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A SYNTHETIC APPROACH TO THE TRICHOTHECENE DEOXYNIVALENOL†

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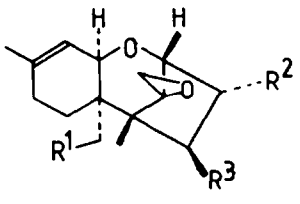
Abstract - Progress towards the total synthesis of deoxynivalenol (8) is described, leading to the advanced intermediate (25). Notable steps include a facile allyl alcohol epimerisation, a regioselective reductive deoxygenation, and a highly stereoselective Claisen allyl enol ether rearrangement.

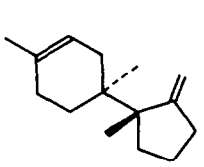
The trichothecenes[1] are a group of complex fungal sesquiterpenoids which can act as antibacterial, antiviral, and cytostatic agents: some are phytotoxic, and all show some degree of animal toxicity. They have been strongly implicated in natural intoxications of man and animals, as their fungal occurrence is ubiquitous. The tolerance level and biological effects of such compounds are of profound importance. Most, however, are difficult to obtain in significant amounts from culture broths. As a group, they therefore present a major synthetic challenge, both in terms of need and of the stereo- and regio-control required for their successful construction. Those non-macrocyclic members which have surrendered to total synthesis[2] include trichodermin[3] (1), trichodermol[4] (2), verrucarol[5] (3), anguidine[6] (4), calonectrin[7] (5), 12,13-epoxytrichothec-9-ene[8] (6), and trichodiene[9] (7).

We achieved the first synthesis[3] of a member of this group, trichodermin (1), and have explored routes[10] to another, verrucarol (3). We wish now to describe our progress on an approach to deoxynivalenol[11] (vomitoxin) (8), a highly oxygenated, non-macrocyclic trichothecene of considerable environmental importance.



(1) R^1, R^2 = H, R^3 = OAc
(2) R^1, R^2 = H, R^3 = OH
(3) R^1, R^3 = OH, R^2 = H
(4) R^1, R^3 = OAc, R^2 = OH
(5) R^1, R^2 = OH, R^3 = H
(6) R^1, R^2, R^3 = H

† Dedicated to Professor Ralph Raphael, for his sixtyfifth birthday.



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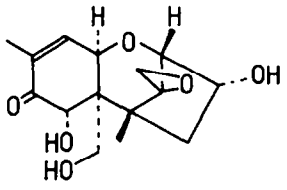
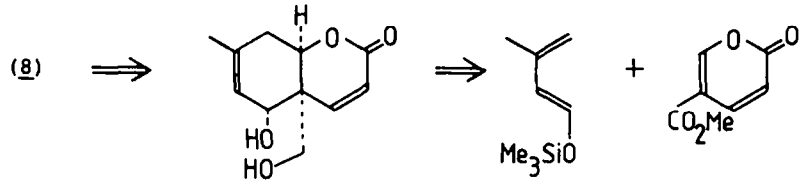


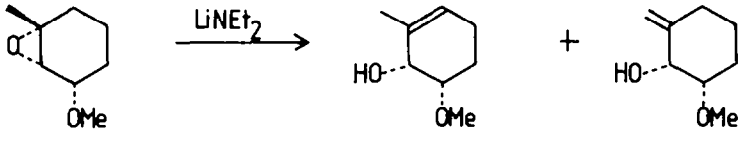
(8)

Our synthetic strategy consists of two main elements. One is formation of the cis-fused AB ring system by a Diels-Alder cycloaddition, the other is to consider the so-created cyclohexene as a masked form of the required enone (Scheme 1).



Scheme 1.

Developing the latter element, which envisages employment of an epoxide-allyl alcohol base-induced rearrangement,[12] an extensive model study[13] showed that the optimum geometry was achieved when there was a syn-relationship between the epoxide and its adjacent oxygen substituent (Scheme 2).

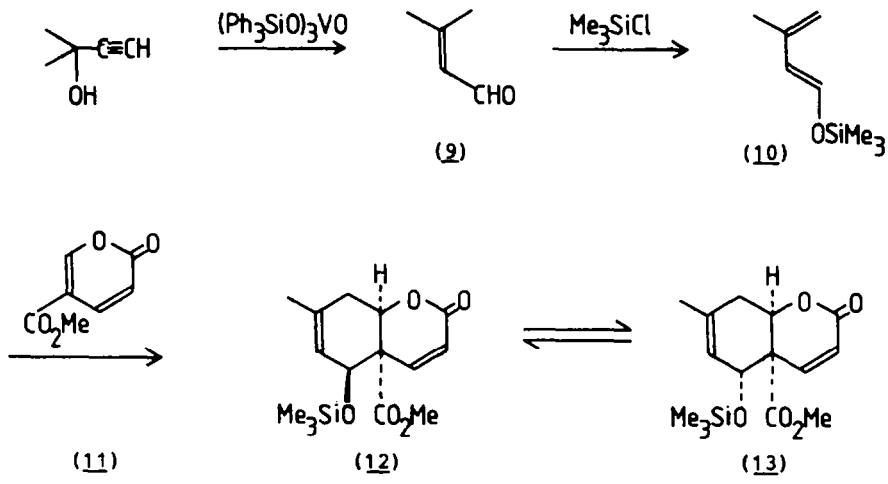


5 : 2

Scheme 2.

Turning to the Diels-Alder reaction, the silyloxydiene (10), obtainable readily[14] from the aldehyde (9) on a large scale as shown (Scheme 3), underwent a regiospecific cycloaddition with methyl coumalate[15] (11). The product (12) was obtained as mainly one epimer, which proved to possess the undesired β-configuration of the silyloxy group. Acid-catalysed desilylation yielded a mixture of two alcohols, in variable proportions. Fortunately, this mixture could be equilibrated to a 1:1 mixture of epimers by stirring over chromatographic silica gel, as a solution in ethyl acetate. Resilylation and triturative crystallisation provided the desired crystalline α-epimer (13), together with the recovered, recyclable oily β-epimer (12). These mild and manipulatively simple processes can be performed on a multi-gram scale.

Reaction of the α-epimer (13) with lithium dimethyl cuprate afforded the product (14) of conjugate addition. The next series of reactions, designed to effect 1,2-transposition of the lactonic carbonyl group following the excellent method of Kraus,[16] required careful manipulation. With caution, these steps can

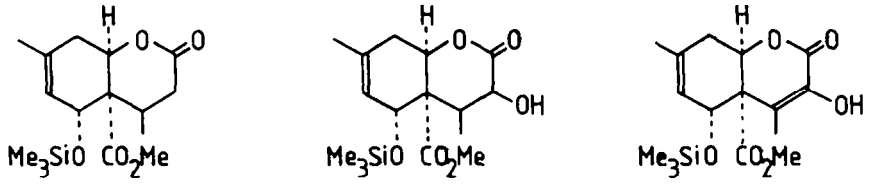


(9) (10) (11) (12) (13)

Scheme 3.

be performed without loss of the trimethylsilyl protecting group: this is a major advantage when one considers the difficult protection/deprotection sequences which would otherwise have been required.

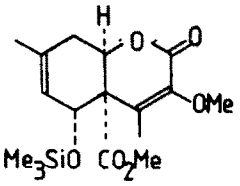
Oxidation of the lactone enolate anion at low temperature with the molybdenum pentoxide reagent of Vedejs[17] gave a diastereoisomeric mixture of hydroxylactones (15). Further oxidation produced the keto-lactone, which existed completely in the enolised form (16).



(14) (15) (16)

The corresponding methyl enol ether (17) was obtained and subjected to single crystal X-ray analysis, the results of which confirmed its structure and relative stereochemistry in all detail. Further, the parent enol (16) underwent smooth alkylation with allyl bromide to give the enol ether (18). Reduction with di-isobutylaluminium hydride produced the unstable lactol (19a), which on further treatment with Et_3SiH in the presence of $BF_3.Et_2O$ under carefully controlled conditions gave the key enol ether (20) in good yield. This second reduction is highly selective, and can be performed equally successfully on the deprotected allylic alcohol (19b).

It was at a related stage in the epimeric series that the β-configuration of the silyloxy/hydroxy group in the initial Diels-Alder adduct was determined. Similar reductive deoxygenation of the lactol (21) gave, in addition to the expected product, the cyclic acetal (22): its structure demanded that the original silyloxy group be on the β-face of the cis-fused bicyclic system in order for it to trap intramolecularly the oxocarbenium ion intermediate involved.



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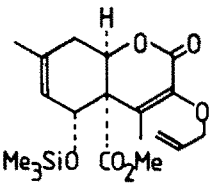

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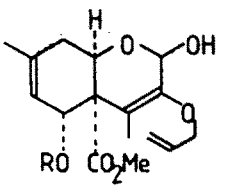
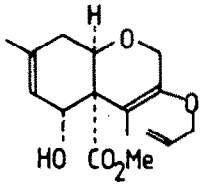


(19a) R = $SiMe_3$
(19b) R = H



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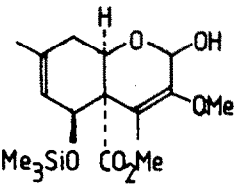

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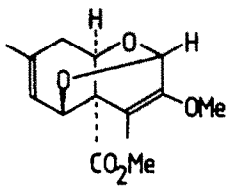
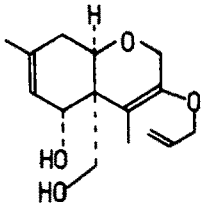


(22)

Ester reduction of (20) under mild conditions gave the diol (23), which underwent a clean and highly stereoselective thermal [3,3]-sigmatropic rearrangement to furnish the ketone (24) and its allyl epimer in a 6:1 ratio. Such stereoselectivity has precedent in a simpler, but related system: the ^1H n.m.r. spectrum of (24) displayed the anticipated[8a] AB spin pattern for the ketonic methylene group. In view of the planned protocol for the elaboration of ring A, diol (24) was converted regio- and stereospecifically by the method of Sharpless[18] into the epoxide and thence the acetonide (25).



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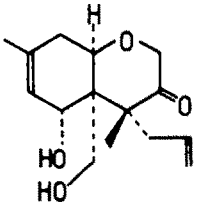

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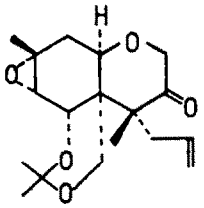

(25)

Oxidative cleavage of the allyl side chain to the nor-aldehyde, aldol cyclisation, transformation of the ketone into an exomethylene unit, rearrangement of ring A, and finally epoxidation are necessary operations to complete the synthesis of deoxynivalenol. Experiments designed to effect these remaining manipulations are under active investigation.

Experimental

Melting points were determined on a Kofler hot-stage melting point apparatus and are uncorrected. ^1H n.m.r. spectra were recorded either on a Perkin-Elmer R32 spectrometer operating at 90 MHz or on a Bruker WP200SY spectrometer operating at 200 MHz. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (0.00 p.p.m.). Infrared spectra were recorded on a Perkin-Elmer 580 spectrometer. Low resolution mass spectra were determined on a VG updated MS 12 instrument and high resolution mass spectra were determined on a MS 902S. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser.

Reactions were carried out under an atmosphere of nitrogen or argon. Anhydrous magnesium sulphate was used to dry reaction mixtures after workup. THF and ether were freshly distilled from sodium/benzophenone. Toluene was distilled from P_2O_5 and stored over 4Å molecular sieves, and dichloromethane was filtered through Grade I basic alumina and stored over 4Å molecular sieves. Dry column flash chromatography[19] and flash chromatography[20] refer to techniques already described.

1-Trimethylsilyloxy-3-methylbuta-1,3-diene (10). A suspension of $ZnCl_2$ (1.5 g, 0.011 mole) in Et_3N (93.5 ml, 0.66 mole) was stirred at room temperature for 1 h. Aldehyde (9)[14] (30 g, 0.36 mole) in benzene (170 ml) was then added, followed by Me_3SiCl (96.6 ml, 0.72 mole). The mixture was stirred at room temperature for 0.5 h, then heated at 40 °C for 24 h. On cooling, the reaction mixture was poured into ether (600 ml), filtered through Celite, and concentrated in vacuo. Ether (600 ml) was added, and the filtration and concentration process repeated. Distillation yielded the diene (10) (35 g, 63%) as a colourless oil, b.p. 45-47 °C at 15 mm Hg (lit.[21] b.p. 47-52 °C at 13 Torr). ^{1}H n.m.r. (90 MHz, $CDCl_3$): δ 0.1 (s, 9H), 1.7 (s, 3H), 4.65 (m, 2H), 5.72 (d, 1H, J 11 Hz) and 6.42 (d, 1H, J 11 Hz).

(±)-(4aα,8aα)-4a-(Carbomethoxy-4a,5,8,8a-tetrahydro-5α-trimethylsilyloxy-7-methyl-2H-1-benzopyran-2-one (13) and its 5β epimer (12). Methyl coumalate (11)[15] (27 g, 0.175 mole), diene (10) (16.5 g, 0.105 mole) and a few crystals of hydroquinone were heated under reflux in toluene (700 ml) for 24 h. At this time more diene (10) (16.5 g, 0.105 mole) was added and reflux continued for a further 24 h. Concentration in vacuo yielded the crude adduct as mainly a single epimer (12). A solution of the crude product (12) (55 g) in THF (800 ml), water (375 ml) and acetic acid (11 ml) was stirred for 12 h at room temperature. The solution was then saturated with salt, and thoroughly extracted with ether. The ethereal extracts were washed with saturated aqueous $NaHCO_3$ solution, brine, and dried. Concentration yielded a mixture of epimeric alcohols (47 g), which was stirred as a solution in ethyl acetate (1300 ml) over silica gel (470 g, ICN Silica TSC) at room temperature for 3.5 days. After this time, ^{1}H n.m.r. spectroscopy indicated a 1:1 mixture of alcohols (vide infra). Filtration and concentration in vacuo gave the crude alcohols (42 g). These could be separated by dry column flash chromatography to give the β-epimeric alcohol as a white crystalline solid, m.p. 84-86 °C; i.r. (CCl_4): 3620, 3595, and 1740 cm^{-1}. ^{1}H n.m.r. (90 MHz, $CDCl_3$): δ 1.68 (bs, 3H), 2-2.8 (m, 2H), 3.72 (s, 3H), 4.68 (m, 1H), 5.0 (t, 1H, J 7 Hz), 5.62 (m, 1H), 6.16 (d, 1H, J 10 Hz), 6.97 (d, 1H, J 10 Hz). MS: m/e 238. (Found: C, 60.77; H, 6.08%. $C_{12}H_{14}O_5$ requires C, 60.50; H, 5.92%.)

The α-epimeric alcohol is also a white crystalline solid, m.p. 106-109 °C; i.r. (CCl_4) 3595, 3550, and 1740 cm^{-1}. ^{1}H n.m.r. (90 MHz, $CDCl_3$): δ 1.7 (bs, 3H), 1.95-2.85 (m, 2H), 3.78 (s, 3H), 4.45 (m, 1H), 5.15 (t, 1H, J 7 Hz), 5.61 (m, 1H), 6.05 (d, 1H, J 10 Hz) and 6.88 (d, 1H, J 10 Hz). MS: m/e 238. (Found: C, 60.66; H, 6.1%.)

However, without purification, to a solution of the crude alcohols (42 g) in ether (1000 ml) and pyridine (142 ml, 1.76 mole) was added Me_3SiCl (112 ml, 0.88 mole) and the mixture stirred at room temperature for 16 h. Water was then added carefully, and the organic layer separated. The organic layer was washed twice with 1N HCl, once with saturated aqueous $NaHCO_3$ solution, once with water, once with brine, and dried. Removal of solvent in vacuo and dry column flash chromatography gave the α-epimer (13) (10 g, 18% based on methyl coumalate) as white crystals after trituration with hexane, m.p. 108.5-109.5 °C; i.r. (CCl_4)

1740 and 1730 cm^{-1}. ^1H n.m.r. (90 MHz, $CDCl_3$): δ 0.01 (s, 9H), 1.68 (bs, 3H), 1.85-2.80 (m, 2H), 3.66 (s, 3H), 4.37 (d, 1H, J 4.5 Hz), 5.19 (dt, 1H, J 7 Hz and 2 Hz), 5.46 (m, 1H), 5.97 (d, 1H, J 10 Hz), 6.70 (dd, 1H, J 10 Hz and 2 Hz). MS: 310.1233 (M^+); calc. for $C_{15}H_{22}O_5Si$: 310.1235. (Found: C, 57.71; H, 7.36%. $C_{15}H_{22}O_5Si$ requires C, 58.04; H, 7.14%.)

The β-epimer (12), slightly contaminated with (13), was obtained as an oil (15.6 g, 29% based on methyl coumalate); i.r. (CCl_4) 1740 and 1730 cm^{-1}. ^1H n.m.r. (90 MHz, $CDCl_3$): δ 0.01 (s, 9H), 1.58 (bs, 3H), 1.8-2.2 (m, 2H), 3.67 (s, 3H), 4.67 (m, 1H), 4.99 (dt, 1H, J 7 Hz and 2 Hz), 5.3 (m, 1H), 6.08 (d, 1H, J 10 Hz), 6.98 (dd, 1H, J 10 Hz and 2 Hz). MS: 310.1251 (M^+).

(±)-(4aα,8aα)-4a-(Carbomethoxy)-3,4,4a,5,8,8a-hexahydro-5α-trimethylsilyloxy-4,7-dimethyl-2H-1-benzopyran-2-one (14). Methyl lithium - lithium bromide complex (1.5M in ether)was added slowly to a suspension of cuprous iodide (1.47 g, 7.72 mmol) in dry ether (40 ml) at 0 °C until the initially formed yellow precipitate had just disappeared. The resulting clear solution was stirred at 0 °C for 5 min, then the α-epimer (13) (2.0 g, 6.45 mmol) in ether (5 ml) added slowly. After addition, the mixture was stirred at 0 °C for 30 min, then poured slowly into a stirred ice-cold saturated NH_4Cl solution (40 ml), and left for 2 min. The resulting mixture was filtered through Celite, and the layers separated. The aqueous layer was extracted twice with ether, and the combined organic extracts were dried and concentrated *in vacuo*. Purification by dry column flash chromatography yielded (14) (1.24 g, 59%) as white crystals, m.p. 144-146 °C; i.r. (CCl_4): 1745 and 1730 cm^{-1}. ^1H n.m.r. (90 MHz, $CDCl_3$), δ 0.10 (s, 9H), 1.12-1.25 (m, 3H), 1.80 (bs, 3H), 1.88-2.05 (m, 5H), 3.80 (s, 3H), 4.51-4.79 (m, 1H), 5.24-5.44 (m, 1H), 5.50-5.65 (m, 1H). MS: 326.1541 (M^+); calc. for $C_{16}H_{26}O_5Si$: 326.1549. (Found: C, 58.95; H, 8.01%. $C_{16}H_{26}O_5Si$ requires C, 58.87; H, 8.02%.)

(±)-(4aα,8aα)-4a-(Carbomethoxy)-3,4,4a,5,8,8a-hexahydro-3-hydroxy-5α-trimethylsilyloxy-4,7-dimethyl-2H-1-benzopyran-2-one (15). To a solution of Pr^i_2NH (0.66 g, 6.57 mmol) in THF (16 ml) at 0 °C was added Bu^nLi (2.5M in hexane, 2.4 ml, 6.0 mmol). After 15 min the solution was cooled to -78 °C, and the cuprate product (14) (1.88 g, 5.77 mmol) in THF (5 ml) added dropwise. After stirring at -78 °C for 30 min, the MoO_5 complex (3.76 g, 8.66 mmol) was added in one portion, and stirring continued for 4 h at -78 °C. The mixture was then allowed to warm to 0 °C over 30 min. Saturated aqueous NH_4Cl solution was added, followed by ether, and the layers separated. The organic layer was washed once with saturated aqueous $NaHCO_3$ solution, brine and dried. Concentration *in vacuo* followed by dry column flash chromatography yielded hydroxylactone (15) (1.44 g, 73%) as an oily mixture of diastereoisomers; i.r. (CCl_4): 3530, 1745, and 1735 cm^{-1}. MS: 342.1527 (M^+); calc. for $C_{16}H_{26}O_6Si$: 342.1498.

(±)-(4aα,8aα)-4a-(Carbomethoxy)-4a,5,8,8a-tetrahydro-3-hydroxy-5α-trimethylsilyloxy-4,7-dimethyl-2H-1-benzopyran-2-one (16). To a solution of N-chlorosuccinimide (0.735 g, 5.51 mmol) in toluene (35 ml) was added Me_2S (0.59 ml, 8.05 mmol) with stirring at 0 °C. The mixture was stirred at 0 °C for 20 min, then cooled to -25 °C. The hydroxylactone (15) (0.64 g, 1.87 mmol) in toluene (10 ml) was added dropwise, and the mixture stirred at -25 °C for 2 h. Triethylamine (0.78 ml, 5.6 mmol) in toluene (1 ml) was added slowly, the cooling bath was removed, the mixture stirred for 5 min, then poured into ether. This solution was washed once with 1N HCl, water, brine, and dried. Concentration *in vacuo* and purification by dry column flash chromatography yielded the enol (16) (0.49 g, 77%) as an oil; i.r. (CCl_4): 3475, 1730, and 1715 cm^{-1}. ^1H n.m.r. (90 MHz, $CDCl_3$): δ 0.01 (s, 9H), 1.62 (bs, 3H), 1.87 (s, 3H), 2.05-2.80 (m, 2H), 3.68 (s, 3H), 4.60

(d, 1H, J 6.5 Hz), 5.34 (t, 1H, J 9 Hz), 5.52 (m, 1H), 5.89 (m, 1H). MS: 268.0953 (M^+, analysed as free alcohol); calc. for $C_{13}H_{16}O_6$: 268.0947.

(±)-(4aα,8aα)-4a-(Carbomethoxy)-4a,5,8,8a-tetrahydro-3-methoxy-5α-trimethylsilyloxy-4,7-dimethyl-2H-1-benzopyran-2-one (17). A mixture of the enol (16) (0.71 g, 2.10 mmol), anhydrous K_2CO_3 (0.34 g, 2.50 mmol) and CH_3I (1.4 ml, 2.25 mmol) in acetone (30 ml) was heated under reflux for 24 h. On cooling, the mixture was poured into ether, filtered through Celite, and concentrated in vacuo. Purification by dry column flash chromatography yielded the methyl enol ether (17) as white crystals, m.p. 137-138 °C, i.r. (CCl_4): 1737 and 1725 cm^{-1}. ^1H n.m.r. (90 MHz, $CDCl_3$): δ 0.02 (s, 9H), 1.66 (bs, 3H), 1.94 (s, 3H), 1.95-2.80 (m, 2H), 3.65 (s, 3H), 3.68 (s, 3H), 4.62 (d, 1H, J 6.5 Hz), 5.26 (t, 1H, J 9 Hz), 5.62 (m, 1H). MS: 354.1472 (M^+); calc. for $C_{17}H_{26}O_6Si$: 354.1498. (Found: C, 57.32; H, 7.57%. $C_{17}H_{26}O_6Si$ requires C, 57.60; H, 7.39%.)

(±)-(4aα,8aα)-4a-(Carbomethoxy)-4a,5,8,8a-tetrahydro-3-allyloxy-5α-trimethylsilyloxy-4,7-dimethyl-2H-1-benzopyran-2-one (18). A mixture of the enol (16) (0.39 g, 1.15 mmol), anhydrous K_2CO_3 (0.19 g, 1.38 mmol) and allyl bromide (0.98 ml, 11.53 mmol) in acetone (30 ml) was heated under reflux for 24 h. On cooling, the mixture was poured into ether, filtered through Celite, and concentrated in vacuo. Purification by dry column flash chromatography gave the allyl enol ether (18) (0.33 g, 76%) as white crystals, m.p. 80-81 °C; i.r. (CCl_4): 1735 and 1725 cm^{-1}. ^1H n.m.r. (90 MHz, $CDCl_3$): δ 0.02 (s, 9H), 1.64 (bs, 3H), 1.92 (s, 3H), 1.93-2.78 (m, 2H), 3.68 (s, 3H), 4.42 (d, 2H, J 7 Hz), 4.60 (d, 1H, J 6.5 Hz), 5.15 (m, 1H), 5.26 (m, 1H), 5.34 (m, 1H), 5.52 (m, 1H), 5.65-6.25 (m, 1H). MS: 308.1267 (M^+, analysed as free alcohol); calc. for $C_{16}H_{20}O_6$: 308.1260. (Found: C, 60.20; H, 7.35%. $C_{19}H_{28}O_6Si$ requires C, 59.97; H, 7.12%.)

(±)-(4aα,8aα)-4a-(Carbomethoxy)-4a,5,8,8a-tetrahydro-2-hydroxy-3-allyloxy-5α-trimethylsilyloxy-4,7-dimethyl-2H-1-benzopyran (19a) and the free alcohol (19b). To a solution of the lactone (18) (0.55 g, 1.45 mmol) in CH_2Cl_2 (20 ml) was added Bu^i_2AlH (1M in hexane, 2.9 ml, 2.9 mmol) at -25 °C with stirring. Stirring was continued for 2 h at -25 °C, then the cooling bath was removed. The mixture was diluted with ether (100 ml), and washed once with 1N HCl, once with water, dried, and concentrated in vacuo. Dry column flash chromatography yielded the lactol (19a) (0.28 g, 50%) as an oily mixture of epimers; i.r. (CCl_4): 3600, 3470, 1755, 1720, and 1676 cm^{-1}. ^1H n.m.r. (90 MHz, $CDCl_3$): δ 0.09 (s, 9H), 1.66 (bs, 3H), 1.88 (s, 3H), 2.1-2.4 (m, 2H), 3.75 (s, 3H), 4.47 (m, 2H), 4.65 (m, 2H), 5.05-5.25 (m, 1H), 5.38 (m, 2H), 5.7-4.2 (m, 1H). MS: 226 (M^+-$C_8H_{16}OSi$, retro-Diels-Alder) and the desilylated lactol (19b) (0.11 g, 23%) as an oily mixture of epimers; i.r. (CCl_4): 3600, 3545, 1725, and 1678 cm^{-1}. ^1H n.m.r. (90 MHz, ($CDCl_3$): δ 1.67 (bs, 3H), 1.81 (s, 3H), 1.99-2.3 (m, 2H), 3.48 (m, 1H), 3.7 (s, 3H), 4.38 (m, 2H), 4.63 (m, 1H), 5.08-5.66 (m, 3H), 5.74-6.21 (m, 1H). MS: 226.0843 (M^+-C_5H_8O, retro-Diels-Alder); calc. for $C_{11}H_{14}O_5$: 226.0841.

(±)-(4aα,8aα)-4a-(Carbomethoxy)-4a,5,8,8a-tetrahydro-3-allyloxy-5α-trimethylsilyloxy-4,7-dimethyl-2H-1-benzopyran (20). To a solution of the silylated lactol (19a) (0.308 g, 0.81 mmol) and Et_3SiH (0.2 ml, 1.26 mmol) in CH_2Cl_2 (10 ml) was added dropwise boron trifluoride etherate (0.1 ml, 0.81 mmol) with stirring at -78 °C. Stirring was continued at -78 °C for 1 h, when excess solid anhydrous K_2CO_3 then saturated aqueous $NaHCO_3$ solution were added. On reaching 0 °C, the mixture was diluted with CH_2Cl_2 (20 ml), washed once with saturated aqueous $NaHCO_3$ solution, dried, and concentrated in vacuo. Purification by dry column flash chromatography gave the alcohol (20) (0.173 g, 73%) as viscous oil; i.r.

(CCl_4): 3550 and 1725 cm^{-1}. ^1H n.m.r. (90 MHz, $CDCl_3$): δ 1.68 (bs, 3H), 1.79 (bs, 3H), 2.08-2.31 (m, 2H), 3.71 (s, 3H), 4.1-4.4 (m, 5H), 5.1-5.32 (m, 2H), 5.4-5.5 (m, 2H), 5.75-6.2 (m, 1H). MS: 253.1094 ($M^+-C_3H_5$); calc. for $C_{13}H_{17}O_5$: 253.1076.

Similar treatment of the desilylated lactol (19b) (0.138 g, 0.44 mmol) with Et_3SiH (0.22 ml, 1.33 mmol) and boron trifluoride etherate (0.11 ml, 0.89 mmol) gave the alcohol (20) (0.092 g, 70%).

Analogous treatment of the methyl enol ether (21) gave, in addition to the expected product, the bridged acetal (22); i.r. ($CHCl_3$): 1735 and 1694 cm^{-1}. ^1H n.m.r. (90 MHz, $CDCl_3$): δ 1.69 (s, 6H), 2.3-2.45 (m, 2H), 3.71 (s, 6H), 4.05-4.2 (m, 2H), 5.24 (s, 1H), 5.75-5.92 (m, 1H). MS: 266.1157 (M^+); calc. for $C_{14}H_{18}O_5$: 266.1154.

(±)-(4aα,8aα)-4a,5,8,8a-Tetrahydro-3-allyloxy-4a-hydroxymethyl-5α-hydroxy-4,7-dimethyl-2H-1-benzopyran (23). To a suspension of $LiAlH_4$ (0.087 g, 2.29 mmol) in ether (2 ml) was added the ester (20) (169 mg, 0.58 mmol) in ether (4 ml) at 0 °C. The mixture was stirred at 0 °C for 30 min, then saturated aqueous Na_2SO_4 solution added dropwise. The mixture was extracted thoroughly with ether, the ethereal extracts were dried and concentrated *in vacuo*. Purification by dry column flash chromatography gave the diol (23) (0.112 g, 73%) as a viscous oil; i.r. (CCl_4): 3630, 3490, and 1680 cm^{-1}. ^1H n.m.r. (90 MHz, $CDCl_3$): δ 1.68 (bs, 3H), 1.81 (bs, 3H), 2.05-2.45 (m, 4H), 3.55-4.3 (m, 7H), 4.49 (m, 1H), 5.1-5.45 (m, 3H), 5.7-6.2 (m, 1H). MS: 225.1118 ($M^+-C_3H_5$); calc. for $C_{12}H_{17}O_4$: 225.1127.

(±)-(4aα,8aα)-4a,5,8,8a-Tetrahydro-4α-allyl-4a-hydroxymethyl-5α-hydroxy-4,7-dimethyl-2H-1-benzopyran-3(4H)-one (24) and its allyl epimer. A solution of the allyl enol ether (23) (0.189 g, 0.71 mmol) in toluene (50 ml) was heated under reflux for 24 h. Concentration *in vacuo* and purification by dry column flash chromatography yielded the ketone (24) (0.134 g, 71%) as a viscous oil; i.r. ($CHCl_3$): 3615, 3530, and 1718 cm^{-1}. ^1H n.m.r. (200 MHz, $CDCl_3$): δ 1.45 (s, 3H), 1.72 (s, 3H), 2.2 (ABq, 2H, J 16 Hz), 2.75 (AB of ABX, 2H, J_{AB} 12 Hz, J_{AX},J_{BX} 5 Hz), 3.69 and 3.84 (ABq, 2H, J 12 Hz), 3.92 and 4.08 (ABq, 2H, J 15 Hz), 4.25 (m, 2H), 5.0-5.1 (m, 3H), 5.28 (m, 1H), 5.42-5.54 (m, 1H). MS: 248.1400 (M^+-H_2O); calc. for $C_{15}H_{20}O_3$: 248.1412 and its allyl β-epimer (0.021 g, 11%) as a viscous oil; i.r. ($CHCl_3$): 3605, 3510, and 1718 cm^{-1}. MS: 266 (M^+), 248 (M^+-H_2O).

(±)-(4aα,8aα)-4a,5,6,7,8,8a-Hexahydro-4α-allyl-4a-hydroxymethyl-5α-hydroxy-6,7α-epoxy-4,7-dimethyl-2H-1-benzopyran-3(4H)-one acetonide (25). A solution of the diol (24) (0.092 g, 0.35 mmol) and $VO(acac)_2$ (few crystals) in CH_2Cl_2 (7.5 ml) was heated at reflux. To this was added dropwise Bu^tOOH (5.4 M in CH_2Cl_2, 0.77 ml, 0.42 mmol), and reflux continued for 6.5 h. On cooling, the mixture was washed twice with saturated aqueous sodium sulphite solution, once with brine, and dried. Concentration *in vacuo* and purification by flash chromatography (ethyl acetate: petrol 7:3) yielded the epoxydiol (0.074 g, 76%): i.r. ($CHCl_3$): 3600, 3500, 3350, and 1720 cm^{-1}. MS: 282.1480 (M^+); calc. for $C_{15}H_{22}O_5$: 282.1467.

A solution of the epoxydiol (0.047 g, 0.17 mmol), 2,2-dimethoxypropane (0.16 ml, 1.3 mmol) and pyridinium tosylate (few crystals) in DMF (3 ml) was stirred at room temperature for 18 h. The mixture was then diluted with ether (50 ml), washed once with water, once with brine, and dried. Concentration *in vacuo* and purification by flash chromatography gave the epoxyacetonide (25) (0.036 g, 67%); i.r. ($CHCl_3$): 1723 cm^{-1}. ^1H n.m.r. (200 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.38 (s, 3H), 1.42 (s, 3H), 1.49 (s, 3H), 2.2 (d, 2H, J 7.5 Hz), 2.5-3.0 (m, 2H), 3.1 (d,

1H, J 3 Hz), 3.65 (1H, t, J 7.5 Hz), 3.7 and 3.65 (ABq, 2H, J 12.5 Hz), 3.85 and 4.25 (ABq, 2H, J 18 Hz), 4.31 (d, 1H, J 3 Hz), 5.1 (m, 2H), 6.0 (m, 1H). MS: 322.1794 (M^+); calc. for $C_{18}H_{26}O_5$: 322.1780.

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