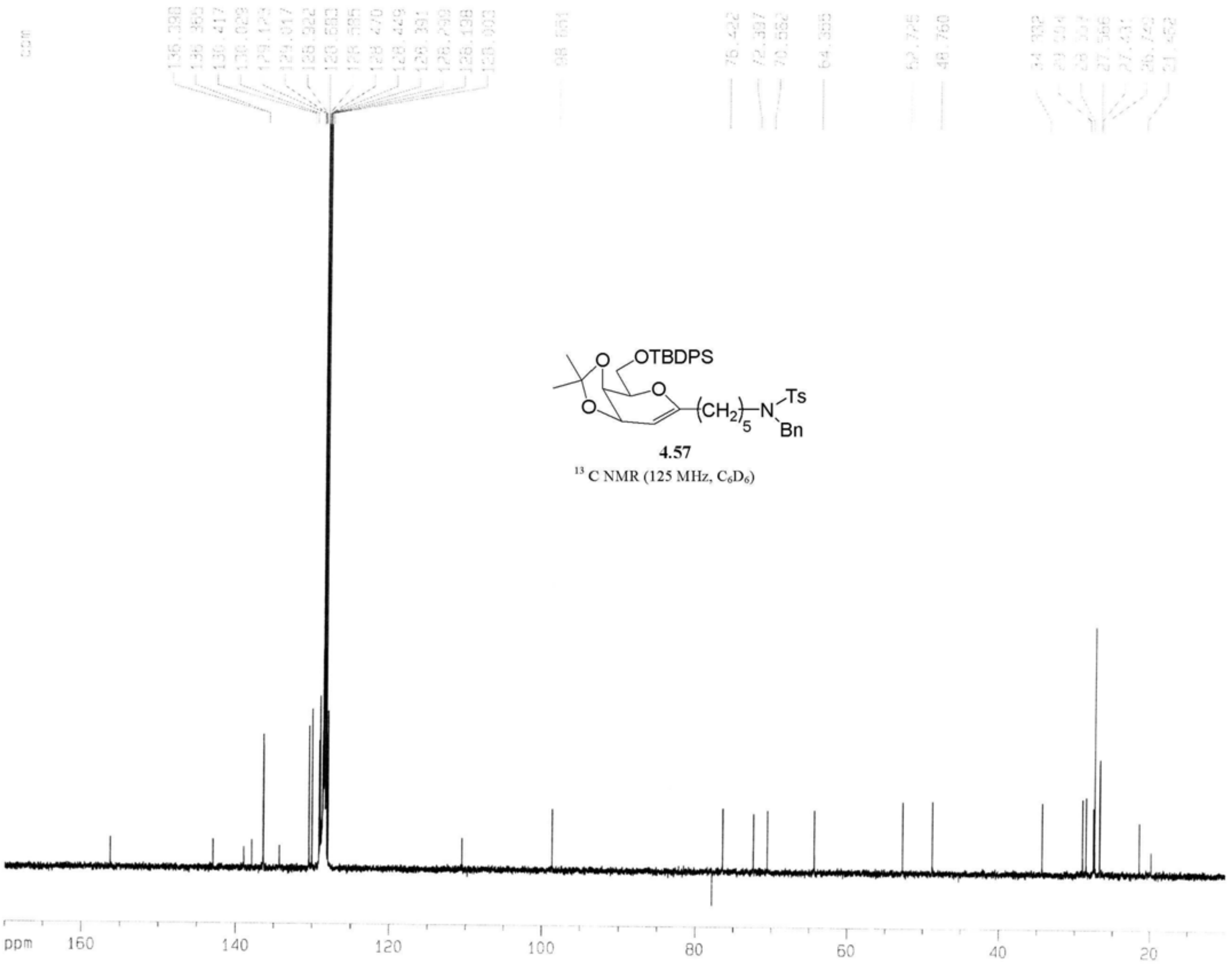
^{13}C NMR (125 MHz, CDCl$_3$)



4.57

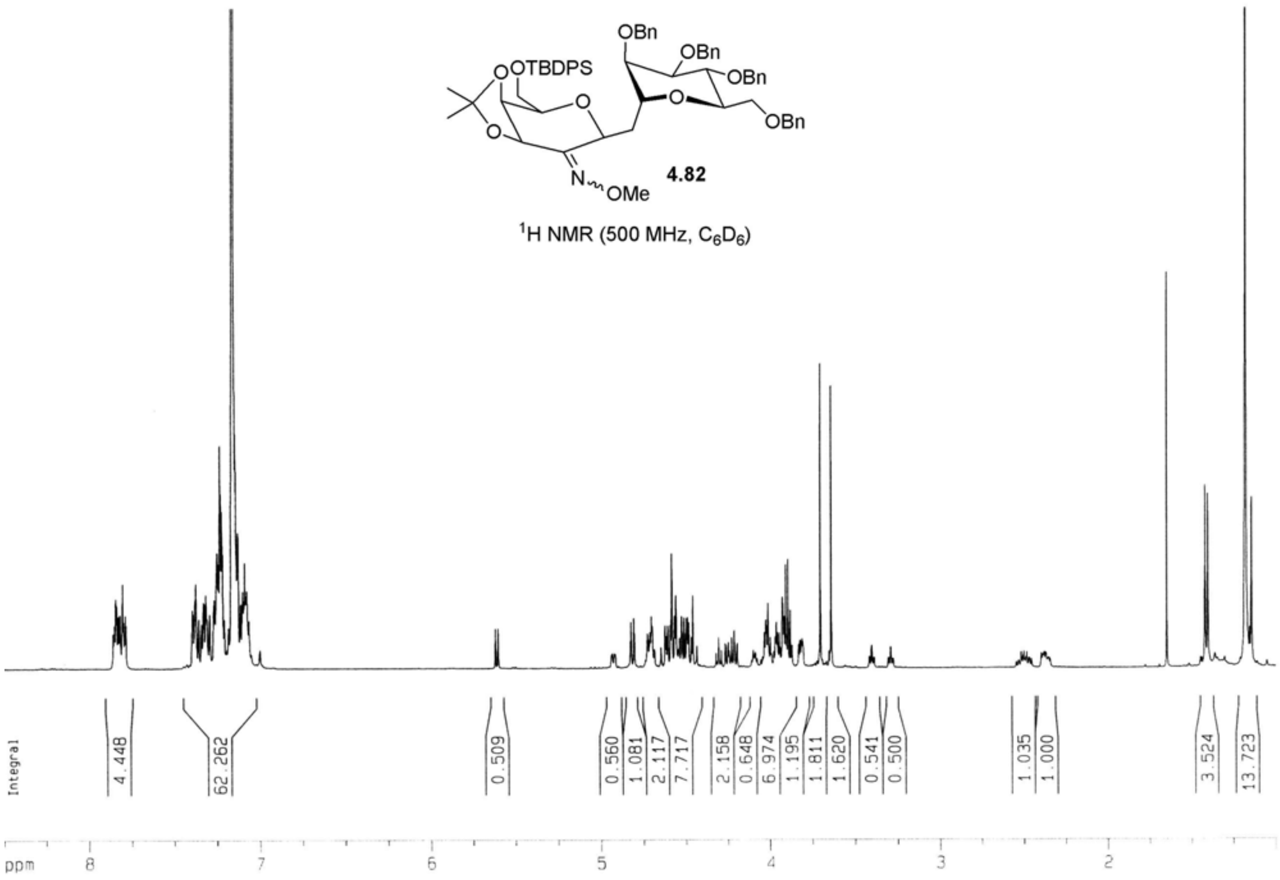
^{1}H NMR (500 MHz, C_6D_6)

```
Current Data Parameters
NAME          09300401
EXPNO                4
PROCNO               1

F2 - Acquisition Paramet
Date_         20040930
Time             14.13
INSTRUM          spect
PROBHD   5 mm DUL 13C-1
PULPROG           zg30
TD               32768
SOLVENT           C6D6
NS                   8
DS                   2
SWH           6666.667 
FIDRES        0.203451 
AQ           2.4577250 
RG                 256
DW              75.000 
DE                6.00 
TE               303.0 
D1          1.00000000 
MCREST      0.00000000 
MCWRK       0.01500000 

======== CHANNEL f1 ====
NUC1                1H
P1                9.30 
PL1              -3.00 
SFO1       500.1330885 

F2 - Processing parameter
SI               32768
SF         500.1300000 
WDW                 EM
SSB                  0
LB                0.30 
GB                   0
PC                1.00

1D NMR plot parameters
CX               22.00 c
CY               25.24 c
F1P              9.000 p
F1             4501.17 H
F2P              0.600 p
F2              300.08 H
PPMCM          0.38182 p
HZCM         190.95872 H
```



4.57

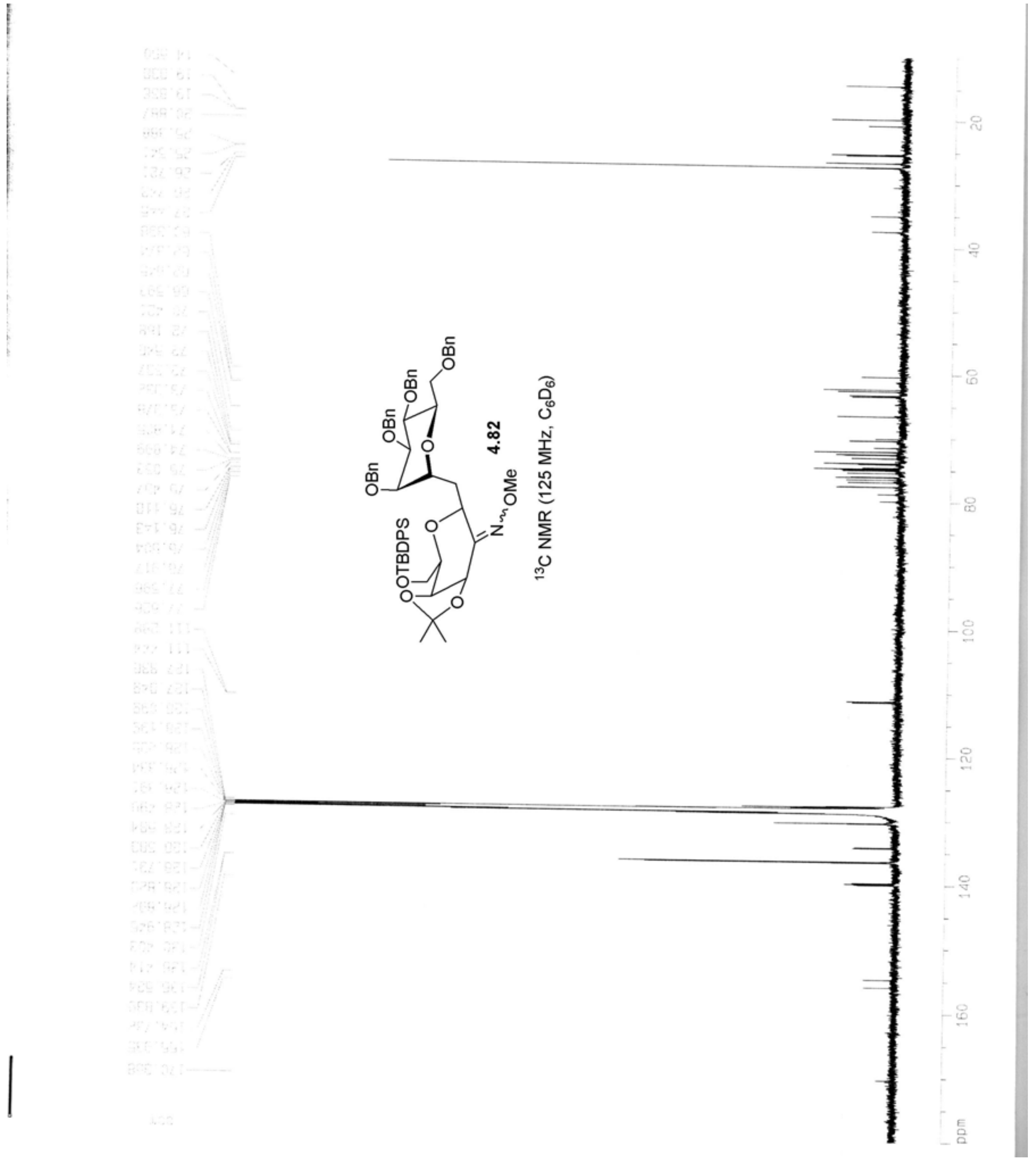
^{13}C NMR (125 MHz, C$_6$D$_6$)



4.82

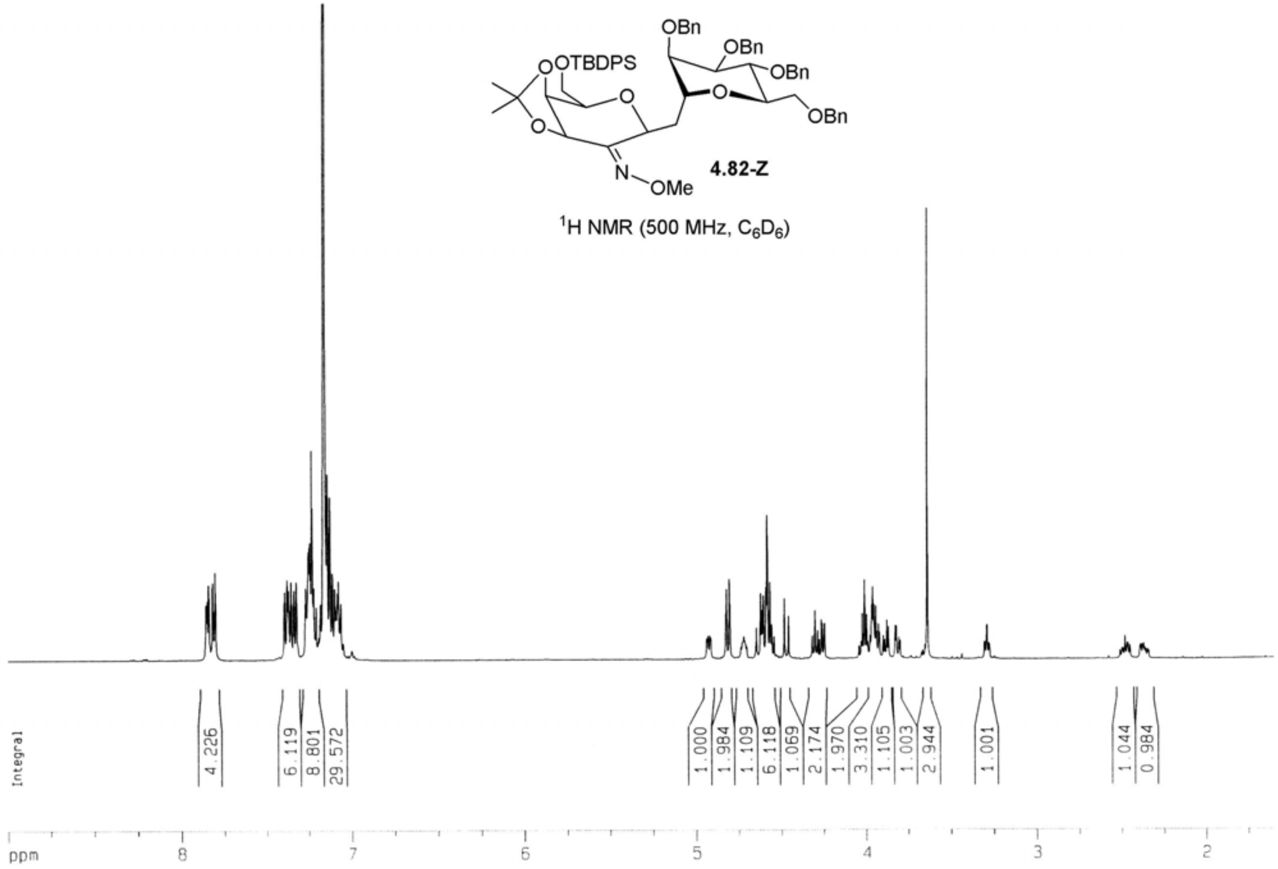
^{1}H NMR (500 MHz, C_6D_6)

```
Current Data Parameters
NAME             11080601
EXPNO                   8
PROCNO                  1

F2 - Acquisition Parameter
Date_            20061108
Time                12.01
INSTRUM             spect
PROBHD   5 mm CPDCH 13C
PULPROG              zg30
TD                  32768
SOLVENT              C6D6
NS                      8
DS                      2
SWH              8012.820 H
FIDRES           0.244532 H
AQ              2.0448356 s
RG                     16
DW                 62.400 u
DE                   6.00 u
TE                  303.0 K
D1             1.00000000 s
MCREST         0.00000000 s
MCWRK          0.01500000 s

======== CHANNEL f1 =====
NUC1                   1H
P1                   9.25 u
PL1                 -0.50 d
SFO1          500.1330885 M

F2 - Processing parameter
SI                  32768
SF            500.1300570 M
WDW                    EM
SSB                     0
LB                   0.30 H
GB                      0
PC                   1.00

1D NMR plot parameters
CX                  22.00 c
CY                  47.83 c
F1P                 8.500 p
F1                4251.10 H
F2P                 1.000 p
F2                 500.13 H
PPMCM             0.34091 p
HZCM            170.49889 H
```



4.82

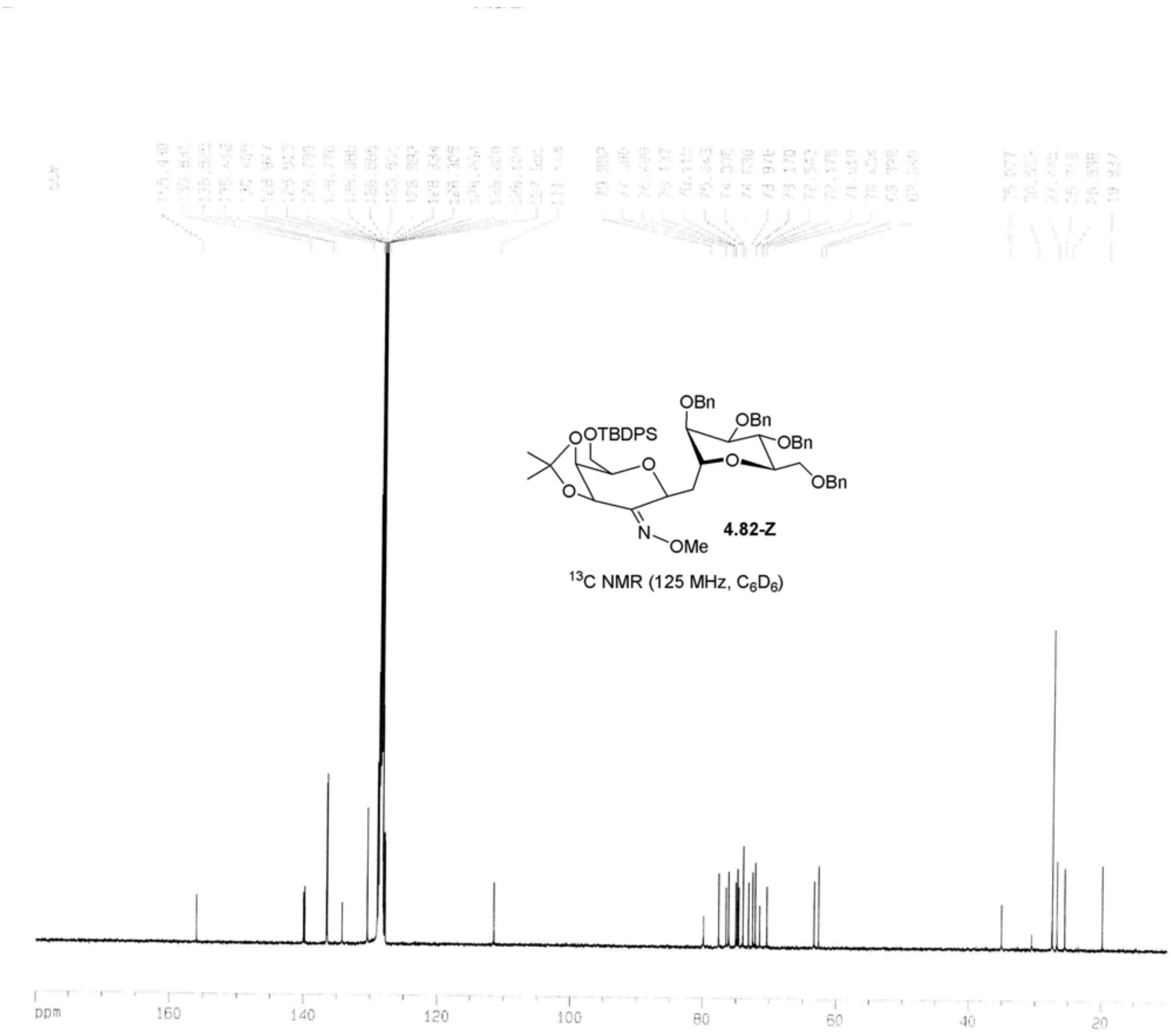
^{13}C NMR (125 MHz, C_6D_6)



4.82-Z

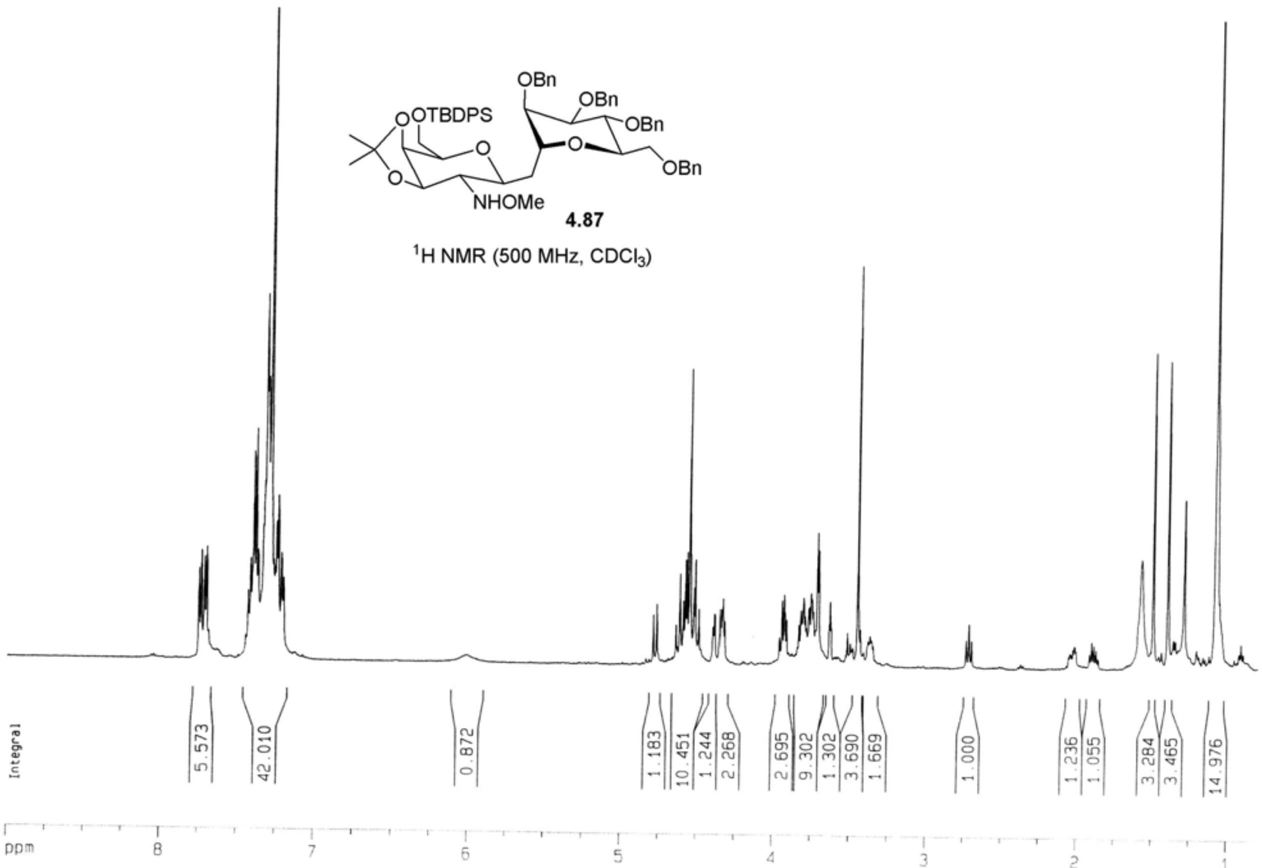
^{1}H NMR (500 MHz, C_6D_6)

```
Current Data Parameters
NAME            11070601
EXPNO                 12
PROCNO                 1

F2 - Acquisition Parameter
Date_           20061107
Time               16.47
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 32768
SOLVENT             C6D6
NS                     8
DS                     2
SWH            8012.820 Hz
FIDRES         0.244532 Hz
AQ            2.0448356 se
RG                  14.3
DW               62.400 us
DE                 6.00 us
TE                303.0 K
D1           1.00000000 se
MCREST       0.00000000 se
MCWRK        0.01500000 se

======== CHANNEL f1 ======
NUC1                  1H
P1                  9.25 us
PL1                -0.50 dB
SFO1         500.1330885 MH

F2 - Processing parameters
SI                 32768
SF           500.1300568 MH
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 22.00 cm
CY                 19.94 cm
F1P                9.000 pp
F1               4501.17 Hz
F2P                1.600 pp
F2                800.21 Hz
PPMCM            0.33636 pp
HZCM           168.22557 Hz
```



4.82-Z

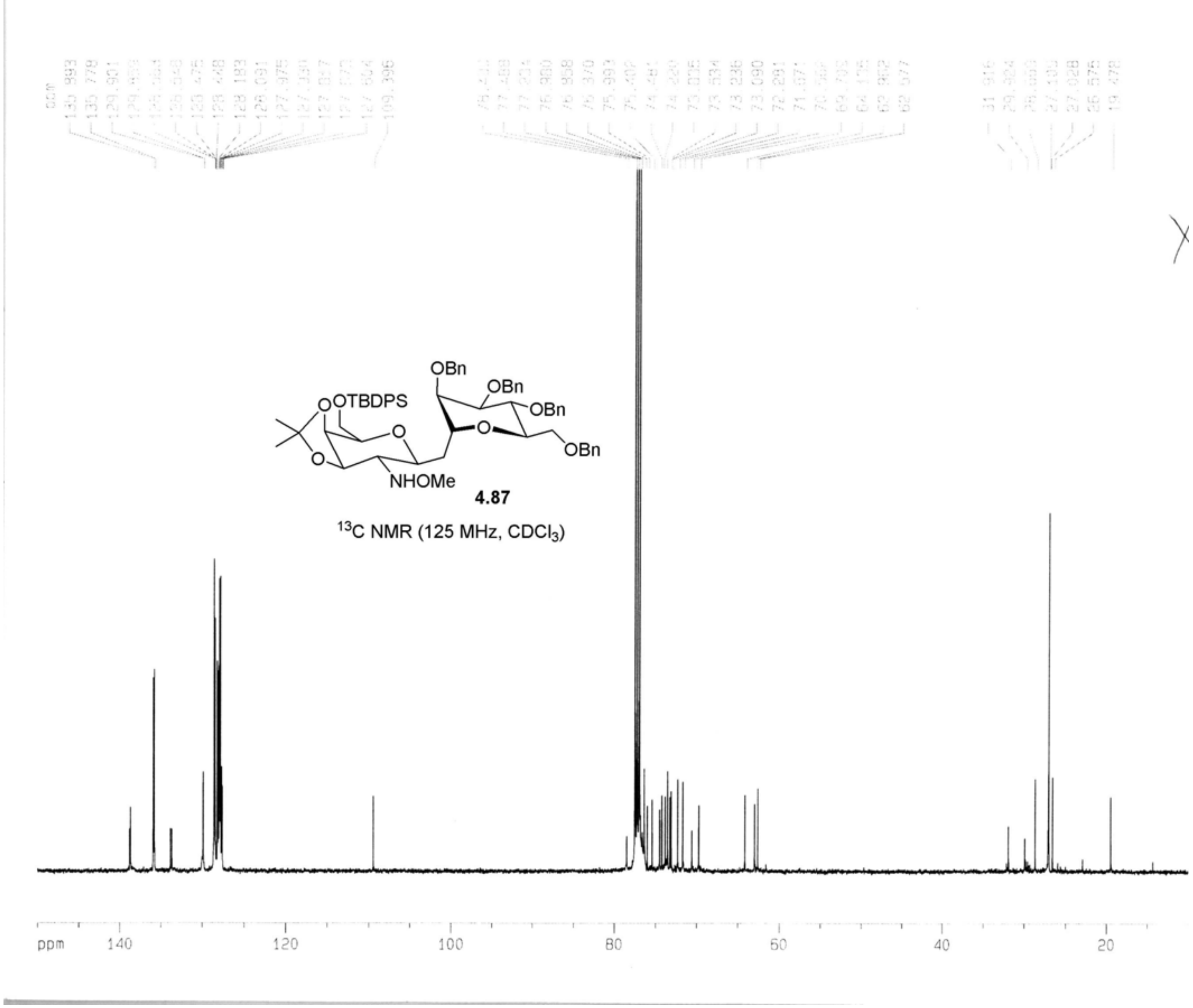
^{13}C NMR (125 MHz, C_6D_6)



4.87

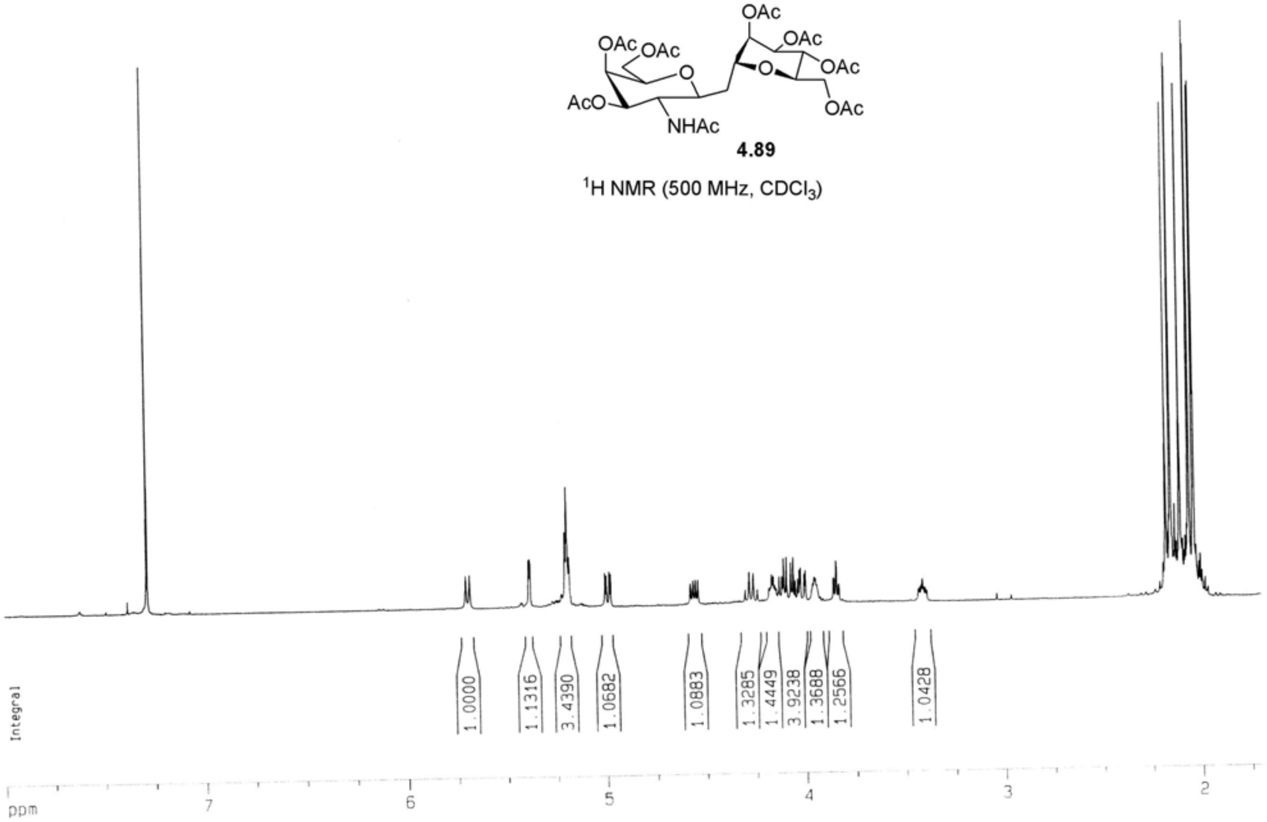
^{1}H NMR (500 MHz, CDCl$_3$)

```
Current Data Parameters
NAME             05220601
EXPNO                   4
PROCNO                  1

F2 - Acquisition Paramete
Date_            20060522
Time                11.15
INSTRUM             spect
PROBHD   5 mm DUL 13C-1
PULPROG              zg30
TD                  32768
SOLVENT              C6D6
NS                     16
DS                      2
SWH              8012.820 H
FIDRES           0.244532 H
AQ              2.0448356 s
RG                    256
DW                 62.400 u
DE                   6.00 u
TE                  303.0 K
D1             1.00000000 s
MCREST         0.00000000 s
MCWRK          0.01500000 s

======== CHANNEL f1 =====
NUC1                   1H
P1                   9.30 u
PL1                 -3.00 d
SF01         500.1330885 M

F2 - Processing parameters
SI                  32768
SF           500.1300000 M
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                  22.00 cm
CY                  20.68 cm
F1P                 9.000 pp
F1                4501.17 Hz
F2P                 0.800 pp
F2                 400.10 Hz
PPMCM             0.37273 pp
HZCM            186.41209 Hz
```



4.87

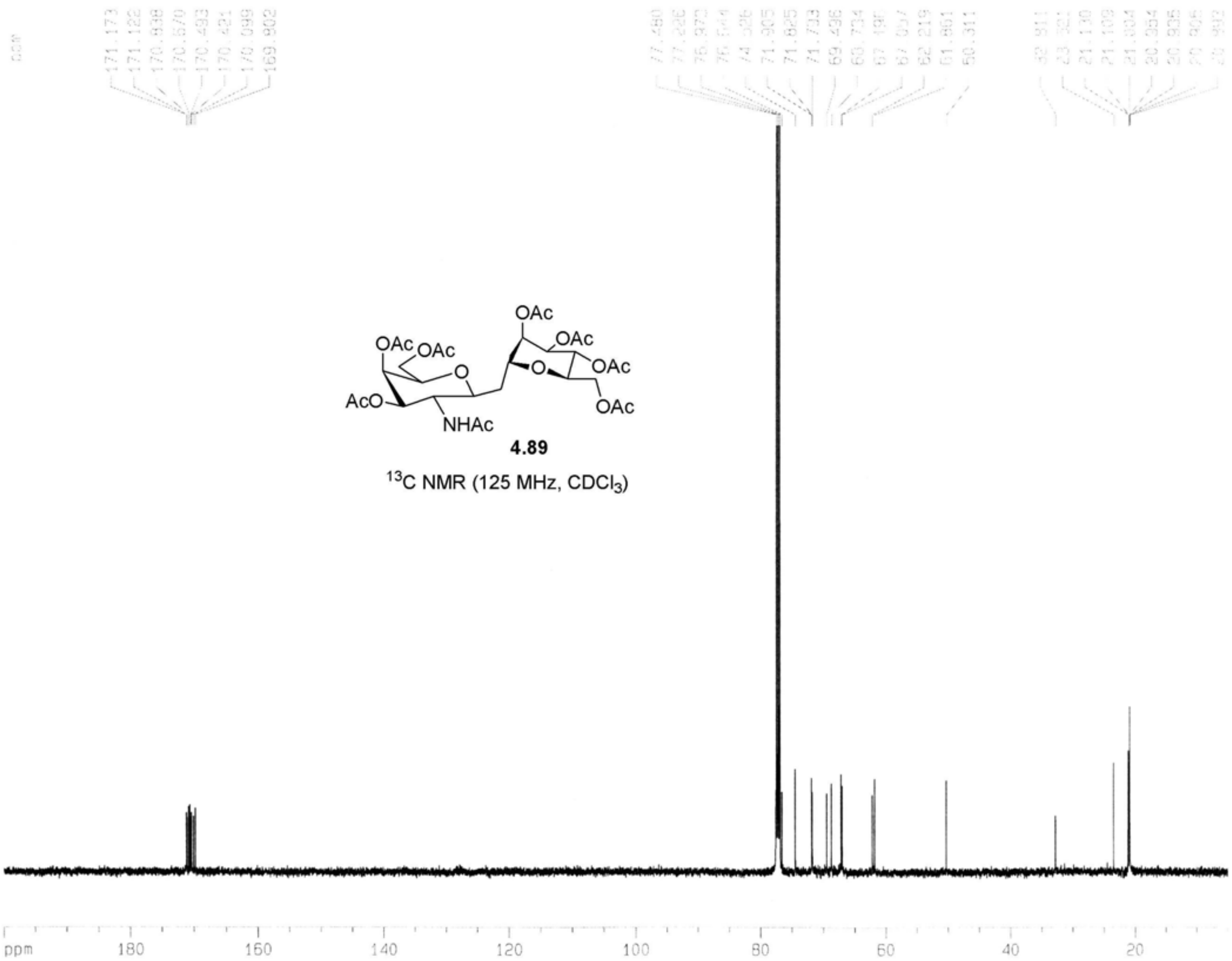
^{13}C NMR (125 MHz, CDCl$_3$)



4.89

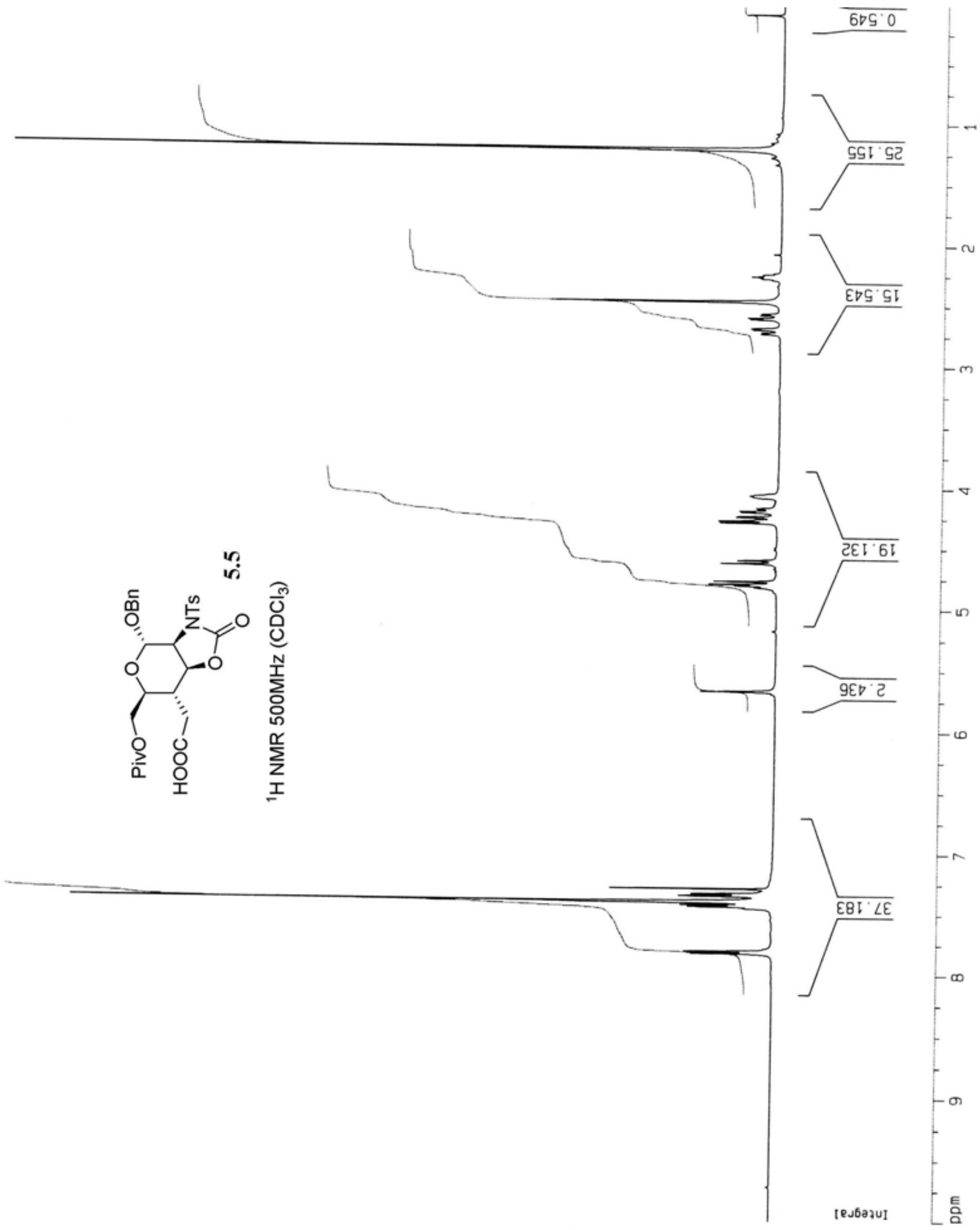
^{1}H NMR (500 MHz, CDCl$_3$)

```
Current Data Parameters
NAME            10300601
EXPNO                 24
PROCNO                 1

F2 - Acquisition Parameters
Date_           20061030
Time               16.39
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 32768
SOLVENT             C6D6
NS                    16
DS                     2
SWH             8012.820 Hz
FIDRES          0.244532 Hz
AQ             2.0448356 se
RG                  14.3
DW                62.400 us
DE                  6.00 us
TE                 304.0 K
D1            1.00000000 se
MCREST        0.00000000 se
MCWRK         0.01500000 se

======== CHANNEL f1 ======
NUC1                  1H
P1                  9.25 us
PL1                -0.50 dE
SF01         500.1330885 MH

F2 - Processing parameters
SI                 32768
SF           500.1300000 MH
WDW                   EM
SSB                    0
LB                  0.30 H:
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 22.00 c
CY                 10.17 c
F1P                8.000 p
F1               4001.04 H
F2P                1.700 p
F2                850.22 H
PPMCM            0.28636 p
HZCM           143.21904 H
```



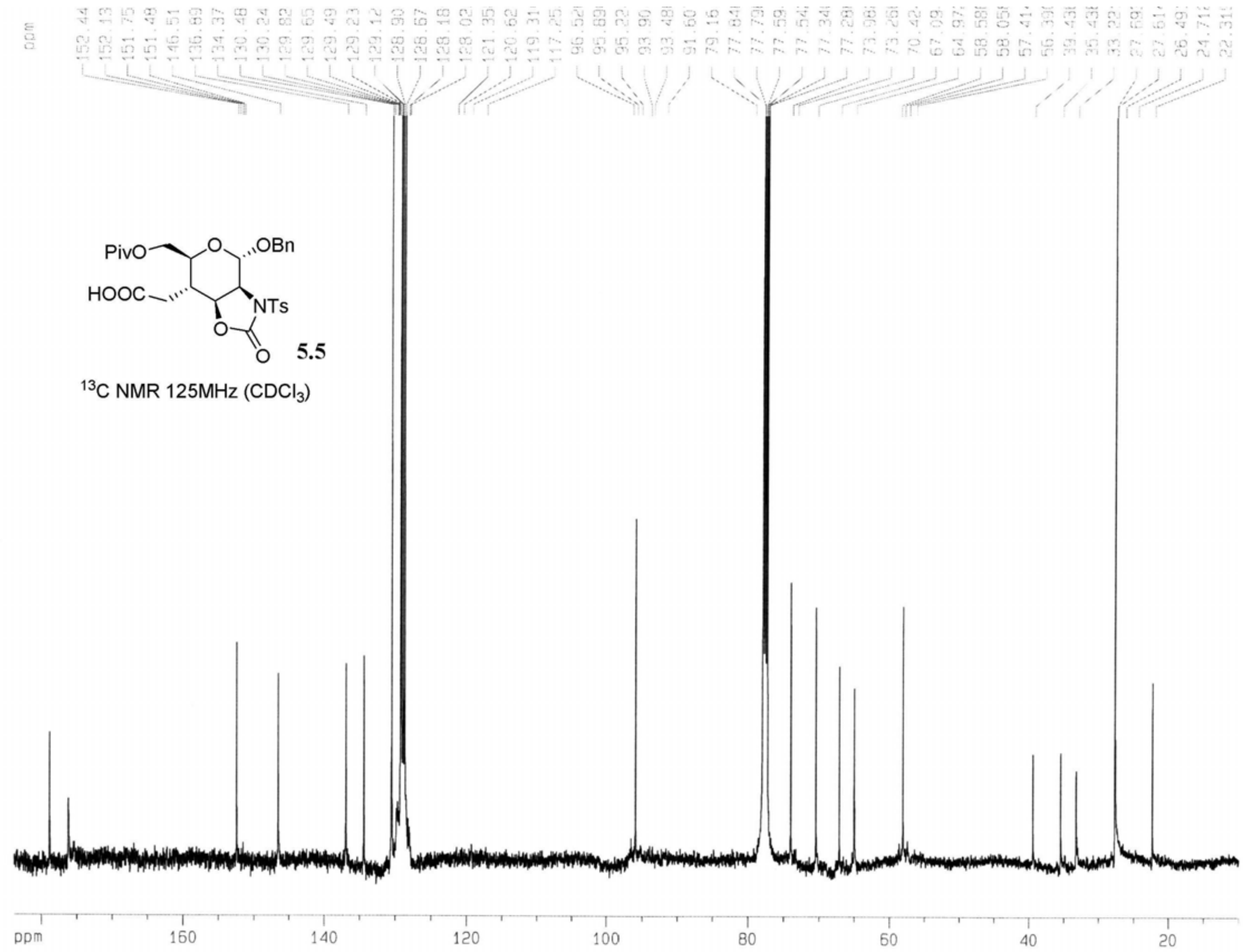
4.89

^{13}C NMR (125 MHz, CDCl$_3$)



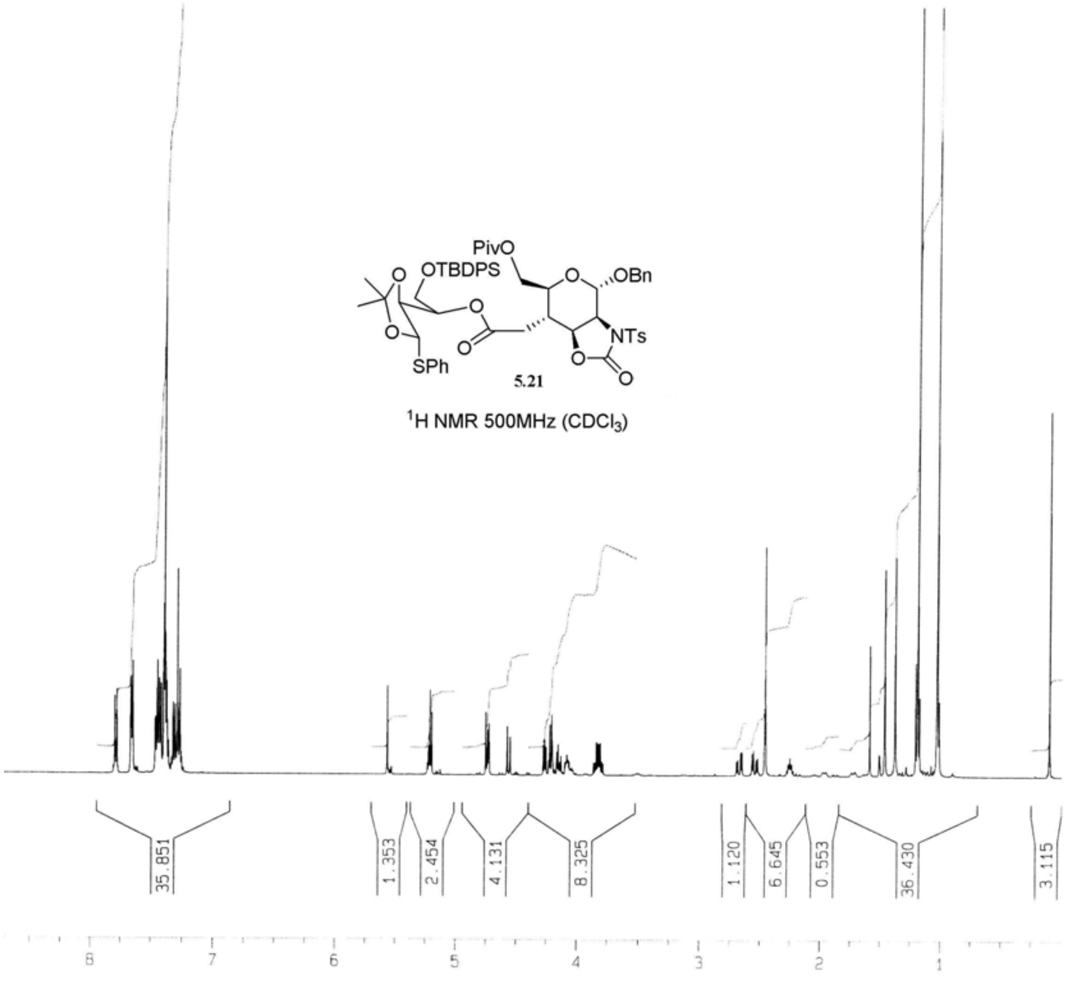
5.5

^{1}H NMR 500MHz (CDCl$_3$)



5.5

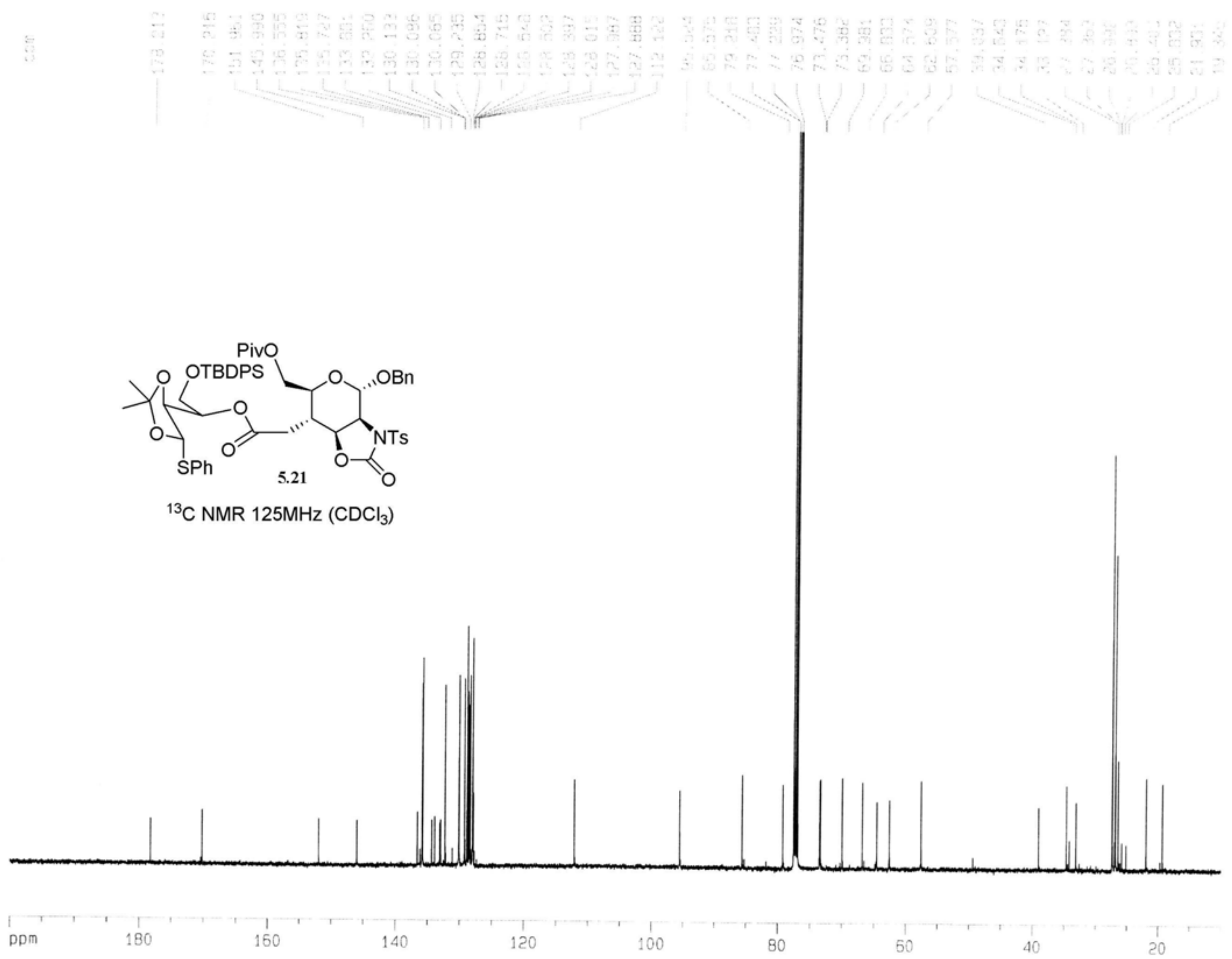
^{13}C NMR 125MHz (CDCl$_3$)



5.21

^{1}H NMR 500MHz (CDCl$_3$)

```
Current Data Parameters
NAME            10250601
EXPNO                 22
PROCNO                 1

F2 - Acquisition Parameter
Date_           20061025
Time               17.27
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 32768
SOLVENT             C6D6
NS                     8
DS                     2
SWH          8012.820 Hz
FIDRES       0.244532 Hz
AQ          2.0448356 se
RG                  14.3
DW            62.400 us
DE              6.00 us
TE              304.0 K
D1         1.00000000 se
MCREST     0.00000000 se
MCWRK      0.01500000 se

======== CHANNEL f1 ======
NUC1                  1H
P1               9.25 us
PL1             -0.50 dB
SFO1      500.1330885 MH

F2 - Processing parameters
SI                 32768
SF        500.1300000 MH
WDW                   EM
SSB                    0
LB               0.30 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX              22.00 cm
CY              20.98 cm
F1P            10.000 ppr
F1            5001.30 Hz
F2P             0.000 ppr
F2               0.00 Hz
PPMCM         0.45455 ppr
HZCM        227.33182 Hz/
```



5.21

^{13}C NMR 125MHz (CDCl$_3$)

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