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(-)-β-PINENE AS CHIRAL PROMOTER. STEREOSPECIFIC ACCESS TO (-)-γ-AMINO-β(R)-HYDROXYBUTYRIC ACID (GABOB) AND (R)-CARNITINE.2[1]

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Abstract - The stereochemical correlation between the ene adducts 2 and 4a and their products of alkaline hydrolysis is reported. Starting from 2, by using a degradative sequence, a stereocontrolled approach to γ-amino-β(R)-hydroxybutyric acid (GABOB) 8f and (R)-carnitine hydrochloride 8g is described.

In the course of studies involving the synthesis of medicinally important compounds, our attention was drawn by the ability of β-pinene 1 to promote, in an ene reaction, the creation of a new chiral center with good to excellent enantiomeric excess. For example, $TiCl_4$-catalysed reaction between (1S,5S)-(-)-β-pinene 1 and chloral led to 2 as the sole diastereomer,[2] whilst $AlCl_3$-catalysed addition of methyl glyoxylate produced a 85:15 mixture of diastereomers.[3] In the latter paper, Gill *et al.* proposed the net retention of stereochemistry at the exocyclic center of 2 during alkaline hydrolysis of the trichloromethyl group. Not long after, Wynberg and Staring[4] claimed the complete inversion of stereochemistry for the same kind of reaction. We therefore decide to clarify these contradictory reports by correlating the adducts 2 and 4a (obtained as major diastereoisomer by reacting 1 with ethyl glyoxylate) as well as their products of alkaline hydrolysis with compounds of known absolute configuration (Scheme I). Herein we describe the conversion of these adducts into (R)-(+)- and (S)-(-)-diethyl malate acetate 8a and 8b, (R)-(+)-diethyl methoxy succinate 8c, (R)-carnitine hydrochloride 8g and (-)-GABOB 8f, thus connecting in a single homogeneous chemical correlation all these compounds.

Phase-transfer catalysed alkaline hydrolysis ($NaOH$,n-$Bu_4N^+HSO_4^-$, CH_2Cl_2-H_2O) of the optically pure 2, known to possess S configuration[5] at the exocyclic center, and subsequent esterification (30%NaOH, EtI, HMPA, r.t.)[6] gave the hydroxy ester 5a,$[\alpha]_D^{20}$ -8.9°(c 2.17,CH_2Cl_2), which was in turn acetylated to produce 5b. Conversion of 5b into 8a was achieved by using a modification of the sequence devised by Spencer and Hill[7a] (Scheme II). The reaction of 5a with m-chloroperbenzoic acid (CH_2Cl_2,0°C,24 h) followed by acid-catalysed rearrangement (acetone, 0.1 N HCl, 3 h, r.t.) provided 7a,$[\alpha]_D^{20}$ -68.9° (c 0.92,CH_2Cl_2). For the degradation of the monoterpenoid moiety, 7a was treated with Jones' oxidant (acetone, 15 min, r.t.) and the resulting crude mixture was further oxidised with RuO_2-$NaIO_4$ in two-

phase system (MeCN-CCl_4-H_2O)[7b] to give, after esterification (oxalyl chloride, CH_2Cl_2, cat. DMF, 2 h, r.t.; EtOH, 2 h, r.t.), (R)-(+)-diethyl malate acetate 8a, $|\alpha|_D^{20}$ +15.7°(c 1.2,CH_2Cl_2) with 84% enantiomeric excess (e.e.).[8]

Inversion of the exocyclic chiral center of 5a, via sequential mesylation followed by solvolysis with cesium acetate in HMPA[9], furnished the acetate 4b,$|\alpha|_D^{20}$ -39.4°(c 1.55,$CHCl_3$), which was subjected to the same degradation pathway leading to (S)-(-)-diethyl malate acetate 8b,$|\alpha|_D^{20}$ -15.4°(c 1.4, $CHCl_3$).

These findings clearly account for a near complete inversion of the configuration at the center bearing the hydroxy group during the alkaline hydrolysis of 2. Moreover, to the adduct 4a,$|\alpha|_D^{20}$-32.4° (c 2.33, CH_2Cl_2), resulting from $FeCl_3$-catalysed ene reaction between 1 and ethyl glyoxylate, the prevalent S configuration (82% d.e.) could be attributed and this was substantiated by conversion to 8b,$|\alpha|_D^{20}$ -15.4°(c 1.4,$CHCl_3$).

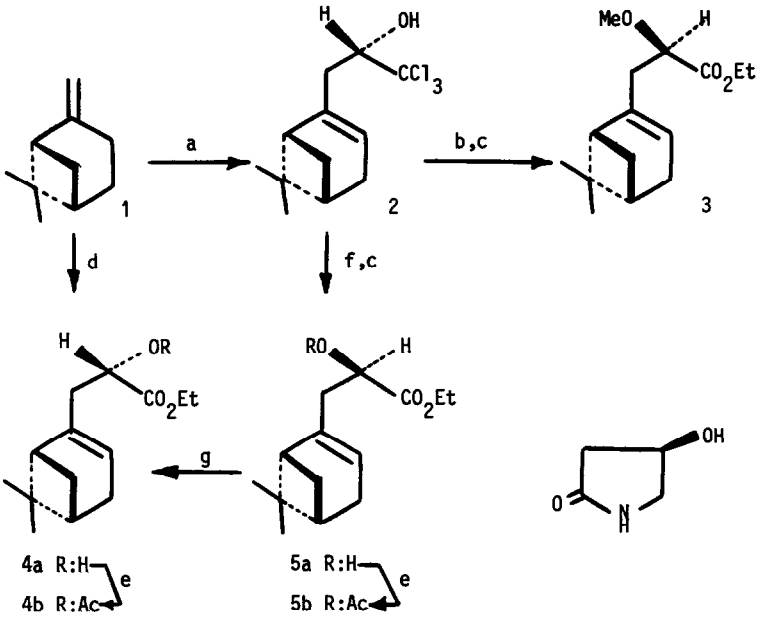
We also established the absolute configuration of the methoxy acid arising from treatment of 2 with sodium methoxide in methanol.[3] (R)-(+)-diethyl methoxy succinate 8c,$|\alpha|_D^{20}$ +42.2°(c 1.2,CH_2Cl_2) was recovered from the usual degradation of 3, further on confirming an almost complete inversion of stereochemistry at the chiral center under investigation. Previous stereochemical assignments for 3[3] must be therefore reversed.

The good feasibility of the synthetic pathway outlined above could be also exploited for a stereo specific access to two pharmacologically important compounds, e.g. (R)-carnitine 8g, a drug widely used for the treatment of myocardial ischemia[10], and (-)-γ-amino-β(R)-hydroxybutyric acid 8f, a nervous inhibitory neurotransmitter[11] extensively clinically tested in the treatment of human epilepsy.[12] Thus, $LiAlH_4$ reduction (THF,4 h, reflux) of the crude hydroxyacid obtained from 2, produced the diol 6a,$|\alpha|_D^{20}$ -19.4°(c 1.9,$CHCl_3$), which was converted, through the agency of PPh_3-CCl_4 system (pyridine, r.t., 4 h)[13], into the chlorohydrin 6b and thence acetylated to afford 6c, $|\alpha|_D^{20}$ -25.4°(c 1.1,CH_2Cl_2). By using the usual degradation pathway, ethyl 4-chloro-3(R)-acetoxybutyrate 8d,$|\alpha|_D^{20}$ +12.3°(c 2.7, $CHCl_3$) was obtained in good overall yield.

The chlorine atom in 8d was instrumental in the development of an efficient three-step process for converting 8d into GABOB 8f. Removal of the acetoxy group in 8d with 3% HCl-EtOH at r.t. for 48 h gave 8e, $|\alpha|_D^{20}$ +19.3° (c 1.2, CH_2Cl_2), in quantitative yield. Exposure of the hydroxy ester 8e to 25% NH_4OH at 80°C for 3 h promoted intramolecular lactamisation to 4(R)-hydroxy-2-pyrrolidinone 9[14],$|\alpha|_D^{20}$ + 56.1°(c 1.3,H_2O), which by subsequent hydrolysis with 1N LiOH(r.t., overnight) afforded (R)-(-)-GABOB 8f, $|\alpha|_D^{20}$ -19.1°(89% e.e.)[15], in 66% overall yield from 8e. Finally, treatment of 8e with dimethylamine in EtOH, followed by acid-catalysed hydrolysis (3N HCl, 3 h, reflux) according to Sih[16], produced (R)-(-)-carnitine 8g as hydrochloride, $|\alpha|_D^{20}$ -20.1°(85% e.e.)[17], m.p. 142-5°C, in 56% overall yield.

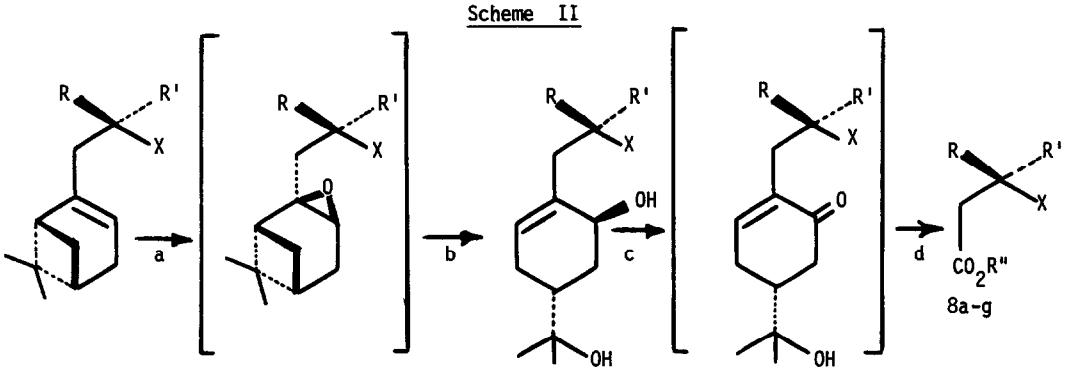
Our findings described above not only correct previous stereochemical assignments but also confirm the absolute configurations proposed for (-)-GABOB[18] and (-)-carnitine and allow a useful entry for a number of four-carbon chiral building blocks.

Scheme I



Reagents: a)Cl_3C-CHO,$FeCl_3$; b)MeONa,MeOH; c)30% NaOH,HMPA,EtI; d)EtO_2C-CHO,$FeCl_3$;
e)Ac_2O,THF,DMAP; f)40% NaOH,CH_2Cl_2-H_2O,$Bu_4N^+HSO_4^-$; g)MsCl-py, then AcOCs,HMPA

Scheme II



3 R:OMe,R':H,X:CO_2Et
4b R:H,R':OAc,X:CO_2Et
5b R:OAc,R':H,X:CO_2Et
6a R:OH,R':H,X:CH_2OH
6b R:OH,R':H,X:CH_2Cl
6c R:OAc,R':H,X:CH_2Cl

7a R:OAc,R':H,X:CO_2Et
7b R:H,R':OAc,X:CO_2Et
7c R:OMe,R':H,X:CO_2Et
7d R:OAc,R':H,X:CH_2Cl

8a R:OAc,R':H,R":Et,X:CO_2Et
8b R:H,R':OAc,R":Et,X:CO_2Et
8c R:OMe,R':H,R"Et,X:CO_2Et
8d R:OAc,R':H,R":Et,X:CH_2Cl
8e R:OH,R':H,R"Et,X:CH_2Cl
8f R:OH,R':H,R":H,X:CH_2NH_2
8g R:OH,R':H,R":H,X:$CH_2NMe_3^+Cl^-$

Reagents: a)MCPBA,CH_2Cl_2; b)acetone-0.1N HCl; c)Jones,acetone; d) $RuO_2(H_2O)_n$-$NaIO_4$,CCl_4-H_2O-MeCN
or $KMnO_4$-$Bu_4N^+HSO_4^-$,CH_2Cl_2-AcOH-H_2O

EXPERIMENTAL

M.p.s. were measured on a Büchi capillary apparatus and are uncorrected. I.r. spectra were recorded on Perkin-Elmer 257 spectrometer as liquid film unless otherwise stated. ^{1}H-N.m.r. spectra were recorded on a Bruker WP-80 (80 MHz) instrument and chemical shifts are quoted in p.p.m. relative to tetramethylsilane as internal standard using deuterochloroform as solvent unless otherwise stated. Optical rotation measurements were obtained in dichloromethane(unless otherwise stated) on a Perkin-Elmer 241 polarimeter. Thin-layer chromatography(t.l.c.) were performed on glass plates pre-coated with Merck Kieselgel 60GF$_{254}$ and spots were located with a vanillin-sulphuric acid-EtOH spray reagent. Silica gel flash chromatography (f.c.) refers to the method of Still et al.(Ref. 19). (-)-α-pinene, $|\alpha|_D^{20}$ -21.0°(neat)(92% e.e.) was purchased from Fluka. Ethyl glyoxylate was prepared according to the procedure of Kelly.[20]

1,1,1-Trichloro-3|(1S,5S)-6,6-dimethylbicyclo|3.3.1|hept-2-enyl|propan-2(S)-ol 2. To a stirred ice-cooled mixture of 1 (15.6 mL, 0.1 mol) and anhydrous chloral (9.8 mL,0.1 mol) under nitrogen was added anhydrous $FeCl_3$ (325 mg, 2 mmol) and stirred overnight. The reaction mixture was dissolved in EtOAc, washed with water, dried and evaporated to dryness. F.c.(cyclohexane-CH_2Cl_2,4:1) provided 2 (21.3 g,75%) as a colourless oil, $|\alpha|_D^{20}$ -50.8°(c 1.11)|lit.[2]: -48.2°(c 0.515,CCl_4)|; R_F(hexane-CH_2Cl_2 1:1) 0.4(violet); δ_H 0.87(3H,s,9-H),1.20(1H,d,J 8.4Hz,7a-H),1.27(3H,s,8-H),2.61(1H,br d,J 4.8Hz,OH), 2.76(1H,d quint,J_{AB} 14.4,$J_{3',2'}$~$J_{3,3'}$~$J_{3,4}$ 2.1Hz,3'-H),3.98(1H,ddd,J 9.1,4.8,2.1Hz,2'-H),5.44(1H,m, 3-H).

Ethyl 2(S)-Hydroxy-3|(1S,5S)-6,6-dimethylbicyclo|3.3.1|hept-2-en-yl|propanoate 4a. Treatment of 1 with ethyl glyoxylate as in the preceding experiment, followed by f.c.(CH_2Cl_2) gave 4a as a colourless oil (60%), $|\alpha|_D^{20}$ -32.4°(c 2.33); R_F(CH_2Cl_2) 0.3(reddish brown); i.r. 3480,1735 cm^{-1}; δ_H 0.81(3H,s, 9-H),1.14(1H,d,J 8.3Hz,7a-H),1.24(3H,s,8-H),1.26(3H,t,J 7.0Hz,CH_2Me),2.58(1H,br d,J 3.8Hz,OH),4.12 (1H,br q,J 4.0Hz,2'-H),4.17(2H,q,J 7.0Hz,CH_2Me),5.35(1H,m,3-H).

Ethyl 2(R)-Methoxy-3|(1S,5S)-6,6-dimethylbicyclo|3.3.1|hept-2-en-2-yl| propanoate 3. To a stirred solution of MeONa (10 g, 185 mmol) in MeOH (200 mL) at 0°C was added dropwise a solution of 2 (10 g, 35 mmol) in MeOH(100 mL). The mixture was stirred overnight at room temperature. After the reaction mixture had been refluxed for 4 h, the bulk of MeOH was removed under reduced pressure and water was added. This solution was extracted with Et_2O and the organic layer was discharged. The aqueous solution was acidified with 10% H_2SO_4 and extracted with Et_2O. The combined extracts were washed with water,dried and evaporated. The resulting residue (5.5 g) was dissolved in HMPA (70 mL), 30% aq NaOH (5 mL) was added and the mixture was stirred for 30 min before addition of EtI (8.5 mL,105 mmol). The solution was allowed to stir overnight, quenched with 10% H_2SO_4 and extracted with Et_2O. The combined organic extracts were washed with sat. $NaHSO_3$ solution, water, dried and evaporated.F.c.(cyclohexane-CH_2Cl_2,1:1) gave 3 (5.6 g,63%) as a colourless oil, $|\alpha|_D^{20}$ +7.3°(c 1.77); R_F(cyclohexane-CH_2Cl_2,1:1) 0.3 (reddish brown); i.r. 1735 cm^{-1}; δ_H 0.81(3H,s,9-H),1.13(1H,d,J 8.3Hz,7a-H),1.25 (3H,s,8-H),1.27(3H,t,J 6.4Hz,2'-H),4.19(2H,q,J 7.1Hz,CH_2Me),5.30(1H,m,3-H).

Ethyl 2(S)-Acetoxy-3|(1S,5S)-6,6-dimethylbicyclo|3.3.1|hept-2-en-2-yl| propanoate 4b. (a) From 5a. 5a(5.0 g, 21 mmol) was dissolved in dry pyridine (50 mL) and mesyl chloride (1.8 mL, 23.2 mmol) was cautiously added at 0°C. The solution was stirred at r.t. for 1 h. The mixture was diluted with Et_2O and washed successively with 10% H_2SO_4, sat. $NaHCO_3$ sol. and brine. The solvent was evaporated to give the crude mesylate which was dissolved in HMPA (50 mL). Cesium acetate (5.0 g,26 mmol) was added and the mixture was heated under stirring at 80°C for 3 h. After cooling, the mixture was diluted with Et_2O, washed thoroughly with water, dried and evaporated. F.c.(cyclohexane-CH_2Cl_2,1:1) yielded 4b (4.4 g, 75%) as a colourless oil, $|\alpha|_D^{20}$ -39.4°(c 1.55); R_F(CH_2Cl_2) 0.25(reddish brown),i.r. 1745 cm^{-1}; δ_H 0.80(3H,s,9-H),1.13(1H,d,J 8.3Hz,7a-H),1.21(3H,s,8-H),1.22(3H,t,J 7.1Hz,MeCH$_2$),2.10(3H,s,OAc) 2.44(2H,m,3'-H),4.15(2H,q,J 7.1Hz,CH_2Me),4.90(1H,dd,J 7.7,6.1Hz,2'-H),5.32(1H,m,3-H).
(b) From 4a. The title compound was obtained as described for 5b in 93% yield, $|\alpha|_D^{20}$-39.3°(c 2.30).

Ethyl 2(R)-Hydroxy-3|(1S,5S)-6,6-dimethylbicyclo|3.3.1|hept-2-en-2-yl| propanoate 5a. To a vigorously stirred solution of 2 (10.0 g, 35.3 mmol) in CH_2Cl_2(100 mL) a solution of NaOH(40.0 g,1 mol) in water (60 mL) and tetra n-butylammonium hydrogensulphate (10.0 g,29.5 mmol) were added. The mixture was stirred at r.t. overnight, then it was cooled,carefully acidified with 20% H_2SO_4 and extracted thoroughly with Et_2O. Usual work-up gave an amorphous residue (5 g). This was treated in the same manner as described for the corresponding methoxy acid (vide supra) to produce, after f.c.(CH_2Cl_2), the corresponding hydroxy ester 5a (5 g, 60%) as a colourless oil, $|\alpha|_D^{20}$-8.9°(C 2.17), R_F(CH_2Cl_2) 0.3(reddish brown), i.r. 3480,1735 cm^{-1}; δ_H 0.83(3H,s,9-H),1.13(1H,d,J 8.1Hz,7a-H),1.17(3H,s,8-H), 1.30(3H,t,J 7.2Hz,MeCH$_2$),2.34(2H,m,3'-H),2.55(1H,br s, OH),4.20(1H,t,J 6.4Hz,2'-H),4.22(2H,q,J 7.2 Hz,CH_2Me),5.35(1H,m,3-H).

Ethyl 2(R)-Acetoxy-3|(1S,5S)-6,6-dimethylbicyclo|3.3.1|hept-2-en-2-yl| propanoate 5b. The hydroxy ester 5a (7.2 g, 30 mmol) was dissolved in dry THF (100 mL) and treated with acetic anhydride (4.3 mL, 45 mmol) and 4-dimethylaminopyridine (1.0 g,8.2 mmol) at r.t. for 3 h. The solution was diluted with EtOAc and washed with 2N H_2SO_4, sat. $NaHCO_3$ sol., water and finally with brine. Removal of the solvent gave a residue which, after f.c.(cyclohexane-CH_2Cl_2, 1:1), gave 5b (7.7g, 91%) as a colour-

less oil, $|\alpha|_D^{20}$ -3.8°(c 1.15); $R_F(CH_2Cl_2)$ 0.25(reddish violet), δ_H 0.80(3H,s,9-H),1.07(1H,d,J 8.6Hz, 7a-H),1.25(3H,s,8-H),1.26(3H,t,J 7.0Hz,CH_2Me),2.06(3H,s,OAc),2.28(1H,br dt,J 8.6,1.8Hz,7b-H),2.46 (2H,m,3'-H),4.19(2H,q,J 7.0Hz,CH_2Me),5.05(1H,t,J 6.6Hz,2'-H),5.34(1H,m,3-H).

1-Chloro-3|(1S,5S)-6,6-dimethylbicyclo|3.3.1|hept-2-en-2-yl| propan-2(R)-yl acetate 6c. The alcohol 6b was acetylated in the same manner as described for 5a to produce the acetate 6c as a colourless oil in 93% yield; $|\alpha|_D^{20}$ -25.4°(c 1.1), R_F(hexane-CH_2Cl_2,1:1) 0.3(violet); δ_H 0.81(3H,s,9-H),1.10(1H, d,J 8.3Hz,7a-H),1.26(3H,s,8-H),2.30(2H,m,3'-H),3.63 and 3.54(AB part of ABX pattern,J 11.5,5.2,4.6 Hz,1'-H),5.03(1H,dddd,J 4.6,5.2Hz,2'-H),5.33(1H,m,3-H).

3-|(1S,5S)-6,6-dimethylbicyclo|3.3.1|hept-2-en-2-yl|propan-1,2(R)-diol 6a. A solution of the crude acid from the hydrolysis of 2 (12.5 g, 59 mmol) in dry THF (125 mL) was dropwise added to a stirred suspension of $LiAlH_4$ (6.7 g, 177 mmol) in dry THF (125 mL) and the reaction mixture was refluxed for 4 h. After cooling to r.t., the reaction was quenched according to Micovic.[21] The organic layer was evaporated and the residue dissolved in EtOAc, washed with sat. ammonium sulphate sol., dried and evaporated in vacuo. F.c.(CH_2Cl_2-Et_2O,7:3) gave 6a (9.8 g, 84%) as a colourless oil, $|\alpha|_D^{20}$ -19.4° (c 1.19); R_F(CH_2Cl_2-Et_2O,7:3) 0.2(brown); i.r. 3380,1650 cm^{-1}; δ_H 0.81(3H,s,9-H),1.10(1H,d,J 8.3Hz,7a-H), 1.24(3H,s,8-H),1.77(1H,br d, J 5.7Hz,OH), 3.36 and 3.44(AB part of ABX pattern,J 11.2,8.5,6.9Hz,1'-H), 3.60(1H,m,2'-H),5.33(1H,m,3-H).

1-Chloro-3|(1S,5S)-6,6-dimethylbicyclo|3.3.1|hept-2-en-2-yl|propan-2(R)-ol 6b. The alcohol 6a(10.4 g, 53 mmol) in dry pyridine (100 mL) was treated at 0°C with PPh_3 (29.0 g,110 mmol) and CCl_4(5.3 mL, 55 mmol). The solution was stirred at r.t. under nitrogen for 4 h, then poured onto 50% H_2SO_4-crushed ice and extracted with EtOAc. Usual work-up followed by f.c.(cyclohexane-CH_2Cl_2,1:1)gave 6b (6.1 g, 53%) as a colourless oil, $|\alpha|_D^{20}$ -25.5°(c 0.86), $R_F(CH_2Cl_2)$ 0.35(violet); δ_H 0.82(3H,s,9-H),1.12 (1H,d,J 8.3Hz,7a-H),1.26(3H,s,8-H),1.98(1H,br s,OH),3.47 and 3.60(AB part of ABX pattern, J11.4,6.4, 3.8Hz,1'-H), 3.80(1H,br dq,J 6.4,3.8Hz,2'-H),5.37(1H,m,3-H).

Ethyl 2(R)-Acetoxy-3|4(R)-(1-hydroxy-1-methylethyl-6(S)-hydroxy-1-cyclohexen-1-yl|propanoate 7a. A solution of 5b (2.8 g, 10 mmol) in CH_2Cl_2 (40 mL) was stirred at 0°C and a slight excess of recrystallised standardised m-chloroperbenzoic acid was added portionwise and the mixture was stirred overnight at r.t. The reaction mixture was diluted with more CH_2Cl_2, washed successively with sat. $NaHCO_3$ sol., brine and dried. Evaporation gave a crude epoxide which was treated with a (1:1) mixture of acetone and 0.1N HCl (40 mL)for 3 h at r.t. Usual work-up followed by f.c.(EtOAc-cyclohexane, 1:1) gave 7a (1.47 g,47%) as white needles,m.p. 98-9°C(Et_2O), $|\alpha|_D^{20}$ -68.9°(c 0.92), R_F(EtOAc) 0.3 (violet); i.r. 3310,3260,1748 cm^{-1}; δ_H 1.19(6H,s,8-H and 9-H),1.27(3H,t,J 6.7Hz,CH_2Me), 2.10 (3H,s,OAc), 2.47 and 2.76(AB part of ABX pattern,J 14.6,8.3,5.6Hz,3'-H),4.16(1H,br t,J 2.4,6-H),4.19 (2H,q,CH_2Me),5.19(X part of ABX,d,J 8.3,5.6Hz,2'-H),5.68(1H,br d,J 5.0Hz,2-H).

Ethyl 2(S)-Acetoxy-3|4(R)-(1-hydroxy-1-methylethyl)-6(S)-hydroxy-1-cyclohexen-1-yl|propanoate 7b. The 2(S)-acetoxy derivative 4b was treated in the same manner as described for the corresponding 2(R)-derivative (vide supra) to produce 7b in 49% yield, m.p. 116-7°C(Et_2O), $|\alpha|_D^{20}$ -87.7° (c 1.10); δ_H 1.20 (6H,s,8-H and 9-H),1.29(3H,t,J 7.1Hz,MeCH$_2$),2.11(3H,s,OAc),2.60(2H,br d,J 6.6Hz,3'-H),4.12(1H,m,6-H), 4.17(2H,q,J 7.1Hz,CH_2Me),5.22(1H,t,J 6.6Hz,2'-H),5.67(1H,br d,J 4.1Hz, 2-H).

Ethyl 2(R)-Methoxy-3|4(R)-(1-hydroxy-1-methylethyl)-6(S)-hydroxy-1-cyclohexen-1-yl|propanoate 7c. This compound was prepared from 3 in a manner identical to that described for 7a. F.c.(EtOAc-cyclohexane,4:1) of the crude product gave the title compound in 53% yield as colourless needles,m.p.94-5°C (Et_2O), $|\alpha|_D^{20}$ -66.3°(c 0.97), R_F(CH_2Cl_2-hexane, 1:1) 0.3(reddish brown), δ_H 1.20(6H,s,8-H and 9-H),1.28 (3H,t,J 7.1Hz,MeCH$_2$),2.35 and 2.62(AB part of ABX syst, J 14.8,9.0,4.4 Hz,3'-H),3.21(1H,br s,OH),3.40 (3H,s,OMe),3.87(1H,dd,J 9.0,4.4 Hz,2'-H),4.06(1H,br t,J 2.4Hz,6-H),4.22(2H,q,J 7.1Hz,CH_2Me),5.71(1H, br d,J 4.1 Hz, 2'-H).

α,α-Dimethyl-4|2(R)-Acetoxy-3-chloro-prop-1-yl|5(S)-hydroxy-3-cyclohexene-1(R)-methanol 7d. This compound was prepared in a manner identical to that described above. F.c.(EtOAc-cyclohexane,4:1) of the crude product gave 7d as colourless needles, m.p. 117-8°C(Et_2O), $|\alpha|_D^{20}$ -65.9° (c 1.11), δ_H 1.18(6H,s, 8-H and 9-H),1.50(1H,br s, OH), 2.02(3H,s,OAc),ABMNX system for 2'-H, 1'-H and 3'-H at 5.25(dddd) 3.56(dd) and 3.67(dd), 2.30(dd) and 2.57(dd), respectively) with J(3',3') 14.4Hz,J(1',1') 11.8,J(2', 3') 7.7 and 5.9,J(1',2') 5.6 and 4.8; 4.16(1H,br s,$W_{\frac{1}{2}}$ 9.5Hz,6-H),5.68(1H,br d,J 4.3Hz,2-H).

(R)-Malic acid diethyl ester acetate 8a. Jones' reagent was added dropwise at r.t. to a stirred solution of 7a (3.2 g,10 mmol) in acetone (70 mL) until the orange colour persisted. After a further 15 min, the mixture was diluted with water and the acetone removed in vacuo. The residue was extracted with EtOAc and extract washed with sat. ammonium sulphate sol. and evaporated to dryness. The residue was dissolved in a mixture of MeCN(45 mL), CCl_4(45 mL) and water (70 mL). Stirring was initiated and $NaIO_4$ (13.0 g, 61 mmol) was added. After several minutes, $RuO_2(H_2O)_n$ (50 mg) was added and stirring was continued overnight. The heterogeneous mixture was filtered and diluted with CH_2Cl_2 (100 mL) and the aq. and organic phases partitioned. The aq. phase was extracted several times with CH_2Cl_2 and the combined organic extracts were concentrated. The resulting residue was dissolved in Et_2O and extracted with sat. $NaHCO_3$ sol. The combined aq. phases were acidified with 20% H_2SO_4 and extracted (3x) with Et_2O.Evaporation of the organic layers gave the crude acid which was dissolved

in CH_2Cl_2 (50 mL) and treated with oxalyl chloride (2.5 mL,29 mmol) in the presence of a drop of DMF. After 2 h the solvent was removed in vacuo and the residue was taken up in THF (30 mL) and added under stirring to dry EtOH (80 mL). The solution was stirred for 2 h and concentrated. F.c.(cyclohexane-EtOAc,4:1) afforded 8a (1.05 g, 45%) as a colourless oil, $|\alpha|_D^{20}$ +15.7°, $|\alpha|_{365}^{20}$ +38.0°(c 1.2,$CHCl_3$)(84% e.e.).

(S)-(-)-Malic diethyl ester acetate 8b. This compound was prepared in a manner identical with that described for 8a in 39% yield; $|\alpha|_D^{20}$ -15.4°, $|\alpha|_{365}^{20}$ -36.6° (c 1.4,$CHCl_3$)(82% e.e.).

Ethyl 4-Chloro-3(R)-acetoxybutyrate 8d. This compound was obtained as described for 8a in 48% yield as a colourless oil, $|\alpha|_D^{20}$ +12.3°(c 2.7,$CHCl_3$);δ_H 1.23(3H,t,J 6.7Hz,$\underline{Me}CH_2$),2.07(3H,s,OAc),4.15(2H,t, J 6.7Hz,CH_2Me); 2.71(d), 3.70(d) and 5.38(tt) for 2-H,4-H and 3-H,respectively(A_2M_2X pattern with $J_{2,3}$ 6.6,$J_{2,4}$ 4.7Hz).

(R)-Methoxy succinic diethyl ester 8c. Jones' reagent was added dropwise at r.t. to a stirred solution of 7a (3.0 g, 10.5 mmol) in acetone (70 mL) until the orange colour persisted. After a further 20 min the mixture was diluted with water and acetone was removed in vacuo. The residue was extracted with EtOAc, the organic layer was dried and evaporated to dryness. The resulting residue dissolved in EtOAc (70 mL) was added dropwise under stirring to a mixture of $KMnO_4$ (6.0 g, 38 mmol) and tetra n-butylammonium hydrogensulphate (720 mg, 2 mmol) dissolved in water-acetic acid (5:1)(85 mL).[22] The reaction was allowed to proceed overnight. Excess $KMnO_4$ was destroyed with MeOH and the MnO_2 ppt was dissolved by adding sodium sulphite to the solution made acidid (pH 1) by 20% H_2SO_4 addition. The clear organic layer was separated and the aqueous layer was extracted (3x) with EtOAc. The combined organic extracts were concentrated and the residue dissolved in Et_2O. In the manner described for the preparation of 8a from 7c, pure 8c was obtained in 40% yield as a colourless oil,$|\alpha|_D^{20}$+42.2° (Lit.[23]: -50.11° for S-enantiomer).

Ethyl 4-Chloro-3(R)-hydroxybutyrate 8e. To a 3% HCl in absolute EtOH (100 mL)|prepared by addition of acetyl chloride (5 mL) to dry EtOH(100 mL)|,8d (5.0 g,24 mmol) was added and the resulting solution was stirred at r.t. for 48 h. The solvent was evaporated in vacuo leaving 8e as a colourless oil (4.0 g,98%),$|\alpha|_D^{20}$ +19.3°(c 1.2) {Lit.[16]: $|\alpha|_D^{23}$ -11.7°(c 5.75,$CHCl_3$) for the prevalent S-enantiomer (55% e.e.)};δ_H 1.29(3H,t,J 6.7Hz,$CH_2\underline{Me}$),3.11(1H,br s, OH),4.16(2H,q,J 6.7Hz,$\underline{CH_2}Me$); 2.62(d), 3.57(d) and 4.20(m) for 2-H,4-H and 3-H,respectively (A_2B_2X system with $J_{2,3}$6.2,$J_{2,4}$ 5.5Hz).

4(R)-Hydroxy-2-pyrrolidinone 9. A stirred mixture of 8e (4.0g, 24 mmol) and 25% NH_4OH (50 mL) was heated at 80°C for 3 h and then evaporated to dryness. F.c.(acetone) of the resulting residue gave 9 (2.0 g, 82%) as colourless cubes,m.p. 157-8°C(acetone),$|\alpha|_D^{20}$ +56.1°(c 1.3,H_2O) |Lit.[14]: +57.3°|; R_F(acetone) 0.15(blue spot, chlorine-benzidine spay);δ_H (D_2O) 2.26(1H,dd,$J_{3,3'}$18.0,$J_{3,4}$,2.5Hz,3-H), 3.81(1H,dd,$J_{3,3'}$,18.0,$J_{3',4}$6.1Hz,3'-H),3.33(1H,dd,$J_{5,5'}$12.2,$J_{4,5}$2.1Hz,5-H),3.73(1H,dd,$J_{5,5'}$,12.2,$J_{4,5'}$ 5.4Hz,5'-H),4.64(1H,dddd,J 6.1,5.4,2.5,2.1Hz,4-H).

4-Amino-3(R)-hydroxybutyric acid 8f. A solution of 9 (2.0 g,20 mmol) in 1N aq. LiOH (80 mL) was stirred at r.t. for 24 h and then poured on a column of ion exchange resin (Amberlite IR-120,H^+). The column was washed with water until the eluate was neutral. Subsequent elution with 10% NH_4OH and evaporation gave a crude product which recrystallised from aq. EtOH to afford pure 8f (2.1 g, 89%), m.p. 210-2°C(dec),$|\alpha|_D^{20}$-19.1°(c 1.6,H_2O) {Lit.[15]: m.p. 210-2°C(dec), $|\alpha|$ -21.4° ; $_H$(D_2O) 2.45(2H, d,2-H),3.15(2H,m,4-H),4.0-4.5(1H,m,3-H).

(R)-Carnitine hydrochloride 8g. A mixture of 8e (2.1g, 12.6 mmol) and 33% ethanolic dimethylamine (70 mL) was refluxed for 6 h. Evaporation of the solution gave a white solid which was taken up in 3H NCl (50 mL) and heated at reflux for 3 h. After evaporation of the solvent, the residue was dissolved in water, the resulting solution was added to an Amberlite IR-120 column in the H^+ form and the column was washed with water until the elute was neutral. The carnitine fraction was then isolated by washing the column with 10% NH_4OH solution. Evaporation of this gave a thick oil which was acidified with concd HCl and evaporation gave crude 8g. Trituration from propan-2-ol gave pure 8g (1.56 g, 56%) as colourless solid, m.p. 144-6°C, $|\alpha|_D^{20}$ -20.6°(c 2.1,H_2O) |Lit.[17]: -23.7°|; δ_H(D_2O) 3.22(9H,s,NMe_3), A_2B_2X system at 2.69(d,2-H),3.50(d,4-H) and 4.69(m,3-H) with $J_{2,3}$6.9 and $J_{3,4}$5.6Hz.

REFERENCES AND NOTES

1. Part 1. R.Pellegata,P.Ventura,M.Villa,G.Palmisano, and G.Lesma,Synth.Commun.,1985,15,165
2. J.P.Benner,G.B.Gill,S.J.Parrot,B.Wallace, and M.J.Begley,J.Chem.Soc.,Perkin Trans 1,1984,315
3. J.P.Benner,G.B.Gill,S.J.Parrot, and B.Wallace,J.Chem.Soc.,Perkin Trans 1,1984,331
4. H.Wynberg and E.G.J.Staring,J.Chem.Soc.,Chem.Commun.,1984,1181
5. M.J.Begley,G.B.Gill, and B.Wallace,J.Chem.Soc.,Perkin Trans 1,1978,93
6. J.E.Shaw ,D.C.Kunerth, and J.J.SherryTetrahedron Lett.,1972,4063
7. a) H.K.Spencer and R.K.Hill, J.Org.Chem.,1975,40,217; b) P.H.J.Carlsen,T.Katsuki,V.S.Martin, and K.B.Sharpless, J.Org.Chem.,1981,46,3936
8. An authentic sample of 8a prepared from (R)-(+)-malic acid with $|\alpha|_D^{20}$ +27±2° (c 5,5, pyridine) showed $|\alpha|_D^{20}$ +18.7, $|\alpha|_{365}^{20}$ +45.5° (c 1.76,$CHCl_3$)
9. Interestingly, the reaction of 5a with PPh_3-diethyl azodicarboxylate-acetic acid under Mitsunobu conditions (O.Mitsunobu, Synthesis, 1981,1] led to the almost complete racemisation at the exo-

cyclic chiral center. See W.H.Kruizinga,B.Strijtveen, and R.M.Kellogg, J.Org.Chem.,1981,46,4323
10. J.R.DiPalma,D.M.Ritchie,and R.F.McMichael, Arch.Int.Pharmacodyn.Ther.,1975,217,246; A.G.Rebuzzi, G.Schiavoni,C.M.Amico,A.S.Montenero,F.Meo,and U.Manzoli, Drugs Exptl.Clin.Res.,1984,10,219; S. Imai, K.Matsui,M.Nakazawa,N.Takatsuka,K.Takeda, and H.Tamatsu, Brit.J.Pharmac., 1984,82,533
11. E.Roberts,D.N.Krause,E.Wong, and A.Mori, J.Neurosci.,1981,1,132
12. T.Hayashi and K.Nagai,'Nervous Inhibition: Proceedings of the Second Friday Harbor Symposium', Florey, Ed.;Pergamon Press: London, 1961, pp. 389-394; see also: T.Hayashi, ibid.,pp.378-388
13. I.M.Downie,J.B.Holmes, and J.B.Lee, Chem.Ind.,1966,800
14. R.Pellegata,M.Pinza, and G.Pifferi, Synthesis,1978,614
15. S.Linstedt and G.Linstedt, Ark.Kemi, 1962,22,93
16. B.Zhou,A.S.Gopalan,F.VanMiddlesworth,W.R.Shieh, and C.J.Sih,J.Am.Chem.Soc.,1983,105,5925
17. E.Strack and I.Lorenz, Z.Physiol.Chem.,1960,318,129
18. T.Kaneko and R.Yoshida, Bull.Chem.Soc.Jap.,1962,35,1153
19. W.C.Still,M.Khan, and A.Mitra, J.Org.Chem.,1978,43,2923
20. T.R.Kelly,T.E.Schmidt, and J.C.Haggerty,Synthesis,1972,544
21. V.Micovic and M.L.J.Mihailovic, J.Org.Chem.,1953,18,1190
22. A.P.Krapcho,J.R.Larson, and J.M.Eldrige, J.Org.Chem.,1977,42,3749
23. Beil.,3,431