Application of New Synthetic Methodologies to access 2,6-*anti*-Tetrahydropyrans: Towards the Total Synthesis of Apicularen A

CHUA SIN SIU

School of Physical and Mathematical Sciences

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

2013

Acknowledgements

William Arthur Ward once said, *"Feeling gratitude and not expressing it is like wrapping a present and not giving it."*

I would not have come so far in my research and consequently, producing this dissertation without the involvement of many parties. The extensive assistance and never-wavering encouragement every one of them showered me with is very humbling. Therefore, I would like to take this opportunity to express my utmost gratitude and deepest appreciation to the following parties:

- **Nanyang Technological University**, for awarding me the ASEAN Undergraduate Scholarship and the Nanyang Research Scholarship for graduate studies. Given my family's financial situation, I would not be able to pursue my tertiary education without the monetary support.

- My supervisor, **Dr. Motoki Yamane**, who has honed my experimental skills in the laboratory since my undergraduate studies and guided me to have more considerations in my ideas before executing them. It has been a great pleasure being under his supervision as he balances the hectic research life with a sense of humour as well as introducing the rich and enchanting Japanese culture to me.

- My co-supervisor, **Prof. Loh Teck Peng**, who has been my pillar of support and light of guidance since the very first day I entered Division of Chemistry and Biological Chemistry as a freshman. Not only did he allow me to follow my interest in Chemistry, he provided me the opportunity to learn by hiring me as a laboratory assistant in his research group. When I decided to focus on natural product synthesis during my PhD studies, he did not hesitate and welcomed me to his research group with open arms. I am truly indebted to Prof. Loh for always being encouraging and making time for consultations despite his busy schedule.

- Other academic staff, especially **Nanyang Professor Koichi Narasaka** and **Prof. Shunsuke Chiba**, who have rekindled my passion for Chemistry when I had almost given up on pursuing my PhD studies.

- Administration and laboratory support staff that efficiently handled my academic matters and patiently addressed my relentless concerns. Special mention goes to Miss Chen Xiaoping, Miss Florence Ng Pei Fan and Miss Celine Hum Wei Mei (academic matters), Miss Seow Ai Hua (Teaching laboratory facilities), Mdm. Zhu Wen Wei (mass spectrometry facilities) as well as Mdm. Goh Ee Ling and Dr. Attapol Pinsa (NMR facilities).

- My mother, **Mdm. Soo Yoke Lin**, who selflessly provided me everything I needed and desired. Ever since the passing of my father, she has been the breadwinner of the family and dedicated her entire life to nurture my brother and me. When I stayed in Singapore, she would call me every night to make sure I returned home safely, rain or shine, and nourish me with delicious home-cooked dishes whenever I return to my hometown.

- **My family members** who have stood by me all the time, providing me comfort and warmth of kinship. I could not thank them enough for never failing to believe in me when I doubt myself as well as being always understanding and patient especially when I am frustrated and not on the best of my behavior.

- **All my colleagues and friends** who have made my graduate studies more meaningful and enjoyable while giving me constructive advice and ideas to my research project. Among them, I would like to specially thank Miss Cheng Jun Kee, Mr. Chok Yew Keong, Mr. Chua Chun Kiang, Miss Kiu Wei Zhen, Mr Jackson Koh Peng Fei, Miss Ng Kim Hong, Miss Nicole Loy, Mr. Stephen Sanjaya, Miss Tnay Ya Lin, Mr. Benny Tong Meng Kiat, Miss Too Pei Chui, Mr Wang Wee Jian, Mr Wong Zhen Zhou and Miss Zhang Shuhua for all the moral support and assistance rendered.

(The list abovementioned is not exhaustive and I apologize for any unintentional omission at the time of printing.)

My indebtedness is beyond describable by merely words and I can only try repaying the kindness by sharing the wisdom and the care that have been shown to me. To quote John Fitzgerald Kennedy: *"As we express our gratitude, we must never forget that the highest appreciation is not to utter words, but to live by them."*

Table of Contents

Index of Abbreviations

δ	chemical shift
Δ	reflux
°C	degree centigrade
1-D	one-dimensional
2-D	two-dimensional
9-I-9-BBN	9-Iodo-9-borabicyclo[3.3.1]nonane
AcOH	acetic acid
Ac_2O	acetic anhydride
aq.	Aqueous
Ar	aryl
BDMS	benzyldimethylsilyl
Bn	benzyl
BOM	benzyloxymethyl acetal
brs	broad singlet
brsm	based on recovered starting material
BuLi	butyl lithium
Bz	benzoyl
calcd.	calculated
cat.	catalytic
CAN	ceric ammonium nitrate
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform
COSY	COrrelation SpectroscopY
CSA	camphorsulfonic acid
d	doublet
DBU	1,8-diazabicycloundec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
dd	doublets of doublet
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
de	diastereomeric excess
(+)-DIPT	(+)-diisopropyl $_L$-tartrate

DMA	dimethylacetamide
DMAP	4-(*N.N*-dimethylamino)pyridine
DMDO	dimethyl dioxirane
DME	1.2-dimethoxyethane
DMF	*N,N*-dimethyl formamide
DMP	Dess-Martin Periodinane
DMS	dimethyl sulfide
DNA	deoxyribonucleic acid
dr	diastereomeric ratio
dt	doublets of triplet
ee	enantiomeric excess
EI	electron impact ionization
equiv.	equivalent
ESI	electron spray ionization
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
FTIR	Fourier Transform Infrared spectroscopy
g	gram
h	hour
H	hydrogen
Hex	hexane
HCl (aq)	hydrochloric acid solution
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple-Quantum Correlation
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
IC_{50}	half maximal inhibitory concentration
Im	imidazole
$Ipc_2Ballyl$	*B*-allyldiisopinocampheylborane
J	coupling constant(s)
kg	kilogram

m	multiplet
M	molar concentration (mol/dm^3)
M^+	parent ion peak (mass spectrum)
*m*CPBA	meta-chloroperoxybenzoic acid
Me	methyl
MEM	2-methoxyethoxymethyl ether
MeOH	methanol
mg	milligram
$MgBr_2$	magnesium bromide
MHz	megahertz
min	minutes
mmol	millimoles
mol	moles
MS	molecular sieves
n.a.	not available
NMR	nuclear magnetic resonance
NMO	N-Methylmorpholine-N-Oxide
NOESY	nuclear Overhauser enhancement spectroscopy
o	ortho
O_3	ozone
OTf	trifluoromethanesulfonate
p	para
Pd/C	palladium on carbon
$Pd(PPh_3)_4$	tetrakis (triphenylphosphine)palladium(0)
PG	protecting group
Ph	phenyl
PhD	Doctor of Philosophy
PhMe	toluene
PMB	*p*-methoxybenzyl ether
PMP	*p*-methoxyphenyl
ppm	parts per million
Py	pyridine
quin	quintet
quar	quartet
quant.	quantitative

R	side chain
r.s.m.	recovered starting material
rt.	room temperature (i.e. 23-25 °C)
RBF	round-bottomed flask
s	singlet
sat.	saturated
SEM	[2-(trimethylsilyl)ethoxy]methyl
SET	single electron transfer
sp.	species
t	triplet
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid
TFP	tetrafluoropropanol
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	trimethylsilyl
TMSCN	trimethylsilyl cyanide
TMSOTf	trimethylsilyl trifluoromethane sulfonate
TPAP	tetrapropylammonium perruthenate
Ts	*para*-toluenesulfonyl
UV	ultraviolet

PREFACE

This dissertation is intended to be a comprehensive research progress report of my pursuit towards a PhD degree in Chemistry at Nanyang Technology University under the tutelage of Dr. Motoki Yamane and Prof. Loh Teck Peng. It would be my honour and pleasure if this dissertation of mine could be of any help to fellow PhD aspirants, undergraduates as well as practitioners of synthetic organic chemistry, who are doing related research.

This dissertation consists of four chapters. The **first chapter** aims to provide a general idea of what total synthetic chemistry is as well as its significance and relevance to both the chemical society and general public. The motif of interest, 2,6-*anti*-tetrahydropyran was then introduced and its prevalence in natural products was illustrated alongside with a discussion on the construction of the 2,6-*anti*-tetrahydropyran motif in total syntheses of three different natural products, namely Swinholide A, Irciniastatin A and (-)-Aspergillide B. Thereafter, the development of our group's methodologies to construct cyclic ethers was showcased in a chronological order.

In the **second chapter**, the target molecule, Apicularen A, was introduced, briefly describing its isolation, structural elucidation as well as its biological significance. We then delved into previously reported synthetic efforts towards the synthesis of Apicularen A by various research groups, highlighting the three key reactions, which are the construction of 2,6-*anti*-tetrahydropyran ring, the formation of 12-membered ring macrolactone and the installation of highly unsaturated side chain.

The **third chapter** consists of our group's synthetic studies towards Apicularen A. The progress from preliminary retrosynthetic analysis, alongside with its synthetic route, to the revised versions, was described and elaborated to the best of the author's knowledge.

Experimental procedures and structural data, complete with supporting spectra and other data analysis, can be found in the **last chapter**.

THIS PAGE IS INTENTIONALLY LEFT BLANK.

Chapter One

Introduction to the Synthesis of Natural Products Containing 2,6-*anti*-Tetrahydropyran Rings

THIS PAGE IS INTENTIONALLY LEFT BLANK.

1.1 Natural Products Synthesis

Today, with rapid developments and discoveries in science and technology, we appreciate and marvel at nature's ingenious molecular architecture and biological systems, more than ever before. By utilizing merely four major classes of molecules, namely nucleic acids, proteins, saccharides and secondary metabolites (which is more commonly known as *natural products*), Mother Nature is able to assemble intricate and efficient living systems. While nature synthesizes these molecules with much ease, using the various types of biological catalysts (i.e. enzymes), it is a daunting challenge for humans to reproduce them, especially so in the construction of natural products. Among the four classes of molecules, natural products have the most extensive and elaborate range of compounds. The variation in both structure and stability is beyond imagination and each compound has its own unique biological properties.

Secondary metabolites, also known as *natural products*, have different roles than that of primary metabolites. Primary metabolites, such as carbohydrates, nucleic acids, lipids and protein, directly participate in growth, development and reproduction of living organisms but secondary metabolites do not. However, secondary metabolites have ecological importance that determines an organism's sustainability, fertility and aesthetics. While the survivability of some organisms heavily depends on their secondary metabolites, humankind utilizes the very same natural products as medicine and flavourings. For example, paclitaxel, which is commercially marketed as Taxol®, was derived from the bark of *Taxus brevifolia*, the Pacific yew tree and is used as a mitotic inhibitor in cancer chemotherapy (**Figure 1.1**). Natural products with analgesic properties such as the alkaloids, epibatidine, that is present on the skin of an endangered Ecuadarian poison dart frog, *Epipedobates tricolor*, and morphine, from opium poppy, *Papaver somniferum*. Another plant-derived natural product, artemisinin, constitutes an integral part of treatments for malaria. The use of natural products as food flavourings is hereby illustrated with cinnamaldehyde (cinnamon flavour), vanillin (vanilla flavour), benzaldehyde (almond flavour), isopentyl acetate (banana flavour) and 2-phenylethyl acetate (sweet, rosy, fruity and honey-like odour).

The syntheses of urea and acetic acid in 1828 and 1845 respectively, ignited synthetic chemists' ambitions and desires to construct even more complex natural products. What the initial intentions were when chemists first embarked on natural

product synthesis, are now obsolete. From being a tool to elucidate and validate natural products' molecular structures, the purpose of total synthesis has evolved. For academia, which enjoys challenges and discovering new methodologies, the construction of natural products that usually requires delicate considerations and exclusive approaches provides ample opportunities for creativity and innovation. On the other hand, total syntheses of natural products can supply sufficient substance when its natural abundance is scarce to biologists for analysis and testing of biological activities. These, in turn allow pharmaceutical companies to explore and subsequently exploit the wondrous biological properties of natural products in their drug design and discovery efforts for greater benefits to mankind. Furthermore, producing natural products synthetically may help to complement the limited natural supply of such entities to meet commercial demands.

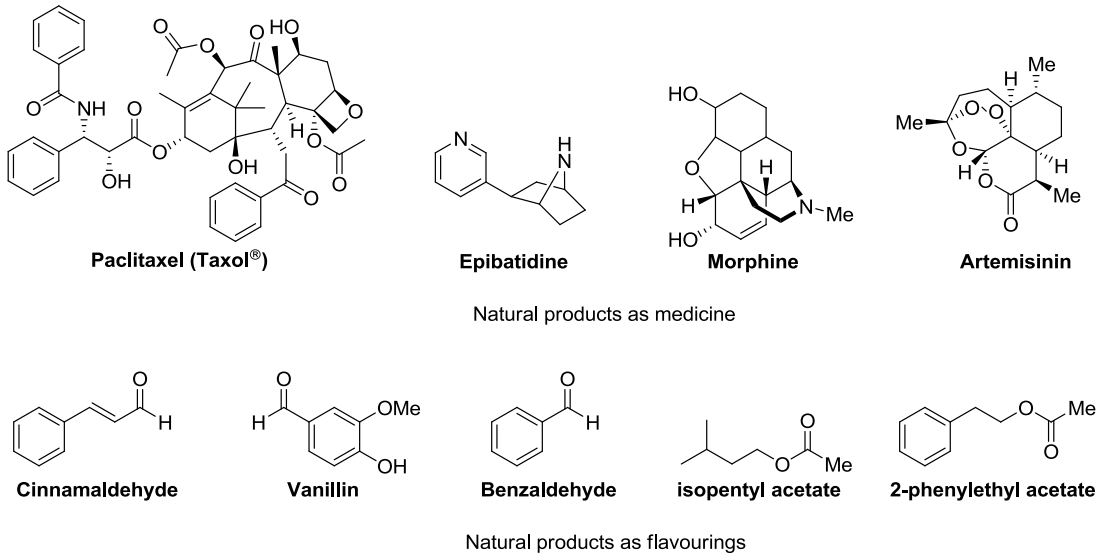


Figure 1.1. Examples of natural products as medicine and flavourings.

Despite being perceived as trivial and its benefits only extend to "educational purposes", what synthetic chemists achieved thus far, is merely the tip of an iceberg. While it may seem as if total synthesis of natural product is merely an application of various methodologies that are discovered by other chemists, the challenges posed should not be underestimated. Contrary to the common belief that this research field has already reached its maturity, synthetic chemistry is in fact at a very preliminary stage if it were to mimic nature. As more and more natural products are identified by the day, it should dawn us that we still have a very long way to catch up with nature even though we are now better equipped with more advanced facilities and methodologies.

1.2 2,6-*anti*-Tetrahydropyran Rings as Motif

Most entities in the world are unique in one way or another. However, often than not, we are able to organize the entities into various categories by sorting them according to certain generalizations and distinctive characteristics. For instance, every individual in our human race is unique, even identical twins may appear slightly different due to external factors despite their identical DNA make-up. We can then be grouped with other individuals to form a community, based on certain traits such as nationality, interests, blood types, skin colour or profession. Likewise, despite the massive library of natural products, they can also be categorized systematically.

While natural products can be sorted according to their sources or commercial values, organic chemists usually classify them with respect to their molecular motifs. Common molecular motifs include polycyclic hydrocarbons, polyenes, cyclic amines and cyclic ethers (**Figure1.2**). Polycyclic hydrocarbons, as illustrated in the molecules cholesterol and camphor, are motifs that consist of two or more fused hydrocarbon ring structures and compounds with polyenes motifs such as Amphotericin B and *β*-carotene have a conjugated system made up of alternating carbon-carbon double and single bonds. Compounds with cyclic amines motifs, for example, quinine and cocaine, comprise of ring structures incorporating nitrogen atoms while those with cyclic ethers motifs, for instance, lactose and Brevetoxin A, involve oxygen atoms into the molecular scaffolds. Amongst the abovementioned, we are interested in cyclic ether motif, and to be more specific, the 2,6-*anti*-tetrahydropyran ring scaffold.

Cyclic ethers have varying ring sizes and number of bridging oxygen atoms. The smallest cyclic ether is ethylene oxide (**Figure 1.3**), which consists of two carbon atoms and one oxygen atom, while cyclic ethers of 5- and 6-membered rings that contain one bridging oxygen atom have suffixes - furan and pyran respectively. Cyclic ethers with more than one bridging oxygen atom are illustrated by 1,3- and 1,4-dioxanes as well as crown ethers, of which their ring sizes increase with monomers (i.e. repeating units) of ethyleneoxy (-CH_2-CH_2-O-).

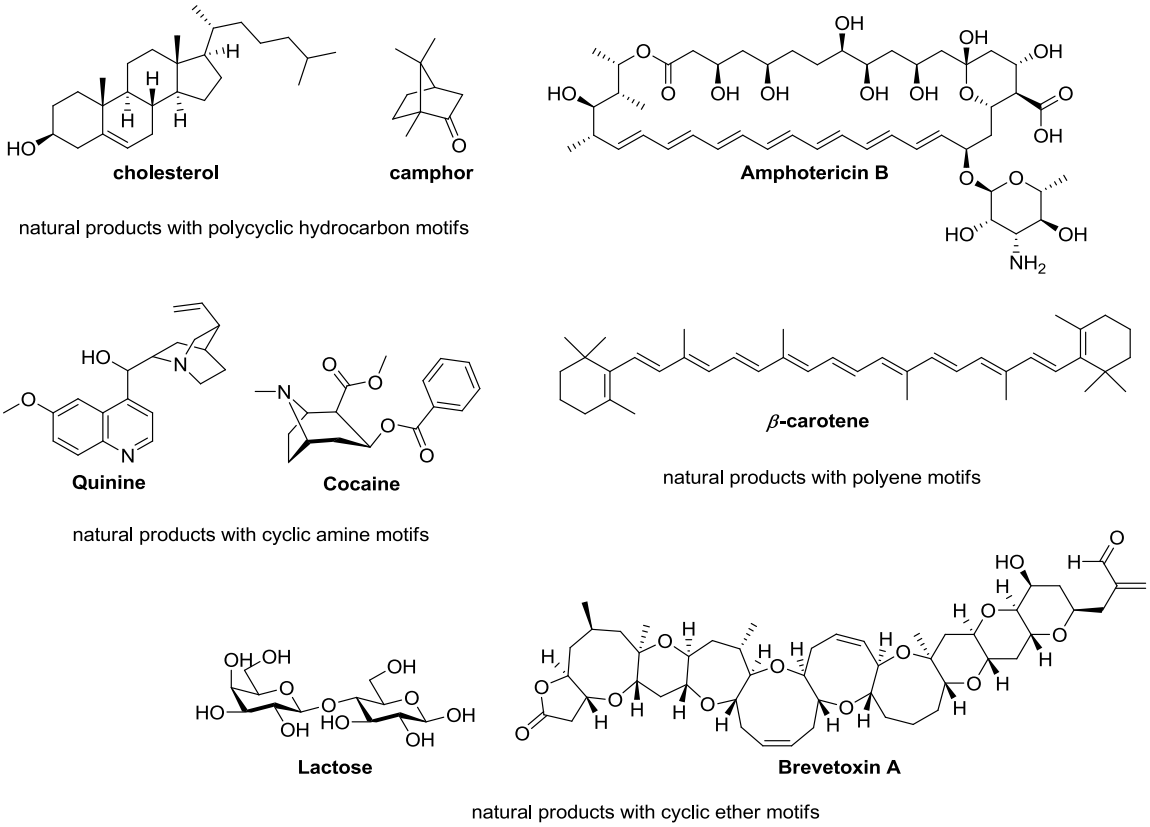


Figure 1.2. Examples of natural products with polycyclic hydrocarbons, polyene, cyclic amine and cyclic ether motifs respectively.

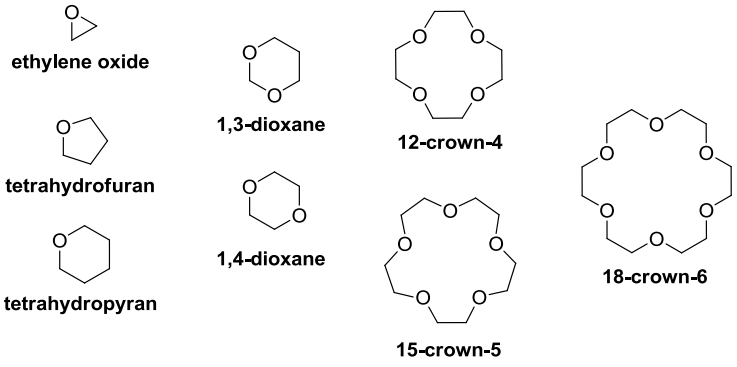


Figure 1.3. Examples of cyclic ethers.

The concern about the stereochemistry of substituted cyclic ethers arises as a consequent of ring conformation of cyclic ethers, which restricts free rotation about the bonds. By convention, an *anti*-isomer has its highest priority groups on the two adjacent atoms of interest, on opposite sides of the molecule while a *syn* isomer has the groups on the same side of the molecule. In accordance with our particular

interest in 2,6-*anti*-tetrahydropyrans, examples in **Figure 1.4** illustrate the presence of such molecular scaffolds in natural products.

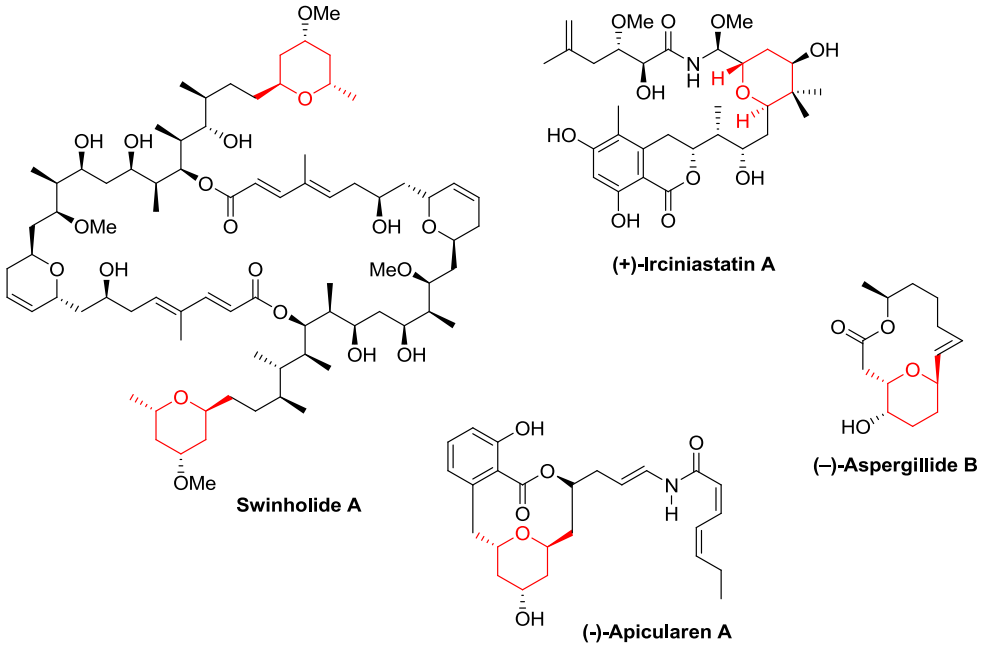


Figure 1.4. Examples of natural products containing 2,6-*anti*-tetrahydropyran motif.

Swinholide A, which is isolated from a species of marine sponge, *Theonella swinhoei*, showcases impressive biological properties especially in antifungal and cytotoxic activities.[1] It consists of an astounding 44-membered macrolide ring and two trisubstituted pyran rings as side chains. This dimeric dilactone structure has two of each following features - conjugated dienes, disubstituted dihydropyran systems and axes of symmetry respectively, embedded within the ring.[2] Its intriguing complex construction with 30 stereogenic centers, its scarcity in nature as well as the beneficial biological properties displayed have aroused chemists' interest to synthesize Swinholide A. To the best of our knowledge, there are only two groups that succeeded in synthesizing the aforesaid molecule so far.[3]

---

[1] Carmely, S.; Kashman, Y. *Tetrahedron Lett.* **1985**, *26*, 511.

[2] (a) Kobayashi, M.; Tanaka, J.; Katori, T.; Matsura, M.; Kitagawa, I. *Tetrahedron Lett.* **1989**, *30*, 2963. (b) Doi, M.; Ishida, T.; Kobayashi, M.; Kitagawa, I. *J. Org.Chem.* **1991**, *56*, 3629. (c) Kitagawa, I.; Kobayashi, M.; Katori, T.; Yamashita, M. *J. Am. Chem. Soc.* **1990**, *112*, 3710. (d) Kobayashi, M.; Tanaka, J.; Katori, T.; Yamashita, M.; Matsuura, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2409. (e) Kobayashi, M.; Tanaka, J.; Katori, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2960.

[3] (a) Paterson, I.; Yeung, K.; Ward, R. A.; Cumming, J. G.; Smith, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 9391. (b) Nicolaou, K. C.; Ajito, K.; Patron, A. P.; Khatuya, H.; Richter, P. K.; Bertinato, P. *J. Am. Chem. Soc.* **1996**,*118*, 3059.

A highly potent cytotoxin, (+)-Irciniastatin A, also known as (+)-Psymberin, was isolated from two different marine sponges, namely *Irnicia ramosa* from the Indo-Pacific and *Psammocinia* sp. from Papua New Guinea by two independent research groups - Pettit and co-workers[4] as well as Crews and co-workers, respectively.[5] Fueled by its limited natural abundance, high cytotoxicity and selective inhibition of tumour cell growth, as well as an interesting molecular architecture (which consists of a *N*,*O*-hemiaminal moiety, a dihydroisocoumarin and a substituted 2,6-*trans*-tetrahydropyran motif), many synthetic chemists jumped onto the bandwagon to reproduce this natural product *via* different approaches. To date, there are seven reported total syntheses of (+)-Irciniastatin A.[6]

(-)-Aspergillide B, on the other hand, is an unprecedented product obtained by Kusumi and co-workers, alongside with Aspergillides A and C,[7] when they substituted natural seawater with bromine-modified artificial seawater to culture fungus *Aspergillus ostianus* strain TUF 01F313 that was isolated from an unknown marine sponge found at Pohnpei, Micronesia.[8] Being one of the earliest reported examples of 14-membered macrolides, in which 2,6-*trans*-substituted tetrahydropyran ring is embedded, Aspergillides A, B and C found themselves in the limelight of synthetic chemists. The molecular structure illustrated in **Figure 1.4** was the revised version suggested by Uenishi and co-workers when they published the first total synthesis of Aspergillide B.[9]

Lastly, Apicularen A, which is our target molecule and hence, the focus in this dissertation, will be discussed in the following chapters with greater depth (*vide infra*).

---

[4] Pettit, G. R.; Xu, J.-P.; Chapuis, J.-C.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schmidt, J. M. *J. Med. Chem.* **2004**, *47*, 1149.

[5] Cichewicz, R. H.; Valeriote, F. A.; Crews, P. *Org. Lett.* **2004**, *6*, 1951.

[6] (a) Jiang, X.; García-Fortanet, J.; DeBrabander, J. K. *J. Am. Chem. Soc.* **2005**, *127*, 11254. (b) Huang, X.; Shao, N.; Palani, A.; Aslanian, R.; Buevich, A. *Org. Lett.* **2007**, *9*, 2597. (c) Smith, A. B., III; Jurica, J. A.; Walsh, S. P. *Org. Lett.* **2008**, *10*, 5625. (d) Crimmins, M. T.; Stevens, J. M.; Schaaf, G. M. *Org. Lett.* **2009**, *11*, 3994. (e) Watanabe, T.; Imaizumi, T.; Chinen, T.; Nagumo, Y.; Shibuya, M.; Usui, T.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2010**, *12*, 1040. (f) Wan, S.; Wu, F.; Rech, J. C.; Green, M. E.; Balachandran, R.; Horne, W. S.; Day, B. W.; Floreancig, P. E. *J. Am. Chem. Soc.* **2011**, *133*, 16668. (g) Byeon, S. R.; Park, H.; Kim, H.; Hong, J. *Org. Lett.* **2011**, *13*, 5816.

[7] Kito, K.; Ookura, R.; Yoshida, S.; Namikoshi, M.; Ooi, T.; Kusumi, T. *Org. Lett.* **2008**, *10*, 225.

[8] Namikoshi, M.; Negishi, R.; Nagai, H.; Dmitrenok, A.; Kobayashi, H. *J. Antibiot.* **2003**, *56*, 755.

[9] Hande, S. M.; Uenishi, J. *Tetrahedron Lett*, **2009**, *50*, 189.

1.3 Examples of the Construction of 2,6-*anti*-Tetrahydropyran Rings

To the best of our knowledge, methodologies dedicated to construct 2,6-*anti*-tetrahydropyran rings are scarce in literature. However, approaches to form 2,6-*anti*-tetrahydropyran rings can be found embedded in various synthetic studies towards natural products that contain such motif. In this section, we will explore how the motif, 2,6-*anti*-tetrahydropyran ring, is constructed in the synthetic studies towards the syntheses of Swinholide A, (+)-Irciniastatin A and (-)-Aspergillide B to illustrate some of the common practices in the literature to form such moiety.

1.3.1 Construction of 2,6-*anti*-tetrahydropyran ring in Swinholide A

1.3.1.1 Keck's approach[10]

Keck and co-workers reported a partial synthesis of Swinholide A, in which they described the assembly of C_{19}-C_{35} fragment (**Figure 1.5**). The synthetic route began with ethyl acetoacetate that underwent several transformations to become a protected homoallylic alcohol intermediate, which was henceforth subjected to ozonolysis. A work-up with dimethyl sulfide and a subsequent treatment with acidic methanol caused the resulting intermediate to cyclize and thus, forming the tetrahydropyran ring.

In the presence of catalytic amount of TMSOTf, trimethylallylsilane attacked the oxonium ion of THP ring from the axial position due to favourable kinetic control, giving rise to a more stable chair conformation and thus resulting in the desired 2,6-*anti*-THP ring configuration. Hereafter, Keck and co-workers completed the C_{19}-C_{35} fragment by employing Evans bis-propionate and Mukaiyama aldol methodologies.

[10] Keck, G. E.; Lundquist, G. D. *J. Org. Chem.* **1999**, *64*, 4482.

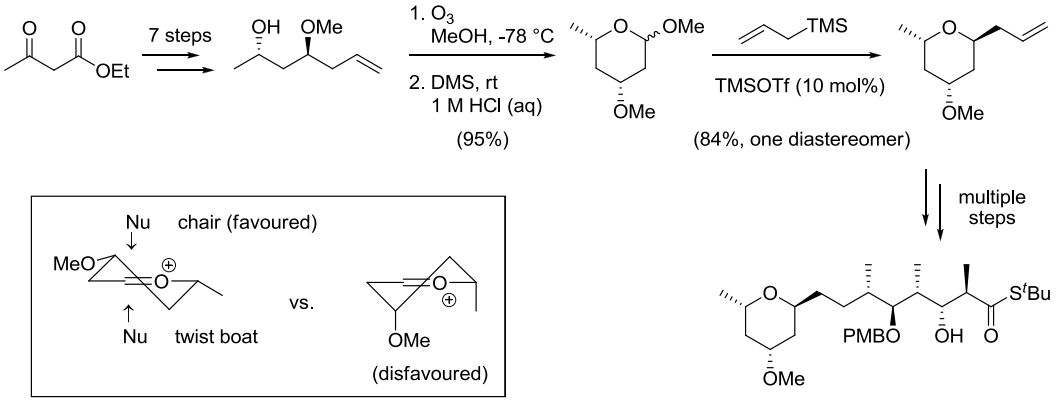


Figure 1.5 Keck's approach towards the construction of 2,6-*anti*-THP ring (C_{27}-C_{32} fragment) in Swinholide A.

1.3.1.2 Mulzer's approach[11]

Mulzer and Meyer prepared the Swinholide A's C_{26}-C_{32} tetrahydropyran motif *via* a highly stereoselective hetero-Diels-Alder reaction between the Danishefsky's diene and (1*R*,2*S*,5*R*)-menthyl glyoxylate, which was mediated by $MgBr_2$ as Lewis acid at 0 °C (**Figure 1.6**). Formation of the desired 2,6-*anti*-THP can be attributed to the chelation of Mg^{2+}-ion with neighbouring carbonyl groups of the glyoxylic ester (dienophile), that preferred the *exo*-transition state to the *endo*-counterpart as the spatial arrangement around the bromine became less cluttered.

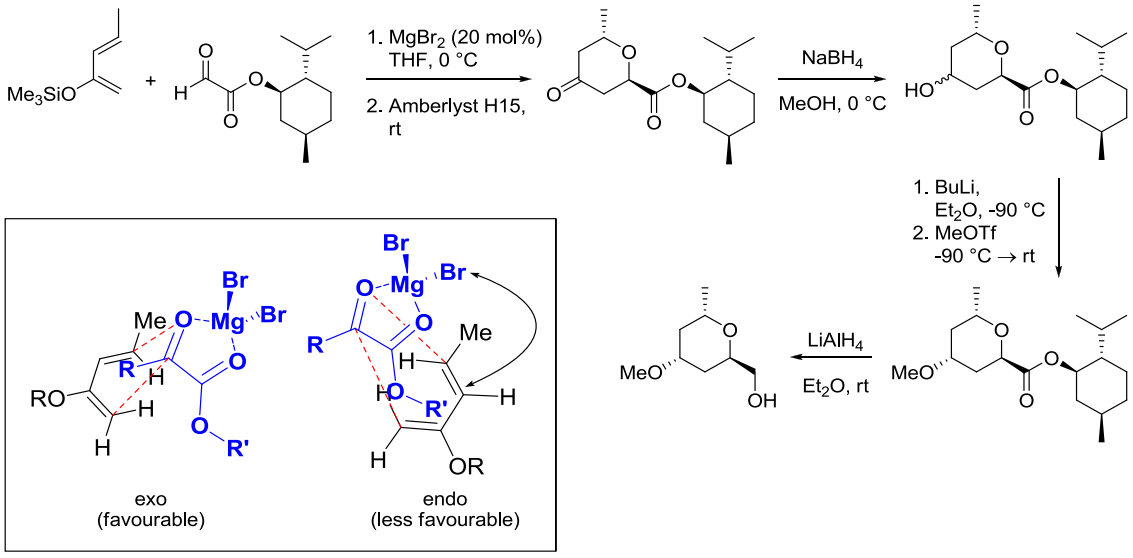


Figure 1.6 Mulzer's approach towards the construction of 2,6-*anti*-THP ring (C_{27}-C_{32} fragment) in Swinholide A.

[11] Mulzer, J.; Meyer, F.; Buschmann, J.; Luger, P. *Tetrahedron Lett.* **1995**, *36*, 3503.

1.3.1.3 Nakata's approach[12]

In the total synthesis of Preswinholide A, Nakata and co-workers transformed (*S*)-threonine into a trisubstituted THP ring that underwent a stereospecific substitution of the anomeric silyloxy group, which was effected by the treatment of allyltrimethylsilane in the presence of a Lewis acid, $BF_3 \cdot OEt_2$. The resulting allylated 2,6-*trans*-THP intermediate was then converted to a ketone *via* ozonolysis, in preparation for a Wittig reaction and subsequent transformations to complete the total synthesis of Preswinholide A (**Figure 1.7**).

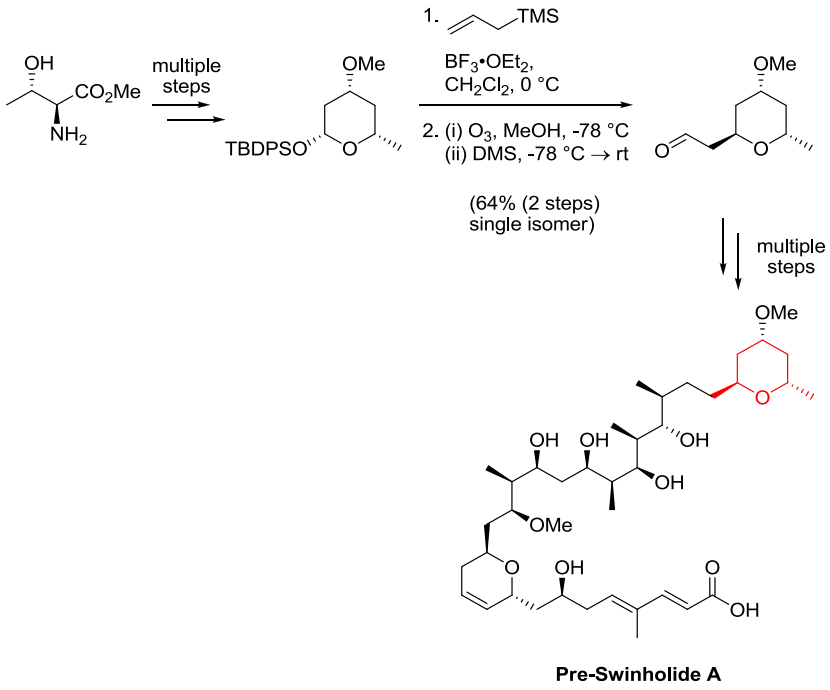


Figure 1.7 Nakata's approach towards the construction of 2,6-*anti*-THP ring (C_{27}-C_{32} fragment) in Swinholide A.

1.3.1.4 Nicolaou's approach[13]

Nicolaou and co-workers employed commercially available L-rhamnose in their total synthesis of Swinholide A (**Figure 1.8**). Fischer glycosidation of the peracetylated L-rhamnose was effected in the presence of $BF_3 \cdot OEt_2$ and TMSOTf to install an allyl moiety in a stereospecific manner. The desired trisubstituted 2,6-*anti*-THP scaffold was revealed soon after several transformations and an imminent deacetylation.

[12] (a) Nakata, T.; Komatsu, T.; Nagasawa, K. *Chem. Pharm. Bull.* **1994**, *42*, 2403. (b) Nagasawa, K.; Shimizu, I.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6885.
[13] Richter, P. K.; Tomaszewski, M. J.; Patron, A. P.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1994**, 1151.

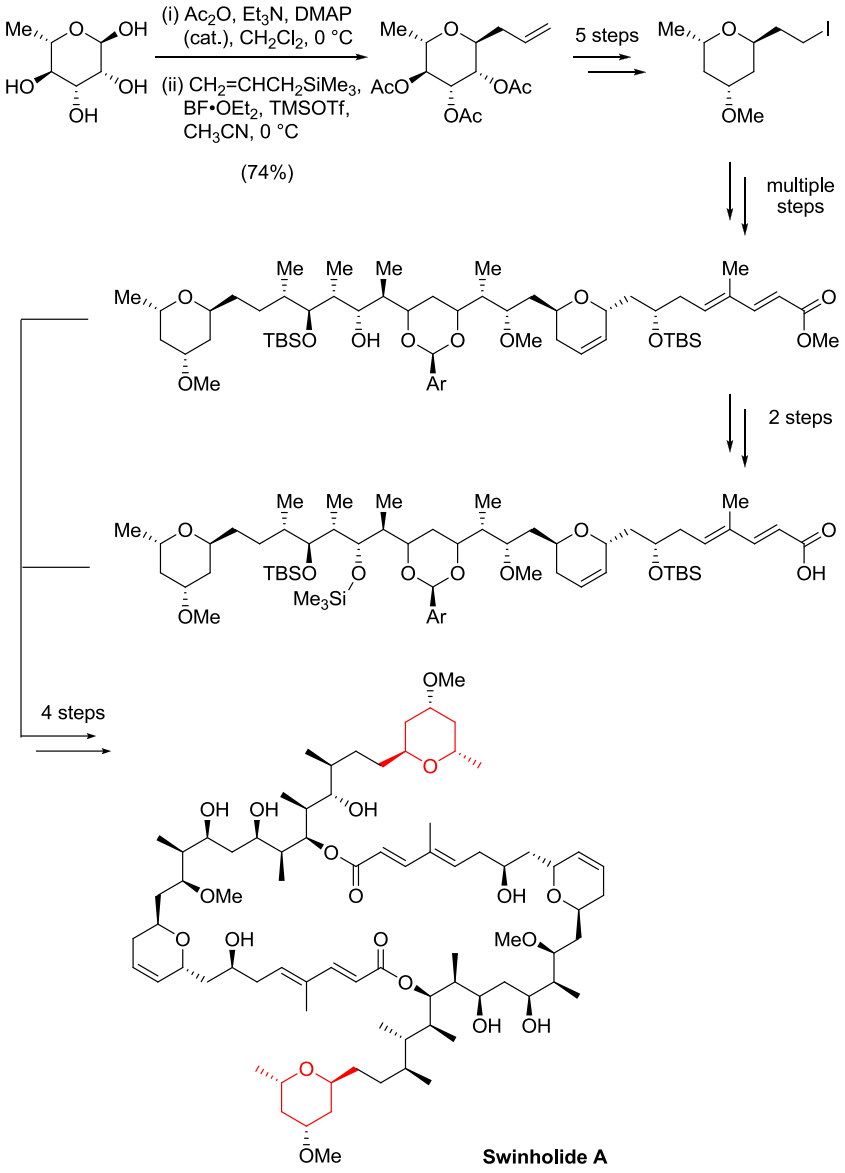


Figure 1.8 Nicolaou's approach towards the construction of 2,6-*anti*-THP ring (C_{27}-C_{32} fragment) in Swinholide A.

1.3.1.5 Paterson's approach[14]

The construction of 2,6-*anti*-THP ring in C_{27}-C_{32} fragment of Swinholide A by Paterson and co-workers first involved a coupling reaction between crotonaldehyde and allyl bromide (**Figure 1.9**). The resultant racemic (*E*)-1,5-heptadien-4-ol then underwent several more transformations and cyclized into a trisubstituted THP ring with a labile acetal group. Rationalizing that the desired 2,6-*anti* configuration can be achieved by

[14] Paterson, I.; Cumming, J. G.; Ward, R. A.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9393.

a kinetically-controlled attack on the oxonium ion intermediate from the axial position, they subjected the acetal and silyloxydiene to a series of Lewis acids and solvents screening. In their studies, TMSOTf proved to be the most efficient Lewis acid and the reaction was best carried out in acetonitrile solution at -20 °C. However, the low yield rendered silyloxydiene a less ideal candidate. Paterson and co-workers revised their synthetic route and substituted silyloxydiene with allyltrimethylsilane, which provided excellent yield, and went on accomplishing the first total synthesis of Swinholide A.

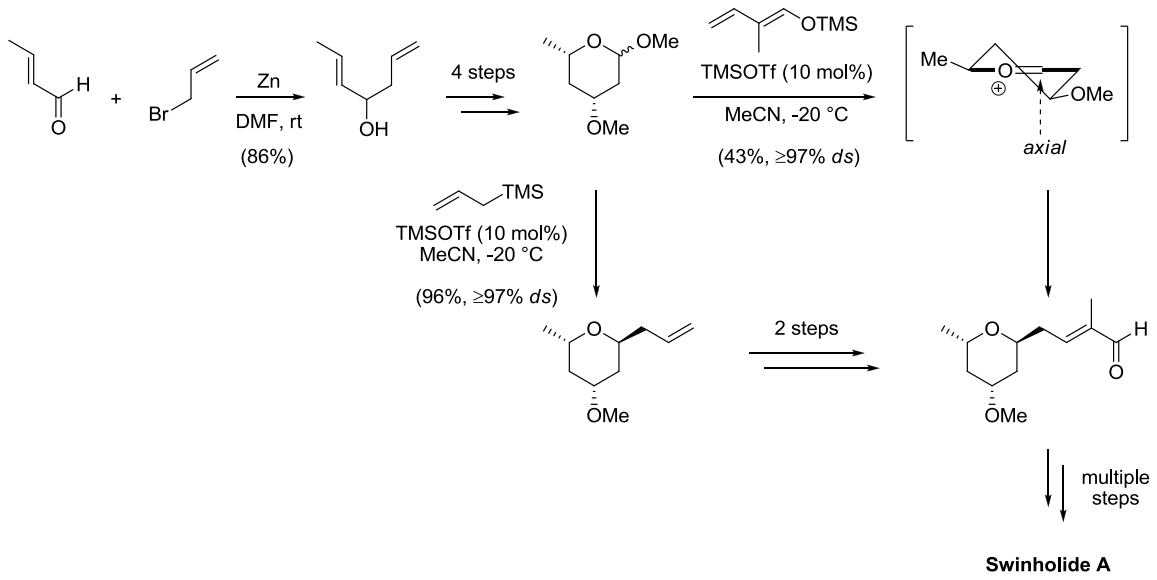


Figure 1.9 Paterson's approach towards the construction of 2,6-*anti*-THP ring (C_{27}-C_{32} fragment) in Swinholide A.

1.3.1.6 A Brief Summary of Methodologies Used To Construct 2,6-anti-tetrahydropyran ring in Swinholide A

Research group	*2,6-anti-THP conformation achieved via*
Keck and co-workers	Lewis-acid TMSOTf-mediated allylation.
Mulzer and Meyer	Lewis-acid $MgBr_2$-mediated hetero-Diels-Alder.
Nakata and co-workers	Lewis-acid $BF_3{\cdot}OEt_2$-mediated allylation.
Nicolaou and co-workers	Lewis-acid $BF_3{\cdot}OEt_2$-mediated allylation in the presence of TMSOTf.
Paterson and co-workers	Lewis-acid TMSOTf-mediated allylation.

1.3.2 Construction of 2,6-*anti*-tetrahydropyran ring in Irciniastatin A

1.3.2.1 Crimmins' approach[15]

In 2009, Crimmins and co-workers delivered (+)-Irciniastatin A in 19 steps from 2-deoxy-$_D$-ribose with an astounding overall yield of 6%. After a two-step transformation from the ribose, they started off their total synthesis with *p*-methoxybenzylidine acetal that would eventually be converted to an acetate precursor in ten steps (**Figure 1.10**). Meanwhile, Crimmins and co-workers also worked on the pentasubstituted arene precursor, in which an enol silane was attached.

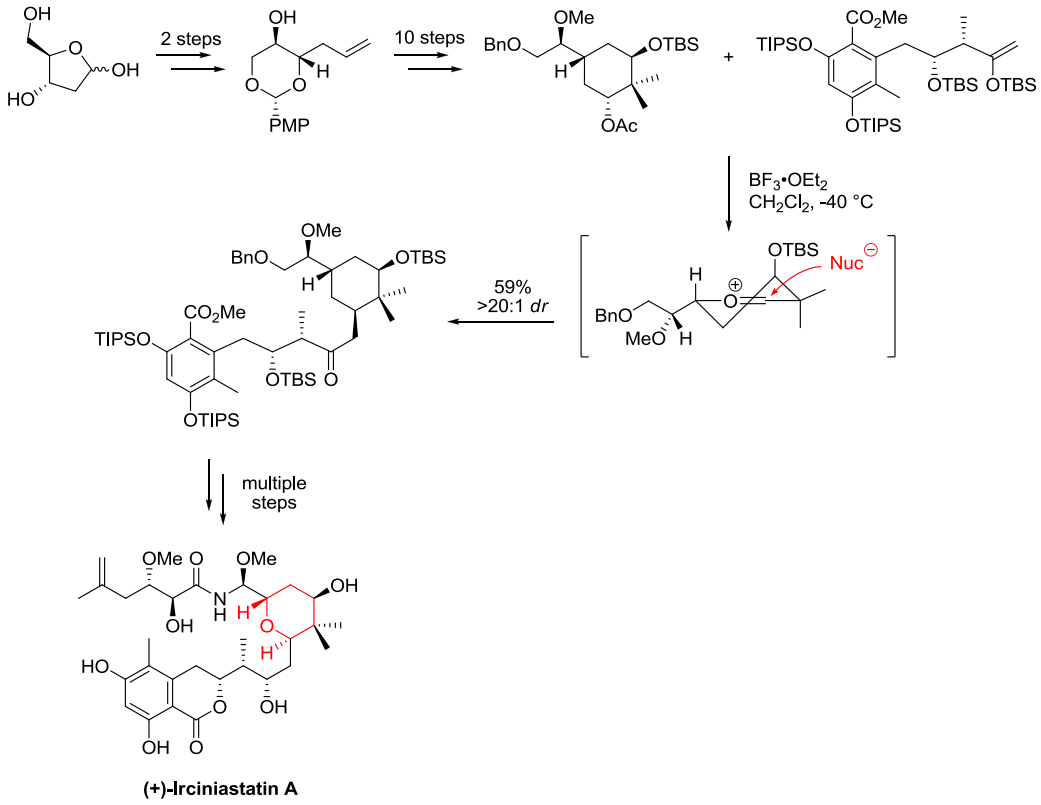


Figure 1.10 Crimmins' approach towards the construction of 2,6-*anti*-THP ring in (+)-Irciniastatin A.

The coupling of both the acetate and aryl enolsilane precursors in the presence of $BF_3{\cdot}OEt_2$ diastereoselectively installed the desired 2,6-anti-THP configuration. Such observation could be attributed to the nucleophile being added in a pseudoaxial manner to the oxocarbenium conformer, where its oxocarbenium ion was likely to be stabilized by the ether on axial position, henceforth leading to a more

[15] Crimmins, M. T.; Stevens, J. M.; Schaaf, G. M. *Org. Lett.* **2009**, *11*, 3990.

thermodynamically stable chair-like conformation.[16] The total synthesis concluded with a late-stage coupling of an advanced hemiaminal core fragment and an acid chloride prior to a universal deprotection.

1.3.2.2 De Brabander's approach[17]

The total synthesis of Irciniastatin A by De Brabander and co-workers relied on three main fragments – one from D-mannitol origin, another from readily available 2,4-dimethoxy-1-methylbenzene and an ethyl ketone formed from a bishomoallyl alcohol that ultimately can be derived from either isobutyraldehyde[18] or 2,2-dimethyl-1,3-propanediol[19] (**Figure 1.11**).

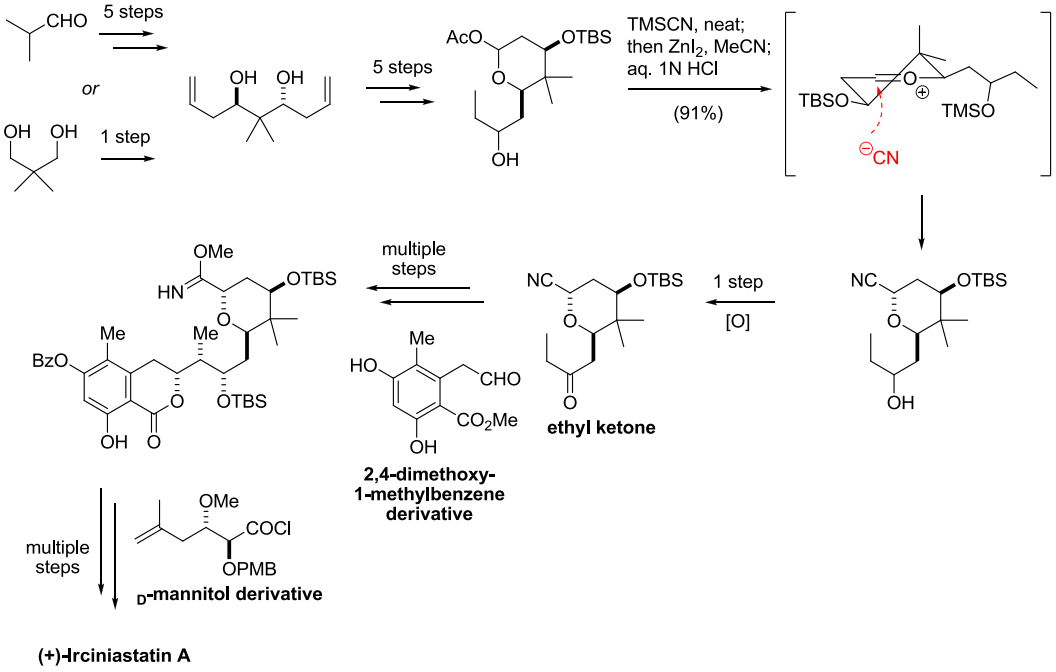


Figure 1.11 De Brabander's approach towards the construction of 2,6-*anti*-THP ring in (+)-Irciniastatin A.

[16] (a) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168. (b) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521.

[17] (a) Jiang, X.; García-Fortanet, J.; De Brabander, J. K. *J. Am. Chem. Soc.* **2005**, *127*, 1124. (b) Feng, Y.; Jiang, X.; De Brabander, J. K. *J. Am. Chem. Soc.* **2012**, *134*, 17083.

[18] (a) Johnson, P. R.; White, J. D.; *J. Org. Chem.* **1984**, *49*, 4424. (b) Kubota, K.; Leighton, J. L. *Angew. Chem. Intl. Ed.* **2003**, *42*, 946.

[19] Lu, Y.; Kim, L.-S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem. Intl. Ed.* **2009**, *48*, 5018.

The formation of 2,6-*anti*-THP ring took place in the construction of the ethyl ketone fragment. The acetal precursor was first treated with TMSCN in the absence of Lewis acid such as boron trifluoride to protect the secondary alcohol, preventing undesired formation of dioxabicyclononane and cyanohydrin side products. Thereafter, the cyanide moiety attacked from the axial position of the resulting oxonium ion, which was initiated in the presence of zinc iodide, providing the required 2,6-*anti*-THP intermediate exclusively in 91%. The ethyl ketone fragment was synthesized in relatively good overall yield of 54% over 7 steps.

1.3.2.3 Floreancig's approach[20]

Rech and Floreancig executed their total synthesis of (+)-Irciniastatin A with a pentasubstituted aryl precursor, which they synthesized in a *de novo* manner *via* [4+2]-cycloaddition of an allene dicarboxylate and a silylketene acetal, and subsequently combined it with an enolsilane to derive an advanced pentasubstituted aryl intermediate with a terminal alkene (**Figure 1.12**).

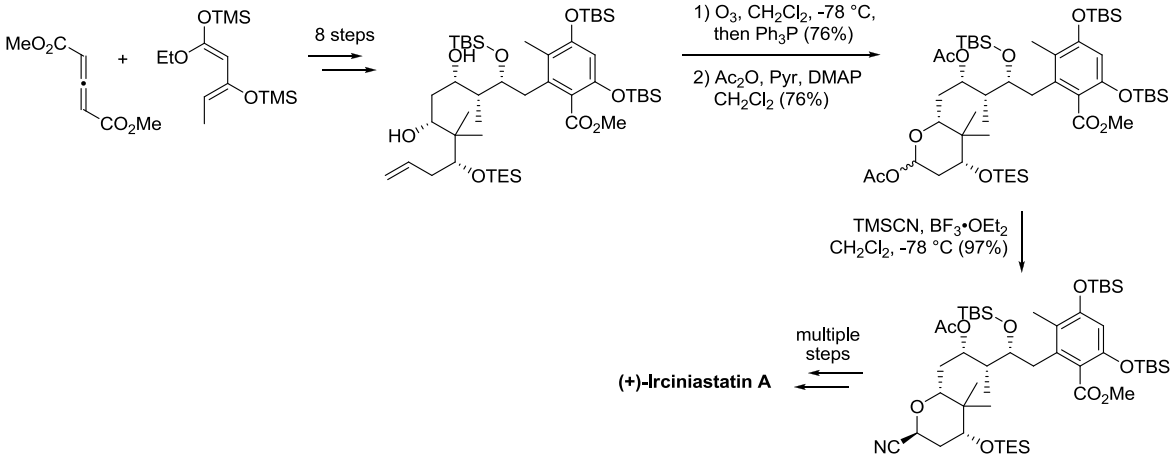


Figure 1.12 Floreancig's approach towards the construction of 2,6-*anti*-THP ring in (+)-Irciniastatin A.

The terminal alkene was then subjected to ozonolysis and acetylated upon a concomitant annulation. Thereafter, the installation of cyanide stereospecifically with TMSCN in the presence of $BF_3{\cdot}OEt_2$ as Lewis acid was carried out smoothly to obtain the desired 2,6-*anti*-THP intermediate in quantitative yield. Alternatively, TMSOTf

[20] (a) Rech, J. C.; Floreancig. P. E. *Org. Lett.* **2005**, *7*, 5175. (b) Wan, S.; Wu, F.; Rech, J. C.; Green, M. E.; Balachandran, R.; Horne, W. S.; Day, B. W.; Floreancig, P. E. *J. Am. Chem. Soc.* **2011**, *133*, 16668.

could be used in place of $BF_3 \cdot OEt_2$ as Lewis acid, allowing the reaction to be carried out at a higher temperature (-20 °C) albeit resulting in a lower yield (88%).

1.3.2.4 Hall's approach[21]

The synthetic studies towards Irciniastatin A carried out by Hall and co-workers was intended to demonstrate the applicability of their new methodologies with organoboron compounds in two non-aromatic subunits, namely the amide and pyran fragments. The amide fragment was prepared from methallyl camphordiol boronate and a protected *α*,*β*-dihydroxy aldehyde *via* their doubly diastereoselective scandium-catalyzed allylboration methodology.[22] While the addition proceeded smoothly in the amide fragment, the 3-component tandem hetero-Diels-Alder/allylboration methodology applied in the construction of the pyran core was trickier and required more cautious and delicate execution.

The polysubstituted THP ring was formed by firstly subjecting 3-boronoacrolein pinacolate and freshly distilled 1-ethoxy-2-methylpropene to a Jacobsen's chiral chromium[23]-catalyzed inverse electron demand [4+2]-cycloaddition[24] (**Figure 1.13**). Although the generation of the transition state was fast, the subsequent conversion from the transition state to the cycloadduct required prolonged reaction time. Thereafter, allylboration with ethyl glyoxylate proceeded smoothly, resulting in 91% yield with 85-90% *ee* and diastereomeric ratio of 10:1. It is noteworthy that even though it is feasible to perform this three-component reaction in one-pot, the Cr(III) catalyst from the hetero Diels-Alder reaction would interfere in the following allylboration reaction and thereby causing undesirable decomposition and lower yields. In light of this, the crude product was passed through silica pad to filter off the Cr(III) catalyst prior to allylboration.

Hall and co-workers then proceeded to functionalize the alkene of 2,6-*anti*-pyran intermediate into an epoxide fragment, which was intended to undergo further

[21] Lachance, H.; Marion, O.; Hall, D. G. *Tetrahedron Lett.* **2008**, *49*, 6061.
[22] (a) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160. (b) Gravel, M.; Lachance, H.; Lu, X.; Hall, D. G. *Synthesis* **2004**, 1290. (c) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518.
[23] (a) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2002**, *41*, 3059. (b) Chavez, D. E.; Jacobsen, E. N. *Org. Synth.* **2005**, *82*, 34.
[24] (a) Gao, X.; Hall, D.G. *J. Am. Chem. Soc.* **2003**, *125*, 9308. (b) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2005**. *127*, 1628. (c) Gao, X.; Hall, D. G.; Deligny, M.; Favre, A.; Carreaux, F.; Carboni, B. *Chem. Eur. J.* **2006**, *13*, 3132.

transformations before combining with an advanced amide fragment *via* a proposed Curtius rearrangement.

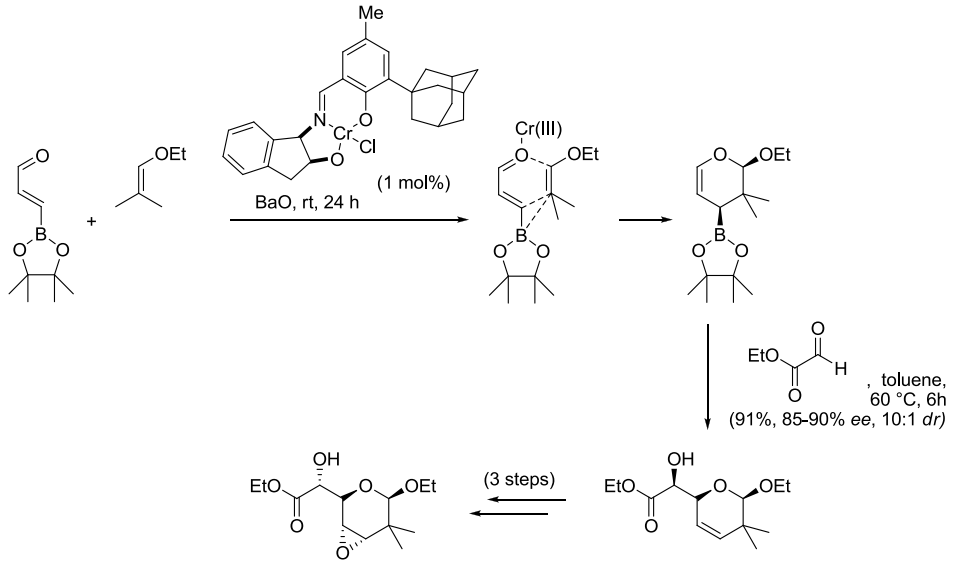


Figure 1.13 Hall's approach towards the construction of 2,6-*anti*-THP ring in (+)-Irciniastatin A.

1.3.2.5 Harrowven's approach[25]

Harrowven and co-workers observed that psymberin (Irciniastatin A), pederin and onnamides D-F shared a common but yet synthetically challenging structural feature – 2,6-*anti*-THP ring, which was constructed with different degrees of success *via* numerous methodologies. Henceforth, they became intrigued by the THP core and delineated an efficient approach to this motif through a stereoselective transformation of *γ*-lactone that was triggered by the presence of ammonia.

Harrowven and co-workers started off with (*S*)-malic acid and converted it into a furanone precursor in six steps (**Figure 1.14**). The furanone would then ring-open into a diol upon amidation when treated with aqueous ammonia in dioxane at ambient temperature. Thereafter, treatment of the diol with basic conditions preferably cyclized the intermediate into the desired 2,6-*anti*-THP, which was coincidentally the kinetic product, in 73% with an approximate diastereomeric ratio of 14:1. Harrowven and co-workers deduced that the kinetic product was favoured most likely because the strong hydrogen bonds remained intact in the corresponding transition state. On the other

[25] Buffman, W. J.; Swain, N. A.; Kostiuk, S. L.; Gonçalves, T. P.; Harrowven, D. C. *Eur. J. Org. Chem.* **2012**, 1217.

hand, the proposed chair-like transition state leading to the thermodynamic product would require breaking strong hydrogen bonds and more drastic conformational changes. Harrowven and co-workers managed to obtain the desired 2,6-*anti*-THP fragment in good diastereoselectivity, after eight steps, with an overall yield of 20%.

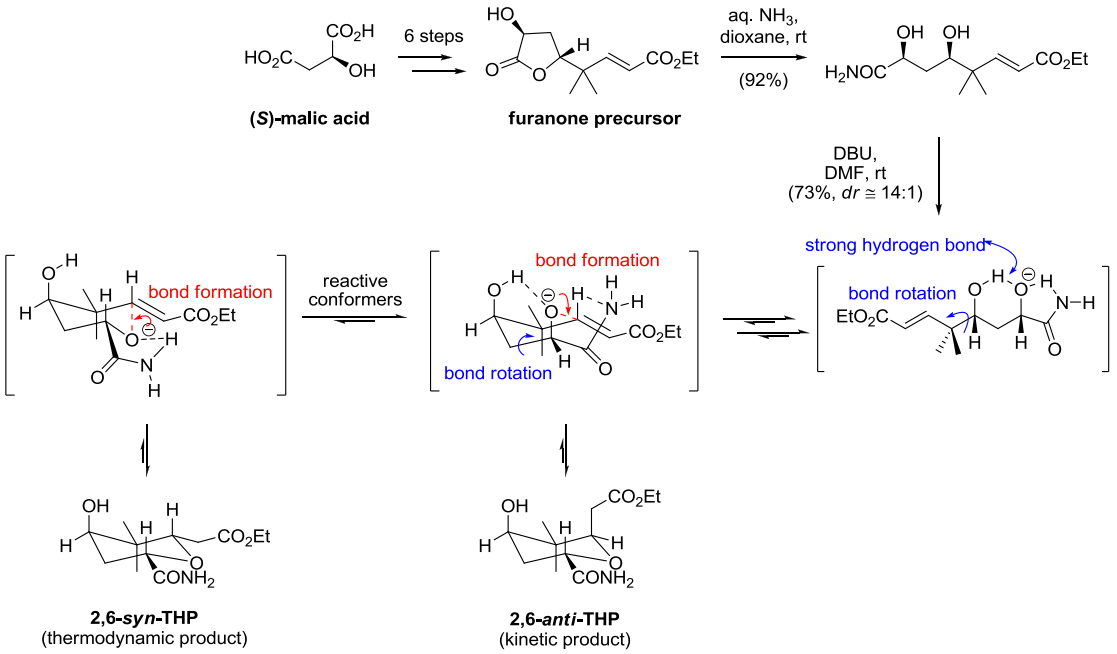


Figure 1.14 Harrowven's approach towards the construction of 2,6-*anti*-THP ring in (+)-Irciniastatin A.

1.3.2.6 Hong's approach[26]

As with De Brabander's approach, Hong and co-workers performed a retrosynthetic analysis and arrived at three similar core fragments. However, they decided that the two non-aryl main fragments – namely the 2,6-*anti*-THP and terminal olefin fragments could be generated from the same chiral epoxide that was derived in 3 steps from readily available (*S*)-(+)-glycidyl benzyl ether[27] (**Figure 1.15**).

The construction of 2,6-*anti*-THP precursor began with a coupling reaction between the aforementioned chiral epoxide and an alcohol, which was prepared in 8 steps

[26] Byeon, S. R.; Park, H.; Kim, H.; Hong, J. *Org. Lett.* **2011**, *13*, 5816.
[27] (a) Whitehead, A.; McParland, J. P.; Hanson, P. R. *Org. Lett.* **2006**, *8*, 5025. (b) Trost, B. M.; Nübling, C. *Carbohyd. Res.* **1990**, *202*, 1. (c) Rama Rao, A. V.; Subhas Bose, D.; Gurjar, M. K.; Ravindranathan, T. *Tetrahedron* **1989**, *45*, 7031. (d) Tanabe, G.; Otani, T.; Cong, W.; Minematsu, T.; Ninomiya, K.; Yoshikawa, M.; Muraoka, O. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3159.

from 2,2-dimethyl-1,3-propanediol [28], to provide a dithiane intermediate. After transforming the dithiane intermediate in another three reactions into a hydroxy ketone, the latter was then subjected to a highly stereoselective, reagent-controlled oxa-conjugate addition reaction, influenced by 9-anthracenecarboxylic acid and (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine in ethyl acetate at 0 °C. The reaction resulted in the desired 2,6-*anti*-THP fragment in 92% and an approximate diastereomeric ratio of 10:1. It is noteworthy that the stereochemical outcome relied heavily on the steric bulkiness of the acid used, which in turn affected the steric repulsions experienced in the undesirable dimeric conformer.

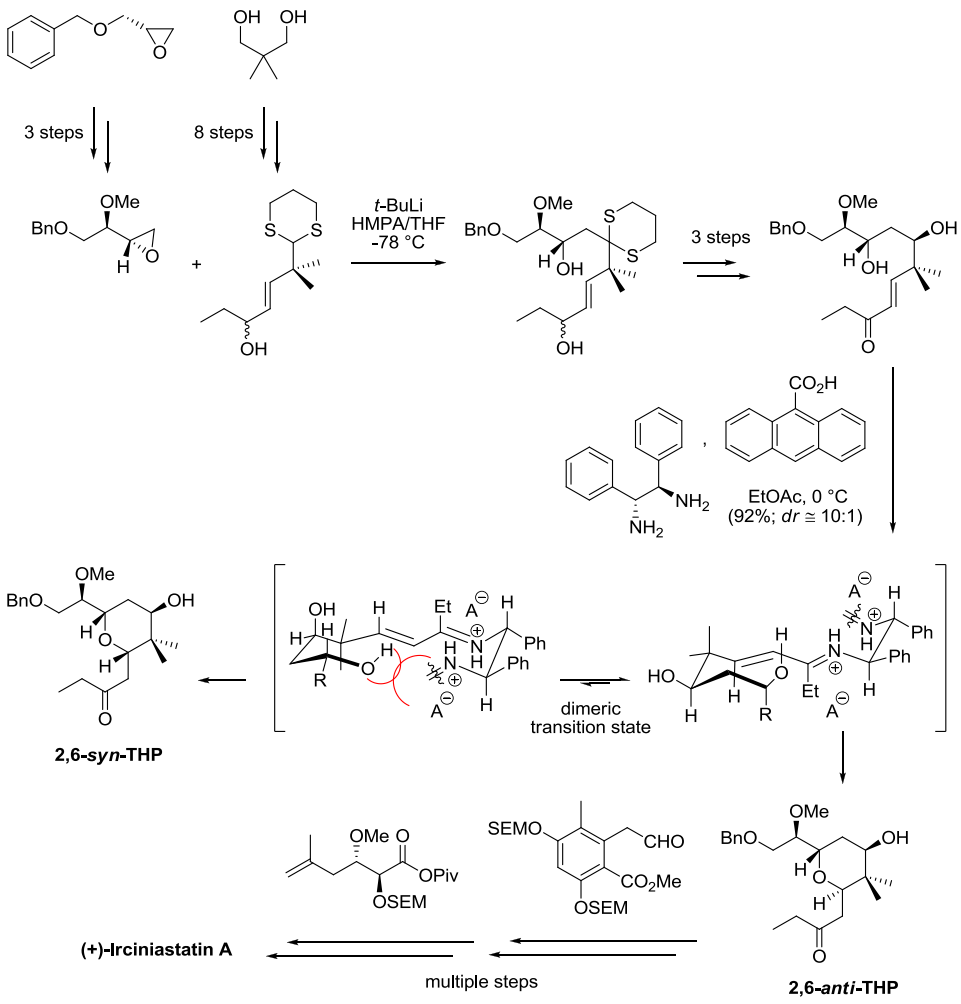


Figure 1.15 Hong's approach towards the construction of 2,6-*anti*-THP ring in (+)-Irciniastatin A.

[28] (a) Armesto, D.; Horspool, W. M.; Gallego, M. G.; Agarrabeitia, A. R.; *J. Chem. Soc., Perkin Trans. I* **1992**, 163. (b) Armesto, D.; Gallego, M. G.; Horspool, W. M.; Agarrabeitia, A. R. *Tetrahedron* **1995**, *51*, 9223.

Hong and co-workers went on and successfully completed the total synthesis of Irciniastatin A in an overall number of 24 steps from 2,2-dimethyl-1,3-propanediol.

1.3.2.7 Huang's approach[29]

In the convergent total synthesis reported by Huang and co-workers, they approached the pyran core of Irciniastatin A with their recent methodology, which presented a $PhI(OAc)_2$-mediated oxidative route to 2-(*N*-acylaminal)-substituted THP from *N*-acyl enamine.[30] The total synthesis began with 2,4,6-trimethoxytoluene to construct the dihydroisocoumarin fragment in 8 steps and was combined with a linker ketone that was synthesized from an aldehyde *via* a 4-step transformation (**Figure 1.16**). The amine subunit, which was constructed from an epoxide after 9 conversions, was attached to the advanced intermediate prior to the requisite annulation.

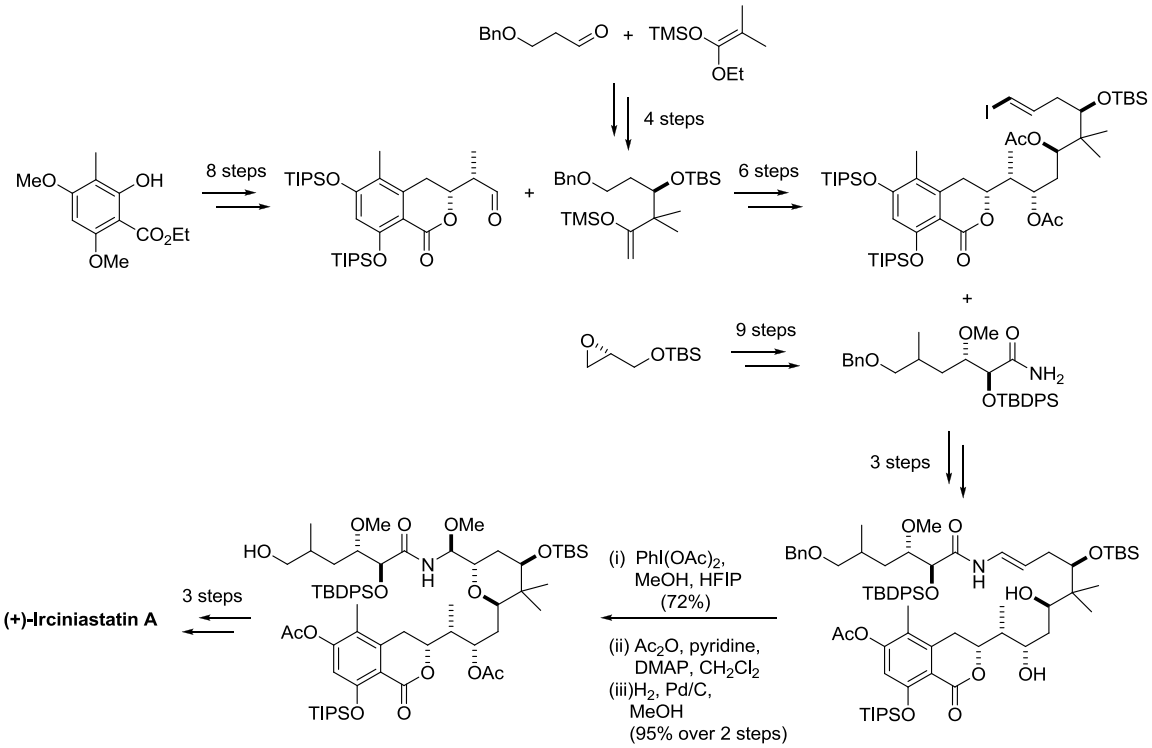


Figure 1.16 Huang's approach towards the construction of 2,6-*anti*-THP ring in (+)-Irciniastatin A.

The $PhI(OAc)_2$-assisted cyclization proceeded to give a mixture of two major diastereomers and other possible isomers in a total yield of 72%, that could be separated upon acetylation and debenzylation. While the possibility of a S_N2' type of

[29] Huang, X.; Shao, N.; Palani, A.; Aslanian, R.; Buevich, A. *Org. Lett.* **2007**, *9*, 2597.
[30] Huang, X.; Shao, N.; Palani, A.; Aslanian, R. *Tetrahedron Lett.* **2007**, *48*, 1967.

mechanism could not be refuted, the variety of products formed could be attributed to and also thereby supporting the radical cationic pathway that was proposed in their previous report (**Figure 1.17**). Finally, Huang and co-workers achieved (+)-Irciniastatin A after 24 steps from commercially available 2,4,6-trimethoxytoluene.

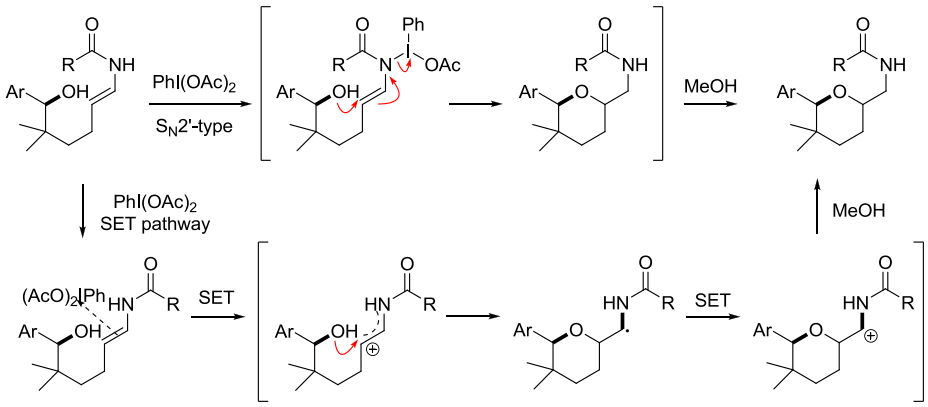


Figure 1.17 Huang's proposed mechanistic pathways for $PhI(OAc)_2$-mediated oxidative route to 2-(*N*-acylaminal)-substituted THP from *N*-acyl enamine.

1.3.2.8 Iwabuchi's approach[31]

In the letter of Iwabuchi and co-workers, they described the syntheses of both (+) and (-) enantiomers of Irciniastatin A and (+)-alkymberin, in which an alkyne was in place of the (+)-Irciniastatin A's terminal olefin. They hypothesized that the two non-aromatic synthons could be derived from two different epoxy alcohol precursors acquired by employing Sharpless asymmetric epoxidation (SAE).

The 2,6-*anti*-THP fragment originated from commercially available (-)-pantolactone that was converted into a preliminary epoxy alcohol[32], which in turn underwent another nine transformations, including the key reaction – Sharpless asymmetric epoxidation, to result in an advanced epoxy alcohol precursor (**Figure 1.18**). The latter then had its primary alcohol protected prior to the treatment of CSA. The acid then ring-opened the epoxide while deprotecting both TES moieties and effected the annulation, yielding the desired 2,6-*anti*-THP intermediate in 83%. This pyran intermediate was subjected to eight more conversions to arrive at the desired 2,6-

[31] Watanabe, T.; Imaizumi, T.; Chinen, T.; Nagumo, Y.; Shibuya, M.; Usui, T.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2010**, *12*, 1040.
[32] Lavallée, P.; Ruel, R.; Grenier, L.; Bissonnette, M. *Tetrahedron Lett.* **1986**, *27*, 679.

anti-THP fragment, awaiting to be combined with two other fragments in the next nine steps to achieve (+)-Irciniastatin A.

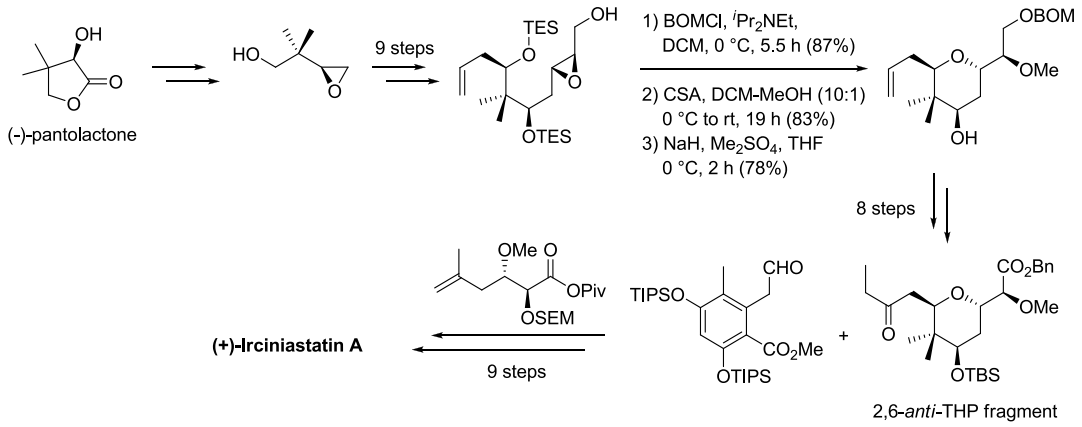


Figure 1.18 Iwabuchi's approach towards the construction of 2,6-*anti*-THP ring in (+)-Irciniastatin A.

1.3.2.9 Konopelski's approach[33]

Konopelski and co-workers described the construction of three main fragments, which were similar to those featured in De Brabander's approach, in their reported synthetic efforts towards the total synthesis of Irciniastatin A. For the assembly of 2,6-*anti*-THP fragment, they followed closely to pyran formation procedure found in Kocienski's synthesis of mycalamides, pederin and theopederin[34] (**Figure 1.19**). Some of the highlights in the construction of 2,6-*anti*-THP fragment include an asymmetric aldol reaction mediated by valine and a Dieckmann condensation. The stereochemistry of 2,6-*anti*-THP was installed *via* 1,4-conjugate addition with vinylMgBr in the presence of CuI, providing the corresponding pyranone in 93%. The resulting pyranone was asymmetrically reduced and protected. The 2,6-*anti*-THP core fragment was furnished as a dimethoxy acetal, masking the unstable aldehyde, upon oxidative cleavage of the terminal olefin.

[33] Brown, L. E.; Landaverry, Y. R.; Davies, J. R.; Milinkevich, K. A.; Ast, S.; Carlson, J. S.; Oliver, A. G.; Konopelski, J. P. *J. Org. Chem.* **2009**, *74*, 5405.

[34] (a) Kocienski, P. J.; Narquizian, R.; Raubo, P.; Smith, C.; Boyle, F. T. *Synlett* **1998**, 1432. (b) Kocienski, P.; Narquizian, R.; Raubo, P.; Smith, C.; Farrugia, L. J.; Muir, K.; Boyle, F. T. *J. Chem. Soc., Perkin Trans. I* **2000**, 2357.

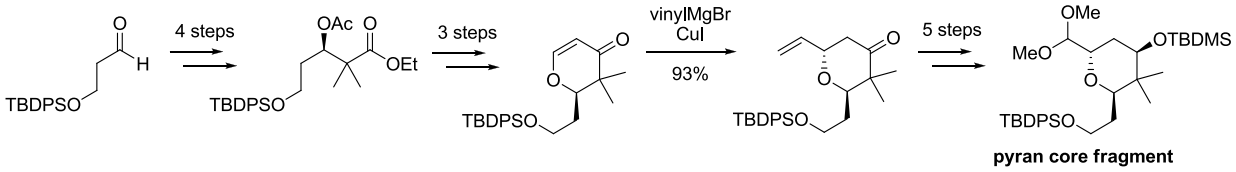


Figure 1.19 Konopelski's approach towards the construction of 2,6-*anti*-THP ring in (+)-Irciniastatin A.

1.3.2.10 Smith III's approach[35]

The construction of 2,6-*anti*-THP fragment in the total synthesis of (+)-Irciniastatin A reported by Smith III in 2008 was built upon 2,2-dimethyl-1,3-propanediol. From the commercially available diol, an epoxide precursor was synthesized through 11 transformations, which was subsequently subjected to a diastereoselective CSA-assisted epoxide ring-opening and a concomitant annulation *via* 6-*exo*-*tet* pathway, to give rise to the desired 2,6-*anti*-THP fragment as the major product in 74% (**Figure 1.20**). Generation of 2,6-*syn*-THP intermediate as side product in 14% could be due to the annulation of unfavourable *α*-hydroxyl epimer during an earlier Paterson aldol reaction. Fortunately, this mixture of products was separable *via* flash column chromatography. The core 2,6-*anti*-THP fragment was then combined with the pentasubstituted arene and acid fragments sequentially, furnishing (+)-Irciniastatin A in 21 steps from 2,2-dimethyl-1,3-propanediol.

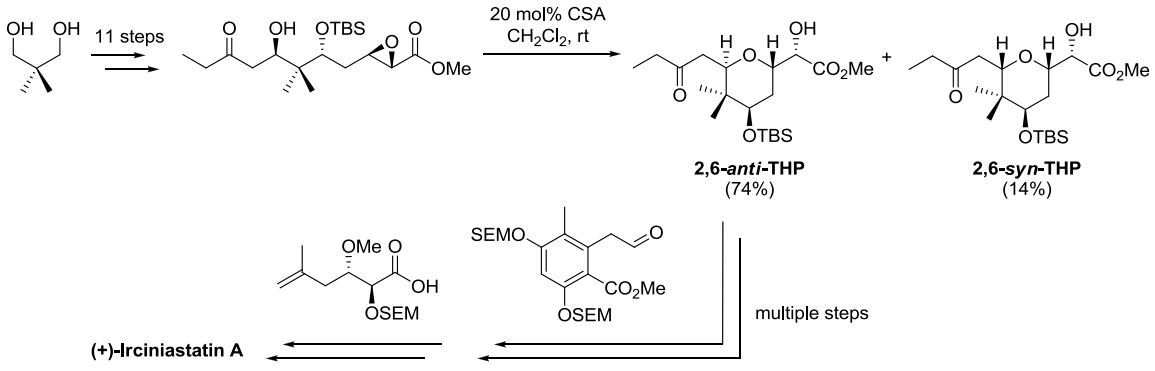


Figure 1.20 Smith III's approach towards the construction of 2,6-*anti*-THP ring in (+)-Irciniastatin A.

[35] Smith III, A. B.; Jurica, J. A.; Walsh, S. P. *Org. Lett.* **2008**, *10*, 5625.

1.3.2.11 Williams' approach[36]

The formal synthesis of (+)-irciniastatin A reported by Williams and co-workers was less conventional compared to its earlier precedents. They prepared the pentasubstituted aryl fragment from aromatization of dimedone *via* an acid-induced rearrangement[37] and a subsequent formylation in the presence of zinc cyanide, $Zn(CN)_2$[38] (**Figure 1.21**).

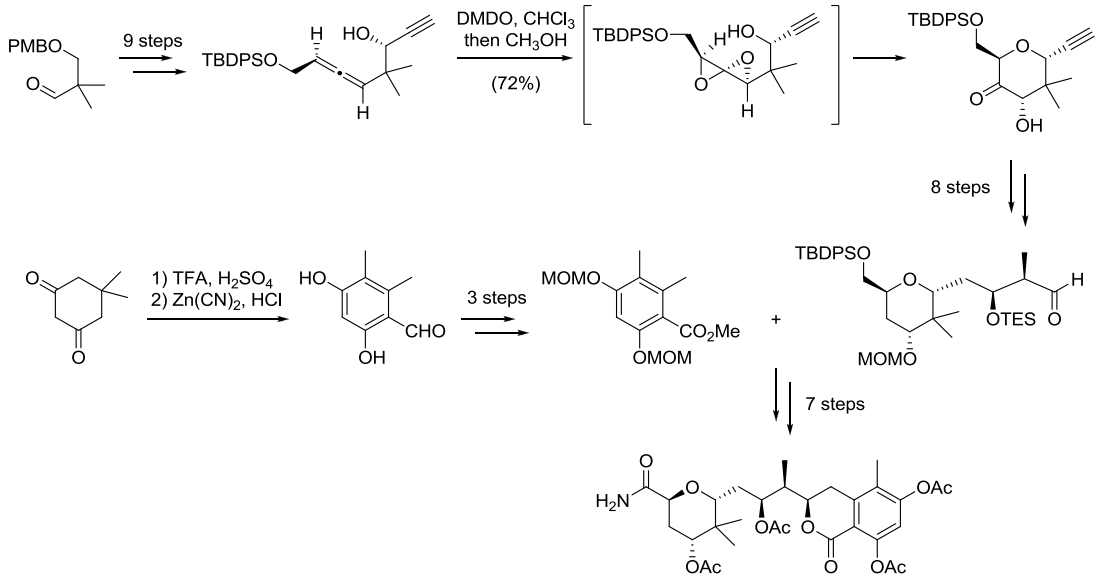


Figure 1.21 Williams' approach towards the construction of 2,6-*anti*-THP ring in (+)-Irciniastatin A.

The desired 2,6-*anti*-THP fragment was constructed from an aldehyde-turned-allene. The allene was preferably oxidized into a stable spirodiepoxide intermediate upon treatment with dimethyl dioxirane (DMDO). Presence of the protected alcohol both stabilized the proximal allenic olefin bond and induced regioselectivity in the oxidation of distal olefinic bond. The subsequent oxidation then took place on the side facing away from the sterically bulky *tert*-butyl-like appendage. Methanol was added as a co-solvent upon complete oxidation of allene to spirodiepoxide, slowly cyclizing the latter intermediate into 2,6-*anti*-THP intermediate. Williams and co-workers concluded their formal synthesis with a truncated core fragment of (+)-Irciniastatin A, a consequent of 7 further manipulations after a more elaborate 2,6-*anti*-THP fragment was combined with the aforementioned pentasubstituted arene.

[36] Ning, S.; Kiren, S.; Williams, L. J. *Org. Lett.* **2007**, *9*, 1093.
[37] Nelson, P. H.; Nelson, J. P. *Synthesis* **1992**, 1287.
[38] Robertson, A.; Whalley, W. B. *J. Chem. Soc.* **1949**, 3033.

1.3.2.12 A Brief Summary of Methodologies Used To Construct 2,6-anti-tetrahydropyran ring in (+)-Irciniastatin A

Research group	*2,6-anti-THP conformation achieved via*
Crimmins and co-workers	Diastereoselective addition of aryl enolsilane to acetate in the presence of $BF_3 \cdot OEt_2$.
De Brabander and co-workers	Axial cyanide attack in the presence of ZnI_2.
Floreancig and co-workers	Lewis-acid $BF_3 \cdot OEt_2$-mediated TMSCN attack.
Hall and co-workers	3-component tandem hetero-Diels-Alder/allylboration.
Harrowven and co-workers	Ammonia-triggered stereocontrolled transformation of γ-lactone.
Hong and co-workers	Stereoselective oxa-conjugate addition reaction of *α,β*-unsaturated ketone in the presence of primary amine and bulky acid.
Huang and co-workers	$PhI(OAc)_2$-mediated oxidative annulation from *N*-acyl enamine.
Iwabuchi and co-workers	CSA-mediated simultaneous epoxide ring-opening and annulation.
Konopelski and co-workers	CuI-mediated 1,4-conjugate addition with vinylMgBr
Smith III and co-workers	Diastereoselective CSA-assisted epoxide ring-opening and a concomitant annulation *via* 6-*exo-tet* pathway.
Williams and co-workers	Oxidation of spirodiepoxide with dimethyl dioxirane (DMDO).

1.3.3 Construction of 2,6-*anti*-tetrahydropyran ring in (-)-Aspergillide B

1.3.3.1 Fuwa's approach[39]

The saying, "Killing two birds with one stone," cannot be more apt to describe the total syntheses of Aspergillides A and B reported by Fuwa and co-workers. Their retrosynthetic analysis led them to a common intermediate, which would result in either 2,6-*syn*-THP or 2,6-*anti*-THP rings by tweaking the reaction conditions of the annulation. An asymmetric allylation with commercially available (*E*)-cinnamaldehyde provided the starting material homoallylic alcohol that would undergo another 10 transformations to obtain the aforementioned common intermediate (**Figure 1.22**).

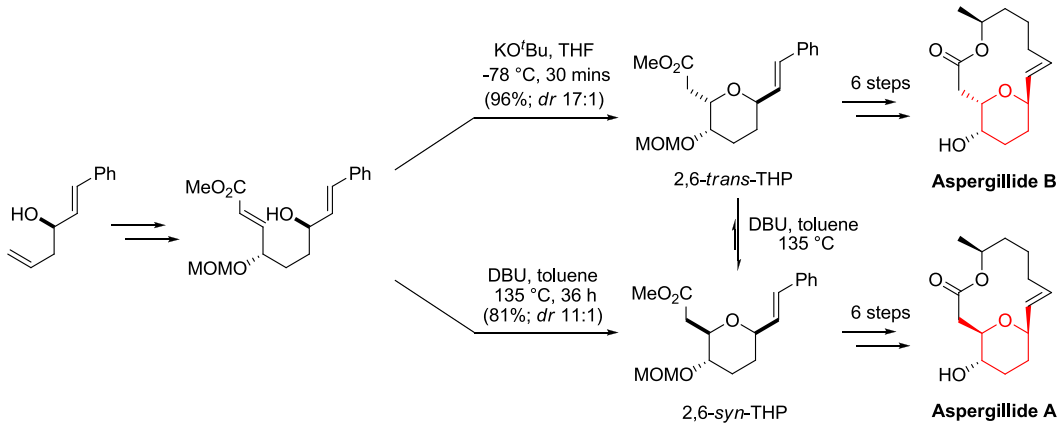


Figure 1.22 Fuwa's approach towards the construction of 2,6-*anti*-THP ring in (-)-Aspergillide B.

Fuwa and co-workers employed KO^{t}Bu at -78 °C in THF for 30 minutes to afford 2,6-*anti*-THP intermediate in 96% (*dr* 17:1). In contrary, the 2,6-*syn*-THP counterpart could only be accessed with harsher conditions by employing DBU at 135 °C in toluene for 36 hours, yielding 81% (*dr* 11:1). The two THP fragments each underwent another six reactions to respectively yield Aspergillides A (*via* 2,6-*syn*-THP) and B (*via* 2,6-*anti*-THP). It is interesting that 2,6-*anti*-THP intermediate could be converted to the more thermodynamically stable 2,6-*syn*-THP counterpart under the DBU conditions.

[39] (a) Fuwa, H.; Yamaguchi, H.; Sasaki, M. *Org. Lett.* **2010**, *12*, 1848. (b) Fuwa, H.; Yamaguchi, H.; Sasaki, M. *Tetrahedron* **2010**, *66*, 7492.

1.3.3.2 Kuwahara's approach[40]

As a spin-off from the total synthesis of Aspergillide C that they reported earlier in the same year[41], Nagasawa and Kuwahara succeeded in their endeavour to synthesize (-)-Aspergillide B in 7 more steps from a common intermediate. The aforementioned common intermediate was derived from an epoxide, which was initially subjected to an addition of a lithium acetylide in the presence of $BF_3{\cdot}OEt_2$, forming an acetylenic alcohol (**Figure 1.23**). After the hydrogenation of the acetylene with Lindlar's catalyst was completed, the resulting intermediate was cyclized into a dihydropyran by the treatment of CSA. The 2,6-*anti*-THP configuration was installed *via* a $BF_3{\cdot}OEt_2$-mediated Ferrier-type reaction involving a silyl ketene acetal, attaining 65% in yield, alongside with 2,6-*syn*-THP isomer in 25%.

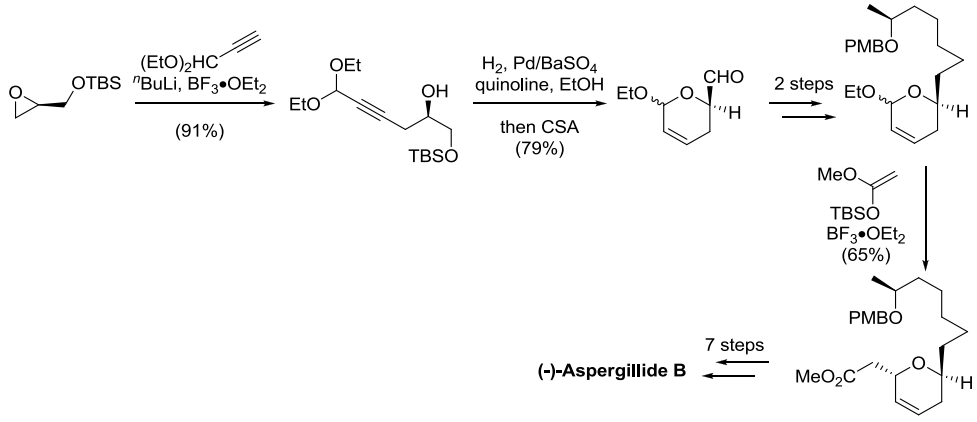


Figure 1.23 Kuwahara's approach towards the construction of 2,6-*anti*-THP ring in (-)-Aspergillide B.

1.3.3.3 Marco's approach[42]

Marco and co-workers first reported their total synthesis of (-)-Aspergillide B in 2009 and later in 2011, as a full article alongside with the total synthesis of Aspergillide A. They started off with an alcohol that subsequently had its carbon chain extended and transformed into a lactone upon selective oxidation of primary alcohol with treatment of $PhI(OAc)_2$/TEMPO [43] (**Figure 1.24**). The resultant lactone was reduced and

[40] Nagasawa, T.; Kuwahara, S. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 1893.
[41] Nagasawa, T.; Kuwahara, S. *Org. Lett.* **2009**, *11*, 761.
[42] (a) Díaz-Oltra, Angulo-Pachón, C. A.; Kneeteman, M. N.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2009**, *50*, 3783. (b) Díaz-Oltra, Angulo-Pachón, C. A.; Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Chem. Eur. J.* **2011**, *17*, 675.
[43] (a) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974. (b) Larrosa, I.; Da Silva, M. I.; Gómez, P. M.; Hannen, P.; Ko, E.; Lenger, S. R.;

acetylated prior to addition of silyl enol ether in the presence of $BF_3{\cdot}OEt_2$ and TMSOTf. The addition provided the desired 2,6-*anti*-THP intermediate in 55% yield, unfortunately together with its 2,6-*syn*-THP counterpart in substantial amounts (21%). After successful separation of the two isomers *via* column chromatography, 2,6-*anti*-THP intermediate was converted to (-)-Aspergillide B in 4 steps.

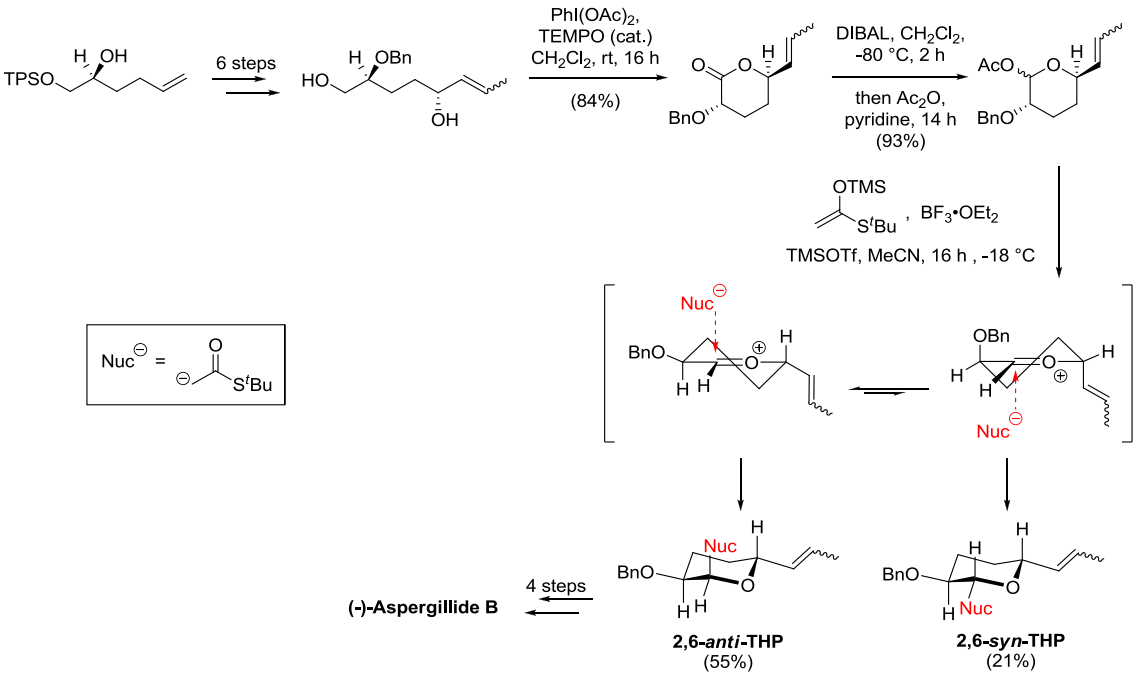


Figure 1.24 Marco's approach towards the construction of 2,6-*anti*-THP ring in (-)-Aspergillide B.

1.3.3.4 Sharma's approach[44]

From L-ascorbic acid, Sharma and Manohar generated an epoxide[45] as the starting material for their formal synthesis of (-)-Aspergillide B. The epoxide was transformed into an allylic alcohol in 11 steps. Treatment of the free secondary alcohol with (+)-DIPT and $Ti(O^iPr)_4$ in the presence of cumene hydroperoxide (CHP) garnered the desired 2,6-*anti*-THP configuration *via* a tandem Sharpless asymmetric epoxidation/6-*exo* annulation sequence, in 85% yield (**Figure 1.25**). Sharma and Manohar believed that the readily available free secondary alcohol as nucleophile played an important role in manoeuvring the reaction to favour the kinetically-controlled 6-*exo* annulation.

Linke, S. R.; White, A. J. P.; Wilton, D.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2006**, *128*, 14042.

[44] Sharma, G. V. M.; Manohar, V. *Tetrahedron: Asymmetry* **2012**, *23*, 252.

[45] Abushnab, E.; Venishetti, P.; Leiby, R. W.; Singh, H. K.; Mikkilineni, A. B.; Wu, D. C. J.; Saibaba, R.; Panzica, P. *J. Org. Chem.* **1988**, *53*, 2598.

It is noteworthy that 5-*exo* cyclization was initially preferred when the PMB-protected secondary alcohol was used in place of the free secondary alcohol. The PMB-protected secondary alcohol was postulated to be a less accessible nucleophile, thereby favouring the thermodynamically stable 5-*exo* cyclization as governed by Baldwin rules[46]. The 2,6-*anti*-THP intermediate was further transformed into a macrolactone intermediate that could be converted to (-)-Aspergillide B according to Marco's protocol[42].

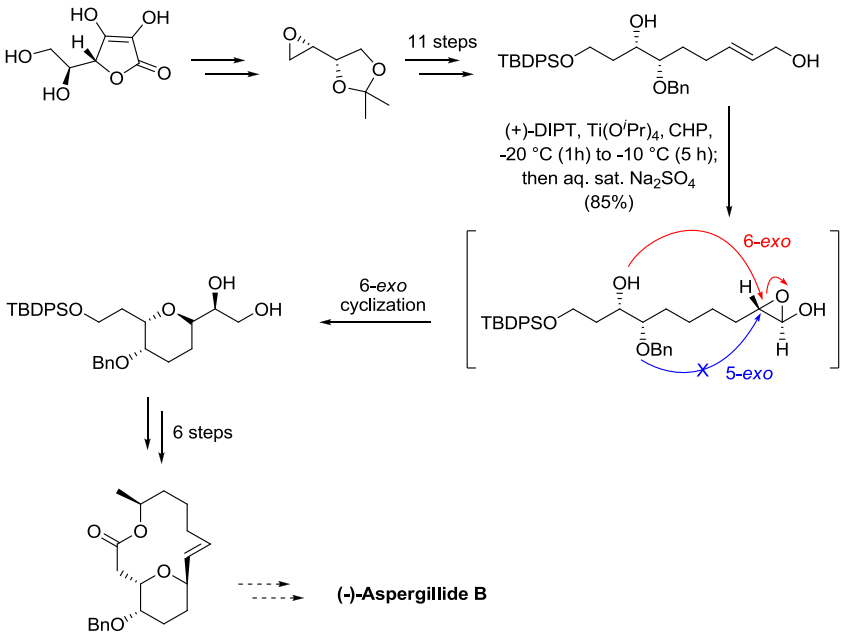


Figure 1.25 Sharma's approach towards the construction of 2,6-*anti*-THP ring in (-)-Aspergillide B.

1.3.3.5 Shishido's approach[47]

In their total synthesis of (-)-Aspergillide B, Shishido and co-workers unconventionally constructed the 14-membered ring macrolactone framework prior to the formation of requisite 2,6-*anti*-THP ring. They began their synthetic approach with an enantiopure enone with a bicyclo[3.2.1]octane structure that was prepared in 6 steps from naturally abundant 2-furfural. The enone was subjected to another 15 conversions, including a Horner-Wadsworth-Emmons reaction to furnish a macrocyclic enone precursor. Transannular oxy-Michael reaction was performed on the macrocyclic

[46] (a) Baldwin, J. E. *J. Chem. Soc. Chem. Comm.* **1976**, 734. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Cruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc. Chem. Comm.* **1976**, 736. (c) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1997**, *42*, 3846.
[47] Kanematsu, M.; Yoshida, M.; Shishido, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 2618.

enone precursor with the treatment of KH and [18]-crown-6 in THF, yielding 96% of 2,6-*anti*-THP intermediate (**Figure 1.26**). It is refreshing that the authors postulated that 2,6-*anti*-THP adduct is the thermodynamic product. This hypothesis was verified when 2,6-*anti*-THP adduct was obtained quantitatively upon subjecting 2,6-*syn*-adduct to the same reaction conditions. The 17-step approach ended with a deprotection in acidic conditions, furnishing the natural product (-)-Aspergillide B in an overall yield of 28%.

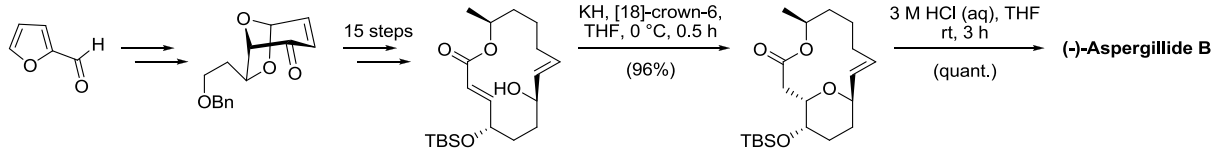


Figure 1.26 Shishido's approach towards the construction of 2,6-*anti*-THP ring in (-)-Aspergillide B.

1.3.3.6 Trost's approach[48]

In their endeavor to design their synthetic approach towards the formal synthesis of (-)-Aspergillide B, Trost and Bartlett intended to apply their zinc-catalyzed asymmetric alkynylation[49] as well as ruthenium-catalyzed *trans*-hydrosilylation-protodesilylation[50] methodologies. Trost and Bartlett first built on pent-1-yne to form the entire carbon backbone of the molecule in ten steps, featuring the zinc-catalyzed asymmetric alkynylation twice, which employed chiral ProPhenol and dimethylzinc under modified conditions (**Figure 1.27**). The consequent elaborate alkyne intermediate was then chemoselectively reduced to (*E*)-alkene *via* hydrosilylation with triethoxysilane ($(EtO)_3SiH$) in the presence of catalytic amount of $Cp^*Ru(CH_3CN)_3PF_6$. The basic reaction conditions promoted a simultaneous intramolecular oxy-Michael addition, thereby delightfully resulting in 2,6-*anti*-THP intermediate in 77% based on recovered starting material (2 steps) upon cuprous iodide-mediated protodesilylation conditions. The 2,6-*anti*-THP intermediate could subsequently undergo another 3 steps in accordance to Fuwa's synthetic approach to achieve (-)-Aspergillide B.

[48] Trost, B. M.; Bartlett, M. J. *Org. Lett.* **2012**, *14*, 1322.
[49] Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963.
[50] (a) Trost, B. M.; Ball, Z. T.; Jöge, T. *Angew. Chem. Int. Ed.* **2003**, *115*, 3537. (b) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644.

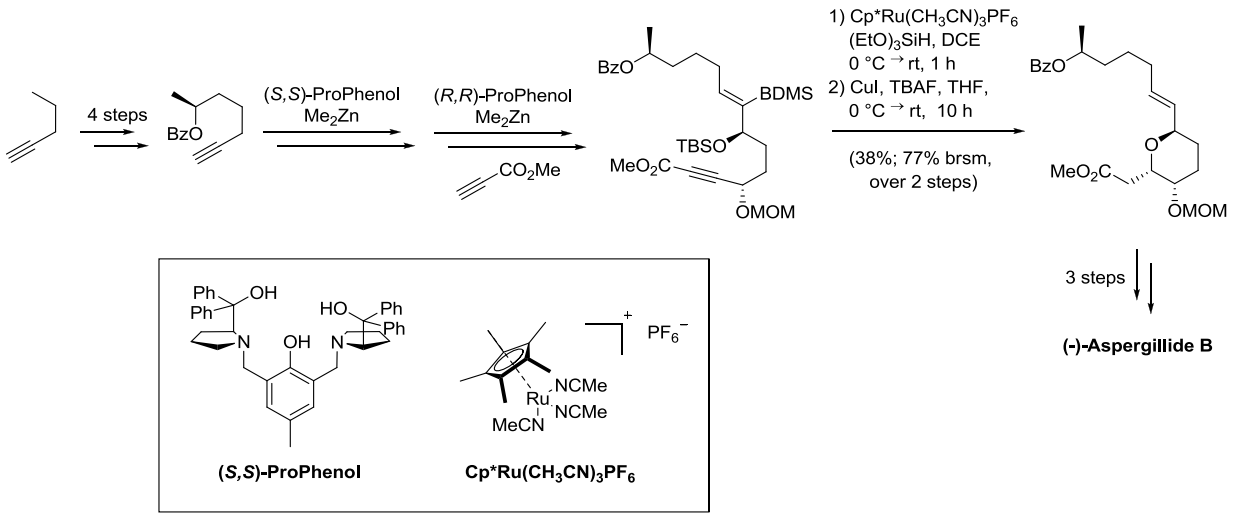


Figure 1.27 Trost's approach towards the construction of 2,6-*anti*-THP ring in (-)-Aspergillide B.

1.3.3.7 Uenishi's approach[51]

Uenishi and Hande undertook the synthesis of (-)-Aspergillide B to demonstrate the utility of their Pd(II)-catalyzed methodology to construct tetrahydropyrans stereospecifically.[52] Derived from tetrafurfuryl alcohol in three steps, methyl (*E*)-7-hydroxyhept-3-enoate became the cornerstone of the total synthesis and underwent seven more transformations to unveil the required precursor. When the precursor was subjected to the key Pd(II)-catalyzed annulation reaction conditions, the desired 2,6-*anti*-THP intermediate was yielded in 76%, along with 3% of 2,6-*syn*-THP counterpart (**Figure 1.28**).

It was previously proposed that the Pd(II) catalyst would selectively coordinate on the olefin in *syn* fashion with reference to chiral allylic alcohol and subsequently undergo *syn* oxypalladation.[53] PdCl(OH) was eliminated thereafter, in a *syn* manner, affording 2,6-*anti*-THP adduct with an *E*-conformation alkene appendage as a major product. Meanwhile, the minor 2,6-*syn*-THP product could be attributed to an *anti* oxypalladation, resulting in a *syn-anti* intermediate that has a *syn* relation between hydroxy and σ-Pd bonds but an *anti*-configuration between the ring and σ-Pd bonds. From the resultant 2,6-*anti*-THP intermediate, Uenishi and Hande performed 7 more

[51] Hande, S. M.; Uenishi, J. *Tetrahedron Lett.* **2009**, *50*, 189.
[52] (a) Uenishi, J.; Ohmi, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 2756. (b) Kawai, N.; Hande, S. M.; Uenishi, J. *Tetrahedron* **2007**, *63*, 9049.
[53] Uenishi, J.; Vikhe, Y. S.; Kawai, N. *Chem. Asian J.* **2008**, *3*, 473.

steps to attain a structure that is now ascertained as (-)-Aspergillide B, thereby proving the inaccuracy of Kusumi's proposed structure of Aspergillide A earlier on.

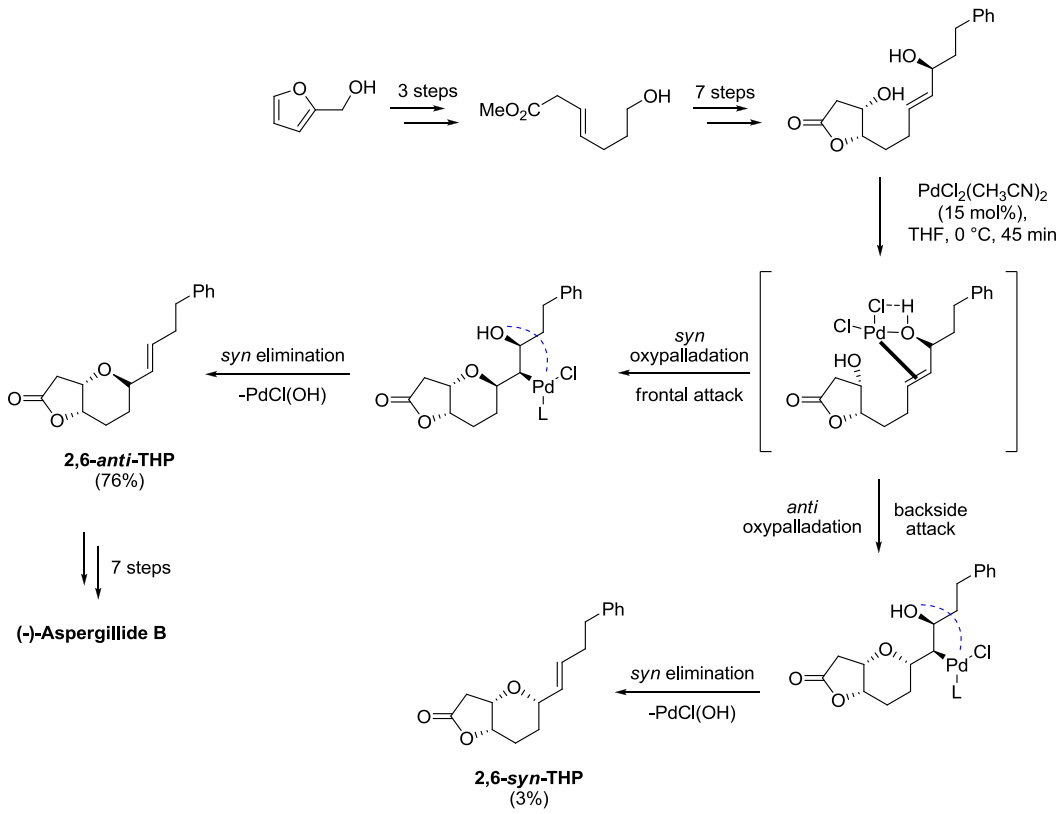


Figure 1.28 Uenishi's approach towards the construction of 2,6-*anti*-THP ring in (-)-Aspergillide B.

1.3.3.9 A Brief Summary of Methodologies Used To Construct 2,6-anti-tetrahydropyran ring in (-)-Aspergillide B

Research group	*2,6-anti-THP conformation achieved via*
Fuwa and co-workers	KO^tBu-mediated annulation.
Kuwahara and Nagasawa	$BF_3{\cdot}OEt_2$-mediated Ferrier-type reaction with silyl ketene acetal.
Marco and co-workers	Addition of silyl enol ether in the presence of $BF_3{\cdot}OEt_2$ and TMSOTf.
Sharma and Manohar	Tandem Sharpless asymmetric epoxidation/6-exo annulation sequence in the presence of cumene hydroperoxide (CHP).
Shishido and co-workers	Transannular oxy-Michael reaction in the presence of KH and [18]-crown-6.
Trost and Bartlett	Spontaneous oxy-Michael transannulation in ruthenium-catalyzed *trans*-hydrosilylation-protodesilylation reaction.
Uenishi and Hande	Pd(II)-catalyzed annulation *via* oxypalladation and 1,3-chirality transfer reactions.

1.3.4 Our research group's development in methodologies to access cyclic ethers

1.3.4.1 $In(OTf)_3$-catalyzed tandem sequence of 2-oxonia [3,3]-sigmatropic rearrangement/cyclization of homoallylic alcohol[54]

Our group serendipitously stumbled upon cyclic ether synthesis while exploring the possibilities to utilize indium(III) triflate ($In(OTf)_3$), which is a strong Lewis acid, in constructing useful prenyl adducts that are quintessential in terpenoids and their synthetic precursors. With the objective to form prenyl adducts in mind, homoallylic alcohol was allowed to stir in dichloromethane for 10 days at ambient temperature, along with catalytic amounts of its corresponding aldehyde and $In(OTf)_3$. From the crude NMR spectrum, it was observed that majority of the starting material was converted and two new sets of peaks appeared. Unfortunately, neither of the new peaks corresponded to the desired prenyl adduct. However, all hopes were not lost. As the saying goes, "Every dark cloud has its silver linings" and such was true when chromatographic separation provided two unprecedented tetrahydrofuran compounds (**Figure 1.29**). These observations captivated our group's interest and henceforth, we embarked on our endeavour in the direction towards the synthesis of cyclic ethers.

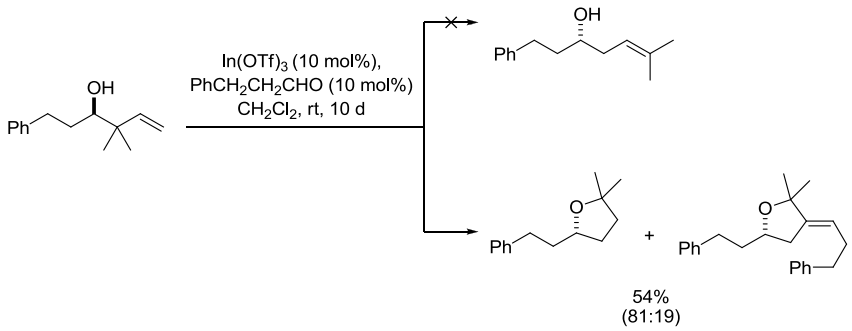


Figure 1.29 Observations of stirring homoallylic alcohol with catalytic amounts of its corresponding aldehyde and $In(OTf)_3$.

Through a series of screenings, it was noted that the increase of $In(OTf)_3$ catalyst loading improved the overall yield but at the expense of selectivity between the two tetrahydrofuran adducts. Stoichiometric amounts of the corresponding aldehyde would favour the generation of a more substituted tetrahydrofuran adduct while catalytic amounts of the aldehyde resulted in a less substituted tetrahydrofuran. It is

[54] Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem. Soc.* **2001**, *123*, 2450.

also proposed that during the course of reaction, the desired prenyl adduct may have formed *via* 2-oxonia [3,3]-sigmatropic rearrangement of an oxocarbenium species[55] before the oxyindiation with indium(III) triflate occurred to provide a tetrahydrofuranyl-indium species. The indium species could either be quenched by a proton source to result in the less substituted tetrahydrofuran or further react with its corresponding aldehyde to give the more substituted tetrahydrofuran product (**Figure 1.30**). This proposed mechanistic pathway was further substantiated when the methodology was applied to construct the tetrahydrofuran side chain of natural product Shidasterone[56] (**Figure 1.31**).

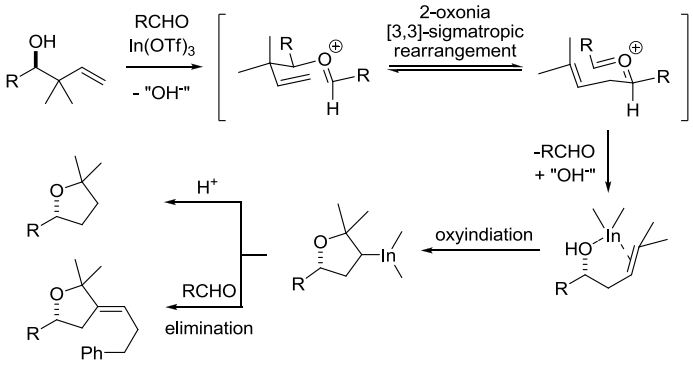


Figure 1.30 Proposed mechanistic pathway of $In(OTf)_3$-catalyzed tandem sequence of 2-oxonia [3,3]-sigmatropic rearrangement/cyclization of homoallylic alcohol.

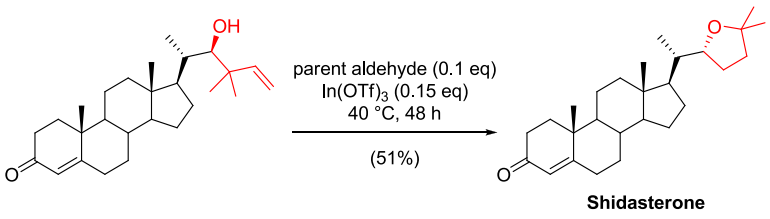


Figure 1.31 Application to the synthesis of tetrahydrofuran side chain of Shidasterone.

[55] (a) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S.I. *J. Am. Chem. Soc.* **1998**, *120*, 6609. (b) Sumida, S. I.; Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc.* **2000**, *122*, 1310. (c) Nokami, J.; Anthony, L.; Sumida, S. I. *Chem. Eur. J.* **2000**, *6*, 2909. (d) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1987**,*109*, 4748. (e) Mikami, K.; Shimazu, M. *Tetrahedron Lett.* **1992**, *33*, 6315.

[56] Takemoto, T.; Okuyama, T.; Arihara, S.; Hikino, Y.; Hikino, H. *Chem. Pharm. Bull.* **1969**, *17*, 1973.

1.3.4.2 In(OTf)$_3$-catalyzed (3,5) oxonium-ene type cyclization[57]

We remained intrigued by the earlier findings[54]and henceforth, delved further into verifying its mechanistic pathway. Our exploration pleasantly surprised us with a new discovery when the similar reaction conditions were carried out at 0 °C. Instead of the two tetrahydrofuran products that we are familiar with, a tetrahydrofuran adduct with a terminal olefin side chain was observed. This unexpected product could be attributed to either Mikami's (3,5) oxonium-ene type annulation[58] or the exocyclic Oppolzer's type III annulation[59], since both pathways are mechanistically similar.

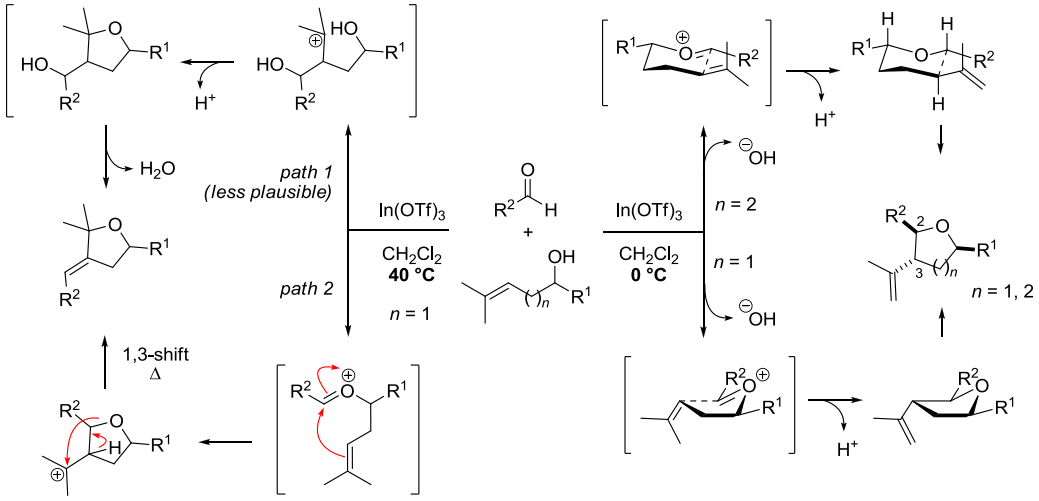


Figure 1.32 Indium(III) triflate-catalyzed annulations and their postulated mechanistic pathways.

When the homoallylic alcohol with longer carbon chain (*n* = 2) was subjected to the reaction conditions at low temperature of 0 °C (**Figure 1.32**, top right section), tetrahydropyranyl adduct with relative stereochemistry of 2,3-*trans*-2,6-*cis* was obtained as major product. This can be resulted from an oxonium-ene type annulation pathway *via* a cyclic six-membered chair-like transition state, with its substituents at equatorial positions. Likewise, the 2,3-*trans*-2,5-*cis* tetrahydrofuran adduct was resulted when *n* = 1, despite the decrease in selectivity due to a less rigid cyclic five-membered transition state (**Figure 1.32**, bottom right section).

[57] Loh, T.-P.; Hu, Q.-Y.; Tan, K.-L.; Cheng, H.-S. *Org. Lett.* **2001**, *3*, 2669.
[58] Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.
[59] (a) Oppolzer, W.; Snieckus, V. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 476. (b) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds.; Pergamon: London, 1991; Vol. 2, pp 527-661.

On the other hand, the reaction of homoallylic alcohol with shorter carbon chain (*n* =1) at an elevated temperature of 40 °C, might proceed in two possible pathways – a Lewis acid-catalyzed nucleophilc addition of an olefin to the carbonyl functionality and a subsequent cyclization (*path 1*), or an oxonium-ene type annulation involving a carbocation intermediate with successive rearrangement *via* 1,3-shift (*path 2*) (**Figure 1.32**, left section). *Path 1* was rendered less plausible since the corresponding benzoate ester of homoallylic alcohol was recovered upon treatment of the reaction conditions, negating the possibility of nucleophilic addition of olefin to carbonyl functionality. Successful conversion of tetrahydrofuran with terminal olefin (consequent of lower reaction temperature) to one with internal olefin at an elevated temperature implied the occurrence of *in situ* generation of a carbocation and the proposed thermodynamic 1,3-shift, thereby validating *Path 2* (**Figure 1.33**). It is also interesting to note that the reaction only proceeds when homoallylic alcohol possesses a prenyl-like disubstituted outer terminus of the alkene.

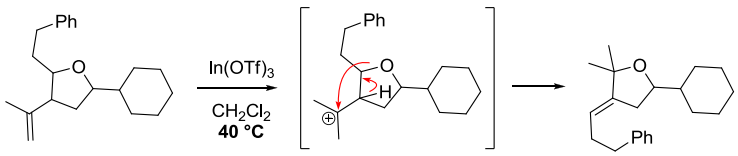


Figure 1.33 Conversion of tetrahydrofuran with terminal olefin to one with internal olefin at elevated temperature.

1.3.4.3 In(OTf)$_3$-catalyzed self-tandem carbonyl-ene/(2,5)-oxonium-ene cyclization[60]

In view of the unprecedented application of indium(III) triflate-catalyzed annulation between homoallylic alcohols and aldehydes, we pondered on the influence of In(OTf)$_3$ on the reaction between methylene cyclohexane and aldehydes. When we subjected methylene cyclohexane and benzaldehyde to catalytic amounts of In(OTf)$_3$ in dichloromethane at ambient temperature, the anticipated carbonyl-ene product was nowhere in sight. Instead, we were pleasantly surprised by the emergence of 2,3-*anti*-2,6-*syn*-tetrahydropyran adduct. To put icing on the cake, the aforementioned tetrahydropyran product was obtained in high yields and diastereoselectivities. This observation implied that a subsequent intramolecular (2,5)-oxonium-ene cyclization took place after the expected homoallylic alcohol product was generated (**Figure 1.34**)

[60] Loh, T.-P.; Feng, L.-C.; Yang, J.-Y. *Synthesis* **2002**, 937.

via a cyclic six-membered chair-like transition state, preferably with its substituents at equatorial positions due to steric considerations.

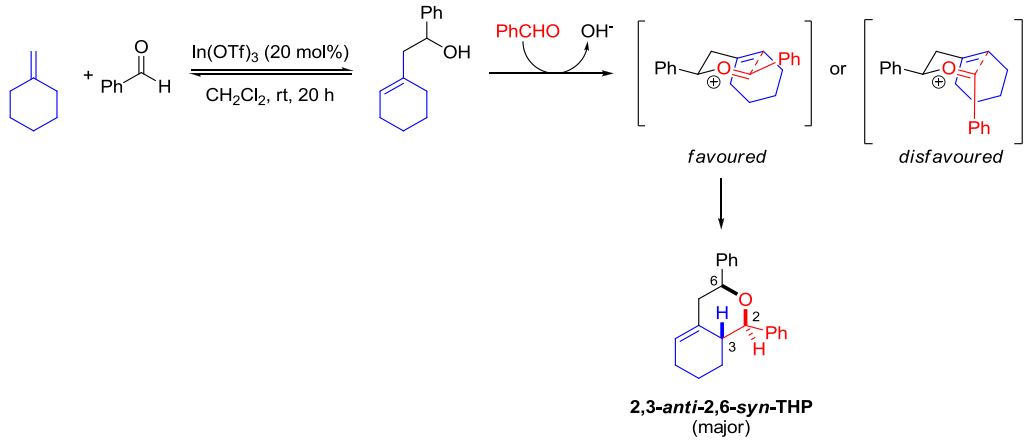


Figure 1.34 $In(OTf)_3$-catalyzed self-tandem carbonyl-ene/(2,5)-oxonium-ene cyclization.

Smith and co-workers timely reported the total syntheses of two natural products consisting 2,6-*syn*-THP moiety, namely dactylolide[61] and zampanolide[62], in which we found an opportunity to employ this recently developed methodology in synthesizing a proposed common 2,6-*syn*-THP intermediate (**Figure 1.35**).

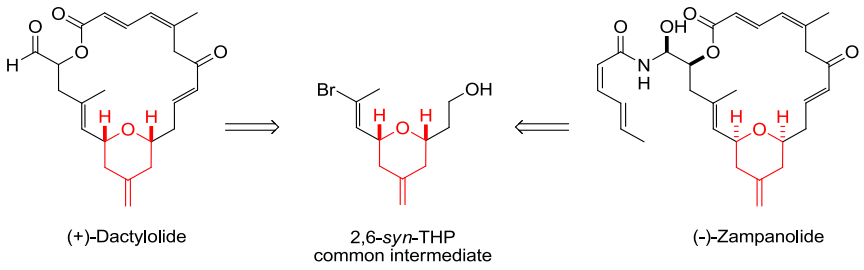


Figure 1.35 Common intermediate for the total syntheses of datcylolide and zampanolide.

[61] Smith, A. B., III; Safonov, I. G. *Org. Lett.* **2002**, *4*, 635.
[62] Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426.

After a series of model studies with benzaldehyde and various homoallylic alcohols, which were prepared by an indium-mediated allylation reaction[63], we slightly modified the reaction conditions shown to obtain the desired 2,6-*syn*-THP intermediate in 70% yield with diastereomeric ratio of *syn* : *anti* = 75 : 25 (**Figure 1.36**).

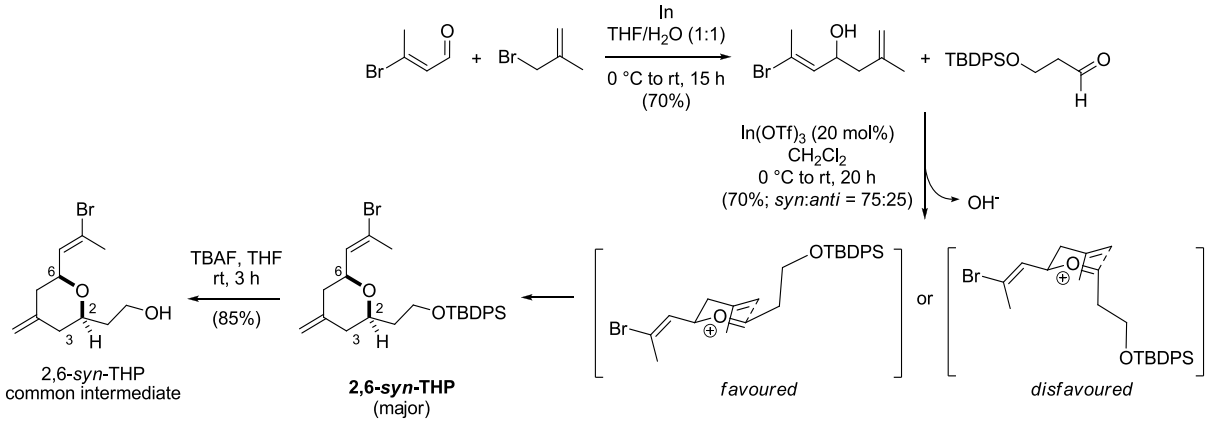


Figure 1.36 Synthetic pathway towards 2,6-*syn*-THP common intermediate.

1.3.4.4 Indium-based Lewis acid-catalyzed stepwise one-pot crossed Prins cyclization[64]

In 1999, Li and co-workers discovered a high-yielding Prins cyclization[65] that was mediated by stoichiometric amounts of Lewis acid $InCl_3$. Motivated by our previous $In(OTf)_3$-catalyzed annulations as well as Li's report, our group set out to formulate a catalyzed stereoselective Prins cyclization, which preferably could tolerate a wider substrate scope, by employing indium-based Lewis acids as catalysts. Our efforts paid off when our initial studies revealed a convenient one-pot Prins cyclization with allylsilanes proceeded in the presence of mild indium-based Lewis acids as catalysts (**Figure 1.37**), affording 2,4,6-trisubstituted THP adducts albeit with the generation of homoallylic alcohol in some cases.

[63] (a) Araki, S.; Ito, H.; Katsumura, N.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831. (b) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (c) Chan, T. H.; Li, C.-J.; Lee, M.-C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181. (d) Cintas, P. *Synlett* **1995**, 1087. (e) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228.
[64] Chan, K.-P.; Loh, T.-P. *Tetrahedron Lett.* **2004**, *45*, 8387.
[65] Yang, J.; Viswanathan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627.

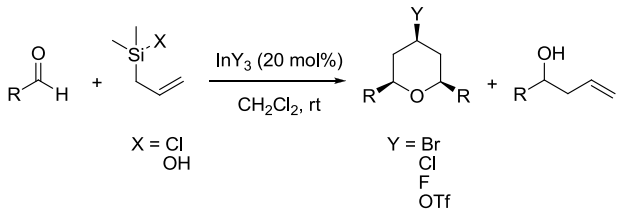


Figure 1.37 Convenient one-pot Prins cyclization with allylsilanes in the presence of catalytic mild indium-based Lewis acids.

2,4,6-trisubstituted THP adducts are best favoured when a stoichiometric amount of allylchlorosilane was used with catalytic amounts of indium(III) triflate in dilute dichloromethane solutions. On the other hand, homoallylic alcohols were preferentially generated when aldehydes were introduced slowly into the reaction mixture, which contained excess amounts of allylchlorosilanes. It is interesting to note that the reaction is moisture-tolerant to a certain extent but does not work well with conjugated aldehydes.

Such observations helped us to design an indium-based Lewis acid-catalyzed stepwise one-pot crossed Prins cyclization, in which two different aldehydes were employed to give rise to two different substituents on 2,6-positions of the THP adduct respectively (**Figure 1.38**). With allylchlorosilanes in excess, homoallylic alcohol was first generated in the presence of indium(III) chloride. Thereafter, larger amounts of aldehyde were added to effect *in situ* Prins cyclization in the presence of catalytic amounts of indium(III) triflate. This stepwise, one-pot homoallylic alcohol formation/Prins cyclization reaction provided both high yields and selectivities of 2,4,6-THP adducts. Unlike in the initial studies, *α,β*-unsaturated aldehydes were tolerated under these optimized conditions.

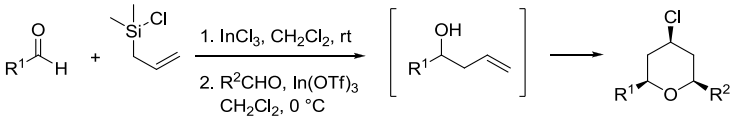


Figure 1.38 Indium-based Lewis acid-catalyzed stepwise one-pot crossed Prins cyclization.

1.3.4.5 Stereoselective indium complex-catalyzed Prins cyclization in the presence of silyl additives[66]

Further investigations following the discovery of $In(OTf)_3$-catalyzed stepwise one-pot crossed Prins cyclization prompted us to elucidate the mechanistic pathway involved and the role of silicon-based reagents. We thus subjected a homoallylic alcohol to a variety of aldehydes in the presence of indium(III) triflate as catalyst and trimethylsilyl halide as additive. The expected Prins cyclization proceeded smoothly and provided moderate to excellent yields of the corresponding 2,4,6-trisubstituted THP in all-*cis* configuration, regardless of trimethylsilyl halide used (**Figure 1.39**). It is noteworthy that the reaction was not affected by steric and electronic factors.

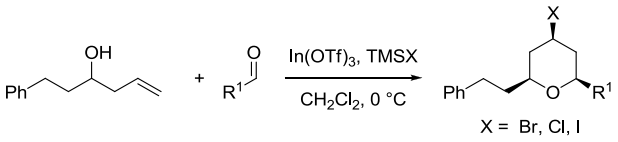


Figure 1.39 Stereoselective indium complex-catalyzed Prins cyclization in the presence of trimethylsilyl halides as additives.

We then applied this methodology to enantioselectively synthesize (-)-Centrolobine, that was isolated from *Centrolobium robustum* (**Figure 1.40**) by constructing the 2,4,6-syn-trisubstituted THP backbone with a further optimized reaction conditions, in which a weaker Lewis acid, indium(III) bromide and trimethylsilyl bromide were used at a lower temperature to suppress epimerization from taking place. We also seized

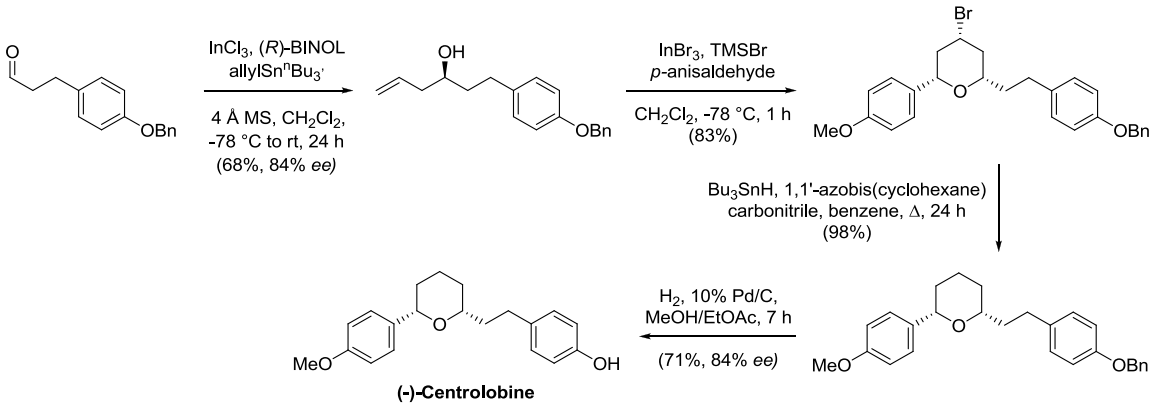


Figure 1.40 Synthesis of (-)-Centrolobine.

[66] Chan, K.-P.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 4491.

this opportunity to showcase another of our recently reported methodologies – an asymmetric allylation of aldehyde with allyltributyltin in the presence of *in situ* generated (*R*)-BINOL indium complex[67], to form the requisite homoallylic alcohol.

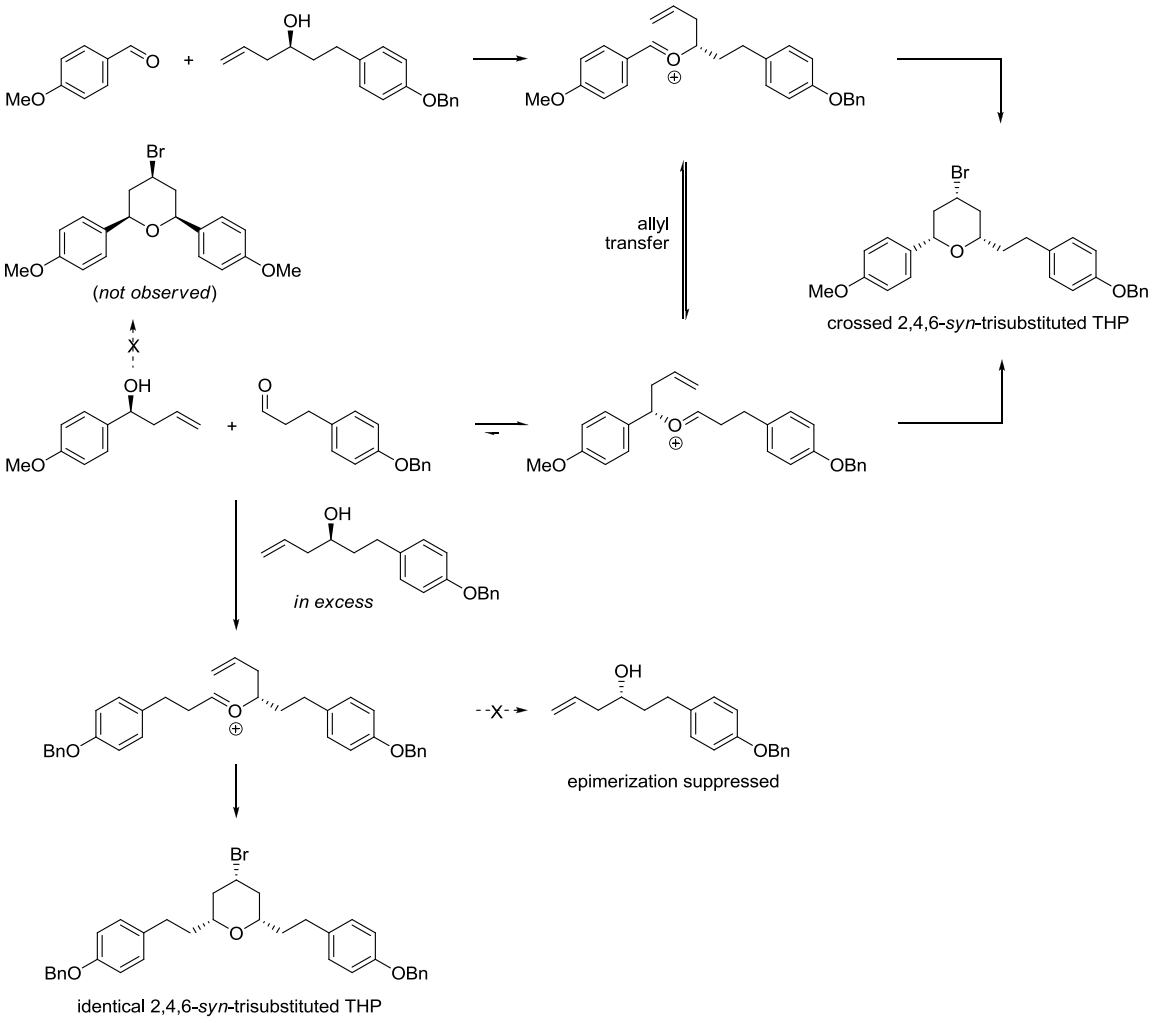


Figure 1.41 Proposed mechanistic pathway for stereoselective indium complex-catalyzed Prins cyclization in the presence of trimethylsilyl halides.

The observations made during the model studies provided valuable mechanistic insights (**Figure 1.41**). We envisaged that $InBr_3$ catalyst, being a Lewis acid in nature, to facilitate in the formation of oxonium ion. The resultant carbocation is then immediately trapped with the halide from trimethylsilyl halide, which may attribute to the absence of epimerized homoallylic alcohol starting material. Self-cyclization of *p*-anisaldehyde was not observed although allyl transfer with retention of its absolute chirality took place to a certain extent. In accordance to an earlier report of $In(OTf)_3$-

[67] Teo, Y. C.; Tan, K. T.; Loh, T. P. *Chem. Commun.* **2005**, *10*, 1318.

catalyzed tandem sequence of 2-oxonia [3,3]-sigmatropic rearrangement/cyclization of homoallylic alcohol[54], it is of no big surprise when identical 2,4,6-*syn*-trisubstituted THP adduct was formed in approximately 5% for all experiments performed in our model studies, as a consequence of the miniscule allyl transfer. Considering the allyl transfer pathway has been retarded, the asymmetric Prins cyclization henceforth became the predominant route, yielding *cis*-4-halo-2,6-*syn*-disubstituted THP adduct.

1.3.4.6 Synthesis of 2,6-anti-tetrahydropyran rings via indium(III) triflate-catalyzed Prins cyclization of homoallylic-α-hydroxy esters[68]

Prins cyclization conventionally provides 2,6-*syn*-tetrahydropyranyl products, resulting from the more favourable all-equatorial chair-like transition state. Generation of 2,6-*anti*-tetrahydropyranyl products is less likely as the chair-like transition state would suffer from a severe 1,3-diaxial interaction (**Figure 1.42**).

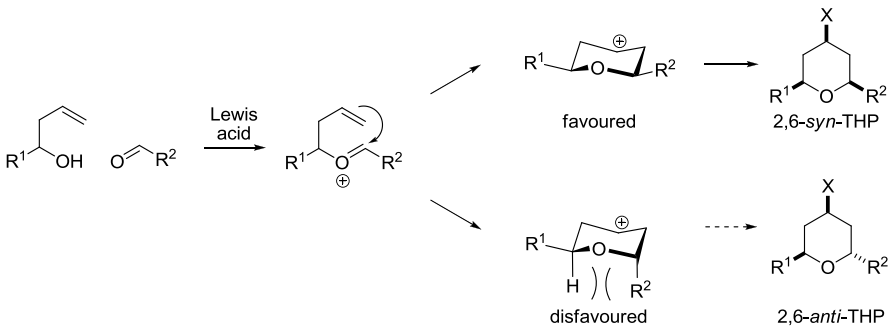


Figure 1.42 Conventional Prins cyclization favouring *syn*-THP ring formation.

Based on our previous report on indium complex-catalyzed Prins cyclization, in which construction of *syn*-4-halo-2,6-disubstituted THP adducts was favoured[64,66], we postulated that the strong yet unfavourable 1,3-diaxial interations could be counteracted with the lone-pair inductive effect provided by a *β*-positioned electron-rich substituent on the homoallylic alcohol, thereby stabilizing the oxonium cation in the chair-like transition state. Henceforth, we subjected homoallylic-*α*-hydroxy esters to Prins cyclization with benzaldehyde in the presence of TMSCl and $In(OTf)_3$ (**Figure 1.43**). Gratifyingly, the reactions generally yielded easily separable diastereomeric mixtures of 2,6-*syn*- and 2,6-*anti*-THP adducts in 1:1 ratio, which may be stemmed from a competition between an electronically-favoured transition state and a sterically-preferred one. It is noteworthy that the chloride from TMSCl attacks

[68] Chan, K.-P.; Seow, A.-H.; Loh, T.-P. *Tetrahedron Lett.* **2007**, *48*, 37.

equatorially and the selectivity of the Prins cyclization is independent of changes in temperature and steric interactions. It is also verified that the Lewis acid-catalyzed enolization between 2,6-*syn*- and 2,6-*anti*-THP adducts is unlikely to take place.

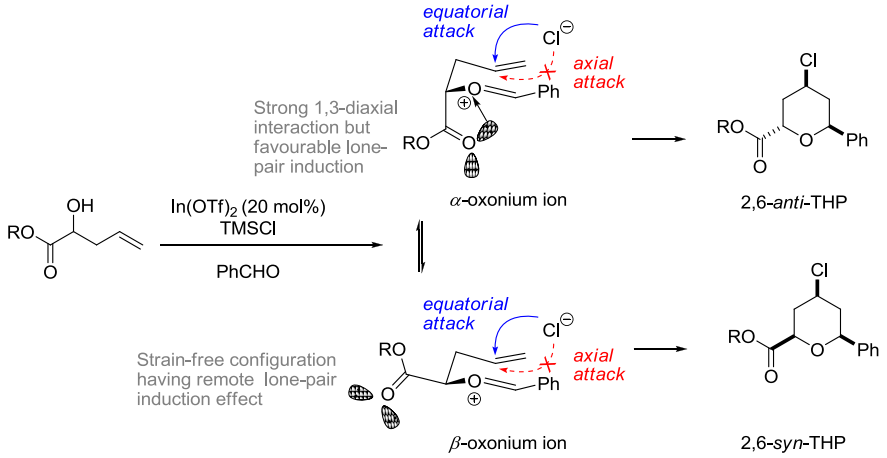


Figure 1.43 Electronic inductive effects on oxonium cations in indium(III) triflate-catalyzed Prins cyclization of homoallylic-*α*-hydroxy esters.

1.3.4.7 Highly stereoselective synthesis of 2,4,5,6-tetrasubstituted tetrahydropyran rings via indium(III) bromide-mediated Prins cyclization of γ-brominated homoallylic alcohols[69]

We extended the substrate scope of indium complex-influenced Prins cyclization to include *γ*-brominated homoallylic alcohols, giving rise to 2,6-*cis*-4,5-dihalo-tetrasubstituted THP adducts, which are useful intermediates to access other functionalized tetrahydropyrans. Upon screening, it was found that stoichiometric amount of $InBr_3$ with slightly excessive TMSBr in CH_2Cl_2 at 0 °C afforded moderate to excellent yields of tetrasubstituted tetrahydropyranyl adducts with high stereoselectivity. This methodology works well with both (*E*)- and (*Z*)-*γ*-brominated homoallylic alcohols to form 2,4,5,6-*cis*- and 2,4,6-*cis*-5-*trans*-THP rings respectively (**Figure 1.44**).

The aforementioned THP products were then subjected to either activated zinc in acetic acid or tributylstannane with 1,1'-azobis(cyclohexane) carbonitrile (ABCCN) in refluxing toluene to afford 2,6-*syn*-dihydropyran upon elimination of both bromides, while treatment with potassium *tert*-butoxide removed the bromide in the 5-position of

[69] Liu, F.; Loh, T.-P. *Org. Lett.* **2007**, *9*, 2063.

the THP ring. The presence of bromine at the axial position in 2,4,5,6-*cis*-THP intermediate rendered it less reactive than 2,4,6-*cis*-5-*trans*-THP counterpart during the subsequent conversions.

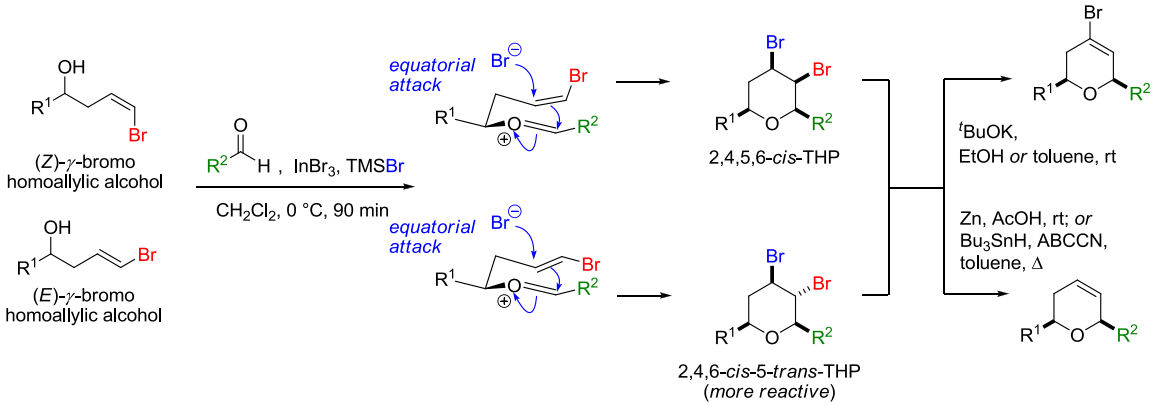


Figure 1.44 Highly stereoselective synthesis of 2,4,5,6-tetrasubstituted THP rings *via* indium(III) bromide-mediated Prins cyclization of *γ*-brominated homoallylic alcohols.

1.3.4.8 Stereoselective synthesis of 2,6-anti-THP rings via indium complex catalyzed Prins cyclization of carboalkoxyl allenic alcohols[70]

We envisaged that the stereoselectivity of our indium complex-promoted Prins cyclization could be improved to favour 2,6-*anti*-THP if the lone pair stabilization of δ^+ oxo-carbenium by the axial carbonyl moiety is capitalized while eliminating the competing consequent 1,3-diaxial interaction. Bearing that in mind, we ventured into the potential of allenic alcohols in our Prins cyclization methodology, in place of homoallylic alcohols, to afford 2,6-*anti*-THP rings in better selectivity (**Figure 1.45**).

To our delight, we indeed obtained very good diastereoselectivities and yields with allenylic alcohols. The efficiency further improved when the Y substituent was switched from methyl to TMS moiety (**Figure 1.45**, right section). Replacement of the ester moiety of the allenic alcohol with alkyl moiety did not yield any crossover 2,6-*anti*-THP products. Instead, a propargylic transfer *via* an oxocarbenium-[3,3]-sigmatropic rearrangement and a subsequent addition of a second aldehyde resulted 2,6-*syn*-THP adducts (**Figure 1.45**, left section)[71]. From these observations, we can conclude that the ester moiety plays an important role in suppressing undesired oxonia-Cope rearrangement due to its electron-withdrawing nature, while stabilizing

[70] Hu, X.; Liu, F.; Loh, T.-P. *Org. Lett.* **2009**, *11*, 1741.
[71] Lee, K. C.; Lin, M. J.; Loh, T. P. *Chem. Commun.* **2004**, 2456.

the δ^+ of oxocarbenium when positioned axially (anomeric effect) through stereoelectronic induction.

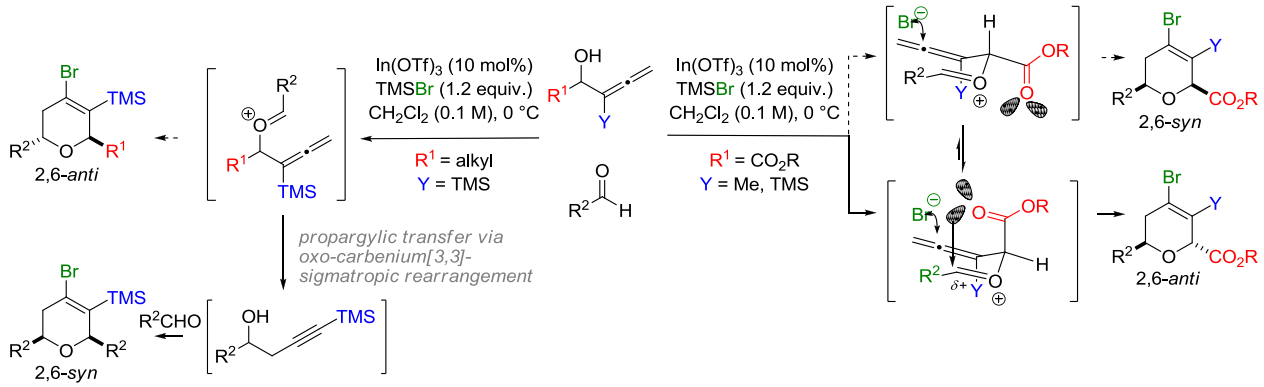


Figure 1.45 Stereoselective synthesis of 2,6-anti-THP rings *via* indium complex catalyzed Prins cyclization of allenic alcohols.

In 2010, this methodology was revisited and modified to provide fluorinated 2,6-*anti*-THP rings, where Lewis acid $BF_3{\cdot}Et_2O$ was applied and acted as both a fluorine source and a promoter, in place of TMSBr and indium(III) bromide.[72] The reaction mechanism is postulated to be similar to the illustration shown on the right section of **Figure 1.45**. However, the reaction conditions are restricted to TMS-tethered carboalkoxyl allenic alcohols as the presence of ester moiety is presumably crucial.

1.3.4.9 A Brief Summary of Our Research Group's Development in Methodologies to access Cyclic Ethers

Our methodologies to access cyclic ethers thus far revolved around oxonium-ene and Prins cyclizations of homoallylic and allenic alcohols respectively. It is noteworthy that most approaches provided substituted cyclic ethers in *syn* configuration, with the exception of the approach discussed in section *1.3.4.8*, that provides 2,6-*anti*-THP adducts. In a later section (*vide infra*), a methodology to access 2,6-*anti*-THP rings *via* Mukaiyama-Michael addition of silyl enol ether, which was developed in the course of our efforts towards the total synthesis of Apicularen A, will be described.

[72] Luo, H.-Q.; Hu, X.-H.; Loh, T.-P. *Tetrahedron Lett.* **2010**, *51*, 1041.

THIS PAGE IS INTENTIONALLY LEFT BLANK.

Chapter Two

Introduction to Apicularen A and Its Previously Reported Synthetic Studies

THIS PAGE IS INTENTIONALLY LEFT BLANK.

2.1 Background of Apicularen A

In search of bioactive metabolites, Jansen and co-workers were particularly intrigued by strains of the species *Chondromyces crocatus*.[73] While some metabolites produced by species *C. crocatus* differ from the other species of the same myxobacterial genus *Chrondromyces* that attribute to its high cytotoxicity and antibiotic activities, there is one common potent metabolite, which is also produced in *C. apiculatus*, *C. lanuginosus*, *C. pediculatus* and *C. robustus*, namely **Apicularen A**.

2.1.1 Isolation and structural elucidation of Apicularen A

Jansen and co-workers cultivated the species *Chondromyces robustus* in a liquid medium for several days with small amounts of neutral adsorber resin present. The culture medium was washed with water and subsequently being extracted with dichloromethane. The organic layer was then subjected to a second extraction in methanol and washed with heptane. The polar fraction was purified *via* silica gel flash chromatography and **Apicularen A** was obtained by recrystallization from methanol, on which an X-ray crystallographic analysis was elucidated (**Figure 2.1**).

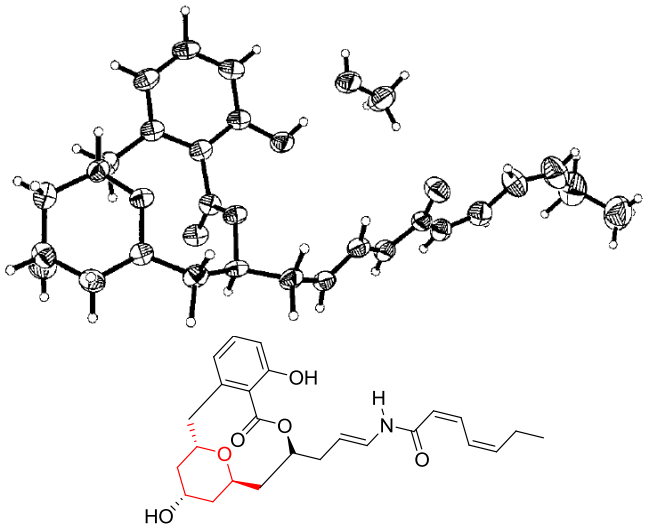


Figure 2.1 X-ray crystallographic structure of Apicularen A with a hydrogen-bonded methanol molecule.

[73](a) Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiotics* **1998**, 1075. (b) Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2000**, 913.

The structure of Apicularen A reveals that it is a 12-membered macrolide, made of a benzolactone and a 2,6-*anti*-THP ring with four stereogenic centers embedded within it. Another interesting feature has to be the highly unsaturated side chain, a distinctive *N*-(2*Z*,4*Z*)-heptadienoylenamine, that is attached to the aforementioned salicylate macrolactone core.

In the same article, Jansen and co-workers reported that Apicularen A has a characteristic broad UV absorption band at λ_{max} = 278 nm whilst its mass spectrum distinctively shows both a molecular ion $[M-H]^-$ at *m/z* = 440 and a fragment ion of [M-108]$^-$. NMR analyses of Apicularen A in [D_6]-acetone, which included 1-D NMR ^{1}H and ^{13}C spectroscopic data as well as discussion on 2-D NMR ^{1}H,^{1}H-COSY, ^{1}H,^{13}C-HMBC and ^{1}H,^{1}H-NOESY spectra, were provided.

2.1.2 Biological activity of Apicularen A

Apicularen A can be a prominent antitumour drug candidate[74] as it possesses antiangiogenesis properties[75]and demonstrates potent cytostatic activity against a variety of human cancer cell lines such as cervix, kidney, leukemia, lung and prostate cells, as indicated by IC_{50} values ranging from 0.23-6.79 nM.[76] Characteristic to the benzolactone enamide family, Apicularen A is capable of selectively inhibiting mammalian vacuolar (H^+)-ATPases that regulates intracellular pH.[77] As a downstream effect of such phenomenon, Apicularen A induces apoptotic-like cell death *via* phosphorylation of mitogen-activated protein kinases.[78] It is also noteworthy that Apicularen A causes the production of nitric oxide[79] as well as abnormal formations of mitotic spindles with multiple spindle poles and bundled actin clusters from the cytoskeleton.

---

[74] Petri, A. F.; Sasse, F.; Maier, M. E. *Eur. J. Org. Chem.* **2005**, 1865.
[75] Kwon, H. J.; Kim, D. H.; Shik, J. S.; Ahn, J. W. *J. Microbiol. Biotechnol.* **2002**, *12*, 702.
[76] Palimkar, S. S.; Uenishi, J.; Ii, H. *J. Org. Chem.* **2012***, 77*, 388.
[77] 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**, *291, 114.*
[78] (a) Hong, J.; Yamaki, K.; Ishihara, K.; Ahn, J.W.; Zee, O.; Ohuchi, K. *J. Pharm. Pharmacol.***2003**, *55*, 1299. (b) Hong, J.; Ishihara, K.; Zee, O.; Ohuchi, K. *Planta Med.* **2005**, *71*, 306.
[79] Hong, J.; Yokomakura, A.; Nakano, Y.; Ban, H. S.; Ishihara, K.; Ahn, J. W.; Zee, O.; Ohuchi, K. *J. Pharmacol. Exp. Ther.* **2005**, *312*, 968.

2.2 Previously Reported Synthetic Efforts Towards Apicularen A

Since the discovery of Apicularen A, the chemical society has vested interest in reproducing the aforesaid natural product. It has captivated the attention of many research groups with its potent biological activities as well as its challenging structural architecture. To the best of our knowledge, there are five total syntheses, four formal syntheses and two reported partial syntheses (*vide infra*). In this section, we will discuss the synthetic efforts towards Apicularen A that have been reported previously, in a chronological order.

2.2.1 Total synthesis of Apicularen A by De Brabander and co-workers[80]

De Brabander and co-workers embarked on their total synthesis with an aldehyde, derived from cheap and commercially-available 2,6-dihydroxybenzoic acid upon several transformations - namely acetal protection of the benzoic acid and an adjacent hydroxy moiety, activation of the free hydroxy group into a triflate moiety for the subsequent Stille coupling and finally, an ozonolysis. The aforementioned aldehyde was subjected to stereoselective hetero-Diels-Alder reaction with Danishefsky's diene[81], in the presence of Jacobsen's chiral chromium(III)-catalyst[82], which was reported to be highly efficient for such combination, resulting in the desired dihydropyranone (84% *ee* prior to recrystallization). A conjugate addition of vinylmagnesium bromide was then effected by copper(I) iodide, thereby installing the 2,6-*anti* configuration, diastereospecifically. The subsequent reduction of the ketone of the tetrahydropyranone unfortunately afforded a racemic mixture of epimeric alcohols at best, despite screening a number of reducing agents. This phenomenon could be attributed to rapid interconversion of the two conformers of the tetrahydropyranone, according to Curtin-Hammett principle, and subsequently being reduced at similar rates, regardless of reducing agents used.

---

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

[81] (a) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400. (b) Danishefsky, S. *Chemtracts: Org. Chem.* **1989**, *2*, 273.

[82] Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem. Int., Ed. Engl.* **1999**, *38*, 2398.

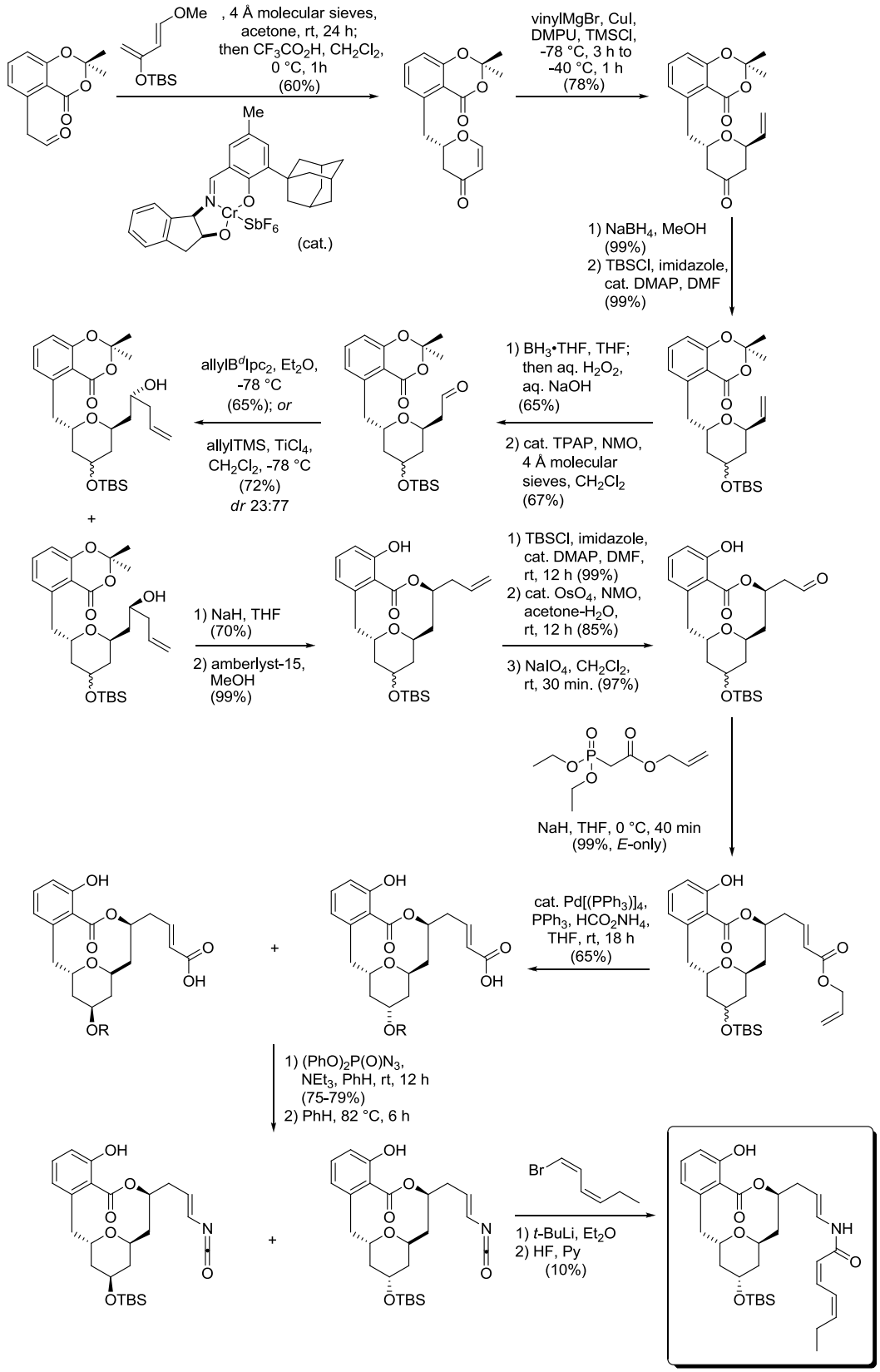


Figure 2.2 Total synthesis of Apicularen A by De Brabander and co-workers.

Fast forward a few steps to the stereoselective allylation, De Brabander initially used Brown's *B*-allyldiisopinocampheylborane ($^{d}Ipc_2Ballyl$) to afford homoallylic alcohols in diastereomeric ratio of 77:23. Application of allyltrimethylsilane in the presence of titanium(IV) chloride ($TiCl_4$) unexpectedly provided better yield, albeit diastereomeric ratio remained unchanged, as chelation of $TiCl_4$ usually favours the *anti*-addition isomer.[83] This mixture of diastereoisomers was only successfully separated during purification *via* preparative thin layer chromatography (pTLC) upon lactonization with sodium hydride (NaH), rendering this synthetic route less practical for large scale synthesis.

Another key step of the total synthesis is the installment of enamine side chain, where De Brabander and co-workers employed the same methodology applied in their previously reported total synthesis of Salicylihalamide A.[84] The requisite (*E*)-vinyl acid was prepared from the truncated Apicularen A core structure through a few conversions that include oxidative cleavage of a terminal alkene and a Horner–Wadsworth–Emmons (HWE) reaction. The carboxylic acid was reacted with an azide source, diphenyl phosphoryl azide to obtain the desired isocyanate *via* an acyl azide intermediate. It is noteworthy that the isocyanate intermediates could provide a versatile handle for various side chain modifications.

Finally, the introduction of lithiated diene to isocyanate and deprotection of alcohols afforded the desired Apicularen A, but unfortunately, in a mixture alongside with two other side products that can only be separated by two successive preparative HPLC. Henceforth, De Brabander's approach is less ideal for large scale synthesis of Apicularen A as tedious purification steps were involved. Moreover, the use of dangerous chemicals such as *t*-BuLi and hydrogen fluoride (HF) in this synthetic route would be best avoided.

De Brabander and co-workers accomplished the total synthesis of Apicularen A (**Figure 2.2**) in approximately 22 steps with an estimated overall yield of less than 0.4%.

---

[83] For examples of *anti*-addition, see: (a) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833. (b) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847.
[84] Wu, Y.; Esser, L.; De Brabander, J. K. *Angew. Chem. Int., Ed. Engl.* **2000**, *39*, 4308.

2.2.2 Formal synthesis of Apicularen A by Taylor and co-workers[85]

Taking on a carbohydrate-based synthetic route to synthesize (+)-Apicularen A, Taylor and co-workers constructed the required THP core from $_D$-glucal in four steps, involving tributyltin hydride-mediated Barton-McCombie-type deoxygenation of a (thiocarbonyl)imidazolide[86]. The primary alcohol was then activated as an unstable triflate-acetal intermediate and was immediately coupled with Kotsuki's salicylate equivalent benzofuryl Grignard reagent[87], which substituted the initial *o*-anisic acid-derived Grignard reagent that was rendered too unstable for the coupling reaction.

Stereospecific allylation of anomeric acetal with allyltrimethylsilane, in the presence of TMSOTf as Lewis acid, afforded the desired 2,6-*anti*-THP configuration in good yield. However, protection of alcohol with another silyl moiety, TBS group, was needed as cleavage of TPS group was observed, which could be due to the acidic conditions of the reaction. A second allylation was effected by Brown's allylB^dIpc$_2$, achieving better stereoselectivity (*dr* 90:10) compared to that reported by De Brabander's group (*dr* 77:23). Interestingly, allylation with allyltrimethylsilane in the presence of $TiCl_4$, which was described to provide better yield in De Brabander's approach, only managed a poor yield of 35% with no selectivity observed. Upon low-yielding macrolactonization *via* Keck's protocol[88], the diastereomeric mixture of intermediates was finally separated before its alcohol moieties being deprotected and reprotected with TBS groups. The 2,6-*anti*-THP core fragment was then finally being converted to (+)-Apicularen A in another 8 steps, following De Brabander's isocyanate route.

This formal synthesis designed by Taylor's group (**Figure 2.3**) acquired an approximately yield of 0.04% in 28 steps.

[85] (a) Lewis, A.; Stefani, I.; Swain, S. A.; Smith, S. A.; Taylor. R. J. K. *Tetrahedron Lett.* **2001**, *42*, 5549. (b) Lewis, A.; Stefani, I.; Swain, S. A.; Smith, S. A.; Taylor. R. J. K. *Org. Biomol. Chem.* **2003**, *1*, 104.
[86] Rasmussen, J. R.; Slinger, C. J.; Kordish, R. J.; Newman-Evans, D. D. *J. Org. Chem.* **1981**, *46*, 4843.
[87] Kotsuki, H.; Araki, T.; Miyazaki, A.; Iwasaki, M.; Datta, P. K. *Org. Lett.* **1999**, *1*, 499.
[88] Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

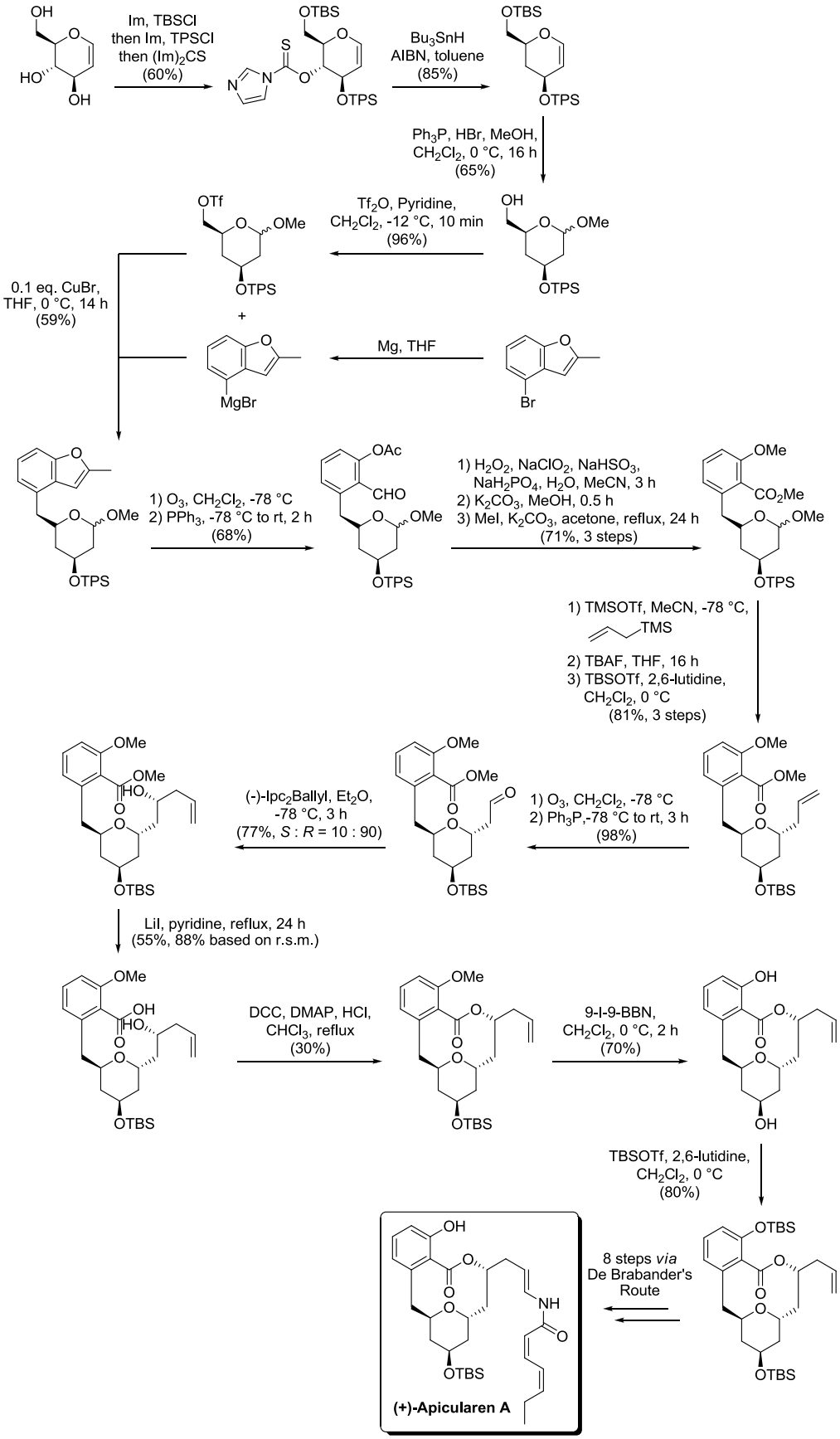


Figure 2.3 Formal synthesis of Apicularen A by Taylor and co-workers.

2.2.3 Total synthesis of Apicularen A by Nicolaou and co-workers[89]

Nicolaou and co-workers derived their inspiration for the total synthesis from Apicularen A's polyacetate-based biosynthesis. Feeding experiments with [1,2-^{13}C]-acetate from previous biosynthetic studies showed that eleven intact molecules of acetate were incorporated into Apicularen A, thereby accounting for all of the carbon atoms in the natural product, with the exception of C-17 (from glycine), C-18 and C-25 (from methionine).[73(b)] Nicolaou and co-workers mimicked nature's biosynthesis of Apicularen A *via* five reiterations of allylation-ozonolysis two-step sequence to introduce acetate-equivalent units.

Nicolaou and co-workers embarked on their synthesis with the same acetonide triflate in De Brabander's route and similarly, employed Stille coupling with allyltributyltin, followed by an ozonolysis (comprising the first allylation-ozonolysis two-step sequence) to result in an aldehyde intermediate. The second allylation-ozonolysis procedure was carried out with Brown's reagent, (-)-Ipc$_2$Ballyl, as the allylating agent and the resultant alcohol was protected prior to ozonolysis. The third allylation was performed with the other isomer of Brown's reagent, (+)-Ipc$_2$Ballyl, and subsequently underwent ozonolysis of the terminal alkene to furnish a hydroxylactol, which was duly acetylated, affording a mixture of anomeric diacetate intermediates (*α*:*β* ca. 3:1). The fourth allylation was performed with allyltrimethylsilane at the anomeric position. The influence of $BF_3 \cdot Et_2O$ present promoted the *anti*-stereochemistry, thereby constructing the desired 2,6-*anti*-THP ring. The final allylation involved (+)-Ipc$_2$Ballyl, giving rise to an alcohol, which would be protected with TBS moiety until the last step, where a concomitant lactonization occurred when the acetal was cleaved in the presence of NaH.

Setting the stage for the installation of enamide side chain, the terminal olefin was transformed into the requisite (*E*)-vinyl iodide intermediate, through an ozonolysis and a subsequent Takai iodo-olefination, in 81% (over 2 steps) as a mixture with its (*Z*)-isomer (*E*:*Z* ca. 9:1). The mixture was coupled with a primary amide in the presence of copper(I) thiophene carboxylate (CuTC) and rubidium carbonate (Rb_2CO_3), thereby stereoselectively installing the enamide side chain in 90% yield (*E*:*Z* ca. 10:1), based on 50% conversion. Upon isolation, the desired (*E*)-enamide underwent deprotection

[89] (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.

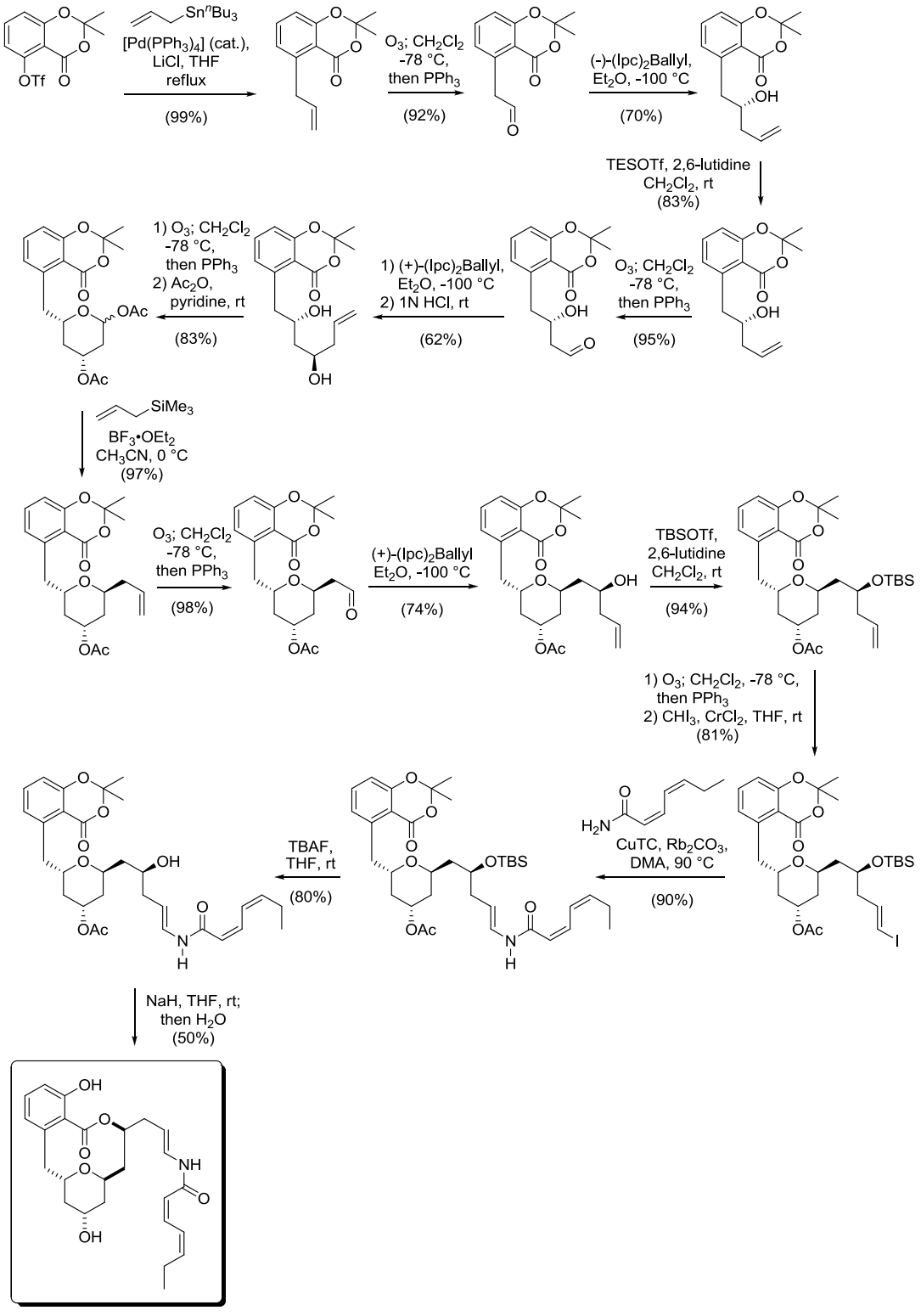


Figure 2.4 Total synthesis of Apicularen A by Nicolaou and co-workers.

of alcohol and ring closure *via* macrolactonization when treated with sodium hydride. This route by Nicolaou's group required approximately 18 steps to achieve total synthesis of Apicularen A (**Figure 2.4**) with an estimated overall yield of 5%.

It is noteworthy that Nicolaou *et.al.* previously attempted two other approaches to attach the enamide side chain, which unfortunately did not provide the desired Apicularen A. However, those failed attempts provided valuable insights and interesting analogues. In the first attempt (**Figure 2.5**, Route A), Nicolaou and co-workers treated the terminal olefin intermediate with *m*CPBA to obtain an epoxide, which was opened regioselectively with sodium azide (NaN_3). The resulting diasteroisomeric mixture of azides was then reduced under Staudinger conditions[90] into a hydroxy amine intermediate, which was subsequently coupled with (*Z,Z*)-diene-carboxylic acid in the presence of EDC (1-[3-dimethylamino]propyl)-3-ethylcarbodiimide hydrochloride) and HOBt (1-hydroxybenzotriazole hydrate), affording a hydroxy amide that was resilient against any dehydration reactions, thereby thwarting any efforts to generate the acylenamine functionality.

Nicolaou and co-workers also explored the possibility of employing a similar strategy by Labrecque *et. al.* in their synthesis of salicylihalamide[91] (**Figure 2.5**, Route B), where hydroboration was performed on the terminal alkene and a subsequent oxidative work-up to reveal a primary alcohol intermediate. The resultant alcohol was oxidized to an aldehyde, using TPAP-NMO conditions. Finally, the aldehyde was subjected to two equivalents of (*Z,Z*)-diene amide under the influence of TMSOTf and a deprotection of alcohols with TBAF to obtain a robust bisamide analogue. Efforts to eliminate one of the amide moieties were proved unfruitful.

In the full paper published in 2003, Nicolaou and co-workers also performed structure activity relationship (SAR) studies and henceforth, established that the acylenamine side chain of Apicularen A is crucial for its antitumour activities. They further reported that the absence of macrolactone does not affect its bioactivity significantly, which opened up a new possibility where more accessible and simpler mimics of Apicularen A could be explored.

[90] (a) Vaultier, M.; Knouzi, N.; Carrié, R. *Tetrahedron Lett.* **1983**, *24*, 763. (b) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.
[91] Labrecque, D.; Charron, S.; Rej, R.; Blais, C.; Lamothe, S. *Tetrahedron Lett.* **2000**, *41*, 8069.

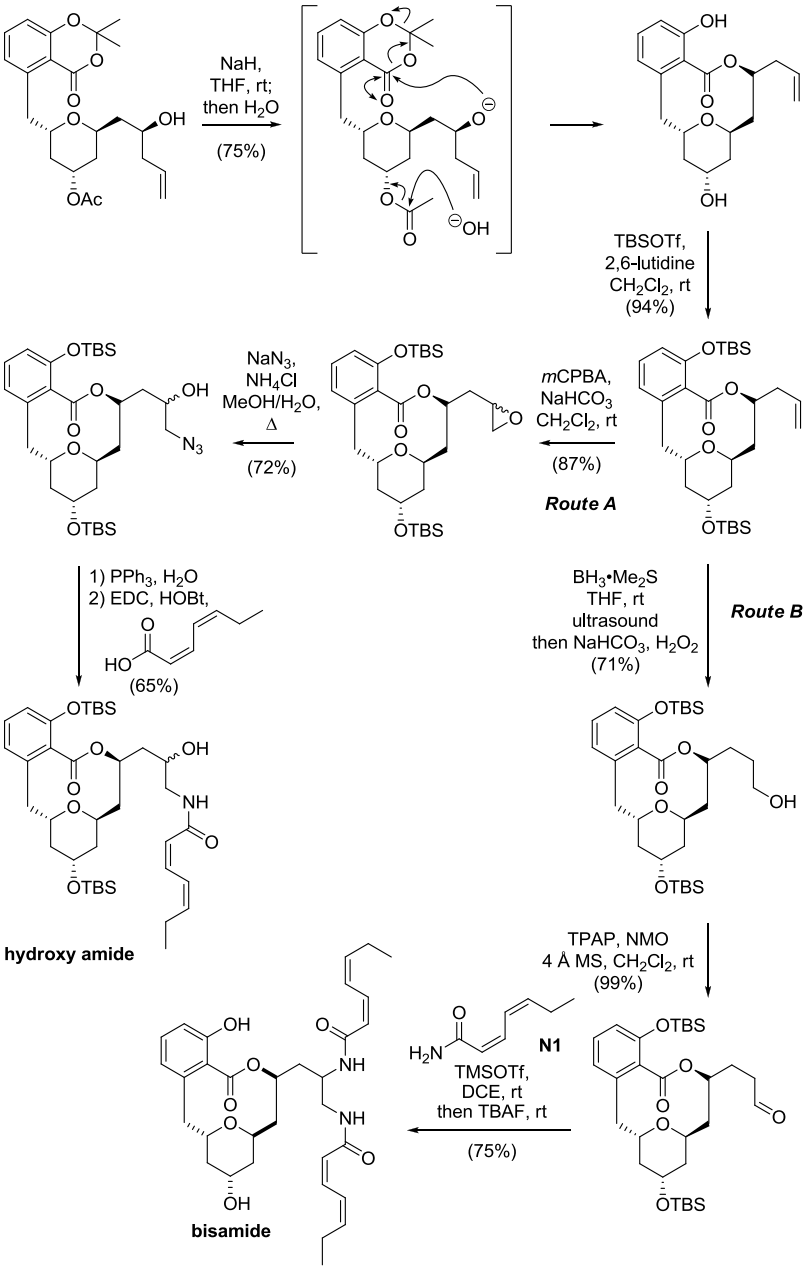


Figure 2.5 Failed attempts to install enamide side chain by Nicolaou and co-workers.

2.2.4 Formal synthesis of Apicularen A by Graetz and Rychnovsky[92]

In 2003, a formal synthesis of Apicularen A reported by Graetz and Rychnovsky featured a convergent strategy, utilizing a cyanohydrin acetonide coupling reaction. The necessary cyanohydrin acetonide was prepared from a *β*-ketoester[93] that underwent a "four-step in three-pot" synthesis and was obtained as a diastereomeric mixture of 1:1 ratio (**Figure 2.6**). On the other hand, its counterpart, the cyanohydrin acetonide electrophile was synthesized from a silylated vinylstannane reagent in four steps, inclusive of a tin-lithium exchange and a Finkelstein reaction, yielding a 1:1 mixture of diastereomeric silylated iodide intermediates.

The cyanohydrin acetonide was treated with LDA and subjected to coupling with its electrophilic iodide counterpart in the presence of *N,N*-dimethylpropyleneurea (DMPU). In the reduction step that followed, it is important to note that the excess lithium should be quenched with isoprene to prevent undesired reduction of vinyl silane to saturated silane and the ammonia solution should be neutralized immediately to avoid cleavage of TES ether.

The stereochemistry of 2,6-*anti*-THP ring was exclusively installed when 2,4-pentadienyltrimethylsilane was treated with an advanced acetal intermediate in the presence of $BF_3{\cdot}OEt_2$, providing quantitative yield. It is also worth mentioning the transesterification between the 2,6-*anti*-THP diol intermediate with a sensitive methyl 3-bromopropiolate that was effected by Otera's distannoxane catalyst[94], albeit in modest yield (44%) alongside with the generation of undesired diester side products in substantial amounts. Although it is possible to perform both the transesterification and the subsequent Diels-Alder together as a one-pot reaction, removal of excess methyl 3-bromopropiolate upon transesterification prior to the Diels-Alder reaction with DDQ would harvest better yield.

Graetz and Rychnovsky initially intended to complete the synthesis of this natural product by coupling the silylated phenol with primary amide **N1** under Porco's conditions[95] but to no avail. Henceforth, they transformed the silylated phenol to a

[92] Graetz, B. R.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3357.
[93] (a) Rychnovsky, S. D.; Rodriguez, C. *J. Org. Chem.* **1992**, *57*, 4793. (b) Claffey, M. M.; Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8267. (c) Kopecky, D. J. ; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420.
[94] Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2383.
[95] Shen, R.; Porco, J. A. *Org. Lett.* **2000**, *2*, 1333.

terminal olefin, of which De Brabander's synthetic route could be employed to achieve Apicularen A.

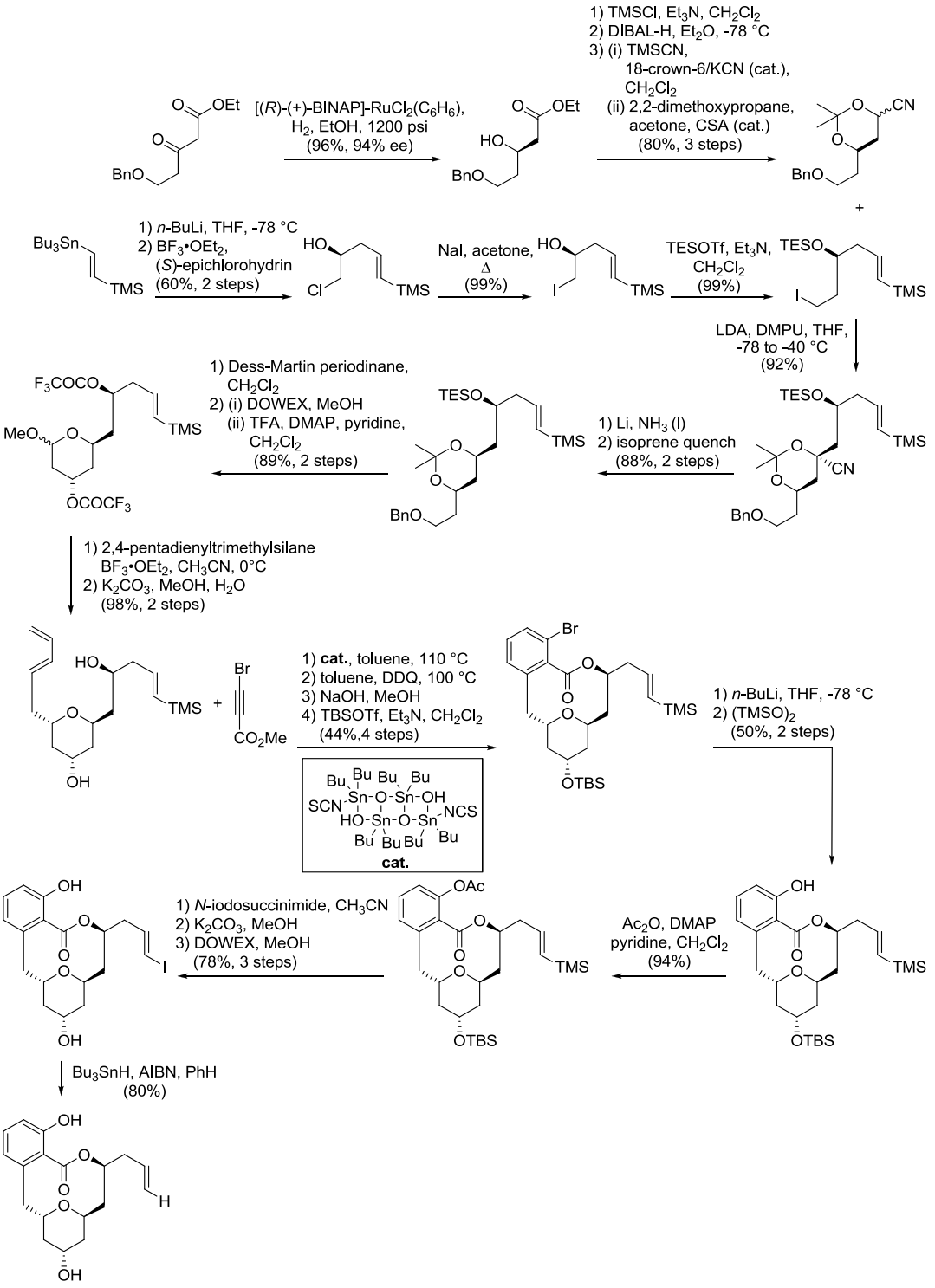


Figure 2.6 Formal synthesis of Apicularen A by Graetz and Rychnovsky.

2.2.5 Total Synthesis of Apicularen A by Maier and co-workers[74,96]

Maier and co-workers kicked off their total synthesis of Apicularen A by employing a four-component coupling reaction between a 1,3-dithiane, an acetylide, an epichlorohydrin and a terminal epoxide, giving rise to a terminal alkyne, which further underwent four more transformations to furnish an acetalized alkyne intermediate (**Figure 2.7**). The alkyne was hydroborated and then transmetallated with tributyltin chloride to exclusively provide (*E*)-vinylstannane in preparation for the requisite Stille coupling with salicylic triflate.

While the macrolactonization could be achieved with Yamaguchi's method in a size-selective manner[97], the yield remained mediocre. Hence, Maier and co-workers explored Trost and Chisholm's procedure[98], in which the carboxylic acid was esterified with ethoxyacetylene precursor in the presence of a ruthenium catalyst prior to macrolactonization by the treatment of sodium hydride, improving the yield from the range of 50% to 63%. Unconventionally, the 2,6-*anti*-THP ring was constructed only after macrolactonization occurred, using mercuric trifluoroacetate, instead of *N*-(phenylseleno)phthalimide that worked well for their previous model studies. This transannular etherification was completed in a matter of minutes and CH_2Cl_2 was substituted with THF as solvent. Reductive demercuration of the intermediate was then performed with lithium borohydride ($LiBH_4$) in the presence of triethylborane[99] to prevent retrocyclization from happening[100]. This strategy further validated the close connection between the salicylihalamide and apicularen.

After several transformations, the aldehyde intermediate was reacted with aluminium carboximidoate, which was generated *in situ* from an amide fragment reacting with DIBAL, thereby forming a diastereomeric mixture (1:1) of hemiaminals. Dehydration of the aforementioned mixture was effected by acetic anhydride and pyridine in refluxing THF, resulting in an *E/Z*-enamide mixture that could be separated upon purification into 46% and 15%, respectively. Upon deprotection of alcohols, the desired Apicularen A was accessed in approximately 24 steps with an overall yield no greater than 9%.

---

[96] (a) Kühnert, S. M.; Maier, M. E. *Org. Lett.* **2002**, *4*, 643. (b) Petri, A. F.; Bayer, A.; Maier, M. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 5821.
[97] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *44*, 3580.
[98] Trost, B, M.; Chisholm, J. D. *Org. Lett.* **2002**, *4*, 3743.
[99] Kang, S. H.; Lee, J. H.; Lee, S. B. *Tetrahedron Lett.* **1998**, *39*, 59.
[100] Griffith, R. C.; Gentile, R. J.; Davidson, T. A.; Scott, F. L. *J. Org. Chem.* **1979**, *44*, 3580.

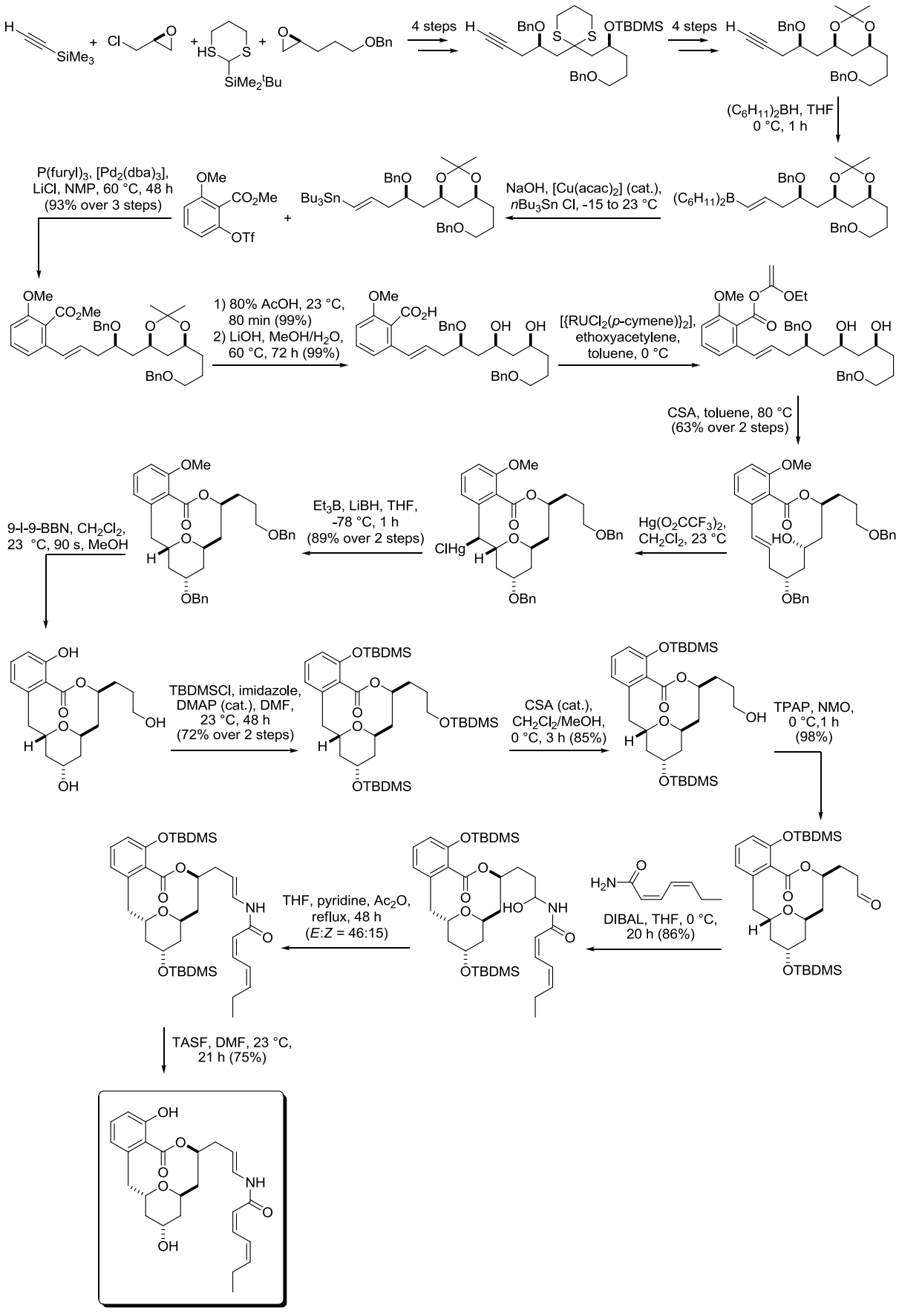


Figure 2.7 Total synthesis of Apicularen A by Maier and co-workers.

2.2.6 Formal Synthesis of Apicularen A by Rizzacasa and co-workers[101]

Rizzacasa's proposed strategy involved allylation of a racemic bis-silylether with (+)-Ipc_2Ballyl that successfully resolved the racemic mixture upon purification (**Figure 2.8**). They then proceeded with both the isomers to perform subsequent modifications in a parallel fashion. The allylated intermediates were transformed into stannane reagents that coupled with a benzyl bromide. Similar to Maier's approach, Rizzacasa and co-workers performed a Mitsunobu macrolactonization using sodium hydride[102] prior to transannular conjugate addition. They also took the liberty of installing a stable methyl ether in place of the free phenol, as the latter may interfere in the subsequent reactions.

Upon global desilylation and a selective oxidation of allylic alcohol, the resulting enones were subjected to refluxing deuterated chloroform, under the influence of acidic Amberlyst-15 to effect a stereoselective oxy-Michael addition. It is noteworthy that both enones converged to provide the anticipated crystalline 2,6-*anti*-pyranone in good yields and selectivities. This outcome is consistent with the previous MM2 calculations, where the 2,6-*anti*-THP ring in twist-boat conformation is more thermodynamically stable than the other three possible diastereomers by more than 10 kJ mol^{-1} under either acidic or basic environments. Rizzacasa and co-workers did attempt transannular conjugate addition in basic conditions in earlier synthetic studies to provide the desired pyranone, however, to no avail.

A non-selective reduction of pyranone was then performed with sodium borohydride in quantitative yield. After separating the undesired isomer from the racemic mixture, it was subjected to a revised Mitsunobu procedure, converting its alcohol into the correct stereochemistry. This formal synthesis of Apicularen A concluded with demethylation to access free phenol in the presence of 9-Iodo-9-borabicyclo[3.3.1]nonane (9-I-9-BBN)[85], affording the truncated core fragment in an overall yield of no more than 20%.

[101] (a) Hilli, F.; White, J. M.; Rizzacasa, M. A. *Tetrahedron Lett.* **2002**, *43*, 8507. (b) Hilli, F.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 1289. (c) Hilli, F.; White, J. M.; Rizzacasa, M. A. *Tetrahedron* **2011**, *67*, 5054.
[102] Mitsunobu,O. *Synthesis* **1981**, 1.

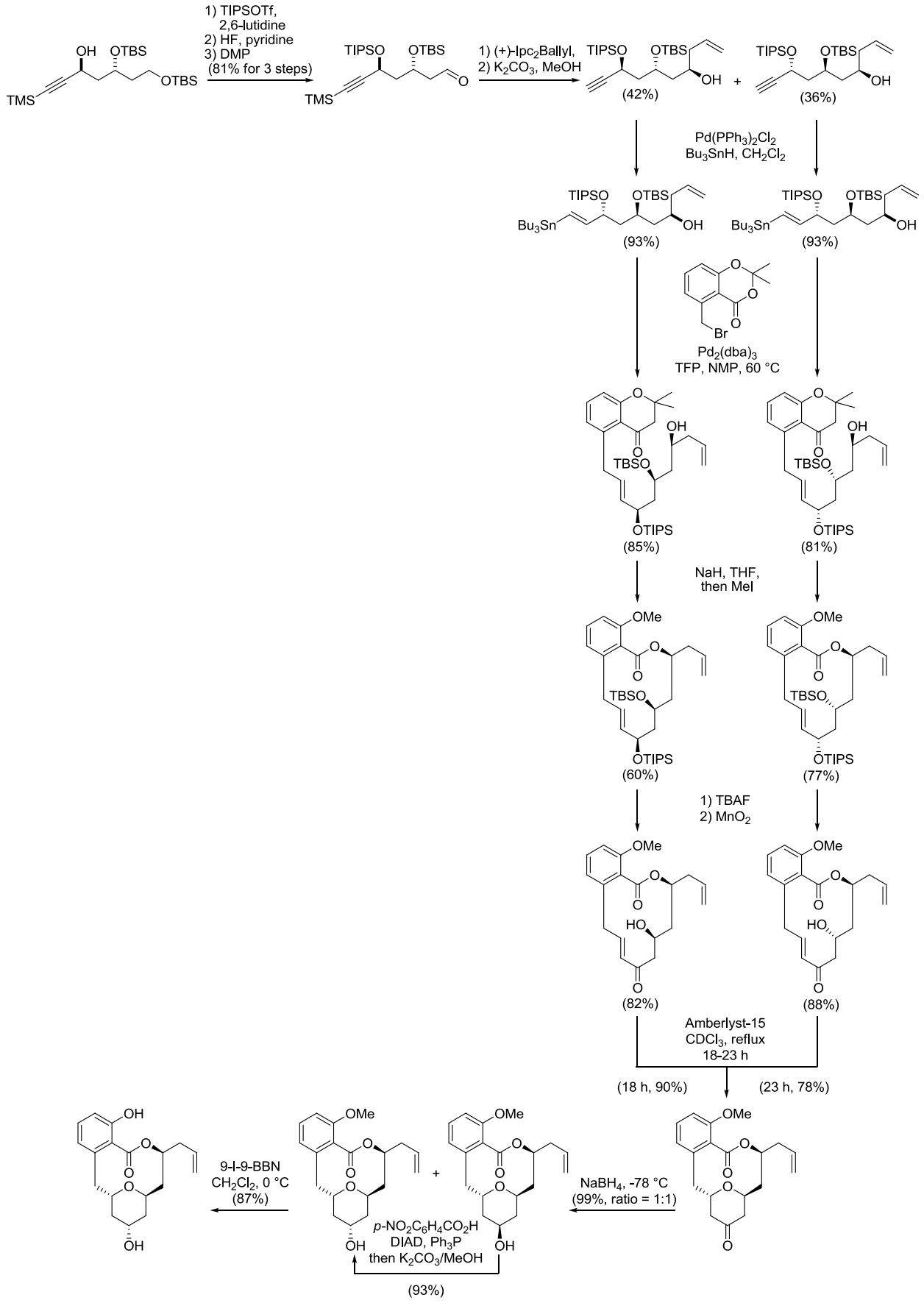


Figure 2.8 Formal synthesis of Apicularen A by Rizzacasa and co-workers.

2.2.7 Total Synthesis of Apicularen A by Su and Panek[103]

Stemming from Panek's previous findings[104], Su and Panek synthesized a 2,6-*anti*-dihydropyran core *via* [4+2]-annulation in the presence of TMSOTf in dichloromethane at -50 °C. In the model studies, they concluded that the stereochemical outcome is not only influenced by the relative stereochemistry of the crotylsilane's silicon and the adjacent -OTMS moiety, but the functional group attached to the crotylsilane also played an important role. After screening through a series of organosilanes, they found crotylsilane with methoxy moiety to provide the desired *anti* conformation while acetate and ester groups gave *syn* conformation as major products. They rationalized these findings by proposing the possible transition states shown in **Figure 2.9**.

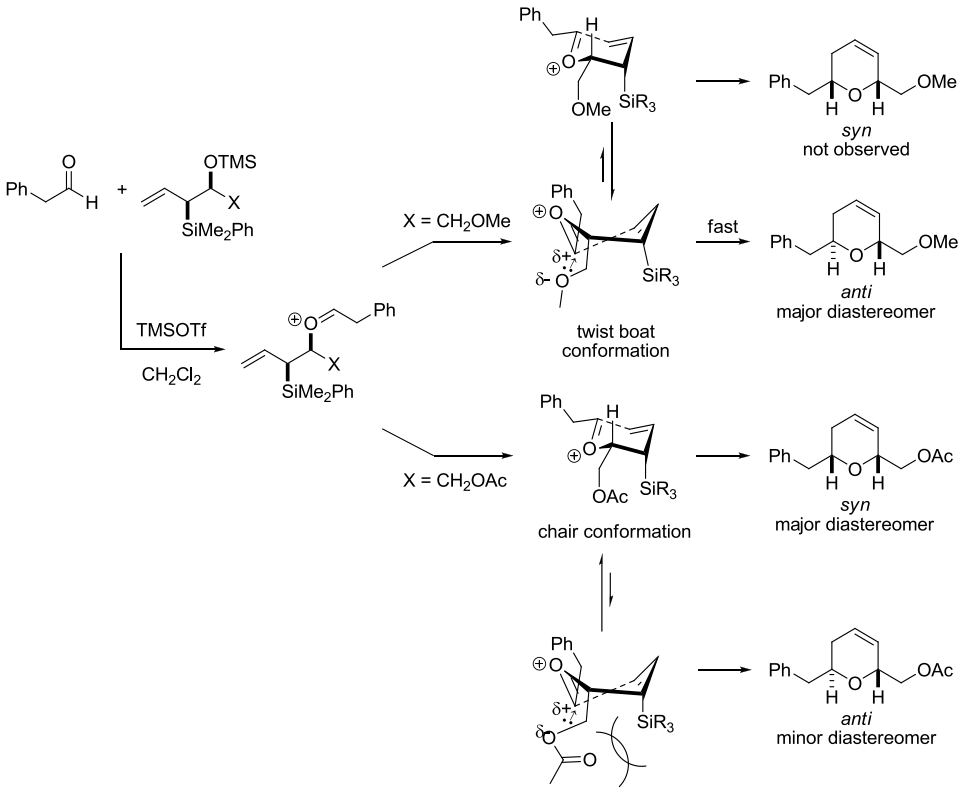


Figure 2.9 Possible transition states for Panek's [4+2]-annulation.

[103] Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425.
[104] Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836.

The silicon group was positioned pseudoaxially in the twist boat and axially in the chair conformations of the possible transition states, where optimal σ-π orbital overlap would occur, to stabilize β-carbocation resulting from the annulation process[105]. Unlike its acetate and ester counterparts, the relatively less bulky methoxy moiety has a non-bonding electron lone pair that may have favourable electrostatic interaction with the positively-charged oxocarbenium, thereby stabilizing the otherwise unfavourable twist boat conformer and expedited the ring formation.

The dihydropyran was then oxidized into an epoxide of which upon ring opening, resulted in secondary alcohol with the incorrect stereochemistry that was rectified using the Mitsunobu's procedure. In accordance to Porco's protocol, macrolactonization was eventually effected by subjecting the salicylic cyano methyl ester to sodium hydride after protecting the free acidic phenol.[106] Finally, the enamide side chain was installed by Porco's CuTC-catalyzed coupling reaction, tweaking the reaction temperature and addition of diamine ligand.[95,107]

This total synthetic route of Apicularen A designed by Su and Panek (**Figure 2.10**) involved approximately 21 steps, achieving an approximate overall yield of no more than 2%.

[105] Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677.
[106] Shen, R.; Lin, C. T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650.
[107] Shen, R.; Lin, C.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889.

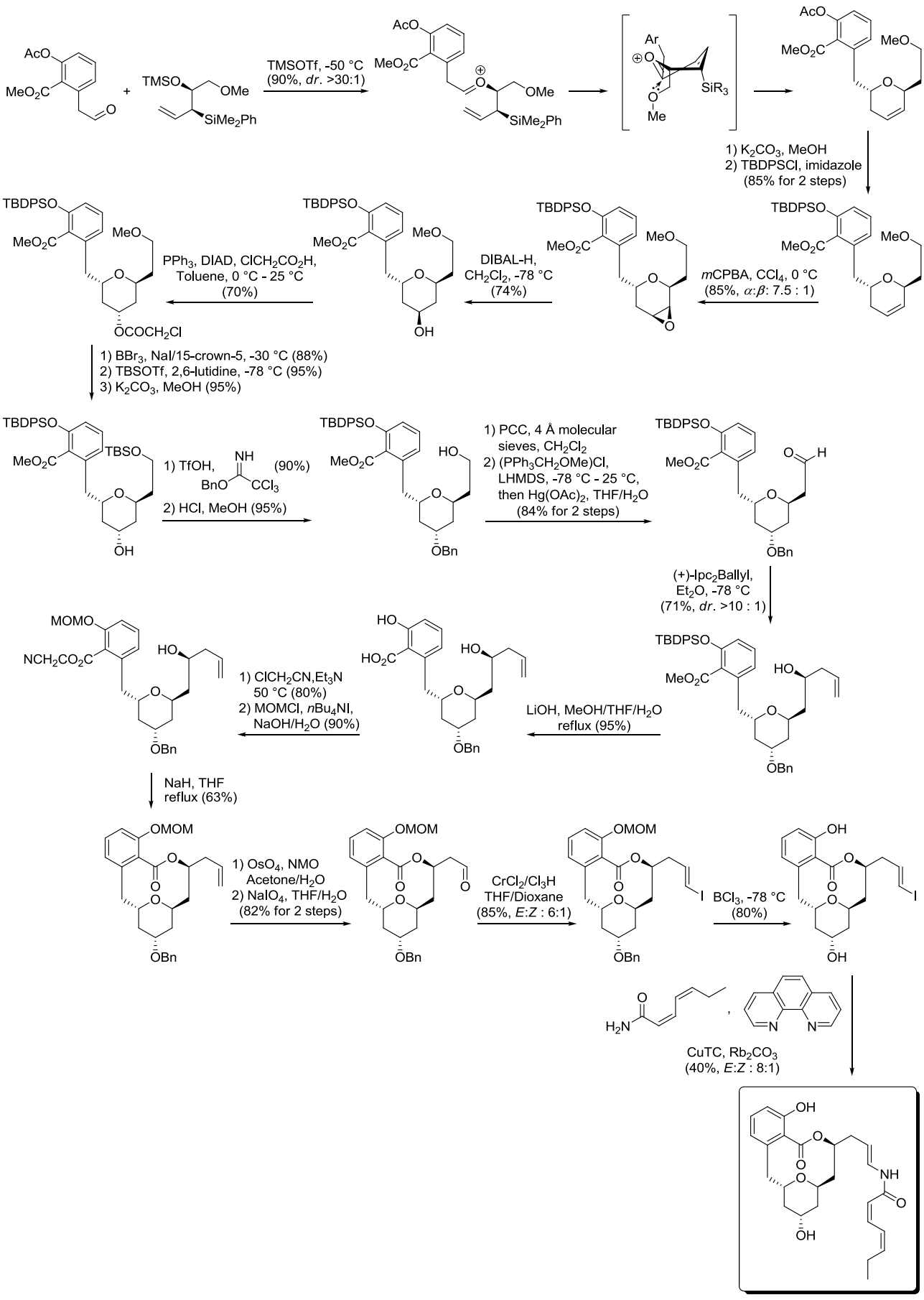


Figure 2.10 Total synthesis of Apicularen A by Su and Panek.

2.2.8 Formal Synthesis of Apicularen A by Li and O'Doherty[108]

Li and O'Doherty were interested in devising a *de novo* synthesis that builds the complex (-)-Apicularen A up from achiral starting materials with the assistance of asymmetric catalysts (**Figure 2.11**). Addition of paraformaldehyde upon lithiation of 1-hexyne provided a propargylic alcohol intermediate, which was treated with *in situ*-generated potassium 3-aminopropylamide (KAPA) to effect alkyne zipper reaction[109] and a triphenylphosphine-promoted isomerization of ynoate to (*E,E*)-dienoate at a later stage.

One of the highlights of this formal synthesis has to be the application of O'Doherty's four-step asymmetric bishydration procedure [110, 111] involving namely Sharpless' asymmetric dihydroxylation, formation of carbonate, palladium-catalyzed reduction as well as Evan's simulataneous diastereoselective hydration and diol protection[112], transforming (*E,E*)-dienoate into the desired benzylidene acetal intermediate in 37% yield over 4 steps. The ester moiety of the aforementioned benzylidene acetal was then reduced to its corresponding aldehyde and was subjected to a diastereoselective allylation with Leighton reagent.

On the other hand, the synthesis of styrene fragment featured a modified Suzuki-Miyaura[113] coupling using Molander's trifluoroborate[114]. Thereafter, both the styrene and allylated benzylidene acetal fragments were combined *via* an olefin metathesis catalyzed by second generation Grubbs reagent[115]. The resultant intermediate then had its diol deprotected and its ester hydrolyzed to an acid, which was subsequently subjected to a Yamaguchi lactonization variant using 2,4,6-trichlorobenzoyl chloride and finally a transannular etherification under basic conditions, completing the formal synthesis in 17 steps with an overall yield of the truncated macrolide in 8%.

---

[108] Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 6087.
[109] (a) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891. (b) Kimmel, T.; Becker, D. *J. Org. Chem.* **1984**, *49*, 2494.
[110] (a) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777. (b) Tosaki, S. Y.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 495. (c) Smith, C. M.; O'Doherty, G. A. *Org. Lett.* **2003**, *5*, 1959.
[111] (a) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 1049. (b) Li, M.; O'Doherty, G. A. *Org. Lett.* **2001**, *8*, 3987.
[112] Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446.
[113] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
[114] Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107.
[115] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

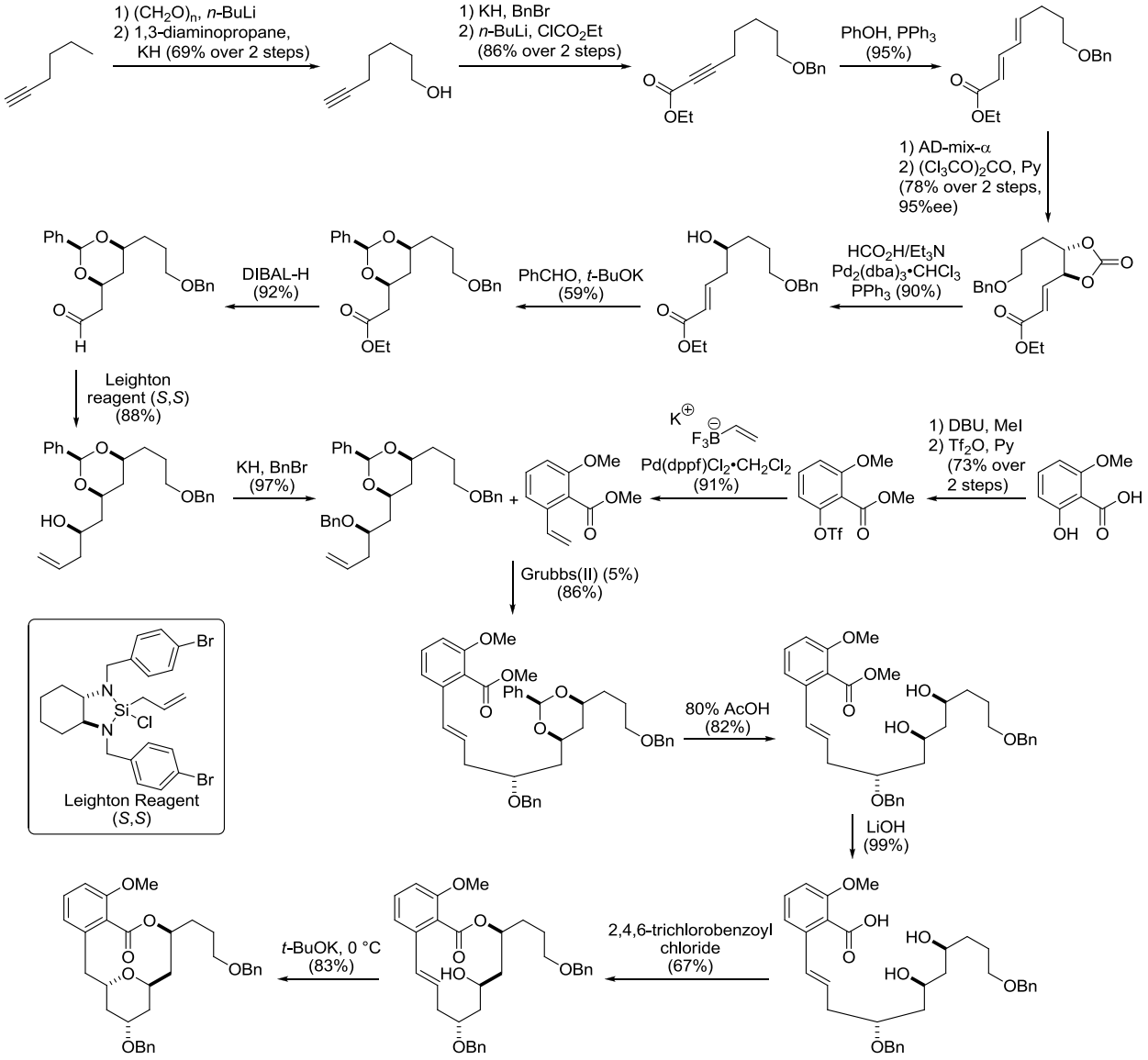


Figure 2.11 Formal synthesis of Apicularen A by Li and O'Doherty.

While Li and O'Doherty worked on their *de novo* formal synthesis of Apicularen A, Yadav and co-workers envisioned a strategy that is very similar to that of the former. In view of the synthetic effort reported by Li and O'Doherty, Yadav and co-workers halted any further development of their synthetic endeavor. Nonetheless, they reported a complementary approach to access the common allylated benzylidene acetal intermediate (**Figure 2.12**). [116]

Yadav and co-workers initiated the synthetic route by subjecting an allyl alcohol to Sharpless asymmetric epoxidation with diisopropyl tartrate [(+)-DIPT], resulting in an epoxy alcohol that underwent regioselective reduction in the presence of sodium

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

bis(2-methoxy-ethoxy)aluminium hydride (Red-Al®) to provide a 1,3-diol. The primary alcohol was then chemoselectively oxidized with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) in the presence of bis(acetoxy)iodobenzene (BAIB) and was subsequently elongated with a two-carbon Wittig reagent to provide (*E*)-vinylester in 50%. The inherent 1,3-diol was reconstructed and protected before preparations for allylation were executed. Yadav and co-workers managed to resolve the racemic mixture of resulting diastereomeric alcohols *via* a series of reactions to afford a 4:1 mixture instead, favouring the desired diastereomer, which was then protected for further transformations.

This route to allylated benzylidene acetal intermediate required 10 steps and achieved an approximate overall yield of 8%. Yadav's approach is less attractive when compared to that of Li and O'Doherty, which provided the same intermediate in 19%, albeit a slightly longer route of 12 steps.

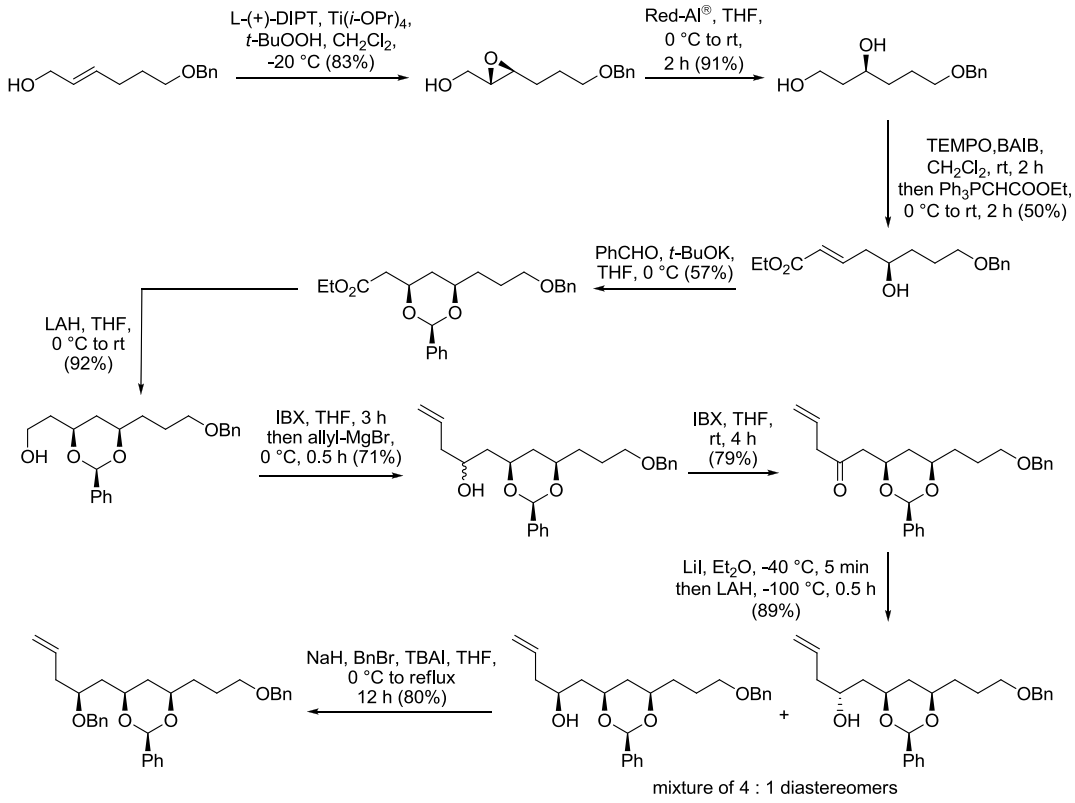


Figure 2.12 Synthesis of allylated benzylidene acetal intermediate by Yadav and co-workers.

2.2.9 Formal Synthesis of Apicularen A by Tae and co-workers[117]

This formal synthetic route by Tae and co-workers was intended to achieve the vinyl iodide intermediate, prior to the imperative coupling with enamide, which was featured in Su and Panek's total synthesis of Apicularen A (**Figure 2.13**). Adopted from an earlier report[118], 1,6-heptadien-4-ol was converted to a chiral hydroxyepoxide *via* Jacobsen's hydrolytic kinetic resolution (HKR) protocol[119]. The hydroxy moiety had its stereochemistry inverted *via* a Mitsunobu reaction and subsequently being protected. Upon attaching an alkynoate, the intermediate was subjected to saponification with an allylated alcohol fragment that was generated from an epoxide of (*S*)-malic acid origin[120]. Tae and co-workers then performed a Diels-Alder reaction under neat conditions, constructing the salicylic core structure, thereby confining the two terminal olefins in closer proximity to each other to enable a more effective macrolactonization *via* a ring-closing metathesis catalyzed by second-generation Grubbs reagent.

After obtaining the desired macrolactone intermediate, the TBS group was desilylated to unmask the alcohol that would undergo transannular etherification. The mercury(II)-mediated annulation that worked well in their model studies, unfortunately did not perform favourably with the target molecule. Tae and co-workers turned to applying phenylselenyl chloride in the presence of pyridine, henceforth obtaining 2,6-*anti*-THP exclusively.[121] They proceeded to install the vinyl iodide moiety by removing the benzyl protecting group, then sequentially performed Dess-Martin oxidation and Takai iodo-olefination, obtaining the desired (*E*)-isomer as the major product (*E:Z* = 2.2:1). Finally, the removal of protecting groups, namely the *p*-methoxyphenyl and methyl moieties with the treatment of ceric ammonium nitrate and 9-iodo-9-BBN respectively, provided Tae and co-workers with the desired vinyl iodide intermediate in an overall yield of 6% after 17 steps. Su and Panek previously achieved the same intermediate in 21 steps with 4% yield.

---

[117] Jung, Y.-H.; Kim, Y.-J.; Lee, J.; Tae, J. *Chem. Asian. J.* **2007**, *2*, 656.
[118] (a) Rádl, S.; Stach, J.; Hajiccek, J. *Tetrahedron Lett.* **2002**, *43*, 2087. (b) Kim, Y.-J.; Tae, J. *Synlett* **2006**, 61.
[119] (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.
[120] (a) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449. (b) Fürstner, A.; Fenster, M. D. B.; Fasching, B.; Godbout, C.; Radkowski, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 5510.
[121] (a) Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J.; Barnetter, W. E.; Lysenko, Z.; Joullie, M. M. *J. Am . Chem. Soc.* **1980**, *102*, 3784. (b) Fettes, A.; Carreira, E. M. *Angew. Chem.* **2002**, *114*, 4272; *Angew. Chem. Int. Ed.* **2002**, *41*, 4098.

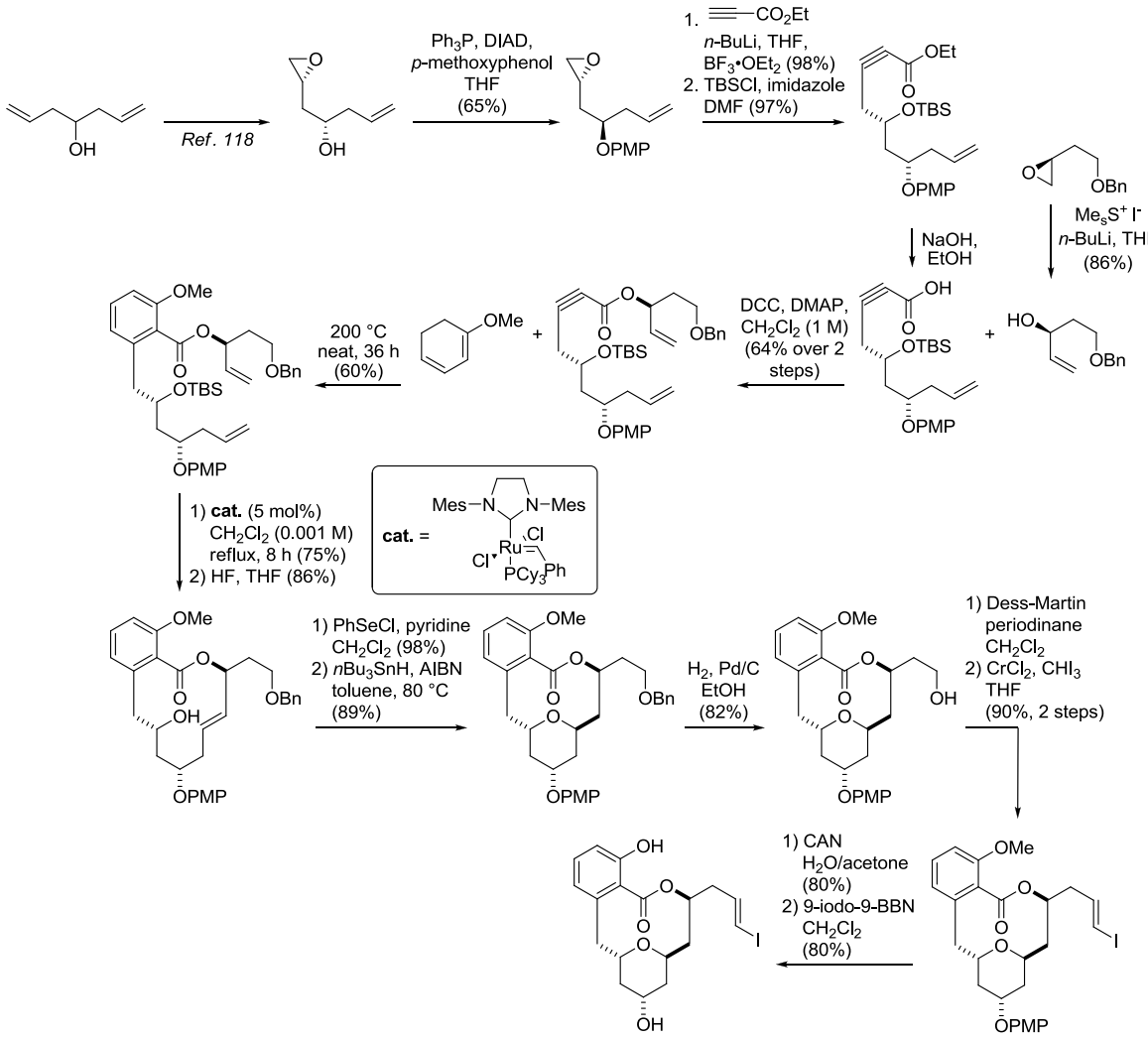


Figure 2.13 Formal synthesis of Apicularen A by Tae and co-workers.

2.2.10 Synthetic studies of Apicularen A by Poniatowski and Floreancig[122]

Inspired by the total synthesis of Apicularen A by Rizzacasa and co-workers, in which transannular etherification of the other C13-epimer leading to the same desired 2,6-*anti*-tetrahydropyranone was described, Poniatowski and Floreancig proposed that isomerization of 2,6-*syn*-tetrahydropyranone upon macrolactonization could likewise result in the desired 2,6-*anti*-THP ring. Poniatowski and Floreancig further postulated that the requisite 2,6-*syn*-tetrahydropyranone could be generated from a homobenzylic ether *via* an electron-transfer-initiated annulation, where the stabilization of radical C13 carbocation is crucial since the geminal methyl moieties present may weaken C8-C9 bond[123], thus favouring the oxidative cleavage of the benzylic carbon-carbon bond[124].

The synthesis of 2,6-*syn*-tetrahydropyranone precursor began with constructing salicylic fragment by subjecting hydroxypyrone to cycloaddition with allenedicarboxylate and subsequently reducing the benzylic ester selectively into aldehyde[125] (**Figure 2.14**). The salicylic fragment was then combined with a diol fragment *via* Noyori's acetalization[126] in the presence of TMSOTf. The racemic diol fragment, on the other hand, was prepared from *p*-fluoroanisole, which was coupled with isobutyronitrile through a Pfizer's base-promoted coupling reaction[127], a subsequent nitrile reduction, allylation of the resulting aldehyde and finally a one-pot reaction of ozonolysis, followed by a reduction with sodium borohydride.

Propargylation of acetal with allenyltrimethylsilane was optimized with Myer's protocol[128], using precooled titanium(IV) chloride to yield the desired alkyne in 50% while suppressing an unfavourable intramolecular Friedel-Crafts reaction. Upon methylation of the phenol moiety and a subsequent ruthenium-promoted addition of AcOH across the terminal alkyne in Markovnikov fashion, the intermediate was treated with cerium(IV) ammonium nitrate at 40 °C, initiating a cyclization into the desired 2,6-*syn*-tetrahydropyranone *via* single-electron oxidation.

---

[122] Poniatowski, A. J.; Floreancig, P. E. *Synthesis* **2007**, 2291.
[123] Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255.
[124] (a) Seiders, J. R. II; Wang, L.; Floreancig, P. E. *J. Am. Chem. Soc.* **2003**, *125*, 2406.
(b) Wang, L.; Seiders, J. R. II; Floreancig, P. E. *J. Am. Chem. Soc.* **2004**, *126*, 12596.
[125] Rech, J. C.; Floreancig, P. E. *Org. Lett.* **2005**, *7*, 5175.
[126] Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.
[127] Caron, S.; Vazquez, E.; Wojcik, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 712.
[128] Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.

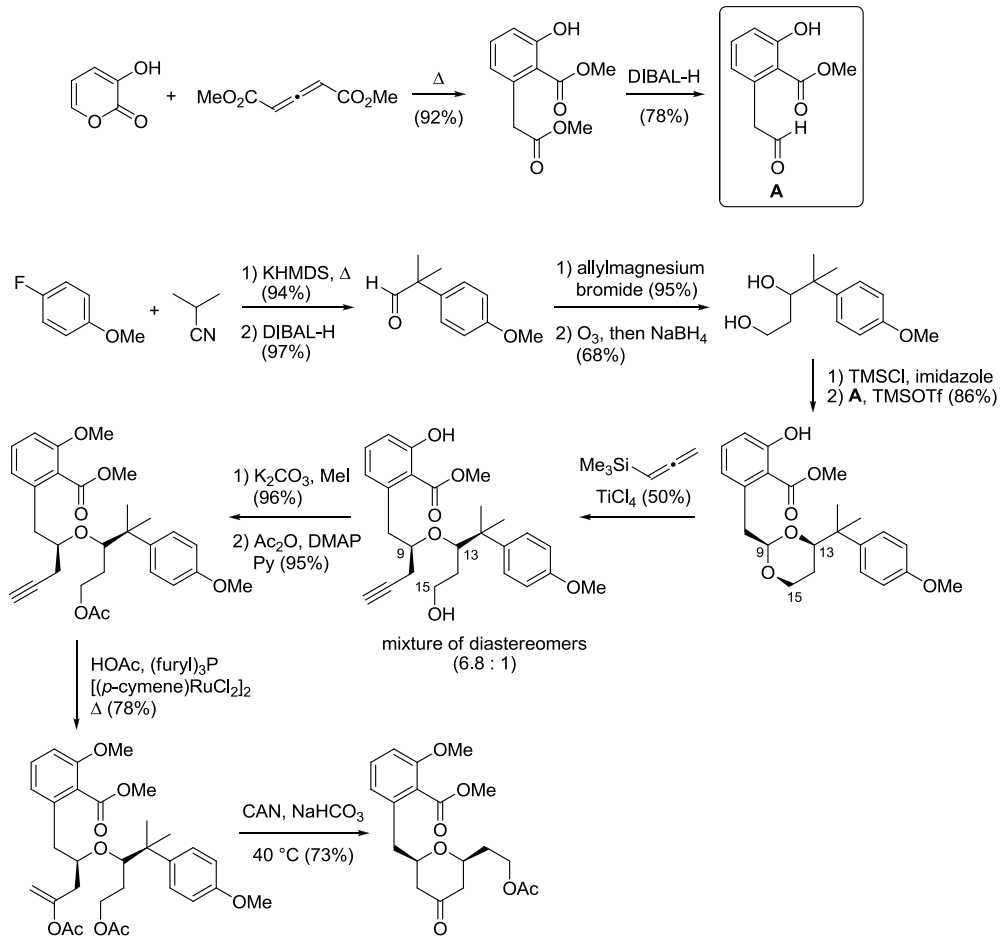


Figure 2.14 Synthetic studies of Apicularen A by Poniatowski and Floreancig.

Poniatowski and Floreancig successfully synthesized their desired 2,6-*syn*-tetrahydropyranone in 11 steps with the yield of 14%. However, there is no further reports by Poniatowski and Floreancig regarding the progress on this synthetic route or model studies pertaining to the hypothesized isomerization of 2,6-*syn*-THP to the corresponding 2,6-*anti*-THP thereafter.

2.2.11 Total Synthesis of Apicularen A by Palimkar and Uenishi [76,129]

The molecular architecture of Apicularen A sparked vested interest of Palimkar and Uenishi, who were eager to demonstrate the applicability of their recent Pd(II)-catalyzed cyclization methodology.[130,131] The initial stage of their strategy required two main fragments – namely the iodoalkene fragment **A** and an aldehyde fragment **B** (**Figure 2.15**).

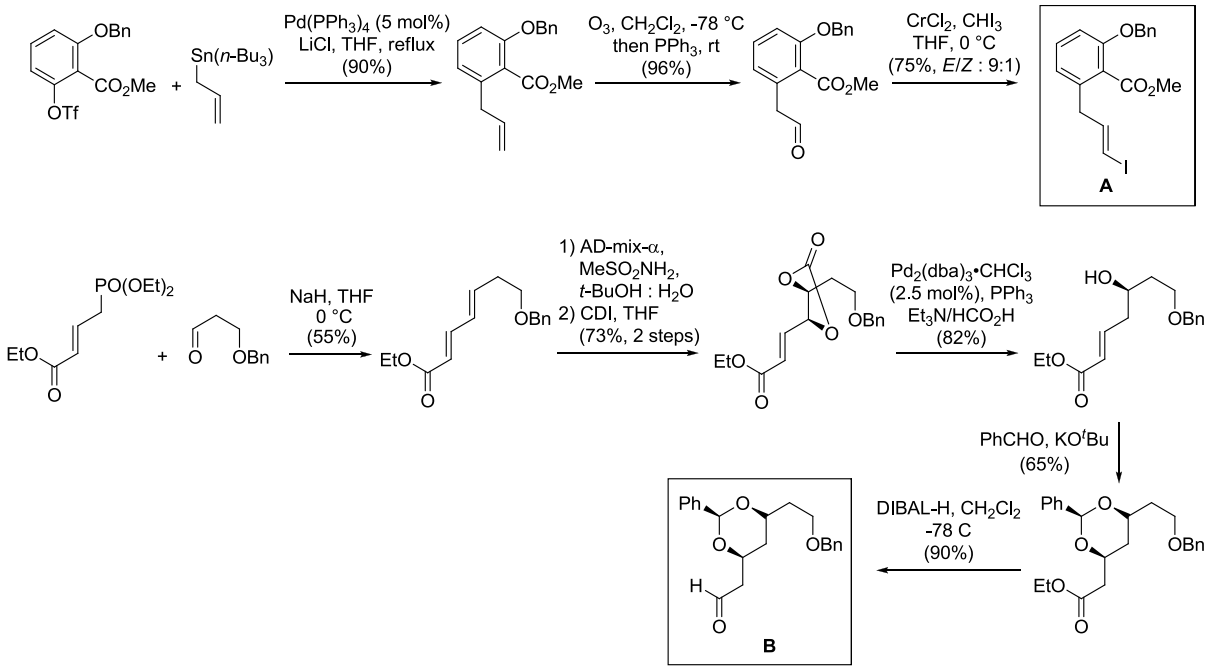


Figure 2.15 Preparation of Precursors in the Total Synthesis of Apicularen A by Palimkar and Uenishi.

The iodoalkene **A** was achieved in three steps from a salicylic precursor by subjecting it to a Stille coupling with allyltributyltin, ozonolysis and finally a Takai olefination. On the other hand, the construction of aldehyde **B** commenced with a Horner-Wadsworth-Emmons reaction between a stabilized ylide and a propanal, to afford a (2*E*,4*E*)-dienoate. This intermediate then underwent Sharpless asymmetric dihydroxylation and a subsequent treatment of carbonyldiimidazole (CDI), resulting in

[129] (a) Palimkar, S. S.; Uenishi, J. *Org. Lett.* **2010**, *12*, 4160.
[130] (a) Uenishi, J.; Ohmi, M.; Ueda, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1299. (b) Kawai, N.; Lagrange, J.-M.; Ohmi, M.; Uenishi, J. *J. Org. Chem.* **2006**, *71*, 4530. (c) Kawai, N.; Lagrange, J.-M.; Uenishi, J. *Eur. J. Org. Chem.* **2007**, 2808. (d) Uenishi, J.; Vikhe, Y. S.; Kawai, N. *Chem. – Asian J.* **2008**, *3*, 473.
[131] (a) Uenishi, J.; Ohmi, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 2756. (b) Hande, S. M.; Uenishi, J. *Tetrahedron Lett.* **2009**, *50*, 189.

a cyclic carbonate, which was reduced into *δ*-hydroxy enoate when treated with formic acid and a Pd catalyst. The resulting *α*,*β*-unsaturated ester was converted to benzylidene acetal according to Evans protocol[132] and finally obtaining the requisite aldehyde **B** upon reduction of ester moiety with DIBAL.

The two fragments were then combined by Nozaki-Hiyama-Kishi (NHK) coupling[133], providing a diastereomeric mixture of allylic alcohols in ratios 1.3:1, giving yields of 43% and 32% respectively (**Figure 2.16**). Fortunately, the undesirable isomer could be "corrected" *via* a two-step protocol involving oxidation by Dess-Martin periodinane and a reduction in a diastereofacial selective manner by proline-derived Corey-Bakshi-Shibata catalyst, (*R*)-CBS[134]. When the precursor triol was unmasked upon deprotection, Uenishi's featured transannular etherification was effected with the treatment of catalytic $PdCl_2(CH_3CN)_2$, transferring the existing 1,3-chirality to exclusively provide 2,6-*anti*-dihydropyran in 72%.

Palimkar and Uenishi then utilized Yamaguchi lactonization to construct the macrolactone ring after obtaining the *seco*-acid from the hydrolysis of methyl ester with LiOH. They proceeded further with an oxymercuration, which was immediately followed by a reductive demercuration that selectively mounted the desired *α*-hydroxy moiety in diastereomeric ratio (with respect to the corresponding *β*-hydroxy) of 3:1.

The macrolactone intermediate underwent a few more manipulations in preparation for the anticipated attachment of the (*Z*,*Z*-enamide) with the vinyl iodide intermediate, by the application of a modified Buchwald's procedure[135]. The coupling reaction successfully took place in the presence of excess CuI and DMF, at room temperature, garnering an excellent yield of 90%, whilst cleaving the acetate moiety simultaneously. Apicularen A was finally achieved upon desilylation of the *α*-hydroxy moiety, in an overall yield of 2% after 19 steps from aldehyde precursor of intermediate **B**.

[132] Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446.
[133] (a) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.
[134] Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986.
[135] Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667.

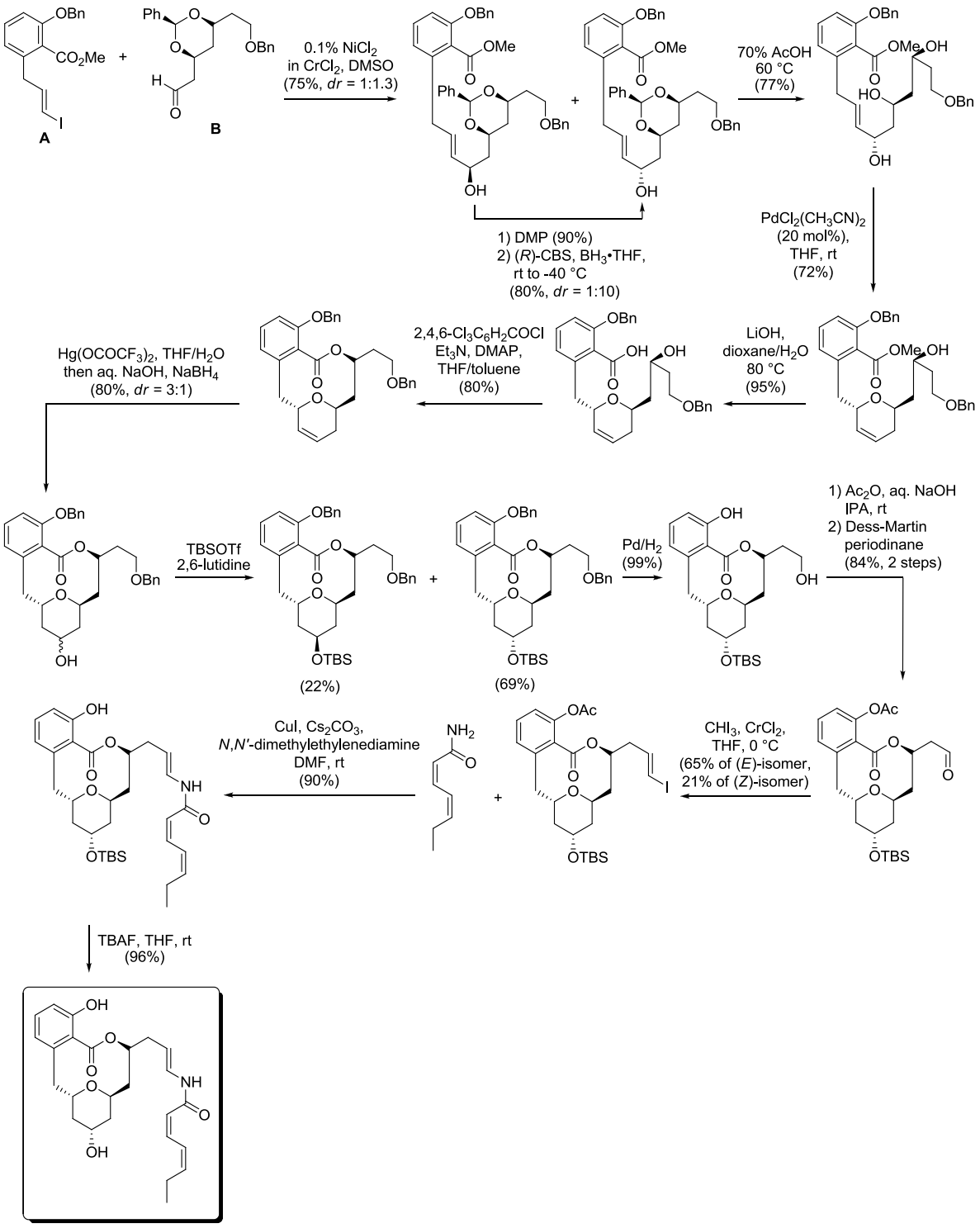


Figure 2.16 Total Synthesis of Apicularen A by Palimkar and Uenishi.

2.2.12 Summary of Reported Synthetic Studies of Apicularen A

Contributor	Type/Order of Synthesis	Protocol Used in the Construction of			Approximate Overall Yield
		(A) 2,6-*anti*-THP	(B) Macrolactone	(C) *Z,Z*-diene enamide	
De Brabander	Total/ A → B → C	Hetero-Diels-Alder with Jacobsen's catalyst and Danieshefsky's diene; then addition of vinylmagnesium bromide.	Sodium hydride esterification.	Coupling of isocyanate and diene.	0.4% (22 steps)
Taylor	Formal/ A → B	D-glucal derivative; then TMSOTf-mediated addition of allylTMS.	DCC-DMAP esterification.	n/a.	0.04% (28 steps)
Nicolaou	Total/ A → C → B	Addition of acetal-like fragments *via* repetitive allylation and ozonolysis; then $BF_3{\cdot}OEt_2$-assisted addition of allylTMS.	Sodium hydride esterification.	Takai iodo-olefination; then coupling of amide in the presence of CuTC-Rb_2CO_3.	5% (18 steps)
Rychnovsky	Formal/ A → B	$BF_3{\cdot}OEt_2$-mediated addition of 2,4-pentadienyltrimethylsilane to acetal intermediate.	Otera's distannoxane catalyzed-transesterification with a sensitive methyl 3-bromopropiolate.	n/a.	4% (26 steps)
Maier	Total/ B → A → C	Mercuric trifluoroacetate-mediated transannular etherification.	Trost-Chisholm macrolactonization.	Dehydration of hemiaminal.	<9% (24 steps)

Contributor	Type/Order of Synthesis	Protocol Used in the Construction of			Approximate Overall Yield
		(A) 2,6-*anti*-THP	(B) Macrolactone	(C) *Z,Z*-diene enamide	
Rizzacasa	Formal/ B → A	Amberlyst-15-mediated transannular etherification.	Sodium hydride- mediated Mitsunobu esterification.	n/a.	20% (14 steps)
Panek	Total/ A → B → C	[4+2] annulation between aldehyde and crotylsilane in the presence of TMSOTf	Sodium hydride- mediated esterification.	Takai iodo-olefination; then Porco's CuTC-catalyzed coupling of amide in the presence of Rb_2CO_3.	<2% (21 steps)
O'Doherty	Formal/ B → A	*t*-BuOK-mediated transannular etherification.	Modified Yamaguchi lactonization with 2,4,6-trichlorobenzoyl chloride.	n/a.	8% (17 steps)
Tae	Formal/ B → A	Transannular etherification with phenylselenyl chloride.	2nd-generation Grubbs' reagent catalyzed-ring-closing metathesis.	n/a.	6% (17 steps)
Floreancig	Synthetic studies/ A	Cyclization initiated by CAN-mediated single-electron oxidation, forming 2,6-***syn***-THP.	n/a.	n/a.	14% (11 steps)
Uenishi	A → B → C	$PdCl_2(CH_3CN)_2$-catalyzed transannular etherification.	Yamaguchi lactonization with 2,4,6-trichlorobenzoyl chloride.	Modified Buchwald's CuI coupling reaction.	2% (19 steps)

Chapter Three

Our Efforts Towards Total Synthesis of Apicularen A

THIS PAGE IS INTENTIONALLY LEFT BLANK.

3.1 Introduction

In line with the burgeoning development in our research group's methodologies to access cyclic ethers (Section 1.3.4), it would be more practical if we could demonstrate their applicability in syntheses of macromolecules and natural products. Apicularen A is one of the few natural products containing cyclic ether framework that we were interested in. By investigating Apicularen A, we initially aimed to apply our indium complex-promoted Prins cyclization to access the 2,6-*anti*-THP core fragment. However, due to some unforeseen circumstances, the intramolecular approach, in which we intended to apply the aforementioned Prins cyclization, did not follow through. We then embarked on a revised strategy – an intermolecular approach involving a Mukaiyama-Michael addition reaction. In this chapter, we recount our synthetic efforts towards the total synthesis of Apicularen A thus far and put forward our plan for future works from thereon.

3.2 The Intramolecular Approach[136]

3.2.1 Retrosynthetic analysis

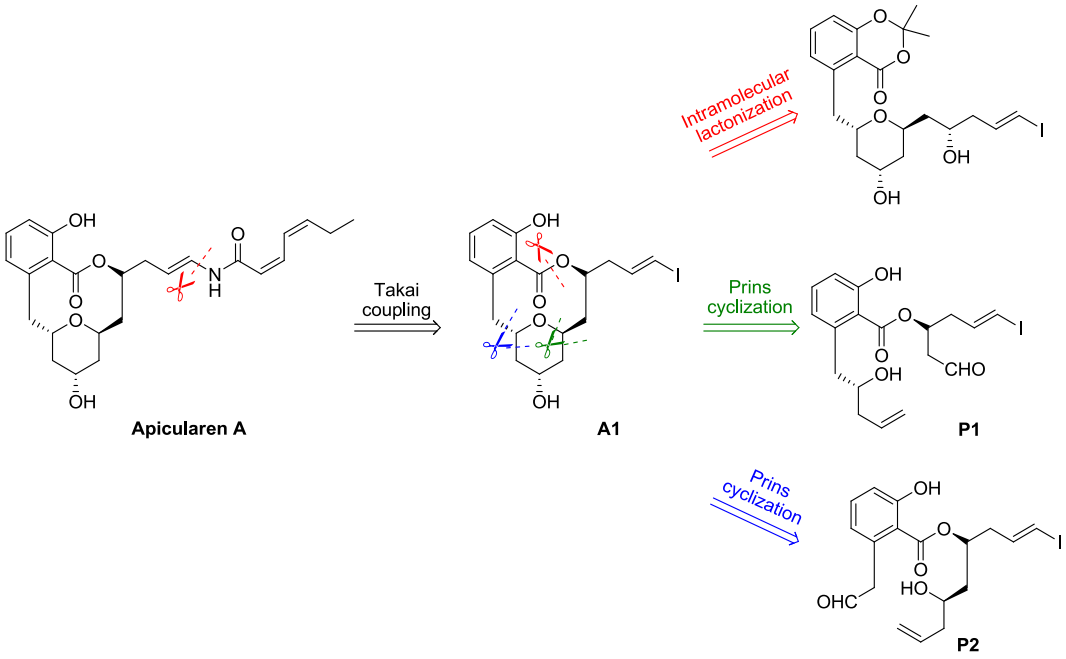


Figure 3.1 Retrosynthetic analysis for intramolecular approach towards Apicularen A.

As with most reported synthetic route, we intended to attach the highly unsaturated amide side chain *via* Takai coupling towards the final stages of the total synthesis. Next, we focused on the macrocyclic core fragment **A1**, in which we envisioned three plausible disconnections – one was originated from an intramolecular lactonization while the other two were devised from Prins cyclization (**Figure 3.1**). The synthetic equivalents **P1** and **P2** intermediates were particularly appealing, considering that we could demonstrate the practicality of our Prins cyclization methodologies.

We postulated that the ring strain resulting from the oxonium ion formation might be able to orientate the transition state to favour 2,6-*anti*-THP configuration (**Figure 3.2**), overriding the then-predominant 2,6-*syn*-THP adducts that were yielded from the Prins cyclization methodologies we have developed until the year 2006. It is noteworthy that the more recent reports of our group's Prins cyclization, which are

[136] Chan, L. J. Towards the Total Synthesis of Apicularen A. Masters Thesis, Nanyang Technological University, Singapore, 2008.

more capable of achieving 2,6-*anti*-THP selectively, were not available at the time we embarked on our synthetic studies of Apicularen A and hence, were not considered for this endeavor.

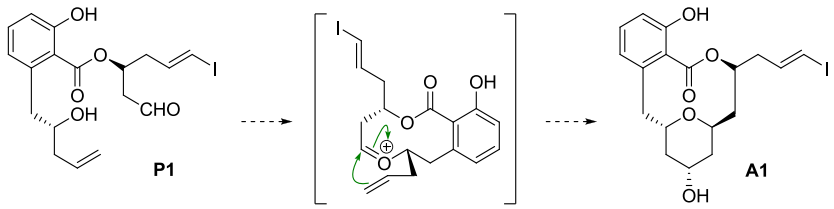


Figure 3.2 Hypothetical Prins cyclization *via* ring-strained oxonium transition state to favour 2,6-*anti*-THP configuration.

3.2.2 Synthetic route

We began our synthetic route by preparing a modified intermediate **P1** *via* esterification of two main fragments – an alcohol **P1-1**, which was derived from 1,3-propanediol, and a carboxylic acid **P1-2**, from 2,6-dihydroxybenzoic acid (**Figure 3.3**).

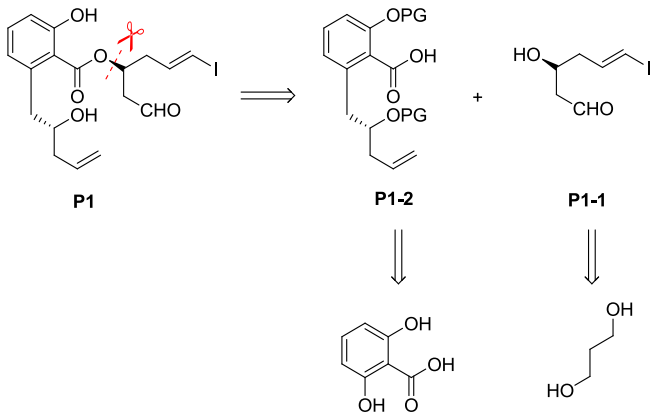


Figure 3.3 Retrosynthetic analysis of intermediate **P1**.

1,3-Propanediol was monoprotected with benzyl moiety prior to oxidation by Dess-Martin periodinane, resulting in the desired aldehyde in 65% over two steps. Thereafter, the aldehyde was subjected to allylation with allyl bromide in the presence of zinc and provided quantitative yield of a racemic mixture of allylated intermediate. The secondary alcohol was then protected by TBS moiety and subsequently being subjected to ozonolysis to convert the terminal olefin to aldehyde. Upon stirring with

methanol in presence of catalytic amount of camphorsulfonic acid, the aldehyde was protected in a methyl acetal form with a concomitant removal of TMS moiety, revealing the secondary alcohol **P1-1**. The required fragment **P1-1** was obtained in an overall yield of 25% (**Figure 3.4**).

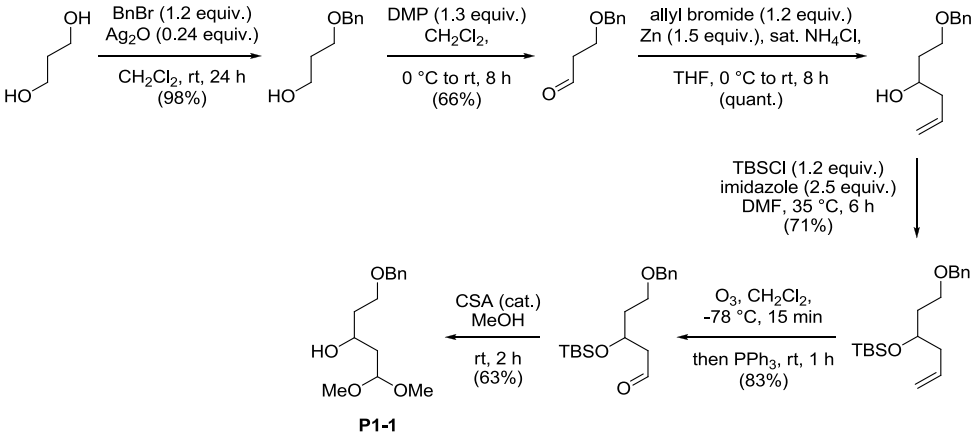


Figure 3.4 Synthesis of alcohol fragment **P1-1**.

The keystone of the carboxylic acid fragment **P1-2**, 2,6-dihydroxybenzoic acid, had its carboxylic acid and one of its hydroxy moieties simultaneously protected as an acetonide while the remaining hydroxy moiety was activated into a triflate as a good leaving group, in preparation for allylation with allyltributyltin *via* Stille coupling (**Figure 3.5**). The consequent terminal alkene underwent ozonolysis and a second allylation with allyl bromide in the presence of zinc. The resultant secondary alcohol was then protected with TMS group, thus providing fragment **P1-2** in an overall yield of 42%.

Having both the necessary fragments at hand, we successfully effected an esterification between fragments **P1-1** and **P1-2** with a strong base, sodium bis(trimethylsilyl)amide (NaHMDS), thereby resulting in the desired intermediate **P1'** in 81% yield. Excitedly, we attempted our Prins cyclization reaction conditions[69] on **P1'** intermediate but to our dismay, the Prins cyclization did not proceed as desired. We rationalized that the acidity of free phenol might have a detrimental effect on the Prins cyclization. Henceforth, we protected the free phenol with a TBS moiety and resubjected it to our Prins cyclization reaction conditions. Unfortunately, the protection did not improve the situation and the desired core macrolactone fragment **A1'** remained elusive. We then synthesized intermediate **P2'** and subsequently subjected it to the Prins cyclization conditions as well. Disappointingly, our efforts were futile.

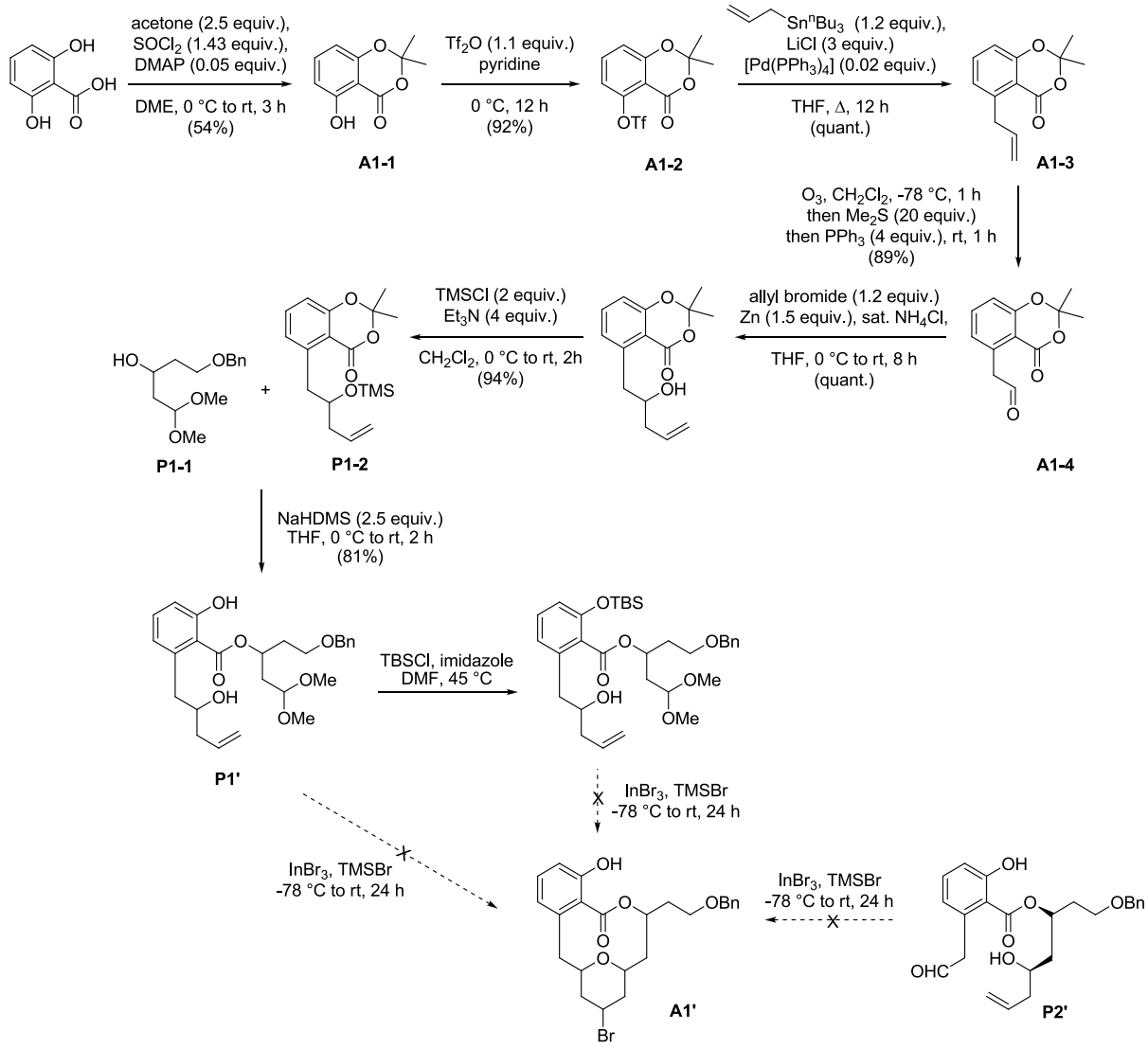


Figure 3.5 Attempts on Prins cyclization of intermediates **P1'** and **P2'**.

We therefore reassessed the effects of the present ring strain, which might impede the Prins cyclization instead of facilitating it to form the desired 2,6-*anti*-THP ring, by reacting fragments **P1-1'** with **P1-2'** and fragments **P2-1'** with **P2-2'** respectively under the Prins cyclization conditions (**Figure 3.6**). It was observed that no desired cyclized adducts was formed, even without any ring strain effect. Starting materials were partially recovered alongside with isolation of common side products, which are possibly lactones by deduction from NMR spectra. The NMR spectra of suspected lactones resembled the NMR spectrum of protected acid **A1-1**, implying that the acetonide moiety may be easily cleaved under the acidic conditions of Prins cyclization. Henceforth, we applied benzophenone instead of acetone for the simultaneous phenol-carboxylic acid acetal protection and the resulting "benzophenonide" fragment was subjected to intermolecular Prins cyclization.

Gratifyingly, the cyclization proceeded smoothly without the generation of side products (**Figure 3.7**). This observation supported our hypothesis involving the instability of acetonide. We proposed that the acidic conditions caused the rupture of acetonide, revealing a free carboxylic acid that may have attacked the free alcohol, which was intended for Prins cyclization, to result in a lactone side product (**Figure 3.6**). Similarly, it can be inferred that the ester moieties in intermediates **P1'** and **P2'** might be labile under acidic conditions of Prins cyclization, thereby hydrolyzed into salicylic acids that reacted with alcohols and aldehydes undesirably. Henceforth, Prins cyclization is rendered ineffective in constructing the 2,6-*anti*-THP ring of the core macrolide fragment **A1**. As a dire consequence, we had to abandon this approach and sought for other alternatives, which turned out to be quite a blessing in disguise.

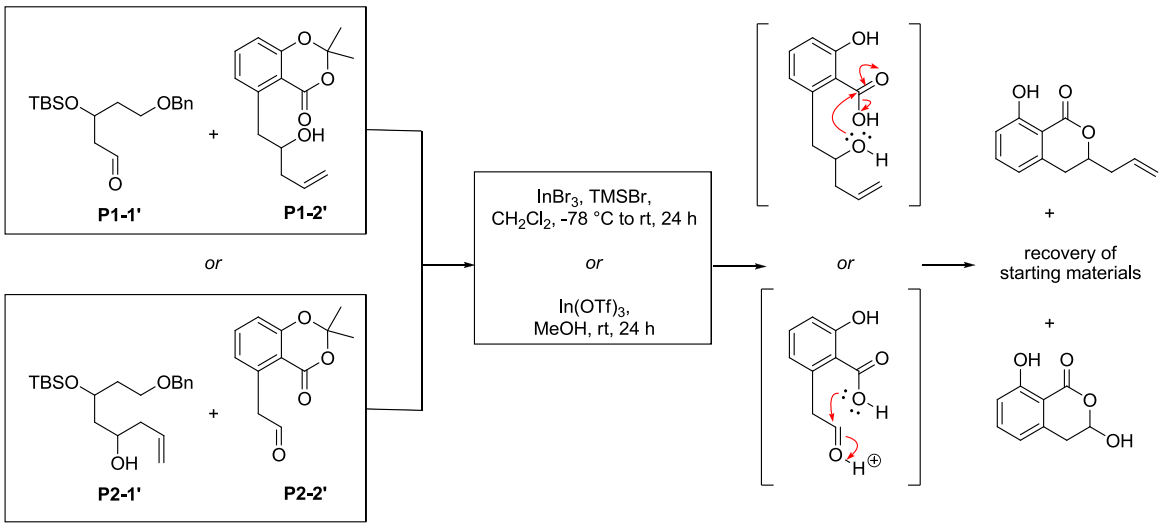


Figure 3.6 Intermolecular versions of the intended Prins cyclization.

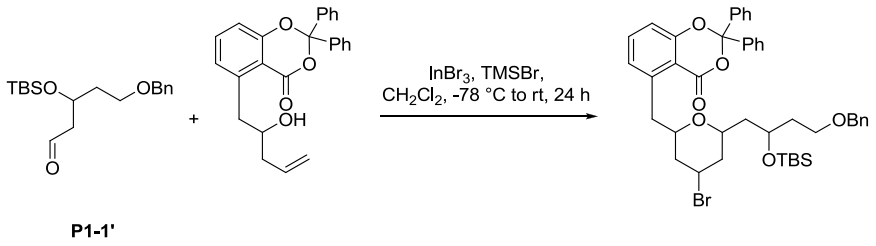


Figure 3.7 Intermolecular Prins cyclization of "benzophenonide".

3.3 The Intermolecular Approach (I)*

3.3.1 Preliminary model studies[136,137]

The unsuccessful attempt with Prins cyclization to construct the necessary 2,6-*anti*-THP ring, required us to revisit as well as build on our previous methodologies. It was then we rediscovered a reported work on $InCl_3$-catalyzed Mukaiyama-Michael addition of silyl enol ethers to *α*,*β*-unsaturated ketones.[138] In the same article, we reported that the reaction generally inclined towards the generation of *anti*-adducts, albeit poor diastereoselectivities were reported (**Figure 3.8**).

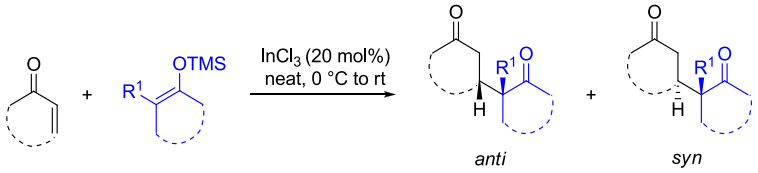


Figure 3.8 Previously reported $InCl_3$-catalyzed Mukaiyama-Michael addition of silyl enol ethers to *α*,*β*-unsaturated ketones.

Inspired by this finding, we applied the methodology onto dihydropyranones, in place of enones. We first subjected racemic 2-phenyl-2H-pyran-4(3H)-one[139] to (1-methoxy-2-methylprop-1-enyloxy)trimethylsilane[140] in the presence of 20 mol% $InCl_3$ under neat conditions at ambient temperature. Delightfully, the reaction provided the desired Mukaiyama-Michael addition adduct in 83% yield as a single *anti* diastereomer, of which the configuration was verified by NOESY experiments. We then extended these model studies to include various dihydropyranones and silyl enol ethers, which we subsequently published an article on the findings (**Figure 3.9**).[141]

---

* References 136,137.

[137] Alni, A. Development of New Synthetic Methodologies and Their Application Towards Synthesis of Natural Products. PhD Thesis, Nanyang Technological University, Singapore, 2010.

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

[139] The aforementioned racemic pyranone was prepared from Lewis acid-catalyzed hetero Diels-Alder reaction of benzaldehyde and Danishefsky's diene. Danishefsky, S. J.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358.

[140] Garst, M. E.; Bonfiglio, J. N.; Grudoski, D. A.; Marks, J. *J. Org. Chem.* **1980**, *45*, 2307.

[141] Chua, S.-S.; Alni, A.; Chan, L.-T. J.; Yamane, M.; Loh, T.-P. *Tetrahedron* **2011**, *67*, 5079.

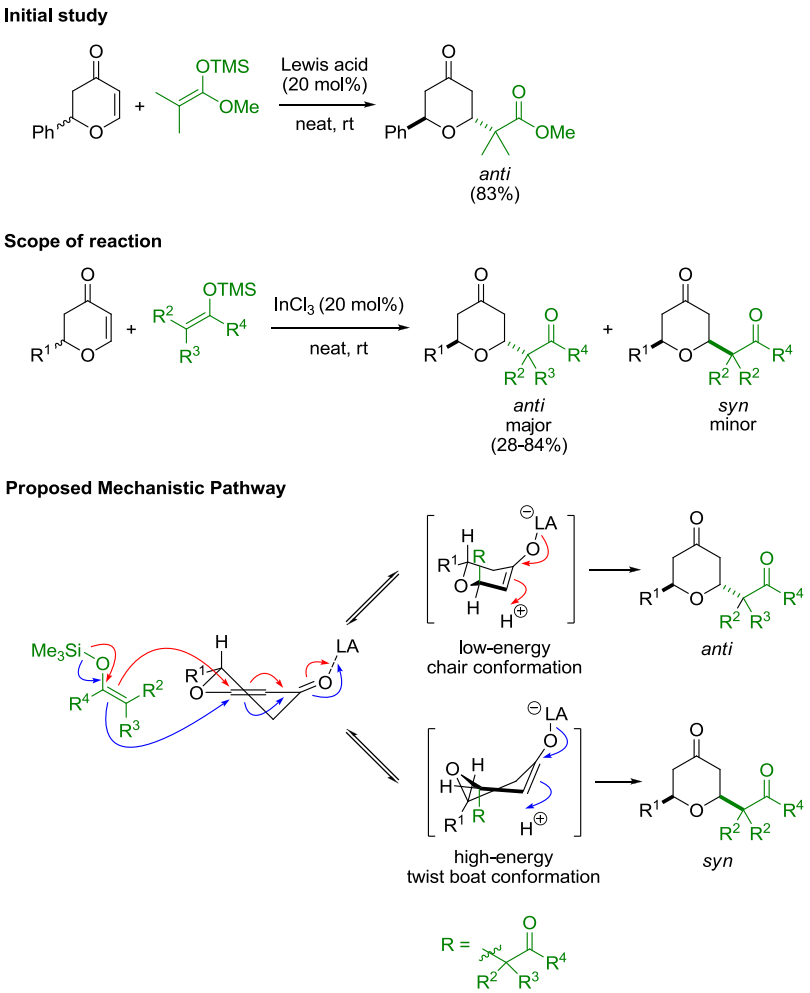


Figure 3.9 Synthesis of 2,6-*anti*-THP rings *via* $InCl_3$-catalyzed Mukaiyama-Michael addition silyl enol ethers to dihydropyranones.

We postulated that $InCl_3$ acts as a Lewis acid, activating the dihydropyranone's conjugated system and thereby increases its susceptibility towards nucleophilic attack of silyl enol ether (**Figure 3.9**). From the findings, we also proposed that an axial attack would most likely occur, leading to a six-membered ring chair conformation transition state, which is of a lower energy state and thus more stable compared to the alternative twist boat transition state, to provide the desired 2,6-*anti*-THP adduct.

Through these preliminary studies, we demonstrated the applicability of $InCl_3$-catalyzed Mukaiyama-Michael addition of silyl enol ethers to dihydropyranones and without further ado, we attempted this methodology to construct the 2,6-*anti*-THP ring in our synthetic endeavour towards the total synthesis of Apicularen A.

3.3.2 Retrosynthetic analysis

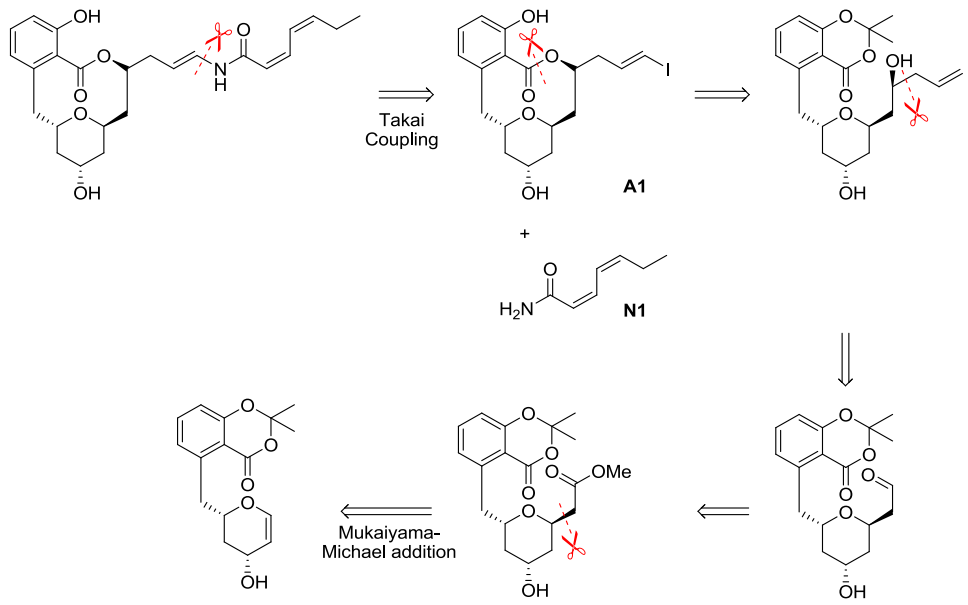


Figure 3.10 Retrosynthetic analysis for intermolecular approach towards Apicularen A.

As with the *intra*molecular approach, our retrosynthetic analysis for *inter*molecular approach kicked off with the disconnection of enamide bond *via* Takai coupling (**Figure 3.10**). The vinyl iodide intermediate would be formed upon a macrolactonization and a prior allylation of a consequent aldehyde from an ester reduction. The preceding ester intermediate would be the desired adduct from our proposed $InCl_3$-catalyzed Mukaiyama-Michael addition of silyl enol ether and dihydropyranone, henceforth attributing to the label – *intermolecular approach* (also note that *intramolecular approach* refers to the Prins cyclization strategy, which would have taken place within a single molecule; see **Figure 3.1**). The dihydropyranone intermediate would resemble that of De Brabander's approach.[80] This retrosynthetic approach suggested a more linear synthetic route since the molecule is gradually constructed by building from a starting material, than the intramolecular convergent one where two major fragments are combined.

3.3.3 Synthetic route

The first portion of this synthetic route, until the procurement of required dihydropyranone **A1-5**, was performed by following closely to De Brabander's approach[80] (**Figure 3.11**). 2,6-dihydroxybenzoic acid had its salicylic moiety protected as an acetonide, leaving a free phenol available for triflate activation that would participate in an upcoming Stille coupling with allyltributylstannane. The ensuing ozonolysis cleaved the terminal alkene, converting it into a homobenzyl aldehyde **A1-4** along with the generation of gaseous formaldehyde. After that, the consequent homobenzyl aldehyde **A1-4** was subjected to stereoselective hetero-Diels-Alder reaction with Danishefsky's diene in the presence of a slightly modified Jacobsen's chromium catalyst, **Catalyst A** [142], furnishing the required dihydropyranone intermediate **A1-5** in an overall yield of 60%.

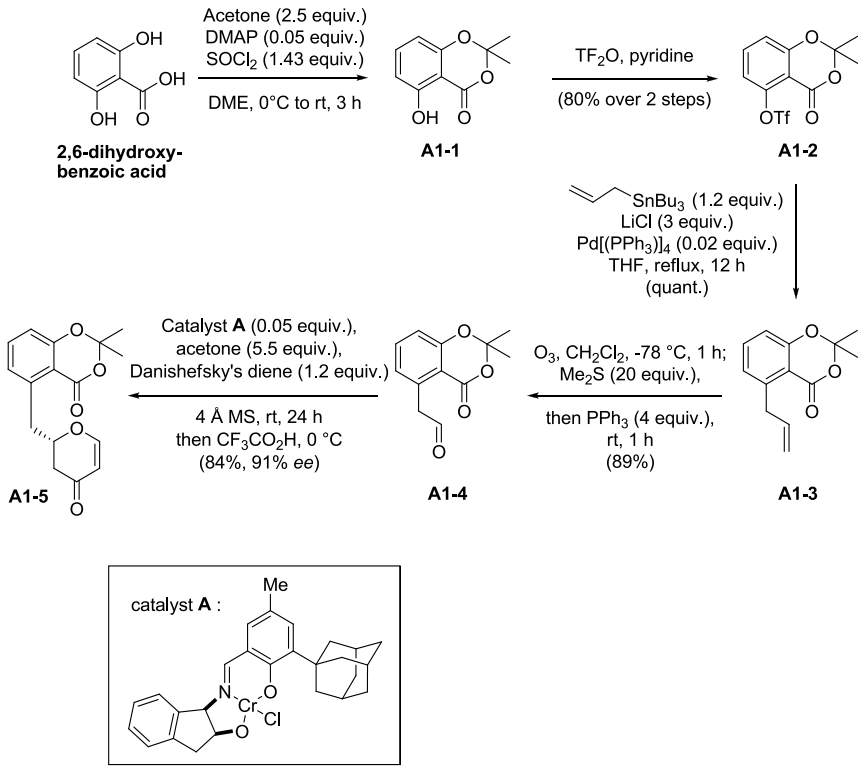


Figure 3.11 Synthesis of dihydropyranone **A1-5** following De Brabander's approach.

With the dihydropyranone **A1-5** at hand, we then excitedly attempted our much anticipated $InCl_3$-catalyzed Mukaiyama-Michael addition of silyl enol ether **A1-5M**.

[142] (a) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999**, *38*, 2398. (b) Chavez, D. E.; Jacobsen, E. N. *Org. Synth.* **2005**, *82*, 34.

Gladly, the desired 2,6-*anti*-THP adduct was exclusively yielded in 80% (**Figure 3.12**). The pyranone was uneventfully reduced into a racemic mixture of secondary alcohols and subsequently being protected with TBS group. Our progress was soon halted by unsuccessful attempts to reduce the methyl ester into the corresponding aldehyde with hydrides such as diisobutylaluminium hydride (DIBAL), lithium borohydride and excess sodium borohydride, which instead resulted in an indistinguishable complex mixture of aldehydes. This complication could be attributed to the lability of acetonides in the presence of hydrides, even at low temperatures.[143] The benzophenone-derived protecting group was as susceptible to reduction by hydrides as the acetonide and hence, resulting in a similar indistinguishable complex mixture of aldehydes.

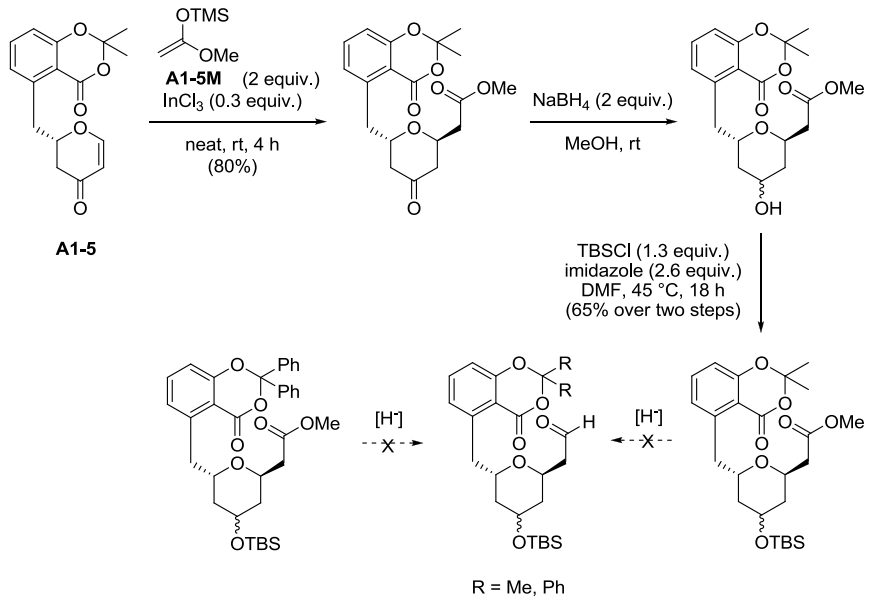


Figure 3.12 $InCl_3$-catalyzed Mukaiyama-Michael addition of silyl enol ether **A1-5M** and subsequent reduction reactions.

Since reduction of methyl ester posed numerous complications, we sought for other moieties that could be conveniently transformed into the requisite aldehyde. Thioesters appealed to us as suitable candidates to replace the problematic methyl ester because reduction of thioesters into aldehydes, which usually occurs in the presence of Pd/C and triethylsilane without the involvement of hydrides, might be sufficiently mild towards the acetonide protecting group.[144] Taking that into consideration, we synthesized a thioester-derived silyl enol ether **A1-5S** and

[143] Bajwa, N.; Jennings, M. P. *J. Org. Chem.* **2006**, *71*, 3646.
[144] Fukuyama, T.; Tokuyama, H. *Aldrichimica Acta* **2004**, *37*, 87.

subjected it to $InCl_3$-catalyzed Mukaiyama-Michael addition. Gratifyingly, the reaction yielded the corresponding 2,6-*anti*-THP adduct exclusively in 80% (**Figure 3.13**). Following the reduction of pyranone and a subsequent TBS protection, the resulting thioester intermediate was successfully reduced into the requisite aldehyde in 86% while keeping the acetonide intact when being treated with Pd/C and triethylsilane. An allylation with (+)-Ipc_2Ballyl and sodium hydride-mediated macrolactonization that followed, provided us with the macrolide core fragment of Apicularen A and thereby concluded our first formal synthesis of the natural product.

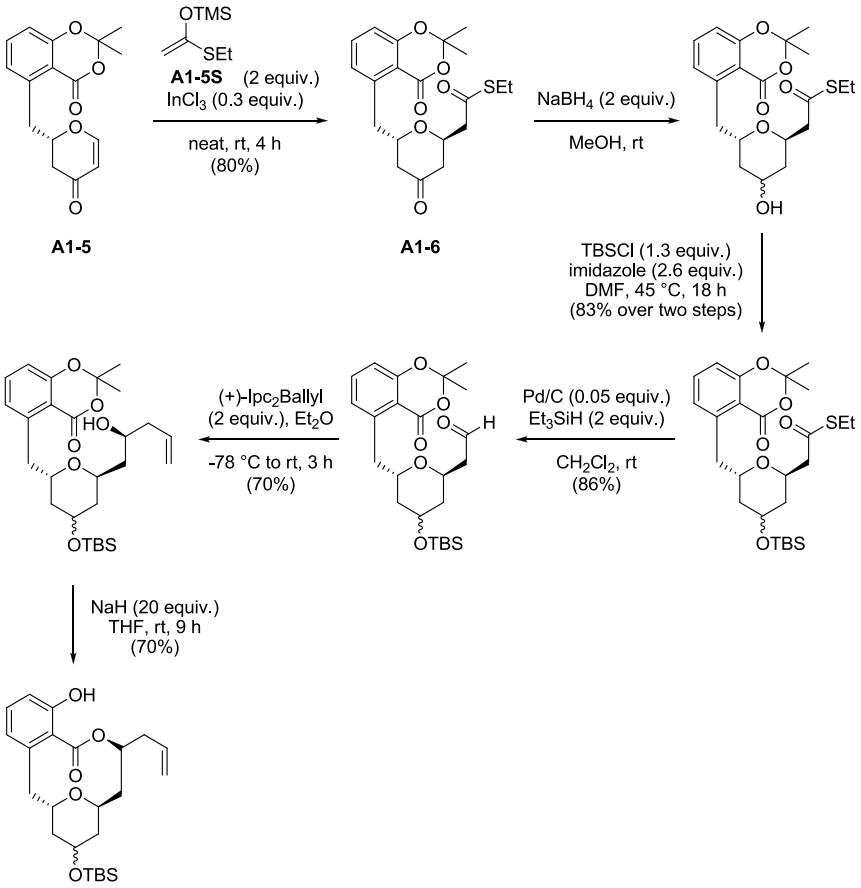


Figure 3.13 Formal synthesis of Apicularen A *via* $InCl_3$-catalyzed Mukaiyama-Michael addition of silyl enol ether **A1-5S**.

3.3.4 Designing tandem one-pot synthesis procedure

Our previously reported one-pot total syntheses of (±)-centrolobine and (±)-civet cat secretion[145] have inspired us to enhance the elegance of our synthetic approach towards the macrolactone core fragment of Apicularen A. With that vision in mind, we then devised a blueprint of one-pot synthetic procedure that preferably encompasses steps from the hetero-Diels-Alder to allylation (**Figure 3.14**). We intended to employ indium complex, particularly indium(III) trichloride, to effect hetero-Diels-Alder reaction, so that it would complement well with the ensuing $InCl_3$-catalyzed Mukaiyama-Michael addition.

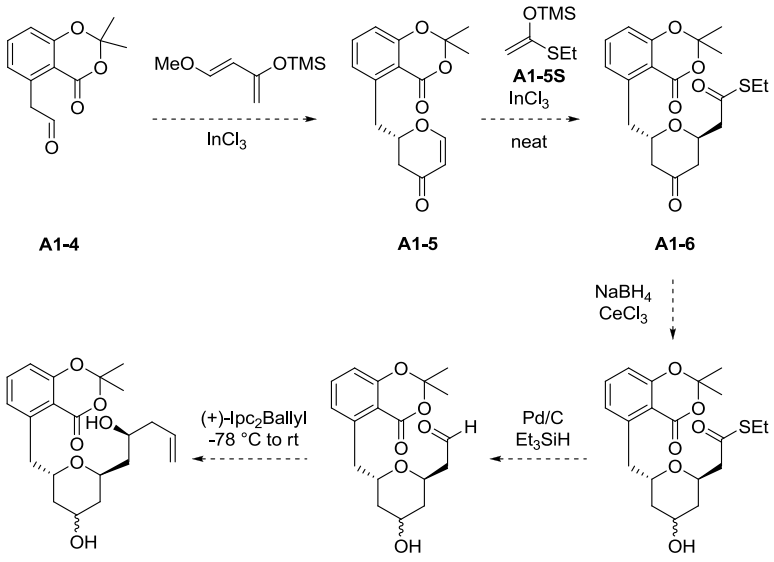


Figure 3.14 Blueprint of tandem one-pot synthesis.

A model study was conducted with benzaldehyde that was first subjected to hetero-Diels-Alder with Danishefsky's diene in the presence of $InCl_3$ as catalyst (**Figure 3.15**). Upon elimination of solvent and trifluoroacetic acid *in vacuo*, the reaction mixture was directly treated with silyl enol ether **A1-5S**. After performing these two reactions, we worked up the mixture and purified the crude product to obtain the desired 2,6-*anti*-THP adduct in 20% yield. We attempted to optimize the reaction conditions by increasing the amounts of dienes used and varying the reaction time but to no avail. Meanwhile, our attempts to incorporate a subsequent $NaBH_4$ reduction step into the one-pot synthetic procedure, were likewise unsatisfactory. These disappointing observations could be attributed to the presence of multiple entities in the reaction

[145] Zhou, H.; Loh, T.-P. *Tetrahedron Lett.* **2009**, *50*, 4368.

mixture, which might have interfered with one another's intended roles and thereby, resulting in unwanted side reactions and decompositions.

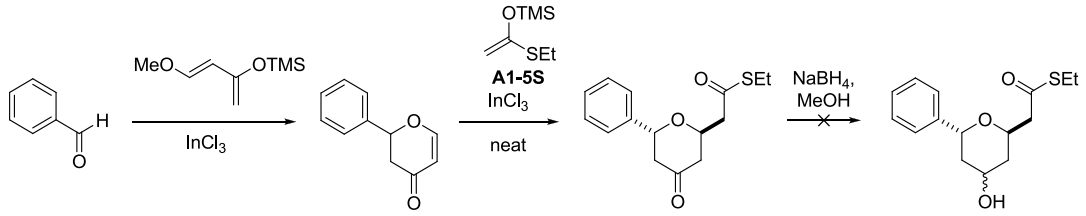


Figure 3.15 Model study of one-pot synthesis route with benzaldehyde.

We detoured to identify the entities that would have affected the one-pot synthetic procedure most. We substituted benzaldehyde with propionaldehyde, which has a lower boiling point, and subjected it to the $InCl_3$-catalyzed hetero-Diels-Alder (**Figure 3.16**). Excess propionaldehyde was evaporated off alongside with the solvent and trifluoroacetic acid. Danishefsky's diene was then directly added to the reaction mixture and expectedly provided the desired 2,6-*anti*-THP adduct. This time, we took a step further with the tandem one-pot synthetic approach by including the sodium borohydride reduction. Satisfyingly, the non-stereoselective reduction proceeded well and four isomers of the resultant alcohol were obtained in an overall yield of 36% over three steps. We tried to push our luck a little further in hope to reduce the thioester with addition of Pd/C and triethylsilane but unfortunately, no distinct aldehyde peak was observed from the crude NMR spectrum. We reckoned that the free hydroxy moiety resulting from the prior pyranone reduction might have obstructed the thioester reduction.

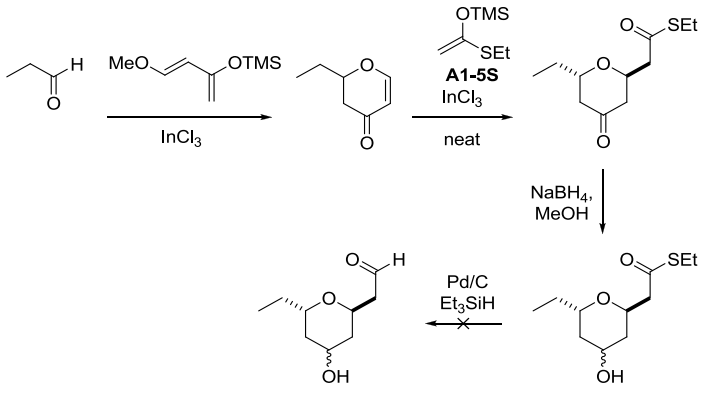


Figure 3.16 One-pot synthesis route with propionaldehyde.

3.4 The Intermolecular Approach (II)

Despite the completion of our formal synthesis of Apicularen A, efforts to improve the synthetic route are still underway. We reviewed our synthetic route and we were especially concerned with the non-stereoselectivity of sodium borohydride reduction of pyranone. With this concern as our motivation, we veered to a new synthetic course, in hope to address the stereoselectivity issue as well as to attempt completing the *total* synthesis of Apicularen A.

3.4.1 Revised synthetic route towards the macrolide core fragment of Apicularen A

In view of the lacklustre sodium borohydride reduction of pyranone, we considered to delay the reduction of pyranone to a later stage, preferably after the installment of macrolactone. We postulated that the formation of macrolactone might be able to restrict free rotation of bonds, which may consequently make one face more available or hindered for attack and thereby influencing a more stereoselective reduction.

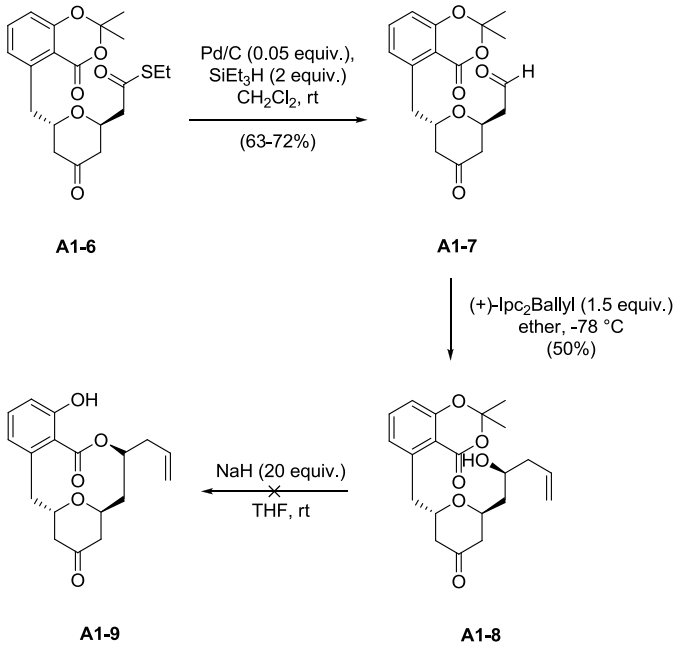


Figure 3.17 Revised synthetic route of Apicularen A's core fragment.

Upon $InCl_3$-catalyzed Mukaiyama-Michael addition to obtain intermediate **A1-6**, we employed Pd/C to effect Fukuyama reduction of thioester into its corresponding aldehyde **A1-7** in good yields of 63-72% (**Figure 3.17**). We then reckoned that the allylation that followed would be chemoselective since aldehyde is usually more reactive than the pyranone moiety, thereby eliminating the need of protection-deprotection of pyranone. To examine our speculation, we introduced 1.5 equivalent of (+)-Ipc_2Ballyl to the aldehyde slowly *via* syringe pump, at a very low temperature of -78 °C. Satisfyingly, the allylation only proceeded at the intended aldehyde, resulting in the desired allylated product **A1-8** in 50%. With minute amount of **A1-8** at hand, we continued to investigate a tandem deprotection of acetonide/macrolactonization reaction mediated by sodium hydride. The reaction unfortunately did not proceed to provide the desired intermediate **A1-9** and no traces of starting material were recovered.

We attempted to regenerate the monoallylated intermediate **A1-8** in larger quantities. However, when we upscaled the reaction, the yield of the **A1-8** decreased, alongside with the generation of unwanted bisallylated product **A1-8B**[146] (**Figure 3.18**). We tried to introduce stoichiometric amount of (+)-Ipc_2Ballyl reagent at an even slower rate but bisallylation product still prevailed. We also attempted to revert the bisallylated **A1-8B** to monoallylated **A1-8** but to no avail.[147] Henceforth, the synthetic route was temporarily shelved aside while we worked on other alternative routes.

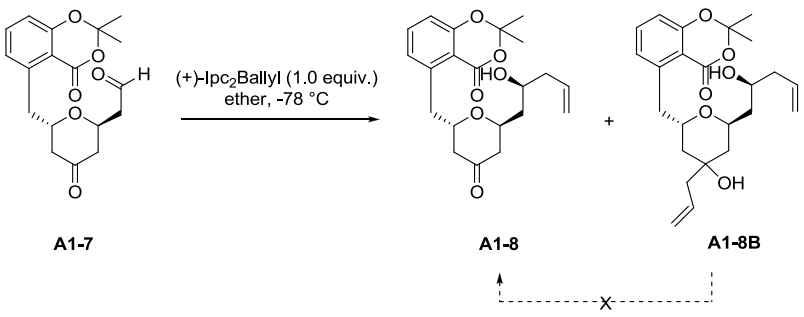


Figure 3.18 Reaction between pyranone **A1-7** and (+)-Ipc_2Ballyl reagent.

Considering the irreproducibility and impracticality of the allylation reaction to provide monoallylated **A1-8** consistently, we decided to protect the pyranone prior to reduction of thioester. We ventured into the possibility of five- and six-membered

[146] See *Appendix* for ^{1}H NMR spectrum of **A1-8B**.
[147] (a) Loh, T.-P.; Lee, C.-L. K.; Tan, K.-T. *Org. Lett.* **2002**, *4*, 2985. (b) Lee, C.-H. A.; Loh, T.-P. *Tetrahedron Lett.* **2004**, *45*, 5819.

rings acetals, which were easily achieved by treating the thioester with ethylene glycol and 1,3-propanediol respectively. We concurrently ran reduction of both protected thioesters into their corresponding aldehydes thereafter and observed that in general, the five-membered ring acetal provided better yields than the six-membered ring acetal counterpart in these two successive reactions (**Figure 3.19**). We thus continued our investigation of the synthetic route only with the five-membered ring acetal intermediate **A1-11A**.

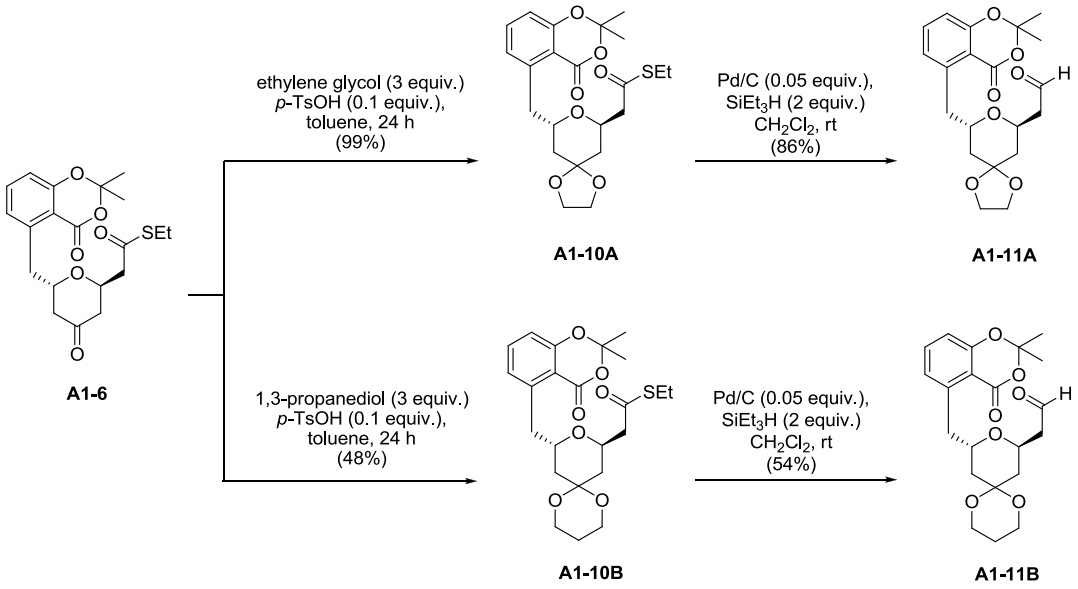


Figure 3.19 Acetal protection and subsequent reduction of thioesters.

We initially obtained good yields of the resulting aldehyde **A1-11A** (86%) with Pd/C but after a few more attempts, the yields deteriorated quite drastically. This might be attributed to the gradual deactivation of palladium on carbon. While Pd/C could be reactivated, we discovered that palladium(II) acetate provided a convenient alternative of Pd/C in Fukuyama reduction with slightly lower but consistent yields. The brownish reaction mixture turning into black suspension is a good indication that the reaction proceeded (**Figure 3.20**). The aldehyde **A1-11A** then underwent allylation with (+)-Ipc$_2$Ballyl[148] and a subsequent macrolactonization without much complications, achieving yields of 75% and 80% respectively (**Figure 3.21**). It is noteworthy that it is necessary for the tandem deprotection of acetonide and

[148] Our efforts thus far have been communicated in: Chua, S.-S.; Alni, A.; Chan, L. J.; Yamane, M.; Loh, T.-P. *Poster Presentation*, 4th EuCheMS Chemistry Congress, Prague, Czech Republic, August 2012; "Towards the synthesis of Apicularen A: An application of new methodology to construct 2,6-*anti*-tetrahydropyran rings." *See Appendix for poster content.*

macrolactonization to conclude with a methyl protection of phenol. Previous attempts to omit the latter protection step yielded an unknown phenolic compound.[149]

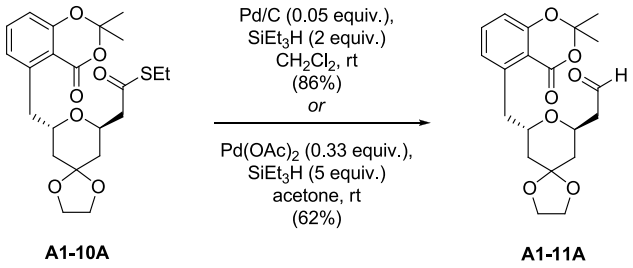


Figure 3.20 Fukuyama-type reduction of thioester.

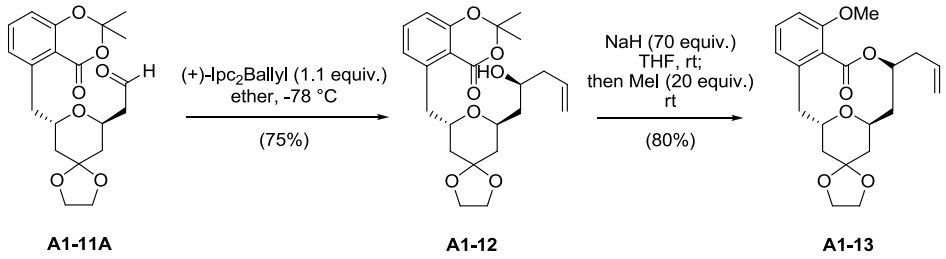


Figure 3.21 Subsequent transformations from aldehyde **A1-11A**.

With macrolactone **A1-13** in hand, we decided to test our hypothesis that the reduction of pyranone would be more stereoselective upon the macrolactone formation. We first attempted to remove the acetal protection, revealing the masked pyranone.[150] However, the acetal moiety appeared to be more robust than expected. We are currently working on the removal of the acetal protecting group and looking forward to reduce the resulting pyranone **A1-14** in a stereoselective manner although in 2011, Rizzacasa and co-workers reported that despite their prior construction of the macrolactone core fragment, no stereoselectivity was observed upon reduction of pyranone with sodium borohydride.[101(c)]

Future developments from macrolactone **A1-13** include ozonolyses of compounds **A1-13** and **A1-14** into aldehydes **A1-16** and **A1-17** respectively, which closely resembled those found in some of the previously reported synthetic approaches such as De Brabander's, Nicolaou's, Rizzacasa's, Panek's, Tae's and Uenishi's.

[149] See *Appendix* for NMR spectra of the unknown phenolic compound.
[150] Borrelly, S.; Paquette, L. A. *J. Am. Chem. Soc.* **1996**, *118*, 727.

Henceforth, we could adopt their strategies to complete the total synthesis of Apicularen A thereon.

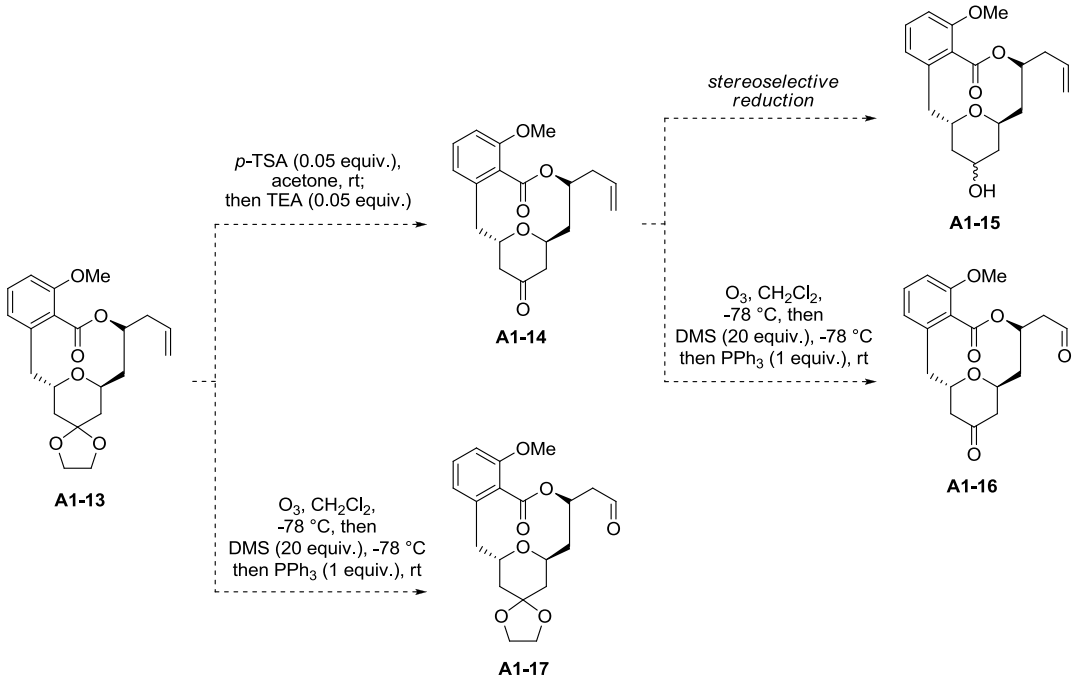


Figure 3.22 Projected developments from macrolactone **A1-13**.

While we were cruising along in this direction towards Apicularen A, we saw an opportunity to demonstrate the applicability of a recently developed methodology involving the coupling of vinylboronic acids and amides (**Figure 3.23**)[151]. Henceforth, we set off to prepare the requisite vinylboronic acid macrolide core fragment **A2** and amide side chain **N2** (**Figure 3.24**).

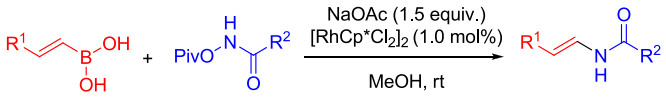


Figure 3.23 Recently developed methodology involving the coupling of vinylboronic acids and amides.

[151] Feng, C.; Loh, T. P. unpublished results.

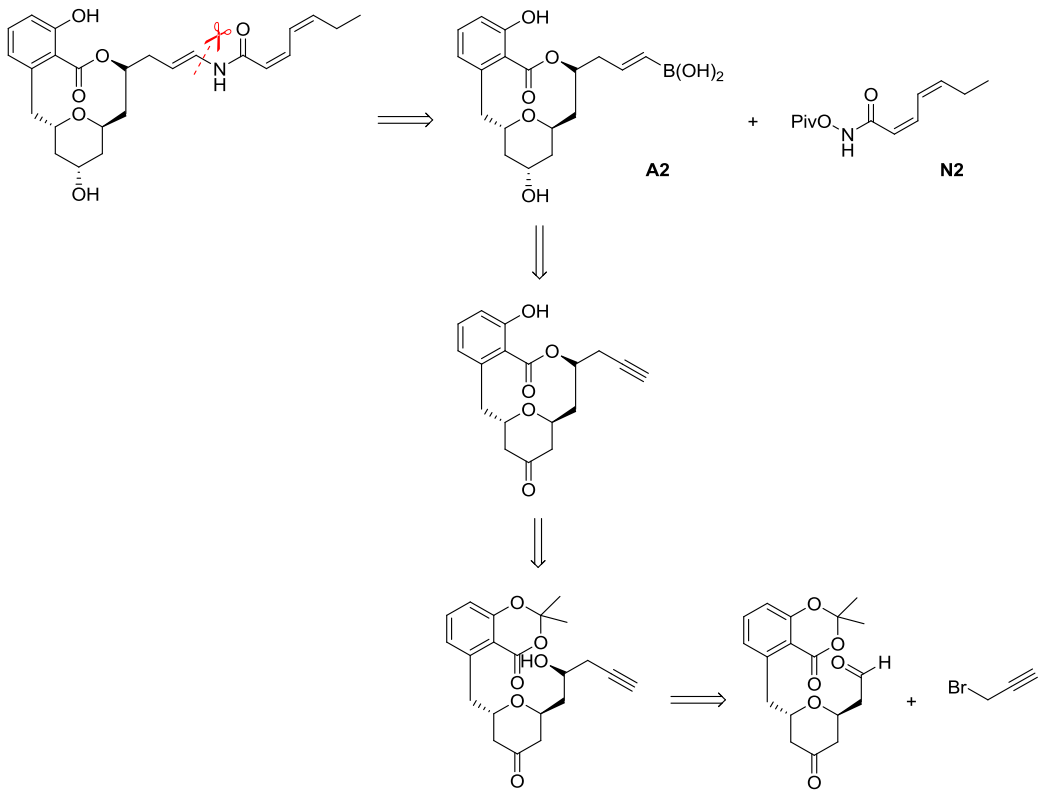


Figure 3.24 Retrosynthetic analysis for the requisite vinylboronic core fragment and corresponding amide side chain.

The vinylboronic acid macrolide core can be derived from a common aldehyde intermediate **A1-11A** *via* a propargylation reaction. While there are many reports to access chiral homopropargylic alcohols[152], the more conventional methods usually provide a mixture of homoallenic and homopropargylic alcohols[153]. This poor selectivity could be attributed to the metallotropic rearrangement, where allenylic and propargylic metal species are present in equilibrium upon transmetalation, and subsequently reacting with aldehyde independently to form two different alcohols – homoallenic and homopropargylic alcohols respectively (**Figure 3.25**).

[152] (a) Moreau, J. L. In *The Chemistry of Kentens, Allenes and Related Compounds*; Patai, S., Ed.; Wiley: New York, 1978; p. 343. (b) Brandsma, L.; Verkruijsse, H. D. In *Synthesis of Acetylenes, Allenes and Cumulenes*; Elseviver, Amsterdam, 1981.

[153] (a) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095. (b) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7667. (c) Yu, C. M.; Yoon, S. K.; Baek, K.; Lee, J. Y. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2392. (d) Yu, C. M.; Yoon, S. K.; Choi, H. S.; Baek, K. *Chem. Commun.* **1997**, 763. (e) Iseki, K.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 2889.

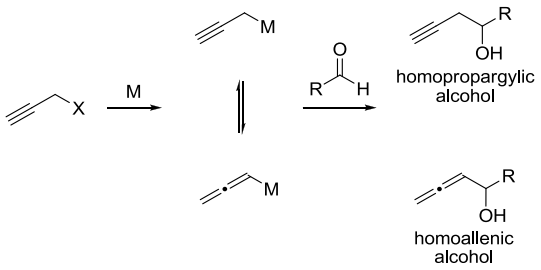


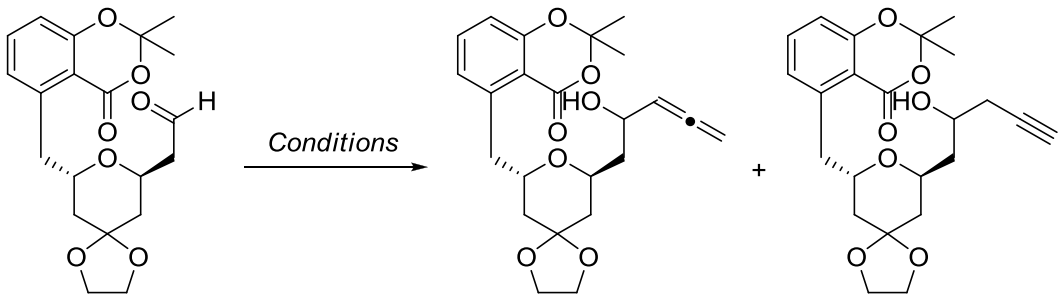
Figure 3.25 Metallotropic rearrangement attributing to poor selectivities.

Previously, our group reported a methodology, in which propargylation of aldehydes favoured the generation of chiral homoproparylic alcohols in the presence of indium and (-)-cinchonidine.[154] Encouraged by the findings, we first attempted a similar indium-mediated propargylation of the core fragment aldehyde **A1-11A** with propargyl bromide at ambient temperature, in the absence of the chirality promoter, (-)-cinchonidine (**Table 3.1**, Entry 1). The reaction proceeded to give rise to three observable products - homoallenic (**A2-1A**) in 23% and the isomers of homopropargylic (**A2-1P**) alcohols in 52%. When we lowered the temperature to 0 °C (**Table 3.1**, Entry 2), no homoallenic alcohol was isolated while combined yield of the isomers of desired homopropargylic alcohol **A2-1P** obtained was 55%.

We also attempted propargylation with *in situ*-generated allenylmagnesium bromide as Grignard reagent at -78 °C (**Table 3.1**, Entry 3),[155] providing the isomers of homopropargylic alcohol **A2-1P** in less than 31% with partial recovery of the starting material **A1-11A**. When aldehyde **A1-11A** was subjected to *B*-allenyl-1,3,2-dioxaborolane[156] (**Table 3.1**, Entry 4), the combined yield of the isomers of desired homopropargylic alcohol **A2-1P** improved to 78%. Finally, propargylation in the presence of zinc dust and mercury(II) chloride amalgam was examined, providing the best combined yields of homopropargylic alcohol **A2-1P** isomers (83%). We then proceeded with the available homopropargylic alcohol **A2-1P** to explore the impending hydroboration.

[154] Loh, T.-P.; Lin, M.-J.; Tan, K.-L. *Tetrahedron Lett.* **2003**, *44*, 507.
[155] (a) Stadler, P. A.; Nechvatal, A.; Frey, A. J.; Eschenmoser, A. *Helv. Chim. Acta* **1957**, *40*, 1373. (b) Sondheimer, F.; Wolovsky, R.; Ben-Efraim, D. A. *J.Am. Chem. Soc.* **1961**, *83*, 1686. (c) Sondheimer, F.; Amiel, Y.; Gaoni, Y. *J. Am. Chem. Soc.* **1962**, *84*, 270. (d) Viola, A.; MacMillan, J. H. *J. Am. Chem. Soc.* **1968**, *90*, 6141. (e) Hopf, H.; Bohm, I.; Kleinschroth, J. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, pp 485.
[156] Barnett, D. S.; Schaus, S. E. *Org. Lett.* **2011**, *13*, 4020.

Table 3.1 Propargylation of **A1-11A**.

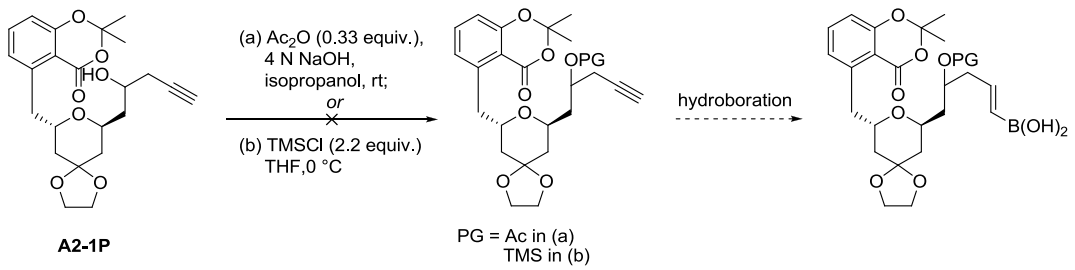


A1-11A **A2-1A** **A2-1P**

Entry	*Conditions*	**A2-1A**	**A2-1P** (isomer 1)	**A2-1P** (isomer 2)
1	Propargyl bromide (6 equiv.), In (2 equiv.), THF, rt, 8 h	23%	27%	25%
2	Propargyl bromide (6 equiv.), In (2 equiv.), THF, 0 °C to rt, 18 h	n.a.	18%	37%
3	Propargyl bromide (1.9 equiv.), Mg (2 equiv.), $HgCl_2$ (0.5 mol%), ether, -78 °C to 0 °C, 18 h	n.a.	<9%[a]	22%
4	*B*-allenyl-1,3,2-dioxaborolane, neat, rt, 18 h	n.a.	40%	38%
5[b]	Propargyl bromide (1.5 equiv.), Zn (4 equiv.), $HgCl_2$ (2 mol%), THF, 60 °C, 24 h	n.a.	47%	36%

[a] Some starting material was recovered alongside with **A2-1P** (isomer 2).

[b] Starting material was recovered in 65%.



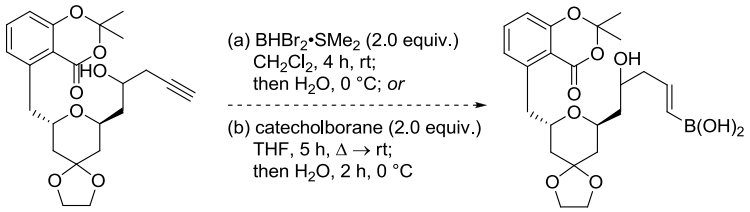
A2-1P

PG = Ac in (a)
TMS in (b)

Figure 3.26 Attempts to protect secondary alcohol of **A2-1P**.

We considered that protection of secondary alcohol present is necessary prior to hydroboration of the terminal alkyne **A2-1P** (**Figure 3.26**). We tried to attach trimethylsilyl[103] and acetyl[76,129] moieties but to no avail. We reckoned that the spatial arrangement about the secondary alcohol may be too crowded and hence, making it challenging to protect the alcohol. Nonetheless, efforts to find a suitable protecting group are currently underway.

We also attempted to waive the protection step off and directly executing hydroboration *via* two different procedures – a modified procedure employing $BHBr_2 \cdot SMe_2$[157] and the other procedure making use of catecholborane[158] (**Figure 3.27**). Neither of these approaches provided the desired vinylboronic acid as well.



A2-1P

Figure 3.27 Attempts to perform hydroboration on secondary alcohol of **A2-1P**.

In view of unsuccessful alcohol protection and direct hydroboration attempts, we then considered tandem deprotection of acetonide/macrolactonization of homopropargylic alcohol **A2-1P** by treatment of excess amounts of sodium hydride, forming macrolide **A2-2** in 40% yield (**Figure 3.28**). We also attempted to extend the tandem one-pot reaction to achieve a protected phenol[101] and **A2-3** was obtained in 28%. Model studies to investigate hydroboration of **A2-2** and **A2-3** are currently underway in the laboratory.

[157] Brown, H. C.; Bhat, N. G.; Somayaji, V. *Organometallics* **1983**, *2*, 1311.
[158] Chen, Y. *et al.*(Hoffmann-La Roche Inc.) 4-Alkenyl and 4-Alkynyloxindoles U. S. Patent 6,130,239, Oct. 10, 2000.

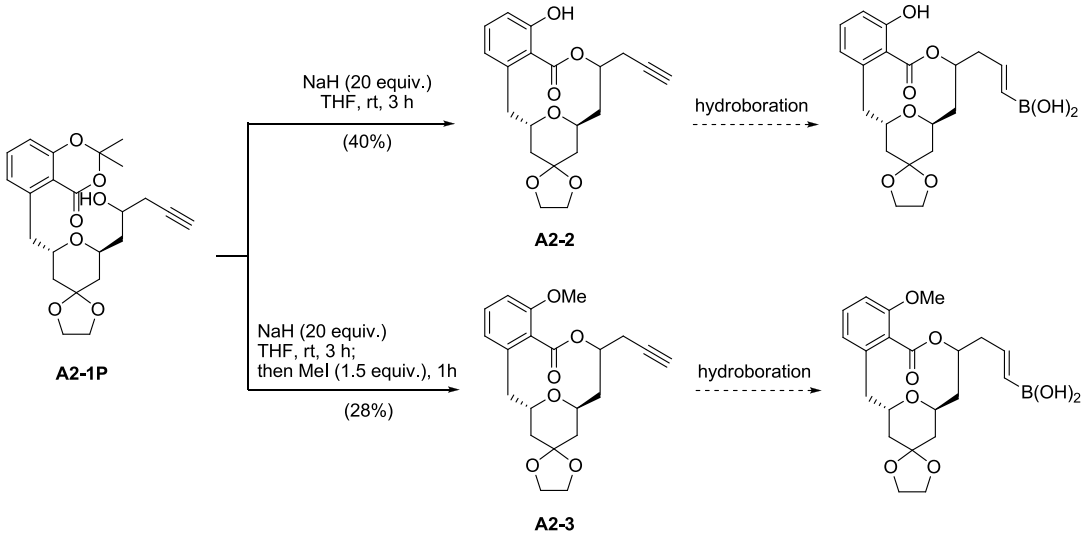


Figure 3.28 Attempts to perform tandem deprotection of acetonide/macrolactonization of **A2-1P**.

3.4.2 Intermissions from the synthetic studies towards the total synthesis of Apicularen A

*3.4.2.1 Synthetic efforts towards the construction of enamides **N1** and **N2***

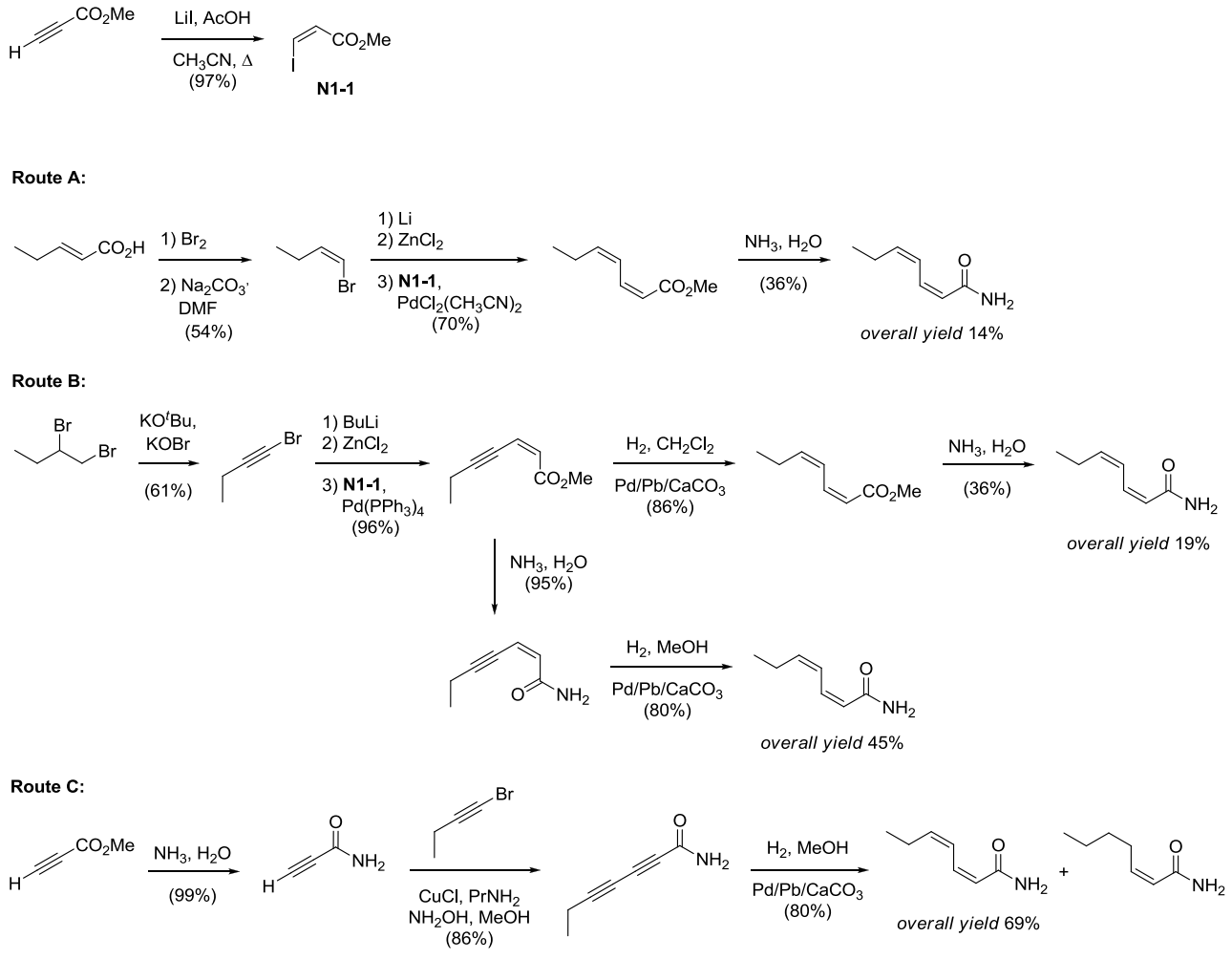


Figure 3.29 Synthetic routes of (*Z,Z*)-heptadienamide **N1** by Bayer and Maier.

While we were working on the core fragment **A1**, we also attempted to prepare the complementary enamide side chain **N1,** in accordance to a report by Bayer and Maier (**Figure 3.29**).[159] We first tried to synthesize 1-bromobut-1-yne as featured in routes B and C as these routes provided more promising yields than Route A. Unfortunately, we were unable to reproduce 1-bromobut-1-yne in appreciable quantities. We then switched tracks to try obtaining 1-bromobut-1-ene as featured in Route A. Our endeavors regrettably came to naught, or otherwise provided meager yields.

[159] Bayer, A.; Maier, M. E. *Tetrahedron* **2004**, *60*, 6665.

Consequentially, we sought for other alternatives with higher boiling points that could be handled more easily.

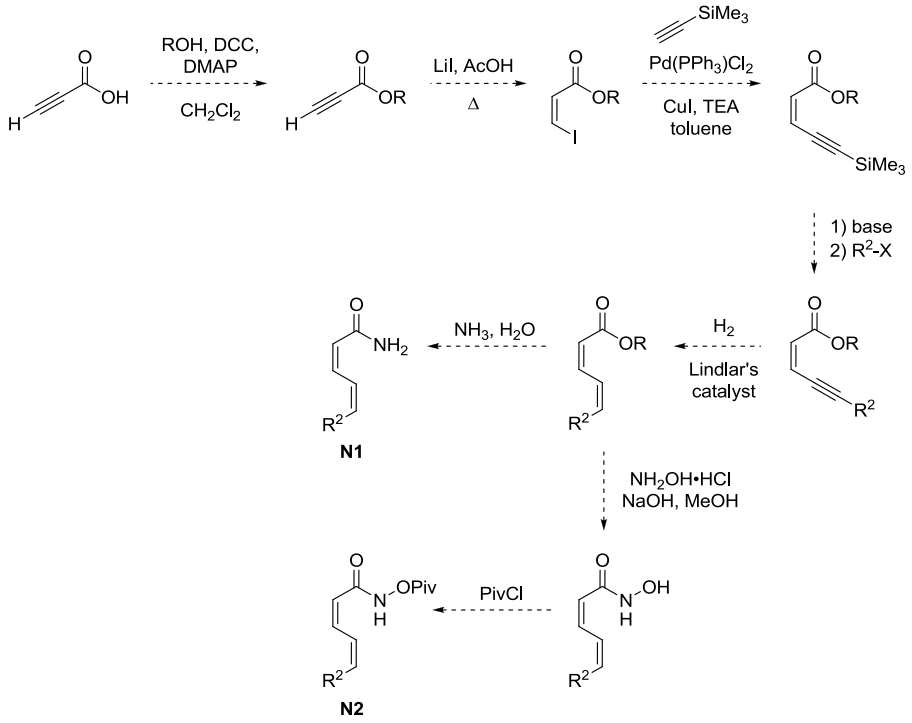


Figure 3.30 Proposed alternative route to access analogues of (*Z,Z*)-heptadienamide **N1** and **N2**.

We contemplated to modify the dispensable methyl esters into bulkier esters since it would eventually be converted to amide moieties, in hope to increase their boiling points (**Figure 3.30**). In line with the idea of decreasing the volatility of intermediates, we also considered substituting the ethyl group attached to both the alkene and alkyne with silyl moieties that could be easily cleaved under basic conditions[160] to eventually install the requisite ethyl moiety. Moreover, silyl moieties are versatile handles that we could exploit to synthesize interesting and useful analogues of Apicularen A. In addition, we decided to do away with the suggested Negishi couplings in Routes A and B as they require very stringent conditions. We envisaged the application of Sonogashira coupling and a successive hydrogenation in the presence of Lindlar's catalyst may be a more convenient approach. The proposed

[160] (a) Scott, L. T.; Cooney, M. J.; Johnels, D. *J. Am. Chem. Soc.* **1990**, *112*, 4054. (b) Cai, C.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 732.

alternative route may also accommodate the synthesis of enamide **N2** by tweaking the amidation step slightly.[161,162]

We set out to investigate the feasibility of this proposed synthetic route by subjecting methyl and ethyl propiolates to lithium iodide in refluxing acetic acid to obtain respective (*Z*)-vinyl iodides. Then, the vinyl iodides underwent Sonogashira coupling with (trimethylsilyl)acetylene to yield the corresponding enyne adducts (**Figure 3.31**).

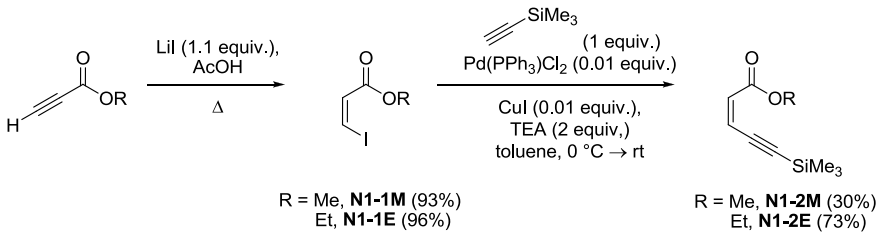


Figure 3.31 Synthesis of enyne adducts **N1-2M** and **N1-2E**.

Concerns about the volatility of intermediates arise again upon substitution of the silyl moiety with smaller functional groups. This catch-22 situation could be evaded if amidation is performed before desilylation takes place. So, we attempted to convert the ester moieties into **N-2**-type hydroxylamides (**Figure 3.32**).[163] Unfortunately, the amidation did not proceed as desired and we reckoned that the presence of the basic-labile (trimethylsilyl)acetylene moiety might have posed complications to the intended amidation reaction. Similarly, the hydroxylamidation was not successful with iodoacrylate **N1-1M** (**Figure 3.33**).

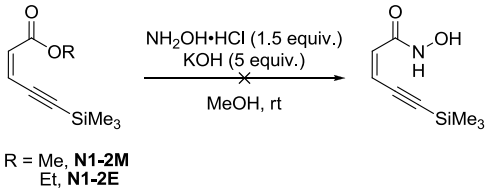


Figure 3.32 Attempt on hydroxylamidation of **N1-2M** and **N1-2E**.

[161] Liu, W.; Lau, F.; Liu, K.; Wood, H. B.;Zhou, G.; Chen, Y.; Li, Y.; Akiyama, T. E.; Castriota, G.; Einstein, M.; Wang, C.; McCann, M. E.; Doebber, T. W.; Wu, M.; Chang, C. H.; McNamara, L.; McKeever, B.; Mosley, R. T.; Berger, J. P.; Meinke, P. T. *J. Med. Chem.* **2011**, *54*, 8541.

[162] Jiang, L.; Chan, T.-H. *J. Org. Chem.* **1998**, *63*, 6035.

[163] In accordance to our more recent strategy, we would be emphasizing on the synthesis of **N2** hereon.

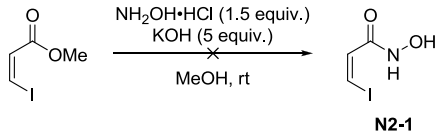


Figure 3.33 Attempt on hydroxylamidation of **N1-1M**.

Henceforth, we suggested that the hydroxylamidation to be performed at an even earlier stage (**Figure 3.34**) and treated propiolic acid with *in situ*-generated hydroxylamine. Disappointingly, the desired hydroxylamide intermediate **N2-1** was not obtained.

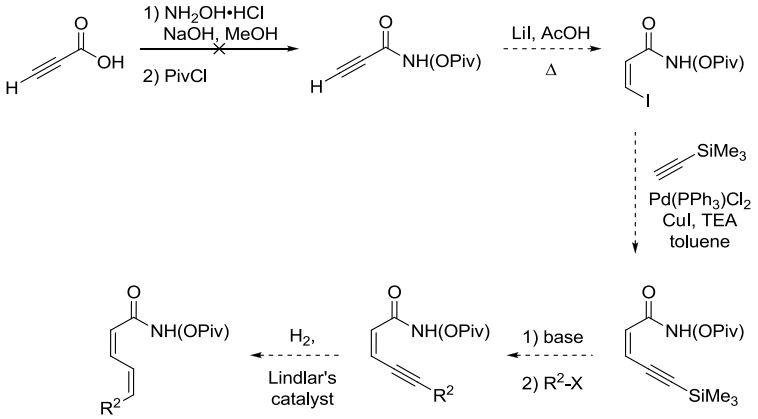


Figure 3.34 Another proposed alternative route to access analogues of (*Z,Z*)-heptadienamide **N2**.

In view of the unsuccessful attempts, we considered to utilize acyl chlorides, which are usually more reactive, in place of the current carboxylic acids and esters. We tried to synthesize the required acyl chloride *in situ* prior to addition of hydroxylamine hydrochloride salts (**Figure 3.35**). The reaction, too, did not provide us with the desired amide intermediate.

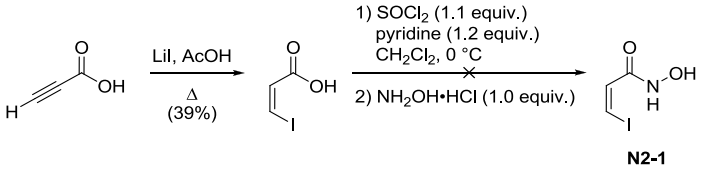


Figure 3.35 An alternative route to access **N2-1**.

Considering that the conventional methods to access hydroxylamides may not be appropriate to synthesize our desired unsaturated hydroxylamide, we discovered a promising route[164] to access (*Z,Z*)-heptadienamide **N2** (**Figure 3.36**) while searching the literature. Laboratory work is currently underway to investigate the feasibility of this approach.

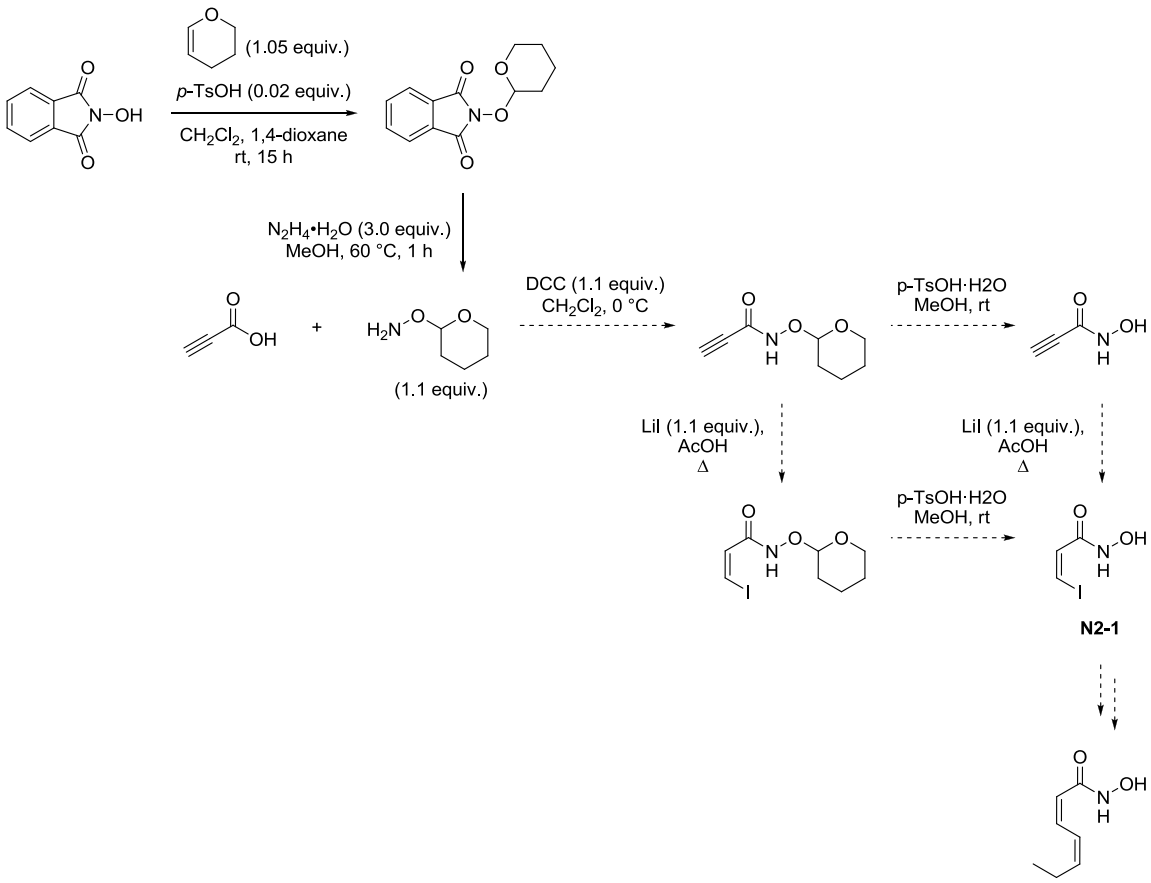


Figure 3.36 Another proposed alternative route to access analogues of (*Z,Z*)-heptadienamide **N2**.

[164] (a) Haslanger, M. F.; Karanewsky, D. S. U.S. Patent 4 604 407, 1986. (b) Martin, N. I.; Woodward, J. J.; Marletta, M. A. *Org. Lett.* **2006**, *8*, 4035. (c) Suzuki, T.; Ota, Y.; Kasuya, Y.; Tsumoto, H.; Nakagawa, H.; Miyata, N.; Mutsuga, M.; Kawamura, Y.; Finn, M. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 6817; *Angew. Chem.* **2010**, *122*, 6969. (d) Suzuki, T.; Ota, Y.; Ri, M.; Bando, M.; Gotoh, A.; Itoh, Y.; Tsumoto, H.; Tatum, P. R.; Mizukami, T.; Nakagawa, H.; Iida, S.; Ueda, R.; Shirahige, K.; Miyata, N. *J. Med. Chem.* **2012**, *55*, 9562.

3.4.2.2 Efforts to develop indium-mediated hetero-Diels-Alder methodology

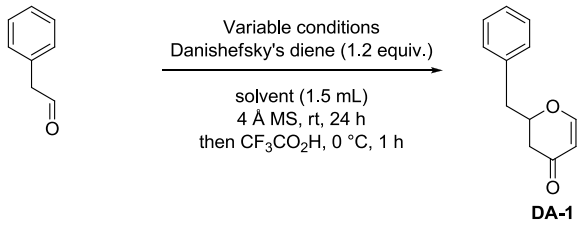
In an earlier section **3.2.4**, we expressed our interest in developing an indium-mediated one-pot tandem synthesis, which, if successful, will comprise of hetero-Diels-Alder, Mukaiyama-Michael addition of silyl enol ethers, reduction of pyranone and the Fukuyama-type reduction of thioester. We have revisited the hetero-Diels-Alder component of the supposed one-pot tandem synthesis and conducted a series of condition screenings with phenylacetaldehyde (**Table 3.2**) and intermediate **A1-4** (**Table 3.3**) respectively.

In **Table 3.3**, some of the reaction conditions prescribed were adapted from our previous methodologies.[165] Among the adapted reaction conditions involving indium complexes, desired pyranones **A1-5** and **DA-1** were obtained only when $InCl_3$ was used in conjunction with **Ligand A** and allyltributylstannane. Entry 2 was initially performed to investigate the significance of ligand in catalyst **A** in providing stereoselectivity. Surprisingly, the absence of the chiral ligand deterred the reaction from proceeding, not to mention providing stereoselectivity. Zinc chloride-mediated Diels Alder reactions were performed to obtain racemic products **DA-1** and **A1-5** respectively.

Further investigations such as optimization of the conditions to determine the enantiomeric excess ratio *via* HPLC elucidation as well as optimization of the one-pot tandem synthesis conditions, are currently underway in our laboratory.

[165] (a) Reaction conditions for entries 4 and 6 were adapted from : Teo, Y.-C.; Loh, T.-P. *Org.Lett.* **2005**, *7*, 2539. (b) Reaction conditions for entry 8 was adapted from : Zhao, J.-F.; Tjan, T.-B. W.; Loh, T.-P. *Tetrahedron Lett.* **2010**, *51*, 5649. (c) Reaction conditions for entry 9 was adapted from : Zhao, J.-F.; Tsui, H.-Y.; Wu, P.-J.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.* **2008**, *130*, 16492.

Table 3.2 Screening of reaction conditions for indium complex-mediated stereoselective hetero Diels-Alder with phenylacetaldehyde.[a]

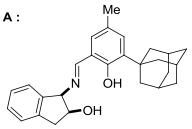


DA-1

Entry	*Metal complex*	*Additives*[b]	*Solvent*	**DA-1**
1	Jacobsen Cr catalyst **A** (0.05 equiv.)	-	acetone	65%
2	$CrCl_3$·3THF (0.05 equiv.)	-	acetone	n.a.
3	$InCl_3$ (0.2 equiv.)	-	CH_2Cl_2	n.a.
4	$InCl_3$ (0.2 equiv.)	Ligand **A** (0.22 equiv.) Allyltributylstannane (0.6 equiv.)	CH_2Cl_2	60%
5	$In(OTf)_3$ (0.2 equiv.)	-	CH_2Cl_2	n.a.
6	$ZnCl_2$ (1.1 equiv.)	-	THF	62%

a Reaction was carried out with 0.25 mmol of phenylacetaldehyde.

b Ligand **A** :



Pybox **B** :

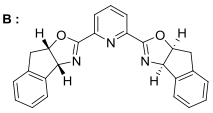
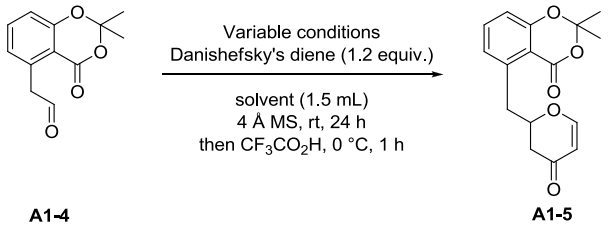


Table 3.3 Screening of reaction conditions for indium complex-mediated stereoselective hetero Diels-Alder with intermediate **A1-4**.[a]

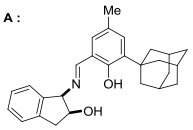


A1-4 **A1-5**

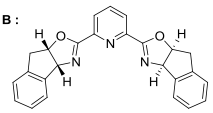
Entry	*Metal complex*	*Additives*[b]	*Solvent*	**A1-5**
1	Jacobsen Cr catalyst **A** (0.05 equiv.)	-	acetone	85%
2	$CrCl_3 \cdot 3THF$ (0.05 equiv.)	-	acetone	n.a.
3	$InCl_3$ (0.2 equiv.)	-	CH_2Cl_2	n.a.
4	$InCl_3$ (0.2 equiv.)	Ligand **A** (0.22 equiv.) Allyltributylstannane (0.6 equiv.)	CH_2Cl_2	58%
5	$In(OTf)_3$ (0.2 equiv.)	-	CH_2Cl_2	n.a.
6	$In(OTf)_3$ (0.05 equiv.)	Pybox **B** (0.06 equiv.) $AgSbF_6$ (0.05 equiv.)	CH_2Cl_2	n.a.
7	$In(OTf)_3$ (0.05 equiv.)	Pybox **B** (0.06 equiv.)	CH_2Cl_2	n.a.
8	$ZnCl_2$ (1.1 equiv.)	-	THF	67%

a Reaction was carried out with 0.25 mmol of **A1-4**.

b Ligand **A** :



Pybox **B** :



3.4.2.3 Application of rhodium(I) complex-catalyzed 1,4-addition of triorgano(vinyl)silanes

Another sideline work that we have undertook was to apply a rhodium(I) complex-catalyzed Michael addition of triorgano(vinyl)silane to pyranone **A1-5**. The aforementioned methodology was built upon an earlier report, in which we described a $[RhCl(CO)_2]_2$-catalyzed acylation of vinylsilanes with acid anhydrides (**Figure 3.37**)[166]. The $[RhCl(CO)_2]_2$ species has an electron-deficient rhodium centre, which is attributed to the electron-withdrawing CO groups attached, favouring transmetalation with the electron-rich silicon centre on the vinylsilanes.

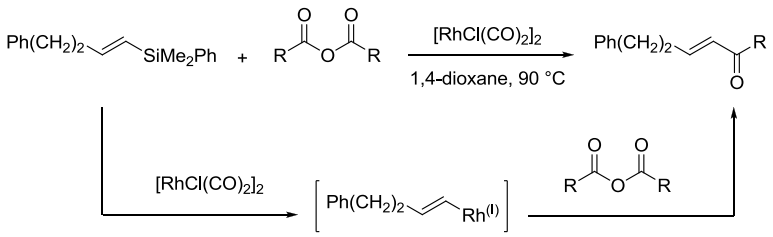


Figure 3.37 Rhodium-catalyzed acylation of vinylsilane with acid anhydrides.

Studies on rhodium(I) complex-catalyzed Michael addition of triorgano(vinyl)silanes to *α*,*β*-unsaturated carbonyl compounds have been carried out previously with much rigor and we found that the reaction is best performed with 5 mol% $[RhCl(CO)_2]_2$, 0.5 M dioxane at 100 °C in the presence of stoichiometric amount of additives (**Figure 3.38**). The additives that were compatible with the reaction conditions are generally Lewis acidic in nature and the few better-yielding additives, namely triethylborane, diethoxydimethylsilane and water, performed comparably well. Our findings have been previously communicated[167] and will not be further elaborated in this dissertation to maintain coherence with the topic in focus.

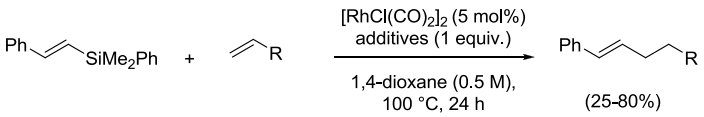


Figure 3.38 Rhodium-catalyzed 1,4-addition of triorgano(vinyl)silane with *α*,*β*-unsaturated carbonyl compounds.

[166] Yamane, M.; Uera, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 477.
[167] Chua, S.-S.; Ng, Y.-R.; Yamane, M. *Poster Presentation*, 6th Asian-European Symposium, Singapore, June 2010; "Rhodium-catalyzed 1,4-Addition of Triorgano(vinyl)silanes."

The application of $InCl_3$-catalyzed Mukaiyama-Michael addition of thioester **A1-5S** to intermediate **A1-5** inspired us to experiment the aforementioned rhodium(I) complex-catalyzed Michael addition on intermediate **A1-5**. When we subjected **A1-5** to the reaction conditions with a non-activated triorgano(vinyl)silane (**Figure 3.39**), the reaction did not proceed and starting material **A1-5** was recovered. We rationalized that pyranones, which were not explored during substrate screening, may not be compliable with the rhodium(I) complex-catalyzed Michael addition as the *β*-position may be less electron-deficient due to the presence of *γ*-oxygen atom. We are currently looking into further optimizing the reaction conditions to expand its substrate scope, especially to encompass staple motifs such as dihydropyranones. We could also bring the utility of the reaction a notch higher by incorporating asymmetrical chemistry *via* chiral catalysts or chiral promoters.

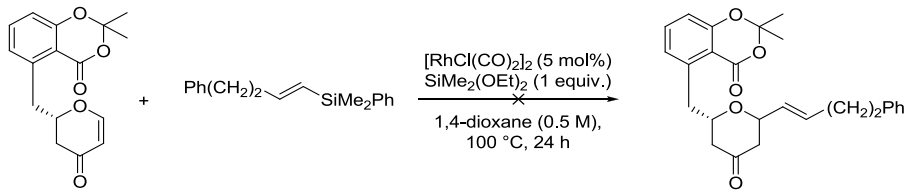


Figure 3.39 Rhodium(I) complex-catalyzed Michael addition of a non-activated triorgano(vinyl)silane on intermediate **A1-5**.

3.4.3 Conclusion

In a nutshell, we have demonstrated the applicability of our $InCl_3$-catalyzed Mukaiyama-Michael addition of silyl enol ether to construct the intrinsic 2,6-*anti*-THP core fragment in good yields, ranging 70-80%. We have yet to establish the feasibility of stereoselective reduction of pyranone **A1-14**, which was envisioned to take place following a macrolactonization. Meanwhile, we have also branched out from the initial route to explore the practicability of a recent methodology, which involved vinylboronic acids and hydroxylamide derivatives in the presence of $[RhCp^*Cl_2]_2$. We are currently working on the hydroboration of propargylic alcohols **A2-2** and **A2-3** as well as the synthesis of complementary amide **N-2**. Initial studies of proposed indium-mediated stereoselective Diels-Alder provided encouraging insights and further extensive investigations are required to establish the methodology and to be applied in the impending tandem one-pot synthesis of Apicularen A. Lastly, we attempted to apply a rhodium(I) complex-catalyzed Michael addition of triorgano(vinyl)silane, which was previously developed, but to no avail as it has not been developed to tolerate pyranone moieties.

THIS PAGE IS INTENTIONALLY LEFT BLANK.

Chapter Four

Experimental Section

THIS PAGE IS INTENTIONALLY LEFT BLANK.

4.1 General Methods

Experiments involving moisture and/or air sensitive components were performed in oven-dried glassware under a positive pressure of nitrogen using either freshly distilled or commercial-grade anhydrous solvents. Commercial-grade solvents and reagents were used without any further purification unless otherwise stated. Reagents and solvents which required more careful and elaborate handling were duly treated with strict accordance to the guidelines of Armarego and co-workers.[168]

Hydrochloric acid (HCl) of varying concentrations were prepared by dilution of commercially available concentrated 37% HCl solution with deionized water while sodium hydroxide (NaOH) solutions were prepared by dissolving sodium hydroxide pearls with deionized water. Saturated solutions of ammonium chloride (NH_4Cl), sodium bicarbonate ($NaHCO_3$), sodium carbonate ($NaCO_3$) and sodium chloride (NaCl, saturated solution is also known as *brine*) were prepared from their respective solids.

Known compounds, while not being fully characterized, are furnished with experimental ^{1}H and ^{13}C NMR data. Further identification and supporting information are duly cited.

Chromatography

Analytical thin layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica gel plate (0.2 mm thickness). Upon subjecting to elution, visualization of plates was conducted with UV radiation (254 nm), absorption of iodine vapour and/or staining with either basic solution of potassium permanganate, acidic solution of ceric molybdate or *p*-anisaldehyde, followed by heating on a hot plate.

Preparative TLC (pTLC) for purification of products from small scale syntheses were performed using Merck 60 F_{254} precoated silica gel plate (0.2 mm thickness). Upon subjecting to elution with appropriate eluent systems, the pTLC was visualized under UV radiation. The desired UV-active band was scraped and made into slurry with ethyl acetate. The slurry was then dried with magnesium sulfate ($MgSO_4$) and

[168] (a) Perrin, D. D. and Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford. 1988. (b) Armarego, W. L. F. and Chai, C. L. L. *Purification of Laboratory Chemicals*; 5th ed., Butterworth-Heinemann, Britain. 2003.

subsequently filtered. The filtrate was evaporated *in vacuo* to obtain purified component. This purification procedure was performed only to isolate UV-active compounds.

Flash column chromatography was performed using Merck Silica Gel 60 (0.010-0.063 nm) and required solvents as stated. Chromatography columns were packed as slurry of silica gel in appropriate solvent prior to use. The solutes were loaded neat or as a concentrated solution in dichloromethane.

Instruments and Equipments

Infrared Spectroscopy

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

Mass Spectroscopy

Mass spectrometry (MS) was carried out on the following equipment: Thermo Finnigan Polaris Q GCMS for MS (EI) spectra; Thermo Finnigan LCQ Deca XP Max for MS (ESI) spectra; and Thermo Finnigan MAT 95 XP for HRMS (EI, ESI). MS and HRMS were reported in units of mass to charge ratio (*m/z*).

Nuclear Magnetic Resonance Spectroscopy

Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR respectively) were recorded on Bruker Avance 400 MHz spectrometer. Chemical shifts were reported as δ in units of parts per million (ppm) downfield from tetramethylsilane ($SiMe_4$) (δ 0.00), using the residual solvent signal as an internal standard: deuterio chloroform-*d*, $CDCl_3$ (^{1}H NMR δ 7.26, singlet; ^{13}C NMR δ 77.0, triplet); deuterio acetone-*d*, CD_3OCD_3 (^{1}H NMR δ 2.05, quintet; ^{13}C NMR δ 29.9, singlet, 206.3, quintet).

Multiplicities were given as: s (singlet), d (doublet), t (triplet), quar (quartet), m (multiplet), br (broad), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublets of doublets) and ddt (doublet of doublets of triplets). Coupling constants (*J*) were recorded in Hertz (Hz). The number of protons (n) for a given resonance was indicated by nH.

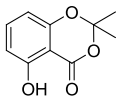
Notes

1. Spectra and data analysis for compounds **A1-5M**, **A1-8B** and **A2-1A** are not provided.
2. Stereochemical assignments of the chiral centres are solely based on previously reported procedures and data. Further structural elucidation *via* optical rotation, HPLC analysis and other instrumental analysis are currently underway. The lack of structural information at the time of printing is deeply regretted.
3. Melting points for solid-state compounds are not furnished at the time of printing as the samples available are minute in amount. Large-scale syntheses of the samples are currently underway.

4.2 Experimental Procedures & Supporting Information

4.2.1 Compound A1-1

5-Hydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one[169]

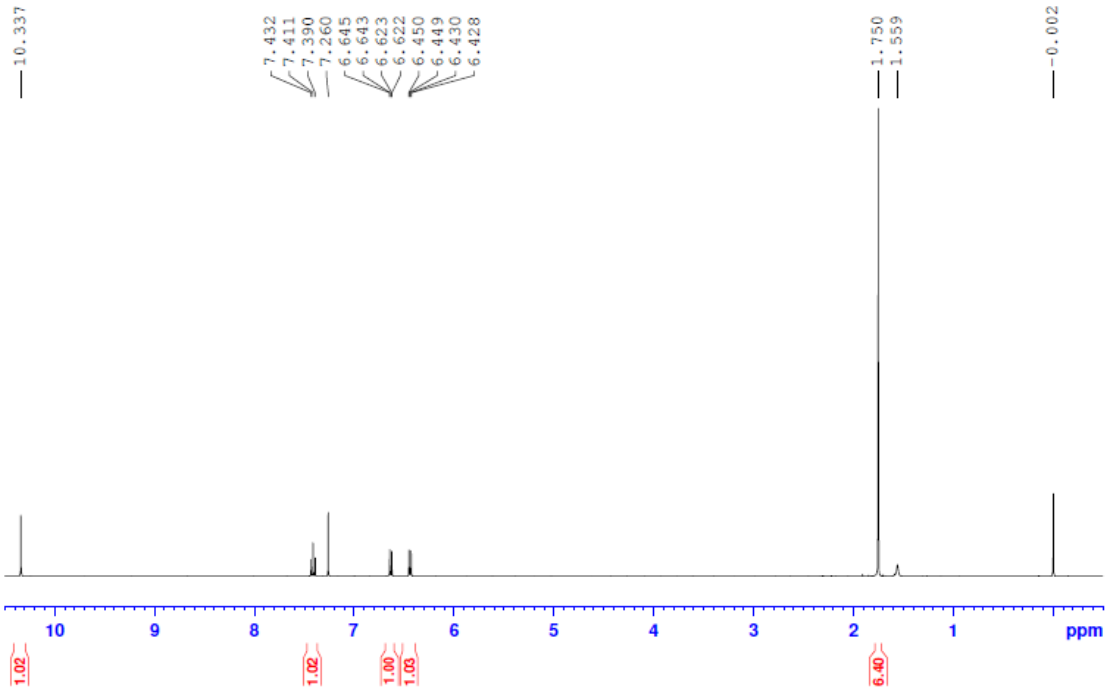


Experimental procedure

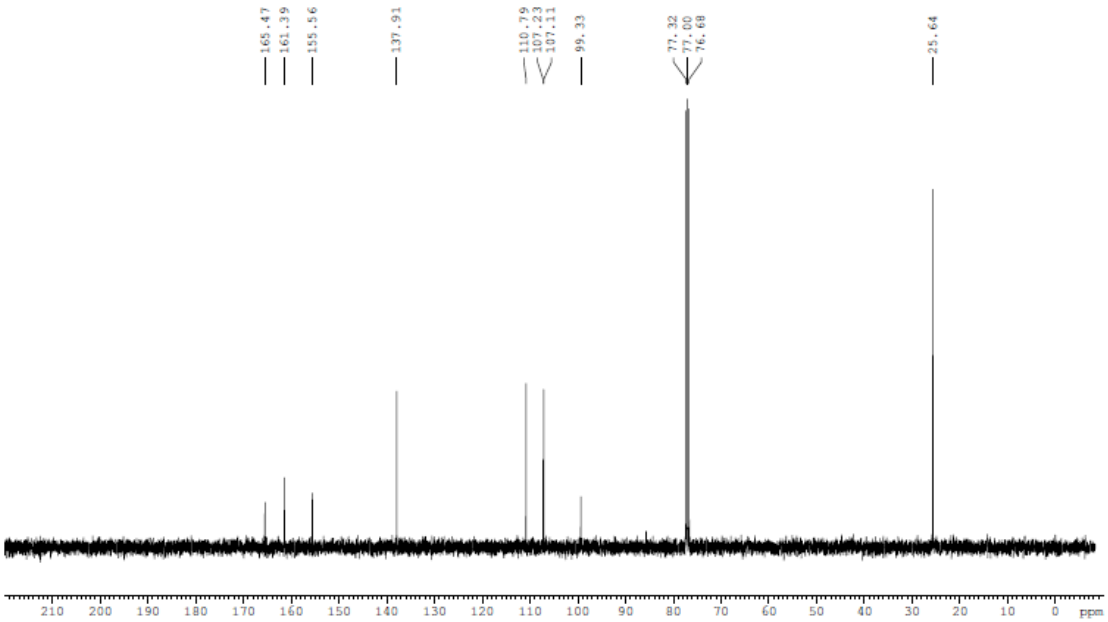
In an oven-dried 2-necked 100 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, 2,6-dihydroxybenzoic acid (15.412 g, 100 mmol, 1 equiv.), 4-dimethylaminopyridine (611 mg, 5 mmol, 0.05 equiv.) and dry acetone (18.4 mL, 250 mmol, 2.5 equiv.) were stirred in 1,2-dimethoxyethane (35 mL). The solution was cooled to 0 °C prior to addition of thionyl chloride (10.2 mL, 140 mmol, 1.4 equiv.) in 1,2-dimethoxyethane (5 mL). The reaction mixture was allowed to warm up to room temperature and to stir for another 5 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (Hexanes : Ethyl acetate = 9 : 1) to afford the protected acid **A1-1** as white solid (14.042 g; 73%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 10.34 (s, 1H), 7.41 (t, J = 8.4 Hz, 1H), 6.63 (dd, J = 8.4, 0.6 Hz, 1H), 6.44 (dd, J = 8.4, 0.6 Hz, 1H), 1.75 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.5, 161.4, 155.6, 137.9, 110.8, 107.2, 107.1, 99.3, 25.6.

[169] (a) Fuerstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, *2*, 3731. (b) Citron, C. A.; Rabe, P.; Dickschat, J. S. *J. Nat. Prod.* **2012**, *75*, 1765.

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

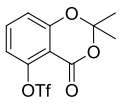


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.2 Compound A1-2

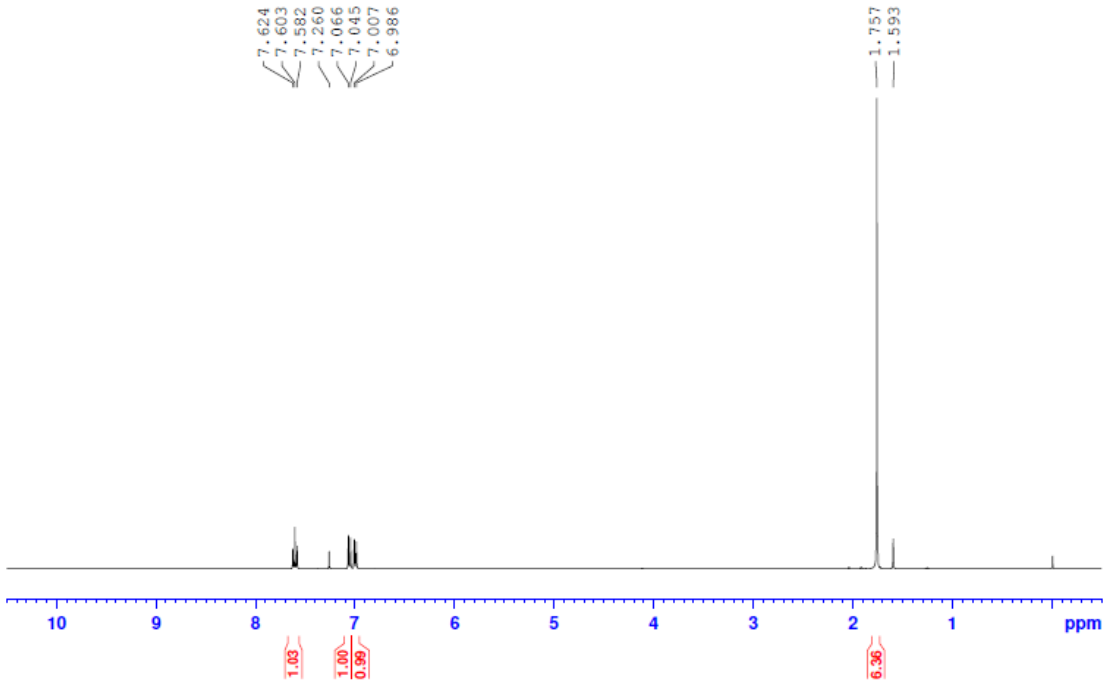
2,2-Dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl trifluoromethane-sulfonate[169]



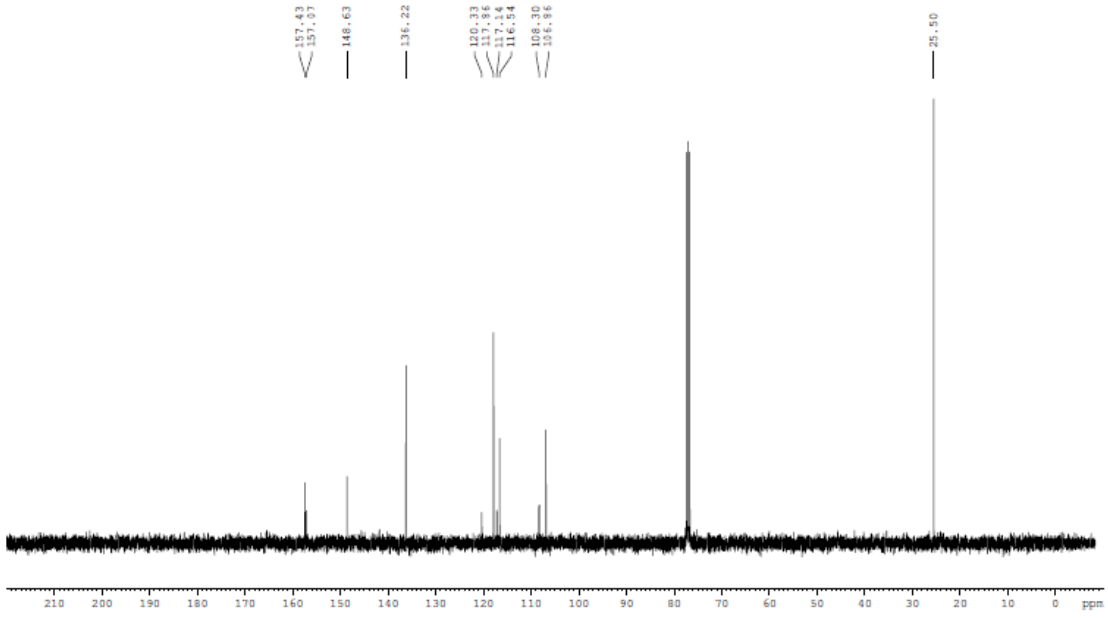
Experimental procedure

In an oven-dried 2-necked 250 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, the protected acid **A1-1** (14.042 g, 72.3 mmol, 1 equiv.) was stirred in pyridine (121 mL). The solution was cooled to 0 °C prior to addition of triflic anhydride (14.6 mL, 86.8 mmol, 1.2 equiv.) in dropwise manner. The reaction mixture was allowed to stir at 0 °C for 12 h. The reaction mixture was then quenched with 75 mL saturated sodium bicarbonate ($NaHCO_3$) solution. The aqueous layer was extracted with diethyl ether (3 x 60 mL). The combined organic extracts were washed with saturated copper(II) sulphate solution (75 mL), water (75 mL) as well as brine (75 mL) and subsequently dried over anhydrous magnesium sulphate ($MgSO_4$). The solution was then filtered and concentrated *in vacuo*. The residual crude product was sufficiently dissolved in ethyl acetate before hexanes was added to crash out colourless needle-like triflate crystals **A1-2** (20.521 g; 87%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.60 (t, J = 8.4 Hz, 1H), 6.63 (dd, J = 8.4, 0.6 Hz, 1H), 6.44 (dd, J = 8.4, 0.6 Hz, 1H), 1.75 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 157.4, 157.1, 148.6, 136.2, 120.3, 117.9, 117.1, 116.5, 108.3, 106.9, 25.5.

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

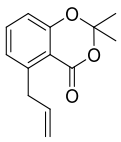


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.3 Compound A1-3

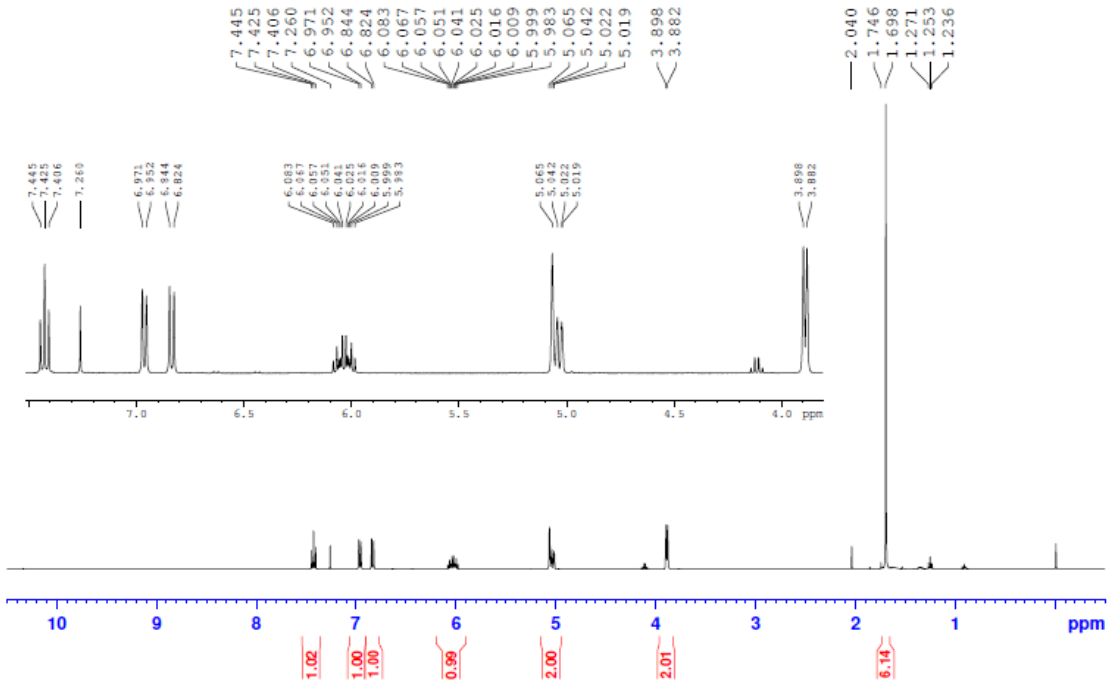
5-Allyl-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one[169]



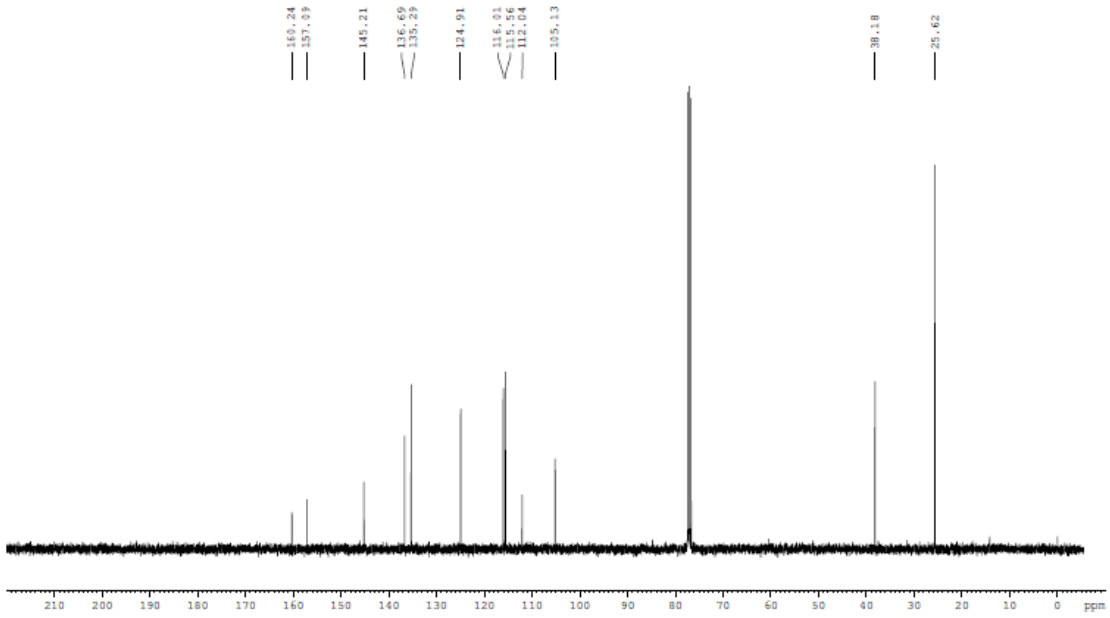
Experimental procedure

In an oven-dried 2-necked 500 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, the triflate **A1-2** (10.002 g, 31 mmol, 1 equiv.), $Pd(PPh_3)_4$ (708 mg, 0.62 mmol, 0.02 equiv.) and LiCl (3.899 g, 93 mmol, 3 equiv.) were stirred in dry, degassed THF (300 mL) at room temperature. After allyltributylstannane (9.5 mL, 31 mmol, 1 equiv.) was added, the reaction mixture was then refluxed for 48 h. After the reaction mixture was cooled down to room temperature, it was extracted with water (100 mL) and subsequently, 10% NH_4OH solution (100 mL). The aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with brine (100 mL) and subsequently dried over anhydrous magnesium sulphate ($MgSO_4$). The solution was then filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hexanes : Ethyl acetate = 95 : 5) to afford the terminal olefin **A1-3** as colourless oil (6.720 g; 99%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.43 (t, J = 7.8 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.08-5.98 (m, 1H), 5.07-5.02 (m, 2H), 3.89 (d, J = 6.4 Hz, 2H), 1.70 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 160.2, 157.1, 145.2, 136.7, 135.3, 124.9, 116.0, 115.6, 112.0, 105.1, 38.2, 25.6.

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

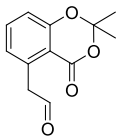


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.4 Compound A1-4

2-(2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl)acetaldehyde[170]

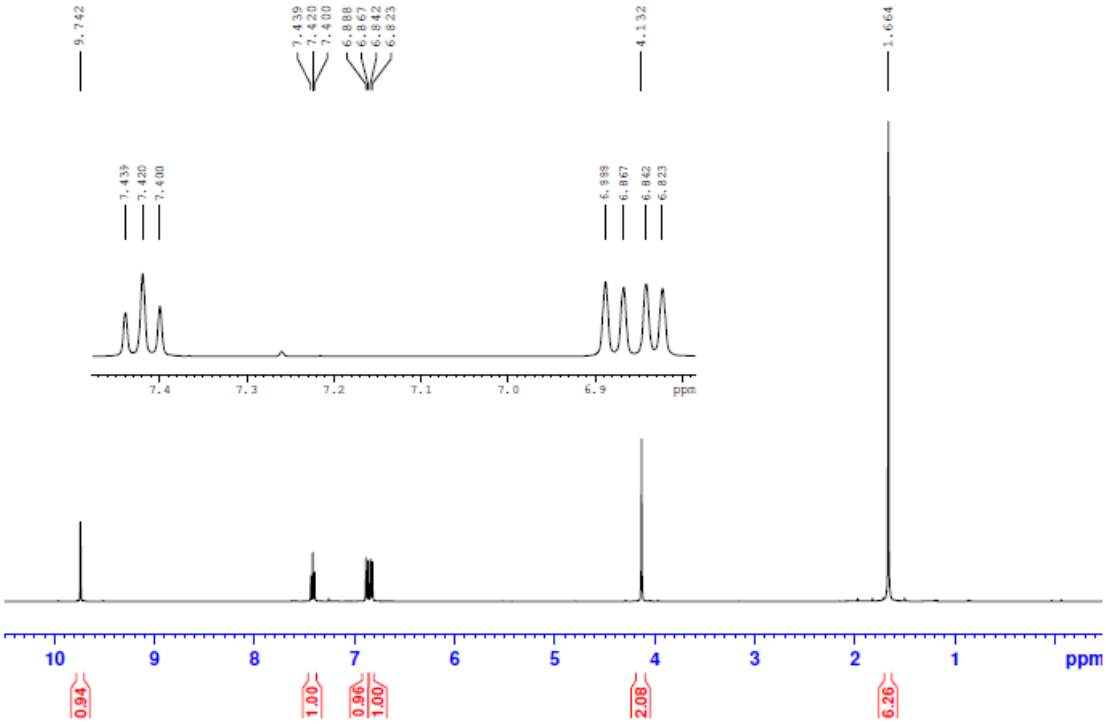


Experimental procedure

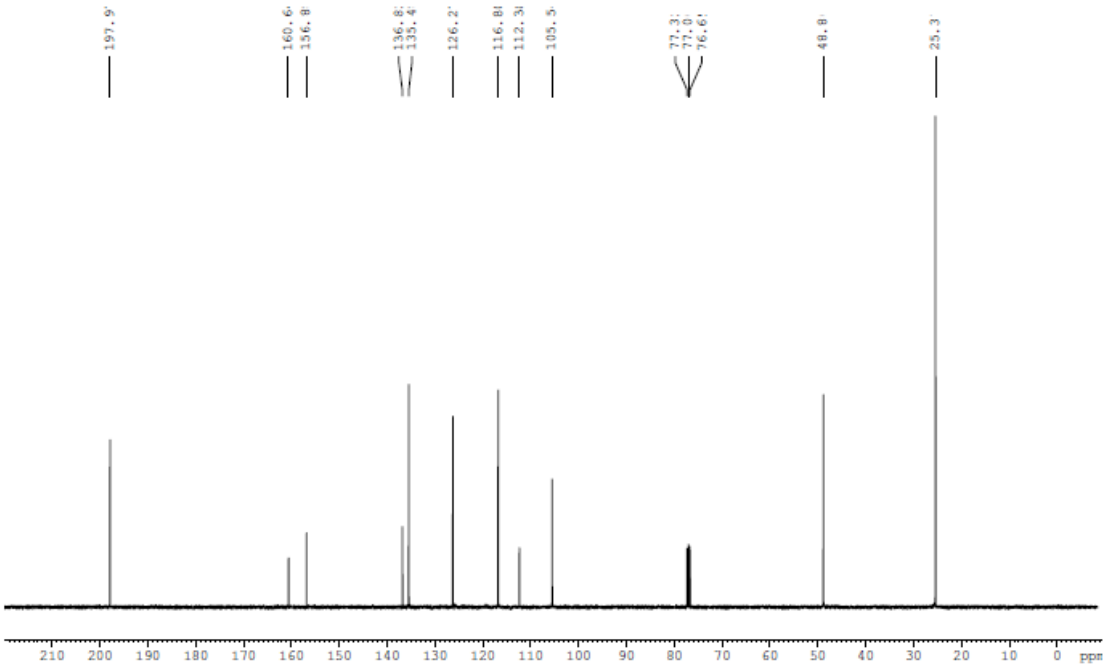
In 1-necked 500 mL round-bottomed flask equipped with a magnetic stirring bar, the terminal olefin **A1-3** (6.5 g, 29.8 mmol, 1 equiv.) was stirred in dichloromethane (280 mL) and the reaction mixture was cooled down to -78 °C. A flow of gaseous ozone was bubbled into the solution until it turned blue in colour. The excess ozone was purged with nitrogen gas and the solution was carefully quenched with dimethyl sulfide (43.8 mL, 596 mmol, 20 equiv.) at -78 °C. After the addition of dimethyl sulfide, the reaction mixture was allowed to warm up to room temperature. Triphenylphosphine (7.82 g, 29.8 mmol, 1 equiv.) was then added and the reaction mixture was allowed to stir for another 5 h at room temperature. The reaction mixture was concentrated *in vacuo* and the residual product was purified by flash column chromatography (Hexanes : Ethyl acetate = 4 : 1) to afford the terminal olefin **A1-3** as yellow solid (5.578 g; 85%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 9.74 (s, 1H), 7.42 (t, J = 7.8 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 4.13 (s, 2H), 1.66 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 198.0, 160.6, 156.9, 136.8, 135.5, 126.3, 116.8, 112.4, 105.5, 48.8, 25.4.

[170] Molander, G. A.; Cavalcanti, L. N. *J. Org. Chem.* **2011**, *76,* 623.

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

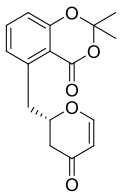


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.5 Compound A1-5

(*S*)-2,2-Dimethyl-5-((4-oxo-3,4-dihydro-2*H*-pyran-2-yl)methyl)-4*H*-benzo[*d*][1,3]dioxin-4-one[171]

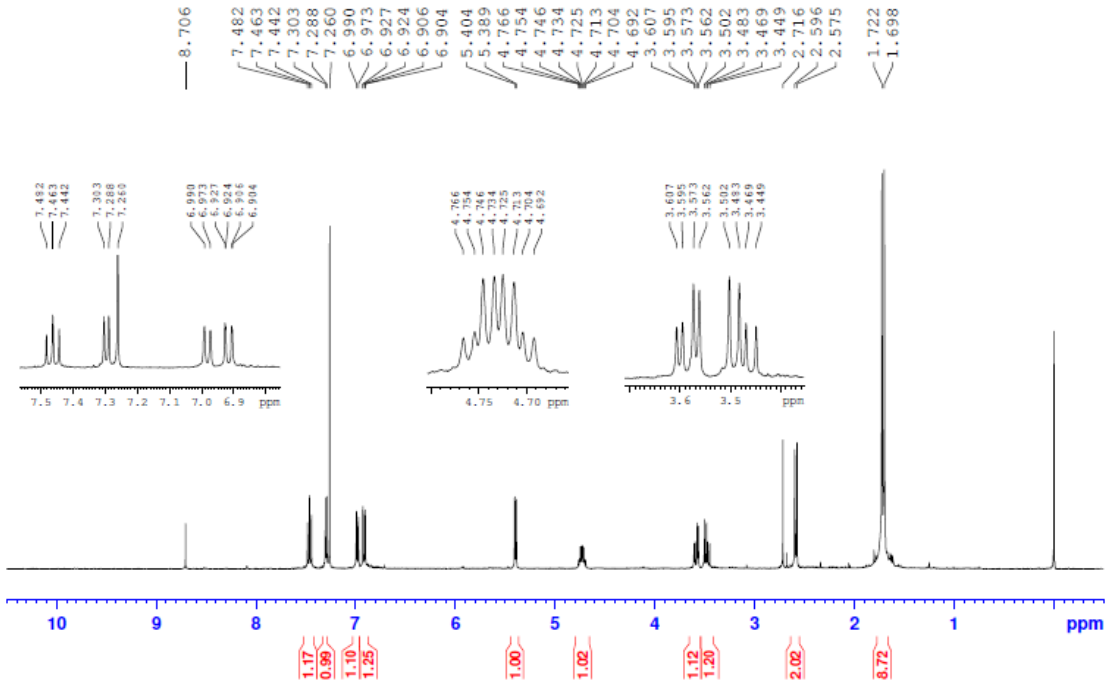


Experimental procedure

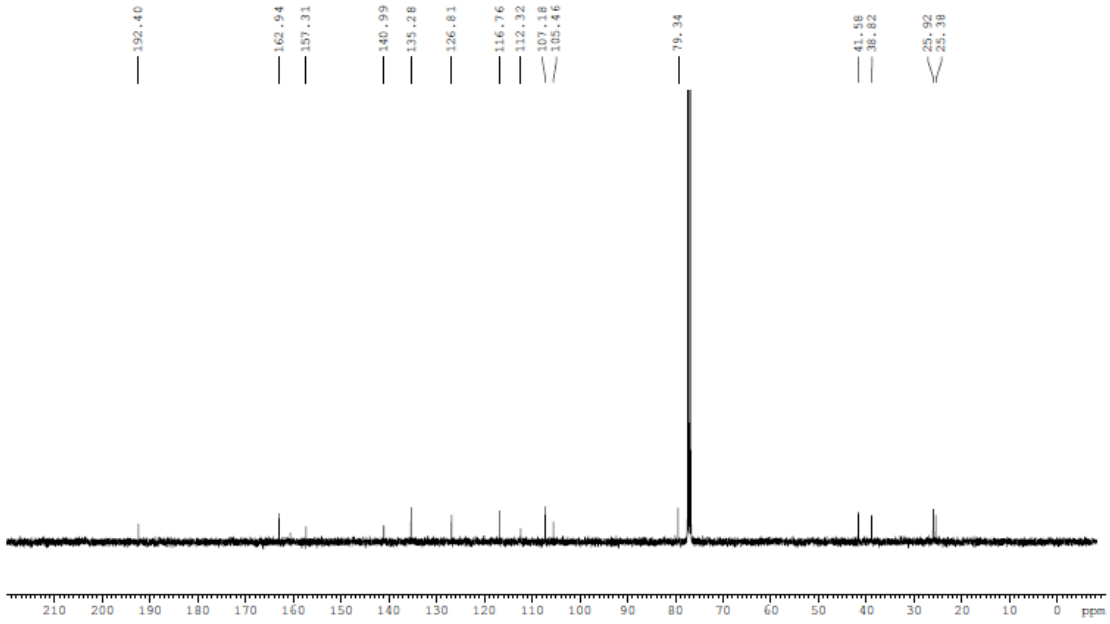
In an oven-dried 2-necked 100 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, aldehyde **A1-4** (11.073 g, 50.3 mmol, 1 equiv.), **catalyst A**[142,172] (1.224 g, 2.514 mmol, 0.05 equiv.) and powdered 4 Å MS (1.5 g) were stirred in dry, degassed acetone (40 mL) at room temperature. Danishefsky's diene (trans-1-methoxy-3-trimethylsiloxy-1,3-butadiene) (11.8 mL, 60.3 mmol,1.2 equiv.) was then added and the reaction mixture was allowed to stir for another 48 h at room temperature before it was subsequently diluted with dichloromethane (5 mL) and cooled down to 0 °C. Trifluoroacetic acid (0.20 mL, 2.5 mmol, 0.05 equiv.) and the reaction mixture was allowed to stir at 0 °C for 1 h. The reaction mixture was then filtered through silica on celite pad, which was subsequently washed copiously with diethyl ether. The filtrate was concentrated *in vacuo* and purified by flash column chromatography (Hexanes : Ethyl acetate = 85 : 15) to afford the dihydropyranone **A1-5** as viscous brown oil (12.235 g; 85%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.46 (t, J = 8.0 Hz, 1H), 7.30 (d, J = 6.4 Hz, 1H), 6.98 (d, J = 6.8 Hz, 1H), 6.92 (dd, J = 8.4, 1.0 Hz, 1H), 5.40 (d, J = 6.0 Hz, 1H), 4.77-4.69 (m, 1H), 3.58 (dd, J = 13.2, 4.6 Hz, 1H), 3.48 (dd, J = 13.4, 7.8 Hz, 1H), 2.59 (d, J = 8.4 Hz, 2H), 1.72 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 192.4, 162.9, 157.3, 141.0, 135.3, 126.8, 116.8, 112.3, 107.2, 105.5, 79.3, 41.6, 38.8, 25.9, 25.4.

[171] Molander, G. A.; Cavalcanti, L. N. *J. Org. Chem.* **2011**, *76,* 623.
[172] As the catalyst has to be prepared, it is noteworthy that the purity of **Catalyst A** is crucial to achieve high yields and selectivities. Otherwise, the yields may vary from 60-85%.

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



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



4.2.6 Compound A1-5S

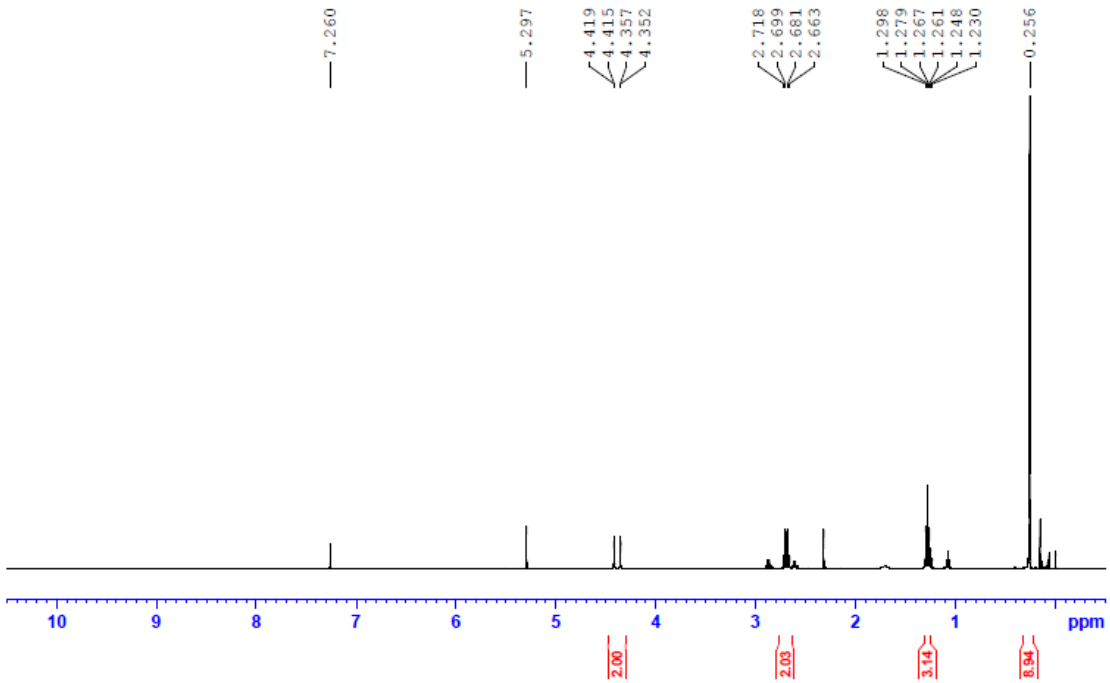
(1-(Ethylthio)vinyloxy)trimethylsilane[173]

Experimental procedure

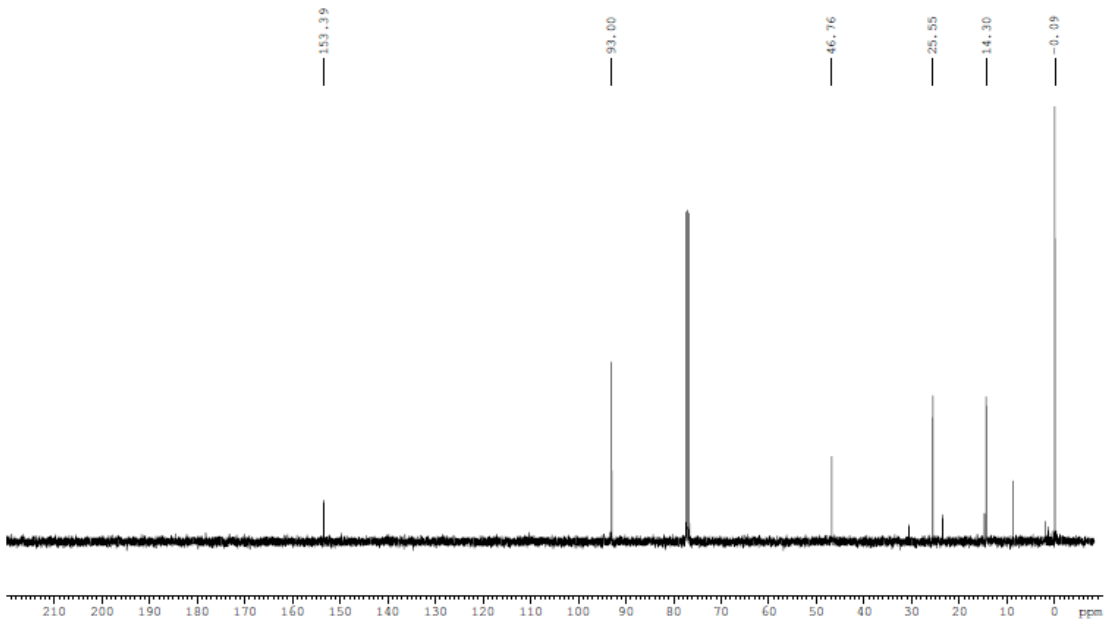
In an oven-dried 2-necked 200 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, ethyl thioacetate (10.06 mL, 100 mmol, 1 equiv.) and triethylamine (16.8 mL, 120 mmol, 1.2 equiv.) were stirred in dry, degassed dichloromethane (100 mL). The reaction mixture was cooled down to 0 °C. Trimethylsilyl trifluoromethanesulfonate (18.0 mL, 100 mmol, 1 equiv.) was added dropwise and the reaction was allowed to stir at 0 °C for another 2 h. The reaction mixture was then concentrated *in vacuo*, resulting in two layers of liquid. The silyl enol ether **A1-5S** was obtained as the upper layer of the residual crude mixture, which was sufficiently pure for perusal in subsequent reactions. The silyl enol ether **A1-5S** was afforded as yellow oil (14.108 g; 80%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 4.42 (d, J = 1.6 Hz, 1H), 4.36 (d, J = 2.0 Hz, 1H), 2.69 (quar, J = 7.3 Hz, 2H), 1.28 (t, J = 7.4 Hz, 3H), 0.26 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 153.4, 93.0, 25.6, 14.3, -0.1.

[173] Shiina, I.; Hashizume, M.; Yamai, Y.; Oshiumi, H.; Shimazaki, T.; Takasuna, Y.; Ibuka, R. *Chem. Eur. J.* **2005**, *11*, 6601.

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

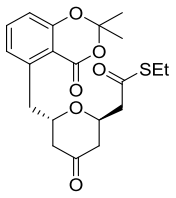


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.7 Compound A1-6

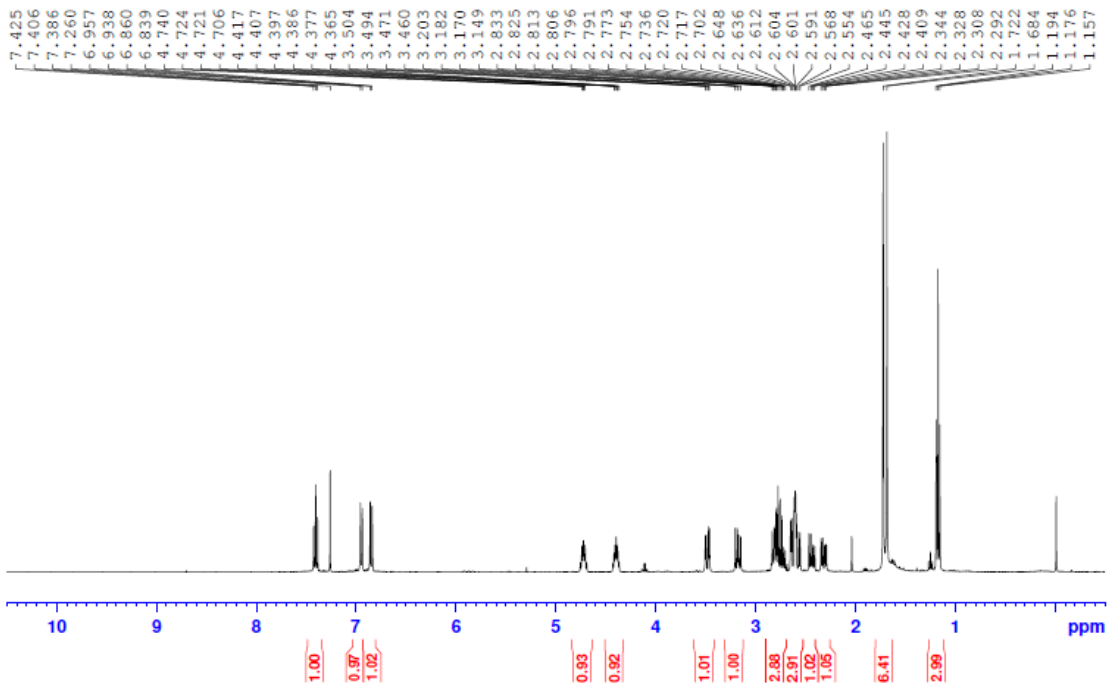
S-Ethyl 2-((2*S*,6*R)*-6-((2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl)methyl)-4-oxotetrahydro-2*H*-pyran-2-yl)ethanethioate



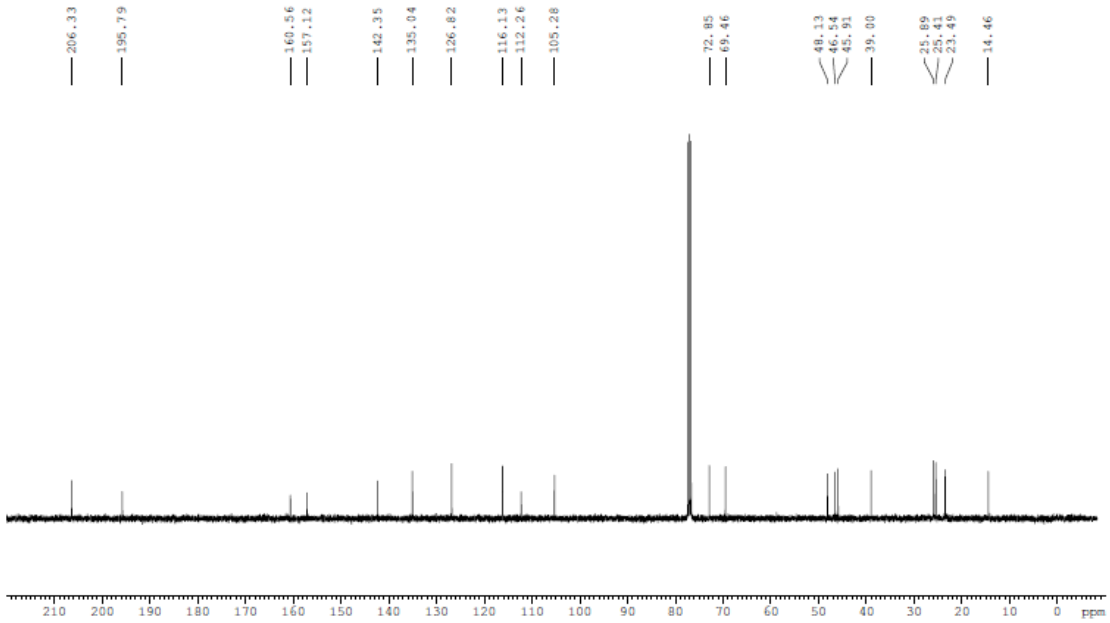
Experimental procedure

To an oven-dried 2-necked 25 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, pyranone **A1-5** (2.290 g, 7.94 mmol, 1 equiv.) and indium trichloride (527 mg, 2.38 mmol, 0.3 equiv.) were added. The reaction mixture was cooled down to 0 °C when silyl enol ether **A1-5S** (3.50 g, 19.86 mmol, 2.5 equiv.) was added to the reaction mixture portionwise. The reaction mixture was allowed to stir in neat condition at ambient temperature for another 15 h. The reaction mixture was diluted with ethyl acetate (30 mL) and subsequently quenched by 1M HCl (5 mL). The reaction mixture was extracted with water (25 mL) and the aqueous layer was extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were washed with brine (25 mL) and subsequently dried over anhydrous magnesium sulphate ($MgSO_4$). The solution was then filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hexanes : Ethyl acetate = 7 : 3) to afford the thioester **A1-6** as viscous brown oil (1.870 g; 60%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.41 (t, J = 7.8 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 4.74-4.71 (m, 1H), 4.42-4.38 (m, 1H), 3.48 (dd, J = 13.2, 4.2 Hz, 1H), 3.18 (dd, J = 13.2, 8.4 Hz, 1H), 2.83-2.68 (m, 3H), 2.65-2.55 (m, 3H), 2.44 (dd, J = 14.4, 7.8 Hz, 1H), 2.32 (dd, J = 14.4 6.4 Hz, 1H), 1.72 (s, 3H), 1.68 (s, 3H), 1.18 (t, J = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 206.3, 195.8, 160.6, 157.1, 142.4, 135.0, 126.8, 116.1, 112.3, 105.3, 72.8, 69.5, 48.1, 46.5, 45.9, 39.0, 25.9, 25.4, 23.5, 14.5. FTIR (neat) : ν_{max} 2932, 1730, 1682, 1607, 1584, 1479, 1449, 1416, 1379, 1346, 1315, 1298, 1269 cm^{-1}. HRMS (EI) *m/z* : Calcd for $C_{20}H_{25}O_6S$ $[M+H]^+$ = 393.1372. Found 393.1365.

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

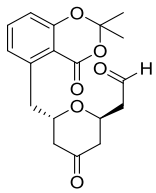


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.8 Compound A1-7

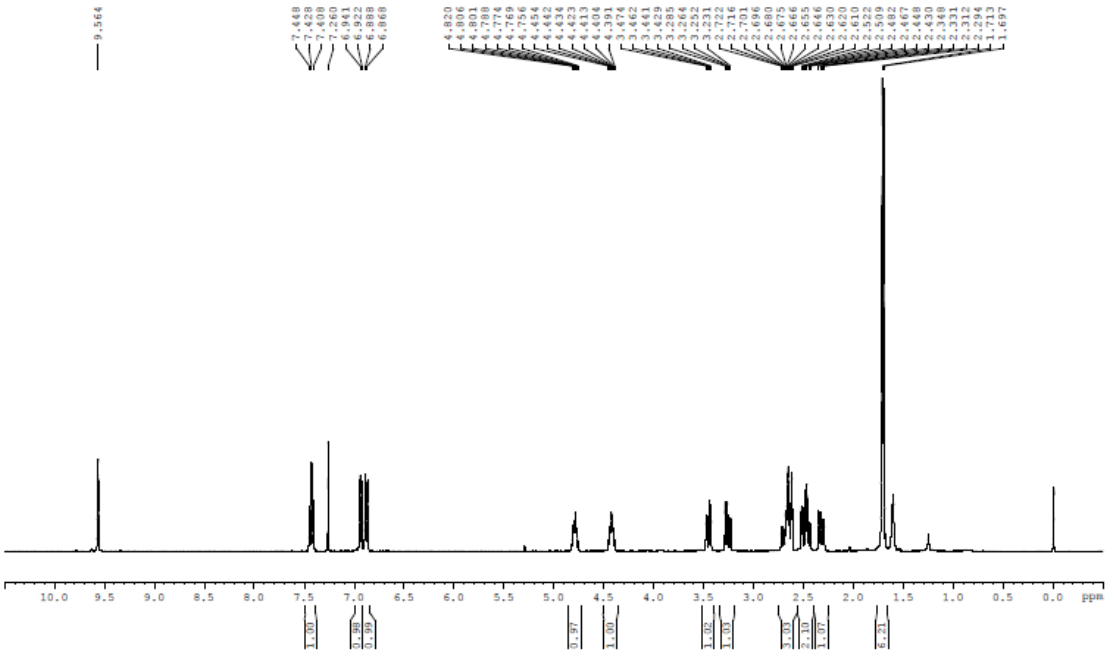
2-((2*S*,6*S*)-6-((2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl)methyl)-4-oxotetrahydro-2*H*-pyran-2-yl)acetaldehyde



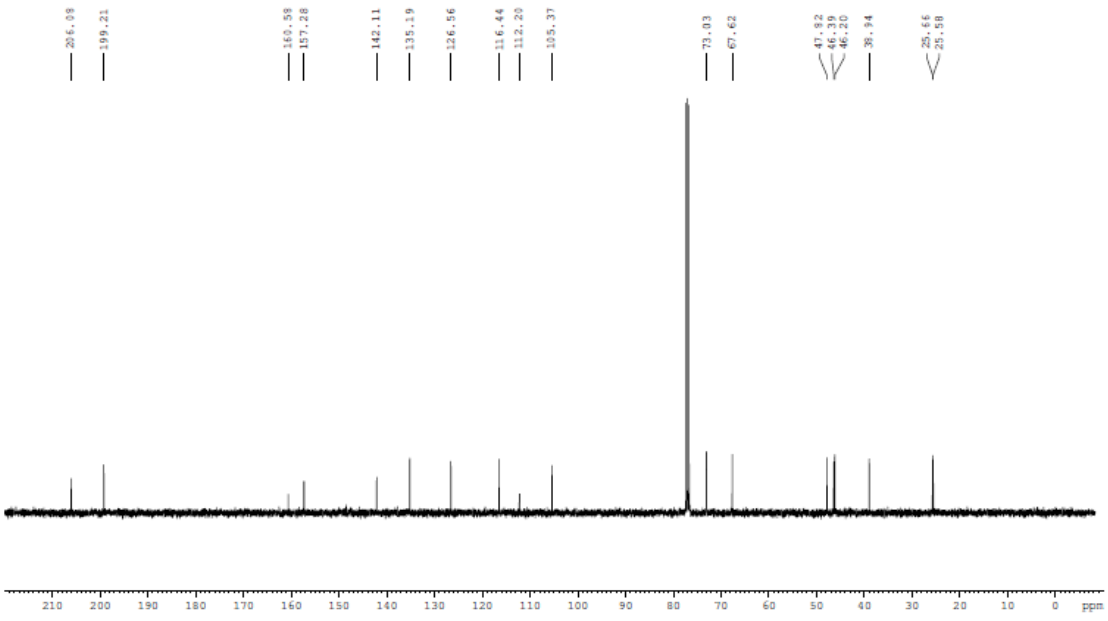
Experimental procedure

In an oven-dried 2-necked 25 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, thioester **A1-6** (205 mg, 0.52 mmol, 1 equiv.) and 10% Pd on carbon (28 mg, 0.026 mmol, 0.05 equiv.) were stirred in dichloromethane (1.5 mL). Triethylsilane (0.17 mL, 1.04 mmol, 2 equiv.) was added to the reaction mixture dropwise. (*Caution* : A needle outlet may be installed to release the hydrogen gas generated.) The reaction mixture was allowed to stir at ambient temperature for another 1 h. The reaction mixture was then filtered through silica on celite pad, which was subsequently washed copiously with dichloromethane. The filtrate was concentrated *in vacuo* and purified by flash column chromatography (Hexanes : Ethyl acetate = 1 : 1) to afford the aldehyde **A1-7** as yellow oil (122 mg; 70%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 9.56 (s, 1H), 7.43 (t, J = 8.0 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 4.82-4.76 (m, 1H), 4.45-4.39 (m, 1H), 3.45 (dd, J = 13.2, 4.8 Hz, 1H), 3.26 (dd, J = 13.2, 8.4 Hz, 1H), 2.72-2.61 (m, 3H), 2.52-2.43 (m, 2H), 2.32 (dd, J = 14.6, 7.0 Hz, 1H), 1.71 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 206.1, 199.2, 160.6, 157.3, 142.1, 135.2, 126.6, 116.4, 112.2, 105.4, 73.0, 67.6, 47.8, 46.4, 46.2, 38.9, 25.7, 25.6. FTIR (neat) : ν_{max} 3005, 2932, 1730, 1717, 1607, 1584, 1479, 1449, 1379, 1317, 1298, 1271 cm^{-1}. HRMS (EI) *m/z* : Calcd for $C_{18}H_{21}O_6$ $[M+H]^+$ = 333.1338. Found 333.1344.

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

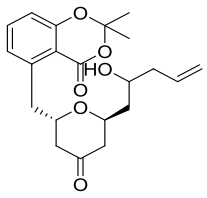


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.9 Compound A1-8

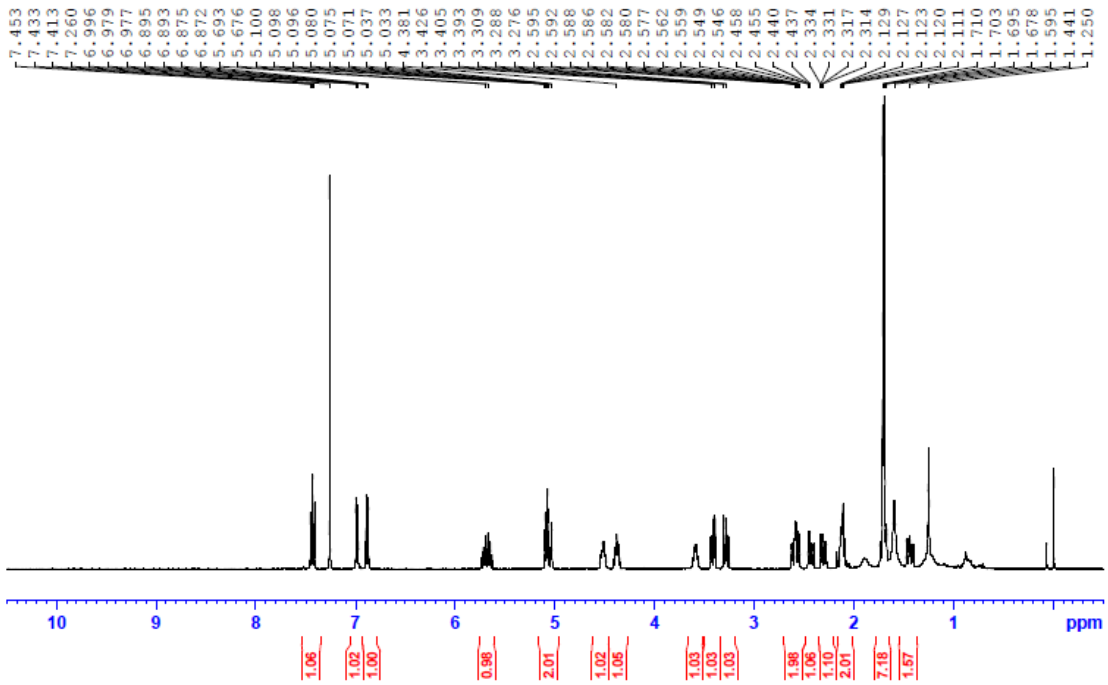
5-(((2*S*,6*S*)-6-(2-hydroxypent-4-enyl)-4-oxotetrahydro-2*H*-pyran-2-yl)methyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one



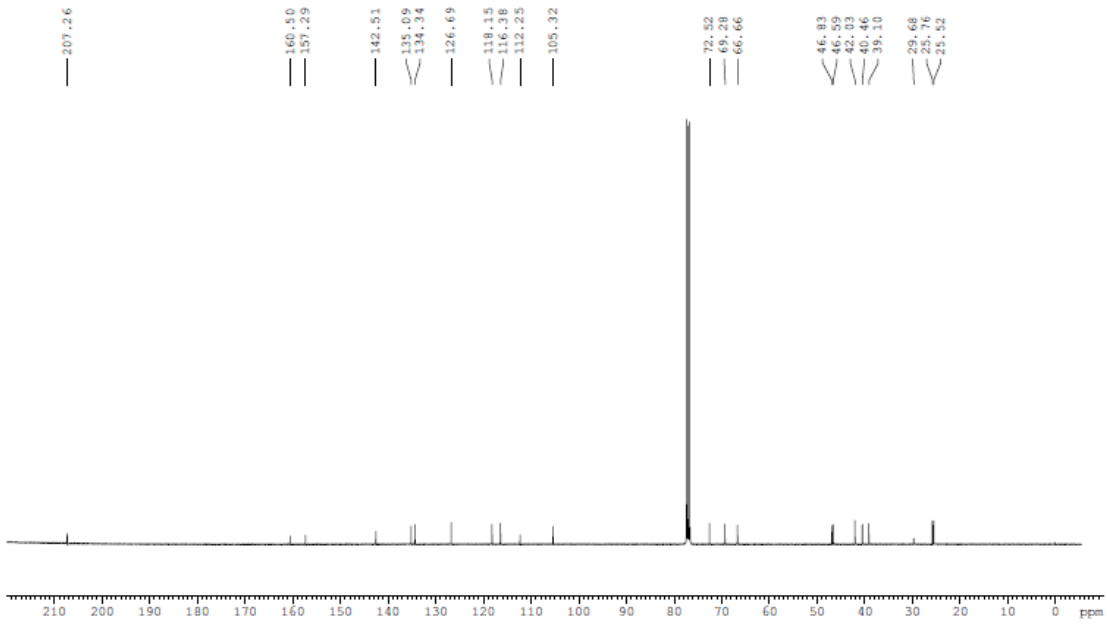
Experimental procedure

In an oven-dried 2-necked 25 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, aldehyde **A1-7** (54 mg, 0.161 mmol, 1 equiv.) was stirred in diethyl ether (1.5 mL) at -78 °C. (+)-*B*-Allyldiisopinocampheylborane solution, 1.0 M in pentane (0.24 mL, 0.242 mmol, 1.5 equiv.) was further diluted with diethyl ether (1 mL) and subsequently added to the reaction mixture slowly *via* syringe pump at the rate of 1 ml/h. The reaction mixture was stirred at -78 °C for another 1 h and warmed up to ambient temperature for 2 h thereafter. The reaction mixture was then cooled down to 0 °C and subsequently quenched with 2 mL of 3:1 (v/v) mixture of 3 M sodium hydroxide and 30% hydrogen peroxide (H_2O_2) for 30 min. The reaction mixture was extracted with water (5 mL) and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (5 mL) and subsequently dried over anhydrous magnesium sulphate ($MgSO_4$). The solution was then filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hexanes : Ethyl acetate = 1 : 1) to afford the homoallylic alcohol **A1-8** as pale yellow oil (30 mg; 50%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.43 (t, J = 8.0 Hz, 1H), 6.99 (dd, J = 7.2, 0.8 Hz, 1H), 6.88 (dd, J = 8.0, 1.0 Hz, 1H), 5.74-5.63 (m, 1H), 5.10-5.03 (m, 2H), 4.55-4.49 (m, 1H), 4.41-4.35 (m, 1H), 3.62-3.56 (m, 1H), 3.42 (dd, J = 13.2, 4.8 Hz, 1H), 3.28 (dd, J = 13.0, 8.2 Hz, 1H), 2.63-2.55 (m, 2H), 2.43 (ddd, J = 14.4, 7.2, 1.2 Hz, 1H), 2.31 (ddd, J = 14.6, 7.0, 1.2 Hz, 1H), 2.14-2.09 (m, 2H), 1.74-1.68 (m, 7H), 1.44 (ddd, J = 14.8, 9.7, 3.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 207.3, 160.5, 157.3, 142.5, 135.1, 134.3, 126.7, 118.2, 116.4, 112.3, 105.3, 72.5, 69.3, 66.7, 46.8, 46.6, 42.0, 40.5, 39.1, 25.8, 25.5. FTIR (neat) : ν_{max} 3431, 2926, 1722, 1607, 1582, 1479, 1447, 1391, 1379, 1317, 1296, 1269 cm^{-1}. HRMS (EI) *m/z* : Calcd for $C_{21}H_{26}O_6Na$ $[M+Na]^+$ = 397.1627. Found = 397.1631.

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

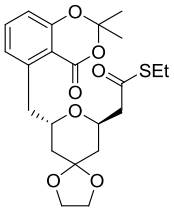


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.10 Compound A1-10A

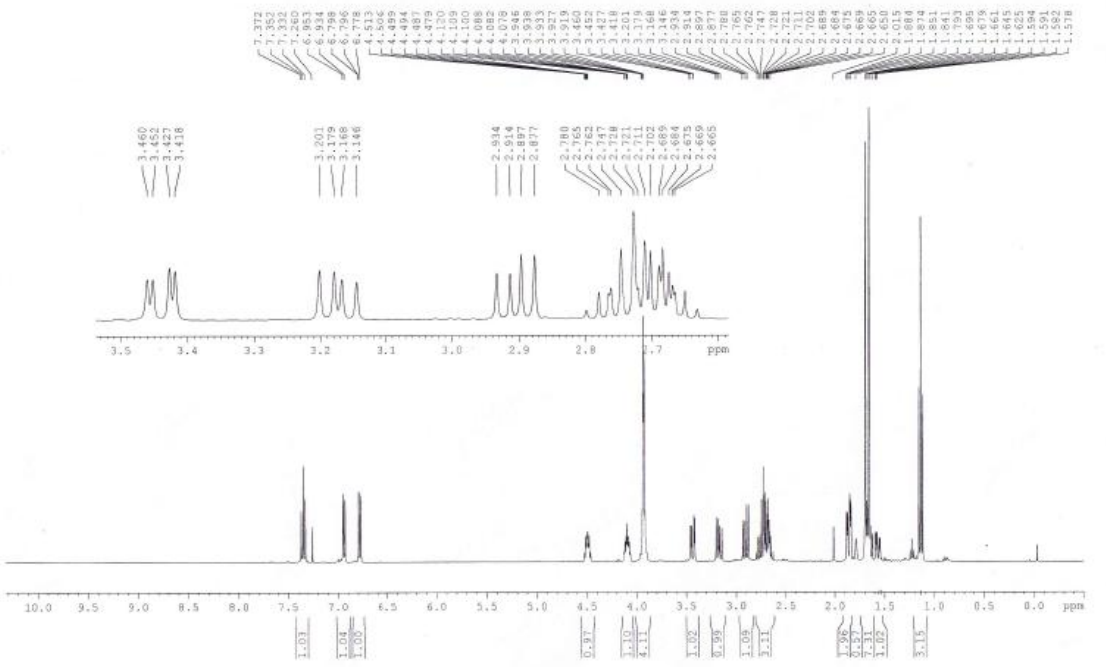
S-Ethyl 2-((7*R*,9*S*)-9-((2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl)methyl)-1,4,8-trioxaspiro[4.5]decan-7-yl)ethanethioate



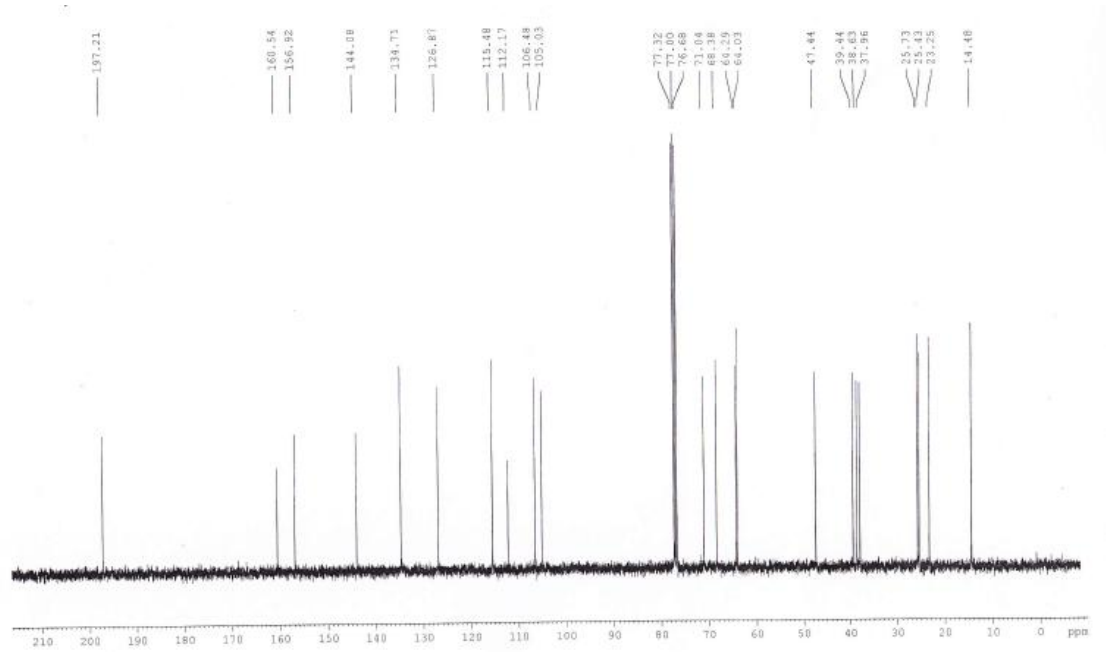
Experimental procedure

In a 1-necked 50 mL round-bottomed flask equipped with a magnetic stirring bar, thioester **A1-6** (1.106 g, 2.82 mmol, 1 equiv.), ethylene glycol (0.48 mL, 8.46 mmol, 3 equiv.) and triethyl orthoformate (1.41 mL, 8.46 mmol, 3 equiv.) were stirred in toluene (28 mL) at ambient temperature. *p*-Toluenesulfonic acid (54 mg, 0.28 mmol, 0.1 equiv.) was then added. The reaction mixture was allowed to stir at ambient temperature for 24 h. The reaction mixture was extracted with saturated sodium bicarbonate ($NaHCO_3$) solution (10 mL) and the aqueous layer was extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were washed with brine (10 mL) and subsequently dried over anhydrous magnesium sulphate ($MgSO_4$). The solution was then filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hexanes : Ethyl acetate = 3 : 1) to afford the acetal **A1-10A** as viscous pale yellow oil (0.923 g; 75%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.35 (t, J = 8.0 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.79 (d, J = 7.2 Hz, 1H), 4.51-4.48 (m, 1H), 4.12-4.08 (m, 1H), 3.95-3.92 (m, 4H), 3.44 (dd, J = 13.4, 3.4 Hz, 1H), 3.17 (dd, J = 13.2, 8.8 Hz, 1H), 2.91 (dd, J = 14.8, 8.0 Hz, 1H), 2.80-2.63 (m, 3H), 1.86 (dd, J = 13.2, 4.0 Hz, 2H), 1.70-1.63 (m, 7H), 1.58 (dd, J = 13.2, 4.4 Hz, 1H), 1.14 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 197.2, 160.5, 156.9, 144.1, 134.7, 126.9, 115.5, 112.2. 106.5, 105.0, 71.0, 68.4, 64.3, 64.0, 47.4, 39.4, 38.6, 38.0, 25.7, 25.4, 23.3, 14.5. FTIR (neat) : ν_{max} 2932, 1728, 1684, 1607, 1582, 1479, 1449, 1389, 1379, 1358, 1315, 1296, 1269 cm^{-1}. HRMS (EI) *m/z* : Calcd for $C_{22}H_{28}O_7SNa$ $[M+Na]^+$ = 459.1453. Found 459.1459.

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

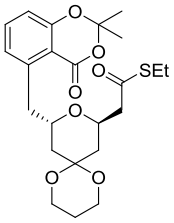


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.11 Compound A1-10B

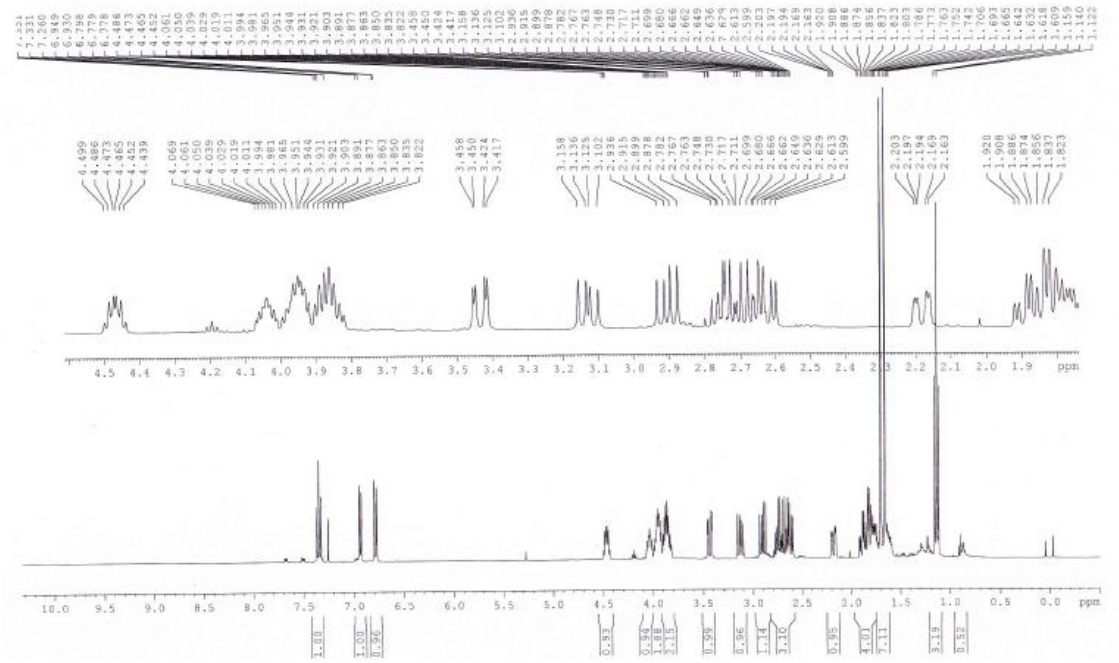
S-Ethyl 2-((8*R*,10*S*)-10-((2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl)methyl)-1,5,9-trioxaspiro[5.5]undecan-8-yl)ethanethioate



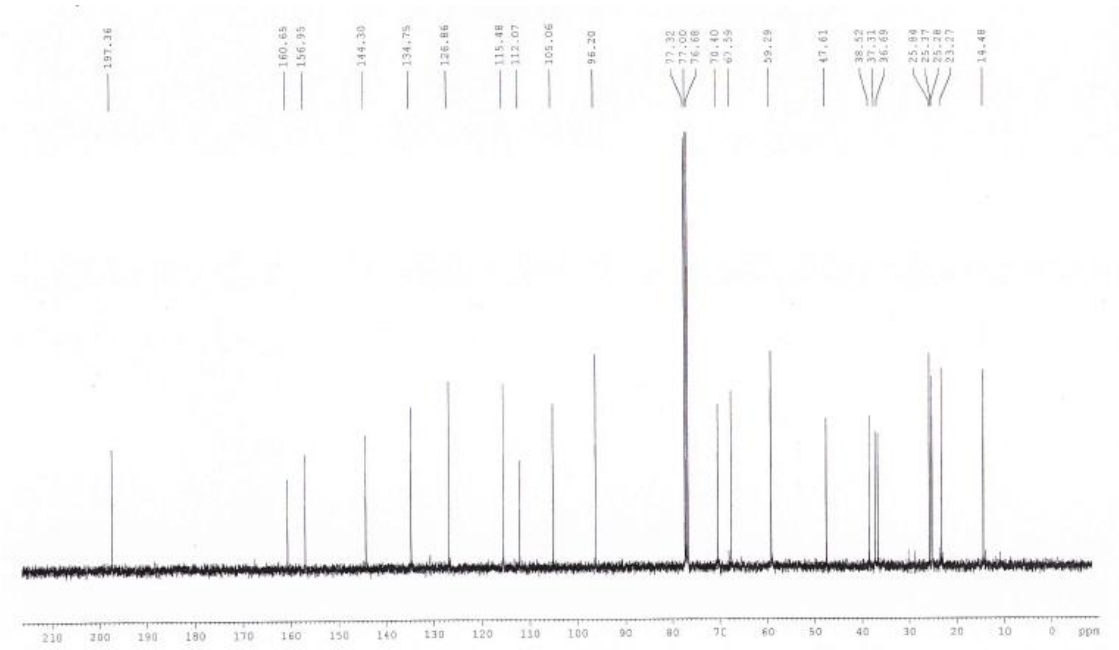
Experimental procedure

In a 1-necked 25 mL round-bottomed flask equipped with a magnetic stirring bar, thioester **A1-6** (0.134 g, 0.342 mmol, 1 equiv.), 1,3-propanediol (0.075 mL, 1.026 mmol, 3 equiv.) and triethyl orthoformate (0.170 mL, 1.026 mmol, 3 equiv.) were stirred in toluene (1 mL) at ambient temperature. *p*-Toluenesulfonic acid (7 mg, 0.034 mmol, 0.1 equiv.) was then added. The reaction mixture was allowed to stir at ambient temperature for 24 h. The reaction mixture was extracted with saturated sodium bicarbonate ($NaHCO_3$) solution (5 mL) and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (5 mL) and subsequently dried over anhydrous magnesium sulphate ($MgSO_4$). The solution was then filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hexanes : Ethyl acetate = 3 : 1) to afford the acetal **A1-10B** as viscous pale yellow oil (0.072 g; 48%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.35 (t, J = 8.0 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 4.50-4.44 (m, 1H), 4.07-3.82 (m, 5H), 3.44 (dd, J = 13.4, 3.0 Hz, 1H), 3.13 (dd, J = 13.4, 9.0 Hz, 1H), 2.91 (dd, J = 14.8, 8.4 Hz, 1H), 2.78-2.60 (m, 3H), 2.20-2.16 (m, 1H), 1.92-1.61 (m, 11H), 1.14 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 197.4, 160.7, 157.0, 144.3, 134.8, 126.9, 115.5, 112.1, 105.1, 96.2, 70.4, 67.6, 59.3, 47.6, 38.5, 37.3, 36.7, 25.8, 25.4, 25.3, 23.3, 14.5. FTIR (neat) : ν_{max} 2967, 2874, 1726, 1682, 1607, 1582, 1479, 1449, 1379, 1315, 1296 cm^{-1}. HRMS (EI) *m/z* : Calcd for $C_{23}H_{30}O_7SNa$ $[M+Na]^+$ = 473.1610. Found 473.1604.

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

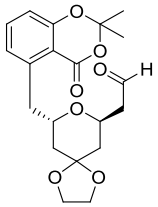


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.12 Compound A1-11A

2-((7*S*,9*S*)-9-((2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl)methyl)-1,4,8-trioxaspiro[4.5]decan-7-yl)acetaldehyde



Experimental procedure

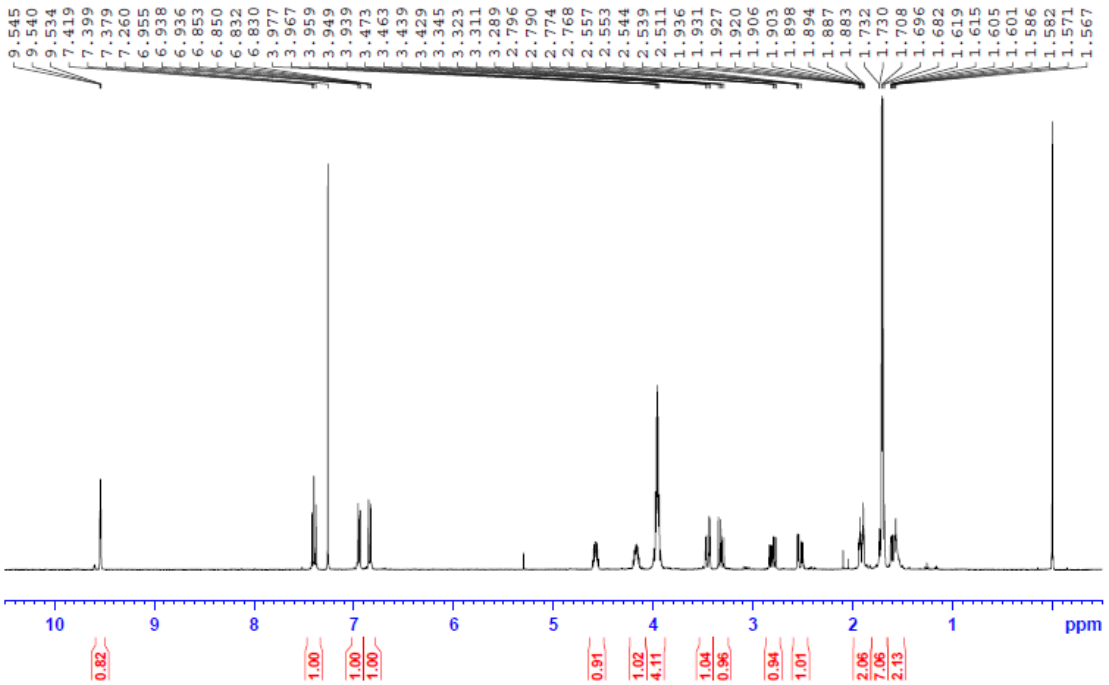
Method 1: In an oven-dried 2-necked 25 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, thioester **A1-10A** (152 mg, 0.347 mmol, 1 equiv.) and 10% Pd on carbon (19 mg, 0.017 mmol, 0.05 equiv.) were stirred in dichloromethane (1.5 mL) at ambient temperature. Triethylsilane (0.12 mL, 0.694 mmol, 2 equiv.) was added to the reaction mixture dropwise. A needle outlet was installed to release the hydrogen gas generated. The reaction mixture was allowed to stir at ambient temperature for another 1 h. The reaction mixture was then filtered through silica on celite pad, which was subsequently washed copiously with dichloromethane. The filtrate was concentrated *in vacuo* and purified by flash column chromatography (Hexanes : Ethyl acetate = 1 : 1) to afford the aldehyde **A1-11A** as viscous pale yellow oil (112 mg; 86%).

Method 2: To an oven-dried 2-necked 100 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, thioester **A1-10A** (884 mg, 2.025 mmol, 1 equiv.), 4 Å molecular sieves (0.5 g) and $Pd(OAc)_2$ (150 mg, 0.668 mmol, 0.33 equiv.) were stirred in degassed acetone (40 mL). Triethylsilane (1.62 mL, 10.126 mmol, 5 equiv.) was added to the reaction mixture dropwise until the brownish reaction mixture turned black. A needle outlet was installed to release the hydrogen gas generated. The reaction mixture was allowed to stir at ambient temperature for another 3 h. The reaction mixture was then filtered through silica on celite pad, which was subsequently washed copiously with ethyl acetate. The filtrate was concentrated *in vacuo* and purified by flash column chromatography (Hexanes : Ethyl acetate = 1 : 1) to afford the aldehyde **A1-11A** as viscous pale yellow oil (655 mg; 86%).

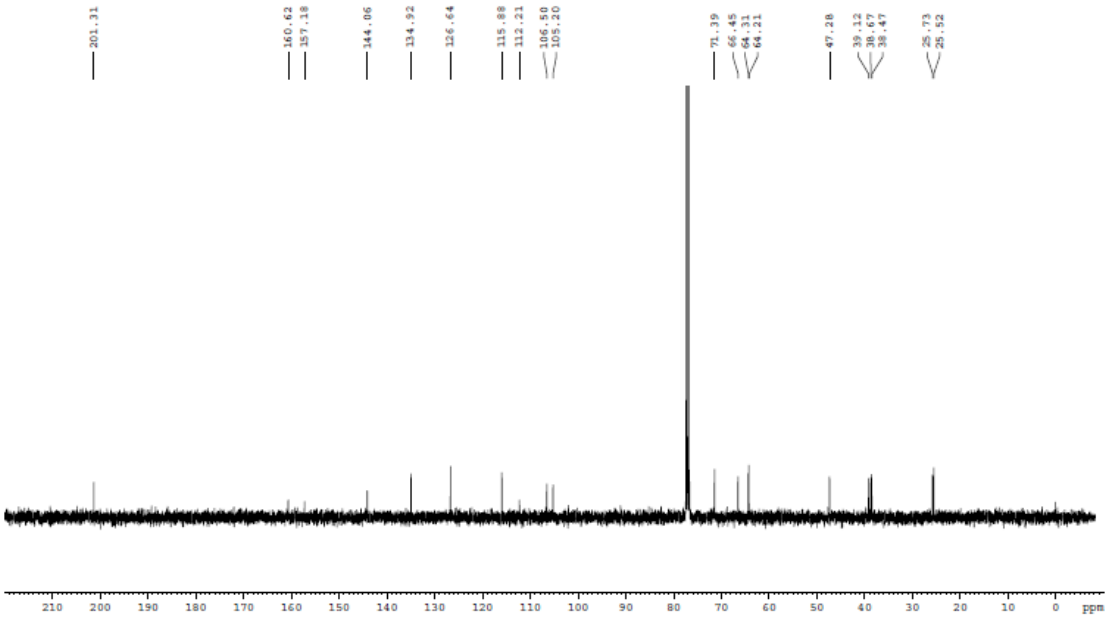
(*Note: This compound is unstable and will decompose over time even when stored at 0 °C*).

^{1}H NMR (400 MHz, $CDCl_3$) : δ 9.54 (t, J = 2.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 7.2 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 4.59-4.55 (m, 1H), 4.20-4.14 (m, 1H), 4.00-3.92 (m, 4H), 3.45 (dd, J = 13.6, 4.0 Hz, 1H), 3.32 (dd, J = 13.6, 8.8 Hz, 1H), 2.80 (ddd, J = 16.4, 8.8, 2.4 Hz, 1H), 2.53 (ddd, J = 16.5, 5.3, 1.9 Hz, 1H), 1.94-1.88 (m, 2H), 1.74-1.68 (m, 7H), 1.62-1.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 201.3, 160.6, 157.2, 144.1, 134.9, 126.6, 115.9, 112.2, 106.5, 105.2, 71.4, 66.5, 64.3, 64.2, 47.3, 39.1, 38.7, 38.5, 25.7, 25.5. FTIR (neat) : ν_{max} 3030, 2930, 1668, 1607, 1576, 1450, 1435, 1450, 1364, 1335, 1294 cm^{-1}. HRMS (EI) *m/z* : Calcd for $C_{20}H_{25}O_7$ $[M+H]^+$ = 377.1600. Found 377.1605.

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

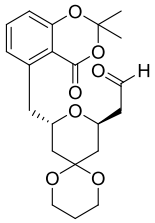


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.13 Compound A1-11B

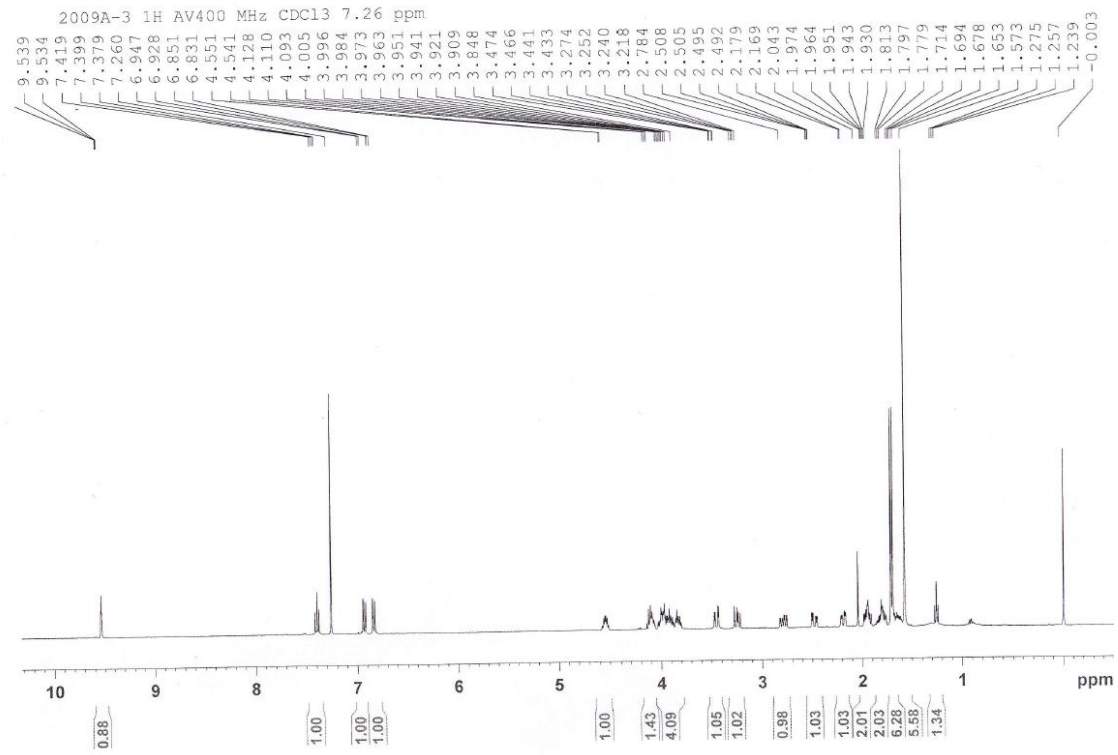
2-((8*S*,10*S*)-10-((2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl)methyl)-1,5,9-trioxaspiro[5.5]undecan-8-yl)acetaldehyde



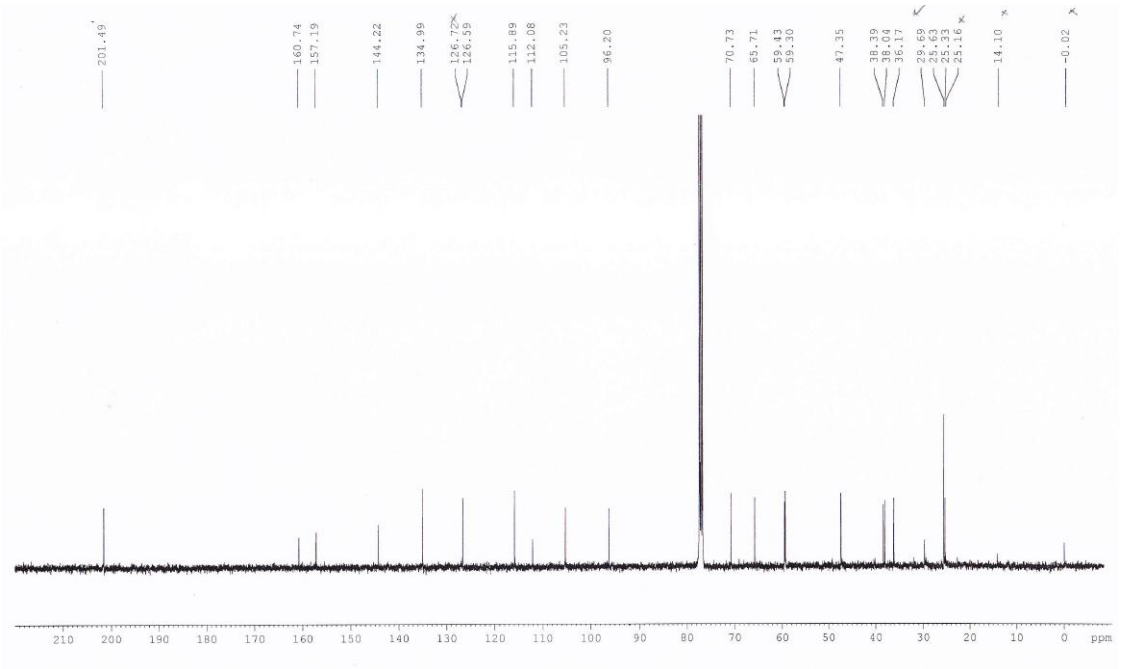
Experimental procedure

In an oven-dried 2-necked 25 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, thioester **A1-10B** (72 mg, 0.160 mmol, 1 equiv.) and 10% Pd on carbon (9 mg, 0.008 mmol, 0.05 equiv.) were stirred in dichloromethane (1.5 mL) at ambient temperature. Triethylsilane (0.05 mL, 0.320 mmol, 2 equiv.) was added to the reaction mixture dropwise. A needle outlet was installed to release the hydrogen gas generated. The reaction mixture was allowed to stir at ambient temperature for 1 h. The reaction mixture was then filtered through silica on celite pad, which was subsequently washed copiously with dichloromethane. The filtrate was concentrated *in vacuo* and purified by flash column chromatography (Hexanes : Ethyl acetate = 1 : 1) to afford the aldehyde **A1-11B** as viscous pale yellow oil (34 mg; 54%). (*Note: This compound is unstable and will decompose over time even when stored at 0 °C*) ^{1}H NMR (400 MHz, $CDCl_3$) : δ 9.54 (t, J = 2.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 4.59-4.51 (m, 1H), 4.13-4.06 (m, 1H), 4.00-3.85 (m, 4H), 3.45 (dd, J = 13.2, 3.2 Hz, 1H), 3.25 (dd, J = 13.6, 8.8 Hz, 1H), 2.79 (ddd, J = 15.8, 8.8, 2.6 Hz, 1H), 2.48 (ddd, J = 16.4, 5.0, 1.9 Hz, 1H), 2.19 (ddd, J = 13.6, 4.1, 1.5 Hz, 1H), 1.97-1.93 (m, 2H), 1.85-1.75 (m, 2H), 1.71 (s, 3H), 1.69 (s, 3H), 1.65-1.61 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 201.5, 160.7, 157.2, 144.2, 135.0, 126.6, 115.9, 112.1, 105.2, 96.2, 70.7, 65.7, 59.4, 59.3, 47.4, 38.4, 38.0, 36.2, 29.7, 25.6, 25.3. FTIR (neat) : ν_{max} 3427, 3028, 3005, 2961, 2930, 2872, 2855, 2731, 1727, 1607, 1584, 1479, 1449, 1388, 1379, 1317, 1296, 1271 cm^{-1}. HRMS (EI) *m/z* : Calcd for $C_{21}H_{27}O_7$ $[M+H]^+$ = 391.1757. Found 391.1754.

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

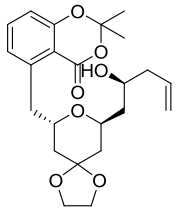


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.14 Compound A1-12

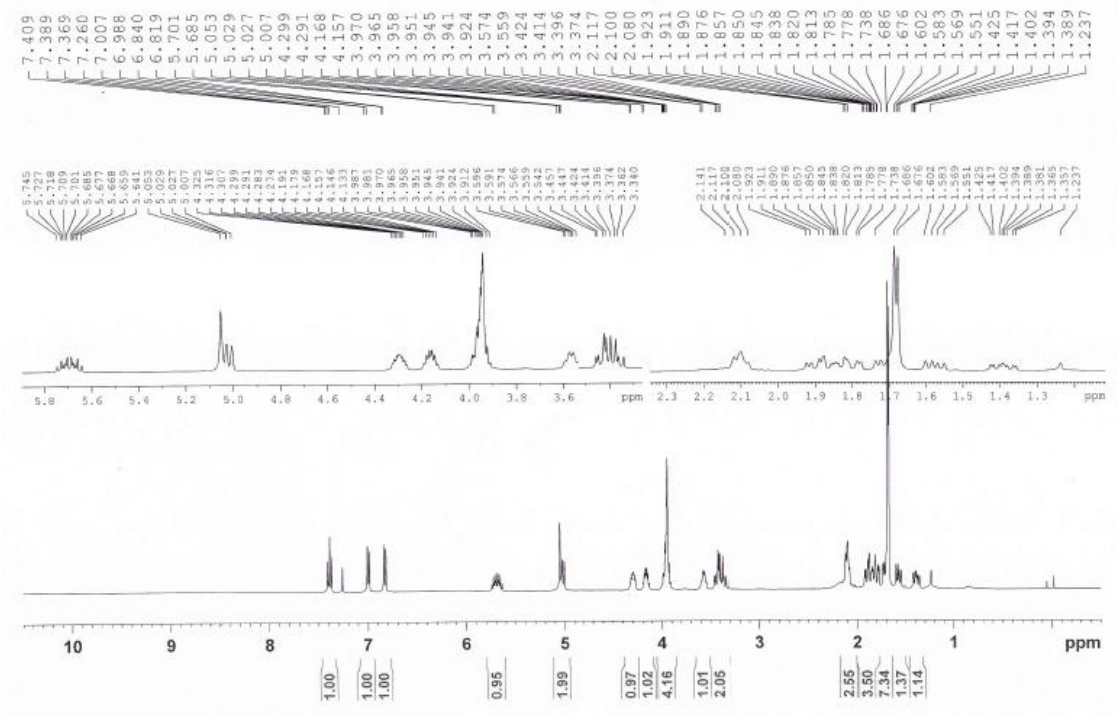
5-(((7*S*,9*S*)-9-((*S*)-2-hydroxypent-4-enyl)-1,4,8-trioxaspiro[4.5]decan-7-yl)methyl)-2,2-dimethyl-4*H*-benzo[d][1,3]dioxin-4-one



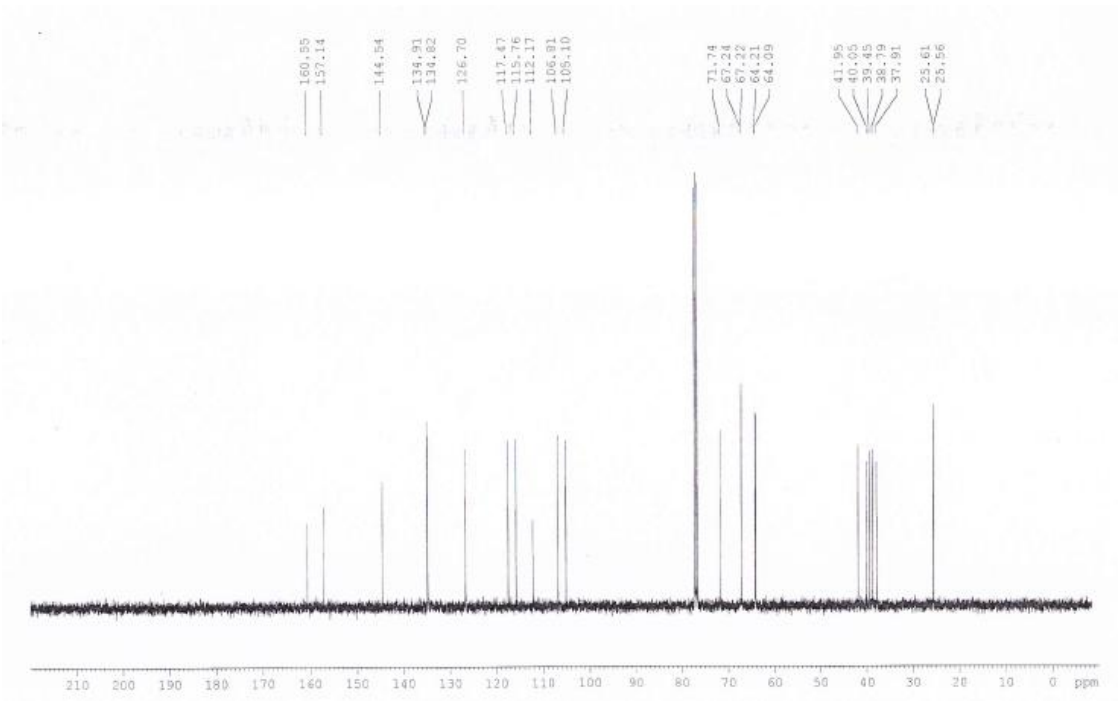
Experimental procedure

In an oven-dried 2-necked XX mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, aldehyde **A1-11A** (0.809 g, 2.15 mmol, 1 equiv.) was stirred in dry diethyl ether (20 mL) at -78 °C. (+)-*B*-Allyldiisopinocampheylborane solution, 1.0 M in pentane (2.37 mL, 2.365 mmol, 1.1 equiv.) was further diluted with diethyl ether (2 mL) and subsequently added to the reaction mixture dropwise. The reaction mixture was stirred at -78 °C for another 1 h and warmed up to ambient temperature for 2 h thereafter. The reaction mixture was then cooled down to 0 °C and subsequently quenched with 8 mL of 3:1 (v/v) mixture of 3 M sodium hydroxide and 30% hydrogen peroxide (H_2O_2) for 30 min. The reaction mixture was extracted with water (10 mL) and the aqueous layer was extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were washed with brine (10 mL) and subsequently dried over anhydrous magnesium sulphate ($MgSO_4$). The solution was then filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hexanes : Ethyl acetate = 1 : 1) to afford the homoallylic alcohol **A1-12** as pale yellow oil (0.700 g; 78%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.39 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 5.70-5.64 (m, 1H), 5.05-5.01 (m, 2H), 4.33-4.27 (m, 1H), 4.19-4.13 (m, 1H), 3.99-3.91 (m, 4H), 3.60-3.54 (m, 1H), 3.46-3.34 (m, 2H), 2.14-2.08 (m, 2H), 1.92-1.67 (m, 11H), 1.58 (dd, J = 13.0, 7.2 Hz, 1H), 1.43-1.36 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 160.6, 157.1, 144.5, 134.9, 134.8, 126.7, 117.5, 115.8, 112.2, 106.8, 105.1, 71.7, 67.2, 67.2, 64.2, 64.1, 42.0, 40.1, 39.5, 38.8, 37.9, 25.6, 25.5. FTIR (neat) : ν_{max} 3503, 2999, 2927, 1728, 1607, 1582, 1477, 1447, 1389, 1379, 1317, 1296, 1269 cm^{-1}. HRMS (EI) *m/z* : Calcd for $C_{23}H_{30}O_7Na$ $[M+Na]^+$ = 441.1889. Found 441.1893.

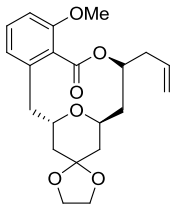
^{1}H NMR spectrum (400 MHz, $CDCl_3$)



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



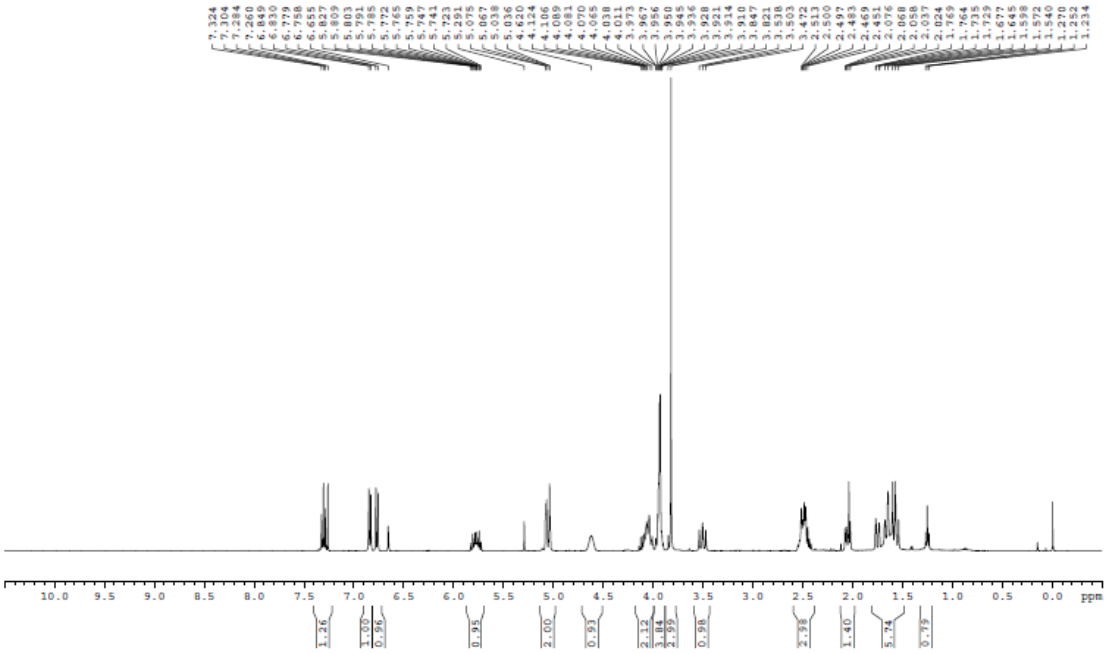
4.2.15 Compound A1-13



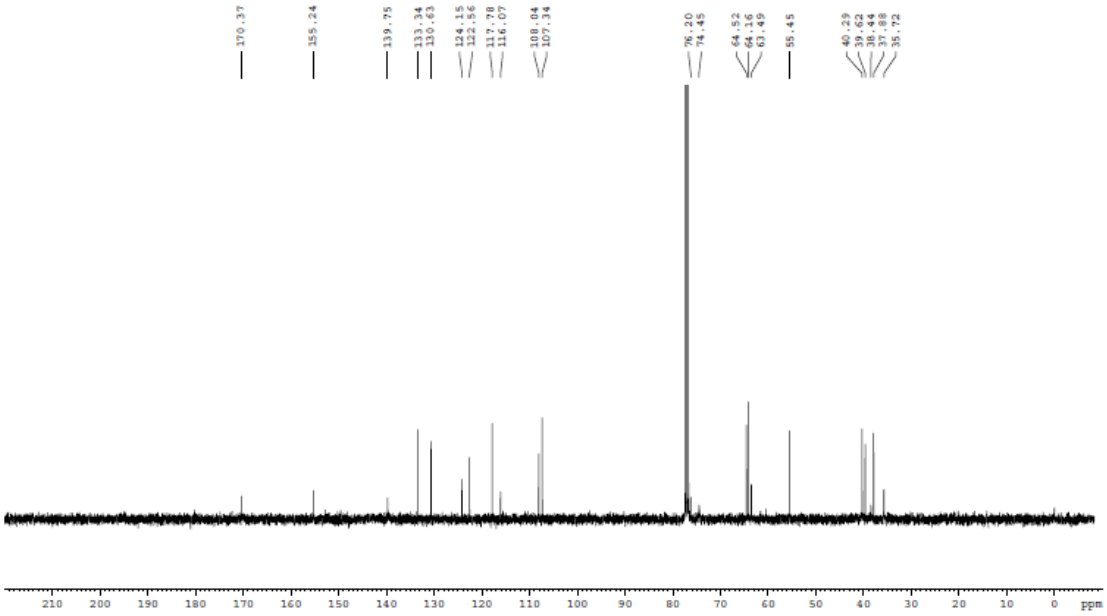
Experimental procedure[101(c)]

In a 2-necked 25 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, mineral oil was decanted from sodium hydride (236 mg, 20.4 mmol, 70 equiv.) with dry hexane and the residue was vacuum-dried. Dry THF (5 mL) and homoallylic alcohol **A1-12** (35 mg, 0.084 mmol, 1 equiv.) in dry THF (1 mL) were added into the reaction flask in that sequence. The reaction mixture was allowed to stir at room temperature for 5 h until the reaction was completed. Iodomethane (0.105 mL, 1.69 mmol, 20 equiv.) was then introduced in a dropwise manner into the reaction mixture at ambient temperature. The reaction mixture was allowed to stir for another 5 h at ambient temperature. The reaction mixture was then cooled down to 0 °C and was acidified to pH3 with 1N aqueous HCl solution. The aqueous layer was extracted with diethyl ether (3 x 50 mL) while the combined organic extracts were washed with brine (20 mL) and subsequently dried over anhydrous magnesium sulphate ($MgSO_4$). The solution was then filtered and concentrated *in vacuo*. The residual crude product was purified by preparative TLC (Hexanes : Ethyl acetate = 1 : 1) to afford the alkyne **A1-13** as white solid (15 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.30 (t, J = 8.0 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 5.83-5.72 (m, 1H), 5.08-5.04 (m, 2H), 4.12-4.01 (m, 2H), 3.97-3.91 (m, 4H), 3.82 (s, 3H), 3.54-3.47 (m, 1H), 2.51-2.45 (m, 3H), 2.08-2.02 (m, 1H), 1.77-1.54 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 170.4, 155.2, 139.8, 133.3, 130.6, 124.2, 122.6, 117.8, 116.1, 108.0, 107.3, 74.5, 64.5, 64.2, 63.5, 55.5, 40.3, 39.6, 38.4, 37.9, 35.7. FTIR (neat) : ν_{max} 2961, 2928, 2887, 2828, 2551, 1715, 1675, 1597, 1584, 1513, 1470, 1435, 1368, 1329, 1308, 1279 cm^{-1}. HRMS (EI) *m/z* : Calcd for $C_{21}H_{27}O_6$ $[M+H]^+$ = 375.1808. Found 375.1808. m.p. : *n.a.*

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

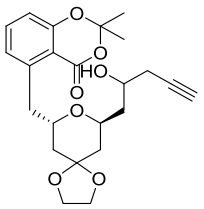


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.16 Compound A2-1P

5-(((7*S*,9*S*)-9-(2-hydroxypent-4-ynyl)-1,4,8-trioxaspiro[4.5]decan-7-yl)methyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one



Experimental procedure

Method 1: In an oven-dried 2-necked 25 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, indium powder (23 mg, 0.193 mmol, 2 equiv.) was stirred in dry THF (1 mL) at ambient temperature. Propargyl bromide (69 mg, 0.58 mmol, 6 equiv.) was added to the reaction mixture dropwise and the reaction mixture was allowed to stir vigourously for 3 h at ambient temperature until it turned into a clear solution. Aldehyde **A1-11A** (35 mg, 0.097 mmol, 1 equiv.) in dry THF (1 mL) was introduced into the reaction mixture in a dropwise manner at 0 °C. The reaction mixture was allowed to stir at 0 °C for 3 h. The reaction mixture was subsequently warmed up to ambient temperature and allowed to stir for another 12 h. The reaction mixture was quenched with 1 M HCl solution (5 mL) and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (5 mL) and subsequently dried over anhydrous magnesium sulphate ($MgSO_4$). The solution was then filtered and concentrated *in vacuo*. The residual crude product was purified by preparative TLC (Hexanes : Ethyl acetate = 1 : 1) to afford the isomers of alkyne **A2-1P** as viscous pale yellow oil (isomer 1: 8 mg, 18%; isomer 2: 15 mg, 37%).

Method 2: In an oven-dried 2-necked 25 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, magnesium turnings (13 mg, 0.50 mmol, 2 equiv.), mercury(II) chloride (2 mg, 0.005 mmol, 0.02 equiv.) and a pearl of iodine were stirred in dry ether (2 mL) at ambient temperature. Propargyl bromide (57 mg, 0.58 mmol, 1.9 equiv.) was added to the reaction mixture dropwise. The reaction mixture was heated to reflux for 2 h. The reaction mixture allowed to cool down to ambient temperature and subsequently to -78 °C. Aldehyde **A1-11A** (91 mg, 0.25 mmol, 1 equiv.) in dry ether (1 mL) was introduced into the reaction mixture in a dropwise manner at -78 °C. The reaction mixture was allowed to stir at -78 °C for 3 h

and then at 0 °C for 12 h. The reaction mixture was quenched with saturated ammonium chloride solution (5 mL) and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (5 mL) and subsequently dried over anhydrous magnesium sulphate ($MgSO_4$). The solution was then filtered and concentrated *in vacuo*. The residual crude product was purified by preparative TLC (Hexanes : Ethyl acetate = 1 : 1) to afford the isomers of alkyne **A2-1P** as viscous pale yellow oil (isomer 1: <10 mg, 9%; isomer 2: 23 mg, 22%).

Method 3:[156] In an oven-dried 2-necked 25 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, magnesium turnings (243 mg, 10 mmol, 1 equiv.), mercury(II) chloride (6 mg, 0.02 mmol, 0.002 equiv.) and a pearl of iodine were stirred in dry diethyl ether (2 mL) at ambient temperature. After the reaction mixture was cooled down to 0 °C, propargyl bromide (1.19 g, 10 mmol, 1 equiv.) was added to the reaction mixture dropwise. When the addition of propargyl bromide was completed, the reaction mixture was allowed to stir at ambient temperature for another 2 h and was cooled down to 0 °C thereafter. This constituted the *in situ*-generated allenylmagnesium bromide solution. In another oven-dried 2-necked 50 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, trimethyl borate (1.1 mL, 10 mmol, 1 equiv.) was stirred in dry diethyl ether (10 mL) at -78 °C. The earlier-prepared solution of allenylmagnesium bromide was added dropwise. Once the Grignard addition was complete, the reaction mixture was allowed to stir at ambient temperature for 1 h. The reaction mixture was then cooled to 0 °C and 3 M HCl solution (10 mL) was added dropwise. The biphasic mixture was stirred until all solids were dissolved and for an additional 20 min. The mixture was extracted with diethyl ether (3 x 5 mL). The combined organic extracts were washed with brine (5 mL) and subsequently dried over anhydrous magnesium sulphate ($MgSO_4$) (5 g). Ethylene glycol (0.84 mL, 15 mmol, 1.5 equiv.) was added to the crude reaction mixture to synthesize dioxaborolane. The suspension was allowed to stir at ambient temperature for 16 h. The reaction mixture was then filtered through a sintered glass funnel and the molecular sieves were washed with diethyl ether. The solution was then concentrated *in vacuo*. The residual crude product was dissolved in 15 mL of pentane and cooled to 0 °C. Excess diol was removed as the bottom layer and any precipitate was filtered through a pad of oven-dried Celite®. The solvent was removed *in vacuo* and the resulting liquid was used in the subsequent step without further purification. In an oven-dried 1-necked 10 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, the crude *B*-allenyl-1,3,2-dioxaborolane (8 mg, 0.066 mmol, 2 equiv.) and aldehyde **A1-11A** (12 mg, 0.033

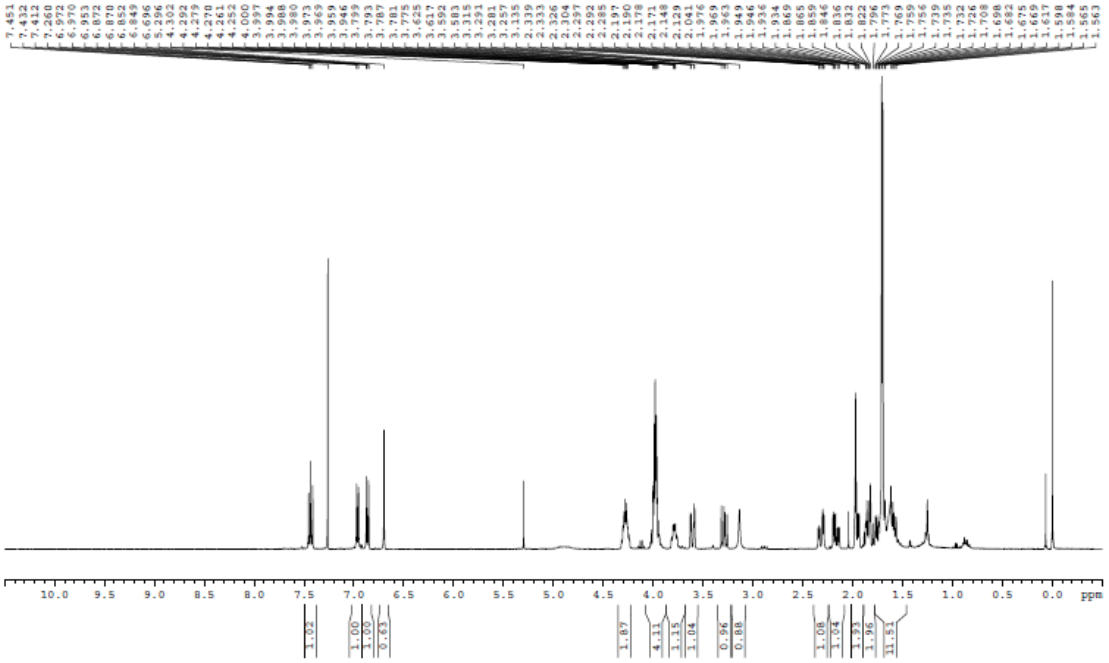
mmol, 1 equiv.) were stirred in neat conditions at ambient temperature for 15 h. The crude reaction mixture was diluted in dichloromethane and was purified by preparative TLC (Hexanes : Ethyl acetate = 1 : 1) to afford the isomers of alkyne **A2-1P** as viscous pale yellow oil (isomer 1: 6 mg, 40%; isomer 2: 5 mg, 38%).

Method 4: In an oven-dried 2-necked 25 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, zinc dust (35 mg, 0.53 mmol, 5 equiv.) and mercury(II) chloride (0.6 mg, 0.002 mmol, 0.02 equiv.) were stirred in dry THF (1 mL) at ambient temperature. Propargyl bromide (26 mg, 0.213 mmol, 2 equiv.) was added to the reaction mixture dropwise. The reaction mixture was heated to reflux for 1 h. The reaction mixture allowed to cool down to ambient temperature and aldehyde **A1-11A** (40 mg, 0.106 mmol, 1 equiv.) in dry THF (1 mL) was introduced into the reaction mixture in a dropwise manner at ambient temperature. The reaction mixture was heated to reflux again and was allowed to stir for another 18 h. The reaction mixture was quenched with water and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (5 mL) and subsequently dried over anhydrous magnesium sulphate ($MgSO_4$). The solution was then filtered and concentrated *in vacuo*. The residual crude product was purified by preparative TLC (Hexanes : Ethyl acetate = 1 : 1) to afford the alkyne **A2-1P** as viscous pale yellow oil (isomer 1: 21 mg, 47%; isomer 2: 19 mg, 36%).

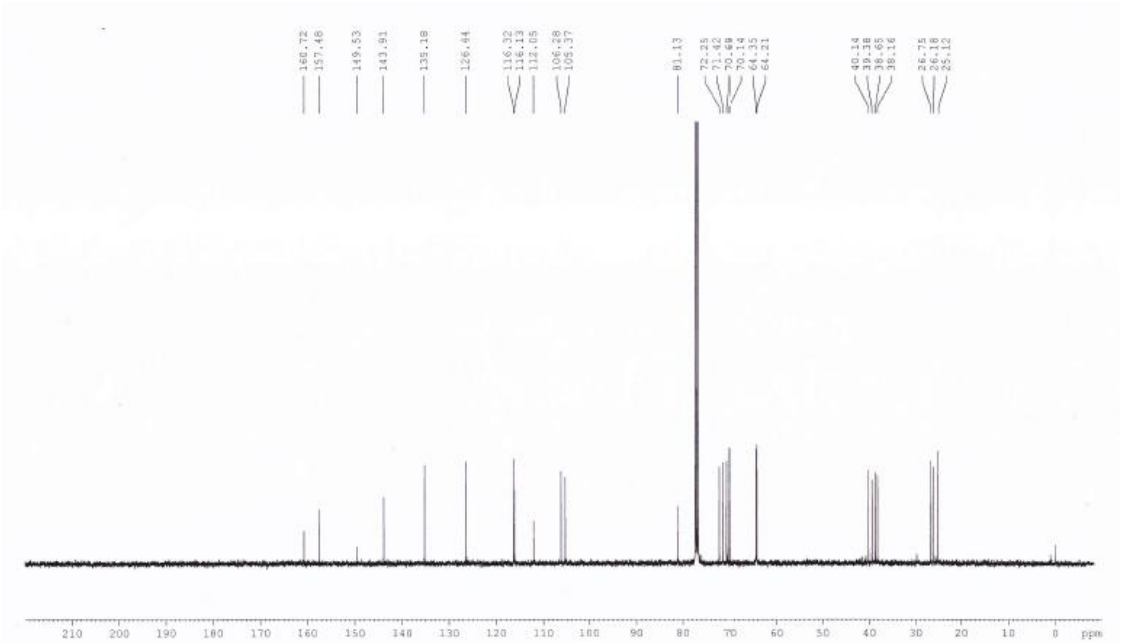
Isomer 1: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.44 (t, J = 7.8 Hz, 1H), 6.96 (d, J = 7.2 Hz, 1H), 6.87 (dd, J = 8.0, 1.0 Hz, 1H), 4.29-4.27 (m, 2H), 4.00-3.96 (m, 4H), 3.82-3.76 (m, 1H), 3.61 (dd, J = 13.6, 3.2 Hz, 1H), 3.29 (dd, J = 13.6, 9.6 Hz, 1H), 3.12 (brs, 1H), 2.32 (ddd, J = 16.6, 5.0, 2.7 Hz, 1H), 2.16 (ddd, J = 16.6, 7.7, 2.7 Hz, 1H), 1.98-1.94 (m, 2H), 1.86-1.67 (m, 10H), 1.62-1.57 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 160.7, 157.5, 143.9, 135.2, 126.4, 116.3, 116.1, 112.1, 106.3, 105.4, 81.1, 72.3, 71.4, 70.7, 70.1, 64.4, 64.2, 40.1, 39.4, 38.7, 38.2, 26.8, 26.2, 25.1.

Isomer 2: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.41 (t, J = 7.8 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 4.34-4.29 (m, 1H), 4.21-4.17 (m, 1H), 4.00-3.92 (m, 4H), 3.72-3.71 (m, 1H), 3.47-3.36 (m, 2H) 2.48 (brs, 1H), 2.42-2.18 (m, 2H), 2.03-1.80 (m, 4H), 1.80-1.65 (m, 7H), 1.65-1.50 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 160.6, 157.2, 144.4, 134.9, 126.7, 115.9, 112.3,106.8, 105.2, 81.0, 71.8, 70.5, 67.2, 66.8, 64.3, 64.1, 39.5, 39.4, 38.8, 38.0, 27.2, 25.7, 25.6. FTIR (neat) : ν_{max} 3304, 3005, 2930, 1727, 1607, 1582, 1479, 1449, 1391, 1379, 1317, 1296, 1317, 1296, 1271 cm^{-1}. HRMS (EI) *m/z* : Calcd for $C_{23}H_{29}O_7$ $[M+H]^+$ = 417.1913. Found 417.1915.

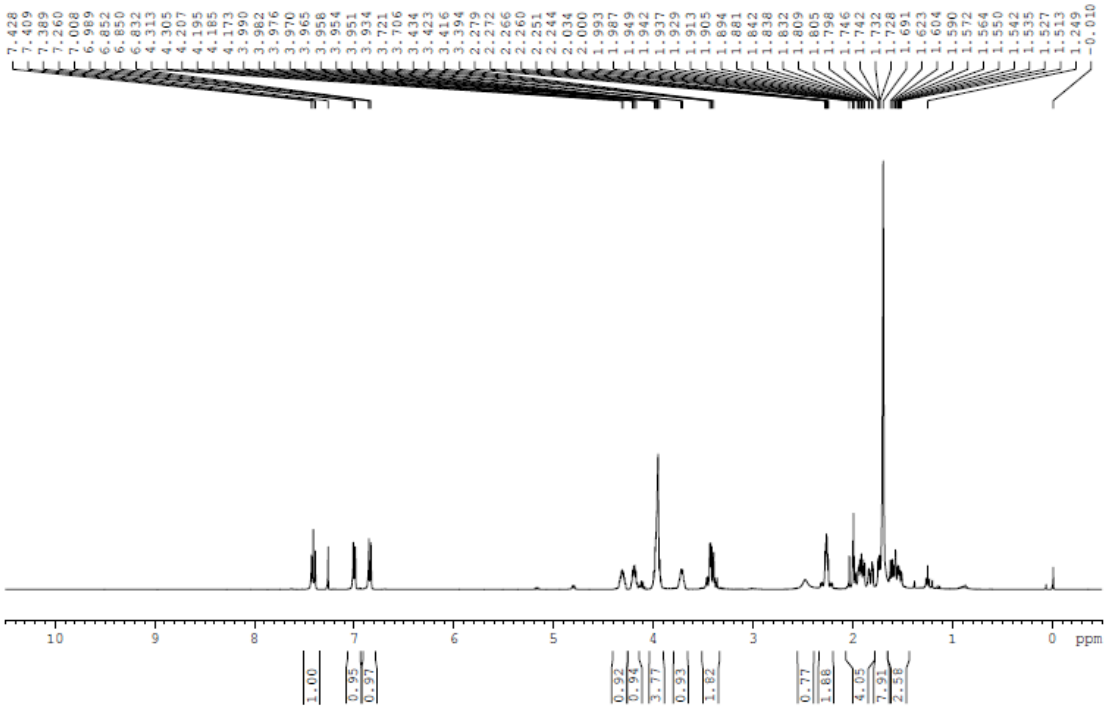
^{1}H NMR spectrum (400 MHz, $CDCl_3$) – Isomer 1



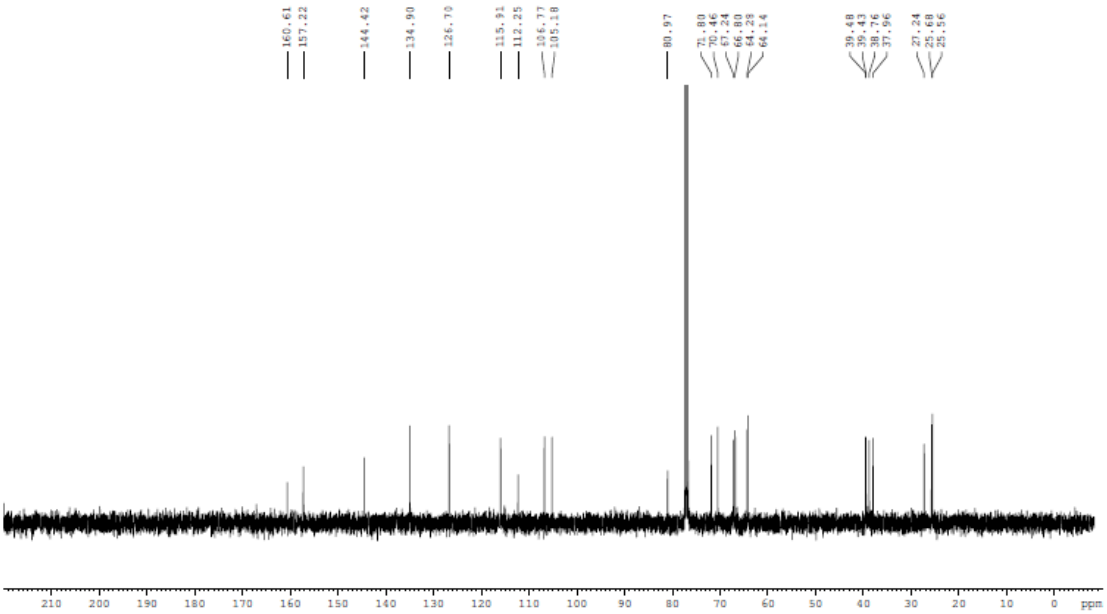
^{13}C NMR spectrum (100 MHz, $CDCl_3$) – Isomer 1



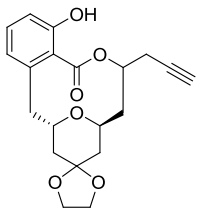
^{1}H NMR spectrum (400 MHz, $CDCl_3$) – Isomer 2



^{13}C NMR spectrum (100 MHz, $CDCl_3$) – Isomer 2



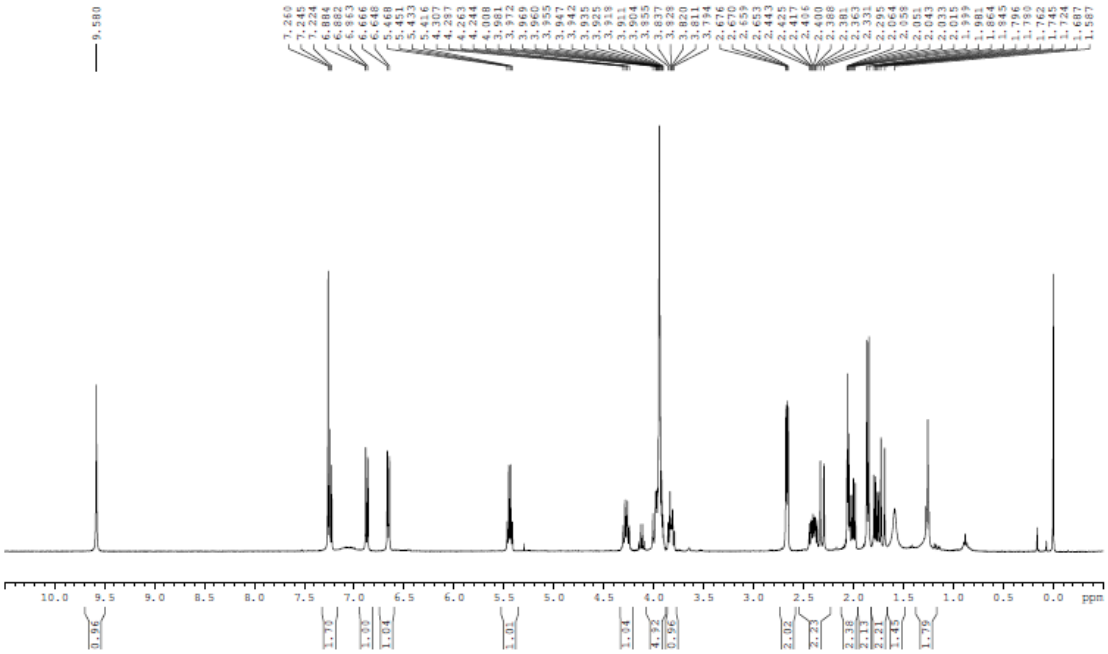
4.2.17 Compound A2-2



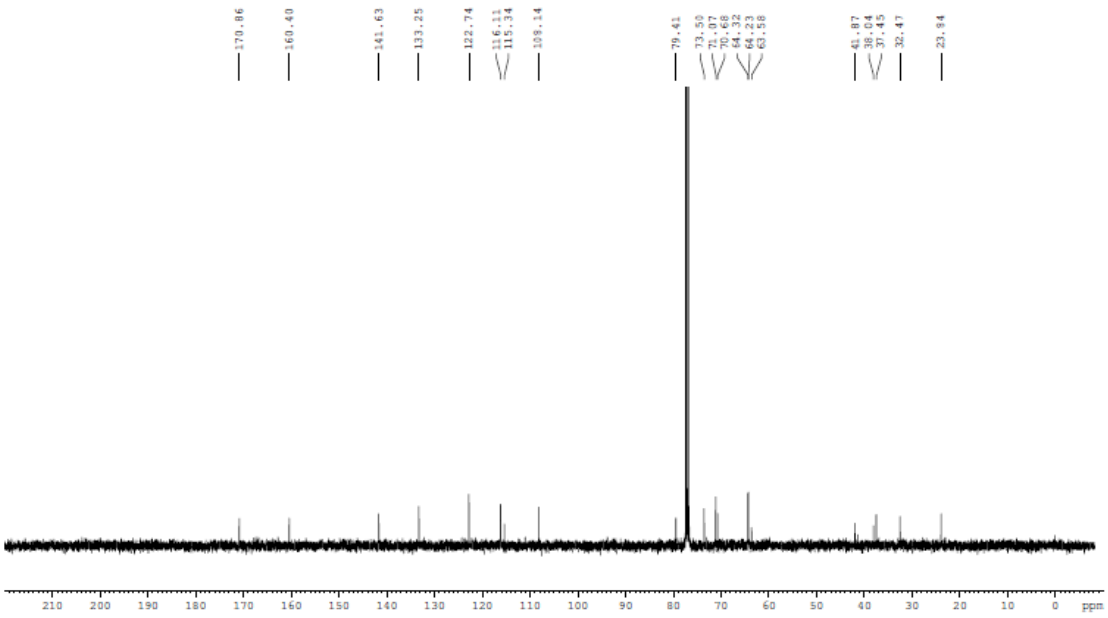
Experimental procedure

In a 2-necked 25 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, mineral oil was decanted from sodium hydride (53 mg, 0.132 mmol, 20 equiv.) with dry hexane and the residue was vacuum-dried. Dry THF (6 mL) and homoallylic alcohol **A2-1P** *(isomer 2)* (27 mg, 0.066 mmol, 1 equiv.) in dry THF (1 mL) were added into the reaction flask in that sequence. The reaction mixture was allowed to stir at room temperature for 18 h. The reaction mixture was quenched with saturated ammonium chloride solution and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (20 mL) and subsequently dried over anhydrous magnesium sulphate ($MgSO_4$). The solution was then filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hexanes : Ethyl acetate = 3 : 1) to afford the macrolactone **A2-2** as white solid (10 mg; 40%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 9.58 (s, 1H), 7.25 (t, J = 8.4 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.66 (d, J = 7.2 Hz, 1H), 5.44 (quar, J = 2.9 Hz, 1H), 4.31-4.24 (m, 1H), 4.00-3.90 (m, 5H), 3.86-3.79 (m, 1H), 2.66 (dd, J = 6.8, 2.4 Hz, 2H), 2.44-2.36 (m, 1H), 2.31 (d, J = 14.4 Hz, 1H), 2.06-1.98 (m, 2H), 1.85 (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 170.9, 160.4, 141.6, 133.3, 122.7, 116.1, 115.3, 108.1, 79.4, 73.5, 71.1, 70.7, 64.3, 64.2, 63.6, 41.9, 38.0, 37.5, 32.5, 23.8. FTIR (neat) : ν_{max} 3304, 2928, 1715, 1668, 1607, 1585, 1450, 1362, 1329, 1292 cm^{-1}. HRMS (EI) *m/z* : Calcd for $C_{20}H_{22}O_6Na$ $[M+Na]^+$ = 381.1314. Found 381.1308.

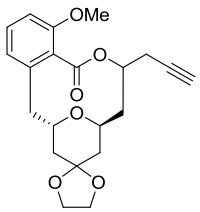
^{1}H NMR spectrum (400 MHz, $CDCl_3$)



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



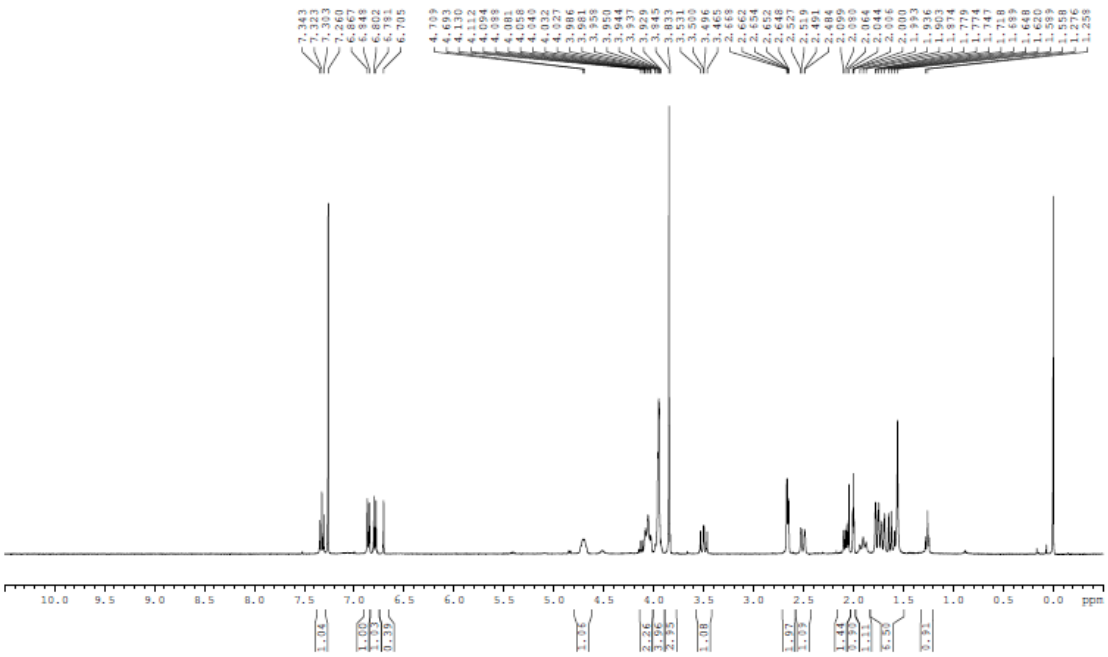
4.2.18 Compound A2-3



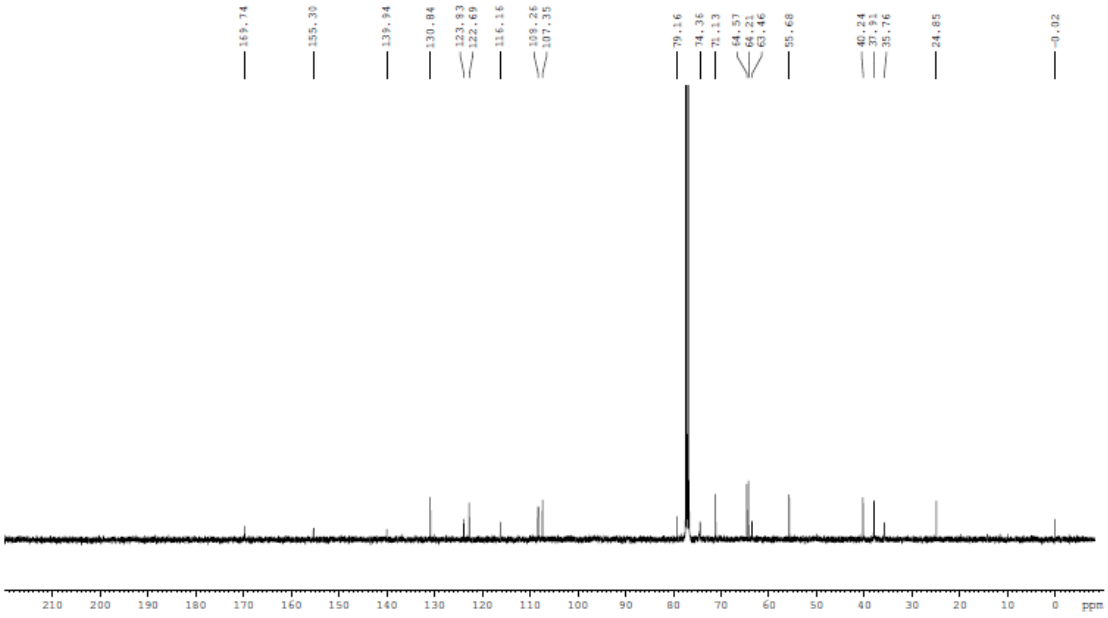
Experimental procedure

In a 2-necked 25 mL round-bottomed flask equipped with a magnetic stirring bar and a nitrogen-filled balloon, mineral oil was decanted from sodium hydride (65 mg, 0.162 mmol, 20 equiv.) with dry hexane and the residue was vacuum-dried. Dry THF (7 mL) and homoallylic alcohol **A2-1P** *(isomer 2)* (34 mg, 0.081 mmol, 1 equiv.) in dry THF (1 mL) were added into the reaction flask in that sequence. The reaction mixture was allowed to stir at room temperature for 8 h before iodomethane (18 mg, 0.122 mmol, 1.5 equiv.) was introduced. The reaction mixture was allowed to stir at room temperature for another 10 h. The reaction mixture was quenched with saturated ammonium chloride solution and the aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined organic extracts were washed with brine (5 mL) and subsequently dried over anhydrous magnesium sulphate ($MgSO_4$). The solution was then filtered and concentrated *in vacuo*. The residual crude product was purified by preparative TLC (Hexanes : Ethyl acetate = 3 : 1) to afford the macrolactone **A2-3** as white solid (9 mg; 28%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.32 (t, J = 8.0 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 4.74-4.66 (m, 1H), 4.09-4.03 (m, 2H), 3.99-3,94 (m, 4H), 3.85 (s, 3H), 3.50 (dd, J = 14.0, 12.4 Hz, 1H), 2.67-2.65 (m, 2H), 2.51 (dd, J = 14.2, 3.0 Hz, 1H), 2.07 (dd, J = 14.2, 8.0 Hz, 1H), 2.00 (t, J = 2.6 Hz, 1H), 1.94-1.87 (m, 1H), 1.78-1.56 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 169.7, 155.3, 139.9, 130.8, 123.8, 122.7, 116.2, 108.3, 107.4, 79.2, 74.4, 71.1, 64.6, 64.2, 63.5, 55.7, 40.2, 37.9, 35.8, 24.9. FTIR (neat) : ν_{max} 3021, 2961, 2926, 2886, 2861, 2408, 2361, 1711, 1584, 1512, 1472, 1458, 1435, 1366, 1329, 1304, 1277 cm^{-1}. HRMS (EI) *m/z* : Calcd for $C_{21}H_{25}O_6$ $[M+H]^+$ = 373.1651. Found 373.1649.

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

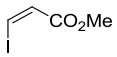


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.19 Compound N1-1M

(*Z*)-Methyl 3-iodoacrylate[174]

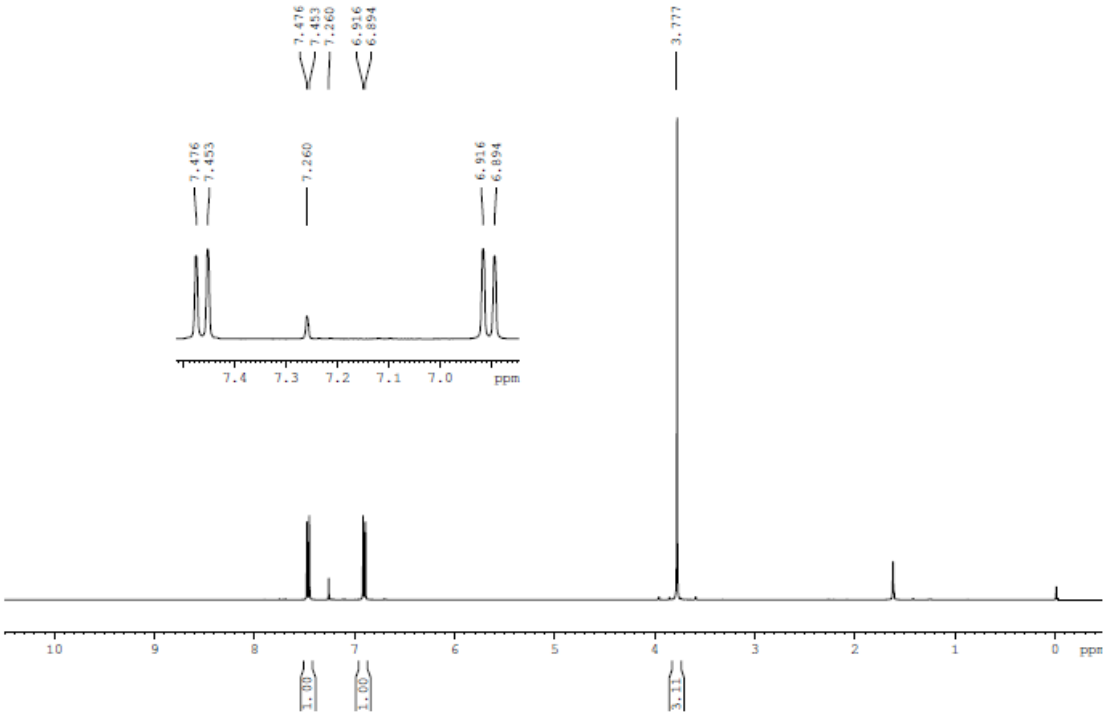


Experimental procedure[175]

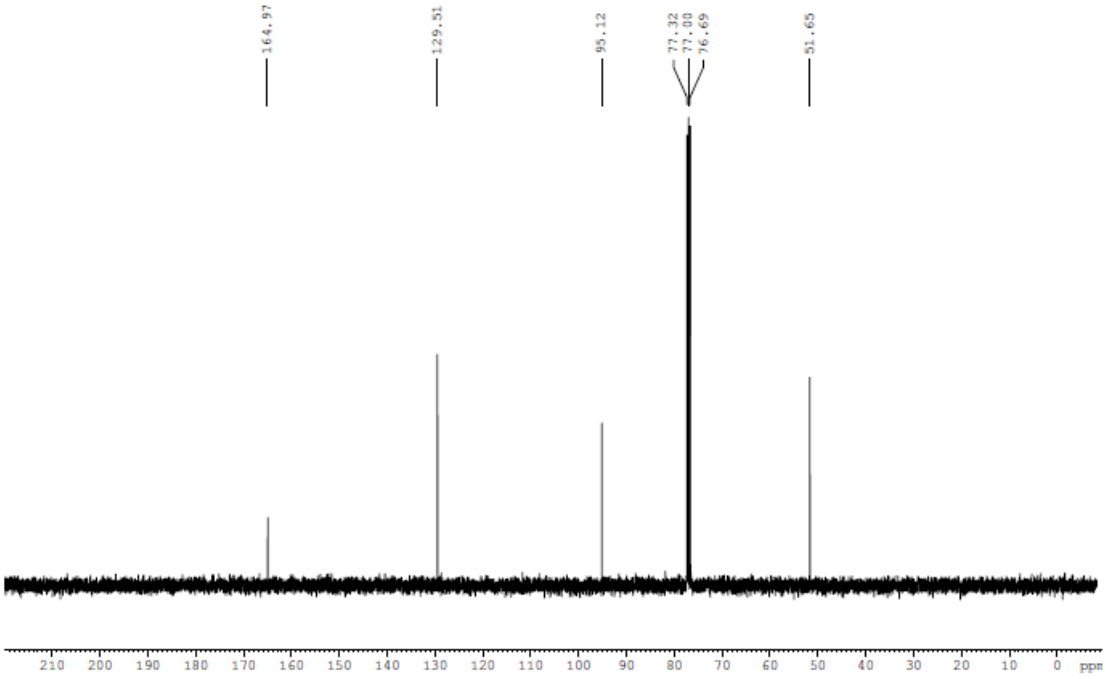
In a 1-necked 100 mL round-bottomed flask equipped with a magnetic stirring bar, methyl propiolate (4.8 mL, 53.96 mmol, 1 equiv.) and lithium iodide (8.000 g, 59.35 mmol, 1.1 equiv.) were stirred in acetic acid (54 mL) at 70 °C for 5 h. After the reaction mixture was cooled ambient temperature, the reaction mixture was diluted with ether and potassium carbonate solids were added until no effervescence observed. The reaction mixture was extracted with water (50 mL) and the aqueous layer was extracted with diethyl ether (3 x 75 mL). The combined organic extracts were washed with brine (50 mL) and subsequently dried over anhydrous magnesium sulphate ($MgSO_4$). The solution was then filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hexanes : Ethyl acetate = 95 : 5) to afford the iodide **N1-1** as pale yellow oil (10.683 g; 93%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.46 (d, J = 9.2 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.0, 129.5, 95.1, 51.7.

[174] (a) Larsson, R.;Sterner, O.; Johansson, M. *Org. Lett.* **2009**, *11*, 657. (b) Bartoli, G.; Cipolletti, R.; Antonio, G. D.; Giovanni, R.; Lanari, S.; Marcolini, M.; Marcantoni, E. *Org. Biomol. Chem.* **2010**, *8*, 3509.
[175] Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709.

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

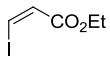


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.20 Compound N1-1E

(*Z*)-Ethyl 3-iodoacrylate[176]

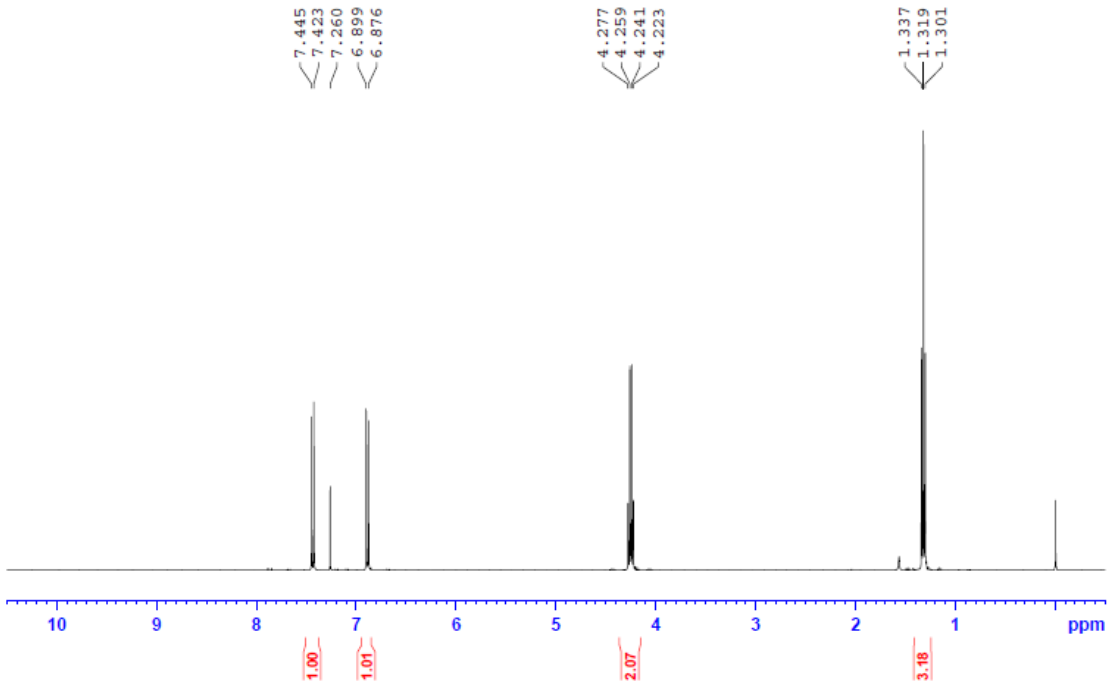


Experimental procedure

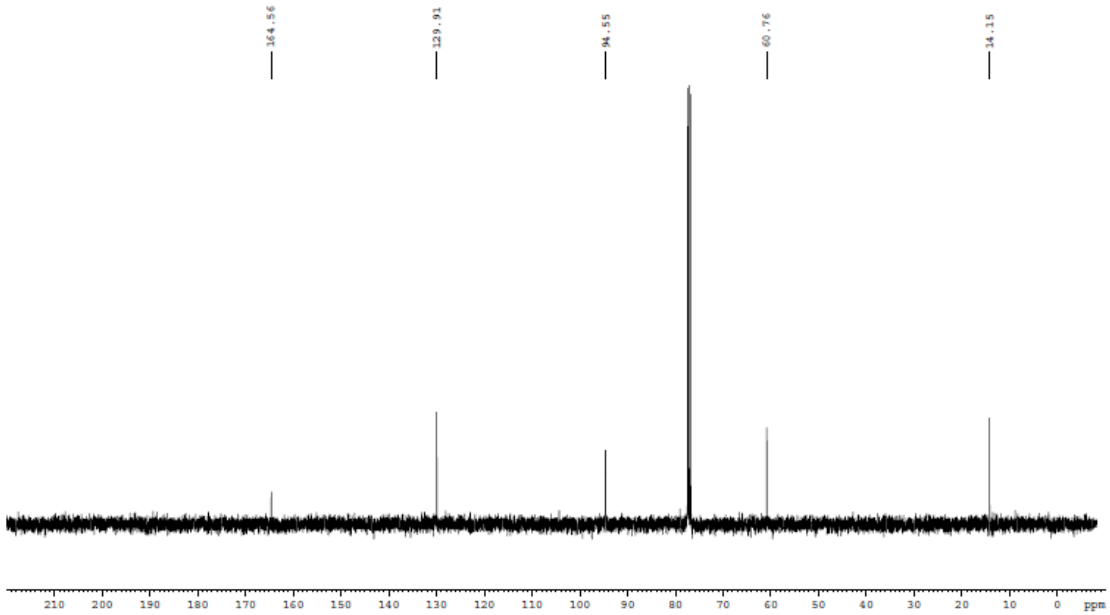
In a 1-necked 100 mL round-bottomed flask equipped with a magnetic stirring bar, methyl propiolate (5.5 mL, 53.96 mmol, 1 equiv.) and lithium iodide (8.000 g, 59.35 mmol, 1.1 equiv.) were stirred in acetic acid (54 mL) at 70 °C for 5 h. After the reaction mixture was cooled ambient temperature, the reaction mixture was diluted with ether and potassium carbonate solids were added until no effervescence observed. The reaction mixture was extracted with water (50 mL) and the aqueous layer was extracted with diethyl ether (3 x 75 mL). The combined organic extracts were washed with brine (50 mL) and subsequently dried over anhydrous magnesium sulphate ($MgSO_4$). The solution was then filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hexanes : Ethyl acetate = 95 : 5) to afford the iodide **N1-1E** as brown oil (11.761 g; 96%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.43 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 9.2 Hz, 1H), 4.25 (quar, J = 7.2 Hz, 1H), 1.32 (t, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 164.6, 129.9, 94.6, 60.8, 14.2.

[176] Dieter, R. K.; Lu, K. *J. Org. Chem.* **2002**, *67*, 847.

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

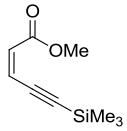


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.21 Compound N1-2M

(*Z*)- Methyl 5-(trimethylsilyl)pent-2-en-4-ynoate[177]



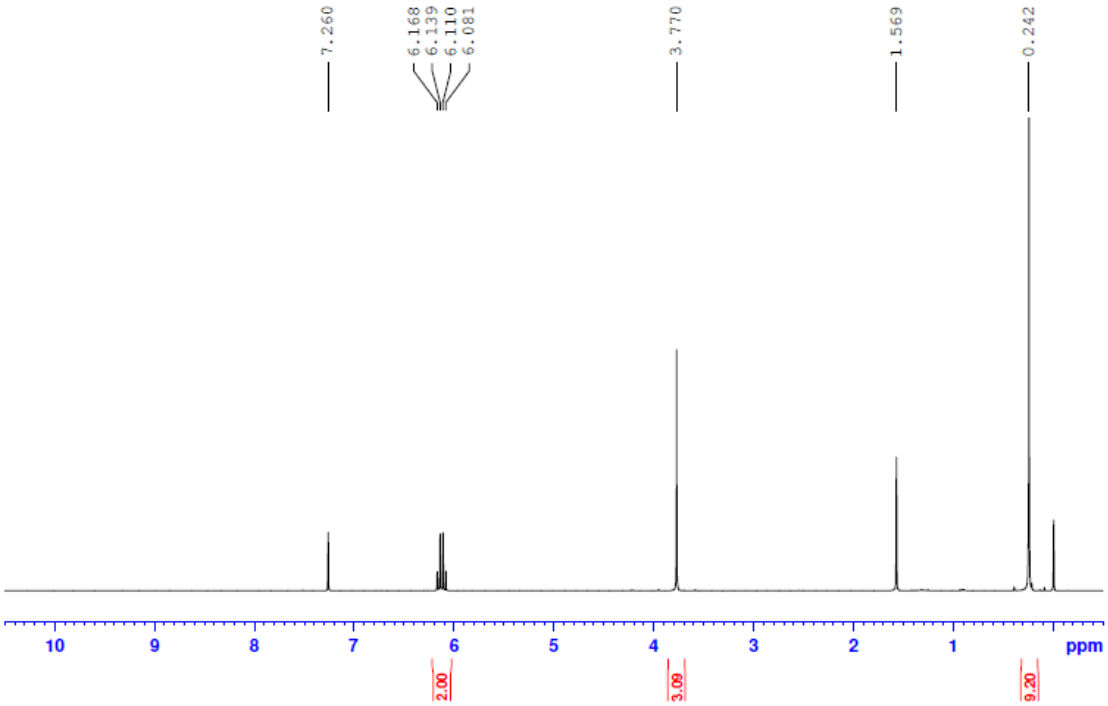
Experimental procedure[178]

In an oven-dried 2-necked 25 mL round-bottomed flask equipped with a magnetic stirring bar, (*Z*)-methyl 3-iodoacrylate **N1-1M** (0.600 g, 0.285 mmol, 1 equiv.), bis-triphenylphosphine-palladium(II) chloride ($PdCl_2(PPh_3)_2$) (20 mg, 0.00285 mmol, 0.01 equiv.), copper(I) iodide (CuI) (5 mg, 0.00285 mmol, 0.01 equiv.) and triethylamine (0.78 mL, 0.57 mmol, 2 equiv.) were stirred in dry THF (7 mL) at 0 °C. (Trimethylsilyl)acetylene (0.39 mL, 0.285 mmol, 1 equiv.) was then added to the reaction mixture at 0 °C. The reaction mixture was allowed to stir for 1 h at 0 °C and for another 16 h at ambient temperature. The reaction mixture was then filtered through silica, which was subsequently washed copiously with diethyl ether. The filtrate was concentrated *in vacuo* and the residual crude product was purified by flash column chromatography (Hexanes : Ethyl acetate = 98 : 2) to afford the ester **N1-2M** as pale yellow oil (155 mg; 30%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.15 (d, J = 11.6 Hz, 1H), 6.10 (d, J = 11.6 Hz, 1H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.0, 129.2, 122.8, 108.5, 100.7, 51.4, -0.4.

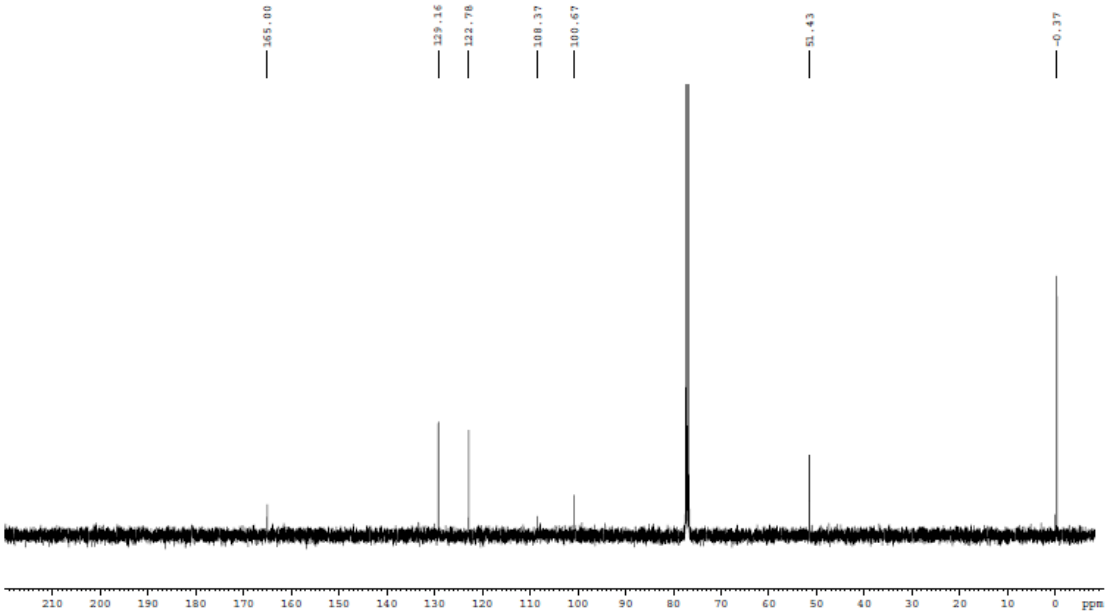
[177] (a) Rossi, R.; Bellina, F.; Catanese, A.; Nannina, L.; Valensin, D. *Tetrahedron* **2000**, *56*, 479. (b) Waser, J.; Gonzalez-Gomez, J. C.; Nambu, H.; Huber, P.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 4249.

[178] Garrais, S.; Turkington, J.; Goldring, W. P. D. *Tetrahedron* **2009**, *65*, 8418.

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

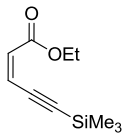


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.22 Compound N1-2E

(*Z*)- Ethyl 5-(trimethylsilyl)pent-2-en-4-ynoate[179]

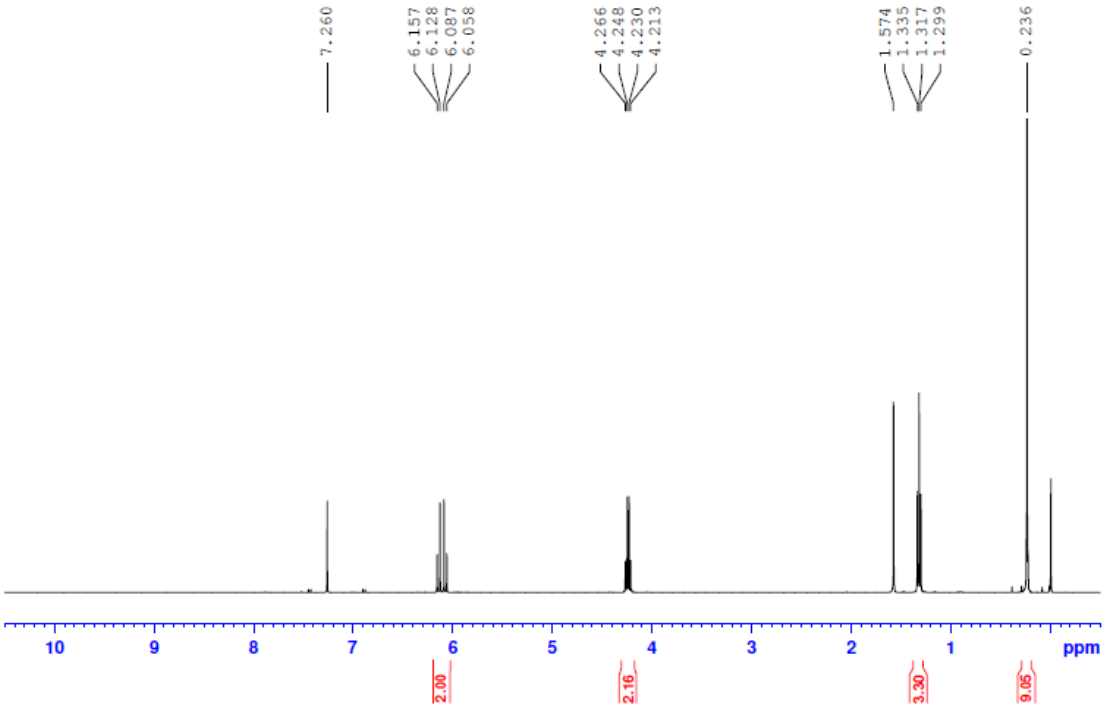


Experimental procedure

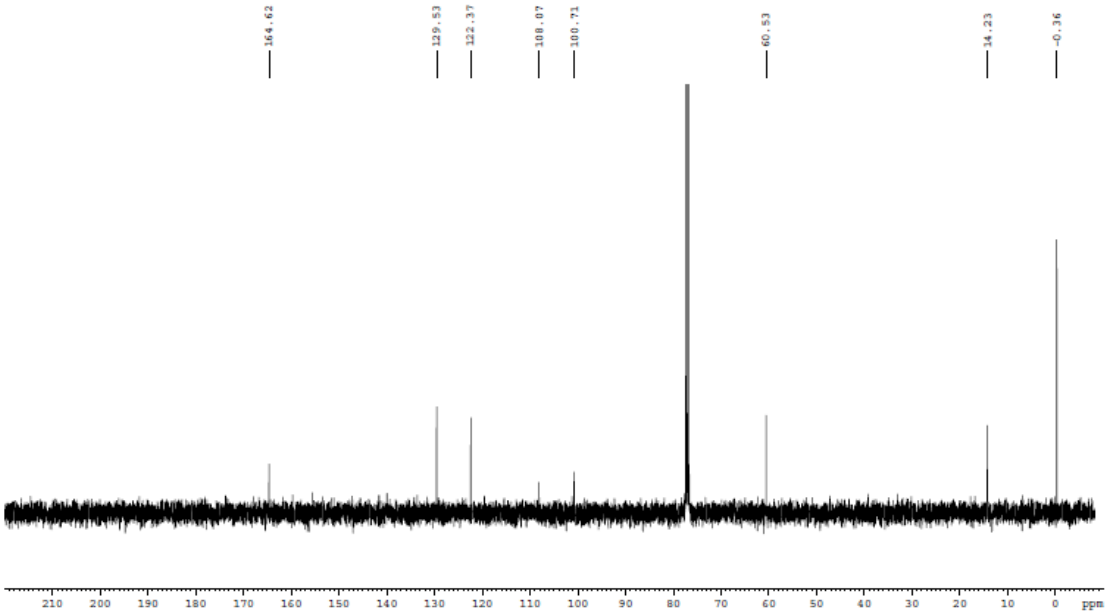
In an oven-dried 2-necked 25 mL round-bottomed flask equipped with a magnetic stirring bar, (*Z*)-ethyl 3-iodoacrylate **N1-1E** (2.260 g, 10 mmol, 1 equiv.), bis-triphenylphosphine-palladium(II) chloride ($PdCl_2(PPh_3)_2$) (70 mg, 0.1 mmol, 0.01 equiv.), copper(I) iodide (CuI) (19 mg, 0.1 mmol, 0.01 equiv.) and triethylamine (2.80 mL, 20 mmol, 2 equiv.) were stirred in dry THF (25 mL) at 0 °C. (Trimethylsilyl)acetylene (1.42 mL, 10 mmol, 1 equiv.) was then added to the reaction mixture at 0 °C. The reaction mixture was allowed to stir for 1 h at 0 °C and for another 16 h at ambient temperature. The reaction mixture was then filtered through silica, which was subsequently washed copiously with diethyl ether. The filtrate was concentrated *in vacuo* and the residual crude product was purified by flash column chromatography (Hexanes : Ethyl acetate = 98 : 2) to afford the ester **N1-2E** as pale yellow oil (1.434 g; 73%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.14 (d, J = 11.6 Hz, 1H), 6.07 (d, J = 11.6 Hz, 1H), 4.24 (quar, J = 7.2 Hz, 1H), 1.32 (t, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 164.6, 129.5, 122.4, 108.1, 100.7, 60.5, 14.2, -0.4.

[179] Ohe, K.; Yokoi, T.; Miki, K.; Nishino, F.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 526.

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

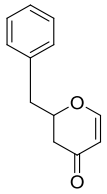


^{13}C NMR spectrum (100 MHz, $CDCl_3$)



4.2.23 Compound DA-1

2-benzyl-2,3-dihydro-4*H*-pyran-4-one[180]

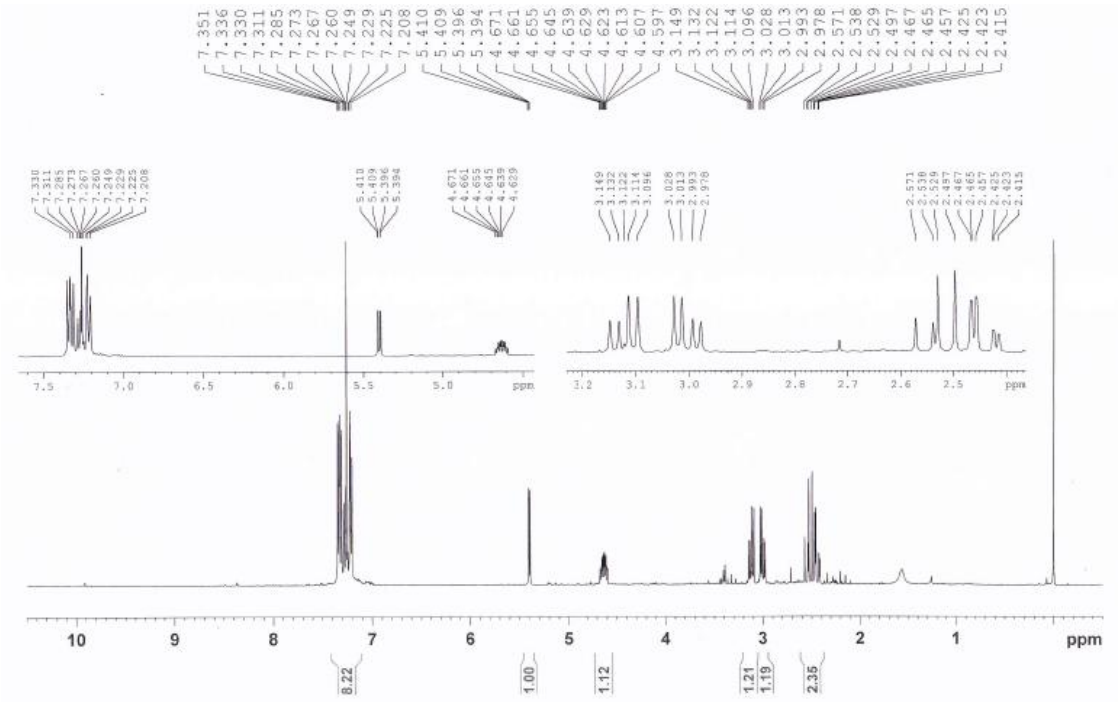


Experimental procedure

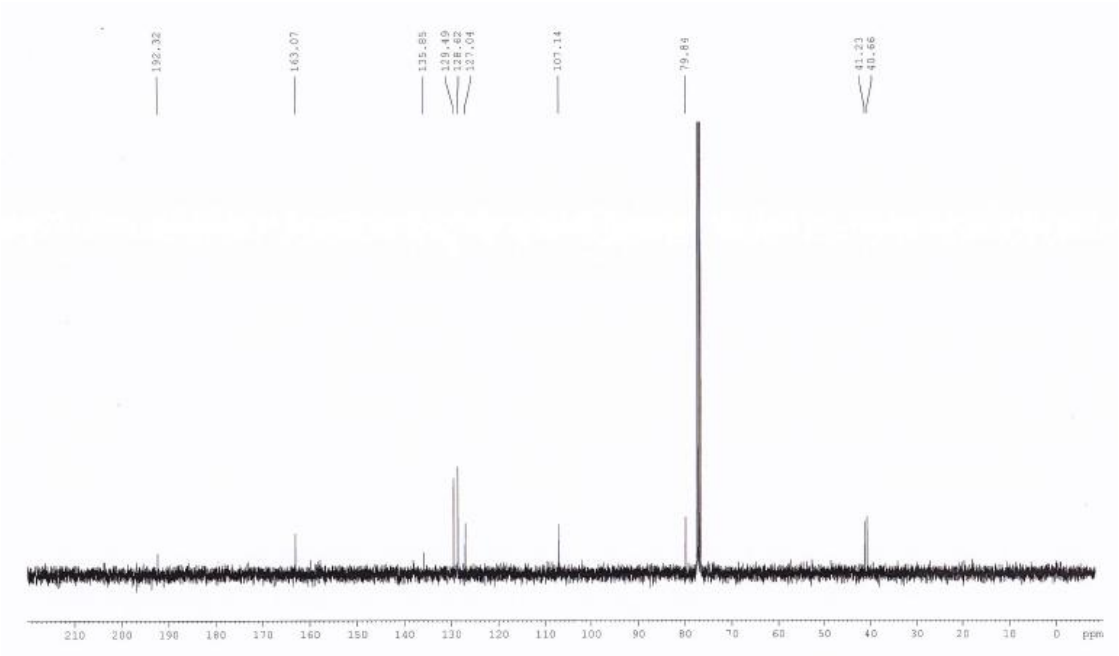
In an oven-dried 8 mL sample vial equipped with a magnetic stirring bar, phenylacetaldehyde (30 mg, 0.25 mmol, 1 equiv.), metal complex (as advised in **Table 3.2**) and powdered 4 Å MS (50 mg) were stirred in dry, degassed solvent (1.5 mL) at room temperature for 30 min. Danishefsky's diene (trans-1-methoxy-3-trimethylsiloxy-1,3-butadiene) (65 mg, 0.375 mmol,1.5 equiv.) was then added and the reaction mixture was allowed to stir for another 24 h at room temperature before it was subsequently diluted with dichloromethane (3 mL) and cooled down to 0 °C. Trifluoroacetic acid (2 mg, 0.0125 mmol, 0.05 equiv.) and the reaction mixture was allowed to stir at 0 °C for 1 h. The reaction mixture was then filtered through silica on celite pad, which was subsequently washed copiously with diethyl ether. The filtrate was concentrated *in vacuo* and purified by preparative TLC (Hexanes : Ethyl acetate = 3 : 1) to afford the dihydropyranone **DA-1** as viscous yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.35-7.21 (m, 6H), 5.40 (dd, J = 5.8, 0.6 Hz, 1H), 4.67-4.60 (m, 1H), 3.12 (dd, J = 14.2, 7.0 Hz, 1H), 3.00 (dd, J = 14.0, 7.0 Hz, 1H), 2.57-2.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 192.3, 163.1, 135.9, 129.5, 128.6, 127.0, 107.1, 79.8, 41.2, 40.7.

[180] (a) Huang, Y.; Rawal, V. H. *Org. Lett.* **2000**, *2*, 3321. (b) Zulauf, A.; Mellah, M.; Guillot, R.; Schulz, E. *Eur. J. Org. Chem.* **2008**, 2118.

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



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



EPILOGUE

Many people perceived that total synthesis may be less interesting than discovering new methodologies. Having tried my hands at both disciplines - methodology and total synthesis, it is only fair to say that each field has its own merits. These two fields work hand-in-hand with each other and have a symbiotic relationship. The synthetic problems faced in total syntheses of natural products fuel the development of new methodologies while more efficient methodologies inspire more elegant synthetic routes.

When I first embarked on my PhD studies, I was involved in developing methodology, which demanded precision, consistency and reproducibility. To meet such requirements, Dr. Motoki Yamane has honed my experimental skills sufficiently, from planning the experiment to executing it with care. He emphasized on the importance of the finer details that may usually be overlooked, as they constitute to more reliable and reproducible findings by minimizing the occurrence of random errors. This set of knowledge better prepared me for my endeavor in total synthesis of natural product.

Beyond the technical adeptness and chemical knowledge instilled in me, the past four years pursuing PhD studies taught me so much more about life that I would have if I chose to pursue a career immediately upon graduation instead. Admittedly, the past four years were not smooth sailing and in fact, it was the most excruciating time of my life thus far. While some, if not many, may argue that the decisions I made and the paths I chose to tread on may not be the wisest options, I take consolation in the fact that I have probably chose what I considered to be the best for myself. In retrospect, there were many things I could have done better and mistakes that could have been avoided. Now, I can only distill the lessons learnt and hopefully, have matured through the years to act after more deliberate and rational considerations.

Lastly, I would like to apologize for my shortcomings that may have frustrated and annoyed the people around me as well as to thank everyone for their graciousness to forgive, tolerate and accept my imperfections. I am truly humbled by the generosity and benevolence that have been shown to me, especially by my co-supervisor, Prof. Loh Teck Peng. We may have our differences but through the years, he has been a father figure to me and without him, I will probably not be what I am today.

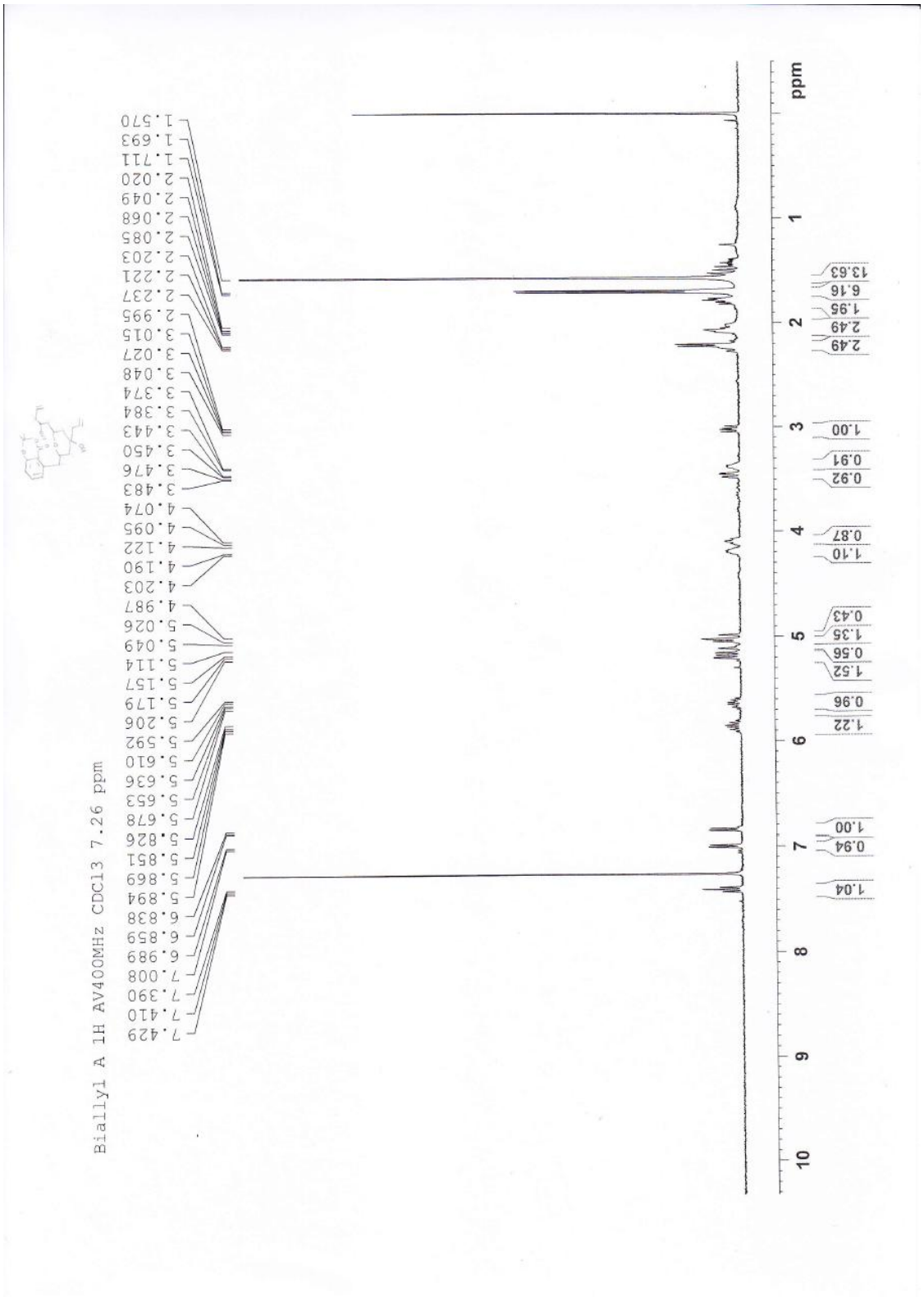
Appendices

Other Supporting Documents

THIS PAGE IS INTENTIONALLY LEFT BLANK.

Reference 146

^{1}H NMR spectrum of **A1-8B**



Reference 148

Poster presentation for 4th EuCheMS Chemistry Congress

P-0878

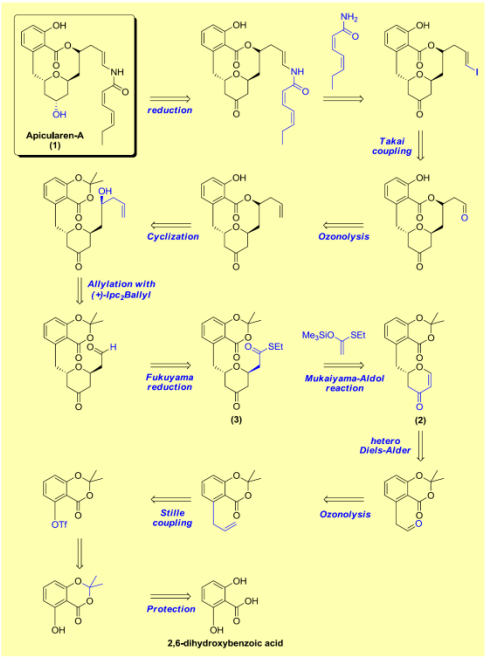
NANYANG TECHNOLOGICAL UNIVERSITY
School of Physical and Mathematical Sciences
Division of Chemistry and Biological Chemistry

Towards the synthesis of Apicularen A: An application of new methodology to construct 2,6-anti-tetrahydropyran rings

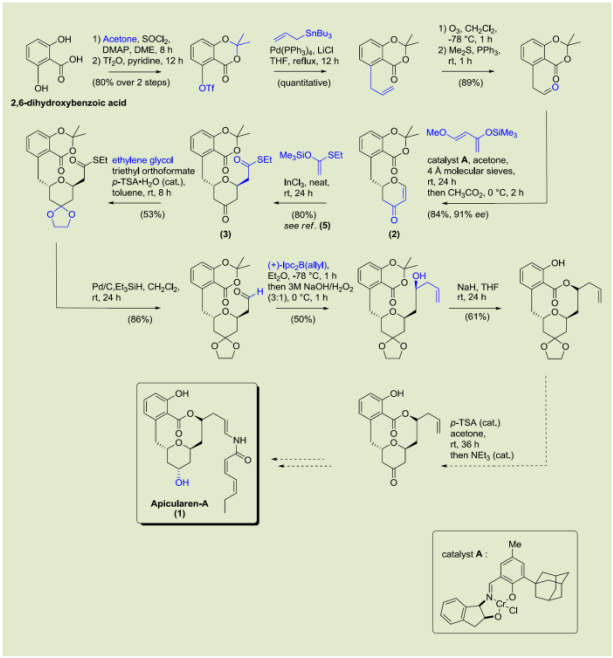
Sin Siu, Chua; Alni, Anita; Teck Peng, Loh*

Since the isolation[1] and the subsequent structural elucidation[2] of Apicularen A, **1**, by Höfle and co-workers, the molecule has been an intriguing molecule to the chemical society due to its wondrous biological properties[3] place Apicularen A as a potential candidate for anticancer drug target and the delicate architecture of the molecule. There are hitherto 11 total syntheses, which includes the first total synthesis successfully reported by De Brabander and co-workers[4], and numerous formal syntheses for this interesting molecule found in the literature.

Retrosynthetic Analysis



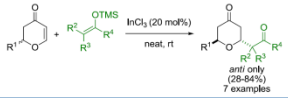
Synthetic Route



Conclusion

We managed to demonstrate the applicability of our methodology in gram-scale in our attempt to synthesize Apicularen A. Total synthesis of this intriguing molecule is currently still underway.

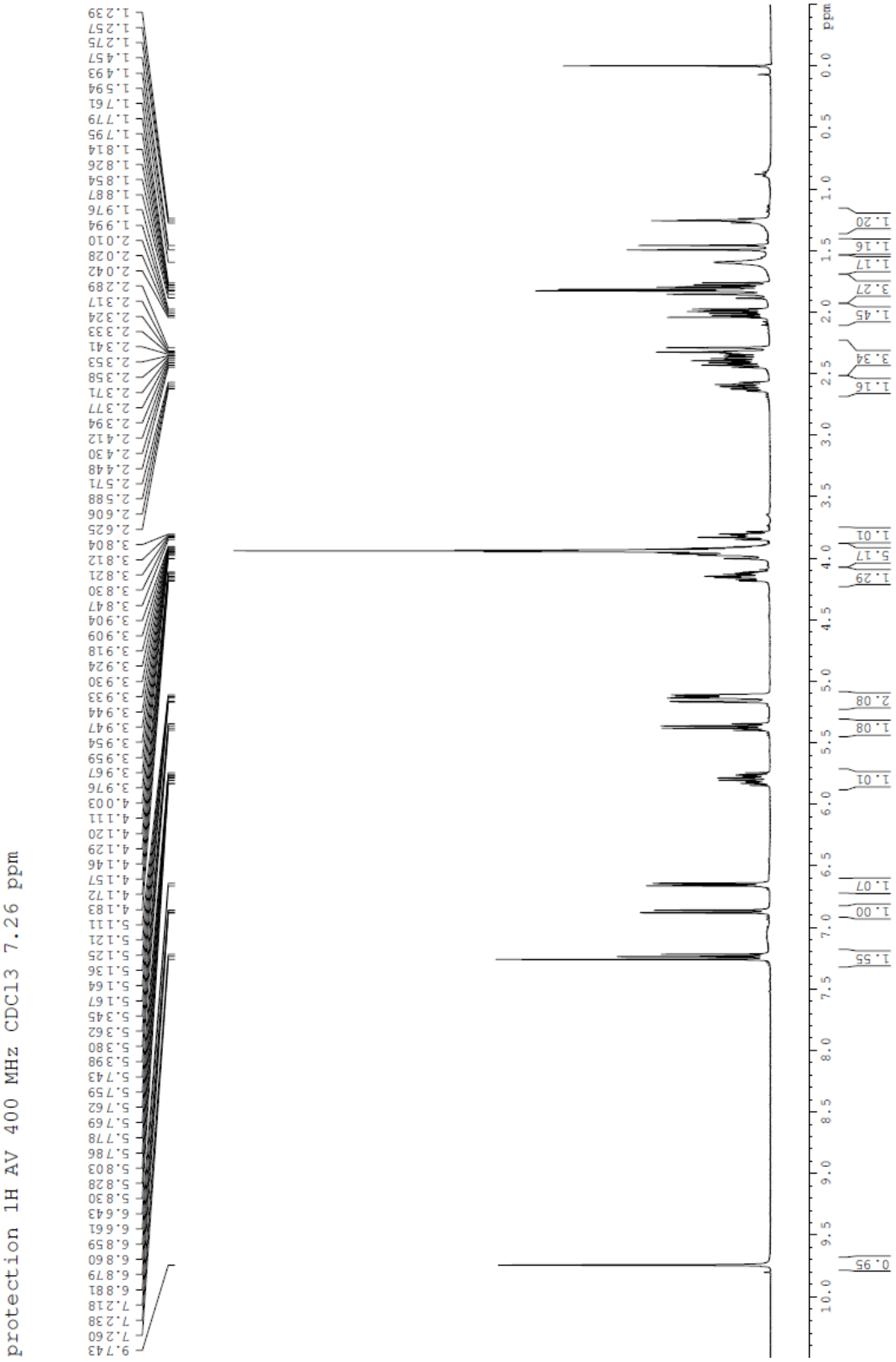
[1] Kunze, B.; Jansen, R.; Sasse, F.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075.
[2] Jansen, R.; Kunze, B.; Reichenbach, H.; Hofle, G. *Eur. J. Org. Chem.* **2000**, *6*, 913.
[3] Boyd, M. R.; Farina, C.; Belfiore, P.; Gagliardi, S.; Kim, J. W.; Hayakawa, Y.; Beutler, J. A.; McKee, T. C.; Bowman, B. J.; Bowman, E. J. *J. Pharmacol.Exp. Ther.* **2001**, *297*, 114.
[4] (a) Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett.* **2000**, *41*, 8069. (b) Bhattacharjee, A.; De Brabander, J. K. *Tetrahedron Lett.* **2001**, *42*, 1217.
[5] Chua, S.-S.; Alni, A.; Chan, L.-T. J.; Yamane, M.; Loh, T.-P. Tetrahedron 2011, 67, 5079.



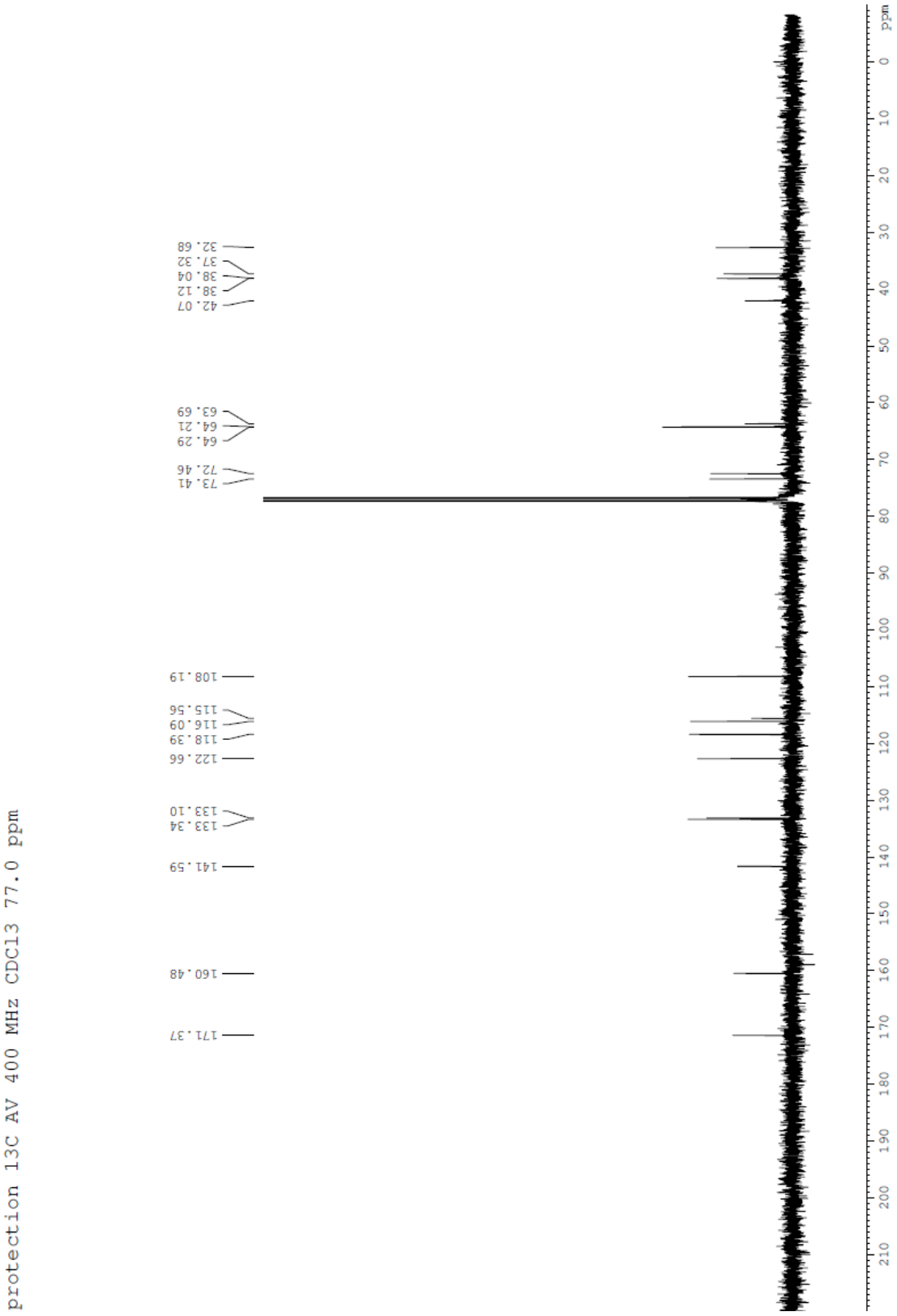
*E-mail address: teckpeng@ntu.edu.sg www.ntu.edu.sg

Reference 149

^{1}H NMR spectrum of unknown phenolic compound



^{13}C NMR spectrum of unknown phenolic compound



Reference 167

Poster presentation for 6th Asian-European Symposium

NANYANG TECHNOLOGICAL UNIVERSITY
School of Physical and Mathematical Sciences
Division of Chemistry and Biological Chemistry

PA26
Poster Session 1

Rhodium-Catalyzed 1,4-Addition of Triorgano(vinyl)silanes

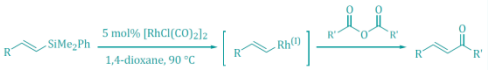
Chua Sin Siu, Motoki Yamane*
yamane@ntu.edu.sg

Introduction

Why is 1,4-conjugate addition important?

- One of the most fundamental and versatile reactions to extend carbon-carbon chain.
- Reported protocols, which utilizes copper catalysts in combination with Grignard or diorganozinc reagents, often require low temperatures and strictly anhydrous reaction conditions.
- In view of its importance, it is necessary to develop milder and more efficient methods.

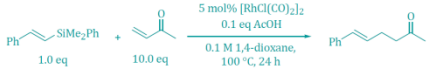
Previous Work



R and R' = alkyl, aryl

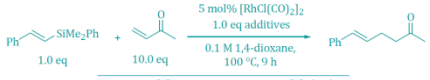
Yamane, M.; Uera, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 477.

Solvent Screening



Solvent	Yield (%)
1,4-dioxane	59
Toluene	15
Acetonitrile	11
1,2-dichloroethane	47
$CDCl_3$	44

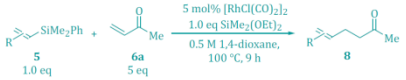
Additive Screening

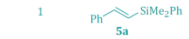
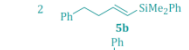


Additives	Yield (%)
-	52
H_2O	67[a]
AcOH	59[a]
Formic acid	64[a]
BEt_3 in 1.0 M THF	80
$B(O^iPr)_3$	71
$Si(OEt)_2Me_2$	79
Zn powder	75
Mg turnings (excess)	76

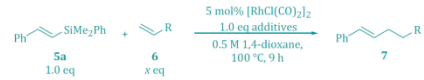
[a] 0.1 eq of additive was added instead of 1.0 eq.

Triorgano(vinyl)silane Scope

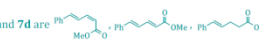


Entry	Vinylsilane	Yield (%)
1	 **5a**	79
2	 **5b**	76
3	 **5e**	53 (Z)-only

Substrate Scope



Entry	Substrate (eq.)	Yield with BEt_3 (%)	Yield with $SiMe_2(OEt)_2$ (%)	Yield with H_2O[a] (%)
1	**6a** (5 eq)	80	79	67
2	**6b** (3 eq)	27 Recovery of **2a** : 47%	67	69
3	**6c** (5 eq)	n.r.	12[b]	25
4[c]	**6d** (5 eq)	35 **7da : 7db : 7d** 2 : 33 : 0 Recovery of **5a** = 42%	78 **7da : 7db : 7d** 6 : 72 : 0 Recovery of **5a** = 6%	56 **7da : 7db : 7d** 3 : 43 : 10 Styrene was formed
5[d]	**6e** (3 eq)	51 **7ea : 7e** 12 : 39 Styrene was formed	45 **7ea : 7e** 15 : 30 Styrene was formed	-
6[e]	**6f** (3 eq)	<59 **7fa : 7f** 42 : <17 Recovery of **5a** = 13%	58 **7fa : 7f** 41 : 17 Styrene was formed	-

[a] 0.1 eq of water is used (according to the previous optimization) unless otherwise stated.
[b] 22% yield is obtained with 15 eq of acrolein.
[c] **7da**, **7db** and **7d** are  respectively.
[d] **7ea** and **7e** are respectively and were isolated as a mixture.
[e] **7fa** and **7f** are  respectively.

Conclusion and Future Work

Rhodium-catalyzed 1,4-conjugate addition with triorgano(vinyl)silanes was demonstrated. The reaction proceeded in the absence of strong additives or promoters. These reaction can also proceed under acidic conditions. Mechanistic studies are currently in progress.

Acknowledgement

The author would like to extend her gratitude to Asst. Prof. Motoki Yamane and his research group for their guidance and assistance. This project would not be possible without the financial as well as technicalsupport provided by Nanyang Technological University.

www.ntu.edu.sg