An Efficient Entry to Highly Functionalised C_4 Chiral Synthons *via* Lewis Acid-Catalysed Ene Reaction of (1*S*)-β-Pinene and α-Keto Esters. Part 4.[1]

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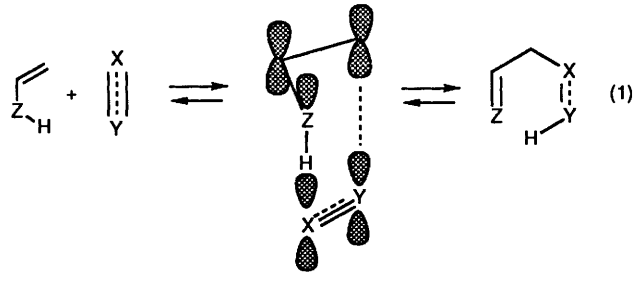
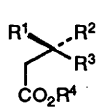
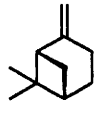
The ene reaction between (1*S*)-β-pinene (**8**) and α-keto esters catalysed by Lewis acids is found to provide a high level of diastereocontrol. The resulting educts have been elaborated into a wide variety of α-hydroxy carboxylic acids with satisfactory yield and excellent optical purity.

The reaction between an alkene bearing an allylic hydrogen (ene) and electron-poor multiple bond (enophile) to form a new bond with migration of the ene double bond followed by 1,5-hydrogen shift [equation (1)] is known as ene reaction (ER). Though lacking appropriate elements of symmetry, it could be considered as a $[_{\pi}2_s + _{\pi}2_s + _{\sigma}2_s]$ pericyclic process, but its activation energy is generally higher than that of Diels–Alder cycloadditions. High temperatures are required for this


(1)

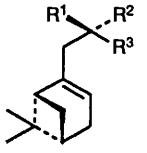
reaction, thus limiting its synthetic utility. Addition of less than one molar equivalent of Lewis acid has been reported to cause a dramatic acceleration of ERs, reducing reaction times and temperatures.[2] Accordingly, many research groups have contributed to the synthetic exploitation of the ene reaction, the most notable contributions being those of Snider,[2] Oppolzer,[3] and Nakai.[4]




(8)

	R^1	R^2	R^3	R^4
(1)	OH	H	CH_2Cl	Et
(2)	OAc	Me	CO_2Me	Me
(3)	OH	Et	CO_2Et	Et
(4)	OH	Et	CO_2H	H
(5)	OAc	CH_2OAc	CO_2Et	Et
(6)	OH	CH_2OH	CO_2H	H
(7)	OAc	Me	CH_2CN	H

Earlier[5] we reported an enantioselective synthesis of (*R*)-ethyl 4-chloro-3-hydroxybutanoate (**1**), a versatile precursor to a diverse array of biologically active compounds, wherein the $FeCl_3$-promoted ER between (1*S*)-(−)-β-pinene (**8**)† and chloral represented the key element for control of stereochemistry. Owing to the stereochemical outcome of this reaction, its mildness, and the inexpensiveness of starting materials, we set out to investigate whether the acid-catalysed ER between the pinene (**8**) and α-keto esters could be employed in construction of highly functionalised optically active synthons with five or more C atoms (*vide infra*).[6] The thermal (165 °C, 96 h) ene addition of compound (**8**) to methyl pyruvate was first investigated by Arnold and Veeravagu,[7] who described the reaction product (55%) as a single diastereoisomer without assessing its stereochemistry. In the 1970s Spencer and Hill[8] examined this reaction more closely and established that Arnold and Veeravagu's adduct was not stereochemically homogeneous but that diastereoisomers (**9**) and (**10**) were formed in approximately equal amounts. The pure adducts, having $[\alpha]_D^{23}$ −33.4° and $[\alpha]_D^{23}$ −12.5°, could be separated



	R^1	R^2	R^3
(9)	OH	Me	CO_2Me
(10)	Me	OH	CO_2Me
(11)	OAc	Me	CO_2Me
(12)	OH	Me	CH_2OH
(13)	OH	Me	CH_2OTs
(14)	OH	Me	CH_2CN
(15)	OAc	Me	CH_2CN
(16)	OH	CH_2Br	CO_2Et
(17)	OH	Et	CO_2Et
(18)	OH	CH_2OAc	CO_2Et
(19)	OAc	CH_2OAc	CO_2Et

only after cumbersome manipulations and the absolute configuration at the newly installed stereocentre in product (**10**) was ascertained as *S* by chemical correlation with dimethyl citramalate (dimethyl 2-methylbutane dionate).

Ene reactions, like the related Diels–Alder reactions, can proceed through an *endo* or *exo* transition states and Gill and Wallace[9] have shown that Lewis acids can dramatically influence the stereochemical outcome of the reaction of β-pinene and chloral. Since it was our intention to obtain

† β-Pinene has been investigated with a wide variety of enophiles; H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 556; R. K. Hill, J. W. Morgan, R. V. Shetty, and M. E. Synerholm, *J. Am. Chem. Soc.*, 1974, **96**, 4201; R. T. Arnold and J. S. Showell, *ibid.*, 1957, **79**, 419.

carboxylic acids containing an oxygenated carbon at the α-position. The Lewis acid-induced ER between the pinene (**8**) and methyl pyruvate seemed more advantageous than the corresponding thermal reaction, wherein a disappointing lack of stereoselectivity has been recorded. A variety of Lewis acids [tin(IV) chloride, titanium tetrachloride, zinc bromide, aluminium chloride, $EtAlCl_2$, and zirconium tetrachloride] was tested and iron(III) chloride was found to be the catalyst of choice.* Thus, when equimolecular amounts of freshly distilled (1*S*)-(−)-β-pinene (**8**) and methyl pyruvate were set aside overnight at room temperature in the presence of iron(III) chloride (0.04 mol equiv.), the adduct (**9**) ($[\alpha]_D^{20}$ −29.9° [lit.,[8] −33.4°]) could be isolated in 51% yield as a stereochemically homogeneous compound as shown by 300 MHz ^1H and 62.5 MHz ^{13}C NMR spectroscopy. The dramatic changeover in diastereoselectivity on switching to the $FeCl_3$-promoted process might be rationalised by assuming a *syn*-complexation of $FeCl_3$ to pyruvate, resulting in the addition to the ene *anti* to the gem-dimethyl groups (*re* face attack). Of the two possible diastereoisomeric transition states, one (**A**) (*exo*-TS) should be favoured over that (**B**) (*endo*-TS) which suffers steric repulsion between the $FeCl_3$ and the incoming ene molecule (see Figure); hence, the isomer (**9**) is expected to be the predominant product.

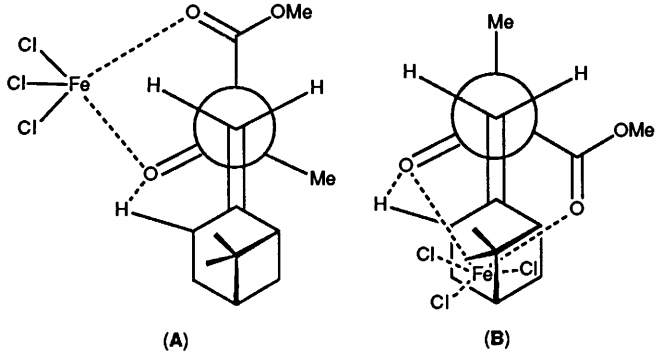
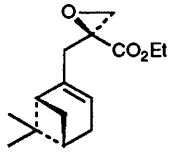


Figure 6.

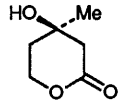
Taking advantage of the high level of diastereofacial selectivity, we next converted compound (**9**) into (*R*)-dimethyl (+)-2-acetoxy-2-methylbutenedioate (**2**) *via* a route in which the (*R*)-configuration of the exocyclic stereogenic centre in compound (**9**) was preserved throughout the reaction sequence. Acetylation of compound (**9**) under standard conditions gave compound (**11**), $[\alpha]_D^{20}$ −5.2° (*c* 1.12, EtOH), which by reaction with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane (room temperature, overnight) followed by acid-catalysed rearrangement (acetone, 0.1M-HCl, room temperature, 3 h) provided the diol (**22**), $[\alpha]_D^{20}$ −51.0° (*c* 1.26, EtOH) in 48% overall yield [from compound (**9**)]. Having performed its function the terpenoid moiety was then removed [with the retention of C-2 (pinane ring numbering) as a *pro*-CO_2H group], thus making the synthesis of optically active non-isoprenoid compounds possible. Accordingly, one-step degradation of diol (**22**) to compound (**2**) was effected in mild yet efficient manner with sodium metaperiodate in the presence of a catalytic amount of ruthenium trichloride in a three-component solvent mixture (MeCN–CCl_4–water) according to the protocol of Sharpless.[10] After the usual work-up, the crude acid was methylated by subsequent treatment with oxalyl dichloride in dry CH_2Cl_2 followed by reaction of the product in stirred, dry MeOH, to furnish (*R*)-dimethyl (+)-2-acetoxy-2-methylbutanedioate (**2**), $[\alpha]_D^{20}$ +33.4° (*c* 1.0, $CHCl_3$) with 96.6% e.e. (compared with the highest reported value of +36.4°).[11] The enantiomeric purity was substantially confirmed (95% e.e.) by use of the chiral solvating agent developed by Pirkle.[12] The ^1H NMR non-equivalence induced by (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol upon its addition to racemic diester (**2**) was sufficiently large and the singlets (δ_H 3.675 and 3.735) due to CO_2Me protons were both split at 300 MHz.

We next turned our attention to the exploitation of compound (**9**) for synthetic purposes. $LiAlH_4$ reduction of compound (**9**) [tetrahydrofuran (THF), reflux, 3 h] gave the diol (**12**), $[\alpha]_D^{20}$ −13.6° (*c* 1.13, EtOH), which by conventional tosylation of the primary OH group led to compound (**13**). One-carbon homologation of the product (**13**) was achieved in excellent yield by an S_N2-displacement reaction of the tosyl group by treatment with tetrabutylammonium cyanide in dichloromethane at room temperature.[13] Acetylation of the tertiary OH group of the resulting cyanide (**14**) [Ac_2O, 4-(*N*,*N*-dimethylamino)pyridine (DMAP), THF][14] [⟶ (**15**)] and degradation of the terpenoid moiety *via* (**23**) as described above yielded, after purification as the dicyclohexylammonium salt, the required (*S*)-(+)-3-acetoxy-4-cyano-3-methylbutanoic acid (**7**), $[\alpha]_D^{20}$ +1.5° (*c* 1.5, EtOH) in 70% overall yield [from (**9**)] and 93% ee.

The ^1H NMR determination of the e.e. for compound (**7**) was possible by observing the different CO_2Me signals for the diastereoisomeric salts formed upon addition of (−)-ephedrine (1 mol equiv.), according to the method of Gais.[15] This step completes the formal synthesis of natural (*R*)-(−)-mevalonolactone (**21**), since transformation of the acid (**7**) to lactone (**21**) has been previously reported by Eliel and Frye.[16] The feasibility of the synthetic pathway outlined above could be also utilised for stereospecific access to a number of malic acid derivative (*vide infra*). Thus, we treated (−)-β-pinene (**8**) with ethyl bromopyruvate in the presence of a catalytic amount of $FeCl_3$ at room temperature and obtained the bromo ester (**16**) as a single diastereoisomer (checked by ^1H NMR spectroscopy) in 53% isolated yield. The absolute configuration and optical purity of the product (**16**) were confirmed by reductive



(**20**)



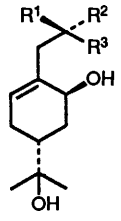
(**21**)

dehalogenation ($LiAlH_4$, THF, reflux) to afford the alcohol (**12**), $[\alpha]_D^{20}$ −13.2° (*c* 1.38, EtOH), identical in all respects with the product obtained from reduction of compound (**9**). Subsequent exposure of ester (**16**) to potassium acetate in hexamethylphosphoric triamide (HMPA) at room temperature for 10 h [or, more efficiently, to potassium fluoride in *N*,*N*-dimethylformamide (DMF) in the presence of dicyclohexyl-18-crown-6[17] at room temperature for 12 h], promoted intramolecular S_N2-type closure to afford the oxirane ring in product (**20**) in 82% [and 94%] yield, respectively. In principle, the epoxide (**20**) represents a versatile synthon which should react selectively with a great number of nucleophiles. In particular, it is well documented that substituted epoxides such as (**20**) are attacked with high selectivity at the less substituted C-atom by *C*-nucleophiles, *e.g.*, Cu^I-catalysed Grignard reagents, organo(cyano)copper(I) lithium reagents R(CN)CuLi, and mixed organocuprates of higher order $R_2Cu(CN)Li_2$.[18] To demonstrate the utility of epoxide (**20**) as a common precursor to (*R*)-α-alkylmalic acids, we tested its reaction with Me_2CuLi. Thus, addition of compound (**20**) in diethyl ether to a stirred

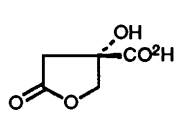
* In our hands, the optical rotation value (EtOH) of the adduct isolated after chromatography ranged from −8.7° to −29.9°, depending on the catalyst, temperature (from −78 °C to room temperature), and the solvent used (CH_2Cl_2, CCl_4, toluene, neat).

solution of lithium dimethylcuprate at 0 °C gave, after acidic work-up, the hydroxy ester (**17**), $[\alpha]_D^{20}$ −22.9° (*c* 1.0, EtOH), in 81% isolated yield. Interestingly, this conversion took place with a regioselectivity >95% according to ^{1}H NMR analysis. The usual stepwise degradation of hydroxy ester (**17**) *via* (**24**) led ultimately to (−)-diethyl α-ethylmalate (**3**), $[\alpha]_D^{20}$ −12.2° (*c* 0.51, $CHCl_3$) in 55% overall yield. The optical purity of compound (**3**) was determined as >95% e.e. by ^{1}H NMR analysis of the Mosher's esters[19] prepared by DMAP-catalysed esterification of the tertiary OH group with both (+)- and (−)-α-trifluoromethyl-α-methoxy(phenyl)acetyl chlorides.* The configuration of compound (**3**) was assessed by conversion of (−)-(**3**) into (*R*)-(−)-α-ethylmalic acid (**4**), $[\alpha]_D^{20}$ −14.4° (*c* 1.02, water), of about the same degree of optical purity based on a value of 15.2° for the maximum rotation reported for the *S*-enantiomer.[20] Since compound (**20**) is also available in the (*S*)-configuration at the exocyclic centre [starting from (1*R*)-(+)-β-pinene *ent*-(**8**)][21] this approach allows an enantioselective entry to (*S*)-α-alkylmalic acids. This sequence does not represent the most concise way to prepare the desired compounds, but selectivity and overall yields are satisfactory and no problems should be encountered in scaling up the amounts.

Finally, reaction of compound (**16**) with a caesium acetate in HMPA at 70 °C for 6 h gave, along with the oxirane (**20**) (53%), the acetate (**18**), $[\alpha]_D^{20}$ −20.1° (*c* 0.65, EtOH) (32%). The latter was converted by the usual protocol into (*S*)-diethyl-acetoxy itatartrate† [(*S*)-diethyl 2-acetoxy-2-acetoxymethyl-butanedioate] (**5**), $[\alpha]_D^{20}$ +10.8° (*c* 0.73, $CHCl_3$) in 48% overall yield. Conversion of the ester (**5**) into itatartaric acid (**6**) was also carried out (alkaline hydrolysis followed by acidic work-up) and the acid was isolated as (*S*)-(+)-3-carboxy-3-hydroxybutyrolactone (**26**) $[\alpha]_D^{20}$ +43.9° (*c* 2.1, water) [lit.,[22] +45.2°] in almost quantitative yield.



	R^1	R^2	R^3
(**22**)	OAc	Me	CO_2Me
(**23**)	OAc	Me	CH_2CN
(**24**)	OH	Et	CO_2Et
(**25**)	OAc	CH_2OAc	CO_2Et



(**26**)

In conclusion, the foregoing results indicate that educts arising from the ene reaction between (1*S*)-β-pinene (**8**) and α-keto esters represent a valuable addition to the chiral pool. These compounds could be elaborated into a wide variety of α-hydroxy carboxylic acids and related structures in satisfactory chemical yield and with excellent optical purity.

Experimental

M.p.s were taken using a Buchi capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrometer as liquid films unless otherwise stated. ^{1}H NMR spectra were recorded on a Bruker WP-80 (80 MHz) spectrometer with $CDCl_3$ as solvent unless otherwise stated ($SiMe_4$ as internal standard). High-field ^{1}H NMR spectra (300 MHz) were obtained with a Bruker CXP-300 spectrometer. ^{13}C NMR were recorded on a Bruker AC250 (62.5 MHz) spectrometer with $CDCl_3$ as solvent. Optical rotation measurements were obtained on a Perkin-Elmer 241 polarimeter. Thin-layer chromatography (TLC) was performed on glass plates pre-coated with Merck kieselgel 60 GF_{254}, and visualisation of the TLC chromatograms was conducted with an AcOH–H_2SO_4–vanillin (98:2:1) mixture followed by heating of the plates at 110 °C for 2–3 min. Silica gel flash chromatography (FC) refers to the method of Still.[23] (1*S*)-(−)-β-pinene (**8**), $[\alpha]_D^{20}$ −21.0° (neat) (92% e.e.), and ethyl bromopyruvate were purchased from Fluka. Organic extracts were dried over Na_2SO_4.

$FeCl_3$-*Catalysed Reaction of* (1S,5S)-β-*Pinene* (**8**) *with Methyl Pyruvate*.—To an ice-cooled stirred mixture of freshly distilled methyl pyruvate (7.5 g, 73.4 mmol) and anhydrous iron(III) chloride (475 mg, 2.94 mmol) was added dropwise, under nitrogen, freshly distilled (−)-β-pinene (**8**) (10.0 g, 73.5 mmol). The mixture was stirred overnight in AcOEt (150 ml) and was then poured into water (200 ml). The separated organic layer was washed twice with water, dried, and evaporated under reduced pressure. FC (cyclohexane–Et_2O, 7:1) of the brown oily residue provided (α*R*)-methyl α-hydroxy-β[(1*S*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]-α-methylpropanoate (**9**) (8.92 g, 57%) as a thick oil, b.p. (0.2 mmHg) 83–85 °C; $[\alpha]_D^{20}$ 29.9° (*c* 1.4, EtOH) (lit.,[8] −33.4°); ν_{max} 3 550, 2 950, and 1 748 cm^{-1}; δ_H(300 MHz) 0.83 and 1.26 (6 H, 2 × s, CMe_2), 1.43 (3 H, s, α-Me), 3.01 (1 H, br s, OH), 3.76 (3 H, s, OMe), and 5.31 (1 H, m, 3-H); δ_C21.0, 26.1, 26.1, 31.5, 31.6, 37.6, 40.3, 46.6, 73.5, 121.6, 143.7, and 177.1.

(α*R*)-*Ethyl* α-*Bromoethyl*-β-[(1S,5S)-6,6-*dimethylbicyclo*-[3.1.1]*hept*-2-*en*-2-*yl*]-α-*hydroxypropanoate* (**16**).—Treatment of compound (**8**) with ethyl bromopyruvate as in the preceding experiment, followed by FC (cyclohexane–dichloromethane, 3:1) gave the *title compound* (**16**) (53% isolated yield) as an oil, $[\alpha]_D^{20}$ −17.8° (*c* 0.82, EtOH) (Found: C, 54.5; H, 6.9. $C_{15}H_{23}BrO_3$ requires C, 54.4; H, 7.0%); δ_H (300 MHz) 0.80 and 1.22 (6 H, 2 × s, CMe_2), 1.27 (3 H, t, *J* 7.0 Hz, $MeCH_2$), 3.48 and 3.67 (AB syst, *J* 10.0 Hz, CH_AH_BBr), 4.25 (2 H, q, *J* 7.0 Hz, $MeCH_2$), and 5.33 (1 H, m, 3-H).

(α*R*)-*Methyl* α-*Acetoxy*-β-[(1S,5S)-6,6-*dimethylbicyclo*-[3.1.1]*hept*-2-*en*-2-*yl*]-α-*methylpropanoate* (**11**).—A solution of the hydroxy ester (**9**) (1.50 g, 6.30 mmol) in dry THF (50 ml) was added to acetic anhydride (6.5 ml) containing DMAP (1.53 g, 12.6 mmol) and the resulting solution was stirred for 4 h under nitrogen. Methanol (8 ml) was added, the mixture was stirred for 1 h, and the solution was diluted with AcOEt (90 ml), and washed successively with 1M-sulphuric acid (× 2), saturated aq. $NaHCO_3$, water, and brine. Removal of the solvent afforded a residue which, after FC (cyclohexane–AcOEt, 8:1), gave the *title compound* (**11**) (1.50 g, 85%) as a viscous oil, $[\alpha]_D^{20}$ −5.2° (*c* 1.12, EtOH) (Found: C, 68.5; H, 8.7. $C_{16}H_{24}O_4$ requires C, 68.5; H, 8.6%); δ_H 0.83 and 1.24 (6 H, 2 × s, CMe_2), 1.54 (3 H, s, α-Me), 2.00 (3 H, s, OAc), and 5.30 (1 H, m, 3-H).

(β*R*)-β-*Acetoxy*-γ-[(1S,5S)-6,6-*dimethylbicyclo* [3.1.1]*hept*-2-*en*-2-*yl*]-β-*methylbutanenitrile* (**15**).—This compound was prepared (76%) from the nitrile (**14**) in a manner identical with that described above. FC (cyclohexane–AcOEt, 13:1) of the crude product gave the title compound as an oil, $[\alpha]_D^{20}$ −16.9° (*c* 2.78, $CHCl_3$); δ_H 0.84 and 1.26 (6 H, 2 × s, CMe_2), 1.55 (3 H, s, β-Me), 2.00 (3 H, s, OAc), 2.80 and 3.05 (AB syst, *J* 16.6 Hz, H_AH_BCN), and 5.40 (1 H, m, 3-H).

* 3,3,3-Trifluoro-2-methoxy-2-phenylpropionyl chloride.

† Itatartaric acid represents a direct product of the fermentation of itaconate by *Aspergillus terreus* [J. Jakubowska, Z. Zakowka, and J. Jeszka, *Zesz. Nauk. Politech. Lodz, Chem. Spozyw.*, 1970, **17**, 21 (*Chem. Abstr.*, 1971, **74**, 136821d)].

(αS)-*Ethyl α-Acetoxy-α-acetoxymethyl-γ-[(1S,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]propanoate* (**19**).—This compound was prepared from compound (**18**) in a manner identical with that described above. FC (cyclohexane–AcOEt, 8:1) of the crude product gave the oily title compound in 86% yield, $[\alpha]_D^{20}$ −5.6° (*c* 0.48, EtOH); δ_H 0.81 and 1.24 (6 H, 2 × s, CM_2), 1.24 (3 H, t, *J* 7.4 Hz, *Me*CH_2), 2.02 and 2.08 (each 3 H, each s, 2 × OAc), 4.16 (2 H, q, *J* 7.4 Hz, MeCH_2), 4.40 and 4.66 (AB syst, *J* 11.7 Hz, H_AH_BOAc), and 5.33 (1 H, m, 3-H).

Treatment of Compound (**11**) *with MCPBA*.—A solution of compound (**11**) (1.45 g, 5.17 mmol) in dry dichloromethane (20 ml) was stirred at 0 °C, a slight excess of recrystallised MCPBA (5.30 g) was added portionwise, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 ml), washed successively with saturated aq. $NaHCO_3$ and brine, and dried. Evaporation gave a crude product, which was treated with a (1:1) mixture of acetone and 0.1M-HCl (40 ml) for 3 h at room temperature. The reaction mixture was diluted with AcOEt (50 ml), and the organic layer was washed with saturated aq. ammonium sulphate, dried, and evaporated under reduced pressure. FC (AcOEt) of the residue afforded (αR)-*methyl α-acetoxy-β-[(4R,6S)-6-hydroxy-4-(1-hydroxy-1-methylethyl)cyclohex-1-enyl]-α-methyl propanoate* (**22**) (910 mg, 56%) as needles (from di-isopropyl ether), m.p. 114–116 °C (Found: C, 61.2; H, 8.3. $C_{16}H_{26}O_6$ requires C, 61.14; H, 8.28%); $[\alpha]_D^{20}$ −51.0° (*c* 1.26, EtOH); δ_H 1.20 (6 H, s, CMe_2), 1.60 (3 H, s, α-Me), 2.08 (3 H, s, OAc), 3.70 (3 H, s, CO_2Me), 4.16 (1 H, br t, *J* 6.6 Hz, 6-H), and 5.70 (1 H, m, 2-H).

(βR)-*Methyl-β-acetoxy-γ(4R,6S)-6-hydroxy-4-(1-hydroxy-1-methyl-ethyl)cyclohex-1-en-1-ylbutanenitrile* (**23**).—This compound was prepared in 50% yield from (**15**) in a manner identical to that described above. FC (AcOEt) of the residue gave the *title compound* as colourless needles (di-isopropyl ether), m.p. 118–120 °C; $[\alpha]_D^{20}$ −83.7° (*c* 2.74, $CHCl_3$); δ_H1.20 (6 H, s, CMe_2), 2.01 (3 H, s, OAc), 2.55 and 2.80 (2 H, AB syst, *J* 16.6 Hz, γ-H_AH_B), 2.92 and 3.06 (2 H, AB syst, *J* 16.6 Hz, α-H_AH_B), 4.18 (1 H, t, *J* 3.0 Hz, 6-H), and 5.80 (1 H, dd, *J* 5.3 and 3.0 Hz, 2-H).

(αS)-*Ethyl α-Acetoxy-α-acetoxymethyl-β-[(4R,6S)-6-hydroxy-4-(1-hydroxy-1-methyl)ethylcyclohex-1-enyl]propanoate* (**25**).—This was prepared as above in 53% yield from compound (**19**). FC (AcOEt–cyclohexane, 4:1) of the residue gave the title compound (**25**) as a glass, $[\alpha]_D^{20}$ −37.0° (*c* 2.55, $CHCl_3$); δ_H 1.20 (6 H, s, CMe_2), 1.25 (3 H, t, *J* 7.0 Hz, *Me*CH_2), 2.10 (6 H, s, 2 × OAc), 4.18 (2 H, q, *J* 7.0 Hz, MeCH_2O), 4.50 and 4.72 (2 H, AB syst, *J* 12.8 Hz, AcO-H_AH_B), and 5.65 (1 H, m, 2-H).

Oxidative Degradation of Compound (**22**) *to* (R)-(+)-*Dimethyl 2-Acetoxy-2-methylbutanedioate* (**2**).—The ester (**22**) (2.05 g, 6.52 mmol) was dissolved in MeCN (84 ml). Water (124 ml) was added, followed by $NaIO_4$ (5.70 g). After the mixture had been stirred to complete dissolution of the periodate, a catalytic amount of $RuCl_3 \cdot 3H_2O$ (100 mg) was added whereupon the colourless solution immediately turned dark; the mixture was stirred overnight, then diluted with dichloromethane (100 ml). The organic layer was separated and the aqueous layer was extracted twice with dichloromethane (2 × 50 ml). The combined organic solutions were dried. The residue obtained on concentration was taken up in Et_2O (200 ml) and extracted twice with saturated aq. $NaHCO_3$ (2 × 50 ml). The combined aqueous phases were acidified with 20% sulphuric acid and extracted (3 ×) with Et_2O. Evaporation of the solvent gave a crude acid, which was dissolved in CH_2Cl_2 (100 ml) and treated with oxalyl dichloride (3.5 ml) in the presence of a drop of DMF. After 2 h, the solvent was removed under reduced pressure and the residue was taken up in THF (50 ml) and added to stirred, dry MeOH (50 ml). The solution was stirred for 3 h at room temperature and concentrated. FC (cyclohexane–AcOEt, 5:1) afforded the title compound (**2**) (1.33 g, 94%) as an oil, $[\alpha]_D^{20}$ +33.4° (*c* 1.0, $CHCl_3$) [lit.,[11] +36.4°] for a product with 96.6% e.e.; (Found: C, 49.4; H, 6.7. Calc. for $C_9H_{14}O_6$: C, 49.5; H, 6.5%); δ_H (300 MHz) 1.65 (3 H, s, 2-Me), 2.065 (3 H, s, OAc), 2.875 and 3.135 (2 H, AB syst, *J* 15.1 Hz, 3-H_AH_B), and 3.675 and 3.735 (each 3 H, s, CO_2Me).

(S)-*Diethyl 2-Acetoxy-2-acetoxymethylbutanedioate* (*Diethyl Itatartrate*) (**5**).—This was obtained in 43% overall yield from compound (**18**) as described for the preparation of ester (**22**); $[\alpha]_D^{20}$ +10.8° (*c* 0.73, $CHCl_3$); δ_H(300 MHz) 1.220 and 1.232 (each 3 H, t, *J* 7.2 Hz, each *Me*CH_2), 2.036 and 2.048 (each 3 H, s, OAc), 3.00 and 3.18 (2 H, AB syst, *J* 17.0 Hz, 3-H_AH_B), 4.12 and 4.21 (each 2 H, q, *J* 7.2 Hz, MeCH_2O), and 4.502 and 4.23 (2 H, AB syst, *J* 15.0 Hz, CH_AH_BOAc).

(R)-*Diethyl 2-Ethyl-2-hydroxybutanedioate* (**3**).—The crude acid (280 mg, 1.047 mmol), obtained from compound (**24**) *via* reaction as described for compound (**22**), was dissolved in HMPA (5 ml) and the mixture was treated with triethylamine (0.2 ml, 1.5 mmol) and stirred for 10 min before addition of iodoethane (0.32 ml, 4.0 mmol). The mixture was stirred overnight, quenched with 10% sulphuric acid, and extracted with diethyl ether (2 × 20 ml). The combined extracts were washed successively with saturated aq. $NaHCO_3$ and water, dried, and evaporated. FC (cyclohexane–AcOEt, 4:1) gave the title compound (**3**) (177 mg) as an oil, $[\alpha]_D^{20}$ −12.2° (*c* 0.51, $CHCl_3$); δ_H (300 MHz) 0.88 (3 H, t, *J* 7.0 Hz, 2-CH_2Me), 1.233 and 1.30 (each 3 H, t, *J* 7.0 Hz, *Me*CH_2O), 1.65 (2 H, dq, *J* 15.0, 7.0 Hz, 2-CH_2Me), 2.66 and 2.90 (2 H, AB syst, *J* 15.2 Hz, 3-H_AH_B), and 4.11 and 4.25 (each 2 H, q, *J* 7.0 Hz, MeCH_2O).

(S)-3-*Acetoxy-4-cyano-3-methylbutanoic Acid* (**7**).—The crude acid obtained from compound (**15**) *via* reaction as described for compound (**5**) was purified *via* its dicyclohexylammonium salt, m.p. 152–153 °C (from di-isopropyl ether), as needles (Found: C, 51.9; H, 5.9; N, 7.7. $C_8H_{11}NO_4$ requires C, 54.9; H, 6.0; N, 7.6%). The pure acid was then obtained as an oil in 60% overall yield, with $[\alpha]_D^{20}$ +1.5° (*c* 1.5 EtOH), and the ^1H NMR spectrum was identical with that reported by Frye and Eliel.[16]

(2R)-3-[(1′S,5′S)-6′,6′-*Dimethylbicyclo*[3.1.1]*hept-2′-en-2′-yl*]-2-*methylpropane*-1,2-*diol* (**12**).—A solution of ester (**9**) (570 mg, 2.4 mmol) in dry THF (10 ml) was dropwise added to a stirred suspension of $LiAlH_4$ (270 mg, 2.4 mmol) in dry THF (10 ml) and the reaction mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was quenched according to the method of Micovic and Mihailovic.[24] The organic layer was evaporated and the residue was dissolved in EtAOc, washed with saturated aq. ammonium sulphate, dried, and evaporated under reduced pressure. FC (cyclohexane–AcOEt, 1:1) gave the *title compound* (**12**) (500 mg, 98%) as an oil, $[\alpha]_D^{20}$ −13.6° (*c* 1.13, EtOH) (Found: C, 74.4; H, 10.6. $C_{13}H_{22}O_2$ requires C, 74.2; H, 10.5%); δ_H 0.85 (3 H, s, C*Me*Me), 1.13 (3 H, s, 2-Me), 1.28 (3 H, s, CMe*Me*), and 5.36 (1 H, m, 3′-H).

Starting from compound (**16**) and using the same procedure, we obtained a compound identical in all respects with the above product (**12**), in 93% yield.

(βR)-γ[(1S,5S)-6,6-*Dimethylbicyclo*[3.1.1]*hept-2-en-2-yl*]-β-*methylbutanenitrile* (**14**).—The alcohol (**12**) (650 mg, 3.09 mmol) was dissolved in dry pyridine (20 ml) and the solution was cooled to 0 °C. To this solution was added toluene-*p*-

sulphonyl chloride (647 mg, 3.40 mmol). The reaction flask was stoppered and kept at 4 °C for 24 h. The mixture was then poured onto ice–water, acidified with 1M-HCl, and the resulting mixture was extracted with AcOEt. The extracts were dried and concentrated. Purification of the residue by FC (cyclohexane–AcOEt, 1:1) gave the tosyl ester (**13**) (912 mg, 81%) as a foam; δ_H 0.80 and 1.24 (each 3 H, s, together CMe_2), 2.42 (3 H, s, Ar*Me*), 3.78 (2 H, s, γ-H_2), 5.30 (1 H, m, 3′-H), and 7.20–7.85 (4 H, AA′BB′ syst, ArH).

To a solution of the foregoing compound (**13**) (415 mg, 1.14 mmol) in dry CH_2Cl_2 (20 ml), was added a solution of tetrabutylammonium cyanide (305 mg, 1.14 mmol) in dry CH_2Cl_2 (5 ml). After 2 h, the mixture was evaporated at room temperature and the residue was directly purified by FC (cyclohexane–AcOEt, 1:1) to give the *title compound* (**14**) (214 mg, 86%) as an oil (Found: C, 76.8; H, 9.7. $C_{14}H_{21}NO$ requires C, 76.7; H, 9.65%); ν_{max} 2 250 cm^{-1}; δ_H 0.85 and 1.27 (each 3 H, s, together CMe_2), 1.31 (3 H, s, β-Me), and 5.45 (1 H, m, 3-H).

Preparation of the Oxirane (**20**) *from the Bromo Derivative* (**16**).—(i) The bromo derivative (**16**) (350 mg, 1.06 mmol) was dissolved in dry DMF (2 ml) and the solution was added dropwise to a stirred suspension of potassium fluoride (125 mg, 2.16 mmol) and dicyclohexyl-18-crown-6 (818 mg, 2.20 mmol) in dry DMF (2 ml) at room temperature under nitrogen. After 12 h, the reaction mixture was poured into pH 7 phosphate buffer (10 ml) and extracted with diethyl ether. The combined extracts were washed with brine and dried. After evaporation of the solvent, the resultant oil was purified by FC (cyclohexane–ether, 8:1) to afford the epoxide (**20**) (249 mg, 94%) as an oil; δ_H 0.80 (3 H, s, C*Me*Me), 1.26 (3 H, t, *J* 8.0 Hz, *Me*CH_2O), 2.75 and 3.99 (2 H, AB syst, *J* 6.5 Hz, oxirane CH_AH_BO), 4.19 (2 H, q, *J* 8.0 Hz, MeCH_2O), and 5.36 (1 H, m, CH=C).

(ii) A mixture of compound (**16**) (112 mg, 3.39 mmol) and potassium acetate (665 mg, 6.78 mmol) in HMPA (5 ml) was vigorously stirred overnight at room temperature. The reaction mixture was then poured into 10% sulphuric acid and extracted with diethyl ether. The combined organic layers were thoroughly washed successively with water and saturated aq. ammonium sulphate and dried. Evaporation under reduced pressure, followed by FC (cyclohexane–diethyl ether, 8:1) gave the epoxide (**20**) (120 mg, 82%).

(αR)-*Ethyl* β-[(1S,5S)-6,6-*Dimethylbicyclo*[3.1.1]*hept*-2-*en*-2-*yl*]-α-*ethyl*-α-*hydroxy propanoate** (**17**).—To a stirred slurry of copper(I) iodide (1.276 g, 6.72 mmol) in dry diethyl ether (25 ml) at 0 °C under nitrogen was added by syringe 1.59M-methyllithium (8.5 ml, 13.44 mmol). The resulting solution of tan lithium dimethylcuprate was stirred at 0 °C for 10 min and then a solution of compound (**20**) (560 mg, 2.24 mmol) in dry diethyl ether (15 ml) was added dropwise during 10 min. The mixture was stirred for an additional 2 h at 0 °C, and then was poured slowly into 1.5M-hydrochloric acid (100 ml). Dilution with diethyl ether (20 ml), separation of organic phase, drying, and removal of the solvent gave a clear oil. Purification by FC (cyclohexane–diethyl ether, 9:1) afforded the *title compound* (**17**) (1.100 g, 81%) as an oil, $[\alpha]_D^{20}$ −22.9° (*c* 1.0, EtOH) (Found: C, 72.2; H, 9.9. $C_{16}H_{26}O_3$ requires C, 72.1; H, 9.8%); δ_H 0.79 (3 H, t, *J* 7.5 Hz, *Me*CH_2), 0.80 and 1.25 each (3 H, s, together CMe_2), 1.29 (2 H, q, *J* 7.5, α-CH_2Me), 3.03 (1 H, s, OH), 4.20 (2 H, q, *J* 7.5 Hz, CH_2O), and 5.27 (1 H, m, CH=C); δ_C 14.3, 21.0, 26.2, 31.5, 32.4, 37.6, 40.4, 46.4, 46.7, 61.5, 78.7, 121.2, 143.9, and 176.3.

* (α*R*)-Ethyl α-[(1*S*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]-methyl-α-hydroxybutanoate.

Treatment of the Bromo Derivative (**16**) *with Caesium Acetate to give Compound* (**18**).—The bromo derivative (**16**) (280 mg, 0.85 mmol) and caesium acetate (190 mg, 1.00 mmol) were combined in HMPA (5 ml) and the mixture was stirred at 70 °C under nitrogen for 6 h. The reaction mixture was then allowed to cool to room temperature, then was diluted with diethyl ether, washed thoroughly with water, dried, and evaporated. The oily residue was purified by FC (cyclohexane–EtOAc, 6:1) to give the epoxide (**20**) (112 mg, 53%) together with the desired *acetate* (**18**) (84 mg, 32%) as an oil, $[\alpha]_D^{20}$ −20.1° (*c* 0.65, EtOH) (Found: C, 65.6; H, 8.5. $C_{17}H_{26}O_5$ requires C, 65.8; H, 8.4%); δ_H 0.80 (3 H, s, C*Me*Me), 1.29 (3 H, t, *J* 7.5 Hz, *Me*CH_2O), 2.05 (3 H, s, Ac), 4.23 (2 H, q, *J* 7.5 Hz, MeCH_2O), and 5.35 (1 H, m, CH=C).

(S)-(+)-3-*Carboxy*-3-*hydroxybutyrolactone* (**26**).—A solution of compound (**5**) (25 mg, 0.082 mmol) in THF–water (1:1) (5 ml) was rendered alkaline by addition of LiOH (10 mg) and left at room temperature for 16 h, then was evaporated to dryness and the residue was taken up in water (5 ml), neutralised with Dowex 50W(H^+), and the solution was concentrated under reduced pressure to give the title compound (**26**) (11 mg, 93%) as needles (from water), m.p. 85–88 °C [lit.,[22] 87–89 °C]; $[\alpha]_D^{20}$ +43.9° (*c* 2.0, water); δ_H[$(CD_3)_2CO$] 2.69 and 3.16 (2 H, AB syst, *J* 1.80 Hz, 2-H_AH_B and 4.34 and 4.64 (2 H, AB syst, *J* 9.6 Hz, 4-H_AH_B).

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