PART A:
SYNTHESIS OF MANNOSIDE GLYCANS OF PHOSPHATIDYLINOSITOL MANNOSIDES (PIMs)

PART B:
SYNTHETIC STUDIES TOWARDS BIELSCHOWSKY SIN MACROCYCLES

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NATIONAL UNIVERSITY OF SINGAPORE
2011
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SYNTHETIC STUDIES TOWARDS BIELSCHOWSKYSIN MACROCYCLES

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Dedication

This thesis is dedicated to all my parents and family members particularly, my wife, Praveena for her immense and incredible support and understanding all through my graduate studies and my cute, lovely daughter Krithika, who become a charming relief to me with her smile every time.
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Summary

The first part of my Ph.D research concentrates on the synthesis of the mannoside glycan portion of phosphatidylinositol mannoses (PIMs). Initially, PIM-6 was sought to provide mechanistic insights into tuberculosis by pathogenic mycobacteria. Preliminarily, a convergent approach was attempted towards the pentamannoside. Later a new and novel synthetic plan was designed to study all homologues of PIMs in order to fully understand the immunogenic roles of PIMs. Accordingly, a linear synthesis of the glycan portion was adopted via the in situ glycosylation method with 1,2-orthoester. This linear synthesis enabled the synthesis of a series of mannoside glycans of PIM-1, PIM-2, PIM-3, PIM-4, PIM-5 and PIM-6 all with terminally differentiated protecting groups that would facilitate future tagging of desired linkers for immunogenic studies of PIMs.

The major part of my research work focused on synthetic studies towards the synthesis of bielschowskysin macrocycles, a highly oxygenated diterpene cembrane isolated in 2004 from *Pseudopterogorgia kallos*. This unprecedented hexacyclic fused ring skeleton displays promising antiplasmodial and anticancer properties. We planned the synthesis of the bielschowskysin carbon framework through the transannular [2+2] cycloaddition of an allene butenolide macrocycle as the key strategy to install the cyclobutane nucleus.

Our efforts initially focused on synthesizing a transannular [2+2] model macrocycle of bielschowskysin (Chapter 2). We recognized a macrocycle encompassing an allene and a butenolide would be made via a ring closing metathesis (RCM)-lactonization or macrolactonization-RCM sequence from linear precursors.
The aldehyde building block was prepared in 8 steps from (S)-malic acid and the alkyne unit from oct-3-yn-1-ol in 3 steps. These building blocks were assembled by acetylide-aldehyde coupling to give a propargylic alcohol that was subsequently converted to an allene by Myers conditions using o-nitrobenzenesulfonylhydrazine (NBSH). After introduction of a conjugated ester by Baylis-Hillman coupling, a macrocyclization study by RCM was not successful. In order to achieve the macrocycle, a seco-acid was obtained by saponification and subsequent Yamaguchi conditions smoothly formed a macrolactone. Again, RCM study with Grubbs I/Grubbs II catalyst to install the butenolide unit was not successful.

Chapter 3 of the thesis focused on the synthesis of bielschowskysin based building blocks. The target molecule was disconnected into two building blocks. The alkyne fragment was synthesized from (S)-malic acid. The conjugated aldehyde synthon was prepared from D-glucose and coupled with an alkyne fragment.

Chapter 4 focused on the synthetic studies of the highly hindered α-(tert)-hydroxy 1,3-disubstituted allene with quaternary carbon centers on both sides. An allene forming reduction protocol was studied on diastereomeric as well as chiral defined propargylic ethers. It was found that the unprotected hydroxyl group was necessary for LiAlH₄ based reductive formation of hindered disubstituted allene from propargylic ethers.

Chapter 5 concentrated on modified methods for the synthesis of aldehyde intermediates, coupling with alkyne synthons, and RCM studies. A terminal alkene was introduced into a D-glucose derived building block via Fe-catalyzed sp²-sp³ coupling and eventual coupling of the alkyne using Grignard exchange protocol gave the propargylic alcohols as
a separable mixture of the diastereomers. While the C5-TES ether was found inert during RCM conditions, the C5-methyl ether gave the desired 14-membered model macrocycle in low yield. RCM reaction with the Grubbs II and Hoveyda-Grubbs II catalysts brought about the macrocyclization with equal productivity and reaction pattern. In conclusion, a RCM route to the carbon framework of bielschowskysin was achieved.

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Abbreviations

4Å MS  4Å molecular sieves
Ac  acetyl
acac  acetylacetonyl
AIBN  2,2′-azo bis(isobutyronitrile)
aq.  aqueous
Ar  aryl
B3LYP  Becke, three-parameter, Lee-Yang-Parr
Bn  benzyl
Bu  butyl
BuLi  butyl lithium
Bz  benzoyl
calcd  calculated
CAN  Ceric ammonium nitrate
cat.  catalytic
CBS  Corey-Bakshi-Shibata
Conc.  concentrated
CM  cross metathesis
CSA  camphorsulfonic acid
cy  cyclohexyl
Δ  heat
DABCO  1,4-diazabicyclo[2.2.2]octane
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DCC  dicyclohexylcarbodiimide
DCM  dichloromethane
DDQ  2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD  diethyl azodicarboxylate
DFT  density functional theory
DIBALH  diisobutylaluminium hydride
DIPEA  N,N-diisopropylethylamine (Hünig’s base)
DMAP  N,N-4-dimethylaminopyridine
DMF  \(N,N\)-dimethylformamide

DMP  Dess-Martin periodinane

DMSO  dimethylsulfoxide

dr  diasteromeric ratio

ee  enantiomeric excess

ESI-MS  electrospray ionization mass spectrometry

Et  ethyl

Grubbs I (or) G I  Grubbs 1\textsuperscript{st} generation catalyst

Grubbs II (or) G II  Grubbs 2\textsuperscript{nd} generation catalyst

GGPP  geranylgeranyl pyrophosphate

h  hour

HG II  Hoveyda-Grubbs 2\textsuperscript{nd} generation catalyst

HMDS  1,1,1,3,3,3-hexamethyldisilazane

HMPA  \(N,N,N',N',N'',N''\)-hexamethylphosphoric triamide

HMQC  heteronuclear multiple quantum coherence

HMTA  hexamethylenetetramine (urotropin)

HRMS  high resolution mass spectrum

hv  irradiation with light

i  iso

Im  imidazole

IR  infrared

L  ligand

LAH  lithium aluminum hydride

LAM  lipoarabinomannan

LC-MS  liquid chromatography-mass spectrometry

LDA  lithium diisopropylamide

LHMDS (or) LiHMDS  lithium bis(trimethylsilyl)amide

LM  lipomannan

M  Molar or mol/litre

m  meta

Me  methyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>full form</th>
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<tbody>
<tr>
<td>Mes</td>
<td>Mesityl (2,4,6-trimethylphenyl)</td>
</tr>
<tr>
<td>mg</td>
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</tr>
<tr>
<td>min</td>
<td>minute</td>
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<tr>
<td>mL</td>
<td>milliliter</td>
</tr>
<tr>
<td>MM2</td>
<td>molecular mechanics 2</td>
</tr>
<tr>
<td>mmol</td>
<td>millimol</td>
</tr>
<tr>
<td>MNBA</td>
<td>2-methyl-6-nitrobenzoic anhydride</td>
</tr>
<tr>
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<td>methoxymethyl</td>
</tr>
<tr>
<td>MS</td>
<td>o-mesitylenesulfonyl</td>
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<tr>
<td>n</td>
<td>normal (e.g., unbranched alkyl chain)</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>sodium bis(trimethylsilyl)amide</td>
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<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
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<td>PIMs</td>
<td>phosphatidylinositol mannosides</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>PMB</td>
<td>p-methoxybenzyl</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>psi</td>
<td>pounds per square inch</td>
</tr>
</tbody>
</table>
$p$-TSA  $p$-toluenesulfonic acid
Py  pyridine
RCM  ring closing metathesis
RT  room temperature
$s$ (or) $sec$  secondary
$S_N1$ or $S_N2$  nucleophilic substitution
$t$ (or) $tert$  tertiary
TBAF  tetra-$n$-butylammonium fluoride
TBAI  tetra-$n$-butylammonium iodide
TBDPS  $t$-butyldiphenylsilyl
TBS  $t$-butyldimethylsilyl
TCA  trichloroacetimidate
TCBC  2,4,6-Trichlorobenzoyl chloride
TES  triethyl silyl
TESOTf  triethylsilyl trifluoromethanesulfonate
Tf  triflate (trifluoromethanesulfonate)
TFA  trifluoroacetic acid
THF  tetrahydrofuran
THP  2-tetrahydropyranyl
TIPS  triisopropylsilyl
TLC  thin layer chromatography
TLR  toll-like receptor
TMEDA  tetramethylethlenediamine
TMS  trimethylsilyl
TMSOTf  trimethylsilyl trifluoromethanesulfonate
Tr  trityl (triphenylmethyl)
Ts  $p$-toluene sulfonyl
uv  ultraviolet
PART A

SYNTHESIS OF MANNOSIDE GLYCANS OF PHOSPHATIDYLINOSITOL MANNOSIDES (PIMs)
1 Background and Introduction

1.1 Phosphatidylinositol Mannosides (PIMs) and Tuberculosis

Tuberculosis (TB) is one the most deadly infectious diseases among the global population and is attributed to cause two million deaths per year. The causative organism of the disease is the acid-fast pathogenic bacteria, *Mycobacterium tuberculosis*. The cell-wall of *M. tuberculosis* is enveloped by a ‘glycocalyx’ which is critical for the integrity of the pathogen that allows infection, survival and propagation in the host.\(^1\) The key components of mycobacterial cell-wall are mycolyl arabinogalactan-peptidoglycan complex (mAGP) and the lipoarabinomannan (LAM) associated lipoglycans. LAMs contain a phosphatidyl myo-inositol anchor that is extended by mannoses to make up phosphatidylinositol “mono”, “di”, “tri”, and “tetramannosides” (PIM-1, PIM-2, PIM-3, PIM-4) and can be further extended by \(\alpha 1\rightarrow 2\) linked mannose to pentamannosides and hexamannosides (PIM-5, PIM-6) (Fig 1). Modification of this lipoglycan backbone with additional mannose linkages results in a branched lipomannann which upon further arabinosylation, forms LAMs.\(^2\)

PIMs are present in the cell-walls of mycobacteria mainly in the form of PIM-2 and PIM-6 (1) and constitute biosynthetic precursors of the lipomannan core and LAMs. This specialized, protective envelope gives *M. tuberculosis* high resilience to external factors such as the cytotoxic oxygen radicals that are generated by human macrophages upon infection. Additionally, PIMs elicit a range of immune responses and act as agonists of toll-like receptor 2 (TLR2) that are involved in innate immunity.\(^3\) They are also known to

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\(^1\) Mycobacterium tuberculosis

\(^2\) Arabinosylation

\(^3\) TLR2

---
recruit natural killer T-cells\(^{3b,4}\) and cause T-cell expansion via binding to the lipid presentation molecule, CD1b.\(^{3b,5}\)

**Fig 1**: Structural Features of PIMs, LM, and LAM

### 1.2 Previous Synthesis of PIMs: Seeberger 4+3 Coupling

There are few reports on the synthesis of PIMs\(^6\), among which only the Seeberger group has reported a total synthesis of PIM-6 (1) via a 4+3 coupling method of the mannose unit 2 with the \textit{myo}-inositol part 3\(^{6c}\).

The tetramannoside building block 2 in turn has been synthesized by reacting mannosyl-trichloroacetimidate donor 4 with alcohol 5 to get a dimannoside, followed by
deprotection of the acetyl group and subsequent iterative glycosylation with the same unit until reaching the tetramannoside (Scheme 1).

Scheme 1: Seeberger Approach to PIM-6

**Scheme 1:** Seeberger Approach to PIM-6$^{6c}$
2 PIMs: 1\textsuperscript{st} Generation Synthetic Plan

To elaborate our understanding of the immunogenic roles of such glycolipids, we started the synthesis of PIMs. A new 5+2 coupling protocol was intended as the key strategy to construct full length PIMs (Scheme 2) in which pentamannoside 6 will be coupled to PIM-1 (7).

![Scheme 2: A 5+2 Coupling Approach to PIMs](image)

2.1 Mannoside Glycan Synthetic Plan 1: A Convergent 3+2 Approach

The pentamannoside unit 6 of PIMs has linear $\alpha 1\rightarrow 2$, $\alpha 1\rightarrow 2$, $\alpha 1\rightarrow 6$, $\alpha 1\rightarrow 6$ glycosidic linkages between monomeric pyranono-mannoses. Thus, the pentamannoside was
envisioned to be built-up via the convergent assembly of trimannoside 9 and dimannoside 10 through $\alpha_1\rightarrow 6$ glycosylation (Scheme 3). The 9 and 10 intermediates could be prepared independently from suitably protected monomeric mannose building blocks.

Scheme 3: A Convergent 3+2 Coupling Approach for Pentamannoside Glycan

2.2 Synthesis of Mannose Building Blocks

2.2.1 Schmidt Donor of Mannose

Mannose was allylated at the anomeric position to give allyl mannose 14 by using BF$_3$ as the catalyst in good yield (Scheme 4). Benzylation of 14 gave the fully protected mannose 15 in 90% yield. The allyl group at the anomeric position was isomerized to propenyl ether by treating with a strong base (KOr-Bu) and subsequent treatment with dilute HCl gave the anomeric free alcohol 16 in quantitative yield. This alcohol was
converted to a trichloroacetimidate 11, a Schmidt donor, in good yield by CCl₃CN in the presence of DBU.⁷

**Scheme 4**: Synthesis of Mannose as a Protected Schmidt Donor 11

### 2.2.2 Mannose With Accessible C2-Hydroxyl Group

**Scheme 5**: Synthesis of C2-Hydroxyl Mannose 12
A stable 6-membered benzaldehyde-dioxane \(17\) was formed between the C4 and C6 hydroxyl groups by treating allyl mannose \(14\) with benzaldehyde dimethyl acetal. From the remaining two hydroxyl groups, protection of the C3-hydroxyl group as its corresponding benzyl ether with stoichiometric reagents (NaH/BnBr) gave all three benzylated possible products. The major product isolated was desired C3-OBn \(12\) in 47% yield (Scheme 5). The free hydroxyl group of this mannose acceptor \(12\) was later engaged in Schmidt glycosylation with the trichloroacetimidate \(11\).

### 2.3 Glycosylation Attempt Towards Dimannoside

With both coupling partners in the hand, the first glycosylation was set as per designed. Thus, Lewis acid mediated glycosyl bond formation between the trichloroacetimidate donor \(11\) and slight excess of alcohol acceptor \(12\) (1.1 eq) proceeded with complete consumption of the donor forming the dimannoside \(18\) (Scheme 6).

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**Scheme 6: Glycosylation to Make Dimannoside 18**
All attempts to purify the dimannoside, however, led to elution of both the dimannoside and acceptor compounds during silica gel column chromatography. Separation at the dimannoside stage and further removal of the allyl group in the presence of the acid sensitive benzylidene acetal ring hampered synthetic progress towards the desired pentamannoside.

3 PIMs: 2\textsuperscript{nd} Generation Synthetic Plan

Scheme 7: PIMs: 2\textsuperscript{nd} Generation Synthetic Plan
In the meantime, we were planning to study the immunogenic roles of PIMs. Immunogenic roles of all homologues of PIM-1, PIM-2, PIM-3, PIM-4, PIM-5 and PIM-6 in order to fully understand the immunogenic roles of PIMs. Accordingly, a new plan for PIMs was formulated so as to make all homologues of PIMs (Scheme 7). This idea required several different mannose glycan units: monomannoside, dimannoside, trimannoside, tetramannoside and pentamannoside. Such glycan units could be synthesized in a linear fashion using monomeric mannose synthons. Importantly, the linear addition of mannose units would require an efficient glycosylation method.8

3.1 Seeberger *in situ* Glycosylation Method

Seeberger *et al.* in 2006 reported the application of glycosyl phosphates 20 generated *in situ* from 1,2-orthoesters 19 as an efficient glycosylation coupling method.9 1,2-Orthoesters upon treatment with dibutyl phosphate generate a stable (and isolable) anomeric phosphate 20 with C2-ester group. During the second step of this one pot reaction, the phosphate in the presence of a Lewis acid, TMSOTf, and molecular sieves at low temperature, initiates glycosyl bond formation with an alcohol (e.g. 21), furnishing a diglycoside 22 with a C2-ester group, typically in excellent yield (Scheme 8).
3.2 Synthetic Plan 2: Iterative *in situ* Coupling of Mannose 1,2-Orthoesters

Due to practical difficulties in the purification of dimannosides, a new synthetic plan for all variations of PIMs was formulated as depicted in Scheme 9.

Here, the dimannoside would be made by regular Schmidt glycosylation between the acetimidate 25 and alcohol 26. Thereafter, *in situ* dibutyl phosphate mediated coupling method in an iterative fashion would propagate to tri- and tetramannosides (Scheme 9).

![Scheme 9: Linear Synthetic Plan for Mannoside Glycan of PIMs](image)

Ultimately, either acetimidate intermediate 11 or 25 could be used in the final glycosylation coupling step with a tetramannoside to complete a pentamannoside glycan (23 or 24), where the case with 24 would lead to a full length PIMs with a selectively accessible hydroxyl group at the primary carbon of the mannose chain.
3.3 Synthesis of Mannose Building Blocks

3.3.1 Mannose with Accessible 1,6-Hydroxyl Groups

In order to synthesize all di-, tri-, tetra- and pentamannosides the simplest building blocks were synthesized with differential protecting groups from commercially available D-mannose.

The mannose acceptor 26 and acetimidate 30 with selectively accessible C6-silyl protecting group were synthesized as shown in Scheme 10.

Initially, the relatively bulky and stable TBS group was used to selectively protect the C6 hydroxyl group of allyl mannose 14; however, this lead to a mixture of products, possibly due to over silylation, therefore a more bulky trityl group was employed at the C6-hydroxyl of allyl mannose to give the allyl-trityl mannose 27 in 85% yield. Blocking all
remaining three hydroxyls with benzyl groups gave a fully protected mannose, which upon treatment with CSA mediated removal of the primary $O$-trityl group giving the acceptor intermediate $26$ (Scheme 10).

Subsequent protection of the primary hydroxyl group with TBS group $28$, followed by removal of the allyl group produced the anomeric hydroxyl intermediate $29$. From here tagging with trichloroacetonitrile furnished the Schmidt donor $30$ in good yield.

### 3.3.2 Synthesis of Methoxy-1,2-Orthoester of Mannose

The 1,2-orthoester of mannose $19$ that would be used for iterative amplification of mannose units by *in situ* dibutyl phosphate mediated glycosylation was constructed from bromo-mannose (Scheme 11) following a reported protocol.$^9$ Perbenzoyl mannose $31$ was obtained by treating $D$-mannose with benzoyl chloride (as the solvent) in the presence of pyridine base. The anomeric benzoyl group of the perbenzoyl mannose was
displaced with HBr to give the bromide 32. Orthoester formation by methanol in the presence of 2,6-lutidine gave the 1,2-orthoester intermediate 33. Deprotection of the three benzoate groups to the trihydroxy mannose 34 and reprotecting with more stable benzyl groups furnished the desired 1,2-orthoester of mannose 19.

3.4 Optimizing in situ Coupling Method; Synthesis of a Model Trimannoside

Having all building blocks in the hand, optimization of the in situ dibutylphosphate mediated coupling method was pursued. Particularly, the coupling method was tested at an advanced stage. To this end, a slight excess of azeotropically pre-dried orthoester intermediate 19 (1.2 eq) in the presence of dibutyl phosphate and molecular sieves was converted to the anomeric glycosyl phosphate, which was utilized for in situ glycosylation with acceptor 26 in the presence of excess Lewis acid, TMSOTf (3.6 eq). This method of glycosylation cleanly produced the dimannoside 35, but with incomplete conversion during the second event (Scheme 12).
Part A: Synthesis of Mannoside Glycans of Phosphatidylinositol Mannosides (PIMs)

Scheme 12: Optimizing in situ Glycosylation

Thereafter, the C2-benzoyl group was removed quantitatively from the C2-position of the dimannoside to give the alcohol 36 using NaOMe/MeOH in DCM. This alcohol was treated again under similar dibutylphosphate mediated coupling conditions with 19 to give the trimannoside 37. Here again, the reaction was incomplete, possibly due to the high sensitivity of the reaction to moisture and dilution of reaction. Nevertheless, the reaction was productive for making the pentamannoside.
3.5 Synthesis of Mannoside Glycan Units of PIMs

3.5.1 Synthesis of Dimannoside of PIMs

The planned glycan synthesis commenced with Schmidt glycosylation of the acetimidate donor 30 with the acceptor 26 to afford α1→6 linked dimannoside 38 in 70% yield (Scheme 13). Deprotection of the silyl ether with TBAF\(^{11}\) gave 39 for the next coupling step to build the mannose units in a linear fashion.

![Scheme 13: Synthesis of Dimannosides](image)

3.5.2 Iterative Glycosylation: Synthesis of Tri-, Tetramannoside Glycan Units of PIMs

A slight excess of the mannose 1,2-orthoester intermediate (19; 1.2 eq) in the presence of dibutyl phosphate generated an anomeric glycosyl phosphate *in situ* which was α1→6 glycosidated with the dimannoside acceptor 39 in the presence of excess TMSOTf to yield the trimannoside 40 in quantitative yield.\(^9\) Releasing the C2-hydroxyl group of this trimannoside by transesterification of benzoate to 41, and repeating a similar *in situ*
glycosylation afforded the tetramannoside 42 in near quantitative yield. Upon opening the C2 hydroxyl group furnished a tetramannoside-acceptor 43 that was suitable for a final glycosylation step (Scheme 14).

Scheme 14: Synthesis of Tri- and Tetramannosides
3.5.3 Synthesis of Petamannosides of PIMs

TMSOTf promoted Schmidt glycosylation between acetimidate-donor 11 and tetramannoside 44 furnished the fully benzyl protected pentamannoside 44 with an anomeric allyl group (Scheme 15).

Subsequent removal of the allyl group using KOt-Bu followed by treatment with 1M HCl in acetone-H$_2$O afforded the pentamannoside 45 with a free anomeric hydroxyl group. Glycan 45 is ready to couple with PIM-1 to afford the eventual target, PIM-6 (Scheme 15).

Scheme 15: Synthesis of Diversified Pentamannosides
Part A: Synthesis of Mannoside Glycans of Phosphatidylinositol Mannosides (PIMs)

Alternatively, Schmidt glycosylation of C6-silyl protected 30 with the tetramannoside acceptor 43 generated the pentamannoside 46 with distinctly accessible protecting groups; a silyl ether at the primary ‘top’ hydroxyl group and allyl group at the ‘bottom’ anomeric position. This differential protecting group would facilitate future tagging of desired linkers for immunogenic studies of PIMs.
4 Summary (Part A)

In this chapter, I summarized the synthesis of the mannose glycan portion of phosphatidylinositol mannoses (PIMs). Initially, PIM-6 was sought to provide mechanistic insights into tuberculosis by pathogenic mycobacteria. Preliminarily, a convergent approach was attempted towards pentamannoside (8). Later a new and novel synthetic plan was designed to study all homologues of PIMs in order to fully understand the immunogenic roles of PIMs. Accordingly, a linear synthesis of glycan portion was adopted via the in situ glycosylation method. This linear synthesis enabled the synthesis of a series of mannose glycans of PIM-1, PIM-2, PIM-3, PIM-4, PIM-5 and PIM-6 all with terminally differentiated protecting groups that would facilitate future tagging of desired linkers for immunogenic studies of PIMs.
References for Part A


Experimental Procedures: Part A
General Techniques and Methods:

All non aqueous reactions were performed in flame dried glassware under nitrogen or argon atmosphere unless stated otherwise. All solvents used in the reactions were purified before use. Dichloromethane (CH₂Cl₂) was distilled over CaH₂ and dry diethyl ether (Et₂O), tetrahydrofuran (THF) was distilled from sodium/benzophenone. All commercially available compounds were used as received without further purification. 4Å molecular sieves were activated by heating at 120-140 °C under high vacuum for 4h before storing in a dry desiccator. The reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm 2E Merck silica gel plates (60F-254) under 254 nm UV lamp and stained by aqueous ceric ammonium molybdate solution or KMnO₄ solution. Flash chromatography was performed on silica gel 60 (0.040 – 0.063 mm). ¹H and ¹³C NMR spectra were recorded on Bruker ACF (300 MHz) and Bruker AMX500 (500 MHz) NMR spectrometers. 2D NMR was performed on a Bruker AMX500 (500 MHz) NMR spectrometer. Chemical shifts are reported in δ (ppm) and calibrated using residual undeuterated solvents as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet, m = multiplet, br = broad. ¹H NMR coupling constants (J) are reported in Hertz (Hz), Mass spectra were obtained on Finnigan MAT95XL-T and Micromass VG7035 double focusing mass spectrometer. High resolution ESI mass spectra were obtained on a Shimadzu LCMS-IT-TOF spectrometer. Infra-red spectra were recorded on Perkin-Elmer FT 1600 spectrometer.
Experimental Procedures (Part A)

2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl trichloroacetimidate (11): D-Mannose (20 g, 111 mmol) was heated at 80 °C for 4h in the presence of BF$_3$·Et$_2$O (1 ml, 7.7 mmol) in allyl alcohol (230 mL). After neutralization with Et$_3$N, excess allyl alcohol was removed under reduced pressure and the residue was purified by flash column chromatography (gradient 10-20% MeOH/CH$_2$Cl$_2$) to afford α/β-mixture of allyl-D-mannopyranoside 14 (19.5 g, 80%) as viscous semi solid. To a stirring solution of above allyl mannose 14 (2 g, 9.5 mmol) in DMF (40 mL) was added BnBr (6 mL, 50.4 mmol), and NaH (60% dispersion in mineral oil, 1.9 g, 49 mmol) portion wise at 0 °C and stirred for 4h at room temperature. After the reaction was completed, excess NaH was quenched by slow addition of methanol, diluted with water and extracted with ether (3x). The combined organic layers were washed with saturated NH$_4$Cl solution, brine, dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (gradient 10-20%, EtOAc/hexanes) to furnish allyl-2,3,4,6-tetra-O-benzyl-α-D-mannopyranose 15 (4.96 g, 90%) as a viscous pale yellow liquid.

The above obtained allyl-2,3,4,6-tetra-O-benzyl-α-D-mannopyranose 15 (1.05 g, 1.76 mmol) was dissolved in DMSO (15 mL) and KOt-Bu (1.9 g, 17.6 mmol) added and stirred at 80 °C for 4h. After completion, the reaction mixture was diluted with ethyl acetate (30 mL) and poured on to ice. The biphasic mixture was separated; the organic layer was washed with brine (30 mL) and concentrated in vacuo. The residue was dissolved in acetone-water (9:1 v/v, 15 mL) and treated with 1N HCl (2 mL) and the reaction mixture was stirred at 40 °C for 30 min. Brine solution (15 mL) was added to the reaction mixture and extracted with ether (3x20 mL), concentrated and purified by flash
column chromatography (gradient 10-20%, EtOAc/hexanes) to afford 2,3,4,6-tetra-O-benzyl-\(\alpha\)-D-mannopyranose 16 (913 mg, 96%) as faint yellow oil.

The above obtained 2,3,4,6-tetra-O-benzyl-\(\alpha\)-D-mannopyranose 16 (1 g, 1.84 mmol) was dissolved in anhydrous toluene (2x) and dried azeotropically by removing solvent under reduced pressure. The compound was dissolved in dichloromethane (15 mL) under argon and cooled to 0 °C. Subsequently, trichloroacetonitrile (740 \(\mu\)L, 7.4 mmol) and DBU (50 \(\mu\)L, 0.37 mmol) were sequentially added and the reaction mixture was stirred at room temperature for 1h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (gradient 10-15%, EtOAc/hexanes) to give 2,3,4,6-tetra-O-benzyl-\(\alpha\)-D-mannopyranosyl trichloroacetimidate 11 (945 mg, 75%) as a faint yellow oil. The NMR data is in agreement with that reported in the literature.\(^1\)

\(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 8.62 (s, 1H, NH), 7.45-.7.26 (m, 20H, aromatic), 6.47 (d, \(J = 3.05\) Hz, 1H), 4.99 (d, \(J = 17.8\) Hz, 1H), 4.87 (s, 2H), 4.79-4.58 (m, 2H), 4.29-4.22 (m, 1H), 4.09-3.96 (m, 3H), 3.93 (dd, \(J = 7.1, 18.6\) Hz, 1H), 3.83 (dd, \(J = 2.75, 18.65\) Hz, 1H). \(^1\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 160.40, 138.27, 138.21, 138.06, 137.88, 129.00, 128.35, 128.32, 128.26, 128.19, 128.14, 127.91, 127.88, 127.78, 127.69, 127.46, 125.26, 96.04, 78.87, 75.31, 74.78, 74.16, 73.48, 73.35, 72.59, 72.30, 68.72.

\textbf{Allyl-3-O-benzyl-4,6-O-benzylidene-\(\alpha\)-D-mannopyranoside (12):} The 2-hydroxyl mannose derivative 12 was synthesized following a reported procedure.\(^2\) Allyl-D-mannopyranose 14 (1.99 g, 9 mmol), benzaldehyde dimethyl acetal (2.32 mL, 10.1 mmol) in anhydrous

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Experimental Procedures (Part A)

acetonitrile were stirred in the presence of camphorsulfonic acid (262 mg, 0.19 mmol) at room temperature for 18h. The reaction contents were neutralized by addition of triethylamine (5 mL) and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (20 mL) and washed successively with saturated NaHCO₃ solution, brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (gradient 40-50%, EtOAc/hexanes) to yield allyl-4,6-O-benzylidene-α-D-mannopyranoside 17 (1.66 g, 60 %) as a white foamy solid.

To a solution of above obtained 17 (3.92 g, 12.7 mmol) in anhydrous DMF (100 mL) was added benzyl bromide (2.17 mL, 22.5 mmol) and NaH (390 mg, 12.7 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 4h. Then excess of NaH destroyed by addition of MeOH, and diluted with EtOAc. The mixture was washed with saturated aq. solution of NaHCO₃, brine and water, dried over anhydrous NaSO₄ and concentrated. Flash column chromatography (gradient 5-10%, EtOAc/hexanes) afforded compound allyl-3-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside 12 (2.38 g, 47%).

Allyl-6-O-trityl-α-D-mannopyranose (27): To a solution of allyl-D-mannopyranoside 14 (2.5 g, 11.35 mmol) in anhydrous pyridine was added trityl chloride (4.74 g, 17.0 mmol) and the reaction mixture was stirred at 80 °C for 24h. After completion, the reaction was quenched with addition of saturated NH₄Cl solution and extracted with ether (3x). The combined organic layers were washed with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (gradient 25-50%, EtOAc/hexanes) to give allyl-6-O-trityl-α-D-mannopyranose 27 (2.2 g,
85%) as a foamy yellow solid. \( ^1H \text{NMR} (\text{CDCl}_3, 500 \text{ MHz}): \delta 7.47-7.44 (m, 6H), 7.31-7.29 (m, 6H), 7.26-7.23 (m, 3H), 5.98-5.87 (m, 1H), 5.33-5.27 (m, 1H), 5.25-5.20 (m, 1H), 4.87 (d, \( J = 1.3 \text{ Hz}, 1H \)), 4.21-4.16 (m, 1H), 4.02-4.00 (m, 1H), 3.96-3.94 (m, 1H), 3.86-3.82 (m, 1H), 3.73-3.72 (m, 1H), 3.52-3.39 (m, 3H). \( ^1H \text{NMR} \) (CDCl3, 500 MHz): δ 7.37-7.27 (m, 15H), 5.87-5.79 (m, 1H), 5.16 (dd, \( J = 1.25, 10.1 \text{ Hz}, 1H \)), 4.95 (d, \( J = 10.7 \text{ Hz}, 1H \)), 4.86 (d, \( J = 1.9 \text{ Hz}, 1H \)), 4.79 (d, \( J = 12.6 \text{ Hz}, 1H \)), 4.71-4.65 (m, 4H), 4.14-4.10 (m, 1H), 4.00 (d, \( J = 9.45 \text{ Hz}, 1H \)), 3.97-3.96 (m, 1H), 3.95-3.90 (m, 1H), 3.86-3.77 (m, 3H), 3.69-3.77 (m, 1H); \( ^13C \text{NMR} \) (CDCl3, 125 MHz): δ 138.45, 138.36, 138.21, 133.59, 128.40, 128.36, 128.06, 127.83, 127.72, 127.70, 127.59, 127.56, 117.35, 97.40, 80.19, 75.24, 75.19.

**Allyl-2,3,4-tri-O-benzyl-α-D-mannopyranose (26):** To a solution of allyl-6-O-trityl-α-D-mannopyranose 27 (4 g, 9.84 mmol) in DMF (50 mL) was added BnBr (4.75 mL, 40 mmol, 45 mmol) and NaH (60% dispersion in mineral oil, 1.8 g, 45 mmol) portion-wise at 0 °C. After 4h at room temperature, excess NaH was quenched by slow addition of methanol, diluted with water (50 mL) and extracted with ether (3x). The combined organic layers were washed with saturated NH₄Cl solution, brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo. To the crude product in dichloromethane (30 mL) was added CSA (0.46 g, 3 mmol) and the reaction mixture was stirred overnight at room temperature. The solvent was distilled in vacuo, and the residue was purified by flash column chromatography (gradient 20-35%, EtOAc/hexanes) to furnish allyl-2,3,4-tri-O-benzyl-α-D-mannopyranose 26 (4.4 g, 91%, 2 steps). \( ^1H \text{NMR} \) (CDCl3, 500 MHz): δ 7.37-7.27 (m, 15H), 5.87-5.79 (m, 1H), 5.16 (dd, \( J = 1.25, 10.1 \text{ Hz}, 1H \)), 4.95 (d, \( J = 10.7 \text{ Hz}, 1H \)), 4.86 (d, \( J = 1.9 \text{ Hz}, 1H \)), 4.79 (d, \( J = 12.6 \text{ Hz}, 1H \)), 4.71-4.65 (m, 4H), 4.14-4.10 (m, 1H), 4.00 (d, \( J = 9.45 \text{ Hz}, 1H \)), 3.97-3.96 (m, 1H), 3.95-3.90 (m, 1H), 3.86-3.77 (m, 3H), 3.69-3.77 (m, 1H); \( ^13C \text{NMR} \) (CDCl3, 125 MHz): δ 138.45, 138.36, 138.21, 133.59, 128.40, 128.36, 128.06, 127.83, 127.72, 127.70, 127.59, 127.56, 117.35, 97.40, 80.19, 75.24,
Experimental Procedures (Part A)


**2,3,4-Tri-O-benzyl-6-O-tert-butyldimethylsilyl-α-D-mannopyranose (29):** To a solution of allyl-2,3,4,-tri-O-benzyl-α-D-mannopyranose 26 (1.89 g, 3.86 mmol) in THF (20 mL), was added TBSCl (0.87 g, 5.8 mmol) and imidazole (0.52 g, 7.7 mmol); and the contents were stirred overnight at room temperature. After the reaction was completed, quenched with saturated NH₄Cl solution and extracted with ether (3x). The combined organic layers were washed with brine solution, dried over anhydrous Na₂SO₄ and concentrated *in vacuo* and subsequently, the residue was dissolved in DMSO (25 mL) and KOt-Bu (4.33 g, 38 mmol) was added and stirred at 80 °C for 4h. After completion, the reaction was diluted with ethyl acetate and poured on to ice. The organic layer was washed with brine and concentrated *in vacuo*. The residue was dissolved in acetone-water (9:1 v/v, 15 mL) and stirred with 1N HCl (2 mL) at 40 °C for 30 min. The reaction mixture was then diluted with brine and extracted with ether (3x), concentrated and purified by flash column chromatography (gradient 10-20%, EtOAc/hexanes) to afford 2,3,4-tri-O-benzyl-6-O-tert-butyldimethylsilyl-α-D-mannopyranose 29 (2.1 g, 90%, 2 steps). **¹H NMR** (CDCl₃, 300 MHz): δ 7.38-7.26 (m, 15H, aromatic), 5.24-5.22 (m, 1H), 4.92 (d, *J* = 11.01 Hz, 1H), 4.78-4.62 (m, 4H), 3.95-3.78 (m, 6H), 3.00 (d, *J* = 3.3 Hz, 1H), 1.64 (s, 1H), 0.89 (s, 9H, TBS), 0.06 (d, *J* = 3.96 Hz, 6H, TBS). **¹³C NMR** (CDCl₃, 5 MHz): δ 166.56, 155.75, 138.71, 138.59, 138.52, 128.32, 128.26, 127.98, 127.70, 127.66, 127.57, 127.52,
2,3,4-Tri-O-benzyl-6-O-tert-butyldimethylsilyl-α-D-mannopyranosyl trichloroacetimidate (30): 2,3,4-Tri-O-benzyl-6-O-tert-butyldimethylsilyl-α-D-mannopyranose 29 (1.3 g, 2.3 mmol) was dissolved in anhydrous toluene and dried azeotropically (2x) by removing the solvent under reduced pressure. The compound was dissolved in dichloromethane (20 mL) under argon and cooled to 0 °C. Subsequently trichloroacetonitrile (700 μL, 7 mmol) and DBU (68 μL, 0.5 mmol) were sequentially added; and the reaction mixture was stirred at room temperature for 1h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (gradient 5-10%, EtOAc/hexanes) to give 2,3,4-,tri-O-benzyl-6-O-tert-butyldimethylsilyl-α-D-mannopyranosyl trichloroacetimidate 1.30 (1.22 g, 75%) as a yellow syrup. ¹H NMR (CDCl₃, 500 MHz): δ 8.48 (s, 1H, NH), 7.42-7.27 (m, 15H, aromatic), 6.33 (s, 1H), 4.94 (d, J = 10.7 Hz, 1H), 4.75 (dd, J = 12, 18.3 Hz, 2H), 4.71-4.66 (m, 3H), 4.62 (d, J = 11.35 Hz, 1H), 4.16 (t, J = 10.1 Hz, 1H), 3.95-3.93 (m, 2H), 3.86 (d, J = 10.7 Hz, 2H), 3.82-3.79 (m, 1H), 0.90 (s, 9H, TBS), 0.08 (d, J = 5.05 Hz, 6H, TBS). ¹³C NMR (CDCl₃, 75 MHz): δ 160.45, 138.55, 138.20, 138.02, 128.37, 128.34, 128.24, 128.11, 127.95, 127.75, 127.69, 127.66, 127.57, 96.25, 78.85, 75.91, 75.32, 74.00, 73.86, 72.52, 72.38, 62.13, 25.86, 18.23, -5.13, -5.31.
Experimental Procedures (Part A)

3,4,6-Tri-\(O\)-benzyl-1,2-\(O\)-(\(\alpha\)-methoxybenzylidene)-\(\beta\)-D-mannopyranose (19):

The orthoester 19 was synthesized following a reported procedure.\(^3\) To a stirring solution of ice-cold \(\alpha\)-D-mannose (7 g, 39 mmol) in \(\text{CH}_2\text{Cl}_2\) (30 mL) and pyridine (30 mL) was added benzoyl chloride (30 mL, 280 mmol) dropwise over 30 min. The reaction was held at room temperature for 24 h after which the yellow reaction mixture was neutralized by slow addition of dil. HCl at 0 °C, extracted with \(\text{CH}_2\text{Cl}_2\) (3x) and the combined organic layers were washed with dil. HCl, \(\text{H}_2\text{O}\), and saturated \(\text{NaHCO}_3\) followed by brine solution and dried over anhydrous \(\text{Na}_2\text{SO}_4\). The solvent was removed \textit{in vacuo} and the crude penta-\(O\)-benzoyl-D-mannose was dissolved in \(\text{CH}_2\text{Cl}_2\) that was subsequently treated with a solution of 30% HBr-AcOH (100 mL) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 12 h after which the reaction found to be completed. The reaction was diluted with \(\text{CH}_2\text{Cl}_2\) and neutralized by slow addition of saturated \(\text{Na}_2\text{CO}_3\) solution at 0 °C, solids were filtered-off, and extracted with \(\text{CH}_2\text{Cl}_2\) (2x) and the combined organic layers were washed with saturated \(\text{NaHCO}_3\), \(\text{H}_2\text{O}\), dil. HCl, and brine solution and dried over anhydrous \(\text{Na}_2\text{SO}_4\) and the solvent was removed \textit{in vacuo} to give 2,3,4,6-tetrabenzoyl-\(\alpha\)-D-mannopyranosyl bromide as a brownish viscous syrup which was dried under high vacuum for 3 h and used without further purification. To a solution of above obtained 2,3,4,6-tetrabenzoyl-\(\alpha\)-D-mannopyranosyl bromide in \(\text{CH}_2\text{Cl}_2\) (100 mL) was added MeOH (6 mL) and 2,6-lutidine (10 mL, 117 mmol) and the reaction was stirred at room temperature for 3 days. The solution was then quenched with water and

diluted with Et₂O (100 mL). The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and the solvent was removed in vacuo. The resulting clear oil was further dried for 2 days under high vacuum to give 1,2-O-(α-methoxybenzylidene)-3,4,6-tri-O-benzoyl-β-D-mannopyranose as a foamy solid. The crude residue of 1,2-O-(α-methoxybenzylidene)-3,4,6-tri-O-benzoyl-β-D-mannopyranose was dissolved in CH₂Cl₂ (100 mL) and MeOH (4 mL) and treated with NaOMe (200 mg, 3.9 mmol). The resulting solution was stirred at room temperature for 24 h. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography (gradient 5-10% MeOH/CH₂Cl₂) to give 34 (5.58 g, 48%, 4 steps) as a colorless semisolid.

To a solution of above obtained 1,2-O-(α-methoxybenzylidene)-β-D-mannopyranose 34 (5.48 g, 18.37 mmol) in DMF (50 mL) was added imidazole (120 mg, 1.8 mmol), benzyl bromide (10 mL, 82 mmol) and NaH (60% dispersion in mineral oil, 2.64 g, 110 mmol) portion wise. The resulting suspension was stirred at room temperature for 2.5 h. Excess NaH was then cautiously quenched by the addition of water and the solution diluted with Et₂O (150 mL). The organic extract were washed with H₂O, saturated NaHCO₃ solution (2x), brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography to give 3,4,6-tri-O-benzyl-1,2-O-(α-methoxybenzylidene)-β-D-mannopyranose 19 (7 g, 82%) as a faint yellow solid. ¹H NMR (CDCl₃, 500 MHz): δ 7.68-7.67 (m, 2H), 7.43-7.41 (m, 2H), 7.36-7.20 (m, 16H), 5.49 (d, J = 3.15 Hz, 1H), 4.88 (d, J = 11.35 Hz, 1H), 4.85 (d, J = 11.95 Hz, 1H), 4.80 (d, J = 12 Hz, 1H), 4.67 (t, J = 3.15 Hz, 1H), 4.62 (d, J = 10.7 Hz, 1H), 4.40 (dd, J = 4.38, 12.0 Hz, 2H), 3.92 (t, J = 8.85, 1H), 3.84 (dd, J = 3.75, 9.45, 1H), 3.65 (dd, J = 5.05, 10.7
Experimental Procedures (Part A)

**1H NMR** (CDCl₃, 300 MHz): δ 8.06-8.06 (m, 2H, aromatic), 7.55-7.15 (m, 32H), 5.87-5.70 (m, 1H), 5.74 (s, 1H), 5.26-5.09 (m, 3H), 4.93-4.85 (m, 3H), 4.74-4.470 (m, 4H), 4.69 (s, 1H), 3.75-3.54 (m, 1H), 3.51-3.48 (m, 1H), 3.26 (s, 3H).


**Allyl (2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1→6)-2-benzoyl-3,4,6-tri-O-benzyl-α-D-mannopyranoside** (35): 2,3,4-Tri-O-benzyl-α-D-mannopyranose acceptor 26 (50 mg, 0.0956 mmol) and 3,4,6-tri-O-benzyl-1,2-O-(α-methoxybenzylidene)-β-D-mannopyranose donor 19 (65 mg, 0.115 mmol) were dried together by azeotropic distillation with anhydrous toluene (3x5 mL) and kept under an argon atmosphere. Activated 4Å MS were added under the flush of argon and the starting materials dissolved in dichloromethane (5 mL) and dibutylphosphate (66 μL, 0.34 mmol) was added. The reaction mixture was stirred at room temperature for 1h during which all the donor converted to glycosyl phosphate (TLC monitoring). Then the reaction mixture was cooled to –30 °C and treated with TMSOTf (62 μL, 0.34 mmol), warmed-up to room temperature and stirred for a further 2h. After completion of the reaction, the solvent was removed under vacuum and the residue was purified by flash column chromatography (gradient 10-15% EtOAc/hexanes) to give 35 (46 mg, 47%) as a transparent viscous colorless liquid while recovering acceptor 26 (25 mg, 53% of used amount). **1H NMR** (CDCl₃, 300 MHz): δ 8.06-8.06 (m, 2H, aromatic), 7.55-7.15 (m, 32H), 5.87-5.70 (m, 1H), 5.74 (s, 1H), 5.26-5.09 (m, 3H), 4.93-4.85 (m, 3H), 4.74-4.4.70 (m, 4H), 4.69 (s,
Experimental Procedures (Part A)

$^2$H), 4.61-4.41 (m, 4H), 4.12-4.02 (m, 3H), 3.94-3.66 (m, 10H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 165.46, 138.61, 138.52, 138.44, 138.29, 137.89, 133.64, 132.95, 130.04, 129.95, 128.32, 128.28, 128.21, 128.15, 127.87, 127.81, 127.68, 127.65, 127.60, 127.47, 127.40, 127.36, 117.41, 98.02, 96.79, 80.27, 77.66, 75.08, 75.00, 74.71, 74.63, 74.19, 73.32, 72.67, 72.04, 71.61, 71.26, 71.08, 68.96, 68.70, 67.75, 66.65. MS (ESI): $m/z$ 1049.3 [M+Na]$^+$. HRMS (ESI): $m/z$ calcd for C$_{64}$H$_{66}$NaO$_{12}$ 1049.4452 [M+Na]$^+$; found 1049.4464.

Allyl (2,3,4-tri-O-benzyl-$\alpha$-D-mannopyranosyl)-(1$\rightarrow$6)-3,4,6-tri-O-benzyl-$\alpha$-D-mannopyranoside (36): The dimannoside 1.35 (45 mg, 0.045 mmol) was dissolved in dichloromethane-methanol (9:1 v/v, 3 mL) and NaOMe (26 mmol, 0.049 mg) was added. The reaction mixture was stirred at room temperature for 24h after which the solvent was removed under reduced pressure. Purification of the residue by flash column chromatography (gradient 15-30% EtOAc/hexanes) afforded the titled dimannoside 36 (45 mg, quantitative) as a colorless viscous syrup. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.37-7.22 (m, 28H, aromatic), 7.16-7.13 (m, 2H, aromatic), 5.88-5.75 (m, 1H), 5.23-5.06 (m, 3H), 4.92-4.43 (m, 13H), 4.10-4.06 (m, 2H), 3.93-3.58 (m, 12H), 2.38 (s, br, 1H, OH). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 138.51, 138.44, 138.26, 137.83, 133.64, 128.44, 128.32, 128.25, 128.20, 127.93, 127.84, 127.78, 127.74, 127.71, 127.63, 127.55, 127.46, 117.44, 99.57, 96.81, 80.21, 79.58, 75.03, 74.93, 74.62, 74.20, 73.34, 72.74, 72.09, 71.59, 71.46, 71.04, 68.83, 68.04, 67.77, 66.24. MS (ESI): $m/z$ 921.0 [M-H]$^-$, 945.3 [M+Na]$^+$. HRMS (ESI): $m/z$ calcd for C$_{57}$H$_{62}$NaO$_{11}$ 945.4190 [M+Na]$^+$; found 945.4190.
Allyl (2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1→6)-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1→2)-2-benzoyl-3,4,6-tri-O-benzyl-α-D-mannopyranoside (37): Here the same one pot glycosylation procedure as mentioned earlier for the synthesis of 36 was adopted. Dimannoside acceptor 36 (45 mg, 0.049 mmol) and 1,2-orthoester donor 19 (33 mg, 0.059 mmol) were dried together by azeotropic distillation with anhydrous toluene (3x5 mL) and kept under an argon atmosphere. Activated 4Å MS were added under the flush of argon and starting material was dissolved in dichloromethane (4 mL) subsequently dibutylphosphate (34 μL, 0.18 mmol) was added. The reaction mixture was stirred at room temperature for 1h during which all the donor converted to glycosyl phosphate (TLC monitoring). Then the reaction mixture was cooled to –30 °C and treated with TMSOTf (31 μL, 0.18 mmol), warmed-up to room temperature and stirred for an additional 2h. After completion of the reaction, the solvent was removed under vacuum and the residue was purified by flash column chromatography (gradient 15-25% EtOAc/hexanes) to give 37 (29 mg, 33%) as a transparent viscous colorless liquid while recovering acceptor 36 (4 mg).

**1H NMR** (CDCl₃, 300 MHz): δ 8.08-8.05 (m, 2H), 7.56-7.51 (m, 1H), 7.37-7.01 (m, 47H), 5.86-5.73 (m, 1H), 5.76 (s, 1H), 5.21-5.01 (m, 4H), 4.89-4.83 (m, 4H), 4.75-4.69 (m, 4H), 4.64-4.40 (m, 11H), 4.12-4.02 (m, 5H), 3.92-3.57 (m, 15H).

**13C NMR** (CDCl₃, 75 MHz): δ 165.42, 138.69, 138.64, 138.59, 138.47, 138.25, 138.19, 138.14, 133.67, 132.92, 130.13, 129.95, 128.35, 128.32, 128.29, 128.23, 128.17, 128.06, 127.89, 127.86, 127.74, 127.69, 127.63, 127.28, 127.53, 127.49, 127.46, 127.41, 127.37, 127.28, 117.43, 99.57, 99.09, 96.89, 80.36, 79.11, 78.18, 77.20, 75.09, 74.96, 74.83, 74.65, 74.53, 74.34, 73.33,
Experimental Procedures (Part A)

73.17, 72.67, 72.09, 71.82, 71.49, 69.21, 67.69, 66.61. MS (ESI): m/z calcd for C_{91}H_{94}NaO_{17} 1481.6389 [M+Na]^+; found, 1481.4.

Allyl (2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-6-O-tert-butyldimethylsilyl-α-D-mannopyranoside (38): The glycosyl donor, 2,3,4-tri-O-benzyl-6-O-tert-butyldimethylsilyl-α-D-mannopyranosyl trichloroacetimidate 30 (1.72 g, 2.43 mmol) and the allyl-2,3,4-O-benzyl-α-D-mannopyranoside acceptor 26 (1.08 g, 2.2 mmol) were dried through azeotropic distillation with anhydrous toluene (2x) before being kept under an argon atmosphere. Then the mixture was dissolved in anhydrous diethyl ether (30 mL) under argon and treated with TMSOTf (25 μL, 0.11 mmol). The reaction mixture was stirred at room temperature for 2h followed by neutralization with Et₃N. Subsequently, distillation of the solvent and flash column chromatography (gradient 10-15% EtOAc/hexanes) of the residue gave the desired dimannoside compound 38 (1.6 g, 70%) as a colorless viscous oil. ¹H NMR (CDCl₃, 300 MHz): δ 7.42-7.26 (30H, aromatic), 5.92-5.80 (m, 1H), 5.27-5.16 (m, 2H), 5.09 (s, 1H), 4.99-4.89 (m, 3H), 4.79-4.52 (m, 10H), 4.15-3.65 (m, 14H), 0.93 (s, 9H, TBS), 0.09 (d, J = 4.08 Hz, 6H, TBS). ¹³C NMR (CDCl₃, 75 MHz): δ 139.03, 138.82, 138.50, 138.27, 133.67, 128.33, 128.29, 128.20, 128.12, 127.80, 127.65, 127.62, 127.54, 127.41, 127.35, 127.23, 117.40, 97.91, 96.92, 80.33, 79.46, 77.42, 75.32, 75.06, 74.91, 74.68, 73.09, 72.83, 72.32, 72.14, 71.78, 71.58, 67.67, 65.85, 62.57, 29.68, 25.93, 18.28, -5.10, -5.33. MS (ESI): m/z calcd for C_{63}H_{76}O_{11}Si 1036.5157 [M]^+; found 1036.4 [M]^+. 
**Experimental Procedures (Part A)**

Allyl (2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside (39): Dimannoside 38 (1.6 g, 1.7 mmol) was dissolved in THF (20 mL) and treated with a drop of acetic acid followed by TBAF (1N in THF, 2 mL, 2 mmol). The reaction mixture was stirred for 3h at room temperature. After completion of the reaction, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (gradient 15-30% EtOAc/hexanes) to give the titled dimannoside 39 (1.28 g, 90%) as a colorless liquid. **\(^1H\) NMR** (CDCl\(_3\), 500 MHz): \(\delta\) 7.37-7.18 (m, 30H, aromatic), 5.85-5.77 (m, 1H), 5.21-5.12 (m, 2H), 5.05 (s, 1H), 4.95-4.89 (m, 2H), 4.84 (s, 1H), 4.73-4.61 (m, 7H), 4.58 (d, \(J = 12\) Hz, 1H), 4.53 (d, \(J = 12\) Hz, 1H), 4.48 (d, \(J = 11.35\) Hz, 1H), 4.09-4.06 (m, 1H), 3.98-3.86 (m, 7H), 3.81 (s, br, 1H), 3.75-3.64 (m, 6H). **\(^{13}C\) NMR** (CDCl\(_3\), 125 MHz): 138.54, 138.51, 138.38, 138.27, 138.15, 133.57, 128.34, 128.31, 128.27, 127.92, 127.83, 127.74, 127.72, 127.70, 127.62, 127.57, 127.55, 127.50, 117.42, 98.23, 96.97, 80.24, 79.35, 75.07, 75.01, 74.77, 74.65, 74.54, 72.85, 72.68, 72.11, 71.58, 67.74, 66.07, 62.23. **MS** (ESI): \(m/z\) calcd for C\(_{57}\)H\(_{62}\)NaO\(_{11}\) 945.4190 [M+Na]\(^+\); found 945.3.

Allyl (2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1→6)-(2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1→6)-2-benzoyl-3,4,6-tri-O-benzyl-α-D-mannopyranoside (40): Dimannoside acceptor 39 (0.4 g, 0.43 mmol) and 1,2-orthoester donor 19 (0.3 g, 0.52 mmol) were together dried by azeotropic distillation with anhydrous toluene (3x) and flushed with argon. Activated 4Å MS were added under the flush of argon and organic content was dissolved in dichloromethane (20 mL), and
dibutylphosphate (300 μL, 1.6 mmol) was added. The reaction mixture was stirred at room temperature for 1h during which all the donor converted to glycosyl phosphate (according to TLC analysis). Then the reaction mixture was cooled to –30 °C and treated with TMSOTf (300 μL, 1.6 mmol), and the contents warmed-up to room temperature and stirred for further 2h. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified by flash column chromatography (gradient 10-20% EtOAc/hexanes) to give the titled trimannoside 40 (0.63 g, quantitative) as a transparent viscous colorless liquid. \(^1\)H NMR (CDCl₃, 500 MHz): \(\delta\) 8.15-8.14 (m, 2H, aromatic), 7.60-7.57 (m, 1H, aromatic), 7.47-7.21 (m, 47H, aromatic), 5.91-5.85 (m, 1H), 5.82 (s, 1H), 5.28-5.15 (m, 4H), 5.02-4.92 (m, 4H), 4.79-4.64 (m, 8H), 4.58-4.49 (m, 6H), 4.16-3.93 (m, 12H), 3.88-3.68 (m, 8H). \(^1\)C NMR (CDCl₃, 125 MHz): \(\delta\) 165.41, 138.82, 138.70, 138.60, 138.50, 138.35, 138.26, 137.95, 133.67, 132.94, 130.17, 130.03, 128.38, 128.34, 128.30, 128.20, 128.18, 127.93, 127.88, 127.85, 127.73, 127.67, 127.61, 127.58, 127.55, 127.50, 127.49, 127.41, 127.39, 127.29, 117.43, 98.26, 98.01, 97.03, 80.38, 79.49, 77.68, 75.11, 75.09, 74.90, 74.60, 74.36, 74.20, 73.36, 72.87, 72.48, 72.19, 71.82, 71.67, 71.38, 71.22, 71.06, 68.96, 68.70, 67.76, 66.50, 66.07, 65.85. MS (ESI): \(m/z\) calcd for C₉₁H₉₄NaO₁₇ 1481.6389 [M+Na]⁺; found 1481.3.

**Allyl (2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1→6)-(2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1→6)-3,4,6-tri-O-benzyl-α-D-mannopyranoside (41):** The trimannoside 40 (451 mg, 0.31 mmol) was dissolved in dichloromethane-methanol (10 mL, 9:1 v/v) and NaOMe (16 mg, 0.3 mmol) was added. The reaction mixture was
stirred at room temperature for 24h after which the solvent was removed under reduced pressure followed by purification of the residue by flash column chromatography (gradient 20-30% EtOAc/hexanes) to afford the titled trimannoside 41 (398 mg, 95%) as a colorless syrup. $^1$H NMR (CDCl$_3$, MHz): δ 7.38-7.17 (m, 45H, aromatic), 5.88-5.80 (m, 1H), 5.25-5.21 (m, 1H), 5.16 (dd, $J = 1.25, 10.1$ Hz, 1H), 5.10 (s, 2H), 4.95-4.82 (m, 4H), 4.77-4.46 (m, 15H), 4.12-4.09 (m, 2H), 3.99-3.82 (m, 11H), 3.59 (dd, $J = 1.9, 10.7$ Hz, 1H). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 138.66, 138.58, 138.50, 138.37, 138.23, 138.10, 137.86, 133.54, 128.37, 128.31, 128.27, 128.20, 128.16, 128.13, 127.88, 127.83, 127.81, 127.77, 127.65, 127.59, 127.51, 127.50, 127.42, 127.28, 117.42, 99.64, 97.81, 96.94, 80.28, 79.48, 79.31, 77.43, 75.02, 74.89, 74.84, 74.76, 74.52, 74.29, 74.14, 73.30, 72.85, 72.51, 72.12, 71.71, 71.44, 71.37, 71.26, 71.01, 68.76, 67.86, 67.68, 65.99, 65.90. MS (ESI): $m/z$ calcd for C$_{84}$H$_{90}$NaO$_{16}$ 1377.6127 [M+Na]$^+$; found 1377.4.

**Allyl (2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1→6)-(2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1→6)-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1→2)-2-benzoyl-3,4,6-tri-O-benzyl-α-D-mannopyranoside (42):** Trimannoside acceptor 41 (200 mg, 0.35 mmol) and 1,2-orthoester donor 19 (397 mg, 0.3 mmol) were dried together by azeotropic distillation with anhydrous toluene (3x5 mL) and flushed with argon. Activated 4Å MS were added under the flush of argon and the organic content was dissolved in dichloromethane (7 mL) and subsequently dibutylphosphate (200 μL, 1 mmol) was added. The reaction mixture was stirred at room temperature for 1h during which all the donor converted to glycosyl phosphates (according
to TLC analysis). Then the reaction mixture was cooled to −30 °C and treated with TMSOTf (190 μL, 1 mmol), the contents were warmed-up to room temperature and stirring continued for further 2h. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified by flash column chromatography (gradient 15-30% EtOAc/hexanes) to give tetramannoside 42 (549 mg, 99%) as a viscous colorless syrup. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 8.16-8.14 (m, 2H, aromatic), 7.63-7.58 (m, 1H, aromatic), 7.43-7.18 (m, 62H, aromatic), 5.93-5.80 (m, 1H), 5.87 (s, 1H), 5.28-5.10 (m, 4H), 5.00-4.90 (m, 5H), 4.84-4.46 (m, 20H), 4.19-4.10 (m, 5H), 4.03-3.57 (m, 21H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 165.35, 138.73, 138.62, 138.53, 138.38, 138.23, 138.09, 133.56, 132.89, 130.06, 129.92, 128.30, 128.18, 128.12, 128.10, 128.05, 127.86, 127.81, 127.76, 127.64, 127.61, 127.54, 127.44, 127.37, 127.23, 127.18, 117.36, 99.47, 99.22, 98.08, 96.96, 80.29, 79.50, 78.96, 78.15, 77.20, 75.02, 74.92, 74.76, 74.49, 74.38, 74.24, 74.16, 73.29, 73.11, 72.79, 72.42, 72.10, 72.04, 71.73, 71.54, 71.41, 71.32, 69.12, 69.06, 67.68, 66.39, 65.99. MS (ESI): $m/z$ calcd for C$_{111}$H$_{118}$O$_{21}$ 1890.8428 [M$^+$/; found, 1891.5 [M+H$^+$].

Allyl (2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1→6)-(2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1→6)-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1→2)-3,4,6-tri-O-benzyl-α-D-mannopyranoside (43): The titled compound was synthesized by the same procedure of debenzoylation as described for the synthesis of 40. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.46-7.19 (m, 60H, aromatic), 5.91-5.83 (m, 1H), 5.27-5.16 (m, 4H), 5.10 (s, 1H), 4.97 (dd, $J = 4.4, 10.75$ Hz, 2H), 4.91
Experimental Procedures (Part A)

(s, br, 1H), 4.88 (dd, \( J = 5 \), 10.7 Hz, 2H), 4.79-4.46 (m, 20H), 4.18 (d, \( J = 10.7 \) Hz, 2H), 4.15-4.12 (m, 1H), 4.04-3.88 (m, 14H), 3.85 (dd, \( J = 3.8 \), 10.7 Hz, 1H), 3.76-3.66 (m, 6H), 3.58-3.55 (m, 2H). \(^{13}\text{C NMR} \) (CDCl\(_3\), 75 MHz): \( \delta \) 138.77, 138.71, 138.63, 138.59, 138.54, 138.42, 138.40, 138.27, 138.24, 138.16, 138.14, 138.09, 138.07, 133.58, 128.35, 128.31, 128.26, 128.23, 128.18, 128.14, 128.10, 128.07, 127.90, 127.83, 127.80, 127.74, 127.72, 127.64, 127.61, 127.53, 127.49, 127.48, 127.42, 127.35, 127.27, 127.18, 127.13, 117.35, 101.05, 99.25, 98.12, 96.97, 80.30, 79.96, 79.52, 78.91, 77.20, 75.00, 74.94, 74.85, 74.67, 74.50, 74.46, 74.27, 74.18, 73.29, 73.10, 72.82, 72.48, 72.11, 72.01, 71.80, 71.75, 71.41, 71.36, 71.31, 69.05, 68.90, 68.59, 67.68, 66.50, 66.08, 65.78. \( \text{MS (ESI):} \) 
\[ m/z \text{ calcd for C}_{111}\text{H}_{118}\text{NaO}_{21} 1809.8063 \ [\text{M+Na}]^+; \text{found, } 1809.5 \ [\text{M+H}]^+. \]

Allyl \((2,3,4\text{-tri-}\text{O-benzyl-}\alpha\text{-D-mannopyranosyl})-(1\rightarrow6)-(2,3,4\text{-tri-}\text{O-benzyl-}\alpha\text{-D-mannopyranosyl})-(1\rightarrow6)-(3,4,6\text{-tri-}\text{O-benzyl-}\alpha\text{-D-mannopyranosyl})-(1\rightarrow2)-(3,4,6\text{-tri-}\text{O-benzyl-}\alpha\text{-D-mannopyranosyl})-(1\rightarrow2)-2,3,4,6\text{-tetra-}\text{O-benzyl-}\alpha\text{-D-mannopyranoside (44):} \) Glycosyl donor 11, (0.125 g, 0.18 mmol) and tetramannoside acceptor 43 (0.27 g, 0.15 mmol) were dried through azeotropic distillation with anhydrous toluene (2x) before being kept under an argon atmosphere. Then the mixture was dissolved in anhydrous diethylether (15 mL) under argon and TMSOTf (4 \( \mu \)L, 0.02 mmol) was added. The reaction mixture was stirred for 2h at room temperature which was followed by neutralization with Et\(_3\)N, removal of the solvent \textit{in vacuo}. The residue was purified by flash column chromatography (gradient 15-30% EtOAc/hexanes) to obtain the desired
Experimental Procedures (Part A)

Pentamannoside 44 (332 mg, 96%) as a faint yellow solid. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.34-7.08 (m, 80H, aromatic), 5.81-5.73 (m, 1H), 5.20-5.09 (m, 4H), 5.05 (d, $J = 1.35$ Hz, 1H), 4.97 (d, $J = 1.35$ Hz, 1H), 4.89-4.84 (m, 2H), 4.82-4.79 (m, 3H), 4.69-4.51 (m, 11H), 4.49-4.28 (m, 3H), 4.16-4.10 (m, 2H), 4.07-4.04 (m, 2H), 3.93-3.76 (m, 17H), 4.67-4.42 (m, 11H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 138.85, 138.81, 138.80, 138.75, 138.69, 138.67, 138.64, 138.61, 138.28, 138.46, 138.43, 138.39, 138.36, 138.29, 138.26, 138.18, 138.06, 128.53, 128.48, 128.42, 128.32, 128.32, 128.28, 128.23, 128.21, 128.18, 128.15, 128.11, 128.08, 128.07, 127.99, 127.85, 127.84, 127.81, 127.80, 127.77, 127.75, 127.73, 127.68, 127.64, 127.62, 127.58, 127.56, 127.52, 127.47, 127.44, 127.40, 127.35, 127.29, 127.26, 127.25, 127.21, 127.10, 117.35, 100.60, 99.29, 99.24, 98.15, 96.99, 80.31, 79.88, 79.80, 79.63, 78.91, 75.03, 74.93, 74.92, 74.86, 74.83, 74.70, 74.64, 74.52, 74.47, 74.28, 74.22, 73.31, 73.24, 73.13, 72.81, 72.51, 72.41, 72.30, 72.14, 72.08, 71.97, 71.81, 71.30, 71.16, 69.32, 69.02, 68.90, 67.68, 66.48, 66.03. MS (ESI): m/z calcd for C$_{145}$H$_{152}$NaO$_{26}$ 2332.0470 [M+Na]$^+$; found 2333.1 [M+H]$^+$. 

(2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1→6)-(2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1→6)-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1→2)-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1→2)-2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside (45): Pentamannoside 44 (223 mg, 0.097 mmol) was dissolved in DMSO (10 mL) to which KOt-Bu (112 mg, 1 mmol) was added and stirred at 80 °C for 4h. After completion of the reaction, the contents were diluted with ethyl acetate and poured on to ice. The layers
were separated; and the organic layer was washed with brine and concentrated *in vacuo*. The crude residue was dissolved in acetone-water (9:1 v/v, 5 mL) and 1N HCl (2 mL) was added and the reaction was held at 40 °C for 30 min. Then H₂O was added to the reaction mixture and extracted with ether (3x), concentrated and purified by flash column chromatography (gradient 30-50%, EtOAc/hexanes) to afford the titled pentamannoside 45 (176 mg, 80%) as a white foamy solid. **¹H NMR** (CDCl₃, 500 MHz): δ 7.32-7.14 (m, 80H), 5.20-5.13 (m, 3H), 5.06-4.96 (m, 2H), 4.88-4.78 (m, 5H), 4.69-4.42 (m, 24H), 4.34-4.30 (m, 2H), 4.23-4.16 (m, 2H), 4.09-4.03 (m, 2H), 3.90-3.75 (m, 17H), 3.69-3.63 (m, 6H), 3.57-3.53 (m, 3H). **¹³C NMR** (CDCl₃, 125 MHz): δ 138.73, 138.68, 138.62, 138.59, 138.54, 138.46, 138.43, 138.33, 138.10, 128.48, 128.43, 128.29, 128.28, 128.25, 128.21, 128.17, 128.09, 128.04, 127.91, 127.79, 127.76, 127.72, 127.67, 127, 64, 127.58, 127.56, 127.53, 127.48, 127.44, 127.42, 127.36, 127.31, 127.28, 127.23, 100.72, 99.32, 98.73, 97.40, 92.46, 89.87, 79.78, 79.69, 78.87, 75.23, 75.04, 74.93, 74.80, 74.71, 74.63, 73.30, 73.26, 73.18, 73.11, 72.78, 72.51, 72.34, 72.29, 72.13, 72.08, 72.00, 71.85, 71.60, 71.43, 71.32, 71.25, 70.98, 69.29, 69.16, 68.99, 66.54, 65.45. **MS** (ESI): *m/z* calcd for C₁₄₂H₁₄₈NaO₂₆ 2292.0157 [M+Na]⁺; found, 2293.4 (100%).

![Diagram](image)

**Allyl (2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1→6)-(2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1→6)-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1→2)-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1→2)-2,3,4-tri-O-benzyl-6-O-tert-butyldimethylsilyl-α-D-mannopyranoside (46):** The glycosylation donor 1.30 (145 mg, 0.2 mmol) and the tetramannoside acceptor 43
(300 mg, 0.17 mmol) were dried together through azeotropic distillation with anhydrous toluene (2x) before being kept under an argon atmosphere. Then the mixture was dissolved in anhydrous diethylether (10 mL) under argon after which TMSOTf (3 μL, 0.01 mmol) was added and stirred at room temperature for 2h. Then the reaction mixture was neutralized with Et3N and concentrated in vacuo and the residue was purified by flash column chromatography (gradient 15-25% EtOAc/hexanes) to obtain the desired pentamannoside 46 (310 mg, 80 %) as a colorless solid. $^{1}H$ NMR (CDCl3, 500 MHz): δ 7.41-7.11 (m, 75H, aromatic), 5.87-5.80 (m, 1H), 5.25-5.13 (m, 5H), 5.01-4.85 (m, 7H), 4.75-4.64 (m, 9H), 4.61-4.41 (m, 13H), 4.45-4.41 (m, 3H), 4.22-4.16 (m, 3H), 4.12-4.08 (m, 1H), 4.01-3.81 (m, 18H), 3.74-3.66 (m, 7H), 3.64-3.61 (dd, $J = 4.4$, 11.35 Hz, 1H), 3.53-3.47 (dd, $J = 10.1$, 20.2 Hz, 2H), 0.91 (s, 9H, TBS), 0.06-0.05 (d, $J = 5.65$ Hz, 6H, TBS). $^{13}C$ NMR (CDCl3, 125 MHz): δ 139.19, 138.78, 138.68, 138.64, 138.60, 138.58, 138.53, 138.41, 138.33, 138.23, 138.15, 137.90, 133.58, 128.46, 128.30, 128.26, 128.21, 128.14, 128.099, 128.04, 127.99, 127.84, 127.80, 127.75, 127.73, 127.699, 127.66, 127.61, 127.57, 127.53, 127.48, 127.41, 127.36, 127.27, 127.21, 127.13, 127.08, 117.33, 100.64, 99.22, 98.88, 98.14, 96.97, 80.29, 79.93, 79.90, 79.61, 78.94, 75.17, 75.01, 74.93, 74.89, 74.83, 74.61, 74.49, 74.42, 74.19, 73.86, 73.35, 73.24, 73.11, 72.81, 72.45, 72.37, 72.33, 72.14, 71.84, 71.79, 71.74, 71.44, 71.28, 71.15, 69.32, 69.01, 67.68, 66.44, 65.99, 61.99, 25.88, 18.25, -5.09, -5.35.
Appendix 1

Spectra (Part A)
Appendix 1: Spectra (Part A)

1H normal range AC300ma03sSrK1064 (exp 1)

13C Standard AC300 ma03SsRk1064
ma03sSrK (exp 2)
### Appendix 1: Spectra (Part A)

**1H AMX500**

SRK 2045_allyl trityl mannosae (s0404 exp 11)

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**Processing Parameters**

**LB** : 0.30 Hz  
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**1H AMX500**

**SRK2049 (ks1404 exp 7)**

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**13C AMX500**

**SRK2049 (ks1404 exp 7)**
Appendix 1: Spectra (Part A)

1H normal range AC300
SRK 1171_6-O-TBDMS, 2,3,4-TRI benzyl mannosae (nv22sk exp 1) 2007

13C Standard AC300
SRK 1171_6-O-TBDMS, 2,3,4-TRI benzyl mannosae (nv22sk exp 2) 2007
Appendix 1: Spectra (Part A)

1H AMX500
SRK 2029 (r0404 exp 1)

13C Standard AC300
1175_ 6a ortho ester (ja17ra exp 2)
Appendix 1: Spectra (Part A)

1H normal range AC300
SRK 1157 glycosylation coupling Pd_lu23exp 1:2007

13C Standard AC300
SRK 1157 glycosylation coupling reaction spot 1B (OC23lu exp 5)
Appendix 1: Spectra (Part A)

1H AMX500
6-OH_DISACHARIDE (pk5519, exp 1)

13C AMX500
6-OH_DISACHARIDE (pk5519, exp 2)
Appendix 1: Spectra (Part A)

1H normal range AC300
SRK 1185 (Bu) Tetrasaccharide (ja28srk exp 1)

13C Standard AC300
SRK 1185 (Bu) Tetrasaccharide (ja28srk exp 2)
Appendix 1: Spectra (Part A)

1H AM5530
OH TETRA (w0527 exp 1) 2008

13C Standard AC300
SRK 1126B_OH Tetra (my26srk exp 2) 2008
Appendix 1: Spectra (Part A)

1H AMX500
1191_allyl Penta mannoside (43304 exp 1) 2008

13C AMX500
SRK 1193 (1-allyl-PENTA) (43303 exp 12)
Appendix 1: Spectra (Part A)

1H AMX500
SRK 1193 (1-OH-Penta)

13C AMX500
SRK 1193 (1-OH-Penta) (rk 0303 exp 2)
Appendix 1: Spectra (Part A)
PART B
SYNTHETIC STUDIES TOWARDS BIELSCHOWSKY'SIN
MACROCYCLES
PART B
CHAPTER 1
BACKGROUND AND INTRODUCTION
1 Background and Introduction

1.1 Bielschowskysin: Isolation, Structural Characterization and Biological Properties

The gorgonian octocorals of the Caribbean Sea encompass a variety of sea plumes, sea whips and sea pans. Specifically, the sea plume genus *Pseudopterogorgia* is a profound source of natural secondary metabolites\(^1,2\) of terpenoids, steroids, and acetogenins. Among several of these are biologically active compounds, exhibiting anti-inflammatory, anti-malarial, anti-tumor, and anti-mycobacterial properties.

The Rodríguez group has contributed enormously towards the isolation of gorgonian metabolites\(^1b-g,2b-d\) in recent years and has reported the highly oxygenated natural product of regular cembrane of the diterpene family, called bielschowskysin (1.1)\(^1e\) in 2004 from the West Indian gorgonian octocoral sea plume, *Pseudopterogorgia kallos* (Bielschowsky, 1918).

Bielschowskysin was isolated from 1.07 kg of air-dried specimen collected near the Old Providence Island, Columbia, located in the Caribbean Sea. By employing thorough extraction techniques, 39.6 mg of pure natural product was isolated as a colorless crystalline solid.
The structure of bielschowskysin (molecular formula: \( \text{C}_{22}\text{H}_{26}\text{O}_9 \)) and relative stereochemistry were elucidated by spectroscopic and single crystal X-ray diffraction analysis and confirmed to be an unprecedented, highly strained, \( \text{tricyclo}[9.3.0.0^{2,10}] \text{tetradecane} \) ring system. This regular diterpene metabolite belongs to the cembranes and comprises a \( \gamma \)-lactone moiety encompassing C10–C12 carbons with a relative \( S \)-configuration. Other highlighting features include two hemiacetals, one of which is a transfused cyclic lactol with an \( \text{exo} \)-cyclic methylene group and a spirocyclic hemiacetal constituted between C3-C6 with a transannular ether linkage. A tetra substituted cyclobutane nucleus embedded in the natural product is a result of transannular bonds between C7-C11 and C6-C12 of the 14-membered cembrane. Two isolated C=C bonds, one acetate group and 11 chiral centers with relative stereochemistry as \( 1\text{S}^*,2\text{S}^*,3\text{S}^*,6\text{S}^*,7\text{S}^*,8\text{S}^*,10\text{S}^*,11\text{S}^*,12\text{R}^*,13\text{R}^* \) are other structural features of bielschowskysin (1.1).

In terms of biological activity, bielschowskysin exhibits antiplasmodial activity against malarial causative organism \( \text{Plasmodium falciparum} \) with IC\(_{50}=10 \mu\text{g/mL} \), as well as profound and specific \textit{in vitro} cytotoxicity against two human cancer cell lines; EKVX non-small cell lung cancer (GI\(_{50}<0.01 \mu\text{M}\)) and CAKI-1 renal cancer (GI\(_{50}=0.51 \mu\text{M}\)).
1.2 Furanocembrane Family: Related Octocoral Diterpenoids

**A. Furanocembranoids:**

- bipinnatin J (1.2)
- rubifolide (1.3)
- acerosolide (1.4)
- providencin (1.5)

**B. Pseudopteranes**

- gorgiacerone (1.6)
- kallolide A (1.7)
- kallolide B (1.8)
- pseudopterolide (1.9)

**C. Rearranged and Complex Polycyclic Furanocembranoids:**

- ciereszkolide (1.10)
- intricarene (1.11)
- vermillin (1.12)
- plumarelilide (1.13)

**Scheme 1.1:** Diterpene Natural Products from *Psuedopterogorgia sp.*

Diterpenes isolated from *Psuedopterogorgia sp.* feature a variety of ring sizes and site specific variable oxidation patterns\(^{1a-f,2b-d,3}\). There are several categories of diterpenes which are interrelated by different rearrangement patterns. The major structural families are classified to be furanocembranoid, pseudopterane, gersolane, ciereszkane, etc., all
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with a macrocyclic skeleton. The typical features among different structural families are a γ-lactone, and a substituted furan. Besides that, internal double bonds or epoxides, e.g., providencin (1.5)\textsuperscript{lc}, pseudopterolide (1.9); exocyclic isoprenyl appendage e.g., bipinnatin J (1.2)\textsuperscript{d}, rubifolide (1.3)\textsuperscript{5}, acerosolide (1.4)\textsuperscript{6}, gorgiacerone (1.6)\textsuperscript{6}, kallolide A (1.7) and kallolide B (2.8)\textsuperscript{1a}; or as a fused ring system, e.g., bielschowskysin (2.1)\textsuperscript{le}, providencin (1.5)\textsuperscript{lc}, ciereszkolide (1.10)\textsuperscript{ld} are some of the commonly observed features.

Fundamental features of the basic macrocyclic core further reorganizes with the formation of additional transannular bonds across the core making the architecturally complex polycyclic diterpene metabolites, e.g., intricarene (1.11)\textsuperscript{lf}, verrillin (1.12)\textsuperscript{lb}, plumarellide (1.13)\textsuperscript{7}.

1.3 Biological Evolution of Diterpene Skeletons: Interrelation Pattern

The basic isoprene appended 14-membered macrocyclic cembrane skeleton (1.15) has been proposed to originate biosynthetically from geranylgeranyl pyrophosphate, GGPP (1.14). Pseudopterane (1.16)\textsuperscript{8}, gersolane (1.17), ciereszkane (1.18)\textsuperscript{ld} with 12, 13 and 13 membered macrocyclic skeletons, respectively, have been proposed to originate from different modes of ring contraction of cembrane 1.15. C2-C17 cyclisation with external isoprenyl group results in the providenciane (1.19) skeleton with a bicyclic 14+4 fusion; whereas transannular bonds across macrocyclic ring generate new classes of fused ring motifs. Tricyclic [6-7-5] ring-system of intricarene (1.20) skeleton is generated by transannulation at C6-C11 and C2-C12. Cyclization by forming the C7-C11 transannular bond gives the bicyclic 5+11 verrillane skeleton (1.21)\textsuperscript{lb}, while simultaneous/consequent
C6-C12 bond formation results in the tricyclic [5-4-9] bielschowskysane skeleton (1.22).
1.4 Bielschowskysin: Proposed Biosynthesis

Polycyclic cembrane metabolites are derived from simple furanocembranoids such as bipinnatin J (1.2) or rubifolide (1.3)\(^3\). Enzymatic oxidations together with transannulation have been proposed to account for the formation of bielschowskysin (1.1). The 2(5\(H\))-furanone-enol-ether 1.26 is conceived to be a potential intermediate, which itself is derived from enzymatic oxidations, though little is known, for example, by cytochrome P450 oxygenase. The origin of the enol-ether 1.26 can be substantiated in 2 ways. Oxidation of \(\Delta^{7,8}\) olefin 1.23 to give epoxide 1.24 followed by ketal intermediate 1.26.
formation by double vinylogous hydrolysis (Path A, Scheme 1.3). Alternatively, oxidative cleavage of trisubstituted furan 1.23 to an ene-dione 1.25 followed by hydrolysis with concomitant cyclization would give the ketal 1.26 (Path B, Scheme 1.3). Eventual transannular [2+2] cyclization between $\Delta^6,7$ enol-ether and $\Delta^{11,12}$ of $\gamma$-lactone 1.26 would deliver the [5-4-9] fused ring motif, bielschowskysin (1.1).

1.5 Gorgonian Diterpenes: Established Synthetic Methods

A significant amount of work has been established towards the synthesis of the growing family of diterpenoid cembranes and related natural products. Yet, aesthetically pleasing synthetic methods are still emerging to construct the structurally complex skeletons. The following methods briefly summarize the major methodologies towards these diterpene molecules.

1.5.1 Paquette Methodology towards Cembranoid Skeletons

The pioneering furanocembranoid chemistry was reported by the Paquette group with the synthesis of gorgiacerone (1.6) completed in 1992. The key methods to build the psuedopterane skeleton comprise construction of the furan ring by glyceraldehyde-acetonide 1.27 condensation with malonate 1.28; Grignard addition to extend furfural 1.29; conjugate addition of allyl stannane 1.30 to an aldehyde 1.31 with concomitant one pot transesterification to $\gamma$-lactone 1.32. Stille sp$^2$-sp$^3$ cross coupling at the remaining side of the furan 1.32 was used to stitch the allyl bromide unit to make-up the furan-lactone 1.33 with all skeletal carbons (Scheme 1.4).
Scheme 1.4: Paquette Methodology: Gorgiacerone (1.6) Synthesis

Eventual cyclization of aldehyde-allyl bromide 1.33 afforded a macrolide with a highly diastereoselective CrCl₂ mediated metallo-ene NHK (Nozaki-Hiyama-Kishi) reaction. Subsequent oxidation of the resulting allylic secondary alcohol to the carbonyl group by Swern oxidation accomplished the pseduopterane diterpene natural product, gorgiacerone (1.6).

The Paquette group successfully employed similar building blocks with conceptually comparable disconnection patterns to construct both furanocembranoid and psuedopterane skeletons. Both skeletons have been achieved by tuning the conditions of addition of allyl stannane 1.30 to the aldehyde 1.31 (Scheme 1.4). BF₃ activation of the reaction proceeds through C-C bond forming conjugate addition at the allylic position of primary allyl stannane; whereas, SnCl₄ mediates rearrangement of the primary allyl stannane 1.30 to a secondary stannane. Next, bond formation at the primary carbon with
the carbonyl of aldehyde 1.34 lead to the furanocembranoid skeleton, 1.35, e.g., acerosolide\(^{10e}\) (Scheme 1.5). Paquette further exploited this methodology to other furanocembranoid natural products.

![Scheme 1.5: Paquette Methodology: Acerosolide (1.4) Synthesis](image)

1.5.2 Marshall Methodology towards Cembrane/Pseudopterane Skeletons\(^{11}\)

The Marshall group is another leading contributor towards the synthesis of macrocyclic diterpenes. They developed a conceptually new methodology to build key elements of these natural products. Both furan\(^{11a}\) and \(\gamma\)-lactone scaffolds were derived pleasingly from an allene (Schemes 1.6 and 1.7).

Macrocyclization by etherification of alcohol-halide 1.40 followed by [2,3]-Wittig ring contraction in a macrocycle (e.g., 1.41) have been employed to build-up psuedopterane macrolides, e.g., the enantiomer of kallolide B 1.8b (Scheme 1.6)\(^{11b,c}\). With similar transformations, the macrocyclization of allenyl tin-aldehyde 1.46 gave the 14-membered cembrane macrocycles; e.g., \textit{ent}-rubifolide 1.3b (Scheme 1.7). The substituted furans (1.39/1.48) were derived from allenones at earlier stages. Lastly, diastereoselective butenolide construction was developed from either the sterically defined allenoate 1.43 or
1.48; which in turn was obtained from stereospecific propargylic alcohol intermediates 1.42 or 1.47 (Schemes 1.6 and 1.7).

Scheme 1.6: Marshall Methodology to Pseudopterane Skeleton
1.5.3 Donohoe RCM Method for Butenolide of Deoxypukalide

The Donohoe group in 2008 demonstrated the tactical application of RCM to construct both the furan and $\gamma$-lactone rings found in the furanocembranoid (-)-(Z)-deoxypukalide\textsuperscript{12} \textit{1.54a}, an enantiomeric form of the natural product (Scheme 1.8).
Diene precursor 1.49 was obtained from (S)-perillyl alcohol in 4 steps. RCM of diene with Grubbs II catalyst 1.50 smoothly formed a cyclic olefin 1.51, which was subsequently aromatized to furan by acid catalysis effectively in one pot. The linear chain with adequately substituted aromatic furan 1.52 was attained by exploiting the regioselective Negishi cross-coupling as the key step. From here, the key macrolactonization of seco-acid 1.52 was best implemented by Shiina protocol to furnish the macrolactone 1.53 in good yield. Finally, RCM with Grubbs II under dilute conditions effected the γ-lactone formation, while exclusively establishing the total synthesis of the target molecule (-)-(Z)-deoxypukalide (1.54a).
1.5.4 Pattenden RCM-CM Method for Cembranoids

The Pattenden group\textsuperscript{13} is another leading contributor towards the synthesis of furanocembrane/pseudopterane members and recently, the macrocyclic furanocembrane (+)-(Z)-deoxypukalide (1.54b) was constructed via the practical and concise functionalization of lactones by exploiting a one pot RCM and cross-metathesis (CM) approach.\textsuperscript{13j} The RCM-CM sequence not only builds the butenolide ring (by RCM) but also gives access to extend the chain further by CM with allyl alcohol 1.58 (Scheme 1.9). The remaining components of the synthesis were well-established Stille sp\textsuperscript{2}-sp\textsuperscript{2} cross-
coupling to bring-in aromatic portion, and the Cr-mediated NHK method for macrocyclization. Eventual oxidation at the final stage furnished the natural product. The broad disconnection pattern is conceptually analogous with known synthetic sequences of furanocembranoids, while the butenolide segment was specifically functionalized with a remarkable RCM-CM protocol.

1.5.5 Trauner Method to Bipinnatin J and Intricarene

The Trauner group has established a concise platform to prepare furanocembranoids via bipinnatin. This group achieved an expedient synthesis of the prototypical gorgonian furanocembranoid, (±)-bipinnatin J in 2006 within 9 linear steps without any protecting group and with high chemoselectivity (Scheme 1.10). The highlights of their synthesis are a strategic ruthenium-catalyzed Trost-Alder-ene reaction of the propiolate 1.62 with allyl alcohol and a subsequent one-pot acid catalyzed intramolecular transesterification to form the butenolide-aldehyde 1.63. The [Ru]-catalyzed Alder-ene transformation not only installed the butenolide but also allowed further functionalization. Stille sp²-sp² cross coupling, with a furan moiety gathered all carbons of the natural product. Finally, diastereoselective CrCl₂-NiCl₂ mediated NHK reaction delivered bipinnatin J (1.2) in good yield. The basis of the diastereoselectivity (dr > 9:1) of anti-alcohol formation during the macrocyclization can be rationalized by conformational rigidity of precursor 1.65, as defined by the remote stereocenter of butenolide driving the metallo-ene reaction via an energetically favored 6-membered chair transition state (1.66).
Shortly after Trauner’s report, Rawal\textsuperscript{15} and Pattenden\textsuperscript{13e} independently published similar strategies in the final stage macrocyclization method to bipinnatin J. In further exploratory studies on cembranoid congeners, Trauner modulated the appropriate stereocenter of lactone by an oxidation–reduction protocol and synthesized pure enantiomer of bipinnatin J (1.2).\textsuperscript{16} He further converted bipinnatin J (1.2) successfully to intricarene (1.11)\textsuperscript{16} by a biosynthetically proposed transannular [3+2]-cycloaddition (Scheme 1.10); the same method to intricarene has also been applied independently by Pattenden\textsuperscript{13e}. 

\textbf{Scheme 1.10}: Trauner Synthesis of Bipinnatin J (1.2) and Conversion to Intricarene (1.11)
1.6 Progress towards Bielschowskysin: Synthetic Reports

1.6.1 Sulikowski Synthesis of Tetracyclic Core

The first report documented towards bielschowskysin was the construction of the tetracyclic core by the Sulikowski group in 2006 by exploiting an intramolecular [2+2] photocycloaddition as the key step.\(^\text{17}\)

![Scheme 1.11: Sulikowski Synthesis of Tetracyclic Core of Bielschowskysin](image)

The synthetic sequence consists of converting the (S)-malic acid derived ester 1.68 to mesitylene acetal 1.69 with the 1°-alcohol accessible for a subsequent oxidation/Still-Genneri olefination sequence. Experience guided them to delay butenolide closure to a late stage, after making the γ-alkylidene butenolide. Sonogashira cross-coupling followed
by oxidization gave the conjugate acid **1.70**. Treatment with AgNO₃ catalysis under Negishi conditions affected cyclization to the alkylidene butenolide **1.71** as a single geometric isomer. The precursor **1.72** for photochemical reaction was obtained by an *in situ* acetal opening-lactonization sequence through transesterification. The key stereoselective intramolecular [2+2] photocycloaddition of sterically congested 5-alkylidene-2(5H)-furanone (**1.72**) under a sun lamp in acetone afforded a 5:1 mixture of the tetracyclic core **1.74** of bielschowskysin in 50% yield for the favored isomer, which was a crystalline solid upon purification (Scheme 1.11).

The anticipated stereo-control during [2+2] cyclization could be defined by the geometry of the exocyclic C4-C5 internal-double bond. Selective formation of the desired diastereomer was hypothesized *via* intermediacy of a dynamically-favored 1,4-biradical species **1.73** in which electrostatic and dipole interactions favor closure to a cyclobutane as compared to other ring series.

**1.6.2 Lear Synthesis of Tricyclic Core**

Our research group independently reported synthesis of a tricyclic core of bielschowskysin (**1.1**) relying on the photochemical [2+2] cycloaddition between an allene appended on a tertiary carbinol and double bond of γ-butyrolactone (Scheme 1.12). This work demonstrated the selective involvement of the internal π-bond of 1,2-cumulated double bonds of the allene **1.79** during [2+2] cycloaddition (rule of five) leading to the cyclobutane containing γ-lactone **1.80** (Scheme 1.12).
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Dioxalane-aldehyde 1.75 was derived from (S)-malic acid in 3 steps. From here, the benzylidene acetal 1.76 was attained by successive Grignard additions and transacetalization. Oxidation and Wittig homologation afforded a conjugate ester 1.77 which was then transformed to the γ-butyrolactone 1.78 via acetal cleavage. The ethynyl carbinol was homologated to the terminal allene 1.79. The allene anchored butenolide 1.79 upon irradiation with UV light by conventional UV lamps smoothly underwent a substrate-controlled, diastereospecific [2+2] cycloaddition to the tricyclic core 1.80 of bielschowskysin.

**Scheme 1.12: Lear Synthesis of Tricyclic Core of Bielschowskysin**

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1.6.3 Nicolaou Synthesis of Tetracyclic Skeleton

Recently, the Nicolaou group synthesized a tetracyclic core skeleton of bielschowskysin by a transannular [2+2] cyclization as the key step (Scheme 1.13). This route provided a five-step enantioselective synthesis of [9.3.0.0] carbocyclic ring framework of the natural product.
The synthetic sequence began with asymmetric reduction of acyl furan 1.81 by Noyori catalyst to give alcohol 1.82. Subsequent ceric ammonium nitrate (CAN) mediated coupling between the furan and the beta keto ester 1.83 provided access to the enol ether motifs 1.84a and 1.84b as separable diastereomers. Treatment of enol ether 1.84a with Grubbs I catalyst resulted in the RCM keto-product 1.85a with a trans double-bond predominantly. Attempts to induce a transannular [2+2] cyclization at this keto stage were unsuccessful. However, NaBH₄ reduction of ketone 1.85a to alcohol 1.86a and subsequent photochemical transannular [2+2] cyclization of macrocycle 1.86a formed tetracyclic framework 1.87a of bielschowskysin as a single diastereomer exclusively. The
relative stereochemistry of the [9.3.0.0] core 1.87a was assigned by X-ray crystal analysis of its corresponding 3,5-dintrobenzoate derivatives. Interestingly, the enantiomeric enol-ether 1.84b was also converted to the tetracyclic core 1.87a employing the same sequence of reactions.

It is noteworthy that the key transannular [2+2] cyclization in 1.86a/1.86b is also presumed to follow the ‘rule of five’ via a diradical species (c.f. 1.73) suggesting diastereoselective control in forming the cyclobutane nucleus.
1.7 Summary: Chapter 1 (Part B)

In this chapter, I introduced the diterpene furanocembrane natural products of marine origin, discussed the common structural features, and described the proposed biosynthetic origin of bielschowskysin (1.1). Also summarized were some established methodologies developed towards the synthesis of these diterpene natural products and published synthetic progress towards bielschowskysin.
References for Chapter 1 (Part B)


PART B

CHAPTER 2

BIELSCHOWSKYSIN: TRANSANNULAR [2+2] MODEL
2.1 Bielschowskysin: Transannular [2+2] Based Synthetic Plan

Bielschowskysin (1.1) is a highly oxygenated member of the furanocembranoid family. It has an unprecedented tricyclo[9.3.0.0²,10]tetradecane ring system. It exhibits a hexacyclic structure with a spirocyclic furan ring, a butenolide moiety and a cyclobutane ring. Additionally, the γ-lactone moiety is conformationally locked in such a way as to be oriented perpendicular to the furan ring.¹

![Bielschowskysin (1.1)](image1)

**Scheme 2.1: Synthetic Overview to Bielschowskysin (1.1)**

With these points in consideration, and upon evaluating possible disconnections of bielschowskysin, the formation of a macrocycle first and successively annulating via transannular bonds was chosen as the central strategy to our synthesis. As illustrated in Scheme 2.1, we visualized the ‘cyclobutane’ core to be introduced via a transannular [2+2] cycloaddition between an allene and a butenolide in a 14-membered macrocycle 2.2. [2+2] cycloaddition involving allenes has literature precedence²,³,⁴ and previously a
model tricyclic core has been synthesized from allene appended butenolide (c.f. Scheme 1.12) in our group. Such a transannular strategy is conceptually analogous to the biosynthetic pathway of the natural product in which the tetrasubstituted four-membered cyclobutane nucleus is implanted by [2+2] cyclization between an enol-ether and butenolide (c.f. Scheme 1.3). Further, there is a literature precedence to construct the tetracyclic core of bielschowskysin as established by the Sulikowski group (Scheme 1.11) and a tetracyclic core skeleton by the Nicolaou group (Scheme 1.12). Such a transannulation technique is envisaged to quickly construct polycyclic ring systems in a desired way. Functionalization of diene 2.1 to the spirocyclic-dihydrofuran would be achieved at a later stage (Scheme 2.1). Hence, an allene was chosen as an appropriate functional element in a [2+2] cyclization approach. The remaining double bond of the allene after transannulation would then enable later transformations to the dihydrofuran moiety.

Mechanistically an intramolecular photochemical [2+2] cyclization could proceed through a concerted or stepwise fashion. This becomes a case of interest, particularly, when a stepwise mechanism progresses through a diradical intermediate (c.f. 1.73, Scheme 1.11). The stability of this diradical intermediate could be a key factor in determining the regioselectivity of allene attack, order of transannular bond formation and feasibility of a [2+2] cyclization. In addition, conformational and geometrical requirements could drive inversion of the planar sp²-radical intermediate of [2+2] addition reaction.

Accordingly the transannular construction of a [5-4-9] fused-ring motif was targeted as a preliminary synthetic study of bielschowskysin, i.e., a ‘model macrocycle’ 2.3
encompassing a butenolide and an allene moiety to mimic the natural product was initially planned in this project.

Our prime objectives of the transannular study were thus:

- to install the cyclobutane core in a [2+2] addition between the double bonds of a butenolide and an allene.
- to probe the mechanism of [2+2] cyclization providing insights into
  - the preferable allene stereochemistry for [2+2] reaction.
  - the regioselective involvement of allene double bond\(^{2a,2d}\).
  - the geometrical outcome of double bond in the product.

To this end, the construction of a model macrocycle 2.3 became essential for the intended transannular studies.

**2.2 Strategy I: Butenolide Construction Followed by Macrocyclization**

Initially, the ‘butenolide’ part was recognized to be prepared by reductive hydroalumination of \(\gamma\)-hydroxypropiolates \(\textit{e.g.,}\) 2.5) and tandem addition onto the aldehyde 2.6 (Scheme 2.2). This strategy forms the butenolide 2.4 and enables assembly of the remaining carbons in one step. Aldehyde would be obtained from 2.4 after deprotection of terminal alcohol and oxidation. The late stage macrocyclization was opted by acetylide addition onto aldehyde. Eventually, after macrocyclization, allene 2.3 evolves from resulting propargylic alcohol in a macrocycle.
2.2.1 Butenolide Construction Studies

2.2.1.1 Background: Reductive Hydroalumination-Addition onto Aldehydes

The idea of reducing propiolates 2.7 by hydroalumination at low temperature and subsequent addition of the resulting α-metallated (E)-acrylates 2.8a onto aldehydes at room temperature to give allylic alcohols 2.9 has literature precedence by Tsuda and co-workers 8 (Scheme 2.3a). This method is a useful option 9 for aliphatic aldehydes when Baylis-Hillman conditions failed and has been extended to β-substituted propiolates 10. Encouraged by this novel methodology, we considered transforming the γ-hydroxypropiolate 2.5 to the butenolide 2.4 in an expedient fashion (Scheme 2.3b).

Scheme 2.3: Reductive Hydroalumination
2.2.1.2 Synthesis of $\gamma$-Hydroxy Propiolate

Synthesis of the left fragment begun with monoprotection of butane-1,4-diol 2.11 (Scheme 2.4). It was monoprotected as its TBDPS-ether 2.12 under stoichiometric control of reagents followed by PCC oxidation of the terminal alcohol to aldehyde 2.13 in good yield. Ethylpropiolate addition to the aldehyde 2.13 produced racemic propargylic alcohols 2.14 in 60% yield.

![Scheme 2.4: Synthesis of $\gamma$-Hydroxypropiolate](image)

2.2.1.3 Hydroalumination-Addition onto Aldehyde Studies

Although DIBALH mediated reductive addition \textit{via} hydralumination is reported to be smooth in the presence of HMPA\textsuperscript{8}, NMO\textsuperscript{11} is an environmentally benign alternative. NMO in our preliminary attempts was unproductive, so, we swapped to HMPA (Scheme 2.5). The results are summarized in Table 2.1.
When γ-hydroxy propiolate 2.14 was treated with DIBALH in the presence of either NMO (entry 1) or HMPA (entry 2), no reaction took place possibly due to interference by the free alcohol during the initial hydroalumination process. Thus, the propargylic alcohol 2.14 was protected as its MOM ether 2.15 before the reduction-addition sequence was attempted. Both HMPA (entry 3) and NMO (entry 4) as additives at low temperatures on protected 2.15 also failed.
Careful survey of the literature revealed reports using electrophilic boranes as additives\(^{12}\) in combination with HMPA that dramatically enhance the reaction for \(\gamma\)-substituted propiolates at -78 °C. Catalytic amounts of \((\text{Bu})_2\text{BOTf}\) along with excess HMPA as additives gave trace amount of allyl alcohol product \(2.10b\) by NMR analysis (entry 6) of crude reaction mixtures. Unfortunately, the allylic alcohol \(2.10b\) could not be fully characterized and several attempts to improve the yield of the product failed.

### 2.3 Strategy II: RCM of allylic Acrylates Followed by Macrocyclization

A RCM approach was planned as a parallel strategy to make the 5-membered lactone ring \(2.4\) (Scheme 2.6).

![Scheme 2.6: Strategy II: RCM Method for \(\gamma\)-Lactone](image)

This cyclization technique by alkene metathesis has been successfully used in construction of lactones of various ring sizes in numerous natural product syntheses\(^{13}\). [Ru]-carbene complexes are particularly significant owing to their wide-range of functional group tolerance and ready availability. Synthetic application using RCM of acrylates was first introduced by Ghosh et al.\(^ {14}\) in 1998 to form \(\gamma\)-and \(\delta\)-lactones.
conveniently. Recent successful RCM-based reports describing the total synthesis of deoxypukalide by Donohoe (Scheme 1.8)\(^9\) and Pattenden (Scheme 1.9)\(^{15}\) are noteworthy. However, the functional reactivity of the RCM precursor 2.16 was uncertain at this time as well as the choice of protecting groups (R, R', and R").

### 2.3.1 Synthesis of Allylic Alcohol Building Block

Protection of 5-hexen-1-ol 2.17 by MOMCl under TBAI catalysis gave the MOM ether 2.18 in good yield (Scheme 2.7). SeO\(_2\) mediated Riley allylic oxidation then gave secondary allylic alcohol 2.19 along with corresponding over oxidized product, the conjugated ketone 2.20. Initially, the same oxidation conditions were employed for the TBS ether of 5-hexen-1-ol (c.f. 2.18), but the TBS group was found to be cleaved during oxidation.

![Scheme 2.7: Allylic Oxidation](image)

#### 2.3.2. Synthesis of Alkynal Synthons

Alkyne-aldehyde 2.23 was prepared in two steps from commercially available 3-octyn-1-ol 2.21 (Scheme 2.8). At first the internal alkyne was isomerized to the terminal position 2.22 in good yield by amide-mediated alkyne-zipping reaction described by Macaulay.\(^{16}\)
The resulting primary alcohol 2.22 was oxidized by PCC in appreciable yields to afford the alkynal 2.23. A portion of the aldehyde was also masked as its corresponding acetal 2.24 with ethylene glycol for further reactions that will be described in forthcoming chapters.

\[
\text{Scheme 2.8: Synthesis of Alkynal Synthons}
\]

### 2.3.3 Synthesis of RCM Precursor

Allylic alcohol 2.25 derived from the alkynal 2.23 was first accessed via Baylis-Hillman reaction\(^1\) with excess acrylate and DABCO (Scheme 2.9). Alternatively, addition of the vinylalane derived from DIBALH reduction of methyl propiolate\(^{8a}\) allowed a quick method for preparation of the Baylis-Hillman adduct 2.25 in good yield which was subsequently protected (Table 2.2).
Scheme 2.9: Synthesis of RCM Precursor

Table 2.2: Protection of Allylic Alcohol (2.25)

<table>
<thead>
<tr>
<th>R</th>
<th>Conditions</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Bn (2.26)</td>
<td>NaH/BnBr, THF, 0 °C</td>
<td>complex mixture no product</td>
</tr>
<tr>
<td>2 Bn (2.26)</td>
<td>BnOTCA, CSA, DCM, 0 °C</td>
<td>complex mixture no product</td>
</tr>
<tr>
<td>3 Me (2.27)</td>
<td>NaH/Mel, THF, 0 °C</td>
<td>complex mixture 7% product</td>
</tr>
<tr>
<td>4 Me (2.27)</td>
<td>Ag2O/Mel, DCM, RT</td>
<td>complex mixture 10% product</td>
</tr>
<tr>
<td>5 MOM (2.28)</td>
<td>MOMCl/DIPEA, DCM, 0 °C</td>
<td>only product 60%</td>
</tr>
</tbody>
</table>
The clean protection of the secondary allylic alcohol 2.25 as its corresponding benzyl ether 2.26 was found difficult both under NaH/BnBr (entry 1) and BnOC(=NH)CCl₃ (entry 2) conditions. Making the methyl ether 2.27 was also inefficient under various conditions (NaH/MeI, entry 3; Ag₂O/MeI, entry 4) and suffered from poor yields with unidentified side products. The complex reactions could be reasoned as a possible consequence of the strong bases employed. Interesting for future studies, etherification with MOMCl/DIPEA (entry 5) was found effective at this location to give the MOM ether 2.28 in good yield.

Subsequent saponification of the methyl ether of the Baylis-Hillman alcohol 2.27 with LiOH smoothly gave the acid 2.29 in moderate yield. Esterification of the acid 2.29 and alcohol 2.19 by the DCC method led only to decomposition of the reactants. Eventually, the allylic acrylate 2.16a was obtained reproducibly under Mitsunobu conditions (Scheme 2.9).

2.3.4 RCM Study to Butenolide

With the dialkene 2.16a in hand, RCM attempts were carried out towards closing to the butenolide 2.4b (Scheme 2.10; Table 2.3). Mechanistically, the first metathesis event of Ru-carbene formation should take place at the allylic terminal, which is sterically and electronically favored. The next metathesis event with the conjugated double bond should then enable cyclization to the lactone.
Scheme 2.10: RCM Attempts to Butenolide

Table 2.3: RCM Conditions

<table>
<thead>
<tr>
<th>Catalyst (eq)</th>
<th>Solvent</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Grubbs I-polymer bound (0.2)</td>
<td>DCM</td>
<td>No reaction</td>
</tr>
<tr>
<td>2  Grubbs I (0.2)</td>
<td>DCM</td>
<td>Decomposed</td>
</tr>
<tr>
<td>3  Grubbs II (0.1)</td>
<td>DCM</td>
<td>No reaction</td>
</tr>
<tr>
<td>4  Grubbs II (0.1)</td>
<td>toluene</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Grubbs I precatalyst 2.30 was first chosen for RCM reaction. There was no reaction with polymer bound Grubbs I (20 mol%) in refluxing DCM (entry 1) and 20 mol% of Grubbs I, reaction decomposed (entry 2). The more efficient Grubbs II 1.50 (10 mol%, entry 3) catalyst in refluxing DCM was found equally ineffective. Grubbs II in refluxing toluene also resulted in no reaction (entry 4).

Although slower than internal alkynes, terminal alkynes were recognized to involve in enyne metathesis with internal [Ru] alkylidene. In retrospect, we suspect the possibility of alkyne involvement in the catalytic cycle of [Ru] alkylidene, which should be protected.
2.4 Strategy III: Allene Making Followed by Macrocyclization

At this juncture, we re-evaluated our synthetic sequence under the concept of RCM for the butenolide ring and followed by the macrocyclization (Scheme 2.6) by changing to acetylide addition onto an aldehyde first (Scheme 2.11). Intermolecular acetylide addition followed by macrocyclization with either RCM or macrolactonization was visualized as a better choice (Scheme 2.11). Here, an early stage allene formation and macrocyclization either by RCM or by macrolactonization would be a versatile choice and further allow RCM to be performed on a macrolactone 2.33.

Furthermore, the C10 chiral center on the butenolide may help govern a stereoselective [2+2] cycloaddition to form tetra-substituted cyclobutanes. Keeping this in mind, we intended to define the C-10 pivotal chiral center in the aldehyde 2.35 from (S)-malic acid via the triol 2.36 (Scheme 2.12).
2.4.1 Synthesis of Chiral Allylic Alcohol

Fischer esterification\textsuperscript{19} of (S)-malic acid followed by NaBH\textsubscript{4} reduction gave triol 2.36. C1-alcohol was left unprotected through 1,3-dioxane ring 2.37 formation using benzaldehyde dimethyl acetal.\textsuperscript{20} The aldehyde 2.38 obtained after Swern oxidation was then immediately used for Wittig olefination (Scheme 2.13). In spite of product formation (30\%) with the preformed Wittig ylide (Ph\textsubscript{3}P=CH\textsubscript{2}), isolation of the highly nonpolar product 2.39 from the Ph\textsubscript{3}P=O byproduct hindered large scale handling. To improve
practical issues, metallic zinc powder with CH₂I₂ in the presence of Ti(i-OPr)₄ were adopted (Nozaki-Takai olefination)²¹ (Scheme 2.14).

Scheme 2.14: Nozaki-Takai Olefination

The reproducibility of olefination was eventually improved by addition of lead (II) chloride that accelerates formation of the key geminal dizinc species 2.41 (Path B, Scheme 2.14) and addition of Ti(Oi-Pr)₄.²² In practice, slow addition of diiodomethane to a stirring solution of freshly activated zinc-dust/PbCl₂ along with CH₂I₂ in THF initiates an exotherm that eventually reaches a reflux. Next, the addition of Ti(Oi-Pr)₄ followed by aldehyde²¹-²³ exclusively forms the alkene 2.39. By virtue of the high sensitivity of Ti-
based intermediates (e.g., 2.42), this methylenation proceeded with variable yields. Nevertheless this procedure was found optimal for a maximum scale of 3g (15 mmol).

![Scheme 2.15](image)

**Scheme 2.15: Reductive Opening of Benzylic Acetal 2.39**

Reductive opening of benzaldehyde acetal 2.39 was less selective with LiAlH₄/AlCl₃ in diethylether²⁴ and gave the internal allyl benzyl ether 2.45 and terminal benzyl ether 2.46 in 4:1 respectively (Condition A, Scheme 2.15). Nevertheless, DIBALH of reliable quality reduced the acetal 2.39 exclusively to the benzyl allyl ether with free terminal alcohol 2.46 in excellent yields (Condition B, Scheme 2.15).²⁵

Mechanistically, the selectivity originates from differentiation of the acetal-oxygen atoms by solvated Lewis acid aggregates, AlCl₃·(Et₂O)ₙ by means of steric environment (Scheme 2.16). Lewis acid coordinates to one of acetal oxygens as shown in 2.47, thereby cleaving the acetal to give the zwitter-ionic alumnioxide 2.48. Finally, benzyl ether 2.45 forms through reduction by hydride transfer from LiAlH₄. Poor selectivity is attributed to little difference in steric imposition for the approaching AlCl₃·(Et₂O)ₙ, *i.e.*, between the
‘vinyl group’ and ‘hydrogen’ in the system of interest 2.39 (Scheme 2.16). On the other hand, the dual property of DIBALH as a Lewis acid, and as a hydride source permits this bulky reagent to efficiently differentiate the less hindered ‘acetal oxygen’.

![Scheme 2.16: Reductive Benzylidene Ring Opening-Mechanism](image)

Next, Dess-Martin oxidation of the terminal alcohol 2.45 gave aldehyde 2.50 which was homologated by one carbon by converting to enol-ether with the Wittig ylide MeOCH=PPh₃²⁶ in THF. The homologated aldehyde 2.35 was then obtained by hydrolysis of crude mixture of E/Z-enol-ethers using mineral acid (1M HCl) in refluxing THF in moderate yield (Scheme 2.17).
2.4.2 Assembly of Fragments, Allene Formation and Baylis Hillman Homologation

With both building blocks in hand, the alkyne-acetal 2.24 as its lithium acetylide was added to the aldehyde 2.35 to give the racemic propargyl alcohol 2.34 (Scheme 2.18) n-BuLi solution was used for the neat acetylide generation; whereas LHMDS produced unidentified side-products. Myers condition of employing \( o\)-nitrobenzenesulphonyl hydridize (NBSH) and PPh\(_3\) in combination with DEAD effectively converted the propargylic alcohol 2.34 in a single step to the internal allene 2.51 in good yield. Mechanistically, the propargylic alcohol gets inverted by substitution by NBSH under Mitsunobu conditions at low temperature to an alkynyl hydridize that spontaneously undergoes sigmatropic elimination of N\(_2\) to form the allene upon warming to ambient temperatures.\(^{27}\) It should be noted that both NBSH\(^{28}\) and PPh\(_3\) need to be freshly recrystallized for reproducible formation of allene.
Scheme 2.18: Synthesis of Macrocyclization Precursor 2.32

Aldehyde 2.52 was released from its acetal 2.51 by acidic hydrolysis and the crude mixture directly subjected to neat Baylis-Hillman conditions employing methyl acrylate and DABCO. Excess reagents were used to speed-up the coupling reaction and a single drop of methanol was used to make a homogeneous reaction mixture. With protecting group experience from previous studies (c.f., Scheme 2.9), the Baylis-Hillman alcohol
2.53 was converted to its MOM ether 2.54 using DIPEA or NaH as the base. Both bases enabled smooth MOM etherification in good yield (Scheme 2.18).

Benzyl group removal from the allylic position was studied next. Although the oxidative cleavage of benzyl ether with DDQ in DCM/H₂O was clean and completed in 2h, larger scales suffered from incomplete reactions regardless of excess reagents and longer reaction times (6h). Also, allylic oxidation advanced with time to give the vinyl ketone 2.55 together with the debenzylated allylic alcohol 2.32 (Scheme 2.18).

2.4.3 Macrocyclization: RCM Attempts in the Presence of Allene

![Diagram of Tentative RCM Pathway for Macrocyclization-Lactonization]

Scheme 2.19: Tentative RCM Pathway for Macrocyclization-Lactonization

RCM macrocyclization of 2.32 at this point, with an unprotected allylic alcohol and a conjugated ester, was speculated to be (Z)-selective (c.f., 2.56), if so, it would facilitate a
spontaneous transesterification to readily install a γ-lactone (Scheme 2.19). However, if the reaction pathway is concerted, transesterification parallels RCM, and thus, γ-lactone formation would be effected spontaneously.

Scheme 2.20: RCM for Macrocyclization

With implementation of the proposed idea, a terminal, (electron-rich) allylic olefin in the presence of an internal allene was attempted with Grubbs I catalyst (Scheme 2.20). This turned out to be ineffective with complete decomposition of dialkene 2.32. The flexible long alkyl chain with a distant, less reactive, electron poor 1,1-disubstituted alkene presumably could not achieve correct C-shape conformation for macrocyclization.
2.4.4 Macrolactonization: Synthesis of Macrolactone

Since a direct RCM macrocyclization was ineffective, we first pursued to make the macrolactone 2.33. This would conceivably align olefin partners for subsequent RCM more appropriately (Scheme 2.21).

According to the modified synthetic plan, the seco-acid 2.31 was obtained by LiOH mediated saponification of the methyl ester 2.32 (Scheme 2.21). Macrolactonization was next accomplished under Yamaguchi conditions by in situ mixed anhydride formation with excess 2,4,6-trichlorobenzoyl chloride (TCBC) and triethylamine. Excess DMAP (10 eq) finally promoted the macrolactonization event under dilute conditions.\textsuperscript{29} Although the macrocyclization suffered from low yields, macrolactone formation to 2.33 was found to be reproducible.

![Scheme 2.21: Macrolactonization](image-url)
2.4.5 Butenolide Installation: RCM Study of Macrolactone

The RCM study with Grubbs catalysts are summarized in Table 2.4. Grubbs I (20 mol%), in refluxing toluene for 16h gave 3 major spots (entry 1). However, purification and characterization of spots was hindered by trace amounts of products being formed. As a next choice, Grubbs II (10 mol%) in refluxing DCM for 20h gave no reaction and recovered starting material (entry 2).

![Scheme 2.22: RCM for γ-Lactone Formation](image)

**Table 2.4: RCM Conditions in a Macrolactone**

<table>
<thead>
<tr>
<th>Catalyst (eq)</th>
<th>Additive</th>
<th>Solvent/Temp</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Grubbs I (0.2)</td>
<td>-</td>
<td>toluene, reflux, 16h</td>
<td>Complex reaction/decomposed</td>
</tr>
<tr>
<td>2 Grubbs II (0.1)</td>
<td>-</td>
<td>DCM, reflux, 20h</td>
<td>SM recovered</td>
</tr>
<tr>
<td>3 Grubbs I (0.2)</td>
<td>Ti(i-PrO)₄ (2 eq)</td>
<td>DCM, reflux, 24h</td>
<td>Complex reaction/decomposed</td>
</tr>
<tr>
<td>4 Grubbs II (0.1)</td>
<td>Ti(i-PrO)₄ (2 eq)</td>
<td>DCM, reflux, 16h</td>
<td></td>
</tr>
</tbody>
</table>
It is postulated that the ester carbonyl of allylic acrylate *(e.g., 2.33)* may form a stable 6-membered chelation ring 2.58 with an internal [Ru] species (Scheme 2.23). This would compete with the formation of a metallacyclobutane intermediate 2.57 and thus, the desired metathesis event to form γ-lactone, *(e.g., 2.3)*. Such interference can be overcome by addition of an external Lewis acid, *(e.g., Ti(i-OPr)_4)*. Hence, Ti(i-OPr)_4 was added along with 20 mol% of Grubbs I in refluxing DCM for 24h (entry 3). Again the reaction mixture was complex and formed trace amounts of unidentified products. Even with 10 mol% of Grubbs II along with Ti(i-OPr)_4 in refluxing DCM (entry 4) the ring closing reaction pattern was found similarly complex.

**Scheme 2.23**: Catalytic Cycle of Grubbs Catalyst with Allylic Acrylates
2.5 Summary: Chapter 2 (Part B)

In this chapter, I explored routes to the alicyclic 14 membered allene macrocyclic model 2.3 of bielschowskysin for future transannular [2+2] cycloaddition studies. Initially, a reductive hydroalumination strategy to a \( \gamma \)-lactone was found unsuccessful. An alternative route to the lactone was attempted via RCM of functionalized allylic acrylate 2.16a. Then, an internal allene 2.51 was synthesized from propargylic alocohol 2.34 employing Myers conditions. Baylis Hillman was used for homologation. Eventually, the synthetic scheme evolved into implementing the RCM of a macrolactone 2.33. A 15-membered macrolactone 2.33 was synthesized under Yamaguchi conditions. RCM attempts by Grubbs I or Grubbs II catalysts to give 2.3 were unfruitful. Titanium based Lewis acids as additives also made no improvement on the RCM reactions.
References for Chapter 2 (Part B)


PART B

CHAPTER 3

RCM METHODS TOWARDS BIELSCHOWSKYSIN MACROCYCLES: SYNTHESIS OF BUILDING BLOCKS
3.1 Towards Bielschowskysin

3.1.1 Bielschowskysin: Retrosynthesis I

As discussed in Chapter 2 (Scheme 2.1), the highly oxygenated, fused hexacyclic scaffold of bielschowskysin was envisioned to be constructed via the transannular [2+2] cycloaddition between a $\Delta^6,7$ double bond of allene and $\Delta^{11,12}$ double bond of butenolide as key element.\(^1\) Such a transannular strategy is conceptually analogous to a bio-synthesis of the natural product, in which the tetrasubstituted cyclobutane nucleus would be implanted by [2+2] cyclization between enol-ether and butenolide functionalities (c.f. Scheme 1.3).\(^2\) Our preliminary synthetic plan towards bielschowskysin is shown in Scheme 3.1.

The key issues to consider from a mechanistic basis are the stereochemistries of the C5-C7 allene and the geometry of the trisubstituted C3-C4 double bond. These factors together can impose ring strain and influence conformational and steric preferences in a 14-membered macrocycle (e.g., 2.2). Eventually, conformation of macrocycle 2.2 would not only dictate the feasibility of the [2+2] cycloaddition reaction, but also the configurational orientation of conjugated double bonds in the [2+2] adduct.

Functionalization of the spirocyclic-dihydrofuran portion of bielschowskysin thereafter would be performed after [2+2] cyclization. Conceivably, the [4+2] cycloaddition of conjugated diene 2.1 with singlet-oxygen would result in an endo-peroxide 3.1 which could be transformed to the dihydrofuran portion using a metal mediated reduction.
In light of our primary focus on bio-mimetically inspired transannulation methods, construction of an appropriate 14-membered macrocycle was envisioned to be pivotal for later stage functionalization. We recognized transition metal catalyzed ring-closing olefin metathesis (RCM) as an appropriate choice for macrocyclization at C11-C12 of a γ-lactone. RCM is a popular technique in modern organic synthesis. [Ru]-carbene complexes are particularly significant owing to their wide-range of functional group tolerance and ready availability. Enormous synthetic applications of this catalytic process
have emerged in crafting a wide variety of small to large rings of diverse natural products.\textsuperscript{3} Recent independent reports describing synthesis of deoxypukalide (1.54b) by Donohoe\textsuperscript{4} (Scheme 1.8) and Pattenden\textsuperscript{5} (Scheme 1.9) to directly install the butenolide moiety evidently provide the potential of RCM routes over other methods\textsuperscript{2b,6} available to prepare furanocembrane congeners.

Herein, two alternative sequences of RCM-(macro)lactonization were envisioned from a linear precursor (3.2). An early stage macrolactonization would facilitate RCM to close conformationally near-located olefins into a $\gamma$-lactone. On the other hand, an initial macrocyclization via RCM by a contemporary transition metal catalyzed reaction enable a subsequent $\gamma$-lactonization.

The allene linear precursor for macrocyclization would be formed by converging alkyne 3.3 with the conjugated aldehyde 3.4. As such, a C-C bond forming acetylide addition of an alkyne unit onto the carbonyl of a conjugated aldehyde building block would afford a propargylic alcohol that could be transformed subsequently into an allene. Thereafter, a Baylis-Hillman reaction would furnish the diene precursor 3.2 for a macrocyclization step. This diene-conjugated ester 3.2 serves as a common intermediate for RCM, as well as a seco-acid for macrolactonization studies (Scheme 3.1).

3.1.2 Alkyne Synthon: 1\textsuperscript{st} Generation Synthesis

The fully functionalized allyl ether building block 3.3 was visualized to be made from a chiral malic acid (Scheme 3.2).\textsuperscript{7} (S)-malic acid is appropriately predisposed with the correct chiral secondary alcohol and a terminal carboxyl groups that allows functionalization via its corresponding triol (2.36).
Scheme 3.2: Alkyne Building Block: Retrosynthesis I

In earlier considerations, it was intended to develop the 3°-alcohol by consecutive Grignard C-C bond formation (Scheme 3.2). A potential advantage of using Grignard reactions is the control of diastereoselectivity through chelation control via the existing chiral center in a locked acetonide 3.6.\textsuperscript{id}

Scheme 3.3: Alkyne-Benzylidene 3.9 Synthesis
Scheme 3.3 illustrates the synthesis of alkyne-benzylidene 3.9. 1,3-Dioxolane of acetonide 3.5 was formed from triol 2.36 by protection in acetone with CuSO₄ and p-TSA catalyst. PCC oxidation of the distant C4-primary alcohol, followed by nucleophilic addition using MeMgBr and subsequent PCC oxidation gave the methyl ketone 3.6. Addition of ethynylmagnesium bromide gave a separable mixture of diastereomeric 3°-propargylic alcohols in a 4:1 preference to the desired diasteromer 3.7. Diastereoselectivity can be rationalized via chelation control of an acetal ring as illustrated earlier. The 1,3-dioxolane ring of acetonide was transformed to the more stable 1,3-dioxane 3.8 using benzaldehyde dimethyl acetal under the influence of an organic acid, CSA. Lastly, methylenation was achieved through a Swern oxidation-Nozaki-Takai reaction sequence to furnish the benzylidene alkyne 3.9.

![Scheme 3.3: Synthesis of Alkyne-Benzylidene 3.9](image)

**Scheme 3.4:** Reductive Opening Study of Benzylidene Acetal Ring 3.9

As proposed, the sequence of early Grignard additions followed by methylenation worked well, however, the selective reductive opening of benzylidene 1,3-dioxane 3.9 was problematic. Benzyl ethers 3.10/3.11 failed to form with both DIBALH⁸ and
NaCNBH₃/dry-HCl⁺ conditions (Scheme 3.4). An alternative plan to maintain orthogonal protections was to form the diol 3.12 and then protect differentially.

![Scheme 3.5: Synthesis of Alkyne Building Block](image)

**Table 3.1: Hydrolytic Cleavage of Benzylidene 3.9**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. p-TSA (1eq) DCM/MeOH (1:1), RT, 4 days</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>2. Conc. HCl (pH=1) THF/H₂O (1:1), 2 days, 50 °C</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>3. Conc. H₂SO₄, (pH=1) THF/H₂O (1:1), 65 °C, O/N</td>
<td>~90%</td>
</tr>
</tbody>
</table>

(60-70% yield)
Hydrolytic cleavage of dioxane 3.9 was incomplete despite long reaction times with $p$-TSA in methanol (Table 3.1; entry 1) and even with conc. HCl at pH=1 (entry 2). Harsh conditions using dibasic mineral acid conc. H$_2$SO$_4$ (pH=1) in refluxing THF-H$_2$O mixture$^{10}$ (entry 3) more efficiently hydrolyzed the strong acetal ring to its corresponding 1,3-diol 3.12 (Scheme 3.5).

However, benzylolation of 1,3-diol 3.12 was not selective as it gave all possible mono and dibenzylated products. The bulky pivaloyl ester group was therefore selected to protect the secondary alcohol selectively as a temporary protecting group, which would be changed to a more robust group at advanced stages.

Diol 3.12 upon treating with pivaloyl chloride with excess pyridine in DCM suffered from sluggish reaction times (10% conversion overnight). However, the use of triethylamine as a base pushed the reaction to completion overnight with exclusive formation of the monoprotected alcohol 3.13, even when excess pivaloyl chloride was used. The differential efficiency of bases can be rationalized from their basic strengths: triethylamine ($pK_a=10.78$) and pyridine ($pK_a=5.25$).

Protection of $\beta$-alcohol as its corresponding TMS ether 3.14 was not effective with 2,6-lutidine ($pK_a=6.99$) and again, triethylamine ($pK_a=10.78$) was found favorable to complete the reaction.

Due to the poor overall protecting group economy, inability of bringing tolerant protecting groups and trace amounts of available material, an alternate scheme was pursued to the alkyne building block.
3.1.3 Alkyne Synthon: 2nd Generation Synthesis

Under an alternative scheme, the aldehyde 2.50 previously synthesized (Scheme 2.17) from (S)-malic acid during [2+2] model study was used to form protected alkyne building block. From this aldehyde 2.50, the modified scheme began with addition of MeMgBr to give an inseparable mixture (1:1) of diastereomeric alcohols 3.15. Methyl ketone 3.16 was obtained by PCC oxidation and HC≡CMgBr addition gave the ethynyl carbinols 3.17 and 3.18 as a 31:10 diasteromeric mixture in preference to anti-alcohol 3.17 (Path A; Scheme 3.6).

Scheme 3.6: Synthesis of Alkyne Building Block 3.3
To investigate the selectivity from chelation control\textsuperscript{1d} the Grignard addition sequence was reversed. Thus, HC≡CMgBr was added first onto the aldehyde 2.50 to give diastereomeric propargylic alcohols 3.20. Mild oxidation to alkynone 3.21 with MnO\textsubscript{2} failed. So, we reserved to conventional Dess-Martin oxidation to obtain alkynone 3.21. Interestingly, the selectivity of MeMgBr addition onto the alkynone 3.21 was equally reversed (10:35) to that of Path A (Path B; Scheme 3.6). This evidence supports a chelation mode of nucleophilic addition from the sterically more favored conformer. Convinently, the diastereomeric 3°-alcohols separated well by TLC, and could be purified by flash column chromatography without difficulty. However, the selectivity could be further improved using additional metal-salts.\textsuperscript{11}

To confirm the stereochemistry at the propargylic alcohol positions, the benzyl ethers 3.17 and 3.18 were separately transformed to the benzylidene acetals 3.9 and 3.22 by treating with DDQ in dry DCM (Scheme 3.7). The resulting benzylidene acetals were compared to authentic sample prepared previously (c.f. Scheme 3.3) This confirmed the \textsuperscript{1}H-NMR of only one acetal 3.9 to exactly match the authentic material.

\[ \text{Scheme 3.7: Confirmation of Stereochemistry} \]
Subsequently, each tertiary alcohol 3.17 and 3.18 was protected as its corresponding TMS ether 3.3 and 3.19 in good yield to afford the desired alkyne synthons.

### 3.1.4 Conjugated Aldehyde Synthon: 1st Generation Synthesis

![Scheme 3.8: Aldehyde building block 3.4: Retrosynthesis I](image)

The *trans*-fused cyclic lactol portion of the natural product 2.1 was visualized to be developed from a conjugated aldehyde *e.g.*, 3.4 as depicted in Scheme 3.1. Conjugated aldehyde in turn would be synthesized from *D*-glucose by a reported procedure *via* the
diacetal 3.24 and PMB ether 3.23. Final selective removal of the exocyclic acetal would then facilitate elaboration towards the conjugated aldehyde 3.4 (Scheme 3.8).

Scheme 3.9: Synthesis of PMB Ether 3.23

To this end, ketone 3.25 was synthesized as shown in Scheme 3.9 using modified procedures. The diacetal glucose 3.24 was formed by treating D-(+)-glucose with acetone in the presence of conc. H₂SO₄ as the catalyst. Recrystallization of crude product from chloroform afforded bright, white, needle-like crystals. Collins oxidation by CrO₃/pyridine in combination with acetic anhydride gave the crude ketone 3.25. Wittig
homologation with the in situ generated stabilized ylide 3.26 yielded the conjugated ester 3.27. Pd-catalysed hydrogenation proceeded in quantitative yield under high pressure of H₂ gas to give 3.28 stereoselectively with (R)-configuration at the C3 position. In addition to X-ray crystallography analysis, the relative stereochemistry was established by NOE correlation between H₃C₃-H₃C₂ & H₃C₂-H₃C₁. We note here that C3-relative stereochemistry is regenerated efficiently under this oxidation-Wittig-hydrogenation sequence (Scheme 3.9). Thereafter, the methyl ester 3.28 was reduced quantitatively by LiAlH₄ to terminal alcohol 3.29 which was subsequently protected as its PMB ether 3.23 for a later stage Baylis-Hillaman coupling.

To elaborate to the conjugated aldehyde 3.4, the exocyclic acetal in 3.23 was selectively cleaved in 75% yield to a diol 3.30 employing 60% aqueous acetic acid keeping the internal acetal intact. Oxidative cleavage of the vicinal diol afforded a sensitive aldehyde 3.31. Attempts to purify by column chromatography failed due to decomposition. Thus the aldehyde was quickly used for Wittig homologation with the preformed ylide 3.32 in DCM to afford the (E)-trisubstituted alkene 3.33 in 72% yield over 2 steps. The conjugated ester 3.33 was next reduced to the allylic alcohol 3.34 by DIBALH in excellent yield with little over reduction of the double bond. Both the products were luckily separable by flash column chromatography. Subsequent allylic oxidation by DMP furnished the desired conjugated aldehyde synthon 3.4 in excellent yield.
3.2 Assembly of Building Blocks: Alkyne Addition onto Aldehyde

3.2.1 Carreira Asymmetric Addition Study

The stereochemistry at the resulting C5-propargylic alcohol (c.f. Scheme 3.11) would determine the chirality of allene. Based on our understanding from minimized energy conformations of appropriate macrocycles by DFT calculations, together with 3-D models, the geometry of allene was conceived to be a crucial aspect for forthcoming events. The specific geometry of the allene would not only conceivably control
Chapter 3: Synthesis of Building Blocks (Part B)

macrocyclization, but also direct [2+2] cycloaddition to follow either a concerted or stepwise pathway. The pathway of [2+2] cyclization would eventually guide the geometry of the remaining unreacted double bond of the allene after cycloaddition (c.f. Scheme 3.1). In addition, the geometry of the allene would also be a determining factor in a macrocycle with a specific ground state conformation.

Under this reasoning, the stereochemical course of C-C bond formation during alkyne addition onto aldehydes was envisioned to be important.

![Scheme 3.11: Proposed Carreira Alkyne Addition](image)

Although challenging in multifunctional substrates, several auxiliary controlled methods have emerged for stereoselective additions forming propargylic alcohol. Amongst these Carreira’s Zn-acetylide method using N-methylephedrine (3.38) auxiliary\(^\text{14}\) is attractive (Scheme 3.12).
To test this method, commercially available hex-5-yn-1-ol (3.40) and cinnamaldehyde (3.41a) were adopted as coupling partners. With little excess of alkyne the reaction was performed in toluene without a chiral auxiliary. Zn(OTf)$_2$ in combination with Et$_3$N gave no observable reaction after 14h at room temperature and even after an additional 8h at 65 °C. After careful analysis of initial reports, toluene was substituted with acetonitrile$^{14a}$, but, this gave similarly no reaction (Scheme 3.13).
Suspecting the free unprotected alcohol hindered the reaction, the coupling was tested with the alkyne 2.2 and cinnamaldehyde (3.41a) in the presence of N-methylephedrine (3.38). Even after 30h, only trace amounts of propargylic alcohol 3.42b was observed (Scheme 3.14). Alkyne 3.38 and an aliphatic conjugated aldehyde 3.41b were also tested under reported coupling conditions without success.

### 3.2.2 Base Mediated Methods

Next, base mediated methods of acetylide addition onto aldehyde were studied. As a first choice, LHMDS was chosen for acetylide generation from alkyne 3.3 and the base was added at -78 °C, followed by addition of the conjugated aldehyde 3.4 after 1h. Despite the raising to room temperature (-78 °C-RT), both reactants were recovered. As a next choice, the base was replaced with n-BuLi and the reaction executed at -78 °C (Scheme
3.15). Unfortunately, [2,3]-Wittig rearrangement paralleled acetylide formation. Ultimately, this competing process hampered formation of the secondary propargylic alcohol 3.35, which was isolated in 21% yield. The diastereomeric propargylic alcohols (10:7) were inseparable by silica gel column chromatography techniques.

Scheme 3.15: Alkyne Addition by \(n\)-BuLi

Eventually, EtMgBr was found effective as the base to generate alkynyl magnesium bromide \textit{in situ} without [2,3]-Wittig rearrangement. This will be described later in Scheme 5.13, chapter 5.
3.3 Summary: Chapter 3 (Part B)

In this chapter, I explored synthetic studies aiming at transannular [2+2] cycloaddition towards a macrocycle core of bielschowskysin (1.1). A Convergent synthesis of the macrocycle was designed by disconnecting the C5-C6 and C11-C12 bonds. Routes to the alkyne synthon 3.3 were further developed from (S)-malic acid via Nozaki-Takai methylenation and a consecutive Grignard addition reactions. The requisite conjugated aldehyde synthon 3.4 was synthesized from D-Glucose in 11 steps. Eventually, alkyne was added onto aldehyde to obtain propargylic alcohol 3.35.
References for Chapter 3 (Part B)


PART B

CHAPTER 4

ALLENE FORMATION AND PHOTOCHEMICAL CYCLOADDITION STUDIES
4.1 Allene Formation Studies

4.1.1 Bielschowskysin: Synthetic Plan

As previously discussed, our central synthetic strategy towards the synthesis of bielschowskysin was based on a transannular [2+2] cycloaddition reaction between an allene and the olefin of a butenolide. As illustrated in Scheme 4.1, we visualized the ‘cyclobutane’ core to be introduced via a transannular [2+2] cycloaddition in a 14-membered macrocycle 2.2. A model tricyclic core 1.80 has been synthesized from allene-butenolide (c.f. Scheme 1.12). Stereochemistry of allene would be one of the determining factors for the conformational orientation of the macrocycle. A concerted or stepwise mechanism would be speculated for intramolecular photochemical [2+2] cyclization.\(^2\)\(^3\) This becomes a case of interest, particularly, when a stepwise mechanism occurs; which could be a key factor in determining the regioselective involvement of the allene double bond\(^1\), the order of transannular bond formation and the eventual feasibility of the [2+2] cyclization. With these points in consideration, we were interested
in the synthesis of chiral defined $\alpha$–hydroxy allene with quaternary carbon centers at both sides.

### 4.1.2 Allenes: Introduction

Allenes were first synthesized in 1887 and are found in as many as 150 natural products of biological origin$^5$ (Fig 4.1). Owing to their unique properties, they have become attractive synthons and extensive chemistry of allenes in several synthetic methods has been developed.$^{4b,4e,6}$

*Fig 4.1: Allenes Containing Natural Products*

Allenes can be synthesized in various ways.$^{6f}$ These methods would be broadly categorized as:

1. Transition Metal-Catalyzed Reactions.


3. Isomerization Reactions.
Based on the proposed synthetic route to bielschowsksysin, a propargylic synthon 4.1 would be advantageous to convert to allene moiety 4.2. In general, allenes could be derived conveniently employing a variety of methods from propargylic systems (Scheme 4.2). Previously, in a model study project, the allene 2.51 was synthesized reproducibly in good yields employing Myers condition7 using NBSH, PPh3 along with DEAD (c.f.: Scheme 2.18).

Scheme 4.2: Allene from Propargylic Alcohol: Synthetic Methods
4.1.3 Synthesis of Propargylic Alcohol and Allene Formation Studies

![Reaction Scheme](image)

**Scheme 4.3:** Allene Synthesis Study from Alkynol

On the basis of the proposed route, propargylic alcohol 4.6 was obtained by addition of alkyne 4.5 onto the conjugated aldehyde 3.6 in good yield (Scheme 4.3). The resulting propargylic alcohol was treated with different allene-forming conditions as summarized in Table 4.1. The recently developed protocol by Ready et al. with the Schwartz reagent Cp₂Zr(H)Cl without a base (entry 1) or in the presence of a Grignard reagent as a base (entry 2, 3) gave no observable reaction. An alternate choice of using Myers method with NBSH, PPh₃ and DEAD was also found ineffective (entry 4).
Table 4.1: Allene from Alkynol

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{1^8}$ Cp$_2$Zr(H)Cl, toluene, 24h</td>
<td>-</td>
</tr>
<tr>
<td>$^{2^8}$ Cp$_2$Zr(H)Cl, EtMgBr toluene, 24h</td>
<td>-</td>
</tr>
<tr>
<td>$^{3^8}$ Cp$_2$Zr(H)Cl, $i$-PrMgCl toluene, 24h</td>
<td>-</td>
</tr>
<tr>
<td>$^{4^7}$ NBSH, PPh$_3$, DEAD, THF</td>
<td>-</td>
</tr>
</tbody>
</table>

At this stage, a model reaction was attempted on a propargylic alcohol 4.10 (Scheme 4.4) to validate the allene formation via the hydroyzirconation of alkynes with the Schwartz reagent Cp$_2$Zr(H)Cl in combination with a Grignard reagent as a base. Here, despite the slow reaction, the expected allene 4.11 was observed while recovering unreacted propargylic alcohol 4.10. From these comparisons, we anticipated, the sterically highly hindered alkyne flanked with quaternary carbon center (c.f. 4.6) would become difficult for approaching reagents. Such a quaternary system would be too bulky and thus it would be difficult to obtain the $\alpha$-hydroxy allene-ene.

![Scheme 4.4: Allene Synthesis by Schwartz Reagent](image)

Scheme 4.4: Allene Synthesis by Schwartz Reagent
4.1.4 Allene Formation by Keck Conditions

Seeking alternative routes to vinyl-allenes\textsuperscript{6f}, we found an efficient preparation of sensitive vinyl-allenes by LiAlH\textsubscript{4} as developed by Keck \textit{et al.}\textsuperscript{9} from ethynyl carbinol \textbf{4.12} (Scheme 4.5). The free hydroxyl group in alkynol \textbf{4.12} facilitates LiAlH\textsubscript{4} to come closer to the sterically hindered alkyne and forms an alanate intermediate \textbf{4.13} by reductive hydroalumination. Simultaneous antiperiplanar elimination of the alkoxy group together with the aluminum species results in the stereoselective\textsuperscript{10} formation of a chiral hydroxymethylvinyl allene \textbf{4.14}.

\begin{align*}
\textbf{4.12} & \xrightarrow{\text{LiAlH}_4} [\textbf{4.13}] \xrightarrow{\text{antiperiplanar elimination}} \textbf{4.14} \\
R = \text{Me, THP}
\end{align*}

\textbf{Scheme 4.5}: Allene Formation by LiAlH\textsubscript{4}\textsuperscript{10}

Anticipating allene formation from \(\gamma\)-hydroxy propargylic ether (\textit{c.f.} \textbf{4.17}), the diastereomeric propargylic alcohol mixture \textbf{4.16} was converted to its corresponding methyl ether (Scheme 4.6). Subsequently, the crude product was desilylated to obtain an inseparable mixture of diastereomeric methyl ethers \textbf{4.17}. At this stage, allene formation from the unprotected \(\gamma\)-hydroxy propargylic ether under Keck conditions was studied (table 4.2).
Chapter 4: Allene Formation and Photochemical Cycloaddition Studies (Part B)

Scheme 4.6: Allene from Methyl Ether of γ-Hydroxy Alkynol

Table 4.2: Allene Formation Conditions from Methyl Ether

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a) LiAlH₄ (3 eq), Et₂O or THF, rt</td>
<td>Allene 4.18 (30%);</td>
</tr>
<tr>
<td>1b) Solid I₂, -78 °C</td>
<td>Incomplete conversion</td>
</tr>
<tr>
<td>2a) LiAlH₄ (5 eq), Et₂O, rt</td>
<td>Allene 4.18 (30%);</td>
</tr>
<tr>
<td>2b) Solid I₂, -78 °C</td>
<td>Complete conversion.</td>
</tr>
<tr>
<td>3 LiAlH₄ (10 eq) Et₂O, rt</td>
<td>Clean allene 4.18 (34%);</td>
</tr>
<tr>
<td>4 Red-Al</td>
<td>No reaction</td>
</tr>
<tr>
<td>5 NBSH, PPh₃, DEAD, THF</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

As described earlier, Keck conditions were tested on the γ-hydroxy propargylic ether 4.17. Either Et₂O or THF as solvent did not affect the reaction course and α-hydroxy allene formation (entry 1), also reaction remained incomplete. When amount of LiAlH₄
was increased (entry 2), the starting material was completely consumed with no improvement in the yield. When, I$_2$ was not used, clean formation of the allene 4.18 was observed, although in an incomplete fashion. The unreacted methyl ether 4.17 was isolated and treated to same conditions, however, to result no observable reaction. Based on the mechanism of allene formation required an antiperiplanar elimination of methoxy group, we anticipated that due to high steric crowd around alkyne, only one diastereomer could interact favorably with Keck conditions to form allene.

4.1.5 Keck Conditions with Stereodefined Propargylic Alcohols

In order to investigate the assumed reactivity of one single diastereomeric propargylic alcohol, the catalytic chiral reduction of ynone was planned to form propargylic alcohols diastereoselectively. With a view to adopt CBS promoted chiral reductions, ynone 4.19 was obtained quantitatively as a single diastereomer by treating propargylic alcohol 4.16 with MnO$_2$ at room temperature (Scheme 4.7). Reduction of ynone 4.19 with the (S)-CBS catalyst in combination with BH$_3$ gave (S)-diastereomer 4.16a and (R)-CBS catalyst afforded (R)-diastereomer 4.16b (c.f. 4.20 and 4.21).
Chapter 4: Allene Formation and Photochemical Cycloaddition Studies (Part B)

Scheme 4.7: Stereodefined Alkynols by CBS Reduction

The stereodefined propargylic systems 4.17a/4.17b under modified Keck conditions were next examined. It was found only the (S)-diasteremer 4.17a reacted to produce the α-hydroxy allene 4.18a in moderate yield with complete conversion of starting material; whereas, the remaining (R)-diastereomer 4.17b was inert to Keck conditions. Based on the mechanism of allene formation with LiAlH₄, the resulting allene from (S)-propargylic ether 4.17a would be postulated to be an (R)-allene (Scheme 4.8).
Chapter 4: Allene Formation and Photochemical Cycloaddition Studies (Part B)

\[ R_1 = \text{H}, R_2 = \text{TES} \quad (4.16a) \]
\[ R_1 = \text{Me}, R_2 = \text{H} \quad (4.17a) \]
\[ \text{a. NaH/Mel} \]
\[ \text{b. TBAF} \]

\[ R_1 = \text{H}, R_2 = \text{TES} \quad (4.16b) \]
\[ R_1 = \text{Me}, R_2 = \text{H} \quad (4.17b) \]
\[ \text{a. NaH/Mel} \]
\[ \text{b. TBAF} \]

**Scheme 4.8: Reductive Allene Formation Pathway**

\[ \text{Keck Conditions} \]

\[ \text{LiAlH}_4, \text{THF} \]

34% No Reaction
4.2 Allene Formation and Photochemical [2+2] Cycloaddition Studies

4.2.1 Allene Formation Studies on Allyl Terminated Propargylic Alcohol

Here again, with the encouraging results obtained previously to obtain allene with quaternary carbon centers on both sides, the catalytic chiral reduction of ‘ynones’ was planned to produce propargylic alcohols diastereoselectively. In order to adopt CBS promoted chiral reductions, the propargylic alcohol 3.37 was oxidized with MnO₂ at room temperature to obtain ynone 4.23 quantitatively as a single diastereomer (Scheme 4.9). Here, reduction with the CBS catalyst in combination with BH₃ however, gave no better selectivity (10:7) than the C-C bond forming assembly (10:7) of synthons. The poor selectivity could be due to the high flexibility of the system around the alkynone.

![Scheme 4.9: Chiral Reduction of Ynone](image)

To move forward, the diastereomeric mixture was, used for subsequent allene formation.

As described earlier, the alkynol 3.35 was protected as its methyl ether 4.24 and the silyl
group was removed by TBAF to obtain the tertiary alcohol **4.25** (Scheme 4.10). Using modified Keck conditions the addition of LiAlH₄ alone produced the allene **4.26** relatively pure in a low yield (18%) from the γ-hydroxy propargylic ether **4.26**, whereas LiAlH₄ with I₂ gave no allene.¹²

**Scheme 4.10: Allene Formation by LiAlH₄**
4.2.2 Photochemical [2+2] Cycloaddition Attempt

Previously, a tricyclic core of bielschowskysin (1.80) was reported by our group photochemical [2+2] cycloaddition between an allene appended on a tertiary carbinol and double bond of γ-butyrolactone as a key step (Scheme 4.11).\(^1\) The allene anchored butenolide 1.79 upon irradiation with UV light by conventional UV lamps smoothly underwent a substrate-controlled, diastereospecific [2+2] cycloaddition to the tricyclic core 1.80 of bielschowskysin. The selective formation of five membered ring during [2+2] cycloaddition (rule of five\(^{13}\)) leading to the cyclobutane containing γ-lactone 1.80 was demonstrated (Scheme 1.12).

**Scheme 4.11: [2+2] Cycloaddition: Tricyclic Core of Bielschowskysin\(^1\)**

**Scheme 4.12: Photochemical [2+2] Cyclization Attempt**
At this juncture, photochemical [2+2] cyclization was attempted on the allyl appended internal allene 4.26 to form the cyclobutane system 4.27. Thus the allene-olefin 4.26 in degassed DCM/hexane (1:1 v/v) mixture was irradiated with two conventional UV lamps (2x6W, \( \lambda = 254 \) nm) over 7h (Scheme 4.12). Unfortunately, this photochemical reaction led to decomposition of the substrate. In retrospect, protection of the free carbinol 4.26, may have given less problems during this photochemical reaction.\(^1\)
4.3 Summary: Chapter 4 (Part B)

In this chapter, I explored synthetic studies to syntheses of a $\alpha$-(tert)-hydroxy 1,3-disubstituted allene with quaternary carbon centers flanking both sides of the allene. Conjugated aldehyde unit 3.6 from $D$- (+)-glucose and an alkyne building block 4.15 from $(S)$-(-)-malic acid were independently prepared and C-C bond forming alkyne addition onto aldehyde resulted required propargylic alcohol 4.16. Allene forming reduction protocol was studied on diastereomeric as well as chiral defined propargylic ethers (4.16a/4.16b). A highly functionalized $\alpha$-(tert)-hydroxy 1,3-disubstituted allene 4.18a was synthesized by reduction of monoprotected propargylic diol employing LiAlH$_4$. The free hydroxyl group found to be necessary for reducing agent such as LiAlH$_4$ to chelate sterically hindered alkyne. In addition, only $(S)$-diasteromer of propargylic ether formed $(R)$-allene, while the other diasteromer was inert to allene forming reduction conditions.

Propargylic alcohol 3.37 was converted to an allene 4.26 under LiAlH$_4$ conditions. Eventual photochemical [2+2] cyclization of the allene, however, failed to yield the desired cycloaddition.
References for Chapter 4 (Part B)


[11] Stereochemistry was predicted based on the mnemonics of CBS catalyzed reduction. The other methods of determining stereochemistry, for example, Mosher’s ester formation were not conclusive due to lack of β-protons.

[12] Attempts by Myers method of allene formation by using NBSH, triphenyl phospine, DEAD conditions were not successful, tentatively, due to high steric congeestion.


PART B

CHAPTER 5

RCM METHODS TOWARDS MACROCYCLIC FRAMEWORK OF BIELSCHOWSKYSIN
5.1 Convergent Synthetic Plan to Macroyclic Framework of Bielschowskysin

5.1.1 Bielschowskysin: Retrosynthesis II

During our previous RCM study, Baylis-Hillman homologation gave a diene 2.53 (c.f. Scheme 2.18), which was found unsuitable for macrocyclic ring closure during RCM (c.f. Scheme 2.20 and Scheme 2.22). As a consequence, the synthetic scheme was revised, so that the adjacent oxidation sites at the olefin were modified (Scheme 5.1). This modification at alkyl chain terminus was envisioned to be a better choice to drive RCM, after which manipulation of the oxidation states would be implemented at a later stage. Thus the olefins were simplified to be un-branched as an allylic alkene in the western alkyne synthon 3.3 and a 1-alkene in the eastern aldehyde synthon 5.4.

Scheme 5.1: Bielschowskysin: Retrosynthesis II
5.2 ‘Modified Conjugated Aldehyde’ Synthon

5.2.2 ‘Modified Conjugated Aldehyde’ Synthon: 1st Generation Synthesis

In our new scheme, a direct sp$^2$-sp$^3$ cross-coupling vinylation method was sought to obtain substrate 5.4 (Scheme 5.2). There are several methods available for C-C bond formation among which, Kumada-type cross-coupling between sp$^2$-sp$^3$ carbons by transition metal catalysis is a prime example. Recently, environmentally benign, inexpensive, Fe-catalyzed direct cross-coupling method has attracted much attention, particularly by the Kochi group. Notably, the Cahiez group has developed convenient systems using Fe(acac)$_3$ and FeCl$_3$ in the presence of hexamethylenetetramine (HMTA) and TMEDA as ligands. While using readily accessible alkenyl-magnesium reagents, unactivated $n$ or $s$-alkyl halide coupling partners can be used in reactions tolerating a variety of functional groups. We thus studied the vinylation to form the modified conjugated aldehyde synthon 5.4 (Scheme 5.2).

![Scheme 5.2: Aldehyde-Alkene Unit 5.4 from PMB Ether 3.34](image)
To this end, the allylic alcohol 3.34 was protected as its corresponding TBS ether and subsequent PMB cleavage by DDQ in DCM-H₂O (9:1 v/v) occurred in 30 min at room temperature to afford the primary alcohol 5.5 in good yield (Scheme 5.3). Further functional group interconversion methods with either Appel halogenation⁵ by CBr₄/PPh₃ (entry 1, Table 5.1) or NBS/PPh₃ (entry 2) to convert the alcohol 5.5 to the alkyl bromide 5.6 resulted in simultaneous cleavage of the delicate TBS group. Re-protection of 5.7 with a TBDPS group to 5.8 also suffered from purification issues. In retrospect, a TBDPS version of 5.5 should be used for this halogenation reaction.

**Scheme 5.3:** Synthesis of Alkyl Bromide
Table 5.1: Bromination of Alcohol 5.5

<table>
<thead>
<tr>
<th>Conditions</th>
<th>5.6 (yield)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPh₃, NBS</td>
<td>5.7</td>
<td>(35%)</td>
</tr>
<tr>
<td>DCM, RT, 30min</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>PPh₃, CBr₄</td>
<td>5.7</td>
<td>(24%)</td>
</tr>
<tr>
<td>DCM, RT, 10min</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Thus the TBDPS appended alcohol 5.9 was prepared from the allylic alcohol 3.34 by silylation and PMB cleavage (Scheme 5.4).

Scheme 5.4: Synthesis of Alkyl Halide
With the TBDPS ether 5.9 in hand, halogenation of alcohol was eventually achieved in an efficient manner with molecular iodine in combination with imidazole and PPh₃ to form alkyl iodide 5.10. It is noteworthy that the iodination process was not practical on small batches (10 mg) perceivably due to moisture sensitivity of the active reagent/reaction; however, the iodination was smooth and exclusive at a relatively large scale.

Now the stage was set to study the cross-coupling reaction of the alkyl iodide 5.10 with vinylmagnesium reagent (Scheme 5.5). The reported catalytic system Fe(acac)₃(5 mol%)/HMTA/TMEDA in a 1:1:1 composition at 0 °C in 30-45 min was first tried with a reasonable excess (1.5-2 eq) of Grignard reagent. Modification of this procedure by adding vinyl magnesium bromide in THF solution slowly via syringe pump over 10 min at 0 °C to stirring solution of the iodide containing HMTA and TMEDA was also tried. Both attempts of vinylation were unsuccessful and starting material was only recovered. Nevertheless, pre-drying of HMTA and the alkyl iodide 5.10 with TMEDA and 10 mol% of catalyst gave consistent results to furnish the terminal alkene 5.11 in good yield.

After vinylation, the silyl ether 5.11 was deprotected by TBAF to obtain the allylic alcohol 5.12 (Scheme 5.5). During silyl group cleavage, some decomposition could not be avoided even when buffered by AcOH. Finally, DMP oxidation of the allylic alcohol 5.12 gave the conjugated aldehyde 5.4 in good yield.
Also during the course of our studies, the $\alpha,\beta$-unsaturated ester 5.13 was prepared (from 3.33 by deprotection of PMB group followed by iodination), but was found inappropriate under the [Fe]-cross coupling conditions. Although tolerating ester functionality in general, this cross coupling technique is perhaps unsurprisingly not applicable to a Michael-type acceptor 5.13.
5.2.4 ‘Modified Conjugated Aldehyde’ Synthon: 2nd Generation Synthesis

Scheme 5.6: Conjugated Aldehyde-Alkene 5.4: Retrosynthesis I

To expedite the formation of aldehyde 5.4, a more convergent synthesis was briefly attempted (Scheme 5.6). To this end, a soft Cu-nucleophile would need to be generated \textit{in situ}. The Mamdapur group, for example, has converted the secondary alicyclic bromide 5.14 into the alkylated product 5.15 under Li$_2$CuCl$_4$ catalyzed Grignard conditions (Scheme 5.7).\(^7\)

Scheme 5.7: C$_{sp^3}$ - C$_{sp^3}$ Coupling
Accordingly, the tosylate 5.18 and iodide 5.19 were (Scheme 5.8) prepared and alkylation studies performed (Table 5.2)

Scheme 5.8: Attempted C<sub>sp3</sub> - C<sub>sp3</sub> Coupling Study on the Ring

<table>
<thead>
<tr>
<th>X</th>
<th>Catalyst system</th>
<th>RMgX</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTs (5.18)</td>
<td>Li&lt;sub&gt;2&lt;/sub&gt;CuCl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>EtMgBr</td>
<td>No reaction;</td>
</tr>
<tr>
<td>I (5.19)</td>
<td>Li&lt;sub&gt;2&lt;/sub&gt;CuCl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>EtMgBr</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>OTs (5.18)</td>
<td>CuI</td>
<td>EtMgBr</td>
<td></td>
</tr>
<tr>
<td>I (5.19)</td>
<td>Fe(acac)&lt;sub&gt;3&lt;/sub&gt;, HMTA, TMEDA</td>
<td>EtMgBr</td>
<td>Complex reaction</td>
</tr>
</tbody>
</table>

In all cases, either under Cu (I) or Fe (III)-mediation, no reaction or a complex mixture was obtained.
5.2.5 ‘Modified Conjugated Aldehyde’ Synthon: 3rd Generation Synthesis

Scheme 5.9: Conjugated Aldehyde-Alkene 5.4: Retrosynthesis II

As elongation by nucleophilic substitution directly by sp³-sp³ coupling failed, a new convergent strategy was formulated to first combine a Wittig homologation then a [Fe]-catalyzed sp²-sp³ vinylation step (Scheme 5.9). Such a plan would eliminate use of PMB/TBDPS protection steps (c.f. Scheme 3.9 and Scheme 3.23).

Scheme 5.10: C_{sp2}-C_{sp3} Cross-coupling
To this end the previously synthesized alcohol 3.29 was converted to the \( n \)-alkyl iodide 5.21 in excellent yield (Scheme 5.10). Under optimized conditions, however, the Fe(acac)₃ catalyzed vinyl addition reaction on a 7.7 g (19 mmol) scale of iodide 5.21 became complex. Here, \( \beta \)-hydride elimination and hydride substitution reactions competed with the intended \( C_{sp2}-C_{sp3} \) cross-coupling reaction. As a result, disproportionation products, \textit{i.e.}, the alkane 5.22 and alkene 5.23 accompanied the desired cross-coupling product 5.20 (Scheme 5.11).\(^9\)

\[ \text{Path A} \]

\[ \text{Path B} \]

\[ \text{Cross-Coupling Product} \]

\[ \text{Disproportionation Products} \]

\[ \text{Scheme 5.11: Mechanistic Basis for Cross-coupling Versus Disproportionation Reactions} \]
Unfortunately, separation of products 5.20 and 5.22 in pure form was impractical at this stage. The mixture was therefore treated with 60% aqueous acetone (Scheme 5.12), the resulting diols (5.26/5.27) were oxidatively cleaved, and the crude aldehydes (5.28/5.29) directly homologated to give (E)-trisubstituted alkenes (5.30/5.31). These conjugated esters were then reduced by DIBALH, and the allylic alcohol 5.12 was separated from the mixture by silica gel column chromatography in 60% overall yield (Scheme 5.12).

Scheme 5.12: Synthesis of Allylic Alcohol 5.12
5.3 Synthesis of Macrocyclic Framework of Bielschowskysin

5.3.1 Assembly of Building Blocks: RMgX Mediated Addition of Alkyne

Having practical quantities of alkyne and aldehyde building blocks in hand, new anionic/basic methods were explored for acetylide addition that circumvented the [2,3]-Wittig rearrangement of 3.3 (Scheme 5.13). To this end, Grignard reagents RMgX (R=alkyl/aryl) were selected to generate alkynyl Grignards \textit{in situ}.\(^{10,11}\)

\begin{center}
\textbf{Scheme 5.13: Assembly by EtMgBr}
\end{center}
Following Sarpong’s protocol\textsuperscript{11}, the alkyne 3.3 should be heated with EtMgBr at reflux for 1h in THF prior to addition of the aldehyde 5.4 as a solution at -20 °C and warming to room temperature. Conveniently, the diastereomeric propargylic alcohols 5.33a and 5.33b could be separated in pure form by column chromatography. The absolute stereochemistry at the C5-epimeric centers was not defined at this stage. Although still somewhat ambiguous, these were deduced later, based on ‘NOE’ correlations in combination with \emph{ab initio} minimum energy conformations of downstream products. Nevertheless, 127 mg of 5.33a and 90 mg of 5.33b could be generated using this procedure (Scheme 5.13).

\textbf{5.3.1 RCM Study}

Although the optimal C5-epimeric configuration was unknown for RCM macrocyclization studies at this critical point, both diastereomers in hand were put forward to cyclize to macrocycles.

Initially, to prevent possible alkyne co-ordination by Grubbs-type catalysts, a relatively bulky triethylsilyl (TES) was chosen to be put on the C5-propargylic alcohols. Both diastereomeric dienes 5.33a/5.33b were thus silylated separately as their corresponding TES ethers 5.34a/5.34b using TESOTf in the presence of Et$_3$N (Scheme 5.14).
Scheme 5.14: RCM Reaction of ‘Dienes with TES Ethers’

Table 5.3: RCM Reaction of Diene with TES Ethers

<table>
<thead>
<tr>
<th>X</th>
<th>Catalyst (mol%)/Addition time</th>
<th>Temp(°C)/Time</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>5.34a</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1) 1.50 (20%)/ direct</td>
<td>1) 100/3h</td>
<td>1) No new spot;</td>
</tr>
<tr>
<td></td>
<td>2) .................................</td>
<td>2) 125/3h</td>
<td>2) No new spot;</td>
</tr>
<tr>
<td></td>
<td>3) + 1.50 (80%)/direct</td>
<td>3) 125/12h</td>
<td>3) complex reaction</td>
</tr>
<tr>
<td>2</td>
<td><strong>5.34b</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>5.36</strong> (20%)/direct</td>
<td>100/3h</td>
<td>No new spot; SM Recovered</td>
</tr>
<tr>
<td>3</td>
<td><strong>5.34b</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>5.36</strong> (20%)</td>
<td>60/3h</td>
<td>No new spot; SM Recovered</td>
</tr>
<tr>
<td></td>
<td>PhOH (50eq)/3h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As can be seen Table 5.3, either Grubbs II or Hoveyda-Grubbs II catalysts gave no reaction or complex mixtures (even when used close to stoichiometry). Even the excess use of PhOH that may promote [Ru]-catalytic cycles (c.f. Forman et al.\textsuperscript{12} and Fukayama et al.\textsuperscript{13}) was found ineffective. Eventually, we decided to reduce possible transannular
steric congestion by replacing the ‘TES’ group with a ‘Me’ group as in 5.37a (Scheme 5.15).

**Scheme 5.15: RCM Reaction of Diene with Methyl Ether 5.37a**

**Table 5.4: RCM Reaction of Diene with Methyl Ether 5.37a**

<table>
<thead>
<tr>
<th>Catalyst (mol%)/ Additive</th>
<th>Solvent (dilution)/ Temp (°C)/Time</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Grubbs II (10) Ti(Or-Pr)₄ (30 mol%)</td>
<td>DCM (1 mM)/60/3h</td>
<td>No reaction SM recovered</td>
</tr>
<tr>
<td>a) 100 mol%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Grubbs II</td>
<td>Toluene (1 mM)/125/2h</td>
<td>SM disappeared 2 new spots; trace macrocycle 5.38a</td>
</tr>
<tr>
<td>b) 50 mol%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) 20 mol%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Hoveyda Grubbs II (20)</td>
<td>Toluene (0.15 mM)/120/2h</td>
<td>2 New spots; trace macrocycle 5.38a</td>
</tr>
<tr>
<td>4 Grubbs II (20)/ 2h addition</td>
<td>Toluene (0.1 mM)/120/30min</td>
<td>2 new spots; 5% macrocycle 5.38a</td>
</tr>
</tbody>
</table>

Table 5.4 summarizes further RCM study on the methyl ether of diene 5.37a. Grubbs II catalyst (10 mol%) in DCM (1 mM) under reflux (60 °C), resulted in no reaction after 3h
even with the addition of Ti(Oi-Pr)$_4$ (entry 1). Grubbs II catalyst (1 eq) in refluxing toluene (1 mM, 125 °C) for 2h was found to produce two new spots with complete consumption of the diene 5.37a (entry 2a), one of which was characterized to be the macrocycle 5.38a based on LC-MS and NMR data. Purification attempts at this stage however suffered from very low yields. Reaction optimization was then sought to improve the yield, but both 20 mol% and 50 mol% catalysts gave similar results (entry 2b, 2c). Switching to the Hoveyda-Grubbs II catalyst gave very similar reaction pattern at 20 mol% in refluxing toluene (0.1 mM) for 2h (entry 3). Adding the catalyst slowly to a refluxing diene solution of 5.37a in toluene (0.1 mM) under Grubbs II catalyst (20 mol% total) generated the macrocycle 5.38a in an isolated yield of 5% (entry 4).

5.3.2 Prediction of Stereochemistry at C5-Propargylic Ether

The major macrocyclic product 5.38a was purified and characterized by NMR (1D and 2D), MS and HRMS analysis. Then, we sought methods to deduce the stereochemistry at C5 position.

Other work in the our group has attempted to establish the stereochmical configuration at the C5 position by means of Mosher’s method and CBS reduction of ynones to give stereoselective propargylic ethers similar to 5.33a and 5.33b. However Mosher’s method was not conclusive due to insufficient protons in the proximity of the C5 chiral center.

Alternatively, NOE correlation analysis from NOESY experiment of synthesized macrocycle was observed as shown in Fig 5.2. The NOE correlation between H$_{C11}$-H$_{C12}$ was characterized to the newly formed $\Delta^{11,12}$ double bond in a Z-configuration.
Fig 5.1: *Ab initio* Calculated Minimum Energy Conformers of Macrocycles and Tentative Diagnostic NOE Correlations

Fig 5.2: Observed Diagnostic NOE Correlations in Macrocycle 5.38a by NOESY
In the meantime, in parallel to the synthetic progress, we evaluated the proposed transannular driven synthetic route and intermediates by means of \textit{ab initio}/DFT calculations. Geometry optimization was performed and minimum energy obtained at the B3LYP/6-31G(d) level. Here, the Geometrical orientation of the key protons in the minimum energy conformations of $Z$-$\Delta^{11,12}$ macrocycles 5.38a and 5.38b (Fig 5.1) were compared to those of the observed NOE correlations (Fig 5.2) in the synthetic material 5.38a. The key difference between the epimeric macrocycles in minimum energy conformations was in the orientation of H$_{C5}$ at chiral center. H$_{C5}$ aligns in the same plane as H$_{C18}$ in the ‘$R$’-configured macrocycle (dihedral angle, $\theta = 26.1^\circ$; nonbonding distance, $d = 2.62\text{Å}$), whereas in the ‘$S$’-configured macrocycle, H$_{C5}$ and H$_{C3}$ arranges in the same spatial plane (dihedral angle, $\theta = 14.9^\circ$; nonbonding distance, $d = 2.19\text{Å}$). Hence, the $R$-configured $Z$-$\Delta^{11,12}$ macrocycle 5.38a is most likely to display H$_{C5}$$\leftrightarrow$H$_{C18}$ NOE correlation while the ‘$S$’-configured $Z$-$\Delta^{11,12}$ macrocycle 5.38b would generate an H$_{C5}$$\leftrightarrow$H$_{C3}$ NOE interaction. Analytically, the synthesized macrocycle has a prominent H$_{C5}$$\leftrightarrow$H$_{C18}$ NOE interaction that implicates the $R_{C5}$ configuration in the macrocycle 5.38a and in its precursors.
5.4 Summary: Chapter 5 (Part B)

In this chapter, I explored synthetic studies aiming at transannular [2+2] cycloaddition towards a macrocycle core of bielschowskysin (1.1). A Convergent synthesis of the macrocycle was designed by disconnecting the C5-C6 and C11-C12 bonds. Routes to the modified conjugated aldehyde synthon 5.4 were explored from D-Glucose by Witting homologation and a Fe(acac)₃ catalyzed sp²-sp³ cross-coupling as key steps.

Eventually, the acetylide addition onto aldehyde 5.4 was effected with EtMgBr by the in situ generation of the organomagnesium compound of alkyne 3.3 to give the separable
propargylic alcohols $5.33\text{a}$ and $5.33\text{b}$. This method prevented [2,3]-Wittig rearrangement of benzyl-allyl ether of the alkyne unit $3.3$.

Finally, the RCM method was studied on a linear framework of bielschowskysin. Although RCM was unsuccessful under C5-TES protection with $5.34\text{a}$ and $5.34\text{b}$, the methyl propargylic ether $5.37\text{a}$ underwent macrocyclization with [Ru]-precatalysts. The slow addition of Grubbs II catalyst to diene $5.36\text{a}$ eventually gave 5% isolable yield of a macrocycle $5.38\text{a}$ with a $Z$-configuration at the newly formed $\Delta^{11,12}$ bond. The absolute configuration at the C5 propargylic position in macrocycle $5.38\text{a}$ was predicted by comparing experimentally observed NOE correlations with the conformational orientation of macrocycles obtained by $ab$-$initio$ energy minimization. Further transannulation studies aiming to functionalize to the natural product (1.1) are in progress.
References for Chapter 5 (Part B)


Experimental Procedures (Part B)

General Techniques and Methods

All non aqueous reactions were performed in flame dried glassware under nitrogen or argon atmosphere unless stated otherwise. All solvents used in the reactions were purified before use. Dichloromethane (CH$_2$Cl$_2$) was distilled over CaH$_2$ and dry diethyl ether (Et$_2$O), tetrahydrofuran (THF) was distilled from sodium/benzophenone. All commercially available compounds were used as received without further purification. 4Å molecular sieves were activated by heating at 120-140 °C under high vacuum for 4h before storing in a dry desiccator. The reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm 2E Merck silica gel plates (60F-254) under 254 nm UV lamp and stained by aqueous ceric ammonium molybdate solution or KMnO$_4$ solution. Flash chromatography was performed on silica gel 60 (0.040 – 0.063 mm). $^1$H and $^{13}$C NMR spectra were recorded on Bruker ACF (300 MHz) and Bruker AMX500 (500 MHz) NMR spectrometer at ambient atmosphere. 2D NMR was performed on a Bruker AMX500 (500 MHz) NMR spectrometer. Chemical shifts are reported in $\delta$ (ppm) and calibrated using residual undeuterated solvents as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, do = doublet of triplet, td = triplet of doublet, m = multiplet, br = broad. $^1$H NMR coupling constants ($J$) are reported in Hertz (Hz), Mass spectra were obtained on Finnigan MAT95XL-T and Micromass VG7035 double focusing mass spectrometer. High resolution ESI mass spectra were obtained on a Shimadzu LCMS-IT-TOF spectrometer. Infra-red spectra were recorded on Perkin-Elmer FT 1600 spectrometer.
Experimental Procedures (Part B)

4-(tert-butyldiphenylsilyloxy)butan-1-ol (2.12): To the stirring solution of 1,4-butanediol 2.11 (10 mL) in dry DCM (30 mL) was added imidazole (1.2 g, 16.5 mmol) and TBDPSCI (3.17 g, 10.9 mmol) at room temperature and the reaction continued overnight. The reaction contents were diluted with ether, washed with H₂O and the layers were separated. The aqueous layer was extracted with ether (2x) and the combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄, The solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography (gradient 10-15% EtOAc/hexanes) to afford 4-(tert-butyldiphenylsilyloxy)butan-1-ol 2.12 (2.14 g, 60%) as a colorless syrup. The NMR data is in agreement with that reported in the literature.¹ ¹H NMR (CDCl₃, 300 MHz): δ 7.72-7.69 (m, 4H), 7.43-7.40 (m, 6H), 3.72 (t, J = 9.85 Hz, 2H), 3.67 (t, J = 10.15 Hz, 2H), 2.29 (s, br, 1H, OH), 1.73-1.63 (m, 4H), 1.08 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz): δ 135.49, 133.60, 129.57, 127.60, 63.94, 62.65, 29.69, 29.18, 26.77, 19.10.

Ethyl 7-(tert-butyldiphenylsilyloxy)-4-hydroxyhept-2-ynoate (2.14): To the stirring solution of 4-(tert-butyldiphenylsilyloxy)butan-1-ol 2.12 (1.86 g, 5.67 mmol) in anhydrous DCM (25 mL) at RT was added PCC (1.6 g, 7.37 mmol) and stirred for 2.5h. Then, the dark orange-black reaction mixture was directly purified by flash column chromatography (gradient 5-10% EtOAc/hexanes) to give aldehyde 2.13 (1.4 g, 76%) as a viscous yellow liquid.

Ethylpropiolate (571 µL, 5.64 mmol) was taken in THF (5 mL) cooled to −78 °C, and LHMDS (5.6 mL, 1M in hexane, 5.6 mmol) was added slowly drop-wise. After 30 min, aldehyde 2.13 (1.4 g, 4.33 mmol) in THF (5 mL) was added and stirred for 2h at −78 °C. Then the reaction was quenched by slow addition of saturated NH₄Cl and extracted with ether (3x). The combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (gradient 10-20% EtOAc/hexane) to afford racemic propargylic alcohol 2.14 (1.43 g, 60%) as a faint yellow oil. ¹H NMR (CDCl₃, 500 MHz): δ 7.68-7.67 (m, 4H), 7.45-7.38 (m, 6H), 4.57 (dd, J = 6.3, 11.95 Hz, 1H), 4.24 (q, J = 6.9 Hz, 2H), 3.74-3.69 (m, 2H), 3.27 (s, br, 1H, OH), 1.96-1.85 (m, 2H), 1.84-1.80 (m, 1H), 1.75-1.70 (m, 1H), 1.31 (t, J = 6.9 Hz, 3H), 1.07 (s, 9H). ¹³C NMR (CDCl₃, 125 MHz): δ 153.41, 135.56, 135.53, 133.28 129.77, 127.73, 87.77, 76.59, 63.75, 62.02, 61.81, 34.27, 27.94, 26.79, 19.11, 13.97. MS (ESI): m/z 395.2 [M-C₂H₅]⁻; 447.1 (100%) [M+Na]⁺. HRMS (ESI): m/z calcd for C₂₅H₃₂O₄SiNa 447.1968 [M+Na]⁺; found 447.1979.

6-(Methoxymethoxy)hex-1-ene (2.18): To a stirring solution of hex-5-enol 2.17 (1 g, 9.8 mmol) and DIPEA (2.5 mL, 25 mmol) in DCM (15 mL) at 0 °C, was added MOMCl (500 µL, 2.93 mmol). After overnight stirring at room temperature, the reaction mixture was quenched by addition of H₂O. The layers were separated and the aqueous layer was extracted with ether (3x). The combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄, filtered and and concentrated in vacuo and the oily residue was purified by flash column chromatography (gradient 2% EtOAc/hexanes) to give 2.18 (850 mg, 60%) as a colorless oily liquid. ¹H
NMR (CDCl₃, 500 MHz): δ 5.78-5.72 (m, 1H), 4.95 (d, J = 17 Hz, 1H), 4.89 (d, J = 10.75 Hz, 1H), 4.55 (s, 2H), 3.48 (t, J = 6.3 Hz, 2H), 3.30 (s, 3H), 2.05-2.01 (m, 2H), 1.57-1.52 (m, 2H), 1.44-1.38 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz): δ 138.47, 114.40, 96.24, 67.44, 54.86, 33.37, 29.07, 25.42; MS (ESI): m/z 144.8 [M]+.

6-(Methoxymethoxy)hex-1-en-3-ol (2.19): To a stirring solution of alkene 2.98 (0.66 g, 4.5 mmol) in DCM (10 mL), SeO₂ (1.2 g, 7 mmol) and t-BuOOH (70% aq. solution, 5 mL, 27 mmol) were added and refluxed for 13h. The reaction was cooled to room temperature and quenched by careful drop wise addition of saturated NaHCO₃ aqueous solution until effervescence ceased. The aqueous layer was extracted with ether (3x) and the combined organic fractions were washed with aq.1M KOH solution, brine and dried over anhydrous Na₂SO₄, filtered and the solvent was removed under vacuum. The crude residue was purified by flash column chromatography (gradient 10-30% EtOAc/hexanes) to give racemic allylic alcohol 2.19 (360 mg, 50%) and over oxidized product 2.20 (140 mg, 20%) both as transparent colorless oils. ¹H NMR (CDCl₃, 500 MHz): δ 5.88-5.81 (m, 1H), 5.23-5.19 (m, 1H), 5.08 (dd, J = 1.25, 8.8 Hz, 1H), 4.59 (s, 2H), 4.13-4.08 (m, 1H), 3.54 (t, J = 6.3 Hz, 2H), 3.33 (s, 1H), 1.73-1.54 (m, 4H). ¹³C NMR (CDCl₃, 125 MHz): δ 141.03, 114.51, 96.30, 72.67, 67.64, 55.14, 33.89, 25.59.
Oct-7-ynal (2.23): The 7-octyn-1-ol 2.22 was obtained by following alkyne isomerization procedure reported by Macaulay. To NaH (60% in mineral oil, 4 g, 100 mmol, washed free of oil three times with distilled hexane) in a two neck round bottom flask (RBF) equipped with a guard tube, was added ethylenediamine (70 mL) and stirred vigorously. Initially, gas evolution was slow and become vigorous to result a brinjal-purple solution. After 15-20 min of vigorous stirring at RT, foaming subsided and the mixture was stirred in a constant-temperature oil bath at 70 °C for 1h. To the resulted brinjal-brown solution, 3-octyn-1-ol 2.21 (2 g, 15.84 mmol) in ethylenediamine (15 mL) was added. The purple brown mixture was stirred at 55 °C overnight and then cooled to 0 °C, quenched with slow addition of ice-cold water (50 mL) with stirring. The aqueous layer was extracted with ether (4x) and the combined ether phases were washed successively with water, dilute HCl and brine solutions and then dried over anhydrous Na₂SO₄. Solids were filtered and the solvents distilled under reduced pressure. The crude product was chromatographed over silica gel (gradient 10-20% EtOAc/hexane) to give 7-octyn-1-ol 2.22 (1.5 g, 75%) as a smelly faint yellow oil.

PCC oxidation: PCC (2.58 g, 12 mmol) was added to the stirring solution of alkynol 2.22 (1 g, 7.92 mmol) in anhydrous DCM (10 mL). After stirring for 2.5h at room temperature, the reaction mixture was directly purified by flash column chromatography (gradient 2-5% EtOAc/hexanes) to give 2.23 (690 mg, 70%) as a smelly, transparent faint yellow oil. The NMR data is in agreement with that reported in the literature.³

¹H NMR


Experimental Procedures (Part B)

2-(Hept-6-ynyl)-1,3-dioxolane (2.24): Alkynal 2.23 (1.44 g, 11.59 mmol), ethyleneglycol (2 mL) and p-TSA (50 mg, 0.58 mmol) were dissolved in toluene (50 mL) in a side neck round bottom flask and refluxed for 12h with removal of water as an azeotroph by using Dean-Stark apparatus. Contents were cooled to room temperature and neutralized by addition of Et$_3$N and the solvent was removed under reduced pressure. Ether was added and washed successively with saturated NaHCO$_3$ solution and brine. The organic layer was concentrated under reduced pressure and the crude residue was purified by flash column chromatography (gradient 1-5% EtOAc/hexane) to give acetal 2.24 (1.9 g, quantitative) as a colorless clear liquid. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 4.84 (t, $J = 4.73$ Hz, 1H), 3.99-3.92 (m, 2H), 3.87-3.80 (m, 2H), 2.18 (dt, $J = 2.55$, 6.95 Hz, 2H), 1.93-1.92 (m, 1H), 1.68-1.64 (m, 2H), 1.57-1.51 (m, 2H), 1.46-1.42 (m, 4H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 104.32, 84.29, 68.11, 64.64, 33.57, 28.45, 28.22, 23.33, 18.10.

Methyl 3-hydroxy-2-methylenedec-9-ynoate (2.25): Methyl acrylate (3 mL) and DABCO (931 mg, 8.3 mmol) were added to a solution of aldehyde 2.23 (343 mg, 2.7 mmol) in MeOH (1-2 drops) and the homogenous solution was stirred at RT for 2 days. The reaction was diluted with 1M HCl, the aqueous phase was extracted with ether and the combined extracts were washed with brine (40 mL), dried over anhydrous Na$_2$SO$_4$, 179
filtered and concentrated. The residue was purified by flash column chromatography (gradient 10-20% EtOAc/hexanes) to furnish Baylis-Hillman adduct 2.25 (425 mg, 75 %) as a colorless clear liquid. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 6.20 (s, 1H), 5.78 (s, 1H), 4.37 (t, br, \(J = 6.09\) Hz, 1H), 3.76 (s, 3H), 2.61 (s, br, 1H, OH), 2.16 (dt, \(J = 2.64, 6.75\) Hz, 2H), 1.92 (t, \(J = 2.64\) Hz, 1H), 1.65-1.60 (m, 2H), 1.56-1.32 (m, 6H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 166.97, 142.44, 124.91, 84.52, 71.59, 68.16, 51.82, 36.01, 28.42, 28.30, 25.25, 18.28.

6-(Methoxymethoxy)hex-1-en-3-yl 3-methoxy-2-methylenedec-9-yonoate (2.16a): NaH (60% in mineral oil, 224 mg, 5.4 mmol) was added to a stirring solution of 2.25 (1.02 g, 4.55 mmol) and MeI (0.5 mL, 7 mmol) in dry THF (20 mL) at 0 °C. After 2h at room temperature, the reaction was diluted with ether (20 mL), quenched with 20 mL of H\(_2\)O. The aqueous layer was extracted with ether (2x) and the combined organic fractions were washed with brine, dried over anhydrous Na\(_2\)SO\(_4\), solids were filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (gradient 4-8% EtOAc/hexanes) to provide 2.27 (65 mg, 7%) as a yellow oil. Ester 2.27 (96 mg, 0.43 mmol) was dissolved in \(i\)-PrOH/H\(_2\)O (1:1 v/v, 4 mL) and treated with LiOH (30 mg, 1.25 mmol). The resulting yellow reaction mixture was stirred at room temperature for 6h. Then the reaction content was diluted with water and the aqueous layer was extracted with Et\(_2\)O (2x) and the combined organic factions were washed with brine, dried over anhydrous Na\(_2\)SO\(_4\) and the solvent removed under reduced pressure. The residue was purified by flash column
chromatography (gradient 10-20% EtOAc/hexane) to obtain acid 2.29 (45 mg, 50%) as a faint yellow oily liquid.

A solution of alcohol 2.22 (91 mg, 0.57 mmol) and Ph₃P (124 mg, 0.48 mmol) in THF (2 mL) was added drop wise at 0 °C to a stirring solution of acid 2.29 (100 mg, 0.48 mmol) and DEAD (75 µL, 0.48 mmol) in THF (2 mL). The reaction was allowed to continue at RT overnight and the mixture was concentrated and the residue purified by flash column chromatography (gradient 5-10% EtOAc/hexanes) to afford the title ester 2.16a (70 mg, 40%) as a clear liquid. ¹H NMR (CDCl₃, 300 MHz): δ 6.29 (s, 1H), 5.85-5.71 (m, 2H), 5.36-5.15 (m, 2H), 4.58 (s, 2H, OCH₂O), 4.06-3.97 (m, 1H), 3.54-3.45 (m, 3H), 3.32 (s, 3H, OMe), 3.24 (s, 3H, OMe), 2.16-2.12 (m, 2H), 1.91-1.89 (t, 1H), 1.76-1.18 (m, 12H).

¹³C NMR (CDCl₃, 75 MHz): δ 165.57, 141.04, 136.12, 124.40, 116.93, 116.71, 106.58, 96.32, 84.52, 79.37, 74.72, 74.63, 68.09, 67.14, 56.95, 55.06, 35.77, 30.92, 28.42, 28.30, 25.31, 24.97. MS (ESI): m/z 375.1 (100%). HRMS (ESI): m/z calcd for C₂₀H₃₂NaO₅ 375.2147 [M+Na]⁺; found 375.2159.

(2S,4S)-4-(Hydroxymethyl)-2-phenyl-1,3-dioxane (2.37): (S)-malic acid was acylated following a procedure adapted from work by Ley et al.⁴ Acetyl chloride (15.5 mL) was added dropwise to MeOH (300 mL) for 15 min at RT with constant stirring and after 10 min, (S)-malic acid (47.0 g, 0.35 mol) was added. The reaction mixture was stirred at RT for 20h and concentrated in vacuo. Flash column chromatography eluting with CH₂Cl₂:MeOH (95:5) afforded the title compound as pale yellow oil. The resulting malic acid ester in absolute

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ethanol (60 mL) was added drop wise to a solution of NaBH₄ (20 g, 0.53 mmol) in THF at 0 °C over 1h with vigorous stirring and the reaction was continued for a further 5h at room temperature with stirring. Then the reaction was quenched by addition of conc. HCl until pH = 7 during which a white solid cake formed. Solids were filtered through a celite pad, the celite was washed thoroughly with methanol and concentrated on a rotary evaporator. The crude residue was purified by flash column chromatography (gradient 5-15% DCM/MeOH) to provide (S)-butane-1,2,4-triol (2.36) as a colorless viscous semi solid.

Triol 2.36 was then converted to beznylidene acetal following a procedure adapted from reported method.⁵ (S)-1,2,4-butanetriol 2.36 (13.5 g, 127 mmol) and benzaldehyde dimethyl acetal (23 mL, 152 mmol) in dry DCM (50 mL) were stirred at room temperature in the presence of camphorsulfonic acid (1.5 g, 6.45 mmol). The reaction mixture was stirred for 20h and the contents were neutralized with triethylamine (5 mL) and concentrated under reduced pressure. Flash column chromatography (gradient 25-40% EtOAc in hexanes) of the resulting residue afforded pure (2-phenyl-1,3-dioxan-4-yl)methanol 2.37 (19.7 g, 80%) as a colorless oil. ¹H NMR (CDCl₃, 500 MHz): δ 7.50 (d, J = 6.3 Hz, 2H), 7.39-7.33 (m, 3H), 5.51 (s, 1H), 4.26 (dd, J = 5.05, 11.35 Hz, 1H), 3.96-3.90 (m, 2H), 3.61 (s, 2H), 2.63 (s, br, 1H, OH), 1.90-1.81 (m, 1H), 1.39 (d, J = 13.25 Hz, 1H). ¹³C NMR (CDCl₃, 100 MHz): 138.29, 128.75, 128.08, 126.02, 101.08, 77.45, 66.45, 65.36, 26.71. MS (ESI): m/z 217.1 [M+Na]⁺. HRMS (ESI): m/z calcd for C₁₁H₁₄NaO₃ 217.0841 [M+Na]⁺; found 217.0842.

**Swern oxidation**: To the stirring dry DCM (10 mL) was added (COCl)₂ (2.1 mL, 24.8 mmol) under argon and cooled to –78 °C. Anhydrous DMSO (3.3 mL, 46 mmol) was added drop wise to the above solution and after 20 min, (2-phenyl-1,3-dioxan-4-yl)methanol 2.37 (3 g, 15.4 mmol) in DCM (5 mL) added. After 30 min, Et₃N (10 mL, 72 mmol) was added at –78 °C and the resulting cloudy solution was stirred for 15 min after which quenched by slow addition of H₂O. The mixture was allowed to warm to room temperature and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic fractions were washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude 2-phenyl-1,3-dioxane-4-carbaldehyde 2.38 was dried azeotropically by dry THF (2x) before being carried forward for the next Nozaki-Takai olefenation.

**Nozaki-Takai Olefenation**: CH₂I₂ (12 mL, 152 mmol) was added slowly drop wise to a solution of freshly activated Zn dust (10 g, 152 mmol) and PbCl₂ (0.43 g, 1.54 mmol) in THF (40 mL) for 15 min with constant stirring under argon. The reaction become vigorous with effervescence and reached reflux within 10 min from the point CH₂I₂ addition begins. Then the reaction was cooled by arranging an external ice-bath as soon as effervescence begins and the grayish solution stirred at room temperature after effervescence ceases. After 1h, Ti(i-OPr)₄ (4.5 mL, 15.2 mmol) was added; and after 30
min at room temperature the crude 2-phenyl-1,3-dioxane-4-carbaldehyde (2.38) in THF (6 mL) was added to the greenish reaction solution. The reaction was allowed to continue overnight, diluted with ether, quenched by addition of 1M HCl (50 mL). The layers were separated, the aqueous layer was extracted with ether (2x30 mL) and the combined organic fractions were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered, concentrated and purified by flash column chromatography (gradient 1-5% Et₂O/hexane) to furnish 2-phenyl-4-vinyl-1,3-dioxane 2.39 (40-60%) exclusively as a transparent colorless oil.

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</table>

\[ ^1H \text{ NMR (CDCl}_3, 500 \text{ MHz): } \delta 7.55-7.52 (m, 2H), 7.40-7.34 (m, 3H), 6.00-5.93 (m, 1H), 5.59 (s, 1H), 5.38-5.34 (m, 1H), 5.21-5.18 (m, 1H), 4.41-4.36 (m, 1H), 4.30 (ddd, \( J = 1.25, 5.05, 11.35 \text{ Hz, } 1\text{H}), 4.04-3.99 (m, 1H), 1.99-1.91 (m, 1H), 1.64-1.60 (m, 1H). \]

\[ ^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz): } \delta 138.58, 137.81, 128.71, 128.15, 126.11, 115.50, 101.12, 77.54, 66.84, 31.12. \]

\((S)-3-(benzyloxy)\text{pent-4-en-1-ol (2.45):} DIBALH (25 \text{ mL, } 1M \text{ in cyclohexane, } 25 \text{ mmol}) \text{ was added slowly drop wise to a solution of 2-phenyl-4-vinyl-1,3-dioxane 2.39 (3.2 g, 16.8 mmol) in DCM (40 mL) at } 0 \text{°C and the}
reaction was allowed to warm gradually to room temperature through 5h. Upon completion, the reaction was quenched by slow addition of 1M HCl solution and after 15min of stirring, cloudy clumps disappeared from the organic phase. The aqueous phase was extracted with ether (2x) and the combined extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated and purified by flash column chromatography (gradient 15-30% EtOAc/hexane) to furnish (S)-3-(benzyloxy)pent-4-en-1-ol 2.45 (2.9 g, 90%) exclusively as a transparent oil. ¹H NMR (CDCl₃, 500 MHz): δ 7.36-7.27 (m, 5H), 5.84-5.77 (m, 1H), 5.29-5.28 (m, 1H), 4.63 (d, J = 11.5 Hz, 1H), 4.37 (d, J = 11.5 Hz, 1H), 4.02 (dt, J = 4.4, 8.2 Hz, 1H), 3.81-3.71 (m, 2H), 2.45 (s, br, 1H, OH), 1.92-1.85 (m, 1H), 1.82-1.76 (m, 1H). ¹³C NMR (CDCl₃, 125 MHz): δ 138.17, 138.10, 128.43, 127.77, 127.65, 117.48, 79.78, 70.27, 60.47, 37.76. MS (ESI): m/z 215.1 (100%) [M+Na]⁺. HRMS (ESI): m/z calcd for C₁₂H₁₆NaO₂ 215.1048 [M+Na]⁺; found, 215.1036.

(S)-3-(benzyloxy)pent-4-enal (2.50): To the stirring solution of (S)-3-(benzyloxy)pent-4-en-1-ol 2.45 (2.5 g, 13 mmol) and NaHCO₃ (10 g, 130 mmol) in dry DCM (40 mL) was added DMP (11 g, 26 mmol) at room temperature and the reaction was continued for 2h at room temperature. The reaction contents were filtered through a celite pad and concentrated on a rotary evaporator and the crude residue was purified by flash column chromatography (gradient 2-5% EtOAc in hexanes) to provide (S)-3-(benzyloxy)pent-4-enal 2.50 (2.12 g, 86%) as a colorless syrup. ¹H NMR (CDCl₃, 500 MHz): δ 9.76-9.75 (m, 1H), 7.36-7.27 (m, 5H), 5.85-5.78 (m, 1H), 5.36-5.30 (m, 2H), 4.62 (d, J = 11.35 Hz, 1H), 4.40 (d, J = 12 Hz, 1H), 4.36-4.32 (m, 1H), 2.74 (ddd, J = 2.5, 8.2, 16.35 Hz, 1H), 2.56 (ddd, J = 1.87, 5.0, 185
16.35 Hz, 1H). $^{13}$C NMR (CDCl₃, 125 MHz): δ 200.65, 137.90, 136.97, 128.36, 128.33, 127.76, 127.67, 118.20, 75.31, 70.32, 49.05.

$(S)$-4-(benzyloxy)hex-5-enal (2.35): To the stirring solution of MeOCH₂PPh₃Cl (6.7 g, 19.5 mmol) in THF was added LHMDS (19.5 mL, 1M in THF, 19.5 mmol) at 0 °C and after 1h, $(S)$-3-(benzyloxy)pent-4-en-1-ol 2.50 (2.12 g, 11.1 mmol) in THF was added at 0 °C. The orange color reaction mixture was allowed to continue with stirring at room temperature overnight. The reaction was diluted with ether and the solids were filtered, washed with 10% K₂CO₃ and the aqueous phase was extracted with ether (2x). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated and purified by flash column chromatography (gradient 2-5% EtOAc/hexane) to yield $(S)$-((6-methoxyhexa-1,5-dien-3-yloxy)methyl)benzene (mixture of E, Z isomers) which was subsequently hydrolyzed by refluxing (60 °C) with 1M HCl/THF (1:1 v/v, 10 mL) for 1h. Then the reaction was diluted with ether and the aqueous phase was extracted with ether (2x) and the combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated and the residue was purified by flash column chromatography (gradient 5-10% Et₂O/hexanes) to accomplish homologated aldehyde, $(S)$-4-(benzyloxy)hex-5-enal 2.35 (50%, 2 steps) as a colorless oily liquid. $^1$H NMR (CDCl₃, 500 MHz): δ 9.74 (t, $J$ = 1.58 Hz, 1H, CHO), 7.36-7.26 (m, 5H, Ph), 5.78-5.71 (m, 1H), 5.28-5.23 (m, 2H), 4.58 (d, $J$ = 11.95 Hz, 1H), 4.33 (d, $J$ = 11.95 Hz, 1H), 3.79 (dd, $J$ = 7.55, 12.6 Hz, 1H), 2.54-2.50 (m, 2H), 1.98-1.86 (m, 2H). $^{13}$C NMR (CDCl₃, 125 MHz): δ 202.13, 138.31, 138.07, 128.31, 127.73, 127.51, 117.74, 79.23, 70.17, 39.90, 27.99.
(3S)-3-(benzyloxy)-13-(1,3-dioxolan-2-yl)tridec-1-en-7-yn-6-ol (2.34): To a solution of 2-(hept-6-ynyl)-1,3-dioxolane 2.24 (321 mg, 1.9 mmol) in THF at –78 °C, n-BuLi (1.80 mL, 1M in hexane, 1.8 mmol) was added and the reaction stirred for 2h. Then (S)-4-(benzyloxy)hex-5-enal 2.35 (195 mg, 0.95 mmol) in THF was added and continued for a further 2h at –78 °C and the reaction was quenched by slow addition of saturated NH₄Cl and extracted with ether (3x). The combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄, filtered and the solvent removed under reduced pressure. The crude residue was purified by flash column chromatography (gradient 10-20% EtOAc in hexanes) to afford (3S)-3-(benzyloxy)-13-(1,3-dioxolan-2-yl)tridec-1-en-7-yn-6-ol 2.34 (350 mg, quantitative) as a colorless syrup while recovering unreacted alkyne. ¹H NMR (CDCl₃, 500 MHz): δ 7.33-7.24 (m, 5H), 5.79-5.72 (m, 1H), 5.25-5.21 (m, 2H), 4.85-4.83 (t, J = 4.73 Hz, 1H), 4.59 (d, J = 12 Hz, 1H), 3.98-3.93 (m, 2H), 3.91-3.76 (m, 2H), 2.39 (s, br, 1H), 2.21-2.17 (m, 2H) 1.85-1.63 (m, 6H), 1.52-1.49 (m, 1H), 1.43-1.42 (m, 1H). ¹³C NMR (CDCl₃, 125 MHz): δ 138.63 and 138.52, 138.43, 138.42, 128.3, 127.75, 127.72, 127.46, 117.34, 104.51, 85.3, 81.23, 80.18 and 80.06, 70.08, 64.79, 62.40 and 62.35, 34.03, 33.93, 33.68, 31.09, 28.68, 28.41, 23.43, 18.54. MS (ESI): m/z 395.2 [M+Na]⁺. HRMS (ESI): m/z calcd for C₂₃H₃₂NaO₄ 395.2198 [M+Na]⁺; found, 395.2188.

⁶ The Multiple C-signals appearing in the spectra are due to diastereotopic carbon centers present in the inseparable mixture of diastereomers.
(14S)-methyl 14-(benzyloxy)-3-hydroxy-2-methylenehexadeca-9,10,15-trienoate (2.51): DEAD (106 µL, 0.67 mmol) was added to a solution of Ph₃P (176 mg, 0.67 mmol) in THF (2 mL) at −15 °C. After 15 min, a solution of propargylic alcohol 2.34 (125 mg, 0.336 mmol) in THF (2 mL) was added to the yellow reaction mixture, 15 min later a solution of NBSH (0.145 g, 0.67 mmol) in THF (2.0 mL) was added. The resulting suspension was held at −15 °C for 1h, after which time TLC analysis indicated complete consumption of the starting alcohol. The reaction mixture was warmed to ambient temperature and allowed to stand overnight. Concentration of the reaction mixture and purification of the residue by flash column chromatography (gradient 5-10% Et₂O in hexanes) afforded the title allene, 2-((11S)-11-(benzyloxy)trideca-6,7,12-trienyl)-1,3-dioxolane 2.51 as a colorless oil (170 mg, 84%).

\[ ^1H \text{ NMR (CDCl}_3, 500 MHz) : \delta 7.35-7.31 (m, 4H), 7.28-7.24 (m, 1H), 5.78-5.71 (m, 1H), 5.74-5.20 (m, 2H), 5.10-5.03 (m, 2H), 4.84 (dt, J = 1.9, 5.05 Hz, 1H), 4.59 (d, J = 12 Hz, 1H), 4.35 (d, J = 12 Hz, 1H), 3.99-3.92 (m, 2H), 3.87-3.78 (m, 2H), 2.14-2.02 (m, 2H), 1.97-1.94 (m, 2H), 1.81-1.73 (m, 1H), 1.68-1.56 (m, 2H), 1.44-1.36 (m, 7H). \]

\[ ^13C \text{ NMR (CDCl}_3, 125 MHz) : \delta 203.86, 203.84, 138.92, 138.76, 128.26, 127.72, 127.68, 127.36, 117.12, 104.61, 91.29, 91.27, 90.46, 90.40, 79.97, 79.78, 70.13, 70.11, 64.78, 38.81, 34.76, 34.75, 33.84, 29.07, 29.06, 28.98, 28.96, 28.79, 24.67, 24.64, 23.86. \]

\[ \text{MS (ESI): } m/z \text{ 379.1 } [M+Na]^+ , \text{ HRMS (ESI): } m/z \text{ calcd for } C_{23}H_{32}NaO_3 \text{ 379.2249 } [M+Na]^+ ; \text{ found, 379.2244.} \]

\[ ^7 \text{ Multiple C-signals appearing in the spectra are due to diastereotopic carbon centers present in the inseparable mixture of diastereomers.} \]
(14S)-methyl 14-(benzyloxy)-3-hydroxy-2-methylenehexadeca-9,10,15-trienoate (2.53): A solution of 2-
((11S)-11-(benzyloxy)trideca-6,7,12-trienyl)-1,3-dioxolane 2.51 (450 mg, 1.26 mmol) in 2M HCl:THF (1:1 v/v, 15 mL)
was stirred overnight at 45 °C and then diluted with Et₂O. The aqueous phase was extracted with Et₂O (2x) and the combined extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude aldehyde 2.52 (450 mg) was subjected to Baylis-Hillman conditions by adding methyl acrylate (0.5 mL, 4.32 mmol) and DABCO (323 mg, 2.88 mmol) and a drop of MeOH to make homogenous solution. After being stirred at ambient temperature for 5 days, the reaction was diluted with 1M HCl and was extracted with ether (2x). The combined extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (gradient 10-20% EtOAc/hexanes) to furnish the Baylis-Hillman adduct, (12S)-12-(benzyloxy)tetradeca-7,8,13-trienal 2.53 (351 mg, 70 %, 2 steps) as a colorless syrup. 

\[ ^1H\text{ NMR (CDCl}_3, 500 MHz) : \delta 7.34-7.24 \text{(m, 5H), 6.2 (s, 1H), 5.78 (s, 1H), 5.76-5.71 (m, 1H), 5.24-5.20 (m, 2H), 5.10-5.03 (m, 2H), 4.58 (d, } J = 12 \text{ Hz, 1H), 4.39-4.37 (m, 1H), 4.35 (d, } J = 12 \text{ Hz, 1H), 3.81-3.77 (m, 1H), 3.77 (s, 3H), 2.59 (s, br, 1H, OH), 2.12-2.01 (m, 2H), 1.98-1.93 (m, 2H), 1.81-1.73 (m, 1H), 1.68-1.57 (m, 3H), 1.46-1.34 (m, 6H). \]

\[ ^13C\text{ NMR (CDCl}_3, 125 MHz) : \delta 203.84, 166.98, 142.53, 138.89, 138.72, 128.27, 127.74, 127.69, 127.37, 124.83, 117.15, 91.32, 91.28, 90.46, 90.39, 79.99, 79.83, 79.80, 71.60, 70.12, 70.10, 51.79, 36.16, 34.78, 34.74, \]

Multiple C-signals appearing in the spectra are due to diastereotopic carbon centers present in the inseparable mixture of diastereomers.
29.05, 28.82, 28.80, 25.62, 25.61, 25.58, 24.65. **MS** (ESI): m/z 421.2 [M+Na]$^+$. **HRMS** (ESI): m/z calcd for C$_{25}$H$_{34}$NaO$_4$ 421.2355 [M+Na]$^+$; found, 421.2350.

**29.**

**Experimental Procedures (Part B)**

14-(benzyloxy)-3-(methoxymethoxy)-2-methylenehexadeca-9,10,15-trienoate (2.54): To a stirring solution of the Baylis-Hillman adduct, (14S)-methyl 14-(benzyloxy)-3-hydroxy-2-methylenehexadeca-9,10,15-trienoate 2.53 (390 mg, 0.98 mmol) in dry DCM (10 mL) were added (i-Pr)$_2$EtN (1 mL, 4.90 mmol) and MOMCl (500 μL, 2.93 mmol) at 0 °C. After overnight at room temperature, the reaction was quenched with addition of H$_2$O. The aqueous layer was extracted with ether (3x) and the combined organic fractions were washed with brine, dried over anhydrous Na$_2$SO$_4$ and filtered. The solvent was removed under vacuum and the resulting residue was purified by flash column chromatography (gradient 2-7% EtOAc in hexanes) to give the MOM ether, (14S)-methyl 14-(benzyloxy)-3-(methoxymethoxy)-2-methylenehexadeca-9,10,15-trienoate 2.54 (370 mg, 86%) as an oily liquid. **1H NMR** (CDCl$_3$, 500 MHz): δ 7.33-7.25 (m, 5H), 6.29 (s, 1H), 5.83 (d, $J = 1.25$ Hz, 1H,) 5.78-5.71 (m, 1H), 5.24-5.20 (m, 2H), 5.10-5.03 (m, 2H), 4.60-4.55 (m, 3H), 4.50-4.48 (t, br, $J = 5.63$ Hz, 1H), 4.36-4.34 (d, $J = 11.35$, 1H), 3.82-3.78 (dd, $J = 6.3$, 13.25 Hz, 1H), 3.75 (s, 3H), 3.75 (s, 3H), 2.13-2.04 (m, 2H), 1.97-1.93 (m, 2H), 1.79-1.73 (m, 1H), 1.69-1.57 (m, 3H), 1.45-1.34 (m, 6H). **13C NMR** (CDCl$_3$, 125 MHz):

δ 203.84, 166.51, 141.36, 138.93, 138.75, 128.24, 127.70, 127.64, 127.34, 125.14, 117.05, 94.85, 91.31, 91.28, 90.43, 90.36, 79.95, 79.77, 74.56, 70.12, 70.11, 55.68, 51.71,

$^9$ Multiple C-signals appearing in the spectra are due to diastereotopic carbon centers present in the inseparable mixture of diastereomers.

**DDQ Reaction:** Benzyl ether, (14S)-methyl 14-(benzyloxy)-3-(methoxymethoxy)-2-methylenehexadeca-9,10,15-trienoate **2.54** (360 mg, 0.81 mmol) was dissolved in DCM/H$_2$O (9:1 v/v, 15 mL) and DDQ (760 mg, 3.34 mmol; 200 mg portions/2h) was added and stirred at room temperature for 9h. The reaction was monitored to be incomplete with orange-red clumps formation. While the allylic oxidation product is accumulating with time, solids were filtered-off through a celite pad, diluted with DCM (15 mL) and washed with saturated NaHCO$_3$. The aqueous layer was extracted with DCM (2x) and the combined organic fractions were washed with brine (30 mL), dried over anhydrous Na$_2$SO$_4$ and filtered. The solvent was removed under reduced pressure and flash column chromatography (gradient 10-20% EtOAc/hexane) of the resulting orange-red residue furnished the title allylic alcohol, (14S)-methyl 14-hydroxy-3-(methoxymethoxy)-2-methylenehexadeca-9,10,15-trienoate **2.32** (127 mg, 50%) as a colorless syrup in addition to allylic oxidation product, methyl 3-(methoxymethoxy)-2-methylene-14-oxohexadeca-9,10,15-trienoate **2.55** (25 mg, 10%) while recovering 27 mg of unreacted starting material, **2.54**.
(14S)-Methyl 14-hydroxy-3-(methoxymethoxy)-2-methylenehexadeca-9,10,15-trienoate (2.32): Debenzylation product.

\[ \text{1H NMR (CDCl}_3, 500 MHz): \delta 6.27 (s, 1H), 5.88-5.83 (m, 1H), 5.82 (s, 1H), 5.22-5.19 (d, J = 17.65 Hz, 1H), 5.09-5.05 (m, 3H), 4.57-4.56 (d, J = 16.35 Hz, 1H), 4.56-4.53 (d, J = 15.75 Hz, 1H) 4.48-4.45 (m, 1H), 4.16-4.12 (q, J = 6.3 Hz, 1H), 3.74 (s, 3H), 3.35 (s, 3H), 2.08-2.02 (m, 2H), 1.98-1.93 (m, 2H), 1.83 (s, br, 1H, OH), 1.68-1.52 (m, 4H), 1.43-1.30 (m, 6H). \]

\[ \text{13C NMR (CDCl}_3, 125 MHz): \delta 203.85, 166.57, 141.29, 141.10, 141.07, 141.03, 125.22, 114.52, 94.81, 91.43, 91.41, 90.32, 74.56, 72.45, 72.43, 55.70, 51.76, 36.22, 36.21, 36.19, 35.68, 35.65, 28.98, 28.95, 28.78, 28.74, 28.71, 25.38, 24.68. \]

\[ \text{MS (ESI): m/z 375.2 (100\%) [M+Na]+. HRMS (ESI): m/z calcd for C}_20\text{H}_32\text{NaO}_5 375.2147 [M+Na]^{+}; \text{found, 375.2139.} \]

Methyl 3-(methoxymethoxy)-2-methylene-14-oxohexadeca-9,10,15-trienoate (2.55): Allylic oxidation product:

\[ \text{1H NMR (CDCl}_3, 500 MHz): \delta 6.39-6.20 (m, 3H), 5.83-5.80 (m, 2H), 5.17-5.07 (m, 2H, allene), 4.59-4.56 (d, J = 16.35 Hz, 1H), 4.58-4.54 (d, J = 17 Hz, 1H), 4.48 (dd, J = 4.4, 7.55 Hz, 1H), 3.76 (s, 3H), 3.37 (s, 3H), 2.71-2.68 (t, J = 7.25 Hz, 2H), 2.32-2.27 (m, 2H), 1.97-1.92 (m, 2H), 1.68-1.64 (m, 1H), 1.58-1.53 (m, 1H), 1.45-1.30 (m, 6H). \]

\[ \text{13C NMR (CDCl}_3, 125 MHz): \delta 203.70, \]

10 Multiple C-signals appearing in the spectra are due to diastereotopic carbon centers present in the inseparable mixture of diastereomers.

11 Multiple C-signals appearing in the spectra are due to diastereotopic carbon centers present in the inseparable mixture of diastereomers.
Experimental Procedures (Part B)

199.97, 166.58, 141.34, 136.57, 127.85, 125.24, 94.88, 92.39, 89.83, 74.60, 55.74, 51.79, 38.50, 35.71, 29.06, 28.90, 28.89, 28.82, 25.42, 22.80. **MS (ESI):** $m/z$ 373.1 $[\text{M+Na}]^+$.  

**(14S)-14-hydroxy-3-(methoxymethoxy)-2-methylenehexadeca-9,10,15-trienoic acid (2.31):** (14S)-methyl 14-hydroxy-3-(methoxymethoxy)-2-methylenehexadeca-9,10,15-trienoate, **2.32** (120 mg, 0.35 mmol) was dissolved in $i$-PrOH/H$_2$O (1:1 v/v, 6 mL) which was subsequently treated with LiOH (30 mg, 1.25 mmol). The yellow color reaction mixture was allowed to stand at room temperature for 6h, after which was diluted with water. The aqueous layer was extracted with Et$_2$O (2x) and the combined organic factions were washed with brine solution, dried over anhydrous Na$_2$SO$_4$ and filtered. The solvent was distilled under reduced pressure and the orange-yellow residue was purified by flash column chromatography (gradient 30-50% EtOAc in hexanes) to furnish *seco*-acid, (14S)-14-hydroxy-3-(methoxymethoxy)-2-methylenehexadeca-9,10,15-trienoic acid **2.31** (41 mg, 35%) as a faint yellow oily liquid. 

**$^1$H NMR (CDCl$_3$, 500 MHz):** $\delta$ 6.40 (s, 1H), 5.88-5.83 (m, 1H), 5.23 (d, $J = 17$ Hz, 1H), 5.13-5.08 (m, 3H), 4.62-4.58 (d, $J = 18.3$ Hz, 1H), 4.60-4.57 (d, $J = 18.95$ Hz, 1H), 4.50-4.48 (m, 1H), 4.22-4.17 (m, 1H), 3.39 (s, 3H), 2.08-2.02 (m, 2H), 2.00-1.96 (m, 2H), 2.00-1.96 (m, 2H), 1.73-1.54 (m, 4H), 1.45-1.38 (m, 6H). **$^{13}$C NMR (CDCl$_3$, 125 MHz)$^{12}$: $\delta$ 203.92, 169.39, 140.89, 140.70, 140.62, 140.57, 127.07, 126.96, 115.09, 115.06, 91.62, 91.60, 91.51, 91.48, 90.43, 90.40, 90.37, 90.33, 74.50, 72.95, 72.93, 72.87, 55.82, 36.05, 36.93, 35.43, 35.36, 35.31, 28.79, 28.73, 28.67, 28.65, 28.57, 28.39, 28.34,

$^{12}$ Multiple C-signals appearing in the spectra are due to diastereotopic carbon centers present in the inseparable mixture of diastereomers.
25.24, 25.22, 25.18, 24.76, 24.68, 34.64. **MS** (ESI): \( m/z \) 337.3 [M-H]; 361.1 [M+Na]^+.


**(15R)-4-(methoxymethoxy)-3-methylene-15-vinyloxacyclopentadec-10,11-dien-2-one**

(2.33): Et\(_3\)N (100 \( \mu \)L, 0.71 mmol) and 2,4,6-trichlorobenzoyl chloride (14 \( \mu \)L, 0.09 mmol) were added sequentially to the stirring solution of pre-dried seco-acid 2.31 (6 mg, 0.0177 mmol) in DCM (30 mL, 0.61 mM dilution) at room temperature. The reaction was held stirring for 20h and then DMAP (22 mg, 0.177 mmol) added and the yellow solution was allowed to continue for 4h at room temperature. Then the reaction mixture was quenched by addition of H\(_2\)O, washed with saturated NH\(_4\)Cl and the aqueous phase was extracted with DCM (2x) and the combined extracts were washed with brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. The yellow residue was purified by flash column chromatography (gradient 2-5% EtOAc in hexanes) to furnish macrolactone 2.33 (4 mg, 63%) as yellow liquid. **\(^1\)H NMR** (CDCl\(_3\), 500 MHz): \( \delta \) 6.33-6.29 (m, 1H), 5.87-5.77 (m, 2H), 5.34-5.31 (m, 1H), 5.27-5.16 (m, 3H), 5.06-4.96 (m, 2H, allene), 4.62-4.53 (m, 2H), 3.42-3.38 (m, 3H, CH\(_3\)), 2.17-2.06 (m, 4H), 1.80-1.69 (m, 4H), 1.61-1.49 (m, 2H), 1.43-1.37 (m, 4H). **\(^{13}\)C NMR** (CDCl\(_3\), 125 MHz): \( \delta \) 206.86, 205.66, 205.40, 204.86, 165.98, 165.70, 165.47, 142.46, 142.18, 142.14, 136.59, 136.22, 136.11, 135.65, 125.22, 124.80, 124.67, 124.57, 116.58, 116.47, 116.28, 116.15, 95.05, 94.89, 94.68, 94.65, 90.82, 90.62, 90.53, 90.26, 89.56, 89.39, 89.19, 88.99, 75.31, 74.67,

\(^{13}\) Multiple C-signals appearing in the spectra are due to diastereotopic carbon centers present in the inseparable mixture of diastereomers.
Experimental Procedures (Part B)

74.60, 74.57, 74.26, 73.70, 73.42, 72.76, 55.86, 55.78, 55.67, 38.18, 36.83, 36.07, 36.00, 35.13, 35.11, 34.30, 33.88, 30.90, 29.69, 29.07, 28.80, 28.18, 27.97, 27.95, 27.82, 27.58, 27.22, 27.20, 27.15, 27.09, 26.08, 25.71, 25.04, 24.92, 24.45, 24.38, 23.97. **MS** (ESI): m/z 320.9 (20%) [M]+; 343.1 (100%) [M+Na]+. **HRMS** (ESI): m/z calcd for C₁₉H₂₈NaO₄ 343.1885 [M+Na]+; found 343.1880.

(2S,4S,6S)-4-ethynyl-4-methyl-2-phenyl-6-vinyl-1,3-dioxane (3.9):

**Acetonide Protection**: Triol 2.36 (4 g, 37.7 mmol), p-TSA (0.8 g, 4.2 mmol) and CuSO₄ (4g, 26 mmol) were taken in acetone (60 mL) and the mixture was held stirring at room temperature for 24h. After the reaction was completed, solids were filtered and the solvent was removed in vacuo and the residue was purified by flash column chromatography (gradient 20-30% EtOAc/hexanes) to give alcohol 3.5 as a faint yellow syrup.

**Swern Oxidation**: At −78°C, DMSO (3.6 mL, 51.2 mmol) was added slowly to a solution of oxalyl chloride (2.6 mL, 30.75 mmol) in 60 mL of CH₂Cl₂ and the mixture was stirred for 30 min. A solution of alcohol 3.5 (3 g, 20.5 mmol) in CH₂Cl₂ (15 mL) was then added to above mixture and after additional stirring for 30 min at −78°C, triethylamine (10.0 mL, 71.5 mmol) was added and the reaction mixture was allowed to warm to room temperature. The mixture was diluted with CH₂Cl₂ and then quenched by addition of water. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄ and concentrated to afford the crude aldehyde.
At –78° C, MeMgBr (10.3 ml, 30.75 mmol, 3.0 M solution in diethyl ether) was added to the above obtained aldehyde in dry Et₂O (60 mL). After stirring for 3h, the reaction mixture was quenched with saturated NH₄Cl and the aqueous layer was extracted with ether. The combined organic extracts were dried over Na₂SO₄ and concentrated to give the crude alcohol.

The above crude alcohol in 10 mL of CH₂Cl₂ was added to the flask containing a PCC reactant-mixture (1:1:1 mixture by weight of PCC : 4Å MS : NaOAc, 25 g, 37.5 mmol) in 45 mL of CH₂Cl₂. The resulting dark solution was stirred for 3h at room temperature and then quenched with ether. The mixture was filtered and washed with ether. The combined organic filtrate was dried and concentrated. The residue was purified through flash column chromatography (gradient 5-10% EtOAc/hexanes) to afford the methyl ketone 3.6 (45%, 3 steps) as a colorless oil.

To a solution of methyl ketone 3.6 (0.5 g, 3.16 mmol) in anhydrous ether (15 mL) was added ethynylmagnesium bromide (16 mL, 8 mmol, 0.5M solution in THF) at –78° C. The resulting reaction mixture was stirred for 15 min at this temperature and then warmed to room temperature and continued for a further 5h. After completion, the reaction was quenched with saturated NH₄Cl and extracted with Et₂O. The organic extracts were combined and washed with brine and dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by flash column chromatography (gradient 15-20% EtOAc/hexanes) to afford ethynylcarbinol 3.7 (410 mg, 70%, dr = 4:1) as a colorless oil.
To a solution of 3.7 (0.4 g, 2.17 mmol) in dry CH$_2$Cl$_2$ (10 mL) were added benzaldehyde dimethyl acetal (630 µL, 4.2 mmol) and camphorsulfonic acid (0.116 g, 0.5 mmol) at 0°C. The resulting reaction mixture was allowed to warm to room temperature and stirred overnight. After completion of the reaction, solid NaHCO$_3$ was added to quench the reaction and the solvent was removed *in vacuo* and the resulting residue was purified by flash column chromatography (gradient 10-20%, EtOAc/hexanes) to afford alcohol 3.8 (0.4 g, 80%) as a pale yellow oil.

To the stirring dry DCM (20 mL) was added oxalyl chloride (0.765 mL, 9 mmol) under argon and cooled to −78 °C then anhydrous DMSO (1.28 mL, 18.08 mmol) was added drop wise slowly. After 20 min, alcohol 3.8 (1.4 g, 6.03 mmol) was added in DCM (6 mL) and 30 min later Et$_3$N (10 mL, 72 mmol) was added at −78 °C, the resulting cloudy solution was stirred for 15 min. Then the reaction was quenched by slow addition of H$_2$O (20 mL) and allowed to warm to room temperature. The aqueous layer was extracted with DCM (3x) and the combined organic fractions were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and the solvent was removed under reduced pressure. The crude aldehyde was dried azeotropically with dry THF (2x) before being carried forward for the Nozaki-Takai olefination.

To a stirring solution of freshly activated Zn dust (3.94 g, 60.27 mmol) and PbCl$_2$ (85 mg, 0.3 mmol) in THF (20 mL) was added CH$_2$I$_2$ (2.45 mL, 30.13 mmol) slowly drop wise under argon for 15 min, where a vigorous exothermic reaction with effervescence started within 10 min from the point CH$_2$I$_2$ addition began. The reaction was cooled by arranging an external ice-bath as soon as effervescence began and the grayish solution was stirred at room temperature for 1h after effervescence ceased. Ti(i-OPr)$_4$ (2.7 mL, 6
mmol) was added; and after 30 min at room temperature the greenish solution was added with freshly synthesized crude aldehyde in THF (6 mL). After stirring overnight, the reaction was diluted with ether (30 mL) and quenched by slow addition of 1M HCl (25 mL). The aqueous layer was extracted with ether (2x) and the combined organic fractions were washed with brine solution, dried over anhydrous Na₂SO₄, filtered, concentrated and purified by flash column chromatography (gradient 2-5% Et₂O in hexanes) to furnish (2S,4S,6S)-4-ethynyl-4-methyl-2-phenyl-6-vinyl-1,3-dioxane 3.9 (0.7 g, 50%, 2 steps) exclusively as a colorless liquid. 

**1H NMR** (CDCl₃, 500 MHz): δ 7.55-7.37 (m, 2H, Ph), 7.35-7.31 (m, 3H, Ph), 6.06 (s, 1H), 5.96-5.89 (m, 1H), 5.39-5.35 (m, 1H), 5.21-5.18 (m, 1H), 4.68-4.64 (m, 1H), 2.64 (s, 1H), 1.86 (dd, J = 2.55, 13.25 Hz), 1.74 (dd, J = 12.65, 11.35 Hz), 1.62 (s, 3H).

**13C NMR** (CDCl₃, 125 MHz): δ 138.37, 137.37, 128.75, 128.19, 126.38, 115.84, 96.82, 83.94, 74.96, 74.45, 70.19, 42.44, 29.78. **MS** (ESI): m/z 267.2 [M+K]⁺. **HRMS** (ESI): m/z calcd for C₁₅H₁₆NaO₂ 251.1048; found 251.1039 [M+Na]⁺.

(3S,5S)-5-hydroxy-5-methylhept-1-en-6-yn-3-yl pivalate (3.13): A solution of benzylidene acetal 3.9 (120 mg, 0.53 mmol) in THF/H₂O (1:1 v/v, 5 mL) was treated with conc. H₂SO₄ until pH = 1 and refluxed overnight at 65 °C. The solvent was removed in vacuo and the residue was purified by flash column chromatography (gradient 20-30% EtOAc/hexanes) to furnish diol 3.12 (52 mg, 70%).

To a stirred solution of above diol 3.12 (53 mg, 0.38 mmol) and Et₃N (235 μL, 1.9 mmol) in dry DCM (5 mL) at 0 °C was added pivaloyl chloride (230 μL, 1.25 mmol). The reaction was allowed to continue overnight at room temperature then diluted with ether and quenched with H₂O (15 mL). The aqueous layer was extracted with ether (3x)
Experimental Procedures (Part B)

and the combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄ and filtered. The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography (gradient 5-10% EtOAc/hexane) to give pivaloyl ester 3.13 (70 mg, 82%) as yellow liquid. \(^1\)H NMR (CDCl₃, 500 MHz): \(\delta\) 5.85-5.78 (m, 1H), 5.65-5.61 (m, br, 1H), 5.25 (d, \(J = 15.05\), 5.14 (d, \(J = 10.05\), 1H), 2.47 (s, 3H), 2.07 (dd, \(J = 9.45, 15.15\) Hz, 1H), 1.97 (dd, \(J = 3.8, 15.15\) Hz, 1H), 1.49 (s, 3H, Me), 1.20 (s, 1H, Piv). \(^1^3\)C NMR (CDCl₃, 125 MHz): \(\delta\) 177.39, 136.43, 116.20, 86.39, 72.74, 72.26, 66.63, 46.97, 38.68, 30.09, 27.03.

(4S)-4-(benzyloxy)hex-5-en-2-ol (3.15): To a stirring solution of (S)-3-(benzyloxy)pent-4-enal 3.50 (541 mg, 2.84 mmol) in anhydrous ether (15 mL) at −78 °C was added MeMgBr (2 mL, 3M in Et₂O, 6 mmol). After 2h of stirring the reaction mixture was quenched by slow addition of 1M HCl (15 mL). The aqueous phase was extracted with ether (2x10 mL) and the combined extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated \(\text{in vacuo}\). The resulting residue was purified by flash column chromatography (gradient 10-15% EtOAc/hexane) to furnish (4S)-4-(benzyloxy)hex-5-en-2-ol 3.15 (2 diastereomers, 440 mg, 75%) as a faint yellow liquid. \(^1\)H NMR (CDCl₃, 500 MHz): \(\delta\) 7.36-7.27 (m, 5H), 5.87-5.72 (m, 1H), 5.30-5.25 (m, 2H), 4.66-4.62 (m, 1H), 4.38-4.35 (m, 1H), 4.12-4.06 (m, 1H), 1.82-1.67 (m, 2H), 1.82-1.15 (m, 1H). \(^1^3\)C NMR (CDCl₃, 125 MHz): \(\delta\) 138.13, 138.06, 138.05, 128.43, 128.38, 127.81, 127.75, 127.67, 127.62, 117.57, 117.09, 81.09, 77.98, 70.33, 70.11, 67.28, 64.52, 44.15, 43.70, 23.37, 23.33. ESI (m/z): calcd for C₁₃H₁₈NaO₂ 229.1204 [M+Na]⁺; found, 229.1.
(S)-4-(benzyloxy)hex-5-en-2-one (3.16): Alcohol 3.15 (440 mg, 2.13 mmol) was dissolved in anhydrous DCM (10 mL) and PCC (690 mg, 3.2 mmol) was added. After stirring overnight at room temperature, the resulting dark orange-black reaction mixture was filtered through a celite pad and the filtrate was concentrated. The thick darker residue was purified by flash column chromatography (gradient 10-15% EtOAc/hexane) to furnish (S)-4-(benzyloxy)hex-5-en-2-one 3.16 (410 mg, 95%) as colorless syrup. 

**1H NMR** (CDCl₃, 500 MHz): δ 7.34-7.27 (m, 5H, Ph), 5.81-5.74 (m, 1H), 5.33-5.25 (m, 2H), 4.57 (d, J = 11.35 Hz, 1H), 4.37 (d, J = 11.35 Hz, 1H), 2.85-2.80 (m, 1H), 2.53 (dd, J = 4.4, 15.78 Hz, 1H), 2.16 (s, 3H).

**13C NMR** (CDCl₃, 125 MHz): δ 206.45, 138.15, 137.42, 128.30, 127.79, 127.56, 117.66, 76.58, 70.58, 49.46, 31.06. **MS** (ESI): m/z 204.9 [M]; 227.0 [M+Na]+. **HRMS** (ESI): m/z calcld for C₁₃H₁₆NaO₂ 227.1048 [M+Na]+; found, 227.1045.

(S)-5-(benzyloxy)hept-6-en-1-yn-3-one 3.21: Ethynylmagnesium bromide (3.6 mL, 0.5 M in Et₂O, 1.8 mmol) was added to the solution of aldehyde 2.50 (172 mg, 0.9 mmol) in anhydrous ether (6 mL) at −78 °C. After 3h of stirring, the reaction mixture was quenched by addition of 1M HCl (15 mL). The aqueous phase was extracted with ether (2x10 mL) and the combined extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated and purified by flash column chromatography (gradient 5-10% EtOAc/hexane) to furnish proargylic alcohol 3.20 (2 diasteriomers, 135 mg, 70%).

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Experimental Procedures (Part B)

To the stirring solution of above propargylic alcohol 3.20 (120 mg, 0.55 mmol) in dry DCM (6 mL) was added DMP (398 mg, 0.94 mmol) at room temperature and the reaction was allowed to stand for 2h at room temperature. Upon complete consumption of alcohol, the reaction contents were filtered through a celite pad and concentrated on a rotary evaporator. The crude residue was purified by flash column chromatography (gradient 1-5% EtOAc in hexanes) to provide (5S)-5-(benzyloxy)hept-6-en-1-yn-3-one 3.21 (52 mg, 42%) as a colorless syrup. 

1H NMR (CDCl3, 500 MHz): δ 7.35-7.27 (m, 5H), 5.82-5.75 (m, 1H), 5.37-5.29 (m, 2H), 4.59 (d, J = 11.95 Hz, 1H), 4.46-4.42 (m, 1H), 4.41 (d, J = 11.35 Hz), 4.46-4.42 (m, 1H), 4.41 (d, J = 11.35 Hz, 1H), 3.21 (s, 1H), 2.97 (dd, J = 8.8, 15.75 Hz), 2.72 (dd, J = 4.4, 15.75 Hz, 1H). 

13C NMR (CDCl3, 125 MHz): δ 184.17, 137.91, 136.73, 128.27, 127.85, 127.59, 118.30, 81.47, 78.88, 76.05, 70.61, 51.11. MS (ESI): m/z 237.0 [M+Na]+. HRMS (ESI): m/z calcd for C14H14NaO2 237.0891 [M+Na]+; found, 237.0881.

5S)-5-(benzyloxy)-3-methylhept-6-en-1-yn-3-ol (3.17/3.18): To a stirring solution of methyl ketone 3.21 (410 mg, 2.0 mmol) in anhydrous ether (20 mL) at −78 °C was added ethynylmagnesium bromide (20 mL, 0.5 M in THF, 10 mmol). Then the reaction mixture was allowed to warm slowly to room temperature over 2h and quenched by addition of 1M HCl (15 mL). The aqueous phase was extracted with ether (2x) and the combined extracts were washed with brine, dried over anhydrous Na2SO4, filtered, concentrated and purified by flash column chromatography (gradient 10-15% EtOAc in hexanes) to furnish
diastereomeric ethynyl carbinols, (3S,5S)-5-(benzyloxy)-3-methylhept-6-en-1-yn-3-ol 3.17 (311 mg) and (3R,5S)-5-(benzyloxy)-3-methylhept-6-en-1-yn-3-ol 3.18 (100 mg) (dr = 31:10 by $^1$H NMR integration, 410 mg, 90%) as a colorless syrup.

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.36-7.26 (m, 5H, Ph), 5.83-5.75 (m, 1H), 5.35-5.28 (m, 2H), 4.91 (s 1H, OH), 4.63 (d, $J = 11.35$ Hz, 1H), 4.56-4.52 (m, 1H), 4.44 (d, $J = 10.75$ Hz, 1H), 2.43 (s, 1H), 1.97 (dd, $J = 14.5$, 11.5 Hz, 1H), 1.78 (dd, $J = 14.5$, 2.5 Hz, 1H), 1.48 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 137.33, 137.30, 128.46, 128.24, 127.88, 117.91, 87.31, 80.32, 71.42, 40.75, 67.45, 47.14, 30.40. MS (ESI): m/z 230.8 [M$^+$], 253.1 [M+Na$^+$]. HRMS (ESI): m/z calcd for C$_{15}$H$_{18}$NaO$_2$ 253.1204 [M+Na$^+$]; found, 253.1196.

(2S,4S,6S)-4-ethynyl-4-methyl-2-phenyl-6-vinyl-1,3-dioxane (3.9): To a stirring solution of benzyl ether 3.17 (7 mg, 0.03 mmol) in dry DCM, was added DDQ (18 mg, 0.09 mmol) and the reaction mixture was held at room temperature for 3h. The reaction solution was filtered through a celite pad, diluted with DCM (10 mL), washed with saturated NaHCO$_3$. The aqueous layer was extracted with DCM (2x) and the combined organic fractions were washed
with brine (15 mL), dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the orange-red residue was purified by flash column chromatography (gradient 2-5% Et₂O in hexane) to furnish benzylidene acetal 3.9.

Analytical data was in good agreement with the compound that was previously synthesized by Nozaki-Takai olefination from 3.8.

(2S,4R,6S)-4-ethynyl-4-methyl-2-phenyl-6-vinyl-1,3-dioxane (3.22): This compound as a colorless syrup was synthesized from 3.18 by following the same procedure as for the synthesis of 3.9 from 3.17. ¹H NMR (CDCl₃, 500 MHz): δ 7.54-7.37 (m, 2H), 7.36-7.32 (m, 3H), 6.06 (s, 1H), 5.95-5.89 (m, 1H), 5.39-5.35 (m, 1H), 5.21-5.18 (m, 1H), 4.68-4.64 (m, 1H), 4.25-4.18 (m, 1H), 2.63 (s, 1H), 2.17 (s, 1H), 1.88-1.84 (m, 1H), 1.76-1.62 (m, 1H), 1.54 (s, 1H).

((3S,5S)-5-(benzyloxy)-3-methylhept-6-en-1-yn-3-yloxy)trimethylsilane (3.3): To a stirring solution of (3S,5S)-5-(benzyloxy)-3-methylhept-6-en-1-yn-3-ol 3.17 (115 mg, 0.50 mmol) and Et₃N (340 µL, 2.5 mmol) in dry DCM (5 mL) at 0 °C, was added TMSOTf (230 µL, 1.25 mmol) and after stirring overnight at room temperature, the reaction was quenched with H₂O. The mixture was diluted with ether (25 mL) and the layers were separated. The aqueous layer was extracted with ether (3x) and the combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄, solids were filtered and the solvent was removed under reduced pressure. The yellow residue was purified by flash column chromatography (gradient 0-5% EtOAc/hexane) to give TMS ether 3.3 (145 mg, 96%)
exclusively as a yellow oil. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.37-7.31 (m, 4H, Ph), 7.28-7.25 (m, 1H, Ph), 5.87-5.79 (m, 2H), 4.57-4.55 (d, $J = 11.35$ Hz, 1H), 4.40-4.38 (d, $J = 11.35$ Hz), 4.13-4.08 (m, 1H), 2.44 (s, 1H), 2.13 (dd, $J = 6.3$, 14.5 Hz), 1.95 (dd, $J = 5.05$, 14.5 Hz), 1.54 (s, 3H), 0.19 (s, 9H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 139.21, 138.71, 128.24, 127.31, 116.33, 88.48, 77.28, 72.31, 70.0, 67.78, 50.18, 31.20, 1.88. MS (ESI): $m/z$ 230.7 [(M-TMS)+H]$^+$; 253.0 [(M-TMS)+H+Na]$^+$. HRMS (ESI): $m/z$ calcd for C$_{15}$H$_{18}$NaO$_2$ 253.1204 [(M-TMS)+H+Na]$^+$; found, 253.1188.

($(3R,5S)$-5-(benzyloxy)-3-methylhept-6-en-1-yn-3-yloxy)trimethylsilane (3.19):

![Diagram](image)

The same procedure was followed as described for synthesis of 3.3. TMS ether 3.19 was obtained as a yellow oil from 3.18.

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.35-7.30 (m 4H), 7.25-7.23 (m, 1H), 5.83-5.76 (m, 1H), 5.28-5.18 (m, 2H), 4.54 (d, $J = 11.35$ Hz, 1H), 4.37 (d, $J = 12$ Hz, 1H), 2.43 (s, 1H), 2.07-2.03 (m, 1H), 1.91-1.87 (m, 1H), 1.53 (s, 3H, Me), 0.17 (s, 9H, TMS). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 139.17, 138.65, 128.21, 127.85, 127.31, 116.08, 87.75, 78.00, 72.76, 70.28, 68.51, 50.52, 30.07, 1.94. MS (ESI): $m/z$ 230.8 [M-TMS+H], 325.1 [M+Na]$^+$. HRMS (ESI): $m/z$ calcd for C$_{18}$H$_{26}$NaO$_2$Si 325.1600 [M+Na]$^+$; found, 325.1599.

1,2:5,6-Di-$O$-isopropylidene-alpha-D-glucofuranose (3.24):

Glucose was acetylated following a procedure described in Preparative carbohydrate chemistry.$^{14}$ To a stirring solution of $\alpha$-D-glucose (50 g) in acetone at ice bath temperature, conc.

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H₂SO₄ (96%, 40 mL) was added in 5 mL portions at 15 min intervals. After addition was completed, contents were allowed to gradually warm-up to ambient temperature over 5h with constant stirring. The solution was cooled again (ice bath) and 50% NaOH (61 g in 75 mL H₂O) was slowly added with vigorous stirring to near neutrality (pH = 7). A pinch of NaHCO₃ was added to maintain near neutrality. After standing overnight, solids were removed by filtration and the solution was concentrated on a rotary-evaporator to thick syrup. This mixture was dissolved in DCM (100 mL) and washed with H₂O (100 mL). The organic layer was concentrated and the crude product was recrystallized from hexanes to give white, shiny, needle-like crystals of diacetal glucose 3.24 (28 g, 40%).

**1H NMR** (CDCl₃, 500 MHz): δ 5.94 (d, J = 3.75 Hz, 1H), 4.53 (d, J = 3.15 Hz, 1H), 4.34-4.10 (m, 2H), 4.18-4.15 (m, 1H), 4.06 (dd, J = 2.5, 7.55, 1H), 3.99-3.96 (m, 1H), 2.58-2.57 (m, 1H, OH), 1.49 (s, 3H), 1.44 (s, 3H), 1.36 (s, 3H).

**13C NMR** (CDCl₃, 125 MHz): δ 111.81, 109.64, 105.28, 85.07, 81.12, 75.22, 73.49, 67.66, 26.83, 26.74, 26.16, 25.12.


**Diacetone ester 3.28**: 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 3.24 (14 g, 53.8 mmol), acetic anhydride (20 mL, 215 mmol) and pyridine (8.6 mL, 107 mmol) were dissolved in dry DCM (150 mL) and cooled to ice-bath temperature with stirring. Solid CrO₃ (21 g, 215 mmol) was added in 4 portions with 15 min intervals and let the reaction warm gradually to room temperature over 3h. When starting material was found to be completely consumed (by TLC), the reaction mixture was filtered through a celite bed, solids were washed with...
DCM and the filtrate was washed with saturated aq. NaHCO$_3$ solution (2x), brine, dried over anhydrous Na$_2$SO$_4$ and filtered. The ketone obtained was directly carried forward for the subsequent Wittig homologation with stabilized ylide.

To the above obtained ketone 3.25 in DCM was added Wittig salt, (2-methoxy-2-oxoethyl)(triphenyl)phosphonium bromide (31 g, 73 mmol) and Et$_3$N (22 mL, 161 mmol) and stirred overnight at room temperature. The solution was concentrated to 50 mL and Ph$_3$P = O was precipitated by adding Et$_2$O (100 mL). A solid clump was filtered-off through a celite bed. The filtrate was concentrated and purified by flash column chromatography (gradient 10-20% EtOAc/hexane) to furnish an E/Z mixture of diastereomers of 3.27.

Pd/C (1.84 g, 20% w/w) was added carefully to the E/Z diastereomeric mixture 3.27 (9.52 g, 30.3 mmol) in MeOH (100 mL) and subsequently shaken by parr hydrogenator under a H$_2$ atmosphere (50 psi) for 5h at room temperature after which all the starting material was consumed (by TLC analysis) with 5 psi consumption of H$_2$. The reaction mixture was filtered through a celite bed and concentrated under reduced pressure. The colored residue was purified by flash column chromatography (30% EtOAc/hexane) to furnish diacetonide ester 3.28 (9.4 g, quantitative) as a single diastereomer. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 5.74 (d, $J = 3.75$ Hz, 1H), 4.77 (t, $J = 4.4$ Hz, 1H), 4.06 (dd, $J = 5.7$, 8.2 Hz, 1H), 3.95-3.88 (m, 2H), 3.67 (s, 3H), 3.65-3.63 (m, 1H), 2.79 (dd, $J = 4.45$, 17.65 Hz, 1H), 2.63 (dd, $J = 10.1$, 17.65, 1H), 2.32-2.27 (m, 1H), 1.46 (s, 3H), 1.37 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 172.65, 111.76, 109.56, 104.96, 81.38, 80.85, 67.82, 51.54, 44.52, 29.67, 26.65, 26.52, 26.27, 25.15. MS (ESI): $m/z$ 339.1 [M+Na]$^+$. HRMS (ESI): $m/z$ calcd for C$_{15}$H$_{24}$NaO$_7$ 339.1420 [M+Na]$^+$; found 339.1416.
Experimental Procedures (Part B)

2-((3aR,5S,6R,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)ethanol (3.29): To the ice cold stirring solution of ester 3.28 (9.3 g, 30 mmol) in THF (150 mL) was added LiAlH₄ (1.34 g, 35 mmol) portion wise for 30 min. The reaction mixture was allowed to warm to room temperature over 1h after which TLC analysis indicated all the ester was consumed. The reaction mixture was cooled to 0 °C and quenched by drop wise addition of saturated aqueous Na₂SO₄ solution (30 mL) with stirring. White solid cake thus formed was refluxed with EtOAc (2x) for 10 min and then filtered. The collective filtrate fractions were washed with brine (40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (gradient 30-50% EtOAc/hexane) of the resulting residue yielded the title compound 3.29 as colorless liquid (8.3 g, 98%).

**¹H NMR** (CDCl₃, 500 MHz): δ 5.4 (d, J = 3.75 Hz, 1H), 4.68 (t, J = 4.45 Hz, 1H), 4.07 (dd, J = 6.3, 8.2 Hz, 1H), 3.98 (dd, J = 6.3, 13.25, 1H), 3.91 (dd, J = 5.65, 8.8 Hz, 1H), 3.76 (d, J = 6.9, 9.45 Hz, 1H), 3.76-3.71 (m, 2H), 2.05-1.8 (m, 4H), 1.48 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H).

**Experimental Procedures (Part B)**

(E)-methyl 3-((3aR,5R,6R,6aR)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-methylacrylate (3.33): To a stirring solution of alcohol 3.29 (4 g, 13.88 mmol) and PMBBr in dry THF (50 mL), was added NaH (60% in mineral oil, 0.61 g, 15.26 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4h. After complete consumption of starting alcohol (by TLC), the reaction was diluted with ether and quenched with addition of H2O, layers were separated and the aqueous layer was extracted with ether (2x). The combined organic fractions were washed with brine, dried over anhydrous Na2SO4, solids were filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (gradient 20-30% EtOAc/hexanes) to give 3.23 (3.96 g, 70%) as a colorless syrup.

The diacetal 3.23 (3.2 g, 7.84 mmol) was dissolved in 60% AcOH/H2O (80 mL) and the reaction mixture was stirred at room temperature for 12h. Upon completion of mono acetal cleavage (by TLC analysis), toluene was added and the solvent was distilled under reduced pressure. The resulting syrup was purified by flash column chromatography (gradient 30-50% EtOAc/hexane) to provide diol 3.30 as a colorless syrup in 75% yield.

**Ylide (3.32) Formation:** Methyl 2-bromopropanoate (3.26 mL, 29.3 mmol) and PPh3 (10 g, 38.12 mmol) were dissolved in EtOAc (50 mL) and stirred at reflux (80 °C) overnight. The reaction mixture was cooled to room temperature and filtered through a fritted funnel to obtain (1-(methoxycarbonyl)ethyl)triphenylphosphonium bromide (7 g, 56%) from which 4.26 g was taken into H2O (10 mL) and NaOH (0.86 g, 21.48 mmol) in H2O (20
mL) added slowly, where the contents instantaneously solidified. DCM (20 mL) was added to dissolve the sticky solids and the yellow solution stirred at room temperature. After 30 min, water was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with DCM (2x) and the combined organic extracts containing ylide 3.32 were dried over anhydrous Na₂SO₄.

**Oxidative Vicinal Diol Cleavage and Wittig**: The vicinal diol 3.30 (1.94 g, 5.26 mmol) was dissolved in MeOH (40 mL) and NaIO₄ (1.46 g, 6.84 mmol) in H₂O (10 mL) was added slowly. The white precipitate formation began with an exothermic reaction. After stirring for 15 min, the reaction solution was filtered through a fritted sintered funnel and the solid was washed with MeOH followed by DCM. The filtrate was diluted with DCM and washed with brine. The aqueous layer was extracted with DCM (3x) and the combined organic fraction was dried over anhydrous Na₂SO₄. The solvent was reduced approximately to half-volume on a rotary evaporator and treated with ylide 3.32 in DCM (20 mL). The reaction mixture was stirred overnight at room temperature and the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (gradient 10-20% EtOAc/hexane) to give the conjugated ester 3.33 (1.5 g, 72%) as an off-white syrup. ¹H NMR (CDCl₃, 500 MHz): δ 7.24 (d, J = 8.2 Hz, 2H), 6.88-6.86 (m, 2H), 6.58 (dd, J = 1.3, 8.9 Hz, 1H), 5.82 (d, J = 3.8 Hz, 1H), 4.60-4.57 (m, 2H), 4.41 (dd, J = 11.3 Hz, 15.1 Hz, 2H), 3.80 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.51 (t, J = 6.9 Hz, 2H), 2.02-1.96 (m, 1H), 1.90 (d, J = 1.25 Hz, 3H, Me), 1.88-1.82 (m, 1H), 1.59-1.53 (m, 1H), 1.53 (s, 3H, Me), 1.27 (s, 3H, Me). ¹³C NMR (CDCl₃, 125 MHz): δ 167.88, 159.20, 138.12, 131.36, 130.39, 129.26, 113.75, 111.61, 105.37, 80.85, 77.43,
Experimental Procedures (Part B)


(E)-3-((3aR,5R,6R,6aR)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-methylprop-2-en-1-ol (3.34): To a stirring solution of conjugated ester 3.33 (500 mg, 1.23 mmol) in dry THF (8 mL) at –78 °C, was added DIBALH (3.1 mL, 1M in cyclohexane, 3.1 mmol) over 10 min. The reaction contents were allowed to warm to room temperature in a dry-ice bath over 4h. After complete consumption of ester, the reaction was quenched by addition of saturated Rochelle salt (potassium sodium tartrate) dropwise (15 mL) and stirred vigorously for 30 min at room temperature during which the initially formed gray-cloud in the organic phases was disappeared slowly and appeared in the water layer. The solution was diluted with ether and the layers were separated. The aqueous layer was extracted with ether (3x) and the combined organic fractions were washed with brine, dried over anhydrous Na_{2}SO_{4}, filtered and concentrated. The resulting syrup was purified by flash column chromatography (gradient 20-30% EtOAc/hexane) to provide allylic alcohol 3.34 (426 mg, 92%) as a colorless syrup along with a trace conjugate reduction product. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.24 (d, \(J = 8.8\) Hz, 2H), 6.87 (d, \(J = 8.2\) Hz, 2H), 5.78 (d, \(J = 3.75\) Hz, 1H), 5.36 (d, \(J = 8.8\) Hz, 1H), 4.57-4.51 (m, 2H), 4.42 (s, 2H), 3.99 (s, 2H), 3.79 (s, 3H), 3.54-3.50 (m, 2H), 1.87-1.80 (m, 3H), 1.71 (s, 3H), 1.59-1.55 (m, 1H), 1.52 (s, 3H), 1.31 (s, 3H). \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 159.14, 141.34, 130.46, 129.22, 122.38, 113.72, 111.24, 104.90, 80.90, 77.38, 72.46, 67.99, 67.71, 55.23, 47.18, 26.65, 26.23, 24.48, 14.30. MS (ESI): m/z 401.1 [M+Na]^+. 
Experimental Procedures (Part B)

(E)-3-((3aR,5R,6R,6aR)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-methylacrylaldehyde (3.4): To the stirring solution of allylic alcohol 3.34 (220 mg, 0.58 mmol) in dry DCM (10 mL) was added DMP (370 mg, 0.87 mmol) at room temperature and the reaction was stirred for 2 h at room temperature. Upon complete consumption of allylic alcohol, the contents were filtered through a celite bed and concentrated on a rotary evaporator. The crude residue was purified by flash column chromatography (gradient 20-30% EtOAc/hexanes) to provide conjugated aldehyde 3.4 (190 mg, 90%) as a colorless syrup. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 9.43 (s, 1 H), 7.23 (m, 2 H) 6.89-86 (m, 2 H) 6.29 (dd, $J$ = 1.3, 8.85 Hz, 1 H), 5.86 (d, $J$ = 3.15 Hz, 1 H), 4.74 (dd, $J$ = 8.8, 18.9 Hz, 1 H), 4.62 (t, $J$ = 4.4 Hz, 1 H), 4.41 (s, 2 H), 3.80 (s, 3 H), 3.53-3.51 (m, 2 H), 2.10-2.04 (m, 1 H), 1.92-1.85 (m, 1 H), 1.79 (d, $J$ = 1.25 Hz, 1 H), 1.58-1.51 (m, 1 H), 1.54 (s, 3 H), 1.33 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 194.63, 159.20, 148.89, 141.09, 130.24, 129.21, 113.74, 111.79, 105.44, 80.77, 77.25, 72.54, 67.47, 55.20, 47.37, 26.62, 26.16, 24.51, 10.07.

Alkyne Addition by BuLi: To a solution of alkyne 3.3 (140 mg, 0.46 mmol) in THF (2 mL) at $-78^\circ$C, n-BuLi (0.9 mL, 0.5 M in hexane, 0.46 mmol) was added. The reaction
was allowed to continue for 2h at –78 °C then, aldehyde 3.4 (191 mg, 0.509 mmol) in THF (2 mL) was added. After 2h at –78 °C, the reaction was quenched by slow addition of saturated NH₄Cl and extracted with ether (3x). The combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by flash column chromatography (gradient 15-50% EtOAc/hexane) to afford coupling product, alkynol 3.35 (65 mg) and [2,3]-Wittig rearrangement product 3.44 (86 mg, 61% of aldehyde used) while recovering 100 mg unreacted aldehyde.

![Chemical Structure](image)

(6S,8S,E)-8-(benzyloxy)-1-((3aR,5R,6R,6aR)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2,6-dimethyl-6-(trimethylsilyloxy)deca-1,9-dien-4-yn-3-ol (3.35): Alkyne addition product.

**¹H NMR** (CDCl₃, 500 MHz): δ 7.35-7.31 (m, 4H), 7.25-7.22 (m, 3H), 6.86 (d, J = 6.86 Hz, 2H), 5.76-5.73 (m, 1H), 5.66-5.53 (m, 3H), 4.76 (s, 1H), 4.71-4.67 (m, 1H), 4.55-4.49 (m, 2H), 4.43-4.38 (m, 2H), 3.79 (m, 3H, OMe), 3.52 (m, 2H), 2.6 (s, br, 1H, OH), 2.53-2.48 (m, 1H), 2.43-2.34 (m, 2H), 2.32-2.27 (m, 1H), 1.89-1.81 (m, 2H), 1.82 (s, 3H, Me), 1.53 (s, 3H, Me), 1.44-1.43 (m, 1H), 1.43 (s, 3H, Me), 0.19-0.17 (m, 9H, TMS).

**¹³C NMR** (CDCl₃, 125 MHz): δ 159.11, 143.88, 143.95, 140.29, 140.29, 130.39, 129.94, 129.90, 129.78, 129.22, 128.26, 127.24, 125.70, 124.64, 124.37, 113.70, 111.28, 104.94, 89.61, 83.92, 83.77, 80.81, 80.76, 77.44, 77.37, 73.20, 73.06, 72.41, 69.57, 67.95, 67.93,

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¹⁵ Multiple C-signals appearing in the spectra are due to diastereotopic carbon centers present in the inseparable mixture of diastereomers.
Experimental Procedures (Part B)

67.11, 66.94, 55.21, 48.41, 48.30, 47.27, 47.23, 42.78, 30.73, 29.62, 26.63, 26.21, 24.35, 13.53, 13.42, 1.91. MS (ESI): m/z 701.2 [M+Na]+.

\((1R,6R,E)-6\text{-methyl-1-phenyl-6-}(\text{trimethylsilyloxy})\text{oct-3-en-7-yn-1-ol (3.44): [2,3] Wittig rearrangement product}\)

\(^1\text{H NMR (CDCl}_3, 500 \text{ MHz):} \delta 7.39-7.28 \text{ (m, 5H, Ph), 5.74-5.68 \text{ (m, 1H), 4.74-4.72 \text{ (m, 1H), 2.59-2.54 \text{ (m, 1H), 2.39-2.35 \text{ (m, 1H), 2.31 \text{ (s, br, 1H, OH), 1.47 \text{ (s, 3H), 0.23 \text{ (s, 9H).}}}})}\)

\(^\text{13C NMR (CDCl}_3, 125 \text{ MHz):} \delta 143.84, 129.95, 129.33, 128.26, 127.28, 125.75, 87.78, 73.05, 72.88, 69.00, 48.23, 42.81, 30.56, 1.87. MS (ESI): m/z 325.1 [M+Na]^+. HRMS (ESI): m/z calcd for \(\text{C}_{18}\text{H}_{26}\text{NaO}_{2}\text{Si} 325.1600 \text{ [M+Na]^+; found, 325.1592.}\)

\((\text{E)-5-}((2S,4S,6S)-6-(\text{tert-butyldimethylsilyloxy)methyl})-4\text{-methyl-2-phenyl-1,3-dioxan-4-yl)-1-}((3aR,5R,6R,6aR)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2\text{-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-methylpent-1-en-4-yn-3-ol (4.6):}\)

To a solution of alkyne 4.5 (469 mg, 1.35 mmol) in THF (6 mL) at \(-78 \text{ °C,} n\text{-BuLi (1.35 mL, 1M in hexane, 1.35 mmol) was added. After stirring 30min at \(-78 \text{ °C, aldehyde 3.4 (340 mg, 0.903 mmol) in THF (6 mL) was added. After 2h at \(-78 \text{ °C, the reaction was quenched by slow addition of saturated NH}_4\text{Cl and extracted with ether (3x). The combined organic fractions were washed with brine, dried over anhydrous Na}_2\text{SO}_4, \text{ filtered and concentrated. The crude residue was purified by flash column chromatography (gradient}} \)
Experimental Procedures (Part B)

15-25% EtOAc/hexane) to afford coupling product, alkynol 4.6 (386 mg, 75%) as a pale yellow syrup with different diastereomeric ratio in different column fractions. 

**1H NMR** (CDCl₃, 500 MHz): δ 7.53-7.52 (m, 2H, Ph), 7.38-7.33 (m, 3H, Ph), 7.25-7.23 (m, 2H, PMB), 6.88-6.85 (m, 2H, PMB), 5.96 (s, 1H), 5.78 (d, J = 3.8 Hz, 1H), 5.61-5.55 (m, 1H), 4.84 (d, J = 5.65 Hz, 1H, epimeric), 4.57-4.4.51 (m, 2H), 4.43-4.38 (m, 2H, CH₂PMP), 4.18-4.14 (m, 1H), 3.81-3.78 (m, 4H), 3.63 (dd, J = 5.7, 10.7 Hz, 1H), 3.52-3.49 (m, 2H), 2.09 (s, br, 1H, OH), 1.90-1.82 (m, 5H), 1.7-1.64 (m, 2H), 1.60 (s, 3H, Me), 1.59-1.56 (m, 1H), 1.54 (s, 3H, Me), 1.32 (s, 3H, Me), 0.90 (s, 9H, TBS), 0.07-0.06 (d, 6H, TBS). 

**13C NMR** (CDCl₃, 125 MHz): δ 159.17, 140.03, 138.39, 130.44, 129.24, 128.64, 128.10, 126.35, 125.42, 124.96, 113.76, 111.39, 105.01, 96.89, 96.84, 86.45, 85.47, 77.42, 77.36, 74.65, 72.49, 70.45, 67.91, 67.46, 67.13, 65.91, 55.25, 47.27, 39.47, 29.94, 26.69, 26.26, 25.89, 24.52, 18.35, 13.58, 13.24, -5.24, -5.30.

(6S,E)-7-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-((3aR,5R,6R,6aR)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2,6-dimethyl-6-(triethylsilyloxy)hept-1-en-4-yn-3-ol (4.16): To a solution of alkyne 4.15 (394 mg, 1.53 mmol) in THF (10 mL) at −78 °C, n-BuLi (1.35 mL, 0.9M in hexane, 1.53 mmol) was added. Dry-ice bath was removed, stirred for 30min, and again cooled to −78 °C, then aldehyde 3.4 (480 mg, 1.28 mmol) in THF (10 mL) was added. After 3h of stirring in a dry-ice bath, the reaction was quenched by slow addition of saturated NH₄Cl and extracted with ether (3x). The combined organic

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16 Multiple C-signals appearing in the spectra are due to diastereotopic carbon centers present in the inseparable mixture of diastereomers.
fractions were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The crude residue was purified by flash column chromatography (gradient 20-30% EtOAc/hexane) to afford coupling product, alkynol 4.16 (610 mg, 76%) as a pale yellow viscous syrup. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.23 (d, $J = 8.2$ Hz, 2H, PMB), 6.86 (d, $J = 8.2$ Hz, 2H, PMB), 5.77 (d, $J = 3.8$ Hz, 1H), 5.50 (d, $J = 8.85$ Hz, 1H), 4.74-4.73 (d, 1H, epimeric), 4.56-4.55 (m, 1H), 4.52-4.48 (t, 1H), 4.44-4.38 (m, 2H, CH$_2$PMP), 4.31-4.26 (m, 1H), 4.11-4.08 (m, 1H), 3.78 (s, 3H, OMe), 3.59-3.55 (m, 1H), 3.53-3.51 (m, 2H), 2.12-2.07 (m, 1H), 1.93-1.83 (m, 3H), 1.81-1.80 (d, 3H, Me), 1.59-1.54 (m, 1H), 1.52 (s, 3H, Me), 1.48 (s, 3H, Me), 1.36 (s, 3H, Me), 1.33 (s, 3H, Me), 1.30 (s, 3H, Me), 0.95-0.92 (t, 9H, TES), 0.67-0.62 (m, 9H, TES). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 159.13, 140.11, 139.84, 130.44, 129.20, 129.18, 124.88, 113.70, 111.29, 107.77, 104.97, 90.15, 90.12, 82.35, 82.33, 80.85, 80.82, 77.36, 77.31, 72.59, 72.44, 72.42, 70.28, 67.96, 67.93, 67.22, 67.10, 55.19, 48.59, 47.27, 47.24, 30.83, 30.78, 26.77, 26.63, 26.21, 25.78, 24.39, 13.26, 13.24, 6.92, 5.98.

$^{17}$ Multiple C-signals appearing in the spectra are due to diastereotopic carbon centers present in the inseparable mixture of diastereomers.
of celite and the solvent was removed in vacuo. The crude residue was purified by flash column chromatography (gradient 10-20% EtOAc/hexanes) to give alkynone 4.19 (77 mg, quantitative) as a colorless liquid. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.23-7.22 (d, 2H, PMB), 6.86-6.85 (d, 2H, PMB), 5.84 (d, $J = 3.75$ Hz, 1H), 4.68 (dd, $J = 8.8, 10.0$ Hz, 1H), 4.62-4.60 (t, 1H), 4.44-4.42 (dd, 2H, CH$_2$PMP), 4.35-4.30 (m, 1H), 3.78 (s, 3H, OMe), 3.59-3.57 (t, 1H), 3.53-3.50 (t, 2H), 2.15 (dd, $J = 4.4, 13.85$ Hz, 1H), 2.04-1.99 (m, 1H), 1.99 (s, 3H, Me), 1.58-1.53 (m, 7H), 1.37 (s, 3H, Me), 1.34 (s, 3H, Me), 1.32 (s, 3H, Me), 0.96-0.93 (t, 9H, TES), 0.69-0.64 (m, 6H, TES).$^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 179.23, 159.21, 144.95, 140.01, 130.28, 129.23, 113.73, 111.79, 108.07, 105.46, 96.30, 80.77, 80.58, 72.57, 72.22, 70.17, 67.64, 67.33, 55.20, 47.99, 47.64, 30.10, 26.80, 26.66, 26.21, 25.77, 24.52, 11.58, 6.89, 5.92.

**Common procedure for CBS/BH$_3$ Reduction:** To a stirring solution of alkynol 2.204 (1 eq) in dry THF (8 mL) at 0 °C was added CBS solution (1M in toluene 2 eq) and BH$_3\cdot$SMe$_2$ (1M in THF, 3 eq). The reaction was allowed to warm gradually to room temperature through 2h, and then quenched by slow addition methanol followed by water at 0 °C. After 15min of vigorous stirring the aqueous phase was extracted with ether (3x) and the combined extracts were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, concentrated and purified by flash column chromatography (gradient 15-25% EtOAc/hexane) to furnish alkynol as a transparent oil.
Experimental Procedures (Part B)

(3S,6S,E)-7-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-((3aR,5R,6R,6aR)-6-(2-(4-methoxybenzyl)oxy)ethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2,6-dimethyl-6-(triethylsilyloxy)hept-1-en-4-yn-3-ol (4.16a):

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\begin{align*}
{^1}H \text{ NMR} \ (\text{CDCl}_3, \ 500 \text{ MHz}): \ & \delta \ 7.25-7.24 \ (d, \ 2H, \ PMB), \\
6.87-6.86 \ (d, \ 2H, \ PMB), \ 5.78 \ (d, \ J = 3.15 \text{ Hz}, \ 1H), \ 5.50 \ (d, \ J = 8.85 \text{ Hz}, \ 1H), \ 4.74 \ (s, \ 1H), \ 4.57-4.56 \ (m, \ 1H), \ 4.52-4.48 \ (m, \ 1H), \ 4.45-4.40 \ (m, \ 2H, \ CH_2PMP), \ 4.32-4.26 \ (m, \ 1H), \\
4.10 \ (dd, \ J = 5.7, \ 8.2 \text{ Hz}, \ 1H), \ 3.79 \ (s, \ 3H, \ OMe), \ 3.59-3.53 \ (m, \ 3H), \ 2.10 \ (dd, \ J = 4.4, \ 13.85 \text{ Hz}, \ 1H), \ 2.02 \ (s, \ br, \ 1H, \ OH), \ 1.93-1.84 \ (m, \ 3H), \ 1.81 \ (s, \ 3H, \ Me), \ 1.60-1.57 \ (m, \ 1H), \ 1.52 \ (s, \ 3H, \ Me), \ 1.49 \ (s, \ 3H, \ Me), \ 1.37 \ (s, \ 3H, \ Me), \ 1.34 \ (s, \ 3H, \ Me), \ 1.31 \ (s, \ 3H, \ Me), \ 0.96-0.93 \ (t, \ 9H, \ TES), \ 0.69-0.61 \ (m, \ 6H, \ TES). \\
{^{13}}C \text{ NMR} \ (\text{CDCl}_3, \ 125 \text{ MHz}): \ & \delta \ 159.19, \ 139.86, \ 130.53, \ 129.23, \ 125.02, \ 113.76, \ 107.84, \ 105.03, \ 90.29, \ 82.33, \ 80.92, \ 77.35, \ 72.63, \ 72.47, \ 70.34, \ 67.98, \ 67.35, \ 67.17, \ 55.25, \ 48.66, \ 47.30, \ 30.82, \ 26.82, \ 26.68, \ 26.26, \ 25.83, \ 24.49, \ 13.27, \ 6.95, \ 6.04. \ MS \ (ESI): \ m/z \ 697.4 \ [M+Na]^+. \ HRMS \ (ESI): \ m/z \ \text{calcd for C}_{37}H_{58}NaO_9Si \ 697.3748 \ [M+Na]^+; \ \text{found,} \ 697.3747.
\end{align*}
\]

(3R,6S,E)-7-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-((3aR,5R,6R,6aR)-6-(2-(4-methoxybenzyl)oxy)ethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2,6-dimethyl-6-(triethylsilyloxy)hept-1-en-4-yn-3-ol (4.16b):

\[
\begin{align*}
{^1}H \text{ NMR} \ (\text{CDCl}_3, \ 500 \text{ MHz}): \ & \delta \ 7.25-7.24 \ (d, \ 2H, \ PMB), \\
6.87-6.86 \ (d, \ 2H, \ PMB), \ 5.79 \ (d, \ J = 3.15 \text{ Hz}, \ 1H), \ 5.51 \ (d, \ J = 8.8 \text{ Hz}, \ 1H), \ 4.57 \ (t, \ J = 3.8 \text{ Hz}, \ 1H), \ 4.51 \ (t, \ J = 9.45 \text{ Hz}, \ 1H), \\
6.87-6.86 \ (d, \ 2H, \ PMB), \ 5.78 \ (d, \ J = 3.15 \text{ Hz}, \ 1H), \ 5.50 \ (d, \ J = 8.85 \text{ Hz}, \ 1H), \ 4.74 \ (s, \ 1H), \ 4.57-4.56 \ (m, \ 1H), \ 4.52-4.48 \ (m, \ 1H), \ 4.45-4.40 \ (m, \ 2H, \ CH_2PMP), \ 4.32-4.26 \ (m, \ 1H), \\
4.10 \ (dd, \ J = 5.7, \ 8.2 \text{ Hz}, \ 1H), \ 3.79 \ (s, \ 3H, \ OMe), \ 3.59-3.53 \ (m, \ 3H), \ 2.10 \ (dd, \ J = 4.4, \ 13.85 \text{ Hz}, \ 1H), \ 2.02 \ (s, \ br, \ 1H, \ OH), \ 1.93-1.84 \ (m, \ 3H), \ 1.81 \ (s, \ 3H, \ Me), \ 1.60-1.57 \ (m, \ 1H), \ 1.52 \ (s, \ 3H, \ Me), \ 1.49 \ (s, \ 3H, \ Me), \ 1.37 \ (s, \ 3H, \ Me), \ 1.34 \ (s, \ 3H, \ Me), \ 1.31 \ (s, \ 3H, \ Me), \ 0.96-0.93 \ (t, \ 9H, \ TES), \ 0.69-0.61 \ (m, \ 6H, \ TES).
\end{align*}
\]
1H), 4.44-4.40 (m, 2H, CH$_2$PMP), 4.32-4.27 (m, 1H), 4.12-4.09 (m, 1H), 3.80 (s, 3H), 3.60-3.57 (m, 1H), 3.54-3.51 (m, 1H), 2.11 (dd, $J = 4.4, 13.25$ Hz, 1H), 1.94-1.83 (m, 4H), 1.81 (s, 3H, Me), 1.58-1.54 (m, 1H), 1.53 (s, 3H, Me), 1.49 (s, 3H, Me), 1.37 (s, 3H, Me), 1.34 (s, 3H, Me), 1.31 (s, 3H, Me), 0.96-0.93 (t, 9H, TES), 0.69-0.61 (m, 6H, TES).

$^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 159.17, 140.09, 130.48, 129.23, 124.93, 113.74, 111.36, 107.82, 105.02, 90.29, 82.33, 80.86, 77.39, 72.63, 72.49, 70.32, 68.00, 67.28, 67.14, 55.25, 48.64, 47.31, 30.86, 26.82, 26.67, 26.26, 25.83, 24.44, 13.32, 6.97, 6.02.

(2S,5S,E)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-methoxy-7-((3aR,5R,6R,6aR)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2,6-dimethylhept-6-en-3-yn-2-ol (4.17a): NaH (60% in mineral oil, 3 mg, 0.07 mmol) was added to a stirring solution of alcohol 4.16a (100 mg, 0.15 mmol) and MeI (22 µL, 0.3 mmol) in dry THF (4 mL) at 0 °C. After 2h of stirring at room temperature, the reaction mixture was diluted with ether (10 mL) and quenched by addition of H$_2$O. The aqueous layer was extracted with ether (2x) and the combined organic fractions were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude methyl ether product was dissolved in dry THF (4 mL) and TBAF (160 µL, 1M in THF, 0.16 mmol) was added. After stirring at room temperature for 30 min, the reaction mixture was diluted by addition of ether (10 mL) and quenched by 10 mL of H$_2$O and the layers were separated. The aqueous layer was extracted with ether (2x) and the combined organic fractions were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The crude residue was purified by flash column chromatography (gradient...
Experimental Procedures (Part B)

40-50% EtOAc/hexane) to give 4.17a (49 mg, 55%, 2 steps) as a colorless syrup. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.25-7.24 (d, 2H, PMB), 6.88-6.86 (m, 2H, PMB), 5.78 (d, \(J = 3.65\) Hz, 1H), 5.49 (d, \(J = 8.9\) Hz, 1H), 4.63-4.51 (m, 3H), 4.45-4.39 (m, 3H), 4.13-4.09 (m, 2H), 3.80 (s, 3H, OMe), 3.58-3.51 (m, 3H), 3.30 (s, 3H, OMe), 1.91-1.81 (m, 4H), 1.78-1.177 (d, 3H), 1.63-1.56 (m, 1H), 1.53 (s, 3H, Me), 1.50 (s, 3H, Me), 1.42 (s, 3H, Me), 1.36 (s, 3H, Me), 1.31 (s, 3H, Me). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): 159.14, 137.95, 130.46, 129.24, 126.57, 113.72, 111.36, 109.73, 105.00, 89.96, 80.81, 80.36, 77.37, 76.02, 74.36, 72.46, 69.48, 67.93, 67.51, 55.13, 55.25, 47.25, 45.65, 30.51, 26.88, 26.67, 26.23, 25.66, 24.46, 13.14. MS (ESI): \(m/z\) 597.3 [M+Na\(^+\)]. HRMS (ESI): \(m/z\) calcd for C\(_{32}\)H\(_{46}\)NaO\(_9\) 597.3040 [M+Na\(^+\)]; found, 597.3048.

(2S,5R,E)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-methoxy-7-((3aR,5R,6R,6aR)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2,6-dimethylhept-6-en-3-yn-2-ol (4.17b): The same procedure was followed as described for the synthesis of 2.01a. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.25-7.24 (d, 2H, PMB), 6.88-6.86 (m, 2H, PMB), 5.78 (d, \(J = 3.15\) Hz, 1H), 5.52 (d, \(J = 8.8\) Hz, 1H), 4.63-4.51 (m, 3H), 4.45-4.38 (m, 3H), 4.11-4.08 (m, 2H), 3.79 (s, 3H, OMe), 3.57-3.52 (m, 3H), 3.29 (s, 3H, OMe), 1.91-1.81 (m, 4H), 1.77 (s, 3H, Me), 1.59-1.54 (m, 1H), 1.52 (s, 3H, Me), 1.49 (s, 3H, Me), 1.41 (s, 3H, Me), 1.35 (s, 3H, Me), 1.31 (s, 3H, Me). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 159.19, 137.95, 130.52, 129.25, 113.76, 111.36, 109.69, 105.03, 90.09, 80.10, 80.60, 77.46, 75.93, 74.37, 72.47, 69.50, 67.94, 67.50, 55.60, 55.25, 47.27, 45.66, 30.50, 26.87, 26.67, 26.26, 25.67, 24.51, 13.19.
(2S,4R,E)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-7-
((3aR,5R,6R,6aR)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-
dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2,6-
dimethylhepta-3,4,6-trien-2-ol (4.18a): To a stirring
solution of ethynyl carbinol 4.17a (35 mg, 0.609 mmol) in
dry Et₂O (5 mL) was added LiAlH₄ (9 mg, 0.244 mmol) at room temperature. After 5 h at
room temperature, the reaction was quenched by slow addition of saturated solution of
sodium potassium tartrate (Rochelle salt) followed by a saturated solution of Na₂S₂O₃.
The contents were stirred for 1 h and then extracted with ether (2x). The combined
organic fractions were washed with brine, dried over anhydrous Na₂SO₄, solids were
filtered and the crude residue was purified by flash column chromatography (gradient 20-
25% EtOAc/hexane) to give the title allene 4.18a (10 mg, 34%) as a colorless liquid
along with an unidentified product. ¹H NMR (CDCl₃, 500 MHz): δ 7.26-7.24 (d, 2H,
PMB), 6.88-6.87 (d, 2H, PMB), 6.00 (d, 1H, J = 6.3 Hz), 5.79 (d, J = 3.8 Hz, 1H), 5.62
(d, J = 3.8 Hz, 1H), 5.29 (d, J = 9.45 Hz, 1H), 4.59-4.55 (m, 2H0, 4.47-4.42 (m, 3H),
4.11-4.09 (m, 1H), 3.80 (s, 3H, Me), 3.58 -3.51 (m, 4H), 1.90-1.76 (m, 7H), 1.62-1.59
(m, 1H), 1.53 (s, 3H, Me), 1.43 (s, 3H, Me), 1.36 (s, 3H, Me), 1.34 (s, 3H, Me), 1.32 (s,
3H, Me). ¹³C NMR (CDCl₃, 125 MHz): δ 202.62, 159.23, 135.52, 135.20, 130.57,
129.26, 126.36, 125.05, 113.80, 111.32, 109.59, 104.98, 103.15, 102.16, 81.02, 77.91,
73.74, 72.53, 71.83, 69.98, 68.02, 55.29, 47.37, 45.07, 32.21, 29.72, 29.69, 26.89, 26.72,
m/z calcd for C₃₁H₄₄NaO₈ 567.2934 [M+Na]⁺; found, 567.2939.
(6S,8S,E)-8-(benzylloxy)-1-((3aR,5R,6R,6aR)-6-(2-(4-methoxybenzylloxy)ethyl)-2,2-dimethyltetrahydrofurano[2,3-d][1,3]dioxol-5-yl)-2,6-dimethyl-6-(trimethylsilyloxy)deca-1,9-dien-4-yn-3-one (4.23): To a stirring solution of propargylic alcohol 3.37 (32 mg, 0.047 mmol) in DCM was added solid MnO₂ portion wise (10 x 5 mg) with 10-15 minutes interval. After stirring overnight at room temperature, the reaction mixture was filtered through a fritted funnel and the solvent was removed in vacuo. The crude residue was purified by flash column chromatography (gradient 20-25% EtOAc/hexanes) to give alkynone 4.23 (30 mg, quantitative).¹H NMR (CDCl₃, 500 MHz): δ 7.36-7.31 (m, 4H), 7.25-7.23 (m, 1H), 7.21 (d, J = 8.85 Hz, 2H), 6.88-6.85 (m, 2H), 5.72 (d, J = 3.8 Hz, 1H), 5.67-5.40 (m, 2H) 4.69-4.65 (m, 2H), 4.54 (t, J = 4.4 Hz, 1H), 4.40 (dd, J = 11.35, 16.4 Hz, 2H), 3.79 (s, 3H, Me), 3.50 (dd, J = 5.7, 6.9 Hz) 2.52-2.36 (m, 5H), 2.07-2.01 (m, 1H), 1.88-1.81 (m, 1H), 1.85 (s, 3H, Me), 1.56-1.51 (m, 4H), 1.48 (s, 3H, Me), 1.30 (s, 3H, Me), 0.18 (s, 9H, TMS).¹³C NMR (CDCl₃, 125 MHz): δ 179.58, 159.22, 144.80, 144.24, 140.19, 130.57, 130.25, 129.26, 128.49,128.31, 127.32, 125.76, 125.73, 113.75, 111.72, 105.39, 96.46, 81.57, 80.68, 73.35, 72.55, 69.45, 67.61, 55.24, 47.87, 47.57. 42.92, 30.02, 29.65, 26.63, 26.16, 24.47, 11.60, 1.81. MS (ESI): m/z 699.2 (100%) [M+Na]^+. HRMS (ESI): m/z calcd for C₃₉H₅₂NaO₈Si 699.3329 [M+Na]^+; found, 699.3330.
Experimental Procedures (Part B)

(3S,5S,E)-3-(benzoyloxy)-8-methoxy-10-((3aR,5R,6R,6aR)-6-(2-(4-methoxybenzoyloxy)ethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-5,9-dimethyldeca-1,9-dien-6-yn-5-ol (4.25): NaH (60% in mineral oil, 3 mg, 0.07 mmol) was added to a stirring solution of alcohol 3.35 (27 mg, 0.032 mmol) and MeI (5 µL, 0.07 mmol) in dry THF (2 mL) at 0 °C. After 2h of stirring at room temperature, the reaction mixture was diluted with ether (10 mL) and quenched with 10 mL of H₂O. The aqueous layer was extracted with ether (2x) and the combined organic fractions were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude methyl ether product 4.24 was dissolved in dry THF and TBAF (40 µL, 1M in THF, 0.038 mmol) was added. After stirring at room temperature for 30 min, the reaction mixture was diluted by addition of ether (10 mL) and quenched with 10 mL of H₂O and the layers were separated. The aqueous layer was extracted with ether (2x) and the combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by flash column chromatography (gradient 40-50% EtOAc/hexane) to give 4.25 (9 mg, 50%, 2 steps) as a colorless syrup. ¹H NMR (CDCl₃, 500 MHz): δ 7.34-7.32 (m, 4H), 7.27-7.22 (m, 3H), 6.87-85 (m, 2H), 5.72,-5.70 (m, 1H), 5.69-5.61 (m, 1H), 5.59-5.49 (m, 2H), 4.70-4.67 (m, 1H), 4.55-4.50 (m, 2H), 4.43-4.36 (m, 3H), 3.79 (s, 3H, Me), 3.53-3.50 (m,2H), 3.28 (s, 3H), 2.51-2.39 (m, 4H), 2.32-2.28 (m, 1H), 1.91-1.80 (m, 2H), 1.77 (s, 3H, Me),1.59-1.57 (m, 1H), 1.56 (s, 3H, Me), 1.52 (s, 3H), 1.44 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 159.19, 144.18, 144.14, 138.20, 137.98, 131.41, 131.37, 18 Multiple C-signals appearing in the spectra are due to diastereotopic carbon centers present in the inseparable mixture of diastereomers.
Experimental Procedures (Part B)

130.44, 130.38, 129.33, 129.26, 128.47, 128.39, 128.37, 128.31, 127.45, 127.42, 126.81, 126.59, 125.83, 125.78, 113.75, 111.38, 111.35, 104.97, 104.95, 90.78, 80.81, 80.24, 77.48, 77.37, 75.98, 75.81, 73.40, 73.29, 72.43, 72.41, 67.89, 67.85, 67.24, 67.14, 55.55, 55.43, 55.27, 47.19, 46.88, 46.86, 42.61, 42.54, 29.67, 29.23, 26.65, 26.21, 24.46, 13.28, 13.12. **MS (ESI):** \(m/z\) 643.2 [M+Na]\(^+\). **HRMS (ESI):** \(m/z\) calcd for C\(_{37}\)H\(_{48}\)NaO\(_8\) 643.3247 [M+Na]\(^+\); found, 643.3226.

\(((3S,5S,E)-3-(benzyloxy)-10-((3aR,5R,6R,6aR)\(-6-(2\-(4\-methoxybenzyloxy)ethyl)-2,2\-dimethyltetrahydrofuro[2,3-\(d\)][1,3]dioxol-5-yl)-5,9-dimethyldeca-1,6,7,9-tetraen-5-\-yloxy)trimethylsilane (4.26):** To a stirring suspension of LiAlH\(_4\) (8 mg, 0.193 mmol) in dry Et\(_2\)O (1 mL), a solution of ethynyl carbinol 4.25 (15 mg, 0.05 mmol) in dry Et\(_2\)O (1 mL) was added dropwise at room temperature. After 10 min at room temperature, the reaction was quenched by slow addition of saturated solution of sodium potassium tartrate (Rochelle salt) followed by a saturated solution of NaS\(_2\)O\(_3\). The contents were stirred for 1h and then extracted with ether (2x). The combined organic fractions were washed with brine, dried over anhydrous Na\(_2\)SO\(_4\), solids were filtered and the crude residue was purified by flash column chromatography (gradient 20-25% EtOAc/hexane) to give the title allene 4.26 (18%) as a faint yellow liquid along with an unidentified product. **\(^1\)H NMR (CDCl\(_3,\) 500 MHz):** \(\delta\) 7.35-7.33 (m, 3H), 7.25-7.23 (m, 5H), 6.88-6.85 (m, 2H, allene), 6.02-6.00 (m, 1H), 5.79-5.78 (m, 1H), 5.60-5.48 (m, 3H), 5.31-5.29 (d, \(J = 8.85\) Hz, 1H), 4.73-4.70 (m, 1H), 4.58-4.55 (m, 2H), 4.42-4.41 (m, 2H), 3.80-3.79 (d, \(J = 3.15\) Hz, 3H, OMe), 3.53-3.51 (m, 2H), 2.53-2.48 (m, 2H), 2.33-2.22 (m, 2H), 1.88-1.82 (m, 3H), 1.53 (s, 3H, Me), 1.43
(s, 3H, Me), 1.31 (s, 3H, Me), 1.25 (s, 3H, Me). **MS** (ESI): \( m/z \) 613.2 [M+Na]^+. **HRMS** (ESI): \( m/z \) calcd for C_{36}H_{46}NaO_{7} 614.3219 [M+Na]^+; found, 613.3144.

**tert-Butyl((E)-3-((3aR,5R,6R,6aR)-6-(2-(4-methoxybenzyloxy)ethyl)-2,2-dimethyl tetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-methylallyloxy)dimethylsilane:** To the stirring solution of allylic alcohol **3.34** (161 mg, 0.42 mmol) in dry DCM (5 mL) was added imidazole (58 mg, 0.84 mmol) and TBSCl (100 mg, 0.84 mmol) at room temperature and stirred overnight. The reaction contents were diluted with ether (15 mL) and H2O (15 mL) was added and the layers were separated. The aqueous layer was extracted with ether (2x15 mL) and the combined organic fractions were washed with brine (20 mL), dried over anhydrous Na2SO4, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (gradient 5-10% EtOAc/ hexanes) to afford TBS ether (188 mg, 90%) as a colorless syrup. **^1H NMR** (CDCl3, 500 MHz): \( \delta \) 7.27 (d, \( J = 8.8 \) Hz, 2H), 6.89 (d, \( J = 8.8 \) Hz, 2H), 5.81 (d, \( J = 3.8 \) Hz, 1H), 5.39 (dd, \( J = 1.27, 8.8 \) Hz, 2H), 4.60-4.55 (m, 2H), 4.45 (dd, \( J = 11.35, 18.9 \) Hz, 2H), 4.04 (s, 2H), 3.82 (s, 3H), 3.55 (t, \( J = 6.3 \) Hz, 2H), 1.88-1.85 (m, 2H), 1.69 (s, 3H), 1.66-1.59 (m, 1H), 1.56 (s, 3H), 1.34 (s, 3H), 0.92 (s, 9H), 0.07 (d, \( J = 1.3 \) Hz, 6H). **^13C NMR** (CDCl3, 125 MHz): \( \delta \) 159.08, 140.87, 130.53, 129.13, 121.39, 113.66, 111.09, 108.87, 80.89, 77.47, 72.33, 68.10, 67.57, 55.19, 47.29, 26.64, 26.25, 25.86, 24.43, 18.30, 14.09, -5.53, -5.41.
Experimental Procedures (Part B)

2-((3aR,5R,6R,6aR)-5-((E)-3-(tert-butyldimethylsilyloxy)-2-methylprop-1-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)ethanol (5.5): The above obtained doubly protected crude alcohol (200 mg, 0.41 mmol) was dissolved in DCM/H2O (10:1 v/v, 15 mL) and DDQ (700 mg, 1.21 mmol) was added. After stirring at room temperature for 30 min, the reaction was determined (by TLC monitoring) to be completed with orange-red clumps formation. The reaction mixture was filtered through a celite pad, diluted with DCM (15 mL), washed with saturated NaHCO3 solution (30 mL). The aqueous layer was extracted with DCM (2x) and the combined organic fractions were washed with brine (30 mL), dried over anhydrous Na2SO4 and concentrated in vacuo. The orange-red residue was purified by flash column chromatography (gradient 20-30% EtOAc/hexane) to furnish the title primary alcohol 5.5 (134 mg, 89%) as a colorless liquid. 

1H NMR (CDCl3, 500 MHz): δ 5.83 (d, J = 3.8 Hz, 1H), 5.37 (dd, J = 1.25, 8.85 Hz, 1H), 4.68 (t, J = 3.8 Hz, 1H), 4.56 (t, J = 9.45 Hz, 1H), 4.00 (s, 2H), 3.72-3.70 (m, 2H), 1.86-1.78 (m, 2H), 1.73-1.70 (m, 1H), 1.67 (s, 3H), 1.59-1.56 (m, 1H), 1.54 (s, 3H), 1.33 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H).


2-((3aR,5R,6R,6aR)-5-((E)-3-(tert-butyldiphenylsilyloxy)-2-methylprop-1-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)ethanol (5.9): To the stirring solution of allylic alcohol 3.34 (220 mg, 0.58 mmol) in dry DCM (10 mL) was added imidazole (370 mg, 0.87 mmol) and TBDPSCl (0.47 mL, 18. mmol) at room temperature and stirred at room
temperature overnight. The reaction mixture was diluted with ether and the layers were separated. The aqueous layer was extracted with ether (3x) and the combined organic fractions were washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was carried forward for subsequent oxidative cleavage of PMB ether.

The above obtained protected crude alcohol (800 mg) was dissolved in DCM/H₂O (10:1 v/v, 15 mL) and DDQ (700 mg, 3.08 mmol) was added and stirred at room temperature. After 30 min, the reaction was determined (TLC monitoring) to be completed with orange-red clumps formation. Then the reaction mixture was filtered through a celite pad, washed with saturated NaHCO₃ solution (30 mL). The aqueous layer was extracted with DCM (2x) and the combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The orange-red residue was purified by flash column chromatography (gradient 20-40% EtOAc/hexane) to furnish the title primary alcohol 5.9 (481 mg, 82%, 2 steps) as a colorless liquid.

**1H NMR** (CDCl₃, 500 MHz): δ 7.67-7.65 (m, 4H), 7.44-7.36 (m, 6H), 5.85 (d, J = 3.8 Hz, 1H), 5.49 (dd, J = 1.25, 8.85 Hz, 1H), 4.70 (t, J = 3.8 Hz, 1H), 4.58 (t, J = 9.45 Hz, 1H), 4.10-4.04 (m, 2H), 3.74-3.72 (m, 2H), 1.87-1.79 (m, 2H), 1.68 (s, 3H), 1.55 (s, 2H), 1.34 (s, 3H), 1.06 (s, 9H).

**13C NMR** (CDCl₃, 125 MHz): δ 140.80, 135.50, 135.56, 129.64, 127.65, 121.40, 111.21, 105.02, 81.02, 77.40, 68.05, 61.36, 47.71, 27.57, 26.80, 26.64, 26.32, 19.27, 14.27.

**MS** (ESI): m/z 519.1 [M+Na]⁺.
**tert-Butyl(\(E\)-3-((3aR,5R,6R,6aR)-6-(2-iodoethyl)-2,2-dimethyltetrahydrofuro[2,3-\(d\])[1,3]dioxol-5-yl)-2-methylallyloxy)diphenylsilane (5.10):** Triphenylphosphine (260 mg, 0.99 mmol) and imidazole (100 mg, 1.48 mmol) were dissolved in DCM (90 mL) and stirred for 10 min at room temperature. The stirring mixture was cooled to ice-bath temperature and iodine as solid was added and stirred at room temperature for 10-15 min after which alcohol 5.9 (246 mg, 0.5 mmol) was added in DCM (10 mL). The reaction mixture was stirred for 1h at room temperature to complete the reaction. The volume was reduced approximately to half and Et\(_2\)O was added to remove Ph\(_3\)P = O by precipitation. The precipitate was filtered and the solvent was concentrated _in vacuo_. The residue was purified by flash column chromatography (gradient 5-10% EtOAc/hexane) to afford the title iodide 5.10 (280 g, 93%) as a colorless liquid.  

**\(^1\)H NMR (CDCl\(_3\), 500 MHz):** \(\delta 7.68\) (d, \(J = 6.9\) Hz, 4H), 7.45 (m, 6H), 5.87 (d, \(J = 3.8\) Hz, 1H), 5.54 (d, 8.8 Hz, 4.66 (t, \(J = 4.4\) Hz, 1H), 4.61 (t, 9.5 Hz, 1H), 4.08 (dd, 14.5, 19.5 Hz, 2H), 3.36-3.32 (m, 1H), 3.25-3.20 (m, 1H), 2.15-2.08 (m, 1H), 1.95-1.89 (m, 1H), 1.85-1.77 (m, 1H), 1.67 (s, 3H, Me), 1.55 (s, 3H, Me), 1.35 (s, 3H, Me), 1.08 (s, 9H, \(t\)-Bu). **\(^{13}\)C NMR (CDCl\(_3\), 125 MHz):** \(\delta 141.10, 135.48, 135.46, 133.51, 129.62, 127.67, 120.90, 111.36, 104.87, 79.99, 76.77, 50.81, 28.75, 26.82, 26.61, 26.28, 19.26, 14.22, 4.03. **MS (ESI):** \(m/z\) 628.9 [M+Na]\(^+\). **HRMS (ESI):** \(m/z\) calcd for C\(_{29}\)H\(_{39}\)INaO\(_4\)Si 629.1560 [M+Na]\(^+\); found, 629.1570.
Experimental Procedures (Part B)

\[(E)-3-((3aR,5R,6R,6aR)-6-(But-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]
dioxol-5-yl)-2-methylallyloxy)(\textit{tert}-butyl)diphenylsilane (5.11):\] Iodide 5.10 (670 mg, 1.1 mmol) was azeotropically dried with THF (2x) and flushed with argon gas. To the RBF with compound was added freshly pre-dried Fe(acac)\(_3\) (77 mg, 0.22 mmol), HMTA (31 mg, 0.22 mmol) and equipped with a magnetic stirring bar. The septum sealed-RBF with contents inside was kept under high vacuum for 5 min and subsequently flushed with argon. The vacuum-Argon cycles were repeated thrice and the flask was equipped with an argon balloon. TMEDA (66 \(\mu\)L, 0.44 mmol) was added and the contents were dissolved in THF (10 mL) and cooled to –20 °C. Vinylmagnesium bromide (1M in THF, 2.2 mL, 2.2 mmol) was added over 15 min to the stirring solution at –20 °C with the aid of a syringe pump. After complete addition, stirring was continued for a further 1h at 0 °C, diluted with ether, quenched by slow addition of 1M HCl (5 mL). The aqueous layer was separated and extracted with ether. The combined organic fractions were washed with brine and dried over anhydrous Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure to give the crude oil. The crude product was purified by the flash column chromatography (gradient 2-8% EtOAc in hexanes) to provide \(sp^2-sp^3\) cross-coupling product 5.11 exclusively (360 mg, 62%) as a yellow syrup. \(^1\)H NMR (CDCl\(_3\), 500 MHz):

\[\delta\ 7.69-7.67\ \text{(d,}\ J=6.9\ \text{Hz,}\ 4\text{H)}\ 7.44-7.37\ \text{(m,}\ 6\text{H)},\ 5.88-5.79\ \text{(m,}\ 1\text{H)},\ 5.84-5.83\ \text{(d,}\ J=\]
3.15 Hz, 1H), 5.49 (d, J = 9.45 Hz, 1H), 5.06 (dd, J = 1.85, 17 Hz, 1H), 5.99 (dd, J = 1.3, 10.1 Hz, 1H), 4.65 (td, J = 3.8, 13.05 Hz, 1H), 4.59-4.54 (m, 1H), 4.11-4.05 (dd, J = 14.5, 18.9 Hz, 2H), 2.30-2.23 (m, 1H), 2.14-2.07 (m, 1H), 1.73-1.70 (m, 1H), 1.68 (s, 3H, Me), 1.65-1.59 (m, 1H), 1.56 (s, 3H, Me), 1.39-1.35 (s, 1H), 1.35 (s, 3H, Me). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 140.47, 140.18, 138.40, 135.48, 135.46, 133.61, 133.58, 129.60, 127.62, 121.87, 121.67, 114.85, 111.17, 111.13, 104.90, 104.88, 80.75, 77.59, 77.52, 68.10, 68.04, 52.45, 49.85, 31.86, 26.77, 26.70, 26.32, 26.21, 23.51, 19.27, 17.49, 14.25, 14.22, 12.42. MS (ESI): m/z 529.1 [M+Na]$^+$. HRMS (ESI): m/z calcd for C$_{31}$H$_{42}$NaO$_4$Si 529.2750 [M+Na]$^+$; found, 529.2765.

**(E)-3-((3aR,5R,6R,6aR)-6-(But-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-methylprop-2-en-1-ol** (5.12): To the stirring solution of silyl ether 5.11 (220 mg, 0.58 mmol) in dry THF (10 mL) was added TBAF (1M in THF, 0.87 mL, 0.87 mmol) at room temperature and the reaction was stirred at room temperature for 4h. The solution was diluted with ether and quenched with water. The biphasic mixture was separated and the aqueous layer was extracted with ether (3x). The combined organic fractions were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (gradient 20-35% EtOAc/hexanes) to provide desilylated allylic alcohol 5.12 (50 mg, 56%) as a colorless syrup. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 5.84-5.76 (m, 1H), 5.81-5.80 (d, J = 3.8 Hz, 1H), 5.37 (dd, J = 1.25, 8.85 Hz, 1H), 5.04 (dd, J = 1.25, 17.05 Hz, 1H), 4.98-4.96 (m, 1H), 4.62 (t, J = 4.4 Hz, 1H), 4.53 (t, J = 9.45 Hz, 1H), 4.05 (s, 2H), 2.27-2.22 (m, 1H), 2.10-2.03 (m, 1H), 1.74 (s, 3H, Me), 1.72-1.63 (m, 2H), 1.54 (s, 3H, Me), 2.29
Experimental Procedures (Part B)

1.37-1.30 (m, 1H), 1.34 (s, 3H, Me). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 141.35, 138.36, 122.53, 114.91, 111.32, 104.93, 80.72, 77.46, 67.84, 49.78, 31.83, 26.71, 26.31, 23.49, 14.38.

$(E)$-Methyl 3-((3a$R$,5$R$,6$R$,6a$R$)-6-(2-iodoethyl)-2,2-dimethyltetrahydrofuro[2,3-$d$][1,3]dioxol-5-yl)-2-methylacrylate (5.13):

PMB ether 3.35 (112 mg, 0.275 mmol) was dissolved in DCM/H$_2$O (10:1 v/v, 4 mL) and DDQ (137 mg, 0.6 mmol) was added and stirred at room temperature during which orange-red clumps formation was observed. After 30 min, the reaction was determined to be completed (TLC monitoring). The reaction mixture was filtered through a celite pad and the filtrate diluted with DCM, washed with saturated NaHCO$_3$ (30 mL). The aqueous layer was extracted with DCM (3x) and the combined organic fractions were washed with brine (30 mL), dried over anhydrous Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The orange-red residue was purified by flash column chromatography (gradient 40-50% EtOAc/hexane) to furnish primary alcohol (85 mg, quantitative) as a viscous colorless oil. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 6.58 (dd, $J = 1.25, 8.8$ Hz, 1H), 5.87 (d, $J = 3.8$ Hz, 1H), 4.73 (t, $J = 3.75$ Hz, 1H), 4.60 (t, $J = 9.4$Hz, 1H), 3.75 (s, 3H, OMe), 3.73-3.72 (m, 2H), 2.01-1.95 (m, 1H), 1.92 (d, $J = 1.25$ Hz, 3H, Me), 1.88-1.81 (m, 1H), 1.57-1.52 (m, 1H) 1.54 (s, 3H, Me), 1.34 (s, 3H, Me). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 167.89, 137.90, 131.57, 111.60, 105.48, 80.82, 77.41, 61.07, 51.99, 47.50, 27.27, 26.63, 26.26, 13.44. MS (ESI):
m/z 309.1 (100%) [M+Na]+. **HRMS** (ESI): m/z calcd for C\textsubscript{14}H\textsubscript{22}NaO\textsubscript{6} 309.1314 [M+Na]+; found, 309.1315.

The above obtained alcohol was used for iodination as follows:

Triphenylphosphine (77 mg, 0.30 mmol) and imidazole (25 mg, 0.36 mmol) were dissolved in DCM (3 mL) and stirred for 10 min at room temperature. The contents were cooled to ice-bath temperature and iodine as solid was added and stirred at room temperature for 10-15 min. Then alcohol (65 mg, 0.22 mmol) was added in DCM (3 mL) and the reaction mixture stirred for 1h at room temperature to complete the reaction. The volume was reduced approximately to half and Et\textsubscript{2}O was added to remove Ph\textsubscript{3}P = O by precipitation. The precipitate was filtered and the solvent was concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (gradient 5-10% EtOAc/hexane) to afford the title iodide \textbf{5.13} (80 mg, 90%) as a colorless oil. \textit{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 500 MHz): δ 6.57 (dd, \(J = 1.3, 8.85\) Hz, 1H), 5.86 (d, \(J = 3.75\) Hz, 1H), 4.67-4.66 (m, 1H), 4.61 (t, \(J = 9.45\) Hz, 1H), 3.75 (s, 3H), 3.32-3.28 (m, 1H), 3.19-3.14 (m, 1H), 2.13-2.06 (m, 1H), 2.03-1.97 (m, 1H), 1.89 (d, \(J = 1.25\) Hz, 3H), 1.79-1.72 (m, 1H), 1.52 (s, 3H), 1.32 (s, 3H). \textit{\textsuperscript{13}C NMR} (CDCl\textsubscript{3}, 125 MHz): δ 167.72, 137.37, 131.79, 111.82, 105.29, 79.77, 52.02, 50.74, 28.37, 26.58, 26.21, 13.41, 3.23. **MS** (ESI): m/z 418.9 [M+Na]+. **HRMS** (ESI): m/z calcd for C\textsubscript{14}H\textsubscript{21}INaO\textsubscript{5} 419.0331 [M+Na]+; found, 419.0330.

(3a\textsuperscript{R},5\textsuperscript{R},6\textsuperscript{S},6a\textsuperscript{R})-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl tetrahydrofuro[2,3-d][1,3]dioxol-6-yl 4-methylbenzenesulfonate (\textbf{5.18}): Diacetal glucose \textbf{3.24} (500 mg, 1.92 mmol), DABCO (600 mg, 5.7 mmol) and TsCl (900mg, 5.7
mmol) were dissolved in DCM (15 mL) and stirred overnight at room temperature. After completion of reaction, the mixture was diluted with ether (20 mL) and the organic layer was washed with dil.HCl (2x). The aqueous layer was extracted with ether (2x) and the combined organic fractions were washed with H₂O, brine and dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (gradient 20-30% EtOAc/hexanes) to give (3aR,5R,6S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxolen-6-yl-4-methylbenzenesulfonate \( \text{5.18} \) (700 mg, 89%) as a white solid. \( ^1\text{H NMR} \) (CDCl₃, 500 MHz): \( \delta \) 7.82 (d, \( J = 8.2 \) Hz, 2H), 7.32 (d, \( J = 8.2 \) Hz), 5.91 (d, \( J = 3.15 \) Hz, 1H), 4.82 (d, \( J = 6.3 \) Hz, 1H), 4.78 (d, \( J = 1.9 \) Hz, 1H), 4.06-3.97 (m, 3H), 3.91-3.88 (m, 1H), 2.44 (s, 3H), 1.47 (s, 3H), 1.30 (s, 3H), 1.18 (s, 3H), 1.14 (s, 3H). \( ^{13}\text{C NMR} \) (CDCl₃, 125 MHz): \( \delta \) 145.05, 132.68, 129.64, 128.40, 112.47, 109.02, 105.07, 83.27, 82.03, 79.83, 71.75, 67.05, 26.58, 26.52, 26.17, 24.86, 21.60. \( \text{MS} \) (ESI): \( m/z \) 414.8 [M]⁺, 437.0 [M+Na]⁺. \( \text{HRMS} \) (ESI): \( m/z \) calcd for C₁₉H₂₆NaO₈S 437.1246 [M+Na]⁺; found, 437.1250.

\[
(3aR,5R,6R,6aS)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-6-iodo-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole \ (5.19) 
\]

Diacetal glucose 3.24 (0.5 g, 1.92 mmol), PPh₃ (1.5 g, 5.76 mmol), imidazole (0.4 g, 5.76 mmol) and iodine (0.97 g, 3.84 mmol) were together taken into toluene (30 mL) and the reaction mixture was refluxed (125 °C) overnight. The solvent was reduced to half volume by distillation on a rotary evaporator and diluted with ether. Solids were filtered and washed with brine solution and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography.
Experimental Procedures (Part B)

(gradient 15-25% EtOAc/hexanes) to obtain the iodo compound **5.19** (0.5 g, 70%) as a solid. 1H NMR (CDCl3, 500 MHz): δ 5.80 (d, J = 3.8 Hz, 1H), 4.58 (t, J = 3.8 Hz, 1H), 4.31-4.28 (m, 1H), 4.24 (dd, J = 3.8, 10.05 Hz, 1H), 4.12-4.09 (m, 1H), 4.06-4.03 (m, 1H), 3.76-3.73 (m, 1H), 1.54 (s, 3H, Me), 1.47 (s, 3H, Me), 1.35 (s, 6H, 2xMe). 13C NMR (CDCl3, 125 MHz): δ 111.66, 109.99, 103.12, 81.73, 81.46, 75.47, 65.75, 26.59, 26.53, 26.39, 25.17, 19.19.

(3aR,5S,6R,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-6-(2-iodoethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole (**5.21**): Triphenylphosphine (7 g, 27 mmol) and imidazole (2.3 mg, 32.3 mmol) were dissolved in DCM (90 mL) and stirred for 10 min at room temperature. The contents were cooled to ice-bath temperature then, iodine as solid was added and stirred at room temperature for 10-15 min. Then alcohol **3.29** (6 g, 20.8 mmol) was added in DCM (10 mL) and the reaction mixture stirred for 1h at room temperature to complete the reaction. The volume was reduced approximately to half and Et2O was added to remove Ph3P = O by precipitation. The precipitate was filtered and the solvent was distilled in vacuo. The residue was purified by flash column chromatography (gradient 5-10% EtOAc/hexane) to afford iodide **5.21** (7.8 g, 95%) as a colorless liquid. 1H NMR (CDCl3, 500 MHz): δ 5.77 (d, J = 3.5 Hz, 1H), 4.66 (t, J = 4.4 Hz, 1H), 4.08 (dd, J = 6.3, 8.2 Hz, 1H), 4.01 (dd, J = 6.9, 12 Hz, 1H), 3.91 (dd, J = 5.0, 8.2 Hz, 1H), 3.80-3.77 (m, 1H), 3.43-3.38 (m, 1H), 3.28-3.23 (m, 1H), 2.26-2.18 (m, 1H), 2.14-2.04 (m, 2H), 1.49 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H). 13C NMR (CDCl3, 125 MHz): δ 111.92, 109.64, 104.91, 81.35, 80.68, 77.58, 67.47, 48.87, 29.07.
Experimental Procedures (Part B)


Cross-Coupling Reaction: Iodide 5.21 (7.7 g, 19.34 mmol) was charged into a 250 mL RBF and azeotropically dried by anhydrous THF (2x) and flushed with argon gas. To the RBF was added freshly pre-dried Fe(acac)₃ (1.36 g, 3.9 mmol), HMTA (0.54 g, 3.9 mmol) and it was equipped with a magnetic stirring bar. The septum sealed-RBF with contents inside was kept under high vacuum for 5 min and subsequently flushed with argon. The vacuum-argon cycles were repeated thrice and equipped with an argon balloon. TMEDA (1.17 mL, 7.74 mmol) was added and the contents were dissolved in THF (10 mL) and cooled to –20 °C. Vinylimagnesium bromide (1M in THF, 29 mL, 29 mmol) was added over 15 min (10 mL/h) to the stirring solution at –20 °C with the aid of syringe pump. After addition being completed, stirring was continued for a further 1h at 0 °C and diluted with ether and quenched by slow addition of 1M HCl (5 mL). The aqueous layer was separated and extracted with ether. The combined organic fractions were washed with brine and dried over anhydrous Na₂SO₄ filtered and concentrated under reduced pressure to give a crude oil. The crude product was purified by flash column chromatography (gradient 5-10% EtOAc/hexane) to provide β-Hydride-
elimination product 5.23 and inseparable mixture of sp²-sp³ coupling product 5.20, along with hydride substitution product 5.22 as oily liquids.

(3aR,5S,6R,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-vinyltetrahydrofuro[2,3-d][1,3]dioxole (2.235): β-Hydride elimination by-product. 

\[
\begin{align*}
\text{1H NMR (CDCl}_3\text{, 500 MHz)}: &\quad \delta 5.89-5.81 (m, 1H), 5.79 (d, J = 3.8 \text{ Hz, 1H}), 5.27-5.19 (m, 2H), 4.60 (t, J = 3.8 \text{ Hz, 1H}), 4.25-4.21 (m, 1H), 4.08 (dd, 3.75, 10.05 \text{ Hz, 1H}), 3.96 (dd, J = 6.35, 8.15 \text{ Hz, 1H}), 3.87 (dd, 6.95, 8.2 \text{ Hz, 1H}), 2.62-2.57 (m, 1H), 1.51 (s, 3H, Me), 1.41 (s, 3H, Me), 1.33 (s, 3H, Me), 1.29 (s, 3H, Me). \\
\text{13C NMR (CDCl}_3\text{, 125 MHz): } &\quad \delta 132.20, 119.03, 111.83, 109.51, 104.68, 83.68, 79.77, 65.27, 50.50, 26.65, 26.34, 26.16, 25.16.
\end{align*}
\]

Acetal Cleavage: The mixture of 5.20 and 5.22 (3.2 g) was dissolved in 60% AcOH/H₂O (100 mL) and the reaction mixture was stirred at room temperature for 12h. Upon completion of terminal acetal hydrolysis (TLC monitoring), toluene was added and concentrated in vacuo. The resulting syrup was purified by flash column chromatography (gradient 30-50% EtOAc/hexane) to provide 5.26 and 5.27 as a partially separable mixture.
(R)-1-((3αR,5S,6R,6αR)-6-(but-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)ethane-1,2-diol (5.26):

$^1$H NMR (CDCl$_3$, 500 MHz): $δ$ 5.85-5.77 (m, 1H), 5.74 (d, $J$ = 3.15 Hz, 1H) 5.07-5.03 (m, 1H), 4.98 (d, $J$ = 10.1 Hz, 1H), 4.62 (t, $J$ = 4.4 Hz, 1H), 3.89 (dd, $J$ = 3.8, 10.1 Hz, 1H), 3.72-3.69 (m, 2H) 2.87 (s, br, 1H, OH), 2.62 (s, br, 1H, OH), 2.31-2.24 (m, 1H), 2.13-2.05 (m, 1H), 1.98-1.90 (m, 1H), 1.78-1.70 (m, 1H), 1.63-1.57 (m, 1H), 1.49 (s, 3H), 1.32 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 125 MHz): $δ$ 138.23, 115.01, 111.77, 104.64, 82.84, 81.06, 72.77, 63.22, 45.60, 31.76, 26.73, 26.37, 24.23. MS (ESI): m/z Calcd for C$_{13}$H$_{22}$O$_5$: 258.1467; found 257.1 [M-H]$^-$; 282.2 [M+Na]$^+$.  

Oxidative Vicinal Diol Cleavage and Wittig: The mixture of 5.26 and 5.27 (3.2 g, 7.16 mmol) was dissolved in MeOH (60 mL) and NaIO$_4$ (2 g, 10.74 mmol) in H$_2$O (15 mL) was added slowly. White precipitate formation began with an exothermic reaction. After stirring for 15 min, the solution was filtered through fritted sintered funnel and the solid was washed with MeOH (20 mL) and DCM (20 mL). The filtrate was diluted with DCM (50 mL) and washed with brine. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried over anhydrous Na$_2$SO$_4$. The solvent was reduced
approximately to half-volume under reduced pressure. Ylide 3.34 in DCM (20 mL) was then added and the reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (gradient 10-15% EtOAc/hexanes) to isolate 5.30 and 5.31 (1.7 g) as an inseparable mixture.

\[(E)-\text{methyl 3-((3aR,5R,6R,6aR)-6-(but-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-methylacrylate (5.30):}\]

\[1^H\text{NMR (CDCl}_3,\text{ 500 MHz): } \delta 6.53, (d, J = 8.8 \text{ Hz, 1H}), 5.80 (d, J = 3.8 \text{ Hz, 1H}), 5.78-5.70 (m, 1H), 5.00-4.93 (m, 2H), 4.61 (t, J = 4.4 \text{ Hz, 1H}), 4.54 (t, J = 10.1 \text{ Hz, 1H}), 3.71 (s, 3H), 2.23-2.16 (m, 1H), 2.06-1.99 (m, 1H), 1.88 (s, 3H), 1.81-1.75 (m, 1H), 1.50 (s, 3H), 1.30-1.26 (m, 4H).\]

\[13^C\text{NMR (CDCl}_3,\text{ 125 MHz): } \delta 167.83, 138.19, 137.93, 131.24, 114.99, 111.52, 105.29, 80.54, 77.44, 51.82, 49.72, 31.61, 26.60, 26.18, 23.37, 13.31. \text{MS (ESI): } m/z 296.9 [M], 319.1 [M+Na]^+. \text{HRMS (ESI): } m/z \text{ calcd for C}_{16}H_{24}NaO_{5} 319.1521 [M+Na]^+; \text{ found, 319.1546.}\]

\[(E)-3-((3aR,5R,6R,6aR)-6-(but-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-methylprop-2-en-1-ol (5.12): \text{To a stirring solution of conjugated esters 5.30 and 5.31 (1.67 g) in dry DCM (25 mL) at } -78 \text{ °C, DIBALH (15 mL, 1M in cyclohexane, 15}\]
mmol) was added over 45 min. The reaction mixture was allowed to warm to room temperature over 4h. After completion of reaction (by TLC) the reaction was quenched by addition of saturated Rochelle salt (sodium potassium tartrate) drop wise (30 mL) and stirred vigorously for 30 min at room temperature, during which the gray cloud in organic phase was dissolved and appeared in water layer. The solution was diluted with ether and the layers were separated. The aqueous layer was extracted with ether (3x) and the combined organic fractions were washed with brine, dried over anhydrous Na$_2$SO$_4$ filtered and concentrated under reduced pressure. The crude syrup was purified by flash column chromatography (gradient 20-30% EtOAc/hexane) to provide desired allylic alcohol, \((E)-3-((3aR,5R,6R,6aR)-6-(but-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-methylprop-2-en-1-ol\) \(5.12\) (1 g) as a colorless syrup, along with trace conjugate reduced product and \(5.32\) (280 mg).

Analytical data of allylic alcohol \(5.12\) is matching in all respects with the product obtained in desilylation of \(5.11\).

\((E)-3-((3aR,5R,6R,6aR)-6-(but-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2-methylacrylaldehyde\) \(5.4\): To the stirring solution of allylic alcohol \(5.12\) (426 mg, 1.58 mmol) in dry DCM (10 mL) was added DMP (1 g, 2.38 mmol) at room temperature and the reaction was stirred for 2h at room temperature. Upon complete conversion of allylic alcohol the contents were filtered through a celite bed and concentrated on a rotary evaporator. The crude residue was purified by flash column
chromatography (gradient 10-20% EtOAc/hexane) to provide the conjugated aldehyde 5.4 (400 mg, 95%) as a colorless syrup. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 9.46 (s, 1H), 6.29 (dd, $J = 1.4$, 8.2 Hz, 1H), 5.87 (d, $J = 3.15$ Hz, 1H), 5.80-5.72 (m, 1H), 5.00 (dd, $J = 1.9$, 1.7 Hz 1H), 4.98 (dd, $J = 1.25$, 10.05 Hz, 1H), 4.73 (t, 9.9 Hz, 1H), 4.68 (t, $J = 4.4$ Hz, 1H), 2.27-2.20 (m, 1H), 2.10-2.02 (m, 1H), 1.90-1.84 (m, 1H), 1.81 (d, $J = 1.3$ Hz, 3H), 1.78-1.70 (m, 1H), 1.54 (m, 3H), 1.35 (s, 3H), 1.33-1.26 (m, 1H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 194.68, 149.08, 141.18, 137.79, 115.30, 111.87, 105.47, 80.53, 77.34, 49.95, 31.61, 26.66, 26.24, 23.42, 10.15.

**Alkyne Addition:** To a stirring solution of alkyne 3.3 (230 mg, 0.76 mmol) in THF at –20 °C, was added EtMgBr (250 μL, 3M in THF, 0.75 mmol) and refluxed (50 °C) for 1h. Then the contents were cooled to –20 °C and aldehyde 5.4 (150 mg, 0.56 mmol) in THF was added. The reaction was gradually warmed to room temperature over 2h after which
Experimental Procedures (Part B)

it was quenched by slow addition of saturated NH₄Cl and extracted with ether (3x). The combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure and the crude residue was purified by flash column chromatography (gradient 20-35% EtOAc/hexane) to yield separable diastereomeric allylic alcohols 5.33a (127 mg), 5.33b (90 mg) as colorless syrups and 50 mg of the mixture (267 mg, 87% overall yield; \( d_r = 10:7 \), based on \(^1\)H NMR integration) while recovering 35 mg of aldehyde and 80 mg alkyne.

\((3R,6S,8S,E)-8-(benzyloxy)-1-((3aR,5R,6R,6aR)-6-(but-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2,6-dimethyl-6-(trimethylsilyloxy)deca-1,9-dien-4-yn-3-ol\) (5.33a):

\(^1\)H NMR (CDCl₃, 500 MHz): \( \delta \) 7.34-7.24 (m, 5H), 5.83-5.74 (m, 3H), 5.52 (d, \( J = 8.85 \) Hz, 1H), 5.25-5.19 (m, 2H), 5.03 (dd, \( J = 1.9, 17.05 \) Hz, 1H), 4.96 (dd, \( J = 1.3, 10.05 \) Hz, 1H), 4.72 (s, br, 1H, OH), 4.62-4.60 (m, 1H), 4.54 (d, \( J = 11.35 \) Hz, 1H) 4.50 (t, \( J = 9.45 \) Hz, 1H), 4.35 (d, \( J = 11.35 \) Hz, 1H), 4.07 (q, \( J = 6.3 \) Hz, 1H), 2.27-2.21 (m, 1H), 2.10 (dd, \( J = 6.3, 14.5 \) Hz, 1H), 2.06-2.02 (m, 1H), 1.93-1.90 (m, 1H), 1.80 (s, 3H, Me), 1.74-1.62 (m, 3H), 1.54 (s, 3H, Me), 1.50 (s, 3H, Me), 1.33 (s, 3H, Me), 0.15 (s, 9H, TMS). \(^{13}\)C NMR (CDCl₃, 125 MHz): \( \delta \) 139.86, 139.20, 138.69, 138.25, 128.26, 127.73, 127.34, 124.75, 116.48, 114.97, 111.34, 105.00, 90.75, 82.52, 80.66, 77.47, 77.28, 69.94, 67.88, 67.19, 50.26, 49.78, 31.78, 31.23, 26.69, 26.29, 23.45, 13.60, 13.59,
1.92. **MS** (ESI): \(m/z\) 567.2 [M-H], 591.2 [M+Na]. **HRMS** (ESI): \(m/z\) calcd for C\(_{33}\)H\(_{48}\)NaO\(_6\)Si 591.3118 [M+Na]; found, 591.3118.

\[
(3S,6S,8S,E)-8-(benzyloxy)-1-((3aR,5R,6R,6aR)-6-(but-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2,6-dimethyl-6-(trimethylsilyloxy)deca-1,9-dien-4-yn-3-ol (5.33b):
\]

**\(^1\)H NMR** (CDCl\(_3\), 500 MHz): \(\delta\) 7.34-7.24 (m, 5H), 5.84-5.74 (m, 3H), 5.48 (d, \(J = 8.85\) Hz, 1H), 5.25-5.19 (m, 3H), 5.03 (ddd, \(J = 1.9, 3.5, 17\) Hz, 1H), 4.98-4.95 (m, 1H), 4.76 (d, \(J = 4.05\) Hz, 1H), 4.62-4.60 (m, 1H), 4.54 (d, \(J = 11.35\) Hz, 1H), 4.52-4.48 (m, 1H), 4.36 (d, \(J = 12\) Hz, 1H), 4.07 (q, \(J = 6.3\) Hz, 1H), 2.27-2.20 (m, 1H), 2.10 (dd, \(J = 6.3, 14.5\) Hz, 1H), 2.08-2.03 (m, 1H), 1.94-1.90 (m, 1H), 1.81 (s, 3H, Me), 1.72-1.63 (m, 3H), 1.54 (s, 3H, Me), 1.50 (s, 3H, Me), 1.34-1.32 (m, 4H), 0.15 (m, 9H, TMS). **\(^{13}\)C NMR** (CDCl\(_3\), 125 MHz): \(\delta\) 140.02, 139.22, 138.70, 138.23, 128.27, 127.74, 127.35, 125.50, 125.09, 116.48, 114.99, 111.37, 105.00, 90.75, 82.54, 80.68, 77.52, 77.28, 69.94, 67.89, 67.43, 50.23, 49.79, 31.77, 31.26, 30.31, 29.68, 26.70, 26.30, 23.46, 13.21, 1.92. **MS** (ESI): \(m/z\) 567.1 [M-H], 591.2 [M+Na]. **HRMS** (ESI): \(m/z\) calcd for C\(_{33}\)H\(_{48}\)NaO\(_6\)Si 591.3118 [M+Na]; found, 591.3124.
Common Procedure for TES Protection of Propargylic Alcohol: To a stirring solution of propargylic alcohol (5.33a or 5.33b) and Et$_3$N (5 eq.) in dry DCM, was added TESOTf (3 eq) at 0 °C and after 2h at room temperature, the reaction was diluted with ether and quenched with addition of H$_2$O. The layers were separated and the aqueous layer was extracted with ether (3x) and the combined organic fractions were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The oily residue was purified by flash column chromatography (gradient 2-5% EtOAc/hexane) to give TES ether (5.34a or 5.34b) as colorless syrup.

(4S,7R)-4-((S)-2-(benzyloxy)but-3-enyl)-7-((E)-1-((3aR,5R,6R,6aR)-6-(but-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)prop-1-en-2-yl)-9,9-diethyl-2,2,4-trimethyl-3,8-dioxo-2,9-disilaundec-5-yne (5.34a):

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.34-7.23 (m, 5H), 5.87-5.73 (m, 3H), 5.22 (dd, $J = 1.25$, 16.4 Hz, 1H), 5.18 (dd, 1.25, 10.1 Hz), 5.02 (dd, $J = 1.85$, 17 Hz, 1H), 4.96 (d, $J = 10.1$ Hz, 1H), 4.73 (s, 1H), 4.61 (t, $J = 3.8$ Hz), 4.53 (d, $J = 11.35$ Hz, 1H), 4.51-4.47 (m, 1H), 4.35 (d, $J = 11.35$ Hz, 1H), 4.08 (dd, $J = 6.3$, 12 Hz), 2.27-2.21 (m,
Experimental Procedures (Part B)

1H), 2.06 (dd, J = 6.3, 14.5 Hz, 1H), 2.05-2.01 (m, 1H), 1.93-1.89 (m, 1H), 1.77 (d, J = 1.25 Hz, 3H, Me), 1.69-1.64 (m, 2H), 1.53 (s, 3H, Me), 1.50 (s, 3H, Me), 1.33 (s, 3H, Me), 0.95 (t, J = 8.15 Hz, 9H, TES), 0.65-0.59 (m, 6H, TES), 0.15 (s, 9H, TMS). MS (ESI): m/z 705.3 (100%) [M+Na]+. HRMS (ESI): m/z calcd for C₃₉H₆₂NaO₆Si 705.3983 [M+Na]+; found, 705.4005.

(4S,7S)-4-((S)-2-(benzyloxy)but-3-enyl)-7-((E)-1-((3aR,5R,6R,6aR)-6-(but-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)prop-1-en-2-yl)-9,9-diethyl-2,2,4-trimethyl-3,8-dioxa-2,9-disilaundec-5-yne (5.34b):

1H NMR (CDCl₃, 500 MHz): δ 7.34-7.30 (m, 4H), 7.27-7.25 (m, 1H), 5.84-5.73 (m, 3H), 5.40 (d, J = 8.85 Hz, 1H), 5.23 (d, J = 17.05 Hz, 1H), 5.18 (dd, J = 1.25, 10.05 Hz, 1H), 5.02 (dd, J = 1.9, 17 Hz, 1H), 4.95 (d, J = 9.45 Hz, 1H), 4.74 (s, 1H), 4.60 (t, J = 3.8 Hz, 1H), 4.36 (d, J = 11.35 Hz, 1H), 4.10 (dd, 6.3, 13.85 Hz, 1H), 2.25-2.18 (m, 1H), 2.07 (dd, 6.3, 13.85 Hz, 1H), 2.05-2.01 (m, 1H), 1.91 (dd, J= 5, 14.5 Hz, 1H), 1.78 (d, J = 1.25 Hz, 3H, Me), 1.70-1.65 (m, 2H), 1.54 (s, 3H, Me), 1.49 (s, 3H, Me), 1.35-1.31 (m, 1H), 1.33 (s, 3H, Me), 0.95 (t, J = 8.2 Hz, 9H, TES), 0.67-0.58 (m, 6H, TES), 0.14 (s, 9H, TMS). 13C NMR (CDCl₃, 125 MHz): δ 140.80, 139.27, 138.78, 138.28, 128.24, 127.70, 127.29, 123.94, 116.09, 114.93, 111.26, 105.01, 88.90, 83.66, 77.65, 77.32, 70.03, 67.94, 67.68, 50.21, 49.92, 31.82, 31.24, 26.69, 26.31, 23.42, 12.90, 6.78, 4.77, 1.87. MS (ESI): m/z 705.2 (100%) [M+Na]+. HRMS (ESI): m/z calcd for C₃₉H₆₂NaO₆Si 705.3983 [M+Na]+; found, 705.4003.
(3S,5S,8R,E)-3-(benzyloxy)-10-((3aR,5R,6R,6aR)-6-(but-3-enyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-8-methoxy-5,9-dimethyldeca-1,9-dien-6-yn-5-yloxy) trimethylsilane (5.37a): NaH (60% in mineral oil, 10 mg, 0.25 mmol) was added to the stirring solution of 5.33a (55 mg, 0.097 mmol) and MeI (15 µL) in dry THF (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. Upon completion, the reaction was diluted with ether (15 mL), quenched with H₂O and the layers were separated. The aqueous layer was extracted with ether (2x) and the combined organic fractions were washed with brine (25 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (gradient % EtOAc/hexane) to obtain methyl ether 5.37a (48 mg, 85%) as a colorless oil. 

1H NMR (CDCl₃, 500 MHz): δ 7.33-7.30 (m, 4H), 7.27-7.24 (m, 1H), 5.82-5.74 (m, 2H), 5.80 (d, J = 3.8 Hz, 1H), 5.49 (d, J = 8.85 Hz, 1H), 5.24-5.19 (m, 2H), 5.02 (dd, 1.9 Hz, 17.05 Hz, 1H), 4.96 (d, J = 10.1 Hz, 1H), 4.62-4.60 (m, 1H), 4.55-4.49 (m, 2H), 4.37-4.34 (m, 2H), 4.08 (dd, J = 6.35, 12.0 Hz, 1H), 3.30 (s, 3H, OMe), 2.27-2.21 (m, 1H), 2.10 (dd, 6.3, 14.5 Hz, 1H), 2.06-2.02 (m, 1H), 1.93 (dd, J = 4.4, 14.5 Hz, 1H), 1.76 (s, 3H, Me), 1.73-1.65 (m, 2H), 1.54 (s, 3H, Me), 1.52 (s, 3H, Me), 1.34-1.32 (m, 1H), 1.33 (s, 3H, Me), 0.15 (s, 9H, TMS). 13C NMR (CDCl₃, 125 MHz): δ 139.14, 138.75, 138.28, 137.74, 137.74, 128.24, 127.72, 127.29, 126.36, 116.36, 114.94, 111.33, 105.02, 91.59, 80.62, 77.49, 75.89, 69.99, 67.97, 55.51, 50.37, 49.81, 31.78, 31.38, 26.70, 26.30, 23.45, 13.55, 1.87. MS (ESI): m/z 605.2 (100%) [M+Na]+. HRMS (ESI): m/z calcd for C₃₄H₅₀NaO₆Si 605.3374 [M+Na]+; found, 605.3271.
**Experimental Procedures (Part B)**

**Macrocyclization by RCM:** Grubbs II catalyst (122 mg, 0.0144 mmol) in degassed toluene (10 mL) was added to a refluxing (120 °C) solution of diene 5.37a (45 mg, 0.077 mmol) in degassed toluene (0.1 mM) over 2h via syringe pump. Upon complete addition, the reaction was refluxed for a further 30 min followed by distillation of the solvent under reduced pressure. The residue was purified by flash column chromatography to isolate macrocycle 5.38a (2mg, 5%) along with other trace unidentified products.

**1H NMR** (CDCl₃, 500 MHz): δ 7.34-7.30 (m, 5H), 5.85 (d, J = 8.85 Hz, 1H), 5.81 (d, J = 5.05 Hz 1H), 5.79 (d, J = 3.75 Hz, 1H), 5.58-5.52 (m, 1H), 4.60-4.54 (m, 4H), 4.50-4.44 (m, 2H), 4.11 (s, br, 1H), 3.27 (s, 3H, OMe), 2.24 (d, J = 2.5 Hz, 1H), 2.24-2.17 (m, 2H), 1.93-1.84 (m, 3H), 1.84 (d, J = 1.25 Hz, 3H, Me), 1.56-5.54 (m, 7H), 1.33 (s, 3H, Me).

**13C NMR** (CDCl₃, 125 MHz): δ 138.84, 137.02, 132.85, 129.03, 128.31, 127.99, 127.68, 127.40, 111.39, 104.95, 93.47, 82.82, 80.95, 77.21, 75.71, 74.16, 70.73, 67.24, 53.93, 47.47, 33.18, 29.58, 26.84, 26.34, 23.22, 15.28, 1.82. **MS** (ESI): m/z 577.2 [M+Na]+.

**HRMS** (ESI): m/z calcd for C₃₂H₄₆NaO₆Si 577.2961 [M+Na]+; found, 577.2962.
Appendix 2

Spectra (Part B)
Appendix 2: Spectra (Part B)

1H normal range AC300

TBDPS

**Current Data Parameters**
- NAME: jl21srk
- EXPNO: 1
- PROCNO: 1

**Acquisition Parameters**
- BF1: 300.1300000 MHz
- LOCNUC: 2H
- NS: 3
- O1: 1853.43 Hz
- PULPROG: zg30
- SFO1: 300.1318534 MHz
- SOLVENT: CDCl3
- SW: 17.9519 ppm

**Processing Parameters**
- LB: 0.30 Hz
- PHC0: 255.079 degree
- PHC1: 1.105 degree

13C Standard AC300

TBDPS

**Current Data Parameters**
- NAME: jl21srk
- EXPNO: 2
- PROCNO: 1

**Acquisition Parameters**
- BF1: 75.4677490 MHz
- LOCNUC: 2H
- NS: 20
- O1: 7924.11 Hz
- PULPROG: zgpg30
- SFO1: 75.4756731 MHz
- SOLVENT: CDCl3
- SW: 238.2968 ppm

**Processing Parameters**
- LB: 0.30 Hz
- PHC0: 121.034 degree
- PHC1: 1.105 degree
### Appendix 2: Spectra (Part B)

#### **1H AMX500**

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- **Current Data Parameters**
  - NAME: rk0721
  - EXPNO: 1
  - PROCNO: 1

- **Acquisition Parameters**
  - BF1: 500.1300000 MHz
  - LOCNUC: 2H
  - NS: 2
  - O1: 3088.51 Hz
  - PULPROG: zg30
  - SFO1: 500.1330885 MHz
  - SOLVENT: CDCl3
  - SW: 20.6557 ppm

- **Processing Parameters**
  - LB: 0.30 Hz
  - PHC0: 38.953 degree
  - PHC1: -0.631 degree

#### **13C AMX500**

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- **Current Data Parameters**
  - NAME: rk0721
  - EXPNO: 2
  - PROCNO: 1

- **Acquisition Parameters**
  - BF1: 125.7577890 MHz
  - LOCNUC: 2H
  - NS: 25
  - O1: 13204.57 Hz
  - PULPROG: zgpg30
  - SFO1: 125.7709936 MHz
  - SOLVENT: CDCl3
  - SW: 238.7675 ppm

- **Processing Parameters**
  - LB: 1.00 Hz
  - PHC0: 31.597 degree
  - PHC1: 38.501 degree
### Appendix 2: Spectra (Part B)

#### 1H AMX500

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#### 13C AMX500

| ppm | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 55 | 60 | 65 | 70 | 75 | 80 | 85 | 90 | 95 | 100 | 105 | 110 | 115 | 120 | 125 | 130 | 135 | 140 | 145 | 150 |
|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| 13C | 138.4763 | 114.4061 | 96.2459 | 95.1237 | 77.2551 | 77.0000 | 76.7449 | 67.4463 | 67.4317 | 54.8610 | 33.3778 | 29.0710 | 25.4200 | 25.4054 |

#### Current Data Parameters
- **NAME**: rk0729
- **EXPNO**: 1
- **PROCNO**: 1

#### Acquisition Parameters
- **BF1**: 500.13000 MHz
- **LOCNUC**: 2H
- **NS**: 2
- **O1**: 3008.51 Hz
- **PULPROG**: zg30
- **SFO1**: 500.133333 kHz
- **SOLVENT**: CDCl3
- **SW**: 20.6557 ppm

#### Processing Parameters
- **LB**: 0.30 Hz
- **PHC0**: 54.430 degree
- **PHC1**: -0.616 degree

#### Current Data Parameters
- **NAME**: rk0729
- **EXPNO**: 2
- **PROCNO**: 1

#### Acquisition Parameters
- **BF1**: 125.757789 MHz
- **LOCNUC**: 2H
- **NS**: 22
- **O1**: 13204.57 Hz
- **PULPROG**: zgpg30
- **SFO1**: 125.770993 MHz
- **SOLVENT**: CDCl3
- **SW**: 238.7675 ppm

#### Processing Parameters
- **LB**: 0.30 Hz
- **PHC0**: 97.363 degree
- **PHC1**: 9.405 degree
Appendix 2: Spectra (Part B)

1H normal range AC300

13C Standard AC300
Appendix 2: Spectra (Part B)

TH AMX500
acetal of octynal (rk0911, exp 1)

13C AMX500
acetal of octynal

*** Current Data Parameters ***
NAME : rk0911
EXPNO : 2
PROCNO : 1

*** Acquisition Parameters ***
BF1 : 125.7577 MHz
LOCNUC : 2H
NS : 15
O1 : 13204.57 Hz
POLPROG : zgpg30
SF01 : 125.7709936 MHz
SOLVENT : CDCl3
SW : 238.7675 ppm

*** Processing Parameters ***
LB : 1.00 Hz
PH0 : 82.866 degree
PH1 : 31.540 degree
Appendix 2: Spectra (Part B)

1H normal range AC300
3136_BHR_bottom

13C Standard AC300
3136_BHR_bottom
### 13C Standard AC300

#### 3139 acid

**Current Data Parameters**
- **NAME**: j29srk
- **EXPNO**: 2
- **PROCNO**: 1

**Acquisition Parameters**
- **BF1**: 75.4677490 MHz
- **LOCNUC**: 2H
- **NS**: 161
- **O1**: 7924.11 Hz
- **PULPROG**: zgpg30
- **SFO1**: 75.4756731 MHz
- **SOLVENT**: CDCl3
- **SW**: 238.2968 ppm

**Processing Parameters**
- **LB**: 1.00 Hz
- **PHC0**: 143.669 degree
- **PHC1**: -37.802 degree

#### 3145 Mitsinobu

**Current Data Parameters**
- **NAME**: ag07srk
- **EXPNO**: 2
- **PROCNO**: 1

**Acquisition Parameters**
- **BF1**: 75.4677490 MHz
- **LOCNUC**: 2H
- **NS**: 200
- **O1**: 7924.11 Hz
- **PULPROG**: zgpg30
- **SFO1**: 75.4756731 MHz
- **SOLVENT**: CDCl3
- **SW**: 238.2968 ppm

**Processing Parameters**
- **LB**: 1.00 Hz
- **PHC0**: 73.594 degree
- **PHC1**: 93.773 degree
**Appendix 2: Spectra (Part B)**

1H AMX500
SRK 4005 Benzylidene alcohol

---

**13C AMX500**
SRK 4005 (rk1002, exp 11)

---

**Current Data Parameters**
- NAME: rk1002
- EXPNO: 10
- PROCNO: 1

**Acquisition Parameters**
- BF1: 500.1300000 MHz
- LOCNUC: 2H
- NS: 2
- O1: 3088.51 Hz
- PULPROG: zg30
- SFO1: 500.1330885 MHz
- SOLVENT: CDCl3
- SW: 20.6557 ppm

**Processing Parameters**
- LB: 0.30 Hz
- PHC0: 56.085 degree
- PHC1: -1.847 degree
**Appendix 2: Spectra (Part B)**

---

### 1H AMX500

**NAME:** rk1007_2  
**EXPNO:** 1  
**PROCNO:** 1

### Acquisition Parameters

- **BF1:** 500.1300000 MHz  
- **LOCNUC:** 2H  
- **NS:** 2  
- **O1:** 3088.51 Hz  
- **PULPROG:** zg30  
- **SFO1:** 500.1330885 MHz  
- **SOLVENT:** CDCl3  
- **SW:** 20.6557 ppm

### Processing Parameters

- **LB:** 0.30 Hz  
- **PHC0:** 159.887 degree  
- **PHC1:** -3.165 degree

---

### 13C AMX500

**NAME:** rk1007_2  
**EXPNO:** 2

---

**Current Data Parameters**  
**NAME:** rk1007_2  
**EXPNO:** 1  
**PROCNO:** 1

### Acquisition Parameters

- **BF1:** 500.1300000 MHz  
- **LOCNUC:** 2H  
- **NS:** 2  
- **O1:** 3088.51 Hz  
- **PULPROG:** zg30  
- **SFO1:** 500.1330885 MHz  
- **SOLVENT:** CDCl3  
- **SW:** 20.6557 ppm

### Processing Parameters

- **LB:** 0.30 Hz  
- **PHC0:** 159.887 degree  
- **PHC1:** -3.165 degree

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Appendix 2: Spectra (Part B)

1H AMX500
SRK 4010_DMP oxdn

*** Current Data Parameters ***
NAME : rk1014
EXPNO : 1
PROCNO : 1

*** Acquisition Parameters ***
BF1 : 500.1300000 MHz
LOCNUC : 2H
NS : 3
O1 : 3088.51 Hz
PULPROG : zg30
SFO1 : 500.1330885 MHz
SOLVENT : CDCl3
SW : 20.6557 ppm

*** Processing Parameters ***
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PHC0 : 49.497 degree
PHC1 : -6.368 degree

13C AMX500
SRK 4010_DMP oxdn (rk1014 <2009> exp 2)

*** Current Data Parameters ***
NAME : rk1014
EXPNO : 1
PROCNO : 1

*** Acquisition Parameters ***
BF1 : 100.6000000 MHz
LOCNUC : 13C
NS : 3
O1 : 300.61 Hz
PULPROG : zg30
SFO1 : 100.6000685 MHz
SOLVENT : CDCl3
SW : 20.6557 ppm

*** Processing Parameters ***
LB : 0.30 Hz
PHC0 : 49.497 degree
PHC1 : -6.368 degree
Appendix 2: Spectra (Part B)

1H AMX500
SRK 4011 spot 2 (h1015 exp. 11) year 2009

13C AMX500
SRK 4011 spot 2 (h1015 exp. 12) year 2009
Appendix 2: Spectra (Part B)

1H AMX 500 MHz (1H NMR spectrum)

13C AMX 500 MHz (13C NMR spectrum)
Appendix 2: Spectra (Part B)

1H AMX500
BHR Pdt_SRK 4037 (rk0205 exp 11)

13C AMX500
BHR Pdt_SRK 4037 (rk0205 exp 12)
Appendix 2: Spectra (Part B)

**1H AMX300**
SRK 4041 MOM protection of BHR Pdt (k0210 exp 1)

**13C AMX300**
SRK 4041 MOM protection of BHR Pdt (k0210 exp 2)
Appendix 2: Spectra (Part B)
Appendix 2: Spectra (Part B)

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500 MHz
4021-macro CDCl3 (pp1120 exp 1)

13C AMX500
4021_Macrolactone (rk1121 exp 2)
Appendix 2: Spectra (Part B)

**1H AMX500**
4018_1 (exp 11)

**13C AMX500**
4018_1 (exp 12)
Appendix 2: Spectra (Part B)

1H AMX500
srk 4049_Pv protection

**Current Data Parameters**
- NAME: rk0309
- EXPNO: 1
- PROCNO: 1

**Acquisition Parameters**
- BF1: 500.1300000 MHz
- LOCNUC: 2H
- NS: 2
- Q1: 3088.51 Hz
- PULPROG: zg30
- SFO1: 500.1330885 MHz
- SOLVENT: CDCl3
- SW: 20.6557 ppm

**Processing Parameters**
- LB: 0.30 Hz
- PHC0: 249.869 degree
- PHC1: 8.011 degree

---

13C AMX500
srk 4049_Pv protection

**Current Data Parameters**
- NAME: rk0309
- EXPNO: 2
- PROCNO: 1

**Acquisition Parameters**
- BF1: 125.7577890 MHz
- LOCNUC: 2H
- NS: 20
- Q1: 13204.57 Hz
- PULPROG: zgpg30
- SFO1: 125.7709936 MHz
- SOLVENT: CDCl3
- SW: 238.7675 ppm

**Processing Parameters**
- LB: 1.00 Hz
- PHC0: 171.499 degree
- PHC1: 32.716 degree
Appendix 2: Spectra (Part B)

1H AMX500
MeMgBr_4051_major_top (60215 exp 1)

13C AMX500
MeMgBr_4051_major_top (60215 exp 2)
Appendix 2: Spectra (Part B)

**Current Data Parameters**
- **NAME**: eey0316
- **EXPNO**: 3
- **PROCNO**: 1

**Acquisition Parameters**
- **LOCNUC**: 2H
- **NS**: 8
- **O1**: 3088.51 Hz
- **PULPROG**: zg30
- **SFO1**: 500.1330885 MHz
- **SOLVENT**: CDCl3
- **SW**: 20.6557 ppm

**Processing Parameters**
- **LB**: 0.30 Hz
- **PHC0**: 158.879 degree
- **PHC1**: 0.332 degree

1H AMX500
RSK4052 PCC

13C Standard AC300
4852_PCC oxdn

[Diagram of spectra with chemical structures and labels 3.16]
Appendix 2: Spectra (Part B)

*** Current Data Parameters ***
NAME : rk0428
EXPNO : 12
PROCNO : 1

*** Acquisition Parameters ***
BF1 : 125.7577890 MHz
LOCNUC : 2H
NS : 55
D1 : 13204.57 Hz
PULPROG : zgpg30
SFO1 : 125.7709936 MHz
SOLVENT : CDCl3
SW : 238.7675 ppm

*** Processing Parameters ***
LB : 1.00 Hz
PHC0 : 87.298 degree
PHC1 : 18.987 degree
Appendix 2: Spectra (Part B)

1H NMR 500
SRK 4054 (n0319 exp 11)
### Appendix 2: Spectra (Part B)

#### 1H AMX500

**SRK 4056_TMS Protection of tert-OH (a: 0322, exp 1)**

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#### 13C AMX500

**SRK 4056_TMS Protection of tert alc (a: 0322 exp 2)**

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### Spectra Diagrams

- **1H AMX500 Spectrum**: Shows the proton NMR spectrum with peaks at various ppm values.
- **13C AMX500 Spectrum**: Shows the carbon NMR spectrum with peaks at various ppm values.

### Additional Notations

- The spectra are labeled with chemical shifts in parts per million (ppm).
- The spectra include peak assignments for specific chemical groups (e.g., OMe, OTMS, 3.3).
- The spectra depict the protection of tert-OH and tert alc groups with tert-butyloxycarbonyl (OBn) and trimethylsilyl (OTMS) groups.
Appendix 2: Spectra (Part B)

1H AMX500
RK 4089_diisopropylidene glucose (H0803 EXP.21...y.2010)

13C AMX500
RK 4089_diisopropylidene glucose (H0803 exp.22, year2010)
Appendix 2: Spectra (Part B)

1H AMX500
SRK 4109_H2/Pd/C (m0817 exp.1; year.2010)

13C AMX500
SRK 4109_H2/Pd/C (m0807 exp.2; year.2010)
Appendix 2: Spectra (Part B)

1H AMX 500
SRK 4110.1AH (A611 exp 1; year 2010)

13C AMX 500
SRK 4110.1AH (A611 exp 2; year 2010)
Appendix 2: Spectra (Part B)
Appendix 2: Spectra (Part B)

HAX500
SRK 4075_3BIAL ch (HAX50A exp 11; year 2010)

13C AMX500
SRK 4075_DIBAL ch (HAX50A exp 13; year 2010)
Appendix 2: Spectra (Part B)

TH AMX500
SRK 4057 (ppm0313-exp 5)

13C AMX500
SRK 4057_aldehyde_RIGHT fragment of PMB (ppm0232-exp 3)
Appendix 2: Spectra (Part B)

1H AMX500
2,3-wittig pdt (k0035 exp 1)

[2,3]-Wittig Rearrangement Product

13C AMX500
SRK 4059_SPOT 1_T0P

[2,3]-Wittig Rearrangement Product
Appendix 2: Spectra (Part B)
Appendix 2: Spectra (Part B)

AMX500
SRK_4134_MnO2_Oxid_alkynone (Exp 2)

AMX500
SRK_4134_MnO2_Oxid_alkynone (Exp 1)
### Appendix 2: Spectra (Part B)

#### AMX500

**SRK 4135 (R)-CBS Reduction (EXPT 1)**

![Spectrum AMX500](image)

#### AMX500

**SRK 4135 (R)-CBS Reduction (EXPT 2)**

![Spectrum AMX500](image)
Appendix 2: Spectra (Part B)

1H AMX500
SRK4132_Allene_pure fraction <RK1027(2011) exp.1>

13C AMX500
rk4137_allene by LAH (rk1027(2011) exp 12)
### Appendix 2: Spectra (Part B)

#### 1H AMX500

SRK-4063_MnO2 oxdn (s6407 exp 1)

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#### 13C AMX500

SRK-4063_MnO2 oxdn (s6407 exp 2)

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O

BnO

TMSO

O

O

PMBO

O

4.23
Appendix 2: Spectra (Part B)

TH AMX500
SRK 4661_TMS cleavage (rk0331, exp 1)

13C AMX500
SRK 4661_TMS cleavage (rk0331, exp 2)
4.26
Appendix 2: Spectra (Part B)

TH AMX500
4068 TBS protection (mH422 (2010) exp 1, 2010)

1H AMX500
4068 TBS protection (mH422 exp 2)

13C AMX500
4068 TBS protection (mH422 exp 2)
Appendix 2: Spectra (Part B)

1H AMX500
SRK 4078_DDQ reaction

13C AMX500
SRK 4078_DDQ reaction

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PROCNO : 1

*** Acquisition Parameters ***
BF1 : 500.1300000 MHz
LOCNUC : 2H
NS : 3
O1 : 3008.51 Hz
PULPROG : zg30
SFO1 : 500.1330885 MHz
SOLVENT : CDCl3
SW : 20.6557 ppm

*** Processing Parameters ***
LB : 0.30 Hz
PHC0 : 73.752 degree
PHC1 : 0.147 degree

140.8009
135.4957
133.5646
129.6440
127.6545
121.4019
111.2142
105.0199
81.0226
77.4081
77.2478
77.0000
76.7449
68.0511
61.3613
47.7120
27.5770
26.8046
26.6443
26.3236
19.2767
14.2776

(1H AMX500
SRK 4078_DDQ reaction)

13C AMX500
SRK 4078_DDQ reaction

*** Current Data Parameters ***
NAME : rk0513
EXPNO : 12
PROCNO : 1

*** Acquisition Parameters ***
BF1 : 125.7577890 MHz
LOCNUC : 2H
NS : 82
O1 : 13204.57 Hz
PULPROG : zgpg30
SFO1 : 125.7709936 MHz
SOLVENT : CDCl3
SW : 238.7675 ppm

*** Processing Parameters ***
LB : 1.00 Hz
PHC0 : 20.630 degree
PHC1 : -0.999 degree

77.4081
77.2478
77.0000
76.7449
68.0511
61.3613
47.7120
27.5770
26.8046
26.6443
26.3236
19.2767
14.2776

(13C AMX500
SRK 4078_DDQ reaction)
**Appendix 2: Spectra (Part B)**

***Current Data Parameters***
- **NAME**: rk0513
- **EXPNO**: 1
- **PROCNO**: 1

***Acquisition Parameters***
- **BF1**: 500.130000 MHz
- **LOCNUC**: 2H
- **NS**: 4
- **O1**: 3088.51 Hz
- **PULPROG**: zg30
- **SFO1**: 500.1330885 MHz
- **SOLVENT**: CDCl3
- **SW**: 20.6557 ppm

***Processing Parameters***
- **LB**: 0.30 Hz
- **PHC0**: 324.580 degree
- **PHC1**: 0.620 degree

---

***Current Data Parameters***
- **NAME**: rk0513
- **EXPNO**: 2
- **PROCNO**: 1

***Acquisition Parameters***
- **BF1**: 125.7577890 MHz
- **LOCNUC**: 2H
- **NS**: 66
- **O1**: 13204.57 Hz
- **PULPROG**: zg30
- **SFO1**: 125.7709936 MHz
- **SOLVENT**: CDCl3
- **SW**: 238.7675 ppm

***Processing Parameters***
- **LB**: 1.00 Hz
- **PHC0**: 357.838 degree
- **PHC1**: 29.769 degree
Appendix 2: Spectra (Part B)

1H AMX500
RK 4090_iodination (rk0603 exp 11)

13C AMX500
RK 4090_iodination (rk0603 exp 12)
Appendix 2: Spectra (Part B)

1H AMX500
SRK 4102_iodination

13C AMX500
SRK 4102_iodination

---

**Current Data Parameters**
- **NAME**: rk0722
- **EXPNO**: 2
- **PROCNO**: 1

**Acquisition Parameters**
- **BF1**: 125.757789 MHz
- **LOCNUC**: 2H
- **NS**: 66
- **O1**: 13204.57 Hz
- **PULPROG**: zgpg30
- **SFO1**: 125.7709936 MHz
- **SOLVENT**: CDCl3
- **SW**: 238.7675 ppm

**Processing Parameters**
- **LB**: 1.00 Hz
- **PHC0**: 74.653 degree
- **PHC1**: 41.704 degree

---

**Current Data Parameters**
- **NAME**: rk0722
- **EXPNO**: 1
- **PROCNO**: 1

**Acquisition Parameters**
- **BF1**: 500.130000 MHz
- **LOCNUC**: 2H
- **NS**: 4
- **O1**: 3088.51 Hz
- **PULPROG**: zg30
- **SFO1**: 500.1330885 MHz
- **SOLVENT**: CDCl3
- **SW**: 20.6557 ppm

**Processing Parameters**
- **LB**: 0.30 Hz
- **PHC0**: 166.704 degree
- **PHC1**: -1.918 degree

---
Appendix 2: Spectra (Part B)

\[ \text{1H AMX500} \]
SRK 4111-Iodination (rk0811, exp 11; year 2010)

\[ \text{13C AMX500} \]
SRK 4111-Iodine (rk0811, exp 12; year 2010)
Appendix 2: Spectra (Part B)

1H AMX500
4112_Fe rxn spot below SM

13C AMX500
4112_Fe rxn

--- Current Data Parameters ---
NAME : rk0813
EXPNO : 11
PROCNO : 1

--- Acquisition Parameters ---
BF1 : 500.1300000 MHz
LOCNUC : 2H
NS : 4
O1 : 3088.51 Hz
PULPROG : zg30
SFO1 : 500.1330885 MHz
SOLVENT : CDCl3
SW : 20.6557 ppm

--- Processing Parameters ---
LB : 0.30 Hz
PHC0 : 138.766 degree
PHC1 : -0.213 degree

--- Current Data Parameters ---
NAME : rk0813
EXPNO : 12
PROCNO : 1

--- Acquisition Parameters ---
BF1 : 125.7577890 MHz
LOCNUC : 2H
NS : 130
O1 : 13204.57 Hz
PULPROG : zgpg30
SFO1 : 125.7709936 MHz
SOLVENT : CDCl3
SW : 238.7675 ppm

--- Processing Parameters ---
LB : 1.00 Hz
PHC0 : 153.125 degree
PHC1 : 39.863 degree
Appendix 2: Spectra (Part B)

1H AMX500D
SRK 4097= right fragment (k6010 exp 11)

13C AMX500D
SRK 4097= right fragment (k6010 exp 12)
Appendix 2: Spectra (Part B)

### 1H AMX500

**SRK 4100 Coupling spot 2 (bottom)**

### 13C AMX500

**SRK 4100 Coupling spot 2 (bottom)**

---

**313**
Appendix 2: Spectra (Part B)

**1H AMX500**

**SRK 4101_NaH/MeI**

---

**13C AMX500**

**SRK 4101_NaH/MeI**

---
### Appendix 2: Spectra (Part B)

DEPT135 AMX500

RCM product of Biels (A0801, 2 nights scanned exp 3)

| ppm  | 132.8431 | 129.0318 | 128.3177 | 127.9752 | 127.6909 | 127.4067 | 104.9471 | 82.8226 | 77.2186 | 75.7028 | 74.1579 | 70.7328 | 53.9282 | 52.9298 | 47.4570 | 33.1883 | 29.6977 | 29.5956 | 26.8483 | 26.3382 | 23.2192 | 15.2978 | 1.8307 |
|------|----------|----------|----------|----------|----------|----------|----------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|

DEPT135 AMX500

RCM product of Biels (A0801, 2 nights scanned exp 3)

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#### F2 - Acquisition Parameters

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<tr>
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<td>D0</td>
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<td>D1</td>
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<td>D16</td>
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<td>IN0</td>
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| ======== CHANNEL f1 ======== |
| NUC1                 | 1H       |
| P0                 | 8.20 usec |
| P1                 | 8.20 usec |
| PL1               | -2.00 dB |
| SFO1        | 500.2320200 MHz |

| ====== GRADIENT CHANNEL ===== |
| P16             | 1500.00 usec |

#### F1 - Acquisition parameters

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#### F2 - Processing parameters

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#### F1 - Processing parameters

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| SI                  | 512      |
| SF                | 500.2300045 MHz |
| WDW               | SINE     |
| SSB                | 0        |
| LB                 | 2.00 Hz  |
| GB               | 2.00 Hz  |

| SI                  | 512      |
| SF                | 500.2300045 MHz |
| WDW               | SINE     |
| SSB                | 0        |
| LB                 | 2.00 Hz  |
| GB                | 2.00 Hz  |
Appendix 2: Spectra (Part B)