Synthesis of 24-heteroatom-substituted cholestanols

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Summary Short syntheses of 24-thia-5α,20ξ-cholestan-3β-ol, 24-methyl-24-aza-5α,20ξ-cholestan-3β-ol, and 24-nor-5α,20ξ-cholan-3β-ol from 3β-hydroxy-5α-pregnan-20-one are described. The products and synthetic intermediates have been fully characterized by the results of proton NMR, infrared, and high and low resolution mass spectral studies.—**Rahman, M.D., H.M. Seidel, and R.A. Pascal, Jr.** Synthesis of 24-heteroatom-substituted cholestanols. *J. Lipid Res.* 1988. **29:** 1543–1548.

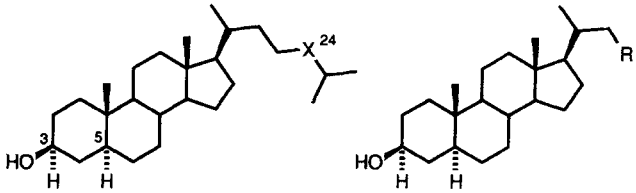
Supplementary key words proton NMR • sulfur-substituted cholestanol derivatives

We recently required a series of 24-heteroatom-substituted sterols for studies of the mechanism and inhibition of biological sterol side chain alkylation. A number of sterols in which heteroatoms have been substituted for carbons 24 and 25 are potent inhibitors of Δ^{24}-sterol methyltransferases in a variety of organisms (1,2); however, most of these compounds contain nuclear double bonds (typically Δ^5 or Δ^8) or "extra" methyl groups (at C-4 and C-14). While compounds containing these groups very closely resemble the natural substrates of the methyltransferases, we wished to minimize, if possible, undesired biochemical processing of the steroid nucleus (such as double bond isomerizations and reductions, and methyl oxidations) in our proposed inhibitors. Remembering that dozens of cholestenols, cholestadienols, and assorted steroid diols and triols are convertible to cholesterol in animal tissues or cell-free preparations (3), we chose to prepare 24-substituted derivatives of the fully saturated sterol 5α-cholestan-3β-ol **(1a).** Reasonable intermediates in such syntheses would be 24-nor-5α-cholan-3β, 23-diol **(2a)** or 3β-hydroxy-24-nor-5α-cholan-23-oic acid **(2b)** or simple derivatives of these compounds. However, published syntheses and physical data for such compounds are at best scarce (4–7),[1] in contrast to the

Abbreviations: NMR, nuclear magnetic resonance; TLC, thin-layer chromatography; GLC, gas-liquid chromatography; IR, infrared; THP, tetrahydropyranyl.

[1]A literature search uncovered a single report of **2a** (4), but no source of the compound was given. Three reports of **2b** were found; in the first (5) the compound was a gift from an industrial source, in the second (6) no source was cited, and in the third (7) a reasonable synthesis of **2b** was described, but the final product was characterized only by melting point and partial IR data.

well-known 3α,5β-epimers which are easily derived from common bile acids.



1a X = CH_2
1b X = S
1c X = NMe

2a R = CH_2OH
2b R = CO_2H

We report here the syntheses of the sulfur- and nitrogen-substituted cholestanol derivatives **1b** and **1c** from relatively inexpensive 3β-hydroxy-5α-pregnan-20-one via suitably protected forms of compounds **2a** and **2b.**

EXPERIMENTAL PROCEDURES AND RESULTS

Materials and general procedures

3β-Hydroxy-5α-pregnan-20-one was purchased from Sigma Chemical Company.

Melting points were recorded in capillary tubes on an Electrothermal apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a Bruker WM250 spectrometer; chemical shifts are reported in parts per million downfield (δ) from tetramethylsilane. Infrared (IR) spectra were recorded on a Perkin-Elmer 283B spectrometer. High and low resolution mass spectra were obtained on a Kratos MS50 spectrometer using an electron beam energy of 70 eV. Thin-layer chromatographic (TLC) analyses were carried out on plates (2.5 cm × 10 cm) of silica gel GF (Analtech). Gas-liquid chromatographic (GLC) analyses were performed on the trimethylsilyl ether derivatives of the sterols using capillary columns (Supelcowax 10 stationary phase, 15 m × 0.53 mm, Supelco) in a Hewlett-Packard 5890A chromatograph with a flame ionization detector.

In the ^{1}H NMR listings of compounds consisting of C-20 epimers, a star (*) following a pair of resonances indicates that the former resonance is due to the 20R-epimer and the latter to the 20S-epimer. All such assignments are tentative.

3β-Tetrahydropyranyloxy-5α-pregnan-20-one (compound 3)

3β-Hydroxy-5α-pregnan-20-one (5.0 g, 15.7 mmol) was suspended in anhydrous ether (125 ml). Dihydropyran (7.15 ml, 78.5 mmol) and concentrated HCl (3 drops) were added, and the solution was stirred for 6 days. Several pellets of NaOH were added, and stirring was continued for 0.5 hr. The solution was filtered, and the solvent was removed by rotary evaporation. The white crystalline residue was dried under vacuum overnight. Recrystallization of the crude product from methanol–ether yielded **3 (Fig. 1)** (6.3 g, 99%), mp 136–137°C. ^{1}H NMR ($CDCl_3$) δ 4.71 (m, 1H, THP methine-H) 3.92 and 3.50 (m's, 2H, THP OCH2), 3.61 (m, 1H, 3-H), 2.52 (t, J = 9.0 Hz, 1H, 17-H), 2.10 (s, 3H, 21-H_3), 0.78 (s, 3H, 19-H_3), 0.59 (s, 3H, 18-H_3); IR (KBr) ν_{max} (cm^{-1}) 2930, 2850, 1705, 1470, 1450, 1390, 1350, 1150, 1130, 1020; MS, m/z 402 (M^+, 2%), 318 (M-DHP, 30), 301 (M-DHP-OH, 100).

Ethyl 3β-tetrahydropyranyloxy-24-nor-5α-chol-20(22)-en-23-oate (compound 4)

n-Butyllithium (11.95 ml of a 1.6 M solution in hexane, 19.1 mmol) was added to a stirred solution of diisopropylamine (2.68 ml, 19.1 mmol) in dry THF (65 ml) at −78°C under an argon atmosphere. After stirring for 15 min, ethyl(trimethylsilyl)acetate (3.5 ml, 19.1 mmol) was added. After 30 min, a solution of **3** (3.5 g, 8.7 mmol) in THF (15 ml) was added. The reaction was allowed to warm to room temperature overnight. After 13 hr, the orange solution was taken up in ether (200 ml) and shaken with water (200 ml). Saturated NaCl solution was added to clear up an emulsion. After separation of the organic layer, the aqueous phase was extracted once more with ether (150 ml). The combined organic phases were washed with dilute $NaHCO_3$ and dried over anhydrous $MgSO_4$. The solvent was evaporated to give a yellow oil (7.45 g). The oil was chromatographed on a silica gel column (hexane–ether 8:1), and fractions that contained the desired compound (R_f 0.27, hexane–ether 8:1) were combined and concentrated to give compound **4** as a light yellow oil, which was crystallized from acetone-water (3.45 g, 84%), mp 87–88°C (melts), 94°C (clears). ^{1}H NMR ($CDCl_3$) δ 5.77 and 5.69 (s's, 1H, vinyl-H, 1:3 *cis* and *trans* isomers), 4.70 (m, 1H, THP methine-H), 4.13 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 3.92 and 3.51 (m's, 2H, THP OCH_2), 3.61 (m, 1H, 3-H), 2.17 (d, J = 1 Hz, 3H, 21-H_3), 1.28 (t, J = 7.0 Hz, 3H, OCH_2CH), 2.17 (d, J = Hz, 3H, 21-H_3), 1.28 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 0.80 (s, 3H, 19-H_3), 0.57 (s, 3H, 18-H_3); IR (KBr) ν_{max} (cm^{-1}) 2940, 2850, 1715, 1630, 1445, 1380, 1215, 1140, 1020; MS, m/z 472 (M^+, 11%), 388 (M-DHP, 45), 370 (M-DHP-H_2O, 39), 355 (M-DHP-H_2O-CH_3, 19), 261 (33), 233 (20), 215 (62). Exact mass 472.3560, calcd for $C_{30}H_{48}O_4$ 472.3553.

Ethyl 3β-tetrahydropyranyloxy-24-nor-5α,20ξ-cholan-23-oate (compound 5)

A solution of compound **4** (0.30 g, 0.64 mmol) in ethanol (30 ml) was hydrogenated (40 psi) over 10%

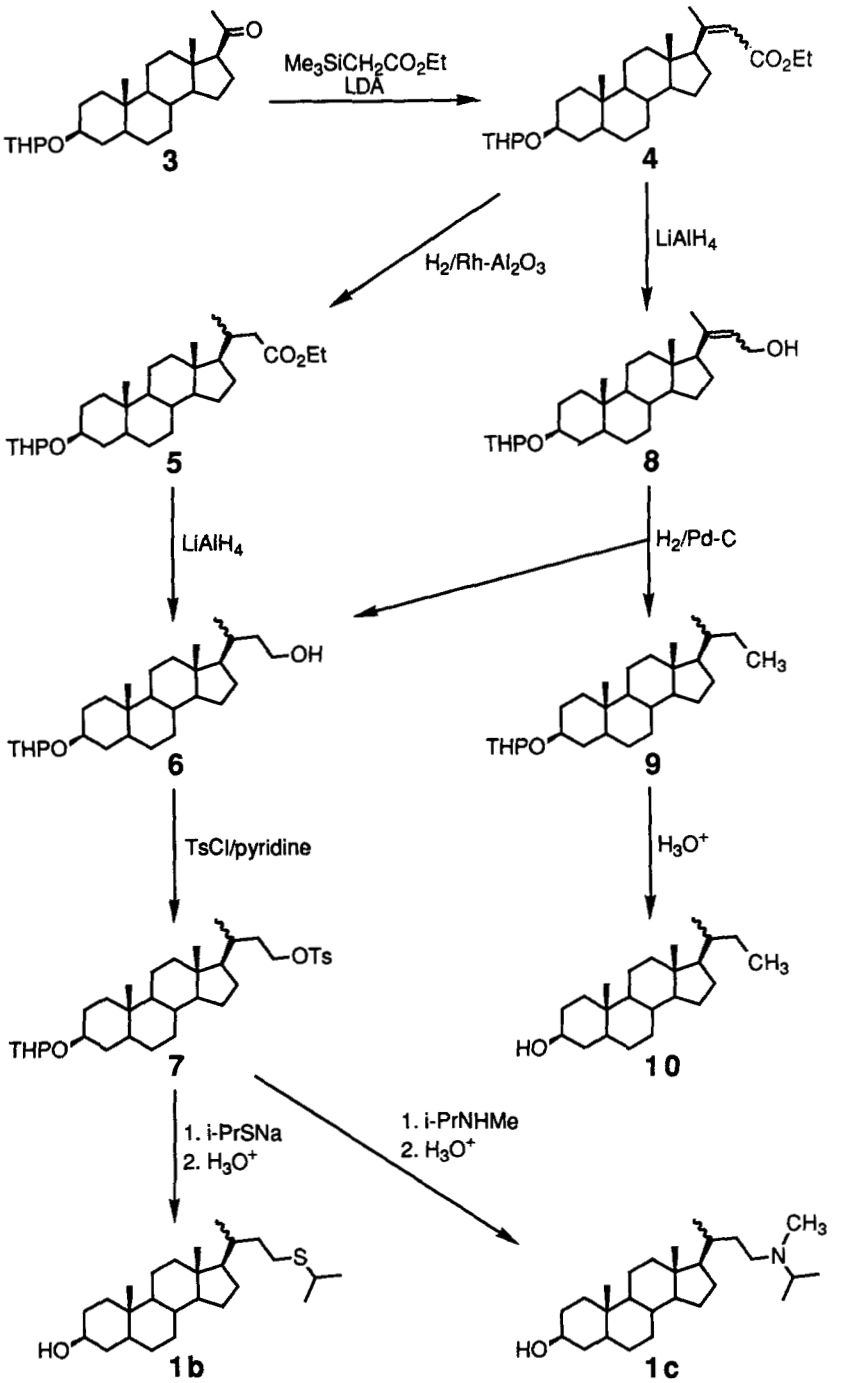


Fig. 1 Scheme for the synthesis of 24-heteroatom-substituted cholestanols.

rhodium on alumina (60 mg) in a Parr apparatus overnight. The reaction mixture was filtered through celite, concentrated, and chromatographed on a small column of silica gel (hexane–ethyl acetate 9:1). Concentration of the appropriate fractions left compound **5** as a white solid which was recrystallized from methanol (0.27 g, 90%), mp 69–70 °C. ^{1}H NMR ($CDCl_3$) δ 4.72 (m, 1H, THP methine-H), 4.11 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 3.92 and 3.48 (m's, 2H, THP OCH_2), 3.59 (m, 1H, 3-H), 1.25 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 0.97 and 0.88* (d's, J = 6.0 Hz, 3H, 21-H_3), 0.80 (s, 3H, 19-H_3), 0.68 (s, 3H, 18-H_3); IR (KBr) ν_{max} (cm^{-1}) 2940, 2850, 1735, 1450, 1155, 1020; MS, m/z 474 (M^+, 2%), 390 (M-DHP, 15), 373 (M-DHP-OH, 100), 327

(M-DHP-H_2O-OEt, 15), 285 (30), 233 (15), 215 (18), 107 (17), 85 (41). Exact mass 474.3724, calcd for $C_{30}H_{50}O_4$ 474.3709. The NMR spectrum indicated an approximately 3:2 ratio of C-20 epimers.

3β-Tetrahydropyranyloxy-24-nor-5α,20ξ-cholan-23-ol (compound 6)

A solution of compound **5** (0.20 g, 0.42 mmol) in anhydrous ether was treated with an excess of $LiAlH_4$ (37 mg, 1 mmol). After stirring for 1 hr, the reaction was quenched by the addition of a few drops of water followed by a few drops of 15% NaOH. The precipitated aluminum salts were filtered away, and the filtrate was dried and concentrated. The resulting oil was chromatographed on silica gel (hexane–ethyl acetate 9:1). Concentration of the appropriate fractions left compound **6** as a white solid which was recrystallized from methanol (0.17 g, 93%), mp 151–152°C (melts), 158°C (clears). ^{1}H NMR ($CDCl_3$), δ 4.70 (m, 1H, THP methine-H), 3.87 and 3.47 (m's, 2H, THP OCH_2), 3.60 (m, 3H, 3-H and 23-H_2), 0.91 and 0.81* (d's, J = 6.5, 3H, 21-H_3), 0.78 (s, 3H, 19-H_3), 0.64 and 0.63* (s's, 3H, 18-H_3); IR (KBr) ν_{max} (cm^{-1} 3450, 2940, 2850, 1445, 1380, 1125, 1020; MS, m/z 432 (M^+, 1%), 348 (M-DHP, 73), 333 (M-DHP-CH_3, 20), 331 (M-DHP-OH, 20), 315 (M-DHP-CH_3-H_2O, 16) 313 (M-DHP-OH-H_2O, 7), 248 (25), 233 (84), 215 (75), 107 (55), 85 (100). Exact mass 432.3589, calcd for $C_{28}H_{48}O_3$ 432.3604. The NMR data indicated an approximately 4:3 ratio of C-20 epimers.

3β-Tetrahydropyranyloxy-23-(*p*-toluenesulfonyloxy)-24-nor-5α,20ξ-cholane (compound 7)

Compound **6** (0.287 g, 0.66 mmol) was dissolved in dry pyridine (20 ml). The solution was cooled in an ice-salt bath, and *p*-toluenesulfonylchloride (0.253 g, 1.32 mmol, freshly recrystallized) was added with stirring. The solution was stirred at 10°C for 16 hr, and then it was poured into ice water (100 ml). A white, sticky precipitate formed immediately. This white solid was collected in a glass frit and the mother liquor was discarded. The frit was rinsed several times with ether, dissolving the tosylate and leaving behind *p*-toluenesulfonic acid as a white solid. The solvent was evaporated to give a colorless oil. This material was chromatographed on a silica gel column (chloroform) to give **7** (0.158 g, 41%) as a white solid which was used without further purification. An analytical sample was recrystallized from methanol, mp 112–113°C (melts), 122°C (clears). ^{1}H NMR ($CDCl_3$) δ 7.79 and 7.34 (AA'BB' system, 4H, Ar-H_4), 4.71 (m, 1H, THP methine-H), 4.07 (m, 2H, 23-H_2), 3.91 and 3.49 (m's, 2H, THP OCH_2), 3.58 (m, 1H, 3-H), 2.45 (s, 3H, Ar-CH_3), 0.82 and 0.74* (d's, J = 6.5, 3H, 21-H_3), 0.79 (s, 3H, 19-H_3), 0.60 and 0.50* (s's, 3H, 18-H_3); IR (KBr) ν_{max} (cm^{-1}) 2940, 2870, 2850, 1600, 1450, 1380, 1360, 1150, 1110, 1020; MS, m/z 502 (M-DHP, 31), 484 (M-DHP-H_2O, 10), 469 (M-DHP-H_2O-CH_3, 248 (73), 233 (70), 215 (100). Exact mass (M-DHP ion) 502.3100, calcd for $C_{30}H_{46}O_4S$ 502.3117. The NMR data indicated an approximately 4:3 ratio of C-20 epimers.

24-Thia-5α,20ξ-cholestan-3β-ol (compound 1b)

Sodium isopropylthiolate (0.65 g, 6.6 mmol) was added to a solution of compound **7** (0.385 g, 0.66 mmol) in argon-saturated ethanol, and the solution was stirred for 30 min at room temperature followed by refluxing for 3 hr. Concentrated hydrochloric acid (3 ml) and water (3 ml) were added, and the mixture was refluxed for 5 hr. After cooling, the reaction mixture was poured into ether (150 ml). The ethereal solution was washed with 1 N NaOH (2 × 150 ml) containing a small amount of sodium dithionite. The organic layer was dried over anhydrous $MgSO_4$. Concentration gave a yellow oil, which was chromatographed on a silica gel column (chloroform). The fractions containing the compound exhibiting TLC R_f 0.20 (chloroform) were combined, the solvent was evaporated, and the residue was recrystallized from methanol–water to give compound **1b** (0.192 g, 71%), mp 102–104°C (melts), 116°C (clears). ^{1}H NMR ($CDCl_3$) δ 3.58 (m, 1H, 3-H), 2.90 (septet, J = 7.0 Hz, 1H, 25-H), 2.58 and 2.44 (m's, 2H, 23-H_2), 1.25 (d, J = 7.0 Hz, 6H, 26-H_3 and 27-H_3), 0.93 and 0.84* (d's, J = 6.5 Hz, 3H, 21-H_3), 0.80 (s, 3H, 19-H_3), 0.66 and 0.65* (s's, 3H, 18-H_3); IR (KBr) ν_{max} (cm^{-1}) 3290, 2930, 2860, 1445, 1380, 1240, 1150, 1080, 1040; MS, m/z 406 (M^+, 11%), 363 (M-C_3H_7, 100), 345 (M-C_3H_7-H_2O, 12), 330 (46), 315 (17), 273 (43), 257 (16), 215 (27). Exact mass 406.3272, calcd for $C_{26}H_{46}OS$ 406.3269. The NMR data indicated an approximately 4:3 ratio of C-20 epimers. This material showed a single component on TLC analysis (chloroform) with R_f 0.20, but GLC analysis (250°C) showed two components in a 58:42 ratio.

24-Methyl-24-aza-5α,20ξ-cholestan-3β-ol (compound 1c)

Isopropyl methyl amine (73 mg, 1.0 mmol) was added to a stirred solution of compound **7** (200 mg, 0.34 mmol) in ethanol (30 ml) under argon. The solution was heated with stirring at 70°C for 2 days. The solvent was evaporated, and the residue was chromatographed on a silica gel column (choloform) to give 3β-tetrahydropyranyloxy-24-methyl-24-azacholestane as an oil [112 mg, 67%; MS, m/z 487 (M^+, 1%), 472 (4), 388 (2), 126 (5), 86 (100)]. A portion of this material (70 mg) was refluxed for 2 hr in a mixture of ethanol

(10 ml), water (1 ml), and conc. HCI (0.5 ml). After cooling, 1 N NaOH (10 ml) and water (25 ml) were added, and the product was isolated by ether extraction (3 × 20 ml). The combined ether extracts were dried over anhydrous Na_2SO_4, and the solvent was removed. The residue was chromatographed on silica gel column (chloroform) to yield compound **1c** (45 mg, 78%), mp 155–156°C (melts), 166°C (clears). ^{1}H NMR ($CDCl_3$) δ 3.56 (m, 1H, 3-H), 2.80 (septet, J = 7.0 Hz, 25-H), 2.2–2.5 (m, 2H, 23-H_2), 2.16 and 2.17 (s's, 3H, NCH_3), 0.99 and 0.97 (d's, J = 7.0 Hz, 6H, 26-H_3 and 27-H_3), 0.90 and 0.81* (d's, J = 6.5, 3H, 21-H_3), 0.78 (s, 3H, 19-H_3), 0.63 (s, 3H, 18-H_3); IR (KBr) ν_{max} (cm^{-1}) 3290, 2970, 2930, 2860, 1450, 1380, 1190, 1130, 1080, 1040; MS, m/z 403 (M^+, 3%) 388 (M-CH_3, 13), 86 (100). Exact mass 403.3809, calcd for $C_{27}H_{49}NO$ 403.3814. The NMR data indicated an approximately 4:3 ratio of C-20 epimers, and GLC analysis (260°C) showed two components in a 56:44 ratio.

3β-Tetrahydropyranyloxy-24-nor-5α-chol-20(22)-en-23-ol (compound 8)

Compound **4** (4.06 g, 8.6 mmol) was dissolved in anhydrous ether (150 ml). $LiAlH_4$ (0.70 g, 18.4 mmol) was added carefully to the solution with stirring. The solution was stirred for 1 hr, and it was quenched by the slow addition of water (0.7 ml), 15% NaOH (2.1 ml), and more water (0.7 ml). After 15 min, a white solid had precipitated. The solids were filtered away, and the etheral solution was dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was dried under vacuum, yielding **8** as a white solid (3.65 g, 99%) which was used without further purification. ^{1}H NMR ($CDCl_3$), δ 5.43 (t, J = 6.5 Hz, 1H, vinyl-H), 4.72 (m, 1H, THP methine-H), 4.20 (d, J = 4.5 Hz, 2H, 23-H_2), 3.94 and 3.53 (m's, 2H, THP OCH_2), 3.63 (m, 1H, 3-H), 1.68 (s, 3H, 21-H_3), 0.80 (s, 3H, 19-H_3), 0.53 (s, 3H, 18-H_3); IR (KBr) ν_{max} (cm^{-1}) 3450, 2940, 2850, 1650, 1445, 1380, 1350, 1190, 1130, 1110, 1050, 1020; MS, m/z 430 (M^+, 41%), 329 (M-DHP-OH, 20), 311 (18), 215 (23), 85 (100). Exact mass 430.3435, calcd for $C_{28}H_{46}O_3$ 430.3447.

3β-Tetrahydropyranyloxy-24-nor-5α,20ξ-cholane (compound 9) and 3β-tetrahydropyranyloxy-24-nor-5α,20ξ-cholan-23-ol (compound 6)

A solution of compound **8** (3.65 g, 8.5 mmol) in ethanol (100 ml) was hydrogenated (40 psi) over 10% Pd/C (365 mg) in a Parr apparatus for 24 hr. The reaction mixture was filtered through celite, concentrated, and passed through a small column of silica gel (ether). The resulting solution was concentrated to yield a clear oil (3.97 g). TLC analysis showed two major spots (toluene; R_fs 0.30 and 0.04). The two compounds were separated by silica gel column chromatography (toluene). The less polar material crystallized from ether–methanol and proved to be compound **9** (1.20 g, 34%), mp 89–91°C. ^{1}H NMR ($CDCl_3$), δ 4.70 (m, 1H, THP methine-H), 3.92 and 3.49 (m's, 2H, THP OCH_2), 3.62 (m, 3H, 3-H and 23-H_2), 0.78–0.86 (m, 9H, overlapping signals from 19-H_3, 21-H_3, and 23-H_3), 0.61 (s, 3H, 18-H_3); IR (KBr) ν_{max} (cm^{-1}) 2940, 2870, 1445, 1380, 1355, 1130, 1110, 1020; MS, m/z 416 (M^+, 1%), 332 (M-DHP, 1) 315 (M-DHP-OH, 100), 245 (10), 205 (12), 149 (13), 85 (64). Exact mass 416.3672, calcd for $C_{28}H_{48}O_2$ 416.3654.

The more polar material proved to be compound **6** (2.06 g, 56%), identical with the material described above.

24-Nor-5α,20ξ-cholan-3β-ol (compound 10)

Compound **9** (0.50 g, 1.2 mmol) was refluxed for 1.5 hr in a mixture of ethanol (40 ml), water (2 ml), and conc. HCl (1 ml). After cooling, the solution was diluted with ether and washed twice with water. The organic phase was dried and concentrated, and the residue was crystallized from ether–methanol to give compound **10** (0.37 g, 93%), mp 131–133°C (melts), 137°C (clears). ^{1}H NMR ($CDCl_3$), δ 3.56 (m, 1H, 3-H), 0.78–0.86 (m, 9H, overlapping signals from 19-H_3, 21-H_3, and 23-H_3), 0.62 (s, 3H, 18-H_3); IR (KBr) ν_{max} (cm^{-1}) 3400, 2930, 2860, 1450, 1380, 1035; MS, m/z 332 (M^+, 100%), 317 (M-CH_3, 42), 301 (24), 273 (11), 248 (17), 234 (75), 233 (96), 206 (23), 165 (11), 147 (24), 135 (27), 121 (42). Exact mass 332.3071, calcd for $C_{23}H_{40}O$ 332.3079. This material showed a single component upon TLC analysis (chloroform) with R_f 0.16, and GLC analysis (240°C) indicated a purity of 94%.

DISCUSSION

We chose compound **6** (the tetrahydropyranyl ether of **2a**) as an ideal intermediate for the synthesis of a wide variety of 24-substituted cholestanols; the tetrahydropyranyl ether moiety is inert to most reaction conditions, and the 23-hydroxyl group can be easily converted to a good leaving group for displacement by a variety of nucleophiles. Two general strategies were considered for the synthesis of **6**. In the first, the side chain of a C_{27} sterol would be degraded to obtain the C_{23} nucleus of **6**; in the second, **6** would be prepared by elaborating the sterol side chain of a smaller precursor. We judged that the former sequence would entail at least one, and possibly two, oxidation steps where the yields would be low and the purification of the products would not be simple. This scheme was

rejected in favor of the second strategy, where we could expect high yields on each synthetic step.

Commercial 3β-hydroxy-5α-pregnan-20-one was converted to the corresponding tetrahydropyranyl ether **3** (Fig. 1), and the side chain was extended by treatment with the lithium enolate of ethyl trimethylsilylacetate (8), which has been used successfully in the construction of other steroidal side chains. Catalytic hydrogenation of compound **4** gave **5** as a mixture of C-20 epimers, which proved to be unresolvable at this or any later stage of the synthesis. The two isomers are formed in roughly a 4:3 ratio. In general it has been found that the 20-methyl groups (C-21) of sterols with the 20β configuration (in our compounds the 20β-isomer has the 20R configuration in standard IUPAC nomenclature) resonate at lower fields than those with the 20α (20S) configuration (9–11). Therefore, on the basis of the proton NMR data for compounds **5, 6, 7, 1b,** and **1c,** we judge the major isomers formed to be the "natural" 20R-epimers,[2] but such assignments must be tentative.

Reduction of the ester **5** with $LiAlH_4$ gave **6** in 70% overall yield from the commercial starting material. Compound **6** was converted to the tosylate **7** by a standard procedure; this material was somewhat unstable and generally used as soon as possible for subsequent reactions. Displacement of the tosylate with sodium isopropylthiolate followed by hydrolysis of the THP ether gave the desired 24-thiacholestanol **1b,** and a similar sequence utilizing isopropyl methyl amine as nucleophile gave the azasterol **1c.**

We also explored the reverse sequence of reductions in the conversion of **4** to **6,** in the hope that a different distribution of C-20 epimers might be obtained. Hydride reduction of the ester **4** gave the allylic alcohol **8** smoothly, and catalytic hydrogenation of **8** gave, not unexpectedly, a mixture of **6** and the deoxygenated product **9.** These two compounds were easily separated, but the epimeric distribution at C-20 in **6** was essentially the same as before. Indeed, the arguments of Nes (12) suggest that hydrogenation of $\Delta^{20(22)}$-sterols should normally give approximately 1:1 mixtures of C-20 epimers. For the preparation of compound **6,** the higher-yielding sequence **4**→**5**→**6** is the one to be preferred.

This work was supported in part by a grant from the National Institutes of Health (AI 24146), and by an Alfred P. Sloan Research Fellowship (to R. A. P.)

Manuscript received 29 March 1988 and in revised form 2 June 1988.

[2]The intermediate tetrahydropyranyl ethers are also epimeric at the methine carbon of the THP groups; however, this has no observable effect on the C-18 and C-21 methyl resonances, from which the C-20 isomeric distributions may be deduced. In any event, the final products **1b** and **1c** have no THP groups, and NMR analyses (as well as GC analyses) of these compounds give the same epimeric ratios.

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