A Novel Synthetic Approach to the Ecdysone Side-chain *via* Furan Derivatives

By **Tetsuji Kametani,*** Hoshi College of Pharmacy, Ebara 2–4–41, Shinagawa-ku, Tokyo 142, Japan
Masayoshi Tsubuki and **Hideo Nemoto,** Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

A new synthesis of (22*R*)-22,25-dihydroxycholesterol (6) and its 6-oxo-derivative (18) from pregnenolone *via* the stereoselective hydrogenation of an olefinic furan derivative (2) as a key reaction is described.

THE importance of steroids having modified side-chains, *e.g.* the ecdysones [1,2] and the metabolites of vitamin D,[3,4] have focussed attention on the synthesis of steroid side-chains as a major challenge of steroid chemistry.[5] The ability to control stereochemistry in the acyclic chain, which contains a functional group suitable for further elaboration, especially at C-20, is crucial to the synthesis of these compounds and a number of solutions to this problem have been presented by various groups.[6–13] Herein we report one of the simplest and yet most versatile syntheses of ecdysone side-chains from pregnenolone by using furan derivatives. As outlined in Scheme 1, the $\Delta^{20(21)}$-furan derivative (2) prepared from pregnenolone acetate (1) in 96% overall yield by reaction of the latter with 2-lithio-5-methylfuran [14] followed by silica-gel dehydration of the product and then acetylation, was hydrogenated on palladium/carbon to give the 20*S*-compound (3) quantitatively in a stereoselective manner. Opening of the furan ring of compound (3) in tetrahydrofuran containing 10% sulphuric acid and acetic acid and then acetylation of the product afforded the diketone (4) in 70% overall yield; this was then treated with methyl-lithium to give the alcohol (5) selectively in 70.8% yield.

TABLE

Reduction of Compound (5)

	Products	
Reagent solvent	Ratio of 22*R* (8) and 22*S* (9)	Yield (%)
$NaBH_4$–MeOH	1 : 3	85
$LiAlOBu^t_3H$–THF	1 : 5	80
$ZnBH_4$–Et_2O	1 : 2	75

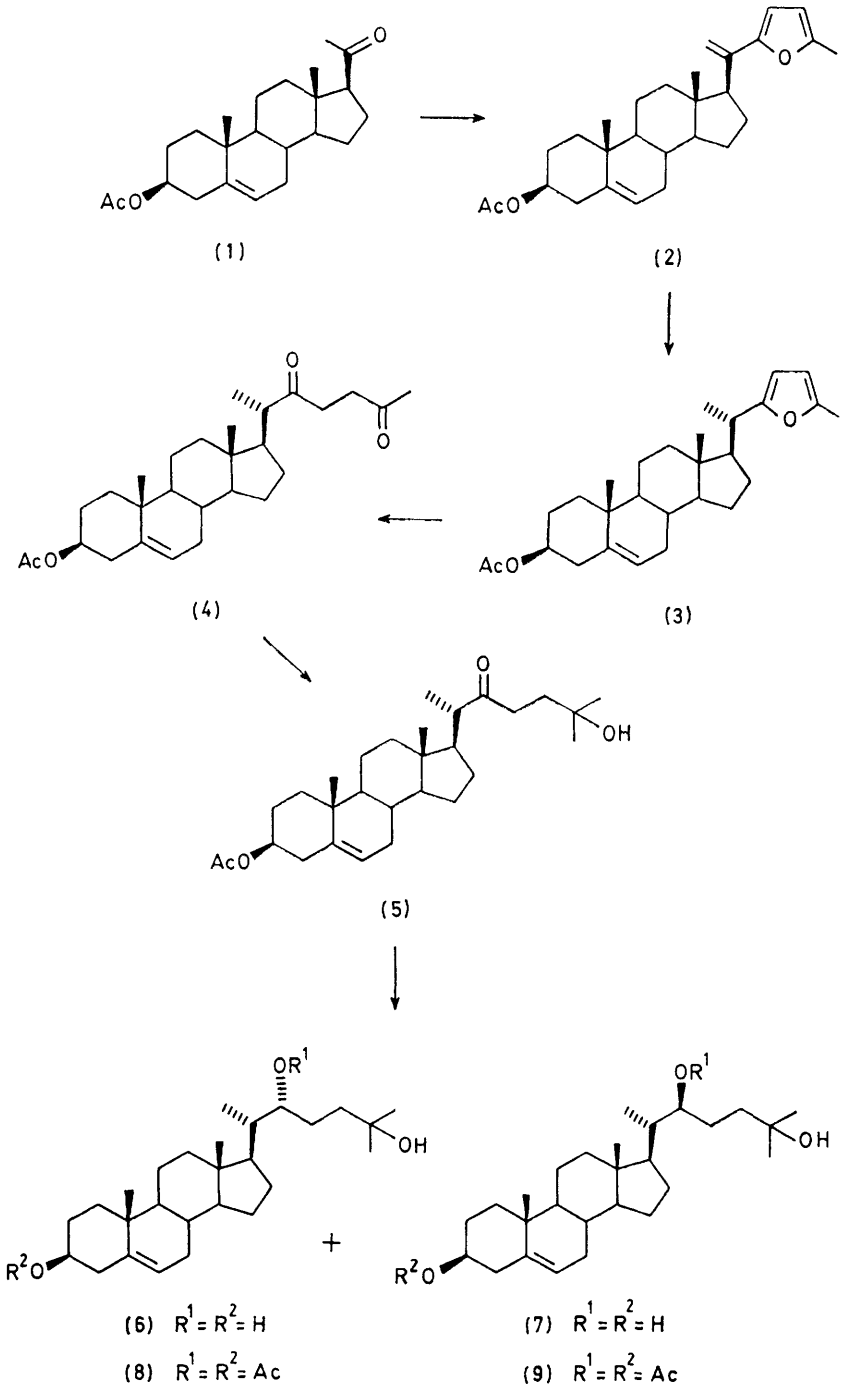
Finally, reduction of compound (5) was carried out under three different conditions to yield a mixture of 22*R*-(6) and 22*S*-(7) compounds as shown in the Table. The diacetates (8) and (9) obtained by acetylation of (6) and (7) were identical with authentic samples derived from (22*R*)-22,25-dihydroxycholesterol and its 22*S*-isomer [6] by acetylation, respectively.

Thus, having devised a simple and effective methodology for the transformation of pregnane-type steroids to cholestane-type we turned our attention to the synthesis of the 6-oxo-analogue (19), a potentially important intermediate of ecdysones. The alcohol (10) prepared in 81.5% yield by hydroboration and oxidation of compound (3) was oxidized with chromium trioxide–pyridine to give the ketone (11) in 85.4% yield; this was treated with ethanedithiol in acetic acid containing boron trifluoride–diethyl ether to yield a mixture of the monothioacetal (12) and the dithioacetal (13) in 21.3% and 77.7% yield respectively. The conversion of the monothioacetal (12) into the dithioacetal (13) was also found to proceed smoothly under the conditions described above. This direct conversion under mild conditions of a furan ring into a masked 1,4-diketone is worthy of note. Reduction of the mono-ketone (13) with sodium borohydride afforded a mixture of the 22*S*-(14) and 22*R*-compounds (15) in 69 and 28.7% yield respectively. The stereochemistry at C-22 was deduced from the n.m.r. spectrum of (14) and (15), in which the C-20 methyl group of (14) was observed at 0.96 p.p.m. and that of (15) at 0.91 p.p.m. This was found to be good agreement with that of compounds (9) and (8) in which the C-20 methyl group of (9) appeared at 1.0 p.p.m. and that of (8) at 0.95 p.p.m. Thus, we tentatively assigned the stereochemistry of (15) and (14) as 22*R* and 22*S* respectively. To increase the yield of the 22*R* compound (15), the 22*S*-compound (14) was recycled *via* a Jones oxidation and reduction of the resulting ketone (13) with sodium borohydride; a high overall yield was achieved. Selective deprotection of the dithioacetal (15) was carried out with methyl iodide in aqueous acetone to give the monothioacetal (16) in 87.3% yield. The diol (17) obtained in 76.4% yield by treating (16) with methyl-lithium was converted into the ketone (18) under the same conditions as those used for compound (15) except for the reaction time; (18) on acetylation furnished the triacetate (19) in 88.4% overall yield.

Thus, we have demonstrated the versatility of our methodology for transformation of pregnane-type steroids to cholestane-type. The remarkable feature of this synthesis is the stereoselective reduction of the olefinic furan derivative (2) to give the 20*S*-compound (3) since the hydrogenation of the double bond between C-20 and the adjacent position is sometimes troublesome and lacking stereoselectivity.[5]

EXPERIMENTAL

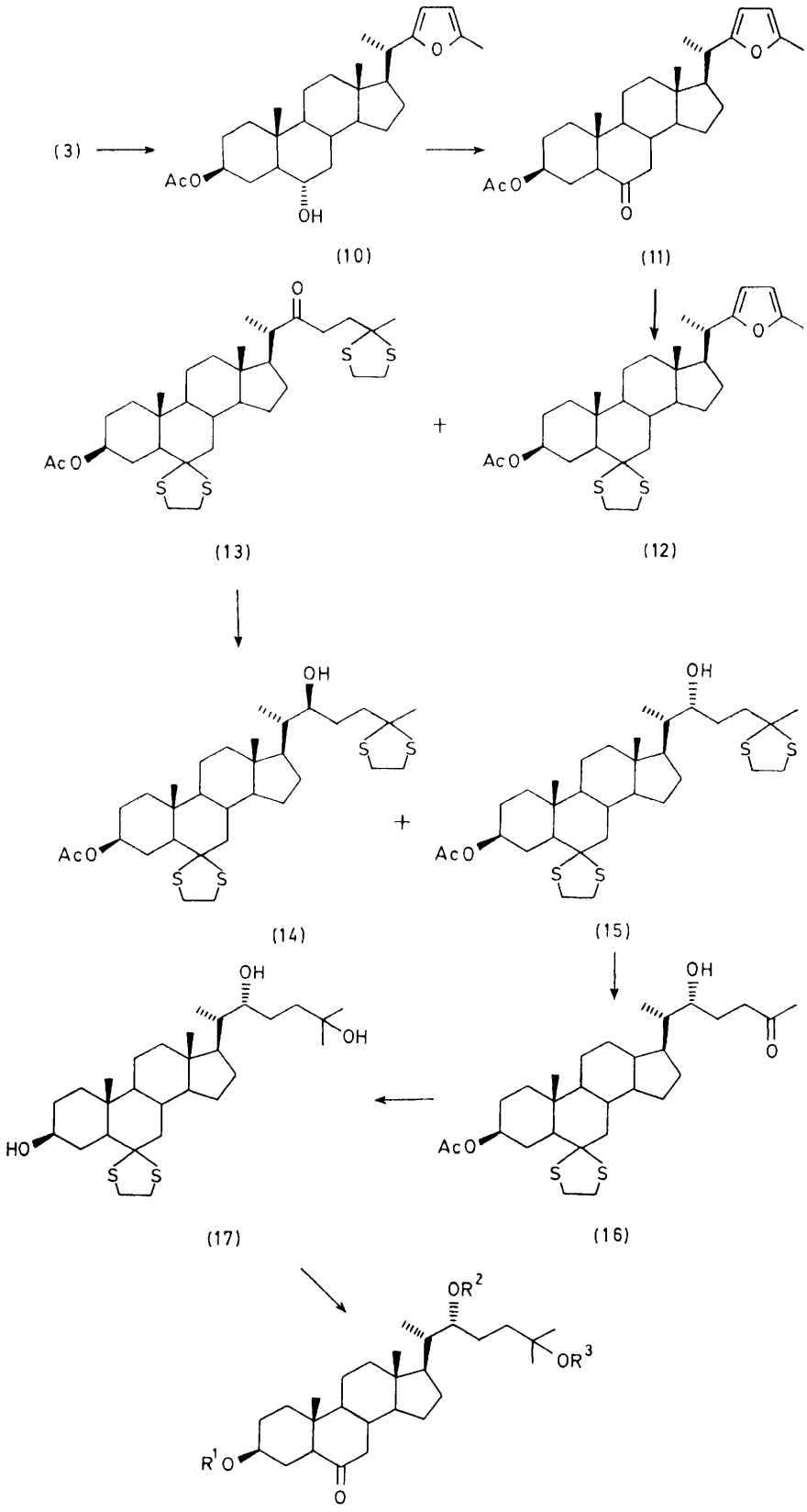
M.p.s were taken with a Yanagimoto micro-melting-point apparatus (MP-S2). I.r. spectra were measured with a Hitachi 260-10 recording spectrophotometer, n.m.r. spectra with a JEOL JNM-PMX60 spectrometer, and mass spectra with a Hitachi M-52G. All optical rotations were obtained



SCHEME 1

on a JASCO-PIP-SL polarimeter at 20 °C using a 1-dm cell in chloroform.

3β-*Acetoxy*-20-(5-*methyl*-2-*furyl*)-*pregna*-5,20(21)-*diene* (2).—To a stirred solution of the ketone (1) (10.6 g, 29.7 mmol) in anhydrous tetrahydrofuran (35 ml) was added 2-lithio-5-methylfuran [prepared from 2-methylfuran (5.85 g, 69.6 mmol) in tetrahydrofuran (100 ml and 1.56M n-butyl-lithium (45 ml, 70.2 mmol)] at −78 °C under a current of nitrogen; the reaction mixture was then stirred for 30 min at the same temperature. After quenching of the reaction with saturated aqueous ammonium chloride (2 ml), the product was isolated by ethyl acetate extraction. On chromatography of the product on silica gel (20 g), elution with dichloromethane gave the styrene. This crude product was acetylated with acetic anhydride (10 ml) and of pyridine (50 ml) at room temperature. The reaction mixture was poured into water (30 ml) and isolation of the product by ethyl acetate extraction gave a red oil which was crystallized from methanol to give the furan (2) (12 g, 96%) as colourless prisms; m.p. 87—88 °C; $\nu_{max.}$ ($CHCl_3$) 1 720 cm^{-1}; δ(CCl_4) 0.6 (3 H, s, Me), 1.0 (3 H, s, Me), 1.95 (3 H, s, OCOMe), 2.3 (3 H, s, ArMe), 4.1—4.8



(18) $R^1 = R^2 = R^3 = H$

(19) $R^1 = R^2 = R^3 = Ac$

SCHEME 2

(1 H, m, 3-H), 4.83 (1 H, s, 21-H), 5.2—5.43 (1 H, m, 6-H), 5.48 (1 H, s, 21-H), 5.7—6.0 (1 H, m, ArH), 6.1 (1 H, d, *J* 3 Hz, ArH); *m/e* 422 (M^+); $[\alpha]_D$ −55° (*c* 0.4) (Found: M^+, 422.2792. Calc. for $C_{28}H_{38}O_3$: 422.2819).

(20*S*)-3-*Acetoxy*-20-(5-*methyl*-2-*furyl*)-*pregn*-5-*ene* (3).—A mixture of 10% palladium carbon (1.2 g) and the styrene (2) (12 g, 28.4 mmol) in benzene (300 ml) was stirred for 8 h under a current of hydrogen. The catalyst was filtered off and the filtrate, evaporated to afford a powder which was crystallized from acetone to give the *furan* (3) (12 g, 99.5%) as colourless prisms, m.p. 179—180 °C; $\nu_{max.}$ ($CHCl_3$) 1 725 cm^{-1}; δ(CCl_4) 0.73 (3 H, s, Me), 1.0 (3 H, s, Me), 1.2 (3 H, d, *J* 7 Hz, 20-Me), 1.92 (3 H, s, OCOMe), 2.3 (3 H, s, ArMe), 4.1—4.8 (1 H, m, 3-H), 5.2—5.5 (1 H, m, 6-H), and 5.62 (2 H, s, ArH); *m/e* 424 (M^+); $[\alpha]_D$ −53° (*c* 1.2) (Found: C, 78.9; H, 9.7. Calc. for $C_{28}H_{40}O_3$: C, 79.2; H, 9.5%).

22,25-*Dioxo*-20-*norcholesterol Acetate* (4).—A solution of acetic acid (1 ml) containing 2 drops of 10% sulphuric acid and the furan (3) (150 mg, 0.35 mmol) in tetrahydrofuran (2 ml) was heated at 70 °C for 8 h with stirring. After cooling, the reaction mixture was poured into water (5 ml) and the product was isolated by ethyl acetate extraction.

The crude product was acetylated with acetic anhydride (1 ml) and pyridine (2 ml) at room temperature. After dilution with water (2 ml), isolation of the product by ethyl acetate extraction gave a red oil which was purified by chromatography on silica gel (5 g) using ethyl acetate–dichloromethane (3 : 97 v/v) to give the *diketone* (4) (110 mg, 70.3%) as colourless prisms (from acetone), m.p. 168—169 °C; $\nu_{max.}$ ($CHCl_3$) 1 715 cm^{-1}; δ($CDCl_3$) 0.7 (3 H, s, Me), 1.01 (3 H, s, Me), 1.12 (3 H, d, *J* 7 Hz, 20-Me), 2.02 (3 H, s, OCOMe), 2.2 (3 H, s, COMe), 2.7 (4 H, s, $COCH_2$-CH_2CO), 4.2—5.0 (1 H, m, 3-H), and 5.2—5.5 (1 H, m, 6-H); *m/e* 442 (M^+); $[\alpha]_D$ −69.1° (*c* 0.72). (Found: C, 75.7; H, 9.55. Calc. for $C_{28}H_{42}O_4$: C, 75.95; H, 9.55%).

25-*Hydroxy*-22-*oxocholesterol Acetate* (5).—To a stirred solution of the diketone (4) (200 mg, 0.456 mmol) in anhydrous tetrahydrofuran (16 ml) was added in portions methyl-lithium tetrahydrofuran (0.32 ml; 1.5M) at −20 °C under a current of nitrogen; the reaction mixture was then stirred for 1 h at the same temperature. After quenching with saturated aqueous ammonium chloride (1 ml), the product was isolated by ethyl acetate extraction. The product was purified by chromatography on silica gel (20 g) using ethyl acetate–dichloromethane (5 : 95, v/v) to give the alcohol (5) (149 mg, 71%) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) 1 725 and 1 715 cm^{-1}; δ($CDCl_3$) 0.7 (3 H, s, Me), 1.0 (3 H, s, Me), 1.13 (3 H, d, *J* 7 Hz, 20-Me), 1.2 (6 H, s, 25-Me_2), 2.02 (3 H, s, OCOMe), 4.3—4.9 (1 H, m, 3-H), 5.2—5.5 (1 H, m, 6-H); *m/e* 442 (M^+); $[\alpha]_D$ −53.3° (*c* 0.3). [Found: M^+ − 18 440.3284. Calc. for $C_{29}H_{46}O_4$: 440.3289 (M^+ − 18)].

Reduction of Compound (5).—(*a*) To a stirred solution of the ketone (5) (150 mg, 0.33 mmol) in methanol (30 ml) was added sodium borohydride (45 mg, 1.185 mmol) at 0 °C and then the reaction mixture was stirred for 1 h at the same temperature. After dilution with water (20 ml), isolation of the product by ethyl acetate extraction gave an oil. This crude product was acetylated with acetic anhydride (15 ml) and pyridine (45 ml). The reaction mixture was stirred for 8 h at room temperature and then poured into water (80 ml). The product was isolated by ethyl acetate extraction to give a yellow oil which was purified by chromatography on silica gel (50 g) using ethyl acetate–dichloromethane (3 : 97, v/v) to give the 22*R*-compound (8) (35 mg, 21%) which was identical with an authentic sample.[6]

Further elution gave the 22*S*-compound (9) (104 mg, 63.2%) which was identical with the authentic sample.[6]

(*b*) To a stirred solution of the ketone (5) (150 mg, 0.33 mmol) in anhydrous tetrahydrofuran (30 ml) was added 0.35M-lithium tri-t-butylaluminium hydride solution (15 ml) in ether at −5 °C under a current of nitrogen. After the reaction mixture had been stirred for 30 min, aqueous ammonium chloride (30 ml) was added and the product was isolated by ethyl acetate extraction.

Acetylation of the product gave the 22*R*-compound (8) (23.9 mg, 14.1%) and the 22*S*-compound (9) (110 mg, 66.8%).

(*c*) To a stirred solution of the ketone (5) (180 mg, 0.39 mmol) in anhydrous ether (12 ml) was added 1.45M-zinc borohydride in ether (9 ml) at room temperature. After the reaction mixture had been stirred for 8 h, water (10 ml) was added and the product was isolated by ethyl acetate extraction.

Acetylation of the product gave the 22*R*-compound (8) (49.4 mg, 25%) and the 22*S*-compound (9) (98 mg, 49.6%).

(20S)-3β-*Acetoxy*-6α-*hydroxy*-20-(5-*methyl*-2-*furyl*)-5α-*pregnane* (10).—To a stirred solution of the olefin (3) (0.6 g, 1.4 mmol) in anhydrous tetrahydrofuran (10 ml) was added 1M-diborane solution (5.5 ml) in tetrahydrofuran at 0 °C under a current of nitrogen. After the reaction mixture had been stirred for 8 h at room temperature, 10% aqueous sodium hydroxide (3 ml) and 10% hydrogen peroxide (3 ml) was added at 0 °C. The reaction mixture was stirred for 4 h at room temperature and was then poured into water (10 ml). Isolation of the product by ethyl acetate extraction gave a yellow oil which was purified by chromatography on silica gel (15 g) using ethyl acetate–dichloromethane (5 : 95 v/v) to give the *alcohol* (0.51 g, 81.5%) (10) as colourless needles (from acetone), m.p. 184—185 °C; $\nu_{max.}$ ($CHCl_3$) 1 725 cm^{-1}; δ($CDCl_3$) 0.7 (3 H, s, Me), 0.82 (3 H, s, Me), 1.2 (3 H, d, *J* 7 Hz, 20-Me), 2.0 (3 H, s, OCOMe), 2.22 (3 H, s, ArMe), 3.1—3.8 (1 H, m, 6-H), 4.3—5.0 (1 H, m, 3-H), and 5.73 (2 H, s, ArH); *m/e* 442 (M^+); $[\alpha]_D$ +11.4° (*c* 2.7). (Found: C, 75.75; H, 9.60. Calc. for $C_{28}H_{42}O_4$: C, 75.95; H, 9.55%).

(20S)-3β-*Acetoxy*-20-(5-*methyl*-2-*furyl*)-6-*oxo*-5α-*pregnane* (11).—To a stirred solution of Sarret reagent [prepared from chromium trioxide (2 g) and pyridine (25 ml)] was added a solution of the alcohol (10) (1.0 g, 2.26 mmol) in pyridine (1 ml) at room temperature. The reaction mixture was stirred for 3 h at room temperature and then saturated aqueous ammonium chloride (5 ml) was added to it. The inorganic compound was filtered off and the product isolated by ethyl acetate extraction to give an oil which was purified by chromatography on silica gel (20 g) using ethyl acetate–dichloromethane (2 : 98 v/v) to give the *ketone* (11) (0.85 g, 85.4%) as colourless needles (from acetone), m.p. 185—186 °C; $\nu_{max.}$ ($CHCl_3$) 1 720 and 1 705 cm^{-1}; δ($CDCl_3$) 0.7 (3 H, s, Me), 0.77 (3 H, s, Me), 1.23 (3 H, d, *J* 7 Hz, 20-Me), 2.0 (3 H, s, OCOMe), 2.21 (3 H, s, ArMe), 4.3—5.0 (1 H, m, 3-H), and 5.73 (2 H, s, ArH); *m/e* 440 (M^+); $[\alpha]_D$ −20.5° (*c* 1.46) (Found: C, 76.15; H, 9.15. Calc. for $C_{28}H_{40}O_4$: C, 76.35; H, 9.15%).

Thioacetalization of Compound (11).—To a stirred solution of the ketone (11) (0.26 g, 0.59 mmol) in acetic acid (3 ml) was added ethanedithiol (0.75 ml) and boron trifluoride–diethyl ether (1 ml) at room temperature. The reaction mixture was stirred for 3 h at the same temperature and was

then poured into water (5 ml). The product was isolated by ethyl acetate extraction and then purified by chromatography on silica gel (6 g) using ethyl acetate–dichloromethane (2 : 98 v/v) to give the thioketal (12) (65 mg, 21.3%) as colourless needles (from acetone), m.p. 87—88 °C; $\nu_{max.}$ ($CHCl_3$) 1 720 cm^{-1}; δ($CDCl_3$) 0.76 (3 H, s, Me), 0.97 (3 H, s, Me), 1.2 (3 H, d, *J* 7 Hz, 20-Me), 1.97 (3 H, s, OCOMe), 2.25 (3 H, s, ArMe), 3.34 (4 H, br s, SCH_2CH_2S), 4.3—4.9 (1 H, m, 3-H), and 5.66 (2 H, s, ArH); *m/e* 516 (M^+); $[\alpha]_D$ +2.2° (*c* 0.36) [Found: 516.2755 (M^+). Calc. for $C_{30}H_{44}O_3S_2$: 516.2732].

Further elution with ethyl acetate–dichloromethane (4 : 96 v/v) gave the dithioketal (13) (280 mg, 77.7%) as colourless needles (from acetone), m.p. 214—215 °C; $\nu_{max.}$ ($CHCl_3$) 1 720 and 1 705 cm^{-1}; δ(CCl_4) 0.72 (3 H, s, Me), 0.96 (3 H, s, Me), 1.07 (3 H, d, *J* 7 Hz, 20-Me), 1.78 (3 H, s, 25-Me), 1.98 (3 H, s, OCOMe), 3.14 (4 H, br s, SCH_2CH_2S), 3.28 (4 H, s, SCH_2CH_2S), and 4.3—5.0 (1 H, m, 3-H); *m/e* 610 (M^+); $[\alpha]_D$ −5.8° (*c* 2.96) [Found: 610.2636 (M^+). Calc. for $C_{32}H_{50}O_3S_4$: 610.2641].

Reduction of Compound (13).—To a stirred solution of the ketone (13) (0.52 g, 0.85 mmol) in dichloromethane (5 ml) and methanol (10 ml) was added in portions sodium borohydride (300 mg) at 0 °C. After the reaction mixture had been stirred for 3 h at room temperature, aqueous ammonium chloride (1 ml) was added; isolation of the product by ethyl acetate extraction gave an oil which was purified by chromatography on silica gel (15 g) using ethyl acetate–dichloromethane (1 : 99, v/v) to give the 22*R*-compound (15) (0.15 g, 28.7%) as a colourless powder (from hexane–acetone), m.p. 130—131 °C; $\nu_{max.}$ ($CHCl_3$) 3 600 and 1 725 cm^{-1}; δ(CCl_4) 0.73 (3 H, s, Me), 0.96 (3 H, s, Me), 0.91 (3 H, d, *J* 7 Hz, 20-Me), 1.75 (3 H, s, 25-Me), 1.98 (3 H, s, OCOMe), 3.15 (4 H, br s, SCH_2CH_2S), 3.3 (4 H, s, SCH_2-CH_2S), and 4.3—5.0 (1 H, m, 3-H); *m/e* 612 (M^+); $[\alpha]_D$ +7.05° (*c* 2.1). [Found: 612.2777 (M^+). Calc. for $C_{32}H_{52}O_3S_4$: 612.2798].

Further elution with the same solvent gave the 22*S*-compound (14) (360 mg, 69.0%) as a colourless powder (from hexane–acetone), m.p. 199—200 °C; $\nu_{max.}$ ($CHCl_3$) 3 590 and 1 725 cm^{-1}; δ(CCl_4) 0.71 (3 H, s, Me), 0.96 (6 H, br s, Me and 20-Me), 1.73 (3 H, s, 25-Me), 1.98 (3 H, s, OCOMe), 3.16 (4 H, br s, SCH_2CH_2S), 3.27 (4 H, s, SCH_2-CH_2S , and 4.3—5.0 (1 H, m, 3-H); $[\alpha]_D$ −5.35° (*c* 0.6) [Found: 612.2815 (M^+) Calc. for $C_{32}H_{52}O_3S_4$: 612.2799].

Jones Oxidation of the 22S-*Compound* (14).—To a stirred solution of the alcohol (14) (0.36 g, 0.588 mmol) in acetone (4 ml) was added 4N Jones reagent (0.5 ml) at 0 °C. The reaction mixture was stirred for 30 min at the same temperature and then poured into water (10 ml). Isolation of the product by ethyl acetate extraction gave an oil which was purified by chromatography on silica gel (2 g) using ethyl acetate–dichloromethane (1 : 99 v/v) to give the ketone (13) (0.35 g, 97.5%) which was identical with the above authentic sample.

(22R)-3β-*Acetoxy*-6,6-(1,2-*ethylenedithio*)-25-*oxo*-26-*norcholestane* (16).—A solution of the dithioketal (15) (0.17 g, 0.28 mmol) in 15% aqueous acetone (15 ml) and methyl iodide (2 ml) was refluxed for 6 h under a current of nitrogen with stirring. After dilution with aqueous ammonium chloride (10 ml), the solvent was evaporated to give the residue which was chromatographed on silica gel (2 g) using ethyl acetate–dichloromethane (3 : 97 v/v) to afford the monoketone (16) (0.13 g, 87.3%) as a colourless powder (from hexane–acetone), m.p. 123—124 °C; $\nu_{max.}$ ($CHCl_3$) 3 600 and 1 725 cm^{-1}; δ($CDCl_3$) 0.7 (3 H, s, Me), 0.86 (3 H, d, *J* 7 Hz, 20-Me), 0.98 (3 H, s, Me), 2.02 (3 H, s, OCOMe), 2.16 (3 H, s, COMe), 3.17 (4 H, br s, SCH_2CH_2S), 3.4—3.8 (1 H, m, 22-H), and 4.3—5.0 (1 H, m, 3-H); $[\alpha]_D$ −4.0° (*c* 0.3). [Found: 518.2877 (M^+ − 18). Calc. for C_{30}-$H_{48}O_4S_2$: 518.2887].

(22R)-6,6-(1,2-*Ethylenedithio*)-3β,22,25-*trihydroxycholestane* (17).—To a stirred solution of the ketone (16) (55 mg, 0.1 mmol) (16) in anhydrous tetrahydrofuran (2 ml) was added 1.5M-methyl lithium in tetrahydrofuran (0.5 ml) at 0 °C under a current of nitrogen. The reaction mixture was stirred for 1 h at the same temperature after which aqueous ammonium chloride (1 ml) was added. Isolation of the product by ethyl acetate extraction gave an oil which was purified by chromatography on silica gel (2 g) using ethyl acetate–dichloromethane (70 : 30, v/v) to give the triol (17) (40 mg, 76.4%) as a colourless powder (from hexane–acetone), m.p. 129—130 °C; $\nu_{max.}$ ($CHCl_3$) 3 600 cm^{-1}; δ($CDCl_3$) 0.7 (3 H, s, Me), 0.9 (3 H, d, *J* 7 Hz, 20-Me), 0.95 (3 H, s, Me), 1.22 (6 H, s, 25-Me_2), and 3.18 (4 H, br s, SCH_2CH_2S); $[\alpha]_D$ +11.43° (*c* 0.56). [Found: 510.3179 (M^+). Calc. for $C_{29}H_{50}O_3S_2$: 510.3199].

(22R)-3β,22,25-*Trihydroxy*-6-*oxocholestane* (19).—A solution of the thioketal (17) (20 mg, 0.039 mmol) in 20% aqueous acetonitrile (6 ml), tetrahydrofuran (2 ml), and methyl iodide (1 ml) was heated for 10 h at 55 °C with stirring under a current of nitrogen. After the mixture had been cooled, aqueous ammonium chloride (10 ml) was added and the solvent was evaporated. Isolation of the product by ethyl acetate extraction gave a colourless solid which, owing to its insolubility, was further characterized as its 3,22,25-triacetate. Thus, the product was acetylated with acetic anhydride (1 ml) and pyridine (3 ml) containing a catalytic amount of 4,4-dimethylaminopyridine at room temperature. The reaction mixture was poured into water (5 ml) and isolation of the product by ethyl acetate extraction gave an oil which was purified by chromatography on silica gel (3 g) using ethyl acetate–dichloromethane (7 : 93, v/v) to afford the triacetate (19) (19.3 mg, 88.4%) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) 1 720 cm^{-1}; δ(CD-Cl_3) 0.67 (3 H, s, Me), 0.77 (3 H, s, Me), 0.92 (3 H, d, *J* 7 Hz, 20-Me), 1.44 (6 H, s, 25-Me_2), 2.02 (9 H, s, 3 × OCOMe), and 4.4—5.2 (2 H, m, 3- and 22-H); $[\alpha]_D$ −7.78° (*c* 0.18). [Found: 501.3571 (M^+ − 59 g). Calc. for $C_{33}H_{52}O_7$: 501.3578].

We thank Professor B. M. Trost, Wisconsin University, for a generous gift of (22*R*)-22,25-dihydroxycholesterol and its 22*S*-isomer which were used in this study and also Mr. K. Kawamura, Miss Y. Enomoto, Mrs. R. Kobayashi, Miss Y. Kato, Miss K. Kikuchi, Miss K. Ohtomo, Miss A. Hareyama, and Miss Y. Watanabe for spectral measurements and for preparation of the manuscript.

[1/738 *Received*, 11*th Ma y*, 1981

REFERENCES

[1] K. Nakanishi, *Pure Appl. Chem.*, 1971, **25**, 167.
[2] H. Hikino and Y. Hikino, *Fortschr. Chem. Org. Naturst.*, 1970, **28**, 256.
[3] H. F. De Luca and H. K. Schnoes, *Annu. Rev. Biochem.*, 1976, **45**, 631.
[4] P. E. Georghiou, *Chem. Soc. Rev.*, 1977, **6**, 85.
[5] For a review on the construction of steroid side-chains, see: D. M. Piatak and J. Wicha, *Chem. Rev.*, 1978, **78**, 199.
[6] B. M. Trost and Y. Matsumura, *J. Org. Chem.*, 1977, **42**, 2036.

[7] B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, 1978, **100**, 3435.
[8] S. R. Schow and T. C. McMorris, *J. Org. Chem.*, 1979, **44**, 3760.
[9] M. Koreeda, Y. Tanaka, and A. Schwartz, *J. Org. Chem.*, 1980, **45**, 1172.
[10] M. Tanabe and K. Hayashi, *J. Am. Chem. Soc.*, 1980, **102**, 862.
[11] J. S. Temple and J. Schwartz, *J. Am. Chem. Soc.*, 1980, **102**, 7381.
[12] W. G. Dauben and T. Brookhart, *J. Am. Chem. Soc.*, 1981, **103**, 237.
[13] M. M. Midland and Y. C. Kwon, *J. Org. Chem.*, 1981, **46**, 229.
[14] G. Büchi and H. Wüest, *J. Org. Chem.*, 1966, **31**, 977.