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DEVELOPMENT OF NEW SYNTHETIC METHODOLOGIES AND THEIR APPLICATION TOWARDS SYNTHESIS OF NATURAL PRODUCTS

ANITA ALNI

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2010

DEVELOPMENT OF NEW SYNTHETIC METHODOLOGIES AND THEIR APPLICATION TOWARDS SYNTHESIS OF NATURAL PRODUCTS

ANITA ALNI
B. Appl. Sc. (Hons.), NUS

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

A thesis submitted to the Nanyang Technological University
In partial fulfillment of the requirement for the degree of
Doctor of Philosophy

2010

For parents,

who never doubt me.

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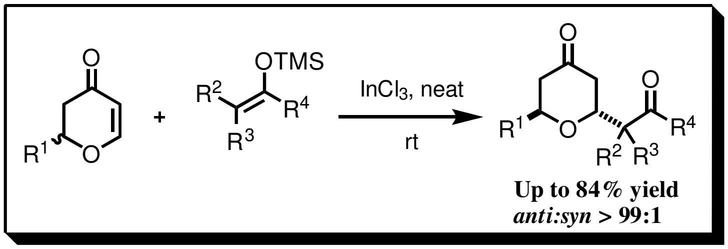
Summary

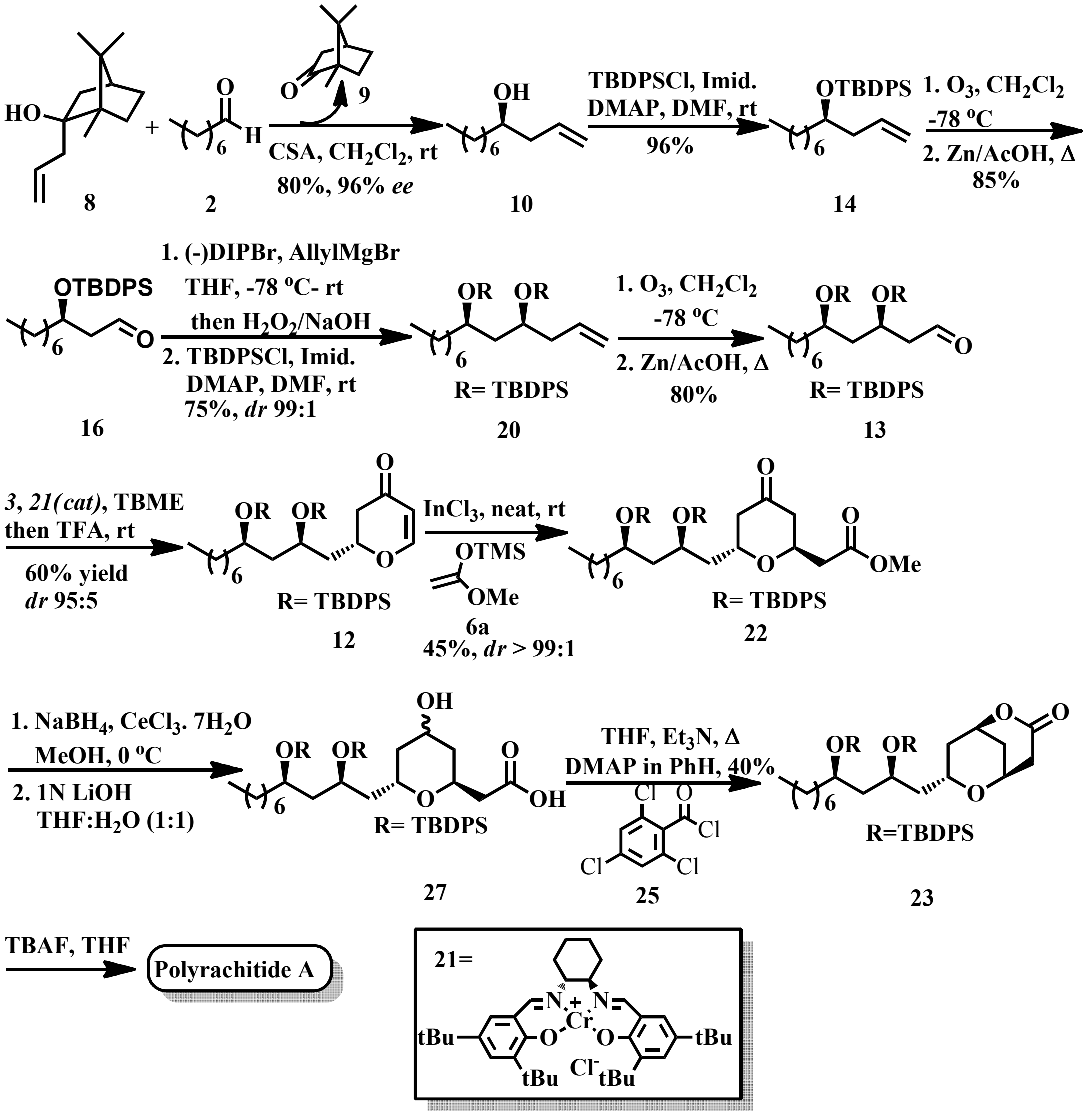
I. Indium (III) chloride catalyzed Mukaiyama-Michael addition

2,6-*anti*-pyran rings are found in many natural products. However, unlike the *syn* isomers, not many methodologies were reported to access this motif. We have developed a new methodology to access the 2,6-*anti*-pyran rings *via* reaction of substituted pyranone with silyl enol ethers or silyl ketene acetals. The Mukaiyama-Michael reactions were catalyzed by indium (III) chloride under neat conditions. The reaction was highly selective and produced only 2,6-*anti*-pyran moiety.



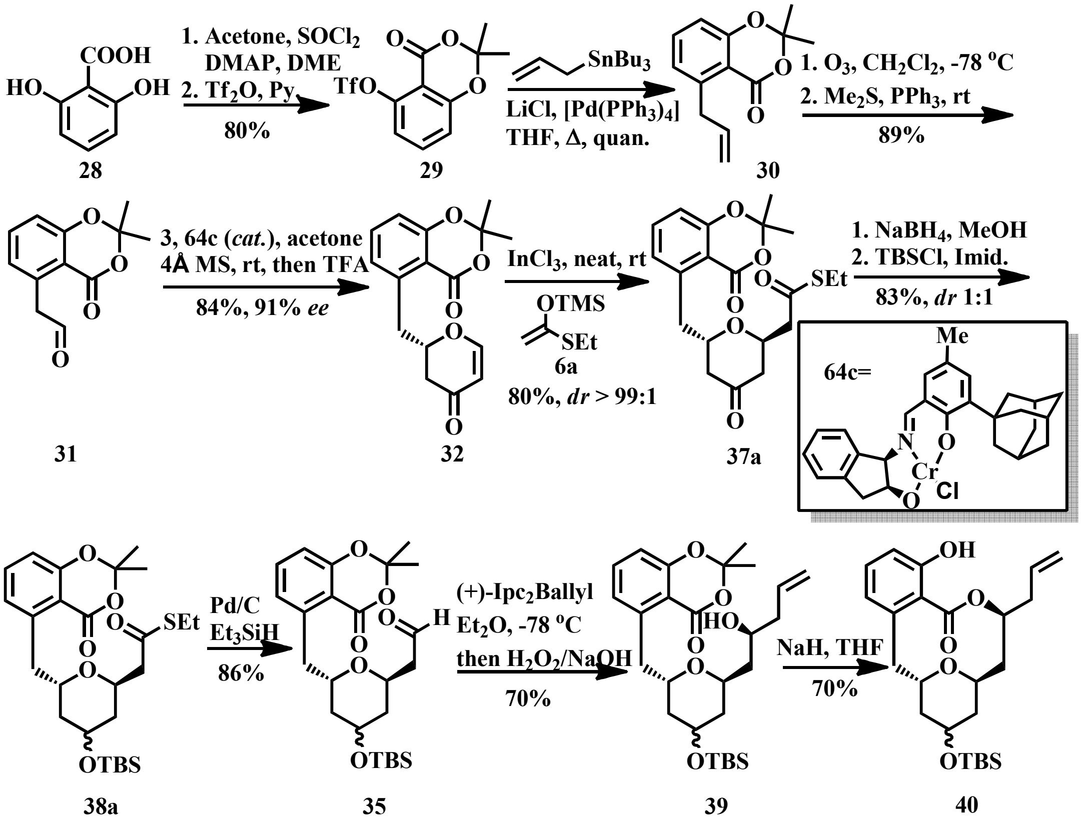
II. Total synthesis of polyrachitide A

We have demonstrated the utilization of allyl transfer *via* camphor scaffold and indium (III) chloride catalyzed Mukaiyama-Michael reactions as the key steps in synthesis of polyrachitide A.


HO
8
+
O
H
6
2
O
9
CSA, CH_2Cl_2, rt
80%, 96% *ee*
OH
6
10
TBDPSCl, Imid.
DMAP, DMF, rt
96%
OTBDPS
6
14
1. O_3, CH_2Cl_2
-78 °C
2. Zn/AcOH, Δ
85%
OTBDPS
6
O
16
1. (-)DIPBr, AllylMgBr
THF, -78 °C- rt
then H_2O_2/NaOH
2. TBDPSCl, Imid.
DMAP, DMF, rt
75%, *dr* 99:1
OR OR
6
R= TBDPS
20
1. O_3, CH_2Cl_2
-78 °C
2. Zn/AcOH, Δ
80%
OR OR
6
O
R= TBDPS
13
3, *21(cat)*, TBME
then TFA, rt
60% yield
dr 95:5
OR OR
6
O
O
R= TBDPS
12
$InCl_3$, neat, rt
OTMS
OMe
6a
45%, *dr* > 99:1
OR OR
6
O
O
O
OMe
R= TBDPS
22
1. $NaBH_4$, $CeCl_3$. $7H_2O$
MeOH, 0 °C
2. 1N LiOH
THF:H_2O (1:1)
OH
OR OR
6
O
O
OH
R= TBDPS
27
THF, Et_3N, Δ
DMAP in PhH, 40%
Cl O
Cl
Cl
Cl
25
OR OR
6
O
O
O
R=TBDPS
23
TBAF, THF
Polyrachitide A
21=
N
+
N
Cr
O
O
tBu
tBu
tBu
tBu
Cl^-

III. Synthetic study towards apicularen A

Previously our group attempted the synthesis of this molecule through Prins cyclization to access the 2,6-*anti*-pyran ring, which however, was unsuccessful. In this attempt, we utilized $InCl_3$ catalyzed Mukaiyama-Michael addition reaction to assemble the 2,6-*anti*-pyran moiety.

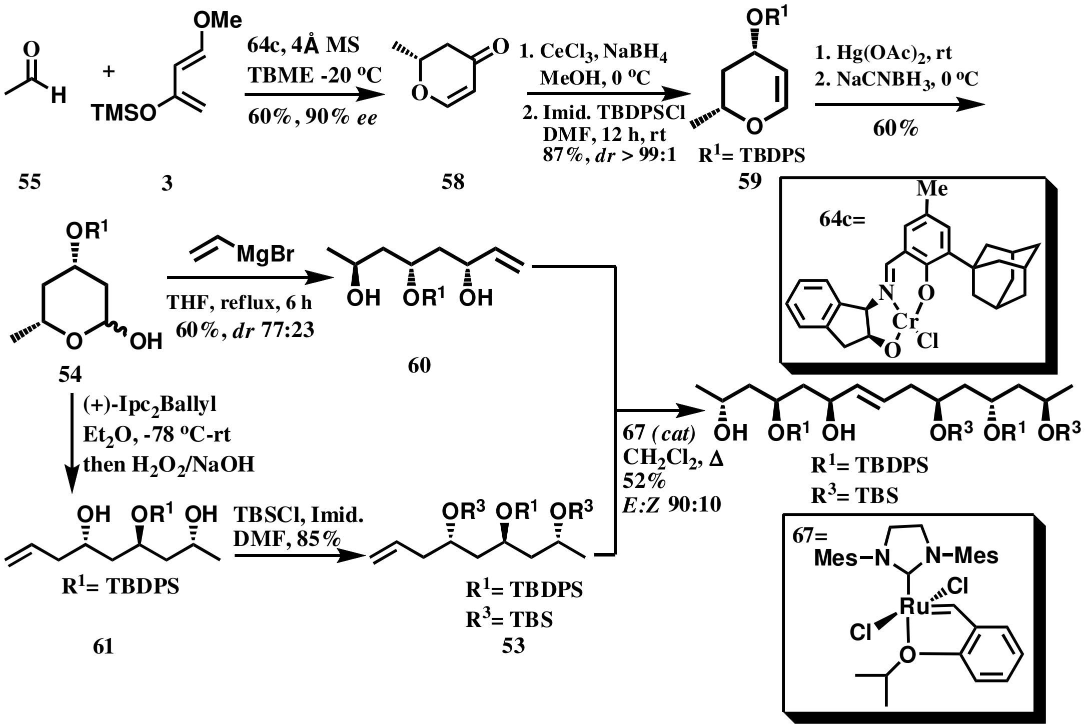

28
1. Acetone, SOCl$_2$ DMAP, DME
2. Tf$_2$O, Py
80%
29
LiCl, [Pd(PPh$_3$)$_4$] THF, Δ, quan.
30
1. O$_3$, CH$_2$Cl$_2$, -78 °C
2. Me$_2$S, PPh$_3$, rt
89%
31
3, 64c (*cat.*), acetone 4Å MS, rt, then TFA
84%, 91% *ee*
32
InCl$_3$, neat, rt
6a
80%, *dr* > 99:1
37a
1. NaBH$_4$, MeOH
2. TBSCl, Imid.
83%, *dr* 1:1
64c=
38a
Pd/C Et$_3$SiH
86%
35
(+)-Ipc$_2$Ballyl Et$_2$O, -78 °C then H$_2$O$_2$/NaOH
70%
39
NaH, THF
70%
40

IV. Synthetic study towards marinomycins

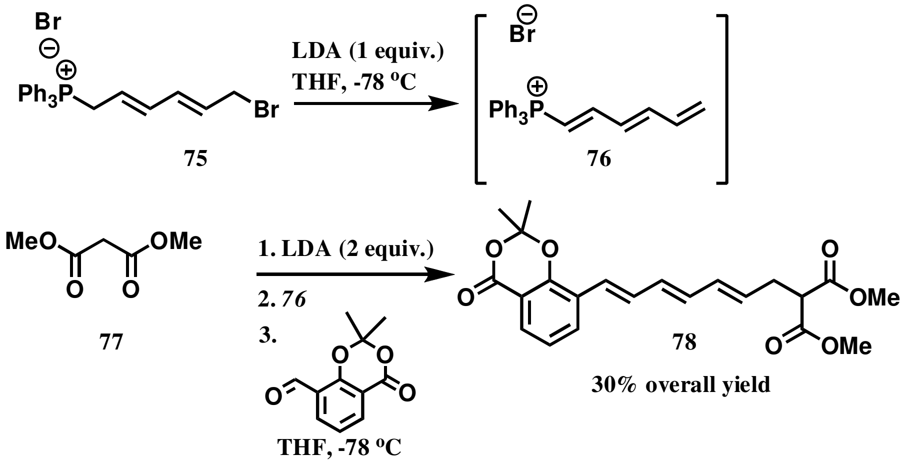
Our strategy towards this macrolide dimer involved macrolactonization, Wittig olefination and Grubbs catalyzed metathesis reactions that divided this molecule into polyene (Fragment A) and polyol (Fragment B). The polyol fragment could be accessed through olefin metathesis coupling of allylic compound **60** and homoallylic compound **53**.

The polyene fragment was more problematic. However, we managed to synthesized intermediate **78** in a tandem manner with 30% overall yield.

Synthetic routes towards Fragment B


55
3
OMe
TMSO
64c, 4Å MS
TBME -20 °C
60%, 90% ee
58
1. $CeCl_3$, $NaBH_4$
MeOH, 0 °C
2. Imid. TBDPSCl
DMF, 12 h, rt
87%, dr > 99:1
OR^1
R^1= TBDPS
59
1. $Hg(OAc)_2$, rt
2. $NaCNBH_3$, 0 °C
60%
64c=
Me
Cr
Cl
54
OH
MgBr
THF, reflux, 6 h
60%, dr 77:23
60
(+)-$Ipc_2Ballyl$
Et_2O, -78 °C-rt
then H_2O_2/NaOH
61
TBSCl, Imid.
DMF, 85%
53
R^3= TBS
67 (cat)
CH_2Cl_2, Δ
52%
E:Z 90:10
OR^3
67=
Mes–N
N–Mes
Ru
Cl

Synthetic routes towards Fragment A


Br
Ph_3P
75
LDA (1 equiv.)
THF, -78 °C
76
MeO
OMe
77
1. LDA (2 equiv.)
2. 76
3.
THF, -78 °C
78
30% overall yield

Index of Abbreviations

δ	chemical shift
Δ	reflux
ºC	degree centrigrade
AcOH	acetic acid
Ac_2O	acetic anhydride
Ad	adamantyl
aq.	aqueous
Bn	benzyl
brs	broad singlet
BuLi	butyl lithium
Bz	benzoyl
t-bu	tert-butyl
cacld	calculated
cat	catalytic
$CDCl_3$	deuterated chloroform
CSA	camphorsulfonic acid
CH_2Cl_2	dichoromethane
$CHCl_3$	chloroform
cm^{-1}	inverse centimeter
d	doublet
dba	dibenzylidene acetone
dd	doublets of doublet
de	diastereomeric excess
DIBAL	diisobutylaluminium hydride
DIEA	diisopropylethylamine
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	N,N-dimethyl formamide
dr	diastereomeric ratio
dt	doublets of triplet
dq	doublets of quartet
ee	enantiomeric excess

EI	electron impact ionization
equiv.	equivalent
ESI	electron spray ionization
Et	ethyl
ether	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl aceate
EtOH	ethanol
FAB	fast atom bombardment
FTIR	Fourier transform infrared spectroscopy
g	gram
h	hour
H	hydrogen
Hex	hexane
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Hz	Hertz
Imid.	Imidazole
IR	infrared
i-Pr	isopropyl
J	coupling constants
kg	kilogram
LDA	lithium diisopropylamide
M	concentration (mol/dm^{-3})
M^+	parent ion peak (mass spectrum)
m	multiplet
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	Megahertz
min	minute
mmol	millimoles
mol	moles

MS	mass spectrum
Ms	methanesulfonyl
MW	microwave
N	concentration (normality)
NBS	*N*-bromosuccinimide
n-Bu	*n*-butyl
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
N.R.	no reaction
OTf	trifluoromethanesulfonate
p	page
PBr_3	phophorus tribromide
Pd/C	palladium on carbon
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
Ph	phenyl
PhMe	Toluene
ppm	parts per million
Py	pyridine
q	quartet
qd	quartets on doublet
quan.	quantitative
quint.	quintet
rt.	room temperature
RBF	round bottom flask
R_f	retention factor
s	singlet
sat'd	saturated
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
t-Bu	*tert*-butyl
td	triplets of doublet

TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
$TiBr_4$	titanium tetrabromide
$TiCl_4$	titanium tetrachloride
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
TMSOTf	trimethylsilyl trifluoromethane sulfonate
Ts	*p*-toluenesulfonyl
TS	transition state
vol	volume

Chapter 1

Introduction to Natural Products Synthesis

1.1. Natural products as inspiration in molecular synthesis

Nature supplies us with tremendous amounts of chemical compounds. Among them are compounds that have therapeutic and medicinal property such as penicillin, a family of amino acid metabolites that have saved millions of lives through its action as potent antibiotic.[1] Some are toxins that can be harmful to the life of human beings when in contact such as coniine, an alkaloid that has been long known as poison.[2] There are also ambiguous natural products such as the steroid cholesterol, which may cause death through heart diseases but at the same time is a vital component of cell walls.[3] All of these classes of compounds can be useful for chemists, for there being many things to learn from these constituents of nature such as utilizing them to find cures for many diseases such as cancer and viral infections (Figure 1) or understanding the biosynthesis of such molecules.[4]

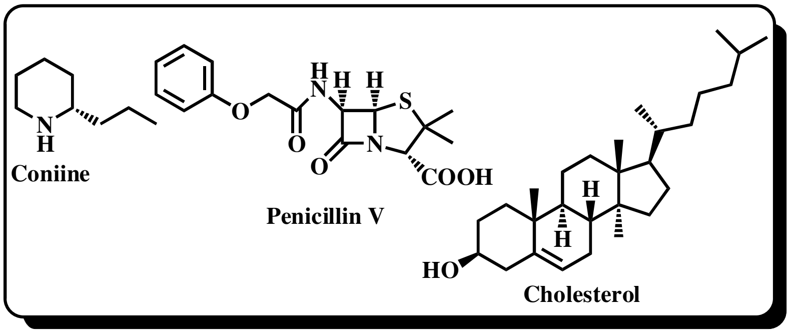


Figure 1. Example of natural products

Nevertheless, in view of the scarce occurrence of many of these compounds, only minute quantity have been isolated and studied for most of them. Hence the field of natural product synthesis remains an exciting field to explore with many promising cases to be studied along the way.

---

[1] (a) Clarke, H. T.; Johnson, J. R.; Robinson, R. Ed. *The Chemistry of Penicillin* , Princeton University Press: Princeton, N.J., 1949. (b) Sammes, P. G. *Chem. Rev*. **1976**, 76, 113. (c) Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1959***, 81,* 5838. (d) Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc*. **1962***, 84,* 2983.

[2] Borrows, E.T.; Holland, D. O. C*hem. Rev*. **1948**, *42*, 611.

[3] (a) Biellmann, J. F. *Chem. Rev*. **2003**, *103,* 2019. (b) Wang, M.; Briggs, M. R. *Chem. Rev*. **2004**, *104* 119. (c) Bloor, W. R. *Chem. Rev*. **1925**, *2*, 243.

[4] Butler, M.S. *J. Nat. Prod***. 2004**, 67, 2141.

We can identify two classes of compounds from nature: primary and secondary metabolites. The former are those chemicals needed in metabolic process of almost all living cells including carbohydrates, lipids, protein and nucleic acids. The latter refer to chemical constituents that are unique and characteristic to certain cells or species. Secondary metabolites are not directly involved in the growth, development or reproduction of living things, but instead provide a functional role, for instance as defense mechanism which the compound is secreted when the species is in danger or they are used as tools for communications among insects known as pheromones. We refer to the latter class of compound as natural products.[5]

Despite the usefulness of natural products, the isolation from natural sources has not always been easy. Many times, tons of sponges need to be taken from the sea to extract a few milligram of useful secondary metabolite; hundreds of species have to be endangered to isolate minute quantities of compounds that they secrete as their defense mechanism.

Epibatidine, an amphibian alkaloid found in Ecuadorian poison frog possesses potent analgesic activity.[6] To isolate 1 mg of this compound 750 frogs need to be endangered and the amount is barely enough for further characterization studies and testing of biological activity (Figure 2).

---

[5] (a) Cragg, G. M.; Newman, D.J.; Snader, K. M. *J. Nat. Prod.* **1997**, *60*, 52. (b) Newman, D.J.; Cragg, G.M.; Snader, K.M. *J. Nat. Prod.* **2003**, *66*, 1022. (c) Newman, D. J.; Cragg, G. M. J. Nat. Prod. **2007**, *70,* 461.

[6] Daly, J. W. *J. Nat. Prod* . **1998**, *61*, 162.

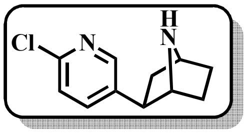


Figure 2. Epibatidine: deadly compound isolated from frog skin

To overcome this problem, chemists need to make this compound in the laboratory from commercially available building blocks.[7] Hence total synthesis of natural product is necessary and will always be, to produce compounds such as drugs, antibiotics that have the same function as those provided by nature.

Total synthesis has dated its way back since the time where analytical tool such as NMR was unheard of, up to now where the characterization of complex molecule has been made easier by the advance in the instrumentation such as NMR, mass spectroscopy, etc. The synthesis of urea, probably the first rational attempt known to chemist was accomplished by Wohler in 1828.[8] The structure might be very simple without any chiral center involved, but it lays the foundation of synthesis for future generation chemists. Nowadays, chemists can celebrate the progress in this field by looking at brevetoxins, an admirable architecture with numerous chiral centers but deadly molecule that has been successfully synthesized by Nicolaou *et al.* in 1995 (Figure 3).[9]

---

[7] For example of the synthesis, see: (a) Broka, C. A. *Tetrahedron Lett.* **1993**, *34*, 3251. (b) Huang, D.F.; Shen, T. Y. *Tetrahedron Lett.* **1993**, *34*, 4477. (c) Corey, E. J.; Loh, T. P.; Achyutha Rao, S.; Daley, D. C.; Sarshar, S. *J. Org. Chem.* **1993**, *58*, 5600. (d) Clayton, S. C.; Regan, A. C. *Tetrahedron Lett.* **1993**, *34*, 7493. (e) Senokuchi, K.; Nakai, H.; Kawamura, M.; Katsube, N.; Nonaka, S.; Sawaragi, H.; Hamanaka, N. *Synlett* **1994**, 343. (f) Trost, B. M.; Cook, G. R. *Tetrahedron Lett.* **1996**, *37*, 7485. (g) Szántai, C.; Kardos-Balogh, Z.; Moldvai, I.; Szántai, C., Jr.; Temesvári-Major, E.; Blasko, G. *Tetrahedron* **1996**, *52*, 11053. (h) Kosugi, H.; Abe, M.; Hatsuda, R.; Uda, H.; Kato, M. *Chem. Commun.* **1997**, 1857. (i) Evans, D. A.; Scheidt, K. A.; Downey, C. W. *Org. Lett.* **2001**, *3*, 3009. (j) Loh, T.P.; Lee, C. L. K. *Org. Lett.* **2005**, *7,* 2965.

[8] Wohler, F. *Ann. Phys. Chem.* **1828**, *12*, 253.

[9] Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao, X. -Y. *J. Am. Chem. Soc.* **1995**, *117*, 1173.

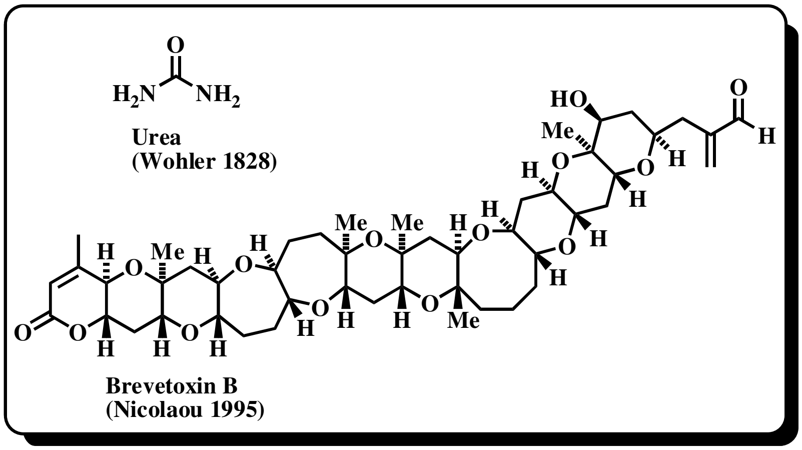


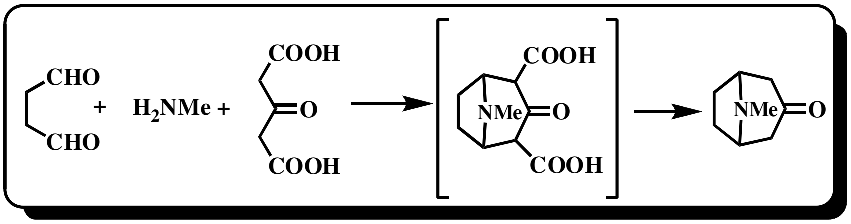
Figure 3. From urea to brevetoxins, the progress of natural product synthesis

Not only to make molecules that represent natural products and mimic the processes that mother nature employs to create the compound, at the same time total synthesis provides insight and limitless source of inspiration for methodology in organic chemistry. It also provides a challenging testing ground for novel methodology to be developed and their application to the synthesis of complex substrates.

Robinson's tropinone synthesis was a classic that represented a bioinspired synthesis reported in 1917.[10] Starting from simple building blocks namely succinaldehyde, methylamine and acetone dicarboxylic acid, he developed a tandem process that lead to tropinone. This molecule was a synthetic precursor to atropine, an anticholinergic drug that was a crucial commodity during World War I. The process itself could be regarded as three component double Mannich reaction which shortened the original synthesis of tropinone from 13 steps to a single step with 17% overall yield (Scheme 1).

---

[10] (a) Robinson, R. *J. Chem. Soc.* **1917**, 762. (b) Robinson, R. *J. Chem. Soc.* **1917**, 876.



Scheme 1. Tropinone synthesis, a classic example of bioinspired synthesis

After almost a century after its conception, numerous reports could be found on the tandem process or one pot synthesis that was believed as the way nature makes many of its products.[11]

Polyene cyclization was another example of bioinspired synthesis that had been established by Stork and Eschenmoser in 1950s.[12] The key feature in this synthesis was the presence of good initiators such as allylic alcohol, acetal, epoxide or even proton. Numerous reports on cationic polyene cyclization could be found such as those by Johnson,[13] Corey,[14] and many others[15] that contributed to this field including its application in natural product synthesis.

---

[11] For reviews, see: (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis,* Wiley-VCH, Weinheim, 2006, p. 672. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed.* **1993**, *32*, 137. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (d) Ho, T. L. *Tandem Organic Reactions*, Wiley, New York, 1992.

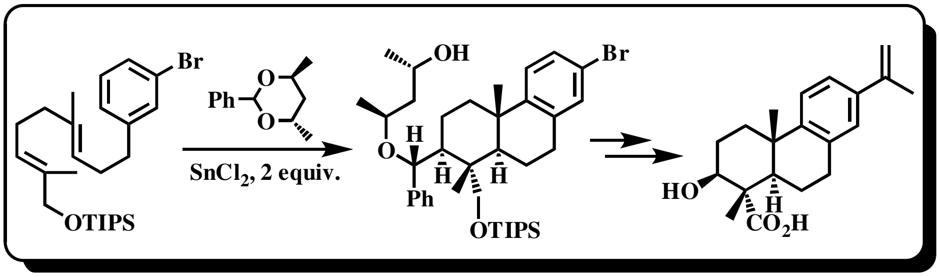
[12] (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (b) Eschenmosher, A.; Ruzika, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta*. **1955**, *38*, 1890.

[13] (a) Johnson, W. S.; Kinnel, R. B. *J. Am. Chem. Soc*. **1966**, *88*, 3861. (b) Johnson, W. S.; Jensen, N. P.; Hooz, J. J. Am. Chem. Soc. 1966, 88, 3859.

[14] (a) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742. (b) Corey, E. J.; Reid, J. G.; Myers, A. G.; Hahl, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 918. (c) Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873. (d) Corey, E. J.; Wood, H. B., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 11982. (e) Corey, E. J.; Staas, D. D. *J. Am. Chem. Soc.* **1998**, *120*, 3526. (f) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999.

[15] (a) Bogenstätter, M.; Limberg, A.; Overman, L. E.; Tomasi, A. L. *J. Am.Chem. Soc.* **1999**, *121*, 12206. (b) Nishizawa, M.; Takenaka, H.; Nishide, H.; Hayashi, Y. *Tetrahedron Lett.* **1983**, *24*, 2581. (c) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Am. Chem. Soc.* **1985**, *107*, 552. (d) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806.

Previously, our group had also developed the methodology in polyene cyclization featuring acetal initiator and $SnCl_4$ as Lewis acid to mediate the cyclization[16]. This methodology was successfully applied to the total synthesis of antiochic Acid (Scheme 2).[17]



Scheme 2. Polyene cyclization in total synthesis of antiochic acid

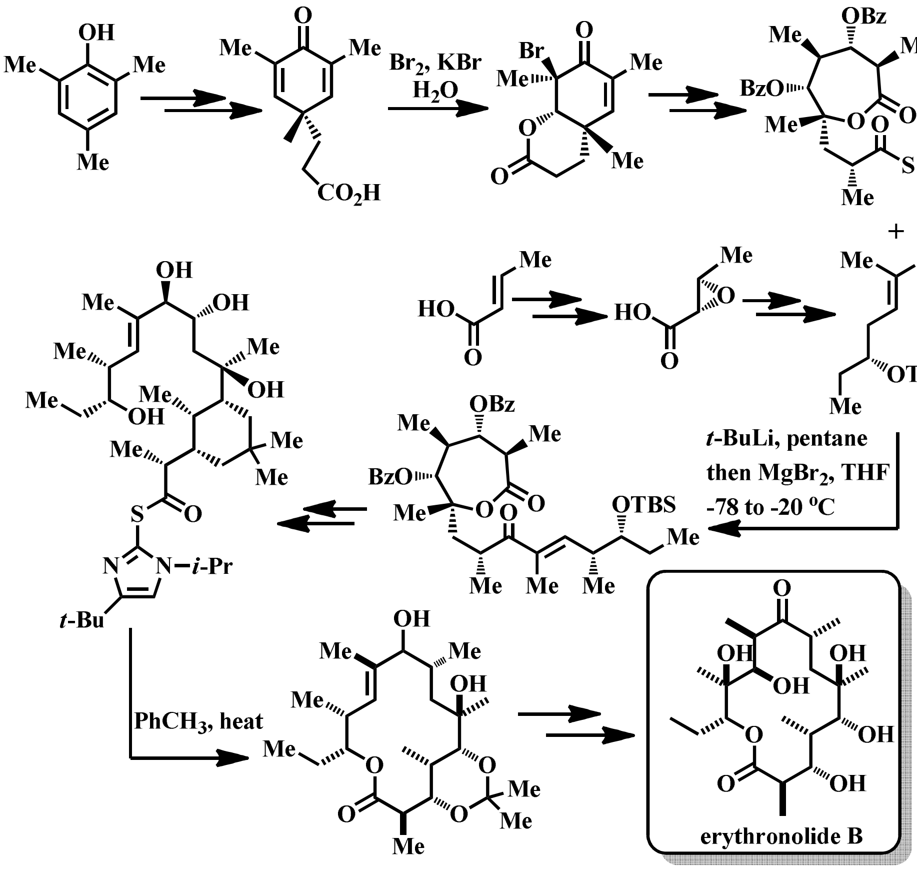
Complexity and unique structures of natural products often lead to discovery of new methodologies in the organic synthesis. For example, in the synthesis of erythronolide B, Corey introduced double activation macrolactonization method for construction of the large ring that later became the foundation for many reactions of this type (Scheme 3)[18].

---

[16] Zhao, Y. J.; Chng, S. S.; Loh, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 492.

[17] Zhao, Y. J.; Loh, T. P. *Org*. Lett. 2008, 10, 2143.

[18] (a) Corey, E. J.; Trybulski, E. J.; Melvin, L. S.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo. S. E. *J. Am. Chem. Soc.* **1978**, *100*, 4618. (b) Corey, E. J.; Kim, S.; Yoo, S. E.; Nicolaou, K. C.; Melvin, L. S. Jr.; Brunelle, D. J.; Flack, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100,* 4620.



Scheme 3. Corey's synthesis of erythronolide B

1.2. Natural products containing *anti*-THP ring

Among the many natural products, tetrahydropyran rings containing structures are found to exist in a wide variety of natural product. Its many possible degree of substitutions and stereochemistry rendered this motif an interesting target for chemists. Some examples of natural products that show this property is shown in Figure 4. Swinholide A is a complex macromolecule that has potential for the treatment of cancer which synthesis has been accomplished by Paterson *et al.*[19]

---

[19] (a) Paterson, I.; Cumming, J. G.; Ward, R. A.; Lamboley, S. *Tetrahedron* **1996**, *51*, 9393. (b) Paterson, I.; Smith. J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413. (c) Paterson, I.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Yeung, K. S. *Tetrahedron* **1995**, *51*, 9437. (d) Paterson, I.; Yeung, K. S.; Ward, R. A.; Smith, J. D.; Cumming, J. G. *Tetrahedron* **1995**, *51*, 9467.

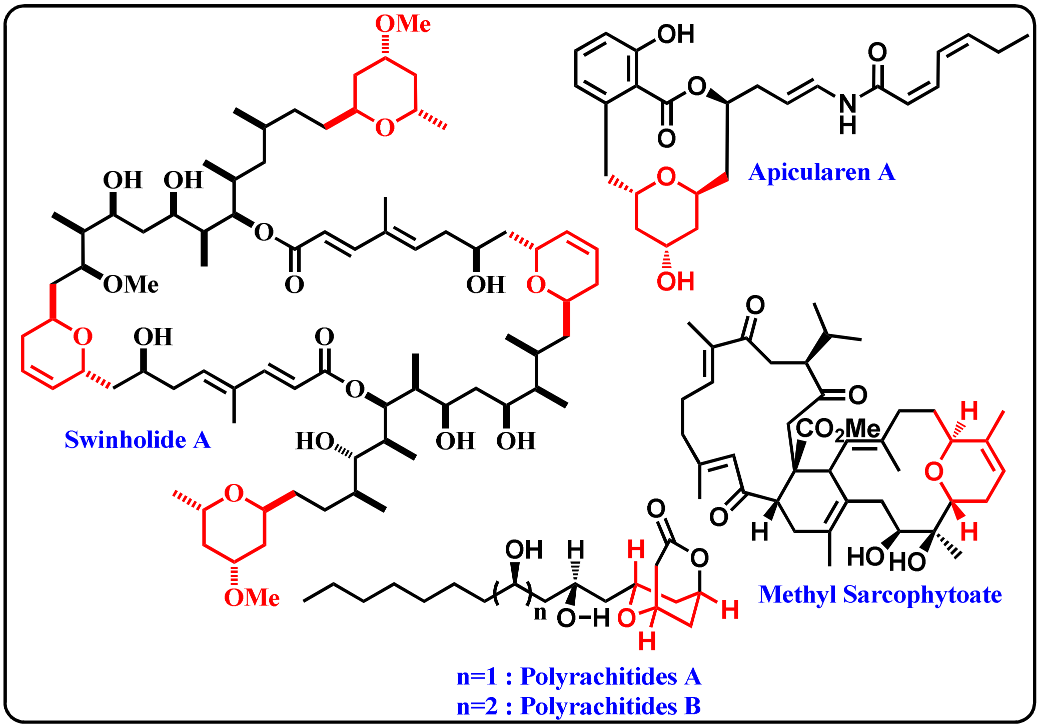


Figure 4. Natural products containing *anti*-pyran ring

Methyl sarcophytoate[20], a natural product isolated from Okinawan soft corals *Sarcophyton glaucum* also shows the presence of 2,6-*anti*-dihydropyran ring. This tetraterpenoid exhibited cytotoxic activity to KB cells and had become an interesting synthetic target after its discovery.[21] Apicularen A and polyrachitides were other examples of natural products possesing the 2,6-*anti*-THP ring which will be discussed further in subsequent chapter (Figure 4).

---

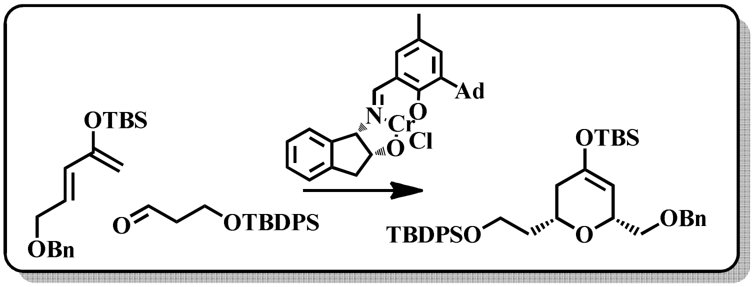
[20] Kusumi,T.; Igari, M.; Ishitsuka,M. O.; Ichikawa, A.; Itezono, Y.; Nakayama, N.; Kakisawa, H. *J. Org. Chem.* **1990,** *55,* 6286.

[21] (a)Takahiro, I.; Yusuke, O.; Naoki, K.; Masaya, N. *J. Org. Chem.* **2009**, *74*, 230.(b)Takahiro, I.; Yusuke, O.; Naoki, K.; Masaya, N. J. Am. Chem.Soc. **2007**, *129*, 9862. (c) Minoru, Y.; Mitsuaki, I.; Yuka, M.; Masaya, N. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1417. (d) Minoru, Y.; Mitsuaki, I; Yuka, M.; Masaya, N. *Synlett* 1997, 899.

1.3. Reported strategy on THP rings formation

1.3.1. Formation of 2,6-*syn*-THP rings

There were many methods for the formation of *syn*-tetrahydropyran available. Hetero Diels-Alder reaction[22] was one of them and breaktrough included the asymmetric version developed by Jacobsen *et al. via* chromium-catalyzed reaction that tolerated wide range of substrates (Scheme 4).[23]



Scheme 4. Hetero Diels-Alder strategy to form THP rings

Hydroxyl cyclization was another alternative to access this moiety such as the one reported by Nicolaou *et al.* in brevetoxin synthesis (Figure 3).[24] The selective formation of the tetrahydropyran ring was achieved using chiral epoxy alcohol under the influence of Brønsted acid (Scheme 5). Nakata[25] and Semmelhack[26] had also contributed to the formation of THP rings *via* this type of cyclization which will not be elaborated further in this section.

---

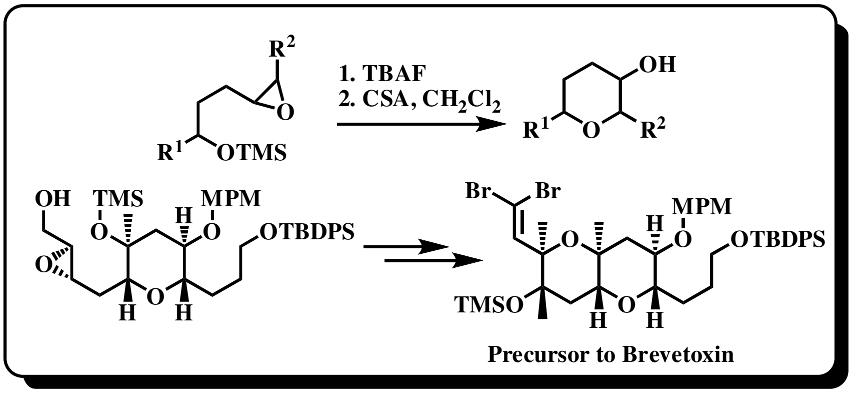
[22] For reviews see (a) JØrgensen, K. A. *Eur. J. Org. Chem.* **2004**, *10*, 2093. (b) Schmidt, R.D. *Acc. Chem. Res.* **1986**, *19*, 250. (c) Herbert, W. *Synthesis* **1994**, *6*, 535. (d) Jorgensen, K.A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558. (e) Weibreb, S.M.; Staib, R.R. *Tetrahedron* **1982**, 38, 3087.

[23] Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772.

[24] (a) Nicolaou, K.C.; Duggan, M.E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 6666.(b) Nicolaou, K.C.; Prasad, C.V.C.; Somers, P.K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (c) Nicolaou, K.C.; Duggan, M.E.; Hwang, C.-K.; Somers, P.K. *J. Chem. Soc. Chem. Commun.* **1985**, *19*, 1359.

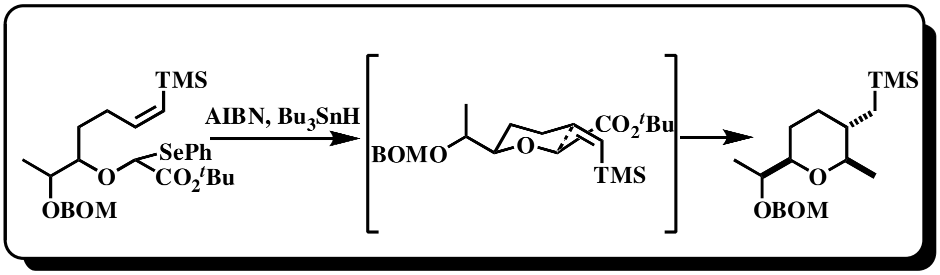
[25] Matsukura, H.; Marimoto, M.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 5545.

[26] (a) Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.* **1989**, *30*, 4925. (b) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1946. (c) Semmelhack, M. F.; Bodurow, C. *Tetrahedron Lett.* **1984**, *30*, 3171. (d) Semmelhack, M. F.; Epa, W. R. *Tetrahedron Lett.* **1993**, *34*, 7205.


1. TBAF
2. CSA, CH2Cl2
R1
R2
OTMS
OH
TMS
MPM
OTBDPS
Br
TMSO
H
Precursor to Brevetoxin

Scheme 5. Hydroxyl cyclization strategy to form THP rings

Burke *et al.* developed the methodology to form THP ring *via* radical cyclization.[27] Excellent control of diastereoselectivity could be achieved using tethered sulfinyl or selenyl ether alkenyl substrate (Scheme 6). Homolytic cleavage of C-Se bond with catalytic amount of AIBN resulted in chair-like transition state to facilitate 6-*exo-trig* radical cyclization. The ring closure followed by entrapment of radical using tributyltin hydride produced a single diastereomer product. Hartung[28] and Lee[29] had also reported AIBN initiated cyclization on different substrates.

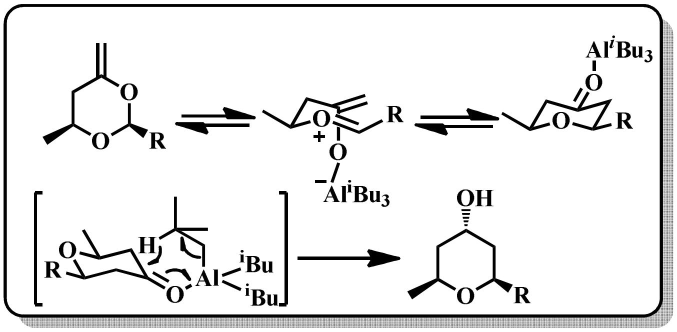

TMS
AIBN, Bu3SnH
SePh
CO2tBu
OBOM
BOMO
CO2tBu
TMS

Scheme 6. THP rings formation *via* radical cyclization

---

[27] Burke, S. D.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 2335.
[28] Hartung, J.; Gottwald, T. *Tetrahedron Lett.* **2004**, *45*, 5619.
[29] (a) Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. *Tetrahedron Lett.* **1993**, *34*, 4831.

THP rings could also be accessed *via* Petasis-Ferrier rearrangement.[30] They had demonstrated that vinyl-acetal could undergo [1,3]-sigmatropic rearrangement initiated by coordination of aluminium with the enolic moiety during the formation of an oxocarbenium ion (Scheme 7).



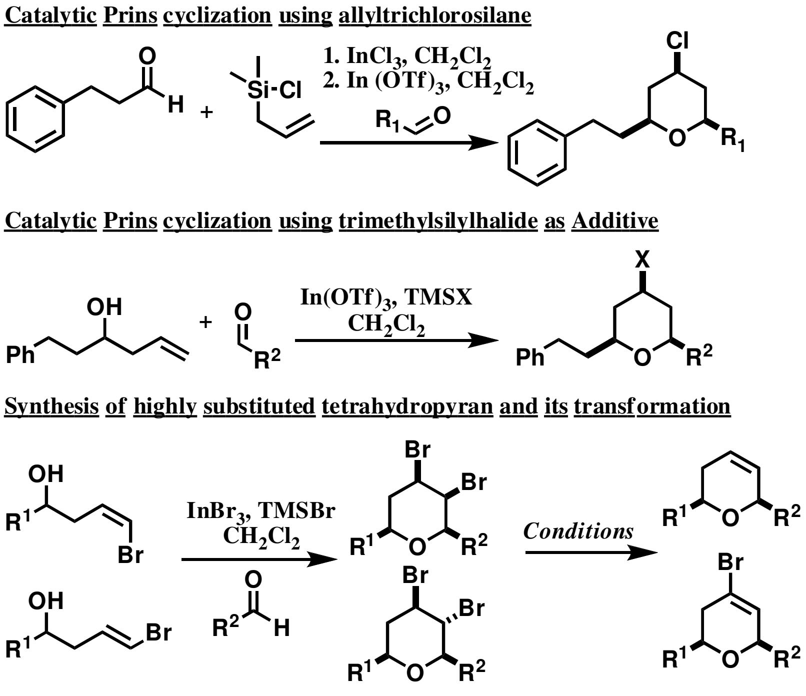
Scheme 7. THP rings formation *via* Petasis-Ferrier rearrangement

Our group had also reported the strategy to form tetrahydropyran rings through indium (III)-catalyzed Prins cyclization and had been applied to synthesis of molecules (Scheme 8).[31]

---

[30] (a) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett*. **1996**, *37*, 141. (b) Petasis, N.A.; Lu, S.-P. *J. Am. Chem. Soc*. **1995**, *117*, 6394.

[31] Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387. (b) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491.(c) Chan, K. P.; Ling, Y. H.; Loh, T. P. *Chem. Commun.* **2007**, *9*, 939. (d) Liu, F.; Loh, T.P. *Org. Lett.* **2007**, *9*, 2063.


Catalytic Prins cyclization using allyltrichlorosilane
1. InCl3, CH2Cl2
2. In (OTf)3, CH2Cl2
Si-Cl
H
R1
O
Cl
Catalytic Prins cyclization using trimethylsilylhalide as Additive
In(OTf)3, TMSX
CH2Cl2
OH
Ph
R2
X
Synthesis of highly substituted tetrahydropyran and its transformation
InBr3, TMSBr
CH2Cl2
Conditions
OH
R1
Br
R2
H
Br

Scheme 8. Our group previous works on THP ring

Many other reports on formation of THP rings were available especially in their application towards natural product synthesis which would not be discussed further in this chapter.[32]

1.3.2. Formation of *anti*-THP rings

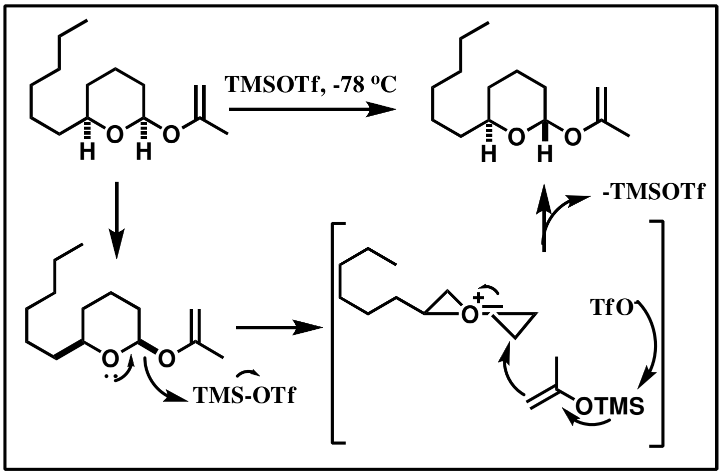
On the contrary to the *syn*-THP rings moiety, there are not many methods available for the formation of *anti*-THP rings. Tate *et al.* reported the formation of this motif *via* isomerization of cyclic acetals.[33]

---

[32] For examples, see: (a) Puglisi, A.; Lee, A.-L.; Schrock, R. R.; Hoveyda, A. H. *Org. Lett.* **2006**, *8*, 1871. (b) Estevez, J. C.; Fairbanks, A. J.; Hsia, K. Y.; Ward, P.; Fleet, W. J. *Tetrahedron Lett.* **1994**, 35. (c) Sanchez, C. C.; Keck, G. E. *Org. Lett.* **2005**, *7*, 3053. (d) Tsurugi, J.; Nakao, R.; Fukumoto, T. *J. Org. Chem.* **1972**, *37*, 76. (e) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, *46*, 2417. (f) Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417.

[33] Dixon, D.J.; Ley, S.V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. I* **1999**, 2665.

Thermodynamically controlled addition of TMSOTf activated the leaving group leading to the formation of oxonium ion and silyl enol ether *in situ*. These compounds recombined kinetically to afford the *anti*-keto-tetrahydropyran product (Scheme 9).



Scheme 9. Formation of *anti*-THP ring *via* isomerization

Rein *et al.*[34] reported that base-mediated Michael type cyclization could afford both *syn* and *anti* isomers of the tetrahydropyran depending on substrate configuration. *(E)*-Hydroxy acrylate provided 2,6-*anti*-isomer with excellent diastereoselectivity while the *(Z)*- isomer led to 2,6-*syn* product. The rationale behind their observation was the conformation stability in the chair-like transition state. In the former substrate, acrylate group adopted an axial position to enhance maximum chelation with the counterion, while in the *(Z)*-isomer, it was confined to the equatorial position leading to corresponding *syn*-product. Hence, in this case, the *anti*-pyran moiety was formed *via* stereochemically controlled cyclization (Scheme 10).

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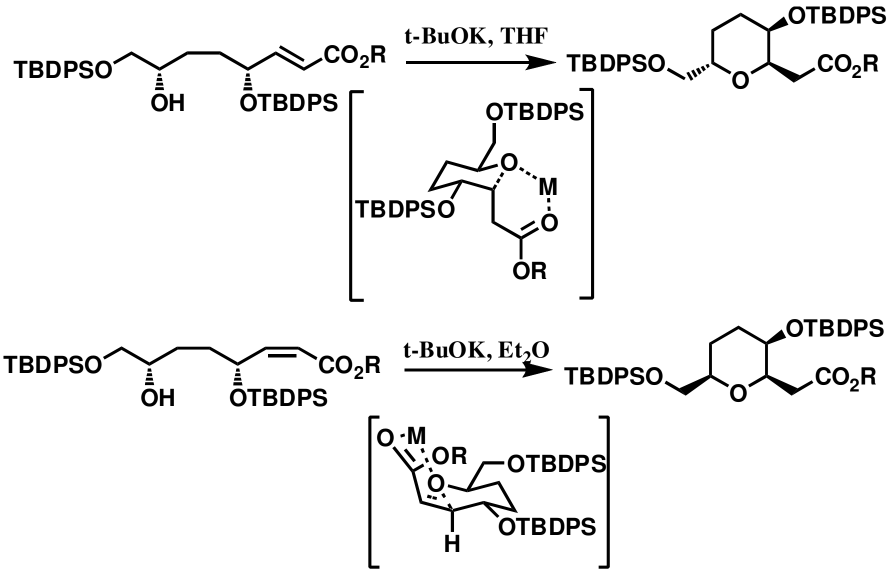
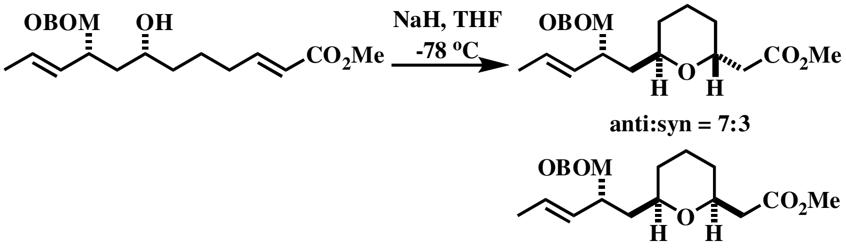
[34] Vares, L.; Rein, T. *J. Org. Chem.* **2002**, *67*, 7226.



Scheme 10. Michael type cyclization to afford *anti*-pyran ring

Bates's group had also reported the formation of *anti*-THP ring through intramolecular Michael addition under kinetic control in their model study towards bistramide D (Scheme 11).[35] The *syn*-THP product was the thermodynamically more stable product. However, referring to the strategy developed by Banwell *et al.*[36] under carefully controlled conditions they managed to obtain the *anti-* THP product (Scheme 13).



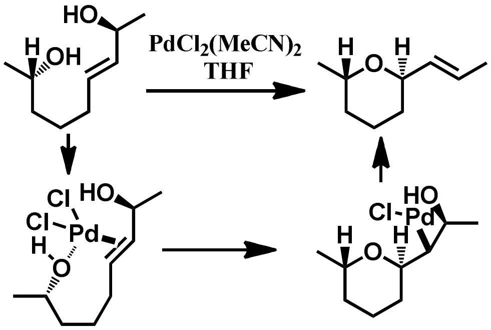
Scheme 11. Intramolecular addition to form *anti*-THP rings

---

[35] Bates, R. W.; Palani, K. *Tetrahedron Lett.* **2008**, *49*, 2832.

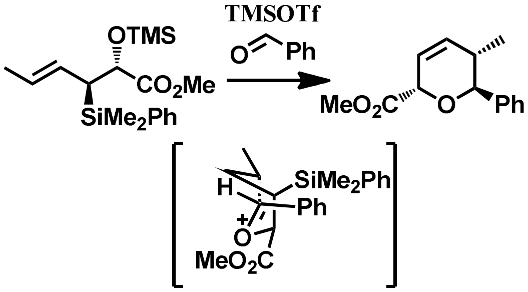
[36] (a) Banwell, M. G.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. *J. Chem. Soc. Perkin. Trans. I* **1996**, 967. (b) Banwell, M. G.; Bisset, B. D.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. *Aust. J. Chem.* **1998**, *51*, 9.

Another example of stereochemical control was palladium-catalyzed cyclization such as those reported by Uenishi *et al.*[37] This transformation occurred *via* a concerted 1,3-chirality transfer cyclic pathway (Scheme 12).


HO
H OH
PdCl2(MeCN)2
THF
H O H
Cl HO
Cl-Pd
H
O
HO
Cl-Pd
H O H

Scheme 12. Oxypalladation reaction to form *anti*-THP ring

Anti-THP rings could also be formed through substrate controlled *anti*-Prins cyclization. The main contribution in this field was introduced by Panek *et al.*[38] relating to the stereoselective synthesis of 2,6-*anti* pyran using [4+2] annulations of chiral *anti*-hydroxycrotylsilane (Scheme 13).


OTMS
CO2Me
SiMe2Ph
TMSOTf
O Ph
MeO2C
O
Ph
H
SiMe2Ph
Ph
+
O
MeO2C

Scheme 13. Panek strategy for substrate controlled cyclization

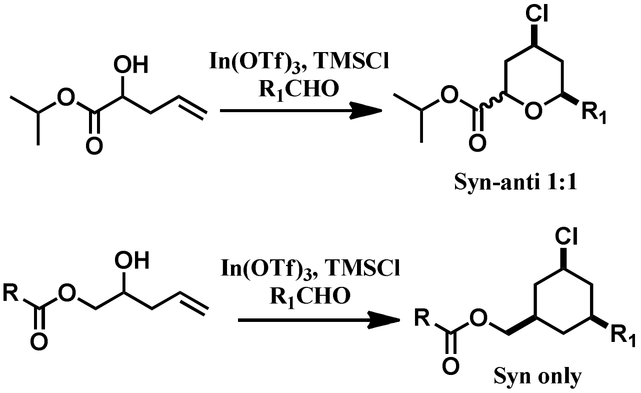
Anti stereochemistry originates from a favorable pseudo-axial orientation for the silyl group hence promoting σ-π overlap in the boat-like transition state. Driven by both steric and electronic factors, the bulky silyl group was oriented *anti* to the ester group that leading to the final product in good diastereoselectivity (dr >30:1). This method was applied to the total synthesis of apicularen A, which will be described in chapter 4.

---

[37] (a) Kawai, N.; Lagrange, J.-M.;Ohmi, M.; Uenishi, J. *J. Org. Chem.* **2006**, *71*, 4530. (b) Uenishi, J.; Ohmi, M.; Ueda, A.; *Tetrahedron: asymmetry*, **2005**, *16*, 1299. (c) Uenishi, J.; Ohmi, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 2756.

[38] Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, **122**, 9836.

Previously our group had also attempted to form *anti*-pyran rings through substrate controlled synthesis.[39] The reaction proceeded with good conversion, however, both *syn* and *anti* isomers were obtained as the products (Scheme 14).



Scheme 14. Our group previous work on *anti*-THP ring

From the experimental results, it was concluded that the carbonyl lone pair inductive effect on the oxonium transition state was significant in determining the configuration of the product. In the absence of this effect, such as when benzoyl ester was used as substrate, only *syn* product was observed.

The need of new methodology in natural products synthesis is endless. Despite proven versatility, some methodology may fail to work on a particular substrate. Hence, we will describe in the next chapter, an alternative to access *anti* tetrahydropyran moiety through indium (III) chloride-catalyzed Mukaiyama-Michael addition of silyl enol ether to substituted pyranone and its application to natural products synthesis in the chapters that follow.

---

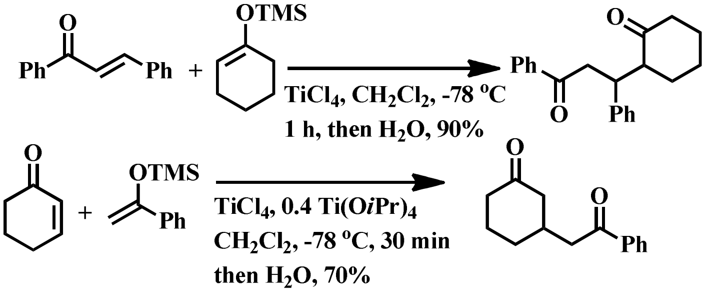
[39] Chan, K. P.; Soew A. H.; Loh, T. P. *Tetrahedron Lett.* **2007**, 37.

Chapter 2

$InCl_3$ Catalyzed Mukaiyama-Michael Addition: Synthesis of 2,6-Anti-Pyran

2.1. Introduction to Mukaiyama-Michael reaction

Mukaiyama-Michael reaction was pioneered by Mukaiyama *et al.*[40] where α,β-unsaturated ketone was treated with silyl enol ether or silyl ketene acetal in the presence of Lewis acid such as $TiCl_4$ (Scheme 15). The significance of this reaction was that it could tolerate base-sensitive acceptors and the by-products due to 1,2-addition or proton transfer could be minimized. Since its conception, this reaction had received much attention and broad range of Lewis acids had been applied.[41]


O
Ph
Ph
OTMS
$TiCl_4$, CH_2Cl_2, -78 °C
1 h, then H_2O, 90%
O
Ph
O
Ph
O
OTMS
Ph
$TiCl_4$, 0.4 $Ti(OiPr)_4$
CH_2Cl_2, -78 °C, 30 min
then H_2O, 70%
O
O
Ph

Scheme 15. Mukaiyama-Michael reaction

Numerous synthetic applications had been reported. Among them were the synthesis of prostaglandins,[42] vitamin D3[43] and functionalized bullvalones[44] that demonstrated the power of this methodology as a tool for C-C bond formation (Scheme 16).

---

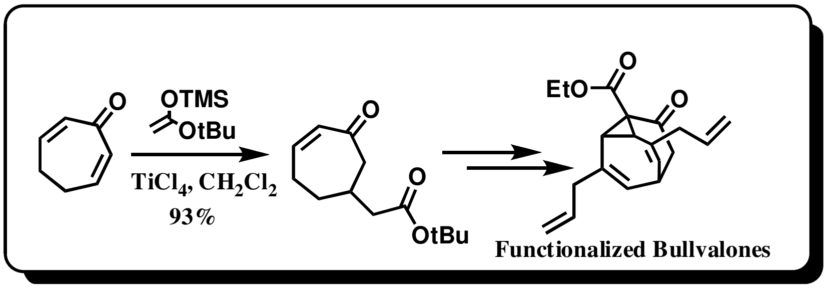
[40] (a) Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223. (b) Narasaka, K.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779. (c) Mukaiyama, T. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 817.

[41] For example see: (a) Gray, B.D.; White, J.D. *J. Chem. Soc. Chem. Commun.* **1985**, 20. (b) Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1987**, 463. (c) Mukaiyama, T.; Matsui, S.; Homma, K.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2687. (d) Duhamel, P.; Dujardin, G.; Hennequin, L.; Poirier, J. M. *J. Chem. Soc. Perkin Trans I.* **1992**, 387. (e) Yura, T.; Iwasawa, N.; Narasaka, K.; Mukaiyama, T. *Chem. Lett.* **1988**, 1025.

[42] Danishefsky, S. J.; Cabal, M.P.; Chow, K. *J. Am. Chem. Soc.* **1989**, 111, 3456.

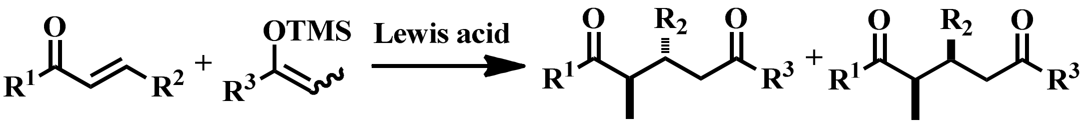
[43] (a) Michallak, K.; Stephanenko, W.; Wicha, J. *Tetrahedron Lett.* **1996**, *37*, 7657. (b) Marczak, S.; Wicha, W. *Tetrahedron Lett.* **1993**, *34*, 6627.

[44] Lippert, A.R.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, 128, 14738.



Scheme 16. Application of Mukaiyama- Michael reaction

Unfortunately, there are not many reports on the diastereoselectivity control of this reaction. Heathcock *et al.*[45] had published an acid-catalyzed Mukaiyama-Michael reaction with control of diastereoselectivity for acyclic substrate (Scheme 17). They reported that silyl enol ethers derived from ketones showed general tendency for *anti* addition regardless of the geometry of the enolates.

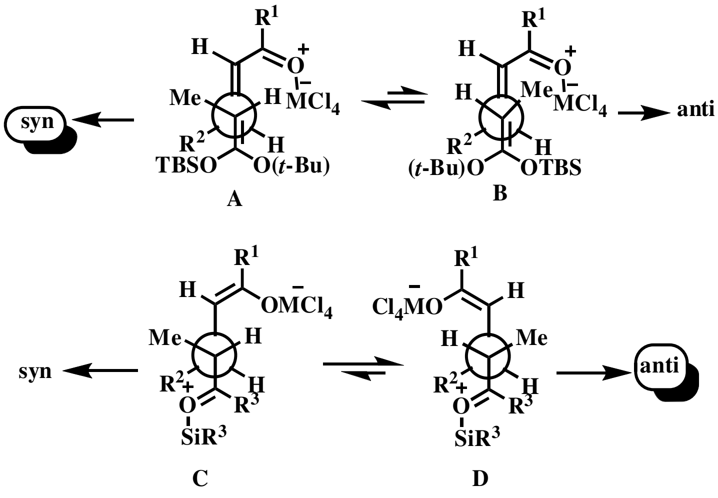


Scheme 17. Mukaiyama-Michael reaction by Heathcock *et al.*

Their explanation for the selectivity was based on partial or complete thermodynamic control in competition of retro-Michael reaction with desilylation. In the case of acyclic *tert*-butyl enones the *syn* selectivity was the result of preference for transition-state conformation **A** relative to **B**. On the other hand, other enol silanes showed *anti* selectivity because gauche interactions are minimized in conformation **D**, relative to **C** (Scheme 18).

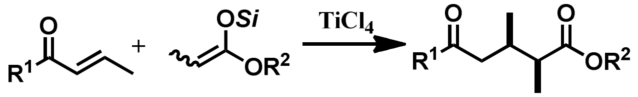
---

[45] Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107,* 2797.



Scheme 18. Mechanistic proposal by Heathcock

Otera *et al.*[46] reported *syn* selectivity of the Mukaiyama-Michael product when the silyl ketene acetals had bulky siloxy or alkoxy group with bulky acyl group in the α-enones. The selectivity could be reversed by decreasing the size of the substituents. In this case, they reported that the stereoselectivity of the products were determined by substrate control (Scheme 19).

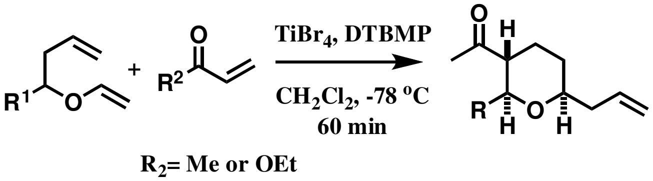


Scheme 19. Otera strategy in selectivity control of the addition product

Rychnovsky *et al.*[47] reported the formation of tetrahydropyran rings using Mukaiyama-Michael cascade reaction in the presence of $TiBr_4$ which was limited to formation of *syn* products (Scheme 20). When methyl vinyl ketone was used as enone, they observed only single diastereomer for most cases. This system tolerated protecting group such as Bn or TIPS that makes it potential for synthetic use in natural products. However, acid labile group such as TBS was not tolerated. Another drawback was that they could not obtain high diastereoselectivity when ethyl acrylate was used as the enolate (*de* 16-32%) (Scheme 20).

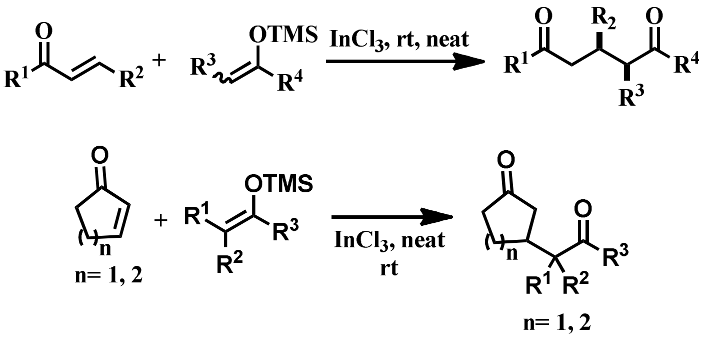
---

[46] Otera, J.; Fujita, Y.; Fukuzumi, S. *Tetrahedron.* **1996**, *52*, 9409.
[47] Bolla, M. L.; Patterson, B.; Rychnovsky, S.D. *J. Am. Chem. Soc.* **2005**, 127, 16044.



Scheme 20. Cascade Mukaiyama-Michael reaction

Previously, we developed the methodology of Mukaiyama-Michael addition of silyl enol ether to α,β-unsaturated carbonyl (ketone and ester) under neat condition catalyzed by indium trichloride (Scheme 21).[48] $InCl_3$ was a mild Lewis acid that allows extension of this methodology to wider range of substrates that were acid sensitive. This reaction was chemoselective in which no Mukaiyama-aldol product was formed. However, the reaction proceeded only with low to moderate diastereoselectivity (4-40% *de*).



Scheme 21. Our previous report on $InCl_3$ catalyzed Mukaiyama-Michael reaction

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[48] Loh, T. P.; Wei, L. L. *Tetrahedron* **1998**, *54*, 7615.

2.2. $InCl_3$ as water-tolerant Lewis acid

Lewis acid can enhance the reactivity of carbonyl-containing compounds, thus promoting the C-C bond formation reactions. However most of the traditional Lewis acids such as BX_3, AlX_3, TiX_4 and SnX_4 are moisture sensitive, hence high loading of the catalysts are often required. Furthermore, the workup is usually carried out by adding water to the reaction, destroying the catalysts, so they cannot be recovered and reused.

Utilization of large amounts of Lewis acids in industries has caused serious environmental problems. Hence the development of water-tolerant Lewis acids that can be recovered and reused can provide significant improvement in the large scale processes.

$InCl_3$ is a water-tolerant Lewis acid that has made it as the choice in several C-C bond formations in water or aqueous solvents.[49] Our group was interested in exploring the catalytic use of $InCl_3$ as recyclable, water-stable catalyst for more than a decade.[50] The first application of $InCl_3$ in our lab was in the Sn-mediated allylation of carbonyl compounds in water.[51] This work showed that the presence of $InCl_3$ was crucial on the final isomer ratios of the products (Scheme 22). The Sn/$InCl_3$ allylation system was also applicable to fluorinated compound which was common entity in pharmacologically active compounds.[52]

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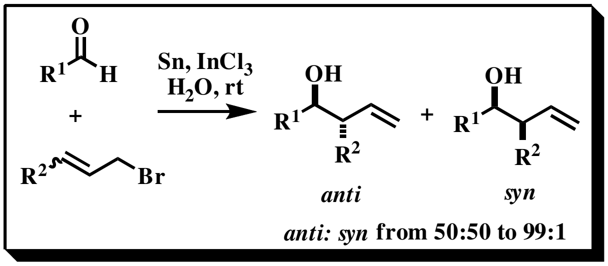
[49] For examples, see: (a) Araki, S.; Jin, S. J.; Idou, Y.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1736. (b) Cho, Y. S.; Kim, H.Y.; Cha, J. H.; Pae, A. N.; Koh, H. Y.; Choi, J. H.; Chang, M.H. *Org. Lett.* **2002**, *4*, 2025.

[50] Loh, T. P.; Chua, G. L. *Chem. Commun.* **2006**, 2739.

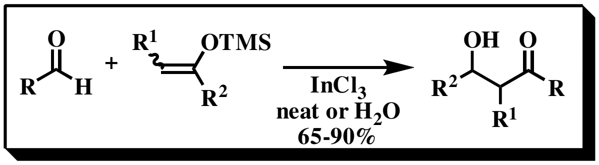
[51] Li, X. R.; Loh, T. P. *Tetrahedron: Asymmetry*, **1996**, *7*, 1535.

[52] Loh, T. P.; Li, X. R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 980.



Scheme 22. $InCl_3$-promoted Sn-mediated allylation of carbonyl compounds in water

Mukaiyama aldol reaction is undoubtedly an important tool in C-C bond formation. This directed aldol reaction could provide the products in high yield and diastereoselectivity. Relating to this fact, our group had reported $InCl_3$-catalyzed Mukaiyama aldol reaction with moderate to high yield (Scheme 23).[53] However, the diastereoselectivity was poor and inconsistent with the effects from sequence of addition of the reactants.



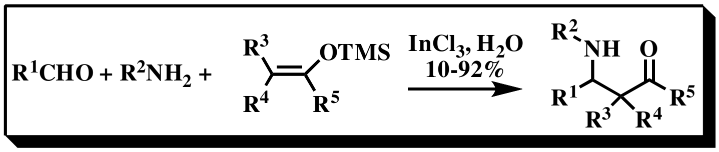
Scheme 23. $InCl_3$ catalyzed Mukaiyama aldol reaction in water

Our group had also expanded the use of $InCl_3$ to catalyze Mannich reaction in water.[54] The yield of the reactions ranged from low to high depends on the substituent combination. This report showed the preferential formation of Mannich products over aldol products. In fact, in the absence of $InCl_3$, aldol products were dominant. $InCl_3$ could be recycled and reused without loss of acitivity (Scheme 24).

---

[53] (a) Loh, T.P.; Pei, J.; Koh, S. V.; Cao, G. Q.; Li, X. R. *Tetrahedron Lett.* **1997**, *38*, 3465. (b) Loh, T. P.; Pei, J.; Cao, G. Q. *Chem. Commun. 1996*, 1819.

[54] (a) Loh, T.P.; Wei, L. L. *Tetrahedron Lett.* **1998**, *39*, 323. (b) Loh, T. P.; Liung, S. B. K. W.; Tan, K. L.; Wei, L. L. *Tetrahedron*, **2000**, *56*, 3227.



Scheme 24. $InCl_3$ catalyzed Mannich reaction in water

Other reactions such as Diels-Alder reaction[55] and amine conjugate additions[56] had also been studied in our group which will not be discussed further in this section.

2.3. Reactions under neat conditions

Most of organic reactions are carried out in liquid phase with organic solvents as reaction medium. Solvents are good medium to transport heat needed or generated during the course of reaction. Dissolving substrates and reagents in solvents provides homogeneous environment that facilitates the molecules to come together rapidly, thus to react more efficiently.[57] However, organic solvents are generally environmentally unfriendly and often been blamed to contribute to global warming phenomenon.

As an alternative to water as more environmentally benign solvent as has been discussed in previous section, we could also carry out a solvent-free reaction or under neat condition. There are many advantages of such reactions. Reaction can be carried out in shorter times, especially when microwave or ultrasound are used to assist the reactions. Solvent-free reactions often require simpler reaction set up and apparatus. The products of the reactions can be isolated by simple extraction with solvents or directly by distillation or sublimation.

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[55] Loh, T. P.; Pei, J.; Lin, M. *Chem. Commun.* **1996**, 2315.

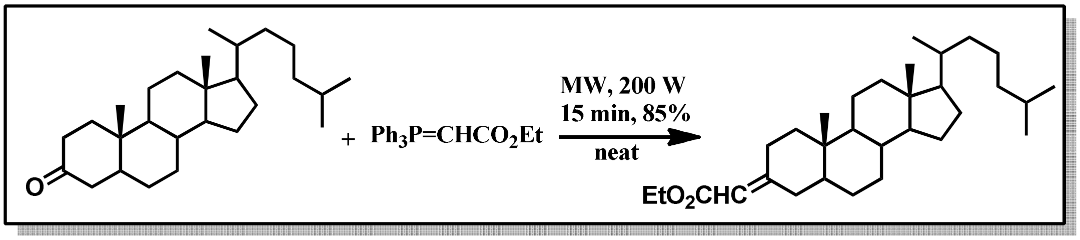
[56] Loh, T.P.; Wei, L. L. *Synlett*, **1998**, 975.

[57] (a) Tanaka, K. *Solvent-free Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2003. (b) Reichardt, C. *Org. Process. Res. Dev.* **2007**, *11*, 105.

Molecular movement is one of the important factors in reactions under neat condition. When all of the reactants are in liquid form, the molecular movement can be regarded as similar to solution reactions. When one or more reactants are solid at the reaction conditions the molecular movements are more complex. However it had been reported that it had minimum effect on several reactions to proceed.[58]

There are several activation mechanisms that can be done in solvent-free conditions such as mechanochemistry (grinding), microwave irradiation, ultrasound irradiation, and conventional thermal heating.[59] Microwave assisted reactions, being the most common in the above mentioned activation method; have received significant attention in recent years.[60]

Wittig reaction is important transformation in organic synthesis. The reaction of stabilized ylides such as $Ph_3P{=}CHCO_2Et$ with aldehydes usually can proceed smoothly. However, high reaction temperature and longer reaction time are needed for the reaction of the ylides with ketone. A solvent-free, microwave assisted process could be the solution to this problem as reported by Soriente *et al.* (Scheme 25).[61]



Scheme 25. Example of microwave assisted reaction

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[58] Toda, F.; Tanaka, K. *Chem. Rev*. **2000**, *100*, 1025.

[59] Martins, M.A.P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev*. **2009**, *109*, 4140.

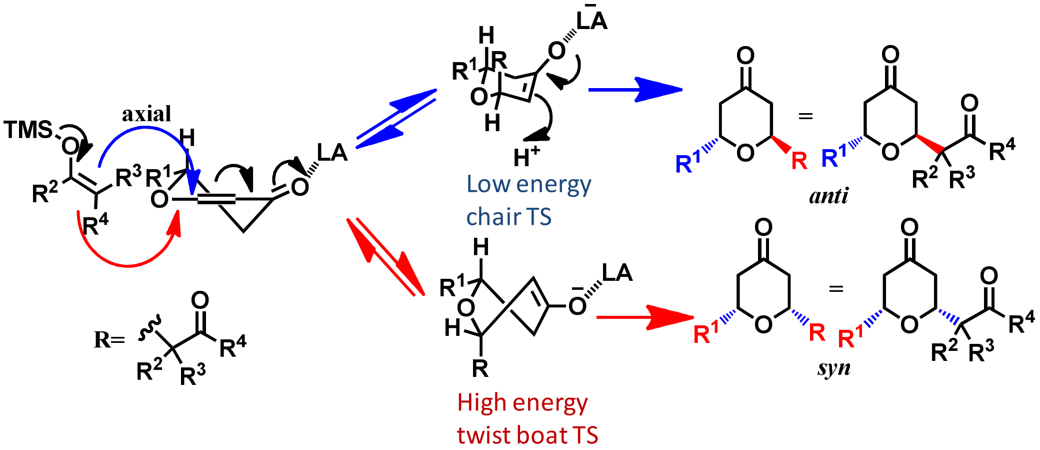
[60] For examples, see: (a) Sabitha, G.; Babu, R. S.; Yadav, J. S. *Synth. Commun.* **1998**, *28*, 4571. (b) Yadav, J. S.; Reddy, B. V. S.; Satheesh, G.; Lakshmi, P. N.; Kumar, S. K.; Kunwar, A. C. *Tetrahedron Lett.* **2004**, *45*, 8587. (c) Deshmukh, M. B.; Jagtap, S. S.; Desmukh, S. A. *J. Indian Chem. Soc.* **2006**, *83*, 1055.

[61] Spinella, A.; Fortunati, T.; Soriente, A. *Synlett* **1997**, 93.

2.4. Results and Discussion

Based on our search to look for alternative method to access *anti*-pyran moiety, we planned to carry out a nucleophilic addition to dihydropyranone, a Mukaiyama-Michael addition, which upon aqueous workup would give the products with the desired stereoselectivity.

We proposed that substituted dihydropyranone could provide stereocontrol by inductive effect which would probably give the *anti*-pyran moiety based on the proposed transition state below:


TMS
axial
R²
R⁴
R³
R¹
H
O
LA
R=
R²
R³
R⁴
H
R¹
R
O
H
LA
H⁺
Low energy
chair TS
R¹
R
anti
R²
R³
R⁴
H
R¹
O
H
R
LA
High energy
twist boat TS
R¹
R
syn
R²
R³
R⁴

Scheme 26. Proposed mechanism for *anti*-selective addition

We initially prepared model substrates to prove our hypothesis. Substituted pyranone was conveniently synthesized from hetero Diels-Alder reaction of aldehyde and Danishefsky diene catalyzed by Lewis acid according to literature procedure (Scheme 27).[62]

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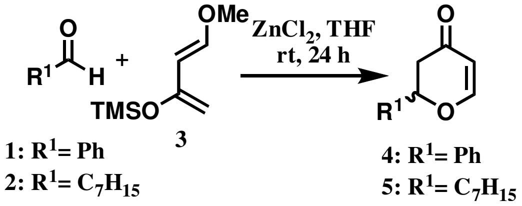
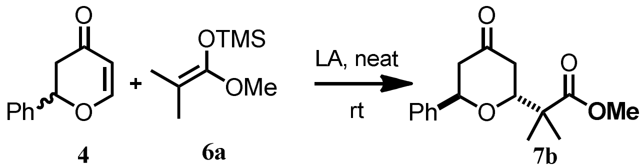
[62] Danishefsky, S. J.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358.



Scheme 27. Preparation of substrate

We initially tested the reaction without addition of Lewis acid and did not observe any products (Table 1, entry 1). Several Lewis acids were then tested towards this reaction and we observed that $InCl_3$ showed the best result with highest yield. This results suggested that $InCl_3$ activates the conjugated system of α,β-unsaturated substrate most efficiently compared to other Lewis acid that we tried (Table 1).

Only trace amount of product was observed when we carried out the reaction with $InOTf_3$, while 12% yield was obtained when we added $InBr_3$ as Lewis acid. The Mukaiyama-Michael reaction also proceeded with $ZnCl_2$, however the yield was significantly lower than the reaction with $InCl_3$. Except for reaction with $InOTf_3$ that we did not manage to analyze the diastereoselectivity, all products were isolated as single diastereomer, which showed the importance of coordination of the carbonyl group with Lewis acid to force the reaction to go through transition state, presumably according to our proposal. We observed a consistent yield when we recycled $InCl_3$ (Table 1, entry 7).



Conditions: 20 mol% Lewis acid, 1 equiv. of 4, 2 equiv. of 6a stirred neat at rt.

Entry	Lewis acid	Yield %	Comments
1	-	0	
2	$InBr_3$	12%	dr >99: 1
3	$InOTf_3$	Trace	Diastereoselectivity not determined
4	$ZnCl_2$	23%	dr >99:1
5	$InCl_3$	83%	dr >99:1
6	$InCl_3$	22%	Without prestirring LA and substrate dr >99:1
7	$InCl_3$	82%	Recycled $InCl_3$, dr >99:1

Table 1. Optimization of reaction conditions

Prestirring of $InCl_3$ and the substituted pyranone was necessary for optimizing yield of the reactions. This was consistent to previous study in our groups[63] due to association of the Lewis acid and the substrate was required before addition of silyl enol ether or silyl ketene acetal. When we carried out the reaction without prestirring of $InCl_3$ and the substrate, we observed significantly lower yield of the product (Table 1, entry 6).

It was also worth noting that only 1,4- addition products were observed (Mukaiyama-Michael product). No 1,2- addition products (Mukaiyama-aldol product) were observed in the reactions. Our group has previously carried out a competitive study between these reactions[64] and concluded that Mukaiyama-Michael reaction occurred preferentially over the aldol reaction in the presence of catalytic amount of $InCl_3$ under neat condition. This showed that $InCl_3$ can effectively discriminate the difference of enones and ketones.

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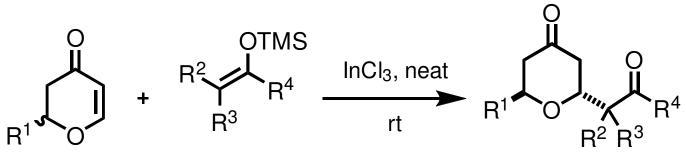
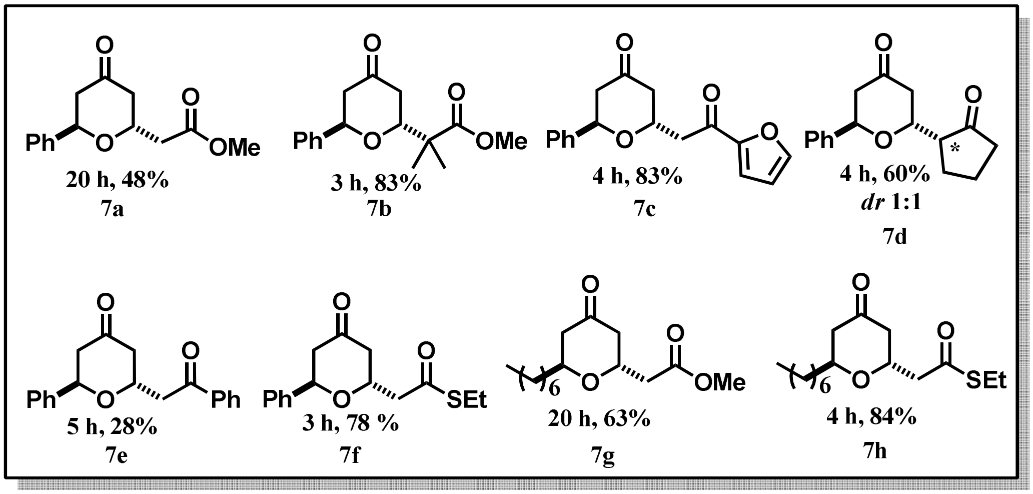
[63] Loh, T.P.; Pei, J.; Koh, S. V.; Cao, G. K.; Li, X. R. *Tetrahedron Lett.* **1997**, *38*, 3465.

With the optimized reaction conditions in hand, we treated the racemic substrate **4** and **5** with $InCl_3$ and silyl enol ether or silyl ketene acetal to undergo the Mukaiyama-Michael addition and the results were shown in Scheme 28.



4 or 5 **6** **7**

Conditions: 20 mol% $InCl_3$, 1 equiv. of 4 or 5, 2 equiv. of 6 stirred at rt.



20 h, 48% **7a**

3 h, 83% **7b**

4 h, 83% **7c**

4 h, 60% ***dr* 1:1** **7d**

5 h, 28% **7e**

3 h, 78 % **7f**

20 h, 63% **7g**

4 h, 84% **7h**

Scheme 28. Indium (III) catalyzed Mukaiyama-Michael reactions

To our delight, the reactions proceeded according to our hypothesis with exclusive *2,6-trans*-stereochemistry in moderate to good yield for both aromatic and aliphatic substituents on the pyranone. In some cases (for example compound **7b**) the *trans*-

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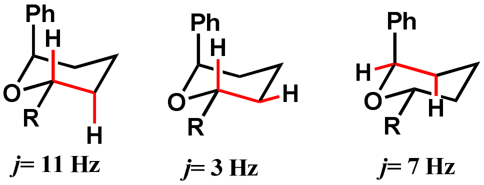
[64] Wei Lin Li, PhD thesis 1998

tetrahydropyranone configuration can be clearly deduced from the coupling constant of the proton that is α to O. The proton that is next to phenyl group shows dd coupling pattern with coupling constant of ~12 Hz and ~3 Hz that suggested that this proton is axial. On the other hand, the other proton that is α to O showed a coupling constant of ~7 Hz and the other is difficult to recognize due to the small coupling, this suggested it is in equatorial position. The coupling patterns of this proton sometimes appear as triplet, while it is probably dd (Scheme 29).



Scheme 29 Coupling constant analysis for anti-configuration

When this α proton next to a methylene group for example in compound **7a, 7c, 7e** and **7f**, the signal appears as multiplet. The coupling pattern is more complicated when the pyranone is alkyl chain substituted (**7g** and **7h**). In this case, both α proton appears as multiplet and to simplify the characterization, we run NOESY experiment for all of the above compounds (**7a-7h**) to confirm that they indeed posses anti configuration.

The reaction gave lower yield when silyl enol ether was used (compound **7e**) as compared to silyl ketene acetals (compound **7a** and **7b**). We also observed that the yields were slightly higher for substrates with aliphatic substituent compared to the aromatic counterpart (e.g. Compound **7a** and **7g**). When we used prochiral substrate as silyl enol ether, we observed 50:50 diastereoselectivy (compound **7d**). When (1-methoxyvinyloxy)trimethylsilane was used as enol ether, we observed that longer reaction time was required for the completion of reaction (Compounds **7a** and **7g**).

2.5. Conclusion

In this chapter we have demonstrated the use of Mukaiyama-Michael addition in the formation of 2,6-*anti*-pyran rings. Typically, Mukaiyama-Michael addition was carried out at low temperature with dichloromethane as the solvent. In this regard, we reported an alternative approach of this reaction at room temperature under solvent-free condition. This reaction provided high diastereoselectivity and we only observed the formation of 2,6-*anti*-pyran products that were confirmed by NOESY analysis. The use of indium (III) chloride as Lewis acid allowed extension of this methodology to acid sensitive substrates. $InCl_3$ can be recycled without losing reactivity. Applications of this methodology to the synthesis of natural products are described in chapter 3 and chapter 4 respectively.

Chapter 3

Total Synthesis of Polyrachitide A

3.1. Background and biological activity of polyrachitides

Polyrachitides A and B were isolated by Jiang *et al.* from Chinese medicinal ants *Polyrachis lamellidens.*[65] It had long been used for the treatment of rheumatoid arthritis and hepatitis as well as inflammation in mainland China.[66] Their studies showed that ethanol extract of this species also demonstrates impressive analgesic and anti-inflammatory activity. However, extensive study of the biological activity had not been reported in literature presumably due to the limited supply of this compound from nature (19.2 mg of polyrachitides B was extracted from 2 kg of ants).

The structure of polyrachitide A featured interesting bicyclic polyketide lactones and poly-hydroxyl group with five stereocenters (C-3, C-5, C-7, C-9, and C-11). Jiang *et al.* reported the structure elucidation through extensive NMR study by applying acetonide and Mosher's MTPA ester methods. Interestingly, the hydrogen bond between C-7-C-9 locked the conformation of this compound in the chair like conformation as shown in Figure 5. This kind of hydrogen bond was also observed in other natural product such as synthetic fragment of maitotoxin as reported by Kishi, *et al.*[67] Polyrachitide B was isolated at the same time with polyrachitide A and the structure differed only by two carbon elongation and one extra hydroxyl group compared to the A counterpart (Figure 5).

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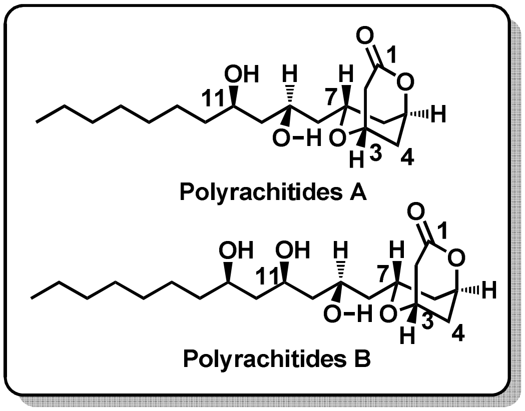
[65] Jiang, Z. H.; Yang, Q.X.; Tanaka, T.; Kouno, I. *J. Nat. Prod.* **2008**, *71*, 724.

[66] (a) Zhang, J. H.; Ma, A. H.; Xie, X. F.; Li, S. L. *Jiangsu J. TCM.* **1996**, *17*, 43. (b) Zhang, R. W.; Shao, S. H. *J. Jiangxi. College. TCM.* **1996**, *8*, 47. (c) Li, S. L.; Ren, Y. J.; Cui, X.; Qian, Z. Z.; Dong, Q., *Chin. Tradit. Pat. Med.* **1994**, *17*, 47.

[67] Cook, L. R.; Oinuma, H.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 7928.

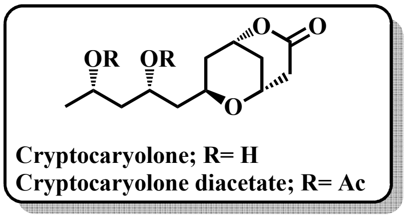


Polyrachitides A

Polyrachitides B

Figure 5. Polyrachitides A and B

Aliphatic polyketides such as polyrachitides A and B were not common in ants unlike their aromatic counterpart that had been isolated previously from Australian ponerine ants.[68] However, similar polyketides featuring bicyclic lactones moiety were found in plants of *Cryptocarya* and *Ocotea* (Lauraceae),[69] *Syncolostemon* (Lamiaceae),[70] *Iboza* (Lamiaceae), [71] and *Euscaphis* (Staphyleaceae).[72]



Cryptocaryolone; R= H
Cryptocaryolone diacetate; R= Ac

Figure 6. Cryptocaryolone class of compounds

Interestingly, cryptocaryolone, and cryptocaryolone diacetate, two similar bicyclic lactones that were isolated from *Cryptocarya latifolia*,[5] had different biological properties as compared to those reported for polyrachitides. The structures differed by changing in the opposite absolute stereochemistry of the hydroxyl groups in addition to the absence of long alkyl chain moiety (Figure 6). Compared to polyrachitides, the latter compounds were known for treatment of headaches and morning sickness to the treatment of cancer, pulmonary diseases, and various bacterial and fungal infections.[73] Further investigation of the crude extract by Van Staden revealed significant activity as cyclooxygenase inhibitors (COX-2/COX-1)[74]. Considering two different sources of these two classes of compounds rendered the study of these materials important in chemical biology as well as ecology.

---

[68] (a) Jones, T. H.; Conner, W. E.; Meinwald, J.; Eisner, H. E.; Eisner, T. *J. Chem. Ecol.* **1976**, *2*, 421. (b) Sun, C. M.; Toia, R. F. *J. Nat. Prod.* **1993**, *56*, 953. (c) Rawlings, B. *J. Nat. Prod.* **1997**, 523.

[69] (a) Drewes, S. E.; Horn, M. M.; Wijewardene, C. S. *Phytochemistry* **1996**, *41*, 333. (b) Drewes, S. E.; Horn, M. M.; Mavi, S. *Phytochemistry* **1997**, *44*, 437.

[70] (a) Collett, L. A.; Davies-Coleman, M. T.; Rivett, D. E. A.; Drews, S. E.; Horn, M. M. *Phytochemistry* **1997**, *44*, 935. (b) Collett, L, A.; Davies-Coleman, M. T.; Rivett, D. E. A. *Phytochemistry* **1998**, *48*, 651.

[71] Puyvelde, L. V.; Dube, S.; Uwimana, E.; Uwera, C.; Dommisse, R. A.; Esmans, E. L.; Schoor, O. V.; Vlietinck, A. J. *Phytochemistry* **1979**, *18*, 1212.

[72] Takeda, Y.; Okada, Y.; Masuda, T.; Hirata, E.; Takushi, A.; Otsuka, S. *Phytochemistry* **1998**, *49*, 2565.

3.2. Previous Synthesis of Polyrachitides

There were a few reported total syntheses of polyrachitides, cryptocaryolone, and cryptocaryolone diacetate. From chemistry point of view, these two classes of compounds have similar features including the bicyclic lactone and poly-hydroxy architectures. However, there was no report of the internal hydrogen bonding in the structure of cryptocaryolone that locked the conformation as reported in polyrachitides.

We will discuss herein, the previous report on total synthesis of cryptocaryolone, cryptocaryolone diacetate and polyrachitides. Efforts towards the synthesis of the architecture of these molecules were reported earlier and would not be discussed further in this section.[75]

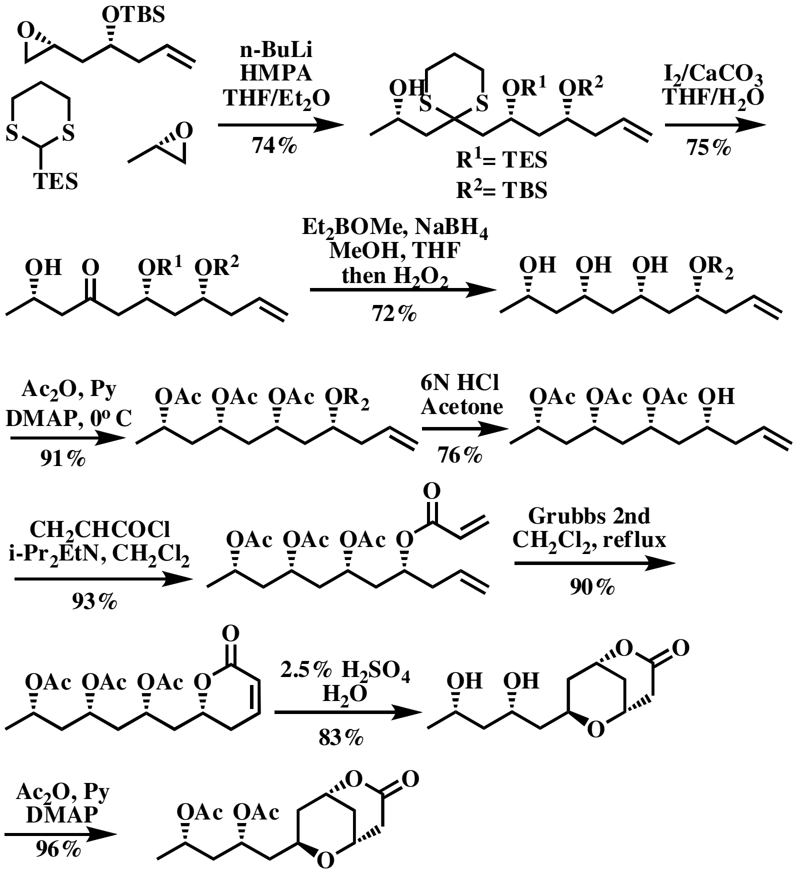
---

[73] Sam, T. W.; Yeu, C. S.; Jodynis-Liebert, J.; Murias, M.; Bloszyk, E. *Planta Med.* **2000**, *66*, 199.

[74] Zschocke, S.; van Staden, J. *J. Ethnopharmacol.* **2000**, *71*, 473.

3.2.1. Cryptocaryolone synthesis by She *et al.*[76]

This group used the linchpin strategy, tandem deacetylation and intramolecular oxa-Michael addition to complete the structure of this molecule (Scheme 30).


OTBS
TES
n-BuLi
HMPA
THF/Et₂O
74%
OH
OR¹ OR²
R¹= TES
R²= TBS
I₂/CaCO₃
THF/H₂O
75%
OH O OR¹ OR²
Et₂BOMe, NaBH₄
MeOH, THF
then H₂O₂
72%
OH OH OH OR₂
Ac₂O, Py
DMAP, 0° C
91%
OAc OAc OAc OR₂
6N HCl
Acetone
76%
OAc OAc OAc OH
CH₂CHCOCl
i-Pr₂EtN, CH₂Cl₂
93%
OAc OAc OAc O
Grubbs 2nd
CH₂Cl₂, reflux
90%
OAc OAc OAc O
2.5% H₂SO₄
H₂O
83%
OH OH
Ac₂O, Py
DMAP
96%
OAc OAc

Scheme 30. Synthesis of cryptocaryolone by She *et al.*

Multi component Linchpin strategy[77] was utilized to install the *syn* 1,3-polyols moiety followed by hydroxyl directed *syn* reduction. Subsequent acetylation and silyl

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[75] (a) Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem.* **2001**, *66*, 2512. (b) Ghosh, A. K.; Bilcer, G. *Tetrahedron Lett.* **2000**, *41*, 1003. (c) Boger, D. L.; Ichikawa, D.; Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4161. (d) Reddy, M. V. R.; Rearick, J. P.; Hoch, N.; Ramachandran, P. V. *Org. Lett.* **2001**, *3*, 19. (e) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777. (f) Garaas, S.; Hunter, T. J.; O'Doherty, G. A. *J. Org. Chem.* **2002**, *67*, 2682. (g) Gao, D.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 1069. (h) Kumar, P.; Gupta, P.; Naidu, S. G. *Chem. Eur. J.* **2006**, *12*, 1397. (i) Georges, Y.; Ariza, X.; Garcia, J. *J. Org. Chem.* **2009**, *74*, 2008. (j) Jorgensen, K. B.; Suenaga, T.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8855.

[76] Wang, X.; Wang, W.; Zheng, H.; Su, Y.; Jiang, T.; He, Y.; She, X. *Org. Lett.* **2009**, *11*, 3136.

deprotection followed by coupling with acrylyl chloride provided the intermediate to undergo olefin metathesis in the presence of Grubbs catalyst. Finally global deacylation with the presence of catalytic amount of H_2SO_4 in water was conveniently followed by oxa-Michael addition to provide the Cryptocaryolone. The acetate counterpart could be easily obtained through acylation of Cryptocaryolone with Ac_2O/Py.

3.2.2. Cryptocaryolone synthesis by O' Doherty *et al.*[78]

Their synthetic route relied on highly *(E)*-selective cross metathesis reaction of benzylidene protected 1,3-diols with acrylates to form trans-δ-hydroxyl-1-enoates followed by Still-Gennari[79] coupling to form the (*Z*)-product. Final transformation was carried out under acidic conditions that accomplished the target molecule synthesis efficiently (Scheme 31).

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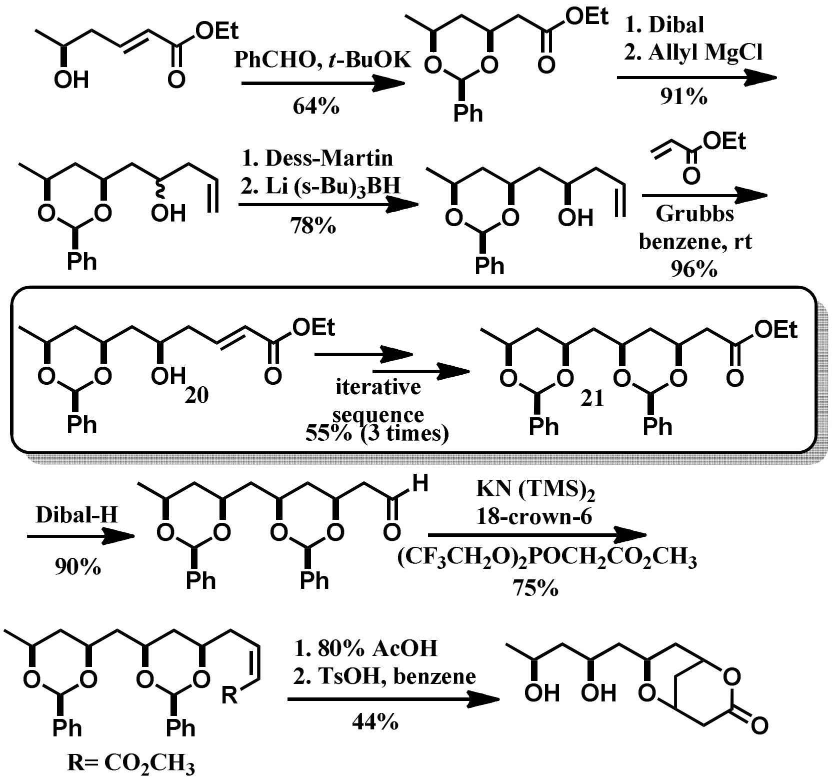
[77] (a) Tieze, L. F.; Gewert, J. A.; Jakobi, U. *Synlett* **1944**, 1. (b) Smith, A. B.; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365. (b) Smith, A. B.; Pitram, S. M.; Boldi, A. M.; Gaunt, M. J.; Sfouggatakis, C.; Moser, W. *J. Am. Chem. Soc.* **2003**, *125*, 14435. (c) Smith, A. B.; Xian, M. *J. Am. Chem. Soc.* **2006**, *128*, 66. (d) Smith, A. B.; Zhuang, L.; Brook, C. S.; Boldi, A. M.; McBriar, M. D.; Moser, W. H.; Murase, N.; Nakayama, K.; Verhoest, P. R.; Lin, Q. *Tetrahedron Lett.* **1997**, *38*, 8667. (e) Smith, A. B.; Zhuang, L.; Brook, C. S.; Lin, Q.; Moser, W. H.; Trout, R. E. L.; Boldi, A. M. *Tetrahedron Lett.* **1997**, *38*, 8671. (f) Smith, A. B.; Lin, Q.; Nakayama, K.; Boldi, A. M.; Brook, C. S.; McBriar, M. D.; Moser, W. H.; Sobukawa, M.; Zhuang, L. *Tetrahedron Lett.* **1997**, *38*, 8675. (g) Smith, A. B.; Pitram, S. M. *Org. Lett.* **1999**, *1*, 2001. (h) Smith, A. B.; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783. (i) Smith, A. B.; Pitram, S. M.; Fuertes, M. J., *Org. Lett.* **2003**, *5*, 2751. (j) Smith, A. B.; Kim, D. *Org. Lett.* **2004**, *6*, 1493.

[78] Smith, C. M.; O' Doherty, G. A. *Org. Lett.* **2003**, 5, 1959.

[79] Still, W. C.; Gennari, C. *Tetrahedron Lett*. **1983**, *24*, 4405.


PhCHO, t-BuOK
64%
1. Dibal
2. Allyl MgCl
91%
1. Dess-Martin
2. Li (s-Bu)3BH
78%
Grubbs
benzene, rt
96%
20
iterative
sequence
55% (3 times)
21
Dibal-H
90%
KN (TMS)2
18-crown-6
(CF3CH2O)2POCH2CO2CH3
75%
1. 80% AcOH
2. TsOH, benzene
44%
R= CO2CH3

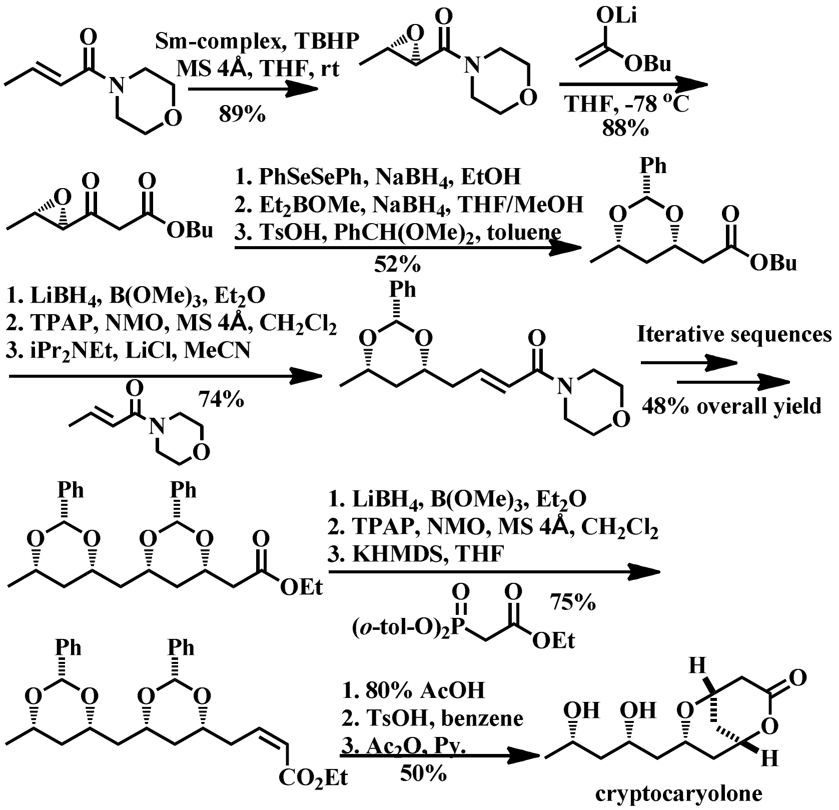
Scheme 31. Synthesis of cryptocaryolone by O' Doherty *et al.*

3.2.3. Cryptocaryolone synthesis by Shibasaki *et al.*[80]

They utilized their group's method to assemble the 1,3-polyols arrays based on catalyst-controlled epoxidation of α,β-unsaturated morpholinyl amides promoted by Sm-BINOL-$Ph_3As=O$ (1:1:1), followed by conversion of the morpholinyl amides to ketone and subsequent diastereoselective reduction. Iterative sequence allowed this methodology to construct the array of all possible 1,3-polyols (Scheme 32).

---

[80] Tosaki, S.Y.; Horiuchi, Y.; Nemoto, T.; Ohsima, T.; Shibashaki, M. *Chem. Eur. J.* **2004**, *10*, 1527.


Sm-complex, TBHP
MS 4Å, THF, rt
89%
OLi
OBu
THF, -78 °C
88%
1. PhSeSePh, NaBH4, EtOH
2. Et2BOMe, NaBH4, THF/MeOH
3. TsOH, PhCH(OMe)2, toluene
52%
1. LiBH4, B(OMe)3, Et2O
2. TPAP, NMO, MS 4Å, CH2Cl2
3. iPr2NEt, LiCl, MeCN
74%
Iterative sequences
48% overall yield
1. LiBH4, B(OMe)3, Et2O
2. TPAP, NMO, MS 4Å, CH2Cl2
3. KHMDS, THF
(o-tol-O)2P
OEt
75%
1. 80% AcOH
2. TsOH, benzene
3. Ac2O, Py.
50%
CO2Et
cryptocaryolone

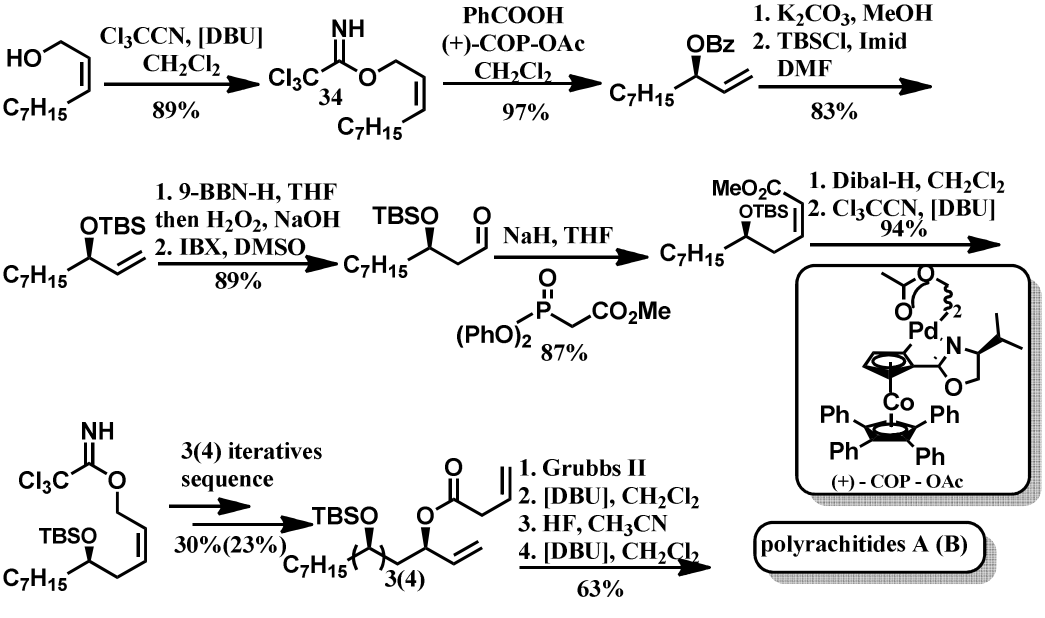
Scheme 32. Synthesis of cryptocaryolone by Shibashaki *et al.*

3.2.4. The first total synthesis of polyrachitides by Kirsch *et al.*[81]

Kirsch *et al.* used the iterative catalyst-controlled synthesis of 1,3-diols moiety that based on Overmann esterification to construct the 1,3-polyols fragment. Olefin metathesis was utilized to assemble the substituted pyrone moiety similar to the O' Doherty's approach. Global deprotection of the silyl group conveniently lead to the natural product *via* spontaneous oxa-Michael addition. Further stirring with DBU completed this target with good overall yield (Scheme 33).

---

[81] Menz, H.; Kirsch, S. F. *Org. Lett.* **2009**, *11*, 5634.


Cl$_3$CCN, [DBU]
CH$_2$Cl$_2$
89%
34
PhCOOH
(+)-COP-OAc
CH$_2$Cl$_2$
97%
1. K$_2$CO$_3$, MeOH
2. TBSCl, Imid
DMF
83%
1. 9-BBN-H, THF
then H$_2$O$_2$, NaOH
2. IBX, DMSO
89%
NaH, THF
87%
1. Dibal-H, CH$_2$Cl$_2$
2. Cl$_3$CCN, [DBU]
94%
(+) - COP - OAc
3(4) iteratives
sequence
30%(23%)
3(4)
1. Grubbs II
2. [DBU], CH$_2$Cl$_2$
3. HF, CH$_3$CN
4. [DBU], CH$_2$Cl$_2$
63%
polyrachitides A (B)

Scheme 33. Synthesis of polyrachitides by Kirsch *et al.*

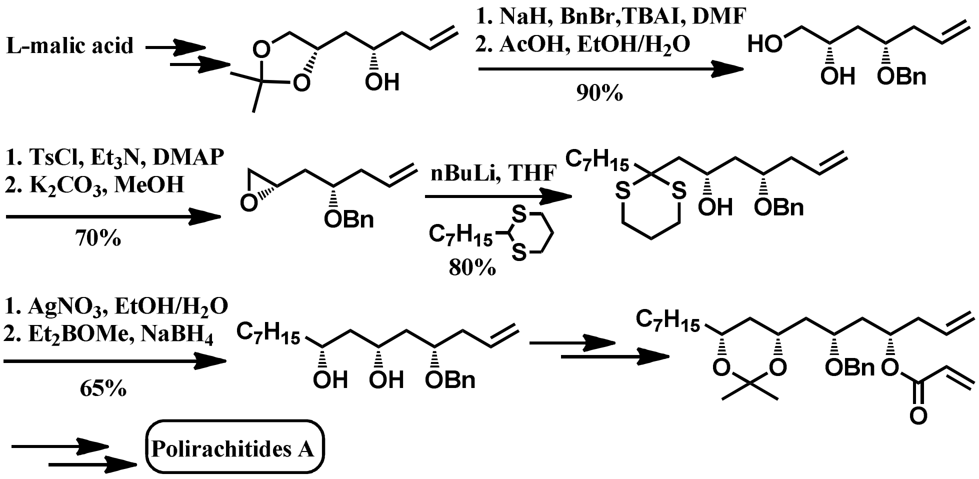
However, despite the successful effort of this synthesis in avoiding the use of stoichiometric amount of chiral reagent such as that of allylic boranes, the process required lengthy alterations of functional groups which were inefficient in terms of atom economy. Eight steps were required for each iteration process as compared to four steps that were required in allyboranes, allyltins or allyl titanium mediated processes.

3.2.5. Polyrachitide A synthesis by Ghosh *et al.*[82]

Ghosh and co worker accessed the synthesis of this compound from L-malic acid that provided the first chiral center. The key steps included chemoselective tosylation of the primary alcohol followed by tosyl displacement to form the epoxide which was then opened at less substituted carbon with anion generated from dithiane. Chain elongation was carried out by substrate-controlled allylation. Finally, the bicyclic lactone was constructed via oxa-Michael reaction that was discussed in previous synthesis (Scheme 34).

---

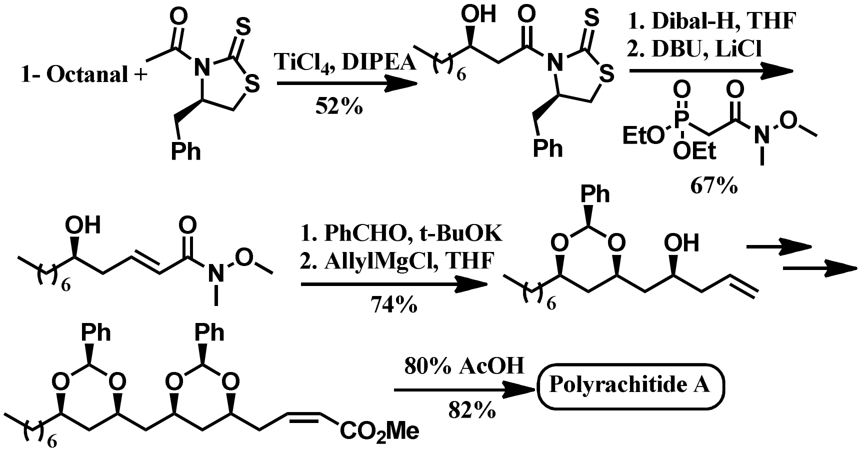
[82] Ghosh, S.; Rao, N. C. *Tetrahedron Lett.* **2010**, 2052.


L-malic acid
1. NaH, BnBr,TBAI, DMF
2. AcOH, EtOH/H2O
90%
1. TsCl, Et3N, DMAP
2. K2CO3, MeOH
70%
nBuLi, THF
80%
1. AgNO3, EtOH/H2O
2. Et2BOMe, NaBH4
65%
Polirachitides A

Scheme 34 Polyrachitide A synthesis by Ghosh *et al.*

3.2.6. Polyrachitide A synthesis by Yadav *et al.*[83]

The key reaction in their synthesis is the utility of asymmetric aldol reaction to establish initial asymmetry. Like previous work, completion of the synthesis was carried out by acid-mediated one-pot dibenzylidene acetal deprotection, lactonization and oxa-Michael reaction (Scheme 35).


1- Octanal +
TiCl4, DIPEA
52%
1. Dibal-H, THF
2. DBU, LiCl
67%
1. PhCHO, t-BuOK
2. AllylMgCl, THF
74%
80% AcOH
82%
Polyrachitide A

Scheme 35 Synthesis of polyrachitide A by Yadav *et al.*

---

[83] Yadav, J. S.; Rajendar, G.; Ganganna, B.; Srihari, P. *Tetrahedron Lett.* **2010**, 2154.

3.3. Total synthesis of Polyrachitide A

3.3.1. Synthesis of 1,3-polyols array *via* allylic camphor auxilary

1,3-Polyols arrays are very common in natural products, hence it is not surprising that numerous methods are developed to access this module. Some methods have been discussed in the previous synthesis of polyrachitides and cryptocaryolone. For many, the initial task to construct this architecture is to introduce the first stereogenic center, followed by elongation method to produce subsequent stereogenic centers. This architecture can also be approached from natural products such as sugar. Based on the structure relation between chiral source and the product, the method of constructing optically pure polyols moiety can be categorized into three approaches.

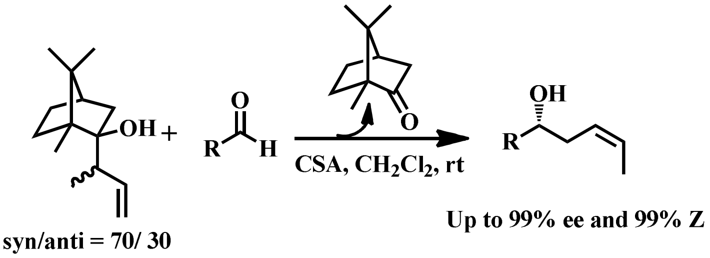
First, iterative allylation and oxidative cleavage involving chiral moiety such as chiral boron[84] or titanium[85] are reagents controlled. This method however is limited due to the need of stoichiometric amount of the chiral auxiliary. Other alternatives in constructing this array is substrate controlled synthesis, such as intramolecular addition of acetal to olefins,[86] hydrosilylation,[87] or intramolecular allylsilylation to carbonyl groups.[88] Compared to the two previously mentioned strategies, only limited number of catalyst controlled strategy has been reported.[89]

---

[84] Selected examples on iterative allylboration: (a) Garcıá, A. B.; Le_mann, T.; Umarye, J. D.; Mamane, V.; Sommer, S.; Waldmann, H. *Chem. Commun.* **2006**, 3868. (b) Umarye, J. D.; Le_mann, T.; Garcıá, A. B.; Mamane, V.; Sommer, S.; Waldmann, H. *Chem. Eur. J.* **2007**, *13*, 3305. (c) Schreiber, S. L.; Goulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8120. (d) Paterson, I.; Wallace, D. J.; Gibson, K. R. *Tetrahedron Lett.* **1997**, *38*, 8911. (e) Smith, A. B. III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942. (f) Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S.; Kole, K. P.; Yamaguchi, J. *J. Am. Chem. Soc.* **2007**, *129*, 1760. (g) Garcıá -Fortanet, J.; Murga, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2003**, *5*, 1447. (h) Murga, J.; Garcıá -Fortanet, J.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2004**, *69*, 7277. (i) Fuwa, H.; Naito, S.; Goto, T.; Sasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4737. (j) Nicolaou, K. C.; Kim, D. W.; Baati, R.; O'Brate, A.; Giannakakou, P. *Chem. Eur. J.* **2003**, *9*, 6177. (k) Paterson, I.; Coster, M. J.; Chen, D. Y.-K.; Gibson, K. R.; Wallace, D. J. *Org. Biomol. Chem.* **2005**, *3*, 2410. (l) Dreher, S. D.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 341. (m) Barrett, A. G. M.; Braddock, D. C.; de Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375. (n) Schneider, C.; Rehfeuter, M. *Chem. Eur. J.* **1999**, *5*, 2850. (o) Hoffmann, R. W.; Stürmer, R. *Synlett* **1990**, 759.

[85] Selected examples on iterative allyltitanation : (a) BouzBouz S.; Cossy, J. *Org. Lett.* **2000**, *2*, 501. (b) BouzBouz, S.; Cossy, J. *Org. Lett.* **2004**, *6*, 3469. (c) Allais, F.; Louvel, M.-C.; Cossy, J. *Synlett* **2007**, 451. (d) Amans, D.; Bellosta, V.; Cossy, J. *Org. Lett.* **2007**, *9*, 1453. (e) Ferriè, L.; Boulard, L.; Pradaux, F.; BouzBouz, S.; Reymond, S.; Capdevielle, P.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 1864. (f) Allais, F.; Cossy, J. *Org. Lett.* **2006**, *8*, 3655. (g) BouzBouz, S.; Cossy, J. *Tetrahedron Lett.* **2000**, *41*, 3363. (h) Knochel, P.; Brieden, W.; Rozema, M. J.; Eisenberg, C. *Tetrahedron Lett.* **1993**, *34*, 5881.

Our group had observed that chiral branched homoallylic sterols successfully transferred their chirality and allyl species to other aldehydes.[90] This showed that an asymmetric steric environment can drive the stereoselective formation of linear homoallylic alcohol. Then, the unusual approach to the synthesis of enantiomerically *cis* linear homoallylic alcohols based on the steric interaction mechanism of camphor scaffold was developed as shown in Scheme 36.[91]



Scheme 36. Crotyl transfer reaction

---

[86] (a) Evans, D. A. ; Gaucht-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446. (b) Miyazawa, M.; Matsuoka, E. ; Sasaki, S.; Oonuma, S.; Maruyama, K. ; Miyashita, M. *Chem. Lett.* **1998**, 56 (c) Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2,* 403.

[87] (a) Y. Ito; Suginome, M. *Pure Appl. Chem.* **1996**, *68*, 505. (b) Shneider, C.; Rehfeuter, M. *Chem. Eur. J.* **1999**, *5*, 2850.(c) O'Malley, S. J.; Leighton, J. L. *Angew. Chem.* **2001**, *113*, 2999; *Angew. Chem. Int. Ed.* **2001**, *40*, 2915. (d) Shneider, C.; Tolksdorf, F.; Rehfeuter, M. *Synlett* **2002**, *12,* 2098. (e) Powell, S. A.; Tenenbaum, J. M.; Woerpel, K. *J. Am. Chem. Soc.* **2002**, *124*, 12 648.

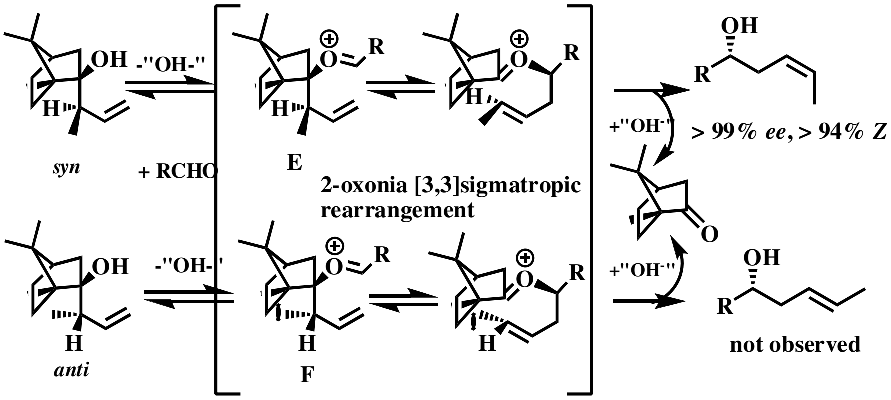
[88] Zacuto, M. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 8587.

[89] (a) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. S. *Angew. Chem., Int. Ed.* **1985**, *24*, 1.(b) Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5018. (c) Hassan, A.; Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3112. (d) Zhang, Z.; Aubry, S.; Kishi, Y. *Org. Lett.* **2008**, *10*, 3077. Kondekar, N. B.; Kumar, P. *Org. Lett.* **2009**, *11*, 2611. (e) Tosaki, S.; Horiuchi, Y.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Chem. Eur. J.* **2004**, *10*, 1527. (f) Gerber-Lemaire, S.; Vogel, P. *Eur. J. Org. Chem.* **2003**, 2959. (g) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2002**, *124*, 8188. (h) Ma, P.; Martin, S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378. (i) Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2005**, *127*, 2866. (j) Binder, J. T.; Kirsch, S. F. *Chem. Commun.* **2007**, 4164. (k) Anderson, C. E.; Kirsch, S. F.; Overman, L. E.; Richards, C. J.; Watson, M. P. *Org. Synth.* **2007**, *84*, 148. (l) Stevens, A. M.; Richards, C. J. *Organometallics* **1999**, *18*, 1346.

[90] Loh, T. P.; Hu, Q. Y.; Chok, Y. K.; Tan, K. T. *Tetrahedron Lett.* **2001**, *42*, 9277.

[91] Loh, T.P.; Lee, C.L.K.; Tan, K.T. *Org. Lett.* **2002**, *4*, 2985.

The proposed mechanism that gave the high selectivity was proposed as shown in Scheme 37.



Scheme 37. Mechanism that account for *Z* homoallylic alcohol

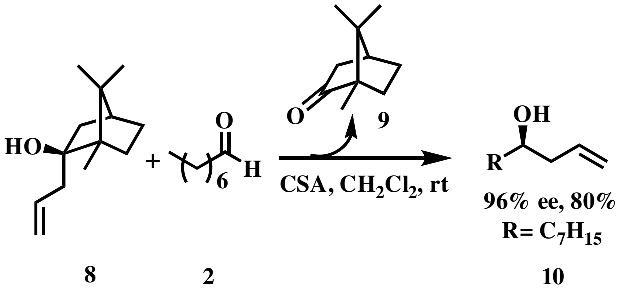
The branched homoallylic alcohol probably formed oxo-carbenium-type ions with aldehyde catalyzed by acid catalyst, revealing two possible transition states. The *anti* branched homoallylic alcohol would most likely adopt a transition state similar to that of **F**, based on Zimmerman-Traxler six membered ring transition state.[92] It was evident that the methyl group from *anti* isomer will develop steric repulsion with C-6 of the camphor scaffold, which explains why the *trans*-linear isomer was not observed at all. On the other hand, transition state **E** showed that the *syn* isomer's methyl group was fixed in a manner where it avoided any close contacts with the camphor's methylene protons before undergoing the rearrangement to furnish the thermodynamically preferred linear regioisomer products.

From the mechanism in Scheme 37, it could be seen that the origin of *Z* selectivity in the homoallylic alcohol product was determined by the *syn* configuration of the substituent on the alkene.

---

[92] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

In the case of polyrachitides, we prepared an allyl camphor auxiliary and to our delight the allyl transfer reaction occurred with high enantiomeric excess (96% *ee*, determined after protection of OH group with UV active protecting group such as Benzyl or TBDPS). We used (-)-*S*-camphor to obtain the desired stereochemistry of the product. Hence we had demonstrated the versatility of this method for allylation to obtain both *R* and *S* stereocenters in high enantioselectivity. The camphor moiety could be recovered and reused (Scheme 38).

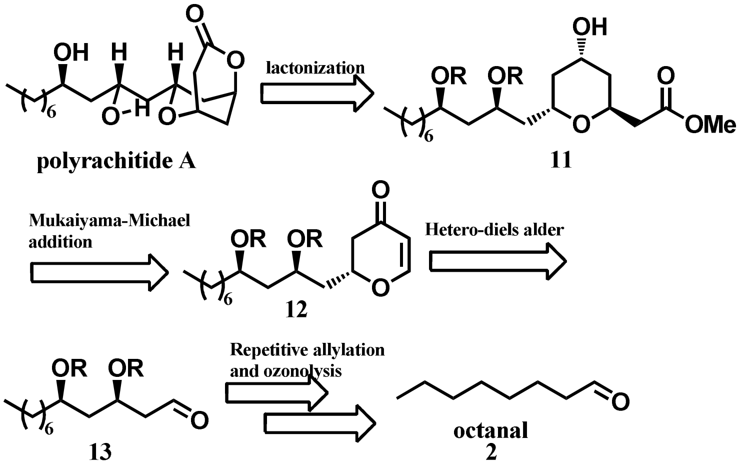


Scheme 38. Allyl transfer catalyzed by CSA

In this chapter, we would like to apply this methodology to install the allylic moiety that will undergo oxidative cleavage followed by the next allylation sequence to afford the intermediate in the synthesis of this natural product.

3.3.2. Retrosynthetic analysis

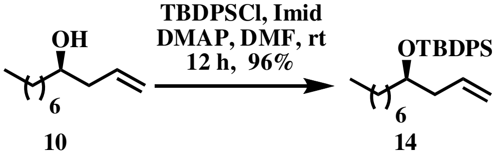
We planned to access the molecules *via* lactonization of carboxylic moiety which can be accessed from our *anti*-selective Mukaiyama-Michael addition of silyl enol ether to pyrone (Chapter 2). The pyrone entity can be formed through chromium-complex catalyzed hetero Diels-Alder reaction of aldehyde **13**. Finally, the polyols moiety could be accessed from our developed camphor derived allylic moiety. Retrosynthetic analysis of polyrachitide A is shown in Scheme 39.


polyrachitide A
lactonization
11
Mukaiyama-Michael addition
12
Hetero-diels alder
13
Repetitive allylation and ozonolysis
octanal
2

Scheme 39. Retrosynthetic analysis of polyrachitide A

3.3.3. Synthetic efforts

We embarked on the synthesis by installing the hydroxyl group using the camphor-derived method followed by TBDPS protection. The reaction proceeded with high yield and selectivity (80% yield, 96% *ee*) and it was feasible to scale up the reaction and recover the camphor moiety (Scheme 40).

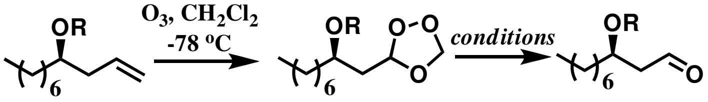

TBDPSCl, Imid
DMAP, DMF, rt
12 h, 96%
10
14

Scheme 40. Synthesis of protected homoallylic alcohol 14

Oxidative cleavage was accomplished by employing ozonolysis. Surprisingly, after treatment with dimethyl sulfide, we isolated mostly the stable ozonide intermediate with only trace amount of aldehyde product. This observation was reported earlier[93] and probably due to the long chain alkyl moiety of the compound that stabilized the ozonide and prevented the cleavage to give the aldehyde product.[94]

---

[93] For example in Nicolaou's total synthesis of Everninomicin: Nicolaou, K.C.; Mitchel, H.C.; Suzuki, H.; Rodriguez, R.M.; Baudoin, O.; Fylaktakidau, K.C. *Angew. Chem.* **1999**, *111*, 3523; *Angew. Chem. Int. ed.* **1999**, *38*, 3334.



R= TBDPS R= TBDPS

14 **15** **16**

Conditions	Observation
DMS (2 equiv.), rt	Mostly ozonide isolated
DMS (2 equiv.), PPh_3 (20 equiv.), rt	Partial convertion after 24 h and difficult separation of product and PPh_3
Zn (2 equiv.), AcOH (2 drops), rt	Partial conversion after 24 h
Zn (2 equiv.), AcOH (2 drops), Δ, 2 h	Complete conversion to aldehyde

Table 2. Conditions for oxidative cleavage

We failed to obtain full conversion after treatment with triphenylphosphine either. Furthermore, the product was non-polar, thus rendering its separation from triphenyl phosphine that was added in excess difficult. We then found the optimum condition of refluxing with zinc in the presence of two drops of AcOH (Table 2). It was also interesting to note that aldehyde **16** gave a distinct smell that was characteristic to insect pheromone such as the one secreted in rice bugs *Leptocorisa oratorius*.[95]

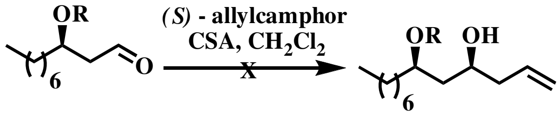
However, when we subjected aldehyde **16** to the next allyl camphor moiety under CSA catalyst, we did not obtain the product and the TLC was quite messy. From the crude NMR we observed the formation of some enone which suggested that silyl protecting group was not able to withstand the highly concentrated acidic medium

---

[94] Mayr, H.; Baran, J.; Will, E.; Yamakoshi, H.; Teshima, K.; Nojima, M. *J. Org. Chem.* **1994**, *59*, 5055.

[95] Gunawardena, N. E.; Bandumathie, M.K. *J. Chem. Eco.* **1993**, *19*, 851.

(0.1 equivalent of CSA at 6 M concentration) and the prolonged stirring of 5 days (Scheme 41).



16: R= TBDPS
17: R= Bn

18: R= TBDPS
19: R= Bn

Scheme 41. Attempt at iterative allyl transfer

However, benzyl protected aldehyde **17**, which we expected to withstand the acidic condition, did not give the required product as well. Upon scale up, the yield dropped tremendously with the formation of the conjugated double bond again as can be seen from the crude NMR. We attempted to decrease the concentration and reaction time, as well as catalyst loading which did not provide promising result.

We thought that addition of MeOH would form the acetal of the aldehyde **17**, which would be more reactive, and hence could shorten the reaction time. We carried out the reaction and compared with the control reaction upon stirring for 3 days but again we observed the formation of conjugated double bond and only trace amount of the product. The yield and selectivity of the reaction were similar with or without addition of methanol. Hence, we assumed that our method was not applicable to β-hydroxy aldehyde due to decomposition of the starting material.

Next, we resorted to the established method to install the subsequent hydroxyl moiety by using allylic borane chemistry[96] followed by oxidative cleavage employing ozonolysis. This step provided aldehyde **13** as starting material for hetero Diels-Alder reaction (Scheme 42).

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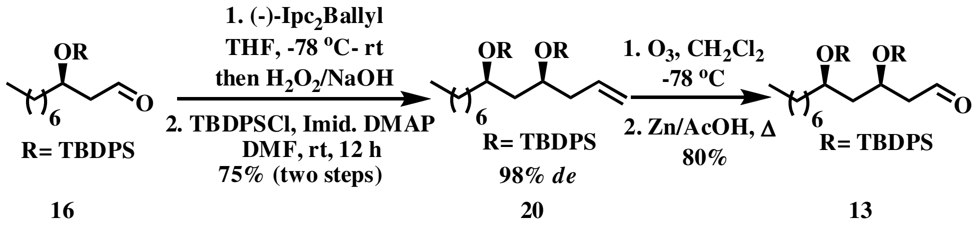
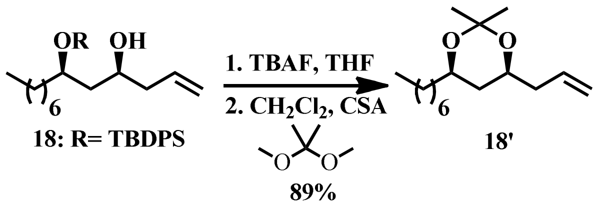
[96] Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.


OR
6
R= TBDPS
16
1. (-)-Ipc$_2$Ballyl
THF, -78 °C- rt
then H$_2$O$_2$/NaOH
2. TBDPSCl, Imid. DMAP
DMF, rt, 12 h
75% (two steps)
OR OR
6
R= TBDPS
98% *de*
20
1. O$_3$, CH$_2$Cl$_2$
-78 °C
2. Zn/AcOH, Δ
80%
OR OR
6
O
R= TBDPS
13

Scheme 42. Synthesis of aldehyde 13

The stereochemistry of the Brown allylation product **18** was established by protecting small amount of the polyhydroxyl group as acetonide 18'. The stereochemistry of the product is apparent from the chemical shifts of the methyl group in the ^{13}C spectrum as reported by Rychnovsky[97] (Scheme 43).

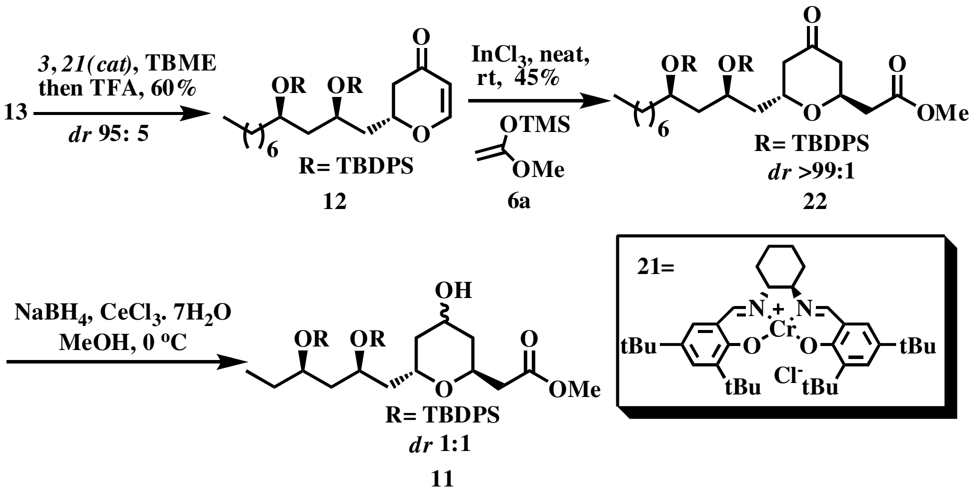

OR OH
6
18: R= TBDPS
1. TBAF, THF
2. CH$_2$Cl$_2$, CSA
O O
89%
O O
6
18'

Scheme 43 Confirmation of the *syn* configuration

The first lactone was introduced by hetero Diels-Alder reaction using Jacobsen catalyst **21**[98] to afford lactone **12** (yield 60%, *dr* 95:5). Next, we applied the InCl$_3$-catalyzed Mukaiyama-Michael[99] addition to give compound **9** with the desired *anti* configuration in good yield as a single isomer (yield 63%, *dr* > 99:1). The anti-configuration was confirmed by NOESY analysis. Treatment with sodium borohydride reduced the ketone according to Luche procedure[100] providing us with compound **11**, albeit with poor diastereoselectivity (*dr* 50:50) (Scheme 44). Nonetheless, based on structural analysis, only one of these isomer would cyclize to form the bicyclic lactone ring.

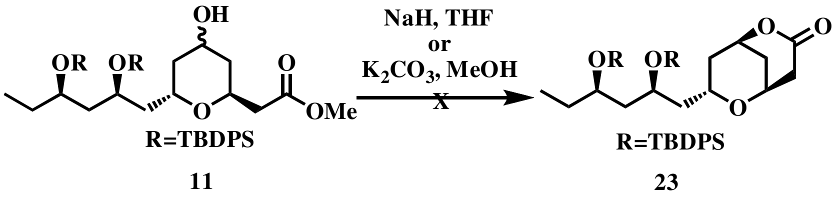
---

[97] Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945.
[98] Jacobsen, E. N.; Dosetter, A. G.; Jamison, T. F. *Angew. Chem. Int. Ed.* **1999**, *38*, 2398.
[99] Refer to chapter 2 of this thesis
[100] Luche, J.L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.


13
3, 21(cat), TBME
then TFA, 60%
dr 95: 5
OR OR
O
O
6
R= TBDPS
12
InCl3, neat,
rt, 45%
OTMS
OMe
6a
OR OR
O
O
O
OMe
6
R= TBDPS
dr >99:1
22
NaBH4, CeCl3. 7H2O
MeOH, 0 °C
OH
OR OR
O
O
OMe
R= TBDPS
dr 1:1
11
21=
N
N
Cr
O
O
tBu
tBu
tBu
tBu
Cl-

Scheme 44. Formation of alcohol 11

We initially sought to perform the cyclization following Brabander's method[101] in the synthesis of apicularen A. However, the reaction with sodium hydride got into complication probably due to migration or cleavage of the silyl protecting group that lead to formation of many possible products. Other basic conditions such as K_2CO_3 in methanol did not work as well (Scheme 45).


OH
OR OR
O
O
OMe
R=TBDPS
11
NaH, THF
or
K2CO3, MeOH
X
OR OR
O
O
O
R=TBDPS
23

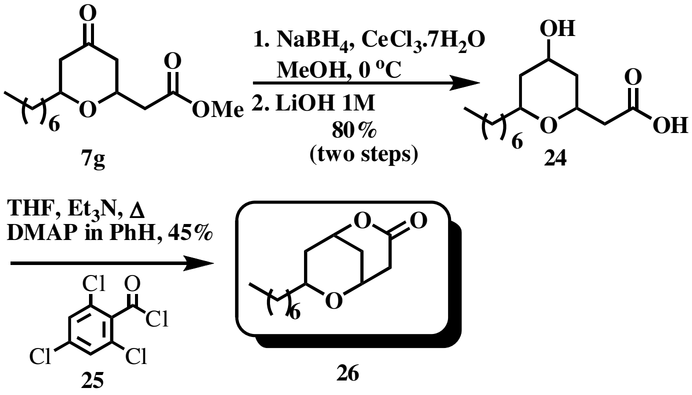
Scheme 45. Attempt to form bicyclic lactone

---

[101] Bhattacharjee, A.; De Brabander, J. K. *Tetrahedron Lett.* **2000**, *41*, 8069.

Hence we resorted to hydrolyze the ester moiety to an acid using LiOH and hoped that it would cyclize to form our target bicyclic lactone. However, we did not observe the formation of bicyclic lactone.

Plummer *et al.*[102] had reported that they obtained the six-membered bilactone as their side product when they performed Yamaguchi procedure to form the macrolactone ring. We then carried out a model reaction by using our previously prepared Mukaiyama-Michael product **7g** and tested out cyclization reaction. To our delight, we managed to get the bicyclic lactone product in good yield (Scheme 46).

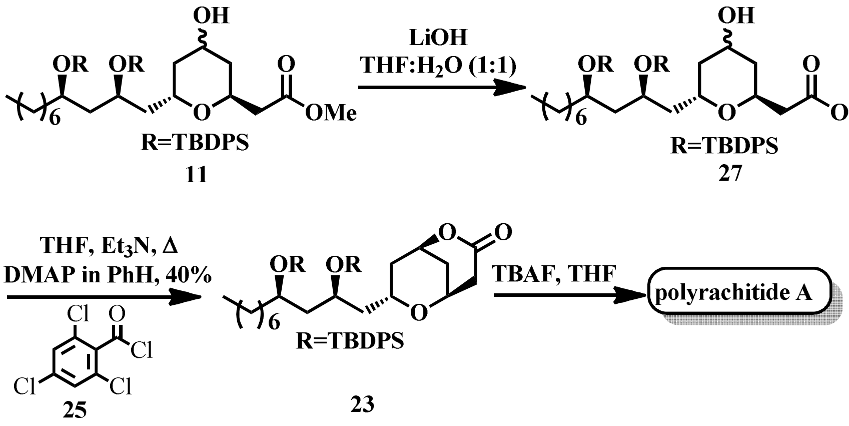

O
O
OMe
6
O
7g
1. NaBH4, CeCl3.7H2O
MeOH, 0 °C
2. LiOH 1M
80%
(two steps)
OH
O
OH
6
O
24
THF, Et3N, Δ
DMAP in PhH, 45%
Cl
O
Cl
Cl
Cl
25
O
O
6
O
26

Scheme 46. Formation of bicyclic lactone on model compound

This reaction worked as expected on the polyrachitides substrate **27** and provided us with the protected bicyclic lactone which upon complete deprotection would provide the natural product polyrachitide A (Scheme 47).

---

[102] Williams, D. R.; Patnaik, S.; Plummer, S. V. *Org. Lett.* **2003**, *5*, 5035.


OH
OR OR
O
OMe
6
R=TBDPS
11
LiOH
THF:H2O (1:1)
OH
OR OR
O
OH
6
R=TBDPS
27
THF, Et3N, Δ
DMAP in PhH, 40%
Cl O
Cl
Cl
Cl
25
OR OR
O
O
6
R=TBDPS
23
TBAF, THF
polyrachitide A

Scheme 47. Completion of synthesis

However, due to the small amount of the protected product **23** , upon deprotection we were not able to fully characterize the natural product Polyrachitide A. The formation of the natural product Polyrachitide A could be observed by HRMS and crude NMR. Completion of the synthesis and full characterization are currently being carried out in our group and will be reported in due course.

3.4. Conclusion

We have demonstrated the versatility of our group methodologies in the efforts to synthesize polyrachitide A. The first hydroxyl group was installed by camphor-assisted allyl transfer reaction. Mukaiyama-Michael addition reaction under neat condition was utilized to construct the 2,6-*anti*-pyran moiety. Finally, we have demonstrated the ability of Yamaguchi lactonization in the formation of a small and constrained ring.

Chapter 4

Synthetic study towards apicularen A

4.1. Introduction to apicularen A[103]

Apicularen A was isolated as a secondary metabolite from myxobacterium *Chrondromyces* sp. in 1998.[104] Its absolute and relative stereochemistries were determined later by the same group in 2000.[105] This biologically active molecule soon attracted the scientific community because of its high cytotoxicity and potent antitumor activity against nine human cancer cell lines with IC_{50} ~0.1-3 ng/mL. It even displays activity against multi-drugs-resistant KB-VI (IC_{50} ~0.4 ng/mL). The mode of action was demonstrated to occur through selective inhibition of the mammalian V-ATPase that is related to regulation of intracellular pH.[106]

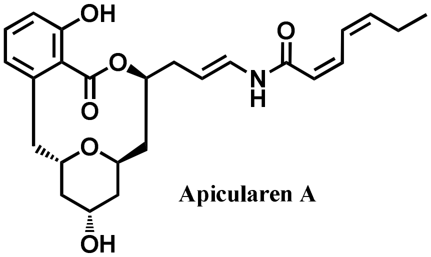


Figure 7 Structure of apicularen A

Apicularen A induced apoptosis by initiating binding of the CD95 ligand to the CD95 receptor, this stimulated receptor clustering and the formation of death-inducing signaling complexes which resulted in caspase-8 activation in a mitochondria-controlled manner. Apicularen A also induced microtubular network disruption by lowering the rate of tubulin synthesis. Microtubules were polymers which showed important roles in many cellular functions, the most important being their role in mitosis, an extremely important cellular function which was crucial survival of cells.

---

[103] This work was done in collaboration with Chan Li Ting, Jocelyn.

[104] Kunze, B.; Jansen, R.; Sasse, F.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075.

[105] Jansen, R.; Kunze, B.; Reichenbach, H.; Hofle, G. *Eur. J. Org. Chem.* **2000**, *6*, 913.

[106] Boyd, M.R.; Farina, C.; Belfiore, P.; Gagliardi, S.; Kim, J. W.; Hayakawa, Y.; Beutler, J. A.; McKee, T. C.; Bowman, B. J.; Bowman, E. J. *J. pharmacol. Exp. Ther.* **2001***, 297*, 114.

In vivo study using mice revealed that during a 15 days period of application, cancerous tumors inserted into the colon shrunk by up to 72%. The study also found that Apicularen A reduced colonisation of the liver by up to 95% when injecting 50 μg per Kg per day.

Apart from its outstanding activity, apicularen A had also attracted synthetic chemist with its interesting chemical structure. It belonged to the benzolactone enamide family of compounds which comprised of a ten-membered macrolide ring that included a salicylic acid residue and a bridging oxygen atom forming a tetrahydropyran residue. In addition, the macrocycle carried a multi-unsaturated chain consisting of an acylenamine moiety and a (*Z,Z*)-diene system. There were four stereogenic centres in the macrocycle of which three resided on a 2,6-*trans*-THP ring (Figure 7).

4.2. Previous synthesis towards apicularen A

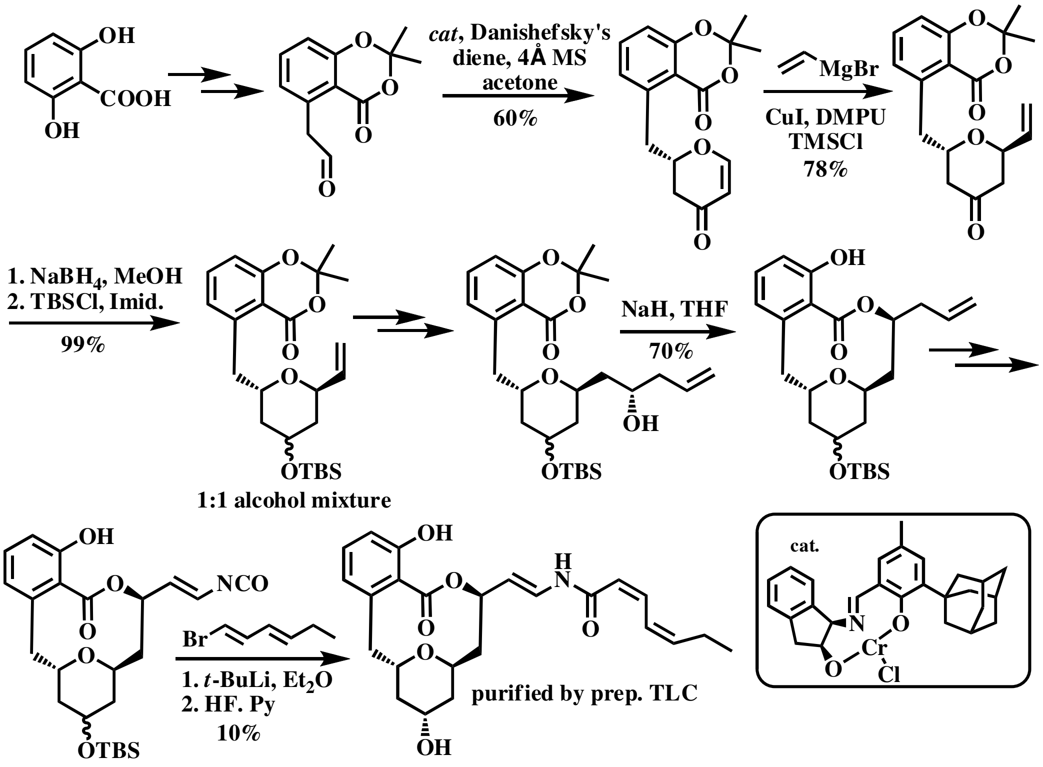
Many groups have reported the total or formal syntheses of apicularen A, among which some are described below.

4.2.1. De Brabander's Approach

The first enantioselective total synthesis of apicularen A was achieved by De Brabander and co-workers.[107] The key steps included a hetero Diels-Alder reaction catalysed by Jacobsen's chiral chromium complex, a base induced macrolactonisation and a coupling reaction involving an isocyanate and diene side chain (Scheme 48).

---

[107] (a) Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett.* **2001**, *42*, 1217. (b) Bhattacharjee, A.; De Brabander, J. K. *Tetrahedron Lett.* **2000**, *41*, 8069.

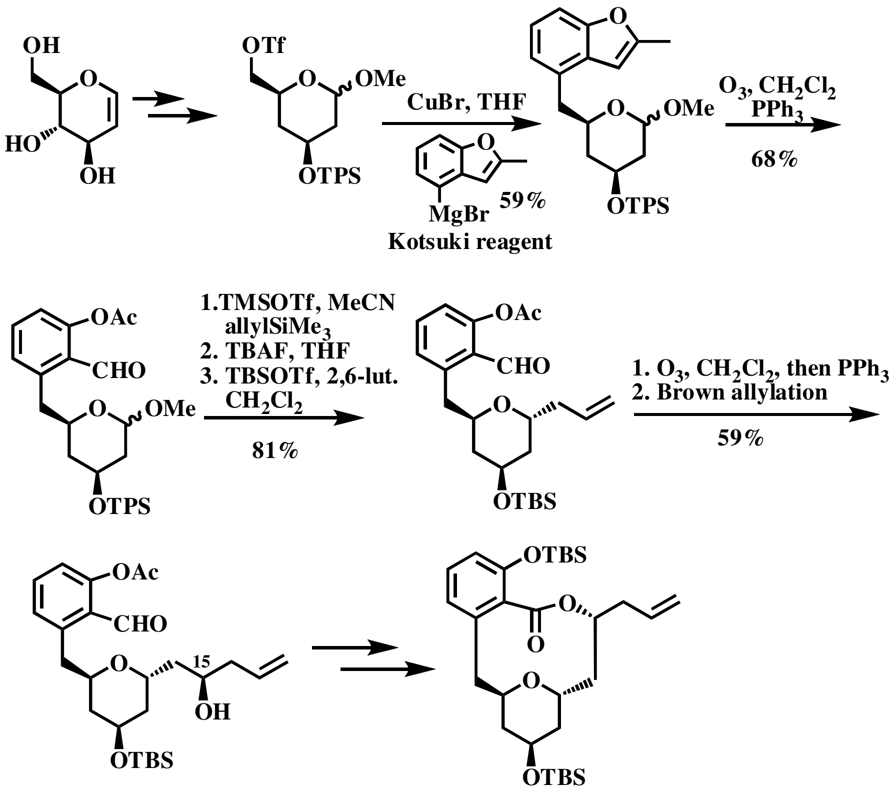

OH
COOH
OH
cat, Danishefsky's diene, 4Å MS acetone
60%
MgBr
CuI, DMPU
TMSCl
78%
1. NaBH4, MeOH
2. TBSCl, Imid.
99%
OTBS
1:1 alcohol mixture
NaH, THF
70%
Br
1. t-BuLi, Et2O
2. HF. Py
10%
NCO
purified by prep. TLC
cat.
N
O
Cr
Cl

Scheme 48. De Brabander's synthetic route

Their group also synthesized some analogues during the synthesis and concluded that the *N*-acyl enamine functionality might be responsible for the bioactivity. One disadvantage of their synthetic strategy was that they were unable to obtain the correct stereochemistry of alcohol with $NaBH_4$ reduction and thus they had to work with a 1:1 alcohol mixture. Preparative TLC was used to separate the diastereomers at the late stage which might not be feasible for large scale synthesis.

4.2.2 Taylor's Approach

Starting from a chiral D-glucal providing half the required chiral centres, Taylor and co-workers[108] achieved a formal synthesis of the molecule by using an organometallic displacement reaction at C-6 carbohydrate triflate with Knochel type and related functionalized, aromatic Grignard reagents (Scheme 49).



OH
HO
OH
OTf
OMe
OTPS
CuBr, THF
MgBr
59%
Kotsuki reagent
OMe
OTPS
O$_3$, CH$_2$Cl$_2$
PPh$_3$
68%
OAc
CHO
OMe
OTPS
1.TMSOTf, MeCN allylSiMe$_3$
2. TBAF, THF
3. TBSOTf, 2,6-lut. CH$_2$Cl$_2$
81%
OAc
CHO
OTBS
1. O$_3$, CH$_2$Cl$_2$, then PPh$_3$
2. Brown allylation
59%
OAc
CHO
15
OH
OTBS
OTBS
O
OTBS

Scheme 49.Taylor's synthetic route

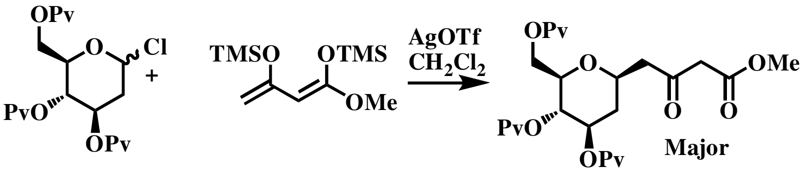
They first tried to perform a Grignard reaction on the sugar using a benzyl Grignard reagent. However, the desired product was not obtained. They then turned to the Kotsuki's reagent[109] which was a salicylate equivalent to give the desired product.

---

[108] (a) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Org. Biomol. Chem.* **2003**, *1,* 104. (b) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2001**, *42*, 5549.

[109] Kotsuki, H.; Araki, T.; Miyazaki, A.; Iwasaki, M.; Datta, P. K. *Org. Lett.* **1999**, *1*, 499.

Taylor's group proceeded to explore installation of the 2,6-*trans*-THP ring using either a silyl enol ether or an allyltrimethylsilane nucleophile. The nucleophilic substitution involving the silyl enol ether did not proceed as expected due to two main problems. The reaction was not regioselective and they were also unstable to the coupling conditions in the latter steps. An interesting result that emerged from the studies was the formation of the *syn* product as shown in Scheme 50.



Scheme 50. Unusual *syn*-THP ring

They then turned to the allyltrimethylsilane moiety. They succeeded in the formation of the α-anomer only to encounter a problem with the stereoselective allylation to install the chiral centre at C-15. Through optimization, they decided to apply Brown's allylation to achieve a good diastereoselectivity of 90: 10 in favour of the desired isomer. The key macrolactonisation step was finally established using the DCC-DMAP procedure.

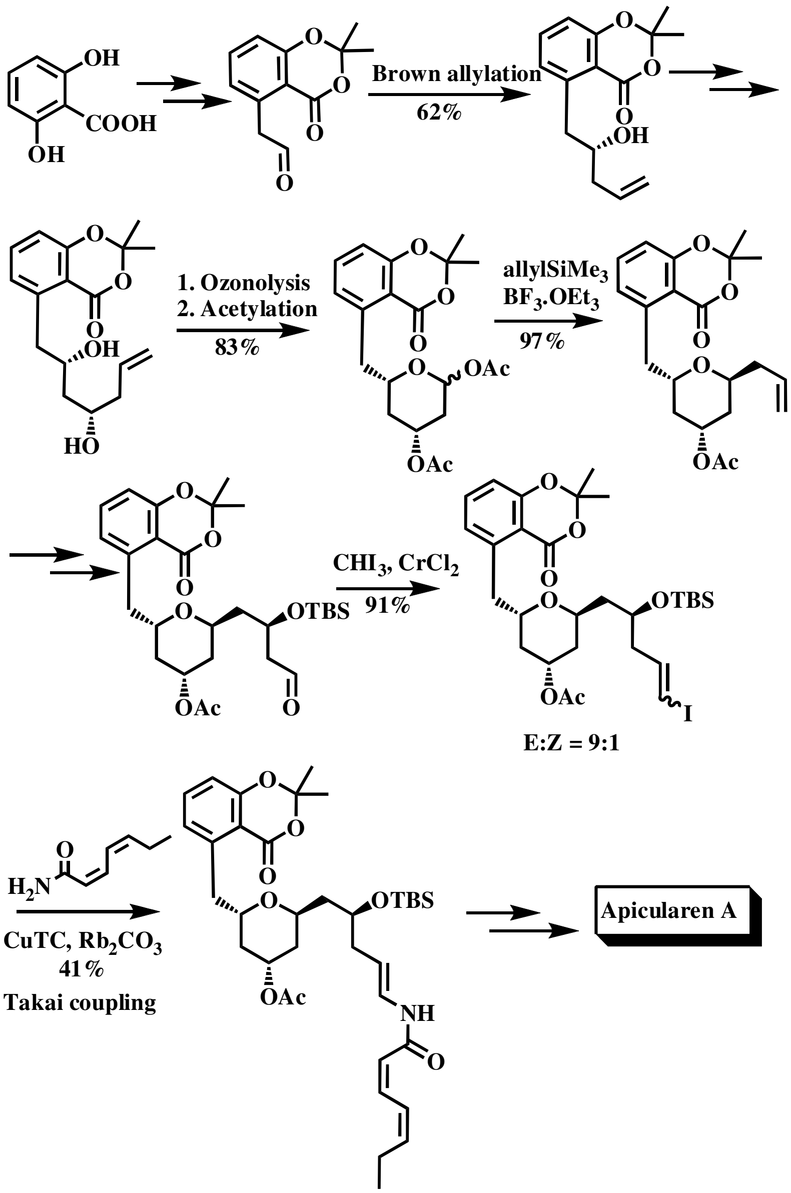
4.2.3. Nicolaou's Approach

Nicolaou's group approached the apicularen A synthesis using a biomimetic method by addition of acetate-like fragments through repetitive allylation and ozonolysis.[110] Their first attempt to attach the enamide chain to the macrolactone *via* the CuTC (copper(I) thiophenecarboxylate) mediated route[111] failed for unknown reasons. After a few unsuccessful attempts to install the side chains moiety, they revisited the CuTC method and upon modification employing an open chain vinyl iodide instead of a cyclic module they managed to obtain the desired product that eventually led to natural products as well as $\Delta^{17,18}$ *Z* isomer (Scheme 51).

---

[110] (a) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 3701. (b) Nicolaou, K. C.; Kim, D. W.; Baati, R.; O' Brate, A.; Giannakakou, P. *Chem. Eur. J.* **2003**, *9*, 6177.

[111] Shen, R; Porco Jr, J. A. *Org. Lett.* **2000**, *2*, 1333.


Brown allylation
62%
1. Ozonolysis
2. Acetylation
83%
allylSiMe$_3$
BF$_3$.OEt$_3$
97%
CHI$_3$, CrCl$_2$
91%
E:Z = 9:1
CuTC, Rb$_2$CO$_3$
41%
Takai coupling
Apicularen A

Scheme 51. Nicolaou's final synthetic route

Nicolaou's group also performed biological tests with some analogues from which they drew the following conclusions. First, the hydroxyl functionality on the THP ring is important for the cytotoxic activity of apicularen A. Second, the geometric arrangement of the enamide side chain affects the activity to a certain extent. Finally, some significant activity was observed in open chain systems that might allow the synthesis of simpler molecules that mimic the activity of apicularen A.

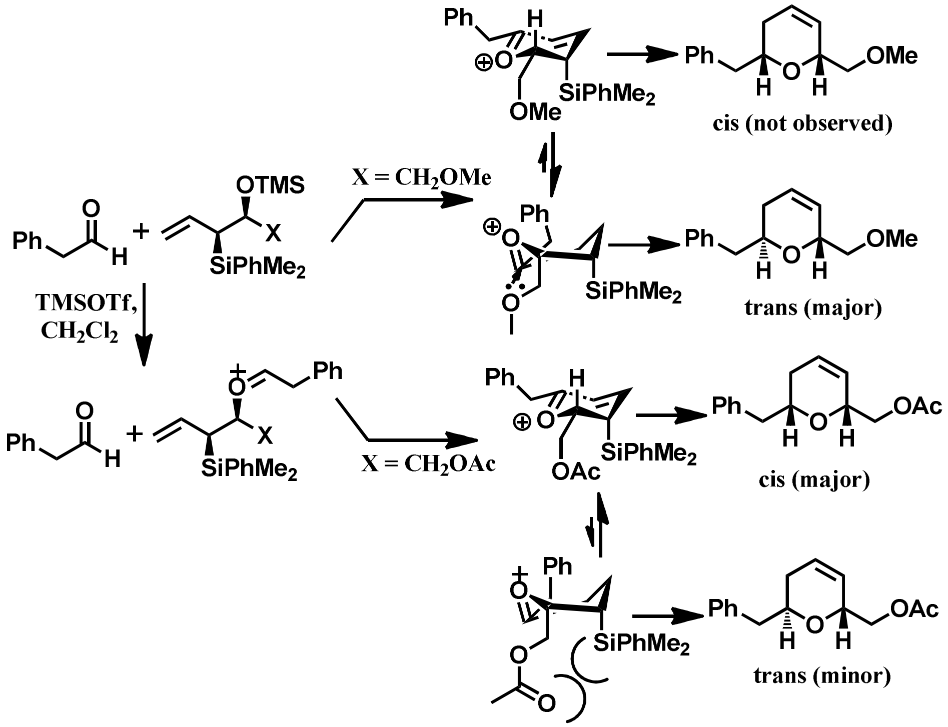
4.2.4. Panek's Approach

Panek and co-worker worked towards the synthesis of apicularen A[112] with the key step of forming the 2,6,-*anti* THP ring which involved a [4+2] annulation between chiral silanes and aldehydes. Contrary to previous results[24] that the stereochemical course of annulation is dependent on the relative stereochemical arrangement (*syn* or *anti*) of the silicon and adjacent silyl ether of the crotylsilane, Panek and co-worker found that the diastereoselectivity of the annulation depends largely on the nature of functional group **X** associated with the organosilanes (Scheme 52).

In order to achieve an effective σ-π orbital overlap for the stabilization of the carbocation, the silicon group is either placed in a pseudoaxial orientation in a twist boat like transition state or an axial position in a chair conformation. They discovered that chiral organosilanes with **X** as a methoxy group gave very high diastereoselectivities in favour of the desired *anti* THP rings.

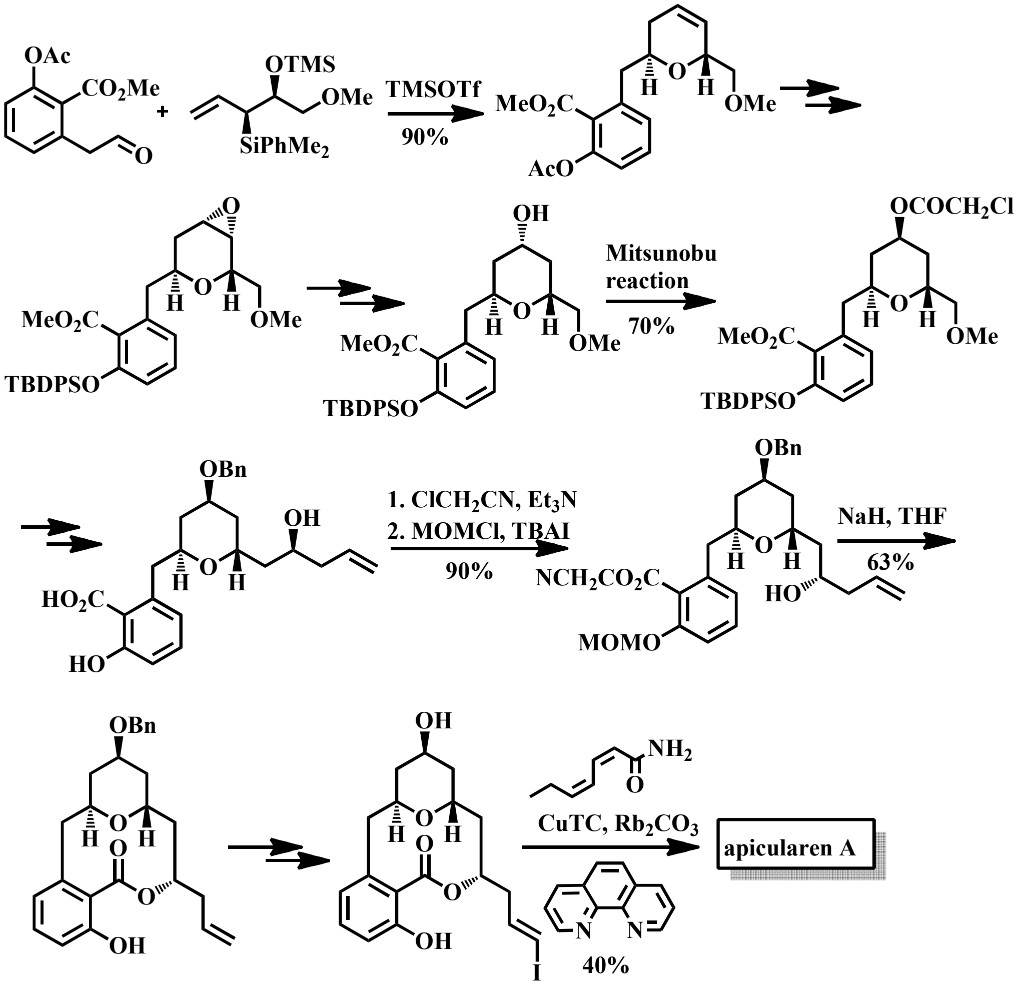
---

[112] Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425.


Ph
H
O
OTMS
X
SiPhMe2
+
TMSOTf, CH2Cl2
X = CH2OMe
X = CH2OAc
OMe
OAc
cis (not observed)
trans (major)
cis (major)
trans (minor)

Scheme 52. Mechanistic explanation on substituent effect on products formed

When they applied the concept onto the intermediate for apicularen A synthesis, they saw the same high selectivity in favour of the desired moiety. The required chiral allylsilane was synthesized using Sharpless asymmetric epoxidation to install the required chiral centres. They then proceeded as shown in Scheme 53.

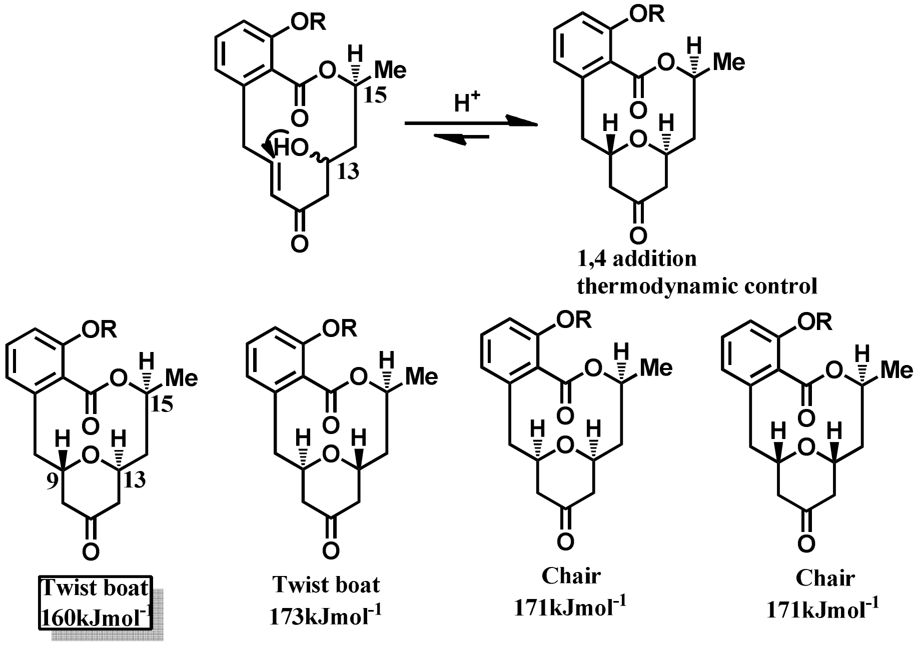

OAc
CO2Me
+
OTMS
OMe
SiPhMe2
TMSOTf
90%
MeO2C
AcO
O
H
H
OMe
MeO2C
TBDPSO
O
OH
Mitsunobu reaction
70%
OCOCH2Cl
OBn
HO2C
HO
OH
1. ClCH2CN, Et3N
2. MOMCl, TBAI
90%
NCH2CO2C
MOMO
HO
NaH, THF
63%
OBn
OH
NH2
O
CuTC, Rb2CO3
N
N
40%
I
apicularen A

Scheme 53. Panek final attempt towards apicularen A

They initially attempted lactonization of the homoallylic alcohol, however, the presence of unprotected phenol prevented the reaction from proceeding. Therefore they sought to complete the lactonization via a protected phenol and activated acid pathway. Finally the coupling of the macrolactone to the enamide chain was achieved using CuTC and Rb_2CO_3 with the necessary addition of the diamine ligand.

4.2.5. Rizzacasa's Approach

Rizzacasa's group began their synthetic analysis by noting a similarity between salicylihalamide and apicularen A.[113] They performed MM2 calculations and found that the desired *trans*-THP ring was more stable by 10 kJ mol^{-1} than other possible isomers assuming that 1,4-addition was thermodynamically controlled and the precursor with a racemic C-13 centre was used as the starting moiety (Scheme 54). This means that stereochemistry at C-13 does not affect the stereochemistry of the product and possible epimerization of C-13 centre under acidic conditions will not affect the product obtained.

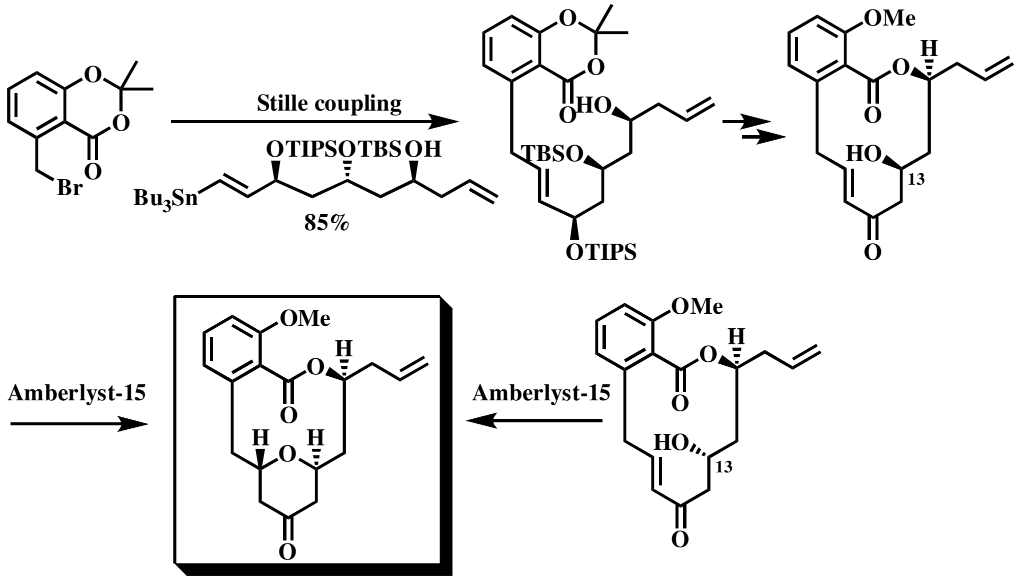

OR
H
Me
15
O
HO
13
O
H+
1,4 addition
thermodynamic control
9
Twist boat
160kJmol-1
Twist boat
173kJmol-1
Chair
171kJmol-1
Chair
171kJmol-1

Scheme 54. MM2 calculation of intramolecular annulation

The group performed the synthesis to find that their calculation was indeed true as the same desired intermediate was obtained regardless of the chirality at C-13. As they proceeded, they encountered a similar problem as De Brabander's group in selectively reducing the ketone on the pyranone ring. They resolved the problem by separating the diastereomers and subjecting the undesired alcohol to an additional Mitsunobu inversion to obtain the desired stereochemistry (Scheme 55).

---

[113] Hilli, F.; White, J. M., Rizzacasa, M. R. *Org. Lett.* **2004**, *6,* 1289.


Stille coupling
Br
O
O
O
Bu3Sn
OTIPS
OTBS
OH
85%
HO
TBSO
OTIPS
OMe
H
HO
13
Amberlyst-15
Amberlyst-15
H
H
HO
13

Scheme 55. Rizzacasa's synthetic efforts

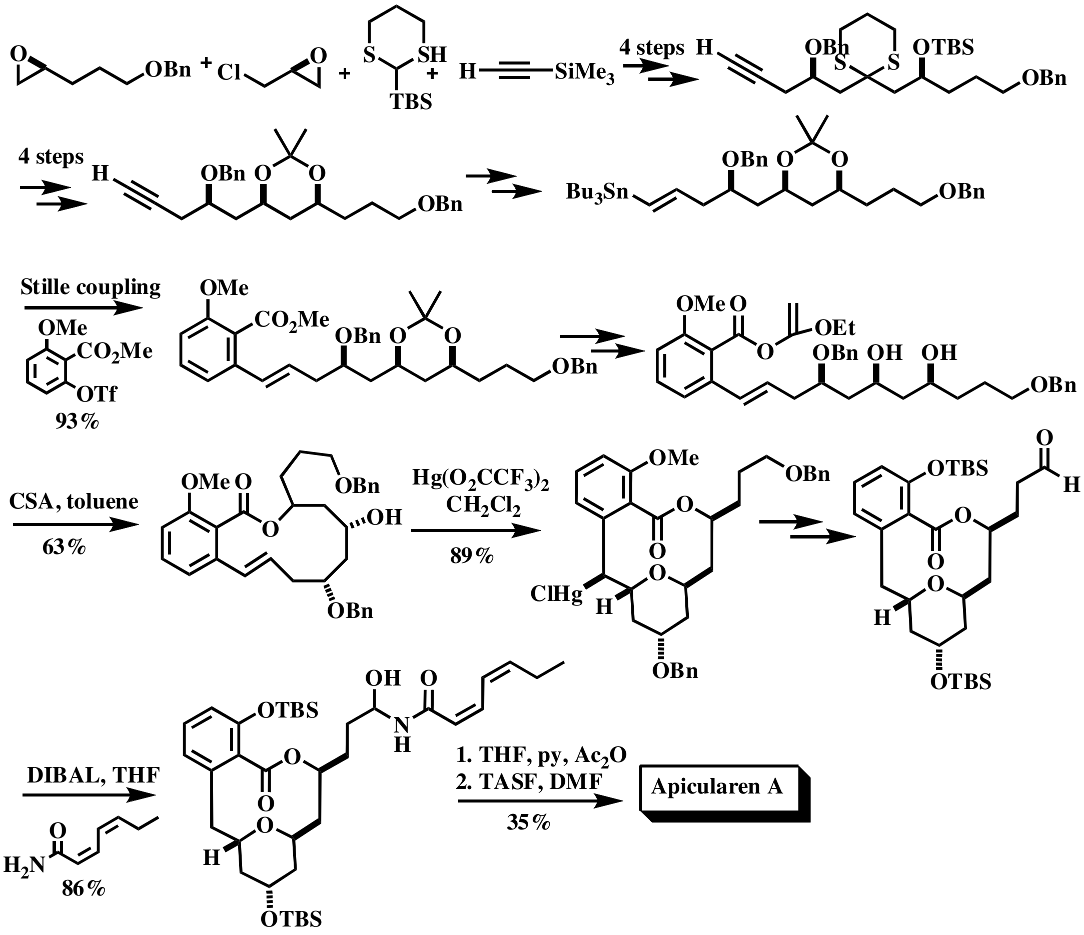
4.2.6. Maier's Approach

The total synthesis of apicularen A was achieved in 2004[114] by Maier's group as shown in Scheme 56. Subsequently they also studied the structure-activity relationship of the analogues.[115]

---

[114] (a) Petri, A. F.; Bayer, A.; Maier, M. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 5821 (b) Kuhnet, S. M.; Maier, M. E. *Org. Lett.* **2002**, *4*, 643.

[115] Petri, A. F.; Sasse, F.; Maier, M. E. *Eur. J. Org. Chem.* **2005**, 1865.


4 steps
4 steps
Stille coupling
93%
CSA, toluene
63%
Hg(O2CCF3)2
CH2Cl2
89%
DIBAL, THF
86%
1. THF, py, Ac2O
2. TASF, DMF
35%
Apicularen A

Scheme 56. Maier's synthetic route

In the synthesis of the lactone by transannular esterification, typical Yamaguchi conditions managed to give selectively the larger macrolactone but the yield was only moderate. The authors then turned to the method of Trost and Chisholm to use an activated acid moiety for the coupling.[116] However the group soon encountered another problem in esterification as previous results from model studies using *N*-(phenylseleno)phthalimide failed to lead to the THP ring formation. They eventually found mercuric trifluoroacetate to be extremely useful in the transannular pyran formation providing high selectivity. The authors believed that the transition state of the kinetically-controlled reaction is product-like leading to the less strained product.

---

[116] Trost, B. M. Chisholm, J. D. *Org. Lett.* **2002**, *4*, 3743.

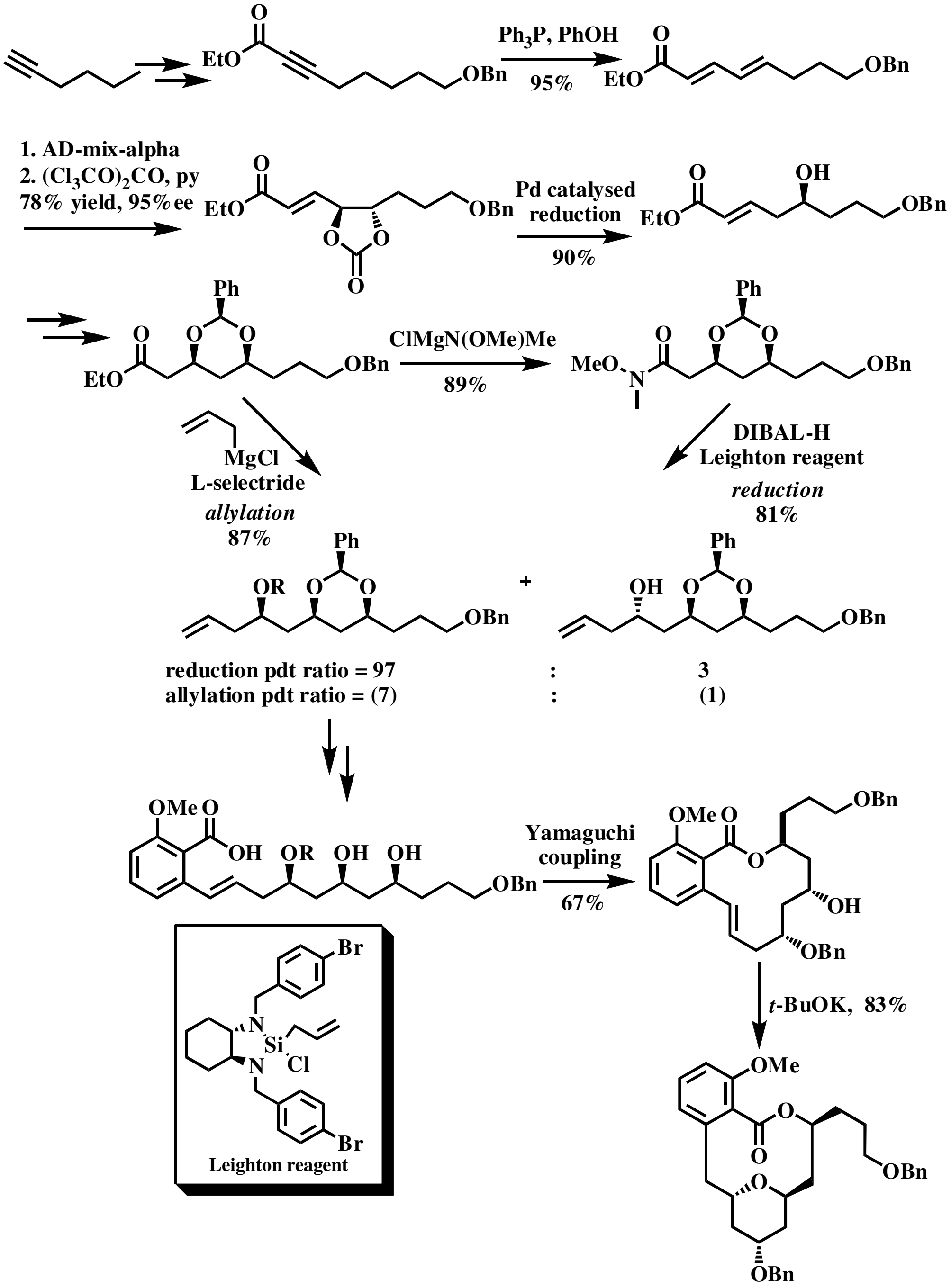
Another explanation may be drawn from Rizzacasa's studies mentioned previously in which intramolecular ether formation is independent of the stereochemistry at C-13 but instead the C-15 stereochemistry determines the outcome.

4.2.7. O' Doherty's Approach

O' Doherty *et al.* [117] started with a terminal alkyne on which they added carbon atoms to form an ynoate over 4 steps. A Rychnovsky variant of Trost isomerisation was applied to convert the triple bond to a highly conjugated ester. The first chiral centre was installed by Sharpless dihydroxylation and a subsequent Pd assisted reduction. The remaining double bond was hydrated diastereoselectively following Evans' protocol.[118] The ester was then converted into a Weinreb amide which was converted to a chiral homoallylic alcohol via two possible pathways either through a Grignard reaction followed by L-selectride reduction or a DIBAL reduction followed by Leighton's allylation.[119] A Yamaguchi lactonization produced the macrocyclic core for transannular esterification. The esterification step was finally established using *t*-BuOK after attempts at Au(I) and Pt(II) catalysis failed. Only one diastereomer was formed to present the intermediate as in Maier's strategy (Scheme 57).

---

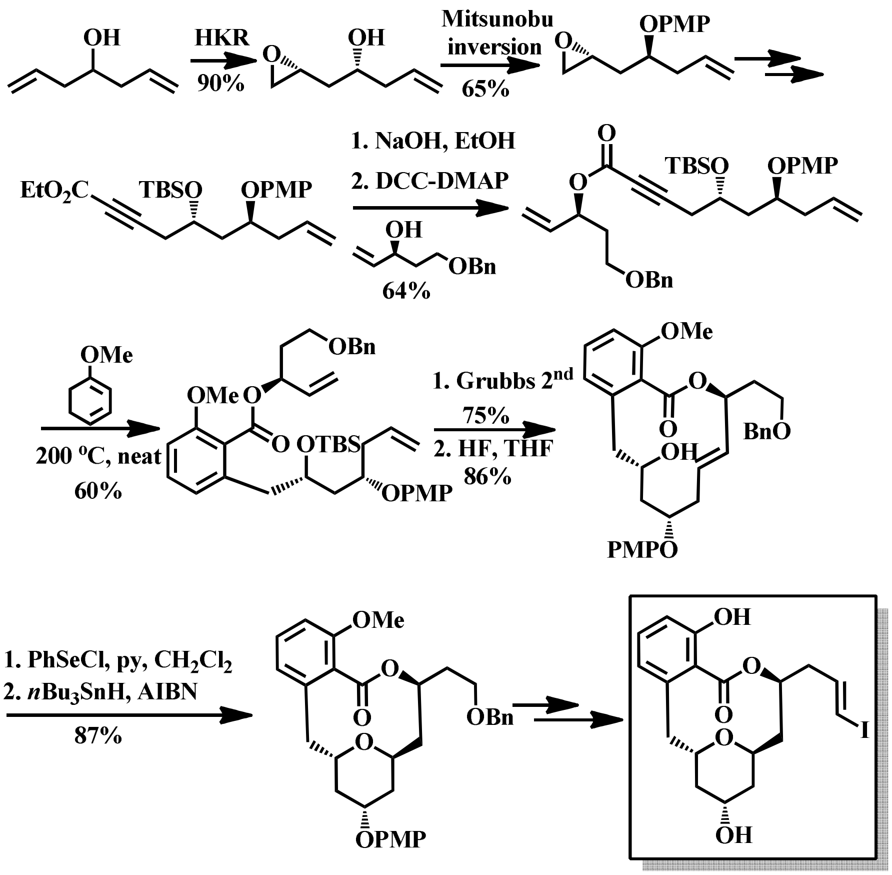
[117] O' Doherty, G.; Li, M. *Org. Lett.* **2006**, *8*, 6087.
[118] Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446.
[119] Kubota, K.; Leighton, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 946.


EtO
OBn
Ph3P, PhOH
95%
1. AD-mix-alpha
2. (Cl3CO)2CO, py
78% yield, 95% ee
Pd catalysed reduction
90%
OH
Ph
ClMgN(OMe)Me
89%
MeO
N
MgCl
L-selectride
allylation
87%
DIBAL-H
Leighton reagent
reduction
81%
OR
+
reduction pdt ratio = 97 : 3
allylation pdt ratio = (7) : (1)
OMe
Yamaguchi coupling
67%
t-BuOK, 83%
Br
Si
Cl
Leighton reagent

Scheme 57. O' Doherty's synthetic pathway

4.2.8. Tae's Approach

Tae's group[120] published the synthesis of the core macrolactone by transannular esterification similar to that of the Maier's approach.


OH
HKR
90%
OH
Mitsunobu inversion
65%
OPMP
EtO$_2$C
TBSO
OPMP
1. NaOH, EtOH
2. DCC-DMAP
OH
OBn
64%
O
TBSO
OPMP
OBn
OMe
200 °C, neat
60%
OMe
O
OBn
O
OTBS
OPMP
1. Grubbs 2nd
75%
2. HF, THF
86%
OMe
O
O
BnO
OH
PMPO
1. PhSeCl, py, CH$_2$Cl$_2$
2. nBu$_3$SnH, AIBN
87%
OMe
O
O
O
OBn
OPMP
OH
O
O
O
I
OH

Scheme 58. Tae's synthetic pathway

Their effort was geared towards the vinyl iodide intermediate in Panek and Su's strategy. The synthesis began with a Jacobsen's hydrolytic kinetic resolution (HKR)[121]. Mitsunobu inversion with *p*-methoxyphenol afforded the first desired stereogenic centre. The chiral epoxide was opened by an acetylide group to give an ethyl enynoate functionality. Base hydrolysis and subsequent protection with a chiral homoallylic alcohol gave the starting material for Diels-Alder reaction. Diels-Alder reaction proceeded regioselectively at 200 °C under neat conditions followed by olefin metathesis facilitated by second-generation Grubbs catalyst. The *anti* THP ring was thereafter formed by reaction with phenylselenyl chloride. Subsequent debenzylation, oxidation and deprotection furnished the advanced intermediate in Panek's synthesis (Scheme 58).

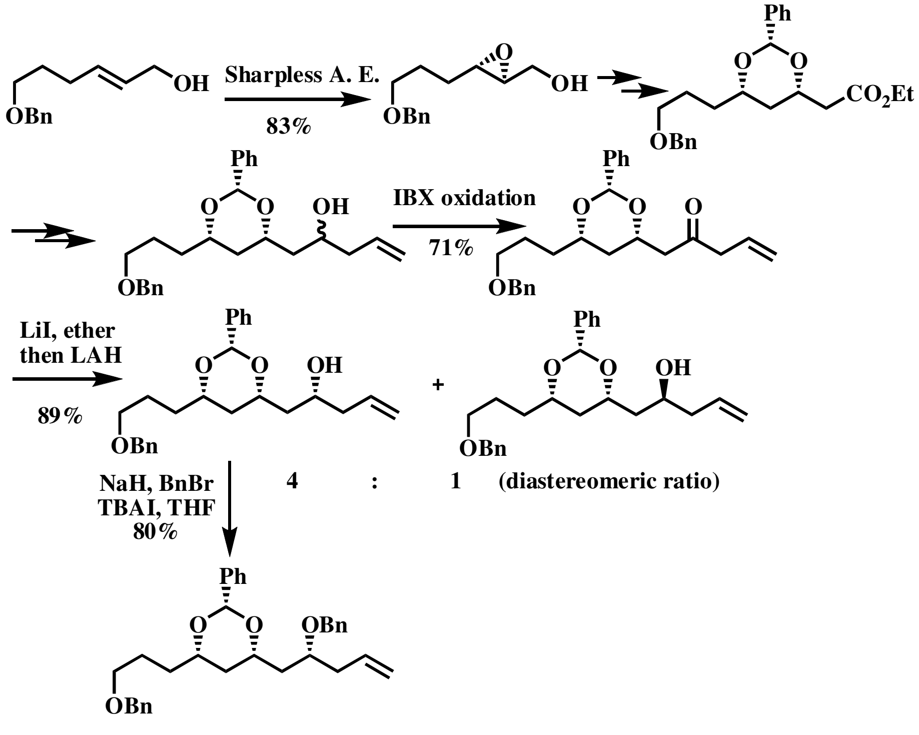
---

[120] Jung, Y.-H.; Kim, Y.-J.; Tae, J. J. *Chem. Asian J.* **2007**, *2*, 656.

[121] (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science*, **1997**, *277*, 936. (b) Brandes, B. D.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **1997**, *8*, 3927.

4.2.9. Yadav's Approach

Yadav[122] and co-workers reported a complementary method to synthesize an intermediate towards apicularen A in O' Doherty's synthetic route.


OBn
OH
Sharpless A. E.
83%
O
OH
OBn
Ph
O
O
CO2Et
OBn
Ph
O
O
OH
OBn
IBX oxidation
71%
Ph
O
O
O
OBn
LiI, ether
then LAH
89%
Ph
O
O
OH
OBn
+
Ph
O
O
OH
OBn
4 : 1 (diastereomeric ratio)
NaH, BnBr
TBAI, THF
80%
Ph
O
O
OBn
OBn

Scheme 59. Yadav's synthetic pathway

The synthesis of the intermediate involved a Sharpless asymmetric epoxidation to achieve the first chiral centre. Thereafter the non-diastereoselective homoallylic alcohol was oxidized to produce a ketone which was subsequently reduced to give a 4:1 ratio of diastereomers in favour of the desired isomer. Finally, benzyl protection was performed on the alcohol (Scheme 59).

---

[122] Yadav, J. S.; Kumar, N. N.; Prasad, A. R. *Synthesis* **2007**, 1175.

4.2.10. Floreancig's Approach

Floreancig and co-worker[123] were inspired by previous postulation by Rizzacasa's group that 2,6-disubstituted tetrahydropyranone could isomerise to the *trans*-isomer following lactone formation. Therefore they set out to synthesize the tetrahydropyranone in the following route (Scheme 60). Their success depended on the selective generation of the C-13 carbocation in preference to the oxidative cleavage of the C-8-C-9 bond using ceric ammonium nitrate (CAN) under basic condition.

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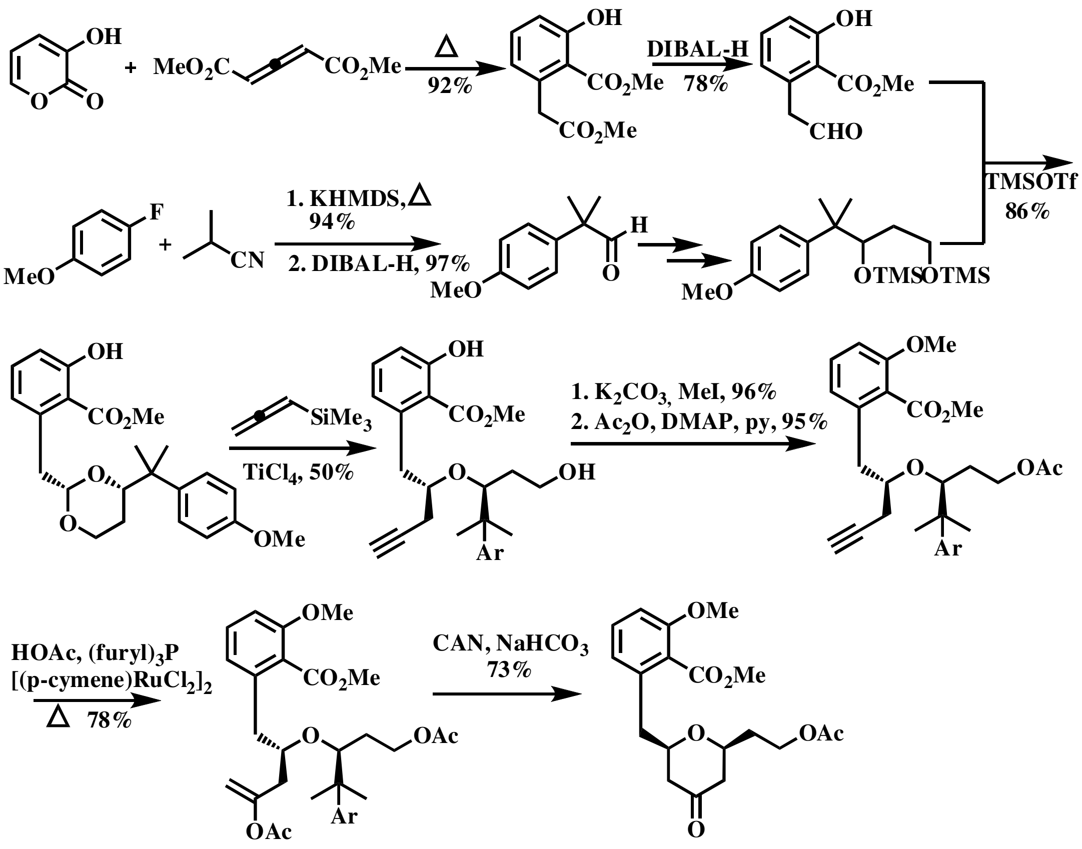
[123] Poniatowski, A. J.; Floreancig, P. E. *Synthesis* **2007**, 2291.


OH
O
O
+ MeO$_2$C
CO$_2$Me
Δ
92%
OH
CO$_2$Me
CO$_2$Me
DIBAL-H
78%
OH
CO$_2$Me
CHO
TMSOTf
86%
F
MeO
+
CN
1. KHMDS,Δ
94%
2. DIBAL-H, 97%
MeO
H
O
MeO
OTMS
OTMS
OH
CO$_2$Me
O
O
OMe
SiMe$_3$
TiCl$_4$, 50%
OH
CO$_2$Me
O
OH
Ar
1. K$_2$CO$_3$, MeI, 96%
2. Ac$_2$O, DMAP, py, 95%
OMe
CO$_2$Me
O
OAc
Ar
HOAc, (furyl)$_3$P
[(p-cymene)RuCl$_2$]$_2$
Δ 78%
OMe
CO$_2$Me
O
OAc
OAc
Ar
CAN, NaHCO$_3$
73%
OMe
CO$_2$Me
O
OAc
O

Scheme 60. Floreancig's synthetic pathway

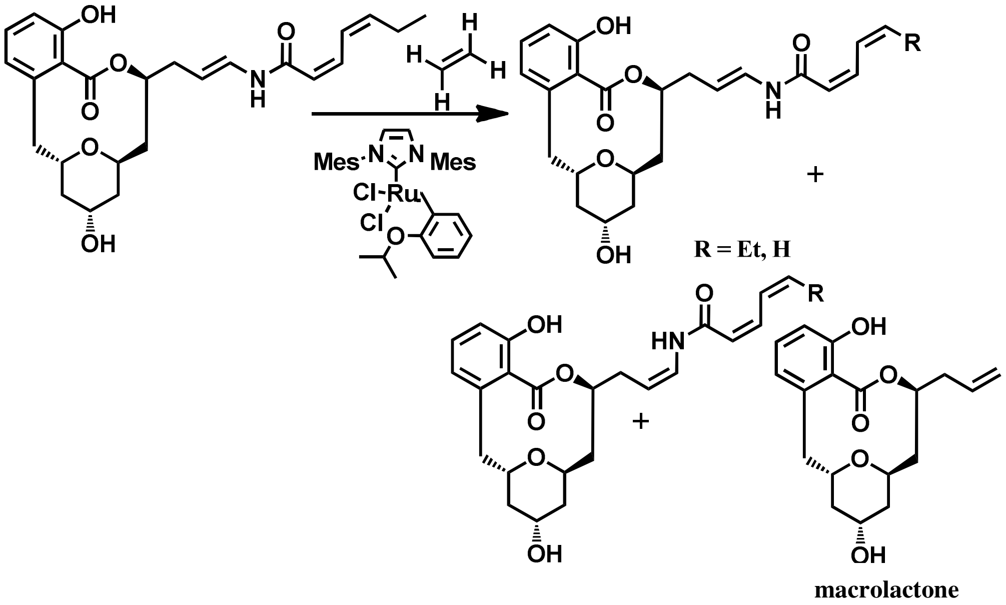
They were able to achieve this due to the dimethyl substitution on the benzyl position of the *para*-methoxybenzyl group which weakens the C-C bond that needs to be broken in order for the THP ring to be formed (Scheme 60).

4.2.11. Höfle's Approach

After reporting the structure elucidation of the natural product, Höfle *et al.* published an alternative method to obtain analogues of the natural product for biological testing.[124] From previous results, it was shown that the enamide side chain plays an important role in the bioactivity of the molecule. In order to shorten the typical 15 to 23- steps procedure to produce the macrocycle core for side chain modification, Höfle and co-worker took a retro route on the basis of the production of apicularen A *via* fermentation. Thereafter, they applied the Hoveyda-Grubbs catalyst to apicularen A in the presence of ethylene to produce mixture of products as shown in Scheme 61.

---

[124] Jundt, L.; Höfle, G. *J. Nat. Prod.* **2007**, *70*, 1377.

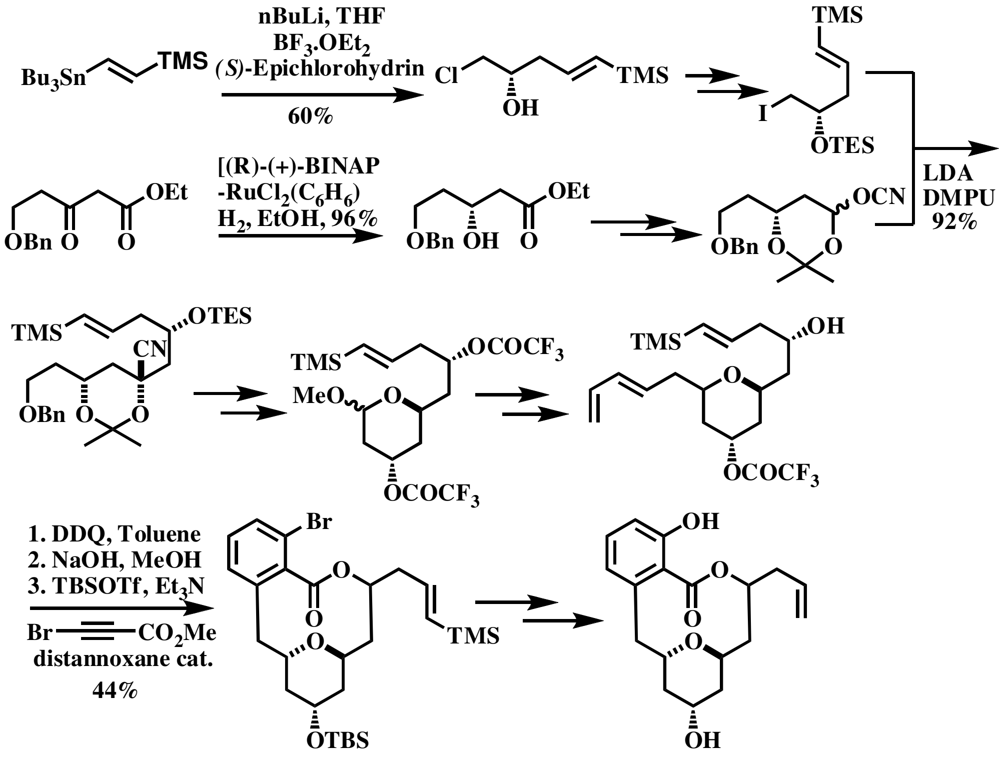


Scheme 61. Höfle's retro route to macrocyclic core

This reaction could give up to 25% yield of the macrolactone, a valuable late-stage intermediate for side chain modifications.

4.2.12. Rychnovsky approach

They approached the synthesis toward apicularen A through the synthesis of cyanohydrin acetonide intermediate and intramolecular Diels-Alder addition sequence.



Bu3Sn
TMS
nBuLi, THF
BF3.OEt2
(S)-Epichlorohydrin
60%
Cl
OH
TMS
TMS
I
OTES
LDA
DMPU
92%
OBn O O
OEt
[(R)-(+)-BINAP
-RuCl2(C6H6)
H2, EtOH, 96%
OBn OH O
OEt
OBn O O
OCN
TMS
OTES
CN
OBn O O
TMS
OCOCF3
MeO
O
OCOCF3
TMS
OH
O
OCOCF3
1. DDQ, Toluene
2. NaOH, MeOH
3. TBSOTf, Et3N
Br—≡—CO2Me
distannoxane cat.
44%
Br
O
O
O
TMS
OTBS
OH
O
O
O
OH

Scheme 62. Rychnovsky synthetic route

The synthesis began with tin-lithium exchange followed by reaction with *(S)*-epichlorohydrin in the presence of Lewis acid to produce enantiopure chlorohydrins. Meanwhile, cyanohydrins acetonide was prepared employing Noyori hydrogenation.[125] The two coupling partners were treated with LDA and DMPU to provide the polyols fragment as a single diastereomer. Upon functional group modification, Otera's distannoxane catalyst[126] was employed for the transesterification which was followed by intramolecular Diels-Alder reaction under thermal condition. Subsequent transformations provided macrocyclic core of apicularen A (Scheme 62).

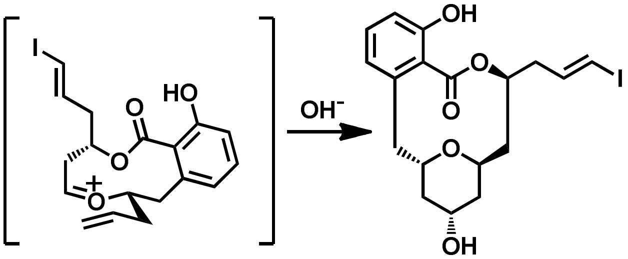
---

[125] (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856. (b) Kitamura, M.; Tokunaga, M.; Ohkum, T.; Noyori, R. *Org. Synth.* **1992**, *71*, 1.

[126] Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2383.

4.2.13. Our previous attempt towards apicularen A

Our previous attempt in synthesis of this molecule was carried out utilizing Prins cyclization to construct the substituted tetrahydropyran moiety.[127] Prins cyclization is one of the most versatile methods to access substituted pyran[128] and our group has developed several methods towards this strategy and applied it to natural product synthesis.[20] However the current limitation of our strategy is that it only forms *syn* and *anti* substituted pyran in 1:1 ratio.[129] In our initial plan for apicularen A synthesis, we expected the ring strain during the transition state to help orientate the oxo-carbenium ion to produce 2,6-*anti*-THP ring (Scheme 63).



Scheme 63. Proposed mechanism for *anti*-THP ring in apicularen A

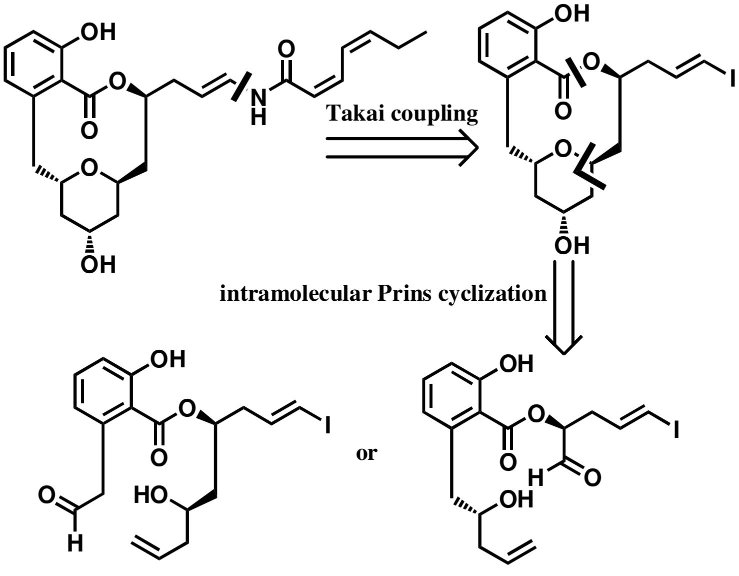
The initial retrosynthetic strategy for this molecule was shown in Scheme 64, where the *anti*-pyran moiety can be accessed from intermediate **I** or **II**.

---

[127] Chan li ting, Jocelyn., master thesis

[128] (a) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 913. (b) Wei, Z. Y.; Li, S. J. Wang, D.; Chan T. H. *Tetrahedron Lett.* **1987**, *28*, 3441. (c) Yang, J.; Viswanathan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627. (d) Patterson, B.; Marumoto, S.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3163. (e) Wei, Z. Y.; Li, S. J. Wang, D.; Chan T. H. *J. Org. Chem.* **1989**, *54*, 5768. (f) Coppi, L.; Ricci, A.; Taddei, M. *Tetrahedron* Lett. **1987**, *28*, 973. (g) Perron, F.; Albizati, K. F. *J. Org. Chem.* **1987**, *52*, 4128. (h) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271. (i) Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387. (j) Ramesh, J.; Vitale, J.; Rychnovsky, S D. *J. Am. Chem. Soc.* **2004**, *126*, 9904. (k) Colobert, F.; Des Mazery, R.; Solladie, G.; Carreno, M. C.; Urbano, A. *J. Org. Chem.* **2003**, *68*, 7779. (l) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426. (m) Dalgard, J. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 15662.

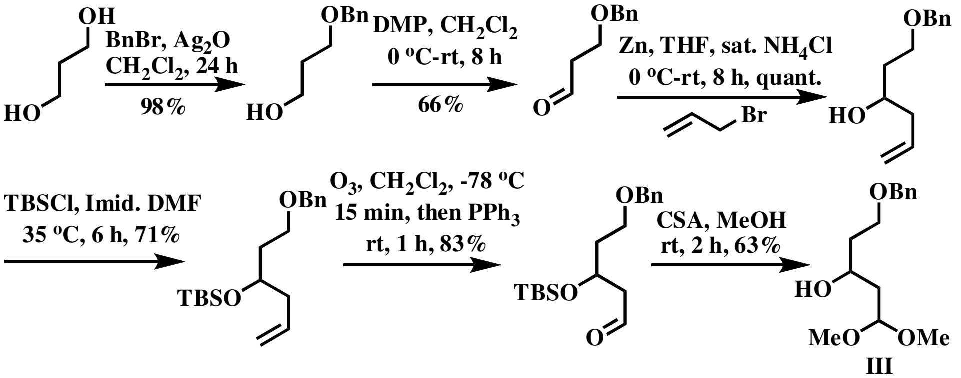
[129] Chan, K. P.; Soew A. H.; Loh, T. P., *Tetrahedron Lett.* **2007**, *48*, 37.


Takai coupling
intramolecular Prins cyclization
or

I II

Scheme 64. Initial retrosynthetic plan toward apicularen A

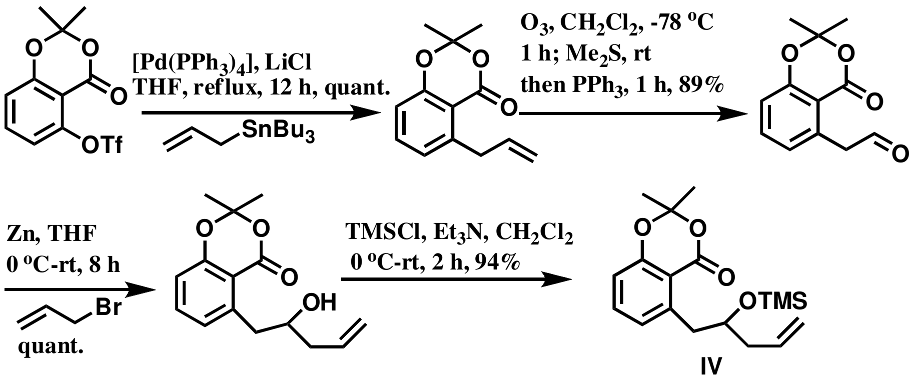
The synthetic efforts commenced with protection of commercially available 1,3-prepanediol followed by a series of transformations to provide acetal **III** (Scheme 65).


BnBr, Ag$_2$O
CH$_2$Cl$_2$, 24 h
98%
DMP, CH$_2$Cl$_2$
0 °C-rt, 8 h
66%
Zn, THF, sat. NH$_4$Cl
0 °C-rt, 8 h, quant.
Br
TBSCl, Imid. DMF
35 °C, 6 h, 71%
O$_3$, CH$_2$Cl$_2$, -78 °C
15 min, then PPh$_3$
rt, 1 h, 83%
CSA, MeOH
rt, 2 h, 63%

III

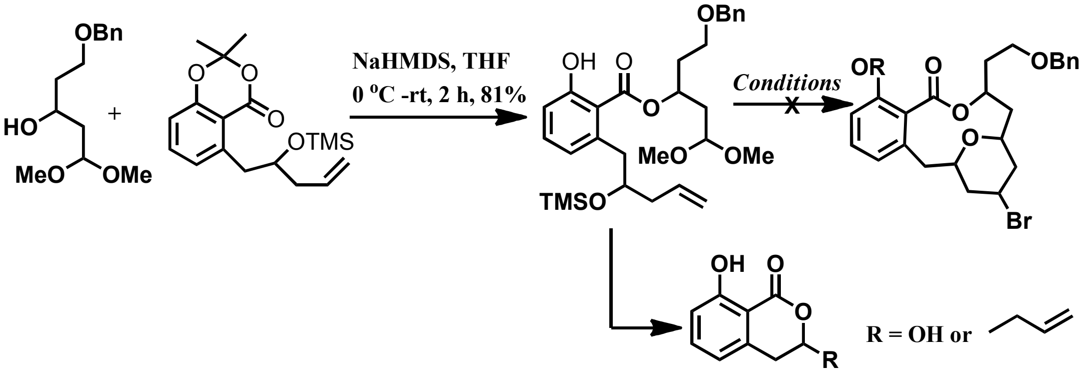
Scheme 65. Preparation of acetal III

Meanwhile, the salicylic moiety **IV** was obtained from triflate moiety that underwent Stille coupling followed by ozonolysis, allylation and protection by TMS group (Scheme 66).


OTf
[Pd(PPh3)4], LiCl
THF, reflux, 12 h, quant.
SnBu3
O3, CH2Cl2, -78 °C
1 h; Me2S, rt
then PPh3, 1 h, 89%
Zn, THF
0 °C-rt, 8 h
Br
quant.
OH
TMSCl, Et3N, CH2Cl2
0 °C-rt, 2 h, 94%
OTMS
IV

Scheme 66. Preparation of intermediate IV

Treatment of fragment **III** and **IV** furnished the Prins intermediate in good yield (81%). However, lactonization under Prins cyclization conditions did not proceed as planned (Table 3).


OBn
HO
MeO
OMe
+
OTMS
NaHMDS, THF
0 °C -rt, 2 h, 81%
OH
MeO
OMe
TMSO
Conditions
OR
OBn
Br
R = OH or

Conditions
InBr$_3$, TMSBr, CH$_2$Cl$_2$, -78 °C-rt, 24 h
In(OTf)$_3$, MeOH, rt, 24h

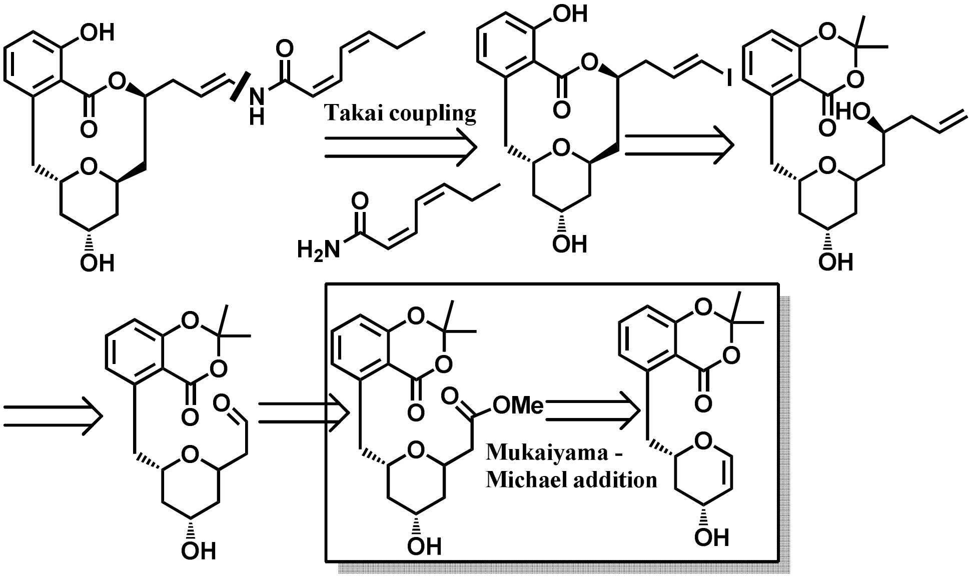
Table 3. Conditions for Prins cyclization

Further investigation suggested that instead of forming the desired THP ring, the ester bond of the salicylic moiety preferably cleaves to form a thermodynamically stable side- product. Since the salicylic moiety is an intrinsic feature of the molecule, we had to revert to the alternative pathway of intramolecular lactonization, a different strategy for the formation of the *anti* THP ring.

4.3. Revised strategy towards the synthesis of apicularen A

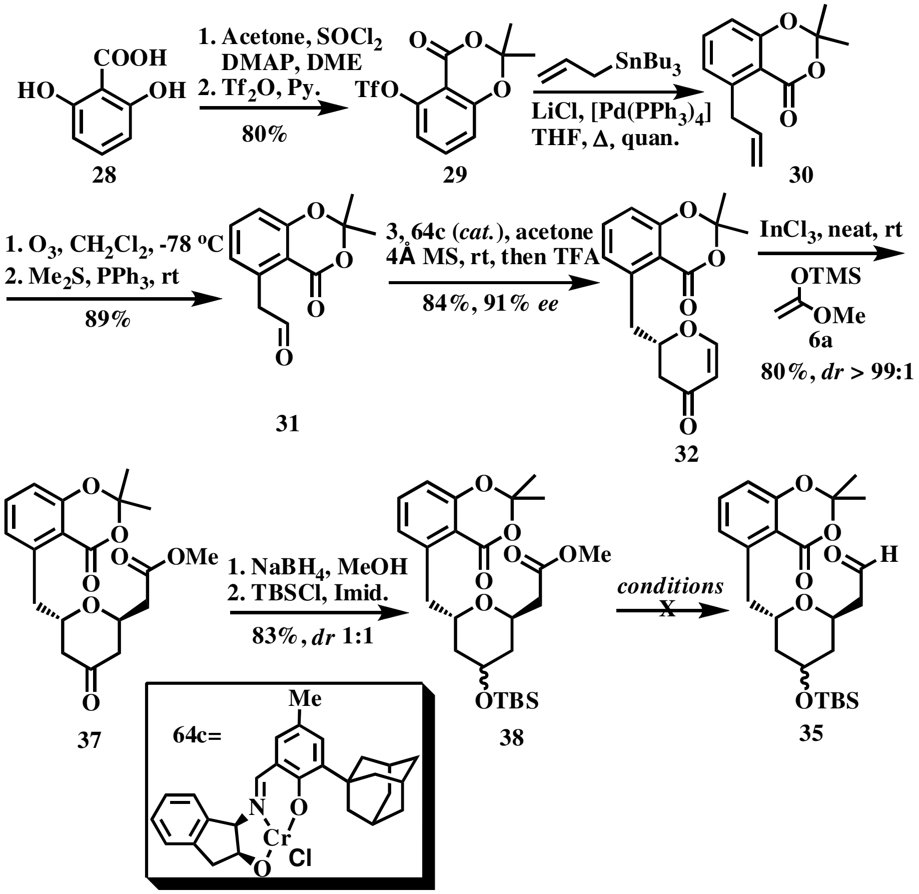
4.3.1. Application of Mukaiyama-Michael reaction toward synthesis of apicularen A

With the advantage of substituent as directing group in the Mukaiyama-Michael addition, we planned our revised strategy towards apicularen A as shown in Scheme 67. The key feature was the use of $InCl_3$-catalyzed Mukaiyama-Michael addition to unsaturated pyrone.



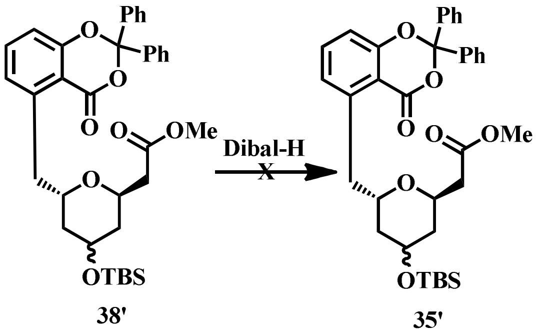
Scheme 67. Revised strategy towards apicularen A

We proceeded with the synthesis of the *anti*-pyran moiety in apicularen A. We followed the synthetic route from the Brabander synthesis of unsaturated pyranone by hetero Diels-Alder reaction and subjected it to our Mukaiyama-Michael condition which successfully gave us the desired product **34**. The anti-pyran configuration was determined based on NOESY experiment. However, we soon encountered problem reducing the ester **34** to obtain the aldehyde **35**, due to instability of the acetonide towards the reduction conditions with hydrides such as DIBAL-H, excess $NaBH_4$ or $LiBH_4$ (Scheme 68).


COOH
HO
OH
28
1. Acetone, SOCl2
DMAP, DME
2. Tf2O, Py.
80%
TfO
29
SnBu3
LiCl, [Pd(PPh3)4]
THF, Δ, quan.
30
1. O3, CH2Cl2, -78 °C
2. Me2S, PPh3, rt
89%
31
3, 64c (cat.), acetone
4Å MS, rt, then TFA
84%, 91% ee
32
InCl3, neat, rt
OTMS
OMe
6a
80%, dr > 99:1
OMe
37
1. NaBH4, MeOH
2. TBSCl, Imid.
83%, dr 1:1
OMe
OTBS
38
conditions
X
H
OTBS
35
64c=
Me
N
O
Cr
O
Cl

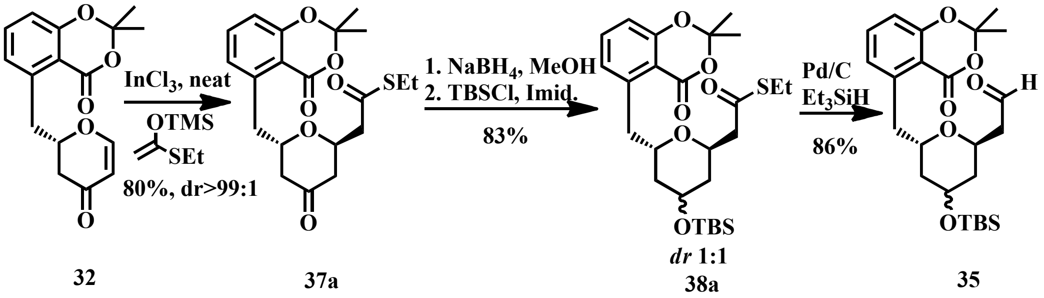
Scheme 68. Synthetic effort towards intermediate 35

When benzophenone was used as the protecting group, we were also unable to reduce the ester moiety to aldehyde (Scheme 69).


Ph
Ph
O
O
O
OMe
Dibal-H
X
OTBS
38'
35'

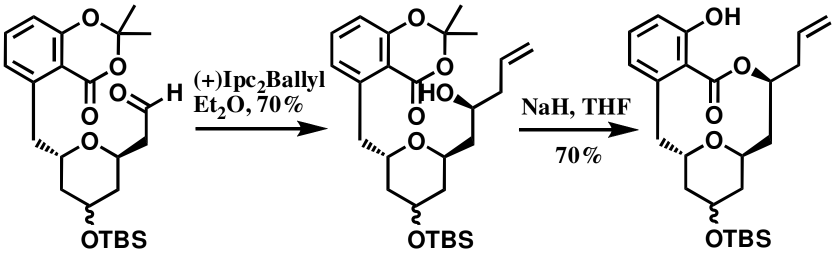
Scheme 69. Failed reduction upon changing protecting group

Fortunately, changing the silyl ketene acetal to thioester functionality reacted successfully to yield the Mukaiyama-Michael product **37a**, in which the absolute stereochemistry was established based on NOESY experiment. Reduction of this moiety in mild condition of Et_3SiH and Pd/C enabled the access to the aldehyde **35** (Scheme 70).


InCl3, neat
OTMS
SEt
80%, dr>99:1
SEt
1. NaBH4, MeOH
2. TBSCl, Imid.
83%
SEt
Pd/C
Et3SiH
86%
H
OTBS
dr 1:1
32
37a
38a
35

Scheme 70. Preparation of aldehyde 35

Aldehyde **35** was treated with (+)-ipc$_2$B-allyl followed by Brabander's method of cyclization in the presence of NaH to furnish the macrolactone core of apicularen A (Scheme 71).



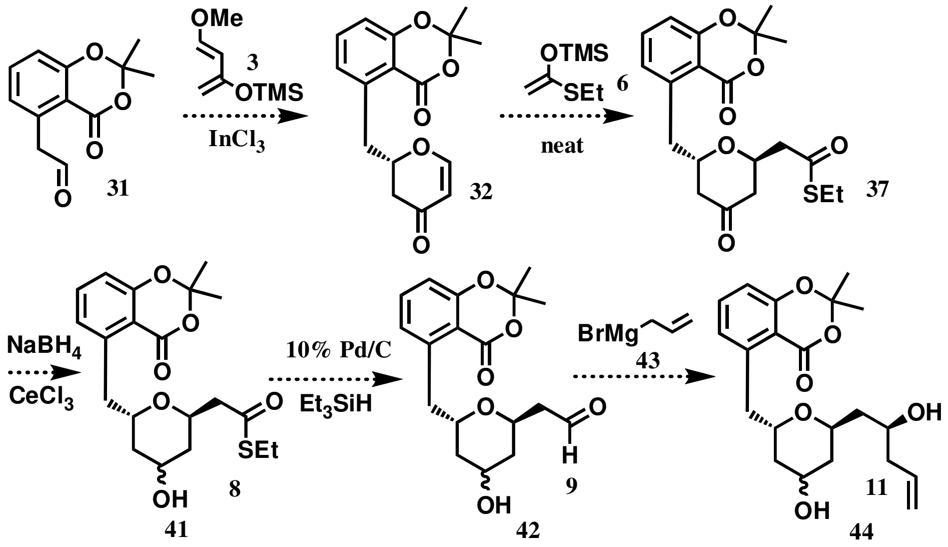
35 **39** **40**

Scheme 71. Completion of macrolactone ring

However, the drawback of this synthetic route was unselective reduction of the lactone **37** (and **37a**) under Luche condition as also reported by Brabander *et al*. This kind of reduction could be inductively selective; however this effect was cancelled out in the *anti*-pyran ring system. We attempted the reduction with K- selectride hoping that the reduction could proceed from the less bulky substituent. However, this did not give good diastereoselectivity either.

4.3.2. One-pot synthesis of apicularen A

Upon establishing the synthetic route to macrolactone part of apicularen A using the indium-catalysed Mukaiyama-Michael strategy, we thought that we could shorten the synthesis by developing a tandem reaction towards a one-pot synthesis of apicularen A. With growing interest in indium chemistry and in an effort to apply the method that we had developed in our group, we came up with a plan for the one-pot synthesis of macrocyclic core of apicularen A as shown in the proposed strategy in the Scheme 72.



Scheme 72. One-pot synthetic plan

We started accessing this possibility by trying with simple aldehyde. There were many Lewis acid that could be used to assist in hetero Diels-Alder reaction, such as $ZnCl_2$ or InX_3 (X = Cl, Br, OTf). Our interest fell on indium since the possibility of complexation with ligand could give a promising method to develop an asymmetric version.

We started with hetero Diels-Alder reaction of benzaldehyde and Danishefsky diene, which was a well-established transformation that could be catalyzed by a wide range of Lewis acid. We found out that $InCl_3$ can conveniently catalyzed the reaction at room temperature, while $In(OTf)_3$ was found highly reactive that complete this transformation in less than one hour at low temperature.[130] For the purpose of subsequent reaction, we employed $InCl_3$ for this transformation.

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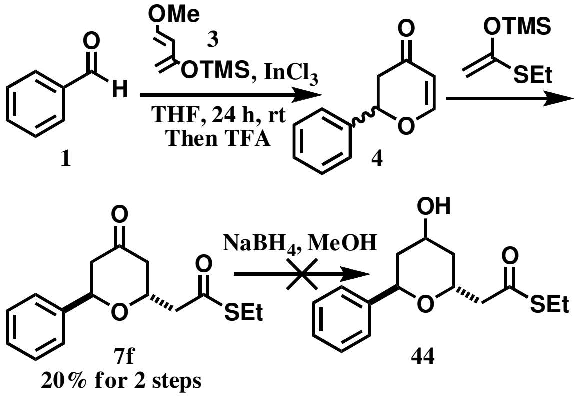
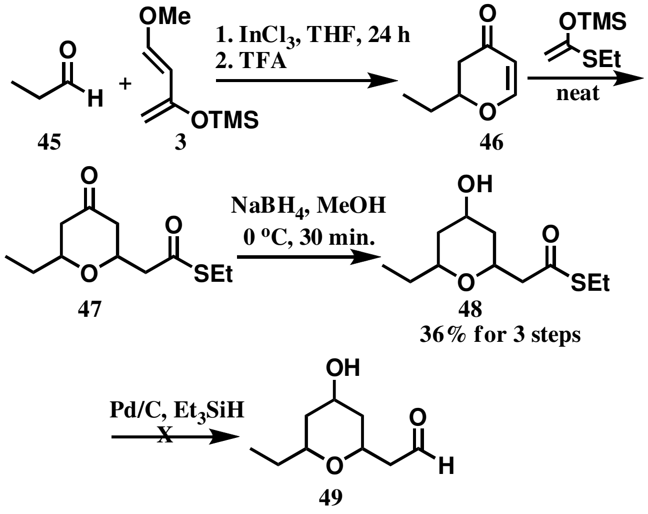
[130] Ali, T.; Chauhan, K.K.; Frost, C.G., *Tetrahedron lett*. **1999**. *40*, 5621.



Scheme 73. One pot synthesis of 2,6-*anti*-pyran ring

After removal of the solvent and trifluoroacetic acid *in vacuo*, we proceeded to the $InCl_3$-catalyzed Mukaiyama-Aldol reaction that provided us with excellent *anti*-selectivity as confirmed by NOESY experiment. However we only obtained low yield (20% two steps) for this transformation probably due to the presence of residual benzalydehyde that interfere in the reaction. Our attempts to push the reaction to completion, such as adding excess diene or prolonging reaction time were not successful. We attempted to carry out one-pot reaction up to the sodium borohydride reduction in this system. However, the result was unsatisfactory due to the presence of many interfering entities in the reaction mixture (Scheme 73).

To prove our hypothesis, we switched to low boiling point aldehyde that can be removed completely after the first step. Reaction of propionaldehyde with the diene followed by vinylogous Michael addition proceeded well to provide 2,6-*anti*-diastereomeric products **47**. Reduction was carried out, and similar to our observation, there was no selectivity in this reaction which left us with four isomers of **48**. This mixture was treated with Pd/C and Et_3SiH to reduce the thioester moiety. However, we did not observe formation of any aldehyde probably due to the presence of unprotected hydroxyl group.


45
+
OMe
OTMS
3
1. InCl3, THF, 24 h
2. TFA
46
OTMS
SEt
neat
47
SEt
NaBH4, MeOH
0 °C, 30 min.
OH
48
36% for 3 steps
Pd/C, Et3SiH
X
49
H

Scheme 74. Model study towards one-pot synthesis

4.4. Conclusion

We have demonstrated the versatility of $InCl_3$-catalyzed Mukaiyama-Michael addition towards the formal synthesis of apicularen A. However, one limitation was failure of the *anti*-pyranone product to be selectively reduced to its hydroxyl counterpart. The enamide side chain can be accessed *via* the already established method reported earlier.

We also have carried out the preliminary study towards the aim for the one-pot synthesis of apicularen A. However, the substrate was limited to low boiling aldehyde moiety unless chromatographic method was used to separate the residual starting material that could interfere with subsequent reaction. Further work and optimization of the reaction are required to actually apply this methodology to the actual substrate.

Chapter 5

Synthetic study towards marinomycins

5.1. Introduction to Marinomycins

Marinomycins A-D were isolated by Fenical *et al* from saline culture of marine actinomycetes (*Marinispora*) obtained from the deep sea offshore of La Jolla, California (Figure 8).[131] Ethyl acetate extracts of the particular strain of this class, CNQ-140, showed *in vitro* cytotoxicity against HCT-116 human colon carcinoma (IC_{50}=1.2 μg/mL). Further characterization and biological testing of this extract identified four compounds that were refer to marinomycins A-D (Figure 8).

Marinomycins A-D which are geometrical isomers, are new structural class of compounds that show significant antitumor-antibiotic activities and selective cancer cell cytotoxicities with MIC values of 0.1-0.6 μM against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faceium* (VREF). In addition, the marinomycins inhibit cancer cell proliferation with average LC_{50} values of 0.2-2.7 μM against the NCI's 60 cancer cell line panel. Interestingly, they only have weak activity against leukemia cell lines. The results suggest that Marinomycins had potent and selective cytotoxicities against six of the eight melanoma cell lines with a unique mechanism of action. However, detailed study on the pharmacology of this compound has not been reported in the literature up to the point of this writing.

Based on its mechanism of action, polyene moiety in natural products would usually leads to antifungal property.[132] Interestingly this property was not observed in marinomycins which suggests that even though the polyene motif was present; these molecules might not be membrane active, hence prohibiting them in proliferation of the cell wall.

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[131] Kwon, H. C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Am. Chem. Soc*. **2006**, *128*, 1622.

[132] (a) Bolard. J. *Biochim. Biophys. Acta* **1986**, *864*, 257. (b) De Kruijff, B.; Demel, R. A. *Biochim. Biophys. Acta* **1974**, *339*, 57. (c) Finkelstein, A.; Holz, R. *Membranes 2: Lipid Bilayers and Antibiotics*; Eisenman, G., Ed., Marcel Dekker: New York, 1973**,** Chapter 5. (d) Matsumori, N.; Yamaji, N.; Oishi, T.; Murata, M. *J. Am. Chem. Soc.* **2002**, *124*, 4180. (e) Matsuoka, S.; Murata, M. *Biochim. Biophys. Acta* **2002**, *1654*, 429.

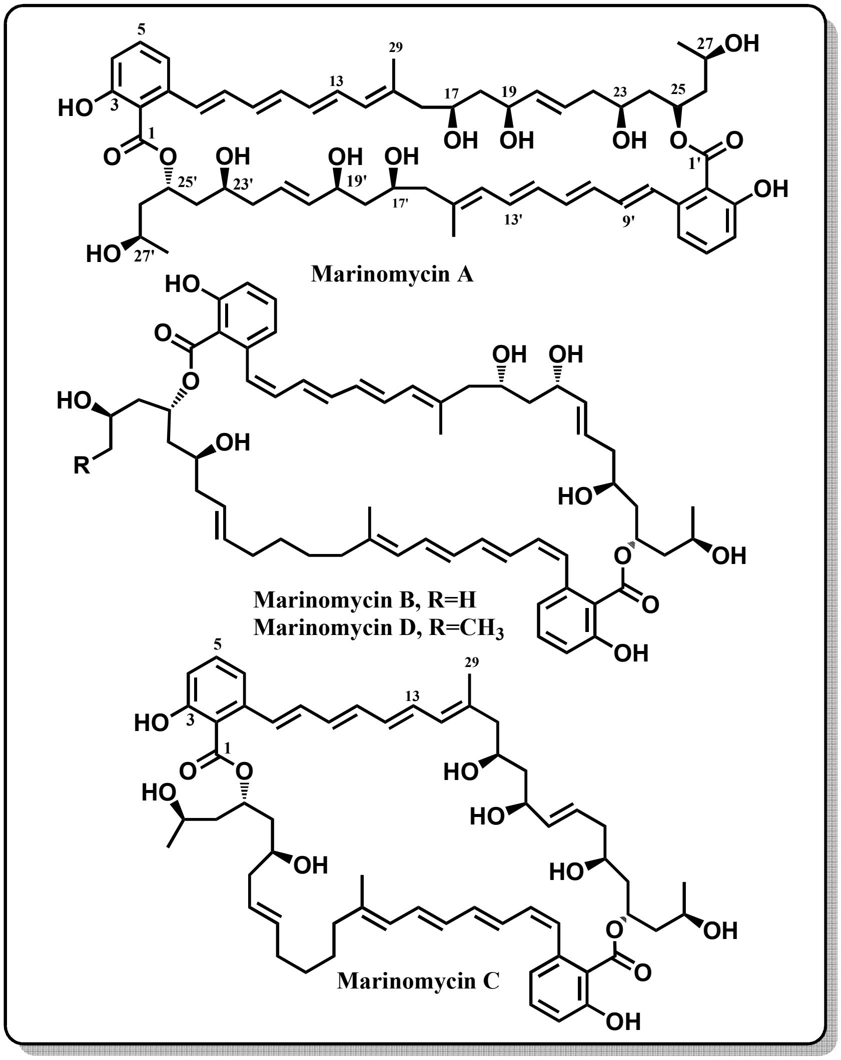


Figure 8. Marinomycins A-D

The unique structural features of these compounds included a macrolide composed of dimeric 2-hydroxy-6-alkenyl-benzoic acid lactones and conjugated tetraene-pentahydroxy polyketide chains which isomerized to its geometrical isomers under room lighting. Marinomycin A, which was proposed to be the true natural product as shown in Figure 8, was isolated and purified as the sole product when isolation was carried out in the dark. In marinomycin A, the polyene moiety had an all *E*-geometry which contributes to transannular hydrogen bonding that was found to be very weak in the other isomers.

Compared to all *trans* polyene geometry in marinomycin A, marinomycins B and D has $\Delta^{8,9} = \Delta^{8',9'}$ *Z* olefin, with the latter having an extra methyl group at C-28. Marinomycin C, on the other hand is an unsymmetrical dimer, with an all *E*- tetraene geometry in one half of the molecule and $\Delta^{8,9} = Z$ olefin in the second half.

Despite their similar structures, the optical rotations of these molecules are significantly different. Marinomycin A showed $[\alpha]_D$ +180°, while marinomycins B-C showed negative $[\alpha]_D$ values of -245° and -151°, respectively. The rotation of marinomycin D was $[\alpha]_D$ -233°, which was similar to marinomycin B, its lower homologue methylene. It was suggested that the all *E*-geometry of marinomycin A played a role in this observation, it caused a positive Cotton effect by exciton coupling between the polyene chromophores of the monomeric units. Since the polyene-polyol chains in marinomycin A adopted an opposing, coplanar, but adjacent to each other, hence placing the polyene chains within very close proximity which enable them to interact, resulting in a ring conformation that was significantly different from the rest of marinomycins.

5.2. Previous Synthesis of Marinomycins

To our knowledge, there were only two reports on synthesis of this molecule so far, one was the total synthesis of marinomycin A and its isomer counterpart by Nicolaou *et al.*[133] and the other was the synthesis of monomeric unit by Cossy *et al.*[134] Since marinomycin A was a dimer of two symmetrical parts, synthetic efforts towards the molecule was correspondingly halved. The challenging part of the molecule was the array of polyol and polyene moieties, numerous chiral centers and dimerization of the monomeric units.

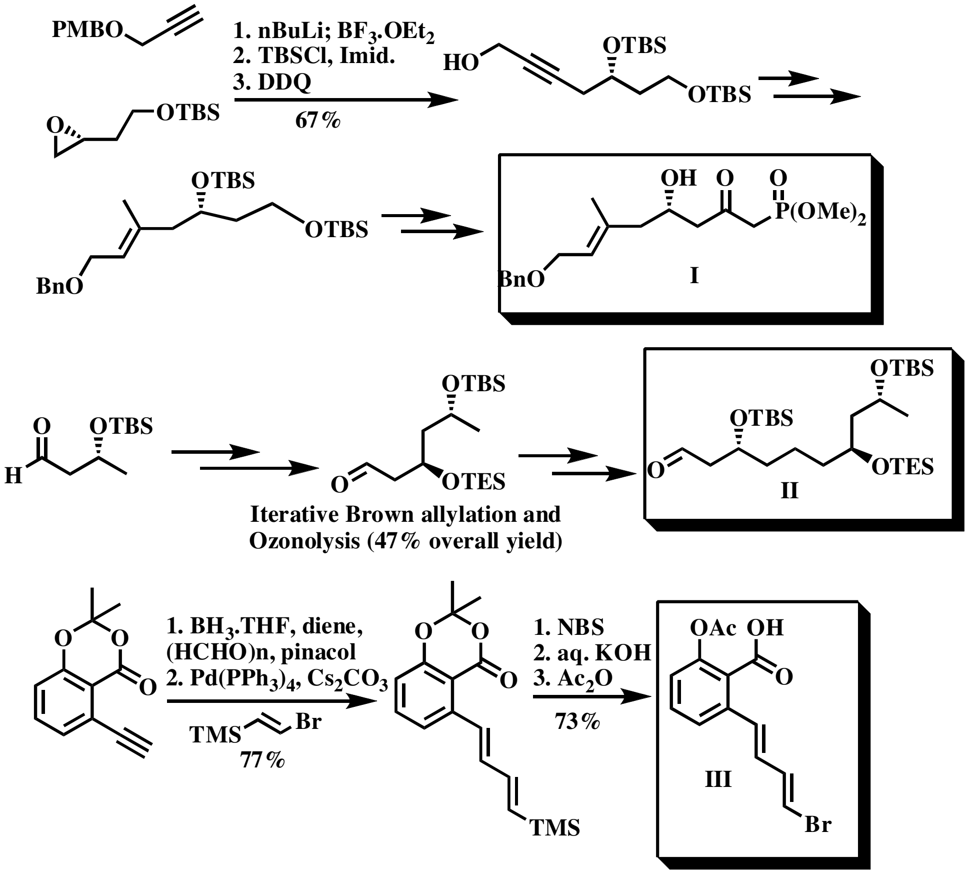
5.2.1. Synthesis by Nicolaou's group

Nicolaou *et al.* reported the total synthesis of marinomycins A-C and their unknown monomeric homologues. Marinomycin A, as mentioned earlier, was the most abundant among the three and isomerizes to marinomycins B and C under room lighting. Hence synthesis of marinomycin A would constitute the synthesis of B and C counterparts. In their effort to the synthesis, they utilized Suzuki coupling reaction as a means to construct the large and complex macrocycle.

---

[133] (a) Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S. *Angew. Chem. Int. Ed.* **2006**, *45*, 1. (b) Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S.; Cole, K. P.; Yamaguchi, J. J. *Am. Chem. Soc*. **2006**, *129,* 1760.

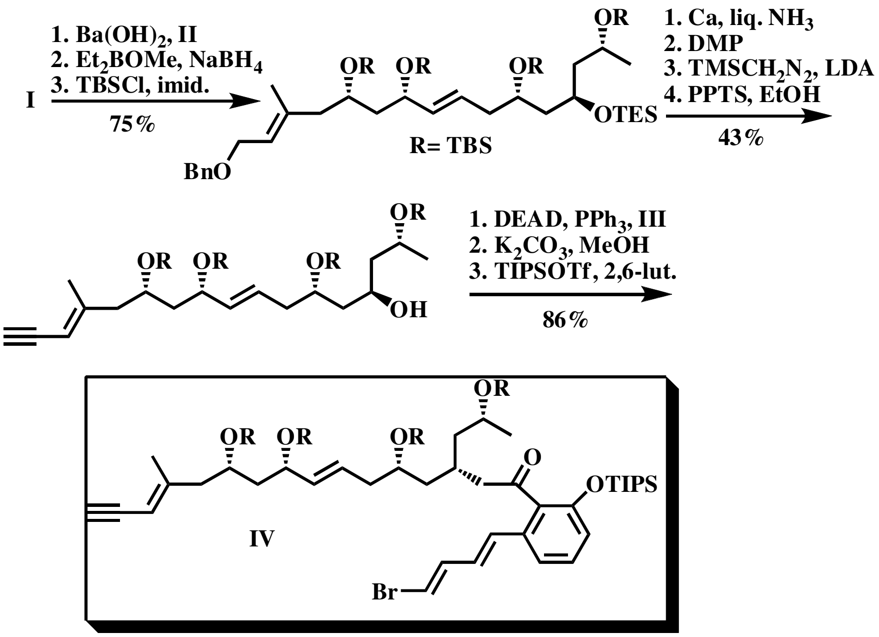
[134] (a) Amans, D.; Bellosta, V.; Cossy, J. *Org. Lett*. **2007**, *9*, 1453. (b) Amans, D.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2009**, *74*, 7665.


PMBO
OTBS
1. nBuLi; BF3.OEt2
2. TBSCl, Imid.
3. DDQ
67%
HO
OTBS
OTBS
OTBS
OTBS
BnO
OH O O
P(OMe)2
BnO
I
O OTBS
H
OTBS
O
OTES
Iterative Brown allylation and
Ozonolysis (47% overall yield)
OTBS
OTBS
O
OTES
II
1. BH3.THF, diene,
(HCHO)n, pinacol
2. Pd(PPh3)4, Cs2CO3
TMS
Br
77%
TMS
1. NBS
2. aq. KOH
3. Ac2O
73%
OAc OH
O
III
Br

Scheme 75. Nicolaou's synthesis of intermediate

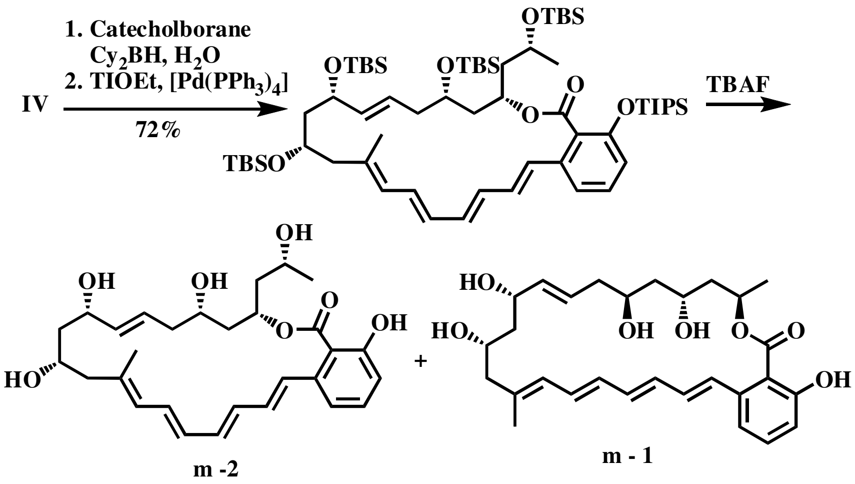
Ketophosphonate **I** was obtained from the known epoxide and propargylic ether which underwent a series of functional group interconversions and protection of the hydroxyl groups. Fragment **II** was obtained from the known aldehyde which underwent two iterations of Brown allylation and ozonolysis. The dienyl bromide carboxylic acid **III** was synthesized from the known acetonide acetylene (Scheme 75).

Assembly of the building blocks to afford the monomeric unit was carried out as shown in Scheme 76. Bromo enyne **IV** was then set for the Suzuki dimerization/ cyclization as initially planned.


1. Ba(OH)$_2$, II
2. Et$_2$BOMe, NaBH$_4$
3. TBSCl, imid.
75%
I
BnO
OR
OTES
R= TBS
1. Ca, liq. NH$_3$
2. DMP
3. TMSCH$_2$N$_2$, LDA
4. PPTS, EtOH
43%
OH
1. DEAD, PPh$_3$, III
2. K$_2$CO$_3$, MeOH
3. TIPSOTf, 2,6-lut.
86%
O
OTIPS
IV
Br

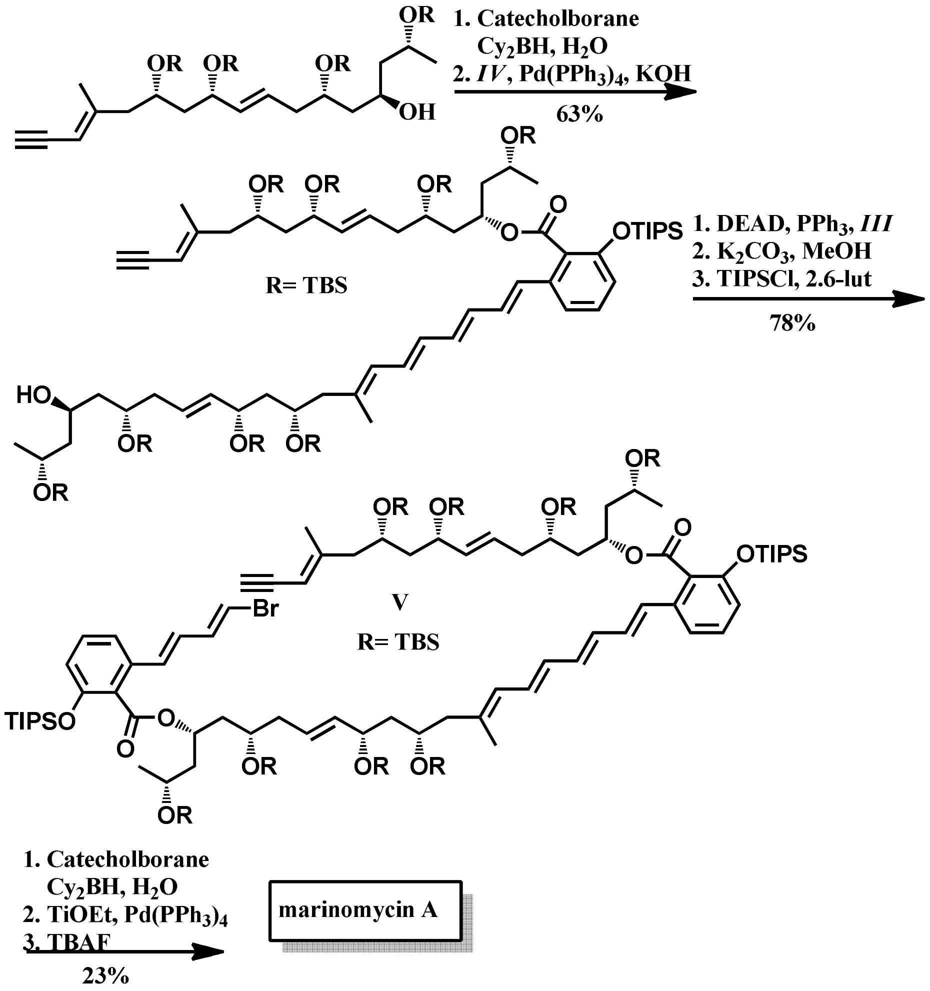
Scheme 76. Assembly of monomeric unit of marinomycin A

In attempt of dimerization according to their initial proposal, treatment of monomeric unit **IV** with catecholborane followed by TiOEt in the presence of palladium provided cyclized monomeric unit which upon global desilylation isomerizes to yield two isomers **m-1** and **m-2** respectively, instead of the intended dimer marinomycin A (Scheme 77).


1. Catecholborane
Cy$_2$BH, H$_2$O
2. TlOEt, [Pd(PPh$_3$)$_4$]
72%
IV
OTBS
TBSO
O
OTIPS
TBAF
OH
HO
m -2
+
m - 1

Scheme 77. Failed effort towards dimerization

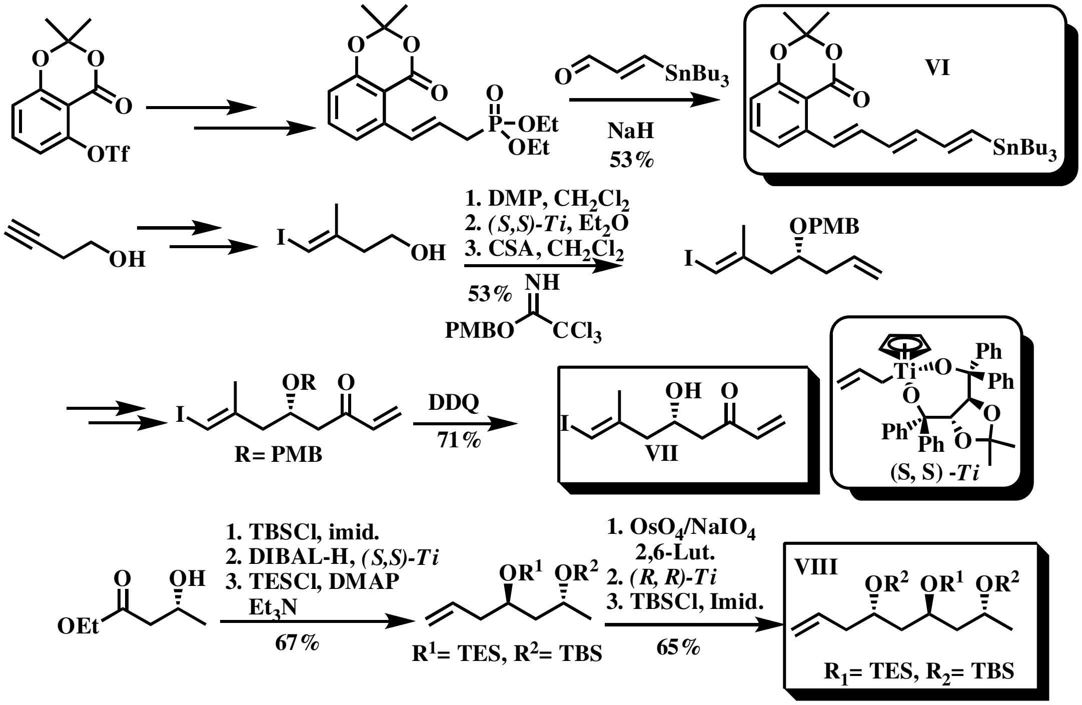
Due to this, they proceeded with stepwise Suzuki coupling followed by Mitsunobu reaction to yield enyene ester **V**. Finally, treatment with cathecolborane followed by excess amount of TiOEt (300 equiv.) and without purification, treatment with palladium furnished the protected macromolecule. Global desilylation provided marinomycin A (Scheme 78).


OR
OR OR OR
OH
1. Catecholborane
Cy2BH, H2O
2. IV, Pd(PPh3)4, KOH
63%
R= TBS
OTIPS
HO
1. DEAD, PPh3, III
2. K2CO3, MeOH
3. TIPSCl, 2.6-lut
78%
Br
V
R= TBS
TIPSO
1. Catecholborane
Cy2BH, H2O
2. TiOEt, Pd(PPh3)4
3. TBAF
23%
marinomycin A

Scheme 78. Completion of marinomycin A synthesis

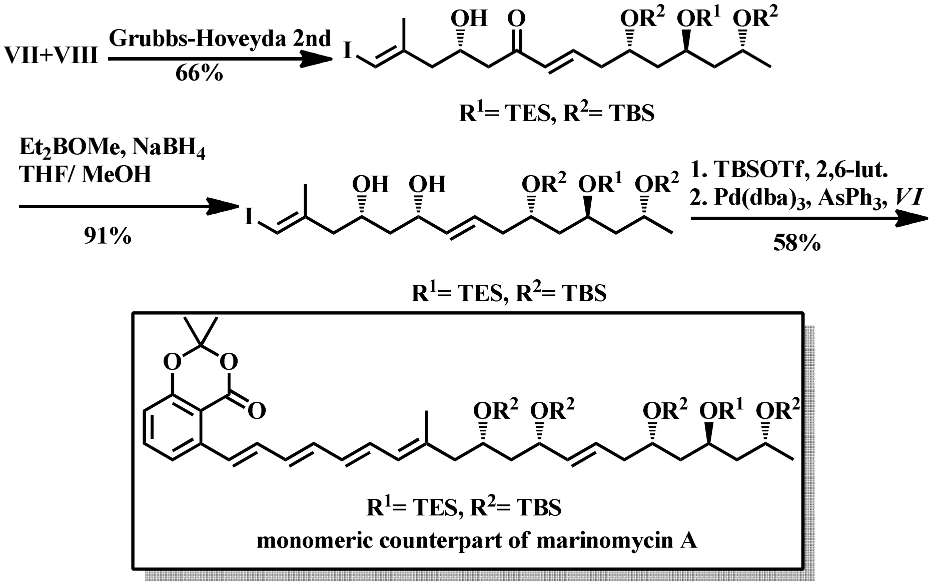
5.2.2. Synthesis by Cossy's group

Cossy *et al.* reported the synthesis of monomeric counterpart of marinomycins by utilizing pallado-catalyzed Stille cross-coupling reaction, Horner-Wardworths-Emmons olefination and metathesis reaction as the key steps. The synthesis of intermediates **VI**, **VII** and **VIII** were shown in Scheme 79. They utilized an optically active allyltitanium complex as a tool in asymmetric allylation procedure.


OTf
SnBu3
NaH
53%
VI
OH
1. DMP, CH2Cl2
2. (S,S)-Ti, Et2O
3. CSA, CH2Cl2
53%
PMBO
CCl3
NH
OPMB
OR
R= PMB
DDQ
71%
OH
VII
Ti
Ph
(S, S) -Ti
OEt
1. TBSCl, imid.
2. DIBAL-H, (S,S)-Ti
3. TESCl, DMAP
Et3N
67%
OR1 OR2
R1= TES, R2= TBS
1. OsO4/NaIO4
2,6-Lut.
2. (R, R)-Ti
3. TBSCl, Imid.
65%
VIII
OR2 OR1 OR2
R1= TES, R2= TBS

Scheme 79. Cossy's synthesis of intermediates

In attempt to complete the synthesis of polyketides marinomycin A, selective deprotection of TES group over TBS group was required. However due to the labile nature of the acetonide protecting group, they had to reassemble protection of the salicylic moiety of the monomeric unit as TIPS and methyl ester moiety. Even so, selective deprotection of TES over TBS group in this regard did not proceed as planned, stopping them from continuation of the synthesis with the dimerization (Scheme 80).

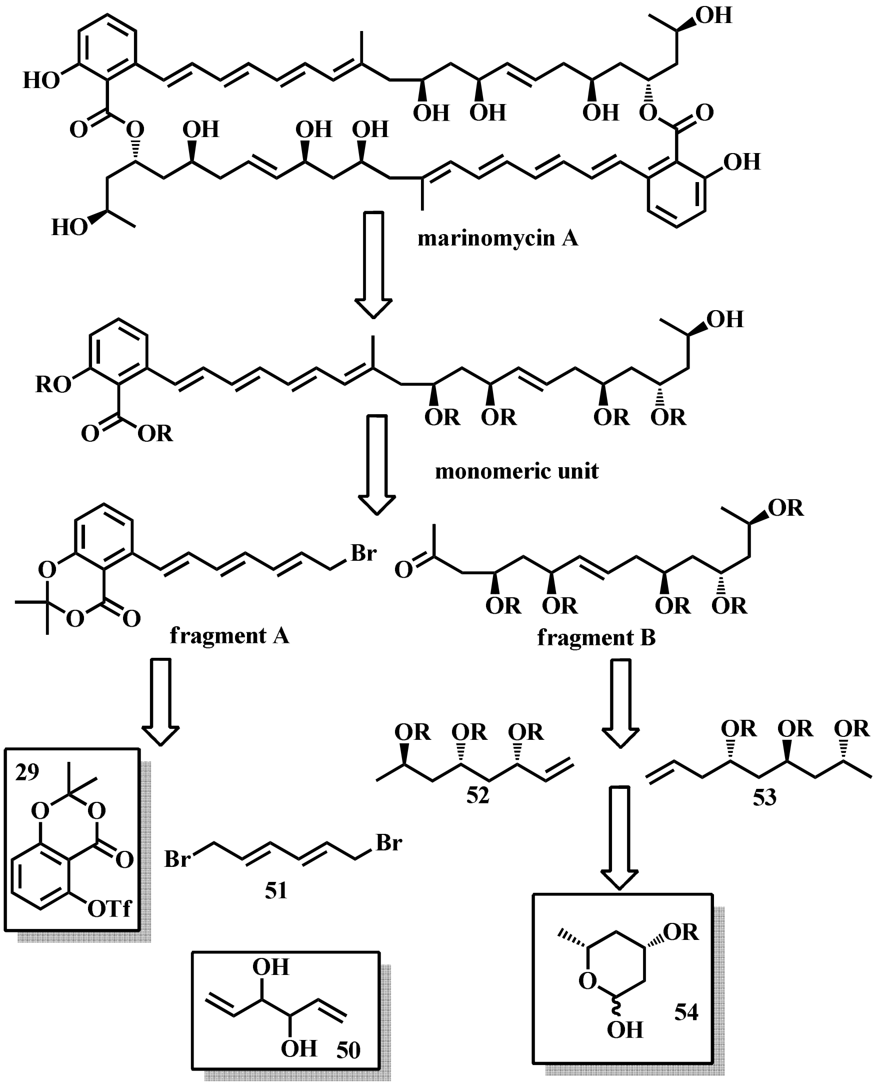

VII+VIII
Grubbs-Hoveyda 2nd
66%
R1= TES, R2= TBS
Et2BOMe, NaBH4
THF/ MeOH
91%
R1= TES, R2= TBS
1. TBSOTf, 2,6-lut.
2. Pd(dba)3, AsPh3, VI
58%
R1= TES, R2= TBS
monomeric counterpart of marinomycin A

Scheme 80. Completion of monomeric synthesis

5.3. Our attempt to marinomycins synthesis

5.3.1. Retrosynthetic analysis

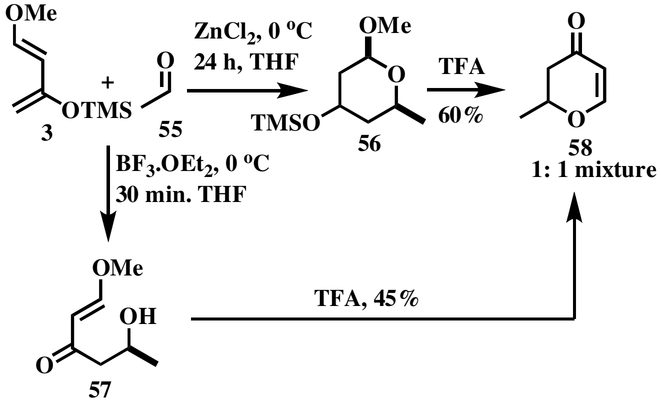
Similar to previously described syntheses, we planned to approach the synthesis of this macrolide from the monomeric counterpart and then adjoining them together through lactonization (Scheme 81). The monomeric unit can be accessed through Wittig type olefination of two key fragment A and fragment B. Furthermore, synthesis of fragment A can be achieved from the key precursor lactol **54**. As for fragment B, we planned to access from the known acetonide **29** that has been previously used by other groups.


HO
OH
OH
OH
OH
OH
OH
OH
O
O
O
O
OH
HO
marinomycin A
RO
O
OR
OH
OR
OR
OR
OR
monomeric unit
Br
O
O
O
O
OR
OR
OR
OR
OR
fragment A
fragment B
29
O
O
O
OTf
Br
Br
51
OR
OR
OR
52
OR
OR
OR
53
OH
OH
50
OR
O
OH
54

Scheme 81. Retrosynthetic analysis of marinomycin A

5.3.2. Synthesis of polyol moiety

We embarked on the racemic synthesis by hetero Diels-Alder reaction of Danishefsky diene **3** with acetaldehyde in the presence of Lewis acids $ZnCl_2$ or $BF_3.OEt_2$ followed by treatment with TFA to give vinylogous lactone **58**. Reaction with $ZnCl_2$ showed higher yield (60%) compared to that with $BF_3.OEt_2$ (45%). This prompted us to go by this route despite its longer reaction time (Scheme 82).



Scheme 82. Hetero Diels-Alder reaction pathway

Even though both $ZnCl_2$ and $BF_3.OEt_2$ resulted in the same products, they actually underwent different mechanisms as reported by Danishefsky *et al.*[135] The reaction catalyzed by $ZnCl_2$ was a true pericyclic reaction *via* an all carbon framework of the classical Diels-Alder process through the intermediate shown in Scheme 82. Reaction with $BF_3.OEt_2$ on the other hand, proceeded through Mukaiyama aldol type reaction to give intermediate **57** which was finally converted to the pyrone after treatment with TFA.

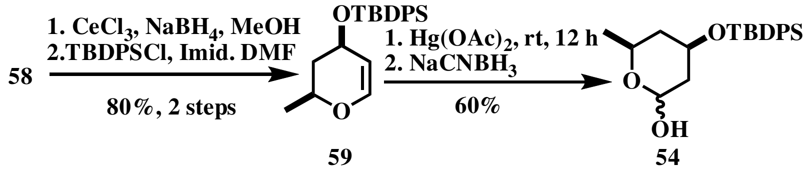
Luche's reduction[136] of **58** followed by TBDPS protection of the hydroxyl group provided us with two isomers of **59** in 1:1 isomer ratio which showed that presence of the methyl group was influential in directing the reduction in a stereoselective manner to give *syn* product. Subsequent oxymercuration[137] followed by treatment with $NaCNBH_3$ provided lactol **54** which was our sole precursor for polyol fragment B (Scheme 83).

---

[135] (a) Danishefsky, S.; Larson, E. R.; Askin, D. *J. Am. Chem. Soc.* **1982**, *104*, 6457. (b) Danishefsky, S.; Pearson, W. H.; Harvey, D. F. *J. Am. Chem. Soc.* **1984**, *106*, 2456. (c) Larson, E. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1982**, *104*, 6458. (d) Larson, E. R.; Danishefsky, S. J. *Tetrahedron. Lett.* **1982**, *23*, 1975.

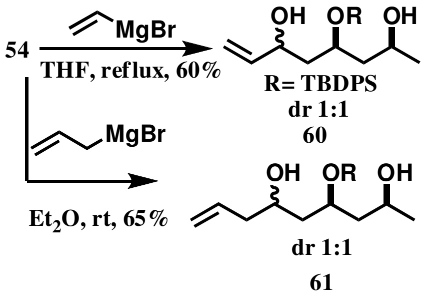
[136] (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Luche, J. L.; Rodriguez-Hahn, L.; Crabbe, P. *J. Chem. Soc. Chem. Commun.* **1978**, 601.

[137] Bordwell, F. G.; Douglass, M. L. *J. Am. Chem. Soc.* **1966**, *88*, 993.


58
1. CeCl3, NaBH4, MeOH
2.TBDPSCl, Imid. DMF
80%, 2 steps
OTBDPS
O
59
1. Hg(OAc)2, rt, 12 h
2. NaCNBH3
60%
OTBDPS
O
OH
54

Scheme 83. Synthesis of lactol 54

We then treated lactol **54** with vinyl Grignard reagent which yielded allyl alcohol **60** as a mixture of isomers. Treatment of the same lactol **49** with allyl magnesium bromide also showed the formation of homoallylic alcohol **53** that rendered our approach feasible in the synthesis of polyol fragment of marinomycin A. We hoped that the substituent in the lactol moiety could provide the necessary directing/ inductive effect to install the next stereogenic centers (Scheme 84).


54
MgBr
THF, reflux, 60%
OH OR OH
R= TBDPS
dr 1:1
60
MgBr
Et2O, rt, 65%
OH OR OH
dr 1:1
61

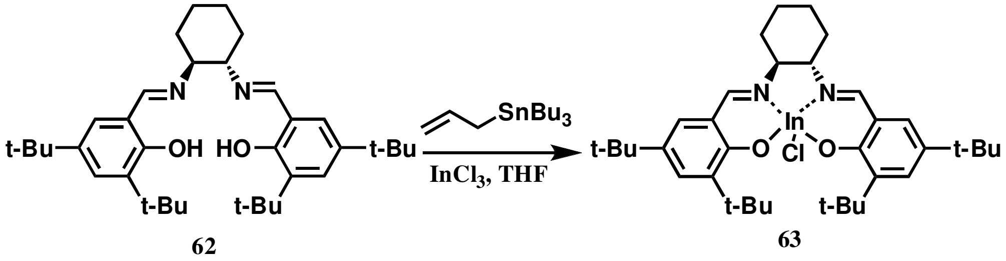
Scheme 84. Proving synthetic route towards fragment A

Inspired by Jacobsen catalyst for catalytic reaction,[138] we initially tried to expand our previous methodology of indium-catalyzed reaction[139] using salen ligand. Jacobsen *et al.* had screened many metals with this particular ligand but not with indium. The catalyst was prepared *in situ* and substrate was added subsequently.

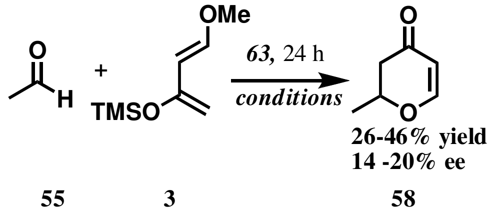
---

[138] Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315.
[139] Teo, Y. C.; Loh, T. P. *Org. Lett.* **2005**, *7*, 2539.

Preparation of Indium Complex:


t-Bu
OH
HO
t-Bu
t-Bu
t-Bu
N
N
SnBu3
InCl3, THF
t-Bu
N
N
In
O
Cl
O
t-Bu
t-Bu
t-Bu
62
63

Testing of HDA

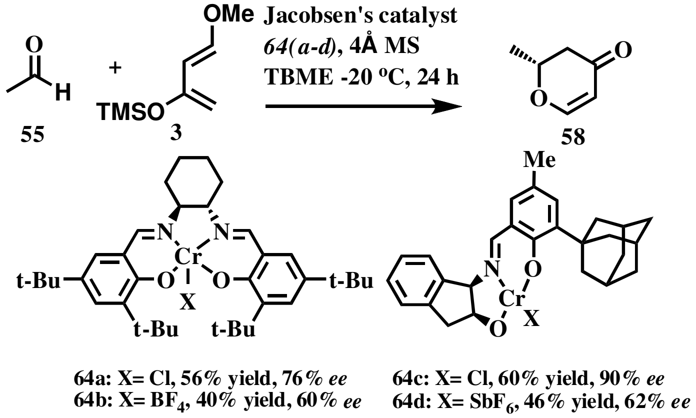

O
H
+
OMe
TMSO
63, 24 h
conditions
O
O
26-46% yield
14 -20% ee
55
3
58

Entry	Solvent	Temp (° C)	Yield (%)	*ee* (%)
1	THF	0	43	14
2	Acetone	0	46	19
3	TBME	0	40	20
4	CH_2Cl_2	0	37	16
5	THF	-20	27	16
6	Acetone	-20	26	20
7	TBME	-20	32	18
8	CH_2Cl_2	-20	28	16

Table 4. Indium complex catalyzed hetero Diels-Alder reaction

However, we only obtained low to moderate yield and poor enantioselectivity for the reactions. We isolated the indium complex and NMR showed the formation of the species as compared to the spectrum of the free ligand. The presence of unreacted $InCl_3$ in the reaction probably interfered with this reaction since $InCl_3$ itself was a Lewis acid that could catalyze this type of reaction. Hence, we did not pursue this strategy further. Asymmetric hetero Diels-Alder with this particular substrate has been reported to give low to moderate enantiomeric excess.[140] The lack of selectivity was particularly observed for saturated aliphatic aldehydes which were not bulky, possibly due to the absence of electronic interaction with the catalyst (Table 4).

We then screened several types of Jacobsen's chromium catalysts **64 (a-d)**[141] in the presence of powdered molecular sieve 4Å. After optimization of condition, with catalyst **64c** we managed to obtain 90% enantiomeric excess and 60% yield of lactone **58** (Scheme 85).


OMe
Jacobsen's catalyst
64(a-d), 4Å MS
TBME -20 °C, 24 h
O
H
+
TMSO
55
3
58
O
O
Me
N
N
Cr
O
O
X
t-Bu
t-Bu
t-Bu
t-Bu
N
O
Cr
O
X
64a: X= Cl, 56% yield, 76% ee
64b: X= BF4, 40% yield, 60% ee
64c: X= Cl, 60% yield, 90% ee
64d: X= SbF6, 46% yield, 62% ee

Scheme 85. Hetero Diels-Alder reaction with Jacobsen's catalyst

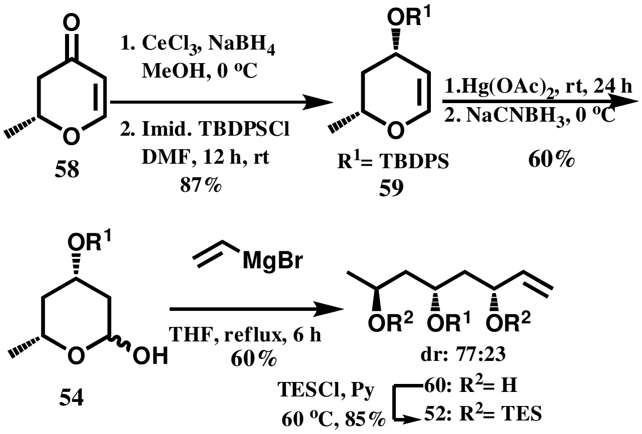
Treatment of lactone **58** with $NaBH_4$ followed by protection with TBDPS gave a single enantiomer which upon NOESY experiment showed *syn* stereochemistry of the product **59**. After that, treatment with mercury acetate gave us lactol **54** which served as building block for both parts of polyol fragment B. We expected the substituent in the lactol moiety to provide inductive effect in driving the reaction towards the desired isomer.

---

[140] (a) US patent no: 5767295, 1998.

[141] (a) Lucas, B. S.; Luther, L. M.; Burke, S. D. *J. Org. Chem.* **2005**, *70*, 3757. (b) Joly, G. D.; Jacobsen, E. N. *Org. Lett.* **2002**, *4*, 1795. (c) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398. (d) Paterson, I.; Luckhurst, C. A. *Tetrahedron Lett.* **2003**, *44*, 3749. (e) Schaus, S. E.; rånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403. (f) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974. (g) Kwiatkowski, P.; Asztemborska, M.; Jurczak, J. *Synlett* **2004**, 1755.

Treatment of lactol **54** with vinylmagnesium bromide provided allylic alcohol **60**, unfortunately only with moderate diastereoselectivity of 77:23 which was probably due to the high temperature needed to complete the reaction. We did not observe meaningful conversion upon addition of the Grignard reagent at room temperature; hence the reaction had to be heated at reflux which compromised its selectivity. The isomers were then separated by column chromatography and protected as the TES ether (Scheme 86). The stereochemistry was established by protecting the polyhydroxyl group as acetonides as reported by Rychnovsky.[97]

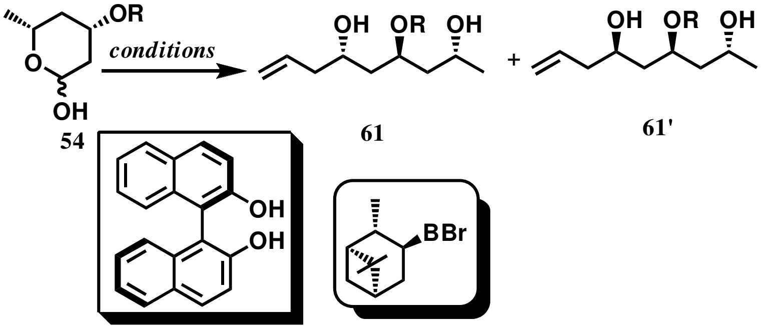


Scheme 86. Synthesis of vinyl alcohol 52

Treatment of lactol **54** with allyl Grignard reagent failed to give the product stereoselectively, but instead as 1:1 mixture of diastereomer. Indium-mediated allylation in water gave diastereoselectvity of 60:40 with the desired isomer as the major product. We then tried the allylation using our own methodology employing

In(III) BINOL-complexes as catalyst[142] which also did not furnish the product; the different nature of the lactol group compare to the conventional aldehyde might have rendered this method unsuitable.

Next, we found out that Brown's allylation[143] could give the desired product, even though without excellent control of the diastereoselectivity due to the mismatch effect, with a diastereomeric ratio of 90:10. The stereochemistry was established by protecting the polyhydroxyl group as acetonides as reported by Rychnovsky.[97] Efforts toward asymmetric allylation of cyclic lactol **54** are summarized in Table 5.



54 **61** **61'**

(*R*)-BINOL **(+) DIPBr**

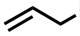
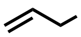
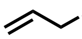
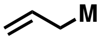
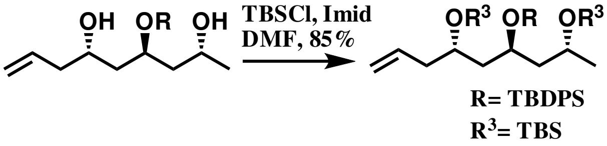
Conditions	Yield	dr (61: 61')
1.  MgBr, Et_2O, rt, 2 h	65%	50: 50
2.  Br , In, THF:H_2O	70%	60: 40
3.  $SnBu_3$, (*R*)-BINOL In (III),MS 4A, CH_2Cl_2	-	-
4.  MgBr , (+) DIPBr, Et_2O	65%	90:10

Table 5 Allylation of lactol

---

[142] Teo, Y. C.; Tan, K. T.; Loh, T.P. *Chem. Commun.* **2005**, 1318.
[143] Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.

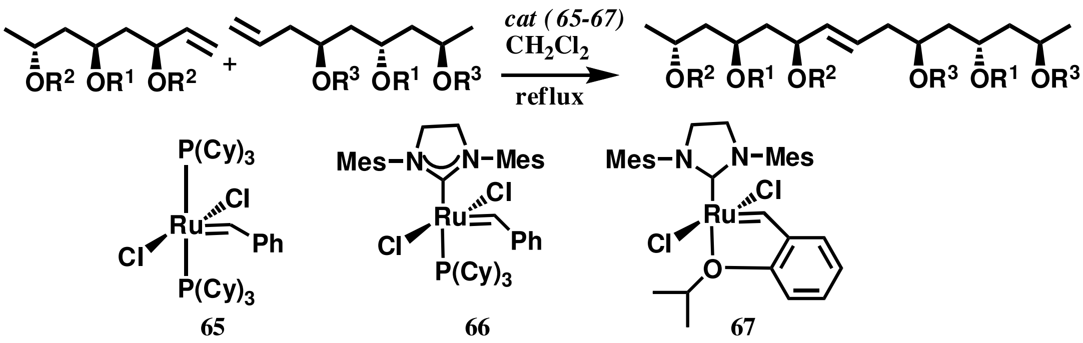
Protection of the desired isomer with TBS group provided us with the protected homoallylic compound **53**. The choice of protecting group was to facilitate selective deprotection that was crucial in the later stage (Scheme 87).



61 **53**

Scheme 87. Protection of intermediate 61

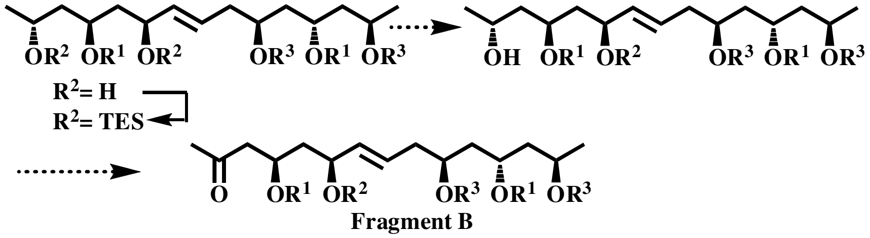
With the two coupling partners **52** and **53**, we carried out olefin metathesis first using the second generation Grubbs catalyst **66**. However the reaction was messy on TLC, probably due to significant amount of homocoupled products. We suspected that this might be due to steric effect of the allylic moiety of compound **53**, hence we carried out the metathesis again with the less bulky first generation of Grubbs catalyst **65**. But to our dismay, this did not give meaningful yield as well. We then attempted to couple the unprotected allyl moiety **52** and protected homoallylic **55** using the second generation Grubbs catalyst **66** and managed to obtain 26% yield with 90:10 *E/Z* selectivity after refluxing for 6 h. Finally, employing the second generation Grubbs-Hoveyda catalyst **67** provided the best yield of 52% with similar diastereoselectivity (*E/Z* 90:10) (Table 6).


OR2 OR1 OR2
+
OR3 OR1 OR3
cat (65-67)
CH2Cl2
reflux
OR2 OR1 OR2
OR3 OR1 OR3
P(Cy)3
Cl
Ru
Ph
Cl
P(Cy)3
65
Mes-N
N-Mes
Cl
Ru
Ph
Cl
P(Cy)3
66
Mes-N
N-Mes
Cl
Ru
Cl
O
67

Entry	R^1	R^2	R^3	Catalyst	Yield (E:Z)
1	TBDPS	TES	TBS	**65**	trace
2	TBDPS	TES	TBS	**66**	trace
3	TBDPS	H	TBS	**66**	26% (90: 10)
4	TBDPS	H	TBS	**67**	52% (90: 10)

Table 6. Olefin metathesis attempts towards polyol fragment B

Subsequent protection and selective deprotection followed by oxidation could furnish the polyol fragment to marinomycin A.


OR2 OR1 OR2
OR3 OR1 OR3
OH OR1 OR2
OR3 OR1 OR3
R2= H
R2= TES
O
OR1 OR2
OR3 OR1 OR3
Fragment B

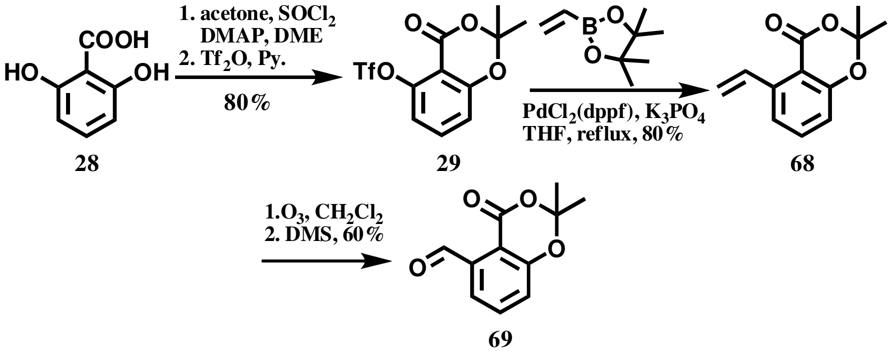
Scheme 88. Completion of fragment B

5.3.3. Synthesis of polyene moiety (fragment A)

We approached the synthesis of fragment A through the known triflate **29**[144] that can be synthesized from commercially available 2,6-dihydroxybenzoic acid **28**. Suzuki coupling of the triflate with [4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane] followed by ozonolysis yielded aldehyde **69** in 80% yield (Scheme 89).

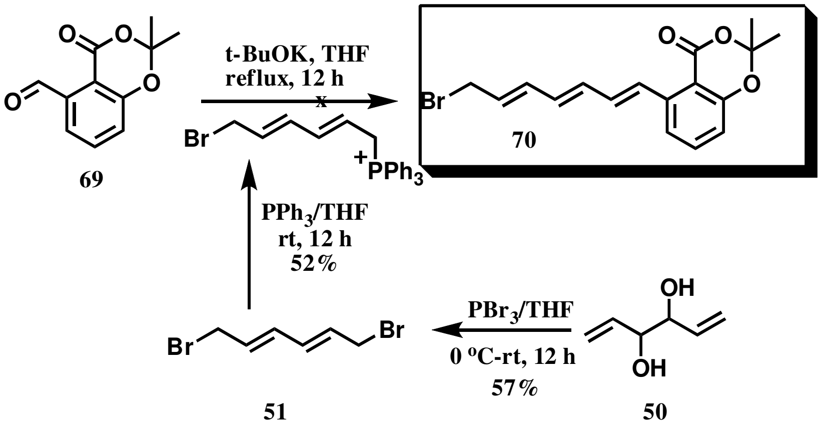
---

[144] Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071.


COOH
HO
OH
1. acetone, SOCl2
DMAP, DME
2. Tf2O, Py.
80%
TfO
O
O
O
B
O
O
PdCl2(dppf), K3PO4
THF, reflux, 80%
28
29
68
1.O3, CH2Cl2
2. DMS, 60%
69

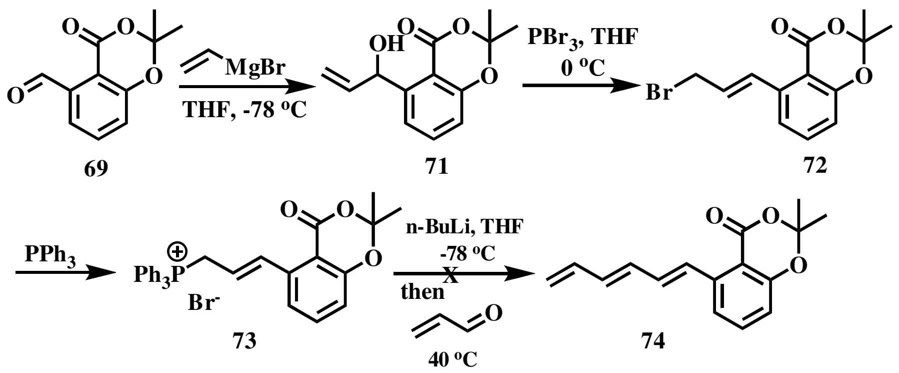
Scheme 89. Synthesis of aldehyde 69

According to our proposal, we then tried to carry out Wittig reaction which unfortunately did not yield the product. After refluxing for 12 h, decomposition of starting material was observed (Scheme 90).


O
O
O
69
t-BuOK, THF
reflux, 12 h
x
Br
+PPh3
Br
70
PPh3/THF
rt, 12 h
52%
Br
Br
51
PBr3/THF
0 °C-rt, 12 h
57%
OH
OH
50

Scheme 90. Alternative approach towards fragment B

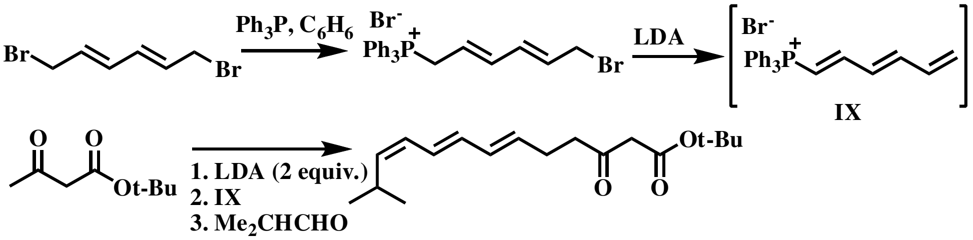
We then tried to invert the coupling partner as shown in Scheme 91. Treatment of aldehyde **69** with vinyl Grignard reagent at low temperature furnished alcohol **71** that underwent bromination to form compound **72** with 80% yield. Treatment with triphenylphosphine was carried out to obtain intermediate **73** which was subjected to Wittig olefination conditions with acrolein.


MgBr
THF, -78 °C
OH
PBr$_3$, THF
0 °C
Br
PPh$_3$
Ph$_3$P
Br$^-$
n-BuLi, THF
-78 °C
X
then
40 °C
69
71
72
73
74

Scheme 91. Attempt towards the synthesis of fragment B

However, again the attempt at Wittig coupling was unsuccessful, even though after changing of the phosphine moiety to the more active phosphonate for Horner-Wadsworth-Emmons reaction. We suspected this could be due to the acetonide protecting group that is unstable to base (Scheme 91).

White *et al.*[145] has reported a tandem nucleophilic addition to a dienylphosphonium salt followed by Wittig reaction that gave *E*-polyene moiety with good selectivity. The sequence involved addition of a nucleophilic anion to the dienyl phosphonium salt to generate *E*-allylphosphorane with suppressed isomerization, which undergoes immediate kinetically-controlled Wittig reaction with an aldehyde (Scheme 92).

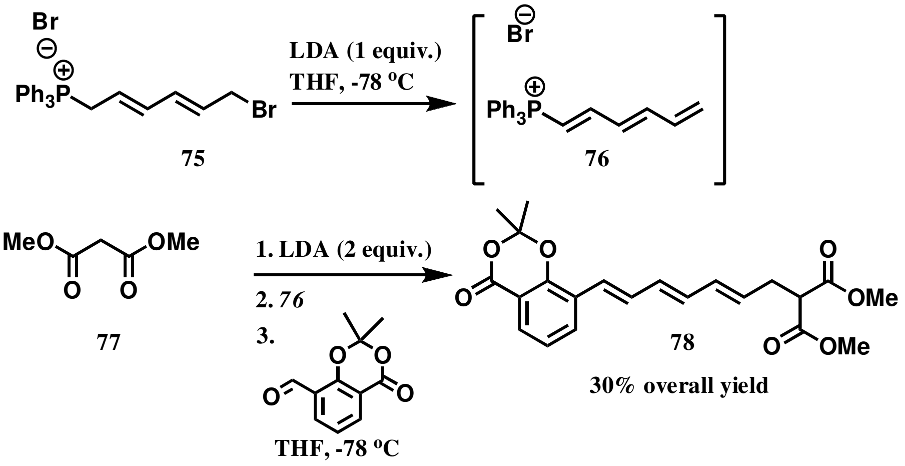

Br
Br
Ph$_3$P, C$_6$H$_6$
Br$^-$
Ph$_3$P
LDA
IX
Ot-Bu
1. LDA (2 equiv.)
2. IX
3. Me$_2$CHCHO

Scheme 92. Tandem Wittig reaction of polyene

---

[145] White, J. D.; Jensen, M. S. *Terahedron. Lett.* **1992**, *33*, 577.

Replacing the nucleophile with dimethyl malonate could drive the deprotonation of the only α-hydrogen available and probably suit our synthetic strategy to install the polyene moiety in a concise tandem manner. We then carried out the reaction and managed to obtain the target product in 30% overall yield (Scheme 93).


Br
Ph3P
Br
75
LDA (1 equiv.)
THF, -78 °C
Br
Ph3P
76
MeO
OMe
O
O
77
1. LDA (2 equiv.)
2. 76
3.
THF, -78 °C
O
O
OMe
OMe
78
30% overall yield

Scheme 93. Synthesis of polyene intermediate

However, we encountered problem with decarboxylation of the coupling product to furnish our target fragment A. We planned to carry out an allylic bromination followed by elimination and decarboxylation to give us the polyene motif. However, our attempts to do the allylic bromination[146] did not proceed as planned after subjecting to various conditions as shown in Table 7.

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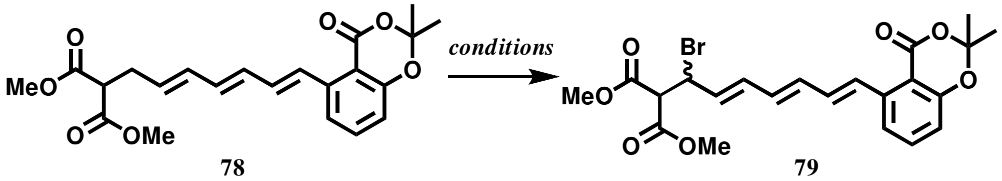
[146] Bauer, D. P.; Macomber, R. S. *J. org. Chem.* **1975**, *40*, 1990.



Conditions	Result
$CuBr_2$, EtOAc: $CHCl_3$ = 1: 1, reflux 4 h	Double bond destroyed
$CuBr_2$, EtOAc: $CHCl_3$ = 1:1, rt	No reaction
$CuBr_2$, EtOAc:$CHCl_3$: THF= 1:1:1, rt	No reaction
NBS, THF, -78°C- rt	No reaction

Table 7. Allylic bromination of intermediate 78

Better methods to access this fragment need to be outlined. During our literature search for a better route to this fragment, we found that β-keto esters can undergo dealkoxycarbonylation which is known as Krapcho reaction (Figure 9).[147]

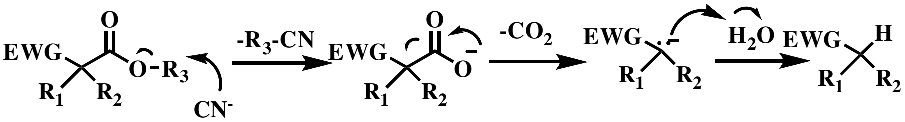


Figure 9. Mechanism of Krapcho reaction

Another ester group can be converted to bromide by treating the corresponding carboxylic acid with bromide source in the presence of silver salt, a reaction that is known as Hunsdiecker reaction[148] to furnish polyene fragment A (Figure 10).

---

[147] (a) Krapcho, A. P.; Glynn, G. A.; Grenon, B. J. *Tetrahedron. Lett.* **1967**, 215. (b) Krapcho, A. P.; Mundy, B. P. *Tetrahedron* **1970**, 26, 5437.

[148] (a) Hunsdiecker, H.; Hunsdiecker, C. *Ber.* **1942**, 75B, 291 (b) Rice, F. A. H. *J. Am. Chem. Soc.* **1956**, 78, 3173. (c) Rice, F. A. H.; Morganroth, W. *J. Org. Chem.* **1956**, 21, 1388. (d) Davis, J. A.; Herynk, J.; Carroll, S.; Bunds, J.; Johnson, D. *J. Org. Chem.* **1965**, 30, 415.
(e) Cristol, S. J.; Firth, W. C. Jr. *J. Org. Chem.* **1961**, 26, 280.

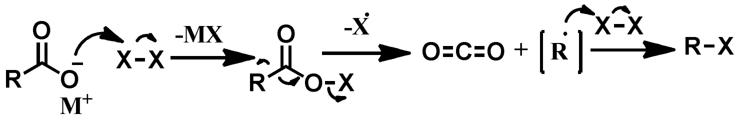
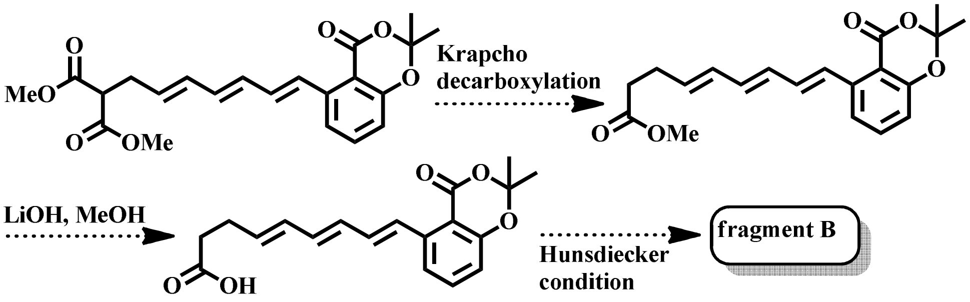


Figure 10. Mechanism of Hunsdiecker reaction

Hence for further study, we proposed the following steps towards the synthesis of polyene moiety.



Scheme 94. Proposed route towards fragment B

5.4. Conclusion

In summary, we have developed a synthetic route to the key precursor of marinomycin A utilizing symmetry driven strategy to construct the polyol moiety from the key intermediate lactol **54**. The challenges included the olefin metathesis reaction and selective protection and deprotection to functionalize the polyol moiety. A variety of silyl protecting groups would provide us with the possibility of selective protection and deprotection.

We also have demonstrated a tandem procedure to install the polyene moiety in a concise manner. However further effort is needed to find a suitable condition to carry out allylic bromination and elimination to get the polyene fragment A to complete the synthesis towards the monomeric unit of marinomycin A.

Chapter 6

Experimental Section

6.1. General Methods

Experiments involving moisture and/or air sensitive components were performed in oven-dried glassware under a positive pressure of nitrogen using freshly distilled solvents. Glassware for extra air sensitive reactions were flame-dried. Commercial grade solvents and reagents were used without further purification unless otherwise stated following the guidelines of Perrin and Armarego.[149] Anhydrous THF was obtained by distillation under nitrogen atmosphere from a deep purple solution resulting from sodium and benzophenone. Anhydrous dichloromethane was distilled over calcium hydride under nitrogen atmosphere.

Azeotropic drying of starting materials or reagents was performed by the addition of the stated amount of anhydrous tetrahydrofuran, ensued by azeotropic removal of tetrahydrofuran with traces of moisture in *vacuo* followed by subsequent purging with nitrogen.

Triethylamine was distilled over calcium hydride and stored over molecular sieves to maintain dryness. Hydrochloric acid was diluted from concentrated 37% solution. 3M sodium hydroxide solution was prepared from sodium hydroxide pearls. Saturated solutions of ammonium chloride, sodium chloride, sodium bicarbonate, and sodium carbonate were prepared from their respective solids.

Chromatography

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were

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[1] Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford. 1988.

visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

Instruments & Equipments

Infrared Spectroscopy

Infrared spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. Samples were either examined neat between NaCl salt plates or as a solution in dichloromethane.

Nuclear Magnetic Resonance Spectroscopy

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on Bruker AMX 300, 400, and 500 MHz spectrophotometer with $CDCl_3$ as solvent. Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.26, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); dt (doublets of triplet); or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a *J* value in Hz.

Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). The proportion of diastereomers and geometric isomers was determined from the integration of ^{1}H NMR and ^{13}C NMR spectra.

Optical Rotation

Optical rotation was measured by using a JASCO P-1030 Polarimeter equipped with a sodium vapour lamp at 589 nm. Concentration is denoted as *c* and was calculated as grams per milliliters (g/100 mL) whereas the solvent was indicated in parentheses (*c*, solvent).

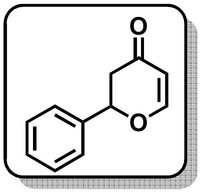
Mass Spectrometry

High resolution mass spectral analysis (HRMS) was performed on Waters Q-Tof Permiers Mass Spectrometer. MS and HRMS were reported in units of mass of charge ratio (*m/z*).

Nomenclature

Systematic nomenclature for the compounds would follow the numbering system as defined by IUPAC. Compounds were named with assistance from CS Chemdraw Ultra 12.0 software.

6.2. Indium (III) Chloride Catalyzed Mukaiyama-Michael Addition



2-Phenyl-2H-pyran-4(3H)-one (4)

A mixture of benzaldehyde (1.05 g, 10.0 mmol, 1 equiv.) and trans-1-methoxy-3-trimethylsiloxy-1,3-butadiene (2.1 mL, 11.0 mmol, 1.1 equiv.) in THF (50 mL) was brought to 0 °C. Zinc chloride (1.36 g, 10.0 mmol, 1 equiv.) in THF (20 mL) was added slowly. The mixture was warmed to room temperature and allowed to stir for 10 h. The reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with diethyl ether (3 × 15 mL). The ether extracts were combined and treated with trifluoroacetic acid (catalytic) for 1 h. Thereafter saturated sodium bicarbonate solution (5 mL) was added to quench the reaction mixture followed by extraction with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hexane: ether, 1:1) to afford the product as a yellow oil (0.75 g, 44% yield).

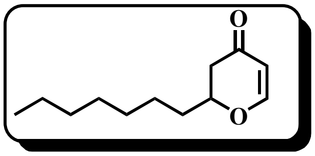
R_f = 0.28 (Hexane: Et_2O, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 6.0 Hz, 1H), 7.45- 7.39 (m, 5H), 5.53 (dd, *J* = 6.0, 1.1 Hz, 1H), 5.43 (dd, *J* = 14.4, 3.3 Hz, 1H), 2.92 (dd, *J* = 16.8, 14.5 Hz, 1H), 2.67 (ddd, *J* = 16.9, 3.4, 1.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): 192.4, 163.4, 138.0, 129.2, 129.1, 126.3, 107.6, 81.3, 43.6.

FTIR (neat): ν_{max} 1667, 1402, 1271, 1038, 698 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{11}H_{10}O_2$ [M^+] = 174.0681. Found 174.0644.



2-Heptyl-2H-pyran-4(3H)-one (5)

Bright yellow oil (0.86 g, 60%)

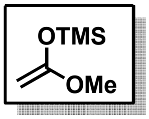
R_f = 0.52 (Hexane: EtOAc, 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, *J*= 6 Hz, 1H), 5.39 (d, *J*=1.6 Hz, 1H), 4.42-4.36 (m, 1H), 2.54-2.40 (m, 2H), 183-1.77 (m, 1H), 1.68-1.61 (m, 1H), 1.31-1.27 (m, 9H), 0.88 (t, *J*= 7.0 Hz, 3H)

^{13}C NMR (500 MHz, $CDCl_3$): δ 192.8, 163.3, 106.9, 79.6, 41.8, 34.4, 31.7, 29.2, 29.0, 24.7, 22.6, 14.1.

FTIR (neat): ν_{max} 1670, 1598, 1404, 1273, 1039, 756 cm^{-1}.

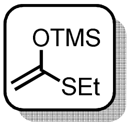
HRMS (ESI) Calcd for $C_{12}H_{20}O_2$ [M^+]: 197.1722 Found: 197.1722



((1-Methoxyvinyl)oxy)trimethylsilane (6b)

To a solution of *i*Pr_2NH (47.8 mL, 34 g, 341 mmol) in THF (330 mL), BuLi (1.56 M solution in hexane, 200 mL, 312 mmol) was added dropwise in an ice bath, and the mixture was stirred for 15 min. After cooling to –78 °C, a mixture of methyl acetate (27.7 mL, 25 g, 284 mmol) and TMSCl (43.5 mL, 37 g, 343 mmol) in THF (170 mL) was added. After the addition was completed, the cooling bath was removed, and the mixture was stirred for 3 h at rt. Then, THF was evaporated and hexane was added. The resulting precipitate was filtrated off through a celite pad, and the residue was washed with hexane. The combined filtrate was evaporated, and the resulting residue was purified by distillation (bp. 70 °C/60 mmHg), giving **6a** in 42% yield (19 g), which contains a trace amount of C–TMS (less than 1/50).

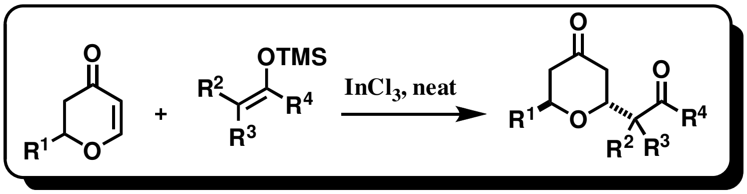
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.47 (d, J = 2.5 Hz, 1H), 3.13 (s, 3H), 3.10 (d, J = 2.5 Hz, 1H), 0.20 (s, 9H)



(1-(Ethylthio)vinyloxy)trimethylsilane (6c)

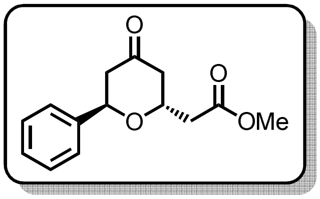
A stirred solution of ethyl thioacetate (5.3 mL, 50 mmol, 1 equiv.) in dichloromethane (50 mL) was added with triethylamine (8.4 mL, 60 mmol, 1.2 equiv.). The mixture was cooled down to 0 °C. Trimethylsilyl trifluomethanesulfonate (9.0 mL, 50 mmol, 1 equiv.) was added dropwise and the reaction stirred at 0 °C for 2 h. Dichloromethane was removed *in vacuo* and the two layers were separated. The upper layer was sufficiently pure for subsequent reactions (7.40 g, 84 % yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.42 (d, J = 1.7 Hz, 1H), 4.36 (d, J = 1.7 Hz, 1H), 2.69 (q, J = 7.4 Hz, 2H), 1.28 (t, J = 7.4 Hz, 3H), 0.26 (s, 9H).



Standard Procedure:

A mixture of pyranone (0.2 mmol, 1 equiv.) and indium trichloride (8.8 mg, 0.04 mmol, and 0.2 equiv.) was stirred neat at room temperature for 15 min. Silyl enol ether (0.4 mmol, 2 equiv.) was added and the mixture stirred for 1 hour. A 1:1 mixture of THF: 1M hydrochloric acid (3 mL) was added and the reaction mixture stirred for 30 min. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography.



Methyl 2-(4-oxo-6-phenyltetrahydro-2H-pyran-2-yl)acetate (7a)

49.7 mg, 48% yield.

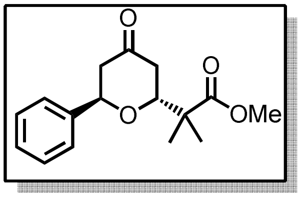
R_f = 0.37 (Hexane: EtOAc, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.28 (m, 5H), 5.31 (t, *J* = 5.4 Hz, 1H), 4.40- 4.31 (m, 1H), 3.68 (s, 3H), 2.92 (ddd, *J* = 14.7, 5.4, 1.2 Hz, 1H), 2.83 (ddd, *J* = 14.7, 5.4, 1.5 Hz, 1H), 2.70 (dd, *J* = 15.0, 7.8 Hz, 1H), 2.59 (ddd, *J* = 14.7, 4.5, 1.5 Hz, 1H), 2.51 (dd, 15.3, 5.7 Hz, 1H), 2.44 (ddd, *J* = 15.0, 8.4, 1.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 206.2, 170.6, 139.4, 128.8, 128.4, 127.2, 74.3, 68.7, 52.0, 46.6, 45.5, 40.1.

FTIR (neat): ν 1721, 1643, 1258, 700 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{14}H_{16}O_4$ = 248.1049. Found 248.1049.



Methyl 2-methyl-2-(4-oxo-6-phenyltetrahydro-2H-pyran-2-yl)propanoate (7b)

45.9 mg, 83% yield

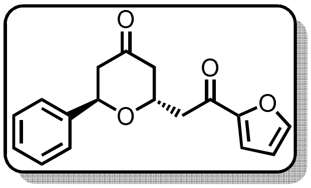
R_f = 0.55 (Hexane: EtOAc, 2:1)

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.37-7.28 (m, 5H), 5.45 (dd, *J* = 7.2, 2.4 Hz, 1H), 3.74 (dd, *J* = 11.6, 2.4 Hz, 1H), 3.60 (s, 3H), 2.98 (d, *J* = 15.2, 1H), 2.89 (dd, *J* = 15.2, 7.2 Hz, 1H), 2.52 (dd, *J* = 14.8, 11.6 Hz, 1H), 2.30 (d, *J* = 14.4 Hz, 1H), 1.20 (s, 3H), 1.09 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 207.4, 176.1, 139.2, 128.6, 128.3, 127.9, 74.6, 74.5, 52.0, 46.4, 43.7, 42.6, 21.3.

FTIR (neat) ν_{max}: 1722, 1643, 1267, 698 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{16}H_{20}O_4$ [M$^+$] = 276.1362. Found 276.1351.



2-(2-(Furan-2-yl)-2-oxoethyl)-6-phenyldihydro-2H-pyran-4(3H)-one (7c)

52 mg, 83% yield

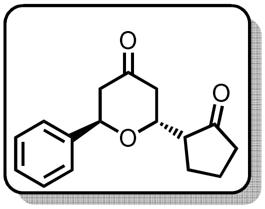
R$_f$ = 0.33 (Hexane: EtOAc, 2:1).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.56 (s, 1H), 7.36- 7.27 (m, 5H), 7.21 (d, *J* = 3.6 Hz, 1H), 6.55- 6.53 (m, 1H), 5.30 (t, *J* = 5.6 Hz, 1H), 4.62- 4.56 (m, 1H), 3.25 (dd, *J* = 15.4, 7.5 Hz, 1H), 2.98 (dd, *J* = 15.4, 5.8 Hz, 1H), 2.92 (dd, *J* = 14.8, 5.6 Hz, 1H), 2.84 (dd, *J* = 14.8, 5.6 Hz, 1H), 2.66 (dd, *J* = 14.8, 4.3 Hz, 1H), 2.48 (dd, *J* = 14.7, 8.2 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 206.5, 185.8, 146.8, 142.8, 139.5, 128.8, 128.3, 127.0, 117.8, 112.7, 74.4, 68.6, 46.9, 45.8, 43.8.

FTIR (neat) ν_{max}: 3063, 1643, 1265, 737 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{17}H_{16}O_4$ [M$^+$] = 284.1049. Found 284.2482.



2-(2-Oxocyclopentyl)-6-phenyldihydro-2H-pyran-4(3H)-one (7d)

48 mg, 60% yield

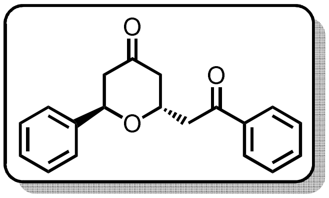
R_f = 0.67 (Hexane: EtOAc, 8:1).

^{1}H NMR (400 MHz, $CDCl_3$) [for two diastereomers]: δ 7.40- 7.29 (m, 5H), 5.40 (dd, *J* = 6.3, 3.8 Hz, 0.5H), 5.28 (t, *J* = 5.4 Hz, 0.5H), 4.12 (dt, *J* = 9.5, 4.3 Hz, 0.5H), 3.90 (dt, *J* = 10.8 , 3.2 Hz, 0.5H), 3.12 (dd, *J* = 15.0, 10.8 Hz, 0.5 H), 2.98- 2.80 (m, 2H), 2.60 (ddd, *J* = 15.0, 9.6, 0.8 Hz, 0.5H), 2.49 (ddd, *J* = 15.0, 3.6, 1.4 Hz, 0.5 H), 2.36- 2.03 (m, 5.5H), 1.96- 1.79 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) [for two diastereomers]: δ 218.9, 217.9, 207.2, 206.9, 139.4, 128.9, 128.8, 128.3, 127.6, 127.2, 74.7, 74.4, 71.2, 70.1, 52.6, 51.1, 45.6, 45.1, 44.7, 44.2, 39.8, 39.2, 26.9, 24.8, 21.0, 20.8.

FTIR (neat): ν 1730, 1450, 1265, 737 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{16}H_{18}O_3$ [M^+] = 258.1256. Found 258.1238.



2-(2-Oxo-2-phenylethyl)-6-phenyldihydro-2H-pyran-4(3H)-one (7e)

22 mg, 28% yield

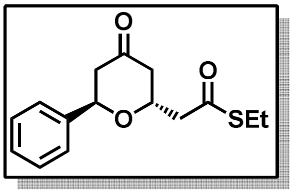
R_f = 0.50 (Hexane: EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.36- 7.31 (m, 5H), 5.29 (t, *J* = 5.6 Hz, 1H), 4.64- 4.57 (m, 1H), 3.40 (dd, *J* = 16.1, 6.5 Hz, 1H), 3.15 (dd, *J* = 16.1, 6.4 Hz, 1H), 2.93 (ddd, *J* = 14.6, 5.8, 1.1 Hz, 1H), 2.84 (ddd, *J* = 14.6, 5.6, 0.9 Hz, 1H), 2.71 (dd, *J* = 13.7, 4.1 Hz, 1H), 2.49 (dd, *J* = 14.8, 8.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.6, 197.0, 139.6, 137.0, 133.6, 128.9, 128.8, 128.3, 127.0 (2C), 74.6, 68.8, 47.0, 45.9, 43.9.

FTIR (neat): ν 1715, 1643, 690, 523 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{19}H_{18}O_3$ [M$^+$] = 294.1256. Found 294.1291.



S-Ethyl 2-((*2R,6R*)-4-oxo-6-phenyltetrahydro-2H-pyran-2-yl)ethanethioate (7f)

32 mg, 78% yield

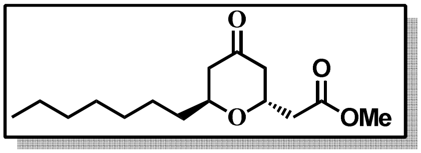
R_f = 0.61 (Hexane: EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.29 (m, 5H), 5.29 (t, *J* = 5.4 Hz, 1H), 4.46-4.37 (m, 1H), 2.98- 2.85 (m, 4H), 2.81 (dd, *J* =15.0, 5.7 Hz, 1H), 2.68 (dd, *J* =15.0, 5.4 Hz, 1H), 2.58 (dd, *J* = 14.7, 4.2 Hz, 1H), 2.42 (dd, *J* = 14.7, 7.8 Hz, 1H), 1.25 (t, *J* = 4.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): 205.8, 195.6, 139.2, 128.6, 127.3, 126.9, 74.1, 68.9, 48.7, 46.3, 45.5, 23.5, 14.6.

FTIR (neat): ν 1722, 1690, 1456, 1232, 756 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{15}H_{18}O_3S$ [M$^+$] = 278.0977. Found 278.0970



Methyl 2-(6-heptyl-4-oxotetrahydro-2H-pyran-2-yl)acetate (7g)

52 mg, 63% yield

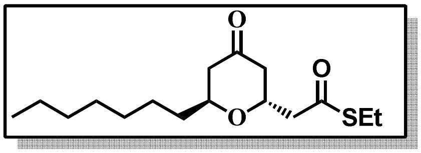
R_f = 0.30 (Hexane: EtOAc, 4:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.54- 4.51 (m, 1H), 4.14-4.08 (m, 1H), 3.70 (s, 3H), 2.68- 2.46 (m, 4H), 1.27- 1.23 (m, 12H), 0.88 (t, *J*= 6.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 206.6, 170.6, 72.9, 68.5, 51.9, 46.7, 46.4, 39.9, 33.9, 31.8, 29.3, 29.2, 25.2, 22.6, 14.1.

FTIR (neat): ν 1732, 1436, 1265, 704 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{15}H_{27}O_4$ [M^+]= 271.1909. Found 271.1909.



S-Ethyl 2-(6-heptyl-4-oxotetrahydro-2H-pyran-2-yl)ethanethioate (7h)

57 mg, 84% yield

R_f = 0.41 (Hexane: EtOAc, 4:1).

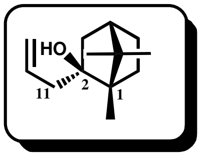
^{1}H NMR (300 MHz, $CDCl_3$) : δ 4.62- 4.53 (m, 1H), 4.16-4.08 (m, 1H), 2.94-2.84 (m, 3H), 2.68- 2.52 (m, 3H), 2.35- 2.26 (m, 2H), 1.29- 1.24 (m, 15 H), 0.88 (t, *J*= 6.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 206.5, 195.5, 72.9, 68.7, 48.7, 46.7, 46.4, 34.1, 31.8, 31.6, 29.3, 29.2, 25.2, 23.5, 22.6, 14.1.

FTIR (neat): ν 1720, 1685, 1456, 1232, 756 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{16}H_{29}O_3S[M+H]^+$ = 301.1837. Found 301.1832.

6.3. Total synthesis of polyrachitide A



(*1S,2S,4S*)-2-Allyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (8)

To a cooled solution of 1-*S*-(-) camphor (7.61 g, 50 mmol, 1 equiv.) in diethyl ether (100 mL) under N_2, was added freshly prepared allylmagnesium bromide (150 mL, 150 mmol, 3 equiv.) dropwise. The reaction mixture was allowed to warm up to room temperature and stirred for 3 h. The reaction mixture was quenched using 40 mL saturated NH_4Cl solution and was extracted with diethyl ether (3 x 50 mL). The combined organic phase was washed with water, brine then dried over $MgSO_4$. The crude mixture was filtered, and concentrated *in vacuo*. The mixture was purified through column chromatography (Hexane: Et_2O, 60: 1)

Colorless oil (7.76 g, 80%)

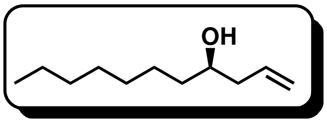
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94-5.90 (m, 1H), 5.18- 5.13 (m, 2H) 2.29- 2.16 (m, 2H), 1.90 (dt, *J*= 12.9, 3.5, 1H), 1.65- 1.32 (m, 6H), 1.03 (s, 3H), 0.78 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.0, 118.8, 79.6, 52.1, 49.4, 46.0, 45.0, 44.5, 30.5, 27.0, 21.4, 20.9, 10.9.

FTIR (neat): ν 3487, 2949, 1638, 1456, 1390, 911 cm^{-1}.

HRMS (EI) Calcd for $C_{13}H_{22}O$ $[M]^+$:194.1671. Found:194.1666.

$[\alpha]_D = +6.5^{o}$ (c = 0.90, CH_2Cl_2)



(*R*)-Undec-1-en-4-ol (10)

Camphorsulfonic acid (460 mg, 0.2 mmol, 0.1 equiv.) and octanal (3.1 mL, 20 mmol, 1 equiv.) were placed into a 250 mL oven-dried round-bottomed flask under nitrogen. Camphor-derived homoallylic alcohol **8** (6.245 g, 30 mmol, 1.5 equiv.) and dichloromethane (10 mL, 6 M) were added to the round-bottomed flask. The reaction mixture was stirred at room temperature for 5 days. The reaction mixture was diluted with 100 mL of diethyl ether, washed with saturated $NaHCO_3$, then by brine, then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified *via* column chromatography (Hexane: Et_2O, 9:1).

Colorless oil (2.43, 80 %).

$R_f = 0.46$ (Hexane: EtOAc, 9:1).

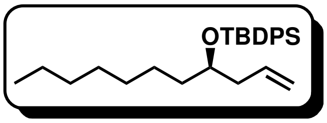
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86-5.75 (m, 1H), 5.11(dd, *J*= 9.6, 4.4 Hz, 2H), 3.62 (m, 1H), 2.32-2.24 (m, 1H), 2.12 (ddd, *J*=14.0, 7.6, 6.7 Hz, 1H), 1.45-1.40 (m, 2H), 1.26 (b, 10H), 0.88 (t, *J*= 6.8 Hz, 3H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 134.9, 117.9, 70.8, 47.2, 41.9, 36.8, 31.8, 29.6, 25.7, 22.6, 14.1.

FTIR (neat): ν 3367, 3076, 2954, 2926, 2856, 2359, 1639, 993, 912 cm^{-1}.

HRMS (ESI) Calcd for $C_{11}H_{20}$ $[M-H_2O]^+$: 152.1565. Found: 152.1564.

$[\alpha]_D = +6.5^\circ$ ($c = 0.90$, CH_2Cl_2)



(*R*)-Tert-butyldiphenyl(undec-1-en-4-yloxy)silane (14)

To a solution of homoallylic alcohol **10** (1.66 g, 9.8 mmol, 1 equiv.) in anhydrous *N,N*-dimethylformamide (10 mL) was added imidazole (1.33 g, 19.6 mmol, 2 equiv.) followed by DMAP (24 mg, 0.19 mmol, 0.02 equiv.). The solution was stirred for 10 min. before *tert*-butyldiphenylsilyl chloride (2.97 g, 10.8 mmol, 1.1 equiv.) was added and the reaction mixture was stirred overnight. The reaction mixture was quenched with H_2O (10 mL) and extracted with ethyl acetate (3 x 30 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using 100% hexane as eluent.

Pale yellow oil (3.84 g, 96 %)

R_f = 0.62 (Hexane: EtOAc, 9:1).

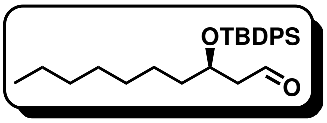
^{1}H NMR: (300MHz, CDCl3): δ 7.68 (d, *J*= 6.8 Hz, 4H), 7.42 (t, *J*= 7.6 Hz, 2H), 7.37 (dd, *J*= 14.6, 6.8Hz, 4H), 5.80-5.70 (m, 1H), 4.94 (dd, *J*=16.8, 9.6 Hz, 2H), 3.75 (dt, *J*=11.6, 5.2 Hz, 1H), 2.25-2.12 (m, 2H), 1.41 (dt, *J*=14.0, 6.3 Hz, 2H), 1.28-1.10 (m, 10H), 1.05 (s, 9H), 0.86 (t, *J*= 7.2 Hz, 3H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 136.0, 135.1, 133.9, 129.8, 129.4, 116.6, 72.9, 41.0, 36.0, 31.8, 29.6, 29.2, 27.1, 24.8, 22.6, 19.4, 14.1.

FTIR (neat): ν 3070, 3049, 2955, 2927, 2857, 1635, 1462, 1427, 1361, 1111, 1057, 912 cm^{-1}.

HRMS (ESI) Calcd for $C_{27}H_{41}OSi$ $[M+ H]^+$: 409.2926 . Found: 409.2923.

$[\alpha]_D = 3.26^o$ (c = 0.545, CH_2Cl_2)



(*R*)-3-((Tert-butyldiphenylsilyl)oxy)decanal (16)

A solution of terminal olefin **14** (4.3 g, 10.5 mmol, 1 equiv.) in dichloromethane (50 mL) was cooled to -78 °C. A flow of ozone was passed through the solution until it turned blue (10 min.). The reaction mixture was quenched with Zn (1.44 g, 22 mmol, 2 equiv.) and two drops of AcOH, at -78 °C then it was allowed to warm to ambient temperature and then refluxed for 2 h. The reaction mixture was filtered through celite and then concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hexane: EtOAc, 98:2) to afford the aldehyde as colorless oil (3.67 g, 85% yield).

R_f = 0.40 (Hexane: EtOAc, 9:1).

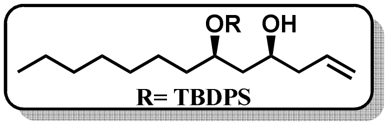
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (t, *J*=2.2 Hz, 1H), 7.72-7.69 (m, 4H), 7.47-7.40 (m, 6H), 4.27-4.15 (m, 1H), 2.52 (dd, *J* = 5.4, 2.0 Hz, 2H), 1.54 (m, 2H), 1.19(m, 10H), 1.09 (s, 9H), 0.90 (t, *J*= 8.5 Hz , 3H).

^{13}C NMR (500 MHz, $CDCl_3$): δ 202.3, 135.9, 133.9, 129.8, 129.7, 69.4, 50.2, 37.4, 31.7, 29.3, 29.1, 27.0, 24.9, 22.6, 19.3, 14.1.

FTIR (neat): ν 2954, 2856, 2719, 1959, 1726, 1111, 1080, 1064, 821, 740, 702 cm^{-1}.

HRMS (ESI) *m/z* Calcd for $C_{26}H_{39}O_2Si$ $[M+H]^+$: 411.2719. Found: 411.2713.

$[\alpha]_D = -11.4^o$ (*c* = 0.900, CH_2Cl_2)



(*4S,6R*)-6-((Tert-butyldiphenylsilyl)oxy)tridec-1-en-4-ol (18)

To an oven dried 150 mL round bottom flask equipped with a magnetic stirring bar was added (-)-DIP-Br (2.91 g, 8 mmol, 1 equiv.) and dry ether (50 mL). The solution was cooled to -78 °C prior to dropwise addition of allylmagnesium bromide (1.0 M in ether, 7.2 ml, 0.9 equiv.) through canula. The mixture was allowed to stir at -78 °C for 1 h and was allowed to warm up to room temperature over 2 h. The mixture was cooled to -78 °C again and was treated with a solution of aldehyde **16** (2.46 g, 6 mmol, 0.75 equiv.) in ether (10 mL) dropwise over 30 min. The reaction mixture was stirred at -78 °C for 1 h and was allowed to warm gradually to room temperature and stirred for 3 h. The solution was cooled to 0 °C and quenched with a pre-formed mixture of 3M NaOH (9 mL) and 30% H_2O_2 (3 mL) and was let to stir overnight. The aqueous layer was extracted with ethyl acetate (3 x 30 mL), and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (Hexane: EtOAc, 98:2) to afford colorless oil (2.17 g, 80% yield, 98% *de*)

R_f = 0.32 (Hexane: EtOAc, 4:1).

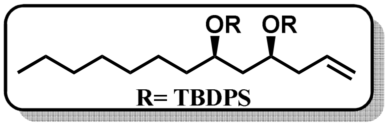
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (t, *J*= 6.0 Hz, 4H), 7.46-7.36 (m, 6H), 5.82-5.70 (m, 1H), 5.07 (dd, *J*= 10.8, 5.6 Hz, 2H) 3.99-3.95 (m, 1H), 3.17 (m, 1H), 2.25-2.05 (m, 2H) 1.67-1.58 (m, 2H), 1.27-1.16 (m, 12H), 1.06 (s, 9H), 0.84(t, *J*= 7.2 Hz, 3H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 135.9, 135.0, 129.8, 127.6, 127.6, 117.2, 72.7, 67.7, 42.2, 40.5, 35.8, 31.7, 29.3, 29.0, 27.0, 25.2, 22.6, 19.2, 14.1.

FTIR (neat): ν 3018, 2985, 2956, 2929, 2319, 1750, 1427, 1265, 1217, 1078, 894, 763 cm^{-1}.

HRMS (ESI) Calcd for $C_{29}H_{42}OSi$ $[M-H_2O]^+$ =434.3005. Found 434.3005.

$[\alpha]_D$ = -7.54 ° (*c* = 7.43, CH_2Cl_2)



(*5S,7R*)-5-Allyl-7-heptyl-2,2,10,10-tetramethyl-3,3,9,9-tetraphenyl-4,8-dioxa-3,9-disilaundecane (20)

To a solution of homoallylic alcohol **18** (4.53 g, 10 mmol, 1 equiv.) in anhydrous *N,N*-dimethylformamide (10 mL) was added imidazole (1.36 g, 19.6 mmol, 2 equiv.) followed by DMAP (24 mg, 0.2 mmol, 0.02 equiv.). The solution was stirred for 10 min before *tert*-butyldiphenylsilyl chloride (3.03 g, 11 mmol, 1.1 equiv) was added and the reaction mixture was stirred overnight at rt. The reaction mixture was quenched with H_2O (10 ml) and extracted with ethyl acetate (3 x 30 ml), washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using 100% hexane as eluent.

Pale yellow oil (6.48 g, 94 %)

R_f = 0.35 (Hexane: EtOAc, 9:1).

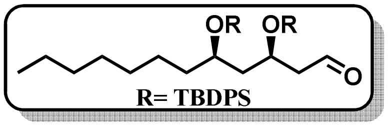
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62-7.58 (m, 8H), 7.40-7. 37 (m, 4H), 7.33-7.29 (m, 8H), 5.67- 5.59 (m, 1H), 5.04 (dd, *J*= 10.6, 5.6 Hz, 2H), 4.88 (dd, *J*= 10.5, 1.5 Hz, 1H), 4.70 (d, *J*= 17.5 Hz, 1H), 2.19-2.02 (m, 2H) 1.55-1.39 (m, 2H), 1.12-1.06 (m, 12H), 1.04 (s, 9H), 1.03 (s, 9H), 0.84 (t, *J*= 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 134.6, 134.5, 134.4, 134.3, 129.5, 129.4, 129.3, 127.5, 127.4, 116.9, 70.7, 70.2, 42.8, 40.8, 34.5, 31.8, 31.6, 29.5, 29.1, 27.0, 25.3, 24.3, 22.7, 19.3, 14.1.

FTIR (neat): ν 3070, 3049, 2370, 1957, 1890, 1830, 1716, 1589, 1471, 1427, 1388, 1377, 1361, 1263, 1188, 1111, 1068, 999, 914, 821, 738, 702 cm^{-1}.

HRMS (ESI) Calcd for $C_{45}H_{63}O_2Si_2$ $[M+H]^+$ = 691.4366 Found 691.4366.

$[\alpha]_D$ = -1.24 ° (c = 7.43, CH_2Cl_2)



(*3R,5R*)-3,5-Bis((tert-butyldiphenylsilyl)oxy) dodecanal (13)

A solution of terminal olefin **20** (4.3 g, 6.2 mmol, 1 equiv.) in dichloromethane (50 mL) was cooled to -78 °C. A flow of ozone was passed through the solution until it turned blue (15 min). The reaction mixture was quenched with Zn (812 mg, 12.4 mmol, 2 equiv.) and two drops of AcOH, at -78 °C. It was allowed to warm to ambient temperature and then refluxed for 3 h. The reaction mixture was filtered through celite, then concentrated *in vacuo*. The residual crude product was purified by flash column chromatography 0-5% ethyl acetate in hexane to afford the aldehyde as colorless oil (5.42 g, 80 % yield).

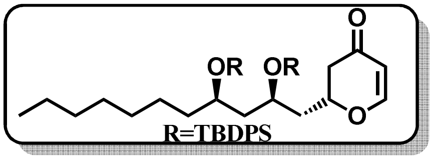
R_f = 0.42 (Hexane: EtOAc, 4:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.52 (t, J=1.8 Hz, 1H), 7.63-7.53 (m, 8H), 7.43-7.29 (m, 12H), 4.41-4.33 (m, 1H), 3.75-3.67 (m, 1H), 2.69-2.42 (m, 2H), 2.26-2.18 (m, 2H), 1.92-1.82 (m, 2H), 1.34-1.21 (m, 10H), 0.99 (s, 9H), 0.95 (s, 9H), 0.89 (t, J= 4.0 Hz, 3H).

^{13}C NMR (300 MHz, $CDCl_3$): δ 201.9, 135.9, 135.8, 134.3, 133.8, 129.9, 129.7, 129.6, 127.7, 70.8, 67.4, 50.2, 45.1, 36.4, 34.7, 31.6, 29.1, 27.0, 26.9, 25.3, 24.4, 22.7, 19.31, 14.1.

HRMS (ESI) Calcd for $C_{44}H_{61}O_3Si_2$ $[M+H]^+$= 693.4160. Found 693.4160.

$[\alpha]_D$ = - 2.97 (c = 7.43, CH_2Cl_2)



***(R)-2-((2S,4R)*-2,4-Bis((tert-butyldiphenylsilyl)oxy)undecyl)-2H-pyran-4(3H)-one (12)**

Into a 50 mL oven-dried round bottomed flask equipped with a magnetic stir bar was charged with 2.75 g of oven dried powdered 4Å molecular sieves and (*S,S*)-(salen)Cr(III)-Cl complex (193 mg, 0.30 mmol, 5 mol %). The flask was sealed with a rubber septum and purged with N_2 for 5 min. Aldehyde **13** (4.158 g, 6.0 mmol, 1 equiv.) was added followed by TBME (6 mL). The flask was further sealed with Teflon tape and parafilm. This mixture was stirred at room temperature for 10 min and then it was cooled to 0 ^{o}C and stirred an additional 10 min. 1-methoxy-3-[(trimethylsilyl)oxy]butadiene (1.238 g, 7.2 mmol, 1.2 equiv.) was added and the reaction was stirred at this temperature for 24 h. Dichloromethane (5 mL) was added followed by 5 drops of TFA. The reaction was allowed to warm to room temperature and stirred for 10 min. The reaction was then filtered through a plug of celite and washed with copious diethyl ether (200 mL). The filtrate was concentrated *in vacuo* and the crude residue was purified by flash chromatography (10% ethyl acetate in hexane) to afford the product as a bright yellow oil.

Bright yellow oil (yield 60%, *dr* 95:5 by chiral HPLC)

R_f = 0.29 (Hexane: EtOAc, 9:1).

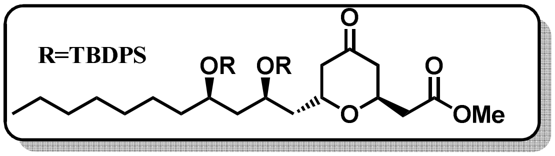
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.56 (m, 8H), 7.43-7.29 (m, 12H), 7.05 (d, *J*= 6 Hz,1H), 5.28 (d, *J*= 6.0 Hz, 1H), 4.46-4.00 (m, 1H), 4.09-4.04(m, 1H), 3.81-3.77 (m, 1H), 2.21-2.05 (m, 2H), 1.94-1.79 (m, 2H), 1.80-1.70 (m, 2H), 1.36-1.22 (m, 12H), 0.99 (s, 9H), 0.95 (s, 9H), 0.89 (t, *J*= 6.0 Hz 3H).

^{13}C NMR (500 MHz, CDCl$_3$): δ 196.7, 148.7, 135.9, 134.8, 134.4, 129.5, 129.3, 127.6, 127.4, 103.9, 70.9, 68.9, 68.3, 65.7, 49.6, 43.9, 41.3, 36.8, 35.6, 31.8, 31.5, 30.2, 29.6, 27.1, 24.5, 23.3, 19.4, 14.7.

FTIR (neat): ν 3070, 3049, 1680, 1597, 1471, 1427, 1273, 1215, 1111, 1068, 1039, 1004, 821, 738 cm^{-1}.

HRMS Calcd for $C_{48}H_{64}O_4Si_2$ [M$^+$]: 761.4421 Found: 761.4404.

$[\alpha]_D = +2.31^o$ (c = 7.43, CH_2Cl_2)



Methyl-2-((*6R*)-6-((*2S,4R*)-2,4-bis((tert-butyldiphenylsilyl)oxy)undecyl)-4-oxotetrahydro-2H-pyran-2-yl)acetate (22)

A mixture of pyranone **12** (152 mg, 0.2 mmol, 1 equiv.) and indium trichloride (8.8 mg, 0.04 mmol, 0.2 equiv.) was stirred neat at room temperature for 15 min. Silyl enol ether (58.5 mg, 0.4 mmol, 2 equiv.) was added and the mixture stirred for 30 min. Another portion of silyl enol ether was added and the reaction mixture was further stirred for 20 h at room temperature. The reaction mixture was quenched with H_2O and stirred for 30 min. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (75 mg, 45% yield, dr >99:1)

R_f = 0.40 (Hexane: EtOAc, 4:1).

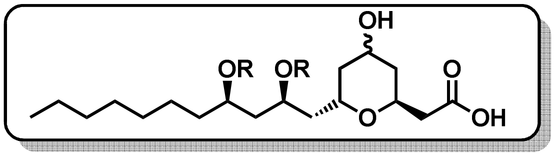
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.65-7.58 (m, 8H), 7.44-7.32 (m, 12H), 4.25-4.20 (m, 1H), 4.14-4.10(m, 1H), 3.75-3.71 (m, 1H), 3.67-3.65 (m, 1H) 3.61 (s, 3H), 2.43 (dd, *J*= 14.0, 4.5 Hz, 2H), 2.40 (dd, *J*=15.6, 5.6 Hz, 2H), 2.37 (d, *J*= 6.0 Hz, 2H), 2.34(d, *J*= 7.0 Hz, 2H) 2.28-2.23 (dd, *J*=14.6, 8.0 Hz, 2H), 1.66-1.61 (m, 2H), 1.47-1.40 (m, 2H), 1.29-1.23 (m, 6H), 1.18-1.08 (m, 2H), 0.96 (s, 9H), 0.95 (s, 9H), 0.88 (t, *J*= 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 206.4, 170.4, 135.9, 134.4, 134.3, 134.2, 129. 6, 129.5, 129.4, 127.6, 70.8, 69.4, 67.8, 67.6, 51.6, 46.3, 45.9, 45.8, 41.0, 39.6, 36.1, 31.8, 29.5, 29.1, 27.0, 26.9, 24.4, 22.6, 19.3, 19.2, 14.1.

FTIR (neat): ν 2956, 2931, 2252, 1718, 1589, 1462, 1427, 1388, 1361, 1265, 1111, 907, 704 cm^{-1}.

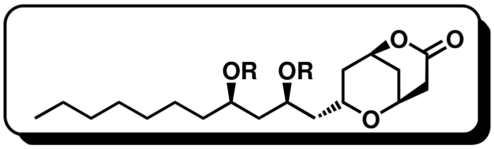
HRMS Calcd for $C_{51}H_{70}O_6Si_2$ [M$^+$]: 835.4789. Found: 835.4788.

$[\alpha]_D$ = +1.76 (*c* =2.4, CH_2Cl_2)



2-((*6R*)-6-((*2S,4R*)-2,4-Bis((tert-butyldiphenylsilyl)oxy)undecyl)-4-oxotetrahydro-2H-pyran-2-yl)acetic acid (27)

To a solution of pyran **65** (167 mg, 0.2 mmol, 1 equiv.) in methanol (2 mL) at 0 °C was added cerium (III) chloride (10 mg, 0.04 mmol, 0.2 equiv.). Sodium borohydride (7.6 mg, 0.2 mmol, 1 equiv) was added and effervescence was observed due to the reduction. The reaction mixture was quenched with saturated sodium sulphate solution after 15 min. The reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was dissolved in 1:1 THF: H_2O (2 mL) and 2 mL LiOH 1M solution was added. The reaction mixture was refluxed for 3 h. After cooling down to room temperature, 1 M HCl was added to the reaction mixture until the solution became pH 4. The mixture was then extracted with ethyl acetate (4 x 10 mL). The combined organic layer was washed with water and brine, and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. The compound was carried out to next step without further purification.



(*1R,5S,7S*)-7-((*2S,4R*)-2,4-Bis((tert-butyldiphenylsilyl)oxy)undecyl)-2,6-dioxabicyclo[3.3.1]nonan-3-one (23)

To a solution of acid **69** (78 mg, 0.09 mmol, 1 equiv.) in THF (0.9 mL) at room temperature was added Et_3N (0.12 ml, 0.9 mmol, 10 equiv.) followed by 2,4,6-trichlorobenzoylchloride (0.09 mL, 0.14 mmol, 1.5 equiv.), and stirring was continued for 2 h. The reaction mixture was diluted with benzene (1.0 mL) and then added dropwise to a refluxing solution of DMAP (129 mg, 1.0 mmol, 11 equiv.) in benzene (2 mL). After refluxing for an additional 1 h, the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL), H_2O (10 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, the aqueous layer was extracted with EtOAc (10 mL), and the organic layers were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified *via* flash silica gel chromatography (Hexane: EtOAc, 4:1) to afford bicyclic lactone **23** (29 mg, 40% yield).

R_f = 0.34 (Hexane: EtOAc, 4:1).

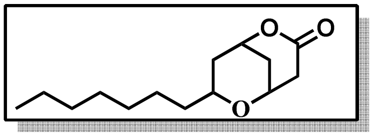
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65-7.58 (m, 8H), 7.44-7.32 (m, 12H), 4.25-4.20 (m, 1H), 4.14-4.10 (m, 1H), 3.75-3.71 (m, 1H), 3.61 (s, 3H), 3.43 (dd, *J*=14.0, 4.5 Hz, 1H), 2.40 (dd, *J*=15.6, 5.6, 2H), 2.37 (d, *J*= 6.0 Hz, 2H), 2.34 (d, *J*= 7.0 Hz, 2H), 2.28-2.23 (dd, *J*= 14.6, 8.0 Hz, 2H), 1.66-1.61 (m, 2H), 1.47-1.40 (m, 2H), 1.29-1.23 (m, 6H), 1.18-1.08 (m, 2H), 0.96 (s, 9 H), 0.95 (s, 9H), 0.88 (t, *J*= 7.0 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ 169.3, 135.9, 134.6, 134.4, 134.1, 129.5, 129.3, 127.6, 127.5, 127.4, 72.9, 70.7, 68.0, 65.4, 62.0, 60.4, 43.7, 42.0, 37.0, 36.6, 36.3, 34.2, 31.8, 29.7, 29.5, 29.2, 27.1, 22.6, 19.3, 14.1.

FTIR (neat): ν 2956, 2929, 2897, 2856, 2252, 1728, 1462, 1427, 1382, 1249, 1111, 1082, 1049, 1028, 908, 732 cm^{-1}.

HRMS Calcd for $C_{50}H_{69}O_5Si_2$ $[M+H]^+$ =805.4684 Found: 805.4684.

$[\alpha]_D$ = + 7.6 (*c* =0.25, CH_2Cl_2)



7-Heptyl-2,6-dioxabicyclo[3.3.1]nonan-3-one (26)

(24 mg, 45 % yield)

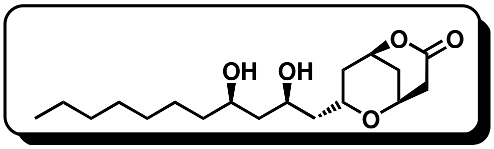
R_f = 0.45 (Hexane: EtOAc, 4:1).

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.90- 4.88 (m, 1H), 4.36- 4.34 (m, 1H), 3.75- 3.70 (m, 1H), 2.88- 2.73 (m, 2H), 2.46-2.40 (m, 2H), 2.03-1.97 (m, 2H), 1.27- 1.25 (m, 12H), 0.87 (t, *J*= 6.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 169.9, 73.2, 65.8, 65.7, 37.0, 36.5, 35.9, 31.7, 29.8, 29.5, 29.2, 25.2, 22.6, 14.1.

FTIR (neat): *ν* 2954, 1728, 1350, 1076, 756 cm^{-1}.

HRMS Calcd for $C_{14}H_{25}O_3[M+H^+]$: 241.1804. Found: 241.2804

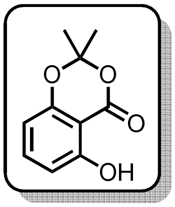


Polyrachitides A

To a solution of bilactone **23** (20 mg, 0.025 mmol, 1 equiv.) in THF (1.0 mL) at room temperature was added TBAF as 1 M solution in THF (0.07 mL, 0.07 mmol, 2.8 equiv.). The reaction mixture was stirred for 2 h. After full consumption of starting material, the solvent was removed in vacuo and the crude product was purified by chromatography (CH_2Cl_2: MeOH, 98:2) to yield polyrachitides A in minute amount (yield not determined).

HRMS (ESI) Calcd for $C_{18}H_{33}O_5$ $[M+H]^+$ = 329.2328. Found 329.2328

6.4. Synthetic study towards apicularen A



5-Hydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one

To a 100 mL round-bottom flask equipped with a magnetic stirring bar was added 2,6-dihydroxybenzoic acid (15.4 g, 0.1 mol, 1 equiv.), 4-dimethylaminopyridine (0.6 g, 5 mmol, 0.05 equiv.), dry acetone (20 mL, 0.25 mol, 2.5 equiv.) and 1,2-dimethoxyethane (35 mL). The solution was cooled to 0 °C prior to addition of thionyl chloride (10.4 mL, 0.143 mol, 1.43 equiv.) in 1, 2-dimethoxyethane (5 mL). The mixture was allowed to warm to room temperature and stir for 5 h. The mixture was evaporated and purified by flash column chromatography (Hexane: EtOAc, 4:1) to afford the protected acid as pale yellow crystals.

(14.90 g, 77% yield).

R_f = 0.54 (Hexane: EtOAc, 4:1).

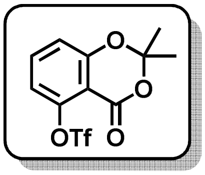
^1H NMR (400 MHz, $CDCl_3$): δ 10.34 (s, 1H), 7.41 (t, J = 8.3 Hz, 1H), 6.63 (d, J = 8.4 Hz, 1H), 6.44 (d, J = 8.2 Hz, 1H), 1.75 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 161.6, 155.8, 138.1, 111.0, 107.5, 107.3, 103.6, 25.9

m.p.: 56 – 57 °C.

FTIR (neat): *v* 3412, 1634, 1472, 1231, 1078 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{10}H_{10}O_4$ [M$^+$] = 194.0597. Found 194.0019.



2,2-Dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl trifluoromethanesulfonate (29)

To an oven-dried 250 mL round-bottom flask equipped with a magnetic stirring bar was placed protected acid (10.5 g, 54 mmol, 1 equiv.) in pyridine (90 mL). The mixture was allowed to cool to 0 °C and triflic anhydride (11 mL, 65 mmol, 1.2 equiv.) was added slowly. The reaction mixture was allowed to stir at 0 °C for 12 h. The mixture was quenched with 50 mL saturated sodium bicarbonate solution. The aqueous layer was extracted with diethyl ether (3 × 40 mL) and the combined organic extracts were washed with saturated copper sulphate solution (50 mL), water (50 mL) and brine (50 mL) and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residual crude product was dissolved in ethyl acetate and crystallised by adding hexane to afford the product as colourless crystals (13.01 g, 92% yield).

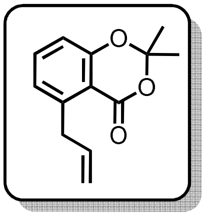
R_f = 0.33 (4:1 Hexane/ EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (t, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 1.76 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 157.3, 148.7, 136.5, 118.1, 116.7, 116.5, 108.4, 107.0, 25.6.

m.p.: 114 – 115 °C.

FTIR (neat): *v* 2087, 1630, 513 cm^{-1}.



5-Allyl-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (30)

To an oven-dried 500 mL round-bottom flask equipped with a magnetic stirring bar was added $Pd(PPh_3)_4$ (0.72 g, 0.62 mmol, 0.02 equiv.) and LiCl (4.0 g, 94 mmol, 3 equiv.) in dry degassed THF (100 mL). A solution of **29** (10.0 g, 31 mmol, 1 equiv.) and tri-n-butylallylstannane (10 mL, 32 mmol, 1 equiv.) in dry degassed THF (200 mL) was added. The mixture was refluxed for 48 h. The solution was cooled to room temperature before diluting with 200 mL diethyl ether. The organic layer was washed with water (100 mL), 10% NH_4OH solution (100 mL) and brine (100 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Henxane: EtOAc, 4:1) to afford the allyl product as yellow oil (6.69 g, quant. yield).

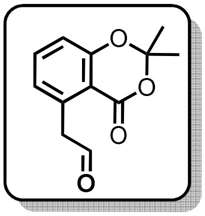
R_f = 0.80 (Henxane: EtOAc, 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (t, *J* = 7.9 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.04 (ddt, *J* = 16.8, 10.3, 6.6 Hz, 1H), 5.07-5.02 (m, 2H), 3.89 (d, *J* = 6.5 Hz, 2H), 1.70 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 157.3, 145.4, 136.9, 135.5, 125.1, 116.2, 115.8, 112.3, 105.3, 38.4, 25.8.

FTIR (neat) ν_{max}: 1732, 1643, 1267, 737 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{13}H_{15}O_3$ $[M+H]^+$ = 218.0943. Found 219.0471.



2-(2,2-Dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)acetaldehyde (31)

A solution of terminal olefin **9** (6.0 g, 27.5 mmol, 1 equiv.) in dichloromethane (260 mL) was cooled to -78 °C. A flow of ozone was passed through the solution until it turned blue. The excess ozone was purged with oxygen and quenched with dimethyl sulfide (40 mL, 54 mmol, 20 equiv.) at -78 °C. It was allowed to warm to ambient temperature. Triphenylphosphine (7.2 g, 27.5 mmol, 1 equiv.) was added and the resulting mixture stirred at room temperature for an additional 5 h before concentrating *in vacuo*. The residual crude product was purified by flash column chromatography (Hexane: EtOAc, 4:1) to afford the aldehyde as bright yellow crystals (5.42 g, 89% yield).

R_f = 0.23 (Hexane: EtOAc, 4:1).

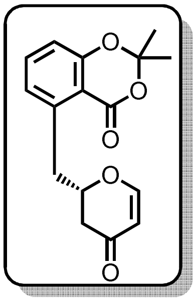
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1H), 7.48, (t, *J* = 7.9 Hz, 1H), 6.94, (d, *J* = 8.2 3Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 4.21 (s, 2H), 1.73 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 161.1, 157.3, 137.2, 135.8, 126.6, 117.2, 112.8, 106.0, 49.2, 25.8.

m.p.: 59 – 60 °C.

FTIR (neat): ν 1732, 1728, 1607, 1296 1045 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{12}H_{12}O_4$ [M^+] = 220.0736. Found 220.0711.



(*S*)-2,2-Dimethyl-5-((4-oxo-3,4-dihydro-2H-pyran-2-yl)methyl)-4H-benzo[d][1,3]dioxin-4-one (32)

A mixture of **31** (1.63 g, 7.39 mmol, 1.0 equiv.), catalyst **64c** (0.18 g, 0.37 mmol, 0.05 equiv.), acetone (3 mL, 40.9 mmol, 5.5 equiv.) and 4Å molecular sieves (1.5 g) was stirred at room temperature. Trans-1-methoxy-3-trimethylsiloxy-1,3-butadiene (1.73 mL, 8.9 mmol, 1.2 equiv.) was added and the mixture allowed to stir for 24 h at room temperature. The mixture was diluted with dichloromethane (5 mL) and brought to 0 ^{o}C. Trifluoroacetic acid (cat.) was added and the mixture allowed to stir at 0 ^{o}C for 1 h. The mixture was then filtered through silica on Celite and the pad washed copiously with Et_2O. The filtrate was concentrated and purified by flash column chromatography (Hexane: EtOAc, 1:1) to yield a brown oil (1.80 g, 84 % yield, 91 % *ee*).

R_f = 0.50 (Hexane: EtOAc, 1:1).

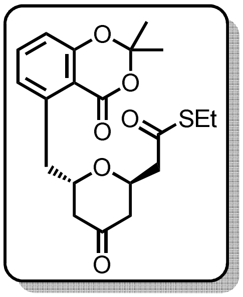
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (t, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 5.8 Hz, 1H), 7.00 (d, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 5.40 (d, *J* = 5.8 Hz, 1H), 4.77- 4.70 (m, 1H), 3.59 (dd, *J* = 13.3, 4.4 Hz, 1H), 3.47 (dd, *J* = 13.3, 8.0 Hz, 1H), 2.59 (d, *J* = 8.6 Hz, 2H), 1.73 (s, 3H), 1.70 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 163.1, 160.6, 157.4, 141.1, 135.4, 126.9, 116.9, 112.4, 107.2, 105.5, 79.4, 41.7, 38.9, 26.0, 25.4.

FTIR (neat): ν 1732, 1672, 1597, 1269, 1045, 735 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{16}H_{16}O_5$ [M^+] = 288.0998. Found 288.0990.

$[\alpha]_D$ = -7.8° (c = 4.6, CH_2Cl_2).



S-Ethyl 2-((*2S,6R*)-6-((2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)methyl)-4-oxotetrahydro-2H-pyran-2-yl)ethanethioate (37a)

Pyranone **32** (1.80 g, 6.3 mmol, 1 equiv.) was added with indium trichloride (0.40 g, 1.8 mmol, 0.3 equiv.) followed by silyl ketene **6b** (1.1 g, 6.3 mmol, 1 equiv.). Another equivalent of silyl ketene **6b** was added after 30 min. The mixture was stirred for a total of 4 h. 1M HCl (1 mL) and ethyl acetate (8 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hexane: EtOAc, 2:1) to afford the product as a brown oil (1.97 g, 80% yield, dr >99:1).

R_f = 0.33 (Hexane:EtOAc, 2:1).

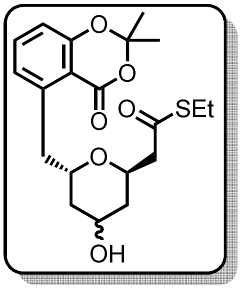
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (t, *J* = 7.9 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 4.76 – 4.70 (m, 1H), 4.40 (m, 1H,), 3.49 (dd, *J* = 13.2, 4.3 Hz, 1H), 3.18 (dd, *J* = 13.2, 8.4 Hz, 1H), 2.84 – 2.69 (m, 3H), 2.66 – 2.55 (m, 3H), 2.44 (dd, *J* = 14.4, 7.9 Hz, 1H), 2.32 (dd, *J* = 14.6, 5.4 Hz, 1H), 1.73 (s, 3H), 1.69 (s, 3H), 1.18 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 206.6, 196.0, 160.8, 157.3, 142.5, 135.2, 127.0, 116.3, 112.4, 105.5, 73.0, 69.7, 48.3, 46.7, 46.1, 39.2, 26.1, 25.6, 23.7, 14.7.

FTIR (neat): ν 2957, 1732, 1680, 1267 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{20}H_{25}O_6S$ $[M+H]^+$ = 392.1294. Found 392.8458.

$[\alpha]^{27}_{D}$ = -33.4° (*c* = 10.8, CH_2Cl_2).



S-Ethyl 2-((*6S*)-6-((2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)methyl)-4-hydroxytetrahydro-2H-pyran-2-yl)ethanethioate (80)

Thiopyranone **37** (0.92 g, 2.34 mmol, 1 equiv.) was dissolved in MeOH (10 mL) and lowered to -78 °C. Sodium borohydride (0.18 g, 4.69 mmol, 2 equiv.) was added to the mixture and allowed to stir at -78 °C for 30 minutes. The reaction mixture was quenched at -78 °C with water (10 mL). The mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated *in vacuo*. The residual crude product was a yellow oil sufficiently pure to be applied to subsequent steps. (0.92 g, quant., d.r. = 1:1).

R_f = 0.28 (Hexane: EtOAc, 2:1).

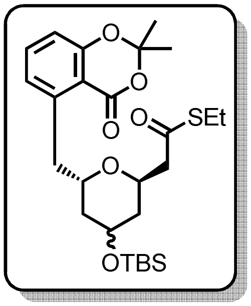
^{1}H NMR (500 MHz, CDCl$_3$) [for 2 diastereomers]: δ 7.39 (t, *J* = 7.9 Hz, 0.5H), 7.37 (t, *J* = 7.9 Hz, 0.5H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 4.58 – 4.54 (m, 0.5 H), 4.34 – 4.27 (m, 1H), 4.19 – 4.15 (m, 0.5 H), 4.02 – 3.99 (m, 0.5 H), 3.89 (tt, *J* = 8.8, 3.1 Hz, 0.5 H), 3.53 (dd, *J* =10.8, 4.1 Hz, 0.5 H), 3.51 (dd, *J* = 9.9, 3.5 Hz, 0.5 H), 3.15 (dd, *J* = 13.5, 9.1 Hz, 0.5 H), 3.05 (dd, *J* = 13.2, 8.4 Hz, 0.5 H), 2.87 (dd, *J* = 14.6, 8.1 Hz, 0.5 H), 2.85 – 2.71 (m, 2 H), 2.68 – 2.62 (m, 1H), 2.55 (dd, *J* = 14.3, 5.0 Hz, 0.5 H), 2.10 (m, 0.5 H), 2.00 (m, 0.5 H), 1.93 (dtd, *J* = 13.0, 4.0, 1.4Hz, 0.5 H), 1.82 (dm, 13.0 Hz, 0.5 H), 1.76 – 1.65 (m, 10 H), 1.42 -1.32 (m, 1H), 1.19 (t, *J* = 7.4 Hz, 1.5 H), 1.14 (t, *J* = 7.5 Hz, 1.5 H).

^{13}C NMR (125 MHz, $CDCl_3$) [for 2 diastereomers]: δ 197.5, 196.9, 160.9, 157.3, 157.1, 144.3, 144.1, 135.2, 135.0, 127.3, 126.7, 115.8, 115.8, 112.3, 112.3, 106.9, 105.4, 77.5, 70.4, 69.3, 67.1, 64.5, 49.9, 46.7, 40.6, 40.4, 38.5, 37.6, 36.6, 26.1, 26.0, 25.7, 25.6, 23.6, 14.8, 14.7.

FTIR (neat) ν_{max}: 3350, 1643, 590 cm^{-1}.

LRMS (ESI) *m/z* Calcd for $C_{20}H_{26}O_6SNa$ $[M+Na]^+$ = 417.15. Found 417.68.

$[\alpha]^{27}_D$ = -97.9 (*c* = 1.1 g/100mL, CH_2Cl_2).



S-Ethyl-2-((*6S*)-4-(tert-butyldimethylsilyloxy)-6-((2,2-dimethyl-4-oxo-4Hbenzo[d][1,3]dioxin-5-yl)methyl)tetrahydro-2H-pyran-2-yl)ethanethioate (38a)

Alcohol **80** (0.92 g, 2.34 mmol, 1 equiv.) was dissolved in N, N'-dimethylformamide (5 mL). Imidazole (0.42 g, 6.20 mmol, 2.6 equiv.) was added followed by *tert*-butylmethyldimethylsilyl chloride (0.45 g, 3.0 mmol, 1.3 equiv.). The mixture was allowed to heat to 45 °C and stirred for 14 h. Saturated sodium bicarbonate solution (5 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate

(3 × 25 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hexane: EtOAc, 4:1) to afford the product as a yellow oil (0.99 g, 83% yield).

R_f = 0.45 (Hexane: EtOAc, 4:1).

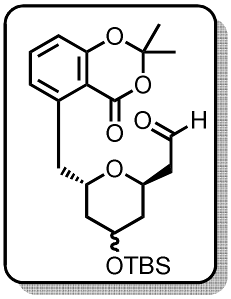
^{1}H NMR (400 MHz, $CDCl_3$) [for 2 diastereomers]: δ 7.38 (t, *J* = 7.9 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 4.56 – 4.51 (m, 0.5 H), 4.37 – 4.31 (m, 0.5H), 4.26 – 4.21 (m, 0.5 H), 4.14 – 4.10 (m, 0.5 H), 4.04-3.91 (m, 1H), 3.33 (td, *J* = 13.1, 3.8 Hz, 1H), 3.16 (dd, *J* = 13.4, 9.0 Hz, 0.5 H), 3.09 (dd, *J* = 13.3, 9.2 Hz, 0.5 H), 3.02 (dd, *J* = 14.8, 8.4 Hz, 0.5 H), 2.82 – 2.63 (m, 1.5 H), 2.55 (dd, *J* = 14.2, 6.3 Hz, 0.5 H), 1.98 (dt, *J* = 13.0, 3.8 Hz, 0.5 H), 1.89 (dt, *J* = 13.3, 3.8 Hz, 0.5 H), 1.75 – 1.64 (m, 2H), 1.71 (s, 3H), 1.69 (s, 3H), 1.53 – 1.37 (m, 2H), 1.17 (t, *J* = 6.8 Hz, 1.5 H), 1.15 (t, *J* = 7.2 Hz, 1.5 H), 0.88 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) [of two diastereomers]: δ 197.7, 197.0, 160.8, 157.2, 157.2, 144.7, 144.5, 135.0, 134.9, 127.3, 134.9, 115.7, 112.4, 112.3, 105.3, 71.2, 70.7, 67.9, 65.2, 65.0, 49.4, 47.6, 40.2, 40.0, 39.0, 38.7, 38.3, 37.7, 31.1, 26.0, 25.8, 25.7, 24.0, 23.5, 18.2, 14.8, 14.7, 0.19, -3.39, -4.43.

FTIR (neat) ν_{max}: 2957, 1736, 1645, 1292 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{26}H_{41}O_6SSi$ $[M+H]^+$ = 508.2315. Found 509.0635.

$[\alpha]^{27}_D$ = -76.7° (*c* = 1.9, CH_2Cl_2).



2-((*6S*)-4-(Tert-butyldimethylsilyloxy)-6-((2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)methyl)tetrahydro-2H-pyran-2-yl)acetaldehyde (35):

Thioacetate **38** (0.99 g, 1.95 mmol, 1 equiv.) was dissolved in dichloromethane (4 mL). 10% palladium on carbon (0.10 g, 0.093 mmol, 0.05 equiv.) was added. Triethylsilane (0.62 mL, 3.90 mmol, 2 equiv.) was added slowly with a needle outlet for release of hydrogen produced. The mixture was stirred for 20 min at room temperature. The mixture was filtered through Celite and the Celite cake washed with dichloromethane. The filtrate was evaporated and the residue purified by flash column chromatography (Hexane: EtOAc, 4:1) to afford the aldehyde as a yellow oil (0.75 g, 86% yield).

R_f = 0.41 (Hexane: EtOAc, 2:1).

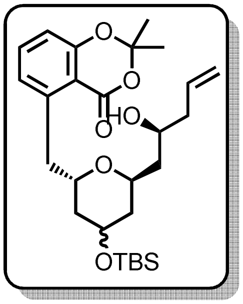
^{1}H NMR (500 MHz, $CDCl_3$) [for 2 diastereomers]: δ 9.54 (t, *J* = 2.1 Hz, 0.5 H), 9.48 (dd, *J* = 2.7, 2.3 Hz, 0.5 H), 7.40 (t, *J* = 7.8 Hz, 0.5H), 7.39 (t, *J* = 7.8 Hz, 0.5H), 6.93 (d, *J* = 7.6 Hz, 0.5H), 6.93 (d, *J* = 7.1 Hz, 0.5H), 6.83 (dd, *J* = 8.2, 0.8 Hz, 0.5 H), 6.82 (dd, *J* = 8.2, 0.8 Hz, 0.5 H), 4.66 – 4.61 (m, 0.5 H), 4.40 – 4.35 (m, 0.5H), 4.28 – 4.23 (m, 0.5 H), 4.16 – 4.12 (m, 0.5 H), 4.06 – 4.01 (m, 0.5 H), 4.00 – 3.96 (m, 0.5 H), 3.49 (d, *J* = 2.9 Hz, 0.5 H), 3.47 (d, *J* = 3.0 Hz, 0.5 H), 3.33 (dd, *J* = 13.6, 9.3 Hz, 0.5 H), 3.21 (dd, *J* = 13.5, 9.1 Hz, 0.5 H), 2.81 (ddd, *J* = 13.7, 8.7, 2.7 Hz, 0.5 H), 2.60 (ddd, *J* = 15.8, 9.4, 3.0 Hz, 0.5 H), 2.52 (ddd, *J* = 16.4, 4.6, 1.8 Hz, 0.5 H), 2.33 (ddd, *J* = 15.8, 4.8, 2.0 Hz, 0.5 H), 1.97 (dt, *J* = 13.2, 4.0 Hz, 0.5 H), 1.92 (dt, *J* = 13.2, 3.9 Hz, 0.5 H), 1.79 – 1.59 (m, 2H), 1.70 (d, J = 2.7 Hz, 3 H), 1.69 (s, 3H), 1.56 (dt, *J* = 13.0, 7.5 Hz, 0.5 H), 1.41 (dt, *J* = 13.0, 7.4 Hz, 0.5 H), 0.88 (d, *J* = 13.8 Hz, 9H), 0.07 – 0.05 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 201.9, 201.3, 160.9, 157.3, 144.8, 144.3, 135.2, 135.1, 126.9, 126.4, 116.0, 116.0, 112.2, 105.4, 71.5, 71.0, 66.2, 65.0, 64.9, 48.8, 47.5, 39.7, 39.2, 38.9, 38.8, 37.6, 26.0, 26.0, 25.9, 25.7, 25.7, 18.2, 18.2, -4.5.

FTIR (neat): ν 1732, 1636, 1292, 781 cm^{-1}.

LRMS (ESI) *m/z* Calcd for $C_{24}H_{36}O_6SiNa$ $[M+Na]^+$ = 471.23. Found 471.47.

$[\alpha]^{27}_D$ = -56.3° (*c* = 2.7, CH_2Cl_2).



5-(((*2S,6S*)-4-(Tert-butyldimethylsilyloxy)-6-((S)-2-hydroxypent-4-enyl)tetrahydro-2H-pyran-2-yl)methyl)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (39):

(-)-DIP-Br (1.22 g, 3.35 mmol, 2 equiv.) in diethyl ether (22 mL) was lowered to -78 °C. 1M allylmagnesium bromide in diethyl ether (2.5 mL) was added slowly to the mixture. The mixture was stirred at -78 °C for 1 h and raised to room temperature to stir for 2 h. The mixture was lowered to -78 °C. Aldehyde **35** (0.75 g, 1.67 mmol, 1 equiv.) in diethyl ether (3 mL) was added dropwise to the preformed (+)-Ipc_2Ballyl mixture and allowed to stir at -78 °C for 1 h. Thereafter, the reaction mixture was raised to room temperature to stir for 2 h. The mixture was cooled to 0 °C before quenching with a 3:1 (v/v) mixture of 3M sodium hydroxide and 30% hydrogen peroxide for 30 min. The mixture was extracted with diethyl ether (3 x 30 mL) and the combined organic layers washed with water (30 mL), brine (30 mL) and dried over anhydrous magnesium sulphate. The solution was filtered and the filtrate dried *in vacuo*. The residue was purified by flash column chromatography (Hexane: EtOAc, 8:1) to afford the product as a yellow oil (0.57 g, 70% yield).

R_f = 0.56 (Hexane:EtOAc, 2:1).

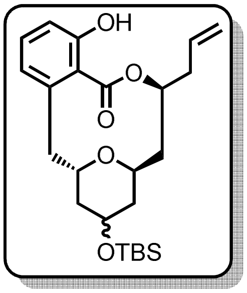
^{1}H NMR (400 MHz, $CDCl_3$) [for 2 diastereomers]: δ 7.43 (t, *J* = 7.9 Hz, 0.5H), 7.41 (t, *J* = 7.8 Hz, 0.5H), 6.95 (d, *J* = 7.0 Hz, 0.5H), 6.94 (d, *J* = 7.2 Hz, 0.5H), 6.86 (d, *J* = 8.2 Hz, 1 H), 5.79 – 5.65 (m, 1H), 5.03 – 4.98 (m, 2H), 4.36 – 4.30 (m, 0.5 H), 4.27 – 4.24 (m, 0.5H), 4.12 – 3.98 (m, 2.5 H), 3.70 – 3.64 (m, 1.5 H), 3.59 (dd, *J* = 13.4, 3.8 Hz, 0.5 H), 3.18 (dd, *J* = 13.4, 9.5 Hz, 0.5 H), 3.16 – 3.09 (m, 1H), 2.19 – 2.00 (m, 3H), 1.85 (dt, *J* = 13.1, 3.5 Hz, 0.5 H), 1.72 (s, 6 H), 1.39 – 1.21 (m, 2H), 0.90 (s, 4.5 H), 0.88 (s, 4.5 H), 0.08 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) [for 2 diastereomers]:: δ 161.0, 160.8, 157.6, 144.3, 144.1, 135.4, 135.2, 135.1, 135.1, 126.9, 126.1, 117.2, 116.4, 112.3, 112.1, 105.6, 105.5, 71.9, 71.9, 71.5, 71.2, 64.9, 64.8, 42.0, 41.8, 41.6, 41.2, 40.8, 40.3, 40.0, 39.9, 39.0, 38.6, 37.3, 26.6, 26.3, 26.0, 26.0, 25.4, 25.2, 18.2, 18.2, -4.4, -4.5.

FTIR (neat): ν 2957, 1732, 1607, 1294, 837 cm^{-1}.

LRMS (ESI) *m/z* Calcd for $C_{27}H_{42}O_6Si$ $[M]^+$ = 490.28. Found 490.82.

$[\alpha]^{27}_D = -68.6^o$ (c = 4.8, CH_2Cl_2).



(*3S,5S,9S*)-3-Allyl-7-((tert-butyldimethylsilyl)oxy)-14-hydroxy-3,4,5,6,7,8,9,10-octahydro-1H-5,9-epoxybenzo[c][1]oxacyclododecin-1-one (40):

Alcohol **39** (89 mg, 0.18 mmol, 1 equiv.) was dissolved in tetrahydrofuran (30 mL). Sodium hydride (0.15 g, 3.6 mmol, 20 equiv.) was added and the reaction allowed to stir at room temperature for 9 h. Saturated ammonium chloride solution (10 mL) was added and the mixture extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with water (30 mL), brine (30 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (Hexane: EtOAc, 4:1) to afford the product as a white powder (57 mg, 70% yield).

R_f = 0.36 (Hexane: EtOAc, 4:1).

^{1}H NMR (400 MHz, d-acetone) [for 2 diastereomers]: δ 8.45 (br, 1H), δ 7.12 (t, *J* = 7.6 Hz, 0.5H), 7.11 (t, *J* = 7.5 Hz, 0.5H), 5.97 – 5.86 (m, 1H), 5.54 – 5.46 (m, 1H), 5.14 (d, *J* = 17.2 Hz, 1H), 5.04 (d, *J* = 10.2 Hz, 1H), 4.36 – 4.31 (m, 0.5 H), 4.17 – 4.01 (m, 2H), 3.96 – 3.86 (m, 1H), 3.49 (dd, *J* = 14.5, 10.6 Hz, 0.5 H), 3.30 (dd, *J* = 13.9, 11.4 Hz, 0.5 H), 2.43 – 2.31 (m, 3H), 1.95 – 1.48 (m, 4H), 1.35 – 1.05 (m, 2H), 0.93 (s, 4.5 H), 0.89 (s, 4.5 H), 0.10 (s, 6H).

^{13}C-NMR (100 MHz, d-acetone): δ 169.9, 169.3, 153.8, 153.6, 140.2, 140.2, 134.9, 134.9, 130.1, 129.9, 125.3, 125.3, 121.9, 121.9, 117.1, 117.1, 114.1, 114.0, 74.5, 74.0, 73.4, 73.3, 68.0, 66.6, 66.2, 41.4, 40.5, 40.0, 39.6, 39.4, 38.9, 37.1, 25.9, 18.2, 18.2, -4.8.

FTIR (neat): ν 1732, 1292, 1107 cm^{-1}.

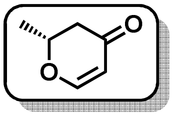
LRMS (ESI) *m/z* Calcd for $C_{24}H_{36}O_5SiNa$ [M+Na]$^+$ = 455.22. Found 455.78.

$[\alpha]^{26}_{D}$ = +73.4 (*c* = 1.00, CH_2Cl_2).

Representative procedure for one-pot synthesis

$InCl_3$ (221 mg, 1 mmol, 0.2 equiv.) was dissolved in THF (5 mL) at 0 °C. Propionaldehyde (0.36 mL, 5 mmol, 1 equiv.) was added and the reaction mixture was stirred at that temperature for 15 min. Danishefsky diene **3** (1.1 mL, 5.5 mmol, 1.1 equiv.) was added to the reaction mixture and it was stirred for 12 h at rt. One drop of TFA was added and the reaction mixture was stirred for another 30 min. After that, solvent and TFA was removed *in vacuo*. 1 mL of CH_2Cl_2 was added followed by addition of silyl ketene **6b** (591 mg, 5 mmol, 1 equiv.) and the reaction mixture was stirred for 1 h at rt. Another portion of **6b** was added and the reaction mixture was stirred for another 3 h. 1M HCl (1 mL) and ethyl acetate (8 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with water and brine. The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated *in vacuo*. The crude product was dissolved in MeOH (5 mL) and sodium borohydride (378 mg, 10 mmol, 2 equiv.) was added in portion. The reaction mixture was allowed to stir at 0 °C for 30 min. The reaction mixture was quenched with water (5 mL). The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with water and brine. The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated *in vacuo* to afford alcohol **48** after 3 steps in one-pot manner.

6.5. Synthetic study towards marinomycins



(*R*)-2-Methyl-2H-pyran-4(3H)-one (58)

A 50 mL oven-dried round bottomed flask equipped with a magnetic stir bar was charged with 3.85 g of oven dried powdered 4Å molecular sieves and (*S,S*)- amino indanol Cr(III)-Cl complex **64c** (0.34 g, 0.70 mmol, 5 mol %). The flask was sealed with a rubber septum and purged with N_2 for 5 min. TBME (15.5 mL) was added and the reaction mixture was cooled down to 0 ^{o}C followed by addition of acetaldehyde (1.86 g, 43 mmol, 3 equiv.). The flask was further sealed with Teflon tape and parafilm. This mixture was stirred at 0 ^{o}C for 15 min. 1-methoxy-3-[(trimethylsilyl)oxy]butadiene (2.43 g, 14.1 mmol, 1 equiv.) was added and the reaction mixture was stirred at this temperature for 24 h. Dichloromethane (5 mL) was added followed by 5 drops of TFA. The reaction mixture was allowed to warm to room temperature and stirred for 15 min. The reaction mixture was then filtered through a plug of celite and washed with copious amount of diethyl ether (300 mL). The filtrate was concentrated *in vacuo* and the crude residue was purified by flash chromatography (Hexane: EtOAc, 93:7). The isolated material was determined to have enantiomeric excess of 90% by chiral HPLC (Daicel Chiracel AS-H column, Hexane: *i*-propanol 99:1, 1 mL/min: t_1 = 26.99 min for the minor isomer, t_2= 30.03 min. for the major isomer).

Yellow oil (0.96 g, 60%)

R_f=0.29 (Hexane:EtOAc = 4:1)

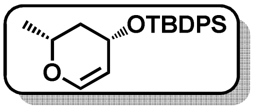
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, *J*= 6.0 Hz, 1H), 5.40 (d, *J*= 6.0 Hz, 1H), 4.57-4.53 (m, 1H), 2.54- 2.42 (m, 2H), 1.45 (d, *J*= 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 192.6, 163.1, 106.7, 75.9, 43.4, 20.2.

FTIR (neat): *v* 2997, 2931, 1732, 1475, 1269, 1043 cm^{-1}.

HRMS (CI) Calcd for $C_6H_9O_2$ $[M+H]^+$: 113.0603. Found: 113.0608.

$[\alpha]_D$ = +137.3 ° (*c* = 4.94, CH_2Cl_2)



Tert-butyl(((*2R,4S*)-2-methyl-3,4-dihydro-2H-pyran-4-yl)oxy)diphenylsilane (59)

To a solution of pyranone **58** (2.0 g, 18 mmol, 1 equiv.) in methanol (50 mL) at 0 °C was added cerium (III) chloride (0.87 g, 3.6 mmol, 0.2 equiv.). Sodium borohydride (0.68 g, 18 mmol, 1 equiv.) was added slowly in portions. The reaction mixture was quenched with saturated sodium sulphate solution after 15 min. The white suspension was filtered through a sintered glass funnel and the residue was flushed with copious ethyl acetate (200 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was immediately dissolved in anhydrous *N,N*-dimethylformamide (50 mL), imidazole (2.45 g, 36 mmol, 2 equiv.) and DMAP (44 mg, 0.36 mmol, 2 mol%) were added and the reaction mixture was stirred for 15 min. *tert*-butyldiphenylsilylchloride (5.61 mL, 21.6 mmol, 1.2 equiv.) was added and the reaction mixture was stirred overnight after which it was quenched with H_2O (25 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography with hexane as eluent.

Pale yellow oil (5.52 g, 87%)

$R_{f=}$ 0.35(Hexane: EtOAc= 9:1)

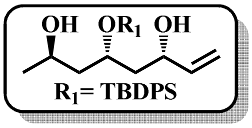
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74-7.71 (m, 4H), 7.48-7.40 (m, 6H), 6.60 (d, *J* = 4 Hz, 1H), 4.68 (dt, *J* = 6.5, 1.5 Hz, 1H), 4.50-4.47 (m, 1H), 3.96- 3.89 (m, 1H), 1.93-1.89 (m, 1H), 1.82-1.75 (m, 1H), 1.26 (d, *J*= 6 Hz, 3H), 1.10 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.4, 135.8, 134.3, 134.2, 129.7, 105.7, 71.0, 64.4, 39.4, 31.7, 26.9, 20.9.

FTIR (neat): *ν* 3068, 2929, 1959, 1890, 1830, 1643, 1471, 1427, 1392, 1265, 1103, 1058, 997, 867, 702 cm^{-1}.

HRMS (ESI) Calcd for $C_{22}H_{29}O_2Si$ $[M+H]^+$: 353.1937 Found: 353.1935.

$[\alpha]_D$ =+ 143.2 ^{o} (*c* =1.2, CH_2Cl_2)



(*2S,4R,6R*)-4-((Tert-butyldiphenylsilyl)oxy)oct-7-ene-2,6-diol (60)

To a solution of dihydropyran **59** (1.97 g, 5.6 mmol, 1 equiv.) in aqueous THF (10 mL, 1:1 THF:H_2O) was added mercury(II) acetate (1.96 g, 6.16 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature for 24 h, then cooled to 0 ^{o}C prior to addition of sodium cyanoborohydride (141 mg, 2.24 mmol, 0.4 equiv.) and stirred for 1 h at that temperature. The grey mixture was passed through a pad of celite and flushed with copious ethyl acetate (250 mL). The filtrate was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude lactol was subsequently dissolved in anhydrous THF (10 mL) and vinylmagnesium bromide in THF (1.0 M, 28 mL, 5 equiv.) was added. The mixture was refluxed for 6 h and stirred at room temperature for 12 h. Saturated ammonium chloride solution was added to the cooled mixture at 0 °C. The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product (77:23 diastereomeric ratio) was separated *via* flash column chromatography (Hexane: EtOAc, 9:1).

Pale yellow oil (1.14 g, 60%)

R_f = 0.24 (Hexane: EtOAc, 1:1).

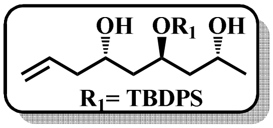
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.68 (m, 4H), 7.46-7.27 (m, 6H), 5.72-5.56 (m, 1H), 5.06 (qt, *J*= 7.5, 1.2 Hz, 1H), 4.97(dd, *J*= 10.2 ,1.2 Hz, 1H), 4.18-4.06 (m, 2H), 3.97-3.89 (m, 1H) 1.83-1.57 (m, 4H), 1.08 (d, *J*= 6.6 Hz, 3H), 1.07 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.9, 136.0, 133.6, 133.1, 129.9, 116.1, 70.5, 69.9, 64.8, 44.5, 43.0, 32.2, 27.0, 23.9.

FTIR (neat): *v* 3379, 3070, 2962, 2931, 2858, 2245, 1961, 1894, 1830, 1705, 1639, 1589, 1512, 1471, 1427, 1375, 1111, 910, 734, 704 cm^{-1}.

HRMS (ESI) Calcd for $C_{24}H_{35}O_3Si$ $[M+H]^+$: 399.2355. Found: 399.2373.

$[\alpha]_D$ = +18.7° (*c* =1.1, CH_2Cl_2)



(*2R,4S,6S*)-4-((Tert-butyldiphenylsilyl)oxy)non-8-ene-2,6-diol (61)

To a solution of dihydropyran **59** (0.84 g, 2.4 mmol, 1 equiv.) in aqueous THF (10 mL, 1:1 THF:H_2O) was added mercury(II) acetate (0.84 g, 2.64 mmol, 1.1 equiv.) and stirred at room temperature for 24 h. The mixture was cooled to 0 °C prior to addition of sodium cyanoborohydride (154 mg, 0.96 mmol, 0.4 equiv.) and stirred for 1 h at that temperature. The grey mixture was passed through a pad of celite and flushed with copious ethyl acetate (100 mL). The filtrate was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude lactol was used without further purification.

In 250 mL round bottom flask, (+) DIP-Br (0.98 g, 2.64 mmol, and 1.1 equiv.) was dissolved in anhydrous ether and the solution was cooled down to -78 ^{o}C. Allyl magnesium bromide (1 M, 3 mL, 1.25 equiv.) was added dropwise and the reaction mixture was stirred at that temperature for 1 h. After that, it was warmed up to room temperature and further stirred for 2 h. The mixture was brought to -78 ^{o}C again and lactol **54** (in 3 mL of dry ether) was added dropwise followed by stirring at that temperature for 1 h then at room temperature for 2 h. The mixture was cooled down to 0 ^{o}C and a premix solution of 3N NaOH/30% H_2O_2 (3:1 v/v) was added slowly and stirred for another 30 min. Then it was extracted with ether (3 x 100 mL), the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product (90:10 diastereomeric ratio) was separated *via* flash column chromatography using 10 % ethyl acetate: hexane solvent mixture.

Pale yellow oil (645 mg, 65%)

R_f = 0.32 (Hexane: EtOAc, 1:1).

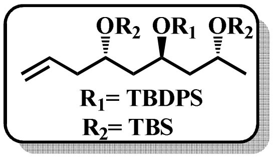
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73-7.69 (m, 4H), 7.45-7.36 (m, 6H), 5.73-5.59 (m, 1H), 5.07- 4.99 (m, 2H), 4.20-4.11(m, 1H), 3.97-3.86(m, 1H), 3.68-3.59 (m, 1H), 2.07-2.00 (m, 2H), 1.82-1.55(m, 4H), 1.07 (s, 9H), 1.05 (d, *J*= 6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 136.0, 135.9, 134.2, 133.6, 129.8, 118.1, 70.6, 67.6, 64.7, 43.6, 42.6, 42.3, 26.9, 23.8.

FTIR (neat): *v* 3053, 2985, 2931, 2858, 2684, 2304, 1427, 1265, 1111, 1064, 999, 894, 738, 705 cm^{-1}.

HRMS (ESI) Calcd for $C_{25}H_{37}O_3Si$ $[M+H]^+$: 413.2512 Found: 413. 2613.

$[\alpha]_D$ = - 16.9 ^{o}(c =0.9, CH_2Cl_2)



((*2R,4S,6S*)-4-(Tert-butyldiphenylsilyl)non-8-ene-2,6-diyl)bis(tert-butyldimethylsilane) (53)

To a solution of homoallylic alcohol **61** (938 mg, 2.27 mmol, 1 equiv.) in dry DMF (5 mL) was added imidazole (618 mg, 6.24 mmol, 4 equiv.) followed by TBSCl (753 mg, 4.99 mmol, 2.2 equiv.). The reaction mixture was stirred for 6 h at room temperature. The reaction mixture was quenched with H_2O (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts was washed with water (3 x 10 mL) followed by brine. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude compound was purified by column chromatography with 5% ethyl acetate in hexane as eluent.

Colorless oil (1.24 g, 85%)

R_f = 0.46 (Hexane:EtOAc, 4:1).

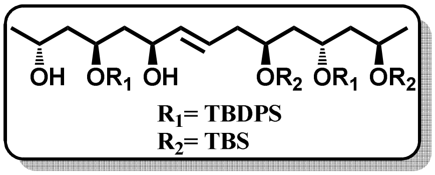
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.42-7.36 (m, 6H), 5.73-5.65 (m, 1H), 4.96- 4.79 (m, 2H), 4.02-3.99(m, 1H), 3.77-3.72(m, 1H), 3.66-3.62 (m, 1H), 2.10-1.87 (m, 2H), 1.73-1.66(m, 2H), 1.54-1.52 (m, 2H), 1.04 (s, 9H), 1.01 (d, *J*= 5.0 Hz, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H), 0.01 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0, 135.8, 135.7, 129.5, 127. 6, 116.8, 69.6, 68.9, 66.2, 48.7, 45.9, 42.2, 32.2, 27.1, 26.9, 23.6, 21.3, 19.4, 18.2, 18.0., -2.9, -4.1.

FTIR (neat): *v* 3070, 2954, 2929, 2856, 1471, 1462, 1388, 1361, 1255, 1111, 1068, 1004, 910, 835, 775, 702 cm^{-1}.

HRMS (ESI) Calcd for $C_{37}H_{65}O_3Si_3$ $[M+H]^+$: 641.4242 Found: 641.4246.

$[\alpha]_D$ =- 12.1 ° (c =4.94, CH_2Cl_2)



(*2R,4S,6S,10S,12S,14R,E*)-10,14-Bis((tert-butyldimethylsilyl)oxy)-4,12-bis((tert-butyldiphenylsilyl)oxy)pentadec-7-ene-2,6-diol

To a heated solution of homoallylic alcohol **53** (169 mg, 0.26 mmol, 1 equiv.) and allyl alcohol **52** (206 mg, 0.52 mmol, 2 equiv.) in 5 mL of argon degassed CH_2Cl_2 was added a solution of Hoveyda Grubbs 2nd generation catalyst (8 mg, 0.013 mmol, 5 mol %) in CH_2Cl_2 (1 mL) dropwise. The reaction mixture was heated to reflux for 6 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by flash column chromatography 10% ethyl acetate: hexane yielded the product as a 9:1 mixture of isomers.

Pale yellow oil (136 mg, 52%)

R_f = 0.26 (Hexane: EtOAc, 4:1).

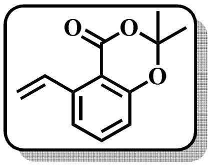
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.66 (m, 8H), 7.44-7.34 (m, 12H), 5.43-5.36 (m, 1H), 5.22-5.09 (m, 1H), 3.96-3.90(m, 3H), 3.88-3.78(m, 1H), 3.76-3.71 (m, 1H), 3.68-3.60 (m, 1H), 1.86-1.65(m, 4H), 1.54-1.46 (m, 2H), 1.07 (s, 9H), 1.02 (s, 9H), 0.81 (s, 9H), 0.80 (s, 9H), 0.03 (s, 6H), 0.01 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0, 135.9, 135.8, 134.8, 133.2, 129.9, 129.6, 129.5, 127.8, 127.7, 127.6, 127.5, 127.4, 70.4, 69.5, 69.3, 69.1, 66.1, 64.6, 60.4, 48.5, 31.6, 26.9, 25.9, 23.6, 22.6, 21.0, 19.3, 19.2, 18.0, 14.2, -4.1, -4.4.

FTIR (neat): *v* 2954, 2929, 2856, 27.08, 2455, 2247, 1957, 1471, 1462, 1427, 1377, 1255, 1111, 1064, 835, 775, 736, 702 cm^{-1}.

HRMS (ESI) Calcd for $C_{59}H_{95}O_6Si_4$ $[M+H]^+$: 1011.6206 Found: 1011.6250.

$[\alpha]_D = + 5.6^{o}$ (c =2.5, CH_2Cl_2)



2,2-Dimethyl-5-vinyl-4H-benzo[d][1,3]dioxin-4-one (68)

Vinylboronate (0.17 mL, 1 mmol, 1 equiv.) and triflate **29** (297 mg, 0.91 mmol, 0.9 equiv.) were added to a mixture of $PdC1_2$(dppf) (73 mg, 0.1 mmol, 10 mol%) and anhydrous K_3PO_4 (318 mg, 1.5 mmol, 1.5 equiv.) suspended in dry THF (5 mL). The mixture was heated to 60 ^{o}C for 6 h. The reaction mixture was diluted with dry THF (5 mL), and treated with a premix 3 N NaOH (0.5 mL) and 30% H_2O_2 (0.5 mL). After 30 min the organic phase was washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (Hexane-Ethyl acetate= 8:1) provided olefin **68** as yellow oil.

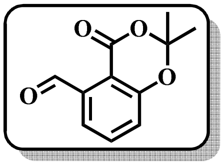
(150 mg, 80%).

^{1}H (300MHz, $CDCl_3$): δ 7.71 (dd, *J*= 13.0, 8.0 Hz, 1H), 7.47 (t, *J*= 6.0 Hz, 1H), 6.89 (dd, *J*=1.0, 6.0 Hz, 1H), 5.44 (dd, *J*= 1.0, 13.0 Hz, 1H), 4.93-4.90 (m, 2H), 1.72 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 152.5, 134.5, 131.3, 128.7, 120.3, 115.9, 114. 3, 113.4, 111.8, 24.7.

FTIR (neat): *v* 3055, 1722, 1693,1631, 1471, 1265,1078, 740 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{12}H_{13}O_3$ [M+H$^+$] = 205.0865. Found 205.0865.



2,2-Dimethyl-4-oxo-4H-benzo[d][1,3]dioxine-5-carbaldehyde (69)

A solution of terminal olefin **68** (2.14 g, 10.5 mmol, 1 equiv.) in dichloromethane (50 mL) was cooled to -78 °C. A flow of ozone was passed through the solution until it turned blue (10 min). The reaction mixture was quenched with dimethyl sulfide (1.54 mL, 22 mmol, 2 equiv.) at -78 °C. It was allowed to warm to ambient temperature and stirred at rt overnight and then concentrated *in vacuo*. The residual crude product was purified by flash column chromatography 0-2% ethyl acetate in hexane to afford the aldehyde as white solid (1.29 g, 60% yield).

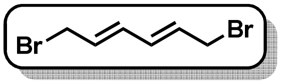
^{1}H (400 MHz, $CDCl_3$): δ 10.89 (s, 1H), 7.66 (d, *J*= 4.4 Hz, 2H), 7.23 (t, *J*=4.4 Hz, 1H), 1.79 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 159.4, 156.4, 138.2, 135.8, 122.3, 122.2, 112.9, 106.2, 60.1, 25.3.

m.p.: 57-60 °C

FTIR (neat): *v* 3055, 2851, 2777, 1693, 1631, 1471, 1265,1078, 740 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{11}H_{11}O_4$ [M+H$^+$] = 207.0579. Found 207.0575.



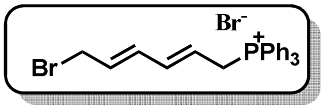
***(2E,4E)*-1,6-Dibromohexa-2,4-diene**

A solution of hexa- 1,6-diene-3,4-diol (228 mg, 2 mmol, 1 equiv.) in anhydrous THF (8 mL) was added dropwise to PBr_3 (0.56 mL, 6 mmol, 3 equiv.) in an ice-bath cooled round-bottomed flask thorugh addition funnel. After the addition was complete, the mixture was allowed to warm to room temperature and was then set aside overnight. It was then poured slowly with stirring into 10 mL ice-water, and the resulting mixture neutralized by careful addition of saturated Na_2CO_3. The product was extracted with ether (3x10 mL) and the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude crystalline dibromide and was recrystallized from ether.

(417 mg, 57%)

^{1}H (400 MHz, $CDCl_3$): δ 6.4-6.2 (m, 2H), 6.1-5.8 (m, 2H), 4.21-4.03 (d, *J*= 7.0 Hz, 4H).

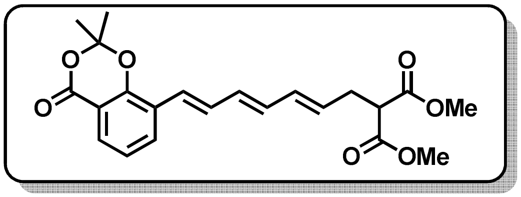
m.p. 85-86



((*2E,4E*)-6-Bromohexa-2,4-dien-1-yl)triphenylphosphonium (75)

1,6-Dibromohexa-2,4-diene (180 mg, 7.5 mmol, 1 equiv.) was weighed rapidly and dissolved in benzene (1 ml) in a 2-1 round-bottomed flask. Triphenylphosphine (2.16 g, 8.25 mmol, 1.1 equiv.) was added. The resulting mixture was rapidly stirred overnight at room temperature after which the phosphonium salt was filtered off, washed several times with fresh toluene to remove traces of unchanged tributylphosphine, and air-dried (376 mg, 52%)

^{1}H (300 MHz, $CDCl_3$): δ 7.89-7.68 (m, 15H), 6.53-6.43 (m, 1H), 6.18-6.09 (m, 1H), 5.88-5.78 (m, 1H), 5.61-5.49 (m, 1H), 5.01 (dd, *J*=7.2 Hz, 2H), 3.93 (d, *J*=7.5 Hz, 2H).



Dimethyl 2-((*2E,4E,6E*)-7-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-8-yl)hepta-2,4,6-trien-1-yl)malonate (78)

To a stirred suspension of **75** (502 mg, 1 mmol, 1 equiv.) in dry THF (3 mL) at -78 °C is added a THF solution of LDA (1 mmol). The mixture is allowed to warm to -40 °C during which it changed to a brown color. To a solution of dimethyl malonate (132 mg, 1 mmol, 1 equiv.) in 1 mL THF was added LDA (2 mL, 2 mmol, 2 equiv.) The anionic solution of dimethyl malonate was then added to a stirred suspension of **75**. The reaction mixture is allowed to warm to 0 °C. Aldehyde **69** (61.8 mg, 0.3 mmol, 1M in THF) was added to the reddish-brown mixture. After 10 min an ice-cold solution of 1% HCl was added and the product was extracted with ether and purified by flash chromatography (36 mg, 30% yield).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.71 (t, *J*= 3.6 Hz, 1H), 7.54-7.42 (m, 2H), 7.31 (d, *J*= 8 Hz, 1H), 7.07-7.02 (m, 2H), 6.90-6.80 (m, 1H), 6.48-6.29 (m, 2H), 4.21 (t, *J*= 7.5 Hz, 1H) 3.75 (s, 6H), 2.49 (t, *J*= 7.6 Hz, 2H), 1.72 (s, 6H).

^{13}C NMR (125 MHz, CDCl$_3$): δ 169.2, 160.1, 156.9, 141.0,135.0, 134.8, 133.3, 130.8, 130.2, 129.1, 128.1, 125.6, 116.2, 111.4, 105.4, 52.6, 51.5, 32.1, 25.7.

FTIR (neat): 2997, 1732, 1597, 1573, 1475, 1317, 1269, 1043, 821 cm^{-1}.

LRMS (ESI) Calcd for $C_{22}H_{24}O_7$ [M]$^+$: 400.15. Found: 400.82.