CHAPTER-4
SYNTHESIS OF TYPE-II LACTONES:
4-\textit{EPI}-MITSUGASHIWARALACTONE AND
MITSUGASHIWARALACTONE
4.1. INTRODUCTION:

After completing the formal synthesis of (+)-iridomyrmecin 10, (-)-isoiridomyrmecin 11 and (+)-teucrimalactone 15 belonging to type-I iridoid lactones, we turned our attention towards the synthesis of type-II lactones. Both types of bicyclic lactones are cis-fused at C4a-C7a, the only difference is that the carbonyl group is at C3 in type-I lactones whereas it is at C1 in type-II lactones. The different methods for the synthesis of mitsugashivalactone 17, onikulactone 18, dihydronepetalactone 20 and isodihydronepetalactone 21 belonging to structural type-II were documented in Chapter-1. A limitation of the reported methods is that all of them, except one, lead to racemic products. So far, only one enantioselective synthesis for (-)-mitsugashivalactone 18 has been reported by Takacs and Myoung [1]. Our aim was to investigate an enantioselective route towards lactones 17,18,20 and 21 employing the HWE protocol.

4.2. SYNTHETIC APPROACH TO DIHYDRONEPETALACTONE AND ISODIHYDRONEPETALACTONE:

From our earlier work on type-I lactones (Chapter-3) we were aware that the stereoselective exo-face hydrogenation of unsaturated lactone 104 gives the cis-fused lactone 59. Hence, the unsaturated lactone 168 was retro analysed as arising from a McMurry coupling of the diketone 169, which can be prepared from anti-pulegenic acid 92. The acid 92 was chosen as starting material because, it has the required anti stereochemistry at C7 and C7a, and also because it is easily prepared from R-pulegone 91.
Thus, *anti*-pulegenic acid 92 was converted to the corresponding carboxylate anion with K$_2$CO$_3$ and alkylated with methallyl chloride 170 in acetone to provide ester 171. The exocyclic methylene protons in ester 171 appeared at $\delta$ 4.98 and 4.90 as singlets in PMR spectrum. Ozonolysis of ester 171 in 1:4 MeOH-CH$_2$Cl$_2$ at -78 °C followed by quenching with DMS afforded triketone as a mixture of keto 169 and enol 172 forms. The hydroxy band at 3450 cm$^{-1}$ in IR spectrum suggested equilibrium with enol form 172 of triketone 169. Attempted cyclisation under McMurry coupling conditions [2] of TiCl$_4$ did not provide the desired unsaturated lactone 168. The failure of the reaction may be due to the 1,3-dicarbonyl moiety in the molecule, which exists predominantly in the enol form 172.
Reagents: i) $\text{K}_2\text{CO}_3$, NaN$_4$, acetone, rt, 12 h; ii) $\text{O}_3$, $\text{NaHCO}_3$, 1:4 $\text{MeOH-CH}_2\text{Cl}_2$, -78°C, then DMS.

A closer inspection of dihydronepetalactone 20, suggested that all the required carbons for the target skeleton are present in anti-pulegenic acid 92 or its methyl ester 161. Therefore, the synthesis of lactone 168 was planned through a tandem allylic oxidation and cyclisation reaction.

The acid 92 and the ester 161 were subjected to allylic oxidation with various oxidising agents such as SeO$_2$ [3], SeO$_2$/TBHP [4], SeO$_2$.SG/TBHP [5], CrO$_3$.2Py [6] and CrO$_3$.DMP [7]. None of these reagents gave the required product. The crude
PMR spectrum showed either unreacted starting material (CrO$_3$.2Py, CrO$_3$.DMP) or a complex unidentified pattern (SeO$_2$/TBHP, SeO$_2$.SG/TBHP). Oxidation with SeO$_2$ in aq. dioxane did not afford the desired allylic alcohol 173. Instead, the intermediate secondary selenyl ester underwent further rearrangement to the tertiary ester, which upon hydrolysis afforded the isolated product. This was tentatively characterised as tert-alcohol 174 based on its PMR spectrum which displayed the olefin proton at $\delta$ 5.72 and also a hydroxy band at 3350 cm$^{-1}$ in IR spectrum.

**Scheme-4**

\[ 161 \xrightarrow{i} \quad CO_2Me \quad \text{HO} \quad \text{S}e \quad \text{OH} \quad \text{H} \quad \text{H} \quad \text{CO}_2\text{Me} \quad \text{CO}_2\text{Me} \quad \text{CO}_2\text{Me} \quad \text{OH} \quad \text{H} \quad \text{H} \quad \text{CO}_2\text{Me} \]

*Reagents: SeO$_2$, aq. dioxane, reflux, 1 h.*
The problems encountered with approaches outlined in Schemes 1 and 3 was a temporary setback. Both the planned routes were elegant and efficient in carbon economy and number of steps. At this juncture we sought recourse to more familiar HWE chemistry.

4.3. SYNTHESIS OF (-)-4-EPI-MITSUGASHI WALACTONE:

Since, the carbonyl at C1 was causing enolisation thereby preventing cyclisation, it appeared that the C1 carbonyl function should be protected. A retrosynthetic analysis is delineated in Scheme-5 which leads to the four lactones (17, 18, 20 and 21) and is also related to our earlier HWE approach. The lactone 168 should arise from hydroxy acetal 175 which can be obtained from the corresponding α, β-unsaturated ester 176. Ester 176 can be prepared by HWE reaction between ketoacetal 177 and phosphonate 178. Depending on the choice of phosphonate reagent 178 (R = H or Me), lactones 17, 18 or 20, 21 can be synthesised. The homoallylic alcohols 159, 160 which are easily available from R-pulegone 91 were the precursors for ketoacetal 177.

Thus, R-pulegone 91 was converted to a 60:40 mixture of syn- and anti-alkene alcohol 159, 160 as described in previous chapter. PCC oxidation [8] of 159, 160 in CH2Cl2 at rt for 1 h provided a mixture of syn- and anti-aldehyde 179. The integration of aldehydic CH doublets at δ 9.34 (syn) and at δ 9.22 (anti) suggested that the ratio is 30:70, respectively. Acetalisation [9] of aldehyde 179 with ethanediol and triethyl orthoformate using catalytic amount of p-TsOH.H2O in benzene at rt provided a 30:70 mixture of syn- and anti-acetal 180. Again, the ratio was determined by the integration of acetal CH doublet at δ 4.94 (syn) and 4.86 (anti) in PMR spectrum. Ozonolysis of exocyclic olefin 180 under buffered conditions (NaHCO3) at -78 °C in
1:4 MeOH-CH$_2$Cl$_2$ provided ketone 177 which was contaminated with acetal cleavage products. Oxidation of 180 with RuCl$_3$/NaIO$_4$ [10] was clean and gave the somewhat unstable syn- and anti-ketoacetal 177 as a 50:50 mixture in 55% yield.

Scheme-5
Reagents: i) LiAlH$_4$, ether, $0^\circ$C, 1 h; ii) PCC, CH$_2$Cl$_2$, rt, 1 h; iii) (CH$_2$OH)$_2$, (EtO)$_3$CH, p-TsOH.H$_2$O, benzene, rt, 4 h; iv) RuCl$_3$, NaIO$_4$, CH$_3$CN, CCl$_4$, H$_2$O, rt, 4 h.
In addition to carrying out this sequence with the mixture of isomers, the anti-
ketooacetal 181 was also prepared in isomerically pure form, without contamination with
its syn-isomer, by starting from anti-methyl pulegenate 161. The PMR spectrum of
181 showed acetel CH doublet at δ 5.16 (J=2 Hz) and CH₃ doublet at δ 1.14 (J=6
Hz). The spectral data on products in isomerically pure series facilitated the
caracterisation of mixtures and assignment of diastereomeric ratios.

The HWE reaction of a 50:50 mixture of syn/anti-ketoacetal with
triethylphosphonopropionate (R=Me) 178 [11] was attempted under different reaction
conditions [12] which are listed in Table-1.

Table-1

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-BuOK/THF, rt, 20 h</td>
<td>E2 + epi</td>
</tr>
<tr>
<td>NaH/THF, rt, 6 h</td>
<td>epi</td>
</tr>
<tr>
<td>NaH/HMPA/THF, rt, 20 h</td>
<td>E2 + epi</td>
</tr>
<tr>
<td>NaH/THF, -20 °C to 15 °C, 20 h</td>
<td>epi</td>
</tr>
<tr>
<td>LiOH.H₂O/ether, rt, 48 h</td>
<td>E2 + epi</td>
</tr>
<tr>
<td>CsCO₃/t-BuOH, rt, 24 h</td>
<td>epi</td>
</tr>
<tr>
<td>DBU/LiCl/CH₃CN, rt, 10 h</td>
<td>E2 + epi</td>
</tr>
<tr>
<td>HMDS/NaH/THF, 0 °C to rt 6 h</td>
<td>epi</td>
</tr>
</tbody>
</table>

E2= elimination; epi= epimerisation.

The coupling between ketone 177 and phosphonate 178 was extremely sluggish
and unreacted ketone 181 was recovered. Under forcing conditions the only product
isolated was the opened dioxolane as a result of β-elimination, which was evidenced

from the appearance of vinyl hydrogen signal at δ 6-7 in PMR spectrum. None of the reaction conditions gave the required product, α,β-unsaturated ester 182, either with the dioxolane group intact or opened up. Spectral analysis of recovered ketoacetal 181 provided information about the relative rates of C=C bond formation vs epimerisation and elimination.

Scheme-7

Reagents: i) Strong bases: NaH, LiOH·H₂O, DBU/LiCl, Cs₂CO₃; ii) Weak bases: t-BuOK, NaHMDS.
Although the reaction was carried out on a mixture of syn/anti diastereomers, the recovered ketoacetal was exclusively the anti-isomer 181. This suggested that α-epimerisation and β-elimination are faster process than the desired C=C forming HWE reaction. Since, the basic HWE reaction conditions converge the syn/anti mixture 177 to anti-ketoacetal 181, the subsequent studies were carried out with the mixture 177 which was synthetically easier to obtain.

The HWE reaction with triethylphosphonopropionate 178 (R=Me) is sluggish, because it leads to the formation of tetrasubstituted olefin 182. In order to accelerate the Horner reaction, diethylphosphonoacetate 178 (R=H) [13] was used which is devoid of a methyl group.

Thus, HWE reaction of ketoacetal 177 with diethylphosphonoacetate 178 [13] under the conditions listed in Table-2 provided a mixture of unsaturated esters 184,185 along with elimination (E2) 183 and epimerisation (epi) 181 products.

Table-2

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMDS/NaH/THF, -20 °C, 6 h</td>
<td>HWE + epi</td>
</tr>
<tr>
<td>HMDS/NaH/HMPA/THF, 0 °C to rt 20 h</td>
<td>HWE + E2 + epi</td>
</tr>
<tr>
<td>DBU/LiCl/CH₃CN, rt, 10 h</td>
<td>E2 + epi</td>
</tr>
<tr>
<td>NaH/THF, rt, 10 h</td>
<td>HWE + epi</td>
</tr>
<tr>
<td>NaH/THF, rt, 3 days</td>
<td>HWE</td>
</tr>
</tbody>
</table>

HWE = unsaturated ester product 184,185; E2 = elimination 183; epi = epimerisation 181.
After experimenting with a number of bases, solvents and reaction temperatures, the following conditions were found to be optimal: addition of ketone 177 to excess phosphonate anion 178 (5 equi, NaH base) in THF and stirring at ambient temperature for 3 days provided a mixture of unsaturated esters 184 and 185 in 60% yield; no elimination product 183 or unreacted ketone 181 was detected in the crude concentrate (TLC, PMR). The esters 184,185 were obtained reproducibly in 40:60 ratio as concluded from PMR integration of vinyl and acetal CH signals corresponding to the major isomer at δ 5.98, 4.92 and the minor isomer at δ 5.84 and 5.24, respectively. Attempted separation of isomeric esters by column chromatography was unsuccessful. The esters 184,185 were reduced to the corresponding allylic alcohols 186,187 with LiAlH₄ in ether at 0 °C. The ratio of the two isomers was again 40:60 as substantiated from its PMR spectrum. The alcohols 186,187 were separated by column chromatography and the isolated yields of the purified alcohols 186 and 187 further confirmed the 40:60 ratio.

At this stage the nature of isomers, as to whether they are diastereomers at carbon adjacent to acetal group (C7a, syn/anti) or geometrical isomers at the newly formed olefin (C4-C4a, Z/E), or both, was deduced in the following manner. (i) The unreacted β-ketoacetal recovered after incomplete reaction was exclusively the anti-acetal 181 and, hence, it is this diastereomer which participates in the Horner-Wadsworth reaction. (ii) The acetal CH doublet of Z-ester 184 was expected to be downfield compared to that of E-ester 185 because of its proximity to the carbonyl group [14]. (iii) Comparison of vinyl and acetal CH shifts in PMR spectrum of allylic alcohols 186 and 187 with those reported for Z- and E-3-methyl-2-pentene-1,5-diol 188 and 189, respectively, [14,15] facilitated in the assignment of isomers as Z-186 and E-187. (iv) Palladium catalysed hydrogenation of allylic alcohols 186,187 produced a single diastereomer 190 as concluded from PMR and CMR spectra. (v) Treatment of
allylic alcohols 186,187 with BF$_3$·Et$_2$O at -78 °C afforded a mixture of lactol 191 and unreacted $E$-alcohol 187.

**Scheme-8**

Reagents: i) NaH, THF, rt, 3 days; ii) LiAlH$_4$, ether, 0 °C, 1 h.

Based on the above evidence it was concluded that the 40:60 mixture of $Z$- and $E$-unsaturated esters 184,185 and alcohols 186,187, are isomeric at the olefinic group and not at the stereogenic allylic centre.
Attempted deprotection-cum-cyclisation of the mixture of allylic alcohols 186,187 with p-TsOH.H2O, PPTS or 2% HCl did not provide the unsaturated lactone 168. The PMR spectrum showed a complicated pattern which did not reveal any signals arising from aldehyde or lactol 191 protons. The substrate presumably decomposes because of the sensitivity of allylic alcohol portion of molecule to such acidic conditions. Cyclisation of alcohol was successful with BF3.Et2O in CH2Cl2 at -78 °C, but the product was difficult to purify and contaminated with unreacted E-isomer 187. Moreover, the cyclised product was a mixture of lactol 191 (R=H) and cyclic acetal 192 (R=CH2CH2OH) because cleavage of the dioxolane group did not proceed to completion. Therefore, the reaction was not synthetically useful but served a crucial role in identification of Z- and E-allylic alcohols 186,187.

Scheme-9

\[
186 + 187 \xrightarrow{i} 191: R=H \quad 192: R=CH_2CH_2OH
\]

Reagents: i) BF3.Et2O, CH2Cl2, -78 °C, 1 h.
In an attempt to perform the hydrolysis of acetal and cyclisation to lactol in a stepwise manner, the alcohols 186,187 were protected as acetates 193,194 and subjected to acetal hydrolysis. Exposure of hydroxy acetates 193,194 to PPTS and p-TsOH.H₂O in aq. acetone produced only unreacted starting material; no aldehyde 195 signals were observed in δ 9-10 region.

Scheme-10

Reagents: i) Ac₂O, Et₃N, DMAP, CH₂Cl₂, 0 °C, 2 h; ii) H₃O⁺.

At this juncture we decided to continue the synthesis with the saturated hydroxy acetal 190. Hydrogenation of allylic alcohols 186,187 with 10% Pd-C in EtOAc at atmospheric pressure provided hydroxy acetal 190 as a single diastereomer. The compound displayed non overlapping acetal CH and CH₃ doublets at δ 4.76 (J=6 Hz) and 4.06 (J=6 Hz) in PMR spectrum and a 11 line (two dioxolane carbons) CMR spectrum. The facial selectivity in the hydrogenation is a consequence of the interplay of steric (syn to hydrogen) and polar (syn to acetal) effects [16]. A rigorous and complete stereochemical assignment of hydroxy acetal 190 was postponed to after cyclisation to lactone.

Hydroxy acetal 190 was subjected to a variety of deprotection-cum-cyclisation conditions [17] which are listed in Table-3.
Table-3

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% HCl, aq. acetone, rt, 10 h</td>
<td>UP</td>
</tr>
<tr>
<td>2% HCl, aq. acetone, rt, 6 h</td>
<td>UP</td>
</tr>
<tr>
<td>PPTS, aq. acetone, rt, 8 h</td>
<td>SM</td>
</tr>
<tr>
<td>p-TsOH.H₂O, aq. acetone, rt, 10 h</td>
<td>SM</td>
</tr>
<tr>
<td>3% HClO₄, THF, 0 °C to rt, 4 h</td>
<td>UP</td>
</tr>
<tr>
<td>10% (COOH)₂/SG, CH₂Cl₂, rt, 4 h</td>
<td>SM</td>
</tr>
<tr>
<td>15% H₂SO₄/SG, rt, 10 h</td>
<td>UP</td>
</tr>
<tr>
<td>3N HCl, CH₃CO₂H, rt, 5 h</td>
<td>197 + SM</td>
</tr>
<tr>
<td>3N HCl, CH₃CO₂H, rt, 15 h</td>
<td>197 + SM + UP</td>
</tr>
<tr>
<td>BF₃.Et₂O, CH₂Cl₂, -78 °C, 1 h</td>
<td>196</td>
</tr>
</tbody>
</table>

UP = Unidentified Products; SM = Starting Material.

Scheme-11

The PMR spectrum showed either unreacted starting material or unidentified products; once again no cyclisation product was observed. Some faint aldehyde signals were detected but optimisation of AcOH/HCl conditions was not fruitful.
Since efforts towards deprotection-cum-cyclisation were unsuccessful, the hydroxy acetal 190 was oxidised to the ester 198 under Deslongchamp's conditions [18]. Ozonolysis of acetal 190 in EtOAc at -78 °C furnished hydroxy ester 198 in quantitative yield, which was evidenced from the carbonyl band at 1728 cm\(^{-1}\) in IR spectrum. Direct cyclisation of ester 198 to lactone with PPTS, p-TsOH.H\(_2\)O or HCl was unsuccessful. Base hydrolysis of ester 198 with 1N NaOH and then acidification with 1N HCl provided hydroxy acid 199.

**Scheme-12**

Reagents: i) 10\% Pd-C, H\(_2\), EtOAc, atmospheric pressure, 4 h; ii) O\(_3\), EtOAc, -78 °C, 10 min; iii) 1N NaOH, then 1N HCl; iv) PPTS, toluene, reflux.
Lactonisation of hydroxy acid 199 with catalytic amount of PPTS in refluxing toluene afforded lactone, but the PMR spectrum of the product was visibly different from that reported for mitsugashiwalactone 17. Lactone 200 exhibited AB CH₂O multiplet at δ 4.46-4.24 and a CH₃ doublet at δ 1.20. Moreover, the C7a downfield proton which appears in mitsugashiwalactone 17 at δ 2.66-2.45 was moved upfield and appeared as part of the aliphatic multiplet above δ 2.30. The CMR spectrum was also different from that reported for lactone 17. Since lactone 200 did not correlate with natural lactone 17 we reasoned that the ring fusion C4a-C7a in 200 should be trans. We were reasonably certain of the C7-C7a anti relationship from the earlier discussion. The stereochemistry at ring junction C4a-C7a is directly dependent on the facial control during the hydrogenation of exocyclic olefin. It is very likely that due to the affinity of polar acetal group and its electronegative oxygen atoms for the palladium surface, the delivery of hydrogen at C4a occurs cis to the acetal group at C7a and the ring fusion C4a-C7a is consequently trans. Therefore, the Pd catalysed hydrogenation is chelation controlled and occurs from the sterically more congested face to produce trans-fused lactone, 4-epi-mitsugashiwalactone 200.

4.4. SYNTHESIS OF (-)-MITSUGASHI WALACTONE:

The natural lactone 17 will be obtained if the hydrogenation occurs under steric control cis to the allylic hydrogen atom. Hence, the hydrogenation was attempted with different catalysts to obtain a cis-fusion at C4a-C7a.

Conjugate reduction of α,β-unsaturated esters 184,185 with NaBH₄/CuCl [19] system also afforded hydroxy acetal 190 with trans C4a-C7a relationship. The methyl group on the β-carbon at C7 has a stronger bearing on the conjugate hydride reduction
than the acetal group on α-carbon at C7a. Therefore, hydride attack occurs anti to C7 methyl group and produces a trans fusion at C4a-C7a.

Hydrogenation of esters 184,185 with homogeneous Wilkinson catalyst RhCl(PPh3)3 [20] was tried in benzene at atmospheric to elevated pressure (60 psi) and under sonication. No reaction occurred and only starting esters 184,185 were recovered. When allylic alcohols 186,187 were subjected to the same conditions isomerisation occurred and E-isomer was isolated; once again no hydrogenation product was observed.

PtO2 catalysed hydrogenation of esters 184,185 in EtOAc at atmospheric pressure provided a mixture of acetal esters 201,202. The integration of acetal CH doublets at δ 4.76 and 4.82 suggested that the two isomers were produced in the ratio of 10:90. When the hydrogenation was performed at elevated pressure (60 psi) the ratio of 201,202 improved to 30:70. Reduction of acetal esters 201,202 with LiAlH4 furnished acetal alcohols 203,190 and again the ratio of two isomers was 30:70. Comparison of the crude PMR spectrum of acetal alcohols 203,190 with that of palladium reduction product indicated that the minor component of the mixture corresponded to the desired stereoisomer having the cis relationship at C4a-C7a. The acetal CH doublet of the cis isomer 203 appeared at δ 4.84, whereas that of the trans isomer 190 exhibited the doublet slightly upfield at δ 4.76. Attempted chromatographic separation of the isomers 203,190 was extremely difficult.
Scheme-13

184 + 185 $\xrightarrow{i}$  
\[ \text{Z:E=40:60} \]
\[ \begin{align*} \text{201} & \quad \text{201:202}=30:70 \\ \text{202} & \quad \end{align*} \]

$\xrightarrow{ii}$

198 + 190 $\xrightarrow{iii}$  
\[ \text{204:198}=30:70 \quad \text{203:190}=30:70 \]

$\xrightarrow{iv}$

\[ \text{17} \quad \text{17:199}=30:70 \]

Reagents: i) PtO$_2$, EtOAc, 60 Psi, 10 min; ii) LiAlH$_4$, ether, 0 °C, 1 h; iii) O$_3$, EtOAc, -78 °C, 10 min; iv) 1N NaOH, then 1N HCl; v) SGC.
The mixture of acetals 203,190 were oxidised to the corresponding hydroxy esters 204,198 under conditions employed earlier with 198. When the esters 204,198 were subjected to base hydrolysis the cis-isomer 204 cyclised, whereas the trans-hydroxy acid 198 remained unreacted. Thus, refluxing 204,198 in 1N NaOH for 30 min. and then acidification to pH 2 with 1N HCl and stirring for 1 h at rt furnished an easily separable mixture of cis-lactone 17 and unreacted trans-hydroxy acid 198. The ready cyclisation of cis-hydroxy acid 204 to mitsugashialactone 17 is in agreement with final stages of Takacs and Myoung synthesis [1].

The crude material accumulated from few batches was combined and purified by SGC to afford mitsugashialactone 17, whose PMR and CMR spectra were identical to the reported data. The AB CH$_2$O pattern (ddd) of lactone 17 appeared at $\delta$ 4.28 and 4.15 and downfield CHCO$_2$ multiplet at $\delta$ 2.66-2.45 in PMR spectrum. The lactone exhibited the expected 9 line CMR spectrum and gave a satisfactory HRMS analysis.

**Scheme-14**

![Scheme-14](image)

**Reagents:** i) $O_3$, CH$_2$Cl$_2$, -78 °C, PPh$_3$; ii) 2% HCl; iii) PCC, CH$_2$Cl$_2$. 
The optical rotation of mitsugashiwalactone 17 obtained from natural sources is not reported in published literature because the value is very low. The recorded optical rotation of \([\alpha]_D^{25} -3.0^\circ\) (CHCl₃, c 0.5) is far superior to the value \([\alpha]_D^{25} -1.9^\circ\) (CHCl₃, c 1.25) reported by Takacs and Myoung [1], who used (-)-citronellene 52 as the starting chiron. Thus, the synthesis of (-)-mitsugashiwalactone 17 was accomplished from R-(+)-pulegone in higher enantiomeric purity than so far reported in the literature.

4.5. EXPERIMENTAL AND SPECTRA:

anti-Pulegenic acid 92:

Ethyl pulegenate 158 (392 mg, 2.0 mmol); KOH (224 mg, 4.0 mmol)

Yield: 238 mg, 71%

IR: cm⁻¹ 3250, 2600, 1690, 1410, 1370, 1290, 1210, 940, 700.

PMR: δ 2.98 (d, J=6 Hz, 1H, CHCO₂H); 2.42-2.26 (m, 3H); 2.08-1.90 (m, 1H); 1.68 (s, 3H, vinyl CH₃); 1.64 (s, 3H, vinyl CH₃); 1.36-1.20 (m, 1H); 1.08 (d, J=6 Hz, 3H, CH₃).

CMR: δ 182.18, 138.76, 126.65, 55.48, 40.73, 33.65, 30.25, 21.47, 21.14, 19.73.

anti-Pulegenic ester 171:

To pulegenic acid 92 (84 mg, 0.5 mmol) in 5 mL of acetone was added K₂CO₃ (138 mg, 1.0 mmol) and stirred for 30 min at rt. Methallyl chloride 170 (100 µL, 90 mg, 1.0 mmol) was added followed by the addition of NaI (150 mg, 1.0 mmol) and stirred for 12 h. The reaction mixture was quenched with 12 mL of H₂O and extracted with ether (3x10 mL). Brine wash and work-up afforded 126 mg of ester which was purified by SGC (hexane to 5% EtOAc/hexane).

Yield: 93 mg, 84%
IR: cm\(^{-1}\) 2900, 1720, 1640, 1440, 1370, 1290, 1220, 1120, 1000, 9000.

PMR: \(\delta\) 4.98 (s, 1H, vinyl H); 4.90 (s, 1H, vinyl H); 4.49 (s, 2H, CO\(_2\)CH\(_2\)); 3.00 (d, \(J=6\) Hz, 1H, CHCO\(_2\)); 2.42-2.12 (m, 3H); 2.08-1.90 (m, 1H); 1.74 (s, 3H, vinyl CH\(_3\)); 1.64 (s, 3H, vinyl CH\(_3\)); 1.60 (s, 3H, vinyl CH\(_3\)); 1.38-1.18 (m, 1H); 1.08 (d, \(J=6\) Hz, 3H, CH\(_3\)).

CMR: \(\delta\) 173.56, 140.18, 134.24, 125.87, 112.82, 67.49, 55.69, 40.59, 33.65, 30.28, 21.21, 20.99, 19.75, 19.43.

**Triketone 169:**

Alkene ester 171 (22 mg, 0.1 mmol); DMS (73 \(\mu\)L, 62 mg, 1.0 mmol).

**Yield:** 10 mg, 53% (keto 169 and enol 172)

IR: cm\(^{-1}\) 3450, 2850, 1720, 1410, 1370, 1270, 1170, 1040, 730.

PMR: (for enol 172) \(\delta\) 4.72 (s, 2H, CO\(_2\)CH\(_2\)CO); 2.74-2.58 (m, 1H, allyl CH); 2.48-2.22 (m, 2H, allyl CH\(_2\)); 2.14 (s, 3H, COCH\(_3\)); 1.62-1.40 (m, 1H); 1.24 (d, \(J=6\) Hz, 3H, CH\(_3\)).

**tert-Alcohol 174:**

Selenium dioxide (22 mg, 0.2 mmol) in 1 mL of moist dioxane (5\% H\(_2\)O) was added to a solution of methyl pulegenate 161 (36 mg, 0.2 mmol) in 1 mL of dioxane. The reaction mixture was refluxed for 2 h. Cooled to rt and filtered through celite. Work-up afforded 23 mg of alcohol 174 along with some amount of unreacted starting material 161.

**Yield:** 13 mg, 34%

IR: cm\(^{-1}\) 3400, 2850, 1710, 1430, 1180, 1110, 820.

PMR: \(\delta\) 5.72 to 5.68 (m, 1H, vinyl H); 3.70 (s, 3H, CO\(_2\)CH\(_3\)); 3.20-3.14 (m, 1H, CHCO\(_2\)); 2.74-2.32 (m, 2H, allyl CH\(_2\)); 1.98-1.84 (m, 1H); 1.64-1.56 (m, 1H); 1.42 (s, 3H, CH\(_3\)C-O); 1.26 (s, 3H, CH\(_3\)C-O); 1.06 (d, \(J=6\) Hz, 3H, CH\(_3\)).
**syn/anti-Alcohols 159,160:**

Ethyl pulegenate 158 (462 mg, 3 mmol); LiAlH₄ (152 mg, 4 mmol).

Yield: 370 mg, 82%

[α]D<sup>25</sup>: +14.4° (CHCl₃, c 2.5)

IR: cm⁻¹ 3356, 2924, 1452, 1373, 1057, 1024, 890.

PMR: δ 3.70 (dd, J = 12, 8 Hz, 1H, OCH<sub>2</sub>); 3.52-3.38 (m, 1H, OCH<sub>2</sub>); 2.75 (q, J = 6 Hz) and 2.46-2.36 (m) (1H, CHCH<sub>2</sub>O); 2.32-2.04 (m, 3H, allyl CH<sub>2</sub> and OH); 2.00-1.78 (m, 1H); 1.74 and 1.70 (s, 3H, vinyl CH₃); 1.73 and 1.63 (s, 3H, vinyl CH₃); 1.54-1.18 (m, 2H); 1.08 and 0.96 (d, J = 6 Hz, 3H, CH₃).

CMR: δ 136.79, 135.34, 124.72, 64.19, 61.72, 52.72, 48.04, 37.55, 36.03, 32.04, 31.43, 29.32, 28.67, 21.49, 21.37, 21.02, 20.93, 20.48, 15.36.

Analysis: Calculated for C₁₀H₁₈O: C = 77.87%, H = 11.76%; Found: C = 77.92%, H = 11.80%.

**syn/anti-Aldehydes 179:**

**syn/anti-Alcohols 159,160** (308 mg, 2.0 mmol); PCC (645 mg, 3.0 mmol).

Yield: 232 mg, 76%

[α]D<sup>25</sup>: +109.6° (CHCl₃, c 2.5)

IR: cm⁻¹ 2955, 1726, 1633, 1456, 1373, 1145, 815.

PMR: δ 9.34 (d, J = 6 Hz) and 9.22 (d, J = 4 Hz) (1H, CHO); 3.22 (t) and 2.84 (br s) (1H, CHCHO); 2.60-2.08 (m, 3H); 2.02-1.70 (m, 1H); 1.64 (s, 3H, vinyl CH₃); 1.54 (s, 3H, vinyl CH₃); 1.40-1.18 (m, 1H); 1.06 and 0.98 (d, J = 6 Hz, 3H, CH₃).

CMR: δ 199.74, 191.72, 131.30, 131.07, 128.95, 127.79, 63.10, 60.00, 39.78, 38.70, 36.09, 35.15, 33.51, 33.43, 24.43, 24.31, 20.27, 20.24, 18.63, 15.53.

**anti-179**: δ 9.22 (d, J = 4 Hz, 1H, CHO); 0.98 (d, J = 6 Hz, 3H, CH₃).
syn/anti-Acetals 180:

Aldehydes 179 (228 mg, 1.5 mmol), ethanediol (0.9 mL, 930 mg, 15.0 mmol), triethyl orthoformate (0.5 mL, 444 mg, 3.0 mmol) containing catalytic amount of p-TsOH.H2O (2.8 mg, 0.15 mmol) in 2 mL of dry benzene were stirred for 3h at rt. The reaction mixture was diluted with ether and washed with NaHCO3 solution and brine. Work-up afforded 368 mg of acetal 180 which was purified by SGC (hexane to 5% EtOAc/hexane).

Yield: 275 mg, 87%

\([\alpha]_D^{25}: +11.6^\circ (\text{CHCl}_3, c 2.5)\)

IR: cm\(^{-1}\) 2900, 1460, 1280, 1120, 1040, 960.

PMR: \(\delta\) 4.94 and 4.86 (d, J=6 Hz, 1H, acetal H); 4.02-3.66 (m, 4H, \((\text{OCH}_2)\)_2); 2.78 (t) and 2.52 (br s) (1H, allyl CH); 2.46-2.08 (m, 3H); 2.02-1.82 (m, 1H); 1.65 (t, 6H, 2xCH\(_3\)); 1.32-1.16 (m, 1H); 1.12 and 0.96 (d, J=6 Hz, 3H, CH\(_3\)).

CMR: \(\delta\) 139.93, 137.72, 125.27, 124.97, 105.87, 105.23, 65.03, 64.92, 64.68, 64.57, 52.91, 48.62, 37.79, 34.27, 32.63, 32.46, 29.76, 29.47, 22.32, 21.61, 21.21, 16.05.

anti-180: \(\delta\) 4.86 (d, J=6 Hz, 1H, acetal H); 0.96 (d, J=6 Hz, 3H, CH\(_3\)).

syn/anti-Ketoacetals 177:

To a solution of alkeneacetals 180 (212 mg, 1.0 mmol) in 1.5 mL of CCl\(_4\), 1.5 mL of CH\(_3\)CN and 2.5 mL of H\(_2\)O was added NaIO\(_4\) (535 mg, 2.5 mmol) and catalytic amount of RuCl\(_3\) (5 mg). The reaction mixture was stirred at rt for 4 h and diluted with 10 mL of CH\(_2\)Cl\(_2\). Washed rapidly with H\(_2\)O (2x5 mL) and then brine. Work-up afforded 372 mg of ketoacetals 177 which was purified by SGC (hexane to 20% EtOAc/hexane).

Yield: 101 mg, 54%

\([\alpha]_D^{25}: +57.2^\circ (\text{CHCl}_3, c 2.5)\)
IR: cm⁻¹ 2900, 1720, 1440, 1360, 1200, 1110, 1050, 950, 810
PMR: δ 5.16 (d, J=2 Hz) and 5.00 (d, J=4 Hz) (1H, acetal H); 4.02-3.72 (m, 4H, (OCH₂)₂); 2.66-1.74 (m, 5H); 1.52-1.32 (m, 1H); 1.14 and 1.10 (d, J=6 Hz, 3H, CH₃).
CMR: δ 217.40, 217.10, 103.29, 102.36, 65.24 (x2); 64.98, 64.41, 58.33, 55.75, 39.01, 36.66, 34.18, 33.20, 31.91, 29.63, 20.75, 15.45.

anti-177=181: δ 5.16 (d, J=2 Hz, 1H, acetal H); 1.14 (d, J=6 Hz, 3H, CH₃).

Z/E-Esters 184,185:

A 50% dispersion of NaH in mineral oil (38 mg, 0.8 mmol) was washed with dry hexane to remove the oil and 1 mL of dry THF was added. To this triethyl phosphonoacetate 178 (R=H) (224 mg, 1.0 mmol) in 1 mL of dry THF was added slowly dropwise at rt and stirred for 30 min. Then ketone 177 (36 mg, 0.2 mmol) in 1 mL of dry THF was added and again stirred for 3 days at ambient temperature. Quenched with 5 mL of H₂O and extracted with CHCl₃ (3x10 mL). The organic layer was washed with brine and usual work-up afforded 125 mg of esters 184,185 which was purified by SGC (hexane to 20% EtOAc/hexane).

Yield: 30 mg, 60%

[α]D²⁵: +21.2° (CHCl₃, c 2.5)
IR: cm⁻¹ 2900, 1710, 1440,1370, 1270, 1120, 1060, 1030, 980, 740.
PMR: δ 5.98 and 5.84 (m, 1H, vinyl H); 5.24 (d, J=2 Hz) and 4.92 (d, J=4 Hz) (1H, acetal H); 4.12 (q, J=6 Hz, 2H, OCH₂); 4.02-3.78 (m, 4H, (OCH₂)₂); 3.20-3.02 (m, 1H); 2.68-2.26 (m, 3H); 2.16-1.90 (m, 2H); 1.28 and 1.22 (d, J=6 Hz, 3H, CH₃); 1.06 (t, J=6 Hz, 3H, CH₂CH₃).
CMR: δ 166.72, 166.25, 114.52, 113.56, 105.58, 104.61, 65.14, 64.99 (x2); 64.92, 59.57, 59.50, 56.27, 52.57, 36.05, 34.82, 33.49, 33.22, 32.38, 32.28, 29.65, 21.64, 20.16, 14.31.
Z/E-Alcohols 186,187:

Unsaturated esters 29,30 (48 mg, 0.2 mmol); LiAlH₄ (15 mg, 0.4 mmol).

Yield: 34 mg, 87%

$[\alpha]_{D}^{25}$: +6.0° (CHCl₃, c 1.0)

IR: cm⁻¹ 3398, 2953, 2872, 1456, 1394, 1145, 1037.

Z-Alcohol 186:

$[\alpha]_{D}^{25}$: -31.0° (CHCl₃, c 1.0)

PMR: δ 5.78 (t, J=6 Hz, 1H, vinyl H); 4.72 (d, J=6 Hz, 1H, acetal H); 4.16-3.78 (m, 7H, 3xOCH₂ and OH); 2.52 (t, J=6 Hz, 1H, allyl H); 2.44-2.14 (m, 2H, allyl CH₂); 2.02-1.82 (m, 1H); 1.42-1.12 (m, 2H); 1.02 (d, J=6 Hz, 3H, CH₃).

CMR: δ 145.82, 123.89, 105.33, 64.88, 64.73, 59.91, 51.42, 35.82, 33.75, 32.27, 21.07.

E-Alcohol 187:

$[\alpha]_{D}^{25}$: +41.0° (CHCl₃, c 1.0)

PMR: δ 5.62 (br s, 1H, vinyl H); 4.92 (d, J=4 Hz, 1H, acetal H); 4.16 (d, J=6 Hz, 2H, OCH₂); 4.04-3.82 (m, 4H, (OCH₂)₂); 2.56-1.82 (m, 6H); 1.44-1.18 (m, 1H); 1.06 (d, J=6 Hz, 3H, CH₃).

CMR: δ 145.56, 122.51, 106.49, 64.90 (x2); 60.66, 54.29, 34.89, 33.61, 28.82, 20.50.

syn/anti-Acetal acetates 193,194:

Pyridine (160 μL, 158 mg, 2.0 mmol), Ac₂O (100 μL, 102 mg, 1.0 mmol) and DMAP (5 mg, 0.04 mmol) were added to alcohol 186, 187 (20 mg, 0.1 mmol) at 0 °C. The reaction mixture was stirred for 4 h and diluted with ether. Organic layer washed
with aq. CuSO₄ solution, saturated NaHCO₃ solution and brine. Work-up afforded 29 mg of acetate 193,194 which was purified by SGC (hexane to 20% EtOAc/hexane).

Yield: 22 mg, 91%

IR: cm⁻¹ 2926, 2856, 1730, 1377, 1116, 1062.

PMR: δ 5.70-5.46 (m, 1H, vinyl H); 4.90 and 4.82 (d, J=6 Hz, 1H, acetal H); 4.74-4.50 (m, 2H, CH₂OC(O)); 4.00-3.76 (m, 4H, (OCH₂)₂); 2.60-2.42 (m, 1H, allyl CH); 2.40-2.22 (m, 2H, allyl CH₂); 2.06 (s, 3H, COCH₃); 2.00-1.80 (m, 1H); 1.42-1.18 (m, 2H); 1.04 (overlapping d, J=6 Hz, 3H, CH₃).

trans-Hydroxyacetal 190:

Allylic alcohol 186, 187 (40 mg, 0.2 mmol); Pd/C (20 mg).

Yield: 30 mg, 75%

[α]D²⁵: -13.6° (CHCl₃, c 2.5)

IR: cm⁻¹ 3422, 2950, 2870, 1460, 1400, 1110, 1050, 950, 875.

PMR: δ 4.76 (d, J=6 Hz, 1H, acetal H); 4.06-3.82 (m, 4H, (OCH₂)₂); 3.74-3.60 (m, 2H, OCH₂); 2.64-2.40 (br s, 1H, OH); 2.14-1.92 (m, 2H); 1.84-1.56 (m, 3H); 1.52-1.14 (m, 3H); 1.06 (d, J=6 Hz, 3H, CH₃); 1.14-0.86 (m, 1H).

CMR: δ 107.20, 65.01, 64.66, 61.15, 54.54, 39.59, 37.40, 36.82, 34.02, 32.51, 20.86.

Analysis: Calculated for C₁₁H₂₀O₃: C=65.97%, H=10.07%; Found C=65.98%, H=9.97%.

trans-Hydroxyester 198:

Hydroxyacetal 190 (10 mg, 0.05 mmol) was dissolved in 1 mL of EtOAc and cooled to -78 °C and ozonised until the blue colour persisted. Excess ozone was removed by flushing with oxygen. The mixture was washed with brine. Work-up gave hydroxyester 198 which was pure enough to carry out the next reaction.
Yield: 11 mg, ~99% (crude)

$[\alpha]D^{25}$: -13.2° (CHCl$_3$, c 2.5)

IR: cm$^{-1}$ 3420, 2953, 2872, 1728, 1456, 1381, 1263, 1159, 1080, 887, 736.

PMR: $\delta$ 4.42-4.12 (m, 2H, OCH$_2$); 3.80 (t, $J=6$ Hz, 2H, CO$_2$CH$_2$); 3.76-3.54 (m 2H, OCH$_2$); 3.60-3.40 (br s, 2H, 2xOH); 2.50-2.14 (m, 2H); 2.02-1.76 (m, 2H); 1.72-1.60 (m, 1H); 1.46-1.14 (m, 3H); 1.10-0.84 (m, 1H); 0.98 (d, $J=6$ Hz, 3H, CH$_3$).

CMR: $\delta$ 176.48, 65.84, 61.03 (x2); 58.59, 40.82, 39.79, 38.71, 33.33, 31.55, 19.71.

**trans-Hydroxyacid 199:**

Hydroxyester 198 (10.8 mg, 0.05 mmol) and 1N NaOH (1 mL) were refluxed for 30 min and cooled to rt. The reaction mixture was extracted with ether to remove the neutral products. Aqueous layer was acidified with 1N HCl (>1 mL) and saturated with NaCl. Extracted with EtOAc (3x10 mL) and washed with brine. Work-up afforded hydroxyacid 199 which was subjected for cyclisation without any purification.

Yield: 8.5 mg, 98% (crude)

$[\alpha]D^{25}$: -12.0° (CHCl$_3$, c 1.0)

IR: cm$^{-1}$ 3300, 2953, 1707, 1381, 1100, 950, 845.

PMR: $\delta$ 7.24-6.70 (br s, 2H, CO$_2$H and OH); 3.68 (t, $J=6$ Hz, 2H, OCH$_2$); 2.76-2.18 (m, 3H); 2.06-1.86 (m, 2H); 1.75-1.62 (m, 1H); 1.48-1.16 (m, 3H); 1.10 (d, $J=6$ Hz, 3H, CH$_3$).


**(-)-4-epi-Mitsugashiwalamacote 200:**

Hydroxyacid 199 (8.6 mg, 0.05 mmol) was dissolved in 20 mL of dry toluene and catalytic amount (~2 mg) of PPTS was added. The solution was heated at 120 °C with slow removal of toluene by short-path distillation. The residue was dissolved in...
10 mL of EtOAc and washed with NaHCO₃ solution and with brine. Usual work-up afforded 6 mg of lactone which was purified by SGC (hexane to 20% EtOAc/hexane).

Yield: 4.3 mg, 56%

[α]D₂₅: -39.0° (CHCl₃, c 0.5)

IR: cm⁻¹ 2955, 2870, 1745, 1462, 1398, 1260, 1165, 1138, 1097, 1057, 941.

PMR: δ 4.46-4.24 (m, 2H, OCH₂); 2.30-2.08 (m, 2H); 2.06-1.86 (m, 2H); 1.82-1.60 (m, 2H); 1.46-1.32 (m, 2H); 1.26-1.12 (m, 1H); 1.20 (d, J=6 Hz, 3H, CH₃). 


Analysis: Calculated for C₉H₁₄O₂: C=70.10%, H=9.15%; Found: C=70.21%, H=9.19%. 

LRMS: 155 (M+1).

cis/trans-Acetalesters 201,202:

Unsaturated ester 186, 187 (12 mg, 0.05 mmol); PtO₂ (5 mg); EtOAc (1 mL); 60 psi; 15 min.

Yield: 11 mg, 90%

[α]D₂₅: +23.0° (CHCl₃, c 1.0)

IR: cm⁻¹ 2953, 1736, 1462, 1375, 1260, 1160, 1120, 1033, 975, 670.

PMR: δ 4.82 and 4.76 (d, J=4 Hz, 1H, acetal H); 4.18-4.06 (m, 2H, CO₂CH₂); 4.00-3.74 (m, 4H, (OCH₂)₂); 2.72-2.52 (m, 2H, CH₂CO₂); 2.44-2.10 (m, 2H); 2.00-1.68 (m, 3H); 1.50-1.36 (m, 1H); 1.28-1.18 (m, 3H, CH₂CH₃); 1.06 and 1.04 (d, J=6 Hz, 3H, CH₃); 1.00-0.86 (m, 1H).

CMR: δ 173.48, 173.12, 106.55, 105.46, 65.24, 64.97 (x2); 64.41, 59.94, 58.36, 55.45, 51.05, 40.81, 38.98, 37.73, 36.16, 35.94, 34.33, 33.70, 33.53, 31.85, 31.27, 29.65, 21.77, 20.94, 20.74.
**cis/trans-Hydroxyacetals 203,190:**

Acetalester **201,202** (25 mg, 0.1 mmol); LiAlH₄ (6 mg, 0.15 mmol).

Yield: 16 mg, 80%

[α]D²⁵ : -20.0° (CHCl₃, c 1.0)

PMR: δ 4.84 (d, J=6 Hz, acetal H).

**cis/trans-Hydroxyesters 204,198:**

Hydroxyacetal **203,190** (10 mg, 0.05 mmol); EtOAc (1 mL); O₃, -78 °C.

Yield: 11 mg, ~99% (crude)

[α]D²⁵ : -21.0° (CHCl₃, c 1.0).

**(-)-Mitsugashiwalactone 17:**

1N NaOH (2 mL) was added to hydroxyester **204,198** (21.6 mg, 0.1 mmol) and refluxed for 30 min. Cooled to rt and extracted with ether to remove the neutral products. Aqueous layer was acidified to pH 2 with 1N HCl (5 mL) and stirred for 1 h at rt. Extracted with EtOAc (3x10 mL) and washed with brine. Work-up afforded a mixture of trans-hydroxyacid **199** and cis-lactone **17** (14 mg) which were seperated by SGC (hexane to 20% EtOAc/hexane, then EtOAc).

Yield: 3 mg, 74%

[α]D²⁵ : -3.0° (CHCl₃, c 0.5)

IR: cm⁻¹ 2924, 2852, 1734, 1462, 1392, 1257, 1178, 1074.

PMR: δ 4.28 (ddd, J=12,6,2 Hz, 1H, OCH₂); 4.15 (ddd, J=12,6,2 Hz, 1H, OCH₂); 2.66-2.45 (m, 1H, CHCO₂); 2.34 (t, J=12 Hz, 1H); 2.30-2.16 (m, 1H); 2.08-1.84 (m, 2H); 1.72-1.44 (m, 2H); 1.32-1.15 (m, 2H); 1.16 (d, J=6 Hz, 3H, CH₃).


HRMS: Calculated for C₉H₁₄O₂: 154.0994; Found 154.0994.
200 MHz PMR spectrum of *anti-180*
200 MHz PMR spectrum of syn/anti-180
200 MHz PMR spectrum of 181
200 MHz PMR spectrum of 177
200 MHz PMR spectrum of 184,185
50 MHz CMR spectrum of 184,185
200 MHz PMR spectrum of 186
50 MHz CMR spectrum of 186
200 MHz PMR spectrum of 187
50 MHz CMR spectrum of 187
200 MHz PMR spectrum of 190
50 MHz CMR spectrum of 190
200 MHz PMR spectrum of 198
200 MHz PMR spectrum of 199
200 MHz PMR spectrum of 200
50 MHz CMR spectrum of 200
2D H-H COSY spectrum of 200
200 MHz PMR spectrum of 201,202
200 MHz PMR spectrum of 17
50 MHz CMR spectrum of 17
4.6. REFERENCES AND NOTES:


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