

Study on the Syntheses of Brassinolide and Related Compounds. Part 14.† Highly Stereoselective Construction of the Side-chain of Brassinosteroids utilizing the β -Alkylative 1,3-Carbonyl Transposition of the Steroidal 22-En-24-one

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A stereoselective synthesis of the side-chain of brassinolide which involves β -alkylative 1,3-carbonyl transposition of the α,β -unsaturated ketone 3,6-diacetoxycholest-22-en-24-one is described. The overall yield of (22*R*,23*R*,24*S*)-22,23-isopropylidenedioxy-24-methyl-5 β -cholestane-3 α ,6 α -diol from 3 α ,6 α -diacetoxy-5 β -pregnane-20-carbaldehyde in six steps is 47%.

Brassinolide (1) and related compounds are known to exhibit plant growth-promoting activity.¹ The outstanding physiological activity and novel structural features of brassinosteroids have impelled us in recent years to develop a synthetic route to these natural products. In particular, the stereoselective construction of this steroidal side-chain has provided a challenging target, because the high activity is reflected in the stereochemistry of the side-chain; *inter alia*, the configuration at C-24.² In continuation of our efforts towards a brassinosteroid side-chain synthesis,³ we report here a practical route to these compounds by means of β -alkylative 1,3-carbonyl transposition⁴ (4) \rightarrow (6). (Scheme).

The 20-carbaldehyde (3) obtained from hydoxycholeic acid by the known procedure⁵ was treated with 'isobutyl carbonyl arsonium ylide'^{6,†} to form the α,β -unsaturated ketone (4) in 90% yield. Oxidation of the tertiary allylic alcohol moiety of compound (5), generated by the 1,2-addition of methyl-lithium to the α,β -unsaturated ketone (4) (98% yield), with pyridinium chlorochromate (PCC) afforded transposed β -alkyl α,β -unsaturated ketone (6)⁴ in 93% yield. Interestingly, the newly introduced methyl group at C-24 was found in only a single configuration, presumed to be the α -orientation due to steric considerations. Stereoselective reduction of enone (6)⁷ with di-isobutylaluminium hydride (DIBAL-H) gave the (22*R*)-22-hydroxy compound (7) in 95% yield. Hydroxy-directed epoxidation of enol (7) with *m*-chloroperbenzoic acid (MCPBA)⁸ gave the desired epoxide (8) in 95% yield. The stereo- and regio-selective opening of the epoxide (8) with inversion at C-24,⁸ followed by treatment with 2,2-dimethoxypropane, gave the known compound (9)⁹ in 64% yield in two steps. The overall yield from aldehyde (3) to the dioxolane (9) in six steps is 47%. This is the best method to date for construction of the side-chain of brassinolide and related compounds.¹⁰ The conversion of compound (9) into brassinolide (1) and typhasterol (2) is known.³

The present procedure is simple, flexible, easy to perform, and provides a high overall yield for the construction of the side-chain of brassinolide and related compounds.

Experimental

The silica gel used for chromatography was GF254 silica gel H 100–200 mesh. M.p.s were measured on a Büchi 535 instrument and are uncorrected. Optical rotations were measured on a Autopol III polarimeter. IR spectra were recorded from KBr discs on a Zeiss-75 model spectrometer. ¹H NMR spectra were recorded on a Varian XL-200 (200 MHz) or a JEOL SX-90 (90

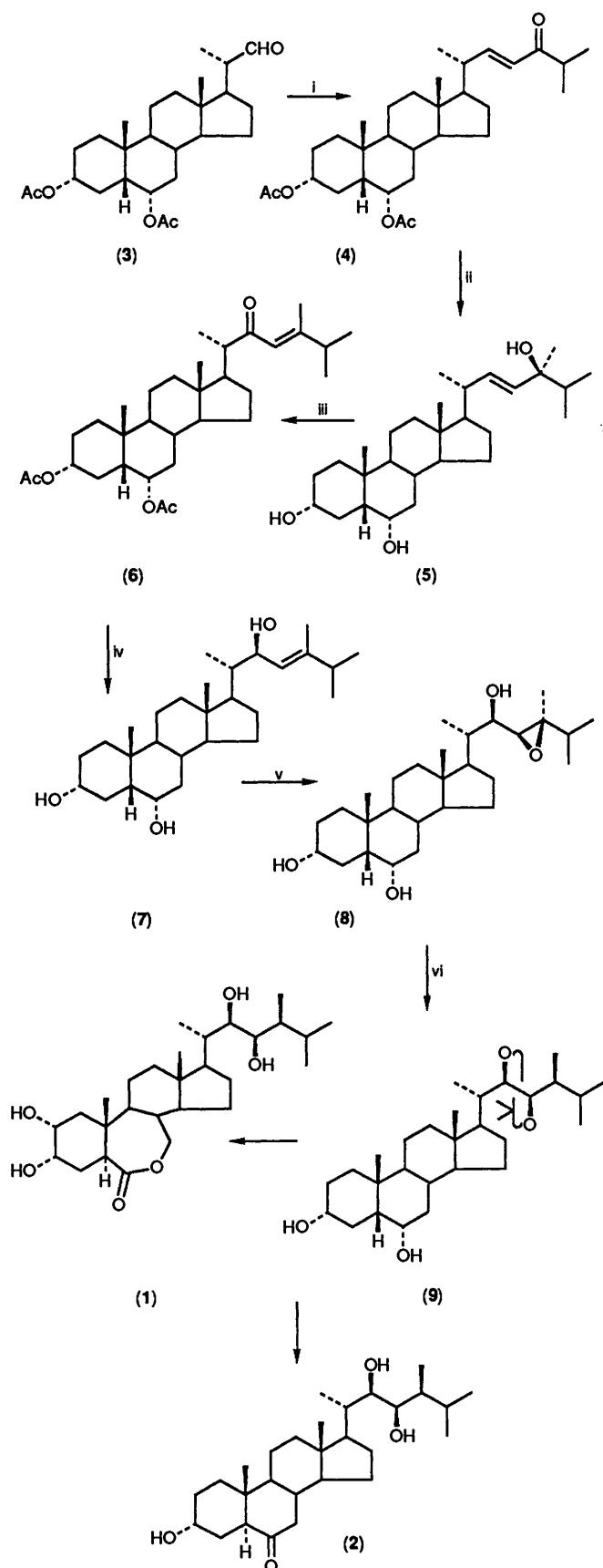
MHz) spectrometer with SiMe₄ as internal standard. Mass spectra were run on a JMS-01U or a MAT-711 instrument. Elemental analyses were performed by the analytical department of this institute. Light petroleum refers to the fraction boiling in the range 60–90 °C.

3 α ,6 α -Diacetoxy-5 β -cholest-22-ene-24-one (4).—A mixture of aldehyde (3) (5 g, 1.14 mmol), (3-methyl-2-oxobutyl)triphenylarsonium bromide (6.98 g, 1.48 mmol), potassium carbonate (2 g, 1.48 mmol), and dichloromethane (30 ml)–tetrahydrofuran (THF) (10 ml)–water (0.4 ml) was stirred at 25 °C for 24 h. After the reaction was complete (TLC), the solvent was removed under reduced pressure. The residue was diluted with water and extracted with dichloromethane. The combined extracts were washed with brine, and dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel [light petroleum–ethyl acetate (9:1) as eluant] to give the *title compound* (4) (5.14 g, 90%), m.p. 141–142 °C (Found: C, 74.0; H, 9.65. C₃₁H₄₈O₅ requires C, 74.36; H, 9.66%); *m/z* 500 (*M*⁺), 440 (*M*⁺ – CH₃COOH), and 380 (*M*⁺ – 2CH₃COOH); ν_{\max} 1 620 (C=C), 1 690 (C=O), and 1 735 cm⁻¹ (OAc); δ_{H} (CDCl₃; 90 MHz) 0.64 (3 H, s, 18-H₃), 0.99 (3 H, s, 19-H₃), 1.02 (3 H, d, 21-H₃), 1.12–1.14 (6 H, d, 26- and 27-H₃), 2.01 (3 H, s, OAc), 2.04 (3 H, s, OAc), 4.66 (1 H, m, 6-H), 5.18 (1 H, m, 3-H), 6.20 (1 H, d, *J* 16 Hz, 23-H), and 6.71 (1 H, dd, *J* 16 and 8 Hz, 22-H).

(24*S*)-24-Methyl-5 β -cholest-22-ene-3 α ,6 α ,24-triol (5).—To a solution of enone (4) (520 mg, 1.04 mmol) in THF (10 ml) at –78 °C under nitrogen was added methyl-lithium (1.0M in diethyl ether; 10 ml, 10 mmol). The reaction mixture was kept at –78 °C for 1 h, then allowed to warm to 20 °C and was stirred at this temperature for 4 h, before being quenched with saturated aq. NH₄Cl. The reaction mixture was extracted with dichloromethane, and the organic layer was washed with brine and dried over Na₂SO₄. Removal of solvent under reduced pressure gave the *title compound* (5) as a solid (441 mg, 98%), m.p. 178.5–180.5 °C; [α]_D –45° (*c* 0.6, CH₂Cl₂) (Found: C, 77.6; H, 11.1. C₂₈H₄₈O₃ requires C, 77.60; H, 11.09%); ν_{\max} 1 630 (C=C) and 3 300 cm⁻¹ (OH); *m/z* 433 (*M*⁺) and 376 (*M*⁺ – C₄H₉); δ_{H} (CDCl₃; 90 MHz) 0.67 (3 H, s, 18-H₃), 0.83 (6 H, s, 26- and 27-H₃), 0.94 (3 H, s, 28-H₃), 0.98 (3 H, s, 19-H₃),

† Part 13, W. S. Zhou, Y. P. Zhou, and B. Jiang, *Synthesis*, 1989, 426.

‡ 3-Methyl-2-oxobutyl(triphenyl)arsonium bromide.



Scheme. Reagents: i, $\text{Ph}_3\text{As}^+\text{CH}_2\text{COCHMe}_2\text{Br}^-$, K_2CO_3 ; ii, MeLi ; iii, $\text{Ac}_2\text{O}-\text{Et}_3\text{N}$; then PCC ; iv, DIBAL-H ; v, MCPBA ; vi, $\text{LiBH}_4-\text{BH}_3$; then $\text{Me}_2\text{C}(\text{OMe})_2$, PTSA .

3.65 (1 H, m, 6-H), 4.02 (1 H, m, 3-H), 5.30 (1 H, d, J 7 Hz, 23-H), and 5.54 (1 H, d, J 7 Hz, 22-H).

3 α ,6 α -Diacetoxy-24-methyl-5 β -cholest-23-ene-22-one (6).—A mixture of compound (5) (90 mg, 0.21 mmol) in triethylamine (1 ml) and Ac_2O (0.5 ml) was kept at room temperature for 24 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed successively with 10% HCl , saturated aq. NaHCO_3 , and brine, and dried over Na_2SO_4 . Removal of solvent under reduced pressure gave an oil.

To a solution of this oily residue in dichloromethane (10 ml) at 0 °C was added PCC (150 mg), and the mixture was stirred at this temperature for 24 h. The solvent was removed in reduced pressure, and the residue was extracted with diethyl ether, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel to give the title compound (6) (100 mg, 93%), m.p. 73–75 °C; $[\alpha]_D^{25} + 36^\circ$ (c 1.86, CH_2Cl_2); m/z 515 (M^+), 455 ($M^+ - \text{CH}_3\text{COOH}$), and 395 ($M^+ - 2\text{CH}_3\text{COOH}$); ν_{max} 1 610 ($\text{C}=\text{C}$), 1 680 ($\text{C}=\text{O}$), 1 740 cm^{-1} (OAc) (Found: C, 74.4; H, 9.9. Calc. for $\text{C}_{32}\text{H}_{50}\text{O}_5$: C, 74.56; H, 9.71%); $\delta_{\text{H}}(\text{CDCl}_3; 90 \text{ MHz})$ 0.67 (3 H, s, 18- H_3), 0.95 (6 H, s, 26- and 27- H_3), 1.09 (3 H, s, 19- H_3), 1.10 (3 H, s, 21- H_3), 1.63 (3 H, s, 24- CH_3), 1.95 and 2.01 (6 H, s, 2 \times Ac), 4.65 (1 H, m, 6-H), 5.10 (1 H, m, 3-H), and 6.05 (1 H, s, 23-H).

(22R)-24-Methyl-5 β -cholest-23-ene-3 α ,6 α ,22-triol (7).—To a solution of compound (6) (1.12 g, 2.17 mmol) in THF (30 ml) at –78 °C under nitrogen was added DIBAL-H (1.0M in Toluene; 10 ml). The temperature of the reaction mixture was kept at –78 °C for 12 h. Additional DIBAL-H (10 ml) was added to the reaction mixture, which was stirred at –78 °C for 4 h and quenched with methanol. After filtration, the solvent was removed under reduced pressure. The solid residue was recrystallized from dichloromethane–light petroleum to give the title compound (7) (0.87 g, 93%), m.p. 173–174 °C; $[\alpha]_D^{25} - 14.59^\circ$ (c 1.1, CHCl_3) (Found: C, 77.4; H, 11.4. $\text{C}_{28}\text{H}_{48}\text{O}_3$ requires C, 77.60; H, 11.09%); ν_{max} 1 630 ($\text{C}=\text{C}$) and 3 300 cm^{-1} (OH); m/z 433 (M^+) and 415 ($M^+ - \text{H}_2\text{O}$); $\delta_{\text{H}}(\text{CDCl}_3; 90 \text{ MHz})$ 0.64 (3 H, s, 18- H_3), 0.90 and 0.92 (6 H, s, 26- and 27- H_3), 0.97 (3 H, s, 19- H_3), 1.04 (3 H, s, 21- H_3), 1.60 (3 H, s, 24- CH_3), 3.60 (1 H, m, 6-H), 4.01 (1 H, m, 3-H), 4.40 (1 H, d, J 7.2 Hz, 22-H), and 5.31 (1 H, d, J 7.2 Hz, 23-H).

(22R,23S,24S)-23,24-Epoxy-24-methyl-5 β -cholestane-3 α ,6 α ,22-triol (8).—A mixture of compound (7) (50 mg) and 85% MCPBA (45 mg) in dichloromethane (10 ml) was stirred at room temperature for 20 h. The reaction mixture was washed successively with saturated aq. NaHCO_3 , brine and water, and dried over Na_2SO_4 . After removal of the solvent under reduced pressure, the solid residue was recrystallized from dichloromethane–light petroleum to give the title compound (8) (48 mg, 93%), m.p. 139–140 °C; $[\alpha]_D^{25} - 9.06^\circ$ (c 0.74, CHCl_3); ν_{max} 1 370 ($\text{C}-\text{O}-\text{C}$) and 3 360 cm^{-1} (OH); m/z 448 (M^+), 330 ($M^+ - \text{C}_6\text{H}_{12}\text{O} - \text{H}_2\text{O}$), and 312 ($M^+ - \text{C}_6\text{H}_{12}\text{O} - 2\text{H}_2\text{O}$) (Found: C, 74.9; H, 10.5. $\text{C}_{28}\text{H}_{48}\text{O}_4$ requires C, 75.00; H, 10.71%); $\delta_{\text{H}}(\text{CDCl}_3; 90 \text{ MHz})$ 0.67 (3 H, s, 18- H_3), 0.91 (6 H, s, 26- and 27- H_3), 0.96 (3 H, s, 19- H_3), 1.03 (3 H, s, 21- H_3), 1.21 (3 H, s, 24- CH_3), 2.80 (1 H, d, J 7.2 Hz, 23-H), 3.60 (1 H, d, J 7.2 Hz, 22-H), 3.65 (1 H, m, 6-H), and 4.05 (1 H, m, 3-H).

(22R,23R,24S)-22,23-Isopropylidenedioxy-24-methyl-5 β -cholestane-3 α ,6 α -diol (9).—To a solution of compound (8) (80 mg, 0.18 mmol) and LiBH_4 (52 mg, 1.5 mmol) in THF (10 ml) was added BH_3-THF (3 ml) at 50 °C. The reaction temperature was kept at 50 °C for 64 h. The reaction mixture was quenched with methanol and water. After the solvent had been removed under reduced pressure, water (10 ml) was added to the residue

and the mixture was kept at room temperature for 0.5 h. To the dried solid dissolved in acetone (5 ml) was added 2,2-dimethoxypropane (1 ml) and PTSA (10 mg). The reaction mixture was stirred at room temperature for 6 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel to give the *title compound* (**9**) (56 mg, 63.6%), 166–167 °C; ν_{\max} 1 130 (C–O–C), 1 450 (C–O–C), and 3 450 cm^{-1} (OH); m/z 491 (M^+) and 472 ($M^+ - \text{H}_3\text{O}$) (Found: C, 75.7; H, 11.0. Calc. $\text{C}_{31}\text{H}_{55}\text{O}_4$: C, 75.76; H, 11.20%); δ_{H} (CDCl_3 ; 200 MHz) 0.647 (3 H, s, 18- H_3), 0.80 and 0.84 (6 H, d, J 8 Hz, 26- and 27- H_3), 0.94 (3 H, d, J 6.8 Hz, 28- H_3), 0.98 (1 H, s, 19- H_3), 1.34 and 1.36 (6 H, s, 2 \times OMe); 3.68 (1 H, m, 6-H), 3.80 (1 H, m, 3-H), 3.82 (1 H, dd, J 9 and 4 Hz, 23-H), and 3.98 (1 H, d, J 9 Hz, 22-H).

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