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Studies on Horner-Wadsworth-Emmons Reaction in Base Sensitive Ketones: Synthesis of (-)-Mitsugashiwalactone and Formal Synthesis of (+)-Iridomyrmecin, (-)-Isoiridomyrmecin and (+)-Teucriumlactone

A. Nangia* and G. Prasuna

School of Chemistry, University of Hyderabad
Central University PO, Hyderabad 500 046, India

Abstract: *The effect of different bases in promoting Horner-Wadsworth-Emmons (HWE) reaction on enolisable cyclopentanones is investigated. NaH is found to be suitable for the intermolecular reaction and DBU/LiCl is optimal for the intramolecular variation. The HWE approach is employed for the enantioselective synthesis of iridoid cyclopentapyranones of type-I (**4,16,52**) and type-II (**5,36**).*

INTRODUCTION

The iridoids are a large class of naturally occurring compounds with over 300 members in the family. They are characterised by a cyclopentane ring *cis*-fused to a dihydropyran, δ-lactol, or δ-lactone.[1] The category of naturally occurring iridoid monoterpenoids which have a cyclopentane ring fused to a δ-lactone is important because of the diverse and interesting physiological and biological activity exhibited by these compounds.[2] They are commonly referred to as cyclopentapyranones and can be further sub-divided into two groups (type-I and II) depending on the regiochemical orientation of the *cis*-annulated lactone ring with respect to the substituted cyclopentane ring. Some prominent examples belonging to type-I are iridomyrmecin **1**, isoiridomyrmecin **2**, teucriumlactone **3**, boschnialactone **4**;[3] and those belonging to type-II are mitsugashiwalactone **5**, onikulactone **6**, dihydronepetalactone **7**, isodihydronepetalactone **8**[4] (Figure 1). Both categories of iridoid lactones have attracted the attention of synthetic chemists over the last three decades. The focal point of various approaches to these

cyclopentapyranones has been the installation of contiguous stereogenic centres on the oxabicyclo[4.3.0]nonane skeleton.

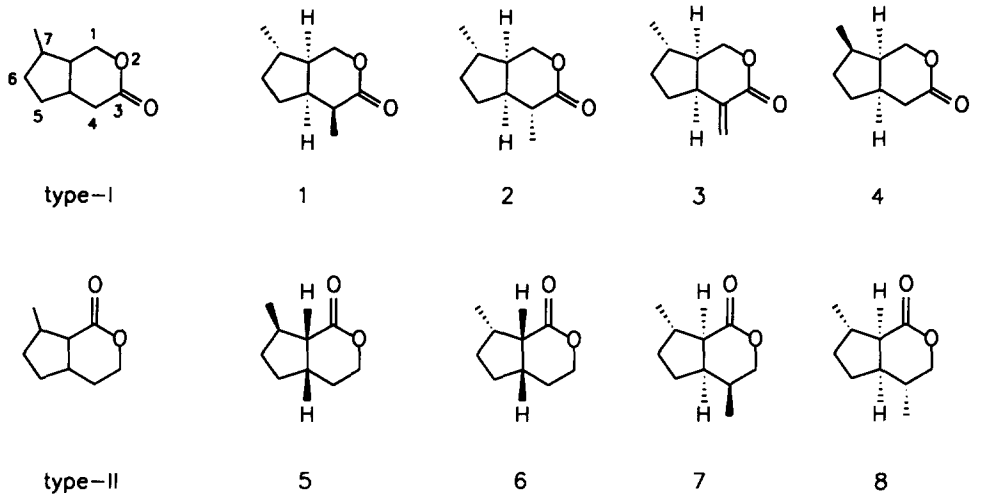
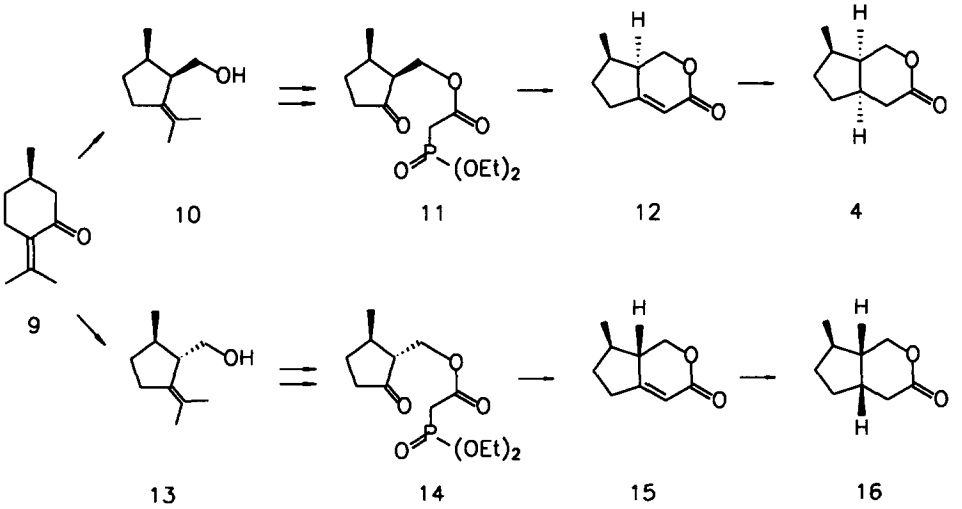


Figure 1: Structures of some prominent iridoid lactones.



Scheme 1: Synthesis of type-I lactones (ref. 5b).

We have employed the intramolecular Horner-Wadsworth-Emmons (IMHWE) reaction as the crucial step to annulate the δ-lactone on to the cyclopentane ring.[5] Using this approach, an enantioselective synthesis of cyclopentapyranones **4** and **16** was carried from the same chiral precursor as

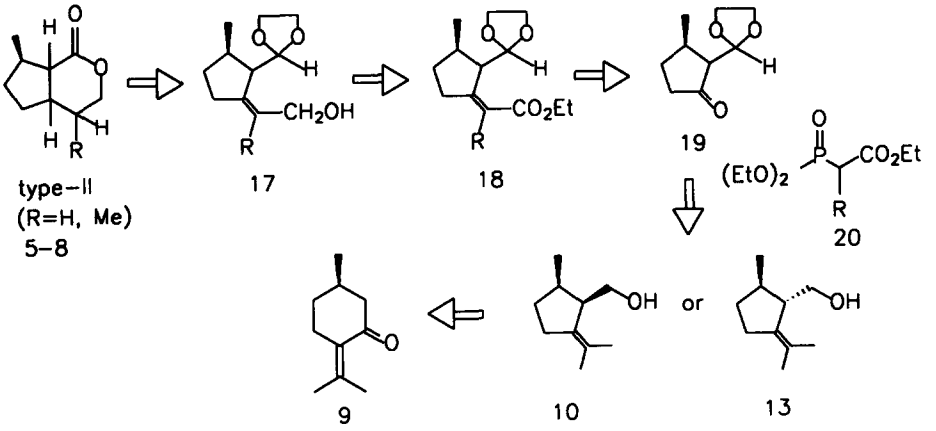
summarised in Scheme 1. Thus, *R*-pulegone **9** was converted to either *syn*- or *anti*-hydroxymethyl cyclopentane **10** or **13** in a few steps. Esterification of resultant β-hydroxyketone with diethylphosphonoacetic acid under neutral conditions of DCC coupling provided phosphonate (**11,14**), which was prone to β-elimination under basic conditions. Employing the original conditions of Blanchette *et al*,[6] optimised subsequently for intramolecular Horner reaction, we obtained the requisite α ,β-unsaturated δ-lactone (**12,15**). Highly stereoselective *exo*-face hydrogenation completed the enantioselective synthesis of target lactones **4** and **16**. Thus, *syn*-alcohol **10** afforded boschnialactone **4**, and *anti*-alcohol **13** provided cyclopentapyranone **16**. The nine carbon lactone **16** is the common penultimate intermediate for the synthesis of target iridoids iridomyrmecin, isoiridomyrmecin and teucriumlactone.

There are three factors which will expand the utility of HWE approach towards the iridoid class of natural products: (i) Cyclopentapyranones **4** and **16** belong to type-I category of natural products. A similar synthetic protocol which will produce lactones of structural type-II (**5-8**) should be desirable. This is because most published reports deal with type-I lactones, and even among those that target type-II lactones only one produces the chiral, non-racemic product.[4f] (ii) The mild and non-epimerising basic conditions used for performing the crucial HWE reaction must be explored in greater detail and on related substrates to establish their generality. Is it possible to decide the best reaction conditions based on substrate structure, phosphonate used, and whether it is intra- or intermolecular HWE condensation? (iii) A minor issue is that lactone **16** derived from *R*-pulegone bears the unnatural *R*-configuration at C7 of iridoids **1-3**. To complete the formal synthesis of natural iridoids, the efficiency of this sequence must be demonstrated with *S*-pulegone as the chiral source. We report in this paper our results with investigations on the HWE protocol to bicyclic δ-lactones and the successful synthesis of naturally occurring iridoid lactones.

RESULTS AND DISCUSSION

Synthesis of (-)-Mitsugashiwalactone (5)

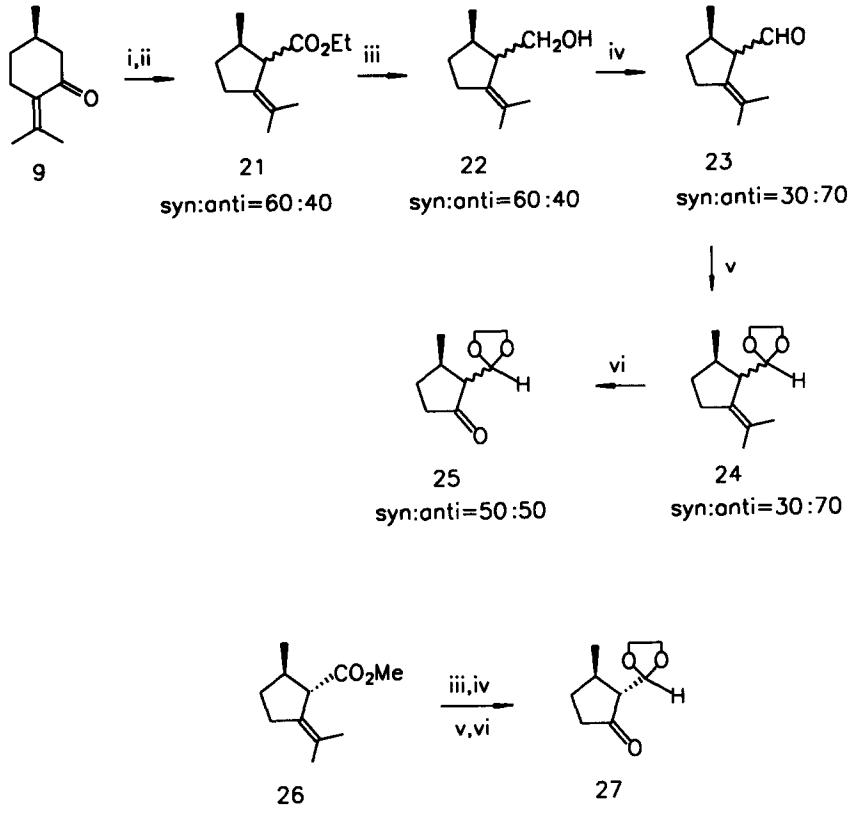
We embarked on the project with the dual objective of finding mild conditions to carry out the Horner-Wadsworth reaction in base sensitive systems, and also to investigate an enantioselective route to type-II lactones **5-8**. From our earlier work on type-I lactones, we were familiar with problems associated with performing intra- and intermolecular HWE reaction on chiral ketophosphonates which are prone to competing α-epimerisation and β-elimination during the carbon-carbon bond forming step.[5] A retroanalysis which was expected to provide all the four lactones in optically enriched form is delineated in Scheme 2. The carbonyl group of lactone is now at C1 instead of C3 and, therefore, an acetal group appeared to be its logical precursor. The allylic alcohol **17** should arise from the corresponding α,β-unsaturated ester **18**, which is the product of a HWE coupling between ketoacetal **19** and phosphonate **20**. Depending on the choice of phosphonate reagent **20** (R=H or Me), lactones **5,6** or **7,8** will be the final products. The easy availability of epimeric ketoacetals **19** from *R*-pulegone was encouraging. The problem of possible epimerisation and elimination during HWE reaction on β-ketoacetal **19** was of concern, but appeared to be surmountable.



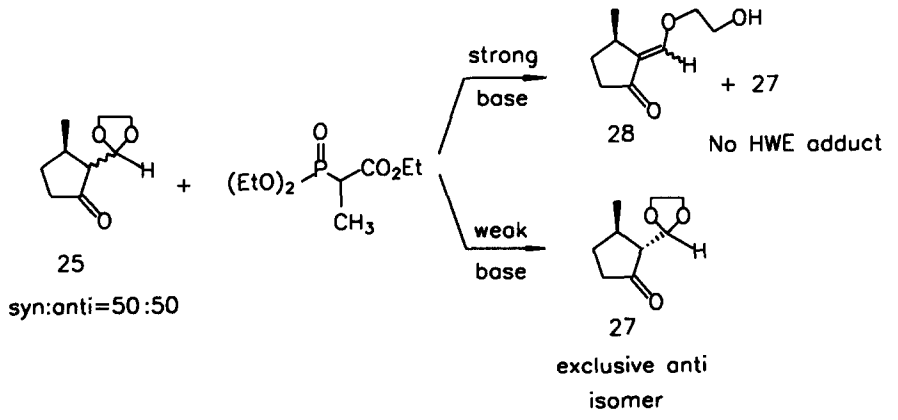
Scheme 2: Retroanalysis of type-II lactones.

In the event, *R*-pulegone **9** (Aldrich, $[\alpha]_D^{25}$ +22°) was converted to a 60:40 mixture of *syn*- and *anti*-ethyl pulegenates **21** when the Favorskii rearrangement was carried out in refluxing EtOH[7] (Scheme 3). The *syn/anti* ratio was unambiguously confirmed by integration of C*H*CO_2Et doublet at δ 3.37 and 2.92, and GC analysis. The mixture of ethyl pulegenates **21** was reduced with LAH to alcohols **22** which were subsequently oxidised to aldehyde **23** with PCC. Acetalisation of the aldehyde ($(CH_2OH)_2$, *p*-TsOH, $HC(OEt)_3$) produced a 30:70 ratio of *syn* and *anti* diastereomers **24** as concluded from integration of acetal C*H* doublets at δ 4.94 and 4.86. Ozonolysis of the exocyclic alkene even under buffered conditions ($NaHCO_3$) at -78°C caused some acetal cleavage. The desired ketoacetal was obtained cleanly as a ~50:50 mixture in 55% yield by oxidation with $RuCl_3/NaIO_4$ system. Additionally, the *anti*-substituted cyclopentanone **27** was prepared in isomerically pure form (δ 5.16, acetal C*H*) uncontaminated with its *syn* isomer by starting from *anti*-methyl pulegenate **26**[8] (Scheme 3). The spectral data on products in the isomerically pure series facilitated the characterisation of mixtures and assignment of diastereomeric ratios. The β-ketoacetal was somewhat unstable and used immediately without extensive purification.

With both *anti*-**27** and a 50:50 mixture of *syn/anti*-**25** in hand, the Horner-Wadsworth reaction with phosphonate **20** (R=Me) was attempted next. The coupling between ketone and phosphonate was extremely sluggish and unreacted ketone was recovered under a variety of conditions.[6,9] Under forcing conditions the only reaction product isolated was the opened dioxolane as a result of β-elimination (δ 6-7, vinyl C*H*); no unsaturated ester product was formed, either with the dioxolane group intact or opened up. It is noteworthy that the recovered ketoacetal was exclusively the *anti* isomer **27** although the reaction was carried out on a mixture of *syn/anti* diastereomers **25** (Scheme 4). This suggested that α-epimerisation and β-elimination are faster processes than the desired C=C bond forming HWE reaction and, therefore, subsequent studies were carried out with the mixture which was synthetically easier to obtain. In any case, the basic Horner conditions converge the mixture **25** to the desired *anti*-acetal **27**.

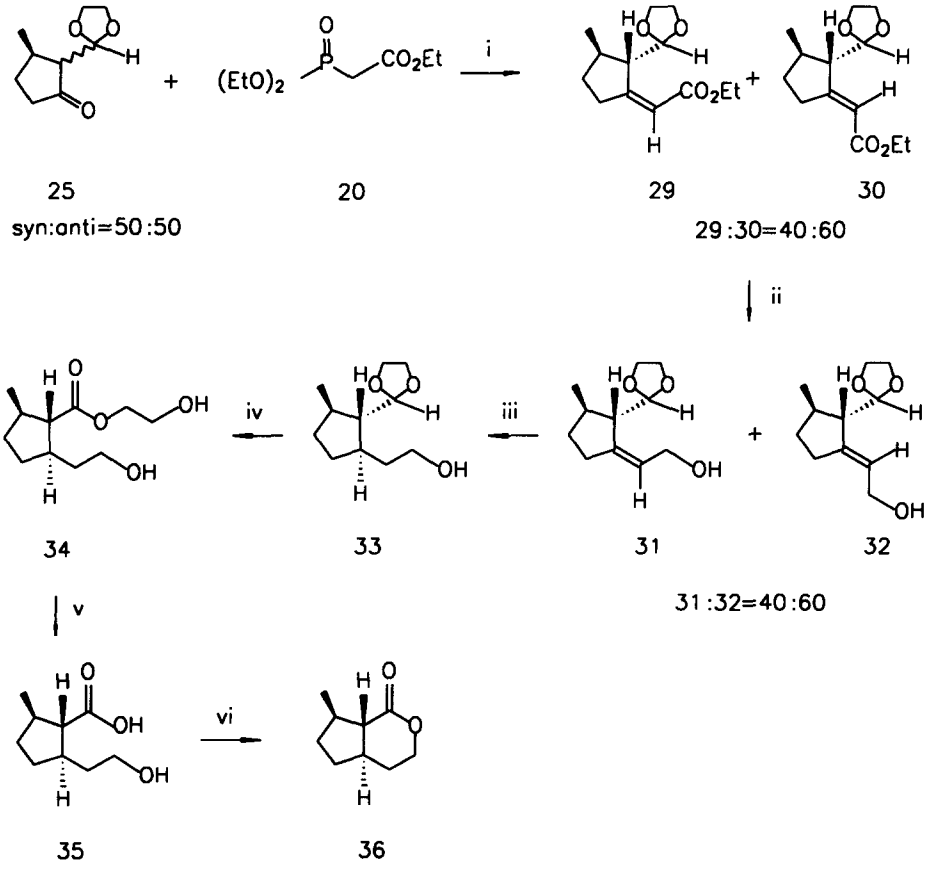


Scheme 3: (i) Br_2, ether; (ii) NaOEt, EtOH; (iii) LAH, ether; (iv) PCC, DCM; (v) $(CH_2OH)_2$, $HC(OEt)_3$, *p*-TsOH; (vi) $RuCl_3$, $NaIO_4$.



Scheme 4: Strong base = NaH, LiOH, DBU/LiCl, Cs_2CO_3; Weak base = *t*-BuOK, NaHMDS.

We reasoned that the HWE reaction with triethyl phosphonopropionate **20** (R=Me) is sluggish because it leads to the formation of tetrasubstituted olefin and, therefore, the only observable products are from competing epimerisation and elimination. In order to facilitate the C=C bond forming reaction, phosphonate **20** (R=H) was used which is devoid of a methyl group. Indeed, reaction of ketone **25** with phosphonate anion at ambient temperature afforded crude material which contained the desired unsaturated esters (Scheme 5). After carrying out the Horner reaction between ketone and phosphonate anion under a variety of conditions,[6,9] the optimal conditions were the following: addition of ketone **25** to excess (5 equi.) phosphonate anion **20** (NaH) in THF and stirring at rt for 3 days. These reaction conditions gave reproducibly a 40:60 mixture of unsaturated esters **29,30** as concluded from PMR integration of vinyl and acetal C*H* signals corresponding to the major (δ 5.98, 4.92) and minor (δ 5.84, 5.24) isomers.



Scheme 5: (i) NaH, THF, rt; (ii) LAH, ether; (iii) 5% Pd/C, EtOAc, H_2; (iv) O_3, -78°C, EtOAc; (v) 1N NaOH; (vi) PPTS, PhMe, reflux.

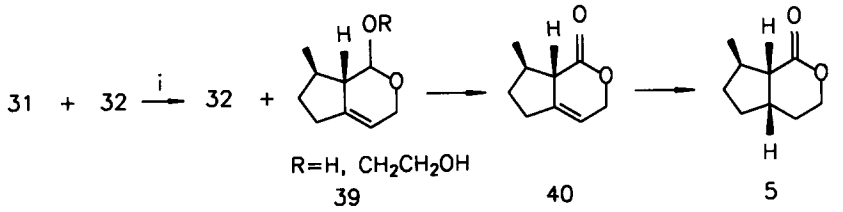
At this stage the nature of isomers, as to whether they are diastereomers at carbon adjacent to acetal group (*syn/anti*) or geometrical isomers at the newly formed olefin (*Z/E*) or both, was deduced in the following manner: (i) The unreacted β-ketoacetal recovered after incomplete reaction was exclusively the *anti*-acetal **27** and, hence, it is this diastereomer which participates in the Horner-Wadsworth reaction. (ii) The acetal C*H* doublet of *Z*-ester **29** was expected to be downfield compared to that of *E*-ester **30** because of its proximity to the carbonyl group.[10] (iii) Comparison of vinyl and acetal C*H* shifts in PMR spectrum of **31** and **32** with those reported for *Z*- and *E*-3-methyl-2-pentene-1,5-diol **37**[11a] and **38**,[11b] respectively, facilitated in the assignment of isomers as *Z*-**31** and *E*-**32**. (iv) Hydrogenation (Pd/C) of the mixture of allylic alcohols **31,32** produced a single diastereomer **33** as concluded from PMR and CMR spectra (*vide infra*). (v) Treatment of mixture of allylic alcohols **31,32** with $BF_3.Et_2O$ at -78°C afforded a mixture of lactol **39** and unreacted *E*-alkene **32** (*vide infra*). Based on the above evidence it was concluded that the 40:60 mixture of *Z*- and *E*-unsaturated esters and alcohols is isomeric at the olefinic group and not at the stereogenic allylic centre; this is illustrated in **29,30** and **31,32**.

Having established the stereochemical integrity of unsaturated esters, their reduction to saturated alcohol **33** was continued. Standard LAH reduction of esters **29,30** and hydrogenation of allylic alcohols **31,32** under heterogeneous catalysis (Pd/C, rt, 6h) proceeded smoothly in EtOAc to furnish hydroxy acetal **33**. Although the facial selectivity in the hydrogenation was debatable because of the combined interplay of steric (*syn* to hydrogen) and polar (*syn* to acetal) effects,[12] examination of the PMR and CMR spectra of the product unambiguously indicated the presence of a single stereoisomer. The compound displayed non-overlapping acetal C*H* and CH_3 doublets at δ 4.76 and 1.06 (PMR) and an 11 line (2 dioxolane carbons) CMR spectrum. A rigorous stereochemical assignment of hydroxy acetal **33** was postponed to after cyclisation to lactone.

Exposure of **33** to a variety of deprotection-cum-cyclisation conditions, such as mineral, organic and polymer-supported acids,[13] afforded crude material which contained either unreacted starting material or unidentifiable products. In no case were any PMR signals arising from aldehyde or lactol detected in the crude residue. This was very surprising in the light of facile cyclisation of hydroxy acetal **43** to its lactol with 2% HCl, and subsequent oxidation with PCC to mitsugashiwalactone **5**.[4f] We proceeded towards our goal with a modified plan (Scheme 5). The ethylene acetal **33** was oxidised under Deslongchamps' conditions[14] (O_3, EtOAc, -78°C) to hydroxy ester **34** in quantitative yield. Direct cyclisation of hydroxy ester to lactone with *p*-TsOH and PPTS catalysis did not proceed to completion. Base hydrolysis of ester **34** to acid **35** and lactonisation with PPTS in refluxing toluene caused facile cyclisation, but the PMR spectrum of **36** was visibly different from that reported for mitsugashiwalactone. Lactone **36** exhibited AB CH_2O multiplet at δ 4.46-4.24 and a CH_3 doublet at δ 1.20. Moreover, the C7a downfield proton which appears in mitsugashiwalactone at δ 2.66-2.45 was surprisingly moved upfield and appeared as part of the aliphatic multiplet above δ 2.30. The 9 line CMR spectrum of **36** was visibly different from that reported for natural **5**. Since lactone **36** was clearly different from the target mitsugashiwalactone **5**, further confirmation of its stereochemistry was mandatory. The C7-C7a *anti* relationship and the C4a-C7a *trans* ring fusion were further confirmed by 2D nOe NMR spectrum of lactone **36**. Whether the ring fusion is *cis* or *trans* is a direct consequence of facial control during the hydrogenation of exocyclic alkene. Because of the affinity of polar acetal group

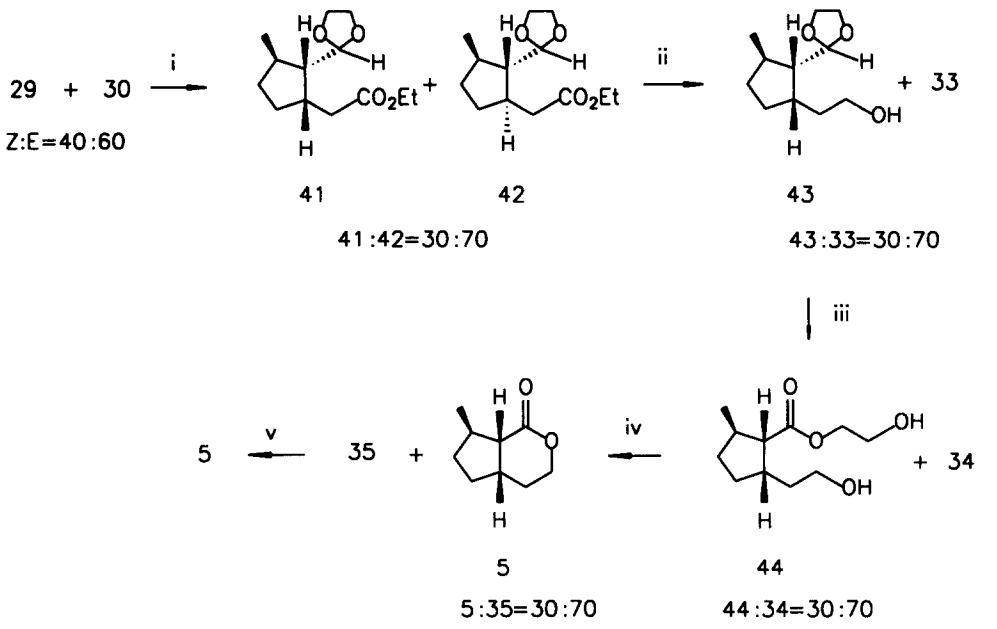
with its electronegative oxygen atoms for the palladium surface, the delivery of hydrogen at C4a occurs *syn* to the acetal group at C7a and the ring fusion C4a-C7a is *trans*.[12] Therefore, the Pd catalysed hydrogenation is chelation-controlled and occurs from the sterically more congested face to produce *trans*-fused bicyclic lactone **36**.

We attempted to overcome the problem posed by acetal-directed hydrogenation by cyclising the mixture of allylic alcohols **31,32** to lactol **39**, and then to lactone **5**. The hydrogenation of unsaturated lactone **40** should occur from the more exposed *exo* face to produce the desired *cis* ring junction at C4a-C7a (Scheme 6). This expectation was based on our earlier observation on the exclusive *exo*-selective hydrogenation of unsaturated lactone **15** with Pd/C.[5b] Exposure of hydroxy acetals **31,32** to mineral and organic acids[13] tried with **33** produced only decomposed material presumably because of the sensitivity of allylic alcohol portion of molecule to such conditions. Cyclisation to lactol **39** was successful with $BF_3.Et_2O$ catalysis in CH_2Cl_2 at -78°C. The utility of this experiment in inferring the *Z/E* stereochemistry of **31,32** was important, but its synthetic usefulness was limited because the product was difficult to purify and contaminated with unreacted *E*-**32**. A better solution was deemed to be one in which the hydrogenation takes place under steric control *syn* to the existing allylic hydrogen atom.[15]



Scheme 6: (i) $BF_3.Et_2O$, DCM, -78°C.

Attempted conjugate reduction of α,β-unsaturated esters **29,30** with $NaBH_4$/CuCl system[16] also afforded product which correlated with acetal **33** having the *trans* C4a-C7a relationship when elaborated to the product. Hydrogenation with homogeneous reagents (Wilkinson catalyst) was explored next. When unsaturated esters **29,30** were reduced with $RhCl(Ph_3P)_3$ in PhH at atmospheric and elevated pressure (60 psi), no reaction occurred. When allylic alcohols **31,32** were subjected to the same conditions isomerisation occurred and *E*-alcohol **32** was isolated; once again no hydrogenation product was observed. Hydrogenation catalysed with PtO_2 was more fruitful (Scheme 7). Thus, reduction of unsaturated esters **29,30** with PtO_2 in EtOAc at 60 psi afforded a 30:70 mixture of two isomeric acetal esters which were reduced to the corresponding alcohols. Comparison of the crude concentrate PMR spectrum with that of palladium reduction products indicated that the minor component of the mixture corresponded to the stereoisomer having the desired *cis* relationship. The *cis* substrates displayed acetal C*H* doublet at δ 4.76 (**41**) and 4.84 (**43**) whereas the *trans* intermediates exhibited the downfield doublet at δ 4.82 (**42**) and 4.76 (**33**). At lower pressure (40, 15 psi) the Pt catalysed hydrogenation gave lesser amount (20, 10%) of the desired *cis* product. A chromatographic separation of the two diastereomeric acetals was understandably difficult, hence difference in their chemical reactivity was exploited.

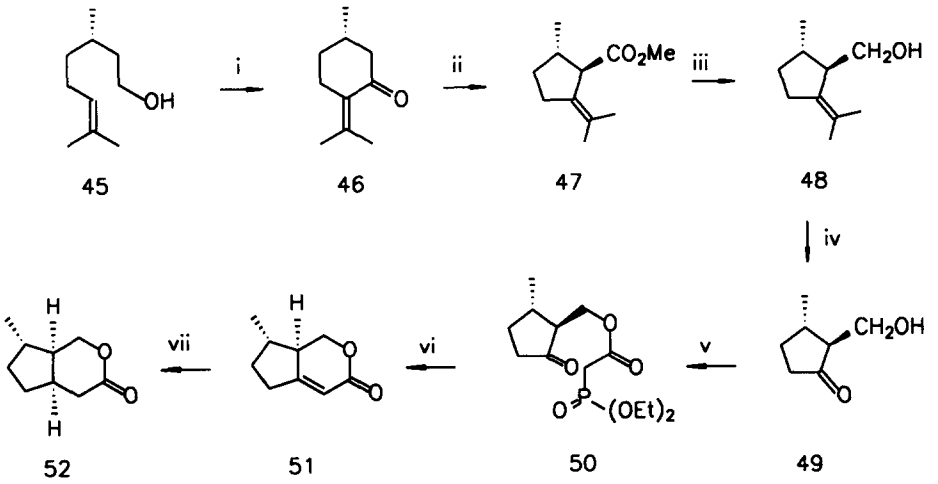


Scheme 7: (i) PtO_2, H_2, EtOAc, 60 psi; (ii) LAH, ether; (iii) O_3, EtOAc, -78°C; (iv) 1N NaOH, then xs 1N HCl, rt, 1h; (v) SGC.

The 30:70 mixture of esters **41,42** was reduced to alcohols **43,33** (LAH), oxidised to hydroxy esters **44,34** (O_3), and hydrolysed with NaOH. Based on the reported facile cyclisation of *cis*-fused hydroxy acetal to lactol[4f] and our own experience with the rather sluggish lactonisation of *trans*-fused hydroxy ester/acid, we reasoned that the selective transformation of isomeric mixture of **44,34** to the desired lactone **5** should be possible under mild reaction conditions. Indeed, base hydrolysis of esters **44,34**, acidification to pH 2, and stirring for 1 h at rt furnished an easily separable mixture of the desired *cis*-lactone **5** and unreacted *trans*-acid **35**. The crude material accumulated from a few batches was combined and purified by silica gel chromatography to furnish mitsugashiwalactone **5** whose PMR and CMR spectra were identical to data published. The AB CH_2O pattern (ddd) appeared at δ 4.28 and 4.15 and the downfield $CHCO_2$ multiplet at δ 2.66-2.45 (PMR). Furthermore, lactone **5** exhibited the expected 9 line CMR spectrum and gave satisfactory HRMS analysis. The optical rotation of mitsugashiwalactone obtained from natural sources is not reported in published literature because the value is very low. We recorded $[\alpha]_D^{25}$ -3.0° which is far superior to the value of -1.9° found by Takacs and Myoung,[4f] who used (-)-citronellene as the starting chiron for their synthesis. Thus, we have synthesised natural (-)-mitsugashiwalactone from *R*-pulegone in significantly higher enantiomeric purity.

Synthesis of Cyclopentapyranone (+)-(52)

Earlier we have synthesised cyclopentapyranone **16** ($[\alpha]_D^{25}$ -92.0°)[5b] which contains the three contiguous, non-epimerisable stereogenic centres and is the penultimate precursor to iridoids **1-3**. Since lactone **16** is derived from *R*-Pulegone ($[\alpha]_D^{25}$ +22.0°) the iridoids produced are the unnatural enantiomers. After examining different procedures available in the literature for the preparation of *S*-pulegone **46**, the one by Corey[17] appeared to be the most attractive in terms of availability of starting material (*S*-β-citronellol **45**, Aldrich, $[\alpha]_D^{25}$ -3.5°), number of steps (two) and overall yield (70%). *S*-Pulegone ($[\alpha]_D^{25}$ -15.3°, 70% ee) was prepared through this route in ~66% yield with the minor modification that *p*-TsOH in refluxing benzene was used instead of NaOH for the isomerisation of isopulegone to pulegone. *S*-Pulegone **46** was converted to *anti*-methyl pulegenate **47**[8] which was uneventfully reduced to alcohol **48** with LAH in Et_2O. Ozonolysis of exocyclic alkene **48** to ketoalcohol **49** proceeded smoothly in $MeOH/CH_2Cl_2$ at -78°C under buffered ($NaHCO_3$) conditions (Scheme 8). The β-keto alcohol was somewhat unstable and hence was esterified immediately without purification with diethylphosphonoacetic acid mediated by neutral DCC reagent. Because facile β-elimination is possible in ketophosphonate **50**, the use of conventional bases such as NaH, *t*-BuOK, NaOEt, LiOH, Cs_2CO_3, LiHMDS, NaHMDS, K_2CO_3, KOH, etc.[9] for carrying out the Horner-Wadsworth reaction was not fruitful. In most cases products arising out of extensive β-elimination were observed with insignificant or none of the desired C=C bond formation adduct. Epimerisation and elimination are much faster processes compared to intramolecular HWE reaction as concluded from studies on different model substrates.[5] Exposure of ketophosphonate **50** to the amine/salt reaction conditions of DBU/LiCl in CH_3CN at ambient temperature furnished the expected α,β-unsaturated δ-lactone **51** in excellent yield.[18] There was no trace of α-epimerisation or β-elimination products as concluded from examination of the crude residue PMR spectrum.



Scheme 8: (i) ref. 17; (ii) ref. 8; (iii) LAH, ether; (iv) O_3, MeOH/DCM, $NaHCO_3$, -78°C, then DMS; (v) $(EtO)_2P(O)CH_2CO_2H$, DCC; (vi) DBU, LiCl, MeCN; (vii) H_2, 5% Pd/C, EtOAc.

Highly stereoselective convex delivery of H_2 (Pd/C) furnished the nine carbon cyclopentapyranone template **52**. Lactone **52** displayed identical PMR, CMR and IR spectra to **16** except optical rotation ([α]$_D^{25}$ +71.8°, 78% ee). The lower ee of lactone **52** compared to its enantiomer **16** is possibly due to the difference in the optical purities of the respective starting chirons. The synthesis of 7*S*-lactone **52** constitutes a formal synthesis of naturally occurring iridoids since homologation of lactone enolate with MeI or Grieco's protocol[19] affords (+)-iridomyrmecin, (-)-isoiridomyrmecin, and (+)-teucriumlactone.

CONCLUSIONS

We have developed a novel approach towards the synthesis of iridoid terpenoids in which either enantiomer of the natural product can be targeted depending on whether the chiron is *R*-pulegone or *S*-citronellol. Both terpenes are commercially available and inexpensive. The transmission of sterogenicity directed by the single asymmetric centre in the starting chiron is excellent and, therefore, complications arising out of diastereomeric mixture of products at the final stage is avoided. The target lactone, mitsugashiwalactone **5**, is produced in higher ee than so far recorded because of better enantiocontrol inherent in the synthetic strategy. The unexpected and anomalous hydrogenation result with palladium catalysis provides an efficient synthesis of 4a-*epi*-mitsugashiwalactone **36**. The synthesis of 7*S*-lactone **52** expands the application of IMHWE protocol to important natural iridoids.

We have also gained a better understanding of the various factors that control the C=C bond forming process compared to competitive epimerisation and elimination pathways in the crucial Horner-Wadsworth-Emmons reaction. It is evident that the optimal conditions for the HWE reaction strongly depend on: (i) structure of the substrate, (ii) intra- *vs* intermolecularity of the reaction, (iii) steric congestion ensuing carbon-carbon bond forming step, and (iv) the possiblity of competitive and degradative pathways. The application of this and related strategies towards the synthesis of complex natural products[9b-d] gives the impetus to continue investigations on the role of base and solvent in directing the course of Wittig-Horner reaction on enolisable ketones.

EXPERIMENTAL SECTION

General: IR spectra were recorded on Jasco 5300 spectrometer. ^1H and ^{13}C NMR (PMR and CMR) were recorded on Bruker ACF 200 instrument. Optical rotations were measured on Autopol II or Jasco DIP 370 polarimeter. Elemental analysis was performed on Perkin Elmer 240C instrument. LRMS and HRMS were recorded on Joel JMS DX303 and Micromass VG70/70H instruments at IICT, Hyderabad. Ozonolysis was carried out on Welsbach model. SGC refers to silica gel chromatography. Work-up means drying of organic extracts with $MgSO_4$, solvent removal on rotary evaporator, and concentration *in vaccuo*. All reactions were carried out using standard syringe-septum techniques in inert nitrogen atmosphere with magnetic stirring. All reagents and solvents were dried and distilled[20] prior to use.

***syn/anti*-Alcohols 22:** To a suspension of $LiAlH_4$ (152 mg, 4 mmol) in 5 mL of dry ether was added a solution of esters **21** (462 mg, 3 mmol) in 5 mL of dry ether slowly at 0 °C and stirred for 1h. Quenched

with 0.16 mL of H_2O, 0.16 mL of 15% NaOH, and 0.5 mL of H_2O. Work-up afforded 412 mg of alcohols **22** which was purified by SGC (hexane to 10% EtOAc/hexane).

Yield: 370 mg, 82%; **$[\alpha]_D^{25}$:** +14.4° ($CHCl_3$, c 2.5); **IR:** cm^{-1} 3356, 2924, 1452, 1373, 1057, 1024, 890; **PMR:** δ 3.70 (dd, J=12,8 Hz, 1H, OCH_2); 3.52-3.38 (m, 1H, OCH_2); 2.75 (q, J=6 Hz) and 2.46-2.36 (m) (1H, $CHCH_2O$); 2.32-2.04 (m, 3H, allyl CH_2 and OH); 2.00-1.78 (m, 1H); 1.74 and 1.70 (s, 3H, vinyl CH_3); 1.73 and 1.63 (s, 3H, vinyl CH_3); 1.54-1.18 (m, 2H); 1.08 and 0.96 (d, J=6 Hz, 3H, CH_3); **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 $C_{10}H_{18}O$: C=77.87%, H=11.76%; Found: C=77.92%, H=11.80%.

***anti*-22:** δ 0.96 (d, J=6 Hz, 3H, CH_3).

***syn/anti*-Aldehydes 23:** To a suspension of PCC (645 mg, 3.0 mmol) in 2 mL of dry CH_2Cl_2 was added a solution of alcohols **22** (308 mg, 2.0 mmol) in 2 mL of dry CH_2Cl_2 at rt. After stirring for 1h the reaction mixture was diluted with 10 mL of ether, filtered through celite, and solvent removed to afford 382 mg of aldehydes **23** which was purified by SGC (hexane).

Yield: 232 mg, 76%; **$[\alpha]_D^{25}$:** +109.6° ($CHCl_3$, 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 CH_3); 1.54 (s, 3H, vinyl CH_3); 1.40-1.18 (m, 1H); 1.06 and 0.98 (d, J=6 Hz, 3H, CH_3); **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*-23:** δ 9.22 (d, J=4 Hz, 1H, CHO); 0.98 (d, J=6 Hz, 3H, CH_3).

***syn/anti*-Acetals 24:** Aldehydes **23** (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.H_2O (2.8 mg, 0.15 mmol) in 2 mL of dry benzene were stirred for 3h at rt. Diluted with ether and washed with $NaHCO_3$ solution and brine. Work-up afforded 368 mg of acetal **24** which was purified by SGC (hexane to 5% EtOAc/hexane).

Yield: 275 mg, 87%; **$[\alpha]_D^{25}$:** +11.6° ($CHCl_3$, c 2.5); **IR:** cm^{-1} 2900, 1460, 1280, 1120, 1040, 960; **PMR:** δ 4.94 and 4.86 (d, J=6 Hz, 1H, acetal H); 4.02-3.66 (m, 4H, $(OCH_2)_2$); 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:** δ 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*-24:** δ 4.86 (d, J=6 Hz, 1H, acetal H); 0.96 (d, J=6 Hz, 3H, CH_3).

***syn/anti*-Ketoacetals 25:** To a solution of alkeneacetals **24** (212 mg, 1.0 mmol) in 1.5 mL of CCl_4, 1.5 mL of CH_3CN and 2.5 mL of H_2O 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_2Cl_2.

Washed rapidly with H_2O (2x5 mL) and then brine. Work-up afforded 372 mg of ketoacetals **25** which was purified by SGC (hexane to 20% EtOAc/hexane).
Yield: 101 mg, 54%; **$[\alpha]_D^{25}$:** +57.2° ($CHCl_3$, 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, $(OCH_2)_2$); 2.66-1.74 (m, 5H); 1.52-1.32 (m, 1H); 1.14 and 1.10 (d, J=6 Hz, 3H, CH_3); **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*-25=27:** δ 5.16 (d, J=2 Hz, 1H, acetal *H*); 1.14 (d, J=6 Hz, 3H, CH_3).

***Z/E*-Esters 29,30:** 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 triethylphosphonoacetate **20** (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 **25** (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 H_2O and extracted with $CHCl_3$ (3x10 mL). The organic layer was washed with brine and usual work-up afforded 125 mg of esters **29,30** which was purified by SGC (hexane to 20% EtOAc/hexane).
Yield: 30 mg, 60%; **$[\alpha]_D^{25}$:** +21.2° ($CHCl_3$, 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, OCH_2); 4.02-3.78 (m, 4H, $(OCH_2)_2$); 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, CH_3); 1.06 (t, J=6 Hz, 3H, CH_2CH_3); **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 31,32:** Unsaturated esters **29,30** (48 mg, 0.2 mmol); $LiAlH_4$ (15 mg, 0.4 mmol).
***Z*-31 and *E*-32: Yield:** 34 mg, 87%; **$[\alpha]_D^{25}$:** +6.0° ($CHCl_3$, c 1.0); **IR:** cm^{-1} 3398, 2953, 2872, 1456, 1394, 1145, 1037;

***Z*-31: $[\alpha]_D^{25}$:** -31.0° ($CHCl_3$, 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, $3xOCH_2$ and O*H*); 2.52 (t, J=6 Hz, 1H, allyl *H*); 2.44-2.14 (m, 2H, allyl CH_2); 2.02-1.82(m, 1H); 1.42-1.12 (m, 2H); 1.02 (d, J=6 Hz, 3H, CH_3); **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*-32: $[\alpha]_D^{25}$:** +41.0° ($CHCl_3$, c 1.0); **PMR:** δ 5.68 (br s, 1H, vinyl *H*); 4.92 (d, J=4 Hz, 1H, acetal *H*); 4.16 (d, J=6 Hz, 2H, OCH_2); 4.04-3.82 (m, 4H, $(OCH_2)_2$); 2.56-1.82 (m, 6H); 1.44-1.18 (m, 1H); 1.06 (d, J=6 Hz, 3H, CH_3); **CMR:** δ 145.56, 122.51, 106.49, 64.90 (x2); 60.66, 54.29, 34.89, 33.61, 28.82, 20.50.

Hydroxyacetal 33: Allylic alcohol **31,32** (40 mg, 0.2 mmol) was dissolved in 4 mL of EtOAc and 20 mg of 10% Pd/C was added. The flask was evacuated to remove air, flushed with H_2 and stirred for 6 h under H_2 atmosphere. Filtration through celite and work-up afforded 38 mg of hydroxyacetal **33** which was purified by SGC (10% to 50% EtOAc/hexane).

Yield: 30 mg, 75%; **$[\alpha]_D^{25}$:** -13.6° ($CHCl_3$, 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, $(OCH_2)_2$); 3.74-3.60 (m, 2H, OCH_2); 2.64-2.40 (br s, 1H, O*H*); 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, CH_3); 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 $C_{11}H_{20}O_3$: C=65.97%, H=10.07%; Found C=65.98%, H=9.97%.

Hydroxyester 34: Hydroxyacetal **33** (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 **34** which was pure enough to carryout the next reaction.

Yield: 11 mg, ~99%; **$[\alpha]_D^{25}$:** -13.2° ($CHCl_3$, c 2.5); **IR:** cm^{-1} 3420, 2953, 2872, 1728, 1456, 1381, 1263, 1159, 1080, 887, 736; **PMR:** δ 4.42-4.12 (m, 2H, OCH_2); 3.80 (t, J=6 Hz, 2H, CO_2CH_2); 3.76-3.54 (m, 2H, OCH_2); 3.60-3.40 (br s, 2H, 2xO*H*); 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:** δ 176.48, 65.84, 61.03 (x2); 58.59, 40.82, 39.79, 38.71, 33.33, 31.55, 19.71.

Hydroxyacid 35: Hydroxyester **34** (10.8 mg, 0.05 mmol) and 1N NaOH (1 mL) were refluxed for 30 min and cooled to rt. 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 **35** which was subjected for cyclisation without any purification.

Yield: 8.5 mg, 98%; **$[\alpha]_D^{25}$:** -12.0° ($CHCl_3$, c 1.0); **IR:** cm^{-1} 3300, 2953, 1707, 1381, 1100, 950, 845; **PMR:** δ 7.24-6.70 (br s, 2H, CO_2H and O*H*); 3.68 (t, J=6 Hz, 2H, OCH_2); 2.76-2.18 (m, 3H); 2.06-1.86 (m, 2H); 1.74-1.62 (m, 1H); 1.48-1.16 (m, 3H); 1.10 (d, J=6 Hz, 3H, CH_3); **CMR:** δ 181.38, 61.45, 58.63, 41.20, 39.86, 38.31, 33.40, 31.35, 19.88.

***trans*-Lactone 36:** Hydroxyacid **35** (8.6 mg, 0.05 mmol) was dissolved in 20 mL of dry toluene and catalytic amount (~2 mg) of PPTS was added. 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 $NaHCO_3$ 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%; **$[\alpha]_D^{25}$:** -39.0° ($CHCl_3$, 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, OCH_2); 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, CH_3); **CMR:** δ 174.42, 68.31, 53.82, 40.37, 33.51, 31.66, 30.25, 28.42, 20.61; **Analysis:** Calculated for $C_9H_{14}O_2$: C=70.10%, H=9.15%; Found: C=70.21%, H=9.19%; **LRMS:** 155 (M+1).

Acetalesters 41,42: Unsaturated ester **29,30** (12 mg, 0.05 mmol); PtO_2 (5 mg); EtOAc (1 mL); 60 psi; 15 min.

Yield: 11 mg, 90%; **[α]$_D^{25}$:** +23.0° ($CHCl_3$, 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, CO_2CH_2); 4.00-3.74 (m, 4H, $(OCH_2)_2$); 2.72-2.52 (m, 2H, CH_2CO_2); 2.44-2.10 (m, 2H); 2.00-1.68 (m, 3H); 1.50-1.36 (m, 1H); 1.28-1.18 (m, 3H, CH_2CH_3); 1.06 and 1.04 (d, J=6 Hz, 3H, CH_3); 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.

Hydroxyacetals 43,33: Acetalester **41,42** (25 mg, 0.1 mmol); $LiAlH_4$ (6 mg, 0.15 mmol).
Yield: 16 mg, 80%; **[α]$_D^{25}$:** -20.0° ($CHCl_3$, c 1.0); **PMR:** δ 4.84 (d, J=6 Hz, acetal *H*).

Hydroxyesters 44,34: Hydroxyacetal **43,33** (10 mg, 0.05 mmol); EtOAc (1 mL); O_3, -78 °C.
Yield: 11 mg, ~99%; **[α]$_D^{25}$:** -21.0° ($CHCl_3$, c 1.0).

Mitsugashiwalactone 5: 1N NaOH (2 mL) was added to hydroxyester **44,34** (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 **35** and *cis*-lactone **5** (14 mg) which were seperated by SGC (hexane to 20% EtOAc/hexane, then EtOAc)
Yield: 3 mg, 74%; **[α]$_D^{25}$:** -3.0° ($CHCl_3$, 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, OCH_2); 4.15 (ddd, J=12,6,2 Hz, 1H, OCH_2); 2.66-2.45 (m, 1H, $CHCO_2$); 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, CH_3); **CMR:** δ 174.51, 66.86, 50.22, 39.49, 36.29, 34.62, 32.68, 29.24, 19.90. **HRMS:** Calculated for $C_9H_{14}O_2$: 154.0994; Found 154.0994.

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