Thromboxane A_2 Analogues from 8-Oxabicyclo[3.2.1]oct-6-en-3-ones

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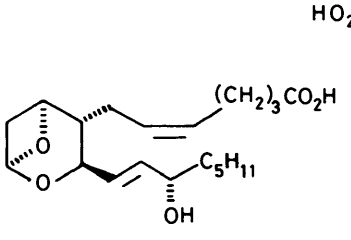
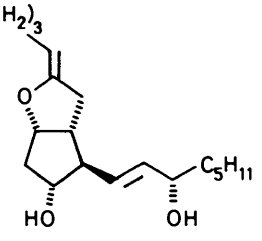
We describe approaches to thromboxane A_2 analogues (**3**), (**4**), and (**32**) which contain 2,6-dioxabicyclo[3.2.1]octane and 2,6-dioxatricyclo[3.3.1.$0^{3,7}$]nonane ring systems. Both were derived from 2-substituted 8-oxabicyclo[3.2.1]oct-6-en-3-ones, which were in turn prepared by cycloadditions of suitable oxyallyls and furans.

The products of the metabolism of arachidonic acid have been under intense investigation for the last 15 years, and hundreds of papers have appeared in the chemical and biological literature.[1] Of the many compounds investigated, thromboxane A_2 (TXA_2) (**1**) is the most enigmatic, since its biological half-life of 30 s under physiological conditions, precludes conventional isolation and structure elucidation.[2] The structure presently accepted was originally proposed on the basis of structural studies carried out on the products of its degradation and metabolism, though Clark Still and co-workers have now confirmed the structure by synthesis.[3] Despite the mystery surrounding its structure, there is no doubt that its major biological function is to cause blood platelets to aggregate and adhere to blood vessel walls. In this respect it exerts an opposite action to prostacyclin (PGI_2) (**2**), and the two compounds



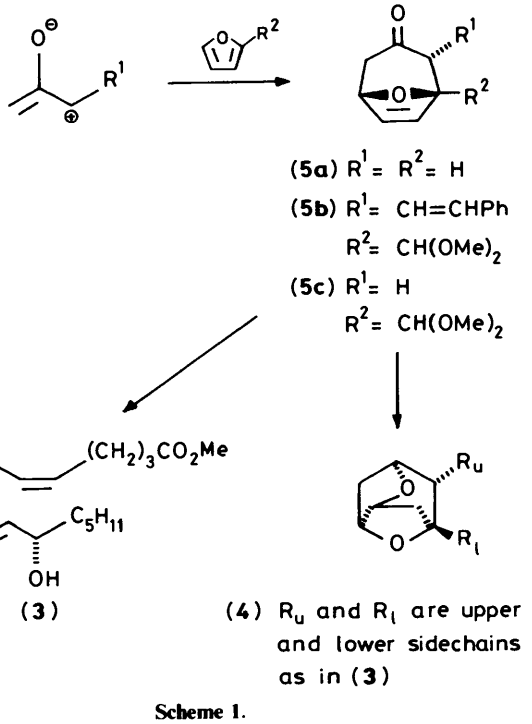
(**1**)



(**2**)

together are involved in maintenance of homeostasis of blood vessels. Undoubtedly the oxetane structure contributes to the instability of TXA_2, and numerous more stable analogues have been prepared in which the oxygen atom(s) are replaced with carbon, or sulphur atoms.[4] Such analogues are of interest for biological studies, and we ourselves have been concerned with the synthesis of the analogues (**3**) and (**4**). Our strategy for the preparation of these compounds is shown in Scheme 1, and both analogues were approached *via* 8-oxabicyclo[3.2.1]oct-6-en-3-ones (**5a**) and (**5b**) prepared from the appropriate oxyallyls[5] and furans.

Our initial efforts were directed towards the synthesis of analogue (**3**). Cycloadduct (**5a**) was prepared by treatment of tetrachloroacetone with triethylamine in a mixture of furan and methanol,[6a,b] with subsequent reduction (zinc/copper couple in methanol containing NH_4Cl) of the trichloro cycloadduct (**6a**). Numerous attempts were made to alkylate the cycloadduct (**5a**) using lithium di-isopropylamide (LDA) and a variety of electrophiles (3-methyl but-2-enyl bromide, ethyl chloroformate, and methyl bromoacetate), but only in the case of ethyl chloroformate was any product isolated, and then in poor yield (30%). An approach *via* the *N,N*-dimethylhydrazone[7] of (**5a**) was also unsuccessful, and these results correspond closely with

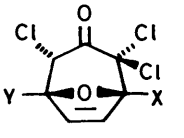


(**5a**) $R^1 = R^2 = H$
(**5b**) $R^1 = CH{=}CHPh$, $R^2 = CH(OMe)_2$
(**5c**) $R^1 = H$, $R^2 = CH(OMe)_2$

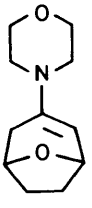
(**3**)

(**4**) R_u and R_l are upper and lower sidechains as in (**3**)

Scheme 1.



(**6a**) X = H, Y = H
(**6b**) X = $CH(OMe)_2$, Y = H
(**6c**) X = H, Y = $CH(OMe)_2$



(**7**)

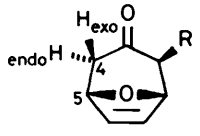
the obvious difficulties encountered by Ansell and co-workers[8] in their alkylation of the related compound (**7**).

The problem was finally solved by conversion of (**5a**) into its enol silyl ether (Me_3SiCl/DBU/refluxing dichloromethane, quantitative yields), and subsequent reaction with methyllithium and electrophiles. When methyl 7-iodoheptanoate was employed, the desired product (**8**) and the dialkylated product (**9**) were obtained as an inseparable mixture in a combined yield of 67%. A ratio of 4.4:1 for (**8**):(**9**) was estimated on the basis of

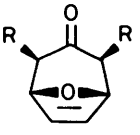
high resolution n.m.r. studies (see Table 1), in particular by integration of 1-H and 5-H. Compound (**8**) possessed two 4-H, and couplings of $J_{4\text{-}endo,5}$ 0.8 Hz, $J_{4\text{-}endo,2}$ 1.0 Hz (W coupling) and $J_{4\text{-}exo,1}$ 0.8 Hz (coupling through 5 bonds) were observed, as well as a geminal coupling of $J_{4,4}$ 16 Hz. The assignment of configuration (*exo*-substituents) in compounds (**8**) and (**9**) was not immediately clear from the *J* values, but MM2 calculations* carried out on (**8**) would appear to indicate a chair conformation with an axial alkyl group. Alkylation from the less hindered *exo* direction would also seem most reasonable.

With this key 2-substituted 8-oxabicyclo[3.2.1]oct-6-en-3-one in hand, we attempted to carry out a selective ozonolysis of (**8**) by the methods of Schreiber *et al.*[9] By incorporation of a variety of reagents in the ozonolysis mixture, these authors described the preparation of aldehydo esters, aldehyde acetals, and acetal esters from cycloalkenes. Attempts to prepare products of this kind from (**8**) were singularly unsuccessful and we could only obtain mixtures of the two possible hemiacetal acetals (**10**) which is completely in accord with our previous ozonolysis studies on similar bicyclo systems.[10]

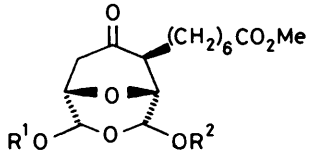
At about this time, Corey published[11] a synthesis of a structural isomer (**11**) of our target analogue, and stated that this was a TXA_2 agonist. It would be preferable to have antagonist activity, and this fact together with the difficulties encountered with the ozonolysis persuaded us to pursue another route.



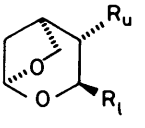
(**8**) R = $-(CH_2)_6CO_2Me$



(**9**) R = $-(CH_2)_6CO_2Me$



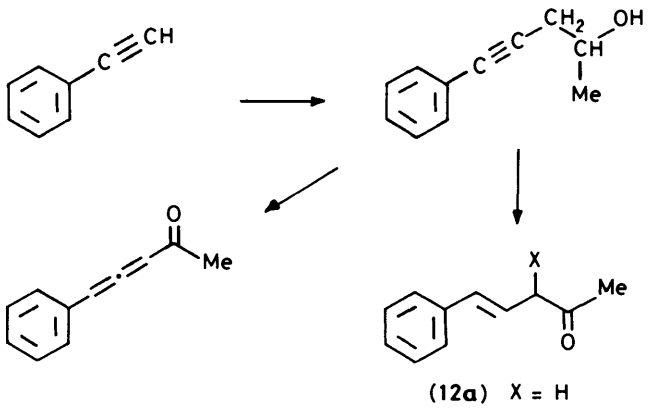
(**10**) R^1 = H, R^2 = Me
and
R^1 = Me, R^2 = H



(**11**)

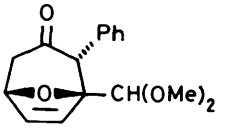
Our second strategy involved the use of the oxyallyl derived from (*E*)-3-bromo-5-phenylpent-4-en-2-one (**12b**), in conjunction with 2-(dimethoxymethyl)furan. We had already shown that the oxyallyl from 1-bromo-1-phenylpropan-2-one gave an excellent yield of cycloadduct (**13**) with this furan, and hoped that the new system, with an allylic rather than a benzylic halide, would prove to be useful in terms of regio- and stereo-selectivity. The desired cycloadduct (**5b**) would have suitable functionality for elaboration into the TXA_2 analogue (**4**).

In the event, the preparation of (**12b**) proved to be more difficult than anticipated. A published route[12] to (*E*)-5-phenylpent-4-en-2-one (**12a**) which employed a Knoevenagel reaction between phenylethanal and pentane-2,4-dione proceeded in at best an overall yield of 24% for two steps. An alternative sequence involving reaction of the acetal (**14**) (derived from 6-methylhept-5-en-2-one by acetalisation then ozonolysis)† with phenylmagnesium bromide produced the desired alcohol (**15a**), but this could not be cleanly dehydrated and deprotected to yield (**12a**). This was surprising since the corresponding chemistry with the acetal (**15b**) proceeded successfully.

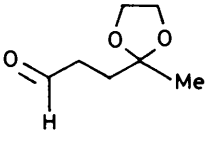


(**12a**) X = H
(**12b**) X = Br

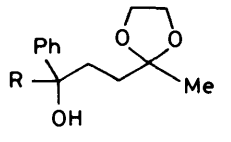
Scheme 2.



(**13**)



(**14**)



(**15a**) R = H
(**15b**) R = Ph

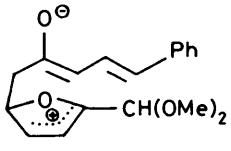
The problem was finally solved by using the route shown in Scheme 2, and only the oxidative step caused difficulty. If oxidation was carried out prior to reduction of the acetylene, an allene was produced in a crude yield of 90% (15% after flash chromatography), having i.r. bands at 1 935 and 1 680 cm^{-1}. Oxidation of the alkenol with pyridinium chlorochromate or Jones reagent proceeded in poor yield, but Collins oxidation,[13] with complete removal of pyridine prior to concentration of the reaction mixture, was very successful (greater than 90% yields).

With quantities of the alkenone (**12a**) available, bromination was carried out (NBS, CCl_4, dibenzoyl peroxide) to produce (**12b**). This was unstable and was always used immediately (and without purification) for cycloadditions with 2-dimethoxymethylfuran (15 equiv.) in 2,2,2-trifluoroethanol containing triethylamine (1.5 equiv.).[6b] The major cycloadduct (**5b**) was obtained with an overall yield of 26% for the two steps, while other isomers (regio- and stereo-) were obtained in a combined yield (for the two steps) of 14%. Obtention of this particular regioisomer (**5b**) accords with Hoffman's results (reviewed in ref. 5*a*), and with our previous synthesis of (**13**). Hoffmann proposed that when a cycloaddition is non-concerted, a bond forms first between the two least encumbered carbon centres. In the

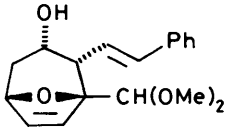
* We thank one of the referees for carrying out the MM2 calculations.
† This ozonolysis provided the acetal (**14**) and the interesting peroxide $Me_2C(OOCMe_2OO)$ without the need to add Me_2S or other reagents. The peroxide was a white crystalline solid (δ 1.6), and slowly disappeared with time, presumably *via* formation of acetone and O_2.

present instance the intermediate (**16**) is perhaps involved. The stereochemistry of the cycloadduct was not clear at this stage, but after reduction with potassium tri-s-butyl borohydride, the axial alcohol (**17**) was obtained, almost exclusively. We have always observed that the olefinic protons (6-H and 7-H) of axial alcohols of this kind resonate at lower field than the signals for the corresponding equatorial alcohols. Those for (**17**) resonated at 6.40 p.p.m., while those for the equatorial alcohol resonated at 6.10 p.p.m. The configuration of the side-chain was established using n.O.e. studies on compounds (**22a**) and (**23a**) (*vide infra*).

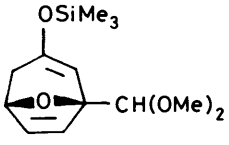
As an alternative approach to a suitably functionalised oxabicycle, we prepared the enol silyltrimethyl ethers (**18**) from cycloadduct (**5c**), and then alkylated this mixture using methyl lithium and (*Z*)-methyl 7-bromohept-5-enoate. The sole product was the unwanted regioisomer (**19**) whose ^{1}H n.m.r. exhibited a singlet for the 5-H proton, and other features fully consistent with the structure shown.



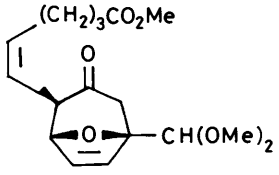
(**16**)



(**17**)

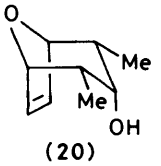


(**18a**) and isomer (**18b**)

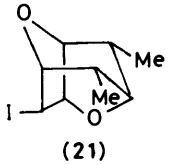


(**19**)

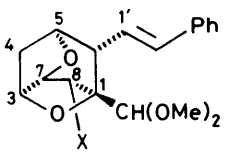
Returning to the main sequence, we had previously shown that iodoetherification of the alcohol (**20**) provided an excellent yield of the tricyclic compound (**21**). The same method was used to convert (**17**) into a mixture of iodoethers (**22a**) and (**23a**) in the ratio (3:2). Structure assignment was achieved through n.m.r. analysis, although shift similarities and the generally small, and in some cases long-range, couplings presented problems. 8-H in each case had to be identified by the distinctive ^{13}C chemical shift of 8-C, plus ^{13}C–^{1}H 2D heteronuclear correlation. Compound (**22a**) yielded positive nuclear Overhauser enhancements between 8-H and 1′-H, showing 8-H and 7-H to be mutually *trans*. 7-H was identified *via* its coupling to



(**20**)

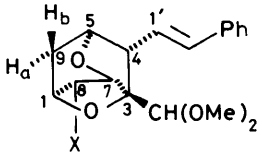


(**21**)



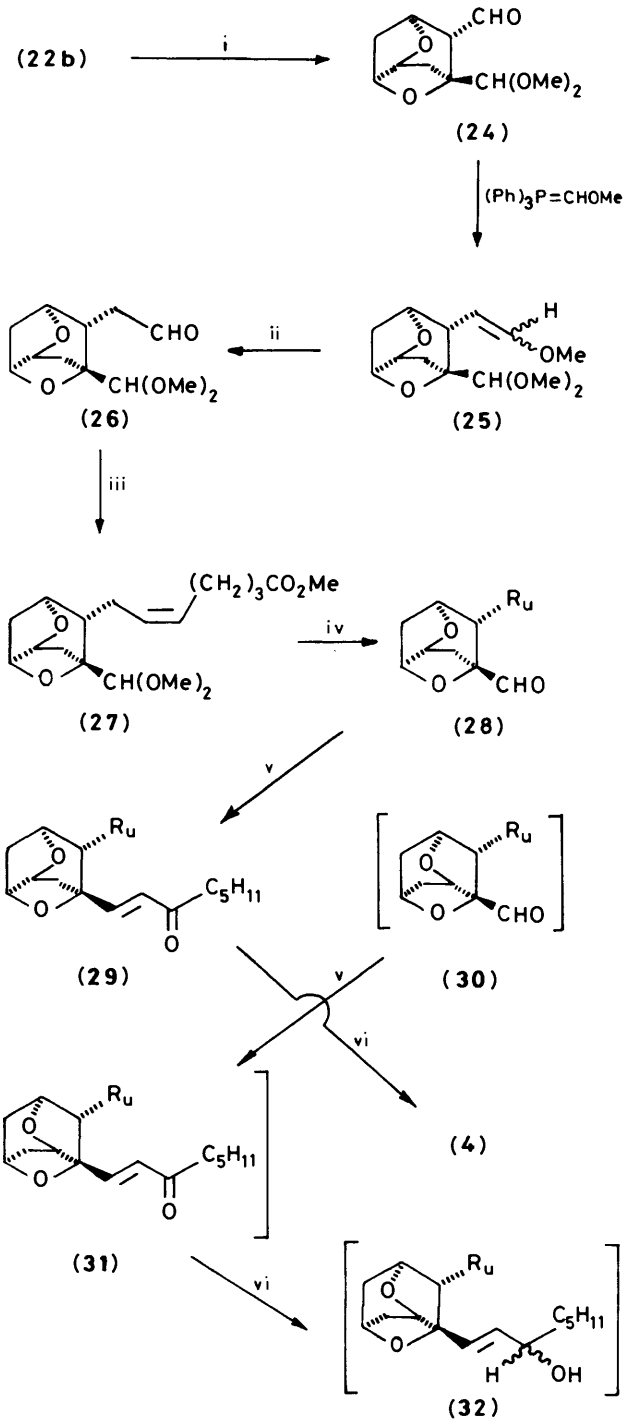
(**22a**) X = I

(**22b**) X = H



(**23a**) X = I

(**23b**) X = H

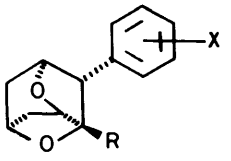


Scheme 3. *Reagents:* i, O_3/CH_2Cl_2, −78 °C then Me_2S; ii, aq. $Hg(OAc)_2$/THF then aq. KI; iii, $Ph_3P{=}CH(CH_2)_3CO_2K$, THF then CH_2N_2; iv, aq. HCl; v, $(MeO)_2POCH_2COC_5H_{11}$, NaH–THF; vi, $NaBH_4$–MeOH

3-H. N.O.e's were as expected except for the absence of 4a-H to 7-H due to a competing 3-spin effect *via* the strongly-enhanced 3-H. Small long-range couplings were observed *via* COSY-45 between 4b-H and 7-H (^4J,W) and even between 4b-H and 8-H (^5J). Compound (**23a**) showed a definite but weaker n.O.e. between 7-H and 1′-H, consistent with their increased separation compared with compound (**22a**). It also showed a small W-coupling (*via* COSY) between 5-H and 7-H and a

substantial n.O.e. but no W-coupling between 9a-H and 8-H, confirming the configuration at 8-C.

Each isomer was now reduced (Bu_3SnH) to yield (**22b**) and (**23b**) respectively, then taken through to the TXA_2 analogues (**4**) and (**32**) using standard prostanoid methodology.[1,4] The sequence is shown (for **22b**) in Scheme 3, and the only step which remains to be optimised is the deprotection of the acetal. Both analogues (as mixtures of epimers at C-15) were tested for biological activity using rabbit platelet-rich plasma. Aggregation of platelets induced by ADP or collagen was potentiated in each instance, and the analogues appear to be acting as TXA_2 agonists. These disappointing results, notwithstanding, the route described does, in principle, allow access to TXA_2 analogues with a variety of side-chains; and compounds of general type (**33**) are easily accessible. These are of interest since prostanoids with a benzene ring inserted into the upper side-chain show interesting biological activity.[14]



(**33**)

Experimental

I.r. spectra were recorded with a Perkin-Elmer 157 double-beam grating spectrophotometer (liquid films for oils and Nujol mulls for solids). ^1H N.m.r. spectra were recorded with a Varian T-60 (60 MHz), Varian HA 100 (100 MHz) instruments, or with a Perkin-Elmer R34 (220 MHz) instrument (tetramethylsilane as internal standard), and unless otherwise stated, all spectra were recorded in deuteriochloroform. Mass spectra were recorded on an A.E.I. MS12 spectrometer. Kieselgel $GF_{254+\ 354}$(Merck) was used for analytical t.l.c., and flash chromatography was performed with Merck silica gel (230—400 mesh). Organic solvents were distilled from calcium hydride when required anhydrous. Light petroleum refers to the fraction boiling in the range 40—60 °C. The abbreviation f.c.c. stands for flash column chromatography.

2,2,4-endo-*Trichloro*-8-*oxabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (**6a**).—In a typical experiment, 1,1,3,3-tetrachloroacetone (TCA) (8.1 ml, 12.93 g, 66 mmol) was added dropwise to a stirred solution of Et_3N (13.8 ml, 10.02 g, 99 mmol) in furan (72 ml) and MeOH (72 ml), under N_2. After addition was complete (*ca.* 40 min), the solution was stirred for 24 h, and then poured into water (600 ml), and extracted with ether (5 × 100 ml). The combined ether extracts were washed with saturated brine (100 ml), dried, and concentrated to a volume of *ca.* 200 ml. After charcoal decolourisation and filtration (Hyflo), concentration gave a pale yellow oil. Addition of ether (10 ml) and light petroleum (10 ml), followed by refrigeration (*ca.* 4 °C) gave the product as a white crystalline solid; these crystals were collected and dried, (3.73 g). Using a similar trituration method, two more crops of crystals were obtained, which were combined and recrystallised to give a further product (2.25 g). Purification of the remaining mother liquor by f.c.c., using 20% ether in light petroleum as eluant gave a further product (1.45 g; total yield 7.43 g, 49%). T.l.c. using petroleum–ether (4:1) gave R_F 0.32, m.p. 88 °C (hexane) (lit.,[6b] m.p. 88—89 °C); $\nu_{max.}(CH_2Cl_2)$ 1 760, 1 335, 1 110, 915, 900, and 855 cm^{-1}; δ (100 MHz; C_6D_6) 4.40 (1 H, dd, $J_{1,2}$ 5 Hz, $J_{1,7}$ 1.5 Hz, 1-H), 4.55 (1 H, d, *J* 5 Hz, 1-H), 4.65 (1 H, d, $J_{5,6}$ 1.5 Hz, 5-H), 5.80 (1 H, dd, $J_{6,7}$ 6 Hz, 6-H), and 5.90 (1 H, dd, 7-H).

8-*Oxabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (**5a**).—In a typical experiment, Zn/Cu couple was prepared as follows: zinc powder (59.93 g, 0.92 mol) was added to a hot, stirred solution of copper(II) acetate monohydrate (3.433 g, 17.2 mmol) in glacial AcOH (300 ml). After being stirred for 1 min, the mixture was cooled, and the AcOH decanted. The Zn/Cu couple was then washed successively with glacial AcOH (250 ml) and ether (5 × 200 ml), with careful decantation after each washing. The resulting Zn/Cu couple was then transferred, as a slurry, with saturated methanolic NH_4Cl (*ca.* 100 ml) into a flask containing the cycloadduct (**6a**) (7.43 g, 32.6 mmol) in saturated methanolic NH_4Cl (150 ml). After being stirred (overhead stirrer) for 16 h, the solution was filtered (Hyflo), and aqueous disodium ethylenediaminetetra-acetate (EDTA) (300 ml; 7% w/v) was added. The solution was then extracted with CH_2Cl_2 (200 ml + 2 × 100 ml), and the combined extracts were dried, concentrated, and purified by f.c.c., using 20% light petroleum–ether as eluant, to give the product (**5a**) as an oil, which crystallised with time (3.82 g, 94%). T.l.c. in ether–petroleum (4:1) gave R_F 0.31, m.p. 38 °C (lit.,[6b,15] 38 °C); $\nu_{max.}(CH_2Cl_2)$, 3 060w, 2 970w, 1 715, 1 610vw, 1 340, 1 180, 950, and 850 cm^{-1}; δ (100 MHz) 2.31 (2 H, d, *J* 16 Hz, 2-H_{endo} and 4-H_{endo}), 2.77 (2 H, dd, *J* 16 Hz and 5 Hz, 2-H_{exo} and 4-H_{exo}), 5.04 (2 H, d, *J* 5 Hz, 1-H and 5-H), and 6.27 (2 H, s, 6-H and 7-H).

3-*Trimethylsiloxy*-8-*oxabicyclo*[3.2.1]*octa*-2,6-*diene*.—In a typical experiment, Me_3SiCl (0.48 ml, 0.41 g, 3.75 mmol) was added to a stirred, refluxing solution of the ketone (**5a**) (310 mg, 2.5 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.58 ml, 0.59 g, 3.85 mmol) in dry CH_2Cl_2 (4 ml), under N_2. After 1 h, the solution was cooled, taken up in light petroleum (20 ml), and washed successively with aqueous HCl (0.5M; 5 ml) and saturated aqueous $NaHCO_3$ (5 ml). The petroleum extract was then dried and concentrated to leave a pale yellow oil (472 mg, 96%). N.m.r. analysis indicated that only a trace of (**5a**) was present, so the product was used without further purification. T.l.c. using ether–light petroleum (1:1) gave R_F 0.55; $\nu_{max.}(CCl_4)$ 3 070w, 2 970, 1 640, 1 360, 1 255, 1 205, 1 060, 890, 850, and 705 cm^{-1}; δ (220 MHz; $CHCl_3$ as internal standard) 0.04 (9 H, s, 3 × Me), 1.55 (1 H, d, *J* 17 Hz, 4-H_{endo}), 2.51 (1 H, dd, *J* 17 Hz and 5 Hz, 4-H_{exo}), 4.72 (1 H, dd, $J_{1,2}$ 5 Hz, $J_{1,7}$ 2 Hz, 1-H), 4.85 (1 H, dd, $J_{5,4exo}$ 6 Hz, $J_{5,6}$ 2 Hz, 5-H), 5.15 (1 H, dt, *J* 5 Hz, 2-H), 5.86 (1 H, dd, $J_{6,7}$ 6 Hz, *J* 2 Hz, 6-H), and 6.42 (1 H, dd, *J* 6 Hz and 2 Hz, 7-H).

2-exo-(6′-*Methoxycarbonylhexyl*)-8-*oxabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (**8**).—MeLi (1.6M soln. in ether; 4.80 ml, 7.65 mmol) was added dropwise to a stirred solution of the silyl enol ether (1.362 g, 6.95 mmol) in dry THF (25 ml), at −78 °C and under N_2. The solution was stirred at −78 °C for 1 h and then at −78 to −30 °C over 1.5 h. A solution of methyl 7-iodoheptanoate (5.63 g, 20.9 mmol) in dry HMPA (8 ml) was added, all at once, and the solution allowed to warm to 0 °C. After 1 h at 0 °C, water (150 ml) was added, and the solution was extracted with light petroleum (2 × 50 ml). The combined petroleum extracts were dried, concentrated, and purified by f.c.c., using 50% light petroleum in ether as eluant, to give the products (**8**) + (**9**), together with recovered iodo ester. High resolution n.m.r. analysis showed that the product contained about 20% of the dialkylated product (**9**) [Yield 1.347 g, 58% of (**8**) + 9% of (**9**)]. T.l.c. using ether–petroleum (1:1) gave R_F 0.22; $\nu_{max.}$(thin film) 2 940, 2 860, 1 740, 1 715, and 1 180 cm^{-1}; n.m.r. (400 MHz)—see Table 1; *m/z* (%) 266.1515(4) ($C_{15}H_{22}O_4$ requires *M*, 266.1518).

5-*Phenylpent*-4-*yn*-2-*ol*.—In a typical experiment, BuLi (9.5M soln. in hexane; 20 ml, 0.19 mol) was added to a stirred solution of phenylacetylene (20.87 ml, 19.41 g, 0.19 mol) in dry THF (200

Table 1.

Signal (δ, p.p.m.)	Multiplicity	*J* (Hz)	Proton assignment (8)	Proton assignment (9)
1.28—1.50	complex m	—	2-H, 1′-H, 5′-H	2-H, 4-H, 1′-H, 5′-H
1.58—1.83	complex m	—	2′-H, 3′-H, 4′-H	2′-H, 3′-H, 4′-H
2.24	d	16 Hz	4-H_{endo}	—
2.30	t	7.6 Hz	6′-H	—
2.30(5)	t	7.6 Hz	—	6′-H
2.79	dd	16 Hz, 5 Hz	4-H_{exo}	—
3.63	s	—	CO_2Me	2 × CO_2Me
4.74	s	—	—	1-H, 5-H
4.79	s	—	1-H	—
4.98	d	5 Hz	5-H	—
6.23	s	—	—	6-H, 7-H
6.26	s	—	6-H, 7-H	—

Other small couplings are mentioned in the text.

ml) at 0 °C, under N_2. After addition was complete (*ca.* 15 min) the solution was stirred at 0 °C for 45 min and then cooled to −78 °C. A solution of 1,2-epoxypropane (42 ml, 34.85 g, 0.60 mol) in dry HMPA (50 ml) was added, and the solution allowed to warm slowly to room temperature (*ca.* 1 h). After being stirred for 1 h at room temperature, the reaction mixture was poured into water (600 ml), and extracted with light petroleum (3 × 150 ml). The combined light petroleum extracts were dried and concentrated to give the crude product as a pale brown oil. Dissolution in ether (20 ml) and light petroleum (100 ml) followed by refrigeration (−15 °C) gave, after filtration and drying, white crystals (19.42 g). Concentration of the mother liquor followed by further trituration/cooling gave a second crop (5.26 g) of crystals. Purification of the remaining mother liquor concentrate (by f.c.c.) gave a further product (4.81 g), as an off-white solid (total yield 29.49 g, 97%). A small amount of the product was recrystallised for spectral purposes, giving lustrous white crystals. T.l.c. using ether–light petroleum (3:2) gave R_F 0.31; 0.41 [ether–light petroleum (2:1)], m.p. 33—34 °C (hexane); lit.,[16] m.p. 37 °C; $\nu_{max.}$(CH_2Cl_2) 3 600, 3 450br, 2 970, 2 930, 2 250w, 1 600w, 1 490, 910, 735, and 695 cm^{-1}; δ (60 MHz) 1.30 (3 H, d, *J* 6 Hz, Me), 2.35 (1 H, br s, OH), 2.55 (2 H, d, *J* 6 Hz, CH_2), 4.00 (1 H, sep, *J* 6 Hz, CH), and 7.05—7.50 (5 H, m, Ph); *m/z* 160 (M^+), 116, 115, and 45.

Attempted Oxidation of 5-*Phenylpent*-4-*yn*-2-*ol*.—A solution of the alcohol (850 mg, 5.3 mmol) in CH_2Cl_2 (5 ml) was added to a stirred suspension of PCC (1.724 g, 8 mmol) in CH_2Cl_2 (10 ml). After being stirred for 5 h, the solution was diluted with ether (75 ml), filtered (Hyflo), concentrated, and purified by f.c.c., using light petroleum–ether (3:1) as eluant, to give a yellow oil (128 mg, 15%). Spectroscopic analysis showed the compound to be the allene 5-phenylpenta-3,4-dien-2-one; T.l.c. using light petroleum–ether (3:1) gave R_F 0.36; $\nu_{max.}$ (thin film) 2 990, 2 920, 1 935, 1 680, 1 600, 1 360, 1 230, 785, 735, and 695 cm^{-1}; δ (60 MHz) 2.30 (3 H, s, Me), 6.10 (1 H, d, *J* 6 Hz, 3-H), 6.60 (1 H, d, *J* 6 Hz, 5-H), and 7.30 (5 H, s, Ph); *m/z* 158 (M^+), 116, 115, 43.

(E)-5-*Phenylpent*-4-*en*-2-*ol*.—In a typical reaction, a solution of $LiAlH_4$ in THF (1M soln.; 100 ml, 100 mmol) was added, dropwise until effervescence ceased, to a stirred solution of 5-phenylpent-4-yn-2-ol (4.00 g, 25 mmol) in dry THF (150 ml), at 0 °C and under N_2. When addition was complete, the solution was heated under reflux, and progress of the reaction was monitored using g.l.c. On completion of reaction (3—5 h) the solution was cooled to 0 °C, and worked up by dropwise and sequential addition of ice-cooled water (20 ml), aqueous HCl (2M; 20 ml), further water (200 ml), and aqueous HCl (2 M; 100 ml). The solution was then extracted with CH_2Cl_2 (3 × 200 ml), and the combined extracts were washed with saturated aqueous $NaHCO_3$ (150 ml) and saturated brine (150 ml), dried, and concentrated to give the product as a colourless oil (4.47 g, quantitative), which could be used in subsequent reactions without purification. T.l.c. using ether–light petroleum (3:2) gave R_F 0.31; $\nu_{max.}$ (thin film) 3 380br, 2 980, 2 940, 1 600w, 1 450, 1 130, 1 080, 970, 750, and 700 cm^{-1}; δ (60 MHz) 1.25 (3 H, d, *J* 6 Hz, Me), 2.25 (1 H, br s, OH), 2.35 (2 H, t, *J* 6 Hz, CH_2), 3.90 (1 H, sext, *J* 6 Hz, 2-H), 6.10 (1 H, dd, *J* 16 Hz and 6 Hz, 4-H), 6.50 (1 H, d, *J* 16 Hz, 5-H), and 7.10—7.45 (5 H, m, Ph).

(E)-5-*Phenylpent*-4-*en*-2-*one* (**12a**).—Collins reagent was prepared by adding CrO_3 (18.13 g, 0.181 mol) to a stirred solution of pyridine (29.2 ml, 28.7 g, 0.363 mol) in CH_2Cl_2 (800 ml). After being stirred for 30 min (overhead stirrer), a solution of (*E*)-5-phenylpent-4-en-2-ol (90% purity; 4.079 g, 22.7 mmol) in CH_2Cl_2 (50 ml) was added, and vigorous stirring was continued for 3 h. The solution was then decanted from the black, tarry material and washed with aqueous HCl (2M; 250 ml). Concentration gave an oil, which was taken up in light petroleum (250 ml), dried, filtered through Hyflo, and concentrated to give the product as a pale yellow oil (3.34 g, 92%), pure by t.l.c. and n.m.r. analysis. T.l.c. using light petroleum–ether (2:1) gave R_F 0.25, 0.32 [light petroleum–ether (1:1)]; $\nu_{max.}$ (thin film) 2 960, 2 920, 1 720, 1 600, 1 580, 1 500, 1 450, 1 360, 1 225, 1 160, 970, 750, and 690 cm^{-1}; δ (100 MHz) 2.14 (3 H, s, Me), 3.29 (2 H, d, *J* 6 Hz, CH_2), 6.22 (1 H, dd, *J* 16 Hz and 6 Hz, 4-H), 6.48 (1 H, d, *J* 16 Hz, 5-H), and 7.14—7.44 (5 H, m, Ph); *m/z* (%) 160.0889 (25) (M^+; $C_{11}H_{12}O$ requires *M* 160.0888), 117.0695 (100) (M^+ − MeCO; C_9H_9 requires 117.0705).

(E)-3-*Bromo*-5-*phenylpent*-4-*en*-2-*one* (**12b**).—In a typical experiment, NBS (2.14 g, 12 mmol) and benzoyl peroxide (few mg, catalytic amount) were added to a solution of (*E*)-5-phenylpent-4-en-2-one (**12a**) (1.92 g, 10 mmol) in CCl_4 (40 ml), and the solution was heated under reflux in the absence of light for 1 h; it was then stirred at room temperature until all the NBS had been converted into succinimide (0—3 h). After this the mixture was filtered and concentrated, and the crude bromide (**12b**) used immediately in the cycloaddition reactions. T.l.c. using ether–light petroleum (1:1) gave R_F 0.43; δ (60 MHz) 2.40 (3 H, s, Me), 5.00 (1 H, d, *J* 8 Hz, CHBr), 6.40 (1 H, dd, *J* 16 Hz and 8 Hz, 4-H), 6.70 (1 H, d, *J* 16 Hz, 5-H), and 7.35 (5 H, m, Ph).

2-*Dimethoxymethylfuran*.—A mixture of freshly distilled 2-furaldehyde (175 ml, 203 g, 2.1 mol), trimethyl orthoformate (253 ml, 245 g, 2.3 mol), and anhydrous NH_4Cl (10.5 g) in AnalaR MeOH (250 ml) was heated under reflux for 3 h. It was then cooled and refrigerated, the precipitated solid filtered off, and the filtrate concentrated, re-filtered and distilled under reduced pressure, to give a quantitative yield of the product, b.p. 63—64 °C at *ca.* 15 mmHg, (lit.,[17] b.p. 62 °C at 12 mmHg). The product was bottled under N_2, and kept in the dark for subsequent use. T.l.c. using ether–light petroleum (1:1) gave R_F 0.49; $\nu_{max.}$ (thin film) 2 940w, 2 835w, 1 190, 1 150, 1 110, 1 060, 980, and 740 cm^{-1}; δ (60 MHz) 3.35 (6 H, s, 2 × OMe), 5.40 [1 H, s, C*H*$(OMe)_2$], 6.35 (2 H, m, 3-H and 4-H), and 7.40 (1 H, m, 5-H).

2,2,4-endo-*Trichloro*-1-*dimethoxymethyl*-8-*oxabicyclo*-[3.2.1]*oct*-6-*en*-3-*one* (**6b**) *and the* 2-endo-4,4-*Trichloro-isomer* (**6c**).—1,1,3,3-Tetrachloroacetone (TCA) (2.0 ml, 3.19 g, 16 mmol) was added dropwise to a stirred solution of Et_3N (4.5 ml,

3.27 g, 32 mmol) in 2,2,2-trifluoroethanol (TFE) (30 ml) and 2-dimethoxymethylfuran (30 ml), under N_2. The mixture was stirred for 75 min after which t.l.c. analysis showed that no TCA was left; after distilling off the TFE (room temperature *ca.* 15 mmHg; condensed in ice–salt-cooled trap), and most of the furan (60—70 °C at *ca.* 15 mmHg), the dark brown oily residue was dissolved in CH_2Cl_2 (100 ml), washed with water (40 ml), dried, and concentrated to give the crude product. More of the furan was removed under reduced pressure (0.1 mmHg; flask heated with heat-gun), and the residue was purified by f.c.c., using 50% light petroleum in ether as eluant, to give the product as a pale brown crystalline solid (3.1 g, *ca.* 64%). Since n.m.r. analysis indicated that there were two isomers present, a small portion of the product was further purified by f.c.c., using CH_2Cl_2–light petroleum–ether (80:18:2%) as eluant, to give the two isomers (**6b**) and (**6c**). These were both recrystallised to give white crystalline solids.

Data for (**6b**). M.p. 80—82 °C (hexane), T.l.c. using ether–light petroleum (1:1) gave R_F 0.29; 0.38 [CH_2Cl_2–light petroleum:ether (80:18:2)]; $\nu_{max.}$(CH_2Cl_2) 2 940, 2 840w, 1 765, 1 120, 1 080, 940, 910, 850, and 730 cm^{-1}; δ (220 MHz) 3.56 and 3.58 (6 H, 2 × s, 2 × OMe), 5.06 [1 H, s, C*H*(OMe)$_2$], 5.19 (1 H, d, *J* 4.5 Hz, 4-H), 5.24 (1 H, dd, $J_{4,5}$ 4.5 Hz, $J_{5,6}$ 1.5 Hz, 5-H), 6.51 (1 H, d, $J_{6,7}$ 6 Hz, 7-H), and 6.58 (1 H, dd, *J* 6 Hz and 1.5 Hz, 6-H); *m/z* (%) no M^+ observed. 272.9485 (1) (M^+ − OMe; $C_9H_8O_3{}^{35}Cl^{37}Cl_2$ requires 272.9480) and 270.9593 (4) (M^+ − OMe; $C_9H_8O_3{}^{35}Cl_2{}^{37}Cl$ requires 270.9510).

Data for (**6c**). *M.p.* 86—88 °C (hexane); T.l.c. using ether–light petroleum (1:1) gave R_F 0.29; 0.34 [CH_2Cl_2–light petroleum–ether (80:18:2); $\nu_{max.}$(CH_2Cl_2) 2 940, 2 840w, 1 760, 1 195, 1 110, 1 080, 1 025, 910, 865, 855, and 730 cm^{-1}; δ (220 MHz) 3.55 and 3.62 (6 H, 2 × s, 2 × OMe), 4.92 [1 H, s, C*H*(OMe)$_2$], 5.25 (1 H, s, 2-H), 5.28 (1 H, s, 5-H), and 6.50 (2 H, s, 6-H and 7-H). Expansion shows small coupling of 5-H to 6-H, J < 1 Hz.

1-*Dimethoxymethyl*-8-*oxabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (**5c**).—Reductive dechlorination of (**6b**)/(**6c**) mixture. The Zn/Cu couple was added, as a slurry in methanolic saturated NH_4Cl (50 ml), to a stirred solution of (**6b**)/(**6c**) (3.10 g, 10.3 mmol) in methanolic saturated NH_4Cl (25 ml). After being stirred for 68 h, the mixture was filtered (Hyflo); the filtrate was then added to aqueous Na_2EDTA (7%, w/v; 150 ml), and extracted with CH_2Cl_2 (150 ml + 25 ml). The combined CH_2Cl_2 extracts were washed with saturated aqueous $NaHCO_3$ (50 ml), dried, and concentrated to give an essentially quantitative yield of the product as a colourless oil (2.1 g). A small portion of the product was purified by f.c.c., using 25% light petroleum in ether as eluant, for characterisation. T.l.c. using ether–light petroleum (3:1) gave R_F 0.25, $\nu_{max.}$ (CH_2Cl_2 soln.) 2 960, 2 940, 2 840w, 1 715, 1 180, and 855 cm^{-1}; δ (220 MHz) 2.32 (1 H, d, *J* 17 Hz, 2-H_{exo} or $_{endo}$), 2.46 (1 H, d, *J* 17 Hz, 2-H_{endo} or $_{exo}$), 2.76 (2 H, d + dd, *J* 17 Hz, $J_{4exo,5}$ 5 Hz, 4-H_{endo} + 4-H_{exo}), 3.57 and 3.60 (6 H, two s, 2 × OMe), 4.40 [1 H, s, C*H*(OMe)$_2$], 5.15 (1 H, dd, $J_{5,6}$ 1.5 Hz, 5-H), 6.24 (1 H, d, $J_{6,7}$ 6 Hz, 7-H), and 6.30 (1 H, dd, 6-H); *m/z* (%) no M^+ observed, 167.0703 (7) (M^+ − OMe: $C_9H_{11}O_3$ requires 167.0708).

1-*Dimethoxymethyl*-3-*trimethylsiloxy*-8-*oxabicyclo*[3.2.1]-*octa*-2,6-*diene* (**18a**) *and the* -3,6-*diene* (**18b**).—Me_3SiCl (0.38 ml, 0.326 g, 3.0 mmol) was added to a stirred, refluxing mixture of the ketone (**5c**) (396 mg, 2.0 mmol) and DBU (0.46 ml, 0.468 g, 3.1 mmol) in CH_2Cl_2 (5 ml), under N_2. After 30 min, the solution was cooled, taken up in light petroleum (30 ml) and washed successively with aqueous HCl (0.5M; 5 ml) and saturated aqueous $NaHCO_3$ (5 ml). The light petroleum extract was then dried and concentrated to give the crude product as a pale brown oil (490 mg). N.m.r. analysis indicated the presence of a small amount of (**5c**) (*ca.* 8%, from integration of the olefinic signal at δ 6.20 p.p.m.), and also showed the product to be a mixture of the 2,6- and 3,6-diene isomers (**18a**) and (**18b**), in a ratio of *ca.* 1:1 [from relative integrations of C*H*(OMe)$_2$ protons]. T.l.c. using light petroleum–ether (2:1) gave R_F's 0.33 and 0.26; δ (60 MHz; CCl_4; C*H*Cl_3 as internal standard) 0.10 (18 H, s, 2 × OSiMe$_3$), 1.40—2.80 [4 H, complex m, 4-H of (**18a**) + 2-H of (**18b**)], 3.50 (12 H, s, 4 × OMe), 4.30 [1 H, s, C*H*(OMe)$_2$], 4.40 [1 H, s, C*H*(OMe)$_2$], 4.80—5.40 [4 H, complex m, 2-H of (**18a**) + 4-H of (**18b**) + 2 × 5-H (both isomers)], 5.90 [2 H, d, *J* 6 Hz, 7-H (both isomers)], and 6.20 [2 H, dd, *J* 6 Hz and 2 Hz, 6-H (both isomers)].

Alkylation of Trimethylsilyl Enol Ethers (**18a**)/(**18b**).—MeLi (1.6M in ether; 1.0 ml, 1.6 mmol) was added dropwise to a stirred solution of the mixture of (**18a**) and (**18b**) (430 mg, 1.5 mmol) in dry THF (10 ml), at −78 °C and under N_2. After being stirred for 1 hour at —78 °C, the solution was allowed to warm to −50 °C, and a solution of (*Z*)-methyl 7-bromohept-5-enoate (968 mg, 4.4 mmol) in dry HMPA (3 ml) was added. The solution was allowed to warm to −20 °C (over 30 min), and then to 0 °C (over 30 min), by which time t.l.c. analysis showed no starting material to be left. Water (50 ml) was added, and the mixture was extracted with light petroleum (2 × 40 ml); the combined light petroleum extracts were then dried, concentrated, and purified by f.c.c., using 50% light petroleum in ether as eluant, to give the product (**19**) (201 mg, 41%), together with a mixture of (**19**) and ketone (**5c**) (35 mg), and unchanged bromide (493 mg, 51% recovery). T.l.c. using ether–light petroleum (1:1) gave R_F 0.21; $\nu_{max.}$ (thin film) 2 960, 2 840w, 1 740, 1 715, 1 200, 1 175, and 1 080 cm^{-1}; δ (220 MHz): 1.62—1.88 (2 H, complex m, 5′-H), 2.07—2.72 (5 H, complex m, 4′-H, 1′-H, 4-H), 2.32 (2 H, t, *J* 7 Hz, 6′-H), 2.36 (1 H, d, *J* 16 Hz, 2-H_{endo}), 2.73 (1 H, d, *J* 16 Hz, 2-H_{exo}), 3.51 and 3.55 (6 H, two s, 2 × OMe), 3.65 (3 H, s, CO_2Me), 4.40 [1 H, s, C*H*(OMe)$_2$], 4.84 (1 H, s, 5-H), 5.36—5.58 (2 H, complex m, 2′-H and 3′-H), 6.18 (1 H, d, *J* 6 Hz, 7-H), and 6.23 (1 H, d, *J* 6 Hz, 6-H); *m/z* (%): no M^+ observed. 307.1536 (1) (M^+ − OMe; $C_{17}H_{23}O_5$ requires 307.1546), 306.1467 (5) (M^+ − MeOH; $C_{17}H_{22}O_5$ requires 306.1467).

1-*Dimethoxymethyl*-2-endo-[(E)-1′-*styryl*]-8-*oxabicyclo*-[3.2.1]*oct*-6-*en*-3-*one* (**5b**).—In a typical experiment, the crude bromide (**12b**) [product from the alkene (**12a**) (1.920 g, 12 mmol)] was dissolved in 2-dimethoxymethylfuran (8 ml) and added to a stirred solution of Et_3N (2.51 ml, 1.82 g, 18 mmol) in trifluoroethanol (24 ml) and 2-dimethoxymethylfuran (16 ml), at 0 °C and under N_2. The mixture was allowed to warm to room temp. and stirred for 20 h; it was then poured into water (200 ml) and extracted with light petroleum (2 × 100 ml). The combined light petroleum extracts were dried, concentrated, and purified by f.c.c., using decreasing percentages (50, 30, 20%) of light petroleum in ether as eluant, to give the product as a pale yellow oil, which crystallised with time [780 mg, 26% from alkene (**12a**), together with the *exo* isomer (270 mg, 9%), and a stereoisomeric mixture of the regioisomers (120 mg, 4%)]. T.l.c. using ether–light petroleum (4:1) gave R_F 0.23, m.p. 108 °C (hexane) (Found: C, 71.8; H, 6.70. $C_{18}H_{20}O_4$ requires: C, 72.0; H, 6.70%); $\nu_{max.}$ (thin film) 2 960, 2 940, 1 715, 1 600w, 1 170, 1 080, 1 015, 970, 750, and 700 cm^{-1}; δ (220 MHz) 2.42 (1 H, d, *J* 16 Hz, 4-H_{endo}), 2.85 (1 H, dd, *J* 16 Hz and 5 Hz, 4-H_{exo}), 3.50 (3 H, s, OMe), 3.56 (3 H, s, OMe), 3.73 (1 H, d, *J* 10 Hz, 2-H), 4.64 [1 H, s, C*H*(OMe)$_2$], 5.25 (1 H, br d, *J* 5 Hz, 5-H), 5.93 (1 H, dd, *J* 16 Hz and 10 Hz, 1′-H), 6.30 (1 H, d, *J* 6 Hz, 7-H), 6.42 (1 H, d, *J* 6 Hz, 6-H), 6.58 (1 H, d, *J* 16 Hz, 2′-H), and 7.26—7.52 (5 H, complex m, Ph).

1-*Dimethoxymethyl*-3-endo-*hydroxy*-2-endo-[(E)-1′-*styryl*]-8-*oxabicyclo*[3.2.1]*oct*-6-*ene* (**17**).—In a typical experiment, potassium tri-s-butylborohydride (K-Selectride) (1M soln. in

THF; 15.4 ml, 15.4 mmol) was added, over *ca.* 10 min, to a stirred solution of the ketone (**5b**) (2.31 g, 7.7 mmol) in dry THF (50 ml), at −78 °C and under N_2. The solution was then allowed to warm to 0 °C and stirred for 4 h at this temperature. A solution of NaOH (10%, w/v; 20 ml) was added, followed by H_2O_2 (30%, v/v; 15 ml), and the mixture was allowed to warm to room temperature and stirred for a further 1 h. The aqueous layer was then separated, and extracted with ether (2 × 50 ml). The combined organic layers were then washed with water (50 ml), saturated aqueous $Na_2S_2O_5$ (50 ml), and brine (50 ml), dried and concentrated to give the crude product (**17**) as a pale brown oil, in quantitative yield (2.74 g). The product was used without further purification. T.l.c. using ether gave R_F 0.27; $\nu_{max.}$ (thin film) 3 480br, 2 950, 2 840w, 1 600, 1 200, 1 080, 1 040, 760, 740m, and 700 cm^{-1}; δ (60 MHz) 1.60—2.30 (4 H, complex m, 2-H + 4-H + OH), 3.20 and 3.30 (6 H, 2 × s, 2 × OMe), 4.00 (1 H, m, 3-H), 4.40 (1 H, s, C*H*(OMe)$_2$], 4.90 (1 H, m, 5-H), 5.90 (1 H, dd, *J* 16 Hz and 10 Hz, 1′-H), 6.40 (2 H, s, 6-H and 7-H), 6.60 (1 H, d, *J* 16 Hz, 2′-H), and 7.10—7.50 (5 H, complex m, Ph).

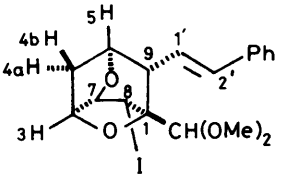
Iodoetherification of the Alcohol (**17**).—The alcohol (**17**) (1.195 g, 3.96 mmol) was dissolved in CH_2Cl_2 (20 ml) and aqueous $KHCO_3$ (10 ml, 10%, w/v) was added followed, with vigorous stirring, by I_2 (1.005 g, 3.96 mmol). After 30 min, the mixture was taken up in further CH_2Cl_2 (30 ml) and washed with aqueous $Na_2S_2O_3$ (2 × 30 ml). The organic layer was then dried, concentrated, and purified by f.c.c., using 20% ether in light petroleum as eluant, to give the tricyclic iodide (**22a**) (474 mg), the isomeric tricycle (**23a**) (190 mg), and a mixture of the two (564 mg); total yield 1.228 g [72% from the ketone (**5b**)]. [N.B. For all of the remaining compounds in this experimental section, the tricyclic ring system has been named by assigning each individual chiral carbon centre as either *R* or *S*, thus depicting the absolute stereochemistry of each centre; all the compounds were obtained and used as their unresolved racemates.]

Data for (1S,3S,5S,7R,8S,9S)-1-*Dimethoxymethyl*-8-*iodo*-9-[(E)-1′-*styryl*]-2,6-*dioxatricyclo*[3.3.1.0^{3,7}]*nonane* (**22a**).—T.l.c. using ether gave R_F 0.65, 0.27 [light petroleum–ether (4:1)], m.p. 125—126 °C (Found: C, 50.6; H, 4.95. $C_{18}H_{21}IO_4$ requires C, 50.5: H, 4.90); $\nu_{max.}$(CCl$_4$) 3 000, 2 040, 2 840w, 1 605, 1 110, 1 085, 1 055, 1 000, 960, 880, 710, and 695 cm^{-1}; n.m.r. (220 MHz): see Table 2.

Data for (1S,3R,4S,5S,7S,8S)-3-*Dimethoxymethyl*-8-*iodo*-4-[(E)-1′-*styryl*]-2,6-*dioxatricyclo*[3.3.1.0^{3,7}]*nonane* (**23a**).—T.l.c. gave R_F 0.65 (ether) and 0.20 [light petroleum–ether (4:1)]; $\nu_{max.}$(CCl$_4$) 2 980, 2 930, 2 840w, 1 600, 1 110, 1 085, 1 055, 990, 970, 720, and 695 cm^{-1}; n.m.r. (220 MHz): see Table 3; *m*/*z* 428 (M^+), 301 (M^+ − I), 283, 269, 126, 117, 115, 91, 81, and 75.

(1R,3S,5S,7S,9S)-1-*Dimethoxymethyl*-9-[(E)-1′-*styryl*]-2,6-*dioxatricyclo*[3.3.1.0^{3,7}]*nonane* (**22b**). Tributyltin(IV) hydride (1.35 ml, 1.45 g, 5.00 mmol) was added to a stirred solution of the iodide (**22a**) (1.427 g, 3.33 mmol) and AIBN (110 mg, 0.67 mmol) in sodium-dried benzene (25 ml), with illumination (150 W tungsten filament lamp) and under N_2. After both 2 h and 4 h, t.l.c. analysis showed some starting material left, so more Bu_3SnH (0.45 ml) and AIBN (55 mg) were added. After a further 2.5 h, saturated aqueous Na_2CO_3 (40 ml) was added, and the mixture stirred vigorously for 20 h. The organic layer was then separated, diluted with more benzene (10 ml), washed with saturated brine (20 ml), dried, and concentrated. Purification by f.c.c., using 20% light petroleum in ether as eluant, gave the product as a colourless oil which crystallised with time (971 mg, 96%). A small portion was recrystallised for characterisation. T.l.c. R_F 0.42 (ether) and 0.33 [ether–light petroleum (4:1)], m.p. 74—75 °C (hexane) (Found: C, 71.2; H, 7.40. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.30%) $\nu_{max.}$ (thin film) 2 990, 2 960, 2 840w, 1 600, 1 100, 1 080, 1 060, 1 010, 980, 850, 755, and 700 cm^{-1}; δ (220 MHz) 1.70—1.84 (2 H, complex m, 4b-H and 8b-H), 2.25 (1 H, d, *J* 11.5 Hz, 4a-H), 2.34 (1 H, d, *J* 11.5 Hz, 8a-H), 2.71 (1 H, d, $J_{9,1'}$ 9 Hz, 9-H), 3.43 and 3.48 (6 H, 2 × s, 2 × OMe), 4.27 [1 H, s, C*H*(OMe)$_2$], 4.35 (1 H, d, $J_{5,4b}$ 4.5 Hz, 5-H), 4.80 (1 H, t, 7-H), 4.89 (1 H, br t, 3-H), 6.33 (1 H, dd, *J* 16 Hz and 9 Hz, 1′-H), 6.54 (1 H, d, *J* 16 Hz, 2′-H), and 7.18—7.44 (5 H, complex m, Ph).

Table 2. ^{1}H N.m.r. data for (**22a**)



(**22a**)

Signal (δ, p.p.m.)	Integration; multiplicity	Coupling constant *J* (H,H)	Proton assignment
1.78	1 H; ddd	12 Hz (4a,4b), 5 Hz (4a,5), 3 Hz, (4a,3)	4a-H
2.26	1 H; d*	12 Hz	4b-H
3.08	1 H; d	8 Hz (9,1′)	9-H
3.44	3 H; s	—	OMe
3.58	3 H; s	—	OMe
4.18	1 H; s	—	$CH(OMe)_2$
4.63	1 H; d	5 Hz (5,4b)	5-H
4.68	1 H; s	—	8-H
4.97	1 H; d	3.5 Hz (7,3)	7-H
5.01	1 H; m	3.5 Hz (3,7), 3.5 Hz (3,4a)	3-H
6.36	1 H; dd	16 Hz, 8 Hz	1′-H
6.58	1 H; d	16 Hz	2′-H
7.20—7.45	5 H; m	—	Ph

* Expansion/spin decoupling reveals small coupling to 3-H

(1S,3R,4S,5S,7R)-3-*Dimethoxymethyl*-4-[(E)-1′-*styryl*]-2,6-*dioxatricyclo*[3.3.1.0^{3,7}]*nonane* (**23b**).—Tributyltin(IV) hydride (0.85 ml, 0.92 g, 3.16 mmol) was added to a stirred solution of a mixture of the iodides (**22a**) and (**23a**) (1.020 g, 2.38 mmol) and AIBN (79 mg, 0.48 mmol) in sodium-dried benzene (20 ml), with illumination (150 W tungsten filament lamp) and under N_2. After 2 h, t.l.c. analysis showed the presence of starting material, so further Bu_3SnH (0.3 ml) and AIBN (30 mg) were added. After a further 2 h, saturated aqueous Na_2CO_3 (30 ml) was added, and the solution stirred vigorously; after a further 1 h, aqueous Na_2CO_3 (20 ml) was added, and stirring was continued for 16 h. The organic layer was then separated, diluted with further benzene (10 ml), washed with saturated brine (10 ml) dried, and concentrated. Purification by f.c.c., using 20% light petroleum in ether as eluant, gave the product (**23b**) as a white crystalline solid, along with some (**22b**), and a mixture of the two. T.l.c. using ether–light petroleum (4:1) gave R_F 0.38; m.p. 115—116 °C; (Found: C, 71.0; H, 7.40. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.30%); $\nu_{max.}$(CCl$_4$) 2 960, 2 840w, 1 600, 1 115, 1 085, 1 055, 1 045, 870, and 695 cm^{-1}; δ (220 MHz) 1.78—1.92 (3 H, complex m, 8a-H, 8b-H, and 9b-H), 2.19 (1 H, d, *J* 11.5 Hz, 9b-H), 3.16 (1 H, d, $J_{4,1'}$ 9 Hz, 4-H), 3.44 and 3.49 (6 H, 2 × s, 2 × OMe), 4.30 (1 H, br s, 5-H), 4.50 [1H, s, C*H*(OMe)$_2$], 4.63 (2 H, d, *J* 3.5 Hz, 1-H and 7-H), 6.20 (1 H, dd, *J* 16 Hz and 9 Hz, 1′-H), 6.58 (1 H, d, *J* 16 Hz, 2′-H), and 7.18—7.44 (5 H, complex m, Ph).

(1R,3S,5S,7S,9S)-1-*Dimethoxymethyl*-9-*formyl*-2,6-*dioxatricyclo*[3.3.1.0^{3,7}]*nonane* (**24**).—A solution of the alkene (**22b**)

(947 mg, 3.14 mmol) in dry CH_2Cl_2 (40 ml) was treated with ozone at −78 °C. DMS (0.8 ml, excess) was then added, and the solution allowed to warm to room temp. and stirred for 16 h. Excess of DMS was removed (under reduced pressure) after which the solution was concentrated and purified by f.c.c., using ether as eluant, to give the product as a colourless oil (530 mg, 74%). T.l.c. using ether gave R_F 0.35; $\nu_{max.}$ (thin film) 3 000, 2 940, 2 840w, 2 760w, 1 720, 1 190, 1 125, 1 105, 1 080, 1 005, 870, and 850 cm^{-1}; δ (60 MHz) 1.60—2.70 (5 H, complex m, both 4-H + both 8-H + 9-H), 3.50 (6 H, s, 2 × OMe), 4.25 [1 H, s, C*H*(OMe)$_2$], 4.65 (1 H, d, *J* 4 Hz, 5-H), 4.79—4.95 (2 H, complex m, 3-H and 7-H), and 9.65 (1 H, d, *J* 3 Hz, CHO) [N.B. Same numbering system as (**22b**)]; *m/z* 228 (M^+), 196 (M^+ − MeOH), 124, 81, and 75.

(1R,3S,5S,7S,9S)-1-*Dimethoxymethyl*-9-(2′-*methoxyvinyl*)-2,6-*dioxatricyclo*[3.3.1.0^{3,7}]*nonane* (**25**).—BuLi (1.55M in hexane; 4.60 ml, 7.14 mmol) was added to a stirred solution of di-isopropylamine (1.00 ml, 0.722 g, 7.14 mmol) in dry THF (25 ml), at 0 °C and under N_2. After 15 min, sodium-dried toluene (10 ml) was added, followed by (methoxymethyl)triphenylphosphonium chloride (2.448 g, 7.14 mmol), and the resulting (deep red) solution was stirred for a further 15 min at 0 °C. A solution of the aldehyde (**24**) (543 mg, 2.38 mmol) in sodium-dried toluene (5 ml) was added, and the solution stirred for 1 h. Water (100 ml) was then added, and the solution was extracted with ether (3 × 50 ml): the combined ether extracts were dried, concentrated, and purified by f.c.c., using ether as eluant, to give the product (**25**) as a mixture of the *cis*- and *trans*-isomers (449 mg, 74%). T.l.c. using ether gave R_F 0.35 and 0.31, $\nu_{max.}$ (thin film) 2 980, 2 950, 2 830w, 1 650, 1 100, 1 080, 1 060, 1 010, and 850 cm^{-1}; δ (220 MHz) 1.63—1.80 (4 H, complex m, 4b-H, 8a-H of both isomers), 2.16—2.29 (4 H, complex m, 4a-H, 8b-H of both isomers), 2.42 (1 H, d, *J* 10 Hz, 9-H of *trans*-isomer), 2.97 (1 H, d, *J* 10 Hz, 9-H of *cis*-isomer), 3.43 (3 H, s, acetal OMe), 3.45 (6 H, s, 2 × acetal OMe), 3.47 (3 H, s, acetal OMe), 3.55 (3 H, s, 2′-OMe), 3.61 (3 H, s, 2′-OMe), 4.17—4.27 (2 H, m, 5-H of both isomers), 4.23 [1 H, s, C*H*(OMe)$_2$], 4.31 [1 H, s, C*H*(OMe)$_2$], 4.51 (1 H, dd, $J_{1',9}$ 10 Hz, $J_{1',2'}$ 6.5 Hz, 1′-H of *cis*-isomer), 4.72 (2 H, m, 7-H of both isomers), 4.78—4.88 (3 H, complex m, 3-H of both isomers + 1′-H of *trans*-isomer), 5.99 (1 H, d, *J* 6.5 Hz, 2′-H of *cis*-isomer), and 6.43 (1 H, d, *J* 13 Hz, 2′-H of *trans*-isomer); *m/z* (%) 256.1312 (11) (M^+; $C_{13}H_{20}O_5$ requires *M*, 256.1310).

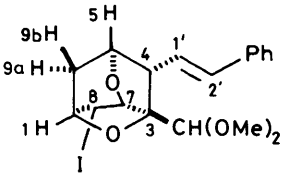
(1R,3S,5S,7S,9S)-1-*Dimethoxymethyl*-9-*formylmethyl*-2,6-*dioxatricyclo*[3.3.1.0^{3,7}]*nonane* (**26**).—Mercuric acetate (1.320 g, 4.14 mmol) was added to a stirred solution of compound (**25**) (424 mg, 1.66 mmol) in THF (18 ml) and water (2 ml). After 4 h, t.l.c. analysis showed the disappearance of all starting material, so aqueous KI (7% w/v; 100 ml) was added, and the solution extracted into benzene (2 × 50 ml). The combined benzene extracts were dried and concentrated to give the crude product (containing some mercuric acetate). This was dissolved in ether (50 ml), washed with saturated brine (30 ml), dried, and concentrated to leave the product (**26**) as a pale brown oil (354 mg, 86% crude yield). This product was used without further purification in the next reaction. T.l.c. using ether gave R_F 0.36 $\nu_{max.}$ (thin film) 2 990, 2 940, 2 840w, 2 730w, 1 725, 1 195, 1 105, 1 080, 1 010, 980, and 850 cm^{-1}; δ (60 MHz) 1.40—1.80 (2 H, complex m, 4b-H and 8a-H), 2.00—2.90 (5 H, complex m, 4a-H, 8b-H, 9-H, 1′-H), 3.40 (6 H, s, 2 × OMe), 4.05 [1 H, s, C*H*(OMe)$_2$], 4.20 (1 H, d, *J* 5 Hz, 5-H), 4.50—4.80 (2 H, m, 3-H and 7-H), and 9.70 (1 H, s, CHO).

(1R,3S,5S,7S,9S)-1-*Dimethoxymethyl*-9-[(Z)-6′-*methoxycarbonylhex*-2′-*enyl*]-2,6-*dioxatricyclo*[3.3.1.0^{3,7}]*nonane* (**27**).—Dry THF (20 ml) was added to potassium t-butoxide (801 mg, 7.15 mmol) and (4-carboxybutyl)triphenylphosphonium bromide (1.584 g, 3.58 mmol) under N_2 and the resulting orange/red suspension was stirred for 30 min. A solution of the aldehyde (**26**) (345 mg; crude product) in dry THF (5 ml) was then added, and the solution stirred for a further 50 min. Saturated aqueous NH_4Cl (50 ml) was added, and the organic layer was separated. The aqueous layer was re-extracted with ether (3 × 30 ml), acidified with aqueous HCl (2M; 20 ml), and again extracted with ether (3 × 30 ml). The combined organic extracts were dried and concentrated to leave the crude product (1.065 g). This was dissolved in ether (20 ml), and an ethereal solution of CH_2N_2 (1.5% w/v; 15 ml) was added, with stirring. After 15 min, the solution was concentrated and purified by f.c.c., using 20% light petroleum in ether as eluant, to give the product (**27**) as a colourless oil [338 mg, 60% from (**25**), 3 steps]. T.l.c. gave R_F 0.47 (ether) and 0.35 [ether–light petroleum (4:1)]; $\nu_{max.}$ (thin film) 2 950, 2 830w, 1 740, 1 190, 1 105, 1 080, 1 010, and 850 cm^{-1}; δ (220 MHz) 1.55—1.82 (5 H, complex m, 4a-H, 8b-H, 9-H, 5′-H), 2.05—2.28 (6 H, complex m, 4b-H, 8a-H, 1′-H, 4′-H), 2.32 (2 H, t, *J* 8 Hz, 6′-H), 3.44 and 3.48 (6 H, 2 × s, 2 × OMe), 3.65 (3 H, s, CO_2Me), 4.22 [1 H, s, C*H*(OMe)$_2$], 4.24 (1 H, d, *J* 4.5 Hz, 5-H), 4.65 (1 H, t, *J* 3.5 Hz, 7-H), 4.76 (1 H, t, *J* 3.5 Hz, 3-H), and 5.40 (2 H, m, 2′-H and 3′-H), *m/z* (%): no M^+ observed. 308.1619 (16) (M^+ − MeOH; $C_{17}H_{24}O_5$ requires 308.1624).

(1R,3S,5S,7S,9S)-1-*Formyl*-9-[(Z)-6′-*methoxycarbonylhex*-2′-*enyl*]-2,6-*dioxatricyclo*[3.3.1.0^{3,7}]*nonane* (**28**).—Compound (**27**) (286 mg, 0.84 mmol) was dissolved in dry, freshly distilled $CHCl_3$ (10 ml). Propan-2-ol (0.4 ml; 4% v/v) and c.HCl (*d* 1.16; 2 ml) were added, and the solution was stirred vigorously for 18 h. Water (20 ml) and ether (30 ml) were then added, and the ethereal layer was separated. The aqueous layer was re-extracted with ether (20 ml), and the combined ether extracts were washed with saturated aqueous $NaHCO_3$ (20 ml), dried, and concentrated to give a colourless oil (*ca.* 200 mg). This product was shown by n.m.r. analysis (see below) to be a mixture of the aldehyde (**28**) and unchanged (**27**), in a ratio of *ca.* 4:1. T.l.c. using ether gave R_F 0.35 ('streak') $\nu_{max.}$($CDCl_3$) 3 000, 2 950, 2 860w, 1 740, 1 440, 1 080, 1 015, and 850 cm^{-1}; δ (60 MHz) 1.40—2.60 (13 H, complex m, 4-H, 8-H, 9-H, 1′-H, 4′-H, 5′-H, 6′-H both compounds), 3.45 and 3.50 (6 H, 2 × s, 2 × acetal OMe), 3.70 (3 H, s, ester OMe), 4.20—4.40 [2 H, m, 5-H + C*H*(OMe)$_2$], 4.60—5.00 (2 H, m, 3-H and 7-H), 5.30—5.60 (2 H, m, 2′-H and 3′-H), and 9.50 (1 H, s, CHO).

(1R,3S,5S,7S,9S)-9-[(Z)-6′-*Methoxycarbonylhex*-2′-*enyl*]-1-[(E)-3″-*oxo*-*oct*-1″-*enyl*]-2,6-*dioxatricyclo*[3.3.1.0^{3,7}]*nonane* (**29**).—NaH (50% dispersion in oil; 90 mg, 1.88 mmol) was washed free of the dispersion oil with light petroleum (2 × 5 ml), and placed under N_2. Dry THF (5 ml) was added, followed by dimethyl (2-oxoheptyl)phosphonate (0.2 ml, 0.21 g, 0.94 mmol), with stirring. After 40 min, a solution of aldehyde (**28**) (200 mg crude product) in dry THF (5 ml) was added. After 80 min, t.l.c. analysis showed no (**28**) remaining; water (20 ml) was added, and the solution was extracted with ether (2 × 30 ml). Saturated brine (20 ml) was added to the aqueous phase, which was then re-extracted with ether (30 ml). The combined ether extracts were dried, concentrated, and purified by f.c.c., using ether–light petroleum (2:1) as eluant, to give the product (**29**) as a colourless oil [78 mg, 21% from (**27**), 2 steps]. (Acidification of the aqueous extract, followed by re-extraction with ether and esterification with CH_2N_2, gave no more product, by t.l.c. analysis). T.l.c. gave R_F 0.43 [ether–light petroleum (4:1), 0.33 [ether–light petroleum (2:1)]; $\nu_{max.}$ ($CDCl_3$ soln.) 2 990, 2 960, 2 940, 2 860w, 1 730, 1 600, 1 440, 1 330, 1 070, 1 005, and 845 cm^{-1}; δ (220 MHz) 0.88 (3 H, t, *J* 4 Hz, 8″-H), 1.20—1.40 (4 H, m, 6″-H + 7″-H), 1.46—1.84 (7 H, complex m, 4a-H, 8b-H, 9-H,

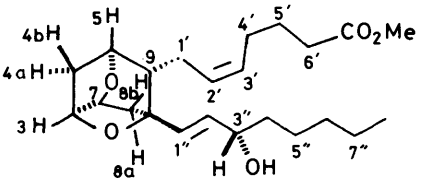
Table 3. ^{1}H N.m.r. data for (**23a**)



(**23a**)

Signal (δ, p.p.m.)	Integration; multiplicity	Coupling constant *J* (H,H)	Proton assignment
1.98	1 H; dd	13 Hz (9a,9b), 4 Hz (9b,1)	9b-H
2.12	1 H; dd	13 Hz, 4 Hz (9a,5)	9a-H
3.25	1 H; d	9 Hz (4,1′)	4-H
3.50	3 H; s	—	OMe
3.54	3 H; s	—	OMe
4.40	1 H; d	4 Hz (5,9a)	5-H
4.52	1 H; s	—	8-H
4.59	1 H; br d	4 Hz	1-H
4.67	1 H; s	—	$CH(OMe)_2$
4.85	1 H; d	1.5 Hz (7,1)	7-H
6.20	1 H; dd	16 Hz, 9 Hz	1′-H
6.48	1 H; d	16 Hz	2′-H
7.16—7.42	5 H; m	—	Ph

Table 4. ^{1}H N.m.r. data for (**4**) (3″*R*-isomer)



Signal (δ, p.p.m.)	Integration; multiplicity	*J*(Hz)	Proton assignment
0.88	3 H; t	4	8″-H
1.20—1.80	14 H; complex m		4a-H, 8b-H, 9-H; 4″H, 6″-H, 7″-H, 5′-H, 5″-H, OH
1.92—2.38	6 H; complex m		4b-H, 8a-H, 1′-H, 4′H
2.32	2 H; t	8	6′-H
3.66	3 H; s		OMe
4.09—4.21	1 H; m*		3′-H
4.26	1 H; d	4.5	5-H
4.75	2 H; m		3-H, 7-H
5.28—5.52	2 H; complex m		2′-H, 3′-H
5.71	1 H; dd*	16, 5	2″-H
5.81	1 H; d	16	1″-H

N.B. 3″-OH≡15-OH.
* Irradiation at δ = 4.14 collapses 2″-H dd to d. The spectrum of the 3″*S*-isomer was identical except for 2″-H, δ = 5.69 and 1″-H, δ = 5.79.

5′-H, and 5″-H), 1.90—2.35 (6 H, complex m, 4b-H, 8a-H, 1′-H, 4′-H), 2.32 (2 H, t, *J* 8 Hz, 6′-H), 2.54 (2 H, t, *J* 8 Hz, 4″-H), 3.66 (3 H, s, OMe), 4.28 (1 H, d, *J* 4.5 Hz, 5-H), 4.75—4.85 (2 H, complex m, 3-H + 7-H), 5.25—5.55 (2 H, complex m, 2′-H + 3′-H), 6.26 (1 H, d, *J* 16 Hz, 2″-H), 6.85 (1 H, d, *J* 16 Hz, 1″-H); *m/z* (%) M^+ 390.2411 (**28**) (M^+; $C_{23}H_{34}O_5$ requires *M*, 390.2406).

(1R,3S,5S,7S,9S)-9-[(Z)-6′-*Methoxycarbonylhex*-2′-*enyl*]-1-[(E)-3″-(R)-*hydroxyoct*-1″-*enyl*)]-2,6-*dioxatricyclo*[3.3.1.0^{3,7}]-*nonane and* 3″-(S)-*Isomer* (**4**).—$NaBH_4$ (20 mg, excess) was added to a stirred solution of the ketone (**29**) (59 mg, 0.15 mmol) in AnalaR MeOH (5 ml) at −40 °C. After 1 h at −35 to −45 °C, water (10 ml) was added, followed by aqueous HCl (2M; 2 ml). The solution was extracted with ether (5 × 10 ml), and the combined ether extracts were dried, concentrated, and purified by f.c.c., using 20% light petroleum in ether as eluant, to give 3″*R*-(**4**) (14 mg), 3″*S*(**4**) (11 mg), and a mixture of the two (32 mg); total yield 57 mg (97%).

Data for the 3″R-*isomer*. T.l.c. using ether–light petroleum (4:1) gave R_F 0.20; $\nu_{max.}$(CCl_4) 3 280, 1 730, 1 070, and 1 000 cm^{-1}; n.m.r. (220 MHz): see Table 4.

Data for 3″S-*isomer*. T.l.c. using ether–light petroleum (4:1) gave R_F 0.14 $\nu_{max.}$ (CCl_4 soln.) 3 280, 1 730, 1 140, and 1 000 cm^{-1}; *n.m.r.* (220 MHz): see Table 4.

Data for mixture: *m/z* (%) no M^+ observed. 291.1578. (M^+ − $CH(OH)C_5H_{11}$; $C_{17}H_{23}O_4$ requires 291.1596).

(1S,3R,4S,5S,7R)-4-[(Z)-6′-*Methoxycarbonylhex*-2′-*enyl*]-3-[(E)-3″-*oxo-oct*-1″-*enyl*]-2,6-*dioxatricyclo*[3.3.1.0^{3,7}]*nonane* (**31**).—Compound (**30**) [tricyclic isomer of (**28**)] was obtained from the tricycle (**23b**), by methods analogous to those used for (**28**), and was used (immediately from the deprotection reaction) in the synthesis of compound (**31**).

NaH (22 mg of (50% dispersion in oil; 22 mg, 0.52 mmol) was dissolved in dry THF (2 ml), under N_2. Dimethyl (2-oxoheptyl)-phosphonate (0.1 ml, 0.5 mmol) was added, and the resulting grey suspension stirred for 30 min. A solution of the aldehyde (**30**) (38 mg, crude product) in dry THF (2 ml) was added, and the solution stirred for 1 h. Water (5 ml) was added, and the solution extracted with ether (2 × 10 ml); the combined ether extracts were dried, concentrated and purified by f.c.c., using ether–light petroleum, 1:1, then 4:1 and finally 9:1 as eluant, to give the product (**31**) as a colourless oil (50 mg). T.l.c. using ether–light petroleum (1:1) gave R_F 0.28; δ (60 MHz) 0.80—2.70 (24 H, complex m, 4-H, 8-H, 9-H, 1′-H, 4′-H, 5′-H, 6′-H, 4″-H, 5″-H, 6″-H, 7″-H, 8″-H), 3.70 (3 H, s, OMe), 4.25 (1 H, d, *J* 5 Hz, 5-H), 4.40—4.80 (2 H, m, 3-H and 7-H), 5.30—5.60 (2 H, m, 2′-H and 3′-H), 6.40 (1 H, d, *J* 16 Hz, 2″-H), and 7.05 (1 H, d, *J* 16 Hz, 1″-H). [N.B. Same numbering system as in (**23b**).]

(1S,3R,4S,5S,7R)-4-[(Z)-6′-*Methoxycarbonylhex*-2-*enyl*]-3-[(E)-3″-*hydroxyoct*-1-*enyl*]-2,6-*dioxatricyclo*[3.3.1.0^{3,7}]*nonane* (**32**).—$NaBH_4$ (20 mg, excess) was added to a stirred solution of the ketone (**31**) (50 mg) in AnalaR MeOH (2 ml) at −40 °C. After 90 min at −35 °C to −45 °C, water (5 ml) and aqueous HCl (2M; 2 ml) were added, and the solution was extracted with ether (3 × 10 ml). The combined ether extracts were dried, concentrated, and purified by f.c.c., using 20% light petroleum in ether as eluant, to give the product (**32**), as a mixture of the 3″-(*R*) and 3″-(*S*) alcohols (15-α- and β-isomers), (35 mg). T.l.c. using ether–light petroleum (4:1) gave R_F 0.28; $\nu_{max.}$ (thin film) 3 460br, 2 960, 2 940, 2 860w, 1 745, 1 590, 1 200, 1 150, 1 050, and 865 cm^{-1}; (220 MHz) 0.88 (3 H, t, *J* 4 Hz, 8″-H), 1.20—1.92 (14 H, complex m, 8b-H, 9a-H, 4-H, 4″-H, 6″-H, 7″-H, 5′-H, 5″-H, OH), 1.98–2.22 (6 H, complex m, 8a-H, 9b-H, 1′-H, 4′-H), 2.30 (2 H, t, *J* 8 Hz, 6′-H), 3.64 (3 H, s, OMe), 4.09—4.27 (2 H, complex m, 5-H and 3″-H), 4.40 (1 H, m, 1-H or 7-H), 4.54 (1 H, t, *J* 4 Hz, 7-H or 1-H), 5.26—5.38 (2 H, m, 2′-H and 3′-H), 5.82 (1 H, dd, *J* 16 Hz and 5 Hz, 2″-H), 5.95 (1 H, d, *J* 16 Hz, 1″-H). *m/z* (%) 374.2438 (1) (M^+ − H_2O; $C_{23}H_{34}O_4$ requires 374.2457), 251.1647 (2) (M^+ − $CH_2CH{=}CH(CH_2)_3CO_2Me$; $C_{15}H_{23}O_3$ requires 251.1647).

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