Stereoselective Synthesis of the Plant-growth-promoting Steroids Dolicholide and Dolichosterone

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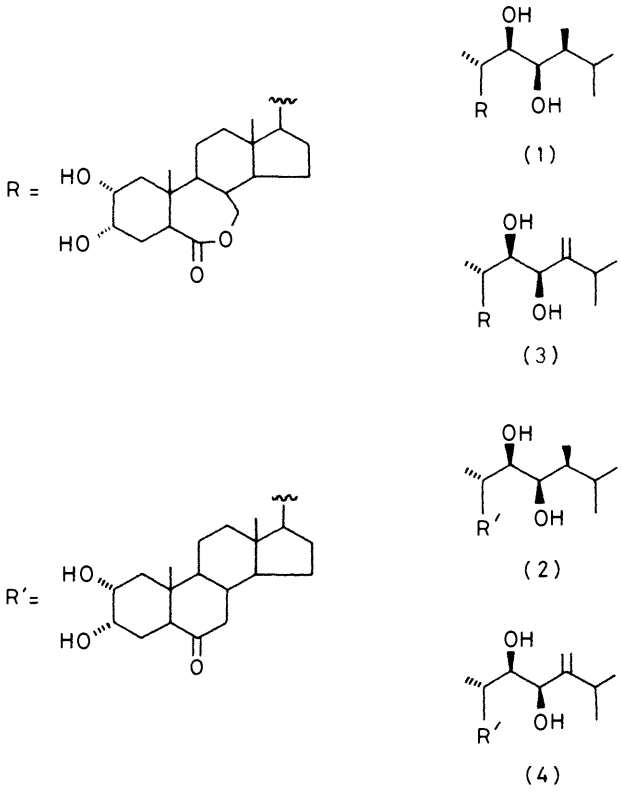
Stereoselective syntheses of dolicholide (3), (22*R*,23*R*)-2α,3α,22,23-tetrahydroxy-B-homo-7-oxa-5α-ergost-24(28)-en-6-one, and dolichosterone (4), (22*R*,23*R*)-2α,3α,22,23-tetrahydroxy-5α-ergost-24(28)-en-6-one, were achieved from the known (22*E*,24*S*)-2α,3α-diacetoxy-5α-stigmast-22-en-6-one (5) which is readily available from stigmasterol. The key step in the construction of the (22*R*,23*R*)-vicinal diol function in the steroidal side-chain was new and used the method of chelation control.

In 1979, a new plant-growth hormone named brassinolide (1) was isolated from the pollen of rape (*Brassica napus* L.) and its structure was determined as (22*R*,23*R*,24*S*)-2α,3α,22,23-tetrahydroxy-B-homo-7-oxa-5α-ergostan-6-one.[1] Brassinolide (1) possesses a wide variety of plant-growth-promoting activities in selected bioassays for auxin, gibberellin, and cytokinin.[2-6] Its unique structural features and remarkable biological activities made brassinolide (1) an attractive synthetic target. Syntheses of brassinolide (1) and many of its analogues were already reported by both us [7-10] and other groups.[11-19] The structure–activity relationship was clarified using a number of bioassay systems.[10,14,20]

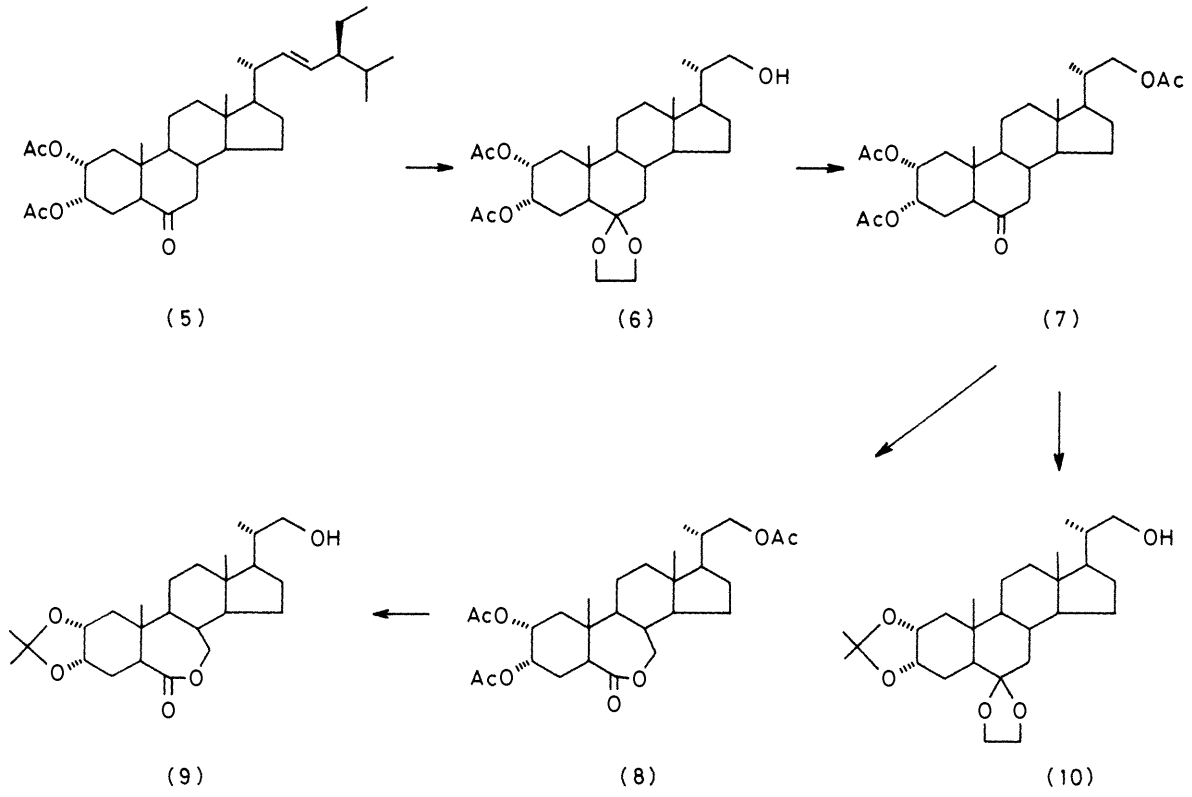
Subsequent to the isolation of brassinolide (1), castasterone (2), (22*R*,23*R*,24*S*)-2α,3α,22,23-tetrahydroxy-5α-ergostan-6-one, was isolated from the insect galls of the chestnut tree (*Castanea* spp).[21] Brassinolide (1) and castasterone (2) were also identified in several other higher plants.[22-25] More recently, dolicholide (3), (22*R*,23*R*)-2α,3α,22,23-tetrahydroxy-B-homo-7-oxa-5α-ergost-24(28)-en-6-one, and dolichosterone (4), (22*R*,23*R*)-2α,3α,22,23-tetrahydroxy-5α-ergost-24(28)-en-6-one, have been isolated from the immature seeds of *Dolichos lablab*.[26,27] From a biosynthetic point of view, it can be assumed that the 6-oxo steroids (2) and (4) might be biosynthetic precursors of the (7-oxa) lactones (1) and (3), respectively.

Because of the scarcity of these brassinosteroids, their chemical synthesis (which is described in this paper in detail) is necessary in order to evaluate their plant-growth-promoting activities. In a preliminary communication we reported the stereoselective synthesis of dolicholide (3).[28]

Since dolicholide (3) and dolichosterone (4) have an allylic alcohol moiety in the side-chain, our synthetic strategy for them is as follows; first, functionalization of the A,B-ring system, then construction of the side-chain part using the chelation-controlled Grignard reaction of α-alkoxy aldehydes. (22*E*,24*S*)-2α,3α-Diacetoxy-5α-stigmast-22-en-6-one (5), which was used for our synthesis of 28-homobrassinolide and related compounds,[9] was the starting material. Compound (5) was easily obtained from stigmasterol in 47% overall yield. The key intermediate, the 2α,3α,22-triacetoxy-6-oxo steroid (7), was prepared from (5) by five steps in 60% overall yield as follows. Protection of the carbonyl group at C-6 as its ethylene acetal, ozonolysis of the 22-ene function, and subsequent sodium borohydride reduction afforded the 22-alcohol (6). This was deacetalized and acetylated to provide the triacetate (7), m.p. 212—213 °C (Scheme 1). Introduction of lactone functionality into the B-ring was achieved by the known Baeyer–Villiger oxidation of the corresponding 6-oxo steroid.[7,29] Oxidation of the 6-oxo steroid (7) with two equivalents of trifluoroperacetic acid in dichloromethane in the presence of disodium hydrogen phosphate at 0 °C for 2 h provided, after chromatographic purification, the desired lactone (8), m.p. 240—241 °C, in 83% yield. The triacetoxy lactone (8) was converted into the aldehyde (11) as follows. Saponification of (8) and acetonide formation gave the 22-alcohol (9), m.p. 193—194 °C, in 95% yield. Oxidation of (9) with pyridinium chlorochromate in the presence of sodium acetate provided the aldehyde (11) in 75% yield. Similarly, the 6-ethylene acetal aldehyde (12), which is a synthetic precursor of dolichosterone (4), was obtained from the triacetoxy 6-oxo steroid (7), *via* the 22-alcohol (10), in 70% overall yield.



Since direct *cis*-hydroxylation of the 22*E*-olefin of the steroidal side-chain with osmium tetraoxide provided the unnatural (22*S*,23*S*)-vicinal diol exclusively,[8-10,13,14,16-18] stereoselective introduction of the (22*R*,23*R*)-vicinal diol function at C-22, and -23 is a crucial step in the synthesis of (22*R*,23*R*)-brassinosteroids. In our previous paper [7] we developed the stereoselective introduction of a (22*R*,23*R*)-vicinal diol using hydroxy-directing epoxidation. However, another stereoselective-introduction method of the (22*R*,23*R*)-vicinal diol function became necessary for the synthesis of the



Scheme 1.

24-methylene-28-norbrassinosteroids (3) and (4). For this purpose, the chelation-controlled Grignard reaction of an α-alkoxy aldehyde [30,31] should be suitable.

The aldehyde (11) was treated with the lithium salt of 1,3-dithiane at −20 °C in tetrahydrofuran (THF), followed by treatment with chloromethyl methyl ether and diethylcyclohexylamine in dioxane, to afford the (22*R*)-dithiane (13) in 85% yield (Scheme 2). The *R* configuration at C-22 was tentatively deduced from the reaction of pregnone-20-carbaldehydes with nucleophiles [32] and was finally confirmed by conversion of (13) into dolicholide (3). Dethioacetalization of the dithiane (13) with red mercury(II) oxide and boron trifluoride–diethyl ether in aqueous THF provided the (22*R*)-carbaldehyde (15) quantitatively, without epimerization at C-22. Chelation-controlled coupling of the aldehyde (15) with the Grignard reagent derived from 2-bromo-3-methylbut-1-ene [33] in THF at −78 °C afforded, exclusively, the (22*R*,23*R*)-22,23-vicinal diol 22-methoxymethyl ether (17) in 73% yield, whose 23*R* stereochemistry was assigned from the prediction reported by Still.[30,31] By the same method, the aldehyde (12) was transformed into the (22*R*,23*R*)-22,23-vicinal diol 22-methoxymethyl ether (18), *via* the (22*R*)-carbaldehyde (16), in 60% overall yield.

In order to remove the methoxymethyl group at C-22 without formation of by-products, protection of the 23-alcohol (as its acetate) was first necessary. Acetylation of the 23-alcohols (17) and (18), followed by treatment with 10% aqueous perchloric acid at 50 °C and subsequent acetylation at 60 °C, provided the dolicholide tetra-acetate (19) and dolichosterone tetra-acetate (20), respectively, in *ca.* 80% yield after chromatographic purification. Saponification of (19) with 5% KOH–MeOH under reflux and acidification afforded dolicholide (3), m.p. 238—242 °C (lit.,[26] 234—238 °C), in 93% yield. The tetra-acetate (20) was saponified to give dolichosterone (4), m.p. 232—235.5 °C (lit.,[27] 233—237 °C), in 92% yield. The ^{1}H-n.m.r. (400.5 MHz) and mass spectra of our synthetic dolicholide (3) and dolichosterone (4) were in complete agreement with those of the natural compounds (3) and (4), respectively.

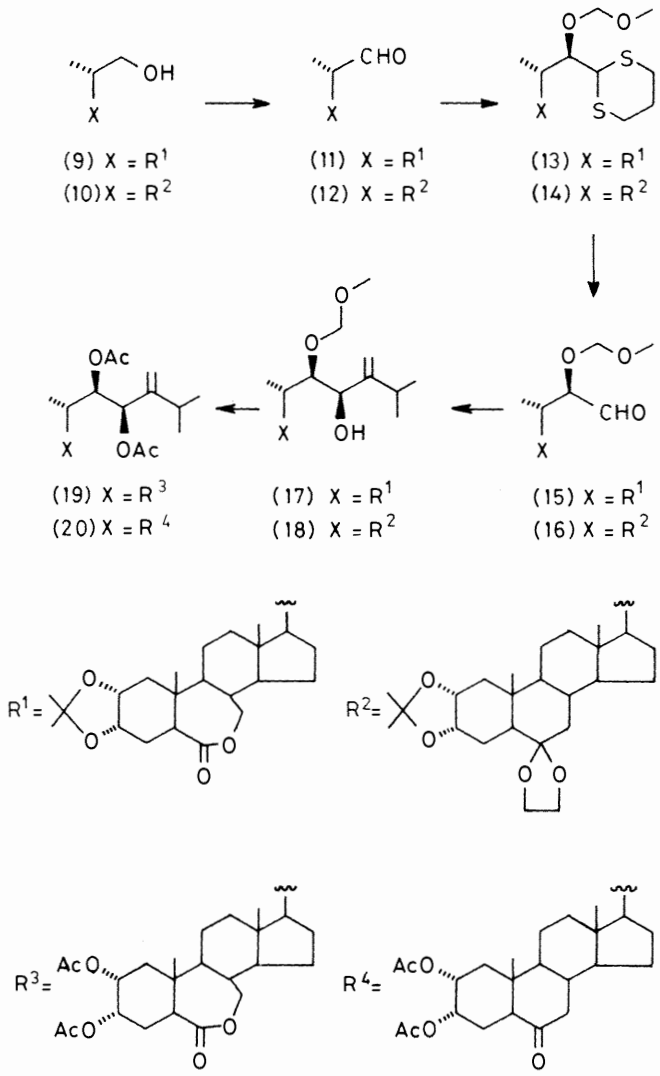
In conclusion, this method of introducing a (22*R*,23*R*)-vicinal diol function at C-22 and -23 of the steroidal side-chain seems to be useful in the synthesis of (22*R*,23*R*)-brassinosteroids with modified side-chains.* Detailed plant-growth-promoting activities of our synthetic dolicholide (3) and dolichosterone (4) will be reported elsewhere.

Experimental

M.p.s were determined with a hot-stage microscope apparatus and were uncorrected. N.m.r. spectra were taken with a Hitachi R-24A, a JEOL PS-100, or a JEOL FX-400 spectrometer with tetramethylsilane as internal standard. Mass spectra were obtained with a Simadzu LKB-9000S and a Hitachi M-80 spectrometer. Column chromatography was performed with silica gel (E. Merck silica gel 60). T.l.c. was carried out on pre-coated plates of silica gel (E. Merck). The usual work-up refers to dilution with water, extraction with an organic solvent, washing until neutrality was attained, drying ($MgSO_4$), filtration, and evaporation under reduced pressure.

2α,3α-*Diacetoxy*-6-*ethylenedioxy*-23,24-*dinor*-5α-*cholan*-22-*ol* (6).—The 6-oxo steroid (5) [9] (15 g, 28.4 mmol) was treated with 2-ethyl-2-methyl 1,3-dioxolane (50 ml) and toluene-*p*-sulphonic acid (0.3 g) under reflux for 2 h. After the mixture had cooled to room temperature saturated aqueous $NaHCO_3$

* According to this synthetic methodology, we synthesized 28-norbrassinolide,[28] brassinolide (1), and castasterone (2). Detailed results of the latter two syntheses will be reported elsewhere.



Scheme 2.

was added. The usual work-up (ethyl acetate for extraction) gave a crude product (15.3 g). Into a solution of this crude product in dichloromethane (500 ml) and methanol (500 ml) was bubbled O_3 at −78 °C. After the solution was saturated with O_3, excess of O_3 was bubbled in for a further 3 h. The excess of O_3 was then removed by bubbling argon into the solution. To this resulting ozonide solution was added sodium borohydride (5 g). This mixture was stirred at room temperature for 2 h. The usual work-up (dichloromethane for extraction) gave the crude 22-*alcohol* (6) (12.4 g). A small portion (500 mg) of this product was submitted to chromatography on silica gel (30 g) with benzene–ethyl acetate (3 : 1) as eluant to provide the 22-alcohol (6) (280 mg) as an amorphous solid; $\delta_H(CDCl_2)$ 0.70 (3 H, s, 18-H_3), 0.85 (3 H, s, 19-H_3), 1.00 (3 H, d, *J* 7 Hz, 21-H_3), 1.98 (3 H, s, acetyl), 2.05 (3 H, s, acetyl), 3.10—3.60 (2 H, m, 22-H_2), 3.90 (4 H, br s, OCH_2-CH_2O), 4.90 (1 H, m, $w_{\frac{1}{2}}$ 23 Hz, 2β-H), and 5.31 (1 H, m, $w_{\frac{1}{2}}$ 9 Hz, 3β-H) [Found: *m/z* 432.2874 ($M^+ - CH_3CO_2H$). $C_{26}H_{40}O_5$ requires *m/z* 432.2877].

2α,3α,22-*Triacetoxy*-23,24-*dinor*-5α-*cholan*-6-*one* (7).—A solution of the crude 22-alcohol (6) (11.9 g) in THF (150 ml) was treated with 10% perchloric acid (20 ml) under reflux for 3 h. The usual work-up (ethyl acetate for extraction) gave a crude product (11.2 g). This was treated with acetic anhydride (20 ml) and pyridine (20 ml) at 60 °C for 17 h. Removal of the solvent under reduced pressure and chromatography on silica gel (200 g) with benzene–ethyl acetate (20 : 1) as eluant provided the *triacetate* (7) [8.38 g, 60% overall from (5)], m.p. 212—213 °C (from methanol); δ_H ($CDCl_3$) 0.69 (3 H, s, 18-H_3), 0.82 (3 H, s, 19-H_3), 0.98 (3 H, d, *J* 7 Hz, 21-H_3), 1.96 (3 H, s, acetyl), 2.01 (3 H, s, acetyl), 2.06 (3 H, s, acetyl), 3.65—4.18 (2 H, m, 22-H_2), 4.82 (1 H, m, $w_{\frac{1}{2}}$ 22 Hz, 2β-H), and 5.30 (1 H, m, $w_{\frac{1}{2}}$ 9 Hz, 3β-H) (Found: C, 68.35; H, 8.7. $C_{28}H_{42}O_7$ requires C, 68.54; H, 8.63%).

2α,3α,22-*Triacetoxy*-B-*homo*-23,24-*dinor*-7-*oxa*-5α-*cholan*-6-*one* (8).—A solution of the 6-oxo steroid (7) (3.7 g, 7.55 mmol) in dichloromethane (16 ml) was treated with trifluoroperacetic acid [2 equiv.; prepared from 90% H_2O_2 (0.8 ml) and trifluoroacetic anhydride (5 ml) in dichloromethane (20 ml) at 0 °C] in the presence of disodium hydrogen phosphate (10 g) at 0 °C for 2 h. The usual work-up (dichloromethane for extraction) gave a crude product (3.7 g) which was applied to a column of silica gel (150 g). Elution with benzene–ethyl acetate (20 : 1) provided the *lactone* (8) (3.15 g, 83%), m.p. 240—241 °C (from methanol); $\delta_H(CDCl_3)$ 0.70 (3 H, s, 18-H_3), 0.95 (3 H, s, 19-H_3), 0.98 (3 H, d, *J* 7 Hz, 21-H_3), 1.96 (3 H, s, acetyl), 2.02 (3 H, s, acetyl), 2.07 (3 H, s, acetyl), 2.98 (1 H, dd, *J* 13 and 6 Hz, 5α-H), 3.80 (2 H, m, 22-H_2), 4.05 (2 H, m, 7a-H_2), 4.82 (1 H, m, $w_{\frac{1}{2}}$ 23 Hz, 2β-H), 5.30 (1 H, m, $w_{\frac{1}{2}}$ 7 Hz, 3β-H) (Found: C, 66.15; H, 8.4. $C_{28}H_{42}O_8$ requires C, 66.38; H, 8.36%).

22-*Hydroxy*-2α,3α-*isopropylidenedioxy*-B-*homo*-23,24-*dinor*-7-*oxa*-5α-*cholan*-6-*one* (9).—The triacetate (8) (3.1 g, 6.13 mmol) was treated with 5% KOH–MeOH (50 ml) under reflux for 1 h. After the mixture had cooled to room temperature, 6M HCl (30 ml) was added. The usual work-up (dichloromethane for extraction) provided a crude product (2.4 g). This was treated with acetone (50 ml) and toluene-*p*-sulphonic acid (50 mg) at room temperature for 2 h. To this reaction mixture was added saturated aqueous $NaHCO_3$ (30 ml). The usual work-up (diethyl ether for extraction) and chromatography on silica gel (50 g) with benzene–ethyl acetate (5 : 1) as eluant provided the *acetonide* (9) (2.45 g, 95%), m.p. 193—195 °C (from methanol); $\delta_H(CDCl_3)$ 0.70 (3 H, s, 18-H_3), 0.85 (3 H, s, 19-H_3), 1.00 (3 H, d, *J* 7 Hz, 21-H_3), 1.28 (3 H, s, acetonide), 1.48 (3 H, s, acetonide), 3.10—3.60 (3 H, m, 5α-H and 22-H_2), 4.05 (2 H, m, 7a-H_2), and 4.32 (2 H, m, 2β- and 3β-H) (Found: C, 71.2; H, 9.65. $C_{25}H_{40}O_5$ requires C, 71.39; H, 9.59%).

(20S)-2α,3α-*Isopropylidenedioxy*-6-*oxo*-B-*homo*-7-*oxa*-5α-*pregnane*-20-*carbaldehyde* (11).—A solution of the alcohol (9) (2.05 g, 4.88 mmol) in dichloromethane (70 ml) was treated with pyridinium chlorochromate (1.5 g, 6.98 mmol) in the presence of sodium acetate (200 mg) at room temperature for 4 h. To this reaction mixture was added diethyl ether (500 ml) was added. Filtration through a short column of Florisil and removal of the solvent under reduced pressure gave a crude product (1.9 g) which was applied to a column of silica gel (50 g). Elution with benzene–ethyl acetate (10 : 1) provided the *aldehyde* (11) (1.54 g, 75%) as an oil; $\delta_H(CDCl_3)$ 0.73 (3 H, s, 18-H_3), 0.85 (3 H, s, 19-H_3), 1.08 (3 H, d, *J* 7 Hz, 21-H_3), 1.27 (3 H, s, acetonide), 1.48 (3 H, s, acetonide), 3.30 (1 H, dd, *J* 8 and 7 Hz, 5α-H), 4.05 (2 H, m, 7α-H_2), 4.32 (2 H, m, 2β- and 3β-H), and 9.55 (1 H, d, *J* 3 Hz, CHO) [Found: *m/z* 403.2484 ($M^+ - CH_3$). $C_{24}H_{35}O_5$ requires *m/z* 403.2486].

6-*Ethylenedioxy*-2α,3α-*isopropylidenedioxy*-23,24-*dinor*-5α-*cholan*-22-*ol* (10).—The triacetate (7) (3.5 g, 7.14 mmol)

was converted, as described for (9), into 22-hydroxy-2α,3α-isopropylidenedioxy-23,24-dinor-5α-cholan-6-one (2.85 g, 94%). This was acetalized, as described for (6), to give the *22-alcohol* (10) (2.9 g, 98%) as an oil; $\delta_H(CDCl_3)$ 0.68 (3 H, s, 18-H_3), 0.82 (3 H, s, 19-H_3), 0.98 (3 H, d, *J* 7 Hz, 21-H_3), and 3.2—4.4 (8 H, m, 2β-H, 3β-H, 22-H_2, and OCH_2CH_2O) (Found: M^+, 448.3191. $C_{27}H_{44}O_5$ requires *M*, 448.3190).

(20S)-6-*Ethylenedioxy*-2α,3α-*isopropylidenedioxy*-23,24-*dinor*-5α-*cholan*-22-*al* (12).*—The 22-alcohol (10) (2.9 g, 6.47 mmol) was oxidized, as described for (11), to provide the *aldehyde* (12) (2.1 g, 73%), m.p. 120—123 °C (from diethyl ether–hexane); $\delta_H(CDCl_3)$ 0.71 (3 H, s, 18-H_3), 0.83 (3 H, s, 19-H_3), 0.98 (3 H, d, *J* 7 Hz, 21-H_3), 3.60—4.40 (6 H, m, 2β-H, 3β-H, and OCH_2CH_2O), and 9.50 (1 H, d, *J* 4 Hz, CHO) (Found: C, 72.45; H, 9.55. $C_{27}H_{42}O_5$ requires C, 72.61; H, 9.48%).

(22R)-2α,3α-*Isopropylidenedioxy*-22-*methoxymethoxy*-6-*oxo*-B-*homo*-24-*nor*-7-*oxa*-5α-*cholan*-23-*al Trimethylene Dithioacetal* (13).†—A solution of n-butyl-lithium in hexane (0.8 ml, 1.25 mmol) was added to a solution of 1,3-dithiane (140 mg, 1.17 mmol) in THF (5 ml) at 0 °C under argon. This mixture was stirred at room temperature for 1 h and was then added dropwise to a solution of the aldehyde (11) (434 mg, 1.04 mmol) in THF (5 ml) at −20 °C under argon. The mixture was stirred at −20 °C for 1 h and was then treated with water. The usual work-up (diethyl ether for extraction) gave a crude product (600 mg), a solution of which in dioxane (10 ml) was treated with chloromethyl methyl ether (2 ml) and *N*,*N*-diethylcyclohexylamine (4 ml) at 50 °C for 19 h. The usual work-up (ethyl acetate for extraction) gave a crude product (755 mg) which was applied to a column of silica gel (30 g). Elution with benzene–ethyl acetate (10 : 1) provided the *dithiane* (13) (507 mg, 85%) as an oil; $\delta_H(CDCl_3)$ 0.70 (3 H, s, 18-H_3), 0.83 (3 H, s, 19-H_3), 0.96 (3 H, d, *J* 7 Hz, 21-H_3), 1.26 (3 H, s, acetonide), 1.47 (3 H, s, acetonide), 2.75 (4 H, m, $SCH_2CH_2CH_2S$), 3.36 (3 H, s, OCH_2OCH_3), 3.58 (1 H, d, *J* 8 Hz, 23-H), 4.07 (2 H, m, 7a-H_2), 4.18 (1 H, d, *J* 8 Hz, 22-H), 4.30 (2 H, m, 2β- and 3β-H), and 4.70 (2 H, s, OCH_2OCH_3) [Found: *m*/*z* 567.2821 ($M^+ - CH_3$). $C_{30}H_{47}O_6S_2$ requires *m*/*z* 567.2816).

(22R)-6-*Ethylenedioxy*-2α,3α-*isopropylidenedioxy*-22-*methoxymethoxy*-24-*nor*-5α-*cholan*-23-*al Trimethylene Dithioacetal* (14).‡—A solution of the aldehyde (12) (1.6 g, 3.59 mmol) in THF (15 ml) was added at −20 °C to a solution of the lithium salt of 1,3-dithiane (1.3 equiv.) which was prepared as described above. This mixture was stirred at −20 °C under argon for 1 h. The usual work-up (diethyl ether for extraction) gave a crude product (2.1 g). This was converted, as described for (13), to the *methoxymethyl ether* (14) (1.85 g, 84%), an oil; $\delta_H(CDCl_3)$ 0.69 (3 H, s, 18-H_3), 0.82 (3 H, s, 19-H_3), 1.00 (3 H, d, *J* 7 Hz, 21-H_3), 1.25 (3 H, s, acetonide), 1.39 (3 H, s, acetonide), 2.76 (4 H, m, $SCH_2CH_2CH_2S$), 3.40 (3 H, s, OCH_2OCH_3), 4.31 (2 H, m, 2β- and 3β-H), and 4.70 (2 H, s, OCH_2OCH_3) [Found: *m*/*z* 595.3132 ($M^+ - CH_3$). $C_{32}H_{51}O_6S_2$ requires *m*/*z* 595.3129].

(22R)-2α,3α-*Isopropylidenedioxy*-22-*methoxymethoxy*-6-*oxo*-B-*homo*-24-*nor*-7-*oxa*-5α-*cholan*-23-*al* (15).—To a suspension of red mercury(II) oxide (200 mg, 0.926 mmol) in THF–H_2O (1 : 1; 20 ml) was added boron trifluoride–diethyl ether (0.1 ml) at room temperature. The mixture was stirred at room temperature for 10 min. To this reagent was added a solution of the dithiane (13) (180 mg, 0.309 mmol) in THF (5 ml) was added at room temperature. The mixture was stirred at room temperature for 30 min. To this reaction mixture was added saturated aqueous $NaHCO_3$ (10 ml). Filtration through Hyplo Super-Cel, extraction with diethyl ether, and the usual work-up provided the *aldehyde* (15) (153 mg, 99%) as an oil; $\delta_H(CDCl_3)$ 0.75 (3 H, s, 18-H_3), 0.88 (3 H, s, 19-H_3), 0.92 (3 H, d, *J* 7 Hz, 21-H_3), 1.32 (3 H, s, acetonide), 1.51 (3 H, s, acetonide), 3.41 (3 H, s, OCH_2OCH_3), 4.08 (2 H, m, 7a-H_2), 4.35 (2 H, m, 2β- and 3β-H), 4.70 (2 H, s, OCH_2OCH_3), and 9.70 (1 H, s, CHO [Found: *m*/*z* 477.2855 ($M^+ - CH_3$). $C_{27}H_{41}O_7$ requires *m*/*z* 477.2853].

(22R)-6-*Ethylenedioxy*-2α,3α-*isopropylidenedioxy*-22-*methoxymethoxy*-24-*nor*-5α-*cholan*-23-*al* (16).—The dithiane (14) (750 mg, 1.23 mol) was converted, in the same manner as described for (15), into the *aldehyde* (16) (650 mg, 99%), an oil; $\delta_H(CDCl_3)$ 0.69 (3 H, s, 18-H_3), 0.82 (3 H, s, 19-H_3), 0.92 (3 H, d, *J* 7 Hz, 21-H_3), 1.25 (3 H, s, acetonide), 1.38 (3 H, s, acetonide), 3.40 (3 H, s, OCH_2OCH_3), 3.88 (4 H, br s, OCH_2CH_2O), 4.67 (2 H, s, OCH_2OCH_3), and 9.69 (1 H, s, CHO) [Found: *m*/*z* 505.3167 ($M^+ - CH_3$), $C_{29}H_{45}O_7$ requires *m*/*z* 505.3167].

(22R,23R)-23-*Hydroxy*-2α,3α-*isopropylidenedioxy*-22-*methoxymethoxy*-B-*homo*-7-*oxa*-5α-*ergost*-24(28)-*en*-6-*one* (17).—The Grignard reagent (0.9 equiv.), prepared from 2-bromo-3-methylbut-1-ene, was added dropwise to a solution of the aldehyde (15) (153 mg, 0.309 mmol) in THF (10 ml) at −78 °C under argon. The mixture was stirred at −78 °C for 2 h. The usual work-up (diethyl ether for extraction) gave a crude product (162 mg) which was applied to a column of silica gel (50 g). Elution with benzene–ethyl acetate (10 : 1) provided the starting material (15) (60 mg) and the (22*R*,23*R*)-23-ol (17) [77 mg, 44%, 73% based on consumed (15)] as an amorphous solid; $\delta_H(CDCl_3)$ 0.69 (3 H, s, 18-H_3), 0.89 (3 H, s, 19-H_3), 1.32 (3 H, s, acetonide), 1.50 (3 H, s, acetonide), 3.32 (3 H, s, OCH_2OCH_3), 3.51 (1 H, m, 22-H), 4.00—4.30 (3 H, m, 7a-H_2 and 23-H), 4.35 (2 H, m, 2β- and 3β-H), 4.60 (2 H, s, OCH_2OCH_3), 4.98 (1 H, br s, $w_{\frac{1}{2}}$ 5 Hz, 28-H), and 5.11 (1 H, d, *J* 6 Hz, 28-H).

(22R,23R)-6-*Ethylenedioxy*-2α,3α-*isopropylidenedioxy*-22-*methoxymethoxy*-5α-*ergost*-24(28)-*en*-23-*ol* (18).—A solution of the aldehyde (16) (600 mg, 1.15 mmol) in THF (10 ml) was treated with the Grignard reagent as described above for (17) to provide, after chromatography, the (22*R*,23*R*)-23-ol (18) (485 mg, 71%) as an amorphous solid; $\delta_H(CDCl_3)$ 0.68 (3 H, s, 18-H_3), 0.84 (3 H, s, 19-H_3), 1.26 (3 H, s, acetonide), 1.40 (3 H, s, acetonide), 3.32 (3 H, s, OCH_2OCH_3), 3.50 (1 H, m, 22-H), 3.60—4.40 (7 H, m, 2β-H, 3β-H, 23-H, and OCH_2CH_2O), 4.60 (2 H, s, OCH_2OCH_3), 4.98 (1 H, br s, $w_{\frac{1}{2}}$ 5 Hz, 28-H), and 5.11 (1 H, d, *J* 6 Hz, 28-H).

(22R,23R)-2α,3α,22,23-*Tetra-acetoxy*-B-*homo*-7-*oxa*-5α-*ergost*-24(28)-*en*-6-*one*, *Dolicholide Tetra-acetate* (19).—The alcohol (17) (77 mg, 0.133 mmol) was treated with acetic anhydride (2 ml) and pyridine (2 ml) at 65 °C for 17 h. Removal of the solvent under reduced pressure gave a crude product (83 mg). This was treated with 10% aqueous perchloric acid (5 ml) and THF (10 ml) at 50 °C for 2 h. The usual work-up (ethyl acetate for extraction) gave a crude product (67 mg). This was acetylated as described above at 65 °C for 19 h. Removal of the solvent under reduced pressure gave a crude product (78 mg) which was applied to a column of silica gel (30 g). Elution with benzene–ethyl acetate (20 : 1)

* 6-Ethylenedioxy-2α,3α-isopropylidenedioxy-5α-pregnane-20-carbaldehyde.

† (22*R*)-22-(1,3-Dithian-2-yl)-2α,3α-isopropylidenedioxy-22-methoxymethoxy-7a-homo-23,24-dinor-7-oxa-5α-cholan-6-one.

‡ (22*R*)-22-(1,3-Dithian-2-yl)-6-ethylenedioxy-2α,3α-isopropylidenedioxy-22-methoxymethoxy-23,24-dinor-5α-cholane.

provided dolicholide tetra-acetate (19) (69 mg, 80%) as an oil; $\delta_H(CDCl_3$; 400.5 MHz) 0.60 (3 H, s, 18-H_3), 0.91 (3 H, s, 19-H_3), 1.02 (3 H, d, *J* 7 Hz, 21-H_3), 1.06 (3 H, d, *J* 7 Hz, 26-H_3), 1.11 (3 H, d, *J* 7 Hz, 27-H_3), 1.93 (3 H, s, acetyl), 1.94 (3 H, s, acetyl), 1.99 (3 H, s, acetyl), 2.06 (3 H, s, acetyl), 2.94 (1 H, dd, *J* 11.4 and 4.3 Hz, 5α-H), 4.04 (2 H, m, 7a-H_2), 4.81 (1 H, m, $w_{\frac{1}{2}}$ 23 Hz, 2β-H), 5.09 (1 H, s, 28-H), 5.16 (1 H, s, 28-H), 5.19 (1 H, d, *J* 9.4 Hz, 22-H), 5.31 (1 H, br s, $w_{\frac{1}{2}}$ 8.6 Hz, 3β-H), and 5.36 (1 H, d, *J* 9.4 Hz, 23-H).

(22R,23R)-2α,3α,22,23-*Tetra-acetoxy*-5α-*ergost*-24(28)-*en*-6-*one*, *Dolichosterone Tetra-acetate* (20).—The alcohol (18) (525 mg, 0.89 mmol) was converted, in the same manner as described for (19), into dolichosterone tetra-acetate (20) (477 mg, 81%), an oil; $\delta_H(CDCl_3$; 100 MHz) 0.64 (3 H, s, 18-H_3), 0.83 (3 H, s, 19-H_3), 1.02 (3 H, d, *J* 7 Hz, 21-H_3), 1.06 (3 H, d, *J* 7 Hz, 26-H_3), 1.11 (3 H, d, *J* 7 Hz, 27-H_3), 2.00 (3 H, s, acetyl), 2.01 (3 H, s, acetyl), 2.06 (3 H, s, acetyl), 2.09 (3 H, s, acetyl), 2.56 (1 H, dd, *J* 9 and 8 Hz, 5α-H), 4.95 (1 H, m, $w_{\frac{1}{2}}$ 23 Hz, 2β-H), 5.09 (1 H, s, 28-H), 5.16 (1 H, s, 28-H), 5.20 (1 H, d, *J* 9 Hz, 22-H), 5.31 (1 H, br s, $w_{\frac{1}{2}}$ 8 Hz, 3β-H), and 5.38 (1 H, d, *J* 9 Hz, 23-H).

(22R,23R)-2α,3α,22,23-*Tetrahydroxy*-B-*homo*-7-*oxa*-5α-*ergost*-24(28)-*en*-6-*one*, *Dolicholide* (3).—The tetra-acetate (19) (69 mg, 0.107 mmol) was treated with 5% KOH–MeOH (10 ml) under reflux for 1 h. After the solution had cooled to room temperature, 6M HCl (10 ml) was added. The mixture was stirred at room temperature for 1 h. The usual work-up (ethyl acetate for extraction) provided dolicholide (3) (47 mg, 93%), m.p. 238—242 °C (from aqueous acetonitrile) (lit.,[26] 234—238 °C); $\delta_H(CDCl_3$; 400.5 MHz) 0.65 (3 H, s, 18-H_3), 0.92 (3 H, s, 19-H_3), 0.95 (3 H, d, *J* 7 Hz, 21-H_3), 1.08 (3 H, d, *J* 8 Hz, 26-H_3), 1.11 (3 H, d, *J* 8 Hz, 27-H_3), 2.26 (1 H, septet, 25-H), 3.11 (1 H, dd, *J* 12.5 and 5 Hz, 5α-H), 3.62 (1 H, d, *J* 8 Hz, 22-H), 3.72 (1 H, m, $w_{\frac{1}{2}}$ 22 Hz, 2β-H), 4.02 (1 H, br s, 3β-H), 4.03 (1 H, d, *J* 8 Hz, 23-H), 4.09 (2 H, m, 7a-H_2), 5.05 (1 H, s, 28-H), and 5.08 (1 H, s, 28-H); *m/z* 379 [M^+ − 99; C-22–C-23 cleavage], 361, 343, 331, 325, 321, 303, 285, 100 (base; 99 + H), 85, and 43 [Found: *m/z* 379.2487 (M^+ − 99). Calc. for $C_{22}H_{35}O_5$: *m/z* 379.2486; *m/z* 100.0875 (99 + H). Calc. for $C_6H_{12}O$: *m/z* 100.0889] (Found: C, 70.15; H, 9.7. $C_{28}H_{46}O_6$ requires C, 70.26; H, 9.69%).

(22R,23R)-2α,3α,22,23-*Tetrahydroxy*-5α-*ergost*-24(28)-*en*-6-*one*, *Dolichosterone* (4).—The tetra-acetate (20) (250 mg, 0.398 mmol) was treated with 5% KOH–MeOH (20 ml) under reflux for 1 h. The usual work-up (ethyl acetate for extraction) provided dolichosterone (4) (170 mg, 92%), m.p. 232—235.5 °C (from aqueous acetonitrile) (lit.,[27] 233—237 °C); $\delta_H(CDCl_3$, 400.5 MHz) 0.62 (3 H, s, 18-H_3), 0.75 (3 H, s, 19-H_3), 0.96 (3 H, d, *J* 7 Hz, 21-H_3), 1.09 (3 H, d, *J* 7 Hz, 26-H_3), 1.11 (3 H, d, *J* 7 Hz, 27-H_3), 1.92 (1 H, dt, *J* 15.7 and 4.3 Hz), 2.26 (1 H, septet, 25-H), 2.29 (1 H, dd, *J* 12.9 and 4.3 Hz), 2.69 (1 H, dd, *J* 13 and 3 Hz, 5α-H), 3.62 (1 H, d, *J* 8 Hz, 22-H), 3.77 (1 H, m, $w_{\frac{1}{2}}$ 23 Hz, 2β-H), 4.03 (1 H, d, *J* 8 Hz, 23-H), 4.05 (1 H, br s, $w_{\frac{1}{2}}$ 8.5 Hz, 3β-H), 5.04 (1 H, s, 28-H), and 5.07 (1 H, s, 28-H); mass spectrum (20 eV) *m/z* 363 [M^+ − 99; C-22–C-23 cleavage], 345, 333, 315, 305, 287, 269, 100 (base; 99 + H), and 85 [Found: *m/z* 363.2538 (M^+ − 99). Calc. for $C_{22}H_{35}O_5$: *m/z* 363.2537; *m/z* 100.0882 (99 + H). Calc. for $C_6H_{12}O$: *m/z* 100.0889] (Found: C, 72.55; H, 9.95. $C_{28}H_{46}O_5$ requires C, 72.69; H, 10.02%).

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