Synthesis of 9,11-Epoxy-9a-homoprostaglandin Analogues [1]

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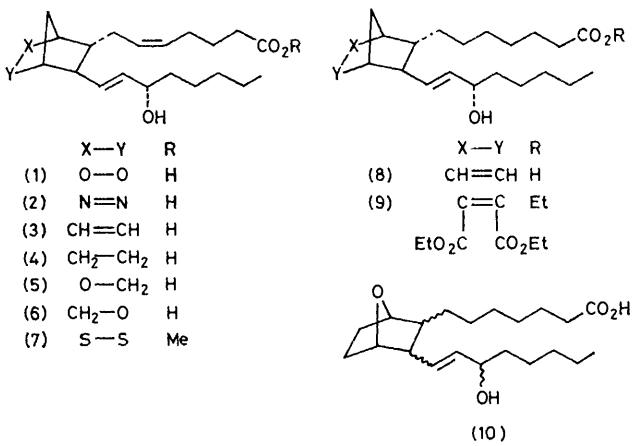
Starting from Diels–Alder adducts of furan with maleic anhydride, maleic acid, and dimethyl acetylenedicarboxylate, the synthesis of prostaglandin-H_1 (PGH_1) analogues, in which the bicyclic part of PGH_1 is replaced by the 7-oxabicyclo[2.2.1]heptane moiety, is described. Isomers with the two side-chains in *exo,exo-*, *exo,endo-*, and *endo,exo*-positions and their C(15)-epimers have been synthesised.

BIOSYNTHESIS of the natural prostaglandins from polyunsaturated C_{20} fatty acids proceeds *via* the *endo*-peroxide intermediates PGG and PGH. Although their existence was postulated many years ago,[2] these highly unstable intermediates have been isolated only recently.[3] The isolated *endo*-peroxides showed high biological activity and for this reason interest has arisen in structural analogues which are more stable than PGG and PGH itself, in order to obtain more information about their mechanism of action.

PGH_2 (1) analogues in which the peroxide bridge is replaced by an azo- (2),[4] an etheno- (3),[5] an ethano- (4),[5b] an epoxymethano- (5, 6),[6] or a dithio-linkage (7) [7] have been synthesised and found to possess interesting biological activities. Compound (2), *e.g.*, showed higher activity than PGG_2 in several assays.[4a] PGH_1 analogues (8) [8] and (9) [9] have also been reported.



SCHEME 1

We now report the synthesis of several isomeric PGH_1 analogues (10) in which the bicyclic moiety of PGH_1 is replaced by a 7-oxabicyclo[2.2.1]heptane system.[10]

[1] Taken in part from the Ph.D. thesis of T. A. Eggelte, University of Amsterdam, 1976.

[2] D. H. Nugteren, R. K. Beerthuis, and D. A. van Dorp, *Rec. Trav. chim.*, 1966, **85**, 405.

[3] D. H. Nugteren and E. Hazelhof, *Biochim. Biophys. Acta*, 1973, **326**, 448; M. Hamberg and B. Samuelsson, *Proc. Nat. Acad. Sci. U.S.A.*, 1973, **70**, 899.

[4] (*a*) E. J. Corey, K. C. Nicolaou, Y. Machida, C. L. Malmsten, and B. Samuelsson, *Proc. Nat. Acad. Sci. U.S.A.*, 1975, **72**, 3355; (*b*) E. J. Corey, K. Narasaka, and M. Shibasaki, *J. Amer. Chem. Soc.*, 1976, **98**, 6417.

[5] (*a*) E. J. Corey, M. Shibasaki, K. C. Nicolaou, C. L. Malmsten, and B. Samuelsson, *Tetrahedron Letters*, 1976, 737; (*b*) T. J. Leeney, P. R. Marsham, G. A. F. Ritchie, and M. W. Senior, *Prostaglandins*, 1976, **11**, 953; (*c*) H. Shimomura, A. Sugie, J. Katsube, and H. Yamamoto, *Tetrahedron Letters*, 1976, 4099.

[6] G. L. Bundy, *Tetrahedron Letters*, 1975, 1957.

[7] H. Miyake, S. Iguchi, H. Itoh, and M. Hayashi, *J. Amer. Chem. Soc.*, 1977, **99**, 3536.

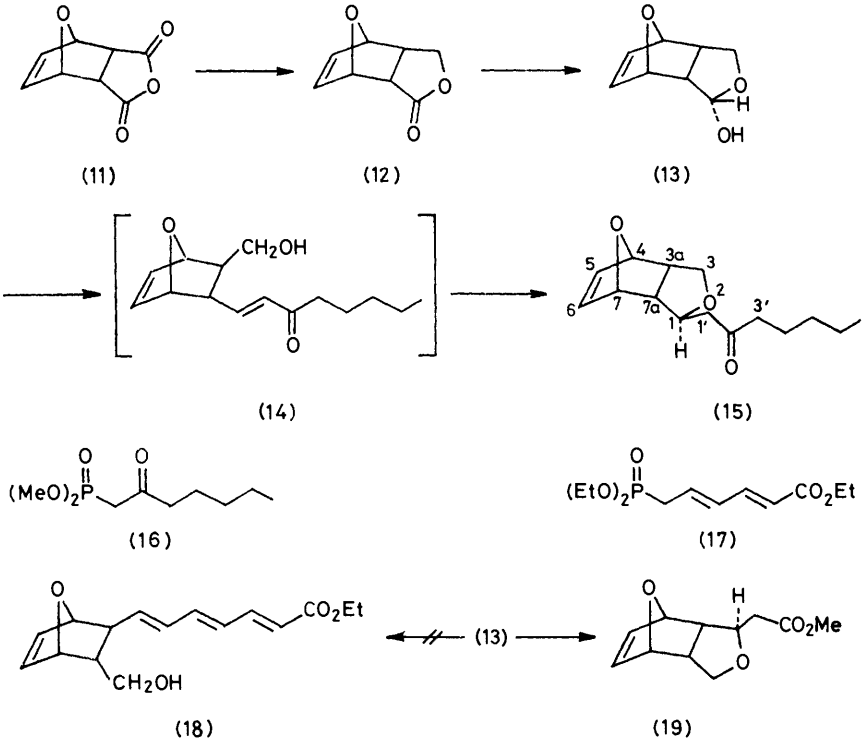
[8] P. Wlodawer, B. Samuelsson, S. M. Albonico, and E. J. Corey, *J. Amer. Chem. Soc.*, 1971, **93**, 2815.

[9] A. G. Abatjoglou and P. S. Portoghese, *Tetrahedron Letters*, 1976, 1457.

[10] Presented in part at the Internat. Conf. on Prostaglandins, Florence, Italy, May 1975; 'Advances in Prostaglandin and Thromboxane Research,' ed. B. Samuelsson and R. Paoletti, Raven Press, New York, 1976, p. 869.

These analogues show also a certain structural relation with the newly discovered thromboxanes.[11] Synthesis of 7-oxabicyclo[2.2.1]heptane compounds is best achieved by Diels–Alder reactions of furan. However, a similar approach as has been used by Corey and his co-workers [8] for the synthesis of (8) (*i.e.* Diels–Alder reaction of cyclopentadiene with 9-cyanonon-2-enal) is not feasible, due to the low reactivity of furan with this type of dienophile. We therefore chose an approach in which readily toluene afforded the lactol (13).† The structure of (13) was deduced from ^{1}H n.m.r. spectra, which showed no coupling of C(7a)–H with C(1)–H and C(7)–H, in conformity with the dihedral angles of about 90° found in Dreiding models.

Attempts to introduce the octenyl side-chain failed because Horner reaction of (13) with the anion of dimethyl 2-oxoheptylphosphonate (16) produced a 5 : 1 mixture of (15) and the isomeric compound with the



SCHEME 2

accessible 7-oxabicyclo[2.2.1]heptane compounds were transformed in such a way that both side-chains could be introduced by Horner reactions with aldehyde functions attached to the bicyclic system. Diels–Alder adducts of furan with maleic anhydride, maleic acid, and dimethyl acetylenedicarboxylate meet the requirement of accessibility [12] and possibility of conversion into the desired functionality.

RESULTS AND DISCUSSION

Synthesis of exo,exo-*Isomers*.—The *exo*-adduct (11) of furan and maleic anhydride was reduced with $NaBH_4$ in dimethylformamide to give the lactone (12),[13,*] which upon treatment with di-isobutylaluminium hydride in side-chain in the α-position, apparently formed from (14) in a subsequent 5-*exo-trig* [14] ring-closure reaction.[15] The thermodynamically more favourable β-position of the side-chain in (15) was proved by the relatively large value (6.5 Hz) found for $J_{1,7a}$ in the ^{1}H n.m.r. spectra, indicating the α-position for the C(1)–H atom. We then tried to introduce the heptanoic acid side-chain first. Horner reaction of (13) with the sodio-derivative of triethyl phosphonosorbate [16] (17), however, led to a complex mixture of products from which only very small amounts of impure (18), presumably containing intramolecular conjugate addition products, could be obtained. A model Horner reaction of (13) with trimethyl

* Recently this compound was also synthesised by S. Takano and K. Ogasawara, *Synthesis*, 1974, 42. However, they assigned the wrong *endo*-configuration to this compound, because they erroneously assumed that upon reaction furan and maleic anhydride give *endo*-adduct (see ref. 13 and references cited therein).

† The compounds described here are racemic although for convenience only one enantiomer is shown.

[11] M. Hamberg, J. Svensson, and B. Samuelsson, *Proc. Nat. Acad. Sci. U.S.A.*, 1975, **72**, 2994. See also G. B. Kolata, *Science*, 1975, **190**, 770.

[12] T. A. Eggelte, H. de Koning, and H. O. Huisman, *Tetrahedron*, 1973, **29**, 2491, and references cited therein.

[13] T. A. Eggelte, H. de Koning, and H. O. Huisman, *Tetrahedron*, 1973, **29**, 2445.

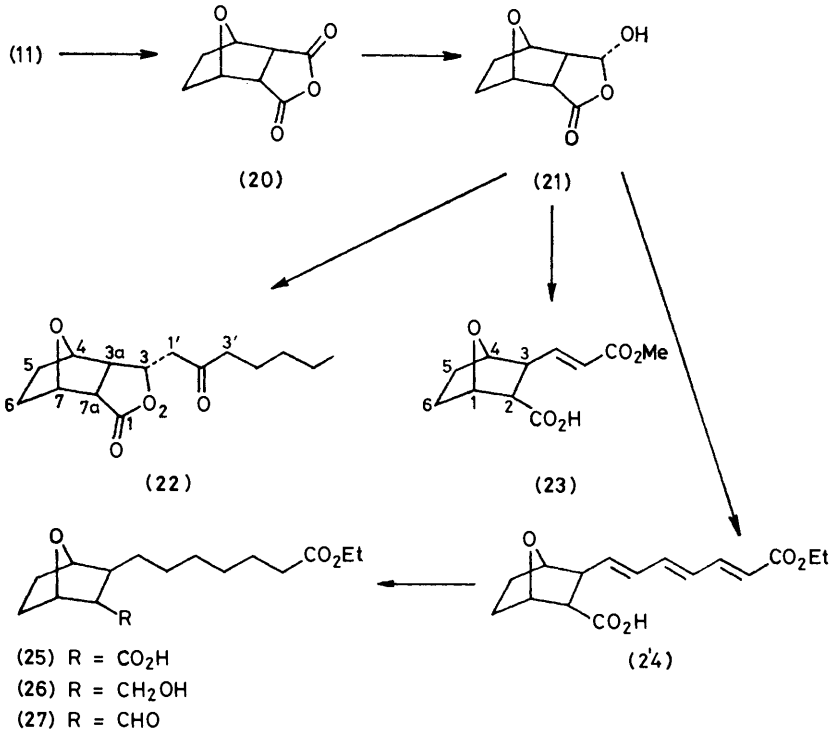
[14] J. E. Baldwin, *J.C.S. Chem. Comm.*, 1976, 734.

[15] A similar reaction was observed by I. T. Harrison, R. Grayshan, T. Williams, A. Semenovski, and J. H. Fried, *Tetrahedron Letters*, 1972, 5151.

[16] H. de Koning, G. N. Mallo, A. Springer-Fidder, K. E. C. Subramanian-Erhart, and H. O. Huisman, *Rec. Trav. chim.*, 1973, **92**, 683.

phosphonoacetate also gave a 4 : 1 mixture of 5-*exo-trig* ring-closure product (19) and its isomer with the side-chain in the α-position. The β-position for the side-chain in (19) was again deduced from the value of $J_{1,7a}$ (6.5 Hz).

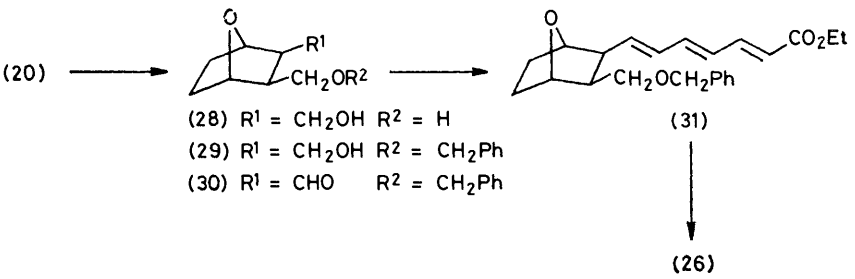
An alternative sequence starting from the *exo*-adduct (11) proved to be more successful. Catalytic hydrogenation of (11) in ethanol over 10% palladium on charcoal (Pd/C) afforded the hydroxy-lactone (21) in almost quantitative yield, whereas in acetone only reduction of the alkene moiety occurred, yielding saturated anhydride (20).[13] Nucleophilic addition of hydroxy-compounds to



SCHEME 3

αβ-unsaturated ketones, carboxylic acid derivatives, *etc.*, proceeds less readily with decreasing basicity of the hydroxy-function, and carboxylic acid derivatives do not react at all.[17] Therefore, Horner reactions of the hydroxy-lactone (21) are less likely to give a subsequent ring-closure product. Horner reaction of (21) with the oxophosphonate (16) in tetrahydrofuran (THF) in the presence of two equivalents of sodium hydride, however, again gave the product of a subsequent 5-*exo-trig* ring-closure reaction, lactone (22). Apparently, the co-planarity of the two *exo*-substituents, providing an ideal conformation for addition of the carboxylate to the enone-system, is a contributing factor in the formation of (22). The position of the heptanone side-chain in (22), *cis* with respect to C(3a)–H, was deduced from the ^{1}H n.m.r. spectrum, displaying $J_{3a,3\beta}$ 3.5 Hz, in accordance with the dihedral angle of *ca.* 125° found in Dreiding models, and with the value of 3.5 Hz observed for $J_{3a,3\beta}$ in the lactone (12).[13]

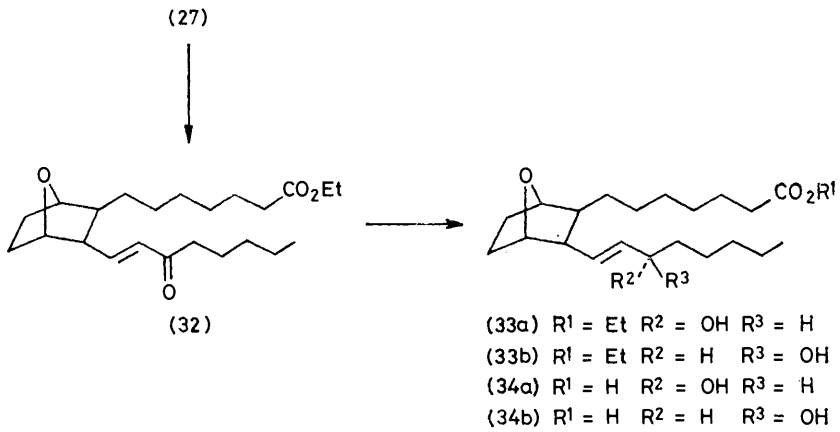
We then reasoned that, in nucleophilic addition reactions, acrylic acid derivatives are less reactive than enones. Thus, a model Horner reaction of the hydroxy-lactone (21) with trimethyl phosphonoacetate and two equivalents of sodium hydride indeed afforded the expected alkene (23), without formation of ring-closure



SCHEME 4

[17] Houben-Weyl, ' Methoden der Organischen Chemie,' ed. E. Müller, Georg Thieme Verlag, Stuttgart, 4th edn., 1972, vol. V/1b, p. 973.

products. Finally, Horner reaction of the hydroxy-lactone (21) with triethyl phosphonosorbate (17) proceeded without complications to furnish the desired heptatrienoic acid derivative (24) in modest yield. Catalytic hydrogenation of the triene (24) provided the saturated compound (25), which was converted into the



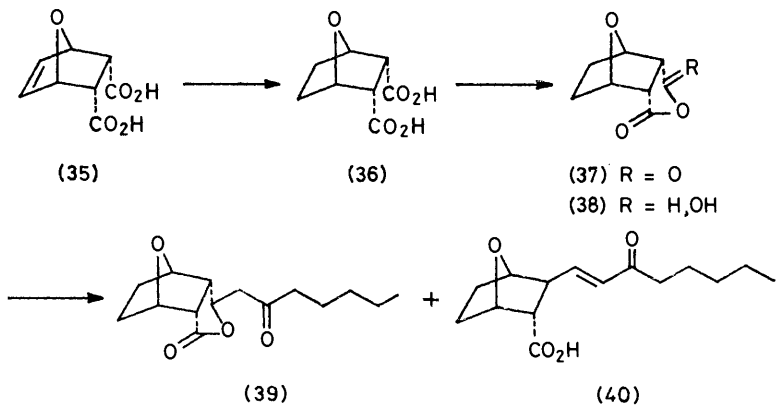
SCHEME 5

alcohol (26) by selective $NaBH_4$ reduction of the carboxy-group *via* the mixed ethyl carbonic anhydride.[18]

The alcohol (26) could also be obtained from (20) through the following sequence. Reduction of (20) with $LiAlH_4$ in THF gave the diol (28) which, upon benzylation of one of the hydroxymethyl groups to give (29) and Moffatt oxidation [19] of the remaining hydroxy-function, could be converted into the aldehyde (30). Subsequent Horner reaction of (30) with triethyl phosphonosorbate (17) furnished the triene (31) which, upon catalytic hydrogenation in ethanol over 10% Pd/C, afforded the saturated alcohol (26).

Moffatt oxidation of (26) gave the aldehyde (27), which in a Horner reaction with the oxophosphonate (16) yielded the enone (32). Reduction of (32) with $Zn(BH_4)_2$ in dimethoxyethane [20] resulted in a mixture of the epimeric enols (33a, b), which could be separated by column chromatography.[21] Saponification of (33a) and (33b) with potassium hydroxide in aqueous methanol furnished the *exo,exo*-prostaglandin analogue (34a) and its C(15)-epimer (34b), respectively.

Synthesis of exo,endo-*Isomers*.—The analogues with the two side-chains in *exo,endo*- and *endo,exo*-positions, (53a, b) and (56a, b) respectively, could be both obtained starting from the Diels–Alder adducts of furan with maleic acid (35) and with dimethyl acetylenedicarboxylate (45). Catalytic hydrogenation of (35) gave the saturated compound (36),[12] which could be converted into the *endo*-anhydride (37) using acetic anhydride and pyridine. Catalytic hydrogenation of (37) over 10% Pd/C in ethanol afforded the *endo*-hydroxy-lactone (38),[13] which upon subsequent Horner reaction with the oxophosphonate (16) yielded two products, the lactone (39) and the enone (40). Formation of the enone (40) can be explained by isomerisation of the *endo*-formyl group preceding the Horner reaction. The *trans*-position of the carboxy-group and the enone system in (40) prevent the ring-closure reaction in this case.

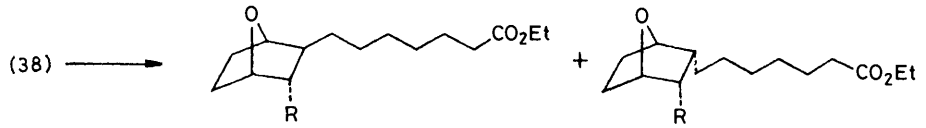


SCHEME 6

Reaction of the hydroxy-lactone (38) with the anion of

[18] K. Ishizumi, K. Koga, and S. Yamada, *Chem. Pharm. Bull. (Japan)*, 1968, **16**, 492.
[19] K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1965, **87**, 5661, 5670.
[20] E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, 1969, **91**. 5675.
[21] D. W. R. Hall and K. D. Jaitly, to be published.

triethyl phosphonosorbate (17), followed by catalytic hydrogenation and reduction of the carboxy-group, also reaction of (49) with triethyl phosphonosorbate (17), and catalytic hydrogenation of the triene (50) thus obtained,



(41) R = CH_2OH
(42) R = CHO
(43) R = CH_2OH
(44) R = CHO

SCHEME 7

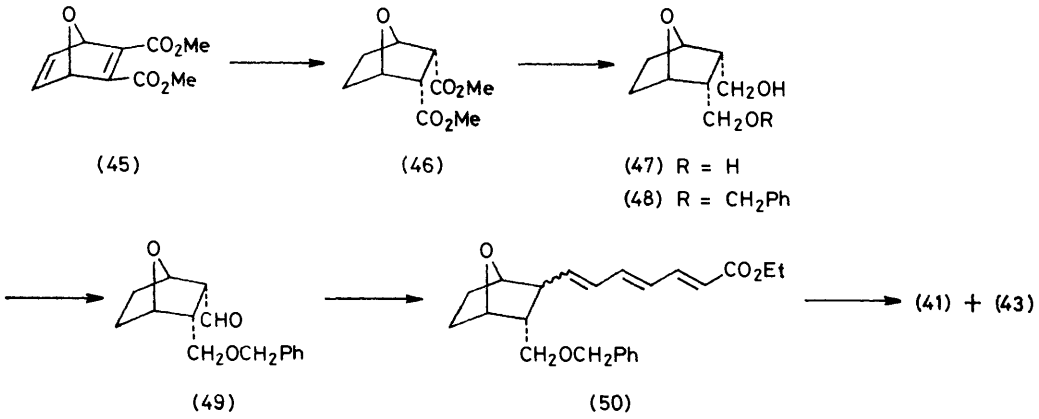
led to a mixture of alcohols, (41) and (43), which could be separated by column chromatography. The ratio of the isomers is dependent on the reaction conditions during the Horner reaction. Stirring of (38) in the presence of base prior to addition of the phosphonosorbate, changed the ratio of (41) and (43) from 1 : 1 to 5 : 1.

A mixture of (41) and (43) could also be obtained starting from adduct (45). Catalytic hydrogenation of (45) gave the *endo*-diester (46),[12] which was reduced with $LiAlH_4$ in THF to furnish the diol (47).

Subsequent monobenzylation to give (48), followed by Moffatt oxidation, provided the aldehyde (49). Horner produced a mixture of (41) and (43), or solely (41) if (49) was isomerised prior to the Horner reaction.

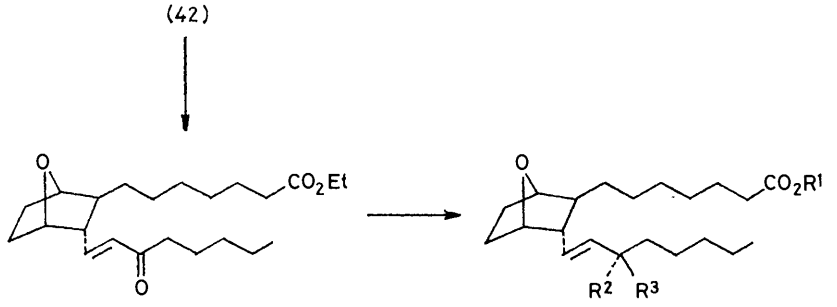
The structures of isomers (41) and (43) could be deduced from the isomerisation experiments and were confirmed by ^1H n.m.r. spectroscopy. The protons adjacent to the oxygen bridge show a broadened triplet if the neighbouring substituent is in the *endo*-position, and a broadened doublet in the case of an *exo*-substituent, because the dihedral angle of the *endo*-proton and the bridge-head proton is close to 90°. This criterion proved to be very useful in configurational assignment of the 7-oxabicyclo[2.2.1]heptane systems.

The alcohol (41) could be converted into *exo,endo*-



(45) (46) (47) R = H (48) R = CH_2Ph (49) (50)

SCHEME 8

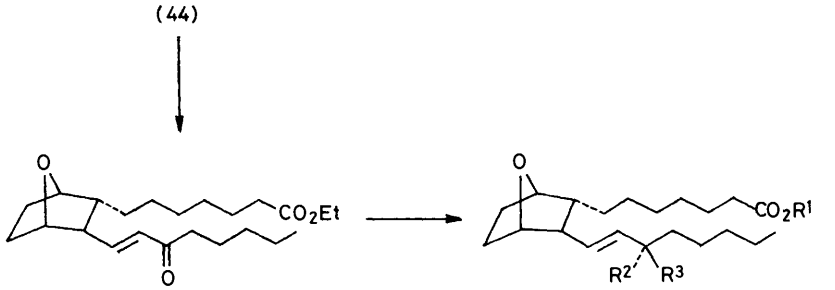


(51)
(52a) R^1 = Et R^2 = OH R^3 = H
(52b) R^1 = Et R^2 = H R^3 = OH
(53a) R^1 = H R^2 = OH R^3 = H
(53b) R^1 = H R^2 = H R^3 = OH

SCHEME 9

prostaglandin analogue (53a) and its C(15)-epimer (53b) *via* the aldehyde (42), the enone (51), and the enols (52a, b),[21] using similar reactions as described for conversion of (26) into (34).

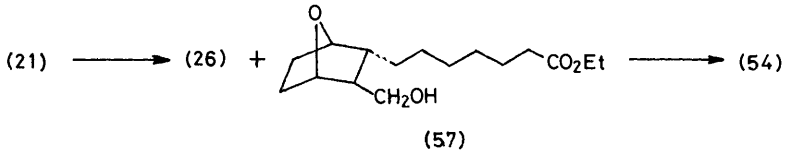
Synthesis of endo,exo-*Isomers*.—Moffatt oxidation of the alcohol (43) gave aldehyde (44), which was treated with the anion of oxophosphonate (16). Under the conditions of the Horner reaction, isomerisation of the formyl group occurred, giving rise to the formation of the enone (54). Assignment of the configuration of (54) was based on its ^{1}H n.m.r. spectrum (which showed a broadened doublet and a broadened triplet for the bridgehead protons) and on an independent synthesis from the hydroxy-lactone (21). Partial isomerisation of (21) in ethanol with sodium ethoxide preceding the Horner reaction with phosphonosorbate (17), and subsequent conversion of the triene ester acid *via* methods described above, provided a mixture of alcohols (26) and (57) which could be separated. Moffatt oxidation of (57) followed by Horner reaction with oxophosphonate (16) furnished the enone (54), which was identical to the enone obtained from alcohol (43).



SCHEME 10

Reduction of the enone (54) with $Zn(BH_4)_2$ in dimethoxyethane gave a mixture of enols (55a) * and (55b), which could be separated. Saponification of the esters gave the *endo,exo*-prostaglandin analogue (56a) and its C(15)-epimer (56b).

Pharmacological Activity.—The prostaglandin analogues (34a, b), (53a, b), and (56a, b) have been screened for pharmacological activity *in vivo* in the anaesthetised guinea-pig on multiple parameters [22] and were found to be potent vasopressors and bronchoconstrictors, but there was no effect on uterine and intestinal contractility. *In vitro* contraction of the rat fundus strip and guinea-pig tracheal chain were observed, but not of the rat uterus. Some interesting structure–activity relationships with respect to the configurations at C(8), C(12), and C(15) were found. Details will be published elsewhere.[21]



SCHEME 11

EXPERIMENTAL

I.r. spectra were recorded on Unicam SP 200 and Perkin-Elmer 257 spectrophotometers with chloroform as solvent, unless otherwise stated. ^{1}H N.m.r. spectra were determined on Varian A-60, A-60D, and HA-100 spectrometers, using deuteriochloroform as solvent; line positions are given in the δ scale downfield from internal tetramethylsilane. Reactions were performed at room temperature, unless otherwise stated.

exo-4,7-*Epoxy*-1,3,3a,4,7,7a-*hexahydroisobenzofuran*-1-*ol* (13).—Di-isobutylaluminium hydride (24 ml; 20% solution in toluene) was added dropwise at 0 °C, under nitrogen, to a suspension of the lactone (12) [13] (4.6 g) in dry toluene (70 ml). The lactone slowly dissolved, and after being stirred for 30 min at room temperature water (10 ml) was added. The precipitate was filtered off and thoroughly extracted with ethanol to give (13) (3.1 g). Evaporation of the toluene filtrate gave another 0.9 g of (13); yield 86%; m.p. 124—126 °C. I.r. (KBr) 3 350 cm^{-1} (OH); n.m.r. [$(CD_3)_2SO$] 2.10 ($J_{3a,7a}$ 7 Hz, 7a-H), 2.34 ($J_{3a,3\alpha}$ 7, $J_{3a,3\beta}$ 2.5, $J_{3a,7a}$ 7 Hz, 3a-H), 3.63 ($J_{3\alpha,3\beta}$ 9, $J_{3a,3\beta}$ 2.5 Hz, 3β-H), 3.95 ($J_{3a,3\alpha}$ 7, $J_{3\alpha,3\beta}$ 9 Hz, 3α-H), 4.71 and 4.88 (s, 4- and 7-H), 5.1 (d, J 5 Hz, 1-H), 5.93 (d, J 5 Hz, exchangeable with D_2O, OH), and 6.38 (s, 5- and 6-H) (Found: C, 62.3; H, 6.6. $C_8H_{10}O_3$ requires C, 62.32; H, 6.54%).

exo-4,7-*Epoxy*-1-(2-*oxoheptyl*)-1,3,3a,4,7,7a-*hexahydroiso*-

* The more polar isomer was tentatively assigned the 15α-configuration, by analogy with the chromatographic behaviour of similar prostaglandin derivatives; *e.g.* see refs. 4*b* and 5*a*. The assignment was confirmed by the higher biological activity of the 15α-isomers; see ref. 21.

[22] D. W. R. Hall and K. D. Jaitly, *Prostaglandins*, 1976, **11**, 573.

benzofuran (15).—Dimethyl 2-oxoheptylphosphonate (16) (440 mg) in dimethoxyethane (10 ml) was added dropwise, under nitrogen, to a suspension of sodium hydride (80 mg, 60% dispersion in oil, washed with n-hexane) in dimethoxyethane (10 ml). After the mixture had been stirred for 15 min, the alcohol (13) (308 mg) was added to it and stirring was continued for 2 h. Water was then added to the mixture which was then extracted with ether. The ethereal solution was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by preparative t.l.c. (silica gel–ethyl acetate) to afford a 5 : 1 mixture (310 mg, 62%) of (15) and its C(1)-isomer. Main isomer (15): i.r. 1 710 cm^{-1} (CO); n.m.r. 0.89 (t, J 6 Hz, CH_3), 2.08 (dd, $J_{1\alpha,7a}$ 6.5, $J_{3a,7a}$ 8 Hz, 7a-H), 2.44 (t, $J_{3',4'}$ 7 Hz, 3'-H), 2.4—2.85 (3a-H, 1'-H), 3.45 (dd, $J_{3a,3\alpha}$ 7, $J_{3\alpha,3\beta}$ 9 Hz, 3a-H), 3.7—4.2 (1-H, 3β-H), 4.67 and 4.97 (s, 4- and 7-H), and 6.36 (s, 5- and 6-H).

exo-1-(*Methoxycarbonylmethyl*)-4,7-*epoxy*-1,3,3a,4,7,7a-*hexahydroisobenzofuran* (19).—Horner reaction of trimethyl phosphonoacetate (910 mg), sodium hydride (200 mg, 60% dispersion), and the alcohol (13) (780 mg) in THF was carried out as described in the preceding experiment to give an oil (860 mg), which was purified on a silica gel column (eluant chloroform) to give a 4 : 1 mixture (680 mg, 65%) of (19) and its C(1)-isomer. Main isomer (19): i.r. 1 735 cm^{-1} (CO_2Me); n.m.r. 2.17 (dd, $J_{1\alpha,7a}$ 6.5, $J_{3a,7a}$ 8 Hz, 7a-H), 2.4—2.85 (3a-H, CH_2CO_2Me), 3.46 (dd, $J_{3\alpha,3\beta}$ 9, $J_{3\alpha,7a}$ 7 Hz, 3α-H), 3.69 (s, OCH_3), 3.6—4.15 (1-H, 3β-H), 4.67 and 4.84 (s, 4- and 7-H), and 6.36 (5- and 6-H) (Found: C, 63.0; H, 6.7. $C_{11}H_{14}O_4$ requires C, 62.84; H, 6.69%).

exo-3α-(2-*Oxoheptyl*)-4,7-*epoxyhexahydrophthalide* (22).—The Horner reaction of the oxophosphonate (16) (448 mg), sodium hydride (100 mg, 60% dispersion), and the hydroxy-lactone (21) [13] (316 mg) was performed as described for (15). The reaction mixture was acidified with dilute HCl and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated to give (22) (350 mg, 71%) as an oil, which slowly crystallised. Recrystallisation from cyclohexane–ethyl acetate afforded the analytical sample, m.p. 57—58.5 °C. I.r. (KBr) 1 760 (lactone) and 1 700 cm^{-1} (ketone); n.m.r. 0.88 (t, J 6 Hz, CH_3), 2.34 ($J_{3.3a}$ 3.5, $J_{3a,7a}$ 8 Hz, 3a-H), 2.42 (t, J 7 Hz, $COCH_2Bu$), 2.85 (7a-H), 2.76 (J 18 and 8 Hz) and 2.99 (J 18 and 5 Hz) ($CHCH_2CO$), 4.45—4.65 (3-H), 4.7 (4-H), and 4.84 (7-H) (Found: C, 61.6; H, 8.8. $C_{15}H_{22}O_4$ requires C, 61.74; H, 8.88%).

exo-3-(2-*Methoxycarbonylethenyl*)-7-*oxabicyclo*[2.2.1]-*heptane*-exo-2-*carboxylic Acid* (23).—The Horner reaction of trimethyl phosphonoacetate (910 mg), sodium hydride (400 mg, 60% dispersion), and the hydroxy-lactone (21) (850 mg) in THF was performed following the procedure described for (15). Water was then added and the mixture was extracted with ether. The aqueous layer was acidified and extracted with ether. The ethereal extract was dried and concentrated to furnish crystalline (23) (310 mg, 27%), m.p. 128—130.5 °C. I.r. (KBr) 3 500—2 700 (CO_2H), 1 730 (CO_2Me), 1 715 (CO_2H), and 1 655 cm^{-1} (C=C); n.m.r. 1.4—1.95 (5- and 6-H_2), 2.85—3.10 (2- and 3-H), 3.71 (s, OCH_3), 4.42 (4-H), 4.94 (1-H), 5.89 (d, J 16.5 Hz, $CH{=}CH{-}CO$), 6.65—7.0 ($CH{=}CH{-}CO$), and 8.95 (CO_2H) (Found: C, 58.6; H, 6.3. $C_{11}H_{14}O_5$ requires C, 58.40; H, 6.24%).

exo-3-(6-*Ethoxycarbonylhexa*-1,3,5-*trienyl*)-7-*oxabicyclo*-[2.2.1]*heptane*-exo-2-*carboxylic Acid* (24).—A solution of triethyl phosphonosorbate (17) [16] (8.5 g) in THF (50 ml) was added to sodium hydride (2.7 g, 60% dispersion in oil, washed with n-hexane) in THF (70 ml) under nitrogen. The mixture was stirred for 30 min and then the hydroxy-lactone (21) (5.1 g) was added, portionwise, to the dark brown solution. After the mixture had been stirred for 18 h, water was added to it. The mixture was extracted with ether; the aqueous layer was acidified and again extracted with ether. The latter extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give 8.4 g of crude product, which was purified by column chromatography (silica gel–ethyl acetate), affording (24) (3.9 g, 45%), m.p. 226—228 °C. I.r. 3 500—2 500 (CO_2H), 1 710 (CO_2H, CO_2Et), and 1 620 cm^{-1} (triene); n.m.r. 1.29 (t, J 7 Hz, CH_3), 1.6—1.95 (5- and 6-H_2), 2.85—3.10 (2- and 3-H), 4.19 (q, OCH_2), 4.38 (4-H), 4.86 (1-H), and 8.6—9.0 (CO_2H); $\lambda_{max.}$(EtOH) 305 nm (ε 4 410) (Found: C, 65.7; H, 7.0. $C_{16}H_{20}O_5$ requires C, 65.74; H, 6.90%).

exo-3-(6-*Ethoxycarbonylhexyl*)-7-*oxabicyclo*[2.2.1]*heptane*-exo-2-*carboxylic Acid* (25).—Hydrogenation of the triene (24) in ethyl acetate in the presence of 10% Pd/C gave the saturated compound (25) in quantitative yield. I.r. 3 500—2 500 (CO_2H) and 1 720 cm^{-1} (CO_2H, CO_2Et); n.m.r. 1.24 (t, J 7 Hz, CH_3), 2.26 (t, J 7 Hz, CH_2CO_2Et), 2.76 (d, $J_{2.3}$ 9 Hz, 2-H), 4.11 (q, J 7 Hz, OCH_2), 4.36 (4-H), 4.75 (1-H), and 8.0—8.3 (CO_2H) (Found: C, 64.2; H, 8.7. $C_{16}H_{26}O_5$ requires C, 64.40; H, 8.78%).

exo-2-(6-*Ethoxycarbonylhexyl*)-exo-3-(*hydroxymethyl*)-7-*oxabicyclo*[2.2.1]*heptane* (26).—(*a*) *From the carboxylic acid* (25). Ethyl chloroformate (0.55 g) was added slowly at −5 °C to a stirred solution of the carboxylic acid (25) (1.3 g) and triethylamine (0.50 g) in THF (10 ml). Stirring was continued for 30 min at 0 °C, after which triethylammonium chloride was filtered off and washed with THF (5 ml). The filtrate was added to $NaBH_4$ (1.0 g) in ethanol (25 ml) at 0 °C and the reaction mixture was stirred for 2 h at room temperature. The mixture was then cooled and the excess of $NaBH_4$ was decomposed with dilute HCl. After addition of water, the mixture was extracted with ether. The extract was washed with sodium hydrogencarbonate solution and brine, dried ($MgSO_4$), and concentrated *in vacuo* to provide 0.80 g (65%) of the alcohol (26) as an oil, homogeneous on t.l.c.

(*b*) *From hydrogenation of* (31). A solution of the benzyl ether (31) (530 mg) in ethanol (25 ml) was hydrogenated over 10% Pd/C (100 mg) for 17 h in a Parr apparatus to give 410 mg (100%) of the alcohol (26). I.r. 3 500 (OH) and 1 725 cm^{-1} (CO_2Et); n.m.r. 1.24 (t, J 7 Hz, CH_3), 1.75—2.1 (2- and 3-H), 2.28 (t, J 7 Hz, CH_2CO_2Et), 2.63 (OH), 3.35—3.75 (CH_2O), 4.11 (q, J 7 Hz, OCH_2CH_3), and 4.25 and 4.49 (1- and 4-H) (Found: C, 67.4; H, 9.9. $C_{16}H_{28}O_4$ requires C, 67.57; H, 9.93%).

exo-2-(6-*Ethoxycarbonylhexyl*)-exo-3-*formyl*-7-*oxabicyclo*-[2.2.1]*heptane* (27).—A mixture of the alcohol (26) (4.6 g), *NN'*-dicyclohexylcarbodi-imide (10.6 g), trifluoroacetic acid (0.8 ml), pyridine (1.6 ml), dimethyl sulphoxide (20 ml), and benzene (20 ml) was stirred for 18 h. After addition of ether (50 ml), oxalic acid (4.5 g) was added carefully. The mixture was stirred for 15 min, then water was added and the precipitated dicyclohexylurea was filtered off. The organic layer was washed with sodium hydrogencarbonate solution and brine, dried ($MgSO_4$), and the solvent evaporated off *in vacuo* to afford 5.5 g of the crude aldehyde (27), which was used without further purification in the next step. N.m.r. 1.21 (t, J 7 Hz, CH_3), 2.26 (t, J 7 Hz,

CH_2CO_2Et), 2.50 (dd, $J_{2,3}$ 8.5, $J_{3,CHO}$ 4.5 Hz, 3-H), 4.10 (q, J 7 Hz, OCH_2), 4.37 (1-H), 4.70 (4-H), and 9.52 (d, J 4.5 Hz, CHO).

exo,exo-2,3-*Bis*(*hydroxymethyl*)-7-*oxabicyclo*[2.2.1]*heptane* (28).—The anhydride (20) [13] (30 g) was added in portions, over a period of 30 min, to $LiAlH_4$ (10 g) in THF (600 ml) at −5 °C under nitrogen. After being stirred for 20 h at room temperature, the mixture was cooled to 0 °C and then water (10 ml), 10% aqueous sodium hydroxide (10 ml), and water (30 ml) were successively added with caution. Stirring was continued for 30 min and then the precipitate was filtered off and washed thoroughly with ether. After evaporation of the solvent *in vacuo*, benzene was added to the residue and this was again evaporated. This procedure was repeated to remove contaminating water, yielding 26.15 g (93%) of the diol (28), m.p. 61—63 °C. I.r. 3 600 and 3 400 cm^{-1} (OH); n.m.r. 1.31—1.8 (5- and 6-H_2), 2.0—2.35 (2- and 3-H), 3.92 (OH), and 4.29 (1- and 4-H) (Found: C, 60.8; H, 8.9. $C_8H_{14}O_3$ requires C, 60.74; H, 8.92%).

exo-2-(*Benzyloxymethyl*)-exo-3-(*hydroxymethyl*)-7-*oxabicyclo*[2.2.1]*heptane* (29).—To sodium hydride (1.0 g, 60% dispersion in oil, washed with n-hexane) in DMF (20 ml) was added, under nitrogen, a solution of diol (28) (4.0 g) in DMF (10 ml). The reaction mixture was stirred until evolution of gas had ceased. Benzyl bromide (5.0 g) in DMF (15 ml) was then added and the mixture was stirred for 20 h at 70 °C. After evaporation of the solvent, water was added to the residue and the mixture was extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified on a silica gel column (elution with cyclohexane–ethyl acetate 1 : 1) to give the diol (28) (0.58 g), dibenzylated product (0.58 g), and monobenzylated product (29) (4.64 g, 74%). I.r. 3 430 (OH) and 1 600 cm^{-1} (phenyl); n.m.r. 1.35—1.85 (5- and 6-H_2), 1.95—2.45 (2- and 3-H), 3.0 (OH), 3.25—3.65 (CH_2O), 4.31 (1- and 4-H), 4.48 (s, OCH_2Ph), and 7.31 (s, C_6H_5) (Found: C, 72.3; H, 8.0. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%).

exo-2-(*Benzyloxymethyl*)-exo-3-*formyl*-7-*oxabicyclo*[2.2.1]-*heptane* (30).—Moffatt oxidation of the alcohol (29) (2.44 g), according to the procedure described for (27), afforded 2.46 g of the crude aldehyde (30), which was used without further purification in the next step. I.r. 1 750 and 1 720 cm^{-1} (CHO); n.m.r. 1.25—1.95 (5- and 6-H_2), 2.35—2.75 (2- and 3-H), 3.25—3.65 (CH_2O), 4.44 (s, OCH_2Ph), 4.44 (1-H), 4.77 (4-H), 7.31 (s, C_6H_5), and 9.6 (d, J 3.5 Hz, CHO). The 2,4-dinitrophenylhydrazone had m.p. 163—165 °C (Found: C, 59.3; H, 5.2; N, 13.1. $C_{21}H_{22}N_4O_6$ requires C, 59.15; H, 5.20; N, 13.14%).

exo-2-(*Benzyloxymethyl*)-exo-3-(6-*ethoxycarbonylhexa*-1,3,5-*trienyl*)-7-*oxabicyclo*[2.2.1]*heptane* (31).—To sodium hydride (500 mg, 60% dispersion in oil, washed with n-hexane) in THF (25 ml), under nitrogen, was added a solution of triethyl phosphonosorbate (17) (4.0 g) in THF (25 ml), and the mixture was stirred for 20 min. The crude aldehyde (30) (2.46 g) in THF (15 ml) was then added to the dark brown solution and stirring was continued for 2 h. Following addition of water, the reaction mixture was extracted with ether and the ethereal extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over silica gel (elution with cyclohexane–ethyl acetate 3 : 1) to afford 1.72 g [48% from (29)] of (31). I.r. 1 700 (CO_2Et), 1 620 (triene), and 1 590 and 1 500 cm^{-1} (phenyl); n.m.r. 1.27 (t, J 7 Hz, CH_3), 1.4—1.9 (5- and 6-H_2), 2.0—2.7 (2- and 3-H), 3.1—3.5 (CH_2O), 4.20 (q, J 7 Hz, OCH_2Me), 4.25 (1-H), 4.42 (s, OCH_2Ph), 4.49 (4-H), 5.6—6.5 and 7.0—7.5 (6 olefinic H), and 7.31 (C_6H_5) (Found: C, 74.9; H, 7.8. $C_{23}H_{28}O_4$ requires C, 74.97; H, 7.66%).

exo-2-(6-*Ethoxycarbonylhexyl*)-exo-3-(3-*oxo-oct*-1-*enyl*)-7-*oxabicyclo*[2.2.1]*heptane* (32).—Horner reaction of dimethyl-2-oxoheptylphosphonate (16) (4.44 g), sodium hydride (800 mg, 60% dispersion), and the crude aldehyde (27) (5.4 g) in THF (80 ml) was performed as described for (15). The crude product was purified by column chromatography on silica gel (eluant cyclohexane–ethyl acetate 4 : 1) to furnish 3.87 g [63% from (26)] of (32). I.r. 1 720 (CO_2Et), 1 665 (C=O), and 1 625 cm^{-1} (C=C); n.m.r. 0.90 (t, J 6 Hz, CH_3), 1.27 (t, J 7 Hz, ester CH_3), 2.1—2.4 (2-H), 2.26 (t, J 7 Hz, CH_2CO_2Et), 2.45—2.70 (3-H), 2.54 (t, J 7 Hz, $COCH_2$), 4.11 (q, J 7 Hz, OCH_2), 4.2—4.4 (1- and 4-H), 6.01 (d, J 16 Hz, CH=C*H*CO), and 6.71 (dd, J 16 and 10 Hz, C*H*=CHCO) (Found: C, 72.9; H, 10.2. $C_{23}H_{38}O_4$ requires C, 72.97; H, 10.12%).

exo-2-(6-*Ethoxycarbonylhexyl*)-exo-3-(3-*hydroxyoct*-1-*enyl*)-7-*oxabicyclo*[2.2.1]*heptane* (33a, b).—A solution of $Zn(BH_4)_2$ in dimethoxyethane (5 ml; 0.5M) was added dropwise to a solution of the enone (32) (1.04 g) in dimethoxyethane (15 ml). The mixture was stirred for 3 h and then a saturated solution of sodium hydrogentartrate was added dropwise until no further evolution of gas was observed. The reaction mixture was extracted with ether and the ethereal extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to provide 1.01 g (97%) of the epimeric enols (33a, b), which showed two spots on t.l.c. (silica gel; cyclohexane–ethyl acetate 1 : 1), R_F 0.34 (33a) and 0.45 (33b). I.r. 3 500 (OH) and 1 720 cm^{-1} (CO_2Et); n.m.r. 0.92 (t, J 6 Hz, CH_3), 1.27 (t, J 7 Hz, ester CH_3), 2.26 (t, J 7 Hz, CH_2CO_2Et), 2.40 (OH), 2.35—2.60 (3-H), 3.95—4.15 (C*H*OH), 4.14 (q, J 7 Hz, OCH_2), 4.15—4.35 (1- and 4-H), and 5.35—5.60 (CH=CH) (Found: C, 72.6; H, 10.6. $C_{23}H_{40}O_4$ requires C, 72.59; H, 10.60%). The isomers (33a) and (33b) could be separated by column chromatography on silica gel (eluant cyclohexane–ethyl acetate 5 : 1).

endo-3,6-*Epoxyhexahydrophthalic Anhydride* (37).—A solution of the *endo*-dicarboxylic acid (36) [12] (15 g) in pyridine (30 ml) and acetic anhydride (30 ml) was stirred for 0.5 h. After partial evaporation, ether was added and the crystalline material was filtered off to give 12.3 g (91%) of the *endo*-anhydride (37), m.p. 166—167 °C; i.r. (KBr) 1 855 and 1 785 cm^{-1} (anhydride).

endo-3-(2-*Oxoheptyl*)-4,7-*epoxyhexahydrophthalide* (39) *and* exo-3-(3-*Oxo-oct*-1-*enyl*)-7-*oxabicyclo*[2.2.1]*heptane*-2-*carboxylic Acid* (40).—The Horner reaction of the *endo*-hydroxylactone (38) [13] with phosphonate (16) in THF, was carried out as described for (22). After addition of water, the mixture was extracted with ether. The aqueous layer was acidified and again extracted with ether. The latter extract was dried, concentrated *in vacuo*, and chromatographed through a silica gel column to give the lactone (39) (30%); i.r. 1 760 (lactone) and 1 710 cm^{-1} (ketone) and the enone (40) (27%); i.r. 3 500—2 500 (CO_2H), 1 700 (CO_2H), 1 665 and 1 620 cm^{-1} (enone); n.m.r. 0.89 (t, J 6.5 Hz, CH_3), 2.55 (t, J 7 Hz, $COCH_2$), 2.8—3.1 (2- and 3-H), 4.47 (4-H), 4.87 (1-H), 6.14 (d, J 16 Hz, CH=C*H*CO), 6.74 (dd, J 16 and 8 Hz, C*H*=CHCO), and 8.0—8.4 (CO_2H).

exo-2-(6-*Ethoxycarbonylhexyl*)-endo-3-(*hydroxymethyl*)-7-*oxabicyclo*[2.2.1]*heptane* (41) *and the* endo,endo-*Isomer* (43).—(*a*) *From the hydroxy-lactone* (38). The alcohols (41)

and (43) were obtained in a 1 : 1 ratio from the *endo*-hydroxy-lactone (38) in the same manner as has been described for the alcohol (26) from the *exo*-hydroxy-lactone (21). If the hydroxy-lactone (38) was stirred for 0.5 h in the presence of 2 equivalents of sodium hydride and a catalytic amount of ethanol, column chromatography (silica gel; cyclohexane–ethyl acetate 2 : 1) of the crude material from the last step afforded (41) (32%) and (43) (7%).

(*b*) ***From the diol*** (47). A mixture of the alcohols (41) and (43) was also prepared from the *endo*-diol (47) through a similar sequence as described for conversion of the diol (28) into the alcohol (26). If the aldehyde (49) was isomerised by stirring it for 15 min with 1 equivalent of sodium hydride and a catalytic amount of ethanol prior to addition of triethyl phosphonosorbate (17), the *trans*-isomer of (50) [40% from (48)] was formed exclusively, thus producing the pure alcohol (41) after catalytic hydrogenation; (41), m.p. 59—60 °C; i.r. 3 500 (OH) and 1 730 cm^{-1} (CO_2Et); n.m.r. 1.24 (t, *J* 7 Hz, CH_3), 2.22 (t, *J* 7 Hz, CH_2CO_2Et), 2.99 (OH), 3.45 and 3.73 (AB part of ABX system, J_{AB} 11, J_{AX} 10, and J_{BX} 5 Hz, CH_2OH), 4.09 (q, *J* 7 Hz, OCH_2), 4.15 (1-H), and 4.55 (4-H) (Found: C, 67.3; H, 9.8. $C_{16}H_{28}O_4$ requires C, 67.57; H, 9.93%); (43), i.r. 3 500 (OH) and 1 730 cm^{-1} (CO_2Et); n.m.r. 1.24 (t, *J* 7 Hz, CH_3), 2.24 (t, *J* 7 Hz, CH_2CO_2Et), 2.1—2.4 (3-H), 3.35—3.65 (CH_2OH), 3.46 (OH), 4.10 (q, *J* 7 Hz, OCH_2), and 4.44 and 4.56 (1- and 4-H) (Found: C, 67.5; H, 9.8. $C_{16}H_{28}O_4$ requires C, 67.57; H, 9.93%).

exo-2-(6-*Ethoxycarbonylhexyl*)-endo-3-*formyl*-7-*oxabicyclo*[2.2.1]*heptane* (42).—Moffatt oxidation of the alcohol (41) gave the crude aldehyde (42), which was not purified. N.m.r. 1.25 (t, *J* 7 Hz, CH_3), 2.25 (t, *J* 7 Hz, CH_2CO_2Et), 2.45—2.70 (3-H), 4.10 (q, *J* 7 Hz, OCH_2), 4.29 (1-H), 4.75 (4-H), and 9.70 (d, *J* 2 Hz, CHO).

endo-2-(6-*Ethoxycarbonylhexyl*)-endo-3-*formyl*-7-*oxabicyclo*[2.2.1]*heptane* (44).—Moffatt oxidation of the alcohol (43) gave the crude aldehyde (44), which was not purified. N.m.r. 1.24 (t, *J* 7 Hz, CH_3), 2.27 (t, *J* 7 Hz, CH_2CO_2Et), 2.70—2.95 (3-H), 4.10 (q, *J* 7 Hz, OCH_2), 4.54 and 4.64 (1- and 4-H), and 9.78 (d, *J* 3 Hz, CHO).

endo,endo-2,3-*Bis*(*hydroxymethyl*)-7-*oxabicyclo*[2.2.1]*heptane* (47).—A solution of the diester (46) [12] (12.5 g) in THF (50 ml) was added at 0 °C to $LiAlH_4$ (4.0 g) in THF (100 ml) under nitrogen. The mixture was stirred for 18 h at room temperature and worked up as described for (28) to afford 9.07 g (98%) of the diol (47), m.p. 88—89 °C. I.r. 3 620 and 3 400 cm^{-1} (OH); n.m.r. 1.57 (5- and 6-H_2), 2.35—2.60 (2- and 3-H), 3.45—3.95 (CH_2OH), and 4.53 (1- and 4-H) (Found: C, 60.7; H, 8.8. $C_8H_{14}O_3$ requires C, 60.74; H, 8.92%).

endo-2-(*Benzyloxymethyl*)-endo-3-(*hydroxymethyl*)-7-*oxabicyclo*[2.2.1]*heptane* (48).—Benzylation of the diol (47), according to the procedure described for (29), provided the monobenzyl ether (48), m.p. 76—78 °C. N.m.r. 1.54 (5- and 6-H_2), 2.25—2.75 (2- and 3-H), 3.05—3.85 (CH_2OH, CH_2O-benzyl), 4.5 (1- and 4-H, OCH_2Ph), and 7.31 (s, C_6H_5) (Found: C, 72.6; H, 8.1. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%).

endo-2-(*Benzyloxymethyl*)-endo-3-*formyl*-7-*oxabicyclo*[2.2.1]*heptane* (49).—Moffatt oxidation of alcohol (48), carried out as described for (27), afforded the crude aldehyde (49), which was not purified. N.m.r. 1.0—2.0 (5- and 6-H_2), 2.8—3.0 (2-H), 3.1—3.75 (CH_2O), 4.5—4.85 (1- and 4-H), 4.49 (s, OCH_2Ph), 7.31 (s, C_6H_5), and 9.81 (d, *J* 2 Hz, CHO).

exo-2-(6-*Ethoxycarbonylhexyl*)-endo-3-(3-*oxo*-*oct*-1-*enyl*)-7-*oxabicyclo*[2.2.1]*heptane* (51).—Horner reaction of the aldehyde (42) with the phosphonate (16), performed as described for (32), furnished the enone (51) [62% from (41)]. I.r. 1 720 (CO_2Et), 1 665 (C=O), and 1 620 cm^{-1} (C=C); n.m.r. 0.92 (t, *J* 6 Hz, CH_3), 1.25 (t, *J* 7 Hz, ester CH_3), 2.29 (t, *J* 7 Hz, CH_2CO_2Et), 2.20—2.45 (3-H), 2.55 (t, *J* 7 Hz, $COCH_2$), 4.13 (q, *J* 7 Hz, OCH_2), 4.27 (1-H), 4.47 (4-H), 6.18 (d, *J* 16 Hz, CH=C*H*CO), and 6.73 (dd, *J* 16 and 8.5 Hz, C*H*=CHCO) (Found: C, 72.8; H, 10.2. $C_{23}H_{38}O_4$ requires C, 72.97; H, 10.12%).

exo-2-(6-*Ethoxycarbonylhexyl*)-endo-3-(3-*hydroxyoct*-1-*enyl*)-7-*oxabicyclo*[2.2.1]*heptane* (52a, b).—Reduction of the enone (51) with $Zn(BH_4)_2$, as described for (33a, b), gave a mixture of the epimeric enols (52a, b). T.l.c. (silica gel; cyclohexane–ethyl acetate 1 : 1), R_F 0.33 (52a) and 0.42 (52b). I.r. 3 500 (OH) and 1 720 cm^{-1} (CO_2Et), n.m.r. 0.89 (t, *J* 6 Hz, CH_3), 1.25 (t, *J* 7 Hz, ester CH_3), 2.1—2.4 (3-H of ring, OH), 2.28 (t, *J* 7 Hz, CH_2CO_2Et), 3.95—4.2 (C*H*OH), 4.11 (q, *J* 7 Hz, OCH_2), 4.20 and 4.36 (1- and 4-H), and 5.25—5.70 (C*H*=C*H*) (Found: C, 72.6; H, 10.5. $C_{23}H_{40}O_4$ requires C, 72.59; H, 10.60%). The isomers (52a) and (52b) were separated by column chromatography on silica gel (eluant cyclohexane–ethyl acetate 5 : 1).

endo-2-(6-*Ethoxycarbonylhexyl*)-exo-3-(3-*oxo*-*oct*-1-*enyl*)-7-*oxabicyclo*[2.2.1]*heptane* (54).—Isomerisation of the crude aldehyde (44) with 1 equivalent of sodium hydride and a catalytic amount of ethanol for 15 min, followed by Horner reaction with the phosphonate (16), gave the enone (54) [66% from (43)]. Moffatt oxidation of the alcohol (57), and subsequent Horner reaction of the crude aldehyde thus obtained, provided the enone (54) in 64% yield. I.r. 1 720 (CO_2Et), 1 660 (C=O), and 1 620 cm^{-1} (C=C); n.m.r. 0.91 (t, *J* 6 Hz, CH_3), 1.26 (t, *J* 7 Hz, ester CH_3), 1.85—2.10 (3-H ring; $J_{2,3}$ 5.5 Hz), 2.29 (t, *J* 7 Hz, CH_2CO_2Et), 2.55 (t, *J* 7 Hz, $CO{\cdot}CH_2$), 4.12 (q, *J* 7 Hz, OCH_2), 4.29 (4-H), 4.50 (1-H), 5.99 (d, *J* 16 Hz, CH=C*H*CO), and 6.72 (dd, *J* 16 and 9 Hz, C*H*=CHCO) (Found: C, 72.8; H, 10.0. $C_{23}H_{38}O_4$ requires C, 72.97; H, 10.12%).

endo-2-(6-*Ethoxycarbonylhexyl*)-exo-3-(3-*hydroxyoct*-1-*enyl*)-7-*oxabicyclo*[2.2.1]*heptane* (55a, b).—Reduction of the enone (54) with $Zn(BH_4)_2$ gave a mixture of the epimeric enols (55a, b). T.l.c. (silica gel; cyclohexane–ethyl acetate 1 : 1) R_F 0.32 (55a) and 0.41 (55b). I.r. 3 500 (OH) and 1 720 (CO_2Et) cm^{-1}; n.m.r. 0.90 (t, *J* 6 Hz, CH_3), 1.26 (t, *J* 7 Hz, ester CH_3), 2.28 (t, *J* 7 Hz, CH_2CO_2Et), 2.3—2.55 (3-H of ring), 3.90—4.15 (C*H*OH), 4.10 (q, *J* 7 Hz, OCH_2), 4.19 (4-H), 4.32 (1-H), and 5.25—5.75 (C*H*=C*H*) (Found: C, 72.5; H, 10.5. $C_{23}H_{40}O_4$ requires C, 72.59; H, 10.60%). The isomers (55a) and (55b) were separated by column chromatography on silica gel (eluant cyclohexane–ethyl acetate 5 : 1).

endo-2-(6-*Ethoxycarbonylhexyl*)-exo-3-(*hydroxymethyl*)-7-*oxabicyclo*[2.2.1]*heptane* (57).—The hydroxy-lactone (21) was added to a solution of sodium (1.4 g) in ethanol (50 ml) and stirred for 3 h. Triethyl phosphonosorbate (17) (8.4 g) was then added and stirring was continued for 3 h. After a work-up as described for (24), a 3 : 2 mixture of the triene (24) and its isomer with an *endo*-carboxy-group was obtained. Catalytic hydrogenation and reduction of the carboxy-function, carried out as described for conversion of (24) into (26), followed by careful column chromatography on silica gel, afforded (24) [14% from (21)] and (57) [11% from (21)]. (57): I.r. 3 500 (OH) and 1 725

cm^{-1} (CO_2Et); n.m.r. 1.25 (t, *J* 7 Hz, CH_3), 2.28 (t, *J* 7 Hz, CH_2CO_2Et), 2.25—2.45 (3-H, OH), 3.40—3.55 (CH_2OH), 4.12 (q, *J* 7 Hz, OCH_2), and 4.40 (1- and 4-H) (Found: C, 67.6; H, 10.1. $C_{16}H_{28}O_4$ requires C, 67.57; H, 9.93%).

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