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Asymmetric Synthesis of Chiral Vinylic Epoxides and α-Hydroxy-β,γ-unsaturated esters via (-)-Menthol based Auxiliary and Enzymatic Resolution Respectively[1]

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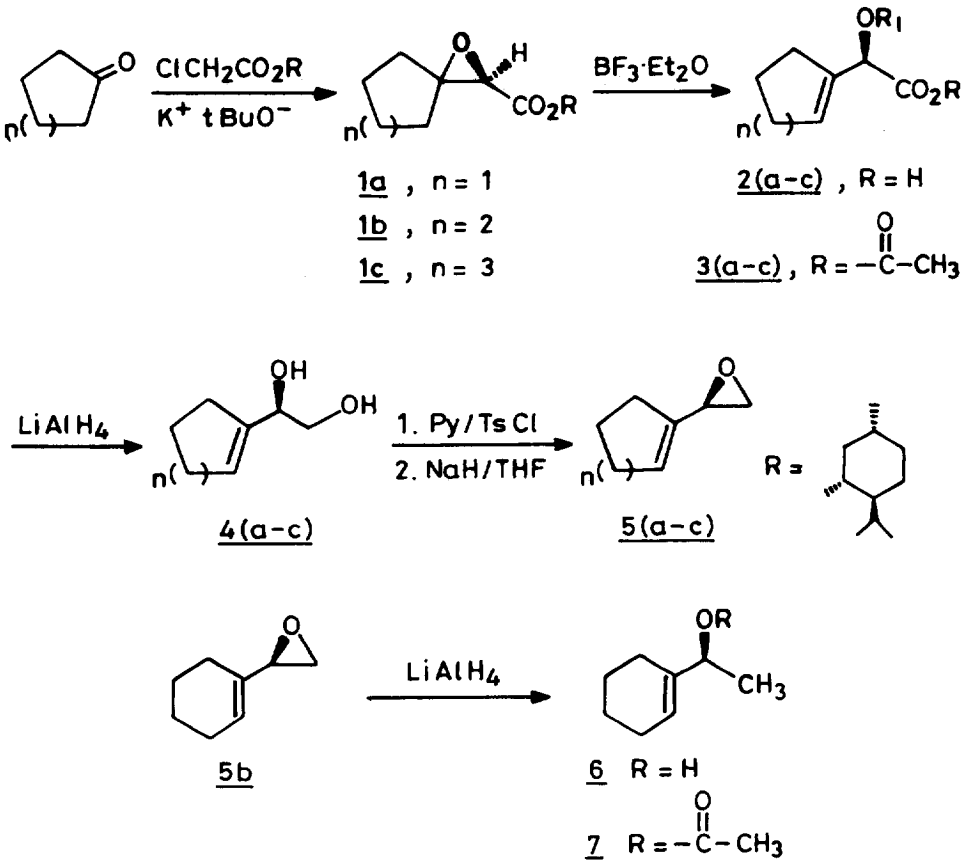
Abstract: Using (-)-menthol as an auxiliary, three chiral vinylic epoxides have been synthesised from the corresponding glycidic esters via α-hydroxy-β,γ-unsaturated esters.Enzymatic resolution of α-acetoxy-β,γ-unsaturated esters using PLAP leads to optically active α-hydroxy- β,γ-unsaturated esters. Copyright © 1996 Elsevier Science Ltd

Vinyl epoxides are useful intermediates in organic synthesis[2]. This functionality offers three electrophilic centres for nucleophilic attack and as a result of this, vinyl epoxides have been employed in the synthesis of a variety of natural products[3]. Recently, we have reported[4] a simple synthesis of vinyl epoxides from glycidic esters via their isomerisation to α-hydroxy-β,γ-unsaturated esters (Scheme 1). As part of a general programme in asymmetric synthesis we became interested in synthesising vinyl epoxides in enantiomerically pure forms by adopting our earlier described[5] procedure.

Our first approach was based on employing (-)-menthol as an auxiliary. To this effect, the formation of glycidic esters **1** from cycloalkanones and (-)-menthyl chloro acetate was studied. Interestingly, the three glycidic esters (Table 1) synthesised in this manner were found to be mixtures (3:1) of two diastereomers as indicated by their ^{1}H NMR spectral analysis. This was apparent from the integration of the two distinct singlets corresponding to the methine protons on the epoxide ring. Thus, for example, in the cyclohexanone case these singlets appeared at δ 3.07 and δ 3.9 in a ratio of 3:1. Isomerisation with $BF_3.Et_2O$ led to the corresponding α-hydroxy-β,γ-unsaturated esters in reasonably good yields (Table1). The diastereomeric ratio after the isomerisation was maintained as 3:1. This was evident from the ^{1}H NMR spectral analysis of the corresponding acetates **3(a-c)** where the signals from the acetate groups appeared as two singlets in the ratio 3:1. Reduction of these hydroxy esters **2(a-c)** with $LiAlH_4$ yielded the corresponding diols **4(a-c)**. Tosylation with p-toluene sulfonyl chloride (TsCl) in the presence of pyridine followed by treatment with NaH furnished the expected vinyl epoxides **5(a-c)**. The absolute configuration of the vinyl epoxide **5b** was established as 'S'on the basis of literature[6] comparison of the sign of the specific rotation value of the corresponding $LiAlH_4$ reduced product **6**. Thus the reduced product showed the rotation $[\alpha]_D^{25}$ = -6.9 (C =1,

$CHCl_3$) whereas the literature value for this compound is $[\alpha]_D^{25}$ = -9.8 (C = 4.25, $CHCl_3$). Further, its enantiomeric excess was confirmed to be 50% by ^1H NMR analysis of the corresponding acetate viz. **7** in the presence of $Eu(hfc)_3$. The two acetate peaks were found to be resolved in the presence of this shift



Scheme 1

reagent. By analogy we presume that the absolute configurations of other vinyl epoxides viz. **5a** and **5c** are also the same, i.e., 'S' as that for **5b**.

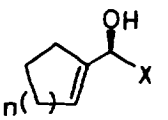
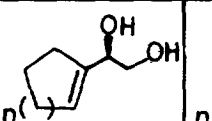
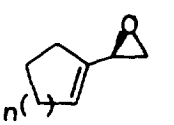
As the asymmetric centres in the isomerised hydroxy esters are neither changed nor destroyed it is expected that the vinyl epoxides continue to have a 3:1 mixture of the two enantiomers. We, therefore, believe that the vinyl epoxides possess an enantiomeric excess (e.e.) of 50%.

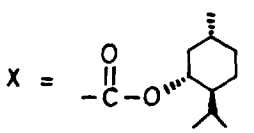
Since the e.e. of these vinyl epoxides which, in turn, depends on the e.e. of α-hydroxy-β,γ-unsaturated esters, was only 50% it was planned to adopt an alternate strategy to improve this. For this purpose, enzymatic resolution[7] strategy using pig liver acetone powder (PLAP)[8] was followed. Initial studies to resolve the hydroxy ester **9b** (Table 2) with PLAP gave a poor yield of the hydrolysed product. More than 95% of the unhydrolysed starting compound was recovered even after several days of the reaction. Although

the recovered hydroxy ester showed a specific rotation value of $[\alpha]_D^{25}$ = + 5.2 (C = 1, $CHCl_3$), the corresponding hydroxy acid could not be isolated in pure state. On the other hand, the acetoxy ester **9c** underwent smooth resolution with PLAP to give the hydrolysed alcohol viz. the hydroxy ester **9d** in 81% yield (Scheme 2). Its specific rotation was found be $[\alpha]_D^{25}$ = + 35.6 (C = 1, $CHCl_3$) and the ^{1}H NMR

Table 1

Synthesis of Chiral Vinylic Epoxides

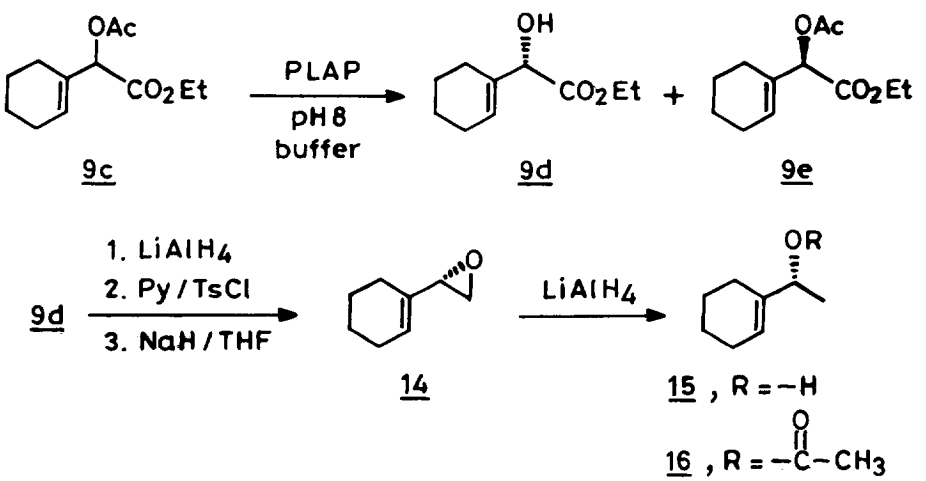
Entry	Glycidic Ester 1	α-Hydroxy Ester 2	Diol 4	Vinylic Epoxide 5 $\{(\alpha)_D^{25}\}$
				
1	n = 1, 1a	2a	4a	5a {-1.2 (C=1, $CHCl_3$)}
2	n = 2, 1b	2b	4b	5b {-4.6 (C=1, $CHCl_3$)}
3	n = 3, 1c	2c	4c	5c {-5.5 (C=1, $CHCl_3$)}

X = 

spectral analysis of its Mosher's ester [derived from R-(+)-α-methoxy-α-(trifluoromethyl)-phenyl acetic acid] indicated it to have 90% e.e. The recovered unhydrolysed acetate **9e** had an e.e. of 54% which was assessed on the basis of its ^{1}H NMR analysis in the presence of (+)-Eu(hfc)$_3$ where the two acetate peaks were clearly separated. Likewise, acetates from a few other α-hydroxy-β,γ-unsaturated esters were hydrolysed with PLAP and good to excellent enantiomeric purity was found in these cases (Table 2).

The hydroxy ester **9d**, obtained in enantiomerically pure form via PLAP hydrolysis was converted into the corresponding vinyl epoxide **14** in a manner analogous to the one described above. Further, its reduction with $LiAlH_4$ gave the desired alcohol **15** (Scheme 2) as one of the products whose rotation value was found to be $[\alpha]_D^{25}$ = +12.2 (C = 1, $CHCl_3$). On the basis of its rotation sign it is clear that it has 'R' configuration. The absolute configuration of α-hydroxy-β,γ-unsaturated esters derived from cyclopentanone and cycloheptanone after PLAP hydrolysis (Table 2) should also be 'R' by way of logical extension. It, therefore, appears that the two methods viz. via (-)-menthol and via PLAP hydrolysis are complementary to each other as they yield products of opposite configurations.

Likewise, glycidic ester of acetophenone viz. **11a** was also isomerised to the hydroxy ester **11b** in 48% yield by using sulfuric acid[9]. Its acetate **11c** upon PLAP hydrolysis yielded the hydroxy ester **11d** in 36% yield having a specific rotation value to be $[\alpha]_D^{25} = +6.7$ (C = 1, $CHCl_3$). On the basis of the ^1H NMR analysis of its Mosher's ester the e.e. was found to be 65%. Again, on the basis of the sign of the specific rotation value it is concluded that the absolute configuration is 'R' as shown in Scheme 2. Glycidic ester derived from acetone was also converted into the racemic acetoxy ester **12c** and subjected to enzymatic resolution with PLAP. However, from the reaction mixture only the acetoxy ester **12e** could be isolated in enantiomerically pure form which possessed a specific rotation value to be $[\alpha]_D^{25} = -15.0$ (C = 1, $CHCl_3$). Its enantiomeric purity was found to be 40% on the basis of $Eu(hfc)_3$ based ^1H NMR spectral studies.



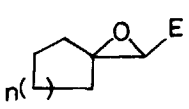
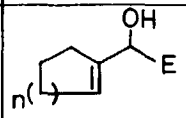
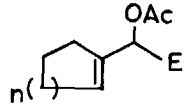
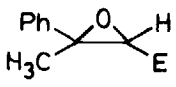
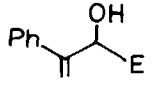
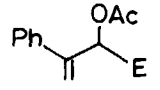
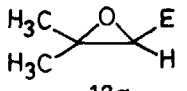
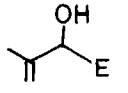
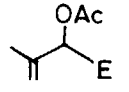
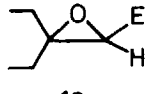
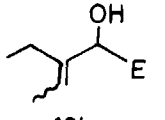
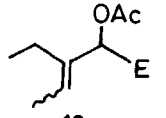
Scheme 2

The acetate **13c** of α-hydroxy-β,γ-unsaturated ester **13b** which was, in turn, derived from 3-pentanone too underwent PLAP hydrolysis. In this case also only the optically active acetoxy ester **13e** was isolated with an enantiomeric purity of only 28% as evidenced by the $Eu(hfc)_3$ based ^1H NMR study. The hydrolysed hydroxy ester could not be seen on the tlc and hence was not isolated.

In summary, it appears that the (-)-menthol based auxiliary allows preparation of α-hydroxy-β,γ-unsaturated esters and the corresponding vinyl epoxides in moderate enantiomeric purities. On the other hand, PLAP based hydrolysis lead to fairly high degree of optical purity of the hydrolysed products viz. α-hydroxy-β,γ-unsaturated esters which are precursors for vinyl epoxides. Further, the two types of products bear opposite configurations. We believe that the present routes should find use in organic synthesis.

Table 2

PLAP Catalysed Hydrolysis of α-Acetoxy-β, γ-Unsaturated Esters

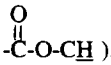
Entry	Glycidic Ester	α-Hydroxy Ester	α-Acetoxy Ester	Chiral α-Hydroxy Ester		Chiral α-Acetoxy Ester	
				$[\alpha]_D^{25}$ = (C=1, $CHCl_3$)	ee(i)	$[\alpha]_D^{25}$ = (C=1, $CHCl_3$)	ee(ii)
							
1	n = 1, 8a	n = 1, 8b	n = 1, 8c	8d +29.016	82%	8e −28.475	44%
2	n = 2, 9a	n = 2, 9b	n = 2, 9c	9d +35.563	90%	9e −28.473	54%
3	n = 3, 10a	n = 3, 10b	n = 3, 10c	10d +108.14	80%	10e −82.56	34%
4	 11a	 11b	 11c	11d +6.69	65%	11e − 8.79	20%
5	 12a	 12b	 12c	—	—	12e −15.033	40%
6	 13a	 13b	 13c	—	—	13e −20.89	29%

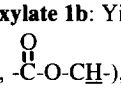
(i) Determined by converting the alcohol into Mosher's ester and its 400 MHz ^1H NMR analysis when the methoxy peaks separated out

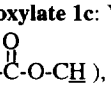
(ii) Determined by 400 MHz ^1H NMR analysis using $Eu(hfc)_3$ when the acetate peaks appeared distinct.

EXPERIMENTAL

General: ^{1}H NMR spectra were recorded on Jeol PMX 60, Bruker WP80 and WM 400 spectrometers with Me_3Si as internal standard. IR spectra were recorded on Perkin-Elmer 1320 spectrophotometer. Mass spectra were recorded at 70 eV on a Jeol MS-300 D mass spectrometer. Elemental analysis were carried out in Coleman automatic analyser. Optical rotations were recorded using Autopol II Rudolph polarimeter. Glycidic esters **8a-13a** were prepared according to literature[9,10] procedures. Glycidic esters **1a-1c** were prepared by following the same procedures[9,10] except that (-)-menthyl ester of chloroacetic acid was used instead of ethyl chloroacetate.

Menthyl-l-oxaspiro-[2,4]-heptan-2-carboxylate 1a:Yield: 60%; Colourless oil; IR (neat): 1750, 1725 cm^{-1} ; ^{1}H NMR (CCl_4): δ 4.75-4.5 (1H, br m, -C(=O)-O-CH), 3.9 and 3.3 (1H, two singlets in 1:3 ratio, ), 2.15-0.65 (26H, m, methylenes, methines and two sets of overlapping doublets for 3 methyls at δ 0.95 and 0.7, with J = 7 Hz). Mass spectrum: m/z 280 (M^+). Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.86; H, 10.0; Found C, 72.23; H, 9.5%.

Menthyl-l-Oxaspiro-[2,5]-octan-2-carboxylate 1b: Yield: 64 %, Colourless oil; IR (neat): 1750, 1725 cm^{-1} ; ^{1}H NMR (CCl_4): δ 4.65-4.45 (1H, br m, -C(=O)-O-CH-), 3.9 and 3.07 (1H, two singlets in 1:3 ratio, ), 2.6-0.7 (28H, m, methylenes, methines and two sets of overlapping doublets for 3 methyls at δ 0.8 and 0.73, with J = 7 Hz). Mass spectrum : m/z 294 (M^+). Anal. Calcd. for $C_{18}H_{30}O_3$: C, 73.47; H, 10.2. Found C, 73.12; H, 9.8%.

Menthyl-l-Oxaspiro-[2,6]-nonan-2-carboxylate 1c: Yield: 45%; Colourless oil; IR (neat): 1750, 1725 cm^{-1} ; ^{1}H NMR (CCl_4): δ 4.75-4.45 (1H, br m, -C(=O)-O-CH), 3.15 (1H, s ), 2.4-0.65 (30 H, m, methylenes, methines and two sets of overlapping doublets for 3 methyls at δ 0.85 and 0.73, with J = 7 Hz). Mass spectrum : m/z 308 (M^+). Anal. Calcd. for $C_{19}H_{32}O_3$: C, 74.03; H, 10.39. Found: C, 73.82; H, 9.4%.

Isomerisation of glycidic esters 1a-1c to α-Hydroxy-β ,γ-Unsaturated Esters 2a-2c: These isomerisations were carried out by following our earlier described procedures[5].

Menthyl-2-hydroxy-2-[cyclopent-1-ene]-acetate 2a: Yield: 22%; Colourless oil; IR (neat): 3500, 1720 cm^{-1} ; ^{1}H NMR (CCl_4): δ 5.67 (1H, br s, olefinic), 5.0-4.33 (2H, br m, -C(=O)-O-CH and -CHOH), 2.75 (1H, br s, -OH, D_2O exchangeable), 2.3-0.65 (24H, m, methylenes, methines and two sets of overlapping doublets for two methyls). Mass spectrum: m/z 280.

Menthyl-2-hydroxy-[cyclohex-1-ene]-acetate 2b: Yield: 65%; A viscous oil; IR (neat) : 3500, 1715 cm^{-1};

^{1}H NMR (CCl_4): δ 5.8 (1H, br s, olefinic), 4.8-4.45 (1H, br m, -C(=O)-O-CH) 4.1 (1H, br s, -CH-OH), 2.97 (1H, br s, OH), 2.6-0.6 (26H, m, methylenes, methines and two overlapping doublets for two methyls). Mass spectrum : m/z 294.

Menthyl-2-hydroxy-2[cyclohept-1-ene]-acetate 2c:Yield: 70%; IR (neat): 3500,1710 cm^{-1}; ^{1}H NMR (CCl_4) :δ 5.75 (1H, t, olefinic, J = 6 Hz), 4.75-4.45 (1H, br m, -C(=O)-O-CH) 4.3 (1H, br s,-CH-OH), 2.75 (1H, br s, -OH), 2.4-0.75 (28H, m, methylenes, methines and two overlapping doublets for two methyls). Mass spectrum: m/z 308.

General Procedure for the Preparation of Acetoxy Esters 3a-3c: A mixture of a hydroxy ester (**2a-2c**) (0.5 mmol), acetic anhydride (204 mg, 2 mmol) and anhydrous pyridine (0.05 ml, 0.6 mmol) in 2 ml of dry dichloromethane was stirred at room temperature for 20 hr. It was then poured into 10 ml of ice cold water and extracted with CH_2Cl_2 (3 x 15 ml). The combined organic layer was washed with 5% HCl (10 ml), water (2 x 15 ml) followed by brine (10 ml) and dried over anhydrous sodium sulfate. Removal of the solvent gave a crude product which was purified by column chromatography [eluent: pet. ether (60-80 ^{0}C) : ethyl acetate = 97:3].

Menthyl-2-acetoxy-2-(cyclopent-1-ene)-acetate 3a: Yield: 85%; A mobile colourless liquid. IR (neat) : 1740 cm^{-1} ; ^{1}H NMR (CCl_4): δ 5.78 (1H, br s, olefinic), 5.4 and 5.0 (1H, 2s, relative area 1:3, -CHOAc), 4.79-4.3 (1H, br m, -COO-CH), 2.45-0.4 (27H, m, methylenes and methines including a singlet for the acetate at δ 2.25 and overlapping doublets for methyls at δ 0.95, 0.8 and 0.68). Mass spectrum: m/z 323 $(M+1)^+$, 322 (M^+), 271 (M^+- 43).

Menthyl-2-acetoxy-2-(cyclohex-1-ene)-acetate 3b: Yield: 92%. A clear liquid. IR (neat): 1735 cm^{-1}. ^{1}H NMR (CCl_4): δ 5.83 (1H, br s, olefinic), 5.01 (1H, s, -CHOAc), 4.75-4.3 (1H, br m, -COOCH), 2.38-0.45 (26H, m, methylenes and methines including two singlets at δ 2.12 and 2.03 for acetate relative area ~1:3 and methyl doublets at δ 0.95, 0.79 and 0.62). Mass spectrum: m/z 337 (M^+), and 293 (M^+-43).

Menthyl-2-acetoxy-2-(cycloheptl-1-ene)-acetate 3c: Yield: 82%. A clear liquid. IR (neat): 1740 cm^{-1}.^{1}H NMR (CCl_4): δ 5.8 (1H, t, olefinic), 4.7 (1H, s, -CHOAc), 4.6-4.3 (1H, br m, -COOCH), 2.3-0.45 (28H, m, methylenes including overlapping doublets at 0.95, 0.8 and 0.63 due to methyls), 2.07 and 2.0 (3H, 2s, relative area 1:3, - $OCOCH_3$). Mass spectrum: m/z 351 $(M+1)^+$, 290 [$(M+1)^+$ - 59].

$LiAlH_4$ reduction of the hydroxy esters 2a-2c to Chiral diols 4a-4c: To a suspension of $LiAlH_4$ (2.5 mmol) in anhydrous THF (5 ml) was slowly added a solution of an α-hydroxy-β,γ-unsaturated ester **2a-2c** (1 mmol) in THF (2 ml) at 5 ^{0}C. After the addition was complete the ice bath was removed and the solution refluxed

for 4 hrs. The excess of $LiAlH_4$ was then slowly destroyed with ethyl acetate (15 ml), followed by water (1 ml) and aq. NaOH (1 ml). The reaction mixture was then filtered through a pad of Na_2SO_4. The filtrate was concentrated under vacuum to yield a thick oil which was purified by column chromatography (eluent : ethyl acetate/pet. ether: 25/75) to obtain a pure diol.

2-(Cyclopentene)-2-hydroxy ethanol 4a: Yield: 77%. A colourless viscous oil. IR (neat) : 3465 cm^{-1}. ^1H NMR (CCl_4): δ 5.5 (1H, br s, olefinic),. 4.3-4.0 (3H, m, -CHOH-CH_2OH), 3.5-3.05 (2H, m, -CHOH-CH_2OH), 2.5-1.1 (6H, m, ring methylenes). Mass spectrum: m/z 128, 110. The specific rotation of the corresponding diacetate was found to be: $[\alpha]_D^{25}$ = -39.0 (C = 1, $CHCl_3$) and the analysis was Calcd. for $C_{11}H_{16}O_4$: C, 62.26; H, 7.56. Found: C, 63.02; H, 7.67%.

2-(Cyclohexene)-2-hydroxy ethanol 4b: Yield: 85%. A colourless oil. IR (neat) : 3460 cm^{-1}. ^1H NMR (CCl_4): δ 5.90 (1H, br s, olefinic), 4.5-4.1 (3H, m, -CHOH-CH_2 OH), 3.8-3.2 (2H, m, CHOH-CH_2 OH), 2.5-2.2 (4H, m, ring allylic methylenes), 2.1-1.8 (4H, m, other ring methylenes). Mass spectrum: m/z 143 (M+1). The specific rotation of the corresponding diacetate was found to be: $[\alpha]_D^{25}$ = -36.8 (C = 1, $CHCl_3$) and the analysis was : Calcd. for $C_{12}H_{18}O_4$: C, 63.72; H, 7.96. Found: C, 63.23; H, 7.47%.

2-(Cycloheptene)-2-hydroxy ethanol 4c: Yield: 82%. A thick oil. IR (neat) : 3455 cm^{-1}. ^1H NMR (CCl_4): δ 5.66 (1H, t, olefinic), 4.15-3.6 (3H, m, -CHOH-CH_2OH), 3.56-3.03 (2H, m, -CHOH-CH_2OH), 2.5-1.1 (10H, m, ring methylenes). Mass spectrum: m/z 156 (M^+), 138 (M^+-H_2O). The specific rotation of the corresponding diacetate was found to be: $[\alpha]_D^{25}$ = -35.7 (C=1, $CHCl_3$) and the analysis was : Calcd. for $C_{13}H_{20}O_4$: C, 65.00; H, 8.33. Found: C, 64.09; H, 9.01%.

Conversion of diols 4a-4c into vinyl epoxides 5a-5c: To a stirred solution of a diol (1 mmol) in dry ether (2 ml) was added pyridine (1.5 mmol) and freshly recrystallized p-tolutene sulfonyl chloride (1.2 mmol) at 0 ^{0}C. The reaction mixture was stirred at 0 ^{0}C-10 ^{0}C for 7 days by the end of which the reaction was generally complete (monitoring by tlc). The solvent was removed under reduced pressure and the crude product so obtained was used without further purification.

A stirred suspension of NaH (1.2 mmol) in dry ether (2 ml) at 0 ^{0}C was treated with a solution of crude tosylate, obtained as above, in ether (2 ml). The reaction mixture was stirred at room temperature for 12 hr. It was then diluted with water (5 ml) and extracted with ether (3 x 10 ml). Evaporation of the solvent yielded a crude product which was purified by column chromatography (eluent: pet. ether/ethyl acetate : 90/10).

Oxirane-2-(cyclopent-1-ene) 5a: Yield: 87%. Clear liquid. $[\alpha]_D^{25}$ = -1.23 (C = l, $CHCl_3$). ^1H NMR (CCl_4): δ 5.74 (1H, br t, olefinic), 3.3 (1H, t, -HC(O)CH_2 , J = 3 Hz), 2.83-1.6 (8H, m, 4 x CH_2 s'). Mass spectrum: m/z 111 $(M+1)^+$, 110 (M^+).

Oxirane-2-(cyclohex-1-ene) 5b: Yield: 79%. A colourless liquid. $[\alpha]_D^{25}$ = -4.6 (C = l , $CHCl_3$). ^1H NMR (CCl_4) : δ 5.75 (1H, br t, olefinic), 3.15 (1H, t, -CH(O)CH_2 , J = 3 Hz), 2.73-2.35 (2H, m, -C(O)CH_2), 2.3-0.75 (8H, m, ring methylenes). Mass spectrum: m/z 125 $(M+1)^+$, 124 (M^+).

Oxirane-2-(cycloheptl-1-ene) 5c: Yield: 82%. A clear liquid. $[\alpha]_D^{25}$ = -5.48 (C = l, $CHCl_3$).^1H NMR (CCl_4): δ 5.83 (1H, t, J = 6 Hz, olefinic), 3.15 (1H, dd, -CH(O)CH_2 , J = 2 Hz), 2.76 -1.16 (12H, m, methylenes). Mass spectrum: m/z 139 $(M+1^+)$, 138 (M^+).

Reduction of 5b with $LiAlH_4$ into 1-(cyclohex-1-ene) ethanol 6: To a stirred suspension of $LiAlH_4$ (152 mg; 4 mmol) in dry THF (3 ml) was slowly added a solution of **5b** (248 mg; 2 mmol) in THF (1 ml) at 0 ^{0}C. The reaction mixture was slowly brought to room temperature and stirred for 4 hr. The reaction was worked up in an analogous manner as described for the preparation of diols **4a-4c** (vide supra) to yield crude **6**. Purification by column chromatography yielded 101 mg of pure **6** (yield: 40%). A colourless mobile liquid. IR (neat) : 3400 cm^{-1}. ^1H NMR (CCl_4): δ 5.52 (1H, br s, olefinic), 4.11 (1H, q, -CHOH, J = 6 Hz), 2.12-1.39 (9H, m, - OH and methylenes), 1.22 (3H, d, $-CH_3$, J = 6 Hz). $[\alpha]_D^{25}$= -6.88(C = l , $CHCl_3$); Lit.[6] value:$[\alpha]_D^{25}$ = -9.8 (C= 4.3, $CHCl_3$).

Ester 7: Acetylation of **6** was carried out in an analogous manner as described above for the preparation of **3a-c**. Yield: 90%. IR (neat) : 1750 cm^{-1}. ^1H NMR (CCl_4) : δ 5.6 (1H, br s, olefinic), 4.96 (1H, q, -CHOAc, J = 7 Hz), 2.15-1.4 (8H, m, 4 methylenes), 2.03 (3H, s, $-OCOCH_3$), 1.33 (3H, d, $-CH_3$, J = 7 Hz). $[\alpha]_D^{25}$: -14.4 (C=1, $CHCl_3$).

Acetylation of α-Hydroxy-β,γ-Unsaturated Esters 8b-13b to 8c-13c: The acetylation procedure was the same as that for the preparation of acetoxy esters **3a-3c**.

Ethyl-2-acetoxy-2-(cyclopent-1-ene)-acetate 8c: Yield: 82%. IR (neat) : 1750, 1740 cm^{-1}. ^1H NMR (CCl_4): δ 5.75 (1H, br s, olefinic), 5.35 (1H, s, -CHOAc), 4.15 (2H, q, $-OCH_2CH_3$, J = 7 Hz), 2.3-1.7 (6H, m, ring methylenes), 1.95 (3H, s, $-OCOCH_3$), 1.15 (3H, t, $-OCH_2CH_3$). Mass spectrum : 212 (M^+), 153 (M^+-59). Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.26; H, 7.54. Found: C, 62.5; H, 7.64%.

Ethyl-2-acetoxy-2-(cyclohex-1-ene)-acetate 9c: Yield: 84%. IR (neat) : 1740 cm^{-1}. ^1H NMR (CCl_4): δ 5.78 (1H, br s, olefinic), 5.15 (1H, s, -CHOAc), 4.25 (2H, q, $-OCH_2CH_3$, J = 7 Hz), 2.5-2.2 (4H, m, allylic methylenes), 2.2-1.2 (4H, m, other ring methylenes), 2.15 (3H, s, $-OCOCH_3$), 1.15 (3H, t, $-OCH_2CH_3$, J = 7

Hz). Mass spectrum : m/z 226 (M^+), 167 (M^+-59). Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.72; H, 7.96. Found: C, 63.5; H, 7.66%.

Ethyl-2-acetoxy-2-(cyclohept-1-ene)-acetate 10c: Yield: 92%. IR (neat) : 1750, 1740 cm^{-1}. ^1H NMR (CCl_4): δ 6.08 (1H, t, olefinic), 5.15 (1H, s, -C<u>H</u>OAc), 4.14 (2H, q, -OC<u>H</u>$_2$CH$_3$, J = 7 Hz), 2.35-1.15 (10H, m, ring methylenes), 2.08 (3H, s, -OCOCH$_3$), 1.3 (3H, t, -OCH$_2$C<u>H</u>$_3$, J = 7 Hz. Mass spectrum : m/z 240 (M^+), 181(M^+ - 59). Anal. Calcd. for $C_{13}H_{20}O_4$: C, 65.05; H, 8.3. Found: C, 65.21; H, 8.12%.

Ethyl-2-acetoxy-3-phenyl-3-butenoate 11c: Yield: 83%. IR (neat): 1750, 1740 cm^{-1}. ^1H NMR (CCl_4): δ 7.12 (5H, m, aromatic), 5.54 (2H, s, olefinic), 5.30 (1H, s, -C<u>H</u>OAc), 3.91 (2H, q, -OC<u>H</u>$_2$CH$_3$, J = 7 Hz), 2.03 (3H, s, -OCOCH$_3$), 1.03 (3H, t, -OCH$_2$C<u>H</u>$_3$, J = 7 Hz). Mass spectrum : m/z 249 $(M+1)^+$, 207 $[(M+1)^+-43]$, 189 (M^+-59). Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.74; H, 6.45. Found: C, 67.66; H, 6.7%.

Ethyl-2-acetoxy-3-methyl-3-butenoate 12c: Yield: 80%. IR (neat): 1740, 1730 cm^{-1}. ^1H NMR (CCl_4): δ 5.35 (2H, s, olefinic), 5.03-4.94 (1H, m, -C<u>H</u>OAc), 4.15 (2H, q, -OC<u>H</u>$_2$CH$_3$, J = 7 Hz), 2.15 (3H, s, -OCOC<u>H</u>$_3$), 1.78 (3H, s, -C<u>H</u>$_3$ -C = CH$_2$, J = 7 Hz), 1.36 (3H, t, OCH$_2$C<u>H</u>$_3$, J = 7 Hz). Mass spectrum : m/z 186 (M^+), 143 (M^+-43), 127 (M^+-59). Anal. Calcd. for $C_9H_{14}O_4$: C, 58.06; H, 7.52. Found: C, 58.5; H, 7.6%.

Ethyl-2-acetoxy-3-ethyl-3-pentenoate 13c: Yield: 75%. IR (neat) : 1745, 1735 cm^{-1}. ^1H NMR (CCl_4): δ 5.54 (1H, q, olefinic, J = 5.7 Hz), 5.06, 5.03 (1H, 2s, -C<u>H</u>OAc), 4.06 (2H, q, -OC<u>H</u>$_2$CH$_3$, J = 7 Hz), 2.03 (3H, s, -OCOCH$_3$), 1.94 (2H, m, allylic CH$_2$), 1.7, 1.63 (3H, m, vinylic methyls from two geometric isomers viz. ratio (1:2), 1.21 (3H, t, C=C(CH$_2$C<u>H</u>$_3$), J = 7 Hz), 0.84 (3H, t, -OCH$_2$C<u>H</u>$_3$, J = 7 Hz). Mass spectrum : m/z 215 $(M+1)^+$, 173 $[(M+1)^+-42]$, 155 (M^+-59). Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.88; H, 8.41. Found: C, 61.5; H, 8.6%.

PLAP catalysed hydrolysis of acetate 8c-13c: Pig liver acetone powder (PLAP) was prepared as reported earlier[8].

To 0.5 M, pH 8.0 KH_2PO_4 /K_2HPO_4 buffer (20 ml), a racemic acetate (500 mg) in ether (10 ml) was added with stirring at 10-15 ^{0}C. PLAP (600 mg) was added to it and stirring continued. Progress of the hydrolysis was monitored by tlc. When an appropriate degree of hydrolysis took place, the reaction mixture was quenched with 2(N) HCl (5 ml) so that the pH was 6.5. To this, sodium chloride (0.3 g) and ethyl acetate (10 ml) were added and the resulting suspension was vigorously stirred for 0.5 hr. The reaction mixture was filtered and the aqueous and the organic layers were separated. The aqueous layer was extracted with ethyl acetate (3x20 ml) and the combined organic layer was washed with brine (10 ml), dried over anhydrous sodium sulfate and concentrated. The crude product so obtained was purified by column chromatography to get optically pure alcohol and enantiomerically enriched unhydrolysed acetate.

Hydrolysis of 8c: This reaction was carried out with 400 mg of **8c** and 480 mg of PLAP for 64 hr to obtain **8d**. Yield of **8d**: 75 mg (47%); $[\alpha]_D^{25}$ = + 29.0 (C = 1, $CHCl_3$); e.e. = 82%. Yield of unhydrolysed **8e**: 250 mg; $[\alpha]_D^{25}$ = - 28.5 (C = 1, $CHCl_3$); e.e. = 44%.

Hydrolysis of 9c: This reaction was carried out with 500 mg of **9c** and 600 mg of PLAP for 72 hr. Yield of **9d** : 165 mg (81%); $[\alpha]_D^{25}$ = + 35.6 (C = 1, $CHCl_3$); e.e. = 90%. Yield of unhydrolysed **9e** : 285 mg; $[\alpha]_D^{25}$ = -28.5 (C = 1, $CHCl_3$); e.e. = 54%.

Hydrolysis of 10c: This reaction was carried out with 480 mg of **10c** and 576 mg of PLAP for 75 hr. Yield of **10d**: 75 mg (35%); $[\alpha]_D^{25}$ = +108.1 (C = 1, $CHCl_3$) ; e/e = 80%. Yield of unhydrolysed **10e**: 250 mg; $[\alpha]_D^{25}$ = -82.6 (C = 1, $CHCl_3$); e.e. = 34%.

Hydrolysis of 11c: This reaction was carried out with 400 mg of **11c** and 480 mg of PLAP for 74 hr. Yield of **11d** : 60 mg (36%); $[\alpha]_D^{25}$ = + 6.7 (C = 1, $CHCl_3$); e.e. 65%. Yield of recovered **11e**: 160 mg; $[\alpha]_D^{25}$ = -8.8 (C = 1, $CHCl_3$); e.e.= 40%.

Hydrolysis of 12c: This reaction was carried out with 462 mg of **12c** and 555 mg of PLAP for 70 hr. Yield of recovered **12e**: 187 mg; $[\alpha]_D^{25}$ = -15.0 (C = 1, $CHCl_3$); e.e. = 40%.

Hydroloysis of 13c: This reaction was carried out with 560 mg of **13c** and 675 mg of PLAP for 85hr. Yield of recovered acetate **13e**: 300 mg; $[\alpha]_D^{25}$ = -20.9 (C = 1, $CHCl_3$); e.e. = 29%.

Conversion of 9d into vinyl epoxide 14: Reduction of **9d** with $LiAlH_4$ followed by its conversion to **14** was carried out by following exactly the same procedure as that for converting **2a-2c** to **5a-5c.** Yield: 72%, $[\alpha]_D^{25}$ = +3.2 (C = 1, $CHCl_3$). Other physical properties were similar to the one as observed for compound **5b**. Reduction of the vinyl epoxide **14** to R-1-(cyclohex-1-ene)-ethanol **15** was performed as that for **5b** to **6**. Yield of **15**: 45%; $[\alpha]_D^{25}$= + 12.2 (C = 1, $CHCl_3$). Enantiomeric excess of this compound was confirmed to be 90% by using shift reagent based ^1H NMR analysis of the corresponding acetate **16**. The yield of the acetate, obtained by adopting a similar acetylation procedure as that for converting compound **6** to **7**, was 85% and showed a specific rotation value to be $[\alpha]_D^{25}$= + 27.4 (C = 1, $CHCl_3$). Other spectroscopic details were similar to the ones observed for compound **6**.

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