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THE SYNTHESIS OF SOME CARBAPROSTACYCLIN PRECURSORS

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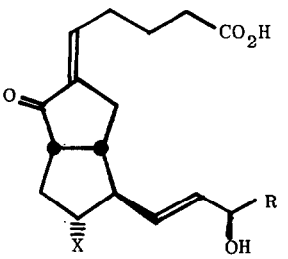
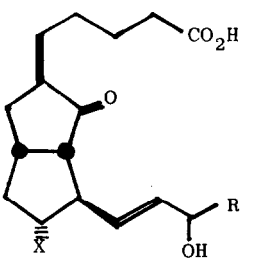
Abstract-Starting from endo-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-diene-3β-ol, which has previously been resolved, a series of transformations are described which provide access to a variety of chiral intermediates for the synthesis of carbaprostacyclin and prostaglandin derivatives. Amongst these precursors are 8-acetoxybicyclo[3.3.0]oct-2-ene, 8-acetoxybicyclo[3.3.0]octane-2-carboxaldehyde and a deoxyCorey lactone derivative.

Several years ago we reported the synthesis of analogues (1) of 11-deoxyprostacyclin in which the 6,9-ether linkage was replaced by a carbonyl group[1]. The biological activities observed for these compounds encouraged us to contemplate the synthesis of both the 11-hydroxy-derivatives (2) and also, for comparison, that of the isomeric analogues (3) and (4). The synthesis of the analogues (4) had recently been reported from another laboratory[2]. Obvious precursors of these compounds are the bicyclo[3.3.0]octane derivatives (5) and (6) or their equivalents. A highly desirable feature of their synthesis was the capability of their production in a state of chiral purity. Consideration of these criteria led us to identify the readily available dicyclopentadienol (7) as a suitable starting material since its



(1) X = H

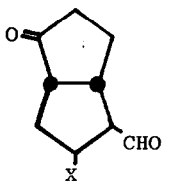
(2) X = OH



(3) X = H

(4) X = OH

optical resolution has been reported[3]. Oxidative cleavage of the norbornene double bond, after reduction of the cyclopentene one, would uncover the bicyclo[3.3.0]octane moiety as in (8). Subsequent removal of either of the carboxyl groups of (8) and appropriate manipulations of the remaining carboxyl and hydroxyl groups would then provide (5) or (6). A particularly interesting feature is that whereas the dicyclopentadienol enantiomer depicted is the appropriate starting point for (3) with the natural prostacyclin absolute configuration, it is the enantiomer of (7) which is required for the corresponding obtention of (1). Thus, in contrast to most situations involving an optical resolution both enantiomers of (7) are of synthetic use. The situation recalls the Newton-Roberts approach to prostaglandin synthesis[4] in which both enantiomers of a key intermediate have been converted to the same product but by employing different sequences of reactions.



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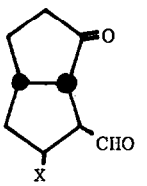

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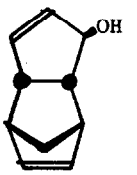

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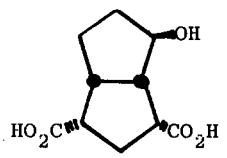

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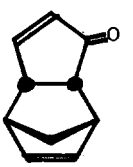

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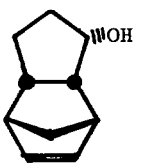

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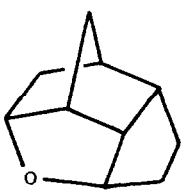

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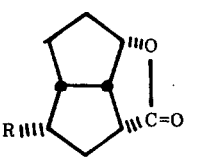
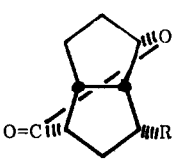


(12) R = CO_2H
(13) R = CH_2OH
(14) R = CH_2OCH_2Ph
(15) R = $CH_2OSiMe_2Bu^t$



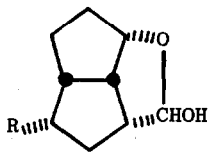
(16) R = CO_2H
(17) R = CH_2OH

As reported in the literature[3] the dicyclopentadienol (7) was readily obtained by selenium dioxide oxidation of dicyclopentadiene. In order to permit ready differentiation of the two carboxyl groups that were to be generated by cleavage of the norbornene double bond we elected to enable one of them to participate in lactonisation with the hydroxyl group. This necessitated inversion of the disposition of the hydroxyl group but could be readily achieved in concert with reduction of the cyclopentene double bond as follows. Oxidation of (7) to the ketone (9)

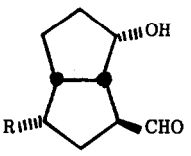
with pyridinium dichromate proved superior to the chromic acid used previously[3]. Reduction of (9) with sodium borohydride to the alcohol (10) proceeded smoothly as long as the originally prescribed[5] acidic work up was eschewed, otherwise the cyclic ether (11) was obtained[6]. Ozonolysis of (10), followed by treatment of the resulting ozonides with hydrogen peroxide and formic acid gave a good yield of an acid lactone whose infrared spectrum displayed a lactone carbonyl frequency of 1750cm^{-1}. This frequency is rather low for a γ-lactone and in line with that observed for strained δ-lactones, hence it was necessary to distinguish between structures (12) and (16) for this compound. A sufficiently detailed analysis of the ^{1}H nmr spectrum of this compound was not possible so it was reduced to the corresponding lactone carbinol with diborane. The utilisation of a combination of proton-proton & carbon-proton decoupling techniques permitted a full assignment of the ^{1}H nmr spectrum of this compound and in particular showed that there were three intervening tertiary C-H's separating the hydroxymethyl methylene protons and the lactonic O-CH as in structure (13), rather than the two tertiary C-H's called for in the alternative (17). Consequently, structure (12) could be assigned with confidence to the acid lactone.

In our original plan we had anticipated that it would be relatively easy to open the γ-lactone under base catalysis and effect the epimerisation of the carboxyl group of (13), especially in view of the steric encumbrance provided by the adjacent hydroxyl and hydroxymethyl groups. However, all attempts to effect such an epimerisation were fruitless. Consequently (13) was converted to its O-benzyl ether (14) and the lactone reduced to the lactol with diisobutylaluminium hydride. Again all attempts to induce the lactol (18) to epimerise to the hydroxy aldehyde (21) were unsuccessful. Efforts to facilitate the process by capturing the hydroxyl group of the hydroxyaldehyde by acetylation merely generated the acetyl derivative of (16), and the lactol also failed to undergo decarbonylation with tris(triphenylphosphine)rhodium (I) chloride. The lactol was eventually opened using a concurrently reported[7] procedure entailing treatment with ethanedithiol in the presence of titanium tetrachloride. Unexpectedly, dithioacetal formation was accompanied by debenzylation yielding (22). However, direct reaction of the unprotected lactol(20) with these reagents gave only a very poor yield of (22). Use of the t-butyldimethylsilyl derivative (19) instead of the benzyl one under these conditions also resulted in partial cleavage of the protecting group with a mixture of (22) and (23) being obtained. The original examples of this lactol opening procedure did not entail the presence of any protecting groups and the present cases constitute the only information so far available on their stability under the reaction conditions. Acetylation of (23) followed by cleavage of the thioacetal with methyl iodide in aqueous acetonitrile yielded the unstable aldehyde (24).

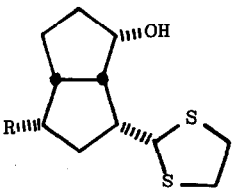
Parallel efforts to convert the acid lactone (12) into (6) or its equivalent also suggested an alternative route to (5). Initially (12) was converted to the acid chloride with thionyl chloride and subsequently decarbonylated by heating with chlorocarbonylbis(triphenylphosphine)rhodium (I) yielding the olefinic lactone (25). However, this method proved rather temperamental and a more reliable one was the oxidative decarboxylation of (12) with lead tetraacetate in the



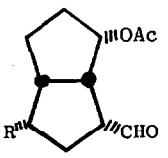
(18) R = CH_2OCH_2Ph
(19) R = $CH_2OSiMe_2Bu^t$
(20) R = CH_2OH



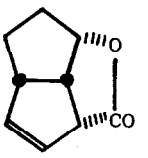
(21) R = CH_2OCH_2Ph



(22) R = CH_2OH
(23) R = $CH_2OSiMe_2Bu^t$



(24) R = $CH_2OSiMe_2Bu^t$



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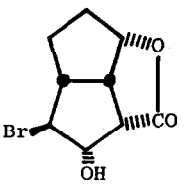

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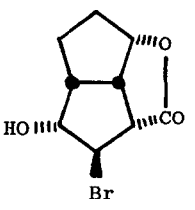

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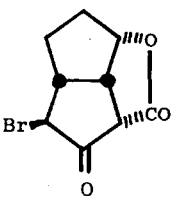

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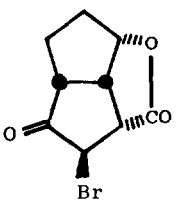

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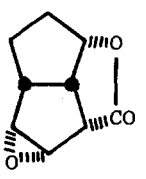

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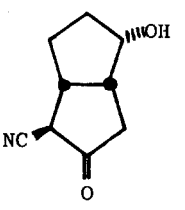

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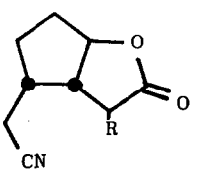
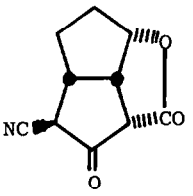


(32) R = H
(33) R = CO_2H

presence of cupric acetate. Addition of hypobromous acid to (25) provided a separable mixture of two bromohydrins (26) and (27), whose orientations were established by oxidation to the corresponding bromketones (28) and (29) which were readily differentiated by their ^1H nmr spectra. The indicated stereochemistry is based upon the reasonable supposition that electrophilic addition to the double bond of (25) is initiated by attack of bromine on the less sterically hindered face. The bromohydrin (27), which was not needed for our studies, could be converted to the epoxide upon exposure to potassium t-butoxide. The epoxide (30) could then be reacted with hydrogen bromide to give a mixture of the bromohydrins (26) and (27), thereby providing a means of recycling the unwanted isomer. Although it had been anticipated that the presence of the β-carbonyl group in (28) would facilitate the

dismantling of the lactone grouping, treatment of (28) with a variety of reagents ostensibly appropriate for the purpose either failed to effect any reaction at all or led to extensive decomposition. The only characterisable product from these studies arose when (28) was heated with sodium cyanide in dimethyl sulphoxide, in the anticipation that replacement of the bromine by a cyano group would be accompanied by decarboxylation[8] leading to an appropriate precursor for (5). The product obtained was not the anticipated (31) but rather the isomeric (32) resulting from



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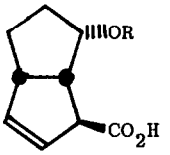
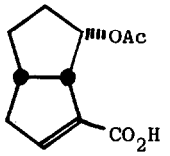


(35) R = H
(36) R = Ac



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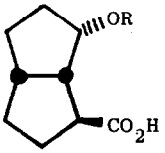
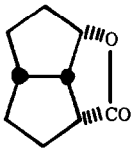


(38) R = H
(39) R = Ac



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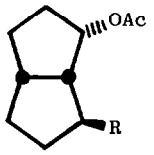


(41) R = CH_2OH
(42) R = CHO
(43) R = $CH{=}CHCOC_5H_{11}$

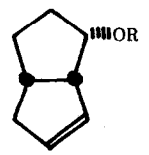
ketonic cleavage of the putatory intermediate (34) to (33) followed by decarboxylation. As at this stage in our studies carbaprostacyclins of type (2) had become available to us by another route[9] we have not pursued the present one any further.

In view of the marked reluctance of compound (13) to undergo base catalysed lactone opening and epimerisation of the carboxyl group we were surprised to find that the unsaturated lactone (25) was readily converted into the hydroxyacid (35) by treatment with sodium methoxide in methanol followed by aqueous alkaline hydrolysis of the intermediary methyl ester. Presumably the lactone opening is facilitated by the additional steric strain introduced into the double bond. Equally unexpected was the failure of the double bond in (35) to move into conjugation with the carboxyl group. The most likely explanation for this is that the carbanion precursor of (35) is preferentially intramolecularly protonated by the hydroxyl group. That (35) has the indicated stereochemistry is demonstrated by its hydrogenation to the hydroxyacid (38), whereas the C-4 epimer of (38) spontaneously cyclises to the lactone (40)[10]. The lactone (40) is of course readily accessible by hydrogenation of (25), and also failed to undergo conversion to (38). The role of the hydroxyl group in the generation of (35) received suport from the observation that reaction with acetic anhydride in pyridine under very mild conditions converted (35) into a separable mixture of (36) and the conjugated isomer (37). For synthetic purposes the acetylation of (35) to (36) could be cleanly effected by acetic anhydride and a catalytic amount of boron trifluoride etherate.

Subsequent catalytic hydrogenation of (36) provided the acetoxyacid (39), and

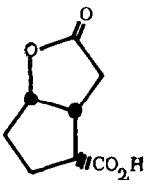
this was reduced to the corresponding carbinol (41) with diborane. Oxidation of (41) with pyridinium chlorochromate provided the unstable aldehyde (42) which was converted into the enone (43) by means of a Wittig-Horner reaction with the sodium salt of dimethyl(2-oxoheptyl)phosphonate. The enone (43) is an obvious precursor of the carbaprostacyclins (3). The original route to the carbaprostacyclins (4)[2] depended on the olefin (44) as an intermediate.This compound, which has also been used as a precursor of carbaprostacyclin[11], is obtained by isomerisation of 3,4-epoxycyclooctene[12]- a route which does not lend itself to the production of chiral material. However, oxidative decarboxylation of the acetoxyacid (39) with lead tetraacetate and cupric acetate provided (45) and is clearly a potential source of either enantiomer.

Finally, ozonolysis of the unsaturated lactone (25) and oxidative work up provided the deoxy-Corey lactone intermediate (46)[13] which is a useful precursor of 11-deoxyprostaglandins[14].



(44) R = H

(45) R = Ac



(46)

EXPERIMENTAL

Except where indicated infrared spectra were measured on liquid films. Unless otherwise stated ^{1}H NMR spectra were recorded at 200 or 250MHz, and ^{13}C NMR spectra at 22.5 or 62.9MHz, for $CDCl_3$ solutions with TMS as internal standard. Spectra at 400MHz were provided by the ULIRS service based at Queen Mary College. Analytical TLC and flash chromatography were carried out on silica gel (Merck, Darmstadt). R_f values were obtained from analytical TLC using the same solvent system as employed for column chromatography. TLC plates were visualised by spraying with either potassium permanganate or phosphomolybdic acid (PMA, 10% in ethanol) or by exposure to iodine vapour.

2α-Carboxybicyclo[3.3.0]octane-4α,6α-carbolactone (12). The dicyclopentadienol(10) (2.45g, 0.016 mol.) was dissolved in dry dichloromethane (30 ml) and cooled to -80°C. Ozonised oxygen was then bubbled through the solution for a period of 2 hours. The system was then flushed with a stream of oxygen and the solvent removed in vacuo without heating. The residue was treated successively with formic acid (6 ml, 90%) and hydrogen peroxide (3 ml, 30%) and heated under reflux until the reaction mixture gave a negative test to starch-potassium iodide paper. The solvent was removed in vacuo and the residue crystallised from ethyl acetate to give the acid lactone (12) (1.9g, 59%), mp 151-153°C. (Found: C, 60.57; H, 6.14. $C_{10}H_{12}O_4$ requires: C, 61.22; H, 6.12%); IR(nujol) 3550-2500, 1750, 1690 cm^{-1}; ^{1}H NMR (200 MHz, C_5D_5N) 1.36-1.72(2H, m, H-8), 1.72-1.90(1H, m, H-7), 2.44-2.98(3H, m, H-1,-3), 3.06-3.36(3H, m, H-2,-4,-5), 4.8-4.91(1H, m, H-6), 12.3-13.8(1H, br, CO_2H); ^{13}C NMR 24.8(C-8), 32.2(C-7), 34.8(C-3), 43.5, 48.9, 49.3, 50.8, 84.6(C-6), 174.9 (C=O), 180.5(C=O) ppm; MS(EI) m/z 152(5), 134(6), 124(15), 80(100); MS(CI-NH_3) m/z 197(M+1, 32), 214(M+NH_4, 44).

2α-Hydroxymethylbicyclo[3.3.0]octane-4α,6α-carbolactone (13). A solution of the acid lactone (12) (1g, 5mmol) in dry tetrahydrofuran (20 ml) under a nitrogen atmosphere was cooled to 0°C and diborane in tetrahydrofuran (5ml of a 1 M soln.) was added dropwise. The solution was stirred at 0°C for 30 minutes and then for 2 hours at room temperature. Saturated ammonium chloride solution (7ml) was then added followed by chloroform (100 ml), The chloroform solution was washed with

saturated aqueous sodium bicarbonate solution (2 x 20ml) and then dried.Subsequent evaporation gave the alcohol (13) as a colourless oil (0.5g, 55%). (Found:C, 66.18; H, 8.01. $C_{10}H_{14}O_3$ requires; C, 65.93; H, 7.69%); IR 3650-3150, 1760 cm^{-1}; ^1H NMR (400MHz) 1.2-1.32(1H, m, H-8), 1.52-1.63(3H, m, H-3,-7,-8), 1.78(1H, s, OH), 2.15 (1H, dd, J=5.5 and 13Hz, H-7), 2.31-2.5(2H, m, H-2,-3), 2.57-2.68(1H, m, H-1), 3.12 (1H, ddd, J=7.5,11 and 11Hz, H-4), 3.31(1H, ddd, J=11, 7.5 and 7.5Hz, H-4), 3.65 (2H, d, J=6.3Hz, CH_2OH), 4.98(1H, t, J=4.7Hz, H-6); ^{13}C NMR 22.4(C-8, 32.4(C-3), 34.6(C-7), 43.3(C-4), 46.4(C-2), 48.1(C-1), 50.4(C-5), 63.3(CH_2OH), 84.5(C-6), 181.1(C=O); MS m/z 182(8), 164(4), 152(68), 134(9), 120(19), 119(17), 79(100).

2α-Benzyloxymethylbicyclo[3.3.0]octane-4α,6α-carbolactone (14). The alcohol (13) (0.4g, 2.2 mmol) and sodium hydride (90mg, 38 mmol) were stirred together in dry dimethylformamide (20ml) under nitrogen for 2 hours, and then benzyl bromide (0.3 ml) was added. The reaction mixture was then stirred overnight. It was subsequently diluted with water (100ml) and extracted with ether (3 x 100ml). The combined extracts were washed with saturated sodium chloride solution (6 x 50ml), dried ($MgSO_4$) and evaporated in vacuo to give the crude ether which was chromatographed (ethyl acetate-petroleum ether 1:3) to give the ether (14) (0.27g, 45%). (Found: C, 74.71; H,7.52. $C_{17}H_{20}O_3$ requires; C, 75.0; H, 7.35%); IR 1760 cm^{-1}; ^1H NMR 1.23 (1H, m), 1.5-1.78(3H, m), 2.11(1H, dd, J=5.7 and 12.8Hz), 2.27-2.7(3H, m), 3.10 (1H, dt, J=7.5, 11 and 11Hz), 3.2-3.35(1H, m), 3.45(2H, d, J=6.8Hz,CH_2OCH_2Ph), 4.96 (1H, t, J=5Hz), 7.35(5H, s, ArH); ^{13}C NMR 22.7(CH_2), 32.7(CH_2), 34.7(CH_2), 43.4 (CH), 44.2(CH), 48.5(CH), 50.4(CH), 71.0(CH_2O), 73.2(CH_2O), 84.5(CHO), 127.6(CH's), 128.4(CH's),129.5(CH),138.3(CCH_2),181.0(C=O); MS m/z 272(8), 181(1), 165(4),91(100).

2α-t-Butyldimethylsilyloxymethylbicyclo[3.3.0]octane-4α,6α-carbolactone (15). The alcohol (13) (1.2g, 6.6 mmol) was dissolved in dimethylformamide (25ml). Imidazole (1.28g) was added followed by t-butyldimethylsilyl chloride (1.48g, 9.8 mmol). The reaction mixture was stirred at room temperature overnight, then poured into ice water and extracted with ethyl acetate. The organic extracts were dried (Na_2SO_4) and evaporated in vacuo to yield a crude oil which was purefied by flash chromatography (ethyl acetate-hexane 4:1) to give (15) (1.5g, 77%).(Found: C, 65.03; H, 9.71. $C_{17}H_{28}O_3Si$ requires; C, 64.84; H, 9.46%); IR 1770 cm^{-1}; ^1H NMR (90MHz) 0.03 (6H, s, CH_3Si), 0.85(9H, s, $(CH_3)_3CSi$), 1.1-1.95(5H, m), 1.95-2.7(5H, m), 3.57(2H, d, J=6Hz, CH_2OSi), 4.85-5.02(1H, m, H-6); MS m/z 296(M^+; 9), 281(37), 263(15), 251 (10), 195(12), 147(18), 133(36), 119(36), 105(21), 84(77), 75(100).

2α-Benzyloxymethylbicyclo[3.3.0]octane-4α,6α-carbolactol (18). Diisobutylaluminium hydride (1M soln in toluene, 1.6 ml) was addded dropwise to a stirred solution of (14) (213mg, 0.78 mmol) in dry toluene (20 ml) at -70°C under a nitrogen atmosphere. The resulting reaction mixture was stirred for 1 hour before pouring into saturated ammonium chloride solution and extracting with ether. The extracts were dried (Na_2SO_4) and evaporated to yield (18) (200mg, 90%). (Found: C,74.81; H, 8.36. $C_{17}H_{22}O_3$ requires: C, 74.45; H, 8.03%); IR 3220-3500 cm^{-1}; ^1H NMR(90MHz) 0.9-3.3 (11H, m), 3.35(2H, d, J=6Hz, CH_2OCH_2Ph), 4.43(2H, s, OCH_2Ph), 4.55-4.75(1H, m, H-6), 5.17(1H, s, CHOH), 7.25(5H, s, ArH).

2α-t-Butyldimethylsilyloxymethylbicyclo[3.3.0]octane-4α,6α-carbolactol (19). This compound was obtained from reduction of (14) in 50% yield following the above procedure. (Found: C, 64.08; H, 9.81. $C_{16}H_{30}O_3Si$ requires; C, 64.41; H, 10.06%); IR 3150-3600 cm^{-1}; ^1H NMR(90MHz) 0.03(6H, s, CH_3Si), 0.85(9H, s, $(CH_3)_3CSi$), 1.18-1.62(4H, m), 1.75-2.66(6H, m), 3.52(2H, d, J=7Hz, CH_2O), 4.55-4.73(1H, m, H-6), 5.2(1H, s, HCOH); MS m/z 297(M-1, 16), 280(15), 241(12), 223(38), 195(9), 149(44), 131(57), 105(25), 75(100).

2α-Hydroxymethylbicyclo[3.3.0]octane-4α,6α-carbolactol (20). This compound was prepared from (13) in 39% yield following the method used for generating (18). (Found: C, 65.45; H, 8.51. $C_{10}H_{16}O_3$ requires; C, 65.22; H, 8.70%); IR 3000-3600cm^{-1}; ^1H NMR(90MHz) 1.2-1.7(3H, m), 1.8-2.8(7H, m, includes OH), 2.97-3.34(1H, m), 3.6 (2H, d, J=7Hz, CH_2OH), 4.6-4.8(1H, m, H-6), 5.21(1H, s, HCOH); MS m/z 184(M^+, 10), 183(18), 167(24), 166(8), 148(5), 120(43), 79(100).

Lactol opening of (23). The lactol (23) (0.7g, 2.35 mmol) was added to dichloromethane (30 ml) with stirring under nitrogen. Ethane-1,2-dithiol (0.2 ml) was then added followed by titanium tetrachloride (1 ml). The reaction mixture was stirred at room temperature for 4 hours, after which time water was added and the aqueous

layer extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to yield a crude oil which was a mixture (tlc) of two products. These were separated by flash chromatography using ethyl acetate/hexane 1:1 as eluant. The more mobile product (R_f 0.75) was the expected thiolane (23). (Found: C, 58.01; H, 9.09. $C_{18}H_{34}O_2S_2Si$ requires: C, 57.74; H, 9.09%) IR 3600-3100 cm^{-1}; ^1H NMR(90MHz) 0.03(6H, s, CH_3Si), 0.85(9H, s, $(CH_3)_3CSi$),1.44-1.74 (5H, m), 1.8-2.02(4H, m), 2.57-2.9(2H, m), 3.18(4H, s, SCH_2CH_2S), 3.4-3.72(1H, m), 3.94-4.4(2H, m), 5.18(1H, d, J=10Hz, $HC(SCH_2)_2$); MS m/z 374(M^+, 10), 317(40), 281 (27), 225(73), 181(20), 167(63), 149(48), 105(32), 75(100). The less mobile product was the desilylated thiolane (22) (R_f 0.26). (Found: C, 55.28; H, 7.91. $C_{12}H_{20}O_2S_2$ requires: C, 54.96; H, 7.63%) IR 3100-3550 cm^{-1}; ^1H NMR(90MHz) 1.36-2.85(12H, m), 3.25(4H, s, SCH_2CH_2S),3.67(2H, d, J=7Hz, CH_2OH), 4.32-4.5(1H, m, H-6), 5.22(1H,d, J=10Hz, $HC(SCH_2)_2$); MS m/z 260(M^+, 10),214(57), 196(4), 181(27), 167(35), 105(100).

Lactol opening of (14). Treatment of the lactol (14) with ethanedithiol and titanium terachloride as above gave solely the debenzylated dithiolane (22).

6α-Acetoxy-2α-t-butyldimethylsilyloxymethylbicyclo[3.3.0]octane-4-carbaldehyde (21)

To the thiolane (23) (110mg, 0.29 mmol) was added acetic anhydride (1 ml) and pyridine (1 ml). The mixture was allowed to stand at room temperature overnight, before being poured into ice-water and extracted with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated to yield the acetyl derivative of (23). IR 1735 cm^{-1}; ^1H NMR(90MHz) 0.9(9H, s, $(CH_3)_3CSi$),1.2-1.9(5H, m), 2.03(3H, s, Ac), 2.1-2.85(5H, m), 3.22(4H, s, SCH_2CH_2S), 3.58-3.75(2H, m), 4.65(1H, d, J=10Hz, $HC(SCH_2)_2$), 5.15-5.42(1H, m, H-6). To this compound in 20% aqueous acetonitrile (20ml) and terahydrofuran (6 ml) was added methyl iodide (2.9 ml). The stirred reaction mixture was heated at 50-70°C for 5 1/2 hours. After cooling, saturated aqueous ammonium chloride solution was added and then extracted with ether. The dried extracts (Na_2SO_4) were evaporated in vacuo to give the aldehyde (21) as an oil (53 mg) which rapidly decomposed. IR 1728 cm^{-1}; ^1H NMR(90MHz) 0.85(9H, s, $(CH_3)_3CSi$), 1.15-2.35(11H, m including singlet for Ac at 2.0), 2.45-3.48(3H, m), 3.60(2H, d, J=6Hz, CH_2OSi), 5.2-5.4(1H, m, H-6), 9.78(1H, s, CHO). MS m/z 359(M^+, 4), 299(5), 271(33), 256(43), 225(19), 196(28), 181(22), 163(48), 149(19), 105(20), 91(10), 43(100).

Bicyclo[3.3.0]oct-2-ene-4α,6α-carbolactone (25).

A) A solution of the acid lactone (12) (0.54g, 2.7 mmol) and thionyl chloride (0.6 ml) in dry benzene (15 ml) was refluxed under nitrogen until the IR carbonyl absorption of the carboxyl group was replaced by that of the acid chloride one. The solution was then filtered and evaporated in vacuo. The residue was taken up in benzene and again evaporated to facilitate removal of traces of thionyl chloride. This process was repeated twice more. The resulting acid chloride was used directly for the next step. IR 1800, 1775 cm^{-1}. The acid chloride was heated at 190°C with chlorocarbonyl-bis(triphenylphosphine)rhodium (I) (20mg) until the infrared absorption at 1800 cm^{-1} had disappeared. The residue was chromatographed and the olefinic lactone (25) eluted with petroleum ether-ethyl acetate 3:1 as a colourless oil (122mg, 39%). (Found: C, 71.83; H, 6.62. $C_9H_{10}O_2$ requires: C, 72.0; H, 6.67%) IR 1770 cm^{-1}; ^1H NMR 1.64-1.96(3H, m, H-7,-8,-8'), 2.07-2.19(1H, m, H-7'), 3.35(1H, m, J=6.2 and 9.5Hz, H-1), 3.49(1H, q, J=9.5Hz, H-5), 3.65(1H, dd, J=6.2 and 9.5Hz), 4.87-4.98(1H, m, H-6), 5.67-5.79(2H, m, $J_{2,3}$=15.3Hz, $J_{1,2}$=6.2Hz, $J_{3,4}$= 6.2Hz, H-2 and H-3); ^{13}C NMR 30.16(CH_2), 33.16(CH_2), 47.7(CH), 51.4(CH), 52.7(CH), 84.3(C-6), 127.2(-CH=), 137.3(-CH=), 177.9(C=O); MS m/z 150(M^+, 5), 106(100), 105(48), 91(90).

B) The acid lactone (12) (1.67g, 8.5 mmol), cupric acetate (428mg, 2.14 mmol) and pyridine (440mg, 5.57 mmol) were stirred together in benzene (60 ml) overnight. Lead tetraacetate (18g, 39.4 mmol) and benzene (250 ml) were added and the solution purged of oxygen by passing a stream of nitrogen through it. The solution was refluxed with exclusion of light for 4 hours, then poured into water and extracted with ether. The combined ether extracts were washed with saturated aqueous sodium bicarbonate solution and dried ($MgSO_4$). Removal of the solvent in vacuo and flash chromatography with petroleum ether/ethyl acetate 3:1 of the residue yielded (25) (1.05g, 83%).

Addition of Hypobromous acid to (25). The olefinic lactone (25) (0.3g, 2.0 mmol) was dissolved in acetone (2 ml) and water (2 ml), and the solution cooled in an ice bath. 1,3-Dibromo-5,5-dimethylhydantoin (304.8mg, 1.03 mmol) was added portionwise

to the stirred solution. On completion of the addition the reaction mixture was allowed to warm to room temperature and stirred overnight. Water was then added, the acetone evaporated and the aqueous medium extracted with ether. The ether extracts were combined, dried ($MgSO_4$) and evaporated to yield an orange oil. This was shown by tlc examination to contain two products which were separated by flash chromatography using hexane/ethyl acetate 2:1 as eluent. The more mobile compound (R_f 0.26) was 3β-bromo-2α-hydroxybicyclo[3.3.0]octane-4α,6α-carbolactone (27) (70 mg, 13%). (Found: C, 43.30; H, 4.59. $C_9H_{11}BrO_3$ requires: C, 43.72; H, 4.45%) IR 3600-3200, 1755 cm^{-1}; ^1H NMR 1.98-2.37(4H, m, H-7,-8), 2.91-3.25(2H, m, OH and H-1), 3.45-3.67(2H, m, H-4,-5), 3.95-4.08(1H, m, H-3), 4.76(1H, dd, J=5.8 and 6.7Hz, H-2), 5.17(1H, dd, J=4.6 and 5.4Hz, H-6); ^{13}C NMR 23.0(CH_2), 35.15(CH_2), 47.0(CH), 48.9 (CH), 53.2(CH), 57.1(CH), 80.4(CH), 85.4(CH), 177.4(C=O); MS m/z 248(46), 246(42), 167(44), 149(100), 81(62), 79(60).

The less mobile compound (R_f 0.17) was 2β-bromo-3α-hydroxybicyclo[3.3.0]octane-4α-,6α-carbolactone (26) (80mg, 16%). (Found: C, 43.81; H, 4.67%) IR 1760 cm^{-1}; ^1H NMR 1.98-2.37(4H, m, H-7,-8), 2.91-3.25(2H, m, H-1 and OH), 3.45-3.67(2H, m, H-4, -5), 4.34-4.49(2H, m, H-2,-3), 4.96-5.11(1H, m, H-6); ^{13}C NMR 28.4(CH_2), 34.0(CH_2), 48.1(CH), 48.7(CH), 53.1(CH), 58.4(CH), 82.0(CH), 85.1(CH), 177.2(C=O).

2α,3α-Epoxybicyclo[3.3.0]octane-4α,6α-carbolactone (30). The bromohydrin (27) (1.2g, 4.9 mmol) and potassium t-butoxide (0.65g, 5.8 mmol) were stirred together in t-butanol for 3 hours. Then water was added and the solution extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and evaporated in vacuo to give the crude epoxide which was crystallised from ether, mp 86-88°C (0.6g, 78%). (Found: C, 64.73; H, 5.92. $C_9H_{10}O_3$ requires: C, 65.06; H, 6.02%) IR 1770 cm^{-1}; ^1H NMR(90MHz) 1.5-1.9 (1H, m, H-8), 1.9-2.3(3H, m, H-7,-7,-8), 2.6-2.9(1H, m, H-1), 3.14(1H, dd, J=4 and 12Hz), 3.45-3.73(2H, m), 3.79(1H, t, J=3Hz), 4.68-4.91(1H, m, H-6); MS m/z 166(M^+, 5), 122(7), 81(100).

Conversion of (30) to (26) and (27). Anhydrous hydrogen bromide was bubbled into a solution of the epoxide (30) (0.5g, 3 mmol) in dry ether 20 ml) at -40°C for 2 hrs. The reaction mixture was allowed to warm to room temperature and then saturated aqueous sodium bicarbonate solution was added dropwise until the solution was neutral. The resulting mixture was then extracted with ethyl acetate, dried ($MgSO_4$) and evaporated in vacuo to give a mixture (0.61g, 82%) of the two bromohydrins (26) and (27) in roughly equal amounts, which could be separated as previously described above.

2β-Bromo-3-oxobicyclo[3.3.0]octane-4α,6α-carbolactone (28). Jones' reagent (8N) was added dropwise to the bromohydrin (26) (166mg, 0.67 mmol) in acetone (4 ml), until no further colour change occurred. The solution was stirred for 3 hours, water was added and the mixture extracted with ethyl acetate. The extracts were washed with saturated sodium bicarbonate solution and dried ($MgSO_4$). Evaporation of the solvent in vacuo gave the bromoketone (28) as a pale orange solid (137mg, 82%), mp 143-145°C. (Found: C, 44.24; H, 3.73. $C_9H_9BrO_3$ requires: C, 44.08; H, 3.67%) IR 1785, 1740 cm^{-1}; ^1H NMR 1.0-1.29(1H, m), 1.7-1.96(1H, m), 2.05-2.36(2H, m), 2.83-3.02(1H, m, H-1), 3.73-3.89(2H, m, H-4,-5), 4.23(1H, s, H-2), 5.14(1H, t, J=5Hz, H-6); ^{13}C NMR 27.9(CH_2), 34.5(CH_2), 49.0(CH), 49.6(CH), 49.9(CH), 83.5(CH), 169.4 (C=O), 199.2(C=O); MS m/z 246(55), 244(55), 201(19), 199(22), 187(30), 185(22), 167(14), 165(14), 121(33), 91(77), 85(66), 83(100).

3β-Bromo-2-oxobicyclo[3.3.0]octane-4α,6α-carbolactone (29). The bromohydrin (27) was oxidised as described for the isomeric (26) above. The ketone (29) was obtained as a white solid, mp. 84-85°C, in 92% yield. (Found: C, 43.93; H, 3.49%). IR 1770, 1745 cm^{-1}; ^1H NMR 1.51-1.75(1H, m), 1.8-2.03(2H, m), 2.18-2.46(1H, m), 3.31(1H, q, J=9Hz, H-1), 3.54(1H, d, J=9Hz , H-4), 3.7-3.86(1H, m, H-5), 4.56(1H, s, H-3), 5.14 (1H, t, J=4.5Hz, H-6); ^{13}C NMR 25.9(CH_2), 35.0(CH_2), 45.6(CH), 47.8(CH), 48.3(CH), 49.9(CH), 51.1(CH), 85.1(CH), 106.5(C=O), 198.1(C=O).

4-Cyanomethylhexahydro-2H-cyclopenta[b]furan-2-one (32). To the bromoketone (28) (213mg, 0.87 mmol) in dry dimethyl sulphoxide (10 ml) was added sodium cyanide (0.1g, 2.04 mmol) and the mixture heated under reflux for 5 hours in a nitrogen atmosphere. After cooling, water was added and the aqueous solution acidified with dilute hydrochloric acid. It was then extracted with ether and the combined extracts dried ($MgSO_4$) and evaporated. Flash chromatography with hexane/ethyl acetate 1:4 yielded (32) (18mg, 14%) (R_f 0.36). IR 3650-3150, 1760 cm^{-1}; ^1H NMR 1.75-2.2(4H, m), 2.3-

2.6(4H, m), 2.72(1H, dd, J=10 and 17.5Hz), 3.1-3.24(1H, m), 5.09(1H, m); ^{13}C NMR 18.6(CH_2), 28.7(CH_2), 28.9(CH_2), 32.8(CH_2), 39.3(CH), 40.2(CH), 85.3(CH), 118(CN), 176.4(C=O); MS m/z 165(M^+, 30), 148(21), 147(18), 139(5), 121(10), 93(18), 91(10), 81(100).

6α-Hydroxybicyclo[3.3.0]oct-2-en-4β-oic acid (35). To a solution of the olefinic lactone (25) (1g, 6.7 mmol) in dry methanol (25 ml) was added sodium methoxide (1.4g, 26 mmol) and the solution refluxed until tlc. examination showed that all of the starting material was consumed. The methanol was evaporated in vacuo, water (25 ml) was added and the solution stirred for 30 minutes. It was then acidified with dilute sulphuric acid and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to give a light brown solid, which was crystallised from chloroform to give the acid (35) as a colourless powder (0.8g, 71%), mp 84-85°C. (Found: C, 64.3; H, 7.4. $C_9H_{12}O_3$ requires: C, 64.3; H, 7.2%). IR(nujol) 3550-3200, 3200-2400, 1700 cm^{-1}, ^{1}H NMR(C_5D_5N) 1.4-1.8(3H, m, H-7,-8), 1.8-1.96(1H, m, H-7), 3.2-3.38(1H, m, H-1), 3.5-3.64(1H, m, H-5), 4.48-4.68(2H, m, H-4,-6), 5.68(1H, m, H-2), 6.07-6.16(1H, m, H-3), 9.2-12.3(2H, br, OH and CO_2H); MS m/z 168(M^+, 2), 150(52), 124(3), 105(100).

Acetylation of (35). Acetic anhydride (5 ml) was added dropwise to the hydroxy acid (35) (0.4g, 2.38 mmol) in pyridine (5 ml) at 10°C. The mixture was stirred for 6 hours at room temperature, then poured into dilute hydrochloric acid and crushed ice and extracted with ethyl acetate. The combined extracts were washed consecutively with 10% aqueous hydrochloric acid, saturated sodium chloride solution and water. After drying ($MgSO_4$) and removal of the solvent in vacuo the residue was flash chromatographed, using hexane/ethyl acetate/formic acid 160:40:1 as eluent, to give the acetate (36) (0.21g, 42%) together with the isomeric acetate (37) (0.15g, 30%). Acetate (36) was obtained as an oil. (Found: C, 63.2; H, 6.88. $C_{11}H_{14}O_4$ requires: C, 62.9; H, 6.71%). IR 3600-2400, 1730, 1700 cm^{-1}; ^{1}H NMR 1.40-1.8(3H, m, H-7,-8), 1.8-1.96(1H, m, H-7), 2.08(3H, s, Ac), 3.16-3.4(2H, m, H-1,-4), 2.64-2.74(1H, m, H-5), 5.04-5.18(1H, m, H-6), 5.66-5.8(2H, m, H-2,-3), 9.25-10(1H, br, CO_2H); MS(E.I.) m/z 193, 192, 165, 150, 105(100); MS(C.I.) m/z 210(M^+). The acetate (37) was obtained as a solid mp 98°C. (Found: C, 63.1; H, 6.78%). ^{1}H NMR 1.36-1.58(1H, m,H-8), 1.7-2.08(3H, m, H-7,-8), 1.96(3H, s, Ac), 2.2-2.4(1H, m, H-1), 2.72-2.84(1H, m, H-2), 2.84-2.96(1H, m, H-2), 3.51-3.68(1H, m,H-5), 5.4(1H, dt, J=8 and 8Hz, H-6), 6.85-6.92(1H, m, H-3), 9.3-10.4(1H, br, CO_2H); MS m/z 193(100), 192, 165, 150, 105.

6α-Hydroxybicyclo[3.3.0]octan-4β-oic acid (38).To a stirred solution of the acid (35) (0.5g, 3 mmol) in ethyl acetate (10 ml) was added 5% palladium on charcoal (63mg). The system was purged with hydrogen gas and kept under a hydrogen atmosphere for 12 hours. The solution was then filtered through a pad of Supercel. Evaporation of the solvent in vacuo gave a solid which was crystallised from ethyl acetate to give (38) (0.43g, 84%), mp 105-106°C. (Found: C, 63.81; H, 8.33. $C_9H_{14}O_3$ requires: C, 63.53; H, 8.24%) IR 3560-3440, 3300-2600, 1720 cm^{-1}; ^{1}H NMR(90MHz, C_5D_5N) 1.5-3.2(11H, m), 4.2-4.45(1H, m, H-6), 8.65-9.5(2H, br, OH and CO_2H).

Bicyclo[3.3.0]octane-4α,6α-carbolactone (40). The olefinic lactone (25) (1.13g, 7.5 mmol) was dissolved in absolute ethanol (30 ml), and 10% palladium on charcoal added. The reaction mixture was hydrogenated at room temperature for 3 hours at 3 atmospheres pressure of hydrogen. The solution was then filtered through a pad of Supercel, dried over sodium sulphate and evaporated in vacuo to give (40) as an oil (1.08g, 96%). (Found: C, 70.62; H, 7.91. $C_{11}H_{12}O_2$ requires: C, 71.05; H, 7.89%). IR 1765 cm^{-1}; ^{1}H NMR(90MHz) 1.3-2.3(8H, m, H-2,-3,-7,-8), 2.4-2.85(1H, m, H-1), 2.9-3.37(2H, m, H-4,-5), 4.85-5.05(1H, m, H-6); MS m/z 153(M+1, 5), 152(M^+, 0.5), 124(2), 108(13), 80(100).

6α-Acetoxybicyclo[3.3.0]oct-2-en-4β-oic acid (36). To a solution of the hydroxyacid (35) (0.4g, 2.38 mmol) in acetic anhydride (5ml) at room temperature was added one drop of boron trifluoride etherate and the solution stirred for 10 minutes. The reaction mixture was then poured into dilute hydrochloric acid and crushed ice, and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and warmed with activated charcoal to remove some brown impurity. Evaporation of the solvent in vacuo gave (36) (0.41g, 82%).

6α-Acetoxybicyclo[3.3.0]octane-4β-carboxylic acid (39). The acid (36) (0.16g, 0.76 mmol) was dissolved in ethyl acetate (10 ml) and 5% palladium on charcoal catalyst was added. The system was purged with hydrogen and the mixture allowed to stir for

12 hours under a hydrogen atmosphere at room temperature. The reaction mixture was then filtered through a pad of Supercel and evaporated in vacuo to give (39) as a colourless solid (0.14g, 87%), mp 64°C. (Found: C, 62.1; H, 7.7. $C_{11}H_{16}O_4$ requires C, 62.2; H, 7.6%). IR(nujol) 3450-2400, 1740, 1690 cm^{-1}; ^1H NMR 1.2-1.46(2H, m), 1.6-1.92(4H, m), 1.92-2.14(2H, m), 2.06(3H, s, Ac), 2.52-2.69(1H, m, H-1), 2.77 (1H, dt, J=7 and 8Hz, H-4), 2.88-3.04(1H, m, H-5), 5.0-5.18(1H, m, H-6), 6.7-8.6 (1H, br, CO_2H); MS m/z 195(M^+-OH, 3), 170(0.5), 169(3), 152(4), 43(100).

6α-Acetoxybicyclo[3.3.0]octan-4β-ylmethanol (41). The acid (39) (0.11g, 0.52 mmol) in dry tetrahydrofuran (5 ml) at -40°C was treated with a solution of diborane in terahydrofuran (0.55 ml, 1M solution) under a nitrogen atmosphere. The reaction mixture was stirred for 1 hour at -40°C, allowed to warm to room temperature over 1 hour and then maintained at 25°C for a further 2.5 hours. The solution was treated with aqueous ammonium chloride solution (5 ml, 10% w/v) and the mixture concentrated in vacuo. Ethyl acetate was added to the residue and the organic extract was washed with water, saturated aqueous sodium bicarbonate solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residual oil flash chromatographed in hexane/ethyl acetate 1:3 to yield (41) as a colourless oil (90 mg, 87%). (Found: C, 66.3; H, 9.5. $C_{11}H_{18}O_3$ requires: C, 66.6; H, 9.1%). IR 3650-3300, 1760 cm^{-1}; ^1H NMR 1.21-1.46(3H, m), 1.6-1.78(2H, m), 1.78-2.0(3H, m), 2.08 (3H, s, Ac), 2.0-2.17(2H, m, H-4 and OH), 2.22-2.40(1H, m, H-1), 2.42-2.6(1H, m, H-5), 3.47(2H, d, J=6Hz, CH_2OH), 5.0-5.12(1H, m, H-6); MS m/z 198, 181, 139, 138, 43(100).

6α-Acetoxybicyclo[3.3.0]octane-4β-carbaldehyde (42). To a solution of the alcohol (41) (50mg, 0.25 mmol) in dry dichloromethane (1.5 ml) was added pyridinium chlorochromate (0.22g, 1.02 mmol) and anhydrous sodium bicarbonate (0.1g). The resulting suspension was stirred for 3.5 hours at room temperature, then filtered and the filtrate directly subjected to flash chromatography. The aldehyde was eluted with hexane/ethyl acetate as an oil (30mg, 61%) which was used immediately for the preparation of (43) on account of its poor stability. ^1H NMR 1.21-1.45(2H, m), 1.6-2.12(6H, m), 2.04(3H, s, Ac), 2.5-2.82(2H, m, H-1,-4), 2.89-3.03(1H, m, H-5), 5.0-5.12(1H, m, H-6), 9.52(1H, d, J=2Hz, CHO); MS m/z 196(M^+, 1), 152(25), 136(2), 43(100).

4β-(3'-Octenyl)bicyclo[3.3.0]octan-6α-yl acetate (43). Dimethyl(2-oxoheptyl)phosphonate (0.73g, 3.15 mmol) in dry tetrahydrofuran (5 ml) was added dropwise to a stirred suspension of sodium hydride (68mg, 2.8 mmol) in tetrahydrofuran (12 ml) under nitrogen. The mixture was stirred for 3 hours, then treated dropwise with a solution of the freshly prepared aldehyde (42) (0.5g, 2.55 mmol) in tetrahydrofuran and finally allowed to stir overnight. The mixture was then filtered and the filtrate evaporated in vacuo. The residue was extracted with ether, and the extracts subsequently washed with water and dried ($MgSO_4$). The solvent was removed in vacuo and the remaining oil was chromatographed in petroleum ether/ethyl acetate 6:1 to give the enone (43) (0.45g, 61%). (Found: C, 74.54; H, 9.93. $C_{18}H_{28}O_3$ requires: C, 73.97; H, 9.59%). IR 1745, 1665, 1620 cm^{-1}; ^1H NMR(90MHz) 0.9(3H, t, J=6Hz, H-8'), 1.0-2.1(17H, m), 1.95(3H, s, Ac), 2.3-2.7(2H, m, H-4,-5), 4.85-5.2(1H, m, H-6), 6.0(1H, d, J=15Hz, H-2'), 6.69(1H, dd, J=8 and 15Hz, H-1'); MS m/z 233(M-OAc, 2), 232(5), 43(100).

6α-Acetoxybicyclo[3.3.0]oct-3-ene (45). The acid (39) (0.7g, 2.2 mmol), cupric acetate (0.19g, 0.95 mmol) and pyridine (0.17g, 2.2 mmol) were stirred together in benzene (23 ml) overnight. Lead tetraacetate (7g, 15.8 mmol) and benzene (100 ml) were added and the solution flushed free of oxygen with nitrogen. The mixture was stirred in the dark for 1 hour at room temperature and then for 3 hours under reflux. The mixture was poured into water and extracted with ether. The organic extracts were washed with saturated aqueous sodium bicarbonate solution and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue chromatographed in petroleum ether/ethyl acetate 20:1 to give the olefin (44) (0.4g, 73%) as a colourless volatile liquid. (Found: C, 72.01; H, 8.43. $C_{10}H_{14}O_2$ requires: C, 72.29; H, 8.43%). IR 1730 cm^{-1}; ^1H NMR(90MHz) 1.2-2.3(5H, m), 2.0(3H, s, Ac), 2.48-2.8 (2H, m), 3.25-3.53(1H, m, H-5), 4.97-5.25(1H, m, H-6), 5.35-5.6(1H, m, H-3), 5.75 (1H, dd, J=2 and 7Hz, H-4).

Hexahydro-2-oxo-2H-cyclopenta[b]furan-4-carboxylic acid (46). The olefinic lactone (25) (0.32g, 2.1 mmol) was dissolved in methanol (5ml) and cooled to -70°C, while a

stream of ozonised oxygen was bubbled through. The methanol was then removed *in vacuo* (0.6 mm Hg) with no external heat being applied. The resulting viscous oil was redissolved in formic acid (1.5 ml) and hydrogen peroxide (0.72 ml, 30%) was cautiously added. The reaction mixture was heated gently until it began to reflux spontaneously. Then no further heat was supplied until refluxing subsided. Refluxing was continued until the reaction mixture gave a negative test for peroxides with potassium iodide-starch paper. The resulting solution was then evaporated *in vacuo* and the liquid thus obtained chromatographed with ethyl acetate as eluent to give (45) as a colourless oil (0.12g, 33%). (Found: C, 56.19; H, 5.55. $C_8H_{10}O_4$ requires: C, 56.47; H, 5.88%). IR 3500-2500, 1790-1700 cm^{-1}; ^1H NMR 1.62-2.1(3H, m), 2.1-2.25(1H, m), 2.50(1H, dd, J=17.3 and 5.0Hz), 2.79(1H, dd, J=17.3 and 10.4 Hz), 2.97(1H, q, J=17.8Hz), 3.1-3.4(1H, m), 5.08(1H, t, J=6.3Hz), 12.9(1H,s,CO_2H); ^{13}C NMR 26.4, 31.7, 32.9, 40.4, 48.8, 85.4, 175.3, 177.2; MS m/z 170(M, 10), 153 (41), 125(18), 81(40), 66(100).

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