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A VERSATILE PROTOCOL FOR β-HYDROXY-α-AMINO ACIDS : AN APPLICATION TO (4R)-4-[(E)-2-BUTENYL]-4,N-DIMETHYL-L-THREONINE (MeBmt)

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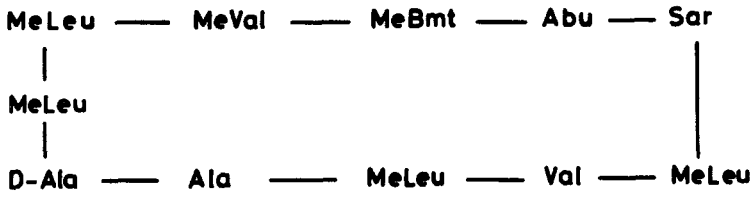
Abstract : *cis-Oxazolidinone derivative (30) readily realised from chiral 2,3-epoxy alcohol (27) had been exploited in the synthesis of (4R)-4-[(E)-2-butenyl]-4,N-dimethyl-L-threonine (2), an unusual β-hydroxy-α-amino acid present in cyclosporin. The intrinsic feature of this approach involved facile isomerisation of cis-oxazolidinone derivative (31) into the trans-isomer (32) whose hydrolysis provided syn-β-hydroxy-α-amino acid.*

β-Hydroxy-α-amino acids[1] form the partial structure of several biologically active peptide molecules[2]. For instance, cyclosporin A (1) contains in its structural framework the unusual and unnatural β-hydroxy-α-amino acid, (4R)-4-[(E)-2-butenyl]-4,N-dimethyl-L-threonine (2). As a part of the ongoing programme, we were interested in developing[3] a versatile methodology which in principle, should provide all the four diastereomers of β-hydroxy-α-amino acids. Our attention was drawn towards readily obtainable[4] optically active cis-oxazolidinone derivative of the type B which



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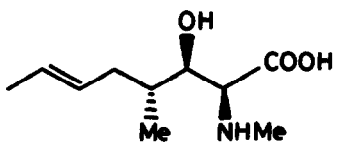

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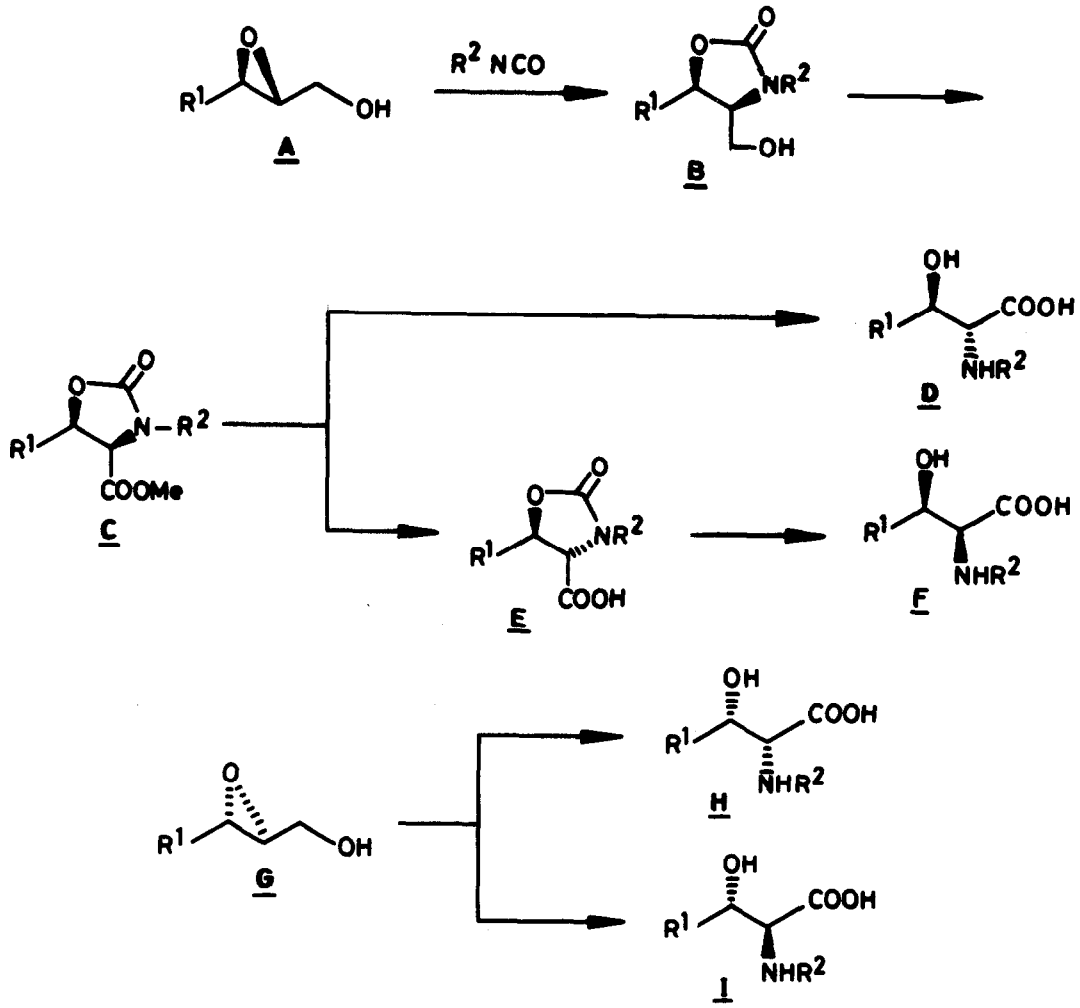
in turn could be realised[5] from optically active 2,3-epoxy alcohol (A). We reasoned that the corresponding oxazolidinone ester (C), obtained by oxidation of the hydroxymethyl group in B, on hydrolysis, should furnish anti-β-hydroxy-α-amino acid (D), whereas subsequent epimerisation[6] of cis-oxazolidinone derivative (C) to a more stable trans-oxazolidinone derivative (E) followed by hydrolysis would give rise to syn-β-hydroxy-α-amino acid (F). Similarly, it becomes apparent that the other

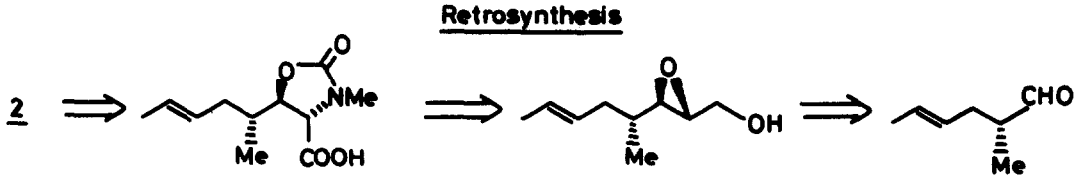
two diastereomers, namely (H) and (I), could be synthesised from the corresponding optically active 2,3-epoxy alcohol[5] (G) (Scheme 1).

Scheme 1



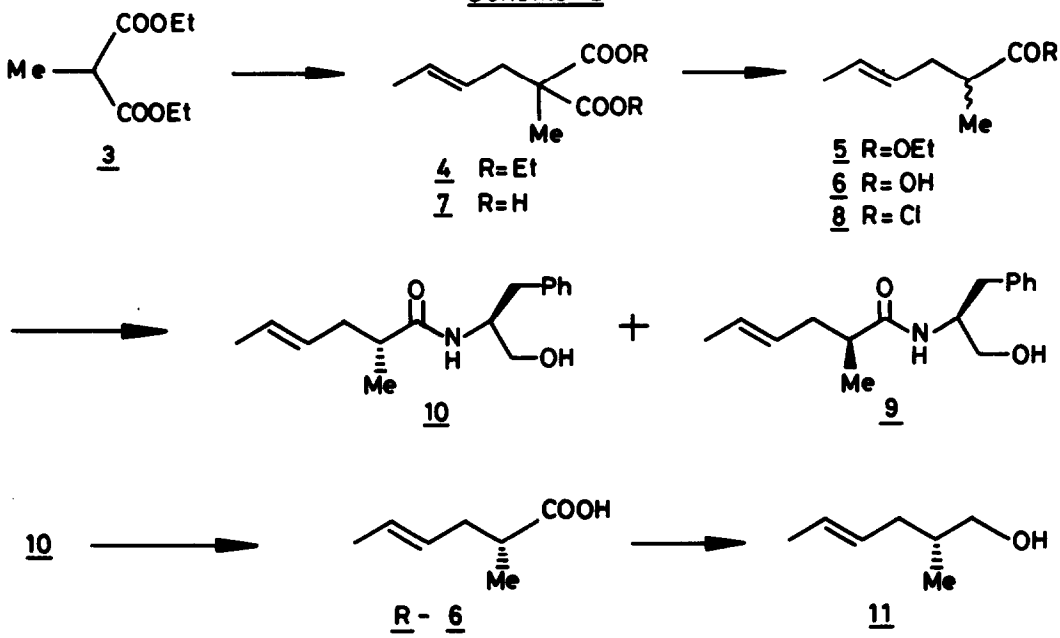
Based on the above approach, MeBmt (2) was re-examined as follows:

Retrosynthesis



Thus, the alkylation of diethyl methylmalonate (**3**) with E-crotyl bromide in the presence of sodium ethoxide gave **4** in almost quantitative yield. Decarboxylative saponification of **4** was then tried employing Krapcho's conditions.[7] Accordingly, **4** and sodium chloride in DMSO containing a trace amount of water were heated under reflux for 18 h to give the monoester (**5**), albeit in only 20% yield. Hydrolysis of **5** with aq. KOH led to the desired acid **6**. In an alternative approach, the diester (**4**) was hydrolysed with an alkali to furnish the solid diacid **7** which consequently underwent facile decarboxylation[8] on distillation to give the monoacid (**6**) in 70% yield (Scheme 2).

Scheme 2

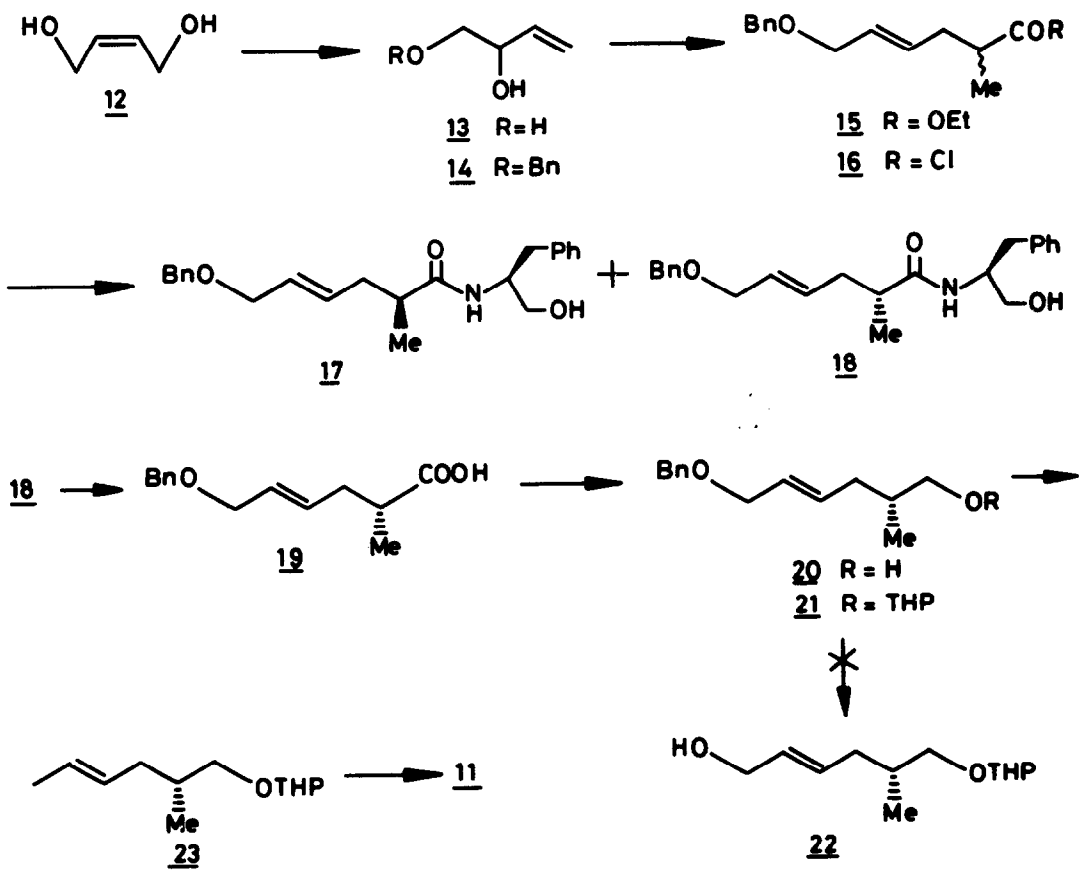


Having obtained the desired monoacid (**6**), the next aim was to resolve the acid as we were interested only in (R)-**6**. The resolution of (±)-**6** was carried out by liquid adsorption chromatography of the diastereomeric mixture of the amides (**9** & **10**) in a directed way - a technique introduced by Helmchen et al.[9] Thus, (±)-**6** was treated with freshly distilled thionyl chloride in dry benzene to give the acid chloride (**8**) which was subsequently treated with phenylalaninol[10] in the presence of triethylamine to give the two diastereomeric amides (**9** & **10**). Both the amides were separated by column chromatography and assigned the structures based on the elution order and proposed postulates of Helmchen et al. The structures (**9** & **10**) were also confirmed by their ^{1}H NMR, IR and mass spectral studies.

The required amide (**10**) on heating with 3N sulphuric acid in a solvent system comprising dioxane and water for 1 h at 90°C gave (R)-**6** in 84% yield. Reduction of (R)-**6** with lithium aluminium hydride in THF under reflux gave the enantiomerically pure alcohol (**11**) in 71% yield. The $[\alpha]_D$ and ^{1}H NMR spectrum of **11** compared well with the reported values; $[\alpha]_D$ +2.4° (c, 1.0, $CHCl_3$), lit.[3b] +2.5° (c, 1.08, $CHCl_3$).

In an alternative approach towards (R)-**6** (Scheme 3), the easily accessible (±)-1-benzyloxy-3-buten-2-ol (**14**) (obtained[11] by the isomerisation of cis-butene-1,4-diol (**12**) to 3-butene-1,2-diol (**13**) followed[12] by monobenzylation) was subjected to Claisen orthoester reaction[13] with triethylorthopropionate containing propionic acid at 140°C to afford **15**. Successive hydrolysis of the ester group with aqueous sodium hydroxide and treatment with thionyl chloride gave the acid chloride (**16**). Treatment of **16** with L-phenylalaninol as a chiral auxillary, in the presence of triethylamine afforded diastereomeric amides (**17** & **18**) which were conveniently separated by silica gel column chromatography. The slower moving fraction containing the required amide (**18**) was hydrolysed

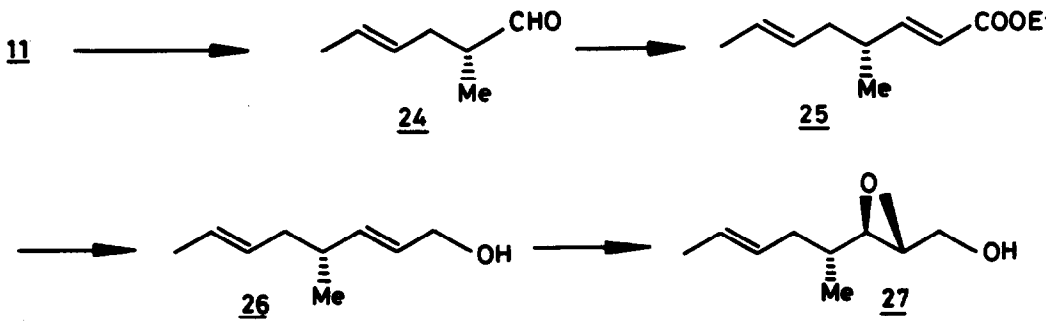
Scheme 3



with dil. sulfuric acid to **19** and then reduced with LAH to the alcohol **20**. After protecting the free hydroxyl group in **20** as a THP ether, the product **21** was reacted with lithium in liquid ammonia[14] for 2 h with the hope to recover the allylic alcohol **22**. However, the major product (90% yield) isolated from the reaction was assigned the structure **23**. The formation of **23** was rather surprising because the cleavage of the C-O bond had occurred between oxygen-allylic group and not between the expected oxygen-benzylic group. Finally, THP group in **23** was cleaved with pyridinium p-toluenesulfonate in refluxing methanol to give **11** (87%) identical with the product obtained

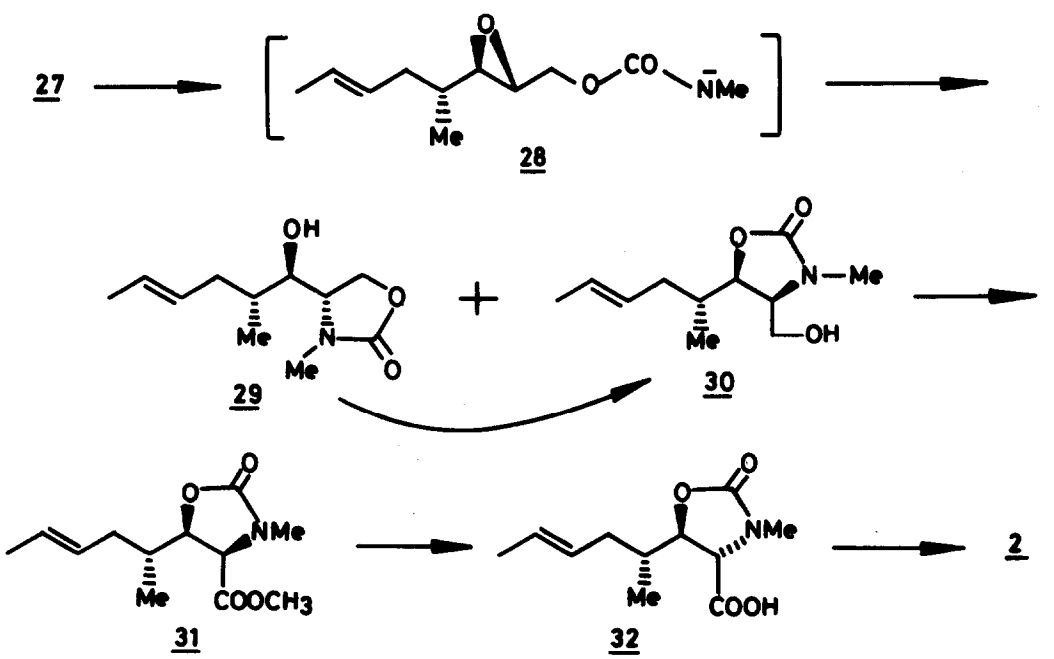
earlier. Swern oxidation of **11** gave a rather unstable aldehyde **24** which without purification was treated with carbethoxymethylenetriphenylphosphorane in benzene to give exclusively the trans-α,β-unsaturated ester (**25**) (Scheme 4). The large coupling constant (16 Hz) between olefinic protons H-2 and H-3 was observed in the ^{1}H NMR spectrum of **25**. Compound **25** was converted into the allylic alcohol derivative **26** with DIBAL-H at -78°C in 80% yield.

Scheme 4



The Sharpless epoxidation[5] of **26**, employing (-) diisopropyl tartrate (DIPT) as a chiral auxillary, at -20°C for 18 h afforded the 2,3-epoxy alcohol (**27**). The stereochemical assignment of **27** was based by taking into account the predictions reported by Sharpless. Compound **27** was treated (Scheme 5) with methyl isocyanate in the presence of sodium hydride in refluxing THF[4] to give

Scheme 5



a chromatographically separable mixture of 1,2- and 2,3-oxazolidinone derivatives (**29** & **30**) in the ratio of 3:2. The cis geometry for **30** was assigned[4] by taking into account the large coupling constant (J = 10.2 Hz) between H-4 and H-5 observed for H-4. The undesired isomer **29** was partially isomerised with NaH to give a further mixture of **29** and **30** in 1:1 ratio.

The combined product **30** was subjected to Jones oxidation and the resulting acid was esterified with diazomethane. The cis-oxazolidinone ester **31** has all the stereochemical centers in conjunction with MeBmt (**2**) except for the C-4 center whose chirality had to be inverted. The transformation of cis product (**31**) into the trans-product (**32**) was successfully effected by employing 0.89 N KOH. The resulting trans-oxazolidinone derivative (**32**) showed small coupling constant (J = 4.7 Hz) between H-4 and H-5 which was in complete agreement with the assigned structure. In addition, $[\alpha]_D$ +30.5° ($CHCl_3$) observed for **32** was in agreement with the literature[3] value (+33.5°).

Finally, **32** was converted into MeBmt (**2**) by the procedure reported by Wenger.[3]

Experimental

FT-IR spectra were determined as neat films or as solutions in $CHCl_3$ using a Perkin-Elmer 683 spectrometer. ^1H NMR spectra were obtained on Varian FT-80 or Jeol PMX-90 spectrometer in $CDCl_3$ containing TMS as an internal standard with chemical shifts (δ) expressed in ppm down field from TMS. Optical rotations were measured on a Jasco DIP 360 polarimeter and all melting points were uncorrected.

(4E)-Ethyl 2-carbethoxy-2-methylhexenoate (4)

To a stirred solution of sodium ethoxide (prepared from 2.9 g of sodium and 300 ml of dry ethanol) was added diethyl methylmalonate (**3**) (20.0 g, 114.9 mmol) at room temperature. After 30 min, E-crotyl bromide (15.5 g, 114.8 mmol) was added dropwise and then the reaction was stirred for 3 h. Solvent was removed and the residue partitioned between water and CH_2Cl_2. The CH_2Cl_2 layer was dried, concentrated to give **4** (22.0 g, 84%); ^1H NMR ($CDCl_3$) : δ 1.24 (t, 6H, J = 7.5 Hz), 1.38 (s, 3H), 1.60 (d, 3H, J = 6.5 Hz), 2.56 (m, 2H), 4.17 (q, 4H, J = 7.5 Hz), 5.45 (m, 2H).

(4E)-2-Methyl hexenoic acid (6)

A solution of **4** (32.0 g, 140 mmol) and 12 N aqueous KOH (59 ml) was heated under reflux for 1 h, cooled and acidified with 6 N HCl. The solid precipitate was filtered, dissolved in acetone and concentrated to give **7** (21.0 g) crystallised from benzene, m.p. 117°C.

Compound **7** (21.0 g) was subjected to distillation at 160°C/11 mm Hg to afford **6** (12.5 g, 70%). ν_{max} (neat) : 3570, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.10 (d, 3H, J = 6.5 Hz), 1.60 (d, 3H, J = 6.0 Hz), 2.20 (m, 3H), 5.40 (m, 2H), 11.0 (bs, 1H). Anal. Calcd. for $C_7H_{12}O_2$: C, 65.6; H, 9.4. Found : C, 65.6; H, 9.35%.

(S)-N-{[(2S,4E)-2-methylhex-4-en]oyl} phenyl alaninol (10) and (S)-N-{[(2R,4E)-2-methylhex-4-en]oyl} phenyl alaninol (9)

Compound **6** (12.5 g, 97 mmol) and thionyl chloride (12 ml) in dry benzene (30 ml) were stirred at room temperature for 16 h and concentrated to afford the acid chloride **8** used as such for next reaction.

8 (14.35 g, 98 mmol) in dry dioxane (50 ml) was added to a solution of phenylalaninol (14.9 g, 98 mmol) and triethylamine (41 ml) in dry dioxan (50 ml) under nitrogen at 5°C. After 1 h, reaction was concentrated, neutralised with 1 N HCl and extracted with CH_2Cl_2. The CH_2Cl_2 layer

was washed with brine, dried and concentrated to afford a mixture of **9** and **10** (20.0 g, 79%). The mixture was subjected to column chromatography on silica gel with ethyl acetate-light petroleum (2:3) as eluent to give the first fraction containing the amide **9** (9.0 g), m.p. 100°C, $[\alpha]_D$ -16.8° (c, 0.24, $CHCl_3$). ν_{max} (KBr) : 3600-3200, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.00 (d, 3H, J = 6.5 Hz), 1.57 (d, 3H, J = 6.3 Hz), 2.0 (m, 4H), 3.78 (d, 2H, J = 7.5 Hz), 3.19 (dt, 2H), 4.0 (bs, 1H), 5.18 (m, 2H), 5.46 (bs, 1H), 7.00 (s, 5H). Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.5; H, 8.9; N, 5.4. Found : C, 73.5; H, 8.8; N, 5.3%.

The second fraction to be isolated gave **10** (8.5 g), m.p. 94°C, $[\alpha]_D$ -28.3°C (c, 0.32, $CHCl_3$). Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.5; H, 8.9; N, 5.4. Found : C, 73.5; H, 8.8; N, 5.3%.

(2R,4E)-2-Methyl-hexen-1-ol (11)

The amide **10** (8.5 g, 32.6 mmol) and 3 N H_2SO_4 (65 ml) were heated at 90°C for 1 h. The reaction mixture was extracted with CH_2Cl_2 and washed with water, dried and concentrated to give (R)-**6** (3.5 g, 84%), $[\alpha]_D$ -11° (c, 0.55, $CHCl_3$).

To **6** (3.5 g, 27.3 mmol) in dry THF (15 ml) was added LAH (1.0 g, 26.3 mmol) at 0°C in small portions and then heated under reflux for 1 h. After usual workup, compound **11** (2.65 g, 71%) was isolated $[\alpha]_D$ +2.4° (c, 1, $CHCl_3$), lit.[3b] $[\alpha]_D$ +2.5° (c, 1.08, $CHCl_3$).

(4E)-Ethyl-6-benzyloxy-2-methyl hexenoate (15)

A mixture of **14** (3.2 g, 17.9 mmol), propionic acid (0.5 ml) and triethylorthopropionate (5.4 ml, 26.9 mmol) was heated at 140°C for 2 h with distillative removal of ethanol. After usual workup followed by purification on silica gel column with ethyl acetate-light petroleum (1:10) as eluent gave **15** (4.2 g, 89%). ν_{max} : 2975, 1740, 1180, 965 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.15 (d, 3H, J = 6 Hz), 1.25 (t, 3H, J = 7.5 Hz), 2.0-2.6 (m, 3H), 3.85 (d, 2H, J = 6 Hz), 4.15 (q, 2H, J = 7.5 Hz), 4.52 (s, 2H), 5.25-5.60 (m, 2H), 7.23 (s, 5H). Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 72.95; H, 8.4%.

(S)-N-{[(2S,4E)-2-Methyl-6-benzyloxyhexen]oyl} phenyl alaninol (17) and (S)-N-{[(2R,4E)-2-methyl-6-benzyloxyhexen]oyl]phenyl alaninol (18)

Compound **15** (2.5 g, 9.54 mmol) was hydrolysed with 2 N aq. KOH (5 ml) in refluxing ethanol (15 ml) for 1 h to afford an acid (2.0 g). The acid and oxalyl chloride (2.18 g, 17.17 mmol) in dry benzene (15 ml) were heated at 70°C for 3 h and then concentrated in vacuo. The resulting residue in dry dioxane (30 ml) was treated with L-phenyl alaninol (1.3 g, 8.5 mmol) and triethylamine (0.8 ml) in dioxane at 5-10°C. After 2 h, it was worked up to afford a crude mixture (2.9 g, 92%) which was chromatographed on a silica gel column with ethyl acetate-light petroleum (1:25). The first fraction to be eluted was **17** (1.36 g), $[\alpha]_D$ -12.2° (c, 2, $CHCl_3$). ν_{max} : 3420, 1665, 1500, 1185, 963 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.10 (d, 3H, J = 6.5 Hz), 2.08 (m, 3H), 2.93 (m, 3H), 3.55 (d, 2H), 3.89 (d, 2H), 4.1 (bs, 1H), 4.52 (s, 2H), 5.62 (m, 2H), 5.78 (bs, 1H), 7.26 (m, 10H).

The second fraction **18** (1.32 g), $[\alpha]_D$ -29.1° (c, 1.4, $CHCl_3$). ν_{max} : 3425, 1664, 1500, 1201, 965 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.15 (d, 3H, J = 6.5 Hz), 2.12 (m, 3H), 2.3 (m, 3H), 3.52 (dd, 2H), 3.92 (d, 2H), 4.05 (bs, 1H), 4.53 (s, 2H), 5.6 (m, 2H), 5.73 (bs, 1H), 7.32 (m, 10H).

(2R,4E)-6-Benzyloxy-2-methyl-hexen-1-ol (20)

A mixture of **18** (1.17 g, 3.18 mmol), 3 N H_2SO_4 (1.5 ml), dioxane (8.2 ml) and water (8.2 ml) was heated at 90°C for 2 h, diluted with water (35 ml) and extracted with chloroform. The

chloroform layer was dried and concentrated to afford the acid **19** (0.63 g, 85%), $[\alpha]_D$ +8.4° (c, 2.6, $CHCl_3$). ^1H NMR ($CDCl_3$) : δ 1.10 (d, 3H, J = 6 Hz); 2.0-2.6 (m, 3H), 3.89 (d, 2H, J = 5 Hz), 4.56 (s, 2H), 5.50-5.75 (m, 2H), 7.25 (s, 5H), 9.75 (bs, 1H).

To a stirred suspension of LAH (0.33 g, 4.2 mmol) in THF (10 ml) was added **19** (0.6 g, 2.5 mmol) in THF (10 ml) at 0°C. The reaction mixture was heated under reflux for 5 h. After usual workup the reaction afforded the alcohol **20** (0.46 g, 85%), $[\alpha]_D$ +4.5° (c, 0.63, $CHCl_3$). ν_{max} : 3400 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.05 (d, 3H, J = 6.5 Hz), 1.60-2.25 (m, 4H), 3.4 (d, 2H), 3.89 (d, 2H), 4.52 (s, 2H), 5.40-5.74 (m, 2H), 7.25 (s, 5H). Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.4; H, 9.1. Found C, 76.25; H, 9.03%.

(2R,4E)-6-Benzyloxy-2-methyl-1-tetrahydropyranyl-hexen-1-ol (21)

A mixture of the **20** (0.8 g, 3.6 mmol), dihydropyran (0.37 g, 4.38 mmol) and toluene-p-sulfonic acid (10 mg) in chloroform (10 ml) was stirred at room temperature for 3 h. After usual workup, the residue was purified by column chromatography on silica gel column with ethyl acetate-light petroleum (1:19) to yield **21** (0.95 g, 86%). ^1H NMR ($CDCl_3$) : δ 1.05 (d, 3H, J = 6.5 Hz), 1.3-2.0 (bs, 6H), 3.2-4.0 (m, 5H), 4.05 (d, 2H), 4.52 (s, 2H), 5.45-5.80 (m, 2H), 7.09 (s, 5H).

(2R,4E)-2-Methyl-hexen-1-ol (11)

Compound **21** (0.85 g, 2.8 mmol) in ether (25 ml) was added slowly to the freshly distilled liq. NH_3 (120 ml) at -33°C. Lithium metal (40 mg, 5.6 mmol) was added over 20 min, and the reaction was stirred for 2 h. It was quenched with solid NH_4Cl and ammonia allowed to evaporate. The residue was partitioned between ether and water. The ethereal layer was washed with brine, dried and concentrated to afford **23** (0.5 g, 90%). ^1H NMR ($CDCl_3$) : δ 1.12 (d, 3H, J = 6.5 Hz), 1.6-2.2 (m, 9H), 3.0-4.1 (m, 6H), 4.52 (s, 1H), 5.4-5.7 (m, 2H).

Compound **23** (0.2 g, 1.0 mmol), PPTS (10 mg) and methanol (10 ml) were heated under reflux for 30 min. After usual workup the crude product was purified on a silica gel column with ethyl acetate-light petroleum (1:4) as eluent to afford **11** (0.1 g, 87%).ν_{max} : 3350 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.93 (d, 3H, J = 7 Hz), 1.62-2.25 (m, 6H), 2.58 (br s, 1H), 3.46 (d, 2H, J = 6.5 Hz), 5.40-5.54 (m, 2H).

(4R,2E,6E)-Ethyl-4-methyl-2,6-octadienoate (25)

To a solution of oxalyl chloride (2.83 ml, 32.4 mmol) in CH_2Cl_2 (50 ml) at -78°C was added dry DMSO (4.68 ml, 66 mmol). After 5 min, **11** (2.65 g, 23.2 mmol) in CH_2Cl_2 (5 ml) was introduced. The resultant white suspension was stirred at -78°C for 30 min and then triethylamine (14.3 ml) was added. After 1 h at -30°C, the reaction mixture was partitioned between water and pentane. The pentane layer was dried, concentrated below 35°C to yield **24** (2.3 g) used as such for next reaction.

24 (2.3 g, 20.5 mmol) and carbethoxymethylenetriphenylphosphorane (7.8 g, 22 mmol) in dry benzene (20 ml) were stirred at room temperature for 2 h and concentrated. The resulting residue was purified by silica gel column chromatography with light petroleum as eluent to afford **25** (2.6 g, 70%), $[\alpha]_D$ -25° (c, 0.5, $CHCl_3$). ν_{max} : 1720 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.03 (d, 3H, J = 6.5 Hz), 1.28 (t, 3H, J = 7 Hz), 1.63 (d, 3H, J = 6.5 Hz), 2.21 (m, 3H), 4.17 (q, 2H), 5.39 (m, 2H), 5.75 (d, 1H, J = 16 Hz), 6.89 (dd, 1H, J = 16.7 Hz).

(2R,3R,4R,6E)-4-Methyl-2,3-epoxy-octa-6-ene-1-ol (27)

To **25** (2.6 g, 14.3 mmol) in CH_2Cl_2 (15 ml) was added DIBAL-H solution in toluene (26 ml, 35 mmol) at -78°C under nitrogen atmosphere. After 30 min, the reaction mixture was worked up by the usual procedure and the residue was chromatographed on silica gel with ethyl acetate-light petroleum (1:4) as eluent to give **26** (1.6 g, 80%), $[\alpha]_D$ -4.7° (c, 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.6-2.0 (m, 4H), 4.1 (m, 2H), 5.51 (m, 4H).

26 (1.6 g, 11.4 mmol) in CH_2Cl_2 (15 ml) was added to a mixture of titanium (IV) isopropoxide (TTIP) (3.4 ml, 11.4 mmol) and (-) diisopropyl tartrate (DIPT) (2.41 ml, 11.34 mmol) in CH_2Cl_2 (20 ml) at -20°C. After 5 min, tert. butyl hydroperoxide (TBHP) (4.3 ml, 22.7 mmol) was added and reaction mixture was stored at -20°C for 18 h. After usual workup the residue was chromatographed on silica gel column with ethyl acetate-light petroleum (1:4) as eluent to give **27** (1.5 g, 85%), $[\alpha]_D$ +22° (c, 0.2, $CHCl_3$). ^1H NMR ($CDCl_3$) : δ 0.91 (d, 3H, J = 6.5 Hz), 1.63 (d, 3H, J = 6 Hz), 2.0 (m, 4H), 2.77 (dd, 1H, J = 6.5 Hz), 2.9 (m, 1H), 3.7 (m, 2H), 3.4 (m, 2H). Anal. Calcd. for $C_9H_{16}O_2$: C, 69.2; H, 10.2. Found : C, 69.0; H, 9.95%.

(4R,5R)-4-Hydroxymethyl-3-N-methyl-5-{[(1R,3E)-1-methyl-3-penten]-1-yl}oxazolidin-2-one (29) and (4R)-3-N-methyl-4-{[(1R,2R,4E)-1-hydroxy-2-methyl-4-hexen]-1-yl} oxazolidin-2-one (30)

A solution of **27** (1.5 g, 9.6 mmol) in dry THF under N_2 was added NaH (0.49 g, 20.6 mmol) followed by methyl isocyanate (0.82 ml, 14.4 mmol). The reaction mixture was heated under reflux for 2 h, cooled to 0°C and decomposed with saturated aqueous ammonium chloride solution. After extracting with ethyl acetate, it was washed with brine, dried and concentrated. The residue was chromatographed on silica gel with ethyl acetate-light petroleum (3:7) as eluent. The first fraction afforded **29** (0.9 g, 44%), $[\alpha]_D$ -15.5° (c, 0.31, $CHCl_3$). ^1H NMR ($CDCl_3$) : δ 0.92 (d, 3H, J = 6.5 Hz), 1.67 (d, 3H, J = 6.5), 2.2 (m, 3H), 2.90 (bs, 1H), 2.96 (s, 3H), 3.6 (m, 1H), 3.8 (m, 2H), 4.06 (dd, 1H, J = 7, 10.2 Hz), 5.4 (m, 2H). Anal. Calcd. for $C_{11}H_{19}NO_3$: C, 62.0; H, 8.9; N, 6.6. Found: C, 61.9; H, 8.9; N, 6.5%.

The second fraction eluted from the column with solvent system ratio (3:1) gave **30** (0.6 g, 29%), $[\alpha]_D$ -10.3° (c, 0.29, $CHCl_3$). ^1H NMR ($CDCl_3$) : δ 0.98 (d, 3H, J = 6.5 Hz), 1.66 (d, 3H, J = 6.5 Hz), 2.25 (m, 3H), 2.90 (bs, 1H), 2.85 (s, 3H), 3.6 (m, 1H), 3.85 (m, 2H), 4.01 (dd, 1H, J = 7, 10.2 Hz), 5.47 (m, 2H). Anal. Calcd. for $C_{11}H_{19}NO_3$: C, 62.0; H, 8.9; N, 6.6. Found : C, 61.9; H, 8.8; N, 6.55%.

(4R,5R)-Methyl-3-N-methyl-5- {[(1R,3E)-1-methyl-3-penten]-1-yl} oxazolidin-2-one-4-carboxylate (31)

To compound **30** (0.6 g, 2.8 mmol) in acetone at 0°C was added Jones reagent (prepared from CrO_3-H_2SO_4-H_2O : 2.67 g - 2.3 ml - 4.0 ml). After 5 h stirring at room temperature, isopropanol (3 ml) was introduced and the mixture filtered. The filtrate was washed with ethyl acetate, dried and concentrated to afford an acid which was treated with excess of diazomethane solution in ether at 0°C followed by concentration. The resulting product was purified by column chromatography on silica gel with ethyl acetate-light petroleum (3:7) as eluent to give **31** (0.46 g, 68%), $[\alpha]_D$ -6.6° (c, 0.4, $CHCl_3$). ν_{max}: 1770 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 0.92 (d, 3H, J = 6.5 Hz), 1.67 (d, 3H, J = 6.3 Hz), 2.22 (m, 3H), 2.96 (s, 3H), 3.77 (s, 3H), 4.22 (dd, 1H, J = 10 Hz), 4.23 (d, 1H), 5.42 (m, 2H). Anal. Calcd. for $C_{12}H_{19}NO_4$: C, 59.75; H, 7.9; N, 5.8. Found : C, 59.7; H, 7.7; N,5.8%.

(4S,5R)-3-N-Methyl-5-[[(1R,3E)-1-methyl-3-penten]-1-yl] oxazolidin-2-on-4-carboxylic acid (32)

A solution of **31** (250 mg, 1.0 mmol) in absolute ethanol (5 ml) and 0.89 N KOH solution (0.2 ml) was heated under reflux for 30 min, concentrated and partitioned between water and ethyl acetate. The aqueous layer was acidified with dil. HCl, extracted with ethyl acetate, dried and concentrated to afford **32** (188 mg, 80%), m.p. 78°C, lit.[3a] m.p. 81-82°C, $[\alpha]_D$ +30.5° (c, 0.26, $CHCl_3$), lit.[3a] $[\alpha]_D$ +33.5° (c, 1, $CHCl_3$). ^1H NMR ($CDCl_3$) : δ 0.96 (d, 3H, J = 6.5 Hz), 1.66 (d, 3H, J = 6.3 Hz), 1.60-2.35 (m, 3H), 2.93 (s, 3H), 4.0 (d, 1H, J = 4.7 Hz), 4.35 (dd, 1H, J = 4.7, 5.3 Hz), 5.4 (m, 2H), 6.60 (bs, 1H).

Partial isomerisation of 29

Compound **29** (0.9 g, 4.2 mmol) and 98% NaH (0.048 g, 2 mmol) in dry THF (10 ml) was stirred at room temperature for 1 h. After usual workup, the residue was chromatographed on a column of silica gel with ethyl acetate-light petroleum (3:7) to afford **29** (0.32 g) and **30** (0.26 g).

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