Synthesis of the Briarane Northern Hemisphere

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SYNTHESIS OF THE BRIARANE NORTHERN HEMISPHERE
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SUMMARY

A large group of marine natural products isolated over the last few years is the briaranes. Over 300 have been isolated, all based on a ring system containing a six membered ring, a ten membered ring and a butenolide, or its oxidised form. Biological studies on the briaranes have revealed a range of activities. Our approach to the synthesis of the briaranes uses a modular approach that should be sufficiently flexible to allow for the synthesis of a variety of these natural products. The preparation of the six-membered ring containing with upper chain as a potential building block was achieved. The Robinson annulation reaction employing β-ketoesters under very mild conditions could not be used to prepare the desired cyclohexenone ester. However, the six-membered ring was obtained by an unusual Diels-Alder reaction of a sulfonyl diene. The Diels-Alder adduct was further manipulated by a series of reactions including oxidative desulfonylation, Eschenmoser-Claisen rearrangement, halo-lactonisation, and enolate hydroxylation using MoOPD.

KEY WORDS: BRIARANES / DIELS-ALDER REACTION / SULFONYL DIENE / ESCHENMOSER CLAISEN REARRANGEMENT / CYCLO-LACTONISATION / ROBINSON ANNULATIONS

CONTENTS

CONTENTS (Cont.)

LIST OF ABBREVIATIONS

ACN	Azocyclohexane-1,1'-dicarbonitrile
AIBN	2,2'-Azobisisobutyronitrile
app.	Apparent
br.	Broad
BSA	*N*,*O*-Bis(trimethylsilyl)acetamide
*n*Bu	*n*-Butyl
*n*BuLi	*n*-Butyllithium
d	Doublet
dd	Doublet of doublets
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	Diisobutylaluminum hydride
cm^{-1}	Wave number
*m*CPBA	3-Chloroperoxybenzoic acid
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMM	Dimethoxymethane
DMP	Dess-Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
equiv	Equivalent

LIST OF ABBREVIATIONS (Cont.)

Et	Ethyl
h	Hour (s)
IBX	2-Iodoxybenzoic acid
LiHMDS	Lithium hexamethyldisilazide
IR	Infrared
J	Coupling constant
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
m	Multiple
M	Molar
M^+	Molecular ion
mp	Melting point
MoOPD	Oxodiperoxymolybdenum (pyridine)-1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidione
Ms	Methanesulfonyl
m/z	A value of mass divided by charge
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
ppm	Part per million
q	Quartet

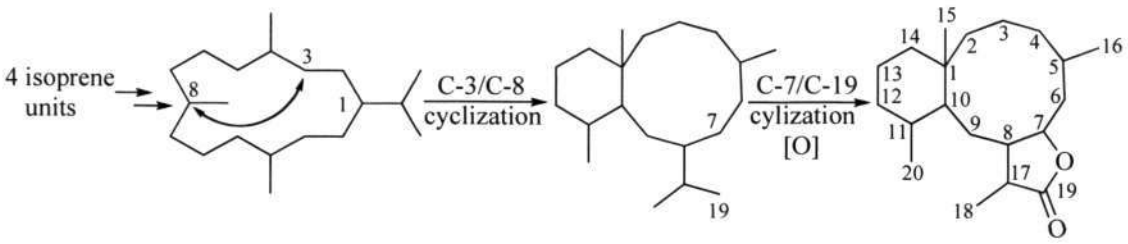
LIST OF ABBREVIATIONS (Cont.)

RT	Room temperature
s	Singlet
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBDPS	*t*-Butyldiphenylsilyl
TBS	*t*-Butyldimethylsilyl
THF	Tetrahydrofuran
Ts	Tosyl (*p*-toluenesulfonyl)
ν_{max}	Maximum absorption frequencies
δ	Chemical shift

CHAPTER I

INTRODUCTION

Since the first discovery of a briarane-type metabolite (briarein A) in 1977 by Burks *et al.*[1] from a West Indian gorgonian coral *Briareum asbestinum*, more than three hundred 3,8-cyclized cembranoid compounds have been reported.[2] They all feature the briarane carbon skeleton (Scheme 1), containing a bicyclo[8.4.0]carbon ring system, and a γ-lactone. The briaranes in this review have been selected from the reviews by Sung *et al.* to illustrate the range of structure.[2] Almost all of the briaranes have been isolated from the soft coral subclass Octocorallia (Phylum cnidaria, class Anthozoa), including Gorgonacea, Pennatulacea, and Stolonifera. Furthermore, some briaranes were obtained from coral and sponges. Briarane-type diterpenoids continue to attract the attentions of investigators because of their structural complexity and the interesting biological activities (e.g., cytotoxicity, antiinflammatory, antiviral, immunomodulatory activity, insect control, antifouling, biotoxin, and ichthyotoxicity) associated with numerous compounds of this type. The briarane-type compounds will be classified taxonomically according to genus and species. It has been proposed that the core skeleton of briaranes is biosynthetically constructs from four isoprene units, followed by a 3+8 linkage to form the 10 and 6 membered rings as shown in Scheme 1. The detail studies or more detailed proposals have, however, not been reported.



Scheme 1 The proposed biosynthetic pathway of briaranes

GORGONACEA

Briareum (family Briareidae)

A. *Briareum asbestinum*

The common Caribbean gorgonian octocoral genus Briareum has been the subject of a number of investigations, which have shown various oxygenated terpenoids, the majority of which possess the briarane skeleton.[2] In 1996, Rodríguez *et al.* reported ten new diterpenoids briareins C-L (**I-3–I-12**) along with two known diterpenoids, briareins A (**I-1**) and B (**I-2**), representative of the briarane skeletal class, isolated from shallow water colonies of the *B. asbestinum* collected at Mona Island near Puerto Rico.[3] The complete spectral data (UV, IR, MS, ^{1}H and ^{13}C NMR) of briareins A-L (**I-1–I-12**) were reported.[3] The structure and the absolute stereochemistry of briarein A (**I-1**) were determined by X-ray analyses.[2] Briarein B (**I-2**) had been reported in the 1980's.[2]

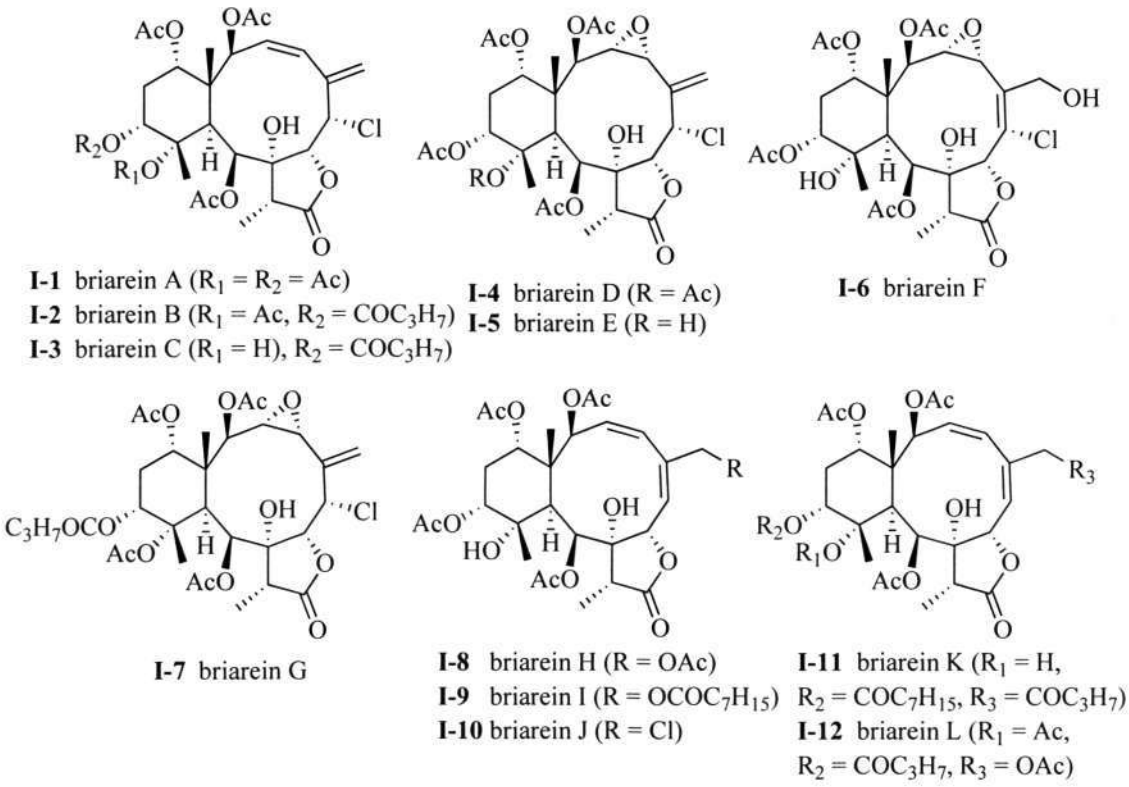


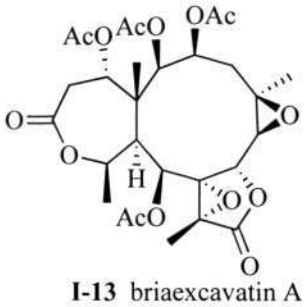
Figure 1 The Briarane-Type Metabolites from *B. asbestinum*

B. *Briareum excavatum*

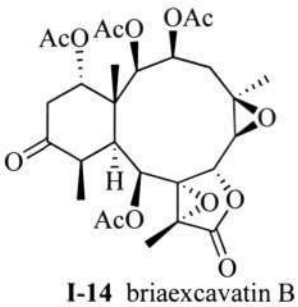
A further study of Taiwanese gorgonian corals, including *B. excavatum* was reported by Sung *et al.*[3-5] Ten new briarane derivatives, briaexcavatins A-F (**I-13–I-18**), I-L (**I-19–I-22**), and three known briaranes, excavatolides B (**I-23**), C (**I-24**), and E (**I-25**), were isolated from the octocoral *B. excavatum* (Figure 2). Compounds **I-13–I-15** possess an unprecedented 5,6-epoxy moiety in the 10-membered ring. The structures were elucidated by spectroscopic methods and the configurations of **I-13** and **I-15** were further supported by molecular mechanics calculations.[3-5] The absolute stereochemistry of **I-24** and **I-25** were determined by X-ray analyses.[6] The absolute configuration were

established by application of modified Mosher's method on **I-23**– **I-25**.[3,6] It may be noted that briaexcavatin A (**I-1**) is the first 11,12-secobriarane possessing an ε-lactone moiety.[3]

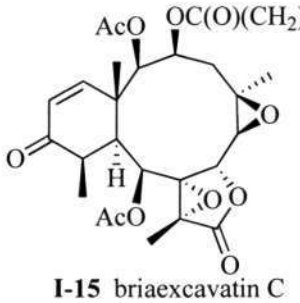
In biological activity testing, briaexcavatin C (**I-15**) has been shown to exhibit mild cytotoxicity toward MDA-MB-231 human breast tumor cells and briaexcavatins E (**I-17**) and excavatolide C (**I-24**) were found to inhibit neutrophil elastase release in humans.[4-5]



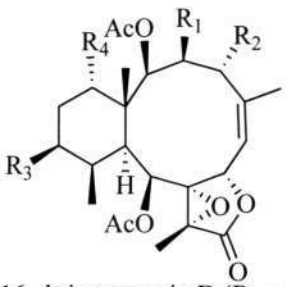
I-13 briaexcavatin A



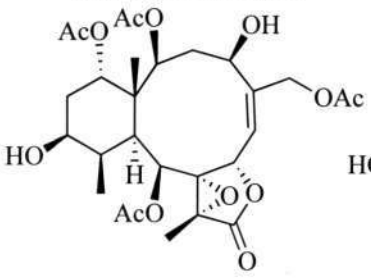
I-14 briaexcavatin B



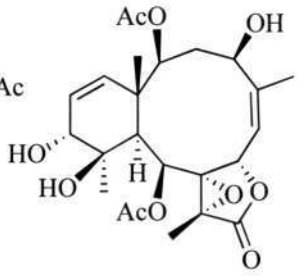
I-15 briaexcavatin C



I-16 briaexcavatin D ($R_1 = R_4 = OAc$, $R_2 = H$, $R_3 = OC(O)(CH_2)_2CH{=}CH_2$)



I-20 briaexcavatin J

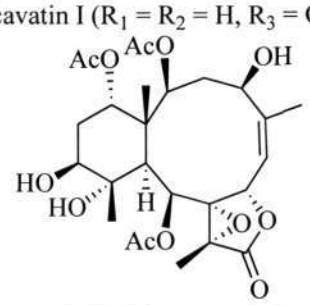


I-21 briaexcavatin K

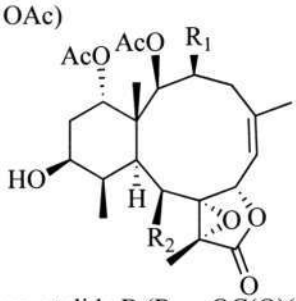
I-17 briaexcavatin E ($R_1 = R_4 = OAc$, $R_2 = H$, $R_3 = OC(O)CH_2CH(CH_3)_2$)

I-18 briaexcavatin F ($R_1 = OC(O)(CH_2)_2CH_3$, $R_2 = H$, $R_3 = OC(O)(CH_2)_2CH{=}CH_2$, $R_4 = OAc$)

I-19 briaexcavatin I ($R_1 = R_2 = H$, $R_3 = OH$, $R_4 = OAc$)



I-22 briaexcavatin L



I-23 excavatolide B ($R_1 = OC(O)(CH_2)_2CH_3$, $R_2 = OAc$)

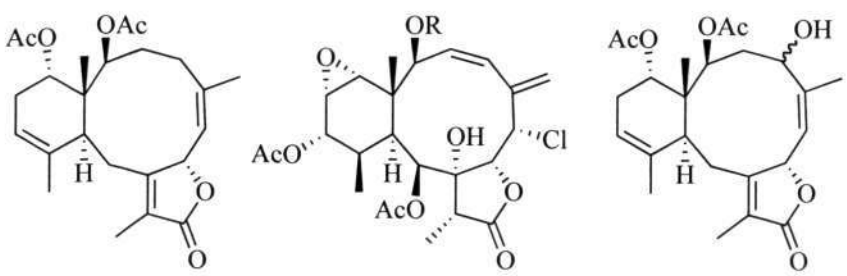
I-24 excavatolide C ($R_1 = R_2 = OAc$)

I-25 excavatolide E ($R_1 = H$, $R_2 = OH$)

Figure 2 The Briarane-Type Diterpenoids from *B. excavatum*

C. Briareum polyanthes

B. polyanthes, *Briareum* species of gorgonian, was discovered at the eastern end of Bermudian waters. This gorgonian coral was found to contain five new Briarane diterpenes, including briantheins W-Z (**I-26–I-29**)[7-9] and an unnamed briarane (**I-30**).[10] The structures and relative stereochemistry of these compounds (**I-26–I-29**) were determined by spectral analyses (IR, UV, MS, ^{1}H and ^{13}C NMR), but the related spectral and physical data for briarane (**I-30**) were not reported.[10] In addition, the absolute configuration of brianthein W (**I-26**) and X (**I-27**) were confirmed by X-Ray diffraction analyses.[7,11] In insecticidal activity testing against grasshoppers, *Melanoplus sanguinipes* and *M. bivitattus*, brianthein Y (**I-28**) exhibited toxicity at a high dose but was inactive at a low dose.[10] Briaranes (**I-26**) and (**I-29**) show *in vitro* cytotoxicity in the P-388 assay, and briaranes (**I-28**) and (**I-29**) displayed antiviral activity, respectively.[6,12] Brianthein W (**I-26**) was also obtained from a Taiwanese soft coral gorgonian genus *Briareum* sp.[12] and briantheins X-Z (**I-27–I-29**) were also found from *Briareum asbestinum*, collected in Caribbean water.[6]



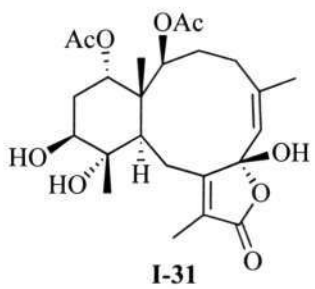
I-26 brianthein W

I-27 brianthein X (R = H)
I-28 brianthein Y (R = COC_3H_7)
I-29 brianthein Z (R = Ac)

I-30

Figure 3 The Briarane-Type Metabolites from *B. polyanthes*

Continuing studies on the chemical constituents of the crude extract of the gorgonian octocoral *B. polyanthes* from Puerto Rico led to a new 7β-hydroxybriarane (**I-31**) of the briarane-type of polycyclized diterpenes (Figure 4).[10] The structure of **I-31** was established on the basis of spectroscopic methods and this compound was found to exhibit antiplasmodial activity.[10]

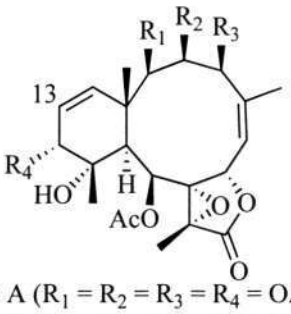


I-31

Figure 4 The Briarane-Type Metabolites from *B. polyanthes*

D. *Briareum sp.*

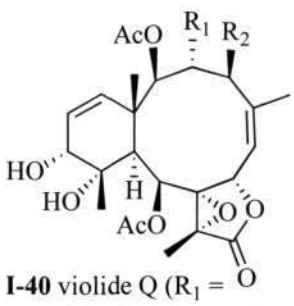
Eight new briaranes diterpenes, which are designated as briarlides A-H (**I-32– I-39**), have been isolated from gorganian coral belonging to the genus *Briareum*, collected at Amami Island, Kagoshima Prefecture, Japan. The relative sterostructures of briaranes (**I-32–I-39**) were elucidated by the interpretation of spectral data analysis (IR, MS, ^{1}H, and ^{13}C NMR spectrum). It has to be noted that all briaranes (**I-32–I-39**) possess a double bond between C-13 and C-14. The structure activity relationships and cytotoxicity of briarlides A-H (**I-32–I-39**) against the African green monkey kidney (Vero) and Madin-Daby Canine Kidney (MDCK) cells are described in the literature.[14]



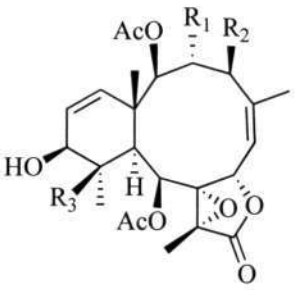
I-32 briarlide A ($R_1 = R_2 = R_3 = R_4 = OAc$)
I-33 briarlide B ($R_1 = R_3 = R_4 = OAc$, $R_2 = OH$)
I-34 briarlide C ($R_1 = R_2 = OH$, $R_3 = R_4 = OAc$)
I-35 briarlide D ($R_1 = R_4 = OAc$, $R_2 = OH$, $R_3 = OCO(CH_2)_6CH_3$)
I-36 briarlide E ($R_1 = R_4 = OAc$, $R_2 = OH$, $R_3 = OCO(CH_2)_4CH_3$)
I-37 briarlide F ($R_1 = R_4 = OAc$, $R_2 = OCO(CH_2)_6CH_3$, $R = OH$)
I-38 briarlide G ($R_1 = R_2 = R_4 = OAc$, $R_3 = H$)
I-39 briarlide H ($R_1 = R_4 = OH$, $R_2 = OAc$, $R_3 = H$)

Figure 5 The Briarane-Type Diterpenoids from *Briareum* sp.

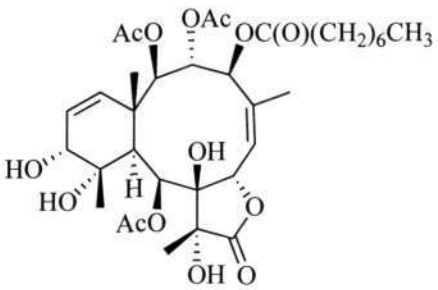
Further investigation of a gorgonian *Briareum* sp., collected in the area of Bonotsu, Kagoshima Prefecture, Japan yielded 24 new briaranes, including, violides Q-U (**I-40–I-44**) and six unnamed derivatives (**I-45–I-50**);[15] briviolides A-D (**I-51–I-54**), 12-*O*-acethylbriviolide D (**I-55**), 9-deacetoxybriviolide D (**I-56**), 4-acetoxybriviolide D (**I-57**), and briviolides E-J (**I-58–I-63**) (Figure 6).[16] The structures of **I-40–I-63** were determined by spectroscopic methods and the structure of briviolide C (**I-53**) was confirmed by X-ray analysis for the first time, indicating that Cl at C-6 and H-7 were α- and β-oriented, respectively.[16] Briaranes (**I-43**, **I-44** and **I-46–I-50**) are examples possessing 17-hydroxy or 17-acyloxy groups.[15] There are no functional groups attached at C-2, C-3, C-4, and C-9 in briviolides G-I (**I-60–I-62**), were rarely found in briarane derivatives.[16] Briviolide I (**I-62**) contained unusual a 7-keto group.[16] Several of above briaranes were shown to exhibit cytotoxicity toward African Green Monkey Kidney (Vero) and Madin-Daby Canine Kidney (MDCK) cells.[15,16]



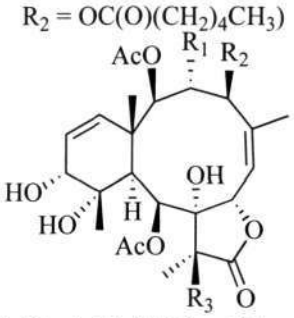
I-40 violide Q (R_1 = $OC(O)(CH_2)_6CH_3$, R_2 = OH)
I-45 unnamed (R_1 = OH, R_2 = $OC(O)(CH_2)_4CH_3$)



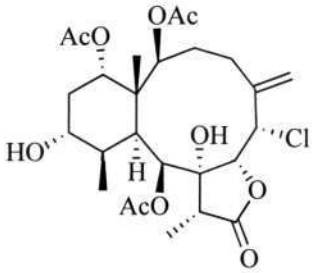
I-41 violide R (R_1 = H, R_2 = $OC(O)(CH_2)_6CH_3$, R_3 = OH)
I-42 violide S (R_1 = R_2 = OAc, R_3 = H)



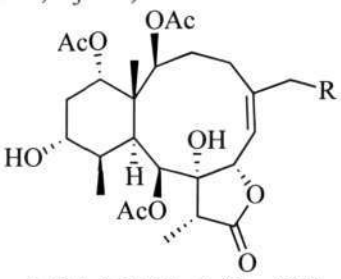
I-50 unnamed



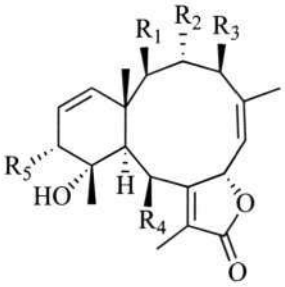
I-43 violide T (R_1 = OAc, R_2 = $OC(O)(CH_2)_6CH_3$, R_3 = OH)
I-44 violide U (R_1 = $OC(O)(CH_2)_2CH_3$, R_2 = OAc, R_3 = OH)
I-46 unnamed (R_1 = H, R_2 = $OC(O)(CH_2)_6CH_3$, R_3 = OH)
I-47 unnamed (R_1 = H, R_2 = $OC(O)(CH_2)_2CH_3$, R_3 = OH)
I-48 unnamed (R_1 = OH, R_2 = $OC(O)(CH_2)_6CH_3$, R_3 = OAc)
I-49 unnamed (R_1 = OH, R_2 = $OC(O)(CH_2)_6CH_3$, R_3 = $OC(O)CH_2CH_3$)



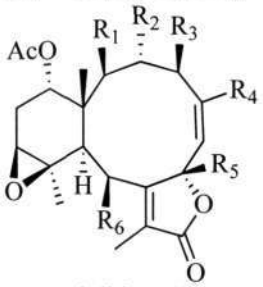
I-53 briviolide C



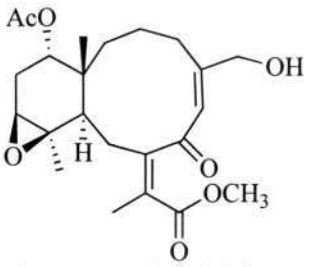
I-51 briviolide A (R = OH)
I-52 briviolide B (R = Cl)



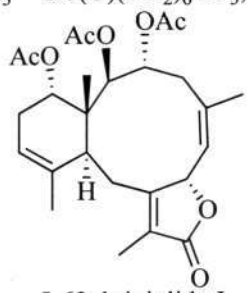
I-54 briviolide D (R_1 = R_2 = R_4 = OAc, R_3 = H, R_5 = OH)
I-55 12-*O*-acethylbriviolide D (R_1 = R_2 = R_4 = R_5 = OAc, R_3 = H)
I-56 9-deacetoxybriviolide D (R_1 = R_2 = OAc, R_3 = R_4 = H, R_5 = OH)
I-57 4-acethylbriviolide D (R_1 = R_2 = R_3 = R_4 = OAc, R_5 = OH)
I-58 briviolide E (R_1 = R_2 = R_5 = OH, R_3 = $OC(O)(CH_2)_6CH_3$, R_4 = OAc)



I-59 briviolide F (R_1 = R_6 = OAc, R_2 = OH, R_3 = $OC(O)(CH_2)_6CH_3$, R_4 = CH_3, R_5 = H)
I-60 briviolide G (R_1 = R_2 = R_3 = R_5 = R_6 = H, R_4 = CH_3)
I-61 briviolide H (R_1 = R_2 = R_3 = R_6 = H, R_4 = CH_2OH, R_5 = OCH_3)



I-62 briviolide I



I-63 briviolide J

Figure 6 The Briarane-Type Diterpenoids from *Briareum sp.*

Ellisella (family Ellisellidae)

A. *Ellisella robusta*

Three new briarane-type diterpenoids, designated as robustolides A-C (**I-64–I-66**), were isolated from the female gorgonian *E. robusta* (Figure 7). The structures of **I-64–I-66** were elucidated by interpretation of spectral data analysis and the structure of **I-64** was confirmed by single-crystal X-ray diffraction analysis.[18] In a previous report, the structure of **I-64** had been named as umbraculolide C.[19] However, by comparison of the NMR data of **I-64** with those of umbraculolide C, the NMR data for **I-64** are significantly different from those of umbraculolide C and the structure of **I-64** (robustolide A) had been further established by X-ray diffraction analysis.[18] The structure for the reported umbraculolide C should be re-examined.[19] In continuing study, six new chlorinated metabolites featuring briarane carbon skeletons, robustolides D-I (**I-67–I-72**), have been isolated from the gorgonian coral *E. robusta,* which was collected from the coast of southern Taiwan (Figure 7).[20,21] The structures of **I-67–I-72** were determined by spectroscopic methods, using 1D and 2D NMR in particular. The absolute stereochemistry of robustolides D (**I-67**), F (**I-69**), G (**I-70**), and I (**I-72**) were directly established by X-ray diffraction analysis.[20,21] It is noteworthy that rebustolide D (**I-67**) is the first metabolite of a briarane possessing two halogen atoms.[20] Compounds **I-69**, **I-70**, and **I-72** had been first reported from a gorgonian *Ellisella* sp., collected in Okinawa, Japan.[22] The absolute configuration of robustolide G (**I-70**) and I (**I-72**) were further confirmed by X-ray analysis indicating that the $\Delta^{3,5,(16)}$-butadiene systems existed in an *s-cis* conjugated system and the structures for these two compounds reported previously should be re-examined.[20-22] Compounds **I-**

64 and **I-65** were found to show weak activity against the bacteria *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[18]

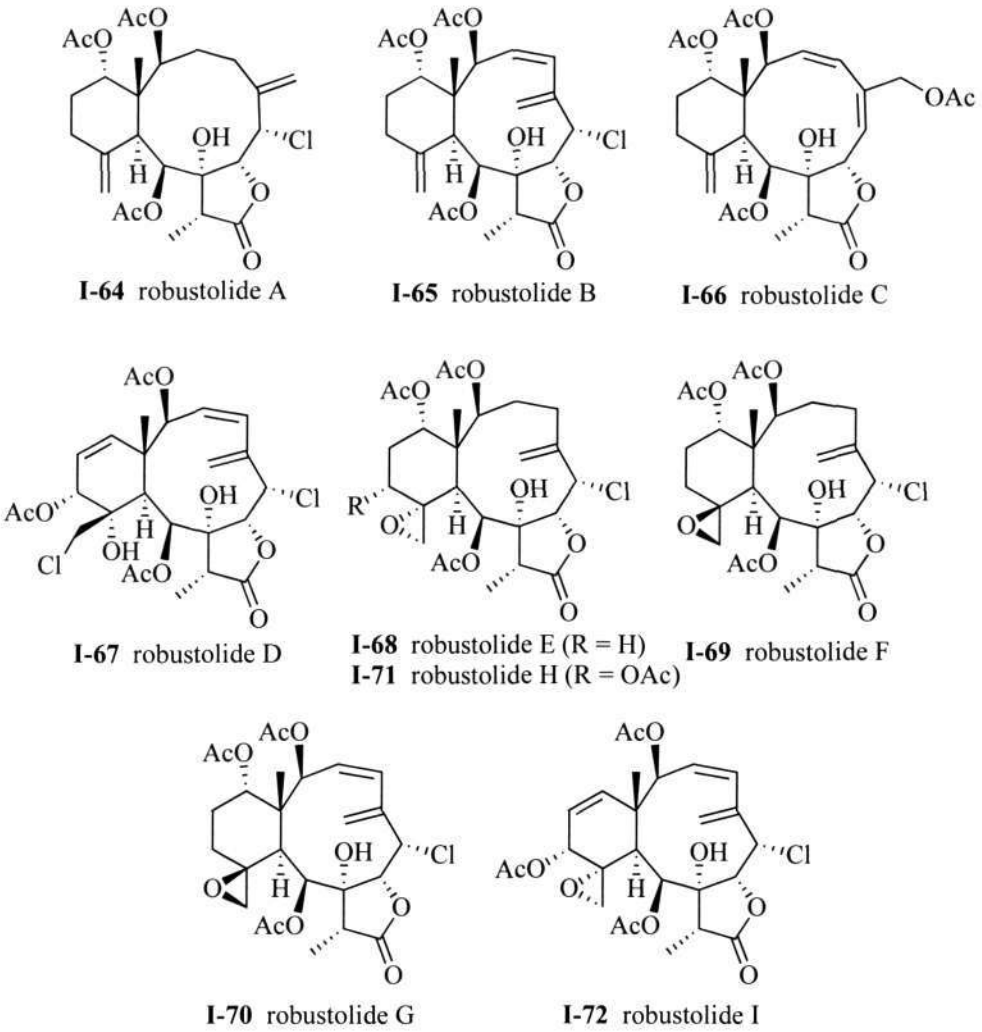
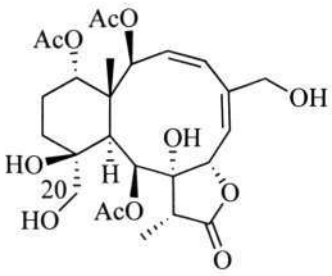


Figure 7 The Briarane-Type Diterpenoids from *E. robusta*

Gorgonella (Ellisellidae)

A. *Gorgonella umbraculum*

Umbraculolide E (**I-73**) is a new tetrahydroxybriarane that has been isolated from an Indian gorgonian coral *G. umbraculum* and its structure was determined by spectral data analysis (Figure 8).[2] It has to be noted that the 20-hydroxy group in **I-73** is rarely found in briarane-type diterpenoid derivatives.



I-73 umbraculolide E

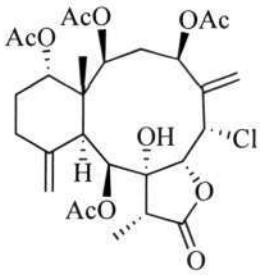
Figure 8 The Briarane-Type Diterpenoid from *G. umbraculum*

***Junceella* (Ellisellidae)**

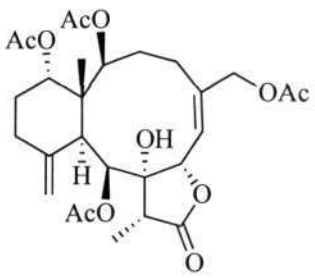
A. *Junceella fragilis*

The gorgonian corals of the genus *Junceella* are known to produce highly oxidized diterpenoids of the briarane class of natural products.[23,24] Five new briarane derivatives, junceellonoids A-E (**I-74–I-78**), were isolated from the extracts of the South China Sea gorgonian coral, *J. fragilis* (Figure 9). The structures of **I-74–I-78** were established by extensive spectroscopic analysis (IR, MS, ^{1}H, and ^{13}C NMR spectrum).[25,26] Junceellonoids C (**I-76**) and D (**I-77**) exhibited mild cytotoxicity against human breast human

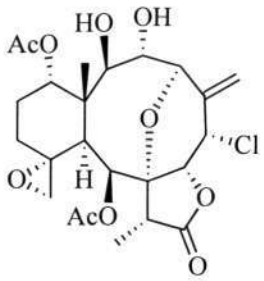
galactophore carcinoma MDA-MB-231 and MCF7 cells.[26] These diterpenoids (**I-74, I-76–I-78**) unusually possess *exo*-methylene group.



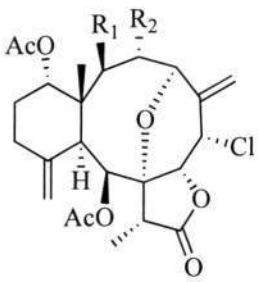
I-74 junceellonoid A



I-75 junceellonoid B



I-76 junceellonoid C



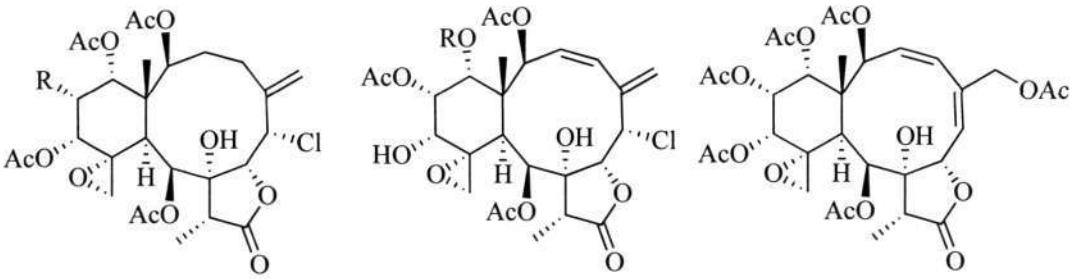
I-77 junceellonoid D ($R_1 = R_2 = OH$)
I-78 junceellonoid E ($R_1 = R_2 = OAc$)

Figure 9 The Briarane-Type Diterpenoids from *J. fragilis*

B. *Junceella gemmacea*

The gorgonian *Junceella gemmacea* collected from Phonpei, Micronesia, yielded six new highly oxidized diterpenoids, gemmacolides A-F (**I-79–I-84**). The structures and relative configurations of gemmacolides A-F (**I-79–I-84**) were elucidated on the basis of extensive NMR studies.[27] Gemmacolide E (**I-83**) is the first briarane-type metabolite bearing the hydroxyl group at C-14. Gemmacolide A (**I-79**) exhibited strong insecticidal activity in a diet overlay assay against the newly hatched larvae of the southern corn rootworm, *Diabrotica undecimpunctata howardi*, and the tobacco budworm, *Heliothis virescens*.[28] Gemmacolides A (**I-79**), B (**I-80**), and D (**I-82**) exhibited selective

immunomodulatory activity with MLR (mixed lymphocyte reaction) to LcV (lymphocyte viability) in ratios of 23, 23, and 11, respectively. The ratios indicate immunosuppressive activity at concentrations significantly lower than the cytotoxicity levels.[2]



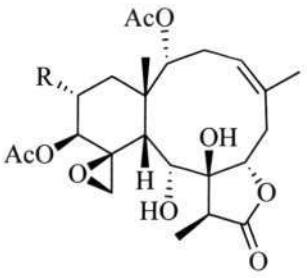
I-79 gemmacolide A (R = OAc)
I-80 gemmacolide B (R = $OCOCH_2CH(CH_3)_2$)
I-81 gemmacolide C (R = H)
I-82 gemmacolide D (R = Ac)
I-83 gemmacolide E (R = H)
I-84 gemmacolide F

Figure 10 The Briarane-Type Metabolites from *J. gemmacea*

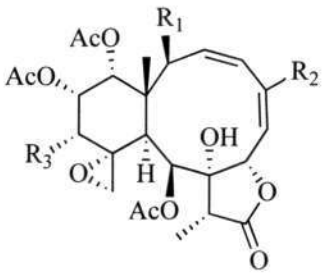
C. *Junceella juncea*

The gorgonian species of the genus *Junceella juncea* also are a rich sourch of several closely related briarane diterenoids having a 10-membered carbocyclic system.[29] Thirteen briaranes, including eleven new metabolites, juncenolide A (**I-85**),[2] juncenolides B-E (**I-86–I-89**),[2,30] and juncins I-N (**I-90–I-95**),[31,32] along with two known diterpenoids junceellin and praelolide,[2] have been isolated from the gorgonian coral *J. juncea*, collected in the Indian Ocean (briaranes **I-85** and **I-90–I-94**) and off the southern Taiwan coast (briaranes **I-86–I-89** and **I-95**), respectively. The structure, including the relative configuration of briaranes (**I-85–I-90**) were elucidated by a combination of extensive spectral data analysis, especially 1D and 2D NMR. It is noteworthy that Juncin N (**I-95**) is the first briarane metabolite containing a carboxylic acid group.[32] Among them,

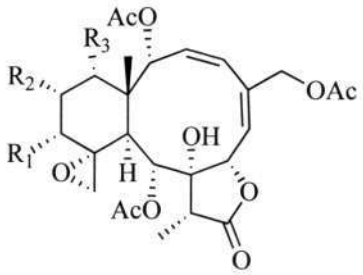
juncenolide C (**I-87**) exhibited mild cytotoxicity against human liver carcinoma (HEPA 59T/VGN) and oral epidemoid (KB-16) carcinoma cells.[30]



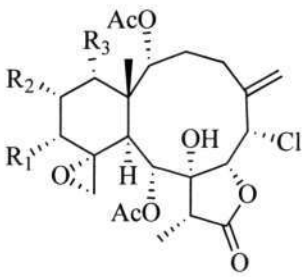
I-85 juncenolide A (R = $OCOCH_2CH(CH_3)_2$)



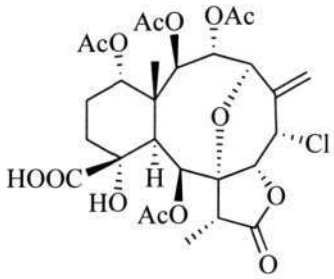
I-86 juncenolide B (R_1 = OAc, R_2 = CH_2OH, R_3 = H)
I-87 juncenolide C (R_1 = R_3 = OAc, R_2 = CH_2OH)
I-88 juncenolide D (R_1 = R_3 = OAc, R_2 = CH_2OCH_3)
I-89 juncenolide E (R_1 = $OCOCH_2CH(CH_3)_2$, R_2 = CH_2OH, R_3 = H)



I-90 juncin I (R_1 = R_3 = OAc, R_2 = $OCOCH_2CH(CH_3)_2$)
I-91 juncin J (R_1 = R_2 = $OCOCH_2CH(CH_3)_2$, R_3 = OAc)
I-92 juncin K (R_1 = R_2 = $OCOCH_2CH(CH_3)_2$, R_3 = H)



I-93 juncin L (R_1 = R_2 = $OCOCH_2CH(CH_3)_2$, R_3 = OAc)
I-94 juncin M (R_1 = R_2 = $OCOCH_2CH(CH_3)_2$, R_3 = H)



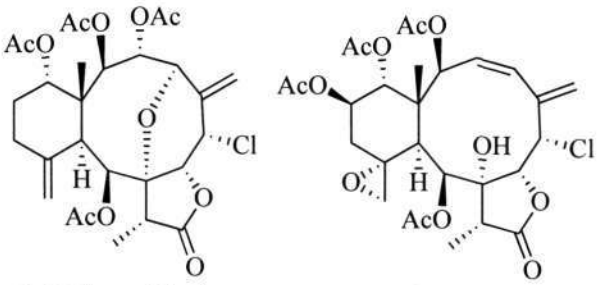
I-95 juncin N

Figure 11 The Briarane-Type Metabolites from *J. juncea*

D. *Junceella squmata*

Two new briarane-type metabolites, junceellins A (**I-96**) and B (**I-97**), have been isolated from *J. squmata* collected in the South China Sea.[2] The structures of briaranes (**I-96**) and (**I-97**) were assigned on the basis of spectral analyses (IR, UV, MS, ^1H and ^{13}C

NMR). Furthermore, the structure and absolute stereochemistry of junceellin A (**I-96**) were established by X-ray diffraction analysis.[2] In addition, the gorgonian corals, *Junceella fragilis* and *Gorgonella umbraculum* were also found to contain Junceellin A (**I-96**).[33-35] Its hydrolysis products showed cytotoxicity toward A-549 tumor cells.[2]



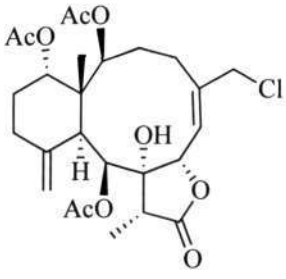
I-96 junceellin A **I-97** junceellin B

Figure 12 The Briarane-Type Metabolites from *J. squmata*

Subergorgia (Subergorgiidae)

A. *Subergorgia retuculata*

A new chlorinated briarane, reticulolide (**I-98**), was isolated from the South China Sea gorgonian *S. reticulata* (Figure 13) and the structure was determined by spectroscopic methods especially in 1D and 2D NMR.[36] This compound is the first briarane derivative isolated from a gorgonian coral belonging to the family Subergorgiidae.



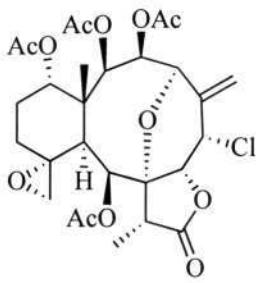
I-98 reticulolide

Figure 13 The Briarane-Type Diterpenoid from *S. reticulata*

Plexaureides (family Plexauridae)

A. *Plexaureides praelonga*

A new diterpenoid with the briarane skeleton, Praelolide (**I-99**), was isolated from *P. praelonga* gorgonian coral collected from the South China Sea. The structure, including the absolute stereochemistry of praelolide (**I-99**) was elucidated by a combination of spectroscopic methods and X-ray crystallographic analyses.[35] This metabolite was also found from both the gorgonian corals *Gorgonella umbraculum* and *Junceella fragilis* collected from the Bay of Bengal, India and the coast of Halmahera Island, Indonesia. Praelolide (**I-99**) showed antiviral activity.[33-35]



I-99 praelolide

Figure 14. The Briarane-Type Metabolite from *P. praelonga*

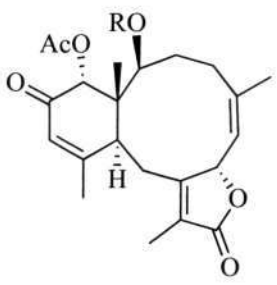
Pennatulacea

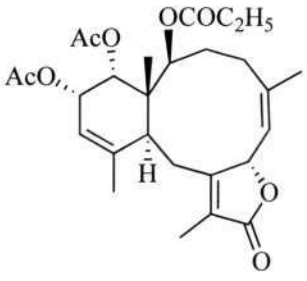
Anthoptilum (family Anthoptilidae)

A. *Anthoptilum* cf. *kukenthali*

Marine coelenterates of the order Pennatulacea have proven to be rich sources of diterpenoids belonging to the skeletal class of briarane. The extraction of Australian sea pen coral, *Anthoptilun* cf. *kukenthali*, afforded five new briarane-type diterpenoids, which

were designated as anthoptilide A-E (**I-100–I-104**). Their structures were determined on the basis of their spectral data (IR, UV, MS, ^{1}H and ^{13}C NMR). The structure of anthoptilide A (**I-100**) was further determined by single-crystal X-ray analyses. The senecioate and benzoate substituents attached to the C-2 positions of anthoptilides A (**I-100**) and D (**I-103**), respectively, are unusual among briarane-type diterpenoids. Briaranes (**I-100–I-104**) inhibited the binding of [^{3}H]1,3-dipropyl-8-cyclopentylxanthine ([^{3}H]DPCPX) to rat-brain adenosine A_1 receptors.[37]





I-100 anthoptilide A (R = $COC(CH_3)$=$CHCH_3$)
I-101 anthoptilide B (R = $COCH(CH_3)_2$)
I-102 anthoptilide C (R = COC_2H_5)
I-103 anthoptilide D (R = COC_6H_5)

I-104 anthoptilide E

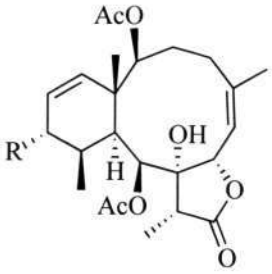
Figure 15 The Briarane-type Metabolites from *A. kukenthali*

Cavernularia (family Veretillidae)

A. *Cavernularia* sp.

Gorgonians belonging to the genus *Cavernularia* are known to produce highly oxidized diterpenoids of the briarane class. An Indian Ocean sea pen coral, *Cavernularia* sp., was discovered at the Eastern Coast of the Bay of Bengal. This gorgonian coral was found to contain two new briaranes, cavernulins A (**I-105**) and B (**I-106**) and their relative

stereostructures were determined by spectral analyses (IR, MS, ^{1}H and ^{13}C NMR spectrum).[2]



I-105 cavernulin A (R = $OCO(CH_2)_2CH_3$)
I-106 cavernulin B (R = OH)

Figure 16 The Briarane-Type Metabolites from *Cavernularia* sp.

Pteroeides (family Pteroeidae)

A. *Pteroeides* sp.

A Sea pen coral, identified as *Pteroeides* sp. and collected off Flores Island, Indonesia, has afforded four new unnamed briarane-type diterpenoids (**I-107–I-110**). The relative stereostructures of briaranes (**I-107–I-110**) were determined on the basis of their spectral data (IR, MS, ^{1}H, and ^{13}C NMR spectrum).[38] It may be notable that two briaranes (**I-107** and **I-108**) contain the *trans* alkene moiety.

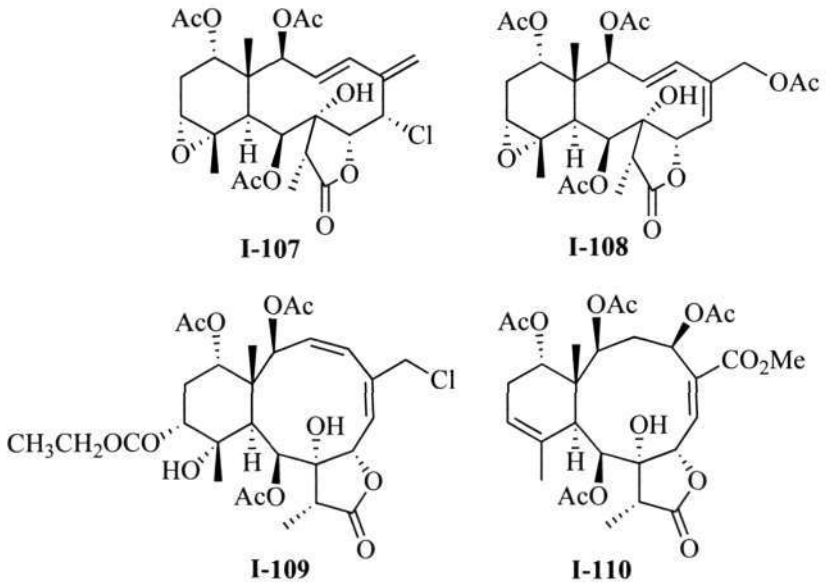


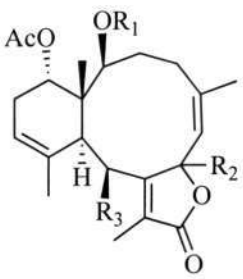
Figure 17 The Briarane-Type Metabolites from *Pteroeides* sp.

Funiculina (family Funiculinidae)

A. *Funiculina quadrangularis*

Marine octocorals are an extremely rich source of novel diterpenoids that often have potent biological activities relevant to drug development.[2] Six new diterpenoids, funicolides A-E (**I-111–I-115**) and 7-epifunicolide A (**I-116**), along with a known metabolite, brianthein W (**I-26**),[7] have been isolated from the luminescent sea pen coral, *F. quadrangularis*, collected in the Vada and Capraia Islands in the Tuscan archipelago, Ligurian Sea. The structures and relative configurations of briaranes (**I-111–I-116**) were elucidated by extensive analysis of spectroscopic data (IR, UV, MS, ^{1}H and ^{13}C NMR) and by comparison with the spectral data from other briarane compounds.[7] Due to the slow flipping rotation in the ten-membered ring, kinetic and equilibrium NMR spectral studies were performed on funicolides A (**I-111**), D (**I-114**), brianthein W (**I-26**), and a chemical derivative of brianthein W, 7-epibrianthein W. These kinetic and equilibrium

NMR spectral observations and molecular mechanics calculations for briaranes (**I-26**, **I-111**, and **I-114**), and 7-epibrianthein A, led to general views on the conformational preferences of diterpenoids of this class.[2]



I-111 funicolide A ($R_1 = COC_2H_5$, $R_2 = H_\beta$, $R_3 = H$)
I-112 funicolide B ($R_1 = COC_2H_5$, $R_2 = \alpha$-OH, $R_3 = H$)
I-113 funicolide C ($R_1 = COC_2H_5$, $R_2 = H_\beta$, $R_3 = OAc$)
I-114 funicolide D ($R_1 = COC_3H_7$, $R_2 = H_\beta$, $R_3 = H$)
I-115 funicolide E ($R_1 = Ac$, $R_2 = \alpha$-OH, $R_3 = H$)
I-116 7-epifunicolide A ($R_1 = COC_2H_5$, $R_2 = H_\alpha$, $R_3 = H$)

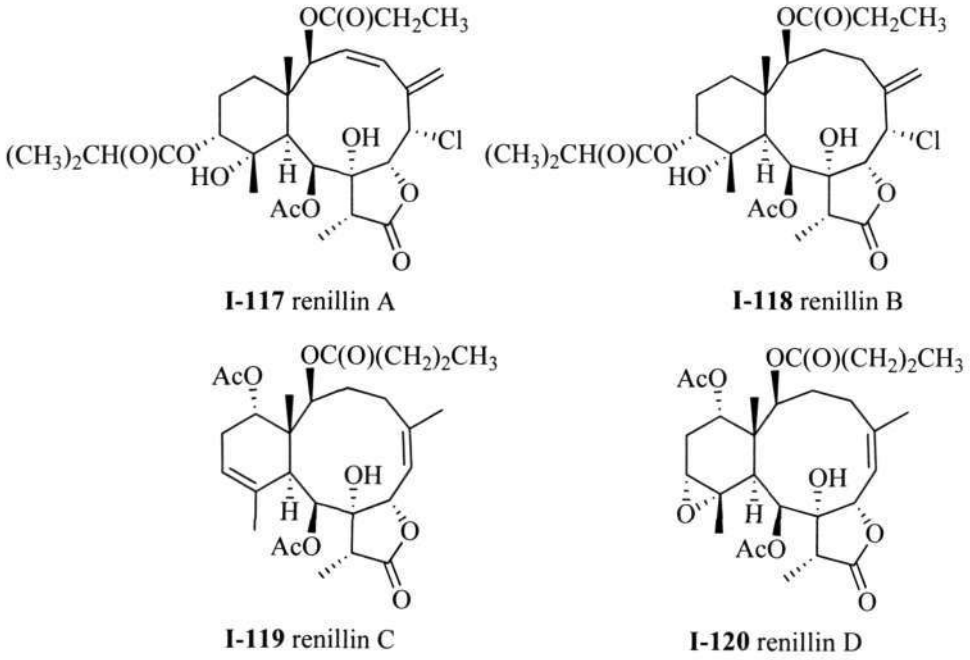
Figure 18 The Briarane-Type Metabolites from *F. quadrangularis*

***Renilla* (Renillidae)**

A. *Renilla reniformis*

Four new briaranes, renillins A-D (**I-117–I-120**) were isolated from the soft-bodied, umbrella-shaped sea peasy coral, which is identified as *R. reniformis*, collected at the sand bars off Wassaw, Little Tybee, and South Cabbage Islands, Georgia, United States (Figure 19).[39] The structures and relative stereochemistry of briaranes **I-117–I-120** were elucidated by the interpretation of spectroscopic data. Interestingly, renillins A (**I-117**) and B (**I-118**) are the first briarane derivatives with fully reduced C-14 centers.[39] Using laboratory feeding assays, briaranes (**I-117–I-120**) tested at natural concentrations

significantly deterred feeding by the predatory lesser blue crab, *Callinectes similis*, while remillins **I-119** and **I-120** also deterred feeding by the predatory mummichog fish, *Fundulus heteroclitus*.



I-117 renillin A

I-118 renillin B

I-119 renillin C

I-120 renillin D

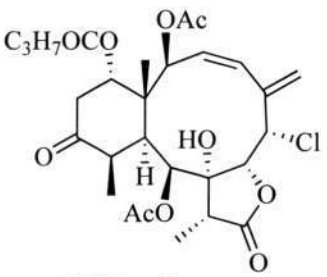
Figure 19 The Briarane-Type Metabolites from *R. reniformis*

Ptilosarcus (family Pennatulidae)

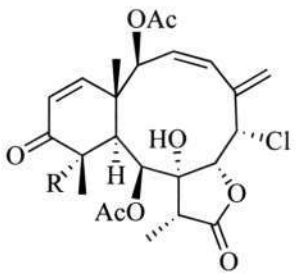
A. *Ptilosarcus gurneyi*

A mild toxic briarane mixture from a North Pacific Ocean sea pen coral, *P. gurneyi*, was found to contain ptilosarcone (**I-121**), and its decomposition product, ptilosarcenone (**I-122**). The gross structures of briaranes (**I-121**) and (**I-122**) were elucidated by NMR data (^{1}H and ^{13}C) and by comparison with those of a known metabolite, briarein A (**I-1**).[40] In a reinvestigation of this marine organism, samples were collected from sites near Sidney, British Columbia, and Seattle, Washington, and afforded

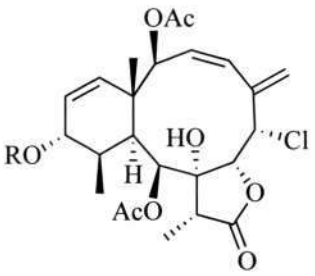
the known ptilosarcone (**I-121**) and ptilosarcenone (**I-122**), along with five new briaranes, 11-hydroxyptilosarcenone (**I-123**), ptilosarcen-12-ol (**I-124**), ptilosarcen-12-acetate (**I-125**), ptilosarcen-12-propionate (**I-126**), and ptilosarcol (**I-127**). The structures and stereochemistry of briaranes **I-121–I-127** were assigned by using 1D and 2D NMR spectral and by comparision with those of the other known briarane.[41] Insecticidal screening activity of Briarane (**I-122**) showed activity against the larvae of the tobacco hornworm, *Manduca sexta*.[41]



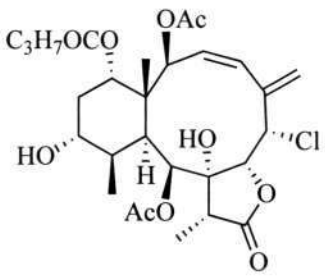
I-121 ptilosarcone



I-122 ptilosarcenone (R =H)
I-123 11-hydroxyptilosarcenone (R = OH)



I-124 ptilosarcen-12-ol (R = OH)
I-125 ptilosarcen-12-acetate (R = Ac)
I-126 ptilosarcen-12-propionate (R = COC_2H_5)



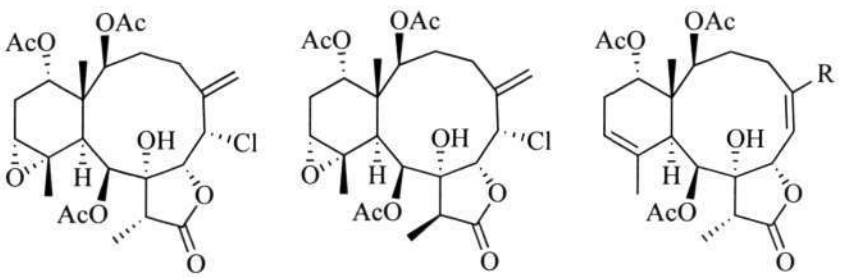
I-127 ptilosarcol

Figure 20 The Briarane-Type Metabolites from *P. gurneyi*.

Stylatula (family Virgulariidae)

A. *Stylatula* sp.

The sea pen *Stylatulide* sp. is a slender, whip-like coelenterate, which was collected in the intertidal zone at Isla Partida, Gulf of California, and was found to contain stylatulide (**I-128**). Briarane **I-128** is the first briarane-type metabolite with toxicity originally from the sea pen coral, *Stylatula* sp. The structure, including the absolute configuration was elucidated by single-crystal X-ray diffraction analyses.[85] In a later study, this organism was found to contain a new metabolite, 17-epistylatulide (**I-129**) and three unnamed new briaranes (**I-130–I-132**), along with known stylatulide (**I-128**). The structures of **I-129–I-132** were determined by basic spectral analyses (UV, IR, MS, ^{1}H and ^{13}C NMR) and chemical methods. Moreover, the complete NMR data (^{1}H and ^{13}C) of stylatulide (**I-128**) were assigned.[86] The stylatulide (**I-128**) was found to be toxic to the larvae of the copepod *Tisbe furcata johnsonii*.[85]



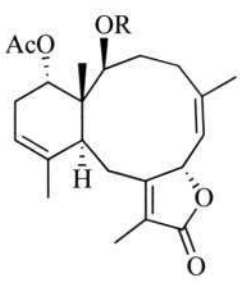
I-128 stylatulide **I-129** 17-epistylatulide **I-130** (R = CH_3)
I-131 (R = CH_2OH)
I-132 (R = $COOCH_3$)

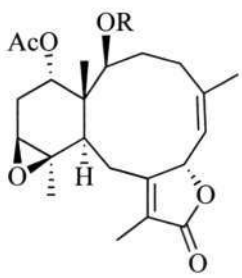
Figure 21 The Briarane-Type Metabolites from *Stylatula* sp.

Veretillum (family Veretillidae)

A. *Veretillum malayense*

The sea pen coral, *V. malayense*, collected near Monado, Sulawesi, Indonesia was found to contain four new briarane diterpenes, which are designed as malayenolides A-D (**I-133–I-136**). The structures of metabolites (**I-133–I-136**) were assigned by using 1D and 2D NMR spectral.[44] The structures of malayenolides A (**I-133**) and C (**I-135**) appear to be identical to funicolide A (**I-111**) and D (**I-114**) except for the C-2 ester group. The benzoate groups in briaranes (**I-133**) and (**I-134**), and the senecioate groups in briaranes (**I-135**) and (**I-136**) are uncommon among marine natural products, although many benzoate-containing metabolites have been isolated from terrestrial plants.[37] Malayenolides A-D (**I-133–I-136**) exhibited toxicity to brine shrimp.





I-133 malayenolide A (R = COC_6H_5) **I-134** malayenolide B (R = COC_6H_5)
I-135 malayenolide C (R = $COCH{=}C(CH_3)_2$) **I-136** malayenolide D (R = $COCH{=}C(CH_3)_2$)

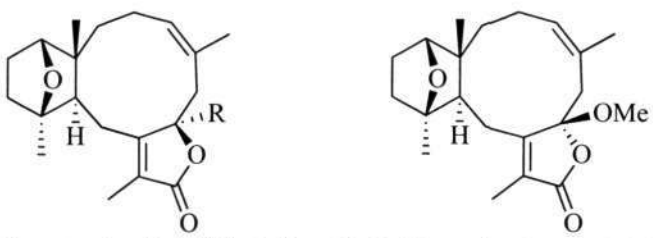
Figure 22 The Briarane-Type Metabolites from *V. malayense*.

Stolonifera

Pachyclavularia (family Tubiporidae)

A. *Pachyclavularia violacea*

Four novel diterpenoids, pachyclavulariolides A-D (**I-137–I-140**), with cembrane and briarane carbon skeletons have been isolated from specimens of *P. violacea*, collected in the shallow reefs near Sek point off Madang, Papua New Guinea. The structures of **I-137–I-140** were elucidated by analyses of spectroscopic data (IR, UV, MS, ^{1}H and ^{13}C NMR). The structure, including the absolute configuration of pachyclavulariolide B (**I-138**) was further confirmed by single X-ray diffraction analyses.[45] It is noteworthy that briaranes (**I-137–I-140**) are the first briarane-type metabolites possessing ether linkage between C-11 and C-14, in the six-membered ring. Furthermore, in the structures of briaranes (**I-138**) and (**I-139**), the C-7 α-oriented oxygen-bearing functional groups were rarely found previously.[2]

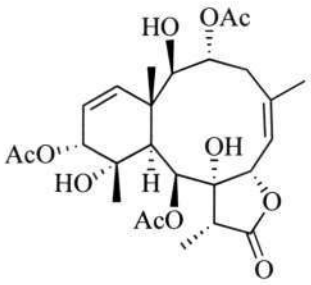


I-137 pachyclavulariolide A (R = H) **I-140** pachyclavulariolide D
I-138 pachyclavulariolide B (R = OH)
I-139 pachyclavulariolide C (R = OMe)

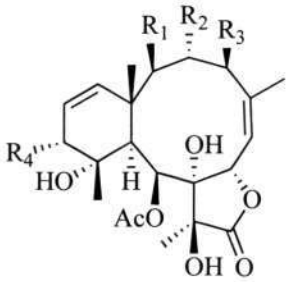
Figure 23 The Briarane-Type Metabolites from *P. violacea*

B. *Pachyclavularia* sp.

The terpenoid fractions of soft coral *Pachyclavularia* sp. collected from an Okinawa octocoral, was found to contain four new briaranes, brianodins A-D (**I-141– I-144**) (Figure 24).[46] The structures and relative of these four natural products were elucidated by spectral data analysis (IR, UV, MS, ^{1}H and ^{13}C NMR). The absolute configurations of **I-143** and **I-144** were further assigned by chemical methods. Brianodin A (**I-141**) showed modest activity toward L1210 (murine leukemia) and KB (human oral epidermoid carcinoma) tumor cells.[46]



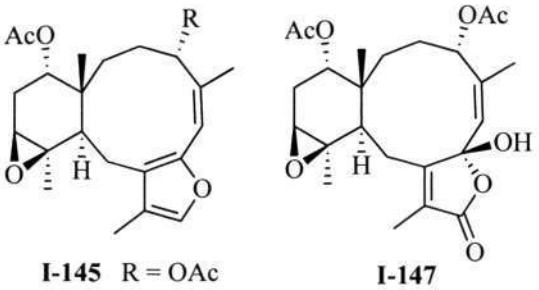
I-141 brianodin A



I-142 brianodin B ($R_1 = R_3 = R_4 = OAc$, $R_2 = OH$)
I-143 brianodin C ($R_1 = R_3 = OAc$, $R_2 = R_4 = OH$)
I-144 brianodin D ($R_1 = R_4 = OH$, $R_2 = OAc$, $R_3 = H$)

Figure 24 The Briarane-Type Metabolites from *Pachyclavularia* sp.

In addition, investigation of the chemical constituents of an octocoral, *Pachyclavularia* sp., collected in the Great Barrier Reef, Australia, led to three new unnamed briaranes (**I-145–I-147**). The structures of diterpenoids (**I-145–I-147**) were determined by analyses of spectroscopic data (Figure 25). Briarane (**I-145**) exhibited ichthyotoxicity toward the mosquito fish, *Gambusia affinis*,[2] and, thus, may be a defense compound.



I-145 R = OAc
I-146 R = H

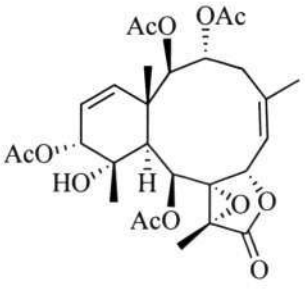
I-147

Figure 25 The Briarane-Type Metabolites from *Pachyclavularia* sp.

Tubipora (family Tubiporidae)

A. *Tubipora* sp.

A Gorgonian soft coral of the genus *Tubipora*, collected at Kuchino-shima Island of the Satsunan archipelago, whose organic extract inhibited the growth of B-16 mouse melanoma tumor cells, was studied for the discovery of potential antitumor agents. A new diterpenoid, tubiporein (**I-148**), was isolated from this organism (Figure 26). The gross structure was detemined by ^{1}H and ^{13}C and the relative configuration was elucidated by the interpretation of NOE experiments. Tubiporein (**I-148**) exhibited cytotoxicity toward B-16 tumor cells.[47]



I-148 tubiporein

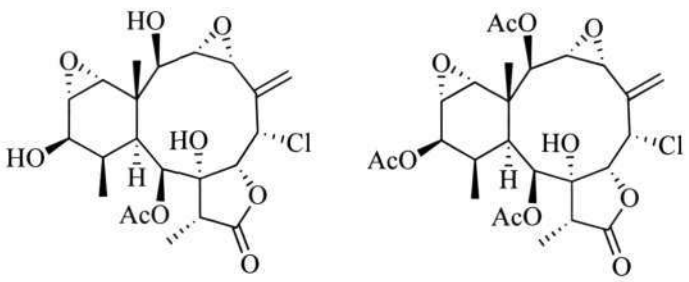
Figure 26 The Briarane-Type Metabolites from *Tubipora* sp.

Sponge

Psammaplysilla (family Verongiidae)

A. *Psammaplysilla purpurea*

Chemical examination of a marine sponge, *P. purpurea*, collected on the coast of Ie island, Okinawa Prefecture, Japan, has afforded a new diterpenoid, bis(deacetyl)solenolide D (**I-149**) (Figure 27). The structure of metabolite (**I-149**) was established by NMR spectral analyses (IR, UV, MS, ^{1}H and ^{13}C NMR) and extensive chemical methods, and by comparison the spectral data with those of a known metabolite, solenolide D (**I-150**).[49] However, the stereochemistry of solenolide D (**I-150**) has been revised,[48] the hydroxyl group attached at the C-12 position in briarane (**I-149**) should be β-oriented. In an antifouling activity assay, bis(deacetyl)solenolide D (**I-149**) exhibited activity to regulate the biofilm formation.[2] Briarane (**I-149**) is the only briarane-type metabolite from a marine sponge.



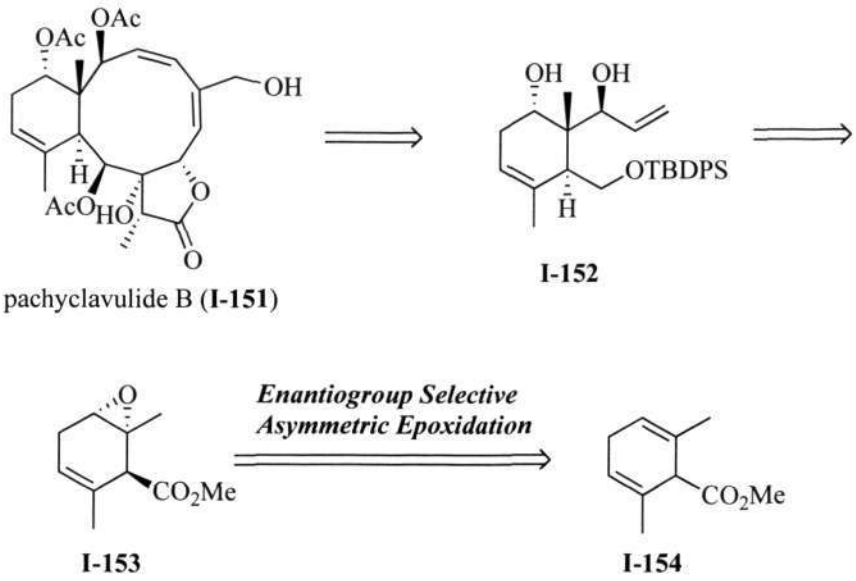
I-149 bis(deacetyl)solenolide D **I-150** solenolide D

Figure 27 The Briarane-Type Metabolites from *P. purpurea*

Synthetic studies

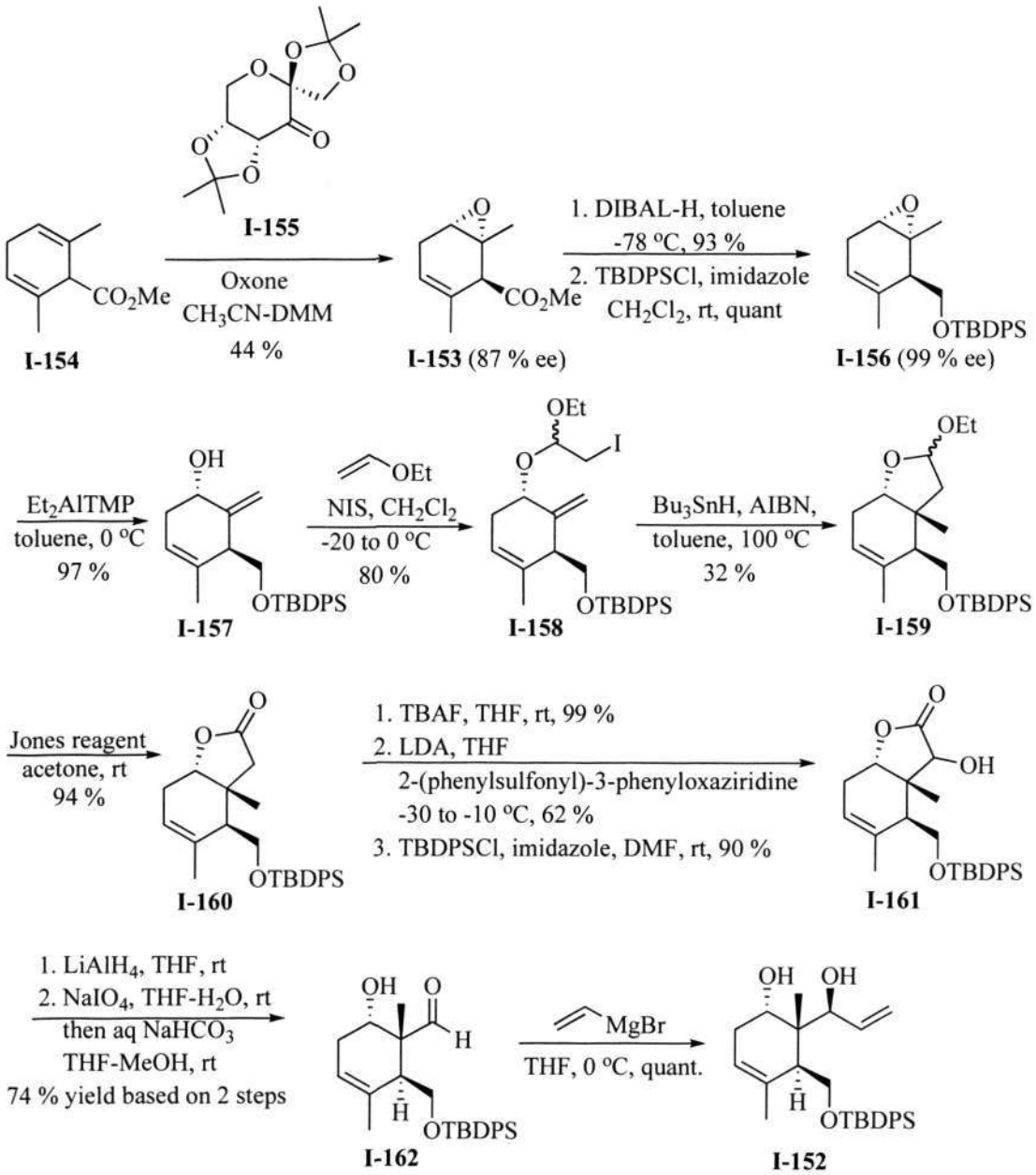
Despite the biological activity and structural challenge of the briaranes, there has been very little synthetic activity. Since 1977 more than 300 briaranes have been reported. However, a total synthesis of briarane-type diterpenoids has not yet been reported. Preliminary, synthetic of briarane-type diterpenoids were reported by several groups.[50] In 2006, Iwasaki *et al.* reported a synthetic study of briarane-type marine diterpenoid, pachyclavulide B,[51] which was isolated from the methanol extraction of soft coral *Pachyclavularia violacea* by the same group.[52] The soft coral *Pachyclavularia violacea* was collected from a coral reef off Ishigaki Island, Okinawa Prefecture, Japan. Pachyclavulide B is a briarane-type diterpenoid containing a highly oxygenated bicyclo[8.4.0]tetradecane skeleton and eight chiral centers. It exhibited moderate growth-inhibitory activity against cancer cells (SNB-75) of the central nervous system.[2]

The synthetic plan for pachyclavulide B (**I-151**) is delineated in Scheme 2. Construction of the 10-membered ring would be achieved through elongation of the carbon chain of **I-152** and ring-closing metathesis. Compound **I-152** could be prepared by a carbon-carbon bond forming reaction with the construction of the quaternary carbon on the cyclohexene ring of compound **I-153**, which could be obtained employing enantio- and diastereoselective asymmetric epoxidation of achiral substrate ester **I-154**. Compound **I-154** can be easily prepared by Birch reduction of 2,6-dimethylbenzoic acid.



Scheme 2 Retrosynthetic analysis of pachyclavulide B (**I-151**).

They employed **I-154** for the synthetic study of pachyclavulide B (**I-151**). The asymmetric epoxidation of **I-154** was performed using **I-155** as a catalyst by Shi's method,[53] which was prepared from D-sorbose,[54] to give compound **I-153** in 44% yield with 81% de and 87% ee (Scheme 3). The reduction of the methoxycarbonyl group followed by TBDPS protection of the corresponding alcohol gave compound **I-156**, which could be purified by recrystallization to provide almost enantiomerically pure **I-156** (99% ee). Treating compound **I-156** with Et_2AlTMP[55] led to allylic alcohol **I-157**, which subsequently reacted with ethyl vinyl ether in the presence of NIS to give the substrate **I-158**.[56] Intramolecular 5-*exo* radical cyclization[57] was performed on **I-158** to construct the quaternary center of the cyclohexene ring to yield compound **I-159** in unsatisfactory yield (32%) along with a significant amount of deiodinated and 6-*endo* cyclized products.[58]



Scheme 3

Pressing forward in the synthetic study, the conversion of acetal **I-159** to aldehyde **I-162** with a carbon degradation was required. Jones reagent was used to oxidize compound **I-159** to lactone **I-160**. The introduction of a hydroxyl group at the α-position of lactone **I-160** was found to be difficult due to the steric repulsion of the TBDPS group;

however, the reaction proceeded with excellent diastereoselectivity (>95% de) after removal of the TBDPS group. Although the stereochemistry of the product **I-161** was not determined, it could be envisaged that the Davis reagent[59] approached from the convex face of lithium enolate of **I-160**. The reduction of **I-161** gave a diol, which was subjected to oxidative cleavage by treatment with $NaIO_4$ to furnish aldehyde **I-162**. The diastereoselective addition reaction of vinylmagnesium chloride to **I-162** was achieved to give the desired adduct **I-152** as a single diastereomer in a quantitative yield. In conclusion, enantio- and diastereoselective asymmetric epoxidation of the symmetric substrate as a key step have succeeded to give the optically active mono-epoxide and the enantionselective preparation of key intermediate **I-152** for the synthesis of the briarane-type diterpenoid, pachyclavulide B (**I-151**) was successfully achieved. Nevertheless, the low yielding formation of the five membered ring remains a stumbling block.

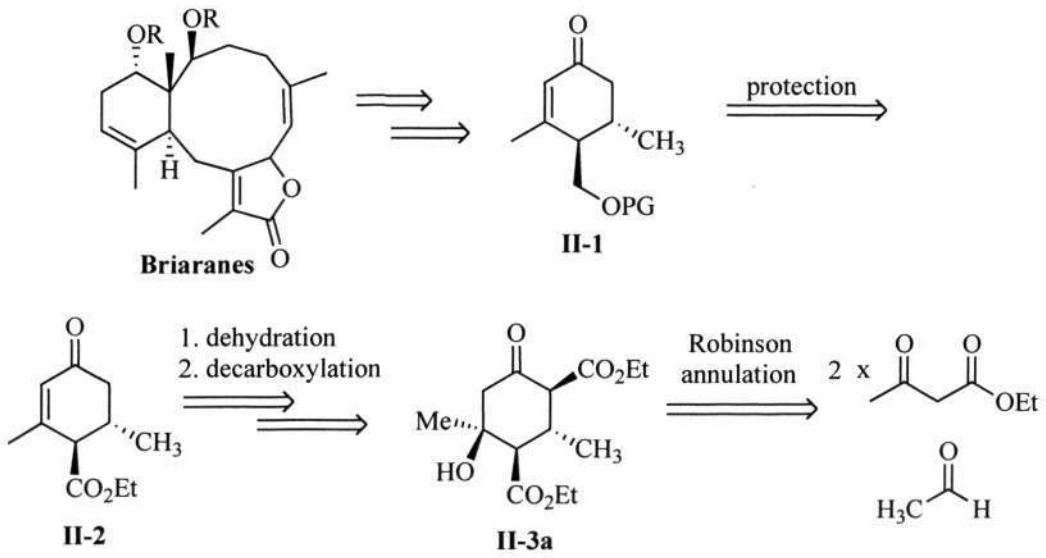
The structural novelty of briarane-type diterpenoids combined with their impressive biological activity poses a challenge for synthetic organic chemists. Its molecular architecture possesses a number of challenging structural elements that would need to be appropriately addressed in a total synthesis. We therefore searched for a new entry to these types of compounds based on the chemistry of unusual Diels-Alder reaction of a sulfonyl diene including oxidative desulfonylation, Eschenmoser modification of the Claisen rearrangement, halo-lactonisation, and enolate hydroxylation.

CHAPTER II

STUDIES ON THE ROBINSON ANNULATIONS

Observation on the Robinson annulation under mild conditions

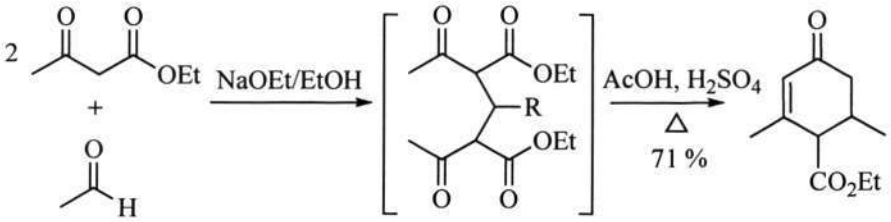
Our approach to the synthesis of the briarane skeleton utilizes compound **II-1** as a building block as shown in Scheme 4 (see page 57). Compound **II-1** could be obtained from protection of cyclohexenone ester **II-2**, which was envisioned to arise from cyclohexanone **II-3a** via Tandem Knoevenagel-Michael condensation, by dehydration and decarboxylation. Alternatively, compound **II-2** might be constructed from a Robinson annulation reaction.



Scheme 4

Tandem or domino processes are multistep reactions providing rapid access to complex structures containing multiple chiral centers. As such, they are powerful

strategy for synthetic transformations. The synthetic efforts have been reported for the construction of methyl-substituted conjugated cyclohexenones,[60] in which an annulation approach from acyclic precursors constituted a useful entry. Horning *et al.* reported a highly efficient synthesis of methyl-substituted conjugate cyclohexenones as shown in Scheme 5.[61]



II-4 **II-5**

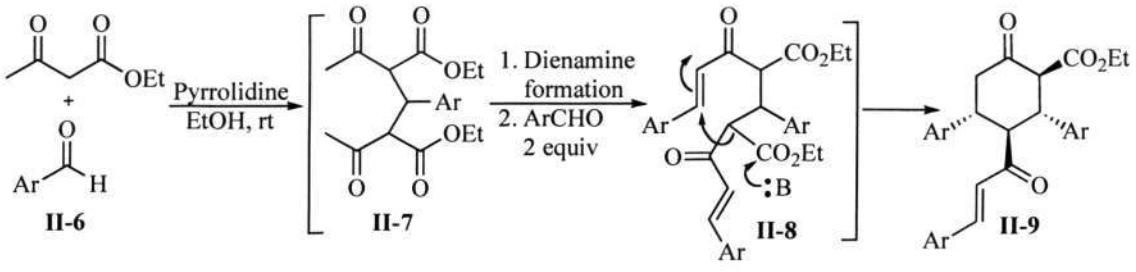
R = methyl, ethyl, *n*-propyl, isopropyl, and *n*-hexyl

Scheme 5

Tandem-Knoevenagel-Michael condensation of 2 equiv of ethyl acetoacetate to aldehydes followed by decarboxylation yields cyclohexenones. This reaction was presumed to proceed through intermediate **II-4**, formed by the conjugate addition of ethyl acetoacetate to the Knoevenagel condensation product of ethyl acetoacetate and an aldehyde, followed by acid catalysed cyclisation and dehydration to give keto ester **II-5**. The reaction has been employed since without discussion as to the true nature of the intermediate.[61] In addition, using the same substrate for the preparation of **II-5** works well by using 35 mol% of piperidine in ethanol[62] or ^{t}BuOK in ^{t}BuOH at reflux.[60]

In addition, Knoevendagel condensation with an extra aldol condensation, has been reported by Perumal *et al.* They reported a one-pot tandem sequence for the diastereoselective synthesis of ethoxycarbonylcyclohexanones **II-9** (Scheme 6) by the

reaction of ethyl acetoacetate with aromatic aldehydes **II-6** in a 2:3 molar ratio in the presence of pyrrolidine at ambient temperature in 58-68% yield.[63] This reaction can be envisaged to occur via an intitial Knoevengal condensation of the aromatic aldehyde with ethyl acetoacetate, followed by Michael addition of a second equiv of ethyl acetoacetate to furnish symmetric intermediate **II-7**. Dione **II-7** could then condense with two molecules of the aromatic aldehyde via dienamine to afford **II-8**, which subsequently could suffer deethoxycarbonylation with concomitant intramolecular Michael addition either simultaneously or in a stepwise manner affording **II-9**.

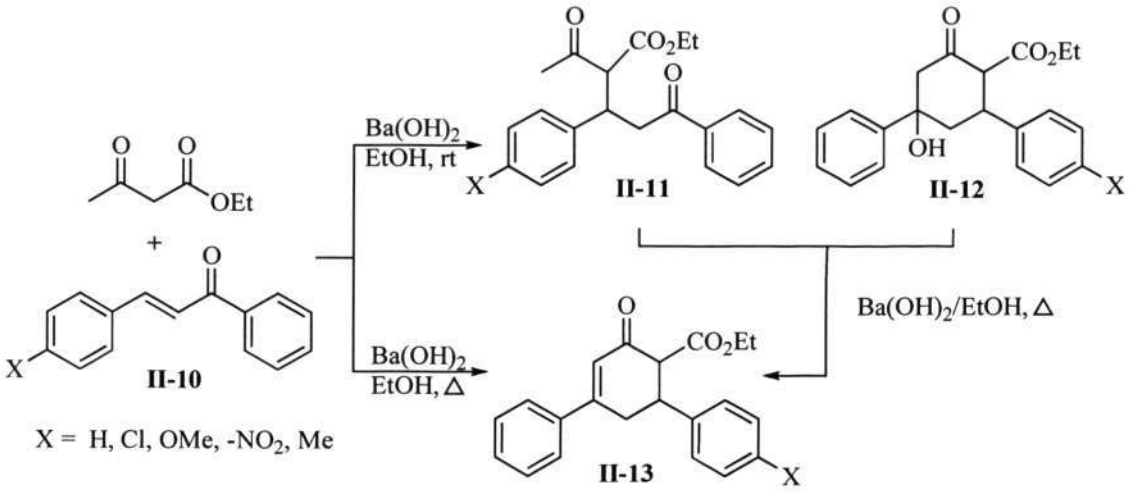


Ar = C_6H_5, 4-ClC_6H_4, 4-$CH_3C_6H_4$, 2-ClC_6H_4, 2-$CH_3OC_6H_4$, 2-$CH_3C_6H_4$

Scheme 6

A tandem Michael reaction-aldol was originally reported in 1912 by Dieckmann *et al.*[64] The highly useful, C-C bond forming Michael reaction is frequently catalyzed by alkali metal hydroxides or alkoxides, but it has been pointed out that better results are obtained with weaker bases such as piperidine, tertiary amines, or quaternary ammonium hydroxides.[65] Improved yields have been reported for certain mild catalysts such as potassium fluoride in both protic and aprotic solvents, and potassium carbonate in acetone. Carcia-Raso *et al.* reported that partially dehydrated commercial barium hydroxide efficiently catalyzes Michael reactions of

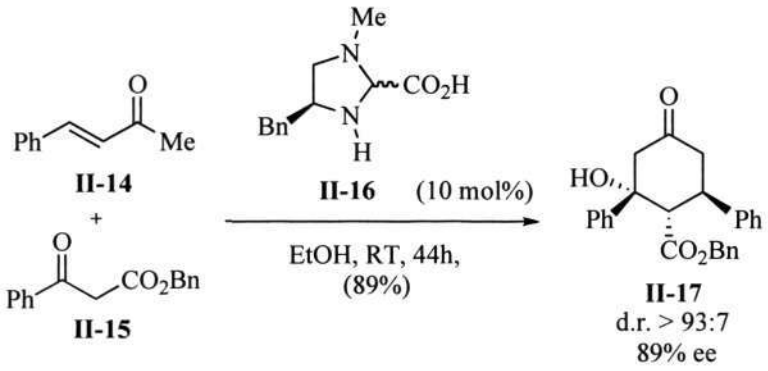
chalcones **II-10** with an active methylene compound, ethyl acetoacetate, as shown in Scheme 7.[65]



Scheme 7

The procedure was performed by stirring the chalcones **II-10** in ethanol containing barium hydroxide by varying the amount of catalyst within the range of 3-10 mol% at room temperature to give Michael adducts **II-11** or cyclized adducts **II-12** in 85-95%, or at reflux to give dehydrated product **II-13** in 55-90% yield. Compounds **II-11** and **II-12** were easily converted to cyclohexenones **II-13** on heating an ethanolic solution in the presence of the catalyst.

The catalytic asymmetric formation of cyclohexenone building blocks with multiple chiral centers represents an increasingly important field in organic chemistry owing to the usefulness of these products in further synthetic transformations. Among the various asymmetric C-C bond forming reactions, the direct catalytic tandem and cycloaddition reactions are of particular interest as multiple stereogenic centers can be formed in a single reaction. Recently Jørgensen *et al*. reported a Robinson annulation involving electrophilic activation using imidazolidine-2-carboxylic acid **II-16** as a catalyst (Scheme 8).[66]



Scheme 8

As shown in Scheme 8, with suitable substrates (**II-14** and **II-15**) an intramolecular aldol reaction mediated by the catalyst **II-16** (with nucleophilic activation) may follow the Michael addition step. This domino reaction sequence afforded cyclohexanones **II-17** with three contiguous stereogenic centers with high enantio- and diastereoselectivities. The transformation can also be applied to β-croyl and β-heteroaroyl β-ketoester, which can be converted readily upon treatment with α,β-unsaturated ketones into valuable building blocks for the synthesis of complex molecules.

Results and Discussion

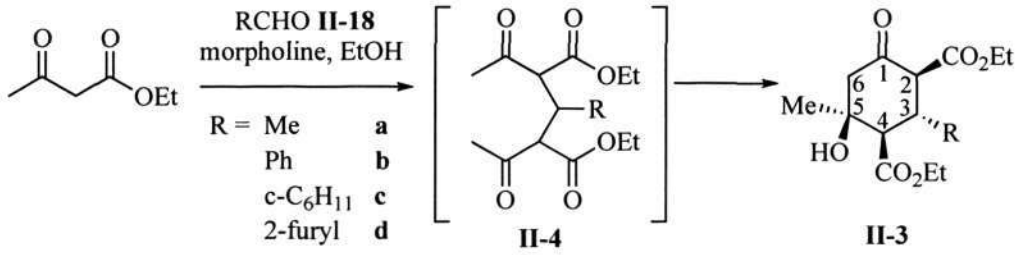
The Robinson annulation, a tandem or domino reaction devised before those names were coined, consists of a sequence of a Michael addition, an intramolecular aldol reaction and an elimination. Although the Robinson annulation has been used for over half a century for the construction of cyclohexanes, it is often considered to be a reaction of limited use, as under relatively strongly basic conditions, various technical problems may arise.[67] The other premier method for the formation of six-membered rings, the Diels-Alder reaction, is often regarded as a superior method as it may, in

principle, result in the formation of four chiral centres with control of relative stereochemistry. We were interested to use the Robinson annulation reaction in order to synthesize a building block for the total synthesis of briarane natural products as shown in Scheme 4.

Preparation of cyclohexanone di-esters II-3

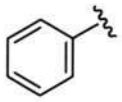
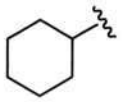
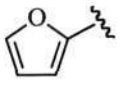
2:1 condensation

We were interested in the construction of highly substituted cyclohexenones. Therefore, we re-investigated the morpholine catalysed 2:1 condensation of ethyl acetoacetate with acetaldehyde **II-18a** (R = Me). The reaction was carried out by employing a sub-stoichiometry amount of morpholine (30 mol%) in ethanol at 0 °C for 3 days. This reaction, originally reported as a two step process in 1944,[61] has been proposed to proceed via bis-ester (**II-4**), a Tandem Knoevenagel-Michael product, followed by acid catalysed cyclisation and dehydration. Variations have also been reported, leading directly to Robinson products with dehydration. Thus, it contains within it a Robinson annulation. Interestingly, in our hands, it was found that the product of the first step was not the bis-ester **II-4** as previously reported.[61] We found that there were no acyl-methyl peaks at 2.3 ppm, however, there were two protons at 2.59 ppm (H-6) and 2.33 ppm (H-6'), with geminal coupling, J=14.3 Hz. The conclusion is that the first step product is the cyclised product from a tandem Knoevenagel-Michael-aldol sequence, cyclohexenone **II-3a**, which was obtained as a single diastereoisomer (Scheme 9). Moreover, the relative stereochemistry of cyclohexenone **II-3a** was determined by single crystal X-ray crystallography (Figure 29). We further investigated the preparation of a series of cyclohexenones **II-3a-d** as summarized in Table 1.



Scheme 9

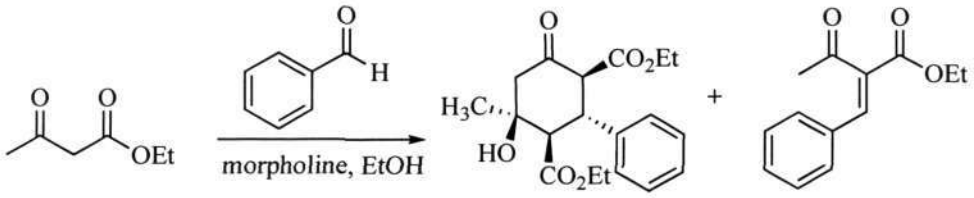
Table 1 2+1 condensation reactions

Entry	Products	R	% Yield[a]
1	**II-3a**	CH_3	57
2	**II-3b**		56[b]
3	**II-3c**		50
4	**II-3d**		48[c]

[a] Isolated yield based on the corresponding aldehydes.
[b] plus 11% of Knoevenagel condensation product.
[c] plus 5% of a diastereoisomer.

In the 2:1 condensation, it may be presumed that an initial Knoevenagel condensation generates a Michael acceptor, by condensation of aromatic aldehyde with ethyl acetoacetate. It is proved that in the case (R = Ph), a small amount of this

compound could be isolated as shown in Scheme 10. It is in agreement with that reported by Perumal *et al.*[63]



II-3b, 56% **II-19**, 11%

Scheme 10

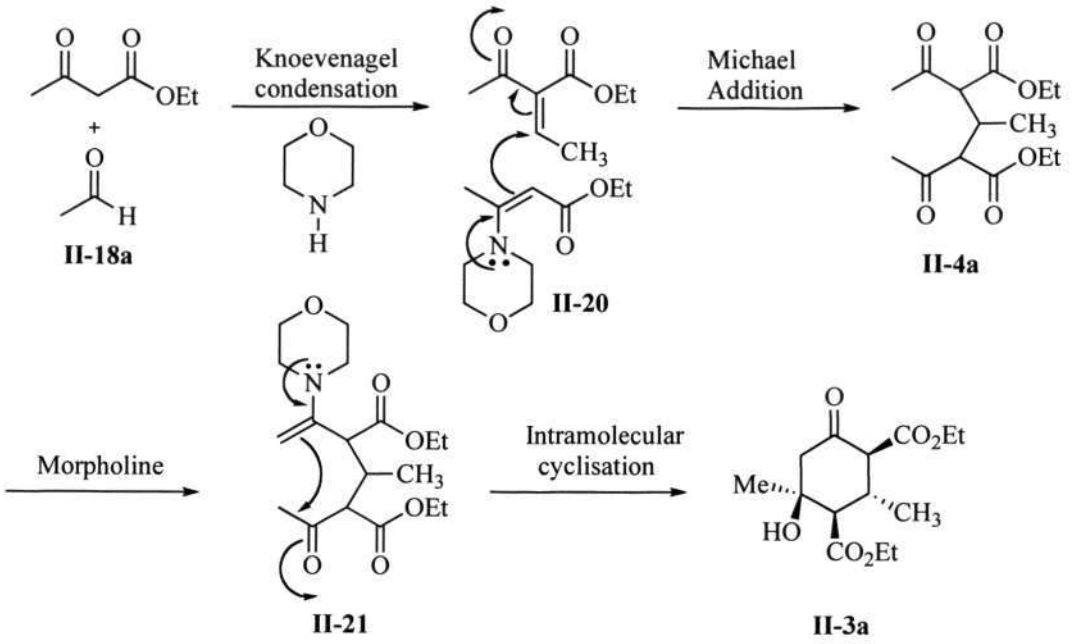
The relative stereochemistry at the 2, 3 and 4–positions could be assigned by the coupling constants ($J_{ax\text{-}ax} \cong 11.5 - 12.2$ Hz) between H-2 and H-3, H-3 and H-4. These appeared in the ^{1}H NMR spectra as a doublets at $\delta = 3.03 - 3.94$ ppm and $\delta = 2.54 - 3.13$ ppm, respectively, as summarized in Table 2. In the case of the substituent being cyclohexyl (**II-3c**), the signals are double doublets (J = 4.8, 1.5 Hz) between H–3 and H–4 that appeared in the ^{1}H NMR spectra as a double of doublets at $\delta = 2.92$ ppm.

Table 2 Some ^{1}H NMR data in $CDCl_3$ of cyclohexenone **II-3a-d**.

Compounds	H-2		H-4	
	δ (ppm)	$J_{2,3}$ (Hz)	δ (ppm)	$J_{3,4}$ (Hz)
II-3a	3.03	12.0	2.54	11.5
II-3b	3.70	12.6	3.05	12.1
II-3c	3.94	12.4	2.92	4.8, 1.5[a]
II-3d	3.72	12.4	3.13	12.2

[a] The ^{1}H NMR spectra appears as a double of doublets

The proposed mechanism for the formation of **II-3a**, in the presence of morpholine, via intermediate **II-4a** is shown in Scheme 11. This reaction can be envisaged to occur via an initial Knoevenagel condensation of the acetaldehyde **II-18a** with ethyl acetoacetate, affording **II-20**, followed by Michael addition of ethyl acetoacetate enamine furnishing symmetrical intermediate **II-4a**. In the presence of morpholine, bis-ester **II-4a** presumably forms monoenamine **II-21**, which undergoes an intramolecular aldol reaction resulting in the formation of the six-membered ring **II-3a**. In addition, when 4-methylmorpholine, a tertiary amine, was employed, no reaction was observed. This evidence proved that the reaction occurs via enamine intermediates.



Scheme 11

Thus, this reaction provides a very mild and general method for the formation of cyclohexanones **II-3** with the control of the relative stereochemistry of four chiral centres. The formation of the isolated diastereoisomers is consistent with the final aldol reaction proceeding via a chair-like conformation as shown in Figure 28, with all major substituents equatorial.

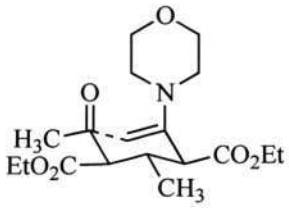
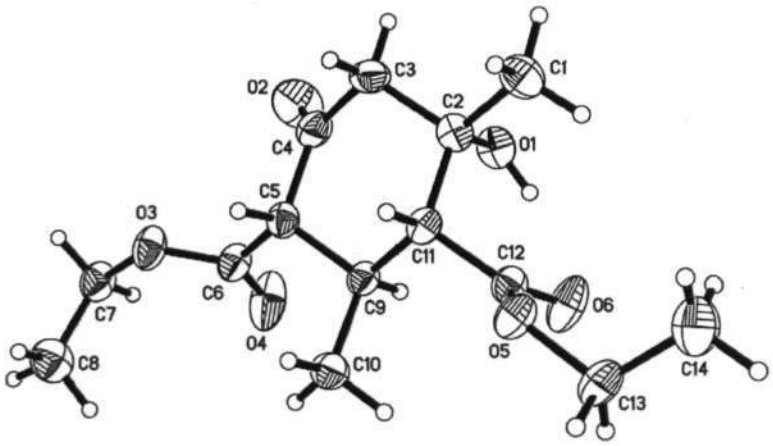


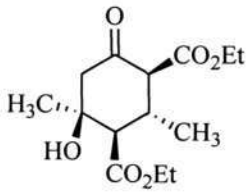
Figure 28

This reaction is very general. Although originally only used with aliphatic aldehydes, a range of aldehydes participate smoothly (Table 1). Of the cases examined, only the use of 2-furaldehyde led to a mixture of stereoisomers. The minor

isomer **II-3d** was found to be epimeric at C-4 in 5% yield. In all other cases, only a single diastereoisomer could be isolated.

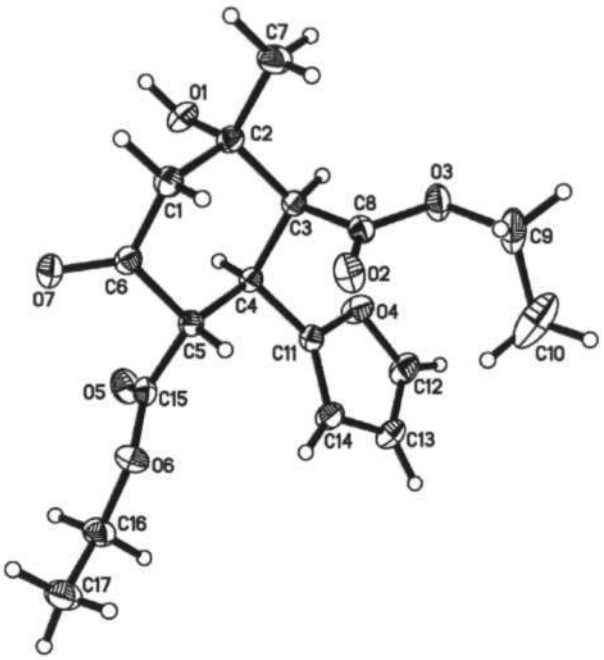
The relative stereochemistry of the cyclohexanone di-ester **II-3a** and **II-3d** were elucidated by NMR spectroscopic data, moreover, further confirmed by single crystal X-ray crystallography as shown in Figure 29 and Figure 30, respectively.

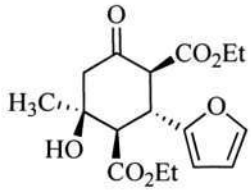




II-3a

Figure 29 X-ray ORTEP diagram of **II-3a**.



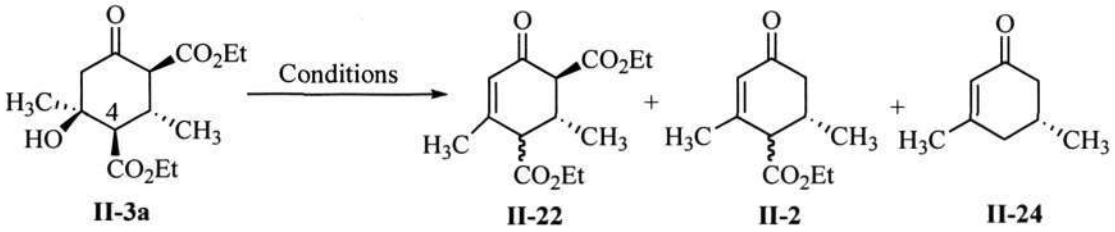


II-3d

Figure 30 X-ray ORTEP diagram of **II-3d**.

Having succeeded in preparing the cyclohexenone **II-3a**, therefore, we tried to use this compound to synthesize the target building block **II-2**. As shown in Scheme 4, cyclohexenone **II-2** might be used as a starting material to synthesize the briarane natural products. However, dehydration and decarboxylation of compound **II-3a** were needed for the preparation of compound **II-2** as shown in Table 3.

Table 3 Optimization of the condition for the preparation of cyclohexenone **II-2**.



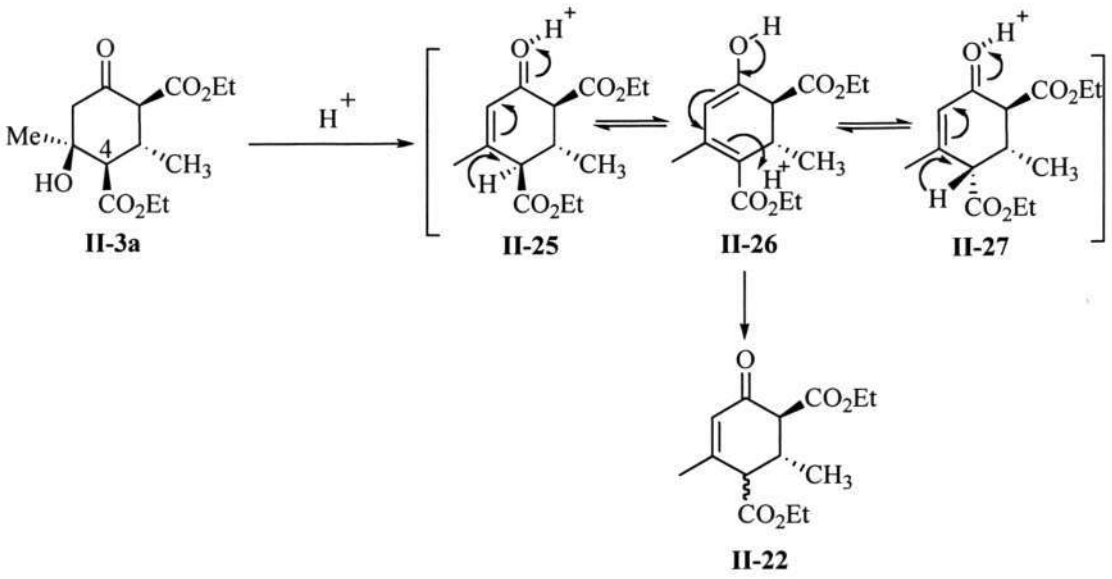
Entry	Conditions	Results
1	AcOH, H_2SO_4 Δ, 1 h	**II-2** (60%)[a] and **II-24** (10%)[a]
2	20 mol% *p*-TsOH, dioxane RT, 20 h	**II-2** (44%)[a] and **II-24** (44%)[a]
3	morpholine, CH_2Cl_2 50 °C, 20 h	**II-2** (84%)[a]
4	$SOCl_2$, pyridine, CH_2Cl_2 0 °C, 20 h	**II-22** (51%)[a]

[a] isolated yield

As shown in Table 3, using a reported procedure[61-66] for dehydro-decarboxylation, the cyclohexanone **II-3a** was treated with acetic acid and sulfuric acid at reflux for 1 h (entry 1, Table 3) to provide the decarboxylated product **II-2** in 60% yield as an inseparable mixture of two diasteroisomers in a ratio of 86:14. The major isomer was determined to be the *trans* isomer by examination of coupling constants. The over decarboxylated product **II-24** was also obtained in 10% yield. Then, we tried to use milder conditions, *p*-toluenesulfonic acid (20 mol%) in dioxane

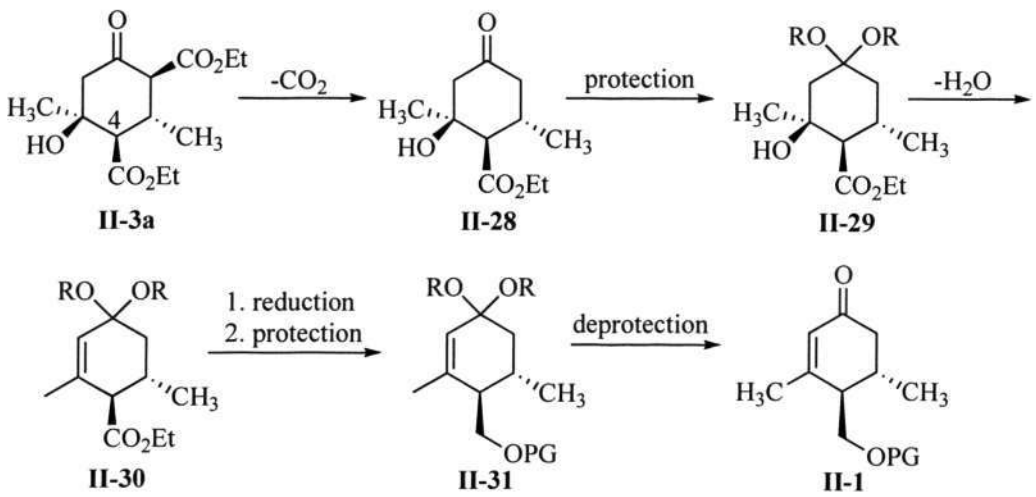
at room temperature for 20 h (entry 2, Table 3) but the overdecarboxylated cyclohexenone **II-24** was still obtained in 44% yield as well as a mixture of diastereoisomers of **II-2** in 44% yield. When morpholine was used for decarboxylation (entry 3, Table 3), only the decarboxylated product **II-2** was obtained in 84% yield, however, the mixture of diastereoisomers was still obtained. In order to prevent the isomerization, we tried to carry on the reaction at 0 °C using $SOCl_2$ and pyridine in CH_2Cl_2 (entry 4, Table 3), unfortunately, the dehydrated product **II-22** was obtained as a mixture of diastereoisomers in 51% yield. In all cases, as long as the dehydration occurred, partial epimerization at C-4 was observed. Therefore by using these procedures, the desired product cyclohexenone **II-2** could not be obtained as a single diasteroisomer.

The proposed mechanism for isomerisation of cyclohexenone **II-22**, is shown in Scheme 12. After dehydration of cyclohexanone **II-3a** gave the cyclohexenone **II-25**. The proton at C-4 of **II-25** is an acidic proton which **II-25–II-27** are in equilibrium under acidic conditions to give a mixture of diastereoisomers **II-22**.



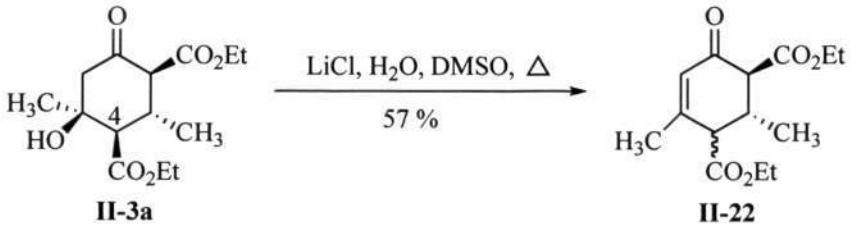
Scheme 12

However, the isomerization at C-4 after dehydration might be prevented by protection of the carbonyl group in the intermediate **II-3a** as proposed in Scheme 13. Therefore, decarboxylation of **II-3a** under Krapcho conditions,[68] could give the mono-decarboxylated product **II-28**. Carbonyl protection and dehydration of the corresponding **II-29** would provide the dehydrated product **II-30**. Subsequent protection of the alcohol would give the intermediate **II-31**. H-4 would no longer be an acidic proton, thus no isomerization would be obtained. Finally, deprotection of the carbonyl group would give the desired building block **II-1**.



Scheme 13

Krapcho decarboxylation was carried out employing lithium chloride in wet DMSO at 100 °C. Surprisingly, dehydration was facile under these conditions to give the dehydrated product **II-22** in 57% yield as a mixture of two diatereoisomers in a ratio of 36:64 as shown in Scheme 14.



II-3a **II-22**

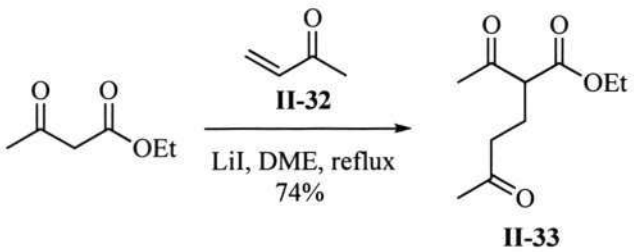
Scheme 14

Due to our inability to control the isomerization, the desired cyclohexenone **II-2** could not be obtained as a single diastereoisomer. To avoiding the unnecessary steps from the protection and deprotection, we move to the alternative pathway employing Robinson annulation in order to synthesize the desired cyclohexenone **II-2**.

Preparation of cyclohexanone mono-esters II-38

Robinson annulation

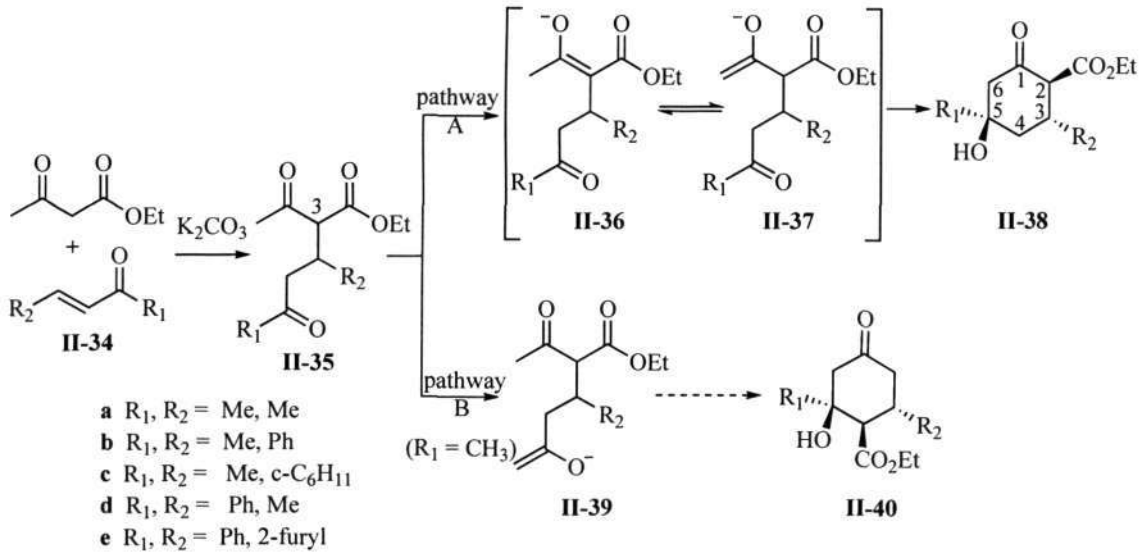
The Michael reaction is widely employed in organic synthesis for effecting C-C bond formation.[113] In particular, many procedures, based on the conjugate addition of β-dicarbonyl compounds under neutral conditions, have been proposed.[69b] Scettri *et al*. reported that lithium iodide is a very efficient catalyst for the conjugate addition of β-ketoesters[70] as shown in Scheme 15. Ethyl acetoacetate reacted with methyl vinyl ketone **II-32** as a Michael acceptor in the presence of catalytic amount of lithium iodide (1%) in dimethoxyethane at reflux, the formation of adduct **II-33** took place in good yield.



II-33

Scheme 15

We were encouraged by the result with the conjugate addition of ethyl acetoacetate to methyl vinyl ketone **II-32**. It is, therefore, a simple extension to combine this with an intramolecular aldol reaction (Scheme 16). In this system, there are then two possible products **II-38** and **II-40** according to the direction of the aldol reaction that terminates the Robinson sequence. Thus, if R^1 = Me, either of two products may be formed, corresponding to pathways A and B.[60] In pathway B, using pent-3-en-2-one (R_1 = R_2 = Me) would give the intermediate **II-40a** which might be used as a starting material to synthesize the desired cyclohexenone **II-2**.

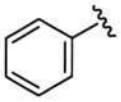
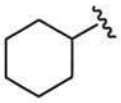
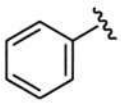
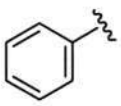


Scheme 16 Robinson annulations

In practice, treatment of ethyl acetoacetate with pent-3-en-2-one[71] **II-34a** in the presence of a catalytic amount of potassium carbonate (20 mol%) at 20 °C for 20 h gave a single product, cyclohexenone **II-38a**. NMR spectroscopic data and single crystal X-ray crystallography (Figure 31) confirmed that this was compound **II-38a** (pathway A). This corresponds to the final aldol of the sequence involving the ketone derived from the β-ketoester **II-36** and **II-37** as the equilibrium enolate component. Deprotonation of C-3, the most acidic proton, would give an intermediate **II-36** which

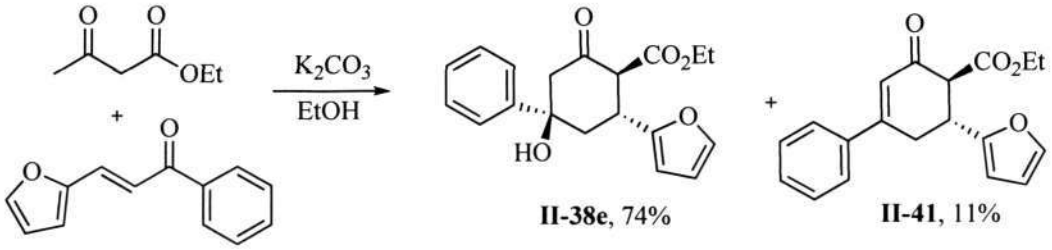
would lead to an unfavourable 4-membered ring adduct. However, the cyclization of the enolate **II-37** is more favored to give the 6-membered ring cyclohexenone **II-38**. From the result, the intermediate **II-40** could not be obtained by this method. However, the Robinson annulation using β-ketoester **II-34a** under very mild conditions is a very simple method to form highly substituted cyclohexenone **II-38a** in one step. Therefore, we further investigated a range of enones to give the products cleanly as single diastereoisomers. The results for the preparation of cyclohexenone mono-ester **II-38a-e** are summarized in Table 4.

Table 4 Robinson annulations

Entry	Products	R^1	R^2	% Yield[a]
1	**II-38a**	CH_3	CH_3	83
2	**II-38b**	CH_3		84
3	**II-38c**	CH_3		86
4	**II-38d**		CH_3	64
5	**II-38e**			74[b]

[a] Isolated yield based on the corresponding ketones.
[b] plus 11% of a dehydrated material **II-41**

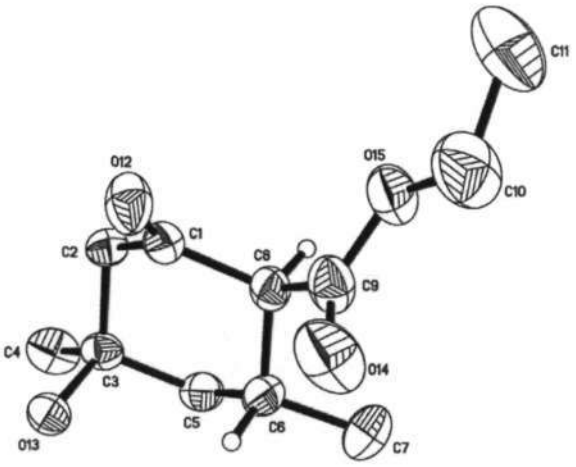
The only exception was **II-38e** with a furyl substituent, using the same reaction conditions as **II-38a**, gave the anticipated cyclohexanone **II-38e** in 74% yield accompanied by a small amount of dehydrated material **II-41** in 11% yield (Scheme 17).

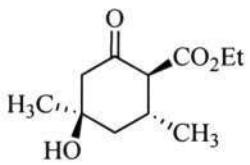


II-38e, 74% **II-41**, 11%

Scheme 17

The relative stereochemistry of the cyclohexenone mono-ester **II-38a** was confirmed by single crystal X-ray crystallography as shown in Figure 31.





II-38a

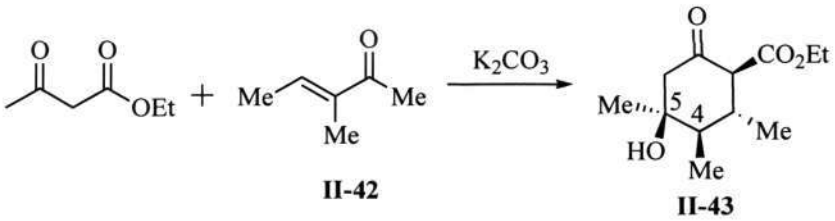
Figure 31 X-ray ORTEP diagram of **II-38a**.

The relative stereochemistry at 2,3-position of compound **II-38** could be assigned by the coupling constants ($J_{axial\text{-}axial} \cong 12.0 - 12.6$ Hz) between H-2 and H-3 that appeared in the ^{1}H NMR spectra as a doublets at $\delta = 2.97 - 3.72$ ppm as summarized in Table 5.

Table 5 Some ^{1}H NMR data in $CDCl_3$ of cyclohexenone **II-38a-e**.

Compounds	H-2	
	δ (ppm)	$J_{2,3}$ (Hz)
II-38a	2.97	12.0
II-38b	3.65	12.6
II-38c	3.26	12.6
II-38d	3.12	12.0
II-38e	3.72	12.3

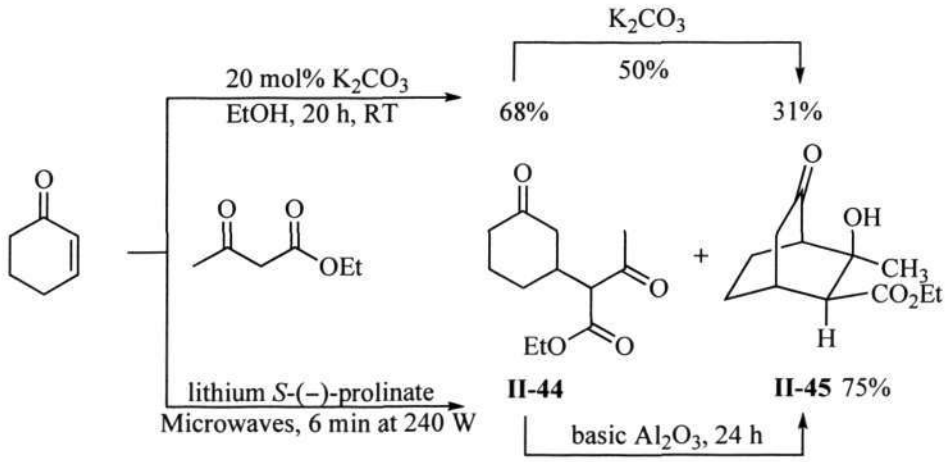
When enone (**II-42**),[72] with an α-substituent, was investigated (Scheme 18), a single isomer of cyclohexanone **II-43** was obtained, but in very low yield (5%) due to the steric interaction around the double bond.



II-42 **II-43**

Scheme 18

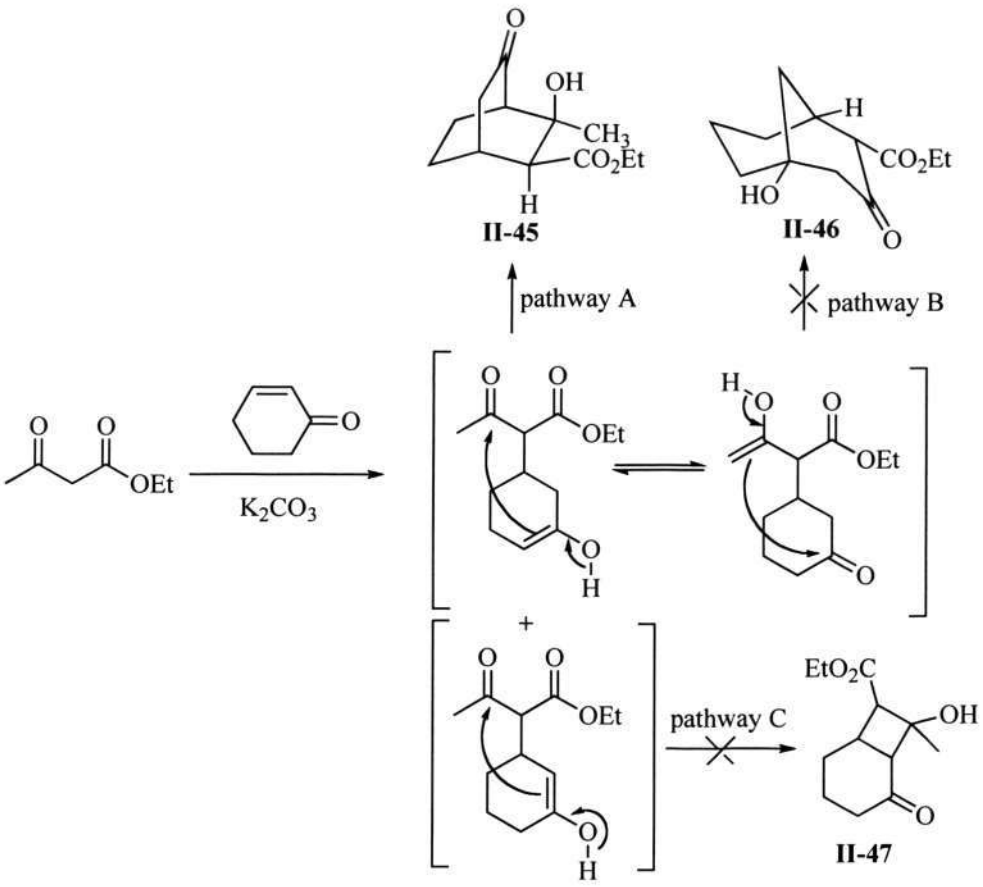
Finally, cyclohexenone was employed as the enone substrate (Scheme 19). Under the reaction conditions, the Robinson product **II-45** was obtained in 31% yield, the major product being the simple Michael adduct **II-44** in 68% yield which could be converted on to the Robinson product **II-45** in 50% yield by further exposure to ethanolic potassium carbonate at room temperature for 7 days. Again the structure of the Robinson product was determined by X-ray crystallography (Figure 32). It is in agreement with that reported by Ranu *et al.*,[73] who employed microwave irradiation of a mixture of cyclohexenone and ethyl acetoacetate adsorbed on the surface of solid lithium *S*-(−)-prolinate followed by basic alumina.



Scheme 19

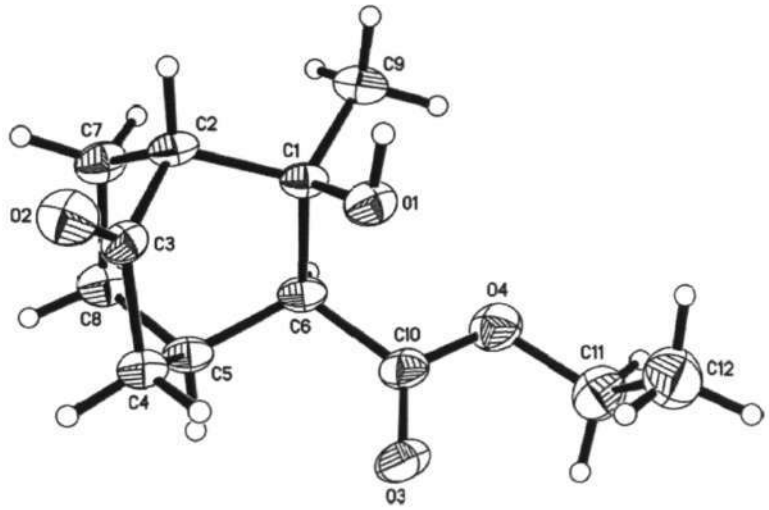
The proposed mechanism in the case of using cyclohexenone as a Michael acceptor in the Robinson annulation reaction is shown in Scheme 20. In this system, there are then three possible products according to the direction of the aldol reaction that terminates the Robinson sequence. Thus, either of three products (**II-45, II-46** and **II-47**) may be formed, corresponding to pathways A, B and C. The result shown that

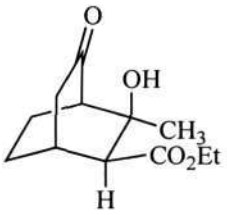
the [2.2.2] bicyclo octane carboxylate **II-45** was obtained (pathway A) as a single diastereoisomer.



Scheme 20

The relative stereochemistry of the oxobicyclo[2.2.2]octane carboxylate **II-45** was confirmed by single crystal X-ray crystallography as shown in Figure 32.





II-45

Figure 32 X-ray ORTEP diagram of **II-45**.

CONCLUSION

We have succeeded in the preparation of highly substituted cyclohexenones by the Robinson annulation reaction employing β-ketoesters under very mild conditions using very simple reagents and starting materials. The tandem reaction proceeds in good yield with high selectivity using morpholine or potassium carbonate as the catalyst. However, the desired cyclohexenone ester **II-2** could not be obtained by these methods. The Tandem-Knoevenagel-Michael (2+1) condensation product could not be decarboxylated to give the desired cyclohexenone ester **II-2** as a single diastereoisomer. Moreover, the Robinson annulations gave the undesired regio-isomer.

CHAPER III

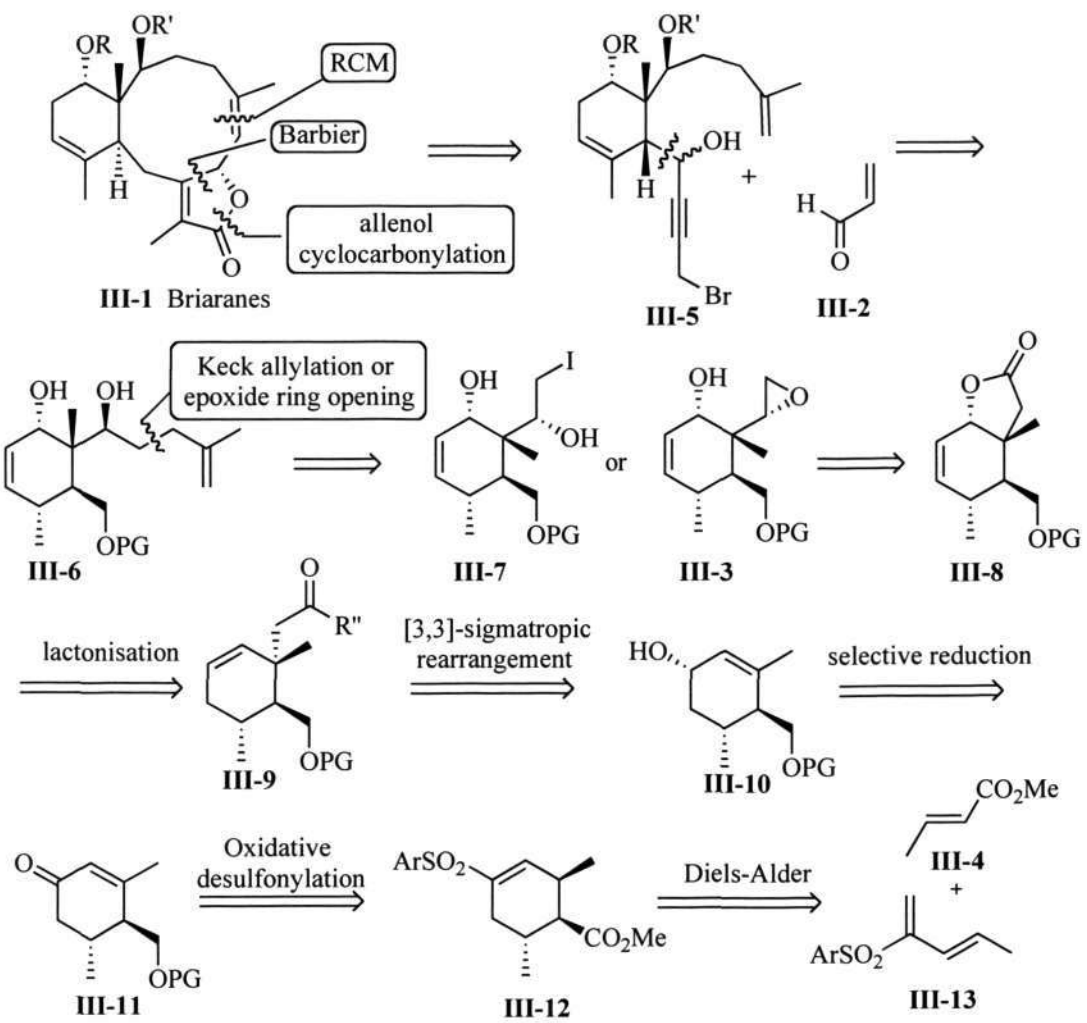
SYNTHESIS OF THE BRIARANE NORTHERN HEMISPHERE

Retrosynthesis of the Briaranes

Our objective was to develop a general route to the briarane skeleton, rather than to target a particular briarane natural products. The revised retrosynthetic analysis of the briaranes is delineated in Scheme 21. We proposed to generate the structure of the briaranes using a modular approach that should be sufficiently flexible to allow for the synthesis of a variety of these natural products.

We envisaged that the macrocyclic 10-membered ring would be achieved by ring closing metathesis. Butenolide might be constructed through an allenol cyclocarbonylation[75] and the intramolecular propargylic Barbier reaction developed by our laboratories,[76] It was intended to generate a cyclohexenol containing the upper chain **III-6** which could be coupled with the lithium derivative of the THP ether of a propargylic alcohol derivative. Cyclohexenol **III-6** was selected as a key building block. It would be obtained through the Keck radical allylation of iodo **III-7** or the epoxide ring opening of epoxide **III-3** for the connecting of the upper chain, which, in turn, could be synthesized from **III-8** by selective hydroxylation and chemoselective iodination. Continuing with the retrosynthesis, lactone **III-8** would be obtained by lactonisation of compound **III-9**. The construction of challenging quaternary carbon of compound **III-9** would be by [3,3]-sigmatropic rearrangement, as a key step, of the corresponding alcohol

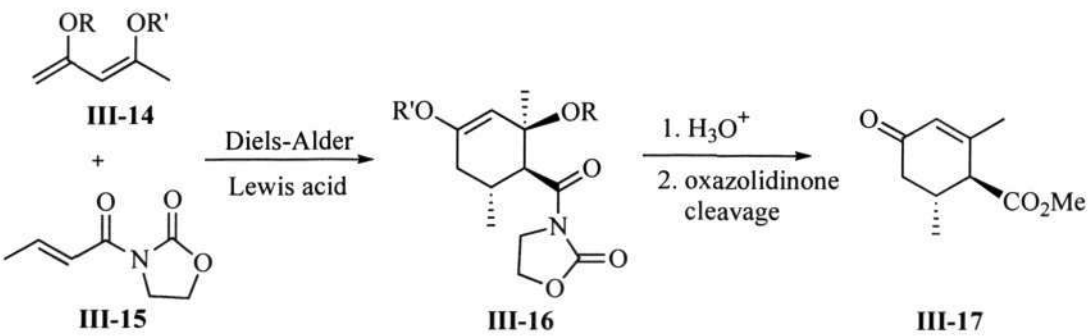
III-10. Selective reduction of **III-11** would give the desired alcohol **III-10**, the stereochemistry of the hydroxyl group would control the stereochemistry of the quaternary carbon in rearrangement product **III-9**. The desulfonylation product **III-11** was predicted to derive from the Diels-Alder adduct **III-12**, which was itself anticipated to arise from the sulfonyl diene **III-13** via an unusual Diels-Alder reaction, as employed by Bäckvall.[77]



Scheme 21

The preparation of cyclohexene ring; Diels-Alder reaction

A dominating feature of the cyclohexane portion of all of the briaranes is the quaternary centre bearing a methyl group. While a Diels-Alder reaction would be a logical choice for the formation of this ring, the steric congestion resulting from this center must be accomodated. As in Scheme 22, we propose to form the 6 membered ring by the Diels-Alder reaction between the electron rich Danishefsky's diene **III-14** and crotonate derivative **III-15**.[78] The difference in electronic character of the partners and the use of Lewis acid catalysis could encourage a facile reaction, despite the crowding, giving Diels-Alder product **III-16**. In addition, the use of crotonates with chiral auxiliaries or the use of asymmetric catalysts, such as lanthanide-pybox complexes,[79] would be considered to give facile access to enantiomerically enriched material. Thus, acidic treatment of the Diels-Alder adduct **III-16** could lead to the enone **III-17**.



III-14a R = R' = TMS
III-14b R = Me, R' = TMS
III-14c R = TMS, R' = Me
III-14d R = Me, R' = TBS

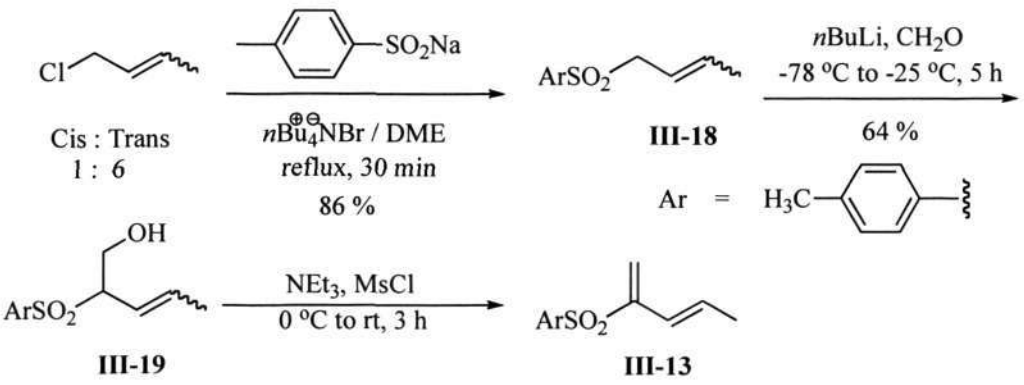
Lewis acid : $Yb(OTf)_3$, $ZnCl_2$, $AlCl_3$, $Ti(OiPr)_4$

Scheme 22

In all cases, attempts to carry out the Diels-Alder reaction between the electron rich dienes **III-14** and crotonoyl oxazolidinone **III-15** under various conditions did not yield the desired cyclohexene Diels Alder product **III-16**, due to decomposition of dienes. Hoping to improve upon this situation, a number of Lewis acids (i.e., $Yb(OTf)_2$, $ZnCl_2$, $AlCl_3$ and $Ti(O^iPr)_4$ were screened in the hope that modulating the strength of the Lewis acid might suppress decomposition or increase the rate of cycloaddition, although these pursuits proved to be fruitless. Finally, we chose the sulfonyl diene for the Diels-Alder reaction because of its robustness under acidic conditions developed by Bäckvall.[77] In addition, the use of sulfinyl diene, containing a chiral sulfoxide, could lead to asymmetric induction.

Our work on the briaranes began with the preparation of sulfonyl diene **III-13**. Bäckvall reported a procedure for the synthesis of sulfonyl-1,3-dienes by a sulfonylmercuration-elimination sequence of a conjugated diene.[77] To avoiding use of toxic mercury we decided to prepare the sulfonyl diene **III-13** by modification of the known procedure[80] as shown in Scheme 23. The first step involved the preparation of allylic *p*-tolyl sulfones by the phase transfer catalysed reaction of *cis*,*trans*-crotyl chloride with sodium *p*-toluenesulfinate in refluxing DME for 30 min. It should be noted that only the *S*-alkylation product **III-18** was obtained, the reaction did not lead to any of the *O*-alkylation product. The second step was the preparation of allylic sulfonyl alcohol **III-19** by generating the lithium allylic sulfone anion, subsequently trapping the anion with formaldehyde. The alcohol **III-19** was treated with 2 equiv of triethylamine and MsCl leading to demesylation to give the desired sulfonyl diene **III-13** as a single geometrical

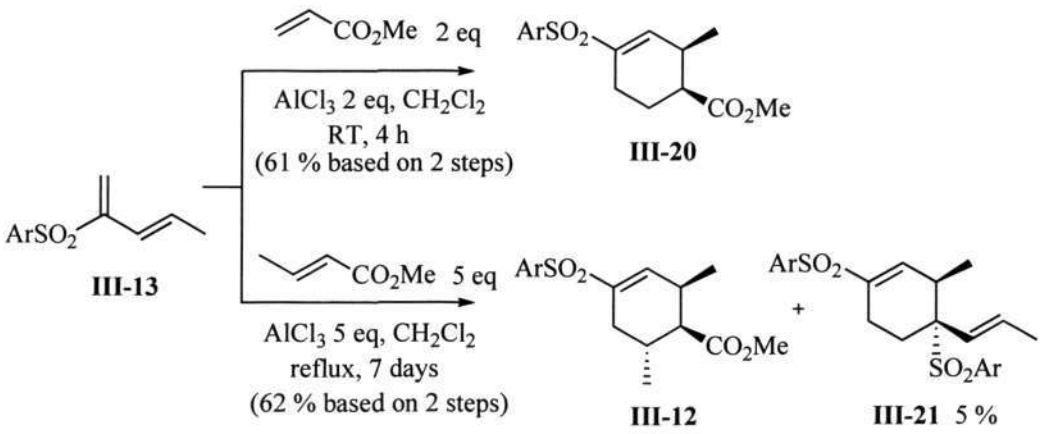
isomer, which could be assigned by the coupling constant (J_{trans} = 15.8 Hz), as the *trans* isomer.



Scheme 23

According to the reports by Hoffmann[81] and Brace,[82] dienes containing an ester or nitrile groups at C-2 normally undergo Diels-Alder dimerization on standing at room temperature. It was found that the *p*-tolylsulfonyl-1,3-diene **III-13** underwent dimerization on standing at room temperature, therefore the diene was usually not isolated before use but handled as a solution in CH_2Cl_2 and stored at –78 °C. Using the modified procedure developed by Bäckvall,[77] the reaction of sulfonyldienes **III-13** with 2 equiv of methyl acrylate in CH_2Cl_2 in the presence of 2 equiv of $AlCl_3$ at room temperature led to complete reaction in 4 h, affording exclusively the adduct **III-20** in 61% yield (Scheme 24). In the case of methyl crotonate as the dienophile, the reaction was slow using 2 equiv of $AlCl_3$ and, in this case, the Diels-Alder dimerization of the sulfonyl diene competed. The *endo*-Diels-Alder product **III-12** was obtained as a single diasteroisomer in 62%

yield accompanied by the dimerization product **III-21** in 5% yield, by employing 5 equiv of $AlCl_3$ in CH_2Cl_2 at reflux for 7 days. When titanium(IV)isopropoxide was used as the catalyst for the reaction, the reaction did not lead to the required product due to competing dimerization.



Scheme 24

The Diels-Alder products **III-20** and *endo* adduct **III-12** were obtained as single diasteroisomers by ^1H NMR; according to the predictions by frontier orbital theory, the formation of *endo*-products are preferable due to the secondary orbital overlap in the transition state. The relative stereochemistry at the 3,4-position of the Diels-Alder products **III-20** and **III-12** could be assigned by the coupling constants ($J_{ax\text{-}eq}$ = 5.5 and 6.1 Hz), which confirmed that the methyl group at C-3 is *cis* to the CO_2Me group at C-4 as shown in Figure 33.

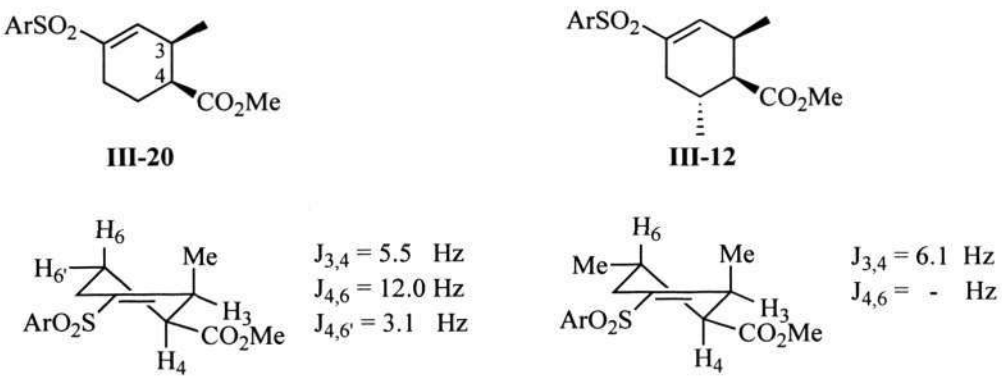


Figure 33

The structure of the Diels-Alder dimer of **III-13** is **III-21**, which was obtained as an *endo*-product, due to the secondary orbital overlap in the transition state as shown in Figure 34. The relative stereochemistry of the Diels-Alder dimerization **III-21** was further confirmed by single crystal X-ray crystallography as shown in Figure 35.

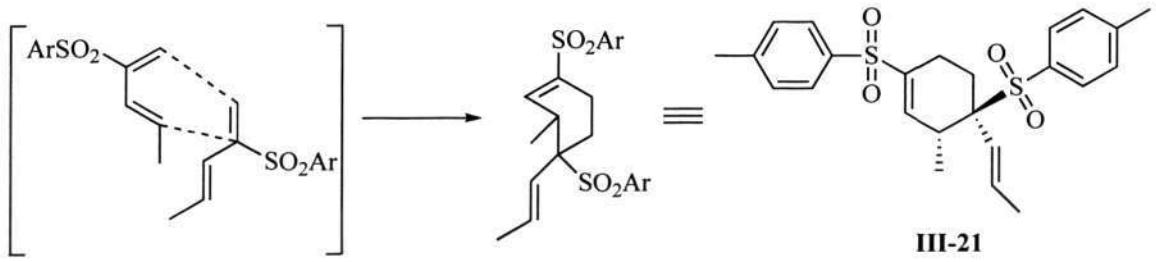
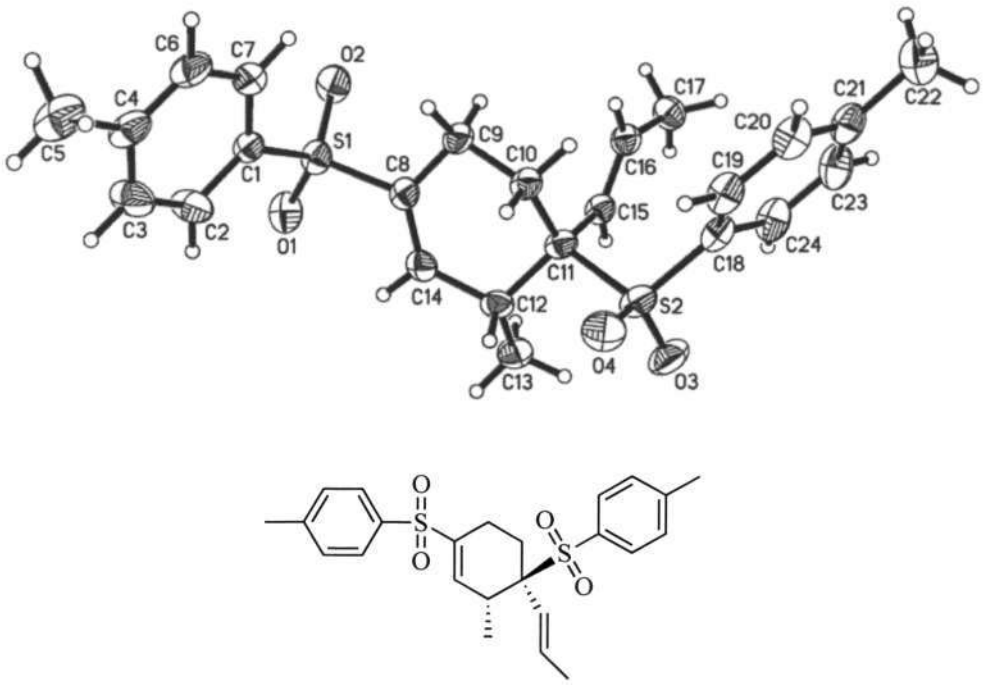


Figure 34



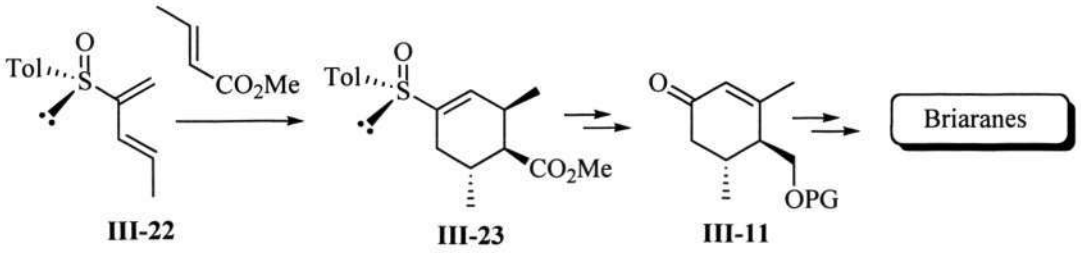
III-21

Figure 35 X-ray ORTEP diagram of Diels-Alder dimerization **III-21**

(±)-Sulfinyl dienes III-29

The preparation of (±) *p*-tolylsulfinyl-1,3-butadienes III-29

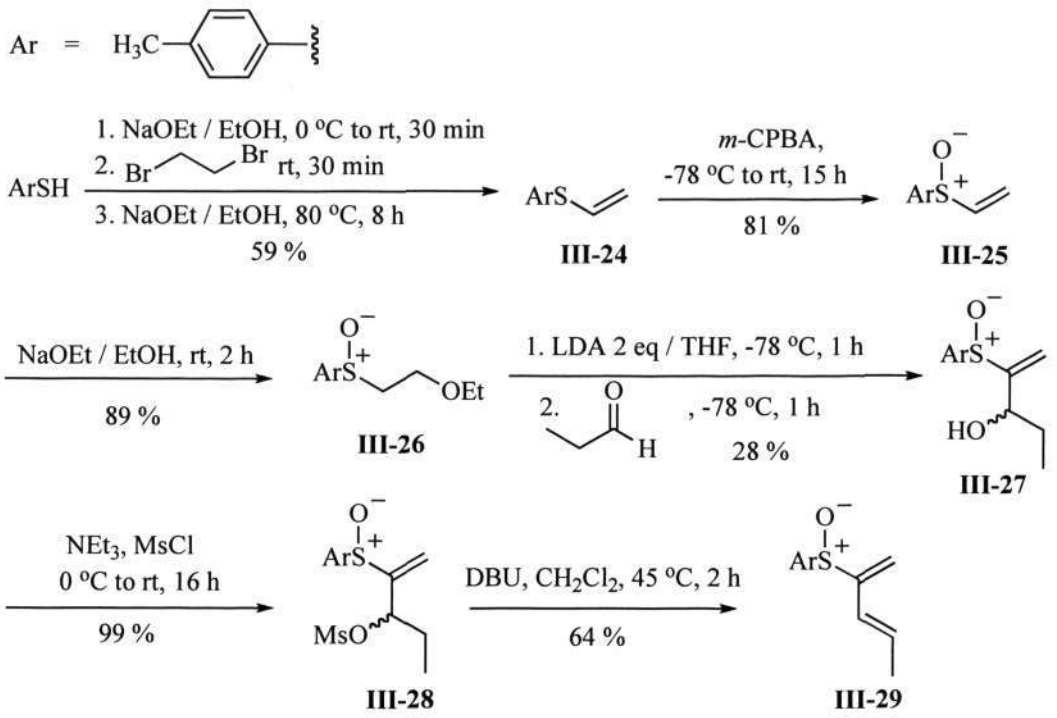
Since the sulfonyl cyclohexene **III-12** was successfully synthesized by the unusual Diels-Alder reaction, we therefore tried to employ the 1-sulfinyl-1,3-butadienes **III-22** as the starting material for syntheses of the optically pure Briaranes. As proposed in Scheme 25, the asymmetic Diels-Alder reaction between chiral sulfinyl diene **III-22** and methyl crotonate as a dienophile could afford the chiral sulfinyl product **III-23**. Desulfinylation of **III-23** would give the optically pure cyclohexenone **III-11**, which could be further used as a building block to synthesize the Briaranes in optically active form.



III-22 III-23 III-11

Scheme 25

The (±)-sulfinyldienes **III-29** could be easily synthesized from *p*-thiocresol as shown in Scheme 26. We attempted to prepare (±)-sulfinyldienes **III-29** by employing the same procedure as the preparation of sulfonyl diene **III-13**, however the reaction did not give the desired product because α-alkylation of the lithium allylic *p*-tolyl sulfinyl was not successful. However, by modifying the known procedure,[83] the vinyl sulfide **III-24** was obtained from the *p*-thiocresol sodium salt by reacting with 1,2-dibromoethane at room temperature for 30 min. In order to avoiding the high corrosive mustard intermediate, (2-bromoethyl)(*p*-tolyl)sulfide, *in situ* dehydrobromination was used, using 1.4 equiv of sodium ethoxide in ethanol at gentle reflux for 8 h. The sulfide **III-24** was oxidized to sulfoxide **III-25** by employing 1 equiv of *m*CPBA in CH_2Cl_2. The synthesis of allylic alcohol **III-27** was completed in two steps from ethoxyethyl sulfoxide **III-26** which was readily prepared in high yield from vinyl sulfoxide **III-25** by Michael addition of sodium ethoxide in excess ethanol. Thus, when the anion of **III-26**, generated by the action of 2 equiv of LDA in THF at –78 °C, reacted with 1 equiv of propionaldehyde, the corresponding allylic alcohol **III-27** was obtained directly in 28% yield along with unidentified decomposition products.[84]

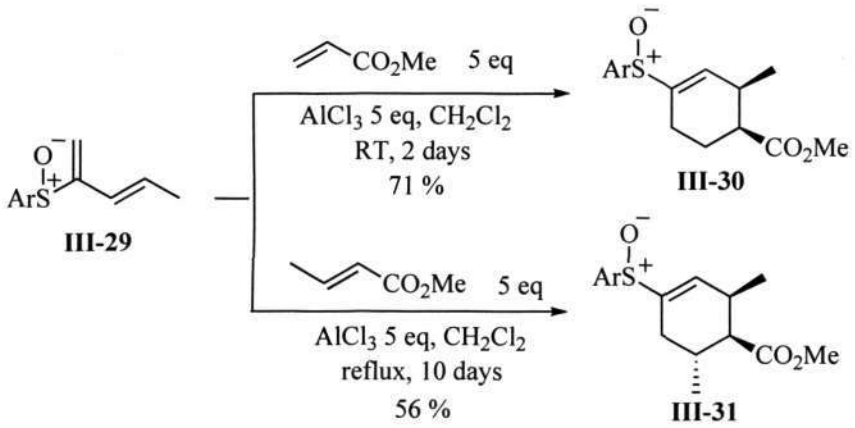


Scheme 26

Reaction of alcohol **III-27** with methanesulfonyl chloride resulted quantitatively in the stable mesylate **III-28**. Subsequent treatment of **III-28** with 2 equiv of DBU in refluxing CH_2Cl_2 for 2 h yielded the desired (±)-*p*-tolylsulfinyl-1,3-diene **III-29**.

The (±)-*p*-tolylsulfinyl-1,3-diene **III-29** proved to be very stable, unlike *p*-tolylsulfonyl-1,3-dienes **III-13**. It could be stored in pure form and purified by column chromatography without any decomposition or dimerization. The reaction of (±)-sulfinyl dienes **III-29** with 5 equiv of methyl acrylate in CH_2Cl_2 in the presence of 5 equiv of $AlCl_3$ at room temperature afforded the cycloaddition product **III-30** in 71% yield as a single diasteroisomer as shown in Scheme 27. However, using 2 equiv of $AlCl_3$ and 2 equiv of methyl acrylate required 7 days for the completion. The use of methyl crotonate as a dienophile in the presence of 5 equiv of $AlCl_3$ in CH_2Cl_2 at reflux required 10 days

for completion to give the corresponding inseparable Diels-Alder product **III-31** in 56% yield as a mixture of diastereoisomers in a ratio of 75:25. The identity of the major isomer was not determined. It can be noted that even with 7 days reaction time the reaction was not completed. Alternatively, the sulfinyl dienes **III-29** decomposed when $TiCl_4$ was used as a Lewis acid in an attempt to improve the rate of cycloaddition.



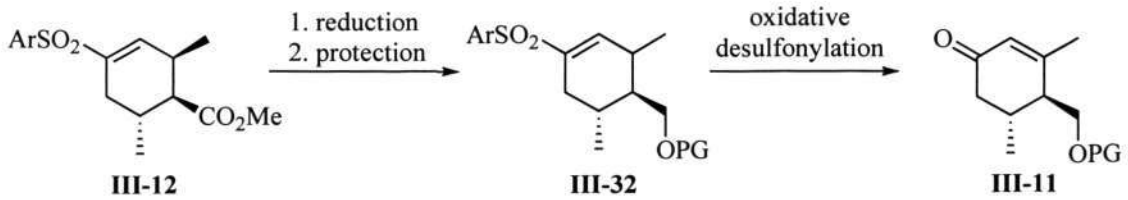
Scheme 27

The reactivity of the sulfonyl diene **III-13** and the sulfinyl diene **III-29** as dienes for the Diels-Alder reaction can be compared, Firstly, by using the same reaction conditions, it can be seen that the sulfonyl diene **III-13** is more reactive than the sufinyl diene **III-29** in the reaction with the dienophiles as shown in Scheme 24 and Scheme 27. The reaction of sulfonyl diene **III-13** with 2 equiv of methyl acrylate went to the completion in 2 h. However, the reaction of the sulfinyl diene **III-29** with 5 equiv of methyl acrylate required 2 days for completion. Secondly, the reaction between methyl crotonate as dienophile with the sulfonyl diene **III-13** gave the desired Diels-Alder product **III-12** as a single diasteroisomer as shown in Scheme 24. In contrast, the sulfinyl

diene **III-29** provided the Diels-Alder product **III-31** as a mixture of diasteroisomers in a ratio of 25:75. Therefore, the *p*-tolylsulfonyl-1,3-butadienes **III-13** would be a better choice of the dienes for the Diels-Alder reaction. However, the racemic Diels-Alder product would be obtained.

The preparation of cyclohexenone III-35

Since the tosylcyclohexenecarboxylate **III-12** was readily synthesized by the Diels-Alder reaction of sulfonyl dienes **III-13** with methyl crotonate, we therefore tried to demonstrate the synthetic utilities of the Diels-Alder product **III-12** as the starting material for syntheses of the cyclohexenone **III-11** which would be a key intermediate for the synthesis of the Briaranes. As proposed in Scheme 28, reduction of the ester group of **III-12**, followed by protection of the free primary alcohol would afford the protected adduct **III-32**. Oxidative desulfonylation of the sulfones **III-32** could provide the desired cyclohexenone **III-11**.

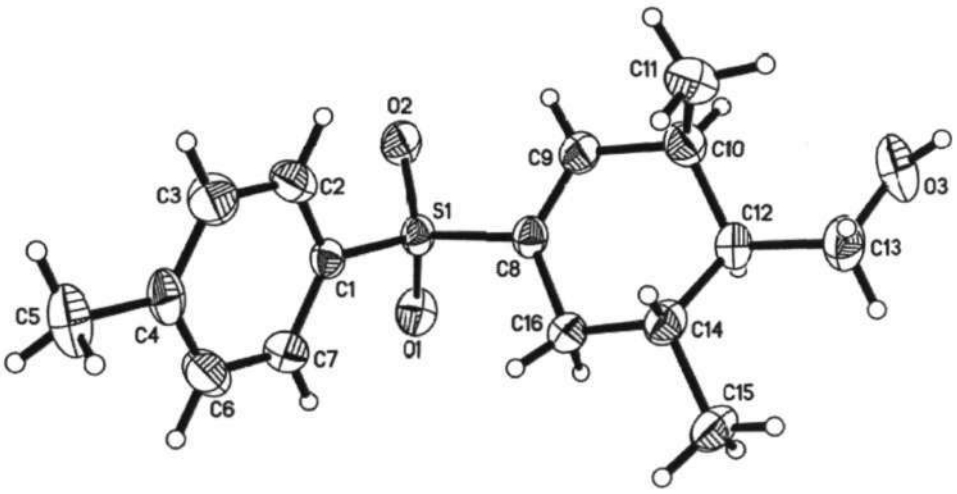


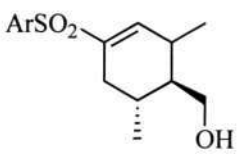
III-12 **III-32** **III-11**

Scheme 28

Having cyclohexenecarboxylate **III-12** in hand, reduction of **III-12** with 2 equiv of DIBAL-H in CH_2Cl_2 at –78 °C for 3 h gave the alcohol **III-33** in excellent yield. The

relative stereochemistry of the Diels-Alder product **III-12** was elucidated from the NMR data and further confirmed by single crystal X-ray crystallography of the reduction product **III-33** as shown in Figure 36.

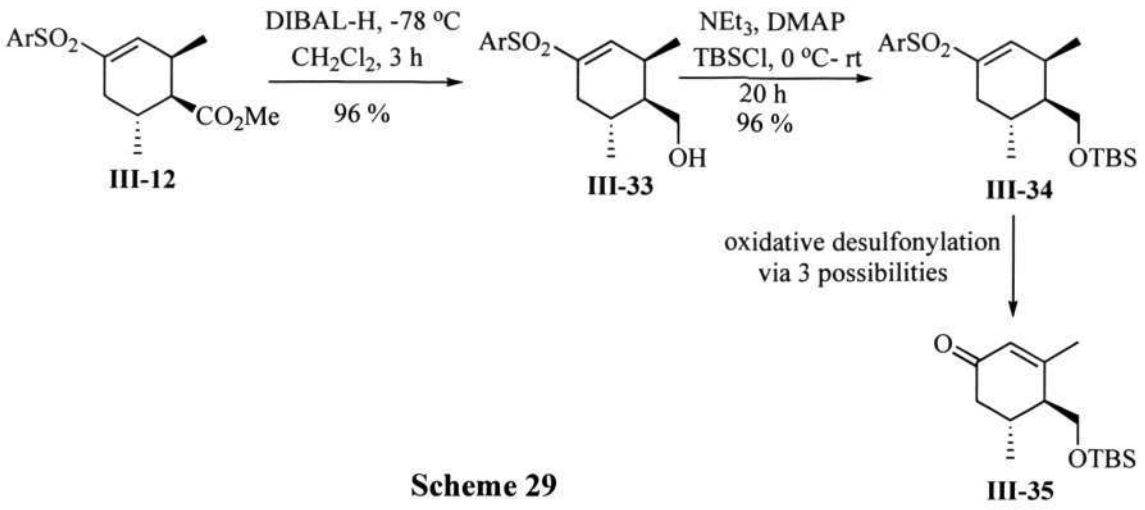




III-33

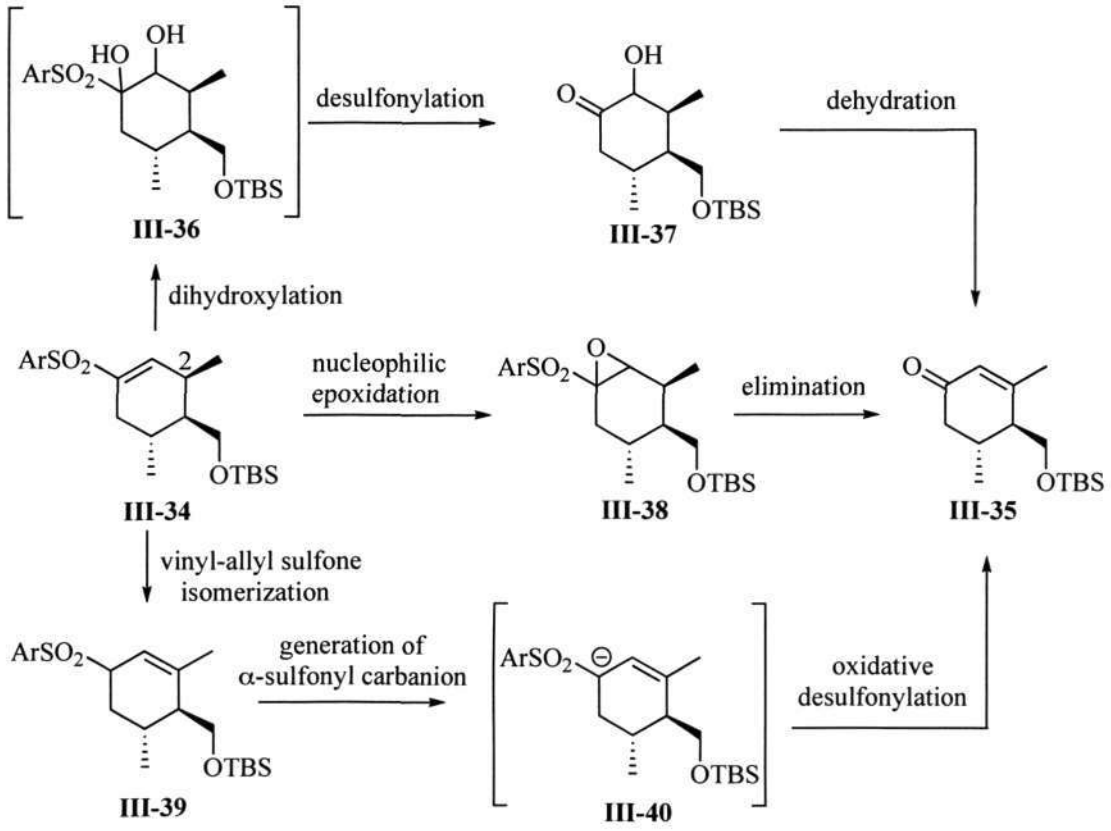
Figure 36 X-ray ORTEP diagram of the sulfonyl alcohol **III-33**

The silylation of the alcohol **III-33** could be achieved by treatment of the alcohol **III-33** with TBSCl, triethylamine as a base and DMAP as a catalyst in THF as shown in Scheme 29. Using imidazole as a base, the yield dropped to 25%. Then, it was necessary to convert the sulfone **III-34** to the cyclohexenone **III-35** by oxidative desulfonylation via 3 possibilities.



Scheme 29

The transformation of **III-34** into **III-35** is proposed in Scheme 30. First, dihydroxylation of **III-34**,[85] followed by *in situ* desulfonylation and subsequent dehydration of the hydroxy ketone adduct **III-37** to afford the desired cyclohexenone **III-35**. Secondly, epoxidation of **III-34**, followed by an elimination reaction of the resulting epoxysulfone **III-38** should give the expected product **III-35**. Thirdly, a vinyl-allyl sulfone isomerization[86] of **III-34** followed by oxidative desulfonylation[86] of the α-sulfonyl carbanion **III-40**, generated from the allyl derivative **III-39**, would provide the cyclohexenone **III-35**.

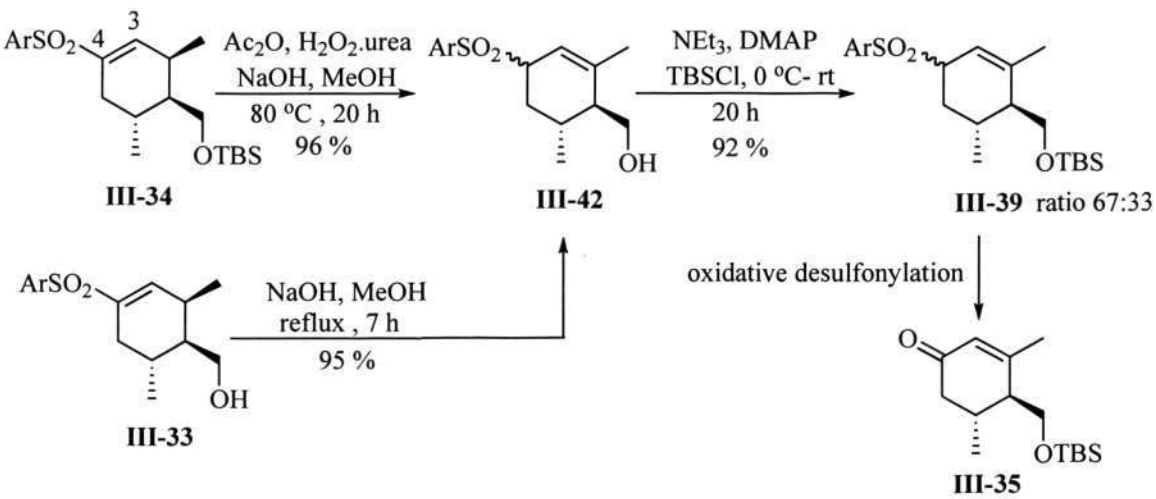


Scheme 30

We began investigating the dihydroxylation of the vinyl sulfone **III-34** by employing oxidizing agents such as $KMnO_4$,[87] $KMnO_4/CuSO_4 \cdot 5H_2O$, OsO_4/NMO,[88] and $OsO_4/K_3Fe(CN)_6$[86] under various conditions. However, all of the reaction failed, leading to recovery of starting material instead. Alternatively, isomerization using ^{n}BuLi or lithium diisopropylamide (LDA) were attempted on the vinyl sulfone **III-34**, yet this reaction did not give the isomerized product. ^{n}BuLi and LDA did not deprotonate H-2 of compound **III-34** at all. In all cases, starting material was recovered. Our dismay from these results made us move on to the last proposed approach. Epoxidation of the vinyl sulfone **III-34** by screening the oxidizing agents such as *t*BuOOLi,[89] *m*CPBA,[90] and

H_2O_2[91] did not lead to the epoxide product **III-38**. In all cases, recovery of the starting material was obtained except in the H_2O_2 case.

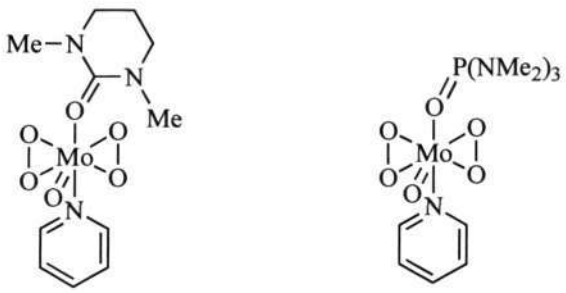
Interestingly and to our surprise, in the case of using urea-hydrogen peroxide (UHP)[91] for epoxidation of the **III-34**, we found that by employing NaOH as a base in refluxing MeOH for 20 h did not lead to the desired epoxide product **III-38** or to recovery of starting material. The recovered material showed spectral data similar to, but not identical to the starting material. We found that the chemical shift of the proton at H-3 changed from 6.95 ppm to 5.53 ppm and there was an extra proton at 3.66 ppm (H-4). It was concluded that the alcohol had isomerized with concomitant removal of the TBS group; **III-42** was obtained in 96% yield as mixture of diastereoisomers, instead of the desired epoxide product **III-38** as shown in Scheme 31. Prototropic shift in vinyl-allyl sulfone isomerizations are common as reported by Arjona *et al.*[86]



Scheme 31

At this point we speculated that the isomerization of **III-33** to **III-42** could occur without the UHP being involved. We further investigated the isomerization of hydroxyl sulfone **III-33** by treatment of compound **III-33** with 7 equiv of NaOH in MeOH at reflux for 7 h. The isomerized product **III-42** was obtained as expected in excellent yield. It may be noted that H-3 was deprotonated by NaOH but it was not deprotonated by *n*BuLi or LDA. Thus, silylation of the alcohol **III-42** by the previous method gave the mixture of epimeric sulfones **III-39** in a ratio of 67:33. The stereochemistry of the major isomer was not determined because the chiral center would be destroyed by oxidative desulfonylation[21] in the next step as described in Scheme 30. Oxidative desulfonylation of sulfones by reaction of the anion with oxidizing agent has been reported by Overman *et al.*[88,106]

Oxodiperoxymolybdenum (pyridine)-1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidione (MoO_5.Py.DMPU; MoOPD; Figure 37) is a versatile enolate anion hydroxylating reagent introduced by Anderson and Smith.[92] MoOPD swiftly hydroxylates anions from lactones, ketones, esters, aldehydes, nitriles, sulfones, amides, and isoxazolines.[93] Beyond functionalizing a wide array of substrates, MoOPD carries out oxidations with excellent regio- and stereoselectivity.[93] Even though, MoOPH (MoO_5·Py·HMPA) has been commonly used as an oxidizing agent, there is still considerable concern regarding the toxicity of the ligand hexamethylphosphoramide (HMPA). For this reason DMPU has been employed as a harmless, non-carcinogenic alternative to HMPA. Thus, MoOPD was selected as an oxidizing agent for the synthetic transformation of the sulfone **III-39** into cyclohexenone **III-35** under various conditions as listed in Table 6. MoOPD could be easily prepared from MoO_3 in 2 steps as shown in Scheme 32.[92]



MoOPD MoOPH

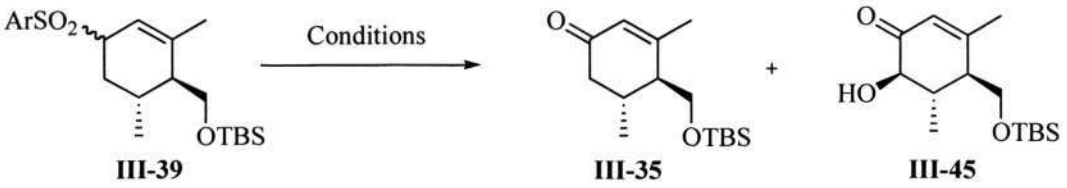
Figure 37

Oxidation of molybdenum (VI) oxide with hydrogen peroxide followed by addition of DMPU provided pale yellow crystals of the monohydrated $MoO_5 \cdot DMPU \cdot H_2O$ complex. After recrystallisation from methanol at 40 °C, dehydration under high vacuum over P_2O_5 and then treatment of the resultant MoO_5.DMPU with one equivalent of pyridine in dry THF at room temperature yielded MoOPD as yellow fine crystals in 56% overall yield. Even though MoOPD is light-sensitive,[92] MoOPD proved to be very stable and could be stored in a fridge at 4 °C for months without any decomposition. However, the complex MoO_5.DMPU is extremely explosive. Pyridine must be added to the complex within 20 h in order to prevent the explosion.

$$MoO_3 \xrightarrow[\text{2. DMPU (1 eq.), 10 °C; recrystallise (MeOH)}]{\text{1. 30\% } H_2O_2 \text{ (aq), 40 °C}} MoO_5.DMPU.H_2O \xrightarrow[\text{2. pyridine (1 eq.), THF}]{\text{1. 1 mm/Hg, } P_2O_5\text{, 20 h}} \boxed{\text{MoOPD}}$$

Scheme 32

Table 6 Optimization of the condition for the preparation of cyclohexenone **III-35**.



III-39 **III-35** **III-45**

Entry	Conditions	Results[a]
1	LDA 1.5 eq, MoOPD 3 eq –78 °C to –40 °C, 20 h	Recovery of **III-39**
2	LDA 3 eq, MoOPD 3 eq –78 °C to –40 °C, 20 h	**III-39** (80%) and **III-35** (13%)
3	LDA 6 eq, MoOPD 4 eq –78 °C, 2 h	**III-39** (11%) and **III-35** (65%)
4	LDA 6 eq, MoOPD 4 eq –78 °C, 3 h	**35** (84%)
5	LDA 6 eq, MoOPD 4 eq –78 °C, 4 h	**35** (51%) and **45** (21%)

[a] isolated yield

As shown in Table 6, attempted preparation of **III-35** by treatment of **III-39** with 1.5 equiv of LDA and 3 equiv of MoOPD was unsuccessful, resulting only in recovery of starting material (entry 1, Table 6). The expected cyclohexenone **III-35** was obtained in 13% yield along with recovery of **III-39** in 80% yield when the amount of LDA and

MoOPD were increased to 3 equiv (entry 2, Table 6). However, the mixture of epimeric sulfones **III-39** could be converted smoothly into the single adduct cyclohexenone **III-35** with the yield climbing up to 84% with 6 equiv of LDA and 4 equiv of MoOPD at –78 °C for 3 h (entry 4, Table 6). Under the same conditions, a lower yield of **III-35** (65%) and recovery of **III-39** (11%) were obtained when the reaction time was shorter (entry 3, Table 6). However, when the reaction time was increased up to 4 h, the expected cyclohexenone **III-35** was obtained in 51% yield together with the over oxidation product **III-45** in 21% yield (entry 5, Table 6).

The hydroxycyclohexenone **III-45** was obtained as a single diasteroisomer which can be rationalized by the assumption that the H_C of **III-35** was deprotonated by a second equiv of LDA to result in formation of the enolate **III-45'** which was approached by MoOPD from the less hindered side avoiding the steric interaction with the nearby methyl group to give the adduct **III-45**. The relative stereochemistry at 5,6-position of the alcohol product **III-45** could be assigned by the coupling constant ($J_{axial\text{-}axial}$ = 12.3 Hz) as shown in Figure 38.

Thus, the conditions in entry 4 (Table 6) were selected as the standard procedure for the oxidative desulfonylation of sulfone **III-39** into **III-35**.

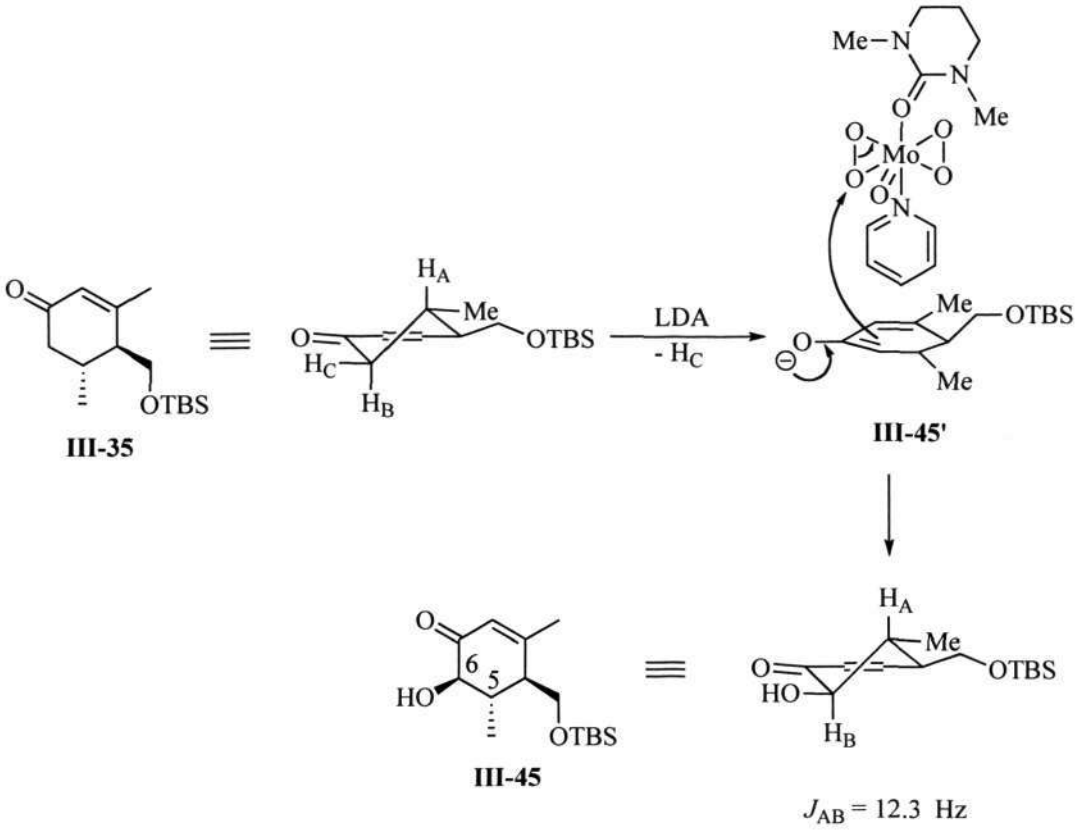
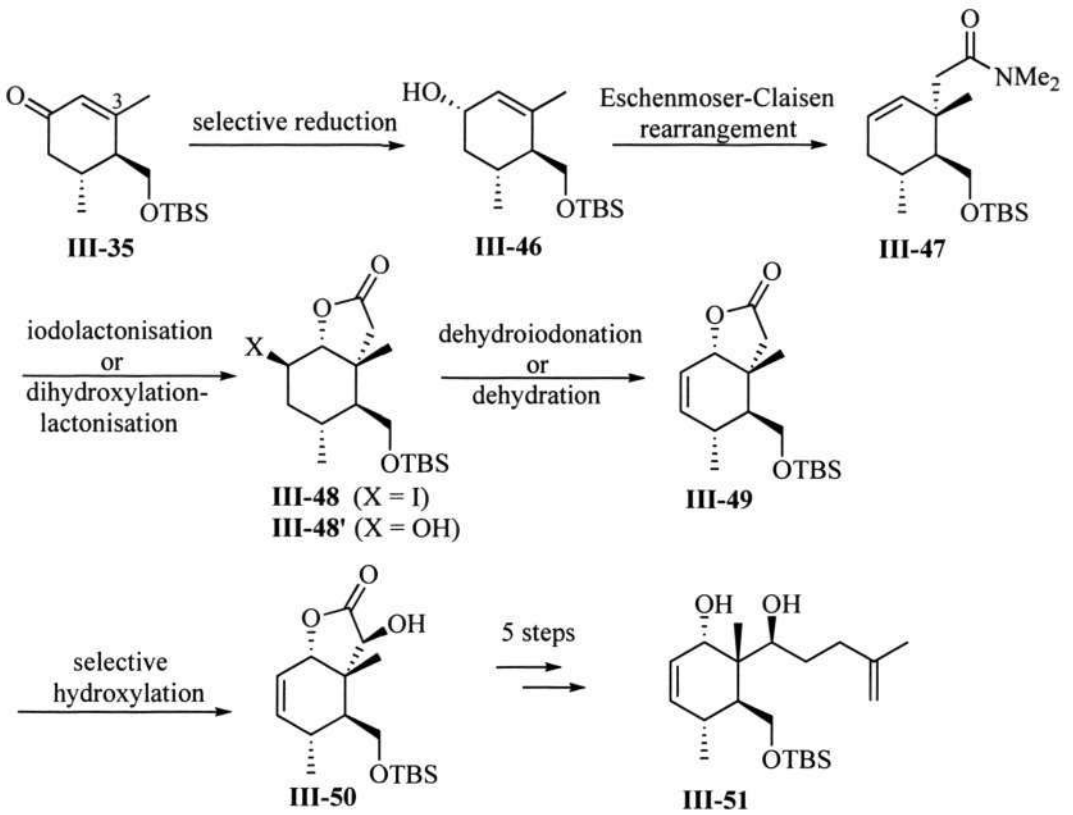


Figure 38

The preparation of hydroxyl-tetrahydrobenzofuranone III-50

Having established the formation of cyclohexenone **III-35**, the next objective was the synthesis of cyclohexenol **III-51** by stereoselective introduction of the requisite side chain at C-3 of **III-35.** As proposed in Scheme 33, compound **III-47** was the key intermediate for synthetic transformation into the **III-51**. Selective reduction of the cyclohexenone **III-35**, followed by the construction of the challenging quaternary carbon at C-3 through an [3,3]-sigmatropic rearrangement of the corresponding alcohol **III-46** would give the intermediate **III-47**. Lactone **III-49** was expected to be obtained by iodolactonisation or dihydroxylation-lactonisation of **III-47,** followed by

dehydroiodonation of the corresponding iodolactone **III-48** or dehydration of the corresponding hydrolactone **III-48′**, respectively. Selective hydroxylation of the lactone ring in adduct **III-49** would provide the hydroxy lactone **III-50** which could be used as a potential adduct to synthesize the desired cyclohexenol **III-51** in 5 steps.



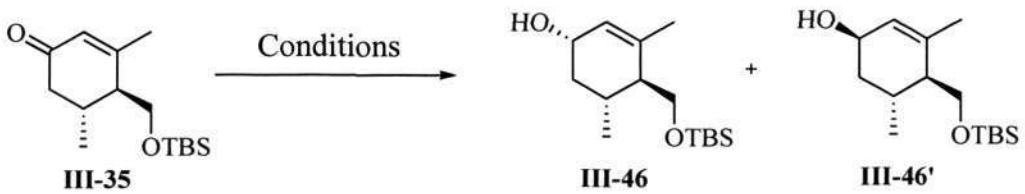
Scheme 33

Selective reduction of cyclohexenone III-35

Having cyclohexenone **III-35** in hand, selective reduction of the **III-35** was studied by using known reducing agents, which were lithium aluminium hydride

($LiAlH_4$)[94] and sodium borohydride ($NaBH_4$),[95] the ketone can be easily converted to the corresponding equatorial alcohol under various conditions as listed in Table 7.

Table 7 Optimization of the condition for the preparation of allylic alcohol **III-46**.



III-35 **III-46** **III-46'**

Entry	Conditions	Results[a]
1	$LiAlH_4$, THF –78 °C, 3 h	dr 80:20 (74%)
2	$NaBH_4$, MeOH –78 °C to RT, 5 h	dr 80:20 (92%)
3	$NaBH_4$, $CeCl_3.7H_2O$, MeOH –78 °C to RT, 5 h	dr 83:17 (91%)
4	$NaBH_4$, MeOH –78 °C to –40 °C, 20 h	dr 92:8 (87%)
5	$NaBH_4$, $CeCl_3.7H_2O$, MeOH –78 °C to –40 °C, 20 h	dr 96:4 (96%)

[a] isolated yield

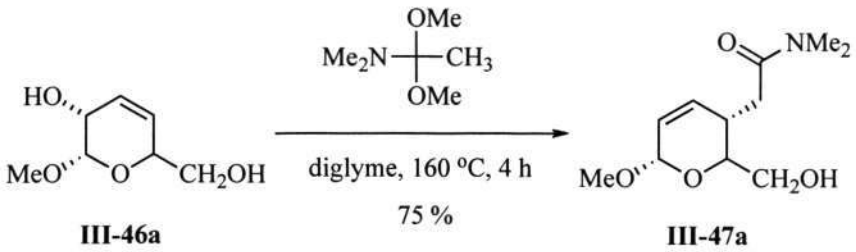
As shown in Table 7, the allylic alcohol **III-46** and **III-46'** were obtained in dr 80:20 by employing $LiAlH_4$ in THF at –78 °C for 3 h (entry 1, Table 7) or using $NaBH_4$ in MeOH at –78 °C then slowly warming to room temperature for 5 h (entry 2, Table 7). Hoping to improve the selectivity, we added $CeCl_3.7H_2O$, anticipating a higher propensity for attack from the more hindered side. It was found that using the same reaction conditions as in entry 2 but with 1 equiv of $CeCl_3.7H_2O$, the selectivity was slightly better (dr 83:17) as shown in entry 3. We envisaged that the temperature would play a role in the reaction selectivity. Thus, the reaction was performed at lower temperature, –78 °C then slowly warming up to –40 °C for 20 h (entry 4, Table 7), as expected, the selectivity was significantly better (dr 92:8). By adding 1 equiv of $CeCl_3.7H_2O$, the allylic alcohol **III-46** was almost exclusively achieved in dr 96:4 as shown in entry 5. Hoping to obtain a single diastereomer of **III-46** failed, the reaction did not go to completion when attempted at –78 °C for 20 h.

Thus, the conditions in entry 5 (Table 7) was selected as the standard procedure for the selective reduction of cyclohexenone **III-35**.

Eschenmoser-Claisen rearrangement of III-46

Since the intermediate **III-46** was readily synthesized, the next intention was the stereoselective introduction of the requisite side chain at C-3 of allylic alcohol **III-46**. The [3,3]-sigmatropic rearrangement (Claisen-type rearrangement) is required based on the nature of both the starting material **III-46** and the final product **III-51**. Corey *et al.*[96] reported that the Eschenmoser-Claisen rearrangement, dimethylamide **III-47a** was obtained from allylic alcohol **III-46a** by heating with several equivalents of the

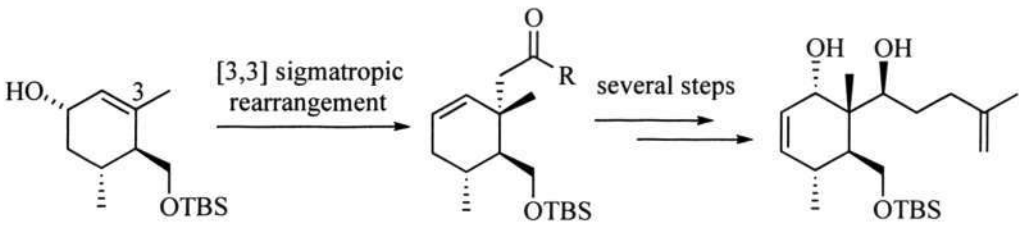
dimethylacetal of *N*,*N*-dimethylacetamide in diglyme as shown in Scheme 34. Thus, we envisaged that the [3,3]-sigmatropic rearrangement would be a logical choice to generate quaternary centre, as the relative configuration of the alcohol will be relayed to the rearranged product.



III-46a **III-47a**

Scheme 34

Therefore, by using [3,3]-sigmatropic rearrangement, compound **III-47r** would be obtained from allylic alcohol **III-46** which might be used as a starting material to synthesize the desired cyclohexenol **III-51** (Scheme 35).

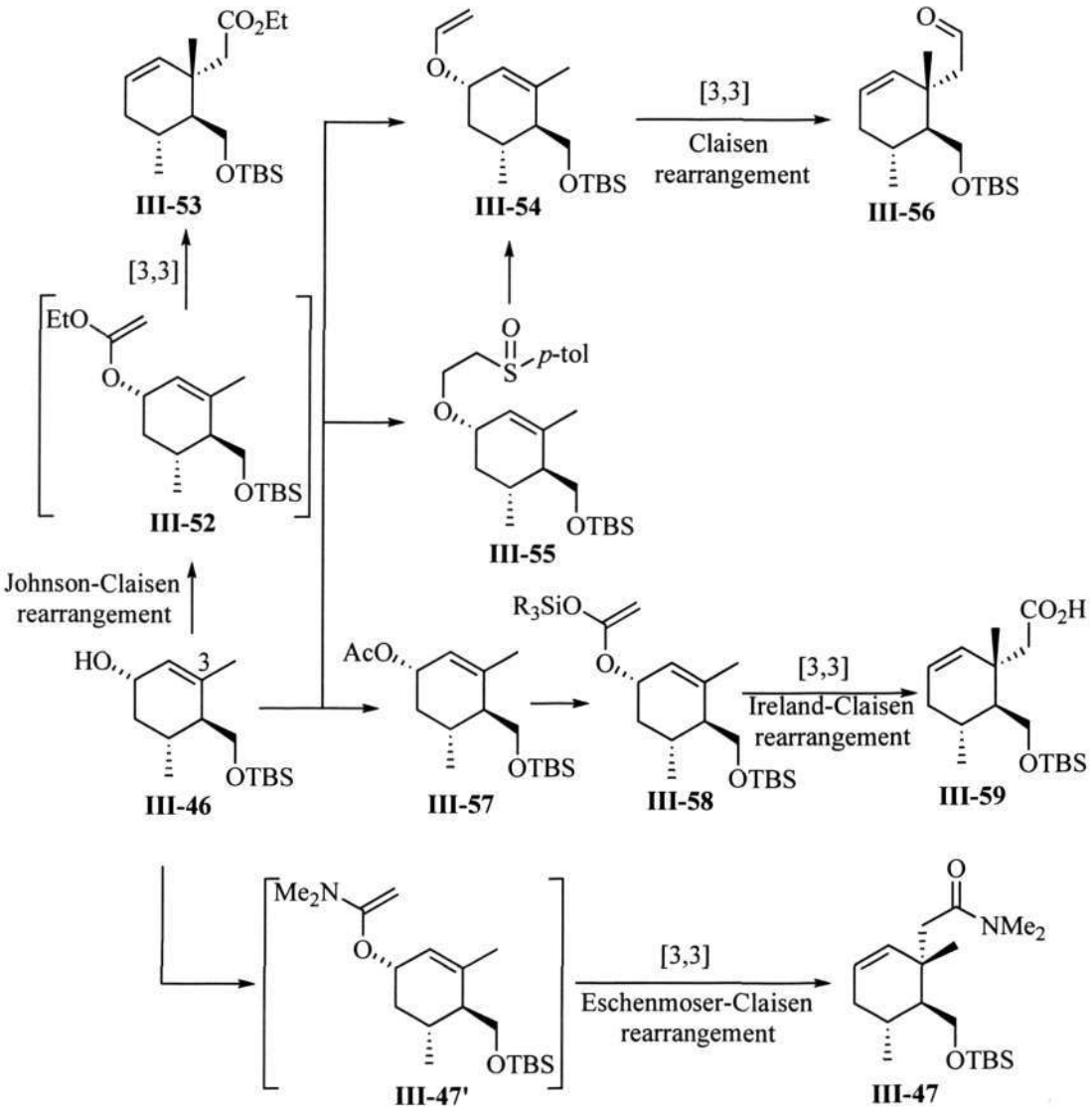


III-46 **III-47r** **III-51**

Scheme 35

For the construction of the quaternary carbon at C-3 we have considered 6 possibilities (Scheme 36). First, Johnson-Claisen (ortho ester) rearrangement[97,98] via intermediate **III-52** would give the ester **III-53**. Secondly and thirdly, Claisen

rearrangement[97,99] via allyl vinyl ether **III-54** and Mandai-Claisen rearrangement[100] via sulfoxide **III-55** may give the aldehyde **III-56** via intermediate **III-54**.

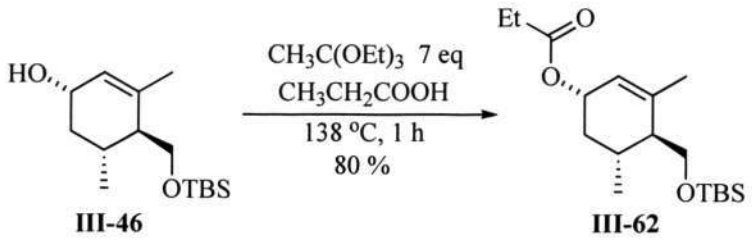


Scheme 36

Fourth, acylation of alcohol **III-46** would afford the ester **III-57** which could be subjected to an Ireland-Claisen rearrangement[101] through silyl ether **III-58**, to afford the

desired acid **III-59**. The final alternative, the construction of quaternary carbon at C_3 through an Eschenmoser Claisen (amide acetal) rearrangement[97] of allylic alcohol **III-46** could give the desired adduct **III-47**.

The Johnson-Claisen (ortho ester) rearrangement,[98] the most common [3,3]-sigmatropic rearrangement, was our first attempt. The allylic alcohol **III-46** was treated with 7 equiv of triethyl orthoacetate (1,1,1-triethoxyethane) in the presence of propionic acid (6 mol%) at 138 °C for 1 h leading to the sole unexpected ester product **III-62** instead of the desired ester **III-53** as shown in Scheme 37. The reaction also failed when 5-10 mol% of pivalic acid was used, giving the undesired acylation product **III-57** and recovery of allylic alcohol **III-46**.

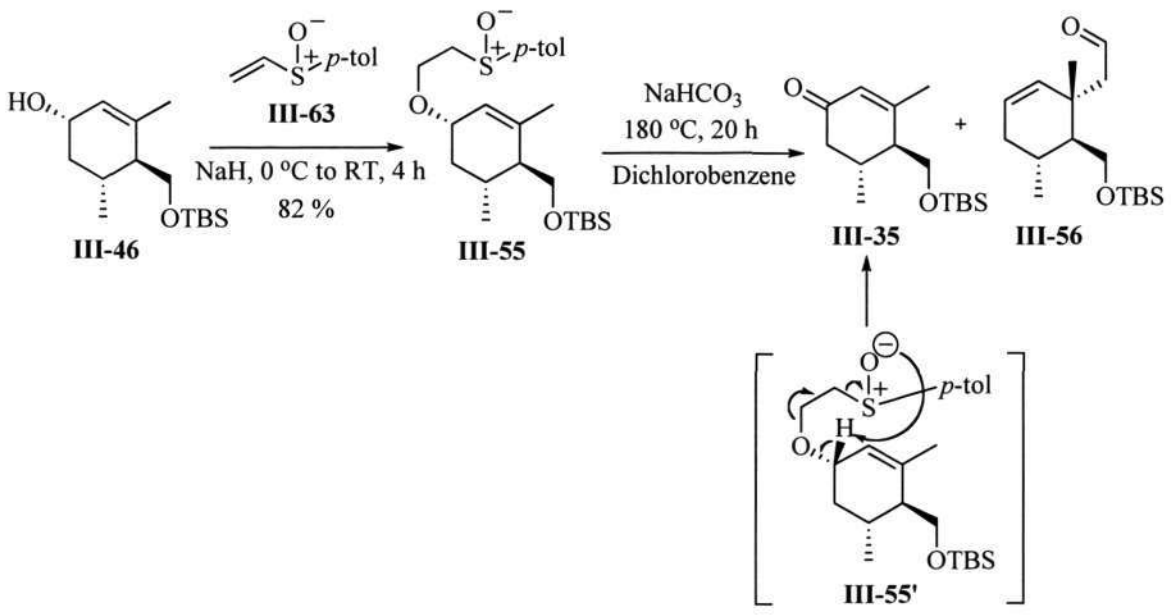


III-46 **III-62**

Scheme 37

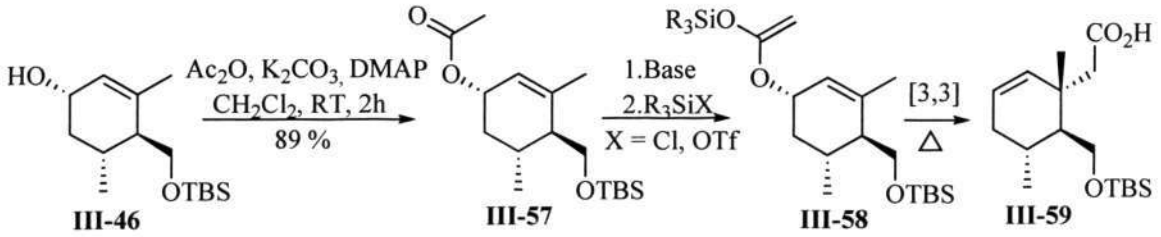
The second attempt was the Claisen rearrangement using the reported procedure,[99] treatment of allylic alcohol **III-46** with 35% mol of mercuric acetate and 9 equiv of ethyl vinyl ether at 100 °C for 2 days. Only a small amount of the required aldehyde **III-56** was observed in the crude ^{1}H NMR spectrum along with unidentified products. We moved to our third attempt, Mandai Claisen rearrangement[100] for the synthetic transformation of **III-46** into **III-56** as shown in Scheme 38. Toward this end, we needed to prepare the

sulfoxide **III-55**, required for the Mandai Claisen rearrangement. Allylic sufoxide **III-63** was reacted allylic alcohol **III-46** in the presence of sodium hydride as a catalyst to furnish the Michael adduct **III-55** in 82% yield. Accordingly, the sulfoxide **III-55** was treated with 20 equiv of $NaHCO_3$ in refluxing dichlorobenzene for 20 h, hoping to induce sulfoxide elimination [3,3]-sigmatropic rearrangement. The reaction led to the undesired and surprising product **III-35** in 8% yield together with a small amount of the inseparable aldehyde **III-56** which was observed in the crude ^{1}H NMR spectrum. The reaction failed when decalin was used as a solvent due to full recovery of starting material. We proposed that the cyclohexenone **III-35** might be obtained via the intermediate **III-55′**. However, the mechanism remains unclear.



Scheme 38

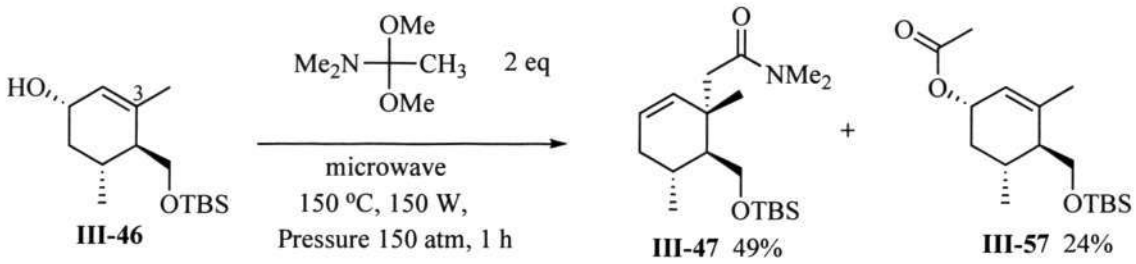
Ireland Claisen (silyl ester) rearrangement was selected for the construction of quaternary carbon at C3 of **III-46** as shown in Scheme 39.[101] For this transformation, the ester **III-57** was required. Treatment of allylic alcohol **III-46** with 4 equiv of acetic anhydride and potassium carbonate as a base at room temperature for 2 h gave the ester **III-57** in 89%. Therefore, we began investigating the preparation of **III-58** by generating the anion of **III-57** using appropriate bases such as LDA, KHMDS and LiHMDS, followed by trapping the resulting anion with TMSCl, TBSCl, and TMSOTf under various conditions. However, all attempts failed, leading to recovery of starting material or in some cases acyl cleavage to result in the allylic alcohol **III-46**. Due to the disappointing results, we consequently moved to the last proposed approach.



Scheme 39

Finally, we were relieved to find that the Eschenmoser-Claisen (amide acetal) rearrangement worked for the transformation of **III-46** into **III-47** (Scheme 40).[97] The allylic alcohol **III-46** was reacted with 2 equiv of *N*,*N*-dimethyl acetamide dimethyl acetal at reflux for 10 h to give the dimethyl amide adduct **III-47** as a single diastereoisomer in 10-30% yield. However, when microwave heating was used without any solvent at 150 W for 1 h the dimethyl amide adduct **III-47** was obtained in 49% yield (based on the major

isomer of **III-46**, in a ratio of 94:6) along with ester **III-57** in 24% yield. The reaction time with microwave heating reaction is 7-10 times shorter than at conventional heating and the yields of isolated products are usually 10-20% higher. Low yields were obtained (20-40% yield) when toluene or xylene was used as a solvent under microwave condition. It may be noted that in our case the [3,3]-sigmatropic rearrangement is difficult due to the hydroxy group is in the equatorial position.

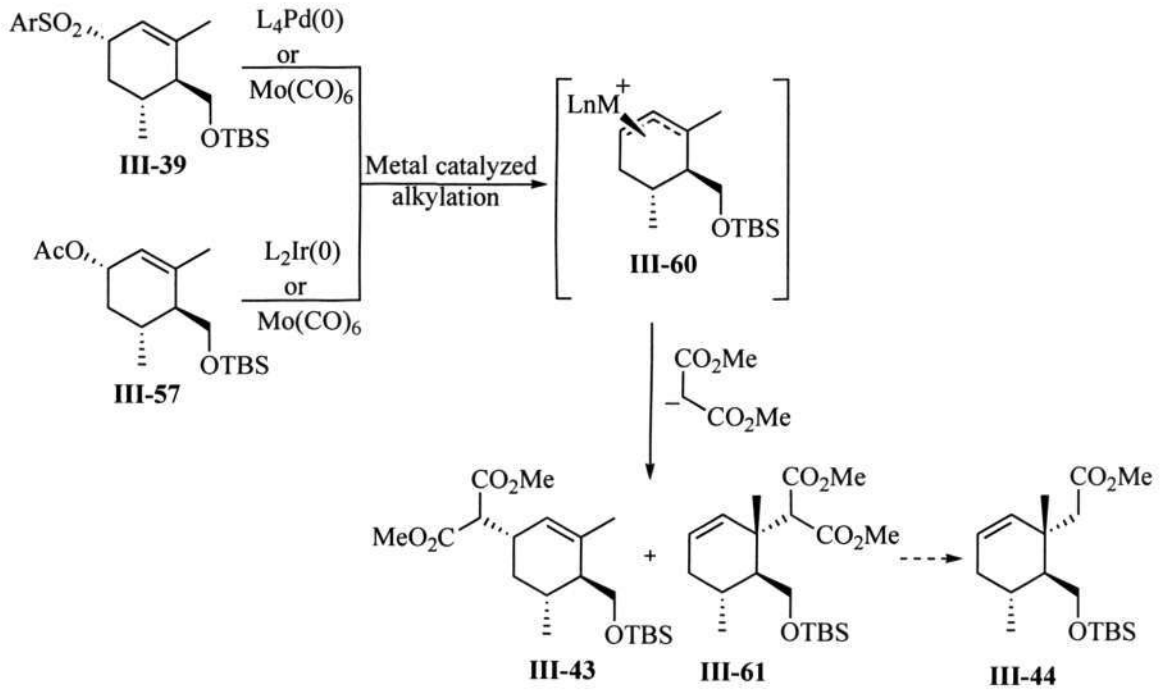


Scheme 40

The metal complex-catalyzed allylic alkylation of allylic sulfone III-39 or allylic ester III-57

Allylation with allylic sulfone **III-39** and ester **III-57** was also attempted for the synthetic transformation of **III-39** or **III-57** into the intermediate **III-61** which could be converted to the desired ester **III-44** through decarboxylation. Trost has reported that allylic sulfones are viable substrates for palladium or molybdenum catalysed allylation.[102] Reaction of sulfone **III-39** with the sodium salt of dimethyl malonate would be expected to result in selective allylation at the less substituted allylic site to give **III-43** as a major product with a palladium (0) catalyst. A quaternary carbon center would be expected by attack at the more substituted allylic site to give **III-61** as a major product, in the case of

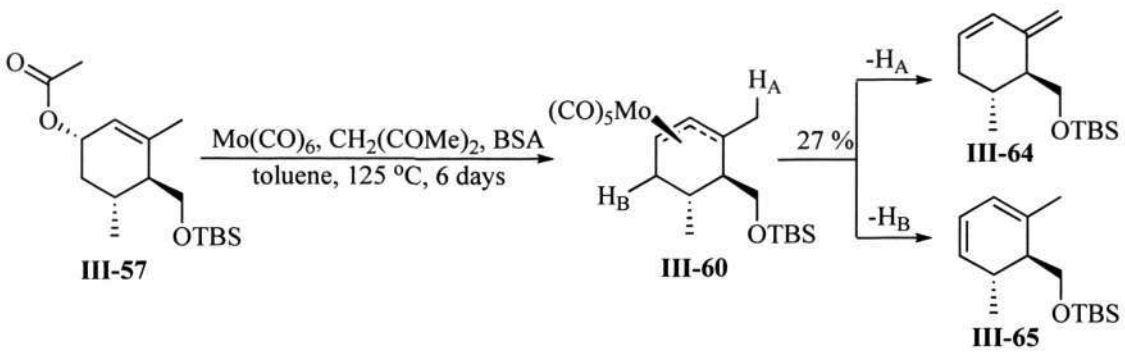
using $Mo(CO)_6$ (Scheme 41). Alternatively, iridium catalyzed allylation might be employed. Takeuchi *et al.*[103] reported the reaction of allylic esters with dialkyl sodiomalonate in the presence of a catalytic amount of $[Ir(COD)Cl]_2/P(OPh)_3$ (Ir/P = 1:1-4).



Scheme 41

To our disappointment, all attempts at allylation using allyl sulfone **III-39** by the Tsuji-Trost chemistry by employing dimethyl malonate sodium salt and 10 mol% $Pd(PPh_3)_4$ catalyst in refluxing THF or 10-20 mol% $Mo(CO)_6$ catalyst in refluxing toluene or dioxane were unsuccessful leading to recovery of the starting material.

The iridium complex-catalyzed or molybdenum complex allylic alkylation using allylic acetate **III-57** were similarly unsuccessful. All attempts under various conditions led to recovery of the starting material **III-57** except when 20 mol% $Mo(CO)_6$ in refluxing toluene for 6 days with 1.5 equiv of BSA was used, providing the dienes **III-64** and **III-65** in a total of 27% yield along with recovery of starting material in 18% yield. We propose that after the π-allyl complex intermediate **III-60** was formed, but deprotonation is faster than the alkylation of dimethyl sodiomalonate due to the steric hindrance of the methyl group to give the undesired dienes **III-64** and **III-65** by loss of proton A and proton B, respectively (Scheme 42).

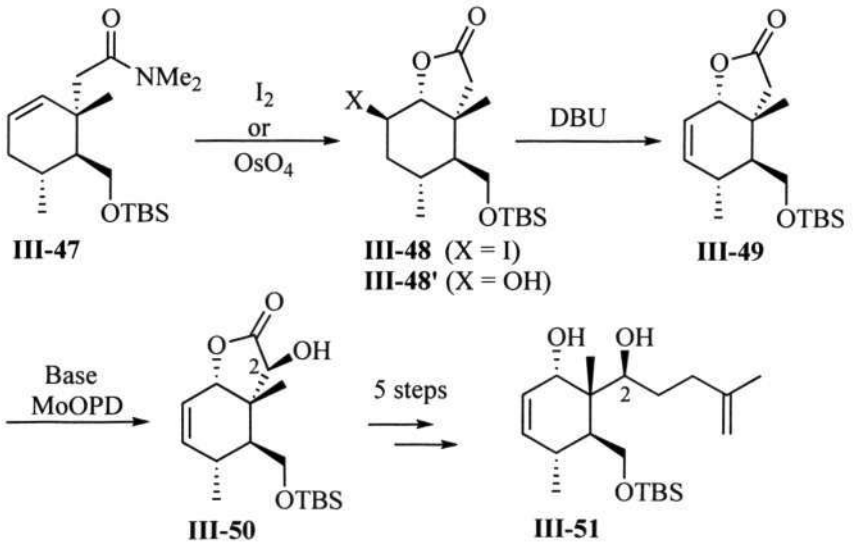


Scheme 42

As the Eschenmoser-Claisen rearrangement had proved successful, metal catalysed allylation was not pursued further.

The preparation of hydroxyl-tetrahydrobenzofuranone III-50

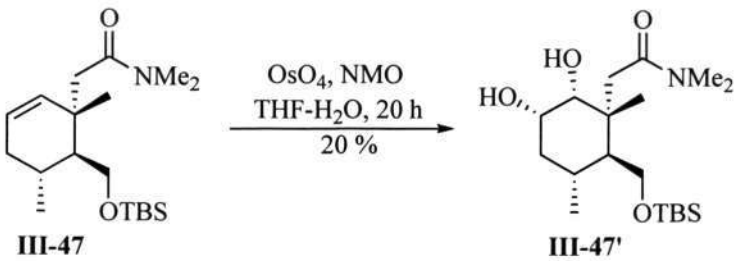
Having succeeded in preparing **III-47**, we next tried to use compound **III-47** as the starting material for synthesis of hydroxyl-tetrahydrobenzofuranone **III-50**. Our first task was lactonisation of **III-47** by iodolactonisation or dihydroxylation-lactonisation to the iodolactone **III-48** or hydroxylactone **III-48′**, respectively, which was expected to undergo de-iodohydronation or dehydration to give lactone **III-49** (Scheme 43). Selective hydroxylation the lactone ring in adduct **III-49** would provide the cyclohexenone adduct **III-50** containing a hydroxyl group at C-2. Compound **III-50** would be used as an intermediate to synthesize the desired cyclohexenol **III-51**.



Scheme 43

Our synthesis began with dihydroxylation-lactonisation:[88] compound **III-47** was treated with osmium tetroxide and NMO as an oxidizing agent in a mixture of THF and water (10:1) to give the dihydroxylation product **III-47′** in 20% yield along with

decomposed unidentified product (Scheme 44). Due to the low yield and the failure of *in situ* lactonisation, therefore, we moved to the alternative synthetic proposal using iodolactonisation[96] hoping that we could avoid additional steps for lactonisation. The failure of *in situ* lactonisation can be attributed to the stabilization of the amide by delocalization of the N-lone pair. This delocalization, however, also makes the amide carbonyl weakly nucleophilic, therefore, we turned to halocyclisation to generate the tetrahydrobenzofuranone.

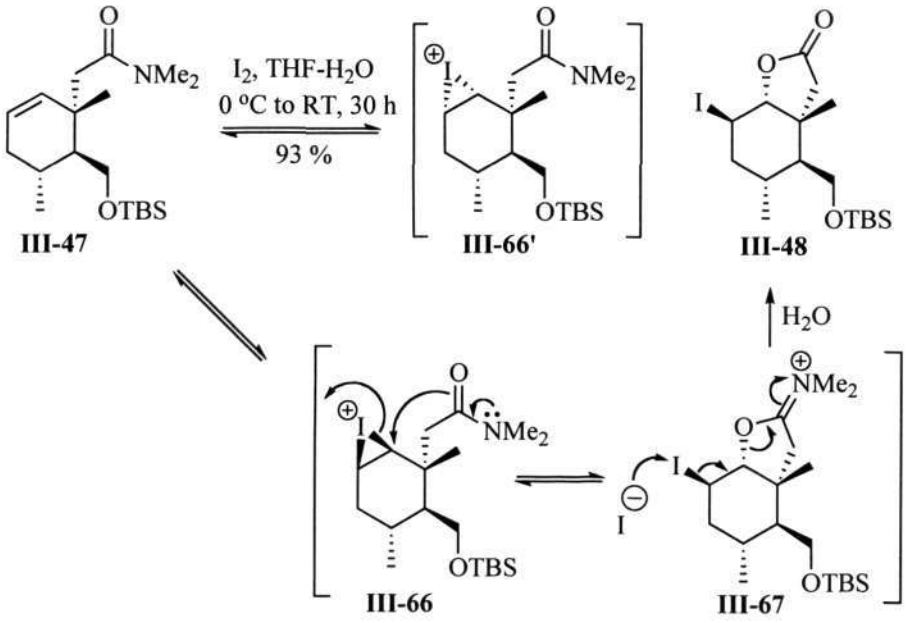


III-47 III-47'

Scheme 44

Compound **III-47** was iodolactonised[96,104] by treatment of **III-47** with 2 equiv of iodine in a mixture of THF:H_2O (10:1) at 0 °C then slowly warmed up to room temperature for 30 h to furnish, almost quantitatively, the iodo lactone **III-48** along with recovery of starting material in 2% yield and the desilylated product in 1% yield. Curiously, if the reaction were quenched and worked up as soon as TLC indicated disappearance of the starting material, then a low yield of the iodolactone **III-48** was obtained, accompanied by unreacted starting material **III-47**. On prolonged reaction, however, an almost quantitative yield of the iodolactone **III-48** could be obtained. We attribute this to fast iodocyclisation via intermediate **III-67**, but slow hydrolysis of this

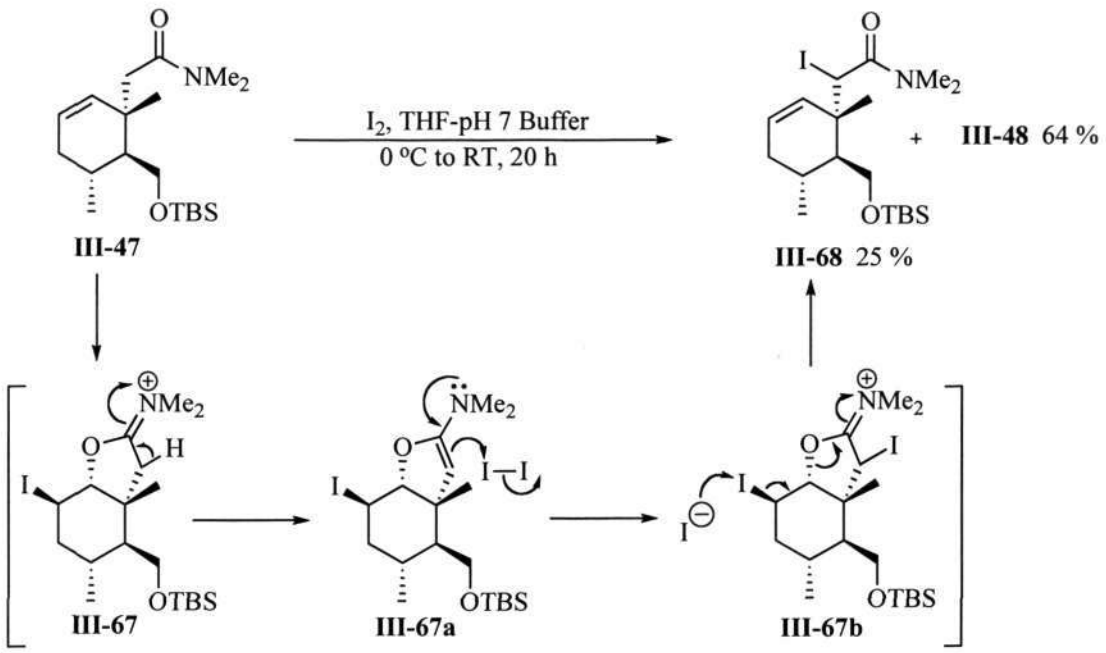
intermediate, with the iodocyclisation reversing under the work up conditions as shown in Scheme 45.



Scheme 45

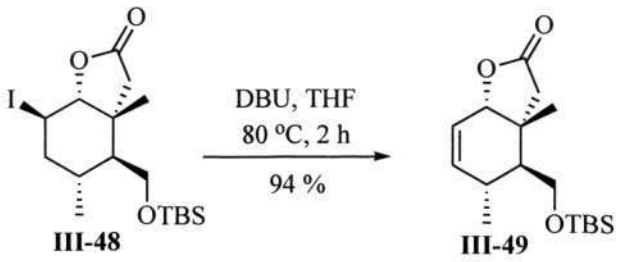
As shown in Scheme 45, the iodo lactone **III-48** was obtained as a single isomer. This can be rationalized by the assumption that iodonium ions **III-66′** and **III-66** are in equilibrium, but only iodonium ion **III-66** can cyclize resulting in the intermediate **III-67,** which was further hydrolyzed to give the iodo lactone **III-48**. We anticipated that the reaction rate might be enhance by increasing the amount of I_2 to 3 equiv. Even though the reaction time was shorter, 20 h, the amount of desilylated product was significantly increased to 12% yield along with the expected product **III-48** in 79% yield. A pH 7 buffer (NaH_2PO_4 and NaOH) solution was used instead of water to prevent cleavage of the TBS group (Scheme 46). However, the expected iodide **III-48** was obtained in only

64% yield along with the undesired product **III-68** in 25% yield. The structure of **III-68** was obtained as a single isomer, and the structure was elucidated from the spectroscopic data. However the stereochemistry was not determined. The proposed mechanism for the formation of iodide **III-68** is shown in Scheme 46. Firstly, α-deprotonation of the intermediate **III-67** yields enamine **III-67a**, subsequently the enamine **III-67a** reacted with a second equivalent of iodine to give α-iodination adduct **III-67b**. Finally, de-iodination of the intermediate **III-67b** gave the iodide **III-68**.



Scheme 46

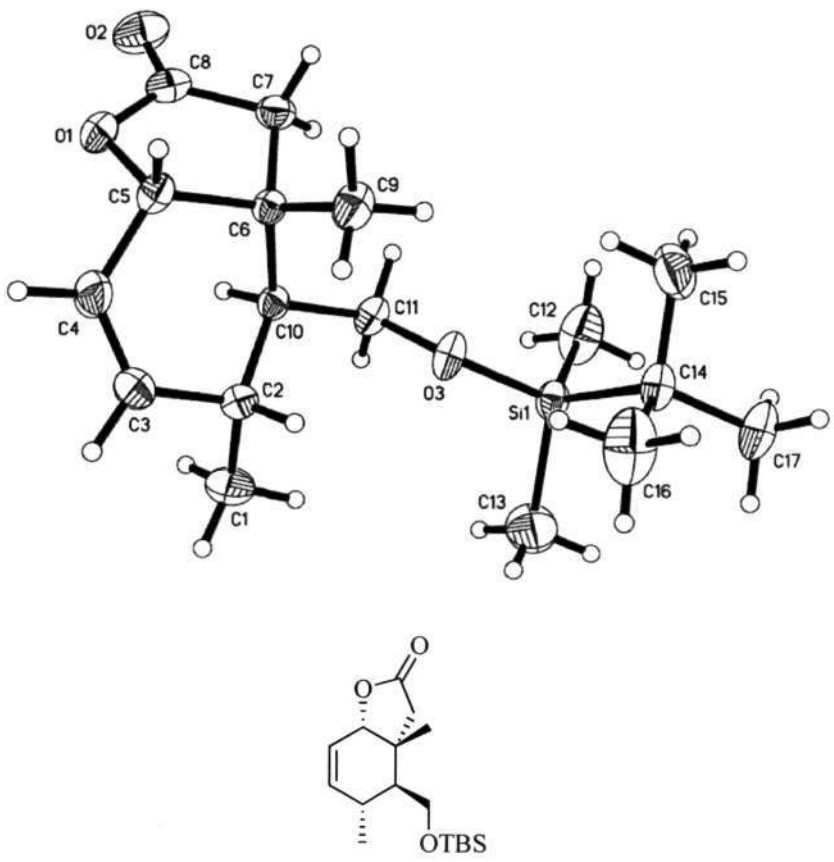
Heating iodo-lactone **III-48** in THF at reflux containing 4 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[105] afforded quantitatively the lactone **III-49** in 2 h (Scheme 47). We attribute this fast elimination to the axial position of the iodine.



III-48 III-49

Scheme 47

The relative stereochemistry of the tetrahydrobenzofuranone **III-49** was confirmed by single crystal X-ray crystallography as shown in Figure 39.

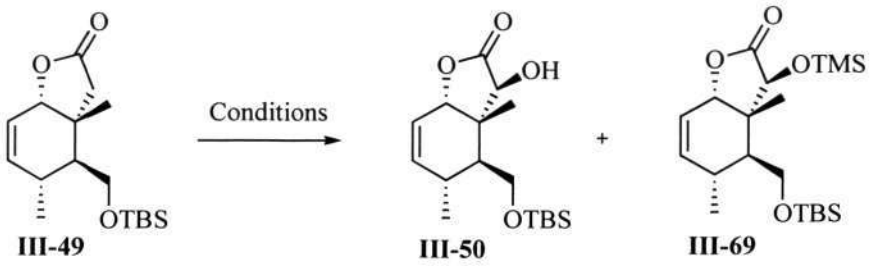


III-49

Figure 39 X-ray ORTEP diagram of tetrahydrobenzofuranone **III-49**

Having lactone **III-49** in hand, selective hydroxylation of the **III-49** was studied using MoOPD as an oxidizing agent and bases such as LDA, KHMDS, LiHMDS under various conditions as listed in Table 8.[86,88,106]

Table 8 Optimization of the condition for the preparation of hydroxyl lactone **III-50**.



III-49 **III-50** **III-69**

Entry	Conditions	Results[a]
1	LDA 2 eq, MoOPD 2 eq –78 °C to –40 °C, 20 h	Recovery of **III-49**
2	KHMDS 2 eq, MoOPD 2 eq –78 °C to –40 °C, 20 h	**III-49** (69%) and **III-50** (20%)
3	KHMDS 3 eq, MoOPD 4 eq –78 °C to –40 °C, 20 h	**III-49** (35%), **III-50** (11%), and **III-69** (24%)
4	KHMDS 5 eq, MoOPD 4 eq –78 °C to –10 °C, 20 h	**III-49** (13%), **III-50** (37%), and **III-69** (20%)
5	LiHMDS 2 eq, MoOPD 2 eq –78 °C to –10 °C, 20 h	**III-50** (87%)

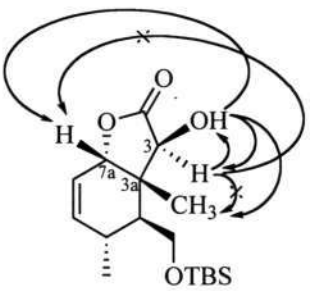
[a] isolated yield

As shown in Table 8, attempted preparation of **III-50** by treatment of **III-49** with 2 equiv of LDA and 2 equiv of MoOPD was unsuccessful with recovery of **III-49** (entry 1, Table 8). Treatment of **III-49** with 2 equiv of LDA and then quenching with D_2O provided recovery of starting material **III-49** without deuteration indicating that deprotonation had not occured. We presumed that the bulk of LDA was preventing deprotonation of the α-position of the lactone ring. At this point, we changed the base to KHMDS. The expected hydroxy lactone **III-50** was obtained in 20% yield along with recovery of **III-49** in 69% yield when 2 equiv of KHMDS was employed as a base (entry 2, Table 8). When the amount of KHMDS was increased to 3 equiv and the amount of MoOPD to 4 equiv, 11% of the desired product **III-50** was obtained, accompanied by 24% of **III-69** and 35% of starting material **III-49** (entry 3, Table 8). However, by increasing the amount of KHMDS to 5 equiv and warming the reaction from –78 °C to –10 °C for 20 h, a 37% yield of **III-50** along with a 20% yield of **III-69** and 13% of the starting material **III-49** (entry 4, Table 8) were obtained. These results led us to use the LiHMDS as a base. Surprisingly, the lactone **III-49** could be converted smoothly into a single hydroxylated lactone **III-50** with a yield sharply increased to 87% yield employing 2 equiv of LiHMDS and 2 equiv of MoOPD at –78 °C then slowly warming up to –10 °C for 20 h (entry 5, Table 8).

Thus, the conditions in entry 5 (Table 8) were selected as the standard procedure for the hydroxylation of lactone **III-49** into **III-50**.

The hydroxy lactone **III-50** was obtained as a single isomer. Inspection of molecular models, supported by NOE studies as shown in Figure 40, indicated hydroxylation *cis* to the methyl group. Irradiation of the H-3 signal resulted in

enhancement of the OH-3 signal, but there was no effect on the CH_3-3a and H-7a signals. Irradiation of OH-3 led to enhancement of the H-3, CH_3-3a and H-7a signal. Therefore, it is likely the MoOPD approaches from the convex face (less hindered side) of lithium enolate of **III-49** avoiding the steric interaction with the cyclohexene ring from the concave side (more hindered side) to give exclusively the alcohol **III-50**. In addition, when KHMDS was used as a base, the hexamethyldisilylamine **III-69** was obtained as a by-product from the reaction. However, when LiHMDS was used as a base, the reaction did not give any silyl ether **III-69** at all. This can be rationalized by the assumption that the reactive potassium alkoxide is silylated by the hexamethyl disilazide by-product, but the lithium alkoxide could not due to the strong bonding interaction between oxygen and lithium.



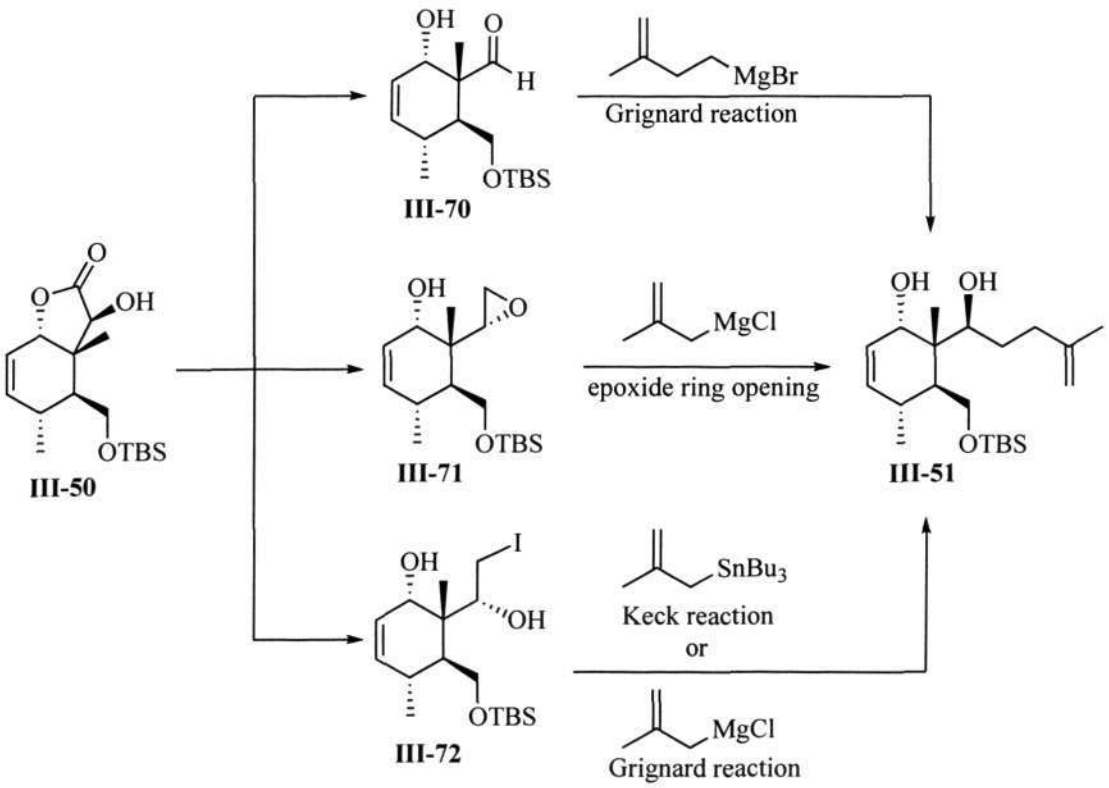
50

Figure 40

The preparation of cyclohexenol III-51

Since the hydroxyl lactone **III-50** was readily synthesized, our next task was to demonstrate the synthetic utility of **III-50** as the starting material for syntheses of the cyclohexenol **III-51,** which contains a side chain. For the transformation of **III-50** to **III-**

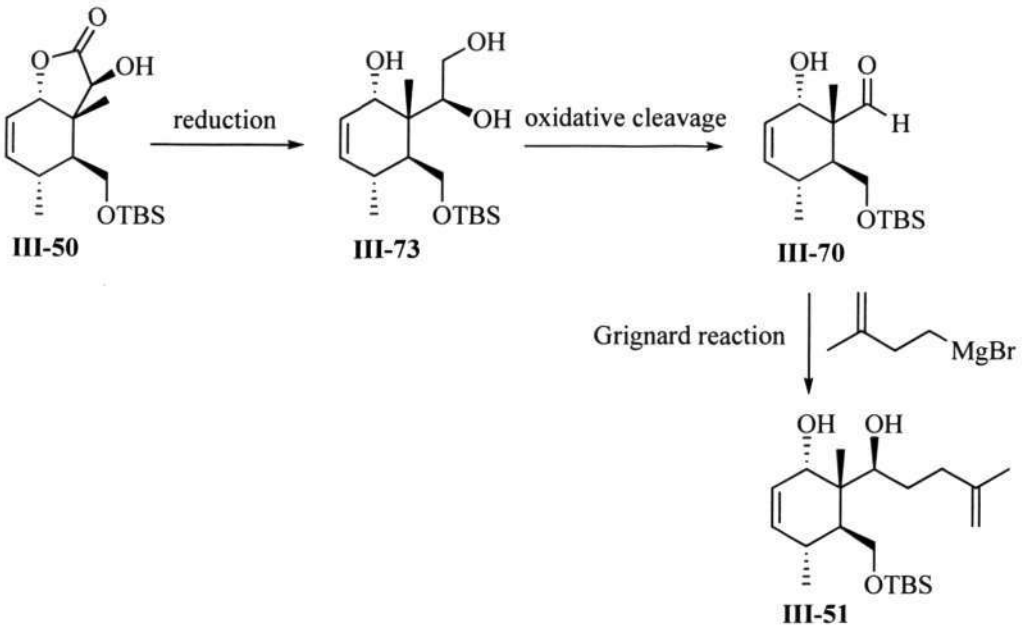
51 we have considered three possibilities (Scheme 48). First, a key diastereoselective nucleophilic addition of a Grignard reagent to aldehyde **III-70** could give **III-51**.[51] Alternatively, epoxide ring opening of **III-71** by methyl allyl magnesium chloride could also afford the desired product **III-51**. Thirdly, Keck allylation[107] or a copper catalyzed Grignard reaction[108] could convert the iodo alcohol **III-72** to the required cyclohexenol **III-51**.



Scheme 48

As proposed in Scheme 49, aldehyde **III-70** will be a key intermediate for synthetic transformation into cyclohexenone **III-51** via a Grignard reaction by a modification of a reported procedure by Iwasaki *et al.*[51] Reduction of lactone **III-50**

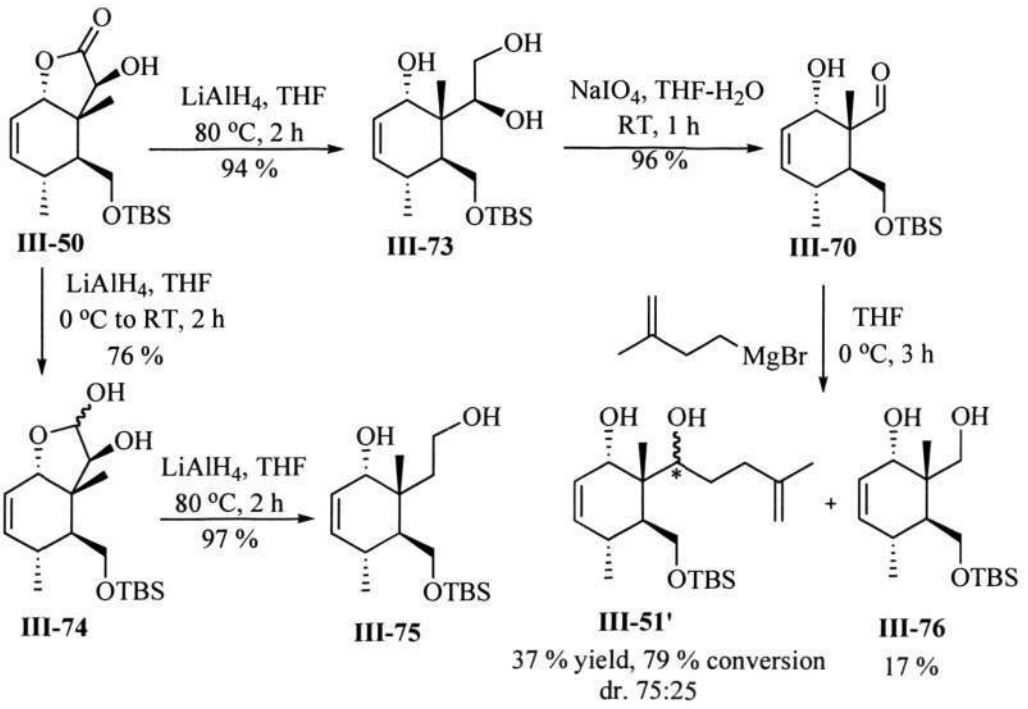
would provide the alcohol **III-73** which would be subjected to oxidative cleavage to afford the aldehyde **III-70**.



Scheme 49

Reduction of hydroxy lactone **III-50** by treatment with 5 equiv of $LiAlH_4$ in refluxing THF for 2 h gave the triol **III-73** in quantitative yield as shown in Scheme 50. When only 2 equiv of $LiAlH_4$ was used at 0 °C then warming up to room temperature for 2 h, intermediate lactol **III-74** was obtained in 76% yield. The diol **III-74** was further subjected to reduction using 5 equiv of $LiAlH_4$ at 80 °C in THF for 2 h unexpectedly gave the over reduction product **III-75** in 97% yield instead of desired alcohol **III-73**. Oxidative cleavage took place smoothly on reaction of **III-73** with 1.5 equiv of sodium periodate in a mixture of THF and H_2O (1:1) to provide the aldehyde **III-70** in 96% yield. The diasteroselective addition reaction of 2-methylbutenylmagnesium bromide to **III-70**

was achieved at 0 °C for 3 h to furnish compound **III-51′** as an inseparable 75:25 mixture of diasteroisomers in 37% yield, based on 79% conversion, along with the reduction product **III-76** in 17% yield.



Scheme 50

The origin of the diastereoselective addition reaction of vinylmagnesium chloride as proposed by Iwasake *et al.*[51] is as shown in Figure 41. Chelation of magnesium between the carbonyl oxygen and the hydroxyl group on the cyclohexene ring fixes the conformation of the aldehyde carbonyl group. The nucleophile approaches one face of the carbonyl group to avoid the steric repulsion of the TBDPS group to create a chiral center bearing a hydroxyl group **I-152** as a single diastereoisomer.

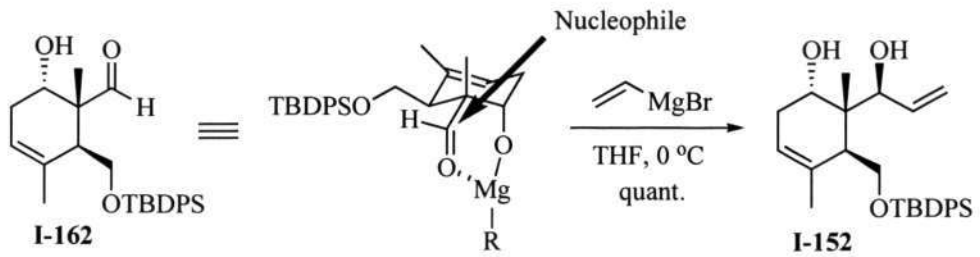


Figure 41

However, in our case, a mixture of diastereoisomers was obtained due to the smaller size of the protecting group (TBS), which could not control the nucleophilic approach. Attempts to improve the selectivity by lowering the temperature to –30 °C in order to control the selectivity of nucleophilic approach, still led to a mixture of diastereoisomers **III-51′**. The best ratio was 75:25 as shown in Scheme 50.

Moreover, the reduction product **III-76** was obtained, which could be explained by hydride transfer from 2-methylbutenylmagnesium bromide to give the alcohol **III-76** after work-up as proposed in Figure 42.

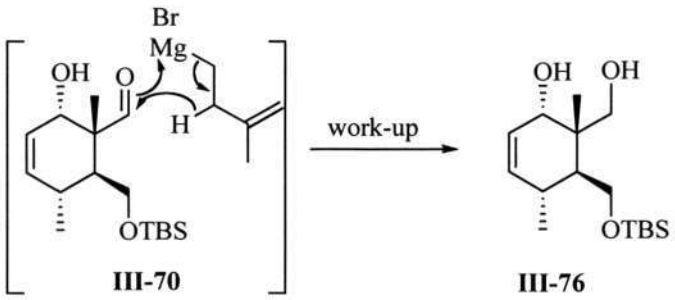
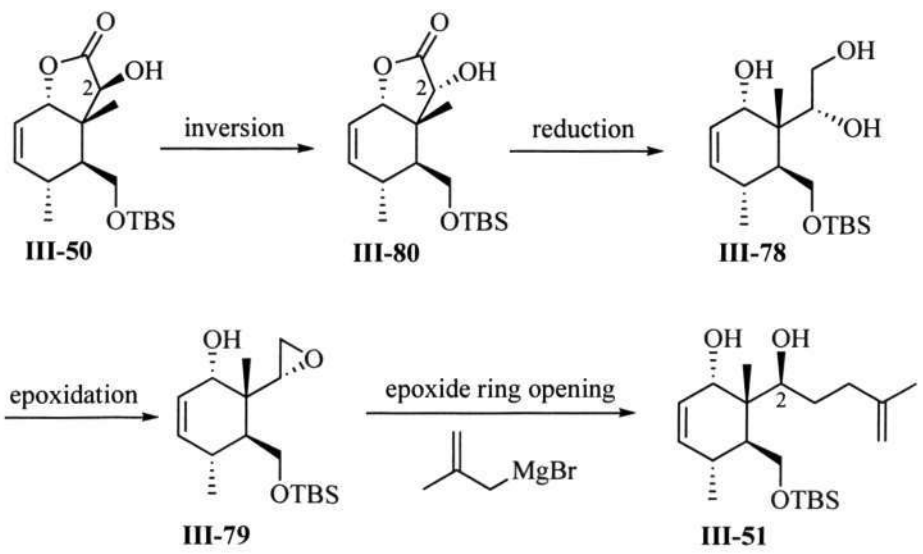


Figure 42

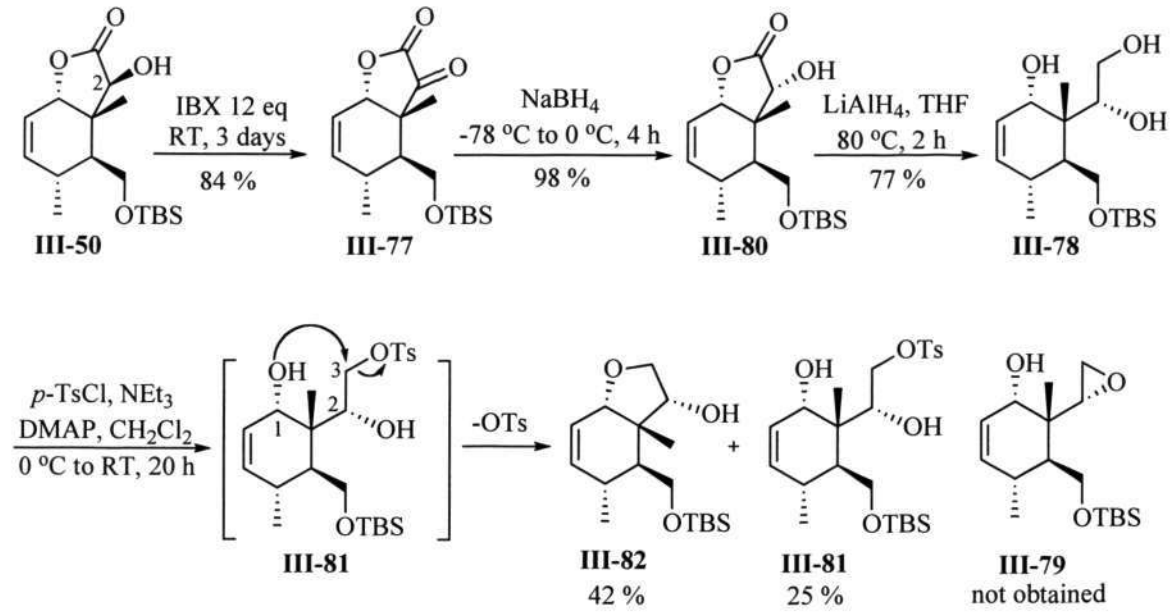
These results made us move on to the second proposed approach. As proposed in Scheme 51, compound **III-79** was selected as a key intermediate for synthetic transformation into cyclohexenone **III-51** via epoxide ring opening or radical allylation (Scheme 53). Comparison of the stereochemistry of the hydroxyl group of **III-50** with the natural products shows that inversion of this chiral centre is required to give the alcohol **III-80**. Reduction of **III-80** and subsequently epoxidation of the corresponding alcohol **III-78** would provide epoxide **III-79** which would be subjected to epoxide ring opening to give the desired cyclohexenol **III-51**.



Scheme 51

As shown in Scheme 52, oxidation of the alcohol **III-50** employing 12 equiv of IBX[100] at room temperature for 3 days gave the keto ester **III-77** in 85% yield. When only 2-6 equiv of IBX were used, a longer reaction time (usually more than 10 days for completion) was required due to the steric hindrance of the α-hydroxy ketoester. Attempts

to improve this oxidation by employing DMP at room temperature for 4 days provided a 11% of diketone **III-77** accompanied by 89% of starting material **III-50**.



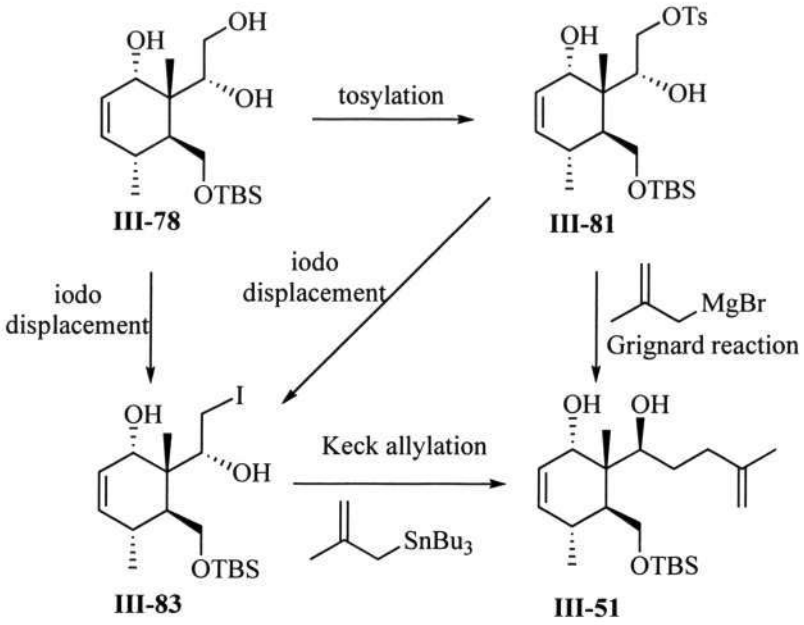
Scheme 52

The β-ketoester **III-77** was reduced using $NaBH_4$ at –78 °C then slowly warming up to 0 °C for 4 h to provide exclusively alcohol **III-80** as a single diastereoisomer which was reduced further by $LiAlH_4$ to give the adduct **III-78** in 77% yield. The high diastereoselectivity observed is due to attack on the convex face by $NaBH_4$ to give solely alcohol **III-80**. Our next task was to use the adduct **III-78** as a starting material to prepare the required epoxide **III-79**. The alcohol **III-78** was treated with *p*-TsCl in a presence of NEt_3 at 0 °C then slowly warming up to room temperature for 20 h. To our disappointment, the undesired tetrahydrofuran **III-82** was obtained in 42% yield instead of the desired epoxide **III-79**, accompanied by 25% of tosylate **III-81** and 5% of starting

material **III-78**. The chemical shift of the proton α- to oxygen in the ^{1}H NMR spectra were clearly inconsistent with an epoxide structure. The desired epoxide **III-79** was not obtained at all from the reaction. It can be suggested that C-3 of intermediate **III-81** was attacked by the hydroxyl group C-1 to produce the 5-membered ring, faster than attack by the hydroxyl group at C-2 which would have produced the desired epoxide.

As the desired epoxide **III-79** was not obtained from the tosylate **III-81**, we considered using protecting groups to ensure that epoxide formation would occur. This would, however, add too many steps. We, therefore, examined Grignard allylation[107] or a Keck free radical allylation[108] which would be logical choices for the synthesis of the desired cyclohexenol **III-51**.

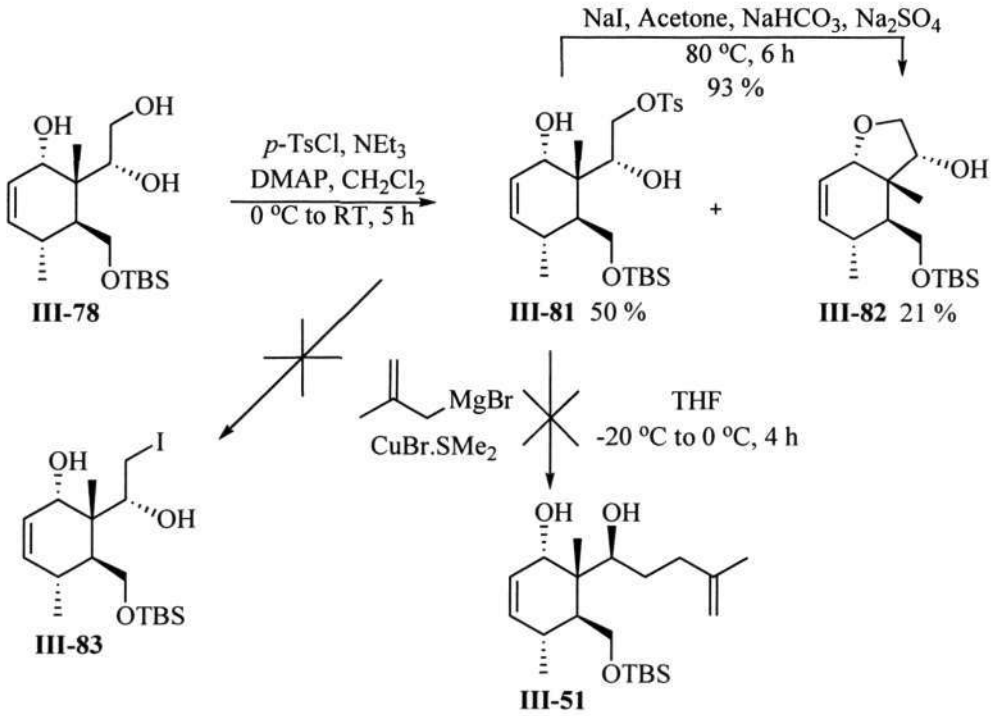
As shown in Scheme 53, we demonstrated the synthetic utilities of adduct **III-83**, which was selected as the key intermediate for the synthetic transformation of **III-83** into **III-51**. Iodide **III-83** could be obtained from triol **III-78** by two possibilities. Firstly, chemoselective iodination of triol **III-78** could furnish intermediate **III-83** directly in one step. Secondly, chemoselective monotosylation of the triol **III-78**, followed by iodide displacement of the resulting tosylate **III-81** should give the required adduct **III-83**. Our desired cyclohexenol **III-51** would be obtained from monotosylate **III-81** by Grignard allylation or iodide **III-83** by Keck free radical allylation as a key step.



Scheme 53

As shown in Scheme 54, our best conditions for the preparation of tosylate **III-81** was to use *p*-TsCl with NEt_3 as a base at 0 °C then slowly warming up to room temperature for 5 h to give the desired tosylate **III-81** in 50% yield along with 21% of the cyclized product **III-82**. However, using 1 equiv of pyridine as a base, 82% of the cyclized product **III-82** accompanied by 14% of the tosylate **III-81** was obtained. Since, we had the tosylate **III-81** in hand, we attempted to convert this compound to iodide **III-83**, using the Finkelstein procedure,[109] by treatment **III-81** with 2 equiv of NaI in the presence of a buffer, $NaHCO_3$, and an iodine scavenger, Na_2SO_3, in refluxing acetone for 6 h. Surprisingly this provided the undesired cyclized product **III-82** in 93% yield. The expected iodide **III-83** was not obtained at all from the reaction. In the absence of the buffer, the cyclized product with desilylation was obtained completely. However, we attempted to use tosylate **III-81** for the preparation of cyclohexenol **III-51** by treatment of

III-81 with allyl magnesium bromide in THF at –20 °C then slowly warmed up to 0 °C for 4 h but unfortunately the reaction failed, leading to decomposition.[107]



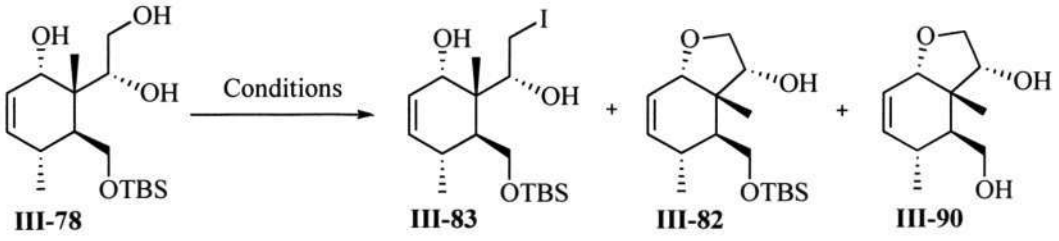
Scheme 54

Due to the unsuccessful results, we moved to the final proposed synthetic by using the triol **III-78** as a starting material for the preparation of the potential iodo adduct **III-83** which could be converted into our target compound **III-51**.

As shown in Table 9, attempted preparation of **III-83** by treatment of **III-78** with 1 equiv of iodine, triphenylphophine and imidazole[110] in a mixture of toluene and CH_2Cl_2 (1:1) at 60 °C for 1 h was unsuccessful furnishing 36% of the tetrahydrofuran **III-82** accompanied by 38% of **III-90** (entry 1, Table 9). To improve the solubility of triol **III-78**, a co-solvent such as acetonitrile or CH_2Cl_2 was needed. However, all attempts failed

leading to the undesired product **III-82** and **III-90**. It was found that low temperature was required for the reaction in order to stop the cyclisation process. As shown in entry 2 (Table 9), treatment of **III-78** with of iodine, triphenylphophine, and imidazole in CH_2Cl_2 at 0 °C for 1 h resulted in a 22% yield of the desired iodide **III-83** along with a 9% yield of the cyclized product **III-82**, and 51% of starting material **III-78**. The triol **III-78** could not be totally dissolved in CH_2Cl_2 at –10 °C, therefore 0 °C was selected for the reaction conditions instead. Finally, we were inspired by a report from Inoue *et. al.*[111] as in entry 3 (Table 9), employing 1.5 equiv of iodine, PPh_3, and imidazole at –30 °C in THF for 3 h. These conditions yielded the desired product **III-83** in 67% yield, accompanied by only 15% of the cyclized product **III-82**.

Table 9 Optimization of the condition for the preparation of iodo **III-83**.



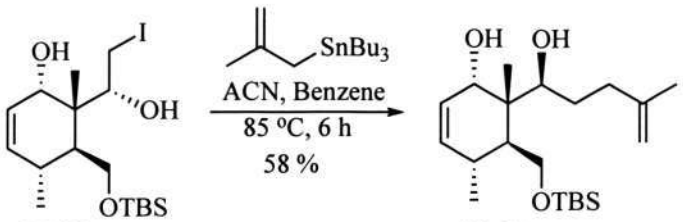
III-78 **III-83** **III-82** **III-90**

Entry	Conditions	Results[a]
1	PPh_3, imidazole, I_2 Toluene:CH_2Cl_2, 60 °C, 1 h	**III-82** (36%) and **III-90** (38%)
2	PPh_3, imidazole, I_2 CH_2Cl_2, 0 °C, 1 h	**III-83** (22%), **III-82** (9%), and **III-78** (51%)
3	PPh_3, imidazole, I_2 THF, –30 °C, 2 h	**III-83** (67%), **III-82** (15%), and **III-78** (11%)

[a] isolated yield

Having compound **III-83** in hand, our next task was to use adduct **III-83** as the starting material to synthesize the desired cyclohexenol **III-51**. By using a modification of a procedure reported by Liu and Postema,[107] compound **III-83** was treated with 2 equiv of allyltributyltin and 30 mol% of ACN as an initiator in refluxing benzene for 6 h to furnish smoothly the desired cyclohexenol **III-51** in 58% yield as shown in Scheme 55. As the major problem was the removal of organotin impurities, therefore, we used a mixture of 10% w/w finely ground KF and 90% w/w silica as the stationary phase in column chromatography for the purification in order to remove the organotin impurities, reported

by Harrowven *et al.*[112] It may be noted that during the free radical methallylation reaction no intramolecular attack on the cyclohexene double bond, presumably due to the equatorial disposition of the radical containing side-chain.



III-83 **III-51**

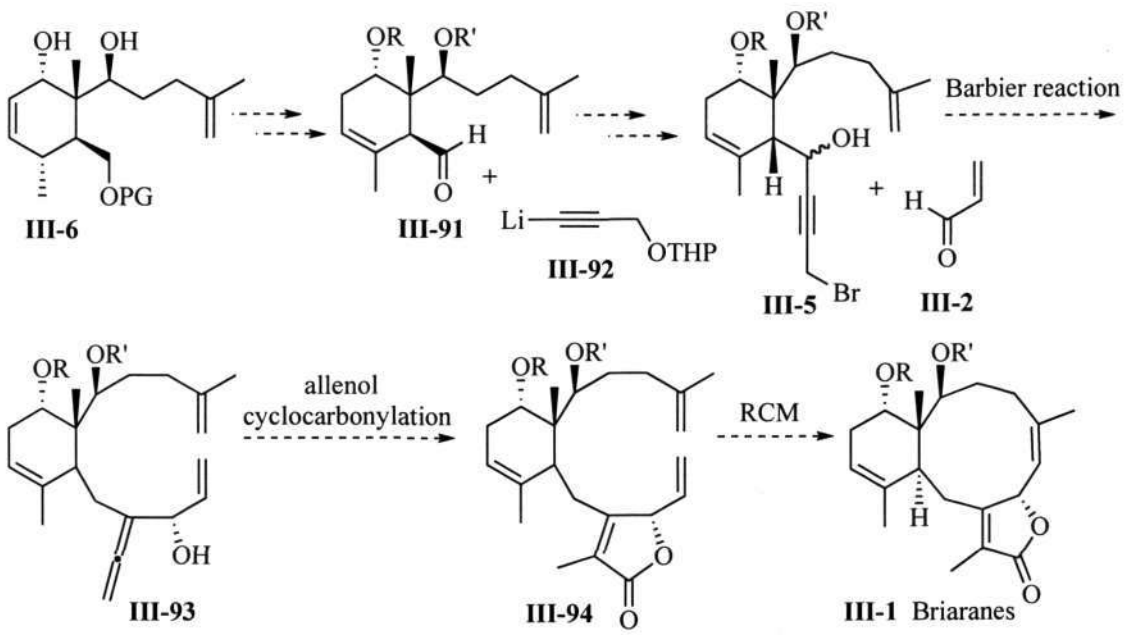
Scheme 55

CONCLUSION

The highly functionalized cyclohexenol containing the upper chain fragment **III-51** corresponding to the skeleton of the briaranes, in racemic form, has been synthesized. The six membered ring was obtained employing a sulfonyl diene Diels-Alder reaction. The Diels-Alder adduct **III-12** was further manipulated by an oxidative desulfonylation, followed by a selective reduction to give the allylic alcohol **III-46**, which was constructed the key quaternary centre of **III-47** by Eschenmoser Claisen rearrangement. The hydroxyl group was introduced to the lactone ring of **III-49**, subsequently inversion the hydroxyl stereochemistry led to the final intermediate **III-51**. After, the reduction and iodination were achieved; the upper chain was installed to iodide **III-83** by free radical Keck allylation. Work on the installation of a butenolide, and closure of the ten membered ring in order to complete the synthesis of the briaranes skeleton is in progress.

FUTURE WORK

We envisaged that the cyclohexenol **III-6** could be employed as a key building block in order to synthesis of a variety of briaranes **III-1** (Scheme 56). The cyclohexenol **III-6** will be converted to aldehyde **III-91** using conventional transformations. The aldehyde **III-91** could be coupled with the lithium derivative of the THP ether of a propargylic alcohol derivative **III-92** to give **III-5**. The butenolide might be constructed through an intramolecular propargylic Barier reaction and allenol cyclocarbonylation to give **III-94**. Finally, the macrocyclic 10-membered ring would be achieved by ring closing metathesis.



Scheme 56

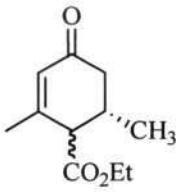
CHAPTER IV

EXPERIMENTAL

General:

The ^{1}H NMR and ^{13}C NMR (500 and 125 MHz respectively) were recorded in $CDCl_3$ solutions using a Brüker AV500. ^{1}H-NMR and ^{13}C-NMR (400 and 100 MHz respectively) were recorded in $CDCl_3$ solutions using a Jeol ECA 400, or on a Jeol ECA 400SL, or on a Brüker AV400. ^{1}H-NMR and ^{13}C-NMR (300 and 75 MHz respectively) were recorded in $CDCl_3$ solutions using a Brüker AV300. The chemical shifts are reported in δ units using $CDCl_3$ as an internal standard (δ 7.26 ppm ^{1}H, δ 77.00 ppm ^{13}C). The coupling constants *J* were recorded in Hz. The following abbreviations for the multiplicity of the peaks are s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), br (broad), m (multiplet) and app (apparent). When required, reactions were carried out under an inert atmosphere of Nitrogen in oven dried glassware. Tetrahydrofuran was distilled from sodium-benzophenone, dichloromethane, acetonitrile, and diisopropylamine were dried by distillation from CaH_2 immediately prior to use. Methanol was distilled from activated magnesium. All other solvents and reagents were used as received, or purified if required, using standard methods. Solvents were removed by using a rotary evaporator at a water-aspirator pressure. Infrared spectra were recored on a Bruker Alpha-E FT-IR, either neat or as nujol mulls. Melting points were obtained using a OptiMelt MPA100. Mass spectra were obtained on a Finnigan LCQ DECA XP MAX with ESI mode. High resolution mass spectra were obtained using a Waters Q-Tof premier also with ESI mode. Elemental analysis was carried out at Nanyang Technological University.

Preparation of ethyl (*S)-2,6-dimethyl-4-oxocyclohex-2-enecarboxylate (II-2)**



Morpholine (0.13 mL, 0.12 mmol) was added to a solution of (**II-3a**) (339.3 mg, 1.19 mmol) in THF (3.5 mL) at room temperature. A condenser and calcium sulfate dying tube were added, and the solution was heated at reflux for 20 h. After the solution was cooled, the mixture was quenched with NH_4Cl (5 mL) and extracted with Et_2O (20 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **II-2**[60] as a colourless liquid as a mixture of two diastereoisomers in a ratio of 86:14 [195.7 mg, 1.00 mmol, 84% yield].

R_f=0.53 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 2980, 1714, 1666, 1536, 1446, 1370, 1242, 1147, 1095, 1024, 934, 859, 735.

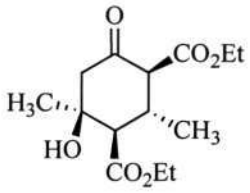
δ_H (300 MHz; $CDCl_3$) 5.97 (s, 1H, C<u>H</u>=CCH$_3$, minor), 5.94 (s, 1H, C<u>H</u>=CCH$_3$, major), 4.17 (dq, 2H, *J*=7.1, 1.8 Hz, CO$_2$C<u>H</u>$_2$CH$_3$, major and minor), 3.15 (d, 1H, *J*=5.1 Hz, C<u>H</u>CO$_2$Et, major), 2.99 (d, 1H, *J*=6.93 Hz, C<u>H</u>CO$_2$Et, minor), 2.59 (dd, 1H, *J*=16.3, 13.4 Hz, COC<u>H</u>H, major and minor), 2.49-2.31 (m, 1H, C<u>H</u>CH$_3$, major and minor), 2.14 (dd, 1H, *J*=16.3, 4.1 Hz, COCH<u>H</u>, major and minor), 1.94 (d, 3H, *J*=1.1 Hz, CH=CC<u>H</u>$_3$, major and minor), 1.25 (t, 3H, *J*=7.1 Hz, COCH$_2$C<u>H</u>$_3$, major and

minor), 1.06 (d, 3H, *J*=6.8 Hz, CHC<u>H</u>$_3$, major), 1.05 (d, 3H, *J*=6.8 Hz, CHC<u>H</u>$_3$, minor).

δ_C (75 MHz; $CDCl_3$) 199.2 (major), 199.0 (minor), 170.1 (major and minor), 156.6 (major and minor), 128.3 (major), 128.1 (minor), 61.2 (minor), 61.1 (major), 54.5 (minor), 52.3 (major), 43.1 (minor), 40.7 (major), 32.9 (minor), 32.0 (major), 23.3 (major), 22.6 (minor), 19.8 (minor), 18.5 (major), 14.3 (major), 14.2 (minor).

m/z; 197 ($M+H^+$, 100%), 162, 145, 129, 122, 118.

Preparation of diethyl (2*S,3*R**,4*R**,5*S**)-5-hydroxy-3,5-dimethyl-1-oxocyclohexane-2,4-dicarboxylate (II-3a)**



Morpholine (90 μL, 1 mmol) in ethanol (0.1 mL) was added to a mixture of ethyl acetoacetate (1.28 mL, 10 mmol) and acetaldehyde (0.28 mL, 5 mmol) at 0 °C. The reaction mixture were stirred at 0 °C for 6 h, and the contents then placed in a refrigerator. The reaction mixture was kept in a refrigerator for 3 days, and a morpholine-ethanol mixture was added each day during this time. The reaction mixture was kept in a refrigerator for an additional 1 day, the crystallization usually occurred near the end of this period, then the reaction mixture was quenched with sat. NH_4Cl (2 mL) and extracted with Et_2O (15 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of

solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **II-3a** as a colourless solid as a single isomer [818 mg, 2.86 mmol, 57% yield].

mp 77–78 °C; R_f=0.40 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3483, 1732, 1712, 1699, 1311, 1298, 1244, 1176, 1147, 1128, 1093, 1024, 825.

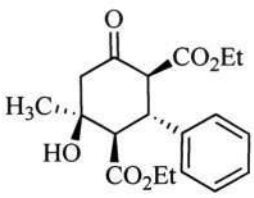
δ_H (500 MHz; $CDCl_3$) 4.19–4.31 (m, 4H, 2×$CO_2C\underline{H}_2CH_3$), 3.49 (d, 1H, *J*=3.0 Hz, OH), 3.03 (d, 1H, *J*=12.0 Hz, $COC\underline{H}CO_2Et$), 2.92 (ddq, 1H, *J*= 12.0, 11.5, 6.5 Hz, $C\underline{H}CH_3$), 2.59 (d, 1H, *J*=14.3 Hz, $COC\underline{H}H$), 2.54 (d, 1H, *J*=11.5 Hz, $C\underline{H}CO_2Et$), 2.33 (dd, 1H, *J*=14.3, 2.0 Hz, $COCH\underline{H}$), 1.33 (t, 3H, *J*=7.3 Hz, $CO_2CH_2C\underline{H}_3$), 1.28 (t, 3H, *J*= 7.3 Hz, $CO_2CH_2C\underline{H}_3$), 1.28 (s, 3H, CH_3), 1.01 (d, 3H, *J*=6.5 Hz, $CHC\underline{H}_3$).

δ_C (125 MHz; $CDCl_3$) 201.8, 174.6, 168.7, 72.9, 63.4, 61.4, 61.2, 57.1, 52.6, 33.9, 28.5, 18.6, 14.3, 14.2.

m/z; 287 (MH^+, 100%), 269, 268, 241, 223.

HRMS Found 286.1413 (M^+, $C_{14}H_{22}O_6$ requires 286.1411).

Preparation of diethyl (2*S,3*R**,4*R**,5*S**)-5-hydroxy-5-methyl-1-oxo-3-phenyl-cyclohexane-2,4-dicarboxylate (II-3b)**



Morpholine (90 μL, 1 mmol) in ethanol (0.1 mL) was added to a mixture of ethyl acetoacetate (1.28 mL, 10 mmol) and benzaldehyde (0.51 mL, 5 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 6 h, and the contents then placed in a refrigerator. The reaction mixture was kept in a refrigerator for 3 days, and a morpholine-ethanol mixture was added each day during this time. Then, the reaction mixture was kept in a refrigerator for an additional 7 days. The crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **II-3b** as a colourless solid as a single isomer [968 mg, 2.78 mmol, 56% yield] and **II-19**[63] as a colourless liquid [248.9 mg, 1.14 mmol, 11 % yield].

mp 147–149 °C; R_f=0.43 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3502, 1732, 1712, 1703, 1346, 1296, 1244, 1205, 1178, 1016, 758, 721, 700.

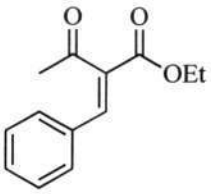
δ_H (400 MHz; $CDCl_3$) 7.33-7.25 (m, 5H, Ar-H), 4.15-3.96 (m, 3H, C<u>H</u>-Ar and $CO_2C\underline{H}_2CH_3$), 3.95-3.80 (m, 2H, $CO_2C\underline{H}_2CH_3$), 3.75 (br.s, 1H, OH), 3.70 (d, 1H, *J*=12.6 Hz, COC<u>H</u>CO_2Et), 3.05 (d, 1H, *J*=12.1 Hz, C<u>H</u>CO_2Et), 2.74 (d, 1H, *J*=14.2 Hz, COC<u>H</u>H), 2.53 (d, 1H, *J*=14.2 Hz, COCH<u>H</u>), 1.37 (s, 3H, CH_3), 1.06 (t, 3H, *J*=7.1 Hz, $CO_2CH_2C\underline{H}_3$), 0.82 (t, 3H, *J*= 7.1 Hz, $CO_2CH_2C\underline{H}_3$).

δ_C (75 MHz; $CDCl_3$) 201.3, 173.9, 167.7, 138.1, 128.6, 128.1, 127.8, 73.0, 62.5, 61.1, 61.0, 57.0, 52.7, 45.3, 28.6, 13.9, 13.6.

m/z; 331 ($M\text{-}OH^+$, 100%), 285, 259.

HRMS Found 348.1560 (M^+, $C_{19}H_{24}O_6$ requires 348.1567).

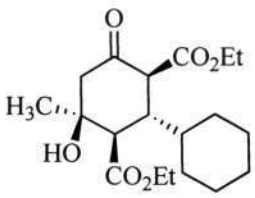
(*E*)-Ethyl 2-benzylidene-3-oxobutanoate (II-19)



δ_H (300 MHz; $CDCl_3$) 7.67 (s, 1H, CH-Ar), 7.37 (br.s, 5H, Ar-H), 4.29 (q, 2H, *J*=7.1 Hz, $CO_2C\underline{H}_2CH_3$), 2.34 (s, 3H, CH_3CO), 1.32 (t, 3H, *J*=7.1 Hz, $CO_2CH_2C\underline{H}_3$).

δ_C (75 MHz; $CDCl_3$) 203.6, 164.4, 140.5, 134.1, 132.9, 130.4, 129.7×2, 128.9×2, 61.5, 31.4, 14.4.

Preparation of diethyl (2*S,3*R**,4*R**,5*S**)-5-hydroxy-5-methyl-3-oxobi(cyclohexane)-2,4-dicarboxylate (II-3c)**



Morpholine (90 μL, 1 mmol) in ethanol (0.1 mL) was added to a mixture of ethyl acetoacetate (1.28 mL, 10 mmol) and cyclohexane carboxaldehyde (0.60 mL, 5 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 6 h, and the contents then placed in a refrigerator. The reaction mixture was kept in a refrigerator for 3 days, and a morpholine-ethanol mixture was added each day during this time. Then, the reaction mixture was kept in a refrigerator for an additional 7 days. The crude product was

purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **II-3c** as a colourless solid as a single isomer [891 mg, 2.51 mmol, 50% yield].

mp 111–112 °C; R_f=0.44 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3466, 1745, 1716, 1701, 1342, 1280, 1238, 1182, 1161, 1138, 1018, 925, 721.

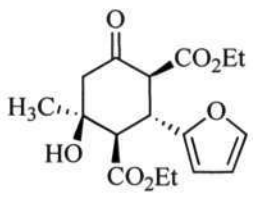
δ_H (500 MHz; $CDCl_3$) 4.28-4.12 (m, 4H, 2×$CO_2C\underline{H}_2CH_3$), 3.94 (d, 1H, *J*=12.4 Hz, $COC\underline{H}CO_2Et$), 3.09 (d, 1H, *J*=15.0 Hz, $COC\underline{H}H$), 2.92 (dd, 1H, *J*=4.8, 1.5 Hz, $C\underline{H}CO_2Et$), 2.86 (ddd, 1H, *J*=12.4, 5.6, 4.8 Hz, C<u>H</u>-cyclohexyl), 2.50 (s, 1H, OH), 2.36 (dd, 1H, *J*=15.0, 1.5 Hz, $COCH\underline{H}$), 1.77-1.52 (m, 5H, cyclohexyl-H), 1.45-1.34 (m, 1H, cyclohexyl-H), 1.31 (t, 3H, *J*=7.2 Hz, $CO_2CH_2C\underline{H}_3$), 1.29 (s, 3H, CH_3), 1.26 (t, 3H, *J*=7.2 Hz, $CO_2CH_2C\underline{H}_3$), 1.25-1.17 (m, 2H, cyclohexyl-H), 0.87-0.76 (m, 1H, cyclohexyl-H).

δ_C (100 MHz; $CDCl_3$) 206.4, 173.6, 170.6, 73.3, 61.0, 60.8, 57.1, 51.5, 50.2, 42.2, 40.4, 30.9, 28.6, 28.5, 26.94, 26.87, 26.5, 14.2, 14.1.

m/z; 337, 291 ($M-63^+$, 100%).

HRMS Found 354.2032 (M^+, $C_{19}H_{30}O_6$ requires 354.2037).

Preparation of diethyl (2*S,3*R**,4*R**,5*S**)-3-(furan-2-yl)-5-hydroxy-5-methyl-1-oxocyclohexane-2,4-dicarboxylate (II-3d)**



Morpholine (90 μL, 1 mmol) in ethanol (0.1 mL) was added to a mixture of ethyl acetoacetate (1.28 mL, 10 mmol) and 2-furaldehyde (0.41 mL, 5 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 6 h, and the contents then placed in a refrigerator. The reaction mixture was kept in a refrigerator for 3 days, and a morpholine-ethanol mixture was added each day during this time. Then, the reaction mixture was kept in a refrigerator for an additional 4 days. The crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **II-3d** as a colourless solid [1.61 g, 4.76 mmol, 48% yield] and **II-3d'** as a colourless solid [179 mg, 0.53 mmol, 5% yield].

mp 76–77 °C; R_f=0.49 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3508, 1735, 1712, 1506, 1340, 1296, 1259, 1209, 1178, 1159, 1012, 852, 738.

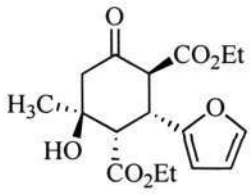
δ_H (500 MHz; $CDCl_3$) 7.34 (d, 1H, *J*=1.9 Hz, furan-H), 6.23 (dd, 1H, *J*=3.2, 1.9 Hz, furan-H), 6.09 (d, 1H, *J*=3.2 Hz, furan-H), 4.18-3.97 (m, 5H, 2×$CO_2C\underline{H}_2CH_3$ and C<u>H</u>-furan), 3.72 (d, 1H, *J*=12.4 Hz, COC<u>H</u>CO_2Et), 3.66 (d, 1H, *J*=2.8 Hz, OH), 3.13 (d, 1H, *J*=12.2 Hz, C<u>H</u>CO_2Et), 2.66 (d, 1H, *J*=14.4 Hz, COC<u>H</u>H), 2.45 (dd, 1H, *J*=14.4, 2.8 Hz, COCH<u>H</u>), 1.32 (s, 3H, CH_3), 1.14 (t, 3H, *J*=7.1 Hz, $CO_2CH_2C\underline{H}_3$), 1.05 (t, 3H, *J*=7.1 Hz, $CO_2CH_2C\underline{H}_3$).

δ_C (100 MHz; $CDCl_3$) 200.8, 173.9, 167.7, 151.7, 142.5, 110.2, 107.8, 72.6, 61.3, 61.2, 60.1, 54.8, 52.6, 39.1, 28.4, 14.0, 13.9.

m/z; 339 ($M+H^+$, 100%), 321, 311, 293.

HRMS Found 338.1362 (M^+, $C_{17}H_{22}O_7$ requires 338.1360).

Preparation of diethyl (2*S,3*R**,4*S**,5*S**)-3-(furan-2-yl)-5-hydroxy-5-methyl-1-oxocyclohexane-2,4-dicarboxylate (II-3d')**



mp 117–118 °C; R_f=0.43 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3419, 1741, 1742, 1701, 1332, 1197, 1184, 1136, 1116, 1037, 1018, 921, 748.

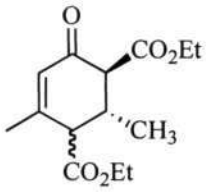
δ_H (500 MHz; $CDCl_3$) 7.30 (dd, 1H, *J*=1.8, 0.8 Hz, furan-H), 6.24 (dd, 1H, *J*=3.3, 1.8 Hz, furan-H), 6.07 (dd, 1H, *J*=3.3, 0.8 Hz, furan-H), 4.34-4.27 (m, 2H, $COC\underline{H}_2$), 4.14 (dq, 2H, *J*=10.7, 7.2 Hz, $CO_2C\underline{H}_2CH_3$), 4.02 (dq, 2H, *J*=10.7, 7.2 Hz, $CO_2C\underline{H}_2CH_3$), 3.30 (d, 1H, *J*=14.5 Hz, $COC\underline{H}CO_2Et$), 3.18 (dd, 1H, *J*=4.3, 1.7 Hz, $C\underline{H}CO_2Et$), 2.44 (dd, 1H, *J*=14.5, 1.7 Hz, C<u>H</u>-furan), 2.32 (s, 1H, OH), 1.35 (s, 3H, CH_3), 1.16 (t, 3H, *J*=7.2 Hz, $CO_2CH_2C\underline{H}_3$), 1.09 (t, 3H, *J*=7.2 Hz, $CO_2CH_2C\underline{H}_3$).

δ_C (100 MHz; $CDCl_3$) 204.0, 171.9, 169.0, 152.9, 141.9, 110.2, 106.5, 73.6, 61.1, 60.9, 56.2, 55.1, 50.6, 37.5, 28.5, 14.1, 13.9.

m/z; 321, 311, 293.

HRMS Found 338.1362 (M^+, $C_{17}H_{22}O_7$ requires 338.1360).

Preparation of diethyl (1*S, 2*R**)-2,4-dimethyl-6-oxocyclohex-4-ene-1,3-dicarboxylate (II-22)**



LiCl (43.7 mg, 1.03 mmol) was added to a mixture of (**II-3a**) (276.6 mg, 1.03 mmol) in DMSO (1.5 mL) and H_2O (20 μL) at room temperature. A condenser and calcium sulfate dying tube were added, and the solution was heated at 100 °C for 20 h. After the solution was cooled, the mixture was quenched with H_2O (3 mL) and extracted with Et_2O (15 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **II-22** as a colourless liquid as a mixture of two diastereoisomers in a ratio of 36:64 [158.4 mg, 0.59 mmol, 57% yield].

R_f=0.46 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 2979, 1732, 1671, 1443, 1379, 1347, 1253, 1174, 1095, 1028, 849.

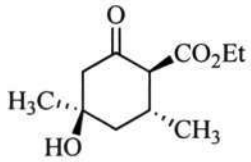
δ_H (300 MHz; $CDCl_3$) 5.96 (app.d, 1H, *J*=1.4 Hz, C<u>H</u>=CCH$_3$, major and minor), 4.23 (q, 4H, *J*=7.1 Hz, CO$_2$C<u>H</u>$_2$CH$_3$, major and minor), 3.17 (d, 1H, *J*=5.1 Hz, C<u>H</u>CO$_2$Et, minor), 3.01 (d, 1H, *J*=7.0 Hz, C<u>H</u>CO$_2$Et, major), 2.58 (d, 1H, *J*=12.3 Hz, COC<u>H</u>CO$_2$Et, minor), 2.57 (d, 1H, *J*=13.0 Hz, COC<u>H</u>CO$_2$Et, major), 2.33-2.18 (m, 1H, C<u>H</u>CH$_3$, major), 2.17-2.03 (m, 1H, C<u>H</u>CH$_3$, minor), 1.95 (s, 3H, CH$_3$, major and minor), 1.29 (d, 6H, *J*=6.7 Hz, 2×CO$_2$CH$_2$C<u>H</u>$_3$, major), 1.28 (d, 6H, *J*=7.1 Hz,

2×$CO_2CH_2C\underline{H}_3$, minor), 1.09 (d, 3H, *J*=6.7 Hz, $CHC\underline{H}_3$, minor), 1.07 (d, 3H, *J*=6.5 Hz, $CHC\underline{H}_3$, major).

δ_C (125 MHz; $CDCl_3$) 197.8 (major), 196.7 (minor), 175.4 (major), 173.2 (minor), 171.8 (major), 170.1 (minor), 156.6 (minor), 155.9 (major), 128.1 (minor), 127.9 (major), 83.6 (major and minor), 61.1 (major and minor), 61.0 (major and minor), 56.2 (minor), 54.3 (major), 52.1 (major), 51.9 (minor), 33.4 (major and minor), 31.9 (major and minor), 23.2 (minor), 22.6 (major), 19.7 (major), 18.4 (minor).

m/z; 269 ($M+H^+$, 100%), 240, 222, 196, 154, 129, 122.

Preparation of ethyl (2*S,3*R**,5*R**)-5-hydroxy-3,5-dimethyl-1-oxocyclohexane-2-carboxylate (II-38a)**



Potassium carbonate (276 mg, 2 mmol) was added to a stirred solution of ethyl acetoacetate (1.28 mL, 10 mmol) and (*E*)-pent-3-en-2-one (0.98 mL, 10 mmol) in ethanol (2 mL) at 20 °C (water bath). The reaction mixture was stirred at that temperature for 20 h, then the reaction mixture was quenched with sat. NH_4Cl (5 mL) and extracted with Et_2O (20 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **II-38a** as a colourless solid as a single isomer [1.78 g, 8.32 mmol, 83% yield].

mp 101–102 °C; R_f=0.27 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3421, 1732, 1697, 1408, 1355, 1323, 1278, 1253, 1176, 1130, 1026, 920.

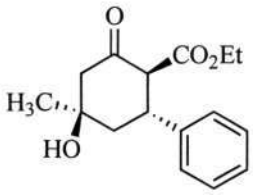
δ_H (500 MHz; $CDCl_3$) 4.29 (dq, 1H, *J*=10.7, 7.2 Hz, CO_2CHHCH_3), 4.23 (dq, 1H, *J*=10.7, 7.2 Hz, CO_2CHHCH_3), 2.97 (d, 1H, *J*=12.0 Hz, $COCHCO_2Et$), 2.73-2.64 (m, 1H, $CHCH_3$), 2.49-2.37 (m, 2H, $COCH_2$), 1.93 (dt, 1H, *J*=14.0, 2.6 Hz, $CHHCHCH_3$), 1.54 (dd, 1H, *J*=14.0, 12.6 Hz, $CHHCHCH_3$), 1.36 (s, 3H, CH_3), 1.28 (t, 3H, *J*=7.2 Hz, $CO_2CH_2CH_3$), 1.04 (d, 3H, *J*=6.5 Hz, $CO_2CH_2CH_3$).

δ_C (125 MHz; $CDCl_3$) 204.7, 169.6, 73.1, 64.3, 61.0, 53.7, 45.3, 31.4, 30.8, 20.5, 14.2.

m/z; 215, 197 ($M\text{-}OH^+$, 100%), 196, 169.

HRMS Found 214.1203 (M^+, $C_{11}H_{18}O_4$ requires 214.1200).

Preparation of ethyl (2*S,3*R**,5*R**)-5-hydroxy-5-methyl-1-oxo-3-phenylcyclo hexane-2-carboxy-late (II-38b)**



Potassium carbonate (152 mg, 1.10 mmol) was added to a stirred solution of ethyl acetoacetate (0.70 mL, 5.51 mmol) and (*E*)-4-phenylbut-3-en-2-one (806 mg, 5.51 mmol) in ethanol (1.5 mL) at 20 °C (water bath). The reaction mixture was stirred at that temperature for 20 h. The crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **II-38b** as a colourless solid as a single isomer [1.28 g, 4.62 mmol, 84% yield].

mp 158–159 °C; R_f=0.31 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3431, 1730, 1701, 1315, 1244, 1151, 1095, 1076, 1018, 923, 754, 700.

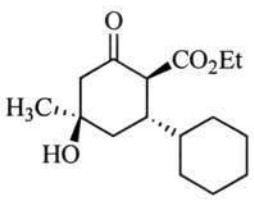
δ_H (500 MHz; $CDCl_3$) 7.35-7.23 (m, 5H, Ar-H), 4.12-4.00 (m, 2H, $CO_2C\underline{H}_2CH_3$), 3.88 (td, 1H, *J*= 12.6, 4.1 Hz, C<u>H</u>-Ar), 3.65 (d, 1H, *J*=12.6 Hz, COC<u>H</u>CO_2Et), 2.65 (d, 1H, *J*=14.2 Hz, COC<u>H</u>H), 2.60 (dd, 1H, *J*=14.2, 2.2 Hz, COCH<u>H</u>), 2.17-2.08 (m, 1H, C<u>H</u>HCH-Ar), 2.04 (app.t, 1H, *J*=13.4 Hz, CH<u>H</u>CH-Ar), 1.72 (s, 1H, OH), 1.44 (s, 3H, CH_3), 1.08 (t, 3H, *J*=7.1 Hz, $CH_2C\underline{H}_3$).

δ_C (125 MHz; $CDCl_3$) 203.9, 168.6 141.6, 128.7, 127.3, 127.1, 73.2, 62.9, 60.9, 53.9, 45.6, 42.3, 30.9, 14.0.

m/z; 277 (MH^+, 100%), 276, 259, 258.

HRMS Found 276.1350 (M^+, $C_{16}H_{20}O_4$ requires 276.1356).

Preparation of ethyl (2*S,3*S**,5*R**)-5-hydroxy-5-methyl-3-oxobi(cyclohexane)-2-carboxylate (II-38c)**



Potassium carbonate (50 mg, 0.36 mmol) was added to a stirred solution of ethyl acetoacetate (0.23 mL, 1.80 mmol) and (*E*)-4-cyclohexylbut-3-en-2-one (274 mg, 1.80 mmol) in ethanol (1 mL) at 20 °C (water bath). The reaction mixture was stirred at that temperature for 20 h. The crude product was purified by column

chromatography (SiO_2, 25% EtOAc in hexanes) to give **II-38c** as a colourless solid as a single isomer [437 mg, 1.55 mmol, 86% yield].

mp 135–136 °C; R_f=0.40 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3427, 1728, 1679, 1319, 1276, 1267, 1238, 1184, 1159, 1045, 1022, 929, 721.

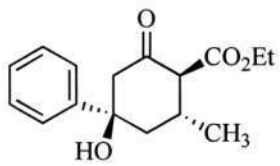
δ_H (300 MHz; $CDCl_3$) 4.25 (q, 2H, *J*=7.1 Hz, $CO_2C\underline{H}_2CH_3$), 3.26 (d, 1H, *J*=12.6 Hz, $COC\underline{H}CO_2Et$), 2.60 (tt, 1H, *J*=12.6, 3.0 Hz, C<u>H</u>-cylohexyl), 2.47 (dd, 1H, *J*=14.1, 2.2 Hz, $COC\underline{H}H$), 2.40 (d, 1H, *J*=14.1 Hz, $COCH\underline{H}$), 1.96-1.50 (m, 7H, $C\underline{H}_2CH$-cyclohexyl, cyclohexyl-<u>H</u>), 1.37 (s, 3H, CH_3), 1.28 (t, 3H, *J*=7.1 Hz, $CO_2CH_2C\underline{H}_3$), 1.27-0.90 (m, 6H, cyclohexyl-<u>H</u>).

δ_C (75 MHz; $CDCl_3$) 205.6, 169.8, 72.9, 60.8, 60.5, 53.9, 40.8, 40.4, 37.6, 31.6, 31.1, 26.9 (2C), 26.7, 26.6, 14.2.

m/z; 283, 265 ($M\text{-}OH^+$, 100%), 237, 219.

HRMS Found 282.1828 (M^+, $C_{16}H_{26}O_4$ requires 282.1826).

Preparation of ethyl (2*S,3*R**,5*R**)-5-hydroxy-3-methyl-1-oxo-5-phenylcyclohexanecarboxylate (II-38d)**



Potassium carbonate (53 mg, 0.39 mmol) was added to a stirred solution of ethyl acetoacetate (0.25 mL, 1.93 mmol) and (*E*)-1-phenylbut-2-en-1-one (283 mg,

1.93 mmol) in ethanol (0.5 mL) at 20 °C (water bath). The reaction mixture was stirred at that temperature for 20 h. The crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **II-38d** as a colourless solid as a single isomer [344 mg, 1.24 mmol, 64% yield].

mp 125–126 °C; R_f=0.53 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3415, 1737, 1703, 1355, 1323, 1273, 1249, 1170, 1143, 1093, 1031, 1012, 698.

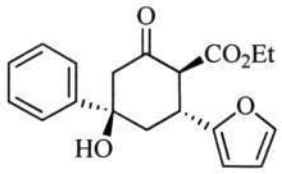
δ_H (500 MHz; $CDCl_3$) 7.50-7.42 (m, 2H, Ar-H), 7.41-7.33 (m, 2H, Ar-H), 7.29 (tt, 1H, *J*=7.3, 1.4 Hz, Ar-H), 4.27 (dq, 1H, *J*=10.8, 7.2 Hz, $CO_2C\underline{H}HCH_3$), 4.22 (dq, 1H, *J*=10.8, 7.2 Hz, $CO_2CH\underline{H}CH_3$), 3.12 (d, 1H, *J*=12.0 Hz, $COC\underline{H}CO_2Et$), 2.94-2.80 (m, 1H, $C\underline{H}CH_3$), 2.89 (d, 1H, *J*=14.1 Hz, $COC\underline{H}H$), 2.63 (dd, 1H, *J*=14.1, 2.8 Hz, $COCH\underline{H}$), 2.33 (s, 1H, OH), 2.11 (ddd, 1H, *J*=13.7, 3.8, 2.8 Hz, $C\underline{H}HCHCH_3$), 1.93 (td, 1H, *J*=13.7, 1.1 Hz, $CH\underline{H}CHCH_3$), 1.28 (t, 3H, *J*=7.2 Hz, $CO_2CH_2C\underline{H}_3$), 1.08 (d, 3H, *J*=6.6 Hz, $CHC\underline{H}_3$).

δ_C (100 MHz; $CDCl_3$) 204.3, 169.5, 146.3, 128.7, 127.6, 124.2, 76.4, 64.4, 61.1, 53.3, 45.7, 31.6, 20.5, 14.2.

m/z; 259 ($M\text{-}OH^+$, 100%), 231.

HRMS Found 276.1355 (M^+, $C_{16}H_{20}O_4$ requires 276.1356).

Preparation of ethyl (2*S,3*R**,5*R**)-3-(furan-2-yl)-5-hydroxy-1-oxo-5-phenylcyclohexane carboxylate (II-38e)**



Potassium carbonate (276 mg, 2 mmol) was added to a stirred solution of ethyl acetoacetate (1.28 mL, 10 mmol) and (*E*)-3-(furan-2-yl)-1-phenylpropyl-2-en-1-one (1.98 g, 10 mmol) in ethanol (2 mL) at 20 °C (water bath). The reaction mixture was stirred at that temperature for 20 h. The crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **II-38e** as a colourless solid as a single isomer [2.42 g, 7.36 mmol, 74% yield] and **II-41** as a colourless solid [347 mg, 1.12 mmol, 11% yield].

mp 141–142 °C; R_f=0.53 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3400, 1735, 1707, 1280, 1259, 1184, 1149, 1029, 1014, 985, 779, 759, 702.

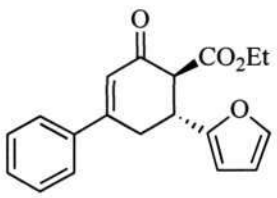
δ_H (500 MHz; $CDCl_3$) 7.57-7.45 (m, 2H, Ar-H), 7.38 (app.t, 2H, *J*=7.7 Hz, Ar-H), 7.35-7.27 (m, 2H, Ar-H and furan-H), 6.26 (dd, 1H, *J*=3.2, 1.9 Hz, furan-H), 6.10 (d, 1H, *J*=3.2 Hz, furan-H), 4.22-4.08 (m, 3H, $C\underline{H}_2CH_3$ and C<u>H</u>-furan), 3.72 (d, 1H, *J*=12.3 Hz, $COC\underline{H}CO_2Et$), 3.01 (d, 1H, *J*=14.1 Hz, COC<u>H</u>H), 2.72 (dd, 1H, *J*=14.1, 2.7 Hz, COCH<u>H</u>), 2.57 (s, 1H, OH), 2.45 (dd, 1H, *J*=14.1, 12.7 Hz, C<u>H</u>HCH-furan), 2.35 (ddd, 1H, *J*=14.1, 4.0, 2.7 Hz, CH<u>H</u>CH-furan), 1.18 (t, 3H, *J*=7.1 Hz, $CO_2CH_2C\underline{H}_3$).

δ_C (100MHz; $CDCl_3$) 203.3, 168.8, 154.8, 145.9, 141.8, 128.7, 127.8, 124.3, 110.2, 105.9, 75.9, 61.2, 61.0, 53.4, 42.6, 36.1, 14.1.

m/z; 311 ($M\text{-}OH^+$, 100%), 243, 205.

HRMS Found 328.1306 (M^+, $C_{19}H_{20}O_5$ requires 328.1305).

Ethyl (2*S,3*R**)-5-(furan-2-yl)-1-oxo-3-phenylcyclohex-2-ene-6-carboxylate (II-41)**



mp 92–93 °C; R_f=0.60 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 1734, 1660, 1165, 767, 688;

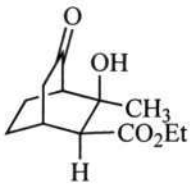
δ_H (500 MHz; $CDCl_3$) 7.60-7.51 (m, 2H, Ar-H), 7.48-7.38 (m, 3H, Ar-H), 7.36 (dd, 1H, *J*=1.8, 0.7 Hz, furan-H), 6.53 (d, 1H, *J*=2.0 Hz, COCH=C), 6.30 (dd, 1H, *J*=3.2, 1.8 Hz, furan-H), 6.15 (d, 1H, *J*=3.2 Hz, furan-H), 4.19 (q, 2H, *J*=7.1 Hz, $CO_2C\underline{H}_2CH_3$), 3.96 (ddd, 1H, *J*=11.7, 10.4, 4.8 Hz, CH-furan), 3.74 (d, 1H, *J*=11.7 Hz, $COC\underline{H}CO_2Et$), 3.20 (dd, 1H, *J*=18.1, 4.8 Hz, $C\underline{H}HCH$-furan), 3.08 (ddd, 1H, *J*=18.1, 10.4, 2.0 Hz, $CH\underline{H}CH$-furan), 1.21 (t, 3H, *J*=7.1 Hz, $CO_2CH_2C\underline{H}_3$).

δ_C (100MHz; $CDCl_3$) 193.3, 169.3, 158.3, 154.2, 142.0, 137.7, 130.6, 128.9, 126.2, 124.1, 110.3, 106.2, 61.3, 57.5, 37.3, 32.5, 14.1.

m/z; 311 ($M\text{-}H^+$, 100%), 243, 108.

HRMS Found 310.1204 (M^+, $C_{19}H_{18}O_4$ requires 310.1205).

Preparation of ethyl (1*R,2*S**,3*R**,4*R**)-3-hydroxy-3-methyl-5-oxobicyclo-[2.2.2]octane-2-carboxylate (II-45)**



Potassium carbonate (276 mg, 2 mmol) was added to a stirred solution of ethyl acetoacetate (1.28 mL, 10 mmol) and cyclohexenone (0.97 mL, 10 mmol) in ethanol (2 mL) at 20 °C (water bath). The reaction mixture was stirred at that temperature for 20 h. The crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **II-45** as a colourless solid as a single isomer [693 mg, 3.06 mmol, 31% yield] and **II-44**[73] as a colourless liquid as a mixture of two diastereoisomers in a ratio of 72:38 [1.53 g, 6.77 mmol, 68% yield].

mp 129–130 °C (80 °C)[73] ; R_f=0.41 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3352, 1734, 1707, 1402, 1327, 1211, 1197, 1168, 1157, 1114, 1043, 864, 829.

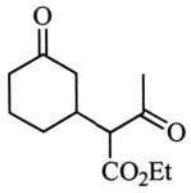
δ_H (500 MHz; $CDCl_3$) 4.19 (q, 2H, *J*=7.1 Hz, $C\underline{H}_2CH_3$), 3.09 (s, 1H, OH), 2.78 (dt, 1H, *J*=18.9, 2.5 Hz), 2.58-2.52 (m, 2H), 2.28 (app.t, 1H, *J*= 3.0 Hz), 2.09 (ddd, 1H, *J*=18.9, 3.3, 2.1 Hz), 1.82-1.73 (m, 2H), 1.68-1.60 (m, 1H), 1.55 (s, 3H, CH_3), 1.54 (m, 1H), 1.27 (t, 3H, *J*=7.1 Hz, $CH_2C\underline{H}_3$).

δ_C (100MHz; $CDCl_3$) 214.1, 172.0, 72.6, 60.8, 55.7, 52.3, 40.5, 30.6, 27.7, 25.4, 19.7, 14.3.

m/z; 227, 226, 209 ($M\text{-}OH^+$, 100%), 181.

HRMS Found 226.1207 (M^+, $C_{12}H_{18}O_4$ requires 226.1200).

Ethyl 3-oxo-2-(3-oxocyclohexyl)butanoate (II-44)



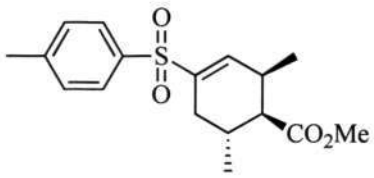
R_f=0.57 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 2937, 1708, 1646, 1448, 1357, 1278, 1215, 1152, 1090, 1040, 911, 841.

δ_H (500 MHz; $CDCl_3$) 4.29-4.15 (m, 4H, $C\underline{H}_2CH_3$, major and minor), 3.55 (d, 1H, *J*=13.6 Hz, $C\underline{H}CO_2Et$, major), 3.37 (d, 1H, *J*=18.2 Hz, $C\underline{H}CO_2Et$, minor), 2.65-2.51 (m, 2H, major and minor), 2.48-2.12 (m, 8H, major and minor), 2.22 (s, 3H, $COCH_3$, major), 2.20 (s, 3H, $COCH_3$, minor), 2.11-1.98 (m, 2H, major and minor), 1.95-1.62 (m, 2H, major and minor), 1.60-1.37 (m, 4H, major and minor), 1.36-1.17 (m, 6H, $CH_2C\underline{H}_3$, major and minor).

m/z; 243 ($M+Na^+$), 226 (M^+, 100%), 208, 170, 130.

Preparation of methyl (1*S,2*S**,6*R**)-2,6-dimethyl-4-tosylcyclohex-3-enecarboxylate (III-12)**



$AlCl_3$ (9.53 g, 71.45 mmol), CH_2Cl_2 (70 mL) and methyl crotonate (7.6 mL, 71.45 mmol) were mixed together and stirred under nitrogen until a homogeneous solution was formed. A 57 mM solution (250 mL) of (**III-13**) (14.29 mmol) in CH_2Cl_2 (6.6 mL) was then concentrated to a volume of 125 mL on a rotary evaporator and added to the first solution during 5 min. The reaction was heated under reflux at 100 °C for 7 days, then the reaction was cooled to 0 °C, quenched with sat NH_4Cl (50 mL) and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-12** as a colourless solid [2.86 g, 8.86 mmol, 62% yield] and **III-21** as a colourless solid [0.33 g, 0.74 mmol, 5% yield].

mp 95–96°C; R_f=0.26 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 2954, 2931, 1732, 1651, 1597, 1454, 1435, 1371, 1300, 1220, 1145, 1089, 1010, 906, 815, 665.

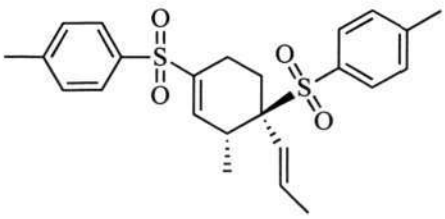
δ_H (500 MHz; $CDCl_3$) 7.70 (d, 2H, *J*=8.2 Hz, Ar-H), 7.31 (d, 2H, *J*=8.2 Hz, Ar-H), 6.92 (app.d, 1H, *J*=3.9 Hz, SO_2C=C<u>H</u>), 3.64 (s, 3H, OCH_3), 2.85-2.74 (m, 1H, C=CHC<u>H</u>CH_3), 2.42 (s, 3H, CH_3), 2.35 (app.t, 1H, *J*=6.1 Hz, C<u>H</u>CO_2CH_3), 2.33 (app.d, 1H, *J*=5.6 Hz, SO_2CC<u>H</u>H), 2.10-1.93 (m, 1H, CH_2C<u>H</u>CH_3), 1.73 (dddd, 1H, *J*=16.8, 9.6, 2.1, 2.1 Hz, SO_2CCH<u>H</u>), 0.98 (d, 3H, *J*=7.3 Hz, CH_3), 0.96 (d, 3H, *J*=6.5 Hz, CH_3).

δ_C (75 MHz; $CDCl_3$) 173.3, 144.3, 140.4, 138.3, 136.1, 129.8×2, 128.0×2, 51.4, 49.2, 31.9, 30.3, 25.5, 21.6, 19.6, 16.1.

m/z; 345 ($M+Na^+$, 100%), 323, 281, 139.

Anal. Calcd. for $C_{17}H_{22}O_4S$: C, 63.33; H, 6.88. Found: C, 63.12; H, 6.98.

Preparation of (3*S, 4*S**)-3-methyl-4-((*E*)-prop-1-enyl)-1,4-tosylcyclohex-1-ene (III-21)**



mp 142–143°C; R_f=0.13 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 1645, 1595, 1288, 1151, 1139, 1091, 970, 800, 707, 655, 594.

δ_H (300 MHz; $CDCl_3$) 7.66 (d, 2H, *J*=8.2 Hz, Ar-H), 7.54 (d, 2H, *J*=8.2 Hz, Ar-H), 7.26 (app.t, 4H, *J*=7.9 Hz, Ar-H), 6.74 (app.d, 1H, *J*=2.4 Hz, SO_2C=C<u>H</u>), 5.51 (dd, 1H, *J*=16.0, 1.3 Hz, C<u>H</u>=CHCH_3), 5.30 (dq, 1H, *J*=16.0, 6.3 Hz, CH=C<u>H</u>CH_3), 3.35-3.15 (m, 1H,

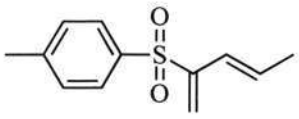
C<u>H</u>CH_3), 2.38 (s, 6H, CH_3×2), 2.28-2.00 (m, 2H, SO_2CCH_2), 1.97-1.78 (m, 2H, $SO_2CCH_2C\underline{H}_2$), 1.61 (dd, 3H, *J*=6.3, 1.3 Hz, CH=CHC<u>H</u>$_3$), 1.39 (d, *J*=7.4 Hz, CH_3).

δ_C (75 MHz; $CDCl_3$) 144.9, 144.3, 141.1, 137.7, 135.8, 133.2, 131.9, 130.6, 129.7×2, 129.1×2, 127.9×2, 121.9×2, 67.8, 33.8, 25.6, 21.59, 21.56, 20.5, 18.5, 16.8.

m/z; 467 ($M+Na^+$, 100%) 445, 413, 391, 363, 287, 205, 167, 149, 131.

Anal. Calcd. for $C_{24}H_{28}O_4S_2$: C, 64.38; H, 6.53. Found: C, 64.72; H, 6.54.

Preparation of (*E*)-1-methyl-4-(penta-1,3-dien-2-ylsulfonyl)benzene (III-13)



To a suspension of 2-(tosylmethyl)but-2-en-1-ol (**III-19**) (3.43 g, 14.29 mmol) in dichloromethane (42 mL) was added triethylamine (4.0 mL, 28.58 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 30 min, then methansulfonyl chloride (2.2 mL, 28.6 mmol) was added dropwise by syringe. A formation of a white precipitate was observed after short time. The reaction mixture was slowly warmed up to room temperature and stirred for an additional for 4 h. The reaction mixture was quenched with H_2O (30 mL) and extracted with CH_2Cl_2 (100 mL × 2). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. The product was usually used in reaction within a few hours, but it can be stored in solution with molecular sieve in a freezer (–78 °C) for several days (<5% dimerization). Since the sulfonyldiene

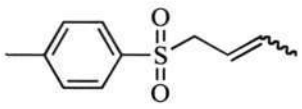
III-13 is reactive toward Diels-Alder dimerization it was kept at low concentration (60 mM) and normally was used for Diels-Alder reaction without purification.

R_f=0.33 (25% ethyl acetate/hexane).

δ_H (400 MHz; $CDCl_3$) 7.72 (app.d, 2H, *J*=7.9 Hz, Ar-H), 7.32 (app.d, 2H, *J*=7.9 Hz, Ar-H), 6.17 (br.s, 1H, C=C<u>H</u>H), 6.13 (dq, 1H, *J*=15.8, 6.5 Hz, CH=C<u>H</u>CH_3), 6.01 (app.d, 1H, *J*=15.8 Hz, C<u>H</u>=$CHCH_3$), 5.83 (br.s, 1H, C=CH<u>H</u>), 2.42 (s, 3H, Ar-CH_3), 1.74 (d, 3H, *J*=6.5 Hz, CH_3).

δ_C (75 MHz; $CDCl_3$) 148.4, 144.4, 136.4, 133.5, 129.7×3, 128.0, 121.9, 121.3, 21.5, 18.5.

Preparation of 1-(but-2-enylsulfonyl)-4-methylbenzene (III-18)



The allylic *p*-tolyl sulphones (**III-18**) were prepared by reaction of the corresponding *cis*,*trans*-crotyl chloride (7.86 mL, 80.12 mmol) was added to a suspension of sodium *p*-toluenesulfinate (15.77 g, 88.18 mmol) and tetrabutyl ammonium bromide (1.29 g, 4.00 mmol) in dimethylformamide (70 mL). The reaction was heated under reflux at 90 °C for 30 min, then cooled the reaction to room temperature, the reaction mixture was quenched with water (20 mL) and extracted with Et_2O (50 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column

chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-18** as a colourless solid as a mixture of the *E* and *Z* isomers in a ratio of 72:28 [14.41 g, 68.53 mmol, 86% yield].

mp 32–34 °C; R_f=0.26 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 1666, 1597, 1433, 1396, 1315, 1300, 1143, 1087, 968, 929, 815, 723, 624.

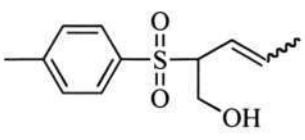
δ_H (400 MHz; $CDCl_3$) 7.86 (d, 2H, *J*=8.1 Hz, Ar-H, cis and trans), 7.29 (d, 2H, *J*=8.1 Hz, Ar-H, cis and trans), 5.77 (dq, 1H, *J*=10.8, 7.0 Hz, C<u>H</u>CH_3, cis), 5.52 (dq, 1H, *J*=15.3, 6.4 Hz, C<u>H</u>CH_3, trans), 5.36 (dtq, 1H, *J*=15.3, 7.3, 1.5 Hz, C<u>H</u>=$CHCH_3$, cis and trans), 3.79 (d, 2H, *J*=7.9 Hz, SO_2CH_2, cis), 3.67 (d, 2H, *J*=7.3 Hz, SO_2CH_2, trans), 2.39 (s, 3H, CH_3, cis and trans), 1.62 (app.d, 3H, *J*=6.4 Hz, CH_3, trans), 1.31 (app.d, 3H, *J*=7.0 Hz, CH_3, cis).

δ_C (100 MHz; $CDCl_3$) 144.6, 136.3, 135.6, 129.6×2, 128.4×2, 117.1, 60.1, 21.6, 18.1;

m/z; 211 ($M+H^+$, 100%), 210, 195.

HRMS Found 211.0785 ($M+H^+$, $C_{11}H_{14}O_2S$ requires 211.0793).

Preparation of 2-tosylpent-3-en-1-ol (III-19)



The 2-(tosylmethyl)but-2-en-1-ol (**III-19**) was prepared by reaction of a suspension of allylic *p*-tolyl sulphones (**III-18**) (4.91 g, 23.36 mmol) and formaldehyde (1.40 g, 46.72 mmol) in THF (70 mL) with a solution of ^{n}BuLi (21.80 mL, 32.71 mmol),

which was added over 5 min at –78 °C under nitrogen. After stirring at this temperature for 1 h, the reaction was gradually raised up to –25 °C over a period of 5 h. The reaction mixture was quenched with NH_4Cl (30 mL) and extracted with Et_2O (50 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give **III-19** as a colourless liquid as a mixture of the *E* and *Z* isomers in a ratio of 64:36 [3.60 g, 14.98 mmol, 64% yield].

R_f=0.25 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3458, 3030, 2920, 1643, 1597, 1494, 1444, 1300, 1141, 966, 815, 709.

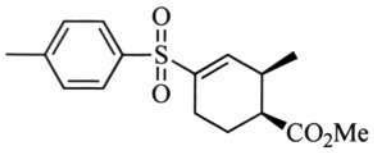
δ_H (400 MHz; $CDCl_3$) 7.73 (d, 2H, *J*=8.2 Hz, Ar-H, cis), 7.70 (d, 2H, *J*=8.2 Hz, Ar-H, trans), 7.34 (d, 2H, *J*=8.2 Hz, Ar-H, cis and trans), 5.81 (dq, 1H, *J*=10.8, 7.0 Hz, C<u>H</u>CH_3, cis), 5.54 (dq, 1H, *J*=15.3, 6.5 Hz, C<u>H</u>CH_3, trans), 5.53-5.10 (m, 1H, C<u>H</u>=$CHCH_3$, cis and trans), 4.30-3.60 (m, 2H, C<u>H_2</u>OH, cis and trans), 2.98 (dt, 1H, *J*=4.6, 3.1 Hz, SO_2CH_2, cis), 2.88 (dt, 1H, *J*=5.6, 2.1 Hz, SO_2CH_2, trans), 2.45 (s, 3H, CH_3, cis and trans), 1.66 (dd, 3H, *J*=6.5, 1.4 Hz, CH_3, trans), 1.31 (dd, 3H, *J*=7.0, 1.7 Hz, CH_3, trans).

δ_C (100 MHz; $CDCl_3$) 145.1, 136.1, 134.1, 129.7, 129.6, 129.1×2, 119.1, 70.4, 60.9, 21.7, 18.3.

m/z; 263 ($M+Na^+$, 100%) 258.

HRMS Found 263.0713 ($M+Na^+$, $C_{12}H_{16}O_3S$ requires 263.0718).

Preparation of methyl (1*S,2*S**)-2-methyl-4-tosylcyclohex-3-enecarboxylate (III-20)**



According to the general procedure as described for compound **III-12**, $AlCl_3$ (0.72 g, 5.39 mmol), CH_2Cl_2 (6 mL) and methyl acrylate (0.49 mL, 5.39 mmol) were mixed together and stirred under nitrogen until a homogeneous solution was formed. A 54 mM solution (50 mL) of (**III-13**) (2.69 mmol) in CH_2Cl_2 was then concentrated to a volume of 25 mL on a rotary evaporator and added to the first solution during 5 min. The reaction was stirred at room temperature for 4 h, then quenched with sat NH_4Cl (10 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-20** as a colourless solid [0.51 g, 1.64 mmol, 61% yield].

mp 81–83 °C; R_f=0.64 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 1737, 1728, 1639, 1593, 1315, 1226, 1205, 1166, 1147, 1083, 1016, 975, 817, 707.

δ_H (500 MHz; $CDCl_3$) 7.72 (d, 2H, *J*=8.2 Hz, Ar-H), 7.32 (d, 2H, *J*=8.2 Hz, Ar-H), 7.03-6.92 (m, 1H, SO_2C=C<u>H</u>), 3.66 (s, 3H, OCH_3), 2.95-2.82 (m, 1H, C<u>H</u>CH_3), 2.59 (ddd, 1H, *J*=12.0, 5.0, 2.9 Hz, C<u>H</u>CO_2CH_3), 2.43 (s, 3H, CH_3), 2.38-2.27 (m, 1H, SO_2CC<u>H</u>H), 2.15-

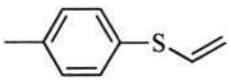
2.05 (m, 1H, $SO_2CCH\underline{H}$), 1.97-1.87 (m, 1H, $SO_2CCH_2C\underline{H}H$), 1.78-1.65 (m, 1H, $SO_2CCH_2CH\underline{H}$), 0.97 (d, 3H, J=7.2 Hz, CH_3).

δ_C (125 MHz; $CDCl_3$) 173.7, 144.3, 140.9, 139.2, 136.1, 129.8×2, 128.1×2, 51.7, 42.2, 31.5, 22.6, 21.6, 19.3, 15.4.

m/z; 309 ($M+H^+$, 100%), 308, 296, 279, 273, 261, 250, 240, 183, 167, 149.

Anal. Calcd. for $C_{16}H_{20}O_4S$: C, 62.31; H, 6.54. Found: C, 62.21; H, 6.55.

Preparation of *p*-tolyl(vinyl)sulfane (III-24)



A solution of the *p*-thiocresol (13.93 g, 112.12 mmol) in EtOH (30 mL) was added rapidly to a solution of sodium ethoxide (7.63 g, 112.12 mmol) in EtOH (40 mL) at 0 °C under nitrogen. The reaction mixture warmed spontaneously and became clear brown solution at room temperature. This solution was transferred over 20 min by cannula to a solution of 1,2-dibromoethane (14.0 mL, 162.57 mmol) in EtOH (30 mL). The reaction mixture was stirred under nitrogen for 30 min, the final bath of sodium ethoxide (16.56 g, 243.29 mmol) solution in EtOH (90 mL) was added to the reaction mixture at room temperature. After heating the reaction mixture under refluxing at 80 °C for 8 h, then the reaction was quenched with water (100 mL) and extracted with Et_2O (3 x 125 mL). The combined organic layers were washed with water, brine and dried over anhydrous

$MgSO_4$. After removal of solvent under reduced pressure, the crude product was distilled under 6 mmHg/112 °C to give **III-24** as a colourless oil [9.91 g, 65.93 mmol, 59% yield].

R_f =0.64 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3020, 2918, 2864, 1722, 1585, 1492, 1446, 1091, 1016, 956, 881, 806.

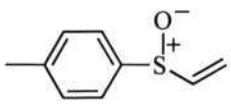
δ_H (500 MHz; $CDCl_3$) 7.42 (d, 2H, *J*=8.2 Hz, Ar-H), 7.25 (d, 2H, *J*=8.2 Hz, Ar-H), 6.33 (dd, 1H, *J*=16.8, 9.8 Hz, SCH), 5.39 (d, 1H, *J*=9.8 Hz, CH=C<u>H</u>H), 5.38 (d, 1H, *J*=16.8 Hz, CH=CH<u>H</u>), 2.45 (s, 3H, CH_3).

δ_C (125 MHz; $CDCl_3$) 137.4, 132.9, 131.4×2, 130.4, 130.1×2, 114.2, 21.2.

m/z; 151 ($M+H^+$, 100%), 145, 142, 136, 133, 131, 128.

HRMS Found 151.0575 ($M+H^+$, $C_9H_{11}S$ requires 151.0581).

Preparation of 1-metyl-4-(vinylsulfinyl)benzene (III-25)



A solution of *m*-chloroperbenzoic acid (0.63 g, 3.63 mmol, 77% dispersion in chlorobenzoic acid) in CH_2Cl_2 (11 mL) was slowly added dropwise to the solution of **III-24** (0.40 g, 2.66 mmol) in CH_2Cl_2 (8 mL) at –78 °C. The reaction was gradually raised up to room temperature stirring for an additional 15 h, then the reaction mixture was quenched with a saturated $NaHCO_3$ solution until its neutral, and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with water, brine and dried over

anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give **III-25** as a colourless oil [0.36 g, 2.16 mmol, 81% yield].

R_f=0.23 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3439, 3415, 1643, 1633, 1492, 1398, 1367, 1303, 1178, 1083, 1049, 1014, 956, 810.

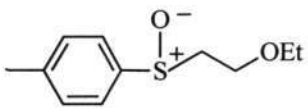
δ_H (400 MHz; $CDCl_3$) 7.50 (d, 2H, *J*=8.0 Hz, Ar-H), 7.30 (d, 2H, *J*=8.0 Hz, Ar-H), 6.56 (dd, 1H, *J*=16.4, 9.6 Hz, SOCH), 6.17 (d, 1H, *J*=16.4 Hz, CH=C<u>H</u>H), 5.86 (d, 1H, *J*=9.6 Hz, CH=CH<u>H</u>), 2.39 (s, 3H, CH_3).

δ_C (100 MHz; $CDCl_3$) 143.1, 141.9, 140.1, 130.1×2, 124.9×2, 120.4, 21.4.

m/z; 167 ($M+H^+$, 100%) 150, 136, 135, 123, 114.

HRMS Found 167.0527 ($M+H^+$, $C_9H_{11}OS$ requires 167.0531).

Preparation of 1-(2-ethoxyethylsulfinyl)-4-methylbenzene (III-26)



A solution of sodium ethoxide (0.35 g, 5.1 mmol) in EtOH (9.6 mL) was slowly added to a solution of *p*-tolyl vinyl sulfoxide (**III-25**) (0.54 g, 3.23 mmol) in EtOH (1.6 mL) at room temperature during 15 min under nitrogen. After stirring the reaction mixture in this temperature for 2 h, the solvent was evaporated, the water (25 mL) was added, and

extracted with Et_2O (20 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give **III-26** as a colourless oil [0.61 g, 2.88 mmol, 89% yield].

R_f = 0.14 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3003, 2872, 1643, 1633, 1492, 1377, 1354, 1215, 1107, 1085, 1041, 806, 754.

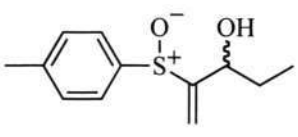
δ_H (500 MHz; $CDCl_3$) 7.54 (d, 2H, *J*=8.1 Hz, Ar-H), 7.32 (d, 2H, *J*=8.1 Hz, Ar-H), 3.89 (ddd, 1H, *J*=10.5, 8.2, 5.2 Hz, C<u>H</u>HOEt), 3.65 (dt, 1H, *J*=10.5, 5.2 Hz, CH<u>H</u>OEt), 3.55 (dq, 1H, *J*=16.4, 7.0 Hz, OC<u>H</u>HCH$_3$), 3.51 (dq, 1H, *J*=16.4, 7.0 Hz, OCH<u>H</u>CH$_3$), 3.04-2.92 (m, 2H, SOC<u>H$_2$</u>), 2.41 (s, 3H, CH_3), 1.21 (t, 3H, *J*=7.0 Hz, CH_3).

δ_C (125 MHz; $CDCl_3$) 141.5, 140.8, 130.0×2, 124.0×2, 66.8, 63.2, 58.3, 21.4, 15.0;

m/z; 213 ($M+H^+$, 100%), 198, 179, 167, 162, 140, 139, 120.

HRMS Found 213.0945 ($M+H^+$, $C_{11}H_{17}O_2S$ requires 213.0949).

Preparation of 2-(*p*-tolylsulfinyl)pent-1-en-3-ol (III-27)



A solution of (**III-26**) (2.76 g, 12.99 mmol) in THF (25 mL) was added dropwise at –78 °C to a solution of lithium diisopropylamide (LDA) under nitrogen [prepared by reacting diisopropylamine (5.85 mL, 32.47 mmol) in THF (32 mL) with *n*-BuLi (1.60 M

in hexane, 17.86 mL, 28.57 mmol) at –78 °C for 30 min]. After stirring at –78 °C for 1 h, a solution of propionaldehyde (1.12 mL, 15.58 mmol) was added to the resulting solution of the anion **III-26**. The mixture was stirred at –78 °C for 3 h, and then quenched with saturated NH_4Cl (30 mL). The mixture was diluted with water (50 mL) and extracted with Et_2O (30 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give **III-27** as a colourless oil [0.81 g, 3.64 mmol, 28% yield].

R_f = 0.17 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3003, 2872, 1643, 1633, 1492, 1377, 1354, 1215, 1107, 1085, 1041, 806, 754.

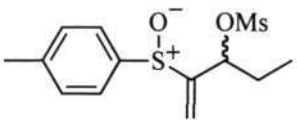
δ_H (500 MHz; $CDCl_3$) 7.55 (d, 2H, *J*=8.1 Hz, Ar-H, minor), 7.52 (d, 2H, *J*=8.1 Hz, Ar-H, major), 7.31 (d, 2H, *J*=8.1 Hz, Ar-H, major), 7.27 (d, 2H, *J*=8.1 Hz, Ar-H, minor), 6.07 (s, 1H, C=C<u>H</u>H, minor), 6.06 (s, 1H, C=C<u>H</u>H, major), 5.85 (s, 1H, C=CH<u>H</u>, major), 5.84 (s, 1H, C=CH<u>H</u>, minor), 4.15-4.03 (m, 1H, C<u>H</u>OH, major and minor), 2.41 (s, 3H, CH_3, major), 2.40 (s, 3H, CH_3, minor), 1.75-1.46 (m, 2H, C<u>H</u>$_2$$CH_3$, major and minor), 0.86 (t, 3H, *J*=7.4 Hz, CH_3, minor), 0.80 (t, 3H, *J*=7.4 Hz, CH_3, major).

δ_C (100 MHz; $CDCl_3$) 156.9 (minor), 156.1 (major), 142.0 (major), 141.9 (minor), 139.7 (minor), 138.9 (major), 130.1×2 (major), 130.0×2 (minor), 125.5×2 (minor), 125.2×2 (major), 117.5 (major), 117.3 (minor), 70.7 (minor), 69.7 (major), 29.4 (minor), 28.4 (major), 21.5 (major and minor), 9.7 (minor), 9.5 (major).

m/z; 225 ($M+H^+$, 100%), 208, 207, 206, 189, 163, 157, 141, 139, 131.

HRMS Found 225.0945 ($M+H^+$, $C_{12}H_{17}O_2S$ requires 225.0949).

Preparation of 2-(*p*-tolylsulfinyl)pent-1-en-3-yl methanesulfonate (III-28)



A solution of methansulfonyl chloride (0.37 mL, 4.81 mmol) in CH_2Cl_2 (1 mL) was added to a solution of **III-27** (0.83 g, 3.70 mmol) in CH_2Cl_2 (18.5 mL) containing triethylamine (0.67 mL, 4.81 mmol) was added at 0 °C under nitrogen. The reaction mixture was stirred and slowly warmed up to room temperature (16 h). The mixture was diluted with NH_4Cl (10 mL), water (10 mL) and extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give **III-28** as a yellow oil [1.11 g, 3.67 mmol, 99% yield].

R_f = 0.37 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3024, 2976, 2937, 1629, 1595, 1492, 1454, 1352, 1174, 1080, 1047, 914, 850, 812.

δ_H (300 MHz; $CDCl_3$) 7.55 (d, 2H, *J*=8.1 Hz, Ar-H, minor), 7.51 (d, 2H, *J*=8.1 Hz, Ar-H, major), 7.32 (d, 2H, *J*=8.1 Hz, Ar-H, major and minor), 6.32 (d, 1H, *J*=0.9 Hz, C=C<u>H</u>H, minor), 6.27 (d, 1H, *J*=0.9 Hz, C=C<u>H</u>H, major), 6.03 (d, 1H, *J*=0.9 Hz, C=CH_2, major and minor), 5.02-4.85 (m, 1H, CH-OMs, major and minor), 2.89 (s, 3H, CH_3, major), 2.60 (s, 3H, CH_3, minor), 2.40 (s, 3H, CH_3, major and minor), 1.92-1.68 (m, 1H, C<u>H</u>HCH_3,

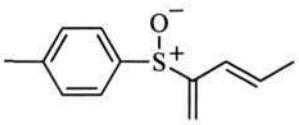
major), 1.63-1.31 (m, 1H, C<u>H</u>HCH$_3$, minor and CH<u>H</u>CH$_3$, major and minor), 0.85 (t, 3H, *J*=7.3 Hz, CH$_3$, major), 0.85 (t, 3H, *J*=7.3 Hz, CH$_3$, minor).

δ_C (75 MHz; $CDCl_3$) 152.6 (major), 152.4 (minor), 142.64 (major), 142.59 (minor), 138.7 (minor), 138.1 (major), 130.3×2 (major), 130.2×2 (minor), 125.6×2 (minor), 125.1×2 (major), 120.71 (major), 120.67 (minor), 78.8 (minor), 77.4 (major), 38.4 (major), 38.3 (minor), 29.4 (major), 29.0 (minor), 21.5 (major and minor), 9.4 (minor), 9.0 (major).

m/z; 303 ($M+H^+$, 100%), 302, 300, 295, 291.

HRMS Found 303.0724 ($M+H^+$, $C_{13}H_{19}O_4S_2$ requires 303.0725).

Preparation of (*E*)-1-methyl-4-(penta-1,3-dien-2-ylsulfinyl)benzene (III-29)



DBU (1.94 mL, 12.98 mmol) was slowly added to a solution of **III-28** (1.96 g, 6.49 mmol) in CH_2Cl_2 (32.5 mL) under nitrogen. The reaction mixture was heated at reflux for 2 h, then the mixture was diluted with NH_4Cl (10 mL) and extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give **III-29** as a yellow solid [0.86 g, 4.16 mmol, 64% yield].

mp 59–60 °C; R_f = 0.54 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3020, 2992, 2850, 1643, 1595, 1492, 1446, 1398, 1377, 1303, 1178, 1082, 1051, 960, 912, 810.

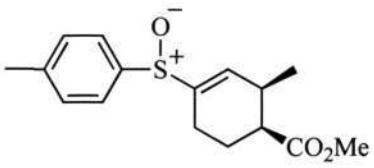
δ_H (300 MHz; $CDCl_3$) 7.52 (d, 2H, *J*=8.1 Hz, Ar-H), 7.25 (d, 2H, *J*=8.1 Hz, Ar-H), 6.10-5.80 (m, 3H, C=C$\underline{H}_2$ and CH=C$\underline{H}$CH$_3$), 5.69 (s, 1H, C$\underline{H}$=CHCH$_3$), 2.36 (s, 3H, CH_3), 1.68 (d, 3H, *J*=5.5 Hz, CH_3).

δ_C (75 MHz; $CDCl_3$) 151.1, 141.8, 140.2, 131.4, 129.9×2, 125.6, 123.5×2, 114.9, 21.4, 18.7.

m/z; 207 ($M+H^+$, 100%), 189, 186, 183, 171, 165, 159, 157, 149, 143.

HRMS Found 207.0840 ($M+H^+$, $C_{12}H_{15}OS$ requires 207.0844).

Preparation of (1*S,2*S**)-methyl 2-methyl-4-(*p*-tolylsulfinyl)cyclohex-3-enecarboxylate (III-30)**



According to the general procedure as described for compound **III-12**, $AlCl_3$ (0.44 g, 3.33 mmol), CH_2Cl_2 (3.5 mL) and methyl acrylate (0.3 mL, 0.29 mmol) were mixed together and stirred under nitrogen until a homogeneous solution was formed. A solution of **III-29** (0.14 g, 0.67 mmol) in CH_2Cl_2 (1.3 mL) was added to the reaction mixture at room temperature. After stirring the reaction mixture for 2 days, then the reaction was cooled to 0 °C, quenched with sat NH_4Cl (5 mL) and extracted with CH_2Cl_2 (20 mL × 3).

The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give **III-30** as a colourless solid as a single diastereoisomers [0.14 g, 0.47 mmol, 71% yield].

mp 71–73 °C; R_f=0.32 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 2966, 1732, 1643, 1597, 1492, 1435, 1375, 1301, 1228, 1203, 1165, 1082, 1035, 810, 752, 665.

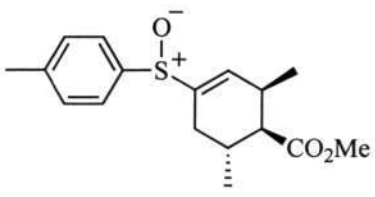
δ_H (500 MHz; $CDCl_3$) 7.44 (d, 2H, *J*=8.1 Hz, Ar-H), 7.26 (d, 2H, *J*=8.1 Hz, Ar-H), 6.57 (app.d, 1H, *J*=4.7 Hz, SO_2C=C<u>H</u>), 3.63 (s, 3H, OCH_3), 2.92-2.80 (m, 1H, C<u>H</u>CH_3), 2.68-2.60 (m, 1H, C<u>H</u>CO_2CH_3), 2.37 (s, 3H, CH_3), 1.96-1.82 (m, 3H, SOCC<u>H</u>$_2$ and $SOCCH_2$C<u>H</u>H), 1.75-1.62 (m, 1H, SO_2CCH_2CH<u>H</u>), 0.97 (d, 3H, *J*=7.1 Hz, CH_3).

δ_C (125 MHz; $CDCl_3$) 173.9, 142.3, 141.4, 139.3, 135.7, 129.9×2, 125.0×2, 51.5, 43.0, 31.8, 21.4, 20.3, 19.8, 15.9.

m/z; 293 ($M+H^+$, 100%), 292, 280, 255, 245, 213, 197, 185, 181, 167, 149, 131.

HRMS Found 293.1206 ($M+H^+$, $C_{16}H_{21}O_3S$ requires 293.1211).

Preparation of (1*S,2*S**,6*R**)-methyl 2,6-dimethyl-4-(*p*-tolylsulfinyl)cyclohex-3-ene-carboxylate (III-31)**



According to the general procedure as described for compound **III-12**, $AlCl_3$ (2.21 g, 16.6 mmol), CH_2Cl_2 (32 mL) and methyl crotonate (3.52 mL, 33.21 mmol) were mixed together and stirred under nitrogen until a homogeneous solution was formed. A solution of **III-29** (0.69 g, 3.32 mmol) was added to the reaction mixture at room temperature. The reaction was heated under reflux at 100 °C for 10 days, then the reaction was cooled to 0 °C, quenched with sat NH_4Cl (30 mL) and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give **III-31** as a colourless oil as a mixture of two diastereoisomers in a ratio of 25:75 [0.57 g, 1.85 mmol, 56% yield].

R_f=0.38 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 2956, 2927, 2874, 1733, 1453, 1433, 1216, 1158, 1082, 1044, 1014, 809, 620.

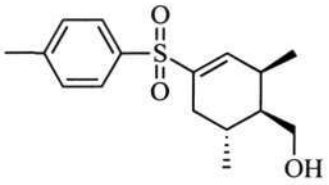
δ_H (300 MHz; $CDCl_3$) 7.27 (d, 2H, *J*=8.0 Hz, Ar-H, major and minor), 7.10 (d, 2H, *J*=8.0 Hz, Ar-H, major and minor), 6.39 (app.s, 1H, SO_2C=C<u>H</u>, major and minor), 3.47 (s, 3H, OCH_3, minor), 3.46 (s, 3H, OCH_3, major), 2.72-2.50 (m, 1H, C=CHC<u>H</u>CH_3, major and minor), 2.25 (dd, 1H, *J*=10.1, 5.8 Hz, C<u>H</u>CO_2CH_3, major and minor), 2.21 (s, 3H, CO_2CH_3, major and minor), 1.93-1.66 (m, 2H, CH_2C<u>H</u>CH_3 and SO_2CC<u>H</u>H, major and minor), 1.42 (ddd, 1H, SO_2CCH<u>H</u>, major and minor), 0.84 (d, 3H, *J*=6.6 Hz, CH_3, minor), 0.82 (d, 3H, *J*=6.7 Hz, CH_3, major), 0.75 (d, 3H, *J*=6.7 Hz, CH_3, major), 0.74 (d, 3H, *J*=6.6 Hz, CH_3, minor).

δ_C (75 MHz; $CDCl_3$) 173.54 (major), 173.48 (minor), 141.5 (major and minor), 141.4 (major and minor), 139.2 (major and minor), 136.5 (minor), 135.4 (major), 129.9×2 (major), 129.8×2 (minor), 125.0 ×2 (major), 124.8 ×2 (minor), 51.3 (major and minor), 50.4 (minor), 50.0 (major), 32.5 (minor), 32.0 (major), 27.9 (major), 26.8 (minor), 25.8 (major), 25.4 (minor), 21.4 (major and minor), 19.7 (major), 19.6 (minor), 16.6 (major), 16.5 (minor).

m/z; 307 ($M+H^+$, 100%), 306, 299, 295, 289, 284.

HRMS Found 307.1363 ($M+H^+$, $C_{17}H_{23}O_3S$ requires 307.1368).

Preparation of ((1*S,2*S**,6*R**)-2,6-dimethyl-4-tosylcyclohex-3-enyl)methan-1-ol (III-33)**



A solution of (**III-12**) (5.74 g, 18.74 mmol) in dry CH_2Cl_2 (95 mL) was cooled under nitrogen to –78 °C. A solution of DIBAL in toluene (65.6 mL of a 1 M solution) was slowly added for 30 min. The reaction was stirred for a further 3 h at –78 °C, then the reaction was quenched with a solution of Rochelle's salt (1.2 M aqueous potassium sodium tartrate, 50 mL). The viscous solution was stirred vigorously for 1 h, after which time it settled to two clear phases. The reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with water, brine and dried over

anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give **III-33** as a colourless solid [5.30 g, 18.03 mmol, 96% yield].

mp 104–105 °C; R_f=0.25 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3441, 1643, 1595, 1300, 1286, 1273, 1149, 1105, 1082, 1004, 806, 669, 623.

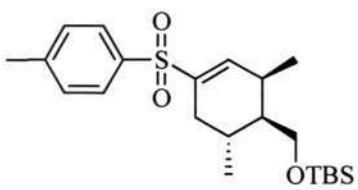
δ_H (400 MHz; $CDCl_3$) 7.70 (d, 2H, *J*=8.1 Hz, Ar-H), 7.30 (d, 2H, *J*=8.1 Hz, Ar-H), 6.94 (app.d, 1H, *J*=4.1 Hz, SO_2C=C<u>H</u>), 3.68 (dd, 1H, *J*=10.1, 6.1 Hz, C<u>H</u>HOH), 3.51 (dd, 1H, *J*=10.1, 10.1 Hz, CH<u>H</u>OH), 2.80-2.66 (m, 1H, C=CHC<u>H</u>CH_3), 2.42 (s, 3H, CH_3), 2.27 (app.d, 1H, *J*=12.2 Hz, SO_2CC<u>H</u>H), 1.85-1.67 (m, 2H, SO_2CCH<u>H</u> and CH_2C<u>H</u>CH_3), 1.63-1.46 (m, 1H, C<u>H</u>CH_2OH), 1.01 (d, 3H, *J*=7.3 Hz, CH_3), 0.87 (d, 3H, *J*=6.2 Hz, CH_3).

δ_C (100 MHz; $CDCl_3$) 144.1, 142.4, 138.0, 136.3, 129.8×2, 127.9×2, 61.7, 43.6, 30.8, 30.7, 26.0, 21.6, 18.7, 14.5.

m/z; 295 ($M+H^+$, 100%), 280, 279, 260, 255, 238, 204, 180, 167, 163, 150.

Anal. Calcd. for $C_{16}H_{22}O_3S$: C, 65.27; H, 7.53. Found: C, 65.33; H, 7.58.

Preparation of *tert*-butyl(((1*S,2*S**,6*R**)-2,6-dimethyl-4-tosylcyclohex-3-enyl)-methoxy) dimethylsilane (III-34)**



To a suspension of (**III-33**) (0.54 g, 1.85 mmol) and 4-(dimethylamino)pyridine (45.0 mg, 0.37 mmol) in THF (9.0 mL) was added triethylamine (0.36 mL, 2.59 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 30 min, then a solution of *t*-butyldimethylsilyl chloride (0.42 g, 2.77 mmol) in THF (8.3 mL) was added drop wise by syringe. The reaction mixture was slowly warmed up to room temperature and stirred for an additional for 20 h. The reaction mixture was quenched with NH_4Cl (15 mL) and extracted with Et_2O (20 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-34** as a colourless solid [0.69 g, 1.68 mmol, 91% yield].

mp 70–72 °C; R_f =0.44 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 1641, 1597, 1467, 1454, 1377, 1300, 1290, 1149, 1112, 1083, 885, 837, 813, 775, 667, 619.

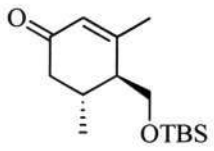
δ_H (500 MHz; $CDCl_3$) 7.71 (d, 2H, *J*=8.1 Hz, Ar-H), 7.31 (d, 2H, *J*=8.1 Hz, Ar-H), 6.45 (app.d, 1H, *J*=4.3 Hz, SO_2C=C<u>H</u>), 3.58 (dd, 1H, *J*=9.9, 6.0 Hz, C<u>H</u>HOTBS), 3.45 (dd, 1H, *J*=9.9, 9.9 Hz, CH<u>H</u>OTBS), 2.75-2.63 (m, 1H, C=CHC<u>H</u>CH_3), 2.42 (s, 3H, Ar-CH_3), 2.26 (app.d, 1H, *J*=12.3 Hz, SO_2CC<u>H</u>H), 1.82-1.66 (m, 2H, SO_2CCH<u>H</u> and CH_2C<u>H</u>CH_3), 1.58-1.46 (m, 1H, C<u>H</u>CH_2OTBS), 0.99 (d, 3H, *J*=7.3 Hz, CH_3), 0.86 (d, 3H, *J*=8.6 Hz, CH_3), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.00 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$).

δ_C (100 MHz; $CDCl_3$) 144.0, 142.7, 138.0, 136.5, 129.7×2, 128.0×2, 61.8, 43.7, 31.1, 31.0, 25.82×3, 25.77, 21.6, 18.6, 18.1, 14.5, –5.4, –5.5.

m/z; 431 ($M+Na^+$, 100%), 409, 389, 357, 339, 335, 279, 254, 233, 222, 206, 166, 140.

HRMS Found 431.2054 ($M+Na^+$, $C_{22}H_{36}O_3SSiNa$ requires 431.2052).

Preparation of (4*S,5*R**)-4-((*tert*-butyldimethylsilyloxy)methyl)-3,5-dimethylcyclohex-2-enone (III-35)**



To a suspension of (**III-39**) (1.91 g, 4.67 mmol) and MoOPD (6.72 g, 17.53 mmol) in THF (55 mL) was added dropwise a solution of lithium diisopropylamide (LDA) at –78 °C under an N_2 atmosphere [prepared by reacting diisopropylamine (5.05 mL, 28.0 mmol) in THF (50 mL) with *n*-BuLi (1.6 M in hexane, 17.5 mL, 28.0 mmol) at –78 °C for 30 min]. The mixture was stirred at –78 °C for 3 h, then quenched with 2 N HCl (30 mL), and extracted with Et_2O (3 x 75 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-35** as a colourless oil [1.06 g, 3.94 mmol, 84% yield].

R_f=0.43 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 2954, 2927, 1647, 1629, 1460, 1438, 1375, 1300, 1251, 1105, 1004, 991, 835, 775.

δ_H (500 MHz; $CDCl_3$) 5.91 (s, 1H, C=CH), 3.80 (app.d, 1H, *J*=1.3 Hz, CHHOTBS), 3.79 (app.d, 1H, *J*=2.5 Hz, CHHOTBS), 2.60 (dd, 1H, *J*=16.9, 5.1 Hz, COCHH), 2.48-2.35 (m,

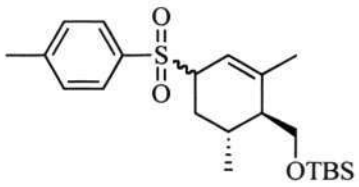
1H, C<u>H</u>CH_3), 2.17-2.06 (m, 2H, COC<u>H</u>H and C<u>H</u>CH_2OTBS), 1.99 (s, 3H, CH_3), 1.05 (d, 3H, *J*=7.0 Hz, CH_3), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.052 (s, 3H, $SiCH_3$), 0.050 (s, 3H, $SiCH_3$).

δ_C (125 MHz; $CDCl_3$) 199.2, 161.1, 127.8, 62.7, 49.8, 41.9, 30.2, 25.8×3, 23.5, 20.0, 18.2, –5.49, –5.52.

m/z; 269 ($M+H^+$, 100%), 268, 239, 223, 185, 137, 107.

HRMS Found 269.1934. ($M+H^+$, $C_{15}H_{29}O_2Si$ requires 269.1937).

Preparation of *tert*-butyl(((1*S,6*R**)-2,6-dimethyl-4-tosylcyclohex-2-enyl)methoxy) dimethylsilane (III-39)**



To a suspension of (**III-42**) (0.66 g, 2.24 mmol) and 4-(dimethylamino)pyridine (0.03 g, 0.22 mmol) in THF (6.7 mL) was added triethylamine (0.48 mL, 3.36 mmol) at 0 ºC under nitrogen. The reaction mixture was stirred at 0 ºC for 30 min, then a solution of *t*-butyldimethylsilyl chloride (0.81 g, 5.38 mmol) in THF (6.7 mL) was added drop wise by syringe. The reaction mixture was slowly warmed up to room temperature and stirred for an additional for 20 h. The reaction mixture was quenched with NH_4Cl (15 mL) and extracted with Et_2O (25 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure,

the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-39** as a colourless solid [0.84 g, 2.06 mmol, 92% yield].

mp 62–64 °C; R_f=0.44 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 1286, 1255, 1220, 1126, 1083, 879, 837, 812, 773, 673, 599, 574, 557, 511;

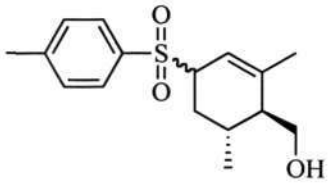
δ_H (500 MHz; $CDCl_3$) 7.71 (d, 2H, *J*=8.1 Hz, Ar-H, minor), 7.68 (d, 2H, *J*=8.1 Hz, Ar-H, major), 7.31 (d, 2H, *J*=8.1 Hz, Ar-H, minor), 7.30 (d, 2H, *J*=8.1 Hz, Ar-H, major), 5.64 (br.s, 1H, C<u>H</u>=CCH_3, minor), 5.58 (br.s, 1H, C<u>H</u>=CCH_3, major), 3.74 (dd, 1H, *J*=11.3, 2.7 Hz, SO_2CH, major), 3.62 (dd, 1H, *J*=10.4, 2.7 Hz, SO_2CH, minor), 3.39 (dd, 1H, *J*=9.9, 4.4 Hz, C<u>H</u>HOTBS, major and minor), 2.85 (dd, 1H, *J*=9.9, 9.9 Hz, CH<u>H</u>OTBS, major and minor), 2.41 (s, 3H, CH_3, minor), 2.40 (s, 3H, CH_3, major), 2.23-2.12 (m, 1H, C<u>H</u>CH_3, major and minor), 1.83-1.50 (m, 3H, SO_2C<u>H</u> and SO_2CHC<u>H_2</u>, major and minor), 1.72 (s, 3H, CH_3, major and minor), 0.95 (d, 3H, *J*=6.6 Hz, CH_3, minor), 0.85 (d, 3H, *J*=7.1 Hz, CH_3, major), 0.82 (s, 9H, $SiC(CH_3)_3$, major), 0.80 (s, 9H, $SiC(CH_3)_3$, minor), –0.03 (s, 6H, $Si(CH_3)_2$, minor), –0.06 (s, 6H, $Si(CH_3)_2$, major).

δ_C (100 MHz; $CDCl_3$) 144.4, 141.0, 133.8, 129.6, 129.4×2, 129.1, 114.4, 64.0, 60.6, 48.5, 28.5, 25.9×2, 25.8, 24.1, 23.7, 21.6, 18.6, 18.2, –5.4, –5.5.

m/z; 431 ($M+Na^+$, 100%), 409, 271, 209.

HRMS Found 431.2048 ($M+Na^+$, $C_{22}H_{36}O_3SSiNa$ requires 431.2052).

Preparation of ((1*S,6*R**)-2,6-dimethyl-4-tosylcyclohex-2-enyl)methanol (III-42)**



To a solution of (**III-33**) (2.39 g, 8.11 mmol) in MeOH (40 mL) was added sodium hydroxide (2.27 g, 56.77 mmol). The reaction mixture was heated under reflux at 100 °C for 7 h, then the reaction was cooled to room temperature, quenched with 2N HCl until neutral and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give **III-42** as a yellow oil [2.28g, 7.74 mmol, 95% yield].

R_f=0.25 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3435, 3419, 3020, 2958, 1637, 1597, 1448, 1379, 1286, 1217, 1143, 1085, 754, 665.

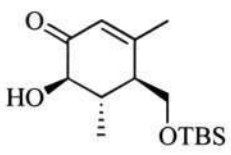
δ_H (400 MHz; $CDCl_3$) 7.66 (d, 2H, *J*=8.2 Hz, Ar-H), 7.28 (d, 2H, *J*=8.2 Hz, Ar-H), 5.53 (br.s, 1H, C<u>H</u>=CCH_3), 3.66 (br.s, 1H, SO_2C<u>H</u>), 3.53 (dd, 1H, *J*=11.1, 3.2 Hz, C<u>H</u>HOH), 3.33 (dd, 1H, *J*=11.1, 6.8 Hz, CH<u>H</u>OH), 2.38 (s, 3H, CH_3), 2.25 (br.s, 1H, OH), 2.22-2.14 (m, 1H, C<u>H</u>CH_3), 1.92 (ddd, 1H, *J*=13.4, 8.0, 4.4 Hz, SO_2CHC<u>H</u>H), 1.77 (br.s, 1H, C<u>H</u>CH_2OH), 1.72 (s, 3H, CH_3), 1.52 (ddd, 1H, *J*=13.4, 6.7, 6.7 Hz, SO_2CHCH<u>H</u>), 0.86 (d, 3H, *J*=6.9 Hz, CH_3).

δ_C (100 MHz; $CDCl_3$) 144.7, 141.9, 134.3, 129.6×2, 129.0×2, 115.0, 62.7, 60.7, 48.5, 26.7, 26.1, 23.0, 21.6, 19.6.

m/z; 317 ($M+Na^+$, 100%), 295, 157.

HRMS Found 317.1183 ($M+Na^+$, $C_{16}H_{22}O_3SNa$ requires 317.1187).

Preparation of (4*S,5*S**,6*R**)-4-((*tert*-butyldimethylsilyloxy)methyl)-6-hydroxy-3,5-dimethyl cyclohex-2-enone (III-45)**



A suspension of **(III-39)** (1.91 g, 4.67 mmol) and MoOPD (6.72 g, 17.53 mmol) in THF (55 mL) was added dropwise a solution of lithium diisopropylamide (LDA) at –78 °C under an N_2 atmosphere [prepared by reacting diisopropylamine (5.05 mL, 28.0 mmol) in THF (50 mL) with *n*-BuLi (1.6 M in hexane, 17.5 mL, 28.0 mmol) at –78 °C for 30 min]. The mixture was stirred at –78 °C for 3 h, then quenched with 2 N HCl (30 mL), and extracted with Et_2O (3 x 75 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-35** as a colourless liquid [5.65g, 21.05 mmol, 51% yield] and **III-45** as a yellow solid [2.45 g, 8.63 mmol, 21% yield].

mp 47–48 °C; R_f=0.34 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3479, 2957, 2928, 2887, 2856, 1657, 1461, 1376, 1251, 1085, 986, 882, 833, 772, 681.

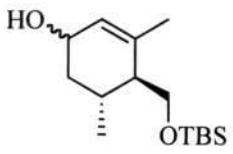
δ_H (500 MHz; $CDCl_3$) 6.03 (s, 1H, C=CH), 3.99 (dd, 1H, *J*=10.6, 2.0 Hz, CHHOTBS), 3.81 (dd, 1H, *J*=10.6, 1.8 Hz, CHHOTBS), 3.81 (br.s, 1H, OH), 3.80 (d, 1H, *J*=12.3 Hz, CHOH), 2.18-2.08 (m, 2H, $CHCH_3$ and $CHCH_2OTBS$), 2.04 (s, 3H, CH_3), 1.23 (d, 3H, *J*=6.0 Hz, CH_3), 0.84 (s, 9H, $SiC(CH_3)_3$), 0.05 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$).

δ_C (125 MHz; $CDCl_3$) 199.2, 164.6, 125.4, 76.7, 59.3, 49.4, 37.9, 25.7×3, 22.1, 18.1, 15.7, –5.6, –5.7.

m/z; 285 ($M+H^+$, 100%), 284, 270, 269, 266, 255, 237, 231, 206, 171, 155, 151.

HRMS Found 285.1887. ($M+H^+$, $C_{15}H_{29}O_3Si$ requires 285.1886).

Preparation of (4*S,5*R**)-4-((*tert*-butyldimethylsilyloxy)methyl)-3,5-dimethylcyclohex-2-enol (III-46)**



To a mixture of $CeCl_3.7H_2O$ (1.98 g, 5.33 mmol) and **(III-35)** (0.95 g, 3.55 mmol) was added methanol (50 mL). The reaction mixture was cooled to –78 °C, then a solid of sodium borohydride (0.67 g, 17.75 mmol) was added slowly under nitrogen. The reaction was gradually raised up to –40 °C stirring for an additional 15 h, then the reaction mixture was quenched with a saturated NH_4Cl solution (20 mL), added 2N HCl until the reaction

mixture became clear, and extracted with Et_2O (3 x 75 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-46** as a colourless oil as a mixture of two diastereoisomer in a ratio of 95:5 [0.87 g, 3.23 mmol, 91% yield].

R_f=0.25 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3348, 3331, 2954, 2927, 2856, 1718, 1664, 1469, 1462, 1384, 1361, 1253, 1112, 1095, 1029, 987, 875, 837, 773.

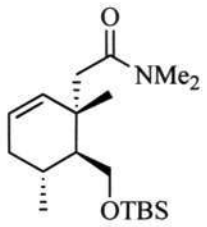
δ_H (300 MHz; $CDCl_3$) 5.51 (s, 1H, C=CH), 4.18 (br.s, 1H C<u>H</u>OH), 3.71 (dd, 1H, *J*=6.1, 2.3 Hz, C<u>H</u>HOTBS), 3.65 (dd, 1H, *J*=6.1, 1.9 Hz, CH<u>H</u>OTBS), 2.02-1.94 (m, 1H, C<u>H</u>HCHCH$_3$), 1.91-1.80 (m, 1H, CHCH$_3$), 1.72 (s, 3H, CH$_3$), 1.68 (br.d, 1H, *J*=3.9 Hz, C<u>H</u>CH$_2$OTBS), 1.40 (br.s, 1H, OH), 1.28-1.18 (m, 1H, CH<u>H</u>CHCH$_3$), 1.03 (d, 3H, *J*=4.0 Hz, CH$_3$), 0.86 (s, 9H, SiC(CH$_3$)$_3$), 0.02 (s, 6H, Si(CH$_3$)$_2$).

δ_C (125 MHz; $CDCl_3$) 137.0, 128.5, 67.3, 61.1, 49.2, 40.5, 27.8, 25.8×3, 21.5, 20.5, 18.2, –5.5×2.

m/z; 293 ($M+Na^+$, 100%), 269, 253, 251, 247, 239, 236, 228, 222, 217, 212, 207, 192.

HRMS Found 293.1917 ($M+Na^+$, $C_{15}H_{30}O_2SiNa$ requires 293.1913).

Preparation of ((1*S,5*R**,6*S**)-6-((*tert*-butyldimethylsilyloxy)methyl)-1,5-dimethyl cyclohex-2-enyl)-*N*,*N*-dimethylacetamide (III-47)**



The allylic alcohol (**III-46**) (3.93 g, 14.5 mmol) and *N*,*N*-dimethylacetamide dimethyl acetate (4.25 mL, 29.07 mmol) were heated under microwave by employing 150 °C, 150 W, pressure 150 Psi for 1 h as a condition. The excess acetal was rotary evaporated to give the crude product which was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-47** as a colourless solid as a single diastereoisomer [2.28 g, 6.73 mmol, 46% yield, 49% conversion from dr. 96:4] and **III-57** as a colourless oil [1.11 g, 3.55 mmol, 24% yield].

mp 65–67 °C; R_f=0.30 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 1653, 1620, 1307, 1253, 1193, 1105, 1058, 991, 862, 837, 773, 719.

δ_H (500 MHz; $CDCl_3$) 5.61 (ddd, 1H, *J*=10.0, 5.2, 1.5 Hz, C<u>H</u>=CH), 5.53 (d, 1H, *J*=10.0 Hz, CH=C<u>H</u>), 3.83 (dd, 1H, *J*=10.8, 3.5 Hz, C<u>H</u>HOTBS), 3.77 (dd, 1H, *J*=10.8, 5.5 Hz, CH<u>H</u>OTBS), 3.04 (s, 3H, NCH_3), 2.95 (s, 3H, NCH_3), 2.54 (s, 2H, C<u>H</u>$_2$N$(CH_3)_3$), 2.10-1.95 (m, 1H, CH=CHC<u>H</u>H), 1.88-1.73 (m, 2H, CH=CHCH<u>H</u> and C<u>H</u>CH_3), 1.72-1.63 (m,

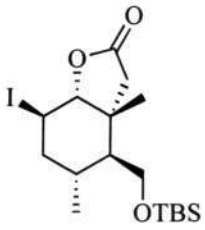
1H, C<u>H</u>CH$_2$OTBS), 1.10 (s, 3H, CH$_3$), 1.01 (d, 3H, *J*=6.0 Hz, CH$_3$), 0.91 (s, 9H, SiC(CH$_3$)$_3$), 0.073 (s, 3H, SiCH$_3$), 0.069 (s, 3H, SiCH$_3$).

δ_C (75 MHz; CDCl$_3$) 171.7, 136.1, 124.3, 61.6, 48.9, 43.5, 39.1, 38.3, 35.4, 35.1, 27.3, 25.9×3, 23.9 19.8, 18.1, –5.6, –5.7.

m/z; 340 (M+H$^+$, 100%), 328, 317, 295, 279, 264, 246, 237, 223, 209, 208, 195, 181.

HRMS Found 340.2675 (M+H$^+$, $C_{19}H_{38}NO_2Si$ requires 340.2672).

Preparation of (3a*R,4*S**,5*R**,7*R**,7a*R**)-4-((*tert*-butyldimethylsilyloxy)methyl)-7-iodo-3a,5-dimethylhexahydrobenzofuran-2(3H)-one (III-48)**



Iodine (1.22 g, 4.81 mmol) was added to a solution of **III-47** (0.82 g, 2.40 mmol) in THF-H$_2$O (9.6 mL: 9.6 mL) at 0 °C. The reaction was gradually raised up to room temperature and stirred for an additional 30 h, then the reaction mixture was quenched with an saturated $Na_2S_2O_3$ solution until the reaction mixture became clear, and extracted with Et$_2$O (3 x 20 mL). The combined organic layers were washed with water, brine and dried over anhydrous MgSO$_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO$_2$, 25% EtOAc in hexanes) to give

III-48 as a colourless solid as a single isomer [0.98 g, 2.23 mmol, 93% yield] and **III-68** as a yellow oil [0.01 g, 0.02 mmol, 1% yield].

mp 77–79 °C; R_f=0.57 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3020, 2954, 2927, 1784, 1637, 1462, 1388, 1327, 1257, 1215, 1195, 1143, 1097, 993, 837, 756.

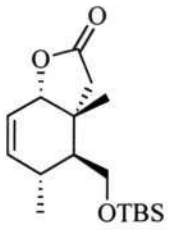
δ_H (500 MHz; $CDCl_3$) 4.66 (d, 1H, *J*=2.8 Hz, CHI), 4.53 (s, 1H, CHO), 3.81 (dd, 1H, *J*=10.6, 3.7 Hz, C<u>H</u>HOTBS), 3.67 (dd, 1H, *J*=10.6, 7.6 Hz, CH<u>H</u>OTBS), 2.97 (d, 1H, *J*=7.2 Hz, C<u>H</u>HCO), 2.37 (d, 1H, *J*=7.2 Hz, CH<u>H</u>CO), 2.08-1.93 (m, 2H, $CHCH_3$ and CHIC<u>H</u>H), 1.92-1.77 (m, 1H, CHICH<u>H</u>), 1.50 (s, 3H, CH_3), 1.41-1.27 (m, 1H, C<u>H</u>CH_2OTBS), 1.02 (d, 3H, *J*=6.3 Hz, CH_3), 0.92 (s, 9H, $SiC(CH_3)_3$), 0.08 (s, 6H, $Si(CH_3)_2$).

δ_C (75 MHz; $CDCl_3$) 174.6, 88.6, 61.6, 47.1, 45.4, 42.7, 39.7, 26.1, 25.9×3, 22.1, 21.9, 19.3, 18.1, –5.6, –5.8.

m/z; 461 ($M+Na^+$, 100%), 439, 414, 413, 403, 393, 344, 330, 275, 257, 223, 209, 180.

HRMS Found 461.0990 ($M+Na^+$, $C_{17}H_{31}O_3SiINa$ requires 461.0985).

Preparation of (3a*R,4*S**,5*R**,7a*S**)-4-((*tert*-butyldimethylsilyloxy)methyl)-3a,5-dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7aH)-one (III-49)**



DBU was added (0.92 mL, 6.19 mmol) to a solution of **III-48** (0.68 g, 1.55 mmol) in THF (7.8 mL) under nitrogen. After heating the reaction mixture under refluxing at 80 °C for 2 h, then the reaction was quenched with NH_4Cl (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-49** as a colourless solid as a single isomer [0.45 g, 1.45 mmol, 94% yield].

mp 97–98 °C; R_f=0.49 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 2956, 2927, 2881, 2854, 1762, 1745, 1460, 1384, 1249, 1222, 1197, 1170, 1126, 993, 833, 773.

δ_H (400 MHz; $CDCl_3$) 5.91 (d, 1H, *J*=10.0 Hz, C<u>H</u>=CH), 5.79 (ddd, 1H, *J*=10.0, 4.6, 2.5 Hz, CH=C<u>H</u>), 4.28 (d, 1H, *J*=4.6 Hz, CHO), 3.79 (dd, 1H, *J*=11.3, 3.3 Hz, C<u>H</u>HOTBS), 3.75 (dd, 1H, *J*=11.3, 5.5 Hz, CH<u>H</u>OTBS), 2.96 (d, 1H, *J*=17.4 Hz, C<u>H</u>HCO), 2.39 (d, 1H, *J*=17.4 Hz, CH<u>H</u>CO), 2.32-2.18 (m, 1H, C<u>H</u>CH_3), 1.37-1.23 (m, 1H, C<u>H</u>CH_2OTBS),

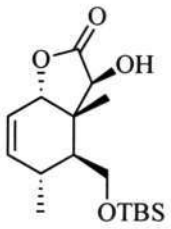
1.11 (s, 3H, CH_3), 1.10 (d, 3H, J=6.0 Hz, CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.06 (s, 6H, $Si(CH_3)_2$).

δ_C (100 MHz; $CDCl_3$) 176.0, 141.0, 119.3, 82.5, 61.1, 44.3, 43.0, 41.2, 29.1, 25.8×3, 19.4, 18.9, 18.1, –5.6, –5.7.

m/z, 333 ($M+Na^+$, 100%), 311, 310, 295, 276, 231, 223, 210, 187, 177, 159, 150.

HRMS Found 333.1853 ($M+Na^+$, $C_{17}H_{30}O_3SiNa$ requires 333.1862).

Preparation of (3*S,3a*S**,4*S**,5*R**,7a*S**)-4-((*tert*-butyldimethylsilyloxy)methyl)-3-hydroxy-3a,5-dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7aH)-one (III-50)**



Lithium bis(trimetylsilyl)amide (1.32 mL, of a 1M solution in THF) was added to a suspension of **III-49** (0.20 g, 0.66 mmol) and MoOPD (0.50 g, 1.32 mmol) in THF (6.5 mL) at –78 °C under nitrogen. The mixture was gradually raised up to –40 °C stirring for an additional 30 min, then raise up to –10 °C stirred for 18 h, then quenched with saturated NH_4Cl solution, and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column

chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-50** as a colourless solid [0.17 g, 0.52 mmol, 79% yield].

mp 96–98 °C; R_f=0.59 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3400, 2954, 2929, 1759, 1666, 1512, 1462, 1359, 1251, 1215, 1116, 991, 835, 752.

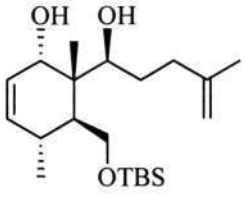
δ_H (500 MHz; $CDCl_3$) 5.86 (dd, 1H, *J*=10.1, 2.0 Hz, C<u>H</u>=CH), 5.72 (ddd, 1H, *J*=10.1, 2.9, 2.9 Hz, CH=C<u>H</u>), 4.62 (app.s, 1H, CHOCO), 4.44 (d, 1H, *J*=3.5 Hz, C<u>H</u>OH), 3.81 (dd, 1H, *J*=10.5, 3.5 Hz, C<u>H</u>HOTBS), 3.66 (dd, 1H, *J*=10.5, 4.5 Hz, CH<u>H</u>OTBS), 2.72 (d, 1H, *J*=3.5 Hz, CHO<u>H</u>), 2.37-2.22 (m, 1H, C<u>H</u>CH_3), 1.49 (app.q, 1H, *J*=4.5 Hz, C<u>H</u>CH_2OTBS), 1.17 (d, 3H, *J*=7.4 Hz, CH_3), 1.12 (s, 3H, CH_3), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.05 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$).

δ_C (100 MHz; $CDCl_3$) 176.6, 138.3, 120.6, 81.0, 74.3, 63.7, 43.9, 43.7, 31.6, 25.8×3, 21.0, 18.1, 14.8, –5.6, –5.7.

m/z; 349 ($M+Na^+$, 100%), 327, 323, 311, 280, 251, 240, 224, 195, 177, 159, 149, 131.

HRMS Found 349.1810 ($M+Na^+$, $C_{17}H_{30}O_4SiNa$ requires 349.1811).

Preparation of (1*S,4*R**,5*S**,6*S**)-5-((*tert*-butyldimethylsilyloxy)methyl)-6-((*S*)-1-hydroxy-4-methylpent-4-enyl)-4,6-dimethylcyclohex-2-enol (III-51)**



Methallyl tri-*n*-butyl tin (0.42 g, 0.12 mmol) was added to a solution of **III-83** (13.2 mg, 0.30 mmol) and 1,1'-azobis(cyclohexanecarbonitrile) (3.0 mg, 0.09 mmol) in benzene (1 mL) at room temperature under nitrogen. After heating at reflux for 6 h at 85 ^{o}C, the reaction mixture was allowed to cool to room temperature, and DBU (0.2 mL) was added. The mixture was stirred for an additional 1 h, diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous $NaSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography using a mixture of 10% w/w finely ground KF and 90% w/w silica as the stationary phase (10% EtOAc in hexanes) to give **III-51** as a colourless oil [6.4 mg, 0.0174 mmol, 58% yield].

R_f =0.46 (25% ethyl acetate/hexane).

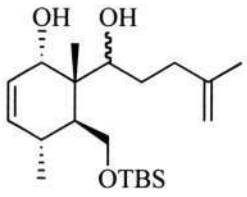
ν_{max}/cm^{-1} 3397, 2956, 2929, 2884, 2857, 1461, 1253, 1102, 1072, 993, 862, 832, 774.

δ_H (300 MHz; $CDCl_3$) 5.79 (ddd, 1H, *J*=9.8, 5.5, 2.0 Hz, C<u>H</u>=CH), 5.63 (dd, 1H, *J*=9.8, 2.2 Hz, CH=C<u>H</u>), 4.72 (br.s, 2H, CH=C<u>H</u>H and OH), 4.71 (s, 1H, C=C<u>H</u>H), 4.41 (d, 1H, *J*=4.4 Hz, OH), 3.99 (d, 1H, *J*=5.5 Hz, CH=CHC<u>H</u>OH), 3.73 (dd, 1H, *J*=10.6, 1.7 Hz, C<u>H</u>HOTBS), 3.70-3.53 (m, 2H, CC<u>H</u>OH and CH<u>H</u>OTBS), 2.39 (ddd, 1H, *J*=14.4, 7.1, 7.1 Hz, $CHOHCH_2C\underline{H}H$), 2.18-2.02 (m, 2H, $CHOHCH_2CH\underline{H}$ and $CHOHC\underline{H}HCH_2$), 1.93-1.77 (m, 3H, C<u>H</u>CH_3, $CHOHCH\underline{H}CH_2$ and C<u>H</u>CH_2OTBS), 1.74 (s, 3H, CH_3), 1.15 (d, 3H, *J*=6.8 Hz, CH_3), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.68 (s, 3H, CH_3), 0.11 (s, 3H, $Si(CH_3)$), 0.10 (s, 3H, $Si(CH_3)$).

δ_C (100 MHz; $CDCl_3$) 145.8, 135.8, 126.5, 110.3, 76.9, 70.8, 61.7, 42.8, 41.7, 35.2, 31.2, 27.7, 25.9×3, 22.6, 19.8, 18.2, 16.1, –5.6×2.

m/z; 391 ($M+Na^+$, 100%), 368, 352, 351, 330, 314, 279, 278, 238, 218, 216, 198, 178. HRMS 391.2653 ($M+Na^+$, $C_{21}H_{40}O_3SiNa$ requires 391.2644).

Preparation of (1*S,4*R**,5*S**,6*S**)-5-((*tert*-butyldimethylsilyloxy)methyl)-6-(1-hydroxy-4-methylpent-4-enyl)-4,6-dimethylcyclohex-2-enol (III-51′)**



A solution of 4-bromo-2-methyl-1-butene (36.3 mg, 0.24 mmol) in THF (0.5 mL) was added dropwise to magnesium turnings (7.1 mg, 0.29 mmol) in THF (0.5 mL) at a rate to maintain gentle reflux under nitrogen. The mixture was then stirred for 30 min at 80 °C. The resulting solution was cooled to room temperature and the precipitate was allowed to settle. The Grignard reagent was slowly added by cannula to a solution of aldehyde **III-70** (28.9 mg, 0.097 mmol) in THF (0.5 mL) at –20 °C under nitrogen. After stirring for 30 min at –20 °C, the reaction mixture was allowed to warm to 0 °C and stirred for 3 h. The reaction was quenched with saturated NH_4Cl solution, and extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with water, brine and dried over anhydrous $NaSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-51′** as a colourless liquid [13.3 mg, 0.036 mmol, 37% yield] as a mixture of

diastereoisomer in a ratio of 78:22, **III-70** as a colourless solid [13.5 mg, 0.045 mmol, 47% yield] and **III-76** as a colourless solid [4.9 mg, 0.016 mmol, 17% yield].

R_f =0.46 (25% ethyl acetate/hexane).

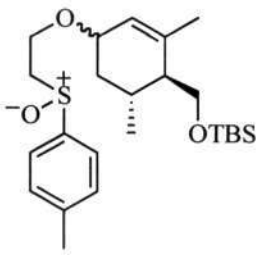
ν_{max}/cm^{-1} 3368, 2955, 2929, 2884, 2857, 1513, 1252, 1102, 1071, 1057, 933, 883, 831, 773.

δ_H (500 MHz; $CDCl_3$) 5.79 (ddd, 1H, *J*=9.8, 5.5, 2.0 Hz, C<u>H</u>=CH, major), 5.75 (ddd, 1H, *J*=9.8, 5.5, 2.3 Hz, C<u>H</u>=CH, minor), 5.65 (dd, 1H, *J*=9.8, 2.3 Hz, CH=C<u>H</u>, minor), 5.64 (dd, 1H, *J*=9.8, 2.3 Hz, CH=C<u>H</u>, major), 4.730 (s, 1H, C=C<u>H</u>H, major and minor), 4.728 (s, 1H, C=CH<u>H</u>, major and minor), 4.72 (s, 1H, OH, major and minor), 4.46 (d, 1H, *J*=6.1 Hz, OH, minor), 4.42 (d, 1H, *J*=4.6 Hz, OH, major), 3.99 (d, 1H, *J*=5.5 Hz, CH=CHC<u>H</u>OH, major and minor), 3.88-3.95 (m, 3H, C<u>H</u>HOTBS, CC<u>H</u>OH and CH<u>H</u>OTBS, major and minor), 2.39 (ddd, 1H, *J*=14.6, 7.1, 7.1 Hz, $CHOHCH_2C\underline{H}H$, major and minor), 2.16-2.02 (m, 2H, $CHOHCH_2CH\underline{H}$ and $CHOHC\underline{H}HCH_2$, major and minor), 1.92-1.76 (m, 3H, $C\underline{H}CH_3$, $CHOHCH\underline{H}CH_2$ and $C\underline{H}CH_2OTBS$, major and minor), 1.74 (s, 3H, CH_3, major and minor), 1.15 (d, 3H, *J*=6.9 Hz, CH_3, major), 1.11 (d, 3H, *J*=6.9 Hz, CH_3, minor), 0.89 (s, 9H, $SiC(CH_3)_3$, major and minor), 0.68 (s, 3H, CH_3, major and minor), 0.115 (s, 3H, $Si(CH_3)$, major), 0.106 (s, 3H, $Si(CH_3)$, major), 0.11 (s, 3H, $Si(CH_3)$, minor), 0.099 (s, 3H, $Si(CH_3)$, minor).

δ_C (125 MHz; $CDCl_3$) 145.8, 135.8, 126.4, 110.2, 76.9, 70.7, 61.6, 42.7, 41.6, 35.1, 31.1, 27.7, 25.8×3, 22.5, 19.7, 18.1, 16.0, –5.6×2.

m/z; 391 ($M+Na^+$, 100%), 352, 351, 332, 323, 306, 301, 288, 268, 260, 250.

Preparation of *tert*-butyl(((1*S,6*R**)-2,6-dimethyl-4-(2-(p-tolylsulfinyl)ethoxy) cyclohex-2-enyl)-methoxy)dimethylsilane (III-55)**



A solution of allylic alcohol **(III-46)** (0.09 g, 0.32 mmol) in THF (0.8 mL) was added drop wise to a suspension of sodium hydride (0.02 g, 0.53 mmol, 60% dispersion in mineral oil) in THF (0.8 mL) at 0 °C and stirred for 10 min. Then, the reaction mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was again cooled to 0 °C and treated with a solution of phenylvinylsulphoxide (0.16 g, 0.96 mmol) in THF (0.8 mL). After being stirred at the same temperature for 10 min, the reaction mixture was slowly warmed to room temperature and stirred for 4 h. The reaction was quenched with NH_4Cl (3 mL), extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give **III-55** as a colourless oil [0.11 g, 0.26 mmol, 82% yield].

R_f=0.20 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3035, 1666, 1597, 1494, 1359, 1317, 1253, 1209, 1184, 1087, 1047, 875, 835, 773.

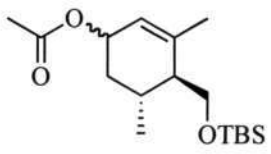
δ_H (300 MHz; $CDCl_3$) 7.52 (d, 2H, *J*=8.1 Hz, Ar-H), 7.30 (d, 2H, *J*=8.1 Hz, Ar-H), 5.57 and 5.47 (s, 1H, C<u>H</u>=CCH_3), 4.03-3.82 (m, 2H, $SOCH_2$), 3.80-3.52 (m, 3H, $C\underline{H_2}$OTBS and C<u>H</u>O), 3.07-2.87 (m, 2H, $OC\underline{H_2}CH_2SO$), 2.39 (s, 3H, CH_3), 2.10-1.50 (m, 3H, C<u>H</u>HCHCH_3, C<u>H</u>CH_3, C<u>H</u>CH_2OTBS), 1.71 (s, 3H, CH_3), 1.40-1.15 (m, 1H, CH<u>H</u>CHCH_3), 1.02 (dd, 3H, *J*=6.6, 3.3 Hz, CH_3), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.01 (s, 6H, $Si(CH_3)_2$).

δ_C (75 MHz; $CDCl_3$) 141.3, 140.9, 137.9, 129.9×2, 125.7, 124.0×2, 75.3, 60.7, 60.7, 58.9, 49.3, 36.5, 27.7, 25.8×3, 21.6, 21.4, 20.4, 18.3, –5.5×2.

m/z; 459 ($M+Na^+$, 100%) 300, 185.

HRMS Found 459.2361 ($M+Na^+$, $C_{24}H_{40}O_3SSiNa$ requires 459.2365).

Preparation of (4*S,5*R**)-4-((*tert*-butyldimethylsilyloxy)methyl)-3,5-dimethylcyclohex-2-enyl acetate (III-57)**



The allylic alcohol (**III-46**) (0.15 g, 0.55 mmol), potassium carbonate (0.31 g, 2.22 mmol), 4-(dimethylamino)pyridine (0.007 g, 0.06 mmol) and CH_2Cl_2 (3 mL) were mixed together at room temperature under nitrogen. The reaction mixture was slowly added

acetic anhydride (0.21 mL, 2.22 mmol). After stirring the reaction mixture for 2 h, then reaction was quenched with NH_4Cl (3 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-57** as a colourless oil as a mixture of two diastereoisomers in a ratio of 12:88 [0.15 g, 0.49 mmol, 89% yield].

R_f=0.37 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 2954, 2927, 2856, 1735, 1469, 1462, 1373, 1242, 1114, 1099, 1026, 873, 837, 775.

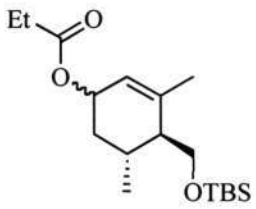
δ_H (500 MHz; $CDCl_3$) 5.47 (s, 1H, CH=C), 5.29 (br.s, 1H, CHOCO), 3.69 (app.d, 2H, *J*=3.1, Hz, C<u>H</u>$_2$OTBS), 2.10-2.20 (m, 1H, C<u>H</u>HCHCH$_3$), 2.05 (s, 3H, OCOCH$_3$), 2.10-1.90 (m, 1H, C<u>H</u>CH$_3$), 1.76 (br.s, 4H, C<u>H</u>CH$_2$OTBS and CH=CC<u>H</u>$_3$), 1.43-1.31 (m, 1H, CH<u>H</u>CHCH$_3$), 1.04 (d, 3H, *J*=6.7 Hz, CH$_3$), 0.88 (s, 9H, SiC(CH$_3$)$_3$), 0.04 (s, 6H, Si(CH$_3$)$_2$).

δ_C (100 MHz; $CDCl_3$) 170.9, 138.9, 123.7, 69.9, 61.3, 49.0, 35.3, 27.4, 25.8×3, 21.8, 21.5, 20.2, 18.2, –5.5×2.

m/z; 335 ($M+Na^+$, 100%) 237, 208, 194, 191.

HRMS Found 335.2020 ($M+Na^+$, $C_{17}H_{32}O_3SiNa$ requires 335.2018).

Preparation of (4*S,5*R**)-4-((*tert*-butyldimethylsilyloxy)methyl)-3,5-dimethylcyclohex-2-enyl propionate (III-62)**



The allylic alcohol **(III-46)** (0.10 g, 0.37 mmol), triethyl orthoacetate (0.5 mL, 2.60 mmol) and propionic acid (2 μL, 0.02 mmol) were mixed together and heated at 138 °C for 1 h. The reaction was quenched with water (3 mL) and extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 5% EtOAc in hexanes) to give **III-62** as a colourless liquid as a mixture of two diastereoisomers in a ratio of 24:76 [0.10 g, 0.30 mmol, 80% yield].

R_f = 0.70 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 2954, 2927, 2881, 2856, 1732, 1462, 1348, 1255, 1188, 1109, 1091, 991, 873, 837, 775, 665.

δ_H (500 MHz; $CDCl_3$) 5.60-5.50 (m, 1H, C=CH, major), 5.44 (app.s, 1H, C=CH, minor), 5.30-5.15 (m, 1H C<u>H</u>OCOEt), major and minor), 3.78-3.60 (m, 2H, C<u>H</u>$_2$OTBS, major and minor), 2.29 (q, 2H, *J*=7.6 Hz, C<u>H</u>$_2$CH$_3$, minor), 2.27 (q, 2H, *J*=7.6 Hz, C<u>H</u>$_2$CH$_3$, major), 2.20-2.07 (m, 1H, CH$_2$C<u>H</u>CH$_3$, major), 1.98-1.90 (m, 1H, CH$_2$C<u>H</u>CH$_3$, minor), 1.80-1.65

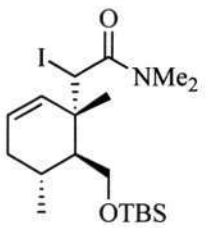
(m, 5H, CH_3 and $C\underline{H}_2CHCH_3$, major and minor), 1.57 (ddd, 1H, *J*=13.6, 8.6, 5.0 Hz, $C\underline{H}CH_2OTBS$, major and minor), 1.08 (q, 3H, *J*=7.5 Hz, $CH_2C\underline{H}_3$, major and minor), 1.01 (d, 3H, *J*=6.8 Hz, CH_3, minor), 0.99 (d, 3H, *J*=6.9 Hz, CH_3, major), 0.87 (s, 9H, $SiC(CH_3)_3$, major), 0.85 (s, 9H, $SiC(CH_3)_3$, minor), 0.033 (s, 3H, $SiCH_3$, major), 0.029 (s, 3H, $SiCH_3$, major), 0.01 (s, 6H, $Si(CH_3)_2$, minor).

δ_C (75 MHz; $CDCl_3$) 174.4, 140.1, 122.2, 68.0, 62.2, 49.0, 33.1, 28.0, 26.3, 25.9×3, 22.1, 19.7, 15.7, 9.2, –5.5×2.

m/z; 349 ($M+Na^+$, 100%), 306, 302, 287, 278, 252, 237, 224, 206, 196, 190, 175, 162.

HRMS Found 349.2167 ($M+Na^+$, $C_{18}H_{34}O_3SiNa$ requires 349.2175).

Preparation of (*R)-2-((1*S**,5*R**,6*S**)-6-((*tert*-butyldimethylsilyloxy)methyl)-1,5-dimethyl cyclohex-2-enyl)-2-iodo-*N*,*N*-dimethylacetamide (III-68)**



According to the general procedure as described for compound **III-48**, iodine (0.29 g, 1.14 mmol) was added to a solution of **III-47** (0.19 g, 0.57 mmol) in THF-Buffer 7 (5 mL: 5 mL) at 0 °C. The reaction was gradually raised up to room temperature and stirred for an additional 20 h, then the reaction mixture was quenched with an aq. $Na_2S_2O_3$ solution until the reaction mixture became clear, and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with water, brine and dried over anhydrous

$MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-68** as a yellow oil [67.2 mg, 0.14 mmol, 25% yield] and **III-48** as a colourless solid as a single isomer [159.6 mg, 0.36 mmol, 64% yield].

R_f =0.55 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3018, 2954, 2929, 1782, 1643, 1462, 1388, 1257, 1215, 1097, 989, 837, 748, 665.

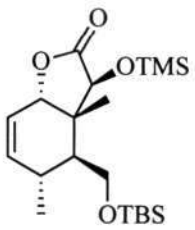
δ_H (500 MHz; $CDCl_3$) 5.79 (app.d, 1H, *J*=10.2 Hz, C<u>H</u>=CH), 5.68-5.57 (m, 1H, CH=C<u>H</u>), 5.20 (s, 1H, CHI), 3.76 (dd, 1H, *J*=10.8, 3.6 Hz, C<u>H</u>HOTBS), 3.64 (dd, 1H, *J*=10.8, 6.3 Hz, CH<u>H</u>OTBS), 3.02 (s, 3H, NCH_3), 2.89 (s, 3H, NCH_3), 1.97 (dt, 1H, *J*=16.8, 4.3 Hz, CH=CHC<u>H</u>H), 1.83 (dt, 1H, *J*=10.6, 2.3 Hz, C<u>H</u>CH_3), 1.81-1.65 (m, 2H, CH=CHCH<u>H</u> and C<u>H</u>CH_2OTBS), 1.12 (s, 3H, CH_3), 0.95 (d, 3H, *J*=6.0 Hz, CH_3), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.054 (s, 3H, $SiCH_3$), 0.052 (s, 3H, $SiCH_3$).

δ_C (100 MHz; $CDCl_3$) 169.8, 136.1, 123.6, 62.3, 44.9, 41.2, 38.2, 38.1, 36.5, 34.6, 29.0, 26.0×3, 25.8, 19.8, 18.4, –5.4, –5.5.

m/z; 466 ($M+H^+$, 100%), 414, 413, 392, 391, 341, 340, 311, 279, 257, 205, 180, 149;

HRMS Found 466.1628 ($M+H^+$, $C_{19}H_{37}NO_2SiI$ requires 466.1638).

Preparation of (3*S,3a*R**,4*S**,5*R**,7a*S**)-4-((*tert*-butyldimethylsilyloxy)methyl)-3a,5-dimethyl-3-(tri-methylsilyloxy)-3,3a,4,5-tetrahydrobenzofuran-2(7aH)-one (III-69)**



Potassium bis(trimetylsilyl)amide (1.25 mL, of a 1M solution) was added a suspension of **III-49** (80 mg, 0.25 mmol) and MoOPD (0.48 g, 1.25 mmol) in THF (2 mL) at –78 °C under nitrogen. The mixture was gradually raised up to –40 °C stirring for an additional 30 min, then raise up to –6 °C stirred for 20 h, then quenched with saturated NH_4Cl solution, and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-49** as a colourless solid [10 mg, 0.03 mmol, 13% recovered], **III-50** as a colourless solid [30 mg, 0.09 mmol, 37% yield] and **III-69** as a colourless solid [20 mg, 0.05 mmol, 20% yield].

mp 47–49 °C; R_f=0.64 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 2956, 2929, 2883, 2856, 1778, 1660, 1512, 1462, 1404, 1359, 1251, 1228, 1097, 989, 939, 837, 775.

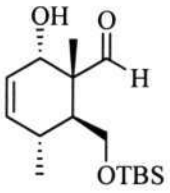
δ_H (500 MHz; $CDCl_3$) 5.87 (dd, 1H, *J*=10.0, 2.2 Hz, C<u>H</u>=CH), 5.76 (ddd, 1H, *J*=10.0, 4.6, 2.4 Hz, CH=C<u>H</u>), 4.54 (d, 1H, *J*=4.6 Hz, CHOCO), 4.35 (s, 1H, C<u>H</u>OTMS), 3.74 (d, 2H, *J*=4.0 Hz, C<u>H</u>$_2$OTBS), 2.35-2.22 (m, 1H, C<u>H</u>CH_3), 1.17 (dt, 1H, *J*=8.9, 4.0 Hz, C<u>H</u>CH_2OTBS), 1.06 (d, 3H, *J*=7.2 Hz, CH_3), 1.00 (s, 3H, CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.19 (s, 9H, $Si(CH_3)_3$), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$).

δ_C (125 MHz; $CDCl_3$) 175.2, 140.2, 119.5, 80.3, 75.3, 62.0, 44.7, 42.9, 30.1, 25.8×3, 19.9, 18.1, 12.5, 0.07×3, –5.5, –5.6.

m/z; 421 ($M+Na^+$, 100%), 399, 391, 349, 327, 267, 249, 221, 195, 177, 159, 146, 131.

HRMS Found 421.2207 ($M+Na^+$, $C_{20}H_{38}O_4Si_2Na$ requires 421.2206).

Preparation of (1*R,2*S**,5*R**,6*S**)-6-((*tert*-butyldimethylsilyloxy)methyl)-2-hydroxy-1,5-dimethyl cyclohex-3-enecarbaldehyde (III-70)**



Sodium periodate (78.0 mg, 0.36 mmol) was added to a solution of **III-73** (80.3 mg, 0.24 mmol) in THF-H_2O (1.2 mL: 1.2 mL) at room temperature. The reaction was stirred at room temperature for 1 h, then the reaction mixture was diluted with a saturated $NaHCO_3$ solution (5 mL), and extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column

chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-70** as a colourless solid [69.9 mg, 0.23 mmol, 96% yield].

mp 47–48 °C; R_f=0.43 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3425, 3415, 3024, 2956, 2929, 2881, 2856, 1712, 1643, 1462, 1257, 1101, 835, 756, 667.

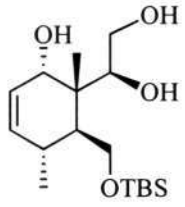
δ_H (300 MHz; $CDCl_3$) 9.78 (s, 1H, CHO), 5.80 (ddd, 1H, *J*=9.8, 5.2, 2.2 Hz, C<u>H</u>=CH), 5.70 (dd, 1H, *J*=9.8, 2.3 Hz, CH=C<u>H</u>), 3.94-3.80 (m, 2H, C<u>H</u>OH and C<u>H</u>HOTBS), 3.53 (dd, 1H, *J*=9.8, 9.8 Hz, CH<u>H</u>OTBS), 2.45-2.25 (m, 2H, C<u>H</u>CH_2OTBS and OH), 2.02-1.86 (m, 1H, C<u>H</u>CH_3), 1.13 (d, 3H, *J*=7.0 Hz, CH_3), 0.95 (s, 3H, CH_3), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$).

δ_C (75 MHz; $CDCl_3$) 208.7, 136.9, 125.1, 71.6, 62.5, 49.7, 42.4, 30.0, 25.8×3, 19.9, 18.2, 12.7, –5.6, –5.7.

m/z; 299 ($M+H^+$, 100%), 295, 281, 280, 268, 263, 251, 229, 212, 180, 166, 148, 131.

HRMS Found 299.2046 ($M+H^+$, $C_{16}H_{31}O_3Si$ requires 299.2042).

Preparation of (*S)-1-((1*R**,2*S**,5*R**,6*S**)-6-((*tert*-butyldimethylsilyloxy)methyl)-2-hydroxy-1,5-dimethylcyclohex-3-enyl)ethane-1,2-diol (III-73)**



A solution of **III-50** (84.6 mg, 0.26 mmol) in THF (2 mL) was slowly added to a suspension of $LiAlH_4$ (78.7 mg, 2.07 mmol) in THF (1.5 mL) at 80 °C under nitrogen. After heating at reflux for 2 h at 80 °C, the reaction mixture was cooled to 0 °C, and quenched with sat NH_4Cl (3 mL), water (5 mL) and stirred for an additional 5 min. The insoluble materials were removed by filtration through Celite and washed with THF, and extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give **III-73** as a colourless solid [80.3 mg, 0.24 mmol, 94% yield].

mp 120–121 °C; R_f=0.21 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3373, 3360, 3020, 2954, 2927, 2885, 2856, 1462, 1390, 1361, 1253, 1103, 1051, 995, 835.

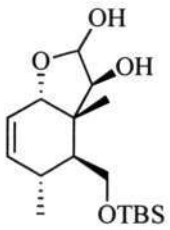
δ_H (500 MHz; $CDCl_3$) 5.75 (ddd, 1H, *J*=9.7, 5.7, 2.2 Hz, C<u>H</u>=CH), 5.65 (dd, 1H, *J*=9.7, 2.3 Hz, CH=C<u>H</u>), 4.82 (br.s, 1H, OH), 3.95-3.64 (m, 6H, C<u>H</u>$_2$OH, C<u>H</u>$_2$OTBS and C<u>H</u>OH×2), 3.09 (br.s, 1H, OH), 2.62 (br.s, 1H, OH), 1.90-1.76 (m, 1H, C<u>H</u>CH_3), 1.66 (ddd, 1H, *J*=10.0, 7.0, 2.6 Hz, C<u>H</u>CHOTBS), 1.09 (d, 3H, *J*=6.9 Hz, C<u>H</u>CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.81 (s, 3H, CH_3), 0.11 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$).

δ_C (100 MHz; $CDCl_3$) 136.9, 125.6, 76.0, 70.8, 62.3, 62.0, 45.5, 42.8, 30.5, 25.8×3, 19.9, 18.1, 13.0, –5.2, –5.5.

m/z; 353 ($M+Na^+$, 100%), 330, 314, 313, 312, 295, 282, 270, 253, 250, 242, 229, 223, 213.

HRMS Found 353.2119 ($M+Na^+$, $C_{17}H_{34}O_4SiNa$ requires 353.2124).

Preparation of (3*S,3a*S**,4*S**,5*R**,7a*S**)-4-((*tert*-butyldimethylsilyloxy)methyl)-3a,5-dimethyl-2,3,3a,4,5,7a-hexahydrobenzofuran-2,3-diol (III-74)**



A solution of **III-50** (54.8 mg, 0.168 mmol) in THF (1 mL) was slowly added to a suspension of $LiAlH_4$ (12.7 mg, 0.34 mmol) in THF (1 mL) at 0 °C under nitrogen. The reaction mixture was allowed to warm up to room temperature and was stirred for 2 h, cooled to 0 °C, and quenched with sat NH_4Cl (3 mL), water (5 mL) and stirred for an additional 5 min. The insoluble materials were removed by filtration through Celite and washed with THF, and extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give **III-74** as a colourless solid [41.6 mg, 0.127 mmol, 76% yield].

mp 100–102 °C; R_f = 0.45 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3292, 2955, 2928, 2883, 2857, 1512, 1461, 1387, 1251, 1105, 1033, 992, 862, 830, 772.

δ_H (500 MHz; $CDCl_3$) 5.80 (ddd, 1H, *J*=10.0, 3.9, 2.3 Hz, C<u>H</u>=CH), 5.75 (d, 1H, *J*=10.0 Hz, CH=C<u>H</u>), 5.52 (d, 1H, *J*=4.0 Hz, OC<u>H</u>OH), 4.18 (app.d, 2H, *J*=4.3 Hz,

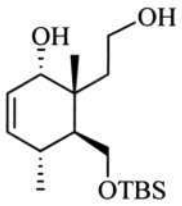
OCHOHCHOH and CHOCHOH), 3.88 (dd, 1H, *J*=10.8, 3.8 Hz, CHHOTBS), 3.76 (dd, 1H, *J*=10.8, 7.1 Hz, CHHOTBS), 2.18-2.05 (m, 1H, $CHCH_3$), 1.29-1.20 (m, 1H, $CHCH_2OTBS$), 1.10 (d, 3H, *J*=7.0 Hz, CH_3), 0.99 (s, 3H, CH_3), 0.92 (s, 9H, $SiC(CH_3)_3$), 0.11 (s, 6H, $Si(CH_3))_2$.

δ_C (75 MHz; $CDCl_3$) 138.3, 122.6, 96.4, 79.6, 78.7, 62.8, 46.9, 44.7, 30.2, 25.9×3, 19.7, 18.3, 14.0, –5.5, –5.6.

m/z; 351 ($M+Na^+$, 100%), 313, 311, 297, 283, 241, 223, 187, 167, 149.

HRMS Found 351.1960 ($M+Na^+$, $C_{17}H_{32}O_4SiNa$ requires 351.1968).

Preparation of (1*S,4*R**,5*S**,6*R**)-5-((*tert*-butyldimethylsilyloxy)methyl)-6-(2-hydroxy ethyl)-4,6-dimethylcyclohex-2-enol (III-75)**



A solution of **III-74** (57.1 mg, 0.174 mmol) in THF (1 mL) was slowly added to a suspension of $LiAlH_4$ (32.0 mg, 0.87 mmol) in THF (1 mL) at 80 °C under nitrogen. After heating at reflux for 2 h at 80 °C, the reaction mixture was cooled to 0 °C, and quenched with sat NH_4Cl (3 mL), water (5 mL) and stirred for an additional 5 min. The insoluble materials were removed by filtration through Celite and washed with THF, and the crude mixture was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under

reduced pressure, the crude product was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give **III-75** as a colourless solid [52.9 mg, 0.168 mmol, 97% yield].

mp 69–70 °C; R_f = 0.25 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3292, 2955, 2928, 2883, 2857, 1512, 1461, 1387, 1251, 1105, 1033, 992, 862, 830, 772.

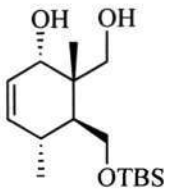
δ_H (300 MHz; $CDCl_3$) 5.73 (app.s, 2H, C<u>H</u>=C<u>H</u>), 3.91 (dd, 1H, *J*=10.8, 3.0 Hz, C<u>H</u>HOTBS), 3.88-3.81 (m, 2H, C<u>H</u>HOH and CH<u>H</u>OTBS), 3.79 (d, 1H, *J*=3.1 Hz, CH<u>H</u>OH), 3.69 (d, 1H, *J*=3.2 Hz, C<u>H</u>OH), 2.78 (br.s, 2H, OH×2), 2.30 (qdd, 1H, *J*=10.2, 7.0, 7.0 Hz, C<u>H</u>CH_3), 1.89 (ddd, 1H, *J*=15.1, 9.0, 4.0 Hz, C<u>H</u>HCH_2OH), 1.72 (ddd, 1H, *J*=15.1, 5.5, 3.1 Hz, CH<u>H</u>CH_2OH), 1.39 (ddd, 1H, *J*=10.2, 3.0, 3.0 Hz, C<u>H</u>CH_2OTBS), 1.07 (d, 3H, *J*=7.0 Hz, CHC<u>H</u>$_3$), 0.91 (s, 3H, CH_3), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.04 (s, 6H, $Si(CH_3)_2$).

δ_C (125 MHz; $CDCl_3$) 138.1, 125.1, 71.4, 60.0, 58.7, 45.7, 39.6, 39.1, 29.9, 25.9×3, 19.4, 19.0, 18.1, –5.5, –5.7.

m/z; 337 ($M+Na^+$, 100%), 309, 301, 297, 294, 289, 281, 264, 251, 247, 241, 232.

HRMS Found 337.2174 ($M+Na^+$, $C_{17}H_{34}O_3SiNa$ requires 337.2175).

(1*S,4*R**,5*S**,6*S**)-5-((*tert*-butyldimethylsilyloxy)methyl)-6-(hydroxymethyl)-4,6-dimethylcyclohex-2-enol (III-76)**



mp 65–67 °C; R_f = 0.19 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1}3211, 2955, 2928, 2883, 2856, 1461, 1384, 1251, 1100, 1028, 992, 862, 831, 770, 701, 629, 589.

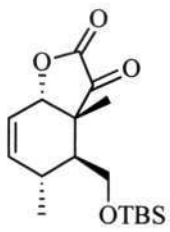
δ_H (300 MHz; $CDCl_3$) 5.76 (ddd, 1H, *J*=9.8, 5.2, 1.0 Hz, C<u>H</u>=CH), 5.65 (dd, 1H, *J*=9.8, 1.3, CH=C<u>H</u>), 3.98-3.56 (m, 7H, C<u>H</u>$_2$OTBS, C<u>H</u>$_2$OH, C<u>H</u>OH and OH×2), 1.94 (br.s, 2H, C<u>H</u>CH$_2$OTBS and C<u>H</u>CH$_3$), 1.13 (d, 3H, *J*=6.6 Hz, CHC<u>H</u>$_3$), 0.91 (s, 9H, SiC(CH$_3$)$_3$), 0.67 (s, 3H, CH$_3$), 0.11 (s, 6H, Si(CH$_3$)$_2$).

δ_C (125 MHz; $CDCl_3$) 136.6, 126.2, 75.1, 70.6, 61.3, 41.6, 39.7, 30.2, 25.8×3, 19.6, 18.2, 15.7, –5.5, –5.6.

m/z; 301 (M+H$^+$, 100%), 278, 252, 248, 222, 207, 196, 190, 186, 182, 175, 163, 148.

HRMS Found 301.2204 (M+Na$^+$, $C_{16}H_{33}O_3Si$ requires 301.2199).

Preparation of (3a*R,4*S**,5*R**,7a*S**)-4-((*tert*-butyldimethylsilyloxy)methyl)-3a,5-dimethyl-4,5-dihydrobenzofuran-2,3(3aH,7aH)-dione (III-77)**



2-Iodoxybenzoic acid (0.18 g, 0.63 mmol) was added to a solution of **III-50** (17.9 mg, 0.055 mmol) in DMSO (1 mL) at room temperature. The mixture was stirred at room temperature for 3 days, then the reaction mixture was diluted with saturated $NaHCO_3$ solution (10 mL), and extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-77** as a colourless solid [15.0 mg, 0.046 mmol, 84% yield].

mp 74–75 °C; R_f=0.61 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 2955, 2929, 2884, 2857, 1787, 1461, 1249, 1110, 990, 952, 909, 832, 775, 675;

δ_H (300 MHz; $CDCl_3$) 6.06 (dd, 1H, *J*=10.1, 1.5 Hz, C<u>H</u>=CH), 5.90 (ddd, 1H, *J*=10.1, 4.3, 2.5 Hz, CH=C<u>H</u>), 4.59 (d, 1H, *J*=4.3 Hz, CHOCO), 3.69 (dd, 1H, *J*=11.3, 3.5 Hz, C<u>H</u>HOTBS), 3.65 (dd, 1H, *J*=11.3, 3.0 Hz, CH<u>H</u>OTBS), 2.60-2.40 (m, 1H, C<u>H</u>CH_3), 1.43

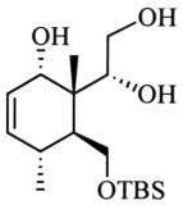
(ddd, 1H, *J*=9.3, 3.5, 3.3 Hz, C<u>H</u>CH$_2$OTBS), 1.24 (s, 3H, CH$_3$), 1.13 (d, 3H, *J*=7.1 Hz, CHC<u>H</u>$_3$), 0.88 (s, 9H, SiC(CH$_3$)$_3$), 0.08 (s, 3H, SiCH$_3$), 0.04 (s, 3H, SiCH$_3$).

δ_C (125 MHz; $CDCl_3$) 197.9, 160.8, 142.1, 119.0, 79.2, 58.7, 48.3, 41.1, 28.5, 25.8×3, 19.0, 18.1, 13.7, –5.7, –5.8.

m/z; 347 (M+Na$^+$, 100%), 325, 324, 311, 306, 298, 280, 278, 266, 261, 257, 242, 238.

HRMS Found 347.1651 (M+Na$^+$, $C_{17}H_{28}O_4SiNa$ requires 347.1655).

Preparation of (*R)-1-((1*R**,2*S**,5*R**,6*S**)-6-((*tert*-butyldimethylsilyloxy)methyl)-2-hydroxy-1,5-dimethylcyclohex-3-enyl)ethane-1,2-diol (III-78)**



A solution of **III-80** (30.8 mg, 0.09 mmol) in THF (1 mL) was slowly added to a suspension of $LiAlH_4$ (10.7 mg, 0.28 mmol) in THF (0.5 mL) at 80 °C under nitrogen. After heating at reflux for 2 h at 80 °C, the reaction mixture was cooled to 0 °C, and quenched with sat NH_4Cl (3 mL), water (5 mL) and stirred for an additional 5 min. The insoluble materials were removed by filtration through Celite, washed with THF, and the crude mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2,

50% EtOAc in hexanes) to give **III-78** as a colourless solid [23.9 mg, 0.07 mmol, 77% yield].

mp 118–120 °C; R_f=0.21 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3368, 2955, 2928, 2884, 2857, 1461, 1253, 1103, 1066, 1026, 995, 864, 834, 774.

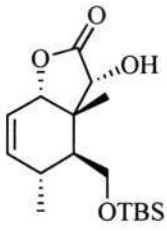
δ_H (300 MHz; $CDCl_3$) 5.73 (ddd, 1H, *J*=9.8, 5.4, 1.8 Hz, C<u>H</u>=CH), 5.65 (dd, 1H, *J*=9.8, 1.9 Hz, CH=C<u>H</u>), 4.58 (app.d, 1H, *J*=5.1 Hz, C<u>H</u>OHCH$_2$OH), 4.12 (br.s, 1H, OH), 3.97-3.65 (m, 6H, C<u>H$_2$</u>OH, C<u>H$_2$</u>OTBS, C<u>H</u>OH, OH), 2.47 (br.s, 1H, OH), 2.10-1.87 (m, 2H, C<u>H</u>CH$_3$, C<u>H</u>CH$_2$OTBS), 1.14 (d, 3H, *J*=6.5 Hz, CHC<u>H$_3$</u>), 0.90 (s, 9H, SiC(CH$_3$)$_3$), 0.76 (s, 3H, CH$_3$), 0.111 (s, 3H, SiCH$_3$), 0.106 (s, 3H, SiCH$_3$).

δ_C (125 MHz; $CDCl_3$) 136.3, 125.8, 78.3, 71.3, 62.3, 61.2, 42.4, 40.8, 30.6, 25.8×3, 19.6, 18.1, 16.3, –5.58, –5.63.

m/z; 353 (M+Na$^+$, 100%), 314, 313, 306, 299, 294.

HRMS 353.2129 (M+Na$^+$, $C_{17}H_{34}O_4SiNa$ requires 353.2124).

Preparation of (3*R,3a*S**,4*S**,5*R**,7a*S**)-4-((*tert*-butyldimethylsilyloxy)methyl)-3-hydroxy-3a,5-dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7aH)-one (III-80)**



Sodium borohydride (93 mg, 2.46 mmol) was slowly portion wise added to a solution of **III-77** (0.16 g, 0.49 mmol) in methanol (5 mL) at –78 °C. The temperature was allowed gradually rise to 0 °C and it was stirred at this temperature for an additional 2 h, then quenched with saturated NH_4Cl solution, and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-80** as a colourless solid [0.16 g, 0.48 mmol, 98% yield].

mp 92–94 °C; R_f=0.26 (50% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3381, 3305, 3018, 2956, 2929, 2883, 2856, 1774, 1462, 1255, 1215, 1141, 958, 835, 756.

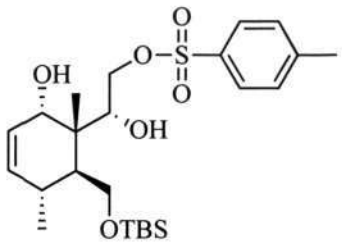
δ_H (300 MHz; $CDCl_3$) 5.91 (dd, 1H, *J*=9.9, 1.9 Hz, C<u>H</u>=CH), 5.81 (ddd, 1H, *J*=9.9, 5.1, 2.3 Hz, CH=C<u>H</u>), 5.73 (app.d, 1H, *J*=10.0 Hz, OH), 4.23-4.12 (m, 2H, C<u>H</u>OCO and C<u>H</u>OH), 3.82 (dd, 1H, *J*=11.3, 1.8 Hz, C<u>H</u>HOTBS), 3.74 (dd, 1H, *J*=11.3, 7.7 Hz, CH<u>H</u>OTBS), 2.05-1.87 (m, 1H, C<u>H</u>CH_3), 1.42 (ddd, 1H, *J*=10.0, 7.7, 1.8 Hz, C<u>H</u>CH_2OTBS), 1.15 (s, 3H, CH_3), 1.13 (d, 3H, *J*=7.0 Hz, CH_3), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.11 (s, 6H, $Si(CH_3)_2$).

δ_C (125 MHz; $CDCl_3$) 175.6, 141.0, 118.9, 79.4, 77.1, 61.0, 45.2, 44.4, 29.7, 25.7×3, 19.9, 18.1, 15.9, –5.4, –5.6.

m/z; 349 ($M+Na^+$, 100%), 326, 311, 279, 274, 256, 240, 220, 213, 200, 180, 177.

HRMS 349.1814 ($M+Na^+$, $C_{17}H_{30}O_4SiNa$ requires 349.1811).

Preparation of (*R)-2-((1*R**,2*S**,5*R**,6*S**)-6-((*tert*-butyldimethylsilyloxy)methyl)-2-hydroxy-1,5-dimethyl-cyclohex-3-enyl)-2-hydroxyethyl 4-methylbenzenesulfonate (III-81)**



Triethylamine (0.04 mL, 0.31 mmol) was added to a solution of **III-78** (92.5 mg, 0.28 mmol), 4-(dimethylamino)pyridine (7 mg, 0.06 mmol) and *p*-TsCl (80 mg, 0.42 mmol) in CH_2Cl_2 (2.8 mL) at 0 °C under nitrogen. The reaction mixture was stirred and slowly warmed up to room temperature (5 h). The mixture was diluted with sat. NH_4Cl (5 mL), water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-81** as a colourless oil [67.8 mg, 50% yield] and **III-82** as a colourless solid [18.8 mg, 21% yield].

R_f=0.57 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3369, 2962, 2926, 2879, 1457, 1357, 1174, 1033, 1009, 970, 814, 682, 665, 553; δ_H (500 MHz; $CDCl_3$) 7.81 (d, 2H, *J*=8.2 Hz, Ar-H), 7.33 (d, 2H, *J*=8.2 Hz, Ar-H), 5.76-5.60 (m, 2H, C<u>H</u>=C<u>H</u>), 4.46 (dd, 1H, *J*=10.6, 2.1 Hz, C<u>H</u>HOTs), 4.28 (dd, 1H, *J*=10.6, 8.1

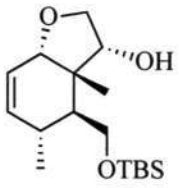
Hz, CHHOTs), 3.96 (dd, 1H, *J*=8.1, 2.1 Hz, CHOHCH$_2$OTs), 3.77 (app.d, 1H, *J*=10.8 Hz, CHHOTBS), 3.73 (app.d, 1H, *J*=5.2 Hz, CH=CHCHOH), 3.69 (dd, 1H, *J*=10.8, 6.6 Hz, CHHOTBS), 2.44 (s, 3H, Ar-CH$_3$), 2.08-1.88 (m, 2H, CHCH$_3$ and CHCH$_2$OTBS), 1.11 (d, 3H, *J*=6.4 Hz, CHCH$_3$), 0.89 (s, 9H, SiC(CH$_3$)$_3$), 0.77 (s, 3H, CH$_3$), 0.09 (s, 6H, Si(CH$_3$)$_2$).

δ_C (75 MHz; CDCl$_3$), 144.7, 138.7, 134.3, 129.9×2, 127.7×2, 121.2, 86.5, 79.7, 71.6, 61.6, 47.1, 44.8, 30.5, 25.8×3, 21.7, 19.6, 18.1, 12.1, –5.5, –5.6.

m/z; 507 (M+Na$^+$, 100%), 485.

HRMS 507.2223 (M+Na$^+$, $C_{24}H_{40}O_6SiSNa$ requires 507.2213).

Preparation of (3*S,3a*S**,4*S**,5*R**,7a*S**)-4-((*tert*-butyldimethylsilyloxy)methyl)-3a,5-dimethyl-2,3,3a,4,5,7a-hexahydrobenzofuran-3-ol (III-82)**



Sodium iodide (14.0 mg, 0.09 mmol), sodium bicarbonate (1.0 mg, 0.009 mmol) and sodium sulfite (0.6 mg, 0.005 mmol) was added to a solution of tosylate **III-81** (22.5 mg, 0.046 mmol) in acetone (0.7 mL) at room temperature. A condenser and calcium sulfate dying tube were added, and the solution was heated at reflux for 6 h. After the solution was cooled, the sodium tosylate was filter off and most of acetone evaporated under reduced pressure. The mixture was diluted with Et$_2$O (10 mL) and water (10 mL),

the layers separated, the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous $NaSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-82** as a colourless solid [13.5 mg, 0.043 mmol, 93% yield].

R_f=0.36 (25% ethyl acetate/hexane).

mp 63–65 °C; R_f=0.36 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3408, 2954, 2928, 2880, 2857, 1461, 1252, 1097, 1074, 1037, 1004, 985, 833, 774.

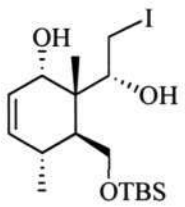
δ_H (500 MHz; $CDCl_3$) 5.84 (ddd, 1H, *J*=10.0, 3.5, 2.6 Hz, C<u>H</u>=CH), 5.65 (d, 1H, *J*=10.0 Hz, CH=C<u>H</u>), 4.45 (dd, 1H, *J*=4.5, 1.6 Hz, OH), 3.96 (dt, 1H, *J*=4.5, 4.5 Hz, C<u>H</u>OH), 3.93-3.86 (m, 2H, OC<u>H</u>H and C<u>H</u>HOTBS), 3.81 (ddd, 1H, *J*=9.4, 4.5, 1.6 Hz, OCH<u>H</u>), 3.65-3.52 (m, 2H, C<u>H</u>OCH_2 and CH<u>H</u>OTBS), 1.93 (dd, 1H, *J*=10.3, 3.9 Hz, C<u>H</u>CH_2OTBS), 1.90-1.82 (m, 1H, C<u>H</u>CH_3), 1.09 (d, 3H, *J*=6.7 Hz, CH_3), 0.97 (s, 3H, CH_3), 0.93 (s, 9H, SiC$(CH_3)_3$), 0.13 (s, 6H, Si$(CH_3)_2$).

δ_C (125 MHz; $CDCl_3$) 136.6, 123.9, 83.3, 81.1, 72.7, 62.8, 45.7, 41.2, 29.7, 25.8×3, 20.3, 18.6, 18.1, –5.6, –5.7;

m/z; 313 ($M+H^+$, 100%), 312, 292, 262, 251, 227, 198, 180, 162.

HRMS 313.2200 ($M+H^+$, $C_{17}H_{33}O_3Si$ requires 313.2199).

Preparation of (1*S,4*R**,5*S**,6*R**)-5-((*tert*-butyldimethylsilyloxy)methyl)-6-((*R**)-1-hydroxy-2-iodoethyl)-4,6-dimethylcyclohex-2-enol (III-83)**



Imidazole (15 mg, 0.21 mmol) was slowly added to a solution of **III-78** (21.2 mg, 0.064 mmol) in CH_2Cl_2 (0.5 mL) followed by a solution of triphenylphosphine (19 mg, 0.07 mmol) in CH_2Cl_2 at –30 °C under nitrogen. A solution of iodine (18 mg, 0.07 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to the stirred reaction mixture. After stirring the reaction mixture for 2 h, the reaction was quenched with saturated sodium thiosulfate (5 mL), and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous $NaSO_4$. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to give **III-83** as a colourless oil [18.9 mg, 0.043 mmol, 67% yield] and **III-82** as a colourless solid [3.1 mg, 0.01 mmol, 15% yield].

R_f =0.27 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3387, 2922, 2851, 1448, 1416, 1374, 1259, 1092, 1031, 987, 892, 838, 578, 553; δ_H (300 MHz; $CDCl_3$) 5.75 (ddd, 1H, *J*=9.8, 5.4, 2.0 Hz, C<u>H</u>=CH), 5.71 (dd, 1H, *J*=9.8, 2.0 Hz, CH=C<u>H</u>), 4.68 (br.s, 1H, OH), 4.45 (br.s, 1H, OH), 4.05 (dd, 1H, *J*=9.5, 4.5 Hz, C<u>H</u>HI), 3.96 (dd, 1H, *J*=8.2, 4.5 Hz, C<u>H</u>HOTBS), 3.84-3.56 (m, 4H, C<u>H</u>OH, C<u>H</u>OHCH$_2$I,

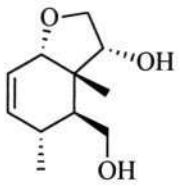
CHHI and CHHOTBS), 1.90-1.79 (m, 1H, CHCH$_2$OTBS), 1.72 (app.d, 1H, *J*=7.1 Hz, CHCH$_3$), 1.13 (d, 3H, *J*=7.1 Hz, CHCH$_3$), 0.92 (s, 9H, SiC(CH$_3$)$_3$), 0.82 (s, 3H, CH$_3$), 0.11 (s, 6H, Si(CH$_3$)$_2$).

δ_C (125 MHz; $CDCl_3$) 137.8, 116.2, 75.3, 70.3, 63.0, 47.4, 42.1, 30.6, 29.7, 25.9×3, 19.9, 18.2, 12.0, –5.3, –5.4.

m/z; 441 ($M+H^+$, 100%), 428, 427, 390, 312, 294, 277, 251, 212, 180, 162, 146;

HRMS 441.1326 ($M+H^+$, $C_{17}H_{34}O_3SiI$ requires 441.1322).

Preparation of (3*S,3a*S**,4*S**,5*R**,7a*S**)-4-(hydroxymethyl)-3a,5-dimethyl-2,3,3a,4,5,7a-hexahydrobenzofuran-3-ol (III-90)**



Sodium iodide (19.5 mg, 0.13 mmol) was added to a solution of tosylate **III-81** (31.6 mg, 0.065 mmol) in acetone (1 mL) at room temperature. A condenser and calcium sulfate dying tube were added, and the solution was heated at reflux for 23 h. After the solution was cooled, the sodium tosylate was filter off and most of acetone evaporated under reduced pressure. The mixture was diluted with Et_2O (10 mL) and water (10 mL), the layers separated, the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous $NaSO_4$. After removal of solvent under reduced pressure, the crude product was purified by

column chromatography (SiO_2, 50% EtOAc in hexanes) to give **III-90** as a colourless oil [10.4 mg, 0.053 mmol, 80% yield].

R_f=0.30 (25% ethyl acetate/hexane).

ν_{max}/cm^{-1} 3408, 2954, 2928, 2880, 2857, 1461, 1252, 1097, 1074, 1037, 1004, 985, 833, 774.

δ_H (300 MHz; $CDCl_3$) 5.89 (dd, 1H, *J*=19.6, 1.2 Hz, C<u>H</u>=CH), 5.81 (dd, 1H, *J*=9.6, 4.5, 2.1 Hz, CH=C<u>H</u>), 4.25 (dd, 1H, *J*=5.4, 2.9 Hz, C<u>H</u>OH), 4.02 (dd, 1H, *J*=6.8, 6.8 Hz), 3.95-3.85 (m, 2H), 3.81 (d, 1H, *J*=4.5 Hz, C<u>H</u>OCH_2), 3.57 (dd, 1H, *J*=12.3, 7.4 Hz, CH<u>H</u>OH), 2.18-2.34 (m, 1H, C<u>H</u>CH_2OH), 2.02 (ddd, 1H, *J*=11.8, 6.2, 6.2 Hz, C<u>H</u>CH_3), 1.08 (d, 3H, *J*=7.0 Hz, CH_3), 0.97 (s, 3H, CH_3).

δ_C (75 MHz; $CDCl_3$) 141.8, 123.9, 88.0, 80.1, 75.3, 69.3, 64.8, 48.8, 29.9, 19.3, 13.0.

m/z; 221 ($M+Na^+$, 100%), 183, 181, 170, 166, 162, 159, 144, 133, 128, 114, 110.

HRMS 221.1161 ($M+Na^+$, $C_{11}H_{18}O_3Na$ requires 221.1154).

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