Notes

(20*R*)- and (20*S*)-Cholest-5-ene-3β,21-diol[1]

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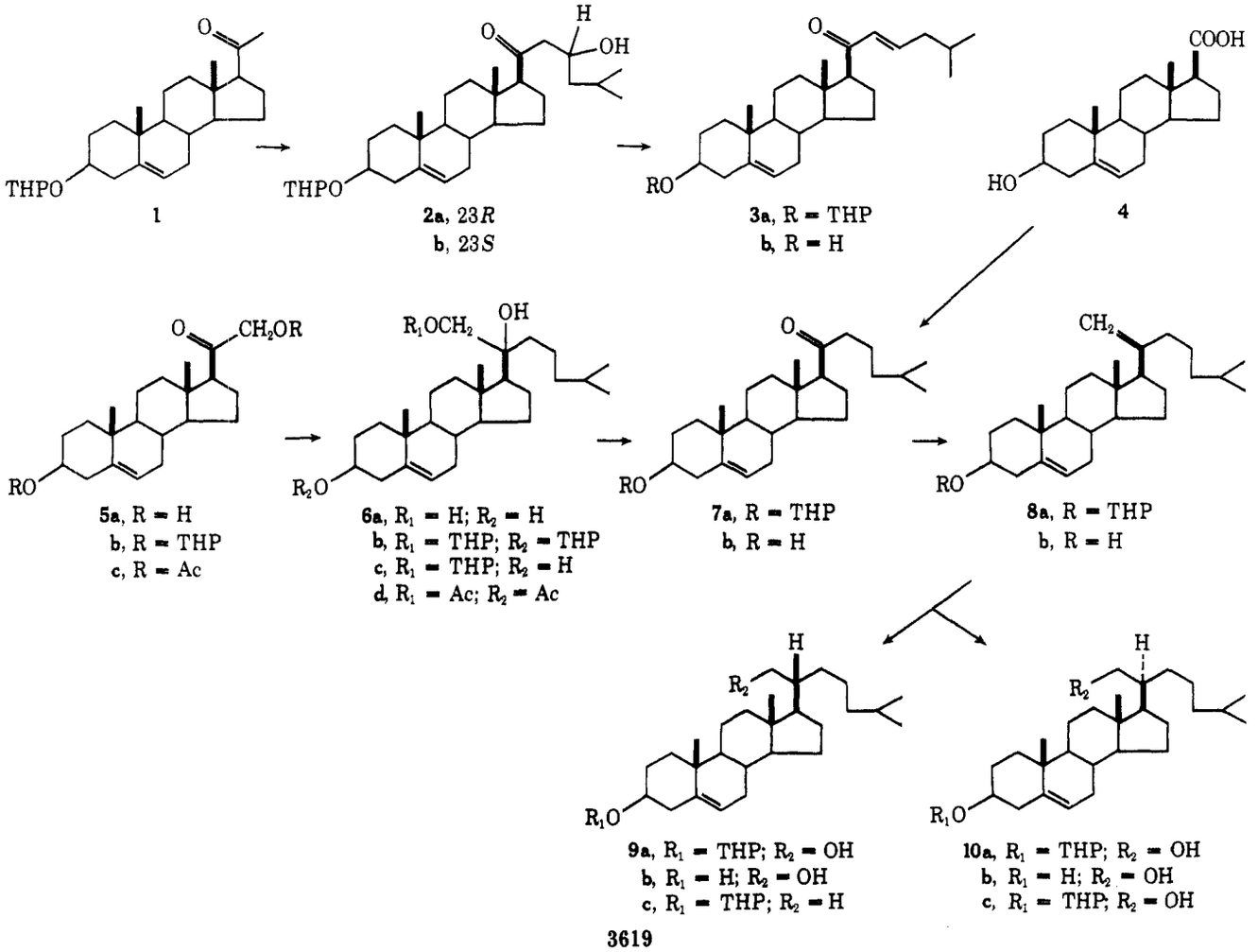
Our interest[2] in inhibitors of the cholesterol side-chain cleavage enzyme system in adrenocortical preparation made it desirable to test (20*R*)- and (20*S*)-cholest-5-ene-3β,21-diol. An approach to these compounds has already been described by Bottin and Fetizon.[3,4]

The starting material, 20-keto-21-norcholesterol can be made in many different ways, as already indicated by Bottin and Fetizon.[3,4] We have explored the regiospecific aldol condensation, as described by Stork et al.,[5] of 3β-hydroxypregn-5-en-20-one tetrahydropyranyl ether (**1**),[6] via its kinetic lithium enolate, with 3-methylbutanal to give 3β,23-dihydroxy-21-norcholest-5-en-20-one 3-tetrahydropyranyl ether (23-isomeric mixture) (**2**). The NMR spectrum indicated the completion of the side chain with a doublet at δ 0.93 for the 26,27-dimethyl group. The two 23 epimers could be separated by preparative TLC and were then analyzed according to the method of Horeau and Kagan.[7] The more polar compound **2a**, mp 134–136 °C, had the 23*R* configuration, while the less polar material was the 23*S* epimer **2b**, mp 151–153 °C. Dehydration of the ketol **2** (23-isomeric mixture) was carried out with *p*-toluenesulfonic acid in boiling benzene. In spite of the short reaction time (10 min), there was a substantial hydrolysis of the 3-tetrahydropyranyl (3-THP) ether (70% **3a** and 10% **3b**, both UV_{max} 228 nm (ε 12 000)). This high extinction (in the UV) together with the coupling constant of 16 Hz for 22-H and 23-H (in the NMR) ascertain the *E* geometry for the 22(23) double bond. In preparative runs the isolated crude product was routinely subjected to a treatment with dihydropyran and a catalytic amount of *p*-toluenesulfonic acid in benzene in order to obtain **3a** as a uniform product. The enone **3a** was then reduced (H_2/PtO_2 or Li/NH_3) to give in good yield the known saturated ketone **7a**.[3,4] Acid hydrolysis of the tetrahydropyranyl ether gave 3β-hydroxy-21-norcholest-5-en-20-one (**7b**),[8] identical in all respects with authentic material.

Another[9] synthesis of the ketone **7** proceeds by reacting 3β,21-dihydroxypregn-5-en-20-one 3,21-ditetrahydropyranyl ether (**5b**) with isohexylmagnesium bromide, followed by acid hydrolysis to give cholest-5-ene-3β,20,21-triol (20-isomeric mixture) (**6a**), which is very similar (NMR and IR) to the known 20*S* isomer.[10] The same product was also obtained from the Grignard reaction on 3β,21-diacetoxypregn-5-en-20-one (**5c**). A lead tetraacetate oxidation of the triol **6a** gave the desired norketone **7b**.

Scheme I



While this study was in progress Danishefsky et al.[11] published a method[12] for the synthesis of the norketone **7b** by the reaction of 3β-hydroxyetiochol-5-enic acid (4) with isohexyllithium.

The ketone **7a** was subjected to a Wittig reaction as described[3,4] to give cholesta-5,20-dien-3β-ol 3-tetrahydropyranyl ether (**8a**), identical with authentic material in all respects. A small aliquot of the ether **8a** was hydrolyzed to give cholesta-5,20-dien-3β-ol (**8b**), mp 109–111 °C. Similarly, the ketone **7b** was reacted with methylene triphenylphosphorane to give the olefin **8b** which was then transformed with dihydropyran and *p*-toluenesulfonic acid to its ether **8a.** The hydroboration of the olefin **8a** with diborane at 0 °C gave a mixture of the two 20*R* and 20*S* alcohols **9a** and **10a** in a ratio of 2:1. The two isomers were separated by adsorption chromatography to give **9a** (mp 155 °C, δ 3.70, s, $-CH_2-OH$) and **10a** (mp 105 °C, δ 3.62, m). The IR spectra of the two epimers are very similar.

Proof of Structure for 9a and 10a. Both alcohols **9a** and **10a** were converted to their tosylates and the crude sulfonates were reduced with lithium aluminum hydride. Thus, the reduction product from the major isomer **9a,** mp 155 °C, gave (20*R*)-cholest-5-en-3β-ol 3-tetrahydropyranyl ether (**9c**) (cholesterol tetrahydropyranyl ether), mp 155–161 °C, identical in all respects with authentic[13] material. The reduction of the minor isomer **10a,** mp 105 °C, gave (20*S*)-cholest-5-en-3β-ol 3-tetrahydropyranyl ether (**10c**) (20-isocholesterol 3β-tetrahydropyranyl ether), mp 96–98 °C, identical in all respects with a sample made from (20*S*)-cholest-5-en-3β-ol.[14] 21-Hydroxycholesterol (**9b**), mp 149–151 °C, was obtained by acid hydrolysis of its tetrahydropyranyl ether **9a,** while (20*S*)-cholest-5-ene-3β,21-diol (**10b**) was obtained in the same fashion from the ether **10a.**

These results contradict those of Bottin and Fetizon,[3,4] since (1) we did not observe (hydroboration with disiamylboran gave similar results) any stereoselectivity (on the Δ^{20} bond) in the hydroboration of olefin **8a** and (2) our hydroxylated material, mp 155–156 °C (Bottin and Fetizon give mp 143–145 °C), belongs to the 20*R* (natural) configuration. This has been ascertained by comparison of the NMR spectra[15] of the 20*R* and the 20*S* configurations, as well as by mixture melting point depression(s). Characteristically, the 21-hydroxy sterols of the 20*R* (natural configuration) series exhibit a resonance at δ 3.70 as a singlet ($-CH_2OH$), while those of the 20*S* configuration show a multiplet centered at δ 3.62. The difference in the NMR spectra of the reduced materials ($21-CH_3$) is also very well documented: cholesterol tetrahydropyranyl ether (**9c**) shows resonances at δ 0.86 (doublet for the 26,27-methyls) and at 0.92 (doublet for the 21-methyl), while (20*S*)-cholest-5-en-3β-ol tetrapyranyl ether (**10c**) gives δ 0.79 (doublet for 21-methyl) and 0.85 (doublet for the 26,27-methyls).

Experimental Section

Melting points were determined on a Kofler melting-point apparatus and are uncorrected. The UV spectra were determined for methanolic solutions on a Cary Model 14 recording spectrophotometer. The NMR spectra were obtained in deuteriochloroform solution on a 60-MHz Varian EM360 and a 100-MHz Varian HA100D-15, with C1024 computer, using tetramethylsilane as an internal reference, and the positions of the proton signals are expressed in parts per million downfield from tetramethylsilane signals.

(23*R*)-3β,23-Dihydroxy-21-norcholest-5-en-20-one 3-Tetrahydropyranyl Ether (2a) and (23*S*)-3β,23-Dihydroxy-21-norcholest-5-en-20-one 3-Tetrahydropyranyl Ether (2b). To the stirred solution of 9.0 g (84 mmol) of lithium diisopropylamide in dry tetrahydrofuran at −78 °C was added at once a solution of 30 g (75 mmol) of 3β-tetrahydropyranyloxypregn-5-en-20-one (1)[6] in 100 mL of dry tetrahydrofuran. To this was added, dropwise, the solution 8.6 mL of 3-methylbutanal dissolved in 20 mL of dry tetrahydrofuran. After 15 min of stirring the cooling was removed and the solution neutralized at once with a solution of acetic acid in ether. The solution was then concentrated in vacuo and diluted with benzene. The organic phase was washed with water several times and dried over anhydrous sodium sulfate, and the solvents were evaporated. The residue, upon crystallization from methanol, gave 30 g of condensation product **2** (23-isomeric mixture): mp 129–150 °C; IR ν 3500 (–OH), 1680 (–CO–), 1030 and 970 cm^{-1} (ether); NMR δ 0.63 (s, 3, 18-CH_3), 0.93 [d, 6, *J* = 6 Hz, 26,27-CH(CH_3)$_2$], 1.01 (s, 3, 19-CH_3), 5.34 ppm (m, 1, 6-H).

Anal. Calcd for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.73; H, 10.41.

A TLC, using as solvents 5–10% acetone in hexane, on 120 mg of the above mixture gave 55 mg of a more polar compound and 46 mg of less polar material. A determination of the configuration at C-23 according to Horeau and Kagan[7] revealed the more polar compound to have the 23*R* configuration, mp 134–136 °C, after two recrystallizations from methanol; IR and NMR are very similar to those of the isomeric mixture.

Anal. Calcd for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.76; H, 10.46.

The less polar compound has the 23*S* configuration and a mp 151–153 °C after recrystallization from methanol; IR and NMR are virtually indistinguishable from those of the mixture or of the 23*R* isomer.

Anal. Calcd for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.55; H, 10.38.

(*E*)-3β-Hydroxy-21-norcholesta-5,22-dien-20-one (3b) and (*E*)-3β-Tetrahydropyranyloxy-21-norcholesta-5,22-dien-20-one (3a). A solution of 24 g of the ketol **2** in 200 mL of benzene containing 250 mg of *p*-toluenesulfonic acid was heated under reflux for 10 min. After cooling, the solution was washed several times with saturated sodium bicarbonate solution, dried over sodium sulfate, and evaporated to dryness in vacuo. Chromatography of a small aliquot (1.25 g) of the residue (either on alumina or on TLC) yielded first the less polar tetrahydropyranyl ether which was recrystallized from hexane to give 793 mg (70%) of **3a:** mp 153–154 °C; UV_{max} (CH_3OH) 228 nm (ε 12 000); IR ν 1680 and 1610 (conj CO), 1030 and 960 cm^{-1} (ether); NMR δ 0.60 (s, 3, 18-CH_3), 0.90 [d, 6, *J* = 6 Hz, 26,27-CH(CH_3)$_2$], 1.00 (s, 3, 19-CH_3), 3.51 (m, 1, 3-H), 5.32 (m, 1, 6-H), 6.12 (d, 1, *J* = 16 Hz, 22-H), 6.78 ppm (t of d, 1, *J* = 8 and 16 Hz, 23-H).

Anal. Calcd for $C_{31}H_{48}C_3$: C, 79.43; H, 10.32. Found: C, 79.21; H, 10.45.

The more polar alcohol was recrystallized from hexane to give 205 mg (10%) of **3b:** mp 110–112 °C, IR ν 3300 (OH), 1670, and 1610 cm^{-1} (conj CO); NMR δ 0.60 (s, 3, 18-CH_3), 0.90 [d, 6, *J* = 6 Hz, 26,27-CH(CH_3)$_2$], 1.00 (s, 3, 19-CH_3), 3.52 (m, 1, 3-H), 5.34 (m, 1, 6-H), 6.10 (d, 1, *J* = 16 Hz, 22-H), 6.78 ppm (t of d, 1, *J* = 9 Hz and 16 Hz, 23-H).

Anal. Calcd for $C_{26}H_{40}O_2$: C, 81.20; H, 10.48. Found: C, 81.55; H, 10.84.

3β-Tetrahydropyranyloxy-21-norcholest-5-en-20-one (7a). (a) Catalytic Reduction. A solution of 500 mg of the conjugated ketone **3a** in 100 mL of ethyl acetate was reduced, at 1 atm, with hydrogen and 40 mg of prereduced platinum oxide. The reaction was stopped after absorption of 1.1 equiv of hydrogen and the mixture was then evapoarted to dryness. The product was dissolved in methylene chloride and the catalyst was removed by filtration through Celite. The filtrate was evaporated to dryness and the residue purified on TLC. In this fashion there was obtained, after recrystallization from ethanol, 443 mg of saturated ketone **7a,** mp 112–119 °C, identical in all respects with an authentic standard.[3,4] This material also had IR and NMR spectra indistinguishable from those obtained from authentic material.

(b) Reduction with Lithium and Ammonia. A solution of 500 mg of the enone **3a** in 20 mL of dry tetrahydrofuran was added rapidly to a well-stirred solution of 300 mg of lithium in liquid ammonia. After 15 min (the color was still deep blue), solid ammonium chloride was added and the ammonia allowed to evaporate. Isolation with methylene chloride gave a crude product which was purified on TLC. Recrystallization from ethanol gave 396 mg of saturated ketone **7a,** identical in all respects with an authentic[3,4] sample.

20-Keto-21-norcholesterol (7b). This product was obtained from the ether **7a** by hydrolysis with hydrochloric acid (5.0 g of **7a**/100 mL of THF/three drops of concentrated HCl/50 °C/3h). The mixture was poured into water, the tetrahydrofuran partially evaporated off in vacuo, and the product extracted with ether. The organic layer was washed with a saturated solution of sodium bicarbonate, dried, and concentrated to give 4.1 g of product **7b** indistinguishable from an authentic[8] sample.

3β-Hydroxycholesta-5,20-diene (8b). A Wittig reaction on the ketone **7b,** exactly as described[3,4] for the 3-tetrahydropyranyl ether, gave the desired diene **8b,** mp 109–111 °C.

(20*R*)- and (20*S*)-Cholest-5-ene-3β,21-diol 3-Tetrahydropyranyl Ether, (9a) and (10a). To 470 mg of olefin **8a** in 5 mL of anhydrous THF was added 1.1 mL of 1 M diborane in THF under a nitrogen atmosphere at 0 °C and the solution was stirred for 30 min at 0 °C. Then 2 mL of 10% sodium hydroxide solution and 2 mL of 30% hydrogen peroxide solution were added dropwise, and stirring was continued for an additional 1 h. After extraction with ethyl acetate, the extract was washed with water and saturated sodium chloride solution and dried (Na_2SO_4). The HPLC separation of this epimeric mixture was carried out in hexane–acetone (4:1) on 2 × 8 ft Porasil A column to give 230 mg of diols. The 20*S* and 20*R* epimers **10a** and **9a** were completely resolved in three recycles in a ratio of 1:2. The former had the longer retention time.

9a: mp 155–156 °C; NMR δ 0.71 (s, 3, 18-CH_3), 0.87 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 1.02 (s, 3, 19-CH_3), 3.70 (s, 2, -CH_2OH), 4.72 (m, 1, -OCHO-), 5.34 ppm (m, 1, 6-H).

10a: mp 105–107 °C; NMR δ 0.69 (s, 3, 18-CH_3), 0.87 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 1.01 (s, 3, 19-CH_3), 3.62 (m, 1, -CH_2OH), 4.72 (m, 1, -OCHO-), 5.34 ppm (m, 1, 6-H).

Anal. Calcd for $C_{32}H_{54}O_3$: C, 78.96; H, 11.18. Found: C, 78.92; H, 11.49.

(20*R*)- and (20*S*)-Cholest-5-ene-3β,21-diol (9b) and (10b). (a) To a solution of 24 mg of THP ether **9a** in 3 mL of THF was added one drop of concentrated HCl and the mixture was allowed to stand at 50 °C for 20 min. Then it was poured into a saturated solution of sodium bicarbonate and the product was extracted with ethyl acetate. The extract was washed with water and dried (Na_2SO_4). Purification of this crude diol **9b** was carried out on TLC (30% acetone in hexane) to give 14 mg of **9b:** mp 149–151 °C; NMR δ 0.70 (s, 3, 18-CH_3), 0.86 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 1.00 (s, 3, 18-CH_3), 3.70 (s, 2, -CH_2OH), 5.34 ppm (m, 1, 6-H).

Anal. calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.31; H, 11.29.

(b) A pure sample (11 mg) of diol **10b** was obtained from 20 mg of THP ether **10a** by the same methods described for the diol **9b.** This compound had: mp 147–149 °C; NMR δ 0.68 (s, 3, 18-CH_3), 0.85 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 1.00 (s, 3, 19-CH_3), 3.62 (m, 2, CH_2OH), 5.34 ppm (m, 1, 6-H).

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: 80.38; H, 11.58.

Cholesterol 3-Tetrahydropyranyl Ether (9c). This sequence (tosylation followed by hydride reduction) was carried out exactly as described by Bottin and Fetizon.[4] The reduction product was purified on a TLC plate which gave, after recrystallization from methanol, clean **9c:** mp 155–161 °C; NMR δ 0.68 (s, 3, 18-CH_3), 0.88 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 0.91 (d, 3, J = 6 Hz, 21-CH_3), 1.00 (s, 3, 19-CH_3), 4.72 (m, 1, -OCHO-), 5.34 ppm (m, 1, 6-H).

(20*S*)-Cholest-5-en-3β-ol 3-Tetrahydropyranyl Ether (10c) from 10a. This was carried out exactly as described above for the 20*R* epimer. The material was recrystallized from methanol to give pure **10c:** mp 96–98 °C; NMR δ 0.68 (s, 3, 18-CH_3), 0.84 (d, 3, J = 6 Hz, 21-CH_3), 0.87 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 1.01 (s, 3, 18-CH_3), 4.72 (m, 1, -OCHO-), 5.34 ppm (m, 1, 6-H).

Anal. Calcd for $C_{32}H_{54}O_2$: C, 81.64; H, 11.56. Found: C, 81.87; H, 11.88.

3β,21-Dihydroxypregn-5-en-20-one 3,21-Ditetrahydropyranyl Ether (5b). To the stirred solution of 9.0 g of 3β,21-dihydroxypregn-5-en-20-one (**5a**) in 20 mL of dry tetrahydrofuran was added 30 mg of *p*-toluenesulfonic acid and 10 mL of dihydropyran. After 3 h, the solution was extracted with benzene. The benzene layer was washed with a sodium bicarbonate solution and with water and dried over sodium sulfate, and the solvent was evaporated off in vacuo. The syrupy residue was crystallized from hexane to give 6.9 g of pure ether **5b:** mp 126–128 °C; IR ν 1725 (CO), 1030 and 965 cm^{-1} (ether); NMR δ 0.63 (s, 3, 18-CH_3), 0.99 (s, 3, 19-CH_3), 4.18 (s, 2, 21-CH_2-O-), 5.32 ppm (m, 1, 6-H).

Anal. Calcd for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Found: C, 74.28; H, 9.66.

3β,20,21-Trihydroxycholest-5-ene 3,21-Ditetrahydropyranyl Ether (20-Isomeric Mixture) (6b). To a stirred Grignard solution, prepared from 6 g of isohexyl bromide and 1.0 g of magnesium turnings in 100 mL of ether, was added dropwise a solution of 8 g of the ketone **5b** in 200 mL of tetrahydrofuran. The solution was heated under reflux for 3 h and left at 50 °C overnight. The mixture was hydrolyzed with a saturated solution of ammonium chloride. The organic material was extracted with ethyl acetate, the organic layer washed with water and dried over sodium sulfate, and the solvent evaporated in vacuo to give a yellow oil. A recrystallization from hexane gave 7.4 g of ether **6b:** mp 121–124 °C; IR ν 3350 (OH), 1025 and 960 cm^{-1} (ether); NMR δ 0.85 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$]; 0.86 (s, 3, 18-CH_3), 0.99 (s, 3, 19-CH_3), 5.35 ppm (m, 1, 6-H).

Anal. Calcd for $C_{37}H_{62}O_5$: C, 75.72; H, 10.65. Found: C, 75.99; H, 10.73.

3β,20,21-Trihydroxycholest-5-ene 21-Tetrahydropyranyloxy Ether (20-Isomeric Mixture) (6c). To 20 mL of dimethyl sulfoxide was added 10.0 mL of water and 4.0 mL of 7% perchloric acid. The resulting solution was cooled to 0 °C and 500 mg of the ether **6b** was added with stirring to the dimethyl sulfoxide solution. If, after 1 h, the steroid had not completely dissolved, 3–4 mL of tetrahydrofuran was added to the solution. The mixture was allowed to stand at room temperature for 3 days, after which time it was poured onto ice and extracted three times with ethyl acetate. These extracts were washed thoroughly with water and once with saturated sodium bicarbonate solution. After drying the organic extracts over sodium sulfate and evaporation, there was obtained a crystalline residue which was purified on TLC. The more mobile fraction gave 198 mg of starting material **6b,** while 225 mg of ether **6c** could be isolated from the more polar fraction. A recrystallization from methanol gave 215 mg of **6c:** mp 168–169 °C; IR ν 3400 (OH), 1020, and 960 cm^{-1} (ether); NMR δ 0.85 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 0.86 (s, 3, 18-CH_3), 1.00 (s, 3, 19-CH_3), 5.35 ppm (m, 1, 6-H).

Anal. Calcd for $C_{32}H_{54}O_4$: C, 76.44; H, 10.83. Found: C, 76.17; H, 10.75.

3β,20,21-Trihydroxycholest-5-ene (20-Isomeric Mixture) (6a). (a) Hydrolysis of Ether 6b. To the solution of 500 mg of the ether **6b** in 50 mL of tetrahydrofuran was added 1 drop of concentrated HCl and the solution was kept at 50 °C for 30 min. Then it was poured into a saturated solution of sodium bicarbonate and the product was extracted with ether. This extract furnished 403 mg of triol **6a,** mp 182–186 °C, after recrystallization from aqueous methanol. This mixture resembled very closely (IR, NMR, mobility on TLC, mixture melting point) the authentic[10] (20*R*) isomer.

(b) Isohexylmagnesium Grignard on 3β,21-Diacetoxypregn-5-en-20-one (5c). This was carried out with **5c** in a very similar fashion to the reaction of identical Grignard reagent with the ether **5b.** This reaction was carried out on a 5-g scale. Purification of the crude triol **6a** was achieved by dissolving the oil in a minimum of benzene, followed by careful addition of hexane to bring about crystallization of 2.9 g of pure product, identical with that obtained from the Grignard reaction on the tetrahydropyranyl ether, and followed by acid hydrolysis.

3β-Hydroxy-21-norcholest-5-en-20-one (7b). To the stirred solution of 3 g of the triol **6a** in 50 mL of dioxan was added dropwise the solution of 3.5 g of lead tetraacetate in 50 mL of benzene. After 18 h, the inorganic material was removed by filtration and washed with benzene. The filtrate was washed with saturated sodium bicarbonate solution and water and dried, and the solvent was evaporated. The syrupy residue was crystallized from methanol to give 2.4 g of pure ketone **7b,** indistinguishable from authentic[8] material.

Registry No.—**1,** 35961-41-2; **2a,** 63216-14-8; **2b,** 63216-15-9; **3a,** 63216-16-0; **3b,** 63216-17-1; **5a,** 1164-98-3; **5b,** 63216-18-2; **5c,** 1693-63-6; (20*R*)-**6a,** 61505-31-5; (20*S*)-**6a,** 26273-31-4; (20*R*) **6b,** 63216-19-3; (20*S*)-**6b,** 63268-04-2; (20*R*)-**6c,** 63268-05-3; **7a,** 34026-85-2; **7b,** 38673-20-0; **8a,** 34153-88-3; **8b,** 41083-90-3; **9a,** 63268-02-0; **9b,** 63216-21-7; **9c,** 6252-45-5; **10a,** 34026-87-4; **10b,** 63268-03-1; **10c,** 34026-88-5; 3-methylbutanal, 590-86-3; isohexylbromide, 626-88-0.

References and Notes

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