Synthesis of the Briarane Northern Hemisphere

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Attapol Pinsa
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 desulfonflylation, Eschenmoser-Claisen rearrangement, halo-lactonisation, and enolate hydroxylation using MoOPD.

KEY WORDS: BRIARANES / DIELS-ALDER REACTION / SULFONYL DIENE / ESCHENMOSEX CLAISEN REARRANGEMENT / CYCLO-LACTONISATION / ROBINSON ANNULATIONS
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LIST OF ABBREVIATIONS

ACN  Azocyclohexane-1,1'-dicarbonitrile
AIBN  2,2'-Azobisisobutyronitrile
app.  Apparent
br.  Broad
BSA  N,N-Bis(trimethylsilyl)acetamide
nBu  n-Butyl
nBuLi  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
mCPBA  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
KHMDIS  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
<table>
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<tr>
<td>RT</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDPS</td>
<td>t-Butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>t-Butyldimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl (p-toluenesulfonyl)</td>
</tr>
<tr>
<td>$\nu_{\text{max}}$</td>
<td>Maximum absorption frequencies</td>
</tr>
<tr>
<td>$\delta$</td>
<td>Chemical shift</td>
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CHAPTER I
INTRODUCTION

Since the first discovery of a briarane-type metabolite (briarein A) in 1977 by Burks et al.\textsuperscript{1} from a West Indian gorgonian coral \textit{Briareum asbestinum}, more than three hundred 3,8-cyclized cembranoid compounds have been reported.\textsuperscript{2} They all feature the briarane carbon skeleton (Scheme 1), containing a bicyclo[8.4.0]carbon ring system, and a \gamma-lactone. The briaranes in this review have been selected from the reviews by Sung \textit{et al.} to illustrate the range of structure.\textsuperscript{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.
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. In 1996, Rodriguez 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. The complete spectral data (UV, IR, MS, $^1$H and $^{13}$C NMR) of briareins A-L (I-1–I-12) were reported. The structure and the absolute stereochemistry of briarein A (I-1) were determined by X-ray analyses. Briarein B (I-2) had been reported in the 1980’s.
B. *Briareum excavatum*

A further study of Taiwanese gorgonian corals, including *B. excavatum* was reported by Sung *et al.* 1-11 Ten new briarane derivatives, briaexcavatins A-F (I-13-1-18), I-L (I-19-1-22), 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. 1-12 The absolute stereochemistry of I-24 and I-25 were determined by X-ray analyses. 1-13 The absolute configuration were
established by application of modified Mosher’s method on I-23–I-25. It may be noted that briaexcavatin A (I-1) is the first 11,12-secobriarane possessing an ε-lactone moiety.

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.

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.\(^6\)

![Figure 3 The Briarane-Type Metabolites from *B. polyanthes*](image-url)
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).\(^\text{10}\) The structure of I-31 was established on the basis of spectroscopic methods and this compound was found to exhibit antiplasmodial activity.\(^\text{10}\)

![Figure 4 The Briarane-Type Metabolites from *B. polyanthes*](image)

**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 stereostructures 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.\(^\text{14}\)
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);\(^{15}\) 12-O-acetylbriviolid E (I-55), 9-deacetoxybriviolid D (I-56), 4-acetoxybriviolid D (I-57), and briviolid 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 briviolid 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 briviolid G-I (I-60–I-62), were rarely found in briarane derivatives.\(^{16}\) Briviolid 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.\(^{15,16}\)
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 (1-64–1-66), were isolated from the female gorgonian E. robusta (Figure 7). The structures of 1-64–1-66 were elucidated by interpretation of spectral data analysis and the structure of 1-64 was confirmed by single-crystal X-ray diffraction analysis. In a previous report, the structure of 1-64 had been named as umbraculolide C. However, by comparison of the NMR data of 1-64 with those of umbraculolide C, the NMR data for 1-64 are significantly different from those of umbraculolide C and the structure of 1-64 (robustolide A) had been further established by X-ray diffraction analysis. The structure for the reported umbraculolide C should be re-examined. In continuing study, six new chlorinated metabolites featuring briarane carbon skeletons, robustolides D-I (1-67–1-72), have been isolated from the gorgonian coral E. robusta, which was collected from the coast of southern Taiwan (Figure 7). The structures of 1-67–1-72 were determined by spectroscopic methods, using 1D and 2D NMR in particular. The absolute stereochemistry of robustolides D (1-67), F (1-69), G (1-70), and I (1-72) were directly established by X-ray diffraction analysis. It is noteworthy that rebustolide D (1-67) is the first metabolite of a briarane possessing two halogen atoms. Compounds 1-69, 1-70, and 1-72 had been first reported from a gorgonian Ellisella sp., collected in Okinawa, Japan. The absolute configuration of robustolide G (1-70) and I (1-72) 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. Compounds 1-
64 and I-65 were found to show weak activity against the bacteria *Pseudomonas aeruginosa* and *Staphylococcus aureus*.¹⁸

![Chemical structures of robustolides](image)

**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](image)

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, ¹H, and ¹³C 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. These diterpenoids (I-74, I-76–I-78) unusually possess exo-methylene group.

![Diagram of diterpenoids](image)

**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. 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*. 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.\(^2\)

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

### C. *Junceella juncea*

The gorgonian species of the genus *Junceella juncea* also are a rich source 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 juncellin 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 epidermoid (KB-16) carcinoma cells.  

![Chemical structures of juncenolides A (I-85), B (I-86), C (I-87), D (I-88), E (I-89), and the juncins I (I-90), J (I-91), K (I-92), L (I-93), M (I-94), and N (I-95).](image)

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

**D. Junceella squamata**

Two new briarane-type metabolites, junceellins A (I-96) and B (I-97), have been isolated from *J. squamata* collected in the South China Sea. The structures of briaranes (I-96) and (I-97) were assigned on the basis of spectral analyses (IR, UV, MS, $^1$H and $^{13}$C...
NMR). Furthermore, the structure and absolute stereochemistry of junceellin A (I-96) were established by X-ray diffraction analysis. In addition, the gorgonian corals, Junceella fragilis and Gorgonella umbraculum were also found to contain Junceellin A (I-96). Its hydrolysis products showed cytotoxicity toward A-549 tumor cells.

![Figure 12](image1)  
**Figure 12** The Briarane-Type Metabolites from *J. squamata*

Subergorgia (Subergorgiidae)

A. *Subergorgia reticulata*

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. This compound is the first briarane derivative isolated from a gorgonian coral belonging to the family Subergorgiidae.

![Figure 13](image2)  
**Figure 13** The Briarane-Type Diterpenoid from *S. reticulata*
Plexaureides (family Plexauridae)

A. Plexaureides praelonga

A new diterpenoid with the briarane skeleton, Praelolide (1-99), was isolated from *P. praelonga* gorgonian coral collected from the South China Sea. The structure, including the absolute stereochemistry of praelolide (1-99) was elucidated by a combination of spectroscopic methods and X-ray crystallographic analyses. 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 (1-99) showed antiviral activity.

![1-99 praelolide](image)

**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, *Anthoptilum* 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 [3H]1,3-dipropyl-8-cyclopentylxanthine ([3H]DPCPX) to rat-brain adenosine A$_1$ receptors.\(^{37}\)

![Chemical structures of anthoptilides A-E](image)

**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).  

![Structural formula of cavernulin A and cavernulin B](image)

**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). It may be notable that two briaranes (I-107 and I-108) contain the *trans* alkene moiety.
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 (1-26, 1-111, and 1-114), and 7-epibrianthein A, led to general views on the conformational preferences of diterpenoids of this class.2

![Chemical structures of funicolide A through E and 7-epifunicolide A.](image)

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

*Renilla* (Renillidae)

**A. Renilla reniformis**

Four new briaranes, renillins A-D (1-117–1-120) 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 1-117–1-120 were elucidated by the interpretation of spectroscopic data. Interestingly, renillins A (1-117) and B (1-118) are the first briarane derivatives with fully reduced C-14 centers.39 Using laboratory feeding assays, briaranes (1-117–1-120) tested at natural concentrations
significantly deterred feeding by the predatory lesser blue crab, *Callinectes similis*, while remillins 1-119 and 1-120 also deterred feeding by the predatory mummichog fish, *Fundulus heteroclitus*.

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 (1-121), and its decomposition product, ptilosarcenone (1-122). The gross structures of briaranes (1-121) and (1-122) were elucidated by NMR data (1H and 13C) and by comparison with those of a known metabolite, briarein A (I-1). 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 bria-ranes, 11-hydroxyptilosarcone (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 bria-ranes I-121—I-127 were assigned by using 1D and 2D NMR spectral and by comparison with those of the other known bria-rane. Insecticidal screening activity of Briarane (I-122) showed activity against the larvae of the tobacco hornworm, *Manduca sexta*.

**Figure 20** The Briarane-Type Metabolites from *P. gurneyi*. 
**Stylatula** (family Virgulariidae)

**A. Stylatula sp.**

The sea pen *Stylatula* 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 1-128 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. 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. The stylatulide (I-128) was found to be toxic to the larvae of the copepod *Tisbe furcata johnsonii*.

![Figure 21 The Briarane-Type Metabolites from Stylatula sp.](image)
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. 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. Malayenolides A-D (I-133–I-136) exhibited toxicity to brine shrimp.

![Diagram of malayenolides A-D](image)

**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. 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.

![Chemical structures](image)

**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). 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.

![Structures of briaranes](image)

**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*, and, thus, may be a defense compound.
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 determined 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.  

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 diterpenoidal, 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). However, the stereochemistry of solenolide D (I-150) has been revised, 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. Briarane (I-149) is the only briarane-type metabolite from a marine sponge.

![Figure 27 The Briarane-Type Metabolites from *P. purpurea*](image-url)
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. In 2006, Iwasaki et al. reported a synthetic study of briarane-type marine diterpenoid, pachyclavulide B, which was isolated from the methanol extraction of soft coral Pachyclavularia violacea by the same group. 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.

The synthetic plan for pachyclavulide B (1-151) is delineated in Scheme 2. Construction of the 10-membered ring would be achieved through elongation of the carbon chain of 1-152 and ring-closing metathesis. Compound 1-152 could be prepared by a carbon-carbon bond forming reaction with the construction of the quaternary carbon on the cyclohexene ring of compound 1-153, which could be obtained employing enantio- and diastereoselective asymmetric epoxidation of achiral substrate ester 1-154. Compound 1-154 can be easily prepared by Birch reduction of 2,6-dimethylbenzoic acid.
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, which was prepared from D-sorbose, 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 Et₂AlTMP led to allylic alcohol I-157, which subsequently reacted with ethyl vinyl ether in the presence of NIS to give the substrate I-158. Intramolecular 5-exo radical cyclization 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.
Pressing forward in the synthetic study, the conversion of acetal 1-159 to aldehyde 1-162 with a carbon degradation was required. Jones reagent was used to oxidize compound 1-159 to lactone 1-160. The introduction of a hydroxyl group at the α-position of lactone 1-160 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 1-161 was not determined, it could be envisaged that the Davis reagent\textsuperscript{59} approached from the convex face of lithium enolate of 1-160. The reduction of 1-161 gave a diol, which was subjected to oxidative cleavage by treatment with NaIO\textsubscript{4} to furnish aldehyde 1-162. The diastereoselective addition reaction of vinylmagnesium chloride to 1-162 was achieved to give the desired adduct 1-152 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 1-152 for the synthesis of the briarane-type diterpenoid, pachyclavulide B (1-151) 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 \textit{et al.} reported a highly efficient synthesis of methyl-substituted conjugate cyclohexenones as shown in Scheme 5.\(^{61}\)

![Scheme 5](image)

\(R = \text{methyl, ethyl, } n\text{-propyl, isopropyl, and } n\text{-hexyl}\)

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 \(^t\text{BuOK}\) in \(^t\text{BuOH}\) at reflux.\(^{60}\)

In addition, Knoevenagel condensation with an extra aldol condensation, has been reported by Perumal \textit{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. This reaction can be envisaged to occur via an initial Knoevenagel 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.

\[
\text{Ar} = \text{C}_6\text{H}_5, 4-\text{ClC}_6\text{H}_4, 4-\text{CH}_3\text{C}_6\text{H}_4, 2-\text{ClC}_6\text{H}_4, 2-\text{CH}_3\text{OC}_6\text{H}_4, 2-\text{CH}_3\text{C}_6\text{H}_4
\]

Scheme 6

A tandem Michael reaction-aldol was originally reported in 1912 by Dieckmann et al. 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. 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.\textsuperscript{65}

\[\text{O} \quad \text{O} \quad \text{O} \quad \text{O}\]

\[\text{II-10} \quad \begin{array}{c}
\text{Ba(OH)}_2 \\
\text{EtOH, } \text{rt}
\end{array} \rightarrow \begin{array}{c}
\text{II-11} \\
\text{II-12}
\end{array}\]

\[\text{Ba(OH)}_2/\text{EtOH, } \Delta \rightarrow \text{Ba(OH)}_2/\text{EtOH, } \Delta \rightarrow \text{Ba(OH)}_2/\text{EtOH, } \Delta \rightarrow \text{Ba(OH)}_2/\text{EtOH, } \Delta
\]

\[\text{II-13} \quad \begin{array}{c}
\text{X = H, Cl, OMe, -NO}_2, \text{Me}
\end{array}\]

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).\textsuperscript{66}
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 \( \beta \)-croyl and \( \beta \)-heteroaroyl \( \beta \)-ketoester, which can be converted readily upon treatment with \( \alpha,\beta \)-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.\(^6\) 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, 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. 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Products</th>
<th>R</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>II-3a</td>
<td>CH₃</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>II-3b</td>
<td>Ph</td>
<td>56ᵇ</td>
</tr>
<tr>
<td>3</td>
<td>II-3c</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>II-3d</td>
<td>2-furyl</td>
<td>48ᶜ</td>
</tr>
</tbody>
</table>

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.\textsuperscript{63}

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Et} & \quad \text{Et} \\
\text{H}_2\text{C} & \quad \text{H}_2\text{C} \\
\text{O} & \quad \text{O} \\
\text{Et} & \quad \text{Et} \\
\text{morpholine, EtOH} & \quad \text{morpholine, EtOH} \\
\end{align*}
\]

Scheme 10

The relative stereochemistry at the 2, 3 and 4-positions could be assigned by the coupling constants ($J_{ax-ax} = 11.5 - 12.2$ 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.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>H-2</th>
<th></th>
<th>H-4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\delta$ (ppm)</td>
<td>$J_{2,3}$ (Hz)</td>
<td>$\delta$ (ppm)</td>
<td>$J_{3,4}$ (Hz)</td>
</tr>
<tr>
<td>II-3a</td>
<td>3.03</td>
<td>12.0</td>
<td>2.54</td>
<td>11.5</td>
</tr>
<tr>
<td>II-3b</td>
<td>3.70</td>
<td>12.6</td>
<td>3.05</td>
<td>12.1</td>
</tr>
<tr>
<td>II-3c</td>
<td>3.94</td>
<td>12.4</td>
<td>2.92</td>
<td>4.8, 1.5$^a$</td>
</tr>
<tr>
<td>II-3d</td>
<td>3.72</td>
<td>12.4</td>
<td>3.13</td>
<td>12.2</td>
</tr>
</tbody>
</table>

$^a$ 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 monoamine 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.
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.

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.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOH, H$_2$SO$_4$, $\Delta$, 1 h</td>
<td>II-2 (60%)$^a$ and II-24 (10%)$^a$</td>
</tr>
<tr>
<td>2</td>
<td>20 mol% p-TsOH, dioxane, RT, 20 h</td>
<td>II-2 (44%)$^a$ and II-24 (44%)$^a$</td>
</tr>
<tr>
<td>3</td>
<td>morpholine, CH$_2$Cl$_2$, 50 °C, 20 h</td>
<td>II-2 (84%)$^a$</td>
</tr>
<tr>
<td>4</td>
<td>SOCl$_2$, pyridine, CH$_2$Cl$_2$, 0 °C, 20 h</td>
<td>II-22 (51%)$^a$</td>
</tr>
</tbody>
</table>

$^a$ 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 diastereoisomers 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 SOCl₂ and pyridine in CH₂Cl₂ (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 diastereoisomer.

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.
However, the isomerization at C-4 after dehydration might be prevented by protection of the carbonyl group in the intermediate \textbf{II-3a} as proposed in Scheme 13. Therefore, decarboxylation of \textbf{II-3a} under Krapcho conditions,\textsuperscript{68} could give the mono-decarboxylated product \textbf{II-28}. Carbonyl protection and dehydration of the corresponding \textbf{II-29} would provide the dehydrated product \textbf{II-30}. Subsequent protection of the alcohol would give the intermediate \textbf{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 \textbf{II-1}.

\begin{center}
\includegraphics[width=\textwidth]{Scheme_13}
\end{center}

\textbf{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 \textbf{II-22} in 57\% yield as a mixture of two diastereoisomers in a ratio of 36:64 as shown in Scheme 14.
Due to our inability to control the isomerization, the desired cyclohexenone II-2 could not be obtained as a single diastereoisomer. To avoid 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. In particular, many procedures, based on the conjugate addition of β-dicarbonyl compounds under neutral conditions, have been proposed. Scettri et al. reported that lithium iodide is a very efficient catalyst for the conjugate addition of β-ketoesters 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.
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 $R_1^1 = \text{Me}$, either of two products may be formed, corresponding to pathways A and B. In pathway B, using pent-3-en-2-one ($R_1^1 = R_2 = \text{Me}$) 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](image)

In practice, treatment of ethyl acetoacetate with pent-3-en-2-one 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Products</th>
<th>R¹</th>
<th>R²</th>
<th>% Yield¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>II-38a</td>
<td>CH₃</td>
<td>CH₃</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>II-38b</td>
<td>CH₃</td>
<td></td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>II-38c</td>
<td>CH₃</td>
<td></td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>II-38d</td>
<td></td>
<td>CH₃</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>II-38e</td>
<td></td>
<td></td>
<td>74ᵇ</td>
</tr>
</tbody>
</table>

¹Isolated yield based on the corresponding ketones.
ᵇplus 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).

Scheme 17

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

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 ($J_{axial-axial} = 12.0 - 12.6$ 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.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>H-2</th>
<th>$\delta$ (ppm)</th>
<th>$J_{2,3}$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-38a</td>
<td></td>
<td>2.97</td>
<td>12.0</td>
</tr>
<tr>
<td>II-38b</td>
<td></td>
<td>3.65</td>
<td>12.6</td>
</tr>
<tr>
<td>II-38c</td>
<td></td>
<td>3.26</td>
<td>12.6</td>
</tr>
<tr>
<td>II-38d</td>
<td></td>
<td>3.12</td>
<td>12.0</td>
</tr>
<tr>
<td>II-38e</td>
<td></td>
<td>3.72</td>
<td>12.3</td>
</tr>
</tbody>
</table>

When enone (II-42), with an $\alpha$-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.

\[
\text{II-42} \xrightarrow{K_2CO_3} \text{II-43}
\]

**Scheme 18**
Finally, cyclohexenone was employed as the enone substrate (Scheme 19). Under the reaction conditions, the Robinson product 11-45 was obtained in 31% yield, the major product being the simple Michael adduct 11-44 in 68% yield which could be converted on to the Robinson product 11-45 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., 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.

\[
\text{Scheme 19}
\]

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 (11-45, 11-46 and 11-47) 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.
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 \(\text{III-6}\) which could be coupled with the lithium derivative of the THP ether of a propargylic alcohol derivative. Cyclohexenol \(\text{III-6}\) was selected as a key building block. It would be obtained through the Keck radical allylation of iodo \(\text{III-7}\) or the epoxide ring opening of epoxide \(\text{III-3}\) for the connecting of the upper chain, which, in turn, could be synthesized from \(\text{III-8}\) by selective hydroxylation and chemoselective iodination.

Continuing with the retrosynthesis, lactone \(\text{III-8}\) would be obtained by lactonisation of compound \(\text{III-9}\). The construction of challenging quaternary carbon of compound \(\text{III-9}\) would be by \([3,3]\)-sigmatropic rearrangement, as a key step, of the corresponding alcohol
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.
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 accommodated. 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. 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, 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.

\[
\text{III-14} + \text{III-15} \xrightarrow{\text{Diels-Alder}} \xrightarrow{\text{Lewis acid}} \text{III-16} \xrightarrow{\text{1. } H_2O^+} \xrightarrow{\text{2. oxazolidinone cleavage}} \text{III-17}
\]

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, ZnCl₂, AlCl₃, 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(OPr)$_4$ 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. To improve upon this situation, a number of Lewis acids (i.e., Yb(OTf)$_2$, ZnCl$_2$, AlCl$_3$ and Ti(OPr)$_4$ 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. In addition, the use of sulfvinyl 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. To avoid use of toxic mercury we decided to prepare the sulfonyl diene III-13 by modification of the known procedure 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 $p$-toluenesulfinato 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 allyl sulfone anion, subsequently trapping the anion with formaldehyde. The alcohol III-19 was treated with 2 equiv of triethylamine and MsCl leading to demesitylation to give the desired sulfonyl diene III-13 as a single geometrical...
isomer, which could be assigned by the coupling constant \( J_{\text{trans}} = 15.8 \text{ Hz} \), as the trans isomer.

![Scheme 23](image)

According to the reports by Hoffmann and Brace, 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\(_2\)Cl\(_2\) and stored at \(-78^\circ\text{C}\). Using the modified procedure developed by Bäckvall, the reaction of sulfonyldienes III-13 with 2 equiv of methyl acrylate in CH\(_2\)Cl\(_2\) 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 diastereoisomer in 62%
yield accompanied by the dimerization product \textbf{III-21} in 5\% yield, by employing 5 equiv of AlCl$_3$ in CH$_2$Cl$_2$ 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.

\\begin{center}
\begin{tikzpicture}
\node at (0,0) {\text{ArSO}_2};
\node at (1,0) {\text{CO}_2\text{Me}};
\node at (2,0) {2 eq};
\node at (3,0) {\text{AlCl}_3};
\node at (4,0) {2 eq, CH$_2$Cl$_2$};
\node at (5,0) {RT, 4 h};
\node at (6,0) {(61 \% based on 2 steps)};
\node at (7,0) {\text{III-20}};
\node at (8,0) {\text{CO}_2\text{Me}};
\node at (9,0) {\text{ArSO}_2};
\node at (10,0) {\text{ArSO}_2};
\node at (11,0) {\text{CO}_2\text{Me}};
\node at (12,0) {5 eq};
\node at (13,0) {\text{AlCl}_3};
\node at (14,0) {5 eq, CH$_2$Cl$_2$};
\node at (15,0) {reflux, 7 days};
\node at (16,0) {(62 \% based on 2 steps)};
\node at (17,0) {\text{III-12}};
\node at (18,0) {\text{III-21} 5 \%};
\end{tikzpicture}
\end{center}

\textbf{Scheme 24}

The Diels-Alder products \textbf{III-20} and \textit{endo} adduct \textbf{III-12} were obtained as single diastereoisomers by $^1$H NMR; according to the predictions by frontier orbital theory, the formation of \textit{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 \textbf{III-20} and \textbf{III-12} could be assigned by the coupling constants ($J_{ax-eq} = 5.5$ and 6.1 Hz), which confirmed that the methyl group at C-3 is \textit{cis} to the CO$_2$Me group at C-4 as shown in 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.
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 asymmetric 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.
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 \( \alpha \)-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 \(-78^\circ C\), reacted with 1 equiv of propionaldehyde, the corresponding allylic alcohol III-27 was obtained directly in 28% yield along with unidentified decomposition products.\(^{84} \)

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$_2$Cl$_2$ in the presence of 5 equiv of AlCl$_3$ at room temperature afforded the cycloaddition product III-30 in 71% yield as a single diastereoisomer 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$_2$Cl$_2$ 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 sulfynyl dienes III-29 decomposed when TiCl₄ 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 sulfynyl 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 sulfynyl 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 sulfynyl 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 diastereoisomer as shown in Scheme 24. In contrast, the sulfynyl
dienen III-29 provided the Diels-Alder product III-31 as a mixture of diastereoisomers 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.

Having cyclohexenecarboxylate III-12 in hand, reduction of III-12 with 2 equiv of DIBAL-H in CH₂Cl₂ 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.

![X-ray ORTEP diagram of the sulfonyl alcohol III-33](image)

**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.
The transformation of **III-34** into **III-35** is proposed in Scheme 30. First, dihydroxylation of **III-34**,\(^8\) 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\(^8\) of **III-34** followed by oxidative desulfonylation\(^8\) of the \(\alpha\)-sulfonyl carbanion **III-40**, generated from the allyl derivative **III-39**, would provide the cyclohexenone **III-35**.
We began investigating the dihydroxylation of the vinyl sulfone III-34 by employing oxidizing agents such as KMnO₄, KMnO₄/CuSO₄·5H₂O, OsO₄/NMO, and OsO₄/K₃Fe(CN)₆ under various conditions. However, all of the reaction failed, leading to recovery of starting material instead. Alternatively, isomerization using "BuLi or lithium diisopropylamide (LDA) were attempted on the vinyl sulfone III-34, yet this reaction did not give the isomerized product. "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 tBuOOLi, mCPBA, and
H$_2$O$_2$ did not lead to the epoxide product **III-38**. In all cases, recovery of the starting material was obtained except in the H$_2$O$_2$ case.

Interestingly and to our surprise, in the case of using urea-hydrogen peroxide (UHP) 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.*

![Scheme 31](image_url)
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 nBuLi 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 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.\textsuperscript{88,106}

Oxodiperoxymolybdenum (pyridine)-1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidione (MoO\textsubscript{5}.Py.DMPU; MoOPD; Figure 37) is a versatile enolate anion hydroxylating reagent introduced by Anderson and Smith.\textsuperscript{92} MoOPD swiftly hydroxylates anions from lactones, ketones, esters, aldehydes, nitriles, sulfones, amides, and isoxazolines.\textsuperscript{93} Beyond functionalizing a wide array of substrates, MoOPD carries out oxidations with excellent regio- and stereoselectivity.\textsuperscript{93} Even though, MoOPH (MoO\textsubscript{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\textsubscript{3} in 2 steps as shown in Scheme 32.\textsuperscript{92}
Oxidation of molybdenum (VI) oxide with hydrogen peroxide followed by addition of DMPU provided pale yellow crystals of the monohydrated MoO$_5$·DMPU·H$_2$O complex. After recrystallisation from methanol at 40 °C, dehydration under high vacuum over P$_2$O$_5$ 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, 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.
Table 6 Optimization of the condition for the preparation of cyclohexenone III-35.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results(^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA 1.5 eq, MoOPD 3 eq -78 °C to -40 °C, 20 h</td>
<td>Recovery of III-39</td>
</tr>
<tr>
<td>2</td>
<td>LDA 3 eq, MoOPD 3 eq -78 °C to -40 °C, 20 h</td>
<td>III-39 (80%) and III-35 (13%)</td>
</tr>
<tr>
<td>3</td>
<td>LDA 6 eq, MoOPD 4 eq -78 °C, 2 h</td>
<td>III-39 (11%) and III-35 (65%)</td>
</tr>
<tr>
<td>4</td>
<td>LDA 6 eq, MoOPD 4 eq -78 °C, 3 h</td>
<td>35 (84%)</td>
</tr>
<tr>
<td>5</td>
<td>LDA 6 eq, MoOPD 4 eq -78 °C, 4 h</td>
<td>35 (51%) and 45 (21%)</td>
</tr>
</tbody>
</table>

\(^{a}\) 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 diastereoisomer which can be rationalized by the assumption that the Hc 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 ($J_{\text{axial-axial}} = 12.3$ 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.
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
dehydrioddonation 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.

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
(LiAlH₄)₉⁴ and sodium borohydride (NaBH₄), 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results⁸</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiAlH₄, THF -78 °C, 3 h</td>
<td>dr 80:20 (74%)</td>
</tr>
<tr>
<td>2</td>
<td>NaBH₄, MeOH -78 °C to RT, 5 h</td>
<td>dr 80:20 (92%)</td>
</tr>
<tr>
<td>3</td>
<td>NaBH₄, CeCl₃.7H₂O, MeOH -78 °C to RT, 5 h</td>
<td>dr 83:17 (91%)</td>
</tr>
<tr>
<td>4</td>
<td>NaBH₄, MeOH -78 °C to -40 °C, 20 h</td>
<td>dr 92:8 (87%)</td>
</tr>
<tr>
<td>5</td>
<td>NaBH₄, CeCl₃.7H₂O, MeOH -78 °C to -40 °C, 20 h</td>
<td>dr 96:4 (96%)</td>
</tr>
</tbody>
</table>

⁸isolated yield
As shown in Table 7, the allylic alcohol III-46 and III-46' were obtained in dr 80:20 by employing LiAlH₄ in THF at -78 °C for 3 h (entry 1, Table 7) or using NaBH₄ 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 CeCl₃.7H₂O, 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 CeCl₃.7H₂O, 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 CeCl₃.7H₂O, 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.

\[
\begin{align*}
\text{HO} & \quad \text{OMe} \\
\text{MeO} & \quad \text{CH}_3 \\
\text{Me}_2\text{N} & \quad \text{I} \\
\text{CH}_3 & \\
\text{MeO} & \\
\end{align*}
\]

\[
\text{III-46a} \quad \text{diglyme, 160 ℃, 4 h} \quad \text{75 %} \quad \text{III-47a}
\]

\text{Scheme 34}

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

\[
\begin{align*}
\text{HO} & \\
\text{OTBS} & \\
\text{III-46} & \quad \text{[3,3] sigmatropic rearrangement} \\
\text{R} & \\
\text{III-47r} & \quad \text{several steps} \\
\text{OH} & \quad \text{OH} \\
\text{III-51} & \\
\end{align*}
\]

\text{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 \text{III-52} would give the ester \text{III-53}. Secondly and thirdly, Claisen
rearrangement\textsuperscript{97,99} via allyl vinyl ether III-54 and Mandai-Claisen rearrangement\textsuperscript{100} via sulfoxide III-55 may give the aldehyde III-56 via intermediate III-54.

\begin{center}
\begin{tikzpicture}
\node (III-53) at (0,0) {\includegraphics[width=0.8\textwidth]{scheme36}};
\node (III-46) at (-4,0) {III-46};
\node (III-52) at (-4,-1.5) {III-52};
\node (III-54) at (2,0) {III-54};
\node (III-55) at (2,-1.5) {III-55};
\node (III-56) at (2,1.5) {III-56};
\node (III-57) at (0,-1.5) {III-57};
\node (III-58) at (0,1.5) {III-58};
\node (III-59) at (2,3) {III-59};
\node (III-47) at (0,3) {III-47};
\node (III-47p) at (-0.5,3.5) {III-47'};
\node (III-54p) at (-0.5,1.5) {III-47''};
\node (III-53p) at (-0.5,0) {III-47'''};
\node (III-54p) at (-0.5,0) {III-47'''};
\end{tikzpicture}
\end{center}

\textbf{Scheme 36}

Fourth, acylation of alcohol III-46 would afford the ester III-57 which could be subjected to an Ireland-Claisen rearrangement\textsuperscript{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.

![Scheme 37](image)

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 sulfoxide 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 NaHCO₃ 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 ¹H 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. 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, KHMSDS and LiHMDS, followed by trapping the resulting anion with TMSCl, TBSCI, 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.

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). 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.

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. 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).

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 α-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).

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.

Our synthesis began with dihydroxylation-lactonisation: 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\(^\text{96}\) 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.

\[
\begin{align*}
\text{III-47} & \quad \text{OsO}_4, \text{NMO} \quad \text{THF-H}_2\text{O}, 20\text{ h} \quad 20\% \quad \text{HO}^-, \\
& \quad \text{III-47'}
\end{align*}
\]

Scheme 44

Compound III-47 was iodolactonised\(^\text{96,104}\) by treatment of III-47 with 2 equiv of iodine in a mixture of THF:H\(_2\)O (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.

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 I₂ 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 (NaH₂PO₄ 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, deiodination of the intermediate III-67b gave the iodide III-68.

Heating iodo-lactone III-48 in THF at reflux containing 4 equiv of 1,8-diazaadamantane-7-ene (DBU)\textsuperscript{105} afforded quantitatively the lactone III-49 in 2 h (Scheme 47). We attribute this fast elimination to the axial position of the iodine.
The relative stereochemistry of the tetrahydrobenzofuranone III-49 was confirmed by single crystal X-ray crystallography as shown in Figure 39.

**Scheme 47**

![Scheme 47](image)

**Figure 39** X-ray ORTEP diagram of tetrahydrobenzofuranone III-49
Having lactone \textbf{III-49} in hand, selective hydroxylation of the \textbf{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.\textsuperscript{86,88,106}

\textbf{Table 8} Optimization of the condition for the preparation of hydroxyl lactone \textbf{III-50}.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA 2 eq, MoOPD 2 eq, -78 °C to -40 °C, 20 h</td>
<td>Recovery of \textbf{III-49}</td>
</tr>
<tr>
<td>2</td>
<td>KHMDS 2 eq, MoOPD 2 eq, -78 °C to -40 °C, 20 h</td>
<td>\textbf{III-49} (69%) and \textbf{III-50} (20%)</td>
</tr>
<tr>
<td>3</td>
<td>KHMDS 3 eq, MoOPD 4 eq, -78 °C to -40 °C, 20 h</td>
<td>\textbf{III-49} (35%), \textbf{III-50} (11%), and \textbf{III-69} (24%)</td>
</tr>
<tr>
<td>4</td>
<td>KHMDS 5 eq, MoOPD 4 eq, -78 °C to -10 °C, 20 h</td>
<td>\textbf{III-49} (13%), \textbf{III-50} (37%), and \textbf{III-69} (20%)</td>
</tr>
<tr>
<td>5</td>
<td>LiHMDS 2 eq, MoOPD 2 eq, -78 °C to -10 °C, 20 h</td>
<td>\textbf{III-50} (87%)</td>
</tr>
</tbody>
</table>

$^a$ 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$_2$O provided recovery of starting material III-49 without deuteration indicating that deprotonation had not occurred. 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.

![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-
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. Alternatively, epoxide ring opening of III-71 by methyl allyl magnesium chloride could also afford the desired product III-51. Thirdly, Keck allylation or a copper catalyzed Grignard reaction could convert the iodo alcohol III-72 to the required cyclohexenol III-51.

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. Reduction of lactone III-50
would provide the alcohol III-73 which would be subjected to oxidative cleavage to afford the aldehyde III-70.

\[
\text{\[
\begin{array}{c}
\text{reduction} \\
\text{III-50} \\
\text{III-73} \\
\text{oxidative cleavage} \\
\text{III-70} \\
\end{array}
\text{Grignard reaction} \\
\text{MgBr} \\
\text{III-71}
\end{array}
\]
\]

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$_2$O (1:1) to provide the aldehyde III-70 in 96% yield. The diastereoselective 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 diastereoisomers 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.\textsuperscript{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.
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.
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.

As shown in Scheme 52, oxidation of the alcohol III-50 employing 12 equiv of IBX\textsuperscript{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.

The β-ketoester III-77 was reduced using NaBH₄ 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 LiAlH₄ to give the adduct III-78 in 77% yield. The high diastereoselectivity observed is due to attack on the convex face by NaBH₄ 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 NEt₃ 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.
As shown in Scheme 54, our best conditions for the preparation of tosylate III-81 was to use p-TsCl with NEt₃ 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, NaHCO₃, and an iodine scavenger, Na₂SO₃, 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

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, triphenylphosphine and imidazole¹¹⁰ in a mixture of toluene and CH₂Cl₂ (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 CH₂Cl₂ was needed. However, all attempts failed
leading to the undesired product 111-82 and 111-90. 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 111-78 with of iodine, triphenylphosphine, and imidazole in CH2Cl2 at 0 °C for 1 h resulted in a 22% yield of the desired iodide 111-83 along with a 9% yield of the cyclized product 111-82, and 51% of starting material 111-78. The triol 111-78 could not be totally dissolved in CH2Cl2 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, PPh3, and imidazole at -30 °C in THF for 3 h. These conditions yielded the desired product 111-83 in 67% yield, accompanied by only 15% of the cyclized product 111-82.
Table 9 Optimization of the condition for the preparation of iodo III-83.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results*</th>
</tr>
</thead>
</table>
| 1     | PPh₃, imidazole, I₂  
       | Toluene:CH₂Cl₂, 60 °C, 1 h | III-82 (36%) and III-90 (38%) |
| 2     | PPh₃, imidazole, I₂  
       | CH₂Cl₂, 0 °C, 1 h | III-83 (22%), III-82 (9%),  
       |     | and III-78 (51%) |
| 3     | PPh₃, imidazole, I₂  
       | 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.\textsuperscript{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.

\begin{center}
\begin{tikzpicture}
\begin{scope}
\node at (0,0) (a) {\includegraphics[width=0.4\textwidth]{scheme55.png}};
\end{scope}
\end{tikzpicture}
\end{center}

\textbf{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 Bruker 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 Bruker AV400. $^1$H-NMR and $^{13}$C-NMR (300 and 75 MHz respectively) were recorded in CDCl$_3$ solutions using a Bruker AV300. The chemical shifts are reported in $\delta$ units using CDCl$_3$ as an internal standard ($\delta$ 7.26 ppm $^1$H, $\delta$ 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 recorded 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 drying tube were added, and the solution was heated at reflux for 20 h. After the solution was cooled, the mixture was quenched with NH₄Cl (5 mL) and extracted with Et₂O (20 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 25% EtOAc in hexanes) to give II-2⁶⁰ as a colourless liquid as a mixture of two diastereoisomers in a ratio of 86:14 [195.7 mg, 1.00 mmol, 84% yield].

Rᵣ=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; CDCl₃) 5.97 (s, 1H, CH=CH₃, minor), 5.94 (s, 1H, CH=CH₃, major), 4.17 (dq, 2H, J=7.1, 1.8 Hz, CO₂CH₂CH₃, major and minor), 3.15 (d, 1H, J=5.1 Hz, CHCO₂Et, major), 2.99 (d, 1H, J=6.93 Hz, CHCO₂Et, minor), 2.59 (dd, 1H, J=16.3, 13.4 Hz, COCHH, major and minor), 2.49-2.31 (m, 1H, CHCH₃, major and minor), 2.14 (dd, 1H, J=16.3, 4.1 Hz, COCHH, major and minor), 1.94 (d, 3H, J=1.1 Hz, CH=CH₃, major and minor), 1.25 (t, 3H, J=7.1 Hz, COCH₂CH₃, major and
minor), 1.06 (d, 3H, $J=6.8$ Hz, CHCH$_3$, major), 1.05 (d, 3H, $J=6.8$ Hz, CHCH$_3$, minor). 

$\delta$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+$\text{H}^+$, 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 (H-3a)**

![Chemical structure](image)

Morpholine (90 $\mu$L, 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$_4$Cl (2 mL) and extracted with Et$_2$O (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).

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

$\delta_h$ (500 MHz; CDCl$_3$) 4.19–4.31 (m, 4H, 2×CO$_2$CH$_2$CH$_3$), 3.49 (d, 1H, $J=3.0$ Hz, OH), 3.03 (d, 1H, $J=12.0$ Hz, COCH$_2$CO$_2$Et), 2.92 (ddq, 1H, $J=12.0$, 11.5, 6.5 Hz, CHCH$_3$), 2.59 (d, 1H, $J=14.3$ Hz, COCH$_2$H), 2.54 (d, 1H, $J=11.5$ Hz, CHCO$_2$Et), 2.33 (dd, 1H, $J=14.3$, 2.0 Hz, COCH$_2$H), 1.33 (t, 3H, $J=7.3$ Hz, CO$_2$CH$_2$CH$_3$), 1.28 (t, 3H, $J=7.3$ Hz, CO$_2$CH$_2$CH$_3$), 1.28 (s, 3H, CH$_3$), 1.01 (d, 3H, $J=6.5$ Hz, CHCH$_3$).

$\delta_c$ (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-phenylcyclohexane-2,4-dicarboxylate (II-3b)**

![Diagram of 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 (SiO₂, 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 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; CDCl₃) 7.33-7.25 (m, 5H, Ar-H), 4.15-3.96 (m, 3H, CH-Ar and CO₂CH₂CH₃), 3.95-3.80 (m, 2H, CO₂CH₂CH₃), 3.75 (br.s, 1H, OH), 3.70 (d, 1H, J=12.6 Hz, COCH₂CO₂Et), 3.05 (d, 1H, J=12.1 Hz, CHCO₂Et), 2.74 (d, 1H, J=14.2 Hz, COCH₃), 2.53 (d, 1H, J=14.2 Hz, COCH₃), 1.37 (s, 3H, CH₃), 1.06 (t, 3H, J=7.1 Hz, CO₂CH₂CH₃), 0.82 (t, 3H, J= 7.1 Hz, CO₂CH₂CH₃).

δ_C (75 MHz; CDCl₃) 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-OH⁺, 100%), 285, 259.

HRMS Found 348.1560 (M⁺, C₁₀H₂₄O₄ requires 348.1567).
(E)-Ethyl 2-benzylidene-3-oxobutanoate (II-19)

\[
\begin{align*}
\delta_H \ (300 \text{ MHz}; \text{CDCl}_3) & \ 7.67 \ (s, \ 1H, \ CH\text{-Ar}), \ 7.37 \ (\text{br.} \ s, \ 5H, \ Ar\text{-H}), \ 4.29 \ (q, \ 2H, \ J=7.1 \ Hz, \ CO_2\text{CH}_2\text{CH}_3), \ \ 2.34 \ (s, \ 3H, \ CH_3\text{CO}), \ 1.32 \ (t, \ 3H, \ J=7.1 \ Hz, \ CO_2\text{CH}_2\text{CH}_3). \\
\delta_C \ (75 \text{ MHz}; \text{CDCl}_3) & \ 203.6, \ 164.4, \ 140.5, \ 134.1, \ 132.9, \ 130.4, \ 129.7\times2, \ 128.9\times2, \ 61.5, \ 31.4, \ 14.4.
\end{align*}
\]

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

\[
\begin{align*}
\text{Morpholine (90 } \muL, \ 1 \text{ mmol) in ethanol (0.1 mL) was added to a mixture of ethyl acetoacetate (1.28 mL, 10 mmol) and cyclohexane carboxaldehyde (0.60 mL, 5 mmol) at 0 \text{ °C. The reaction mixture was stirred at 0 °C for 6 h, and the contents then placed in a refrigerator. The reaction mixture was kept in a refrigerator for 3 days, and a morpholine-ethanol mixture was added each day during this time. Then, the reaction mixture was kept in a refrigerator for an additional 7 days. The crude product was}
\end{align*}
\]
purified by column chromatography (SiO₂, 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; CDCl₃) 4.28-4.12 (m, 4H, 2×CO₂CH₂CH₃), 3.94 (d, 1H, J=12.4 Hz, COCHCO₂Et), 3.09 (d, 1H, J=15.0 Hz, COCHH), 2.92 (dd, 1H, J=4.8, 1.5 Hz, CH(CO₂Et)), 2.86 (ddd, 1H, J=12.4, 5.6, 4.8 Hz, CH-cyclohexyl), 2.50 (s, 1H, OH), 2.36 (dd, 1H, J=15.0, 1.5 Hz, COCHH), 1.77-1.52 (m, 5H, cyclohexyl-H), 1.45-1.34 (m, 1H, cyclohexyl-H), 1.31 (t, 3H, J=7.2 Hz, CO₂CH₂CH₃), 1.29 (s, 3H, CH₃), 1.26 (t, 3H, J=7.2 Hz, CO₂CH₂CH₃), 1.25-1.17 (m, 2H, cyclohexyl-H), 0.87-0.76 (m, 1H, cyclohexyl-H).

δ_C (100 MHz; CDCl₃) 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⁺, C₁₉H₃₀O₆ requires 354.2037).

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

![Image of the compound structure](image-url)
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 (SiO₂, 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].

\[ \text{mp } 76-77 \degree \text{C; } R_f = 0.49 \text{ (50\% ethyl acetate/hexane).} \]

\[ \nu_{\text{max/cm}^{-1}}: 3508, 1735, 1712, 1506, 1340, 1296, 1259, 1209, 1178, 1159, 1012, 852, 738. \]

\[ \delta_{\text{H}} (500 \text{ MHz; CDCl}_3): 7.34 (\text{d, } 1\text{H, } J=1.9 \text{ Hz, furan-H}), 6.23 (\text{dd, } 1\text{H, } J=3.2, 1.9 \text{ Hz, furan-H}), 6.09 (\text{d, } 1\text{H, } J=3.2 \text{ Hz, furan-H}), 4.18-3.97 (\text{m, } 5\text{H, } 2\times \text{CO}_2\text{CH}_2\text{CH}_3 \text{ and CH-furan}), 3.72 (\text{d, } 1\text{H, } J=12.4 \text{ Hz, COCHCO}_2\text{Et}), 3.66 (\text{d, } 1\text{H, } J=2.8 \text{ Hz, OH}), 3.13 (\text{d, } 1\text{H, } J=12.2 \text{ Hz, CHCO}_2\text{Et}), 2.66 (\text{d, } 1\text{H, } J=14.4 \text{ Hz, COCHH}), 2.45 (\text{dd, } 1\text{H, } J=14.4, 2.8 \text{ Hz, COCHH}), 1.32 (\text{s, } 3\text{H, CH}_3), 1.14 (\text{t, } 3\text{H, } J=7.1 \text{ Hz, CO}_2\text{CH}_2\text{CH}_3), 1.05 (\text{t, } 3\text{H, } J=7.1 \text{ Hz, CO}_2\text{CH}_2\text{CH}_3). \]

\[ \delta_{\text{C}} (100 \text{ MHz; CDCl}_3): 200.8, 173.9, 167.7, 151.7, 142.5, 110.2, 107.8, 72.6, 61.3, 61.2, 60.1, 54.8, 52.6, 39.1, 28.4, 14.0, 13.9. \]

\[ \text{m/z: 339 (M+H\textsuperscript{+}, 100\%), 321, 311, 293.} \]

HRMS Found 338.1362 (M\textsuperscript{+}, C\textsubscript{17}H\textsubscript{22}O\textsubscript{7} requires 338.1360).
Preparation of diethyl (2S*,3R*,4S*,5S*)-3-(furan-2-yl)-5-hydroxy-5-methyl-1-oxocyclohexane-2,4-dicarboxylate (II-3d*)

\[
\text{mp 117–118 °C; } R_f = 0.43 (50\% \text{ ethyl acetate/hexane}).
\]

\[
\nu_{\text{max/cm}^{-1}} 3419, 1741, 1742, 1701, 1332, 1197, 1184, 1136, 1116, 1037, 1018, 921, 748.
\]

\[
\delta_H (500 \text{ MHz; } \text{CDCl}_3) 7.30 (\text{dd}, 1H, J=1.8, 0.8 \text{ Hz, furan-H}), 6.24 (\text{dd}, 1H, J=3.3, 1.8 \text{ Hz, furan-H}), 6.07 (\text{dd}, 1H, J=3.3, 0.8 \text{ Hz, furan-H}), 4.34-4.27 (m, 2H, COCH_2), 4.14 (dq, 2H, J=10.7, 7.2 \text{ Hz, CO_2CH_2CH_3}), 4.02 (dq, 2H, J=10.7, 7.2 \text{ Hz, CO_2CH_2CH_3}), 3.30 (d, 1H, J=14.5 \text{ Hz, COCHC_2Et}), 3.18 (dd, 1H, J=4.3, 1.7 \text{ Hz, CHCO_2Et}), 2.44 (dd, 1H, J=14.5, 1.7 \text{ Hz, CH-furan}), 2.32 (s, 1H, OH), 1.35 (s, 3H, CH_3), 1.16 (t, 3H, J=7.2 \text{ Hz, CO_2CH_2CH_3}), 1.09 (t, 3H, J=7.2 \text{ Hz, CO_2CH_2CH_3}).
\]

\[
\delta_C (100 \text{ MHz; } \text{CDCl}_3) 204.0, 171.9, 169.0, 152.9, 141.9, 110.2, 106.5, 73.6, 61.1, 60.9, 56.2, 55.1, 50.6, 37.5, 28.5, 14.1, 13.9.
\]

m/z; 321, 311, 293.

HRMS Found 338.1362 (M^+; C_{17}H_{22}O_7 requires 338.1360).
Preparation of diethyl (1S*, 2R*)-2,4-dimethyl-6-oxocyclohex-4-ene-1,3-dicarboxylate (II-22)

\[
\begin{align*}
\text{CO}_2\text{Et} & \\
\text{CH}_3 & \\
\end{align*}
\]

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 H₂O (20 μL) at room temperature. A condenser and calcium sulfate drying tube were added, and the solution was heated at 100 °C for 20 h. After the solution was cooled, the mixture was quenched with H₂O (3 mL) and extracted with Et₂O (15 mL x 3). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 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].

R₁ = 0.46 (50% ethyl acetate/hexane).

νmax/cm⁻¹ 2979, 1732, 1671, 1443, 1379, 1347, 1253, 1174, 1095, 1028, 849.

δ'H (300 MHz; CDCl₃) 5.96 (app.d, 1H, J=1.4 Hz, CH=CCH₃, major and minor), 4.23 (q, 4H, J=7.1 Hz, CO₂CH₂CH₃, major and minor), 3.17 (d, 1H, J=5.1 Hz, CHCO₂Et, minor), 3.01 (d, 1H, J=7.0 Hz, CHCO₂Et, major), 2.58 (d, 1H, J=12.3 Hz, COCHCO₂Et, minor), 2.57 (d, 1H, J=13.0 Hz, COCHCO₂Et, major), 2.33-2.18 (m, 1H, CHCH₃, major), 2.17-2.03 (m, 1H, CHCH₃, minor), 1.95 (s, 3H, CH₃, major and minor), 1.29 (d, 6H, J=6.7 Hz, 2xCO₂CH₂CH₃, major), 1.28 (d, 6H, J=7.1 Hz,
2\times\text{CO}_2\text{CH}_2\text{CH}_3, \text{minor}), 1.09 (d, 3H, \ J=6.7 ~\text{Hz}, \text{CHCH}_3, \text{minor}), 1.07 (d, 3H, \ J=6.5 ~\text{Hz}, \text{CHCH}_3, \text{major}).

\delta_\text{C} (125 ~\text{MHz; CDCl}_3) 197.8 \text{ (major)}, 196.7 \text{ (minor)}, 175.4 \text{ (major)}, 173.2 \text{ (minor)}, 171.8 \text{ (major)}, 170.1 \text{ (minor)}, 156.6 \text{ (minor)}, 155.9 \text{ (major)}, 128.1 \text{ (minor)}, 127.9 \text{ (major)}, 83.6 \text{ (major and minor)}, 61.1 \text{ (major and minor)}, 61.0 \text{ (major and minor)}, 56.2 \text{ (minor)}, 54.3 \text{ (major)}, 52.1 \text{ (major)}, 51.9 \text{ (major and minor)}, 33.4 \text{ (major and minor)}, 31.9 \text{ (major and minor)}, 23.2 \text{ (minor)}, 22.6 \text{ (major)}, 19.7 \text{ (major)}, 18.4 \text{ (minor)}.

m/z; 269 (M+H\text{\textsuperscript{+}}, 100\%), 240, 222, 196, 154, 129, 122.

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

Potassium carbonate (276 \text{mg}, 2 \text{mmol}) was added to a stirred solution of ethyl acetoacetate (1.28 mL, 10 \text{mmol}) and (E)-pent-3-en-2-one (0.98 mL, 10 \text{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. \text{NH}_4\text{Cl} (5 mL) and extracted with \text{Et}_2\text{O} (20 mL \times 3). The combined organic layers were washed with water, brine and dried over anhydrous MgSO\textsubscript{4}. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO\textsubscript{2}, 25% EtOAc in hexanes) to give II-38a as a colourless solid as a single isomer [1.78 \text{g}, 8.32 \text{mmol}, 83\% yield].
mp 101–102 °C; Rf = 0.27 (50% ethyl acetate/hexane).

νmax/cm⁻¹: 3421, 1732, 1697, 1408, 1355, 1323, 1278, 1253, 1176, 1130, 1026, 920.

δH (500 MHz; CDCl₃) 4.29 (dq, 1H, J = 10.7, 7.2 Hz, CO₂CH₂CH₃), 4.23 (dq, 1H, J = 10.7, 7.2 Hz, CO₂CH₃CH₂CH₃), 2.97 (d, 1H, J = 12.0 Hz, COCH₂CO₂Et), 2.73-2.64 (m, 1H, CH₂CH₃), 2.49-2.37 (m, 2H, COCH₂), 1.93 (dt, 1H, J = 14.0, 2.6 Hz, CHHCHCH₃), 1.54 (dd, 1H, J = 14.0, 12.6 Hz, CHHCHCH₃), 1.36 (s, 3H, CH₃), 1.28 (t, 3H, J = 7.2 Hz, CO₂CH₂CH₃), 1.04 (d, 3H, J = 6.5 Hz, CO₂CH₂CH₃).

δC (125 MHz; CDCl₃) 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-OH⁺, 100%), 196, 169.

HRMS Found 214.1203 (M⁺, C₁₁H₁₈O₄ requires 214.1200).

**Preparation of ethyl (2S⁺,3R⁺,5R⁺)-5-hydroxy-5-methyl-1-oxo-3-phenylcyclohexane-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 (SiO₂, 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; Rf = 0.31 (50% ethyl acetate/hexane).

νmax/cm⁻¹ 3431, 1730, 1701, 1344, 1151, 1095, 1076, 1018, 923, 754, 700.

δH (500 MHz; CDCl₃) 7.35-7.23 (m, 5H, Ar-H), 4.12-4.00 (m, 2H, CO₂CH₂CH₃), 3.88 (td, 1H, J= 12.6, 4.1 Hz, CH-Ar), 3.65 (d, 1H, J=12.6 Hz, COCHCO₂Et), 2.65 (d, 1H, J=14.2 Hz, COCHH), 2.60 (dd, 1H, J=14.2, 2.2 Hz, COCHH), 2.17-2.08 (m, 1H, CHHCH-Ar), 2.04 (app.t, 1H, J=13.4 Hz, CHHCH-Ar), 1.72 (s, 1H, OH), 1.44 (s, 3H, CH₃), 1.08 (t, 3H, J=7.1 Hz, CH₂CH₃).

δC (125 MHz; CDCl₃) 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⁺, C₁₆H₂₀O₄ requires 276.1356).

**Preparation of ethyl (2S*,3S*,5R*)-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...
Attapol Pinsa

chromatography (SiO₂, 25% EtOAc in hexanes) to give **II-38c** as a colourless solid as a single isomer [437 mg, 1.55 mmol, 86% yield].

<table>
<thead>
<tr>
<th>mp</th>
<th>135–136 °C; R_f=0.40 (50% ethyl acetate/hexane).</th>
</tr>
</thead>
<tbody>
<tr>
<td>νmax/cm⁻¹</td>
<td>3427, 1728, 1679, 1319, 1276, 1267, 1238, 1184, 1159, 1045, 1022, 929, 721.</td>
</tr>
<tr>
<td>δ_H (300 MHz; CDCl₃)</td>
<td>4.25 (q, 2H, J=7.1 Hz, CO₂CH₂CH₃), 3.26 (d, 1H, J=12.6 Hz, COCHCO₂Et), 2.60 (tt, 1H, J=12.6, 3.0 Hz, CH-cylohexyl), 2.47 (dd, 1H, J=14.1, 2.2 Hz, COCHH), 2.40 (d, 1H, J=14.1 Hz, COCHH), 1.96-1.50 (m, 7H, CH₂CH-cyclohexyl, cyclohexyl-H), 1.37 (s, 3H, CH₃), 1.28 (t, 3H, J=7.1 Hz, CO₂CH₂CH₃), 1.27-0.90 (m, 6H, cyclohexyl-H).</td>
</tr>
<tr>
<td>δ_C (75 MHz; CDCl₃)</td>
<td>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.</td>
</tr>
<tr>
<td>m/z</td>
<td>283, 265 (M-OH⁺, 100%), 237, 219.</td>
</tr>
<tr>
<td>HRMS Found</td>
<td>282.1828 (M⁺, C₁₆H₂₆O₄ requires 282.1826).</td>
</tr>
</tbody>
</table>

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

![](image)

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 (SiO2, 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; Rf = 0.53 (50% ethyl acetate/hexane).

νmax/cm⁻¹ 3415, 1737, 1703, 1355, 1323, 1273, 1249, 1170, 1143, 1093, 1031, 1012, 698.

δH (500 MHz; CDCl₃) 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, CO₂CHHCH₃), 4.22 (dq, 1H, J=10.8, 7.2 Hz, CO₂CHHCH₃), 3.12 (d, 1H, J=12.0 Hz, COCH₂CO₂), 2.94-2.80 (m, 1H, CH₂CH₃), 2.89 (d, 1H, J=14.1 Hz, COCHH), 2.63 (dd, 1H, J=14.1, 2.8 Hz, COCHH), 2.33 (s, 1H, OH), 2.11 (ddd, 1H, J=13.7, 3.8, 2.8 Hz, CHHCHCH₃), 1.93 (td, 1H, J=13.7, 1.1 Hz, CHHCHCH₃), 1.28 (t, 3H, J=7.2 Hz, CO₂CH₂CH₃), 1.08 (d, 3H, J=6.6 Hz, CHCH₃).

δC (100 MHz; CDCl₃) 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-OH⁺, 100%), 231.

HRMS Found 276.1355 (M⁺, C₁₆H₂₀O₄ requires 276.1356).
Preparation of ethyl (2S*,3R*,5R*)-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 (SiO₂, 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; Rᵣ=0.53 (50% ethyl acetate/hexane).

νmax/cm⁻¹ 3400, 1735, 1707, 1280, 1259, 1184, 1149, 1029, 1014, 985, 779, 759, 702.

δH (500 MHz; CDCl₃) 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, CH₂CH₃ and CH-furan), 3.72 (d, 1H, J=12.3 Hz, COCHCO₂Et), 3.01 (d, 1H, J=14.1 Hz, COCHH), 2.72 (dd, 1H, J=14.1, 2.7 Hz, COCHH), 2.57 (s, 1H, OH), 2.45 (dd, 1H, J=14.1, 12.7 Hz, CHCHCH-furan), 2.35 (ddd, 1H, J=14.1, 4.0, 2.7 Hz, CHCH-furan), 1.18 (t, 3H, J=7.1 Hz, CO₂CH₂CH₃).
Ethyl (2S*,3R*)-5-(furan-2-yl)-1-oxo-3-phenylcyclohex-2-ene-6-carboxylate (II-41)

\[
\begin{align*}
\delta_C \text{ (100MHz; CDCl}_3) & \quad 203.3, 168.8, 154.8, 145.9, 141.8, 128.7, 127.8, 124.3, 110.2, 105.9, 75.9, 61.2, 61.0, 53.4, 42.6, 36.1, 14.1. \\
m/z \; 311 \text{ (M-OH}^+, 100\%), 243, 205. \\
\text{HRMS Found 328.1306 (M}^+, \text{ C}_{19}\text{H}_{20}\text{O}_5 \text{ requires 328.1305).}
\end{align*}
\]

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

\[\nu_{\text{max}}/\text{cm}^{-1} \quad 1734, 1660, 1165, 767, 688;\]

\[\delta_H \text{ (500 MHz; CDCl}_3 \quad 7.60-7.51 \text{ (m, 2H, Ar-H), 7.48-7.38 (m, 3H, Ar-H), 7.36 (dd, 1H, } J=1.8, 0.7 \text{ Hz, furan-H), 6.53 (d, 1H, } J=2.0 \text{ Hz, COCH=C), 6.30 (dd, 1H, } J=3.2, 1.8 \text{ Hz, furan-H), 6.15 (d, 1H, } J=3.2 \text{ Hz, furan-H), 4.19 (q, 2H, } J=7.1 \text{ Hz, CO}_2\text{CH}_2\text{CH}_3, 3.96 (\text{ddd, 1H, } J=11.7, 10.4, 4.8 \text{ Hz, CH-furan), 3.74 (d, 1H, } J=11.7 \text{ Hz, COCHCO}_2\text{Et), 3.20 (dd, 1H, } J=18.1, 4.8 \text{ Hz, CHHCH-furan), 3.08 (dd, 1H, } J=18.1, 10.4, 2.0 \text{ Hz, CHHCH-furan), 1.21 (t, 3H, } J=7.1 \text{ Hz, CO}_2\text{CH}_2\text{CH}_3).}\]

\[\delta_C \text{ (100MHz; CDCl}_3 \quad 193.3, 169.3, 158.3, 154.2, 142.0, 137.7, 130.6, 128.9, 126.2, 124.1, 110.3, 106.2, 61.3, 57.5, 37.3, 32.5, 14.1. \\
m/z \; 311 \text{ (M-H}^+, 100\%), 243, 108. \\
\text{HRMS Found 310.1204 (M}^+, \text{ C}_{19}\text{H}_{18}\text{O}_4 \text{ requires 310.1205).}
\]
Preparation of ethyl (1R*,2S*,3R*,4R*)-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 (SiO₂, 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 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) ; 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; CDCl₃) 4.19 (q, 2H, J=7.1 Hz, CH₂CH₃), 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, CH₃), 1.54 (m, 1H), 1.27 (t, 3H, J=7.1 Hz, CH₂CH₃).

δ_C (100MHz; CDCl₃) 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-OH⁺, 100%), 181.
HRMS Found 226.1207 (M^+, C\textsubscript{12}H\textsubscript{18}O\textsubscript{4} requires 226.1200).

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

\[
\text{\includegraphics[width=0.2\textwidth]{image}}
\]

R\textsubscript{f} = 0.57 (50% ethyl acetate/hexane).

\[\text{\nu}_{\text{max}}/\text{cm}^{-1} 2937, 1708, 1646, 1448, 1357, 1278, 1215, 1152, 1090, 1040, 911, 841.\]

\[\delta_\text{H} (500 \text{ MHz; CDCl}_3) 4.29-4.15 \text{ (m, 4H, CH}_2\text{CH}_3, \text{ major and minor)}, 3.55 \text{ (d, 1H, } J=13.6 \text{ Hz, CHCO}_2\text{Et, major)}, 3.37 \text{ (d, 1H, } J=18.2 \text{ Hz, CHCO}_2\text{Et, minor)}, 2.65-2.51 \text{ (m, 2H, major and minor)}, 2.48-2.12 \text{ (m, 8H, major and minor)}, 2.22 \text{ (s, 3H, COCH}_3, \text{ major)}, 2.20 \text{ (s, 3H, COCH}_3, \text{ minor)}, 2.11-1.98 \text{ (m, 2H, major and minor)}, 1.95-1.62 \text{ (m, 2H, major and minor)}, 1.60-1.37 \text{ (m, 4H, major and minor)}, 1.36-1.17 \text{ (m, 6H, CH}_2\text{CH}_3, \text{ major and minor)}.\]

\[m/z; 243 (\text{M+Na}^+), 226 (\text{M}^+, 100\%), 208, 170, 130.\]
Preparation of methyl (1S*,2S*,6R*)-2,6-dimethyl-4-tosylcyclohex-3-enecarboxylate (III-12)

\[
\begin{align*}
\text{AlCl}_3 (9.53 \text{ g, 71.45 mmol), CH}_2\text{Cl}_2 (70 \text{ mL) and methyl crotonate (7.6 mL, 71.45 mmol) were mixed together and stirred under nitrogen until a homogeneous solution was formed. A 57 mM solution (250 mL) of (III-13) (14.29 mmol) in CH}_2\text{Cl}_2 (6.6 mL) was then concentrated to a volume of 125 mL on a rotary evaporator and added to the first solution during 5 min. The reaction was heated under reflux at 100 °C for 7 days, then the reaction was cooled to 0 °C, quenched with sat NH}_4\text{Cl (50 mL) and extracted with CH}_2\text{Cl}_2 (50 mL \times 3). The combined organic layers were washed with water, brine and dried over anhydrous MgSO}_4. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO}_2, 25% EtOAc in hexanes) to give III-12 as a colourless solid [2.86 g, 8.86 mmol, 62% yield] and III-21 as a colourless solid [0.33 g, 0.74 mmol, 5% yield].
\end{align*}
\]

mp 95–96°C; R\text{f}=0.26 (25% ethyl acetate/hexane).

\[\nu_{\text{max}}/\text{cm}^{-1} 2954, 2931, 1732, 1651, 1597, 1454, 1435, 1371, 1300, 1220, 1145, 1089, 1010, 906, 815, 665.\]
\[ \delta_1 \ (500 \text{ MHz}; \text{CDCl}_3) \ 7.70 \ (d, \ J=8.2 \text{ Hz, Ar-H}), \ 7.31 \ (d, \ 2H, \ J=8.2 \text{ Hz, Ar-H}), \ 6.92 \ (\text{app.d}, \ 1H, \ J=3.9 \text{ Hz, SO}_2\text{C=CH}), \ 3.64 \ (s, \ 3H, \text{OCH}_3), \ 2.85-2.74 \ (m, \ 1H, \text{C=CHCHCH}_3), \ 2.42 \ (s, \ 3H, \text{CH}_3), \ 2.35 \ (\text{app.t}, \ 1H, \ J=6.1 \text{ Hz, CHCO}_2\text{CH}_3), \ 2.33 \ (\text{app.d}, \ 1H, \ J=5.6 \text{ Hz, SO}_2\text{CCHH}), \ 2.10-1.93 \ (m, \ 1H, \text{CH}_2\text{CHCHCH}_3), \ 1.73 \ (\text{ddddd}, \ 1H, \ J=16.8, \ 9.6, \ 2.1, \ 2.1 \text{ Hz, SO}_2\text{CCHH}), \ 0.98 \ (d, \ 3H, \ J=7.3 \text{ Hz, CH}_3), \ 0.96 \ (d, \ 3H, \ J=6.5 \text{ Hz, CH}_3).
\]

\[ \delta_c \ (75 \text{ MHz; CDCl}_3) \ 173.3, \ 144.3, \ 140.4, \ 138.3, \ 136.1, \ 129.8 \times 2, \ 128.0 \times 2, \ 51.4, \ 49.2, \ 31.9, \ 30.3, \ 25.5, \ 21.6, \ 19.6, \ 16.1.
\]

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

Anal. Calcd. for C\(_{17}\)H\(_{22}\)O\(_4\)S: C, 63.33; H, 6.88. Found: C, 63.12; H, 6.98.

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

![Diagram](image)

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

\[ \nu_{\text{max}}/\text{cm}^{-1} \ 1645, \ 1595, \ 1288, \ 1151, \ 1139, \ 1091, \ 970, \ 800, \ 707, \ 655, \ 594.
\]

\[ \delta_H \ (300 \text{ MHz; CDCl}_3) \ 7.66 \ (d, \ 2H, \ J=8.2 \text{ Hz, Ar-H}), \ 7.54 \ (d, \ 2H, \ J=8.2 \text{ Hz, Ar-H}), \ 7.26 \ (\text{app.t}, \ 4H, \ J=7.9 \text{ Hz, Ar-H}), \ 6.74 \ (\text{app.d}, \ 1H, \ J=2.4 \text{ Hz, SO}_2\text{C=CH}), \ 5.51 \ (\text{dd}, \ 1H, \ J=16.0, \ 1.3 \text{ Hz, CH=CHCH}_3), \ 5.30 \ (\text{dq}, \ 1H, \ J=16.0, \ 6.3 \text{ Hz, CH=CHCH}_3), \ 3.35-3.15 \ (m, \ 1H,
CH\textsubscript{3}), 2.38 (s, 6H, CH\textsubscript{3}\times2), 2.28-2.00 (m, 2H, SO\textsubscript{2}CCH\textsubscript{2}), 1.97-1.78 (m, 2H, SO\textsubscript{2}CCH\textsubscript{2}CH\textsubscript{2}), 1.61 (dd, 3H, J=6.3, 1.3 Hz, CH=CHCH\textsubscript{3}), 1.39 (d, J=7.4 Hz, CH\textsubscript{3}).

δ\textsubscript{C} (75 MHz; CDCl\textsubscript{3}) 144.9, 144.3, 141.1, 137.7, 135.8, 133.2, 131.9, 130.6, 129.7\times2, 129.1\times2, 127.9\times2, 121.9\times2, 67.8, 33.8, 25.6, 21.59, 21.56, 20.5, 18.5, 16.8.

m/z; 467 (M+Na\textsuperscript{+}, 100%) 445, 413, 391, 363, 287, 205, 167, 149, 131.

Anal. Calcd. for C\textsubscript{24}H\textsubscript{28}O\textsubscript{4}S\textsubscript{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\textsubscript{2}O (30 mL) and extracted with CH\textsubscript{2}Cl\textsubscript{2} (100 mL \times 2). The combined organic layers were washed with water, brine and dried over anhydrous MgSO\textsubscript{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).

$\delta_H$ (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=CHH), 6.13 (dq, 1H, $J=15.8$, 6.5 Hz, CH=CHCH$_3$), 6.01 (app.d, 1H, $J=15.8$ Hz, CH=CHCH$_3$), 5.83 (br.s, 1H, C=CHH), 2.42 (s, 3H, Ar-CH$_3$), 1.74 (d, 3H, $J=6.5$ Hz, CH$_3$).

$\delta_C$ (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)**

![Structure of 1-(but-2-enylsulfonyl)-4-methylbenzene](image)

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$_2$O (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 (SiO₂, 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).

v max/cm⁻¹: 1666, 1597, 1396, 1315, 1300, 1143, 1087, 968, 929, 815, 723, 624.

δ_H (400 MHz; CDCl₃) 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, CH₂CH₃, cis), 5.52 (dq, 1H, J=15.3, 6.4 Hz, CH₂CH₃, trans), 5.36 (dtq, 1H, J=15.3, 7.3, 1.5 Hz, CH=CHCH₃, cis and trans), 3.79 (d, 2H, J=7.9 Hz, SO₂CH₂, cis), 3.67 (d, 2H, J=7.3 Hz, SO₂CH₂, trans), 2.39 (s, 3H, CH₃, cis and trans), 1.62 (app.d, 3H, J=6.4 Hz, CH₃, trans), 1.31 (app.d, 3H, J=7.0 Hz, CH₃, cis).

δ_C (100 MHz; CDCl₃) 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⁺, C₁₁H₁₄O₂S requires 211.0793).

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

![Structure of III-19](image)

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 nBuLi (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 NH₄Cl (30 mL) and extracted with Et₂O (50 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 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; CDCl₃) 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, CHCH₃, cis), 5.54 (dq, 1H, J=15.3, 6.5 Hz, CHCH₃, trans), 5.53-5.10 (m, 1H, CH=CHCH₃, cis and trans), 4.30-3.60 (m, 2H, CH₂OH, cis and trans), 2.98 (dt, 1H, J=4.6, 3.1 Hz, SO₂CH₂, cis), 2.88 (dt, 1H, J=5.6, 2.1 Hz, SO₂CH₂, trans), 2.45 (s, 3H, CH₃, cis and trans), 1.66 (dd, 3H, J=6.5, 1.4 Hz, CH₃, trans), 1.31 (dd, 3H, J=7.0, 1.7 Hz, CH₃, trans).

δ_C (100 MHz; CDCl₃) 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⁺, C₁₂H₁₆O₃S requires 263.0718).
Preparation of methyl (1S*,2S*)-2-methyl-4-tosylecyclohex-3-enecarboxylate (III-20)

According to the general procedure as described for compound III-12, AlCl₃ (0.72 g, 5.39 mmol), CH₂Cl₂ (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 CH₂Cl₂ 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 NH₄Cl (10 mL) and extracted with CH₂Cl₂ (10 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 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; CDCl₃) 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, SO₂C=CH₂), 3.66 (s, 3H, OCH₃), 2.95-2.82 (m, 1H, CHCH₃), 2.59 (ddd, 1H, J=12.0, 5.0, 2.9 Hz, CHCO₂CH₃), 2.43 (s, 3H, CH₃), 2.38-2.27 (m, 1H, SO₂CHCH₃), 2.15-
2.05 (m, 1H, SO\textsubscript{2}CCHH), 1.97-1.87 (m, 1H, SO\textsubscript{2}CCH\textsubscript{2}CHH), 1.78-1.65 (m, 1H, SO\textsubscript{2}CCH\textsubscript{2}CHH), 0.97 (d, 3H, J=7.2 Hz, CH\textsubscript{3}).

\[ \delta_C \text{ (125 MHz; CDCl}_3 \text{) 173.7, 144.3, 140.9, 139.2, 136.1, 129.8\times2, 128.1\times2, 51.7, 42.2, 31.5, 22.6, 21.6, 19.3, 15.4.} \]

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

Anal. Calcd. for C\textsubscript{16}H\textsubscript{20}O\textsubscript{4}S: 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\textsubscript{2}O (3 x 125 mL). The combined organic layers were washed with water, brine and dried over anhydrous...
MgSO₄. 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).

\( \nu_{\text{max}}/\text{cm}^{-1} \): 3020, 2918, 2864, 1722, 1585, 1492, 1446, 1091, 1016, 956, 881, 806.

\( \delta_\text{H} \) (500 MHz; CDCl₃) 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=CHH), 5.38 (d, 1H, \( J = 16.8 \) Hz, CH=CHH), 2.45 (s, 3H, CH₃).

\( \delta_\text{C} \) (125 MHz; CDCl₃) 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⁺, \( \text{C}_9\text{H}_9\text{S} \) requires 151.0581).

**Preparation of 1-methyl-4-(vinylsulfinyl)benzene (III-25)**

\[ \text{\begin{tikzpicture}
\begin{scope}[scale=0.5]
\draw[thick] (-1,0) -- (1,0);
\draw[thick] (0,-1) -- (0,1);
\draw[thick] (-0.5,0.5) -- (0.5,0.5);
\draw[thick] (0.5,-0.5) -- (-0.5,-0.5);
\draw[thick] (-0.5,0.5) -- (-0.5,-0.5);
\draw[thick] (0.5,0.5) -- (0.5,-0.5);
\draw[thick] (0,0) -- (0,0.5);
\draw[thick] (0,0) -- (0,-0.5);
\node at (0,0) {\textbf{O}};
\node at (0,0.5) {\textbf{S}};
\end{scope}
\end{tikzpicture}}\]

A solution of \( m \)-chloroperbenzoic acid (0.63 g, 3.63 mmol, 77% dispersion in chlorobenzoic acid) in CH₂Cl₂ (11 mL) was slowly added dropwise to the solution of III-24 (0.40 g, 2.66 mmol) in CH₂Cl₂ (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 NaHCO₃ solution until its neutral, and extracted with CH₂Cl₂ (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).

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

$\delta_H$ (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=CHH), 5.86 (d, 1H, $J$=9.6 Hz, CH=CHH), 2.39 (s, 3H, CH$_3$).

$\delta_C$ (100 MHz; CDCl$_3$) 143.1, 141.9, 140.1, 130.1x2, 124.9x2, 120.4, 21.4.

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

HRMS Found 167.0527 (M+H$^+$, C$_9$H$_{11}$OS requires 167.0531).

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

![Chemical structure of III-26](image)

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<sub>2</sub>O (20 mL x 3). The combined organic layers were washed with water, brine and dried over anhydrous MgSO<sub>4</sub>. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO<sub>2</sub>, 50% EtOAc in hexanes) to give **III-26** as a colourless oil [0.61 g, 2.88 mmol, 89% yield].

R<sub>f</sub> = 0.14 (50% ethyl acetate/hexane).

ν<sub>max</sub>/cm<sup>-1</sup> 3003, 2872, 1643, 1633, 1492, 1377, 1354, 1215, 1107, 1085, 1041, 806, 754.

δ<sub>H</sub> (500 MHz; CDCl<sub>3</sub>) 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, CHCHOEt), 3.65 (dt, 1H, J=10.5, 5.2 Hz, CHCHOEt), 3.55 (dq, 1H, J=16.4, 7.0 Hz, OCHHCH<sub>3</sub>), 3.51 (dq, 1H, J=16.4, 7.0 Hz, OCHHCH<sub>3</sub>), 3.04-2.92 (m, 2H, SOCH<sub>2</sub>), 2.41 (s, 3H, CH<sub>3</sub>), 1.21 (t, 3H, J=7.0 Hz, CH<sub>3</sub>).

δ<sub>C</sub> (125 MHz; CDCl<sub>3</sub>) 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<sup>+</sup>, 100%), 198, 179, 167, 162, 140, 139, 120.

HRMS Found 213.0945 (M+H<sup>+</sup>, C<sub>14</sub>H<sub>17</sub>O<sub>2</sub>S requires 213.0949).

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

![Chemical structure of 2-(p-tolylsulfinyl)pent-1-en-3-ol (III-27)](attachment:image)

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 NH₄Cl (30 mL). The mixture was diluted with water (50 mL) and extracted with Et₂O (30 mL x 3). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 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).

\[ \nu_{\text{max/cm}^{-1}}: 3003, 2872, 1643, 1633, 1492, 1377, 1354, 1215, 1107, 1085, 1041, 806, 754. \]

\[ \delta_{\text{H}} (500 \text{ MHz; CDCl}_3): 7.55 (d, 2H, J=8.1 \text{ Hz, Ar-H, minor}), 7.52 (d, 2H, J=8.1 \text{ Hz, Ar-H, major}), 7.31 (d, 2H, J=8.1 \text{ Hz, Ar-H, major}), 7.27 (d, 2H, J=8.1 \text{ Hz, Ar-H, minor}), 6.07 (s, 1H, C=CHH, minor), 6.06 (s, 1H, C=CHH, major), 5.85 (s, 1H, C=CHH, major), 5.84 (s, 1H, C=CHH, minor), 4.15-4.03 (m, 1H, CHOH, major and minor), 2.41 (s, 3H, CH₃, major), 2.40 (s, 3H, CH₃, minor), 1.75-1.46 (m, 2H, CH₂CH₃, major and minor), 0.86 (t, 3H, J=7.4 Hz, CH₃, minor), 0.80 (t, 3H, J=7.4 Hz, CH₃, major).

\[ \delta_{\text{C}} (100 \text{ MHz; CDCl}_3): 156.9 \text{ (minor), 156.1 \text{ (major), 142.0 \text{ (major), 141.9 \text{ (minor), 139.7 \text{ (minor), 138.9 \text{ (major), 130.1×2 \text{ (major), 130.0×2 \text{ (minor), 125.5×2 \text{ (minor), 125.2×2 \text{ (major), 117.5 \text{ (major), 117.3 \text{ (minor), 70.7 \text{ (minor), 69.7 \text{ (major), 29.4 \text{ (minor), 28.4 \text{ (major), 21.5 \text{ (major and minor), 9.7 \text{ (minor), 9.5 \text{ (major).}}}

\[ m/z: 225 \text{ (M+H}^+ \text{, 100%), 208, 207, 206, 189, 163, 157, 141, 139, 131. \]

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)

![Structure](image)

A solution of methansulfonyl chloride (0.37 mL, 4.81 mmol) in CH₂Cl₂ (1 mL) was added to a solution of III-27 (0.83 g, 3.70 mmol) in CH₂Cl₂ (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 NH₄Cl (10 mL), water (10 mL) and extracted with Et₂O (3 x 25 mL). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 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; CDCl₃) 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=CH₂, minor), 6.27 (d, 1H, J=0.9 Hz, C=CH₂, major and minor), 5.02-4.85 (m, 1H, CH-OMs, major and minor), 2.89 (s, 3H, CH₃, major), 2.60 (s, 3H, CH₃, minor), 2.40 (s, 3H, CH₃, major and minor), 1.92-1.68 (m, 1H, CHHCH₃),
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major), 1.63-1.31 (m, 1H, CHHCH₃, minor and CHHCH₃, major and minor), 0.85 (t, 3H, J=7.3 Hz, CH₃, major), 0.85 (t, 3H, J=7.3 Hz, CH₃, minor).

δC (75 MHz; CDCl₃) 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⁺, C₁₃H₁₉O₄S₂ 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 CH₂Cl₂ (32.5 mL) under nitrogen. The reaction mixture was heated at reflux for 2 h, then the mixture was diluted with NH₄Cl (10 mL) and extracted with Et₂O (3 x 25 mL). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 50% EtOAc in hexanes) to give III-29 as a yellow solid [0.86 g, 4.16 mmol, 64% yield].

mp 59–60 °C; Rf = 0.54 (50% ethyl acetate/hexane).
\( \nu_{\text{max}}/\text{cm}^{-1} \) 3020, 2992, 2850, 1643, 1595, 1492, 1446, 1398, 1377, 1303, 1178, 1082, 1051, 960, 912, 810.

\( \delta_H \) (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\(=\)CH\(_2\) and CH\(=\)CHCH\(_3\)), 5.69 (s, 1H, CH\(=\)CHCH\(_3\)), 2.36 (s, 3H, CH\(_3\)), 1.68 (d, 3H, J=5.5 Hz, CH\(_3\)).

\( \delta_C \) (75 MHz; CDCl\(_3\)) 151.1, 141.8, 140.2, 131.4, 129.9\(\times\)2, 125.6, 123.5\(\times\)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 (1S*,2S*)-methyl 2-methyl-4-(p-tolylsulfanyl)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\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\) (1.3 mL) was added to the reaction mixture at room temperature. After stirring the reaction mixture for 2 days, the reaction was cooled to 0 °C, quenched with sat NH\(_4\)Cl (5 mL) and extracted with CH\(_2\)Cl\(_2\) (20 mL × 3).
The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 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; Rf = 0.32 (50% ethyl acetate/hexane).

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

\[ \delta_{\mathrm{H}} \] (500 MHz; CDCl₃) 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, SO₂C=CH), 3.63 (s, 3H, OCH₃), 2.92-2.80 (m, 1H, CHCH₃), 2.68-2.60 (m, 1H, CHCO₂CH₃), 2.37 (s, 3H, CH₃), 1.96-1.82 (m, 3H, SOCCCH₃ and SOCCCH₂CHH), 1.75-1.62 (m, 1H, SO₂CCCH₂CHH), 0.97 (d, 3H, J=7.1 Hz, CH₃).

\[ \delta_{\mathrm{C}} \] (125 MHz; CDCl₃) 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⁺, C₁₆H₂₁O₃S requires 293.1211).

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

![Structure of III-31](image-url)
According to the general procedure as described for compound III-12, AlCl$_3$ (2.21 g, 16.6 mmol), CH$_2$Cl$_2$ (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 ºC for 10 days, then the reaction was cooled to 0 ºC, quenched with sat NH$_4$Cl (30 mL) and extracted with CH$_2$Cl$_2$ (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).

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

$\delta$$_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$_2$C=CH, major and minor), 3.47 (s, 3H, OCH$_3$, minor), 3.46 (s, 3H, OCH$_3$, major), 2.72-2.50 (m, 1H, C=CHCHCH$_3$, major and minor), 2.25 (dd, 1H, $J$=10.1, 5.8 Hz, CHCO$_2$CH$_3$, major and minor), 2.21 (s, 3H, CO$_2$CH$_3$, major and minor), 1.93-1.66 (m, 2H, CH$_2$CHCH$_3$ and SO$_2$CCHH, major and minor), 1.42 (ddd, 1H, SO$_2$CCHH, 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).
δC (75 MHz; CDCl3) 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.


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

![Chemical structure](attachment:image.png)

A solution of (III-12) (5.74 g, 18.74 mmol) in dry CH₂Cl₂ (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 CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with water, brine and dried over
anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 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<sub>f</sub>=0.25 (50% ethyl acetate/hexane).

ν<sub>max</sub>/cm⁻¹ 3441, 1643, 1595, 1300, 1286, 1273, 1149, 1105, 1082, 1004, 806, 669, 623.

δ<sub>H</sub> (400 MHz; CDCl₃) 7.70 (d, 2H, <i>J</i>=8.1 Hz, Ar-H), 7.30 (d, 2H, <i>J</i>=8.1 Hz, Ar-H), 6.94 (app.d, 1H, <i>J</i>=4.1 Hz, SO₂C=CH), 3.68 (dd, 1H, <i>J</i>=10.1, 6.1 Hz, CHHOH), 3.51 (dd, 1H, <i>J</i>=10.1, 10.1 Hz, CHHOH), 2.80-2.66 (m, 1H, C=CHCH(CH₃)), 2.42 (s, 3H, CH₃), 2.27 (app.d, 1H, <i>J</i>=12.2 Hz, SO₂CCHH), 1.85-1.67 (m, 2H, SO₂CCHH and CH₂CHCH₃), 1.63-1.46 (m, 1H, CHCH₂OH), 1.01 (d, 3H, <i>J</i>=7.3 Hz, CH₃), 0.87 (d, 3H, <i>J</i>=6.2 Hz, CH₃).

δ<sub>C</sub> (100 MHz; CDCl₃) 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.


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

![Structure](attachment:structure.png)
To a suspension of (III-33) (0.54 g, 1.85 mmol) and 4-(dimethylamino)pyridine (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 NH₄Cl (15 mL) and extracted with Et₂O (20 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 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).

$\nu_{\text{max}}$/cm⁻¹: 1641, 1597, 1467, 1454, 1377, 1300, 1290, 1149, 1112, 1083, 885, 837, 813, 775, 667, 619.

$\delta_H$ (500 MHz; CDCl₃) 7.71 (d, 2H, $\delta = 8.1$ Hz, Ar-H), 7.31 (d, 2H, $\delta = 8.1$ Hz, Ar-H), 6.45 (app.d, 1H, $\delta = 4.3$ Hz, SO₂C=CH), 3.58 (dd, 1H, $\delta = 9.9, 6.0$ Hz, CHHOTBS), 3.45 (dd, 1H, $\delta = 9.9, 9.9$ Hz, CHHOTBS), 2.75-2.63 (m, 1H, C=CHCH₃), 2.42 (s, 3H, Ar-CH₃), 2.26 (app.d, 1H, $\delta = 12.3$ Hz, SO₂CCHH), 1.82-1.66 (m, 2H, SO₂CCHH and CH₂CHCH₃), 1.58-1.46 (m, 1H, CH₂CHOTBS), 0.99 (d, 3H, $\delta = 7.3$ Hz, CH₃), 0.86 (d, 3H, $\delta = 8.6$ Hz, CH₃), 0.85 (s, 9H, SiC(CH₃)₃), 0.00 (s, 3H, SiCH₃), 0.01 (s, 3H, SiCH₃).

$\delta_C$ (100 MHz; CDCl₃) 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_{3}SSiNa requires 431.2052).

Preparation of (4S*,5R*)-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 N₂ 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 Et₂O (3 x 75 mL). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 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; CDCl₃): 5.91 (s, 1H, C=CH), 3.80 (app.d, 1H, J=1.3 Hz, CH_{HOTBS}), 3.79 (app.d, 1H, J=2.5 Hz, CH_{HOTBS}), 2.60 (dd, 1H, J=16.9, 5.1 Hz, COCHH), 2.48-2.35 (m,
1H, CHCH$_3$), 2.17-2.06 (m, 2H, COCHH and CHCH$_2$OTBS), 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$_3$).

$\delta$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$_{18}$H$_{29}$O$_2$Si requires 269.1937).

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

![Structure of the compound]

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 °C under nitrogen. The reaction mixture was stirred at 0 °C for 30 min, then a solution of tert-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$_4$Cl (15 mL) and extracted with Et$_2$O (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 (SiO₂, 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, 599, 574, 557, 511;

δ_H (500 MHz; CDCl₃) 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, CH=CCH₃, minor), 5.58 (br.s, 1H, CH=CCH₃, major), 3.74 (dd, 1H, J=11.3, 2.7 Hz, SO₂CH, major), 3.62 (dd, 1H, J=10.4, 2.7 Hz, SO₂CH, minor), 3.39 (dd, 1H, J=9.9, 4.4 Hz, CHHOTBS, major and minor), 2.85 (dd, 1H, J=9.9, 9.9 Hz, CHHOTBS, major and minor), 2.41 (s, 3H, CH₃, minor), 2.40 (s, 3H, CH₃, major), 2.23-2.12 (m, 1H, CHCH₃, major and minor), 1.83-1.50 (m, 3H, SO₂CH and SO₂CHCH₂, major and minor), 1.72 (s, 3H, CH₃, major and minor), 0.95 (d, 3H, J=6.6 Hz, CH₃, minor), 0.85 (d, 3H, J=7.1 Hz, CH₃, major), 0.82 (s, 9H, SiC(CH₃)₃, major), 0.80 (s, 9H, SiC(CH₃)₃, minor), −0.03 (s, 6H, Si(CH₃)₂, minor), −0.06 (s, 6H, Si(CH₃)₂, major).

δ_C (100 MHz; CDCl₃) 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⁺, C₂₂H₃₆O₃SSiNa requires 431.2052).
Preparation of ((1S*,6R*)-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 CH₂Cl₂ (50 mL × 3). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 50% EtOAc in hexanes) to give III-42 as a yellow oil [2.28g, 7.74 mmol, 95% yield].

R₇=0.25 (50% ethyl acetate/hexane).

νₓmax/cm⁻¹ 3435, 3419, 3020, 2958, 1637, 1597, 1448, 1379, 1286, 1217, 1143, 1085, 754, 665.

δH (400 MHz; CDCl₃) 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, CH=CCH₃), 3.66 (br.s, 1H, SO₂CH), 3.53 (dd, 1H, J=11.1, 3.2 Hz, CHHOH), 3.33 (dd, 1H, J=11.1, 6.8 Hz, CHHOH), 2.38 (s, 3H, CH₃), 2.25 (br.s, 1H, OH), 2.22-2.14 (m, 1H, CHCH₃), 1.92 (ddd, 1H, J=13.4, 8.0, 4.4 Hz, SO₂CHCHH), 1.77 (br.s, 1H, CHCH₂OH), 1.72 (s, 3H, CH₃), 1.52 (ddd, 1H, J=13.4, 6.7, 6.7 Hz, SO₂CHCHH), 0.86 (d, 3H, J=6.9 Hz, CH₃).
\( \delta_c \) (100 MHz; CDCl\(_3\)) 144.7, 141.9, 134.3, 129.6\times2, 129.0\times2, 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\(^+\), Ce\(_{16}H_{22}O_3\)Na requires 317.1187).

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

![Chemical Structure](image)

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 \(-78^\circ\)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 \(-78^\circ\)C for 30 min]. The mixture was stirred at \(-78^\circ\)C for 3 h, then quenched with 2 N HCl (30 mL), and extracted with Et\(_2\)O (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 [5.65 g, 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).
\[ \nu_{\text{max/cm}^{-1}} \] 3479, 2957, 2928, 2887, 2856, 1657, 1461, 1376, 1251, 1085, 986, 882, 833, 772, 681.

\[ \delta_{\text{H}} \] (500 MHz; CDCl\textsubscript{3}) 6.03 (s, 1H, C=CH), 3.99 (dd, 1H, J=10.6, 2.0 Hz, CH\textsubscript{HOTBS}), 3.81 (dd, 1H, J=10.6, 1.8 Hz, CH\textsubscript{HOTBS}), 3.81 (br.s, 1H, OH), 3.80 (d, 1H, J=12.3 Hz, CH\textsubscript{OH}), 2.18-2.08 (m, 2H, CH\textsubscript{CH\textsubscript{3}} and CH\textsubscript{CH\textsubscript{2}OTBS}), 2.04 (s, 3H, CH\textsubscript{3}), 1.23 (d, 3H, J=6.0 Hz, CH\textsubscript{3}), 0.84 (s, 9H, SiC(CH\textsubscript{3})\subscript{3}), 0.05 (s, 3H, SiCH\textsubscript{3}), 0.04 (s, 3H, SiCH\textsubscript{3}).

\[ \delta_{\text{C}} \] (125 MHz; CDCl\textsubscript{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\textsuperscript{+}, 100%), 284, 270, 269, 266, 255, 237, 231, 206, 171, 155, 151.

HRMS Found 285.1887. (M+H\textsuperscript{+}, C\textsubscript{15}H\textsubscript{29}O\textsubscript{3}Si requires 285.1886).

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

To a mixture of CeCl\textsubscript{3}.7H\textsubscript{2}O (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\textsubscript{4}Cl solution (20 mL), added 2N HCl until the reaction
mixture became clear, and extracted with Et$_2$O (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).

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

$\delta_H$ (300 MHz; CDCl$_3$) 5.51 (s, 1H, C=CH), 4.18 (br.s, 1H CHOH), 3.71 (dd, 1H, $J$=6.1, 2.3 Hz, CHHOTBS), 3.65 (dd, 1H, $J$=6.1, 1.9 Hz, CHHOTBS), 2.02-1.94 (m, 1H, CHHCHCH$_3$), 1.91-1.80 (m, 1H, CHCH$_3$), 1.72 (s, 3H, CH$_3$), 1.68 (br.d, 1H, $J$=3.9 Hz, CHCH$_2$OTBS), 1.40 (br.s, 1H, OH), 1.28-1.18 (m, 1H, CHHCHCH$_3$), 1.03 (d, 3H, $J$=4.0 Hz, CH$_3$), 0.86 (s, 9H, SiC(CH$_3$)$_3$), 0.02 (s, 6H, Si(CH$_3$)$_2$).

$\delta_C$ (125 MHz; CDCl$_3$) 137.0, 128.5, 67.3, 61.1, 49.2, 40.5, 27.8, 25.8x3, 21.5, 20.5, 18.2, -5.5x2.

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$_{13}$H$_{30}$O$_2$SiNa requires 293.1913).
Preparation of ((1S*,5R*,6S*)-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 (SiO₂, 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; Rf=0.30 (25% ethyl acetate/hexane).

νmax/cm⁻¹ 1653, 1620, 1307, 1253, 1193, 1105, 1058, 991, 862, 837, 773, 719.

δH (500 MHz; CDCl₃) 5.61 (ddd, 1H, J=10.0, 5.2, 1.5 Hz, CH=CH), 5.53 (d, 1H, J=10.0 Hz, CH=CH), 3.83 (ddd, 1H, J=10.8, 3.5 Hz, CHHOTBS), 3.77 (dd, 1H, J=10.8, 5.5 Hz, CHHOTBS), 3.04 (s, 3H, NCH₃), 2.95 (s, 3H, NCH₃), 2.54 (s, 2H, CH₂N(CH₃)₃), 2.10-1.95 (m, 1H, CH=CHCHH), 1.88-1.73 (m, 2H, CH=CHCHH and CHCH₃), 1.72-1.63 (m,
1H, CH\(\text{CH}_2\text{OTBS})\), 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\(_3\)).

\[\delta_{C} (75 \text{ MHz; CDCl}_3) 171.7, 136.1, 124.3, 61.6, 48.9, 43.5, 39.1, 38.3, 35.4, 35.1, 27.3, 25.9 \times 3, 23.9, 19.8, 18.1, -5.6, -5.7.\]

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\(_{38}\)N\(_2\)Si requires 340.2672).

**Preparation of (3aR\(^{\ast}\),4S\(^{\ast}\),5R\(^{\ast}\),7R\(^{\ast}\),7aR\(^{\ast}\))-4-((\text{tert-butyldimethylsilyloxy)methyl})-7-iodo-3a,5-dimethylhexahydrobenzofuran-2(3H)-one (III-48)**

![Chemical structure of III-48](image)

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\(_2\)S\(_2\)O\(_3\) 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; Rf=0.57 (25% ethyl acetate/hexane).

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

$\delta_H$ (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, CHHOTBS), 3.67 (dd, 1H, $J$=10.6, 7.6 Hz, CHHOTBS), 2.97 (d, 1H, $J$=7.2 Hz, CHHCO), 2.37 (d, 1H, $J$=7.2 Hz, CHHCO), 2.08-1.93 (m, 2H, CHCH$_3$ and CHICH$_2$), 1.92-1.77 (m, 1H, CHICH$_2$), 1.50 (s, 3H, CH$_3$), 1.41-1.27 (m, 1H, CHCH$_2$OTBS), 1.02 (d, 3H, $J$=6.3 Hz, CH$_3$), 0.92 (s, 9H, SiC(CH$_3$)$_3$), 0.08 (s, 6H, Si(CH$_3$)$_2$).

$\delta_C$ (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$_2$SiNa requires 461.0985).
Preparation of (3aR*,4S*,5R*,7αS*)-4-((tert-butyldimethylsilyloxy)methyl)-3α,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 NH₄Cl (5 mL) and extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 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; Rf = 0.49 (25% ethyl acetate/hexane).

νmax/cm⁻¹ 2956, 2927, 2881, 2854, 1762, 1745, 1460, 1384, 1249, 1222, 1197, 1170, 1126, 993, 833, 773.

δH (400 MHz; CDCl₃) 5.91 (d, 1H, J=10.0 Hz, CH=CH), 5.79 (ddd, 1H, J=10.0, 4.6, 2.5 Hz, CH=CH), 4.28 (d, 1H, J=4.6 Hz, CHO), 3.79 (dd, 1H, J=11.3, 3.3 Hz, CHHOTBS), 3.75 (dd, 1H, J=11.3, 5.5 Hz, CHHOTBS), 2.96 (d, 1H, J=17.4 Hz, CHHCO), 2.39 (d, 1H, J=17.4 Hz, CHHCO), 2.32-2.18 (m, 1H, CHCH₃).
1.11 (s, 3H, CH₃), 1.10 (d, 3H, J=6.0 Hz, CH₃), 0.89 (s, 9H, SiC(CH₃)₃), 0.06 (s, 6H, Si(CH₃)₂).

δC (100 MHz; CDCl₃) 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⁺, C₁₇H₃₀O₃SiNa requires 333.1862).

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

Lithium bis(trimethylsilyl)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 NH₄Cl solution, and extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column
chromatography (SiO₂, 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).

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

\( \delta_\text{H} \) (500 MHz; CDCl₃) 5.86 (dd, 1H, \( J = 10.1, 2.0 \text{ Hz} \), CH=CH), 5.72 (ddd, 1H, \( J = 10.1, 2.9, 2.9 \text{ Hz} \), CH=CH), 4.62 (app.s, 1H, CHOCO), 4.44 (d, 1H, \( J = 3.5 \text{ Hz} \), CHOH), 3.81 (dd, 1H, \( J = 10.5, 3.5 \text{ Hz} \), CHHOTBS), 3.66 (dd, 1H, \( J = 10.5, 4.5 \text{ Hz} \), CHHOTBS), 2.72 (d, 1H, \( J = 3.5 \text{ Hz} \), CHOH), 2.37-2.22 (m, 1H, CHCH₃), 1.49 (app.q, 1H, \( J = 4.5 \text{ Hz} \), CHCH₂OTBS), 1.17 (d, 3H, \( J = 7.4 \text{ Hz} \), CH₃), 1.12 (s, 3H, CH₃), 0.87 (s, 9H, Si(CH₃)₃), 0.05 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃).

\( \delta_\text{C} \) (100 MHz; CDCl₃) 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⁺, C₁7H₃₀O₄SiNa requires 349.1811).

**Preparation of (1S*,4R*,5S*,6S*)-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 °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 CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na₂SO₄. 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].

Rᵣ=0.46 (25% ethyl acetate/hexane).

νₑₘₐₓ/cm⁻¹ 3397, 2956, 2929, 2884, 2857, 1461, 1253, 1102, 1072, 993, 862, 832, 774.

δₜ (300 MHz; CDCl₃) 5.79 (ddd, 1H, J=9.8, 5.5, 2.0 Hz, CH=CH), 5.63 (dd, 1H, J=9.8, 2.2 Hz, CH=CH), 4.72 (br.s, 2H, CH=CHH and OH), 4.71 (s, 1H, C=CHH), 4.41 (d, 1H, J=4.4 Hz, OH), 3.99 (d, 1H, J=5.5 Hz, CH=CHCHOH), 3.73 (ddd, 1H, J=10.6, 1.7 Hz, CHHOTBS), 3.70-3.53 (m, 2H, CCHOH and CHHOTBS), 2.39 (ddd, 1H, J=14.4, 7.1, 7.1 Hz, CHOCH₂CHH), 2.18-2.02 (m, 2H, CHOCH₂CHH and CHOCHHCH₂), 1.93-1.77 (m, 3H, CH₃CH₃, CHOCHHCH₂ and CH₂OTBS), 1.74 (s, 3H, CH₃), 1.15 (d, 3H, J=6.8 Hz, CH₃), 0.91 (s, 9H, SiC(CH₃)₃), 0.68 (s, 3H, CH₃), 0.11 (s, 3H, Si(CH₃)), 0.10 (s, 3H, Si(CH₃)).

δₙ (100 MHz; CDCl₃) 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 \((M+Na^+), C_{21}H_{40}O_3SiNa\) requires 391.2644).

**Preparation of \((1S^\star,4R^\star,5S^\star,6S^\star)-5-((\text{tert/}{-}\text{butyldimethylsilyloxy})\text{methyl})-6-\text{(1-hydroxy-4-methylpent-4-enyl)}-4,6\text{-dimethylcyclohex-2-enol (III-51')}\)**

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\(_4\)Cl solution, and extracted with Et\(_2\)O (3 x 15 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na\(_2\)SO\(_4\). After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO\(_2\), 25% Et\(_2\)OAc 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).

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

δ_{H} (500 MHz; CDCl₃) 5.79 (dd, 1H, J=9.8, 5.5, 2.0 Hz, CH=CH, major), 5.75 (ddd, 1H, J=9.8, 5.5, 2.3 Hz, CH=CH, minor), 5.65 (dd, 1H, J=9.8, 2.3 Hz, CH=CH, minor), 5.64 (dd, 1H, J=9.8, 2.3 Hz, CH=CH, major), 4.730 (s, 1H, C=CHH, major and minor), 4.728 (s, 1H, C=CHH, 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=CHCHOH, major and minor), 3.88-3.95 (m, 3H, CHHOTBS, CCHOH and CHHOTBS, major and minor), 2.39 (ddd, 1H, J=14.6, 7.1, 7.1 Hz, CHOHCH₂CHH, major and minor), 2.16-2.02 (m, 2H, CHOHCH₂CHH and CHOHCH₃CH₂, major and minor), 1.92-1.76 (m, 3H, CHCH₃, CHOHCH₃CH₂ and CHCH₂OTBS, major and minor), 1.74 (s, 3H, CH₃, major and minor), 1.15 (d, 3H, J=6.9 Hz, CH₃, major), 1.11 (d, 3H, J=6.9 Hz, CH₃, minor), 0.89 (s, 9H, SiC(CH₃)₃, major and minor), 0.68 (s, 3H, CH₃, major and minor), 0.115 (s, 3H, Si(CH₃)₃, major), 0.106 (s, 3H, Si(CH₃)₃, major), 0.11 (s, 3H, Si(CH₃)₃, minor), 0.099 (s, 3H, Si(CH₃)₃, minor).

δ_{C} (125 MHz; CDCl₃) 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 \textit{tert}-butyl((1S*,6R*)-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 NH₄Cl (3 mL), extracted with Et₂O (2 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 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).
\[ v_{\text{max}}/\text{cm}^{-1} 3035, 1666, 1597, 1494, 1359, 1317, 1253, 1209, 1184, 1087, 1047, 875, 835, 773. \]

\[ \delta_H (300 \text{ MHz}; \text{CDCl}_3) 7.52 (d, 2H, J=8.1 \text{ Hz}, \text{Ar-H}), 7.30 (d, 2H, J=8.1 \text{ Hz}, \text{Ar-H}), 5.57 \text{ and } 5.47 (s, 1H, \text{CH} = \text{CCH}_3), 4.03-3.82 (m, 2H, \text{SOCH}_2), 3.80-3.52 (m, 3H, \text{CH}_3\text{OTBS and CHO}), 3.07-2.87 (m, 2H, \text{OCH}_2\text{CH}_2\text{SO}), 2.39 (s, 3H, \text{CH}_3), 2.10-1.50 (m, 3H, \text{CHHCHCH}_3, \text{CHCH}_3, \text{CHCH}_2\text{OTBS}), 1.71 (s, 3H, \text{CH}_3), 1.40-1.15 (m, 1H, \text{CHHCHCH}_3), 1.02 (dd, 3H, J=6.6, 3.3 \text{ Hz}, \text{CH}_3), 0.85 (s, 9H, \text{SiC(CH}_3)_3), 0.01 (s, 6H, \text{Si(CH}_3)_2). \]

\[ \delta_C (75 \text{ MHz}; \text{CDCl}_3) 141.3, 140.9, 137.9, 129.9 \times 2, 125.7, 124.0 \times 2, 75.3, 60.7, 60.7, 58.9, 49.3, 36.5, 27.7, 25.8 \times 3, 21.6, 21.4, 20.4, 18.3, -5.5 \times 2. \]

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

HRMS Found 459.2361 (M+Na^+, \text{C}_{24}\text{H}_{40}\text{O}_3\text{SiNa requires } 459.2365). 

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

![Chemical Structure](attachment:image.png)

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\text{Cl}_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 NH₄Cl (3 mL) and extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 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].

Rᶠ=0.37 (25% ethyl acetate/hexane).

νmax/cm⁻¹ 2954, 2927, 2856, 1735, 1469, 1462, 1373, 1242, 1114, 1099, 1026, 873, 837, 775.

δH (500 MHz; CDCl₃) 5.47 (s, 1H, CH=C), 5.29 (br.s, 1H, CHOCO), 3.69 (app.d, 2H, J=3.1, Hz, CH₂OTBS), 2.10-2.20 (m, 1H, CHHCHCH₃), 2.05 (s, 3H, OCOCH₃), 2.10-1.90 (m, 1H, CHCH₃), 1.76 (br.s, 4H, CHCH₂OTBS and CH=CCH₃), 1.43-1.31 (m, 1H, CHHCHCH₃), 1.04 (d, 3H, J=6.7 Hz, CH₃), 0.88 (s, 9H, SiC(CH₃)₃), 0.04 (s, 6H, Si(CH₃)₂).

δC (100 MHz; CDCl₃) 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⁺, C₁₇H₂₀O₃SiNa requires 335.2018).
Preparation of \((4S^*,5R^*)-4-(\text{tert-butyldimethylsilyloxy})\text{methyl}-3,5\text{-dimethylcyclohex-2-enyl propionate (III-62)}\)

The allylic alcohol \((\text{III-46})\) (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 Et₂O (2 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 5% EtOAc in hexanes) to give \text{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).

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

\(\delta_H\) (500 MHz; CDCl₃) 5.60-5.50 (m, 1H, C=CH, major), 5.44 (app.s, 1H, C=CH, minor), 5.30-5.15 (m, 1H CHO COEt, major and minor), 3.78-3.60 (m, 2H, CH₂OTBS, major and minor), 2.29 (q, 2H, \(J=7.6\) Hz, \(\text{CH}_2\text{CH}_3\), minor), 2.27 (q, 2H, \(J=7.6\) Hz, \(\text{CH}_2\text{CH}_3\), major), 2.20-2.07 (m, 1H, \(\text{CH}_2\text{CHCH}_3\), major), 1.98-1.90 (m, 1H, \(\text{CH}_2\text{CHCH}_3\), minor), 1.80-1.65
(m, 5H, CH₃ and CH₂CHCH₃, major and minor), 1.57 (ddd, 1H, J=13.6, 8.6, 5.0 Hz, CHCH₂OTBS, major and minor), 1.08 (q, 3H, J=7.5 Hz, CH₂CH₃, major and minor), 1.01 (d, 3H, J=6.8 Hz, CH₃, minor), 0.99 (d, 3H, J=6.9 Hz, CH₃, major), 0.87 (s, 9H, SiC(CH₃)₃, major), 0.85 (s, 9H, SiC(CH₃)₃, minor), 0.033 (s, 3H, SiCH₃, major), 0.029 (s, 3H, SiCH₃, major), 0.01 (s, 6H, Si(CH₃)₂, minor).

δ_C (75 MHz; CDCl₃) 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⁺, C₁₈H₃₄O₃SiNa requires 349.2175).

Preparation of (R *)-2-((1S*,5R*,65*)-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. Na₂S₂O₃ solution until the reaction mixture became clear, and extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with water, brine and dried over anhydrous...
MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 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].

\[R_f=0.55 \text{ (25\% ethyl acetate/hexane).}\]

\[\nu_{\text{max/cm}^{-1}} \quad 3018, 2954, 2929, 1782, 1462, 1388, 1257, 1215, 1097, 989, 837, 748, 665.\]

\[\delta_{\text{H}} \ (500 \text{ MHz; CDCl}_3) \quad 5.79 \text{ (app.d, 1H, } J=10.2 \text{ Hz, CH=CH), 5.68-5.57 \text{ (m, 1H, CH=CH), 5.20 (s, 1H, CHI), 3.76 (dd, 1H, } J=10.8, 3.6 \text{ Hz, CHHOTBS), 3.64 (dd, 1H, } J=10.8, 6.3 \text{ Hz, CHHOTBS), 3.02 (s, 3H, NCH}_3, 2.89 \text{ (s, 3H, NCH}_3, 1.97 \text{ (dt, 1H, } J=16.8, 4.3 \text{ Hz, CH=CHCHH), 1.83 \text{ (dt, 1H, } J=10.6, 2.3 \text{ Hz, CHCH}_3, 1.81-1.65 \text{ (m, 2H, CH=CHCHH and CHCH}_2\text{OTBS), 1.12 (s, 3H, CH}_3, 0.95 \text{ (d, 3H, } J=6.0 \text{ Hz, CH}_3, 0.88 \text{ (s, 9H, SiC(CH}_3)_3, 0.054 (s, 3H, SiCH}_3, 0.052 (s, 3H, SiCH}_3).\]

\[\delta_{\text{C}} \ (100 \text{ MHz; CDCl}_3) \quad 169.8, 136.1, 123.6, 62.3, 44.9, 41.2, 38.2, 38.1, 36.5, 34.6, 29.0, 26.0 \times 3, 25.8, 19.8, 18.4, -5.4, -5.5.\]

\[m/z; \quad 466 \text{ (M+H}^+, 100\%), 414, 413, 392, 391, 341, 340, 311, 279, 257, 205, 180, 149;\]

HRMS Found 466.1628 (M+H\(^+\), \(\text{C}_{19}\text{H}_{37}\text{NO}_2\text{Si}) \text{ requires 466.1638).}\]
Preparation of \( (3S^*,3aR^*,4S^*,5R^*,7aS^*)-4-((\text{tert-butyldimethylsilyloxy})\text{methyl})-3a,5\text{-dimethyl}-3-(\text{tri-methylsilyloxy})-3,3a,4,5\text{-tetrahydrobenzofuran-2(7aH)}\text{-one} \) (III-69)

Potassium bis(trimethylsilyl)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\(_4\)Cl solution, 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-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).

\( \nu_{\text{max}}/\text{cm}^{-1} \) 2956, 2929, 2883, 2856, 1778, 1660, 1512, 1462, 1404, 1359, 1251, 1228, 1097, 989, 939, 837, 775.
\( \delta_H \) (500 MHz; CDCl\(_3\)) 5.87 (dd, 1H, \( J=10.0, 2.2 \) Hz, CH=CH), 5.76 (ddd, 1H, \( J=10.0, 4.6, 2.4 \) Hz, CH=CH), 4.54 (d, 1H, \( J=4.6 \) Hz, CHOCO), 4.35 (s, 1H, CHOTMS), 3.74 (d, 2H, \( J=4.0 \) Hz, CH\(_2\)OTBS), 2.35-2.22 (m, 1H, CHCH\(_3\)), 1.17 (dt, 1H, \( J=8.9, 4.0 \) Hz, CHCH\(_2\)OTBS), 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\(_3\)).

\( \delta_C \) (125 MHz; CDCl\(_3\)) 175.2, 140.2, 119.5, 80.3, 75.3, 62.0, 44.7, 42.9, 30.1, 25.8x3, 19.9, 18.1, 12.5, 0.07x3, -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\(_4\)Si\(_2\)Na requires 421.2206).

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

\[
\begin{align*}
\text{OH} & \quad \text{H} \\
\text{OTBS} &
\end{align*}
\]

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\(_2\)O (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\(_2\)O (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).

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

$\delta$$_H$ (300 MHz; CDCl$_3$) 9.78 (s, 1H, CHO), 5.80 (ddd, 1H, $J$=9.8, 5.2, 2.2 Hz, CH=CH), 5.70 (dd, 1H, $J$=9.8, 2.3 Hz, CH=CH), 3.94-3.80 (m, 2H, CHOH and CHHOTBS), 3.53 (dd, 1H, $J$=9.8, 9.8 Hz, CHHOTBS), 2.45-2.25 (m, 2H, CHCH$_2$OTBS and OH), 2.02-1.86 (m, 1H, CHCH$_3$), 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$_3$).

$\delta$$_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$_{33}$O$_3$Si requires 299.2042).

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

![Chemical Structure](attachment:image.png)
A solution of **III-50** (84.6 mg, 0.26 mmol) in THF (2 mL) was slowly added to a suspension of LiAlH4 (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 NH4Cl (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 Et2O (3 x 15 mL). The combined organic layers were washed with water, brine and dried over anhydrous MgSO4. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO2, 50% EtOAc in hexanes) to give **III-73** as a colourless solid [80.3 mg, 0.24 mmol, 94% yield].

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

\[ \text{v}_{\text{max}}/\text{cm}^{-1} 3373, 3360, 3020, 2954, 2927, 2885, 2856, 1462, 1390, 1361, 1253, 1103, 1051, 995, 835. \]

\[ \delta_\text{H} (500 \text{ MHz; CDCl}_3) 5.75 (\text{ddd, 1H, } J=9.7, 5.7, 2.2 \text{ Hz, CH} = \text{CH}), 5.65 (\text{dd, 1H, } J=9.7, 2.3 \text{ Hz, CH} = \text{CH}), 4.82 (\text{br.s, 1H, OH}), 3.95-3.64 (\text{m, 6H, CH}_2\text{OH, CH}_3\text{OTBS and CHOHx2)}, 3.09 (\text{br.s, 1H, OH}), 2.62 (\text{br.s, 1H, OH}), 1.90-1.76 (\text{m, 1H, CHCH}_3), 1.66 (\text{ddd, 1H, } J=10.0, 7.0, 2.6 \text{ Hz, CHCHOTBS}), 1.09 (\text{d, 3H, } J=6.9 \text{ Hz, CHCH}_3), 0.89 (\text{s, 9H, SiC(CH}_3)_3), 0.81 (\text{s, 3H, CH}_3), 0.11 (\text{s, 3H, SiCH}_3), 0.10 (\text{s, 3H, SiCH}_3). \]

\[ \delta_\text{C} (100 \text{ MHz; CDCl}_3) 136.9, 125.6, 76.0, 70.8, 62.3, 62.0, 45.5, 42.8, 30.5, 25.8x3, 19.9, 18.1, 13.0, -5.2, -5.5. \]

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 \((3S^*, 3aS^*, 4S^*, 5R^*, 7aS^*)-4-(\text{tert-butyldimethylsilyloxy})\text{methyl})\text{-3a,5-dimethyl-2,3,3a,4,5,7a-hexahydrobenzofuran-2,3-diol (III-74)}\)

A solution of \textbf{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\(_4\)Cl (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\(_2\)O (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 \textbf{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).

\(\nu_{\text{max}}/\text{cm}^{-1}: 3292, 2955, 2928, 2883, 2857, 1512, 1461, 1387, 1251, 1105, 1033, 992, 862, 830, 772\).

\(\delta_H\) (500 MHz; CDCl\(_3\)) 5.80 (ddd, 1H, \(J=10.0, 3.9, 2.3\) Hz, CH=CH), 5.75 (d, 1H, \(J=10.0\) Hz, CH=CH), 5.52 (d, 1H, \(J=4.0\) Hz, OCH\(_2\)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, CHCH₂OTBS), 1.10 (d, 3H, J=7.0 Hz, CH₃), 0.99 (s, 3H, CH₃), 0.92 (s, 9H, SiC(CH₃)₃), 0.11 (s, 6H, Si(CH₃)₂).

δC (75 MHz; CDCl₃) 138.3, 122.6, 96.4, 79.6, 78.7, 76.2, 54.9, 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⁺, C₁₇H₃₂O₄SiNa requires 351.1968).

**Preparation of (1S*,4R*,5S*,6R*)-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 LiAlH₄ (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 NH₄Cl (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 Et₂O (3 x 15 mL). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under
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reduced pressure, the crude product was purified by column chromatography (SiO₂, 50% EtOAc in hexanes) to give III-75 as a colourless solid [52.9 mg, 0.168 mmol, 97% yield].

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

ν max/cm⁻¹ 3292, 2955, 2928, 2883, 2857, 1512, 1387, 1251, 1105, 1033, 992, 862, 830, 772.

δH (300 MHz; CDCl₃) 5.73 (app.s, 2H, CH=CH), 3.91 (dd, 1H, J=10.8, 3.0 Hz, CHHOTBS), 3.88-3.81 (m, 2H, CHHOH and CHHOTBS), 3.79 (d, 1H, J=3.1 Hz, CHHOH), 3.69 (d, 1H, J=3.2 Hz, CHHO), 2.78 (br.s, 2H, OH×2), 2.30 (qdd, 1H, J=10.2, 7.0, 7.0 Hz, CHCH₃), 1.89 (ddd, 1H, J=15.1, 9.0, 4.0 Hz, CHHCH₂OH), 1.72 (ddd, 1H, J=15.1, 5.5, 3.1 Hz, CHHCH₂OH), 1.39 (ddd, 1H, J=10.2, 3.0, 3.0 Hz, CHCH₂OTBS), 1.07 (d, 3H, J=7.0 Hz, CHCH₃), 0.91 (s, 3H, CH₃), 0.88 (s, 9H, SiC(CH₃)₃), 0.04 (s, 6H, Si(CH₃)₂).

δC (125 MHz; CDCl₃) 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⁺, C₁₇H₃₄O₃SiNa requires 337.2175).
(1S*,4R*,5S*,6S*)-5-((tert-butyldimethylsilyloxy)methyl)-6-(hydroxymethyl)-4,6-dimethylcyclohex-2-enol (III-76)

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

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

$\delta_{\text{H}}$ (300 MHz; CDCl$_3$): 5.76 (ddd, 1H, $J$=9.8, 5.2, 1.0 Hz, CH=CH), 5.65 (dd, 1H, $J$=9.8, 1.3, CH=CH), 3.98-3.56 (m, 7H, CH$_2$OTBS, CH$_2$OH, CHO and OH×2), 1.94 (br.s, 2H, CHCH$_2$OTBS and CHCH$_3$), 1.13 (d, 3H, $J$=6.6 Hz, CHCH$_3$), 0.91 (s, 9H, SiC(CH$_3$)$_2$), 0.67 (s, 3H, CH$_3$), 0.11 (s, 6H, Si(CH$_3$)$_2$).

$\delta_{\text{C}}$ (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$_2$Si requires 301.2199).
Preparation of (3aR*,4S*,5R*,7aS*)-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 NaHCO₃ solution (10 mL), and extracted with Et₂O (3 x 15 mL). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 25% EtOAc in hexanes) to give III-77 as a colourless solid [15.0 mg, 0.046 mmol, 84% yield].

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

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

\( \delta_H \) (300 MHz; CDCl₃) 6.06 (dd, 1H, J=10.1, 1.5 Hz, CH=CH), 5.90 (ddd, 1H, J=10.1, 4.3, 2.5 Hz, CH=CH₂), 4.59 (d, 1H, J=4.3 Hz, CHOCO), 3.69 (dd, 1H, J=11.3, 3.5 Hz, CHHOTBS), 3.65 (dd, 1H, J=11.3, 3.0 Hz, CHHOTBS), 2.60-2.40 (m, 1H, CHCH₃), 1.43
(ddd, 1H, J=9.3, 3.5, 3.3 Hz, CHCH₂OTBS), 1.24 (s, 3H, CH₃), 1.13 (d, 3H, J=7.1 Hz, CHCH₃), 0.88 (s, 9H, SiC(CH₃)₃), 0.08 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃).

δC (125 MHz; CDCl₃) 197.9, 160.8, 142.1, 119.0, 79.2, 58.7, 48.3, 41.1, 28.5, 25.8 x 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⁺, C₁₇H₂₈O₄SiNa requires 347.1655).

Preparation of (R*)-1-((1R*,2S*,5R*,6S*)-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 LiAlH₄ (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 NH₄Cl (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 Et₂O (3 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂,
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).

\( \nu_{\text{max}}/\text{cm}^{-1} \) 3368, 2955, 2928, 2884, 1461, 1253, 1103, 1066, 1026, 995, 864, 834, 774.

\( \delta_H \) (300 MHz; CDCl\(_3\)) 5.73 (ddd, 1H, \( J=9.8, 5.4, 1.8 \) Hz, CH=CH), 5.65 (dd, 1H, \( J=9.8, 1.9 \) Hz, CH=CH), 4.58 (app.d, 1H, \( J=5.1 \) Hz, CHOHCH\(_2\)OH), 4.12 (br.s, 1H, OH), 3.97-3.65 (m, 6H, CH\(_2\)OH, CH\(_2\)OTBS, CHOH, OH), 2.47 (br.s, 1H, OH), 2.10-1.87 (m, 2H, CHCH\(_3\), CHCH\(_2\)OTBS), 1.14 (d, 3H, \( J=6.5 \) Hz, CHCH\(_3\)), 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\(_3\)).

\( \delta_C \) (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\(_4\)SiNa 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 NH₄Cl solution, and extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 25% EtOAc in hexanes) to give III-80 as a colourless solid [0.16 g, 0.48 mmol, 98% yield].

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

νmax/cm⁻¹ 3381, 3305, 3018, 2956, 2929, 2883, 2856, 1774, 1462, 1255, 1215, 1141, 958, 835, 756.

δ_H (300 MHz; CDCl₃) 5.91 (dd, 1H, J=9.9, 1.9 Hz, CH=CH), 5.81 (ddd, 1H, J=9.9, 5.1, 2.3 Hz, CH=CH), 5.73 (app.d, 1H, J=10.0 Hz, OH), 4.23-4.12 (m, 2H, CHOCO and CHOH), 3.82 (dd, 1H, J=11.3, 1.8 Hz, CHHOTBS), 3.74 (dd, 1H, J=11.3, 7.7 Hz, CHHOTBS), 2.05-1.87 (m, 1H, CHCH₃), 1.42 (ddd, 1H, J=10.0, 7.7, 1.8 Hz, CHCH₂OTBS), 1.15 (s, 3H, CH₃), 1.13 (d, 3H, J=7.0 Hz, CH₃), 0.91 (s, 9H, SiC(CH₃)₃), 0.11 (s, 6H, Si(CH₃)₂).

δ_C (125 MHz; CDCl₃) 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⁺, C₁₇H₃₀O₄SiNa requires 349.1811).
Preparation of (R*)-2-((1R*,2S*,5R*,6S*)-6-((tert-butyldimethylsilyloxy)methyl)-2-hydroxy-1,5-dimethyl-cyclohex-3-enyl)-2-hydroxyethyl 4-methylbenzenesulfonate (III-81)

\[
\begin{align*}
\text{R}^* & = 0.57 (25\% \text{ ethyl acetate/hexane}). \\
\nu_{\text{max/cm}^{-1}} & = 3369, 2962, 2926, 2879, 1457, 1357, 1174, 1033, 1009, 970, 814, 682, 665, 553; \\
\delta_H (500 \text{ MHz; CDCl}_3) & = 7.81 (d, 2H, \text{J}=8.2 \text{ Hz, Ar-H}), 7.33 (d, 2H, \text{J}=8.2 \text{ Hz, Ar-H}), 5.76-5.60 (m, 2H, CH=CH), 4.46 (dd, 1H, \text{J}=10.6, 2.1 \text{ Hz, CHHOTs}), 4.28 (dd, 1H, \text{J}=10.6, 8.1 \text{ Hz, CHHOTs}).
\end{align*}
\]
Hz, CHHOTs), 3.96 (dd, 1H, J=8.1, 2.1 Hz, CHOHCH2OTs), 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-CH3), 2.08-1.88 (m, 2H, CHCH3 and CHCH2OTBS), 1.11 (d, 3H, J=6.4 Hz, CHCH3), 0.89 (s, 9H, SiC(CH3)3), 0.77 (s, 3H, CH3), 0.09 (s, 6H, Si(CH3)2).

δC (75 MHz; CDCl3), 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+, C24H40O6SiNa requires 507.2213).

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

![Chemical Structure](image)

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 drying 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 Et2O (10 mL) and water (10 mL),
the layers separated, the aqueous layer was extracted with Et₂O (2 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous NaSO₄. After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO₂, 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; CDCl₃) 5.84 (ddd, 1H, J=10.0, 3.5, 2.6 Hz, CH=CH), 5.65 (d, 1H, J=10.0 Hz, CH=CH), 4.45 (dd, 1H, J=4.5, 1.6 Hz, OH), 3.96 (dt, 1H, J=4.5, 4.5 Hz, CHOH), 3.93-3.86 (m, 2H, OCHH and CHHOTBS), 3.81 (ddd, 1H, J=9.4, 4.5, 1.6 Hz, OCHH), 3.65-3.52 (m, 2H, CHOCH₂ and CHHOTBS), 1.93 (dd, 1H, J=10.3, 3.9 Hz, CHCH₂OTBS), 1.90-1.82 (m, 1H, CHCH₃), 1.09 (d, 3H, J=6.7 Hz, CH₃), 0.97 (s, 3H, CH₃), 0.93 (s, 9H, Si(C(CH₃))₃), 0.13 (s, 6H, Si(CH₃)₂).

δ_C (125 MHz; CDCl₃) 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⁺, C₁₇H₃₃O₃Si requires 313.2199).
Preparation of \((1S^*,4R^*,5S^*,6R^*)-5-((\text{tert-butyldimethylsilyloxy})\text{methyl})-6-((R^*)-1\text{-hydroxy-2-iodoethyl})-4,6\text{-dimethylcyclohex-2-enol}\) (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\(_2\)Cl\(_2\) (0.5 mL) followed by a solution of triphenylphosphine (19 mg, 0.07 mmol) in CH\(_2\)Cl\(_2\) at -30 °C under nitrogen. A solution of iodine (18 mg, 0.07 mmol) in CH\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\) (3 x 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na\(_2\)SO\(_4\). After removal of solvent under reduced pressure, the crude product was purified by column chromatography (SiO\(_2\), 25% EtOAc in hexanes) to give IIIm-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).

\(\nu_{\text{max}}/\text{cm}^{-1}\) 3387, 2922, 2851, 1448, 1416, 1374, 1259, 1092, 1031, 987, 892, 838, 578, 553;
\(\delta_{\text{H}}\) (300 MHz; CDCl\(_3\)) 5.75 (ddd, 1H, \(J=9.8, 5.4, 2.0\) Hz, CH=CH), 5.71 (dd, 1H, \(J=9.8, 2.0\) Hz, CH=CH), 4.68 (br.s, 1H, OH), 4.45 (br.s, 1H, OH), 4.05 (dd, 1H, \(J=9.5, 4.5\) Hz, CHH), 3.96 (dd, 1H, \(J=8.2, 4.5\) Hz, CHHOTBS), 3.84-3.56 (m, 4H, CHOH, CHOHCH\(_2\)I,
CHHII and CHHOTBS), 1.90-1.79 (m, 1H, CHCH\textsubscript{2}OTBS), 1.72 (app.d, 1H, J=7.1 Hz, CHCH\textsubscript{3}), 1.13 (d, 3H, J=7.1 Hz, CHCH\textsubscript{3}), 0.92 (s, 9H, SiC(CH\textsubscript{3})\textsubscript{3}), 0.82 (s, 3H, CH\textsubscript{3}), 0.11 (s, 6H, Si(CH\textsubscript{3})\textsubscript{2}).

\(\delta_C\) (125 MHz; CDCl\textsubscript{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\textsuperscript{+}, 100%), 428, 427, 390, 312, 294, 277, 251, 212, 180, 162, 146;

HRMS 441.1326 (M+H\textsuperscript{+}, C\textsubscript{17}H\textsubscript{34}O\textsubscript{3}Si requires 441.1322).

Preparation of (3S\textsuperscript{*},3aS\textsuperscript{*},4S\textsuperscript{*},5R\textsuperscript{*},7aS\textsuperscript{*})-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 drying 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\textsubscript{2}O (10 mL) and water (10 mL), the layers separated, the aqueous layer was extracted with Et\textsubscript{2}O (2 × 10 mL). The combined organic layers were washed with water, brine and dried over anhydrous NaSO\textsubscript{4}. After removal of solvent under reduced pressure, the crude product was purified by
column chromatography (SiO₂, 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).

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

$\delta_{\text{H}}$ (300 MHz; CDCl₃) 5.89 (dd, 1H, $J = 19.6$, 1.2 Hz, CH=CH), 5.81 (dd, 1H, $J = 9.6$, 4.5, 2.1 Hz, CH=CH), 4.25 (dd, 1H, $J = 5.4$, 2.9 Hz, CHOH), 4.02 (dd, 1H, $J = 6.8$, 6.8 Hz), 3.95-3.85 (m, 2H), 3.81 (d, 1H, $J = 4.5$ Hz, CHOCH₂), 3.57 (dd, 1H, $J = 12.3$, 7.4 Hz, CH₂OH), 2.18-2.34 (m, 1H, CH₂CH₂OH), 2.02 (ddd, 1H, $J = 11.8$, 6.2, 6.2 Hz, CHCH₃), 1.08 (d, 3H, $J = 7.0$ Hz, CH₃), 0.97 (s, 3H, CH₃).

$\delta_{\text{C}}$ (75 MHz; CDCl₃) 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⁺, C₁₁H₁₈O₃Na requires 221.1154).
REFERENCES


