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A synthesis of (±)-sparteine

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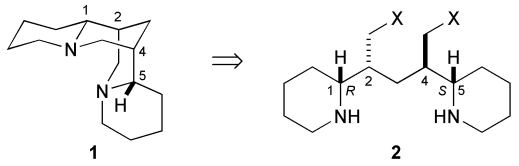
In a synthesis of racemic sparteine, Diels–Alder reaction between dimethyl bromomesaconate **14** and dicyclopentenyl **4**, followed by cyclopropane formation, set up the stereochemistry at C-1 and C-5 as *S* and *R*, respectively, in a meso intermediate **8**. The stereochemistry at C-2 and C-4 was then secured by a moderately diastereoselective protonation of the bis-enolate **17** derived from the diester **8** by reductive cleavage with lithium in liquid ammonia. The C=C in the racemic diester **19** was ozonolysed and the diketone converted by Beckmann rearrangement into the bis-lactam **25**. Reduction of the bis-lactam with lithium aluminium hydride and intramolecular nucleophilic displacement gave racemic sparteine **1**. Some ideas for making this synthesis amenable to a synthesis of enantiomerically enriched sparteine are presented.

Introduction

(−)-Sparteine **1** has been used to induce absolute stereocontrol in a number of lithiations,[1] but is readily available only in one enantiomeric series. Its importance has excited much interest in its synthesis, first of the racemic alkaloid,[2,3] but only relatively recently of the unnatural (+)-enantiomer.[4] Equally interesting has been the successful quest to find simpler analogues.[5] We reported some of our work on a synthesis of the racemic alkaloid in a preliminary communication,[6] and we report it in full here.

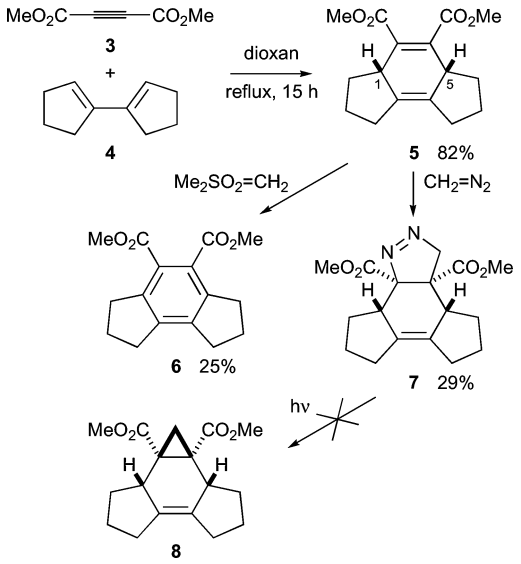


1 **2**

In our retrosynthetic analysis, the disconnection **1** ⇒ **2** is similar to that used in the earliest, but stereochemically random, synthesis of (±)-sparteine by Leonard and Beyler.[2] In particular, we sought to find an intermediate in which the two stereocentres numbered as C-1 and C-5 were firmly set up as *R* and *S*, respectively, in a meso intermediate, and later to set up the two stereocentres C-2 and C-4, either both *R* or both *S*, in such a way as to make either enantiomer equally easy to prepare. In the event we have synthesised racemic sparteine using this design, showing that the approach is workable. We have not had time to test its applicability to an enantiocontrolled synthesis, although there are many intriguing ways in which this might be achieved.

Results and discussion

The key meso intermediate was the cyclopropane **8**, and our first route to it (Scheme 1) was to be the known Diels–Alder reaction[7] between dimethyl acetylenedicarboxylate **3** and the diene **4**, reliably setting up the stereochemical relationship between C-1 and C-5 in the adduct **5**, which was to be subjected to a methylene insertion. The dimethylsulfoxonium methylide[8] is known to



Scheme 1

insert into α,β-unsaturated esters,[9] but in practice it was too basic for our compound **5**. Instead of insertion it gave only the aromatic compound **6** even with careful exclusion of air. Our second attempt at methylene insertion, inspired by a Woodward synthesis,[10] was to use diazomethane. The cycloaddition to give the adduct **7** took place, but very slowly, taking many days and giving, even so, a low yield. Furthermore, all our attempts to extrude the nitrogen were unavailing. Even when we had an authentic sample of the cyclopropane **8**, and of its stereoisomer **16**, we were unable to detect either of them in the photolysis mixtures.

In our second route, we tried to introduce the methylene group by treating another known Diels–Alder adduct[11] **9** with an excess of lithium diisopropylamide (LDA) and methylene bromide, and obtained the bromomethyl compound **10** in low yield (Scheme 2). On further treatment with LDA, this gave us what we wanted for the first time, the cyclopropane **8**, but the overall yield was much too low.

In our third route, we turned to a Diels–Alder reaction between a dienophile that would carry the extra carbon with it, allowing a cyclopropane to be created in much the same way that Eschenmoser did in a synthesis of colchicine.[12] As our first dienophile with this feature, we tried bromomethylmaleic

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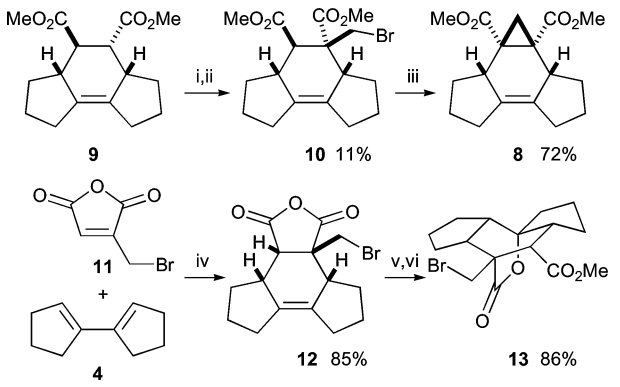
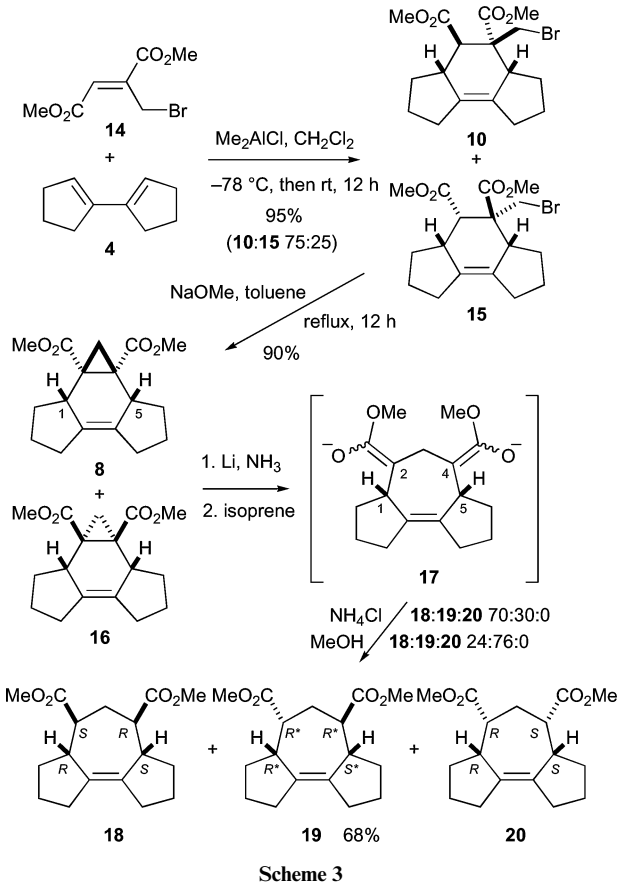


Scheme 2 *Reagents*: i, 2 equiv. LDA; ii, CH_2Br_2; iii, 1 equiv. LDA; iv, Et_2O, rt, 4 h; v, NaOMe, MeOH, reflux, 2.5 h; vi, 3 N HCl workup.

anhydride **11**, and obtained the adduct **12** in good yield (Scheme 2). This did not give a cyclopropane when treated with lithium tetramethylpiperidide, and so we tried opening the anhydride ring first. Using sodium methoxide, we obtained only the lactone **13**, presumably formed by an exceptionally easy protonation of the double bond during the mild acidic workup. Hoping to avoid this problem, we tried to carry out a Diels–Alder reaction between the diene **4** and the corresponding diester, dimethyl bromocitraconate, which we prepared from the anhydride **11** by treating it with methanol and sulfuric acid. This Diels–Alder reaction failed to take place, with or without Lewis acid catalysis. A planar anhydride is a better dienophile than a maleate ester, but our total failure to induce a Diels–Alder reaction was disappointing. We simply recovered the starting materials.

Finally, the Diels–Alder reaction of the corresponding *Z*-diester, dimethyl bromomesaconate **14**, took place smoothly to give a mixture of adducts **10** and **15** in a ratio of 75 : 25 (Scheme 3). On treatment with sodium methoxide this mixture gave a mixture of the cyclopropanes **8** and **16** in the same ratio.



Scheme 3

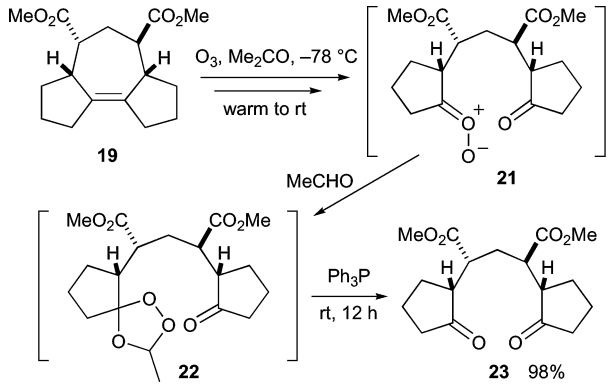
Except to characterise the major isomers, we did not separate the bromides or the cyclopropanes before they were used in the next step. Having a mixture of cyclopropanes was of no consequence, beyond mild inconvenience, because the next step was to remove the difference between them. Treatment with lithium in liquid ammonia cleaved the bond between the carbonyl groups, and gave the bis-enolate **17**. This key intermediate is still essentially a meso compound, if one ignores enolate geometry.

The interesting step, creating the stereochemistry at C-2 and C-4, is the protonation of the bis-enolate. There are three possible diastereoisomeric products, two of which, the *R*,*S*,*R*,*S* and the *R*,*R*,*S*,*S* isomers **18** and **20**, are meso, and the third of which, the *R**,*R**,*R**,*S** isomer **19**, the diastereoisomer required for the synthesis of sparteine, is not. The isomers **18** and **20**, being meso, will each have a singlet for the methoxy protons in their ^{1}H NMR spectra, whereas the racemic isomer **19** will have two methoxy singlets, which we hoped would be resolved. In practice we obtained only two, **18** and **19**, of the three isomers in the many conditions for protonation that we tried, with no trace of the isomer **20** at any stage. The isomer **18** was distinguished from the other meso isomer **20** by single crystal X-ray structural analysis, and the racemic isomer **19** did have the two methoxy singlets which identified it unambiguously.

When isoprene was not used to quench the excess of solvated electrons, yields were low and the proportions of the esters **18** and **19** varied as a consequence of the different rates at which they were reduced, giving us at first a misleading impression of selectivity in favour of the desired racemic isomer **19**. Once isoprene was added before the protonation, yields were reliably high, and the only problem was to raise the proportion of the racemic isomer **19**. We tried several reduction conditions, including sodium in the presence of trimethylsilyl chloride,[13] and lithium 2,6-di-*tert*-butylbiphenyl,[14] but our best results were with lithium in liquid ammonia, quenching with various proton sources. In summary, quenching with ammonium chloride gave the meso isomer as the major product (**18** : **19** = 70 : 30), and quenching with methanol gave the racemic isomer as the major product (**18** : **19** = 24 : 76). Crystallisation of the latter mixture, followed by chromatography of the mother liquors, gave a total yield of the diester **19** of 68% based on the mixture of cyclopropanes **8** and **16**.

Equilibration of the esters using sodium methoxide in methanol unhelpfully gave the same two esters in a ratio even more in favour of the meso isomer (**18** : **19** = 84 : 16), with still no sign of the other meso isomer **20**. This result more or less agreed with a calculated difference in energy between the isomers **18** and **19** of 5.55 kJ mol^{-1} in favour of the meso isomer, with the other meso isomer **20** higher again in energy by 6.46 kJ mol^{-1}.

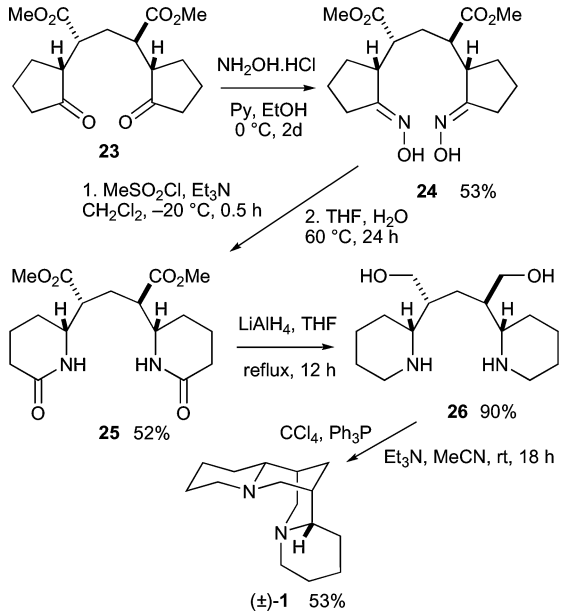
With the relative stereochemistry set up, the remaining steps looked, and eventually were, straightforward. The next step, however, gave us some trouble, in spite of appearing to be uncomplicated. Ozonolysis of the alkene **19** in dichloromethane solution took place at low temperature as expected, but workup with dimethyl sulfide or triphenylphosphine gave us mixtures of isomeric diketones instead of a single diketone **23**. We deduced that one or more of the four stereocentres had to some extent lost its configuration. Although all four are in principle equilibratable, we did not at first see why any of them should have been so easily disturbed in essentially neutral conditions at low temperature. The explanation we offer is that the molozonide is formed as usual, but an intermediate ketone oxide **21** (Scheme 4) derived from it does not rapidly undergo the usual dipolar cycloaddition to give the ozonide, because the ring size for the intramolecular reaction is unfavourable—the smallest of the rings which would be formed is 8-membered. The ketone oxide group in the intermediate **21** is effectively an activated carbonyl group, and its unusually long life allows epimerisation by the equivalent of enolisation. We do not, of course, know on which side of the molecule epimerisation occurs, and so the particular ketone oxide drawn as **21** is an arbitrary choice.



Scheme 4

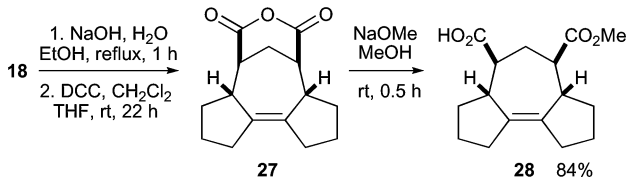
The solution to the problem, which also supports our analysis, was to carry out the ozonolysis in acetone, allowing the ketone oxide to be trapped by the solvent. Under these conditions we obtained the diketone **23** with 4% of epimerisation. Better still was to add acetaldehyde to the acetone to trap the ketone oxide, even more efficiently, as the ozonide **22**. In this way we detected among the products only the diketone **23**, and isolated it in 98% yield.

The remaining steps (Scheme 5) were relatively uneventful, but were not optimised. The bis-oxime **24** was separable in 53% yield from the geometrically isomeric oximes by chromatography and crystallisation. The mixture of oxime byproducts—geometrical isomers and mono-oximes—could almost certainly have been recycled, but we did not test this. Beckmann rearrangement took place when the bis-oxime methanesulfonate was warmed in aqueous tetrahydrofuran. The bis-lactam **25** gave the bis-piperidine diol **26** on reduction with lithium aluminium hydride, and the diol gave (±)-sparteine **1** when treated with carbon tetrachloride and triphenylphosphine.



Scheme 5

Although we did not investigate the synthesis of an enantiomerically enriched sparteine, we did prepare for one route by which it might be achieved (Scheme 6). The meso diester **18** gave the corresponding dicarboxylic acid on hydrolysis, without epimerisation, since acid gave back the diester **18** on treatment with trimethylsilyldiazomethane. The dicarboxylic acid gave the corresponding anhydride **27**, and the anhydride could be opened with methanol to give the monoester **28** in good overall yield, again without epimerisation, since it also gave the meso diester



Scheme 6

18 on treatment with trimethylsilyldiazomethane. Were we to have used a chiral and enantiomerically enriched alcohol or amine,[15] there is some hope that we would have been able to make an enantiotopically differentiated version of the monoester. Unfortunately, the monoester **28** was not epimerised by sodium methoxide in refluxing methanol over three days, and so more work needs to be done to find a route to the enantiomerically enriched natural or unnatural product following these more-or-less conventional ideas.

There are several other ideas like this which might work, but the most elegant solution to the problem would be to find an enantiomerically enriched acid which was constitutionally either *R*- or *S*-selective in the protonation of an enolate. It might be better to delay the protonation until after the ozonolysis, in order to avoid any steric bias imparted by the tricyclic framework in the bis-enolate **17**, but, at whatever stage the protonation of the bis-enolate is carried out, an enantioselective proton source would provide an extraordinarily simple way to set up the stereochemistry at C-2 and C-4, in either sense. If only there were such a reagent. . .

Experimental

General

Infrared spectra were recorded on a Perkin–Elmer FT-IR 1620 infrared spectrometer and wave numbers measured relative to polystyrene (1603 cm^{-1}), using sodium chloride solution cells (0.1 mm path length). ^{1}H and ^{13}C NMR spectra were recorded on Bruker NMR spectrometers (Avance 700, Avance 500 Cryo Ultrashield, DPX 400 and DPX 250). Chemical shifts were measured relative to tetramethylsilane (δ_H 0.00) or chloroform (δ_H 7.27) as internal standards. The coupling constant J is expressed in Hertz (Hz). In ^{13}C attached proton test (APT) spectra, + denotes a signal in the same direction as the solvent signal. ^{1}H and ^{13}C NMR assignments were made in all but the most simple compounds from COSY, HMQC, HMBC and NOESY spectra. Mass spectra were recorded on Kratos Concept (EI) and Micomas Q-TOF (ESI) spectrometers. X-Ray structures were determined with a Nonius Kappa CCD. Mass spectra and X-ray crystallography were carried out by technical staff. Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh ASTM) and Merck LiChroprep RP-18 (25–40 μm). Thin layer chromatography (TLC) was performed on glass plates coated to a thickness of 1 mm with Merck Kieselgel 60 PF_{254} and RP-18F_{254s}. R_f values refer to TLC on Kieselgel 60 PF_{254} plates. Melting points were determined using Gallenkamp melting point apparatus and stand uncorrected. Tetrahydrofuran (THF) and ether were freshly distilled from lithium aluminium hydride under argon. Dichloromethane, carbon tetrachloride, acetonitrile, methanol, light petroleum, hexane and toluene were freshly distilled from calcium hydride under argon. Light petroleum refers to the fraction boiling in the range 40–60 °C. Ether refers to diethyl ether.

Dimethyl 1,2,3,3a,5a,6,7,8-octahydro-*as*-indacene-4,5-dicarboxylate 5[7]

Dicyclopentenyl[16] (4.0 g, 0.03 mol), dimethyl acetylenedicarboxylate (4.26 g, 0.03 mol, freshly distilled), hydroquinone (0.1 g) and dioxan (13 cm^3, freshly distilled from calcium hydride) were refluxed under nitrogen for 15 h. Dioxan was removed

under reduced pressure, pentane (20 cm^3) was added to the light yellow residue, the pentane-soluble portion decanted off and the solution kept at −20 °C overnight. The adduct (6.74 g, 82%) was filtered off as large needles, mp 42–43 °C (from hexane) (no mp in lit.; the mp of 127 °C given for **5**[16] is actually that of the aromatic compound **6**, as revealed by Courtot and Clément[7]); R_f(Et_2O–light petroleum, 1 : 1) 0.52; ν_{max}($CDCl_3$)/cm^{-1} 2952 (CH), 2870 (CH), 2841 (CH), 1716 (C=O) and 1258 (C–O–C); δ_H(400 MHz, $CDCl_3$) 3.78 (6 H, s, 2 × OMe), 3.15 (2 H, br s, 2 × =CCH), 2.23–2.13 (6 H, m, 2 × $=CCH_2$ and 2 × CH_ACH_B), 1.87–1.80 (2 H, m), 1.75–1.64 (2 H, m) and 1.32 (2 H, qd, *J* 11.8 and 7.5, 2 × CH_AH_BCH); δ_C(100 MHz, $CDCl_3$) 168.7+, 137.1+, 130.7+, 51.9−, 43.8−, 31.9+, 27.3+ and 23.7+.

Dimethyl 1,2,3,6,7,8-hexahydro-*as*-indacene-4,5-dicarboxylate 6[7,16]

The diester **5** (2.5 g, 9 mmol) in dry DMSO (3 cm^3) was added to the trimethylsulfoxonium methylide[8] (9 mmol). A mild exothermic reaction took place and the mixture turned initially slightly yellow (then orange, and finally dark brown with no precipitate). The mixture was stirred at room temperature for 4 h, and poured into ice and hydrochloric acid (3 mol dm^{-3}, 30 cm^3). The mixture was extracted with ether (3 × 50 cm^3), dried ($MgSO_4$), and filtered. The solvents were removed, and pentane (40 cm^3) was added to the oil. The pentane-soluble portion was decanted and kept at −20 °C overnight. The only recognisable product, the aromatic diester (0.62 g, 25%), separated as yellow needles, mp 135–136 °C (from EtOH) (lit.,[7] 130 °C); R_f(Et_2O–light petroleum, 1 : 1) 0.48; ν_{max}($CDCl_3$)/cm^{-1} 2952 (CH_3), 2878 (CH_3), 2840 (CH_2), 1721 (C=O), 1583 (Ph) and 1287 (C–O–C); δ_H(400 MHz; $CDCl_3$) 3.86 (6 H, s, 2 × OMe), 3.05 (4 H, t, *J* 7.5, 2 × $CH_2CH_2CH_2$), 2.83 (4 H, t, *J* 7.5, 2 × $CH_2CH_2CH_2$) and 2.10 (4 H, quintet, *J* 7.5, 2 × $CH_2CH_2CH_2$); δ_C(100 MHz; $CDCl_3$) 168.8+, 143.6+, 142.9+, 126.0+, 52.1−, 32.5+, 31.4+, 25.0+.

Dimethyl (3a*RS*,3b*RS*,9a*SR*,9b*SR*)-3b,4,5,6,7,8,9,9a-octahydro-3*H*-1,2-diazatrindene-3a,9b-dicarboxylate 7

Diazomethane (16.6 mmol, alcohol-free solution in ether)[17] was added to a solution of Diels–Alder adduct **5** (0.765 g, 2.78 mmol) in dry ether (10 cm^3). The solution was kept in the dark, adding further aliquots of freshly prepared diazomethane (16.6 mmol, alcohol-free solution in ether) after 3, 5 and 7 days, successively. After 18 days, glacial acetic acid was added. The mixture was filtered, the filtrate washed with aqueous sodium hydrogen carbonate and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The ^{1}H NMR spectrum showed 46% conversion of the starting material. Diazomethane (16.6 mmol, alcohol-free solution in ether) was added to a solution of the residue in dry ether (10 cm^3). The solution was again kept in the dark and diazomethane (16.6 mmol, alcohol-free solution in ether) added after 4 and 6 days, successively. After 14 days, glacial acetic acid was added. The mixture was filtered, the filtrate washed with aqueous sodium hydrogen carbonate and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, light petroleum–EtOAc, 4 : 1) to give the *pyrazoline* (0.25 g, 29%) as needles, mp 85–86 °C (from EtOAc–hexane); R_f(Et_2O–light petroleum, 1 : 1) 0.38; ν_{max}($CDCl_3$)/cm^{-1} 2954 (CH_3), 2872 (CH_3), 2834 (CH_2), 1747 (C=O) and 1255 (C–O–C); δ_H(500 MHz; $CDCl_3$) 5.05 (1 H, d, *J* 18.7, $CH_AH_BN_2$), 4.23 (1 H, d, *J* 18.7, $CH_AH_BN_2$), 3.71 (3 H, s, CO_2Me), 3.64 (3 H, s, CO_2Me), 3.05 (1 H, m, $CHCCO_2MeN_2$), 2.84 (1 H, m, $CHCCO_2MeCH_2N_2$), 2.45 (1 H, dt, *J* 20.3, 7.2, $CH_AH_BCHCCO_2MeN_2$), 2.27–2.13 (3 H, m, 2 × CH_AH_BC=C and $CH_AH_BCHCCO_2Me)N_2$], 1.82 [1 H, dquintet, *J* 19.7 and 3.7, $CH_AH_BCH_2CHC(CO_2Me)CH_2N_2$], 1.71–1.61 [3 H, m, $CH_AH_BCH_2CHC(CO_2MeCH_2N_2$ and $CH_2CH_2CHCCO_2MeN_2$) and 1.29 (1 H, m dq, *J* 17.0 and 8.4, $CH_AH_BCHCCO_2MeCH_2N_2$); δ_C(100 MHz; $CDCl_3$) 173.8+ ($CHCCO_2MeCH_2N_2$), 170.0+ ($CHCCO_2MeN_2$), 134.0+ (C=C), 133.4+ (C=C), 106.7+ ($CHCCO_2MeN_2$), 83.8+ (CH_2N_2), 58.5+ ($CHCCO_2MeCH_2N_2$), 52.6− ($CHCCO_2Me$-CH_2N_2), 52.5− ($CHCCO_2MeN_2$), 47.6− ($CHCCO_2MeN_2$), 45.9− ($CHCCO_2MeCH_2N_2$), 30.0+, 29.8+, 29.75+, 28.5+ ($CH_2CHCCO_2MeN_2$), 26.8+ (CH_2CH_2C=C) and 26.5+ (CH_2CH_2C=C); *m*/*z* (ESI) 341 (M + Na)$^+$ (Found: M + Na^+, 341.1469. $C_{17}H_{22}N_2O_4$ requires *M* + Na, 341.1477). The aromatic compound **6** was also present in other chromatographic fractions.

Dimethyl (3a*RS*,4*SR*,5*SR*,5a*SR*)-1,2,3,3a,4,5,5a,6,7,8-decahydro-*as*-indacen-4,5-dicarboxylate 9[11]

Diene **4** (2 g, 14.9 mmol) and dimethyl fumarate (2.22 g, 15.4 mmol) were refluxed in toluene (30 cm^3) for 4 h. Toluene was removed under reduced pressure to give a pale yellow oil, which was dissolved in *n*-pentane (20 cm^3) and kept at −20 °C overnight to give the diester (3.81 g, 92%) as plates, mp 75–75.5 °C (from *n*-pentane) (lit.,[11] 72–74 °C; R_f(Et_2O–light petroleum, 1 : 1) 0.27; ν_{max}($CDCl_3$)/cm^{-1} 2954 (CH), 2870 (CH) and 1731 (C=O); δ_H(400 MHz; $CDCl_3$) 3.69 (3 H, s, CO_2Me), 3.67 (3 H, s, CO_2Me), 3.25 (1 H, dd, *J* 15.0 and 12.0, $CHCO_2Me$), 2.67 (1 H, m, $CHCHCO_2Me$), 2.31 (1 H, m, $CHCHCO_2Me$), 2.20–2.12 (5 H, m, 2 × CH_2C=C and $CHCO_2Me$), 1.92 (1 H, quintet, *J* 6.0), 1.81–1.51 (5 H, m), 1.25 (1 H, quintetd, *J* 12.0 and 6.8, CH_AH_BCH) and 1.05 (1 H, dtt, *J* 21.3, 10.3 and 2.2, $CH_AH_BCH_2C$=C).

2-Bromo-2-bromomethylsuccinic acid[18]

Bromine (16 cm^3, 50 g, 313 mmol) in acetic acid (50 cm^3) was added dropwise over 2 h with stirring to itaconic acid (29 g, 300 mmol) in acetic acid (50 cm^3) at room temperature, and the mixture was refluxed for 1.5 h. Acetic acid and bromine were removed under reduced pressure. Carbon tetrachloride (100 cm^3) was added and evaporated. Additional carbon tetrachloride (50 cm^3) was added to the residue and the solution stored at −20 °C overnight to give the dibromide (60.7 g, 70%) as plates, mp 166–167 °C (from $CHCl_3$–light petroleum) (lit.,[18] 167–168 °C); ν_{max}(CD_3OD)/cm^{-1} 1732 (C=O); δ_H(400 MHz; CD_3OD) 4.32 (1 H, d, *J* 10.0, CH_AH_BBr), 4.30 (1 H, d, *J* 10.0, CH_AH_BBr), 3.36 (1 H, d, *J* 18.0, CH_AH_BCOOH) and 3.31 (1 H, d, *J* 18.0, CH_AH_BCOOH).

3-Bromo-3-(bromomethyl)dihydrofuran-2,5-dione[18]

Trifluoroacetic anhydride (42 cm^3, 61.6 g, 195 mmol) was added to the dibromide (40 g, 138 mmol) under nitrogen at room temperature, and the mixture refluxed for 30 min. The solvent was removed under reduced pressure, and traces of trifluoroacetic acid and trifluoroacetic anhydride were removed under high vacuum to give the anhydride (37 g, 99%) as needles, mp 59–60 °C (from $CHCl_3$–light petroleum) (lit.,[18] 58–60 °C); ν_{max}($CDCl_3$)/cm^{-1} 2926 (CH), 2855 (CH), 1873 (C=O, antisym.) and 1802 (C=O, sym.); δ_H(250 MHz; $CDCl_3$) 4.23 (1 H, d, *J* 10.6, CH_AH_BBr), 3.93 (1 H, d, *J* 19.5, CH_AH_BCO), 3.87 (1 H, d, *J* 10.6, CH_AH_BBr) and 3.44 (1 H, d, *J* 19.5, CH_AH_BCO).

3-Bromomethylfuran-2,5-dione 11[10]

Dry 2,6-lutidine (16.5 cm^3, 15.17 g, 141.6 mmol) was added dropwise over 30 min to a vigorously stirred solution of the anhydride (35 g, 128.7 mmol) in dry toluene (450 cm^3) under nitrogen at 0 °C, and the mixture was kept at room temperature for 1.5 h. The solvent was removed under reduced pressure. Kugelrohr distillation gave the anhydride (15.67 g, 64%) as a yellowish oil, bp 90 °C at 0.3 mmHg (lit.,[10] 116–117 °C at 1.2 mmHg); ν_{max}($CDCl_3$)/cm^{-1} 2926 (CH), 2855 (CH), 1873 (C=O, antisym.) and 1802 (C=O, sym.); δ_H(250 MHz; $CDCl_3$) 6.94 (1 H, t, *J* 1.5, CH=C) and 4.22 (2 H, d, *J* 1.5, CH_2).

(3a*RS*,3b*SR*,9a*SR*,9b*RS*)-3a-Bromomethyl-3a,3b,4,5,6,7,8,9,9a,9b-decahydro-2-oxatrindene-1,3-dione 12

Bromomethyl anhydride **11** (3.82 g, 20 mmol) and the diene **4** (2.71 g, 20.2 mmol) were kept in ether (8 cm^3) at room temperature for 24 h. The solvent was evaporated under reduced pressure. The residue was chromatographed (SiO_2, Et_2O–light petroleum, 15 : 85) to give the *anhydride* (5.51 g, 85%) as needles, mp 66–67 °C (from *n*-pentane); R_f(Et_2O–light petroleum, 1 : 1) 0.52; ν_{max}($CDCl_3$)/cm^{-1} 1852 (C=O, antisym.) and 1776 (C=O, sym.); δ_H(500 MHz; $CDCl_3$) 3.89 (1 H, d, *J* 10.6, CH_AH_BBr), 3.53 (1 H, d, *J* 6.2, C*H*CO), 3.49 (1 H, d, *J* 10.6, CH_AH_BBr), 2.57 (1 H, m, C*H*CHCO), 2.40–2.33 (2 H, m, C*H*CCOCH_2Br and C$H_A$$H_B$CHCCOC$H_2$Br), 2.26–2.21 (2 H, m, CH_2C=C), 2.19–2.16 (2 H, m, CH_2C=C), 2.07–1.99 (3 H, m, CH_AH_B CHCCOCH_2Br and CH_2CHCHCO), 1.89 (1 H, qt, *J* 12.0 and 7.0, CH_AH_BCH_2CHCCOCH_2Br), 1.81 (1 H, qt, *J* 12.0 and 7.0, CH_AH_BCH_2CHCHCO) and 1.69–1.60 (2 H, m, CH_AH_BCH_2CHCCOCH_2Br and CH_AH_BCH_2CHCHCO); δ_C (125 MHz; $CDCl_3$) 171.4+ C(CH_2Br*C*O), 170.1+ (CH*C*O), 136.7+ (C=*C*CHCH(CO), 133.1+ (*C*=CCHCHCO), 56.7+ (*C*CH_2Br), 49.5− (*C*HCOO), 46.9− (*C*HCCOCH_2Br), 40.9− (*C*HCHCO), 35.0+ (CH_2Br), 29.3+ (*C*H_2C=C), 28.9+ (*C*H_2C=C), 27.6+ (*C*H_2CHCOCH_2Br), 27.5+ (*C*H_2CHCHCO), 26.1+ (*C*H_2CH_2CHCOCH_2Br) and 25.9+ (*C*H_2CH_2CHCHCO) (Found: C, 55.4; H, 5.25; Br, 24.7. $C_{15}H_{17}BrO_3$ requires C, 55.4; H, 5.27; Br, 24.6%).

Methyl (1*RS*,2*RS*,3*SR*,7*RS*,8*RS*,12*SR*)-1-bromomethyl-14-oxa-13-oxotetracyclo[5.5.2.0^{3,7}.0^{8,12}]-tetradecane-2-carboxylate 13

Freshly prepared sodium methoxide (150 mg) in methanol (3 cm^3) and the anhydride **12** (1 g, 3.1 mmol) were refluxed in methanol (25 cm^3) for 2.5 h. The methanol was removed under reduced pressure. Dilute hydrochloric acid (3 mol dm^{-3}; 10 cm^3) was added to the residue and the mixture was extracted with ether (3 × 5 cm^3). The extract was washed with brine (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, Et_2O–light petroleum, 85 : 15) to give the *lactone* (953 mg, 86%) as needles, mp 158–159 °C (from EtOH); R_f(Et_2O–light petroleum, 1 : 1) 0.30; ν_{max}($CDCl_3$)/cm^{-1} 2957 (CH), 2874 (CH) and 1748 (C=O); δ_H(500 MHz; $CDCl_3$) 3.87 (1 H, d, *J* 11.5, CH_AH_BBr), 3.70 (3 H, s, CO_2Me), 3.66 (1 H, d, *J* 11.5, CH_AH_BBr), 3.41 (1 H, d, *J* 11.7, C*H*CO_2Me), 2.67 (1 H, q, *J* 9.6, C*H*CCH_2BrCOO), 2.27 (1 H, td, *J* 12.5 and 7.0, CHC–O–CO), 2.22 (1 H, q, *J* 10.5, C*H*CHCO_2Me), 2.07 (1 H, m, CH_AH_BC–O–CO), 1.97–1.88 (2 H, m, CH_AH_BCHCCH_2BrCOOC and CH_AH_BCH_2CHCCH_2BrCOOC), 1.84 (1 H, quintet, *J* 6.6 CH_AH_BCHCHCO_2Me), 1.78–1.70 (4 H, m, CH_AH_BC–O–CO, CH_AH_BCH_2CHCCH_2BrCOOC, CH_AH_BCH_2CHCHCO_2Me and CH_AH_BCHC–O–CO), 1.55–1.45 (2 H, m, CH_AH_B-CHCHCO_2Me) and CH_AH_BCH_2CHCHCO_2Me), 1.37–1.19 (1 H, m, CH_AH_BCHC–O–CO) and 1.12 [1 H, dddd, *J* 18.8, 9.8, 6.3 and 3.5, CH_AH_BCHCCH_2BrCOOC; δ_C(125 MHz; $CDCl_3$) 172.4+ (C–O–*C*O), 171.1+ (*C*O_2Me), 92.4+ (*C*–O–CO), 51.6− (CO_2*Me*), 46.6+ (*C*COOCCH_2Br), 46.1− (*C*HCO_2Me), 45.6− (*C*HCHCO_2Me), 44.4− (*C*HC–O–CO), 42.6− (*C*HCCOOCCH_2Br), 34.0+ (CH_2Br), 31.7+ (*C*H_2C–O–CO), 28.5+ (*C*H_2CHCCOOCCH_2Br), 27.3+ (*C*H_2CHCHCO_2Me), 25.9+ (*C*H_2CH_2C–O–CO), 25.4+ (*C*H_2CHC–O–CO) and 21.6+ (CH_2CH_2CHCHCOOCCH_2Br) (Found: C, 53.7; H, 5.90; Br, 22.7. $C_{16}H_{21}BrO_4$ requires C, 53.8; H, 5.90; Br, 22.4%). Refluxing the anhydride **12** (572 mg, 1.76 mmol) and concentrated sulfuric acid (1 cm^3) in methanol (20 cm^3) for 12 h gave the same lactone in slightly better yield (570 mg, 91%).

Crystal data for 13. $C_{16}H_{21}BrO_4$, M = 357.24, monoclinic, space group $P2_1/n$, a = 9.3004(5) Å, b = 14.8301(9) Å, c = 11.6244(4) Å, β = 108.53(1)°, U = 1520.20(13) Å^3, Z = 4, μ(Mo–Kα) = 2.717 mm^{-1}, 8450 reflections measured at 180(2) K using an Oxford Cryosystems Cryostream cooling apparatus, 2640 unique (R_{int} = 0.044); R_1 = 0.047, wR_2 = 0.116 [$I>2\sigma(I)$]. The structure was solved with SHELXS-97 and refined with SHELXL-97.[19]

CCDC reference number 263438. See http://www.rsc.org/suppdata/ob/b5/b502213d/ for crystallographic data in CIF or other electronic format.

Dimethyl 2-bromo-2-(bromomethyl)succinate[20]

Bromine (56.6 g, 354 mmol) in dichloromethane (20 cm^3) was added to a stirred solution of dimethyl itaconate (49.2 g, 311 mmol) in dichloromethane (200 cm^3) at 0 °C, and the mixture was refluxed for 16 h. The solvent was evaporated under reduced pressure and dichloromethane (100 cm^3) was added to the residue. The mixture was stirred with aqueous sodium sulfite solution (100 cm^3) for 30 min. The organic layer was washed with distilled water (50 cm^3), brine (50 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the dibromide (97.76 g, 99%); ν_{max}($CDCl_3$)/cm^{-1} 1725 (C=O); δ_H(250 MHz; $CDCl_3$) 4.34 (1 H, d, *J* 10.7, CH_AH_BBr), 4.25 (1 H, d, *J* 10.7, CH_AH_BBr), 3.85 (3 H, s, CO_2Me), 3.73 (3 H, s, CO_2Me) and 3.42 (2 H, s, CH_2CO_2Me).

Dimethyl (*Z*)-2-(bromomethyl)but-2-enedioate 14[20]

The dibromosuccinate (97.6 g, 307 mmol) and triethylamine (51 cm^3, 37.14 g, 367 mmol) were kept in dichloromethane (600 cm^3) at room temperature for 4 h. The mixture was filtered, and the filtrate was washed with dilute hydrochloric acid (200 cm^3), aqueous sodium hydrogencarbonate (100 cm^3), brine (100 cm^3), and dried ($MgSO_4$). The volatiles were evaporated under reduced pressure. Kugelrohr distillation gave the bromomesaconate (53.72 g, 73%) as a greenish oil, oven temperature 110 °C at 3 mmHg (lit.,[20] 72 °C at 0.1 mmHg); R_f(Et_2O–light petroleum, 1 : 1) 0.49; ν_{max}($CDCl_3$)/cm^{-1} 2955 (CH), 1727 (C=O) and 1644 (C=C); δ_H(400 MHz; $CDCl_3$) 6.83 (1 H, s, HC=C), 4.72 (2 H, s, CH_2Br), 3.88 (3 H, s, CO_2Me) and 3.83 (3 H, s, CO_2Me).

Dimethyl (*E*)-2-(bromomethyl)but-2-enedioate

The anhydride **11** (10.04 g, 52.6 mmol) and concentrated sulfuric acid (0.5 cm^3) were refluxed in methanol (10 cm^3) for 3 h. The mixture was diluted with distilled water (20 cm^3) and extracted with ether (4 × 10 cm^3). The extract was washed with brine (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, Et_2O–light petroleum, 5 : 95) to give the (bromomethyl)maleate (5.56 g, 45%) as a greenish oil; R_f(Et_2O–light petroleum, 1 : 1) 0.40; ν_{max}($CDCl_3$)/cm^{-1} 2953 (CH), 1735 (C=O) and 1635 (C=C); δ_H(400 MHz; $CDCl_3$) 6.24 (1 H, t, *J* 1.0, HC=C), 4.13 (2 H, d, *J* 1.0, CH_2Br), 3.85 (3 H, s, CO_2Me) and 3.77 (3 H, s, CO_2Me).

Dimethyl (3a*RS*,4*SR*,5*RS*,5a*RS*)-4-bromomethyl-1,2,3,3a,4,5,5a,6,7,8-decahydro-*as*-indacene-4,5-dicarboxylate 10

Method A. The diester **9** (0.557 g, 2.00 mmol) in THF (2 cm^3) was added dropwise to a stirred solution of LDA (0.84 mol dm^{-3} in THF–hexane, 5 cm^3, 4.20 mmol) at −78 °C. After 1 h, dibromomethane (3 cm^3, 7.43 g, 42.7 mmol) was added at −50 °C. The mixture was kept at −50 °C for another 3 h, and then at room temperature for 12 h. The mixture was quenched with aqueous ammonium chloride (10 cm^3) and extracted with ether (3 × 10 cm^3). The extract was washed with brine (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, Et_2O–light petroleum, 15 : 85) to give the *bromide* (81 mg, 11%); R_f(Et_2O–light petroleum, 1 : 1) 0.59; ν_{max}($CDCl_3$)/cm^{-1} 2953 (CH_3), 2872 (CH_3) and 1731 (C=O); δ_H(500 MHz; $CDCl_3$) 3.88 (1 H, d, *J* 10.4, CH_AH_BBr),

3.82 (1 H, d, J 10.4, CH_AH_BBr), 3.69 (3 H, s, CO_2Me), 3.65 (3 H, s, CO_2Me), 3.01 (1 H, d, J 7.8, $CHCO_2Me$), 2.80 (1 H, m, $CHCCO_2MeCH_2Br$), 2.51 (1 H, m, $CHCHCO_2Me$), 2.26–2.05 (5 H, m, 2 × CH_2C=C and $CH_AH_BCHCHCO_2Me$), 1.86 (1 H, dt, J 13.0 and 8.2, $CH_AH_BCHCCO_2Me)CH_2Br$), 1.80 (1 H, dt, J 12.4 and 7.3, $CH_AH_BCH_2CHCHCO_2Me$), 1.71 [1 H, m, $CH_AH_BCH_2CHCCO_2MeCH_2Br$], 1.62–1.51 (3 H, m, $CH_AH_BCH_2CHCHCO_2Me$), $CH_AH_BCHCCO_2MeCH_2Br$ and $CH_AH_BCH_2CHCCO_2MeCH_2Br$) and 1.37 (1 H, qd, J 11.6 and 6.9, $CH_AH_BCHCHCO_2Me$); δ_C(125 MHz; $CDCl_3$) 174.5+ (C=O), 172.7+ (C=O), 133.1+ (*C*=C), 131.7+ (C=*C*), 54.8+ (*C*CO_2MeCH_2Br), 51.7− (CO_2*Me*), 51.5− (CO_2*Me*), 50.7− (*C*HCO_2Me), 46.4− (*C*$HCCO_2MeCH_2Br$), 43.0− (*C*$HCHCO_2Me$), 36.8+ (*C*H_2Br), 33.4+ (*C*$H_2CHCHCO_2Me$), 28.6+ (*C*$H_2CHCCO_2MeCH_2Br$), 28.3+ (*C*H_2C=C), 28.2+ (*C*H_2C=C), 24.31+ (*C*H_2CH_2C=C) and 24.26+ (*C*H_2CH_2C=C) (Found: M + Na^+, 393.0673. $C_{17}H_{23}{}^{79}BrO_4$ requires M + Na, 393.0677).

Method B. Dimethyl aluminium chloride (1 mol dm^{-3} solution in hexanes, 20.3 cm^3, 20.3 mmol) was added dropwise to a stirred solution of bromomethyl fumarate **14** (4.81 g, 20.3 mmol) in dichloromethane (60 cm^3) at −78 °C. After 20 min, diene **4** (3 g, 22.3 mmol) in dichloromethane (15 cm^3) was added at −78 °C. The mixture was allowed to warm slowly to room temperature and stirred for 12 h. The mixture was quenched dropwise with aqueous sodium hydrogencarbonate (15 cm^3) at 0 °C, and extracted with ether (3 × 25 cm^3). The extract was washed with brine (25 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Traces of solvent and unreacted diene were removed under high vacuum to give a mixture of the adducts **10** and **15** (7.46 g, 99%; 75 : 25 using the signals δ_H 3.65 of the major diastereoisomer and 3.60 of the minor). The diastereoisomeric mixture was used in the next step without further purification. On one occasion the mixture was chromatographed (SiO_2, Et_2O–light petroleum, 2 : 98 to 5 : 95) to obtain a pure sample of the major diastereoisomer, as a colourless oil, identical with the earlier sample.

Method C. Bromomethyl fumarate **14** (15.79 g, 66 mmol) and the diene **4** (8.80 g, 65.56 mmol) were kept at 45 °C for 18 h. The mixture was chromatographed (SiO_2, Et_2O–light petroleum, 15 : 85) to give the same mixture of bromides (20.74 g, 85%; 88 : 12).

Dimethyl (3a*RS*,3b*RS*,9a*RS*,9b*RS*)-1-oxo-1,3b,4,5,6,7,8,9,9a,9b-decahydro-2-oxatriindene-3a-carboxylate

When the Diels–Alder reaction was carried out at 250 °C, the *lactone*, formed by displacement of the bromide in the major adduct by the *cis* ester group, was obtained as needles, mp 98–99 °C (from Et_2O–*n*-pentane); R_f(Et_2O–light petroleum, 1 : 1) 0.37; ν_{max}($CDCl_3$)/cm^{-1} 2955 (C-H), 2873 (C–H), 2848 (C–H), 1760 (C=O, lactone) and 1731 (C=O, ester); δ_H(500 MHz; $CDCl_3$) 4.50 (1 H, d, J 9.1, CH_AH_BO), 4.16 (1 H, d, J 9.1, CH_AH_BO), 3.77 (3 H, s, CO_2Me), 3.60 (1 H, m, CHC=O), 2.68 (1 H, m, $CHCCO_2MeCH_2O$), 2.49 (1 H, m, CH_AH_BC=C), 2.45–2.36 (3 H, m, CH_AH_BC=C, $CHCHC$=O) and C*H_AH_BC=C), 2.18 (1 H, m, C*H_AH_BC=C), 1.88–1.83 (2 H, m, CH_2CH_2C=C), 1.78 (1 H, m, $CH_AH_BCHCCO_2MeCH_2O$), 1.70 (1 H, qd, J 12.9 and 7.5, $CH_AH_BCHCCO_2MeCH_2O$), 1.64–1.52 (2 H, m, $CH_AH_BCHCHCOO$ and $CH_AH_BCH_2C$=C), 1.45 (1 H, m, $CH_AH_BCH_2C$=C) and 1.21 (1 H, m, $CH_AH_BCHCHCOO$); δ_C(125 MHz; $CDCl_3$) 174.22+ (C=O), 174.15+ (C=O), 138.6+ (C=*C*$CHCCO_2Me$), 126.0+ (C=*C*$CHCHC$=O), 72.8+ (CH_2O), 53.6+ ($CHCCO_2Me$), 52.6− (CO_2*Me*), 42.3− (*C*$HCOO$), 40.1− (*C*$HCHCO$)O), 37.5− (*C*$HCOO$), 33.3+ (*C*H_2C=C), 33.0+ (*C*H_2C=C), 29.0+ (*C*H_2CHCCO_2Me), 26.8+ (*C*$H_2CHCHCOO$), 22.6+ (*C*$H_2CH_2CHCHCOO$) and 21.5+ (*C*$H_2CH_2CHCCO_2Me$) (Found: C, 69.6; H, 7.30. $C_{16}H_{20}O_4$ requires C, 69.5; H, 7.30%).

Dimethyl (3a*RS*,4*SR*,5*RS*,5a*RS*)-4-chloromethyl-1,2,3,3a,4,5,5a,6,7,8-decahydro-*as*-indacene-4,5-dicarboxylate

Dimethyl ester **9** (0.566 g, 2.03 mmol) in THF (2 cm^3) was added to LDA (0.89 mol dm^{-3} solution in THF–hexane, 5 cm^3, 4.47 mmol) at −78 °C. After 1 h, bromochloromethane (2.72 cm^3, 5.25 g, 40.6 mmol) was added. The mixture was kept at −78 °C for another 3 h, and then at room temperature for 25 h. The mixture was worked up in the same way as for the corresponding bromide **10** to give the *chloride* (53 mg, 8%); R_f(Et_2O–light petroleum, 1 : 1) 0.56; ν_{max}($CDCl_3$)/cm^{-1} 2955 (CH_3), 2928 (CH_2), 2870 (CH_3), 2861 (CH_2), 1728 (C=O) and 1261 (C–O–C); δ_H(500 MHz; $CDCl_3$) 3.99 (1 H, d, J 11.4, CH_AH_BCl), 3.95 (1 H, d, J 11.4, CH_AH_BCl), 3.70 (3 H, s, CO_2Me), 3.68 (3 H, s, CO_2Me), 2.96 (1 H, d, J 8.5, $CHCO_2Me$), 2.74 (1 H, m, $CHCCO_2MeCH_2Cl$), 2.55 (1 H, m, $CHCHCO_2Me$), 2.27–2.12 (5 H, m, 2 × CH_2C=C and $CH_AH_BCHCHCO_2Me$), 1.87–1.77 [2 H, m, $CH_AH_BCHCHCO_2MeCH_2Cl$ and $CH_AH_BCH_2C$=C), 1.75 (1 H, m, $CH_AH_BCH_2C$=C), 1.63–1.50 (3 H, m, $CH_AH_BCHCHCO_2MeCH_2Cl$ and CH_2CH_2C=C) and 1.31 (1 H, dq, J 11.4 and 7.0, $CH_AH_BCHCHCO_2Me$); δ_C(125 MHz; $CDCl_3$) 174.6+ (C=O), 173.1+ (C=O), 133.5+ (*C*=C), 131.9+ (C=*C*), 54.4+ (*C*CO_2MeCH_2Cl), 51.9− (CO_2*Me*), 51.7− (CO_2*Me*), 50.8− (*C*HCO_2Me), 47.9+ (*C*H_2Cl), 45.8− (*C*$HCCO_2MeCH_2Cl$), 42.6− (*C*$HCHCO_2Me$), 33.7+ (*C*$H_2CHCHCO_2Me$), 29.1+, 28.6+, 28.2+ (*C*H_2C=C), 24.5+ (*C*H_2CH_2C=C) and 24.4+ (*C*H_2CH_2C=C); m/z (+ESI) 349 (100%, M + Na^+) and 291 (15%, M − Cl) (Found: M + Na^+, 349.1190. $C_{17}H_{23}{}^{35}ClO_4$ requires M + Na, 349.1183).

meso-Dimethyl (1a*S*,1b*S*,7a*R*,7b*R*)-1b,2,3,4,5,6,7,7a-octahydrocyclopropa[*e*]-*as*-indacene-1a,7b-dicarboxylate 8

Method A. The bromide **10** (0.802 g, 2.16 mmol) in THF (5 cm^3) was added dropwise to a stirred solution of LDA (0.84 mol dm^{-3} in THF–hexane, 5 cm^3, 4.20 mmol) at −78 °C. The mixture was kept for 1 h at −78 °C, and then at room temperature for 3 h. The mixture was quenched with aqueous ammonium chloride (10 cm^3) and extracted with ether (3 × 10 cm^3). The extract was washed with brine (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, Et_2O–light petroleum, 15 : 85) to give the *cyclopropane* (321 mg, 72%) as plates, mp 77–78 °C (from *n*-pentane); R_f(Et_2O–light petroleum, 1 : 1) 0.44; ν_{max}($CDCl_3$)/cm^{-1} 2952 (CH_3), 2870 (CH_3) and 1728 (C=O); δ_H(500 MHz; $CDCl_3$) 3.59 (6 H, s, 2 × CO_2Me), 2.31 (1 H, d, J 5.2, $CCO_2MeCH_aH_bCCO_2Me$), 2.29 (2 H, m, 2 × CH_AH_BC=C), 2.22 (2 H, m, 2 × CH_AH_BC=C), 2.02 (2 H, m, 2 × $CH_AH_BCHCCO_2Me$), 1.98 (2 H, m, 2 × $CHCCO_2Me$), 1.92 (2 H, ddd, J 15.4, 7.4 and 3.8, 2 × $CH_AH_BCH_2C$=C), 1.77 (2 H, quintet, J 9.0, 2 × $CH_AH_BCHCCO_2MeCH_2$), 1.57 (2 H, m, 2 × $CH_AH_BCH_2C$=C) and 0.88 (1 H, d, J 5.2, $CCO_2MeCH_aH_bCCO_2Me$); δ_C(125 MHz; $CDCl_3$) 171.4+ (2 × C=O), 134.0+ (2 × *C*=C), 51.4− (2 × CO_2*Me*), 45.5− (2 × *C*$HCCO_2Me$), 37.6+ (2 × $CHCCO_2Me$), 30.2+ (2 × *C*H_2CHCCO_2Me), 28.5+ (2 × CH_2C=C), 28.3+ ($CO_2MeCH_2CO_2Me$) and 25.5+ (2 × *C*H_2CH_2C=C) (Found: C, 70.2; H, 7.65. $C_{17}H_{22}O_4$ requires C, 70.3; H, 7.65%).

Method B. The corresponding chloride (47 mg, 0.144 mmol) in THF (2 cm^3) under similar conditions gave the same *cyclopropane* (13 mg, 32%).

Method C. The 75 : 25 diastereoisomeric mixture of bromomethyl dicarboxylates **10** and **15** (10.43 g, 28.1 mmol) in toluene (50 cm^3) was added dropwise to a stirred solution of freshly prepared sodium methoxide (6.68 g, 123.6 mmol) in toluene (250 cm^3) at room temperature, and refluxed for 12 h. The mixture was quenched with dilute hydrochloric acid (150 cm^3) and extracted with ether (3 × 50 cm^3). The extract was washed with distilled water (100 cm^3), brine (100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give an

impure mixture of *cyclopropanes* **8** and **16** (75 : 25 measured using δ_H 3.59 of the major diastereoisomer and δ_H 3.67 of the minor). The residue was chromatographed (SiO_2, Et_2O–light petroleum, 10 : 90) to give the pure mixture (7.34 g, 90%). Recrystallisation from *n*-pentane gave the pure major *cyclopropane*.

Method D. The 88 : 12 diastereoisomeric mixture of bromomethyl dicarboxylates **10** and **15** (5.06 g, 13.6 mmol) in toluene (50 cm^3) was added dropwise to a stirred solution of freshly prepared potassium *tert*-butoxide (4.31 g, 38.4 mmol) in toluene (100 cm^3) at 75 °C, and kept at 40 °C for 3 h. The mixture was worked up as in Method C to give the mixture of *cyclopropanes* (3.43 g, 87%; 88 : 12).

Method E. Bromomethyl dicarboxylate **10** (5.12 g, 13.8 mmol) in toluene (50 cm^3) was added to a stirred solution of freshly prepared potassium amyloxide (4.5 g, 51.2 mmol) in toluene (100 cm^3) at 70 °C, and kept at 40 °C for 5.5 h. The mixture was worked up as in Method C to give the *cyclopropane* **8** (1.29 g, 32%).

meso-Dimethyl (3a*R*,4*S*,6*R*,6a*S*)-2,3,3a,4,5,6,6a,7,8,9-decahydro-1*H*-cyclopenta[*e*]azulene-4,6-dicarboxylate 18

The flask, condenser and glass-coated stirrer bar were dried twice with a heat gun under high vacuum before distilling ammonia (250 cm^3) into the flask. Lithium (290 mg, 41.8 mmol) was dissolved in the ammonia, and the mixture cooled to −78 °C under argon. The 75 : 25 diastereoisomeric mixture of cyclopropanes **8** and **16** (1.319 g, 4.54 mmol) in ether (10 cm^3) was added with stirring to the dark blue solution, and the mixture kept for 0.5 h. Freshly distilled isoprene (5 cm^3, 51 mmol) was added dropwise until the colour disappeared. The mixture was quenched with ammonium chloride (8.64 g, 159 mmol) over 30 s. The ammonia was allowed to evaporate, water (100 cm^3) was added and the mixture extracted with ether (3 × 30 cm^3). The extract was washed with brine (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the mixture of *diesters* (1.197 g, 90%; 70 : 30 measured using the signals at δ_H 3.65 from both methoxy groups of the major diastereoisomer **18** and one of those of the minor isomer **19**, and δ_H 3.64 from the other methoxy signal of the minor isomer **19**). The mixture was crystallised from *n*-pentane to give the pure *meso* diester **18** (479 mg, 36%) as plates, mp 68–69 °C (from *n*-pentane); R_f(Et_2O–light petroleum, 1 : 1) 0.40; $\nu_{max}(CDCl_3)/cm^{-1}$ 2953 (C–H), 2863 (C–H) and 1731 (C=O); δ_H(500 MHz; $CDCl_3$) 3.65 (6 H, s, 2 × CO_2Me), 2.60 [2 H, m, C(3a)H and C(6a)H], 2.29 [2 H, dd, *J* 16.0 and 7.0, C(1)H_A and C(9)H_A], 2.17–2.06 [5 H, m, C(1)H_B, C(9)H_B, C(4)H, C(6)H and C(5)H_b], 1.99 [1 H, dt, *J* 13.5 and 12.0, C(5)H_a], 1.89 [2 H, dt, *J* 12.5 and 6.0, C(3)H_A and C(7)H_A], 1.71 [2 H, m, C(2)H_A and C(8)H_A] and 1.31 [2 H, m, C(3)H_B and C(7)H_B]; δ_C(125 MHz; $CDCl_3$) 175.7+ (2 × C=O), 136.8+ (2 × *C*=C), 51.5− (2 × CO_2*Me*), 49.0− [C(4) and C(6)], 45.8− [C(3a) and C(6a)], 36.8+ [C(5)], 33.85+, 33.80+ and 24.8+ [C(2) and C(8)] (Found: M + Na^+, 315.1592. $C_{17}H_{24}O_4$ requires *M* + Na, 315.1572).

Crystal data for 18. $C_{17}H_{24}O$, $M = 292.36$, triclinic, space group $P\bar{1}$, $a = 9.6393(2)$ Å, $b = 9.6637(2)$ Å, $c = 17.7208(4)$ Å, $\alpha = 78.73(1)°$, $\beta = 79.019(1)°$, $\gamma = 76.781(1)°$, $U = 1557.50(6)$ $Å^3$, $Z = 4$, μ(Mo–Kα) = 0.087 mm^{-1}, 9537 reflections measured at 180(2) K using an Oxford Cryosystems Cryostream cooling apparatus, 3046 unique ($R_{int} = 0.031$); $R_1 = 0.038$, $wR_2 = 0.088$ [$I > 2\sigma(I)$]. The structure was solved with SHELXS-97 and refined with SHELXL-97.[19]

CCDC reference number 263439. See http://www.rsc.org/suppdata/ob/b5/b502213d/ for crystallographic data in CIF or other electronic format.

Dimethyl (3a*RS*,4*RS*,6*RS*,6a*RS*)-2,3,3a,4,5,6,6a,7,8,9-decahydro-1*H*-cyclopenta[*e*]azulene-4,6-dicarboxylate 19

Similarly, lithium (1.3 g, 187 mmol), ammonia (300 cm^3) and the mixture of cyclopropanes **8** and **16** (7.599 g, 26.17 mmol) in ether (30 cm^3) were kept at −78 °C for 0.5 h. Freshly distilled isoprene (26.22 cm^3, 262 mmol) was added dropwise until the colour disappeared, and methanol (53 cm^3, 1.31 mol) was added rapidly but cautiously through the top of the condenser immediately afterwards. The ammonia was allowed to evaporate, water (150 cm^3) was added and the mixture extracted with ether (1 × 100 cm^3 and 3 × 50 cm^3) to give the mixture of *diesters* (7.322 g, 96%; 76 : 24 measured using the same signals as before). The residue was crystallised from *n*-pentane; the mother liquor was evaporated under reduced pressure and chromatographed (SiO_2, Et_2O–light petroleum, 2 : 98 to 10 : 90). Recrystallisation of the combined crops gave the pure *diester* **19** (5.17 g, 68%) as needles, mp 83–84 °C (from *n*-pentane); R_f(Et_2O–light petroleum, 1 : 1) 0.48; $\nu_{max}(CDCl_3)/cm^{-1}$ 2952 (C-H), 2866 (C–H) and 1731 (C=O); δ_H(500 MHz; $CDCl_3$) 3.65 (3 H, s, CO_2Me), 3.64 (3 H, s, CO_2Me), 2.85 [1 H, d, *J* 3.0, C(4)H], 2.65 [1 H, m, C(3a)H], 2.61 [1 H, m, C(6a)], 2.34–2.27 [4 H, m, C(6)H, C(5)H_b, C(1)H_A, and C(9)H_A], 2.17–2.12 [2 H, m, C(1)H_B, and C(9)H_B], 1.97 [1 H, m, C(5)H_a], 1.92 [1 H, m, C(3)H_A], 1.86 [1 H, m, C(7)H_A], 1.77 [1 H, m, C(2)H_A], 1.72–1.64 [2 H, m, C(3)H_B and C(8)H_A], 1.50–1.39 [2 H, m, C(2)H_B and C(8)H_B] and 1.33 [1 H, m, C(7)H_B]; δ_C(125 MHz; $CDCl_3$) 175.9+ (C=O), 173.3+ (C=O), 136.6+ (*C*=C), 134.4+ (C=*C*), 51.4− (CO_2*Me*), 51.2− (CO_2*Me*), 45.9− [C(6)], 45.8− [C(6a)], 45.1− [C(3a)], 43.7− [C(4)], 35.9+ [C(5)], 33.65+, 33.61+, 33.2+, 32.8+, 25.3+ [C(2)] and 25.1+ [C(8)] (Found: C, 69.8; H, 8.30. $C_{17}H_{24}O_4$ requires C, 69.8; H, 8.25%).

Equilibration of diesters 18 and 19

The racemic diester **19** (216 mg, 0.74 mmol) in methanol (10 cm^3) and freshly prepared sodium methoxide (1 g, 18.5 mmol) in methanol (13.5 cm^3) were refluxed for 3 days under nitrogen. The mixture was quenched with dilute hydrochloric acid (8 cm^3) and most of the methanol was evaporated off under reduced pressure. The remaining aqueous layer was extracted with ether (4 × 5 cm^3). The extract was washed with brine (8 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Traces of solvents were removed under high vacuum to give the mixture of diesters (216 mg; **18** : **19** = 84 : 16 measured using the same signals as before). Similarly, the meso diester **18** (459 mg, 8.5 mmol) gave the mixture of diesters (450 mg; **18**:**19** = 84 : 16), and a 30 : 70 mixture of the diesters (140 mg, 0.48 mmol) also gave the mixture of diesters (140 mg; **18** : **19** = 84 : 16).

Formation and reprotonation of the enolate of diester 18

Dimethyl dicarboxylate **18** (0.848 g, 2.9 mmol) in THF (5 cm^3) was added dropwise to a stirred solution of LDA (0.45 mol dm^{-3} solution in THF–hexane, 6.44 cm^3, 2.9 mmol) at −78 °C. After 1 h, the mixture was allowed to warm slowly up to room temperature. The reaction was quenched by adding equal volumes (3 cm^3) of it to four different solutions [MeOH (15 cm^3), MeOH–AcOH (15 cm^3 : 0.05 cm^3), HCl (3 mol dm^{-3}, 60 cm^3) and aqueous NH_4Cl (25 cm^3)] at room temperature and the four solutions were stirred for 1 h. The methanolic solutions were diluted with distilled water (15 cm^3) and acidified where necessary. All four aqueous solutions were extracted with ether (3 × 10 cm^3), washed with brine (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Traces of solvents were removed under high vacuum to give the mixtures of diesters (**18** : **19** = 69 : 31 from MeOH, MeOH–AcOH and aqueous NH_4Cl, and 62 : 38 from HCl). Recombined, the four samples gave recovered diester (806 mg, 95%).

Dimethyl (2*RS*,4*RS*)-2-[(*SR*)-2-oxocyclopentyl]-4-[(*RS*)-2-oxocyclopentyl]pentanedioate 23

A stream of ozone was bubbled through a solution of the diester **19** (2.064 g, 7.06 mmol) in freshly distilled acetone (133 cm^3) and freshly distilled acetaldehyde (13.35 g, 17 cm^3, 0.3 mol) at −78 °C. After the appearance of a faint blue colour, a stream

of oxygen was passed through the solution for 10 min, and triphenylphosphine (4.64 g, 17.7 mmol) was added. The mixture was kept at −78 °C for 1 h and at room temperature for 12 h. The solvent was evaporated off under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–light petroleum, 40 : 60) to give the *diketone* (2.236 g, 98%) as an oil; R_f(EtOAc–light petroleum, 6 : 4) 0.29; $\nu_{max}(CDCl_3)/cm^{-1}$ 2956 (CH), 2878 (CH) and 1732 (C=O, coincident ketone and ester); δ_H(500 MHz; $CDCl_3$) 3.75 (3 H, s, CO_2Me), 3.70 (3 H, s, CO_2Me), 2.90 (1 H, dt, *J* 10.0 and 5.0, C*H*CO_2Me), 2.77 (1 H, ddd, *J* 10.5, 6.5 and 4.0, C*H*CO_2Me), 2.52 (1 H, dt, *J* 12.0 and 7.0, CHC=O), 2.39–2.29 (2 H, m, 2 × C*H*$_A$H$_B$C=O), 2.29–2.02 (7 H, m, CHCO, 2 × C*H*$_A$H$_B$CHCHCO$_2$Me, 2 × CH$_A$*H*$_B$C=O and 2 × C*H*$_A$H$_B$CH$_2$C=O), 1.99 (1 H, ddd, *J* 14.0, 10.0 and 4.5, $CHCO_2MeCH_AH_B$), 1.89 (1 H, ddd, *J* 14.0, 10.0 and 4.0, $CHCO_2MeCH_AH_B$) and 1.86–1.65 (4 H, m, 2 × CH$_A$*H*$_B$-CHCHCO$_2$Me and 2 × CH$_A$*H*$_B$CH$_2$CO); δ_C(125 MHz; $CDCl_3$) 218.1+ (C=O), 217.9+ (C=O), 175.0+ (*C*O_2Me), 173.6+ (*C*O_2Me), 51.9− (CO_2*Me*), 51.8− (CO_2*Me*), 51.2− (*C*HCHCO$_2$Me), 50.7− (*C*HCHCO$_2$Me), 43.4− (*C*HCO$_2$Me), 42.5− (*C*HCO$_2$Me), 38.0+ (*C*H$_2$C=O), 37.9+ (*C*H$_2$C=O), 30.3+ ($CHCO_2MeCH_2$), 26.9+ (*C*H$_2$CHCHCO$_2$Me), 26.2+ (*C*H$_2$CHCH(CO$_2$Me), 20.53+ (*C*H$_2$CH$_2$C=O) and 20.49+ (*C*H$_2$CH$_2$C=O); *m/z* (ESI) 347 (100%, M^+ + Na) and 279 (95%, M − C_2H_5O) (Found: M + Na^+, 347.1472. $C_{17}H_{24}O_6$ requires *M* + Na, 347.1471).

Dimethyl (2*RS*,4*RS*)-2-{(*SR*)-2-[(*E*)-hydroxyimino]cyclopentyl}-4-{(*RS*)-2-[(*E*)-hydroxyimino]cyclopentyl}pentanedioate 24

The diketone (2.044 g, 6.3 mmol), hydroxylamine hydrochloride (2.19 g, 31.51 mmol) and pyridine (2.0 cm^3, 1.99 g, 25.2 mmol) were kept in ethanol (80 cm^3) at 0 °C for 2 days at 0 °C. Most of the ethanol was evaporated off under reduced pressure. The remaining solid was dissolved in warm chloroform (50 cm^3) and washed with dilute hydrochloric acid (2 × 20 cm^3). The aqueous layer was extracted with warm chloroform (2 × 15 cm^3). The combined organic layers were dried (K_2CO_3) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, EtOAc–CH_2Cl_2, 80 : 20) to give the *dioxime* (1.185 g, 53%) as needles, mp 147–148 °C (from $CHCl_3$–hexane); R_f(EtOAc–CH_2Cl_2, 4:6) 0.18; $\nu_{max}(CDCl_3)/cm^{-1}$ 3291 (OH), 2958 (CH), 2876 (CH), 1727 (C=O) and 1684 (C=N); δ_H(500 MHz; $CDCl_3$) 7.55 (2 H, br s, 2 × C=NOH), 3.67 (6 H, s, 2 × CO_2Me), 2.83 (1 H, q, *J* 8.0, C*H*CHCO$_2$Me), 2.72 (1 H, q, *J* 7.0, C*H*CHCO$_2$Me), 2.64–2.53 (4 H, m, 2 × C*H*CO$_2$Me and 2 × C*H*$_A$H$_B$C=N), 2.38–2.27 (2 H, m, 2 × CH$_A$*H*$_B$C=N), 2.07 (1 H, ddd, *J* 13.5, 11.5 and 3.0, $CHCO_2MeCH_AH_B$), 1.95 (1 H, m, C*H*$_A$H$_B$CHCHCO$_2$Me), 1.89 (1 H, ddd, *J* 13.5, 11.0 and 3.0, $CHCO_2MeCH_AH_B$), 1.88–1.77 (3 H, m, C*H*$_{A*}$H$_{B*}$CHCHCO$_2$Me and 2 × C*H*$_A$H$_B$CH$_2$C=N) and 1.65–1.48 (4 H, m, 2 × CH$_A$*H*$_B$CH$_2$C=N, CH$_{A*}$*H*$_{B*}$CHCHCO$_2$Me and CH$_A$*H*$_B$CHCHCO$_2$Me); δ_C(125 MHz; $CDCl_3$) 175.1+ (*C*O_2Me), 174.5+ (*C*O_2Me), 166.39+ (*C*=N), 166.38+ (*C*=N), 51.71− (CO_2*Me*), 51.66− (CO_2*Me*), 45.5− (*C*HCO$_2$Me), 45.25− (*C*HCHCO$_2$Me), 45.23− (*C*HCHCO$_2$Me), 44.5− (*C*HCO$_2$Me), 30.4+ ($CHCO_2MeCH_2$), 29.2+ (*C*H$_2$CHCH-CO$_2$Me), 29.1+ (*C*H$_2$CHCHCO$_2$Me), 27.1+ (*C*H$_2$C=N), 27.0+ (*C*H$_2$C=N), 22.3+ (*C*H$_2$CH$_2$ C=N) and 22.1+ (*C*H$_2$CH$_2$ C=N) (Found: M + Na^+, 377.1683. $C_{17}H_{26}N_2O_6$ requires *M* + Na, 377.1689).

Dimethyl (2*RS*,4*RS*)-2-[(*SR*)-6-oxopiperidin-2-yl]-4-[(*RS*)-6-oxopiperidin-2-yl]pentanedioate 25

Methanesulfonyl chloride (0.9 cm^3, 1.34 g, 11.65 mmol) was added over 10 min to a stirred solution of triethylamine (2.2 cm^3, 1.57 g, 15.5 mmol) and the dioxime (917 mg, 2.59 mmol) in dichloromethane (50 cm^3) at −20 °C under nitrogen, and the mixture kept for 0.5 h. The mixture was allowed to warm up to room temperature, washed with dilute hydrochloric acid (2 × 10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Traces of solvent were removed under high vacuum to give crude O-*mesylate* (1.313 g, 99%) as a viscous, yellowish oil; R_f(CH_2Cl_2–Et_2O, 6 : 4) 0.55. The crude mesylate was used directly in the next step without further purification because it partly rearranged during attempted purification. The *O*-mesylate (1.313 g, 2.57 mmol) was stirred in a mixture of THF (60 cm^3) and distilled water (30 cm^3) at 60 °C for 24 h. Most of the THF was evaporated off under reduced pressure. The remaining aqueous solution was saturated with sodium chloride and extracted with chloroform (5 × 10 cm^3). The extract was dried (K_2CO_3) and concentrated under reduced pressure. The residue was chromatographed (SiO_2, MeOH–CH_2Cl_2, 5 : 95 to 20 : 80) to give the *bis-lactam* (471 mg, 52%) as plates, mp 158–159 °C (from THF); R_f(MeOH–CH_2Cl_2, 1 : 9) 0.35; $\nu_{max}(CDCl_3)/cm^{-1}$ 2952 (CH), 2922 (CH), 2853 (CH), 1734 (C=O, ester), 1663 (C=O, lactam) and 1453 (NH); δ_H(500 MHz; $CDCl_3$) 6.28 (1 H, br s, NH), 6.17 (1 H, br s, NH), 3.72 (3 H, s, CO_2Me), 3.71 (3 H, s, CO_2Me), 3.66 [1 H, m, C*H*CH(CO_2Me)], 3.62 [1 H, m, C*H*CH(CO_2Me)], 2.48–2.33 [4 H, m, 2 × C*H*(CO_2Me) and 2 × C*H*$_A$H$_B$C(O)N], 2.31–2.21 [2 H, m, 2 × CH$_A$*H*$_B$C(O)N], 1.95–1.82 [5 H, m, CH(CO_2Me)C*H*$_2$CH(CO_2Me), 2 × C*H*$_A$H$_B$CH$_2$C(O)N and C*H*$_A$H$_B$CHCH(CO_2Me)], 1.81–1.62 [3 H, m, C*H*$_{A*}$H$_{B*}$CHCH(CO_2Me) and 2 × CH$_A$*H*$_B$CH$_2$C(O)N] and 1.56–1.45 [2 H, m, CH$_{A*}$*H*$_{B*}$CHCH(CO_2Me) and CH$_A$*H*$_B$CHCH(CO_2Me)]; δ_C(125 MHz; $CDCl_3$) 173.6+ (*C*O_2Me), 172.9+ (*C*O_2Me), 172.4+ [*C*(O)N], 172.3+ [*C*(O)N], 54.3− [*C*HCH(CO_2Me)], 54.2− [*C*HCH(CO_2Me)], 52.32− (CO_2*Me*), 52.28− (CO_2*Me*), 48.8− [*C*H(CO_2Me)], 47.7− [*C*H(CO_2Me)], 31.2+ [2 × *C*H$_2$C(O)N, 2 coincident peaks], 26.1+ [CH(CO_2Me)*C*H$_2$CH(CO_2Me)], 25.31+ [*C*H$_2$CHCH(CO_2Me)], 25.28+ [*C*H$_2$CHCH(CO_2Me)], 19.7+ [*C*H$_2$CH$_2$C(O)N] and 19.3+ [*C*H$_2$CH$_2$C(O)N] (Found: M + Na^+, 377.1674. $C_{17}H_{26}N_2O_6$ requires *M* + Na, 377.1689).

(2*RS*,4*RS*)-2-[(*SR*)-Piperidin-2-yl]-4-[(*RS*)-piperidin-2-yl]pentane-1,5-diol 26

The bis-lactam (455 mg, 1.28 mmol) and lithium aluminium hydride (585 mg, 15.4 mmol) were refluxed in THF (55 cm^3) for 12 h. The mixture was quenched sequentially with aqueous potassium sodium tartrate (1.9 cm^3), aqueous potassium hydroxide [15% (w/v), 1.9 cm^3] and aqueous potassium sodium tartrate (5 cm^3) at 0 °C. After stirring the resulting suspension for 0.5 h at room temperature, the supernatant was decanted off and the remaining inorganic salts were washed with dichloromethane (5 × 5 cm^3). The combined extracts were dried (K_2CO_3) and evaporated under reduced pressure. Traces of solvents were removed under high vacuum to give the *diol* (311 mg, 90%) as a viscous, oil; R_f(RP-18, MeOH–H_2O–TFA, 20 : 80 : 2.5) 0.26; $\nu_{max}(CDCl_3)/cm^{-1}$ 3418 (OH and NH), 2940 (CH), 2860 (CH) and 1642 (NH); δ_H(500 MHz; $CDCl_3$) 3.90 (1 H, d, *J* 11.0 and 2.5, C*H*$_A$H$_B$OH), 3.69–3.60 (2 H, m, C*H*$_{A*}$*H*$_{B*}$OH), 3.49 (1 H, dd, *J* 11.0 and 4.0, CH$_A$*H*$_B$OH), 3.03 (2 H, m, C*H*$_A$H$_B$NH and C*H*$_{A*}$H$_{B*}$NH), 2.75 (1H, dt, *J* 11.0 and 2.5, C*H*NH), 2.60 (1 H, dd, *J* 6.0 and 3.0, C*H*NH), 2.56–2.45 (2 H, m, CH$_A$*H*$_B$NH and CH$_{A*}$*H*$_{B*}$NH), 1.85–1.77 (2 H, m, C*H*$_A$H$_B$CH$_2$CH and C*H*$_{A*}$H$_{B*}$CH$_2$CH), 1.68 (6 H, m, C*H*CH$_2$OH, C*H*$_A$H$_B$CHCH, C*H*$_{A*}$H$_{B*}$CHCH, 2 × C*H*$_A$H$_B$CH$_2$NH and CHCH$_2$OHC*H*$_A$H$_B$), 1.43–1.25 (7 H, m, C*H*CH$_2$OH, CH$_A$*H*$_B$CHCH, 2 × CH$_A$*H*$_B$CH$_2$NH, CHCH$_2$OHCH$_A$*H*$_B$, CH$_A$*H*$_B$CH$_2$CH and CH$_{A*}$*H*$_{B*}$CH$_2$CH) and 1.21 (1 H, q, *J* 9.0, CH$_{A*}$*H*$_{B*}$CHCH); δ_C(125 MHz; $CDCl_3$) 64.9+ (*C*H$_2$OH), 64.2+ (*C*H$_2$OH), 61.80− (*C*HNH), 61.77− (*C*HNH), 47.3+ (*C*H$_2$NH), 47.1+ (*C*H$_2$NH), 42.09− (*C*HCH$_2$OH), 42.07− (*C*HCH$_2$OH), 30.8+ (*C*H$_2$CHCH), 26.6+, 26.5+, 26.25+, 26.23+, 24.57+ (*C*H$_2$CH$_2$CH) and 24.55+ (*C*H$_2$CH$_2$CH)); *m/z* (ESI) 293 (82%, M^+ + Na) and 253 (84%, M − OH) (Found: M + Na^+, 293.2198. $C_{15}H_{30}N_2O_2$ requires *M* + Na, 293.2205).

(±)-Sparteine 1

Following Oinuma, Dan and Kakisawa,[21] the diaminodiol (37 mg, 0.137 mmol), triphenylphosphine (144 mg, 0.547 mmol), carbon tetrachloride (40 mm^3, 63 mg, 0.410 mmol) and triethylamine (76 mm^3, 55 mg, 0.547 mmol) were stirred in acetonitrile (2 cm^3) at room temperature for 18 h. The solvent was evaporated off under reduced pressure and the residue was dried under high vacuum for 2 h. Trifluoroacetic acid (53 mm^3, 78 mg, 0.684 mmol) and LiChroprep RP-18 (300 mg) were added to a solution of the residue in dichloromethane (5 cm^3). The solvent was evaporated under reduced pressure and the remaining, solvent-free LiChroprep RP-18 was loaded onto a column. Column chromatography gave (±)-sparteine as its bis-trifluoroacetic acid salt (LiChroprep RP-18, MeOH–H_2O–TFA, 20 : 80 : 2.5); R_f(RP-18, MeOH–H_2O–TFA, 20 : 80 : 2.5) 0.17. All product-containing fractions were combined, basified with potassium hydroxide (350 mg, pH 15), extracted with dichloromethane (5 × 5 cm^3) and dried (K_2CO_3). The extract was concentrated under reduced pressure to give (±)-sparteine (17 mg, 53%) as a pale yellow oil, identical (IR, ^{1}H NMR and ^{13}C NMR) with a sample of (–)-sparteine (Aldrich); $\nu_{max}(CDCl_3)/cm^{-1}$ 2927, 2854, 2757, 1464, 1442, 1350, 1288, 1266, 1180, 1145, 1125, 1113, 1073, 1015, 974, 881, 844, 785 and 734; δ_H(500 MHz; $CDCl_3$)[22] 2.78 [1 H, d (not first order), C(15)H_A], 2.74–2.64 [2H, m, C(17)H_A and C(2)H_A], 2.52 [1 H, dt, *J* 11.0 and 2.5, C(10)H_A], 2.33 [1 H, dd, *J* 11.0 and 3.5, C(17)H_B], 2.08–1.89 [5 H, m, C(8)H_A, C(15)H_B, C(10)H_B, C(11)H and C(2)H_B], 1.83 [1 H, m, C(9)H], 1.74–1.65 [3 H, m, C(6)H, C(4)H_A and C(13)H_A], 1.61–1.43 [6 H, m, C(3)H_2, C(14)H_2, C(12)H_A and C(7)H], 1.42–1.14 [5 H, m, C(5)H_2, C(12)H_B, C(4)H_B and C(13)H_B] and 1.05 [1 H, dt, *J* 12.0 and 2.5, C(8)H_B]; δ_C(125 MHz; $CDCl_3$)[22] 66.5− [C(6)], 64.4− [C(11)], 62.0+ [C(10)], 56.2+ [C(2)], 55.4+ [C(15)], 53.6+ [C(17)], 36.1− [C(7)], 34.7+ [C(12)], 33.0− [C(9)], 29.3+ [C(5)], 27.6+ [C(8)], 25.9+ [C(3) or C(14)], 25.8+ [C(3) or C(14)], 24.8+ [C(4) or C(13)] and 24.7+ [C(4) or C(13)] (Found: M^+, 234.2088. $C_{15}H_{26}N_2$ requires *M*, 234.2096).

(3a*R*,4*S*,6*R*,6a*S*)-2,3,3a,4,5,6,6a,7,8,9-Decahydro-1*H*-cyclopenta[*e*]azulene-4,6-dicarboxylic acid

The diester **18** (723 mg, 2.47 mmol) and sodium hydroxide (920 mg, 23 mmol) in distilled water (17 cm^3) and ethanol (8 cm^3) were refluxed for 1 h. Most of the ethanol was distilled off under reduced pressure, the remaining aqueous solution was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (5 × 10 cm^3). The extract was washed with brine (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Traces of solvent were removed under high vacuum to give the crude *dicarboxylic acid* (637 mg, 98%) as needles, mp 117–120 °C (dec.) (from hexane–EtOH); ν_{max}(film)/cm^{-1} 3408 (OH), 2923 (CH), 2851 (CH) and 1689 (C=O); δ_H(700 MHz; CD_3OD) 2.57 (2 H, m, 2 × C*H*CHCOOH), 2.34 (2 H, ddd, *J* 16.0, 5.0 and 2.0, 2 × C$H_A$$H_B$C=C), 2.16 (2 H, m, CH_AH_BC=C), 2.12 (1 H, dt, *J* 13.5 and 2.0, CHCOOHC$H_A$$H_B$CHCOOH), 2.05 (2 H, td, *J* 11.0 and 2.0, 2 × C*H*COOH), 1.98 (2 H, m, C$H_A$$H_B$CHCHCCOOH), 1.94 (1 H, dt, *J* 13.5 and 12.0, CHCOOHC$H_A$$H_B$CHCOOH), 1.74 (2 H, m, C$H_A$$H_B$$CH_2$C=C) and 1.49–1.45 (4 H, m, CH_AH_BCHCHCCOOH and $CH_AH_B$$CH_2$C=C); δ_C(175 MHz; CD_3OD) 179.2+ (2 × C=O), 138.0+ (2 × *C*=C), 50.7− (2 × C*H*COOH), 47.0− (2 × C*H*CHCOOH), 38.7+ (CHCOOH*C*H_2CHCOOH), 35.1+ (2 × *C*H_2CHCHCOOH), 34.8+ (2 × *C*H_2C=C) and 25.9+ (2 × *C*$H_2$$CH_2$C=C) (Found: M + Na^+, 287.1253. $C_{15}H_{20}O_4$ requires *M* + Na, 287.1259).

Methylation of *meso*-dicarboxylic acid

Trimethylsilyldiazomethane (2.0 mol dm^{-3} in hexane, 0.1 cm^3, 0.2 mmol) was added dropwise to the dicarboxylic acid (5 mg, 0.02 mmol) in methanol (1 cm^3) at room temperature, and the mixture kept for 30 min. Acetic acid (0.1 cm^3) was added and the mixture stirred for 30 min. Distilled water (2 cm^3) was added and the mixture was extracted with ether (3 × 1 cm^3). The extract was dried ($MgSO_4$) and evaporated under reduced pressure. Traces of solvents were removed under high vacuum to give the diester **18** (5.5 mg, 100%), identical (^{1}H NMR) with the earlier sample.

(3a*R*,4*S*,6*R*,6a*S*)-2,3,3a,4,5,6,6a,7,8,9-Decahydro-1*H*-cyclopenta[*e*]azulene-4,6-dicarboxylic acid anhydride 27

Method A. 1,3-Dicyclohexylcarbodiimide (505 mg, 2.45 mmol) in anhydrous dichloromethane (1.7 cm^3) was added to a stirred suspension of the *meso*-dicarboxylic acid (588 mg, 2.22 mmol) in anhydrous THF (8 cm^3), and the mixture kept for 22 h. Ether (10 cm^3) was added, the mixture was cooled in an ice-bath for 0.5 h to precipitate insoluble dicyclohexylurea, and filtered through a sinter. The filter cake was washed with cold ethyl acetate (3 × 10 cm^3). The filtrate was evaporated under reduced pressure to give the crude *anhydride* (600 mg) as a yellow oil, which was used directly in the next step without further purification.

Method B. Trifluoroacetic anhydride (5 cm^3, 7.35 g, 35 mmol) was added to the *meso*-dicarboxylic acid (557 mg, 2.12 mmol) under nitrogen at room temperature, and the mixture refluxed for 1 h. The solvent was removed under reduced pressure. Traces of trifluoroacetic acid and trifluoroacetic anhydride were removed under high vacuum to give the crude *anhydride* (555 mg) as a yellow oil, which was used directly in the next step without further purification; $\nu_{max}(CDCl_3)/cm^{-1}$ 2924 (CH), 2855 (CH), 1847 (C=O, antisym.) and 1760 (C=O, sym.).

Methyl (3a*RS*,4*SR*,6*RS*,6a*SR*)-2,3,3a,4,5,6,6a,7,8,9-decahydro-1*H*-cyclopenta[*e*]azulene-4,6-dicarboxylate 28

Freshly prepared sodium methoxide (862 mg, 15.96 mmol) in methanol (10 cm^3) was added to the crude anhydride **27** (600 mg) under nitrogen at room temperature, and the mixture was stirred for 0.5 h. The mixture was acidified with dilute hydrochloric acid (5 cm^3) and extracted with ether (5 × 10 cm^3). The extract was washed with brine (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the *monoester* (531 mg, 86% from the dicarboxylic acid) as needles, mp 126–127 °C (from hexane–$CHCl_3$); R_f(Et_2O–light petroleum, 1 : 1) 0.28; $\nu_{max}(CDCl_3)/cm^{-1}$ 3453 (OH), 2949 (CH), 2937 (CH), 2861 (CH), 1733 (C=O, ester) and 1698 (C=O, acid); δ_H(700 MHz; $CDCl_3$) 3.66, (3 H, s, CO_2Me), 2.60 (2 H, m, 2 × C*H*CHCOO), 2.30 (2 H, ddd, *J* 16.0, 5.0 and 2.0, C$H_A$$H_B$C=C), 2.20–2.09 (5 H, m, 2 × CHCOO, 2 × CH_AH_BC=C and $CHCO_2MeCH_AH_B$), 2.01 (2 H, m, $CHCO_2MeCH_AH_B$ and C$H_A$$H_B$CHCHCOO), 1.89 (1 H, m, C$H_{A*}$$H_{B*}$CHCHCOO), 1.72 (2 H, m, 2 × C$H_A$$H_B$$CH_2$C=C), 1.48–1.35 (3 H, m, CH_AH_BCHCHCOO and 2 × $CH_AH_B$$CH_2$C=C) and 1.32 (1 H, tdd, *J* 12.0, 10.0 and 6.0, $CH_{A*}H_{B*}$CHCHCOO); δ_C(175 MHz; $CDCl_3$) 180.8+ (CO_2H), 175.6+ (*C*O_2Me), 137.1+ (*C*=C), 136.7+ (C=*C*), 51.6− (CO_2*Me*), 48.92− *C*HCOO), 48.88− (*C*HCOO), 45.9− (*C*HCHCOO), 45.5− (*C*HCHCOO), 36.7+ ($CHCO_2MeCH_2CHCO_2H$), 33.91+ (2 coincident peaks), 33.90+, 33.85+, 24.89+ (*C*$H_2$$CH_2$C=C) and 24.88+ (*C*$H_2$$CH_2$C=C) (Found: M + Na^+, 301.1418. $C_{16}H_{22}O_4$ requires *M* + Na, 301.1416).

Methylation of monoester 28

Trimethylsilyldiazomethane (2.0 mol dm^{-3} in hexane, 0.1 cm^3, 0.2 mmol) was added dropwise at room temperature to the monoester **28** (5 mg, 0.02 mmol) in methanol (1 cm^3) and the mixture kept for 30 min. Acetic acid (0.1 cm^3) was added and the mixture stirred for 30 min. Distilled water (2 cm^3)was added and the mixture was extracted with ether (3 × 1 cm^3), the extracts dried ($MgSO_4$) and evaporated under reduced pressure.

Traces of solvents were removed under high vacuum to give the diester **18** (5.3 mg, 100%), identical (^{1}H NMR) with the earlier sample.

Compounds prepared for another route

The following compounds were prepared in anticipation of a route in which reduction of the esters preceded the ozonolysis and Beckmann rearrangement.

(3a*RS*,4*RS*,6*RS*,6a*SR*)-6-Hydroxymethyl-2,3,3a,4,5,6,6a,7,8,9-decahydro-1*H*-cyclopenta[*e*]azulen-4-ylmethanol

Diester **19** (0.117 g, 0.4 mmol) in ether (5 cm^3) was added dropwise to a stirred solution of lithium aluminium hydride (91 mg, 2.4 mmol) in ether (5 cm^3) maintaining a gentle reflux, and the mixture kept for 1 h at room temperature. The mixture was quenched with ice-water, made homogeneous with dilute hydrochloric acid and extracted with ether (6 × 5 cm^3). The extract was washed with brine (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, MeOH–CH_2Cl_2, 10 : 90) to give the *diol* (87.2 mg, 92%) as needles, mp 117.5–118.5 °C (from hexane–EtOH); R_f(MeOH–CH_2Cl_2, 1 : 9) 0.38; ν_{max}($CDCl_3$)/cm^{-1} 3458 (OH); δ_H(500 MHz; CD_3OD) 3.58 (2 H, m, 2 × CH_AH$_B$OH), 3.46 (2 H, m, 2 × CH$_A$$H_B$OH), 2.69 (1 H, m, C*H*CHCH$_2$OH), 2.29–2.26 (4 H, m, C*H*CHCH$_2$OH, 2 × CH_AH$_B$C=C and CHCH$_2$OHCH_AH$_B$CH), 2.07–2.05 (3 H, m, 2 × CH$_A$$H_B$C=C and C$H_AH_B$CHCHCH$_2$OH), 1.92–1.89 (2 H, m, C*H*CH$_2$OH and CH_{A*}H$_{B*}$CHCHCH$_2$OH), 1.73 (2 H, m, 2 × CH_AH$_B$-CH$_2$C=C), 1.64 (1 H, m, CH$_{A*}$$H_{B*}$CHCHCH$_2$OH) and 1.54–1.30 (5 H, m, CHCH$_2$OHCH$_A$$H_B$, C*H*CH$_2OH, CH_A$$H_B$-CHCHCH$_2$OH and 2 × CH$_A$$H_BCH_2$C=C); δ_C(125 MHz; CD_3OD) 137.1+ (*C*=C), 136.3+ (C=*C*), 67.2+ (*C*H$_2$OH), 61.5+ (*C*H$_2$OH), 47.4− (*C*HCHCH$_2$OH), 46.5− (*C*HCH-CH$_2$OH), 42.0− (*C*HCH$_2$OH), 39.8− (*C*HCH$_2$OH), 35.0+ (CHCH$_2$OH*C*H$_2$), 34.9+ (*C*H$_2$C=C and *C*H$_2$CHCHCH$_2$OH, coincident peaks], 34.0+ (*C*H$_2$C=C), 33.2+ (*C*H$_2$CHCH-CH$_2$OH), 26.9 (*C*H$_2$CH$_2$C=C) and 26.3 (*C*H$_2$CH$_2$C=C) (Found: C, 76.2; H, 10.10. $C_{15}H_{24}O_2$ requires C, 76.2; H, 10.25%).

(3a*RS*,4*RS*,6*RS*,6a*SR*)-4,6-Bis(toluene-*p*-sulfonyloxymethyl)-2,3,3a,4,5,6,6a,7,8,9-decahydro-1*H*-cyclopenta[*e*]azulene

The diol (80 mg, 0.34 mmol), *p*-methylbenzenesulfonyl chloride (0.142 g, 0.74 mmol) and pyridine (95 mg, 1.2 mmol, 0.1 cm^3) were kept in ethanol-free chloroform (5 cm^3) for 1 h. The mixture was diluted with ether (10 cm^3) and washed with dilute hydrochloric acid (5 cm^3), water (5 cm^3), brine (5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, Et_2O–light petroleum, 30 : 70) to give the *ditosylate* (0.152 g, 82%) as needles, mp 100.5–101.5 °C (from EtOH); R_f(Et_2O–light petroleum, 1 : 1) 0.32; ν_{max}($CDCl_3$)/cm^{-1} 2869 (CH), 1598 (Ph), 1355 (SO_2O, antisym.) and 1179 (SO_2O, sym.); δ_H(500 MHz; $CDCl_3$) 7.78 (2 H, d, *J* 8.0, 2 × *o*-Ts), 7.75 (2 H, d, *J* 8.0, 2 × *o*-Ts), 7.36 (2 H, d, *J* 8.0, 2 × *m*-Ts), 7.33 (2 H, d, *J* 8.0, 2 × *m*-Ts), 4.04 (1 H, dd, *J* 10.0 and 4.5, CH_AH$_B$OTs), 3.93 (1 H, t, *J* 10.0, CH$_A$$H_B$OTs), 3.87 (1 H, dd, *J* 9.0 and 5.0, CH_AH$_B$OTs), 3.77 (1 H, dd, *J* 9.0 and 2.0, CH$_A$$H_B$OTs), 2.60 (1 H, m, C*H*CHCH$_2$OTs), 2.47 (3 H, s, Me), 2.45 (3H, s, Me), 2.25–2.19 (3 H, m, C*H*CHCH$_2$OTs, 2 × CH_AH$_B$C=C), 2.06 (1 H, m, C*H*CH$_2$OTs), 1.89–1.83 (5 H, m, 2 × CH$_A$$H_B$C=C, CHCH$_2$OTsC$H_AH_B$, C$H_AH_B$CHCHCH$_2$OTs and C$H_{A*}H_{B*}$CHCHCH$_2$OTs), 1.65 (1 H, m, C$H_AH_BCH_2$C=C), 1.60–1.50 (2 H, m, CH_{A*}H$_{B*}$-CH$_2$C=C and CHCH$_2$OTsCH$_A$$H_B$), 1.45–1.35 (2 H, m, CH$_{A*}$$H_{B*}$CHCHCH$_2$OTs and CH$_{A*}$$H_{B*}CH_2$C=C), 1.26 (1 H, m, CH$_A$$H_BCH_2$C=C), 1.17 (1H, m, C*H*CH$_2$OTs) and 1.08 (1 H, m, CH$_A$$H_B$CHCHCH$_2$OTs); δ_C(125 MHz; $CDCl_3$) 144.5+ (2 × *ipso*-C), 136.0+ (*C*=C), 134.6+ (C=*C*), 132.8+ (*p*-C), 132.6+ (*p*-C), 129.63− (2 × *o*-C), 129.57− (2 × *o*-C), 127.6− (4 × *m*-C), 74.1+ (*C*H$_2$OTs), 68.8+ (*C*H$_2$OTs), 45.1− (*C*HCHCH$_2$OTs), 44.5− (*C*HCHCH$_2$OTs), 37.3− (*C*HCH$_2$OTs), 35.7− (*C*HCH$_2$-OTs), 35.1+ (CHCH$_2$OTs*C*H$_2$), 33.8+ (*C*H$_2$C=C), 33.4+ (*C*H$_2$-CHCHCH$_2$OTs), 33.1+ (*C*H$_2$C=C), 32.0+ (*C*H$_2$CHCHCH$_2$-OTs), 25.6+ (*C*H$_2$CH$_2$C=C), 24.9+ (*C*H$_2$CH$_2$C=C), 21.63− (Me) and 21.59− (Me) (Found: C, 63.9; H, 6.65. $C_{29}H_{36}O_6S_2$ requires C, 63.9; H, 6.65%).

(3a*RS*,4*RS*,6*RS*,6a*SR*)-4,6-Bis(benzoyloxymethyl)-2,3,3a,4,5,6,6a,7,8,9-decahydro-1*H*-cyclopenta[*e*]azulene

The diol (404 mg, 1.71 mmol), benzoyl chloride (1.2 g, 8.55 mmol, 1 cm^3) and pyridine (5 cm^3) were kept at 0 °C for 1 h. The mixture was diluted with distilled ice-water (15 cm^3) and extracted with ether (3 × 20 cm^3). The extract was washed with dilute hydrochloric acid (2 × 10 cm^3), aqueous sodium hydrogencarbonate (5 cm^3), water (5 cm^3), brine (5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, Et_2O–light petroleum, 2 : 98 to 5 : 95) to give the *dibenzoate* (721 mg, 95%) as an oil; R_f(Et_2O–light petroleum, 1 : 1) 0.65; ν_{max}($CDCl_3$)/cm^{-1} 2865 (CH), 1725 (C=O) and 1610 (Ph); δ_H(500 MHz; $CDCl_3$) 7.97 (2 H, d, *J* 8.0, *o*-H), 7.95 (2 H, d, *J* 8.0, *o*-H), 7.50 (2 H, q, *J* 7.0, 2 × *p*-H), 7.36–7.29 (4 H, m, 2 × *m*-H), 4.40 (1 H, dd, *J* 11.0 and 4.5, CH_AH$_B$OBz), 4.34 (1 H, dd, *J* 11.0 and 3.0, CH_{A*}H$_{B*}$OBz), 4.30 (1 H, t, *J* 11.0, CH$_A$$H_B$OBz), 4.17 (1 H, dd, *J* 11.0 and 7.0, CH$_{A*}$$H_{B*}$OBz), 2.81 (1 H, m, C*H*CHCH$_2$OBz), 2.48–2.26 (5 H, m, C*H*CHCH$_2$OBz, C*H*CH$_2$OBz, 2 × CH_AH$_B$C=C and CH_AH$_B$CHCHCH$_2$OBz), 2.18–2.04 (3 H, m, 2 × CH$_A$$H_B$C=C and C$H_{A*}H_{B*}$CHCHCH$_2$OBz), 1.99 (1 H, m, CHCH$_2$OBz-C$H_AH_B$) 1.82–1.64 (5 H, m, C*H*CH$_2$OBz, CH$_{A*}$$H_{B*}$CHCHCH$_2$-OBz, C$H_AH_BCH_2$C=C, C$H_{A*}H_{B*}CH_2$C=C and CHCH$_2$OBz-CH$_A$$H_B$), 1.54–1.42 (2 H, m, CH$_A$$H_B$CHCHCH$_2$OBz and CH$_{A*}$$H_{B*}CH_2$C=C) and 1.37 (1 H, m, CH$_A$$H_BCH_2$C=C); δ_C(125 MHz; $CDCl_3$) 166.8+ (*C*=O), 166.7+ (*C*=O), 136.3+ (*C*=C), 135.3+ (C=*C*), 132.8− (*p*-C), 132.7− (*p*-C), 130.34+ (*ipso*-C), 130.33+ (*ipso*-C), 129.5− (2 × *o*-C), 129.4− (2 × *o*-C), 128.4− (2 × *m*-C), 128.3− (2 × *m*-C), 69.1+ (*C*H$_2$OBz), 64.0+ (*C*H$_2$OBz), 45.9− (*C*HCHCH$_2$OBz), 45.7− (*C*HCHCH$_2$OBz), 37.5− (*C*HCH$_2$OBz), 36.1− (*C*HCH$_2$OBz), 34.0+ (*C*H$_2$CHCH-CH$_2$OBz), 33.8+ (*C*H$_2$CHCHCH$_2$OBz), 33.2+ (2 × *C*H$_2$C=C, coincident peaks), 32.2+ (CHCH$_2$OBz*C*H$_2$), 25.8+ (*C*H$_2$CH$_2$-C=C) and 25.3+ (*C*H$_2$CH$_2$C=C) (Found: M + Na$^+$, 467.2203. $C_{29}H_{32}O_4$ requires *M* + Na, 467.2198).

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