Stereoselective Alkylation of Dianions derived from Chiral Half-Esters of Monosubstituted Malonic Acids: Asymmetric Synthesis of α-Alkyl α-Amino Acids and Key Synthetic Intermediates for *Hunteria* and *Aspidosperma* Indole Alkaloids

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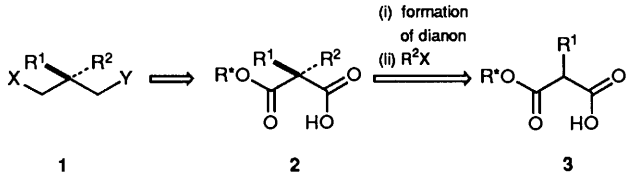
Substitution of the chiral half-esters of monosubstituted malonic acids with halides leads to the formations of mixtures of the diastereoisomeric alkyl- or benzyl-malonic half-esters. The (*R*)-isomers (**13A** and **15A–22A**) were obtained from the phenylmenthyl half-ester **14** of methylmalonic acid in high diastereoisomeric excess. The same stereoisomers were also produced by reaction of the half-esters **9**, **23** and **24** with methyl iodide. Their absolute configurations were determined by transforming the major products into the known α-alkyl α-amino acid derivatives **30**, **33** and **35**. The major product **43**, prepared by allylation of the half-ester **9**, was converted into two lactones **41** and **42**, key intermediates for synthesis of indole alkaloids of the *Hunteria* and *Aspidosperma* types. The mechanism of the above alkylation is discussed.

Recently we developed a new methodology for the synthesis of optically pure chiral propane-1,3-diols from monosubstituted malonic acids, with the possibility of obtaining high enantioselection due to crystallisation-induced asymmetric transformation at the chiral half-esters stage.[1,2] As a further extension of this study, the kinetically controlled alkylation of chiral half-esters **3** of monoalkylmalonic acids (Scheme 1) was investigated, with the expectation of diastereoselective construction of a quaternary asymmetric centre (as shown in structure **2**). The stereoselective transformation of prochiral malonic acids into unsymmetrical molecules would appear to be one of the favourite methods for providing versatile chiral building blocks[3] in the organic synthesis of biologically active compounds. While this type of asymmetric synthesis is common in enzymatic conversions,[4] examples of its use in chemical transformation are rare.[5] We now describe an efficient synthesis of chiral precursors **1** possessing a quaternary carbon centre with high optical purity, and their transformation into α-alkyl α-amino acids and synthetic intermediates for indole alkaloids.[6]



1 2 3

Scheme 1 Strategy for construction of a quaternary asymmetric centre

Results and Discussion

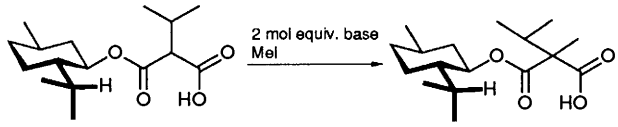
Reaction of Dianions with Alkyl Halides.—It was considered that dianions derived from chiral half-esters **3** of monosubstituted malonic acids were strong nucleophiles and would react, in a diastereoselective manner, with alkyl halides. First, conditions for the methylation of (1*R*,3*R*,4*S*)-*p*-menthan-3-yl hydrogen isopropylmalonate **4** with a variety of bases were examined. With excess of a lithium base, such as lithium diisopropylamide (LDA) or lithium hexamethyldisilazide (LHMDS), a dianion smoothly formed at −78 °C in dry tetrahydrofuran (THF) and reacted with methyl iodide at the same temperature to produce, in excellent yield, a mixture of two diastereoisomers **5** in the ratio 2.4:1 (Table 1). There was no fundamental difference in results between LDA and LHMDS. The ratio of the two diastereoisomers was decreased by addition of hexamethylphosphoramide (HMPA); this indicated the operation of an intramolecular chelation effect. The presence of metal ions such as copper(I) did not effect any improvement of either yield or selectivity. Therefore the alkylations shown in Table 1 were carried out using an excess of LDA in dry THF. The ratios of the two epimers formed were determined by ^{1}H NMR (500 MHz) spectroscopy.

Next, the effect of chiral auxiliaries on the selectivity between the two stereoisomers was investigated as shown in Table 2. Among α-phenylethyl alcohol, 2-(1-naphthyl)-3-borneol,[7] menthol and 8-phenylmenthol,[8] the last compound gave the best selectivity on methylation of ethylmalonic acid. Therefore 8-phenylmenthol was chosen as the chiral auxiliary for the present work.

The dianion derived from 8-phenylmenthyl hydrogen methylmalonate **14** was allowed to react with number of alkyl halides as shown in Table 3. Reactions with ethyl iodide and propyl iodide at −25 °C for 10 h afforded two diastereoisomers in the ratio 4:1. Treatment with allyl iodide or with methallyl iodide (2-methylprop-2-enyl iodide) at −78 °C for 12 h yielded a mixture of two isomers in the ratio 7:1 and 6:1, respectively. Reactions with benzyl bromide and analogues were carried out at −25 °C. The ratios of the two stereoisomers ranged between 8:1 and 16:1.

Reactions of the phenylmenthyl half-esters **9**, **23** and **24** of ethyl-, propyl- and benzyl-malonic acid with methyl iodide at −78 °C furnished a mixture of two diastereoisomers in the ratio of 5:1, 5:1 and 15:1, respectively (Table 4). It was unexpectedly found that the same stereoisomers (**A**) were produced as major products, with similar selectivity, both on alkylation of the methylmalonate **14** and on methylation of the alkylmalonates. The structure of the products was assigned by conversion of the major products into known compounds as discussed in the following section. The substrates for the substitution reaction were prepared by condensation of monosubstituted malonic acids with 8-phenylmenthol in the presence of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP),[1] except for the half-ester **24** of benzylmalonic acid. The half-ester **24** was synthesized by

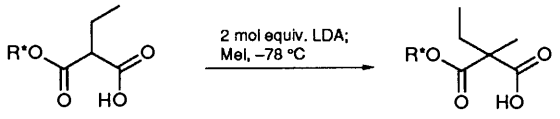
Table 1 Methylation of (1*R*,3*R*,4*S*)-*p*-menthan-3-yl hydrogen isopropylmalonate



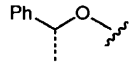
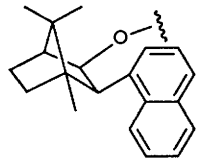
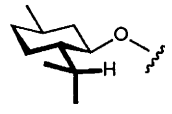
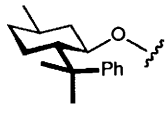
4 **5**

Entry	Conditions	Yield (%)	Ratio of two diastereoisomers
1	LDA, THF, −78 °C	87	2.4:1
2	LHMDS, THF, −78 °C	87	2.4:1
3	LDA, THF, HMPA, −78 °C	83	1.4:1
4	LDA, CuBr·SMe_2, THF, −78 °C	52	1.5:1

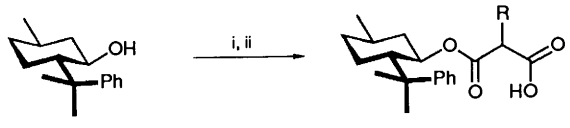
Table 2 Methylation of chiral half-esters of ethylmalonic acid



6 – 9 **10 – 13**

Entry	R*O		Yield (%)	Ratio of two diastereoisomers
1		**6**	78	1.1:1 **10**
2		**7**	90	3:1 **11**
3		**8**	89	2:1 **12**
4		**9**	80	5:1 **13**

condensation of 8-phenylmenthol with malonic acid, followed by benzylation of the acid **25** in the presence of LDA (Scheme 2).

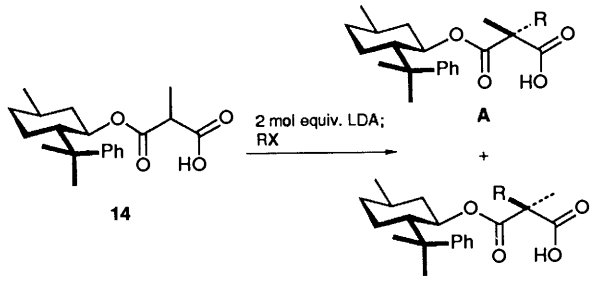


25 R = H
24 R = $PhCH_2$

Scheme 2 *Reagents:* i, $HO_2CCH_2CO_2H$, DCC, DMAP; ii, LDA, $PhCH_2Br$

Transformation of the Acids into Known Compounds: Asymmetric Synthesis of α-Akyl α-Amino Acids.—The product **13**, obtained by the reaction of the half-ester **14** of methylmalonic acid and ethyl iodide, in the ratio 4:1, was converted into the homologous methyl ester **26** by Arndt–Eistert reaction, namely chlorination with oxalyl dichloride, reaction with diazomethane and treatment with silver(I) benzoate in methanol. After separation of two diastereoisomers by high-performance liquid chromatography (HPLC), the major ester **26** was reduced with lithium aluminium hydride (LAH), and the resulting diol was treated with *p*-nitrobenzoyl chloride in the presence of pyridine and DMAP. Comparison of the specific rotation, $[\alpha]_D^{24}$ −1.93° (*c* 1.52, $CHCl_3$) of the product, m.p. 154 °C, with that of the authentic (*R*)-(−)-isomer **27** {lit.,[9] $[\alpha]_D^{20}$ −1.8° (*c* 3.3, $CHCl_3$); m.p. 154 °C}, determined the (*R*)-configuration of the major product (Scheme 3).

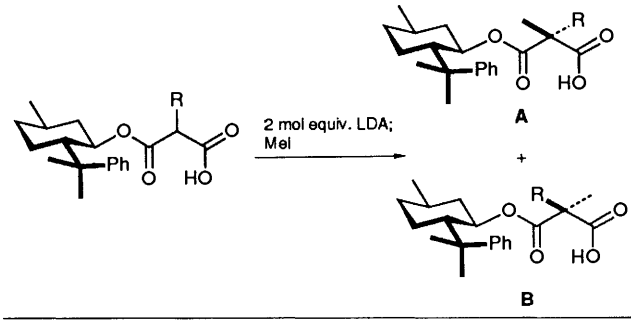
Table 3 Alkylation of (1*R*,3*R*,4*S*)-8-phenyl-*p*-menthan-3-yl hydrogen methylmalonate **14**



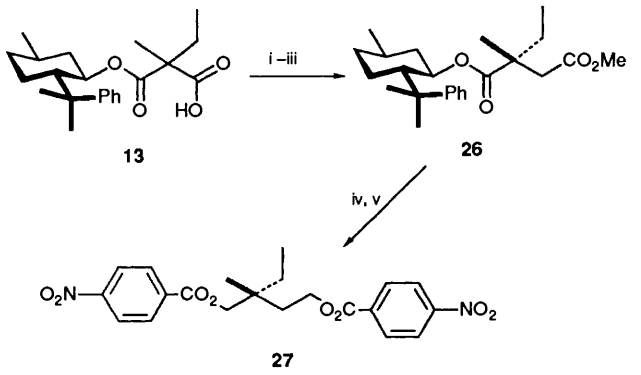
14

Entry	RX	Yield (%)	Ratio of two diastereoisomers
1	EtI	83	4:1 **13A** and **13B**
2	Pr I	72	4:1 **15A** and **15B**
3	CH_2=$CHCH_2I$	77	7:1 **16A** and **16B**
4	CH_2=$CMeCH_2I$	91	6:1 **17A** and **17B**
5	Benzyl bromide	72	12:1 **18A** and **18B**
6	2-Nitrobenzl bromide	94	10:1 **19A** and **19B**
7	4-Nitrobenzyl bromide	95	8:1 **20A** and **20B**
8	4-Methoxybenzyl bromide	71	12:1 **21A** and **21B**
9	2-Methoxybenzyl bromide	73	16:1 **22A** and **22B**

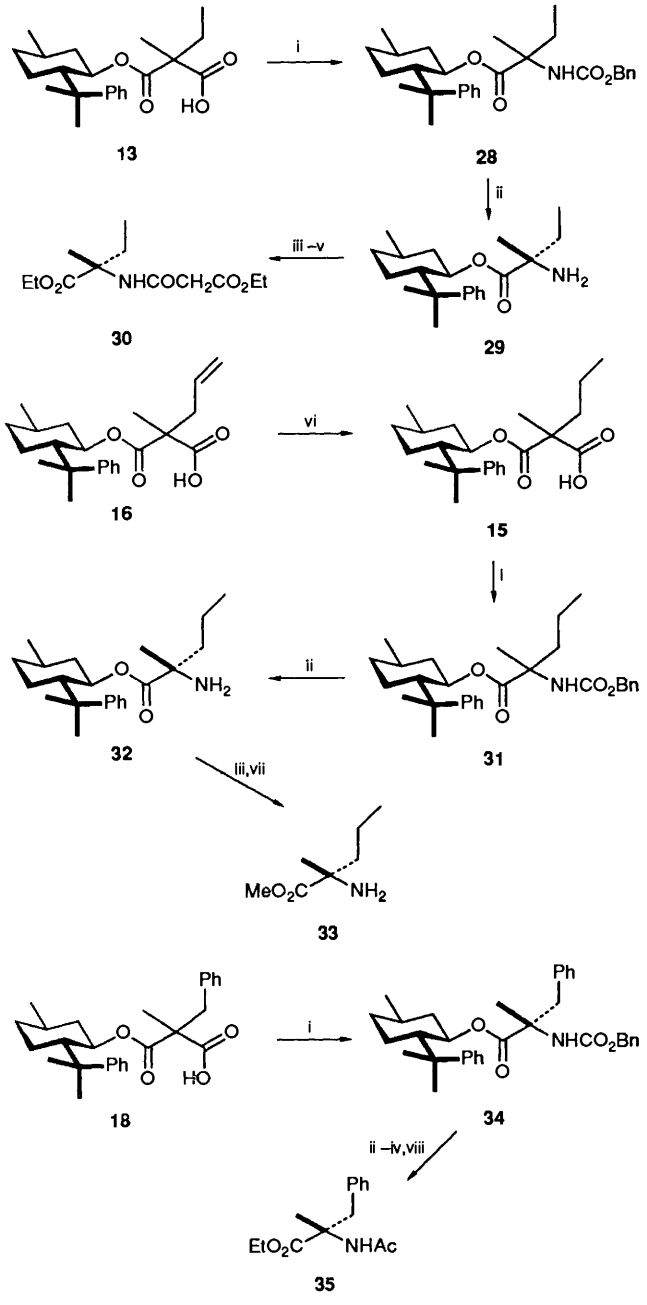
Table 4 Methylation of (1*R*,3*R*,4*S*)-8-phenyl-*p*-menthan-3-yl hydrogen monoalkylmalonates



Entry	R		Yield (%)	Ratio of two diastereoisomers
1	Et	**9**	80	5:1 **13A** and **13B**
2	Pr	**23**	84	5:1 **15A** and **15B**
3	$PhCH_2$	**24**	61	15:1 **18A** and **18B**



Scheme 3 *Reagents:* i, $(COCl)_2$; ii, CH_2N_2; iii, AgOCOPh, MeOH; iv, LAH; v. *p*-nitrobenzoyl chloride, pyridine, DMAP



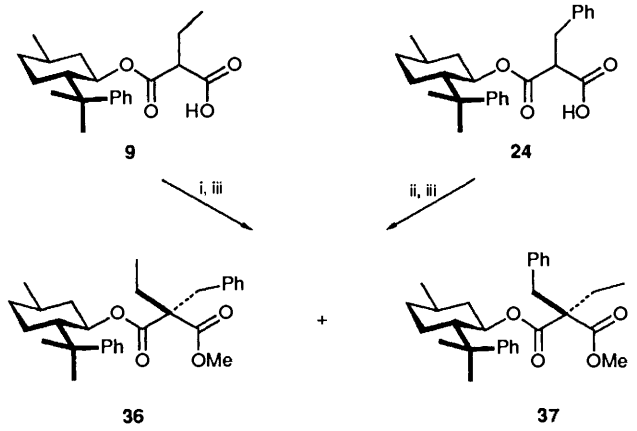
Scheme 4 *Reagents:* i, $(PhO)_2PON_3$, Et_3N, $PhCH_2OH$; ii, Pd–C, cyclohexene; iii, KOH, 18-crown-6; iv, HCl, EtOH; v, EtO_2CCH_2COCl, DMAP; vi, H_2, Pd–C; vii, HCl, MeOH; viii, Ac_2O, DMAP

The 5:1 mixture of compounds **13**, produced by reaction of the half-ester (**9**) of ethylmalonic acid with methyl iodide, was subjected to Curtius-type rearrangement.[10] The urethane **28**, obtained in 86% yield, was deprotected by hydrogenolysis with 10% palladium on carbon and cyclohexene in hot ethanol. The major amine **29**, separated by reverse-phase HPLC, was converted into the amide **30** by the successive hydrolysis of the ester group with potassium hydroxide in the presence of 18-crown-6, esterification with ethanolic hydrogen chloride, and finally reaction with ethyl (chloroformyl)acetate in the presence of DMAP. Comparison of the specific rotation $[\alpha]_D^{20}$ +5.3° (*c* 0.86, benzene) of the amide **30** with the reported data,[11] $[\alpha]_D^{20}$ +5.0° (*c*. 2.096, benzene) of the (*S*)-(+)-isomer **30** indicated the (*S*)-configuration of our product **30** (Scheme 4).

The major components of the product **15**, obtained by two reactions, (i) methylation of the half-ester (**23**) of propylmalonic acid and (ii) propylation of the half-ester (**14**) of methylmalonic acid, were identical with the major product from the hydrogenation of half-ester **16**, prepared by the reaction of half-ester **14** with allyl iodide. Curtius-type reaction of compound **15**, followed by hydrogenolysis of the resulting urethane **31** and HPLC separation, produced the major amine **32**. Hydrolysis of the phenylmenthyl ester group of compound **32**, followed by esterification (methanolic hydrogen chloride), furnished the amino ester **33**. The (*S*)-configuration of our product **33** was determined by its specific rotation, $[\alpha]_D^{28}$ +13.37° (*c* 0.70, EtOH) {(R)-(−)-isomer: lit.,[12] $[\alpha]_D$ −13.0° (*c* 1.5, EtOH)} (Scheme 4).

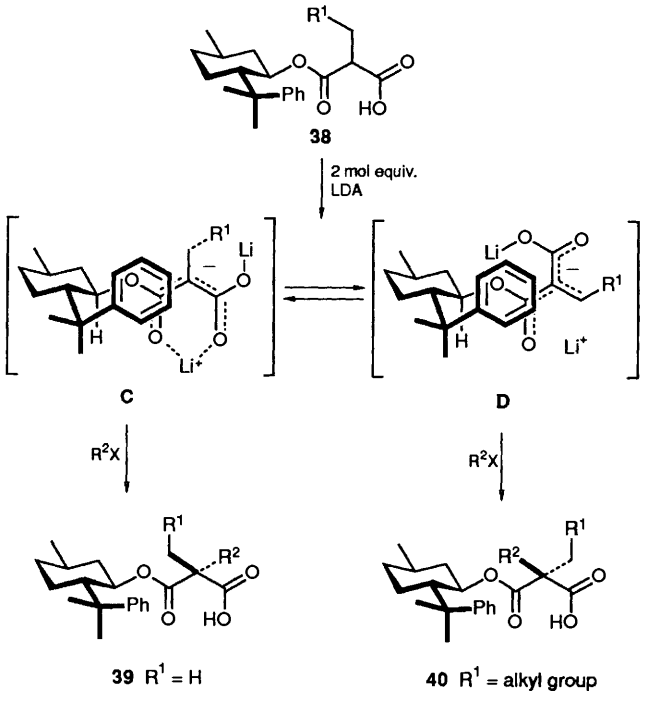
The half-esters **18**, obtained by benzylation of compound **14**, were similarly converted into urethanes, whose HPLC separation gave the major compound **34**, which was transformed into the acetamide **35**. On the basis of its specific rotation, $[\alpha]_D^{27}$ +49.20° (*c* 0.56, $CHCl_3$) {(*R*)-(−)-isomer: lit.,[13] $[\alpha]_D$ −47.8° (*c* 1, $CHCl_3$)}, the absolute configuration of our product **35** was assigned as (*S*) (Scheme 4).

The above transformations not only established the stereochemistry of the major products, but also provided an efficient route to α-alkyl α-amino acids, the subject of much attention in the biological community.[14]



Scheme 5 *Reagents:* i, LDA, $PhCH_2Br$; ii, LDA, EtI; iii, CH_2N_2

Mechanism of Substitution Reactions.—The above unexpected results, the formation of the same major products on alkylation in both sequences, may be due to alkylation at different conformations of dianions. It is interesting that the major product, formed by the benzylation of the half-ester (**9**) of ethylmalonic acid, was different from that obtained by ethylation of the half-ester (**24**) of benzylmalonic acid, although these selectivities were not high (Scheme 5). On the assumption of a *syn* planar arrangement between the alkoxy hydrogen on the phenylmenthol and the ester carbonyl oxygen atom,[15] two conformations (**C** and **D**) arising from different geometries must



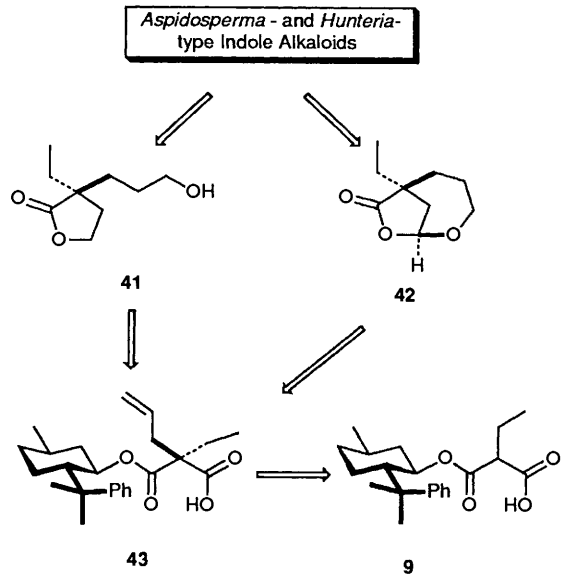
Scheme 6 Putative conformations of dianions reacting to give major products

be considered for the alkylation reaction (Scheme 6). It was assumed from the stereostructures of the major products that the major pathway of the alkylation of the half-ester **14** of methylmalonic acid would be access of the electrophile from the less hindered α-side of the conformation **C**, leading to product **39**, while the other conformation **D** would be preferred for the reaction of the dianions derived from monoalkylmalonates **9**, **23** and **24**. The above results suggested that conformation **C** would be more thermodynamically stable than **D**, although the difference in enthalpy between conformations **C** and **D** would be small. In conformation **C**, the alkyl group (R^1) directed to the α-side would prevent the approach of the electrophile from the same side. In conformation **D**, the rotation of the alkyl group (R^1) is not so restricted compared with the case of conformation **C**, and this transition state **D** leading to product **40** would be more important for the reaction of half-esters of monosubstituted malonic acids **38** (except methylmalonic acid).* We therefore deduced from the above considerations that the major product on benzylation of compound **9** would be compound **37**, whereas the major one from ethylation of compound **24** would be compound **36**.

Asymmetric Synthesis of Key Intermediates for Aspidosperma- *and* Hunteria-*type Indole Alkaloids.*—Recently, Takano *et al.*[17] and Fuji and co-workers[18] have independently accomplished asymmetric total synthesis of *Aspidosperma*- and *Hunteria*-type indole alkaloids. We considered that their synthetic intermediates **41**[18] and **42**[17,18] could be derived from the acid **43**, which would in turn be diastereoselectively obtained by allylation of the half-ester **9** of ethylmalonic acid. Thus the synthetic approach as shown in Scheme 7 was examined in order to confirm the usefulness of this approach and the validity of the above working hypothesis concerning the reaction mechanism.

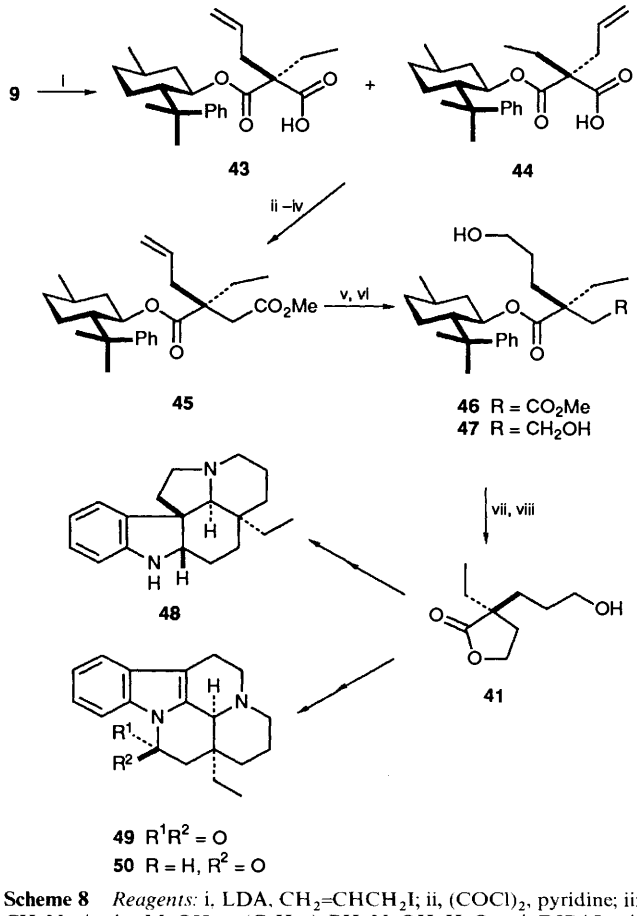
In expectation of the preferred formation of the (*S*)-isomer **43** from the above mechanistic considerations, the half-ester **9** was treated with excess of LDA, followed by allyl iodide at

* A similar geometry was recently proposed for the product of Michael addition of the α-formyl ester derived from 2-(1-naphthyl)-3-borneol.[16]



Scheme 7 Strategy for synthesis of key intermediates **41** and **42** to the indole alkaloids

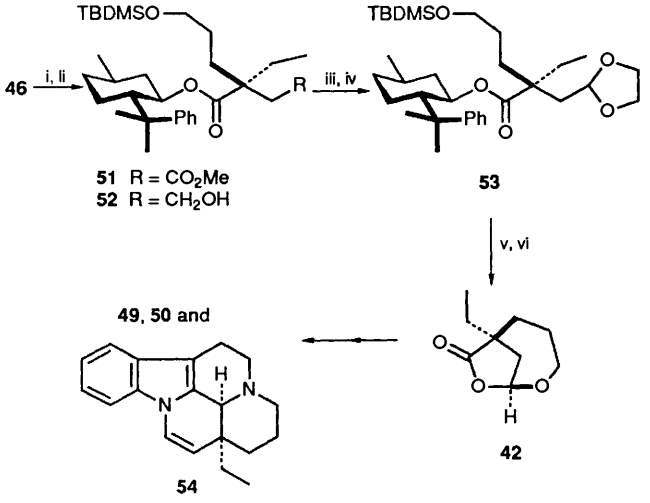
−78 to −50 °C to give (quantitatively) a mixture of two diastereoisomers **43** and **44** in the ratio 2.6:1 (Scheme 8). The epimeric mixture of **43** and **44** was treated with oxalyl dichloride in the presence of pyridine to afford the acid chloride, which was treated with diazomethane. The formed diazo ketone was irradiated in methanol through a Pyrex filter with a 400 W high-pressure mercury lamp to give, in 76% overall yield for the three steps, the methyl ester, whose major isomer **45** was



Scheme 8 *Reagents:* i, LDA, CH_2=$CHCH_2I$; ii, $(COCl)_2$, pyridine; iii, CH_2N_2; iv, *hν*, MeOH; v, $(C_6H_{11})_2BH$, NaOH, H_2O_2; vi, DIBAL; vii, KO_2, 18-crown-6; viii, HCl

isolated by HPLC. Hydroboration of the alkene **45**, using dicyclohexylborane, followed by oxidation, provided the primary alcohol **46** in 92% yield. Reduction of compound **46** with diisobutylaluminium hydride (DIBAL) gave, in 72% yield, the diol **47**, whose phenylmenthyl group was removed by potassium superoxide in the presence of 18-crown-6[19] at room temperature. The crude acid was heated with 9% hydrochloric acid to produce the lactone **41** in 87% overall yield for two steps. The lactone **41**, whose spectral data were identical with those of the authentic compound,[18] had previously been transformed into (−)-aspidospermidine **48**, (−)-eburnamonine **49** and (+)-eburnamine **50**.[18]

Since the specific rotation of the butanolide **41** had not been previously recorded in the literature,[18] the alcohol **46** was converted into the bicyclic lactone **42**[17,18] for the determination of the stereochemistry of the major product (Scheme 9).



Scheme 9 *Reagents:* i, TBDMSCl, DMAP, Et_3N; ii, DIBAL; iii, Swern ox.; iv, $(CH_2OH)_2$, CSA; v, KO_2, 18-crown-6; vi, $HClO_4$

Protection of the hydroxy group of compound **46** with t-butyldimethylsilyl (TBDMS) group (93% yield), followed by reduction of the resulting ester **51** with DIBAL, gave the hydroxy ester **52** in 76% yield. After Swern oxidation of the alcohol function of compound **52**, the resulting aldehyde was converted, in the presence of (1*R*)-camphor-10-sulphonic acid (CSA), into the acetal **53** in 79% overall yield for two steps. The phenylmenthyl group of compound **53** was deblocked with potassium superoxide in the presence of 18-crown-6[19] in refluxing benzene and the acid thus formed was treated with perchloric acid in hot THF to give the bicyclic lactone **42**, m.p. 78–82 °C (lit.,[17] 82–85 °C; lit.,[18] 89–90 °C) in 58% overall yield, whose spectral and chromatographic properties were identical with those of an authentic specimen.[17] The specific rotation, $[\alpha]_D^{24}$ +8.16° (*c* 0.46, CH_2Cl_2) {lit.,[17] $[\alpha]_D$ +6.7° (*c* 0.42, CH_2Cl_2); lit.,[18] $[\alpha]_D^{22}$ +5.4° (*c* 1.47, CH_2Cl_2)} determined the absolute configuration of lactone **42** as depicted. The bicyclic lactone **42** had previously been converted into (−)-eburnamonine **49**, (+)-eburnamine **50** and (−)-eburnamenine **54**.[17]

The consistency of the absolute configuration of the major product **43** with the expected configuration would suggest the validity of the previous mechanistic considerations. Thus the stereochemistry of the major product of alkylation of phenylmenthyl half-esters could be correctly anticipated according to the above reaction mechanisms. In summary, a new method for the enantioselective construction of a quaternary asymmetric carbon centre was developed. The possible production of optically pure building blocks by separation of two diastereoisomers, as well as the possible assignment of their stereostructures, are characteristic merits of this methodology.

Experimental

General Methods.—M.p.s were determined on a Yanako micromelting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IR-Report-100 spectrophotometer. NMR spectra were measured for $CDCl_3$ solutions on a JEOL-FX-90A or a JNM-GX-500 spectrometer. Chemical shifts are reported relative to internal $SiMe_4$, and *J*-values are given in Hz. Mass spectra were taken on a JEOL-JMS-01SG-2, JEOL-DX-300 or JEOL-DX-303 spectrometer. Optical rotations were determined on a JASCO-DIP-340 polarimeter. All reactions except hydrogenation were run under dry nitrogen or argon. Solvents were freshly distilled prior to use: THF and Et_2O were distilled from sodium–benzophenone; CH_2Cl_2 was distilled from P_2O_5; acetonitrile was distilled from CaH_2. Unless otherwise noted, all reaction mixtures were dried, after work-up, over anhydrous Na_2SO_4. Silica gel column chromatography was carried out with Merck Kieselgel 60 (70–230 mesh), while flash chromatography was performed on Merck Kieselgel 60 (230–400 mesh). TLC was carried out on Merck Kieselgel 60 F_{254} (0.25 mm). HPLC was carried out with a Gilson HPLC system Model 302/303 and monitored by UV absorption and refractive-index measurements.

(1R,3R,4S)-p-*Menthan*-3-*yl Hydrogen Isopropyl(methyl)malonates* **5**.—To a stirred solution of diisopropylamine (0.144 cm^3, 1.1 mmol) in dry THF (1 cm^3) at −78 °C was added butyllithium (1.54 mol dm^{-3} solution: 0.68 cm^3, 1.05 mmol) and the mixture was stirred for 30 min at −78 °C. To the resulting mixture was added a solution of the half-esters **4**[1] (142 mg, 0.5 mmol) in dry THF (1.5 cm^3). After the mixture had been stirred for 45 min at −78 °C, MeI (0.12 cm^3, 2.0 mmol) was added at the same temperature. The mixture was stirred for 2 h at −78 °C before the addition of Et_2O (50 cm^3). The resulting mixture was washed successively with 5% HCl, 0.1 mol dm^{-3} aq. $Na_2S_2O_3$, and brine, dried, and evaporated under reduced pressure to give a residue, which was subjected to flash chromatography. Elution with CH_2Cl_2–MeOH (99:1 v/v) afforded the diastereoisomeric mixture of the *acids* **5** (130 mg, 87%) as a syrup [Found: (M^+ + H), 299.2237. $C_{17}H_{31}O_4$ requires *m/z*, 299.2222]; δ_H(500 MHz) 0.73 and 0.74 [3 H (1:2.4), each d, each *J* 7.5, 1-Me], 1.37 and 1.38 [3 H (1:2.4), each s, 2′-Me] and 4.71 and 4.74 [1 H (1:2.4), each dt, each *J* 4.5 and 10.5, 3-H].

(R)-α-*Phenylethyl Hydrogen Ethylmalonates* **6**.—To a stirred solution of (*R*)-(+)-α-phenylethyl alcohol (200 mg, 1.64 mmol), ethylmalonic acid (345 mg, 2.61 mmol), DMAP (39 mg, 0.32 mmol) and MeCN (4 cm^3) in CH_2Cl_2 (4 cm^3) at −37 °C was slowly added a solution of DCC (348 mg, 1.69 mmol) in CH_2Cl_2 (4 cm^3) and the mixture was stirred for 15 h at −37 °C. After concentration under reduced pressure, the residue was taken up into Et_2O and the solution was then filtered. The filtrate was washed successively with saturated aq. $KHSO_4$ and brine, dried and evaporated. The residue was purified by silica gel column chromatography with benzene–AcOEt (95:5 v/v) as eluent to give the *half-esters* **6** (239 mg, 62%) as a pale yellow oil (Found: M^+, 236.1049. $C_{13}H_{16}O_4$ requires M, 236.1047); $[\alpha]_D^{24}$ +51.87° (*c* 2.27, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1740 (C=O); δ_H(500 MHz) 0.96 and 0.99 [3 H (1.16:1), each t, each *J* 7.5, CH_2Me], 1.57 (3 H, d, *J* 6.5, PhCH*Me*), 1.97 (2 H, m, CH_2Me), 3.35 (1 H, br t, *J* 7.5, $CHCO_2H$), 5.95 (1 H, q, *J* 6.5, PhC*H*) and 7.26–7.38 (5 H, m, Ph).

(R)-α-*Phenylethyl Hydrogen Ethyl(methyl)malonates* **10**.—The mixture of half-esters **6** (74 mg, 0.31 mmol) was methylated at −78 °C under the same conditions as for compound **4** and the product was purified by silica gel column chromatography. Elution with benzene–acetone (4:1 v/v) afforded the *acids* **10** (62 mg, 78%) as a yellowish syrup (Found: C, 67.2; H, 7.7.

$C_{14}H_{18}O_4$ requires C, 67.2; H, 7.2%); $[\alpha]_D^{26}$ +38.01° (*c* 0.63, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1725 (C=O); δ_H(500 MHz) 0.857 and 0.864 [3 H (1.11:1), each t, each *J* 7.5, CH_2Me], 1.45 (3 H, s, 2′-Me), 1.56 (3 H, d, *J* 6.5, PhCH*Me*), 1.94–2.02 (2 H, m, CH_2Me), 5.95 and 5.96 [1 H (1:1.11), each q, each *J* 6.5, PhC*H*] and 7.26–7.38 (5 H, m, Ph); *m/z* 250 (M^+).

(2R,3R)-4,7,7-*Trimethyl*-3-(1-*naphthyl*)*bicyclo*[2.2.1]*heptan*-2-*yl Hydrogen Ethyl*(*methyl*)*malonates* **11**.—The mixture of half-esters **7** (34 mg, 0.086 mmol) was methylated under the same conditions as for compound **4** and the crude product was purified by flash chromatography. Elution with hexane–AcOEt (7:1 v/v) gave the *acid* **11** (32 mg, 90%) as a syrup (Found: M^+, 408.2309. $C_{26}H_{32}O_4$ requires M, 408.2299); $[\alpha]_D^{22}$ −134.78° (*c* 0.61, $CHCl_3$); δ_H(500 MHz) 0.15 and 0.31 [3 H (1:3), each t, each *J* 7.5, CH_2Me], 0.42 and 0.55 [3 H (1:3), each s, Me] and 5.51 and 5.56 [1 H (3:1), each d, each *J* 9.0, 2-H].

(1R,3R,4S)-p-*Menthan*-3-*yl Hydrogen Ethyl*(*methyl*)*malonates* **12**.—The mixture of menthyl esters **8**[1] (135 mg, 0.5 mmol) was methylated under the same conditions as for compound **4** and the product was purified by flash chromatography. Elution with CH_2Cl_2–MeOH (98.5:1.5 v/v) afforded the *acids* **12** (126 mg, 89%) as a syrup [Found: (M^+ + H), 285.2063. $C_{16}H_{29}O_4$ requires *m/z*, 285.2066]; δ_H(500 MHz) 0.74 (3 H, d, *J* 7.5, 1-H), 0.88–0.92 (9 H, m, $CHMe_2$ and CH_2Me), 1.44 (3 H, s, 2′-Me) and 4.71 and 4.72 [1 H, (1:2), each dt, each *J* 4.5 and 12.0, 3-H].

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Hydrogen Ethyl*(*methyl*)*malonates* **13A** *and* **13B**.—*Method A*. The mixture of half-esters **9** (173 mg, 0.5 mmol) was methylated under the same conditions as for compound **4** and the product was purified by flash chromatography. Elution with CH_2Cl_2–MeOH (47:3 v/v) afforded the *acids* **13A** and **13B** (144 mg, 80%) as a syrup (Found: M^+, 360.2286. $C_{22}H_{32}O_4$ requires M, 360.2298); δ_H(500 MHz) 0.84–0.89 (6 H, m, 1-Me and CH_2Me), 1.21 and 1.32 (each 3 H, each s, $CPhMe_2$), 1.23 and 1.28 [3 H (5:1), each s, 1′-Me] and 4.89 and 4.93 [1 H (1:5), each dt, each *J* 4.5 and 11.0, 3-H].

Method B. To a solution of LDA [prepared from diisopropylamine (0.048 cm^3, 0.34 mmol) and butyllithium (1.56 mol dm^3; 0.183 cm^3, 0.29 mmol)] in dry THF (1 cm^3) at −78 °C was added a solution of the phenylmenthyl half-esters (**14**) (38 mg, 0.11 mmol) of methylmalonic acid in dry THF (1 cm^3). After having been stirred for 30 min at −78 °C, and then treated with ethyl iodide (0.027 cm^3, 0.34 mmol), the mixture was stirred for 10 h at −25 °C. After dilution with Et_2O (50 cm^3), the mixture was poured into 5% HCl. The aq. layer was thoroughly extracted with Et_2O. The extract was washed with brine, dried and evaporated to give a residue, which was subjected to flash chromatography. Elution with CH_2Cl_2–MeOH (47:3 v/v) afforded the acids **13A** and **13B** (34 mg, 83%) as a syrup; δ_H(500 MHz) 1.23 and 1.28 [3 H (4:1), each s, 1′-Me] and 4.89 and 4.93 [1 H (1:4), each dt, each *J* 4.5 and 11.0, 3-H]; other spectral properties were identical with those of the sample prepared by method A.

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Hydrogen Methyl*(*propyl*)*malonates* **15A** *and* **15B**.—*Method A*. The mixture of half-esters **14** (41 mg, 0.12 mmol) was treated with propyl iodide (0.036 cm^3, 0.37 mmol) at −25 °C for 10 h under the same conditions as method B for the preparation of **13**, and the product was purified by flash chromatography. Elution with hexane–AcOEt (7:3 v/v) gave the *acids* **15A** and **15B** (33 mg, 72%) as a syrup (Found: M^+, 374.2410. $C_{23}H_{34}O_4$ requires M, 374.2455); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (C=O); δ_H(500 MHz) 0.84–0.93 (6 H, m, 1-Me and CH_2Me), 1.22 and 1.32 (each 3 H, each s, $CPhMe_2$), 1.23 and 1.29 [3 H (4:1), each s, 2′-Me] and 4.89 and 4.92 [1 H (1:4), each dt, each *J* 4.5 and 10.5, 3-H].

Method B. The mixture of half-esters (**23**) (1.02 g, 2.83 mmol) of propylmalonic acid was methylated under the same conditions as for compound **4** and the product was purified as above to give the acids **15A** and **15B** (890 mg, 84%) as a syrup; δ_H(500 MHz) 1.23 and 1.29 [3 H (5:1), each s, 2′-Me] and 4.89 and 4.92 [1 H (1:5), each dt, each *J* 4.5 and 10.5, 3-H]; other spectral data were identical with those of the specimen prepared by method A.

Method C. A mixture of the olefinic acids **16** (30 mg, 0.08 mmol) and 10% Pd–C (30 mg) in THF (5 cm^3) was stirred for 24 h at room temperature under H_2 (1 atm). After filtration, followed by evaporation of the filtrate under reduced pressure, the residue was taken up into Et_2O. The organic solution was washed with brine, dried and evaporated under reduced pressure. The residue was subjected to flash chromatography to give the acids **15A** and **15b** (28 mg, 93%) as a syrup; δ_H(500 MHz) 1.23 and 1.29 [3 H (7:1), each s, 2′-Me] and 4.89 and 4.92 [1 H (1:7), each dt, each *J* 4.5 and 10.5, 3-H]; other spectral data were identical with those of the above samples.

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Hydrogen Allyl*(*methyl*)*malonates* **16A** *and* **16B**.—The mixture of half-esters **14** (81 mg, 0.243 mmol) was treated with allyl iodide (409 mg, 2.44 mmol) for 12 h at −78 °C as above and the product was purified by flash chromatography with hexane–AcOEt (4:1 v/v) as eluent to afford the *acids* **16A** and **16B** (69 mg, 77%) as a syrup (Found: M^+, 372.2259. $C_{23}H_{32}O_4$ requires M, 372.2299); $[\alpha]_D^{24}$ −13.47° (*c* 1.28, $CHCl_3$); δ_H(500 MHz) 0.86 (3 H, d, *J* 7.5, 1-Me), 1.22 and 1.27 [3 H (7:1), each s, 2′-Me], 1.23 and 1.32 (each 3 H, each s, $CPhMe_2$), 4.89 and 4.91 [1 H (1:7), each dt, each *J* 4.5 and 11.0, 3-H], 5.06–5.15 (2 H, m, 2 × olefinic H) and 5.60–5.72 (1 H, m, olefinic H).

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Hydrogen Methyl*(2-*methylallyl*)*malonates* **17A** *and* **17B**.—The mixture of half-esters **14** (54 mg, 0.16 mmol) was treated with methallyl iodide (296 mg, 1.62 mmol) for 12 h at −78 °C under the same conditions as above and the product was subjected to flash chromatography with hexane–AcOEt (4:1 v/v) as eluent to give the *acids* **17A** and **17B** (57 mg, 91%) as a syrup (Found: M^+, 386.2419. $C_{24}H_{34}O_4$ requires M, 386.2455); $[\alpha]_D^{23}$ −13.27° (*c* 3.69, $CHCl_3$); δ_H(500 MHz) 0.86 (3 H, d, *J* 7.5, 1-Me), 1.22 and 1.29 [3 H (6:1), each s, 2′-Me], 1.24 and 1.32 (each 3 H, each s, $CPhMe_2$), 1.67 and 1.68 [3 H (6:1), each s, 4′-Me], 4.65 and 4.73 [1 H (6:1), each s, olefinic H], 4.83 and 4.86 [1 H (6:1), each t, each *J* 0.5, olefinic H] and 4.88 and 4.91 [1 H (1:6), each dt, each *J* 4.5 and 11.0, 3-H].

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Hydrogen Benzyl*(*methyl*)*malonates* **18A** *and* **18B**.—*Method A*. The mixture of half-esters **14** (60 mg, 0.18 mmol) was treated with benzyl bromide (0.21 cm^3, 1.80 mmol) for 14 h at −25 °C as above and the product was purified by flash chromatography. Elution with hexane–AcOEt (7:3 v/v) gave the *acids* **18A** and **18B** (55 mg, 72%) as a syrup (Found: M^+, 422.2438. $C_{24}H_{34}O_4$ requires M, 422.2455); $[\alpha]_D^{29}$ −17.15° (*c* 3.80, $CHCl_3$); δ_H(500 MHz) 0.83 (3 H, d, *J* 7.5, 1-Me), 1.16 (3 H, s, 2′-Me), 1.23 and 1.32 (each 3 H, each s, $CPhMe_2$), 2.97 and 3.03 [1 H (12:1), each d, each *J* 13.5, C*H*HPh], 3.11 and 3.14 [1 H, (12:1), each d, each *J* 13.5, CH*H*Ph] and 4.90 (1 H, dt, *J* 4.5 and 11.0, 3-H).

Method B. The mixture of half-esters (**24**) (32 mg, 0.078 mmol) of benzylmalonic acid was methylated under the same conditions as for compound **4** and the product was purified as above to give the acids **18A** and **18B** (20 mg, 61%) as a syrup; δ_H(500 MHz) 2.97 and 3.03 [1 H (15:1), each d, each *J* 13.5, C*H*HPh] and 3.11 and 3.14 [1 H (15:1), each d, each *J* 13.5,

CH*H*Ph]; other spectral data were identical with those of the sample prepared by method A.

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Hydrogen Methyl*(2-*nitrobenzyl*)*malonates* **19A** *and* **19B**.—The mixture of half-esters **14** (110 mg, 0.33 mmol) was treated with 2-nitrobenzyl bromide (715 mg, 3.31 mmol) for 14 h at −25 °C under the same conditions as the case of the conversion of compounds **14** into compounds **13**, and the product was purified by flash chromatography. Elution with hexane–AcOEt (4:1 v/v) afforded the acids **19A** and **19B** (146 mg, 94%) as a yellowish syrup, $[\alpha]_D^{26}$ +10.82° (*c* 2.18, $CHCl_3$); δ_H(500 MHz) 0.82 (3 H, d, *J* 7.5, 1-Me), 1.14 (3 H, s, 2′-Me), 1.20 and 1.29 (each 3 H, each s, CPh*Me*$_2$), 3.49 and 3.56 [1 H (10:1), each d, each *J* 14.0, C*H*HAr], 3.54 and 3.59 [1 H (10:1), each d, each *J* 14.0, CH*H*Ar] and 4.89 and 4.92 [1 H (10:1), each dt, each *J* 4.5 and 11.0, 3-H].

The above acids **19A** and **19B** were treated with excess of CH_2N_2 in the usual manner and the product was purified by flash chromatography with hexane–AcOEt (95:1 v/v) as eluent to give the corresponding *methyl esters* as a yellowish syrup (Found: M^+, 481.2461. $C_{28}H_{35}NO_6$ requires M, 481.2462); $[\alpha]_D^{24}$ −2.23° (*c* 0.36, $CHCl_3$); δ_H(500 MHz) 0.82 (3 H, d, *J* 7.5, 1-Me), 1.07 and 1.24 [3 H (1:10), each s, 2′-Me], 1.20 and 1.30 (each 3 H, each s, CPh*Me*$_2$), 3.68 (3 H, s, OMe) and 4.89 and 4.93 [1 H (10:1), each dt, each *J* 4.5 and 11.0, 3-H].

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Hydrogen Methyl*(4-*nitrobenzyl*)*malonates* **20A** *and* **20B**.—The mixture of half-esters **14** (60 mg, 0.18 mmol) was treated with 4-nitrobenzyl bromide (390 mg, 1.80 mmol) for 14 h at −25 °C as above and the product was purified by flash chromatography with hexane–AcOEt (3:2 v/v) as eluent to give the acids **20A** and **20B** (83 mg, 95%), which were converted (CH_2N_2) into the corresponding methyl esters. Flash chromatography with hexane–AcOEt (95:5 v/v) as eluent afforded the *esters* as a yellowish oil (Found: M^+, 481.2440. $C_{28}H_{35}NO_6$ requies M, 481.2462); δ_H(500 MHz) 0.82 (3 H, d, *J* 7.5, 1-Me), 2.90 and 3.09 [1 H (8:1), each d, each *J* 13.0, C*H*HAr], 3.24 and 3.26 [1 H (1:8), each d, each *J* 13.0, CH*H*Ar], 3.70 and 3.72 [3 H (8:1), each s, OMe] and 4.90 and 4.93 [1 H (8:1), each dt, each *J* 4.5 and 11.0, 3-H].

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Hydrogen* 4-*Methoxybenzyl*(*methyl*)*malonates* **21A** *and* **21B**.—The mixture of half-esters **14** (97 mg, 0.29 mmol) was treated with 4-methoxybenzyl bromide (587 mg, 2.92 mmol) for 14 h at −25 °C as above and the product was purified by flash chromatography to give the acids **21A** and **21B** (97 mg, 71%). Treatment of acids **21** with CH_2N_2, followed by flash chromatography with hexane–AcOEt (95:5 v/v) as eluent, afforded the corresponding *methyl esters* as a syrup (Found: M^+, 466.2719. $C_{29}H_{38}O_5$ requires M, 466.2717); $[\alpha]_D^{23}$ −18.8° (*c* 0.79, $CHCl_3$); δ_H(500 MHz) 0.83 (3 H, d, *J* 7.5, 1-Me), 1.20 and 1.26 [3 H (1:12), each s 2-Me], 1.22 and 1.32 (each 3 H, each s, CPh*Me*$_2$), 2.87 and 2.99 [1 H, (12:1), each d, each *J* 13.0, C*H*HAr], 3.16 and 3.19 [1 H (1:12), each d, each *J* 13.0, CH*H*Ar], 3.70 and 3.72 [3 H (12:1), each s, OMe], 3.76 (3 H, s, OMe), 4.89 and 4.92 [1 H (12:1), each dt, each *J* 4.5 and 11.0, 3-H] and 6.80 and 7.02 (each 2 H, each d, each *J* 8.5, 4 × ArH).

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Hydrogen* 2-*Methoxybenzyl*(*methyl*)*malonates* **22A** *and* **22B**.—The mixture of half-esters **14** (97 mg, 0.29 mmol) was treated with 2-methoxybenzyl bromide (587 mg, 2.92 mmol) for 14 h at −25 °C as above and the product was purified by flash chromatography with hexane–AcOEt (9:1 v/v) as eluent to give the *acids* **22A** and **22B** (97 mg, 93%) as a syrup (Found: M^+, 452.2577. $C_{28}H_{36}O_5$ requires M, 452.2561); $[\alpha]_D^{25}$ −13.92° (*c* 6.82, $CHCl_3$); δ_H(500 MHz) 0.84 (3 H, d, *J* 7.5, 1-Me), 1.13 (3 H, s, 2′-Me), 1.24 and 1.34 (each 3 H, each s, CPh*Me*$_2$), 3.10 and 3.19 [1 H (16:1), each d, each *J* 14.0, C*H*HAr], 3.25 and 3.29 [1 H (16:1), each d, each *J* 14.0, CH*H*Ar] and 4.89 and 4.91 [1 H (1:16), each dt, each *J* 4.5 and 11.0, 3-H].

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Hydrogen Malonate* **25**.—To a stirred solution of (−)-phenylmenthol[2] (525 mg, 2.26 mmol), malonic acid (470 mg, 4.52 mmol), DMAP (20 mg, 0.16 mmol) and MeCN (25 cm^3) in CH_2Cl_2 (25 cm^3) at −35 °C was slowly added a solution of DCC (699 mg, 3.39 mmol) in CH_2Cl_2 (25 cm^3) and the mixture was stirred for 10 h at −30 °C. After evaporation, the residue was taken up into Et_2O and the solution was filtered through Celite. The filtrate was washed successively with saturated aq. $KHSO_4$ and brine, dried, and evaporated. The residue was subjected to flash chromatography with benzene–acetone (4:1 v/v) as eluent to afford a solid, which was recrystallised from benzene to give the *acid* **25** (705 mg, 98%) as needles, m.p. 111–112 °C (Found: M^+, 318.1838. $C_{19}H_{26}O_4$ requires M, 318.1831); $[\alpha]_D^{22}$ +3.19° (*c* 3.32, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1748 and 1695 (C=O); δ_H(90 MHz) 0.87 (3 H, d, *J* 6.9, 1-Me), 1.20 and 1.32 (each 3 H, each s, CPh*Me*$_2$), 2.31 and 2.72 (each 1 H, each d, each *J* 18.0, C*H*$_2$CO$_2$H), 4.93 (1 H, dt, *J* 4.8 and 11.4, 3-H) and 7.22–7.41 (5 H, m, Ph).

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Hydrogen Benzylmalonates* **24**.—To a stirred solution of LDA [prepared from diisopropylamine (0.16 cm^3, 1.13 mmol) and butyllithium (1.56 mol dm^{-3}; 0.54 cm^3, 0.85 mmol)] in dry THF (5 cm^3) at −78 °C was added a solution of the above acid **25** (90 mg, 0.28 mmol) in dry THF (5 cm^3). After having been stirred for 30 min, and then treated with benzyl bromide (0.12 cm^3, 0.99 mmol), the mixture was stirred for 10 h at −25 °C. After the same work-up as previously, the product was purified by flash chromatography with hexane–AcOEt (4:1 v/v) as eluent to give the *half-esters* **24** (83 mg, 72%) as a syrup (Found: M^+, 408.2298. $C_{26}H_{32}O_4$ requires M, 408.2299); $[\alpha]_D^{26}$ +15.30° (*c* 3.49, $CHCl_3$); δ_H(500 Hz) 0.82 and 0.85 [3 H (9:11), each d, each *J* 7.5, 1-Me], 1.09 and 1.12 [3 H (9:11), each s, 8-Me], 1.19 and 1.27 [3 H (9:11), each s, 8-Me], 2.85–3.06 (3 H, m, C*H*C*H*$_2$Ph) and 4.80 (1 H, dt, *J* 4.5 and 11.0, 3-H).

4-*Methyl* 1-[(1′R,3′R,4′S)-8′-*Phenyl*-p-*menthan*-3-*yl*] (R)-2-*Ethyl*-2-*methylbutanedioate* **26**.—A mixture of the half-esters **13** (118 mg, 0.32 mmol), prepared by method B, and oxalyl dichloride (0.5 cm^3) in dry CH_2Cl_2 (3 cm^3) was stirred for 20 h at room temperature, before evaporation under reduced pressure. The acid chloride thus formed was used in the next reaction without purification.

The product was taken up into benzene (2 cm^3) and then treated with an excess of CH_2N_2 in Et_2O. After having been stirred for 5 h at room temperature the mixture was evaporated under reduced pressure. The crude diazo ketone was subjected to the next reaction without purification.

A mixture of the above product, silver(I) benzoate (7.6 mg, 0.32 mmol) and Et_3N (0.4 cm^3) in MeOH (5 cm^3) was stirred for 14 h at room temperature. After dilution with benzene (30 cm^3) and filtration, the filtrate was washed successively with saturated aq. $KHSO_4$, brine, saturated aq. $NaHCO_3$ and brine, dried, and evaporated under reduced pressure. The residue was purified by flash chromatography with hexane–Et_2O (95:5 v/v) as eluent to give a epimeric mixture of esters **26** (64 mg, 51%), whose ^1H NMR spectrum (500 MHz) and HPLC chromatogram determined the ratio of two diastereoisomers as 4.1. Separation of stereoisomers by HPLC on a 10 × 250 mm column of Dynamax microsorb silica 5 μm with hexane–AcOEt (98:2 v/v) as eluent (4 cm^3 min^{-1}) gave the major, (R)-*isomer*

26 as an oil (Found: M^+, 388.2628. $C_{24}H_{36}O_4$ requires M, 388.2616); $[\alpha]_D^{24}$ −17.40° (*c* 0.91, $CHCl_3$); δ_H(500 MHz) 0.82 (3 H, t, *J* 8.0, CH_2*Me*), 0.85 (3 H, d, *J* 7.5, 1′-Me), 1.15, 1.24 and 1.37 (each 3 H, each s, 3 × Me), 2.28 and 2.59 (each 1 H, each d, each *J* 16.5, CH_2CO_2Me), 3.63 (3 H, s, OMe) and 4.85 (1 H, dt, *J* 4.5 and 11.0, 3′-H).

(2R)-2-*Ethyl*-2-*methylbutane*-1,4-*diazo Bis*-(4-*Nitrobenzoate*) **27**. To a stirred mixture of LAH (50 mg, 1.35 mmol) in dry Et_2O (2 cm^3) was added a solution of the diester **26** (50 mg, 0.128 mmol) in dry Et_2O (3 cm^3) and the mixture was heated for 1.5 h under reflux. After having been cooled, followed by successive addition of water (0.05 cm^3), 15% aq. NaOH (0.05 cm^3) and water (0.15 cm^3), the mixture was filtered through Celite and washed with Et_2O. The combined filtrate was dried and evaporated to give a residue, which was used in the following reaction without purification.

A mixture of the crude product, 4-nitrobenzoyl chloride (40 mg, 0.22 mmol), DMAP (5 mg, 0.04 mmol) and pyridine (1 cm^3) in dry CH_2Cl_2 (2 cm^3) was stirred for 24 h at room temperature. After dilution with benzene, the mixture was washed successively with saturated aq. $KHSO_4$ and brine, dried, and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography with hexane–AcOEt (9:1 v/v) as eluent to give the bisnitrobenzoate **27** (43 mg, 78%) as a solid, recrystallisation of which from EtOH–AcOEt afforded fine needles, m.p. 154 °C; $[\alpha]_D^{24}$ −1.93° (*c* 1.52, $CHCl_3$) {for (*R*)-(−)-isomer: lit.,[9] m.p. 154 °C; $[\alpha]_D^{20}$ −1.8° (*c* 3.3, $CHCl_3$)}.

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl* 2′-*Benzyloxycarbonyl*-*amino*-2′-*methylbutanoates* **28**.—To a solution of the half-esters **13** (251 mg, 0.69 mmol), prepared by method A, in dry benzene (20 cm^3) were added diphenylphosphoryl azide (0.45 cm^3, 2.092 mmol) and Et_3N (0.32 cm^3, 2.30 mmol) and the mixture was heated for 2 h under reflux. After addition of benzyl alcohol (0.29 cm^3, 2.79 mmol) the resulting mixture was heated for 20 h under reflux. After evaporation under reduced pressure, the residue was taken up into AcOEt. The organic solution was washed successively with 5% aq. citric acid, water, saturated aq. $NaHCO_3$ and brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography with hexane–AcOEt (95:5 v/v) to give the *urethanes* **28** (276 mg, 86%) as a pale yellowish oil (Found: M^+, 465.2880. $C_{29}H_{39}NO_4$ requires M, 465.2879); $[\alpha]_D^{24}$ −5.03° (*c* 1.29, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3470 and 3440 (NH) and 1720 (C=O); δ_H(500 MHz) 0.76 (3 H, t, *J* 7.5, CH_2*Me*), 0.86 (3 H, d, *J* 7.5, 1-Me), 1.20 and 1.22 [3 H, (1:5), each s, Me], 1.32 (3 H, s, Me), 1.37 and 1.40 [3 H (1:5), each s, Me], 4.86 and 4.88 [1 H (1:5), each dt, each *J* 4.5 and 11.0, 3-H] and 5.17 and 5.37 [1 H (1:5), each br s, NH].

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl* (2′S)-2′-*Amino*-2′-*methylbutanoate* **29**.—A mixture of the urethanes **28** (237 mg, 0.51 mmol), 10% Pd–C (150 mg) and cyclohexene (3 cm^3, 0.03 mol) in EtOH (8 cm^3) was heated for 45 min under reflux. After having been cooled, the mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was partitioned between 10% aq. ammonia and CH_2Cl_2. The aq. layer was thoroughly extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel with hexane–isopropyl alcohol (9:1 v/v) as eluent to afford the epimeric mixture of *amines* **29** (135 mg, 81%) as a pale yellowish syrup. HPLC separation on a 4.6 × 250 mm column of Dynamax microsorb C18 5 μm with 5% aq. $(NH_4)_2CO_3$–MeOH (1:4 v/v) as eluent (1 cm^3 min^{-1}) gave the *major amine* **29** as a syrup (Found: M^+, 331.2462. $C_{21}H_{33}NO_2$ requires M, 331.2511); $[\alpha]_D^{24}$ −9.48° (*c* 1.24, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3380 and 3320 (NH) and 1710 (C=O); δ_H($CDCl_3$) 0.81 (3 H, t, *J* 7.1, CH_2*Me*), 0.87 (3 H, d, *J* 7.0, 1-Me), 1.04, 1.20 and 1.33 (each 3 H, each s, 3 × Me), 4.86 (1 H, dt, *J* 4.5 and 11.0, 3-H) and 7.26–7.33 (5 H, m, Ph).

Ethyl (2S)-2-(*Ethoxycarbonylacetamide*)-2-*methylbutanoate* **30**.—To a solution of the above amine **29** (15.5 mg, 0.046 mmol) in toluene (3 cm^3) were added 18-crown-6 (15 mg, 0.057 mmol) and KOH (150 mg, 2.68 mmol) and the mixture was heated for 24 h under reflux. After addition of water (3 cm^3), the separated aq. layer was further washed with Et_2O and then acidified with conc. HCl. Evaporation of the resulting mixture under reduced pressure gave a residue, which was taken up into anhydrous EtOH. Filtration of the mixture, followed by evaporation of the filtrate, gave a residue, which was further taken up into EtOH. After filtration, followed by evaporation, the residue was treated with HCl–EtOH (10 w/v %; 3 cm^3) and the mixture was heated for 20 h under reflux. After evaporation under reduced pressure, the residue was partitioned under $CHCl_3$ and 10% aq. ammonia. The aq. layer was thoroughly extracted with $CHCl_3$. The combined extracts were washed with brine, dried and evaporated under reduced pressure to give a residue, which was subjected to silica gel column chromatography. Elution with $CHCl_3$ gave the amino ester as a pale yellowish oil, which was dissolved in dry CH_2Cl_2 (2 cm^3). To the solution were added ethyl (chloroformyl)acetate (0.085 cm^3, 0.664 mmol) and DMAP (100 mg, 0.818 mmol) and the mixture was stirred for 24 h at room temperature. After dilution with Et_2O (30 cm^3), the mixture was washed successively with 10% aq. $KHSO_4$, brine, saturated aq. $NaHCO_3$ and brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography with hexane–AcOEt (9:1 v/v) as eluent to give the (*S*)-amide **30** (8.6 mg, 71% from **29**, $[\alpha]_D^{20}$ +5.3° (*c* 0.86, benzene) {for (*S*)-(+)-isomer: lit.,[11] $[\alpha]_D^{20}$ +5.0° (*c* 2.096, benzene)}.

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl* 2′-*Benzyloxycarbonyl*-*amino*-2′-*methylpentanoates* **31**.—The mixture of propyl compounds **15** (349 mg, 0.93 mmol), prepared by method B, was transformed, according to the same procedure as for compound **28**, into the *urethanes* **31** (408 mg, 91%) as a pale yellowish oil (Found: C, 75.2; H, 8.65; N, 2.95. $C_{30}H_{41}NO_4$ requires C, 75.15; H, 8.55; N, 2.9%); $[\alpha]_D^{25}$ +0.28° (*c* 3.56, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3460 and 3430 (NH) and 1730 (C=O); δ_H(500 MHz) 0.86 (3 H, d, *J* 7.0, 1-Me), 0.87 (3 H, t, *J* 7.0, CH_2*Me*), 1.22, 1.32 and 1.40 (each 3 H, each s, 3 × Me), 4.88 (1 H, dt, *J* 4.5 and 11.0, 3-H) and 5.23 and 5.36 [1 H (1:5), each br s, NH]; *m*/*z* 479 (M^+).

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl* (2′S)-2′-*Amino*-2′-*methylpentanoate* **32**. Hydrogenolysis of the above urethanes **31** (852 mg, 1.78 mmol) was carried out under the same conditions as for compound **28** and the product was purified by silica gel column chromatography with hexane–isopropyl alcohol (95:5 v/v) to give an epimeric mixture of amines (**32** and its epimer) (609 mg, 99%) as a yellowish syrup. HPLC separation on a 4.6 × 250 mm column of Dynamax microsorb C18 5 μm with 5% aq. $(NH_4)_2CO_3$–MeOH (1:4 v/v) as eluent (1 cm^3 min^{-1}) gave the *major amine* **32** as a syrup (Found: M^+, 345.2637. $C_{22}H_{35}NO_2$ requires M, 345.2668); $[\alpha]_D^{21}$ −5.04° (*c* 2.4, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3360 and 3300 (NH) and 1710 (C=O); δ_H($CDCl_3$, 500 MHz) 0.87 (3 H, d, *J* 7.5, 1-Me), 0.90 (3 H, t, *J* 8.0, CH_2*Me*), 1.04, 1.20 and 1.32 (each 3 H, each s, 3 × Me), 4.84 (1 H, dt, *J* 4.5 and 11.5, 3-H) and 7.26–7.33 (5 H, m, Ph).

Methyl (2S)-2-*Amino*-2-*methylpentanoate* **33**.—A mixture of

the above amine **32** (90 mg, 0.26 mmol), 18-crown-6 (36 mg, 0.14 mmol) and KOH (158 mg, 2.82 mmol) in toluene (3 cm^3) was heated for 12 h under reflux. After addition of water (5 cm^3), the aq. layer was washed with Et_2O and then acidified by addition of conc. HCl. Evaporation of the aq. solution under reduced pressure gave a residue, which was taken up into anhydrous MeOH. Filtration, followed by evaporation of the filtrate under reduced pressure, afforded a residue, to which was added 10 w/v % HCl–MeOH (4 cm^3). The resulting mixture was heated for 6 h under reflux. After evaporation under reduced pressure, the residue was partitioned between $CHCl_3$ and 10% aq. ammonia. The aq. layer was thoroughly extracted with $CHCl_3$. The combined extracts were washed with brine, dried and evaporated under reduced pressure to give a residue, which was purified by silica gel column chromatography. Elution with $CHCl_3$ gave the (*S*)-amino ester **33** (24.9 mg, 66%) as an oil; $[\alpha]_D^{28}$ +13.37° (*c* 0.70, EtOH) {for (*R*)-(−)-isomer: lit.,[12] $[\alpha]_D$ −13.0° (*c* 1.5, EtOH)}.

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl* (2′S)-2′-*Benzyloxycarbonylamino*-2′-*methyl*-3′-*phenylpropanoate* **34**.—The mixture of benzyl compounds **18** (37 mg, 0.087 mmol), prepared by method A, was transformed, according to the same procedure as for compound **28**, into the title urethanes (**34** and its epimer) (36 mg, 80%) as a syrup whose ^1H NMR (500 MHz) and HPLC analyses determined the ratio of two diastereoisomers as 12:1. HPLC separation on a 4.6 × 250 mm column of Dynamax microsorb silica 5 μm with hexane–AcOEt (95:5 v/v) as eluent (1 cm^3 min^{-1}) gave the *major* (S)-*isomer* **34** as a solid, m.p. 129–130 °C [Found: ($M^+ - CH_2Ph$), 436.2491. $C_{27}H_{34}NO_4$ requires *m/z*, 436.2486]; $[\alpha]_D^{25}$ −0.8° (*c* 1.0, $CHCl_3$); δ_H(500 MHz) 0.86 (3 H, d, *J* 7.5, 1-Me), 1.08 and 1.10 (each 3 H, each s, 2 × Me), 3.03 and 3.11 (each 1 H, each d, each *J* 13.0, CCH_2Ph) and 5.00 (1 H, br s, NH).

Ethyl (2S)-2-*Acetamido*-2-*methyl*-3-*phenylpropanoate* **35**.—A mixture of the above urethane **34** (22.1 mg, 0.041 mmol), 18-crown-6 (15 mg, 0.056 mmol) and KOH (105 mg, 1.944 mmol) was heated for 24 h under reflux. After evaporation under reduced pressure, the residue was taken up into MeOH and then acidified by addition of 10 w/v% HCl–MeOH. Filtration, followed by evaporation of the filtrate under reduced pressure, gave a residue, which was dissolved in anhydrous EtOH. After filtration, followed by evaporation under reduced pressure, the residue was treated with 5 w/v % HCl–EtOH. The mixture was heated for 15 h under reflux and then evaporated under reduced pressure. The residue was partitioned between $CHCl_3$ and 10% aq. ammonia. The aq. phase was thoroughly extracted with $CHCl_3$. The combined organic phases were washed with brine, dried and evaporated to give a residue, which was dissolved in dry CH_2Cl_2 (2 cm^3). To the resulting mixture were added DMAP (100 mg) and acetic anhydride (0.3 cm^3), and the mixture was stirred for 14 h at room temperature. After addition of Et_2O (20 cm^3), the mixture was washed successively with saturated aq. $KHSO_4$, saturated aq. $NaHCO_3$ and brine, dried, and evaporated under reduced pressure. The residue was purified by flash chromatography with hexane–AcOEt (1:1 v/v) as eluent to give the (*S*)-amide **35** (7.1 mg, 68%) as an oil; $[\alpha]_D^{27}$ +49.20° (*c* 0.56, $CHCl_3$) {for (*R*)-(−)-isomer: lit.,[13] $[\alpha]_D$ −47.8° (*c* 1, $CHCl_3$)}.

Methyl (1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl* (R)- *and* (S)-*Benzyl*(*ethyl*)*malonates* **36** *and* **37**.—*Method A*. The mixture of half-esters **9** (77 mg, 0.24 mmol) was treated with benzyl bromide (0.264 cm^3, 2.21 mmol) for 20 h at −20 °C under the same conditions as for compound **4**. After chromatography on silica gel with hexane–AcOEt (7:3 v/v) as eluent, the product in MeOH (5 cm^3) was treated with excess of CH_2N_2 in Et_2O. After having been stirred for 30 min, the mixture was evaporated under reduced pressure to give a residue, which was taken up into Et_2O. The solution was washed successively with saturated aq. $KHSO_4$, brine, saturated aq. $NaHCO_3$ and brine, and dried, and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography with hexane–AcOEt (95:5 v/v) as eluent to afford the *esters* **36** and **37** (63 mg, 63%) as an oil (Found: M^+, 450.2793. $C_{29}H_{38}O_4$ requires M, 450.2770); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O); δ_H(500 MHz) 0.83–0.95 (6 H, m, 2 × Me), 1.20 and 1.26 [3 H (5.5:3), each s, Me], 1.22 and 1.31 [3 H (5.5:3), each s, Me], 3.06 and 3.14 [1 H (3:5.5), each d, each *J* 14.0, C*H*HPh], 3.20 and 3.30 [1 H (5.5:3), each d, each *J* 14.0, CH*H*Ph], 3.66 and 3.72 [3 H (3:5.5), each s, OMe] and 4.89 and 4.90 [1 H (3:5.5), each dt, each *J* 4.5 and 11.0, 3-H].

Method B. The mixture of half-esters **24** (5 mg, 0.012 mmol) was treated with ethyl iodide (0.012 cm^3, 0.151 mmol) for 20 h at −20 °C as above and the product was similarly converted into the methyl esters **36** and **37** (3.3 mg, 60%) as an oil; δ_H(500 MHz) 0.83–0.95 (6 H, m, 2 × Me), 1.20 and 1.26 [3 H (3:5), each s, Me], 1.22 and 1.31 [3 H (3:5), each s, Me], 3.06 and 3.14 [1 H (5:3), each d, each *J* 14.0, C*H*HPh], 3.20 and 3.30 [1 H (3:5), each d, each *J* 14.0, CH*H*Ph], 3.66 and 3.72 [3 H (5:3), each s, OMe] and 4.89 and 4.90 [1 H (5:3), each dt, each *J* 4.5 and 11.0, 3-H].

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Hydrogen Allyl*(*ethyl*)*malonates* **43** *and* **44**.—The mixture of half-esters **9** (271 mg, 0.78 mmol) was treated with allyl iodide (0.8 cm^3, 8.83 mmol) for 15 h at −78 to −50 °C under the same conditions as for compound **4** and the product was purified by silica gel column chromatography. Elution with hexane–AcOEt (7:3 v/v) gave the mixture of *diastereoisomeric acids* **43** and **44** (302 mg, 99%) as a syrup (Found: 72.0; H, 8.7. $C_{24}H_{34}O_4 \cdot 0.7H_2O$ requires C, 72.25; H, 8.9%); $[\alpha]_D^{22}$ −17.02° (*c* 1.44, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3700–2100 (OH) and 1725 and 1715 (C=O); δ_H(500 MHz) 0.73–0.92 (6 H, m, 2 × Me), 1.23 and 1.34 (each 3 H, each s, CPh*Me*$_2$), 2.37–2.48 (1 H, m, C*H*HCH=CH_2), 2.51–2.59 (1 H, m, CH*H*CH=CH_2), 4.86–4.94 (1 H, m, 3-H) and 7.14–7.34 (5 H, m, Ph); *m/z* 386 (M^+).

The above product was converted, using CH_2N_2 as usual, into the diastereoisomeric mixture of the *corresponding methyl esters* as an oil (Found: M^+, 400.2634. $C_{25}H_{36}O_4$ requires M, 400.2614); ν_{max}(neat)/cm^{-1} 1740 and 1730 (C=O); δ_H(500 MHz) 0.81 (3 H, t, *J* 8.0, CH_2*Me*), 0.85 (3 H, d, *J* 7.5, 1-Me), 1.22 and 1.23 [3 H (1:2.6), each s, Me), 1.35 and 1.38 [3 H (1:2.6), each s, Me], 3.63 and 3.64 [3 H (1:2.6), each s, OMe], 4.84 and 4.85 [1 H (1:2.6), each dt, each *J* 4.5 and 11.0, 3-H], 5.05–5.13 (2 H, m, 2 × olefinic H) and 5.62–5.71 (1 H, m, olefinic H).

4-*Methyl* 1-[(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl*] (2′S)-2′-*Allyl*-2′-*ethylbutanedioates* **45**.—To a stirred solution of $(COCl)_2$ (0.43 cm^3, 4.93 mmol) in dry benzene (15 cm^3) were added a solution of the acids **43** and **44** (798 mg, 2.07 mmol) in dry benzene (5 cm^3) and pyridine (0.20 cm^3, 2.48 mmol), and the resulting mixture was stirred for 5.5 h at room temperature. Filtration through Celite, followed by evaporation of the filtrate under reduced pressure, gave the acid chloride as an oil; ν_{max}(neat)/cm^{-1} 1810 and 1740 (C=O), which was directly used in the following reaction.

To a solution of the above product in dry benzene (8 cm^3) at 0 °C was slowly added an excess of CH_2N_2 in Et_2O and the mixture was stirred for 3 h at 0 °C and for 9 h at room temperature. Evaporation of solvents and the reagent gave the crude diazo ketone as a yellowish oil; ν_{max}(neat)/cm^{-1} 2110 (N≡N) and 1720 and 1640 (C=O), which was subjected to the next reaction without purification.

A solution of the above product in MeOH (80 cm^3) was

irradiated for 3 h through a Pyrex filter with a 400 W high-pressure mercury lamp under ice cooling. After evaporation under reduced pressure, the residue was purified by chromatography on silica gel with hexane–AcOEt (99:1 v/v) as eluent to give the esters **45** and its epimer [647 mg, 76% from (**43** and **44**)] as an oil. HPLC separation on a 10 × 250 mm column of Dynamax microsorb silica 5 μm with hexane–AcOEt (98:2 v/v) as eluent (4 cm^3 min^{-1}) gave the *major isomer* **45** as an oil (Found: C, 75.15; H, 9.2. $C_{26}H_{38}O_4$ requires C, 75.3; H, 9.25%); $[\alpha]_D^{23}$ −4.85° (*c* 1.03, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1740 and 1720 (C=O); δ_H(500 MHz) 0.81 (3 H, t, *J* 7.8, CH_2Me), 0.86 (3 H, d, *J* 6.0, 1-Me), 1.23 and 1.38 (each 3 H, each s, $CPhMe_2$), 2.29 and 2.51 (each 1 H, each d, each *J* 16.6, CH_2CO_2Me), 2.36 and 2.41 (each 1 H, each dd, each *J* 8.0 and 14.0, $CH_2CH{=}CH_2$), 3.64 (3 H, s, OMe), 4.85 (1 H, dt, *J* 4.0 and 10.5, 3-H), 5.03–5.11 (2 H, m, 2 × olefinic H), 5.63–5.72 (1 H, m, olefinic H) and 7.13–7.35 (5 H, m, Ph); *m/z* 414 (M^+).

4-*Methyl* 1-[(1R,3R,4S)-8-*Phenyl*-9-*menthan*-3-*yl*] (S)-2′-*Ethyl*-2′-(3-*hydroxypropyl*)*butanedioate* **46**.—To a stirred, ice-cooled solution of 10 mol dm^{-3} $BH_3{\cdot}SMe_2$ (0.30 cm^3, 3.0 mmol) in dry THF (5 cm^3) was added cyclohexene (0.9 cm^3, 8.89 mmol) and the mixture was stirred for 30 min. The resulting mixture was slowly added to a stirred, ice-cooled solution of the above olefin **45** (108 mg, 0.26 mmol) in dry THF (5 cm^3) and the mixture was stirred for a further 2 h at the same temperature. To the resulting mixture were successively added MeOH (2.5 cm^3), 3 mol dm^{-3} aq. NaOH (0.4 cm^3, 1.2 mmol) and 30% aq. H_2O_2 (0.2 cm^3, 1.76 mmol) and the mixture was stirred for 1 h at the same temperature. After evaporation under reduced pressure, the residue was partitioned between 5% aq. $KHSO_4$ and Et_2O. The aq. layer was thoroughly extracted with Et_2O. The combined organic phases were washed successively with saturated aq. $NaHCO_3$ and brine, dried, and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography with hexane–AcOEt (7:3 v/v) as eluent to give the *alcohol* **46** (104 mg, 92%) as an oil (Found: C, 69.7; H, 9.0. $C_{20}H_{40}O_5{\cdot}0.8H_2O$ requires C, 69.9; H, 9.3%); $[\alpha]_D^{26}$ −13.18° (*c* 1.55 $CHCl_3$); ν_{max}(neat)/cm^{-1} 3450 (OH) and 1740 and 1720 (C=O); δ_H(500 MHz) 0.80 (3 H, t, *J* 7.6, CH_2Me), 0.86 (3 H, d, *J* 6.6, 1-Me), 1.22 and 1.36 (each 3 H, each s, $CPhMe_2$), 2.32 and 2.51 (each 1 H, each d, each *J* 15.8, CH_2CO_2Me), 3.51–3.73 (2 H, m, CH_2OH), 3.64 (3 H, s, OMe), 4.85 (1 H, dt, *J* 4.5 and 11.0, 3-H) and 7.12–7.37 (5 H, m, Ph); *m/z* 432 (M^+).

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl* (2′S)-2′-*Ethyl*-5′-*hydroxy*-2′-(2-*hydroxyethyl*)*pentanoate* **47**.—To a stirred, ice-cooled solution of the above ester **46** (17.4 mg, 0.04 mmol) in dry 1,2-dimethoxyethane (DME) (2 cm^3) was added 1 mol dm^{-3} DIBAL in hexane (0.12 cm^3, 0.12 mmol), and the mixture was stirred for 3 h at the same temperature. After addition of water (0.14 cm^3), the mixture was stirred for 1 h at room temperature, and then filtered through Celite. The filtrate was dried and evaporated under reduced pressure to give a residue, which was purified by silical gel column chromatography. Elution with benzene–acetone (7:3 v/v) afforded the *diol* **47** (11.7 mg, 72%) as a syrup [Found: (M^+ − phenylmenthyloxy), 173.1180. $C_9H_{17}O_3$ requires *m/z*, 173.1177]; $[\alpha]_D^{24}$ −13.59° (*c* 2.67, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3450–3350 (OH) and 1720 (C=O); δ_H(500 MHz) 0.78 (3 H, t, *J* 7.5, CH_2Me), 0.86 (3 H, d, *J* 6.3, 1-Me), 1.21 and 1.35 (each 3 H, each s, $CPhMe_2$), 3.57–3.62 (4 H, m, 2 × CH_2O), 4.86 (1 H, dt, *J* 4.5 and 11.0, 3-H) and 7.14–7.38 (5 H, m, Ph).

(2S)-2-*Ethyl*-2-(3-*hydroxypropyl*)*butan*-4-*olide* **41**.—To a solution of the diol **47** (41.4 mg, 0.102 mmol) and 18-crown-6 (13.7 mg, 0.052 mmol) in benzene (3 cm^3) was added KO_2 (21.9 mg, 0.308 mmol), and the mixture was stirred for 15 h at room temperature, and was then poured into water. After acidification with 6 mol dm^{-3} HCl, the aq. layer was thoroughly extracted with Et_2O. The combined organic layers were dried and evaporated to give a residue, which was dissolved in saturated aq. K_2CO_3. The mixture was washed with Et_2O (× 2), then acidified with 6 mol dm^{-3} HCl, and extracted thoroughly with Et_2O. The combined extracts were dried and evaporated under reduced pressure to give a residue, which was treated with 9% aq. HCl (3 cm^3). After being heated for 10 h under reflux, the mixture was saturated with crystalline NaCl and was then thoroughly extracted with $CHCl_3$. The combined extracts were washed with brine, dried, and evaporated under reduced pressure to afford a residue, which was subjected to chromatography on silica gel. Elution with benzene–acetone (4:1 v/v) gave the lactone **41** (15.3 mg, 87% from **47**) as a syrup; $[\alpha]_D^{22}$ +1.85° (*c* 1.10, $CHCl_3$), whose IR and NMR spectra were identical with those of the authentic compound.[18]

4-*Methyl* 1-[(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl*] (2′S)-2′-(3-*t*-*Butyldimethylsiloxy*)-2′-*ethylbutanedioate* **51**.—To a stirred, ice-cooled solution of the alcohol **46** (64 mg, 0.15 mmol) and DMAP (7.4 mg, 0.13 mmol) in dry CH_2Cl_2 (3 cm^3) were added a solution of TBDMSCl (40 mg, 0.26 mmol) in dry CH_2Cl_2 (1 cm^3) and Et_3N (0.03 cm^3, 0.22 mmol), and the mixture was stirred for 7 h at room temperture. After addition of benzene (30 cm^3), the resulting mixture was washed successively with 5% aq. $KHSO_4$, saturated aq. $NaHCO_3$ and brine, dried, and evaporated under reduced pressure. The residue was purifed by chromatography on silica gel with hexane–AcOEt (95:5 v/v) as eluent to afford the *TBDMS ether* **51** (75 mg, 93%) as an oil (Found: C, 69.05; H, 9.85. $C_{32}H_{54}O_5Si{\cdot}0.67H_2O$ requires C, 68.8; H, 9.7%); $[\alpha]_D^{22}$ −11.09° (*c* 1.10, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1740 and 1720 (C=O); δ_H(90 MHz) 0.04 (6 H, s, $SiMe_2$), 0.89 (9 H, s, Bu^t), 1.23 and 1.36 (each 3 H, each s, $CPhMe_2$), 2.27 and 2.53 (each 1 H, each d, each *J* 15.9, CH_2CO_2Me), 3.44–3.69 (2 H, m, CH_2O), 3.63 (3 H, s, OMe), 4.85 (1 H, dt, *J* 4.5 and 11.0, 3-H) and 7.15–7.40 (5 H, m, Ph); *m/z* 315 (M^+ − phenylmenthyloxy).

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl* (2′S)-5′-(*t*-*Butyldimethylsiloxy*)-2′-*ethyl*-2′-(2-*hydroxyethyl*)*pentanoate* **52**.—To a stirred, ice-cooled solution of the above diester **51** (89 mg, 0.16 mmol) in dry THF (4 cm^3) was slowly added 1 mol dm^{-3} DIBAL in hexane (0.6 cm^3, 0.6 mmol) and the mixture was stirred for 2 h at the same temperature. After addition of water (0.6 cm^3), the mixture was further stirred for 1 h at room temperature and was then filtered through Celite. The filtrate was dried and evaporated under reduced pressure to give a residue, which was subjected to chromatography on silica gel. Elution with hexane–AcOEt (4:1 v/v) afforded the *alcohol* **52** (64 mg, 76%) as an oil [Found: (M^+ − phenylmenthyloxy), 287.2039. $C_{15}H_{31}O_3Si$ requires *m/z*, 287.2043]; $([\alpha]_D^{22}$ −8.40° (*c* 3.44, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3450–3400 (OH) and 1720 (C=O); δ_H (90 MHz) 0.05 (6 H, s, $SiMe_2$), 0.90 (9 H, Bu^t), 1.21 and 1.35 (each 3 H, each s, $CPhMe_2$), 3.46–3.73 (4 H, 2 × CH_2O), 4.85 (1 H, dt, *J* 4.5 and 11.0, 3-H) and 7.14–7.36 (5 H, m, Ph).

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl* (2′S)-5′-(*t*-*Butyldimethylsiloxy*)-2′-[(1,3-*dioxolan*-2-*yl*)*methyl*]-2′-*ethylpentanoate* **53**.—To a stirred solution of $(COCl)_2$ (0.025 cm^3, 0.286 mmol) in dry CH_2Cl_2 (4 cm^3) at −78 °C was added dimethyl sulphoxide (DMSO) (0.025 cm^3, 0.353 mmol) and the mixture was stirred for 15 min at −78 °C. After addition of a solution of the above alcohol **52** (64 mg, 0.124 mmol) in dry CH_2Cl_2 (2 cm^3) at −78 °C, the mixture was stirred for 20 min at −78 °C. After addition of Et_3N (0.08 cm^3, 0.575 mmol) at −78 °C, the mixture was stirred for 1 h at −78 °C to room

temperature. After dilution with hexane (50 cm^3), the resulting mixture was washed with brine, dried, and evaporated under reduced pressure to give the crude aldehyde as an oil, which was used in the following reaction without purification.

A mixture of the above product, CSA (7.6 mg, 0.033 mmol) and ethylene glycol (0.035 cm^3, 0.63 mmol) in dry benzene (4 cm^3) was heated for 1.5 h under reflux in a Dean–Stark apparatus to remove any water formed. After dilution with benzene, the mixture was washed successively with saturated aq. $NaHCO_3$ and brine, dried, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel with hexane–AcOEt (95:5 v/v) as eluent to afford the *acetal* **53** (55 mg, 76% from **52**) as an oil [Found: (M^+ – phenylmenthyloxy), 329.2112. $C_{17}H_{33}O_4Si$ requires *m/z*, 329.2148]; $[\alpha]_D^{23}$ −12.67° (*c* 0.43, $CHCl_3$): ν_{max}(neat)/cm^{-1} 1716 (C=O); δ_H(500 MHz) 0.05 (6 H, s, $SiMe_2$), 0.80 (3 H, t, *J* 7.6, CH_2Me), 0.84 (3 H, d, *J* 6.1, 1-Me), 0.90 (9 H, s, Bu^t), 1.24 and 1.38 (each 3 H, each s, $CPhMe_2$), 3.53–3.61 (2 H, m, $CH_2OTBDMS$), 3.74–3.82 and 3.88–3.96 (each 2 H, each m, OCH_2CH_2O), 4.82–4.90 (2 H, m, 3-H and CHO_2) and 7.14–7.33 (5 H, m, Ph).

(1S,4S)-6-*Ethyl*-2,8-*dioxabicyclo*[4.2.1]*nonan*-7-*one* **42**.—To a solution of the above acetal **53** (27.8 mg, 0.05 mmol) and 18-crown-6 (7.3 mg, 0.028 mmol) in benzene (3 cm^3) was added KO_2 (16.9 mg, 0.238 mmol), and the mixture was heated for 2 days under reflux. After evaporation under reduced pressure, followed by addition of water (5 cm^3), the resulting mixture was washed with Et_2O, acidified with 6 mol dm^{-3} HCl, and then thoroughly extracted with Et_2O. The extracts were dried and evaporated under reduced pressure to give a residue, which was dissolved in THF (1 cm^3). To the mixture was added 70% $HClO_4$ (0.15 cm^3, 1.04 mmol) and the mixture was stirred for 12 h at room temperature and heated for 1 h under reflux. After evaporation under reduced pressure, the residue was taken up into CH_2Cl_2. The organic solution was washed with brine, dried, and evaporated under reduced pressure to give a residue, which was subjected to chromatography on silica gel. Elution with hexane-AcOEt (85:5 v/v) afforded the bicyclic lactone **42** (4.9 mg, 58% from **53**) as scales, m.p. 79–82 °C; $[\alpha]_D^{24}$ +8.16° (*c* 0.49, CH_2Cl_2) {lit.,[17] m.p. 82–85 °C; $[\alpha]_D$ +6.7° (*c* 0.42, CH_2Cl_2); lit.,[18] m.p. 89–90 °C; $[\alpha]_D^{22}$ +5.4° (*c* 1.47, CH_2Cl_2)}, the spectral data of which were identical with those of the authentic compound.

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