Studies on Synthesis of Plant Growth Hormone Steroids. Part 16.† Stereoselective Synthesis of 26,27-Dinorbrassinolide

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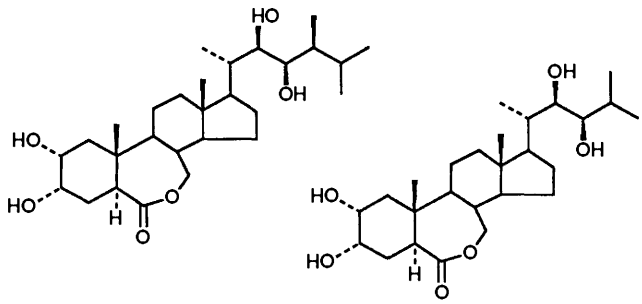
26,27-Dinorbrassinolide, having a (20*S*,22*R*,23*R*)-22,23-dihydroxy-unit side-chain, was stereoselectively synthesized from hyodeoxycholic acid *via* successive lactonization, oxidation, and reduction of the key intermediate (*Z*)-(**7**).

Since the discovery of the new plant growth promoter brassinolide (**1**) from the pollen of rape (*Brassica napus*),[1] much effort has been expended to synthesize its analogues and to study the relationship between structure and biological activity.[2] In 1984, Ikekawa and co-workers first synthesized 26,27-dinorbrassinolide (**2**) and found that it had almost the same activity as brassinolide (**1**) in both the Raphanus and rice-lamina inclination tests.[3] In 1987, Kametani *et al.* also synthesized compound (**2**), by another synthetic route.[4] Compound (**2**) may find practical application in agriculture because of its simple structure and high biological activity.



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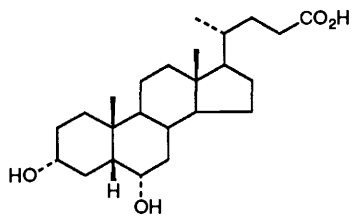


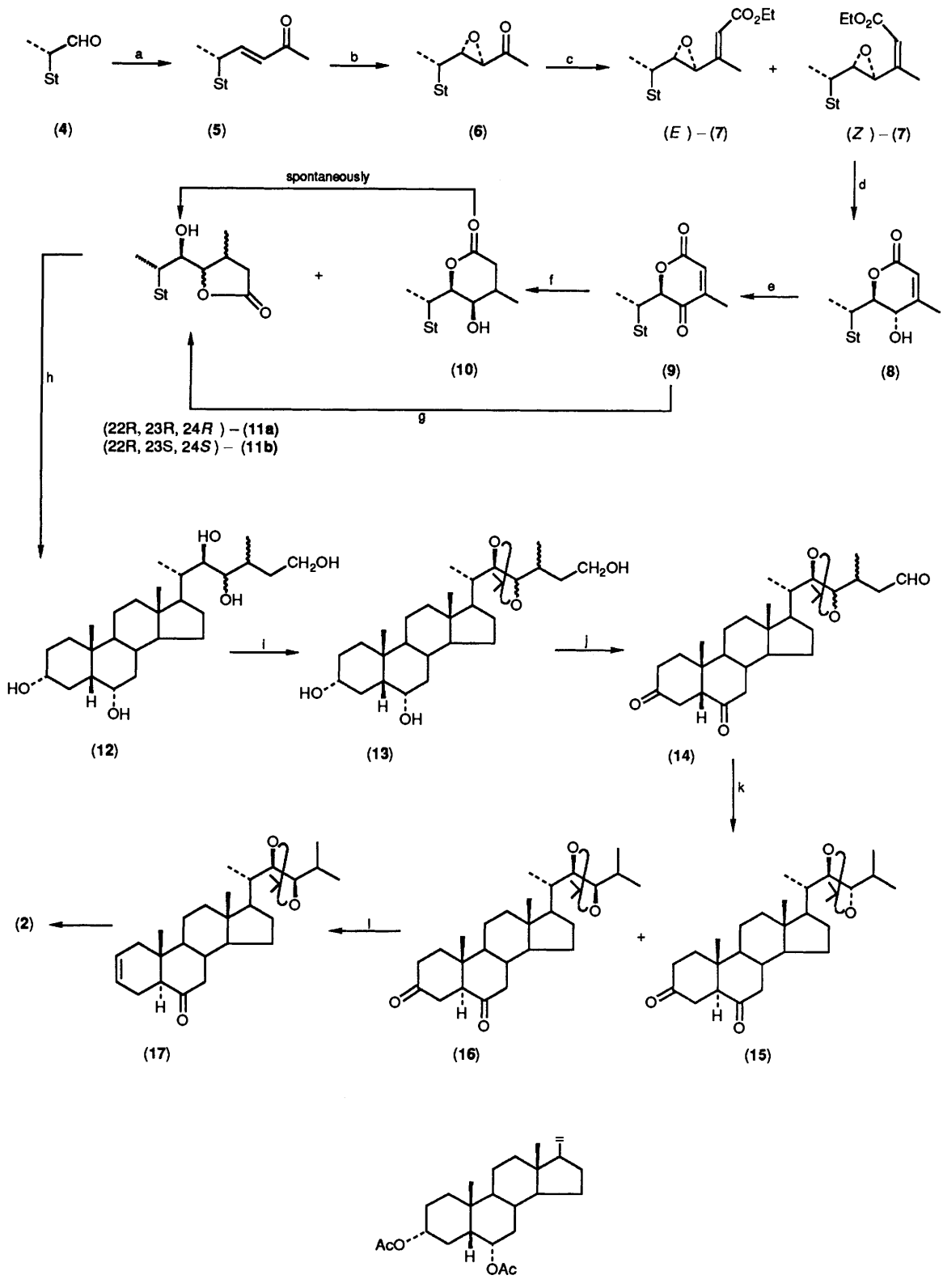
(3)

Recently, one of us developed a new method for the construction of the brassinolide side-chain, from which brassinolide and its analogues were synthesized.[5] This method involves the stereoselective transformation of (*Z*)-γ,δ-epoxy-α,β-unsaturated acid esters under acidic conditions to form the (22*R*,23*S*)-22,23-dihydroxy-α,β-unsaturated δ-lactone [*cf.* (**7**) ⟶ (**8**)]. We now report the synthesis of 26,27-dinorbrassinolide (**2**) from hyodeoxycholic acid (**3**) by this method (Scheme 1).

The 20-carbaldehyde (**4**) obtained from hyodeoxycholic acid (**3**) *via* oxidative decarboxylation and ozonization[6] was treated with (2-oxopropyl)triphenylarsonium bromide[7] in the presence of potassium carbonate to form α,β-unsaturated ketone (**5**) in 84% yield. From the doublet peak of the 21-H_3 signal (1.09, *J* 6.6 Hz) in the ^{1}H NMR spectrum, it is obvious that the configuration of the 20-CH_3 group remains unchanged.[8] From the *J*-value of 22-H and 23-H (15.5 Hz), the configuration of the double bond in compound (**5**) was shown to be *E*. Epoxidation of compound (**5**) with 30% H_2O_2–4M-NaOH[9] provided the α-epoxy ketone (**6**) in 97% yield. The Wittig–Horner reaction of ethoxycarbonylmethylphosphonic acid dimethyl ester[10] with ketone (**6**) furnished a mixture of *Z*- and *E*-γ,δ-epoxy-α,β-unsaturated acid ester (*Z*)-(**7**) and (*E*)-(**7**) in 99% yield in the ratio 2.6:1 which was determined on the basis of the ratio of the integrations of (*Z*)-(**7**), 4.41 (1 H, s, 23-H) and (*E*)-(**7**), 3.02 (1 H, s, 23-H) in the ^{1}H NMR spectrum. The mixture of (*Z*)-(**7**) and (*E*)-(**7**) could be separated by flash column chromatography or simply by recrystallization. Attempted photoisomerization of (*E*)-(**7**) to (*Z*)-(**7**) failed.[11] This key intermediate (*Z*)-(**7**) was lactonized with 30% perchloric acid[10] to give (22*R*)-α,β-unsaturated δ-lactone (**8**), formed stereoselectively by the carboxylate-aided epoxide ring opening of (*Z*)-(**7**) with inversion of configuration at C-22 in quantitative yield. The 22*R*-configuration of δ-lactone (**8**) was determined by its circular dichroism (CD) spectrum which showed a strong negative peak at 256 nm.[10] The 23*S*-hydroxy group of (**8**) could be easily converted into a 23*R*-hydroxy compound by successive oxidation and stereoselective reduction.[12] Thus, oxidation of compound (**8**) with pyridinium chlorochromate (PCC) gave keto compound (**9**) in quantitative yield; low-pressure catalytic hydrogenation of ketone (**9**) at 30 °C with platinum dioxide then afforded quantitatively a mixture of thermodynamically stable γ-lactones (**11a**) (77%) and (**11b**) (23%).‡ A small amount of pure lactone (**11a**) could be obtained from the mixture of (**11a** and **b**) (see Experimental section) and the configuration at C-22 and C-23 in (**11a**) was assigned as *R*,*R* on comparison with its analogues by ^{1}H NMR spectroscopy.[5,12] Catalytic hydrogenation of lactone (**9**) with platinum dioxide at 10 °C provided a mixture of δ-lactone (**10**) and γ-lactones (**11a** and **b**), in the ratio 1:1 [(**10a**):(**11a** and **b**)] as shown in ^{1}H NMR spectroscopy, in quantitative yield. Pure compound (**10**) could not be obtained because it spontaneously gave γ-lactone (**11a**). Its presence was assumed from the ^{1}H NMR signals at 4.25 (1 H, s, 22-H) and 3.74 (1 H, s, 23-H) of the aforementioned mixture of (**10**) and (**11a** and **b**).[5] Catalytic hydrogenation of compound (**9**) with 5% palladium–carbon in ethanol at room temperature provided γ-keto-δ-lactone (**18**) in 72% yield (Scheme 2), its stereoisomeric γ-keto-δ-lactone (**19**) in

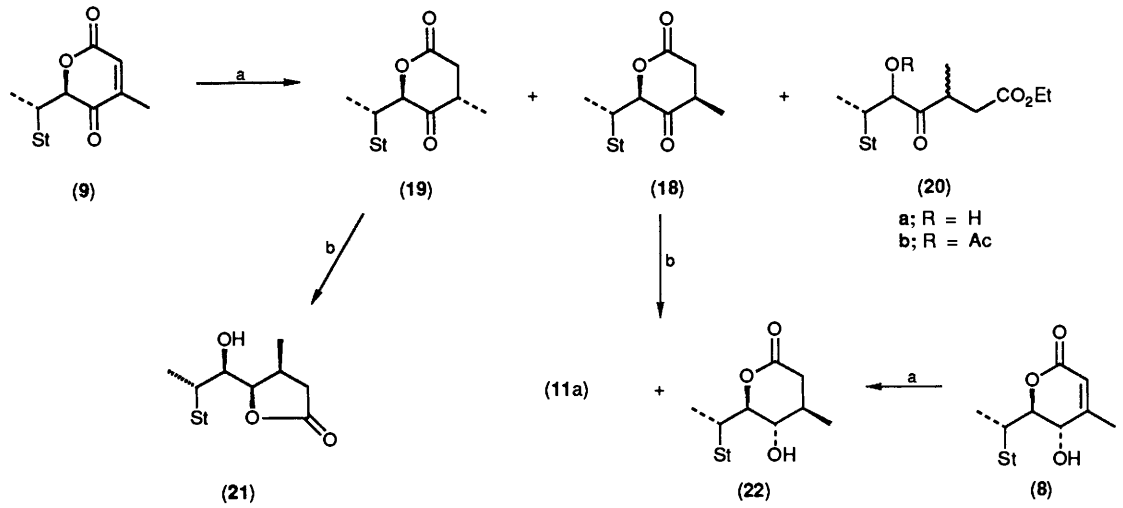
† Part 15, Formal Synthesis of Brassinolide *via* Stereoselective Sulphenate–Sulphoxide Transformation, W. S. Zhou and Z. W. Shan, *J. Chem. Soc., Chem. Commun.*, submitted for publication.

‡ The proportions of lactones (**11a** and **b**) in the mixture were calculated from the later conversion of the mixture into the 26,27-dinorbrassinolide-22,23-acetonides.



Scheme 1. *Reagents and conditions:* (a) $Ph_3As^+CH_2Ac$, Br^-–K_2CO_3–CH_2Cl_2–THF–trace water, room temp. overnight; (b) i, 30% H_2O_2–4M-NaOH–EtOH, 35 °C, 2 h; ii, Ac_2O–Py; (c) i, $(MeO)_2P(O)CH_2CO_2Et$–NaH–THF, room temp., 2 h; ii, Ac_2O–Py; (d) 30% $HClO_4$–MeOH, room temp., 0.5 h; (e) PCC–CH_2Cl_2, room temp.; (f) H_2/PtO_2–EtOH, 10 °C; (g) H_2/PtO_2–EtOH, 30 °C; (h) $LiAlH_4$–THF, reflux, 4 h; (i) $(MeO)_2CMe_2$–acetone–p-TsOH, room temp., 1 h; (j) PDC–CH_2Cl_2– 4 Å MS, room temp.; (k) i, $Rh(PPh_3)_3Cl$–toluene, reflux, 6 h; ii, *p*-TsOH–acetone, room temp., overnight; (l) Zn(Hg)–Me_3SiCl–THF, room temp., 12 h.

4% yield, and ester-exchanged product (**20a**) in 20% yield. Reduction of compound (**19**) with sodium borohydride gave quantitatively the known compound (22*R*,23*R*,24*S*)-22,23-dihydroxy-24-methyl-γ-lactone (**21**).[13] Reduction of compound



Scheme 2. *Reagents and conditions:* (a) 5% Pd/C–H_2–EtOH, room temp.; (b) $NaBH_4$–CH_2–Cl_2–MeOH, room temp.

(**18**) with sodium borohydride afforded γ-lactone (**11a**) (89% yield) and γ(α)-hydroxy-δ-lactone (**22**) (10% yield), which could also be obtained quantitatively from catalytic hydrogenation of compound (**8**) with 5% palladium–carbon in ethanol (Scheme 2).

Stereoselectivity in the reduction of compound (**9**) can be rationalized by assuming that reduction will occur mostly from the less hindered side of the lactone as shown in the Figure (see Structures A, B).[12,14,15] Catalytic hydrogenation of compound (**8**) with 5% palladium–carbon in ethanol at room temperature gave (quantitatively) 24β-methyl compound (**22**) in high stereoselectivity which results not only from the steric hindrance but also from the interaction between the catalyst and the hydroxy group, the so-called hydroxy-group effect.[16] (Figure, structure C).

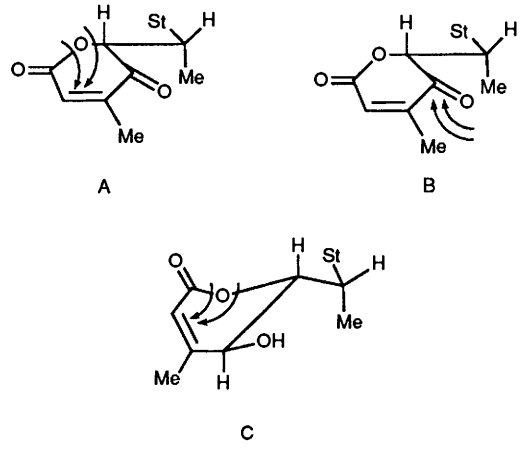


Figure.

In conclusion, catalytic hydrogenation of compound (**9**) with platinum dioxide in ethanol at 30 °C gave γ-lactone (**11a**) in 77% yield in one step, whereas catalytic hydrogenation with 5% palladium–carbon in ethanol at room temperature provided γ-keto-δ-lactone (**18**) in 72% yield; the product was reduced with sodium borohydride to give γ-lactone (**11a**) in 89% yield. The overall yield of the two steps is 64%.

The next task was to synthesize the target compound (**2**) from compound (**11a**). The mixture of lactones (**11a**) and (**11b**) was directly reduced with lithium aluminium hydride to give the hydroxy compound (**12**) in 96% yield. Compound (**12**) was treated with 2,2-dimethoxypropane to form the 22,23-acetonide (**13**) (87% yield), oxidation of which with pyridinium dichromate (PDC) in the presence of 4 Å molecular sieves gave aldehyde (**14**) in 76% yield. Compound (**14**) was submitted to catalytic decarbonylation with tris(triphenylphosphine)-rhodium chloride[17] followed by 5-H isomerization with toluene-*p*-sulphonic acid (PTSA) to afford a mixture of isomers (**15**) and (**16**) in 71% yield, which was separated by flash column chromatography to give (22*R*,23*R*)-(**16**) (55%) and (22*R*,23*S*)-(**15**) (16%). Compound (**16**) was subjected to reductive elimination by treatment with chlorotrimethylsilane (TMSCl) and zinc amalgam[18] to give Δ^2-6-oxo compound (**17**)[3] in 57% yield. Compound (**17**) can be converted into target compound (**2**) by a known procedure.[3] Thus, compound (**17**) has been stereoselectively synthesized from hyodeoxycholic acid (**3**) in 14 steps in 9% total yield.

Experimental

M.p.s were determined on a Kofler heating-stage microscope and are uncorrected. IR spectra were recorded on a Shimazhi IR-440 spectrophotometer. ^1H NMR spectra were obtained on a JEOL FX90Q (90 MHz), Varian XL200 (200 MHz), or a Bruker AM400 (400 MHz) spectrometer with tetramethylsilane as internal reference. Mass spectra were measured with a Finnigan 4021 spectrometer. High-resolution mass spectra were measured with a Finnigan MAT 8430 spectrometer. CD spectra were determined on a Jasco J-500C spectropolarimeter. Optical rotations were recorded on a Autopol-III polarimeter. Flash column chromatography was performed on silica gel H.

Usual work-up refers to dilution with water, extraction with dichloromethane or ethyl acetate, washing of the extract with saturated brine to neutrality, drying ($MgSO_4$), and removal of the solvent under reduced pressure. Light petroleum refers to the fraction boiling over the range 60–90 °C.

Preparation of Compound (**5**).—A solution of the Δ^{22}-steroid (12.5 g, 29.1 mmol), obtained from hyodeoxycholic acid (**3**)[6] in pyridine (10 ml), anhydrous dichloromethane (130 ml), and methanol (60 ml) was cooled to −78 °C and ozonized until the colour of solution became blue. The solution was then bubbled with N_2 and dimethyl sulphide (10 ml) was added. The mixture was stirred at room temperature for 1.5 h. The solvent was then removed under reduced pressure, and acetone (100 ml) was added. The solution was acidified with 10% hydrochloric acid. Usual work-up gave crude product (**4**), used directly for the next step.

Compound (**4**) was dissolved in dichloromethane–THF (3:1,

100 ml), and (2-oxopropyl)triphenylarsonium bromide (17.3 g, 39 mmol), potassium carbonate (5.4 g, 39 mmol), and water (1 ml) were added. The mixture was stirred at room temperature under N_2 overnight, then filtered and evaporated, and the residue was purified by flash column chromatography [light petroleum–ethyl acetate (4:1) as eluant] to give α,β-unsaturated ketone (**5**) as a solid (11.5 g, 84%), m.p. 148–150 °C (from light petroleum) (lit.,[9] 152–153 °C); the spectroscopic data were identical with those reported.[9]

Epoxidation of Enone (**5**) *with Hydrogen Peroxide to give the Oxirane* (**6**).—To a solution of compound (**5**) (11 g, 25.5 mmol) in 95% ethanol (600 ml) were added 4M-NaOH (30 ml) and 30% H_2O_2 (20 ml). The mixture was stirred at 35 °C for 2 h and then evaporated. After usual work-up, the residue was dissolved in acetic anhydride (20 ml) and anhydrous pyridine (40 ml), and the solution was stirred at room temperature overnight. Usual work-up followed by flash column chromatography [light petroleum–ethyl acetate (4:1)] gave compound (**6**) as a solid (11 g, 97%), m.p. 85–86 °C (lit.,[9] 85–88 °C); the spectroscopic data were identical with those reported.[9]

Wittig-Horner Reaction of Ketone (**6**) *to give the Unsaturated Ester* (**7**).—80% NaH (6.57 g, 0.217 mol; washed with anhydrous light petroleum) was suspended in anhydrous THF (500 ml), and a solution of ethoxycarbonylmethylphosphonic acid dimethyl ester (43 g, 0.219 mol) in THF (100 ml) was added. The mixture was stirred at room temperature for 1 h and then a solution of the ketone (**6**) (11 g, 22.5 mmol) in THF (100 ml) was added. The reaction mixture was stirred at room temperature for 2 h and the solvent was removed under reduced pressure. After usual work-up, the residue was dissolved in acetic anhydride (30 ml) and anhydrous pyridine (50 ml), and the solution was stirred at room temperature overnight. Usual work-up gave a mixture of esters (*Z*)-(**7**) and (*E*)-(**7**) (12.5 g, 99%). (*Z*)-(**7**) and (*E*)-(**7**) were separated by flash column chromatography [light petroleum–ethyl acetate (15:1)] or recrystallization. *Ester* (*Z*)-(**7**) had m.p. 96–98 °C; $[\alpha]_D$ +97.4° (*c* 0.52, $CHCl_3$) (Found: C, 70.9; H, 9.5. $C_{33}H_{50}O_7$ requires C, 70.94; H, 9.02%); ν_{max}(KCl) 1 720 and 1 630 cm^{-1}; δ_H(200 MHz; $CDCl_3$) 0.66 (3 H, s, 18-H_3), 0.99 (3 H, s, 19-H_3), 1.06 (3 H, d, *J* 6.06 Hz, 21-H_3), 1.30 (3 H, t, *J* 7.12 Hz, OCH_2Me), 1.71 (3 H, d, *J* 1.30 Hz, 25-H_3), 2.03 and 2.06 (6 H, s, AcO), 2.74 (1 H, dd, *J* 6.6, 1.8 Hz, 22-H), 4.20 (2 H, q, *J* 7.12 Hz, OCH_2Me), 4.41 (1 H, s, 23-H), 4.74 (1 H, m, 3-H), 5.20 (1 H, m, 6-H), and 5.88 (1 H, s, 26-H); *m/z* 543 ($M^+ - CH_3$).

Compound (*E*)-(**7**) had $[\alpha]_D$ +14.95° (*c* 3.15, $CHCl_3$) (Found: C, 71.5; H, 9.45%); ν_{max}(film) 1 720 and 1 660 cm^{-1}; δ_H(200 MHz; $CDCl_3$) 0.61 (3 H, s, 18-H_3), 0.94 (3 H, s, 19-H_3), 1.06 (3 H, d, *J* 6.06 Hz, 21-H_3), 1.30 (3 H, t, *J* 7.12 Hz, OCH_2Me), 1.71 (3 H, d, *J* 1.30 Hz, 25-H_3), 2.04 (6 H, s, AcO), 2.60 (1 H, dd, *J* 6.6 and 1.8 Hz, 22-H), 3.02 (1 H, s, 23-H), 4.20 (2 H, q, *J* 7.12 Hz, OCH_2Me), 4.68 (1 H, m, 3-H), 5.10 (1 H, m, 6-H), and 5.85 (1 H, s, 26-H); *m/z* 558 (M^+), 438 ($M^+ - 2 \times CH_3CO_2H$).

Lactonization of Ester (*Z*)-(**7**) *to Compound* (**8**).—To a solution of compound (*Z*)-(**7**) (500 mg, 0.9 mmol) in methanol (50 ml) at 0 °C was added dropwise 30% perchloric acid (5 ml). Then the mixture was stirred at room temperature for 0.5 h and neutralized with 4M-NaOH. After evaporation, usual work-up followed by flash chromatography [light petroleum–ethyl acetate (2:1)] quantitatively gave *compound* (**8**) as a solid, m.p. 258–259 °C; $[\alpha]_D$ +25.95° (*c* 0.50, $CHCl_3$) (Found: C, 70.2; H, 8.8. $C_{31}H_{46}O_7$ requires C, 70.16; H, 8.74%); CD (*c* 0.055 MeOH); λ_{max} 256, θ −9 100, λ_{max} 229 nm, θ +8 700; ν_{max}(KCl) 3 350, 1 740, 1 690, and 1 640 cm^{-1}; δ_H(200 MHz; $CDCl_3$) 0.69 (3 H, s, 18-H_3), 0.98 (3 H, s, 19-H_3), 1.03 (3 H, d, *J* 6.6 Hz, 21-H_3), 2.03 (3 H, s, Ac), 2.07 (3 H, s, Ac), 4.20 (1 H, d, *J* 10.6 Hz, 23-H), 4.35 (1 H, br s, 22-H), 4.90 (1 H, m, 3-H), 5.20 (1 H, m, 6-H), and 5.77 (1 H, s, 26-H); *m/z* 531 ($M^+ + 1$), 470 ($M^+ - CH_3CO_2H$), and 410 ($M^+ - 2 \times CH_3CO_2H$).

Oxidation of Compound (**8**) *with PCC to Compound* (**9**).—To a solution of compound (**8**) (400 mg, 0.75 mmol) in anhydrous dichloromethane (6 ml) was added PCC (800 mg, 3.71 mmol). The mixture was stirred at room temperature, and the reaction was monitored by TLC [light petroleum–ethyl acetate (3:1)] until the reaction was complete; anhydrous diethyl ether was then added, the mixture was filtered and evaporated, and the residue was purified by flash column chromatography [light petroleum–ethyl acetate (3:1)] to give compound (**9**) as a solid in quantitative yield, m.p. 215–216 °C; $[\alpha]_D$ +107° (*c* 0.7, $CHCl_3$) (Found: C, 70.4; H, 8.6. $C_{31}H_{44}O_7$ requires C, 70.43; H, 8.39%); ν_{max}(KCl) 1 720, 1 690, and 1 640 cm^{-1}; δ_H(90 MHz; $CDCl_3$) 0.65 (3 H, s, 18-H_3), 0.88 (3 H, d, *J* 6.3 Hz, 21-H_3), 0.99 (3 H, s, 19-H_3), 2.00 (3 H, s, Ac), 2.03 (3 H, s, Ac), 4.88 (1 H, s, 22-H), 5.10 (1 H, m, 6-H), and 6.68 (1 H, s, 26-H); *m/z* 529 ($M^+ + 1$), 510 ($M^+ - H_2O$), 408 ($M^+ - 2 \times CH_3CO_2H$).

Catalytic Hydrogenation of Enone (**9**) *with Platinum Dioxide to give Compounds* (**10**) *and* (**11a** *and* **b**).—To a solution of compound (**9**) (30 mg) in ethanol (20 ml) was added $PtO_2 \cdot 2H_2O$ (6 mg) and the mixture was hydrogenated at 30 °C and 10 °C respectively. The catalyst was filtered off and the solvent was removed to give a mixture of compounds (**11a**) and (**11b**) (30 °C) and a mixture of compounds (**10**), (**11a**), and (**11b**) (10 °C), both in quantitative yield. A small amount of pure *compound* (**11a**) was obtained from the mixture of (**11a**) and (**11b**) by flash column chromatography [light petroleum–ethyl acetate (2:1)], m.p. 125–126 °C; $[\alpha]_D$ −8.15° (*c* 0.38, $CHCl_3$) (Found: C, 69.4; H, 9.3. $C_{31}H_{48}O_7$ requires C, 69.90; H, 9.08%); ν_{max}(KCl) 3 400, 1 780, and 1 730 cm^{-1}; δ_H(400 MHz; $CDCl_3$) 0.64 (3 H, s, 18-H_3), 0.95 (3 H, s, 19-H_3), 0.97 (3 H, d, *J* 5.1 Hz, 21-H_3), 1.99 (3 H, s, Ac), 2.02 (3 H, s, Ac), 3.59 (1 H, d, *J* 5.4 Hz, 22-H), 4.04 (1 H, dd, *J* 5.4 and 5.4 Hz, 23-H), 4.68 (1 H, m, 3-H), and 5.11 (1 H, m, 6-H); *m/z* 532 (M^+), 454 ($M^+ - CH_3CO_2H - H_2O$), and 412 ($M^+ - 2 \times CH_3CO_2H$).

Catalytic Hydrogenation of Enone (**9**) *with 5% Palladium–Carbon in Ethanol to give Compounds* (**18**), (**19**), *and* (**20a**).—To a solution of compound (**9**) (800 mg) in ethanol (100 ml) was added 5% palladium–carbon (100 mg). The mixture was hydrogenated at room temperature. After the reaction had finished, the mixture was filtered and evaporated; flash column chromatography [light petroleum–ethyl acetate, (3:1)] of the residue then gave compound (**18**) as a solid (574 mg, 72%), compound (**19**) as solid (32 mg, 4%) and oily ester (**20a**) (170 mg, 20%).

Compound (**18**) had m.p. 219–220 °C; $[\alpha]_D$ +58.1° (*c* 9.3, $CHCl_3$) (Found: C, 70.0; H, 9.2. $C_{31}H_{46}O_7$ requires C, 70.16; H, 8.74%); ν_{max}(KCl) 1 760 and 1 730 cm^{-1}; δ_H(90 MHz; $CDCl_3$) 0.65 (3 H, s, 18-H_3), 0.88 (3 H, d, *J* 7.2 Hz, 21-H_3), 0.98 (3 H, s, 19-H_3), 2.02 (3 H, s, Ac), 2.06 (3 H, s, Ac), 2.80 (1 H, m, 24-H), 4.70 (1 H, d, *J* 2 Hz, 22-H), 4.71 (1 H, m, 3-H), and 5.10 (1 H, m, 6-H); *m/z* 471 ($M^+ - CH_3CO_2$), 470 ($M^+ - CH_3CO_2H$), and 410 ($M^+ - 2 \times CH_3CO_2H$).

Compound (**19**) had m.p. 212–214 °C; $[\alpha]_D$ +111.6° (*c* 0.25, $CHCl_3$) (Found: C, 70.1; H, 8.2%); ν_{max}(KCl) 1 765 and 1 725 cm^{-1}; δ_H(90 MHz; $CDCl_3$) 0.69 (3 H, s, 18-H_3), 0.90 (3 H, d, *J* 6.3 Hz, 21-H_3), 0.96 (3 H, s, 19-H_3), 2.00 (3 H, s, Ac), 2.04 (3 H, s, Ac), 2.64 (1 H, m, 24-H), 4.60 (1 H, d, *J* 1.80 Hz, 22-H), 4.68 (1 H, m, 3-H), and 5.12 (1 H, m, 6-H); *m/z* 471 ($M^+ - CH_3CO_2$), 470 ($M^+ - CH_3CO_2H$), and 410 ($M^+ - 2 \times CH_3CO_2H$).

Compound (**20a**) had $[\alpha]_D$ −25.65° (*c* 6.0, $CHCl_3$) (Found: C, 68.5; H, 9.1. $C_{33}H_{52}O_8$ requires C, 68.72; H, 9.09%); ν_{max}(film) 3 500 and 1 730 cm^{-1}; δ_H(90 MHz; $CDCl_3$) 0.72 (3 H, s, 18-H_3), 0.76 (3 H, d, *J* 5.4 Hz, 25-H_3), 0.98 (3 H, s, 19-H_3), 1.02 (3 H, d, *J*

7.2 Hz, 21-H_3), 1.24 (3 H, t, *J* 7.2 Hz, OCH_2Me), 3.28 (1 H, m, 24-H), 4.08 (2 H, q, *J* 7.2 Hz, OCH_2Me), 4.40 (1 H, s, 22-H), 4.68 (1 H, m, 3-H), and 5.12 (1 H, m, 6-H); δ_C(90 MHz; $CDCl_3$) 170.4 (2 C, $MeCO_2$), 171.5 (1 C, CO_2), and 215.5 (1 C, CO); *m/z* 577 ($M^+ + 1$), 517 ($M^+ - CH_3CO_2$), 457 ($M^+ - CH_3CO_2H - CH_3CO_2$), and 439 ($M^+ - CH_3CO_2H - CH_3CO_2 - H_2O$).

Reduction of Compound (**19**) *with Sodium Borohydride to afford Compound* (**21**).—To a solution of δ-lactone (**19**) (25 mg, 0.047 mmol) in dichloromethane (3 ml) and methanol (3 ml) at 0 °C was added sodium borohydride (3 mg, 0.086 mmol). The mixture was stirred at room temperature for 0.5 h and ammonium chloride was then added to stop the reaction. Usual work-up gave (quantitatively) the γ-lactone as a solid, m.p. 120–122 °C (lit.,[13] 120–124 °C). The spectroscopic data were identical with those reported.[13]

Acetylation of Compound (**20a**) *to afford the Triacetate* (**20b**).—Compound (**20a**) (20 mg) was dissolved in acetic anhydride (1 ml) and pyridine (2 ml). The mixture was stirred at room temperature overnight. Usual work-up gave (quantitatively) the oily *compound* (**20b**), $[\alpha]_D$ −21.95° (*c* 2.0, $CHCl_3$) (Found: C, 67.9; H, 8.65. $C_{35}H_{54}O_9$ requires C, 67.93; H, 8.80%); ν_{max}(film) 1 720 cm^{-1}; δ_H(90 MHz; $CDCl_3$) 0.72 (3 H, s, 18-H_3), 0.88 (3 H, d, *J* 7.2 Hz, 25-H_3), 0.98 (3 H, s, 19-H_3), 1.00 (3 H, d, *J* 5.4 Hz, 21-H_3), 1.25 (3 H, t, *J* 7.2 Hz, OCH_2Me), 2.00 (3 H, s, Ac), 2.02 (3 H, s, Ac), 2.16 (3 H, s, Ac), 4.12 (2 H, q, *J* 7.2 Hz, OCH_2Me), 4.68 (1 H, m, 3-H), 5.10 (1 H, m, 6-H), and 5.28 (1 H, s, 22-H); *m/z* 439 ($M^+ - CH_3CO_2H - CH_3CO_2$).

Reduction of δ-*Lactone* (**18**) *with Sodium Borohydride to afford Compounds* (**11a**) *and* (**22**).—To a solution of compound (**18**) (90 mg, 0.17 mmol) in dichloromethane (3 ml) and methanol (3 ml) at 0 °C was added sodium borohydride (14 mg, 0.4 mmol). The mixture was stirred at room temperature for 0.5 h, and ammonium chloride was then added to stop the reaction. Usual work-up, followed by flash column chromatography [light petroleum–ethyl acetate (2:1)], gave γ-lactone (**11a**) as a solid (80 mg, 89%) and oily hydroxy lactone (**22**) (9 mg, 10%). Compound (**22**) was also obtained (quantitatively) from the catalytic hydrogenation of compound (**8**) with 5% palladium–carbon in ethanol.

Compound (**22**) had $[\alpha]_D$ +22.5° (*c* 1.9, $CHCl_3$) (Found: C, 70.1; H, 8.8. $C_{31}H_{48}O_7$ requires C, 69.90; H, 9.08%); ν_{max}(film) 3 440 and 1 730 cm^{-1}; δ_H(90 MHz; $CDCl_3$) 0.66 (3 H, s, 18-H_3), 0.94 (3 H, d, *J* 5.4 Hz, 21-H_3), 0.96 (3 H, s, 19-H_3), 2.00 (3 H, s, Ac), 2.04 (3 H, s, Ac), 3.36 (1 H, t, *J* 9 Hz, 23-H), 4.04 (1 H, d, *J* 9 Hz, 22-H), 4.60 (1 H, m, 3-H), and 5.10 (1 H, m, 6-H); *m/z* 472 ($M^+ - CH_3CO_2H$), 412 ($M^+ - 2 \times CH_3CO_2H$).

For γ-lactone (**11a**), the m.p., R_f-value, and spectroscopic data were identical with those reported above.

Reduction of a Mixture of γ-*Lactones* (**11a**) *and* (**11b**) *with Lithium Aluminium Hydride to afford the Pentaol* (**12**).—Lithium aluminium hydride (600 mg, 15.8 mmol) was added to a solution of a mixture of lactones (**11a**) and (**11b**) (500 mg, 0.94 mmol) in anhydrous THF (70 ml). The mixture was stirred at room temperature for 0.5 h, then refluxed for 4 h, and ethyl acetate (20 ml) was added to destroy the excess of $LiAlH_4$. After filtration and evaporation, usual work-up gave compound (**12**) as a solid (415 mg, 96%) (Found: C, 70.5; H, 11.0. $C_{27}H_{48}O_5 \cdot 0.5H_2O$ requires C, 70.24; H, 10.72%); ν_{max}(KCl) 3 330 cm^{-1}; δ_H[90 MHz; $(CD_3)_2CO$] 0.66 (3 H, s, 18-H_3), 0.88 (3 H, s, 19-H_3), 0.90 (3 H, d, *J* 3.6 Hz, 21-H_3), 3.10 (5 H, s, OH), 3.50 (1 H, m, 3-H), and 3.96 (1 H, m, 6-H); *m/z* 331 ($M^+ - H_2O - C_5H_{11}O_2$), 133 ($C_6H_{13}O_3$), 115 ($C_6H_{11}O_2$), and 103 ($C_5H_{11}O_2$).

Reaction of Pentaol (**12**) *with* 2,2-*Dimethoxypropane to afford Compound* (**13**).—To a solution of pentaol (**12**) (415 mg, 0.9 mmol) in acetone (15 ml) were added 2,2-dimethoxypropane (6 ml) and PTSA (10 mg). The mixture was stirred at room temperature for 1 h. Removal of solvent, followed by flash column chromatography [acetone–ethyl acetate (1:2)], gave *compound* (**13**) as a solid (397 mg, 87%) (Found: C, 70.3; H, 10.25. $C_{30}H_{52}O_2 \cdot H_2O$ requires C, 70.13; H, 10.64%); ν_{max}(KCl) 3 350 cm^{-1}; δ_H(90 MHz; $CDCl_3$) 0.64 (3 H, s, 18-H_3), 0.90 (3 H, s, 19-H_3), 1.24 (3 H, s, acetonide), 1.34 (3 H, s, acetonide), and 3.5–4.0 (6 H, m, 3-, 6-, 22-, and 23-H, and 26-H_2); *m/z* 477 ($M^+ - CH_3$).

Oxidative of Triol (**13**) *with PDC to give the Aldehyde* (**14**).—To a solution of the triol (**13**) (300 mg, 0.588 mmol) in anhydrous dichloromethane (20 ml) were added powdered 4 Å molecular sieves (20 mg) and PDC (3 g, 7.98 mmol). The mixture was stirred at room temperature until the starting material had been consumed [TLC; light petroleum–ethyl acetate (2:1)]. The solution was diluted with anhydrous diethyl ether, filtered, and evaporated, and the residue was purified by flash column chromatography [light petroleum–ethyl acetate (2:1)] to give the *aldehyde* (**14**) as a solid (216 mg, 76%); HRMS (Found: M^+, 486.3324. $C_{30}H_{46}O_5$ requires *M*, 386.3345); ν_{max}(KCl) 1 720 cm^{-1}; δ_H(90 MHz; $CDCl_3$) 0.64 (3 H, s, 18-H_3), 0.94 (3 H, s, 19-H_3), 0.96 (3 H, d, *J* 3.6 Hz, 21-H_3), 1.34 (6 H, s, acetonide), 3.4–3.8 (2 H, m, 22- and 23-H), and 9.83 (1 H, s, CHO); *m/z* 487 ($M^+ + 1$), 486 (M^+), and 471 ($M^+ - CH_3$).

Decarbonylation and Isomerization of Aldehyde (**14**) *to give Diones* (**15**) *and* (**16**).—To a solution of compound (**14**) (130 mg, 0.267 mmol) in anhydrous toluene (20 ml) was added tris(triphenylphosphine)rhodium chloride (200 mg). The mixture was refluxed for 6 h and filtered. Acetone (5 ml) and PTSA (2 mg) were added. The mixture was stirred at room temperature overnight. Removal of solvent, followed by flash column chromatography [light petroleum–ethyl acetate (3:1)], gave compound (**16**) (67 mg, 55%) and compound (**15**) (20 mg, 16%).

Compound (**16**) had m.p. 164–165 °C; $[\alpha]_D$ −32.34° (*c* 1.45, $CHCl_3$) HRMS [Found: ($M^+ - CH_3$) 443.3141. $C_{28}H_{43}O_4$ requires 443.3161]; ν_{max}(KCl) 1 710 cm^{-1}; δ_H(90 MHz; $CDCl_3$) 0.70 (3 H, s, 18-H_3), 0.96 (3 H, s, 19-H_3), 0.98 (3 H, d, *J* 5.4 Hz, 21-H_3), 1.25 (6 H, s, 25- and 26-H_3), 1.34 (3 H, s, acetonide), 1.38 (3 H, s, acetonide), 3.41 (1 H, dd, *J* 7.2 and 7.2 Hz, 23-H), and 3.91 (1 H, d, *J* 7.2 Hz, 22-H); *m/z* 459 ($M^+ + 1$) and 443 ($M^+ - CH_3$).

Compound (**15**) had $[\alpha]_D$ −26.33° (*c* 0.3, $CHCl_3$); ν_{max}(film) 1 720 cm^{-1}; δ_H(90 MHz; $CDCl_3$) 0.71 (3 H, s, 18-H_3), 0.96 (3 H, s, 19-H_3), 0.97 (3 H, d, *J* 5.4 Hz, 21-H_3), 1.34 (3 H, s, acetonide), 1.46 (3 H, s, acetonide), 3.74 (1 H, dd, *J* 10.8 and 7.2 Hz, 23-H), and 4.12 (1 H, d, *J* 7.2 Hz, 22-H); *m/z* 459 ($M^+ + 1$) and 458 (M^+).

Reductive Elimination of Compound (**16**) *to afford Enone* (**17**).—To a solution of compound (**16**) (20 mg, 0.044 mmol) were added zinc amalgam (200 mg) and TMSCl (300 μl). The mixture was stirred at room temperature overnight under N_2, then filtered and evaporated, and the residue was purified by flash column chromatography (benzene) to give compound (**17**) as a solid (11 mg, 57%), m.p. 175–176 °C (lit.,[3] 176–178 °C); $[\alpha]_D$ +40° (*c* 0.1, $CHCl_3$); HRMS (Found: M^+, 442.3468. Calc. for $C_{29}H_{46}O_3$: *M*, 442.3447); ν_{max}(KCl) 1 720 and 1 630 cm^{-1}; *m/z* 444 ($M^+ + 2$), 443 ($M^+ + 1$), and 442 (M^+). The ^1H NMR data were identical with those previously reported.[3]

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