PART I

CASCADE REACTION: MUKAIYAMA-ALDOL-PRINS (MAP) AND MUKAIYAMA-ALDOL-ENE (MAE)

PART II

SYNTHETIC STUDIES TOWARDS THE TOTAL SYNTHESIS OF CYTOCHALASANS

APPENDIX

DIASTEREOSELECTIVE ALLYLATION OF PLANAR CHIRAL SUBSTITUTED FERROCENECARBOXALDEHYDE

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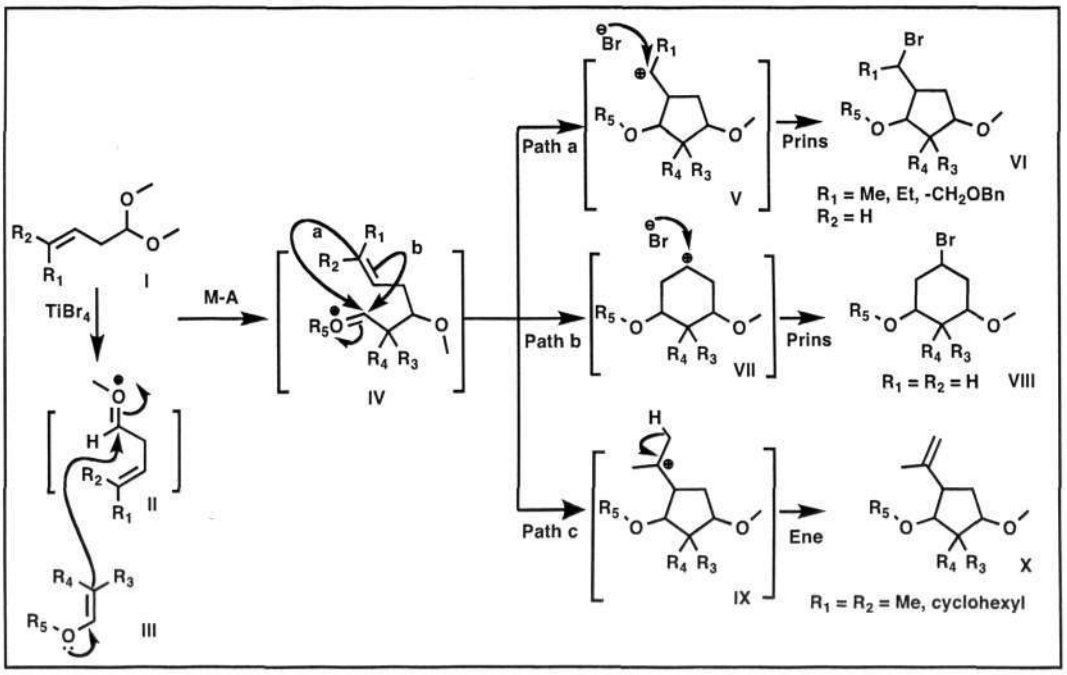
TABLE OF CONTENTS

SUMMARY

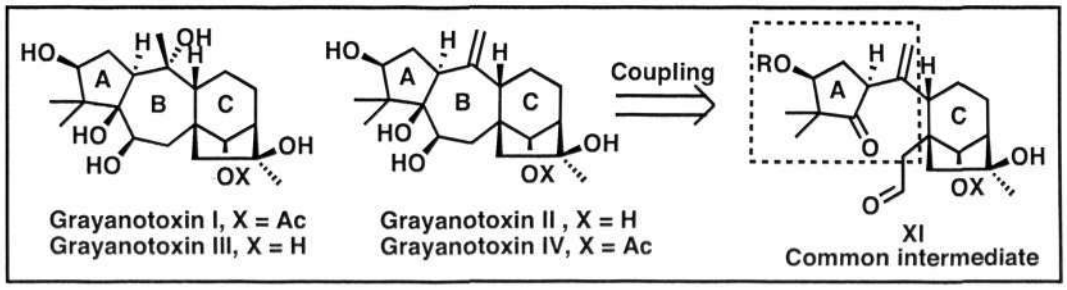
Part I



Mukaiyama-Aldol and Prins reactions have been testified as highly efficient methods in C-C bond formation since they were discovered several decades ago. Since both reactions gave the same common intermediate, called oxocarbonium **II**, we intend to combine the two reactions into a domino process, which means the formation of multiple C-C bonds and stereogenic centers in one pot without isolation of any intermediates. We envisage that the domino reactions involving the Mukaiyama-Aldol reaction of silyl enol ether **III** and acetal **I** treated with Lewis acid (*e.g.* $TiBr_4$) will produce an oxonium intermediate **IV** which upon trapping by an alkene functionality in an intramolecular Prins cyclization fashion will generate the cyclopentyl ring system **VI** (path a).

By careful tuning the stability of the carbocation formed *via* the variation of the acetal olefinic substitutents **I**, we envisaged that a six-membered ring **VIII** (pathway b) or a different type of five-membered ring **X** (pathway c) could be

obtained. Herein, we report a novel cascade reaction involving the Mukaiyama-Aldol-Prins (MAP) and Mukaiyama-Aldol-Ene cascade reaction to create highly functionalized six-membered and five-membered ring systems with the generation of up to 4 new stereogenic centers in a one-pot manner. This method provides fast access to a wide variety of cyclohexane and cyclopentyl derivatives which are important building blocks for the synthesis of complex molecules.

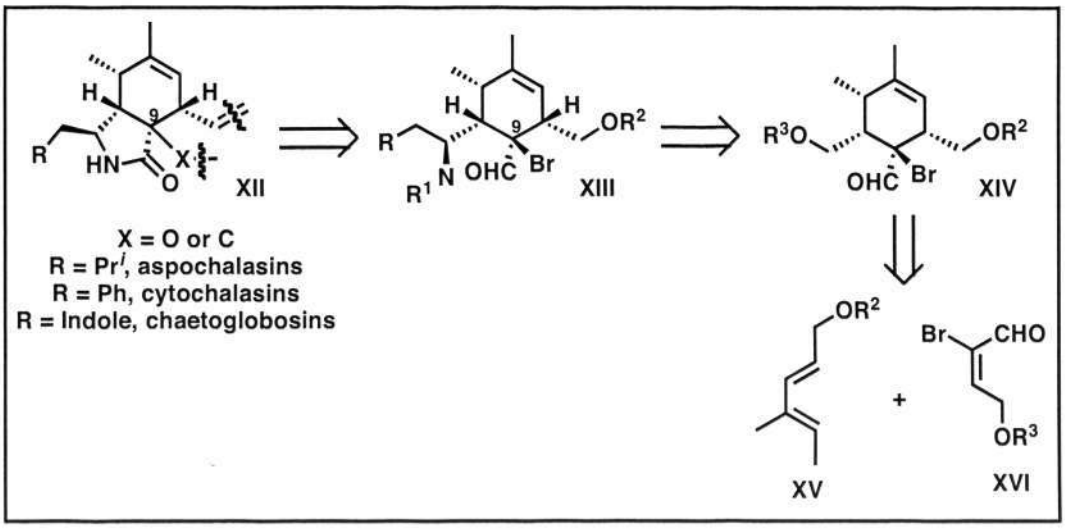


The versatility of our methodology greatly enhanced its synthetic value. In Chapter 3, we will discuss the application of Mukaiyama-Aldol-Ene (MAE) cascade reaction in the synthetic studies of Grayanotoxin. The five-membered ring A **XI** can be generated using our MAE cascade reaction.

Part II

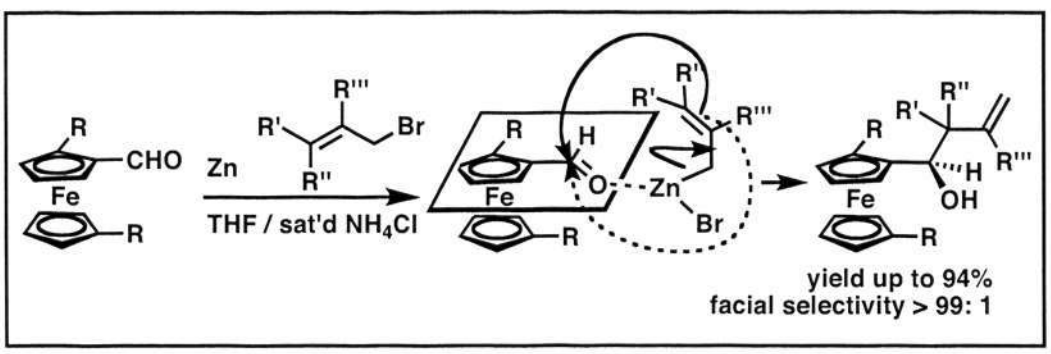
In Part II of this thesis, synthetic studies towards the total synthesis of cytochalasan is described. Cytochalasan is proposed to be derived from intermediate **XIII** which can be obtained from intermediate **XIV**. Intermediate **XIV** was envisaged to be constructed from a Lewis acid catalyzed intermolecular Diels-Alder reaction of diene **XV** and dienophile **XVI**. Several strategies were tried with a wide range of dienophiles in the construction of cyclohexyl ring system. The desired cycloadduct is successfully constructed in high yield and diastereoselectivity. Along the studies, we

have discovered an interesting finding on the Diels-Alder cyclization reaction which depends on the geometry of the dienophile used.



Appendix

In appendix, we described the diastereoselective allylation of planar chiral substituted ferrocenecarboxaldehyde to provide an efficient entry to chiral ferrocenyl ligands. 2,2'-Disubstituted ferrocenecarboxaldehydes are subjected to zinc mediated allylation to form homoallylic ferrocenyl alcohols. The effects of *ortho*-substituted functional groups on facial selectivities of planarly chiral aldehydes were studied and it was found that the corresponding homoallylic alcohols were obtained as single diastereomers in excellent yields.



INDEX OF ABBREVIATIONS

δ	chemical shift
Δ	reflux
°C	degree centrigrade
Ac	acetyl
AcOH	acetic acid
AIBN	*azo-bis*-isobutyronitrile
aq.	aqueous
Bn	benzyl
BOC	tert-butoxycarbonyl
brs	broad singlet
BuLi	butyl lithium
Bz	benzoyl
t-bu	tert-butyl
cacld	calculated
cat	catalytic
Cbz	benzyloxycarbonyl
$CDCl_3$	deuterated chloroform
COSY	correlated spectroscopy
CSA	camphorsulfonic acid
CH_2Cl_2	dichoromethane
$CHCl_3$	chloroform
cm^{-1}	inverse centimeter
cyc	cyclohexane; cyclohexenyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
dd	doublets of doublet
de	diastereomeric excess
DIBAL	diisobutylaluminium hydride

DIEA	diisopropylethylamine
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
dt	doublets of triplet
dq	doublets of quartet
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
ee	enantiomeric excess
EI	electron impact ionization
equiv.	equivalent
ESI	electronspray ionization
Et	ethyl
ether	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl aceate
EtOH	ethanol
FAB	fast atomic bombardment
Fmoc	9-fluorenylmethyl
FTIR	Fourier transform infrared spectroscopy
g	gram
h	hour
H	hydrogen
Hex	hexane
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum correlation
HOBt	1-hydroxybenzotriazole
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
i-Pr	isopropyl
J	coupling constants

kg	kilogram
LDA	lithium diisopropylamide
LiHMDS	Lithium hexamethyl disilazide
M	concentration (mol/dm^{-3})
M^+	parent ion peak (mass spectrum)
m	multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
MAE	Mukaiyama-Aldol-Ene
MAP	Mukaiyama-Aldol-Prins
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	Megahertz
min	minute
mmol	millimoles
mol	moles
MS	mass spectrum
Ms	methanesulfonyl
N	concentration (normality)
NaHMDS	sodium hexamethyl disilazide
NBS	*N*-bromosuccinimide
n-Bu	*n*-butyl
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
NOESY	nuclear overhauser enhancement spectroscopy
N.R.	no reaction
obsd.	observed
OTf	trifluoromethanesulfonate
p	page
PBr_3	phophorus tribromide
PCC	pyridinium chlorochromate
Pd/C	palladium on carbon
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)

Ph	phenyl
PhMe	Toluene
ppm	parts per million
Py	pyridine
q	quartet
qd	quartets on doublet
quint.	quintet
rt.	room temperature
RBF	round bottom flask
R_f	retention factor
s	singlet
sat'd	saturated
t	triplet
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethyl silyl
TBDPS	*tert*-butyldiphenyl silyl
t-BOC	*tert*-butoxycarbonyl
t-Bu	*tert*-butyl
td	triplets of doublet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropyl silyl
$TiBr_4$	titanium tetrabromide
$TiCl_4$	titanium tetrachloride
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
TMSBr	trimethylsilyl bromide
TMSOTf	trimethylsilyl trifluoromethane sulfonate
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl
T.S.	transition state
vol	volume

PART I

Chapter 1

Cascade reactions in organic synthesis

1.1 INTRODUCTION

In the past fifty years, synthetic organic chemistry has developed in a fascinating way with the invention of new methodologies and the synthesis of challenging molecules. The "Golden Age" of organic chemistry has heralded the increased structural complexity of the targeted synthetic molecules. Additionally, aspects of the stereo-control has taken on more significant roles in synthetic chemistry aided by modern advanced analytical tools (e.g. MS, HPLC, NMR).[1]

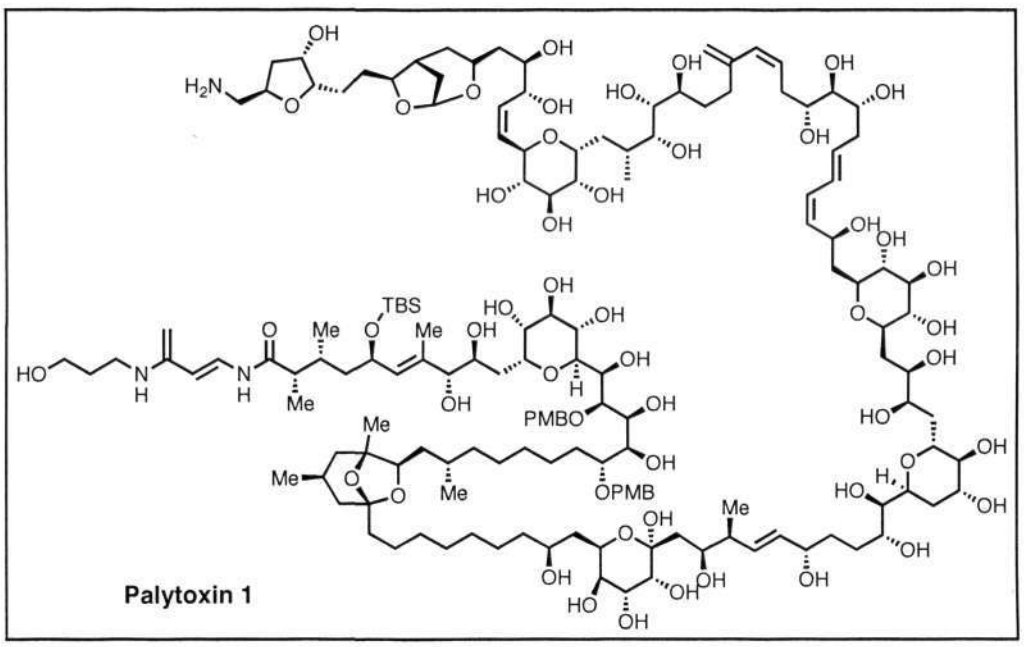


Figure 1-1

Synthesis of the natural product, palytoxin **1** (Figure 1-1) with 64 stereocenters demonstrates the elegant application of modern organic synthetic tools.[2] However,

[1] (a) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods (I)*, New York , Wiley-VCH, 1996; (b). Nicolaou, K. C.; Snyder, S. *A. Classics in Total Synthesis II: More Targets, Strategies, Methods.* New York ,Wiley-VCH, 2003; (c) Nicolaou K. C.; Montagnon, T. *Molecules That Changed the World,* New York, Wiley-VCH, 2008.

[2] (a) Suh, E. M.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11205; (b) Cha, J. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, L. L.; Ko, S. S.; Leder, J.; McWhorter, W. W.; Pfaff, K. -P.; Yonaga, M. *J. Am. Chem. Soc.* **1982**, *104,* 7369; (c) Armstrong, R. W.; Beau, J. -M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W. -H.; Hawkins, L. D.; Jin, H.; Kang, S. H. *J. Am. Chem. Soc.* **1989**, *111,* 7525; (d) Armstrong, R. W.; Beau, J. -M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W. -H.; Hawkins, L. D.; Jin, H.; Kang, S. H. *J. Am. Chem. Soc.* **1989**, *111,* 7530.

the ever-larger improvements of synthetic chemistry to our quality of life (*e.g.* medication, textile) seems to be overshadowed by critical issues tailing in its wake. The two major problems are: low synthetic yields resulting from long and tedious synthetic routes and the various concerns of environmental pollutants accumulated in the process. Therefore, the study of novel environmental friendly (*i.e.* less waste generating) and cost-effective methodologies is currently one of the most important tasks for modern synthetic chemists.[3]

Strategies which involve the synthesis of target molecule *via* stepwise formation of individual bonds of the target molecule from the starting material are cumbersome. The increase in the numbers of synthetic steps also impose a greater risk on the overall work, especially when any key synthetic step turns out to be unsuccessful at the later stage.[4]

Synthesis can evolve to be more elegant if we could construct several bonds in one step without isolation of any reaction intermediates. Obviously, comparing to stepwise synthesis, this type of reaction has the intrinsic advantage on the minimization of chemical waste. The cost of chemical reagents, solvents, energy and other related materials will also be greatly reduced. Time costs are additionally saved with much reduced work-up, separation and purification steps. This type of reaction is called cascade reaction, also known as domino reaction or tandem reaction.[5]

These reactions share a common definition: A process involving two or more

[3] (a) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233; (b) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267; (c) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice, Oxford University Press, Oxford*, **2000**, p. 135; (d) Matlack, A. S. *Introduction to Green Chemistry*, Marcel Dekker, New York, **2001**, p. 570.

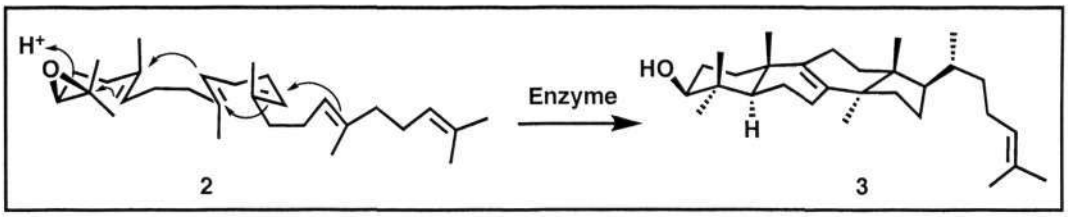
[4] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259.

[5] (a) Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed.* **1993**, *32*, 137; (b) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619; (c) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143; (d) Domling, A.; Ugi. I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168; (e) Domling, A. *Chem. Rev.* **2006**, *106*, 17; (f) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831; (g) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103; (h) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195; (i) Ho, T. -L. *Tandem Organic Reactions*, Wiley, New York, **1992**, p 502.

bond-forming transformations (usually C-C bonds) taking place under the same reaction conditions without adding additional reagents and catalysts. Additionally, the subsequent reactions result as a consequence of the functionality formed in the previous step.[6]

1.2 CASCADE REACTION

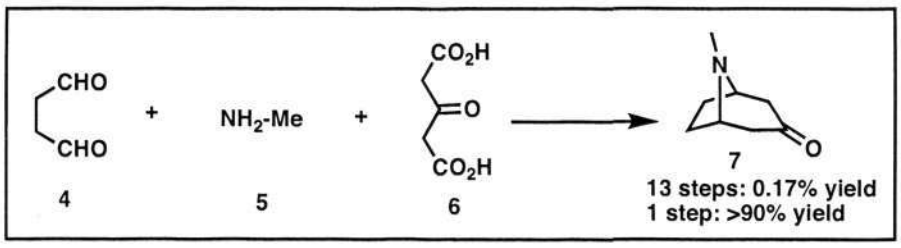
Cascade reaction is not a new invention. Nature has employed this approach for billions of years. For example, in the highly efficient and stereoselective biosynthesis of lanosterol **3** from (*S*)-2,3-oxidosqualene **2** in organism (Scheme 1-1),[7] four new bonds are constructed in a one-pot manner in the presence of enzyme catalysts.



Scheme 1-1 Biosynthesis of Lanosterol **3**

Robinson's[8] one-pot synthesis of tropinone in 1917 is one of the first cascade reactions developed by mankind. The synthesis is based on a three component double Mannich reaction. This route shortened the original synthesis from 13 steps to a single step and the yield was improved from 0.17% to more than 90% (Scheme 1-2).

[6] (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2006, p. 672; (b) Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed.* **1993**, *32*, 137; (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (d) Ho, T. -L. *Tandem Organic Reactions*, Wiley, New York, 1992.
[7] Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem. Int. Ed.* **2000**, *39*, 2812.
[8] (a) Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762; (b) Robinson, R. *J. Chem. Soc.* **1917**, *111*, 876; (c) Willstatter, R. *Justus Liebigs Ann. Chem.* **1901**, *317*, 204; (d) Schopf, C.; Lehmann G.; Arnord, W. *Angew. Chem.* **1937**, *50*, 779.



Scheme 1-2 Tropinone synthesis (Robinson, 1917)

1.3 CLASSIFICATION OF CASCADE REACTION

For the purpose of comparison and development of new cascade processes, cascade reactions have been grouped into five categories. Nucleophilic (anionic) reaction, electrophilic (cationic) reaction, radical mediated reaction, pericyclic reaction and transition-metal-catalyzed processes.[9] The classification is dependant on the character of the key "step". For case of comprehension, representative examples for each category will be provided in the following sections.

1.3.1 Nucleophilic (Anionic) Cascade Reaction

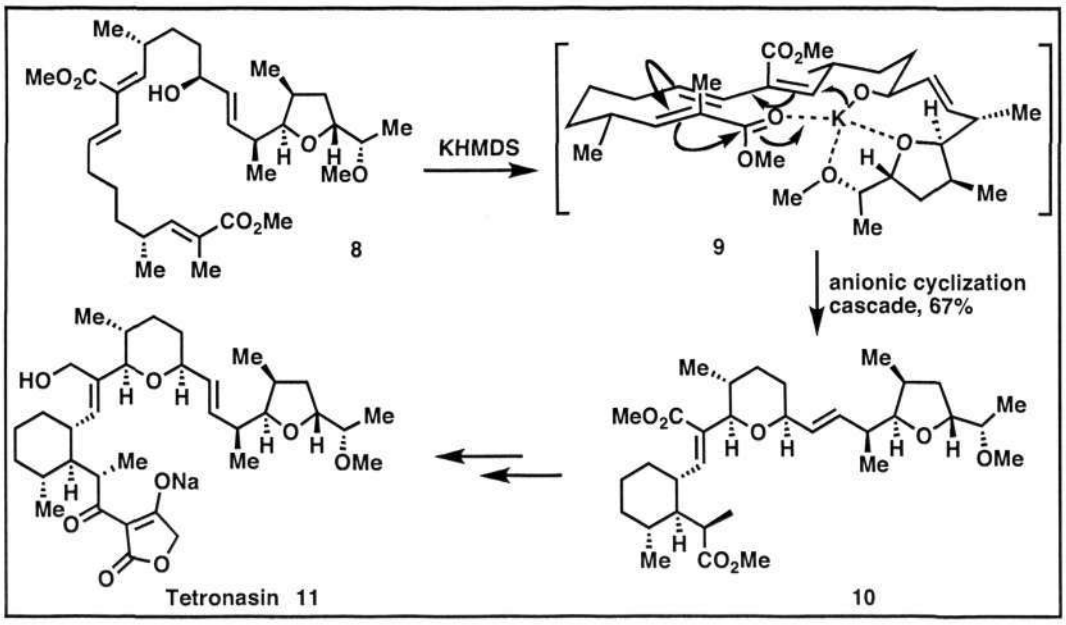
Anionic cascade reaction involves the attack of a nucleophile either an anion (*e.g.* carbanion, enolate or an alkoxide) or a pseudo anion (*e.g.* an amine, or an alcohol), onto an electrophilic center. A bond is formed with the creation of a new or pseudo anionic functionality, which can undergo further transformations. The sequence can then be terminated either by the addition of a proton or by the elimination of an X^- group.[10]

[9] Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134.
[10] For a recent review related to nucleophilic cascade reaction, see: Guo, H. -C.; Ma, J.-A. *Angew. Chem. Int. Ed.* **2006**, *45*, 354.

The well-known Robinson annulation,[11] double Michael reaction,[12] Pictet-Spengler cyclization,[13] reductive amination[14] *etc.*, all fall into this category.

Nucleophilic cascade reaction has been widely used in the synthesis of many natural products. One of the examples is the biomimetic total synthesis of tetronasin **11** as reported by Ley and co-workers.[15] They employed a nucleophilic cascade reaction as the key step (Scheme 1-3). Treatment of the putative cascade precusor **8** with potassium hexamethyldisilazide in toluene at 0 °C gave an efficient cyclization to produce **10** in 67% yield. Further chemical transformations afforded tetronasin **11**.

[11] (a) Robinson, R. *J. Chem. Soc.* **1917**, 111, 762; (b) Robinson, R. *J. Chem. Soc.* **1917**, 111, 876.
[12] (a) Hagiwara, H.; Morii, A.; Yamada, T.; Hoshi, T.; Suzuki, T. *Tetrahedron Lett.* **2003**, *44*, 1595; (b) Nicolaou, K. C.; Lim, Y. H.; Papageorgiou, C. D.; Piper, J. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 7917.
[13] (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1800; (b) Whaley, W. M.; Govindachari, T. R. *The Pictet-Spengler Synthesis of Tetrahydroisoquinolines and Related Compounds. In Organic Reactions*; Adams, R., Ed.; John Wiley and Sons: New York, 1951; Vol. VI, p 151; (c) Konda, M.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 1063; (d) Konda, M.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1977**, *25*, 69.
[14] Beshore, D. C.; Dinsmore, C. J. *Org. Lett.*, **2002**, *4*, 1201.
[15] a) Hailes, H. C.; Jackson, C. M.; Leadlay, P. F.; Ley, S. V.; Staunton, J. *Tetrahedron Lett.* **1994**, *35*, 307; b) Hailes, H. C.; Handa, S.; Leadlay, P. F.; Lennon, I. C.; Ley, S. V.; Staunton, J. *Tetrahedron Lett.* **1994**, *35*, 311; (c) Hailes, H. C.; Handa, S.; Leadlay, P. F.; Lennon, I. C.; Ley, S. V.; Staunton, J. *Tetrahedron Lett.* **1994**, *35*, 315; (d) Boons, G. -J.; Brown, D. S.; Clase, J. A.; Lennon, I. C.; Ley, S. V. *Tetrahedron Lett.* **1994**, *35*, 319; (e) Boons, G. -J.; Lennon, I. C.; Ley, S. V.; Owen, E. S. E.; Staunton, J.; Wadsworth, D. J. *Tetrahedron Lett.* **1994**, *35*, 323; (f) Ley, S. V.; Brown, D. S.; Clase, J. A.; Fairbanks, A. J.; Lennon, I. C.; Osborn, H. M. I.; Stokes, E. S. E. (nee Owen); Wadsworth, D. J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2259; (g) Hori, K.; Kazuno, H.; Nomura, K.; Yoshii, E. *Tetrahedron Lett.* **1993**, *34*, 2183.



Scheme 1-3 Tetronasin **11** synthesis *via* an anionic cascade cyclization (Ley *et al.*, 1998)

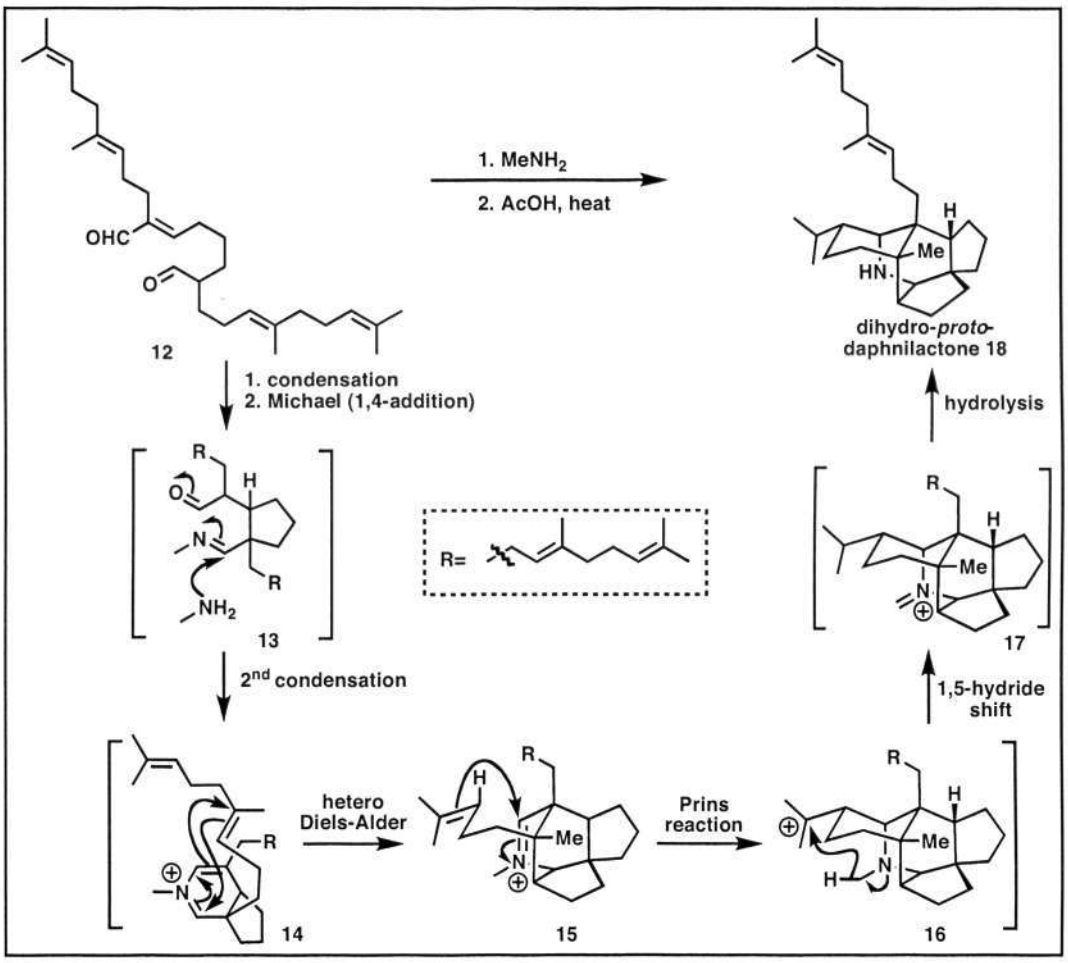
1.3.2 Electrophilic (Cationic) Cascade Reaction

The class of electrophilic cascade reaction covers processes in which carbocations or iminium ions are generated in the initial step. The formation of a carbocation can easily be achieved by treatment of an alkene or an epoxide with a Bronsted or Lewis acid, elimination of water from alcohol or an alcohol from an acetal, or by reaction of carbonyl compounds and imines with a Bronsted or Lewis acid.

Heathcock and co-workers[16] reported a remarkable example of electrophilic cascade process in the synthesis of polycyclic alkaloids of the *Daphniphyllum* family. They reported the one-step synthesis of dihydro-*proto*-daphniphylline **18**, which is a

[16] (a) Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath. J. C. *J. Org. Chem.* **1992**, *57*, 2544; (b) Heathcock, C. H.; Piettre, S.; Ruggeri, R. B.; Ragan, J. A.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2554; (c) Heathcock, C. H. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 665; (d) Heathcock, C. H. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 14323.

precursor to *Daphniphyllum* alkaloids, *via* iminium chemistry (Scheme 1-4). Treatment of acyclic di-aldehyde **12** with methylamine and acetic acid gave the target compound in 65% yield through a process that formed five new rings and installed eight new stereogenic centers in a completely diastereoselective fashion.



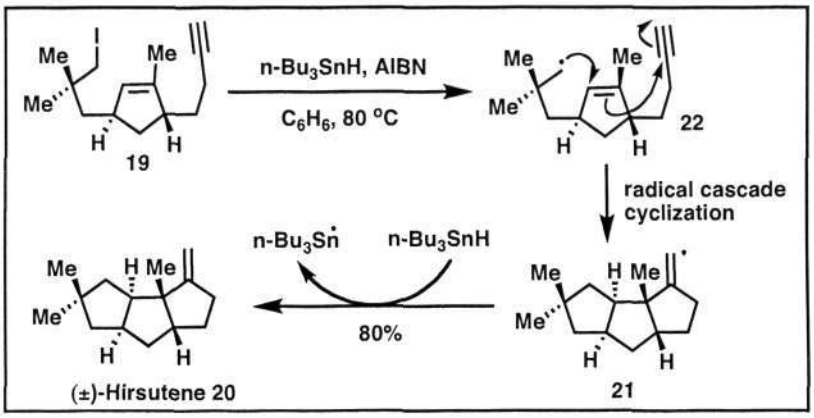
Scheme 1-4 One-step synthesis of dihydro-*proto*-daphniphylline **18** (Heathcock *et al.*, 1992)

1.3.3 Radical Cascade Reaction

Radical based transformations have drawn much attention from organic chemists as an indispensable alternative of a nonpolar method for the connection of carbon atoms. In marked contrast to polar processes, radical transformations can

proceed in most cases in the presence of free hydroxyl and amino groups, as well as keto and ester functionalities. Another advantageous feature of utilizing radicals is the fact that they are equally feasible in adding to inactivate double and triple bonds as to substrates bearing polarizing groups.[17]

Curran's radical cascade cyclization strategy in the total synthesis of Hirsutene **20** is a prominent example in this field.[18] The key feature of Curran's strategy is illustrated in Scheme 1-5. The tri-*n*-butyltin radical generated *in-situ* reacts with iodide **19** to give the transient radical **22** which participates in a facile 5-*exo*-trig radical cyclization, followed by a 5-*exo*-dig radical cyclization to give the tricylic vinyl radical **21**. **21** then undergoes radical termination by abstraction of a hydrogen atom from tri-*n*-butyltin hydride to afford Hirsutene **20**.



Scheme 1-5 A radical cascade cyclization in the total synthesis of Hirsutene (Curran *et al.*, 1985)

[17] For general reviews of radical chemistry, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds, Pergamon, Oxford,* 1986, p. 294; (b) Giese, B. *Radicals in Organic Synthesis, Vols. 1&2* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, 2001, p. 1110; (c) Zard, S. Z. *Radical Reactions in Organic Synthesis, Oxford University Press, Oxford,* 2003, p. 256; (d) Albert, M.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Top. Curr. Chem.* **2006**, *264*, 1; (e) McCarroll, A. J.; Walton, J. C. *Angew. Chem. Int. Ed.* **2001**, *40*, 2224.

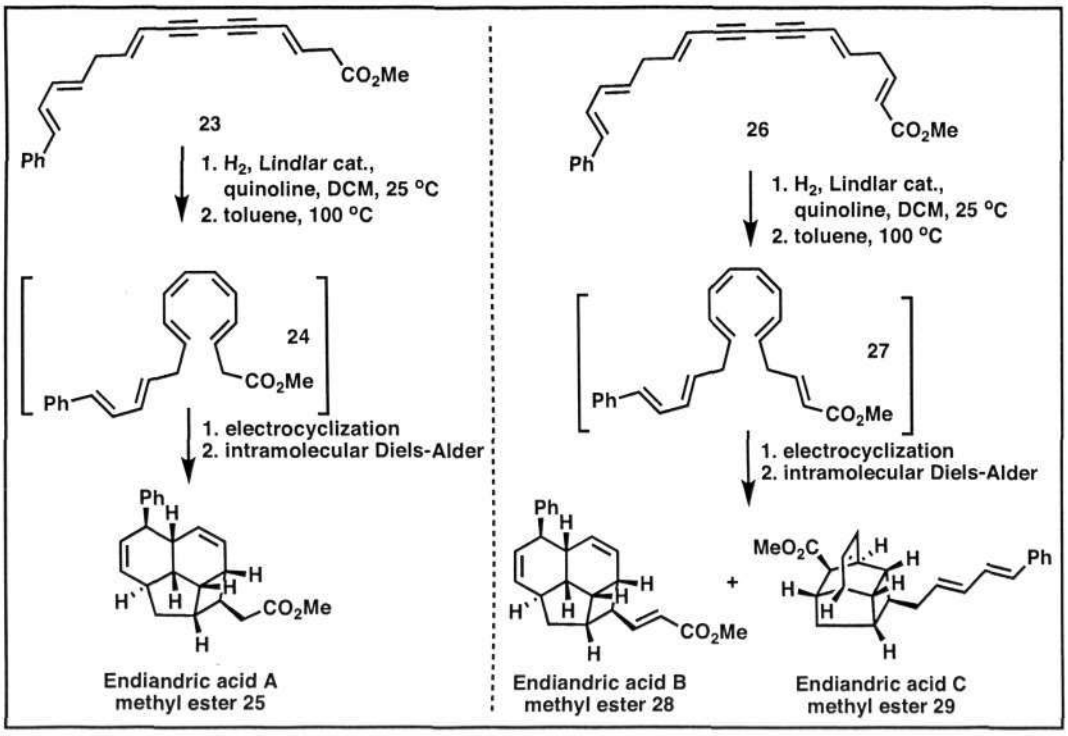
[18] (a) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448; (b) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron*, **1985**, *41*, 3943.

1.3.4 Pericyclic Cascade Reaction

Pericyclic reaction is perhaps the most common processes encountered in cascade reactions. One of the most famous examples is the Diels-Alder reaction.[19] Pericyclic reactions include cycloadditions, sigmatropic rearrangements, and electrocyclic reactions, all of which have been employed in cascades *en route* to natural product targets.

Nicolaou's one-step approach towards Endiandric acid (A-D) is an excellent illustration.[20] The polyunsaturated compound **23** was first prepared to serve as a precursor for the cascade process. A mild hydrogenation was undertaken, followed by brief heating at 100 °C in toluene. In this amazing single-step cascade reaction, a simple achiral polyene is converted into the complex tetracyclic framework of endiandric acid methyl ester (A-C) **25, 28** and **29** respectively with complete control over eight stereogenic centers (Scheme 1-6).

[19] For a review of tandem Diels–Alder reactions, see: Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167.
[20] (a) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E.; Uenishi, J. *J. Am. Chem. Soc.* **1982**, *104*, 5555; (b) Nicolaou, K. C.; Petasis, N. A.; Uenishi, J.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5557; (c) Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J. Am. Chem. Soc.* **1982**, *104*, 5558; (d) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5560; (e) Bandaranayake, W. M.; Banfield, J. E.; Black, D. St. C.; Fallon, G. D.; Gatehouse, B. M. *J. Chem. Soc. Chem. Commun.* **1980**, 162; (f) Bandaranayake, W. M.; Banfield, J. E.; Black, D. St. C. *J. Chem. Soc. Chem. Commun.* **1980**, 902; (g) Bandaranayake, W. M.; Banfield, J. E.; Black, D. St. C. *Aust. J. Chem.* **1981**, *34*, 1655; (h) Bandaranayake, W. M.; Banfield, J. E.; Black, D. St. C. *Aust. J. Chem.* **1982**, *35*, 557; (i) Bandaranayake, W. M.; Banfield, J. E.; Black, D. St. C.; Fallon, G. D.; Gatehouse, B. M. *Aust. J. Chem.* **1982**, *35*, 567; (j) Banfield, J. E.; Black, D. St. C.; Johns, S. R.; Willing, R. I. *Aust. J. Chem.* **1982**, *35*, 2247.



Scheme 1-6 The endiandric acid cascade reaction (Nicolaou *et al.*, 1982)

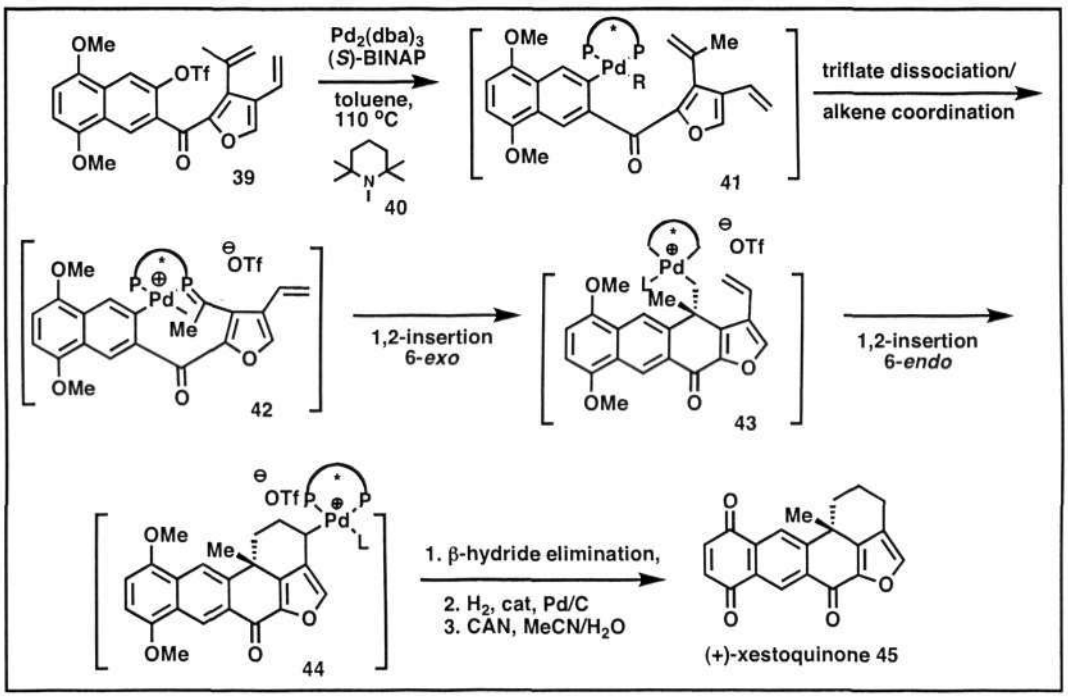
1.3.5 Transition-Metal-Catalyzed Cascade Reaction

Transition-metal-catalyzed cascade reactions have blossomed into extraordinarily powerful tools for carbon-carbon and carbon-heteroatom bond formation in synthetic organic chemistry within the last 25 years. In particular, Pd-catalyzed cascade transformation with the Heck reaction is one of the most widely utilized cascade processes.[21] Other transition metals-catalyzed related cascade reactions involving rhodium, ruthedium, cobalt, nickel, copper, titanium and iron had also been widely explored in past years.[22]

[21] (a) Heck, R. F.; Nolley, Jr. J. P. *J. Org. Chem.* **1972**, *37*, 2320; (b) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581; (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009; (d) Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533.

[22] (a) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*, Wiley-VCH Weinheim, 1998, Vol, 1 and Vol. 2; (b) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed., University Science Books, Sausalito, 1999, p. 337; (c) *Comprehensive Organometallic Chemistry II, Vol. 12*, Pergamon, Oxford, 1995, p. 1359; (d) *Asymmetric Organocatalysis* (Eds.: A. Berkessel, H. Gröger), Wiley-VCH, Weinheim, 2005, p. 440; (e) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719; (f) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. (g) Tietze, L. Z.;

Keay and co-workers[23] employed an asymmetric polyene Heck cyclization in their enantioselective synthesis of (+)-xestoquinone **45** (Scheme 1-7), in which achiral aryl triflate **39** was converted in a single step into pentacyclic compound **45** under the conditions shown.



Scheme 1-7 (+)-xestoquinone (*Keay et al.*, 1996)

Hiriyakkanavar, I.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453; (h) Negishi, E. Handbook of Organopalladium Chemistry for Organic Synthesis, John Wiley & Sons, Inc, Hoboken NJ, **2002**, *2*, 1689;

[23] (a) Maddaford, S. P.; Andersen, N. G.; Cristofoli, W. A.; Keay, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10766; (b) Cristofoli, W. A.; Keay, B. A. *Synlett.* **1994**, 625.

1.4 SUMMARY

To date, the application of various cascade reactions in total syntheses have been reported. The enormous benefits associated with cascade reactions are still under development and exploitation in organic synthesis. Construction of complex molecules in an efficient way, as nature does, has been a great mission to every synthetic organic chemist. Based on the beautiful and ingenious development in cascade reactions, this great mission will be achieved in the near future. Herein, we will report the methodology developments of titanium catalyzed cascade reaction with acetals and enol ethers as substrates and it's application in natural product synthesis. The result will be discussed in more detail in the next section.

Chapter 2

Mukaiyama-Aldol-Prins Cascade Reaction

2.1 INTRODUCTION

2.1.1 Mukaiyama-Aldol Reaction

Mukaiyama-Aldol reaction is a Lewis acid mediated addition of enol silanes to carbonyl compounds discovered by T. Mukaiyama and K. Narasaka in the early 1970's[1] (Sheme 2-1). Lewis acids such as $TiCl_4$, $SnCl_4$, $AlCl_3$, $BCl_3{\cdot}OEt_2$, and $ZnCl_2$ were required to mediate this transformation. The importance of Mukaiyama-Aldol[2,3] reaction is unquestionable, as a highly efficient method in C-C bond formation. The sheer volume of corresponding publications testified its utility. The diastereoselectivity of this reaction can be controlled if substrates and conditions are carefully chosen. The asymmetric Mukaiyama-Aldol reaction has also been extensively investigated with both chiral Lewis acid complexes and Lewis bases.[4]

The mechanism of the classical Lewis acid catalyzed Mukaiyama-Aldol reaction involves the silyl enol ether, which functions as a nucleophile. The carbonyl group of electrophile **1** is activated by the Lewis acid coordination (intermediate **5**) followed by carbon-carbon bond formation to form intermediate **6**. After aqueous work-up, the final products **3** or **4** were generated. The stereochemical outcome of the

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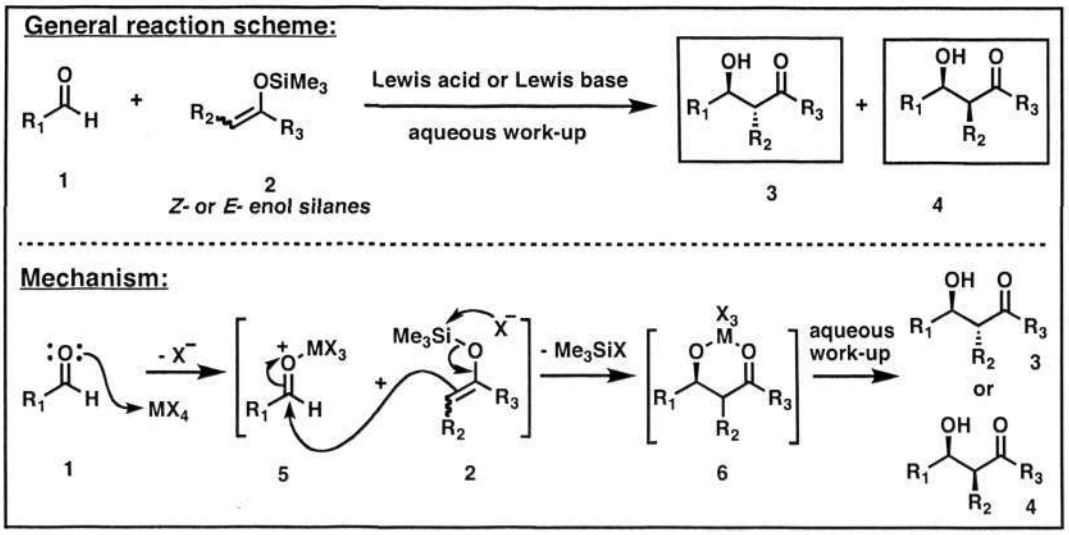
[1] Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011; (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.***1974**, *96*, 7503.

[2] (a) Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem.Lett.* **1975**, 989; (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203; (c) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16,* 817; (d) Mukaiyama, T. *Aldrichimica Acta* **1996**, *29*, 59.

[3] (a) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109; (b) Heathcock, C. H. in *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: Amsterdam, **1984**; Part B, Chapter 4; (c) Heathcock, C. H. in *Asymmetric Synthesis*; Morrison, D. J., Ed.; Chapter 2, Academic: New York, **1984**; Vol. 3, Part. B, p. 111; (d) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1; (e) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1; (f) Braun, M.; Sacha, H. *J. Prakt. Chem.* **1993**, *335*, 653; (g) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M. Ed.; Pergamon: Oxford, **1993**; Vol. 2, Chapter 1, 6; (h) Heathcock, C. H. *Mod. Synth. Meth.* **1992**, 1; (i) Heathcock, C. H. *Aldrichimica Acta* **1990**, *23*, 99; (j) Heathcock, C. H. *Science* **1981**, *214*, 395; (k) Mukaiyama, T. *Org. React.***1982**, *28*, 203.

[4] (a) Carreira, E. M. *Mukaiyama aldol reaction: Comprehensive Asymmetric Catalysis I-III* **1999**, *3*, 997; (b) Kazuaki, I.; Yamamoto, H. *Modern Aldol Reactions*, **2004**, *2*, 25.

reaction is generally dependent on steric- and dipolar effects[5] of the transition state, determining the resulting *syn* or *anti* configuration.



Scheme 2-1 Mechanistic interpretation of Mukaiyama-Aldol reaction

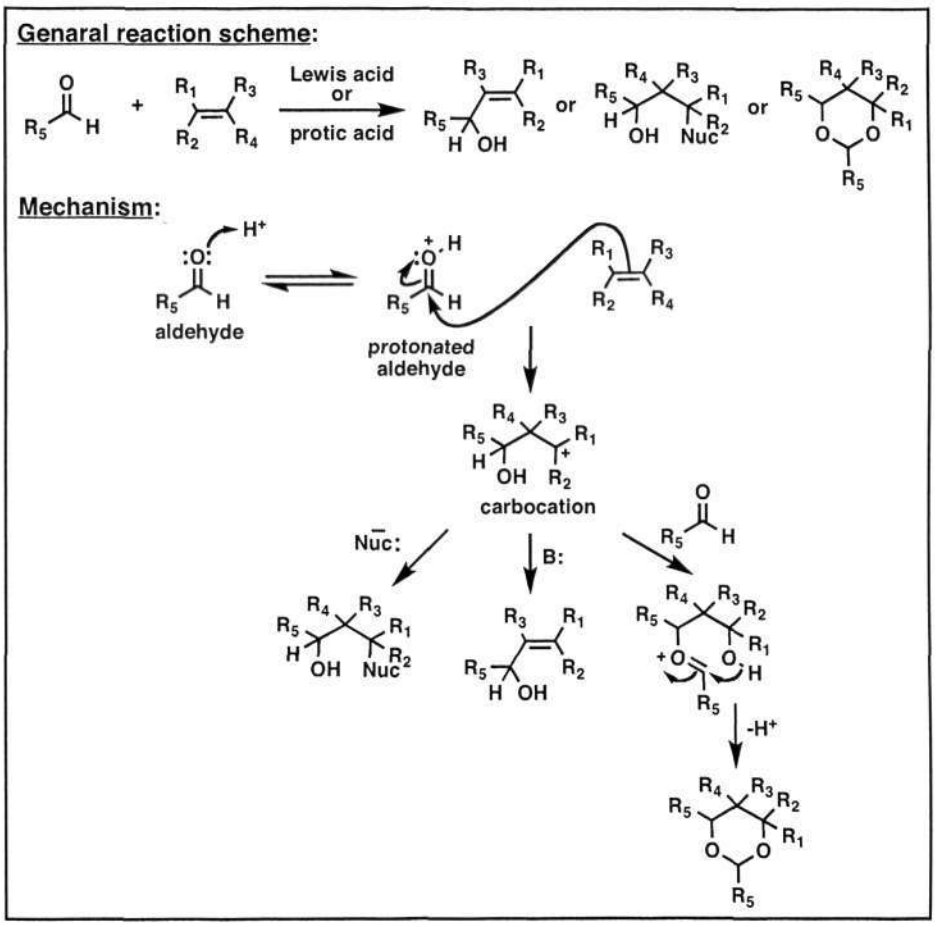
2.1.2 Prins Reaction

Prins reaction is an acid catalyzed addition of alkene to an aldehye established by Hendrik Jacobus Prins[6] in 1919. The final product obtained varies according to the different reaction conditions employed. Similar to the Mukaiyama-Aldol reaction, the Prins reaction is also an eminent named reaction in carbon-carbon bond formation reactions.[7] It has been widely applied in methodology studies and natural product synthesis.[8] Our research group has also been actively involved in the development of

[5] (a) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095; (b) Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, 2005.
[6] (a) Prins, H. J. *Chem. Weekblad*, **1919**, *16*, 1510; (b) Prins, H. J. *Chem. Weekblad*, **1919**, *16,* 1072.
[7] (a) Arundale, E., Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505; (b) Snider, B. B. *Comp. Org. Synth.* 1991, p. 527; (c) Zhang, W.-C., Viswanathan, G. S., Li, C.-J. *Chem. Commun.* **1999**, 291; (d) Keh, C. C. K., Li, C. -J. *Green Chem.* **2003**, *5*, 80; (e) Tian, G. -Q; Shi, M. *Org. Lett.*, **2007**, *9*, 2405; (f) Yadav, J. S.; Reddy, B. V. S.; Kumar, G.; Aravind, S. *Synthesis*, **2008**, 395.
[8] (a) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919; (b) Kwon, M. S.; Woo, S. K.; Na, S. W.; Lee, E. *Angew. Chem. Int. Ed.* **2008**, *47*, 1733; (c) Ko, H. M.; Lee, D. G.; Kim, M. A.; Kim, H. J.; Park, J.; Lah, M. S.; Lee, E. *Org. Lett.*, **2007**, *9*, 141.

versatile and practical Prins cyclization for the construction of tetrahydropyran (THP) rings.[9]

The Prins reaction mechanism involves an acid activation of the aldehyde, followed by attack from an electron-rich alkene moiety.[10] The resultant carbocation formed can then undergo elimination, nucleophilic attack, or acetalization with excess aldehydes to form different products *via* a stepwise mechanism[11] (Scheme 2-2).



Scheme 2-2 Mechanistic interpretation of Prins reaction

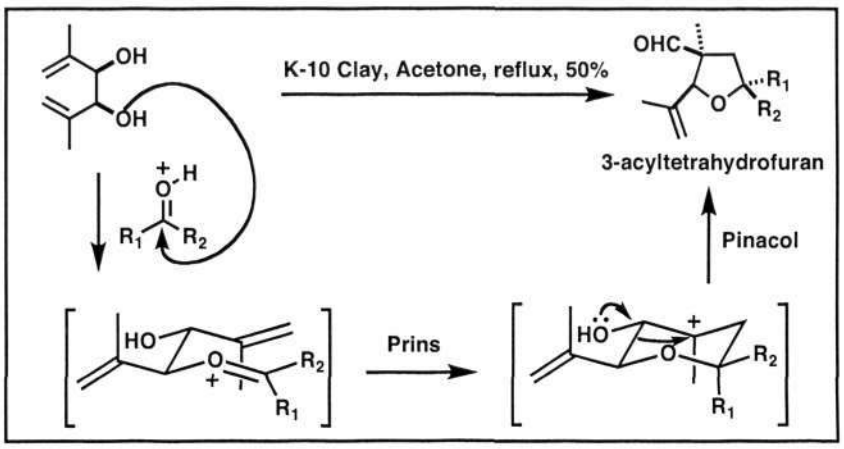
[9] (a) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491; (b) Liu, F.; Loh, T.-P. *Org. Lett.*, **2007**, *9*, 2063.
[10] (a) Alder, K.; Von, B. H. *Liebigs. Ann. Chem.* **1962**, *651*, 141; (b) Carruthers, E. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press, 1990; (c) Oppolzer, W.; Snieckus, V. *Angew. Chem. Int. Ed.* **1978**, *17*, 476; (d) Benn, F. R.; Dwyer, J.; Chappel, I. *J Chem. Soc. Perkin. Trans. 2*, **1977**, *5*, 533; (e) Jenner, G.; Salem, B.; Elyanor, B.; Gonikberg, E. M. *J. Chem. Soc. Perkin Trans. 2*, **1989**, *11*, 1671; (f) Snider, B. B. *Acc. Chem. Res.*, **1980**, *13*, 426.
[11] (a) Dolby, L. J.; Schwarz, M. J. *J. Org. Chem.* **1965**, *30*, 3581; (b) Dolby, L. J.; Meneghini, F. A.; Koizumi, T. *J. Org. Chem.* **1968**, *33*, 3060; (c) Dolby, L. J.; Wilkins, C. L.; Rodia, R. M. *J. Org. Chem.* **1968**, *33*, 4155; (d) Schowen, K. B.; Smissman, E. E.; Schowen, R. L. *J. Org. Chem.* **1968**, 33, 1873; (e) Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, 2005.

2.1.3 Mukaiyama-Aldol and Prins in Cascade reaction

2.1.3.1 Overman Prins-Pinacol cascade reaction

The Prins-pinacol rearrangement is one of the prominent cascade reaction developed by Overman in 1987.[12] This cascade reaction is catalyzed by a Lewis acid mediated rearrangement to generate a highly substituted tetrahydrofuran derivative *via* formation of two C-C bonds, one C-O bond and two new stereogenic centres.

Overman proposed that the ketone was condensed with the diol to give an oxocarbenium ion. The reaction terminates *via* Prins cyclization to afford a β-hydroxy carbenium ion intermediate and a pinacol rearrangement, giving rise to a 3-acyltetrahydrofuran[13] (Scheme 2-4).



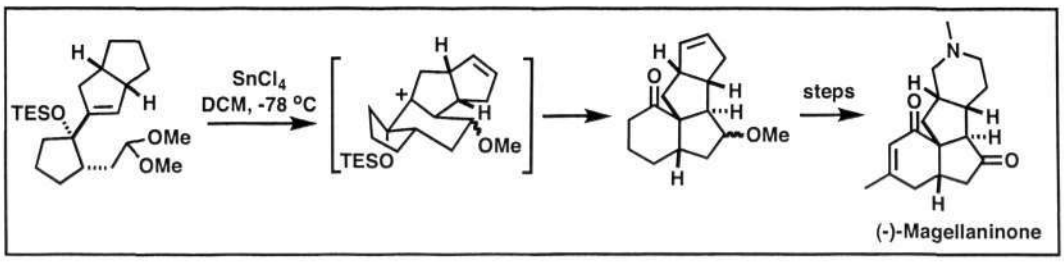
Scheme 2-4

Subsequent studies conducted by the Overman group have broadened the scope of this transformation, refining in the assembly of oxacyclic ring system and the

[12] Hopkins, M. H.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 4748.
[13] Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143.

construction of carbocylic ring systems, which are featured widely in many natural products.[14]

The total synthesis of *lycopodium* alkaloids of the magellanane group has demonstrated the prowess of the Prins-pinacol rearrangement strategy as reported by Overman.[15] The angularly fused all-carbon tetracylic framework of (-)-magellaninone was constructed using the ring-expansion Prins-Pinacol rearrangement as the key step (**Scheme 2-5**).



Scheme 2-5

2.1.3.2 Rychnovsky Mukaiyama-Aldol-Prins Cascade Reaction

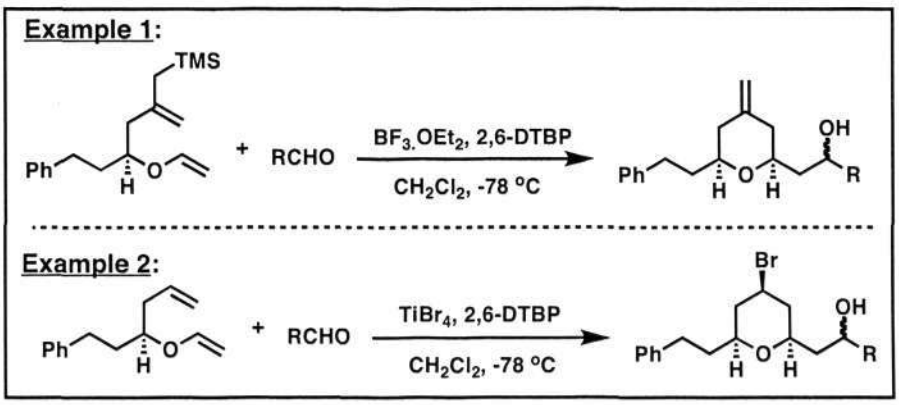
The Mukaiyama-Aldol-Prins reaction is another attractive cascade reaction reported by Rychnovsky in 2001 in the construction of tetrahydropyran (THP) moiety.[16] A mixture of an unsaturated enol ether and an aldehyde undergoes an aldol

[14] (a) Brown, M. J.; Harrison, T.; Herrinton, P. M., Hopkins, M. H.; Hutchinson, K. D.; Overman, L. E.; Mishra, P. *J. Am. Chem. Soc.* **1991**, *113*, 5365; (b) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378. (c). Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354; (d) Overman, L. E *Acc. Chem. Res.* **1992**, *25*, 352; (e) Overman, L. E. *Aldrichimica Acta* **1995**, *28*, 107; (f) Ando, S.; Minor, K. P.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 6379; (g) Minor, K. P.; Overman, L. E. *Tetrahedron* **1997**, *53*, 8927; (h) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092; (i) Gahman, T. C.; Overman, L. E. *Tetrahedron* **2002**, *58*, 6473; (j) Burke, B. J.; Lebsack, A. D.; Overman, L. E. *Synlett* **2004**, 1387; (k) Hanaki, N.; Link, J. T.; MacMillan, D. W. C.; Overman, L. E.; Trankle, W. G.; Wurster, J. A. *Org. Lett.* **2000**, *2*, 223; (l) Cohen, F.; MacMillan, D. W. C.; Overman, L. E.; Romero, A. *Org. Lett.* **2001**, *3*, 1225; (m) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, *125*, 6650; (n) Lebsack, A. D.; Overman, L. E.; Valentekovich, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 4851.

[15] Hirst, G. C.; Johnson, T. O. Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992.

[16] Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420.

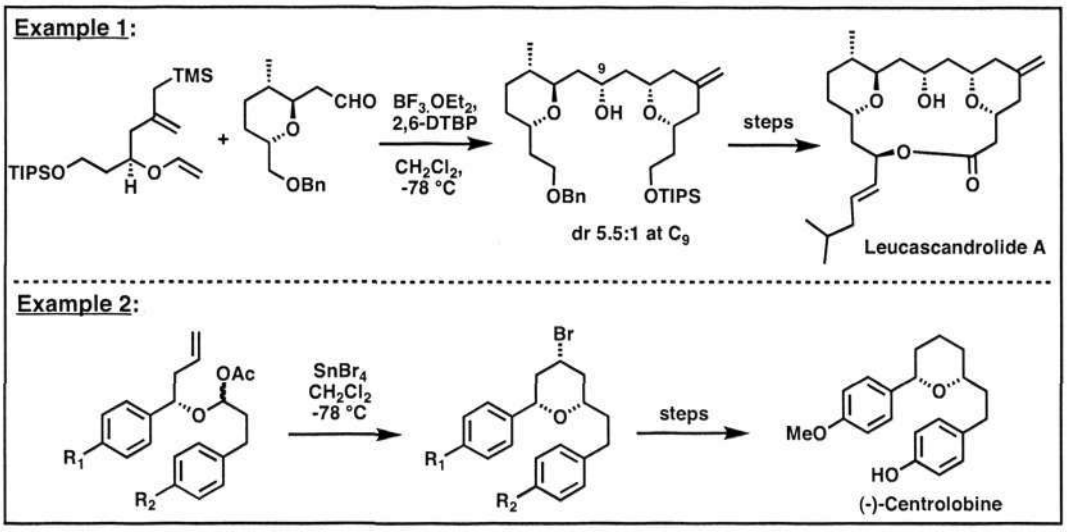
type reaction in the presence of a Lewis acid, followed by a Prins cyclization to form a tetrahydropyran ring[17] (Scheme 2-6).



Scheme 2-6 Lewis acids promoted Mukaiyama-Aldol-Prins cyclization

Tandem Mukaiyama-Aldol-Prins cyclization has been utilized in the synthesis of natural products such as macrolide leucascandrolide A[18] and (-)-centrolobine[19] by Rychnovsky. A tetrahydropyran ring system is a key feature in the reported synthesis and is constructed *via* the Mukaiyama-Aldol-Prins cyclization (Scheme 2-7).

[17] (a) Bahnck, K. B.; Rychnovsky, S. D. *J. Am Chem.Soc.* **2008**, *130*, 13177; (b) Orden, K. L. V.; Patterson, B. D.; Rychnovsky. S. D. *J. Org. Chem.* **2007**, *72*, 5784; (c) Jasti, R.; Rychnovsky, S. D. *Org. Lett.* **2006**, *8*, 2175; (d) Patterson, B.; Rychnovsky, S. D. *Syn. Lett.* **2004**, 543; (e) Patterson, B.; Marumoto, S.; Rychnovsky. S. D. *Org. Lett.* **2003**, *5*, 3163; (f) Graetz, B.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3357.
[18] Kopecky, D. J.; Rychnovsky, S. D.; *J. Am. Chem. Soc.* **2001**, *123*, 8420.
[19] Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919.



Scheme 2-7 Total synthesis of the leucascandrolide A and (-)-centrolobine

2.2 APPLICATION OF MUKAIYAMA-ALDOL-PRINS CASCADE REACTION

Discovery of efficient methods towards the construction of complex molecules with multiple stereogenic centers in excellent regio-, diastereo- and enantioselectivity has been an important goal for both academic and industrial researchers.[20] In particular, asymmetric domino and cascade reactions which allow the formation of multiple C-C bonds and many stereogenic centers in a one-pot manner are useful for the synthesis of natural products and synthetic building blocks.[21] Accordingly, much effort has been focused on the development of new stereoselective cascade reactions, including recent reports by Enders *et. al.* on an elegant asymmetric domino reaction for the construction of cyclohexane derivatives in excellent stereoselectivities.[22] Whilst research in this area is gaining momentum, the development of highly

[20] Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134.
[21] Guo, H. -C.; Ma, J. -A. *Angew. Chem. Int. Ed.* **2006**, *45*, 354.
[22] Enders, D.; Grondal, C.; Huttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570.

stereoselective cascade reaction for the synthesis of cyclopentane derivatives remains a challenge.[23]

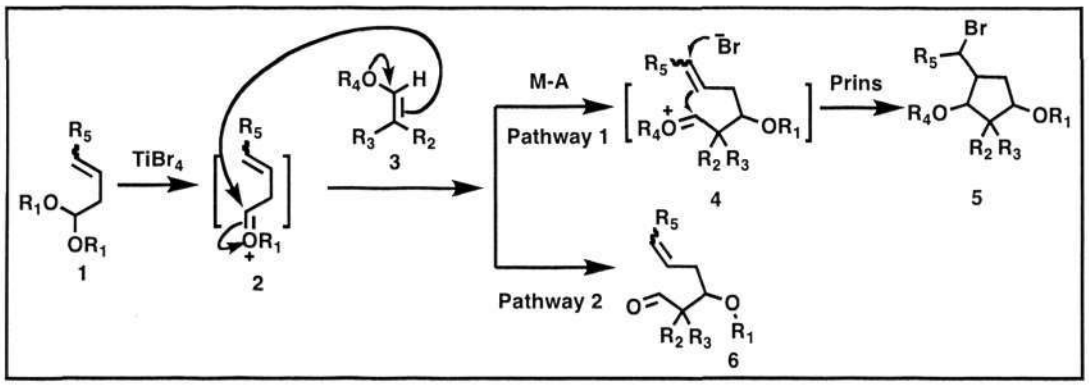
2.2.1 Construction of Five-Membered Ring System

Our research group has been engaged in the research of Mukaiyama-Aldol reaction[24] and Prins reaction[25] for many years. Since both reactions give the same common intermediate, an oxocarbenium, we intend to combine the two reactions into a cascade process for the synthesis of highly substituted ring system. In addition, variation of the substrates and simple manipulation of the products will allow the construction of a diverse library of polyfunctionalized cyclopentane derivatives, which can serve as building blocks for the synthesis of complex molecules.

We envisage that the cascade reactions involving the Mukaiyama-Aldol reaction of silyl enol ether **3** with acetal **1** will produce an oxocarbenium intermediate **4**,[26] which upon trapping by an alkene functionality in an intramolecular Prins cyclization fashion[27] may generate the cyclopentyl ring system **5** (Scheme 2-10).

---

[23] Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604.
[24] (a) Loh, T. P.; Pei, J.; Cao, G. Q. *J. Chem. Soc., Chem. Commun.* **1996**, 1819; (b) Loh, T. P.; Pei, J.; Koh, K. S. V.; Cao, G. Q.; Li, X. R. *Tetrahedron Lett*, **1997**, *38*, 3465; (c) Loh, T. P.; Chua, G. L.; Vital, J. J.; Wong, M. W. *J. Chem. Soc., Chem Commun.* **1998**, 861; (d) Loh, T. P.; Li, X. R. *Tetrahedron,* **1999**, *55*, 10789; (e) Loh, T. P.; Huang, J. M.; Goh, S. H. *Org Lett*. **2000**, 1291; (f) Loh, T. P.; Feng, L. C. *Tetrahedron*, **2001**, *57*, 4231; (g) Chen, S. L.; Ji, S. J.; Loh, T. P. T*etrehedron lett.* **2004**, *45*, 375.
[25] (a) Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387; (b) Chan, K. P.; Loh, T. P. *Org. Lett*, **2005**, 4491; (c) Chan, K. P.; Seow, A. H.; Loh, T. P. *Tetrahedron Lett*, **2007**, 48, 37; (d) Chan, K. P.; Ling, Y. H.; Loh, T. P. *Chem. Comm.* **2007**, 939.
[26] Balme, G.; Gore, J. *J. Org. Chem.* **1983**, *48*, 3336.
[27] (a) Chan, K. P.; Loh, T. P. *Org. Lett*. **2005**, *7*, 4491; (b) Liu, F.; Loh, T. P. *Org. Lett*. **2007**, *9*, 2063.

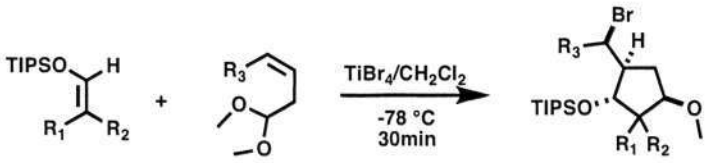


Sheme 2-10 Our proposed hypothesis

In our initial studies, we reacted the mono substituted acetal (Scheme 2-10, R_1 = Me, R_5 = Et) with silyl enol ether (Scheme 2-10, R_2, R_3 = Me, R_4 = TMS) in the presence of titanium tetrabromide ($TiBr_4$). Unfortunately, the desired domino process did not occur. Only the Mukaiyama-Aldol reaction product **6** was obtained (Scheme 2-10).

Next, we replaced the labile trimethyl silyl group with more robust silicon protecting group such as triisopropyl silane (TIPS). To our delight, the desired product **9** was obtained in very high yield with excellent diastereoselectivity (Table 2-1, entry 1). Using different silyl enol ethers (Table 2-1, entries 2-3), the domino process proceeded in the same manner to give the desired products in high yields with excellent diastereoselectivities. In all cases, a single isomer was obtained, three new bonds and four new stereocenters were generated from this highly efficient cyclization process.

Table 2-1 MAP reactions with mono-substituted acetal (Z-8)[a]



7 8 9

Entry	R_1	R_2	R_3[b]	Yield[c]	*dr*[d]
1	CH_3	CH_3	Et	90	>99:1
2	CH_3CH_2-	CH_3CH_2-	Et	91	>99:1
3	-$(CH_2)_3$-		Et	86	>99:1
4	CH_3, Br (Z/E = 85:15)[e]		Et	80 (87:13)	>99:1
5	CH_3	CH_3	CH_2OBn	81	>99:1
6	CH_3CH_2	CH_3CH_2	CH_2OBn	85	>99:1
7	-$(CH_2)_3$-		CH_2OBn	93	>99:1
8	-$(CH_2)_2$-		CH_2OBn	90	>99:1

[a]Mukaiyama-Aldol-Prins reactions were run with 2 equiv of $TiBr_4$, 1 equiv of acetal and 1.2 equiv of silyl enol ether under N_2 atmosphere. [b]Mono-substituted acetals (*Z*-8) were prepared by Wittig reactions. MAP reaction cannot proceed using mono-substituted acetal (*E*-8). [c]Isolated yield. [d]Diastereomeric ratios were based on ^1H and ^{13}C NMR analyses. [e]MAP reaction proceeds smoothly with *Z* or *E* silyl enol ether.

A noteworthy point in this study is the intriguing bromo substituted silyl enol ether. In this case, five new chiral centers were formed contiguously in a one-pot reaction with high yield and excellent diastereoselectivity (Table 1, Entry 4). The *E/Z* isomers (85/15) of the silyl enol ether which could not be separated were retained in the product. This reaction further expanded the scope of this method. The MAP domino process could also proceed smoothly with -CH_2OBn substituted acetal to afford the products in high yields and excellent diastereoselectivities. Based on the X-

ray analysis of a MAP product (Table 2-1, entry 7 analog[28]), the relative configuration of the five-membered rings system was established as shown in Figure 2-1.

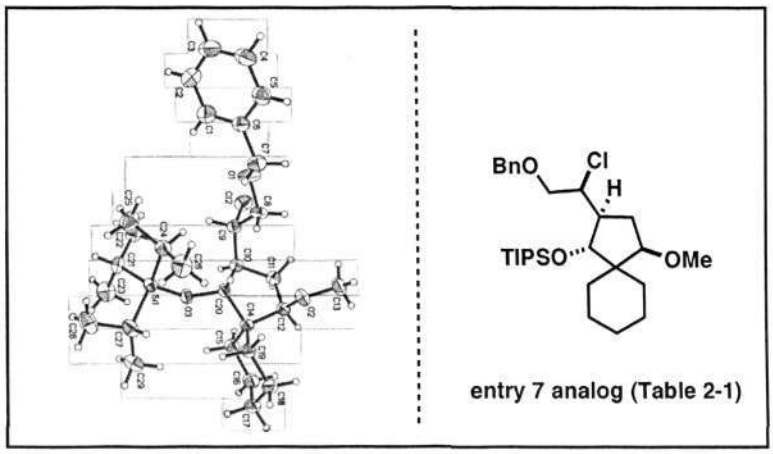
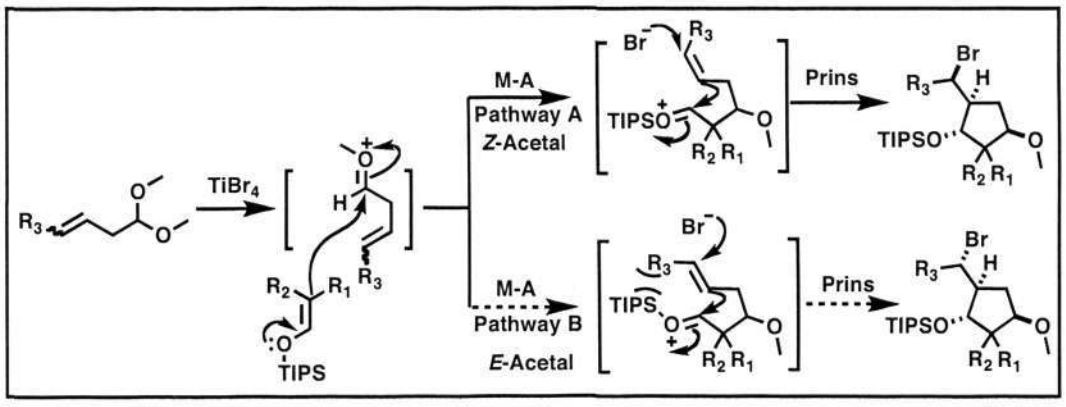


Figure 2-1 X-ray of chloride analogue (Table 2-1, entry 7)

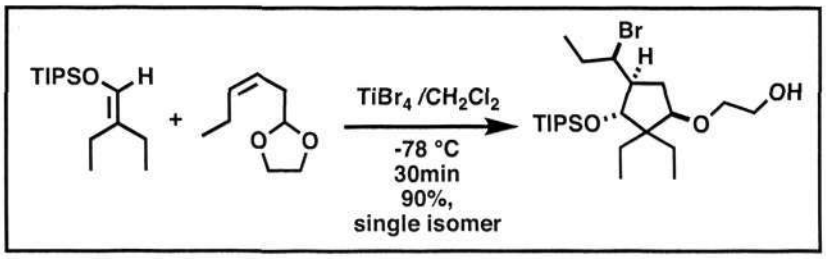
Of mechanistic interest is that no reaction was observed when the *E* isomer of the acetal was used in this reaction. Based on this information and the stereochemistries observed in the products, a plausible mechanism for the formation of the five-membered ring products was proposed as shown in Scheme 2-11. We believe that the steric repulsion between bulky OTIPS and R_3 in the *E*-isomer disfavored pathway B.



Scheme 2-11 Mechanism of five-membered rings system formation

[28] $TiCl_4$ as replacement of $TiBr_4$ also been explored in this MAP study. We found that $TiCl_4$ gave lower yield as compared to $TiBr_4$. So, we mainly focus on $TiBr_4$ as Lewis acid. Attempts to grow a crystal in both series of product were tried, but only crystal structure from chloride analog was obtained.

Besides the acyclic acetal, we also looked into the cyclic acetal version (Scheme 2-12). Treatment of the TIPS silyl enol ether with cyclic acetal under the same reaction condition gave the desired product as a single isomer in excellent yield.

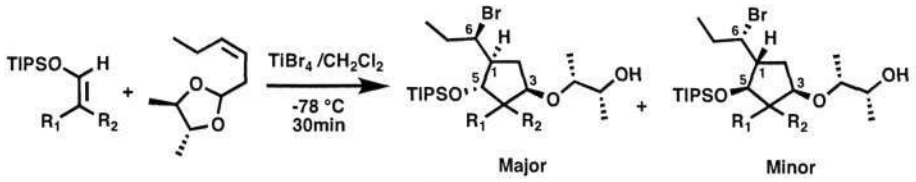


Scheme 2-12 MAP reactions using cyclic acetal

These encouraging results set the stage for carrying out studies for the asymmetric version of this methodology. Inspired by our research work on chiral acetal initiated intermolecular polyene cyclization,[29] we decided to introduce asymmetric element by using optically pure cyclic acetal. In all cases, the cyclization reaction using cyclic mono-substituted acetal provided the desired products in high yields and excellent stereoselectivities (Table 2-2).

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

Table 2-2 MAP reactions in asymmetric version for five-membered rings[a]



Entry	R_1	R_2	Yield	*dr*
1	CH_3	CH_3	93%	90:10
2	CH_3CH_2	CH_3CH_2	94%	89:11
3	$-(CH_2)_3-$	$-(CH_2)_3-$	90%	92: 8
4	CH_3, Br (Z/E = 85:15)		80% (90:10)	>99:1

[a]Optically pure cyclic acetals (*Z*) were prepared using (2*R*,3*R*)-(-)-butanediol

The absolute stereochemistry of the minor isomer was determined by X-ray crystallography analysis (Figure 2-2; entry 4, Table 2-2) while the relative configuration of the major isomer is assumed to be the same as the racemic product as shown in Table 2-1. We managed to confirm the absolute configuration of the major isomer as (1*S*, 3*R*, 5*R*) after a series of synthetic manipulations (Scheme 2-13).[30]

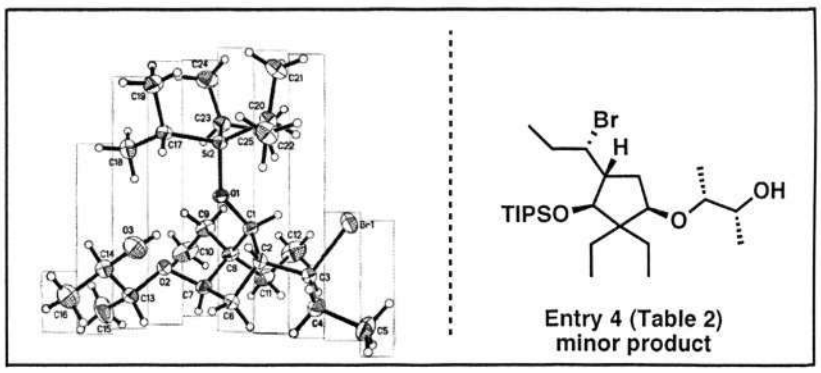
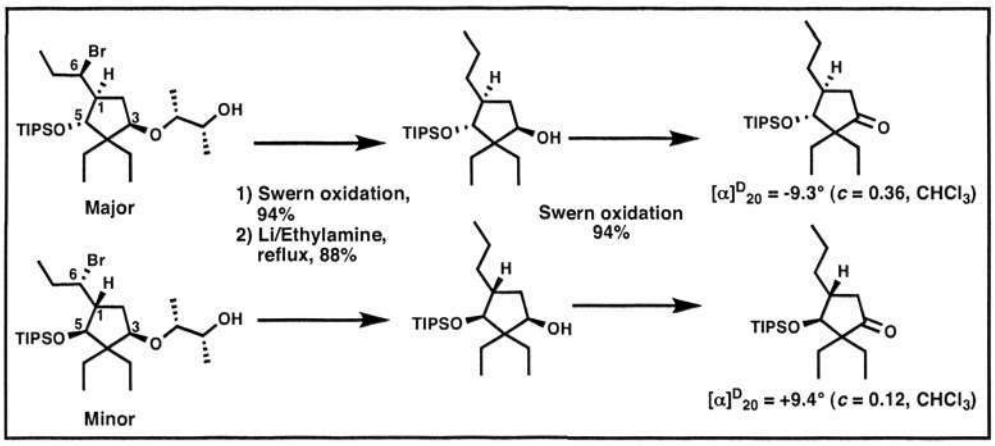


Figure 2-2 X-ray structure of minor product of entry 4, Table 2

[30] Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. E.; Stipanovic, R. D. *J. Am. Chem. Soc.*, **1976**, *98*, 6188.



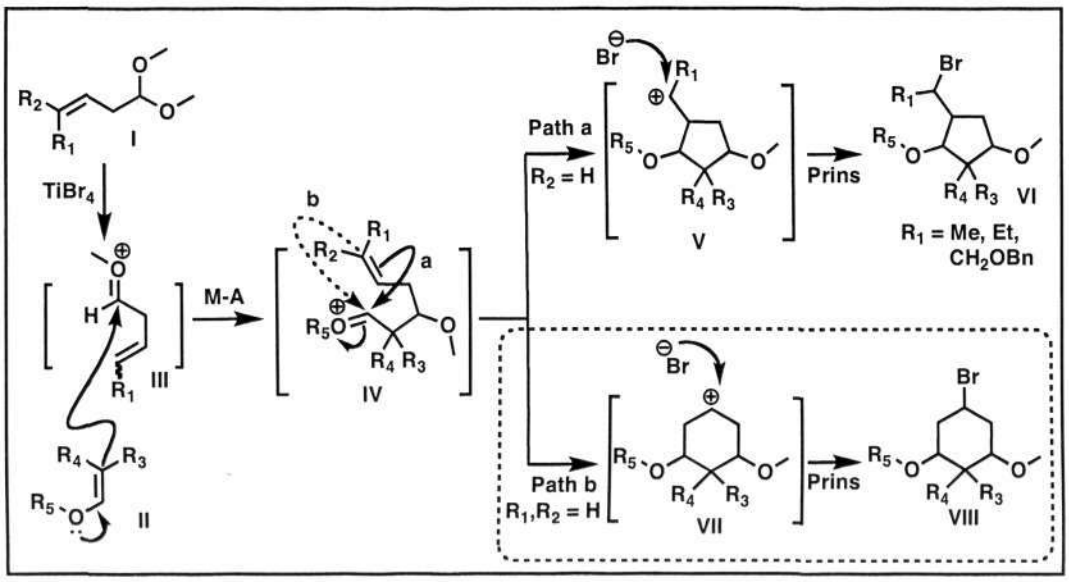
Scheme 2-13 Determination of absolute stereochemistry of major product

In conclusion, we have developed a highly stereoselective domino reaction, accomplished with easily accessible starting materials. The novelty of this domino reaction is the ability to construct five membered-ring systems with up to five new chiral centers in a one-pot manner in high yields with excellent diastereo-, and enantioselectivities. This new methodology provides a simple and practical method for the synthesis of polyfunctional cyclopentane building blocks.

2.2.2 Construction of Six-Membered Ring System

We have developed an efficient method for the synthesis of highly functionalized five-membered rings in high yields, excellent regio-, diastereo-, enatioselectivities using Mukaiyama-Aldol-Prins (MAP) reaction (Scheme 2-14, Path a). We envisage that by tuning the stability of the carbocation formed *via* the variation of the acetal olefinic substitutents **I**, six-membered rings **VIII** can be obtained instead of the five-membered rings **VI** (Scheme 2-14, Path b). Therefore, if a non-substituted acetal **I** (R_1, R_2 = H) is utilized, six-membered ring **VIII** could be formed through pathway b. This method can provide fast access to a wide variety of cyclohexane

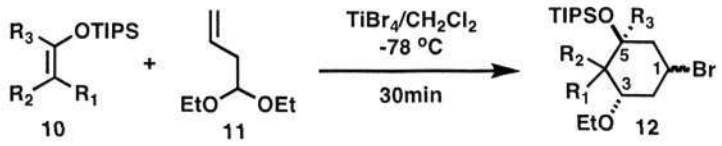
derivatives which are important building blocks for the synthesis of complex molecules.

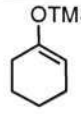
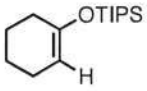
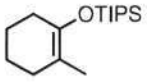
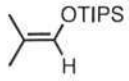
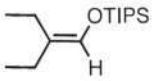
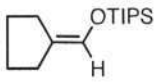
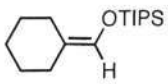
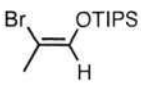


Scheme 2-14 Our proposed hypothesis

Initially, cyclohexyltrimethylsilane (Table 2-3, entry 1) was reacted with the commercially available 4,4-diethoxy-but-1-ene **11** in the presence in $TiBr_4$. Unfortunately, only the Mukaiyama-Aldol product was obtained (Table 2-3, entry 1). Similar to the results reported earlier, replacing the trimethyl silyl group with the more robust triisopropylsilyl (TIPS) group afforded the desired product, albeit in low yield (Table 2-3, entry 2). Fortunately, the yield of the product could be increased dramatically when β- disubstituted silyl enol ethers were used (Table 2-3, entries 3-8). The desired product was obtained as a single isomer at C_3/C_5 but moderate diastereoselectivity at C_3/C_1 (*ca.* 2:1 diastereomeric mixture).

Table 2-3 Mukaiyama-Aldol-Prins to form six-membered ring[a,b]



Entry	Silyl enol ether[c]	Yield[d]	*Dr*[e] C_3:C_5 (C_3:C_1)
1		70	-
2		20	-
3		81	>99:1 (66:34)
4		86	>99:1 (63:37)
5		84	>99:1 (70:30)
6		84	>99:1 (65:35)
7		92	>99:1 (79:21)
8	 *Z*/*E*=85:15	75	>99:1 (75:25)

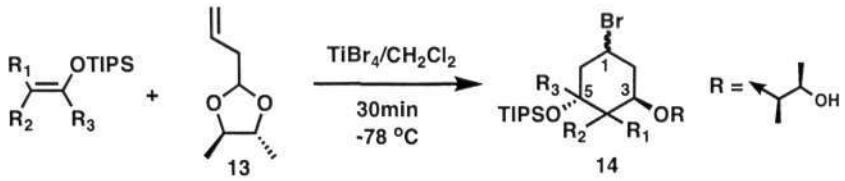
[a]Mukaiyama-Aldol-Prins reactions were run with 2 equiv of $TiBr_4$, 1 equiv of acetal and 1.2 equiv of silyl enol ether under N_2 atmosphere. [b]Non-substituted acetal was purchased from Sigma-Aldrich. [c]Silyl enol ethers were prepared following method reported by E. J. Corey. [d]Isolated yield. [e]Diastereomeric ratios were based on ^1H and ^{13}C NMR analyses.

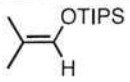
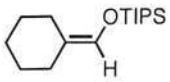
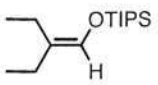
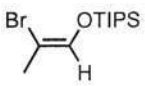
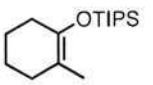
These results suggest that the substituted group on the β position of silyl enol ether plays an important role in the cascade process. Especially noteworthy is that β-substituted brominated silyl enol ether could react with acetal to afford the desired product in good yield (Table 2-3, entry 8). This further expands the scope and synthetic utility of our methodology as the bromide can be easily removed or

functionalized, providing wider range of cyclohexane building blocks. The isomer ratios were retained in the products.

Next we investigated the asymmetric version of this reaction using optically pure cyclic acetal **13**. The results are summarized in Table 2-4. In all cases, the desired products were obtained in good yields. Similar to the non-asymmetric version, the two diastereomers were obtained and easily separated by column chromatography. It is important to note that both the diastereomers were obtained as a single isomer (>99:1) as determined by ^{13}C NMR.

Table 2-4 MAP reactions in a asymmetric version[a]



Entry	Silyl enol ether[b]	Yield[c]	*Dr*[d] C_3:C_5 (C_3:C_1)
1		80%	>99:1 (65:35)
2		90%	>99:1 (62:38)
3		89%	>99:1 (57:43)
4	 *E/Z*=85:15	76%	>99:1 (60:40)
5		85%	>99:1 (75:25)

[a]Mukaiyama-Aldol-Prins reactions were run with 2 equiv of $TiBr_4$, 1 equiv of acetal and 1.2 equiv of silyl enol ether under N_2 atmosphere. [b]Silyl enol ethers were prepared following method reported by E. J. Corey. [c]Isolated yield. [d]Diastereomeric ratios were based on ^1H and ^{13}C NMR analyses .

The relative (Table 2-3, entry 3 analog) and absolute (Table 2-4, entry 5) stereochemistries of the major product were confirmed by the X-ray crytallography (Figure 2-3). The relative and absolute stereochemistries of minor products were determined *via* radical initiated debromination of both diastereomers in entry 3 (Table 2-4) led to an identical compound as shown in ^{1}H NMR and ^{13}C NMR (Scheme 2-15).

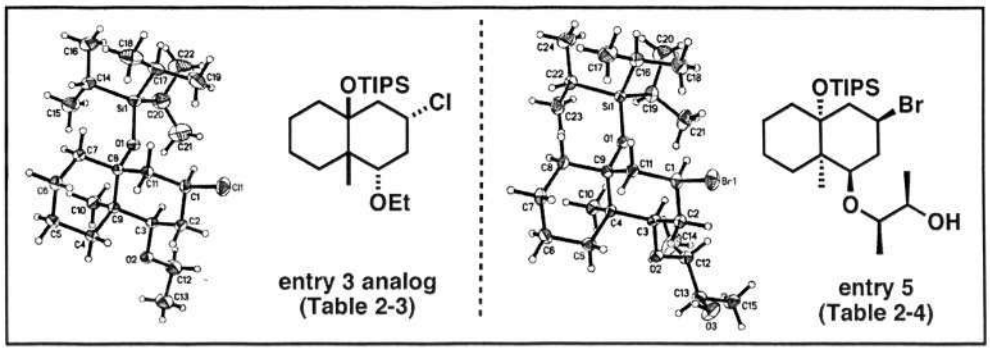
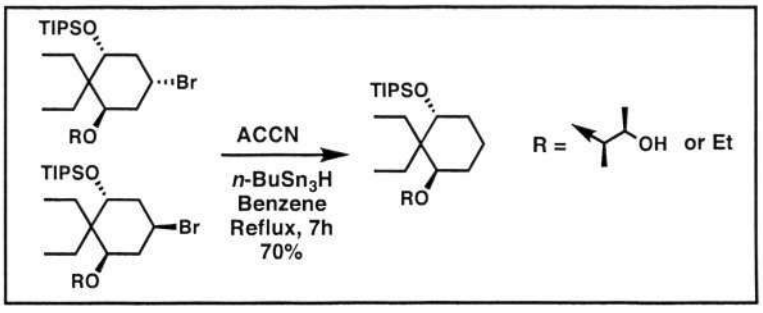


Figure 2-3 X-Ray crystallography of the major products (Table 2-4, entry 5 and Table 2-3, entry 3 analog[31])



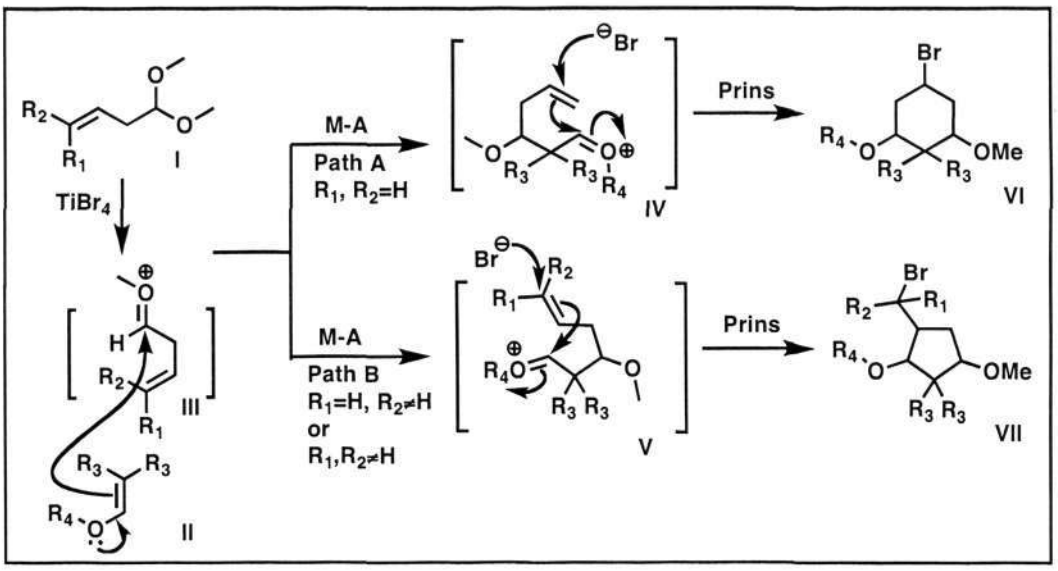
Scheme 2-15 Confirmation of relative and absolute stereochemistry of minor product

In summary, we have developed a highly efficient three component cascade reactions using cheap commercial and easily accessible starting materials to construct highly functionalized six membered-rings with 3 to 4 chiral centers in high yields. Single enantiomers were obtained when chiral acetals were employed.

[31] Entry 3 analog (Table 2-3) was obtained from $TiCl_4$ as Lewis acid.

2.2.3 Exploration of MAP Reaction with Enol Ether

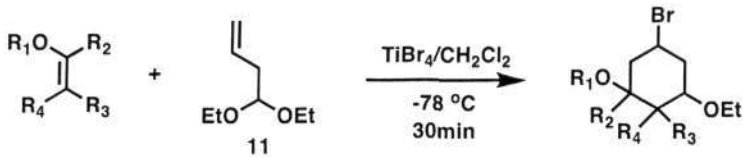
We have developed a new convergent annulation cascade reaction that is a formally four-carbon plus two-carbon reaction [4+2] (Scheme 2-16, Path A) or three-carbon plus two-carbon [3+2] (Scheme 2-16, Path B) ring-forming reaction through tuning the stability of oxocarbenium to form six, or five-membered ring. In both cases, the nucleophile, silyl enol ether **II** (R_4 = TIPS) reacts with a carbonyl compound, an intermediate **III**, generated from acetal **I** in the presence of strong Lewis acid, $TiBr_4$ to give aldol-type product, intermediate **IV** or **V**. This is followed by a Prins reaction to terminate the cascade process giving rise to **VI** or **VII** respectively. As silyl reagents are more expensive and cyclic ethers are not applicable in this method, we plan to replace the silyl enol ether with alkyl enol ether or other structure-akin substrates to perform the cascade Mukaiyama-Aldol-Prins (MAP) reaction for the syntheses of highly substituted cyclopentyl or cyclohexyl ring system.

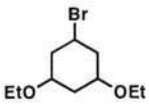
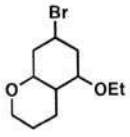
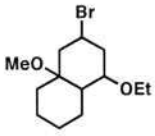
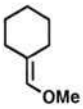
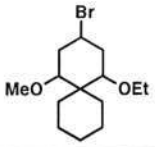


Scheme 2-16 MAP cascade reaction

In our initial studies, commercially available acetal **11** (we previously used in section 2.2.2, Table 2-3) was subjected to cyclization using various alkyl enol ethers, or equivalents in the presence of $TiBr_4$ (Table 2-5). Treatment of ethyl enol ether (Table 2-5, entry 1) with acetal **11** under the standard conditions, generated the cyclization product in low yields and diastereoselectivities. Four isomers were observed from ^1H NMR. When dihydropyran (Table 2-5, entry 2), an equivalent of alkyl enol ether was employed, the desired product was isolated in high yield (83%) but with low diastereoselectivity. Though the selectivity was low, it is still worthy to mention that the cyclized product (Table 2-5, entry 2) can be converted into a versatile multifunctionalized six-membered ring system through a pyran ring opening.

Table 2-5 Screening of various alkyl enol ethers[a,b]



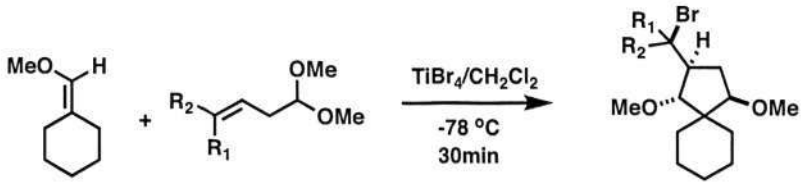
Entry		Product	Yield[c]	*Dr*[d]
1			15%	-
2			83%	56:22:11:11
3			80%	50:13:25:12
4			85%	67:33

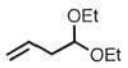
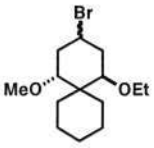
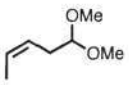
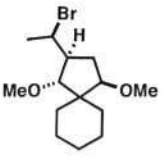
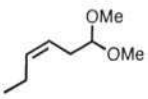
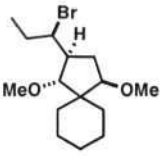
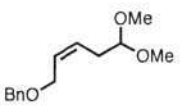
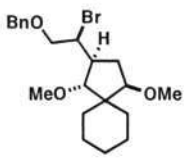
[a]Mukaiyama-Aldol-Prins reactions were run with 2 equiv of $TiBr_4$, 1 equiv of acetal and 1.2 equiv of silyl enol ether under N_2 atmosphere. [b]Non-substituted acetals were purchased from Sigma-Aldrich. [c]isolated yield. [d]Diastereomeric ratios were based on ^1H and ^{13}C NMR analyses.

Extended study of enol ether generated from cyclohexanone (Table 2-5, entry 3) also produced annulation product in high yield. However diastereoselectivity issues persisted. When enol ether generated from cyclohexanylcarboxaldehyde (Table 2-5, entry 4) was employed, cyclization product was obtained in good yield and with moderate diastereoselectivity. After removing the bromide of both pure diastereomers (*via* silica gel column chromatography) respectively, an identical product was obtained. This outcome indicates that racemization occurs in the Prins reaction. Based on our findings, we believe that the dialkyl substituent at the terminal double bond of enol ether induces conformational restriction and also aid in stabilizing the cation of the proposed intermediate **IV** (Scheme 2-16) through hyperconjugation, generating high yields.

With the optimized reaction substrate in hand, cyclization of various acetals with methoxy enol ether was carried out and the results were summarized in Table 2-6. In all cases, the desired products were obtained in high yields and diastereoselectivities.

Table 2-6 MAP reactions with mono- or di-substituted acetal[a]

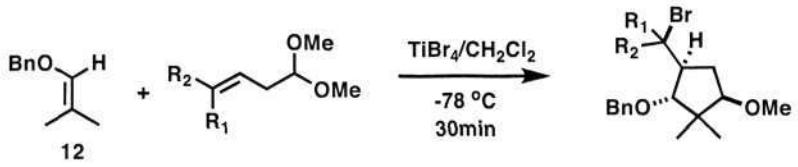


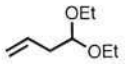
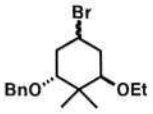
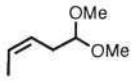
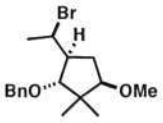
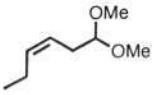
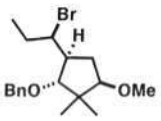
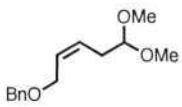
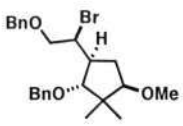
Entry	Acetal[b]	Product	Yield[c]	*Dr*[d]
1			85%	2:1
2			72%	>99:1
3			76%	>99:1
4			67%	>99:1

[a]Mukaiyama-Aldol-Prins reactions were run with 2 equiv of $TiBr_4$, 1 equiv of acetal and 1.2 equiv of silyl enol ether under N_2 atmosphere. [b]Mono-, di-substituted acetals were prepared by Wittig reactions. [c]Isolated yield. [d]Diastereomeric ratios were based on ^1H and ^{13}C NMR analyses.

To promote the ease in modification of the cyclized product, we carried out an in-dept study by changing the methoxy enol ether to benzyloxy enol ether. The results are delineated in Table 2-7. Yields and diatereoselectivities are similar to that of methoxy enol ether as shown in Table 2-5.

Table 2-7 MAP reactions with *Z*-mono- and di-substituted acetal[a]

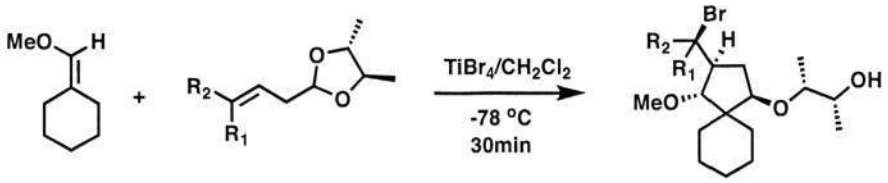


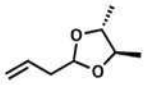
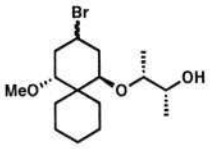
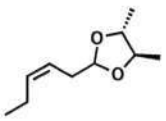
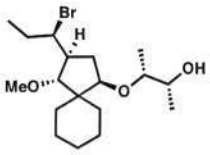
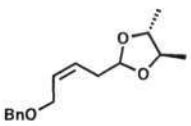
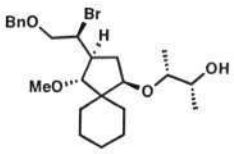
Entry	Acetal	Product	Yield[b]	*Dr*[c]
1			79%	64:36
2			80%	>99:1
3			80%	>99:1
4			75%	>99:1

[a]Mukaiyama-Aldol-Prins reactions were run with 2 equiv of $TiBr_4$, 1 equiv of acetal and 1.2 equiv of silyl enol ether under N_2 atmosphere. [c]Isolated yield. [d]Diastereomeric ratios were based on ^1H and ^{13}C NMR analyses.

Subsequently, we performed the asymmetric version of this methodology using chiral acetal in the cascade process. Various chiral acetals were subjected to the reaction with methoxy enol ether and benzyloxy enol ether under the standard conditions. The results are shown in Tables 2-8 and 2-9.

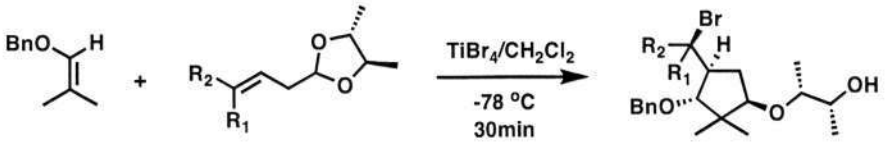
Table 2-8 MAP reactions with chiral mono- or di-substituted acetal[a]

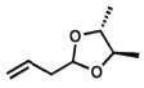
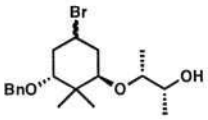
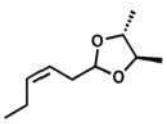
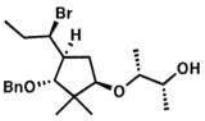
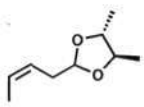
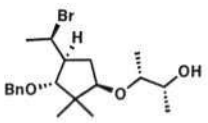


Entry	Acetal	Product	Yield[b]	*Dr*[c]
1			82%	80:20
2			80%	>92:8
3			70%	>92:8

[a]Mukaiyama-Aldol-Prins reactions were run with 2 equiv of $TiBr_4$, 1 equiv of acetal and 1.2 equiv of silyl enol ether under N_2 atmosphere. [b]Isolated yield. [c]Diastereomeric ratios were based on ^1H and ^{13}C NMR analyses.

Table 2-9 MAP reactions with chiral mono- or di-substituted acetal[a]

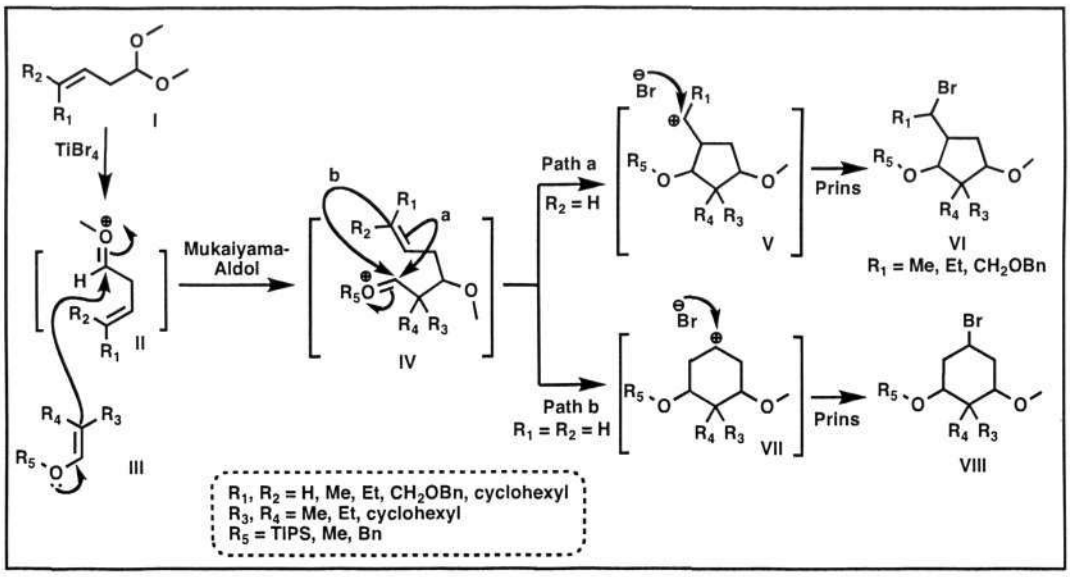


Entry	Acetal	Product	Yield[b]	*Dr*[c]
1			82%	80:20
2			80%	>92:8
3			70%	>92:8

[a]Mukaiyama-Aldol-Prins reactions were run with 2 equiv of $TiBr_4$, 1 equiv of acetal and 1.2 equiv of silyl enol ether under N_2 atmosphere. [b]Isolated yield. [c]Diastereomeric ratios were based on ^1H and ^{13}C NMR analyses.

2.3 CONCLUSION

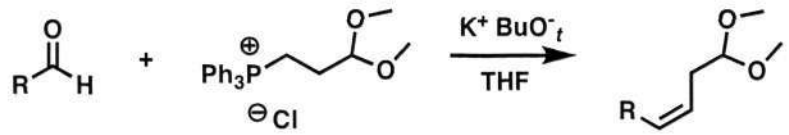
In conclusion, we have developed a highly stereoselective three component domino reaction, Mukaiyama-Aldol-Prins (MAP), accomplished with easily accessible starting materials. The novelty of this domino reaction resides in the ability to construct five or six membered-ring systems with up to 5 new chiral centers in a one-pot manner in high yields with excellent diastereo, and enatioselectivities (Scheme 2-17). This new methodology provides a simple and practical method for the synthesis of polyfunctional cyclopentyl and cyclohexyl building blocks.



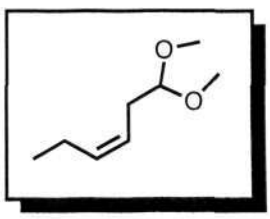
Scheme 2-17

2.6 EXPERIMENTAL

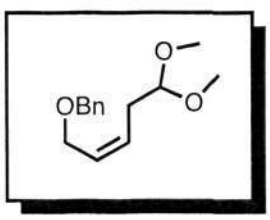
Representative experimental procedure for the synthesis of acylic acetals



Into a 25mL round bottom flask equipped with a magnetic stirrer, 5mmol of aldehyde (5mmol) was added and cooled using a salt/ice freezing mixture. 1.5 equivalents of the yellow-orange phosphonium ylide was added and the solution was stirred from -10°C to room temperature. The reaction was quenched using saturated sodium bicarbonate solution and extracted three times with ethyl acetate. The combined organic extracts were washed with saturated sodium chloride and dried over anhydrous magnesium sulphate. The solvent was removed *in vacuo*, and the yellowish liquid was purified using flash column chromatography with 20% ethyl acetate/hexanes to give (about 70% purified yield) of the colorless Wittig acetal product.



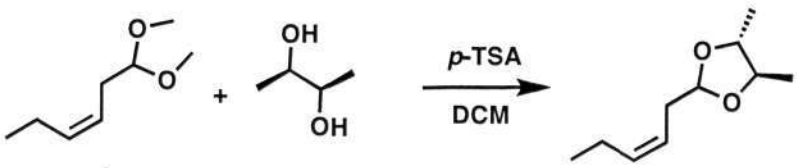
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.54-5.47 (1H, m), 5.37-5.30 (1H, m), 4.38 (1H, t, *J* = 5.6 Hz), 3.33 (6H, s), 2.40-2.36 (2H, m), 2.10-2.02 (2H, m), 0.97 (3H, t, *J* = 7.2 Hz); **^{13}C NMR ($CDCl_3$, 75.4 MHz):** δ 134.1, 122.7, 104.2, 52.9×2, 30.8, 20.7, 14.1;



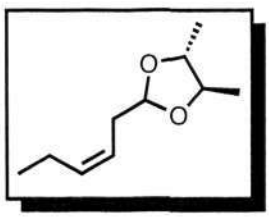
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.27 (5H, m), 5.77-5.57 (2H, m), 4.52 (2H, s), 4.37 (1H, t, J = 5.6Hz), 4.08 (2H, bd, J = 6.8Hz), 3.32 (6H, s), 2.40-2.37 (2H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 138.2, 129.6, 128.7 (×2), 128.4 (×2), 127.6, 127.3, 103.9, 72.2, 65.8, 53.1 (×2), 31.4;

Representative experimental procedure for the synthesis of cylic acetals (optically pure)



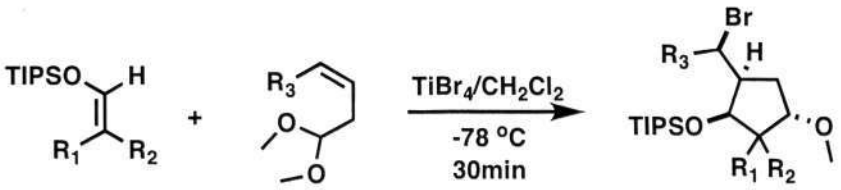
To a solution of cyclic acetal (5 mmol) and (2*R*,3*R*)-butanediol (6 mmol) in dichloromethane (20 mL) was added in 0.05 equivalents of *p*-TSA. The whole was stirred at room temperature for 6h. The reaction was quenched using saturated sodium bicarbonate solution and extracted with ethyl acetate (x3). The combined organic extracts were washed with saturated sodium chloride and dried over anhydrous magnesium sulphate. The solvent was removed *in vacuo*, and the yellowish liquid was purified using flash column chromatography with 20% ethyl acetate/hexanes to give (~95% purified yield) of the colorless cyclic acetal



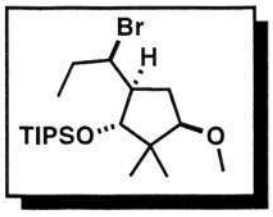
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.58-5.52 (1H, m), 5.44-5.37 (1H, m), 5.06 (1H, t, J = 4.8 Hz), 3.66-3.58 (2H, m), 2.42-2.39 (2H, m), 2.10-2.03 (2H, m), 1.29 (3H, d, J = 5.6 Hz), 1.23 (3H, d, J = 5.6 Hz), 0.97 (3H, t, J = 7.5 Hz);

^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 134.8, 122.0, 102.8, 79.8, 78.2, 32.9, 20.8, 17.2, 16.9, 14.1;

General procedure for the Mukaiyama-Aldol-Prins domino reaction



To a solution of $TiBr_4$ in dichloromethane was added in the mixture of silyl enol ether and acetal (pre-dissolved in dichloromethane) at -78 °C. After 30 minute, the reaction mixture was quenched by saturated sodium bicarbonate and extracted with dichloromethane (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo* to give the crude product. Purification with silica gel column chromatography using hexane as eluent afforded the desired product.



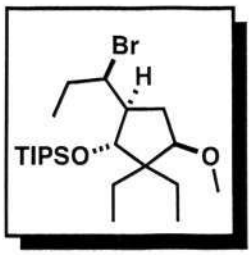
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.20 (1H, ddd, J = 10.8, 4.8, 1.6 Hz), 3.90 (1H, d, J = 6.8 Hz), 3.27 (3H,s), 3.23 (1H, dd, J = 5.2, 3.2 Hz), 2.66-2.59 (1H, m), 2.20-2.12 (1H, m), 1.91-1.82 (1H, m), 1.75-1.57 (2H, m), 1.06 (24H, brs) 0.98 (3H, s), 0.95 (3H, s);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 87.5, 82.0, 62.3, 57.0, 53.5, 47.4, 28.0, 27.1, 21.0, 20.8, 18.4 (×3), 18.3 (×3), 13.2 (×3), 12.8;

R_f = 0.64 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1130, 1066, 677;

HRMS (EI, m/z (M - C_3H_7)] calcd (found) for $C_{20}H_{41}BrO_2Si$: 377.1511 (377.1445)



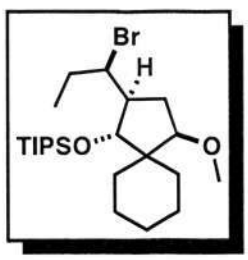
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.20 (1H, ddd, *J* = 10.5, 5.0, 1.5 Hz), 4.03 (1H, d, *J* = 6.0 Hz), 3.41 (1H, dd, *J* = 6.5, 5.0 Hz), 3.24 (3H, s), 2.63-2.58 (1H, m), 2.15-2.09 (1H, m), 1.90-1.83 (1H, m), 1.69-1.54 (4H, m), 1.43-1.34 (2H, m), 1.08 (24H, brs), 0.92 (3H, t, *J* = 7.6 Hz), 0.86 (3H, t, *J* = 7.5 Hz);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 85.7, 82.5, 62.7, 56.6, 53.7, 52.3, 28.3, 27.3, 24.5, 23.9, 18.4×3, 18.3×3, 13.4×3, 12.7, 9.3, 9.1;

R_f = 0.67 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1130, 1066, 677;

HRMS (EI, m/z (M- C_3H_7)] calcd (found) for $C_{22}H_{45}BrO_2Si$: 405.1824 (405.1701).



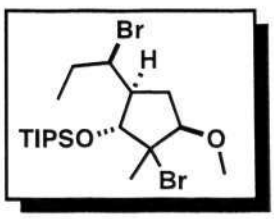
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.23 (1H, ddd, *J* = 11.0, 4.0, 2.0 Hz), 3.85 (1H, d, *J* = 7.5 Hz), 3.54 (1H, d, *J* = 5.0 Hz), 3.25 (3H, s), 2.70-2.64 (1H, m), 2.10-2.03 (1H, m), 1.90-1.81 (1H, m), 1.78-1.75 (1H, m), 1.73-1.55 (6H, m), 1.39-1.14 (5H, m), 1.10-1.07 (24H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 81.9, 81.4, 62.5, 56.6, 52.9, 51.2, 29.2, 26.8, 26.7, 26.4, 26.3, 23.4, 22.6, 18.4 (×3), 18.3 (×3), 13.3 (×3), 12.9;

R_f = 0.63 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1118, 1056, 687;

HRMS (EI, m/z (M- C_3H_7)] calcd (found) for $C_{23}H_{45}BrO_2Si$: 417.1824 (417.1911).



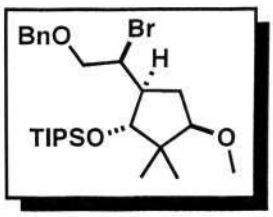
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.61 (1H, d, *J* = 0.8Hz), 4.35 (1H, td, *J* = 9.2, 2.4Hz), 3.36 (3H, s), 3.43-3.30 (1H, m), 2.41-2.31 (2H, m), 1.98-1.92 (1H, m), 1.86 (3H,s), 1.78-1.66 (2H, m), 1.60-1.54 (1H, m), 1.25-1.19 (2H,m), 1.11-1.09 (21H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 85.9, 84.1, 76.1, 63.1, 58.3, 52.4, 31.8, 29.2, 25.1, 18.4 (×3), 18.3 (×3), 13.0 (×3), 11.7;

R_f = 0.63 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1444, 1282, 1115;

HRMS (EI, m/z (M-C_3H_7)] calcd (found) for $C_{19}H_{38}Br_2O_2Si$: 441.0460 (441.0392).



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (1H, s), 7.34 (1H, s), 7.33-7.27 (3H, m), 4.57 (2H, s), 4.41 (1H, ddd, *J* = 11.2, 4.8, 1.7Hz), 3.98 (1H, d, *J* = 6.0Hz), 3.82 (1H, dd, *J* = 11.2, 3.2Hz), 3.66 (1H, dd, *J* = 10.4, 8.0Hz), 3.22 (3H, s), 3.23-3.21 (1H, m), 2.60-

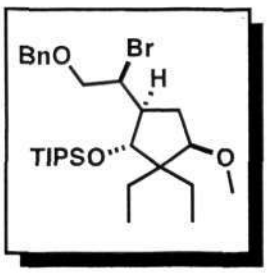
2.53 (1H, m), 2.20-2.12 (1H, m), 1.54-1.48 (1H, m), 1.07 (21H, s), 0.95 (3H, s), 0.93 (3H, s);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 137.8, 128.4 (×2), 127.8 (×2), 127.7, 87.6, 82.1, 73.3, 72.4, 57.0, 55.7, 51.4, 47.2, 28.5, 21.1, 20.7, 18.4 (×3), 18.3 (×3), 13.2 (×3).

R_f = 0.45 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1463, 1093, 883;

HRMS (ESI, m/z [M+Na]$^+$) calcd (found) for $C_{26}H_{45}BrNaO_3Si$: 535.2219 (535.2289).



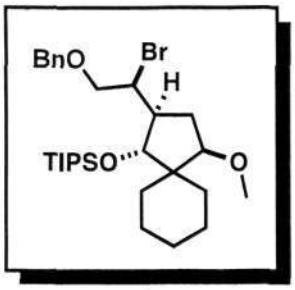
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.27 (5H,m), 4.60 (2H,s), 4.41 (1H, ddd, *J* = 8.8, 5.6, 3.2 Hz), 4.11 (1H, d, *J* = 5.6 Hz), 3.81 (1H, dd, *J* = 11.2, 3.2Hz), 3.63 (1H, dd, *J* = 11.2, 7.9 Hz), 3.40 (1H, t, *J* = 4.72 Hz), 3.20 (3H, s), 2.61-2.54 (1H, m), 2.17-2.09 (1H, m), 1.63-1.47 (3H, m), 1.42-1.30 (2H, m), 1.07 (21H, s), 0.91 (3H, t, *J* = 7.6Hz), 0.84 (3H, t, *J* = 7.6 Hz);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 137.8, 128.2 (×2), 127.8 (×2), 127.7, 86.0, 82.5, 73.2, 72.5, 56.7, 56.1, 52.2, 51.6, 28.8, 24.5, 23.5, 18.4 (×3), 18.3 (×3), 13.3 (×3), 9.2, 9.0;

R_f = 0.46 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1443, 1097, 863;

HRMS (ESI, m/z (M+Na)]$^+$calcd (found) for $C_{28}H_{49}BrNaO_3Si$: 563.2532 (563.2571).



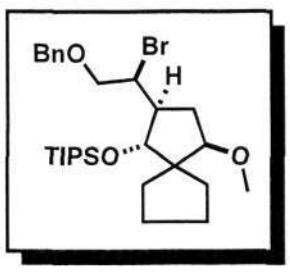
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.27 (5H, m), 4.57 (2H, s), 4.49-4.45 (1H, m), 3.94 (1H, d, J = 7.6 Hz), 3.83 (1H, dd, J = 11.3, 3.0 Hz), 3.64 (1H, dd, J = 11.3, 8.4 Hz), 3.52 (1H, d, J = 4.4 Hz), 3.20 (3H, s), 2.66-2.59 (1H, m), 2.12-2.05 (1H, m), 1.78-1.68 (2H, m), 1.65-1.50 (5H, m), 1.35-1.10 (4H, m), 1.07 (21H, s);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 137.9, 128.3 (×2), 127.9 (×2), 127.7, 82.1,81.5, 73.3, 72.2, 56.6, 55.7, 51.2, 51.0, 29.1, 27.4, 26.9, 26.3, 23.4, 22.6, 18.4 (×3), 18.3 (×3), 13.2 (×3);

R_f = 0.45 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1454, 1124, 1091;

HRMS (ESI, m/z (M+Na)]$^+$ calcd (found) for $C_{29}H_{49}BrNaO_3Si$: 575.2532 (575.2592).



^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.28 (5H, m), 4.60 (1H, d, J = 12Hz), 4.56 (1H, d, J = 12 Hz), 4.33 (1H, td, J = 7.6, 3.2 Hz), 4.11 (1H, d, J = 5.2 Hz), 3.81 (1H, dd, J = 10.4, 2.4 Hz), 3.65 (1H, dd, J = 10.4, 7.6 Hz), 3.34 (1H, t, J = 5.2 Hz), 3.23 (3H, s),

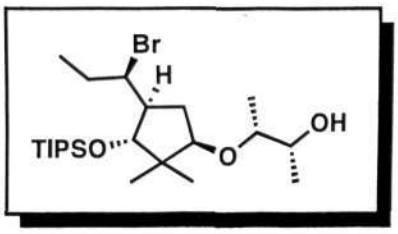
2.50-2.45 (1H, m), 2.19-2.11 (1H, m), 2.00-1.96 (1H, m), 1.88-1.82 (1H, m), 1.59-1.49 (4H, m), 1.46-1.39 (1H, m), 1.27-1.17 (2H, m), 1.08-1.06 (21H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 137.9, 128.4 (×2), 127.8 (×2), 127.7, 85.8, 80.9, 73.3, 72.5, 58.9, 57.1, 56.3, 50.9, 30.1, 29.7, 29.6, 26.0, 25.5, 18.4 (×6), 13.2 (×3);

FTIR (neat, cm^{-1}): ν 1444, 1104, 1051;

R_f = 0.43 (Hex:EA = 5:1);

HRMS (ESI, m/z (M+Na)]$^+$ calcd (found) for $C_{28}H_{47}BrNaO_3Si$: 561.2376 (561.2398).



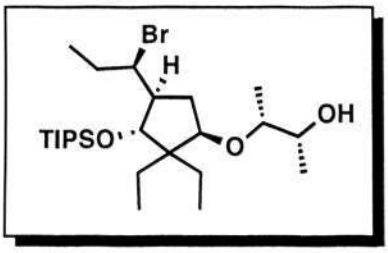
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.13 (1H, ddd, *J* = 9.8, 5.6, 2.3Hz), 3.91 (1H, d, *J* = 5.7 Hz), 3.58 (1H, t, *J* = 6.0 Hz), 3.52 (1H, qd, *J* = 7.6, 3.2Hz), 3.18 (1H, q, *J* = 6.0 Hz), 2.61 (1H, d, *J* = 2.4 Hz), 2.52-2.48 (1H, m), 2.30-2.22 (1H, m), 1.86-1.70 (2H, m), 1.44-1.35 (1H, m), 1.14 (3H, d, *J* = 6.4 Hz), 1.10-1.06 (27H, m), 0.97 (3H, s), 0.91 (3H, s);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 82.3, 81.8, 78.0, 71.1, 62.0, 53.2, 46.6, 30.3, 28.0, 21.2, 20.8, 18.5 (×3), 18.4 (×3), 15.3, 13.2 (×3), 12.5, 12.3;

R_f = 0.49 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 2866, 1380, 997;

HRMS (ESI, m/z (M+Na)]$^+$ calcd (found) for $C_{23}H_{47}BrNaO_3Si$: 501.2376 (501.2183).



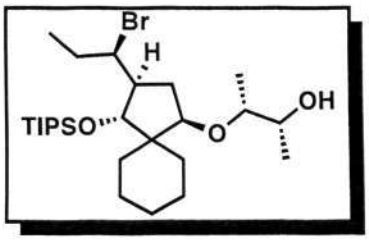
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.13-4.12 (2H, m), 3.91 (1H, t, *J* = 6.9 Hz), 3.58-3.52 (1H, m), 3.24 (1H, q, *J* = 6.0 Hz), 2.62 (1H, d, *J* = 2.8 Hz), 2.50-2.45 (1H, m), 2.31-2.30 (1H, m), 1.88-1.50 (6H, m), 1.40-1.24 (2H, m), 1.17-1.09 (29H, m), 0.96-0.89 (6H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 81.3, 80.8, 76.6, 71.3, 62.2, 53.2, 51.3, 30.7, 28.4, 25.0, 21.6, 18.4 (×3), 18.4 (×3), 14.8, 13.0 (×3), 12.3, 12.2, 8.9, 8.6;

R_f = 0.38 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 2891, 1262, 997;

HRMS (ESI, m/z (M+Na)]$^+$ calcd (found) for $C_{25}H_{51}BrNaO_3Si$: 529.2689 (529.2616).



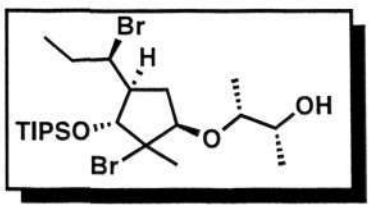
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.21-4.17 (1H, m), 3.95 (1H, d, *J* = 11.6 Hz), 3.84 (1H, dd, *J* = 2.8, 5.2 Hz), 3.55 (1H, qd, *J* = 6.4, 2.8 Hz), 3.24 (1H, q, *J* = 6.0 Hz), 2.64-2.57 (1H, m), 2.49 (1H, d, *J* = 2.8 Hz), 2.22-2.14 (1H, m), 1.80-1.68 (4H, m), 1.62-1.50 (4H, m), 1.39-1.20 (6H, m), 1.14 (3H, d, *J* = 6.4 Hz), 1.09-1.08 (26H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 80.7, 76.4, 71.1, 61.8, 52.2, 50.3, 28.8, 28.6, 27.1, 27.0, 26.1, 23.0, 22.8, 18.6, 18.4 (×3), 18.3 (×3), 17.8, 14.7, 13.4 (×3), 12.7;

R_f = 0.39 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 2941, 1381, 908;

HRMS (ESI, m/z (M+Na)]$^+$ calcd (found) for $C_{26}H_{51}BrNaO_3Si$: 543.2688 (543.2721).



^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.65 (1H, d, *J* = 0.8 Hz), 4.34 (1H, td, *J* = 9.6, 1.2 Hz), 3.63 (1H, dd, *J* = 8.8, 4.8 Hz), 3.60-3.56 (1H, m), 3.29-3.22 (1H, m), 2.94 (1H, d, *J* = 1.6 Hz), 2.40-2.27 (2H, m), 2.00-1.89 (1H, m), 1.84 (3H, s), 1.74-1.64 (1H, m), 1.55-1.47 (1H, m), 1.26-1.12 (9H, m), 1.10-1.19 (21H, m);

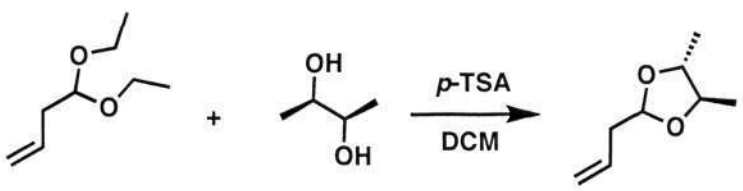
^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 84.1, 80.4, 78.8, 77.6, 71.1, 63.3, 52.8, 33.0, 29.5, 24.8, 18.4 (×3), 18.3 (×3), 18.2, 15.6, 13.0 (×3), 11.6;

R_f = 0.38 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 2966, 1122, 1087;

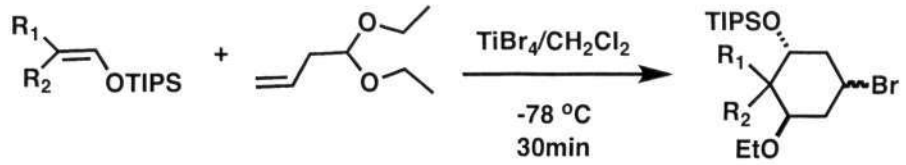
HRMS (ESI, m/z (M+Na)]$^+$ calcd (found) for $C_{22}H_{44}Br_2NaO_3Si$: 565.1324 (565.1313).

Representative experimental procedure for the synthesis of cylic acetals (optically pure)

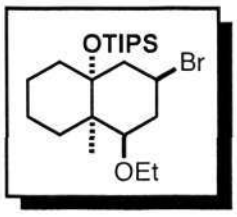


To a solution of cyclic acetal (5mmol) and (2*R*,3*R*)-butanediol (6mmol) in dichloromethane (20 mL) was added in 0.05 equivalents of *p*-TSA. The whole was stirred at room temperature for 6h. The reaction was quenched using saturated sodium bicarbonate solution and extracted with ethyl acetate (x3). The combined organic extracts were washed with saturated sodium chloride and dried over anhydrous magnesium sulphate. The solvent was removed *in vacuo*, and the yellowish liquid was purified using flash column chromatography with 20% ethyl acetate/hexanes to give (~95% purified yield) of the colorless cyclic acetal.

General procedure for the Mukaiyama-Aldol-Prins cascade reaction



To a solution of $TiBr_4$ in dichloromethane was added in the mixture of silyl enol ether and acetal (pre-dissolved in dichloromethane) at -78 °C. After 30 minute, the reaction mixture was quenched by saturated sodium bicarbonate and extracted with dichloromethane (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo* to give the crude product. Purification with silica gel column chromatography using hexane as eluent afforded the desired product.



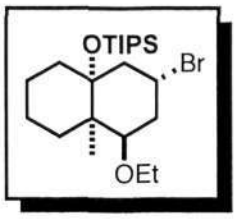
^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.87 (1H, tt, *J* = 3.5, 13.5 Hz), 3.66-3.60 (1H, m), 3.47 (1H, dd, *J* = 4.5, 12 Hz), 3.40-3.34 (1H, m), 2.39-2.35 (1H, m), 2.16 (1H, t, *J* = 12.5 Hz), 1.96-1.92 (1H, m), 1.80 (1H, q, *J* = 12.5 Hz), 1.76-1.65 (2H, m), 1.59-1.36 (6H, m), 1.16 (3H, *J* = 7.0 Hz), 1.10-1.09 (21H, m), 0.95 (3H, s);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 76.3, 75.2, 65.6, 53.5,46.7, 43.7, 37.3, 34.2, 29.7, 21.4, 21.1, 18.7 (×3), 18.6 (×3), 16.8, 15.7, 13.9 (×3);

R_f = 0.68 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1707, 1094, 1050;

HRMS (ESI, m/z (M + Na)] calcd (found) for $C_{22}H_{43}BrNaO_2Si$: 469.2113 (469.2110).



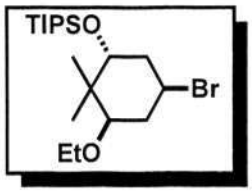
^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.21 (1H, tt, *J* = 4.5, 12.0 Hz), 3.66-3.60 (1H, m), 3.45 (1H, dd, *J* = 4.5, 12 Hz), 3.38-3.32 (1H, m), 2.38-2.30 (2H, m), 1.87-1.77 (3H, m), 1.64-1.61 (1H, m), 1.52-1.36 (6H, m), 1.15 (3H, t, *J* = 8Hz), 1.13 (3H, s), 1.10-1.07 (21H, m);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 81.0, 79.1, 65.9, 54.8, 43.5, 43.3, 36.9, 36.1, 27.5, 23.6, 20.4, 18.6 (×3), 18.5 (×3), 18.0, 15.5, 13.8 (×3);

FTIR (neat, cm^{-1}): ν 1440, 1100, 1063;

R_f = 0.70 (Hex:EA = 5:1);

HRMS (ESI, m/z (M + Na)] calcd (found) for $C_{22}H_{43}BrNaO_2Si$: 469.2113 (469.2110).



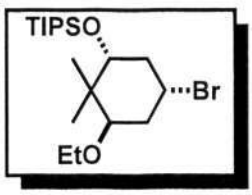
^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.80 (1H, tt, *J* = 3.6, 10.0 Hz), 3.65-3.59 (1H, m), 3.38-3.33 (2H, m), 2.73 (1H, dd, *J* = 3.2, 9.2 Hz), 2.41-2.36 (1H, m), 2.28-2.24 (1H, m), 2.04-1.81 (2H, m), 1.17 (3H, t, *J* = 6.9 Hz), 1.07 (3H, s), 1.06 (21H, s), 0.86 (3H, s);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 82.1, 75.9, 65.8, 43.2, 42.4, 41.7, 38.1, 25.0, 22.7 ,18.3 (×3), 18.2 (×3), 15.5, 12.9 (×3);

FTIR (neat, cm^{-1}): ν 1464, 1164, 848;

R_f = 0.75 (Hex:EA = 5:1);

HRMS (EI, m/z (M+H)] calcd (found) for $C_{19}H_{40}BrO_2Si$: 407.1981 (407.1990).



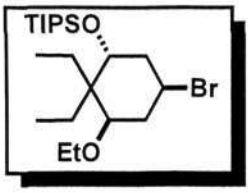
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.20 (1H, tt, *J* = 4.4 12.6 Hz), 3.86 (1H, dd, *J* = 4.36, 11.3 Hz), 3.55 (1H, dq, *J* = 9.24, 7.04 Hz), 3.28 (1H, dq, *J* = 9.2, 7.0 Hz), 3.05 (1H, t, *J* = 2.8 Hz), 2.34-2.27 (2H, m), 2.04-1.95 (2H, m), 1.14 (3H, t, *J* = 7.0 Hz), 1.08 (21H, s), 1.06 (3H, s), 0.89 (3H, s);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 83.9, 72.8, 65.3, 54.1, 41.8, 40.2, 35.4, 24.0, 18.7, 18.3 (×3), 18.2 (×3), 15.4, 12.9 (×3);

FTIR (neat, cm^{-1}): ν 1464, 1102, 678;

R_f = 0.73 (Hex:EA = 5:1);

HRMS (ESI, m/z (M+H)] calcd (found) for $C_{19}H_{40}BrO_2Si$: 407.1981 (407.1990).



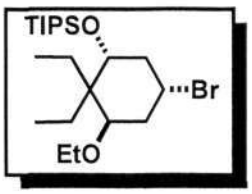
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.19 (1H, tt, *J* = 4.7, 17.2 Hz), 3.95 (1H, dd, *J* = 4.2, 11.5 Hz), 3.56 (1H, dq, *J* = 7.0, 8.76 Hz), 3.26-3.18 (2H, m), 2.34 (1H, t, *J* = 3.9 Hz), 2.31 (1H, t, *J* = 3.96 Hz), 2.18 (1H, q, *J* = 12.1 Hz), 1.91-1.68 (3H, m), 1.58-1.49 (1H, m), 1.30-1.17 (1H, m), 1.14 (3H, t, *J* = 6.96 Hz), 1.07 (21H, s), 0.94 (3H, t, *J* = 7.56 Hz), 0.82 (3H, t, *J* = 7.52 Hz);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 80.3, 75.3, 64.5, 45.6, 44.1, 42.6 35.1, 24.6, 22.6, 18.34 (×2), 18.30 (×4), 15.6, 13.0 (×3), 9.5, 8.0;

FTIR (neat, cm^{-1}): ν 1464, 1186, 882;

R_f = 0.75 (Hex:EA = 5:1);

HRMS (ESI, m/z (M + H) calcd (found) for $C_{21}H_{44}BrO_2Si$: 435.2294 (435.2268).



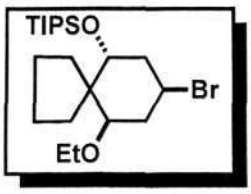
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.31 (1H, tt, *J* = 4.7, 17.0 Hz), 3.87 (1H, t, *J* = 2.8 Hz), 3.60 (1H, dq, *J* = 9.04, 7.0 Hz), 3.40 (1H, dd, *J* = 4.3,11.4 Hz), 3.29 (1H, dq, *J* = 9.04, 7.0 Hz), 2.47-2.43 (1H, m), 2.21-1.95 (3H, m), 1.82-1.66 (2H, m), 1.55-1.43 (1H, m), 1.32-1.25 (1H, m), 1.14 (3H, t, *J* = 6.8 Hz), 1.09 (21H, s), 0.90 (3H, t, *J* = 7.56 Hz), 0.84 (3H, t, *J* = 7.52 Hz);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 81.7, 75.0, 65.4, 45.8, 43.9, 40.5, 38.1, 25.8, 20.8, 18.7, 18.3 (×3), 18.30 (×3), 15.5, 12.9 (×3), 8.9, 8.1;

FTIR (neat, cm^{-1}): ν 1444, 1282, 1098;

R_f = 0.73 (Hex:EA = 5:1);

HRMS (ESI, m/z (M + H) calcd (found) for $C_{21}H_{44}BrO_2Si$: 435.2294 (435.2268).



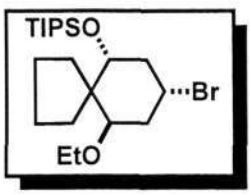
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.21 (1H, tt, *J* = 4.0, 12.0 Hz), 3.75 (1H, t, *J* = 2.0 Hz), 3.68-3.62 (1H, m), 3.41 (1H, dd, *J* = 4.0, 11 Hz), 3.37-3.31 (1H, m), 2.46-2.41 (1H, m), 2.18-2.14 (1H, m), 1.89-1.74 (3H, m), 1.66-1.45 (7H, m), 1.15 (3H, t, *J* = 7 Hz),1.07-1.06 (21H, brs);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 78.8, 76.2, 65.3, 53.9, 52.0, 40.9, 39.3, 33.9, 30.4, 27.2, 26.3, 18.3 (×3), 18.2 (×3), 15.6, 12.9 (×3);

FTIR (neat, cm^{-1}): ν 1463, 1097, 883;

R_f = 0.71(Hex:EA = 5:1);

HRMS (EI, m/z (M^+–C_3H_7) calcd (found) for $C_{18}H_{34}BrO_2Si$: 389.1511 (389.1503).



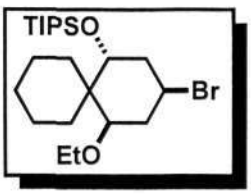
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.08 (1H, tt, *J* = 4.5, 12.0 Hz), 3.97 (1H, dd, *J* = 4.0, 11.5 Hz), 3.60-3.54 (1H, m), 3.30-3.24 (1H, m), 3.13 (1H, t, *J* = 2.0 Hz), 2.31-2.27 (2H, m), 1.92-1.86 (1H, m), 1.75-1.26 (10H, m), 1.15 (3H, t, *J* = 7.0 Hz), 1.07(21H, brs);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 81.4, 71.7, 65.0, 53.8, 52.3, 43.5, 35.6, 32.4, 29.2, 26.7, 25.8, 18.3 (×3), 18.2 (×3), 15.5, 13.0 (×3);

FTIR (neat, cm^{-1}): ν 1464, 1158, 854;

R_f = 0.70 (Hex:EA = 5:1);

HRMS (EI, m/z (M^+-C_3H_7) calcd (found) for $C_{18}H_{34}BrO_2Si$: 389.1511 (389.1503).



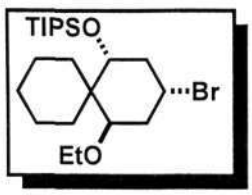
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.22 (1H, tt, *J* = 4.6, 17.2 Hz), 3.79 (1H, dd, *J* = 11.0, 4.5 Hz), 3.71 (1H, t, *J* = 2.75 Hz), 3.59 (1H, dq, *J* = 7.0, 9.1 Hz) , 3.28 (1H, dq, *J* = 7.0, 9.0 Hz), 2.36-2.33 (1H, m), 2.26 (1H, dtd, *J* = 12, 4.5, 2.0 Hz), 2.06 (1H, q, *J* = 12 Hz), 1.95 (1H, ddd, *J* = 14.0, 12.5, 2.5 Hz) 1.78-1.75 (1H, m), 1.68-1.62 (2H, m), 1.56-1.51 (5H, m), 1.37-1.22 (2H, m), 1.18-1.11 (1H, m)1.15 (3H, t, *J* = 7 Hz), 1.07 (21H, s);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 76.4, 73.2, 65.1, 45.7, 42.4, 41.6, 35.1, 29.0, 26.5, 24.9, 21.6, 21.3, 18.3 (×3), 18.3 (×3), 15.6, 12.9 (×3);

FTIR (neat, cm^{-1}): ν 1463, 1092, 1068;

R_f = 0.74 (Hex:EA = 5:1);

HRMS (EI, m/z (M + Na) calcd (found) for $C_{22}H_{43}BrNaO_2Si$: 469.2113(469.2118).



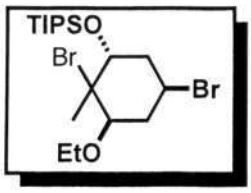
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.32 (1H, tt, *J* = 12.0, 4.5 Hz), 4.29 (1H, *J* = 2.0 Hz), 3.62 (1H, dq, *J* = 9.5, 7.0 Hz), 3.34 (1H, dq, *J* = 9.5, 7.0 Hz), 3.24 (1H, dd, *J* = 11.4, 4.2 Hz), 2.39 (1H, dtd, *J* = 12.5, 4.5, 2.0 Hz), 2.26-2.21 (1H, m), 2.15 (1H, ddd, *J* = 14.0, 12.0, 2.0 Hz), 1.97 (1H, *J* = 12.5 Hz), 1.71-1.68(1H, m), 1.62-1.50 (8H, m), 1.44-1.37 (1H, m), 1.29-1.22 (3H, m), 1.16 (3H, t, *J* = 7.0 Hz), 1.09 (21H, s);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 79.5, 77.2, 71.4, 65.8, 45.8, 42.1, 40.1, 29.0, 26.5, 26.3, 21.8, 21.5, 18.3 (×6), 15.5, 13.0 (×3);

R_f = 0.72 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1463, 1094, 882;

HRMS (EI, m/z (M + Na) calcd (found) for $C_{22}H_{43}BrNaO_2Si$: 469.2113(469.2118).



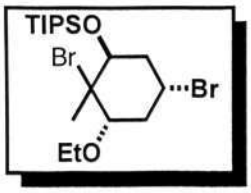
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.27 (1H, tt, *J* = 4.0, 12.8 Hz), 4.23 (1H, t, *J* = 4.0 Hz), 3.78-3.70 (1H, m), 3.52-3.44 (1H, m), 3.16 (1H, dd, *J* = 4.0, 11.2Hz), 2.79 (1H, td, *J* = 12.8, 2.0 Hz), 2.54-2.49 (1H, m), 2.30-2.18 (2H, m), 1.89 (3H, s), 1.22 (3H, t, *J* = 6.8 Hz), 1.09-1.08 (21H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 78.4, 77.9, 71.8, 65.7, 43.2, 40.6, 40.0, 27.3, 18.2 (×3), 18.1 (×3), 15.4, 12.7 (×3);

R_f = 0.72(Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1464, 1105, 678;

HRMS (ESI, m/z (M+H)] calcd (found) for $C_{18}H_{37}Br_2O_2Si$: 471.0930 (471.0928).



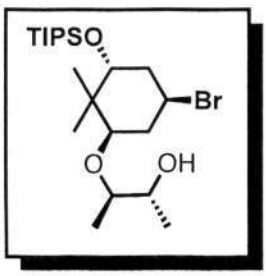
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.35 (1H, dd, *J* = 4.8, 10.8 Hz), 4.30 (1H, tt, *J* = 4.8, 12.0 Hz), 3.66-3.58 (2H, m), 3.54 (1H, dd, *J* = 3.2, 4.0 Hz), 2.44-2.38 (1H, m), 2.36-2.30 (1H, m), 2.10-1.94 (2H, m), 1.75 (3H, s), 1.21 (3H, t, *J* = 6.8 Hz), 1,12-1.10 (21H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 74.4, 73.0, 66.7, 42.9, 37.7, 23.2, 18.3 (×3), 18.2 (×3), 15.3, 12.8 (×3);

R_f = 0.70 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1475, 1103, 679;

HRMS (ESI, m/z (M+H)] calcd (found) for $C_{18}H_{37}Br_2O_2Si$: 471.0930(471.0928).



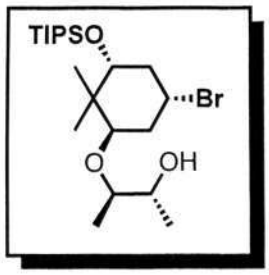
^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.29 (1H, tt, *J* = 4.5, 12.0 Hz), 3.73 (1H, t, *J* = 3Hz), 3.50 (1H, dq, *J* = 6.5, 2.0 Hz), 3.45 (1H, dd, *J* = 4.0, 11 Hz), 3.22 (1H, q, *J* = 6.5 Hz), 2.64 (1H, bs,), 2.52-2.47 (1H, m), 2.23-2.13 (2H, m), 1.86 (1H, q, *J* = 12Hz), 1.13 (3H, d, *J* = 6 Hz), 1.08 (21H, brs), 1.03 (3H, d, *J* = 6H), 1.07 (3H, s), 0.89 (3H, s);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 78.3, 77.4, 76.1, 71.0, 44.9, 40.8, 39.8, 38.3, 24.3, 19.2, 18.6, 18.2 (×3), 18.3 (×3), 12.7 (×3), 12.2;

R_f = 0.49 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 2942, 11635, 883;

HRMS (ESI, m/z (M+Na)] calcd (found) for $C_{21}H_{43}BrNaO_3Si$: 473.1886 (473.1952).



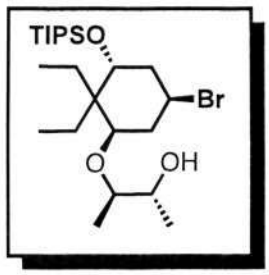
^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.14 (1H, tt, *J* = 4.5, 8, 12.5Hz), 3.83 (1H, dd, *J* = 4.5, 11.5Hz), 3.62-3.56 (1H, m), 3.27 (1H, t, *J* = 3Hz), 3.24 (1H, q, *J* = 6.5Hz), 2.37-2.28 (1H, m), 2.14 (1H, d, *J* = 4.5Hz), 2.07-1.99 (1H, m), 1.60 (2H, m) 1.15 (3H, d, *J* = 6.5Hz), 1.07 (3H, d, *J* = 6.4Hz), 1.06 (21H, brs), 1.04 (3H, s), 0.93 (3H, s);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 80.6, 76.4, 73.3, 71.1, 44.8, 42.5, 40.0, 35.5, 24.4, 19.0, 18.8, 18.3 (×3), 18.2 (×3), 14.9, 12.9 (×3);

R_f = 0.45 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 2944, 1465, 735;

HRMS (ESI, m/z (M+Na)] calcd (found) for $C_{21}H_{43}BrNaO_3Si$: 473.1886 (473.1952).



^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.27 (1H, tt, *J* = 4.8, 12.4 Hz), 3.88 (1H, t, *J* = 2.6 Hz), 3.57 (1H, dd, *J* = 4.1, 11.5 Hz), 3.49 (1H, qd, *J* = 6.4, 3.0 Hz), 3.19 (1H, q, *J* = 6.2 Hz), 2.53 (1H, d, *J* = 2.8 Hz), 2.50-2.45 (1H, m), 2. 22-2.19 (1H, m), 2.14-2.07 (1H,

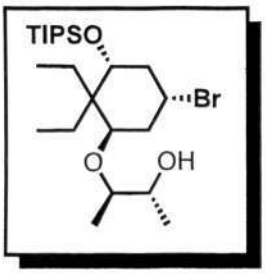
m), 1.98 (1H, q, J = 12.3 Hz), 1.80-1.67 (2H, m), 1.52-1.46 (1H, m), 1.30-1.20 (1H, m), 1.13 (3H, d, J = 6.3 Hz), 1.08 (21H, s), 1.05 (3H, d, J = 6.3 Hz), 0.90-0.85 (6H, m);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 78.0, 77.1, 74.9, 71.1, 45.1, 43.8, 40.4, 37.7, 24.9, 21.1, 18.7, 18.3 (×6), 15.2, 13.0, 12.8 (×3), 8.7, 8.6;

R_f = 0.49 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 2889, 1464, 732;

HRMS (ESI, m/z (M+Na)] calcd (found) for $C_{23}H_{47}BrNaO_3Si$: 501.2376 (501.2335).



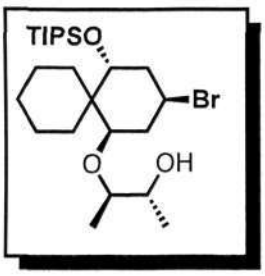
^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.11 (1H, tt, J = 4.9, 7.7, 12.5 Hz), 3.96 (1H, dd, J = 4.2, 11.5 Hz), 3.62-3.57 (1H, m), 3.47 (1H, t, J = 2.6 Hz), 3.33 (1H, q, J = 5 Hz), 2.38-2.31 (2H, m), 2.22 (1H, q, J = 12 Hz), 2.13 (1H, d, J = 5.5 Hz), 1.94-1.74 (3H, m), 1.52-1.45 (1H, m), 1.25-1.19 (1H, m), 1.16 (3H, d, J = 6.5 Hz), 1.06 (3H, d, J = 7.5 Hz), 1.06 (21H, brs), 0.96 (3H, t, J = 8.5 Hz), 0.84 (3H, t, J = 8.0 Hz);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 75.2, 75.1, 74.2, 71.3, 44.6, 44.0, 42.3, 33.9, 24.0, 22.7, 19.0, 18.3 (×3), 18.2 (×3), 14.3, 12.9 (×3), 9.4, 7.8;

FTIR (neat, cm^{-1}): ν 2891, 1380, 677;

R_f = 0.45 (Hex:EA = 5:1);

HRMS (ESI, m/z (M+Na)] calcd (found) for $C_{23}H_{47}BrNaO_3Si$: 501.2376 (501.2335).



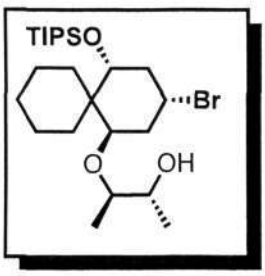
^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.32-4.31 (1H, m), 4.29 (1H, tt, *J* = 4.0, 8.0, 11 Hz), 3.53 (1H, dq, *J* = 2.5, 6 Hz), 3.40 (1H, dd, *J* = 4.5, 11.5 Hz), 3.20 (1H, q, *J* = 6.5 Hz), 2.61 (1H, d, *J* = 3.0 Hz), 2.45-2.40 (1H, m), 2.27-2.14 (2H, m), 1.94 (1H, q, *J* = 12 Hz), 1.70-1.40 (1H, m), 1.27-1.19 (2H, m), 1.14 (3H, d, *J* = 5.5 Hz), 1.09 (21H, brs), 1.04 (3H, d, *J* = 6.0 Hz);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 77.5, 75.9, 71.3, 71.0, 45.0, 41.7, 40.0, 29.1, 26.5, 26.2, 21.8, 21.5, 18.6, 18.3 (×3), 18.3 (×3), 15.5, 13.0 (×3), 12.2;

FTIR (neat, cm^{-1}): ν 2941, 1653, 817;

R_f = 0.48 (Hex:EA = 5:1);

HRMS (ESI, m/z (M+Na)] calcd (found) for $C_{24}H_{47}BrNaO_3Si$: 491.2376 (491.2382).



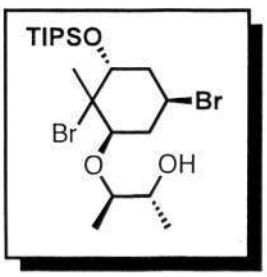
^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.14 (1H, tt, *J* = 4.5, 12.5 Hz), 3.94 (1H, t, *J* = 3.0 Hz), 3.80 (1H, dd, *J* = 4.5, 11.5 Hz), 3.63-3.58 (1H, m), 3.35 (1H, q, *J* = 6.0 Hz), 2.39-2.34 (1H, m), 2.30-2.26 (1H, m), 2.16-2.08 (2H, m), 2.00-1.94 (1H, m), 1.73-1.64 (3H, m), 1.60-1.50 (4H, m), 1.37-1.19 (2H, m), 1.17 (3H, d, *J* = 6.5 Hz), 1.08 (3H, d, *J* = 6.0 Hz), 1.06 (21H, bs);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 74.7, 73.0, 71.9, 71.3, 44.7, 42.2, 41.5, 33.9, 28.6, 26.3, 25.2, 21.4, 21.3, 19.0, 18.3 (×3), 18.2 (×3), 14.6, 12.9 (×3);

FTIR (neat, cm^{-1}): ν 2892, 1464, 759;

R_f = 0.44 (Hex:EA = 5:1);

HRMS (ESI, m/z (M+Na)] calcd (found) for $C_{24}H_{47}BrNaO_3Si$: 491.2376 (491.2382).



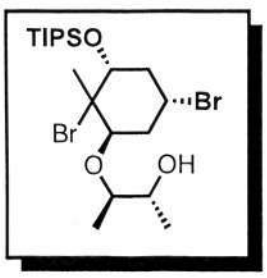
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.29-4.20 (2H, m), 3.57 (1H, dq, *J* = 2.0, 6.8 Hz), 3.35-3.28 (2H, m), 2.82-2.75 (1H, m), 2.71 (1H, d, *J* = 2.0 Hz), 2.57-2.51 (1H, m), 2.31-2.26 (1H, m), 2.22-2.13 (1H, m), 1.86 (3H, s), 1.15 (3H, d, *J* = 6.0 Hz), 1.14-0.98 (m, 24H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 77.9, 77.3, 74.8, 71.5, 70.8, 42.6, 40.6, 39.4, 27.5, 18.5, 18.2 (×3), 18.1 (×3), 15.5, 12.7 (×3);

R_f = 0.44 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 2990, 1272, 997;

HRMS (ESI, m/z (M+Na)] calcd (found) : $C_{20}H_{40}Br_2NaO_3Si$: 537.1011 (537.1014).



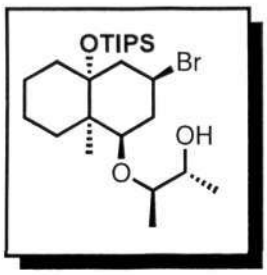
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.33 (1H, dd, *J* = 4.8, 10.4 Hz), 4.25 (1H, tt, *J* = 4.8, 11.6 Hz), 3.78 (1H, q, *J* = 2.0 Hz), 3.66 (1H, q, *J* = 6.0 Hz), 3.46 (1H, q, *J* = 6.0 Hz), 2.47-2.42 (1H, m), 2.39-2.33 (1H, m), 2.15-2.00 (3H, m), 1.80 (3H, s), 1.21-1.19 (6H, m), 1.13-1.08 (21H, m);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 77.2, 74.1, 71.2, 42.5, 36.8, 19.5, 18.3 (×3), 18.2 (×3), 15.2, 12.8 (×3);

R_f = 0.44 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 2892, 1457, 882;

HRMS (ESI, m/z (M+Na)] calcd (found): $C_{20}H_{40}Br_2NaO_3Si$: 537.1011(537.1014).



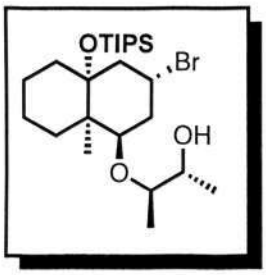
^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.28 (1H, tt, *J* = 6.0, 10.5, 16 Hz), 3.61 (1H, dd, *J* = 5.5, 14.5 Hz), 3.52-3.47 (1H, m), 3.24-3.17 (1H, m), 2.60-2.46 (2H, m), 2.00-1.81 (2H, m), 1.66-1.39 (7H, m), 1.14-1.04 (32H, m);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 79.7, 77.5, 77.1, 71.0, 45.9, 44.2, 43.2, 37.3, 36.0, 27.5, 23.5, 20.2, 18.6 (×3), 18.4 (×3), 18.3, 15.4, 13.8, 12.3 (×3);

R_f = 0.45 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 2966, 1122,1087;

HRMS (EI, m/z (M+Na)] calcd (found) for $C_{24}H_{47}BrNaO_3Si$: 513.2376 (513.2338)



^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.96 (1H, tt, *J* = 4.8, 14.5 Hz), 3.58 (1H, dd, *J* = 4.4, 11.2 Hz), 3.55-3.48 (1H, m), 3.23 (1H, q, *J* = 7.2 Hz), 2.54-2.50 (2H, m), 2.34 (1H, t, *J* =12.8 Hz), 2.06-2.02 (1H, m), 1.92 (1H, q, *J* = 11.6 Hz), 1.78-1.23 (9H, m), 1.14-1.06 (26H, m), 0.97 (3H, s);

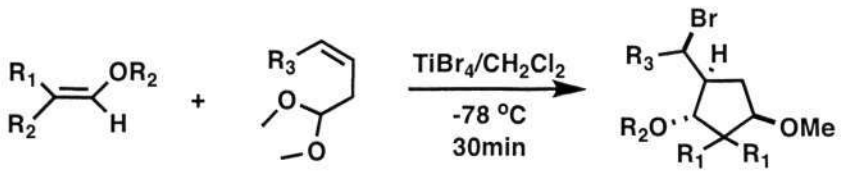
^{13}C NMR ($CDCl_3$, 100 MHz): δ 77.0, 72.2, 71.0, 47.7, 43.7, 43.5, 37.9, 34.1, 29.5, 21.1, 21.0, 18.6 (×3), 18.5 (×3), 16.8, 15.8, 13.8 (×3);

R_f = 0.43 (Hex:EA = 5:1);

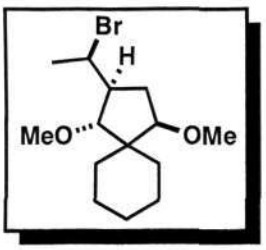
FTIR (neat, cm^{-1}): ν 2989, 1132,1087;

HRMS (EI, m/z (M+Na)] calcd (found) for $C_{24}H_{47}BrNaO_3Si$: 513.2376 (513.2338)

General procedure for the Mukaiyama-Aldol-Prins domino reaction



To a stirred solution of $TiBr_4$ in dichloromethane was added in the mixture of silyl enol ether and acetal (pre-dissolved in dichloromethane) at -78 °C. After 30 minute, the reaction mixture was quenched by saturated sodium bicarbonate and extracted with dichloromethane (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo* to give the crude product. Purification with silica gel column chromatography using hexane as eluent afforded the desired product.



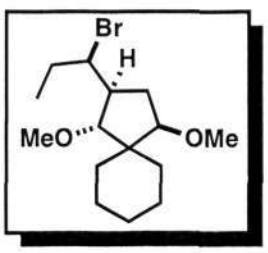
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.27 (1H, q, *J* = 6.4 Hz), 3.50-3.46 (1H, m), 3.45 (3H, s), 3.39 (1H, d, *J* = 6.4 Hz), 3.29 (3H, s), 2.39-2.31 (1H, m), 2.18-2.10 (1H, m), 1.78-1.73 (1H, m), 1.70 (3H, d, J = 6.8 Hz) , 1.67-1.60 (1H, m), 1.54-1.20 (9H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 89.2, 83.7, 59.3, 57.1, 54.2, 50.7, 49.9, 29.8, 29.0, 28.4, 26.2, 23.3, 23.0, 22.8;

R_f = 0.64 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1413, 1066, 679;

HRMS (ESI, m/z (M +Na)] calcd (found) for $C_{14}H_{25}BrNaO_2$: 327.0936 (327.0934).



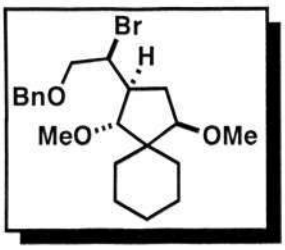
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.05-4.00 (1H, m), 3.50-3.46 (1H, d, m), 3.45 (3H, s), 3.28 (3H, s), 2.40-2.32 (1H, m), 2.20-2.12 (1H, m), 1.99-1.90 (1H, m), 1.82-1.20 (13H, m), 1.08 (3H, t, *J* = 7.6 Hz);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 89.1, 84.1, 64.2, 60.4, 59.2, 30.5, 29.3, 28.8, 28.7, 26.2, 22.9, 22.8, 21.0, 14.2, 12.5;

R_f = 0.67 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1130, 1092, 968;

HRMS (ESI, m/z (M + Na)] calcd (found) for $C_{15}H_{27}BrO_2$: 341.1092 (341.1133).



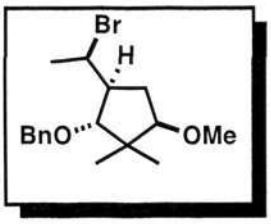
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37-7.28 (5H, m), 4.59 (2H, dd, *J* = 12.0, 19.5Hz), 4.25-4.22 (1H, m), 3.82 (1H, dd, *J* = 4.5, 11.0 Hz), 3.72 (1H, dd, *J* = 7.5, 11.0Hz), 3.55 (1H, d, *J* = 6.0 Hz), 3.45 (1H, t, *J* = 5.0 Hz), 3.42 (3H, s), 3.26 (3H, s), 2.41-2.38 (1H, m), 2.14-2.08 (1H, m), 1.78-1.75 (1H, m), 1.65-1.60 (1H, m), 1.50-1.20 (9H, m);

^{13}C NMR ($CDCl_3$, 100MHz) δ 137.8, 128.4 (×2), 127.8 (×2), 127.7, 89.1, 83.7, 73.2, 73.1, 59.2, 57.9, 57.0, 49.6, 45.8, 30.5, 29.1, 28.5, 26.2, 22.9, 22.8;

R_f = 0.63 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1452, 1272, 982;

HRMS (ESI, m/z (M +H)] calcd (found) for $C_{21}H_{31}BrNaO_3$: 433.1354 (433.1344).



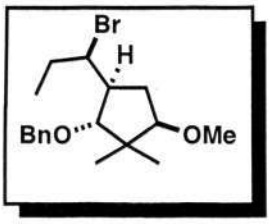
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.28 (5H, m), 4.61 (2H, dd, *J* = 11.2, 16.4 Hz), 4.24 (1H, q, *J* = 6.4 Hz), 3.52 (1H, d, *J* = 6.4 Hz), 3.31 (3H, s), 3.32-3.29 (1H, m), 2.44-2.36 (1H, m), 2.20-2.12 (1H, m), 1.63 (3H, d, *J* = 8.0 Hz), 1.49-1.42 (1H, m), 1.07 (3H, s), 1.05 (3H, s);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 138.7, 128.4 (×2), 127.9 (×2), 127.6, 89.0, 87.6, 73.2, 57.4, 53.9, 51.1, 46.1, 30.3, 23.3, 21.9, 21.6;

R_f = 0.45 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 3420,1696, 1070, 753;

HRMS (ESI, m/z (M + Na)]$^+$ calcd (found) for $C_{17}H_{25}BrNaO_2$: 363.0936 (363.1008).



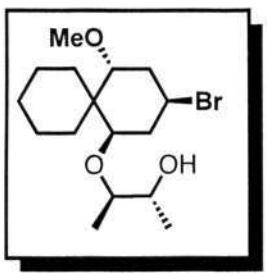
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.28 (5H, m), 4.60 (2H, dd, *J* = 11.2, 14.0 Hz), 4.05-4.00 (1H, m), 3.59 (1H, d, *J* = 6.4 Hz), 3.33 (1H, t, *J* = 6.0 Hz) 3.31 (3H, s), 2.46-2.38 (1H, m), 2.21-2.14 (1H, m), 1.89-1.80 (1H, m), 1.78-1.70 (1H, m), 1.49-1.42 (1H, m), 1.09 (3H, s), 1.04 (3H, s), 1.02 (3H, t, *J* = 7.2 Hz);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 138.8, 128.3 (×2), 127.8 (×2), 127.5, 89.2, 87.5, 73.0, 63.7, 57.5, 49.7, 45.8, 30.9, 29.3, 21.8, 21.6, 12.6;

R_f = 0.46 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 3421,1443, 1097, 863;

HRMS (ESI, m/z (M +Na)]calcd (found) for $C_{18}H_{27}BrNaO_2$: 377.1092 (377.1064).



Major

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.14 (1H, tt, *J* = 4.4, 12.8 Hz), 3.63 (1H, t, *J* = 2.4 Hz), 3.51 (1H, qd, *J* = 6.8, 2.4 Hz), 3.32 (3H, s), 3.28 (1H, dd, *J* = 4.0, 11.6 Hz), 3.16 (1H,

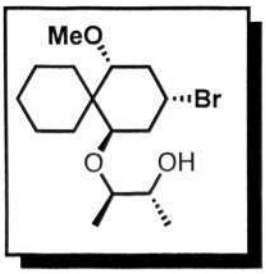
q, J = 6.4 Hz), 2.57 (1H, d, J = 2.4 Hz), 2.44-2.40 (2H, m), 1.99-1.86 (2H, m), 1.70-1.16 (10H, m), 1.13 (3H, d, J = 6.4 Hz), 1.04 (3H, d, J = 6.4 Hz);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 78.5, 77.6, 76.3, 71.0, 57.5, 44.6, 41.2, 37.4, 34.1, 29.1, 26.2, 25.9, 21.4, 21.1, 18.6, 15.7;

R_f = 0.49 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 3501, 2936, 1278, 603;

HRMS (ESI, m/z (M+Na)]calcd (found) for $C_{16}H_{29}BrNaO_3$: 371.1198 (371.1199).



Minor

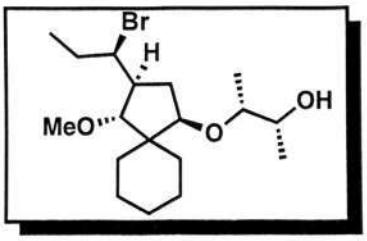
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.18 (1H, tt, J = 4.8, 12.0Hz), 3.89 (1H, t, J = 3.2Hz), 3.62-3.58 (1H, m), 3.33 (3H, s), 3.36-3.30 (1H, m), 3.06 (1H, dd, J = 4.0, 11.2Hz), 2.47-2.33 (2H, m), 2.18 (1H, d, J = 4.0Hz), 2.03-1.89 (2H, m), 1.70-1.48 (7H, m), 1.36-1.22 (3H, m), 1.18 (3H, d, J = 6.4Hz), 1.09 (3H, d, J = 6.4 Hz);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 81.6, 75.3, 72.4, 71.3, 58.0, 44.8, 41.4, 34.2, 28.2, 26.2, 26.1 (×2), 21.3, 21.2, 19.0, 14.9;

R_f = 0.38 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 3522, 2862, 1262, 713;

HRMS (ESI, m/z (M+Na)]calcd (found) for $C_{16}H_{29}BrNaO_3$: 371.1198 (371.1199).



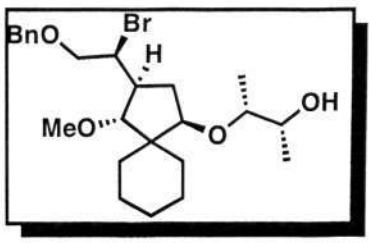
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.02-3.97 (1H, m), 3.71(1H, t, *J* = 6.4 Hz), 3.60 (1H, d, *J* = 4.8 Hz), 3.54-3.50 (1H, m), 3.46 (3H, s), 3.19-3.12 (1H, m), 2.77 (1H, d, *J* = 1.6 Hz), 2.30-2.19 (2H, m), 1.99-1.65 (4H, m), 1.50-1.28 (7H, m), 1.24-1.18 (2H, m), 1.13 (3H, d, *J* = 6.4Hz), 1.09-1.03 (6H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 88.2, 79.0, 77.8, 71.2, 64.7, 58.8, 49.0, 48.7, 32.5, 30.1, 28.9, 28.0, 26.1, 23.1, 22.5, 18.5, 15.2, 12.5;

R_f = 0.39 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 2941, 1381, 908;

HRMS (ESI, m/z (M +Na)]$^+$ calcd (found) for $C_{18}H_{33}BrNaO_3$: 399.1511 (399.1503).



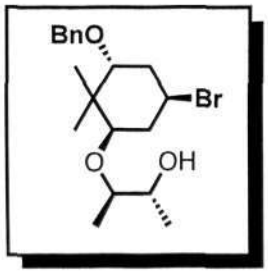
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.28 (5H, m), 4.59 (1H, dd, *J* = 12.0, 20.8 Hz), 4.22 (1H, dd, *J* = 6.0, 12.0 Hz), 3.84-3.70 (3H, m), 3.64 (1H, d, *J* = 6.4 Hz), 3.55-3.49 (1H, m), 3.42 (3H, s), 3.17-3.10 (1H, m) , 2.88 (1H, bs), 2.41-2.33 (1H, m), 2.18-2.12 1.75-1.63 (4H, m), 1.47-1.36 (7H, m), 1.25-1.17 (2H, m), 1.13 (3H, d, *J* = 6.0Hz), 1.05(3H, d, *J* = 6.0 Hz);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ = 137.8, 128.4 (×2), 127.8 (×2), 127.0, 88.5, 77.6, 73.2, 73.0, 71.1, 63.4, 59.1, 58.4, 49.1, 44.9, 32.1, 28.5, 28.4, 26.1, 22.9, 22.6, 18.5, 15.1;

R_f = 0.38 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 3566, 1122, 712;

HRMS (ESI, m/z (M +Na)] calcd (found) for $C_{24}H_{37}BrNaO_4$: 491.1773 (491.1786).



Major

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.28 (5H, m), 4.58 (1H, d, *J* = 11.6Hz), 4.38 (1H, d, *J* = 11.6Hz), 4.23 (1H, tt, *J* = 4.8, 12.4Hz), 3.54-3.45 (2H, m), 3.24-3.17 (2H, m), 2.57 (1H, d, *J* = 2.8Hz), 2.52-2.39 (2H, m), 2.09-2.02 (1H, m), 1.86 (1H, q, *J* = 12.0 Hz), 1.13 (3H, d, *J* = 6.4 Hz), 1.08 (3H, s), 1.05 (3H, , d, *J* = 6.4 Hz), 0.92(3H, s);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 138.4, 128.4 (×2), 127.7, 127.6 (×2), 84.3, 77.5, 76.6, 71.7, 71.0, 44.6, 39.1, 38.5, 35.9, 23.9, 19.2, 18.6, 15.7;

R_f = 0.49 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 2974, 1456, 839;

HRMS (ESI, m/z (M +Na)] for $C_{19}H_{29}BrNaO_3$: 407.1198 (407.1194).

Minor

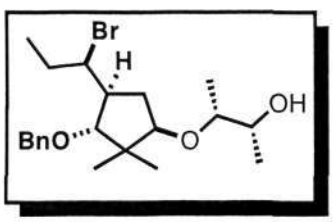
^{1}H NMR ($CDCl_3$, 400 MHz)) δ 7.38-7.28 (5H, m), 4.62 (1H, d, *J* = 11.6 Hz), 4.43 (1H, d, *J* = 11.6 Hz), 4.18 (1H, tt, *J* = 4.8, 12.0 Hz), 3.62-3.55 (1H, m), 3.40 (1H, dd, *J* = 4.4, 11.2 Hz), 3.27-3.23 (2H, m), 2.58-2.53 (1H, m), 2.34-2.29 (1H, m), 2.16 (1H, d, *J* = 4.4 Hz), 2.09-1.94 (2H, m), 1.17 (3H, d, *J* = 6.0 Hz), 1.07 (3H, d, *J* = 6.0 Hz), 1.06 (3H, s), 0.99 (3H, s);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 138.4, 128.4 (×2), 127.7, 127.5 (×2), 80.7, 80.0, 76.7 71.9, 71.0, 44.8, 39.2, 38.1, 35.7, 23.9, 19.6, 19.1, 15.1;

R_f = 0.38 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 2974, 1635, 995;

HRMS (ESI, m/z (M +Na)] for $C_{19}H_{29}BrNaO_3$: 407.1198(407.1194).



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.28 (5H, m), 4.62 (2H, s), 4.06-4.00 (1H, m) , 3.64 (1H, d, *J* = 5.2 Hz), 3.60-3.51 (2H, m), 3.18-3.11 (1H, m), 2.78 (1H, brs), 2.40-2.32 (1H, m), 2.24-2.18 (1H, m), 1.90-1.78 (2H, m), 1.42-1.26 (3H, m), 1.13 (3H, d, *J* = 6.0 Hz), 1.09 (3H, s), 1.06-1.02 (4H, m), 1.00 (3H, s);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 138.7, 128.4 (×2), 127.8 (×2), 127.6, 89.2, 82.0, 78.4, 73.0, 71.1, 64.2, 49.4, 45.4, 32.6, 30.0, 21.8, 21.3, 18.5, 15.5, 12.5;

R_f = 0.45 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1463, 1093, 883;

HRMS (ESI, m/z $(M + H)]^+$ calcd (found) for $C_{21}H_{33}BrO_3$: 413.1691 (413.1686).

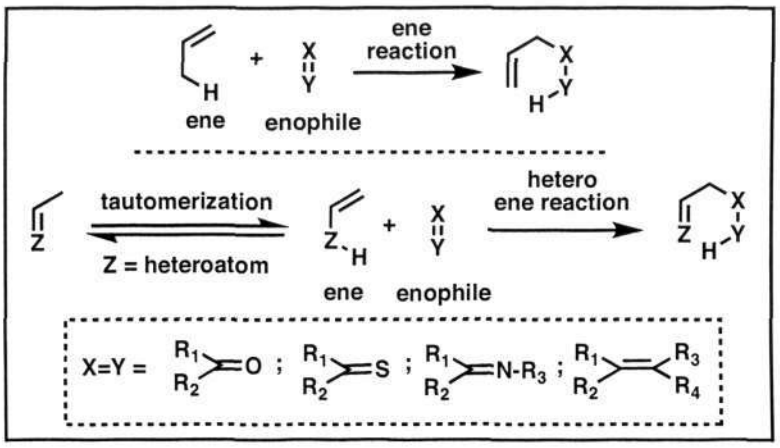
Chapter 3

Mukaiyama-Aldol-Ene Cascade Reaction

3.1 INTRODUCTION

3.1.1 Ene Reaction

The ene reaction was first recognized by Alder[1] in 1943. It is another classic reaction to form a C-C bond. The principle of ene reaction involves the addition of alkenes (referred to 'ene') to multiple bonds (C=C or C≡C, referred to 'enophile') leading to an ether moiety. However, when the enophile is a carbonyl compound (C=O), an alcohol will be formed. This reaction is known as the carbonyl-ene reaction.[2] In most examples, the ene is electron-rich whereas the enophile is electron-deficient. Usually, high temperature or Lewis acids (*e.g.* $AlCl_3$, $SnCl_4$, $TiCl_4$, $RAlX_2$)[3] are required as promoters or catalysts (Scheme 3-1).



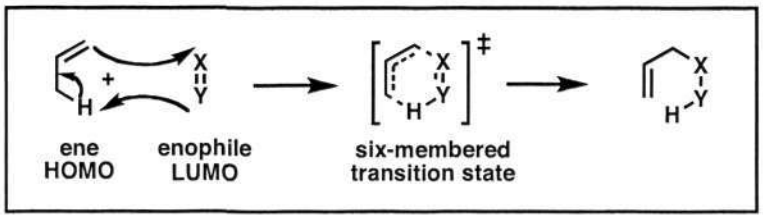
Scheme 3-1 General ene reaction

[1] Alder, K.; Pascher, F.; Schmidt, H. *Ber. Dtsch. Chem. Ges.*, **1943**, *76*, 27; (b) *Nobel Lectures-Chemistry*, **1942**; Elsevier: Amsterdam, **1964**, p. 253.

[2] (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556; (b) Gollnick, K.; Kuhn, H. *J. Org. Chem.* **1979**, *40*, 287; (c) Oppolzer, W. *Angew. Chem.* **1984**, *96*, 840; (d) Trost, B. M. *Acc. Chem. Res.***1990**, *23*, 34; (e) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett.* **1992**, 255; (f) Prein, M., Adam, W. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 477; (g) Weinreb, S. M. *J. Heterocycl. Chem.* **1996**, *33*, 1429; (h) Leach, A. G.; Houk, K. N. *Chem. Commun.* **2002**, 1243; (i) Chen, J. S.; Houk, K. N.; Foote, C. S. *J. Am. Chem. Soc.* **1997**, *119*, 9852.

[3] For a recent review, see: (a) Mikami, K.; Terada, M. In *Comprehensive Asymmetric Catalysis I-III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Wiley: New York, 2000; Vol. 3, Chapter 32, p. 1140; (b) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021; (c) Mikami, K. *Pure Appl. Chem.* **1996**, *68*, 639; (d) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426; (e) Dubac, J.; Laporterie, A. *Chem. Rev.* **1987**, *87*, 319. (f) Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, 2005.

The ene reaction is mechanistically related to the well-known Diels-Alder reaction, which is believed to proceed *via* a six-membered transition state.[4] The mechanism of Lewis acid-promoted ene reaction is slightly different from thermal ene reactions. The general consensus for the Lewis acid-promoted ene reaction involves a stepwise mechanistic pathway, whereas the thermal ene reaction mainly proceed *via* a concerted reaction mechanism.



Scheme 3-2

Upon development of the ene-reaction, it has been widely applied in methodology studies and natural product synthesis.[5] Heathcock[6] reported a remarkable example of ene cyclization process in the total synthesis of Daphnilactone A (as described in Chapter 1). A pentacyclic system was produced from the cyclization. Barriault[7] showed the asymmetric total synthesis of (+)-arteannuin M using Tandem oxy-cope/transannular ene cyclization as the key step to construct the bicyclic core of natural product. Our research group[8] also employed ene-reaction in

[4] (a) Paderes, G. D.; Jorgensen, W. L. *J. Org. Chem.* **1992**, *57*, 1904; (b) Achmatowicz, O.; Bialecka-Florjanczyk, E. *Tetrahedron* **1996**, *52*, 8827

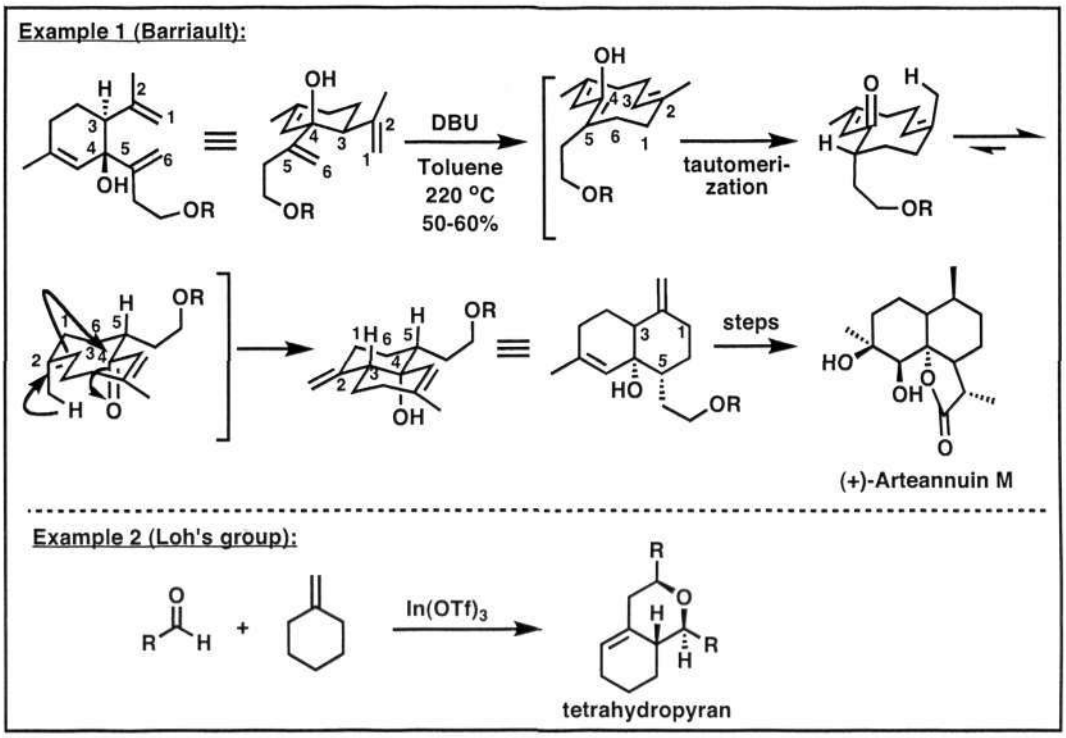
[5] (a) Ripoll, J. L.; Vallee, Y. *Synthesis* **1993**, 659; (b) Berrisford, D. J.; Bolm, C. *Angew. Chem., Int. Ed. Engl.***1995**, 34, 1717; (c) Borzilleri, R. M., Weinreb, S. M. *Synthesis* **1995**, 347; (d) Mikami, K. *Adv. in Asymmetric Synth.* **1995**, *1*, 1; (e) Mikami, K.; Terada, M.; Nakai, T. *Adv. Catal. Processes* **1995**, *1*, 123; (f) Adam, W.; Bottke, N.; Engels, B.; Krebs, O. *J. Am. Chem. Soc.* **2001**, *123*, 5542; (g) Musch, P. W.; Engels, B. *J. Am. Chem. Soc.* **2001**, *123*, 5557; (h) Morao, I.; McNamara, J. P.; Hillier, I. H. *J. Am. Chem. Soc.* **2003**, *125*, 628; (i) Mackewitz, T. W.; Regitz, M. *Synthesis* **1998**, 125.

[6] (a) Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath. J. C. *J. Org. Chem.* **1992**, *57*, 2544; (b) Heathcock, C. H.; Piettre, S.; Ruggeri, R. B.; Ragan, J. A.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2554.

[7] Barriault, L.; Deon, D. H. *Org. Lett.* **2001**, 3, 1925.

[8] (a) Loh, T. P.; Feng, L. C.; Zhou, Y.; Yang, J. Y. *Tetrohedron Lett.* **2002**, *43,* 7193; (b) Loh, T. P.; Feng, L. C.; Yang, J. Y. *Synthesis* **2002**, 937; (c) Loh, T. P.; Hu, Q. Y.; Ma, L. T. *J. Am. Chem. Soc.* **2001**, *123,* 2450; (d) Loh, T. P.; Tan, K. T.; Hu, Q. Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 2921.

the synthesis of highly stereoselective annulated tetrahydropyrans catalyzed by $In(OTf)_3$ (Scheme 3-3).



Scheme 3-3 Application of ene reaction

3.2 MUKAIYAMA-ALDOL-ENE TYPE CASCADE REACTION

3.2.1 Synthesis of Highly Functionalized Five-Membered Rings

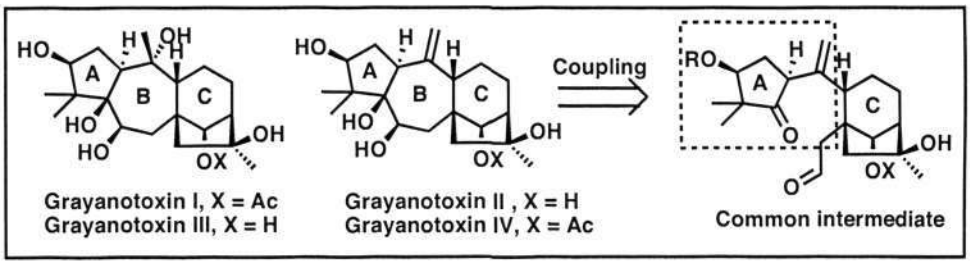
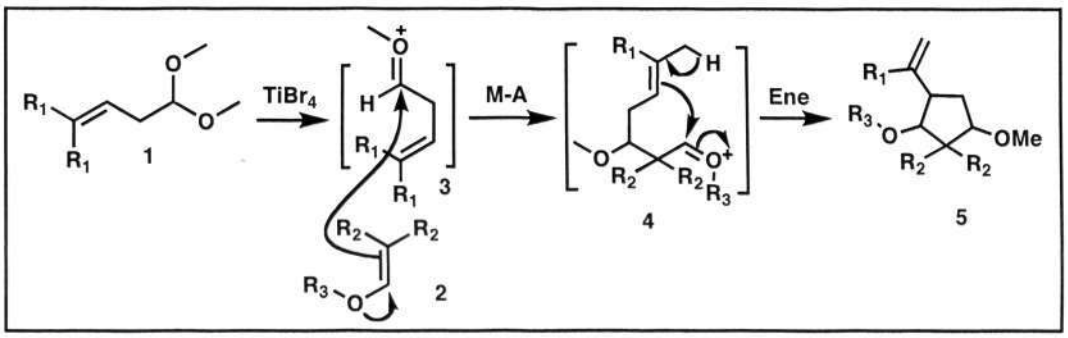


Figure 3-1 Grayanotoxins I - IV

In connection with our interest in the synthesis of natural products, we are interested in the development of a new strategy to obtain five-membered rings having

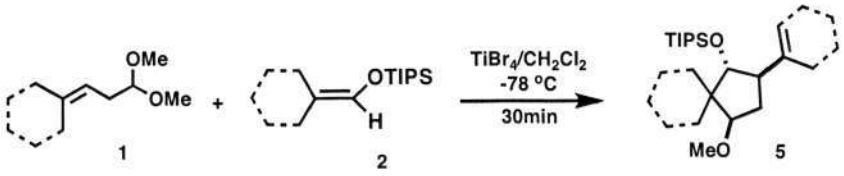
the structural scaffold as shown in Figure 3-1. We envisage that the cascade reaction involving disubstituted acetal **1** will proceed through a Mukaiyama-Aldol-Ene (MAE) cascade reaction to afford the desired five-membered ring **5** (Scheme 3-4). To expand our work on Mukaiyama-Aldol cascade reaction, we report a highly diastereo- and enantioselective cascade Mukaiyama-Aldol-Ene type (MAE) reaction to generate functionalized five-membered ring systems **5** with the generation of up to three stereogenic centers in a one-pot manner.

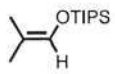
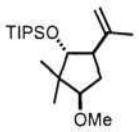
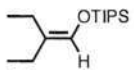
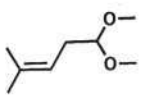
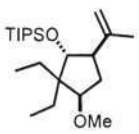
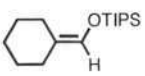
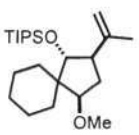
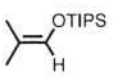
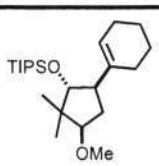
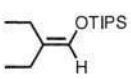
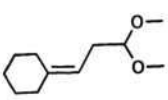
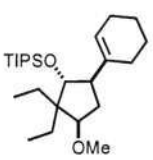
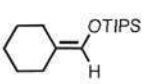
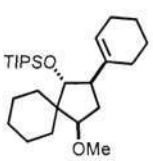


Scheme 3-4 Our proposed hypothesis on Mukaiyama-Aldol-Ene type reaction

Various studies were carried out using dialkyl substituted acetal **1** with disubstituted silyl enol ether **2** in the presence of $TiBr_4$ in dichloromethane at -78 °C. The results from the series of studies are shown in Table 3-1. Interestingly, the desired MAE products were obtained as a single stereoisomer in all cases, as observed in ^{1}H and ^{13}C NMR. Variation of the silyl enol ethers generated similar results (Table 3-1, entries 2, 3). Besides acyclic acetal (dimethyl substituted), cyclic acetal such as cylclohexanyl substituted acetal was employed in the cascade process. Gratifyingly, MAE Cascade reaction proceeded smoothly and gave the desired products with high yields and high diastereoselectivities.

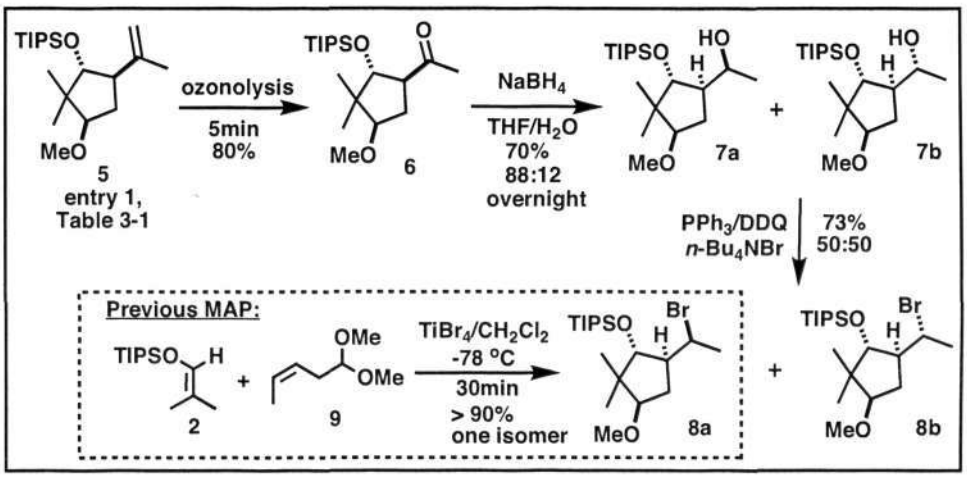
Table 3-1 MAE reactions with 1,1-disubstituted acetal[a]



Entry	Silyl enol ether	Acetal[b]	Product	Yield[c]	*dr*[d]
1				70	>99:1
2				75	>99:1
3				81	>99:1
4				86	>99:1
5				85	>99:1
6				80	>99:1

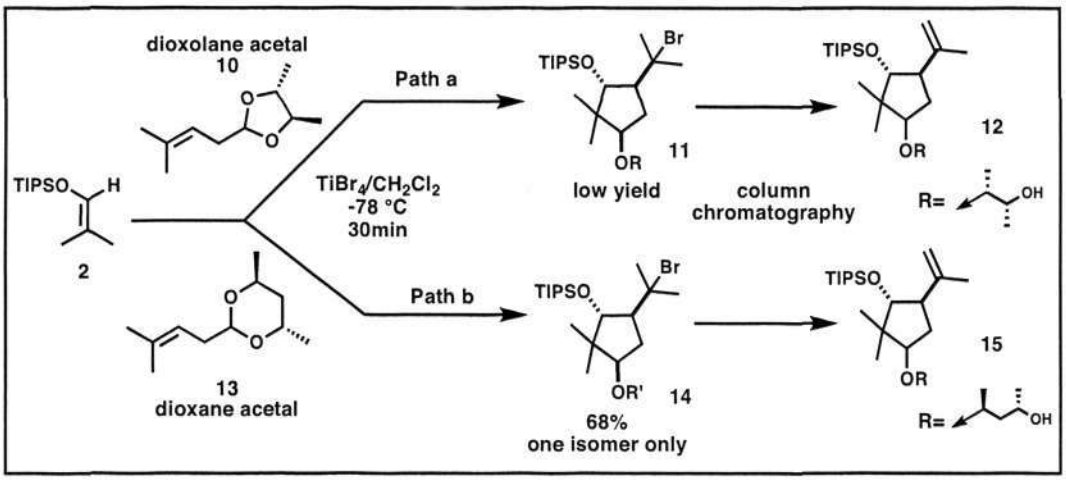
[a]Mukaiyama-Aldol-Ene reactions were run with 2 equiv of $TiBr_4$, 1 equiv of acetal and 1.2 equiv of silyl enol ether under N_2 atmosphere. [b]Disubstituted acetals were prepared by Wittig reactions. [c]Isolated yield. [d]Diastereomeric ratios were based on ^1H and ^{13}C NMR analyses.

Though we attained good diastereoselectivity of the final MAE product, the relative stereochemistry of the compounds we obtained remain unknown. Attempts to crystallize the MAE products were unsuccessful. In order to determine the relative stereochemistry of the cyclopentane ring, a series of chemical transformations was performed. Product **5** in entry 1 (Table 3-1) was converted to the known MAP product **8** (characterized in Chapter 2).



Scheme 3-5 Determination of the relative stereochemistry of MAE Product

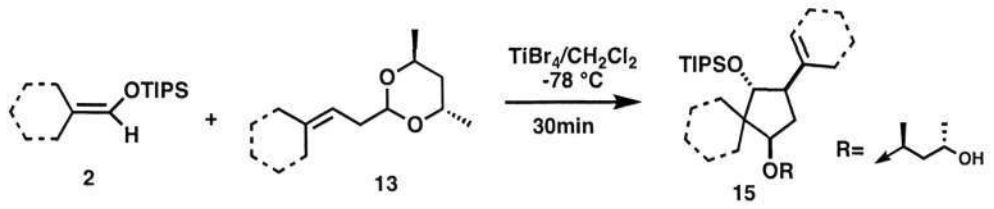
Ozonolysis followed by reduction with sodium borohydride ($NaBH_4$), generate a hydroxyl group **7** as a mixture of diastereomer (ratio = 88:12). It was further converted to a bromide with *n*-Bu_4NBr in the presence of PPh_3 and DDQ to give a fully racemized brominated product **8** in high yield. Both diastereomers **8** were separated *via* silical gel column chromatography. One of this diastereoisomers **8a** was identical to the sole product generated from MAP reaction as we have reported earlier (Chapter 2). Comparison of ^{1}H and ^{13}C NMR suggests to us the relative stereochemistry on the five-member ring system generated from MAE process is the same as that from our MAP reaction (Scheme 3-5).

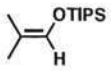
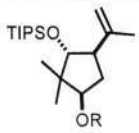
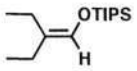
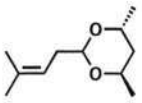
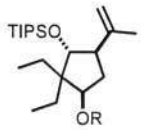
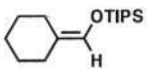
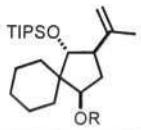
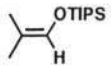
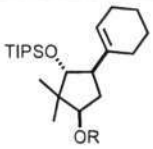
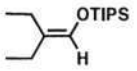
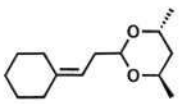
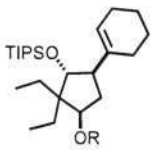
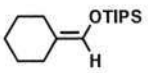
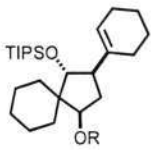


Scheme 3-6 Introduce asymmetric element into MAE type reaction

Adhering to the strategy we reported earlier, optically pure dioxolane acetal **10** was applied to the MAE cascade process in hopes that we can introduce an asymmetric element to the system (Scheme 3-6, Path a). Unfortunately, in contrast to what we observed for the achiral version in Table 3-1, MAE cyclization product was isolated in very low yields. Gratifyingly, when the optically pure dioxane acetal **13** was used (Scheme 3-2, Path b), the domino reaction proceeded in high yield and diastereoselectivity to give product **15** after column chromatography. From our detail observation and comparing the ^{1}H and ^{13}C NMR of crude and purified product, we found that the initial generated MAP product **14** was further undergoes a HBr elimination to MAE product **15** after silica gel flash column chromatography, even when soaked in $CDCl_3$ overnight. The results are shown in Table 3-2. On the basis of the final product obtained, we name the whole cascade process a Mukaiyama-Aldol-Ene type reaction.

Table 3-2 MAE type reactions in a asymmetric version[a]

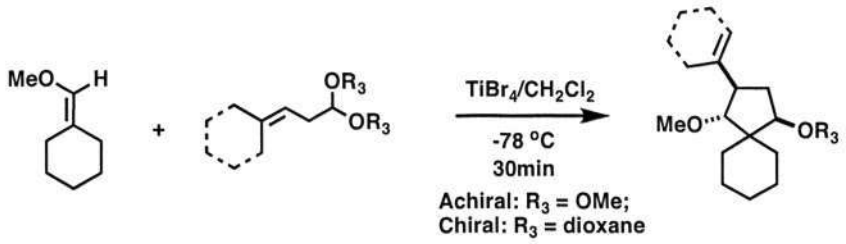


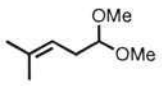
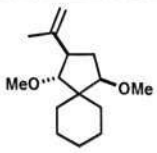
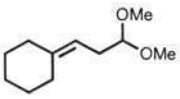
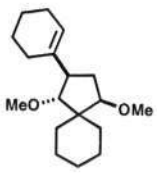
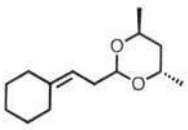
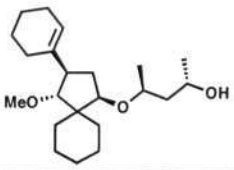
Entry	Silyl enol ether	Acetal	Product	Yield[b]	*Dr*[c]
1				68%	85:15
2				71%	84:16
3				75%	85:15
4				69%	84:16
5				86%	84:16
6				75%	87:13

[a]Mukaiyama-Aldol-Ene type reactions were run with 2 equiv of $TiBr_4$, 1 equiv of acetal and 1.2 equiv of silyl enol ether under a N_2 atmosphere. [b]Isolated yield. [c]Diastereomeric ratios were based on ^1H and ^{13}C NMR analyses.

Apart from silyl enol ether, we also explored the disubstitute alkyl enol ether for both chiral and achiral system, the results are similar in term of selectivities and yields as we observed in MAP reaction. The results are summarized in Table 3-3.

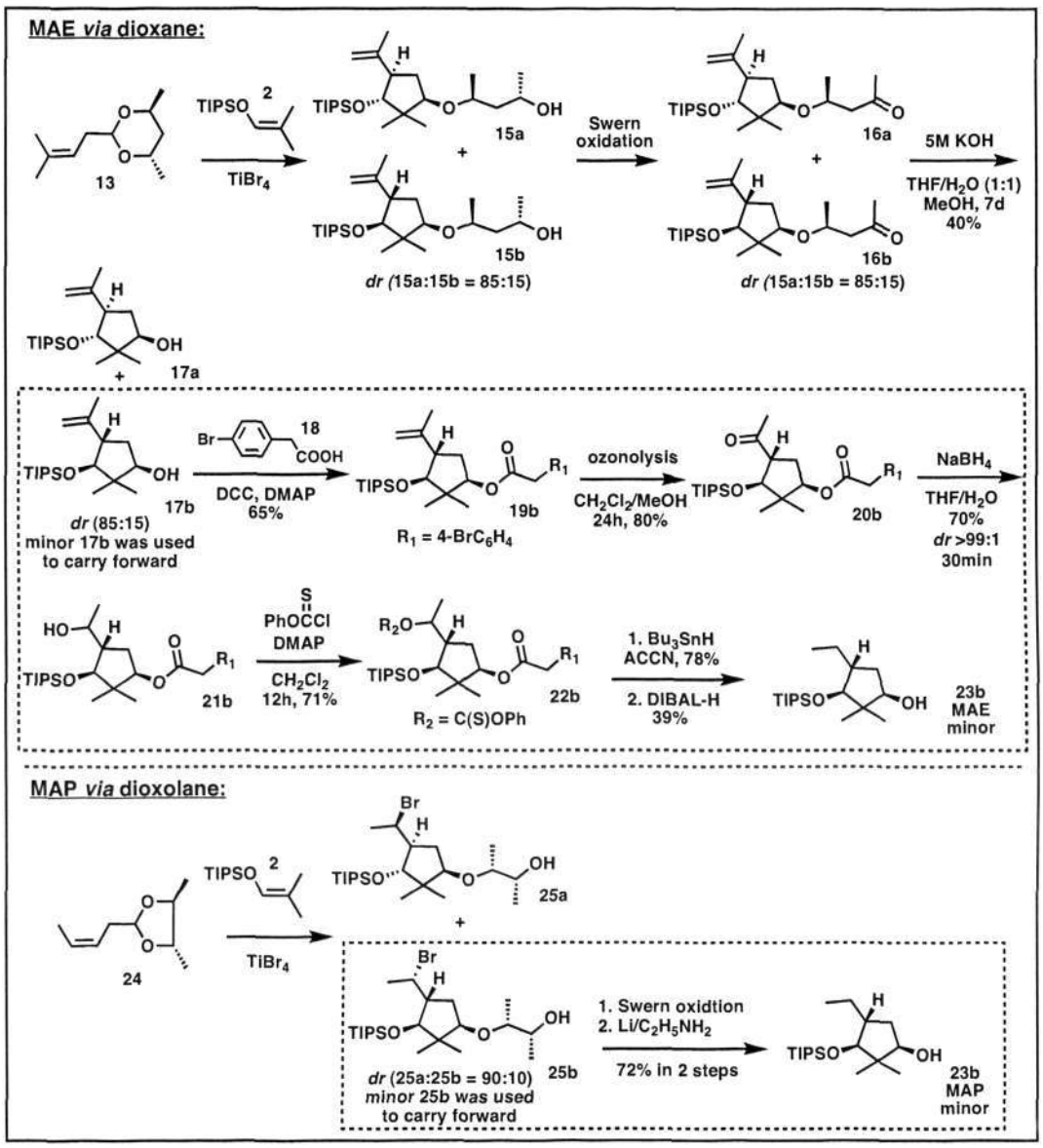
Table 3-3 MAP reactions with mono- or di-substituted acetal[a]



Entry	Acetal	Product	Yield[c]	*Dr*[d]
1			78%	>99:1
2			70%	>99:1
3			74%	>99:1

[a]Mukaiyama-Aldol-Prins reactions were run with 2 equiv of $TiBr_4$, 1 equiv of acetal and 1.2 equiv of silyl enol ether under N_2 atmosphere. [b]Isolated yield. [c]Diastereomeric ratios were based on ^1H and ^{13}C NMR analyses.

After much attempts in growing crystal failed, we decided to confirm the stereochemistry by make a comparison to reported compound in MAP reaction as we did for the achiral version in Scheme 3-5. Two series of chemical transformations were performed on the products generated from MAP and MAE cascade reaction respectively. The strategy is shown in Scheme 3-7.

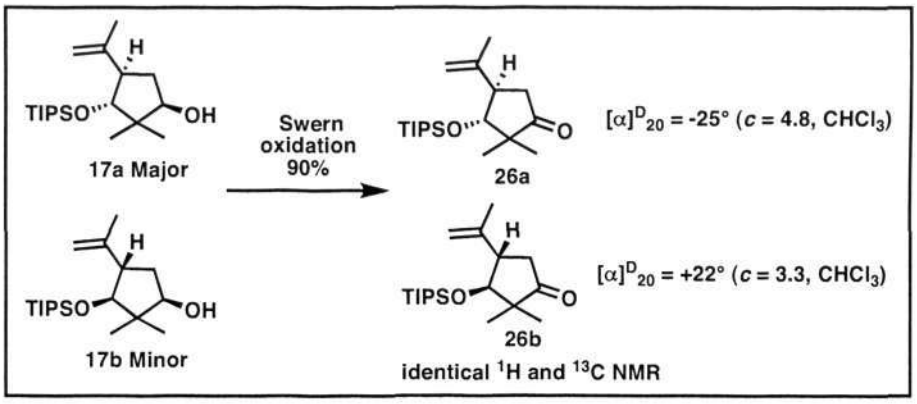


Scheme 3-7 Confirming of the absolute stereochemistry of MAE product

The MAE product **15** (*dr*=85:15) derived from dioxane **13** and silyl enol ether **2** was subjected to Swern oxidation and removal of the side chain under basic condition gave alcohol **17**. At this stage, we were able to separate out both diastereomers and the minor compound **17b** was subsequently coupled with **18** followed by ozonolysis and $NaBH_4$ reduction to afford **21b**. Barton-McCombie

radical deoxygenation reaction[9] was employed in the deoxygenation step to generate **23b**. On the other hand, the minor MAP product **25b** was subjected to Swern oxidation and Li/$EtNH_2$ to give an identical compound as **23b** from MAE product **17b** (Scheme 3-7).

Now we know the absolute stereochemistry of the minor product, the major product should be its enantiomer. To confirm this assumption, both pure major **17a** and minor alcohol **17b** were oxidized *via* Swern oxidation respectively. Both ketones **26a** and **26b** show identical ^{1}H and ^{13}C NMR but opposite optical rotation sign. This confirms that both alcohols are enantiomers (Scheme 3-8).



Scheme 3-8

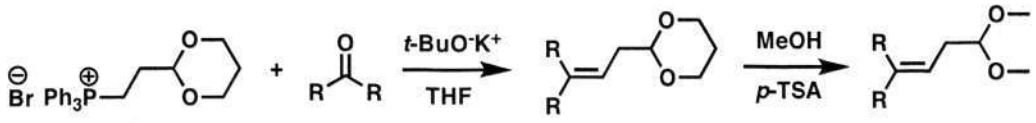
[9] (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574; (b) Barrett, A. G. M.; Prokopiou, P. A.; Barton, D. H. R. *J. Chem. Soc., Chem. Commun.* **1979**, 1175; (c) Luzzio, F. A.; Fitch, R. W. *J. Org. Chem.* **1999**, *64*, 5485.

3.3 CONCLUSION

In conclusion, we have developed a highly stereoselective Mukaiyama-Aldol-Ene (MAE) cascade reaction, accomplished with easily accessible starting materials. The novelty of this cascade reaction lies in the ability to construct five membered-ring systems in a one-pot manner in high yields with excellent diastereo, and enatioselectivities. In all cases, the products were obtained as single isomers. This new methodology provides a simple and practical method for the synthesis of polyfunctional cyclopentane building blocks.

3.4 EXPERIMENTAL

General Experimental Procedure for the synthesis of starting materials (acetals)



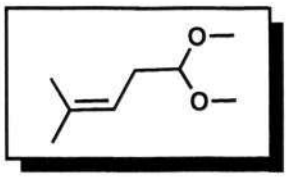
Step 1:

Into a 250 ml oven dried round bottom flask equipped with magnetic stirrer, THF (100 ml), phosphonium salt (46 g, 100 mmol, 1.0 equiv.) and 1M t-BuOK in butanol (110 ml, 110 mmol, 1.1 equiv.) was added and the mixture was allowed to stir for 20 minutes at -15 °C. Ketone (300 mmol, 3 equiv.) was then added into the reaction mixture after which the temperature of the reaction mixture was allowed to slowly rise to 0 °C in 30 minutes. The reaction was quenched using saturated sodium bicarbonate solution and extracted three times with diethyl ether. The combined organic extracts were washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in *vacuo*, and the yellowish liquid was purified using flash column chromatography with 20% ethyl acetate/hexane to give the colorless Wittig acetal products (~90% yield).

Step 2:

Into a 500 ml oven dried round bottom flask equipped with magnetic stirrer, acetal (90 mmol, 1 equiv.), *p*-TSA monohydrate (1.71 g, 9.0 mmol, 0.1 equiv.) and methanol (250 ml) were added and the mixture was allowed to stir and refluxed at 70 °C for 1 hour. Sodium bicarbonate (1.5 g, 18 mmol, 0.2 equiv.) was then added into the reaction mixture and the reaction was stirred for another 30 minutes after which excess sodium bicarbonate was removed by simple filtration. Crude product was

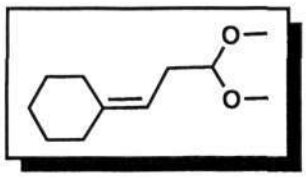
obtained after excess methanol was removed in *vacuo*. Diethyl ether (100 ml) was then added into the crude product and the resulted solution was washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. The organic layer was concentrated to give the colorless acetal products (~90% yield).



^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.11 (1H, t, J = 6.8 Hz), 4.35 (1H, t, J = 6.0 Hz), 3.32 (6H, s), 2.31 (2H, dd, J = 6.0, 6.8 Hz), 1.71 (3H, s), 1.62 (3H, s);

^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 134.4, 118.3, 104.37, 52.8, 31.8, 25.8, 17.9;

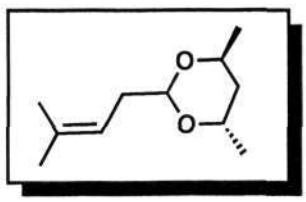
R*f* = 0.63 (Hexane : Ethyl Acetate = 5:1);



^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.16 (1H, t, J = 7.0 Hz), 4.50 (1H, t, J = 5.3 Hz), 4.11 (1H, d, J = 4.9 Hz), 4.09 (1H, d, J = 4.9Hz), 3.75 (1H, dt, J = 12, 2.2 Hz), 2.30 (1H, t, J = 5.9 Hz), 2.16-2.02 (1H, m), 1.71 (3H, s), 1.61 (3H, s), 1.30-1.25 (2H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 134.2, 117.9, 102.2, 66.9, 34.3, 25.8, 25.7, 17.9;

R*f* = 0.75 (Hexane : Ethyl Acetate = 5:1);

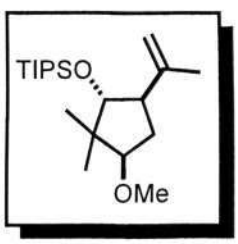


^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.16 (1H, t, J = 6.8 Hz), 4.82 (1H, J = 5.3 Hz), 4.34-4.27 (1H, m), 3.99-3,91 (1H, m), 2.29 (1H, t, J = 5.7 Hz), 1.88-1.80 (1H, m), 1.71 (3H, s), 1.60 (3H, d, J = 7.0 Hz), 1.35 (3H, d, J = 7.0 Hz), 1.20 (1H, d, J = 6.2 Hz);

^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 133.9, 118.3, 94.3, 68.0, 67.5, 36.8, 34.5, 25.8, 21.9, 18.0, 17.2;

General Experimental Procedure for MAE Reaction

To a stirred solution of $TiBr_4$ (2 equiv.) in DCM was added solution of silyl enol ether (1.5 equiv.) and acetal (1 equiv.) in DCM at -78 °C (in dry ice / acetone bath). After 30 minutes, the reaction mixture was quenched by saturated sodium bicarbonate and extracted 3 times with DCM. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo* to give the crude product. Purification with silica gel column chromatography using hexane as eluent afforded the desired product (yield range from 70 to 86%).



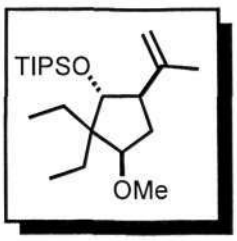
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.78 (1H, bs), 4.73(1H, bs), 4.03 (1H, d, J = 6.8 Hz), 3.27 (3H, s), 3.21 (1H, dd, J = 4.4, 5.6 Hz), 2.57-2.51 (1H, m), 2.20-2.12 (1H, m), 1.72 (3H, brs), 1.47-1.41 (1H, m), 1.06 (21H, brs), 0.99 (3H, s), 0.95 (3H, s);

^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 146.6, 111.5, 88.0, 81.8, 57.0, 52.5, 46.8, 32.3, 21.2, 21.0, 19.7, 18.4 (x3), 18.4 (x3), 13.3 (x3);

R_f = 0.63 (Hexane : Ethyl Acetate = 5 : 1)

FTIR (neat, cm^{-1}): ν 3155, 3075, 2944, 1643, 1465, 1385, 1094;

HRMS (ESI, m/z M +H] Calcd (Found) for $C_{20}H_{40}NaO_2Si$**:** 363.2695 (363.2690).



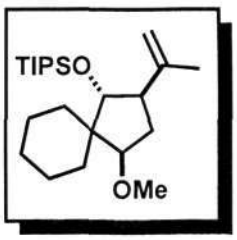
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.78 (1H, brs), 4.74 (1H, brs), 4.15 (1H, d, *J* = 6.4 Hz), 3.39 (1H, t, *J* = 5.6 Hz), 3.25 (3H, s), 2.59-2.53 (1H, m), 2.15-2.08 (1H, m), 1.72 (3H, bs), 1.63-1.53 (2H, m), 1.47-1.36 (3H, m), 1.05 (21H, brs), 0.93 (3H, t, *J* = 7.6 Hz), 0.89 (3H, t, *J* = 0.76 Hz);

^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 146.9, 111.4, 86.1, 82.0, 56.6, 52.7, 51.6, 32.4, 24.8, 23.8, 19.9, 18.5 (x3), 18.4 (x3), 13.4 (x3), 9.37, 9.09;

R_f = 0.64 (Hexane: Ethyl Acetate =5 : 1)

FTIR (neat, cm^{-1}): ν 3075, 2944, 1463, 1463, 1374, 1094;

HRMS (ESI, m/z M +Na] Calcd (found) for C22H44NaO2Si**:** 391.3008 (391.3011).



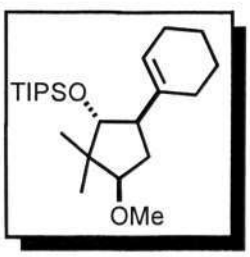
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.78 (1H, brs), 4.73-4.72 (1H, m), 4.03 (1H, d, *J* = 7.6 Hz), 3.51 (1H, dd, *J* = 2.0, 5.6 Hz), 3.26 (3H, s), 2.62-2.55 (1H, m), 2.15-2.08 (1H, m), 1.71 (3H, brs), 1.06 (21H, brs), 1.80-0.96 (11H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 146.8, 111.8, 82.7, 81.5, 56.6, 51.7, 50.6, 31.6, 29.0, 26.9, 26.4, 23.5, 22.8, 19.1, 18.5 (x3), 18.4 (x3), 13.4 (x3);

R_f = 0.63 (Hexane : Ethyl Acetate = 5 : 1)

FTIR (neat, cm^{-1}): ν 3074, 2943, 1643, 1463, 1380, 1097;

HRMS (ESI, m/z M +Na] Calcd (Found) for C23H44NaO2Si: 403.3008 (403.3026).



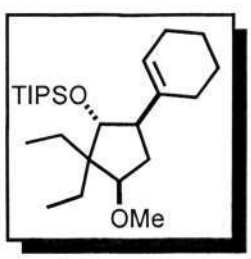
^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.49 (1H, m), 3.99 (1H, d, *J* =7.5 Hz), 3.26 (3H, s), 3.16 (1H, dd, *J* = 3.2, 4.8Hz), 2.45-2.40 (1H, m), 2.11-2.04 (1H, m), 2.00-1.92 (4H, m), 1.63-1.52 (3H, m), 1.46-1.41 (1H, m), 1.08-1.04 (22H, m), 0.99 (3H, s), 0.93 (3H, s);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.1, 122.9, 88.1, 81.5, 57.0, 52.9, 46.6, 31.8, 25.4, 25.1, 23.0, 22.6, 21.2, 18.5 (x3), 18.4 (x3), 17.8, 13.3(x3);

R_f = 0.67 (Hexane : Ethyl Acetate = 5 : 1)

FTIR (neat, cm^{-1}): ν 3159, 2943, 1687, 1463, 1378, 1093;

HRMS (EI, m/z M +Na] Calcd (found) for C23H44NaO2Si: 403.3008 (403.3026).



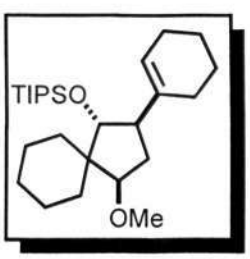
^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.49 (1H, brs), 4.12 (1H, dd, *J* = 7.2 Hz), 3.33 (1H, t, *J* = 5.2 Hz), 3.24 (3H, s), 2.48-2.42 (1H, m), 2.06-1.94 (5H, m), 1.65-1.52 (6H, m), 1.49-1.34 (3H, m), 1.08-1.06 (21H, m), 0.93 (3H, t, *J* = 7.6 Hz), 0.87 (3H, t, *J* = 7.6 Hz);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.4, 122.9, 85.9, 82.0, 56.5, 53.1, 51.3, 31.9, 25.4, 25.1, 24.8, 24.3, 23.0, 22.6, 18.5 (x6), 13.5 (x3), 9.4, 9.2;

R_f = 0.70 (Hexane : Ethyl Acetate = 5 : 1)

FTIR (neat, cm^{-1}): ν 3162, 2942, 1663, 1463, 1382, 1093;

HRMS (EI, m/z M+H] Calcd (Found) for $C_{25}H_{48}O_2Si$: 409.3502 (409.3498)



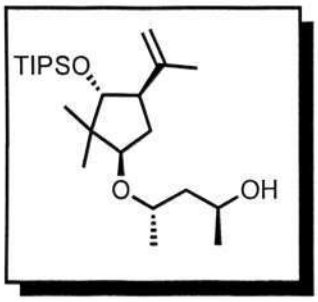
^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.47 (1H, m), 3.97 (1H, d, *J* = 10 Hz), 3.48 (1H, dd, *J* = 1.0, 6.5 Hz), 3.25 (3H, s), 2.50-2.43 (1H, m), 2.09-1.93 (5H, m), 1.78-1.45 (11H, m), 1.37-1.15 (4H, m), 1.06-1.05 (21H, m);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.4, 123.1, 82.5, 81.4, 56.6, 52.0, 50.5, 31.3, 29.2, 26.8, 26.4, 25.5, 24.7, 23.6, 23.0, 22.8, 22.7, 18.6 (x3), 18.5 (x3), 13.5 (x3);

R_f = 0.67 (Hexane : Ethyl Acetate = 5 : 1)

FTIR (neat, cm^{-1}): ν 3156, 2940, 1715, 1465, 1383, 1095;

HRMS (ESI, m/z (M + H] Calcd (Found) for $C_{26}H_{49}O_2Si$: 421.3502 (421.3497).



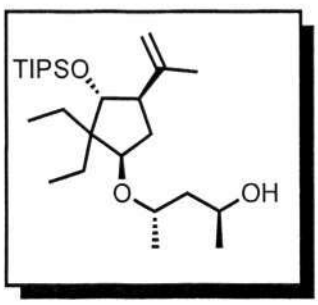
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.77 (1H, brs), 4.73 (1H, brs), 4.15-4.09 (1H, brs), 3.83-3.79 (2H, m), 3.40 (1H, t, *J* = 8.4 Hz), 3,33 (1H, d, *J* = 3.6Hz), 2.65-2.58 (1H , m), 1.92-1.83 (1H, m), 1.76-1.71 (1H, m), 1.72 (3H, s), 1.68-1.56 (2H, m), 1.17 (6H, t, *J* = 6.8 Hz), 1.07-1.03 (24H, m), 0.85 (3H, s);

^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 146.2, 111.9, 81.4, 81.0, 71.4, 64.6, 51.1, 45.6, 44.2, 33.2, 25.3, 23.3, 19.6, 18.9, 18.4 (x3), 18.3 (x3), 14.7, 13.3 (x3);

R_f = 0.43 (Hexane : Ethyl Acetate = 5 : 1)

FTIR (neat, cm^{-1}): 3392, 2867, 1464;

HRMS (ESI, m/z (M+H)] calcd (found) for $C_{24}H_{48}O_3Si$**:** 413.3451 (413.3460)



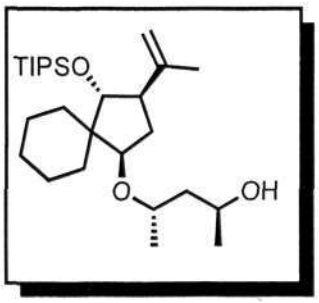
^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.77 (1H, brs), 4.74 (1H, brs), 4.13-4.10 (1H, m), 4.01 (1H, d, *J* = 5.2 Hz), 3.85-3.81 (1H, m), 3.59 (1H, t, *J* = 4.4 Hz), 3.14 (1H, d, *J* = 4.4 Hz), 2.82-2.76 (1H, m), 2.09-2.02 (1H, m), 1.78-1.70 (1H, m), 1.72 (3H, m), 1.61 (1H, t, *J* = 5.6Hz), 1.55-1.52 (1H, m), 1.43-1.23 (4H, m), 1.17 (3H, d, *J* = 6.4 Hz), 1.40 (3H, d, *J* = 6.4 Hz), 1.05 (21H, brs), 0.88 (6H, dt, *J* = 1.6, 7.2 Hz);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.3, 110.5, 80.8, 79.4, 69.6, 64.6, 54.7, 52.4, 44.8, 33.7, 26.3, 23.4, 20.8, 19.6, 18.4 (x3), 18.4 (x3), 17.7, 13.1 (x3), 12.3, 9.02, 8.20;

R_f = 0.43 (Hexane : Ethyl Acetate = 5 : 1)

FTIR (neat, cm^{-1}): 2963, 1457, 1067;

HRMS (ESI, m/z (M+H)] calcd (found) for $C_{26}H_{52}O_2Si$**:** 441.3764 (441.3760)



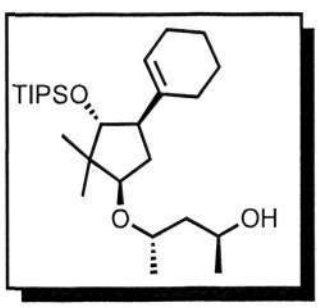
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.79 (1H, brs), 4.75 (1H, brs), 4.17-4.12 (1H, m), 4.07 (1H, d, *J* = 7.2 Hz), 3.84-3.79 (2H, m), 2.56-2.51 (1H, m), 2.21-2.14 (1H, m), 1.75 (3H, s), 1.69-1.27 (10H, m), 1.20 (3H, d, *J* = 6.4 Hz), 1.17 (3H, d, *J* = 6.4 Hz), 1.05 (21H, s), 0.90-0.83(4H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 146.7, 111.3, 80.6, 77.9, 77.2, 70.4, 64.2, 51.4, 49.9, 44.5, 32.9, 28.7, 27.2, 26.2, 23.6, 23.1, 22.9, 20.3, 18.5 (x3), 18.5 (x3), 13.4 (x3);

R_f = 0.44 (Hexane : Ethyl Acetate = 5 : 1)

FTIR (neat, cm^{-1}): 2941, 1663, 1382, 678;

HRMS (ESI, m/z (M+H)] calcd (found) for $C_{27}H_{52}O_3Si$**:** 453.3764 (453.3759)



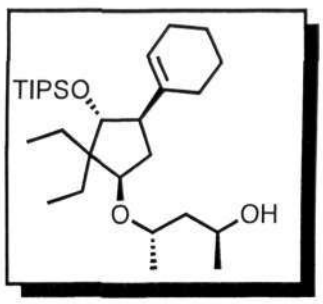
^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.50 (1H, t, *J* = 3.5 Hz), 4.15-4.11 (1H, m), 3.95 (1H, d, *J* = 7.0 Hz), 3.81-3.78 (1H, m), 3.47 (1H, t, *J* = 6.0 Hz), 3.40 (1H, d, *J* = 2.5 Hz), 2.93-2.34 (1H, m), 2.13-2.07 (1H, m), 2.00-1.94 (4H, m), 1.70-1.51 (6H, m), 1.43-1.37 (1H, m), 1.17 (3H, d, *J* = 1.5 Hz), 1.16 (3H, d, *J* = 1.5 Hz), 1.05-1.04 (21H, m), 0.95 (3H, s), 0.93 (3H, s);

^{13}C NMR ($CDCl_3$, 100 MHz): **δ** 137.9, 122.5, 77.1, 83.1, 81.3, 71.4, 64.4, 53.0, 45.8, 44.2, 33.2, 26.0, 25.4, 23.5, 23.0, 22.6, 21.5, 21.4, 18.4 (x3), 18.3 (x3), 13.2 (x3);

R_f = 0.46 (Hexane : Ethyl Acetate = 5 : 1)

FTIR (neat, cm^{-1}3182, 1643, 1380, 1073;

HRMS (ESI, m/z (M+H)] calcd (found) for $C_{27}H_{52}NaO_3Si$**:** 475.3583 (475.3665).



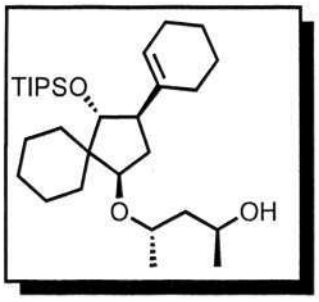
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.50 (1H, t, *J* = 3.5 Hz), 4.12-4.10 (1H, m), 3.95(1H, d, *J* = 4.8 Hz), 3.84-3.81 (1H, m), 3.56 (1H, t, *J* = 4.4 Hz), 3.18 (1H, d, *J* = 3.6 Hz), 2.71-2.66 (1H, m), 2.00-1.90 (5H, m), 1.72-1.66 (1H, m), 1.64-1.52 (5H, m), 1.43-1.40 (1H, m), 1.34-1.28 (3H, m), 1.17 (3H, d, *J* = 4.8 Hz), 1.14 (3H, d, *J* = 4.8 Hz), 1.07-1.05 (21H, m), 0.90-0.86 (6H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz): **δ** 138.4, 122.3, 80.4, 79.0, 77.2, 69.6, 64.6, 54.7, 51.7, 44.7, 33.1, 26.5, 25.8, 25.4, 23.3, 23.0, 22.5, 19.9, 18.5 (x3), 18.4 (x3), 13.3 (x3), 9.17, 8.24;

R_f = 0.45 (Hexane : Ethyl Acetate = 5 : 1)

FTIR (neat, cm^{-1}): 3279, 1464, 734;

HRMS (ESI, m/z (M+Na)] calcd (found) for C29H56NaO3Si**:** 503.3896(503.3894).



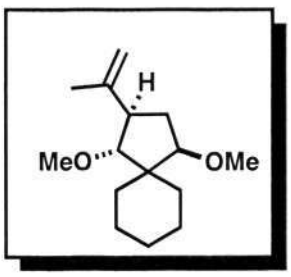
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.50 (1H, t, *J* = 3.5Hz), 4.13-4.07 (1H, m), 3.85-3.80 (1H, m), 3.73-3.71 (1H, m), 3.16 (1H, d, *J* = 4.8 Hz), 2.65-2.65 (1H, m), 1.99-1.77 (6H, m), 1.64-1.33 (17H, m), 1.18 (3H, d, *J* = 6.8 Hz), 1.16 (3H, d, *J* = 6.5 Hz), 1.06 (21H, brs);

^{13}C NMR ($CDCl_3$, 75.4 MHz): **δ** 137.9, 122.6, 82.7, 80.8, 69.6, 64.7, 54.4, 49.0, 44.9, 36.3, 32.7, 26.7, 26.3, 25.8, 25.3, 23.4, 23.3, 23.1, 23.0, 22.6, 18.6, 18.5 (x3), 18.4 (x3), 13.3 (x3);

R_f = 0.46 (Hexane : Ethyl Acetate = 5 : 1)

FTIR (neat, cm^{-1}): 3145,1663, 1363, 997;

HRMS (ESI, m/z (M+Na)] calcd (found) for $C_{30}H_{56}NaO_3Si$**:** 515.3896 (515.3901).



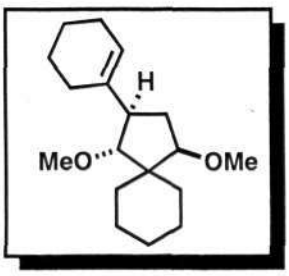
^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.55 (1H, brs), 3.43 (1H, dd, *J* = 3.6, 6.0 Hz), 3.36 (3H, s), 3.35 (1H, brs), 3.27 (3H, s), 2.52-2.47 (1H, m), 2.10-2.00 (5H, m), 1.76-1.73 (1H,m), 1.66-1.20 (14H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 139.3, 121.9, 89.3, 83.4, 59.4, 56.8, 49.8, 49.0, 31.6, 29.3, 27.9, 26.2, 25.5, 25.4, 23.3, 23.2, 22.8, 22.7;

R_f = 0.63 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1656, 1470, 1094, 650;

HRMS (ESI, m/z (M + H)] calcd (found) for $C_{15}H_{27}O_2$: 239.2011(239.2007).



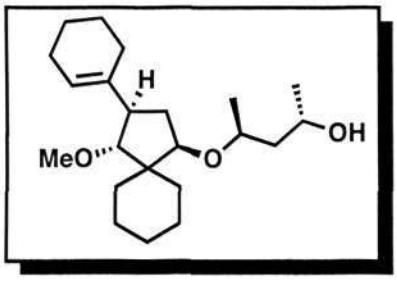
^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.55 (1H, brs), 3.43 (1H, dd, *J* = 3.6, 6.0 Hz), 3.36 (3H, s), 3.35 (1H, brs), 3.27 (3H, s), 2.52-2.47 (1H, m), 2.10-2.00 (5H, m), 1.76-1.73 (1H,m), 1.66-1.20 (14H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 139.3, 121.9, 89.3, 83.4, 59.4, 56.8, 49.8, 49.0, 31.6, 29.3, 27.9, 26.2, 25.5, 25.4, 23.3, 23.2, 22.8, 22.7;

R_f = 0.63 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 1647, 1418, 1385, 769;

HRMS (ESI, m/z (M +Na)] calcd (found) for $C_{18}H_{30}NaO_2$: 301.2144 (301.2129).



^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.54 (1H, brs), 4.12-4.08 (1H, m), 3.84-3.80 (1H, m), 3.55 (1H, d, J = 3.2 Hz), 3.28 (3H, s), 3.22 (1H, d, J = 4.4 Hz), 2.75-2.69 (1H, m), 1.99-1.90 (5H, m), 1.71-1.21 (18H, m), 1.18 (3H, d, J = 6.4 Hz), 1.13 (3H, d, J = 6.4 Hz);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 139.6, 120.6, 89.7, 82.7, 69.6, 64.2, 58.1, 52.5, 49.3, 44.6, 35.0, 32.5, 27.2, 27.1, 26.2, 25.4, 23.3, 23.1, 23.0, 22.9, 22.7, 18.5;

R_f = 0.38 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): ν 2989, 1650, 769;

HRMS (ESI, m/z (M+H)] for $C_{22}H_{39}O_3$: 351.2899 (351.2894).

Chapter 4

Synthetic Studies Towards the Total Synthesis of Grayanotoxin

4.1 BACKGROUND

4.1.1 Structural and Biological Aspects of Grayanotoxin

Grayanotoxin (Figure 4-1) is a toxin found in the pollen and nectar of plants belonging to the family *Ericaceae*, mainly in the genera *Rhododendrons*. It has long been known as "mad honey" in the Black Sea region in the first century B.C., commonly used as weapon against their enemy troops. Grayanotoxin poisoning has been documented to induce hallucination, delirium and incapacitation by laxative effects.[1]

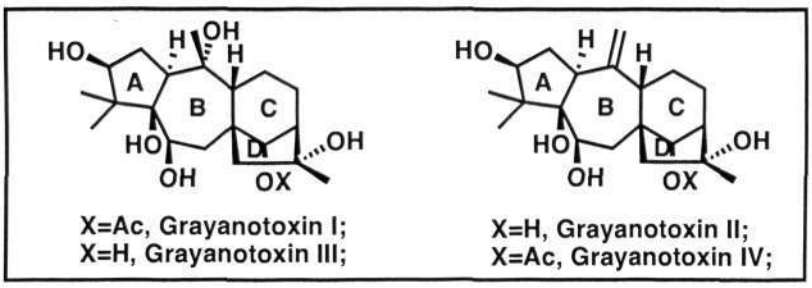


Figure 4-1

The first isolation of Grayanotoxin I, II and III[2] were reported in 1960's and Grayanotoxin IV[3] in 1990's. It is a unique class of neurotoxic polyhydroxylated cyclic diterpenoid with an unusual rigid tetracylic carbon framework. This class of neurotoxin has been found to interfere with the cell membranes transmission potential by binding to sodium channels.[4] Grayanotoxins prevents deactivation of the sodium channel, leaving excitable cells depolarized and increase the permeability of sodium ions in the excitable membranes. Symptoms associated with this effect are

[1] (a) Gossinger, H.; Hruby, K.; Pohl, A.; Davogg, S.; Sutterlutti, G.; Mathis, G. *Dtsch. Med. Wochenschr* **1983**, *108*, 1555; (b) Grunduz, A.; Turedi, S.; Uzun, H.; Topbas, M. *Am. J. Emerg. Med.* **2006**, *24*, 595.
[2] (a) Tallent, W. H.; Riethof, M. L.; Horning, E. C. *J. Am. Chem. Soc.*, **1957**, *79*, 4548; (b) Tallent, W. H. *J. Org. Chem*, **1964**, *29*, 2756.
[3] Burke, J. W.; Doskotch, R. W. *J. Nat. Prod.* **1990**, *53*, 131.
[4] Kimura, T.; Kinoshita, E.; Yamaoka, K.; Yuki, T.; Yakehiro, M.; Seyama, I. *FEBS Lett.* 465, *1*, 18.

hypotension, respiratory depression, altered mental status and in some cases, life threatening bradycardia.[5]

Their remarkable physiological activities and complicated structure distinguish these molecules as unusually attractive targets for total synthesis. In addition, grayanotoxins possess significant value in research as a pharmacological tool for probing the mechanism of sodium channels.

4.1.2 Reported Synthesis of Grayanotoxin

The first and only total synthesis of grayanotoxin was reported by Shirahama[6] in 1994. Shirahama has demonstrated an efficient synthesis of the molecule using the highly diastereoselective Diels-Alder reaction and SmI_2-mediated radical cyclization as the key steps.

Shirahama's strategy is shown in Scheme 4-1. Dienophile **2** was prepared in a practical synthetic route from commercially available starting material, ethyl (*S*)-lactate.[7] Thermal Diels-Alder reaction under neat condition afforded **3** in high yield. Rings D, A, and C were constructed *via* a SmI_2-mediated cyclization in three steps, with some alternate functional group interconversions and C-C bond formations to give Grayanotoxin **10**.

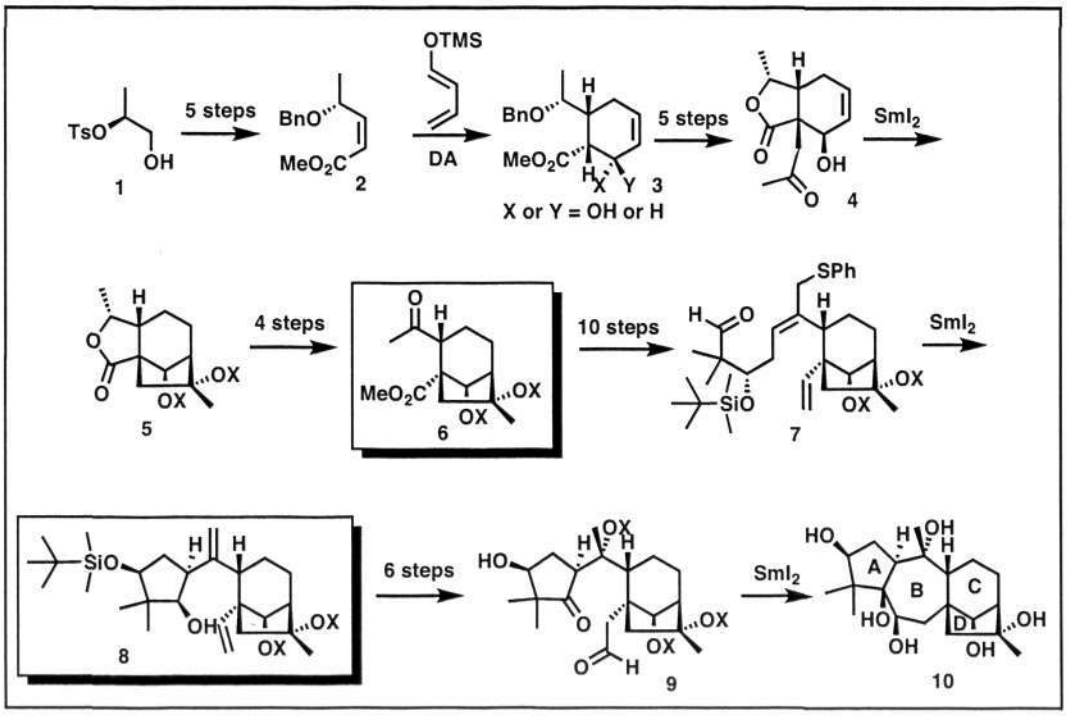
Shirahama's strategy hinges on the advantage of SmI_2-induced cyclization to construct rings A, C and D. Though the synthesis has been completed, their linear route narrowing its accessibility towards diversification and scaled-up synthesis.

---

[5] (a) Ozhan, H.; Akdemir, R.; Yazici, M.; Gunduz, H.; Duran, S.; Uyan, C. *Emerg. Med. J.* **2004**, *21*, 742; (b) Moran, N. C.; Dresel, P. E.; Perkins, M. E.; Richardson, A. P. *J. Phormacol. Exp. Ther.* **1954**, *110*, 415.

[6] (a) Kan, T.; Matsuda, F.; Yanagiya, M.; Shirahama, H. *Synlett.* **1991**, 391; (b) Kito, M.; Sakai, T.; Yamada, K.; Matsuda, F.; Shirahama, H. *Synlett.* **1993**, 158; (c) Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5532.

[7] Johnston, B. D.; Slessor, K. N. *Can. J. Chem.* **1979**, *57*, 233.

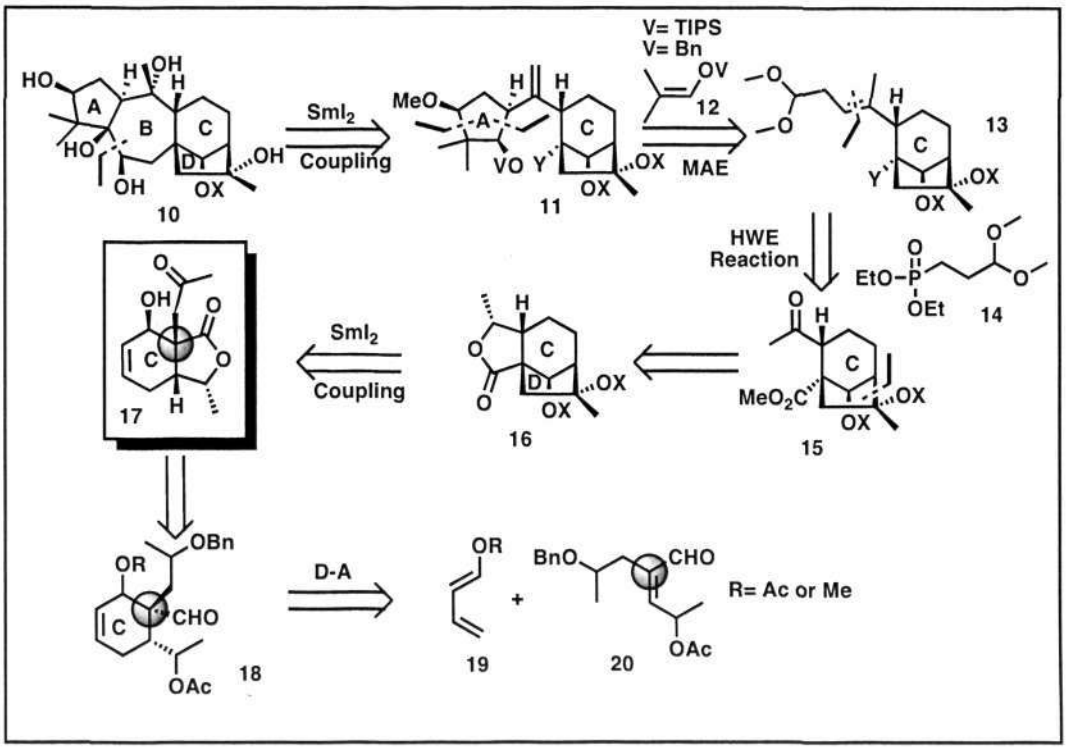


Scheme 4-1 Total synthesis of Grayanotoxin (Shirahama *et al.*)

4.2 RETROSYNTHETIC ANALYSIS OF GRAYANOTOXIN

4.2.1 First Generation

In the previous chapters, we demonstrated a highly efficient cascade process: The Mukaiyama-Aldol-Prins and Ene Type reaction, leading to the construction of five and six-membered ring systems. In conjunction with our interest in the natural product synthesis, we believe these novel strategies can be applied to the total synthesis of Grayanotoxins. The retrosynthetic analysis is delineated in Scheme 4-2.



Scheme 4-2 The first generation of retrosynthetic analysis

The key feature of our strategy is to construct ring A *via* an efficient cascade approach. This is contrary to Shirahama's ten steps linear synthesis, which constitutes a major drawback in terms of poor overall yield.

Ring B can be modeled after Shirahama's strategy by using SmI_2-induced cyclization. The five-membered ring A in **11** is constructed adopting our Mukaiyama-Aldol-Ene type protocol starting from silyl enol ether **12** and disubstituted acetal **13**.

Retrosynthetic cleavage of the indicated double bond in **13** furnished ketone **15** and precursor **14** *via* a classic Wittig reaction or Horner-Wadsworth-Emmons Olefination. Ring D in **16** can be envisioned from SmI_2 coupling as reported in Shirahama's strategy. Retro-Diels-Alder cyclization of ring C leads to commercially available diene **19** and a synthetically viable fragment: α,β-unsaturated dienophile **20**. Although we have demonstrated multifunctionalized Diels-Alder reaction on reactive

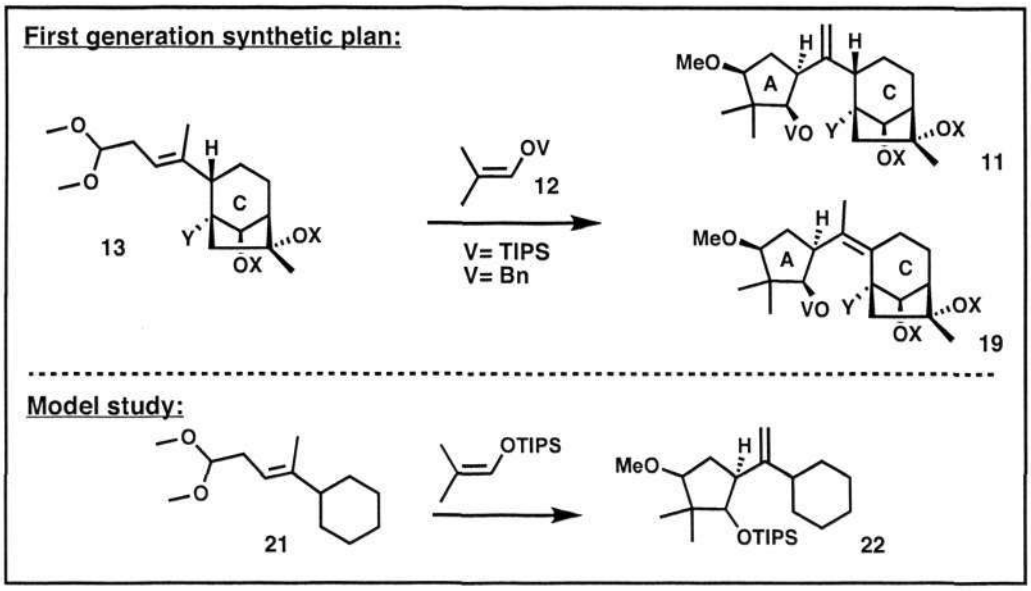
dienophiles (refer to Chapter 5), we envisaged that the assembly of these two fragments might pose a considerable level of difficulty due to the constrains imposed by differential reactivity of the dienophile and selectivity issues.

4.2.2 Synthesis

4.2.2.1 Model study

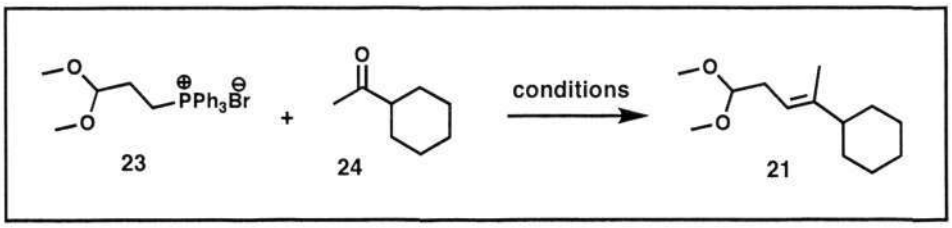
One of the highlights in this formal synthesis is the demonstration of the versatility of $TiBr_4$-catalyzed Mukaiyama-Aldol-Ene-Type reaction applied to natural product synthesis. Although we have demonstrated that our Mukaiyama-Aldol-Ene reaction methodology was tolerant to a wide range of silyl enol ethers and disubstituted acetals substrate,[8] the coupling of fragments **12** and **13** was deemed to be synthetically challenging (Scheme 4-3). Two different substituents on the terminal double bond of acetal **13** might cause discrepancy. The cascade reaction could be terminated *via* two possible pathways: giving either **11** (desired product) or **19** (undesired product) as shown in Scheme 4-3. Hence, it was crucial to perform a model study before executing the formal synthesis of Grayanotoxin **10**. A simpler version of disubstituted acetal **21** was designated for the model study.

[8] For demonstration Mukaiyama-Aldol-Ene reaction on simple silyl enol ethers and disubstituted acetals, refer to Chapter 3 in this thesis.



Scheme 4-3

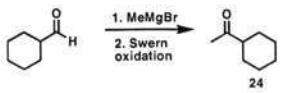
The synthesis of intermediate **21** was attempted using Wittig reaction in the presence of base (e.g. *t*-BuOK and *n*-BuLi), under various reaction conditions (-78 °C, -10 °C or room temperature). Unfortunately, no desired product was isolated.



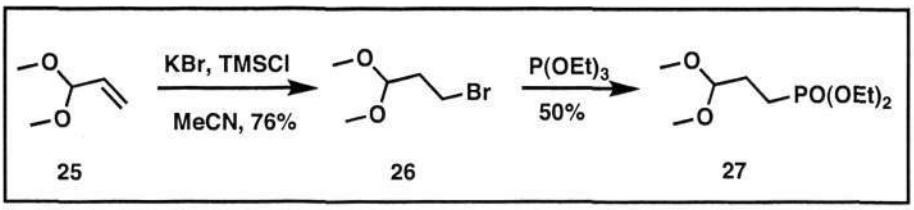
Scheme 4-4 Preparation of acetal **21**[9]

In our attempts to synthesize **21**, the Horner-Wadsworth-Emmons (HWE) reaction was employed as an alternative. It has been reported that there are significant advantages of utilizing phosphonate carbanion over the traditional triphenyl

[9] Ketone **24** was prepared in two steps as described bellow:



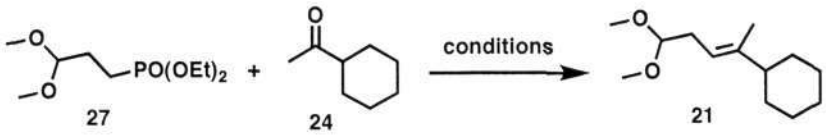
phosphorous ylides in the Wittig reaction.[10] The phosphonate **27** was synthesized in two steps with moderate yield as shown in Scheme 4-5.[11]



Scheme 4-5

With ample amounts of phosphonate **27** in hand, we screened various HWE conditions as summarized in Table 4-1. In most cases, only trace or no desired product was obtained. Based on the structural analysis of **21**, we believe that the failure could be attributed to the bulkiness of the cyclohexyl ring and constraints imposed on the bond formation by steric hindrance from the adjacent methyl moiety.

Table 4-1 Preparation of acetal for model study using HWE reaction



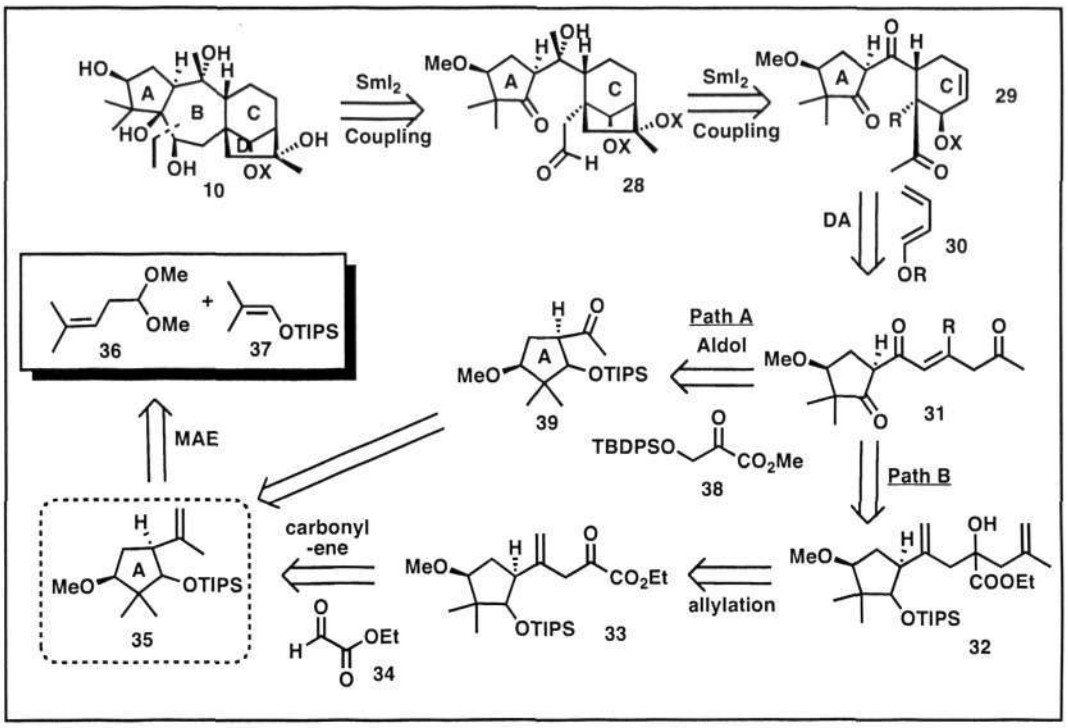
Entry	Base	Temperature (°C)	Time (h)	Yield
1	*t*-BuOK	-10	2	Trace
2	*t*-BuOK	0	2	Trace
3	*t*-BuOK	25	2	-
4	*n*-BuLi	-78 to 25	12	-

[10] Maryanoff, B. M.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
[11] Arbuzov, A. *J. Russ. Phys. Chem. Soc.* **1906**, *38*, 687.

The failure to obtain intermediate **21** for model study outweighed the advantages that were proposed earlier. However, this setback did not discourage us to continue the synthesis of Grayanotoxin. A second generation retrosynthetic strategy is proposed in the next section.

4.2.3 Second Generation Retrosynthesis

Similar to the first generation retrosynthesis, we adopted SmI_2 mediated coupling to construct the ring B and D in **10** and **28** respectively (Scheme 4-6).



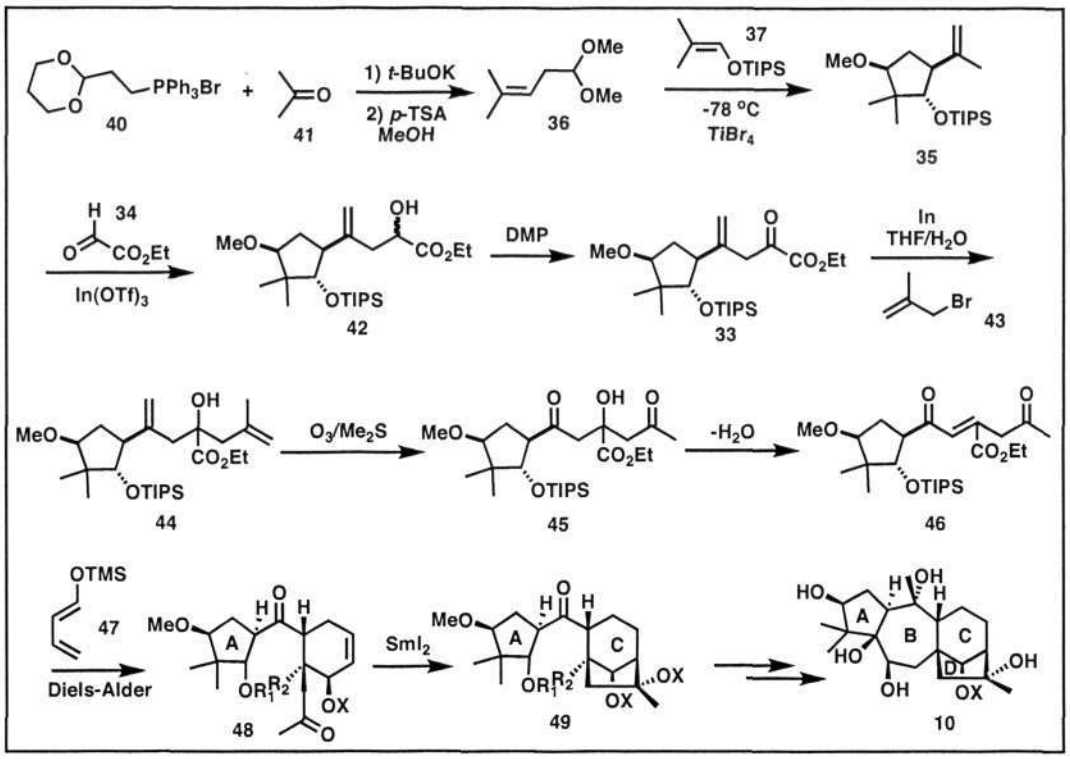
Scheme 4-6

The key subunit in intermediate **28** is a six-membered ring, which can be generated from a classic Diels-Alder reation with diene **30** and dienophile **31** respectively. Dienophile **31** can be derived in two ways. Pathway A employs aldol

reaction between ketone **39** and glycolate **38**[12] as developed by Evans.[13] Pathway B uses carbonyl-ene (**33**) and allylation (**32**) to elongate the carbon chain as established in our group.[14,15] Both pathways will share a common intermediate **35**, which can be further disconnected into silyl enol ether **37** and disubstituted acetal **36** *via* Mukaiyama-Aldol-Ene cascade reaction.

4.3 SYNTHETIC STUDIES ON GRAYANOTOXIN 10

The forward synthethic plan of Grayanotoxin **10** is outlined in Scheme 4-7.

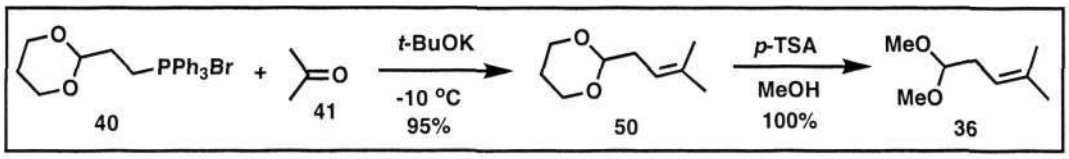


Scheme 4-7

[12] Choi, D.; Stables, J. P.; Kohn, H.; *Bioorg. Med. Chem.* **1996**, *4*, 2105.
[13] Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686.
[14] Zhao, J.-F.; Tsui, H.-Y.; Wu, P.-J.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.* **2008**, *130*, 16492.
[15] Loh, T. P.; Huang, J.-M.; Xu, K.-C.; Goh, S.-H. *Tetrahedron Lett.* **2000**, *41*, 6511.

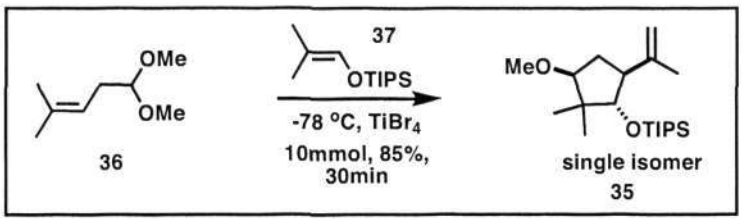
4.3.1 Synthesis of dimethyl acetal 36

Our convergent strategy commences with the synthesis of a dimethyl acetal **36** from a commercially available Wittig salt **40**[16] and acetone **41** in the presence of potassium *t*-butoxide, which was subsequently subjected to re-acetalation to form acylic acetal **36** (95% yield, 2 steps, Scheme 4-8).



Scheme 4-8

4.3.2 Mukaiyama-Adol-Ene reaction



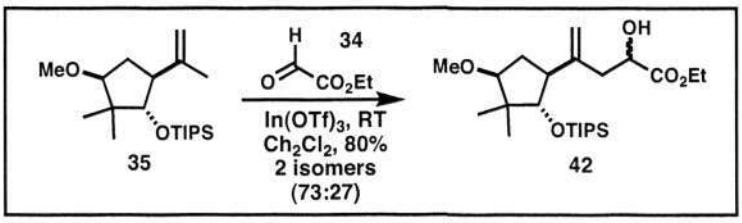
Scheme 4-9

In our previous works, we demonstrated the highly efficient, diastereoselective and enantioselective Mukaiyama-Aldol-Ene type reaction catalyzed by $TiBr_4$. Acetal **36** and silyl enol ether **37** were subjected to Mukaiyama-Aldol-Ene type cascade reaction to give the desired five-membered ring product **35** in high yield and stereoselectivity. It is also worthy to note that the cascade reaction can be performed in large scale, up to 50 mmol without any lose in yield and diastereoselectivity (Scheme 4-9).

[16] CAS: 69891-92-5

4.3.3 Synthesis of Dienophile 46 - Pathway B

4.3.3.1 Carbonyl-ene reaction



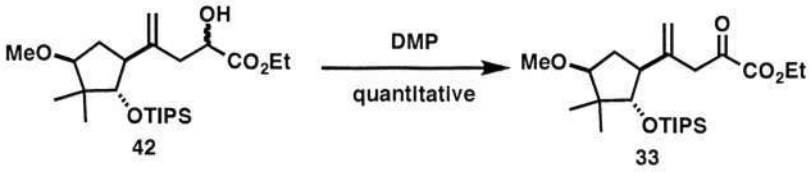
Scheme 4-10

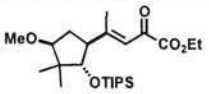
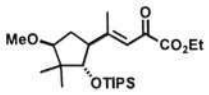
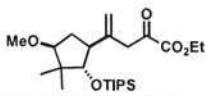
$In(OTf)_3$ catalyzed carbonyl-ene reaction has been well established by our research group. Reaction of the alkene intermediate **35** and ethyl glyoxylate **34** in the presence of $In(OTf)_3$ generated the desired product **42** in high yield with moderate selectivity (Scheme 4-10).

4.3.3.2 Oxidation

The isolated alcohol **42** was first subjected to pyridinyl chlorochromate (PCC) oxidation to form the corresponding pyruvate **33**, but proved to be unsuccessful. Swern oxidation was subsequently employed to no avail. Eventually oxidation with Dess-Martin periodinane (DMP) proceeded smoothly to give **33**. The difficulties encountered in this oxidation was mainly attributed to the instability of **33**, where the double bond easily rearranges to a conjugated product (entries 1 and 2, Table 2). We also found that **33** is unstable on silica gel. Rearrangement occurs during purification by flash column chromatography. The reaction mixture from DMP oxidation was filtered and carried forward to the next step without further purification. Quantitative yield assumed.

Table 4-2



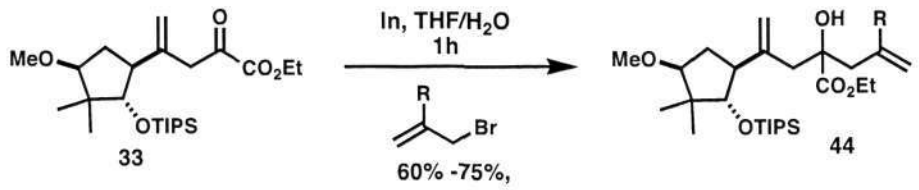
Entry	Oxidant	Product	Yield
1	PCC		-
2	Swern		-
3	DMP		quantitative

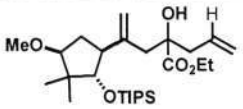
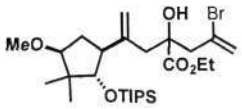
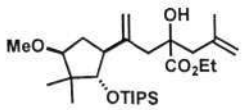
4.3.3.3 Allylation Reaction

With pyruvate **33** in hand, we investigated various allylation methodology studies. Three allyl bromides were screened using the well-established allylation methods developed by our research group.[17] The results are summarized in Table 4-3. In our case, a highly selective transformation was not necessary. As chiral centre in the tertiary alcohol would be eventually destroyed in the subsequent synthetic steps. The advantageous utility of these series of compounds lie in the versatility of their double bond, which can be easily transformed to the aldehyde (Entry 1, Table 3), ester (Entry 2, Table 3) or ketone (Entry 3, table 3) functionalities respectively.

[17] Loh, T. P.; Huang, J.-M.; Xu, K. C.; Goh, S.-H. *Tetrahedron Lett*, **2000**, *41*, 6511.

Table 4-3

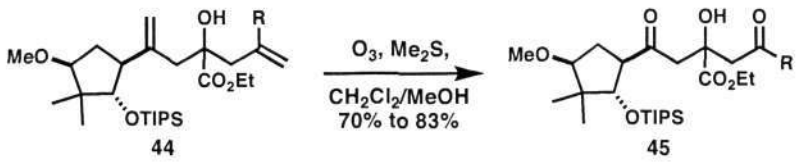


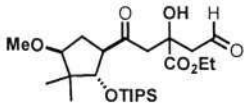
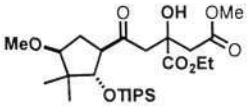
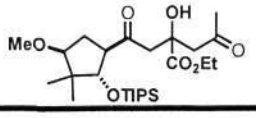
Entry	R	Product	Yield (%)	*Dr*
1	H		63	64:36
2	Br		60	60:40
3	Me		75	63:37

4.3.3.4 Ozonolysis

Ozonolysis of compound **44** was achieved upon treatment with ozone followed by dimethyl sulfide treatment to give **45** with yields ranging from 70-83%.

Table 4-4

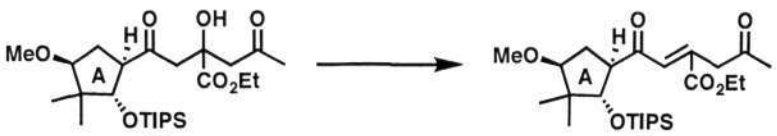


Entry	R	Product	Yield (%)
1	H		76
2	Br		70
3	Me		83

4.3.3.5 Dehydration[18]

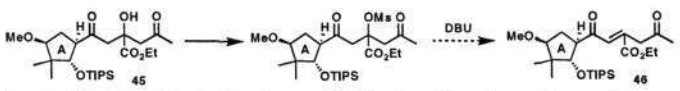
The synthesis proceeded smoothly until the dehydration step. Several kinds of dehydration methods were experimented as shown in Table 4-4. Acidic conditions failed to initiate dehydration. When pyridine-$SOCl_2$ was used as solvent, dehydration products were obtained in 30% yield. $(Boc)_2O$ and DMAP in CH_2Cl_2 as solvent was the most desirable condition, yielding 80% of desired product as a mixture of chromatographically inseparable isomers (*dr* = 2:1) as shown by ^1H NMR. We hypothesize that the carbonyl group in the Boc group is less bulky as compared to that of the sulfonyl counterpart in the mesyl group, imparting greater accessibility to the quaternary carbon center of compound **41**.

Table 4-5



Entry	Reagent	Solvent	Time (h)	Yield (%)	Comment
1	*p*-TSA	CH_2Cl_2	12	-	S.M remain
2	*p*-TSA	Benzene	12	-	S.M remain
3	*p*-TSA	Toluene	12	-	S.M remain
4	Py-$SOCl_2$	Pyridine	5	30	S.M remain partially
5	$(Boc)_2O$, DMAP	CH_2Cl_2	12	80	Two isomers *dr* = 67:33

18

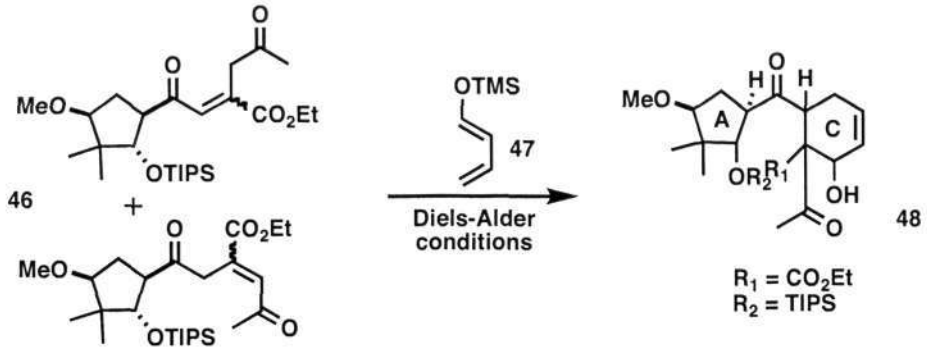


An indirect method also been tried, steps involves the replacement of hydroxyl group by mesyl group which is then attempted for elimination by DBU. Unfortunately, the elimination reaction did not work.

4.3.4 Diels-Alder Reaction

The two chromatographically inseparable dienophiles **46** were used for the Diels-Alder reaction without further purification. Two conditions were tried with commercial available diene **47** (Table 5). Heating the mixture of dienophile **46** and diene **47** in a seal tube at 160 °C for 16 hours afforded cyclized product **48** in low yield and poor diastereoselectivity (~4 isomers observed in ^{1}H NMR). Additionally, the Diels-Alder methodology developed by Shibasaki[19] employing a Ba(i-PrO)$_2$ and CsF combination was not viable. Lewis acid conditions such as $BF_3.OEt_2$ and In(OTF)$_3$ did not offer any product but resulted in diene decomposition.

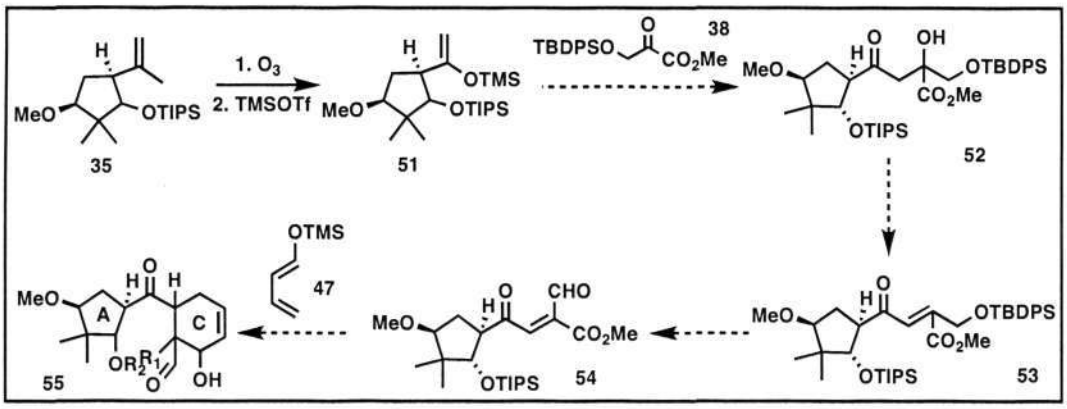
Table 4-6



Entry	Condition	Result
1	Toluene, Hydroxyquinone, Seal tube (160 °C), 16h,	30% (4 inseparable isomers)
2	Ba(i-PrO)$_2$, CsF, -20 °C, 3days	No reaction
3	$BF_3.OEt_2$ or In(OTf)$_3$	No reaction

[19] Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 1070.

4.4 FUTURE WORK: EVANS ALDOL REACTION (PATHWAY A)



Scheme 4-11

Although we are able to construct the desired A and C rings of Grayanotoxin **10**, low yield and poor selectivity was obtained. In our proposed pathway A, we intend to adopt Evans's catalytic enantioselective aldol addition of enolsilanes to pyruvate ester. The availability of intermediate **35**, obtained in high yield and selectivity from MAE cyclization, was subjected to ozonolysis to give the ketone derivative which was subsequently transformed to a silyl enol ether using TMSOTf. Attempts to perform the Evan's aldol reaction by incorporation of pyruvate type ester **38**[20] in the presence of $Cu(OTf)_2$ failed to give the desired product.

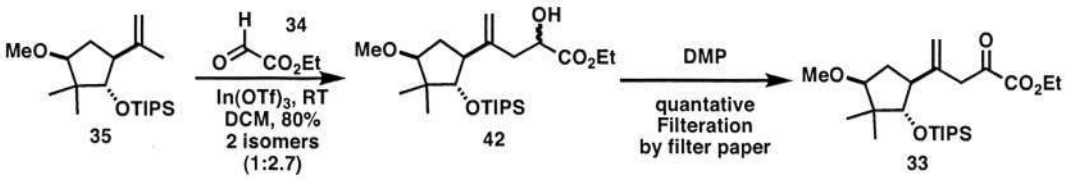
Prior to the discovery of the advantageous of aldehyde-ester **54** as a reactive dienophile in Diels-Alder cyclization (chapter 5), the chance of obtaining product **55** in good yield and selectivity is feasible. Effort along pathway A is currently in progress in our research group.

20

Pyruvate ester **38** was synthesized in 3 steps from methyl acrylate.

4.5 EXPERIMENTAL

Ene reaction and Dess-Martin Oxidation Reaction



Into a 250 ml oven dried round bottom flask equipped with magnetic stirrer, compound **35** (6.80 g, 20 mmol, 1 equiv.) and ethyl glyoxylate (8.30 g) were added with DCM (150 ml) as solvent. After that, $In(OTf)_3$ (1.12 g, 2 mmol, 0.1 equiv.) was added as catalyst of the reaction. The reaction mixture was allowed to stir at room temperature for 3 hours after which the reaction mixture was extracted three times with diethyl ether. The combined organic extracts were washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in *vacuo*, and the yellowish liquid was purified using flash column chromatography with 15% ethyl acetate/hexanes to give the colorless products **42** (6.67 g, 15 mmol, 75% yield).

Two isomers could not be separated by column, the mixture was carried forward to the next step without structural characterization.

Into a 250 ml oven dried round bottom flask equipped with magnetic stirrer, compound **42** (6.67 g, 15 mmol, 1 equiv) and Dess Martin reagent (7.00 g, 16.5 mmol, 1.1 equiv.) was added with dry DCM (100 ml) as solvent. The reaction mixture was allowed to stir at room temperature for 20 minutes and then subjected simple filtration for 3~4 times to eliminate the Dess-Martin reagent. The solvent was removed in vacuo, and the yellowish crude product was directly taken into the next step without any further purification.

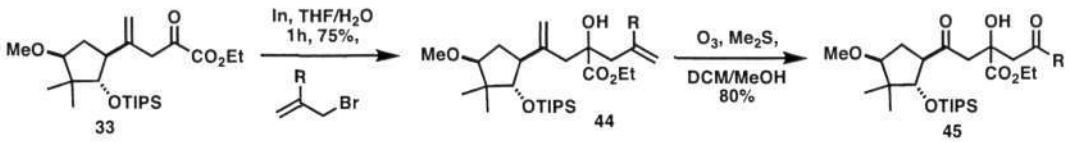
^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.13 (1H, brs), 4.84(1H, brs), 4.31(2H, q, J = 7.2 Hz), 4.01(1H, d, J = 6.8 Hz), 3.64 (1H, d, J = 16.4 Hz), 3.47(1H, d, J = 16 Hz), 3.25 (3H, s), 3.17 (1H, q, J = 3.2 Hz), 2.64-2.58(1H, m), 2.26-2.17(1H, m), 1.54-1.49(1H, m), 1.36(3H, t, J = 7.2 Hz), 1.04 (21H, brs), 1.00 (3H, s), 0.92 (3H, s);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.5, 161.4, 142.6, 115.9, 88.1, 82.6, 62.4, 57.0, 52.5, 47.0, 43.6, 32.3, 20.9, 20.8, 18.4 (x3), 18.3 (x3), 14.0, 13.3 (x3);

R_f = 0.63 (Hexane : Ethyl Acetate = 5:1);

HRMS (EI, m/z (M - C_3H_7)$^+$] Calcd (Found) for $C_{24}H_{44}O_5Si$: 397.20 (397.18).

Allylation Reaction and Ozonolysis



Into a 250 ml oven dried round bottom flask equipped with magnetic stirrer, crude product of compound **33**, indium powder (2.59 g, 22.5 mmol, 1.5 equiv.) and 3-bromo-2-methylprop-1-ene (6.07 g, 45 mmol, 3 equiv.) was added with H_2O/THF (1:1, 150 ml) as solvent. The reaction mixture was allowed to stir at room temperature over night. The reaction mixture was was extracted three times with diethyl ether and the combined organic extracts were washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the crude product was purified using flash column chromatography with 10% ethyl acetate/hexanes to give the colorless compound **44** (5.07 g, 10.2 mmol, 68% yield). Two isomers could not be separated by column chromatography, the mixture was carried forward to the next step without structural characterization.

Into a 250 ml oven dried round bottom flask equipped with magnetic stirrer, compound **44** (2.50g, 5.0 mmol, 1 equiv.) was added with MeOH/DCM (1:10, 100ml) as solvent. The mixture was then allowed to cool down to -78 °C using dry ice / acetone bath after which O_3 gas was directed in to the reaction system constantly using O_3 generator for 10 minutes until the color of the solution turned light blue. PPh_3 (3.14 g, 12 mmol, 2.4 equiv.) was then added into the solution and the reaction mixture was allowed to rise to room temperature over 1 hour. The reaction mixture was then allowed to stir over night. The reaction mixture was extracted three times with DCM and the combined organic extracts were washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the crude product was purified using flash column chromatography with 40 % ethyl acetate/hexanes to give the colorless compound **45a** (1.125 g, 2.25mmol, 45% yield) and **45b** (0.92 g, 1.85 mmol, 37% yield).

Major isomer

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.37 (1H, d, J = 4.8 Hz), 4.27 (1H, bs), 4.24-4.18 (2H, m), 3.32 (1H, t, J = 5.6 Hz), 3.27 (3H, s), 3.07 (1H, d, J = 16.8 Hz), 2.93-2.81 (4H, m), 2.41-2.33 (1H, m), 2.19 (3H, s), 1.62-1.55 (1H, m), 1.26 (3H, t, J = 7.2 Hz), 1.06-1.02 (21H, m), 0.96 (3H, s), 0.87 (3H, s);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.1, 206.7, 173.8, 87.4, 78.4, 73.9, 62.0, 58.0, 57.6, 50.6, 48.8, 46.8, 31.7, 30.2, 21.2, 19.8, 18.3 (x3), 18.2 (x3), 14.0, 13.3 (x3);

R_f = 0.33 (Hexane : Ethyl Acetate = 1:1);

FTIR (neat, cm^{-1}): ν 3448 (br), 2944, 1734, 1715, 1710, 1463, 1385;

HRMS (EI, m/z (M - C_3H_7)$^+$] Calcd (Found) for $C_{26}H_{48}O_7Si$: 501.31 (501.02).

Minor isomer

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.37 (1H, d, J = 4.8 Hz), 4.26-4.17 (3H, m), 4.24-4.18 (2H, m), 3.31 (1H, t, J = 5.6 Hz), 3.25 (3H, s), 3.01-2.76 (5H, m), 2.40-2.33 (1H, m), 2.18 (3H, s), 1.61-1.54 (1H, m), 1.27 (3H, t, J = 7.2 Hz), 1.06-1.02 (21H, m), 0.95 (3H, s), 0.86 (3H, s);

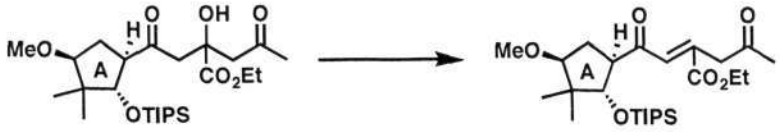
^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.1, 206.7, 173.8, 87.4, 78.4, 73.9, 62.0, 58.0, 57.6, 50.6, 48.8, 46.8, 31.7, 30.2, 21.2, 19.8, 18.3 (x3), 18.2 (x3), 14.0, 13.3 (x3);

R_f = 0.4 (Hexane : Ethyl Acetate = 1:1);

FTIR (neat, cm^{-1}): ν 3510 (br), 2941, 1734, 1719, 1703, 1465, 1388;

HRMS (EI, m/z (M - C_3H_7)$^+$] Calcd (Found) for $C_{26}H_{48}O_7Si$: 501.31 (500.94).

Dehydration Reaction



45 46

Into a 50 ml oven dried round bottom flask equipped with magnetic stirrer, compound **45** (0.50 g, 1 mmol, 1 equiv.), $(Boc)_2O$ (0.54 g, 2.5 mmol, 2.5 equiv.) and DMAP (0.18 g, 1.5 mmol, 1.5 equiv.) was added with dry DCM (15ml) as solvent. The reaction mixture was allowed to stir for 12 hrs and then extracted three times with DCM and the combined organic extracts were washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the crude product was purified using flash column chromatography with 40 % ethyl acetate/hexanes to give slightly red inseparable mixture of compound **46a** & **46b** (0.34 g, 0.7 mmol, 70% yield).

PART II

Chapter 1

Synthetic Studies Towards The Total Synthesis of Cytochalasans

1.1 BACKGROUND

Cytochalasans **1** (Figure 1-1) are a group of fungal secondary metabolites, related by their chemical structure and biological properties.[1] It was discovered by the Pharmaceuticals Division of Imperial Chemicals Industries in 1964. The name cytochalasin comes from the Greek words (cytos = cell; chalasis = relaxation) and is coined to describe the unique response which the compounds incite on mammalian cells in tissue culture.[2] Some distinctive biological effects including cytotoxicity,[3] antibiotic[4] and antitumor activities,[5] CNS activity,[6] inhibitory activity against the HT29 colonic adenocarcinoma cell line,[7] inhibit growth and sugar uptake,[8] In addition, some have been recognized for their potential as mycotoxins[9] (Figure 1-2).

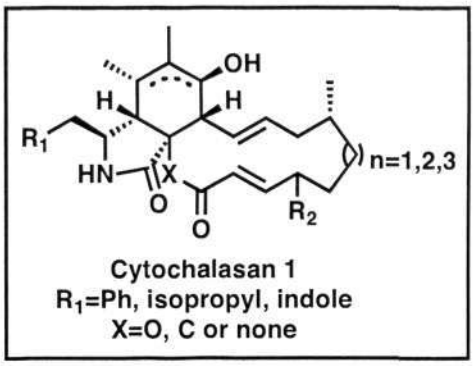


Figure 1-1 General structure of cytochalasan

[1] (a) Aldridge, D. C.; Armstrong, J. J.; Speaks, R. N.; Turner, W. B. *J. Chem. Soc.* **1967**, 1667; (b) Aldridge, D. C.; Turner, W. B. *J. Chem. Soc.* **1969**, 923; (c) Aldridge, D. C.; Burrows, F. F.; Turner, W. B. *Chem. Commun.* **1972**, 148; (d) Aldridge, D. C.; Greatbanks, D.; Turner, W. B. *Chem. Commun.* **1973**, 551; (e) Pendse, G. S. *Experientia* **1974**, *30*, 107; (f) Padwardhan, S. A.; Pandey, R. C.; Dev, S.; Pendse, G. S. *Phytochemistry* **1974**, *13*, 1985; (g) Deshmukh, P. G.; Kanitkar, U. K.; Pendse, G. S. *Acta Microbiol. Acad. Sci. Hung.* **1975**, *22*, 253.
[2] S. B. Carter, *Nature*, **1967**, *213*, 261.
[3] (a) Cole, R.; Cox, R. H. *Handbook of Toxic Fungal Metabolites*, Academic Press; New York, **1981**, 264; (b) Turner, W. B. *Fungal Metabolites*; Academic Press, New York, **1971**, p 352; (c) Turner, W. B.; Aldridge, D. C. *Fungal Metabolites II*; Academic Press, New York, **1983**, p 459; (d) Himes, R. H. *Biochim. Biophys. Res. Commun.* **1976**, *68*, 1362; (e) Fox, E. B.; Phillips, D. R. *Nature* **1981**, 292.
[4] Betina, V.; Micekova, D. *Z. Allg. Mikrobiol.* **1972**, *12*, 355.
[5] Katagiri, K.; Matsuura, S. *J. Antifiot.* **1971**, *24*, 722.
[6] Kuo, S. -C.; Lampen, J. O. *Biochim Biophys. Acta* **1975**, *389*, 145.
[7] Alvi, K. A.; Nair, B.; Pu, H.; Ursino, R.; Gallo, C.; Mocek, U. *J. Org. Chem.* **1997**, *62*, 2148.
[8] Kuo, S. -C.; Lampen, J. O. *Ann. N.Y. Acad. Sci.* **1974**, *235*, 137.
[9] Glinsukon, T.; Shank, R. C.; Wogan, G. N.; Newberne, P. M. *Toxical. Appl. Pharmacol.* **1975**, *32*, 135.

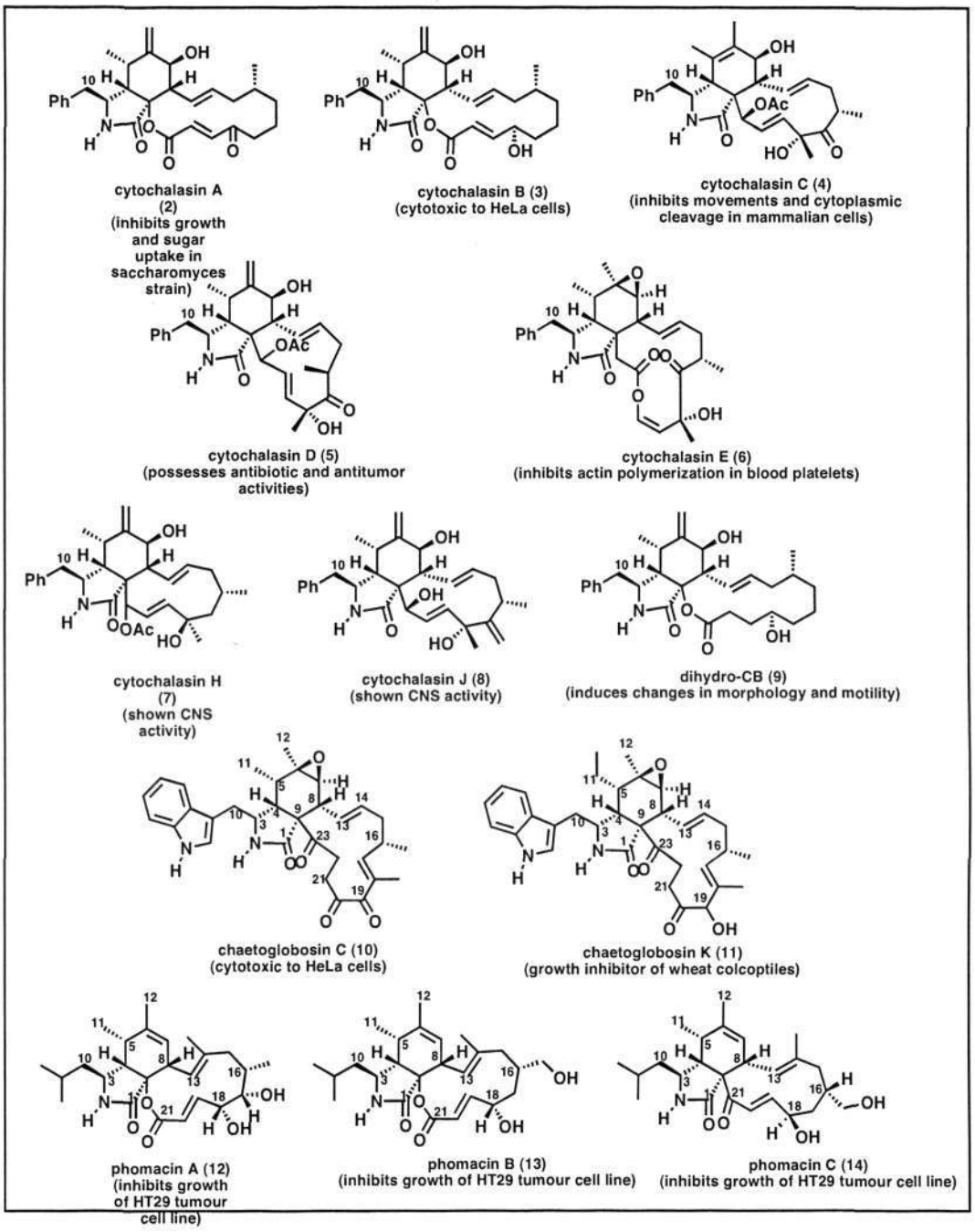


Figure 1-2[2,3,7]

[2] Carter, S. B. *Nature* **1967**, *213*, 261.
[3] (a) Cole, R.; Cox, R. H. *Handbook of Toxic Fungal Metabolites*, Academic Press; New York, **1981**, 264; (b) Turner, W. B. *Fungal Metabolites*; Academic Press, New York, **1971**, p. 352; (c) Turner, W. B.; Aldridge, D. C. *Fungal Metabolites II*; Academic Press, New York, **1983**, p. 459; (d) Himes, R. H. *Biochim. Biophys. Res. Commun.* **1976**, *68*, 1362; (e) Fox, E. B.; Phillips, D. R. *Nature*, **1981**, 292.
[7] Alvi, K. A.; Nair, B.; Pu, H.; Ursino, R.; Gallo, C.; Mocek, U. *J. Org. Chem.* **1997**, *62*, 2148.

The cytochalasans can be divided into three general groups based on whether they contain an indole, phenyl or isopropyl moiety at position 10 of the perhydroisoindole ring system as shown in Figure 1-3. Those that contain an indole moiety are generally referred to as the chaetoglobosins (**10**). Cytochalasans containing phenyl and isopropyl moieties are referred to as cytochalasins (**4**) and aspochalasins (**15**) respectively.[3]

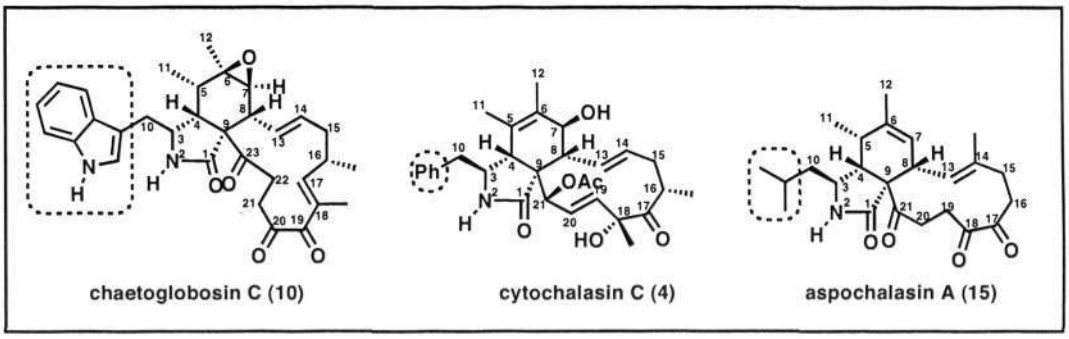


Figure 1-3 Types of cytochalasans

Since their commercial availability in the early 1970's, this group of compounds has become the subject of intense cytological research, which has led to the discovery of many new effects and a large library of synthetic cytochalasan derivatives. Literature abounds with reports and reviews on various aspects of their pharmacology.

[3] (a) Cole, R.; Cox, R. H. *Handbook of toxic Fungal Metabolites*, Academic Press; New York, **1981**, 264; (b) Turner, W. B. *Fungal Metabolites*; Academic Press, New York, **1971**, p. 352; (c) Turner, W. B.; Aldridge, D. C. *Fungal Metabolites II*; Academic Press, New York, **1983**, p. 459; (d) Himes, R. H. *Biochim. Biophys. Res. Commun.* **1976**, *68*, 1362; (e) Fox, E. B.; Phillips, D. R. *Nature*, **1981**, 292.

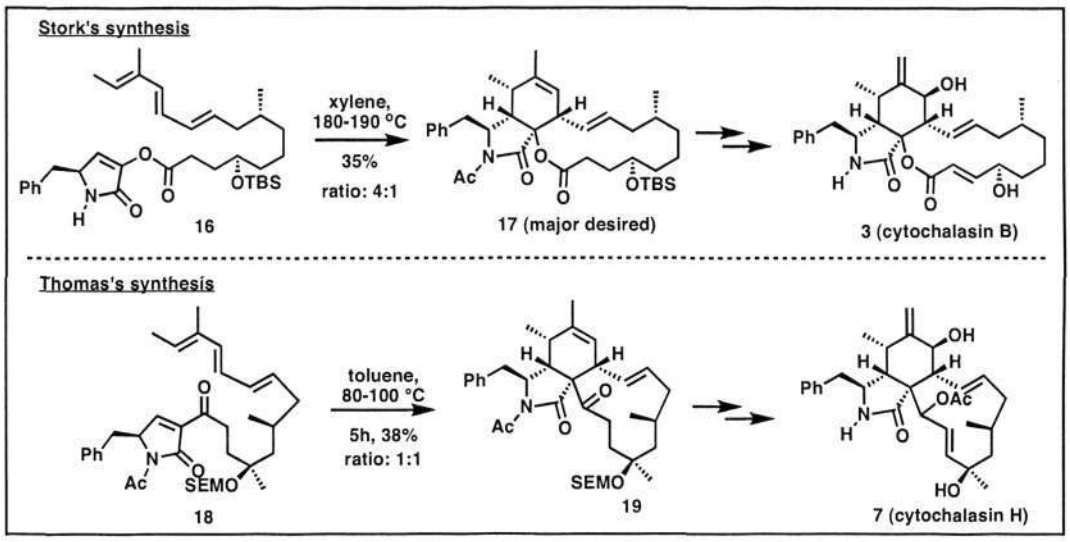
1.2 PREVIOUS SYNTHETIC WORKS

1.2.1 Introduction

Due to the unique biological activities and structural complexities of this group of compounds, cytochalasans have been the targets of much synthetic endeavors. Thermal Diels-Alder cyclization (either intermolecular or intramolecular) has been centered on formation of the six-membered core ring system together with the macrocyclic lactone or carbocyclic ring.

1.2.2 Literature Reviews

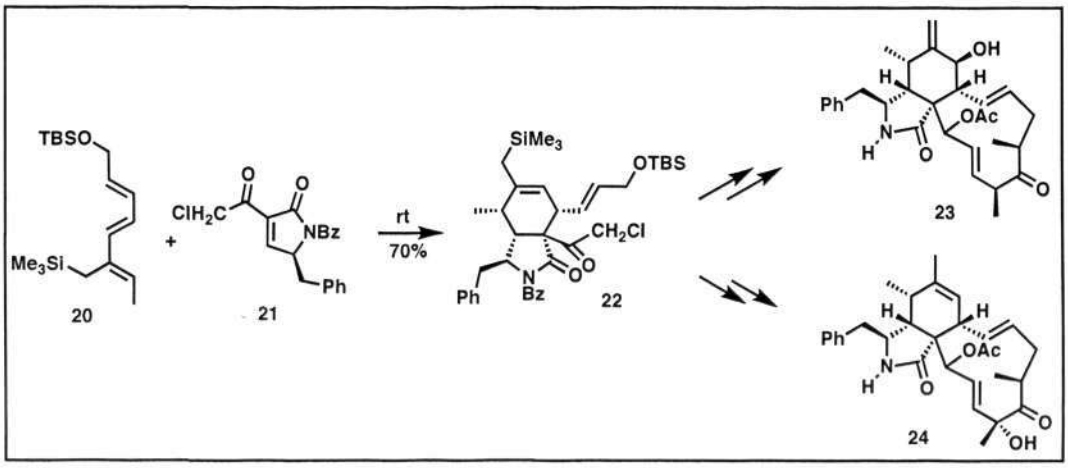
Stork[10] and Thomas[11] reported the synthesis of cytochalasans employing a thermal intramolecular Diels-Alder reaction as the key step. A long chain triene-pyrrolinone was used as the precursor to construct the six-membered ring system, followed by subsequent synthetic manipulations to give the title compound (Scheme 1-1).



Scheme 1-1

[10] Stork, G.; Nakamura, E. *J. Am. Chem. Soc.* **1983**, *105*, 5510.
[11] (a) Thomas, E. J.; Whitehead, J.W.F. *J. Chem. Soc., Perkin Trans. I.* **1989**, 507; (b) Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Perkin Trans. I.*, **1989**, 519.

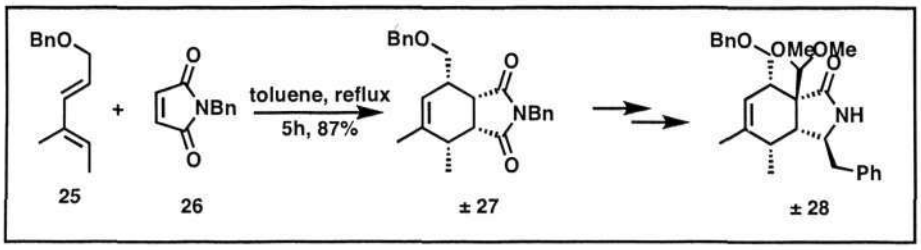
On a separate account, Vedejs[12] delivered the total synthesis of cytochalasan, featuring an intermolecular thermal Diels-Alder reaction using complex triene **20** and a reactive dienophile **21** to build the key six-membered ring. Further synthetic manipulations afforded the title compound, cytochalasin D analogs **23** and zygoporin G **24** respectively (Scheme 1-2).



Scheme 1-2

Hungate[13] also worked on the synthetic studies of cytochalasan. The cyclohexyl ring structure of cytochalasans was synthesized *via* thermal intermolecular Diels-Alder reaction using diene **25** and a symmetrical dienophile **26**.[14] Intermediate **27** underwent a further seven steps to give the racemic core ring structure **28** (Scheme 1-3).

[12] (a) Vedejs, E.; Reid, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 4618; (b) Vedejs, E.; Rodgers, J. D.; Wittenberger, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 4822; (c) Vedejs, E.; Rodgers, J. D.; Wittenberger, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 4351.
[13] Hungate, R. W.; Chen, J. L.; Starbuck, K. E.; Macaluso, S. A.; Rubino, R. S. *Tetrahedron Lett.* **1996**, *37*, 4113.
[14] Weinreb, S. M.; Starlett, Jr., J. E.; Kim, Y. M. *J. Org. Chem.* **1981**, *46*, 5383.



Scheme 1-3

All the reported syntheses of cytochalasans involved the use of thermal intramolecular or intermolecular Diels-Alder reaction as the key step, thus requiring harsh reaction condition. Besides, these methodologies cannot be employed with heat- or acid-sensitive compounds that are often featured in complex and multi-step syntheses.[15] Furthermore, the precursors reported for the cyclizations usually require activated dienophiles which are generally made *via* a tedious synthetic manipulations.

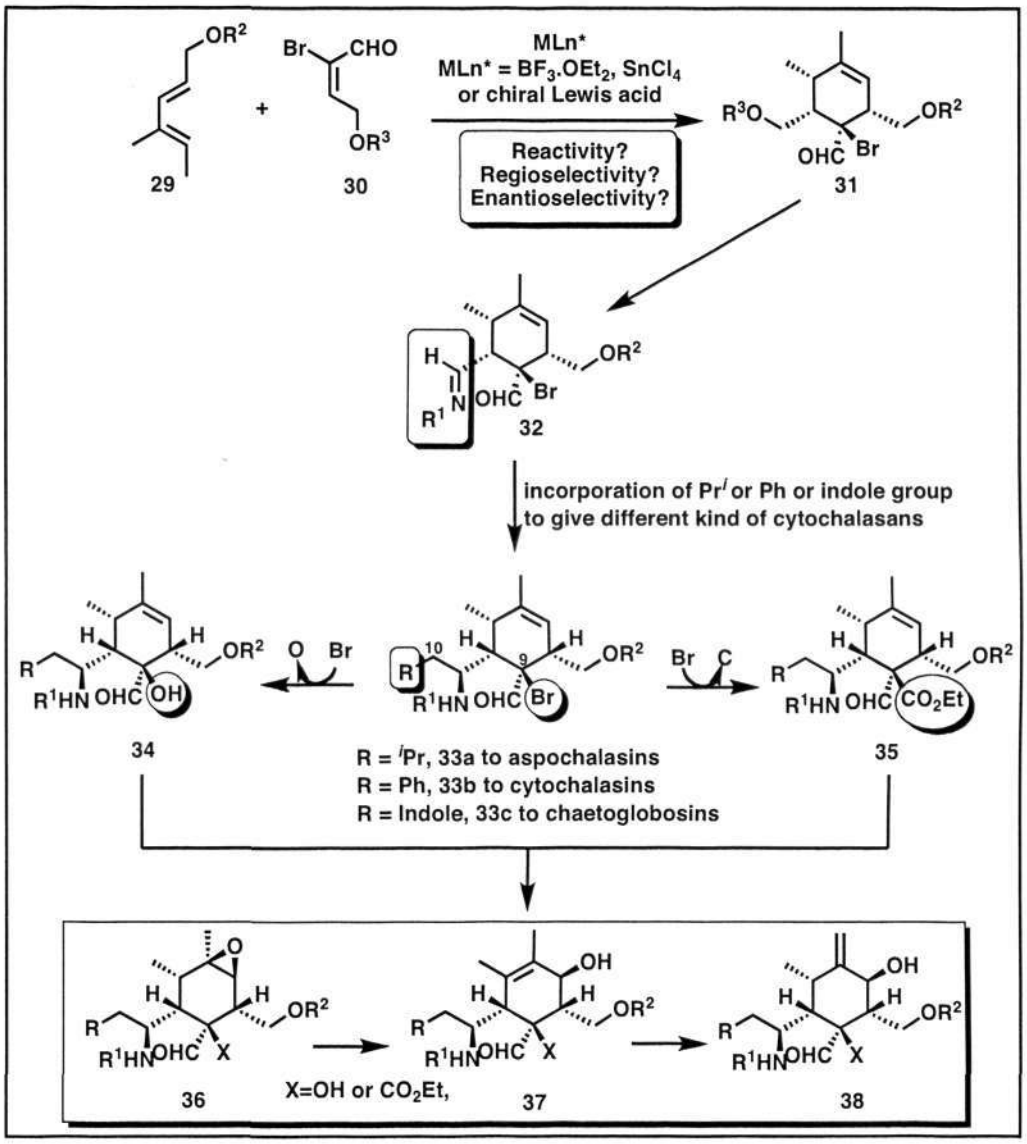
1.3 OUR SYNTHETIC PLAN

Diels-Alder reaction is probably one of the most efficient methods for the construction of six-membered rings. Efficient and practical asymmetric versions continue to emerge but fundamental problems related to reactivity as well as regioselectivity of the intermolecular Diels-Alder reaction between highly functionalized dienes and dienophiles remain to be solved.[16]

Our strategy is to adopt Lewis acid catalyzed intermolecular Diels-Alder reaction to construct the six-membered ring (Scheme 1-4). Lewis acid catalysts allow the reaction to proceed under mild conditions (at room temperature or below) with satisfactory yields. Reactions with less reactive dienes and dienophiles are also made possible, and the cycloaddition products are often highly regio- and stereo-selective.

[15] Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, *33*, 6815.
[16] (a) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807; (b) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400; (c) Danishefsky, S. *Chemtracts: Org. Chem.* **1989**, *2*, 273.

Furthermore, Lewis acids are capable of increasing both the reaction rate and selectivity, contrary to other catalyzed reactions where an increase in reaction rate is typically accompanied by a decrease in selectivity.[17]



Scheme 1-4

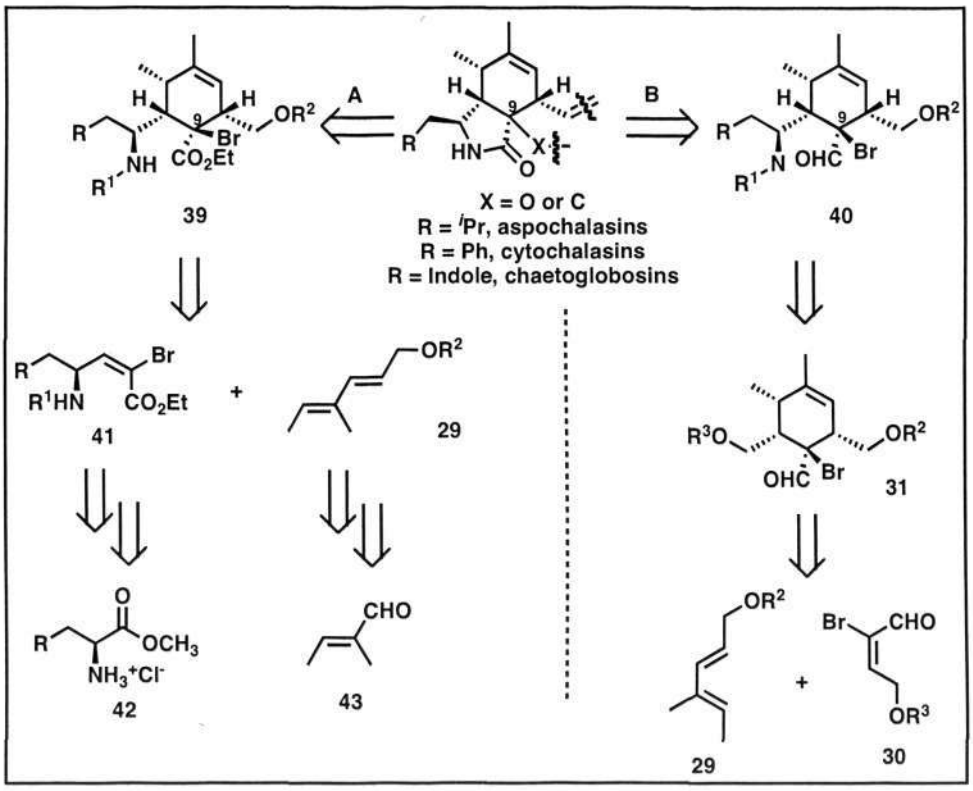
[17] Fringuelli, F.; Taticchi, A. *The Diels-Alder Reaction Selected Practical Methods*, Wiley & Sons, England, **2002**, 99.

Our interest in the total synthesis of cytochalasan,[18] has encouraged us to investigate the intermolecular Diels-Alder reaction between highly functionalized dienes and dienophiles with control of the stereochemistry on all the six carbons of the cyclohexane ring.

The key feature of our synthetic plan is the versatility of the key intermediates **32** as shown in Scheme 1-4. The phenyl, isopropyl and indole groups can be incorporated from an imine containing functionality in intermediate **32** to afford intermediates **33** for the syntheses of aspochalasins, cytochalasins and chaetoglobosins respectively. The presence of bromide in the six-membered core ring system will enable us to introduce oxygen or carbon substituents in the C-9 position affording intermediate **34** and **35** for the syntheses of cytochalasans with the macrocyclic lactone or carbocyclic rings. Further synthetic manipulations on the cyclohexane ring will allow us to synthesize almost all the known cytochalasans.

Two possible synthetic approaches were proposed to construct the six-membered ring system. The main difference between the two approaches is on the substituents on the amine functionality. In approach A, the substituents on the amine group are incorporated in the diene's synthesis while in approach B, they are introduced in the later part of the synthesis (Scheme 1-5).

[18] Collaborative work with Lee Kiew Ching, unpublished results.



Scheme 1-5

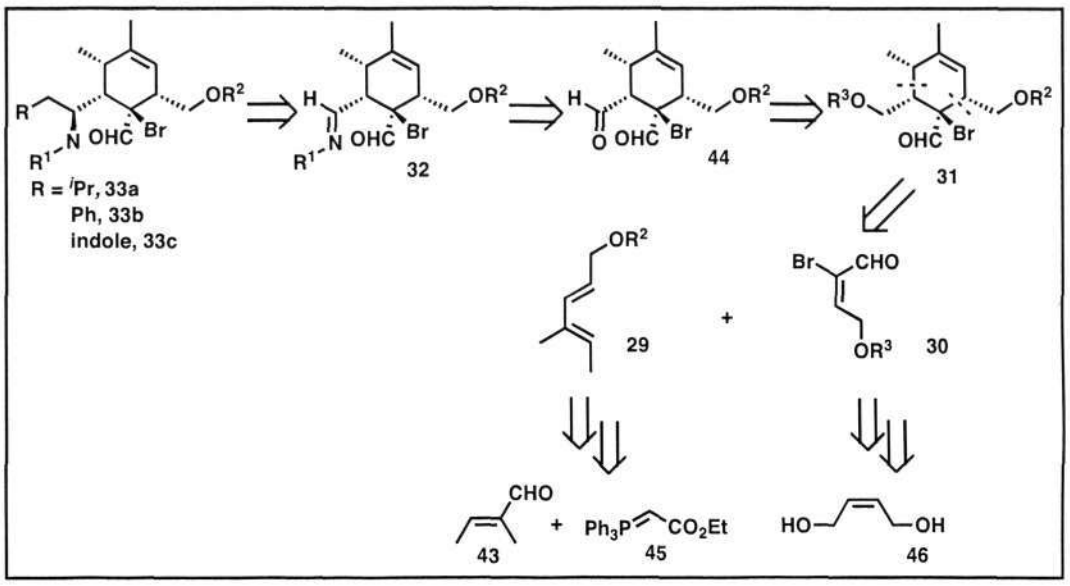
In our previous synthetic studies with approach A,[19] various Lewis acids catalyzed and thermal intermolecular Diels-Alder reaction using diene **29** (R^2 = Bn, TBS) and dienophile **41** (R = isopropyl, R^1 = CBz) have been carried out. Unfortunately, no desired product was obtained. We postulate that this can be attributed to the ester functionality on dienophile **41** being not sufficiently electron-withdrawing for promoting the Diels-Alder reactions. A attempts to make a more reactive dienophile had failed.

[19] Lim Zeyi, Honours thesis, **1998** - unpublished results.

1.3.1 Approach B

In our synthetic approach B, the substituents on the amine group are introduced in the later part of the synthesis. The use of a chiral Lewis acid[20] in the Diels-Alder reaction will enable us to control the relative as well as the absolute stereochemistry in the six-membered ring intermediate **38**.

Retrosynthetic analyses of intermediates **33** using a sequence of functional group interconversions lead to **31** *via* compound **32** and **44** (Scheme 1-6). Disconnection of the six-membered ring system **31** provides diene **29** and dienophile **30**. Dienophile **30** can be envisaged from a commercially available *cis*-1,4-butendiol **46**. Meanwhile diene **29** can be derived form tiglic aldehyde **43** and stabilized ylide **45**.



Scheme 1-6

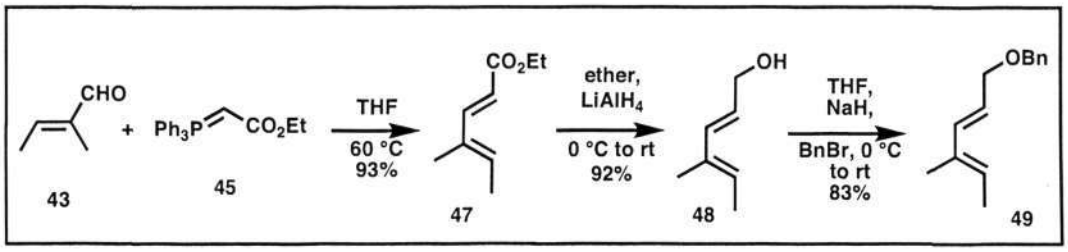
[20] Loh, T. P.; Corey, E. J. *Tetrahedron Lett.* **1993**, *34*, 3979.

1.4 RESULTS AND DISCUSSIONS

With the plan in mind, we proceed to the syntheses of the diene and dienophiles in order to investigate the Diels-Alder reaction.

1.4.1 Synthesis of Diene 49

Diene **49** was prepared in four steps from tiglic aldehyde **43**. Treatment of **43** with carb(ethoxymethylene)triphenylphosphorane **45** in THF at 60 °C gave ester **47** in 93% yield. As expected, the *trans* isomer was the only product been isolated. When ester **47** was reduced using lithium aluminium hydride in ether at 0 °C, alcohol **48** was obtained in 92% yield. Protection of the alcohol functionality was carried out using benzyl bromide in the presence of sodium hydride in THF at 0 °C, giving the benzyl protected alcohol **49** in 83% yield.

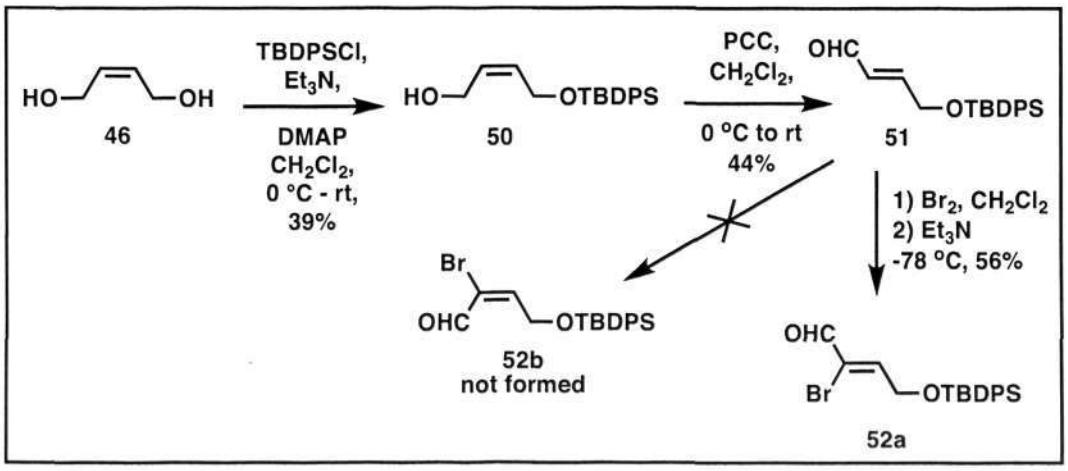


Scheme 1-7

1.4.2 Synthesis of dienophile 52a and 52b

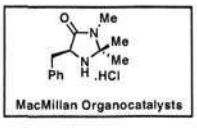
Synthesis of dienophiles **52a** and **52b** were carried out from a commercially available *cis*-1,4-buten-2-diol **46** (Scheme 1-8). Diol **46** underwent *t*-butyldiphenylsilylchloride (TBDPSCl) protection in the presence of triethylamine and DMAP in CH_2Cl_2 at 0 °C to give monoprotected alcohol **50** in 39% yield. Oxidation

of alcohol **50** with pyridinium chlorochromate (PCC) in CH_2Cl_2 at 0 °C afforded the more stable *trans* isomer, dienophile **52a** in 44% yield. The latter was brominated with bromine in CH_2Cl_2 followed by dehydrobromination by triethylamine at -78 °C to give undesired *E*-dienophile **52a** as the sole product in 56% yield.



Scheme 1-8

With both diene **49** and dienophile **52a** and **52b** in hand, a series of studies using various conditions were tried. Different Lewis acids such as $BF_3.(OEt)_2$, $SnCl_4$, $AlCl_3$, $In(OTf)_3$ and $Sm(OTf)_3$ were experimented. In most cases, diene **49** decomposed gradually in the reaction mixture, even under mildly acidic condition. Mild organocatalyst such as MacMillan's catalysts[21] were employed but no desired product was obtained. Thermal conditions were also employed, however, no product was obtained and only the decomposition or polymerization of diene **49** resulted. Such observations could be attributed to the incorrect *E*-dienophile we made. Another possible explanation is that the dienophile is not reactive enough to initiate the cyclization.

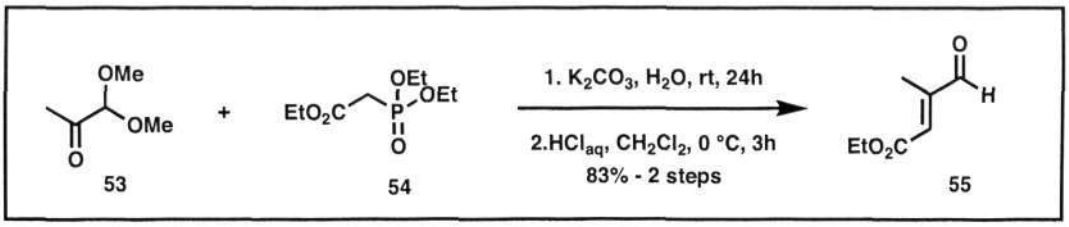
21 

MacMillan Organocatalysts

These failed results led us to exploit a more reactive dienophile, aldehyde-ester as reported by Corey.[22] A series of α-substituted aldehyde-ester were synthesized and subjected to the optimized reaction conditions from previous study, which utilized $BF_3.OEt_2$ as the Lewis acid.

1.4.3 Synthesis of dienophile 55

Dienophile **55** was prepared in 83% yield by Horner-Emmons reaction of commercially available 1,1-dimethoxyacetone (**53**) and ethyl 2-(diethoxyphosphoryl) acetate (**54**), followed by acid hydrolysis with 3N HCl/CH_2Cl_2 at 0 °C for 3 hours (Scheme 1-9).

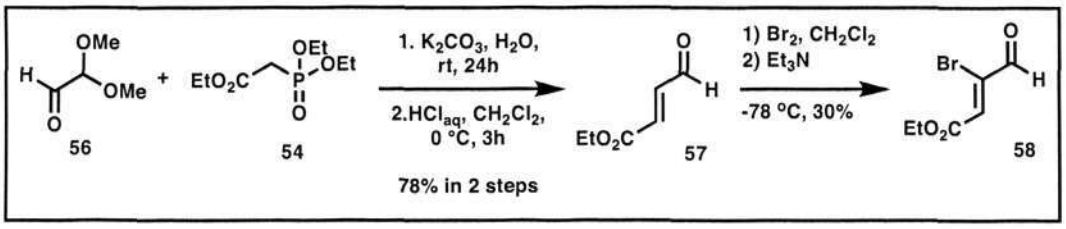


Scheme 1-9

1.4.4 Synthesis of dienophile 57 and 58

Dienophile **57** was prepared in 78% yield by Horner-Emmons reaction of commercially available 1,1-dimethoxyacetaldehyde **56** and ethyl 2-(diethoxyphosphoryl) acetate **54**, followed by acid hydrolysis with 3N HCl/CH_2Cl_2 at 0 °C for 3 hours. Further bromination of aldehyde **57** with bromine in CH_2Cl_2 followed by dehydrobromination by triethylamine at -78 °C gave dienophile **58** as *E*-isomer in 30% yield (Scheme 1-10).

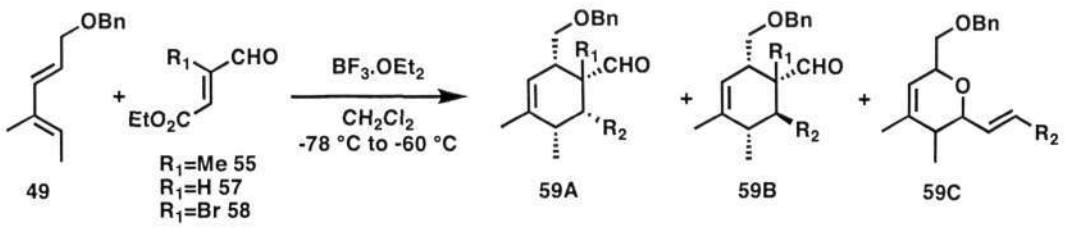
[22] (a) Hu, Q. -Y; Rege, P. D.; Corey, E. J. *J. Am Chem. Soc.* **2004**, *126*, 5984; (b) Hu, Q. -Y; Zhou, G.; Corey, E. J. *J. Am Chem. Soc.* **2004**, *126*, 13708.

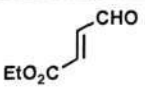
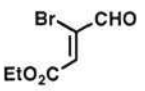
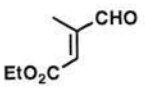
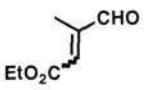


Scheme 1-10

The aldehyde-esters (**55**, **57** and **58**) were subjected to Diels-Alder cyclization catalyzed by $BF_3.OEt_2$ with diene **49** and the results are shown in Table 1-1. Two competing reactions, [4 + 2] cycloaddition and hetero Diels-Alder, were observed in this study.

Table 1-1



Entry	Dienophile	Yield (%)	Ratio A:B:C
1		83	0:50:50
2		56	**C** only
3		42	**C** only
4	 **E/Z (4:1)**	45	78:0:22

An interesting trend was observed from these studies. Three different compounds were isolated from the reaction mixture. When we reacted non-alpha-

substituted aldehyde-ester **57** (Table 1-1, entry 1), products **B** and **C** were obtained in high yield (1:1 mixture). Interestingly, when employing alpha-substituted aldehyde-esters such as methyl (**55**, weak electron donating group) and Br (**58**, electron withdrawing group) (Table 1-1, entry 2 and 3), only product **C**, which is the hetero-Diels-Alder product, was isolated.

A noteworthy finding from this study is when we tried a *E*/*Z* mixture of methyl alpha-substituted aldehyde-ester (**55**, Table 1-1, entry 4), we were able to obtain the product **A**, product **C** and recover some of the unreacted *E*-**55**. This shows that reaction characteristics differ depending on the geometry of the dienophile. From α-substituted *E*-dienophile, hetero addition was the dominant reaction pathway, and product **C** was obtained. While from *Z*-dienophile, *endo* selective Diels-Alder gave the cycloadduct **A**.

The relative stereochemistry of cycloadducts **59b** (Table 1-1, entry 1) and **59a** (Table 1-1, entry 4) was confirmed by NOESY experiment showing the interactions between corresponding protons. High degree of interaction exists between the aldehydic proton and that of the neighbouring proton H-1 and H-5. We were unable to observe the interaction between H-6 and H-1 for **59b** (Table 1-1, entry 1) due to the overlap between the two protons. From 1D and 2D NMR experimental data, we concluded that H-5 and H-6 are in the *anti* configuration. NOESY analysis for **59a** (Table 1-1, entry 4) showed strong interaction between the aldehydic proton with H-1 and H-4 with H-5. These interactions confirmed the *cis* configuration of **59a** (Table 1-1, entry 4) (Figure 1-4).

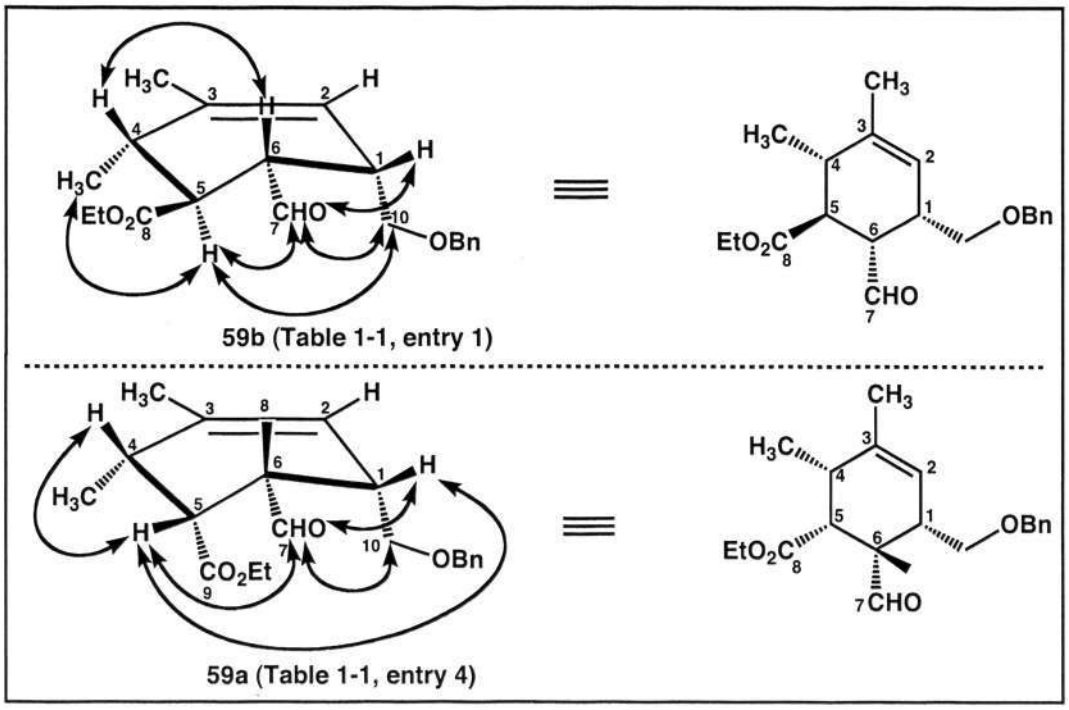


Figure 1-4

With cycloadduct **59b** (Table 1-1, entry 1) and **59a** (Table 1-1, entry 4) in hand, we still need to tackle further challenges. One of the major problems lies in the methyl group at C_6 of **59a** (Table 1-1, entry 4) being very difficult to functionalize to the proposed compound as mentioned in our retroanalysis plan (Scheme 1-5). Meanwhile the CHO and CO_2Et functionalities on **59b** (Table 1-1, entry 1) are in the *anti*-position.

To overcome these synthetic problems, we plan to make a more elegant dienophile which can be applied to our system. Our initial attempt was to make the dialdehyde **60** as shown in Figure 1-5. However, attempts to synthesis **60** failed. Thus, we changed our focus to aldehyde-diester **61**. The procedure is described in following section.

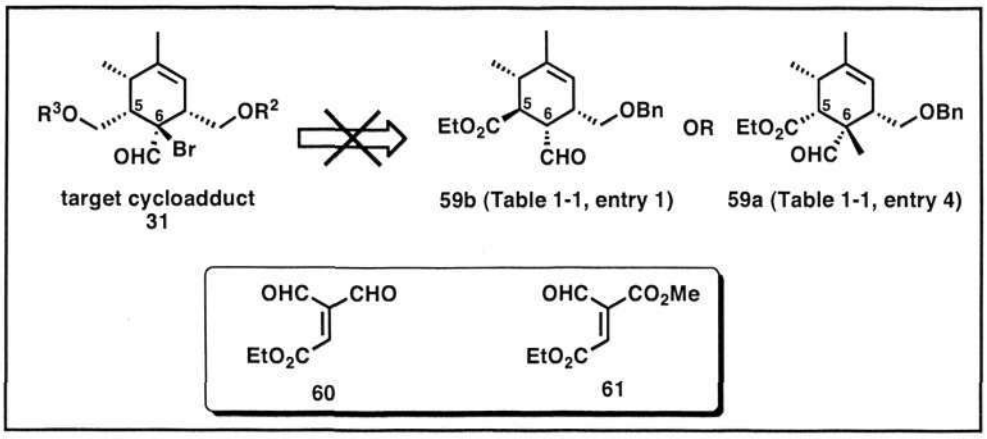
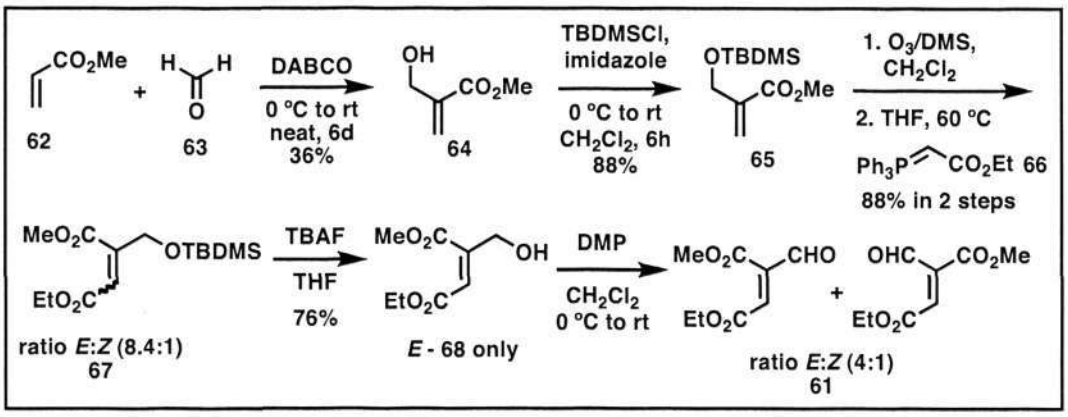


Figure 1-5

1.4.5 Synthesis of Dienophile 61

Synthesis of dienophile **61** was completed in 6 steps from the commercially available formaldehyde **63** and methyl acrylate **62** (Scheme 1-11). Alcohol **64** was prepared by Baylis Hilman reaction between formaldehyde **63** and methyl acrylate **62** in the presence of a catalytic amount of DABCO. Protection of alcohol **64** with TBDMSCl and pyridine in CH_2Cl_2 gave the protected alcohol **65** in 88% yield. Ozonolysis followed by Wittig reaction with a stabilized ylide **66** afforded 88% yield of α,β-unsaturated ester **67** (inseparable *E/Z* mixture, 8.4:1) in two steps. TBDMS deprotection of the mixture of **67** give mainly *E*-**68**. Final DMP oxidation leads to the corresponding aldehyde **61** (*E/Z* mixture, 4:1). We found that the aldehyde **61** was very unstable and all attempts at purification failed. Subsequently the reaction mixture was filtered and used for the Diels-Alder reaction without any further purification.



Scheme 1-11

The structural configuration of **61**, **67** and **68** were determined *via* NMR studies (^{1}H and NOE experiments). The major product obtained from the Wittig reaction is the undesired (*E*)-isomer. After desilylation, alcohol **68** was obtained as a single isomer with the (*E*)-configuration. The desired (*Z*)-isomer was only obtained as a minor product during the DMP oxidation where isomerization occurred. ^{1}H NMR showed two aldehyde peaks at 9.65 ppm and 10.16 ppm which correspond to *E* and *Z* isomer respectively (Figure 1-6).

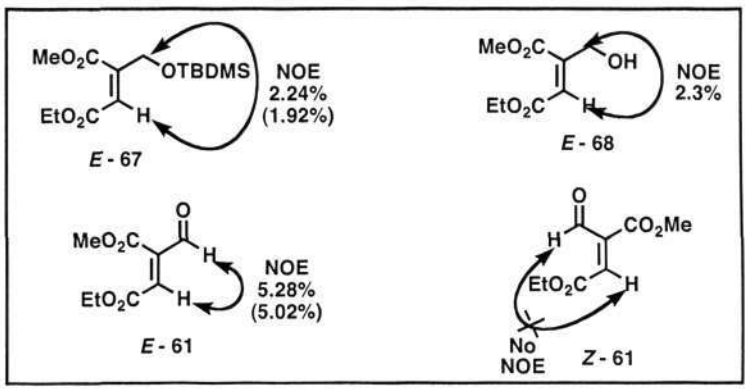


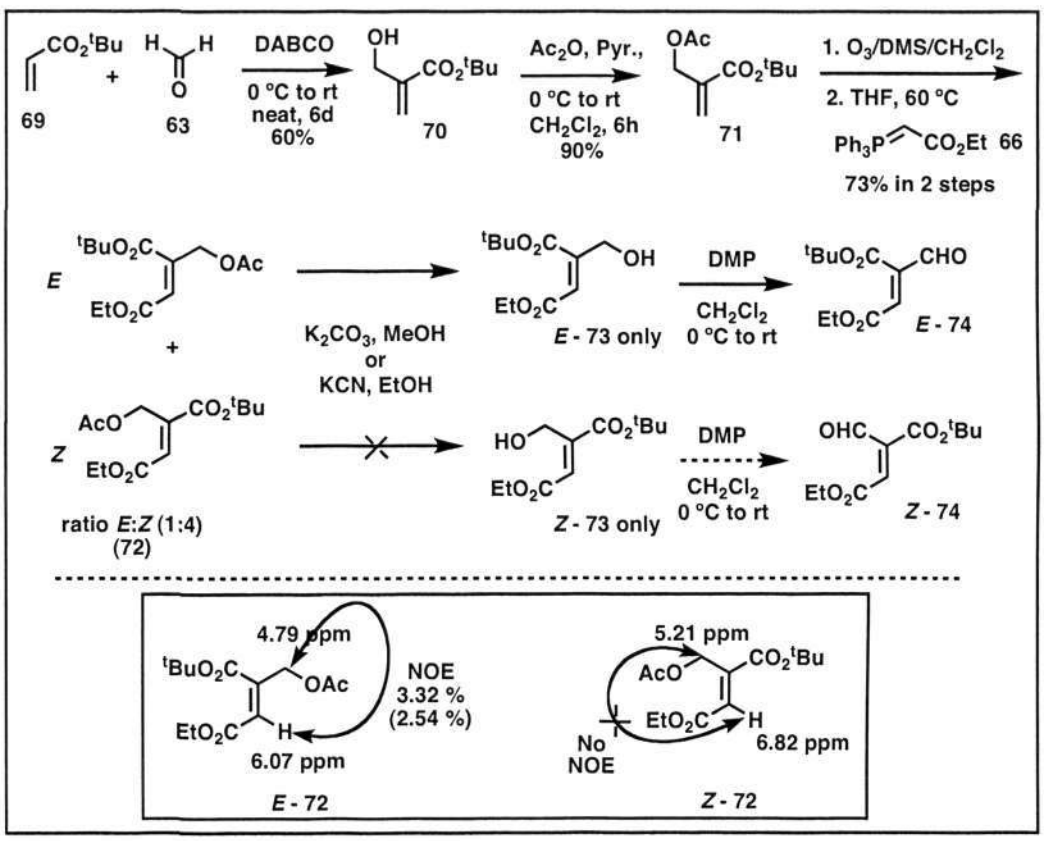
Figure 1-6

Since our desired dienophile is (*Z*)-isomer **61**, we needed to seek for other alternatives in order to carry on this synthesis. One of the alternatives is to change the

methyl ester to *t*-butyl ester. We expect that the steric hindrance provided by the bulky *t*-butyl group would give the desired (*E*)-isomer as the major product.

1.4.6 Synthesis of Dienophile 74

Efforts to synthesize the (*Z*)-isomer was carried out as shown in Scheme 1-12. Alcohol **70** was prepared by a Baylis-Hilman reaction between formadehyde **63** and *t*-butyl acrylate **69** in the presence of a catalytic amount of DABCO. Protection of the alcohol **70** was carried out with acetic anhydride with pyridine in CH_2Cl_2, giving the protected alcohol **71** in 90% yield. Ozonolysis followed by Wittig reaction with a stabilized ylide **66** gave the α,β-unsaturated ester **72** in 73% yield (2 steps) with 1:4 ratio, where the major product is the desired *Z* isomer. With diester **72** in hand, several deacetylation methods were test, but we failed to obtain alcohol *Z*-**73**.

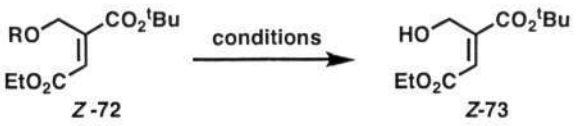


Scheme 1-12

The desired (Z)-isomer was obtained as a major product from the Wittig reaction and the structural comfirmation was studied (Figure 1-7). However, all attempts at deprotection of *Z*-**72** were futile. The compound either decomposed or in some cases, the undesired cyclized product was obtained.

Other alternative routes were employed. Returning to alcohol **70** as starting material, protection with several different protecting moieties were investigated. It was our hope that other deprotection method would give the alcohol-ester *Z*-**73**, which can then be oxidized to aldehyde-ester **74**. However, the deprotection failed and only the cyclized product was obtained from the reaction mixture (Table 1-2).

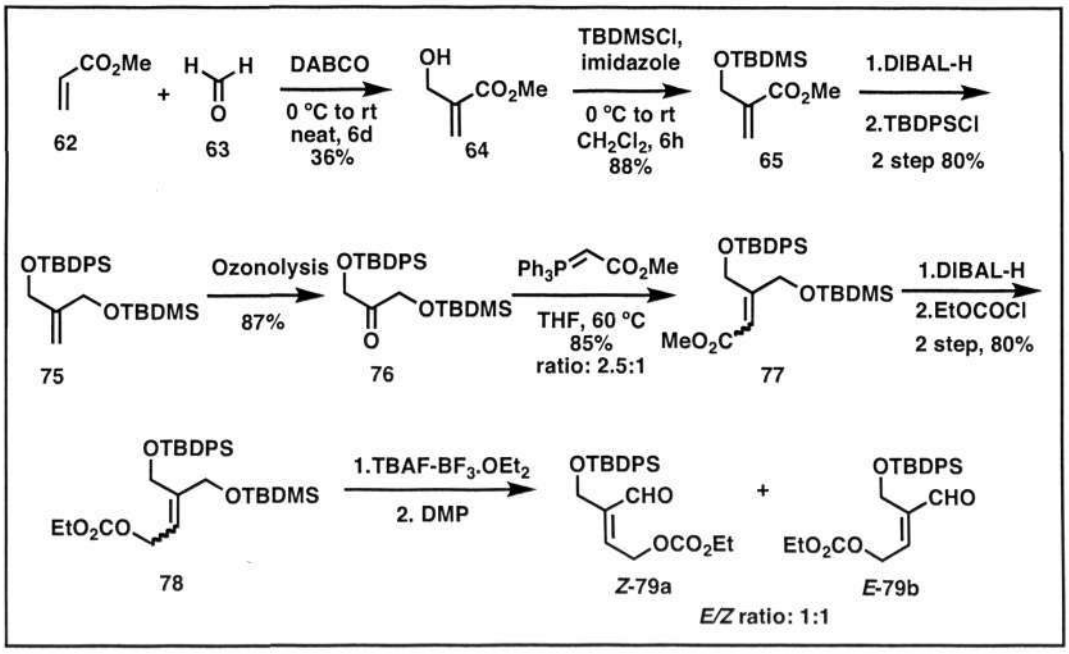
Table 1-2



Z-72 *Z*-73

Entry	R	Conditions	Results
1	Ac	K_2CO_3 / MeOH	transesterification occured, cyclized product
2	Ac	KCN / EtOH	no desired product
3	TMS	-	TMS cleavage during ozonolysis
4	TBDMS	TBAF / THF	some cyclized product, decomposition
5	TBDMS	HF.Pyr / THF	cyclized product

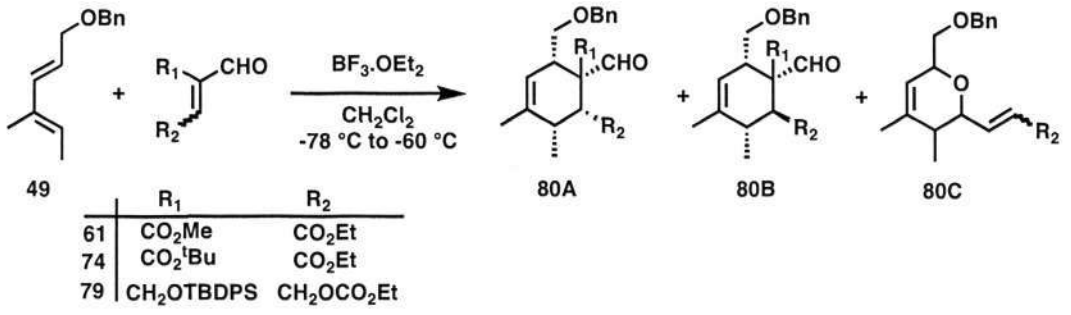
1.4.7 Synthesis of Dienophile 79

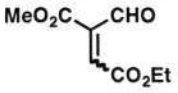
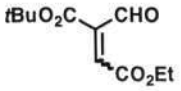
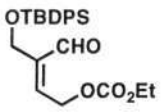
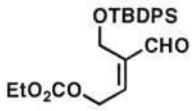


Scheme 1-13

As different deprotection methods did not work, a longer synthetic route was explored. Using intermediate **65** as the starting point, DIBAL reduction of **65** followed by TBDPSCl protection gave **75** in 80% yield (2 steps). Subsequent ozonolysis and Wittig reaction provided **77** as (2.5:1) *E*/*Z* mixture. **77** was underwent DIBAL reduction and $EtOCO_2Cl$ protection to generate **78**. The latter was subjected to a selective desilylation using TBAF/BF_3.OEt complex and DMP oxidation to give both **Z-79** and ***E*-79** dienophiles with a ratio of 1:1 respectively, in 78% yield over 2 steps. Both isomers were separated *via* flush column chromatography (Scheme 1-13).

Table 1-3



Entry	Dienophile	Yield (%)	Ratio A:B:C
1	 E/Z (4:1)	23 (91:9)	Only A
2	 E/Z (4:1)	22 (90:10)	Only A
3		89 (90:10)	Only A
4		No reaction	-

Treating the dienophiles (**61, 74, 79**) with diene **49** in the presence of $BF_3.OEt_2$ and CH_2Cl_2 as solvent at -60 °C overnight, cycloadduct **80a** was isolated as the main product with yields ranging from 23-89% from the crude mixture (Table 1-3). From these series of *Z*-dienophiles, we were able to obtain the desired cycloadduct with desired stereochemistries on the six-membered ring system. As with respect to previous observation, no desired was obtained when *E*-**79** (Table 1-3, entry 4) was employed.

The relative stereochemistry of cycloadducts **80** (Table 1-3, entries 1-3) were confirmed by 2D NOESY and are consistent with the proposed structure (Figure 1-7). Cycloadduct **A** shows a high degree of interaction between the aldehydic proton and

that of the neighbouring proton H-1, H-5 and H-10 attached to the newly formed ring system. NOESY effect of H-4 and H-5 further confirmed the relative stereochemistry. The anomalous NOESY effect of H-5 with H-1; H-1 and H-5 with aldehydic proton can explained by the boat conformation adopted due to restriction about the alkene bond, effectively causing the molecule to adopt a bent axis about the C_3-CH_3 or CO_2Me/CHO and CO_2Bu_t/CHO groups, so that interaction is now possible.

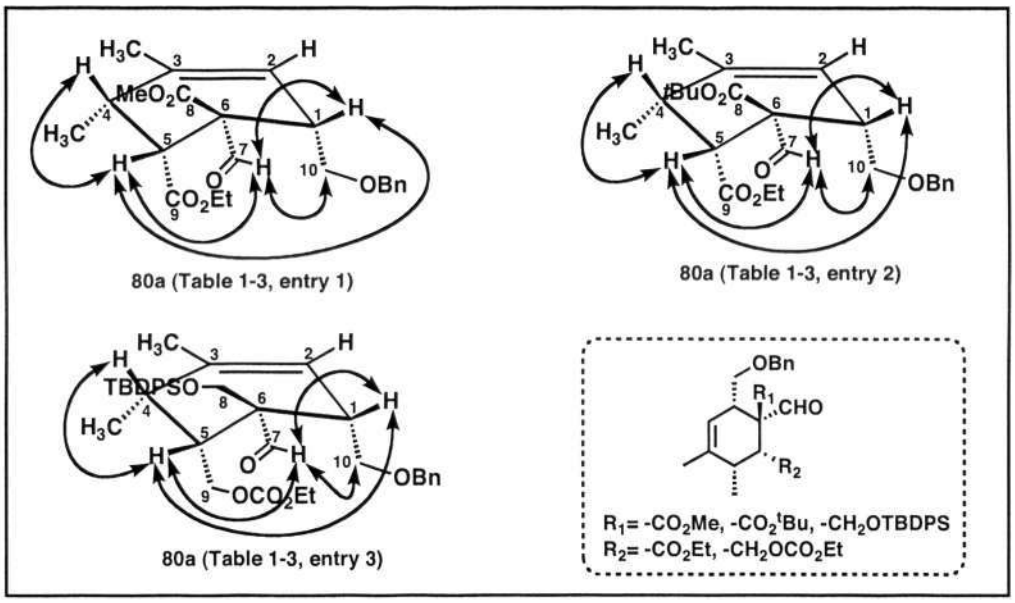
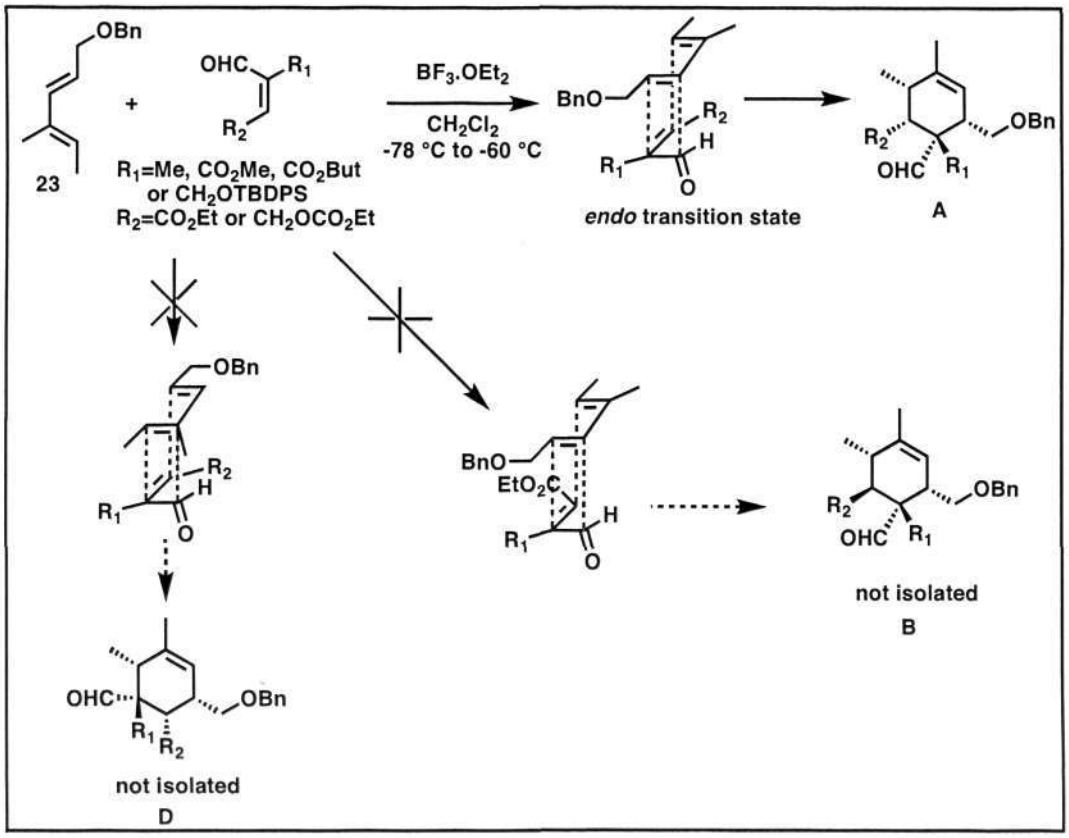


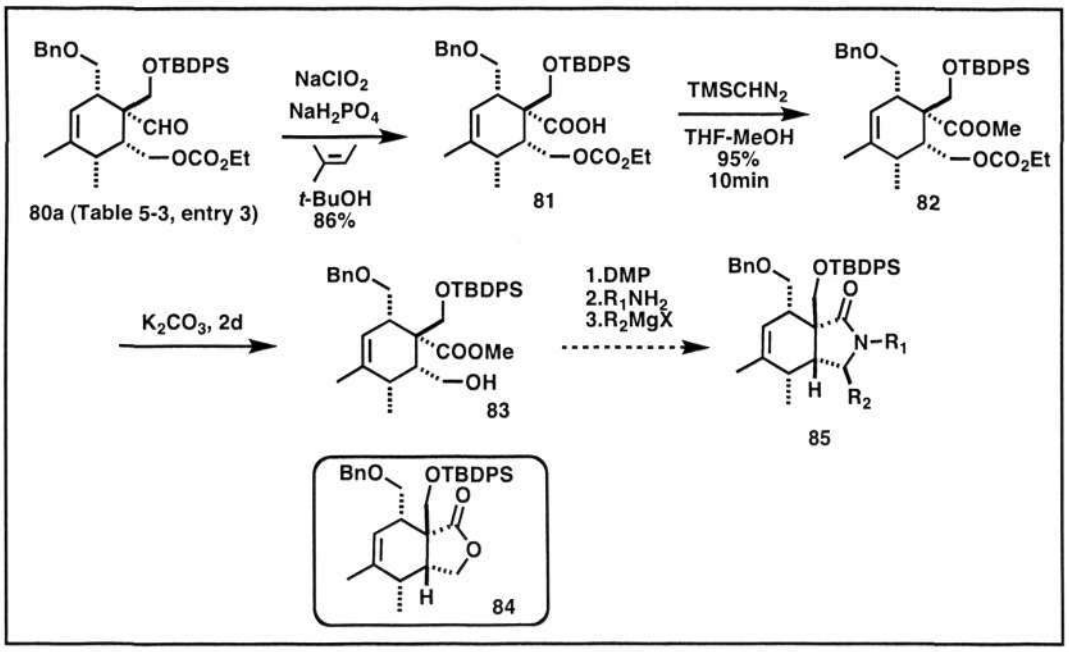
Figure 1-7

Since cycloadduct **80d** was not isolated, the formation of **80a** suggested that the CH_2OBn group and the 3-methyl group have a greater directing effect than that of the 4-methyl group on diene **49**. Besides, cycloadduct **80b** was also not observed from the reaction mixture. This might be due to the steric effect of the *endo* ester group which prevents the cycloaddition from occurring. In this series of dienophiles, no hetero-Diels-Alder product **80c** was detected. The bulkiness of CO_2Me/CHO or CO_2Bu^t/CHO groups might hinder the coupling process (Scheme 1-14).



Scheme 1-14

With this cycloaddition product **80a** (Table 5-3, entry 3) in hand, we took the synthetic a step forward, oxidizing the CHO to COOH **81** in 86% yields. Methyl ester **82** was obtained in 95% yield with TMS diazomethane. After deprotection of **82** under basic condition, lactone **84** was generated in high yield, instead of desired product **83**. This undesired result further confirmed the *cis* configuration of intermediate **80a** (Table 1-3, entry 3) obtained from the $BF_3.OEt_2$ catalyzed Diels-Alder reaction (Scheme 1-15).



Scheme 1-15

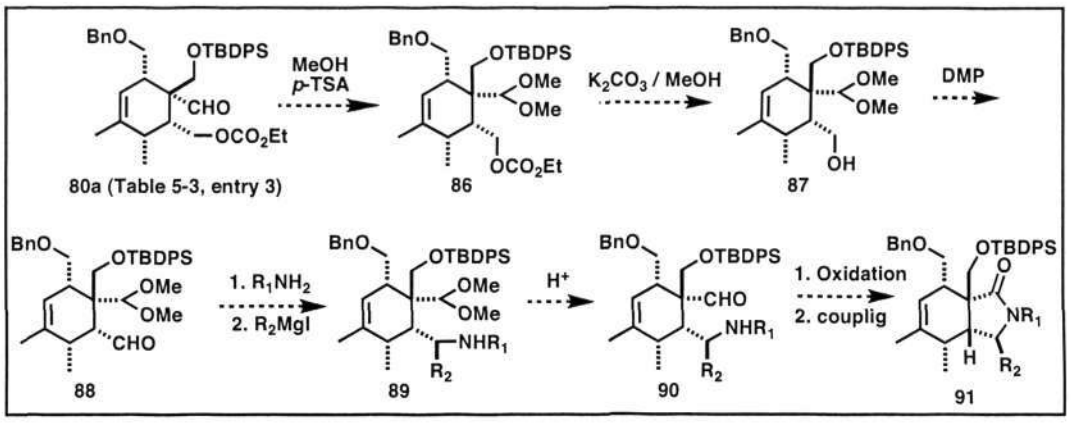
1.5 CONCLUSION

We have successfully demonstrated the use of Lewis acid catalyzed intermolecular Diels-Alder reaction between highly functionalized dienes and dienophiles. Two competing reactions, hetero Diels-Alder and normal Diels-Alder cyclization were observed when we employed aldehyde-ester with or without α-substitution. We found that reaction characteristics differ depending on the geometry of the dienophile. From α-substituted *E*-dienophile, hetero addition was the dominant reaction pathway. While from *Z*-dienophile, *endo* selective Diels-Alder give raise to the desired cycloadduct, with correct stereochemistries as that in the core ring skeleton found in the cytochalasans class of natural products. Further synthetic studies towards the total synthesis of cytochalasan are in progress.

1.6 FUTURE WORKS

We have achieved the synthesis of cycloadduct **80a** (Table 1-3, entry 3) in high yield and diastereoselectivity. The next target in our synthetic exploration focuses on the development of strategies for the introduction of the lactam ring containing either indole, phenyl or isopropyl which will allow us to synthesize almost all the known cytochalasans.

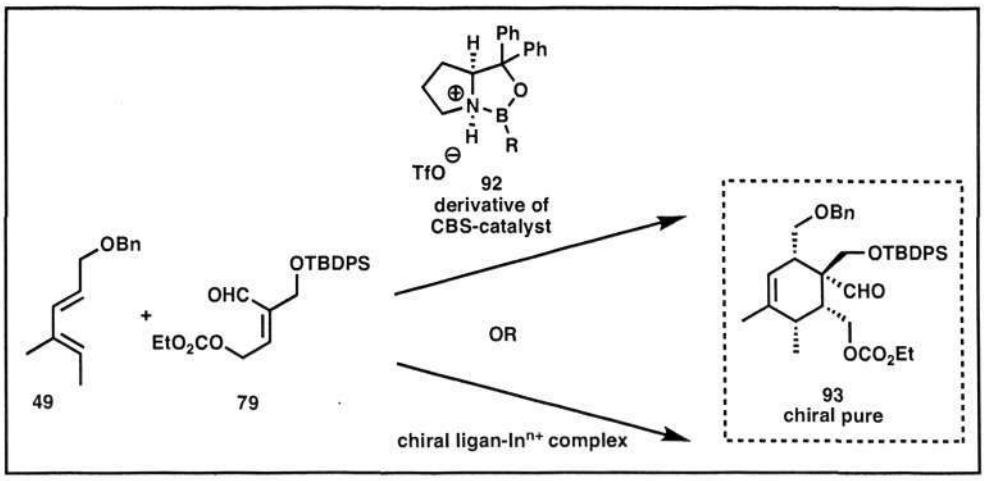
A proposed synthetic route to intermediate **91** is listed in Scheme 1-16. The synthesis involves aldehyde protection, ester hydrolysis, oxidation and incorporation of R_2 *via* imine and Grignard reaction to give **89**. Subsequent acid hydrolysis frees the aldehyde **90**, following by oxidation to acid and finally amide coupling to the lactam ring **91**.



Scheme 1-16

Base on findings of this methodology, exploration of an enantioselective synthesis route is feasible. An enantioselective version of the Diels-Alder reaction can be explored by the use of a chiral ligand such as CBS-catalyst (Corey-Bakshi-Shibata-

catalyst[23], **86**) in the form of oxazoborolidinium cations or indium catalyst[24] as developed in our research group (Scheme 1-17).

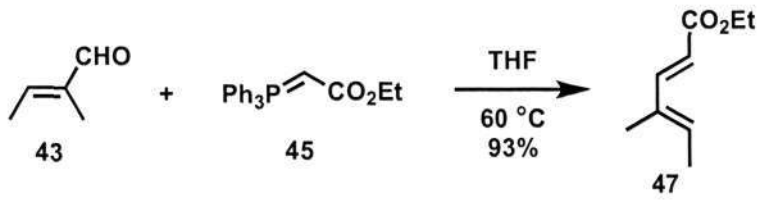


Scheme 1-17

[23] (a) Liu, D.; Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 1498; (b) Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 9536.
[24] Teo, Y. -C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2539.

1.7 EXPERIMENTAL

(2*E*,4*E*)-Ethyl-4-methyl-2,4-hexadienoate (47)



Tiglic aldehyde **43** (10 g, 0.12 mol, 11.5 mL) was added to a solution of carb(ethoxymethylene) triphenyl phosphorane **45** (60 g, 0.18 mol) in THF (250 mL) at 60 °C. The reaction was stirred overnight at 60 °C. The reaction mixture was filtered. The filtrate was concentrated *in vacuo*. Purification *via* column chromatography afforded 93% (17.2 g) product **47**.

$\mathbf{R}_f$ = 0.77 (Hexane:EtOAc, 1:1);

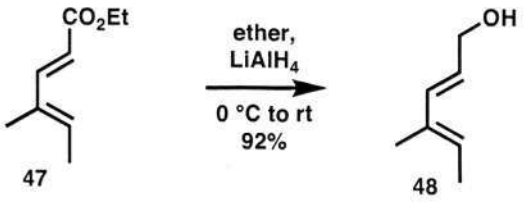
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (3H, t, *J* = 6.87 Hz, -$OCH_2C\mathbf{H}_3$), 1.74 (3H, s, $H_3CHC{=}CC\mathbf{H}_3$), 1.78 (3H, d, *J* = 7.05 Hz, $\mathbf{H}_3CHC{=}CCH_3$), 4.17 (2H, q, *J* = 6.87 Hz, -$OC\mathbf{H}_2CH_3$), 5.75 (1H, d, *J* = 15.4 Hz, HC=C**H**CO_2Et), 5.95 (1H, q, *J* = 7.05 Hz, $H_3C\mathbf{H}C{=}CCH_3$), 7.28 (1H, d, *J* = 15.4 Hz, **H**C=$CHCO_2$Et) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.7 ($\mathbf{C}H_3$), 14.3 (-$\mathbf{C}H_3$), 14.4 (-$\mathbf{C}H_3$), 60.0 (-$O\mathbf{C}H_2$-), 115.2 (-**C**H=CH-), 133.7 (-**C**H=C-), 136.2 (-**C**=CH-), 149.4 (-**C**H=CH-), 167.6 (-**C**=O) ppm;

FTIR (neat, cm^{-1}): 2985, 2940, 2870, 1704, 1621, 1446;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_9H_{14}O_2]^+$ = 154.0994, found = 154.0996.

(2*E*,4*E*)-Ethyl-4-methyl-2,4-hexadien-1-ol (48)



47 (16.8 g, 0.10 mol) in dry ether (200 mL) was added dropwise to a suspension of lithium aluminium hydride at 0 °C under nitrogen. The reaction mixture was warmed slowly to room temperature and stirred for 4h. The mixture was quenched by adding saturated Na_2SO_4 solution dropwise at 0 °C. The mixture was filtered and the residue washed with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and rotary evaporated to give 92% (10.3 g) product **48**.

$\mathbf{R_f}$ = 0.52 (Hexane:EtOAc, 1:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (3H, s, $H_3CHC{=}CC\mathbf{H}_3$), 1.72 (3H, d, *J* = 6.77 Hz, $\mathbf{H}_3CHC{=}CCH_3$), 4.17 (2H, d, *J* = 6.18 Hz, -C$\mathbf{H}_2$OH), 5.56 (1H, q, *J* = 6.77 Hz, $CH_3\mathbf{H}C{=}CCH_3$), 5.69 (1H, dt, *J* = 15.6, 6.18 Hz, -CH=C**H**CH_2OH), 6.24 (1H, d, *J* = 15.6 Hz, -C**H**=$CHCH_2$OH) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9 (-$\mathbf{C}H_3$), 13.7 (-$\mathbf{C}H_3$), 63.8 (-$\mathbf{C}H_2$OH), 124.6 (-**C**H=C-), 127.4 (-**C**H=CH-), 133.7 (-CH=**C**H-), 136.2 (-CH=**C**-) ppm;

FTIR (neat, cm^{-1}): 3401, 2988, 2926, 2866, 1671, 1452;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_7H_{12}O]^+$ = 112.0888, found = 112.0896.

(2*E*,4*E*)-1-(Benzyloxy)-4-methyl-2,4-hexadien-1-ol (49)

48 (4.00 g, 36 mmol) was added to a solution of sodium hydride (8.72 g, 0.36 mol) in THF (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes after which benzyl bromide (6.82 g, 39 mmol, 4.8 mL) was added. The reaction was warmed slowly to room temperature and stirred for 3h. Saturated NH_4Cl solution was added drop-wise at 0 °C to quench the reaction. The reaction mixture was filtered, and washed with ethyl acetate. The combined organic layer was washed with water (1 x 100 mL), brine (1 x 100 mL), dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. Purification *via* flash column chromatography yielded 83% (6.05 g) of product **49**.

$\mathbf{R}_f$ = 0.84 (Hexane:EtOAc, 2:1);

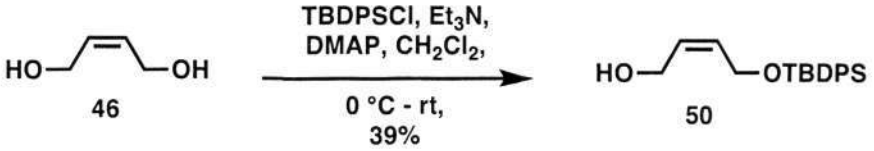
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (3H, s, $H_3CHC{=}CC\mathbf{H}_3$), 1.76 (3H, d, *J* = 6.81 Hz, $\mathbf{H}_3CHC{=}CCH_3$), 4.10 (2H, d, *J* = 6.35 Hz, -$C\mathbf{H}_2OBn$), 4.54 (2H, s, $OC\mathbf{H}_2C_6H_5$), 5.59 (1H, q, *J* = 6.81 Hz, $H_3C\mathbf{H}C{=}CCH_3$), 5.69 (1H, dt, *J* = 15.76, 6.35 Hz, $HC{=}C\mathbf{H}CH_2OBn$), 6.29 (1H, d, *J* = 15.76 Hz, $\mathbf{H}C{=}CHCH_2OBn$), 7.30 – 7.39 (5H, m, -$OCH_2C_6\mathbf{H}_5$) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9 (-$\mathbf{C}H_3$), 13.7 (-$\mathbf{C}H_3$), 71.0 (-$O\mathbf{C}H_2$-), 71.8 (-$O\mathbf{C}H_2$-), 122.1 (-**C**H-), 127.3 (-**C**H-), 127.4 (-**C**H-), 127.5 (-**C**H-), 127.7 (-**C**H-), 128.2 (-**C**H-), 133.8 (-**C**-), 137.9 (-**C**-) ppm;

FTIR (neat, cm^{-1}): 3040, 2997, 2920, 2853, 1709, 1452;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_{14}H_{18}O]^+$ = 202.1358, found = 202.1353.

(2*Z*)-1-(*tert*-Butyldiphenylsilyloxy)-1,4-butendiol (50)



Triethylamine (11.1 g, 0.11 mol, 16 mL) was added to a solution of dimethyl aluminium hydride (1.4 g, 0.01 mol) in CH_2Cl_2 (150 mL). But-2-ene-1,4 diol **46** (10.0 g, 0.11 mol, 9.5 mL) was added to the reaction mixture followed by *t*-butyldiphenylsilylchloride (31.2 g, 0.11 mol, 30 mL) at 0 °C. The mixture was stirred overnight. The reaction was quenched by adding ice water. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layer was washed with water (1 x 50 mL), brine (1x 50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. Purification *via* column chromatography eluted the pure product **50** in 39% (14.1 g) yield.

$\mathbf{R_f}$ = 0.45 (Hexane:EtOAc, 2:1);

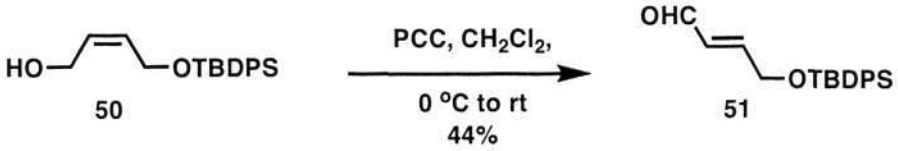
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (9H, s, $OSi(C_6H_5)_2C(CH_3)_3$), 1.91 (1H, brs, O**H**), 4.02 (2H, d, *J* = 5.70 Hz, C**H**$_2$OH), 4.29 (2H, d, *J* = 4.62 Hz, C**H**$_2$OTBDPS), 5.60 -5.69 (1H, m, C**H**CH$_2$OH), 5.71 – 5.77 (1H, m, C**H**CH$_2$OTBDPS), 7.40 – 7.76 (10H, m, $OSi(C_6H_5)_2C(CH_3)_3$) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0 (-**C**$(CH_3)_3$), 26.7 (-C(**C**$H_3)_3$), 58.5 (-O**C**H_2-), 60.1 (-O**C**H_2-), 127.6 (-**C**H-), 129.7 (-**C**H-), 129.8 (-**C**H-), 130.7 (-**C**H-), 133.3 (-**C**H-), 135.5 (-**C**-) ppm;

FTIR (neat, cm^{-1}): 3447, 3019, 2928, 2861, 1428;

HRMS (EI [M-C_4H_9]$^+$): *m/e* calculated for $[C_{16}H_{17}O_2Si]^+$ = 269.0998, found = 269.0998.

(2*E*)-4-(*tert*-Butyldiphenylsilyloxy)-2-butenal (51)



50 (9.07 g, 28 mmol) in CH_2Cl_2 (30 mL) was added to pyridinium chlorochromate (56 g, 56 mmol), 4Å molecular sieve (9 g) and silica gel (9 g) in CH_2Cl_2 (150 mL) at 0 °C. The reaction mixture was warmed slowly to room temperature and stirred for 4h. The reaction mixture was filtered through a sintered glass funnel packed with silica gel and washed with CH_2Cl_2. The filtrate was dried over $MgSO_4$ and rotary evaporated. Purification through column chromatography yielded 44% (4.0 g) product **51**.

R_f = 0.63 (Hexane:EtOAc, 2:1);

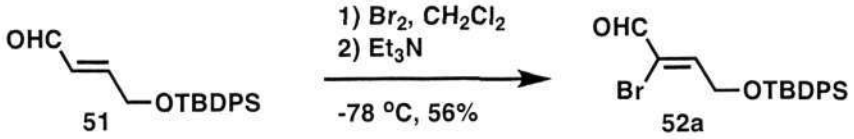
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (9H, s, -C(CH_3)$_3$), 4.45 (2H, d, *J* = 2.37, -CH_2OTBDPS), 6.57 (1H, dd, *J* = 15.5, 8.10 Hz, -CHCHO), 6.84 (1H, dt, *J* = 15.5, 2.37 Hz, -CHCH$_2$OTBDPS), 7.40-7.67 (10H, m, -Ph-H), 9.60 (1H, d, *J* = 8.10 Hz, -CHO) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1 (-C(CH$_3$)$_3$), 26.6 (-C(CH$_3$)$_3$), 62.8 (-OCH$_2$-), 127.7 (-CH-), 129.8 (-CH-), 130.6 (-CH-), 132.6 (-CH-), 135.3 (-C-), 155.8 (-CH-), 193.0 (-C=O) ppm;

FTIR (neat, cm^{-1}): 3073, 2965, 2939, 2860, 1658, 1472;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_{20}H_{24}O_2Si]^+$ = 324.1546 found = 324.1546.

(*Z*)-2-bromo-4-(*tert*-butyldiphenylsilyloxy)but-2-enal (52a)



To a solution of **51** (0.60 g, 1.8 mmol) in CH_2Cl_2 (20 mL) was treated with Br_2 (0.29 g, 1.8 mmol) at -78 °C. The resulting colourless solution was treated with additional Br_2 until reddish brown colour persisted. The reaction mixture was warmed to 0 °C and stirred for 20 minutes. The mixture was then cooled to -78 °C and Et_3N (0.18 g,

1.8 mmol) was added dropwise with vigorous stirring. After completed, the reaction mixture was filtered through sintered glass funnel and the residue was washed with copious amount of dry ether. The filtrate was washed with saturated $Na_2S_2O_3$ solution, brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was chromatographed (hexane:ether = 99:1) affording 0.42 g of **52a** as a colourless oil (56%).

$\mathbf{R_f}$ = 0.50 (Hexane:Ether, 6:1);

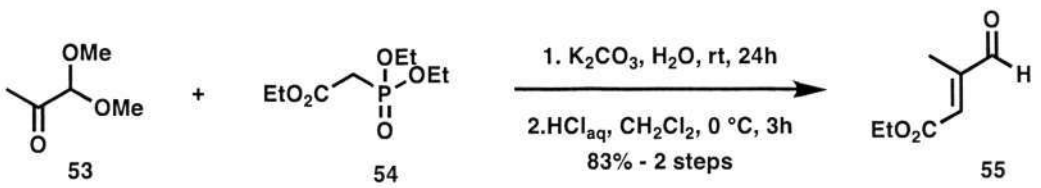
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (9H, s, -C($\mathbf{CH_3}$)$_3$), 4.62 (2H, d, *J* = 4.79 Hz, -$\mathbf{CH_2}$-OTBDPS), 7.31 (1H, t, *J* = 4.79 Hz, -C=C**H**-), 7.39-7.69 (10H, m, -Ph-**H**), 9.15 (s, 1H -C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1 (-**C**(CH_3)$_3$), 26.6 (-C(**C**H_3)$_3$), 63.9 (-O**C**H_2-), 122.0 (-**C**H-), 127.8 (-**C**H-), 130.0 (-**C**-), 132.6 (-**C**H-), 135.4 (-**C**-), 154.5 (-**C**H-), 185.0 (-**C**=O) ppm;

FTIR (neat, cm^{-1}): 3057, 2963, 2930, 2858, 1709, 1622, 1428;

HRMS (EI [M-C_4H_9]$^+$): *m/e* calculated for [$C_{16}H_{14}O_2Si^{79}Br$]$^+$ = 344.9946 found = 344.9956.

(*E*)-ethyl 3-methyl-4-oxobut-2-enoate (55)



A mixture of 1,1-dimethoxyacetone (**53**) (5.91 g, 50 mmol) and ethyl 2-(diethoxyphosphoryl)acetate (**54**) (13.45 g, 60 mmol) was added dropwise to a suspension of K_2CO_3 (17.28 g) in 10 mL of water at room temperature. After the addition was complete, stirring was continued at room temperature for an additional

24h. The insoluble matter was then removed by filtration and washed with ether. The organic phase was separated and washed with brine to neutrality. After drying and evaporation of solvent, the product was purified by distillation under vacuum, which yields a mixture of *E* and *Z* acetal esters as a colorless oil.

HCl (3N, 15 mL) was added dropwise to a solution of the above obtained *E* and *Z* acetal esters in 15 mL CH_2Cl_2 at 0 °C. The resulting mixture was stirred for another 2h at 0 °C. The organic layer was separated and washed with a saturated aqueous solution of $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Solvent was removed under vacuum. The crude product was purified by vacuum distillation to yield 5.9 g of the *E* isomer of **55** (yield: 83%).

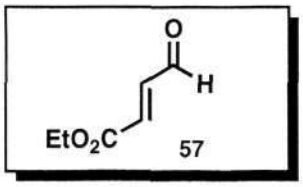
$\mathbf{R}_f$ = 0.45 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (3H, t, *J* = 7.03 Hz, -OCH$_2$C**H**$_3$), 2.16 (3H, d, *J* = 1.76 Hz, -CC**H**$_3$), 4.28 (2H, q, *J* = 7.03 Hz, -OC**H**$_2$CH$_3$), 6.50 (1H, q, *J* = 1.76 Hz, -C**H**=C-), 9.55 (1H, s, C**H**O) ppm;

(*E*)-ethyl 4-oxobut-2-enoate (75) and (*Z*)-ethyl 3-bromo-4-oxobut-2-enoate (57)

Following the described procedure for the preparation of dienophile **55**; dienophile **57** was obtained in 78% (2 steps) and dienophile **58** was obtained in 30% yield.

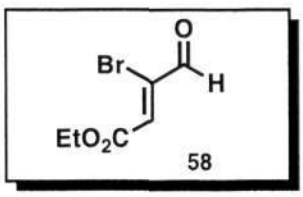
(*E*)-ethyl 4-oxobut-2-enoate (57)



$\mathbf{R}_f$ = 0.43 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (3H, t, *J* = 6.96 Hz, -$OCH_2C\mathbf{H}_3$), 4.30 (2H, q, *J* = 6.96 Hz, -$OC\mathbf{H}_2CH_3$), 6.72 (1H, q, *J* = 16.02 Hz, -C**H**=CH-), 6.97 (1H, dd, *J* = 7.65, 16.02 Hz, -CH=C**H**-), 9.76 (1H, dd, *J* = 7.65, 0.69 Hz, -C**H**O) ppm

(Z)-ethyl 3-bromo-4-oxobut-2-enoate (58)

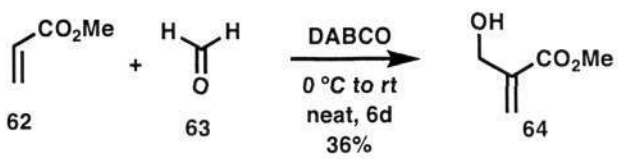


$\mathbf{R}_f$ = 0.62 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (3H, t, *J* = 7.32 Hz, -$OCH_2C\mathbf{H}_3$), 4.34 (2H, q, *J* = 7.32 Hz, -$OC\mathbf{H}_2CH_3$), 7.28 (1H, s, -C=C**H**-), 9.26 (1H, s, -C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (-$OCH_2\mathbf{C}H_3$), 61.8 (-$O\mathbf{C}H_2CH_3$), 133.9 (-**C**=CH-), 136.0 (-C=**C**H-), 163.1 (-**C**O_2Et), 185.9 (-**C**HO) ppm;

methyl 2-(hydroxymethyl)acrylate (64)



Methyl acrylate (**62**) (1 mol, 86.1 g), DABCO (0.1 mol, 11.2 g) and formaldehyde (**63**) (1.5 mol, 41,7 mL) were stirred at room temperature for six days. The product

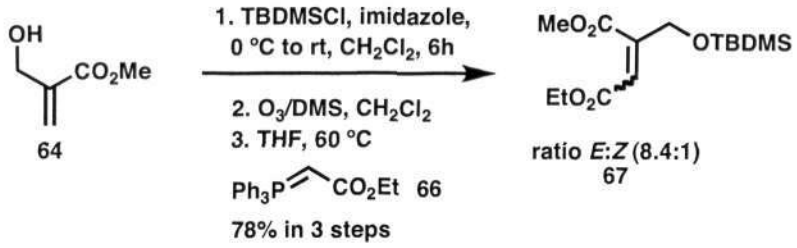
was extracted with ethyl acetate (x3). The organic extracts were washed with brine, dried with anhydrous $MgSO_4$, concentrated in *vacuo* and purified by distillation, affording 41.8 g of pure **64** as colourless oil (36% yield). Bp: 105 °C / 4.5 mmHg.

$\mathbf{R_f}$ = 0.25 (Hexane:EtOAc, 2:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (3H, s, -C**H**$_3$), 4.30 (2H, d, *J* = 5.57 Hz, -C**H**$_2$OH), 5.82 (1H, d, *J* = 1.21 Hz, -C=C**H**$_2$-), 6.22 (1H, s, -C=C**H**$_2$-) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 51.8 (-OC**H**$_3$), 62.2 (-**C**H$_2$OH), 125.6 (-C=**C**H$_2$), 139.4 (-**C**=CH$_2$), 166.7 (-**C**=O) ppm

4-ethyl 1-methyl 2-((*tert*-butyldimethylsilyloxy)methyl)but-2-enedioate (86)



To a solution of **64** (5 g, 43 mmol) in CH_2Cl_2 (100 mL) was added imidazole (5.85 g, 86 mmol) at 0 °C. After imidazole was dissolved, TBDMSCl (7.13 g, 47.3 mmol) was added to the reaction mixture. The mixture was at 0 °C to room temperature for 6h. The reaction was poured into ice water and extracted with ethyl acetate (x3). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed in *vacuo*. The crude product was then used for ozonolysis at -78 °C in CH_2Cl_2 as the solvent. The reaction was quenched by adding DMS (3 equiv) and let it stirred for overnight at room temperature. After washed with water, dried over $MgSO_4$ and concentrated, the crude product was further subjected for Wittig reaction with **66** (22.47 g, 64.5 mmol) in THF at 60 °C for 12h. The solvent was removed and

purification *via* column chromatography eluted the pure product **67** in 78% (10.15 g) yield in 3 steps. (*Z*:*E* = 8.4:1)

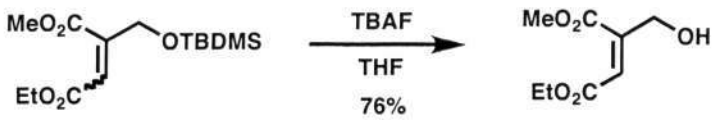
Major *E* isomer:

$\mathbf{R}_f$ = 0.73 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.07 (6H, s, -Si-($C\mathbf{H}_3$)$_2$), 0.89 (9H, s, -C($C\mathbf{H}_3$)$_3$), 1.27 (3H, t, *J* = 7.1 Hz, -$OCH_2C\mathbf{H}_3$), 3.78 (3H, s, -$CO_2\mathbf{Me}$), 4.18 (2H, t, *J* = 7.1 Hz, -$OC\mathbf{H}_2CH_3$), 4.36 (2H, d, *J* = 2.05 Hz, -$C\mathbf{H}_2$OTBDMS), 6.15 (1H, t, *J* = 2.05 Hz, -C=C**H**-) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ -5.6 (-Si($\mathbf{C}H_3$)$_2$), 14.1 (-$\mathbf{C}H_3$), 18.2 (-$\mathbf{C}$(CH_3)$_3$), 25.7 (-C($\mathbf{C}H_3$)$_3$), 52.2 (-O**Me**), 60.9 (-$O\mathbf{C}H_2$-), 62.5 (-$O\mathbf{C}H_2$-), 120.1 (-**C**H=C-), 147.1 (-CH=**C**-), 165.5 (-**C**=O), 167.2 (-**C**=O) ppm;

***E*-4-ethyl 1-methyl 2-(hydroxymethyl)maleate (68)**



ratio *E*:*Z* (8.4:1)
67

E - 68 only

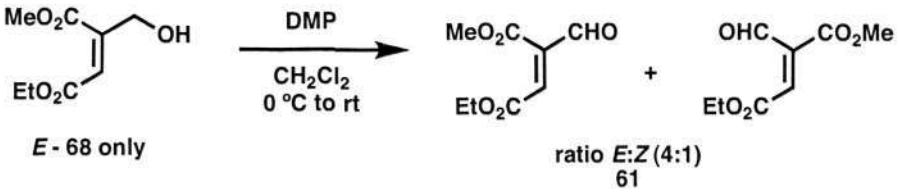
To a solution of **67** (0.91 g, 3 mmol) in THF (9 mL) was treated with TBAF (4.5 mL, 1.0 M in THF solution, 4.5 mmol) at room temperature. The mixture was stirred for 30 minutes. After the reaction was completed (monitor by TLC), THF was removed in *vacuo*. The residue was purified by flash chromatography on silica gel to afford *E*-alcohol **68** as a colorless oil, 0.43 g (76%).

$\mathbf{R}_f$ = 0.15 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (3H, t, *J* = 7.1 Hz, -$OCH_2C\mathbf{H}_3$), 3.82 (3H, s, -$CO_2\mathbf{Me}$), 4.21 (2H, q, *J* = 7.1 Hz, -$OC\mathbf{H}_2CH_3$), 4.39 (2H, d, *J* = 1.6 Hz, -$C\mathbf{H}_2$OH), 6.20 (1H, t, *J* = 1.6 Hz, -C=C**H**-) ppm;

2.3% NOE

4-ethyl 1-methyl 2-formylmaleate (61)



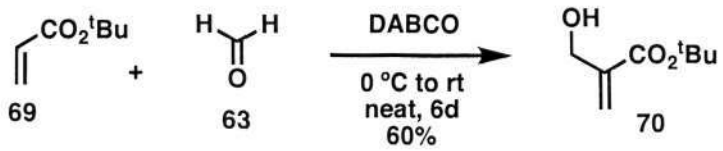
To a solution of Dess-Martin reagent (0.64 g, 1.5 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise of **68** (0.19 g, 1 mmol) prediluted in CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was stirred under nitrogen at 0 °C for 30 minutes. After completion, the reaction mixture was filtered through selite and rinse with ether. The combine etherate layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo* to give **61** as a colorless oil, quantitative yield assumed (**61** is sensitive to purification, NMR determination was done from the crude product ^{1}H NMR).

$\mathbf{R}_f$ = 0.43 (Hexane:EtOAc, 4:1);

major ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (3H, t, *J* = 7.1 Hz, -$OCH_2\mathbf{CH_3}$), 3.88 (3H, s, -$CO_2\mathbf{Me}$), 4.28 (2H, q, *J* = 7.1 Hz, -$OC\mathbf{H_2}CH_3$), 6.74 (1H, s, -C=C**H**-), 9.65 (1H, s, -C**H**O) ppm

minor ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (3H, t, *J* = 7.1 Hz, -$OCH_2\mathbf{CH_3}$), 3.86 (3H, s, -$CO_2\mathbf{Me}$), 4.28 (2H, q, *J* = 7.1 Hz, -$OC\mathbf{H_2}CH_3$), 7.09 (1H, s, -C=C**H**-), 10.17 (1H, s, -C**H**O) ppm

***tert*-butyl 2-(hydroxymethyl)acrylate (70)**



Tert-butyl acrylate (**69**) (10 mL, 68.9 mmol), DABCO (7.7 g, 68.9 mmol) and formaldehyde (**63**) (0.689 mol, 100 mL) were stirred at room temperature for six

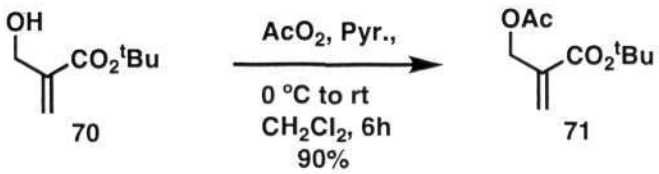
days. The product was extracted with ether (x5). The organic extracts was washed with brine, dried with anhydrous $MgSO_4$, concentrated in *vacuo* and purified by column chromatography, affording 6.54 g of pure **70** as colourless oil (60% yield).

$\mathbf{R}_f$ = 0.41 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (9H, s, -C($\mathbf{CH}_3$)$_3$), 4.28 (2H, d, J = 6.83 Hz, -$\mathbf{CH}_2$OH), 5.74 (1H, d, J = 1.21 Hz, -C=C$\mathbf{H}_2$-), 6.15 (1H, s, -C=C$\mathbf{H}_2$-) ppm

^{13}C NMR (75 MHz, $CDCl_3$): δ 28.0 (-OC($\mathbf{CH}_3$)$_3$), 62.7 (-$\mathbf{CH}_2$OH), 81.3 (-O$\mathbf{C}$(CH$_3$)$_3$), 124.7 (-C=$\mathbf{CH}_2$), 140.9 (-$\mathbf{C}$=CH$_2$), 165.7 (-$\mathbf{C}$=O) ppm

***tert*-butyl 2-(acetoxymethyl)acrylate (71)**



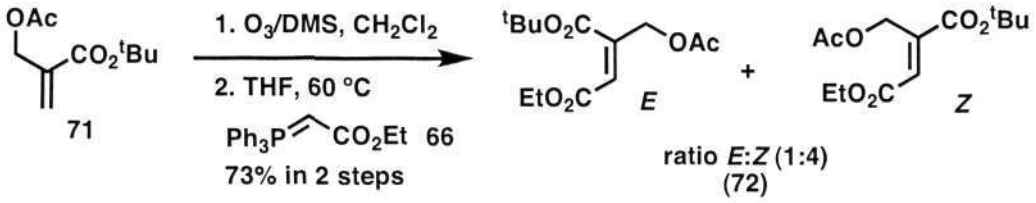
To a solution of **70** (6.4 g, 40.4 mmol) in CH_2Cl_2 (100 mL) was added pyridine (6.54 mL, 80.8 mmol) at 0 °C. After stirred for 10 minutes, acetic anhydride (7.7 mL, 80.8 mmol) was added to the reaction mixture. The mixture was at 0 °C to room temperature for 6h. The reaction was poured into ice water and extracted with ether (x3). The combined organic layer was washed with copper sulfate solution, water, brine and dried over anhydrous $MgSO_4$. The solvent was removed in *vacuo*. Purification by column chromatography provided **71** in 90% yield (7.30 g).

$\mathbf{R}_f$ = 0.57 (Hexane:EtOAc, 4:1);

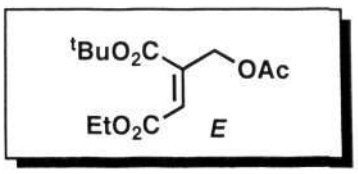
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (9H, s, -C($\mathbf{CH}_3$)$_3$), 2.06 (3H, s, O**Ac**), 4.73 (2H, s, -$\mathbf{CH}_2$OAc), 5.69 (1H, s, -C=C$\mathbf{H}_2$-), 6.21 (1H, s, -C=C$\mathbf{H}_2$-) ppm

^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7 (-O**Ac**), 27.9 (-OC($\mathbf{CH}_3$)$_3$), 62.5 (-O$\mathbf{CH}_2$-), 81.2 (-O$\mathbf{C}$(CH$_3$)$_3$), 125.9 (-C=$\mathbf{CH}_2$), 136.8 (-$\mathbf{C}$=CH$_2$), 164.2 (-$\mathbf{C}$=O), 170.2 (-$\mathbf{C}$=O) ppm

1-*tert*-butyl 4-ethyl 2-(acetoxymethyl)maleate (72)



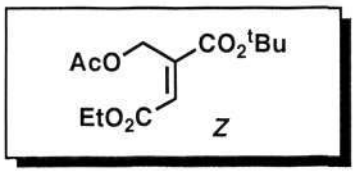
To a solution of **71** (5 g, 25 mmol) in CH_2Cl_2 was subjected for ozonolysis at -78 °C. After completion (~30 minutes), the reaction was quenched by adding DMS (3 equiv) and let it stirred for overnight at room temperature. After washed with water, dried over $MgSO_4$ and concentrated, the crude product was further subjected for Wittig reaction with **66** (13 g, 37.5 mmol) in THF at 60 °C for 12h. The solvent was removed and purification *via* column chromatography eluted the pure product **72** in 73% (4.96 g) yield in 2 steps. (*Z*:*E* = 4:1)



$\mathbf{R}_f$ = 0.59 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (3H, t, *J* = 7.2 Hz, -$OCH_2C\mathbf{H}_3$), 1.53 (9H, s, -$C(C\mathbf{H}_3)_3$), 2.12 (3H, s, -O**Ac**), 4.23 (2H, q, *J* = 7.2 Hz, -$OC\mathbf{H}_2CH_3$), 4.79 (2H, d, *J* = 1.55 Hz, -$C\mathbf{H}_2OAc$), 6.07 (1H, t, *J* = 1.65 Hz, -C=C**H**-) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (-$\mathbf{C}H_3$), 20.6 (-$\mathbf{C}H_3$), 27.9 (-$OC(\mathbf{C}H_3)_3$), 61.0 (-$O\mathbf{C}H_2$-), 63.1 (-$O\mathbf{C}H_2$-), 83.0 (-$O\mathbf{C}(CH_3)_3$), 122.5 (-**C**H=C-), 141.8 (-CH=**C**-), 164.4 (-**C**=O), 164.8 (-**C**=O), 169.9 (-**C**=O) ppm



$\mathbf{R}_f$ = 0.63 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (3H, t, *J* = 7.1 Hz, -$OCH_2\mathbf{CH_3}$), 1.51 (9H, s, -$C(\mathbf{CH_3})_3$), 2.06 (3H, s, -**OAc**), 4.26 (2H, q, *J* = 7.1 Hz, -$\mathbf{OCH_2}CH_3$), 5.21 (2H, s, -$\mathbf{CH_2}OAc$), 6.82 (1H, s, -C=C**H**-) ppm

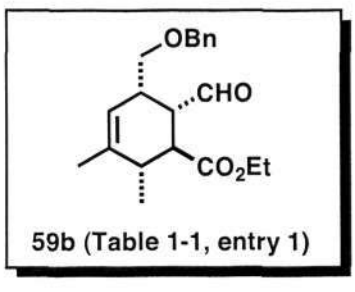
^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (-$\mathbf{C}H_3$), 20.7 (-$\mathbf{C}H_3$), 28.0 (-$OC(\mathbf{C}H_3)_3$), 58.1 (-$O\mathbf{C}H_2$-), 61.2 (-$O\mathbf{C}H_2$-), 82.5 (-$O\mathbf{C}(CH_3)_3$), 130.0 (-**C**H=C-), 141.6 (-CH=**C**-), 164.3 (-**C**=O), 164.9 (-**C**=O), 170.2 (-**C**=O) ppm

Diels-Alder Reactions

General Procedure using $BF_3.OEt_2$ as Catalyst

The dienophile (1 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a stirred solution of 4Å molecular sieve (100 mg, excess) and cooled to -78 °C for 15 minutes. Then boron trifluoride dietherate (0.06 mL, 0.5 mmol) was added dropwise. Subsequently, the diene (3 mmol) pre-diluted in CH_2Cl_2 (1 mL) was added dropwise. The whole reaction was maintained at -78 °C with constant stirring for 16h. The reaction was quenched with saturated $NaHCO_3$ (2 mL). The organic layer was extracted with CH_2Cl_2 (3 x 5 mL), washed with saturated $NaHCO_3$ (2 x 5 mL), and dried over anhydrous $MgSO_4$. The filtrate was filtered and concentrated. Purification by flash column chromatography afforded the pure compound.

ethyl 5-(benzyloxymethyl)-6-formyl-2,3-dimethylcyclohex-3-enecarboxylate (77b)



59b (Table 1-1, entry 1)

Yield = 42%;

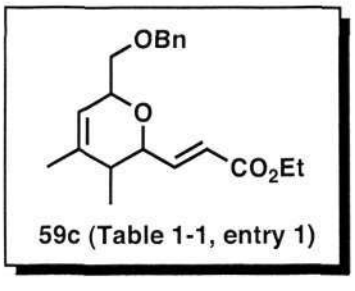
R_f = 0.44 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (3H, d, *J* = 6.9 Hz, CHC**H**$_3$), 1.30 (3H, dd, *J* = 6.9, 7.4 Hz, -OCH$_2$C**H**$_3$), 1.67 (3H, d, *J* = 1.4 Hz, -CH=CC**H**$_3$), 2.25 (1H, dq, *J* = 7.9, 7.4 Hz, -C**H**CH$_3$), 2.50 (1H, dd, *J* = 10.2, 9.7 Hz, -C**H**CO$_2$Et), 3.03-3.09 (2H, m, -C**H**CHO, -C**H**CH$_2$OBn), 3.11 (1H, q, *J* = 8.8 Hz, -C**H**$_2$OBn), 3.40 (1H, dd, *J* = 8.8, 2.3 Hz, -C**H**$_2$OBn), 4.20 (2H, ddd, *J* = 14.3, 7.16, 1.4 Hz, -OC**H**$_2$CH$_3$), 4.30 (1H, d, *J* = 11.55 Hz, OC**H**$_2$C$_6$H$_5$), 4.40 (1H, d, *J* = 12 Hz, OC**H**$_2$C$_6$H$_5$), 5.38 (1H, d, *J* = 3.70, 1.35 Hz, -C**H**=C-), 7.26-7.35 (5H, m, OCH$_2$C$_6$**H**$_5$), 9.72 (1H, s, C**H**O) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2 (-OCH$_2$**C**H$_3$), 17.5 (-CH-**C**H$_3$), 21.2 (-CH=C-**C**H$_3$), 36.7 (-**C**HCH$_2$OBn), 37.6 (-**C**H-CH$_3$), 44.2 (-**C**HCO$_2$Et), 52.1 (-**C**HCHO), 60.6 (-O**C**H$_2$CH$_3$), 70.3 (-CH-**C**H$_2$OBn), 73.0 (-O**C**H$_2$Ph), 120.1 (-**C**H=C-CH$_3$), 127.6 (Ph-**C***p*), 127.8 (Ph-**C***o* x2), 128.3 Ph-**C***m* x2), 137.6 (Ph-**C***q*), 139.5 (-CH=**C**-CH$_3$), 175.5 (**C**O$_2$Et), 200.9 (**C**HO) ppm;

HRMS (EI [M]$^+$): *m/e* calculated for [$C_{20}H_{26}O_4$]$^+$ = 330.1831, found = 330.1821.

ethyl 3-(6-(benzyloxymethyl)-3,4-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)acrylate (59c, Table 1-1, entry 1)



59c (Table 1-1, entry 1)

Yield = 41%;

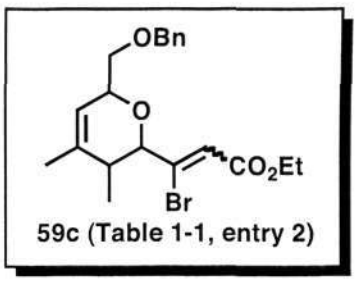
R_f = 0.48 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (3H, d, *J* = 6.96 Hz, CHC**H**$_3$), 1.29 (3H, t, *J* = 7.32 Hz, -OCH$_2$C**H**$_3$), 1.74 (3H, s, -C=CC**H**$_3$), 1.94-1.99 (1H, m, C**H**CH$_3$), 3.47 (1H, dd, *J* = 9.93, 4.71, Hz, -C**H**$_2$OBn), 3.55 (1H, dd, *J* = 10.11, 6.63 Hz, -C**H**$_2$OBn), 4.20 (2H, q, *J* = 7.32 Hz, -OC**H**$_2$CH$_3$), 4.29-4.32 (1H, m, -OC**H**CH=CH-), 4.37-4.40 (1H, m, -C**H**CH$_2$OBn), 4.58 (1H, d, *J* = 12.54 Hz, -OC**H**$_2$C$_6$H$_5$), 4.63 (1H, d, *J* = 12.54 Hz, -OC**H**$_2$C$_6$H$_5$), 5.32 (1H, s, -C**H**=C-), 6.14 (1H, dd, *J* = 15.66, 1.74 Hz, -CH=C**H**CO$_2$Et), 6.90 (1H, dd, *J* = 15.66, 3.84 Hz, -C**H**=CHCO$_2$Et), 7.26-7.35 (5H, m, -OCH$_2$C$_6$**H**$_5$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.4 (-CH-**C**H$_3$), 14.2 (-OCH$_2$**C**H$_3$), 21.5 (-CH=C-**C**H$_3$), 37.4 (-**C**H-CH$_3$), 60.1 (-O**C**H$_2$CH$_3$), 73.1 (-CHCH$_2$O**C**H$_2$Ph), 73.3 (-CH**C**H$_2$OBn), 74.9 (-O**C**HCH$_2$OBn), 75.3 (-O**C**HCH=CHCO$_2$Et), 120.0 (-**C**H=C-CH$_3$), 120.8 (-CH=**C**HCO$_2$Et), 127.4 (Ph-**C***p*), 127.6 (Ph-**C***o* x2), 128.2 (Ph-**C***m* x2), 138.3 (-CH=**C**CH$_3$), 139.2 (Ph-**C***q*), 146.5 (-**C**H=CHCO$_2$Et), 166.5 (**C**O$_2$Et) ppm;

HRMS (EI [M]$^+$): *m/e* calculated for [C$_{20}$H$_{26}$O$_4$]$^+$ = 330.1831; found = 330.1828

Ethyl 3-(6-(benzyloxymethyl)-3,4-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)-3-bromoacrylate (59c, Table 1-1, entry 2)



59c (Table 1-1, entry 2)

Mixture of diastereomers.

Yield = 56%;

Diastereomer 1:

R$_f$ = 0.57 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (3H, d, *J* = 6.9 Hz, CHC**H**$_3$), 1.32 (3H, dd, *J* = 6.95, 6.90 Hz, -OCH$_2$C**H**$_3$), 1.78 (3H, s, -CH=CC**H**$_3$), 2.45 (1H, d, *J* = 6.9 Hz, -C**H**CH$_3$), 3.48 (1H, dd, *J* = 9.95, 4.65 Hz, -C**H**$_2$OBn), 3.55 (1H, dd, *J* = 9.95, 6.45 Hz, -C**H**$_2$OBn), 4.24 (2H, q, *J* = 6.95 Hz, -OC**H**$_2$CH$_3$), 4.30 (1H, brs, -C**H**CH$_2$OBn), 4.41 (1H, brs, -OC**H**C-Br), 4.61 (2H, s, -OC**H**$_2$C$_6$H$_5$), 5.33 (1H, s, -C**H**=C-), 6.83 (1H, s, -C=C**H**CO$_2$Et), 7.28-7.36 (5H, m, -OCH$_2$C$_6$**H**$_5$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.4 (-CH**C**H$_3$), 14.2 (-OCH$_2$**C**H$_3$), 21.7 (-CH=C-**C**H$_3$), 35.7 (-**C**HCH$_3$), 60.4 (-O**C**H$_2$CH$_3$), 72.9 (-O**C**H$_2$Ph), 73.3 (-**C**H$_2$OBn), 75.7 (-O**C**HCH$_2$OBn), 80.4 (-O**C**HC=CHCO$_2$Et), 119.0 (-**C**H=C-), 119.7 (-C=**C**H-), 127.5 (Ph-**C***p*), 127.6 (Ph-**C***o* x2), 128.3 (Ph-**C***m* x2), 137.9 (**C***q*), 138.2 (**C***q*), 139.2 (**C***q*), 164.4 (-**C**O$_2$Et) ppm;

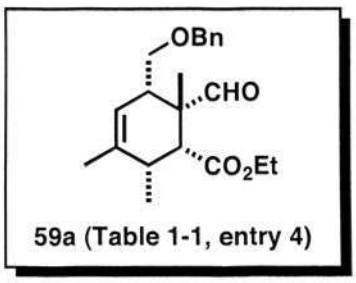
Diastereomer 2:

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05 (3H, d, *J* = 6.95 Hz, CHC**H**$_3$), 1.32 (3H, dd, *J* = 7.40, 6.95 Hz, -OCH$_2$C**H**$_3$), 1.75 (3H, s, -CH=CC**H**$_3$), 2.50 (1H, d, *J* = 6.9 Hz, -C**H**CH$_3$), 3.49 (1H, dd, *J* = 9.70, 4.15 Hz, -C**H**$_2$OBn), 3.57 (1H, dd, *J* = 9.70, 6.5 Hz, -C**H**$_2$OBn), 4.14 (1H, d, *J* = 5.55 Hz, -C**H**CH$_2$OBn), 4.23 (2H, q, *J* = 6.95 Hz, -OC**H**$_2$CH$_3$), 4.39 (1H, brs, -OC**H**CBr-), 4.59 (2H, s, -OC**H**$_2$C$_6$H$_5$), 5.29 (1H, s, -C**H**=C-), 6.47 (1H, s, -C=C**H**CO$_2$Et), 7.28-7.35 (5H, m, -OCH$_2$C$_6$**H**$_5$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (-CH**C**H$_3$), 16.2 (-OCH$_2$**C**H$_3$), 21.2 (-CH=C-**C**H$_3$), 35.4 (-**C**HCH$_3$), 60.7 (-O**C**H$_2$CH$_3$), 71.7 (-O**C**HCH$_2$OBn), 72.0 (-O**C**H$_2$Ph), 73.2 (-**C**H$_2$OBn), 81.4 (-O**C**HC=CHCO$_2$Et), 119.9 (-**C**H=C-), 122.1 (-C=**C**H-), 127.6 (Ph-**C***p*), 127.8 (Ph-**C***o* x2), 128.3 (Ph-**C***m* x2), 135.8 (**C***q*), 138.2 (**C***q*), 139.6 (**C***q*), 164.1 (**C**O$_2$Et) ppm;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_{20}H_{25}BrO_4]^+$ = 408.0936, found = 408.0920.

ethyl 5-(benzyloxymethyl)-6-formyl-2,3,6-trimethylcyclohex-3-enecarboxylate (59a, Table 1-1, entry 4)



59a (Table 1-1, entry 4)

Yield = 35%

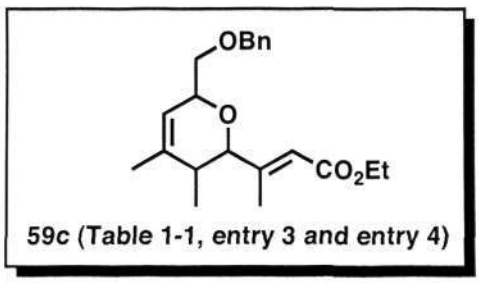
R_f = 0.41 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (3H, d, *J* = 7.4 Hz, CHC**H**$_3$), 1.21(3H, s, -CC**H**$_3$), 1.26 (3H, dd, *J* = 7.4, 6.95 Hz, -OCH$_2$C**H**$_3$), 1.78 (3H, d, *J* = 0.95 Hz, -CH=CC**H**$_3$), 2.35 (1H, m, -C**H**CH$_2$OBn), 2.62 (1H, dq, *J* = 7.4, 6.95 Hz, -C**H**CH$_3$), 2.96 (1H, d, *J* = 6.45 Hz, -C**H**CO$_2$Et), 3.32 (1H, dd, *J* = 6.95, 6.95 Hz, -C**H**$_2$OBn), 3.55 (1H, dd, *J* = 9.25, 4.15 Hz, -C**H**$_2$OBn), 4.15 (2H, ddd, *J* = 14.32, 7.15, 0.95 Hz, -OC**H**$_2$CH$_3$), 4.40 (1H, d, *J* = 12.05 Hz, -OC**H**$_2$C$_6$H$_5$), 4.44 (1H, d, *J* = 12.00 Hz, -OC**H**$_2$C$_6$H$_5$), 5.47 (1H, d, *J* = 1.4 Hz, -C**H**=C-), 7.26-7.34 (5H, m, -OCH$_2$C$_6$**H**$_5$), 9.91 (1H, s, C**H**O) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (-OCH$_2$**C**H$_3$), 16.4 (-CH-**C**H$_3$), 20.5 (-C-**C**H$_3$), 21.7 (-CH=C-**C**H$_3$), 34.9 (-**C**H-CH$_3$), 45.7 (-**C**H-CH$_2$OBn), 48.5 (-**C**-CHO), 54.6 (-**C**H-CO$_2$Et), 60.5 (-O**C**H$_2$CH$_3$), 69.9 (-CH-**C**H$_2$OBn), 73.1 (-CH-CH$_2$O**C**H$_2$Ph), 121.8 (-**C**H=C-CH$_3$), 127.5 (Ph-**C***p*), 127.6 (Ph-**C***o* x2), 128.3 (Ph-**C***m* x2), 135.6 (-CH=**C**-CH$_3$), 138.0 (Ph-**C***q*), 172.6 (-**C**O$_2$Et), 203.2 (**C**HO) ppm;

HRMS (EI $[M]^+$): *m/e* calculated for $[C_{21}H_{28}O_4]^+$ = 344.1988; found = 344.1988.

(*E*)-ethyl 3-(6-(benzyloxymethyl)-3,4-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)but-2-enoate (59c, Table 1-1, entry 3 and entry 4)



59c (Table 1-1, entry 3 and entry 4)

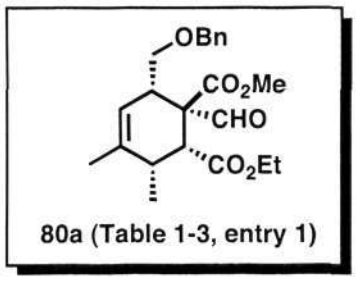
Yield = 42% (entry 3) and 9% (entry 4);

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

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (3H, d, *J* = 6.7 Hz, -C**H**$_3$), 1.30 (3H, t, *J* = 7.1 Hz, -OCH$_2$C**H**$_3$), 1.77 (3H, s, -C**H**$_3$), 2.11 (3H, s, -C**H**$_3$), 2.30-2.34 (1H, m, -C**H**CH$_3$), 3.49 (1H, dd, *J* = 10.1, 4.85, Hz, -C**H**$_2$OBn), 3.50 (1H, dd, *J* = 10.1, 6.25 Hz, -C**H**$_2$OBn), 4.06 (1H, brs, -OCH-), 4.14-4.21 (2H, m, -OC**H**$_2$CH$_3$), 4.37 (1H, brs, -OC**H**-), 4.43-4.51 (1H, m, -OC**H**-), 4.63 (2H, s, -OC**H**$_2$C$_6$H$_5$), 5.37 (1H, s, -C**H**=C-), 6.13 (1H, s, -CH=C**H**CO$_2$Et), 7.27-7.38 (5H, m, -OCH$_2$C$_6$**H**$_5$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.9 (-**C**H$_3$), 14.4 (-**C**H$_3$), 15.9 (-**C**H$_3$), 21.8 (-**C**H$_3$), 35.8 (-**C**H-), 59.6 (-O**C**H-), 73.2 (-O**C**H-), 73.4 (-**C**H-), 75.2 (-O**C**H$_2$-), 79.4 (-O**C**H$_2$-), 115.1 (-**C**H=C-), 120.2 (-C=**C**H-), 127.6 (Ph-**C***p*), 127.7 (Ph-**C***o* x2), 128.4 (Ph-**C***m* x2), 138.4 (-CH=**C**-), 139.3 (Ph-**C***q*), 155.8 (-**C**=CH-), 167.1 (-**C**O$_2$Et) ppm;

2-ethyl 1-methyl 6-(benzyloxymethyl)-1-formyl-3,4-dimethylcyclohex-4-ene-1,2-dicarboxylate (80a, Table 1-3, entry 1)



80a (Table 1-3, entry 1)

Yield = 22%

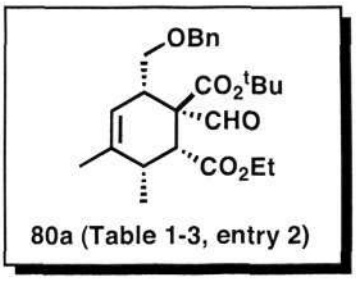
$\mathbf{R}_f$ = 0.30 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21 (3H, d, *J* = 6.95 Hz, CHC**H**$_3$), 1.24 (3H, dd, *J* = 7.4, 6.95 Hz, -OCH$_2$C**H**$_3$), 1.69 (3H, s, -CH=CC**H**$_3$), 2.64 (1H, dq, *J* = 7.85, 6.95 Hz, -C**H**CH$_3$), 3.04 (1H, d, *J* = 9.25 Hz, -C**H**CO$_2$Et), 3.18 (1H, m, -C**H**CH$_2$OBn), 3.29 (1H, dd, *J* = 8.8, 8.3 Hz, 1H, -C**H**$_2$OBn), 3.45 (1H, dd, *J* = 10.17, 3.25 Hz, -C**H**$_2$OBn), 3.71 (3H, s, CO$_2$**Me**), 4.16 (2H, dd, *J* = 12.0, 7.4 Hz, -OC**H**$_2$CH$_3$), 4.35 (1H, d, *J* = 11.55 Hz, OC**H**$_2$C$_6$H$_5$), 4.41 (1H, d, *J* = 12.05 Hz, -OC**H**$_2$C$_6$H$_5$), 5.28 (1H, d, *J* = 6.05 Hz, -C**H**=C-), 7.26-7.35 (5H, m, -OCH$_2$C$_6$**H**$_5$), 9.89 (1H, s, C**H**O) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9 (-OCH$_2$**C**H$_3$), 19.8 (-CH**C**H$_3$), 21.3 (-CH=C-**C**H$_3$), 34.3 (-**C**HCH$_3$), 42.0 (-**C**HCH$_2$OBn), 46.3 (-**C**HCO$_2$Et), 52.2 (-CO$_2$**Me**), 61.0 (-O**C**H$_2$CH$_3$), 61.9 (-**C**-CHO), 69.9 (-CH**C**H$_2$OBn), 72.8 (-CHCH$_2$O**C**H$_2$Ph), 117.8 (-**C**H=C-CH$_3$), 127.6 (Ph-C*p*), 127.7 (Ph-C*o* x2), 128.3 (Ph-C*m* x2), 137.4 (Ph-C*q*), 140.5 (-CH=**C**-CH$_3$), 170.6 (-**C**O$_2$Me), 173.0 (-**C**O$_2$Et), 198.1 (**C**HO) ppm;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_{22}H_{28}O_6]^+$ = 388.1886, found = 388.1888.

1-*tert*-butyl 2-ethyl 6-(benzyloxymethyl)-1-formyl-3,4-dimethylcyclohex-4-ene-1,2-dicarboxylate (80a, Table 1-3, entry 2)



80a (Table 1-3, entry 2)

$\mathbf{R}_f$ = 0.31 (Hexane:EtOAc, 4:1);

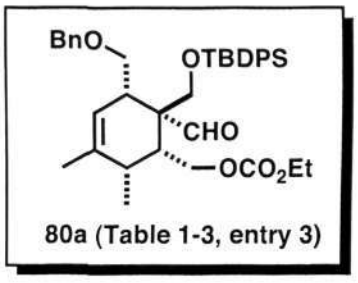
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (3H, d, *J* = 6.9 Hz, -CHC**H**$_3$), 1.26 (3H, t, *J* = 7.2 Hz, -OCH$_2$C**H**$_3$), 1.43 (9H, s, -OC(C**H**$_3$)$_3$), 1.71 (3H, s, -CH=CC**H**$_3$), 2.64 (1H,

dq, J = 14.1, 7.2 Hz, -C**H**-), 3.05 (1H, d, J = 9.0 Hz, -C**H**-), 3.17 (1H, brs , -C**H**CO_2Et), 3.32 (1H, dd, J = 10.5, 8.4 Hz, 1H, -C**H**$_2$OBn), 3.44 (1H, dd, J = 10.5, 3.9 Hz, -C**H**$_2$OBn), 4.17 (2H, q, J = 7.2 Hz, -OC**H**$_2$CH$_3$), 4.38 (1H, d, J = 12.0 Hz, -OC**H**$_2$C$_6$H$_5$), 4.44 (1H, d, J = 12.0 Hz, -OC**H**$_2$C$_6$H$_5$), 5.34 (1H, d, J = 6.0 Hz, -C**H**=C-), 7.28-7.37 (5H, m, -OCH$_2$C$_6$**H**$_5$), 9.89 (1H, s, C**H**O) ppm;

^{13}C NMR (125 MHz, CDCl$_3$): δ 14.0 (-OCH$_2$**C**H$_3$), 20.2 (-CH**C**H$_3$), 21.3 (-CH=C-**C**H$_3$), 27.8 (-C(**C**H$_3$)$_3$), 34.6 (-**C**HCH$_3$), 42.2 (-**C**HCH$_2$OBn), 46.3 (-**C**HCO$_2$Et), 60.8 (-**C**-CHO),), 62.2 (-O**C**H$_2$CH$_3$), 70.0 (-CH**C**H$_2$OBn), 72.8 (-CHCH$_2$O**C**H$_2$Ph), 82.1 (-O**C**(CH$_3$)$_3$), 118.4 (-**C**H=C-CH$_3$), 127.7 (Ph-C*p*), 127.8 (Ph-C*o* x2), 128.3 (Ph-C*m* x2), 137.6 (Ph-C*q*), 140.3 (-CH=**C**-CH$_3$), 169.2 (-**C**O$_2$Bu$_t$), 173.0 (-**C**O$_2$Et), 198.9 (**C**HO) ppm;

HRMS (EI [M]$^+$): *m/e* calculated for [C$_{22}$H$_{28}$O$_6$]$^+$ = 388.1886, found = 388.1888.

5-(benzyloxymethyl)-6-((*tert*-butyldiphenylsilyloxy)methyl)-6-formyl-2,3-dimethylcyclohex-3-enyl)methyl ethyl carbonate (80a, Table 1-3, entry 3)



80a (Table 1-3, entry 3)

^{1}H NMR (CDCl$_3$, 400 MHz): δ 9.80 (1H, s), 7.62-7.59 (4H, m), 7.44-7.26 (9H, m), 7.17 (2H, d, J = 6.8Hz), 5.39 (1H, bs), 4.42 (1H, dd, J = 4.4, 10.8Hz), 4.23-4.18 (3H, m), 4.13-4.02 (2H, m), 3.61 (1H, d, J = 11.2), 3.20 (1H, dd, J = 4.0, 9.6Hz), 3.01 (1H, dd, J = 5.2, 9.6Hz), 2.88-2.83 (1H, m), 2.49-2.45 (1H, m) 1.75 (3H, s), 1.31 (3H, t, J = 7.2Hz), 1.08 (2H, s), 1.06 (9H, s), 0.98 (3H, d, J = 7.2Hz).

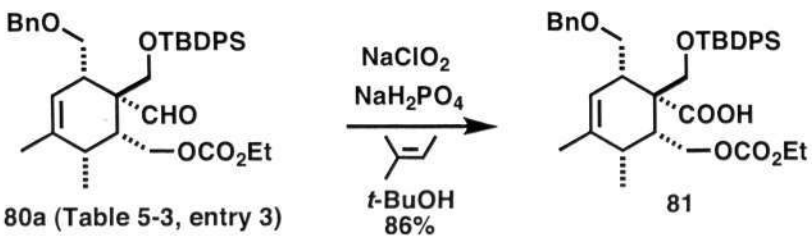
^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.3, 154.9, 137.8, 137.7, 135.8 (x2) , 135.7 (x2), 134.8, 133.0, 132.8, 129.9, 129.8, 128.3 (x2), 127.8 (x2), 127.7 (x2), 127.6, 122.1, 73.3, 69.8, 65.8, 64.0, 61.0, 53.9, 40.0, 39.9, 34.0, 27.0 (x4), 21.9, 19.3, 14.8, 14.3.

R_f = 0.49 (Hexane : Ethyl Acetate = 5 : 1).

FTIR (neat, cm^{-1}): 2957, 2857, 1751, 1453, 966.

HRMS (ESI, m/z (M +H)] Calcd (Found) for $C_{38}H_{48}O_6Si$: 629.3298 (629.3290)

2-(benzyloxymethyl)-1-((*tert*-butyldiphenylsilyloxy)methyl)-6-((ethoxycarbonyloxy)methyl)-4,5-dimethylcyclohex-3-enecarboxylic acid (81)



To a cooled (10 °C) stirred solution of the intermediate aldehyde (630 mg, 1mmol) in 5:1.2 *t*-BuOH/2-methyl-2-butene (10 mL) was added $NaClO_2$ (0.45g, 5mmol) slowly dropwise. The reaction mixture was stirred for 3h and then quenched with ice water. The mixture was extracted with EtOAc (30ml ×3). The combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude was purified via column chromatography, eluted with 50% ethyl acetate/hexane to give the product 81 (553 mg, colorless oil).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63-7.62 (4H, m), 7.42-7.26(9H, m), 7.17(2H, d, *J* = 6.8Hz), 5.49 (1H, bs), 4.43 (2H, s), 4.35-4.14 (3H, m), 3.88 (1H, d, *J* =12Hz), 3.77(1H, d, *J* = 10.4), 3.57 (1H, dd, *J* = 3.6, 8.8Hz), 3.48 (1H, t, *J* = 8.4Hz), 2.79-2.72 (2H, m), 2.34-2.31 (1H, m), 1.66 (3H, s), 1.31(3H, t, *J* = 7.2Hz), 1.08 (2H, s), 1.05 (9H, s), 0.93 (3H, d, *J* = 7.2Hz).

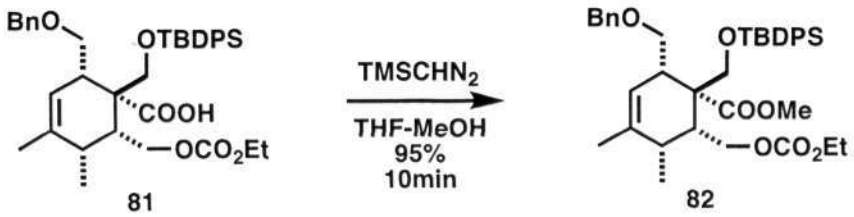
^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.8, 155.0, 138.2, 137.7, 135.9, 135.8 (x2) 135.7 (x2), 135.6, 135.5, 130.0, 129.9, 129.8, 128.4 (x2), 127.8 (x2), 127.7 (x2), 127.5, 122.2, 73.1, 71.6, 66.7, 63.9, 61.0, 50.9, 40.0, 39.8, 33.6, 27.0 (x4), 21.7, 19.3, 14.8, 14.3, 13.2.

R_f = 0.25 (Hexane : Ethyl Acetate = 5 : 1).

FTIR (neat, cm^{-1}): 2955, 2928, 1756, 1266.

HRMS (ESI, m/z (M +H)] Calcd (Found) for $C_{38}H_{48}O_7Si$: 645.3248 (645.3252).

methyl 2-(benzyloxymethyl)-1-((*tert*-butyldiphenylsilyloxy)methyl)-6-((ethoxycarbonyloxy)methyl)-4,5-dimethylcyclohex-3-enecarboxylate (82)



To a stirred solution of **81** (553 mg, 0.86 mmol) in diethyl ether (5 mL) in ice bath, was added $TMSCH_2N_2$ (1M in diethyl ether, 1.5 ml). The reaction mixture was stirred at 0 °C for 15min. The mixture was quenched with 1M HCl and extracted with diethyl ether (20 ml x3). The combined organics were dried and concentrated. The crude was purified via column chromatography eluted with 10% ethyl acetate/hexane to give the desired product **82** (537 mg, colourless oil).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (4H, d, *J* = 7.2Hz), 7.44-7.26 (11H, m), 5.52 (1H, bs), 4.45 (2H, bs), 4.32 (1H, dd, *J* = 3.2, 10.4Hz), 4.25-4.17 (3H, m), 3.86 (1H, d, *J* = 10.4), 3.77 (1H, d, *J* = 10.4 Hz), 3.56 (1H, dd, *J* = 3.6, 8.8Hz), 3.52 (3H, s), 3.48 (1H, d, *J* = 8.8Hz), 2.77-2.73 (2H, m), 2.34-2.30 (1H, m), 1.65 (3H, s), 1.32 (3H,t, *J* = 6.8Hz), 1.06 (9H, s), 0.91 (3H, d, *J* = 7.2Hz).

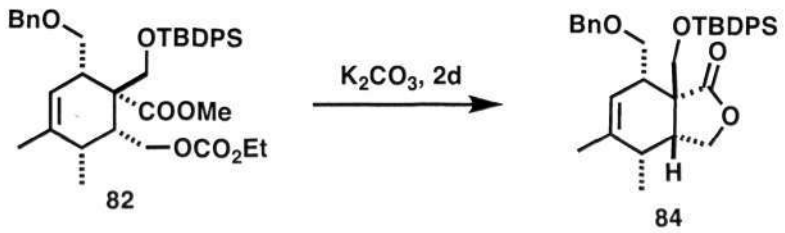
^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.5, 155.0, 138.5, 135.7 (x2) , 135.6 (x2), 135.2, 132.9, 132.8, 130.0, 129.7, 128.3 (x2), 127.7 (x2), 127.6 (x2), 127.5 (x2), 122.6, 73.0, 72.1, 67.1, 66.0, 63.8, 51.2, 50.8, 40.4, 39.4, 33.4, 26.8 (x4), 21.6, 19.3, 14.3, 13.3.

R_f = 0.57 (Hexane : Ethyl Acetate = 5 : 1).

FTIR (neat, cm^{-1}): 3301, 1761,1265, 1112.

HRMS (ESI, m/z (M +H)] Calcd (Found) for $C_{39}H_{50}O_7Si$: 659.3404 (659.3410).

7-(benzyloxymethyl)-7a-((*tert*-butyldiphenylsilyloxy)methyl)-4,5-dimethyl-3a,4,7,7a-tetrahydroisobenzofuran-1(3*H*)-one (84)



82 (537 mg, 0.8 mmol) was dissolved in 1 % K_2CO_3 in MeOH solution at room temperature. The solution was stirred at room temperature for 48 hours. The mixture was concentrated and the residue was diluted with water (30 ml) and extracted with ethyl acetate (20 ml x3). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel to afford **83** as colorless oil, 0.32 g (70%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67-7.63 (4H, m), 7.40-7.36 (7H, m), 7.30-7.26 (4H, m), 5.51 (1H, bs), 4.45 (2H, dd, *J* = 11.6, 19.6Hz), 4.20 (1H, t, *J* = 8.8Hz), 4.00 (1H, d, *J* = 10.0Hz), 3.82 (1H, d, *J* = 9.6Hz), 3.73 (1H, dd, *J* = 4.0, 9.2Hz), 3.63 (1H, d, *J* = 9.6Hz), 3.50 (1H, dd, *J* = 7.6, 9.2Hz), 3.07 (1H, dt, *J* = 4.8, 9.2Hz), 2.35-2.34 (1H, m), 2.15-2.14 (1H, m), 1.72 (3H, s), 1.34-1.26 (3H, m), 1.05 (9H, s), 0.91 (3H, d, *J* = 7.2Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.0, 138.3, 137.3, 135.8 (x2), 135.6x2, 133.2, 132.8, 132.8, 129.7, 128.3 (x2), 127.8 (x4), 127.7 (x2), 127.5, 124.4, 73.3, 70.4, 68.1, 66.6, 51.3, 44.2, 37.9, 31.8, 26.8 (x2), 20.7, 19.3, 14.7, 1.05.

R_f = 0.57 (Hexane : Ethyl Acetate = 5 : 1).

FTIR (neat, cm^{-1}): 2955, 2928, 2855, 1682, 1429.

HRMS (EI, m/z (M +H)] Calcd (Found) for $C_{35}H_{45}O_4Si$: 555.2931 (555.2935).

Appendix

Diastereoselective allylation of planar chiral substituted ferrocenecarboxaldehyde

A.1 INTRODUCTION

Ferrocene[1] is an organometallic compund consisting of two cyclopentadienyl rings bound to a ferric atom (Fe) at the central. It was discovered by Pauson and Kealy in 1951. Due to the unique sandwich structure of the ferrocene, it's derivative had been the symbol for an international conference on organometallic chemisty.[2]

In addition to its unique structure, ferrocene has ideal properties such as low price, thermal stability, and high tolerance to moisture, oxygen, and many types of reagents. Interestingly, its behaviour as an electron-rich aromatic compound in electrophilic aromatic substitutions (*e.g.* Friedel-Crafts reaction), facile lithiation and dilithiation (at the 1,1'-positions), and the extraordinary ability to stabilize carbocations at the benzylic-like position are key chemical properties that provided very practical ways for the synthesis of functionalized, substituted ferrocenes[3] (Figure A-1).

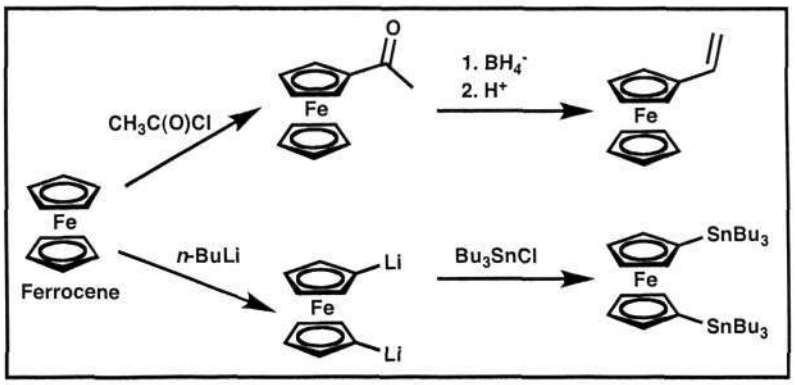


Figure A-1

[1] (a) Keally, T. J.; Pauson, P. J. *Nature* **1951**, *168*, 1039. (b) Wilkinson, G.; Rosenblum, M.; Whiting, M. C.; Woodward, R. B. *J. Am. Chem. Soc.* **1952**, *74*, 2125.
[2] Dai, L. X.; Tu, T.; You, S. L.; Deng, W. P.; Hou, X. L. *Acc. Chem. Res.* **2003**, *36*, 659.
[3] Ramón, G. A.; Javier A.; Juan, C. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 7674.

Unlike the benzene aromatic derivatives, ferrocenes showed a unique structural feature, which make it the subject of intense research in chemistry field. It has been reported that disubstituted ferrocene derivatives with two different substituents on the same ring (1,2 or 1,3) is considered a chiral compound. It is due to the loss of the plane of symmetry of ferrocene, known as planar chirality. Owing to this interesting property, it has been intensively investigated as an importance tool in the synthesis of chiral ligands used in asymmetric catalysis.[4]

In connection with our interest in application of chiral carbenium in controlling the selectivity of C-C bond formation, we intend to explore the possibility to prepare stabilized carbocations associated with a ferrocene system. We envisage that the existing planar chirality property of ferrocene could induce a chiral control of the latter product. In addition, the utilitization of stable α-chiral carbenium of ferrocene substrates may open up new areas of asymmetric catalysis.

There are many literature reports on the application of chiral carbocation in organic synthesis. For example, Denmark and Chen[5] described the preparation of chiral triarylcarbonium ions for Mukaiyama aldol addition. Whereas, Kagan and co-workers[6] reported the synthesis of chiral carbocations linked to a ferrocene unit for Diels-Alder reaction.

Adhering to our interest in α-chiral carbenium of ferrocene carbenium chemistry, we intend to incorporate an alcohol functionality unto a ferrocene chiral planarity *via* allylation chemistry, which have been well established in our research

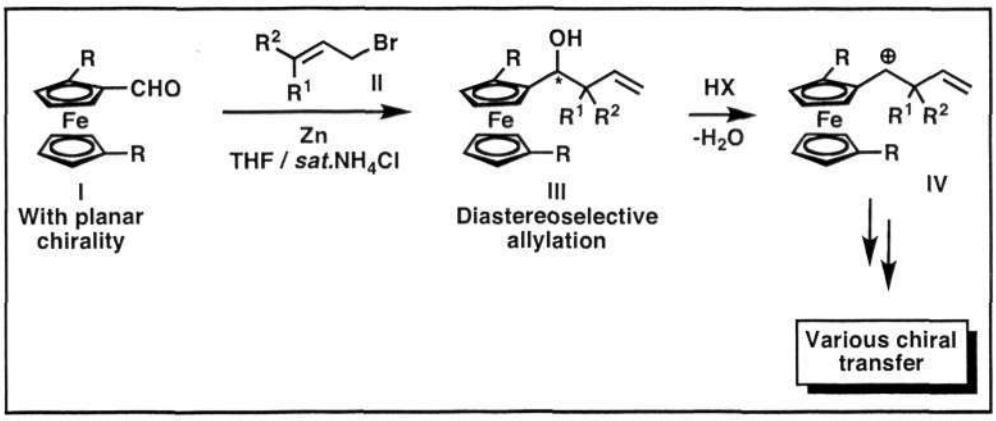
[4] For reviews, see: (a) Hayashi, T. *Asymmetric Catalysis with Chiral Ferrocenylphosphine Ligands*. In *Ferrocenes*, ed. Togni, A. and Hayashi, T. VCH, Weinheim, 1995, p. 105; (b) Togni, A. *New Chiral Ferrocenyl Ligands for Asymmetric Catalysis*. In *Metallocenes*, ed. Togni, A. and Halterman, R. L. VCH, Weinheim, 1998, vol. 2, p. 689; (c) Kagan, H. B.; Riant, O. *Adv. Asymmetric Synth.* **1997**, *2*, 189.

[5] Denmark, S. E.; Chne, C. T. *Tetrahedron Lett.* **1994**, *35*, 4327.

[6] Taudien, S.; Riant, O.; Kagan, H. B. *Tetrahedron Lett.* **1995**, *36*, 3513.

group. The generated secondary hydroxy group **III** can later been converted to a chiral carbenium **IV** through acidic elimination (Scheme A-1).

Thus, we required an efficient and practical method to obtain α-chiral alcohols with high selectivities. There have been tremendous efforts directed towards the development of new methods to obtain optically pure α-chiral ferrocenyl alcohols.[7] Based on our long-standing experience with the allylation of aldehyde in aqueous media, we developed an efficient method utilizing the existing planar chirality of ferrocene to generate chiral ferrocenyl alcohols for various chiral transfer (Scheme A-1).



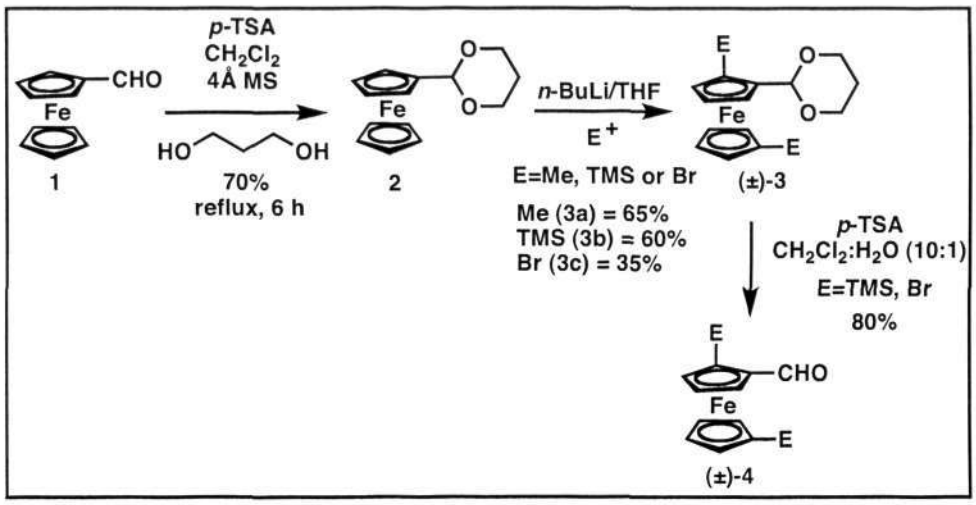
Scheme A-1 Synthetic scheme to chiral ferrocenyl alcohols for chiral transfer

[7] Fukuzawa, S. I.; Tsuchiya, D.; Sasamoto, K.; Hirano, K.; Ohtaguchi, M. *Eur. J. Org. Chem.* **2000**, 2877.

A.2 RESULTS AND DISCUSSION

A.2.1 Preparation of Ferrocenecarboxaldeyhe Substrate with Planar Chirality

The 2,2'-substituted ferrocenecarboxaldehydes were prepared using the following general procedure. [8] Ferrocenecarboxaldehyde **1** was quantitatively converted to the acetal **2** by heating with 1,3-propanediol in the presence of *p*-TSA in dichloromethane. Deprotonation of the acetal using *n*-BuLi (2.2 eq) in THF at room temperature for 4 h, followed by quenching with different electrophiles (TMSCl or dibromoxylene) to give intermediate **3** and finally deprotection furnished the respective desired 2,2'-substituted ferrocenecarboxaldehydes **4** (Scheme A-2).

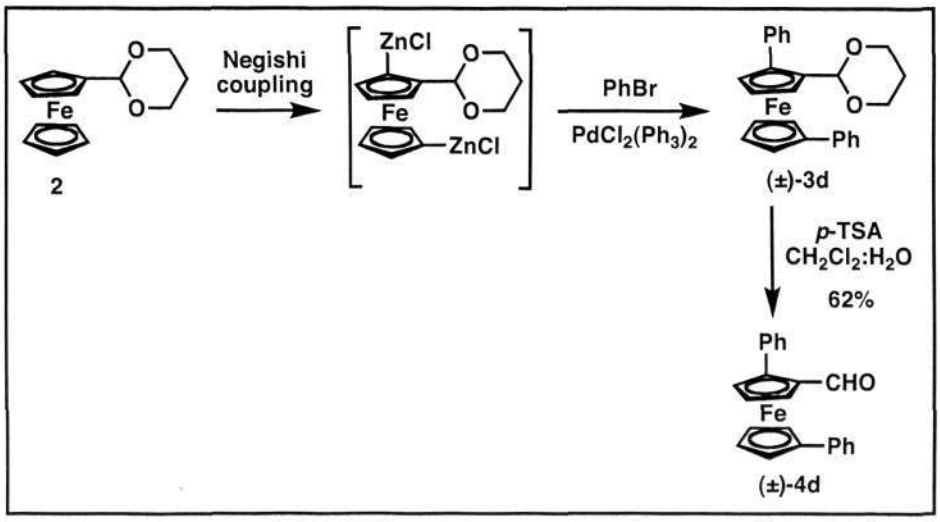


Scheme A-2 Synthesis of 2,2'-disubstituted ferrocenecarboxaldehydes

Phenylferrocenecarboxaldehyde **(±)-4d** was obtained using the Negishi coupling reaction.[9] After lithiation of ferrocenylacetal with *n*-BuLi, the *ortho* lithiated intermediate obtained was transmetalated with $ZnCl_2$ and cross-coupled with

[8] (a) Riant, O.; Samuel, O.; Kagan, H. B. *J. Am. Chem. Soc.* **1993**, *115*, 5835; (b) Riant, O.; Samuel, O.; Flessner, T.; Tauben, S.; Kagan, H. B. *J. Org. Chem.* **1997**, *62*, 6733.
[9] Mamane, V.; Fort, Y. *J. Org. Chem.* **2005**, *70*, 8220.

bromobenzene in the presence of a catalytic amount of $PdCl_2(Ph_3)_2$ to afford **(±)-4d** as shown in Scheme A-3.



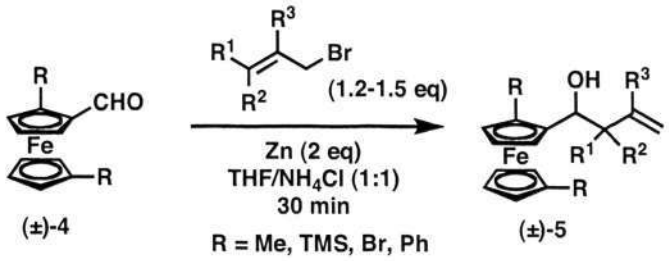
Scheme A-3 Negishi coupling reaction

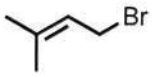
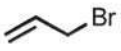
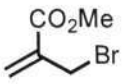
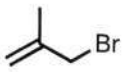
A.2.2 Allylation Reactions

The 2,2'-disubstituted ferrocenecarboxaldehydes prepared were then subjected to allylation reactions.[10] Various allyl bromides were used in the presence of zinc powder and the results are summarized in Table A-1.

[10] For a review, see: Loh, T. P.; Chua, G. L. *Yuki Gosei Kagaku Kyokaishi* **2005**, *63*, 1137.

Table A-1 Allylation of 2,2'-disubstituted ferrocenecarboxaldehydes with various allyl bromides[a]



Entry	R	Allyl bromide	Yield[b]	*Dr*[c]
1	Me		83	75:25
2	TMS		92	67:33
3	Br		89	>99:1
4	Ph		85	>99:1
5	TMS		67	67:33
6	Br		84	>99:1
7	Ph		90	>99:1
8	TMS		94	52:48
9	Br		94	>99:1
10	Ph		76	>99:1
11	TMS		87	76:24
12	Br		90	>99:1
13	Ph		92	>99:1

[a]All reactions were carried out on a 0.5 mmol scale in an ice bath with 6 mL of solvent. [b]Isolated yield. [c]Diastereoselectivity was determined by ^{1}H and ^{13}C NMR spectroscopy.

In all cases, the zinc-mediated allylation proceeded smoothly to give the desired products in moderate to good yields (Table A-1). When R = TMS or Me, the prenylated products were obtained with low selectivities (entries 1 and 2). This contrasts with the high facial selectivities for R = Br or Ph (entries 3 and 4). A similar trend was observed for allylation (entries 5-7), where TMS gave no preference in facial selectivity while Ph and Br gave the products essentially as single isomers.

Furthermore, Ph and Br substituted ferrocenecarboxaldehyde also gave excellent selectivities with α-substituted bromide (entries 9, 10, 12 and 13). The relative stereochemistry of the alcohol product (Table A-1, entry 3) was confirmed by X-ray crystallography (Figure A-1).

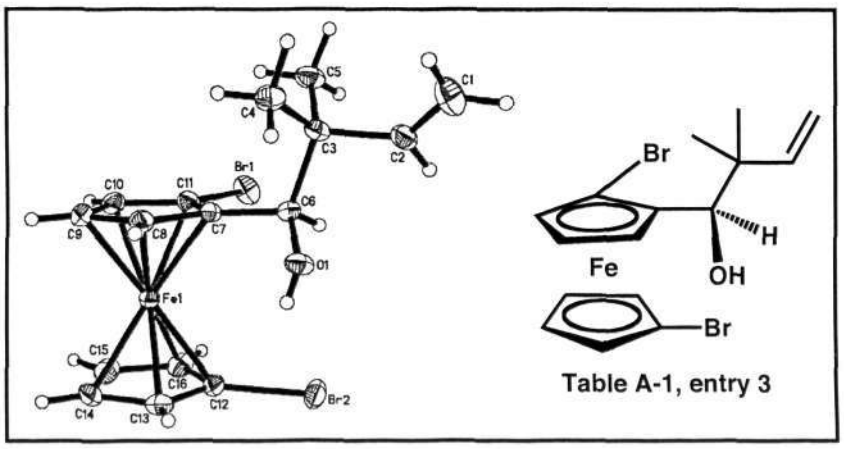
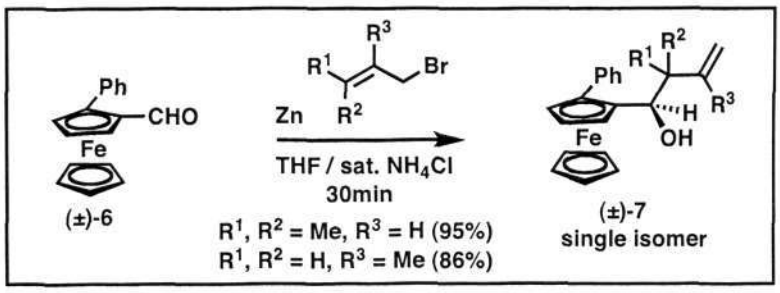


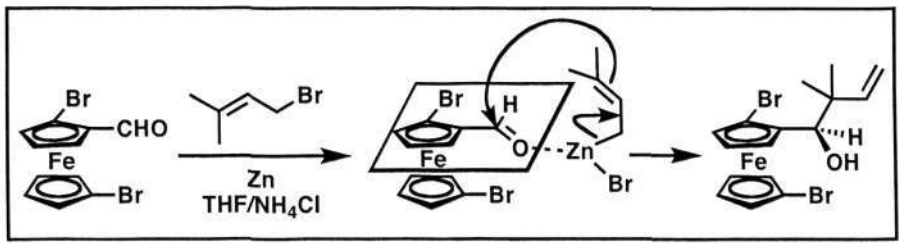
Figure A-1 X-ray crystal structure of the allylation product

Furthermore, simple 2-substituted ferrocenecarboxaldehyde **(±)-6** was also subjected to the same zinc allylation conditions, giving similar yields and facial selectivities as shown in Scheme A-4. This suggests that the key factor in determining the diastereoselectivity of the allylation process is the substituted group on the upper cyclopentadienyl ring.



Scheme A-4 Allylation of 2-substituted ferrocenecarboxaldehyde with allyl bromide

A transition state can be proposed to account for the observed stereochemistry. Organozinc reagents attack the formyl group from the less hindered side, away from the sterically hindered lower cyclopentadienyl ring to afford the product with the stereochemistry as shown in Scheme A-5.



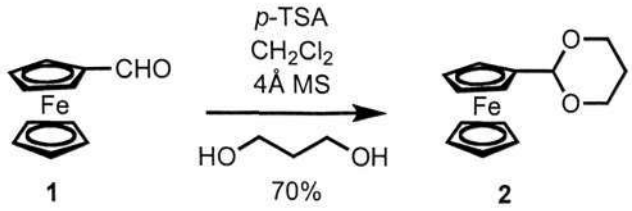
Scheme A-5 Proposed mechanism for the allylation of 2,2'-disubstituted ferrocene-carboxaldehyde with allyl bromide

A.3 SUMMARY

In conclusion, a series of 2,2'-disubstituted ferrocenecarboxaldehydes have been synthesized and applied in allylation reactions using various allylic bromides. TMS and Me substituents did not give good selectivity. However, Ph and Br substituents gave excellent diastereoselectivities (>99:1). A series of chiral ferrocenyl complexes are currently being derived from 2,2'-disubstituted ferrocene-carboxaldehydes and the further work on chiral transfer is in progress in our research group.

A.4 EXPERIMENTAL

Ferrocenyl-1,3-dioxane (2)



1 2

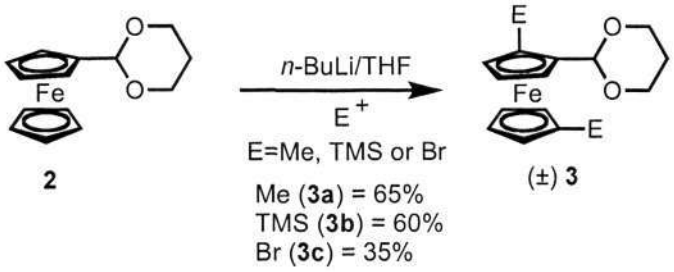
Ferrocenecarboxaldehyde **1** (0.57 g, 2.6 mmol) in 20 mL dried CH_2Cl_2 was added 1,3-propanediol (0.73 mL, 7.8 mmol), 4 Å molecular sieves and catalytic amount of *p*-TSA. The reaction mixture was refluxed for 16 hours. After completion (monitored by TLC), the reaction mixture was filtered, concentrated and purified by column chromatography with 10% ethyl acetate in hexane gave the product **2** in 70% (0.67 g) yield.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.36 (1H, s), 4.31 (2H, t, J = 1.8 Hz), 4.23-4.21 (1H, m), 4.18 (5H, s), 4.12 (2H, J = 1.9), 3.96-3.87 (2H, m), 2.23-2.07 (1H, m), 1.41-1.36 (1H, m);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 100.6, 86.2, 68.9 (x5), 68.0, 67.3, 66.4, 25.8 (x2);

R_f = 0.51 (Hex:EA = 5:1);

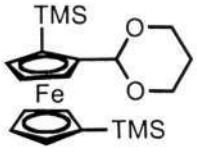
2,2'-substituted ferrocenecarboxaldehydes:



2 (±) 3

To the solution of acetal **2** (1.26 g, 4.6 mmol) in THF (20 mL) was added in *n*-BuLi (1.6 M in hexane, 16 mL, 10 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 hours before TMSCl (1 mL, 9.2 mmol) was added dropwise. After that, the reaction mixture was stirred for 16 hours at room temperature. The reaction mixture was quenched using saturated NH_4Cl solution and extracted with diethyl ether (x3). The combined organic layers was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification *via* column chromatography with 2% ethyl acetate in hexane gave the product **3** in 61% (0.83 g) yield.

2,2'-trimethylsilyl-ferrocenyl-1,3-dioxane (3b)



(±) **3b**

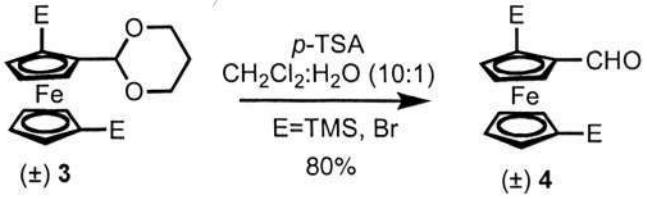
^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.43 (1H, s, -C<u>H</u>-$(OCH_2)_2$), 4.59-4.58 (1H, m), 4.32-4.29 (2H, m), 4.24-4.22 (2H, m), 4.14-4.10 (1H, m), 4.07-4.06 (2H, m), 4.04-4.03 (1H, m), 3.94-3.82 (2H, m), 2.20-2.07 (1H, m), 1.39-1.35 (1H, m), 0.28 (9H, s, TMS-<u>H</u>), 0.24 (9H, s, TMS-<u>H</u>);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 100.8, 90.4, 74.5, 74.1, 72.8, 72.5, 71.6, 70.0 (x4), 67.0, 66.7, 25.7, 0.3 (x3), -0.3 (x3);

R_f=0.73 (Hex:EA = 4:1);

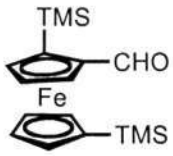
FTIR (neat, cm^{-1}): 3427, 3412, 2955, 1630;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{20}H_{32}O_2FeSi_2$: 416.1285 (416.1282);



To the acetal **3** (0.93 g, 2.2 mmol) in CH_2Cl_2 : H_2O (10:1; 20 mL), was added in *p*-TSA (85 mg, 0.44 mmol). The reaction mixture was stirred for 30 minutes and excess of H_2O was added in and extracted with CH_2Cl_2 (x3). The combined organic layers was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo* to give the desired product which will be used for next step without purification.

2,2'-trimethylsilyl-ferrocenecarboxaldehyde (4b)



(±) **4b**

^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.01 (1H, s, C<u>H</u>O), 4.93 (1H, s), 4.67 (1H, s), 4.50 (2H, s), 4.41 (1H, s), 4.25 (1H, s), 4.10 (1H, s), 0.32 (9H, s, TMS-H), 0.22 (9H, s, TMS-<u>H</u>);

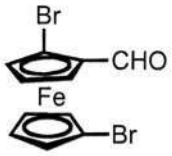
^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 194.3 (<u>C</u>HO), 83.5, 79.7, 74.9, 74.8, 74.4, 74.2, 74.1, 73.9, 72.5, 72.5, 0.45 (x3), -0.35 (x3);

R_f = 0.43 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): 2955, 2928, 2855, 1682, 1429;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{17}H_{26}OFeSi_2$: 358.0866 (358.0861);

2,2'-bromo-ferrocenecarboxaldehyde (4c)



(±) **4c**

^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.15 (1H, s, -CHO), 4.90 (1H, brs), 4.81-4.80 (1H, m), 4.63-4.61 (1H, m), 4.53-4.52 (2H, m), 4.28-4.27 (2H, m);

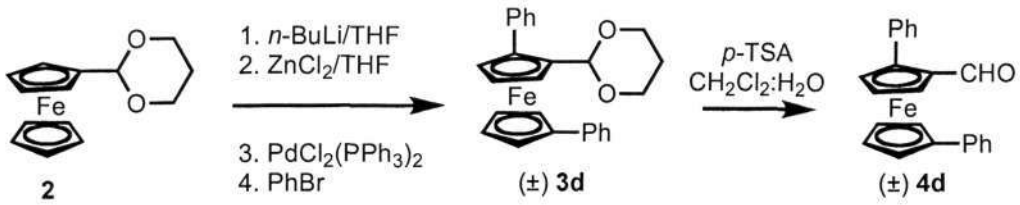
^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 192.9 (CHO), 80.7, 78.9, 77.8, 74.5, 74.0, 73.6, 71.7, 71.1, 68.7;

R_f = 0.38 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): 3422, 3408, 1674;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{11}H_8OBr_2Fe$: 371.8265 (371.8265)

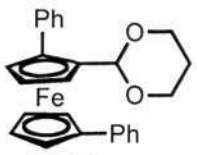
Phenylferrocenecarboxaldehyde (4d)



To a solution of **2** (0.46 g, 1.67 mmol) in dry THF (20 mL) at -78 °C under nitrogen was added slowly a solution of *n*-BuLi (1.6 M in hexane, 2 mL, 3.3 mmol). After 20 min the temperature was raised to 0 °C for 1 hour. The orange solution was cooled to -78 °C, a solution of $ZnCl_2$ in 10 mL THF (0.45 g, 3.3 mmol) was added slowly, the temperature was raised to room temperature, and the reaction mixture was stirred for 1 hour. To the orange suspension were successively added phenylbromide (0.35 mL, 3.3 mmol) and $PdCl_2(PPh_3)_2$ (58 mg, 0.08 mmol), and the mixture was

stirred at room temperature for overnight. Brine was added, and the mixture was extracted with ethyl acetate, dried over anhydrous $MgSO_4$ and concentrated. The residue was dissolved in CH_2Cl_2:H_2O (10:1) and *p*-TSA (20 mg) were added, and the mixture was stirred at room temperature for 2 hours under exclusion of light. A saturated solution of sodium bicarbonate was added, and mixture was extracted with ethyl acetate, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane:ether, 100:5) to afford compound **4d** as a yellowish oil in 62% yield.

2,2'-phenyl-ferrocenyl-1,3-dioxane (3d)



(±) **3d**

^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.51 (2H, d, *J* = 7.35 Hz), 7.35 (2H, d, *J* = 7.35 Hz), 7.28-7.15 (6H, m), 5.21 (1H, s, -C<u>H</u>-$(OCH_2)_2$), 4.55 (2H, brs), 4.45 (1H, s), 4.33 (1H, brs), 4.27 (1H, s), 4.21 (1H, brs), 4.14 (1H, t, *J* = 6.3 Hz), 4.11-4.09 (2H, m), 3.84-3.67 (2H, m, -OC<u>H</u>$_2$), 2.21-2.05 (1H, m, -OCH_2-C<u>H</u>$_2$-), 1.32 (1H, brd, *J* = 13.4 Hz, -OCH_2-C<u>H</u>$_2$-);

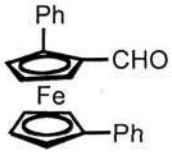
^{13}C NMR (CDCl$_3$, 75.4 MHz) δ 138.1, 137.8, 128.8 (x2), 128.1 (x2), 127.9 (x2), 126.2 (x2), 126.1, 125.9, 99.5, 86.7, 86.5, 83.8, 72.1, 71.8, 71.7, 69.8, 69.4, 69.2, 68.1, 67.4, 67.1, 25.6;

R_f = 0.49 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): 3059, 2963, 2849, 1601, 1510, 1452;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{26}H_{24}O_2Fe$: 424.1120 (424.1130);

2,2'-phenyl-ferrocenecarboxaldehyde (4d)



(±) **4d**

^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.07 (1H, s, -CHO), 7.40-7.34 (4H, m, Ph-H), 7.29-7.20 (6H, m), 4.83 (1H, dd, J = 2.5, 1.4 Hz), 4.72-4.70 (1H, m), 4.67-4.65 (2H, m), 4.49 (1H, t, J = 2.5 Hz), 4.37-4.35 (2H, m).

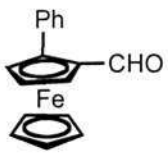
^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 193.2, 136.2, 135.3, 129.5 (x2), 128.5 (x2), 128.2 (x2), 127.2, 126.8, 126.1 (x2), 92.7, 88.0, 76.6, 74.2, 72.4, 72.0, 71.1, 70.2, 68.8 (x2);

R_f = 0.42 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): 3412, 1654, 1628, 1265;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{23}H_{18}OFe$: 366.0702 (366.0693)

2-phenyl-ferrocenecarboxaldehyde (6)



(±) **6**

^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.21 (1H, s, -CHO), 7.54-7.52 (2H, m), 7.39-7.32 (3H, m) 5.01-5.00 (1H, m), 4.85-4.84 (1H, m), 4.72-4.71 (1H, m), 4.25 (5H, s);

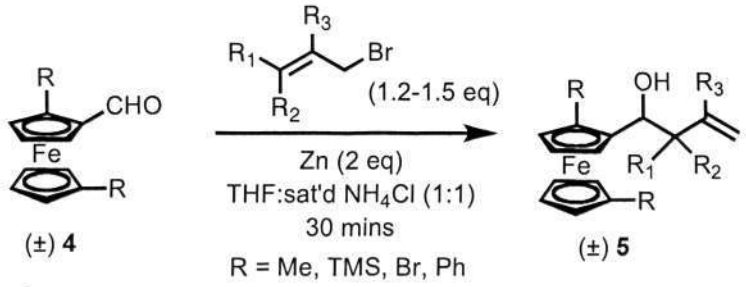
^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.1, 136.0, 129.7 (x2), 128.3 (x2), 127.3, 92.7, 75.1, 72.0, 71.1 (x5), 69.6, 68.4;

R_f = 0.42 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): 3412, 1654, 1628, 1265;

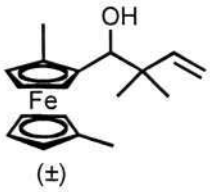
HRMS (EI, m/z (M^+)] calcd (found) for $C_{17}H_{14}OFe$: 290.0389 (290.0387)

General procedure for allylation reaction:



2, 2'-disubstituted ferrocenecarboxaldehyde (1 eq, 0.2 mmol) in a solution of THF:NH_4Cl (1/1 v/v) (4 mL) was added zinc powder (26 mg, 0.4 mmol, 2 eq) and allylbromide (1.2-1.5 eq). The reaction mixture was allowed to stir vigorously for 30 minutes at room temperature. The reaction mixture was extracted with diethylether (x3), washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. Purification *via* column chromatography with 5% ethyl acetate in hexane gave the desired product as yellowish oil.

(Entry 1, Table 1)



Major diastereomer:

^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.93 (1H, dd, *J* = 17.3,11.0 Hz, -C<u>H</u>=CH_2), 5.05-4.99

(2H, m, -CH=C<u>H</u>$_2$), 4.14-3.95 (8H, m), 2.09 (3H, s), 1.98 (3H, s), 1.01 (3H, s), 0.99 (3H, s);

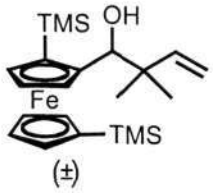
Minor diastereomer:

^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.93 (1H, dd, *J* = 17.3, 11.0 Hz, -C<u>H</u>=CH$_2$), 5.03-4.95 (2H, m), 4.19-4.00 (8H, m), 1.97 (3H, s), 1.95 (3H, s), 0.99 (3H, s), 0.97 (3H, s);

^{13}C NMR ($CDCl_3$, 75.4 MHz)(major+minor diastereomer) δ 146.0, 145.6, 112.2, 112.1, 90.4, 87.9, 84.3, 84.2, 81.8, 79.5, 77.6, 76.7, 74.3, 72.0, 71.3, 70.7, 70.6, 70.4, 69.6, 69.5, 69.4, 68.9, 68.5, 68.4, 68.3, 68.2, 67.9, 67.5, 67.4, 66.9, 66.8, 66.1, 65.8, 65.7, 42.5, 42.2, 24.5, 23.7, 22.4, 22.3, 22.2, 15.1, 14.1, 14.0, 13.9;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{18}H_{24}OFe$: 312.2177 (312.1168);

(Entry 2, Table 1)



Minor diastereomer:

^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.90 (1H, dd, *J* = 17.2 Hz, 11.2 Hz, -C<u>H</u>=CH$_2$), 5.06-5.00 (2H, m -CH=C<u>H</u>$_2$), 4.33-4.27 (5H, m), 4.07-4.04 (3H, brs), 1.78 (1H, d, *J* = 3.24 Hz), 1.01 (6H, s, 2×C<u>H</u>$_3$), 0.31 (9H, s, TMS-<u>H</u>), 0.22 (9H, s, TMS-<u>H</u>);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 145.9, 112.6, 93.6, 78.8, 75.2, 73.7, 73.2, 73.0, 72.7, 72.4, 71.7, 70.8, 69.3, 42.2, 24.1, 23.3, 1.8 (x3), -0.2 (x3).

R_f = 0.50 (Ether:Hex = 1:10);

Major diastereomer:

^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.92 (1H, dd, *J* = 17.4, 10.9 Hz, -C<u>H</u>=CH_2), 5.00 (1H, dd, *J* = 10.9, 1.41 Hz, -CH=C<u>H</u>$_2$), 4.98 (1H, dd, *J* = 17.45, 1.41 Hz, -CH=C<u>H</u>$_2$), 4.43-4.42 (1H, m), 4.38-4.36 (1H, m), 4.35-4.33 (1H, m), 4.29 (1H, t, *J* = 2.4 Hz), 4.12 (1H, *J* = 1.71 Hz), 4.09 (1H, brs), 4.06 (1H, dd, *J* = 2.34, 1.21 Hz), 2.48 (1H, s), 0.99 (3H, s, C<u>H</u>$_3$), 0.95 (3H, s, C<u>H</u>$_3$), 0.30 (9H, s, TMS-<u>H</u>), 0.22 (9H, s, TMS-<u>H</u>);

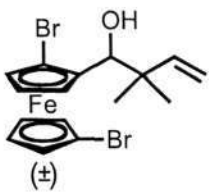
^{13}C NMR (CDCl3, 100 MHz) δ 145.6, 112.3, 97.8, 75.3 (x2), 73.9, 73.7, 72.9, 72.8, 72.4, 71.3, 71.2, 68.9, 41.6, 24.8, 22.7, 1.3 (x3), -0.2 (x3).

R_f = 0.56 (Ether:Hex = 1:10);

FTIR (neat, cm^{-1}): 3566, 3080, 2959, 1640, 1462;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{22}H_{36}OFeSi_2$: 428.1649 (428.1641);

(Entry 3, Table 1)



^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.94 (1H, dd, *J* = 17.5, 10.7 Hz, -C<u>H</u>=CH_2), 5.05 (1H, dd, *J*=10.4, 1.4 Hz, -CH=C<u>H</u>$_2$), 4.99 (1H, dd, *J* = 17.5, 1.4 Hz, -CH=C<u>H</u>$_2$), 4.48-4.42 (3H, m), 4.38 (1H, s), 4.25-4.15 (4H, m), 1.04 (3H, s, -C<u>H</u>$_3$), 0.95 (3H, s, -C<u>H</u>$_3$);

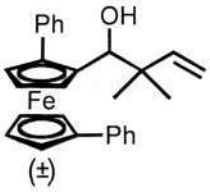
^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 144.8, 113.1, 90.9, 80.0, 78.4, 73.8, 73.0, 72.8, 72.6, 70.9, 70.4, 69.0, 67.4, 42.7, 24.3, 22.0;

R_f = 0.38 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): 3427, 3059, 1636, 1628, 1601, 1450;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{16}H_{18}OBr_2Fe$: 411.9048 (411.9048);

(Entry 4, Table 1)



^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43-7.36 (4H, m), 7.30-7.14 (6H, m), 5.69 (1H, dd, *J* = 17.5, 11.0 Hz, -C<u>H</u>=CH_2), 4.85-4.72 (3H, m), 4.59-4.47 (2H, m), 4.34-4.30 (2H, m), 4.21-4.19 (2H, m), 4.06-4.04 (1H, m), 1.97 (1H, d, *J* = 2.1 Hz), 0.66 (3H, s, -CH_3), 0.61 (3H, s, -CH_3);

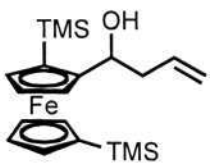
^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 145.1, 137.9, 137.8, 130.2 (x2), 128.6 (x2), 127.9 (x2), 126.5, 126.4, 126.0 (x2), 112.2, 90.4, 90.3, 86.3, 74.0, 71.7, 70.8, 70.4, 70.0, 68.8, 68.2, 66.7, 42.4, 24.1, 22.0;

R_f = 0.47 (Hex:EA = 5:1);

FTIR (neat, cm^{-1}): 3427, 2963, 1636, 1265;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{22}H_{24}OFe$ **[M-Ph]$^+$** : 360.1171 (360.1168)

(Entry 5, Table 1)



Major diastereomer

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.01-5.94 (1H, m), 5.23-5.18 (2H,m), 4.58-4.07 (8H, m), 2.77-2.14 (2H, m), 0.33-0.25 (18H, m);

Minor diastereomer

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.89-5.79 (2H, m), 5.11-5.06 (2H, m), 4.58-4.07 (8H, m), 2.77-2.14 (2H, m), 0.33-0.25 (18H, m);

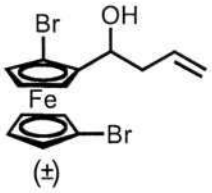
^{13}C NMR ($CDCl_3$, 100 MHz) (major+minor diastereomer) δ 135.6, 135.1, 117.7, 117.2, 100.8, 99.2, 95.0, 77.3, 77.0, 76.7, 75.0, 74.0, 73.5, 73.3, 73.1, 72.8, 72.5, 72.2, 71.7, 71.6, 71.5, 71.2, 71.0, 70.5, 70.5, 70.0, 69.9, 69.6, 69.5, 68.8, 67.8, 67.0, 43.8, 41.3, 0.7 (x6), -0.2 (x3), -0.2 (x3).

R_f = 0.46 (Hex:Ether = 8:1)

FTIR (neat, cm^{-1}): 3447, 3080, 2955, 1734, 1636, 1423, 1265, 1248;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{20}H_{32}OFeSi_2$: 400.1336 (400.1327)

(Entry 6, Table 1)



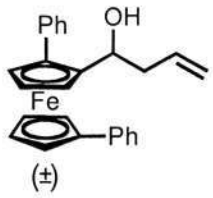
^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.78-5.92 (1H, m, -C<u>H</u>=CH_2), 5.09-5.15 (2H, m, -CH=C<u>H</u>$_2$), 4.74 (1H, dt, *J* = 7.2, 3.6 Hz, C<u>H</u>-OH), 4.46-4.38 (3H, m), 4.29-4.28 (1H, m), 4.22-4.17 (3H, m), 2.49-2.41 (1H, m), 2.36-2.29 (1H, m), 2.27 (1H, d, *J* = 3.0 Hz);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 134.3, 118.0, 92.4, 78.6, 78.0, 73.5, 72.4, 72.3, 70.7, 69.9, 68.5, 67.5, 66.5, 42.4;

FTIR (neat, cm^{-1}): 3452, 3111, 1637, 1412;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{14}H_{14}OBr_2Fe$: 413.8713 (413.8735)

(Entry 7, Table 1)



^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43-7.39 (4H, m), 7.29-7.18 (6H, m), 5.76-5.58 (1H, m, -C<u>H</u>=CH_2), 4.95-4.90 (2H, m), 4.68-4.62 (3H, m), 4.33-4.23 (4H, m), 4.13-4.11 (1H, m), 2.20 (2H, td, J = 6.8, 1.0 Hz), 1.92 (1H, d, J = 2.6 Hz, O<u>H</u>);

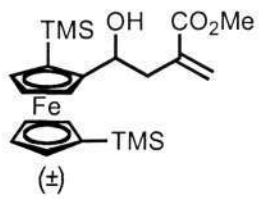
^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 137.7, 137.3, 134.7 (x2), 129.1 (x2), 128.6 (x2), 128.0 (x2), 126.4 (x2), 125.7 (x2), 117.0, 92.6, 87.4, 86.0, 71.0, 70.9, 70.6, 69.2, 67.8, 67.7, 67.1, 42.8;

R_f = 0.60 (Hex:EA = 5:1)

FTIR (neat, cm^{-1}): 3564, 3447, 3063, 2930, 1639, 1601, 1506, 1452;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{26}H_{24}OFe$: 408.1171 (408.1166);

(Entry 8, Table 1)



Major diastereomer

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.33 (1H, d, J = 1.5 Hz, -C=C<u>H</u>$_2$), 5.74 (1H, s, -C=C<u>H</u>$_2$), 4.71-4.66 (1H, m), 4.43-4.07 (7H, m), 3.81 (3H, s, CO_2<u>Me</u>), 2.68-2.31 (2H, m), 0.30 (9H, s, TMS-<u>H</u>), 0.23 (9H, s, TMS-<u>H</u>);

Minor diastereomer

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.24 (1H, d, *J* = 1.56 Hz, -C=C$\underline{H}_2$), 5.65 (1H, s, -C=C$\underline{H}_2$), 3.74 (3H, s, -$CO_2\underline{Me}$), 4.60-4.57 (1H, m), 4.43-4.07 (7H, m), 3.17 (1H, d, *J* = 13.8 Hz), 2.68-2.31 (2H, m), 0.30 (9H, s, TMS-$\underline{H}$), 0.22 (9H, s, TMS-$\underline{H}$);

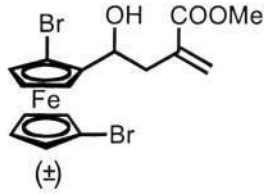
^{13}C NMR ($CDCl_3$, 75.4 MHz) (major+minor diastereomer) δ 167.7, 167.6, 137.5, 137.2, 128.0, 127.9, 99.2, 94.7, 74.9, 74.1, 73.5, 73.4, 73.2, 72.6, 72.4, 72.0, 71.6, 71.2, 70.7, 68.9, 68.8, 67.8, 67.7, 52.0, 51.9, 42.2, 39.8, 0.6 (x3), 0.5 (x3), -0.1 (x3), -0.2 (x3);

R_f= 0.60 (Hex:EA = 5:1)

FTIR (neat, cm^{-1}): 3445, 2953, 1718, 1630, 1439;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{22}H_{34}O_3FeSi_2$: 458.1390 (458.1376);

(Entry 9, Table 1)



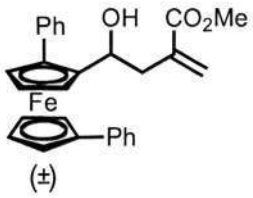
^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.22 (1H, d, *J* = 1.5 Hz, -C=C$\underline{H}$), 5.60 (1H, d, *J* = 1.2 Hz, -C=C$\underline{H}$), 4.86 (1H, dt, *J* = 7.6, 3.7 Hz, -C$\underline{H}$-OH), 4.44-4.39 (3H, m), 4.28 (1H, t, *J* = 3.4), 4.20-4.17 (3H, m), 3.75 (3H, s), 2.80 (1H, d, *J* = 3.3 Hz, O$\underline{H}$), 2.68 (1H, dd, *J* = 14.0, 3.4 Hz), 2.58 (1H, ddd, *J* = 14.0, 7.9, 0.7 Hz);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.2, 136.6, 128.4, 92.1, 78.6, 78.0, 73.2, 72.7, 72.4, 70.6, 70.1, 68.5, 67.6, 66.4, 52.1, 40.8;

R_f=0.21 (Hex:EA=5:1);

HRMS (EI, m/z (M^+)] calcd (found) for $C_{16}H_{16}O_3Br_2Fe$: 471.8790 (471.8796);

(Entry 10, Table 1)



^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44-7.39 (4H, m), 7.31-7.19 (6H, m), 6.05 (1H, d, *J* = 1.5 Hz, -C=C$\underline{H}_2$), 5.36 (1H, d, J = 1.5Hz, -C=C$\underline{H}_2$), 4.84-4.81 (1H, m), 4.67-4.63 (2H, m), 4.32-4.25 (4H, m), 4.12-4.11 (1H, m), 3.57 (3H, s, CO$\underline{Me}$), 2.45-2.48 (2H, m, -C$\underline{H}_2$-CHOH), 2.21 (1H, *J* = 3.0 Hz, O$\underline{H}$);

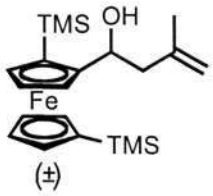
^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.6, 137.7, 137.3, 136.7, 129.3 (x2), 128.6 (x2), 127.9 (x2), 127.8, 126.4 (x2), 125.8 (x2), 92.4, 87.7, 86.1, 71.2, 71.0, 70.7, 69.5, 68.0, 67.7, 67.5, 66.6, 51.7, 41.2;

R_f = 0.56 (Hex:EA = 5:1)

FTIR (neat, cm^{-1}): 3562, 3059, 2951, 1715, 1630, 1601, 1506, 1439;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{28}H_{26}O_3Fe$: 466.1234 (466.1226);

(Entry 11, Table 1)



Major diastereomer

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.86 (1H, s, -C=C$\underline{H}_2$), 4.82 (1H, s, -C=C$\underline{H}_2$), 4.53-4.56 (1H, m), 4.45 (1H, brs), 4.37 (1H, brs), 4.34 (1H, brs), 4.26 (1H, brs) , 4.14 (1H, brs), 4.12 (1H, brs), 4.07 (1H, brs) 2.21-2.23 (2H, m), 1.78 (3H, s), 0.28 (9H, s, TMS-

H), 0.23 (9H, s, TMS-H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.9, 113.0, 99.6, 74.0, 72.7, 71.6, 71.2, 67.8, 67.2, 48.3, 30.3, 22.6, 0.6 (x3), -0.2 (x3).

R_f = 0.49 (Hex:Eher = 8:1);

Minor diastereomer

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.95 (1H, s, -C=CH$_2$), 4.88 (1H, s, -C=CH$_2$), 4.68 (1H, d, J = 10.6 Hz), 4.33 (1H, s), 4.30 (1H, s), 4.25 (1H, s), 4.18 (1H, s) , 4.09 (2H, s), 4.06 (1H, s) 2.71 (1H, d, J = 13.6 Hz), 2.40-2.47 (1H, dd, J = 13.6, 10.6 Hz), 1.87 (3H, s), 0.31 (9H, s, TMS-H), 0.22 (9H, s, TMS-H);

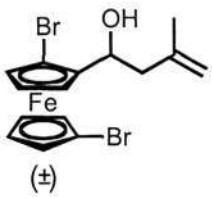
^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.80, 113.5, 94.9, 74.9, 73.3, 73.1, 72.2, 71.8, 71.5, 70.6, 69.3, 67.4, 45.3, 22.4, 0.6 (x3), -0.2 (x3);

R_f = 0.51 (Hex:Eher = 8:1);

FTIR (neat, cm^{-1}): 3414, 3057, 2957, 1713, 1645, 1362, 1267, 1223;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{21}H_{34}OFeSi_2$: 414.1492 (414.1487)

(Entry 12, Table 1)



(±)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.89 (1H, s), 4.81-4.77 (2H, m), 4.45-4.43 (2H, m), 4.42-4.40 (1H, m), 4.32-4.31 (1H, m), 4.21-4.19 (3H, m), 2.35 (1H, dd, J = 10.3, 2.1 Hz), 2.26 (1H, brs), 2.21 (1H, dd, J = 10.3, 7.2 Hz), 1.82 (3H, s);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.5, 113.6, 92.5, 78.7, 78.0 73.3, 72.6, 72.2, 70.6,

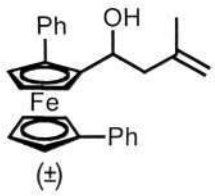
70.1, 68.5, 66.2, 66.1, 50.0, 22.4;

R_f= 0.66 (Hex:EA = 3:1);

FTIR (neat, cm^{-1}): 3424, 3076, 2980, 1645, 1412, 1383, 1265;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{15}H_{16}OBr_2Fe$: 427.8891 (427.8894);

(Entry 13, Table 1)



^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43-7.41 (4H, m), 7.30-7.20 (6H, m), 4.74-4.62 (5H, m), 4.34-4.29 (4H, m), 4.14-4.13 (1H, m), 2.19-2.07 (2H, m), 1.81 (1H, s), 1.58 (3H, s);

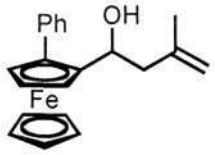
^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.6, 137.8, 137.5, 129.2 (x2), 128.6 (x2), 128.0 (x2), 126.5, 126.4, 125.9 (x2), 112.8, 93.0, 87.5, 86.2, 71.2, 71.1, 70.6, 69.3, 68.0, 67.9, 67.7, 65.7, 47.2, 22.1;

R_f = 0.30 (Hex:Ether = 8:1)

FTIR (neat, cm^{-1}): 3057, 2963, 2930, 1620, 1453, 1265;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{27}H_{26}OFe$: 422.1328 (422.1329)

Monosubstituted (2-substituted ferrocenecarboxaldehyde) allylation products:



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50-7.48 (2H, m), 7.34-7.23 (3H, m), 4.80 (1H, ddd,

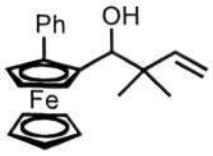
J = 8.8, 4.0, 2.7 Hz), 4.74 (1H, brs), 4.69 (1H, brs), 4.47 (1H, brs), 4.42 (1H, brs), 4.30 (1H, brs), 4.22 (5H, s), 2.30 (1H, dd, J = 14.0, 8.8 Hz), 2.20 (1H, dd, J = 14.0, 4.0 Hz), 2.23 (1H, d, J = 2.7 Hz, O<u>H</u>), 1.59 (3H, s);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.7, 137.8, 129.4 (x2), 128.0 (x2), 126.5, 112.9, 93.0, 87.9, 69.8 (x5), 69.1, 67.1, 65.8, 65.3, 47.4, 22.2;

R_f = 0.27 (Hex:Ether = 8:1);

FTIR (neat, cm^{-1}): 3445, 3053, 2982, 2934, 1650, 1601, 1443, 1265;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{21}H_{22}OFe$: 346.1015 (346.1015);



^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.30 (2H, m), 7.27-7.25 (3H, m), 5.76 (1H, dd, J = 17.5, 10.8 Hz), 4.89 (1H, dd, J = 10.8, 1.2 Hz), 4.84 (1H, dd, J = 17.5, 1.6 Hz), 4.49 (1H, brs), 4.43 (1H, brs), 4.36 (1H, brs), 4.31 (1H, brs), 4.22 (5H, s), 0.72 (3H, s), 0.66 (3H, s);

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 145.1, 138.2, 130.3 (x2), 127.9 (x2), 126.5, 112.1, 90.5, 90.3, 73.9, 69.8 (x5), 68.3, 67.1, 66.1, 42.2, 24.0, 21.9;

R_f = 0.39 (Hex:Ether = 8:1);

FTIR (neat, cm^{-1}): 3556, 2780, 1661;

HRMS (EI, m/z (M^+)] calcd (found) for $C_{22}H_{24}OFe$: 360.1171 (360.1165);

PUBLICATIONS

1. Control of up to 5 stereocenters in a cascade reaction: Synthesis of highly functionalized five-membered rings; Hao Li and Teck-Peng Loh; *Journal of the American Chemistry Society*, 2008, 130 (23) pp 7194.
2. Diastereoselective allylation of planar chiral substituted ferrocenecarboxaldehyde: an efficient entry to chiral ferrocenyl ligands; Hao Li, Hin-Soon Cheng, Ai-Hua Seow and Teck-Peng Loh; *Tetrahedron Letters*, 2007, 48(12), pp 2209.
3. Mukaiyama-Aldol-Ene Type cascade reaction: Synthesis of Highly Functionalized Five-membered Rings. Hao Li and Teck-Peng Loh, Manuscript in preparation.
4. Mukaiyama-Aldol-Prins cascade reaction: Synthesis of highly functionalized six-membered ring system. Hao Li and Teck-Peng Loh. Manuscript in preparation.
5. Mukaiyama-Aldol-Prins, Ene cascade reaction: Employ alkyl enol ether to construct multifunctional five, six-membered ring system. Hao Li and Teck-Peng Loh. Manuscript in preparation.

CONFERENCES

1. Control of up to 5 stereocenters in a cascade reaction: Synthesis of highly functionalized five-membered rings. Hao Li and Teck-Peng Loh,17th International Conference on Organic Synthesis (ICOS), 22-27th Jun 2008, Daejeon, Korea. (poster presentation)

2. An Efficient Entry to Chiral Ferrocenyl Ligands. Hao Li and Teck-Peng Loh. The Fifth PERCH Annual Scientific Congress, 6-9 May 2007, Pattaya, Thailand (poster presentation).
3. A facile method for highly substituted six-membered rings: Mukaiyama-Aldol-Prins (MAP) domino reaction. Hao Li and Teck-Peng Loh, International Symposium on Catalysts and Fine Chemicals 2007, 16-21 Dec 2007 (poster presentation).