Preparation and Hydrolysis of Some 4-Substituted Bicyclo[3.1.0]hex-2-ene-6-carbaldehydes: Synthesis of the Prostaglandin A_2 Analogue possessing a Butyl Group in Place of the Octenol Side Chain

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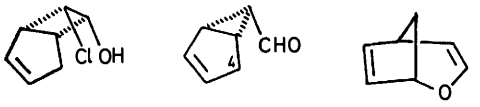
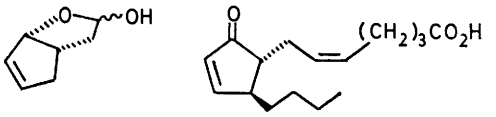
The halogenoesters (7) and (13) were treated with various nucleophiles to give a range of 4,6,7-trisubstituted bicyclo[3.2.0]heptenes (8)—(12) and (14)—(20). The esters (11), (12), and (17)—(20) were treated with hydroxide or methoxide ion to give the corresponding bicyclo[3.1.0]hexene-6-*endo*-carbaldehyde (21), (22), and/or the bicyclo[3.1.0]hexene-6-*exo*-carbaldehyde (24)—(27). The *endo*-aldehydes (21) and (22) were readily hydrolysed under acid catalysis to give the lactols (32) and (33): the *exo*-aldehydes (24)—(26) were hydrolysed to the corresponding lactols (32)—(34) under more forcing conditions. The lactol (32) was converted into the prostaglandin A_2 analogue (5) by a Wittig reaction followed by a Jones oxidation.

It has been demonstrated that on treatment with aqueous sodium hydroxide the chlorohydrin (1) gave bicyclo[3.1.0]hex-2-ene-6-*endo*-carbaldehyde (2) [1] and that this aldehyde exists in equilibrium with the enol-



(1) (2) (3)



(4) (5)

ether (3).[2] Moreover, mild acid-catalysed hydrolysis of the enol-ether (3) gave the lactol (4).[3] We reasoned that if we could prepare various 4-substituted bicyclohexene-6-carbaldehydes then hydrolysis should furnish lactols that might be readily converted into analogues of prostaglandin A_2, *e.g.* (5).

RESULTS AND DISCUSSION †

The chlorohydrin (1) was readily acetylated to give the chloroester (6). Irradiation of (6) in carbon tetrachloride containing *N*-bromosuccinimide gave a mixture of the dihalogenoacetates (7) and (13) [99%; ratio (7) : (13) *ca.* 1 : 1]. The ester (7) was purified by fractional crystallization while a small quantity of the isomer (13) was obtained by high-pressure liquid chromatography (h.p.l.c.). Column chromatography of the mixture of (7) and (13) over silica using ethanol in chloroform as the eluant gave only the ethers (8) and (14) and the alcohols (9) and (15). Similarly, reaction of the esters (7) and (13) with a paste of silica and acetic acid gave the alcohols (9) and (15) and also the diesters (10) and (16).

Morpholine reacted with the bromoesters (7) and (13) at room temperature to give a mixture of the amines (11) and (17) while lithium dibutylcuprate reacted with a mixture of (7) and (13) (ratio 1 : 1) at low temperature to give the chloroacetates (12) and (18) (ratio 1 : 1). It was interesting to note that under the same reaction conditions the pure ester (7) gave only the butylated derivative (18) in 95% yield through an S_N' *syn*-process.[4] Potassium thiophenoxide also reacted specifically *via* an S_N' *syn*-process with the ester (7) to give the thioether (19) in 95% yield.

Treatment of the butylchloroacetates (12) and (18) with aqueous sodium hydroxide gave the *endo*-aldehyde (21) [5] while employment of more basic reaction conditions for the rearrangement led to the formation of the *exo*-aldehyde (24). The *endo*-aldehyde (21) was also converted into the *exo*-aldehyde (24) on photolysis in acetone.[6] The chlorothio ester (19) gave a mixture of the *endo*- (22) and *exo*-carbaldehyde (25) [(ratio (22) : (25) was 1 : 3] when set aside in methanol containing potas-

(6) R = H
(7) R = Br
(8) R = OEt
(9) R = OH
(10) R = OAc
(11) R = —N O
(12) R = n-C_4H_9
R = SPh
R = -CH=CHCHC$_5H_{11}$ (OSi)

(13)
(14)
(15)
(16)
(17)
(18)
(19)
(20)

(21) R = n-C_4H_9
(22) R = SPh
(23) R = -CH=CHCHC$_5H_{11}$ (OSi)

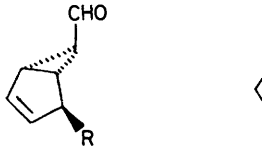
sium carbonate. The former compound was hydrolysed preferentially on heating the mixture in water containing oxalic acid (*vide infra*) allowing the *exo*-aldehyde (25) to be isolated by chromatography. A pure sample of the *endo*-aldehyde (22) was obtained as follows. The chloroester (19) was treated with an excess of lithium aluminium hydride in ether to give the chlorohydrin (28) and the primary alcohol (29). Controlled oxidation of the

† All substrates and products are racemic: only one enantiomer is illustrated in the diagrams.

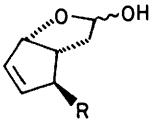
alcohol (29) gave the *endo*-aldehyde (22). Potassium carbonate in methanol at ambient temperature converted the aminochloroacetates (11) and (17) into the *exo*-aldehyde (26).

N.m.r. spectral data indicated that at room temperature in chloroform solution the aldehyde (21) was in equilibrium with the enol-ether (30) (ratio 4 : 1): similarly the aldehyde (22) and the enol-ether (31) equilibrate to a 8 : 1 mixture through a Cope rearrangement.

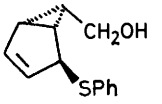
As expected from earlier work by Dreiding,[3] the mixtures (21) ⇌ (30) and (22) ⇌ (31) were easily hydrolysed in water containing a catalytic quantity of oxalic acid to give the lactols (32) and (33) respectively. In contrast the corresponding *exo*-aldehydes (24) and (25) were not readily hydrolysed although the use of more vigorous hydrolysis conditions (*e.g.* aqueous acetic acid at 80 °C) still led to a high yield of the appropriate lactols (32) : (33). The aminoaldehyde (26) was not hydrolysed using oxalic or acetic acid as the catalyst but furnished the lactol (34) on treatment with aqueous perchloric acid. The lactol (34) gave the lactone (35) on Jones oxidation, while the lactol (33) gave the sulphonolactone (36) under the same conditions.



(24) R = n-C_4H_9
(25) R = SPh



(32)
(33)
(34)



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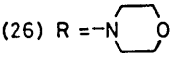
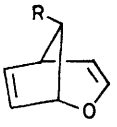
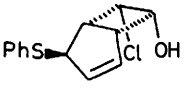


(26) R = -N O

(27) R = -CH=CHCHC$_5$H$_{11}$ (OSi)



(30) R = n-C_4H_9
(31) R = SPh



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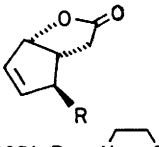
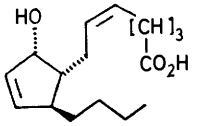


(35) R = -N O

(36) R = SO_2Ph

$Ph_3\overset{+}{P}\overset{-}{C}H[CH_2]_3CO_2^-$

(37)



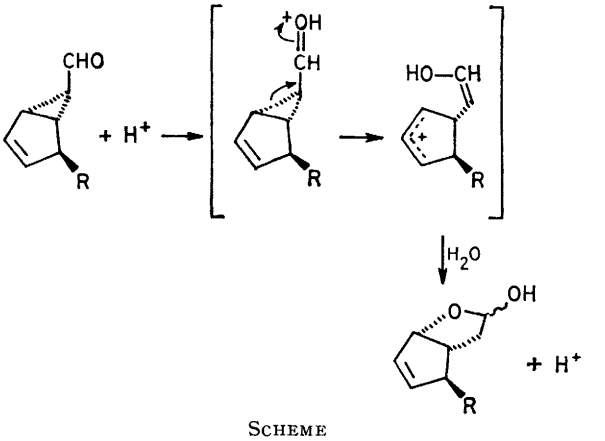
(38)

LiCu[CH=CHCH(OSi)C_5H_{11}]$_2$

(39)

Presumably, the *exo*-aldehydes (24)—(26) are hydrolysed by initial protonation of the carbonyl group and cyclopropyl bond cleavage to give an intermediate allyl carbonium ion as illustrated in the Scheme.

Reaction of the lactol (32) with the Wittig reagent (37) gave the hydroxy-acid (38) which was converted into the prostanoid (5) by a Jones oxidation. Thus the sequence (1)→[(7) + (13)]→[(12) + (18)]→(21)→(32)→(38)→(5) provides a prostaglandin A_2 congener in an overall yield of 35%.[7]



SCHEME

We attempted to prepare the useful aldehyde (23) [8] using the same strategy. Reaction of the halogeno-ester (7) with the cuprate reagent (39) gave the desired product (20) in a disappointing 40% yield. Moreover the chloroacetate (20) was inert to aqueous sodium hydroxide and the use of more basic media (*e.g.* potassium carbonate in methanol) to promote the ester hydrolysis/ring contraction process led to the formation of the *exo*-aldehyde (27). Treatment of the aldehyde (27) with a variety of aqueous acids gave complex mixtures of products in all cases.

EXPERIMENTAL

M.p.s were determined by the capillary tube method. The Buchi Kügelrohr (bulb-to-bulb) system was used for distillations and the b.p.s reported are oven temperatures at distillation. I.r. spectra were recorded on a Perkin-Elmer 257 spectrometer for neat films unless otherwise stated. N.m.r. spectra were recorded on a Varian EM-360 or Perkin-Elmer R-32 spectrometer (CCl_4 or $CDCl_3$ solvent). Column chromatography was performed using silica gel M.F.C.: t.l.c. was accomplished using silica gel G (Merck). Anhydrous sodium sulphate was used as a drying agent for solutions in organic solvents. Unless otherwise stated petroleum refers to the fraction boiling at 60—80 °C.

7-endo-*Chlorobicyclo*[3.2.0]*hept*-2-*en*-6-endo-*ol* (1).—This compound was prepared following the literature procedure.[1]

6-endo-*Acetoxy*-7-endo-*chlorobicyclo*[3.2.0]*hept*-2-*ene* (6).—A solution of the chlorohydrin (1) (2.7 g) in pyridine (50 ml) was treated with acetic anhydride (3.0 g) and the resulting solution was allowed to stand in the dark at room temperature for 48 h. Water was added to the mixture and organic material was extracted with ether (3 × 100 ml). The combined extracts were washed with 10% aqueous hydrochloric acid (100 ml), dried, and evaporated to leave an oil which was distilled to give the required *chloroacetate* (6) as a colourless oil (3.08 g, 82%), b.p. 75 °C at 0.05 mmHg; $\nu_{max.}$ 1 740 and 1 618 cm^{-1}; δ 6.00 (1 H, dd, *J* 6, 2 Hz, H-2 or H-3), 5.66 (1 H, dd, *J* 6, 2.5 Hz, H-3 or H-2), 5.40 (1 H, dt, *J* 2.5, 7 Hz, H-6), 4.80 (1 H, t, *J* 7 Hz, H-7), 3.70 (1 H, m, H-1), 3.17 (1 H, ddq, *J* 1, 3, 7.5 Hz, H-5), 2.50 (2 H, m, 2 ×

H-4), and 2.07 (3 H, s, $OCOCH_3$) (Found: M^+ 186.044 4. $C_9H_{11}ClO_2$ requires M 186.044 6).

Bromination of the Chloroacetate (6) *with* N-*Bromosuccinimide*.—To a solution of 6-*endo*-acetoxy-7-*endo*-chlorobicyclo-[3.2.0]hept-2-ene (6) (7.5 g) in anhydrous carbon tetrachloride (150 ml) was added freshly recrystallised *N*-bromosuccinimide (7.2 g) and the mixture was refluxed for 1½ h under irradiation by a 500 W light bulb. The mixture was filtered and the filtrate was washed with 10% aqueous hydrochloric acid. Evaporation of the solvent after drying afforded a mixture of the bromochloroacetates (7) and (13) (10.6 g, 99%) as a solid. H.p.l.c. showed the isomer ratio to be 1 : 1. Recrystallisation from carbon tetrachloride–petroleum gave 6-endo-*acetoxy*-4-exo-*bromo*-7-endo-*chlorobicyclo*[3.2.0]*hept*-2-*ene* (7)(1.5 g, 15%) as white prisms m.p. 85—88 °C; $\nu_{max.}$ 1 745, and 1 605 cm^{-1}; δ 6.25 (1 H, dd, *J* 6, 2 Hz, H-3 or H-2), 5.95 (1 H, dd, *J* 6, 2 Hz, H-2 or H-3), 5.46 (1 H, dt, *J* 2, 8 Hz, H-6), 5.17 (1 H, t, *J* 2 Hz, H-4), 4.80 (1 H, t, *J* 8 Hz, H-7), 4.00 (1 H, m, H-1), 3.50 (1 H, t, *J* 8 Hz, H-5), and 2.07 (3 H, s, $OCOCH_3$) (Found: C, 40.6; H, 3.9. $C_9H_{10}BrClO_2$ requires C, 40.7; H, 3.8%). A sample of 7-endo-*acetoxy*-4-exo-*bromo*-6-endo-*chlorobicyclo*[3.2.0]*hept*-2-*ene* (13), m.p. 70—75 °C, was obtained by h.p.l.c.; $\nu_{max.}$ 1 745 and 1 600 cm^{-1}; δ 6.24 (1 H, dm, *J* 6 Hz, H-3 or H-2), 5.96 (1 H, dm, *J* 6 Hz, H-2 or H-3), 5.38 (1 H, t, *J* 8 Hz, H-7), 5.29 (1 H, s, H-4), 4.82 (1 H, tt, *J* 8, 2 Hz, H-6), 4.02 (1 H, m, H-1), 3.44 (1 H, t, *J* 8 Hz, H-5), and 2.10 (3 H, s, $OCOCH_3$) (Found: P^+ 185.036 8. $C_9H_{10}BrClO_2$ requires M — Br 185.036 0).

Substitution Reactions with the Bromochloroacetates (7) *and* (13).—(*a*) A 1 : 1 mixture of the bromoacetates (7) and (13) (10 g) was chromatographed on a silica column with chloroform containing a small amount of ethanol as eluant and from the earlier fractions collected was obtained a mixture of 6-endo-*acetoxy*-7-endo-*chloro*-4-exo-*ethoxybicyclo*[3.2.0]*hept*-2-*ene* (8) and 7-endo-*acetoxy*-6-endo-*chloro*-4-exo-*ethoxybicyclo*[3.2.0]*hept*-2-*ene* (14) (0.5 g), b.p. 75 °C at 0.3 mmHg; $\nu_{max.}$ 1 750 cm^{-1} (Found: P^+ 195.101 9. $C_{11}H_{15}ClO_3$ requires M — Cl 195.102 0).

From the later fractions collected was obtained a mixture of 6-endo-*acetoxy*-7-endo-*chloro*-4-exo-*hydroxybicyclo*[3.2.0]-*hept*-2-*ene* (9) and 7-endo-*acetoxy*-6-endo-*chloro*-4-exo-*hydroxybicyclo*[3.2.0]*hept*-2-*ene* (15) (4 g), $\nu_{max.}$ 3 400 and 1 740 cm^{-1} (Found: M^+ 202.039 5. $C_9H_{11}ClO_3$ requires M 202.039 6).

(*b*) A slurry of the bromoacetates (7) and (13) in glacial acetic acid and silica was left for 3 days and then chromatographed to give a mixture of the two chlorohydroxyacetates (9) and (15) (39%) and a mixture of 6-endo, 4-exo-*diacetoxy*-7-endo-*chlorobicyclo*[3.2.0]*hept*-2-ene (10) and 7-endo, 4-exo-*diacetoxy*-6-endo-*chlorobicyclo*[3.2.0]*hept*-2-*ene* (16) (22%), b.p. 90 °C at 3 × 10^{-1} mmHg, $\nu_{max.}$ 1 735 cm^{-1} (Found M^+ 244.049 9. $C_{11}H_{13}ClO_4$ requires M 244.050 2).

(*c*) 6-endo-*Acetoxy*-7-endo-*chloro*-4-exo-*morpholinobicyclo*-[3.2.0]*hept*-2-*ene* (11) and 7-endo-*acetoxy*-6-endo-*chloro*-4-exo-*morpholinobicyclo*[3.2.0]*hept*-2-*ene* (17).—A 1 : 1 mixture of the bromo-acetates (7) and (13) was dissolved in morpholine (0.5 g in 10 ml). After 1 h water was added (100 ml) and the product extracted with chloroform (3 × 50 ml). The extracts were washed with water, dried, and evaporated to leave a residue which was chromatographed over alumina using ethyl acetate as eluant to give a 1 : 1 mixture of the two *morpholino-acetates* (11) and (17) (0.45 g, 88%), $\nu_{max.}$ 1 725 cm^{-1} (Found: M^+ 271.097 3. $C_{13}H_{18}ClNO_3$ requires M 271.097 4).

(*d*) 7-endo-*Acetoxy*-6-endo-*chloro*-4-exo-*phenylthiobicyclo*-[3.2.0]*hept*-2-*ene* (19).—To a solution of 6-*endo*-acetoxy-4-*exo*-bromo-7-*endo*-chlorobicyclo[3.2.0]hept-2-ene (7) (0.4 g) in anhydrous tetrahydrofuran (20 ml) was added sodium thiophenoxide (0.21 g) with stirring. After 4 h at room temperature the mixture was filtered and the filtrate evaporated to dryness to leave a sample of the *phenylthioacetate* (19) (>95%) which was shown by t.l.c. and n.m.r. spectroscopy to be >95% pure: $\nu_{max.}$ 1 745 and 1 583 cm^{-1}; δ 7.28 (5 H, s, Ph), 5.95 (1 H, d, *J* 6 Hz, H-3 or H-2), 5.67 (1 H, d, *J* 6 Hz, H-2 or H-3), 5.12 (1 H, t, *J* 7 Hz, H-7), 4.70 (1 H, td, *J* 7, 3 Hz, H-6), 4.44 (1 H, s, H-4), 3.47 (1 H, s, H-1), 3.06 (1 H, t, *J* 7 Hz, H-5), and 2.00 (3 H, s, $OCOCH_3$) (Found: M^+ 294.048 1. $C_{15}H_{15}ClO_2S$ requires M 294.048 1).

(*e*) 7-endo-*Acetoxy*-4-exo-*butyl*-6-endo-*chlorobicyclo*[3.2.0]-*hept*-2-*ene* (18).—To a solution of butyl-lithium (12.3 ml of a 1.2M-solution) in anhydrous tetrahydrofuran (20 ml) at −70 °C was added a previously prepared solution of dimethylsulphide–copper bromide complex (1.56 g) in dimethyl sulphide (10 ml) and anhydrous tetrahydrofuran (25 ml). The reaction was conducted under an atmosphere of argon. After 15 min a solution of the 6-*endo*-acetate (7) (1 g) in anhydrous tetrahydrofuran (25 ml) was added dropwise with stirring. After a further 6 h a saturated solution of ammonium chloride was added to the reaction mixture which was then allowed to warm to room temperature. The mixture was extracted with chloroform and the combined extracts were dried and evaporated to leave an oil. Chromatography over silica using 5% ethyl acetate–petroleum as eluant gave the *acetate* (18) (0.87 g, 95%), b.p. 70 °C at 0.03 mmHg; $\nu_{max.}$ 1 745 and 1 620 cm^{-1}; δ 5.89 (1 H, dt, *J* 6, 2 Hz, H-3 or H-2), 5.56 (1 H, dt, *J* 6, 2 Hz, H-2 or H-3), 5.18 (1 H, dt, *J* 1, 7 Hz, H-7), 4.73 (1 H, dt, *J* 3, 7.5 Hz, H-6), 3.65 (1 H, m, H-1), 2.98 (1 H, m, H-4), 2.72 (1 H, t, *J* 7.5 Hz, H-5), 2.00 (3 H, s, $OCOCH_3$), 1.27 (6 H, s, 3 × CH_2), and 0.89 (3 H, t, *J* 5 Hz, CH_3) (Found: M^+ 242.106 9. $C_{13}H_{19}ClO_2$ requires M 242.107 2).

(*f*) 6-endo-*Acetoxy*-4-exo-*butyl*-7-endo-*chlorobicyclo*[3.2.0]-*hept*-2-*ene* (12) and 7-endo-*Acetoxy*-4-exo-*butyl*-6-endo-*chlorobicyclo*[3.2.0]*hept*-2-*ene* (18).—A 1 : 1 mixture of the two bromo-acetates (7) and (13) reacted with lithium dibutyl cuprate, as described above to give 96% of a 1 : 1 mixture of (18) and the *acetate* (12), b.p. 65 °C at 0.3 mmHg; $\nu_{max.}$ 1 750 cm^{-1}; δ 5.96 (1 H, dm, *J* 6 Hz, H-2 or H-3), 5.63 (1 H, dt, *J* 6, 2 Hz, H-3 or H-2), 5.36 (1 H, td, *J* 7, 2 Hz, H-6), 4.71 (1 H, t, *J* 7 Hz, H-7), 3.66 (1 H, m, H-1), 2.77 (2 H, m, H-4 and H-5), 2.02 (3 H, s, $OCOCH_3$), 1.27 (6 H, m, 3 × CH_2), and 0.89br (3 H, t, CH_3) (Found: M^+ 242.107 1. $C_{13}H_{19}ClO_2$, requires M 242.107 2).

Base Hydrolyses of the 4-*Substituted Chloro-acetates*.

(*a*) 4-exo-*Butylbicyclo*[3.1.0]*hex*-2-*ene*-6-endo-*carbaldehyde* (21).—A mixture of the butyl-acetate (18) (0.94 g) and an aqueous 1M-solution of sodium hydroxide (70 ml) was stirred at room temperature for 16 h. The product was extracted with chloroform and the extracts were dried and evaporated to give the *carbaldehyde* (21) (0.62 g, 97%), $\nu_{max.}$ 1 700 and 1 620 cm^{-1}; δ 9.19 (1 H, d, *J* 7 Hz, CHO), 5.85 (2 H, s, H-2 and H-3), 2.68 (2 H, m), 2.10 (1 H, t, *J* 7 Hz), 1.73 (1 H, q, *J* 7 Hz), 1.40 (6 H, s, 3 × CH_2), and 0.91 (3 H, t, *J* 4 Hz, CH_3) (Found: M^+ 164.120 1. $C_{11}H_{16}O$ requires M 164.120 1).

There are other signals in the n.m.r. spectrum which correspond to the *enol-ether* (30) in the equilibrium mixture; δ 6.26 (1 H, dd, *J* 6, 3 Hz), 5.22 (1 H, dd, *J* 6, 3 Hz), 4.99 (1 H, t, *J* 6 Hz), and 4.54 (1 H, s).

Similarly, the mixture of the two butyl acetates (12) and (18) was hydrolysed to give the aldehyde (21) in >95% yield.

(*b*) 4-exo-*Butylbicyclo*[3.1.0]*hex*-2-*ene*-6-exo-*carbaldehyde* (24).—A mixture of the two butyl acetates (7) and (13) (40 mg) was dissolved in methanol (3 ml) and 10% aqueous sodium hydroxide (3 ml). After the mixture had been heated under reflux for 1½ h water was added to it and the product extracted with chloroform. Drying and evaporation of the combined extracts gave the exo-*aldehyde* (24) (25 mg); $\nu_{max.}$ 2 750, 1 710, and 1 600 cm^{-1}; δ 9.31 (1 H, d, *J* 4 Hz, CHO), 5.88 (1 H, d, *J* 5 Hz, H-3 or H-2), 5.50 (1 H, dm, *J* 5 Hz, H-2 or H-3), 3.0—1.7 (4 H), 1.37 (6 H), and 0.90 (3 H, t, *J* 5 Hz, CH_3) (Found: M^+ 164.120 1. $C_{11}H_{16}O_2$ requires *M* 164.120 0).

The *exo*-aldehyde (24) is obtainable from the *endo*-aldehyde (21) by treating the latter compound with methanol containing sodium hydroxide (100% yield) or by photolysis of a solution of the *endo*-aldehyde in acetone (25%).

(*c*) 4-exo-*Phenylthiobicyclo*[3.1.0]*hex*-2-*ene*-6-endo-*carbaldehyde* (22) *and* 4-exo-*Phenylthiobicyclo*[3.1.0]*hept*-2-*ene*-6-exo-*carbaldehyde* (25).—A solution of the phenylthioacetate (19) in methanol was treated with potassium carbonate with stirring. After 7½ h water was added and the product extracted into chloroform. The extracts were dried and evaporated to leave a 1 : 3 mixture of endo-(22) and exo-*carbaldehyde* (25) in >95% yield. A pure sample of the *exo*-aldehyde (25) was obtained after partial hydrolysis of the mixture—see later. The *endo*-aldehyde (22) was identified by comparison with an authentic sample prepared from the corresponding *endo*-hydroxymethyl compound (29) (see later).

(*d*) 4-exo-*Morpholinobicyclo*[3.1.0]*hex*-2-*ene*-6-exo-*carbaldehyde* (26).—A 1 : 1 mixture of the morpholinoacetates (11) and (17) was hydrolysed for 8 h as in (b) above to give the exo-*carbaldehyde* (26), m.p. 55—57 °C (>95%); $\nu_{max.}$ 2 720, 1 700, and 1 590 cm^{-1}; δ 9.38 (1 H, d, *J* 4 Hz, CHO), 6.27 (1 H, d, *J* 6 Hz, H-3 or H-2), 5.66 (1 H, dd, *J* 6, 2 Hz, H-2 or H-3), 3.72 (4 H, m, CH_2–O–CH_2), 2.60 (6 H, m, CH_2–N–CH_2, H-1 and H-5), 1.35 (1 H, m, H-6) (Found: M^+ 193.110 2. $C_{11}H_{15}NO_2$ requires *M* 193.110 2).

Acid Hydrolysis of exo- *and* endo-*Aldehydes*

(*a*) 6-exo-*Butyl*-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*ol* (32).—A mixture of the 4-*exo*-butyl-*endo*-aldehyde (21) (0.62 g), water (40 ml), and a catalytic amount of oxalic acid (*ca.* 20 mg) was stirred at room temperature for 24 h. The product was extracted with chloroform and the combined extracts were dried and evaporated to give the γ-*lactol* (32) (0.62 g), b.p. 85 °C at 2 × 10^{-2} mmHg; $\nu_{max.}$ 3 400 and 1 621 cm^{-1}; δ 5.65 (2 H, s, H-7 and H-8), 5.30 (1 H, d, *J* 5 Hz, H-1), 5.06 (1 H, t, *J* 7 Hz, H-3), 4.50 (1 H, s, OH), 3.0—1.7 (4 H, m, H-5, H-6 and 2 × H-4), 1.30 (6 H, s, 3 × CH_2), and 0.80 (3 H, t, *J* 5 Hz, CH_3) (Found: M^+, 182.129 8. $C_{11}H_{18}O_2$ requires *M*, 182.130 6). The *exo*-aldehyde (24) could also be hydrolysed in a 2 : 1 mixture of acetic acid and water to give the *lactol* (32) (90%).

The *exo*-aldehyde (24) was heated under reflux with a mixture of water and a catalytic amount of oxalic acid for ¾ h. Work-up led to the isolation of the lactol (32) (70%). If the reaction was allowed to run for 3 h, only a very low yield of the lactol (32) was obtained.

(*b*) 6-exo-*Phenylthio*-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*ol* (33).—A 3 : 1 mixture of the *exo*- and *endo*-thiophenoxy-aldehydes (25) and (22) was heated under reflux in water containing a catalytic amount of oxalic acid for 1 h. On cooling the product was extracted with chloroform and the extracts were dried and evaporated to leave an oil which was chromatographed over silica using 40% ethyl acetate–petroleum as eluant, to give the *thiophenoxylactol* (33), m.p. 64—65 °C, $\nu_{max.}$ 3 360 cm^{-1}; δ 7.30 (5 H, m, C_6H_5), 5.78 (2 H, m, H-7 and H-8), 5.38 (1 H, d, *J* 5 Hz, H-3), 5.08 (1 H, dd, *J* 7, 3 Hz, H-1), 3.90 (1 H, s, H-6), 3.10 (1 H, m, H-5), and 2.2—1.5 (2 H, m, 2 × H-4) (Found: C, 66.4; H, 6.2. $C_{13}H_{14}O_2S$ requires C, 66.6; H, 6.0%) which was further characterised *via* oxidation to the phenylsulphonyl compound (36) (see later). The major product from this reaction was the unchanged 4-exo-*phenylthiobicyclo*[3.1.0]*hex*-2-*ene*-6-exo-*carbaldehyde* (25), m.p. 34—35 °C; $\nu_{max.}$ 2 700 and 1 690 cm^{-1}; δ 9.33 (1 H, d, *J* 4 Hz, CHO), 7.33 (5 H, m, Ph), 6.00 (1 H, dm, *J* 6 Hz, H-3 or H-2), 5.56 (1 H, dm, *J* 6 Hz, H-2 or H-3), 4.05 (1 H, s, H-4), 2.50 (2 H, m, H-1 and H-5), and 1.31 (1 H, m, H-6) (Found: C, 72.2; H, 5.6. $C_{13}H_{14}OS$ requires C, 71.8; H, 5.9%).

The *exo*-carbaldehyde (25) was hydrolysed in 90% aqueous acetic acid at 80 °C for 18 h. Water was then added and the product extracted with chloroform. The extracts were dried and evaporated to leave the exo-*thiophenoxylactol* (33) (90%).

(*c*) 6-exo-*Morpholino*-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*ol* (34).—The 4-*exo*-morpholino-6-*exo*-carbaldehyde (26) was dissolved in tetrahydrofuran (10 ml) and perchloric acid (3 ml of 70% aqueous solution) and the resultant solution was heated under reflux for 3 h. The product mixture was poured into an aqueous sodium carbonate solution and extracted with chloroform. The extracts were dried and evaporated to leave 6-exo-*morpholino*-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*ol* (34); $\nu_{max.}$ 3 350, 1 100, 1 050, and 985 cm^{-1}, which was characterized by oxidation to the stable lactone (35) (see later).

Reduction of 7-*endo*-*Acetoxy*-6-endo-*chloro*-4-exo-*phenylthiobicyclo*[3.2.0]*hept*-2-*ene* (19).—A solution of the thiophenoxyacetate (19) (0.6 g) in anhydrous tetrahydrofuran (20 ml) was treated with an excess of lithium aluminium hydride at room temperature. The mixture was heated under reflux for 15 h and then set aside for a further 18 h at room temperature. Water was added to the mixture followed by 10% aqueous hydrochloric acid and the products were extracted with chloroform. The extracts were dried and evaporated to leave an oil which was chromatographed over silica using 40% ethyl acetate in petroleum as eluant. The less-polar product was 6-endo-*chloro*-7-endo-*hydroxy*-4-exo-*phenylthiobicyclo*[3.2.0]*hept*-2-*ene* (28) (0.27 g); $\nu_{max.}$ 3 400 cm^{-1}; δ 7.36 (5 H, s, Ph), 6.05 (1 H, m, H-3 or H-2), 5.78 (1 H, m, H-2 or H-3), 4.82 (1 H, td, *J* 7, 3 Hz, H-6), 4.47 (1 H, s, H-4), 3.52 (1 H, m, H-1), 3.02 (1 H, t, *J* 7 Hz, H-5), and 2.20 (1 H, s, OH) (Found: M^+ 252.037 4. $C_{13}H_{13}ClOS$ requires *M* 252.037 5). The more-polar product was 6-endo-*hydroxymethyl*-4-exo-*phenylthiobicyclo*[3.1.0]*hex*-2-*ene* (29) (0.12 g); $\nu_{max.}$ 3 340 cm^{-1}; δ 7.47 (5 H, m, Ph), 5.72 (2 H, m, H-2 and H-3), 3.83 (1 H, s, H-4), 3.40 (2 H, d, *J* 8 Hz, CH_2–O), 2.40 (1 H, s, OH), 2.00 (2 H, t, *J* 8 Hz, H-1 and H-5), and 1.39 (1 H, q, *J* 8 Hz, H-6) (Found: M^+ 218.076 4. $C_{13}H_{14}OS$ requires *M* 218.076 4).

Oxidation Reactions

(*a*) 4-exo-*Phenylthiobicyclo*[3.1.0]*hex*-2-*ene*-6-endo-*carbaldehyde* (22).—To a solution of the primary alcohol (29) in methylene chloride was added a suspension of pyridinium chlorochromate in methylene chloride. After 1 h ether was

added and the mixture was filtered, dried, and evaporated to leave an oil which was purified chromatographically to give the endo-*aldehyde* (22); $\nu_{max.}$ 2 730 and 1 696 cm^{-1}; δ 9.13 (1 H, d, *J* 6 Hz, CHO), 7.28 (5 H, m, Ph), 5.85 (2 H, s, H-2 and H-3), 4.23 (1 H, d, *J* 2 Hz, H-4), 2.55 (2 H, m, H-1 and H-5), and 1.89 (1 H, ddd, *J* 7, 7, 6 Hz, H-6) (Found: M^+ 216.060 6. $C_{13}H_{12}OS$ requires *M* 216.060 2. The n.m.r. spectrum showed low-intensity signals assignable to the enol-ether (31).

(*b*) 6-exo-*Morpholino*-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*one* (35).—The crude morpholino-lactol (34) was dissolved in ether and oxidized with Jones reagent to give the *lactone* (35), m.p. 98—99 °C; $\nu_{max.}$ 1 770 and 1 640 cm^{-1}; δ 6.12 (2 H, s, H-7 and H-8), 5.52 (1 H, d, *J* 6 Hz, H-1), 3.70 (5 H, m, H-6 and CH_2OCH_2), 3.28 (1 H, m, H-5), and 3.2—2.2 (6 H, m, 2 × H-4 and CH_2–N–CH_2) (Found: C, 62.9; H, 7.3. $C_{11}H_{15}NO_3$ requires C, 63.1; H, 7.2%).

(*c*) 6-exo-*Phenylsulphonyl*-2-*oxabicyclo*[3.3.0]*oct*-7-*en*-3-*one* (36).—The impure thiophenoxy-lactol (33) was oxidized with Jones reagent to give the *sulphonyl-lactone* (36), m.p. 140—143 °C; $\nu_{max.}$ 1 760, 1 570, 1 295, and 1 140 cm^{-1}; δ 7.65 (5 H, m, Ph), 6.22 (1 H, d, *J* 5.5 Hz, H-7), 5.88 (1 H, dd, *J* 5.5, 2 Hz, H-8), 5.38 (1 H, d, *J* 7 Hz, H-1), 4.18 (1 H, s, H-6), 3.55 (1 H, m, H-5), 2.86 (1 H, dd, *J* 18, 10 Hz, H-4), and 2.25 (1 H, dd, *J* 18, 7 Hz, H-4) (Found: M^+ 264.045 4. $C_{13}H_{12}O_4S$ requires *M* 264.045 4).

7-(5′-*Butyl*-2′-*hydroxycyclopent*-3′-*enyl*)*hept*-5-*enoic Acid* (38).—The ylide (37) was generated by adding a solution of (4-carboxybutyl)triphenylphosphonium bromide (4.77 g) in anhydrous dimethyl sulphoxide (10 ml) at 0 °C to a solution of sodium hydride (0.51 g) in dimethyl sulphoxide (10 ml). After 15 min at room temperature a solution of the lactol (32) (0.65 g) in dimethyl sulphoxide (10 ml) was added dropwise with stirring. After a further 16 h water was added and non-acidic material was extracted with chloroform. The aqueous layer was acidified with 10% aqueous hydrochloric acid and re-extracted with ether. The combined ether extracts were washed with water (× 3), dried, and evaporated to leave the *hydroxy-acid* (38) (0.27 g); $\nu_{max.}$ 3 650—2 200 and 1 710 cm^{-1}; δ 7.27 (1 H, s, CO_2H), 5.85 (2 H, m, H-3′ and H-4′), 5.45 (2 H, m, H-5 and H-6), 4.68 (1 H, dm, *J* 6 Hz, H-2′), 2.7—1.0 (17 H, m), and 0.88 (3 H, t, *J* 4.5 Hz, CH_3). The neutral extracts were dried and evaporated to give recovered lactol (32) (0.45 g).

7-(5′-*Butyl*-2′-*oxocyclopent*-3′-*enyl*)*hept*-5-*enoic Acid* (5).—To a solution of the hydroxy-acid (38) (0.14 g) in ether (4 ml) at 0 °C was added dropwise with stirring Jones reagent (0.1 ml). After 1½ h at room temperature the product was extracted with chloroform and the combined extracts were dried and evaporated to leave an oil. Chromatography over silica using 10% methanol in ethyl acetate as eluant gave the *keto-acid* (5) (0.065 g); $\nu_{max.}$ 3 600—2 300, 1 710, and 1 595 cm^{-1}; δ 9.47 (1 H, s, CO_2H), 7.63 (1 H, dd, *J* 6, 3 Hz, H-4′), 6.13 (1 H, dd, *J* 6, 2 Hz, H-3′), 5.40 (2 H, m, H-5 and H-6), 2.8—1.1 (16 H, m), and 0.90 (3 H, t, *J* 4 Hz, CH_3) (Found: P^+ 248.177 4. $C_{16}H_2O_2$ requires $M - H_2O$ 248.177 4).

7-endo*Acetoxy*-4-exo-(3′-*t*-*butyldimethylsilyloxyoct*-1′-*enyl*)-6-endo-*chlorobicyclo*[3.2.0]*hept*-2-*ene* (20).—The cuprate reagent (39) was generated from 3-t-butyldimethylsilyloxy-1-iodo-oct-1-ene, butyl-lithium, and dimethylsulphide–copper bromide complex. To a solution of the reagent in anhydrous tetrahydrofuran was added the bromo-acetate (7) at −70 °C. Work-up and chromatography gave recovered bromo-acetate (7) and the *octenylbicycloheptene* (20) (40%); $\nu_{max.}$ 1 750, 1 240, and 1 100 cm^{-1}; δ 5.80 (2 H, m, H-2 and H-3), 5.40 (2 H, m, H-1′ and H-2′), 5.25 (1 H, t, *J* 7 Hz, H-7), 4.81 (1 H, td, *J* 7, 2 Hz, H-6), 4.3—3.5 (3 H, m, H-1, H-4 and H-3′), 2.83 (1 H, t, *J* 7 Hz, H-5), 2.05 (3 H, s, $OCOCH_3$), 1.34 (8 H, s, 4 × CH_2), 0.90 [12 H, s, $C(CH_3)_3$ and CH_3], 0.0 [6 H, s, $Si(CH_3)_2$].

4-exo-(3′-*t*-*Butyldimethylsilyloxyoct*-1′-*enyl*)*bicyclo*[3.1.0]-*hex*-2-*ene*-6-exo-*carbaldehyde* (27).—A mixture of the octenylbicycloheptene (20), potassium carbonate, and methanol was stirred at ambient temperature for 3 h. Water was added to the mixture and the product extracted with chloroform. The combined extracts were dried and evaporated to give a crude sample of the *exo*-aldehyde (27); $\nu_{max.}$ 1 705 cm^{-1}; δ 9.17 (1 H, d, *J* 5 Hz, CHO), 5.76 (2 H, m, H-2 and H-3), 5.35 (2 H, m, H-1′ and H-2′), 5.0—3.3 (2 H, H-4, H-3′), 3.0—1.7 (3 H, m, H-1, H-5 and H-6), 1.20 (8 H, m, 4 × CH_2), 0.8 [12 H, s, CH_3 and $C(CH_3)_3$], and 0.00 [6 H, s, $Si(CH_3)_2$] (Found: M^+ 348.248 3. $C_{21}H_{36}O_2Si$ requires *M* 348.248 3). No reaction was observed when (20) was treated with an aqueous 1M-solution of sodium hydroxide for 16 h at room temperature.

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