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A NEW SYNTHETIC ROUTE TO (±)-FORSKOLIN

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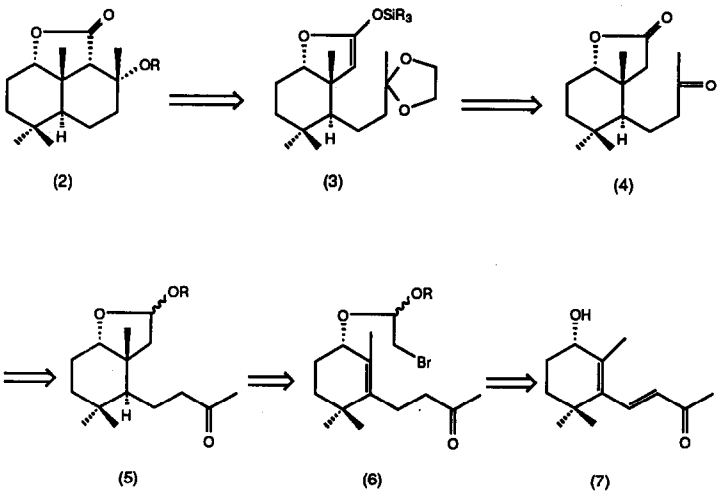
Summary: The trans-decalin lactone (35) has been elaborated in five steps from the bromo-acetal (10) using a novel stereoselective intramolecular radical mediated cyclisation reaction, viz (10)→(12) in tandem with an intramolecular Mukaiyama aldolisation, viz (34)→(35). Treatment of (35) with methanolic potassium hydroxide next led to the βγ-unsaturated lactone (37), which on oxidation with pyridinium dichromate t-butylhydroperoxide complex then gave the enone (40). Since the enone (40) has previously been converted to (±) -forskolin (1), the sequence constitutes a new synthetic route to this natural product. Some chemistry relating to elaboration of the cis-decalin lactone (49) to analogues of forskolin, e.g. (55), (56) and (57), incorporating a cis-ring fused decalin core structure, is also described.

Forskolin (1) is a highly oxygenated labdane diterpene isolated from the roots of the Indian herb Coleus forskohlii, a species which has been used locally as a medicine for centuries[1]. Interest in the medicinal properties of forskolin soared with the discovery that the molecule is a potent positive ionotropic agent, as well as being a potent bronchodilator and hypotensive agent. In addition, forskolin displays platelet aggregation inhibitory activity and can reduce intraocular pressure in man. This broad-range physiological spectrum is related to the ability of forskolin to directly stimulate adenylate cyclase, a membrane bound enzyme, and thus increase intracellular AMP[2].

(1)

Forskolin is one of the most oxygenated secondary metabolites yet isolated. In addition, its decalin based molecular framework accommodates eight asymmetric centres, seven of which are contiguous. These structural features, together with its wide pharmacological profile have combined to make forskolin a challenging target for synthesis. Indeed, three total

syntheses of this target molecule from the research groups of Ziegler[3], Corey[4] and Ikegami[5], have recently been accomplished, and a number of synthetic approaches have been published[6]. The overwhelming majority of the published synthetic approaches to forskolin have been based on intramolecular cycloaddition, with the ubiquitous intramolecular Diels-Alder reaction predominant. In this paper, we describe a conceptually new approach to the decalin carbon framework in forskolin, which is based on a novel stereoselective intramolecular radical mediated cyclisation reaction viz (6)→(5), in tandem with an intramolecular Mukaiyama aldolisation viz (3)→(2) (Scheme).[7] Elaboration of the decalin (2) to the Ziegler intermediate (40)[3] then culminated in a new formal synthesis of (±)-forskolin (1).



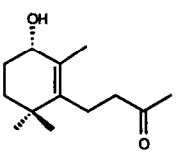
Scheme

Thus, the known and readily available hydroxy β-ionone (7)[8] was first converted to the vinyl ether (9) following reduction with tri-n-butyltin hydride and treatment of the resulting γδ-unsaturated ketone (8) with ethyl vinyl ether in the presence of mercuric acetate. Reaction between the vinyl ether (9) and N-bromosuccinimide in methanol at -20°C then led to a mixture of diasterioisomers of the bromo-acetal (10).

When a solution of the bromo-acetal (10) in benzene was heated in the presence of tri-n-butyltin hydride (Bu_3SnH) in the presence of 2,2'-azobis-(2-methylpropionitrile (AIBN), it underwent smooth stereoselective 5-exo-trigonal radical cyclisation to produce a mixture of the cyclic acetals (11) and (12) in 95% overall yield[9]. Subsequent hydrolysis and oxidation of the mixture of diastereoisomeric acetals, using Jones reagent at 0°C, then gave a 3:1 mixture of equatorial (cis-) and axial (trans-) isomers of the corresponding bicyclic lactones (13) and (14) respectively. The isomeric lactones were separated by

chromatography and crystallisation to give the trans-isomer (14) as an oil and the cis-isomer (13) as colourless crystals. The stereochemistry of (14) followed conclusively from n.O.e. experiments, whereas the structure and stereochemistry of the cis-isomer (13) was confirmed by X-ray crystallographic analysis.

The formation of a 3:1 mixture of cis- (11) and trans- (12) isomers† from cyclisation of (10) in the presence of tri-n-butyltin hydride was unacceptable



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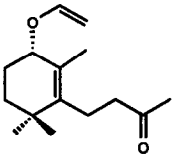

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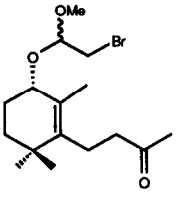

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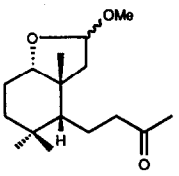

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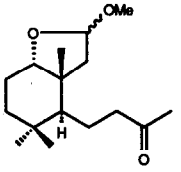

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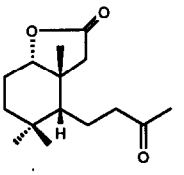

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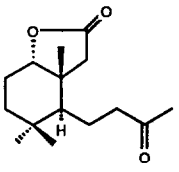

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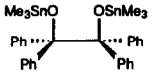

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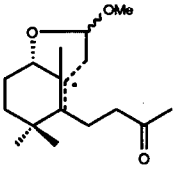


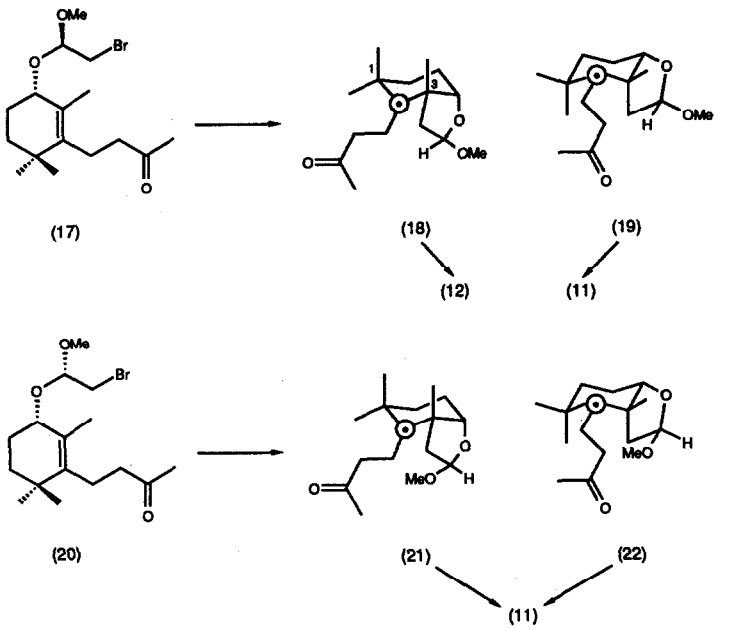
(16)

and disappointing. Accordingly, a range of alternative reaction conditions and radical-initiating procedures were investigated in order to optimise the formation of the required trans-isomer (12) for our projected synthesis of forskolin. Alterations in the nature of the solvent e.g. xylene, tetrahydrofuran, or the mode of initiation e.g. peroxide or ultraviolet irradiation, in the tri-n-butyltin hydride cyclisation of (10) had no effect on the stereochemical outcome of the reaction. However use of hexaphenylditin (1.5 equivalents, 450W Hanovia lamp, 25°C) or more

†Throughout this paper the trivial terminology cis- and trans (referring to the orientation of the C-5-H relative to the C-10-Me) will be used to designate the equatorial (13) and axial (14) isomers respectively.

conveniently bis(trimethylstannyl)benzopinacolate (15)[10] (reflux, benzene) in the cyclisation of (10) both led to entirely the trans-isomer (12) of the corresponding cyclic acetal, which on Jones oxidation produced the oily trans- lactone (14). Even more interesting was the observation that when the cyclisation of (10) was effected in the presence of catalytic cobalt(I), generated electrochemically in methanol-lithium perchlorate from vitamin B_{12} at -1.8 volts[11], analysis of the crude product by n.m.r. data showed that it was almost entirely the required trans bicyclic acetal (12), containing less than 5% of the corresponding cis-isomer (11). Thus, using either hexaphenylditin, bis(trimethylstannyl)benzopinacolate or cobalt(I) we were able to effect the desired 5-exo-trig cyclisation of (10) to the required equatorial (trans)-isomer of the bicyclic acetal (12) en route to forskolin.

The interesting dichotomous behaviour in the stannane- and cobalt-mediated radical cyclisations of (10) leading to stereocontrolled synthesis of the cis- (>75%, Bu_3SnH) and trans-[>95%, Co(I) Ph_6Sn_2 or (15)] acetals (11) and (12) respectively, is without precedent in radical chemistry. To a large extent the origin of the dichotomy can be traced to the nature and



geometry of the acetal moiety in (10)[12]. Thus, chromatography of the mixture of diastereoisomeric bromo-acetals produced by treatment of the vinyl ether (9) with N-bromosuccinimide in methanol resulted in the separation of a solid diastereoisomer, m.p. 90.5-92.5°C together with a liquid diastereoisomer. When a solution of the liquid diastereoisomer was heated in benzene in the presence of Bu_3SnH and AIBN, radical cyclisation was stereoselective and led to only the cis-isomer (11) of the adduct. Surprisingly, radical cyclisation of the corresponding solid diastereoisomeric bromo-acetal under the same

conditions led to a 1:1 mixture of the cis and trans-isomers (11) and (12), whereas cyclisation of either of the diastereoisomeric acetals (10) in the presence of Co(I) produced only the trans- isomer (12).

Inspection of Dreiding molecular models suggests that the differing stereoselectivity observed in the Bu_3SnH cyclisations of (10) could have its origin in the preferred conformations adopted by the transition state (16)/product radical centre (18) in the two reactions. These will no doubt assume conformations whereby unfavourable 1,3- diaxial interactions between groups associated with carbons C_1 and C_3 are kept to a minimum. Thus, the diastereoisomer (17) most likely promotes formation of the trans-isomer (12) when the C_1-C_3 methyl groups are 1,3-diaxial, [as in (18)], whereas all other 1,3-interactions i.e. (19), (21) and (22) from both the diastereoisomers (17) and (20) would be expected to favour formation of the cis- isomer(11). This crude analysis was vindicated when it was established by X-ray crystallographic analysis that the crystalline diastereoisomer of (10), which was found to lead to the trans-isomer (12), did in fact have the β-methoxy stereochemistry anticipated, i.e. (17).

Interactive graphics work, whereby the butanone side chain in the trigonal product radical (16) was subjected to minimisation and systematic analysis, shed even more light on the problem. This analysis revealed two major minima in the conformational space, and these are shown in Figure 1 (high energy) and Figure 2 (low energy)[13]. The conformers differ in energy

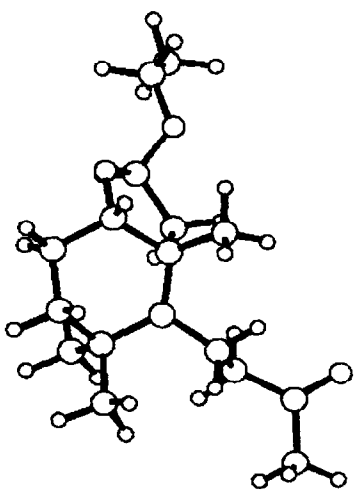


FIGURE 1

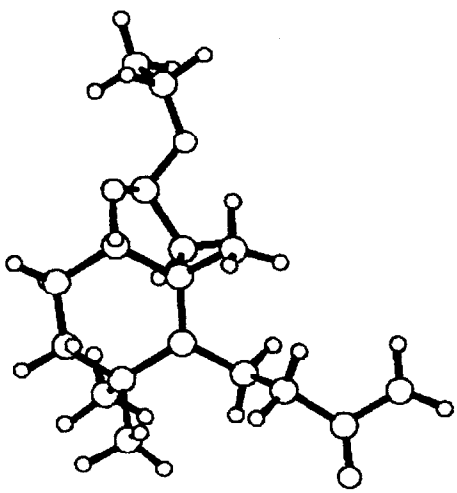
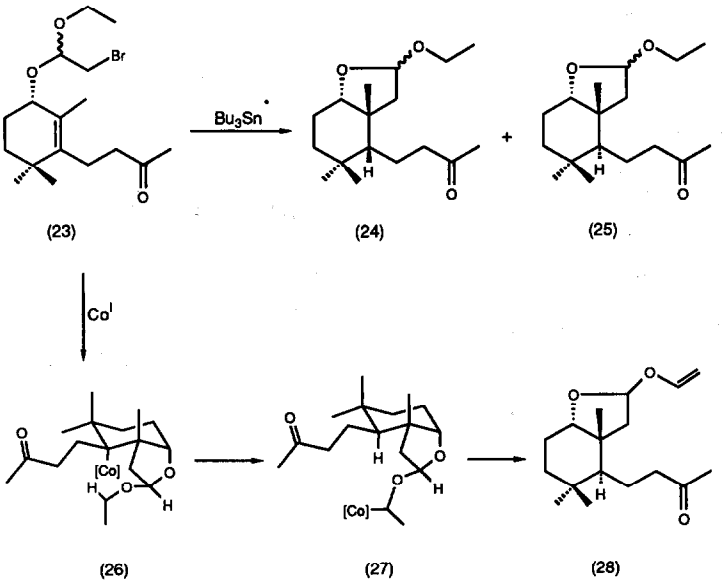


FIGURE 2

by 4 Kcals and there is a large energy barrier (> 20 Kcals) between the two. The low energy conformer (Figure 2) has the butanone side chain orientated

trans(anti)-to the five ring acetal residue, thereby impeding H• quench from this face which would lead ultimately to the trans-isomer (12) of the product. By contrast the high energy conformer (Figure 1), with the butanone side chain orientated cis(syn)-to the acetal residue, would be expected to lead to the corresponding cis-isomer (11) of the product. Thus, if the two conformers (Figures 1 and 2) are produced in a kinetic distribution in the Bu_3SnH reaction with (10), quenching by H• should favour formation of the cis-product (11). Correspondingly, radical initiation conditions [i.e. Ph_6Sn_2 -hν, reagent (15), cobalt (I)] which incorporate slower hydrogen donors, would allow the product radical to acquire thermodynamic equilibrium, thereby populating the lower energy conformation (Figure 2), leading largely to the trans-product (12), as observed.

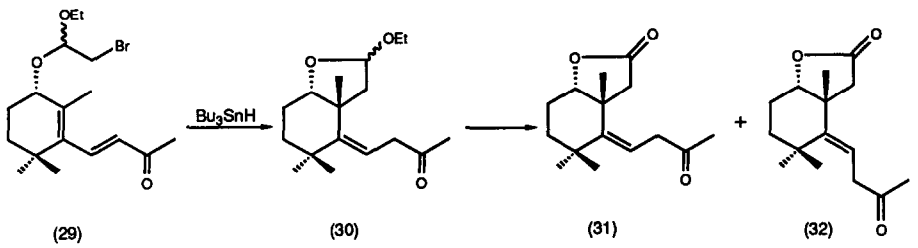
Although we were not able to separate the diastereoisomers of the ethyl acetal (23) produced when (8) was treated with 1,2-dibromoethyl ethyl ether, radical cyclisation of a 1:1 mixture of diastereoisomers of (23) in the presence of Bu_3SnH-AIBN, like the methyl acetal, led to a 3:1 mixture of cis- and trans- isomers, (24) and (25), of cycloadduct. Much more interesting however was the outcome of the reaction between (23) and catalytic Co(I) produced from electrolytic reduction of vitamin B_{12}. This reaction led to a 1:1 mixture of the ethyl acetal (25) and the ethylene acetal (28) in a combined yield of 70%; furthermore both (25) and (28) were produced with the trans-stereochemistry. In the light of our contemporaneous studies involving oxidative free radical carbon-to-carbon bond forming reactions via cobalt complexes[14], it is tempting to suggest that the transformation (23)→(28)



(23) (24) (25)

(26) (27) (28)

in the presence of Co(I) most likely occurs via the transient organo-cobalt (27). Instead of undergoing de-hydrocobaltation to (30), molecular models suggest that the organocobalt intermediate (26) resulting from initial cyclisation of (23) could undergo intramolecular Co-H exchange, with retention of stereochemistry, involving the C-H bond associated with the methylene group of the ethyl acetal in (26). 1,2-Elimination of Co-H from (27) would then lead to the observed ethylene acetal (28) whereas C-Co bond cleavage accompanied by hydrogen atom addition would produce the corresponding ethyl acetal (25). In a separate experiment we were able to prepare the unsaturated acetal (30) following radical cyclisation of the bromo-dienone (29) in the presence of Bu_3SnH-AIBN. Attempts to implicate (26) and/or (27) in the conversion of (23) to (28) were unsuccessful however, when all attempts to effect hydrocobaltation of (30) and in situ intramolecular hydrogen transfer in the presence of Co-H catalysis met with failure.[15]

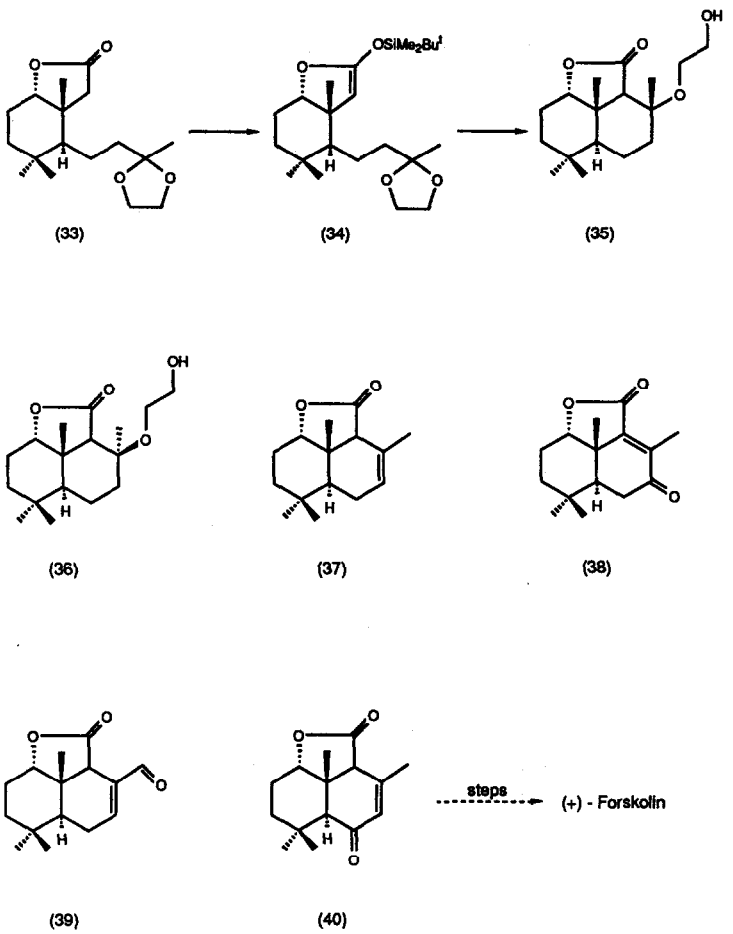


(29) (30) (31) (32)

With a successful, high-yielding, stereocontrolled synthesis of the keto- lactone (14), resulting from radical cyclisation of the bromo-acetal (10), we next proceeded to examine the intramolecular Mukaiyama aldolisation reaction to access the trans-decalin (35). Thus, conversion of (14) to the corresponding dioxolan (33) followed by treatment with lithium hexamethyldisilazide and quenching the resulting enolate with t-butyldimethylsilyl chloride first provided the silyl ether (34). Addition of (34) to a cold solution of titanium tetrachloride in methylene dichloride at -78°C resulted in smooth intramolecular Mukaiyama cyclisation leading to a 3:1 mixture of α- and β- C-8 epimers, (35) and (36) respectively, of the substituted decalin, in a combined yield of 62%. The geometry assigned to the major C-8 β-methyl epimer (35), followed conclusively from n.O.e. experiments.

The formal synthesis of (±)-forskolin (1) was now completed following conversion of the 3:1 mixture of (35)/(36) to the βγ-unsaturated lactone (37) using methanolic potassium hydroxide,[16] and oxidation of (37) to (40) in the presence of pyridinium dichromate - t-butylhydroperoxide.[17] The specific oxidation of (37) to the enone (40) was difficult as well as capricious. Several oxidation conditions led to either recovered starting material or

intractable tars, whilst others led to the transposed ketone (38) or to the aldehyde (39). The combination of pyridinium dichromate and t-butylhydroperoxide led to a mixture of (38) and (40) from which the enone (40) was separated and crystallised. The enone (40) was identical with the material synthesised by Ziegler et.al[3] and used by them in their total synthesis of forskolin. The synthesis of (40) based on the tandem radical cyclisation-intramolecular Mukaiyama approach (Scheme) thus constituted a new formal synthesis of (±)-forskolin.



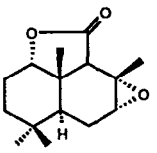
(33) (34) (35)

(36) (37) (38)

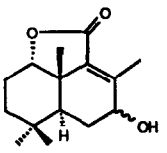
(39) (40)

In one of a number of alternative proposed routes of forskolin (1) from the β γ-unsaturated lactone (37) we envisaged the cyclohexadiene lactone (43) as a key intermediate. This intermediate could then be processed in a number of ways (e.g. vicinal oxidation at C6-C7, nucleophilic opening of the 5-ring lactone) to several more advanced intermediates towards the final target. In the event however, although the cyclohexadiene could be produced from (37),

following epoxidation to (41), conversion of the epoxide (41) to the allylic alcohol (42), and elimination from (42) in the presence of methanesulphonic anhydride- triethylamine, the molecule proved to be remarkably labile, and readily underwent isomerisation to the cis-ring fused diene (44) and to the isomeric diene (45) on leaving at room temperature for a few hours.



(41)
a. α-epoxide
b. β-epoxide



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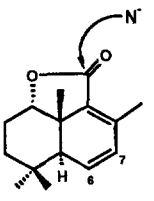

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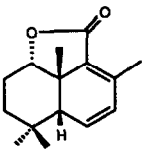

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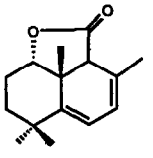
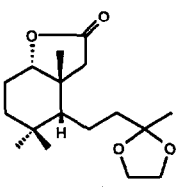


(45)

As a corollary to our synthetic investigations towards natural forskolin (1), we also evaluated the use of the readily available cis-bicyclic lactone



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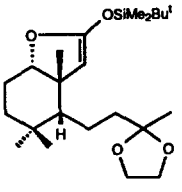

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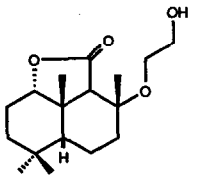

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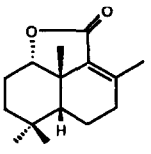

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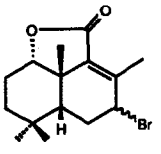

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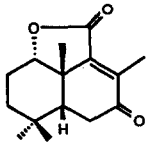
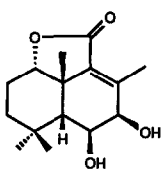
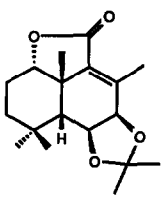


(51)

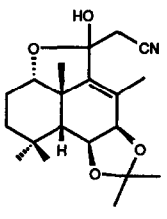
(13) resulting from Bu_3SnH-AIBN initiated cyclisation of (10), in the synthesis of analogues of forskolin e.g. (55), (56), (57) incorporating cis-ring fused decalin core structure. Thus, in four simple steps starting with the bicyclic lactone (13) we were able to synthesis the tricyclic α,β-unsaturated lactone (49) via (46), (47) and (48). Bromination of (49) to the allylic bromide (50), followed by dehydrobromination in the presence of 1,8-diazabicycloundecene then led to the 1,3-diene (44) together with minor amounts of the corresponding enone (51). Treatment of (44) with osmium tetroxide next led to the vicinal diol (52) which was protected as the corresponding acetonide (53). The lactone-acetonide (53) was then reacted with a range of nucleophilic reagents i.e. lithium acetonitrile, methyllithium, lithium aluminium hydride, lithium propyne, leading to high yields of the products (54), (55a), (56) and (55b) respectively. Interestingly, the adduct (51) underwent smooth dehydration to the crystalline diene nitrile (57) in the presence of p-toluenesulphonic acid. Unfortunately the diene (57) failed to participate in any further interesting chemistry which might have led to precursors to forskolin containing a cis-ring fused decalin system.



(52)



(53)



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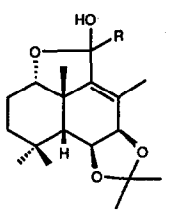
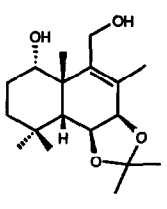
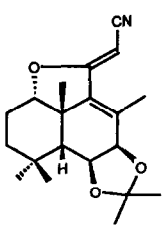


(55)

a R = Me
b R = ≡Me



(56)



(57)

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were obtained using a Pye Unicam SP3-100 or Philips PU9706 spectrometer, as liquid films on sodium chloride discs or as solutions in the solvent stated. P.m.r.spectra were recorded on either a Bruker WM250 or a Bruker AM400 instrument. The spectra were recorded as dilute solutions in deuteriochloroform unless otherwise stated. The chemical shifts are recorded relative to internal tetramethylsilane, and the multiplicity of a signal is a singlet unless otherwise stated, when the following abbreviations are used: d, doublet; t, triplet; q, quartet; m, multiplet; br., broad. C.m.r. spectra were recorded as dilute samples in deuteriochloroform unless otherwise stated. The chemical shifts are reported relative to internal tetramethylsilane in a broad band decoupled mode. The multiplicities were obtained using either a DEPT program or from an off resonance spectrum.

Mass spectra were recorded on an AEI MS-902 or VG MM-7070F instrument at high resolution. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser.

Column chromatography was carried out using Merck Kieselgel 60, Art. 9385 silica, and light petroleum (b.p. 40°-60°C) was redistilled before use. Analytical t.l.c. plates (Polygram Sil G/UV_{254} on plastic sheets) were visualised with basic potassium permanganate solution, with acidic anisaldehyde solution or with ethanolic dodecamolybdophosphoric acid.

Routinely, dry organic solvents were stored under nitrogen, over freshly activated molecular sieves. Ether, benzene and toluene were dried over sodium wire. Other organic solvents were distilled from the following drying agents: dichloromethane (calcium hydride), tetrahydrofuran (sodium wire), ethanol (magnesium ethoxide), dimethylformamide (calcium hydride at reduced pressure). Evaporation of organic solutions refers to solvent removal on a Büchi rotary evaporator under water aspirator pressure (12mmHg). Where necessary reactions were carried out under a nitrogen or argon atmosphere.

4-(3-Hydroxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one (7)[8].- A solution of 1-epoxy-α-ionone (8.9 g, 1.0 equiv.)[18] in methanol (170 ml) was heated under reflux in the presence of anhydrous potassium carbonate (11.9 g, 2.0 equiv.) for 1 hr. The mixture was cooled to 25°C and then poured into water (500 ml). The aqueous solution was extracted with ether (3 x 150 ml) and the combined ether extracts were then washed with brine (2 x 200 ml), dried and evaporated to leave the alcohol (9 g, 98%) as an orange oil, ν_{max}

(film) 3500 (br.), 1660, 1610, 1260 cm.$^{-1}$, δ_H 7.3 (d, J 16Hz, HC:CHCO), 6.25, (d, J 16Hz, HC:CHCO), 4.05 (dd, J 4Hz, CH-O), 3.0 (br, -OH), 2.33 (CH_3CO), 2.0-1.0 (4H, m), 1.88 (CH_3C:), 1.09 (CH_3), 1.05 (CH_3); (Found: C, 74.9; H, 9.5; Calc. for $C_{13}H_{20}O_2$: C, 75.0; H, 9.6%).

The hydroxyionone was also obtained from β-ionone following the procedure described by Henbest.[8]

4-(3-Hydroxy-2,6,6,-trimethyl-1-cyclohexen-1-yl)-2-butanone (8).- Tri-n-butyltin hydride (5.55 ml., 2.2 equiv.) was added to a degassed (N_2) solution of the enone (7) (1.94 g., 1.0 equiv.) in dry benzene (30 ml), and the mixture was then heated under reflux for 24 h. The solution was cooled to room temperature, and the solvent was then evaporated in vacuo. The residue was purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (4:1 then 1:2) as eluant to give the keto-alcohol (1.93 g; 98%) as a colourless oil, ν_{max} (film) 3400 (br), 1710 cm.$^{-1}$, δ_H 3.94 (m, CHOH), 2.7-2.1 [m, $C(O)CH_2CH_2C$:C], 2.15 ($COCH_3$), 1.70 (:CCH_3), 2.0-1.0 [m, $C(OH)CH_2CH_2$- and -OH], 1.03 (CH_3), 0.96 (CH_3), (Found: m/z 192.1512. $C_{13}H_{20}O$ ($M-H_2O$) requires: 192.1505).

4-[3-Ethenoxy-2,6,6-trimethylcyclohexen-1-yl]-2-butanone (9). - A solution of the alcohol (8) (3.95 g; 1.0 equiv.) in ethyl vinyl ether (40 ml) was heated under reflux in the presence of mercuric acetate (0.6 g., 0.1 equiv.) under nitrogen for 3 days. The mixture was cooled to room temperature, and then poured into water (100 ml). The aqueous solution was extracted with ether (3 x 50 ml), and the combined ether extracts were then washed with water (2 x 30 ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by chromatography using light petroleum (b.p. 40-60°C)-ether (5:1, then 2:3) as eluant to give the vinyl ether (2.54 g; 57%) as a pale-yellow oil, ν_{max} (film) 2940, 1710, 1630, 1180 cm.$^{-1}$, δ_H 6.35 (dd, J 14 and 6 Hz, :CH), 4.35 (dd, J 14 and 2 Hz, CH-O), 4.04 (m,:CH_2), 2.7-2.45 (m, CH_2CO), 2.45-2.15 (m, :CCH_2), 2.15 (CH_3C:), 1.68 (CH_3), 2.0-1.1 (4H, m), 1.04 (CH_3), 0.98 (CH_3), [Found: m/z 193.1568. $C_{13}H_{21}O$ ($M-CH_2$:CH-O) requires: 193.1585].

4-[3-(1-Methoxy-2-bromoethoxy)-2,6,6-trimethylcyclohex-1-yl]-2- butanone (10). - N-Bromosuccinimide (838 mg; 1.1 equiv.) was added in one portion to a solution of the vinyl ether (9) (1.01 g; 1.0 equiv.) in dry methanol (20 ml) maintained at -23°C under nitrogen. The mixture was stirred at -23°C for 0.5 h, (during which time a thick, white precipitate formed), and then poured into water (50 ml). The aqueous solution was extracted with ether (3 x 30 ml), and the combined ethereal extracts were then washed with 1M hydrochloric

acid (1 x 20 ml) and water (2 x 20 ml), and dried ($MgSO_4$). The solvent was evaporated in vacuo to leave a 1:1 mixture of diastereoisomers of the bromo-acetal (1.40 g; 98%) as a pale-yellow oil which partially crystallised on standing. Light petroleum (b.p. 40-60°C) was added to the residue, and the precipitated crystalline diastereoisomer (180 mg; 12%) was isolated by filtration. The filtrate was evaporated in vacuo, and the residue was then purified by repeated chromatography using light petroleum (b.p. 40-60°C)-ether (12:1) as eluant to give : (i) the oily diastereoisomer (20) (428 mg; 29%), ν_{max} (film) 2940, 1715, 1650, 1020 $cm.^{-1}$, δ_H 4.70 (dd, J 5 and 5 Hz, OCHO), 3.72 (m, CH-O), 3.42 (CH_2Br), 3.40 (OCH_3), 2.7-2.4 (CH_2CO), 2.4-2.1 (CH_2C:), 2.18 (CH_3C:), 1.72 (CH_3), 2.0-1.1, (4H, m), 1.05 (CH_3), 0.99 (CH_3), (Found: m/z 235.1685. $C_{15}H_{23}O_2$ (M-HBrOMe) requires: 235.1698); (ii) the crystalline diastereoisomer (17) (234 mg; 28%) which recrystallised from a mixture of light petroleum (b.p. 40-60°C) and ether, and had m.p. 90.5-92.5°C, ν_{max} ($CHCl_3$) 2950, 1715, 1020 $cm.^{-1}$, δ_H 4.71 (dd, J 5 and 5 Hz, OCHO), 3.88 (m, CH-O), 3.43 (OCH_3), 3.35 (m, CH_2Br), 2.7-2.4 (m, CH_2CO), 2.4-2.1 (m, CH_2C:), 2.18 (CH_3C:), 1.74 (CH_3), 1.9-1.2 (4H, m), 1.04 (CH_3), 0.98 (CH_3), (Found: C, 55.85; H, 8.1, m/z 235.1696; $C_{16}H_{27}O_3$ requires: C, 55.4, H, 7.8%; (M-HBrOMe) 235.1698). Despite repeated chromatography a proportion of the mixture (323 mg; 22%) remained unseparated.

4-[3-(1-Ethoxy-2-bromoethoxy)-2,6,6-trimethyl-cyclohexen-1-yl]-2-butanone (23). - Triethylamine (0.3 ml; 0.2 equiv.) was added to a stirred solution of bromine (1.06 ml, 2.0 equiv.) in dry dichloromethane (40 ml) maintained at -78°C under nitrogen, and the mixture was then titrated with ethyl vinyl ether (~2.0 ml) until a colourless solution resulted. The mixture was stirred at -78°C for 10 min., and then a solution of the alcohol (8) (2.17 g: 1.0 equiv.) and triethylamine (3.3 ml; 2.3 equiv.) in dry dichloromethane (20 ml) was added. The mixture was allowed to warm to room temperature where it was then stirred for 6 h. The mixture was poured into water (200 ml), and the separated aqueous phase was then extracted with ether (3 x 50 ml). The combined organic phases were washed with water (2 x 50 ml), then dried and evaporated in vacuo to leave a brown oil. Chromatography using light petroleum (b.p. 40°-60°C)-ether (4:1) as eluant gave a mixture of diastereoisomers of the bromo-acetal (2.73 g; 73%) as a colourless oil, ν_{max} (film) 1710, 1030 $cm.^{-1}$, δ_H 4.75 (dd, J 5.5 and 5.5Hz, OCHOEt), 4.71 (dd, J 5.5 and 5.5Hz, OCHOEt), 3.94-3.55 (m, OCHC:C and CH_3CH_2O), 3.5-3.3 (m, CH_2Br), 2.65-2.5 [m, $C(O)CH_2$], 2.35-2.20 (m, $C:CCH_2$), 2.15 ($COCH_3$), 1.90-1.60 (m, $-CH_2CH_2-$), 1.75 (CH_3C:C), 1.25 (t, J 7.0Hz, CH_3CH_2O), 1.02 (CH_3), 0.96 (CH_3), (Found: C, 56.7; H, 8.0; $C_{17}H_{29}BrO_3$ requires: C, 56.5; H, 8.1%).

3a,4β,5,6,7,7aβ-Hexahydro-4(3-oxobut-1-yl)-3aβ,5,5-trimethyl-2(3H)-benzofuranone (13). - Tri-n-butyltin hydride (15.9 ml; 1:2 equiv.) was added to a degassed (N_2) solution of the bromo-acetal (10) (17.7 g; 1.0 equiv.) and AIBN (1.6g; 0.2 equiv.) in dry benzene (700 ml) and the solution was then heated under reflux for 4 h. The mixture was allowed to cool to room temperature, and the solvent was then removed *in vacuo*. The residue was purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (9:1 then 1:1) as eluant to give a mixture of the corresponding diastereoisomeric *cis*- and *trans*- bicyclic acetals (11) and (12) (12.4 g; 90%) as a pale yellow oil, which was not separated. A stirred solution of the mixture of cyclic acetals (12.4 g) in acetone (200 ml) was cooled to 5°C (ice-bath), and then titrated with Jones reagent during 0.5 h. to a permanent red end-point. The acetone was evaporated *in vacuo* and the aqueous residue was then extracted with ether (3 x 150 ml). The combined ethereal extracts were washed with saturated sodium bicarbonate solution (2 x 100 ml) and brine (1 x 100 ml), then dried and evaporated *in vacuo*. Chromatography of the residue using light petroleum (b.p. 40°-60°C)-ether (1:1 then pure ether) as eluant gave a 1:3 mixture of the *trans*- and *cis*-bicylic lactones, (14) and (13) (8.1 g: 73%) respectively, which was separated by repeated crystallisation from ether at 0°C to give: (i) the oily "*trans*"-isomer (14); which showed identical spectroscopic data to those of an authentic sample (see below), and (ii) the "*cis*"-isomer (13), m.p. 81-81.5°C (ether); ν_{max} ($CHCl_3$) 2950, 1770, 1710 $cm.^{-1}$, δ_H 4.07 (dd, J 10.5 and 6Hz, C*H*-O), 2.74 (d, J 17Hz, C*H*CO_2), 2.58 (m, C*H*$_2$CO), 2.16 (C*H*$_3$CO), 2.09 (d, J 17Hz, C*H*CO_2), 2.03-1.25 (6H, m), 1.19 (C*H*$_3$CCO), 1.04 (dd, J 4.5 and 4.5Hz, C*H*CH_2), 0.97 (C*H*$_3$), 0.93 (C*H*$_3$); δ_C 207, 176, 86, 51, 46, 43, 37.2, 36.9, 34, 32, 30, 29, 26, 22, 20, (Found: C, 71.6; H, 9.9; m/z 252.1717; $C_{15}H_{24}O_3$ requires: C, 71.4; H, 9.6%; *M* 252.1726).

Crystallographic Analysis of Lactone (13) and Bromoacetal (17)

Crystal data of Lactone (13). - $C_{15}H_{24}O_3$, M_{os} = 252.36, Orthorhombic, a= 8.101(1), b=10.377(1), c=17.338(1) Å, U=1457.64 Å, z=4, Dc=1.15 g $cm.^{-3}$, F(000)=552, Space group $P2_12_12_1$, Cu-$k_\alpha\lambda$ radiation λ=1.54178 Å, μ (Cu-K_α)=6.33 $cm.^{-1}$. Crystal data of Bromoacetal (17). - $C_{16}H_{27}BrO_3$, M= 347.31, Triclinic, a=8.399(3), b=10.849(3), c=12.820(5) Å, α= 90.54(3), β=93.31(3), γ=131.95(2)°, U=865.51 $Å^3$, z=2, Dc=1.33 g $cm.^{-3}$, F(000)=412, Space group $P\bar{1}$, Cu-k α radiation λ=1.54178 Å, μ (Cu-k_α)=36.05 $cm.^{-1}$.

Crystals of approximate dimensions 0.5 x 0.4 x 0.1 mm for (13) and 0.6 x 0.5 x 0.2 mm for (17) were mounted on an Enraf-Nonius CAD4 diffractometer and 25 reflections were used to determine accurate lattice parameters.

Intensity data were collected using an $\omega/2\theta$ scan for $1° < \theta < 76°$. Totals of 1759 (13) and 3614 (17) independant reflections were measured of which 1218 and 2248 respectively had $I > 3\sigma(I)$ and were considered observed and used in the subsequent refinement. Diffraction maxima for (17) were

broad and poorly defined as seen in the larger standard deviations of the unit cell dimensions and the large scan angle (2.2°) used in data collection. The crystal of (17) also deteriorated during data collection as shown by periodic measurement of a standard reflection, whose intensity declined by 25%, and all intensities were scaled to allow for this. The data were corrected for Lorentz and polarisation factors but no absorption corrections were made. Crystallographic calculations were performed using the CRYSTALS system of programs. The structures were solved by direct methods using the MULTAN program. Least squares refinement including anisotropic thermal parameters for non-hydrogen atoms and isotropic refinement of hydrogen atoms located in a difference Fourier synthesis terminated at R 0.0367 (R_w 0.0473) for (13). The poorer data for (17) did not allow refinement of the similarly located hydrogen atoms and terminated at R 0.0813 (R_w 0.1032). Final difference maps showed no features in excess of 0.2 $e\text{Å}^{-3}$ for (13), but two peaks of 1.2 $e\text{Å}^{-3}$ in the neighbourhood of the bromine atom and no other features in excess of 0.4 $e\text{Å}^{-3}$ for (17).

The refined fractional atomic coordinates are shown in Tables 1 and 2 respectively and the resulting molecular structures are illustrated in Figures 3 and 4. In (13) the cyclohexane ring adopts the expected chair conformation while the lactone ring is in the envelope conformation with the tetra-substituted carbon atom out of the plane containing the other four atoms. In (17) the cyclohexene ring is in the half-chair form. The geometric data for both structures are unexceptional. Observed and calculated structure factors, thermal parameters, bond lengths and bond angles are all listed in a Supplementary Publication. See Notice to Authors, Tetrahedron, 40(2), ii (1984).

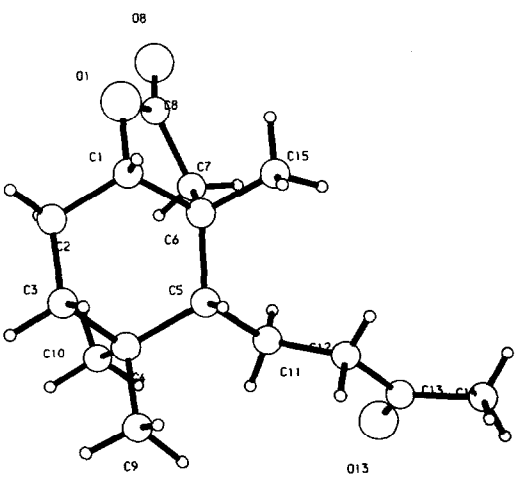


Figure 3

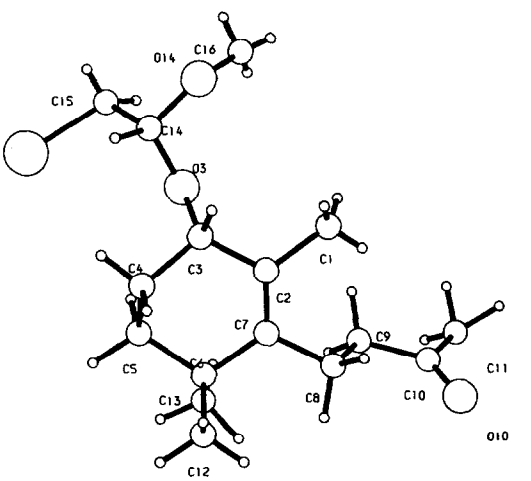


Figure 4

Table 1. Fractional Atomic Coordinates for (13)

Atom	x/a	y/b	z/c
C(1)	0.3696(4)	0.7679(3)	0.3140(2)
C(2)	0.2264(5)	0.8603(3)	0.3045(2)
C(3)	0.1027(5)	0.8406(3)	0.3683(2)
C(4)	0.0268(4)	0.7055(3)	0.3681(2)
C(5)	0.1685(3)	0.6045(2)	0.3760(1)
C(6)	0.3210(3)	0.6249(2)	0.3233(1)
C(7)	0.3081(4)	0.5845(3)	0.2386(2)
C(8)	0.4359(5)	0.6694(5)	0.2001(2)
C(9)	-0.0835(6)	0.6937(5)	0.4397(2)
C(10)	-0.0828(4)	0.6871(4)	0.2971(2)
C(11)	0.1035(4)	0.4641(3)	0.3723(2)
C(12)	0.1598(6)	0.3774(3)	0.4371(2)
C(13)	0.0868(4)	0.2440(3)	0.4354(2)
C(14)	0.1645(7)	0.1478(3)	0.4878(2)
C(15)	0.4705(4)	0.5544(3)	0.3583(2)
O(1)	0.4724(3)	0.7703(3)	0.2457(2)
O(8)	0.5013(4)	0.6535(4)	0.1388(2)
O(13)	-0.0281(4)	0.2168(2)	0.3943(1)

Table 2. Fractional Atomic Coordinates for (17)

Atom	x/a	y/b	z/c
Br(1)	0.4240(1)	0.7360(1)	0.42838(7)
C(1)	0.695(1)	0.5595(8)	0.8301(5)
C(2)	0.4976(8)	0.5327(6)	0.8018(4)
C(3)	0.5396(9)	0.6674(6)	0.7386(4)
C(4)	0.362(1)	0.6678(8)	0.7366(5)
C(5)	0.1463(9)	0.4919(8)	0.7122(4)
C(6)	0.1010(9)	0.3761(7)	0.7982(4)
C(7)	0.3028(8)	0.4053(6)	0.8305(4)
C(8)	0.2713(9)	0.2798(7)	0.9018(4)
C(9)	0.272(1)	0.1561(8)	0.8466(5)
C(10)	0.293(1)	0.0596(8)	0.9190(5)
C(11)	0.316(1)	-0.0526(9)	0.8704(6)
C(12)	0.029(1)	0.408(1)	0.8938(5)
C(13)	-0.081(1)	0.1961(9)	0.7518(5)
C(14)	0.7200(9)	0.7902(6)	0.5822(4)
C(15)	0.664(1)	0.7547(8)	0.4658(5)
C(16)	0.994(1)	0.7728(9)	0.5751(6)
O(3)	0.5725(6)	0.6434(4)	0.6330(3)
O(10)	0.289(1)	0.0689(9)	1.0128(4)
O(14)	0.9350(7)	0.8608(5)	0.6102(3)

3a,4α,5,6,7,7aβ-Hexahydro-4-(3-oxobut-1-yl)-3aβ,5,5,trimethyl-2(3H)-benzofuranone (14). - A range of complementary radical cyclisation methods were used to produce the required "trans"-stereochemistry at the ring juncture in the bicyclic ketone. Thus, (i) Using hexaphenylditin. - Hexaphenylditin (0.7 g, 1.0 equiv.) was added to a degassed (N_2) solution of the bromo-acetal (10) (361 mg; 1.0 equiv.) in dry benzene (50 ml) and the stirred suspension was then irradiated through pyrex with a 450W Hanovia lamp for 22h. The solvent was evaporated in vacuo, and the residue was then triturated with light petroleum (b.p. 40-60°C). The precipitated solid was removed by filtration and then washed thoroughly with light petroleum. The filtrates were evaporated in vacuo to leave the crude cyclic acetal as a pale-yellow oil. The cyclic acetal was dissolved in acetone (2 ml), and the cooled (water bath) solution was then titrated with Jones reagent to a permanent red end-point. The mixture was poured into brine (10 ml), and the aqueous solution was then extracted with ether (3 x 5 ml). The combined ethereal extracts were washed with saturated sodium bicarbonate solution (2 x 5 ml) and brine (1 x 5 ml), then dried and evaporated in vacuo to leave a pale yellow oil. Chromatography using light petroleum (b.p. 40°-60°C)-ether (4:1 then 1:2) as eluant gave the trans-bicyclic lactone (100 mg; 40%) as a colourless oil, ν_{max} (film) 1770, 1710 $cm.^{-1}$, δ_H 4.25 (dd, J 2.8 and 2.8Hz, -CH-O), 2.66 (ddd, J 16.5, 11.0 and 5.5Hz, CHCO), 2.52 (d, J 17Hz, $CHCO_2$), 2.48 (ddd, J 16.5, 11.0 and 5.5Hz, CHCO), 2.23 (d, J 17Hz , $CHCO_2$), 2.14 [$C(O)CH_3$], 2.05-1.40 (5H, m), 1.23 (1H, ddd, J 13.5, 3.5 and 3.5Hz), 1.16 (CH_3), 1.05 (1H, m), 0.92 (CH_3), 0.91 (CH_3), (Found; C, 71.1; H, 9.4; m/z 252.1722; $C_{15}H_{24}O_3$ requires: C, 71.4; H, 9.6%; M 252.1726).

(ii) Using Cobalt(I), generated Electrochemically. - Both compartments of a standard H-electrochemical cell were filled with 0.1M methanolic lithium perchlorate solution. A stirred mercury pool was used as the cathode, and a graphite rod was used for the anode; the reference electrode comprised a silver wire in 0.01M methanolic silver nitrate solution. The bromo-acetal (10) (216 mg; 1.0 equiv.) was added to the cathodic half-cell, and the solution was then degassed with nitrogen at -1.8V until the current had dropped to 0.5mA. Vitamin B_{12} (40 mg; 0.05 equiv.) was added to the cathodic section of the cell, and the reaction mixture was then stirred at -1.8V for 24 h. The mixture was poured into water (30 ml) and the aqueous solution was then extracted with a 1:1 mixture of light petroleum (b.p. 40-60°C) and ether (3 x 20 ml). The combined organic extracts were washed with brine (2 x 15 ml) then dried and the solvent was evaporated in vacuo to yield the crude diastereoisomeric mixture of the trans-fused bicyclic acetals (160 mg) as a colourless oil. The crude cyclisation product (160 mg) was dissolved in

acetone (6 ml) and titrated with Jones reagent at 10°C to a permanent red end-point. The acetone was evaporated in vacuo and the residue was then diluted with water (10 ml). The aqueous solution was extracted with ether (3 x 10 ml), and the combined ethereal extracts were then washed with water (2 x 10 ml), dried and evaporated in vacuo. Chromatography of the residue using light petroleum (b.p. 40-60°C)-ether(2:1) as eluant gave the trans-fused bicyclic lactone (117 mg; 75%) as a colourless oil, which contained less than 5% of the corresponding cis-fused isomer.

(iii) Using bis (trimethylstannyl)benzopinacolate. - Bis(trimethylstannyl) benzopinacolate (632 mg; 1:1 equiv.)[10] was added to a degassed (N_2) solution of the bromo acetal (23) (300 mg; 1.0 equiv.) in dry benzene (42 ml), and the mixture was then heated under reflux for 2 h. A further 262 mg (0.4 equiv.) of bis(trimethylstannyl)benzopinacolate was added, and the mixture was heated under reflux for a further 0.5 h. The mixture was allowed to cool to room temperature, and the solvent was then removed in vacuo. The residue was purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (6:1) as eluant to give a mixture of diastereoisomers of the cyclic acetal (200 mg; 85%) as a colourless oil. A solution of the cyclic acetal (200 mg) in acetone (5 ml) was cooled to 10°C and titrated with Jones reagent to a permanent red end-point. The mixture was poured onto water (20 ml) and the aqueous solution was then extracted with ether (3 x 10 ml). The combined ether extracts were washed with saturated sodium bicarbonate solution (2 x 10 ml) and brine (1 x 10 ml), then dried ($MgSO_4$). Evaporation of the solvent in vacuo left an oily residue which was purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (1:2) as eluant to give the trans-bicyclic lactone (114 mg; 64%) which showed spectroscopic data identical to those described above.

Radical Cyclisation of the Crystalline (β-Methoxy, α-oxy) Acetal (17) using tri-n-Butyltin Hydride. - Tri-n-butyltin hydride (79 µl; 2.0 equiv.) was added to a degased (N_2) solution of the crystalline methyl bromo-acetal diastereoisomer (17) (51 mg; 1.0 equiv.) and AIBN (5 mg; 0.2 equiv.) in dry benzene (7.5 ml) and the solution was then heated under reflux for 2 h. The mixture was allowed to cool to room temperature, and the solvent was then removed in vacuo. The residue was purified by chromatography using light petroleum (b.p. 40-60°C)-ether (6:1) as eluant to give a 1:1 mixture of (11) and (12) (38 mg., 98%) as a colourless oil. Treatment of the mixture of isomers with Jones reagent gave a 1:1 mixture of the corresponding cis- and trans-lactones, (13) and (14) respectively, which showed identical spectroscopic data to those described earlier.

Radical Cyclisation of the Liquid (α-Methoxy, α-oxy) Acetal (20) using tri-n-Butyltin Hydride. - Treatment of the liquid methyl bromo-acetal diastereoisomer (29) (85.5 mg; 1.0 equiv.) with tri-n-butyltin hydride under identical conditions to those described previously, followed by work-up gave a single diastereoisomer of the cis-fused cyclic acetal (11) (57 mg; 86%) as a colourless oil, ν_{max} (film) 2950, 1720, 1030 $cm.^{-1}$, δ_H 5.04 (dd, J 5 and 5 Hz, OCHO), 3.52 (dd, J 10, 7 Hz, CH-O), 3.37 (OCH_3), 2.55 (m, $COCH_2$), 2.15 (CH_3CO), 2.05 (1H, dd, J 9, 4.5 Hz), 1.9-1.1 (8H, m, methylene envelope), 1.08 (CH_3), 0.98 (CH_3), 0.87 (CH_3), (Found: m/z 236.1779. $C_{15}H_{24}O_2$ (M-MeOH) requires: 236.1776).
Treatment of the acetal with Jones reagent gave the cis-lactone (13), m.p. 80-81°C, which showed identical spectroscopic data to those described earlier

Electrochemical Cyclisation of 4-[3-(1-Ethoxy-2-bromoethoxy)-2,6,6-trimethylcyclohexen-1-yl]-2-butanone (23). - The bromoacetal (130 mg) was electrolysed in the presence of Vitamin B_{12} at -1.8V, under identical conditions to those described earlier. The mixture was poured into water (30 ml) and the aqueous solution was then extracted with a 1:1 mixture of light petroleum (b.p. 40-60°c) and ether (3 x 20 ml). The combined organic extracts were washed with brine (2 x 15 ml) then dried ($MgSO_4$) and evaporated in vacuo. Chromatography of the residue using light petroleum (b.p. 40-60°C)-ether (6:1) as eluant gave:
(i) the ethenyl acetal (28) (23 mg; 23%) as a colourless oil, δ_H 6.39 (dd, J 14 and 6 Hz, $CH:CH_2$), 5.32 (br. d, J 6 Hz, OCHO), 4.4 (dd, J 14 and 1.5 Hz, :CHH), 4.1 (dd, J 6 and 1.5 Hz, :CHH), 3.7 (dd, J 3 and 3 Hz, CH-O), 2.6 (m, CH_2CO), 2.15 (CH_3CO), 2.1-1.1 (9H, m, methylene envelope), 1.01 (CH_3), 0.9 (CH_3), 0.88 (CH_3), (ii) the corresponding ethyl acetal (25) (20 mg; 20%) as a colourless oil. A solution of the cyclic acetals (25) and (28) (43 mg) in acetone (2 ml) was cooled to 10°C and titrated with Jones reagent to a permanent red end point. The mixture was poured into water (10 ml) and the aqueous solution was then extracted with ether (3 x 5 ml). The combined ether extracts were washed with water (2 x 5 ml), dried ($MgSO_4$) and the solvent was then evaporated in vacuo. Chromatography of the residue using light petroleum (b.p. 40-60°C) -ether (1:1) as eluant gave the trans-lactone (14) (34 mg; 90%) as a colourless oil, which displayed identical spectral data to those described earlier.

4-[3-(1-Ethoxy)-2-bromoethoxy)-2,6,6-trimethylcyclohexen-1-yl]-but-3-en-2-one (29). - Hydroxy-β-ionone (7) (2.5g) was converted into the corresponding bromo-acetal using the procedure described for the preparation of (23).

Work-up, followed by chromatography using light petroleum (b.p. 40°-60°C)-ether (5:1) as eluant gave the bromo-acetal (3.0g; 70%) as a pale-yellow oil, ν_{max} (film) 2930, 1665, 1605, 1025 cm.$^{-1}$, δ_H 7.12 (br. d, J 16 Hz; CH:CHCO), 6.07 (br. d, J 16 Hz, CHCO), 4.70 (dd, J 5 and 5 Hz, OCHO), 4.0-3.3 (m, CH_2 Br, OCH_2CH_3 and CH-O), 2.26 (CH_3CO), 1.81 (CH_3C:), 2.0-1.2 (4H, m, methylene envelope), 1.22 (t, J 7 Hz, CH_3CH_2O), 1.06 (CH_3), 1.02 (CH_3), (Found: m/z 359.1000; $C_{17}H_{27}BrO_3$ requires M, 359.1002).

Radical Cyclisation of the Dienone Acetal (29). - Treatment of the bromo-acetal (29) (3.0g; 1.0 equiv.) with tri-n-butyl tin hydride (2.0 equiv.) and AIBN (0.6 equiv.) in refluxing dry benzene (400 ml) for 3.5h, followed by work-up and chromatography using light petroleum (b.p. 40°-60°C)-ether (4:1) as eluant, gave the corresponding acetal (30) (2.05g; 88%) as a mixture of acetal epimers (and double bond isomers) showing, ν_{max} (film) 2930, 1710 cm.$^{-1}$, δ_H 5.6 (dd, J 8 and 8Hz, :CH), 5.1 (m, OCHO), 4.0-3.2 (m, :CH_2CO, OCH_2CH_3, and CH-O), 2.18 (CH_3CO). (Found: m/z 280.2038. $C_{17}H_{28}O_3$ requires M, 280.2039). A solution of the mixture of cyclic acetals (2.0g; 1.0 equiv.) in acetone (60 ml) was cooled to 10°C and titrated with Jones reagent to a permanent red end-point. The mixture was diluted with water (300 ml), and the aqueous solution was then extracted with ether (3 x 100 ml). The combined ethereal extracts were washed with water (2 x 50 ml), then dried ($MgSO_4$) and the solvent was evaporated in vacuo. Chromatography of the residue using light petroleum (b.p. 40-60°C)-ether (2:3) as eluant gave:- (i) the (E)-isomer of the bicyclic lactone [259 mg; 12% from (29)] as a crystalline, white solid, m.p. 116-117.5°C, (ether), ν_{max} ($CHCl_3$) 1760, 1715 cm.$^{-1}$, δ_H 5.74 (dd, J 7 and 7 Hz, CH:), 4.29 (dd, J 5 and 5 Hz, CH-O), 3.41 (m, :$CHCH_2CO$), 2.86 (d, J 18 Hz, $CHCO_2$), 2.42 (d, J 18 Hz, $CHCO_2$), 2.19 (CH_3CO), 1.90 (1H, m), 1.79 (1H, m), 1.65 (1H, ddd, J 13.5, 10.5 and 3 Hz), 1.40 (CH_3), 1.33 (1H, ddd, J 14, 8 and 3 Hz), 1.26 (CH_3), 1.23 (CH_3). Irradiation at δ1.4 (bridgehead methyl) gave a positive n.O.e. enhancement at δ 2.42, 4.29 and 5.74. (Found: C, 71.7; H, 9.2%; m/z 250.1567. $C_{15}H_{22}O_3$ requires C, 72.0; H, 8.9%; M, 250.1569), and (ii) the (Z)-isomer (31) of the bicyclic lactone (783 mg; 37% from (29)] as a crystalline, white solid, m.p. 70.5-71.5°C [light petroleum (b.p. 40°-60°C)- ether] ν_{max} ($CHCl_3$) 2940, 1770, 1710, 1660 cm.$^{-1}$, δ_H 5.73 (dd, J 7 and 7 Hz, CH:), 4.37 (dd, J 8 and 3.5 Hz, CH-O), 3.2 (m, :$CHCH_2CO$), 2.74 (d, J 17 Hz, $CHCO_2$), 2.63 (d, J 17 Hz, $CHCO_2$), 2.17 (CH_3CO), 1.95 (1H, m), 1.60 (2H, m), 1.38 (1H, m)., 1.37 (CH_3), 1.16 (CH_3) 1.12 (CH_3). Irradiation at δ3.20 gave a positive n.O.e. enhancement at δ2.63 and δ2.74. (Found: C, 72.1; H, 9.2; m/z 250.1555; $C_{15}H_{22}O_3$ requires C, 72.90; H, 8.9%; M, 250.1569).

3a,4a,5,6,7,7aβ-Hexahydro-4-(3-oxobut-1-yl)-3aβ,5,5-trimethyl-2(3H)-benzofuranone, ethylene acetal (33). A solution of the keto-lactone (14) (270 mg; 1.0 equiv.), ethylene glycol (0.3 ml; 5.0 equiv.) and p-toluenesulphonic acid (1 crystal) in dry benzene (20 ml) was heated under reflux using a Dean and Stark water separator for 2h. The mixture was cooled to room temperature and then poured into saturated sodium bicarbonate solution (20 ml). The two phases were separated and the aqueous phase was then extracted with ether (3 x 10 ml). The combined organic phases were washed with water (2 x 20 ml), then dried and evaporated in vacuo to leave a yellow oil. Chromatography using light petroleum (b.p. 40°-60°C)-ether (3:2) as eluant gave the ketal (294 mg; 93%) as a white crystalline solid, m.p. 75°-76°C, ν_{max} ($CHCl_3$) 1760 $cm.^{-1}$, δ_H 4.23 (dd, J 3.0 and 3.0 Hz, -CH-O), 3.94 (OCH_2CH_2O), 2.57 (d, J 17 Hz, $CHCO_2$), 2.19 (d, J 17 Hz, $CHCO_2$), 2.1-1.0 (9H,m), 1.31 (CH_3), 1.14 (CH_3), 0.92 (2 x CH_3), (Found: C; 68.7, H; 9.7; m/z 281.1763. $C_{17}H_{28}O_4$ requires: C; 68.9; H; 9.5%; ($M-CH_3$) 281.1753).

2aβ,3,4,5,5aα,6,7,8,8aβ,8b-Decahydro-3β-(2-hydroxyethoxy)-3a,6,6,8bβ-tetramethyl-2H-naphtho[1,8-bc]furan-2-one (36), and 2aβ,3,4,5,5aα,6,7,8,8aβ,8b-decahydro-3α-(2-hydroxyethoxy)-3β,6,6,8bβ-tetramethyl-2H-naphtho[1,8-bc]furan-2-one (35). - Lithium hexamethyldisilazide (1M solution in hexane; 6.0 ml; 2.0 equiv.) was added to a stirred solution of the ketal (33) (886 mg; 1.0 equiv.) in dry tetrahydrofuran (15 ml) maintained at -78°C under nitrogen, and the mixture was then stirred at - 78°C for 0.75h. The mixture was allowed to warm to 0°C where it was stirred for a further 2h., after which time it was re-cooled to -78°C. Freshly sublimed tert-butyldimethylsilyl chloride (900 mg; 2.0 equiv.) was added in one portion and the mixture was stirred at -78°C for 30 min., then at 0°C for 1h. The mixture was evaporated to dryness in vacuo, and the residue was then triturated with light petroleum (b.p. 40°-60°C) and filtered through a pad of celite. The filtrate was evaporated in vacuo to leave the silyl enol ether (34) (1.42 g) as a pale yellow oil, ν_{max} (film) 1660, 1260, 850 $cm.^{-1}$, δ_H 4.0 (dd, J 3.0 and 3.0 Hz, -CH-O), 3.88 (OCH_2CH_2O and C:CH), 1.25 (CH_3), 1.00 (CH_3). 0.89 ($CH_3)_3C$-), 0.85 (CH_3), 0.80 (CH_3) 0.15 (2 x $SiCH_3$) which was used without further purification.

A solution of the crude silyl enol ether (1.24 g; 1.0 equiv.) in dry methylene chloride (10 ml) was added dropwise during 5 min. to a stirred solution of titanium tetrachloride (360 µl; 1.1 equiv.) in dry methylene chloride (10 ml) maintained at -78°C under nitrogen. The resulting brown suspension was stirred at -78°C for a further 10 min. and then poured into water (25 ml). The two phases were separated, and the aqueous layer was then

extracted with ether (3 x 20 ml). The combined organic extracts were washed with water (2 x 20 ml), then dried and evaporated in vacuo to leave a brown oil. Chromatography using light petroleum (b.p. 40°-60°C)-ethyl acetate (1:1) as eluant gave: (i) the minor (α-methyl) isomer of the hydroxy ether (36) (151 mg; 17%), ν_{max} (film) 3480 (br), 1765 cm.$^{-1}$, δ_H 4.00 (dd, J 4.0 and 4.0 Hz, -CH-O), 3.71 (br, CH_2OH), 3.43 (m, OCH_2), 2.40 (d, J 1.8 Hz, $CHCO_2$), 2.1-1.2 (10H, m, methylene envelope and -OH), 1.49 (CH_3), 1.31 (CH_3), 0.90 (CH_3), 0.87 (CH_3), and (ii) the major (β-methyl) isomer of the hydroxy ether (35) (328 mg; 37%), ν_{max} (film) 3480 (br), 1765 cm.$^{-1}$, δ_H 4.03 (dd, J 3.5 and 3.5 Hz, -CH-O), 3.7-3.4 (m, OCH_2CH_2OH), 2.41 ($CHCO_2$) 2.0-1.2 (9H, m, methylene envelope), 1.40 (CH_3), 1.20 (CH_3), 0.89 (CH_3), 0.86 (CH_3); irradiation at δ2.41 gave an n.O.e. enhancement at δ1.20, δ1.40 and δ4.03 of 5.1%, 3.2% and 3.9% respectively. (Found: m/z 296.1991. $C_{17}H_{28}O_4$ requires M 296.1988).

2aβ,5,5aα,6,7,8aβ,8b-Octahydro-3,6,6,8bβ-tetramethyl-2H-naptho[1,8-bc]furan-2-one (37). - A stirred mixture of the hydroxy-ethers (32) and (33) (479 mg; 1.0 equiv.) in methanol (10 ml) containing solid potassium hydroxide (484 mg; 5.0 equiv.) was heated under reflux for 2.5h. The mixture was cooled to 0°C and then acidified by the addition of 2M hydrochloric acid. The aqueous solution was extracted with ether (2 x 10 ml), and the combined ether extracts were washed with water (2 x 10 ml) and brine (1 x 10 ml), and then dried. The solvent was removed in vacuo to leave a brown oil which was purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (9:1, then 1:1) as eluant to give the enone (310 mg; 82%) as colourless needles, m.p. 63°-66°C (petroleum ether [b.p. 40°-60°C]-ether), ν_{max} (film) 1765 cm.$^{-1}$, δ_H 5.61 (m, :CH), 4.20 (dd, J 3Hz and 3Hz, -CH-O), 2.49 (br, $CHCO_2$), 1.91 (br, $:CCH_3$), 2.13-1.75 (3H, m), 1.54 (1H, ddd, J 13, 13 and 5 Hz), 1.40-1.25 (3H, m), 1.10 (CH_3), 0.9 (CH_3), 0.89 (CH_3). δ_C 176.4, 127.4, 124.5 (d), 82.5 (d), 58.4 (d), 42.5 (d), 40.4, 35.0 (t), 31.4 (q), 29.5, 22.3 (q), 31.7 (t), 21.3 (t), 20.1 (q); 16.6 (q), (Found: C, 76.6; H, 9.7; m/z 234.1612. $C_{15}H_{22}O_2$ requires: C, 76.9; H, 9.4%; M, 234.1602).

4-Oxo-4,5,5aα,6,7,8,8aβ,8b-octahydro-3,6,8bβ-tetramethyl-2H-naphtho[1,8-bc]furan- 2-one (35), and 5-oxo-2aβ,5,5aα,6,7,8,8aβ,9b-octahydro-3,6,6,8bβ-tetramethyl-2H- naphtho[1.8-bc]furan-2-one (40). - A mixture of the enone (37) [30 mg; 1.0 (equiv.)], t-butylhydroperoxide (80% solution in di-t-butylperoxide, 70 µl; 4.3 equiv.), pyridinium dichromate (190 mg) and celite (160 mg) in benzene (3 ml) was stirred at room temperature for 24

h. A further 50 µl (3.1 equiv.) of t-butyl hydroperoxide was added, and stirring was then continued at room temperature for a further 24 h. The mixture was diluted with ether (20ml), then celite (0.5 g) was added and the mixture was filtered through a pad of celite. The celite was washed with ether (3 x 10 ml), and the combined ether solutions were then evaporated in vacuo to leave an oil. Chromatography using light petroleum (b.p. 40-60°C)-ether (4:1) as eluant gave: (i) recovered starting material (28) (eluted first) (5.7 mg; 19%); (ii) the enone (35) (eluted second) (8.7 mg: 34%) as a colourless oil, ν_{max} ($CHCl_3$) 2970, 1760, 1685, 1475, 1190, 1040 cm.$^{-1}$, δ_H 4.28 (dd, J 11.2 and 6.2 Hz, CH-O), 2.64-2.43 (2H, m, AB of ABX, J_{AB} 13.3, J_{BX} 4.9 Hz), 2.14 (CH_3C:), 2.05 (2H, m), 1.65 (2H, m), 1.29 (CH_3), 1.27 (1H, m), 1.00 (CH_3), 0.96 (CH_3), δ_C 200.6, 168.6, 147.6, 139.4, 85.4 (d), 41.1, 34.8 (t), 34.3 (t), 31.0, 30.0 (q), 25.7 (q), 24.5 (t), 23.6 (q), 10.5 (q); (Found: m/z 248.1421; $C_{15}H_{20}O_3$ requires: M 248.1431); (iii) the enone (12) (eluted third) (9.3 mg; 37%) as colourless crystals, m.p. 111-116°C (petroleum ether[b.p. 80°-100°C]-ether, lit[19] m.p. 109-110°C), ν_{max} (KBr disc) 2920, 1765, 1375, 1305, 1175, 975 cm.$^{-1}$, δ_H5.83 (CH:), 4.29 (dd, J 2.8 and 2.8 Hz, CH-O), 2.89 (COCHC:), 2.44 (COCH), 2.17 (CH_3C:), 2.1-1.8 (2H,m), 1.49-1.2 (2H,m), 1.24 (CH_3), 1.16 (CH_3), 1.10 (CH_3), δ_C 197.9, 173.0, 148.2, 128.8 (d), 82.4 (d), 59.6 (d), 54.3 (d), 47.90, 35.5 (t), 31.4 (q), 30.9 (q), 22.7 (q), 20.(t), 20.3 (q), 18.1 (q); (Found; m/z 248.1418; $C_{15}H_{20}O_3$ requires: M 248.1426).

2aβ,3,4,5aα,6,7,8,8aβ,8b-Decahydro-3,4-epoxy-3,6,6,8bβ-tetramethyl-2H-naphtho [1.8-bc]furan-2-one (41). - m-Chloroperbenzoic acid (85%, remainder m-chlorobenzoic acid; 428 mg; 1.1 equiv.) was added to a solution of the enone (34) (450 mg; 1.1 equiv.) in dry methylene chloride (15 ml), and the colourless solution was then stirred at room temperature for 4 h. during which time a white precipitate formed. The mixture was diluted with ether (20 ml) and the ether solution was then washed successively with saturated sodium bicarbonate solution (2 x 10 ml) and brine (1 x 10 ml), and dried. The solvent was evaporated in vacuo to leave a waxy solid residue. Chromatography using light petroleum (b.p. 40°-60°C)-ether (2:1 then pure ether) as eluant gave: (i) the β-epoxide (190 mg; 40%) as a crystalline white solid, m.p. 120-122°C [petroleum ether (b.p. 80-100°C)-ether], ν_{max} ($CHCl_3$) 1755, 990, 980 cm.$^{-1}$, δ_H 4.05 (dd, J 2.8 and 2.8 Hz, CHOC(O)-), 3.20 (d, J 5.7 Hz, CHOC), 2.62 ($CHCO_2$), 2.1-1.1 (7H, m, methylene envelope), 1.61 (CH_3), 1.17 (CH_3), 0.90 (CH_3), 0.88 (CH_3); (Found: m/z 250.1583. $C_{15}H_{22}O_3$ requires: M 250.1563);

(ii) the α-epoxide (160 mg; 33%) as a crystalline white solid, m.p. 150°-151°C [petroleum ether (b.p.80-100°C)-ether], ν_{max} ($CHCl_3$) 1655, 995, 970 $cm.^{-1}$, δ_H 4.10 (dd, J 3.0 and 3.0 Hz, CHOC(O)-), 3.10 (br.m), CHOC), 2.51 ($CHCO_2$), 2.0-1.2 (7H, m, methylene envelope), 1.50 (CH_3), 1.15 (CH_3), 0.88 (2 x CH_3); (Found: m/z 250.1543. $C_{15}H_{22}O_3$ requires: M 250.1563).

4α,5,5aα,6,7,8,8aβ,8b-Octahydro-4-hydroxy-3,6,6,8b-tetramethyl-2H-naphtho[1,8,bc]furan-2-one (42). - A solution of the β-epoxide (41b) (190 mg; 1.0 equiv.) in dry tetrahydrofuran (5 ml) was cooled to -78°C under nitrogen, and then treated with lithium hexamethyldisilazide (1.0M solution in hexanes; 840 µl; 1.1 equiv.). The solution was allowed to warm to 0°C, and stirring was continued at this temperature for 14 h. The mixture was acidified with 2M hydrochloric acid, and the aqueous solution was then extracted with ether (3 x 10 ml). The combined ethereal extracts were washed with water (1 x 10 ml) and brine (1 x 10 ml), and then dried. The solvent was evaporated in vacuo to leave a residue which was purified by chromatography using light petroleum (b.p. 40-60°C)-ether (1:2) as eluant to give the allylic alcohol (120 mg; 63%) as a colourless oil, ν_{max} ($CHCl_3$) 3410 (br.), 1730, 1660, 910 $cm.^{-1}$, δ_H 4.24 (dd, J 7.6 and 7.6 Hz, CHOH), 4.10 (dd, J 11.4 and 6.0 Hz, CHOC(O)-), 2.13 (CH_3C:C), 2.1-1.2 (8H, m, methylene envelope and -OH), 1.19 (CH_3), 0.88 (CH_3), 0.85 (CH_3); (Found: m/z 250.1577. $C_{15}H_{22}O_3$ requires M 250.1563).

[Under identical reaction conditions to those described above, the α-epoxide (41a) (190 mg; 1.0 equiv.) gave the corresponding α-allylic alcohol (124 mg; 65%) as a colourless oil, ν_{max} ($CHCl_3$) 3410 (br.), 1730, 1660, 910 $cm.^{-1}$, δ_H 4.40 (d, J 8.5 Hz, CHOH), 4.10 (dd, J 11.0 and 6.1 Hz, CHOC(O)-), 2.17 (d, 1.2 Hz CH_3C:C), 1.9-1.4 (8H, m, methylene envelope and -OH), 1.03 (CH_3), 0.89 (CH_3), 0.87 (CH_3); (Found: m/z 250.1573. $C_{15}H_{22}O_3$ requires M 250.1569).]

5aα,6,7,8,8aβ-Hexahydro-3,6,6,8bβ-tetrahydro-2H-naphtho[1.8-bc]furan-2-one (43).- A solution of the allylic alcohol (42) (81 mg; 1.0 equiv.), methanesulphonic anhydride (169 mg; 3.0 equiv.) and dry triethylamine (226 µl; 5.0 equiv.) in dry benzene (5 ml) containing catalytic dimethylaminopyridine was heated under reflux in a nitrogen atmosphere for 16 h. The solution was cooled to room temperature and then poured into water (5 ml). The organic layer was separated, and the aqueous phase was then extracted with ether (3 x 5 ml). The combined organic extracts were washed successively with 2M hydrochloric acid solution (5 ml), saturated sodium bicarbonate solution (5 ml), and brine (5 ml), then dried and the

solvent was removed in vacuo. The residue was purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (2:1) as eluant to give the diene (62 mg; 84%) as a colourless oil, ν_{max} ($CHCl_3$), 1720, 1645, 905 $cm.^{-1}$, λ_{max} 304.8 nm, δ_H 6.1 (2H, olefinic), 4.3-4.1 (dd, J 10.4 and 6.7 Hz, CH-O), 3.44 (CHC:C), 2.17 (CH_3C:C), 1.7-1.2 (4H, m, -CH_2CH_2-), 1.17 (CH_3CC:C), 1.08 (CH_3), 0.98 (CH_3); (Found: m/z 232.1439. $C_{15}H_{20}O_2$ requires: M 232.1415).

3a,4β,5,6,7,7aβ-Hexahydro-4-(3-oxobut-1-yl)-3aβ,5,5-trimethyl-2(3H)-benzofuranone, ethylene acetal (46). - A solution of the ketone (13) (8.1g; 1.0 equiv.), ethylene glycol (9 ml; 5.0 equiv.) and p-toluene-sulphonic acid (cat.) in dry benzene (300 ml) was heated under reflux using a Dean and Stark water separator for 2h. The mixture was allowed to cool to room temperature and then poured into saturated sodium bicarbonate solution (600 ml). The phases were separated, and the aqueous phase was extracted with ether (3 x 200 ml). The combined organic phases were washed with water (2 x 200 ml) then dried and evaporated in vacuo. The residue was purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (3:2) as eluant to give the ketal (8.7 g; 93%) as a crystalline white solid, m.p. 88.5-89.5°C [light petroleum (b.p. 40°-60°C)-ether 1:1, -78°C]. ν_{max} (film) 2950, 1770, 1060 $cm.^{-1}$, δ_H 4.05 (m, CH-O), 3.94 (OCH_2CH_2O), 2.76 (br. d, J 17 Hz, $CHCO_2$), 2.08 (d, J 17 Hz, $CHCO_2$), 2.1-1.2 (9H, m, methylene envelope), 1.31 (CH_3). 1.20 (CH_3), 0.96 (2 x CH_3); (Found: C, 68.8; H, 9.8; m/z 281.1770. $C_{17}H_{28}O_4$ requires: C, 68.9; H, 9.5%; ($M-CH_3$) 281.1753).

2aβ,3,5,5,5aβ,6,7,8,8aβ,8b-Decahydro-3α-(2-hydroxyethoxy)-3α,6,6,8bβ-tetramethyl- 2H-naphtho [1,8-bc]furan-2-one, and 2aβ,3,4,5,5aβ,6,7,8,8aβ,8b-decahydro-3β-(2- hydroxyethoxy)-3β,6,6,8bβ-tetramethyl-2H-naphtho[1,8-bc]furan-2-one (48). - n-Butyl lithium (1.6M solution in hexane; 21.2 ml; 1.5 equiv.) was added dropwise to a cooled solution of diisopropylamine (4.75 ml; 1.5 equiv.) and 1,10 phenanthroline (1 crystal) in dry tetrahydrofuran (75 ml) and the deep red solution was then stirred at -78°C for 40 min. A solution of the lactone (46) (6.7g; 1.0 equiv.) in dry tetrahydrofuran (75 ml) was added via a cannular needle, and the mixture was then stirred at -78°C for 30 min. and finally at 0°C for 1h. The mixture was recooled to -78°C, and freshly sublimed t-butyldimethylsilyl chloride (5.13 g; 1.5 equiv.) was added in one portion. The solution was allowed to warm to 0°C, where it was stirred for a further 45 min., before the solvent was removed in vacuo. Light

petroleum (b.p. 40°-60°C, 100 ml) was added to the residue, and the resulting suspension was filtered through a pad of celite and washed with light petroleum (2 x 50 ml). The filtrate was evaporated in vacuo to leave the silyl ketene acetal (47) (9.0 g; 97%) as a viscous oil which was used without further purification, ν_{max} (film) 2960, 2870, 1670, 845 cm.$^{-1}$, δ_H 3.90 (m, -CHO), 3.90 (OCH_2CH_2O), 3.70 (:CH), 1.9-1.0 (9H, m, methylene envelope), 1.28 (CH_3), 1.06 (CH_3), 0.89 (CH_3), 0.82 (CH_3), 0.15 (2x$SiCH_3$). Using the procedure already described for the synthesis of the corresponding trans-decalin (35), treatment of the silyl ketene acetal with titanium tetrachloride followed by work-up and chromagraphy using light petroleum (b.p. 40°-60°C)-ether (2:3 as eluant) gave, in order of elution:- (i) a mixture of deketalised starting material (28%) and the β-epimer of the hydroxy ether (14%), and (ii) the α-epimer of the hydroxy ether (23%) as a colourless oil, ν_{max} (film) 3440 (br), 2940, 1755 cm.$^{-1}$, δ_H 4.29 (dd, J 8.4 and 5 Hz, CH-O), 3.8-3.6 (m, CH_2O), 3.52-3.38 (m, CH_2O), 3.0 (br, -OH), 2.33 ($CHCO_2$), 2.2-1.2 (9H, m, methylene envelope), 1.45 (CH_3), 1.36 (CH_3), 1.11 (CH_3), 0.97 (CH_3). Irradiation at δ1.36 (bridgehead methyl) gave a positive n.O.e. enhancement at δ2.33 and δ4.29, while irradiation at δ2.33 gave a positive n.O.e. enhancement at δ1.36, 1.45 and 4.29 respectively; δ_C 177.5, 83.5 (d), 73.5, 62.5 (t), 62 (t), 59.5 (d), 47.5 (d), 40.5, 33.5 (q), 33.4 (t), 33.2 (q), 33, 32 (q), 30 (t), 26 (q), 23 (t), 22.5 (t); (Found: m/z 296.20915. $C_{17}H_{28}O_4$ requires M, 296.1988).

4,5,5aβ,6,7,8,8aβ,8b-Octahydro-3,6,6,8bβ-tetramethyl-2H-naptho[1,8-bc]furan-2-one (49). - 1M Aqueous potassium hydroxide solution (100 ml) was added to a solution of the crude Mukaiyama product (48) (8.3 g) in methanol (130 ml), and the mixture was heated at 90°C for 35 min. The mixture was allowed to cool to room temperature, then poured onto a mixture of ice and 1M hydrochloric acid solution (130 ml). The aqueous solution was extracted with ether (4 x 100 ml), and the combined ethereal extracts were washed with brine (2 x 50 ml) and then dried. Evaporation of the solvent in vacuo left a residue which was purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (6:1) as eluant to give the enone (4.05 g; 76%) as a crystalline white solid, m.p. 82-83°C (light petroleum, [b.p.40°-60°C]), ν_{max} ($CHCl_3$) 2930, 1730, 1680, 1150, 980 cm.$^{-1}$, δ_H 4.15 (dd, J 10.5 and 6 Hz, CH-O), 2.20 (m, CH_2C:), 2.09 (CH_3:), 2.0-1.20 (6H, m, methylene envelope), 1.46 (dd, J 7 and 2 Hz, $CHC(CH_3)_2$), 1.18 (CH_3), 0.95 (CH_3), 0.78 (CH_3), δ_C 170.0, 149.4, 125.1, 84.3 (d), 45.7 (d), 40.6, 36.9 (t) 33.3, 32.0 (q), 31.2 (t), 30.3 (q), 27.1 (t), 21.7 (q), 18.6 (t),

18.1 (q), (Found: C,77.0; H, 9.5; m/z 234.1627; $C_{15}H_{22}O_2$ requires: C, 77.2; H, 9.6%; M 234.1620).

4-Bromo-4,5,5aβ,6,7,8,8aβ,8b-octahydro-3,6,6,8bβ-tetramethyl-2H-naphtho[1,8-bc]furan-2-one (50). - A mixture of the lactone (49) (4.0 g; 1.0 equiv.), N-bromosuccinimide (3.35 g; 1:1 equiv.) and AIBN (50 mg; 0.02 equiv.) in carbon tetrachloride (200ml) was heated under reflux for 15 min. while being irradiated with a 300W sun-lamp. The mixture was cooled to room temperature, then filtered through a pad of celite and the filtrate was then evaporated in vacuo to leave the bromide (5.3 g; 99%) as a crystalline white solid, m.p. 148-158°C (light petroleum [b.p. 40-60°C]-ether), ν_{max} ($CHCl_3$) 2860, 1735, 1670, 1145 $cm.^{-1}$, δ_H 4.75 (dd, J 9.5 and 9.5 Hz, CHBr), 4.2 (m, CH-O), 2.78-2.54 (2H, m), 2.28 (CH_3C:), 2.05 (1H, m), 1.64 (1H, m), 1.32 (CH_3), 2.45-1.15 (3H, m), 0.99 (CH_3), 0.80 (CH_3); (Found: m/z 314.0682; $C_{15}H_{21}BrO_2$ requires M 314.0705).

5aβ,6,7,8,8aβ,8b-Hexahydro-3,6,6,8bβ-tetramethyl-2H-naphtho[1,8-bc]furan-2-one (44) and 4,5,5aβ,6,7,8.8aβ,8b-Octahydro-4-oxo-3,6,6,8bβ-tetramethyl-2H-naphtho[1,8-bc]furan-2-one (51). - A solution of the bromide (47) (60 mg; 1.0 equiv.) and 1,8-diazabicycloundecene (100 µl; 3.5 equiv.) in dry toluene (4 ml) was heated under reflux for 16 h. The mixture was cooled to room temperature, and then poured onto 1M hydrochloric acid solution (4 ml). The phases were separated, and the aqueous phase was extracted with ether (3 x 4 ml). The combined organic phases were washed with water (2 x 5ml) and then dried. The solvent was evaporated in vacuo to leave an oil which was purified by chromatography using light petroleum (b.p.40-60°C)-ether (5:1) as eluant to give: (i) the diene (44) (26 mg; 58%) as a crystalline white solid, m.p. 128.5-130°C [light petroleum (b.p. 40°C-60°C)], ν_{max} ($CHCl_3$) 1725, 1670 $cm.^{-1}$, δ_H 6.09 (d, J 9.5Hz, CH:), 6.0 (dd, J 9.5 and 6Hz, CH:), 4.22 (dd, J 10 and 7Hz, CHO), 2.22 (CH_3C:), 2.08 (d, J 6Hz, :C-CH), 2.04 (1H, m), 1.46-1.20 (3H, m), 1.12 (CH_3), 0.98 (CH_3), 0.74 (CH_3). Irradiation at δ1.12 (bridgehead methyl group) gave a positive n.O.e. enhancement at δ2.08 and δ4.22. (Found: C, 77.7; H, 8.9; m/z 232.1461. $C_{15}H_{20}O_2$ requires C, 77.6; H, 8.7%; M 232.1463), and (ii) the keto-lactone (51) (6.5 mg; 14%), ν_{max} ($CHCl_3$) 1750, 1670 $cm.^{-1}$, δ_H 4.25 (m, CH-O), 2.80 (dd, J 18 and 6Hz, CHCO), 2.68 (dd, J 18 and 2Hz, CHCO), 2.16 (1H, m), 2.15 (CH_3C:), 1.96 (1H, dd, J 6.5 and 2Hz), 1.44 (CH_3), 1.5-1.2 (3H, m, methylene envelope), 0.97 (CH_3), 0.72 (CH_3). (Found: m/z 248.1421. $C_{15}H_{20}O_3$ requires M 248.1413).

4,5,5aβ,6,7,8,8aβ,8b-Octahydro-4β,5β-dihydroxy-3,6,6,8-tetra methyl-2H-naphtho [1,8-bc]furan-2-one (52). - A solution of osmium tetroxide (1.1g; 1.03 equiv.) in dry pyridine (15ml) was added dropwise during 15 min. to a solution of the diene (44) (980 mg; 1.0 equiv.) in dry pyridine (10 ml) and the resulting dark brown solution was stirred at room temperature for a further 2 h. The mixture was poured onto saturated copper sulphate solution (50ml) and the aqueous solution was extracted with ethyl acetate (4 x 30ml). The combined ethyl acetate extracts were washed successively with saturated copper sulphate solution (1 x 30ml), 1M hydrochloric acid solution saturated with sodium chloride (1 x 30ml), and then brine (2 x 30ml). The solvent was evaporated in vacuo to leave the diol (1.0g; 88%) as a crystalline white solid, m.p. 190.5-191°C (ethyl acetate), ν_{max} ($CHCl_3$) 3400(br.), 2920, 1740, 1685, 1005 $cm.^{-1}$, δ_H 4.31 (ddd, J 8, 6 and 1Hz, :CCH-OH), 4.22 (m, CH-OH), 4.12 (m, CH-O), 2.82 (d, J 3Hz, CHCHOH), 2.67 (d, J 8Hz, :CCHOH), 2.25 (d, J 1Hz, CH_3C:), 2.06 (d, J 1.5Hz, $CHC(CH_3)_2$), 2.0 (1H, m), 1.46 (CH_3), 0.77 (CH_3); (Found: C, 68.0; H, 8.5; m/z 266.1510. $C_{15}H_{22}O_4$ requires C, 67.7; H, 8.3%; M 266.1518).

4,5-di-O-Isopropylidene-4β,5β-dihydroxy-4,5,5aβ,6,7,8,8aβ,8b-octahydro-3,6,6,8bβ- tetramethyl-2H-naphtho[1,8-bc]furan-2-one (53). A solution of the diol (52) (1.0g) and dimethoxypropane (10ml) in acetone (40ml) containing p-toluene sulphonic acid (20mg, cat.) was stirred at room temperature for 16 h. The solvent was removed in vacuo, and water (30ml) was then added to the residue. The aqueous solution was extracted with ether (3 x 20ml), and the combined ethereal extracts were then washed with brine (2 x 15ml) and dried. The solvent was evaporated in vacuo to leave a residue which was purified by chromatography using light petroleum (b.p. 40-60°C)-ether (4:1) as eluant to give the acetonide (1.05g; 91%) as a crystalline white solid, m.p. 165.5-166.5°C (light petroleum (b.p. 40°-60°C)-ether), ν_{max} (CCl_4), 2950, 1760, 1695, 1390, 1150, 1010 $cm.^{-1}$, δ_H 4.46 (d, J 1Hz, :CCHO), 4.44 (dd, J 7 and 1Hz, CHCHO), 4.13 (m, CH-O), 2.25 (CH_3C:), 2.08 (1H, br.), 2.02 (1H, m), 1.44 (CH_3), 1.41 (CH_3), 1.40 (CH_3), 1.40-1.25 (3H, m), 1.10 (CH_3), 0.71 (CH_3); (Found: C, 70.7; H, 8.8; m/z 306.1832. $C_{18}H_{26}O_4$ requires: C, 70.6; H, 8.6%; M 306.1831).

2-Cyanomethyl-4,5-di-O-isopropylidene-4,5,5aβ,6,7,8,8aβ,8b-octahydro-2,3β,5β- trihydroxy-3,6,6,8bβ-tetramethyl-2H-naphtho [1,8-bc]furan (54). - n-Butyllithium (1.6M in hexane; 625 µl; 5.0 equiv.) was added dropwise to a cooled (-78°C) solution of acetonitrile (52 µl, 5.0 equiv.) in dry tetrahydrofuran (6ml) and the pink solution was then stirred at -78°C for

1 h. The lactone (53) (61mg; 1.0 equiv.) was added in one portion, and the mixture was stirred at -78°C for 15 min. and then at 0°C for 45 min. The mixture was poured onto 1M hydrochloric acid solution (10ml) and the aqueous solution was extracted with ether (3 x 15ml). The combined ethereal extracts were washed with brine (2 x 10ml) and then dried. The solvent was evaporated in vacuo to leave a residue which was purified by chromatography using light petroleum (b.p.40°-60°C)- ether (2:1) as eluant to give the hydroxy nitrile (59mg; 86%) as a crystalline white solid, m.p. 144-6°C (light petroleum (b.p. 40°-60°C)-ether), ν_{max} ($CHCl_3$) 3560(s), 3450(br), 2950, 2240, 1380, 1020 $cm.^{-1}$, δ_H 4.39 ($C\underline{H}_2CN$), 3.82 (dd, J 10 and 8Hz, C<u>H</u>-O), 3.10 (d, J 17Hz, C<u>H</u>-O), 3.05 (O<u>H</u>), 2.74 (d, J 17Hz, C<u>H</u>-O), 1.95 (1H,s), 1.91 ($C\underline{H}_3C$:), 1.43 ($C\underline{H}_3$), 1.39 ($C\underline{H}_3$), 1.34 ($C\underline{H}_3$), 1.9-1.1 (4H, m, methylene envelope), 1.05 ($C\underline{H}_3$), 0.73 ($C\underline{H}_3$); (Found: m/z 347.2087. $C_{20}H_{29}O_4N$ requires M 347.2097).

2-Cyanomethylene-4β,5β-dihydroxy-4,5-di-O-isopropylidene-4,5,5aβ,6,7,8,8aβ,8b-octahydro-3,6,6,8bβ-tetramethyl-2H-naphtho[1,8-bc]furan (54). - A solution of the hydroxynitrile (54) (73 mg) and p-toluenesulphonic acid (1mg, cat.) in dry benzene (3ml) was heated under reflux for 10 min. The mixture was cooled to room temperature, then diluted with ether (20ml) and filtered through a pad of silica gel. The filtrate was evaporated in vacuo to leave a residue which was purified by chromatography using light petroleum (b.p.49-60°C)-ether (3:1) as eluant to give the diene (61mg; 89%) as a crystalline white solid, m.p. 115-116°C° (ether). ν_{max} ($CHCl_3$) 2210, 1705, 1610 $cm.^{-1}$, δ_H 4.52 (:C<u>H</u>CN), 4.45 (2 x C<u>H</u>-O), 2.06 (1H, s), 2.0 ($C\underline{H}_3C$:), 1.42 ($C\underline{H}_3$), 1.40 ($C\underline{H}_3$), 1.32 ($C\underline{H}_3$), 1.9-1.1 (4H, m, methylene envelope), 1.09 ($C\underline{H}_3$), 0.69 ($C\underline{H}_3$). (Found: m/z 329.1992: $C_{20}H_{27}O_3N$ requires: M 329.1991).

4,5-Di-O-isopropylidene-4,5,5aβ,6,7,8,8aβ,8b-octahydro-2,3,6,6,8bβ-pentamethyl-2,4β,5β-trihydroxy-2H-naphtho[1,8-bc]furan (55a). - Methyl lithium (1.4M solution in ether; 1.05ml; 5.0 equiv.) was added dropwise to a solution of the lactone (53) (90mg; 1.0 equiv.) in dry tetrahydrofuran (7ml) maintained at -78°C under nitrogen, and the mixture was then stirred at -78°C for 1 h. and afterwards at 0°C for 15 min. Water (10ml) was added, and the aqueous solution was extracted with ether (3 x 10ml). The combined ethereal extracts were washed with brine (2 x 5ml) and then dried. The solvent was evaporated in vacuo to leave a residue which was purified by chromatography using light petroleum (b.p.40-60°C)-ether (3:1) as eluant to give the lactol (46mg; 71% based

on recovered starting material) as a crystalline white solid, m.p. 120-124°C (light petroleum (b.p.40°-60°C)-ether), ν_{max} ($CHCl_3$) 3590(s), 3500(br), 2920, cm.$^{-1}$, δ_H 4.39 (2 x C<u>H</u>-O), 3.7 (dd, <u>J</u> 10 and 8Hz, C<u>H</u>-O), 2.58 (br,-O<u>H</u>), 1.91 (C<u>H</u>$_3$C:), 1.66 (C<u>H</u>$_3$COH), 1.46 (C<u>H</u>$_3$), 1.39 (C<u>H</u>$_3$), 1.32 (C<u>H</u>$_3$), 1.04 (C<u>H</u>$_3$), 2.0-1.0 (5H, m, methylene envelope), 0.76 (C<u>H</u>$_3$); (Found: m/z 322.2150: $C_{19}H_{30}O_4$ requires: <u>M</u> 322.2144).

<u>1-Hydroxymethyl-3,4,4aβ,5,6,7,8,8a-octahydro-3,4-di-O-isopropylidene - 2,5,5, 8aβ- tetramethyl-4β,5β,8α-trihydroxynaphthalene</u> (56). - Lithium aluminium hydride (38mg; 4.0 equiv.) was added in one portion to a solution of the lactone (53) (77mg; 1.0 equiv.) in dry tetrahydrofuran (5ml) maintained at 0°C under nitrogen. The mixture was heated under reflux for 4 h. then cooled to room temperature and poured into a mixture of ice and 1M hydrochloric acid solution (10ml). The aqueous solution was extracted with ethyl acetate (3 x 10ml) and the combined organic extracts were washed with brine (2 x 5ml) and then dried. The solvent was evaporated in vacuo to leave a residue which was purified by chromatography using light petroleum (b.p.40°-60°C)-ether (1:1) as eluant to give the <u>diol</u> (66mg; 85%) as a crystalline white solid, m.p.176-178°C (ethyl acetate), ν_{max} ($CHCl_3$) 3410(br), 2940, 1380, 1015 cm.$^{-1}$, δ_H 4.4 (m, C<u>H</u>$_2$O), 4.0 (br., 2 x C<u>H</u>-O), 3.46 (dd, <u>J</u> 10 and 4Hz, C<u>H</u>-O), 1.93 (C<u>H</u>$_3$C:), 1.9-1.5 (5H, m, methylene envelope), 1.51 (C<u>H</u>$_3$), 1.49 (C<u>H</u>$_3$), 1.42 (C<u>H</u>$_3$), 1.08 (C<u>H</u>$_3$), 0.70 (C<u>H</u>$_3$); (Found: C, 69.7; H, 9.5; m/z 292.2029: $C_{18}H_{30}O_4$ requires: C, 69.6; H, 9.7%; (<u>M</u>-H_2O) 292.2039).

4,5-<u>Di</u>-0-<u>isopropylidene</u>-4,5,5aβ,6,7,8,8aβ,8b-<u>octahydro</u>-2-<u>propyne</u>-3,6,6,8bβ-<u>tetramethyl</u>-2,4β,5β-<u>trihydroxy</u>-2H-<u>naptho</u>[1,8-bc]<u>furan</u> (55<u>b</u>) (C.J.Walker). - Methyl acetylene was bubbled through a cooled (-5°C) solution of <u>n</u>-butyllithium (1.5M solution in hexanes; 1.5 ml; 5.2 equiv.) in dry tetrahydrofuran (3 ml) for 15 min. during which time a fine white precipitate was formed. A solution of the lactone (53) (130 mg; 1.0 equiv.) in dry tetrahydrofuran (1.5 ml) was added, and the mixture was stirred for 30 min. at -5°C and then for 20 h. at room temperature. The mixture was poured into 1<u>M</u>-hydrochloric acid (20 ml), and the aqueous solution was then extracted with ether (3 x 10 ml). The combined ethereal extracts were washed with brine (1 x 10 ml), then dried ($MgSO_4$), and the solvent was evaporated in vacuo to leave the <u>lactol</u> (111 mg; 75%) as a crystalline white solid, m.p. 198-199°C; [light petroleum (b.p. 40°-60°C)-ether] ν_{max} ($CHCl_3$) 3590, 2940, 2260, 1380, 980 cm.$^{-1}$, δ_H 4.41 (m, 2 x C<u>H</u>-O), 3.81 (m, C<u>H</u>-O), 3.23 (br, -O<u>H</u>), 1.98 (C<u>H</u>$_3$), 1.88 (C<u>H</u>$_3$), 1.8

($C\underline{H}_3$), 1.8-1.7 (2H, m), 1.49 ($C\underline{H}_3$) 1.41 ($C\underline{H}_3$), 1.40 ($C\underline{H}_3$), 1.4-1.1 (3H, m), 1.05 ($C\underline{H}_3$), 0.75 ($C\underline{H}_3$); (Found: C, 72.4; H, 9.0%; m/z 346.2136; $C_{21}H_{30}O_4$ requires: C, 72.8; H, 8.7%; M, 346.2136).

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REFERENCES

1 Bhat,S.V.; Bajwa,B.S.; Dornauer,H.; de Souza,N.J.; and Fehlhaber,H.; Tetrahedron Lett., **1977**, 1669.

2 See: Seamon,K.B.; Annu.Rept., Med Chem., **1984**, 19, 293. For additional physiological spectrum see: Seamon,K.B.; Padgett,W.; and Daly,J.W. Proc. Natl.Acad.Sci.U.S.A., **1981**, 78, 3363. Worley,P.F.; Baraban,J.M.; De Souza,E.B.; and Snyder,S.H. Proc.Natl.Acad.Sci.U.S.A., **1986**, 83, 4053. Metzger,H.; and Linder,E. Drug Res. **1981**, 31, 1248: I.R.C.S.Med.Sci., **1981**, 9, 99. De Souza,N.J.; Dohadwalla,A.N.; and Reden,J. Med.Res.Rev., 1983, 3(2), 201. Bhat,S.V.; Dohadwalla,A.N.; Bajwa,B.S.; Dadkar,N.K.; Dornauer,H.; and de Souza,N.J. J.Med.Chem., **1983**, 26, 486. Capripoli,J.; Sears,M.; Bausher,L.; Gregory,D.; and Mead,A. Inves.Ophth. and Vis.Sci., **1984**, 25, 268. Lickey,J.; Friedrich,T.; Priesnitz,M.; Biamino,G.; Usinger,P.; and Huckauf,H.; The Lancet, **1983**, 1, 958. Caprioli,J.; Drug.Dev.Res., **1985**, 6, 193. Erhardt,P.W. J.Med.Chem., **1987**, 30, 231. De Souza,N.J.; Dohadwalla,A.H.; and Rupp,R.H. Forskolin - Its Chemical, Biological and Medical Potential : Hoechst India Ltd., Bombay (**1986**).

3 Ziegler,F.E.; Jaynes,B.H.; and Saindane,M.T.; J.Am.Chem.Soc., **1987**, 109, 8115.

4 Corey,E.J.; Jardine,P.D.; and Rohloff,J.C. J.Am.Chem.Soc., 1988, 110, 3672

5 S. Hashimoto, S. Sakata, M. Sonegawa and S. Ikegami, J.Am.Chem.Soc., 1988, 110, 3670.

6 See: Jenkins,P.R.; Menear,K.A.; Barraclough,P.; and Nobbs,M.S. J.Chem.Soc., Chem.Commun., **1984**, 1423; Nicolau,K.C.; and Li,W.S. J.Chem.Soc., Chem.Commun., **1985**, 421; Ziegler,F.E.; Jaynes,B.H.; and Saindane,M.T. Tetrahedron Lett., **1985**, 26, 3307; Baraldi,P.G.; Barco,A.; Benetti,S.; Pollini,G.P.; Polo,E.; and Simoni,D. J.Chem.Soc.,Chem.Commun., **1986**, 757; Hashimoto,S.; Sonegawa,M.; Sakata,S.; and Ikegami,S.; J.Chem.Soc.,Chem.Commun., **1987**, 24; Bold,G.; Chao,S.; Bhide,R.; Wu,S.; Patel,D.V.; and Sih,C.J. Tetrahedron Lett., **1987**, 28, 1973; Kozikowski,A.P.; Jung,S.H.; and Springer,J.P. J.Chem.Soc.,Chem.Commun., **1988**, 167; Ziegler,F.E.; and Jaynes,B.H. Tetrahedron Lett., **1987**, 28, 2339;

Koft,E.R.; Kotnis,A.S.; and Broadbent,T.A. Tetrahedron Lett., **1987**, 28, 2799; Delpech,B.; and Lett,R. Tetrahedron Lett., **1987**, 28, 4061; Liu,Z.; Zhou,X.; and Wu,Z. J.Chem.Soc.,Chem.Commun., **1987**, 1868; Ziegler,F.E.; and Jaynes,B.H.; Tetrahedron Lett., **1988**, 29, 2031; Li,T.; and Wu,Y. Tetrahedron Lett., **1988**, 29, 4039; Sherkenbeck,J.; Barth,M.; Thiel,U.; Metten,K.; Tetrahedron, **1988**,44, 6325; Paquette,L.A.; and Oplinger,J.A. Tetrahedron, **1989**, 45, 107.

7 Preliminary communications: Hutchinson,J.H.; Meyers,P.L.; and Pattenden,G. Tetrahedron Lett., **1987**, 28, 1313.

8 Heubest,H.B. J.Chem.Soc., **1951**, 1074.

9 For the first applications of this protocol in synthesis see: Stork,G.; Mook,R.; Biller,S.A.; and Rychnovsky,S.D. J.Am.Chem.Soc., **1983**, 105, 3741.

10 Hart,D.J.; and Seely,F.L. J.Am.Chem.Soc., **1988**, 110, 163. We thank Dr. Hart for making the details of the preparation of (15) available to us.

11 cf. Scheffold,R.; Rytz,G. and Walder,L. 'Modern Synthetic Methods', **1983**, Vol.3, 355. Edit., Scheffold,R.

12 Preliminary communication: Begley,M.J.; Bhandal,H.; Hutchinson,J.H.; and Pattenden,G. Tetrahedron Lett., **1987**, 28, 1317.

13 We are grateful to Paul Wight of this department for carrying out these calculations.

14 e.g. Bhandal,H.; Pattenden,G.; and Russell,J.J. Tetrahedron Lett.,**1986**, 27, 2299; Patel,V.F.; Pattenden,G.; and Russell,J.J. ibid., **1986**, 27, 2303.

15 cf. Okamoto,T; and Oka,S. J.Chem.Soc., Chem.Commun., **1984**, 289 and refs. cited therein.

16 In earlier studies (Ref.7) we had found that treatment of the glycol ether (48) containing a cis-fused decalin, with 1M aqueous potassium hydroxide in methanol (reflux, 2h) led exclusively to the conjugated lactone (49). In a similar manner, treatment of the 3:1 mixture of (35)/(36) with 1M aqueous potassium hydroxide in methanol, led largely to the conjugated lactone corresponding to (37) [i.e. 2.5:1 ratio of conjugated and deconjugated enone (37); yield 80%]. Treatment of (35)/(36) with solid potassium hydroxide in methanol however, gave exclusively the deconjugated lactone (37) in 82% yield. We infer from these data that the conjugated lactone corresponding to (37) is the kinetic product produced by elimination from (35)/(36) whereas (37) containing the trans-fused decalin system, is the thermodynamic product of the reaction.

17 Chidambaram,N.; and Chandrasekaran,S. J.Org.Chem., **1987**, 52, 5048.

18 Nicolaou,K.C.; and Li,W.S.; J.Chem.Soc., Chem.Commun., **1985**, 421.

19 Ziegler,F.E.; Jaynes,B.H.; and Saindane,Manohar T. Tetrahedron Lett., **1985**, 26, 3307.