A Simple Approach to the Bicyclo[5.3.1]undecane System Present in Taxanes

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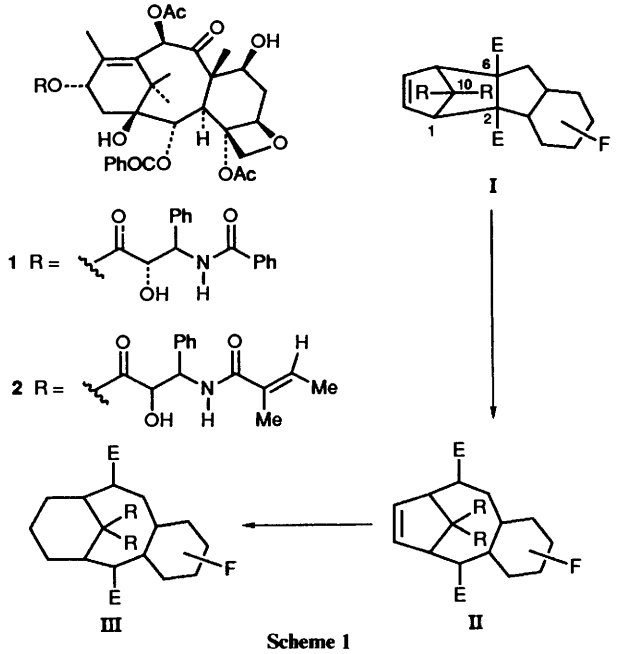
A simple route for the synthesis of the bicyclo[5.3.1]undecane ring system present in taxanes has been developed. The key steps involve the cleavage of a carbon–carbon bond in the tricyclo-[5.2.1.$0^{2,6}$]decane system **5** and a one-carbon ring enlargement of the latter to the bicyclo-[5.3.1]undecane system **23**. The potential generality of this ring cleavage process has been examined using various tricyclo[5.2.1.$0^{2,6}$]decane derivatives **5**, **10** and **13** which have been prepared either through a [4 + 2] cycloaddition reaction or by annelation *via* alkylation of the vicinal dianion. The scope and limitations of both these routes to the synthesis of the tricyclo[5.2.1.$0^{2,6}$]decane derivatives have been demonstrated.

The taxane diterpenes[1] have emerged as one of the most challenging synthetic targets because of their high level of structural and stereochemical complexities and the highly promising antitumour and antileukemic activites exhibited by a few member *e.g.* taxol **1**[2] and cephalomannine **2**.[3] Despite an extraordinary amount of synthetic effort, only a synthesis[4] of a relatively simple member, taxusin, has been achieved. Hence, the quest to secure routes[5] for access to the active members **1** and **2** is continuing.

As part of our interest[6] in the use of tricyclo[5.2.1.$0^{2,6}$]decane derivatives towards the synthesis of condensed and bridged-ring natural products, we envisaged that a carbon–carbon bond cleavage in the tricyclo[5.2.1.$0^{2,6}$]decane derivative **I** (Scheme 1) would provide compound **II** which with a one carbon ring enlargement might lead to the tricyclo[9.3.1.$0^{3,8}$]pentadecane structure **III** present in taxanes. We report here the results[7] of our investigation based on this concept.



Scheme 1

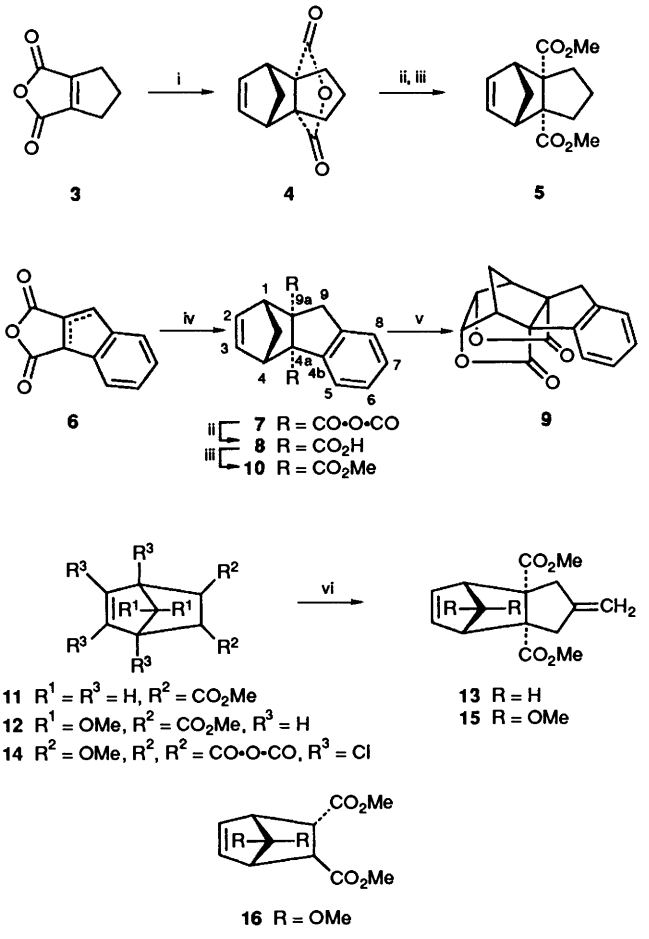
Results and Discussion

Design and Synthesis of Tricyclo[5.2.1.$0^{2,6}$]*decanes.*—The concept adopted here for achieving the cleavage of the C-2–C-6 bond in **I** is based on an earlier observation[8] that the reaction of a few strained succinic ester derivatives with Na or K in NH_3(l) under certain condition leads to fission of the central C–C bond. Accordingly, the tricyclo[5.2.1.$0^{2,6}$]decane derivative **I** is designed with two ester moieties at C-2 and C-6 (in **I**, R must be CO_2Me). In principle, the diester derivative **I** may be available through a cycloaddition between a cyclopentadiene derivative and an appropriately constructed maleic anhydride derivative. The investigation was initiated with the synthesis of simpler analogues of **I** and their subsequent transformations in accord with the plan delineated in Scheme 1. The reaction[9] of cyclopentadiene with cyclopentene-1,2-dicarboxylic anhydride **3** afforded, in excellent yield, the adduct **4** (Scheme 2) which was transformed to the dimethyl ester **5** through hydrolysis and treatment with diazomethane. Refluxing a toluene solution of the bicyclic anhydride **6**[10] with cyclopentadiene gave the *endo*-adduct **7** in 74% yield. While the gross structure of **7** became apparent from its ^{1}H NMR spectroscopic data, the assignment of *endo*-configuration to **7** was made by its nearly quantitative transformation to the dilactone **9** through the dicarboxylic acid **8**. The dicarboxylic acid **8** on treatment with ethereal diazomethane afforded the dimethyl ester **10**.

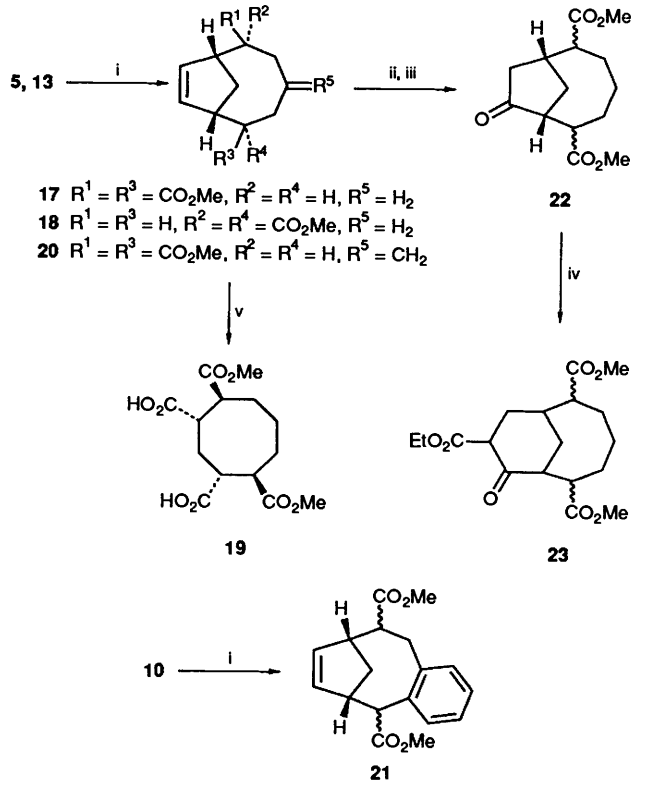
For the synthesis of tricyclo[5.2.1.$0^{2,6}$]decane derivative **I** (R = Me), required for elaboration to the natural products, it was necessary to have a cycloaddition of the anhydride **3** or **6** with a 5,5-disubstituted cyclopentadiene derivative. However, the anhydride **3** was found to be inert towards cycloaddition with 5,5-diethoxycyclopentadiene or 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene.[9a] This necessitated the development of an alternative route† for access to the derivatives of the general structure **I**. We considered a ring annelation *via* alkylation[12] of the vicinal dianions derivable, in principle, from the diesters **11** and **12** with α,ω-dihalides. Thus, treatment of the readily available diester **11** with LDA (lithium diisopropylamide) (2.5 equiv.) in THF (tetrahydrofuran) followed by treatment with 3-chloro-2-chloromethylpropene in presence of HMPA (hexamethylphosphoramide) afforded the ring annelated product **13**‡ in excellent yield. The stereochemical assignment of **13** was made by analogy to the alkylation of dienolate of **11** which was reported[12e] to occur exclusively from the *exo*-face. Annelation of the 7,7-dimethoxy derivative **12** was next examined. The diester **12**[14] was prepared from the tetrachloro

† For a different approach to a 10-substituted tricyclo[5.2.1.$0^{2,6}$]decane see ref. 11.

‡ For an alternative synthesis of this compound see ref. 13.



Scheme 2 *Reagents and conditions:* i, cyclopentadiene, THF, $AlCl_3$, 0 °C; ii, $NaHCO_3$, EtOH, H_2O, reflux; iii, CH_2N_2, Et_2O; iv, cyclopentadiene, toluene, reflux; v, I_2, KI, $NaHCO_3$, NaOH, H_2O; vi, LDA, THF, HMPA, 3-chloro-2-chloromethylpropene, −78 °C to room temp.



Scheme 3 *Reagents and conditions:* i, Na, $NH_3(l)$, −55 °C; ii, BH_3, THF, 0 °C, 3 mol dm^{-3} NaOH, 30% H_2O_2; iii, acetone, Jones reagent, 0 °C; iv, $Et_3O^+BF_4^-$, CH_2Cl_2, N_2CHCO_2Et, 0 °C to room temp.; v, $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O, room temp., 3 h

adduct **14**[15] through sequential hydrolysis, dechlorination with Na–$NH_3(l)$ and esterification. Attempted annelation of **12** with 3-chloro-2-chloromethylpropene under the conditions used for annelation of **11** failed to produce the corresponding ring annelated product **15**. The most remarkable change in the ^1H NMR spectrum of the only product obtained, in 75% yield, from the attempted alkylation of **12**, is the appearance of two doublets of doublets at δ 6.10 and 6.34 (J 6, 4 Hz) for the C-5,-6-olefinic protons and two singlets at δ 3.70 and 3.76 for two CO_2Me groups in contrast to the symmetrical spectral pattern (a triplet at δ 6.32 for the C-5, -6-olefinic protons and a singlet at δ 3.64 for the CO_2Me groups) for the starting dimethyl ester **12**. The unsymmetrical nature of the spectrum clearly indicates that the two CO_2Me groups are *anti* to each other and structure **16** is assigned to the product of attempted alkylation of **12**. The failure of the enolate of **12** to undergo alkylation may possibly be attributed to the steric hindrance imposed by the rigidly held 7-OMe groups in the *exo* face as well as by the C_5–C_6 olefinic bridge in the *endo* face. Although the C-10-functionalised analogue of the structure **1** could not be synthesised, the two routes developed have provided easy access to a number of diesters **5**, **10** and **13** for further elaboration.

Transformation of Tricyclo[5.2.1.$0^{2,6}$]*decane System to the Bicyclo*[5.3.1]*undecane System.*—An ethereal solution of the dimethyl ester **5** when treated with sodium (12 equiv.) in $NH_3(l)$ at −55 °C for 12–15 min afforded exclusively compound **17** (Scheme 3), m.p. 76 °C in 70% yield. The diagnostic information that 2,6-bond breaking in **5** has, in fact, taken place was available from ^1H and ^{13}C (DEPT) NMR spectroscopic data. While the ^1H NMR spectrum of **17** showed the appearance of a two proton doublet of doublet at δ 3.34 (J 10.4,4.4) assigned to 2-,6-protons, the ^{13}C NMR spectrum showed the presence of an additional methine resonance at δ 46.75. The conclusive evidence that C-2–C-6 bond has been cleaved was shown by the fact that the diester **17** could be epimerised on treatment with NaOMe–MeOH at room temperature for 24 h to a mixture containing more that 80% (from integration of olefinic H in ^1H NMR spectrum of the reaction mixture) of the epimerised product **18**. The stereochemical assignment of the ring cleaved product **17** was made by comparison of the ^1H NMR spectroscopic data of **17** with those of **18**. Of the two diastereoisomers, the olefinic protons at C-8 and C-9 in the isomer with the CO_2Me and the olefinic bridge *syn* to each other is expected to be deshielded. Thus, the isomer with the olefinic protons appearing at δ 5.94 was assigned the structure **18** while the isomer with 8,9-protons resonating at δ 5.71 was assigned the structure **17**. Oxidative fission of the C-8,C-9-olefinic bridge in **17** using a catalytic amount of $RuCl_3$ in the presence of $NaIO_4$ afforded the dicarboxylic acid **19**, m.p. 174 °C. Thus, the combination of a reductive and an oxidative carbon–carbon bond fission of the diester derivative **5** offers an excellent route for the synthesis of highly functionalised cyclooctane derivative **19**.

After successfully achieving the C–C bond cleavage in **5**, the more functionalised diesters **13** and **10** were next subjected to the reduction under the condition developed above. Thus, the diester **13** gave the ring cleaved product **20** in 76% yield. The structural and stereochemical assignment of **20** was made by comparison of the change in chemical shift (0.48 ppm) of the 8,9-olefinic protons in the transformation **13**→**20** with those

observed (0.58 ppm) for the 8,9-protons in the transformation **5**→**17**. However, the diester **10**, under identical conditions, gave the ring cleaved product **21** in only 33% yield as an inseparable diastereoisomeric mixture (from ^{1}H NMR spectroscopy). Thus the C-2–C-6 bond in the diesters **5**, **10** and **13** could be induced to undergo facile cleavage leading to bridged eight-membered derivatives **17**, **21** and **20**, respectively, in moderate to good yield.

Finally, the feasibility of the transformation of a bicyclo[5.2.1]decane derivative to a bicyclo[5.3.1]undecane system is demonstrated. Treatment of the bicyclo[5.2.1]decane **17** with BH_3–THF at 0 °C followed by oxidation of the intermediate organoborane with alkaline hydrogen peroxide afforded, in 88% yield, the hydroxy diester which was directly oxidised with Jones reagent to give the keto diester **22** as a 1:1 diastereoisomeric mixture in 75% overall yield. One-carbon ring expansion of cyclopentanone unit in compound **22** was achieved in 51% yield to produce the β-keto ester derivative **23** by reaction with ethyl diazoacetate using triethyloxonium tetrafluoroborate as the catalyst. The regiochemical assignment of the keto ester moiety in **23** is based on the well known trend[16] of the methylene unit to undergo preferential migration over the methine unit during ring expansion of unsymmetrical ketones with ethyl diazoacetate.

Thus, the present investigation has provided a simple short route for access to the bicyclo[5.3.1]undecane system functionalised in both the six and eight membered rings at appropriate centres for elaboration to taxanes.

Experimental

The compounds described are all racemates. M.p.s were measured in open capillary tubes and are uncorrected. IR spectra of solids (KBr) and liquids (film) were recorded on a Perkin-Elmer model PE-298 instrument. ^{1}H NMR spectra were recorded at 200 MHz on Varian Associates XL-200 spectrometers for solutions in $CDCl_3$ with $SiMe_4$ as internal standard. *J* values are given in Hz. The organic extracts were dried over anhydrous Na_2SO_4. Column chromatography was performed on silica gel (60–200 mesh). Light petroleum refers to the fraction boiling at 60–80 °C. Elemental analyses were performed by Mr. P. P. Bhattacharya and Mr. S. Pal of this laboratory.

Dimethyl Tricyclo[5.2.1.0^{2,6}]*dec*-8-*ene*-2,6-*dicarboxylate* **5**.—The dimethyl ester **5** was prepared in 91% yield according to the literature procedure[9] through cycloaddition of the anhydride **3** with cyclopentadiene followed by hydrolysis of the resulting adduct **4** and esterification with diazomethane; m.p. 60 °C; δ_H 1.48–2.22 (6 H, m, 3 × CH_2), 2.34–2.48 (2 H, m), 2.83 (2 H, m, 1-, 7-H), 3.62 (6 H, s, CO_2Me) and 6.29 (2 H, t, *J* 1.5, 8-, 9-H).

endo-1,4,4a,9a-*Tetrahydro*-1,4-*methanofluorene*-4a,9a-*dicarboxylic Anhydride* **7**.—A solution of the anhydride **6** [900 mg, 4.83 mmol in toluene (12 cm^3)] was refluxed with freshly distilled cyclopentadiene (12 cm^3) for 5 h. Removal of solvent and volatile material under reduced pressure afforded a viscous mass which was chromatographed using ethyl acetate–light petroleum (1:19) as eluent to afford compound **7** (930 mg, 78%), m.p. 102 °C (Found: C, 76.4; H, 4.95. $C_{16}H_{12}O_3$ requires C, 76.17; H, 4.79%); ν_{max}/cm^{-1} 1855, 1830 and 1775; δ_H 1.63 (H, d, *J* 9.8, 10-H), 1.87 (H, d, *J* 9.7, 10-H), 3.16 (H, d, *J* 18.1 9-H), 3.34 (H, br s, 1-H), 3.40 (H, br s, 4-H), 3.76 (H, d, *J* 18.1, 9-H), 6.52 (H, dd, *J* 4.8, 2.9, 2-H), 6.62 (H, dd, *J* 5.8, 2.9, 3-H), 7.31–7.48 (3 H, m, ArH) and 7.68 (H, m, ArH).

Dimethyl 1,4,4a,9a-*Tetrahydro*-1,4-*methanofluorene*-4a,9a-*dicarboxylate* **10**.—The reaction mixture obtained by refluxing the anhydride **6** (1.12 g, 6.02 mmol) with cyclopentadiene (8 cm^3) in toluene (15 cm^3) was directly hydrolysed by refluxing for 2 h with $NaHCO_3$ (2.75 g, 32.7 mmol), water (5 cm^3) and ethanol (25 cm^3) in the same reaction flask. On cooling to room temp., the reaction mixture was extracted with ether (4 × 20 cm^3) to remove unhydrolysed material. The aqueous part was cooled in ice and acidified with concentrated hydrochloric acid. The white solid which crystallised out was collected by filtration. The solid obtained was dried under vacuum to afford the dicarboxylic acid **8** (1.4 g, 88%), m.p. 188 °C (decomp.); ν_{max}/cm^{-1} 1720.

The dicarboxylic acid **8** (1.14 g, 4.22 mmol) was treated with ethereal diazomethane for 2 h. The residue after removal of diethyl ether was filtered through a short column of neutral alumina to afford the dimethyl ester **10** (1.15 g, 92%), m.p. 59 °C (Found: C, 72.45; H, 6.2. $C_{18}H_{18}O_4$ requires C, 72.45; H, 6.0%); ν_{max}/cm^{-1} 1735; δ_H 1.32 (2 H, dd, *J* 22, 9, 10-H), 2.95 (H, br s, 1-H), 3.05 (H, d, *J* 17.6, 9-H), 3.11 (H, br s, 4-H), 3.57 (3 H, s, CO_2Me), 3.64 (3 H, s, CO_2Me), 3.83 (H, d, *J* 17.6, 9-H), 6.17 (H, dd, *J* 5.4, 2.9, 2-H), 6.55 (H, dd, *J* 5.4, 2.8, 3-H) and 7.26 (4 H, s, ArH).

Transformation of the Dicarboxylic Acid **8** *to the Dilactone* **9**.—To a solution of the dicarboxylic acid **8** (500 mg, 1.86 mmol) in methanol (2.5 cm^3) was added successively 20% aqueous NaOH (1.2 cm^3), 5% aqueous $NaHCO_3$ (10 cm^3) and aqueous iodine solution (3 cm^3) [prepared from iodine (500 mg), potassium iodide (1 g) and water (3 cm^3)]. This mixture was kept in the dark at room temp. for 2 d and then boiled for 30 min. On cooling, the reaction mixture was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3 × 15 cm^3). The organic extract was dried and concentrated to afford the dilactone **9** (380 mg, 76%), m.p. 218 °C (decomp.) (Found: C, 71.6; H, 4.55. $C_{16}H_{12}O_4$ requires C, 71.63; H, 4.51%); ν_{max}/cm^{-1} 1785 and 1765; δ_H 1.83 (H, dt, *J* 1.8, 12.9, 10-H), 1.91 (H, dt, *J* 1.5, 12.9, 10-H), 2.97 (H, *J* 17.2, 9-H), 3.28 (H, br s, 1-H), 3.41 (H, br s, 4-H), 3.86 (H, d, *J* 17.5, 9-H), 4.78 (2 H, m, 2-, 3-H) and 7.14–7.54 (4 H, m, ArH).

Dimethyl 4-*Methylenetricyclo*[5.2.1.0^{2,6}]*dec*-8-*ene*-2,6-*dicarboxylate* **13**.—To a magnetically stirred solution of diisopropylamine (2.6 ml, 18.75 mmol) in anhydrous THF (16 cm^3) under a nitrogen atmosphere, cooled to −78 °C, was added dropwise BuLi (10 cm^3, 18.75 mmol, 12% solution in hexane). After the addition was complete, the reaction mixture was warmed to −10 °C and stirred for additional 15 min. The reaction mixture was again cooled to −78 °C and to it was added dropwise a solution of the dimethyl ester **11** (1.6 g, 7.62 mmol) in THF (10 cm^3). Immediately, the solution became orange. The reaction mixture was stirred at −78 °C for 1 h and at −30 °C for a further 1 h. Then it was again cooled to −78 °C and to it HMPA (hexamethylphosphoramide) (4 cm^3, 22.9 mmol) followed by 3-chloro-2-chloromethylpropene (1.2 g, 9.60 mmol) were added. The reaction mixture was stirred at −78 °C for 1 h, at −10 °C for 1 h, at 0 °C for 2 h and finally left at room temp. overnight. The reaction mixture was acidified with cold 6 mol dm^{-3} HCl and extracted with diethyl ether (3 × 60 cm^3). The ether extract was washed with brine and dried. Removal of solvent afforded a reddish liquid. Chromatography of the crude product using ethyl acetate–light petroleum (1:19) as the eluent furnished the ring annelated dimethyl ester **13** (1.60 g, 80%) as a colourless liquid (Found: C, 69.15; H, 7.25. $C_{15}H_{18}O_4$ requires C, 68.68; H, 6.92%); ν_{max}/cm^{-1} 1730; δ_H 1.44 (H, d, *J* 9, 10-H), 2.14 (H, d, *J* 9, 10-H), 2.42 (2 H, d, *J* 16, 3-, 5-H), 2.94 (2 H, br s, 1-, 7-H), 3.34 (2 H, d, *J* 16, 3-, 5-H), 3.72 (6 H, s, 2 × CO_2Me), 4.94 (2 H, br s, C=CH_2) and 6.40 (2 H, s, 8-, 9-H).

Dimethyl 7,7-*Dimethoxybicyclo*[2.2.1]*hept*-5-*ene*-2,3-*dicarboxylate* **12**.—A mixture of maleic anhydride (150 mg, 1.50

mmol) and 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene (400 mg, 1.51 mmol) in anhydrous benzene (3 cm^3) was refluxed for 12 h with magnetic stirring under nitrogen atmosphere. Removal of solvent under reduced pressure afforded a white solid **14** (540 mg, 99%), m.p. 112 °C (lit.,[15] m.p. 90–100 °C), ν_{max}/cm^{-1} 1835 and 1775; δ_H 3.60 (3 H, s, OMe), 3.66 (3 H, s, OMe) and 3.90 (2 H, s, 2-, 3-H).

A solution of the above anhydride **14** (400 mg, 0.96 mmol) in ethanol (1.5 cm^3) and water (5 cm^3) was refluxed with sodium hydrogen carbonate (200 mg, 2.4 mmol) for 4 h. The reaction mixture was cooled to room temp. and extracted with diethyl ether to remove unhydrolysed material. The aqueous part was acidified with 6 mol dm^{-3} HCl and extracted with diethyl ether (3 × 30 cm^3). The diethyl ether extract was washed with brine, dried and evaporated to dryness to afford the corresponding dicarboxylic acid (410 mg, 98%), m.p. 183 °C.

To magnetically stirred NH_3(l) (70 cm^3) (distilled from sodium) was added small pieces of sodium (180 mg, 7.8 mmol). The deep blue solution was cooled to −78 °C and to it a solution of the diacid obtained as above (200 mg, 0.53 mmol) in anhydrous THF (1.5 cm^3) containing ethanol (60 mg, 1.3 mmol) was added dropwise. After being stirred at this temperature for 8 min, the reaction mixture was quenched by addition of powdered ammonium chloride. Ammonia was then allowed to evaporate. The residue was diluted with ice water (5 cm^3) and acidified with 6 mol dm^{-3} HCl. The organic mass was extracted with diethyl ether (3 × 30 cm^3). The ether extract was washed with brine (3 × 20 cm^3) and dried. Removal of solvent furnished a solid, m.p. 110 °C, which on treatment with ethereal diazomethane yielded the dimethyl ester **12**[14] (130 mg, 91%); ν_{max}/cm^{-1} 1735; δ_H 3.18 (5 H, s merged with t, OMe and 1-, 4-H), 3.24 (3 H, s, OMe), 3.52 (2 H, m, 2-, 3-H), 3.64 (6 H, s, CO_2Me) and 6.32 (2 H, t, *J* 1.5).

Attempted Alkylation of **12**. *Synthesis of Dimethyl* 2-endo-3-exo-7,7-*Dimethoxybicyclo*[2.2.1]*hept-5-ene*-2,3-*dicarboxylate* **16**.—To a magnetically stirred solution of LDA [prepared from diisopropylamine (0.125 cm^3, 0.88 mmol) in anhydrous THF (2 cm^3) and BuLi (0.47 cm^3, 0.88 mmol, 12% solution in hexane)] was added dropwise a solution of the diester **12** (100 mg, 0.37 mmol) in THF (1 cm^3) at −78 °C. Immediately, a yellow colour was generated. The reaction mixture was stirred at −78 °C for 1 h and at −30 °C for a further 1 h and then cooled to −78 °C. To the cooled mixture, HMPA (0.1 cm^3, 0.57 mmol) followed by 3-chloro-2-chloromethylpropene (50 mg, 0.4 mmol) was added. The reaction mixture was stirred at −78 °C for 1 h, at −10 °C for 1 h, at 0 °C for 2 h and finally stood at room temp. overnight. The reaction mixture was acidified with cold 6 mol dm^{-3} HCl and extracted with diethyl ether (3 × 20 cm^3). The diethyl ether layer was washed with brine, and dried. Removal of diethyl ether afforded a yellowish liquid which on column chromatography using light petroleum–ethyl acetate (19:1) as the eluent furnished compound **16** as a colourless liquid (75 mg, 75%) (Found: C, 57.45; H, 6.8. $C_{13}H_{18}O$ requires C, 57.77; H, 6.71%); ν_{max}/cm^{-1} 1730; δ_H 2.76 (H, d, *J* 4, 4-H), 3.16 (3 H, s, OMe), 3.18 (3 H, s, OMe), 3.25 (H, m, 1-H), 3.42 (H, m, 3-H), 3.64 (H, m, 2-H), 3.70 (3 H, s, CO_2Me), 3.76 (3 H, s, CO_2Me), 6.10 (H, dd, *J* 6, 4, 5-H) and 6.34 (H, dd, *J* 6, 4, 6-H).

Dimethyl exo-*Bicyclo*[5.2.1]*dec*-8-*ene*-2,6-*dicarboxylate* **17**.—To magnetically stirred NH_3(l) (100 cm^3) (distilled from sodium) was added sodium (375 mg, 16.3 mmol) in small pieces. After complete addition, the deep blue solution was cooled to −55 °C. A solution of the diester **5** (300 mg, 1.2 mmol) in anhydrous ether (7.5 cm^3) was added dropwise to it. After being stirred at this temperature for 15 min, the reaction mixture was quenched by addition of powdered ammonium chloride. Ammonia was then allowed to evaporate. The residue was diluted with water (20 cm^3) and extracted with diethyl ether (3 × 30 cm^3). The diethyl ether extract was washed with brine (3 × 20 cm^3) and dried. Removal of solvent furnished a semisolid mass (200 mg). The aqueous part after acidification with cold 6 mol dm^{-3} HCl was extracted with ethyl acetate (3 × 15 cm^3). The organic extract was washed with brine (3 × 10 cm^3), dried and concentrated under reduced pressure. The residue (70 mg) was treated with ethereal diazomethane. The combined mass obtained as above was chromatographed (light petroleum) to afford the diester **17** (210 mg, 70%), m.p. 76 °C (Found: C, 66.3; H, 8.3. $C_{14}H_{20}O_4$ requires C, 66.64; H, 7.99%); ν_{max}/cm^{-1} 1730; δ_H 1.33–1.77 (5 H, m), 2.12–2.26 (3 H, m), 2.75 (2 H, dd, *J* 7.8, 4, 1-, 7-H), 3.34 (2 H, dd, *J* 10.4, 4.4, 2-, 6-H), 3.68 (6 H, s, CO_2Me) and 5.71 (2 H, s, 8-, 9-H); δ_C 19.6 (C-10), 28.5 (C-4), 29.0 (C-3, -5), 44.4 (C-1, -7), 46.7 (C-2, -6), 51.4 (OMe), 134.6 (C-8, -9) and 175.18 (CO_2Me).

Equilibration of **17** *with* NaOMe–MeOH.—The diester **17** (40 mg, 0.16 mmol) was treated with 10% methanolic sodium methoxide (2 cm^3) at room temp. for 16 h. The mixture, after acidification with 6 mol dm^{-3} HCl was extracted with diethyl ether. Removal of the diethyl ether afforded a liquid, which on treatment with ethereal diazomethane, furnished a mixture of the epimers **17** and **18** (30 mg, 75%) in a ratio of *ca.* 1:4 (by integration of the olefinic singlets in the ^1H NMR spectrum); δ_H (for **18** from mixture of **17** and **18**) 1.22–2.04 (8 H, m), 2.61 (2 H, d, *J* 12, 1-, 7-H), 3.15 (2 H, d, *J* 10, 2-, 6-H), 3.70 (6 H, s, CO_2Me) and 5.94 (2 H, s, 8-, 9-H).

4,8-*Dimethoxycarbonyloctane*-1,3-*dicarboxylic Acid* **19**.—To a stirred suspension of $NaIO_4$ (500 mg, 2.33 mmol) in CCl_4 (3 cm^3), CH_3CN (3 cm^3) and water (5.2 cm^3), the diester **17** (100 mg, 0.4 mmol) was added followed by addition of a pinch of $RuCl_3$ at room temp. and the mixture was stirred for 3 h. The reaction mixture was extracted with ethyl acetate (3 × 10 cm^3). The ethyl acetate extract was washed with aqueous NaOH (5%, 3 × 5 cm^3). The aqueous part, after acidification with cold 6 mol dm^{-3} HCl was extracted with ethyl acetate (3 × 10 cm^3). Removal of solvent from the dried organic extract afforded the dicarboxylic acid **19** as a white solid (100 mg, 80%), m.p. 174 °C (Found: C, 52.8; H, 6.25. $C_{14}H_{20}O_8$ requires C, 53.16; H, 6.37%); δ_H [as the tetramethyl ester (CH_2N_2)] 1.52–2.60 (8 H, m), 2.76–3.20 (4 H, m) and 3.70 (12 H, s, CO_2Me).

Dimethyl 4-*Methylenebicyclo*[5.2.1]*dec*-8-*ene*-2,6-*dicarboxylate* **20**.—To magnetically stirred NH_3(l) (75 cm^3) was added sodium (180 mg, 7.8 mmol) in small pieces. The deep blue solution was cooled to −55 °C and to it was added a solution of the diester **13** (200 mg, 0.76 mmol) in anhydrous diethyl ether (4 cm^3). After being stirred for 15 min at −55 °C, the reaction mixture was quenched by addition of powdered ammonium chloride. The ammonia was then allowed to evaporate. The reaction mixture was worked up with diethyl ether as described above to furnish a yellowish liquid which on chromatography [light petroleum–ethyl acetate (19:1)] afforded a colourless liquid **20** (150 mg, 76%) (Found: C, 68.2; H, 7.9. $C_{15}H_{20}O_4$ requires C, 68.16; H, 7.63%); ν_{max}/cm^{-1} 1725; δ_H 1.70–2.60 (6 H, m), 2.79 (2 H, dd, *J* 12.2, 1-, 7-H), 3.19 (2 H, d, *J* 8, 2-, 6-H), 3.72 (6 H, s, CO_2Me), 5.06 (2 H, br s, C=CH_2) and 5.92 (2 H, s, 8-, 9-H).

Dimethyl 6,9,10,11-*Tetrahydro*-6,9-*methano*-5H-*benzocyclononene*-5,10-*dicarboxylate* **21**.—To a cold (−55 °C) deep blue solution prepared by adding sodium (150 mg, 6.52 mmol) to distilled NH_3(l) (50 cm^3), was added dropwise a solution of the diester **10** (150 mg, 0.5 mmol) in anhydrous diethyl ether (3 cm^3). After stirring for an additional 15 min, the blue colour was discharged by adding powdered ammonium chloride. Ammonia

was allowed to evaporate and the residue after dilution with water (10 cm^3) was extracted with diethyl ether (3 × 20 cm^3). The diethyl ether extract was dried and concentrated to afford a viscous mass (50 mg). The aqueous part, after acidification with 6 mol dm^{-3} HCl, was extracted with ethyl acetate (3 × 20 cm^3). The organic extract after drying and concentrating gave a further 50 mg. The combined mass (100 mg) was chromatographed [ethyl acetate–light petroleum (1:19)] to afford the diester **21** (50 mg, 33%) as a viscous liquid; δ_H 2.02–3.18 (6 H, m), 3.34–3.60 (H, m), 3.70, 3.72, 3.74, 3.76 (6 H, all s, CO_2Me), 3.95 (H, m), 5.32–6.34 (2 H, m) and 7.04–7.48 (4 H, m, ArH); *m/z* (%), 300 (M^+, 5), 268 (23), 256 (23), 264 (36), 162 (47), 131 (87) and 77 (100). An analytically pure sample could not be obtained.

Dimethyl 8-Oxobicyclo[5.2.1]*decane-2,6-dicarboxylate* **22**.—A solution of the diester **17** (100 mg, 0.39 mmol) in THF (2 cm^3) was treated with a solution of borane (0.8 cm^3, 3.47 mmol, 34%) in THF at 0 °C for 3 h. A few drops of water was then added followed by addition of aqueous sodium hydroxide (1.20 cm^3, 30%). The reaction mixture was stirred at room temp. for 1 h and then extracted with diethyl ether (3 × 25 cm^3). The diethyl ether extract was washed with brine, dried and concentrated to afford the hydroxy diester (45 mg) as a viscous mass. The aqueous part was acidified with cold 6 mol dm^{-3} HCl and extracted with ethyl acetate (3 × 25 cm^3). The organic extract was washed with brine, dried and concentrated to afford a semi-solid mass which after treatment with ethereal diazomethane furnished a further 50 mg of the hydroxy diester. The combined mass without further characterisation was oxidised to the keto diester according to the following procedure. To an ice cold magnetically stirred solution of the above hydroxy diester (95 mg, 0.35 mmol) in acetone (3 cm^3) was added, dropwise, Jones reagent (1.5 cm^3; 0.7 mol dm^{-3}). Stirring was continued for an additional 30 min at that temperature. The reaction mixture, after dilution with water, was extracted with diethyl ether (3 × 30 cm^3). The diethyl ether extract was washed with aqueous sodium hydrogen carbonate, brine and dried. Removal of solvent furnished a viscous liquid which on chromatography [light petroleum–ethyl acetate (3:1)] afforded the keto diester **22** (80 mg, 75%) as a liquid (Found: C, 62.45; H, 7.60. $C_{14}H_{20}O_5$ requires C, 62.67; H, 7.51%); ν_{max}/cm^{-1} 1745 and 1725; δ_H 1.16–2.68 (10 H, m), 2.84–3.14 (4 H, m, 1-, 2- 6-, 7-H), 3.68, 3.76 (3 H, s, CO_2Me for one diastereoisomer) and 3.72, 3.74 (3 H, s, CO_2Me for the other diastereoisomer).

9-Ethyl 2,6-Dimethyl 8-Oxobicyclo[5.3.1]*undecane-2,6,9-tricarboxylate* **23**.—To a magnetically stirred solution of the keto diester **22** (600 mg, 2.23 mmol) in dry CH_2Cl_2 (12 cm^3) at 0 °C triethyloxonium tetrafluoroborate (1.0 g, 5.2 mmol) was added followed by ethyl diazoacetate (770 mg, 6.75 mmol). The reaction mixture was stirred at 0 °C for 6 h and at room temp. for 16 h. After careful addition of saturated aqueous sodium hydrogen carbonate (15 cm^3), the reaction mixture was extracted with CH_2Cl_2 (3 × 50 cm^3) and dried. Removal of solvent furnished a viscous liquid. The crude mass was chromatographed [light petroleum–ethyl acetate (9:1)] to afford the β-keto ester **23** (220 mg, 51%, based on recovered ketone) as a viscous liquid (Found: C, 60.9; H, 7.45. $C_{18}H_{26}O_7$ requires C, 61.00; H, 7.40%); ν_{max}/cm^{-1} 1730 and 1650; δ_H 2.10–2.78 (14 H, m), 2.88–3.20 (2 H, m), 3.50 (2 H, q, *J* 8), 3.68, 3.76 (3 H, s, CO_2Me for one diastereoisomer), 3.72, 3.74 (3 H, s, CO_2Me for the other diastereoisomer) and 4.12–4.44 (2 H, m) and the keto diester **22** (270 mg, 45%).

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