Regioselective aryl radical cyclisation. Part 2.[1] Synthesis of octahydro-1*H*-dibenzo[*a*,*d*]cycloheptenes through 7-*endo* ring closure

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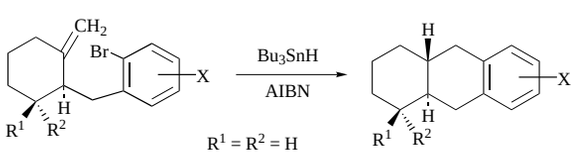
A simple convergent synthesis of *trans*- and *cis*-octahydro-1*H*-dibenzo[*a*,*d*]cycloheptenes 15a–c and 16a–c and 20a–c and 21a–c through implementation of a regioselective 7-*endo*-*trig*-aryl radical cyclisation of the respective 2-(*o*-bromoarylethyl)-1-methylenecyclohexanes 6a–c and 8a–c with tributyltin hydride is described. The scope of the 7-*endo* aryl radical cyclisation has been further demonstrated by the synthesis of (2*SR*,4a*RS*,11a*SR*)-methyl 1,1-dimethyl-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a*,*d*]cycloheptene-2-carboxylate 29.

Intramolecular free-radical cyclisations have emerged as extremely useful synthetic methods for five- and six-membered carbo- and hetero-cyclic ring structures.[2] In contrast, although such reactions have been extended to a limited extent to construct a small number of seven-membered hetero ring structures,[3a–m] a heteroatom replacing a methylene group in the newly formed rings, the formation of carbocyclics by a similar carbon-centred radical process is rare. Prior to our own work described here,[4] there were only two definitive reports[5–8] of the formation of a cycloheptane ring in the tributyltin hydride-mediated radical cyclisation. More recently, a cyclopropane ring fused cycloheptene derivative has been reported[9] by a Bu_3SnH-induced 7-*endo* radical cyclisation. Cycloheptene derivatives have also been synthesized by tandem oxidative free-radical cyclisations using manganese(III)[10] and cobalt(I)[11] reagents.

In a previous paper[1] we demonstrated an exclusive regio- and stereo-selective 6-*endo*-aryl radical cyclisation in some 2-(*o*-bromobenzyl)methylenecyclohexanes **A** to the respective *trans*-octahydroanthracenes **B** through preferred radical attack at the least substituted exocyclic methylene carbon centre (Scheme 1). We present in this paper the detailed results of our

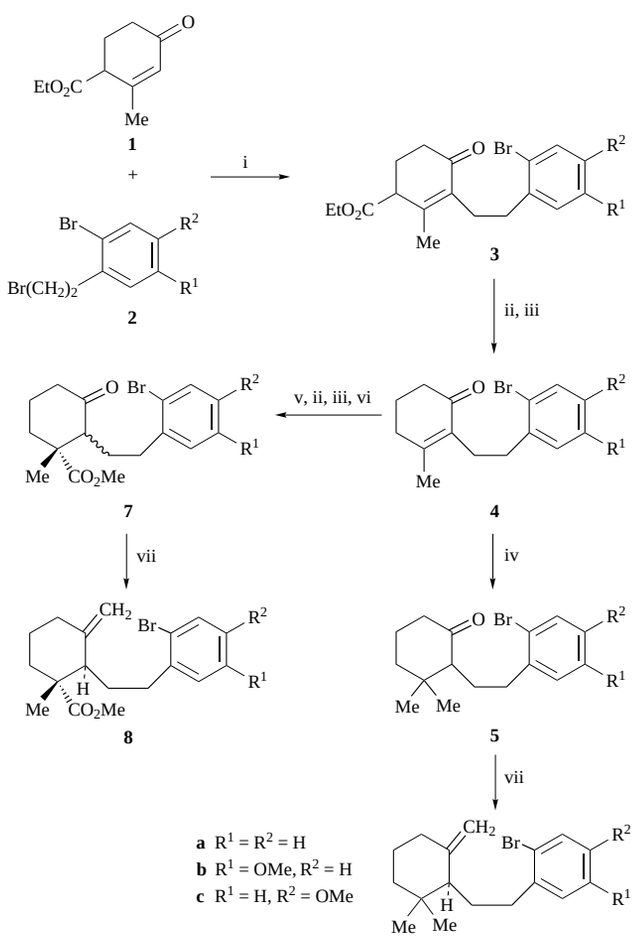


Scheme 1

study revealing that such a strategy may be efficiently employed for convergent synthesis of octahydro-1*H*-dibenzo[*a*,*d*]cycloheptene derivatives, some of which are potential intermediates for the synthesis of 9(10 ⟶ 20)-*abeo*-abieta-8,11,13-triene diterpenoids and the related bio-active natural products[12,13] through a highly regioselective 7-*endo*-aryl radical cyclisation.

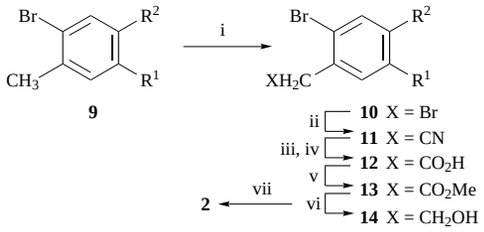
Results and discussion

The (*o*-bromophenylethyl)cyclohexanones **5a–c** and the keto esters **7a–c**, the key intermediates for the corresponding olefins **6a–c** and the olefinic esters **8a–c**, were obtained in good yields through the corresponding cyclohexenones **4a–c** by adopting standard routes involving conjugate addition of a methyl group[14] and a cyanide group,[15] respectively (Scheme 2). The



Scheme 2 *Reagents:* i, Bu^{t}OK, Bu^{t}OH; ii, KOH–H_2O–EtOH; iii, aq. HCl (6 mol dm^{-3}); iv, $LiMe_2Cu$–BF_3·Et_2O; v, EtOH–KCN; vi, CH_2N_2–Et_2O, vii, $Ph_3P^+MeI^-$-*tert*-$C_5H_{11}ONa$ in toluene

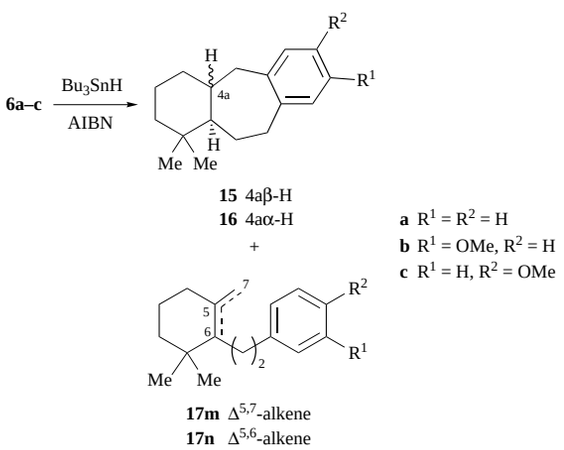
cyclohexenones **4a–c** were prepared by alkylation[14] of Hagemann's ester **1** with the bromides **2a–c**, respectively, followed by alkaline hydrolytic decarboxylation of the corresponding C-3 alkylated products **3a–c**. The bromides **2b** and **2c** were prepared by the sequence of reactions outlined in



Scheme 3 *Reagents:* i, Br_2–CCl_4–$(PhCO_2)_2$; ii, KCN–DMSO; iii, KOH–EtOH–H_2O; iv, aq. HCl (6 mol dm^{-3}); v, MeOH–H_2SO_4(conc); vi, $LiAlH_4$–Et_2O; vii, PBr_3–C_6H_6

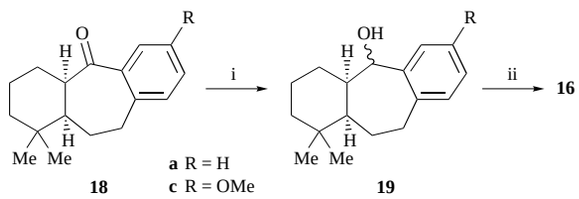
Scheme 3 (see Experimental section). The ketones **5a–c** were smoothly transformed into the respective alkenes **6a–c** by a Wittig reaction under forcing conditions.[12,16] In parallel with our earlier observation with the corresponding *o*-bromobenzylcyclohexanone esters,[1] the Wittig olefination of the epimeric mixture of the enolisable keto esters **7a–c** produced, in each case, a single epimer of the respective *exo*-methylene esters in excellent yields. The stereochemical assignments of the olefinic esters **8a**, **8b** and **8c** are based upon the analogy.[1]

The radical cyclisation of the alkene **6a** with Bu_3SnH and a catalytic amount of azoisobutyronitrile (AIBN) in refluxing benzene (Scheme 4) after work-up and chromatography fur-



Scheme 4

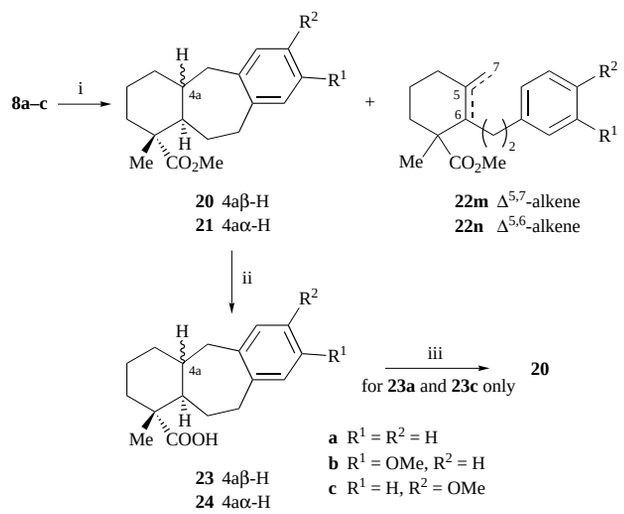
nished a mixture of the *trans*- and *cis*-hydrocarbons† **15a** and **16a** and the debrominated olefin mixture **17ma**[12] and **17na**‡ in a ratio of *ca.* 9:1 in a very good yield. Chromatography of this mixture after treatment with an excess of diborane followed by oxidation with alkaline hydrogen peroxide eliminated the olefins and afforded an inseparable mixture of the epimeric hydrocarbons **15a** and **16a** in a ratio of *ca.* 55:45. Similarly, radical cyclisations of the methylenecyclohexanes **6b** and **6c**, under the same conditions, produced mixtures of the respective *trans*- and *cis*-cyclised ethers **15b** and **16b**, and **15c** and **16c** along with the respective debrominated olefinic ethers. From these products *ca.* 60:40 mixtures of the *trans*- and *cis*-ethers **15b** and **16b**, and **15c** and **16c** were isolated in 42 and 49% yields, respectively. The structural and stereochemical assignments for **15a** and **16a**, and **15c** and **16c** followed directly from ^{1}H NMR spectroscopic comparison with the corresponding pure *cis*-epimers **16a** and **16c**, prepared by Pd–C (10%) catalysed hydrogenolysis of the respective epimeric alcohols **19a** and **19c**, derived from $NaBH_4$ reduction of the known[12] *cis*-ketones **18a** and **18c** (Scheme 5). The stereochemical assign-



Scheme 5 *Reagents:* i, $NaBH_4$–EtOH; ii, Pd–C(10)–EtOH, H_2

ments of the *cis*- and *trans*-ethers **15b** and **16b** have been made from the comparison of the ^{1}H NMR chemical shifts of the *gem*-dimethyl groups of the isomeric ethers **15c** and **16c**.

The radical cyclisation of the alkene ester **8c** with Bu_3SnH–AIBN in boiling benzene furnished a complex mixture of the cyclised *trans*- and *cis*-esters **20c** and **21c** along with a substantial amount of the debrominated unsaturated esters **22mc** and **22nc**. The unsaturated esters were eliminated by hydroxylation[17] of the mixture with $NaIO_4$ in the presence of a catalytic amount of $RuCl_3 \cdot 3H_2O$ followed by careful chromatography to afford a *ca.* 70:30 mixture of the *trans* and *cis*-esters **20c** and **21c** in 40–45% yields (Scheme 6). From this mixture pure

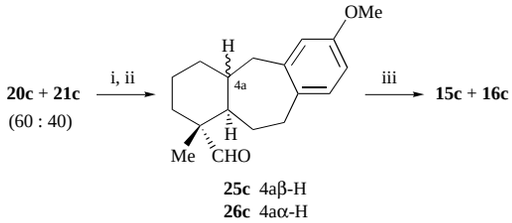


Scheme 6 *Reagents:* i, Bu_3SnH–AIBN–C_6H_6; ii, Bu^tOK–DMSO; iii, CH_2N_2–Et_2O

trans-acid **23c** has been separated by fractional crystallisations of the mixture of acids obtained by dimethyl sulfoxide–Bu^tOK mediated ester cleavage.[18] The stereochemistry of the major and the minor esters **20c** and **21c** were conclusively established by comparisons of the epimeric ethers mixture **15c** and **16c** obtained through chemical transformations of the esters mixture following the sequence of standard reactions[1] **20c** + **21c** ⟶ **25c** + **26c** ⟶ **15c** + **16c** (Scheme 7) with that of the mixtures derived from the radical cyclisation of **6c**. Similarly, the radical cyclisations of each of the olefinic esters **8a** and **8b** gave the respective *trans*- and *cis*-esters mixtures **20a** and **21a**, and **20b** and **21b** in a ratio of *ca.* 70:30, after separations from the corresponding uncyclised debrominated olefinic esters. The pure *trans*-acid **23a** has been isolated from the mixture of the acids **23a** and **24a**, obtained through ester cleavage of a mixture of **20a** and **21a**.

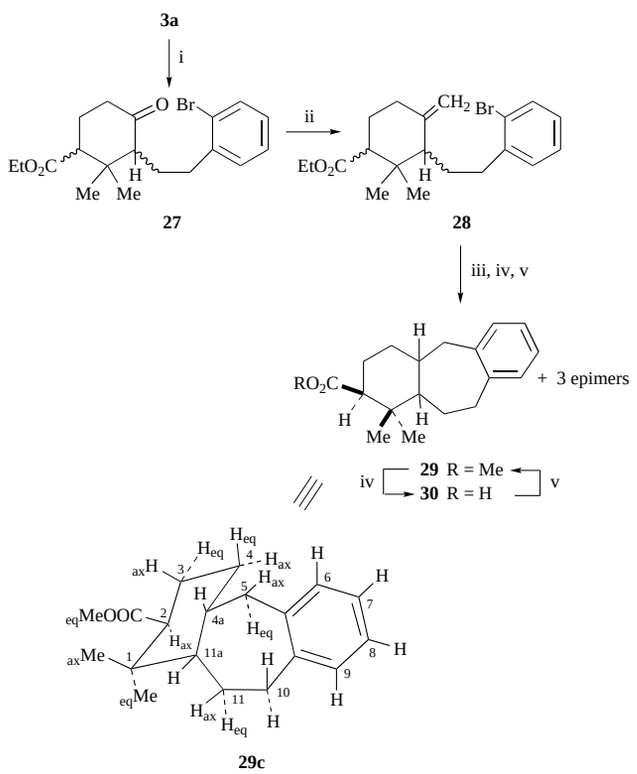
† The formation of the hydrocarbons **15a** and **16a** from **6a** most likely proceeds through a direct 7-*endo*-*trig* process in preference to the alternative 6-*exo*-*trig* path followed by neophyl radical rearrangement (*cf.* ref. 3*g*). This was supported by the analyses of the products from the reactions of **6a** with Bu_3SnH, in much higher concentrations, in which no hydrocarbons, namely, *trans*- or *cis*-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octohydrophenanthrene (ref. 14), the expected hydrogen quenched product of the corresponding 6-*exo*-*trig* radical intermediate, could be detected in the mixtures, incorporating only the minor cyclised products **15a** and **16a**, and the major debrominated olefins **17ma** and **17na**.

‡ The tetrasubstituted olefin **17na** possibly arises *via* the intermediate allyl radical resulting from a 1,5-shift of the C-2 hydrogen of the initially generated aryl radical from the *exo*-olefin **6a** (D. P. Curran and J. Xu, *J. Am. Chem. Soc.*, 1996, **118**, 3142 and references cited therein).



Scheme 7 *Reagents:* i, $LiAlH_4$, Et_2O; ii, PCC, CH_2Cl_2; iii, NH_2NH_2–H_2O, $(HOCH_2CH_2)_2O$, KOH

Finally, we examined the radical cyclisation of a mixture of diastereoisomeric alkene esters **28**. A *ca.* 40 : 60 epimeric mixture of the alkene esters **28** with an undefined stereochemistry was prepared by Wittig olefination of the epimeric keto esters **27**, which were obtained in an excellent yield from the unsaturated keto esters **3a** by conjugate addition of a methyl group. The Bu_3SnH–AIBN induced radical cyclisation of the epimeric mixture of **28**, after work-up gave a complex mixture of products which was directly subjected to ester cleavage with DMSO–$KOBu^t$. The resulting acids, on transformation to their methyl esters, were treated with $NaIO_4$ and $RuCl_3{\cdot}3H_2O$ for hydroxylation of the presumably debrominated uncyclised olefinic esters. The careful chromatography of the product gave a mixture of the major epimeric ester **29** along with three other possible diastereoisomeric cyclised esters (by ^1H NMR) in a good yield. The pure acid **30** was separated from the diastereoisomeric mixture of the acids by fraction crystallisation of the crude product produced by ester cleavage of the epimeric esters mixture (Scheme 8). The structural and stereochemical assign-



Scheme 8 *Reagents:* i, $LiMe_2Cu$–BF_3–Et_2O; ii, Ph_3P–MeI-*tert*-$C_5H_{11}ONa$ in toluene; iii, Bu_3SnH–AIBN–C_6H_6; iv, Bu^tOK–DMSO; v, CH_2N_2–Et_2O

ments of the major epimeric ester **29** (from the ^1H NMR spectrum) was established on the basis of several pieces of evidence. Thus, the ring-junction protons (H-4a and H-11a) at C-4a and C-11a (shown in **29c**) indicated a *cis gauche* relationship to each other, because: (i) H-11a showed NOE with both CH_3(ax) and CH_3(eq) and also with H-4a; (ii) $J_{\mathbf{H\text{-}4a,H\text{-}11a}}$ is ~4 Hz, as derived from the pattern of H-4a and NOE experiments [irradiation of CH_3(ax) and CH_3(eq)]. The NOE showed that H-11a is dt (*J* 12 and 4 Hz). The proposed stereostructure was supported by several cross peaks in the NOESY spectrum as well as the *J* coupling. The methyl singlet at δ 1.10 has been assigned to CH_3(ax) as it showed NOE with H-11a, H-4a and H-3(ax), while the CH_3(eq) singlet at δ 0.94 showed NOE between H-11a, H-2 and H-11(eq). The H-11(ax) showed NOE with H-2 and H-4(ax) implying that it is *trans* to the ring junction proton H-11a. Therefore, H-11(eq) is *gauche* to H-11a. The couplings $J_{\mathbf{H\text{-}11(eq),H\text{-}11a}}$, 4 Hz and $J_{\mathbf{H\text{-}11(ax)'H\text{-}11a}}$, 12 Hz are consistent with the assigned stereostructure of **29**.

The stereochemical outcome[3g,19] in the 7-*endo-trig* cyclisation of **6a–c** and **8a–c** leading to the mixtures of the respective *trans*- and *cis*-products **15a–c** and **16a–c**, and **20a–c** and **21a–c**, unlike that observed in the 6-*endo-trig* cyclisation in the lower homologues leading only to the respective *trans*-products (*cf*. Scheme 1), is possibly due to the increasing flexibility in the former cases in lowering the corresponding transition states energies in the formations of the respective *trans*- and *cis*-products. The formation of predominately the *cis*-product **29** from the radical cyclisation of the olefinic ester **28** most likely has its origin in the change of conformational preference of the cyclohexyl ring in the transition state.

The intrinsic preference for a 7-*endo-trig*-aryl radical cyclisation at the terminal carbon atom[20] of an *exo*-methylene group, constituting a relatively efficient method of preparing octahydrodibenzo[*a*,*d*]cycloheptene intermediates described in the present work, if general in nature, has significant potential for the synthesis of seven-membered fused-ring carbocycles having other structural features.

Experimental

General details

The compounds described are all racemates. Melting and boiling points are uncorrected, and melting points were taken in open capillaries in sulfuric acid. IR spectra of solids (KBr) and liquids (film) were recorded on a Perkin-Elmer model PE 298 spectrometer. UV spectra were recorded on a Beckman DU instrument for solutions in ethanol (95%). The ^1H NMR spectra were taken at 60 MHz on a Varian EM-360L, at 100 MHz on a JEOL FX-100, at 200 MHz on a Varian Gemini-200 and at 400 MHz on a Bruker AM 400 instrument; unless stated otherwise the spectra were taken in dilute $CDCl_3$ solutions with $SiMe_4$ as internal standard, with *J* values given in Hz. Analytical GLC was performed on a Shimadzu GC-9A model with a FID detector employing 1.5% OV-17 (6.5 ft × 0.25 in) column with N_2 as the carrier gas. Column chromatography was performed on silica gel [Glaxo Laboratories (India) Ltd] or on neutral alumina (Brockmann Grade 1, of BDH, India). Light petroleum refers to the fraction of bp 60–80 °C. Ether refers to diethyl ether. Elemental analyses were performed by P. P. Bhattacharyya, S. Sarkar and B. Pathak of I.A.C.S.

2-(2-Bromo-5-methoxyphenyl)ethanol 14b

To a stirred solution of **9b** (40 g, 199 mmol) in dry, refluxing carbon tetrachloride (400 cm^3) containing dry benzoyl peroxide (4.8 g, 19.8 mmol) was added dry bromine (9.98 cm^3, 19 mmol) in dry carbon tetrachloride (50 cm^3) dropwise over a period of 1 h. After an additional 1 h under reflux the cooled reaction mixture was washed with aqueous NaOH (5%) and water, dried (Na_2SO_4) and evaporated to give the crude bromide. This on crystallisation from CH_2Cl_2–light petroleum gave 2-bromo-5-methoxybenzyl bromide **10b** (38.8 g, 69%), mp 96 °C; δ_H(60 MHz, CCl_4), 3.80 (3H, s, ArOMe), 4.53 (2H, s, ArCH_2Br), 6.70 (1H, dd, *J* 9 and 2, 4-ArH), 6.97 (1H, d, *J* 2, 6-ArH) and 7.40 (1H, d, *J* 8, 3-ArH).

The bromide **10b** (60 g, 214 mmol) in DMSO (60 cm^3) was added to a well-stirred cooled (0–10 °C) solution of potassium cyanide (16.9 g, 257 mmol) in DMSO (200 cm^3). After the add-

ition was completed stirring was continued further for 45 min at room temperature. The reaction mixture was then diluted with ice–water and extracted with ether to give the cyanide **11b** (48 g) as a pale yellow oil (ν_{max}/cm^{-1} 2250) after evaporation of the dried (Na_2SO_4) extract. The crude cyanide was refluxed with a solution of KOH (47 g) in water (150 cm^3) and EtOH (120 cm^3) for 14 h. After removal of most of the EtOH under reduced pressure the cooled reaction mixture was acidified with aqueous HCl (6 mol dm^{-3}) and extracted with ether. The combined ether layers were washed once with water and the acidic material was washed with aqueous NaOH (10%; 3 × 30 cm^3) and once with water. The combined aqueous alkaline layers were acidified with aqueous HCl (6 mol dm^{-3}) and the crude acid **12b** (43.7 g), (ν_{max}/cm^{-1} 1700) was isolated by extraction with ether. The crude dried acid was esterified directly by refluxing for 7 h with anhydrous MeOH (160 cm^3) containing concentrated H_2SO_4 (6 cm^3) to afford the ester **13b** (33.2 g, 73%) as a colourless oil, bp 120–125 °C (0.2 mmHg); ν_{max}/cm^{-1} 1730; δ_H(60 MHz, CCl_4), 3.72 (3H, s, CO_2Me), 3.76 (2H, s, CH_2Ar), 3.80 (3H, s, ArOMe), 6.65 (1H, dd, *J* 8 and 2, 4-ArH), 6.80 (1H, d, *J* 2, 6-ArH) and 7.40 (1H, d, *J* 8, 3-ArH).

To a well stirred ice-cold slurry of $LiAlH_4$ (3.4 g, 88.3 mmol) in dry ether (150 cm^3), the ester **13b** (22.7 g, 88.3 mmol) was added dropwise. After addition was over, the mixture was stirred for 2 h at room temperature (25–30 °C). Work-up yielded the alcohol **14b** (19 g, 93%) as a colourless oil (Found: C, 46.4; H, 4.5. $C_9H_{11}O_2Br$ requires C, 46.77; H, 4.80%); δ_H(60 MHz, CCl_4), 2.86 (2H, t, *J* 6, $ArCH_2$), 3.33 (1H, br s, OH), 3.57–3.93 (5H, OCH_2 overlapped with the ArOMe s at 3.67), 6.57 (1H, dd, *J* 8 and 2, 4-ArH), 6.76 (1H, d, *J* 2, 6-ArH) and 7.40 (1H, d, *J* 8, 2-ArH).

2-(2-Bromo-4-methoxyphenyl)ethanol 14c

The bromomethoxytoluene **9c** (40 g, 1.99 mmol) was converted in the same way as described into the bromide **10c** (42 g, 75%), mp 98 °C; δ_H(60 MHz, CCl_4), 3.70 (3H, s, ArOMe), 4.53 (2H, s, $ArCH_2Br$), 6.67 (1H, dd, *J* 8 and 2, 5-ArH), 7.06 (1H, d, *J* 2, 3-ArH) and 7.30 (1H, d, *J* 8, 6-ArH).

The bromide **10c** (60 g, 214 mmol) in DMSO (200 cm^3) was treated with potassium cyanide (16.9 g, 257 mmol) in DMSO (60 cm^3), following the same procedure as described for **11b**, into the cyanide **11c** (45 g) (ν_{max}/cm^{-1} 2250) which was directly hydrolysed with KOH (35 g) in water (120 cm^3) and EtOH (80 cm^3) to give the acid **12c** (39.3 g); ν_{max}/cm^{-1} 1700. This was esterified with dry MeOH (150 cm^3) in the presence of concentrated H_2SO_4 (5 cm^3) to afford the ester **13c** (30 g, 66%), bp 122–125 °C (0.2 mmHg); ν_{max}/cm^{-1} 1730; δ_H(60 MHz, CCl_4), 3.53 (3H, s, CO_2Me), 3.73 (2H, s, CH_2Ar), 3.76 (3H, s, ArOMe), 6.73 (1H, dd, *J* 8 and 2, 5-ArH), 7.03 (1H, d, *J* 2, 3-ArH) and 7.13 (1H, d, *J* 8, 6-ArH).

The ester **13c** (22.7 g, 88.3 mmol) was reduced with $LiAlH_4$ (3.4 g, 88.3 mmol) in dry ether (200 cm^3), in the same way as described for **13b**, to afford the alcohol **14c** (18.5 g, 90.5%) as a colourless oil (Found: C, 46.5; H, 4.6. $C_9H_{11}O_2Br$ requires C, 46.77; H, 4.80%); δ_H(60 MHz, CCl_4) 2.83 (2H, t, *J* 6, $ArCH_2$), 3.53–3.83 (3H, OCH_2 and OH overlapped with ArOMe), 3.67 (3H, s, ArOMe), 6.66 (1H, dd, *J* 8 and 2, 5-ArH), 6.96 (1H, d, *J* 2, 3-ArH) and 7.10 (1H, d, *J* 8, 6-ArH).

2-(2-Bromo-5-methoxyphenyl)ethyl bromide 2b

To a stirred ice-cold solution of the alcohol **14b** (19 g, 82.2 mmol) in dry benzene (70 cm^3), PBr_3 (11.1 cm^3, 41.12 mmol) in dry benzene (20 cm^3) was added dropwise during 20 min. After being stored overnight at room temperature the reaction mixture was heated at 70–80 °C for 2 h and then poured into ice–water. The neutral substance isolated upon work-up, when distilled, afforded the bromide **2b** (11.8 g, 49%), bp 118–122 °C (0.2 mmHg); δ_H(60 MHz, CCl_4), 3.23 (2H, t, *J* 6, $ArCH_2$), 3.47 (2H, t, *J* 6, CH_2Br), 3.74 (3H, s, Ar-OMe), 6.46–6.93 (2H, m, 4- and 6-ArH) and 7.43 (1H, d, *J* 8, 3-ArH). An analytically pure sample could not be obtained.

2-(2-Bromo-4-methoxyphenyl)ethyl bromide 2c

The alcohol **14c** (20 g, 86 mmol) in dry benzene (70 cm^3) was treated with PBr_3 (11.6 cm^3) in dry benzene (20 cm^3) in a similar way to that described for **2b** to give the bromide **2c** (12 g, 49.8%), bp 115–118 °C (0.2 mmHg); δ_H(60 MHz, CCl_4), 3.23 (2H, t, *J* 6, $ArCH_2$), 3.43 (2H, t, *J* 6, CH_2Br), 3.77 (3H, s, ArOMe), 6.78 (1H, dd, *J* 8 and 2, 5-ArH), 7.10 (1H, d, *J* 2, 3-ArH) and 7.16 (1H, d, *J* 6). An analytically pure sample could not be obtained.

Ethyl 3-[2-(2-bromophenyl)ethyl]-4-oxocyclohex-2-enecarboxylate 3a

This compound was prepared adopting a general method[14] developed in this laboratory. Hagemann's ester **1** (13.8 g, 75.7 mmol) was alkylated with the bromide **2a** (20 g, 75.7 mmol) in the presence of Bu^{t}OK, prepared from potassium metal (2.95 g, 75.71 mmol) in Bu^{t}OH, to afford the desired alkylation product **3a** (16.6 g, 60%), bp 190–198 °C (0.04 mmHg) (Found: C, 59.2; H, 5.81. $C_{18}H_{21}O_3Br$ requires C, 59.17; H, 5.79%); ν_{max}/cm^{-1} 1730 (ester) and 1665 (α,β-unsaturated ketone); δ_H(60 MHz, CCl_4), 1.26 (3H, t, *J* 7, CO_2CH_2*Me*), 1.76 (3H, s, vinyl Me), 1.86–2.50 (4H, m), 2.53–3.00 (4H, m, $COCH_2$ and $ArCH_2$), 3.03–3.35 (1H, m, methine), 4.17 (2H, q, *J* 7, CO_2CH_2Me), 6.83–7.40 (3H, m, 4, 5 and 6-ArH) and 7.40–7.57 (1H, d, *J* 8 and 2, 3-ArH).

Ethyl 3-[2-(2-bromo-5-methoxyphenyl)ethyl]-4-oxocyclohex-2-enecarboxylate 3b

Hagemann's ester **1** (12.3 g, 68.2 mmol) was alkylated with the bromide **2b** (20 g, 68 mmol) in the presence of Bu^{t}OK prepared from potassium metal (2.72 g, 68 mmol) in Bu^{t}OH to afford the desired alkylation product **3b** (16.7 g, 62%), bp 215–220 °C (0.05 mmHg) (Found: C, 57.8; H, 5.9. $C_{19}H_{23}O_4Br$ requires C, 57.72; H, 5.86%); ν_{max}/cm^{-1} 1725 (ester) and 1655 (α,β-unsaturated ketone); λ_{max}(EtOH) nm 205 (log ε 4.44), 230 (4.27) and 282 (3.35); δ_H(60 MHz, CCl_4), 1.26 (3H, t, *J* 7, CO_2-CH_2Me), 1.79 (3H, s, vinyl Me), 1.86–2.50 (4H, m), 2.50–3.00 (4H, m, $COCH_2$, $ArCH_2$), 3.00–3.35 (1H, m, methine), 3.76 (3H, s, ArOMe), 4.17 (2H, q, *J* 7, CO_2CH_2Me), 6.57 (1H, dd, *J* 8 and 2, 4-ArH), 6.72 (1H, d, *J* 2, 6-ArH) and 7.39 (1H, d, *J* 8, 3-ArH).

Ethyl 3-[2-(2-bromo-4-methoxyphenyl)ethyl]-2-methyl-4-oxocyclohex-2-enecarboxylate 3c

Hagemann's ester **1** (15.47 g, 85.03 mmol) was alkylated with the bromide **2c** (25 g, 85.03 mmol) in the presence of Bu^{t}OK, prepared from potassium metal (3.32 g, 85.03 mmol), in Bu^{t}OH to afford the desired alkylation product **3c** (20.84 g, 62%), bp 212–218 °C (0.04 mmHg) (Found: C, 57.7; H, 5.85. $C_{19}H_{23}O_4Br$ requires C, 57.72; H, 5.86%); ν_{max}/cm^{-1} 1725 (ester), 1665 (α,β-unsaturated ketone); λ_{max}(EtOH) nm 206 (log ε 4.41), 225 (4.17), 280 (3.39) and 288 (3.3); δ_H(60 MHz, CCl_4), 1.26 (3H, t, *J* 7, CO_2CH_2*Me*), 1.79 (3H, s, vinyl Me), 1.86–2.50 (4H, m, methylenes), 2.53–3.00 (4H, m, $COCH_2$ and $ArCH_2$), 3.03–3.35 (1H, m, methine), 3.76 (3H, s, ArOMe), 4.17 (2H, q, *J* 7, $COOCH_2$Me), 6.74 (1H, dd, *J* 8 and 2, 5-ArH), 7.03 (1H, d, *J* 2, 3-ArH) and 7.08 (1H, d, *J* 8, 6-ArH).

2-[2-(2-Bromophenyl)ethyl]-3-methylcyclohex-2-enone 4a

The keto ester **3a** (16 g, 43.8 mmol) was refluxed with a solution of KOH (7.3 g, 130.4 mmol) in water (10 cm^3) and EtOH (60 cm^3) under N_2 for 14 h. The cooled reaction mixture was acidified with aqueous HCl (6 mol dm^{-3}). Work-up followed by distillation afforded the enone **4a** (10.2 g, 79%); bp 185–190 °C (0.04 mmHg) (Found: C, 61.5; H, 5.8. $C_{15}H_{17}OBr$ requires C, 61.43; H, 5.84%); ν_{max}/cm^{-1} 1660 (α,β-unsaturated ketone); λ_{max}(EtOH) nm 205 (log ε 4.28), 240 (3.97) and 282 (3.2); δ_H(60 MHz, CCl_4), 1.73 (3H, s, vinyl Me), 1.83–2.47 (6H, m), 2.50–3.00 (4H, m), 6.83–7.35 (3H, m, 4, 5 and 6-ArH) and 7.37 (1H, dd, *J* 8, 3-ArH).

2-[2-(2-Bromo-5-methoxyphenyl)ethyl]-3-methylcyclohex-2-enone 4b

The keto ester **3b** (16 g, 40.47 mmol) was converted, in the same way as described for **4a**, into the α,β-unsaturated ketone **4b** which was obtained as an oil (10.2 g, 78%), bp 190–195 °C (0.05 mmHg) (Found: C, 59.4; H, 5.9. $C_{16}H_{19}O_2Br$ requires C, 59.44; H, 5.92%); ν_{max}/cm^{-1} 1660 (α,β-unsaturated ketone); λ_{max}(EtOH) nm 205 (log ε 4.43), 230 (4.23) and 281 nm (3.34); δ_H(60 MHz, CCl_4) 1.76 (3H, s, vinyl Me), 1.83–2.50 (6H, m, methylenes), 2.53–3.00 (4H, m, $COCH_2$ and $ArCH_2$), 3.73 (3H, s, ArOMe), 6.52 (1H, dd, *J* 8 and 2, 4-ArH), 6.79 (1H, d, *J* 2, 6-ArH) and 7.4 (1H, d, *J* 8, 3-ArH).

2-[2-(2-Bromo-4-methoxyphenyl)ethyl]-3-methylcyclohex-2-enone 4c

The keto ester **3c** (20 g, 50.63 mmol) was converted in the same way as described for **4a** into the α,β-unsaturated ketone **4c** which was obtained as an oil (12.92 g, 79%), bp 195–205 °C (0.08 mmHg) (Found: C, 59.4; H, 5.9. $C_{16}H_{19}O_2Br$ requires C, 59.44; H, 5.92%); ν_{max}/cm^{-1} 1660 (α,β-unsaturated ketone); λ_{max}(EtOH) nm 206 (log ε 4.4), 225 (4.16), 281 (3.4) and 288 (3.36); δ_H(60 MHz, CCl_4), 1.76 (3H, s, vinyl Me), 1.83–2.46 (6H, m, methylenes), 2.50–3.00 (4H, m, $COCH_2$ and $ArCH_2$), 3.76 (3H, s, ArOMe), 6.80 (1H, dd, *J* 8 and 2, 5-ArH), 7.10 (1H, d, *J* 2, 3-ArH) and 7.20 (1H, d, *J* 8, 6-ArH).

2-[2-(2-Bromophenyl)ethyl]-3,3-dimethylcyclohexanone 5a

This compound was prepared adopting the procedure described earlier.[14,21] To a stirred suspension of CuI (15.6 g, 81.9 mmol) in dry ether (20 cm^3) under N_2 at −25 °C was added MeLi in ether (1.6 mol dm^{-3}; 51 cm^3, 8.19 mmol). The resulting yellow suspension was cooled to −50 °C and $BF_3{\cdot}Et_2O$ (5 cm^3, 40.95 mmol) was added to it. After 5 min the cyclohexenone **4a** (4 g, 13.64 mmol) in ether (10 cm^3) was added dropwise to the mixture which was then stirred at −30 °C for 15 min. Additional $BF_3{\cdot}Et_2O$ (5 cm^3, 40.95 mmol) was added to the mixture and stirring continued at −30 °C for 1 h. After this the mixture was allowed to warm to 0 °C and then quenched with aqueous NH_4Cl. Work-up followed by chromatography over silica gel (25 g) using light petroleum as eluent afforded the cyclohexanone **5a** (3.5 g, 84%) as a colourless oil (Found: C, 62.0; H, 6.9. $C_{16}H_{21}OBr$ requires C, 62.12; H, 6.84%); ν_{max}/cm^{-1} 1705 (CO); δ_H(60 MHz, CCl_4) 0.72 (3H, s, Me), 1.03 (3H, s, Me), 1.40–2.15 (7H, m, methylenes), 2.15–3.00 (4H, m, $COCH_2$ and $ArCH_2$), 6.83–7.38 (3H, m, 4, 5 and 6-ArH) and 7.50 (1H, dd, *J* 8 and 2, 3-ArH).

2-[2-(2-Bromo-5-methoxyphenyl)ethyl]-3,3-dimethylcyclohexanone 5b

The α,β-unsaturated ketone **4b** (4.4 g, 13.6 mmol) was converted, in the same way as described for **5a**, into the ketone **5b** (3.88 g, 84%) (Found: C, 60.2; H, 6.85. $C_{17}H_{23}O_2Br$ requires C, 60.17; H, 6.83%); ν_{max}/cm^{-1} 1705 (CO); δ_H(60 MHz, CCl_4) 0.73 (3H, s, Me), 1.00 (3H, s, Me), 1.40–2.13 (7H, m, methylenes and methine), 2.14–3.00 (4H, m, $COCH_2$ and $ArCH_2$), 3.70 (3H, s, ArOMe), 6.53 (1H, dd, *J* 8 and 2, 4-ArH), 6.73 (1H, d, *J* 2, 6-ArH) and 7.30 (1H, d, *J* 8, 3-ArH).

2-[2-(2-Bromo-4-methoxyphenyl)ethyl]-3,3-dimethylcyclohexanone 5c

The α,β-unsaturated ketone **4c** (4.4 g, 13.6 mmol) was converted, in the same way as described for **5a**, into the ketone **5c** (3.9 g, 84.4%) (Found: C, 60.0; H, 6.8. $C_{17}H_{23}O_2Br$ requires C, 60.17; H, 6.83%); ν_{max}/cm^{-1} 1705 (CO); δ_H(60 MHz, CCl_4) 0.73 (3H, s, Me), 1.03 (3H, s, Me), 1.40–2.10 (7H, m, methylenes and methine), 2.13–2.90 (4H, m, $COCH_2$ and $ArCH_2$), 3.73 (3H, s, ArOMe), 6.70 (1H, dd, *J* 8 and 5-ArH), 8.00 (1H, d, *J* 2, 3-ArH) and 7.10 (1H, d, *J* 8, 6-ArH).

Methyl 2-[2-(2-bromophenyl)ethyl]-1-methyl-3-oxocyclohexanecarboxylate 7a

A procedure described[15] earlier was adopted. A solution of the unsaturated ketone **4a** (4 g, 13.6 mmol) in 95% EtOH (40 cm^3) was heated under reflux with a solution of KCN (3.6 g, 55.4 mmol) in water (10 cm^3) for 14 h when the colour turned to brown. The cyano derivative, without isolation, was hydrolysed by refluxing it with KOH (5 g) in water (60 cm^3) for 96 h. Most of the EtOH was then removed. The organic phase was acidified with aqueous HCl (6 mol dm^{-3}) and repeatedly extracted with ether. The combined extracts were repeatedly washed with 10% aqueous KOH until alkaline. The cooled basic washings after acidification with aqueous HCl (6 mol dm^{-3}) were extracted with ether. The extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude acid thus obtained was esterified with an excess of diazomethane in ether. The methyl ester was purified by chromatography over silica gel (25 g) and eluted with ether–light petroleum (1:9) to afford a diastereoisomeric mixture of the keto esters **7a** (3 g, 68%) (Found: C, 57.8; H, 6.0. $C_{17}H_{21}O_3Br$ requires C, 57.78; H, 5.99%); ν_{max}/cm^{-1} 1730 (CO_2Me) and 1710 (CO); δ_H(100 MHz) 1.02 and 1.28 (3H, each s, Me for the major and the minor isomers, respectively) in a ratio of *ca.* 3:2; 1.40–2.28 (7H, m, methylenes and methine), 2.30–3.04 (4H, m, $COCH_2$ and $ArCH_2$), 3.64 (3H, br s, CO_2Me for both isomers), 6.96–7.40 (3H, m, 4, 5 and 6-ArH) and 7.52 (1H, dd, *J* 8 and 2, 1-ArH).

Methyl 2-[2-(2-bromo-5-methoxyphenyl)ethyl]-1-methyl-3-oxocyclohexanecarboxylate 7b

The α,β-unsaturated ketone **4b** (4 g, 12.37 mmol) was converted, in the same way as described for **7a**, into a diastereoisomeric mixture of the keto esters **7b** (3.37 g, 71%) (Found: C, 56.37; H, 6.0. $C_{18}H_{23}O_4Br$ requires C, 56.39; H, 6.04%); ν_{max}/cm^{-1} 1730 (CO_2Me) and 1710 (CO); δ_H(100 MHz) 1.03 and 1.28 (3H, each s, Me, for the major and minor isomers) in a ratio of *ca.* 3:2; 1.40–2.28 (7H, m, methylenes and methine), 2.30–3.04 (4H, m, $COCH_2$ and $ArCH_2$), 3.64 (3H, s, CO_2Me), 3.80 (3H, s, ArOMe), 6.65 (1H, dd, *J* 8 and 2, 6-ArH), 6.78 (1H, d, *J* 2, 4-ArH) and 7.40 (1H, d, *J* 8, 1-ArH).

Methyl 2-[2-(2-bromo-4-methoxyphenyl)ethyl]-1-methyl-3-oxocyclohexanecarboxylate 7c

The α,β-unsaturated ketone **4c** (4 g, 12.37 mmol) was converted, in the same way as described for **7a**, into a diastereoisomeric mixture of the keto esters **7c** (3.2 g, 67%) (Found: C, 56.4; H, 6.1. $C_{18}H_{23}O_4Br$ requires C, 56.39; H, 6.04%); ν_{max}/cm^{-1} 1730 (CO_2Me), 1710 (CO); δ_H(100 MHz) 1.03 and 1.28 (3H, each s, Me, for the major and the minor isomers) in a ratio of *ca.* 3:2; 1.40–2.26 (7H, m, methylenes and methine), 2.28–3.00 (4H, m, $COCH_2$ and $ArCH_2$), 3.64 (3H, s, CO_2Me), 3.80 (3H, s, ArOMe), 6.80 (1H, dd, *J* 8 and 2, 5-ArH), 7.10 (1H, dd, *J* 2, 1-ArH) and 7.12 (1H, d, *J* 8, 4-ArH).

2-[2-(2-Bromophenyl)ethyl]-3,3-dimethyl-1-methylenecyclohexane 6a

This compound was prepared adopting a procedure described earlier.[12,16] A suspension of methyl(triphenyl)phosphonium iodide (7.8 g, 19.4 mmol) in toluene (5 cm^3) and a toluene solution of freshly prepared sodium 2,2-dimethylpropanolate (2.25 mol dm^{-3} solution; 8.6 cm^3) was stirred at room temperature (*ca.* 25 °C) for 20 min. The ketone **5a** (2g, 6.47 mmol) in toluene (3 cm^3) was added dropwise to the mixture after which it was refluxed for 2 h and then quenched with saturated aqueous NH_4Cl and extracted with ether. The extract was washed with aqueous NH_4Cl and water, dried (Na_2SO_4) and evaporated to yield an oil. This was purified by chromatography on silica gel (25 g) using ether–light petroleum (1:49) as eluent to give the pure alkene **6a** (1.77 g, 90%) as a colourless oil (Found: C, 66.5; H, 7.55. $C_{17}H_{23}Br$ requires C, 66.43; H, 7.54%); ν_{max}/cm^{-1} 1640 (C=C); δ_H(100 MHz) 0.83 (3H, s, Me), 0.92 (3H, s, Me), 1.16–

2.00 (7H, m, methylenes and methine); 2.00–2.36 (2H, m, allylic CH_2), 2.40–2.92 (2H, m, $ArCH_2$), 4.68 and 4.84 (2H, each m, $C{=}CH_2$), 6.96–7.32 (3H, m, 4, 5 and 6-ArH) and 7.52 (1H, dd, *J* 8 and 2, 3-ArH).

2-[2-(2-Bromo-5-methoxyphenyl)ethyl]-3,3-dimethyl-1-methylenecyclohexane 6b

The ketone **4b** (2 g, 5.89 mmol) was converted in the same way as described for **6a** into the alkene **6b**, obtained as a colourless oil (1.85 g, 93%) (Found: C, 64.0; H, 7.5. $C_{18}H_{25}OBr$ requires C, 64.08; H, 7.47%); ν_{max}/cm^{-1} 1640 (C=C); δ_H(100 MHz, $CDCl_3$) 0.83 (3H, s, Me), 0.94 (3H, s, Me), 1.16–2.00 (7H, m, methylenes and methine), 2.00–2.34 (2H, m, allylic CH_2), 2.36–2.88 (2H, m, $ArCH_2$), 3.80 (3H, s, ArOMe), 4.68 and 4.86 (2H, each m, $C{=}CH_2$), 6.62 (1H, dd, *J* 8 and 2, 4-ArH), 6.78 (1H, d, *J* 2, 6-ArH) and 7.43 (1H, d, *J* 8, 3-ArH).

2-[2-(2-Bromo-4-methoxyphenyl)ethyl]-3,3-dimethyl-1-methylenecyclohexane 6c

The ketone **4c** (2 g, 5.89 mmol) was converted in the same way as described for **6a** into the alkene **6c** (1.8 g, 90%) (Found: C, 64.0; H, 7.5. $C_{18}H_{25}OBr$ requires C, 64.08; H, 7.47%); ν_{max}/cm^{-1} 1640 (C=C); δ_H(100 MHz, $CDCl_3$) 0.84 (3H, s, Me), 0.94 (3H, s, Me), 1.16–2.00 (7H, m, methylenes and methine), 2.00–2.32 (2H, m, allylic CH_2), 2.34–2.88 (2H, m, $ArCH_2$), 3.80 (3H, s, ArOMe), 4.68 and 4.84 (2H, each m, $C{=}CH_2$), 6.80 (1H, dd, *J* 8 and 2, 5-ArH), 7.10 (1H, d, *J* 2, 3-ArH) and 7.14 (1H, d, *J* 8, 6-ArH).

Methyl 2-[2-(2-bromophenyl)ethyl]-1-methyl-3-methylenecyclohexanecarboxylate 8a

The keto ester **7a** (2 g, 5.66 mmol) was converted in the same way as described for **6a** into the alkene ester **8a** (1.75 g, 88%) (Found: C, 61.55; H, 6.7. $C_{18}H_{23}O_2Br$ requires C, 61.53; H, 6.59%); ν_{max}/cm^{-1} 1730 (CO_2Me) and 1645 (C=C); δ_H(100 MHz) 1.05 (3H, s, Me), 1.20–2.48 (9H, m, methylenes and methine), 2.48–3.00 (2H, m, $ArCH_2$), 3.64 (3H, s, CO_2Me), 4.82 and 4.94 (2H, each br s, $C{=}CH_2$), 6.97–7.40 (3H, m, 4, 5 and 6-ArH) and 7.52 (1H, dd, *J* 8 and 2, 1-ArH).

Methyl 2-[2-(2-bromo-5-methoxyphenyl)ethyl]-1-methyl-3-methylenecyclohexanecarboxylate 8b

The mixture of keto esters **7b** (2 g, 5.22 mmol) was converted in the same way as described for **6a** into the alkene ester **8b** (1.7 g, 85%) (Found: C, 59.7; H, 6.6. $C_{19}H_{25}O_3Br$ requires C, 59.83; H, 6.61%); ν_{max}/cm^{-1} 1730 (CO_2Me) and 1640 (C=C); δ_H(100 MHz) 1.03 (3H, s, Me), 1.20–2.43 (9H, m, methylenes and methine), 2.45–3.00 (2H, m, $ArCH_2$), 3.64 (3H, s, CO_2Me), 3.76 (3H, s, ArOMe), 4.80 and 4.93 (2H, each br s, $C{=}CH_2$), 6.60 (1H, dd, *J* 8 and 2, 4-ArH), 6.70 (1H, d, *J* 2, 6-ArH) and 7.40 (1H, d, *J* 8, 3-ArH).

Methyl 2-[2-(2-bromo-4-methoxyphenyl)ethyl]-1-methyl-3-methylenecyclohexanecarboxylate 8c

The keto ester **7c** (2 g, 5.22 mmol) was converted in the same way as described for **6a** into the alkene ester **8c** (1.8 g, 90%) (Found: C, 59.8; H, 6.6. $C_{19}H_{25}O_3Br$ requires C, 59.83; H, 6.61%); ν_{max}/cm^{-1} 1730 (CO_2Me) and 1645 (C=C); δ_H(60 MHz, CCl_4) 1.03 (3H, s, Me), 1.20–2.43 (9H, m, methylenes and methine), 2.44–3.00 (2H, m, $ArCH_2$), 3.64 (3H, s, CO_2Me), 3.74 (3H, s, ArOMe), 4.80 and 4.90 (2H, each br s, $C{=}CH_2$), 6.73 (1H, dd, *J* 8 and 2, 5-ArH), 7.03 (1H, d, *J* 2, 3-ArH) and 7.06 (1H, d, *J* 8, 6-ArH).

***cis*-1,1-Dimethyl-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a*,*d*]cycloheptene 16a**

$NaBH_4$ (389 mg, 10.3 mmol) was added portionwise to a stirred solution of the *cis*-ketone **18a**[12] (500 mg, 2.06 mmol) in 95% EtOH (15 cm^3). The mixture was left overnight after which the excess of $NaBH_4$ was decomposed with water. Work-up afforded *cis*-5-hydroxy-1,1-dimethyl-2,3,4,4a,5,10,11,11a-octahydro-2*H*-dibenzo[*a*,*d*]cycloheptene **19a** (460 mg, 91%) as a solid epimeric mixture (Found: C, 83.4; H, 9.8. $C_{17}H_{24}O$ requires C, 83.55; H, 9.90%); ν_{max}/cm^{-1} 3340br (OH); δ_H(60 MHz, CCl_4) 0.70 and 0.73 (each s, CMe_2, major epimer), 0.90 and 0.97 (each s, CMe_2, minor epimer) in a ratio of *ca.* 2:1; 0.86–1.90 (8H, m, methylenes and methines), 2.02–2.28 (2H, m), 2.66–2.90 (2H, m, $ArCH_2$), 4.66 (1H, *J* 8, C*H*OH) and 7.08–7.54 (4H, m, ArH).

The epimeric mixture of **19a** (400 mg, 1.6 mmol) was subjected to hydrogenolysis in EtOH (20 cm^3) in the presence of 70% $HClO_4$ (3 drops) and Pd–C (10%) (40 mg) at room temperature and pressure. The uptake of hydrogen was very rapid and was complete within 2 h. Work-up followed by chromatography over silica gel with light petroleum as eluent furnished the pure *cis*-hydrocarbon **16a** (336 mg, 90%) as a colourless oil (Found: C, 89.3; H, 10.4. $C_{17}H_{24}$ requires C, 89.41; H, 10.51%); ν_{max}/cm^{-1} 2930, 1610 and 1590; δ_H(60 MHz, CCl_4), 0.72 and 0.92 (6H, each s, CMe_2), 1.16–2.30 (10H, m, methylenes and methine), 2.33–2.90 (4H, m, 2 × $ArCH_2$) and 6.97 (4H, br s, ArH).

***cis*-1,1-Dimethyl-7-methoxy-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a*,*d*]cycloheptene 16c**

The *cis*-ketone **18c**[12] (500 mg, 1.8 mmol) in 95% EtOH (15 cm^3) was reduced with $NaBH_4$ (340 mg, 9.1 mmol) as described for **19a** into the 7-methoxy alcohol **19c** (460 mg, 90%) as a solid mixture of two epimers; ν_{max}/cm^{-1} 3400 (br, OH); δ_H(60 MHz, CCl_4) 0.72 and 0.76 (each s, CMe_2, one epimer) and 0.95 and 0.98 (each s, CMe_2, other epimer) in a ratio of *ca.* 1:1; 1.0–1.90 (8H, methylenes), 2.02–2.28 (2H, m), 2.50–2.85 (2H, m, $ArCH_2$), 3.78 and 3.82 (3H, each s, ArOMe), 4.46–4.70 (1H, m, C*H*OH) and 6.60–7.20 (3H, m, ArH).

The epimeric mixture of the alcohols **19c** (400 mg, 1.45 mmol) on hydrogenolysis in EtOH (20 cm^3) and 70% $HClO_4$ (3 drops) in the presence of Pd–C (10%) (40 mg) gave the pure *cis*-ether **16c** (350 mg, 92%) as a colourless oil after chromatography over silica gel using ether–light petroleum (1:10) as eluent (Found: C, 83.4; H, 10.2. $C_{18}H_{26}O$ requires C, 83.66; H, 10.14%); ν_{max}/cm^{-1} 2930, 1610 and 1590; δ_H(60 MHz, CCl_4) 0.72 and 0.93 (6H, each s, CMe_2), 1.03–2.06 (10H, m, methylenes and methines), 2.10–2.91 (4H, m, CH_2), 3.70 (3H, s, ArOMe), 6.53 (2H, dd, *J* 8 and 2, 6 and 7-ArH) and 6.91 (1H, d, *J* 8, 9-ArH).

Radical cyclisation of 6a to *trans*-1,1-dimethyl-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a*,*d*]cycloheptene 15a and its 4a-epimer 16a

Tributyltin hydride (566 mg, 1.95 mmol) was added dropwise over 10 min to a stirred solution of the alkene **6a** (500 mg, 1.62 mmol) and AIBN (20 mg) in refluxing benzene (244 cm^3) under a nitrogen atmosphere for 10 h, and then cooled to room temperature. After removal of the solvent the residue was taken up in ether (120 cm^3) and stirred vigorously for 10 h with saturated aqueous KF (75 cm^3). The white precipitate was filtered off and washed with ether. The combined ether layers were separated and the aqueous layer was extracted with ether. The combined organic layer and extracts were dried (Na_2SO_4) and evaporated under reduced pressure and the residual oil after chromatography on silica gel using light petroleum as eluent afforded a colourless liquid (340 mg, 91%) consisting of an inseparable mixture of the *trans*- and *cis*-hydrocarbons **15a** and **16a** and the debrominated olefins **17ma** and **17na** in a ratio of *ca.* 90:10 (co-injection with pure **16a** and **17ma**[12] in GLC and from the ^1H NMR spectrum). The mixture was taken up in dry THF (10 cm^3) and the solution cooled to 0 °C, through which an excess of diborane gas [prepared from $NaBH_4$ (460 mg, 11.9 mmol) in $BF_3{\cdot}Et_2O$ (2 cm^3) in diglyme (5 cm^3)] was passed for 3 h under a continuous slow stream of N_2. The cooled mixture was carefully decomposed with cold water (*ca.* 0–10 °C) and added to

aqueous NaOH (3 mol dm^{-3}; 15 cm^3). To the well-stirred cooled mixture (*ca.* 0–10 °C) H_2O_2 (30% v/v; 5 cm^3) was added dropwise. Stirring was continued for an additional 30 min after which further H_2O_2 (2 cm^3) was added to the mixture which was then set aside overnight. After this it was extracted with ether and the extract washed with water, dried (Na_2SO_4) and evaporated to afford a colourless oil. This was purified by careful chromatography on silica gel using light petroleum as eluent to give an inseparable mixture of the *trans*- and the *cis*-hydrocarbons **15a** and **16a** (211 mg, 65%) (Found: C, 89.3; H, 10.4. $C_{17}H_{24}$ requires C, 89.41; H, 10.51%); ν_{max}/cm^{-1} 2930, 1610 and 1590; δ_H(60 MHz, CCl_4) 0.72 and 0.92 (each s, CMe_2, *cis*-isomer), 0.86 and 1.03 (each s, CMe_2, *trans*-isomer) in a ratio of *ca.* 45:55; 1.16–2.30 (10H, m), 2.33–3.16 (4H, m, 2 × $ArCH_2$) and 6.97 (4H, br s, ArH); *m/z* 228 (M^+, 100%), 214 (36), 179 (77), 143 (65), 129 (82) and 104 (84).

Radical cyclisation of 6c to *trans*-7-methoxy-1,1-dimethyl-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a*,*d*]cycloheptene 15c and its 4a-epimer 16c

Treatment of the olefin **6c** (500 mg, 1.48 mmol) in benzene (222 cm^3) with Bu_3SnH (516 mg, 1.78 mmol) and AIBN (20 mg) according to the procedure described for the *trans* and *cis*-hydrocarbons **15a**/**16a** gave a mixture of the *trans* and *cis*-ethers **15c** and **16c** and the corresponding debrominated olefins **17mc** and **17nc** in a ratio of *ca.* 1:1 (from ^1H NMR). The hydroboration oxidation followed by chromatography on silica gel gave an inseparable mixture of **15c** and **16c** (187 mg, 49%) (Found: C, 83.6; H, 10.2. $C_{18}H_{26}O$ requires C, 83.66; H, 10.14%); ν_{max}/cm^{-1} 2930, 1610 and 1590; δ_H(100 MHz) 0.71 and 0.92 (each s, CMe_2, *cis* isomer), 0.86 and 0.12 (each s, CMe_2, *trans* isomer) in a ratio of *ca.* 2:3; 1.16–2.40 (10H, m, methylenes and methines), 2.42–3.10 (4H, m, 2 × $ArCH_2$), 3.76 (3H, s, ArOMe), 6.60–6.80 (2H, m, 6 and 7-ArH) and 7.00 (1H, d, *J* 8, 9-ArH); *m/z* 258 (M^+, 100%), 244 (20), 173 (25) and 134 (90).

Radical cyclisation of 6b to *trans*-8-methoxy-1,1-dimethyl-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a*,*d*]cycloheptene 15b and its 4a-epimer 16b

Treatment of the olefin **6b** (500 mg, 1.48 mmol) in benzene (222 cm^3) with Bu_3SnH (516 mg, 1.78 mmol)–AIBN (20 mg) and purification of the resulting product according to procedure described for preparation of **15a**/**16a**, gave the *trans* and *cis* ethers **15b** and **16b** as a mixture (160 mg, 42%) (Found: C, 83.5; H, 10.1. $C_{18}H_{26}O$ requires C, 83.66; H, 10.14%); ν_{max}/cm^{-1} 2930, 1610 and 1590; δ_H 0.71 and 0.92 (each s, CMe_2, *cis* isomer), 0.86 and 1.04 (each s, CMe_2, *trans* isomer) in a ratio of *ca.* 2:3; 1.16–2.24 (10H, m, methylenes and methine), 2.24–3.08 (4H, m, 2 × $ArCH_2$), 3.76 (3H, s, ArOMe), 6.61 (2H, dd, *J* 8 and 2, 7 and 9-ArH) and 6.95 (1H, d, *J* 8, 6-ArH); *m/z* 258 (M^+, 84%), 244 (22), 173 (25) and 134 (100).

Radical cyclisation of 8c to (1*RS*,4a*RS*,11a*RS*)-Methyl 7-methoxy-1-methyl-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a*,*d*]cycloheptene-1-carboxylate 20c and its 4a-epimer 21c

Treatment of a solution of the olefinic ester **8c** (500 mg, 1.31 mmol) in benzene (196 cm^3) with Bu_3SnH (456 mg, 1.57 mmol) and AIBN (20 mg) according to the procedure described for **15a**/**16a** after the removal of the tin compounds with KF, on chromatography over silica gel gave a mixture of esters **20c** and **21c**, and the debrominated olefinic esters **22mc** and **22nc** in the fractions eluted with ether–light petroleum (1:9) (revealed from GLC and ^1H NMR). This mixture was then vigorously stirred[17] in EtOAc (1.6 cm^3) and MeCN (1.6 cm^3), with a solution of $RuCl_3 \cdot 3H_2O$ (0.018 mmol) and $NaIO_4$ (0.39 mmol) in water (0.5 cm^3) at 0 °C for 3 min. The reaction mixture was then quenched with saturated aqueous $Na_2S_2O_3$ (10 cm^3) and extracted with ether. The combined organic extracts were washed with water, dried (Na_2SO_4) and evaporated under reduced pressure to leave a thick oil. This was carefully chromatographed on silica gel using ether–light petroleum (1:9) as eluent to give a mixture of the *trans*- and *cis*-esters **20c** and **21c** (160 mg, 42%) in a ratio of *ca.* 70:30 (GLC) (Found: C, 75.6; H, 8.6. $C_{19}H_{26}O_3$ requires C, 75.46; H, 8.67%); ν_{max}/cm^{-1} 1730 (CO_2Me); δ_H(200 MHz) 0.60–0.95 (1H, m), 1.00 and 1.08 (3H, each s, Me, *cis* and *trans* isomers, respectively), 1.15–2.20 (8H, m, methylenes), 2.28–2.50 (1H, m), 2.52–3.15 (4H, m, 2 × $ArCH_2$), 3.70 (3H, br s, CO_2Me), 3.76 (3H, br s, ArOMe), 6.55–6.70 (2H, m, 6 and 7-ArH) and 6.90–7.05 (1H, m, 9-ArH). This mixture of **20c** and **21c** (310 mg, 1.02 mmol) was stirred with $KOBu^t$ (1.15 g, 10.26 mmol) in dry DMSO (15 cm^3) at room temperature[18] for 4 h after which it was poured onto ice–water and acidified with aqueous HCl (6 mol dm^{-3}). The mixture of liberated acids was extracted with ether and the extract washed with water, dried (Na_2SO_4) and evaporated to afford a yellowish solid mixture of the acids **23c** and **24c**. This on crystallisation once from ether–light petroleum gave a colourless solid, mp 185–198 °C. Fractional crystallisation of the mixture from EtOAc–light petroleum gave pure *trans*-acid **23**, mp 204–205 °C. A small portion of this acid was esterified with an excess of ethereal diazomethane to afford the pure *trans*-ester **20c** (Found: C, 75.7; H, 8.6. $C_{19}H_{26}O_3$ requires C, 75.46; H, 8.67%); ν_{max}/cm^{-1} 1730 (CO_2Me); δ_H(200 MHz) 0.60–0.85 (1H, m), 1.08 (3H, s, Me), 1.10–1.95 (8H, m), 2.35–2.50 (1H, m), 2.50–3.15 (4H, m, 2 × $ArCH_2$), 3.72 (3H, s, CO_2Me), 3.77 (3H, s, ArOMe), 6.66–6.67 (2H, m, 6 and 7-ArH) and 6.98 (1H, d, *J* 8, 9-ArH).

Conversion of the epimeric esters mixture of 20c and 21c to an epimeric mixture of the ethers 15c and 16c

An ethereal solution of the aforementioned (*ca.* 7:3) mixture of *trans*- and *cis*-esters **20c** and **21c** (130 mg, 0.43 mmol) was added to a stirred suspension of $LiAlH_4$ (33 mg, 0.86 mmol) in ether (10 cm^3) and the resulting mixture was refluxed for 4 h. After being cooled to 0 °C, the excess of $LiAlH_4$ was decomposed by slow addition of saturated aqueous Na_2SO_4. The ethereal layer was separated and filtered and the residual slurry was washed well with ether. The combined ether layer and washings were washed with water, dried (Na_2SO_4) and evaporated to give a mixture of two epimeric alcohols (107 mg, 91%); ν_{max}/cm^{-1} 3400 (br, OH); δ_H(60 MHz, CCl_4) 1.06 and 0.86 (3H, each s, Me, *trans* and *cis* isomers respectively) in a ratio of *ca.* 7:3; 1.15–2.30 (10H, m, methylenes and methines), 2.50–3.06 (4H, m, 2 × $ArCH_2$), 3.10–3.60 (2H, m, OCH_2), 3.68 (3H, s, ArOMe), 6.46 (2H, m, 6 and 8-ArH) and 6.83 (1H, d, *J* 8, 9-ArH). This mixture of epimeric alcohols (80 mg, 0.29 mmol) in CH_2Cl_2 (3 cm^3) was then added to a magnetically stirred suspension of pyridinium chlorochromate (94 mg, 0.43 mmol) in CH_2Cl_2 (5 cm^3) at 0 °C and stirring at this temperature was continued for 1 h followed by stirring for 30 min at room temperature. After work-up the product was chromatographed over silica gel using ether–light petroleum (1:10) as the eluent to afford an epimeric mixture of the aldehydes **25c** and **26c** (70 mg, 88%); ν_{max}/cm^{-1} 1730 (C=O); δ_H 0.82 and 0.89 (3H, each s, Me, *cis* and *trans* isomers, respectively) in a ratio of *ca.* 3:7; 1.03–2.00 (9H, m, methylenes and methine), 2.03–2.40 (1H, m, methine), 2.49–3.20 (4H, m, 2 × $ArCH_2$), 3.70 (3H, s, ArOMe), 6.47–6.67 (2H, m, 6 and 8-ArH), 6.90 (1H, d, *J* 8, 9-ArH) and 9.36 and 9.46 (1H, each s, CHO).

The above diastereoisomeric mixture of the aldehydes **25c** and **26c** (54.5 mg, 0.2 mmol) in diethylene glycol (3 cm^3) and hydrazine hydrate (0.80 cm^3) was heated at 120–130 °C (graphite bath for 2 h under a dry N_2 atmosphere) with a continuous distillation system. The reaction mixture was cooled to *ca.* 70 °C after which KOH (225 mg, 4 mmol) was added to it and the temperature raised to 210–220 °C. After 2.5 h at this temperature, the reaction mixture and the distillate were poured into water and extracted with ether. The combined ether

extracts were washed with water, dried (Na_2SO_4) and evaporated to give a gum which was purified by chromatography on silica gel (10 g) using light petroleum as eluent to afford a mixture of the *trans*- and the *cis*-ethers **15c** and **16c** (41.3 mg, 80%); δ_H(100 MHz) 0.71 and 0.92 (each s, CMe_2, *cis* isomer), 0.86 and 1.04 (each s, CMe_2, *trans* isomer) in a ratio of *ca.* 3:7, 1.16–2.40 (10H, m, methylenes and methines), 2.42–3.10 (4H, m, 2 × $ArCH_2$), 3.76 (3H, s, ArOMe), 6.60–6.80 (2H, m, 6 and 7-ArH) and 7.00 (1H, d, *J* 8, 9-ArH).

Radical cyclisation of 8a to (1*RS*,4a*RS*,11a*RS*)-methyl 1-methyl-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo-[*a*,*d*]cycloheptene-1-carboxylate 20a and its 4a-epimer 21a

Treatment of the alkene ester **8a** (500 mg, 1.42 mmol) in benzene (293 cm^3) with Bu_3SnH (495 mg, 1.7 mmol)–AIBN (20 mg) using an identical procedure to that described for the epimeric esters **20c** and **21c** gave, after purification of the products, a gum which on chromatography over silica gel using ether–light petroleum (1:9) as eluent afforded a mixture of the epimeric esters **20a** and **21a** (160 mg, 42%) (Found: C, 79.4; H, 8.9. $C_{18}H_{24}O_2$ requires C, 79.37; H, 8.88%); ν_{max}/cm^{-1} 1730 (CO_2Me); δ_H(100 MHz) 0.60–0.95 (1H, m), 1.00 and 1.05 (3H, each s, Me, *cis* and *trans* epimers, respectively), 1.16–2.20 (8H, m, methylenes and methine), 2.28–2.50 (1H, m, methine), 2.56–3.20 (4H, m, 2 × $ArCH_2$), 3.72 and 3.70 (3H, each s, CO_2Me, *trans*- and *cis*-isomers, respectively) in a ratio of *ca.* 7:3 and 7.08 (4H, br s, ArH).

The above epimeric mixture of the esters **20a** and **21a** (150 mg, 0.55 mmol) was treated with $KOBu^t$ (560 mg, 5 mmol) in dry DMSO (12 cm^3) using an identical procedure to that described for **23c** and **24c** to afford a solid mixture of the acids **23a** and **24a** which on fractional crystallisation from EtOAc–light petroleum gave the pure *trans* acid **23a**, mp 244–245 °C. A small sample of the acid was esterified with an excess of diazomethane in ether to give the pure *trans*-ester **20a** (Found: C, 79.5; H, 8.65. $C_{18}H_{24}O_2$ requires C, 79.37; H, 8.88%); δ_H(100 MHz) 0.60–0.95 (1H, m), 1.05 (3H, s, Me), 1.12–2.20 (8H, m), 2.36–2.52 (1H, m), 2.58–3.20 (4H, m), 3.72 (3H, s, CO_2Me) and 7.12 (4H, br s, ArH).

Radical cyclisation of 8b to (1*RS*,4a*RS*,11a*RS*)-methyl-8-methoxy-1-methyl-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a*,*d*]cycloheptene-1-carboxylate 20b and its 4a-epimer 21b

Treatment of a solution of the alkene ester **8b** (500 mg, 1.3 mmol) in benzene (196 cm^3) with Bu_3SnH (456 mg, 1.57 mmol)–AIBN (20 mg), using a procedure identical with that described for the synthesis of **20c** and **21c** gave the mixture of the *trans*- and *cis*-esters **20b** and **21b** (158 mg, 40%) (Found: C, 75.7; H, 8.6. $C_{19}H_{26}O_3$ requires C, 75.46; H, 8.67%); ν_{max}/cm^{-1} 1730 (CO_2Me); δ_H(100 MHz) 0.60–0.95 (1H, m), 1.00 and 1.08 (3H, each s, Me, *cis*- and *trans*-isomers, respectively) in a ratio of *ca.* 3:7; 1.16–2.20 (9H, m, methylenes and methine), 2.28–2.52 (1H, m, methine), 2.56–3.14 (4H, m, 2 × $ArCH_2$), 3.70 (3H, br s, CO_2Me, both isomers), 3.76 (3H, s, ArOMe), 6.60 (1H, dd, *J* 8 and 2, 7-ArH), 6.64 (1H, s, 9-ArH) and 6.92 (1H, d, *J* 8, 6-ArH).

Ethyl 3-[2-(2-bromophenyl)ethyl]-2,2-dimethyl-4-oxocyclohexanecarboxylate 27

The enone ester **3a** (5 g, 13.68 mmol) was subjected to methylation using a procedure identical with that described for **5a**. Chromatography of the crude product on neutral alumina using light petroleum as eluent gave a diastereoisomeric mixture of **27** (4.5 g, 88%) as a faint yellow oil (Found: C, 59.7; H, 6.7. $C_{19}H_{25}BrO_3$ requires C, 59.83; H, 6.61%); ν_{max}/cm^{-1} 1735 (CO_2Et) and 1720 (C=O); δ_H(200 MHz) 0.80 and 1.08 (s, Me, major isomer), 0.92 and 1.05 (s, Me, minor isomer) in a ratio of *ca.* 68:32; 1.25 (t, *J* 7, $CO_2CH_2CH_3$, major isomer), 1.40 (t, *J* 7, $CO_2CH_2CH_3$, minor isomer), 1.57–2.95 (10H, m, benzylic, methylenes and methine), 4.08–4.40 (m, $CO_2CH_2CH_3$, isomers) and 6.98–7.58 (m, ArH, isomers).

Ethyl 3-[2-(2-bromophenyl)ethyl]-2,2-dimethyl-4-methylene cyclohexanecarboxylate 28

The diastereoisomeric mixture of the keto ester **27** (2.5 g, 6.55 mmol) was converted in the same way as described for **8a** into the diastereoisomeric mixture of the alkene esters **28** (2.15 g, 85%) as an oil (Found: C, 63.15; H, 7.0. $C_{20}H_{27}BrO_2$ requires C, 63.31; H, 7.17%); ν_{max}/cm^{-1} 1735 (CO_2Et) and 1650 (s, C=C); δ_H(200 MHz) 0.77 and 1.02 (s, Me, minor isomer), 0.97 and 0.99 (s, Me, major isomer) in a ratio of *ca.* 40:60; 1.16–1.28 (m, $CO_2CH_2CH_3$, isomers), 1.50–3.00 (m, methylenes, methine and benzylic), 3.62 (br s), 4.02–4.17 (m, $CO_2CH_2CH_3$, isomers), 4.65–5.02 (2H, m, C=CH_2) and 6.98–7.58 (m, ArH, isomers).

Radical cyclisation of 28 to (2*SR*,4a*RS*,11a*SR*)-methyl 1,1-dimethyl-2,3,4,4a,5,10,11,11a-octahydro-1*H*-dibenzo[*a*,*d*]-cycloheptene-1-carboxylate 29

Treatment of the alkene ester **28** (1 g, 2.64 mmol) in benzene (250 cm^3) with Bu_3SnH (920 mg, 3.16 mmol)–AIBN (60 mg) under reflux for 13 h and work-up by an identical procedure to that described for **20c**/**21c** gave a thick, light-yellow oil which was subjected to ester cleavage with $KOBu^t$ in dry DMSO. The crude acids mixture was directly esterified with ethereal diazomethane and the product on chromatography on alumina using light petroleum as eluent gave a complex mixture (^1H NMR) of the ester **29** along with its diastereoisomers and the corresponding debrominated alkene esters (650 mg, 86%). This mixture was vigorously stirred in EtOAc (2 cm^3) and MeCN (2 cm^3) with a solution of $RuCl_3 \cdot 3H_2O$ (0.24 mmol) and $NaIO_4$ (0.513 mmol) in distilled water (0.7 cm^3) at 0 °C for 2 min. Work-up as described for the **20c**/**21c** mixture gave a thick yellow oil. This on chromatography on alumina using light petroleum as eluent gave a thick colourless oil (543 mg, 72%) containing the major epimer **29** along with the remaining three diastereoisomers of undetermined stereochemistries in a ratio of *ca.* 73:10:8:9 (GLC analyses); ν_{max}/cm^{-1} 1735 (CO_2Me); δ_H-(200 MHz) 0.97 and 1.13 (each s, CMe_2, major epimer, 0.65–0.90 (1H, m, methine), 1.00–2.05 (m, methylenes), 2.22–2.46 (benzylic and methine), 2.60–3.09 (m, methine methylene and benzylic), 3.62 (s, CO_2Me, major epimer), 3.64, 3.65 and 3.68 (s, CO_2Me, minor epimers) and 7.00–7.35 (m, ArH). This was subjected to ester cleavage with $KOBu^t$ in DMSO as described for the **20c**/**21c** mixture to give a gummy mixture of acids (475 mg) which on fractional crystallisation from ether–light petroleum afforded the *cis*-acid **30**, mp 184–186 °C as the sole isolable pure diastereoisomer. This on esterification with diazomethane in ether afforded the methyl ester **29**, mp 96–97 °C (Found: C, 79.5; H, 9.0. $C_{19}H_{26}O_2$ requires C, 79.68; H, 9.15%); ν_{max}/cm^{-1} 1735 (CO_2Me); δ_H(400 MHz), 0.75 (1H, qd, *J* 13.5 and 4.5, 4_{ax}-H), 0.94 (3H, s, eq-Me), 1.10 (3H, s, ax-Me), 1.24 (1H, m, 4_{eq}-H), 1.36 (1H, m, 11_{ax}-H), 1.50 (2H, m, 3_{eq}-H and 11a-H), 1.76 (1H, qd, *J* 13.5 and 4.5, 3_{ax}-H), 1.93 (1H, m, 11_{eq}-H), 2.25 (1H, dd, *J* 13 and 4.1, 2-H), 2.34 (1H, m, 4a-H), 2.64 (1H, dd, *J* 13.9 and 6.5, 5_{ax}-H), 2.71 (2H, m, 10_{ax} and 10_{eq}-H_2), 2.99 (1H, dd, *J* 13.9 and 2.0, 5_{eq}-H), 3.58 (3H, s, CO_2Me) and 7.00–7.08 (4H, m, ArH).

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