Studies on Steroids. Part XXIX.[1] Synthesis of Allenic Analogues of Fucosterol and Desmosterol

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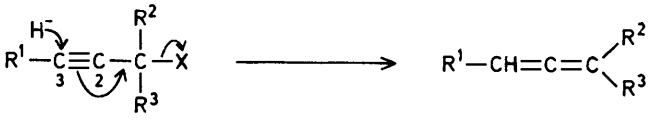
As potential specific inhibitors of sterol biosynthesis, two steroidal allenes, stigmasta-5,24(28),28-trien-3β-ol (6) and cholesta-5,23,24-trien-3β-ol (22), have been synthesized *via* a reductive S_N2' reaction(lithium aluminium hydride–aluminium chloride) of the corresponding αβ-acetylenic alcohols.

SOME allenic analogues of normal substrates have been shown to be potent and specific inhibitors of β-hydroxydecanoyl thioester dehydrase, a key enzyme system in unsaturated fatty acid biosynthesis.[2] On the basis of these findings, we felt that steroidal allenes might act as specific inhibitors of sterol biosynthesis. In the terminal stages of sterol biosynthesis fucosterol and desmosterol are important intermediates;[3] we therefore considered that the analogous allenic sterols (6) and (22) might exert an inhibitory effect on phytosterol dealkylation in insects,[4] on liver Δ^{24}-sterol reductase,[5] on yeast sterol C-24 methyl transferase,[6] and/or on phytosterol side-chain biosynthesis.[7] We describe here the synthesis of the allenes (6) and (22).[8]

Of various methods of preparing allenes,[9] we selected a reductive S_N2' reaction of an acetylene derivative with



SCHEME 1

a suitable leaving group at the adjacent position (Scheme 1). In this Scheme, the leaving group (X) may be halogen, quarternary ammonium salt, sulphonate, acetate, ether, epoxide, or hydroxide and the reducing reagent[10] Zn, Zn–Cu, Na–Hg, $LiAlH_4$, $LiMe_2Cu$, or $LiAlH_4$–$AlCl_3$.

24-Oxocholesterol tetrahydropyranyl (Thp) ether (1)[11] was treated with sodium acetylide in liquid ammonia[12] to yield the 24-ethynyl alcohol, which was then treated with methanolic hydrogen chloride followed by acetic anhydride in pyridine. Chromatography of the product on a silica gel column afforded the acetate (2) (61%), and 20% of the 24-ketone was recovered. The corresponding diacetate (3) was prepared in 34% yield by acetylation with acetic anhydride catalysed by calcium hydride.[13] An alternative acetylation with acetic anhydride in the presence of toluene-*p*-sulphonic acid afforded the diacetate (3) (26%), accompanied by the enyne (5) (26%) (Scheme 2).

An attempt to effect a reductive S_N2' reaction of the diacetate (3) by refluxing with zinc dust in bis-(2-methoxyethyl) ether[14] failed; the starting material was recovered. Similarly, when the acetate (2) was treated with lithium aluminium hydride in tetrahydrofuran, only the diol (4) was obtained in good yield. However, reduction of (2) with lithium aluminium hydride–aluminium chloride (3 : 1) in tetrahydrofuran[15,16] gave the expected allene (6) (46%) and the allylic alcohol, saringosterol (7)[12] (42%). In an attempt to increase the yield of

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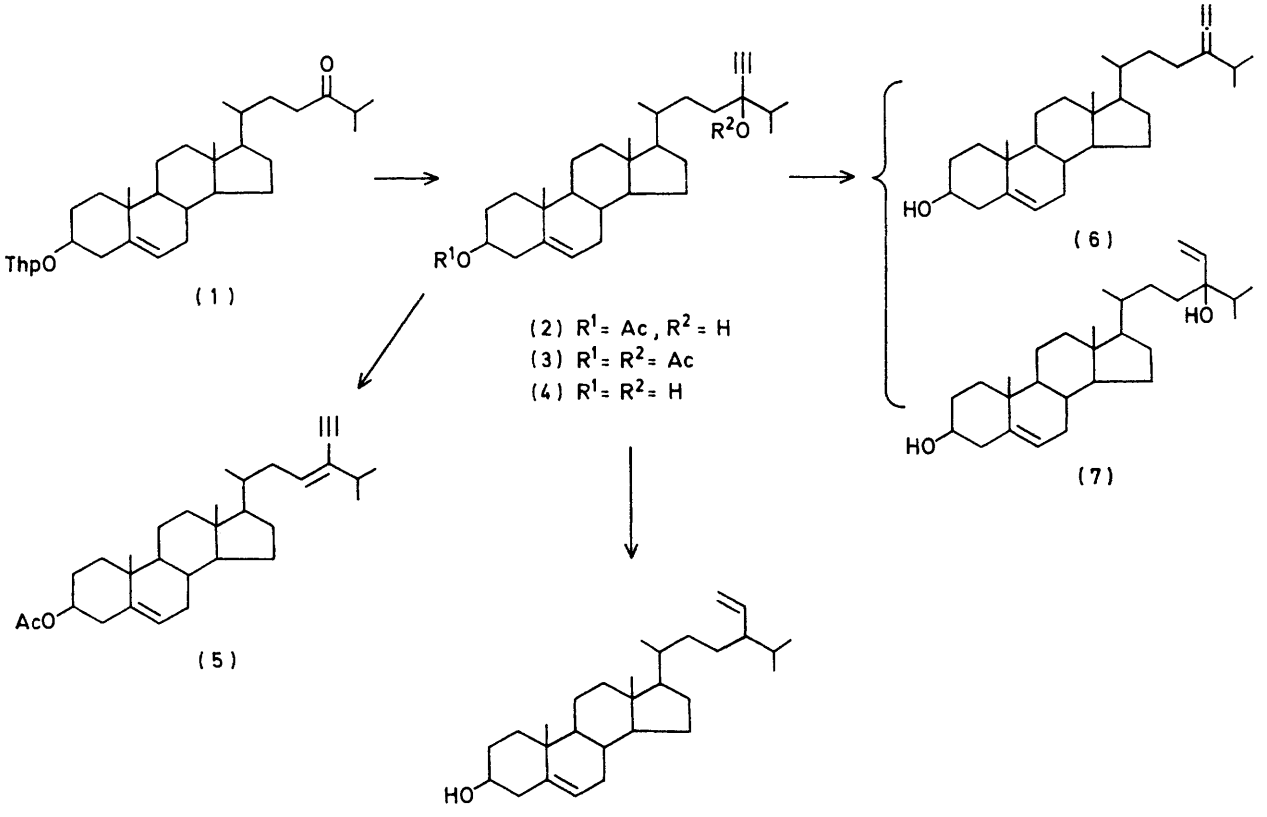
allene (6), the aluminium chloride was replaced by titanium tetrachloride: however, this afforded the deoxygenated olefin (8) (50%).*

The allene (22) was synthesized as in Scheme 3. The tosylate (11) was synthesized in a straightforward manner in 70% overall yield from the methyl ester (9) of commercially available 3-acetoxybisnorcholenic acid. from the crude product of the coupling reaction by silica gel column chromatography. The monoacetate (18) and the diacetate (19) were prepared by treatment of the diol (17) with acetic anhydride–pyridine at 15 or 120 °C, respectively. Attempted mesylation of the monoacetate (18) with mesyl chloride in triethylamine [18] induced dehydration to give the enyne (20) (75%). The



SCHEME 2

The tosyl group was readily displaced with a variety of nucleophiles affording the bromide (12), the azide (13), or the methyl ether (14). However C–C bond formation by reaction with the lithium acetylide derived from (15) was not easily achieved. On treatment of (11) with two equivalents of the acetylide in tetrahydrofuran or tetrahydrofuran–hexamethylphosphoric triamide (4 : 1), no reaction occurred. An excess of reagent or increasing the proportion of the phosphoramide induced hydrolysis of the tosylate giving the alcohol (10). Success was finally attained by the use of a recently reported method.[17] Thus the tosylate (11) was refluxed in dioxan with 4 equiv. of the reagent, and then both Thp groups of the crude product were cleaved by acidic treatment. Subsequent chromatography on a silica gel column provided the acetylenic alcohol (17) (70%) and the starting 3,22-diol (10%). A crystalline di-Thp ether (16) was obtained

* Details of the hydrogenolysis of acetylenic and allylic alcohols with lithium aluminium hydride–titanium tetrachloride will be published elsewhere.

same enyne (20) was also obtained by attempted acetylation of the diol (17) with acetic anhydride–toluene-*p*-sulphonic acid.

Reduction of the diol (17) or the diacetate (19) with lithium aluminium hydride in tetrahydrofuran produced only the allylic alcohol (21) in good yield, accompanied by a trace (1—2% by g.l.c. analysis) of the allene (22). The Thp ether (16) was unchanged under the same conditions. The desired S_N2' reaction occurred on treatment of the diol (17) or the diacetate (19) with lithium aluminium hydride–aluminium chloride (3 : 1),[15,16] to afford the allene (22) (13%) and the allylic alcohol (21) (80%). The Thp ether (16) resisted reaction even under these conditions. Combination of lithium aluminium hydride with titanium tetrachloride induced concomitant deoxygenation as observed above [*i.e.* (2) ⟶ (8)], leading to the olefin (23).

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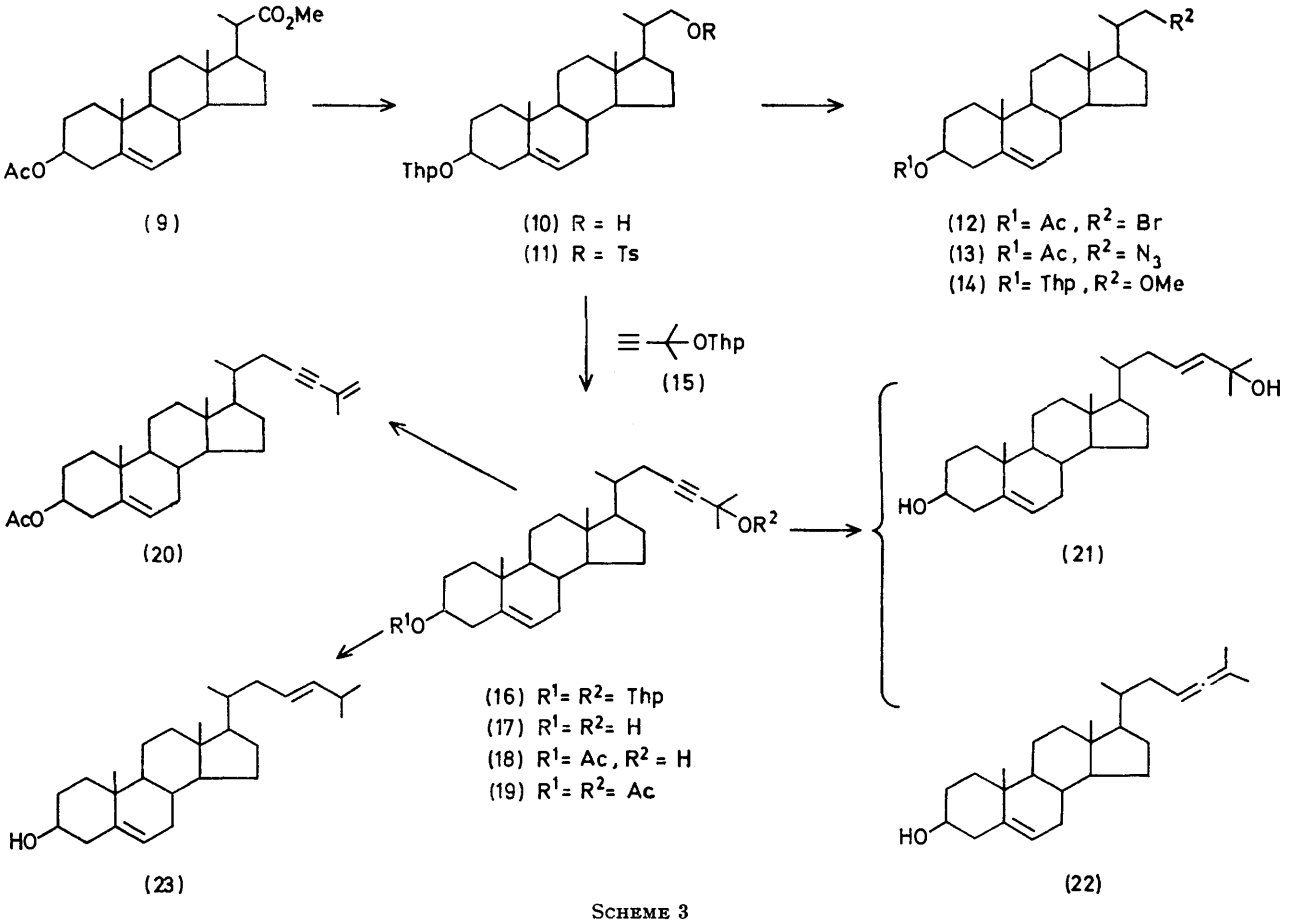
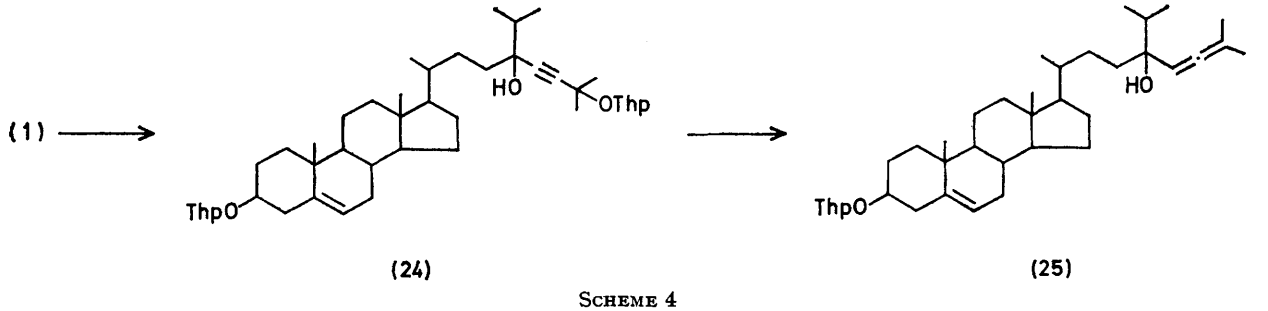
The extreme unreactivity of the Thp ether (16) suggests that an extra hydroxy-group at the adjacent position is essential for the S_N2' reaction of αβ-acetylenic Thp ethers to give allenic alcohols.[19,20] In fact, an analogous Thp ether (24) prepared from the 24-ketone and (17) is of interest. In the absence of aluminium chloride, aluminium may bind to oxygen and the hydride may be delivered intramolecularly to C-2 exclusively,[21] giving the allylic alcohol (Scheme 5), as exemplified in the case (17) ⟶ (21). However the hydroxy-group



SCHEME 3



SCHEME 4

(1) by coupling with the lithium salt of (15) yielded the allene (25) in an excellent yield on treatment with lithium aluminium hydride in ether (Scheme 4).

In connection with the mechanism of the reduction of αβ-acetylenic alcohols by lithium aluminium hydride, a comparison of the results observed with compounds (2) of (2) appears to be too highly hindered to complex with the reducing agent, thus preventing reaction. Addition of a Lewis acid ($AlCl_3$) to the reaction medium may increase the leaving group character of OH and result in formation of allene by hydride attack on C-3 (Scheme 1).

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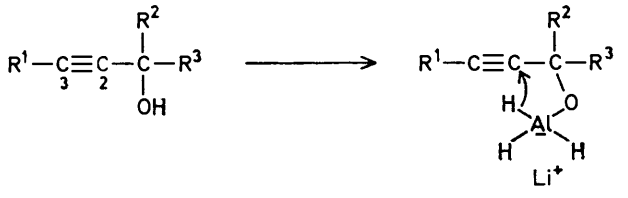
[21] B. Grant and C. Djerassi, *J. Org. Chem.*, 1974, **39**, 968.

Position 29 of the terminal acetylene (2) may be more susceptible to hydride attack than C-23 of the internal acetylene (17), in agreement with the observed product ratio of allene to allylic alcohol.



SCHEME 5

At least one of the above allenes [*i.e.* the allene (6)] is a specific inhibitor of sterol metabolism in the silkworm *Bombyx mori*.*

EXPERIMENTAL

M.p.s were determined with a hot-stage microscope. I.r. spectra were taken with a Hitachi ESI-G_2 spectrometer for solutions in chloroform solution unless otherwise stated, u.v. spectra with a Hitachi ESP-3T apparatus with ethanol as solvent, and ^{1}H n.m.r. spectra with a Varian T-60 or JEOL JNM-4H-100 spectrometer with deuteriochloroform as solvent unless otherwise cited, and tetramethylsilane as internal reference. Mass spectra were determined with an LKB-9000S instrument. Column chromatography was carried out with Wako silica gel C-200. T.l.c. was carried out with Merck precoated Kieselgel 60 F_{254} plates (0.25 mm thick). 'The usual work-up' refers to dilution with water, extraction with organic solvent, washing to neutrality, drying ($MgSO_4$), filtration, and evaporation under vacuum.

Stigmast-5-en-28-yne-3β,24-diol 3-Acetate (2).—Dry acetylene was passed into a solution of sodium (800 mg) in liquid ammonia (300 ml) until the blue colour was discharged. To the stirred suspension of sodium acetylide was then added 24-oxocholesterol Thp ether (1) (2.7 g) in dry tetrahydrofuran (Thf) (20 ml). The mixture was stirred for 1 h and worked up by addition of solid ammonium chloride (1.9 g), evaporation of ammonia, addition of water, and extraction with ether. The organic layer was washed with water, dried ($MgSO_4$), and evaporated and the residue was treated with 1N-HCl (5 drops) in methanol (35 ml)–Thf (15 ml) at room temperature for 3 h. The usual work-up gave a white solid, which was kept in dry pyridine (10 ml) and acetic anhydride (20 ml) at room temperature overnight. The solution was poured into ice–water and extracted with ether. The extract was chromatographed on a silica gel column. Elution with hexane–benzene (1 : 1) gave unchanged 24-oxocholesterol acetate (500 mg, 20%). Further elution with benzene afforded the *acetate* (2) (1.56 g, 61%), m.p. 205—207° (from methanol), $\nu_{max.}$ 3 600, 3 260, and 1 720 cm^{-1}, δ 0.67 (3 H, s, 13-Me), 1.01 (3 H, s, 10-Me), 1.01 (6 H, d, *J* 6.0 Hz, 25-Me_2), 2.01 (3 H, s, Ac), 2.40 (1 H, s, HC≡C), 4.6 (1 H, m, 3α-H), and 5.4br (1 H, 6-H) (Found: C, 79.9; H, 10.45. $C_{31}H_{48}O_3$ requires C, 79.45; H, 10.3%).

Stigmast-5-en-28-yne-3β,24-diol Diacetate (3).—To a mixture of acetic anhydride (0.2 ml) and dry xylene (1.5 ml) was added powdered calcium hydride (21 mg). After refluxing under a stream of nitrogen for 1 h, the acetate (2) (40 mg) was added and refluxing was continued for 15 h. Saturated aqueous sodium hydrogen carbonate was then added and the mixture was extracted with ether. The crude product obtained by the usual work-up was purified by preparative layer chromatography (p.l.c.), to give the *diacetate* (3) (15 mg, 34%) as an amorphous solid, $\nu_{max.}$ 3 300 and 1 730 cm^{-1}, δ 0.67 (3 H, s, 13-Me), 1.00 (3 H, s, 10-Me), 2.01 (6 H, s, 2 × Ac), 2.5 (1 H, s, HC≡C), 4.6 (1 H, m, 3α-H), and 5.4 (1 H, m, 6-H), *m/e* 510 (M^+), 450 (M^+—AcOH), and 390 (M^+ — 2AcOH) (Found: M^+, 510.3731. $C_{33}H_{50}O_4$ requires *M*, 510.3712).

Stigmast-5-en-28-yne-3β,24-diol (4).—(*a*) A solution of the acetate (2) (200 mg) in methanolic 5% potassium hydroxide (5 ml) was stirred at room temperature for 5 h, then poured into cold water and extracted with ethyl acetate. The usual work-up gave the diol (4) (170 mg, 93%), m.p. 185—186° (from methanol) (lit.,[12] 184—184.5°), $\nu_{max.}$ 3 600, 3 450, and 3 300 cm^{-1}, δ 0.67 (3 H, s, 13-Me), 1.00 (3 H, s, 10-Me), 1.01 (6 H, d, *J* 6.0 Hz, 25-Me_2), 2.39 (1 H, s, HC≡), 3.5 (1 H, m, 3α-H) and 5.4 (1 H, m, 6-H), *m/e* 426 (M^+).

(*b*) To a suspension of $LiAlH_4$ (100 mg) in dry Thf (2 ml), a solution of the acetate (2) (47 mg) in dry Thf (2 ml) was added. After refluxing for 10 h under nitrogen, the mixture was cooled and the excess of hydride was decomposed with water. The mixture was extracted with ether and usual work-up gave the diol (4) (39 mg, 91%).

Stigmasta-5,23-dien-28-yn-3β-yl Acetate (5).—A mixture of the acetate (2) (100 mg), acetic acid (2.25 ml), acetic anhydride (0.225 ml), and toluene-*p*-sulphonic acid monohydrate (90 mg) was kept at room temperature for 2 h. The usual work-up (ether for extraction; purification by p.l.c.) afforded the diacetate (3) (28 mg, 26%) as an amorphous solid and the *enyne* (5) (25 mg, 26%), m.p. 95—98° (from methanol), $\lambda_{max.}$ 224 nm (ε 10 000), δ 0.66 (3 H, s, 13-Me), 1.01 (3 H, s, 10-Me), 1.09 (6 H, d, *J* 6.5 Hz, 25-Me_2), 2.01 (3 H, s, Ac), 3.09 (1 H, s, HC≡C), 4.5 (1 H, m, 3α-H), 5.4 (1 H, m, 6-H), and 5.76 (1 H, t, *J* 6.5 Hz, 23-H) (Found: M^+, 450.3501. $C_{31}H_{46}O_2$ requires *M*, 450.3497).

Attempted Reduction of the Diacetate (3).—To the diacetate (3) (10 mg) in dry bis-(2-methoxyethyl) ether (2 ml) was added freshly activated zinc dust (6.5 mg) and the mixture was refluxed under nitrogen overnight. The mixture was filtered and the filtrate extracted with ether. The extract was washed with water, dried, and evaporated to give starting material (identified by t.l.c. and n.m.r.).

Stigmasta-5,24(28),28-trien-3β-ol (6).—To a suspension of $LiAlH_4$ (500 mg) and $AlCl_3$ (500 mg) in dry Thf (10 ml) was added a solution of the ethynyl alcohol (2) (450 mg) in dry Thf (10 ml). The mixture was refluxed for 10 h. The excess of reagent was decomposed by addition of moist ether and the mixture was extracted with ether. The usual work-up and column chromatography on silica gel [benzene–ethyl acetate (50 : 1)] afforded the *allene* (6) (200 mg, 46%), m.p. 105—106° (from methanol), $\nu_{max.}$ (CCl_4) 3 600, 1 950, and 850 cm^{-1}, δ 0.67 (3 H, s, 13-Me), 1.00 (3 H, s, 10-Me), 1.01 (6 H, d, *J* 6 Hz, 25-Me_2), 3.5 (1 H, m, 3α-H), 4.68 (2 H, m, 29-H_2), and 5.4 (1 H, m, 6-H) (Found: M^+, 410.3586. $C_{29}H_{46}O$ requires *M*, 410.3548).

Further elution with benzene–ethyl acetate (10 : 1) gave the allylic alcohol (7) (190 mg, 42%), m.p. 159.5—161° (from methanol) (lit.,[12] 160—161°), *m/e* 428 (M^+), identical with authentic saringosterol.[12]

Stigmasta-5,28-dien-3β-ol (8).—A solution of the diol (4) (50 mg) in dry Thf (2 ml) was added to a mixture of $TiCl_4$ (30 μl) and dry Thf (2 ml) under argon. The mixture

* Details of the biological activity of the allenic compounds (6) and (22) will be described in a forthcoming paper.

was stirred for 10 min and added to a suspension of $LiAlH_4$ (38 mg) in dry Thf (3 ml). The mixture then turned black; it was refluxed for 5 h and then moist ether was added. The organic layer was washed with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated to dryness. Crystallization from methanol gave the deoxygenated olefin (8) (24 mg, 50%), m.p. 123—127°, *m/e* 412 (M^+).

Acetylation of (8) and crystallization from methanol gave the corresponding *acetate*, m.p. 130—132°, δ 0.70 (3 H, s, 13-Me), 1.00 (3 H, s, 10-Me), 4.6 (1 H, m, 3α-H), and 4.8—5.8 (4 H, m, 6- and 28-H and 29-H_2) (Found: C, 82.0; H, 11.3. $C_{31}H_{50}O_2$ requires C, 81.9; H, 11.1%).

23,24-*Bisnorchol*-5-*ene*-3,22-*diol* 3-*Thp Ether* (10).—To a solution of the methyl ester (9) (10 g) in ethanol (400 ml) was added a 5% solution of KOH in methanol–water (3 : 1) (44.3 ml). The mixture was stirred at room temperature for 3 h. After neutralization with 1N-HCl, the mixture was concentrated *in vacuo* and poured into ice–water. The precipitate was collected, washed with water, and dried *in vacuo* to afford methyl 3β-hydroxybisnorchol-5-en-22-oate, m.p. 138—141° (from methanol). This was dissolved in CH_2Cl_2 (400 ml) and dihydropyran (4.5 ml) and a catalytic amount of toluene-*p*-sulphonic acid were added. The solution was stirred for 1.5 h at room temperature. Work-up as usual (CH_2Cl_2 for extraction) gave the 3-Thp ether (8.7 g), m.p. 137.5—138.5° (from methanol–acetone). To a suspension of $LiAlH_4$ (2.0 g) in dry ether (100 ml) was added a solution of the Thp ether (8.7 g) in dry ether (200 ml) at 0 °C. The mixture was stirred for 1 h at room temperature. After addition of 1N-NaOH, the mixture was extracted with ether. The usual work-up gave the 22-*alcohol* (10) (7.9 g), m.p. 148.5—150° (methanol), δ 0.67 (3 H, s, 13-Me), 1.00 (3 H, s, 10-Me), 3.1—4.2 (5 H, m, 3α-H, 22-H_2, and 6′-H_2 of Thp), 4.75 (1 H, m, 2′-H of Thp), and 5.4 (1 H, m, 6-H) (Found: C, 78.0; H, 10.85. $C_{27}H_{44}O_3$ requires C, 77.85; H, 10.65%).

22-*Tosyloxy*-23,24-*bisnorchol*-5-*en*-3β-*yl*-*Thp Ether* (11).—To a solution of the 22-alcohol (10) (7.9 g) in pyridine (30 ml) was added toluene-*p*-sulphonyl chloride (5.0 g), and the mixture was left at 0 °C overnight, poured into cold water, and extracted with ether. The usual work-up gave the tosylate (11) (10.0 g) [70% overall yield from (9)], m.p. 143—145° (from acetone–methanol), δ 0.65 (3 H, s, 13-Me), 1.00 (3 H, s, 10-Me), 2.45 (3 H, s, aromatic Me), 3.2—4.2 (5 H, m, 3α-H, 22-H_2, and 6′-H_2 of Thp), 4.73 (1 H, m, 2′-H of Thp), 5.35 (1 H, m, 6-H), and 7.6 (4 H, m, aromatic) (Found: C, C, 71.45; H, 8.95. $C_{34}H_{50}O_5S$ requires C, 71.55; H, 8.85%).

22-*Bromo*-23,24-*bisnorchol*-5-*en*-3β-*yl Acetate* (12).—A mixture of the tosylate (11) (235 mg), lithium bromide (130 mg), and dry acetone (4 ml) was refluxed under argon for 30 min and then extracted with ether. The organic layer was washed with water, dried, and evaporated to dryness. The residue was treated with acidic methanol to remove the Thp group and acetylated with acetic anhydride–pyridine to afford the 22-*bromide* (12) (140 mg, 72%), m.p. 151—153° (from methanol), δ 0.70 (3 H, s, 13-Me), 1.00 (3 H, s, 10-Me), 2.0 (3 H, s, Ac), 3.3 (1 H, dd, *J* 10 and 5 Hz, 22-H_a), 3.55 (1 H, dd, *J* 10 and 3 Hz, 22-H_b), 4.6 (1 H, s, 3α-H), and 5.4 (1 H, m, 6-H) (Found: C, 66.05; H, 8.65. $C_{24}H_{37}BrO_2$ requires C, 65.9; H, 8.55%).

22-*Azido*-23,24-*bisnorchol*-5-*en*-3β-*yl Acetate* (13).—A mixture of the tosylate (11) (190 mg), sodium azide (43 mg), and dry dimethyl sulphoxide (10 ml) was heated at 90—100° for 1 h under nitrogen, and then extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated to dryness. A procedure similar to that described for (12) gave the *azide* (13) (200 mg, 90%), m.p. 137—139° (from acetone), $\nu_{max.}$ 2 100 and 1 730 cm^{-1}, δ 0.70 (3 H, s, 13-Me), 1.00 (3 H, s, 10-Me), 2.01 (3 H, s, Ac), 3.04 (1 H, dd, *J* 12 and 8 Hz, 22-H_a), 3.41 (1 H, dd, *J* 12 and 4 Hz, 22-H_b), 4.6 (1 H, m, 3α-H), and 5.4 (1 H, m, 6-H) (Found: C, 72.5; H, 9.5; N, 10.55. $C_{24}H_{37}N_3O_2$ requires C, 72.15; H, 9.35; N, 10.5%).

23,24-*Bisnorchol*-5-*ene*-3β,22-*diol* 22-*Methyl Ether* 3-*Thp Ether* (14).—To a solution of sodium methoxide [from sodium (46 mg) and dry methanol (3 ml)] was added a solution of the tosylate (11) (235 mg) in dry Thf (3 ml). The mixture was refluxed for 2 h under nitrogen. The usual work-up (ether for extraction; recrystallization from methanol) gave the 22-*methyl ether* (14), m.p. 118—119.5°, δ 0.71 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 3.34 (3 H, s, OMe), and 5.4 (1 H, m, 6-H) (Found: C, 78.05; H, 10.7. $C_{28}H_{46}O_3$ requires C, 78.1; H, 10.75%).

1,1-*Dimethylprop*-2-*ynyl Thp Ether* (15).—A mixture of 2-methylbut-3-yn-2-ol (15 g), CH_2Cl_2 (60 ml), dihydropyran (27 g), and a catalytic amount of toluene-*p*-sulphonic acid was stirred at 0 °C for 30 min. Saturated aqueous $NaHCO_3$ (5 ml) was then added and stirring was continued for 20 min. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with water, dried ($MgSO_4$), and evaporated at room temperature. The oily residue was purified by fractional distillation, to give the Thp ether (15) (26.9 g, 90%), b.p. 71° at 11 mmHg (lit.,[17] 30—33° at 0.5 mmHg), δ 1.43 and 1.46 (6 H, s, Me_2), 2.35 (1 H, s, HC≡C), and 5.05br (1 H, s, 2′-H of Thp) (Found: C, 71.4; H, 9.6. $C_{10}H_{16}O_2$ requires C, 71.4; H, 9.6%).

Attempted Coupling between Compounds (11) *and* (15) *in Thf or Thf–Hexamethylphosphoric Triamide* (*HMPA*).—(*a*) A solution of n-butyl-lithium (0.4 mmol) in n-hexane (Tokyo Kasei) was added to a mixture of the Thp ether (15) (67 mg) and Thf (5 ml). To the resulting lithium acetylide, a solution of the tosylate (11) (115 mg, 0.2 mmol) in Thf (5 ml) was added at 0 °C under argon. The mixture was stirred overnight at room temperature or at reflux. Extraction with ether and the usual work-up gave starting material in each case.

(*b*) When a five- or ten-fold excess of the acetylide (15) was similarly treated in Thf (4 ml)–HMPA (1 ml), the di-Thp ether (16) was obtained in 20% yield after chromatography; the starting compound was recovered when a twofold excess of reagent was used.

(*c*) A combination of 1.0 mmol of (15) and 0.2 mmol of (11) in Thf (4 ml)–HMPA (4 ml) at reflux afforded the 22-alcohol (10).

Cholest-5-*en*-23-*yne*-3β,25-*diol Di-Thp Ether* (16).—To a stirred mixture of the Thp ether (15) (1.34 g) and dry dioxan (10 ml) cooled in ice under argon was added a solution of n-butyl-lithium in hexane (Tokyo Kasei) (8 mmol). After stirring at room temperature for 30 min, a solution of the tosylate (11) (1.14 g) in dry dioxan (20 ml) was added. The mixture was refluxed overnight. The usual work-up (ether for extraction) gave a brown oily residue, which was chromatographed on silica gel. A fraction eluted with benzene, recrystallized from methanol, gave the *di-Thp ether* (16) (1.01 g, 75%), m.p. 100—105°, δ 0.68 (3 H, s, 13-Me), 1.00 (3 H, s, 10-Me), 1.45 and 1.49 (6 H, s, 5-Me_2), 4.71br (1 H, s, 2′-H of Thp at C-3), and 5.06br (1 H, s, 2′-H of Thp at C-25) (Found: C, 78.55; H, 10.45. $C_{37}H_{58}O_4$ requires C, 78.4; H, 10.3%).

Cholest-5-*en*-23-*yne*-3β,25-*diol* (17).—The crude product

(1.35 g) from another run of the above coupling reaction was treated with 1N-HCl (5 drops) and methanol (20 ml)–Thf (10 ml) and, after the usual work-up, the residue obtained was chromatographed on silica gel. Elution with benzene–acetate (150 : 1) afforded 23,24-bisnorchol-5-ene-3,22-diol 22-tosylate (97 mg, 10%), m.p. 103—104° (from methanol), δ 0.65 (3 H, s, 13-Me), 0.99 (3 H, s, 10-Me), 2.48 (3 H, s, aromatic Me), 3.5—4.1 (3 H, m, 22-H_2 and 3α-H), and 5.35 (1 H, m, 6-H). Elution with benzene–ethyl acetate (100 : 1) afforded the *diol* (17) (560 mg, 70%), m.p. 154—156° (from acetone–methanol), $\nu_{max.}$ 3 600, 3 450, and 2 250 cm^{-1}, δ 0.68 (3 H, s, 13-Me), 1.00 (3 H, s, 10-Me), 1.50 (6 H, s, 25-Me_2), 3.5 (1 H, m, 3α-H), and 5.35 (1 H, m, 6-H) (Found: C, 81.5; H, 10.8. $C_{28}H_{42}O_2$ requires C, 81.35; H, 10.6%). The bistrimethylsilyl ether showed *m/e* 542 (M^+).

Further elution with benzene–ethyl acetate (50 : 1) afforded 23,24-bisnorchol-5-ene-3,22-diol (66 mg, 10%), m.p. 206—206.5° (ethyl acetate).

Cholest-5-en-23-yne-3β,25-diol 3-Acetate (18).—A mixture of the diol (17) (160 mg), pyridine (1 ml), and acetic anhydride (1 ml) was left at room temperature overnight to give the *monoacetate* (18) (104 mg, 80%), m.p. 173—175.5° (from methanol), δ 0.69 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 1.49 (6 H s, 25-Me_2), 2.02 (3 H, s, Ac), 4.6 (1 H, m, 3α-H), and 5.4 1 H, m, 6-H) (Found: C, 78.9; H, 10.15. $C_{29}H_{44}O_3$ requires C, 79.05; H, 10.05%).

Cholest-5-en-23-yne-3β,25-diol Diacetate (19).—A mixture of the diol (17) (400 mg), pyridine (3 ml), and acetic anhydride (3 ml) was heated at 120 °C for 2 h to give the *diacetate* (19) (415 mg, 86%), m.p. 99—101° (from methanol), δ 0.70 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 1.63 (6 H, s, 25-Me_2), 2.00 and 2.03 (6 H, s, 2 × Ac), 4.6 (1 H, m, 3α-H), and 5.4 (1 H, m, 6-H) (Found: C, 77.15; H, 9.75. $C_{31}H_{46}O_4$ requires C, 77.15; H, 9.6%).

Cholesta-5,25-dien-23-yn-3β-yl Acetate (20).—(*a*) To a solution of the monoacetate (18) (150 mg) in CH_2Cl_2 (2 ml) containing triethylamine (70 μl) was added methanesulphonyl chloride (40 μl) at 0 °C. Stirring was continued for 10 min at 0 °C. The usual work-up (CH_2Cl_2 for extraction) gave the *enyne* (20) (100 mg, 75%), m.p. 97—101° (from methanol), $\lambda_{max.}$ 224 (ε 13 400) and 233 nm (11 600), δ 0.70 (3 H, s, 13-Me), 1.01 (3 H, s, 10-Me), 1.86 (3 H, t, *J* 1 Hz, 25-Me), 2.00 (3 H, s, Ac), 4.6 (1 H, m, 3α-H), 5.14br (2 H, s, 27-H_2), and 5.4 (1 H, m, 6-H) (Found: *M* — AcOH, 362.2926. $C_{27}H_{38}$ requires 362.2975).

(*b*) A mixture of the diol (17) (27 mg), acetic acid (1.35 ml), acetic anhydride (0.135 ml), and toluene-*p*-sulphonic acid monohydrate (27 mg) was kept at room temperature for 1.5 h. The usual work-up gave the enyne (20) (25 mg, 70%).

Cholesta-5,23-diene-3β,25-diol (21).—To a suspension of $LiAlH_4$ (20 mg) in dry Thf (3 ml), a solution of the diol (17) (40 mg) in dry Thf (3 ml) was added. After refluxing for 10 h under nitrogen, the excess of reagent was decomposed with moist ether. The usual work-up gave a residue [containing 1—2% of the allene (22), by g.l.c. analysis] which was crystallized from acetone–methanol to afford the *allylic alcohol* (21) (32 mg, 80%), m.p. 151—152.5° (from acetone–methanol), δ 0.69 (3 H, s, 13-Me), 1.01 (3 H, s, 10-Me), 1.29 (6 H, s, 25-Me_2), 3.5 (1 H, m, 3α-H), 5.4 (1 H, m, 6-H), and 5.58br (2 H, s, 23- and 24-H), (Found: C, 81.35; H, 11.05. $C_{27}H_{44}O_2$ requires C, 80.95; H, 11.05%).

Cholesta-5,23,24-trien-3β-ol (22).—A solution of the diol (17) (400 mg) in dry Thf (10 ml) was added to a suspension of $LiAlH_4$ (154 mg) and $AlCl_3$ (133 mg) in dry Thf (10 ml). After refluxing for 10 h under argon, the mixture was cooled in ice and the excess of reagent was decomposed by slow addition of water. The mixture was then filtered and the filtrate was extracted with ether; the extract was washed with water, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on a silica gel column. Elution with benzene–ethyl acetate (150 : 1) afforded the *allene* (22) (50 mg, 13%), m.p. 109—111° (from methanol), $\nu_{max.}$ (CCl_4) 3 620, 3 350, and 1 970 cm^{-1}, δ 0.69 (3 H, s, 13-Me), 1.00 (3 H, s, 10-Me), 1.65 (6 H, d, *J* 3 Hz, 25-Me_2), 3.5 (1 H, m, 3α-H), 4.85 (1 H, m, 23-H), and 5.4 (1 H, m, 6-H) (Found: M^+, 382.3229. $C_{27}H_{42}O$ requires *M*, 382.3235).

Further elution with ethyl acetate gave the allylic alcohol (21) (320 mg, 80%).

Cholesta-5,23-dien-3β-ol (23).—A solution of the diol (17) (40 mg) in dry Thf (2 ml) was added to a mixture of $TiCl_4$ (22 μl) and dry Thf (2 ml) under argon. The mixture was stirred for 10 min and added to a suspension of $LiAlH_4$ (38 mg) in dry Thf (3 ml). The resulting black mixture was refluxed for 5 h, and then moist ether was added. The organic layer was washed with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated to dryness. Crystallization from methanol gave the diene (23) (30 mg, 78%), m.p. 116—118°, δ 0.68 (3 H, s, 13-Me), 1.00 (3 H, s, 10-Me), 3.5 (1 H, m, 3α-H), and 5.3 (3 H, m, 6-, 22-, and 23-H), *m/e* 384 (M^+), 369, 366, 351, 283 (20,22-cleavage — H_2O), and 271. Acetylation of (23) and crystallization from methanol gave the corresponding *acetate*, m.p. 87—88°, $\nu_{max.}$ 1 730 and 966 cm^{-1}, *m/e* 366 (base peak, M^+ — AcOH), 351, 340, 283, 255, and 253 (Found: C, 82.1; H, 11.1. $C_{29}H_{46}O_2$ requires C, 81.65; H, 10.85%).

24-(3-*Methyl*-3-*tetrahydropyran*-2-*yloxybut*-1-*ynyl*)*cholest*-5-*ene*-3β,24-*diol* 3-*Thp Ether* (24).—To the lithium salt prepared from the Thp ether (15) (170 mg) and n-butyl-lithium (1.0 mmol) in dry Thf (3 ml), was added a solution of the 24-ketone (1) (240 mg) in dry Thf (5 ml) at −15 °C under argon. After 30 min stirring, saturated aqueous ammonium chloride was added and the mixture was extracted with ether. Work-up in the usual way afforded a residue which was crystallized from acetone to afford the *acetylenic alcohol* (24) (250 mg, 79%), m.p. 122—125°, δ 0.70 (3 H, s, 13-Me), 1.01 (3 H, s, 10-Me), 1.52 and 1.56 (3 H × 2, s, 25-Me_2), 4.75br (1 H, s, 2′-H of Thp at C-3), 5.1br (1 H, s, 2′-H of Thp at C-25), and 5.4 (1 H, m, 6-H) (Found: *M*—ThpOH, 550.4336. $C_{37}H_{58}O_3$ requires 550.4389).

24-(3-*Methylbuta*-1,2-*dienyl*)*cholest*-5-*ene*-3β,24-*diol* 3-*Thp Ether* (25).—To a suspension of $LiAlH_4$ (50 mg) in dry ether (3 ml) was added a solution of the acetylenic alcohol (24) (100 mg) in dry ether (3 ml) at 0 °C under nitrogen. After stirring for 6 h at room temperature, the excess of reagent was decomposed by addition of water. The mixture was extracted with ether and the extracts chromatographed on a silica gel column to afford the *allene* (25) (60 mg, 71%), $\nu_{max.}$ 1 970 cm^{-1}, δ 0.69 (3 H, s, 13-Me), 1.74 (6 H, d, *J* 4 Hz, allenic Me_2), and 5.4 (1 H, m, 6-H) (Found: M^+ 552.4705, $C_{37}H_{60}O_3$ requires *M*, 552.4546).

[5/876 *Received, 9th May,* 1975]